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Cette thèse intitluée:

The Development of an Expedient Method for the Synthesis of a Diverse Series of Cyclopropane α-Amino Acids.

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Sommaire

Cette thèse présente un ensemble de réalisations accomplies dans le domaine de la cyclopropanation d'oléfines par des réactifs diazo. Cette recherche a été appliquée à la synthèse d'acides aminés cyclopropanés. Ces motifs sont présents tant dans les produits naturels que synthétiques. De plus ils possèdent des propriétés biologiques intéressantes.

Une voie rapide et efficace a été developpée pour la préparation des α-nitro-α-diazocarbonyles. Ces derniers ont par la suite été utilisés dans des réactions de cyclopropanation d'oléfines catalysées par des complexes de Rh(II) ou Cu(I). Une version asymétrique a aussi été développée qui permet la synthèse des 1-nitro-cyclopropanecarbonyles avec des énantioselectivités modestes.

La réaction de cyclopropanation peut être effectuée dans l'eau, un résultat surprenant puisque les composés diazo sont reconnus pour procéder à des réactions d'insertion O-H avec des rendements élevés. Une méthodologie permettant la génération *in situ* de diazo acétate d'éthyle a également été developpée. Ceci représente un progrès majeur pour l'industrie car l'utilisation de composés diazo à grande échelle peut être dangeureux due à la nature explosive de ces derniers. Cette méthode permet donc la génération contrôlée dans le milieu, de petites quantités du diazo.

Une méthode de génération *in situ* d'ylures d'iodonium, qui sont des équivalents de diazo sans toutefois posséder leur caractère explosif, a aussi été developpée pour remplacer les α-nitro-α-diazocarbonyles. Ces ylures peuvent aussi être utilisés dans la réaction de cyclopropanation catalysée par Rh(II) au même titre que les diazos.

La réduction de nitro cyclopropanes a finalement été effectuée avec succès, malgré l'extrême sensibilité du motif cyclopropane aux nucléophiles et aux acides. Les catalyseurs de Pd qui sont souvent utilisés pour la réduction ont conduit à la destruction du motif cyclopropane, mais en utilisant de la fine poudre de zinc dans le 2-propanol, une réduction efficace a été observée, conduisant aux produits désirés avec des rendements élevés.

Le motif nitro cyclopropane sert aussi comme un synthon utile dans la synthèse organique. La synthèse de dihydropyrroles a été accomplie en traitant les 1-nitro-cyclopropanecarbonyles avec des amines primaires. Un oxydation peut donner accès à des pyrroles hautement fonctionnalisées. De plus, l'ouverture des cyclopropanes donne accès à des isoxazolines *N*-oxydes qui par la suite peuvent participer dans une cycloaddition 1,3-dipolaire. Cette stratégie a été envisagée pour la synthèse des β-lactames fonctionnalisées.

MOTS CLÉS: Acides aminés cyclopropanés
α-Nitro-α-diazocarbonyles
La catalyse asymétrique
La génération *in situ* de réactifs diazo
Ylures d'iodonium

Summary

This thesis presents a collection of developments made in the field of diazo chemistry involving the cyclopropanation of olefins. The main goal of this research was to develop a new and efficient synthetic methodology for the synthesis of cyclopropane α-amino acids. This class of amino acids appears in natural and synthetic products and has been shown to have very interesting biological properties.

An expedient and efficient method was developed for the preparation of α-nitro-α-diazocarbonyls. These diazo compounds undergo efficient cyclopropanation reactions with olefins catalyzed by Rh(II) and Cu(I) complexes. Accordingly, the presence of chiral ligands on these metal complexes allow for the catalytic asymmetric preparation of 1-nitro cyclopropanecarboxylates in modest enantioselectivities.

The cyclopropanation reaction was also found to proceed in aqueous media, an interesting observation due to the synthetic efficiency of O-H insertion reactions with diazo compounds. This led to the development of an *in situ* method for generation of ethyl diazoacetate. This methodology permits the controlled formation of ethyl diazoacetate in the reaction mixture, representing a safe alternative for diazo-mediated cyclopropanations on a large scale.

A method involving the *in situ* generation of phenyliodonium ylides derived from α-nitrocarbonyls, which represent synthetic equivalents of diazos, was also developed to eliminate potential explosion hazards associated with the use of α-nitro-α-diazocarbonyls. These ylides undergo Rh(II)-catalyzed cyclopropanation reactions in a very similar manner to those observed with the corresponding diazo compounds.

The sensitive nature of 1-nitro cyclopropanecarboxylates made their reduction very challenging. Pd-based hydrogenation catalysts, which are often used to reduce nitro groups, led only to the destruction of the cyclopropane moiety. However, zinc dust in 2-propanol enabled an efficient reduction of these cyclopropanes to the desired cyclopropane amino esters in excellent yields. These compounds can then be easily transformed into the desired cyclopropane α-amino acids upon saponification of the ester.

The nitro cyclopropanecarbonyl moiety can also serve as a useful synthon in organic synthesis. Dihydropyrroles could be prepared upon treatment of 1-nitro-1-ketocyclopropanes with a variety of primary amines. Oxidation of these dihydropyrroles then allows rapid access to densely functionalized pyrroles. 1-Nitro cyclopropane carboxylates can also participate in cascade reactions. A cascade reaction involving an intramolecular rearrangement to an isoxazoline *N*-oxide followed by a 1,3-dipolar cycloaddition reaction with an olefin was developed. A strategy was envisioned using this approach for the synthesis of densely functionalized β-lactams.

KEY WORDS:

Cyclopropane α-amino acids
α-Nitro-α-diazocarbonyls
Asymmetric catalysis
In situ generation of diazos
Phenyliodonium ylides

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List of Abbreviations

$[\alpha]_D$	optical rotation
Å	angström
Ac	acetyl
ACC	amino cyclopropanecarboxylate
anal.	elementary analysis
aq.	aqueous
Ar	aromatic group
atm	atmosphere
Bn	benzyl
Boc	*tert*-butylcarbonyl
b.p.	boiling point
br	broad
^oC	degrees Celsius
calcd	calculated
cat.	catalytic
δ	chemical displacement
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
Decomp.	decomposed
DMAP	dimethylaminopyridine
DMF	dimethylformamide
E	entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
FAB	fast atom bombardment

g	gram
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i-Pr	isopropyl
IR	infrared
J	coupling constant
Lit.	literature
M	molar
MAB	metastable atom bombardment
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm Hg	millimeters of mercury
mmol	millimole
μL	microliter
M.p.	melting point
NBS	*N*-bromosuccinimide
n-Pr	*n*-propyl
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PG	protecting group
Ph	phenyl
ppm	parts per million
p-TsOH	*para*-toluene sulfonic acid
pyr	pyridine
ref.	reference
R_f	relative mobility
rt	room temperature

TBDPS	tertiary butyl diphenylsilyl
t-Bu	tertiary butyl
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
t_r	retention time
Z	zusammen

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CHAPTER 1

Cyclopropane α-Amino Acids

1.1 Introduction

Cyclopropane chemistry is amazingly diverse and continues to fascinate scientists from a broad range of backgrounds. Theoreticians, synthetic or structural chemists and biochemists with interests in natural product or medicinal chemistry have all shown great interest in this field. This cyclic three-membered carbon ring also represents a source of great wonder for the fundamental aspects of bonding and challenges the skills of organic chemists in the preparation of highly strained molecules.

On a more practical basis, the cyclopropane moiety has a significant role in medicinal chemistry. It is estimated that by the year 2010, 10% of all the pharmaceuticals on the market will contain a cyclopropane subunit.[1] This compares even more favorably than the biaryl subunit, which appears in approximately 4.3% of pharmacologically active compounds.[2] This virtually ubiquitous three-membered carbocycle may serve a variety of purposes in drug design including: the rigidification of molecular conformations, as in the cyclopropane analogue of tamoxifen (**1**),[3] an effective medication for the treatment and possible prevention of breast cancer; or its introduction into peptides **2**, where it rigidifies the three-dimensional conformation of the peptide acting as an excellent mimic of the bound state (Fig. 1).[4]

Nature has also chosen to use a cyclopropane skeleton to design a defense mechanism for certain pyrethrum flowers against insect attack.[5] In the case of *trans*-

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1.(a) Communication S. Nguyen OMCOS 12, Toronto, ON, July 6-10, 2003. For a review on cyclopropane chemistry see: (b) de Meijere, A. Small Ring Compounds in Organic Synthesis VI Vol 207 *Top. Curr. Chem*. Springer: New York, 2000.
2. Communication K. Fagnou 14th QOMSBOC, Montréal, QC, December 5-7, 2003.
3. Davies, H. M. L.; Nagashima, T.; Klino III, J. L. *Org. Lett*. **2000**, *2*, 823-826.
4. Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 205-215.
5. Faust, R. *Angew. Chem., Int. Ed*. **2001**, *40*, 2251-2253.

chrysanthemic acid (**3**), isolated from the petals of these plants,[6] the cyclopropane is a very effective antifeedant for herbivores. It represents a broad spectrum insect repellent with low mammalian toxicity. This insecticide's efficiency has led to commercial production of a class of biomimetic insecticides produced to a tune of over $1.5 billion (US) annually.[7]

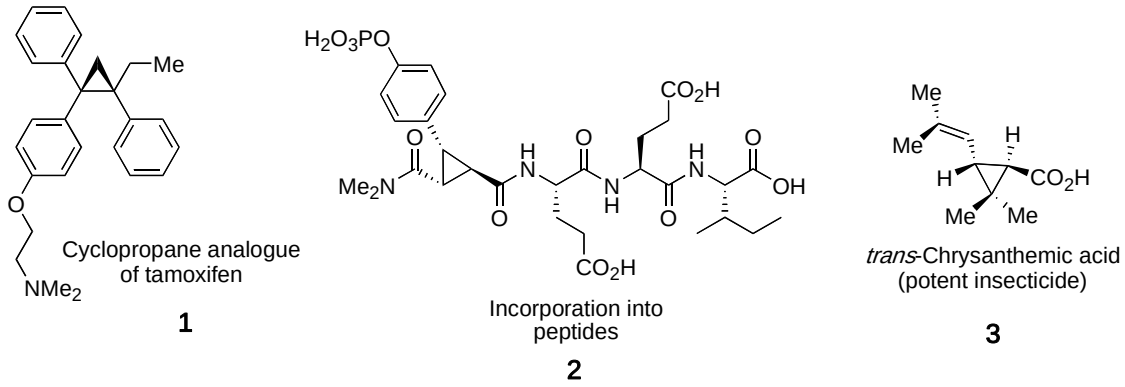
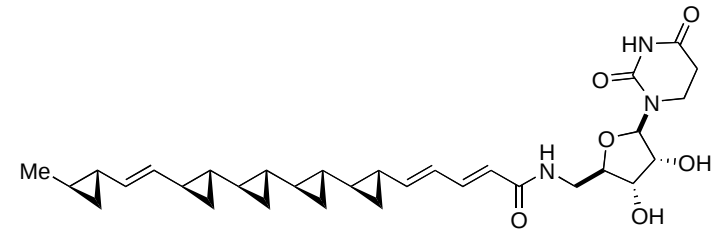


Figure 1. Applications of cyclopropanes.

Multiply cyclopropanated analogues also occur in nature. Yoshida *et al*. isolated the potent antifungal agent FR-900848 (**4**) from the fermentation broth of *Streptoverticillium fervens,* which contains four contiguous and one isolated cyclopropane unit.[8] Another related natural product isolated from *Streptomyces sp*., U-106305 (**5**), was found to act as an effective inhibitor of the cholesteryl ester transfer protein in the blood and can, thus, be envisioned to slow the progression of atherosclerosis (Fig. 2).[9]

6. Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 177-235.
7. Faust, R.; Knaus, G.; Siemeling, U. *World Records in Chemistry* (Ed. Quadbeck-Seeger, H.- J.), Wiley-VCH, Weinheim, **1999**, pg. 95.
8. Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiotics* **1990**, *18*, 748-754.
9. Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P.; *J. Am. Chem. Soc*. **1995**, *117*, 10629-10634.



(-)-FR-900848
Potent antifungal agent

4

(-)-U-106305
Cholesteryl ester transfer protein inhibitor

5

Figure 2. Natural products containing multiple cyclopropane subunits.

The medicinal importance of these cyclopropane containing products justifies the keen interest in the development of new methods for the construction of cyclopropanes in a stereo-controlled fashion.[10] Many current methods rely on toxic or highly pyrophoric reagents, thus the development of new methodologies that can avoid use of these reagents are of great interest. In the context of the development of a commercially viable methodology, the availability and toxicity of the implicated reagents must be carefully examined. Attempts to accommodate these issues in a new cyclopropanation methodology will be addressed in the following chapters.

1.2 Naturally occurring cyclopropane α-amino acids

The design and synthesis of amino acids with enhanced properties has been an ongoing subject of research in the Charette group. As a result, we became interested in the preparation of α,α-disubstituted amino acids due to their important role in the design of peptides with enhanced properties. This area of peptidomimetics has inspired keen interest in the scientific community. In conjunction with the group's

10. For a recent review on stereo-controlled cyclopropanations see: Lebel, H.; Marcoux, J.- F.; Molinaro, C.; Charette, A. B. *Chem. Rev*. **2003**, *103*, 977-1050.

successes in the stereo-controlled synthesis of cyclopropanes, the synthesis of cyclopropane α-amino acids containing chiral quaternary centers[11] represents a particularly attractive and challenging research goal.

Many researchers have paid particular attention to the special characteristics that the cyclopropane ring confers on a peptide in which it is incorporated. The introduction of the cyclopropane unit imposes the formation of new stereocenters in addition to the creation of new stereoisomers. Therefore, a very interesting way to decrease the conformational freedom of peptides is to incorporate amino acids containing a cyclopropane subunit.

There are few known examples of naturally occurring cyclopropane α-amino acids and only one of which is abundant in nature. The parent compound, 1-amino-1-cyclopropane carboxylic acid, (ACC, (**6**), Fig. 3) occurs in every green plant.[12] It was discovered by two independent research groups in 1957, where it was isolated from perry pears and cider apples by Burroughs[13] and extracted from cowberries by Vähätalo and Virtanen.[14] This cyclopropane amino acid **6** represents the eighty-eighth natural amino acid to be discovered.

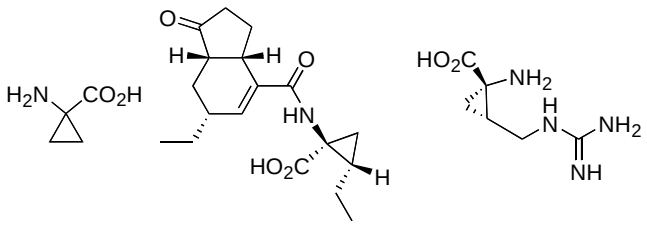


Figure 3. Naturally occurring cyclopropane α-amino acids.

11. For reviews on the catalytic enantioselective construction of molecules with quaternary carbon stereocenters see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 4591-4597. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 388-401. (c) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037-2066.
12. Yang, S. F.; Hoffman, N. E.; *Annu. Rev. Plant Physiol*. **1984**, *35*, 155-189.
13. Burroughs, L. F. *Nature* **1957**, *179*, 360-361.
14. Vähätalo, M. L.; Virtanen, A. I. *Acta Chem. Scand*. **1957**, *11*, 741-743.

ACC (**6**) plays a very important role in plants as it serves as the direct synthetic precursor to the plant hormone, ethylene. Since ethylene is a volatile gas, plants have evolved an ingenious method for ethylene fixation, storing it in the form of a simple, non-volatile amino acid. Ethylene gas can be released upon action of the Ethylene Forming Enzyme (EFE) on this amino acid **6**. Ethylene is a phytohormone that initiates and regulates many aspects of plant growth including fruit ripening, wound healing, germination of seeds, senescence (wilting and other catabolisms, such as Fall colors), abscission (dropping of Fall leaves) and responses to environmental stress.[15]

The role of ACC (**6**) in plants has a great impact to human activities as well. If you consider the tremendous losses of agricultural products due to over-ripening, the development of products to control the production of ethylene could have a profound value to the global food supply. Progress made towards the understanding and development of inhibitors of the EFE with this in mind will be the topic of further discussion in Section 1.3.1 along with the structure-activity relationships of substituted ACC's and the Ethylene Forming Enzyme (EFE).

Coronatine (**7**), is another naturally occurring cyclopropane α-amino acid produced by the bacteria *Pseudomonas coronafacience var. atropurpurea* (Fig. 3).[16] Infection of host plants by these bacteria induces chlorosis on the leaves, due to production of **7**. In addition, this phytotoxin also induces hypertrophy of potato cells, inhibits root elongation in corn and stimulates ethylene biosynthesis at concentrations below 1.0 μM.[16] Plant defense against herbivores involves the release of volatile substances, which act as SOS signals attracting predators that prey on herbivores. It has been shown that coronatine (**7**) is superior to jasmonic acid in inducing the biosynthesis and emission of volatiles.[17]

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15. Pirrung, M. C. *Acc. Chem. Res*. **1999**, *32*, 711-718.
16. Ichihara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *66*, 636-637.
17. Boland, W.; Hopke, J.; Donath, J.; Nüske, J.; Bublitz, F. *Angew. Chem., Int. Ed*. **1995**, *34*, 1600-1602.

Carnosadine (**8**) was isolated from the red algae, *Grateloupia carmasa* and its biological activities are yet unknown (Fig. 3).[18] The asymmetric synthesis of carnosadine (**8**) and its protected analogues have been reported for use in the incorporation into peptides where it represents conformationally constrained surrogates of arginine.[19]

1.3 Applications of cyclopropane α-amino acids

1.3.1 Applications of cyclopropane α-amino acids as low molecular weight inhibitors

Considerable interest has been devoted to cyclopropane α-amino acids (ACC's) in recent years on account of their biological activities as low molecular weight inhibitors. The understanding and development of inhibitors related to the Ethylene Forming Enzyme (EFE) have been research interests for many groups. Yang and Ichihara found that *allo*-coronamic acid (**9**) is preferred over its other stereoisomers as a substrate for the production of 1-butene in plants.[20] As a result, a variety of analogues were prepared to study their inhibition abilities of the EFE. Hydroxymethyl-ACC (**10**) was found to be a good inhibitor with a $K_i/K_m = 1$.[21] The cyclopropene analogue (**11**) of ACC (**6**) was found to be one of the best competitive inhibitors with a $K_i/K_m = 0.6$, forming acetylene by plant tissue, but at a rate of only 0.2% of the rate ACC (**6**) is converted to ethylene (Fig. 4).[22]

18.(a) Wakamiya, T.; Nakamoto, H.; Shiba, T. *Tetrahedron Lett.* **1984**, *25*, 4411-4412. (b) Wakamiya, T.; Oda, Y.; Fujita, H.; Shiba, T. *Tetrahedron Lett*. **1986**, *27*, 2143-2144.

19. Burgess, K.; Ho, K.-K. *Tetrahedron Lett*. **1992**, *33*, 5677-5680.

20. Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant Physiol*. **1982**, *70*, 195-199.

21. Pirrung, M. C.; McGeehan, G. M.; *Angew. Chem., Int. Ed.* **1985**, *24*, 1044-1045.

22. Pirrung, M. C.; Trinks, U. P. *J. Chem. Soc., Chem. Commun.* **1989**, 857-859.

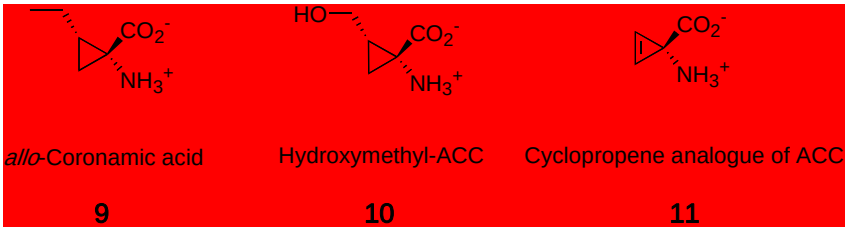
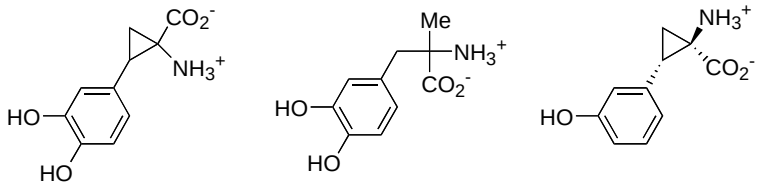


Figure 4. Inhibitors of the Ethylene Forming Enzyme (EFE).

Since there are few known naturally occurring cyclopropane α-amino acids, specific enzymes for their degradation in mammals are rare. Amino acids that are substituted with a cyclopropane have very similar electrostatic and steric profiles. Modification of an amino acid through incorporation of the cyclopropane moiety leads to only a small increase in overall steric bulk. As a result, binding of these modified amino acids to substrates tends to resemble that of the parent amino acid. However, the presence of the cyclopropane moiety greatly decreases the rate of enzymatic degradation, hence the metabolism of the modified amino acid. This in turn could result in the inhibition of certain enzymes. This represents an area of potential interest for applications in the pharmaceutical industry.

A number of 2-substituted cyclopropane α-amino acid derivatives are efficient inhibitors of DOPA carboxylase. For instance 2-(3,4-dihydroxyphenyl) cyclopropane amino acid **12**, due to its structural analogy with α-methyl DOPA (**13**), is a reversible, time-dependent inhibitor of DOPA carboxylase and of tyrosine amino transferase (Fig. 5).[23] In related research, the four possible cyclopropane analogues of *m*-tyrosine were prepared, assayed and proven to be competitive inhibitors of pig liver L-aromatic amino acid decarboxylase against D-*m*-tyrosine. It was found that the (+)-(*E*)-enantiomer **14** corresponding to that of a D-amino acid was the most potent inhibitor, showing a K_i of 22 μM, 45-fold greater than that of D-*m*-tyrosine (Fig. 5).[24]

23. Suzuki, M.; Kumar, S. D.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 4769-4771.
24. Ahmad, S.; Phillips, R. S.; Stammer, C. H. *J. Med. Chem.* **1992**, *35*, 1410-1417.



2-(3,4-Dihydroxyphenyl) cyclopropane amino acid

α-Methyl DOPA

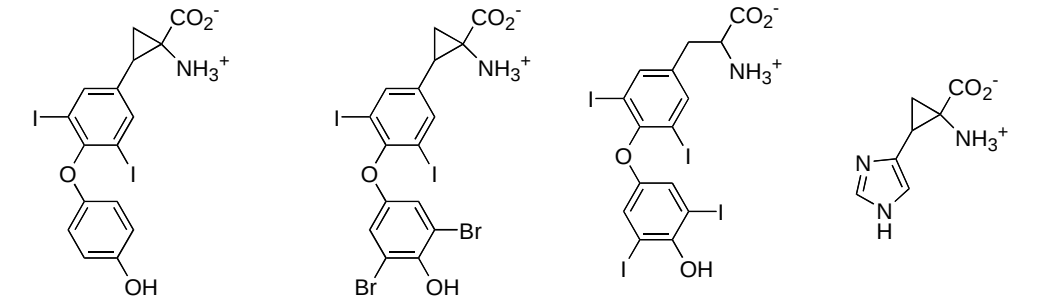
Cyclopropane analogue of *m*-tyrosine

12 **13** **14**

Figure 5. Hydroxy(2-aryl) substituted cyclopropane α-amino acid based inhibitors.

(*Z*)-2,3-Methanothyronine (**15**) and its dibromo derivative **16** have comparable activities with thyroxine (**17**), a thyroid hormone, which exhibited thyromimetic activity in basal metabolism and antigoiter tests (comparison of oxygen consumption and heart rate in normal and thyroidectomized rats), but did not have an inhibitory action on the metabolism developed by triiodothyronine (Fig. 6).[25]

(*Z*)-2,3-Methanohistidine (**18**) was also found to be an effective inhibitor of histidine decarboxylase when tested on rat liver (Fig. 6).[26]



(*Z*)-2,3-Methanothyronine

(*Z*)-2,3-Methanothyronine dibromo analogue

Thyroxine

(*Z*)-2,3-Methanohistidine

15 **16** **17** **18**

Figure 6. Cyclopropane analogues of thyronine and histidine.

The cyclopropane analogues of a variety of β-lactam antibiotics have also been prepared.[27] The cyclopropane derivative of penicillin G, (2,3)-β-methylenepenam

25. Pages, R. A.; Burger, A. *J. Med. Chem*. **1967**, *10*, 435-440.
26. Pages, R. A.; Burger, A. *J. Med. Chem*. **1966**, *9*, 766-768.

(**19**), containing an imbedded cyclopropane α-amino acid subunit, was found to possess reduced antibacterial potency when compared to its penam counterpart. Despite its poor antibacterial effectiveness, it proved to be a substrate for several β-lactamases.[28] When the cyclopropane analogue was tested in several strains of β-lactamase producing bacteria, it was found to serve as a β-lactamase inhibitor to protect the β-lactam antibacterials. A broad-spectrum β-lactamase inhibitor sulbactam (**20**) showed similar half-maximal inhibitory concentration (IC_{50}) values with its cyclopropane analogue **21** against some β-lactamases such as *Staphylococcus aureus* and *Escherichia coli R1* (Fig. 7).[28]

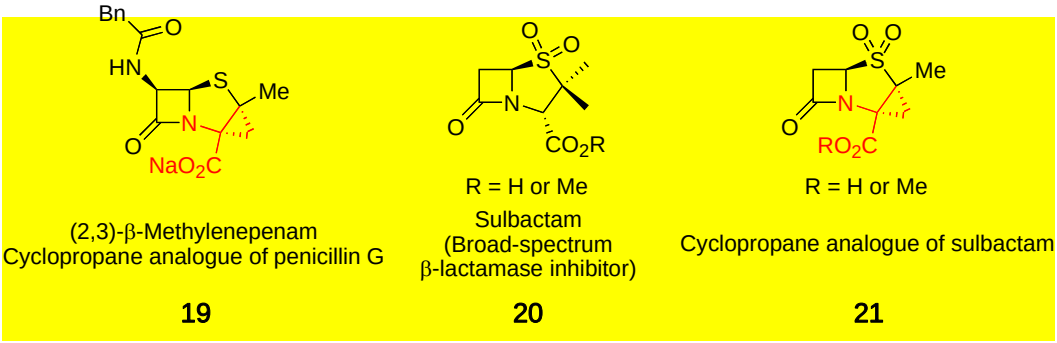


Figure 7. 2,3-Methylenepenams as β-lactamase inhibitors.

Additionally, these cyclopropane analogues exhibit greater stability towards hydrolysis, which may explain their large differences in antibacterial activity. Once they are bound, they do not acylate the enzyme to make the attachment irreversible. Furthermore, the cyclopropane analogues are locked in an unique conformation, whereas penams are less rigid and can exist in a variety of conformations.

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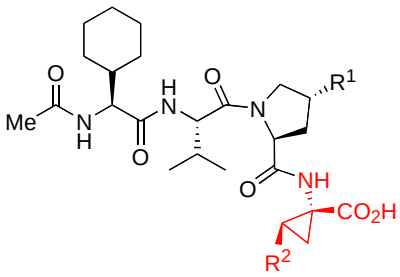
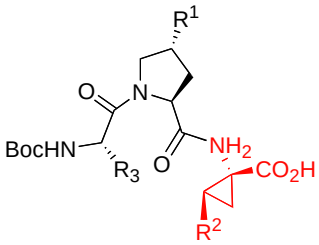
27. Kamiya, T.; Teraji, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *J. Am. Chem. Soc.* **1975**, *97*, 5020-5021.
28. Keith, D. D.; Tengi, J.; Rossman, P.; Tobaro, L.; Weigele, M. *Tetrahedron* **1983**, *39*, 2445-2458.

1.3.2 Applications of cyclopropane α-amino acids in macrocycles

Researchers at Boehringer Ingelheim recently incorporated substituted cyclopropane amino acids into small peptides[29] resulting in potent NS3 protease inhibitors against the hepatitis C virus (HCV). The first generation inhibitor was a *tetra*-peptide **22** incorporating ACC (**6**) as a terminal subunit. Its truncated analogue **23a** was a poor inhibitor of the NS3 enzyme *in vitro* but upon incorporation of 2-vinyl-ACC **23b** its potency again increased (Table 1).



22a $R^1 = R^2 = H$
22b $R^1 = X^1$, $R^2 = H$
22c $R^1 = X^1$, $R^2 = CH{=}CH_2$



23a $R^1 = R^2 = H$, $R^3 = Me$
23b $R^1 = X^2$, $R^2 = CH{=}CH_2$, $R^3 = (CH_2)_4CH_3$

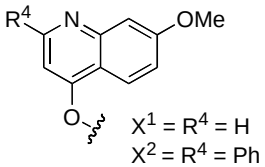


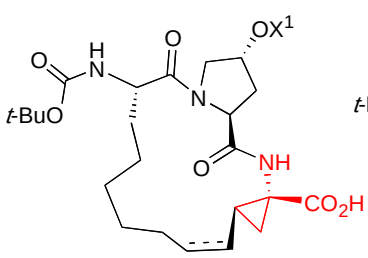
Table 1. Potency of the HCV NS3 protease inhibitors in enzymatic (IC_{50}) and cell-based assays (EC_{50}).

compound	IC_{50} (μM)[a]	EC_{50}(μM)[b]
22a	>1000	---
22b	1.4	>20.0
22c	0.047	>5.0
23a	>1000	---
23b	0.400	n.d.

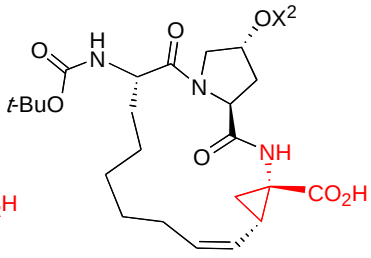
a) IC_{50} – half maximal inhibitory concentration.
b) EC_{50} – mean 50% effective concentration.

29.(a) Poupart, M.- A.; Cameron, D. R.; Chabot, C.; Ghiro, E.; Goudreau, N.; Goulet, S.; Poirier, M.; Tsantrizos, Y. S. *J. Org. Chem*. **2001**, *66*, 4743-4751. (b) Rancourt, J.; Cameron, D. R.; Gorys, V.; Lamarre, D.; Poirier. M.; Thibeault, D.; Llinàs-Brunet, M. *J. Med. Chem*. **2004**, *47,* 2511-2522.

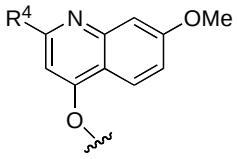
An elaborated second generation NS3 protease inhibitor included a 15-membered macrocycle with an imbedded vinyl cyclopropane amino acid subunit.[30] The researchers found that upon binding of the *tri*-peptide **23b**, the terminal carboxylic acid rotated 180° to bind in the enzyme pocket. Introduction of a macrocycle locked this optimum binding conformation.[31] The vinylic cyclopropane α-amino acid subunit was found to be 2-fold more potent that its saturated analogue (**24c** versus **24d**, Table 2). The stereochemistry of the cyclopropane was also found to be important, with the *E*-isomer 200-times more potent than its *Z*-isomer (**24c** versus **25**, Table 2).



24a R^1 = H, unsaturated bridge
24b R^1 = X^1, unsaturated bridge
24c R^1 = X^2, unsaturated bridge
24d R^1 = X^2, saturated bridge



25



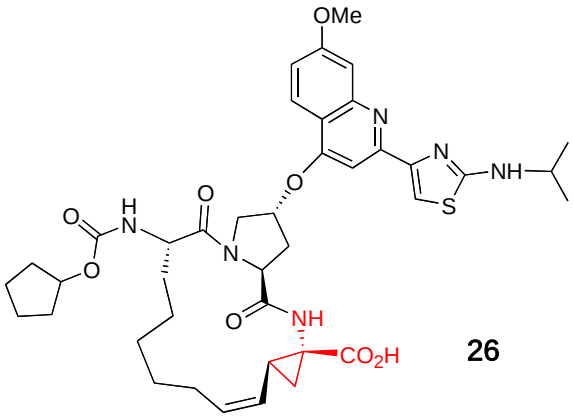
X^1 = R^4 = H
X^2 = R^4 = Ph

Table 2. Potency of macrocyclic HCV NS3 protease inhibitors in enzymatic (IC_{50}) and cell-based assays (EC_{50}).

compound	IC_{50} (μM)	EC_{50}(μM)
24a	400.0	---
24b	0.024	1.20
24c	0.011	0.077
24d	0.028	0.12
25	2.00	---

30. Tsantrizos, Y. S.; Bolger, G.; Bonneau, P.; Cameron, D. R.; Goudreau, N.; Kukolj, G.; LaPlante, S. R.; Llinàs-Brunet, M.; Nar, H.; Lamarre, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1355-1360.
31. M. Llinàs-Brunet, 14th Québec-Ontario Minisymposium on Bio-Organic and Synthetic Chemistry, Montréal, QC, December 5-7, 2003.

Additional modifications to the hydroxy-proline region of the macrocycle led to the introduction of an amino thiazole subunit, which gave a further increase in potency. The stability of the macrocycle was also increased upon replacement of the "Boc" protecting group present in macrocycles **24** and **25** with a more stable cyclopentanol derived carbamate analogue **26** (Fig. 8).[32]



26

Figure 8. Refined NS3 protease inhibitor containing a 2-vinyl ACC subunit.

This NS3 protease inhibitor was well tolerated at doses ranging from 5 to 2,000 mg in human clinical trials. Unspecific intestinal adverse events were observed at the highest dose (2,400 mg), probably due to local gastrointestinal irritations caused by the large quantity of drug. In small proof-of-concept trials this pharmaceutical **26** has been shown to reduce the hepatitis C RNA detectable in plasma and it represents the first of its kind in a new class of hepatitis C inhibitors. Macrocycle **26** possesses IC_{50} values of 4.0 and 3.0 nM for the HCV replicon 1a and 1b, respectively, and EC_{50} values of 1.2 nM. It has an apparent selectivity index with the addition of 50% human serum of 10,000 in Huh-7 cells, making it highly specific for the desired NS3 protease.

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32. Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Bös, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; Laplante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St. George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.- L.; Llinàs-Brunet, M. *Nature*, **2003**, *426*, 186-189.

1.3.3 Applications of cyclopropane α-amino acids in peptides

As alluded to in Section 1.2, perhaps the greatest pharmacological potential for cyclopropane α-amino acids exists in the field of conformationally constrained peptide mimetics.[33] It has been observed that their incorporation into peptides influences the 3-dimensional conformation of the peptide leading to more compact structures. This compression of the peptide results in reduced rates of hydrolysis, therefore, resulting in increased bioavailability of the peptide.[34] In principle, incorporation of a cyclopropane analogue could be rationally applied to almost any bioactive peptide, so the scope for this type of modification is virtually unlimited.[35]

Many examples of bioactive cyclopropane α-amino acid containing peptido-mimetics have already emerged. For instance, Asp-Acc-O(*n*-Pr) was found to be 250-300 times sweeter than sucrose,[36] while replacement of phenyl alanine by its cyclopropane analogue gave tasteless analogues of aspartame (in Asp-Phe-OMe).[37]

The influence on conformation of adding a cyclopropane analogue into peptides is well documented in the research of Burgess *et al*. Peptidomimetics of the antiopiate neuropeptide (Phe-Met-Arg-Phe-NH_2) were synthesized by exchanging methionine (Met) with each of the four isomers of its cyclopropane analogue **27**. All four peptidomimetics precipitated more morphine abstinence signs in morphine addicted rats, although the *in vitro* receptor binding studies have shown that the analogues were less strongly bound than the parent peptide (Fig. 9).[38]

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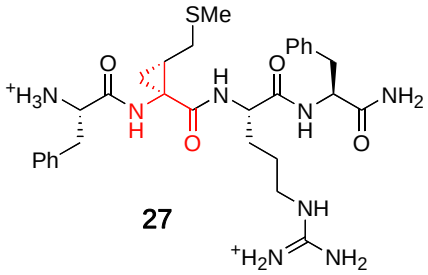
33. For a review see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517-3599.
34.(a) Burgess, K.; Ke, C.- Y. *J. Org. Chem.* **1996**, *61*, 8627-8631. (b) Hillier, M. C.; Davidson, J. P.; Martin, S. F. *J. Org. Chem*. **2001**, *66*, 1657-1671. (c) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305-1318.
35. Burgess, K.; Ho. K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575-583.
36. Tsang, J. W.; Schmeid, B.; Nyfeler, R.; Goodman, M. *J. Med. Chem*. **1984**, *27*, 1663-1668.
37. Mapelli, C.; Stammer, C. H.; Lok, S.; Mierke, D. F.; Goodman, M. *Int. J. Pept. Protein Res.* **1988**, *32*, 484-487.
38. Burgess, K.; Ho, K.-K.; Pettitt, B. M.; *J. Am. Chem. Soc*. **1995**, *117*, 54-66.



27

Phe-(*2S,3S*-cyclo-Met)-Arg-Phe-NH_2

Antiopiate *tetra*-peptide

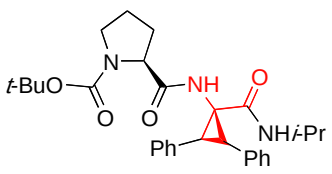
Figure 9. Antiopiate *tetra*-peptide containing a cyclopropane analogue of methionine.

The parent sequence (Phe-Met-Arg-Phe-NH_2) was found to have the expected random coil conformation in solution, however, introduction of cyclopropane analogues of methionine (Met) showed a bias toward defined secondary structures in solution. For example, the Phe-((*2S,3S*)-cyclo-Met)-Arg-Phe-NH_2 analogue **27** was found to have good correlation indicating a bias toward a γ-turn structure in solution (Fig. 9).[38]

In addition to the induction of three-dimensional conformational preferences in solution, both enkephalin[39] and Phe-Met-Arg-Phe-NH_2 peptides[40] containing cyclopropane analogues had exceptional proteolytic stability towards carboxypeptidase or leucine aminopeptidase digestion respectively. This implies that substitution with cyclopropane analogues can generally provide proteolytically stable materials.

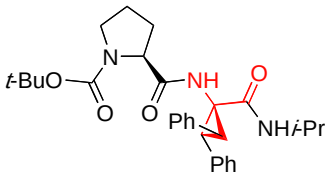
Cativiela *et al*. have also reported the presence of a γ-turn induced by the introduction of a highly constrained cyclopropane analogue of phenylalanine into a *tri*-peptide. In solid state, one enantiomer **28** adopts a classical βII-turn while the other enantiomer **29** adopts a γ-turn centered at the cyclopropane (Fig. 10).[41]

39. Kimura, H.; Stammer, C. H.; Shimohigashi, Y.; Cui, R. L.; Stewart, J. *Biochem. Biophys. Res. Commun*. **1983**, *115*, 112-115.
40. Malin, D. H.; Lake, J. R.; Ho, K.-K.; Corriere, L. S.; Garber, T. M.; Waller, M.; Benson, T.; Smith, D. A.; Luu, T.-A.; Burgess, K. *Peptides* **1993**, *14*, 731-734.
41. Jiménez, A. I.; Cativiela, C.; Marraud, M. *Tetrahedron Lett.* **2000**, *41*, 5353-5356.



Tri-peptide which exhibits a βII-turn

28

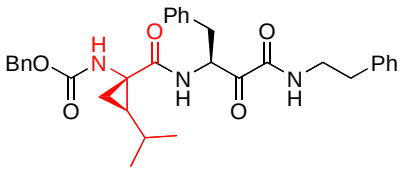


Tri-peptide which exhibits a γ-turn

29

Figure 10. The induction of β- and γ-turns in *tri*-peptides using cyclopropane analogues of phenylalanine.

The influence of incorporating cyclopropane α-amino acids into *tri*-peptides was also studied in calpain inhibitors, a cytosolic calcium-activated neutral protease. The enzyme has been implicated in a number of pathological conditions including neurological disorders (eg. stroke), cataracts, cardiac ischemia and thrombotic platelet aggregation. A *tri*-peptide, already known to have good inhibition of the enzyme, was modified by the introduction of the four possible stereoisomers of leucine **30**. These cyclopropane analogues were studied and found to have pronounced effects on inhibition of calpain I. The cyclopropane analogues of leucine, unfortunately, led to a 10-fold decrease in potency, but significant gains in selectivity of the peptide were observed when assayed in the presence of cathepsin B (Fig. 11).[42]



Tri-peptide based inhibitor of calpain I

30

Figure 11. *Tri*-peptide based inhibitor of calpain I containing the cyclopropane analogue of leucine.

Incorporation of cyclopropane α-amino acids into peptides provide a means to manipulate their conformations, and in turn bioactivities, as briefly illustrated above.

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42. Donkor, I. O.; Zheng, X.; Miller, D. D. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2497-2500.

Their introduction can also be greatly beneficial to the proteolytic stability of the peptide as well. However, the number of proven cases is minimal in comparison with the vast potential for this type of peptidomimetic. The main obstacle to further progress has been inaccessibility of optically pure cyclopropane α-amino acids. Consequently, efficient asymmetric syntheses of these materials are both timely and important.

1.4 Preparation of cyclopropane α-amino acids

1.4.1 Preparation of ACC

In order to gain insights into the synthesis of substituted cyclopropane α-amino acids, one has to first examine the synthesis of the simplest member of the family, namely, 1-amino-1-cyclopropanecarboxylic acid (ACC, **6**). Although it is naturally occurring, it is too costly to isolate this amino acid from natural sources due to its low concentrations. There have been a number of interesting strategies for its synthesis, many of which have been applied to the synthesis of more synthetically challenging substituted cyclopropane α-amino acids.

One method of synthesis of ACC (**6**) includes the method of Häner and Seebach involving the nitration of a di-*tert*-butylhydroxyanisole (DBHA) derived cyclopropanecarboxylate enolate. This enolate was prepared upon treatment of DBHA cyclopropanecarboxylate (**31**) with *t*-BuLi.[43] Reduction of the resulting nitro cyclopropane **32** was accomplished using Pd on carbon (1 atm H_2) for 48 h, followed by oxidative removal of the ester using hydrogen peroxide and formic acid (Scheme 1).

Another expedient synthesis of ACC (**6**) was realized upon dialkylation of isocyanide ethylester (**33**) with 1,2-dibromoethane, affording cyclopropane **34** in 58% yield.[44] Hydrolysis and saponification of this ester **34** and treatment with HCl afforded **6** (Scheme 1) in quantitative yield. This method can also be applied to the synthesis of other cyclic amino acids.

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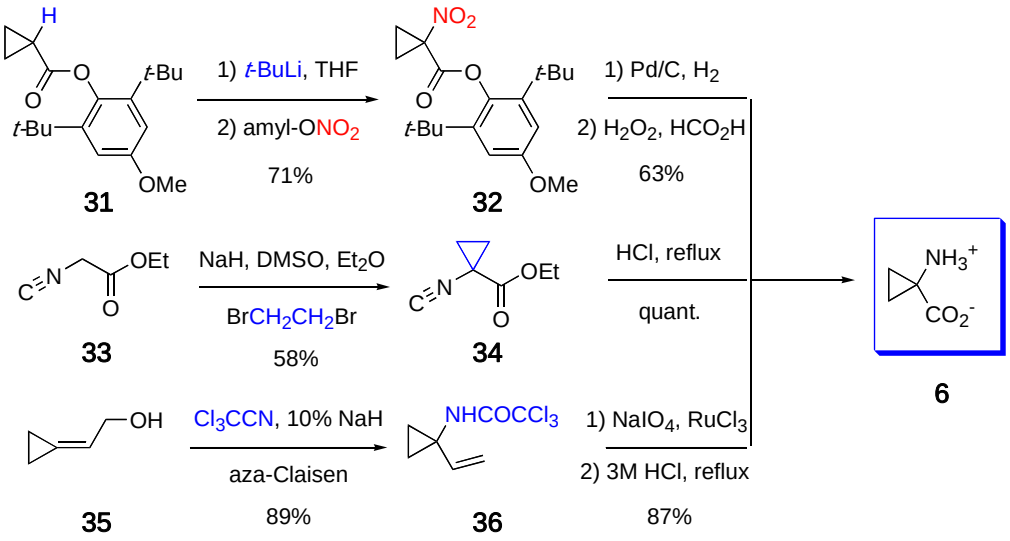
43. Häner, R.; Seebach, D. *Chimia*, **1985**, *39*, 356-357.
44. Schöllkopf, U.; Hoppe, D.; Jentsch, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 331-333.

An aza-Claisen rearrangement has also been used for the synthesis of ACC (**6**). In this approach, the readily available cyclopropylidine-ethanol (**35**) rearranges thermally, *via* a [3,3] sigmatropic rearrangement to provide the trichloroacetamide **36** in 89% yield. Oxidative cleavage of the olefin followed by refluxing in 3M HCl affords ACC (**6**) in 87% (Scheme 1).[45]

Scheme 1. Synthetic strategies for the synthesis of ACC (**6**).



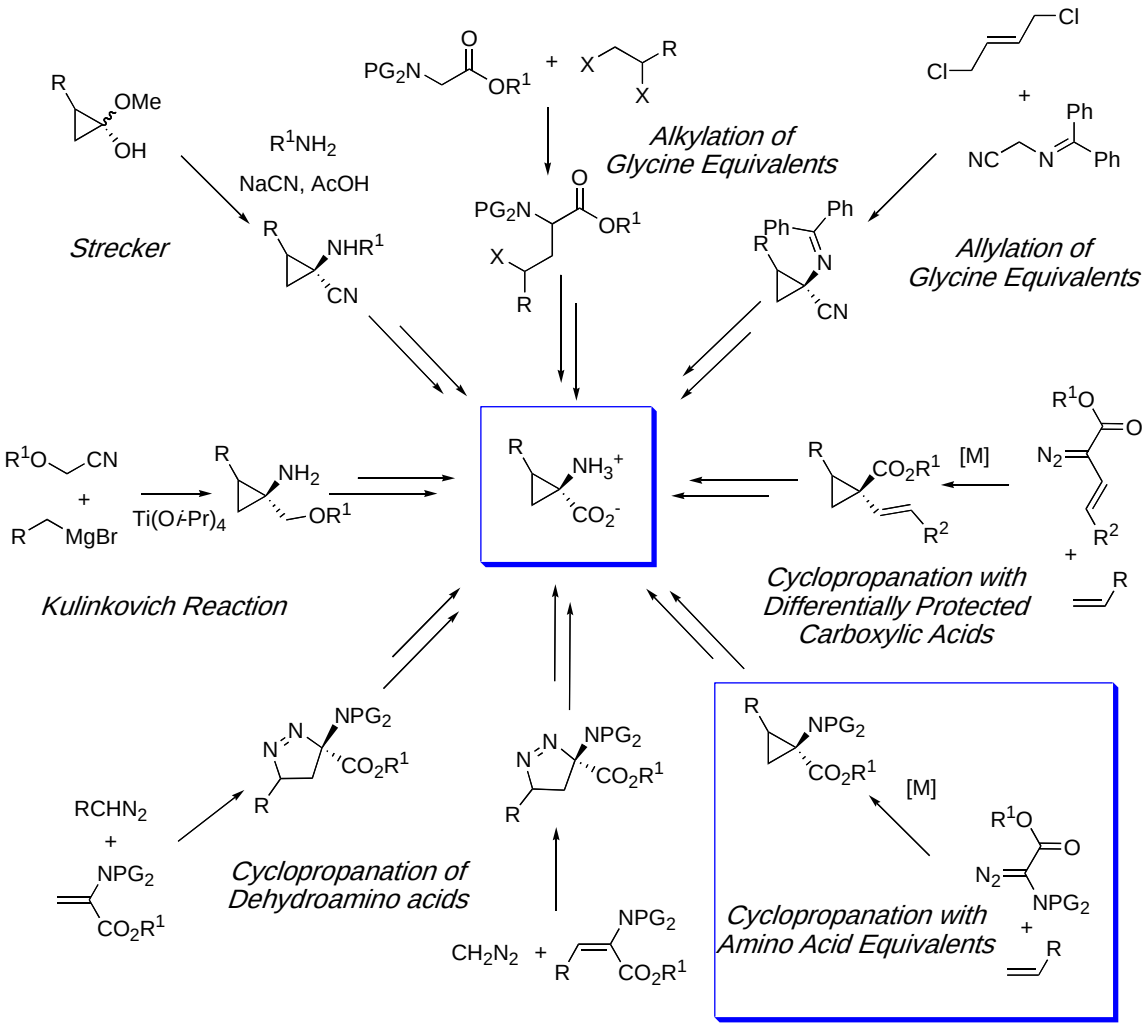
Since few naturally occurring substituted cyclopropane α-amino acids exist, their isolation from natural sources for large-scale use is impossible. Consequently, diastereoselective and enantioselective methods for their preparation become important. The stereo-controlled synthesis of chiral quaternary carbon stereocenters makes these molecules very challenging indeed. Further elements of complexity arise from the presence of the often sensitive cyclopropane moiety. To date, more than 50 synthetic methodologies have been developed to tackle this challenging problem in organic synthesis. A brief summary of these methods will follow in addition to some of the perceived benefits and drawbacks of each method.

The general strategies for the synthesis of cyclopropane α-amino acids can be placed into six main categories including: a) cyclopropanation of functionalized α,β-

45. Estieu, K.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1995**, *36*, 2975-2978.

dehydroamino acids, b) Curtius or Hofmann rearrangements of differentially protected cyclopropane dicarboxylic acids, c) double alkylations of glycine anion equivalents, d) cyclopropanation using amino acid equivalents, e) Strecker or allylations and f) modified Kulinkovich reactions (Scheme 2).

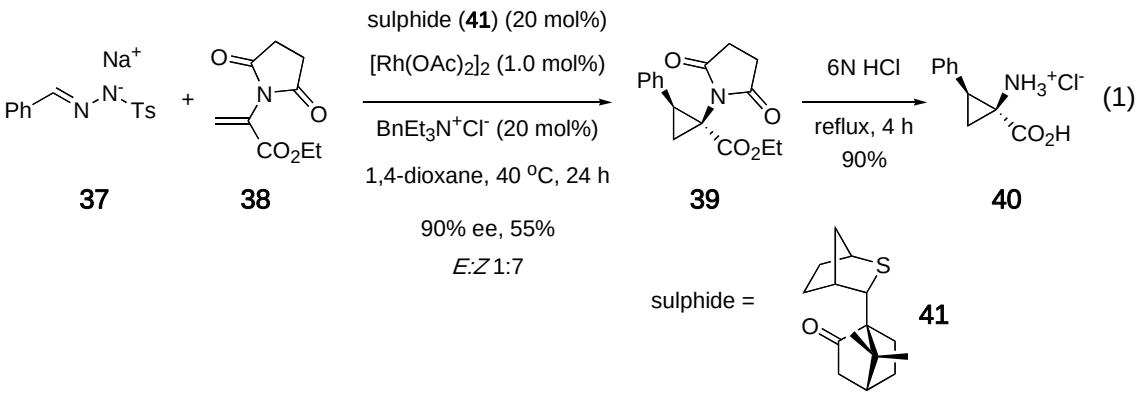
Scheme 2. Strategies for the preparation of cyclopropane α-amino acids.



1.4.2 Cyclopropanation of functionalized α,β-dehydroamino acids

Probably one of the most popular methods for the synthesis of cyclopropane α-amino acids involves the addition of diazo compounds or ylides to dehydroamino

acids. A catalytic asymmetric variation of this strategy involving Michael additions of sulfur ylides to dehydroamino acids is a good illustrative example, which was recently reported by Aggarwal *et al.*[46] In this methodology, phenyl diazomethane is formed *in situ* upon treatment of the insoluble tosylhydrazone salt **37** with a phase transfer catalyst ($BnEt_3N^+Cl^-$). Upon formation of phenyl diazomethane, $[Rh(OAc)_2]_2$ catalyzes the formation of a sulfur ylide derived from chiral sulphide **41**. A highly enantioselective Michael addition then occurs with dehydroamino acid **38**, affording the protected cyclopropane amino acid **39** in modest yields of 55% (Eq. 1). The reaction proceeds with reasonable diastereoselectivities (*E:Z* = 1:7) and with excellent enantiomeric excess (90%). Cleavage of the protecting groups was accomplished upon refluxing in 6N HCl, revealing the *Z*-cyclopropane analogue of phenylalanine (**40**, Eq. 1). Cyclopropanation of the di-Boc protected α-amino acrylate derivative of **38** gave slightly higher yields (72%), reduced diastereoselectivities (*E:Z* = 1:6) and similar enantioselectivities (92% ee).

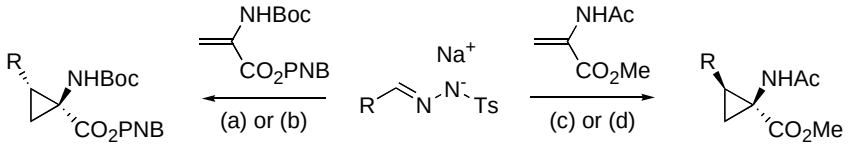


In a follow-up of this research, the scope of a related racemic methodology involving the direct cyclopropanation of protected amino acrylates **38** was explored. In this case, the absence of the chiral sulfide **41** makes the reaction mechanistically different than described in Eq. 1. The reaction scope was expanded to include other aromatic and α,β-unsaturated hydrazones **43** as diazo precursors. Table 3 summarizes

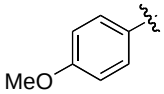
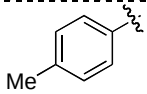
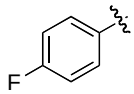
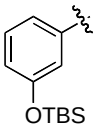
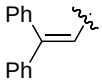
46. Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433-1436.

the yields and diastereoselectivities possible for the racemic synthesis of 2-substituted cyclopropane α-amino acids.[47]

Table 3. Reaction scope for the tosylhydrazone-mediated cyclopropanation.



Cond. (a) $BnEt_3N^+Cl^-$ (5 mol%), toluene, 40 °C, 60 h.
(b) Starting with RCH=NNHTs (i) LiHMDS, THF, -78 °C to rt;
(ii) $BnEt_3N^+Cl^-$ (5 mol%), toluene, 40 °C, 60 h.
(c) ClFeTPP (1 mol%), $BnEt_3N^+Cl^-$ (5 mol%), toluene, 40 °C, 60 h.
(d) Starting with RCH=NNHTs (i) LiHMDS, THF, -78 °C to rt;
(ii) ClFeTPP (1 mol%), $BnEt_3N^+Cl^-$ (5 mol%), toluene, 40 °C, 60 h.

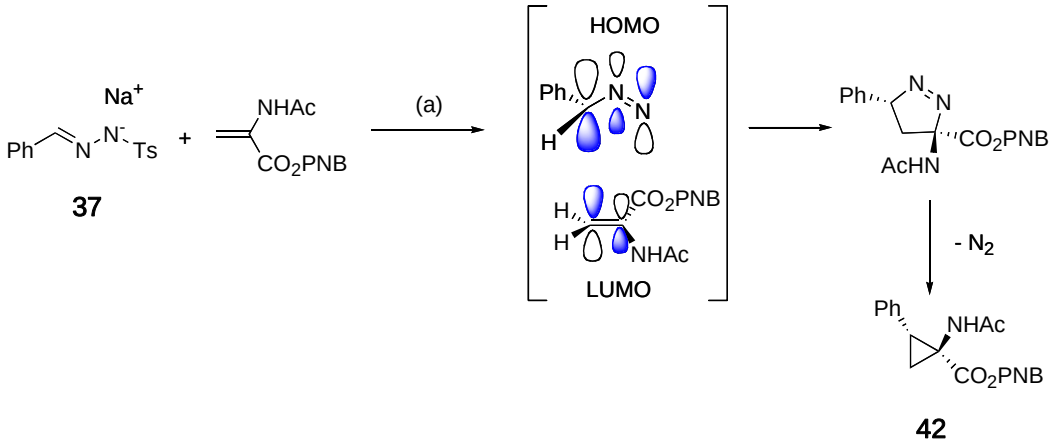
entry	R	cond.[a]	yield (%)	*E:Z* ratio
1		(a)	50	95:5
2		(c)	84	19:81
3		(a)	72	95:5
4	MeO	(c)	52	12:88
5		(a)	52	89:11
6	Me	(c)	49	14:86
7		(a)	62	87:13
8	F	(c)	82	14:86
9		(b)	47	96:4
10	OTBS	(d)	44	16:84
11		(a)	76	66:34
12	Ph Ph	(c)	82	8:92
13		(b)	36	72:28

a) 2.0 equiv of the dehydroamino acid was used.

47. Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vincente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433-9440.

This methodology attempts to address the difficult task of selectively forming *E*- or *Z*-diastereomers by using two different sets of reaction conditions. In the case of the *E*-selective non-catalyzed cyclopropanation reaction conditions (a) or (b), the authors propose a 1,3-dipolar cycloaddition of the diazo compound with the dehydroamino acid followed by ring contraction and extrusion of nitrogen affording the *E*-diastereomer of the cyclopropane (**42**, Scheme 3). In contrast, the iron porphyrin catalyst leads to *Z*-selective cyclopropane **44** formation, presumably *via* an iron-carbene intermediate (Table 3). Unfortunately, this methodology is plagued by long reaction times (60 h) and the reaction yields with many aromatic or α,β-unsaturated hydrazones remain only modest (Table 3). Furthermore, issues of enantioselectivity were not addressed and the preparation of more highly functionalized cyclopropanes, such as 2,2- or 2,3-disubstituted cyclopropane α-amino acids, is not possible using this protocol.

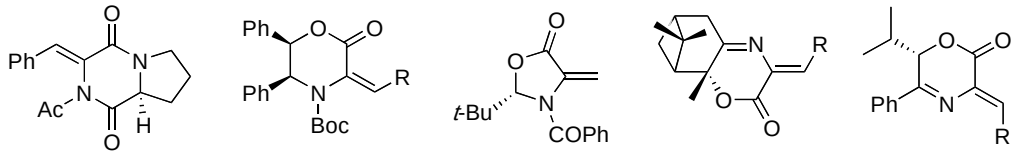
Scheme 3. Cyclopropane formation *via* a 1,3-dipolar cycloaddition pathway.



A variety of chiral auxiliaries representing dehydroamino acids have also been developed for application to related cyclopropanation reactions including: **45**,[48] **46**,[49]

48. Fernández, M. D.; de Frutos, M. P.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett*. **1989**, *30*, 3101-3104.
49. Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796-8806.

Seebach's dehydroalanine derivative **47**,[50] **48** derived from (*1R,2R,5R*)-2-hydroxy pinan-3-one[51] and **49** (Fig. 12).[52] Cyclopropanation can occur with a variety of reagents including diazomethane,[48,49] sulfur ylides[49,51,52] and phosphorus ylides. Often cyclopropanations using these auxiliaries affords mixtures of diastereomers, which must then be separated. Cleavage of the auxiliary affords the desired amino acid, which also must be separated from the auxiliary.



45 **46** **47** **48** **49**

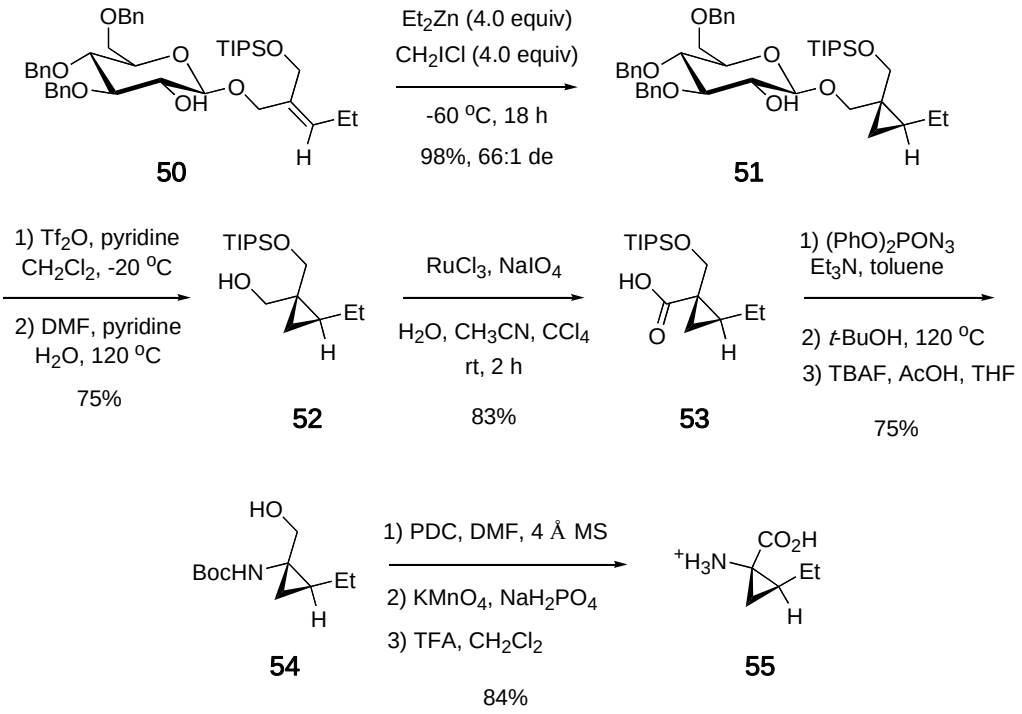
Figure 12. Auxiliaries based on dehydroamino acids.

1.4.3 Cyclopropane α-amino acid synthesis *via* Curtius or Hofmann rearrangements

Another popular method for the synthesis of cyclopropane α-amino acids involves the use of Curtius or Hofmann rearrangements for incorporation of the quaternary amine. In this strategy, a cyclopropane containing two differentially protected carboxylic acid equivalents is selectively transformed into an amine. This approach was used in the Charette laboratories for the preparation of the four possible isomers of coronamic acid employing a Simmons-Smith protocol for the highly diastereomeric preparation of **55** (Scheme 4).[53]

50. Chinchilla, R.; Nájera, C. *Tetrahedron Lett*. **1993**, *34*, 5799-5802.
51. Calmes, M.; Daunis, J.; Escale, F. *Tetrahedron: Asymm*etry **1996**, *7*, 395-396.
52. Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *J. Org. Chem*. **2000**, *65*, 3034-3041.
53. Charette, A. B.; Côté, B.; *J. Am. Chem. Soc.* **1995**, *117*, 12721-12732.

Scheme 4. Simmons-Smith approach to coronamic acid (**55**).

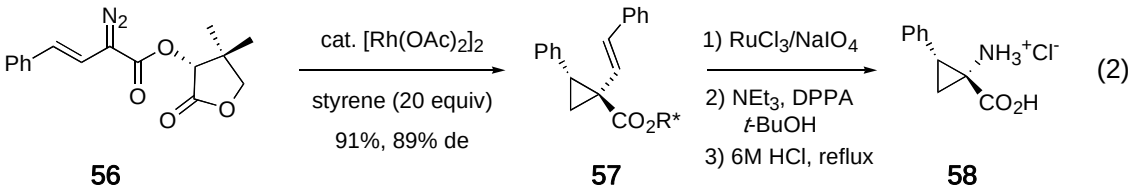


This method allows the preparation of the four-isomers of coronamic acid in excellent yields and excellent diastereomeric excesses, albeit a rather lengthy sequence is required. The key step of the synthesis involves use of a sugar (D-glucose) derived auxiliary in a highly diastereoselective Simmons-Smith cyclopropanation reaction yielding cyclopropane **51**. Cleavage of the auxiliary followed by oxidation of the free alcohol **52** to the corresponding carboxylic acid **53** enables a Curtius rearrangement for introduction of the quaternary amine. Deprotection and oxidation of the alcohol and removal of the "Boc" protecting group affords coronamic acid (**55**, Scheme 4).[53] The other three-isomers can be accessed using the same sugar derived auxiliary, either with protecting group inter-conversions or using the *E*-isomer of olefin **50**.

Perhaps, the most expedient and reliable approach to date for the synthesis of substituted cyclopropane α-amino acids was reported by Davies *et al.*[54] employing a similar strategy. The synthesis of *Z*-(*2R*,*3R*)-2-phenyl-cyclopropane-1-amino acid

54. Davies, H. M. L.; Cantrell Jr. W. R. *Tetrahedron Lett.* **1991**, *32*, 6509-6512.

(**58**) was accomplished upon cyclopropanation of styrene with a benzylidene diazoester **56** containing a (*R*)-(-)-pantolactone chiral auxiliary. Oxidative cleavage of the benzylidene cyclopropane **57**, Curtius rearrangement of the resulting carboxylic acid and hydrolysis resulted in the desired cyclopropane **58** in 17% overall yield (Eq. 2).

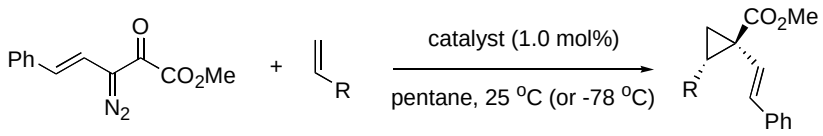


56 **57** **58** (2)

The catalytic asymmetric variant of this approach, using chiral rhodium catalysts based on (*S*)-*N*-benzenesulfonylprolinates **61** or **62**, resulted in highly enantioselective cyclopropanation reactions.[55] Additionally, the scope of the cyclopropanation reaction with various olefin substrates allowed for the synthesis of a broad range of cyclopropanes (**60**, Table 4).

55. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897-6907.

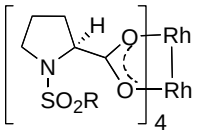
Table 4. Catalytic asymmetric cyclopropanations with benzylidene diazoesters.



59 **60**

catalyst	temp. (°C)	R	ee (%)	yield (%)
61	25	Ph	90	79
62	-78	Ph	98	68
61	25	*p*-ClPh	89	91
62	-78	*p*-ClPh	>97	70
61	25	*p*-MeOPh	83	87
62	-78	*p*-MeOPh	90	41
61	25	AcO	76	40
62	-78	AcO	95	26
61	25	EtO	59	83
62	-78	EtO	93	65
61	25	*n*-Bu	>90	63
61	25	Et	>95	65
61	25	*i*-Pr	95	58

catalyst =



R = 4-*t*-BuC_6H_4 (**61**),
R = 4-($C_{12}H_{25}$)C_6H_4 (**62**)

This method takes advantage of the wealth of commercially available olefins, thus lending it great scope. One of the few drawbacks, however, is the incompatibility of sensitive functionalities. The oxidative cleavage of the benzylidene, necessary for incorporation of the quaternary amine *via* a Curtius rearrangement, is the source of this limitation. It should also be mentioned that the Curtius rearrangement requires the use of freshly distilled reagents in order to obtain reasonable yields. Furthermore, in an industrial setting, the use of azides and diazo-based reagents would be strongly discouraged due to their inherent toxicities and potential for explosions.

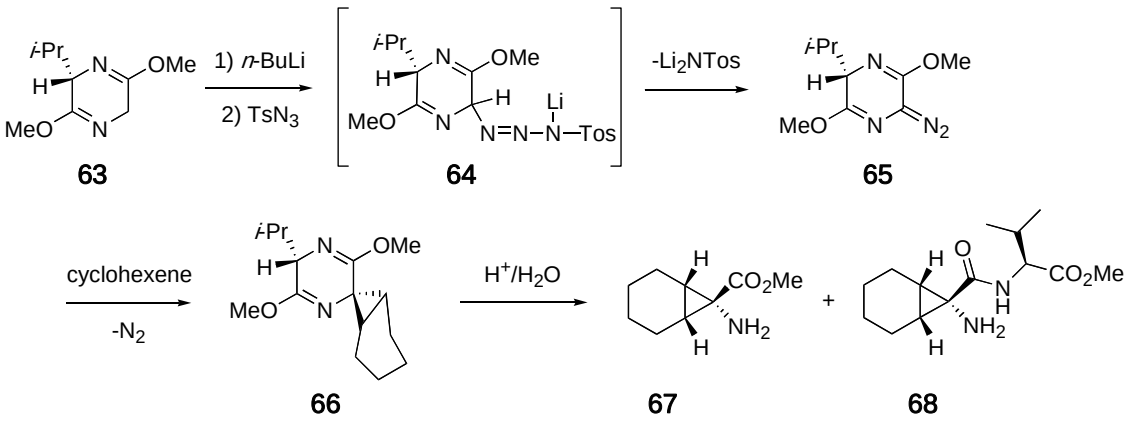
1.4.4 Cyclopropanations with amino acid equivalents

In light of the inherent disadvantages associated with the use of Curtius and Hofmann rearrangements previously outlined, a cyclopropanation reaction involving amino acid equivalents represents an attractive approach. It has the potential to reduce the length of the synthetic sequence necessary to prepare the cyclopropane α-amino acids and broaden the reaction scope, since an oxidative cleavage step is not necessary.

Schöllkopf *et al.* reported the first example of a cyclopropanation reaction involving an aminocarboxycarbene equivalent.[56] The aminocarboxydiazo substrate **65** was formed upon lithiation of a bislactim ether **63** and treatment with tosyl azide *via* intermediate **64**. The aminocarboxydiazo **65** was found to be stable at -70 ^{o}C but upon warming to room temperature, the diazo decomposed into its free carbene. The presence of a large excess of olefin (30 mL of cyclohexene to 3.0 mmol bislactim), allowed isolation of the corresponding spiro compound **66**, which could be recovered in reasonable yields (71%). Hydrolysis of the bislactim ether **66** was achieved upon stirring in 0.25N HCl for 7 days, affording a mixture of the *endo*-aminocyclopropane methyl ester **67** (43%) and the dipeptide ester (**68**, 38%, Scheme 5). This precedence setting cyclopropanation reaction with an amino acid equivalent clearly defined the challenges of using this strategy. The reactivity of this carbene and the difficulty of cleavage of the bislactim ether **66** were clearly limitations.

56. Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed.* **1986**, *25*, 192-193.

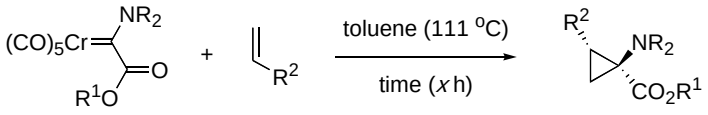
Scheme 5. Schöllkopf's bislactim ether method.



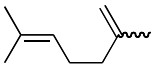
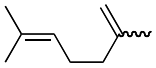
Another report of a cyclopropanation reaction using aminocarboxycarbenes was reported by Barluenga *et al*.[57] In this case, a cyclopropanation reaction of a variety of olefins with chromium(0) carbonyl carbene complexes **69** proceeded in modest yields, affording the corresponding amino cyclopropanecarboxylates **70**, often with good diastereoselectivities (Table 5). However, one obvious drawback is the necessity for stoichiometric use of the toxic chromium complex **69**.

57. Barluenga, J.; Aznar, F.; Gutiérrez, I.; Garcia-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett*. **2002**, *4*, 4273-4276.

Table 5. Cyclopropanation with chromium(0)-based aminocarboxycarbenes.



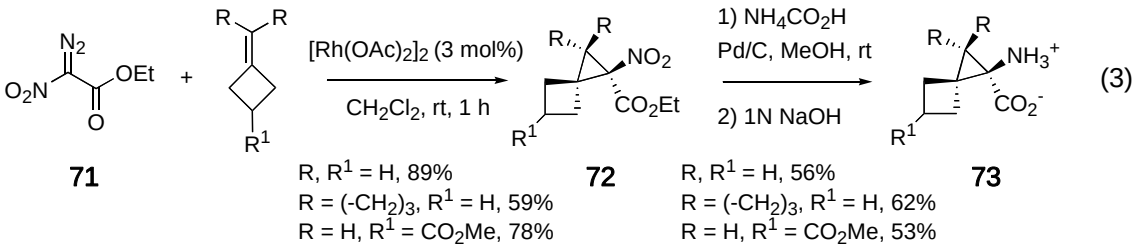
69 **70**

NR_2	R^1	R^2	time (h)	*E*:*Z* ratio	yield (%)
NMe_2	*t*Bu	Ph	24	>95:5	79
NMe_2	*t*Bu	hexyl	50	>95:5	68
NMe_2	*t*Bu	CH_2OTBS	30	1:1	91
NMe_2	*t*Bu		48	70:30	70
NBn_2	Me	Ph	24	>95:5	35
morpholine	Me	Ph	30	>95:5	70
morpholine	Me		20	>95:5	69

An α-nitro-α-diazoester can also be viewed as an amino acid equivalent upon reduction of the nitro group. A number of researchers have been interested in cyclopropanations involving these substrates including O'Bannon and Dailey,[58] Snider and Che[59] and Kuznetsova *et al*.[60] α-Nitro-α-diazocarbonyls represent a much more stable amino acid equivalent and they undergo efficient cyclopropanations with a variety of olefin substrates, including tetrasubstituted examples, in the presence of rhodium catalysts. This type of diazo substrate **71** was recently applied to the synthesis of a variety of spirohexane amino acids (Eq. 3).[60a] The cyclopropanation reaction went smoothly with di- and tetrasubstituted olefins in short reaction times (1 h) affording nitro cyclopropanecarboxylates **72** in modest to excellent yields.

58. The research of O'Bannon and Dailey will be discussed in depth in Chapter 3.
59. Snider, B. B.; Che, Q. *Tetrahedron* **2002**, *58*, 7821-7827.
60.(a) Yashin, N. V.; Averina, E. B.; Gerdov, S. M.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett*. **2003**, *44*, 8241-8244. (b) Ivanova, O. A.; Yashin, N. V.; Averina, E. B.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirov, N. S. *Russ. Chem. Bull., Int. Ed*. **2001**, *50*, 2101-2105.

Reduction of the nitro group was possible using ammonium formate (NH_4CO_2H) in the presence of Pd on carbon followed by treatment with sodium hydroxide (Eq. 3).[60a]



71

R, R^1 = H, 89%
R = $(-CH_2)_3$, R^1 = H, 59%
R = H, R^1 = CO_2Me, 78%

72

R, R^1 = H, 56%
R = $(-CH_2)_3$, R^1 = H, 62%
R = H, R^1 = CO_2Me, 53%

73

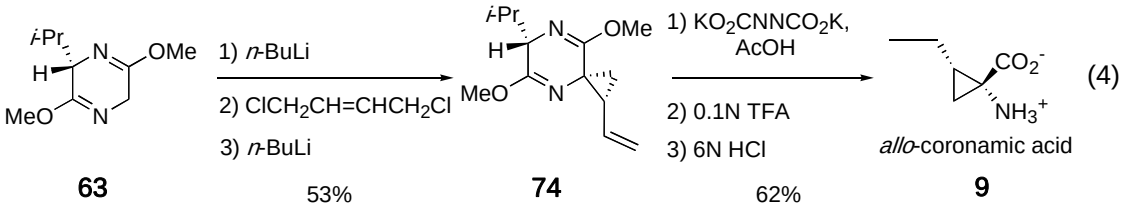
(3)

Use of these diazo compounds in a cyclopropanation methodology also benefits from the widespread availability of olefins as reaction partners, making the rapid synthesis of a diverse series of cyclopropane α-amino acids possible. Our progress in this field will be the subject of this thesis and the advantages and disadvantages of the method will be discussed in the following chapters.

1.4.5 Double alkylations of glycine equivalents

Another intuitively straightforward method for the synthesis of cyclopropane α-amino acids involves the double alkylation of glycine equivalents.[61] Schöllkopf's bislactim ethers **63** have also been employed in this approach to make selected amino acids including *allo*-coronamic acid (**9**). Thus, bislactim ether **63** was treated with *trans*-1,4-dichloro-2-butene and two equivalents of *n*-BuLi to give vinyl cyclopropane **74** in 83% yield with an additional 17% of material corresponding to the other three possible diastereomers. Diastereomerically pure material was isolated in 53% yield after chromatographic separation. Diimine reduction of **74**, followed by hydrolysis of the chiral auxiliary afforded *allo*-coronamic acid (**9**) in 62% yield (Eq. 4).[62]

61. See for example: Aitken, D. J.; Royer, J.; Husson, H.- P. *J. Org. Chem*. **1990**, *55*, 2814-2820.
62. Groth, U.; Halfbrodt, W.; Schöllkopf, U. *Liebigs Ann. Chem*. **1992**, 351-355.

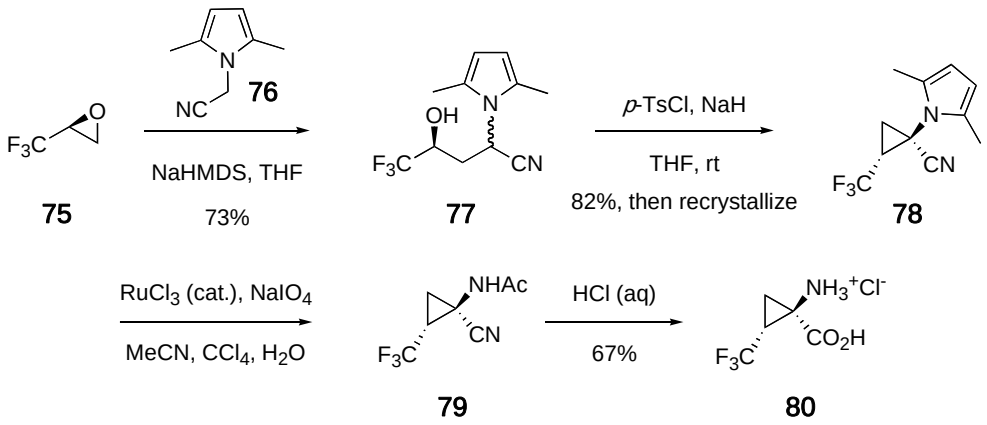


63 53% **74** 62% **9** (4)

The treatment of epoxides with glycine equivalents can also lead to the synthesis of cyclopropane α-amino acids. The synthesis of optically active trifluoronorcoronamic acid (**80**) was realized using this strategy by Uneyama *et al*. from the optically active 2,3-epoxy-1,1,1-trifluoropropane (**75**).[63] Thus, treatment of **75** with an α-cyanopyrrole **76** led to cyanohydrin **77** in 30% de. The diastereomeric mixture was then cyclized to cyanocyclopropane **78**, yielding only one diastereomer in 75% ee which could be enriched to >99% ee upon recrystallization (70%). Oxidative degradation of the pyrrole portion of **78** liberated acetylated amine **79**, which upon acid hydrolysis afforded the optically pure trifluoronorcoronamic acid (**80**, Scheme 6).

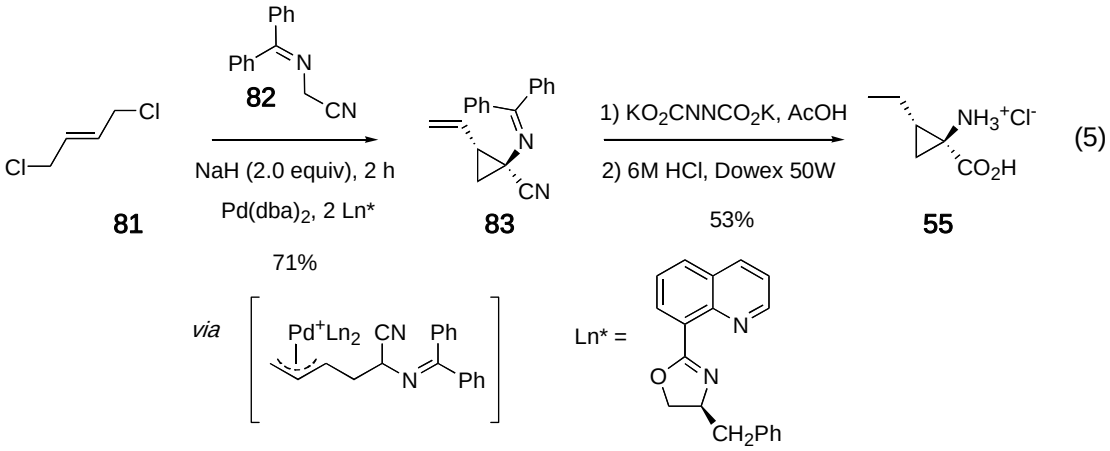
63. Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett*. **2000**, *2*, 2423-2425.

Scheme 6. Synthesis of trifluoronorcoronamic acid from a chiral epoxide.



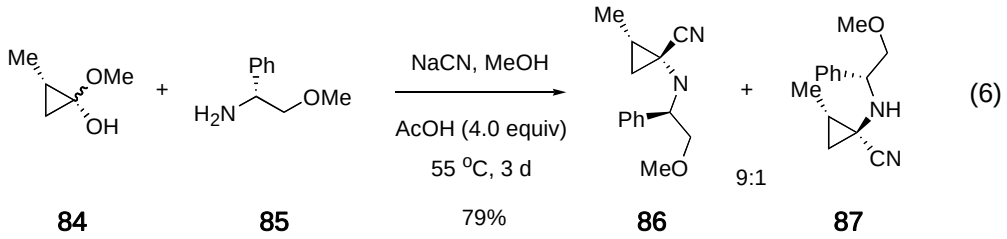
1.4.6 The allylation and Strecker approach

A related method to the alkylation with glycine equivalents is the less commonly used allylation methodology. A catalytic asymmetric synthesis of coronamic acid (**55**) using 1,4-dichlorobut-2-ene (**81**) was realized upon treatment of *N*-(diphenylmethyleneamino) acetonitrile (**82**) with a Pd(0) complex and a chiral oxazoline-based ligand. This afforded the cyanocyclopropane **83**, which after diimide reduction and acid hydrolysis, afforded coronamic acid (**55**) in 20% ee (Eq. 5).[64]



64. Zhou, Y. B.; Ma, J. A.; Wang, L. X.; Zhou, Q. L. *Chin. Chem. Lett*. **2002**, *13*, 939-941.

A diastereoselective Strecker reaction has also been used to prepare cyclopropane α-amino acids. In this approach, a chiral cyclopropanone hemiacetal **84** and a chiral amine **85** were submitted to standard Strecker conditions to afford a 9:1 mixture of cyanocyclopropanes **86** and **87** in 79% isolated yield (Eq. 6). Hydrolysis of the nitrile to the amide, hydrogenolysis of the benzyl amine using palladium on carbon, followed by hydrolysis of the amide afforded the desired cyclopropane amino acid.[65]

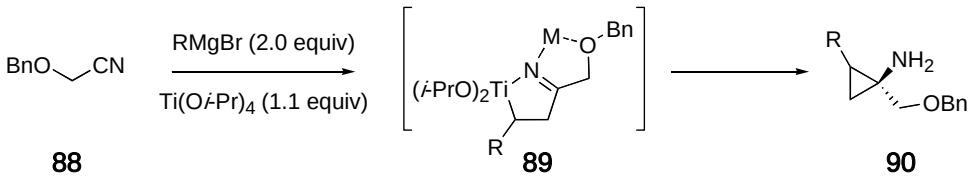


1.4.7 Modified Kulinkovich reaction

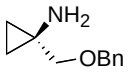
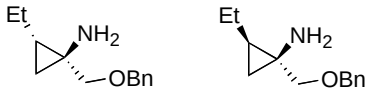
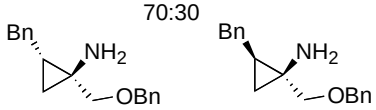
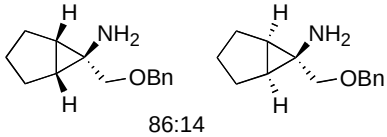
An attractive approach for the racemic synthesis of cyclopropylamines directly from α-benzyloxy nitriles and Grignard reagents also provides an expedient strategy for the synthesis of cyclopropane α-amino acids. In this approach, α-benzyloxy nitrile (**88**) was converted to the corresponding cyclopropylamine **90** in 74% yield upon treatment with EtMgBr (2.0 equiv) and Ti(O*i*-Pr)$_4$ (1.1 equiv) in THF *via* intermediate **89**. The scope of this reaction could be extended to include other Grignard reagents, affording the substituted cyclopropylamines in modest yields (Table 6).[66] The corresponding amino acids can be prepared upon protection of the amine, removal of the benzyl ether protecting group (hydrogenolysis), followed by oxidation of the liberated alcohol and deprotection of the amine.

65. Fadel, A.; Khesrani, A. *Tetrahedron: Asymm*etry **1998**, *9*, 305-320.
66. Bertus, P.; Szymoniak, J. *J. Org. Chem*. **2002**, *67*, 3965-3968.

Table 6. Ti(IV) mediated conversion of α-benzyloxy nitriles to cyclopropylamines.



88 89 90

entry	RMgBr	product	yield (%)
1	EtMgBr		74
2	BuMgBr	 70:30	61
3	Ph(CH$_2$)$_3$MgBr	 64:36	64
4	*c*-C$_5$H$_9$MgCl	 86:14	45

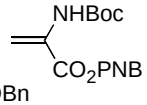
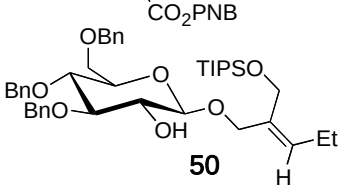
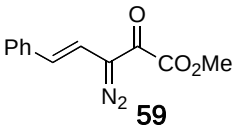
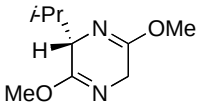
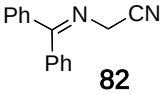
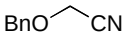
1.5 Conclusions

The preparation of 1-aminocyclopropanecarboxylic acid derivatives has been the subject of numerous synthetic efforts in recent years. This interest stems from their diverse biological activities and potential use in conformationally constrained peptides. Applications of these amino acids in low molecular weight inhibitors and as components in macrocycles have also been shown to be of great value.

This brief survey of synthetic methodologies for the preparation of cyclopropane α-amino acids would suggest that there still remains room for improvement. Few available methods are expedient in terms of the number of synthetic manipulations required and even fewer methods offer broad reaction scope to allow the rapid preparation of a large number of derivatives. Table 7 summarizes six syntheses of coronamic acid (**55**) using different methods. There is a great deal of variation in the

number of synthetic steps required to isolate the desired amino acid, but overall, the isolated yields are quite similar.

Table 7. A summary of various syntheses of coronamic acid.

entry	author (ref.)	starting material	synthetic steps	ee (%)	overall yield (%)
1	Aggarwal (47)		4	racemic	17
2	Charette (53)	 **50**	9	97	38
3	Davies (55)	 **59**	7	>95	ca. 32
4	Schöllkopf (62)	 **63**	5	ca. 98[a]	33
5	Zhou (64)	 **82**	3	20	37
6	Szymoniak (66)	 **89**	5	racemic	31

a) Led to the synthesis of *allo*-coronamic acid.

In the above cases, the methodology usually lacked one or more elements of control, including diastereoselectivity, enantioselectivity, or required the use of rearrangements (Curtius or Hofmann) for the incorporation of the quaternary amine. These factors resulted in long synthetic sequences and low overall isolated yields. The development of a new methodology taking into account all of these considerations will be the topic of this doctoral thesis. The details of the progress made will be revealed in the following chapters.

CHAPTER 2

The Synthesis of α-Diazocarbonyl Compounds

2.1 Introduction

α-Diazocarbonyl compounds have an extensive history of useful applications in organic chemistry. They can be prepared from readily available precursors and undergo a wide variety of chemical transformations under very mild conditions. Their exceptional synthetic flexibility arises from the wide array of diazo compounds that can be utilized in this chemistry.[67] Furthermore, the loss of nitrogen can be induced in a number of different ways including thermal, photochemical or *via* organometallic catalyzed reaction pathways.

The synthetic utility of diazo chemistry for the synthesis of cyclopropanes has been well documented in the literature over the last several decades. Presently, it represents one of the most efficient means for the preparation of these three-membered carbocycles, allowing the expedient synthesis of diversely functionalized cyclopropanes. However, many challenges remain including the control of diastereoselectivities and enantioselectivities in these cyclopropanation reactions. Consequently, this subject represents an extremely active field of research today.[68]

In addition to cyclopropanation reactions, numerous other synthetically useful transformations are possible with diazo compounds, thus illustrating their great synthetic utility. These transformations include C-H insertions, aromatic cycloadditions, α,α-disubstitution reactions,[69] dipolar cycloadditions, cascade reactions resulting from ylide generation,[70] olefinations,[71] electrophilic aromatic

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67. For a review on organic synthesis with diazo compounds see: Ye, T.; McKervey, M. A. *Chem. Rev*. **1994**, *94*, 1091-1160.
68. Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* Vol 57; John Wiley & Sons: Toronto, 2001, pg. 1-326.
69. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998.
70. Padwa, A.; Weingarten, D. *Chem. Rev*. **1996**, *96*, 223-269.

substitutions, Y-H insertions (Y = O, N, S, P, Se, Si), epoxidations,[72] aziridinations[72,73] and rearrangements or transfer reactions involving ylides.[74] The types of transformations possible are largely dictated by the intrinsic reactivities of the diazo compounds in question. In particular, the substitutions that flank the diazo functionality have the greatest influence on its reactivity.

New methods for the expedient synthesis of various diazo compounds has been an area of research enabling further expansion of substrates for testing in the above transformations. Among the synthetic strategies used for the preparation of disubstituted diazo compounds, many have been diminished somewhat in usefulness since the introduction of the diazo transfer reaction. The transfer of a diazo subunit, typically using a sulfonyl azide, represents one of the most straightforward and practical methods for their synthesis.

2.2 Research objectives

Cyclopropane α-amino acids are useful for the preparation of peptidomimetics with enhanced properties or as low molecular weight inhibitors. However, their full pharmacological potential appears largely hampered by the availability of these cyclopropanes. This problem of availability is directly related to the difficulties associated with their preparation. Although numerous seemingly attractive methods have been developed, their practicality often suffers from very time consuming or lengthy reaction sequences and is invariably limited in terms of reaction scope. Presently, few of the existing methodologies can deliver a diverse series of cyclopropane α-amino acids in an expedient and enantioselective manner.

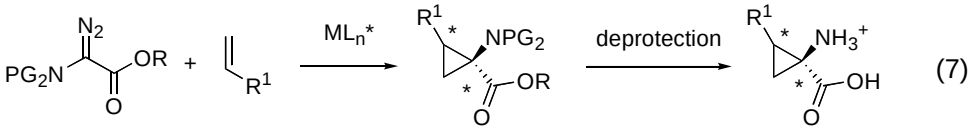
71.(a) Doyle, M. P.; Yan, M. *J. Org. Chem*. **2002**, *67*, 602-604. (b) Mirafzal, G.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc*. **2002**, *124*, 176-177. (c) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett*. **1997**, *38*, 8125-8128. (d) Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed*. **1991**, *30*, 1641-1643.

72. Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett*. **2001**, *3*, 933-935.

73. Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **1995**, *34*, 676-678.

74. Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev*. **2001**, *30*, 50-61.

The ultimate goal of this doctoral research project was, therefore, to develop an expedient and practical methodology for the catalytic asymmetric construction of cyclopropane α-amino acids. The envisioned strategy involves a challenging retro-synthetic disconnection in which a diazo compound, representing an amino acid equivalent **92**, reacts with an olefin forming a protected quaternary amino acid **70**. The amino acid **93** can then be revealed upon removal of the protecting groups (Eq. 7). In a transition metal catalyzed bond-forming scenario, the potential for asymmetric induction exists through use of chiral ligands on the metal.[68]



92 **70** **93** (7)

Masked aminodiazocarboxylate compounds **92**, or their synthetic equivalents may satisfy the envisioned strategy since transition metals can potentially catalyze bond forming reactions between diazo compounds and olefins to afford cyclopropanes. Thus, the first goal of this research was to find a suitable diazo compound representing an amino acid equivalent, which could be readily synthesized.

One advantage of the proposed strategy is the elimination for the need of Hofmann or Curtius type degradations for the introduction of the quaternary amine (Chapter 1, Section 1.4.3). Consequently, the number of synthetic manipulations necessary would be reduced, potentially leading to a more expedient synthesis of cyclopropane α-amino acids. Furthermore, in an industrial setting, azide reagents including diphenyl phosphorazidate ($(PhO)_2PON_3$) or sodium azide used in Curtius rearrangements are neurotoxic and represent explosion hazards on large-scale.[75,76]

The proposed strategy also benefits from the use of olefins as reaction substrates since they represent one of the most abundant chemical functionalities available

75. Azides are toxic and unstable: Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*, Academic Press: London 1986.
76. The hazards associated with the use of diazo compounds will be addressed in Chapter 4 and 5.

commercially. They are often inexpensive (eg. styrene $188.40 for 16.5 L) and easy to handle. Recent advances in the field of ring closing metathesis,[77] olefin cross-metathesis[78] and methylenations[79] are making structurally diverse olefins available with increasing ease.

A large number of transition metal-based complexes have been reported to successfully catalyze cyclopropanation reactions between diazo compounds and olefins. Catalysts based on Fe, Co, Ru, Rh and Cu are particularly efficient with highly reactive diazo compounds including diazomethane, diazoketones and ethyl diazoacetate (Fig. 13). On the other hand, Rh-based catalysts can be extremely active for cyclopropanations involving less reactive diazo compounds.[80]

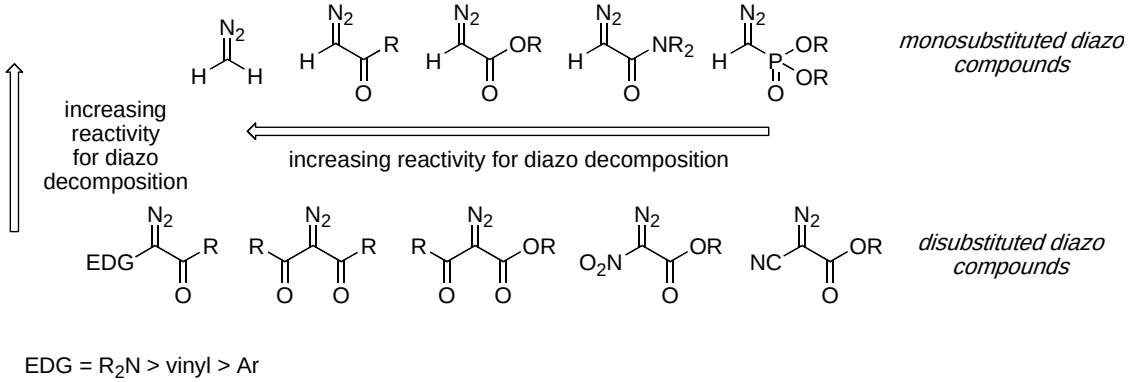


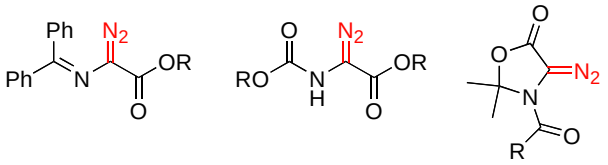
Figure 13. Relative reactivities of diazo compounds.

Tremendous advances in catalyst ligand design and catalyst efficiency have been realized in the last decade. Surprisingly, there have been few reports of

77.(a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18-29. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446-452.
78.(a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370. (b) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 4035-4037. (c) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2001**, *123*, 7767-7778.
79.(a) Lebel, H.; Paquet, V.; Proulx, C. *Angew Chem., Int. Ed*. **2001**, *40*, 2887-2890. (b) Lebel, H.; Paquet, V. *J. Am. Chem. Soc*. **2004**, *126*, 320-328. (c) Matsubara, S.; Sufihara, M.; Utimoto, K. *Synlett* **1998**, 313-315.
80. Cyclopropanation with α-aryl- and α-vinyl-α-diazoesters have been successfully catalyzed with loadings of 1.0 x 10^{-5} mol% using Rh(II) carboxylate catalysts see: Davies, H. M. L.; Venkataramani, C. *Org. Lett*. **2003**, 5, 1403-1406.

cyclopropanation reactions concerning diazo compounds that represent amino acid equivalents (see Chapter 1, Section 1.4.4) and no reports involving these types of diazo compounds in successful asymmetric cyclopropanation reactions. Therefore, this proposed strategy for the synthesis of cyclopropane α-amino acids represents a novel approach with little literature precedence.

Three criteria were desired for a suitable diazo compound which could permit the development of a successful methodology including: a) availability and ease of synthesis, b) stability and c) reactivity with transition metals containing chiral ligands. Synthetic efforts initially focused on the preparation of a variety of glycine based diazo compounds (**93-95**, Fig. 14) with these criteria in mind.



93 **94** **95**

Figure 14. Diazo compounds representing amino acid equivalents.

Significant efforts were undertaken to prepare the desired glycine based diazo compounds using a variety of synthetic strategies. However, all attempts resulted predominantly in the decomposition of the starting materials. The difficulty encountered in the synthesis of the above diazo compounds likely resulted from their inherent instabilities. The pioneering work of Schöllkopf, involving the synthesis of an α-aminodiazocarboxylate derived from a bislactim ether **65**, illustrated that decomposition of this diazo compound occurred simply upon warming to room temperature. This would suggest that the isolation and purification of diazo compounds **93-95** would also be challenging.

In light of the anticipated difficulties with product stability, the focus shifted to diazo compounds bearing two electron-withdrawing substituents. The stabilities of these diazo compounds are enhanced by the presence of two electron-withdrawing groups (see reactivity trends in Fig. 13). This led to the examination of α-nitro

carbonyls as potential amino acid equivalents in which the amine is protected as a nitro group.

The syntheses of various α-nitro-α-diazocarbonyls have been previously described in the literature and it has been highlighted that these diazo compounds are reasonably stable and can be purified on silica gel.[81] Moreover, examples of olefin cyclopropanations with these substrates using $[Rh(OAc)_2]_2$ as a catalyst were found to be high yielding.[81c,d] Another attractive feature of these diazo compounds is the commercial availability of several α-nitrocarbonyls, which could serve as potential synthetic precursors. Unfortunately, one major drawback associated with the use of α-nitro-α-diazocarbonyls is their synthesis. The examples present in the literature could be best described as tedious and low yielding.

2.3 Preparation of α-nitro-α-diazocarbonyls

2.3.1 Introduction and precedence

Although there have been numerous synthetic methodologies developed for the preparation of diazo compounds, few compete with the simplicity of the diazo transfer technique introduced by Regitz in 1967.[82] This method of synthesis represents the standard preparative route for diazo compounds, with the diazo donor almost invariably derived from a sulfonyl azide.

Previous to our contributions to the synthesis of α-nitro-α-diazocarbonyls, few methods existed in the literature, and those which did, were largely inefficient. In 1966, Balli and Löw reported a diazo transfer reaction to prepare α-nitro-α-diazocarbonyls. In this case, treatment of methyl nitroacetate (**94**) or benzoylnitromethane (**95**) with a thiazolium azide reagent **96**, followed by sodium

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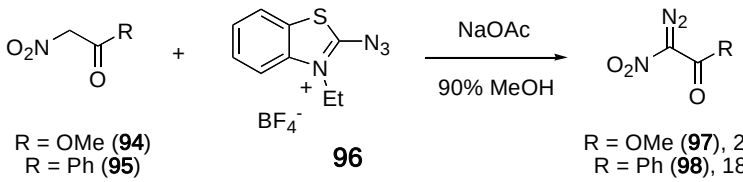
81. See for example: (a) Schöllkopf, U.; Tonne, P.; Schäfer, H.; Markusch, P. *Liebigs Ann. Chem*. **1969**, *722*, 45-51. (b) Schöllkopf, U.; Markusch, P. *Liebigs Ann. Chem*. **1971**, *753*, 143-150. (c) O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1989**, *54*, 3096-3101. (d) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341-7358.
82. (a) Regitz, M. *Angew. Chem., Int. Ed*. **1967**, *6*, 733-749. (b) Regitz, M. *Synthesis* **1972**, 351-373.

acetate in 90% methanol afforded the corresponding α-nitro-α-diazocarbonyls **97** and **98** in 23% and 18% yields, respectively, after purification on basic alumina (Eq. 8).[83]



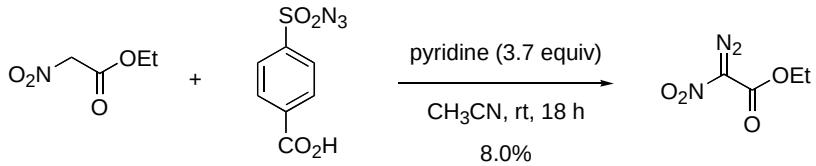
R = OMe (**94**)
R = Ph (**95**)

96

R = OMe (**97**), 23%
R = Ph (**98**), 18%

(8)

In 1968, Hendrickson and Wolf also reported the preparation of ethyl nitro diazoacetate (**71**) using a diazo transfer reaction. Treatment of ethyl nitroacetate (**99**) with *p*-carboxybenzenesulfonazide (**100**) in acetonitrile, followed by addition of pyridine afforded ethyl nitro diazoacetate (**71)** in only 8.0% yield (Eq. 9).[84]

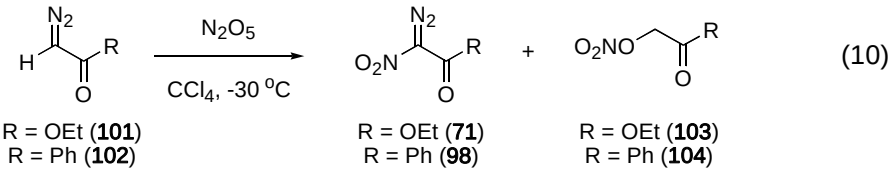


99 **100** **71**

(9)

Perhaps the most efficient method to access various α-nitro-α-diazocarbonyls was the method reported by Schöllkopf[81a] involving the nitration of diazo compounds (Eq. 10). This procedure typically affords up to 40% yield of the corresponding α-nitro-α-diazocarbonyls based on starting material. Unfortunately, the reaction yields cannot exceed 50% as one equivalent of the mono-substituted diazo substrate is consumed as a base during the nitration, producing a nitrate ester **103** or **104** as a reaction byproduct. To further complicate this reaction, the nitrate ester byproduct has to be removed from the desired diazo compound usually *via* distillation followed by column chromatography.

83. Balli, H.; Löw, R. *Tetrahedron Lett*. **1966**, *7*, 5821-5822.
84. Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem*. **1968**, *33*, 3610-3618.



R = OEt (**101**)
R = Ph (**102**)

R = OEt (**71**)
R = Ph (**98**)

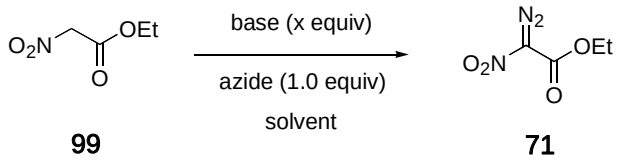
R = OEt (**103**)
R = Ph (**104**)

Although this nitration protocol can be successfully applied to the synthesis of several diazo compounds, the preparation of the nitrating reagent, N_2O_5, requires the treatment of nitrogen dioxide (toxic at levels < 100 ppm) with ozone gas. The reaction temperatures must be maintained below –10 °C to prevent degradation of the reagent back into nitrogen dioxide and ozone.[85] Carbon tetrachloride's role as the reaction solvent also adds additional elements of undesirable toxicity to this reaction making it unattractive for lab-scale preparation of these diazo compounds, let alone on an industrial scale.

2.3.2 Development of a diazo transfer methodology

The literature methods for the preparation of α-nitro-α-diazocarbonyls were highly disadvantageous for the development of an expedient methodology to access cyclopropane α-amino acids. Therefore, a new method for their preparation was sought. The use of *p*-toluenesulfonyl azide (TsN_3) has been well established in diazo transfer reactions for the preparation of 2-diazo-1,3-dicarbonyls, 2-diazo-3-ketoesters[86] and other α-acidic carbonyls. Consequently, it and a variety of structurally related sulfonyl azides were prepared and tested in a diazo transfer reaction involving ethyl nitroacetate (**99**, Eq. 11). A variety of reaction conditions and bases were also screened including TsN_3 using K_2CO_3 as a base[87] and methanesulfonyl (mesyl) azide with Et_3N, all with limited success.

85. Gruenhut, N. S.; Goldfrank, M.; Cushing, M. L.; Caesar, G. V. *Inorg. Synth*. Vol III, **1950**, 78-81.
86. Taber, D. F.; Ruckle, R. E. Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077-4078.
87. Koskinen, A. M. P.; Muñoz, L. *J. Chem. Soc., Chem. Commun*. **1990**, 652-653.



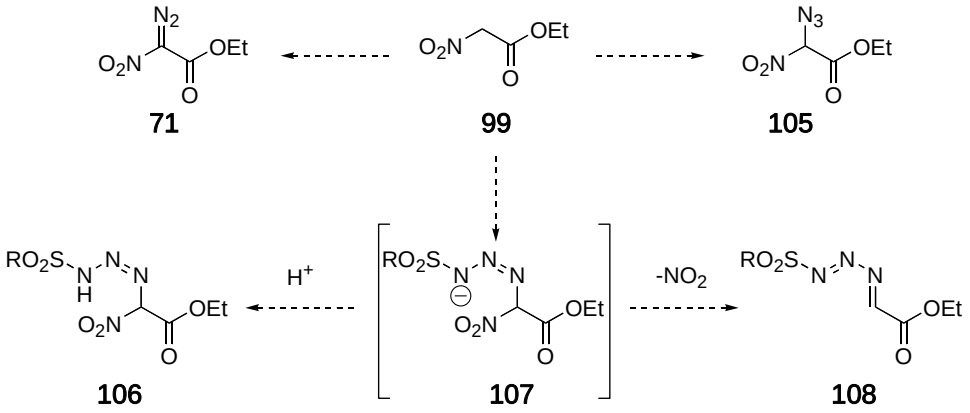
99 **71** (11)

Aromatic substituted sulfonyl azides containing electron-withdrawing groups, such as pentafluorophenyl, *p*-chlorophenyl and *p*-nitrophenyl derivatives were also tested, anticipating that a more electrophilic azide would allow diazo transfer to the highly stabilized anion of ethyl nitroacetate (**99**). All of these aromatic sulfonyl azides failed to afford reasonable yields of the desired ethyl nitro diazoacetate (**71**). Other azide reagents including diphenyl phosphorazidate (DPPA)[88] were also tested, but again only degradation of the starting materials resulted.

The failure of these azide reagents to efficiently transfer a diazo subunit to ethyl nitroacetate was particularly intriguing since all of these reagents efficiently transfer diazo subunits to other α-acidic substrates such as diethyl malonate. In the case of ethyl nitroacetate, a variety of possible side-reactions are believed to occur including: the formation of the α-azido derivative **105**, resulting from azide transfer; or the formation of triazenes **106** and **108**[89] *via* intermediate **107** which could ultimately lead to degradation upon work-up (Scheme 7).[90]

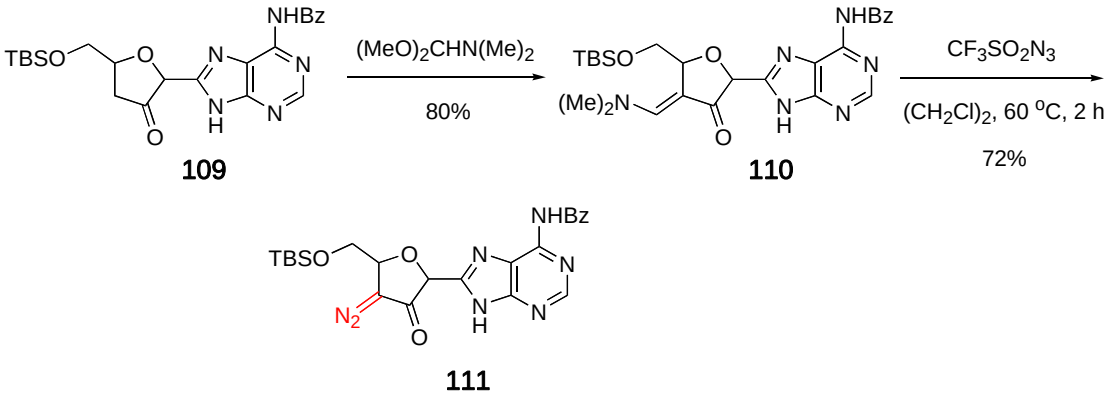
88. DPPA's use in a diazo transfer reaction to prepare α-diazoamides see: Villalgordo, J. M.; Enderli, A.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 1983-1998.
89. Koft, E. R. *J. Org. Chem*. **1987**, *52*, 3466-3468.
90. For a good discussion on the various reaction pathways involved in the reactions of stabilized carbanions with arylsulfonyl azide reagents see: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc*. **1990**, *112*, 4011-4030.

Scheme 7. Possible side-reactions in the attempted diazo transfer reaction to ethyl nitroacetate.



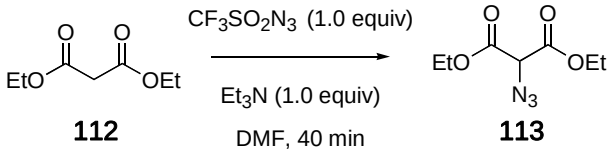
We reasoned that use of a more electrophilic sulfonyl azide and appropriate base may prevent these undesirable side-reactions and provide efficient access to this class of synthetically useful diazo compounds. Our focus turned to trifluoromethane-sulfonyl azide (triflyl azide) which had been previously used by Norbeck and Kramer to affect a diazo transfer reaction with enamino ketone **110** affording an α-diazoketone in 72% yield (Scheme 8).[91] It is also noteworthy to mention that other azides, such as TsN_3, failed to afford the desired diazo compound in this case.

Scheme 8. The use of triflyl azide in a diazo transfer reaction for the synthesis of an α-diazoketone.

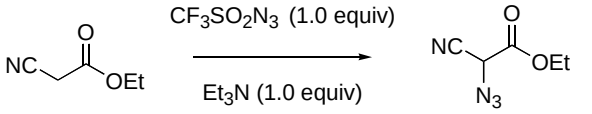


91. Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc*. **1988**, *110*, 7217-7218.

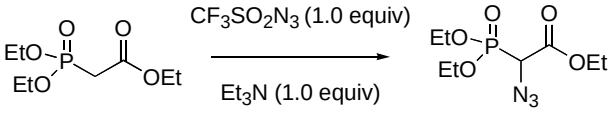
In contrast to the reactivity of triflyl azide in Scheme 8, Hakimelahi and Just reported the treatment of diethyl malonate (**112**), ethyl cyanoacetate (**114**) and ethyl diethylphosphonoacetate (**116**) with triflyl azide and triethyl amine in DMF to afford azides **113**, **115**, **117**, respectively, in 40-60% yields (Eq. 12-14).[92] In these cases, triflyl azide now transfers an azide subunit instead of the desired diazo subunit affording trifluoromethane sulfoxide as the reaction byproduct.



112 **113** 50-60% (12)

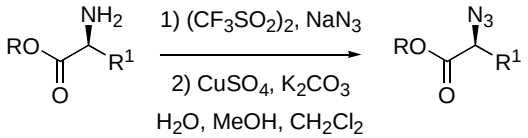


114 **115** 50-60% (13)



116 **117** 40% (14)

Triflyl azide, generated *in situ*, has also been used for the protection of primary amines as azides.[93] Treatment of a primary amine **118** with triflic anhydride/NaN_3, followed by the addition of Cu(II)SO_4 and K_2CO_3 affects a net overall diazo transfer reaction affording azide **119**. In this case, trifluoromethane sulfonamide is the reaction byproduct (Eq. 15).



118 **119** (15)

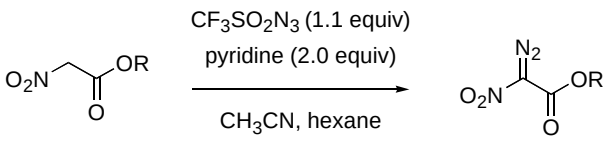
92. Hakimelahi, G. H.; Just, G. *Synth. Commun*. **1980**, *10*, 429-435.
93.(a) Lundquist, J. T. IV; Pelletier, J. C. *Org. Lett*. **2001**, *3*, 781-783. (b) Alper, P. B.; Hung, S. C.; Wong, C. H. *Tetrahedron Lett*. **1996**, *37*, 6029-6032.

Triflyl azide was then tested in the diazo transfer reaction involving ethyl nitroacetate (Eq. 11). A 1.0M solution of triflyl azide in hexane[94] was added to ethyl nitroacetate (**99**) in acetonitrile.[95] Upon the addition of 2.0 equivalents of pyridine, a bright yellow solution resulted and after stirring overnight at room temperature, ethyl nitro diazoacetate (**71**) could be isolated from the reaction mixture in 92% isolated yield.[96] The chemical yields of the diazo transfer reaction can be further improved if the reaction mixture is initially cooled to 0 ^{o}C during pyridine addition, affording uniformly high yields with α-nitroester and α-nitroketone substrates.[97]

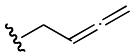
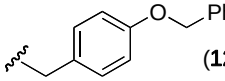
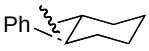
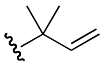
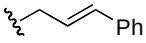
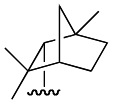
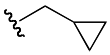
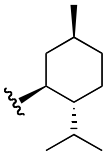
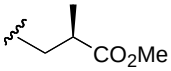
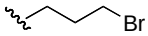
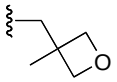
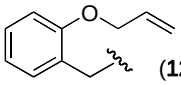
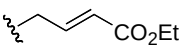
The diazo transfer reactions are normally allowed to stir overnight (*ca*. 14 h). In reduced reaction times, 65% conversion can be obtained for ethyl nitroacetate (**99**) in 3 h, while complete conversions can be achieved for α-nitroketone substrates due to their increased acidities. It is notable to mention that prolonged reaction times are not detrimental and do not lead to a decrease in isolated yields due to decomposition. The scope of the diazo transfer reaction was found to be excellent. To date, over 60 substrates have been successfully transformed to the corresponding α-nitro-α-diazocarbonyls **121** in high yields, making this diazo transfer reaction highly reliable (Table 8).

94. Fritschi, S.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2024-2034.
95. Triflyl azide has a boiling point of 30 ^{o}C and it can be stored for > 6 months in the freezer (-20 ^{o}C) in a hexane solution without loss of its effectiveness.
96. Charette, A. B.; Wurz, R. P.; Ollevier, T. *J. Org. Chem*. **2000**, *65*, 9252-9254.
97. Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468-4484.

Table 8. Diazo transfer reaction scope with α-nitroester substrates.



120(a-r) **121(a-r)**

entry	R-group	yield (%)[a]	entry	R-group	yield (%)[a]
1	Me (**97**)	90	13	 (**121k**)	91
2	Et (**71**)	92			
3	*i*-Pr (**121a**)	86	14	 (**121l**)	85
4	*t*-Bu (**121b**)	90			
5	Allyl (**121c**)	88	15	 (**121m**)	61
6	 (**121d**)	73			
7	 (**121e**)	81	16	 (**121n**)	96
8	 (**121f**)	96			
9	 (**121g**)	72	17	 (**121o**)	99
10	 (**121h**)	68	18	 (**121p**)	83
11	 (**121i**)	87	19	 (**121q**)	99
12	 (**121j**)	81	20	 (**121r**)	75

a) Isolated yields after chromatography on silica gel.

Sterically hindered substrates are often transformed to their corresponding diazo compounds in high yields (Table 8, entries 4,6,15-17). The diazo transfer reaction is also tolerant of functional groups including: oxetanes, α,β-unsaturated esters, alkyl bromides and unprotected alcohols using the standard protocol (Table 8, entries 11,12,18,20). Generally, isolated yields of above 80% can be expected. However, several of the more polar compounds have a high affinity for the silica gel, resulting in slightly compromised reaction yields (Table 8, entries 10,15,20). One additional

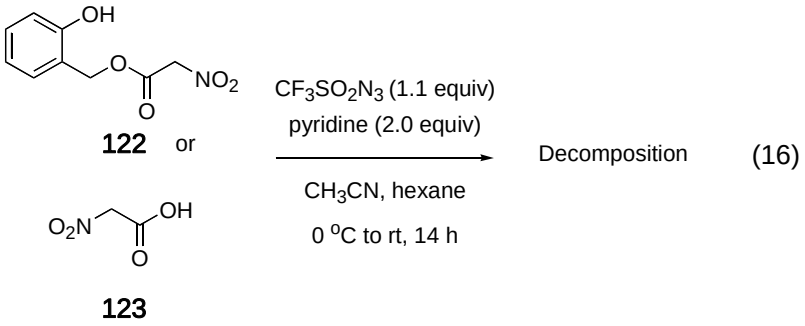
benefit of the reaction is complete consumption of the starting materials. ^{1}H NMR analyses of the crude reaction mixtures always indicates the absence of starting α-nitroester substrates which simplifies the purification to a straightforward filtration of the crude residues on a column of silica gel.

Purification of α-nitro-α-diazocarbonyls on silica gel did not result in decomposition of these diazo compounds. Furthermore, chromatography can be followed visually as the diazo compound elutes as a compact yellow band. Interestingly, it was found that purification of these diazo compounds was best-performed using chloroform as an eluent. This eluent serves to decrease the solubility of the sulfonamide byproduct, allowing for its efficient removal. When other eluents are used, such as mixtures of EtOAc and hexane, co-elution of the sulfonamide with the diazo results.[98]

The α-nitro-α-diazocarbonyls are pleasant to handle and are quite stable on silica gel and open to air on the bench-top. However, it is suggested that they be kept in the freezer at –20 ^{o}C for long-term storage. Samples of ethyl nitro diazoacetate (**71**) have been stored for up to three years in the refrigerator at 5 ^{o}C and found to be absent of any noticeable signs of decomposition. These samples also performed as expected in cyclopropanation reactions when compared to the freshly prepared reagent.

Few substrates failed to afford the desired diazo compounds under standard reaction conditions. Substrate **122**, containing an unprotected phenol, led only to decomposition (Eq. 16), whereas unprotected alcohols were successfully converted (Table 8, entry 20). Direct diazo transfer to nitroacetic acid (**123**) is also unsuccessful as it undergoes spontaneous decarboxylation in the presence of a base.

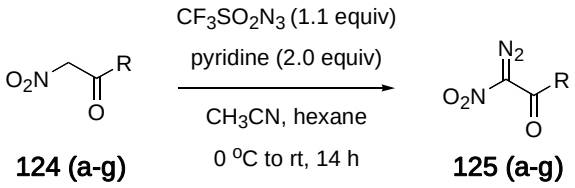
98. If the sulfonamide is present, the addition of chloroform will precipitate a white, flaky solid.

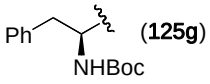


(16)

The diazo transfer reaction also performs equally well for α-nitroketone substrates **124** as illustrated in Table 9. These substrates are much more acidic, leading to decreased reaction times for the diazo transfer reaction.

Table 9. Diazo transfer reaction scope with α-nitroketone substrates.



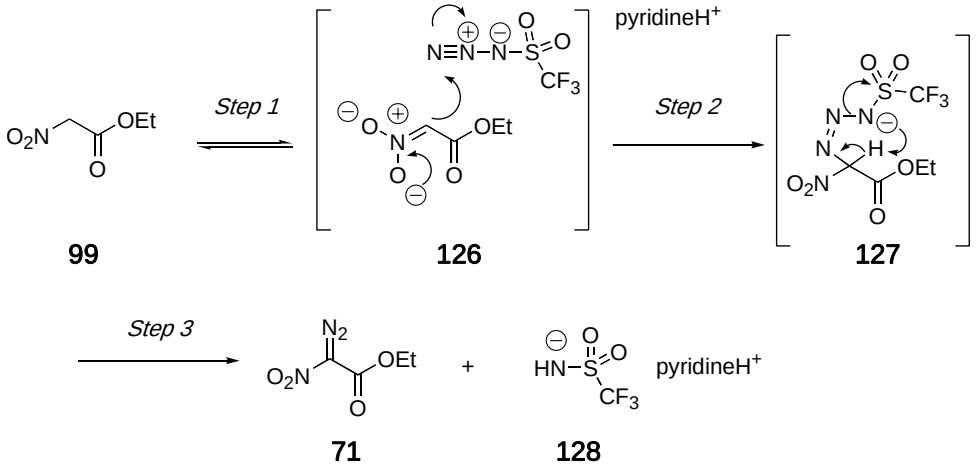
entry	R-group	yield (%)
1	Me (**125a**)	83
2	Ph (**98**)	90
3	*i*-Pr (**125b**)	93
4	*t*-Bu (**125c**)	80
5	Cyclohexyl (**125d**)	78
6	$(CH_2)_2CH_3$ (**125e**)	81
7	1-Adamantyl (**125f**)	93
8	 (**125g**)	80

It is noteworthy to mention that *tert*-butyl nitro diazoketone (**125c**, Table 9, entry 4) decomposes slowly at room temperature and should be stored in the freezer. α-

nitro-α-diazoketones **125** generally exhibit lower stabilities than their diazoester counterparts.[99]

The mechanism of the diazo transfer reaction may provide some insights into the success of triflyl azide and the failure of other sulfonyl azide reagents tested. A reversible deprotonation of ethyl nitroacetate (**99**) by pyridine (Scheme 9, *Step 1*) is expected to occur affording, in a small quantity, a highly stabilized anion. The extent of the deprotonation is expected to be small since the pK_a (H_2O) of pyridine·HCl is 5.2, whereas the pK_a (DMSO) of ethyl nitroacetate is *ca*. 10.[100] Nucleophilic attack of the nitroacetate anion **126** onto the electrophilic triflyl azide (Scheme 9, *Step 2*), is followed by an intramolecular proton abstraction, expulsing the sulfonamide **128** (Scheme 9, *Step 3*). Mesyl azide ($MeSO_2N_3$) likely fails in this reaction due to its reduced electrophilicity. Other azide reagents of the general form EWG-$ArSO_2N_3$ may not be sufficiently electrophilic to promote *Step 2*, or may fail in *Step 3* where sterics inhibit approach of the sulfonamide intermediate **127** for intramolecular proton abstraction.

Scheme 9. Proposed mechanism for the diazo transfer reaction.



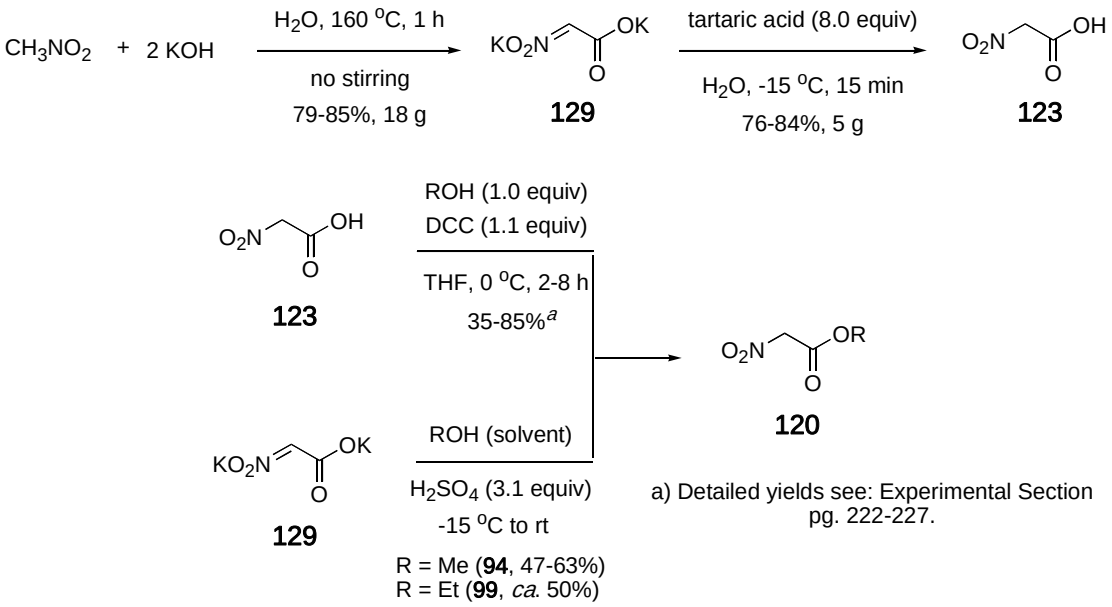
99. Caution should be exercised when handling α-nitro-α-diazocarbonyl compounds due to their potential for explosion. Low molecular weight compounds such as methyl nitro diazoacetate (**97**) are shock sensitive in solid form.

100. The pK_a is reported as being 5.82 in 50% aqueous dioxane solutions see: Bell, R. P. The Proton in Chemistry, Cornell University Press: Ithica, **1959**.

Preparation of the α-nitroester substrates can be accomplished from readily available starting materials according to Scheme 10. Treatment of nitromethane with potassium hydroxide in water at 160 ^{o}C for 1 h results in its deprotonation, dimerization and oxidation (ammonia is a byproduct) affording dipotassium nitroacetate (**129**), a pale peach-colored solid that is stable to air.[101] The reaction is routinely conducted on a 20 g scale and is high yielding (79-85%).[102] Protonation of the salt **129** with an aqueous tartaric acid solution affords nitroacetic acid (**123**) as pale yellow crystalline needles (76-84%).[103] Nitroacetic acid (**123**) and the desired alcohol can then be coupled using dicyclohexyl carbodiimide (DCC), affording the desired α-nitroesters **120**.[104] Alternatively, the dipotassium nitroacetate (**129**) can be esterified upon treatment with concentrated sulfuric acid and the desired alcohol to afford the corresponding α-nitroesters **120**.[102,105] This method represents an expedient approach to access α-nitroesters derived from inexpensive primary alcohols such as methyl and ethyl nitroacetate (Scheme 10).

101. The crude dipotassium nitroacetate (**129**) can be recrystallized from hot 50% KOH solutions, however, it was found that the crude was sufficiently pure for the following steps.
102. Koyama, Z. M.; Koto, S. *Org. Synth*. **1988**, *C.V. 6*, 797-799.
103. Kurth, M. J.; Olmstead, M. M.; Lee, E. H.; Huang, K. S. *J. Org. Chem*. **2000**, *65*, 499-503.
104. Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett*. **1999**, *40*, 875-878.
105. Matthews, V. E.; Kubler, D. G. *J. Org. Chem*. **1959**, *25*, 266-268.

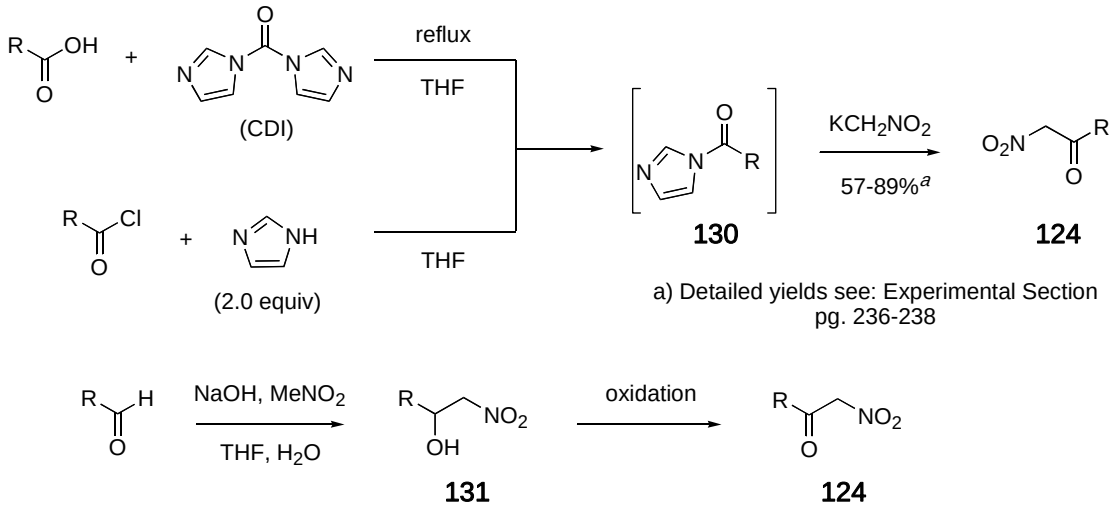
Scheme 10. Synthesis of α-nitroesters.



α-Nitroketone substrates **124** can be prepared in an equally expedient manner. The treatment of carboxylic acids with carbonyl diimidazole (CDI) forms an imidazolide intermediate **130**, which upon treatment with nitromethane potassium salt, affords the corresponding α-nitroketone **124** in excellent yields.[106] If acid chlorides are available, treatment with two equivalents of imidazole again forms intermediate **130**.[107] Alternatively, treatment of an aldehyde with nitromethane in the presence of a base undergoes a Henry reaction leading to β-nitro alcohols **131**.[108] Oxidation of the β-nitro alcohols with IBX[109] or Jone's reagent then allows access to the corresponding α-nitroketones. All three approaches were routinely employed for the preparation of these substrates, all affording excellent yields of the desired α-nitroketones (Scheme 11).

106. Baker, D. C.; Putt, S. R. *Synthesis* **1978**, 478-479.
107. Nudelman, A.; Nudelman, A. *Synthesis* **1999**, 568-570.
108. Edmont, D.; Williams, D. M. *Tetrahedron Lett*. **2000**, *41*, 8581-8585.
109. More, J. D.; Finney, N. S. *Org. Lett*. **2002**, *4*, 3001-3003.

Scheme 11. Synthesis of α-nitroketones.



The success of the diazo transfer reaction has been proven unambiguously by a crystal structure of methyl nitro diazoacetate (**97**, Fig. 15).[97] Crystals of methyl nitro diazoacetate (**97**) were grown from a $CHCl_3$ solution. They crystallized in an orthorhombic unit cell.[110]

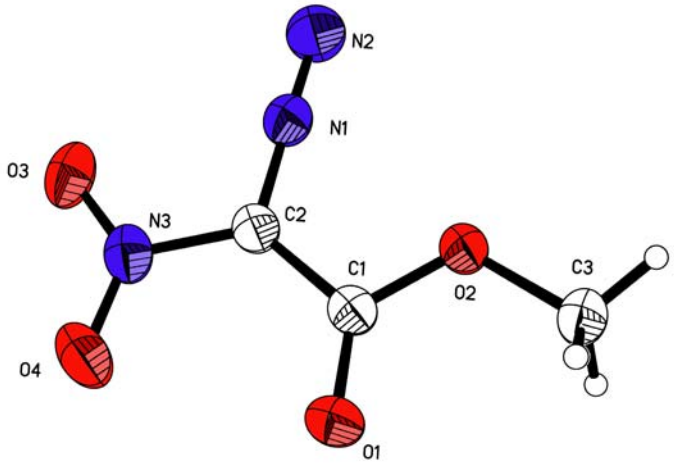


Figure 15. ORTEP representation of the crystal structure of methyl nitro diazoacetate.

110. See Appendix I for the complete structural data concerning the crystal structure of methyl nitro diazoacetate (**97**). The crystallographic data has been deposited with the *Cambridge Crystallographic Data Centre* as CCDC-189718.

The solid-state structure of methyl nitro diazoacetate (**97**) possesses a short N1-N2 bond length of 1.11 Å approaching N≡N triple bond character (N≡N 1.098 Å).[111] The N3-C2 bond length of 1.41 Å is somewhat contracted in comparison to a single C-N bond (eg. nitromethane C-NO_2 1.48 Å),[112] suggesting conjugation between the nitro group and the carbene carbon (C2). The virtually planar N2-N1-C2 bond angle of 178.7° also suggests conjugation with C2. Additionally, the overall planarity of the molecule suggests complete delocalization of electron density of the diazo carbon (C2) into the strongly electron-withdrawing nitro and ester groups (Fig. 15). [113]

Table 10. Selected geometric parameters for the crystal structure of methyl nitro diazoacetate (**97**).

atoms	bond length (Å)	atoms	bond angle (°)
O1-C1	1.205(2)	C1-O2-C3	116.89(16)
O2-C1	1.329(3)	N2-N1-C2	178.7(2)
O2-C3	1.444(3)	O4-N3-O3	124.1(2)
O3-N3	1.236(2)	O4-N3-C2	118.3(2)
O4-N3	1.211(3)	O3-N3-C2	117.6(2)
N1-N2	1.111(3)	O1-C1-C2	125.27(19)
N3-C2	1.413(3)	O2-C1-C2	108.43(17)
C1-C2	1.450(3)	N1-C2-N3	112.61(19)
N1-C2	1.327(3)	N1-C2-C1	119.43(17)

2.4 Expansion of the scope of the diazo transfer reaction

The application of triflyl azide as a reagent in a new diazo transfer methodology for the preparation of α-nitro-α-diazocarbonyls prompted further examination of related substrates. We reasoned that other highly acidic substrates that possess pK_a

111. CRC Handbook of Chemistry and Physics, *1st Student's Edition*, CRC Press Inc.: Boca Raton, 1991, pg. F-107.
112. CRC Handbook of Chemistry and Physics, *1st Student's Edition*, CRC Press Inc.: Boca Raton, 1991, pg. F-106.
113. For a related X-ray crystal structure of nitro diazoacetic acid see: O'Bannon, P. E.; Carroll, P. J.; Dailey, W. P. *Tetrahedron Lett*. **1988**, *47*, 6031-6032.

values similar to those of α-nitroesters and ketones would be potential candidates. Attempts to apply the standard diazo transfer conditions used for the α-nitrocarbonyl substrates to the synthesis of diazo malonates (pK_a = 15.7 in DMSO) resulted in recovery of the starting materials. This is probably due to the reduced acidities of these substrates and the inability of pyridine to affect deprotonation to a significant degree. This led to the testing of other substrates and bases to examine both the tolerance of the triflyl azide to various reaction conditions and the scope of the diazo transfer.

Among the substrates tested, we were particularly interested in α-cyanocarbonyls which would allow the synthesis of α-cyano-α-diazocarbonyls. These diazo compounds could have synthetic potential for the preparation of cyclopropane α-amino acids and β-amino acids. A cyanoester represents two differentially protected carboxylic acid equivalents and, although the amine component would need to be introduced using a Curtius or Hofmann type rearrangement, these substrates possess the added benefit of significant steric differentiation between the two groups.

A number of methods for the preparation of α-cyano-α-diazocarbonyls already exist including direct diazo transfer reactions[114] or more lengthy reaction sequences involving preparation of carbonyl cyanide hydrazones, followed by treatment with oxidants such as $Pb(OAc)_4$ or Ag_2O.[115] The synthesis of α-cyano-α-diazocarbonyls using a direct diazo transfer reaction facilitated by triflyl azide would offer an attractive alternative to previously known methods due to the ease of preparation of the reagent and its handling (stored as a solution in hexane).

Treatment of ethyl cyanoacetate (**132a**) with triflyl azide (1.5 equiv) was found to cleanly afford the corresponding diazo compound **133a** in 79% (Table 11, entry 1). It was found that 1.5 equivalents of triflyl azide were necessary to obtain optimal

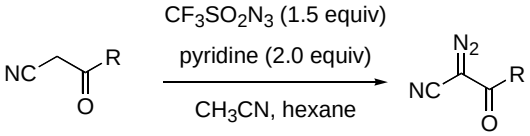
---

114. For examples see: (a) Balli, H.; Löw, R.; Müller, V.; Rempfler, H.; Sezen-Gezgin, A. *Helv. Chim. Acta* **1978**, *61*, 97-103. (b) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P. Jr.; Semones, M. A.; Padwa, A. *Tetrahedron* **1996**, *52*, 2489-2514. (c) Alloum, A. B.; Villemin, D. *Synth. Commun*. **1989**, *19*, 2567-2571.

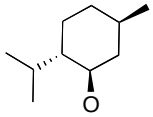
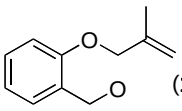
115.(a) Ciganek, E. *J. Org. Chem*. **1965**, *30*, 4198-4204. (b) Ciganek, E. *J. Org. Chem*. **1969**, *35*, 862-864.

reaction yields compared with only 1.1 equivalents in the diazo transfer reaction involving α-nitrocarbonyls. The preparation of a variety of other α-cyanoester substrates allowed examination of the reaction scope (Table 11).

Table 11. Scope of the diazo transfer reaction with α-cyano-α-diazocarbonyl substrates.



132(a-j) **133(a-j)**

entry	R-group	yield (%)[a]
1	OEt (**133a**)	79[b]
2	OCH_2CF_3 (**133b**)	81[b]
3	OPh (**133c**)	93
4	$OCH_2CH{=}CH_2$ (**133d**)	86
5	OBn (**133e**)	86
6	 (**133f**)	71[c]
7	(*Z*)-$OCH_2CH{=}CHCH_2CH_3$ (**133g**)	84
8	 (**133h**)	91
9	Ph (**133i**)	94
10	(*E*)-CH=CHPh (**133j**)	99

a) Isolated yields after purification by flash chromatography.
b) Product is volatile. c) (1*R*, 2*S*, 5*R*)-(-)-Menthol.

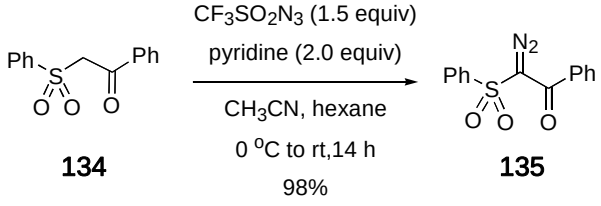
Gratifyingly, the scope of this diazo transfer reaction was found to be equally broad as it was for the synthesis of α-nitro-α-diazocarbonyls.[116] Even sterically demanding esters were transformed in excellent yields (Table 11, entries 6 and 8).

116. Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett*. **2003**, *44*, 8845-8848.

The diazo transfer reaction involving α-cyanoketones (Table 11, entries 9 and 10), prepared from cyanoacetic acid and the corresponding acid chloride,[117] were also found to proceed in excellent yields. The α-cyanoester substrates were readily prepared in an analogous fashion to α-nitroesters using a DCC coupling of the desired alcohol with cyanoacetic acid. Cyanoacetic acid is commercially available and the coupling reactions proceed to completion with reaction times of less than 2 h affording excellent yields (> 80%) at room temperature.[118]

In the case of α-cyanoketones, the diazo transfer is greatly accelerated when compared to their α-cyanoester counterparts, due to their increased acidities (pK_a of benzoylacetonitrile = 10.2 versus 13.1 for ethyl cyanoacetate in DMSO). For reactions involving α-cyanoketones, yields exceeding 90% could be achieved in only 6 h.

To further expand the scope of the diazo transfer protocol, a variety of other α-acidic carbonyl substrates with similar pK_a values were chosen. For example, the pK_a of 2-(phenylsulfonyl) acetophenone (**134**, pK_a = 11.4 in DMSO) was also found to be similar with that of benzoylacetonitrile. Thus, upon treatment of this commercially available substrate with triflyl azide under the standard reaction conditions, diazo compound **135** was obtained in 98% yield after purification by flash chromatography (Eq. 17).[116]



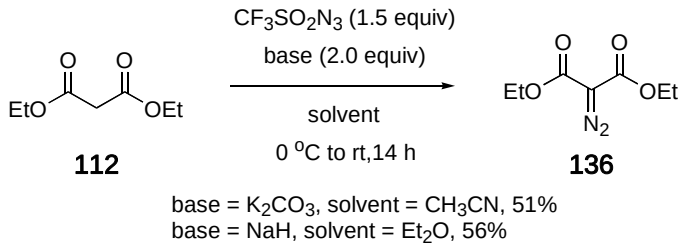
(17)

117. For the synthesis of cyanomethyl ketones see: (a) Krauss, J. C.; Cupps, T. L.; Wise, D. S.; Townsend, L. B. *Synthesis* **1983**, 308-309. (b) Chen, Y.; Sieburth, S. M. *Synthesis* **2002**, 2191-2194.

118. For cyanoacetate synthesis see: (a) Nahmany, M.; Melman, A. *Org. Lett*. **2001**, *3*, 3733-3735. Synthesis of phenyl cyanoacetate see: (b) Bruice, T. C.; Hegarty, A. F.; Felton, S. M.; Donzel, A.; Kundu, N. G. *J. Am. Chem. Soc*. **1970**, *92*, 1370-1378.

2.4.1 The influence of the base in the diazo transfer reaction

Diethyl malonate (**112**) is much less acidic (pK_a = 15.7 in DMSO) than the other successful substrates and treatment with triflyl azide and pyridine resulted in isolation of the starting materials. A variety of reaction conditions were then screened and it was found that modest yields of the corresponding diazo **136** could be obtained upon judicious choice of the base used. Accordingly, yields of 51% and 56% resulted using K_2CO_3 and NaH, respectively (Eq. 18). In these cases, the irreversible nature of the deprotonation appears to be beneficial since participation of the conjugate acid in various side-reactions is not possible.



(18)

Another important observation was the dramatic influence of various bases upon diazo transfer reaction yields. This observation was made when a variety of bases were screened during the optimization of the reaction yields according to Table 12. Benzyl cyanoacetate (**132e**)[119] was treated with 1.5 equivalents of triflyl azide followed by the slow dropwise addition of 2.0 equivalents of base in these reactions. The yields were found to closely correspond to the pK_a (of the conjugate acid) of the base used (Table 12). Stronger bases, such as Hünig's base (*i*-Pr_2NEt), led to only decomposition (Table 12, entry 1), while weaker bases such as pyridine and 2,6-lutidine gave optimal yields of the desired diazo compound **133e**.

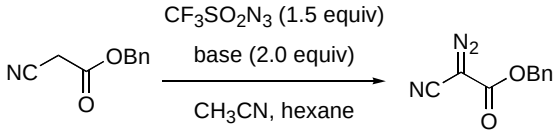
Intuitively, one would expect the inverse since stronger bases should affect a more rapid deprotonation of the substrate leading to faster product generation. However, this was not the case in this diazo transfer reaction. We then reasoned that

119. Benzyl cyanoacetate (**132e**) was chosen as the substrate since ethyl cyano diazoacetate (**133a**) was found to be slightly volatile under reduced pressure.

the highly electrophilic diazo compound could be sensitive to the base. To test this hypothesis, the pure diazo compound **133e** was treated with 2.0 equivalents of Hünig's base under the diazo transfer conditions. The reaction mixture rapidly darkened leading to complete degradation of the diazo compound, thus confirming this hypothesis. In contrast, when inorganic bases such as potassium carbonate and sodium hydride were tested, good to excellent yields of the corresponding diazo compound **133e** resulted (Table 12, entries 9 and 10). In these cases, the bases and/or their conjugate acids cannot interfere with the desired diazo compound allowing its isolation in high yields.

Finally, pyridine was chosen for this diazo transfer reaction as the base of choice due to its simplicity of handling over sodium hydride. Although sodium hydride performed well in the reaction, it is supplied as a suspension in mineral oil, therefore, must be first rinsed with hexane before use. Furthermore, when sodium hydride is used as a base the reaction is more time-consuming as the substrate must be first subjected to an initial deprotonation period prior to treatment with triflyl azide.

Table 12. Influence of the base on the yield of the diazo transfer reaction.



132e **133e**

entry	base	pK_a of conjugate acid (H_2O)	yield (%)
1	*i*-Pr_2NEt	*ca.* 11	Decomp.
2	DBU	*ca.* 12[a]	19
3	Et_3N	10.8	32
4	DMAP	9.2	53
5	morpholine	8.4	48
6	4-methylmorpholine	7.4	83
7	2,6-lutidine	6.8	86
8	pyridine	5.2	86
9	K_2CO_3	10.3	67
10	NaH	35[b,c]	86

a) Refers to the pK_a (of the conjugate acid) in DMSO. b) pK_a of hydrogen.
c) Reaction performed in Et_2O.

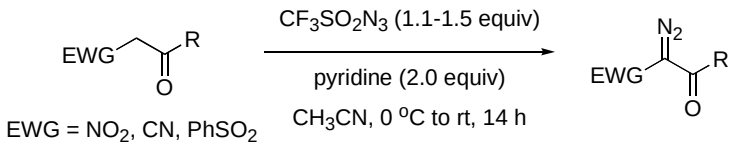
2.5 Conclusions

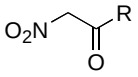
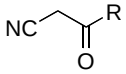
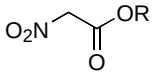
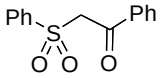
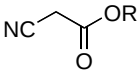
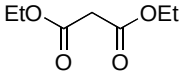
In conclusion, the new diazo transfer methodology developed for the preparation of α-nitro-α-diazocarbonyls offers several advantages over previously reported methodologies in terms of reaction yields and experimental simplicity. The precursor to triflyl azide, triflic anhydride, is commercially available or can be readily prepared.[120] The diazo transfer reaction is robust and performs with equal efficiency when the pyridine or reaction solvents are used directly from the bottle in an unpurified form.

The triflyl azide reagent was also found to be effective in diazo transfer reactions for the preparation of other α-acidic diazo compounds including α-cyano-α-diazocarbonyls **133**, 2-(phenylsulfonyl) diazoacetophenone **135** and diethyl diazomalonate **136**. Rationalization of these successes can be attributed to the pK_a's of the substrates (Table 13).

120. Triflic anhydride can be readily prepared by dehydration of triflic acid with P_2O_5.

Table 13. Summary of diazo transfer reaction scope with triflyl azide.



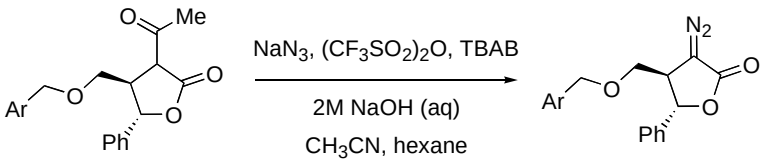
entry	substrate	substrate pK_a (DMSO)	diazo transfer yield (%)
1		R = Ph, 7.7	78-93
2		R = Ph, 10.2	94-99
3		R = Et, *ca.* 10	61-99
4		11.4	98
5		R = Et, 13.1	71-93
6		15.7	56[a]

a) NaH used as a base in Et_2O as a solvent.

It is also important to highlight that the previous reports by Hakimelahi and Just involving the treatment of α-acidic substrates with triflyl azide and triethylamine in DMF resulted in the transfer of an azide subunit to the substrates (Eq. 12-14). This research has shown that the solvent and base have a significant influence on the course of the reaction. The replacement of DMF with CH_3CN as the reaction solvent led to an efficient diazo transfer reaction instead of an azide transfer reaction using the same reagent.

Since our initial communication describing the synthesis of α-nitro-α-diazocarbonyls, other researchers have also recognized the utility of triflyl azide in diazo transfer reactions. Swain *et al*. recently reported its application for the

preparation of α-diazo lactones **138** using acetyl activation **137**.[121] In this case, triflyl azide was formed *in situ* upon addition of triflic anhydride to an aqueous biphasic mixture of substrate and sodium azide (Eq. 19).



137 **138** (19)

Finally, with a reliable synthesis for the preparation of α-nitro-α-diazocarbonyls in hand, the first criterion in the proposed strategy for the synthesis of cyclopropane α-amino acids is met. Chapter 3 will focus on the applications of α-nitro-α-diazocarbonyls in a transition metal-catalyzed cyclopropanation reactions with olefins.

121.(a) Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Chem. Soc., Chem. Commun*. **2002**, 2042-2043. (b) Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem*. **2004**, *69*, 122-129.

CHAPTER 3

Cyclopropanation Reactions with α-Nitro-α-Diazocarbonyls

3.1 Introduction and precedence

There have been relatively few reports concerning the use of α-nitro-α-diazocarbonyls in the literature, despite the existence of methods for their preparation for over 40 years. This was likely related to the tedious and low yielding means reported for their preparation. Following the development of a facile and efficient diazo transfer methodology, as described in Chapter 2, exploration of their full synthetic potential is now much more convenient.

Schöllkopf *et al*. conducted pioneering research involving α-nitro-α-diazocarbonyl compounds in the late 1960's to early 1970's. Their research involved irradiation and photolysis of these diazo compounds to produce presumably "free nitro carbenes" which rapidly fragmented, releasing various gases.[81a,b]

Two decades later, O'Bannon and Dailey demonstrated in a preliminary report that ethyl nitro diazoacetate (**71**) underwent a nitroso "ene" reaction with 2,3-dimethyl-2-butene[122] affording the corresponding hydroxylamine **143** and a nitroso hetero-Diels-Alder reaction with 9,10-dimethylanthracene affording adduct **144** in 67% yield.[123] These transformations were performed in either refluxing $CHCl_3$ or at room temperature in CH_2Cl_2 using $[Rh(OAc)_2]_2$ as a catalyst. The proposed mechanism for these transformations involves an initial Wolff rearrangement *via* intermediates **139** and **140** forming the reactive acyl nitroso compound **141** which reacts with the substrates present (Scheme 12).

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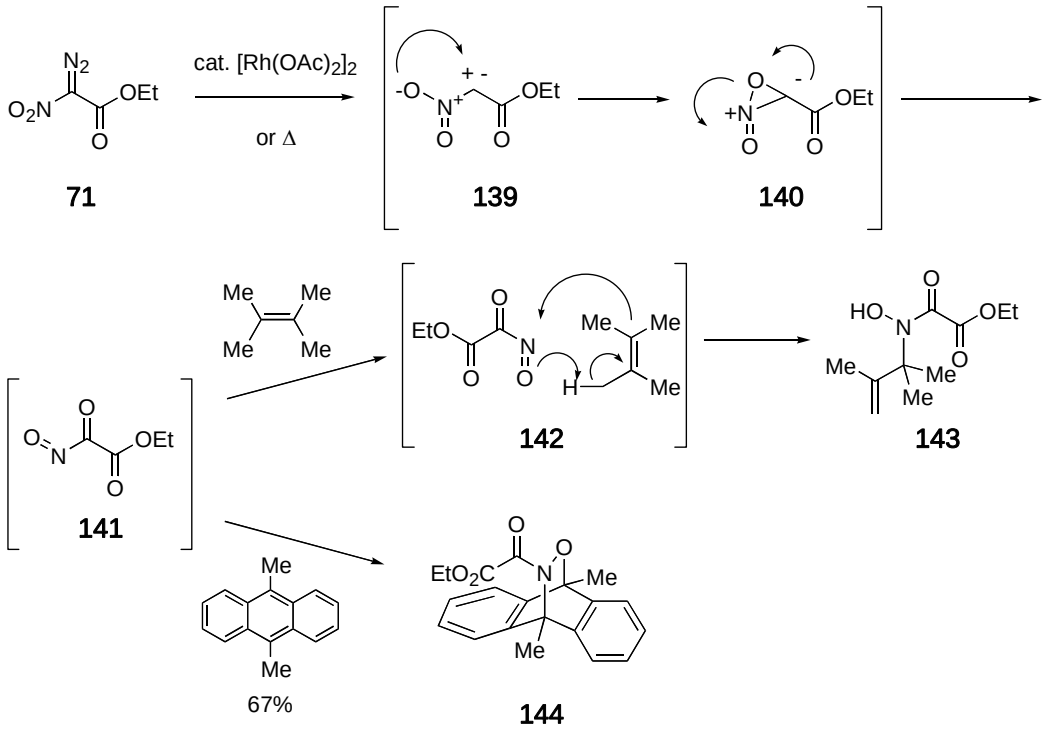
122. No yield was reported for this reaction, however, the authors state that it is surprisingly high yielding.
123. O'Bannon, P. E.; Dailey, W. P. *Tetrahedron Lett*. **1988**, *29*, 5719-5722.

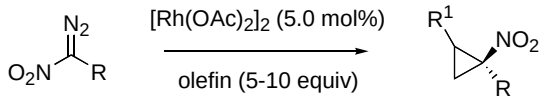
Scheme 12. Wolff rearrangement followed by nitroso "ene" or a hetero-Diels-Alder reaction.



O'Bannon and Dailey were also the first researchers to use α-nitro-α-diazocarbonyl compounds in transition metal-catalyzed cyclopropanation reactions. Their research focused on the efficiency of this reaction with a diverse array of olefin substrates catalyzed by $[Rh(OAc)_2]_2$.[124,81c,d] The results of their findings are summarized in Table 14.

124. O'Bannon, P. E.; Dailey, W. P. *Tetrahedron Lett*. **1989**, *30*, 4197-4200.

Table 14. Scope of the cyclopropanation reaction with various α-nitro-α-diazo compounds.



145 **146**

olefin	R = H		R = CN		R = CO_2Et		R = CO_2*t*-Bu		R = COPh	
	yield (%)	*trans:cis*	yield (%)	*E:Z*	yield (%)	*E:Z*	yield (%)	*E:Z*	yield (%)	*E:Z*
styrene	54	2.4	55	3.0	75	8.0	83	2.0	75	0.16
iso-butene	50	--	50	--	75	--	80	--	58	--
1-hexene	50	1.4	55	3.0	35	1.0	nd	--	nd	--
cis-2-butene	50	1.0	40	15	65	4.0	59	4.0	45	0.10
cyclohexene	30	3.0	40	>20	35	6.0	30	4.0	20	>0.05
2,3-dimethyl-2-butene	35	--	35	--	0	--	0	--	0	--
trans-2-butene	40	--	30	--	0	--	nd	--	nd	--

As illustrated in Table 14, α-nitro-α-diazo compounds derived from esters and ketones (**145**, R = CO_2Et, CO_2*t*-Bu, COPh) often afforded modest to excellent yields of the corresponding nitro cyclopropanes **146** with electron-rich olefins such as styrene, *iso*-butene and *cis*-butene. However, trisubstituted and *trans*-substituted olefins gave consistently inferior yields of the corresponding cyclopropanes. In the latter two cases, approach of the olefins towards the intermediate "metal-carbene complex" is impeded due to steric repulsions, thus resulting in reduced yields or "ene" reaction products.

Since the investigations conducted by O'Bannon and Dailey, few other reports concerning the use of α-nitro-α-diazocarbonyl compounds have appeared in the literature. Among these, Kuznetsova *et al*. have recently disclosed the preparation of nitro-substituted triangulanes[60b] and spirohexane amino acids[60a] as previously described in Chapter 1 (Eq. 3). It is also noteworthy to mention that these researchers were able to successfully cyclopropanate certain tetrasubstituted olefin substrates in modest yields.

Aside from these cited examples, the synthetic utility of these interesting diazo compounds has remained largely unexplored. Consequently, this chapter will more closely examine the synthetic scope of the cyclopropanation reaction with these diazo compounds, both in terms of olefinic substrates and the ability to control diastereoselectivities in the cyclopropanation reaction. In addition, our extensive efforts to achieve a highly enantioselective cyclopropanation reaction using various transition metal-catalysts possessing chiral ligands will be described. High yielding intramolecular cyclopropanations have been achieved for the first time with α-nitro-α-diazocarbonyl compounds and this will also be a topic of discussion in this chapter.

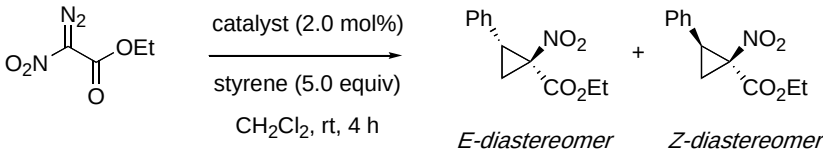
3.2 Intermolecular cyclopropanation reactions

3.2.1 Catalyst influence on cyclopropanation diastereoselectivities and yields

Since the pioneering research of O'Bannon and Dailey, the field of transition metal-catalyzed cyclopropanation reactions with diazo compounds has seen tremendous advances. Their research involving α-nitro-α-diazocarbonyl compounds focused solely on cyclopropanation reactions employing $[Rh(OAc)_2]_2$ as a catalyst. Due to the important synthetic utility of diazo compounds, many achiral Rh(II) catalysts are now commercially available. Hence, we became interested in exploring the influence that the ligands of the achiral catalysts had on the cyclopropanation reaction. The cyclopropanation reaction between styrene and ethyl nitro diazoacetate (**71**) was used as a probe reaction. A variety of catalysts were prepared containing ligands that varied in terms of their electronic and steric properties. The results are tabulated in Table 15.

The cyclopropanation reactions between styrene and ethyl nitro diazoacetate (**71**) were conducted in the following way; a 1.0M solution of ethyl nitro diazoacetate (**71**) was added slowly (over a period of 30 minutes) to a solution of styrene and the appropriate catalyst. Active catalysts resulted in a vigorous effervescence of nitrogen gas. Following the addition of the diazo solution, the reaction mixture was stirred an additional 4 h before the solvent was removed and the products purified by flash chromatography on silica gel.

Table 15. The influence of the Rh(II) catalyst on the yields and diastereoselectivities of the cyclopropanation reaction.



E-diastereomer *Z-diastereomer*

71 **147**

entry	catalyst	yield (%)	*E:Z* ratio
1	$[Rh(Cap)_2]_2$[a]	Decomp.	---
2	$[Rh(CF_3CO_2)_2]_2$	24	92:8
3	$[Rh(OAc)_2]_2$	79	88:12
4	$[Rh(Oct)_2]_2$[b]	76	90:10
5	$[Rh(Ph_3CCO_2)_2]_2$	78	68:32
6	$[Rh(OPiv)_2]_2$[c]	84	85:15
7	$[Rh(1\text{-Adaman})_2]_2$[d]	90	88:12

a) Cap = caprolactam. b) Oct = octanoic acid. c) OPiv = trimethyl acetic acid. d) 1-Adaman = 1-adamantane carboxylic acid.

The commercially available Rh(II) carboxamidate catalyst, $[Rh(Cap)_2]_2$, was found to be inactive in the cyclopropanation reaction, leading only to decomposition of the diazo compound (Table 15, entry 1). Following this result, attention turned to various Rh(II) carboxylate catalysts. The catalyst derived from trifluoroacetic acid, $[Rh(CF_3CO_2)_2]_2$, was also rather unreactive with ethyl nitro diazoacetate (**71**), affording the corresponding cyclopropane **147** in 24% isolated yield (Table 15, entry 2). In contrast to $[Rh(Cap)_2]_2$, it was possible to recover 41% of unreacted ethyl nitro diazoacetate (**71**) from the crude reaction mixture. Rh(II) catalysts derived from non-sterically demanding electron-rich ligands, such as $[Rh(OAc)_2]_2$ and $[Rh(Oct)_2]_2$, afforded excellent yields of the corresponding cyclopropane **147** with excellent diastereoselectivities favoring the *E*-diastereomer (Table 15, entries 3 and 4). Increasing the steric bulk of the carboxylate ligand to triphenyl acetate resulted in a drastic decline in diastereoselectivities to 68:32 *E:Z* while maintaining respectable yields (Table 15, entry 5). However, when catalysts possessing sterically demanding electron-rich ligands were used, such as $[Rh(OPiv)_2]_2$ or $[Rh(1\text{-Adaman})_2]_2$, yields

surpassing 80% were possible (Table 15, entries 6 and 7). Again, excellent diastereoselectivities were observed favoring the *E*-diastereomer in approximately a 9:1 *E:Z* ratio.

Rh(II) carboxylate catalysts (**148**, Fig. 16), such as $[Rh(OAc)_2]_2$, are 16 electron, diamagnetic complexes possessing D_{4h} symmetry with two vacant axial coordination sites (depicted as L, Fig. 16). The axial ligands form much weaker bonds than the bridging ligands and can often be removed by simply heating under vacuum. Ligands that can typically occupy these axial coordination sites include water, ethyl acetate and acetonitrile. However, olefins generally do not coordinate well.[125] Rh(II) carboxylate complexes containing electron deficient ligands, such as $[Rh(CF_3CO_2)_2]_2$, serve as exceptions and are able to coordinate olefins.[126] This coordination may account for the reduced reactivity of $[Rh(CF_3CO_2)_2]_2$ in the cyclopropanation reaction with ethyl nitro diazoacetate (Table 15, entry 2).

The axial ligands also have a small influence on the Rh-Rh bond length. This, in turn, may be partially responsible for the reactivity of the carbenoid since the axial position is believed to be the site of binding with the carbene carbon.[127] For example, the introduction of small quantities of strongly coordinating ligands to the reaction mixture, such as phosphines, can effectively inhibit the cyclopropanation reaction presumably because the diazo compound cannot access the reactive axial coordination site. Triphenyl phosphine, as an axial ligand, will increase the Rh-Rh bond length of $[Rh(OPiv)_2]_2$ from 2.37 Å (L = H_2O) to 2.58 Å (L = PPh_3).[127]

125. Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem*. **1980**, *45*, 695-702.
126. Doyle, M. P.; Colsman, M. R.; Chinn, M. S. *Inorg. Chem*. **1984**, *23*, 3684-3685.
127. Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed*. **1994**, *33*, 1797-1815.

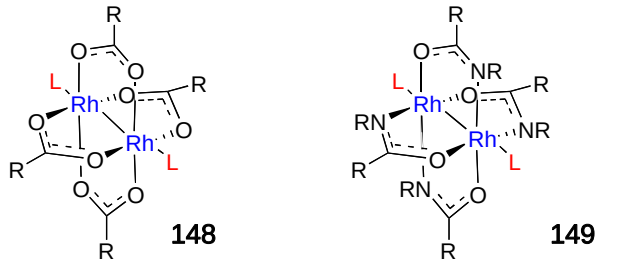


Figure 16. Rh-Rh bond lengths with various bridging and axial ligands.

Rh(II) carboxamidate (**149**, Fig. 16) derived catalysts have reduced activities compared to their Rh(II) carboxylate counterparts making reactions with these catalysts generally more selective.[128] Binding of the carbamate ligands occurs in a (2,2-*cis*) geometry with "like" binding orientations of the amide ligands (eg. Rh-N versus Rh-O) *cis* to one another (Fig. 16). The ligated carbamate functionality is also expected to increase the electron density at Rh, thereby influencing the Rh-Rh bond lengths.

The trends in reactivity observed with this series of achiral catalysts (Table 15) in cyclopropanation reactions with ethyl nitro diazoacetate (**71**) contrasts those involving ethyl diazoacetate (**101**). Teyessie *et al*. found that $[Rh(Oct)_2]_2$ gave the highest yields (95%) in cyclopropanation reactions between ethyl diazoacetate (**101**) and styrene, whereas the more sterically demanding $[Rh(OPiv)_2]_2$ catalyst afforded yields of only 60%. Furthermore, Rh(II) carboxamidate catalysts are quite active in cyclopropanation reactions involving ethyl diazoacetate (**101**), whereas decomposition results in reactions involving ethyl nitro diazoacetate (**71**). The origins of these contrasting reactivity patterns are not obvious but are characteristic of diazo chemistry in general. Diazo compounds which are structurally similar to α-nitro-α-diazocarbonyls, such as diazo malonates and α-cyano-α-diazocarbonyls, display very different reactivities.

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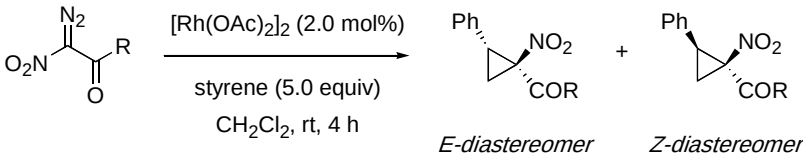
128. Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc*. **1993**, *115*, 9968-9978.

3.2.2 Control of diastereoselectivity in the cyclopropanation reaction

The development of a cyclopropanation methodology which could provide both *E*- and *Z*-diastereomers is highly desirable. The pioneering research of O'Bannon and Dailey illustrated that *E*- or *Z*-selective cyclopropanation reactions were possible through use of either ethyl nitro diazoacetate (**71**) or nitro diazoacetophenone (**98**), respectively (see Table 14).[81d] The origin of this reversal in diastereoselectivities was then further examined upon preparation of a variety of different α-nitro-α-diazoesters and ketones.

Table 16. The influence on diastereoselectivities of the cyclopropanation reactions by the R-group of the diazo compound.



125 **150(a-g)**

entry	R-group	yield (%)[a]	*E*:*Z* ratio	product
1	OMe	78	91:9	**150a**
2	O*i*-Pr	80	88:12	**147**
3	O*t*-Bu	78	75:25	**150b**
4	Me	81	55:45	**150c**
5	*n*-Pr	77	78:22	**150d**
6	Ph	74	81:19	**150e**
7	*t*-Bu	74[b]	16:84	**150f**
8		55[b]	20:80	**150g**

a) Isolated yields after column chromatography. b) 15% (entry 7) and 30% (entry 8) yields of the corresponding isoxazoline *N*-oxides were isolated.

Gratifyingly, a highly diastereoselective cyclopropanation reaction favoring the *E*-diastereomer resulted when α-nitro-α-diazoesters containing small R-groups were used (Table 16, entries 1 and 2). Increasing the steric bulk of the R-group to an *iso*-propyl ester or a *tert*-butyl ester led to an increase in the *Z*-diastereomer (Table 16,

entries 3 and 4). Furthermore, upon variation of the R-groups of the α-nitro-α-diazoesters, the isolated yields of the desired cyclopropanes **147** or **150a-c** remained effectively unchanged, ranging from 78-81%.

When α-nitro-α-diazoketone compounds were used, an *E*-selective cyclopropanation ensued for small R-groups (Table 16, entries 5 and 6). However, the *Z*-diastereomer predominated when the R-group was a phenyl or *tert*-butyl substituent (Table 16, entries 7 and 8). It is noteworthy to mention that the *E*- and *Z*-diastereomers could be readily separated by flash chromatography allowing a respectable yield of the pure *Z*-diastereomer for cyclopropane **150f** derived from α-nitro-α-diazoacetophenone (**98**). Cyclopropane **150g**, derived from nitrodiazomethyl *tert*-butyl ketone showed compromised stability on untreated silica gel, resulting in the isolation of 30% of an isoxazoline *N*-oxide byproduct.[129] Other sterically demanding nitrodiazomethyl ketones (eg. R = Cy or 1-adamantane) also resulted in unstable cyclopropanes which were prone to rearrange to their corresponding isoxazoline *N*-oxides.

The diastereoselectivities of the cyclopropanation reactions were determined upon integration of the appropriate signals in the ^{1}H NMR spectrum of the crude reaction mixture. Assignment of the signals to *E*- or *Z*-diastereomers corresponds with the findings of O'Bannon and Dailey.[81c,d] A representative ^{1}H NMR spectrum of a mixture of *E*- and *Z*-diastereomers (70:30 *E:Z*) of ethyl-2-phenylnitrocyclopropane carboxylate (**147**) is depicted in Figure 17. This ^{1}H NMR spectrum illustrates the significant downfield shifts of the peaks corresponding to the cyclopropyl protons due to the presence of the two strong electron-withdrawing groups.

129. Further discussions concerning this rearrangement are included in Chapter 8.

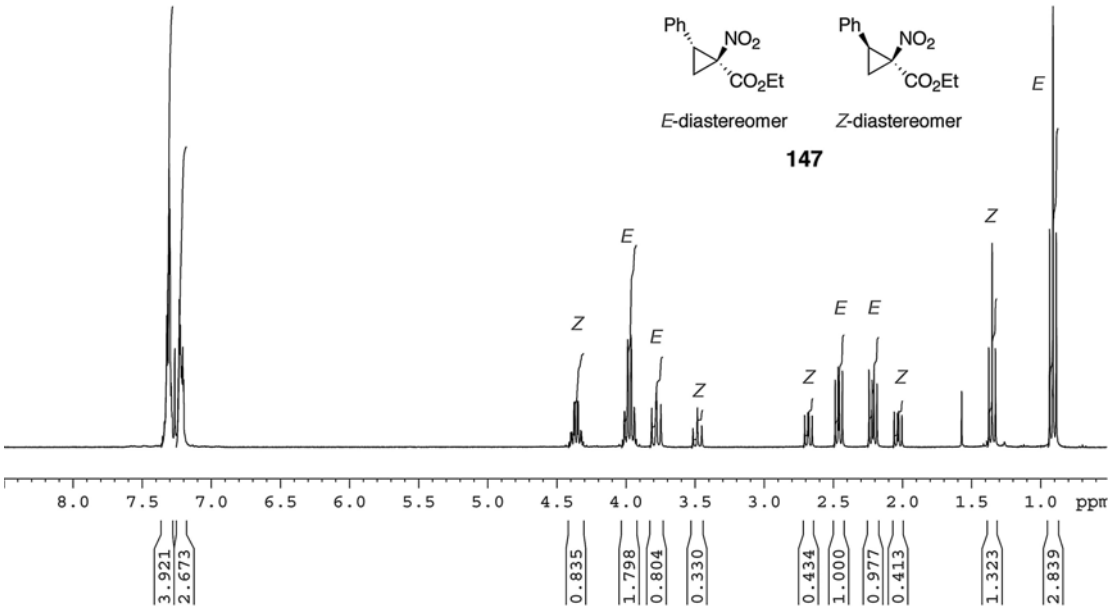


Figure 17. Representative ^{1}H NMR spectrum of ethyl-2-phenyl-1-nitrocyclopropane carboxylate (**147**).

The methylene protons of the cyclopropane for both diastereomers lie between 2.00-2.71 ppm, which is uncharacteristically high. Cyclopropyl protons *syn* to the nitro group appear 0.25 ppm downfield relative to *anti* protons in the case of the methylene protons of the *E*-diastereomer (Fig. 17). There is an even greater difference in chemical shifts between the *syn* and *anti* protons for the methylene protons of the *Z*-diastereomer due to the influence of the phenyl group. In this case the separation between the two is increased to 0.65 ppm. The multiplicities of the methylene cyclopropyl protons are invariably well-defined doublet of doublets with coupling constants of 6.9 and 9.9 Hz.

The assignment of the ^{1}H NMR signals to *E*- or *Z*-diastereomers has also been confirmed unambiguously by X-ray crystallography. The ORTEP representation of (*E*)-1[2-(4-fluorophenyl)-1-nitrocyclopropyl]ethanone (**151**, Fig. 18) clearly establishes the *trans*-relationship between the nitro and 4-fluorophenyl group. Crystals of this compound were grown from an EtOAc/hexane solution crystallizing

in a triclinic unit cell.[130] The bond angle between C(4)-C(3)-N(3) is 115.6º, illustrating the effect of the cyclopropane moiety on the optimum bond angle of a sp^3-hybridized carbon of 109.5º.

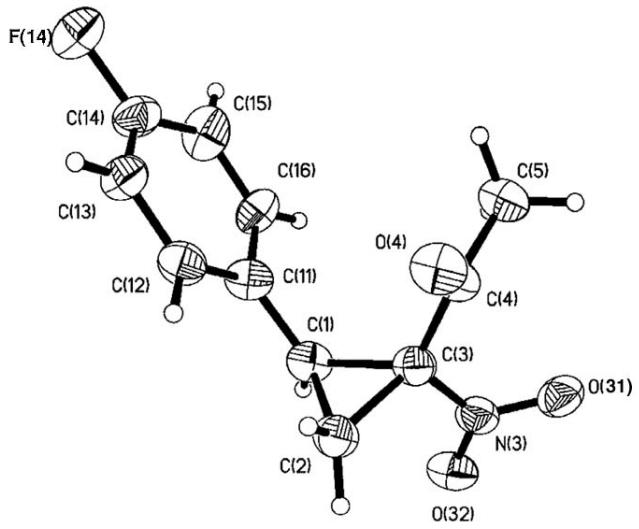


Figure 18. ORTEP representation of the crystal structure of (*E*)-1-[2-(4-fluoro-phenyl)-1-nitrocyclopropyl] ethanone (**151**).

One of the desired attributes of a useful methodology for the synthesis of cyclopropane α-amino acids is the ability to prepare both *E*- and *Z*-diastereomers. In order to access *Z*-cyclopropane α-amino acids, oxidation of the cyclopropyl ketones to esters must first be achieved. A number of reports in the literature give precedence for Baeyer-Villiger type oxidations of related cyclopropyl ketones. In these cases, the migratory aptitudes of *iso*-propyl and phenyl ketone substituents were found to exceed the cyclopropyl subunit.[131] Using this approach, one can envision a method by which the *Z*-nitro cyclopropylketones can be transformed into the desired esters. Once this is achieved, reduction of the nitro group and saponification of the ester would afford the corresponding *Z*-cyclopropane α-amino acids.

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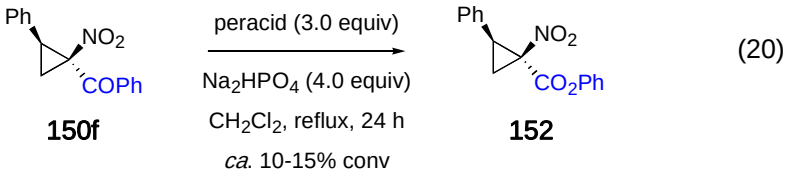
130. See Appendix II for the complete structural data concerning the crystal structure of (*E*)-1[2-(4-fluorophenyl)-1-nitrocyclopropyl] ethanone (**151**).
131.(a) Ma, D.; Cao, Y.; Yang, Y.; Cheng, D. *Org. Lett*. **1999**, *1*, 285-287. (b) Sauers, R. R.; Ubersax, R. W. *J. Am. Chem. Soc*. **1965**, *87*, 3939-3941.

Unfortunately, preliminary results involving the treatment of *Z*-2-phenyl-nitrocyclopropyl acetophenone (**150f**) with various peracids, including *m*-chloroperbenzoic acid and trifluoroperacetic acid resulted in low conversions (*ca*. 10-15%) of the desired corresponding phenyl carboxylate (**152**, Eq. 20). Unreacted starting material represented the mass balance. The oxidation could be impeded by the steric hindrance of the α-nitro group, however, further experimentation is needed.

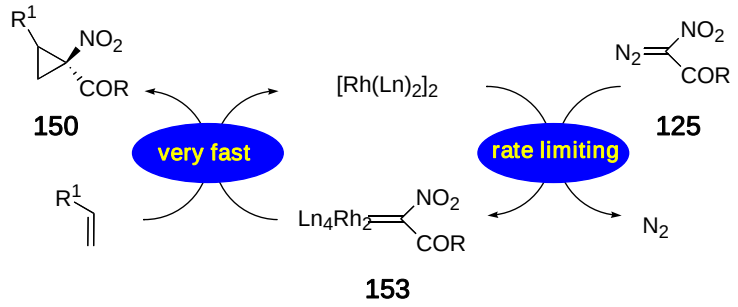


(20)

3.2.3 Cyclopropanation reaction mechanism

Despite the great synthetic utility of diazo compounds in cyclopropanation reactions, definitive mechanistic studies on the metal-catalyzed cyclopropanations are lacking. There still remains much debate over the exact nature of the intermediates in the associated mechanism. This is largely due to the rapid catalytic turnovers of these reactions making structural information about the intermediates difficult to obtain. However, it is generally accepted that the reaction involves an intermediate rhodium-carbene complex **153**. In its simplest depiction, the catalytic cycle consists of two steps, Rh-catalyzed nitrogen extrusion from the diazo compound, forming a Rh-carbene complex **153**, followed by C-C bond formation with the olefin which regenerates the catalyst (Scheme 13).

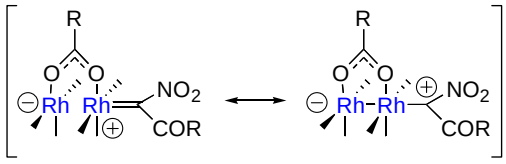
Scheme 13. Schematic representation of the catalytic cycle of a Rh(II) catalyzed cyclopropanation of an α-nitro-α-diazocarbonyl and an olefin.



The exact nature of the intermediate carbene complex **153** is still under debate since this highly reactive intermediate has never been isolated or observed by spectroscopic techniques. Furthermore, the reactive intermediate may vary depending on the particular diazo compound used, accounting for the diverse reactivities and reaction rates observed. This intermediate **153** may also be involved in other synthetic transformations involving diazo compounds, including C-H bond activation reactions in which a number of transition states have been proposed.[132] However, a general consensus has yet to be met in the scientific community.

The resonance forms **154** and **155** have been postulated to further describe the nature of the rhodium-carbene complex (**153**, Scheme 13). These two proposed resonance forms rationalize the experimental observation that electron-rich olefins are preferred substrates in cyclopropanation reactions involving α-nitro-α-diazocarbonyls (Fig. 19).

132. On the mechanism of C-H bond activations see: (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc*. **2002**, *124*, 7181-7192. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc*. **1993**, *115*, 958-964. (c) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc*. **1996**, *118*, 547-556.



154 **155**

Figure 19. Proposed rhodium-carbene complexes.

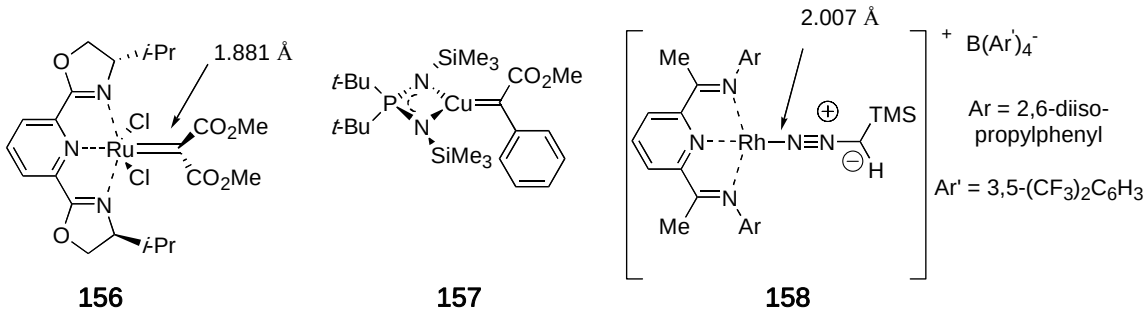
There are a variety of examples giving indirect crystallographic evidence to both support and oppose the existence of metal-carbene intermediates. Unfortunately, these examples involve different transition metals and diazo compounds than those in question. Two notable pieces of evidence supporting the presence of metal-carbene complexes with disubstituted diazo compounds involve Ru and Cu-based catalysts. In the case of the Ru-based catalyst, extrusion of nitrogen from methyl diazo malonate occurred upon refluxing the diazo compound with the catalyst at 60 ^{o}C for 24 h. A stable bis(methoxycarbonyl)carbene complex **156** was isolated in 92% yield. A crystal structure was also obtained of this metal-carbene complex (Fig. 20).[133] However, complex **156** reacted very slowly with styrene and after refluxing at 110 ^{o}C for 48 h, only 11% conversion to the corresponding cyclopropane was observed.

Another example involving the spectroscopic determination of a copper(I) carbene species **157** was possible upon treatment of methyl 2-phenyl-2-diazoacetate with a copper(I) ethylene complex. Complex **157** was only stable for several hours at –33 ^{o}C.[134] It is debatable whether these two distantly related metal-carbene complexes would be relevant to the active intermediates involved in Rh-catalyzed reactions of α-nitro-α-diazocarbonyls.

133.(a) Nishiyama, H.; Aoki, K.; Itoh, H.; Iwamura, T.; Sakata, N.; Kurihara, O.; Motoyama, Y. *Chem. Lett.* **1996**, 1071-1072. For an example involving a chiral metalloporphyrin carbene complex see: (b) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z. Y. *J. Am. Chem. Soc*. **2001**, *123*, 4119-4129.

134.(a) Straub, B. F.; Hofmann, P. *Angew. Chem., Int. Ed*. **2001**, *40*, 1288-1290. For an example involving an η^1-bound diazophenanthrone with the same Cu(I) complex see: (b) Straub, B. F.; Rominger, F.; Hofmann, P. *Organometallics* **2000**, *19*, 4305-4309.

Another mechanistic possibility that one also has to consider is that the catalyst does not form a rhodium-carbene complex, but rather complexes the nitrogen in a Lewis acid-Lewis base type interaction.[135] Brookhart *et al*. have recently reported a crystal structure involving an η^1-*N*-bound diazoalkane complex that contains a proton at the α-carbon atom lending evidence to the existence of these types of interactions (**158**, Fig. 20).[136] The diazoalkane obviously lacks resonance stabilization provided by ester or nitro groups and this case involves a Rh(I) complex instead of a Rh(II) complex. Again, whether direct analogies can be made with intermediates involving Rh(II) catalysts and α-nitro-α-diazocarbonyls is debatable.



156 **157** **158**

Figure 20. Examples of metal-carbene complexes and diazo-metal adducts.

To help rationalize the trends for the *E*- and *Z*-selectivities observed in cyclopropanation reactions involving α-nitro-α-diazocarbonyls, Doyle's model can be applied.[137] Rh-catalyzed cyclopropanation reactions of olefins with diazoacetates and diazoamides exhibit a preference for *trans*-products. Doyle attempted to explain this preference by the presence of a stabilizing interaction with the electrophilic β-carbon by the carbonyl group (Scheme 14). Doyle suggests that the greater the

135. Rh(II) carboxylates and carboxamidates acts as Lewis acids to catalyst hetero-Diels-Alder reactions see: Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc*. **2001**, *123*, 5366-5367.

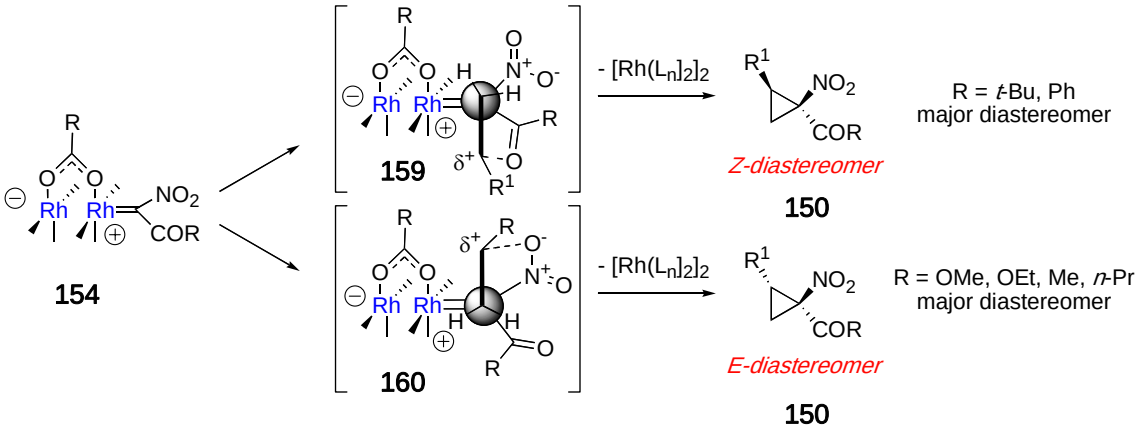
136.(a) Dias, E. L.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 2442-2443. For examples of Rh(I) carbene complexes see: (b) Werner, H.; Schwab, P.; Bleuel, E.; Mahr, N.; Steinert, P.; Wolf, J. *Chem. Eur. J*. **1997**, *3*, 1375-1384. (c) Gandelman, M.; Rybtchinski, B.; Ashkenazi, N.; Gauvin, R. M.; Milstein, D. *J. Am. Chem. Soc*. **2001**, *123*, 5372-5373.

137. Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53-61.

nucleophilic ability of the substrate, the greater the *trans*-preference (eg. diazoamides are more nucleophilic than diazoacetates). Additionally, steric bulk on the diazo compound or olefin favors formation of the *trans*-isomer.

Cyclopropanation reactions involving α-nitro-α-diazocarbonyl compounds give much higher diastereoselectivities than those commonly observed in cyclopropanations involving diazoamides or diazoacetates. In cases where R = OMe, OEt, Me and *n*-Pr, the *E*-diastereomer predominates by as much as 6-9:1 (Table 16). This preference for the *E*-diastereomer may reflect the increased ability of the oxygen atoms of the nitro group to stabilize the electrophilic β-carbon of the olefin, thus controlling the diastereoselectivities in the cyclopropanation (Scheme 14).[137] An interesting reversal to the *Z*-diastereomer is observed for sterically demanding nitro diazoketones (Table 16). This likely arises from the cooperative nucleophilic abilities of the carbonyl oxygen and the size and proximity of the ketone substituent to the carbene center resulting to outweigh the directing power of the nitro group.

Scheme 14. Rationalization of diastereoselectivities using Doyle's Model.



Based on the above arguments, one would expect nitro diazomethane to undergo highly diastereoselective cyclopropanation reactions due to the excellent directing ability of the nitro group and the absence of competing directing groups or sterically demanding groups. Surprisingly, nitro diazomethane is one of the least selective nitro diazo-based compounds in cyclopropanation reactions. For example, when styrene

was used as a substrate, the cyclopropanation reaction proceeded in a ratio of 2.4:1 *trans:cis* versus 9:1 *E:Z* when methyl nitro diazoacetate (**97**) was used (see: Table 14 and 16). This suggests that the directing ability of the nitro group may not be the only factor contributing to the high diastereoselectivities in these cyclopropanation reactions.

A number of other factors including reaction rates may account for the varying degrees of diastereoselectivities in these reactions. In the case of sterically hindered diazo compounds, approach of the olefin to the rhodium-carbene complex is more difficult for steric reasons. With diazo compounds, such as nitro diazomethane, the cyclopropanation reaction may occur before any degree of differentiation can occur. A change in reaction mechanism could be another plausible explanation. Different binding modes of the diazo compound with the metal catalyst could alter its reactivity, hence diastereoselectivities.

In an alternative scenario, the presence of two electron-withdrawing groups on the diazo compound may allow a greater build-up of positive charge on the β-carbon, thus magnifying the ability of the nitro groups to direct the cyclopropanation reaction. Unfortunately, at this time, the origins of the diastereoselectivities in the cyclopropanation reaction are not fully understood. Further experimentation is needed to clarify this issue.

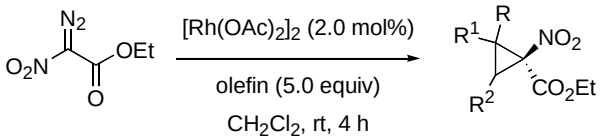
Doyle's Model also rationalizes the favorable yields resulting from cyclopropanation reactions involving α-stabilized olefins compared to non-α-stabilized olefins. Styrene, an α-stabilized olefin, is more capable of accommodating a build-up of positive charge on the β-carbon due to conjugation with the aromatic ring. As a result, cyclopropanation reactions with this substrate proceed rapidly and in excellent yields. In contrast, when 1-hexene is used as a substrate, reduced yields and greatly diminished reaction rates are observed (Table 14).

3.2.4 Scope of the intermolecular cyclopropanation reaction

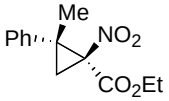
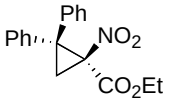
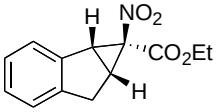
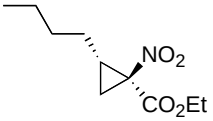
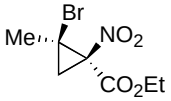
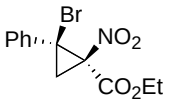
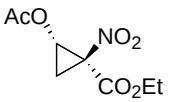
A large variety of olefinic substrates are commercially available or can be readily prepared. These building blocks will allow for the preparation of a diverse series of

cyclopropane α-amino acid analogues upon reduction of the nitro group. The reaction scope of the cyclopropanation reaction with α-nitro-α-diazocarbonyls has only been briefly examined. To further explore the scope of this reaction, a number of previously untested substrates were submitted to the cyclopropanation reaction (Table 17).

Table 17. Scope of the cyclopropanation reaction.



71 **161(a-g)**

entry	olefin	product[a]		yield (%)[b]	*E*:*Z* ratio
1	α-methylstyrene		(**161a**)	95	72:28
2	1,1'-diphenylethene		(**161b**)	97	---
3	1*H*-indene		(**161c**)	85	97:3
4	1-hexene		(**161d**)	40	60:40
5	2-bromopropene		(**161e**)	50	20:80
6	α-bromostyrene		(**161f**)	77	25:75
7	vinyl acetate		(**161g**)	51	77:23

a) Major diastereomer is depicted. b) Isolated yields after chromatography.

It is generally believed that the highest yields can be obtained with electron-rich, terminal, α-stabilized and *cis*-configured olefins (Table 17, entries 1-4,7). Surprisingly, when the cyclopropanation reaction was performed with somewhat electron-deficient olefin substrates,[138] such as 2-bromopropene and α-bromostyrene, the corresponding cyclopropanes **161e** and **161f** were indeed isolated in modest to excellent yields (Table 17, entries 5 and 6). Success with these substrates could be due to favorable polarization of the substrate towards the β-carbon. *Cis*- and *trans*-β-bromostyrenes were also submitted to the same reaction conditions and only trace amounts of the corresponding cyclopropane could be isolated. Considering a concerted formation of the nitro cyclopropanecarboxylate as proposed by Doyle *et al*. for related systems, the polarization of the β-bromostyrene would result in a destabilization of the intermediates, thus decreasing the potential for cyclopropane formation.[139] Accordingly, polarization also appears to play an important role in substrates, such as *cis*-stilbene and *cis*-1,4-dichloro-2-butene, as they failed to yield cyclopropanes under standard reaction conditions, whereas *cis*-2-butene gave excellent yields (Table 14).

Sterically hindered substrates, such as 3,3-dimethyl butene, also failed to afford reasonable yields of the corresponding cyclopropanes. Vinyl acetate was successfully cyclopropanated in modest yields (Table 17, entry 7). In contrast, tetrahydropyran and ethyl vinyl ether gave a mixture of degradation products, presumably due to the "push-pull" nature of the cyclopropane formed, facilitating its ring opening and degradation *via* an oxonium intermediate.

The diastereoselectivities observed in the cyclopropanation reactions were generally good. The nitro cyclopropanecarboxylate resulting from the cyclopropanation of indene **161c** gave excellent yields (85%) and almost exclusively the *exo*-diastereomer (Table 17, entry 3). When methyl nitro diazoacetate (**97**) was used as the diazo compound, exclusive formation of the *exo*-diastereomer **162** was

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138. For an ethyl diazoacetate cyclopropanation of α-fluorostyrene see: Meyer, O. G. J.; Fröhlich, R.; Haufe, G. *Synthesis* **2000**, 1479-1490.
139. Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44-52.

observed. The stereochemistry of this cyclopropane was confirmed unambiguously by X-ray crystallography (Fig. 21).[140]

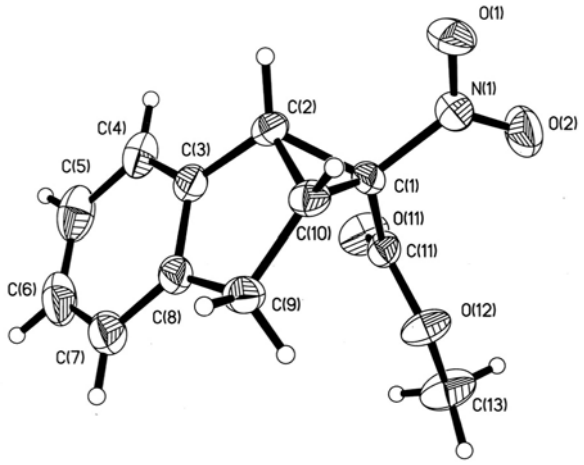


Figure 21. ORTEP representation of the crystal structure of *exo*-1,1a,6,6a-tetrahydro-1-nitrocyclopropa[*a*]indene-1-carboxylate (**162**).

The scope of the cyclopropanation reaction will be further explored in following chapters. As a general trend, α-nitro-α-diazocarbonyl compounds undergo efficient cyclopropanation reactions with a diverse series of olefins making this cyclopropanation strategy very attractive for the preparation of these densely functionalized nitro cyclopropylcarbonyls.

3.3 Enantioselective intermolecular cyclopropanation reactions

3.3.1 Evaluation of chiral Rh(II) carboxylate and carboxamidate catalysts

Diazo compounds bearing two electron-withdrawing groups are substantially less reactive than mono-substituted diazo compounds bearing only one electron-withdrawing group. For this reason, more active catalysts are required to generate the corresponding metal-carbene intermediate. At the present time, results reported for the Rh(II)-catalyzed asymmetric cyclopropanations of styrenes with diazomalonates

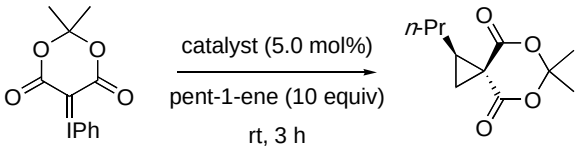
140. See Appendix III for the complete structural data concerning the crystal structure of *exo*-1,1a,6,6a-tetrahydro-1-nitrocyclopropa[*a*]indene-1-carboxylate (**162**).

are quite unsatisfactory. For example, the $[Rh(S\text{-}MEAZ)_2]_2$ (**163a**) catalyzed cyclopropanation of styrene with dimethyl diazomalonate results in 97% yield of the desired cyclopropane but in only 50% ee.[141]

If the diazo compound prepared from Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is used, slightly higher enantioselectivities are possible. Müller *et al*. have shown that this diazo compound can be replaced with its corresponding iodonium ylide **164**, serving as a synthetic equivalent of the diazo functionality.[142,143] Accordingly, upon screening a variety of chiral Rh(II) catalysts, asymmetric cyclopropanations of up to 63% ee could be obtained with pent-1-ene (Table 18).[144]

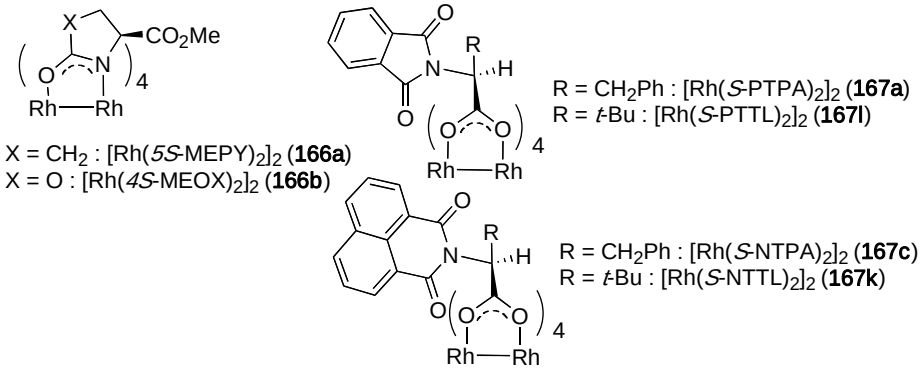
141. Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett*. **2000**, *2*, 1145-1147.
142. Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947-958.
143. Chapter 5 will describe in greater detail the use of iodonium ylides as synthetic equivalents of diazo compounds.
144. Müller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, *14*, 779-785.

Table 18. Asymmetric cyclopropanations with iodonium ylide **164** derived from Meldrum's Acid.



164 **165**

entry	catalyst	yield (%)	ee (%)	comment
1	[Rh(*5S*-MEPY)$_2$]$_2$	80	0	
2	[Rh(*4S*-MEOX)$_2$]$_2$	96	0	
3	[Rh(*S*-PTPA)$_2$]$_2$	95	22	
4	[Rh(*S*-PTTL)$_2$]$_2$	100	48	
5	[Rh(*S*-NTPA)$_2$]$_2$	96	26	
6	[Rh(*S*-NTTL)$_2$]$_2$	93	63	0<*T*<5 ^{o}C
7	[Rh(*S*-NTTL)$_2$]$_2$	84	37	styrene used



The results in Table 18 also serve to illustrate the differences in reactivity patterns between α-nitro-α-diazocarbonyl compounds and ylide **164**. Even though ylide **164** also has two strong electron-withdrawing groups flanking the carbene-carbon, its behavior in cyclopropanation reactions with olefin substrates appears different. For example, when 1-hexene was used as a substrate in a cyclopropanation reaction with ethyl nitro diazoacetate (**71**), it was found to give only modest yields (40%) of the corresponding cyclopropane **161d** (Table 17, entry 4). With the iodonium ylide **164**, nearly quantitative yields resulted for many of the catalysts tested (Table 18). Furthermore, Rh(II) carboxamidates **166a-b** were found to be completely inactive in cyclopropanation reactions involving ethyl nitro diazoacetate (**71**), whereas in

reactions involving iodonium ylide **164**, excellent yields of 80% and 96% resulted (Table 18, entries 1 and 2).

Cyclopropanation reactions involving aryl- and vinyldiazoester compounds have been widely used in asymmetric catalysis.[145] Rh(II) prolinate-based catalysts **61** and **62** in non-polar solvents are capable of providing excellent levels of enantiocontrol and often complete diastereocontrol (see: Table 4, Chapter 1). The presence of an electron-donating substituent (vinyl or aryl group) and an electron-withdrawing group was found to be crucial for high diastereoselectivities. Presumably, the approach of the olefin occurs on the side of the electron-withdrawing group. Heteroaryl diazoacetates containing both electron-rich and electron-deficient heterocycles, such as thiophene, furan, pyridine, indole, oxazole, isoxazole and benzoxazole, were also found to lead to highly diastereoselective and enantioselective cyclopropanations.[146]

Asymmetric cyclopropanation reactions employing α-nitro-α-diazocarbonyl compounds have been only briefly mentioned by O'Bannon and Dailey[81d] involving the $Cu(OAc)_2$-based catalysts reported by Brunner and Miehling[147] and Kunz and Reissig.[148] They noted that the material obtained using these chiral catalysts did exhibit optical activity, but the optical purity was not determined and the cyclopropanation yields were low. Asymmetric cyclopropanations involving these diazo compounds were not further pursued to the best of our knowledge.

Rh(II) carboxylate catalysts initially appeared to be the most attractive for the development of a high yielding enantioselective cyclopropanation. Accordingly, a large library of chiral rhodium catalysts was prepared. The chiral carboxylic acids ligands were based mainly from protected amino acid derivatives. The synthesis of Rh(II) catalysts is generally straightforward, usually consisting of heating the rhodium source with 6-10 equivalents of the desired chiral carboxylic acid. When $[Rh(OAc)_2]_2$ is used as a precursor, the equilibrium of the ligand exchange can be driven to completion through distillation of the reaction solvent (chlorobenzene) at

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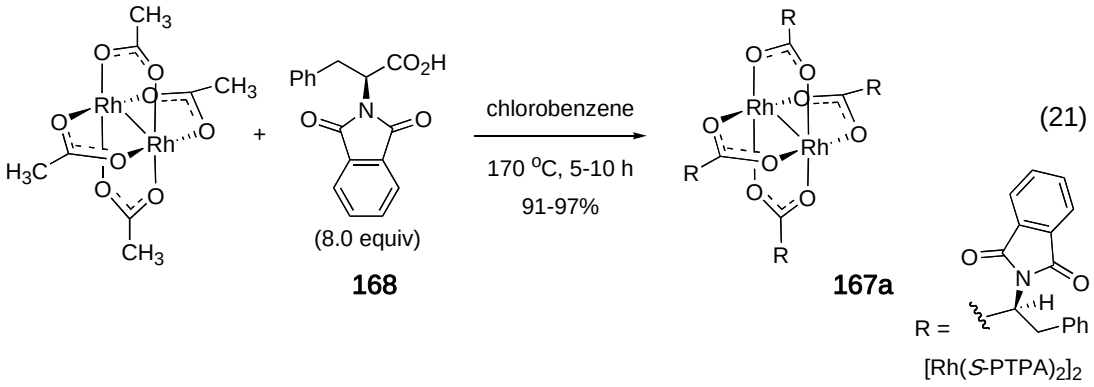
145. For a review on asymmetric transformations using these types of diazo compounds see: Davies, H. M. L. *Eur. J. Org. Chem*. **1999**, 2459-2469.
146. Davies, H. M. L.; Townsend, R. J. *J. Org. Chem*. **2001**, *66*, 6598-6603.
147. Brunner, H.; Miehling, W. *Monatsh. Chem*. **1984**, *115*, 1237-1254.
148. Kunz, T.; Reissig, H.-U. *Tetrahedron Lett.* **1989**, *30*, 2079-2082.

170 °C over a 3-6 h period[149] or by trapping of the acetic acid using a soxhlet extractor containing a mixture of sodium carbonate and sand (Eq. 21).



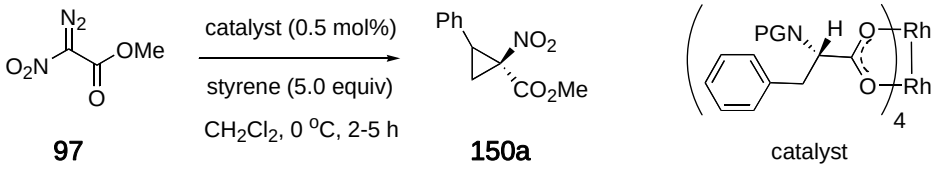
(21)

Rhodium tetrakis(carbonate), $[Rh(CO_3)_2]_2$, can also be used as a starting material when the desired carboxylic acid ligands are soluble in water. In this case, the ligand exchange is driven by the irreversible formation of carbon dioxide and water. The reaction is performed in aqueous media, requiring 2-3 h of heating at 80 °C for completion of the reaction. Upon cooling of the reaction mixture, the desired Rh(II) carboxylate precipitates from the reaction mixture and can be recovered by filtration.[150] This method of synthesis also reflects the robust nature of these catalysts to air and water and their ease of preparation and handling.

To examine the activities and levels of asymmetric induction for the catalysts prepared, a cyclopropanation reaction involving methyl nitro diazoacetate (**97**) and styrene was used. The first class of ligands surveyed was derived from the amino acid L-phenyl alanine. A diverse variety of amine protecting groups were tested and the results are reported in Table 19.

149. Callot, H. J.; Metz, F. *Tetrahedron*, **1985**, *41*, 4495-4501.
150. Buck, R. T.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *Tetrahedron: Asymm*etry **2003**, *14*, 791-816.

Table 19. Influence of the amine-protecting group on asymmetric induction.



97 **150a** catalyst **167(a-h)**

entry	protecting group (PG)	catalyst abbrev. (product)	yield (%)[a]	*E*:*Z* ratio	ee (%)[b] *E*-isomer	ee (%)[b] *Z*-isomer
1	phthalic anhydride	(*S*)-PTPA (**167a**)	75	86:14	30	13
2	maleic anhydride	(*S*)-MPA (**167b**)	75	83:17	24	5
3	1,8-naphthalic anhydride	(*S*)-NTPA (**167c**)	83	85:15	18	6
4	2,4-dioxo-3-azabicyclo [3.2.1]oct-3-yl anhydride	(*S*)-BCPA (**167d**)	75	90:10	26	12
5	tetrafluoro-phthalic anhydride	(*S*)-TFPTPA (**167e**)	76 (72)[c]	81:19 (77:23)	35 (34)	45 (61)
6	tetrachloro-phthalic anhydride	(*S*)-TCPTPA (**167f**)	77	84:16	8	46
7	tetrabromo-phthalic anhydride	(*S*)-TBPTPA (**167g**)	75	77:23	*ca*. 0	39
8	4-NO_2-$PhSO_2$-	(*S*)-NSPA (**167h**)	32	83:17	1	17

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis. c) The number in parenthesis corresponds to the results obtained at -50 °C.

The results from Table 19 illustrate that the protecting group on the amine portion of the ligand has a marked influence on the enantioselectivies in the cyclopropanation reaction. When phthalic anhydride was used as a protecting group, the resulting catalyst, $[Rh(S\text{-PTPA})_2]_2$ (**167a**), led to excellent isolated yields of the desired cyclopropane (**150a**, Table 19, entry 1). The diastereoselectivities were comparable to those observed when $[Rh(OAc)_2]_2$ was used as a catalyst at around 6:1 favoring the *E*-diastereomer. However, only low levels of asymmetric induction were observed, to the extent of 30% ee, for the major *E*-diastereomer and 13% for the *Z*-diastereomer (Table 19, entry 1).

The nature of the protecting group on the amine was further explored. Replacement of phthalic anhydride by maleic anhydride $[Rh(S\text{-MPA})_2]_2$ (**167b**), a much less bulky anhydride, resulted in a small decline in the observed enantioselectivities from 30% ee to 24% ee for the major diastereomer (Table 19,

entry 2). When the steric bulk of the anhydride was increased to the more bulky naphthalic anhydride, the resulting catalyst [Rh(*S*-NTPA)$_2$]$_2$ (**167c**), also gave low levels of asymmetric induction, declining from 30% ee for [Rh(*S*-PTPA)$_2$]$_2$ (**167a**) to only 18% ee for the major diastereomer (Table 19, entry 1 versus entry 3). In an attempt to determine whether π-stacking with the amine protecting group had an influence, a catalyst derived from a saturated bulky anhydride 2,4-dioxo-3-azabicyclo[3.2.1]oct-3-yl [Rh(*S*-BCPA)$_2$]$_2$ (**167d**) was prepared (Table 19, entry 4). This anhydride was derived from the Diels-Alder adduct between maleic anhydride and cyclopentadiene followed by olefin hydrogenation. Catalyst **167d** did not serve to enhance the enantioselectivities above the benchmark catalyst, [Rh(*S*-PTPA)$_2$]$_2$ (Table 19, entry 1 versus entry 4).

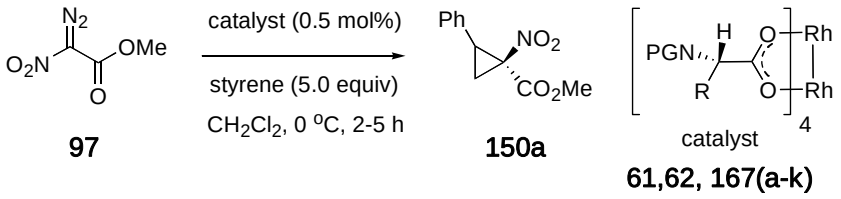
Next, the electronic properties of the phthalic anhydride amine-protecting group were modified. The catalyst derived from L-phenyl alanine with *tetra*-fluorophthalic anhydride as the protecting group, [Rh(*S*-TFPTPA)$_2$]$_2$ (**167e**),[151] gave somewhat promising results. Asymmetric induction of the major *E*-isomer slightly improved to 35% ee, while the *Z*-isomer rose sharply to 46% ee (Table 19, entry 5). At –50 ^{o}C, the enantioselectivity observed for the *E*-isomer remained unchanged (34% ee) while the level of asymmetric induction for the *Z*-isomer rose to 61% ee. Surprisingly, the catalyst derived from *tetra*-chlorophthalic anhydride, [Rh(*S*-TCPTPA)$_2$]$_2$ (**167f**), again showed modest enantioselectivities for the minor *Z*-isomer, but enantioselectivities for the *E*-isomer were completely eroded (Table 19, entry 6). The catalyst derived from *tetra*-bromophthalic anhydride, [Rh(*S*-TBPTPA)$_2$]$_2$ (**167g**), was slightly inferior to the *tetra*-chloro analogue (Table 19, entry 7).

These somewhat encouraging preliminary results prompted the exploration of other protecting groups in an attempt to boost the enantioselectivities. When the catalyst [Rh(*S*-NSPA)$_2$]$_2$ (**167h**), derived from phenyl alanine using *p*-nitrobenzenesulfonyl chloride as the protecting group, was tested the yields and enantioselectivities of the cyclopropanation reaction were completely lost (Table 19,

151. Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817-821.

entry 8). We then examined a variety of other amino acids to determine if this portion of the catalyst could be optimized (Table 20).

Table 20. Dirhodium catalysts derived from other amino acids.



entry	R-group	protecting group (PG)	catalyst abbrev. (product)	yield (%)[a]	*E*:*Z* ratio	ee (%)[b] *E*-isomer	ee (%)[b] *Z*-isomer
1	Bn	phthalic anhydride	(*S*)-PTPA (**167a**)	75	86:14	30	13
2	Me	phthalic anhydride	(*S*)-PTA (**167i**)	81	83:17	25	0
3	*i*-Pr	tetrachloro-phthalic anhydride	(*S*)-TCPTL (**167j**)	85	88:12	3	61
4	*t*-Bu	1,8-naphthalic anhydride	(*S*)-NTTL (**167k**)	88	89:11	19	15
5	proline[c]	4-($C_{12}H_{25}$)$C_6H_4SO_2$	(*S*)-DOSP (**62**)	74	79:21	8	10
6	proline[c]	4-(*t*-Bu)$C_6H_4SO_2$	(*S*)-TBSP (**61**)	89	89:11	2	17

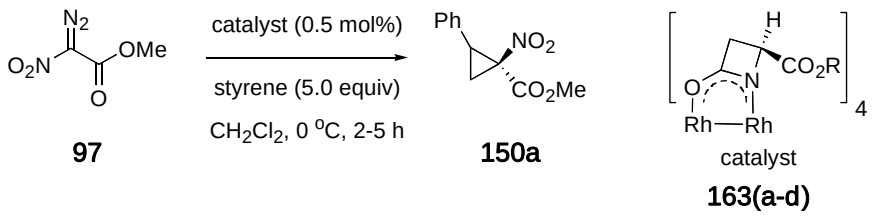
a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis. c) Amino acid derived from L-proline.

The catalyst derived from L-alanine with phthalic anhydride as a protecting group, [Rh(*S*-PTA)$_2$]$_2$ (**167i**), was tested and found to give slightly inferior levels of asymmetric induction when compared to the [Rh(*S*-PTPA)$_2$]$_2$ (**167a**) in terms of asymmetric induction. The catalyst derived from L-leucine protected with *tetra*-chlorophthalic anhydride, [Rh(*S*-TCPTL)$_2$]$_2$ (**167j**), was also prepared and the enantioselectivities were modest for the *Z*-isomer of 61% ee (Table 20, entry 3). When *tert*-leucine was protected with 1,8-napthalic anhydride and used as a ligand to make catalyst [Rh(*S*-NTTL)$_2$]$_2$ (**167k**), only a slight improvement in enantioselectivity resulted when compared to its phenylalanine analogue (19% ee versus 18% ee for *E*-isomer, Table 20, entry 4). However, this *tert*-leucine derived ligand did have an influence on reaction yields, improving to 88% (Table 20, entry 4). This trend was also observed with bulky ligands such as the achiral [Rh(OPiv)$_2$]$_2$ catalyst (Table 15, entry 6). L-proline derived catalysts, [Rh(*S*-DOSP)$_2$]$_2$ (**62**) and [Rh(*S*-TBSP)$_2$]$_2$ (**61**), showed dismal levels of asymmetric induction, however,

excellent yields of the corresponding cyclopropanes were observed (Table 20, entries 5 and 6).

Originally, it was found that the dirhodium carboxamidate catalyst, $[Rh(Cap)_2]_2$, was completely inactive in cyclopropanation reactions, leading only to degradation of the diazo compound (Table 15, entry 1). In general, this type of catalyst is not sufficiently reactive to promote cyclopropanations with α-nitro-α-diazo compounds even under forcing conditions (refluxing toluene). However, azetidine-based dirhodium catalysts proved to be an exception as Doyle *et al.* have proposed that the ligand strain on the Rh(II) framework results in higher reactivities towards diazo decomposition relative to other Rh(II) carboxamidate-type catalysts.

Table 21. Asymmetric cyclopropanations with Rh(II) azetidine-based catalysts.



97 **150a** catalyst **163(a-d)**

entry	R-group	catalyst abbrev. (product)	yield (%)[a]	*E:Z* ratio	ee (%)[b] *E*-isomer	ee (%)[b] *Z*-isomer
1	Me	(*S*)-MEAZ (**163a**)	76	86:14	33	0
2	*i*-Bu	(*S*)-IBAZ (**163b**)	46	90:10	45	8
3	Bn	(*S*)-BNAZ (**163c**)	28	86:14	28	7
4	4-F-Ph	(*S*)-FBNAZ (**163d**)	<5	92:8	18	5

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis.

Accordingly, $[Rh(S\text{-MEAZ})_2]_2$ (**163a**) was prepared and tested in a cyclopropanation reaction with methyl nitro diazoacetate (**97**) resulting in 76% isolated yield of the desired cyclopropane **150a**. The enantioselectivities were modest for this catalyst with 33% ee for the major diastereomer (Table 21, entry 1). The steric bulk of the azetidine-ester ligand was then increased to an *iso*-butyl group affording catalyst $[Rh(S\text{-IBAZ})_2]_2$ (**163b**). With this catalyst, the enantioselectivities increased to 45% for the *E*-diastereomer while maintaining a respectable *E:Z* ratio of

9:1 favoring the *E*-isomer. These improvements in enantioselectivities came at the expense of the reaction yields, which declined to 46% (Table 21, entry 2). The catalysts derived from azetidine benzyl or 4-fluorobenzyl esters, [Rh(*S*-BNAZ)$_2$]$_2$ (**163c**) and [Rh(*S*-FBNAZ)$_2$]$_2$ (**163d**), were surprisingly inactive as the enantioselectivities dropped precipitously as did the reaction yields (Table 21, entries 3 and 4).

In an attempt to predict the origin of asymmetric induction from the [Rh(*S*-MEAZ)$_2$]$_2$ (**163a**) catalyst, the metal-carbene complex was modeled using Spartan. This three-dimensional image depicts the projection of the ester groups into the axial positions potentially leading to the observed levels of enantiodescrimination. What is not obvious, however, is the orientation of diazo compound in the metal-carbene complex (Fig. 22).

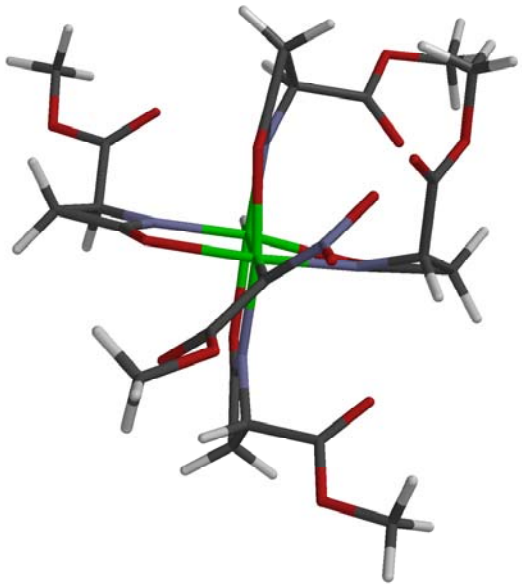
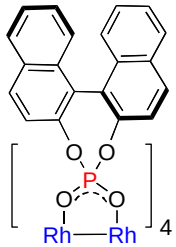


Figure 22. Spartan three-dimensional depiction (using MMFF 94 level) of the [Rh(*S*-MEAZ)$_2$]$_2$-carbene complex with methyl nitro diazoacetate.

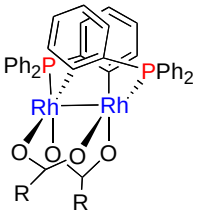
Various other rhodium-based catalysts were tested in the cyclopropanation reaction with little success including the commercially available Doyle's catalysts [Rh(*5S*-MEPY)$_2$]$_2$ (**166a**) and [Rh(*4S*-MEOX)$_2$]$_2$ (**166b**), which were found to be completely inactive. The BINOL-phosphate based catalyst, [Rh(*R*-BNP)$_2$]$_2$ (**169),**

(Fig. 23)[152] afforded respectable yields (71%) of the desired cyclopropane **150a** with an *E:Z* ratio of 75:25. However, the enantioselectivities were low of only 13% and 16% ee for the *E*- and *Z*-diastereomers, respectively. This is likely related to the lack of chiral projection by the ligands towards the axial binding sites in this catalyst. The Rh(II) phosphine-based catalysts **170a-b**, designed for the enantioselective intramolecular cyclopropanation of diazoketones by Taber *et al*.[153] were completely inactive with methyl nitro diazoacetate (**97**) due to their low reactivities (Fig. 23).



$[Rh(R\text{-BNP})_2]_2$

169



R = L-proline, **170a**
R = CF_3, **170b**

Figure 23. Other miscellaneous catalysts tested.

One unique characteristic of the cyclopropanation reactions involving α-nitro-α-diazocarbonyl compounds is that additions of the diazo compounds to the catalyst/olefin mixture can be done very rapidly (< 30 min) without the formation of dimers. With many diazo compounds dimers often result from self-condensation of two diazo molecules if addition rates to the catalyst are too rapid. For this reason, most diazo compounds are usually added to the catalyst/olefin mixtures *via* a syringe pump.

152.(a) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett*. **1992**, *33*, 5987-5990. (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *J. Chem. Soc., Chem. Commun*. **1999**, 2185-2186.

153.(a) Taber, D. F.; Malcolm, S. C. *J. Am. Chem. Soc*. **1999**, *121*, 860-861. See also: (b) Barberis, M.; Lahuerta, P.; Pérez-Prieto, J.; Sanaú, M. *J. Chem. Soc., Chem. Commun*. **2001**, 439-440. (c) Estevan, F.; Herbst, K.; Lahuerta, P.; Barberis, M.; Pérez-Prieto, J. *Organometallics* **2001**, *20*, 950-957. (d) Barberis, M.; Pérez-Prieto, J.; Herbst, K.; Lahuerta, P.; *Organometallics* **2002**, *21*, 1667-1673.

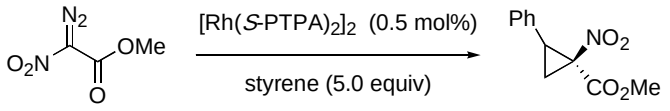
3.3.2 Influence of solvents on the enantioselectivity of the cyclopropanation reaction

Often, the levels of asymmetric induction in cyclopropanation reactions are largely dictated by the polarity of the reaction medium.[154] This, often dramatic, influence of reaction solvent is best illustrated by the enantioselective cyclopropanations reported by Davies *et al*. involving [Rh(*S*-TBSP)$_2$]$_2$ (**61**) and methyl benzylidene diazoacetate (**59**).[55] They propose that the ligand arrangement of the Rh(II) prolinate catalysts **61** or **62** exists in the D_2-symmetric form in non-polar solvents, which are believed to be the most stereo-discriminating conformer of the catalyst. For this reason, we were interested in performing the asymmetric cyclopropanation reaction involving methyl nitro diazoacetate (**97**) and styrene in a variety of solvents.

To examine the influence of various solvents on the enantioselectivities of the cyclopropanation reaction, a standard cyclopropanation reaction between methyl nitro diazoacetate (**97**) and styrene was used. [Rh(*S*-PTPA)$_2$]$_2$ (**167a**) was used as a catalyst as it gave one of the highest levels of asymmetric induction in previous cyclopropanation reactions. The results of these cyclopropanations are reported in Table 22.

154. Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc*. **2000**, *122*, 7638-7647.

Table 22. Influence of solvent on enantioselectivity.



97 **150a**

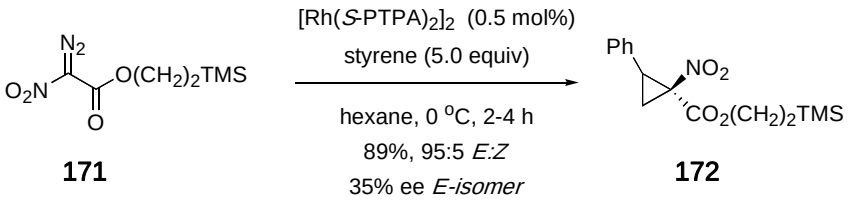
entry	solvent[a]	yield (%)[b]	*E*:*Z* ratio	ee (%)[c] *E*-isomer	ee (%)[c] *Z*-isomer
1	CH_2Cl_2	75	86:14	28	13
2	benzene	81	90:10	27	12
3	DME	65	89:11	25	6
4	Et_2O[d]	75	89:11	28	9
5	THF	32	94:6	25	0
6	acetone	81	88:12	22	18
7	CH_3CN	78	80:20	24	22

a) A 1.0 M solution of **97** in the corresponding solvent was added to the catalyst/ styrene mixture. b) Isolated yields after column chromatography. c) The ee's were determined by SFC analysis. d) A 0.5 M solution was used.

A diverse range of different solvents was tested in the cyclopropanation reaction and, surprisingly, there was little influence on the levels of asymmetric induction in the reaction. Enantioselectivities ranged from 22-28% for the major isomer (Table 22).[155] However, the isolated yields varied to a greater extent. THF was found to be quite detrimental to the reaction with yields dropping to 32% (Table 22, entry 5). This solvent probably reacts with the carbene intermediate forming oxonium ylides, which presumably decompose.

Due to the insolubility of methyl nitro diazoacetate (**97**) in hexane, the trimethylsilylethyl ester derivative **171** was prepared. Cyclopropanation with this diazo compound led to a small improvement in asymmetric induction to 35% ee for the major *E*-diastereomer (Eq. 22) versus 28% ee (Table 22, entry 1). For the sake of comparison, cyclopropanation with the trimethylsilylethyl ester **171** was also performed in CH_2Cl_2 and the enantioselectivity was found to be 29% ee for the *E*-diastereomer and 0% ee for the minor *Z*-diastereomer in a 93:7 *E:Z* ratio and 86% isolated yield.

155. Charette, A. B.; Wurz, R. P. *J. Mol. Catal. A: Chem*. **2003**, *196*, 83-91.

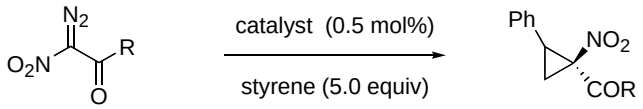


171 **172** (22)

3.3.3 Influence of the diazo compound on enantiomeric excess

Clearly, the solvent polarity had little influence on the levels of asymmetric induction, in contrast to the findings of Davies *et al*. We then reasoned that the low levels of asymmetric induction could result from the inability of the catalyst to differentiate between the nitro and ester groups. The influence of the R-groups of the diazo compound was then examined in cyclopropanation reactions involving several Rh(II) carboxylate catalysts.

Table 23. The influence of the diazo compound on the levels of asymmetric induction.



125 **150(a-f)**

entry	R-group	catalyst	yield (%)[a]	*E*:*Z* ratio	ee (%)[b] *E*-isomer	ee (%)[b] *Z*-isomer
1	OMe	[Rh(*S*-PTPA)$_2$]$_2$ (**167a**)	75	86:14	28	13
2	OEt	[Rh(*S*-PTPA)$_2$]$_2$ (**167a**)	72	90:10	30	0
3	O*t*-Bu	[Rh(*S*-PTPA)$_2$]$_2$ (**167a**)	68	89:11	41[c]	6[c]
4	Ph	[Rh(*S*-PTPA)$_2$]$_2$ (**167a**)	64	39:61	31	13
5	Ph	[Rh(*S*-TFPTPA)$_2$]$_2$ (**167e**)	81	37:63	13	37
6	Ph	[Rh(*S*-TCPTPA)$_2$]$_2$ (**167f**)	71	12:88	3	65

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis. c) The ee was determined by upon $LiAlH_4$ reduction to the nitro cyclopropylmethanol followed by typical SFC analysis.

In reactions involving [Rh(*S*-PTPA)$_2$]$_2$ (**167a**) as a catalyst, a slight increase was observed in the levels of asymmetric induction for the cyclopropanation reaction upon increasing the size of the R-group. When the methyl ester was used, 28% ee was

obtained and this value increased to 41% ee for the *tert*-butyl ester (Table 23, entry 1 versus 3). As observed in the case of achiral catalysts, the diastereoselectivities were compromised.

Interesting results were also observed when the nitro diazoacetophenone (**98**) was used as a substrate in the cyclopropanation reaction. When [Rh(*S*-PTPA)$_2$]$_2$ (**167a**) was used as a catalyst, a modest enantioselectivity for the minor *E*-diastereomer of 31% ee resulted, while the *tetra*-fluoro or *tetra*-chloro derived catalysts **167e** and **167f** gave modest enantioselectivities for the major *Z*-diastereomer up to 65% ee (Table 23, entries 5 and 6). This result represents one of the highest levels of asymmetric induction observed for an intermolecular cyclopropanation involving a diazoketone derivative. In fact, it is quite surprising that the reactivities of the nitro diazoketones and esters are so similar.

Presumably, the difficulty in achieving higher levels of asymmetric induction in these cyclopropanation reactions can be attributed to two factors: the high electrophilicity of the diazo compound, thus allowing little time for facial discrimination during the cyclopropanation reaction; and the steric and electronic similarities of the nitro and carbonyl groups. The latter idea could be supported by the slight improvements observed in the enantioselectivities between the methyl and *tert*-butyl derived esters (Table 23, entries 1 versus 3).

Improvement of catalyst design to include more rigid ligands with projection of chirality into the axial sites of the catalyst may allow for higher levels of enantioselection. However, the preferred binding orientation of the diazo compound is not immediately obvious, thus making rational catalyst design extremely difficult. Presently, dirhodium-based catalysts remain the most attractive catalysts due to their robust nature and high activities. Furthermore, the ease of preparation of these catalysts provides an additional benefit. To date, the levels of asymmetric induction in the Rh(II)-catalyzed intermolecular cyclopropanation reactions remain only modest.

3.3.4 Copper-catalyzed intermolecular cyclopropanations

In light of the disappointing levels of asymmetric induction possible with dirhodium-based catalysts, copper-based catalysts were briefly examined in intermolecular cyclopropanation reactions. Copper catalysts are known to be much more selective in intermolecular cyclopropanation reactions with diazo compounds such as ethyl diazoacetate,[156] hence, this trend should also be expected with α-nitro-α-diazocarbonyl compounds. However, their increased selectivities come at the expense of reduced reactivities, which led O'Bannon and Dailey to abandon their work involving asymmetric cyclopropanations with α-nitro-α-diazocarbonyls.[81d]

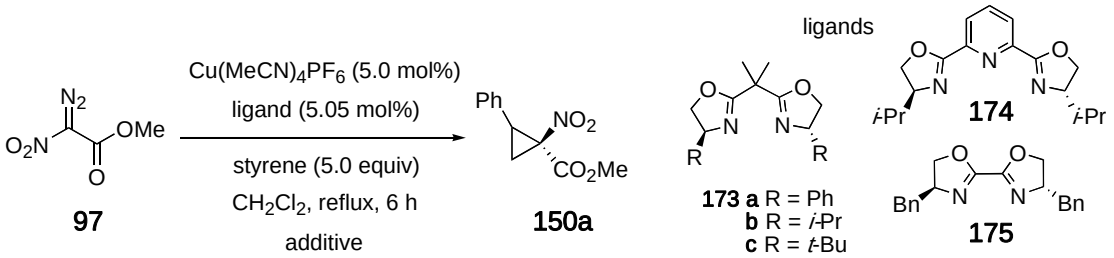
We were particularly interested in testing the catalysts reported by Evans *et al*. containing C_2 symmetric bis(oxazoline) ligands. Initially, cyclopropanations using these catalysts were plagued by low yields. One intriguing observation was that consistently low yields resulted regardless of reaction time, ligand, solvent or reaction temperature. In contrast, reactions catalyzed by the same Cu-source and ligands with ethyl diazoacetate were efficient, eliminating the possibility that the Cu-source had been improperly handled. Furthermore, methyl nitro diazoacetate (**97**) did not decompose under the cyclopropanation reaction conditions, even upon refluxing in toluene, and could be recovered along with small quantities of the desired cyclopropane **150a** with greater than 90% mass recovery.

We then resorted to methods to activate the copper catalyst by addition of additives. One report in the literature outlined the use of benzoyl peroxide to increase yields in copper-catalyzed cyclopropanations involving diazo malonates.[157] When methyl nitro diazoacetate (**97**) was used in the presence of 10 mol% of benzoyl peroxide as an additive, only slight improvements in reaction yields resulted (Table 24, entry 1). Given that the cyclopropanation reaction involving ethyl diazoacetate is always high yielding, we reasoned that this diazo compound could be used to activate the catalyst, potentially *via* simple displacement of coordinating solvent (eg.

156. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728.
157. Peace, B. W.; Carman, F.; Wulfman, D. S. *Synthesis* **1971**, 658-661.

CH_3CN), liberating a free site. Thus, pre-treatment of the Cu(I)$(MeCN)_4PF_6$ ligand complex **173a** with 20 mol% of ethyl diazoacetate followed by addition of a 1.0M solution of methyl nitro diazoacetate (**97**) resulted in a substantial increase in reaction yields. This new protocol also showed improved reproducibility (Table 24, entry 2).

Table 24. Copper-catalyzed cyclopropanations of styrene and methyl nitro diazoacetate.



entry	ligand	additive (equiv)	yield (%)[a]	*E*:*Z* ratio	ee (%)[b] *E*-isomer	ee (%)[b] *Z*-isomer
1	**173a**	$(BzO)_2$ (10%)	27	90:10	N/d	N/d
2	**173a**	EDA (20%)[c]	55	90:10	72	51
3	**173a**	EDA (10%)[d]	52	90:10	66	49
4	**173a**	$PhNHNH_2$[e]	39	90:10	70	49
5	**173b**	EDA (10%)[c]	16	95:5	68	N/d
6	**173c**	EDA (10%)[c]	7	95:5	63	N/d

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis. c) The catalyst was pretreated with a solution of ethyl diazoacetate in CH_2Cl_2. d) The ethyl diazoacetate was mixed with **97** in CH_2Cl_2. e) $Cu(OTf)_2$ was used as the copper source.

The copper-catalyzed cyclopropanations using the phenyl bis(oxazoline) ligand **173a** showed improved asymmetric induction for the formation of cyclopropane **150a** when compared to the Rh(II) carboxylate catalysts. Diastereoselectivities up to 9:1 *E*:*Z* and enantioselectivities up to 72% ee for the major *E*-diastereomer were possible (Table 24, entry 2). Unfortunately, the yields remained modest with the mass balance being unreacted methyl nitro diazoacetate (**97**). This material could be recovered from the reaction mixture and re-submitted to the reaction conditions if so desired.

Increased reaction times did not increase the conversions nor did the use of a variety of other copper sources including Cu(I)OTf. When ethyl diazoacetate was

mixed with the methyl nitro diazoacetate (**97**), similar yields could be obtained (Table 24, entry 3) and the enantioselectivities declined slightly. Finally, the use of Cu(II)OTf_2 as the copper source followed by pre-activation with phenyl hydrazine (2.0 equiv based on Cu) also produced a slightly inferior yield of the desired cyclopropane (**150a**, Table 24, entry 4).

Other ligands were also screened and it was discovered that the reaction was very sensitive to steric bulk on the ligands. The yields declined dramatically using *iso*-propyl **173b** and *tert*-butyl **173c** derivatives of the bis(oxazoline) ligand and enantioselectivities were also diminished (Table 24, entries 5 and 6). In an attempt to use less sterically demanding ligands, *i*-Pr pybox **174**[158] and the phenyl alanine derived bis(oxazoline) **175**[159] were tested, resulting in drastic decreases in enantioselectivities to 12% ee and 0% ee, respectively.

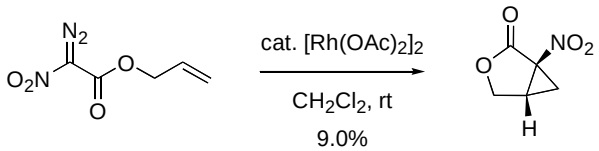
3.4 Enantioselective intramolecular cyclopropanation reactions

One of the most successful applications of Rh(II) catalysts is in the intramolecular cyclopropanations of mono- and disubstituted diazo compounds. Numerous examples of highly enantioselective cyclopropanations have been reported. However, few examples of enantioselective intramolecular cyclopropanations of the highly unreactive diazo malonates have been reported thus far.[160] To date, only modest enantioselectivities have been obtained in these types of transformations.

To our knowledge, only one example of an intramolecular cyclopropanation involving α-nitro-α-diazocarbonyl compounds has been attempted (Eq. 23). Snider and Che recently described this achiral example for the attempted synthesis of the 5-membered nitrocyclopropyl lactone **176**.[59] The cyclopropanation proceeded in low

158. Totleben, M. J.; Prasad, J. S.; Simpson, J. H.; Chan, S. H.; Vanyo, D. J.; Kuehner, D. E.; Deshpande, R.; Kodersha, G. A. *J. Org. Chem*. **2001**, *66*, 1057-1060.
159. Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem*. **1997**, *62*, 3375-3389.
160. For selected examples see: (a) Taber, D. F.; Amedio, J. C.; Ramand K. *J. Org. Chem*. **1988**, *53*, 2984-2990. For Cu-catalyzed intramolecular cyclopropanations see: (b) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093-1111. (c) Müller, P.; Boléa, C. *Synlett* **2000**, 826-828.

yield (9.0%) and this report appeared shortly following our publication of the expedient new synthesis of these diazo compounds.

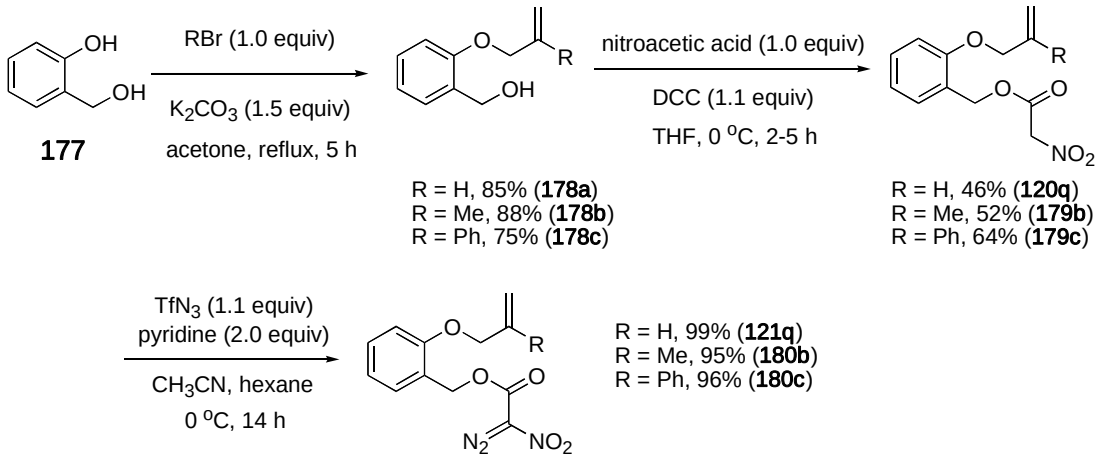


121c **176** (23)

The low yield of the intramolecular cyclopropanation is not surprising given the difficulty at which non-α-stabilized substrates are cyclopropanated, such as 1-hexene (Table 17, entry 4). With this in mind, a series of suitable substrates were prepared for the intramolecular cyclopropanation employing 2-hydroxybenzyl alcohol (**177**) as a scaffold. We were also interested in determining if enhanced enantioselectivities could be achieved in this intramolecular cyclopropanation using chiral Rh(II) catalysts. Preparation of the diazo compounds **121q, 180b-c** was readily accomplished in three high yielding steps involving allylation of the 2-hydroxybenzyl alcohol (**177**)[161] with the appropriate allyl bromide; followed by DCC coupling of nitroacetic acid (**123**) with the substituted benzene methanol **178a-c** then diazo transfer to afford the corresponding diazo compounds **121q**, **180b-c** (Scheme 15).[96,97]

161. Lachapelle, A.; St.-Jacques, M. *Tetrahedron* **1988**, *44*, 5033-5044.

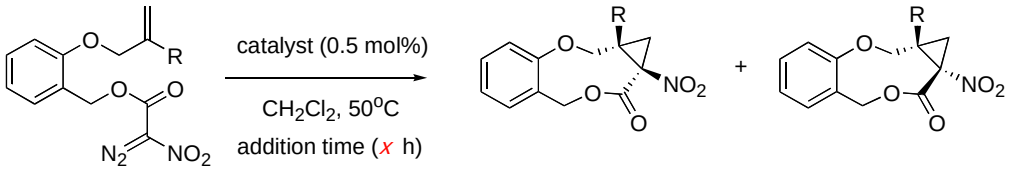
Scheme 15. Preparation of diazo compounds for intramolecular cyclopropanations.



Gratifyingly, asymmetric intramolecular cyclopropanations with these substrates proceeded with greater levels of enantioselection than observed in the intermolecular cyclopropanations. Surprisingly, the [Rh(*S*-DOSP)$_2$]$_2$ (**62**) catalyst gave consistently higher yields than the corresponding achiral catalysts [Rh(OPiv)$_2$]$_2$ or [Rh(Oct)$_2$]$_2$ which were required for preparation of racemic material.

The yields of the intramolecular cyclopropanation reactions follow the trend observed of ease at which various olefins are cyclopropanated (Table 14). Accordingly, it is not surprising that the cyclopropanations with the allyloxy compound (**121q**, Table 25, entries 1 and 2) were lower yielding. In these cases, the mass balance is presumably polymeric material resulting from competing intermolecular cyclopropanation reactions. The diastereoselectivitites observed in these intramolecular cyclopropanations were also particularly satisfying as only one diastereomer could be detected in almost all of the cases studied.

Table 25. Asymmetric intramolecular cyclopropanations for the synthesis of 9-membered nitrocyclopropyl lactones.



121q R = H
180b R = Me
180c R = Ph

181a R = H
181b R = Me
181c R = Ph

182a R = H
182b R = Me
182c R = Ph

entry	substrate	catalyst	addition time (h)	yield (%)[a]	ratio **181:182**	ee (%)[b] **181**
1	**121q**	$[Rh(OPiv)_2]_2$	3	14	>95:5	---
2	**121q**	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	3	33	>95:5	45
3	**180b**	$[Rh(Oct)_2]_2$	3	31	92:8	---
4	**180b**	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	2	58	>95:5	50
5	**180c**	$[Rh(Oct)_2]_2$	4	28	>95:5	---
6	**180c**	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	2.5	66	>95:5	61

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis.

The methyl-substituted compound **180b** afforded modest yields (31% and 58%) of the corresponding cyclopropane **181b** with an enantiomeric excess of 50% (Table 25, entry 4). This reaction is higher yielding than the allyl derived compound **121q** presumably because the presence of the methyl substitution is better able to accommodate the formation of partial positive charge on the β-carbon. In a similar fashion, the phenyl substituted diazo compound **180c** displayed even higher yields, affording 66% of the corresponding cyclopropane **181c**, and gave the highest levels of asymmetric induction observed of 61% ee (Table 25, entry 6).

The relative stereochemistry of cyclopropane **181c** was confirmed by X-ray crystallography, clearly establishing the *syn*-relationship of the phenyl and nitro groups of the macrocycle (Fig. 24).[162] By analogy, the major diastereomers of the other cyclopropanes were also assigned as *syn*-cyclopropanes.

162. See Appendix IV for the complete structural data concerning the crystal structure of 10a-nitro-1a-phenyl-1,1a,2,10a-tetrahydro-8*H*,10*H*-benzo[*b*]cyclopropa[*g*][1,5]dioxonin-10-one (**181c**).

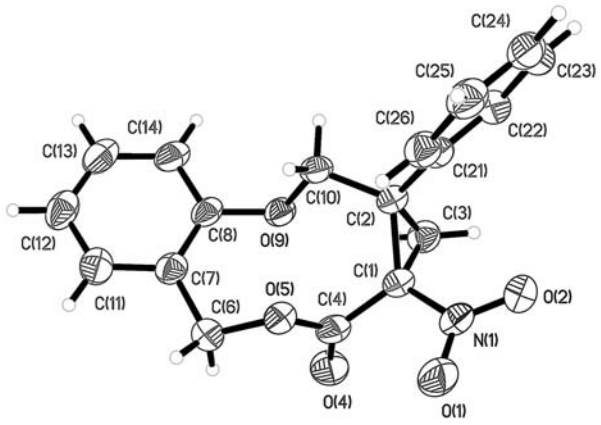
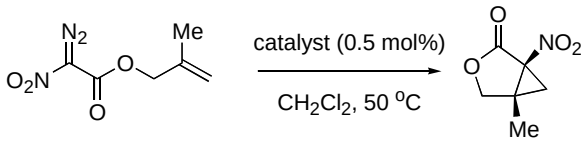


Figure 24. ORTEP representation of the crystal structure of 10a-nitro-1a-phenyl-1,1a,2,10a-tetrahydro-8*H*,10*H*-benzo[*b*]cyclopropa[*g*][1,5]dioxonin-10-one (**181c**).

A variety of other chiral Rh(II) catalysts were screened in the intramolecular cyclopropanation reaction with the above diazo compounds and found to give greatly inferior enantioselectivities, although modest to high yields were often possible. Surprisingly, the catalysts that gave the highest enantioselectivities in the intermolecular cyclopropanations gave very low levels of enantioselection in the intramolecular cyclopropanations.

Initially, we believed that the success of the intramolecular cyclopropanation was related to its ability to cyclopropanate certain types of olefin substrates. As was the case in intermolecular cyclopropanations, terminal disubstituted electron-rich double bonds appeared to undergo cyclopropanation reactions with the greatest ease. To further study this intramolecular cyclopropanation, catalyst-ligand effects were examined in the cyclopropanation reaction of 2-methylallyl nitro diazoacetate (**182a**). The yields of the cyclopropanation were also found to be highly dependent on the reaction conditions including temperature, solvent and catalyst used (Table 26).

Table 26. The influence of the Rh(II) catalyst on the yields of the intramolecular cyclopropanations.



182a **183a**

entry	catalyst	yield (%)[a]	ee (%)[b]
1	$[Rh(OAc)_2]_2$	20	---
2	$[Rh(OPiv)_2]_2$	79	---
3	$[Rh(1\text{-Adaman})_2]_2$	82	---
4	$[Rh(1\text{-Adaman})_2]_2$	trace[c]	---
5	$[Rh(S\text{-MEAZ})_2]_2$ (**163a**)	0[d]	---
6	$[Rh(S\text{-PTPA})_2]_2$(**167a**)	76	<2
7	$[Rh(S\text{-TBSP})_2]_2$ (**61**)	7	15
8	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	37	10
9	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	<5[e]	N/d
10	$[Rh(S\text{-DOSP})_2]_2$ (**62**)	0[f]	N/d

a) Isolated yields after column chromatography. b) The ee's were determined by SFC analysis. c) Reaction performed at room temperature. d) Recovered 57% of **182a**. e) Solvent = toluene. f) Solvent = $(CH_2Cl)_2$.

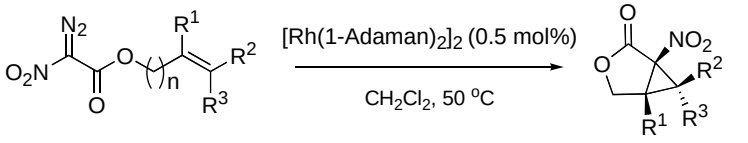
Slow addition of a dilute (0.1M) solution of the 2-methallyl nitro diazoacetate (**182a**) to a solution containing $[Rh(OAc)_2]_2$ at 50 °C led to only 20% yield of the desired cyclopropane **183a** as a single diastereomer (Table 26, entry 1). More active catalysts such as $[Rh(OPiv)_2]_2$ or $[Rh(1\text{-Adaman})_2]_2$ afforded respectable yields of the desired cyclopropane **183a** ranging from 79-82% yield (Table 26, entries 2 and 3). Surprisingly, when the cyclopropanation reaction was performed at room temperature with $[Rh(1\text{-Adaman})_2]_2$, only traces of the cyclopropane **183a** were detectable along with the unreacted starting material. Upon heating this reaction mixture at 50 °C for 2.5 h, the cyclopropanation reaction did not progress further (Table 26, entry 4).

Several chiral catalysts were then screened in asymmetric intramolecular cyclopropanation reactions. $[Rh(S\text{-MEAZ})_2]_2$ (**163a**) was completely inactive for the formation of cyclopropane **183a** and 57% of the 2-methallyl nitro diazoacetate (**182a**) could be recovered from the crude reaction mixture. $[Rh(S\text{-PTPA})_2]_2$ (**167a**) was also tested, yielding 76% of the desired cyclopropane **183a**, however, the

enantioselectivities were < 2% ee (Table 26, entry 6). Proline derived catalysts [Rh(*S*-TBSP)$_2$]$_2$ (**61**) and [Rh(*S*-DOSP)$_2$]$_2$ (**62**) gave low yields and enantioselectivities with CH_2Cl_2 being the solvent of choice (Table 26, entries 7-10).

Following these results, a variety of other diazo compounds were prepared. The results of the intramolecular cyclopropanations involving these compounds are summarized in Table 27.

Table 27. Scope of the Rh(II)-catalyzed intramolecular cyclopropanation reaction.



121c,e 182(b-h) **176, 183(b-h)**

entry	n	R^1	R^2	R^3	product	yield (%)[a]
1	1	H	H	H	**176**	20
2	1	H	Ph	H	**183b**	36
3	1	*n*-Pr	H	H	**183c**	39
4	1	Bn	H	H	**183d**	37
5	1	H	Me	Me	**183e**	50
6	1	H	Me	R[b]	**183f**	30
7	2	Me	H	H	**183g**	80
8	3	Me	H	H	**183h**	95

a) Isolated yields after column chromatography. b) Allylic alcohol derived from geraniol.

The cyclopropanation yields were quite sensitive to the substitution pattern on the diazo compound. Allyl nitro diazoacetate (**121c**) afforded 20% yield using the optimum reaction conditions and catalyst. The α-nitro-α-diazocarbonyl compound derived from cinnamyl alcohol **121e** was also prepared and tested, affording only 36% yield of the corresponding cyclopropane **183b**. In an attempt to approximate the electronic environment of the successful 2-methallyl compound **182a**, *n*-propyl **182c** and benzyl **182d** derivatives were prepared. Upon submission of these diazo compounds to the optimal cyclopropanation reaction conditions, surprisingly low yields of 39% **183c** and 37% **183d** resulted, respectively (Table 27, entries 3 and 4).

This is presumably a result of increasing unfavorable steric repulsions in the transition state.

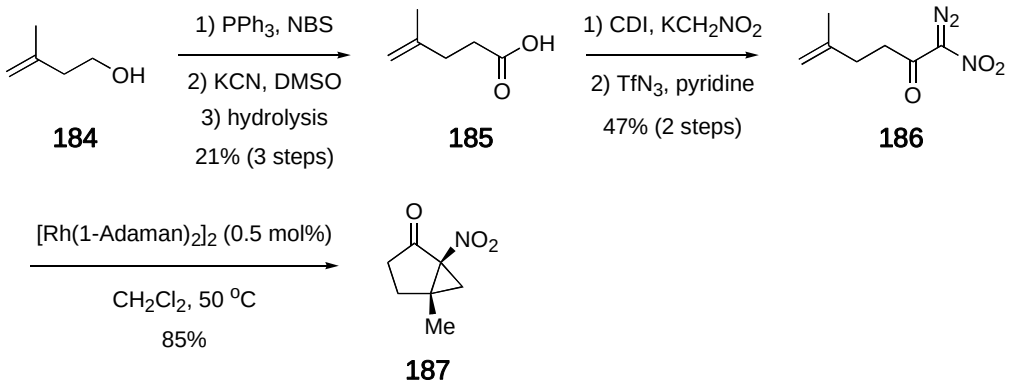
The synthesis of the highly functionalized pentasubstituted nitrocyclopropyl lactone **183e**, derived from diazo compound **182e**, was possible in 50% yield. Unfortunately, the yield precipitously declined when $[Rh(S\text{-DOSP})_2]_2$ (**62**) was used as a catalyst and all attempts to determine the enantioselectivities of this reaction were thwarted due to its transparency to UV/Vis detectors and its high melting point. A diazo compound derived from the allylic alcohol, geraniol **182f**, was also tested and found to give only modest yields of the corresponding 5-membered nitrocyclopropyl lactone **183f**.

The influence of the cyclopropanation reaction yield on ring size was also briefly studied upon preparation of the homoallylic and bis(homo)allylic diazo compounds **182g** and **182h**. Satisfyingly, the cyclopropanation reactions yielded the corresponding 6- and 7-membered nitrocyclopropyl lactones **183g** and **183h** in excellent yields of 80% and 95%, respectively. Again, only one diastereomer was observed.

We also wondered if the same reactivity would be observed if α-nitro-α-diazoketone compounds were submitted to the reaction conditions. Accordingly, 4-methylpent-4-enoic acid (**185**)[163] was prepared from the commercially available 3-methyl-but-3-enol (**184**) and transformed into the corresponding diazo compound **186** *via* the sequence depicted in Scheme 11. The intramolecular cyclopropanation proceeded with excellent yields, affording the corresponding 5-membered cyclopropylketone **187** in 85% isolated yield (Scheme 16). When $[Rh(S\text{-DOSP})_2]_2$ (**62**) was used as a catalyst, the cyclopropanation was equally high yielding (84%) but the isolated material was found to be racemic.

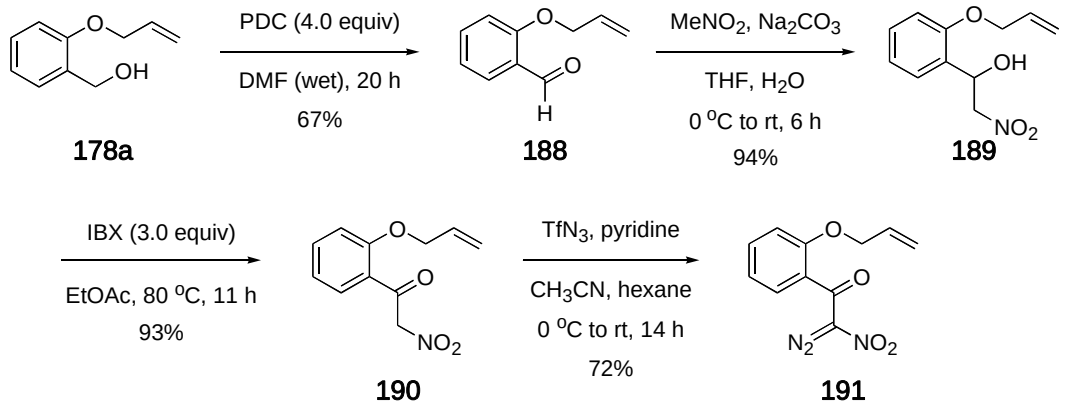
163. Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1815-1827.

Scheme 16. Synthesis and intramolecular cyclopropanation of an α-nitro-α-diazoketone.



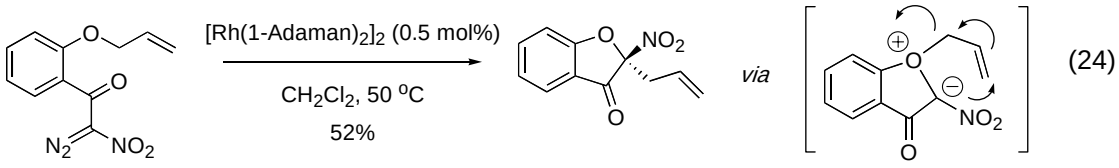
To further examine the intramolecular cyclopropanations involving α-nitro-α-diazoketones, diazo compound **191** was prepared using the 2-hydroxybenzyl alcohol (**177**) scaffold. Synthesis of this diazo compound required a Henry reaction for synthesis of the α-nitroketone **190** due to the challenges associated with the oxidation of benzyl alcohol **178a** to a carboxylic acid in the presence of an olefin (Scheme 17).[164]

Scheme 17. Synthesis of an α-nitro-α-diazoketone compound based on a 2-hydroxy benzyl alcohol scaffold.



164. The procedure involving TEMPO and bleach reported by Merck led to chlorination of the olefin see: Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem*. **1999**, *64*, 2564-2566.

When α-nitro-α-diazoketone **191** was submitted to the cyclopropanation reaction conditions, no cyclopropanes were recovered from the reaction mixture. Instead, product **192** derived from an oxonium rearrangement resulted. This rearrangement is believed to occur through the formation of an oxonium ylide intermediate **193** as depicted in Eq. 24.[165]



191 **192** **193**

3.5 Conclusions

Intermolecular cyclopropanations of styrene with α-nitro-α-diazocarbonyl compounds using achiral Rh(II) carboxylate catalysts were found to proceed in modest to high yields. Catalysts containing electron-rich sterically demanding carboxylate ligands performed the best in terms of reaction yields (Table 15).

Asymmetric intermolecular cyclopropanations using chiral Rh(II) carboxylate and carboxamidate catalysts were also explored and, although excellent yields were generally observed, only low to modest levels of asymmetric induction could be obtained (Tables 19-21). Other experimental parameters including solvent polarity (Table 22) and steric bulk of the diazo compounds (Table 23) were varied with limited success. For the intermolecular cyclopropanation of styrene with methyl nitro diazoacetate (**97**), copper-based catalysts were found to give the highest levels of enantioselection. With these catalysts, ee's up to 72% could be obtained, however, yields were generally modest (Table 24).

The first high-yielding intramolecular cyclopropanations of α-nitro-α-diazocarbonyl compounds have been achieved, allowing for the preparation of a

165.(a) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett*. **1992**, *33*, 5983-5986. (b) Pierson, N.; Fernández-Garcia, C.; McKervey, M. A. *Tetrahedron Lett*. **1997**, *38*, 4705-4708. (c) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett*. **1997**, *38*, 6471-6472.

variety of nitro cyclopropyl lactones with varying ring sizes. Enantioselectivities up to 61% ee were possible for the 9-membered nitro cyclopropyl lactones (Table 25). The yields in the intramolecular cyclopropanation reactions were also found to be quite sensitive to the substitution pattern of the olefin and reaction conditions (Tables 26 and 27)

These preliminary results involving asymmetric cyclopropanations of α-nitro-α-diazocarbonyls are quite encouraging. The design and synthesis of new chiral Rh(II) catalysts will ultimately lead to highly enantioselective cyclopropanations involving these α-nitro-α-diazocarbonyls in the near future. Presently, however, there remains room for improvement in the field of asymmetric cyclopropanation reactions involving disubstituted diazo compounds.

CHAPTER 4

Transition Metal-Catalyzed Cyclopropanations in Water and In Situ Generation of Ethyl Diazoacetate

4.1 Introduction

The cyclopropane subunit occurs frequently in biologically active compounds, both of natural and synthetic origins. Recent developments in organic synthesis have also shown cyclopropanes to be versatile synthetic intermediates for the preparation of functionalized cycloalkanes[166] and acyclic compounds.[167] Transition metal-catalyzed cyclopropanations of alkenes with diazo compounds represents a direct approach for the preparation of various cyclopropanes. Unfortunately, in an industrial setting, this approach has been generally avoided[168,169] due to the toxicities and potential for explosion of some diazo compounds.[170]

In an effort to improve the viability of large-scale diazo-mediated cyclopropanations, we envisioned a methodology which could use water as a reaction solvent. One of the recent demands for organic synthesis and catalysis, with environmental concerns in mind, has been for reactions to be carried out in non-

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166. For a review on the divinylcyclopropane rearrangement see: (a) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pg. 971. For a review on the vinylcyclopropane rearrangement see: (b) Hudlicky, T.; Reed, J. W.; In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pg. 899.

167. For reviews on cyclopropane opening reactions see: (a) Nonhebel, D. C. *Chem. Soc. Rev*. **1993**, 347-359. (b) Salaün, J. R. Y. *Top. Curr. Chem*. **1988**, *144*, 1-71.

168.(a) Aratani, T. *Pure & Appl. Chem*. **1985**, *57*, 1839-1844. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc*. **1980**, *102*, 6163-6165.

169.(a) Scott, J. W. *Organ. Chem. (Abstr. Am. Chem. Soc. Div. Org. Chem.)* **2002**, *186*, 223. (b) Simpson, J. H.; Godfrey, J.; Fox, R.; Kotnis, A.; Kacsur, D.; Hamm, J.; Totelben, M.; Rosso, V.; Mueller, R.; Delaney, E.; Deshpande, R. P. *Tetrahedron: Asymmetry* **2003**, *14*, 3569-3574.

170. Regitz, M.; Maas, G. *Diazo Compounds; Properties and Synthesis* Academic Press: Orlando, 1986.

halogenated solvents or in aqueous and/or protic media. There are many potential advantages associated with using water as a reaction medium including the following: 1) *Cost*. Water is one of the most economical solvents; 2) *Safety*. Frequently, the organic solvents used are carcinogenic and inflammable posing an explosion risk; 3) *Environmental concerns*. The chemical industry is a major contributor to environmental pollution and the use of water may diminish the problems associated with the use of organic solvents; and 4) *Separation*. From an industrial point of view, the use of a two-phase system allows for easy separation of the products from byproducts.[171]

It is important that the above listed benefits of using water as a solvent are not gained at the expense of synthetic efficiency. Even a small decrease in yield, catalyst turnover, or selectivity of a reaction can lead to a substantial increase in cost and the amount of waste generated. Fortunately, many practical advantages of the use of water as a solvent for organic synthesis exist, some of which will be described in this chapter.

As organic chemists, we generally consider water as a contaminant and we often take extreme measures to ensure that trace quantities of water do not come into contact with the reagents or the reaction vessel used for the reaction. Nevertheless, in recent years chemists have begun investigating the possibility of using water as a solvent for organic reactions, sometimes with surprising and unforeseen results. One contribution that led to a heightened interest in the use of water in organic synthesis was the observation of the positive influence of water on the reaction rates and selectivities of Diels-Alder reactions observed in the laboratories of Breslow[172] and Grieco[173] in the early 1980's.

In the decades following this discovery, significant progress has been made using aqueous solvents. The list of transformations that can be performed efficiently in

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171. For reviews on stereoselective organic reactions in water see: (a) Lindström, U. M. *Chem. Rev*. **2002**, *102*, 2751-2772. (b) Sinou, D. *Adv. Syn. Catal*. **2002**, *344*, 221-237.

172.(a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc*. **1980**, *102*, 7816-7817. (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901-1904. (c) Breslow, R.; Maitra, U. *Tetrahedron Lett*. **1984**, *25*, 1239-1240.

173. Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem*. **1983**, *48*, 3137-3139.

aqueous solvents continues to grow. Other recent and notable examples include Pt-catalyzed C-H bond activations of amino acids,[174] stereoselective aldol reactions,[175] olefin epoxidations,[176] and epoxide resolutions[177] to mention a few. Even olefin polymerizations of styrene catalyzed by metallocene-based catalysts have been shown to be possible in water.[178]

Before a reaction is to be done in water, several issues must first be considered. The reagents and the catalyst must be compatible with this reaction medium. In the case of diazo compounds, O-H insertion reactions are well-documented transformations with this functionality. Furthermore, the viability of O-H insertion reactions demonstrates that diazo compounds and the catalysts used to affect the transformation are compatible with aqueous and protic media. One must also consider that this facile O-H insertion process could be a competing side-reaction should we wish to perform a cyclopropanation reaction in aqueous media.

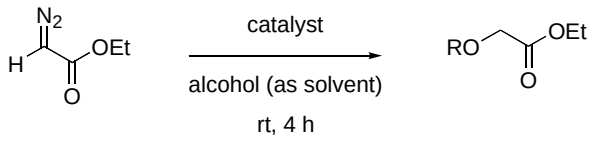
4.1.1 O-H insertion reactions with diazo compounds

Generally speaking, cyclopropanation reactions employing diazo compounds are performed under rigorously anhydrous conditions to prevent possible O-H insertion reactions from protic sources. It has been well documented that diazo compounds, such as ethyl diazoacetate (EDA, **101**), undergo facile O-H insertion reactions with alcohols and water in the presence of a catalyst. Teyssié *et al*. documented the first examples of such transformations in 1973 upon treatment of an alcoholic solution containing a rhodium catalyst with EDA (**101**). Additionally, they found that several rhodium sources including $[Rh(OAc)_2]_2$, $RhCl_3 \cdot 3H_2O$ or $RhCl(PPh_3)_3$ were efficient

174. Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc*. **2001**, *123*, 8149-8150.
175. Mori, Y.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2001**, *40*, 2816-2818.
176. Lane, B. S.; Burgess, K. *J. Am. Chem. Soc*. **2001**, *123*, 2933-2934.
177. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938.
178. Manders, B.; Sciandrone, L.; Hauck, G.; Kristen, M. O. *Angew. Chem., Int. Ed.* **2001**, *40*, 4006-4007.

in promoting an O-H insertion reaction between EDA (**101**) and alcohols (Table 28).[179]

Table 28. Rh-catalyzed O-H insertion reactions of alcohols with EDA (**101**).



101 **194**

entry	catalyst	alcohol	yield (%)
1	$[Rh(OAc)_2]_2$[a]	methanol	93
2	$[Rh(OAc)_2]_2$[a]	ethanol	88
3	$[Rh(OAc)_2]_2$[a]	*i*-propanol	83
4	$[Rh(OAc)_2]_2$[a]	*t*-butanol	82
5	$[Rh(OAc)_2]_2$[a]	water	80
6	$RhCl_3 \cdot 3H_2O$[b]	ethanol	64
7	$RhCl_3 \cdot 3H_2O$[b]	*t*-butanol	58
8	$RhCl(PPh_3)_3$[b]	ethanol	49

a) Catalyst loadings of 0.2 mol% used. b) Catalyst loadings of 0.8 mol% used.

As illustrated in Table 28, the carbene resulting from treatment of the Rh-catalyst with EDA (**101**) is inserted with equal efficiency into the O-H bonds of primary to tertiary alcohols. Yields in excess of 80% were observed for examples catalyzed by $[Rh(OAc)_2]_2$ (Table 28, entries 1-4). Water was also a good substrate for this reaction as the O-H insertion product could be isolated in 80% yield (Table 28, entry 5).

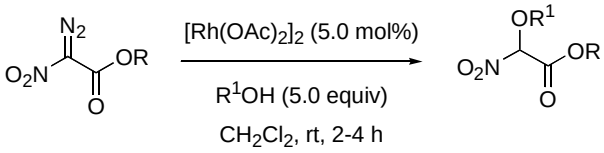
A competition experiment was also reported, which demonstrated that primary alcohols reacted faster than more hindered secondary and tertiary alcohols in the following relative ratios: ethanol 2.12, *iso*-propanol 1.20 and *tert*-butanol 1.00. This observed trend follows the order of decreasing acidity of the alcohols as well as the order of increasing steric hindrance. Other catalysts, including cupric chloride, were also tested resulting in low yields of the corresponding O-H insertion products. In

179. Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *14*, 2233-2236.

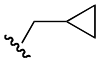
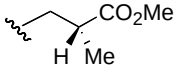
contrast to the more robust Rh-derived catalysts, the Cu-catalyst is presumably deactivated by the protic media.

Since no reports of O-H insertion processes involving α-nitro-α-diazocarbonyl compounds are found in the literature, we were interested in determining if these reactions were possible. The products resulting from O-H insertions of these diazo compounds, α-alkoxy-α-nitrocarbonyls, represent a novel class of compounds that could serve as interesting synthons for the preparation of α-alkoxy amino acids. A typical O-H insertion experiment was conducted in the following way. A 1.0M solution of the diazo compound in CH_2Cl_2 was added in a dropwise manner to a solution containing the catalyst and the desired alcohol. After complete addition of the diazo compound, the solution was allowed to stir an additional 2-4 h before work-up and purification. The results of these experiments are reported in Table 29.

Table 29. O-H insertion reactions of alcohols with α-nitro-α-diazoester compounds.



71 or **121c** **195(a-h)**

entry	product	R	R^1	yield (%)[a]
1	**195a**	Et	allyl	84
2	**195b**	Et	Bn	99
3	**195c**	Et	*t*-Bu	45
4	**195d**	Et		87
5	**195e**	Et		74[b]
6	**195f**	Bn	allyl	92
7	**195g**	Bn	Bn	84
8	**195h**	Bn	menthyl	79[b,c]

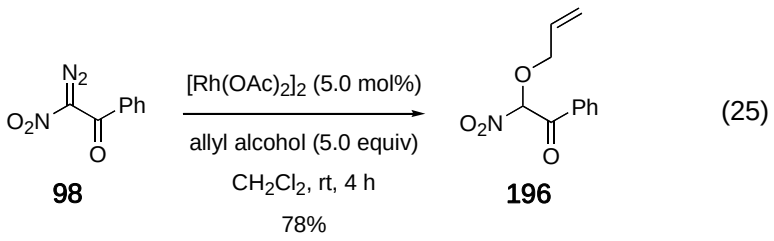
a) Isolated yields after chromatography. b) Isolated as *ca.*a 1:1 mix of diastereomers. c)(1*R*, 2*S*, 5*R*)-(-)-menthol.

$[Rh(OAc)_2]_2$ was found to be an efficient catalyst for the preparation of these α-alkoxy-α-nitrocarbonyl compounds. The O-H insertion reaction proceeds with

respectable efficiency for a range of primary to tertiary alcohols (Table 29). When allyl alcohol was used as a substrate, no competing cyclopropanation was observed in the crude reaction mixtures (Table 29, entries 1 and 6). Reaction yields were typically excellent except for the case involving the tertiary alcohol, *tert*-butanol, which afforded the O-H insertion product in only 45% yield (Table 29, entry 3).

Non-racemic chiral alcohols such as (*R*)-2-(methoxycarbonyl)propanol and (1*R*, 2*S*, 5*R*)-(-)-menthol did not lead to significant levels of diastereoselective induction at the created α-center (Table 29, entries 5 and 8).[180] Treatment of these substrates with D_2O or MeOD did not result in deuterium incorporation, therefore, the diastereoselectivities observed probably arose from the O-H insertion process not through an epimerization process at the highly acidic α-center.

Nitro diazoacetophenone (**98**) also underwent an O-H insertion reaction with similar efficiency observed for the α-nitro-α-diazoester compounds. Again, reaction with allyl alcohol gave exclusive O-H insertion affording the corresponding 1-(allyloxy)-1-nitro-2-phenylethan-2-one (**196**) in 78% yield (Eq. 25).



(25)

To further investigate the facile nature of the O-H insertion reaction, the relative rates of O-H insertions versus cyclopropanations were examined in a series of competition experiments. Accordingly, ethyl nitro diazoacetate (**71**) was added to a mixture containing styrene (5.0 equiv), an alcohol (5.0 equiv) and $[Rh(OAc)_2]_2$. The results are reported in Table 30.

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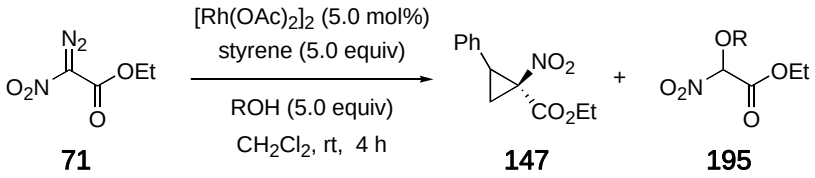
180. For examples of diastereoselective O-H insertions reactions with diazo compounds using chiral auxiliaries on the diazo compound see: (a) Aller, E.; Cox, G. G.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 5949-5952. (b) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem.* **1995**, *60*, 4449-4460.

Table 30. Cyclopropanation O-H insertion competition experiments.



71 **147** **195**

entry	insertion product	R	**147:195**	yield of **147** + **195** (%)[a]
1	**195c**	*t*-Bu	10:1	77
2	**195i**	*i*-Pr	1:1	78
3	**195b**	Bn	1:4	94

a) Isolated yields after chromatography based on theoretical yield of product from crude ratios.

The cyclopropanation of styrene predominated over the O-H insertion process in the case of the sterically hindered *tert*-butyl alcohol (Table 30, entry 1), while the rates of cyclopropanation and O-H insertion were similar when styrene and *iso*-propyl alcohol were subjected to the competition experiment (Table 30, entry 2). In the case of benzyl alcohol, the O-H insertion pathway was found to be four times faster than cyclopropanation with styrene (Table 30, entry 3). If the analogous experiments are conducted with EDA (**101**), similar trends are observed. In light of these results, we believed that it would be quite challenging to perform a chemoselective cyclopropanation reaction in water.

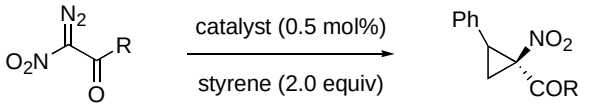
4.2 Cyclopropanations in aqueous media

4.2.1 Cyclopropanations with α-nitro-α-diazocarbonyls in aqueous media

Given that O-H insertion reactions are possible with α-nitro-α-diazocarbonyls and that the products are stable and can be isolated in high yields, it seems unlikely that cyclopropanation reactions in aqueous media would be efficient. Nevertheless, we were fascinated with the compatibility of the cyclopropanation reaction with a large range of different solvents including: THF, DME, benzene, CH_2Cl_2, hexane, Et_2O and acetone (Table 22). This prompted us to try water as well.

Three α-nitro-α-diazocarbonyl compounds were found to be soluble in water, thus suitable for cyclopropanation reactions in aqueous media. The test reaction was conducted in the following way. The diazo compound was dissolved in water by heating in a warm-water bath if necessary. Once the diazo compound had been fully dissolved, it was added slowly dropwise to a biphasic aqueous solution containing a Rh(II) catalyst and styrene. A variety of Rh(II) catalysts were screened and the results are reported in Table 31.

Table 31. Aqueous cyclopropanation reactions involving α-nitro-α-diazocarbonyl compounds: catalyst optimization.



R = OMe, **97**
R = OEt, **71**
R = Me, **125a**

R = OMe, **150a**
R = OEt, **147**
R = Me, **150d**

entry	R-group	catalyst	yield (%)[a]	*E:Z* ratio
1	OMe	$[Rh(OAc)_2]_2$	<10	87:13
2	OMe	$[Rh(1\text{-Adaman})_2]_2$	74	94:6
3	OMe	$[Rh(Oct)_2]_2$	77	90:10
4	OMe	$[Rh(OPiv)_2]_2$	91	93:7
5	OEt	$[Rh(OPiv)_2]_2$	76	90:10
6	Me	$[Rh(1\text{-Adaman})_2]_2$	46	86:14

a) Isolated yields after column chromatography.

As illustrated in Table 31, the aqueous cyclopropanation reaction involving methyl nitro diazoacetate (**97**) proceeded with surprising efficiency for several catalysts. $[Rh(OAc)_2]_2$ led to very low isolated yields (<10%) of the desired cyclopropane (**150a**, Table 31, entry 1), whereas all the other catalysts tested gave remarkably good yields of the cyclopropane **150a**. Ethyl nitro diazoacetate (**71**) was also tested and although it was an oil, it could be dissolved in water upon vigorous stirring. The aqueous cyclopropanation reaction using this compound was found to be slightly less efficient than that observed with methyl nitro diazoacetate (**97**).

Nonetheless, it afforded the corresponding cyclopropane **147** in 76% yield (Table 31, entry 5). The α-nitro-α-diazoketone, 1-nitro-1-diazo-2-propanone (**125a**), was also submitted to the cyclopropanation conditions affording 46% isolated yield of the corresponding cyclopropane (**150d**, Table 31, entry 6). This is also an interesting result due to the increased reactivities of diazoketones.

The diastereoselectivities of the cyclopropanation reactions were found to be similar to those observed in organic solvents. They remain synthetically useful at around 9:1 favoring the *E*-diastereomer. Moreover, the *E*- and *Z*-diastereomers can be easily separated by column chromatography so diastereomically pure cyclopropanes can be easily obtained.

Initially, we were intrigued by these results. Why should $[Rh(OAc)_2]_2$ be so ineffective in aqueous media when it undergoes cyclopropanation reactions with similar efficiency as the other catalysts tested in organic solvents? Upon examination of the reaction mixtures, the reason for the failure of $[Rh(OAc)_2]_2$ was obvious. Catalysts which afforded respectable yields were found to be soluble in the organic phase (eg. it consists of beads of styrene). This is obvious visually since the phase of preference for the catalyst is brightly colored (usually purple). $[Rh(OAc)_2]_2$ resided in the aqueous phase instead of the organic phase as indicated by the green color of the water. This suggests that the hydrophilicity or hydrophobicity of the catalyst plays an important role in the success of the reaction.

The cyclopropanation reaction likely proceeds in the following manner. The diazo compound slowly diffuses from the aqueous phase into the organic phase (styrene) driven by a concentration gradient and/or by hydrophobic effects.[181] If the catalyst is hydrophobic in nature, it will also reside in the organic phase making the effective concentration of olefin to water very high. This hydrophobic effect results in a chemoselective cyclopropanation even though the diazo compound was originally dissolved in water. More correctly stated, the cyclopropanation is not actually occurring in the aqueous phase at all, but within the organic phase.

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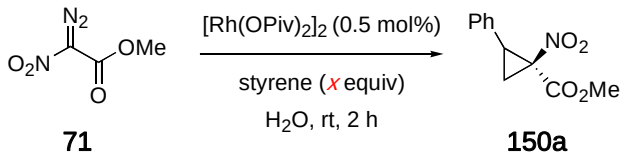
181. Nitro groups are surprisingly organic-like in nature and this explains the limited solubilities of the diazo compounds in water.

The results of Table 31 seem to support the above hypothesis since the most hydrophobic catalysts afforded the highest yields of cyclopropane **150a**. In fact, the cyclopropanation reaction under these conditions proceeded with such high efficiency that the yield actually surpassed that observed for the analogous cyclopropanation reaction in anhydrous CH_2Cl_2 (Table 31, entry 4). In view of the fact that the cyclopropanation reaction is occurring in the styrene phase, it can be regarded as being the equivalent of performing the reaction neat in the olefin substrate. This led to the desire to reduce the olefin equivalents further, allowing for an atom-economical cyclopropanation reaction. For these experiments, $[Rh(OPiv)_2]_2$ was chosen as the optimal catalyst (Table 32).

Table 32. Aqueous cyclopropanations of α-nitro-α-diazocarbonyl compounds: influence of olefin equivalents on reaction yields.



71 **150a**

entry	styrene equiv.	yield (%)[a]	*E*:*Z* ratio
1	5.0	89	93:7
2	2.0	91	93:7
3	1.5	80	91:9
4	1.0	74	90:10

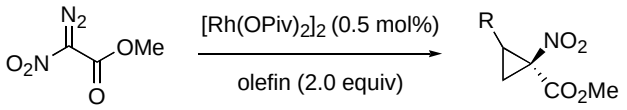
a) Isolated yields after column chromatography.

Through systematic reduction in the equivalents of the olefin substrate used, it was found that a slight excess of olefin was important for optimal yields (Table 32). When 2-5 equivalents of the olefin substrate were used, the yields and diastereoselectivities were effectively constant within experimental errors (Table 32, entries 1 and 2). Acceptable yields of 74% were still possible using only 1.0 equivalent of styrene (Table 32, entry 4).

Various olefin substrates were then screened to examine the scope of the cyclopropanation reaction in aqueous media. For the sake of comparison, an

analogous reaction was also performed in anhydrous CH_2Cl_2 using the same catalyst and olefin equivalents (Table 33).

Table 33. Scope of the aqueous cyclopropanation reaction with α-nitro-α-diazocarbonyls.



97 **150a, 162, 197(a-f)**

entry	olefin (product)	yield % (CH_2Cl_2)[a]	*E:Z* ratio (CH_2Cl_2)
1	indene (**162**)	87 (84)	100:0 (100:0)
2	styrene (**150a**)	91 (90)	93:7 (90:10)
3	4-Cl-styrene (**197a**)	84 (87)	87:13 (91:9)
4	4-MeO-styrene (**197b**)	84 (91)[b]	86:14 (86:14)
5	α-methylstyrene (**197c**)	77 (91)	67:33 (87:13)
6	1,1'-diphenylethene (**197d**)	71 (63)[b]	N/a
7	2,3-dimethylbutadiene (**197e**)	31 (62)	100:0 (100:0)
8	4-phenyl-1-butene (**197f**)	32 (30)	57:43 (58:42)

a) The numbers in parentheses corresponds to the isolated yields of the cyclopropanation reactions performed in CH_2Cl_2. b) The cyclopropane rearranges on silica gel to afford the isoxazoline *N*-oxide.

For most cases, the efficiency of the cyclopropanation reaction in aqueous media closely resembled those conducted in 1.0M CH_2Cl_2 as a reaction solvent (Table 33). In some cases, the reaction yields of the cyclopropanation reactions performed in aqueous media slightly exceeded those performed in organic solvents. These surprising results prompted the question whether other diazo compounds would exhibit similar behaviors.

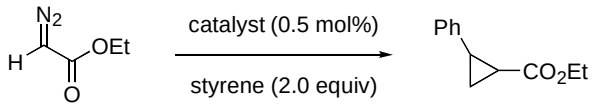
4.2.2 Cyclopropanation reactions with EDA in aqueous media

As previously described, new methods allowing safer handling of ethyl diazoacetate (EDA, **101**) could represent a substantial advancement for the use of EDA (**101**) in industrial applications. The cyclopropanation reaction involving EDA

in aqueous media would potentially serve to reduce some of the hazards associated with its handling in addition to reducing the amount of organic solvents needed to perform the reaction.

In an analogous manner to the α-nitro-α-diazocarbonyl compounds, a number of Rh(II) carboxylate catalysts were screened in an EDA-mediated cyclopropanation reaction of styrene in water (Table 34). Satisfyingly, modest yields of the desired cyclopropane carboxylate **198** could be obtained with low catalyst loadings, olefin equivalents and relatively rapid addition rates of the aqueous diazo solution (< 1 h).[182] These results are reported in Table 34.

Table 34. The influence of the catalyst on cyclopropanation efficiencies of styrene with EDA (**101**) in aqueous media.



101 **198a**

entry	catalyst	yield (%)[a]	*t:c* ratio
1	$[Rh(OAc)_2]_2$	26	1.6
2	$[Rh(CF_3CO_2)_2]_2$	11	1.0
3	$[Rh(Oct)_2]_2$	72	1.5
4	$[Rh(Oct)_2]_2$	47[b]	1.4
5	$[Rh(OPiv)_2]_2$	61	1.5
6	$[Rh(1\text{-}Adaman)_2]_2$	58	1.5

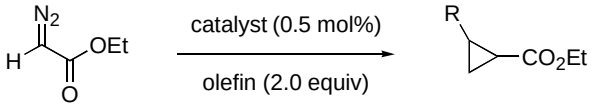
a) Isolated yields after column chromatography. b) 1.0 equiv of styrene used.

The highest cyclopropanation efficiencies again resulted when hydrophobic ligands on the Rh(II) catalysts were used (Table 34, entries 3-6). The $[Rh(Oct)_2]_2$ catalyst (Table 34, entry 3) was found to be the most efficient with this substrate,[183] affording 47% yield of the desired cyclopropane **198a** even when 1.0 equivalent of styrene was used (Table 34, entry 4).

182. Wurz, R. P.; Charette, A. B. *Org. Lett*. **2002**, *4*, 4531-4533.
183. The superiority of the $[Rh(Oct)_2]_2$ catalyst over $[Rh(OPiv)_2]_2$ was also observed by Teyssié *et al.* see: ref. 125.

The scope of the cyclopropanation reaction was extended to a variety of other olefin substrates using the two most efficient catalysts (Table 35). For the sake of comparison, the reactions were also performed in anhydrous CH_2Cl_2 with the same catalyst and olefin loadings.

Table 35. Scope and comparison of cyclopropanation reactions involving EDA (**101**) in aqueous media.



101 **198(a-f)**

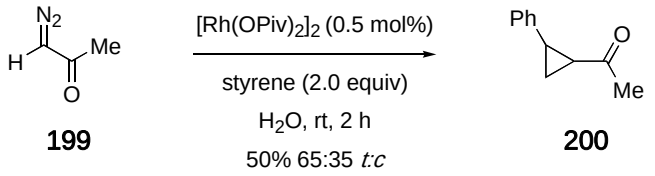
entry	olefin (product)	catalyst	yield (%)[a] (CH_2Cl_2)[b]	*t:c* ratio (CH_2Cl_2)
1	styrene (**198a**)	$[Rh(OPiv)_2]_2$	61 (72)	1.5 (1.5)
2	" "	$[Rh(Oct)_2]_2$	72 (84)	1.5 (1.5)
3	4-Cl-styrene (**198b**)	$[Rh(OPiv)_2]_2$	73 (77)	1.5 (1.3)
4	α-methyl styrene (**198c**)	$[Rh(OPiv)_2]_2$	72 (75)	1.1 (1.2)
5	cyclohexa-1,4-diene (**198d**)	$[Rh(OPiv)_2]_2$	53 (55)	2.2 (2.0)
6	2-vinyl napthalene (**198e**)	$[Rh(OPiv)_2]_2$[b]	52 (57)	1.5 (1.5)
7	" "	$[Rh(Oct)_2]_2$	49 (64)	1.5 (1.5)
8	Ph (**198f**)	$[Rh(OPiv)_2]_2$	59 (64)	1.5 (1.5)
9	" "	$[Rh(Oct)_2]_2$	56 (61)	1.0 (1.1)

a) Isolated yields after column chromatography. b) The reaction was performed in CH_2Cl_2 (0.5 M) with the same catalyst. c) The substrate was treated with 0.5 mL toluene.

The results in Table 35 suggest that the aqueous-based cyclopropanation reaction proceeds with similar efficiencies to those performed in anhydrous CH_2Cl_2 using the same addition rates of the diazo compound and reaction times. The diastereoselectivities of the reactions were nearly identical for all cases. Solid substrates, such as 2-vinyl naphthalene, can also be submitted to this cyclopropanation by addition of a small amount of toluene to create a liquid organic phase (Table 35, entry 6).

To further extend the methodology, other diazo compounds were briefly examined. Methyl diazoketone (**199**) was found to yield cyclopropane **200** in a

modest 50% yield (Eq. 26). This is a surprising result since α-diazoketones are much more reactive than the corresponding α-diazoesters. Methyl diazophosphonate was also found to give modest yields with a variety of olefin substrates under aqueous conditions.[184]



199 **200** (26)

When dimethyl diazomalonate was submitted to the same reaction conditions, isolation of the reaction mixture afforded a 1:1 mixture of cyclopropane to O-H insertion products resulting in only 25% isolated yield of the cyclopropane. The difference in reactivity between dimethyl diazomalonate and α-nitro-α-diazocarbonyl compounds is intriguing. One would expect these two diazo compounds to have similar reactivities since both of the carbene-carbons are flanked by two strong electron-withdrawing groups. In the case of dimethyl diazomalonate, the propensity for O-H insertions must be greater than the other diazo compounds tested. Finally, one can conclude that cyclopropanation in aqueous media is a somewhat general trend, however, the efficiencies of the cyclopropanation reaction should be expected to vary from case to case depending on the reactivity of the diazo compound.

4.3 Enantioselective cyclopropanation reactions involving EDA in water

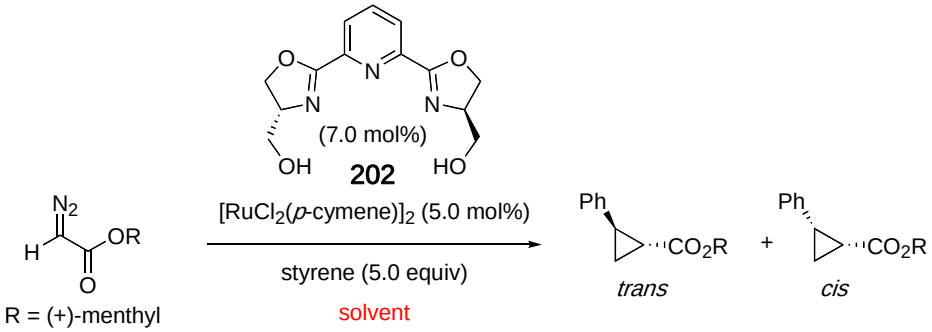
4.3.1 Introduction and precedence

Jessop *et al.* have reported that the dielectric constant of the solvent, such as supercritical carbon dioxide, can have a large negative influence on the levels of asymmetric induction in cyclopropanation reactions with certain diazo compounds. We became interested in determining whether it was possible to perform highly asymmetric cyclopropanation reactions in aqueous conditions.

184. J.-E. Bouchard, unpublished results.

A survey of the literature indicated that few researchers have attempted asymmetric cyclopropanations in protic media, let alone water. One example was reported by Nishiyama in 2001, outlining the use of a water-soluble Ru(*hm*-pybox)Cl_2 (**202**) for the asymmetric cyclopropanation of styrene with (+)-menthyl diazoacetate (**201a**) in biphasic media.[185] In their strategy, the water-soluble catalyst would reside in the aqueous phase and cyclopropanation would occur at the interface between the aqueous and organic phases (Table 36).

Table 36. Nishiyama's asymmetric biphasic cyclopropanation using a water-soluble Ru(II) catalyst.



201a **203a**

entry	initial solvent (mL)	diazo solvent (mL)	yield (%)	*t:c* ratio	% ee (*trans*)
1	THF (3.0)	THF (3.0)	39	83:17	8
2	toluene (3.0)	toluene (3.0)	38	89:11	8
3	THF (2.0) + H_2O (1.0)	THF (3.0)	46	95:5	78
4	toluene (2.0) + H_2O (1.0)	toluene (3.0)	56	96:4	88
5	toluene (0.5) + H_2O (0.5)	toluene (1.5)	57	97:3	94
6	---	toluene (1.5)[a]	62	97:3	97

a) Catalyst solution reused from previous trial.

The reactions were conducted in the following way. The ligand **202** and the Ru(II) source were dissolved in the *initial solvent* (Table 36), then the diazo compound was added in the *diazo solvent*, which consisted of either THF or toluene due to the insolubility of (+)-menthyl diazoacetate (**201a**) in water (Table 36). The

185. Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *J. Chem. Soc., Chem. Commun*. **2001**, 59-60.

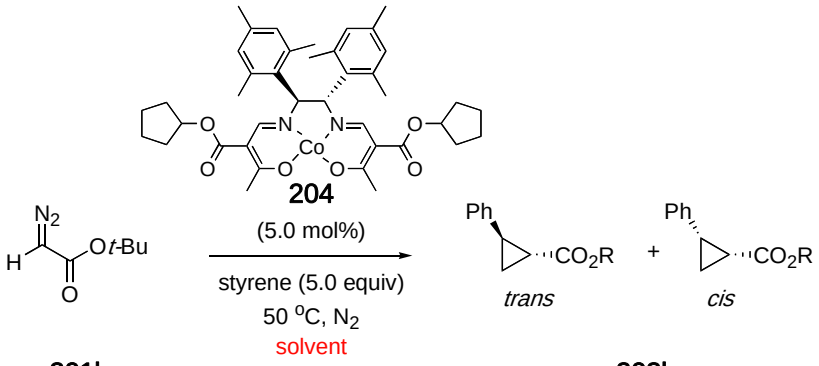
reaction proceeded with low enantioselectivity (8% ee) in pure THF or toluene (Table 36, entries 1 and 2). However, when water was added (to the *initial solvent*), a dramatic increase in enantioselectivity resulted with formation of cyclopropane **203a** in 78% ee in THF/H_2O 2:1 and 94% ee in toluene/H_2O 1:1 (Table 36 entries 3-5). Although the yields remained modest, the diastereoselectivity of the cyclopropanation reaction was excellent up to 97:3 favoring the *E*-diastereomer. It is noteworthy to mention that it was possible to recycle the aqueous-phase containing the catalyst and resubmit it to the cyclopropanation conditions, resulting in an improved enantioselectivity (Table 36, entry 6).

In a recently published follow-up of this work, Nishiyama *et al*. found that various alcohols such as ethanol and 2-propanol had a positive influence on the enantioselectivities. The scope of the cyclopropanation reaction was also extended to include other electron-rich terminal olefins including substituted styrenes and vinyl ethers to afford functionalized chiral cyclopropanes. Furthermore, they also demonstrated that intramolecular cyclopropanations were possible with modest levels of enantioselectivity.[186]

Another example involving cyclopropanation reactions in alcoholic or aqueous media involved the use of an optically active β-ketoiminato Co(II) complex **204** and was reported by Yamada *et al*.[187] These researchers found that water and alcohols enhanced the reaction rate and increased the diastereomeric and enantiomeric excesses of the cyclopropane products. The results of their research are summarized in Table 37.

186. Iwasa, S.; Tsushima, S.; Nishiyama, K.; Tsuchiya, Y.; Takezawa, F.; Nishiyama, H. *Tetrahedron: Asymmetry* **2003**, *14*, 855-865.
187. Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, 406-408.

Table 37. The influence of various solvents on asymmetric cyclopropanation reactions using a β-ketoiminato Co(II) complex **204**.



201b **203b**

entry	solvent	time (h)	yield (%)	*t*:*c* ratio	% ee (*trans*)
1	$CHCl_3$	34	40	70:30	76
2	toluene	34	31	72:28	76
3	THF	10	39	77:23	87
4	THF + H_2O^a	8	58	78:22	88
5	MeOH	7	88	83:17	93
6	MeOH + H_2O^a	7	89	83:17	92

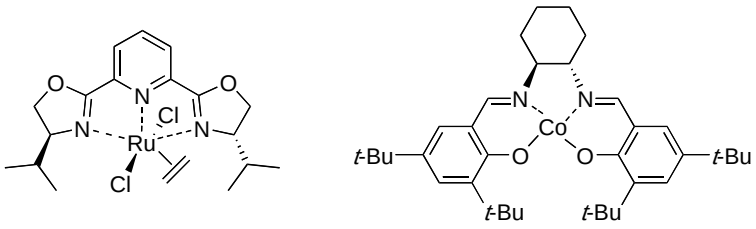
a) 5% Aqueous solvents used.

The scope of the cyclopropanation reaction could be extended to include a wide variety of other terminal substituted olefins giving enantioselectivities in excess of 90% ee using 5% aqueous MeOH as the optimal reaction solvent. When a series of other alcohols were tested, inferior enantioselectivities resulted. It was found that the enantioselectivity of the product was positively affected by the increasing dielectric constant of the solvent, contrary to the results reported by Jessop *et al*.

4.3.2 Enantioselective cyclopropanation reactions involving EDA in water

Since highly enantioselective cyclopropanation reactions involving Rh(II)-based catalysts and EDA (**101**) are rare, this prompted us to turn to other known cyclopropanation catalysts to determine their compatibility with water as a reaction solvent. Again, we desired that the catalysts be hydrophobic in nature so that they

would reside in the organic phase encouraging a cyclopropanation reaction instead of the competing O-H insertion reaction. The Ru(II)-based catalyst **205** reported by Nishiyama *et al*.[188] and the Co(II)-based catalyst **206** reported by Katsuki *et al*.[189] were both tested for their cyclopropanation efficiencies in water (Fig. 25).



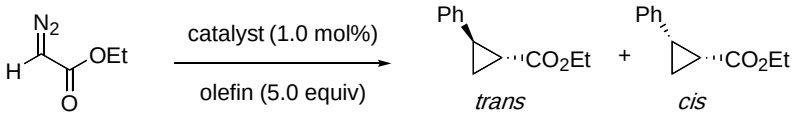
205 **206**

Figure 25. Catalysts for asymmetric cyclopropanations in water involving EDA.

These two catalysts were found to be active for cyclopropanation reactions in aqueous media, leading to modest to high diastereoselective and enantioselective formation of cyclopropanes **198(a-h)**. Furthermore, the enantioselectivities were often similar to those performed in organic solvents (Table 38).

188. Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc*. **1994**, *116*, 2223-2224.
189. Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647-3651.

Table 38. Catalytic asymmetric cyclopropanation reactions involving EDA in water.



101 **198(a-h)**

entry	olefin (product)	catalyst	yield (%) (CH_2Cl_2)[a]	*t/c* ratio (CH_2Cl_2)	% ee (*trans*) (CH_2Cl_2)
1	styrene (**198a**)	**205**	46 (48)	19 (24)	90 (86)
2	4-Cl-styrene (**198b**)	**205**	31 (40)	24 (24)	83 (89)
3	4-MeO-styrene (**198g**)	**205**	42 (77)	19 (19)	87 (85)
4	1,1'-diphenyl ethene (**198h**)	**205**	44 (74)	n/a	86 (83)
5	styrene (**198a**)	**206**[b]	61 (20)[d]	2.0 (n/d)	22 (n/d)
6	styrene (**198a**)	**206**[b,c]	80 (62)[d]	1.5 (1.5)	47 (56)
7	4-Cl-styrene (**198b**)	**206**[b,c]	60 (78)[d]	1.8 (1.3)	47 (46)

Reaction conditions: A 0.18 M solution of **101** was added over 2 h to a mixture of catalyst **205** and the olefin, then stirred an additional 4 h; or a 0.18 M solution of **101** was added in one portion to a mixture of catalyst **206** and the olefin and the mixture was stirred 24 h under Ar. a) Isolated yields after column chromatography. b) 5.0 mol% of catalyst **206** was used in Ar purged water. c) 10 mol% *N*-methyl imidazole was used as an additive. d) Reaction performed in THF for comparison.

Cyclopropanation reactions with the Ru(II)-based catalyst **205**, reported by Nishiyama *et al*., led to modest yields (31-46%) of cyclopropanes **198(a-h)** in a highly diastereoselective and enantioselective manner. Satisfyingly, the enantioselectivities observed were nearly identical to those performed in CH_2Cl_2. If the rate of addition of EDA (**101**) was too rapid, significant quantities of dimerization resulted. This observation suggests that performing the reaction at higher temperatures (eg. 40 ^oC) might reduce this side-reaction.

The Co(II)-based catalyst **206**, popularized by Katsuki, was also found to be active in the cyclopropanation reaction in aqueous media. In fact, the presence of water led to a substantial improvement in reaction yields in the absence of NMI (Table 38, entry 5). It is also noteworthy to mention that argon-purged water was necessary to prevent deactivation of the catalyst. Addition of 10 mol% of *N*-methyl-imidazole as an additive was also found to improve both the chemical yields and

enantioselectivities of the cyclopropanation reaction.[190] Unfortunately, the enantioselectivities observed in water were slightly inferior to those observed in THF (Table 38, entries 6 and 7). However, with this catalyst dimerization of the EDA (**101**) was never observed, even when the reagent was added in one portion to the catalyst.

4.4 *In situ* generation of EDA followed by cyclopropanation

4.4.1 Introduction and precedence

There has been considerable research efforts devoted to the development of safe alternatives to diazo compounds or to their *in situ* generation in recent years. Among the noteworthy contributions made to this field of research are those of Aggarwal and co-workers involving the *in situ* preparation of vinyl- and aryl-diazomethane-based compounds. Their approach involves the treatment of aryl tosyl hydrazone salts with a phase-transfer catalyst, which leads to the formation of substituted diazomethane compounds in solution. If this is done in the presence of a catalyst, such as $[Rh(OAc)_2]_2$, then preparation of chiral epoxides,[191] aziridines[192,46] and cyclopropanes, are possible. This method effectively eliminates the hazards associated with preparation and manipulation of these diazo reagents.

Another approach to non-stabilized diazoalkanes reported by May and Stoltz[193] involved heating *N*-aziridinyl imines **207** in 1,2-dichloroethane. Heating was sufficient to promote a Bamford-Stevens rearrangement, liberating a reactive diazo

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190. For use of this additive see: (a) Yamada, T.; Ikeno, T.; Sekino, H.; Sato, M. *Chem. Lett*. **1999**, 719-720. (b) Ikeno, T.; Sato, M.; Yamada, T. *Chem. Lett*. **1999**, 1345-1346.

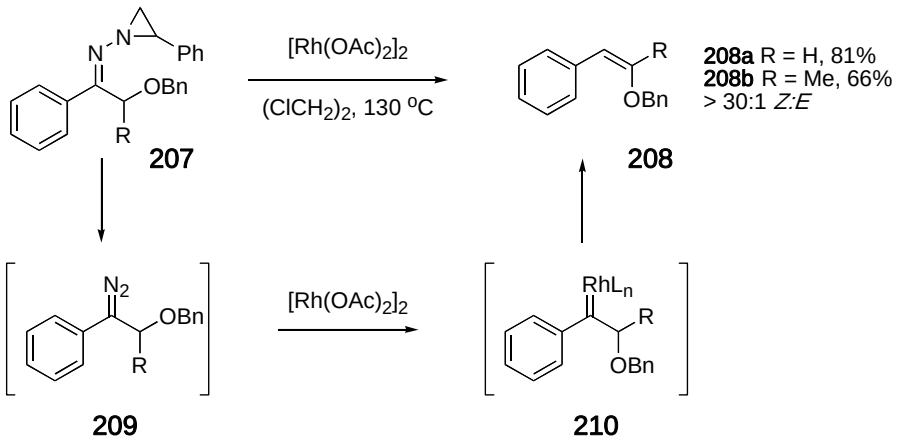
191.(a) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430-1433. (b) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc*. **2002**, *124*, 5747-5756. (c) Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274-3278.

192. Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159-3166.

193. May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 12426-12427.

compound, which underwent additional transformations in the presence of $[Rh(OAc)_2]_2$ (Scheme 18).[194]

Scheme 18. *In situ* generation of non-carbonyl stabilized diazo compounds.



In order to address the potentially unstable nature of ethyl diazoacetate (**101**) and to make it more attractive for use on an industrial scale, an *in situ* procedure for its generation was envisioned. Generation of EDA (**101**) *in situ* would eliminate hazards associated with its handling and use. Moreover, if generation of EDA (**101**) could occur in a slow and controlled manner in the presence of an active cyclopropanation catalyst, the quantity of EDA (**101**) present at any one time would be quite small, eliminating risks derived from explosions and toxicity.

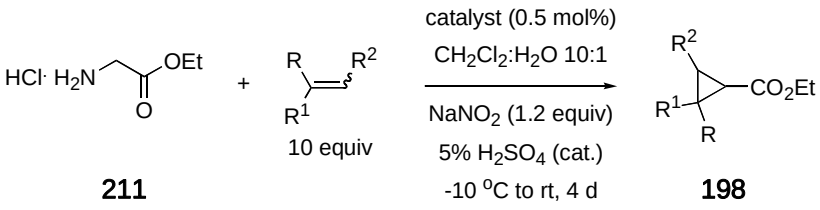
Since prior results in this chapter have established that cyclopropanation reactions involving ethyl diazoacetate (**101**) can proceed in aqueous media with surprising efficiency, the question arose, could a procedure be developed to form the EDA reagent (**101**) in the same reaction vessel? The envisioned strategy would involve the amalgamation of two known procedures; the procedure used for the preparation of EDA (**101**) and the previously developed methodology employing hydrophobic Rh(II)-catalysts to affect cyclopropanations in aqueous media.

A few months prior to final publication of our findings outlining a new procedure for the *in situ* generation of EDA (**101**), Barrett and co-workers published an article

194. See also: Lee, H.-Y.; Kim, Y. *J. Am. Chem. Soc*. **2003**, *125*, 10156-10157.

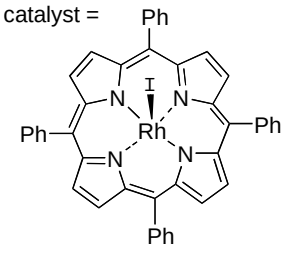
proposing a similar idea, although their findings and strategy were slightly different.[195] In their account, *in situ* generation of EDA (**101**) involved treatment of glycine ethyl ester (**211**) with $NaNO_2$. To catalyze the ensuing cyclopropanation reaction, a variety of catalysts were tested including Cu(I), Cu(II), Rh(II) or Rh(III) and were all found to be inefficient. Finally, they found that a Rh(III) porphyrin catalyst **212** provided modest yields of the desired cyclopropanes. Under optimal conditions, the reaction was carried out using $NaNO_2$ (1.2 equiv), 5% H_2SO_4 (catalytic) and Rh(III) porphyrin **212** (0.5 mol%) in a 1:10 mixture of H_2O:CH_2Cl_2 at room temperature (Table 39).

Table 39. *In situ* generation of EDA followed by cyclopropanation reported by Barrett *et al.*



211 **198**

entry	olefin	yield (%)
1	styrene	62
2	4-Me-styrene	72
3	4-Cl-styrene	54
4	1-octene	59
5	allyl benzene	53
6	1,2-dihydronaphthalene	53
7	cyclohexene	50
8	α-methylstyrene	60



212

It was found that excess olefin (10 equiv) was necessary for modest conversions in the cyclopropanation reaction. Unfortunately, this catalyst gave little *syn/anti* selectivity, typically around 1:1 for all of the examples tested. The dilution of the

195. Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem*. **2001**, *66*, 8260-8263.

reaction was also quite high, which presumably decreases the rates of reaction. Furthermore, the cyclopropanation reaction required 4 days to go to completion. This extended reaction time is quite unattractive since comparable yields for this cyclopropanation reaction can be achieved in only 2 h using EDA (**101**) directly in CH_2Cl_2. This method also involves the use of chlorinated solvents, which are the solvents best avoided due to environmental concerns.

4.4.2 Development of a new *in situ* EDA generation cyclopropanation methodology

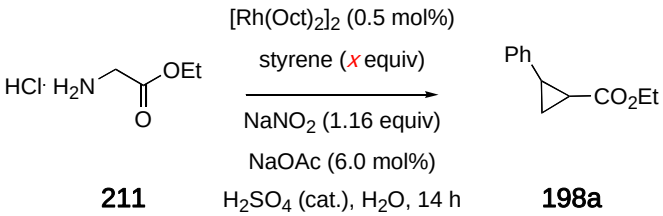
In our approach, previous experimental results led us to believe that efficient cyclopropanations could result if we could efficiently supply a source of EDA (**101**) to the catalyst/olefin mixture in water. One of the most economical and expedient methods for the preparation of EDA (**101**) involves the treatment of glycine ethyl ester hydrochloride salt (**211**) with $NaNO_2$ in water, followed by the extraction of the reagent with toluene. The compatibility of the cyclopropanation catalysts with aqueous media has already been established. However, it was uncertain if the catalysts would be compatible with nitrous acid. Nitrous acid is formed upon treatment of $NaNO_2$ with catalytic quantities of H_2SO_4 in aqueous media. This reagent is necessary to transform glycine ethyl ester hydrochloride (**211**) into EDA (**101**).

To test the envisioned *in situ* strategy, the standard procedure for EDA preparation was followed.[196] Additionally, styrene containing the hydrophobic $[Rh(Oct)_2]_2$ catalyst was added to the reaction mixture. The idea was that the styrene phase containing the catalyst would serve to extract the EDA (**101**) from the aqueous phase upon formation and convert it to the desired cyclopropane **198a**. In our preliminary experiment, the characteristic evolution of nitrogen gas was observed on the surface of the rapidly stirring styrene beads. After 1 h, the reaction mixture was extracted with EtOAc and 35% yield of the corresponding cyclopropane **198a** could be isolated.

196. Womack, E. B.; Nelson, A. B. *Org. Synth*. **1964**, *C. V. 3*, 392-393.

The yields could be further improved through slight modifications of the reaction conditions. The optimum conditions involved the following proportions of reagents; styrene (3.0 equiv), $[Rh(Oct)_2]_2$ (0.5 mol% based on **211**), glycine ethyl ester hydrochloride (**211**, 1.0 equiv), $NaNO_2$ (1.16 equiv) and NaOAc (6.0 mol%) to serve as a buffer. The reaction mixture was initially cooled to –5 ^oC in an ice bath (using brine) before 2 drops of 10% H_2SO_4 was added to catalyze EDA (**101**) formation. The reaction mixture was then allowed to slowly warm to room temperature overnight (14 h). The equivalents of styrene were varied to determine the maximum efficiency of the cyclopropanation reaction (Table 40).

Table 40. *In situ* generation of EDA (**101**) followed by cyclopropanation.



211 **198a**

entry	styrene equiv.	yield (%)[a]	*t/c* ratio
1	3.0	70	1.5
2	2.0	66	1.3
3	2.0[b]	54	1.1
4	1.0	45	1.2

a) Isolated yields after column chromatography. b) Reaction time was 5 h.

Cyclopropane **198a** could be isolated in 70% yield using 3.0 equivalents of styrene (Table 40, entry 1), while 2.0 equivalents of styrene allowed for an isolation of a modest 66% yield (Table 40, entry 2). These yields compare nicely with those reported for the cyclopropanation reaction involving pure EDA (**101**) in water which afforded 72% isolated yield using $[Rh(Oct)_2]_2$ (Table 35, entry 2). Interestingly, in only 5 h, 54% yield of the cyclopropane could be recovered suggesting that the rate of the reaction is initially very rapid and then diminishes. Fortunately, there were only traces of the fumarate and maleate esters derived from dimerization of the EDA (**101**) reagent, ranging from 1-3%. This indicates that the rate of EDA (**101**)

formation and diffusion into the styrene phase does not exceed the rate at which the catalyst is able to consume it, thus preventing an accumulation of EDA (**101**) which would lead to the formation of dimers.

Since glycine ethyl ester (**211**) is inexpensive,[197] it is likely that the olefin substrate will constitute most of the cost in this reaction. When stoichiometric quantities of styrene and glycine ethyl ester (**211**) are used, 45% yield can be recovered of the desired cyclopropane **198a**. When 4-methoxystyrene (1.0 equiv) was used as an olefin substrate, 47% yield of **198g** could be obtained in a 52:48 *t/c* ratio. When the reaction was performed on a 3.0 g scale, it was found to proceed with similar efficiency and with excellent reproducibility.

A preferable method for generation of EDA (**101**) was recently reported. It involves using $Na_2B_4O_7 \cdot 10H_2O$ as a buffer and a 2% H_3PO_4 aqueous solution as the catalyst.[169a,198] Using this method, EDA (**101**) has been prepared on a 1000 mole scale (*ca*. 114 kg) in process at Bristol-Myers Squibb for the synthesis of a melatonin agonist containing a *trans*-substituted cyclopropane carboxylic acid subunit.[169b] These conditions for EDA generation are milder than those previously reported and less prone to exotherms on large-scale. Accordingly, these conditions were also tested and the cyclopropanation was found to proceed with equal or greater efficiencies than those reported in Table 40.

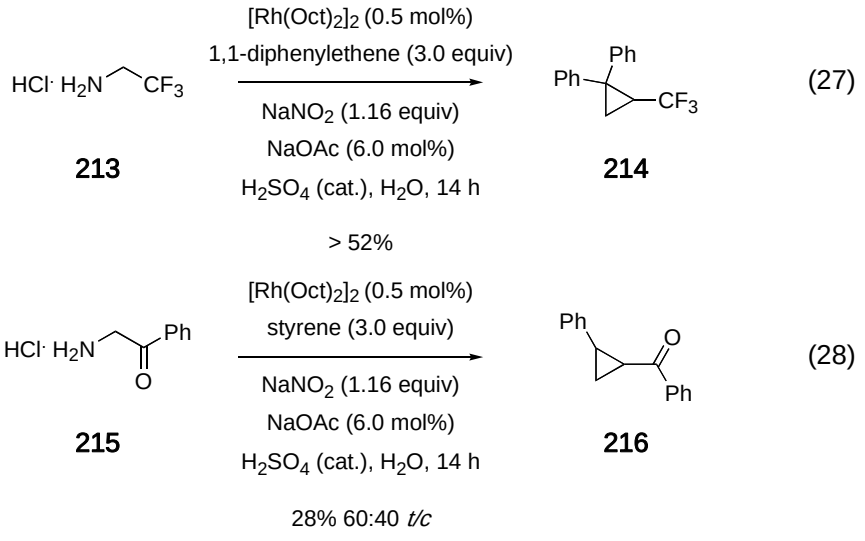
As an obvious extension to the methodology, we were also interested in testing other amino esters using this *in situ* approach. Glycine methyl and *tert*-butyl esters were tested and found to be inferior to glycine ethyl ester. In the case of the *tert*-butyl ester, the cyclopropanation completely failed, presumably due to its affinity for the organic phase. This prevented conversion of the amine into the corresponding diazo compound. Other amino esters, such as phenyl glycine methyl ester and alanine methyl ester, were also tested and only traces (< 20%) of the desired cyclopropane could be recovered. This is not surprising since these disubstituted diazo compounds

197. The Aldrich Chemical Company (2003-2004) glycine ethyl ester hydrochloride (**211**) 500 g = $56.60.

198. Kotnis, A. S.; Simpson, J. H.; Deshpande, R. P.; Kacsur, D. J.; Hamm, J.; Kodersha, G.; Merkl, W.; Domina, D.; Wang, S. S. Y. *Org. Proc. Res. Develop.*, *In Press*.

exhibit greatly different reactivities than those of EDA (**101**). Barrett and co-workers also reported similar findings in their attempts to extend the methodology with their Rh(III) porphyrin catalyst **212**.

Some success was realized when 2,2,2-trifluoroethyl amine hydrochloride salt (**213**) was used as a diazo source, affording > 52% yield of the corresponding cyclopropane **214** when 1,1'-diphenylethene was used as a substrate (Eq. 27). Unfortunately, due to the highly non-polar nature of the cyclopropanes formed with this diazo compound, purification is difficult. α-Aminoacetophenone (**215**) was also submitted to the *in situ* cyclopropanation conditions and found to afford 28% of the corresponding cyclopropane **216** in a 60:40 *t/c* ratio (Eq. 28). Optimization of the protocol could possibly result in higher yields but this has not yet been pursued.



One drawback of the *in situ* cyclopropanation methodology is that the diastereoselectivity of the cyclopropanation reaction is not synthetically useful. This lack of diastereoselectivity is directly related to the catalyst used and not the reaction conditions. Additionally, we wanted to apply this *in situ* methodology to asymmetric cyclopropanations. Unfortunately, when Nishiyama's Ru(II)-pybox catalyst **205** and Katsuki's Co(II)-salen catalyst **206** were submitted to the *in situ* protocol, no cyclopropanes could be recovered from the reaction mixtures. Presumably, the metals are prone to undergo redox processes due to the presence of the nitrous acid, which

ultimately results in deactivation of the catalysts. However, if a chiral hydrophobic Rh(II) catalyst were available, this methodology would likely be efficient, representing an alternative for industrial applications due to the cost advantages associated with using glycine ethyl ester (**211**) and the simplicity of the procedure.

4.5 Conclusions

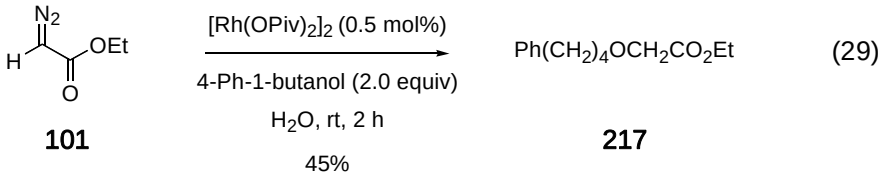
The synthetic efficiency of O-H insertion reactions into alcohols was demonstrated with α-nitro-α-diazocarbonyls (Table 29). Following this result, these diazo compounds were found to undergo efficient cyclopropanation reactions in water upon judicious choice of the Rh(II) carboxylate catalyst. Rh(II) carboxylate catalysts bearing hydrophobic ligands performed the best under these conditions due to their affinity for the olefin substrate, thereby increasing the effective concentration of the olefin substrate with respect to water (Table 31).

Following the aqueous cyclopropanation results with α-nitro-α-diazocarbonyl compounds, this methodology was extended to include ethyl diazoacetate (**101**). Even though this diazo compound undergoes a high yielding O-H insertion reaction with water (80%), high yields in aqueous cyclopropanation reactions could nevertheless be achieved if hydrophobic Rh(II) catalysts were used (Table 34).

Cyclopropanations in aqueous media not only allow for the elimination of environmentally destructive chlorinated solvents, but also led to the development of an *in situ* diazo generation cyclopropanation procedure. This *in situ* approach involves treatment of glycine ethyl ester (**211**) with $NaNO_2$ in the presence of styrene and a catalyst resulting in formation of modest to high yields of the corresponding cyclopropane (Table 40). This method could have potentially important implications for industry since handling of the hazardous reagent has been largely avoided.

Finally, to further illustrate the idea that the catalyst's partitioning into the organic phase can affect the reaction outcomes for biphasic reaction mixtures, we attempted a chemoselective O-H insertion of a hydrophobic alcohol in water. The O-H bond of a hydrophobic primary alcohol, 4-phenyl-1-butanol, could undergo a selective insertion reaction under aqueous conditions when using a hydrophobic catalyst $[Rh(OPiv)_2]_2$

(Eq. 29). Although the yield of the corresponding α-alkoxy ester **217** is only a modest 45%, the ratios between the two potential substrates (water and 4-Ph-1-butanol) are in excess of 100:1, respectively. Furthermore, when the analogous reaction was performed with 2.0 equivalents of ethanol as a substrate (ethanol is miscible with water), only trace amounts of the product corresponding to insertion in the ethanolic O-H bond resulted. This outcome demonstrates the positive influence that the biphasic nature of the reaction mixture can have on the reaction.



(29)

We also desired a method for the *in situ* preparation of α-nitro-α-diazocarbonyl compounds. The present strategy used for ethyl diazoacetate (**101**) obviously could not be applied. Hence, Chapter 5 will focus on the development of a new strategy for the *in situ* generation and cyclopropanation of these diazo compounds.

CHAPTER 5

Phenyliodonium Ylides as Safe Alternatives to α-Nitro-α-Diazocarbonyl Compounds

5.1 Introduction and precedence

The organic chemistry of polyvalent iodine compounds has experienced explosive development during the last decade of the 20th century. The surging interest in these compounds is mainly due to their very useful oxidizing properties and unique reactivities, combined with their benign environmental character and commercial availability.[199] In addition, iodine(III) compounds have also been found to have broad applications in organic synthesis. In particular, phenyliodonium ylides and iminoiodinanes have been extensively explored for their applications to the fields of carbene and nitrene chemistry, respectively.

A formal analogy between the reactivities of β-dicarbonyl phenyliodonium ylides and β-dicarbonyl-α-diazo compounds has been drawn.[200] Iodonium salts of the type $ArI{=}CR_2$ can serve as synthetic equivalents of diazo compounds as "metal-carbene" sources upon treatment with the appropriate transition-metal catalyst. Moreover, the use of iodonium ylides as carbene equivalents can have additional advantages over diazo compounds, as they do not suffer certain drawbacks. Phenyliodonium ylides are non-explosive, non-toxic and non-carcinogenic. Therefore, they represent a more industrially friendly reagent for use on multi-gram quantities. For these reasons, we became interested in developing a methodology involving the use of phenyliodonium ylides to replace α-nitro-α-diazocarbonyl compounds for the synthesis of nitro cyclopropanecarboxylates.

199.(a) Stang, P. J. *J. Org. Chem*. **2003**, *68*, 2997-3008. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2002**, *102*, 2523-2584. (c) Ochiai, M.; Kitagawa, Y. *J. Synth. Org. Chem. Jpn.* **2000**, 1048-1056.

200.(a) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc*. **1989**, *111*, 6443-6444. (b) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947-958.

5.1.1 Cyclopropanation reactions with phenyliodonium ylide reagents

The mechanism by which cyclopropanation reactions proceed with phenyliodonium ylides and diazo compounds remains a subject of debate. Certain researchers have proposed that treatment of active cyclopropanation catalysts (Rh or Cu) with phenyliodonium ylides or diazo compounds, both form the same metallo-carbene intermediate.[200b] To the contrary, other researchers have placed greater value on the subtle differences in reactivities observed between phenyliodonium ylides and diazo compounds and have proposed alternative mechanistic pathways to account for these observations.[200a] Irrespective of the mechanism, however, the reactivities between the phenyliodonium ylides and diazo compounds are indeed quite similar in cyclopropanation reactions,[201] thus serving their purpose to be effective replacements for the potentially hazardous diazo compounds.

Phenyliodonium ylides **219** derived from β-dicarbonyl compounds are reasonably stable and can be prepared in modest to excellent yields. This typically involves treatment of an α-acidic methylene compound **218** with bis(acetoxy)iodobenzene, $PhI(OAc)_2$, in aqueous or alcoholic solutions of KOH (Eq. 30).[202] Purification of the phenyliodonium ylide is usually achieved by recrystallization. A large number of β-dicarbonyl phenyliodonium ylides have been prepared in modest to excellent yields from the corresponding α-acidic methylene compounds in this manner. In addition, other classes of α-acidic compounds including β-disulfonyl, β-sulfonyl-β-keto and β-dinitro phenyliodonium ylides have been reported.[203]

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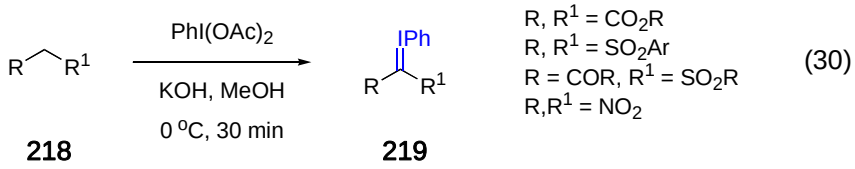
201. For a review on cyclopropanation reactions with iodonium ylides see: Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243-251.
202. Schank, K.; Lick, C. *Synthesis* **1983**, 392-395.
203.(a) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2002**, *85*, 483-494. (b) Hajiarapoglou, L. P.; Schank, K. *Tetrahedron* **1997**, *53*, 9365-9376. (c) Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett*. **1973**, *14*, 25-28. (d) Zhu, S.-Z.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun*. **1990**, 1459-1460.



218 **219** (30)

Phenyliodonium ylides have been compared extensively to their diazo counterparts in cyclopropanation reactions. As a general trend, β-dicarbonyl derived phenyliodonium ylides were found to be more reactive than their corresponding diazo analogues.[203a,204] The enhancement in reactivities of these substrates allowed metal-catalyzed transformations to occur at lower reaction temperatures. As a result, the potential for increasing the levels of asymmetric induction in asymmetric cyclopropanation reactions exists.

5.1.2 Hypervalent iodine(III) reagents for the *in situ* preparation of nitrenes

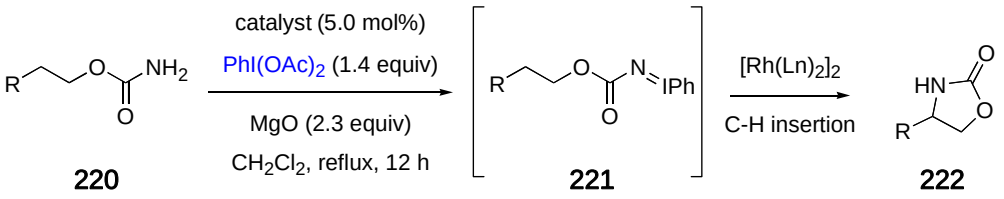
In addition to the utility of hypervalent iodine(III) reagents as precursors to carbenes, their efficacy in the formation of nitrene precursors has also been an emerging area of research. Perhaps some of the most important developments in the field of hypervalent iodine(III) chemistry, in recent years, has been in the field of nitrene chemistry. In particular, the research of Espino and Du Bois involving Rh-catalyzed C-H insertion reactions for the oxidative conversion of carbamates **220** to oxazolidinones **222** clearly demonstrates the synthetic utility of hypervalent iodine(III) reagents.[205] This transformation established that an *in situ* protocol could be successfully applied for the preparation of iminoiodinane intermediates **221**. It avoids the often tedious purification and handling of the sensitive iminoiodinane reagents. Furthermore, the practicality of the reaction improves substantially.

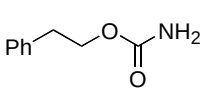
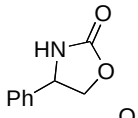
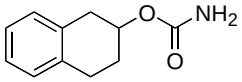
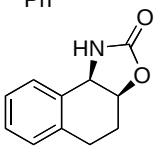
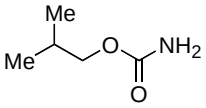
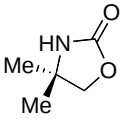
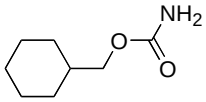
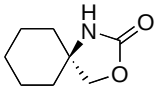
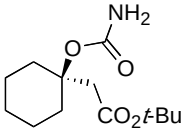
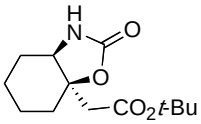
Experimentally speaking, Espino and Du Bois reported the treatment of carbamates **220** with the hypervalent iodine(III) reagent, $PhI(OAc)_2$ (1.4 equiv) and MgO (2.3 equiv) in the presence of a Rh(II) catalyst (5.0 mol%). Refluxing the reaction mixture in CH_2Cl_2 for 12 h afforded, in excellent yields, the corresponding

204. Müller, P.; Boléa, C. *Synlett* **2000**, 826-828.
205. Espino, C. G.; Du Bois, J. *Angew*. Chem., *Int. Ed*. **2001**, *40*, 598-600.

oxazolidinones **222**. This presumably results from an *in situ* iminoiodinane **221** formation followed by intramolecular C-H insertion *via* a metal-nitrene intermediate (Table 41).

Table 41. Oxidative cyclization of carbamates using $PhI(OAc)_2$ *via in situ* formation of iminoiodinane intermediates.



entry	substrate	product	catalyst	yield (%)
1			B	74
2			B	77
3			A	83
4			A B	77 79
5			A	82

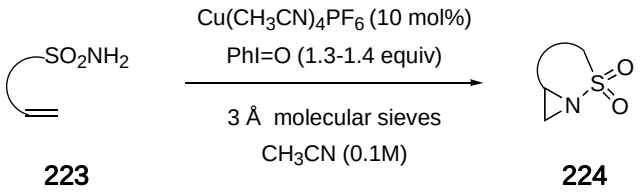
Catalyst A: $[Rh(OAc)_2]_2$, B: $[Rh(Ph_3CCO_2)_2]_2$.

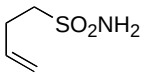
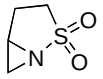
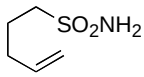
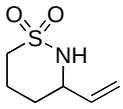
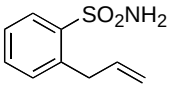
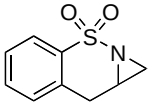
In the presence of a Rh(II) catalyst, iodobenzene is expulsed, resulting in the formation of a metal-nitrene complex. This metal-nitrene complex then undergoes intramolecular C-H insertion. MgO is added to scavenge the AcOH byproduct from

the reaction mixture. This protocol has since been successfully extended to include C-H insertions[206] and aziridinations[207] of sulfonamide substrates.

Shortly following the first report by Espino and Du Bois, Dodd *et al*. showed that copper-catalyzed aziridinations mediated by iodosylbenzene (PhI=O) were also efficient processes.[208] Again, a related *in situ* strategy enabled the formation of iminoiodinane intermediates derived from sulfonamide substrates (Table 42). This methodology has since been extended to include asymmetric intramolecular aziridinations involving chiral Rh(II) catalysts with modest levels of asymmetric induction.[209]

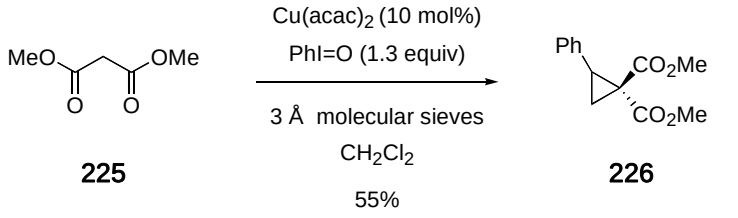
Table 42. The *in situ* formation of iminoiodinane intermediates using PhI=O, followed by copper-catalyzed intramolecular aziridinations or C-H insertions.



entry	substrate	product	yield (%)
1			62
2			51
3			69

206. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc*. **2001**, *123*, 6935-6936.
207. Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc*. **2002**, *124*, 13672-13673.
208. Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc*. **2001**, *123*, 7707-7708.
209. Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett*. **2003**, *44*, 5917-5920.

Dodd *et al*. also demonstrated the similarities between carbene and nitrene formation by including the application of this new *in situ* methodology to a cyclopropanation reaction involving dimethyl malonate (**225**) as a substrate. Although only modest yields were obtained of the corresponding cyclopropane **226**, it illustrates that the *in situ* generation of a phenyliodonium ylide followed by its subsequent cyclopropanation is a feasible process (Eq. 31).



225 **226** (31)

5.2 Cyclopropanation of olefins with *in situ* generated phenyliodonium ylides derived from α-nitrocarbonyls

The transition metal-catalyzed cyclopropanation of olefins with α-nitro-α-diazocarbonyl compounds represents a direct approach for the formation of nitro cyclopropane carboxylates. These cyclopropanes will serve as direct synthetic precursors to the desired cyclopropane α-amino acids in our envisioned synthetic strategy. However, the potentially explosive nature[210] of α-nitro-α-diazocarbonyl compounds precludes their use for the large-scale preparation of nitro cyclopropane carboxylates. Consequently, the development of a carbene-transfer reaction avoiding diazo precursors was of considerable interest.

Developments in the Charette group and others[191,193,195] to circumvent the intrinsic drawbacks of diazo chemistry have led to the development of several new *in situ* diazo generation protocols. However, diazo compounds can be avoided entirely using hypervalent iodine(III) reagents, an idea which has been gaining in popularity.

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210. During melting point determination, solid methyl nitro diazoacetate (**97**) exploded when heated. Diazo compounds with higher molecular weights (lower nitrogen to carbon ratios) are presumably more stable.

Furthermore, these iodine reagents are available commercially in large quantities and are generally inexpensive.

As outlined in Section 5.1.1, the classic method used for preparation of a phenyliodonium ylide involved treatment of an α-acidic carbonyl compound with methanolic KOH followed by the addition of a solution containing $PhI(OAc)_2$ (Eq. 30). Unfortunately, when this protocol was applied to a variety of α-nitro carbonyl compounds, the desired iodonium ylides could not be isolated. Presumably, complications arose from a variety of sources including the instability of the α-nitro carbonyl compounds to KOH and the limited solubility and stability of the phenyliodonium ylides themselves. Originally it was believed that phenyliodonium ylides could be practically isolated in pure form only when the substituents of their carbanionic center were of the same type. If the two substituents were different, the ylides tended to be rather labile.[203b,211] Since this time, however, phenyliodonium ylides derived from β-sulfonyl-β-carbonyl compounds were found to have enhanced stabilities. Presently, this class of compounds represents one of the few examples that can be purified by chromatography on silica gel.[203a]

In order to circumvent the difficulties associated with isolation and purification of the desired iodonium ylides, an *in situ* approach was envisioned involving generation of the iodonium ylide in the presence of a Rh(II) carboxylate catalyst and the olefin substrate. This "one pot" approach would not only avoid isolation of the potentially unstable phenyliodonium ylide intermediates,[212] but also serve to eliminate an additional synthetic operation resulting in a more expedient cyclopropanation procedure.

Inspired by the *in situ* approaches reported by Dodd *et al*. and Espino and Du Bois involving the preparation of the related iminoiodinane intermediates, a similar strategy was envisioned. Previous experience with the reactivities of α-nitro-α-diazocarbonyl compounds in cyclopropanation reactions also indicated that the dimerization process between two molecules of the diazo compound was unlikely.

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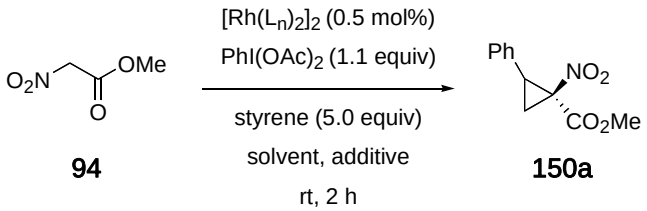
211. Surprisingly, there are few examples of phenyliodonium ylides containing two different substituents α– to the ylide carbon.

212. Isolation of iodonium ylides is not always high yielding see: Moriarty, R. M.; May, E. J.; Guo, L.; Prakash, O. *Tetrahedron Lett.* **1998**, *39*, 765-766.

This would suggest that an *in situ* protocol should be possible and that addition of all of the reagents simultaneously should be tolerated.

Various experimental conditions including the influence of the iodine(III) source, the reaction solvent, the base and the concentration of the reaction were explored to test cyclopropanation efficiency. These preliminary results are reported in Table 43.[213]

Table 43. Cyclopropanation of styrene using an *in situ* generated phenyliodonium ylide derived from methyl nitroacetate: optimization of reaction conditions.



94 **150a**

entry	solvent	catalyst	additive (equiv)	yield (%)[a]	*E:Z* ratio
1	CH_2Cl_2	$[Rh(OAc)_2]_2$	3 Å MS	20[b,c]	92:8
2	CH_2Cl_2	$[Rh(OAc)_2]_2$	MgO (5.0)	52[c]	92:8
3	CH_2Cl_2	$[Rh(OAc)_2]_2$	Na_2CO_3 (2.0)	32[c]	90:10
4	H_2O	$[Rh(OPiv)_2]_2$	Na_2CO_3 (2.0)	86	93:7
5	H_2O	$[Rh(OPiv)_2]_2$	none	85	93:7
6	none	$[Rh(OAc)_2]_2$	none	41	90:10
7	none	$[Rh(Oct)_2]_2$	none	71	91:9
8	none	$[Rh(OPiv)_2]_2$	none	83	92:8
9	none	$[Rh(OPiv)_2]_2$	none	67[d]	92:8

a) Isolated yields after purification by column chromatography. b) PhI=O was used as the hypervalent iodine source. c) Reaction time was 6 h in refluxing CH_2Cl_2. d) 2.0 equiv of styrene were used.

In a typical reaction, all the reagents were simply added to the reaction vessel, the solvent was introduced and the reaction allowed to stir for 2-6 h. Iodosylbenzene, (PhI=O),[214] was originally tested as the hypervalent iodine(III) source. 3 Å molecular sieves were also added to scavenge water, which is presumably generated according

213. Wurz, R. P.; Charette, A. B. *Org. Lett*. **2003**, *5*, 2327-2329.
214. For preparation of this reagent see: Saltzman, H.; Sharefkin, J. G. *Org. Synth*. **1973**, *C. V. 5*, 658-659.

to the protocol reported by Dodd *et al*.[208] Upon refluxing the reaction mixture for 6 h in CH_2Cl_2, an encouraging 20% yield of the desired cyclopropane **150a** could be recovered from the crude reaction mixture (Table 43, entry 1).

The reaction conditions employed by Espino and Du Bois for the *in situ* formation of iminoiodinane intermediates were also tested. This protocol involved using $PhI(OAc)_2$ as the hypervalent iodine(III) source. Espino and Du Bois also found that addition of MgO was necessary to scavenge the AcOH byproduct. These conditions improved the reaction yield of the desired cyclopropane **150a** to 52% (Table 43, entry 2). Unfortunately, the presence of MgO severely complicated purification efforts since the insoluble fine powder made filtration and chromatography difficult. This additive also left an insoluble white film on the glassware, which could not be easily removed. Replacement of MgO with other inorganic bases including Na_2CO_3 and BaO resulted in no improvement in the reaction yields (Table 43, entry 3).

Motivated by our previous success with aqueous cyclopropanation reactions involving α-nitro-α-diazocarbonyl compounds[215] and EDA (**101**), water was tested as the reaction solvent. A hydrophobic catalyst, $[Rh(OPiv)_2]_2$,[216] and 2.0 equivalents of Na_2CO_3 dissolved in water were added to a mixture of styrene, methyl nitroacetate (**94**) and $PhI(OAc)_2$ resulting in a biphasic reaction mixture. Vigorous stirring for 2 h afforded a respectable 86% isolated yield of cyclopropane **150a** with excellent diastereoselectivities of 93:7 *E:Z* favoring the *E*-diastereomer (Table 43, entry 4). The utility of the base in this reaction was questionable due to the high acidity of the methyl nitroacetate (**94**). Subsequently, conducting the reaction in absence of base resulted in nearly identical yields, indicating that it was unnecessary for progression of the reaction (Table 43, entry 5).

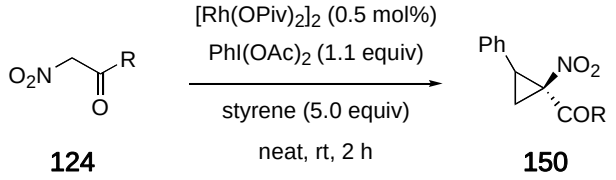
In an attempt to further simplify the reaction protocol, the water was removed. By performing the reaction neat in the olefin substrate, no extractions were necessary upon completion of the reaction, thus further reducing the necessity for organic solvents. When the reaction was performed under solvent-less conditions in 5.0

215. See the results of Chapter 4, Section 4.2.1.
216. The use of hydrophobic catalysts in aqueous cyclopropanation reactions was found to be critical for their success see: Chapter 4.

equivalents of styrene using $[Rh(OAc)_2]_2$ or $[Rh(Oct)_2]_2$ as catalysts, the reaction yields were somewhat inferior to those observed if $[Rh(OPiv)_2]_2$ was used (83%) as a catalyst (Table 43, entries 6, 7 versus 8). However, it is noteworthy to mention that if the reaction times with these catalysts were prolonged to 14 h, then isolated yields between 70% and 80% could be obtained, respectively. Finally, reduction of the equivalents of styrene resulted in isolation of a modest 67% yield of the desired cyclopropane **150a** (Table 43, entry 9).

Next, the scope of the cyclopropanation reaction was examined. Several α-nitrocarbonyl substrates were tested and, satisfyingly, the yields were found to be respectable for all examples tested (Table 44).

Table 44. Cyclopropanation of styrene using an *in situ* generated phenyliodonium ylide: variation of the α-nitrocarbonyl substrate.



124 **150**

entry	product	R-group	yield (%)[a]	*E*:*Z* ratio
1	**150h**	Oallyl	71	90:10
2	**150i**	OBn	83	84:16
3	**150b**	O*i*-Pr	64[b]	82:18
4	**150f**	Ph	61	9:91
5	**150f**	Ph	75[c]	10:90
6	**150j**	*c*-C_3H_5	72	72:28

a) Isolated yields after purification by column chromatography. b) Reaction time was 3 h. c) Reaction was heated at 40 ºC for 3 h.

These results suggest that the *in situ* protocol can be efficient for a wide variety of α-nitrocarbonyl substrates. Of particular interest is the tolerance for α-nitroester substrates containing olefins. In the case of allyl nitroacetate (**120c**), the reaction proceeded smoothly and exclusively in an intermolecular fashion (Table 44, entry 1). The increased steric bulk imposed by the presence of an *iso*-propyl ester **120a** slowed

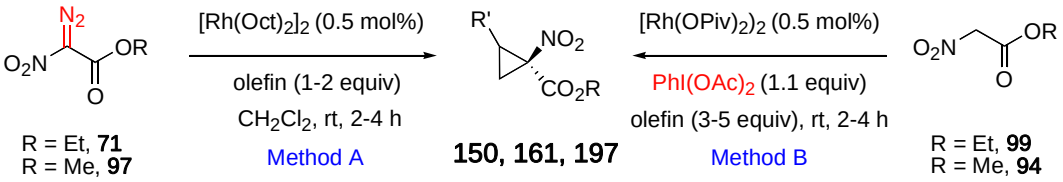
the rate of cyclopropanation, resulting in only 64% yield after stirring for 3 h (Table 44, entry 3). Examination of the crude reaction mixture indicated incomplete consumption of the nitroacetate substrate but no degradation. The reaction involving the corresponding *tert*-butyl ester **120b** was also tested, affording 42% isolated yield of cyclopropane **150g** in 2 h (70:30 *E:Z*) favoring the *E*-diastereomer. In this case, water was used as the reaction solvent.

α-Nitro acetophenone (**95**) also performed well in the cyclopropanation reaction, affording modest yields under standard conditions. The yields could be further improved to 75% upon heating at 40 ˚C for 3 h (Table 44, entry 5). The excellent *Z*-selectivity observed in this reaction closely corresponds to that obtained when the cyclopropanation reaction was performed using the corresponding diazo compound.

This *in situ* protocol has also been successfully scaled-up with reduced catalyst loadings. Ethyl nitroacetate (**99**) and styrene undergo an efficient cyclopropanation reaction in the presence of $PhI(OAc)_2$ (1.05 equiv) and $[Rh(Oct)_2]_2$ (0.04 mol%). The reaction was heated at 40 ^oC for 4.5 h, affording 79% isolated yield of cyclopropane **147** in a 92:8 *E:Z* ratio on a 3.0 g scale. Moreover, purification of cyclopropane **147** could be readily accomplished on a silica gel column requiring only 200-300 mL of organic solvent.

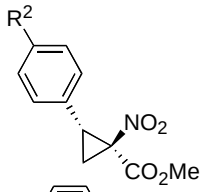
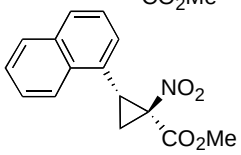
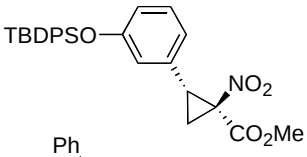
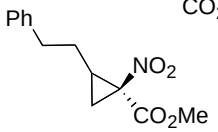
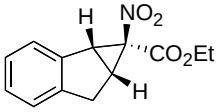
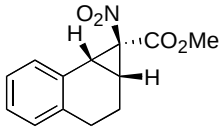
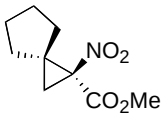
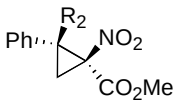
To further examine the scope of the cyclopropanation reaction with phenyliodonium ylide reagents, a number of olefin substrates were tested using the standard cyclopropanation protocol. For the sake of comparison, an analogous reaction was also performed using the corresponding diazo compound with 2.0 equivalents of the olefin. The results of these experiments are reported in Table 45.

Table 45. Comparison of the diazo-mediated cyclopropanation reaction to the *in situ* generated phenyliodonium ylide protocol.



R = Et, **71**
R = Me, **97**

R = Et, **99**
R = Me, **94**

entry	cyclopropane product		method	yield (%)[a]	*E:Z* ratio[b]
1		R^2 = H (**150a**)	A B	90 84	93:7
2		R^2 = Cl (**197a**)	A B	87 80	91:9
3		R^2 = OMe (**197b**)	A B	91 82	N/a
4		(**197g**)	A B	86 87[c]	95:5
5		(**197h**)	A B	92 50	92:8
6		(**197f**)	A B	70[c,d] 0	53:47
7		(**161c**)	A B	79 83	97:3[e]
8		(**197i**)	A B	84 72[f]	97:3[e]
9		(**197j**)	A B	83 73[f]	N/a
10		R^2 = Me (**197c**)	A B	91 80	97:3
11		R^2 = Ph (**197d**)	A B	97 63[f]	N/a

a) Isolated yields after purification by column chromatography. b) The major isomer is depicted. c) Reaction allowed to stir overnight. d) 5.0 equiv of olefin used. e) Refers to *exo:endo* ratio. f) Reaction required heating at 40 ^{o}C for 3 h.

Cyclopropanation of olefin substrates including substituted styrenes, indene, 1,2-dihydronaphthalene and α-methyl styrene generally afforded the corresponding cyclopropanes with similar chemical yields using methods A or B. One noteworthy exception among these examples was the 3-hydroxystyrene derivative protected with the bulky TBDPS group (Table 45, entry 5). The steric bulk associated with this protecting group appears to be the only factor influencing the reduced chemical yield when method B was employed. Electronic factors should be well tolerated on styrene substrates since 4-chlorostyrene (Table 45, entry 2) and 4-vinyl anisole (Table 45, entry 3) both undergo efficient cyclopropanation reactions using methods A and B.

Another curiosity noticed in the comparison between the two methods was in the cyclopropanation reactions with 4-phenyl-1-butene as an olefin substrate. Method B completely failed to afford the cyclopropane **197f** even upon addition of a variety of additives including toluene (to aid in the solubility of $PhI(OAc)_2$), aqueous KBr solutions (known to activate PhI=O by depolymerizing the reagent),[217] molecular sieves, MgO and other bases to try and improve the reaction yields. The inability of the phenyliodonium ylides to cyclopropanate this olefin substrate could be related to the decreased reactivity of these carbene precursors for entropic reasons. This is in contrast to the findings of other researchers.[203a,204] Cyclopropanation reactions with phenyliodonium ylides release iodobenzene upon treatment with a metal catalyst, whereas diazo compounds release nitrogen gas. In entropic terms, the release of a gas is greatly favored over the release of a liquid. Additionally, one has to consider that 4-phenyl-1-butene is unable to stabilize the build-up of positive charge on the β-carbon. Presumably, phenyliodonium ylides are more sensitive to this effect than the corresponding diazo compounds.

Methylene cyclopentane and 1,1'-diphenylethene were also somewhat problematic under the standard reaction conditions. However, acceptable yields of the desired cyclopropanes **197j** and **197d** of 73% and 63%, respectively, could be obtained when the reaction mixtures were heated to 40 ^{o}C for 3 h (Table 45, entries 9 and 11).

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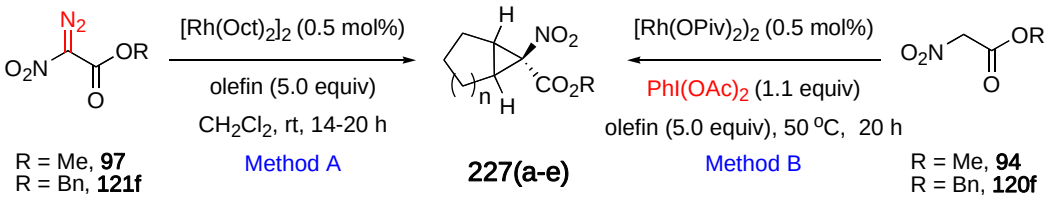
217. Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed*. **2000**, *39*, 1306-1308.

Cyclopropanation reactions employing methods A and B allowed access to a structurally diverse series of nitro cyclopropane carboxylates. In most cases, similar chemical yields and diastereoselectivities[218] could be obtained for a variety of substrates using either method A or B. Electron-rich terminal olefins or *cis*-olefins with potential for stabilization of the β-carbon appear to be the most efficient substrates in these cyclopropanation reactions.

A series of symmetric nitro cyclopropanecarboxylates were also prepared upon cyclopropanation of a variety of cyclic *cis*-olefin substrates. The reaction yields with these substrates were found to vary according to ring size of the olefin substrate. These results are reported in Table 46.

Table 46. Preparation of a series of symmetric nitro cyclopropanecarboxylates.



entry	n	R	method	cyclopropane	yield (%)[a]	*exo:endo* ratio
1	1	Bn	A	**227a**	81	87:13
2	1	Bn	B		47	
3	2	Me	A	**227b**	55	88:12
4	2	Bn	A	**227c**	39	86:14
5	4	Bn	A	**227d**	66	80:20
6	4[b]	Bn	A	**227e**	71	74:26
7	4[b]	Bn	B		50	

a) Isolated yields after purification by column chromatography. b) Cyclooctadiene used as substrate.

Cyclopropanation of cyclopentene afforded excellent yields of the corresponding cyclopropane **227a** using benzyl nitro diazoacetate (**121f**) with a preference for the *exo*-diastereomer (Table 46, entry 1). When the same reaction was performed using

218. The diastereoselectivities for the two methods vary less than ± 2%.

the *in situ* generated phenyliodonium ylide protocol (method B), only 47% yield could be obtained after heating at 50 ^{o}C in a sealed tube overnight (Table 46, entry 2).

In contrast to cyclopentene, cyclohexene proved to be a less reactive substrate as cyclopropanation with methyl and benzyl nitro diazoacetates (method A) gave disappointing yields of the corresponding cyclopropanes **227b** and **227c** (Table 46, entries 3 and 4). The benzyl ester was desirable since upon reduction of the nitro group, the corresponding cyclopropylamine was volatile. Cyclooctene and cyclooctadiene derived cyclopropanes **227d** and **227e** could also be prepared with acceptable yields (Table 46, entries 5 and 6). Attempts to cyclopropanate cyclooctadiene using the phenyliodonium ylide derived protocol resulted in only modest yields (50%) of the corresponding cyclopropane **227e** after 20 h (Table 46, entry 7). The fact that the reactions must be conducted in sealed tubes to avoid evaporation of the olefin substrate may play a role in the reduced yields in these reactions. Again, these results seem to be in contrast with the findings of other researchers where iodonium ylide derived substrates had enhanced reactivities when compared to their diazo counterparts.[203a,204]

5.2.1 Modification and attempted reoxidation of the iodine(III) reagent

A variety of other bis(acetoxy)iodobenzene derivatives of the form $ArI(O_2CR)_2$ can be easily prepared upon treatment of the corresponding iodobenzene with reagents such as peracetic acid[219] or sodium perborate/acetic acid.[220] Bis(trifluoroacetoxy)iodobenzene ($PhI(O_2CCF_3)_2$) was also prepared by stirring $PhI(OAc)_2$ in trifluoroacetic acid.[221] When tested under a similar set of reaction conditions, there appeared to be no advantage in using structurally modified iodonium(III) reagents since reaction yields were found to be inferior to those obtained with the commercially available $PhI(OAc)_2$ reagent (Eq. 32).

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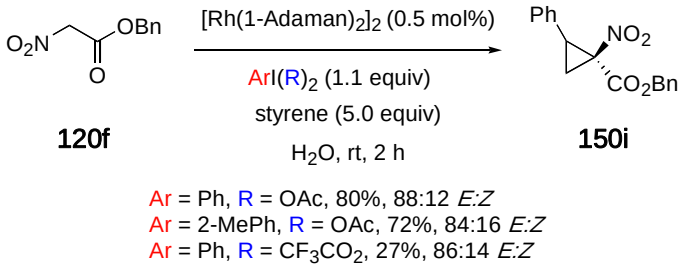
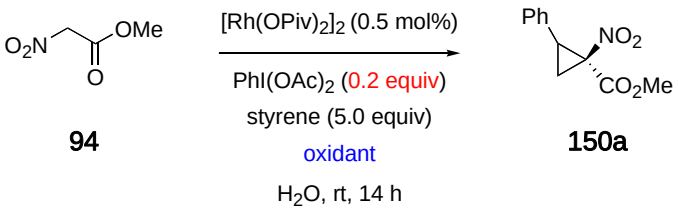
219. Sharefkin, J. G.; Saltzman, H. *Org. Synth*. **1973**, *C. V. 5*, 660-663.
220. McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299-3306.
221. Merkushev, E. B.; Novikov, A. N.; Makarchenko, S. S.; Moskal'chuk, A. S.; Glushkova, V. V.; Kogai, T. I.; Polyakova, L. G. *J. Org. Chem. USSR* **1975**, *11*, 1246-1249.



(32)

The cyclopropanation reaction involving nitroacetates and $PhI(OAc)_2$ can simplistically be viewed as an oxidation reaction. The nitroacetate is being oxidized by the iodine(III) reagent, while iodobenzene and acetic acid are the reaction byproducts. In light of this realization, reoxidation of the iodobenzene back into an iodine(III) reagent *in situ* was attempted according to Eq. 33.



(33)

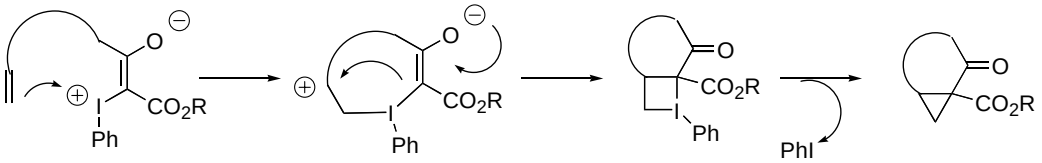
If successful, this protocol would allow for a cyclopropanation requiring only catalytic quantities of the $PhI(OAc)_2$ reagent and stoichiometric quantities of an inexpensive oxidant. A variety of reagents, including oxone, $NaBO_3 \cdot 4H_2O$ and H_2O_2, were screened in an attempt to reoxidize the iodobenzene. These preliminary reactions did not exceed yields of 20% (eg. corresponding to 0.2 equiv of reagent) due presumably to the catalytic destruction of the oxidant by the Rh(II) catalyst.

5.2.2 The mechanism of the cyclopropanation reaction using phenyliodonium ylides

As previously mentioned, there remains some debate whether the mechanisms for the cyclopropanation reactions involving phenyliodonium ylides and diazo compounds actually proceed through the same metal-carbene intermediate. The

source of this debate stems from small differences in reactivities observed between the two-carbene sources. Moriarty *et al*. has suggested a step-wise electrophilic addition of the iodonium center to the double bond, followed by reductive elimination of iodobenzene to afford the cyclopropane ring (Scheme 19).[200a,212,222] Since these reactions can be catalyzed by CuCl, its catalytic effect was tentatively ascribed to electron-transfer from the catalyst to the ylide. Furthermore, in many instances no catalyst was required for the cyclopropanation to occur, albeit these uncatalyzed processes were usually lower yielding.

Scheme 19. Proposed intramolecular cyclopropanation reaction mechanism involving phenyliodonium ylides.



228 **229** **230** **231**

The proposed mechanism for the cyclopropanation proceeds in a step-wise manner as depicted in Scheme 19. Initially, an electrophilic addition occurs to the iodonium center from the double bond **228**, followed by a transannular alkylation of the, thus formed, carbocation by the enolate **229**. This is then followed by reductive elimination of **230**, expulsing iodobenzene and ligand coupling to yield the corresponding cyclopropane **231**.

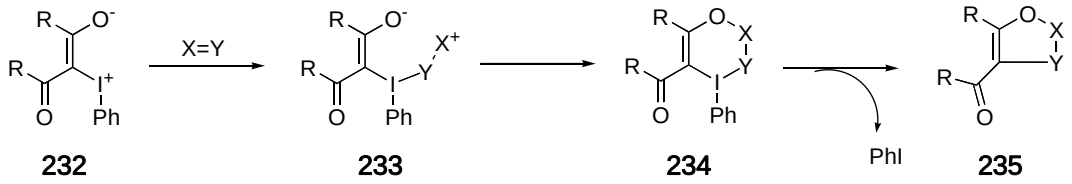
The findings of Gallos *et al.* also led them to agree with the mechanism proposed by Moriarty *et al.* In their case, various intramolecular cyclopropanations were conducted using a glycoside scaffold. They found that the resulting diastereoselectivities from the cyclopropanation reaction were almost completely reversed between phenyliodonium ylides and the corresponding diazo compounds.[223] They suggest that, depending on the reaction conditions (solvent, temperature and

222. Moriarty, R. M.; Kim, J.; Guo, L. *Tetrahedron Lett*. **1993**, *34*, 4129-4132.
223. Gallos, J. K.; Koftis, T. V.; Massen, Z. S.; Dellios, C. C.; Mourtzinos, I. T.; Coutouli-Argyropoulou, E.; Koumbis, A. E. *Tetrahedron* **2002**, *58*, 8043-8053.

catalyst) and the nature of the substrate, a stepwise electrophilic addition of the iodonium center to the double bond or the formation of the metal-carbenoid intermediate can occur.

Moriarty *et al*. also concludes that carbenoid intermediates are not involved in metal-catalyzed processes involving iodonium ylides for a number of other reasons. First, phenyliodonium ylides undergo a number of cycloaddition reactions leading to the formation of five-membered heterocycles (**235**, Scheme 20).[200a] These include reactions with CS_2, phenylisothiocyanate, acetonitrile and olefins.[224] Secondly, no Wolff-type rearrangement products were formed in these reactions, although the analogous α-keto-carbene from α-diazo ketones has been shown to follow this pathway. This suggests that an α-keto-carbene is not involved in the phenyliodonium ylide reactions.

Scheme 20. Formation of five-membered heterocycles with iodonium ylides.



232 **233** **234** **235**

Another unique property of the iodonium ylides that was unobserved with diazo compounds was acid catalyzed N-H insertion reactions. Kume *et al*. reported a method for the preparation of β-lactam antibiotics using this approach.[225]

In contrast to the mechanism proposed by Moriarty *et al*., Müller *et al*. have been led to believe that cyclopropanation reactions involving phenyliodonium ylides proceed in the same fashion as those involving diazo compounds. This idea stemmed from research conducted in 1995 in which a number of different diazo-mediated processes including intermolecular cyclopropanations and cyclopropenations, 1,3-dipolar cycloaddition reactions to furans, intramolecular C-H insertion reactions,

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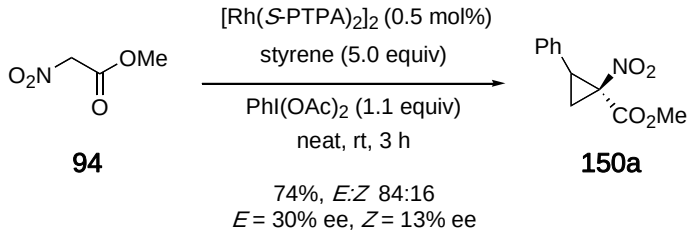
224.(a) Hadjiarapoglou, L. *Tetrahedron Lett.* **1987**, *28*, 4449-4450. (b) Papadopoulou, M.; Spyroudis, S.; Varvoglis, A. *J. Org. Chem*. **1985**, *50*, 1509-1511.
225. Kume, M.; Ooka, H.; Ishitobi, H. *Tetrahedron* **1997**, *53*, 1635-1646.

intramolecular cyclopropanation versus intramolecular C-H insertion competition experiments and asymmetric induction in C-H insertion reactions were conducted both with diazo compounds and the analogous phenyliodonium ylides.[200b] For all of the cases examined, nearly identical product distributions were observed for the Rh(II)-catalyzed processes involving both diazo and iodonium ylide substrates. These results suggest that they both proceed through the same metallo-carbene intermediate. Among the processes examined, perhaps the strongest evidence is the fact that both substrates gave nearly identical levels of asymmetric induction. In the mechanism proposed by Moriarty *et al*. the role of the catalyst and its impact on asymmetric processes would be expected to be greatly limited or at least different.

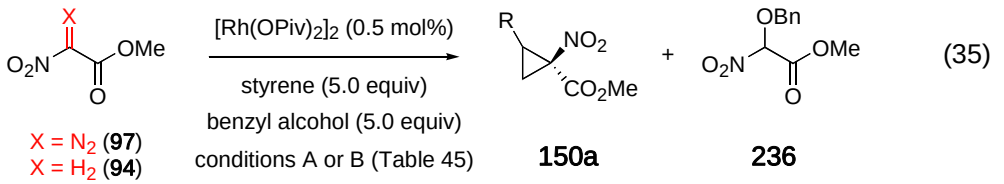
In order to gain further insight into the reaction mechanism governing cyclopropanation reactions involving α-nitrocarbonyl substrates, an asymmetric cyclopropanation reaction involving the *in situ* protocol using phenyliodonium ylides was briefly examined. For example, when a $[Rh(S\text{-PTPA})_2]_2$ catalyzed cyclopropanation was performed using iodonium ylides (Eq. 34), the yields and levels of asymmetric induction closely resembled those obtained with the corresponding diazo compound (75% yield in a 86:14 *E:Z* ratio; *E* = 30% ee, *Z* =12% ee). It is, therefore, highly unlikely that two different mechanisms be operating given the similarity of these two results.



(34)

Next a competition experiment was performed between O-H insertion and cyclopropanation processes using benzyl alcohol and styrene as substrates (Eq. 35). To our surprise, when the *in situ* generated phenyliodonium ylides protocol was used, exclusive formation of the cyclopropane product **150a** was observed in 70% isolated yield. In contrast, use of methyl nitro diazoacetate (**97**) afforded a mixture of

cyclopropane **150a** and the O-H insertion product **236** in a 1.7:1 ratio, respectively, in 90% of the theoretical yield based of ratio of two products (Eq. 35).



(35)

In fact, all our attempts to affect an O-H insertion reaction with phenyliodonium ylides derived from α-nitrocarbonyls have been unsuccessful. Moreover, the corresponding α-alkoxy-α-nitrocarbonyls have never been observed in the crude reaction mixtures. If phenyliodonium ylide and diazo compounds both go through the same metallo-carbene intermediate, then one would also expect they should react in a similar way with alcohols. To further establish that the presence of $PhI(OAc)_2$ and its byproducts (AcOH and PhI) were not affecting in some way the observed differences in reactivity, a number of control reactions were performed. Accordingly, the presence of AcOH, PhI or $PhI(OAc)_2$ did not affect the outcome of the diazo-mediated process as O-H insertion was always observed. In light of these unexpected results, one can only conclude that there is some degree of divergence between the reactivities of the two carbene precursors for certain processes.

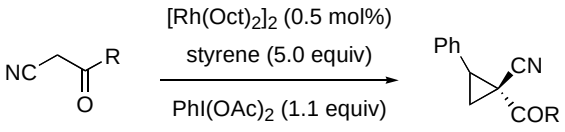
5.3 Expansion of the reaction scope: cyclopropanation with α-cyanomethyl ketones

The simplicity of the cyclopropanation reaction protocol involving the *in situ* generation of the phenyliodonium ylide reagents clearly enjoys many benefits over use of the corresponding diazo compounds. As a result, we wished to extend the scope of the cyclopropanation methodology using the *in situ* protocol to include other types of substrates. To help select likely candidates for the *in situ* cyclopropanation protocol, we resorted to comparing the pK_a values of the α-acidic substrates to those of α-nitro carbonyls. A similar approach was taken for the successful expansion of

the scope of the diazo transfer methodology. Accordingly, we decided to test α-cyanomethyl carbonyls **132** under the conditions used for the *in situ* generation of phenyliodonium ylides involving α-nitrocarbonyls.

The results of a variety of cyclopropanation reactions involving α-cyano-α-diazoesters **133a-h** and olefins were quite variable. Some substrates led to high yields while others resulted in complete inactivity. On the other hand, α-cyano-α-diazoketones **133i-j** were uniformly high yielding in the cyclopropanation reactions. When various α-cyanomethyl ketones were treated with bis(acetoxy)iodobenzene in the presence of styrene and a Rh(II) catalyst, modest yields of the corresponding cyclopropanes could be obtained. A variety of reaction conditions were tested and the results are reported in Table 47.

Table 47. Optimization of the *in situ* generation of the phenyliodonium ylides with α-cyanomethyl ketones.



132 **237**

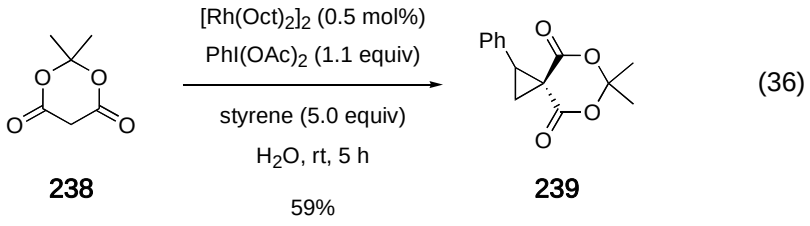
entry	R-group	solvent	additive	yield (%)[a]	*E:Z* ratio
1	Ph (**237a**)	none	none	63	86:14
2	" "	CH_2Cl_2	4 Å MS[b]	64	86:14
3	" "	CH_2Cl_2	Al_2O_3[c]	52	89:11
4	" "	CH_2Cl_2	Al_2O_3 + 4 Å MS[b]	63	87:13
5	" "	CH_2Cl_2	Na_2CO_3 + 4 Å MS[b]	72 (88)[d]	90:10
6	" "	H_2O	none	52	87:13
7	Bn (**237b**)	none	none	57	75:25
8	Bn (**237b**)	CH_2Cl_2	Na_2CO_3 + 4 Å MS[b]	47 (64)[d]	76:24
9	4-MeO-Ph (**237c**)	CH_2Cl_2	Na_2CO_3 + 4 Å MS[b]	63 (72)[d]	94:6
10	styryl (**237d**)	none	none	65 (67)[d]	55:45

a) Isolated yields after column chromatography. b) 1:1 wt/wt with the cyano substrate. c) 2.3 equiv of the additive was used. d) The number in parenthesis corresponds to the yield obtained upon stirring for 18 h.

The optimized cyclopropanation conditions in reactions with benzoyl acetonitrile (**133i**) were found to involve the use of sodium carbonate and 4 Å MS as additives and 1.0M CH_2Cl_2 as the reaction solvent, affording yields of 72% of the corresponding cyclopropane (**237a**, Table 47, entry 5). Generally speaking, the additives and solvent had little influence on the yields of the cyclopropanation reaction. For example, changing the reaction solvent to water also led to 52% isolated yield of the desired cyclopropane **237a** in 5 h (Table 47, entry 6).

When other α-cyanomethyl ketones were tested, modest yields of the desired cyclopropanes **237b-d** could be obtained, however, the optimal conditions varied for each substrate (Table 47, entries 7-10). For example, improved yields of the cyclopropane **237b** resulted in the absence of additives and solvent compared to the optimal conditions involving the benzoylacetonitrile (**133i**) substrate. The 4-methoxy-benzoylacetonitrile substrate did not perform well under solvent-less conditions since this substrate was insoluble in styrene. If the reactions were allowed to stir for longer periods of time (18 h), then the yields of the cyclopropanation reactions could be further improved (see yields in parenthesis, Table 47).

Meldrum's acid (**238**) was also used a substrate for a cyclopropanation reaction involving aqueous conditions. Accordingly, the cyclopropanation reaction was found to proceed with modest efficiency, affording 59% isolated yield of the corresponding cyclopropane (**239**, Eq. 36).



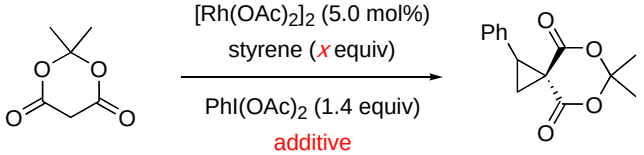
(36)

5.4 Conclusions

Directly following publication of our results involving the cyclopropanation with the *in situ* generation of phenyliodonium ylides derived from α-nitro carbonyls,

Müller and Ghanem reported an extension of the scope of this methodology. This involved the use of Meldrum's Acid (**238**) as a substrate (Table 48).

Table 48. Extension of the *in situ* generated phenyliodonium ylide methodology to Meldrum's Acid.



238 **239**

entry	styrene equiv.	additive[a]	yield (%)
1	10	none	23
2	10	MgO	67
3	10	K_2CO_3	69
4	10	Al_2O_3	51
5	10	MS 4 Å	33
6	10	MgO + 4 Å MS	80
7	10	K_2CO_3 + 4 Å MS	73
8	10	Al_2O_3 + 4 Å MS	85
9	6	Al_2O_3 + 4 Å MS	58
10	4	Al_2O_3 + 4 Å MS	49
11	2	Al_2O_3 + 4 Å MS	24

a) 2.3 equiv of additive was used.

The optimal reaction conditions in this cyclopropanation were found to involve a large excess of olefin (10 equiv), catalyst loadings of 5.0 mol% and the addition of $PhI(OAc)_2$ (1.4 equiv), Al_2O_3 (2.3 equiv) and 4 Å molecular sieves (Table 48, entry 8).[226] These authors also demonstrated that modest levels of asymmetric induction could be obtained under these conditions with enantioselectivities up to 70% ee. These levels are some of the highest reported for cyclopropanation reactions involving diazo or diazo equivalents with two electron-withdrawing substituents.

In conclusion, hypervalent iodine(III) reagents were successfully applied to cyclopropanation reactions involving α-nitro carbonyl compounds. They were shown

226. Müller, P.; Ghanem, A. *Synlett* **2003**, 1830-1833.

to be safe alternatives to α-nitro-α-diazocarbonyl compounds. Cyclopropanation reactions involving the *in situ* generation of phenyliodonium ylides were found to proceed with similar yields and diastereoselectivities compared to cyclopropanation reactions using α-nitro-α-diazocarbonyl compounds for most olefin substrates (Table 45). Unfortunately, attempts to extend this protocol to O-H insertions and intramolecular cyclopropanations involving α-nitrocarbonyls have not yet been possible. This suggests that the methodologies involving both diazo compounds and phenyliodonium ylides will remain complementary.

The mechanism of the cyclopropanation reaction involving diazo and iodonium ylide substrates was briefly examined and preliminary results suggest that the implicated mechanisms are quite similar. However, there appears to be an unexplained divergence in the reactivity patterns between the two substrates in O-H insertion reactions (Eq. 35). As of yet, no explanations can be offered with confidence for this surprising observation.

The cyclopropanation procedure involving the *in situ* generation of phenyliodonium ylides was also successfully extended to include cyclopropanations with α-cyanomethyl ketones (Table 47). The reaction yields involving these substrates were modest to excellent. This also represents an efficient synthesis of valuable synthons whose utility will be described in Chapter 7.

Finally, a replacement for the potentially toxic and explosive α-nitro-α-diazocarbonyl compounds was successful with the development of a methodology employing hypervalent iodine(III) reagents. Using this methodology, the synthesis of a diverse series of α-nitro cyclopropanecarboxylates can be successfully achieved in one step from commercially available starting materials in short reaction times. The robust nature of the reaction, the inexpensive reagents involved and the high activities of the catalysts used make this an attractive method for the preparation of these precursors to cyclopropane α-amino acids. Chapter 6 will outline the conditions necessary to achieve successful reductions of the nitro cyclopropanecarboxylates.

CHAPTER 6

Reduction of Nitro Cyclopropanecarboxylates

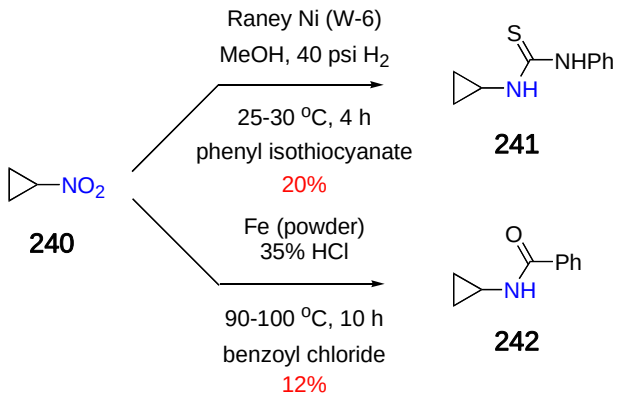
6.1 Introduction and precedence

Two reliable methods for the synthesis of a series of structurally diverse nitro cyclopropanecarboxylates in modest to excellent yields have been developed. These methods involve cyclopropanation reactions employing α-nitro-α-diazoesters or iodonium ylides generated *in situ*. In our envisioned synthetic strategy, nitro cyclopropanecarboxylates would serve as direct synthetic precursors to the desired cyclopropane α-amino acids upon reduction of the nitro group and hydrolysis of the ester. There exist numerous examples in the literature outlining successful hydrolyses of amino cyclopropyl esters. Therefore, the remaining challenge was the development of a successful reduction protocol for the nitro cyclopropanecarboxylates. This seemingly straightforward reduction proved to be much more challenging than anticipated.

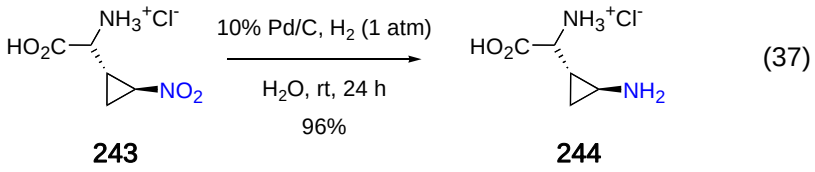
Several examples concerning the reduction of nitro cyclopropanes have been reported in the literature. Hass and Shechter reported one of the earliest examples involving the reduction of nitrocyclopropane (**240**). They found that reductions involving Raney nickel or iron powder and HCl were able to successfully reduce nitrocyclopropane (**240**) to cyclopropylamine in low yields. Cyclopropylamine was isolated as either *N*-cyclopropyl-*N'*-phenylthiourea (**241**) or *N*-cyclopropylbenzamide (**242**) for ease of purification (Scheme 21).[227]

227.(a) Hass, H. B.; Shechter, H. *J. Am. Chem. Soc.* **1953**, *75*, 1382-1384. See also: (b) Asunskis, J.; Shechter, H. *J. Org. Chem.* **1968**, *33*, 1164-1168.

Scheme 21. Reduction of nitrocyclopropane.



Zindel and de Meijere reported a method for the synthesis of 2-(*trans*-2'-aminocyclopropyl)glycine hydrochloride (**244**), which also relied on the reduction of a nitro cyclopropane **243**. This reduction was accomplished in excellent yields using 10% Pd on carbon as the hydrogenation catalyst. The reduction was achieved by stirring the reaction mixture under a hydrogen atmosphere in aqueous media for 24 h (Eq. 37).[228]



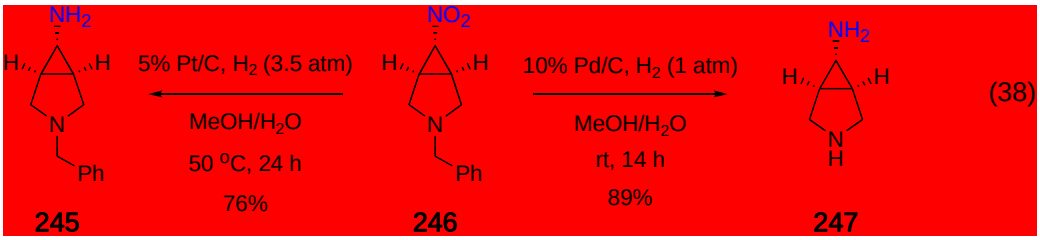
(37)

The cyclopropylamine subunit of the antibiotic, Trovafloxacin, was also prepared through reduction of nitro cyclopropane **246**. In this case, a variety of reducing conditions were tested including Pt on carbon, Pd on carbon, zinc-HCl and Raney nickel-hydrazine.[229] Reduction of the nitro cyclopropane **246** with Pt on carbon was found to be the most convenient method, leaving the benzyl protecting group intact

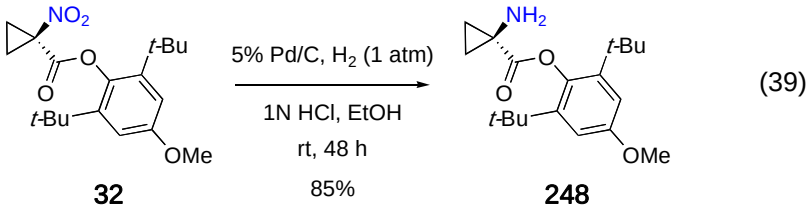
228.(a) Zindel, J.; de Meijere, A. *Synthesis* **1994**, 190-194. See also: (b) Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O. V.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Synlett* **2000**, 1741-1744.

229. Norris, T.; Braish, T. F.; Butters, M.; DeVries, K. M.; Hawkins, J. M.; Massett, S. S.; Rose, P. R.; Santafianos, D.; Sklavounos, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1615-1622.

(**245**, Eq. 38). The corresponding diamine **247** could be isolated following reduction of the nitro cyclopropane **246** with Pd on carbon (Eq. 38).



To the best of our knowledge, only two examples exist for the reduction of nitro cyclopropanecarboxylates. Häner and Seebach reported the reduction of the unsubstituted nitro cyclopropanecarboxylate **32** possessing a bulky phenol-derived ester.[230] This reduction was successfully accomplished in excellent yields by stirring for 48 h under a hydrogen atmosphere using 5% Pd on carbon (**248**, Eq. 39).



Kuznetsova *et al*. also recently reported the reductions of three structurally related 2,2-disubstituted nitro cyclopropanecarboxylates in their synthesis of spirohexane amino acids (Eq. 3).[60a] Pd on carbon was again used as the hydrogenation catalyst, however, ammonium formate (NH_4CO_2H) was the hydrogen source for these reductions.[231] It is also noteworthy to mention that these three examples did not possess aromatic functional groups directly attached to the cyclopropane ring. Moreover, the amino cyclopropyl esters were not isolated but submitted directly to the saponification conditions affording the corresponding cyclopropane α-amino

230. See also Scheme 1, Chapter 1.
231. Reduction conditions: The nitro cyclopropane carboxylate **72** was dissolved in EtOH (anhydr.) followed by the addition of 10% Pd/C (10 mol%), NH_4CO_2H (10 equiv). The mixture was stirred for 40 h at room temperature.

acids in respectable yields.[60a] Lengthy reaction times for the reductions were again necessary, similar to those reported by Häner and Seebach (Eq. 39).

6.2 Development of a new reduction methodology for nitro cyclopropane carboxylates

Since there exists considerable literature precedence for the reduction of nitro cyclopropanes and two examples for reductions involving nitro cyclopropanecarboxylates, we were confident that a general reduction protocol would be easy to develop. In fact, it was often assumed that reductions of these nitro cyclopropanecarboxylates were straightforward when other authors cited publications concerning nitro cyclopropanecarboxylates. This assumption was made despite the absence of reports in the literature concerning the reduction of nitro cyclopropanes containing aromatic groups directly attached to the cyclopropane ring.[232]

In an attempt to develop a general reduction protocol, we focused on what we perceived as the most challenging case, methyl-2-phenyl-1-nitrocyclopropane carboxylate **150a**. This cyclopropane was submitted to standard reduction conditions involving 10% Pd on carbon under a hydrogen atmosphere. Surprisingly, the reducing conditions resulted in isolation of amine **250**, the product corresponding to the hydrogenolysis of the cyclopropane ring. Discouraged by this result, the hydrogen source was changed to ammonium formate (NH_4CO_2H). These reduction conditions then afforded the corresponding hydroxylamine **249** in respectable yields (Scheme 22). It has been suggested that reductions with Pd catalysts are preferable for only partial reduction of α-carboxy nitro groups to hydroxylamines. This is presumably due to the resulting stabilization imparted by intramolecular hydrogen bonding.[233]

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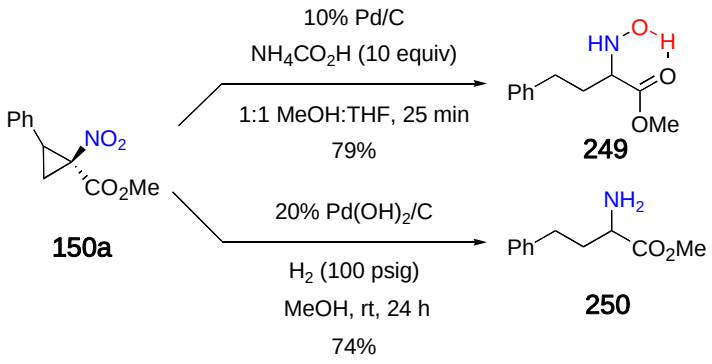
232. See: pg. 9434, ref. 47.

233.(a) Fu, Y.; Hammarström, L. G. J.; Miller, T. J.; Fronczek, F. R.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem.* **2001**, *66*, 7118-7124. (b) Freifelder, M. In *Catalytic Hydrogenation in Organic Synthesis, Procedures and Commentary*; John Wiley & Sons: New York, 1978; pg. 26-39. (c) Rylander, P. In *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; pg. 113-125. (d) Boger, D. L.; Lerner, R. A.; Cravatt, B. F.; *J. Org. Chem*. **1994**, *59*, 5078-5079.

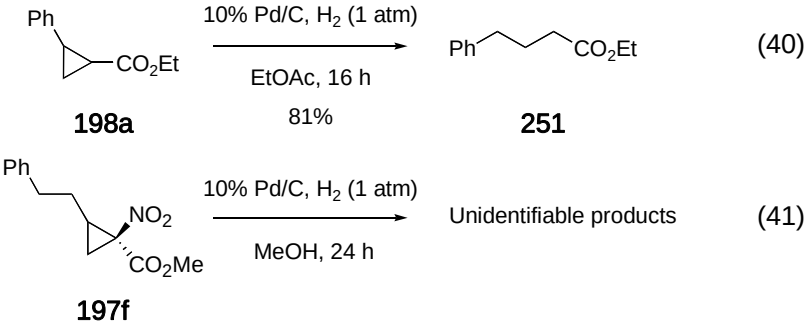
In an attempt to fully reduce the nitro cyclopropane to the desired amine, higher pressures of hydrogen were used in combination with a more active hydrogenation catalyst $Pd(OH)_2$. These conditions led to the complete hydrogenolysis of the cyclopropane ring affording methyl 2-amino-4-phenylbutanoate (**250**) in 74% isolated yield (Scheme 22). In both cases, the hydrogenolysis of the cyclopropane ring was found to be regiospecific as only one of the two possible products was observed in the crude reaction mixtures.

Scheme 22. Pd-catalyzed reduction of methyl 2-phenyl-1-nitrocyclopropane carboxylate (**150a**).



Several potential variables were then examined in an attempt to clarify the factors contributing to the ease of hydrogenolysis of the cyclopropane ring. For example, the presence of radical species on the nitro group α– to the cyclopropane ring during reduction could ultimately result in ring opening.[167a] Alternatively, hydrogenolysis efficiency could be derived from the aromatic substituent in the 2-position, thus facilitating ring opening. To test these two hypotheses, ethyl 2-phenylcyclopropanecarboxylate (**198a**) was subjected to the standard hydrogenation conditions resulting in excellent yields of product **251** corresponding to hydrogenolysis of the cyclopropane ring (Eq. 40). Methyl 1-nitro-2-(2-phenethyl) cyclopropanecarboxylate (**197f**), which lacks an aromatic group directly attached to

the cyclopropane ring, was also submitted to the reduction conditions. Accordingly, only small quantities of the desired amino ester could be recovered (Eq. 41).[234]



These two results suggested that reduction of nitro cyclopropanecarboxylates containing an aromatic group directly attached to the cyclopropane ring would be particularly problematic using Pd-catalysts. Accordingly, a variety of known reduction conditions for nitro groups were screened including Raney Ni,[229,235] Fe-HCl, and Zn-AcOH,[233a,236] Electrochemical reduction methods using Devarda's Alloy (45% Al, 50% Cu, 5% Zn) were also briefly examined.[237] Unfortunately, all of these conditions led to the recovery of unidentifiable products corresponding mainly to the decomposition of the highly activated cyclopropanes.[238] Vinylic and

234. It is noteworthy to mention that Stammer *et al*. have reported the cleavage of the benzyl ester of benzyl *Z*-1-amino-2-phenylcyclopropanecarboxylate in high yields without hydrogenolysis of the cyclopropane ring see: King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270-3273.

235. Reductions of α-nitrocarboxylates in the presence of a cyclopropane see: (a) Yun, Y. K.; Godula, K.; Cao, Y.; Donaldson, W. A. *J. Org. Chem*. **2003**, *68*, 901-910. For an example involving an α,α-disubstituted ethyl nitroacetate see: (b) Fu, Y.; Etienne, M. A.; Hammer, R. P. *J. Org. Chem*. **2003**, *68*, 9854-9857.

236. For reductions of α-nitrocarboxylates with Zn, AcOH/Ac_2O see: (a) v. Seebach, D.; Häner, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507-1515.

237.(a) Chan-Shing, E. S.; Boucher, D.; Lessard, J. *Can. J. Chem*. **1999**, *77*, 687-694. (b) Cyr, A.; Huot, P.; Belot, G.; Lessard, J. *Electrochim. Acta* **1990**, *35*, 147-152.

238. Activated cyclopropanes can potentially undergo anionic polymerizations initiated by nucleophiles see: (a) Penelle, J.; Xie, T. *Macromolecules* **2001**, *34*, 5083-5089. (b) Penelle, J.; Xie, T. *Macromolecules* **2000**, *33*, 4667-4672. (c) Penelle, J.; Clarebout, G.; Balikdjian, I. *Polym. Bull*. **1994**, *32*, 395-401.

benzylic[239] nitro cyclopropanecarboxylates undergo rearrangements to the corresponding isoxazoline *N*-oxides under mildly acidic or Lewis acidic conditions,[81d] which precludes the use of harsh reduction conditions. Cyclopropane ring opening in the presence of a variety of nucleophiles is an efficient process,[81d,240] further necessitating the use of mild reducing conditions.

After several years of fruitless attempts to successfully reduce the nitro cyclopropanecarboxylates without the destruction of the cyclopropane moiety, reduction conditions involving zinc were re-examined. Zinc dust has been the reducing agent of choice for reductions involving sterically encumbered α,α-disubstituted nitrocarboxylates and various other tertiary and quaternary nitro groups.[233a,241] A variety of acid sources (NH_4Cl,[242] AcOH, HCl) were screened along with various stoichiometries of acid and zinc. Finally, using zinc dust (20 equiv) and aqueous 1N HCl (10 equiv) in methanol (0.05M), an efficient reduction of ethyl 2-phenyl-1-nitro cyclopropanecarboxylate (**147**) was possible with only traces of the hydrogenolysis product. Further optimization of the reduction conditions indicated that 2-propanol was a superior reaction solvent as it aided in substrate solubility and led to increases in yields of 5-10% compared to methanol. The scope of the reduction was then examined for a variety of nitro cyclopropanecarboxylates containing an aromatic group directly attached to the cyclopropane ring (Table 49).[243]

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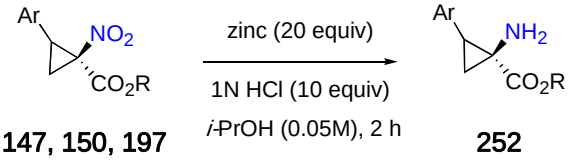
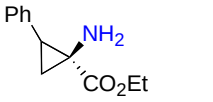
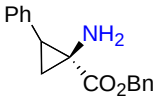
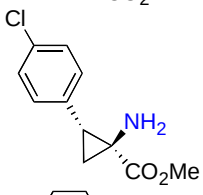
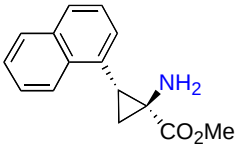
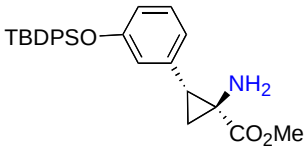
239. Refers to nitro cyclopropanecarboxylates containing an olefin or an aromatic group directly attached to the cyclopropane ring.
240. Vettiger, T.; Seebach, D. *Liebigs Ann. Chem*. **1990**, 195-201.
241. Zn/HOAc see: (a) Battersby, A. R.; Baker, M. G.; Broadbent, H. A.; Fookes, C. J. R.; Leeper, F. J.; *J. Chem. Soc., Perkin Trans. 1* **1987**, 2027-2048. (b) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem*. **1998**, *63*, 3528-3529.
242. Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546-14547.
243. Wurz, R. P.; Charette, A. B. *J. Org. Chem*. **2004**, *69*, 1262-1269.

Table 49. Reduction of nitro cyclopropanecarboxylates containing an aromatic group using zinc dust.



147, 150, 197 **252**

entry	amino cyclopropane	product	yield (%)[a]
1		**252a**	49[b]
2			67[c]
3			77
4		**252b**	75
5		**252c**	76
6		**252d**	76
7		**252e**	74

a) Isolated yields after purification by column chromatography. b) AcOH used as the acid. c) MeOH used as solvent.

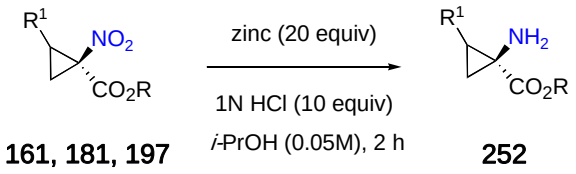
Initially, when acetic acid and 2-propanol were used, nitro cyclopropane carboxylate **147** was reduced to ethyl 1-amino-2-phenylcyclopropanecarboxylate (**252a**) in 49% yield (Table 49, entry 1). When the acid source was changed to HCl, an isolated yield of 67% of the corresponding amino ester **252a** could be obtained in methanol (Table 49, entry 2). This protocol afforded acceptable yields for most of the examples tested except for cyclopropane **197h**, which only gave 32% isolated yield of the corresponding amino ester **252e**. This poor result was probably related to the limited solubility of the cyclopropane in methanol causing conglomeration of the

reagents. Upon replacement of methanol with 2-propanol, more general reduction conditions resulted. Finally, the best results (77%, Table 49, entry 3) were obtained when the zinc dust was added in small portions over 15 min (reaction is exothermic) to the acidic 2-propanol solution containing the cyclopropane. In contrast, however, slow addition of 1N HCl to the heterogeneous mixture of cyclopropane, alcohol and zinc dust gave increased degradation. Other zinc(0) sources, including zinc powder, were also tested and found to give inferior results.

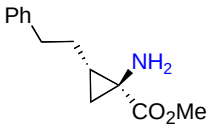
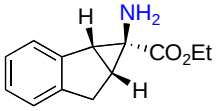
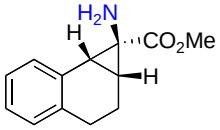
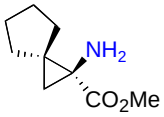
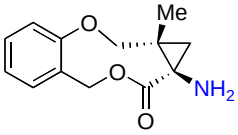
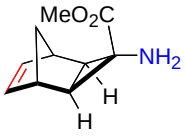
Cyclopropane **150i**, containing a benzyl ester, underwent smooth reduction affording the corresponding amino ester **252b** in 75% yield (Table 49, entry 4). The 4-chlorophenyl and 1-naphthyl derivatives **197a** and **197g** were also transformed to the corresponding amino esters **252c** and **252d** without incident, both in 76% isolated yield (Table 49, entries 5 and 6). Reduction of cyclopropane **197h** in 2-propanol gave acceptable yields of 74%. This amino cyclopropyl ester **252e** serves as a precursor to Cyclo-*m*-tyr (**14**, Fig. 5).

These sensitive cyclopropanes containing aromatic substituents could be consistently reduced in respectable yields ranging from 74-77%. To further examine the scope of the reduction protocol, a structurally diverse series of nitro cyclopropane carboxylates were then submitted to the standard reaction conditions with satisfying results (see Table 50).

Table 50. Reduction of a structurally diverse series of nitro cyclopropane carboxylates using zinc dust.



161, 181, 197 **252**

entry	amino cyclopropane	product	yield (%)[a]
1	 60:40 *E:Z*	**252f**	93
2		**252g**	79
3		**252h**	86
4		**252i**	54
5		**252j**	70
6		**252k**	80

a) Isolated yields after purification by column chromatography.

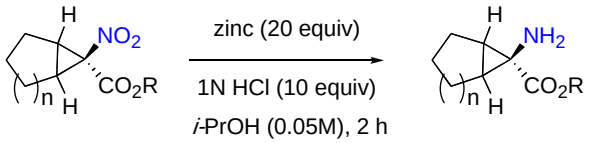
The *E*- and *Z*-isomers of cyclopropane **197f** derived from 4-phenyl-1-butene, which do not contain an aromatic substituent directly attached to the cyclopropane ring, gave an excellent yield (93%) of the corresponding amino esters (**252f**, Table 50, entry 1). It is noteworthy to mention that the *E*- and *Z*-isomers (of **252f**) could now be easily separated by column chromatography. Cyclopropane **161c** derived from indene, and its homolog **197i**, also underwent smooth reductions affording the

corresponding amino esters **252g** and **252h** in 79% and 86% yields, respectively (Table 50, entries 2 and 3).

Surprisingly, the reduction of cyclopropane **197j** under the standard reduction conditions gave disappointing results, yielding a modest 54% yield of the pure amino ester **252i** (Table 50, entry 4). Several attempts to reduce this cyclopropane under the conditions reported by Kuznetsova *et al.*[60a] yielded only traces of the desired amino ester **252i**. In addition, products corresponding to the hydroxylamine and ring opening of the cyclopropane were also isolated. The nitro cyclopropyl lactone **181b** prepared by intramolecular cyclopropanation was also successfully reduced to its amine **252j** in 70% isolated yield (Table 50, entry 5). One advantage to using zinc as a reducing source is its ability to chemoselectively reduce nitro groups in the presence of olefins. Accordingly, reduction of cyclopropane **197k**, derived from norbornadiene, gave 80% isolated yield of the desired cyclopropane **252k** without affecting the olefin (Table 50, entry 6).

Next, a series of symmetric nitro cyclopropanecarboxylates were submitted to the standard reduction protocol. This robust series of cyclopropanes were found to undergo clean nitro reductions resulting in excellent isolated yields of the corresponding amino esters (Table 51). The *endo*- and *exo*-diastereomers could now be easily separated by column chromatography on silica gel.

Table 51. Reduction of symmetric nitro cyclopropanecarboxylates using zinc dust.



227(a-e) **253(a-e)**

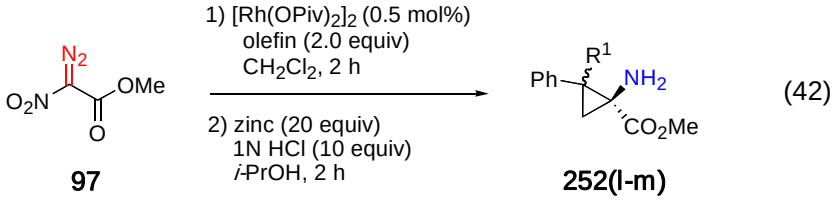
entry	n	R	product	yield (%)[a]
1	1	Bn	**253a**	88
2	2	Me	**253b**	74[b]
3	2	Bn	**253c**	87
4	4	Bn	**253d**	>99
5	4[c]	Bn	**253e**	94

a) Isolated yields after purification by column chromatography. b) Product was volatile. c) Olefin derived from cyclooctadiene.

Cyclopropane **227b**, derived from cyclohexene, was found to be volatile affording amino ester **253b** in 74% yield (Table 51, entry 2). Consequently, the benzyl ester was prepared **227c** and reduced in 87% yield, affording amino ester **253c** (Table 51, entry 3). Satisfyingly, reduction of the unsaturated nitro cyclopropane **227e** again resulted in the chemospecific reduction of the nitro group in the presence of the olefin. The desired amino ester **253e** was obtained in 94% yield (Table 51, entry 5).

6.3 Development of a "one pot" cyclopropanation reduction procedure

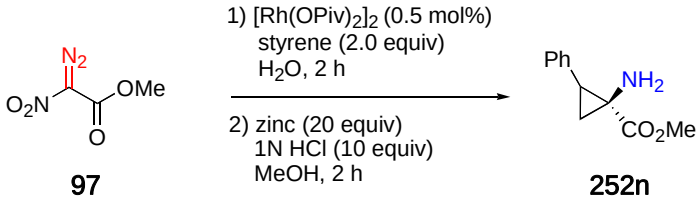
The reduction of more sensitive cyclopropanes, such as 2,2-diphenyl-1-nitro-cyclopropanecarboxylate (**197d**), represent more challenging examples as they readily rearrange to the corresponding isoxazoline *N*-oxides on silica gel if it is not pretreated with triethylamine. To avoid such rearrangements, these cyclopropanes were prepared using the standard cyclopropanation reaction protocol. Upon removal of the solvent, the crude material was subjected directly to the reduction conditions. Modest yields were obtained (62% and 57%, respectively) for the two-step sequence with the total reaction time amounting to only 4 h (Eq. 42).



(42)

olefin = 1,1'-diphenylethene 57% **252l** (R^1 = Ph)
α-methyl styrene 62% (*E*:*Z* 82:12) **252m** (R^1 = Me)

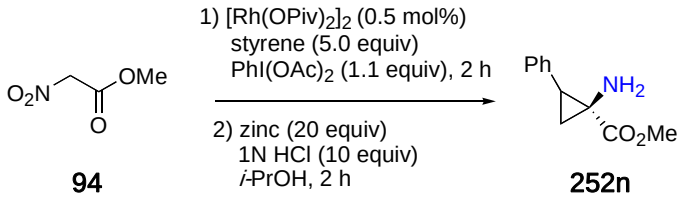
This "one pot" cyclopropanation reduction procedure can also be applied to biphasic, aqueous cyclopropanations.[244] An aqueous solution of methyl nitro diazoacetate (**97**) was added over 30 min to a mixture of styrene (2.0 equiv) and catalyst, resulting in an efficient cyclopropanation reaction. Treatment of the reaction mixture after 2 h with 2-propanol, 1N HCl and zinc dust afforded the corresponding amino cyclopropanecarboxylate **252n** in a respectable 66% yield for 2 steps (Eq. 43).



(43)

66%, *E*:*Z* = 71:29

In a similar fashion, the cyclopropanation protocol involving the *in situ* generated iodonium ylides could also be applied. This practical method offers the advantage of avoiding handling of the potentially dangerous diazo compounds in addition to elimination of a purification step for the nitro cyclopropane. Again, a respectable yield of 65% could be obtained (Eq. 44).

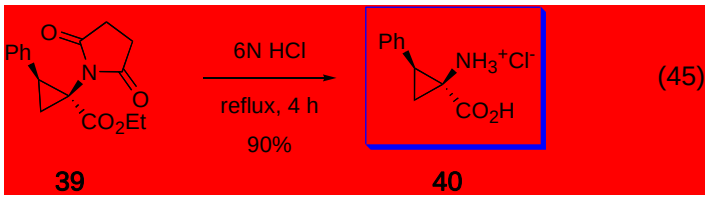


(44)

65%, *E*:*Z* = 65:35

244. See the results reported in Chapter 4.

Finally, the amino esters can be converted to the corresponding amino acids by saponification of the ester according to previously reported methods.[60a] For example, Aggarwal reported the isolation of *Z*-1-amino-2-phenyl-cyclopropanecarboxylic acid (**40**) in 90% yield upon refluxing ethyl ester **39** in 6N HCl for 4 h (Eq. 45).



6.4 Mechanism for reduction of nitro groups using zinc(0)

The ease of hydrogenolysis of nitro cyclopropanecarboxylates containing an aromatic group directly attached to the cyclopropane ring was quite unsettling. This competing process made development of mild reducing conditions for the nitro cyclopropanecarboxylates a necessity. It also precluded the use of Pd-based hydrogenation catalysts since these catalysts were found to be particularly efficient in promoting the hydrogenolyses of cyclopropanes. After rigorous optimization, the reducing conditions involving zinc(0) led to only traces of the compound corresponding to cyclopropane ring opening. In this case, the ring opening presumably arises from radical processes.

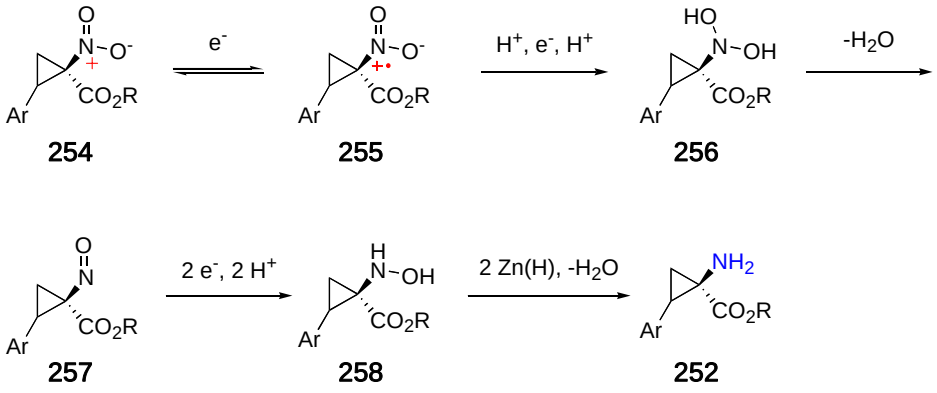
Cyclopropane ring opening in a zinc-mediated reduction is presumably due to the presence of a radical intermediate α– to the cyclopropane ring. The presence of an aromatic group in the 2-position of the cyclopropane is known to greatly accelerate the rate of ring opening, as it favors migration of the radical to the more stabilized benzylic position. For example, a phenyl group in the 2-position of a cyclopropyl methyl radical opens 2500 times faster than the parent compound.[245] In contrast, substituents in the 1-position did not substantially affect the rate of ring opening.[167a]

245.(a) Newcomb, M.; Glen, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275-277. (b) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915-10921.

Additionally, ring opening with cyclopropylaminyl radicals were found to be faster than cyclopropylmethyl radicals.[246]

The mechanism of the nitro reduction likely proceeds as depicted in the cartoons in Scheme 23. The outcome of the reduction largely depends on two factors: whether one or two electrons are transferred from the zinc and the related rates of electron transfer and migration of the radical species to the more stable benzylic position.

Scheme 23. The proposed mechanism of the zinc-mediated reduction of nitro cyclopropanecarboxylates.



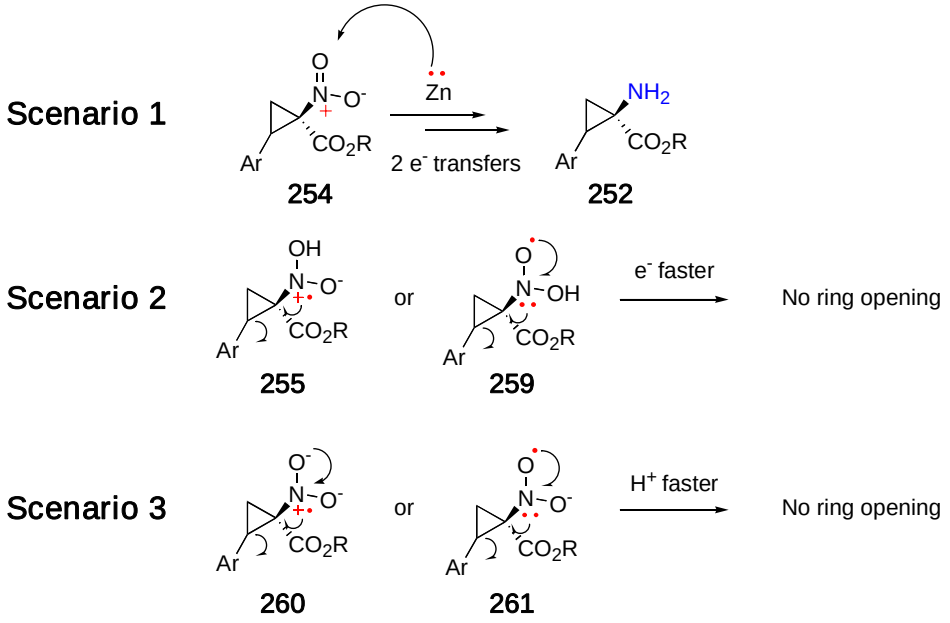
If two electrons are simultaneously transferred from zinc to the nitro group, there will be no radical species involved. The electron transfer to the nitro group will be followed by protonation resulting in formation of a hydroxylamine. Further protonation will result in the loss of water until it is reduced fully to the amine (Scenario 1, Scheme 24). If reduction of the nitro group occurs through a series of one-electron transfers, the potential for cyclopropane ring opening by migration of the radical to the more stable benzylic position is greater. Whether or not ring opening will occur is governed by the relative rates of radical migration versus electron transfer by zinc. It also depends on the relative stabilities of the radical species. For example, upon formation of the hydroxylamine intermediate, the radical can reside on either the nitrogen **255** or on the oxygen atom **259**. Migration of the

246. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States* P. de Mayo, Academic: New York, **1980**, Vol. 1, Chapter 4.

radical to the benzylic position will result in ring opening if the rate of electron transfer is a slow process as depicted (Scenario 2, Scheme 24).

Alternatively, rearrangement of the radical intermediates can occur before proton transfer. If the rate of protonation is slow, then the radicals residing on the nitronate **260** or **261** can migrate to the benzylic position resulting in cyclopropane ring opening (Scenario 3, Scheme 24). This could explain why higher yields were possible in the reductions when stronger acids (eg. HCl) were used and why weaker acids (NH_4Cl, AcOH) led to comparatively lower yields.

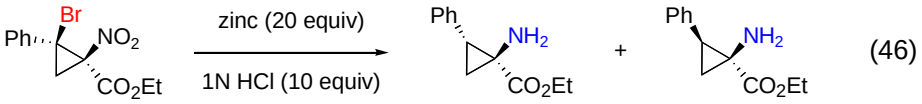
Scheme 24. Mechanism of cyclopropane ring opening during reduction.



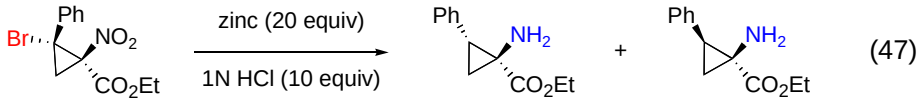
Another intriguing observation made during the reduction of nitro cyclopropane carboxylates substituted with an aromatic group was that a small amount of isomerized product was observed in the crude reaction mixtures. In other words, if diastereomerically pure *E*-isomer was submitted to the reduction conditions, it was possible to obtain 10-15% of the corresponding *Z*-isomer of the amino cyclopropane ester. This baffling result suggests either that the cyclopropane ring is in fact opening and re-closing with a small amount of inversion at the 2-position during the reduction, or that intramolecular hydride abstraction is occurring resulting in

formation of the stabilized benzylic radical as an intermediate. This erosion of diastereomeric purity was not observed for cases involving nitro cyclopropanes derived from indene (**161c**), its homologue (**197i**) or for cases where the substitutions directly attached to the cyclopropane were not aromatic.

Another interesting experiment performed that further illustrates this isomerization process, involved reductions of the two diastereomers of ethyl 2-bromo-2-phenyl-1-nitro cyclopropanecarboxylate (**161f**). In these cases, the diastereomerically pure cyclopropanes were separately submitted to the reduction conditions resulting in the expected dehalogenation[247] and reduction of the nitro group, but also isomerization of the cyclopropane. The *Z*-diastereomer (bromine *cis* to the nitro group) afforded 57% isolated yield of the corresponding dehalogenated amino ester **252a** in a 90:10 *E:Z* ratio (Eq. 46). In contrast, the *E*-diastereomer (bromine *trans* to the nitro group) afforded 33% isolated yield of the corresponding dehalogenated amino ester **252a** in a 60:40 *E:Z* ratio, indicating a large amount of isomerization has occurred (Eq. 47). The low isolated yields are likely a result of increased decomposition during the dehalogenation reduction process.



Z-**161f**

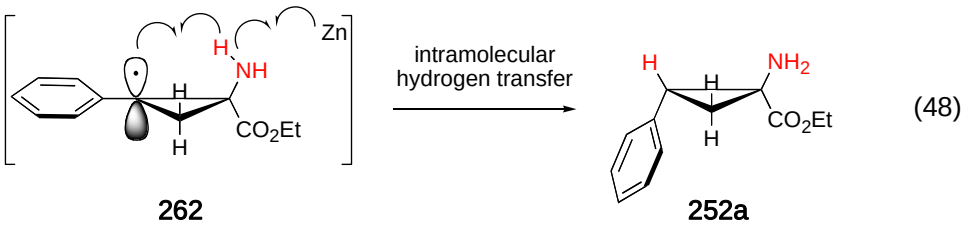


E-**161f**

The isomerization process for the 2-bromocyclopropanes could be a result of stabilization or quenching of a benzylic radical by an intramolecular transfer of hydrogen from the amine *via* intermediate **262**. This could account for the increased

247.(a) Formanovskii, A. A.; Bolesov, I. G. *J. Org. Chem. USSR* **1982**, *18*, 2030-2035. (b) Mehta, G.; Kapoor, S. K. *J. Organomet. Chem*. **1974**, *80*, 213-218.

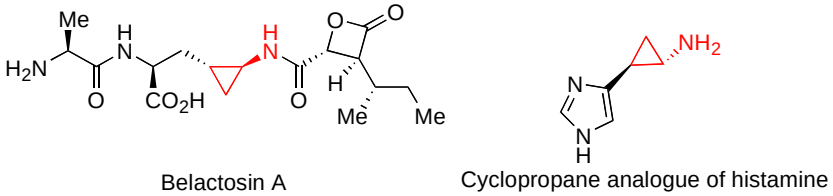
preference for formation of the *E*-diastereomer of the cyclopropane amino ester **252a**. A possible mechanistic scenario is depicted (Eq. 48).



262 **252a**

6.5 Application of the methodology to the expedient synthesis of aryl-substituted cyclopropylamines

Recently, there has been much interest in the preparation of cyclopropylamines due to the presence of this structural motif in a number of biologically active products. Belactosin A (**263**), isolated from a *Streptomyces* metabolite, has potential interest as an antitumor agent.[228b,248] Additionally, cyclopropane analogues of histamine, such as **264**, show significant activities as histamine H_3 receptor agonists (Fig. 26).[249]



Belactosin A

263

Cyclopropane analogue of histamine

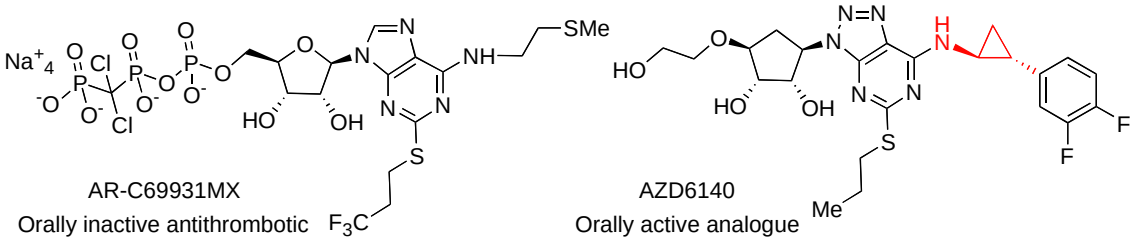
264

Figure 26. Biologically active cyclopropylamines.

Researchers at AstraZeneca also found interesting benefits of cyclopropylamines. The antithrombotic AR-C69931MX (**265**), with its bulky triphosphate group, was not compatible with oral activity. They found that upon replacement of the triphosphate group with a simple alcohol, a series of metabolically stable compounds with

248. Armstrong, A.; Scutt, J. N. *Org. Lett*. **2003**, *5*, 2331-2334.
249. Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem*. **2003**, *46*, 1980-1988.

potential for oral activity resulted. The change initially had an adverse effect on potency but the researchers were able to recover the potency by optimizing other parts of the structure. A key structural alteration was the introduction of a difluorinated phenylcyclopropyl group which substantially boosted potency and stability. The result was AZD6140 (**266**), a potent, selective, orally active $P2Y_{12}$-receptor antagonist that is presently in development (Fig. 27).[250]



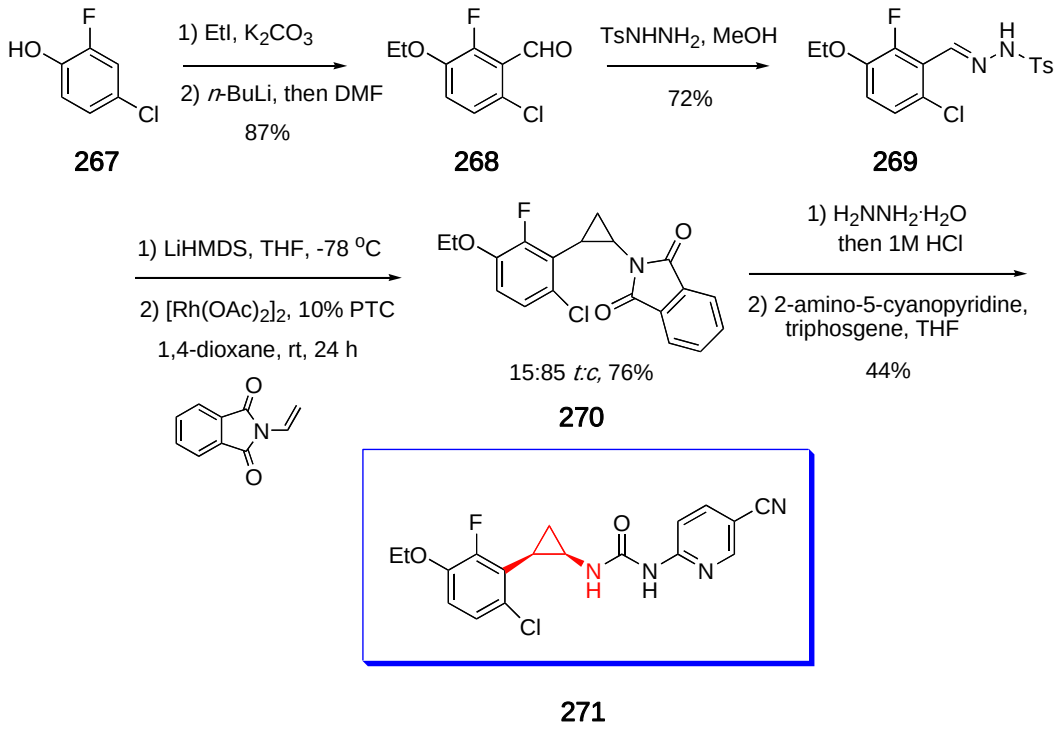
265 **266**

Figure 27. Introduction of cyclopropylamines in antithrombotic therapeutics.

Recently, urea derivatives of aryl cyclopropylamines have emerged as a new class of highly effective HIV-1 reverse transcriptase inhibitors.[251] Aggarwal *et al*. prepared one of the most active members of this class of HIV-1 reverse transcriptase inhibitors **271** *via* a diazo-mediated cyclopropanation where the diazo compound was generated *in situ*. Introduction of the amine was achieved by cyclopropanation of a *N*-vinylphthalimide, which is subsequently deprotected using hydrazine (Scheme 25).

250. Borman, S. *Chem. Eng. News, May 23*, **2003**, *81*, 30-31.
251. Sahlberg, C.; Noréen, R.; Engelhardt, P.; Högberg, M.; Kangasmetsä, J.; Johansson, N. G.; Öberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B.-L.; Unge, T.; Lövgren, S.; Fridborg, K.; Bäckbro, K. *J. Med. Chem*. **1999**, *42*, 4150-4160.

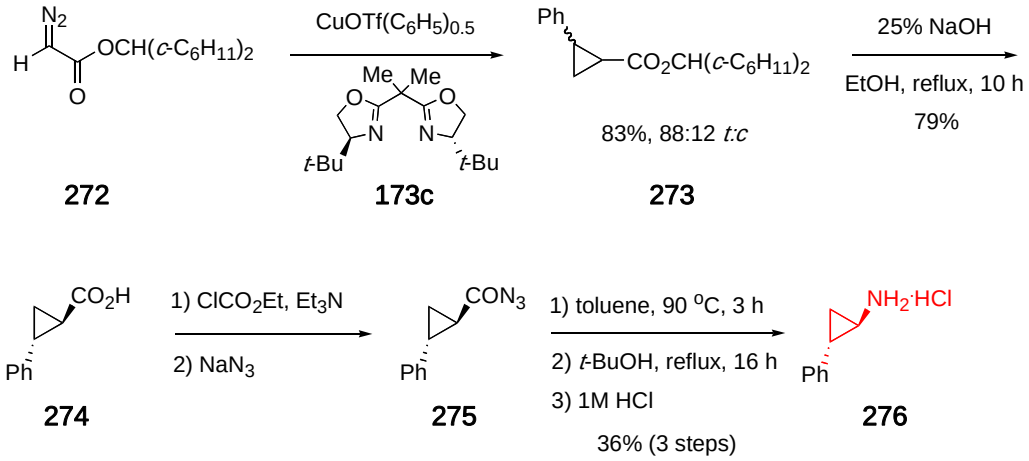
Scheme 25. Synthesis of a *cis*-aryl cyclopropylamine using an *in situ* diazo generation protocol.



trans-2-Phenylcyclopropylamine, tranylcypromine (**276**) is a commercially available pharmaceutical agent for treatment of depression, acting as a monoamine oxidase inhibitor. It is also used in therapy in its racemic form. Aryl cyclopropylamines are generally prepared from the corresponding ester using a three-step sequence. For example, enantiomerically pure tranylcypromine (**276**) was prepared employing a copper(I) triflate catalyzed cyclopropanation of diazoacetate **272** with styrene followed by a Curtius rearrangement for the incorporation of the amine (Scheme 26).[252]

252.(a) Shu, F.- C.; Zhou, Q.-L. *Synth. Commun*. **1999**, *29*, 567-572. See also: (b) Csuk, R.; Schabel, M. J.; v. Scholz, Y. *Tetrahedron: Asymm*etry **1996**, *7*, 3505-3512. (c) Wang, M.-X.; Feng, G.-Q. *Tetrahedron Lett*. **2000**, *41*, 6501-6505.

Scheme 26. Synthesis of enantiomerically pure tranylcypromine (**276**).



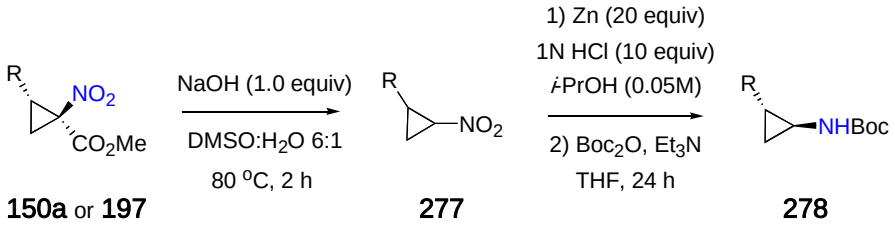
Surprisingly, the preparation of aryl cyclopropylamines *via* reduction of the corresponding nitro cyclopropane has no literature precedence, despite several methods for the preparation of aryl and alkyl nitro cyclopropanes.[227b,253] One method for the synthesis of nitro cyclopropanes **277** includes the decarboxylation of nitro cyclopropanecarboxylates **150** as reported by O'Bannon and Dailey.[60a,254] Accordingly, a slightly modified procedure from that reported by O'Bannon and Dailey was used to prepare a variety of aryl substituted nitro cyclopropanes. It involved the treatment of nitro cyclopropanecarboxylates **150** or **197** with NaOH in aqueous DMSO followed by heating to 80 °C. This resulted in ester hydrolysis followed by decarboxylation. The corresponding nitro cyclopropanes **277** could be isolated in excellent yields following extraction of the reaction mixture with Et_2O.

253. For the synthesis of nitro cyclopropanes see: (a) Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D.; Kalinowski, H.-O. *Helv. Chim. Acta* **1982**, *65*, 137-161. (b) Yu, J.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1992**, *57*, 3757-3759. (c) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267-3276. (d) Russel, G. A.; Makosza, M.; Hershberger, J. *J. Org. Chem.* **1979**, *44*, 1195-1199. (e) Arai, S.; Nakayama, K.; Hatano, K.-; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 9572-9575. (f) Galley, G.; Hübner, J.; Anklam, S.; Jones, P. G.; Pätzel, M. *Tetrahedron Lett.* **1996**, *37*, 6307-6310.

254.(a) O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1990**, *55*, 353-355. (b) O'Bannon, P. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 9244-9245.

Slight erosion of their diastereomeric integrity was observed.[255] These cyclopropanes **277** were then submitted to the standard reduction conditions using zinc dust and HCl and found to efficiently yield the corresponding cyclopropylamines. These amines were protected as their *tert*-butyl carbamates (Boc) for ease of purification (**278**, Table 52)

Table 52. Preparation of aromatic substituted *trans*-cyclopropylamines.



150a or **197** **277** **278**

entry	R-group	decarboxylation yield (%)	*trans:cis* ratio	reduction yield (%)[a]
1	phenyl (**150a**)	91 (**277a**)	81:19	60 (**278a**)
2	1-naphthyl (**197g**)	79 (**277b**)	82:18	66 (**278b**)
3	4-Cl-phenyl (**197a**)	96 (**277c**)	83:17	67 (**278c**)

a) Refers to the isolated yield for 2 steps on reduction of pure *trans*-isomer and protection as its *tert*-butyl carbamate.

Reduction of *trans*-1-nitro-2-phenylcyclopropane (**277a**) afforded the desired cyclopropylamine. This procedure represents an intuitively straightforward, yet novel synthesis of the antidepressant (±) transcycloamine (**276**).[256] Reductions involving nitro cyclopropanes **277b-c** also proceeded with similar efficiencies affording ≥ 66 % for the two-step sequence (Table 52).

255. The *cis* and *trans*-isomers of the corresponding nitro cyclopropanes can be easily separated by column chromatography. Only the pure *trans*-isomers were submitted to the reduction conditions.

256. A monoaminooxidase inhibitor (MAOI) tranylcypromine (Parnate®, Jatrosom® N) is an oral MAOI-type antidepressant used to treat major depression in patients who have not responded to other antidepressant therapies.

6.6 Conclusions

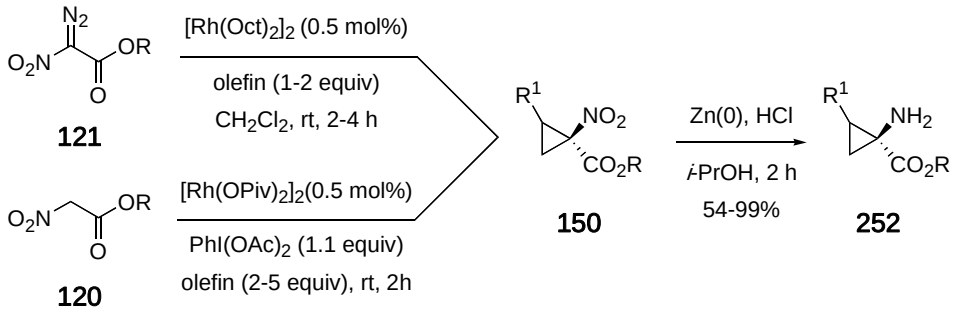
The development of a novel reduction protocol for nitro cyclopropane carboxylates allows for the expedient preparation of a structurally diverse series of cyclopropane α-amino acids as illustrated in Tables 49-51. Furthermore, the reduction conditions developed (zinc-HCl) tolerate the presence of sensitive functionalities on the cyclopropane ring. As such, the synthesis of cyclopropane α-amino acids containing these functionalities would not be possible using previously available methods. Both the cyclopropanation and reduction procedures are expedient (requiring only 2 h each), thus allowing the rapid preparation of cyclopropane α-amino esters. This is in stark contrast to most Pd-catalyzed reductions of nitro cyclopropanes which typically require > 24 h.

Another noteworthy achievement was the reduction of nitro cyclopropane carboxylates and nitro cyclopropanes containing aromatic substituents. This reduction protocol, in combination with the cyclopropanation methodologies developed for the synthesis of nitro cyclopropanecarboxylates (Chapters 3 and 5), represents an attractive synthetic strategy for the preparation of symmetric or racemic cyclopropane α-amino acids (ACCs). Furthermore, commercially available α-nitroesters and olefins are used as starting materials.

Presently, the preparation of enantiomerically enriched nitro cyclopropane carboxylates up to 72% ee is possible. This area is currently under investigation and the design of new chiral catalysts will ultimately lead to higher levels of asymmetric induction for the cyclopropanation reaction. In the meantime, it should be mentioned that a variety of methods exist for the resolution of cyclopropane α-amino acids allowing access to enantiomerically pure materials.[18b,24,39,257] Scheme 27 summarizes the optimized conditions developed for the cyclopropanation and reduction methodologies.

257.(a) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. H.; *Tetrahedron Lett*. **1985**, *26,* 485-488. (b) Kimura, H.; Stammer, C. H.; *J. Org. Chem*. **1983**, *48*, 2440-2441.

Scheme 27. Synthesis of amino cyclopropanecarboxylates: summary of preparative methods.



The difficulties encountered during the reductions of the nitro cyclopropane carboxylates gave many valuable insights into the reactivity of these highly activated cyclopropanes. The ease by which the nitro cyclopropylcarbonyls undergo ring-opening reactions with a variety of different nucleophiles, or rearrange to give the corresponding isoxazoline *N*-oxides was further examined. One cannot neglect the fact that cyclopropanes also serve as useful synthetic intermediates in synthesis. As such, Chapters 7 and 8 will focus on the use of various nitro cyclopropylcarbonyls as synthons.

CHAPTER 7

Synthesis of Densely Substituted Dihydropyrroles and Pyrroles

7.1 Introduction and precedence

There has been a tremendous emphasis placed on the applications of cyclopropanes as synthons in organic chemistry in the past several decades.[258] Depending on the functionalities present on the cyclopropane ring, fragmentation of these three-membered carbocycles represents an extremely useful method for the construction of a wide variety of carbon skeletons. These processes benefit from a potent thermodynamic driving force, derived from relief of ring strain of the cyclopropane.[258b]

Of particular interest to our research was the synthetic potential of doubly activated cyclopropanes. This field of research has also inspired other researchers to develop methodologies for the preparation of complex synthetic[259] and natural products.[260] Many possible outcomes result upon treatment of these doubly activated cyclopropanes with various nucleophiles. These include anionic polymerizations,[238] intermolecular aminolysis with secondary amines,[261] *spiro* and *fused* modes of intramolecular ring openings[262] and ring-opening coupling reactions,[263] to mention a few.

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258. For reviews on the chemistry of related cyclopropanes see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151-1196. (b) Wong, H. N. C.; Hon, M.- Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev*. **1989**, *89*, 165-198. (c) Rappoport, Z. In *The chemistry of the Cyclopropyl Group*, John Wiley & Sons: Toronto; **1987**, 809-878.

259.(a) Palucki, M.; Um, J. M.; Yasuda, N.; Conlon, D. A.; Tsay, F.-R.; Hartner, F. W.; Hsiao, Y.; Marcune, B.; Karady, S.; Hughes, D. L.; Dormer, P. G.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5508-5516. (b) Lim, Y.-H.; McGee, K. F. Jr.; Sieburth, S. M. *J. Org. Chem*. **2002**, *67*, 6535-6538.

260. See for example: (a) Fischer, C.; Meyers, C.; Carreira, E. *Helv. Chim. Acta* **2000**, *83*, 1175-1181. (b) Taber, D. F.; Krewson, K. R.; Raman, K.; Rheingold, L. *Tetrahedron Lett.* **1984**, *25*, 5283-5286. (c) Danishefsky, S.; Dynak, J.; Hatch, E.; Yamamoto, M. *J. Am. Chem. Soc.* **1974**, *96*, 1256-1259.

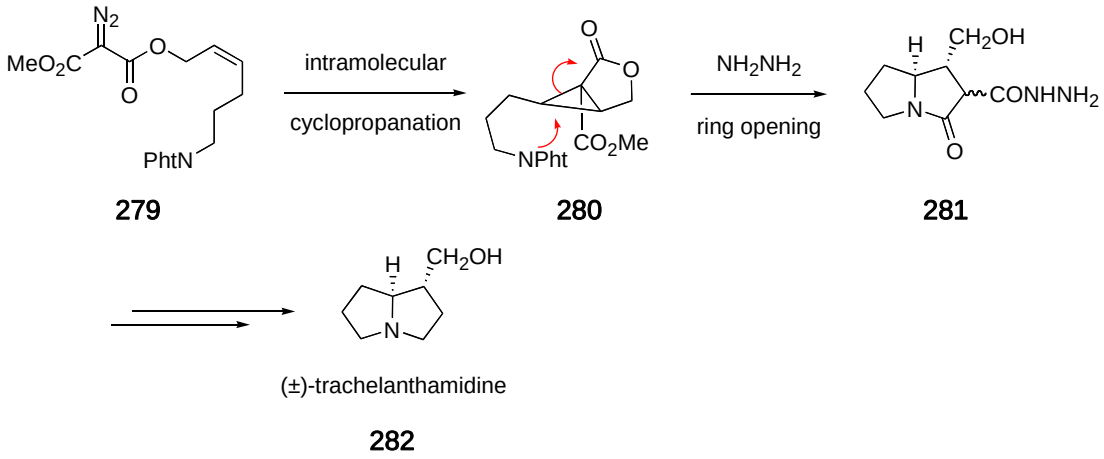
261. Blanchard, L. A.; Schneider, J. A. *J. Org. Chem*. **1986**, *51*, 1372-1374.

262. Danishefsky, S. *Acc. Chem. Res*. **1979**, *12*, 66-72.

263. Ma, S.; Zhang, J.; Cai, Y.; Lu, L. *J. Am. Chem. Soc*. **2003**, *125*, 13954-13955.

The addition of nucleophiles to doubly activated cyclopropanes can be viewed as a homologous (or 1,5) version of the classical Michael reaction. Its synthetic utility can be illustrated in an elegant example of an intramolecular *spiro* mode of nucleophilic ring opening.[264] This approach was applied to the total synthesis of (±)-trachelanthamidine (**282**) reported by Danishefsky *et al*.[265] The key synthetic step involved the deprotection of a phthalimide protected amine **280** triggering an intramolecular ring opening of the doubly activated cyclopropane. Ring opening was followed by condensation of the resulting secondary amine with the ester, affording a bicyclic lactam **281**. This bicyclic lactam **281** could then be easily transformed to the desired (±)-trachelanthamidine (**282**) with complete retention of the initial stereochemical integrity of the cyclopropane (Scheme 28).

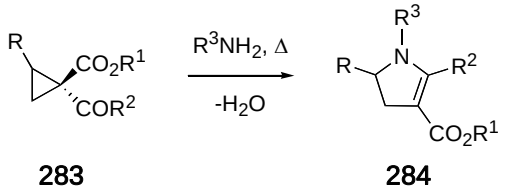
Scheme 28. Total synthesis of (±)-trachelanthamidine *via* an intramolecular ring opening of a doubly activated cyclopropane.



Doubly activated cyclopropanes have also been used as synthons for the regiospecific synthesis of dihydropyrroles. Lhommet *et al*. found that treatment of 1-acyl-cyclopropanecarboxylic esters **283** with a primary amine at 140 °C led to the isolation of the corresponding dihydropyrroles **284** in low to modest yields of 25-72%

264. Danishefsky, S.; Rovnyak, G. *J. Org. Chem.* **1975**, *40*, 114-115.
265. Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc*. **1977**, *99*, 4783-4788.

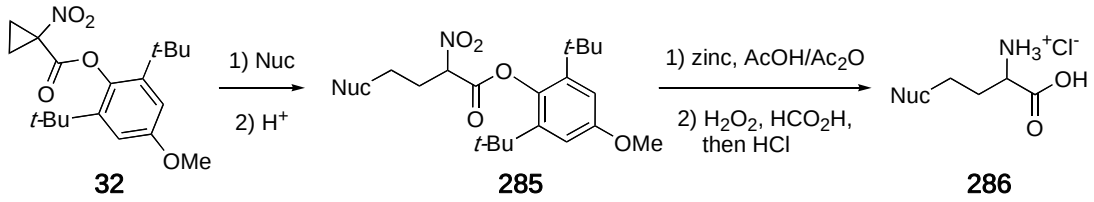
(Eq. 49).[266] These biologically active dihydropyrroles were tested for their insecticidal properties against termites *Reticulitermes (lucifugus) grassei*.[266b]



283 **284** (49)

There have been few reports involving the use of nitro cyclopropanecarbonyls as synthons. They have served as precursors for the preparation of nitro cyclopropanes *via* decarboxylation as mentioned in Chapter 6. Their synthetic potential has also been examined in ring opening reactions.[81d] Seebach *et al*. found that ring opening of the highly activated cyclopropane **32** with a variety of C-, N-, O- and S-nucleophiles in DMF or alcohol gave excellent yields of 2-nitrobutanoates **285** with the newly introduced substituent in the 4-position (Scheme 29). Nitro reduction and oxidative cleavage of the ester led to the preparation of γ-substituted α-amino acids **286** in excellent yields (Scheme 29).[236,240]

Scheme 29. The synthesis of γ-substituted α-amino acids from nitro cyclopropanes.



32 **285** **286**

266.(a) Jacoby, D.; Célérier, J. P.; Haviari, G.; Petit, H.; Lhommet, G. *Synthesis* **1992**, 884-887. (b) Célérier, J. P.; Haddad, M.; Jacoby, D.; Lhommet, G. *Tetrahedron Lett.* **1987**, *28*, 6597-6600.

7.1.1 Objectives

To the best of our knowledge, the research involving the use of nitro cyclopropanecarbonyls as synthons was not further pursued beyond these few examples. Methodologies described in previous chapters have illustrated that substituted nitro cyclopropanecarbonyls are readily available *via* diazo- or iodonium ylide-mediated cyclopropanation reactions. Therefore, as a logical extension of this research, the use of nitro cyclopropanecarbonyls as potentially useful synthons was also examined.

Inspired by the findings of Lhommet *et al*., densely substituted dihydropyrroles and pyrroles represent attractive synthetic targets due to their prevalence in a tremendous range of natural products and biologically active molecules.[267] Furthermore, the classic condensation reactions devised for the synthesis of these five-membered aza-heterocycles, including Hantzsch[268] and Paal-Knoor[269] procedures, are often limited by their efficiency, functional group compatibility, regiospecificity or the variety of substituents that can be introduced around the pyrrole.

In recent years, there has been renewed interest in the development of novel strategies for the synthesis of pyrroles including [3+2] cycloadditions between nitriles and donor-acceptor cyclopropanes,[270] multi-component coupling reactions[271] and dimerization of enamine-esters,[272] to mention a few. The use of doubly activated cyano and nitro cyclopropanecarbonyls should also be suitable synthons for the preparation of pyrroles. In particular, a method was desired that would allow access

267. *Pyrroles, Part II*; Jones, R. A., Ed.; Wiley: New York, 1992.
268. Hantzsch, A. *Ber*. **1890**, *23*, 1474-1483.
269.(a) Paal, C. *Ber*. **1885**, *18*, 367-371. (b) Knorr, L. *Ber*. **1885**, *18*, 299-311.
270. Yu, M.; Pagenkopf, B. L. *Org. Lett*. **2003**, *5*, 5099-5101.
271. For Pd-catalyzed couplings see: (a) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc*. **2004**, *126*, 468-469. For microwave assisted couplings see: (b) Ranu, B. C.; Hajra, A.; Jana, U. *Synlett* **2000**, 75-76.
272. Zhang, P.-F.; Chen, Z.-C. *Synth. Commun*. **2001**, *31*, 1619-1624.

to the synthetically challenging non-symmetrical tetrasubstituted pyrroles. These could be prepared upon oxidative aromatization[273] of the dihydropyrroles.

The 4-nitropyrrole skeleton is a structural subunit found within many biologically active products including pharmaceuticals, fungicides and herbicides.[274] This subunit also exists in several naturally occurring examples of the pyrrolomycin class of antibiotics.[275] For example, tri- and tetrasubstituted 4-nitropyrrole cores are present in the pyrrolomycin A (**287**) and B (**288**) antibiotics, respectively (Fig. 28).[276] 4-Nitropyrroles can also be used as synthetic precursors to the highly coveted 4-aminopyrroles through reduction of the nitro group.[277] 4-Aminopyrroles also serve as structural subunits in a large number of biologically active products. [278]

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273. For the synthesis of symmetric 4-nitropyrroles *via* oxidative rearomatization of 4-nitropyrrolidines see: Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem*. **2000**, 903-912.

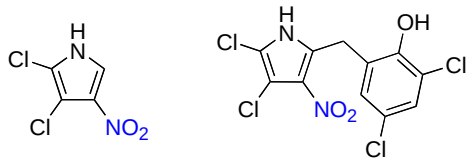
274.(a) Ono, N.; Muratani, E; Ogawa, T. *J. Heterocyclic Chem*. **1991**, *28*, 2053-2055. (b) Niskiwaki, N.; Nakanishi, M.; Hida, T.; Miwa, Y.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *J. Org. Chem*. **2001**, *66*, 7535-7538. (c) Ono, N.; Muratani, E; Fumoto, Y.; Ogawa, T.; Tazima, K. *J. Chem. Soc., Perkin Trans. 1,* **1998**, 3819-3824.

275. First isolation of members of this class of antibiotics see: (a) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiotics* **1981**, *34*, 1366-1368. (b) Koyama, M.; Kodama, Y.; Tsuruoka, T.; Ezaki, N.; Niwa, T.; Inouye, S. *J. Antibiotics* **1981**, *34*, 1569-1576. (c) Koyama, M.; Ezaki, N.; Tsuruoka, T.; Inouye, S. *J. Antibiotics* **1983**, *36*, 1483-1489.

276. Koyama, M.; Ohtani, N.; Kai, F.; Moriguchi, I.; Inouye, S. *J. Med. Chem*. **1987**, *30*, 552-562.

277.(a) Lee, M.; Coulter, D. M.; Lown, J. W. *J. Org. Chem*. **1988**, *53*, 1855-1859. (b) Almerico, A. M.; Cirrincione, G.; Aiello, E.; Dattolo, G. *J. Heterocyclic Chem*. **1989**, *26*, 1631-1633. (c) Aiello, E.; Dattolo, G.; Cirrincione, G. *J. Chem. Soc., Perkin Trans. I* **1979**, 1-3.

278. See for example: (a) Marcotte, F.-A.; Lubell, W. D. *Org. Lett*. **2002**, *4*, 2601-2603. (b) Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1981**, *46*, 3492-3497. See also references cited therein.



Pyrrolomycin A Pyrrolomycin B

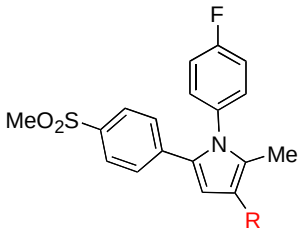
287 **288**

Figure 28. Examples of the pyrrolomycin class of antibiotics containing a 4-nitropyrrole core.

Although electrophilic substitution is a powerful method for the introduction of nitro groups *via* nitration, α-nitration is predominant in the case of pyrrole rings. If nitration in the 4-position is desired, then the 2-position must be occupied by an electron-withdrawing group,[274b] which inevitably restricts the structural diversity of the pyrroles that can be prepared. Therefore, alternative methods for the introduction of the nitro group into the pyrrole ring can allow expedient access to compounds that, otherwise, would be synthetically challenging to prepare.

The use of doubly activated cyclopropanes, such as 1-cyano-cyclopropane carbonyls, could also serve as valuable synthetic precursors for preparation of a variety of tetrasubstituted pyrroles. Tetrasubstituted 4-cyanopyrrole derivatives have been tested as nonsteroidal anti-inflammatory drugs (NSAIDS). In particular, several derivatives were found to have modest potencies as COX-2 inhibitors.[279] For example, the tetrasubstituted 4-cyanopyrrole **289a** was found to be fairly potent with an IC_{50} of 0.75 μM (COX-2). Its selectivity for the COX-2 enzyme is also noteworthy since its potency for COX-1 is IC_{50} of >100 μM. In contrast, the 4-bromo derivative **289b** has higher potency for the COX-2 enzyme, but displayed no selectivity for the two enzymes (Fig. 29).[279a] Furthermore, functional group transformations possible with the cyano substitution lend it additional synthetic value.

279.(a) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1619-1633. (b) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem*. **1995**, *38*, 3895-3901. (c) Wilkerson, W. W.; Galbraith, W.; Gans-Brangs, K.; Grubb, M.; Hewes, W. E.; Jaffee, B.; Kenney, J. P.; Kerr, J.; Wong, N. *J. Med. Chem*. **1994**, *37*, 988-998.

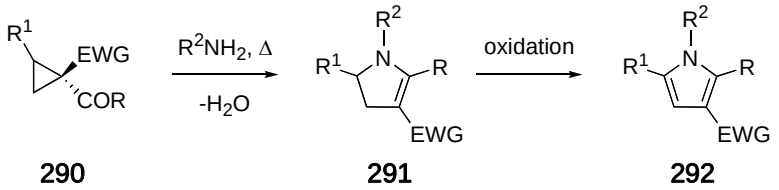


289a R = CN, IC_{50} 0.75 μM
289b R = Br, IC_{50} 0.02 μM

Figure 29. Biologically active tetrasubstituted pyrroles as NSAID COX-2 inhibitors.

The cyclopropanation methodologies developed using α-nitro-α-diazocarbonyls or the *in situ* generation of iodonium ylides allows for the expedient preparation of a variety of doubly activated cyclopropanes. Therefore, our strategy for the preparation of dihydropyrroles **291** would involve the use of these substituted cyclopropyl ketones **290** as synthons. Oxidation of these dihydropyrroles would then allow access to the desired densely substituted pyrroles (**292**, Scheme 30).

Scheme 30. Synthetic strategy for the synthesis of densely functionalized pyrroles.



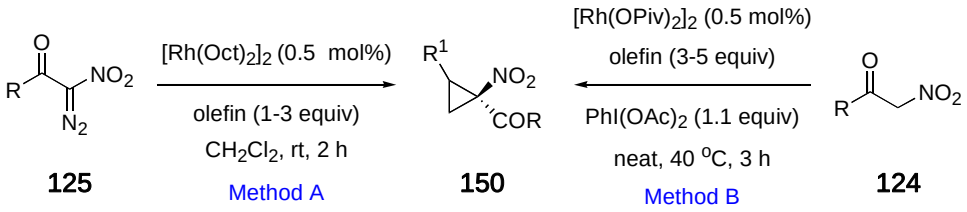
290 **291** **292**

7.2 Synthesis of dihydropyrroles using doubly activated cyclopropanes

7.2.1 Synthesis of 4-nitro-dihydropyrroles

A structurally diverse series of 1-nitro-1-ketocyclopropane synthons could be prepared using the two previously developed cyclopropanation methodologies (Table 53).

Table 53. Preparation of a structurally diverse series of substituted 1-nitro-1-ketocyclopropanes.



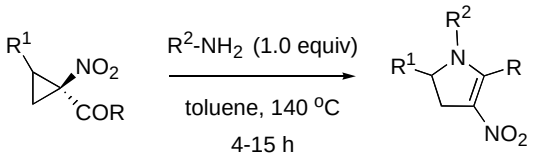
entry	product	R	R^1	method	yield (%)[a]	*E:Z* ratio
1	**150d**	Me	Ph	A	77	78:22
2	" "	" "	" "	B	59[b]	78:22
3	**150e**	*n*-propyl	Ph	A	74	81:19
4	" "	" "	" "	B	62[b]	88:12
5	**150f**	Ph	Ph	A	74	16:84
6	" "	" "	" "	B	75	10:90
7	**150j**	*c*-C_3H_5	Ph	A	69	76:24
8	" "	" "	" "	B	73	74:26
9	**151**	Me	4-F-Ph	A	63[c]	73:27
10	**150k**	Me	1-naphthyl	A	52[c]	79:21
11	**150l**	Me	phenethyl	A	36	53:47

a) Isolated yields after column chromatography. b) Stirred at room temperature for 20 h. c) 1.0 equiv of olefin was used.

A variety of 1-nitro-1-ketocyclopropanes **150** were prepared in respectable yields. When stoichiometric amounts of the olefin and 1-diazo-1-nitro-propan-2-one (**125a**) were used, modest yields of the corresponding cyclopropanes could still be obtained (Table 53, entries 9 and 10). These cyclopropanation reactions were not repeated using method B as higher loadings of the costly olefin are required for acceptable reaction yields. The cyclopropanation reaction with 4-phenyl-1-butene proved to be sluggish with 1-diazo-1-nitro-propan-2-one (**125a**), resulting in a disappointing 36% isolated yield of the corresponding cyclopropane (**150l**, Table 53, entry 11).

E:Z mixtures of 1-nitro-1-ketocyclopropanes **150** were then treated with a variety of primary amines at elevated temperatures. Satisfyingly, the corresponding 4-nitro-dihydropyrroles **293** were isolated in modest to excellent yields allowing efficient preparation of a number of derivatives (Table 54).

Table 54. Preparation of tetrasubstituted 4-nitro-dihydropyrroles by treatment of 1-nitro-1-ketocyclopropanes with primary amines.



150 **293**

entry	product	R	R^1	R^2	yield (%)[a]
1	**293a**	Me	Ph	Ph	91
2	**293b**	*n*-propyl	Ph	Ph	78
3	**293c**	Ph	Ph	Ph	91
4	**293d**	*c*-C_3H_5	Ph	Ph	79
5	**293e**	*c*-C_3H_5	Ph	4-MeO-Ph	97
6	**293f**	Me	Ph	allyl	48
7	**293g**	Me	Ph	benzyl	35
8	**293h**	Me	Ph	*(R)*-(+)-α-methylbenzyl	84[b]
9	**293i**	Me	Ph	*t*-Bu	47
10	**293j**	Me	Ph	4-Cl-Ph	95
11	**293k**	Ph	Ph	4-MeO-Ph	96
12	**293l**	Me	4-F-Ph	Ph	99
13	**293m**	Me	1-naphthyl	Ph	84
14	**293n**	Me	phenethyl	Ph	18[c]

a) Isolated yields after column chromatography. b) A 55:45 mixture of the 2 diastereomers were isolated. c) The remainder of the mass was unreacted cyclopropane **150l.**

The ketone substituents (R) could be easily modified with little influence on the yields of the corresponding dihydropyrroles **293** when aniline was used as the primary amine reaction partner (Table 54, entries 1-4). A cyclopropyl group as the R-substituent gave exclusive dihydropyrrole **293d-e** formation resulting from reaction with the doubly activated cyclopropane (Table 54, entries 4 and 5). Variation of the primary amine component (R^2NH_2) demonstrated that aniline and its derivatives generally gave the highest yields (Table 54, entries 5-11). Reactions with volatile amines, such as allyl and *tert*-butylamine, were conducted in sealed tubes and modest yields were possible (Table 54, entries 6 and 7). Amines that were non-nucleophilic in nature, such as carbamates, were completely unreactive in the dihydropyrrole

formation reaction. In these cases, the starting materials could be recovered quantitatively after heating for 15 h at 140 ^{o}C.

The influence of the nature of the 2-substitution (R^1 on the cyclopropane ring) on reaction yields was also examined. The yields of the corresponding dihydropyrroles were found to be respectable when aromatic groups were used (Table 54, entries 12 and 13). However, the cyclopropane derived from 4-phenyl-1-butene **150l** (R^1 = phenethyl) exhibited reduced rates of reaction. In this case, the cyclopropane starting material **150l** could be recovered unaltered from the crude reaction mixture. This would suggest that aromatic substituents serve to activate the cyclopropanes, allowing rearrangement to the corresponding dihydropyrroles.

It is also important to mention that the dihydropyrroles **293** were formed in a regiospecific manner. ^{1}H NMR analysis of the crude reaction mixtures could not detect traces of any regioisomers formed in the reaction. Moreover, the rates of consumption of the *E*- and *Z*-diastereomers of the nitro cyclopropanes **150** were found to be quite similar, indicating that these mixtures of cyclopropanes are tolerated. Finally, this strategy enabled the synthesis of 4-nitro-dihydropyrroles **293** in a highly modular fashion allowing the preparation of a large number of derivatives in an expedient manner. This modular construction is attractive for library creation with applications in medicinal chemistry.

The regiospecificity of the dihydropyrrole formation was confirmed by X-ray crystallography of 4-nitro-1,2-diphenyl-5-propyl-2,3-dihydro-1*H*-pyrrole (**293b**, Fig. 30). Crystals of dihydropyrrole **293b** were grown from a 20% EtOAc/Hexane solution upon slow evaporation of the solvent. They crystallized in a monoclinic unit cell.[280]

280. See Appendix V for the complete structural data concerning the crystal structure of 4-nitro-1,2-diphenyl-5-propyl-2,3-dihydro-1*H*-pyrrole (**293b**).

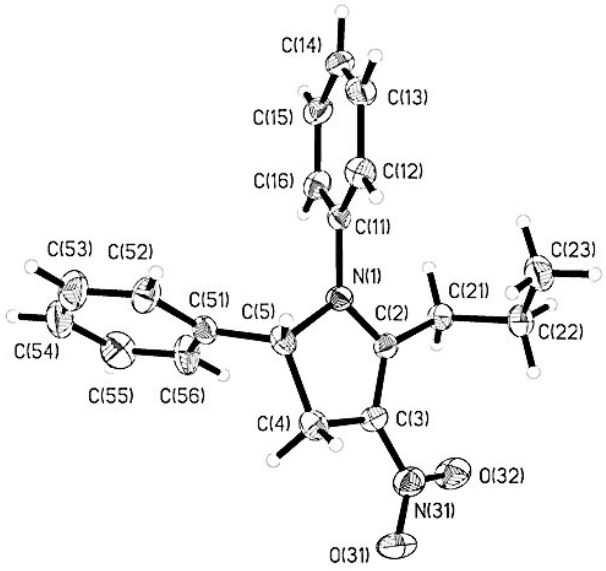
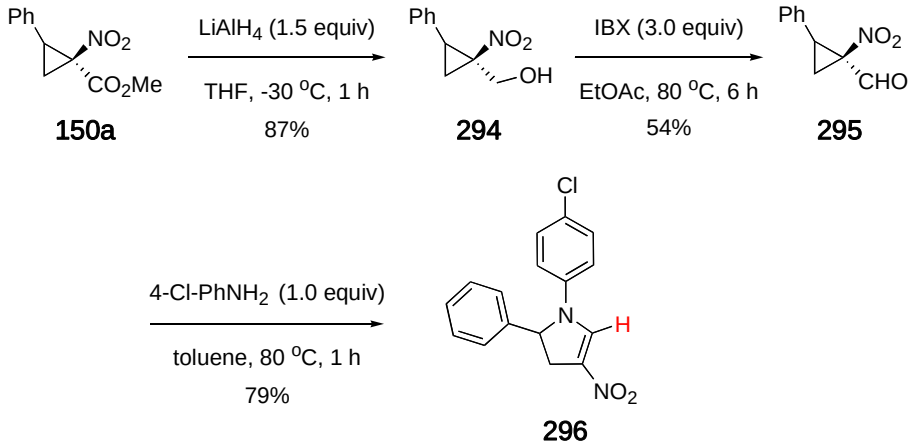


Figure 30. ORTEP representation of the crystal structure of 4-nitro-1,2-diphenyl-5-propyl-2,3-dihydro-1*H*-pyrrole (**293b**).

In order to access trisubstituted 4-nitro-dihydropyrroles **296** (R = H), 1-nitro-2-phenyl-cyclopropanecarbaldehyde (**295**) was prepared through reduction of cyclopropane **150a** with $LiAlH_4$.[81d] Oxidation of the (1-nitro-2-phenyl-cyclopropyl)-methanol (**294**) to the corresponding aldehyde **295** was achieved in 54% yield using IBX as an oxidant. Treatment of this aldehyde **295** with 4-chloroaniline for 1 h at 80 ^{o}C afforded the desired 4-nitro-1-(4-chlorophenyl)-2-phenyl-2,3-dihydro-1*H*-pyrrole (**296**) in 79% yield (Scheme 31).

Scheme 31. Synthesis of a trisubstituted 4-nitro-dihydropyrrole.

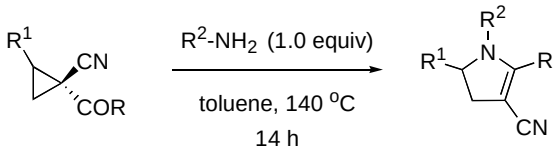


7.2.2 Synthesis of 4-cyano-dihydropyrroles

Given that the preparation of 1-cyano-1-ketocyclopropanes **237** was also found to be possible using the *in situ* generated iodonium ylide method,[281] they were tested as reaction partners for the synthesis of 4-cyano-dihydropyrroles. Accordingly, the 1-cyano-1-ketocyclopropanes **237** were treated with various primary amines and heated to 140 °C in toluene. Satisfyingly, the desired 4-cyano-dihydropyrroles **297** could be isolated (Table 55).

281. See Chapter 5, Section 5.3.

Table 55. Preparation of densely substituted 4-cyano-dihydropyrroles.



237 **297**

entry	product	R	R^1	R^2	yield (%)[a]
1	**297a**	styryl	Ph	4-Cl-Ph	82
2	**297b**	Bn	Ph	4-Cl-Ph	91
3	**297c**	Ph	Ph	Ph	97
4	**297d**	Ph	Ph	4-Cl-Ph	99
5	**297e**	4-MeO-Ph	Ph	Ph	77

a) Isolated yields after column chromatography.

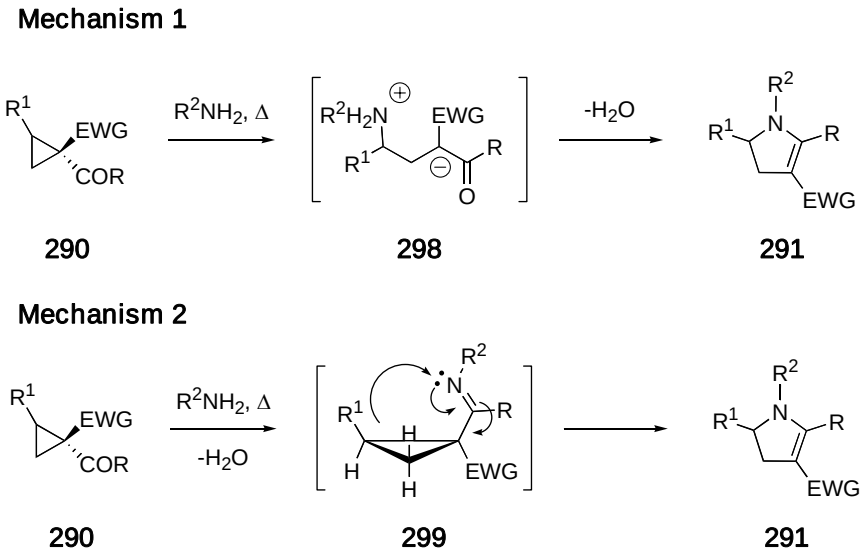
Excellent yields were observed for the five examples tested involving 1-cyano-1-ketocyclopropanes **237** as substrates. Aniline or 4-chloroaniline (R^2 = Ph, 4-Cl-Ph) were used as the primary amine component and the cyclopropanes tested were all derived from styrene (R^1 = Ph). The 4-cyano-dihydropyrroles **297** generally precipitated from the reaction mixtures upon formation and could be easily purified using column chromatography on silica gel in a similar fashion to the 4-nitro-dihydropyrroles **293**.

7.2.3 Mechanism of dihydropyrrole formation

One can envision two possible mechanistic scenarios for the formation of dihydropyrroles upon treatment of doubly activated cyclopropanes with a primary amine. The mechanism could involve either nucleophilic ring opening of the cyclopropane by the primary amine followed by intramolecular dehydration (mechanism 1, Scheme 32), or imine formation with the ketone followed by a cyclopropyl iminium ion rearrangement (mechanism 2, Scheme 32).[282]

282. This rearrangement is usually promoted by the presence of an acid to form the necessary iminium ion. Since no acid was added, it is depicted in neutral form.

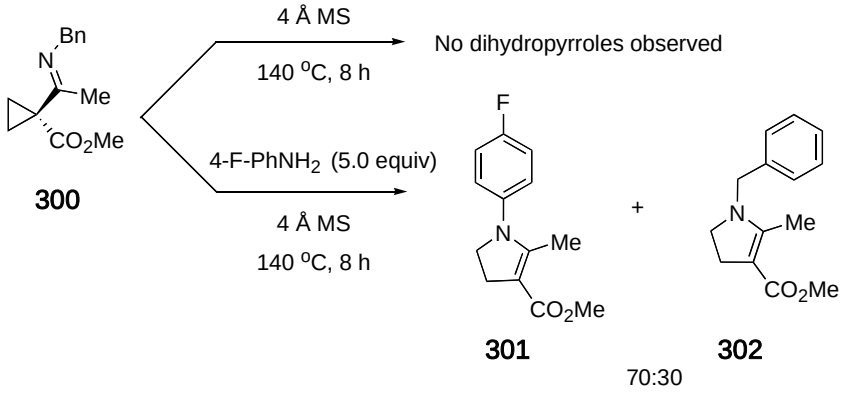
Scheme 32. Two possible mechanisms proposed for the formation of dihydropyrroles.



The cyclopropyl iminium ion rearrangement (mechanism 2, Cloke's rearrangement)[283] was ruled out by Lhommet *et al*. for cases involving 1-acyl-cyclopropanecarboxylic esters (Eq. 49).[266b] This conclusion was drawn after heating imine **300** for 8 h at 140 ^{o}C in the presence of molecular sieves (Scheme 33). These conditions did not lead to the formation of dihydropyrrole **302**.[266b] However, dihydropyrroles **301** and **302** could be isolated when the cyclopropyl imine **300** was treated with an excess of primary amine (5.0 equiv) under the same conditions. The proportions of the dihydropyrroles obtained depended on the nature of the amines used (Scheme 33). A *trans*-imination process was invoked to explain why both of the amines were found to be separately incorporated into the dihydropyrrole products.

283. Cloke, J. B. *J. Am. Chem. Soc*. **1929**, *51*, 1174-1187.

Scheme 33. Mechanistic studies by Lhommet *et al*.[266b]



The presence of acid in Cloke's rearrangement (mechanism 2, Scheme 32) presumably serves as a nucleophile to affect ring opening of the activated cyclopropane. Kuduk *et al*. have recently proposed a ring opening mechanism catalyzed by iodide in thioimidate cyclopropane rearrangements.[284] However, in our case, the absence of nucleophiles other than primary amines would suggest that mechanism 1 (Scheme 32) is the process that leads to dihydropyrrole formation. Thus, the primary amine reacts with the highly activated cyclopropane *via* a homologous (or 1,5) Michael reaction followed by an intramolecular dehydration as demonstrated by Danishefsky.

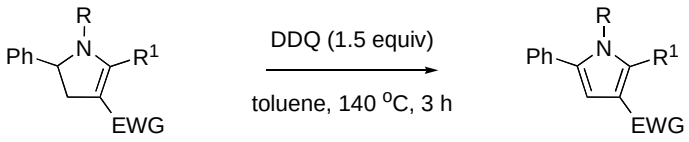
It should be mentioned that the presence of a nucleophile or an acid in catalytic quantities could possibly change the mechanistic course of this reaction.[285] For example, Jabin *et al*. observed dihydropyrrole formation upon heating α-cyclopropyl imines in the presence of catalytic quantities of trifluoroacetic acid.[286] Wasserman and Dion also observed that catalytic quantities of acid also successfully promoted dihydropyrrole formation among an assortment of dicyclopropylketimines.[287]

284. Kuduk, S. D.; Ng, C.; Chang, R. K.; Bock, M. G. *Tetrahedron Lett*. **2003**, *44*, 1437-1440.
285. A more detailed discussion concerning this idea will be covered in Chapter 8.
286. Jabin, I.; Monnier-Benoit, N.; Le Gac, S.; Netchitaïlo, P. *Tetrahedron Lett*. **2003**, *44*, 611-614.
287. Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett*. **1983**, *24*, 3409-3412.

Grotjahn and Vollhardt successfully applied this rearrangement to the synthesis of the pentacyclic alkaloid γ-lycorane.[288]

7.3 Oxidation of dihydropyrroles to pyrroles

Finally, the 4-nitro- and 4-cyano-dihydropyrroles **291** (EWG = NO_2, CN) could be efficiently oxidized to the desired pyrroles **292** using DDQ in refluxing toluene (Eq. 50).[289] Dell'Erba *et al*. reported a similar method for the oxidative aromatization of symmetrical aryl-substituted 4-nitropyrrolidinines.



(50)

291 **292**

292a EWG = NO_2 R, R^1 = Ph 77%

292b EWG = CN R,R^1 = Ph 94%

292c EWG = CN, R = 4-Cl-Ph, R^1 = styryl 91%

Since the solvent and reaction temperatures are exactly the same as those used for the preparation of the dihydropyrroles, a "one pot" procedure was envisioned. Accordingly, the above examples were submitted to a "one pot" procedure and afforded yields ranging from 75-80% for two steps starting from the doubly activated cyclopropanes.

7.4 Conclusions

An expedient method for the synthesis of a variety of 4-nitro- and 4-cyano-dihydropyrroles has been developed. This research serves as an extension to the reaction scope published by Lhommet *et al.* in their dihydropyrrole synthesis (Eq. 49).[266] The newly developed methodology relies on the readily available 1-nitro- or 1-

288. Grotjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579-605.
289. Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc*. **2003**, *125*, 4692-4693.

cyano-1-ketocyclopropane as synthons for the modular construction of these dihydropyrroles. Oxidation to the corresponding pyrroles upon treatment with DDQ in refluxing toluene is also possible in excellent yields (Eq. 50). This method represents a straightforward route to access a wide variety of densely substituted dihydropyrroles and pyrroles, which could have potentially interesting biological activities.

Some limitations were encountered in terms of reaction scope. For example, nucleophilic primary amines, such as substituted anilines, generally gave excellent yields of the dihydropyrroles while reaction yields declined when non-nucleophilic amines were used. Aromatic groups directly attached to the cyclopropane ring were also found to be necessary for respectable reaction yields. Fortunately, modifications of the ketone substitution were not found to significantly influence reaction yields.

This method allows the regiospecific synthesis of densely substituted symmetrical and unsymmetrical dihydropyrroles and pyrroles. The reaction is chemospecific as the reaction occurs preferentially with doubly activated cyclopropanes in the presence of mono-activated cyclopropanes under the standard reaction conditions. Furthermore, the synthesis is atom-economical as stoichiometric quantities of the required reagents can be used, providing in respectable reaction yields. Chapter 8 will focus on further research efforts to use nitro cyclopropanecarboxylates as synthons in organic synthesis.

CHAPTER 8

A Tandem Cyclopropane Rearrangement 1,3-Dipolar Cycloaddition: Pericyclic Nitrosoacetal Synthesis

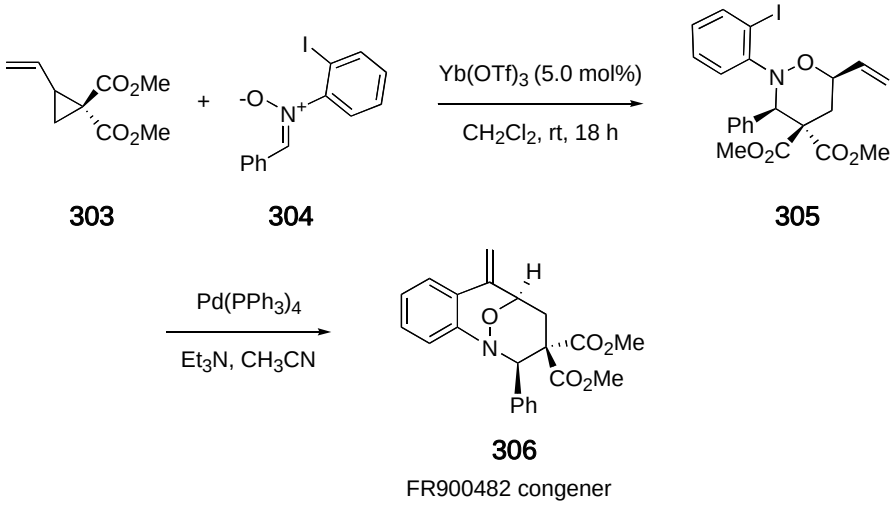
8.1 Introduction and precedence

As demonstrated in Chapter 7, doubly activated cyclopropanes can serve as useful synthons in organic synthesis. Their reactivity parallels classic α,β-unsaturated carbonyl compounds in the presence of nucleophiles, yielding the homologous (or 1,5) addition products. Although many nucleophiles have been found to be useful in ring opening reactions involving various cyclopropanes, Young and Kerr recently made an interesting contribution to this area of research.

Young and Kerr exploited the reactivity of doubly activated cyclopropanes **303** to extend the scope of nucleophilic ring opening to include nitrones **304**.[290] Their contribution, entitled "Homo [3+2] dipolar cycloadditions: the reaction of nitrones with cyclopropanes," led to the elegant construction of tetrahydro-1,2-oxazine rings **305**.[290a] In one proposed mechanistic scenario, the nucleophilic portion of the nitrone **304** (oxygen atom) induced ring opening of the cyclopropane followed by intramolecular cyclization of the resulting malonate onto the imminium species. The net result was C-O and C-C bond formation in a single step. This reaction was applied to the two-step preparation of skeletal congeners of FR900482 **306**. The tetrahydro-1,2-oxazine core **305** can be transformed into the bicyclic scaffold of FR900482 **306** *via* an intramolecular Heck reaction (Scheme 34).

290.(a) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed*. **2003**, *26*, 3023-3026. (b) Young, I. S.; Kerr, M. A. *Org. Lett*. **2004**, *6*, 139-141.

Scheme 34. The synthesis of FR900482 congeners from doubly activated cyclopropanes and nitrones.

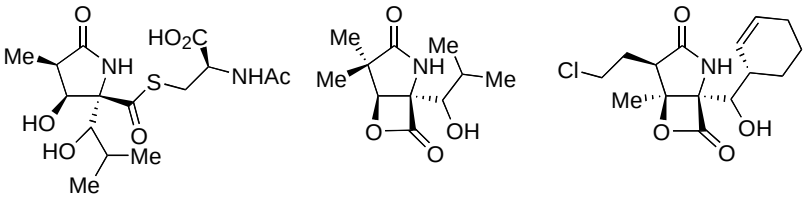


8.1.1 Objectives

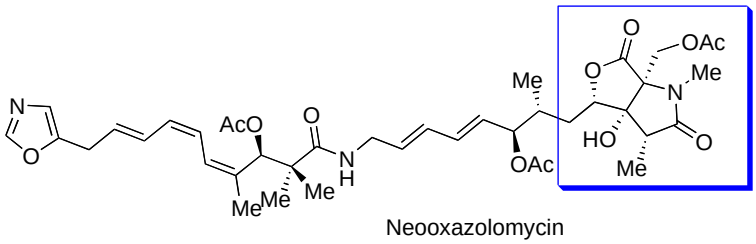
A strategy related to the one developed by Young and Kerr was envisioned in the Charette laboratories for the synthesis of a series of γ-lactams. Naturally occurring γ-lactams, including lactacystin (**307**),[291] α-methylomuralide (**308**),[292] salinosporamide A (**309**)[293] and neooxazolomycin (**310**),[294] are densely functionalized biologically active molecules (Fig. 31). The functionalization of these 5-membered aza-heterocycles makes them challenging synthetic targets. Furthermore, a number of these γ-lactams, including lactacystin (**307**) and α-methylomuralide (**308**), represent important members of a class of proteasome inhibitors. These inhibitors have

291. Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726-731.
292. For a total synthesis see: (a) Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760-2764.
293. Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355-357.
294. Isolation see: (a) Takahashi, K.; Kawabata, M.; Uemura, D. *Tetrahedron Lett.* **1985**, *26*, 1077-1078. For a total synthesis see: (b) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070-4072.

significant therapeutic value as they increase the sensitivity of cancer cells to apoptosis (biochemically regulated cell death).



307 **308** **309**



310

Figure 31. Examples of densely functionalized γ-lactams.

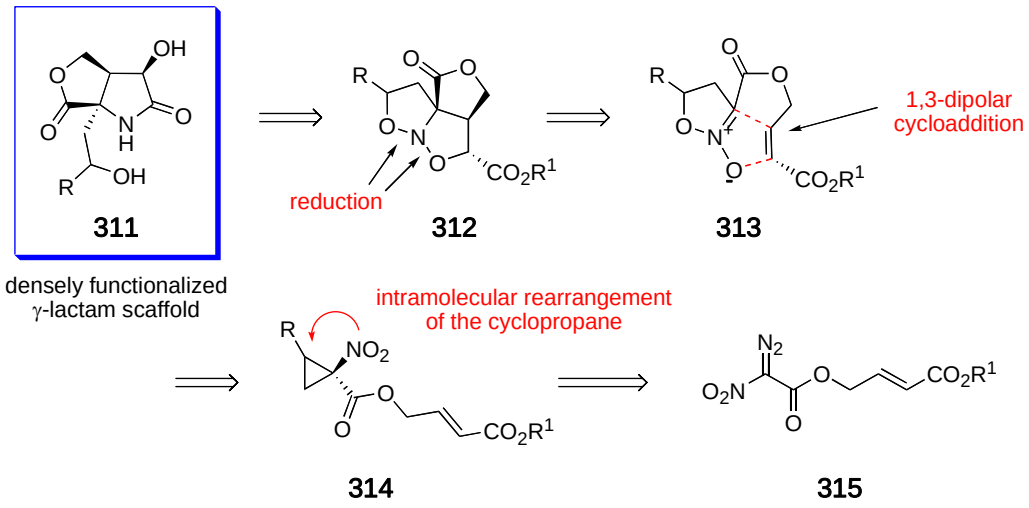
The important biological activities exhibited by this class of synthetically challenging γ-lactams make the development of new strategies for their preparation of great interest. In the context of using doubly activated cyclopropanes as synthons, a new approach was envisioned, which exploits the reactivity patterns of nitro cyclopropanecarboxylates discussed in previous chapters. Preparation of various derivatives of these cyclopropanes has revealed that certain substitution patterns on the cyclopropane promote facile intramolecular rearrangements to isoxazoline *N*-oxides **313** on silica gel (Scheme 35).

The new envisioned strategy differs from the one used by Young and Kerr. In this case, the 1,3-dipole (a cyclic nitrone) would be derived from a nitro cyclopropanecarboxylate **314**. Trapping of this 1,3-dipole **313** in an intramolecular fashion by an olefinic dipolarophile[295] would allow the expedient construction of densely functionalized nitrosoacetals **312**. The nitrosoacetals would then serve as

295. For a review on the synthesis, reactions and properties of ONO systems see: Rudchenko, V. F. *Chem. Rev*. **1993**, *93*, 725-739.

synthetic precursors to the desired γ-lactams **311** upon reductive cleavage of the N-O bonds (Scheme 35).[296]

Scheme 35. Envisioned retrosynthetic strategy for the construction of densely functionalized γ-lactam scaffolds.



If the envisioned strategy was to be successful, four issues would have to be addressed including: 1) Could an intermolecular cyclopropanation reaction (**315** to **314**) be favored over an intramolecular cyclopropanation with substrates already containing olefins? 2) What substitutions (R) on the cyclopropane would facilitate its rearrangement to isoxazoline *N*-oxide **313**? 3) Would the intramolecular 1,3-dipolar cycloaddition[297] be a high yielding process? 4) Would reduction of the nitrosoacetal **312** lead to the formation of the desired γ-lactam **311**?

296.(a) Denmark, S. E.; Kramps, L. A.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4122-4125. (b) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett*. **2001**, *3*, 1367-1369.

297. For examples of low yielding intermolecular 1,3-dipolar cycloadditions with similar substrates see: Shimizu, T.; Hayashi, Y.; Teramura, K. *J. Org. Chem*. **1983**, *48*, 3053-3058.

8.2 Rearrangements of activated cyclopropanes to isoxazoline *N*-oxides and dihydrofurans

During the development of new cyclopropanation methodologies for the syntheses of various nitro cyclopropanecarboxylates, certain derivatives were found to be prone to intramolecular rearrangements during chromatography on mildly acidic silica gel. As mentioned in Chapter 6, prevention of these rearrangements was the impetus for the development of a "one pot" cyclopropanation reduction procedure, allowing the synthesis of 2,2-diphenyl- and 2-phenyl-2-methyl-substituted cyclopropane α-amino esters from the corresponding nitro cyclopropanecarboxylates (Eq. 42).

The presence of electron-rich aromatic rings or vinyl groups (eg. styryl) directly attached to the nitro cyclopropanecarboxylates facilitated their rearrangement to the corresponding isoxazoline *N*-oxides **318**.[298] For example, 2-substituted cyclopropanes containing 4-methoxy-phenyl **197b** or 3-indole-1-*tert*-butylcarbamate **316a** groups could be identified in the crude reaction mixtures directly following a cyclopropanation reaction. However, these cyclopropanes would rapidly rearrange to the corresponding isoxazoline *N*-oxides **318** upon column chromatography.[299] Bands in the infrared spectra in the 1595-1625 cm^{-1} and 1230-1240 cm^{-1} regions corresponding to the *N*-oxide **318** provided evidence that a rearrangement had occurred.[300]

This rearrangement presumably occurs *via* heterolytic cleavage of the cyclopropane ring promoted by traces of acid (eg. from silica gel). Intramolecular trapping of the zwitterion **317** by the nitronate directly follows (Eq. 51). This rearrangement can also be induced by Lewis acids, suggesting that an incremental

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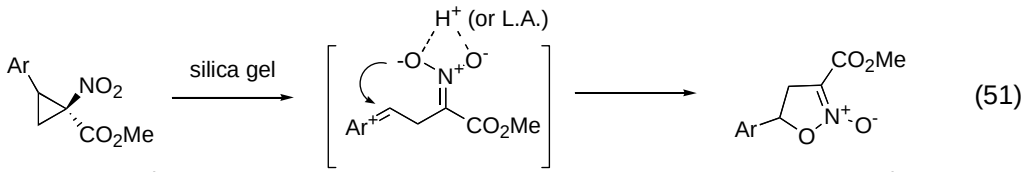
298. For examples involving the syntheses of isoxazoline *N*-oxides see: (a) Scardovi, N.; Casalini, A.; Peri, F.; Righi, P. *Org. Lett*. **2002**, *4*, 965-968. (b) Kunetsky, R. A.; Dilman, A. D.; Ioffe, S. L.; Struchkova, M. I.; Strelenko, Y. A.; Tartakovsky, V. A. *Org. Lett.* **2003**, *5*, 4907-4909. (c) Galli, C.; Marotta, E.; Righi, P.; Rosini, G. *J. Org. Chem.* **1995**, *60*, 6624-6626. (d) Mélot, J.-M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1988**, 558-560.

299. If the silica gel is pretreated with 5:20:75 Et_3N:EtOAc/Hexane prior to column chromatography this rearrangement can be avoided.

300. Dean, F. M.; Johnson, R. S. *J. Chem. Soc., Perkin Trans. I* **1980**, 2049-2053.

enhancement in the electron-withdrawing ability of the nitro group weakens the cyclopropane bond sufficiently, allowing for intramolecular nucleophilic trapping.



197b Ar = 4-MeO-Ph
316a Ar = 3-indole-1-Boc
316b Ar = styryl

317

318a Ar = 4-MeO-Ph
318b Ar = 3-indole-1-Boc
318c Ar = styryl

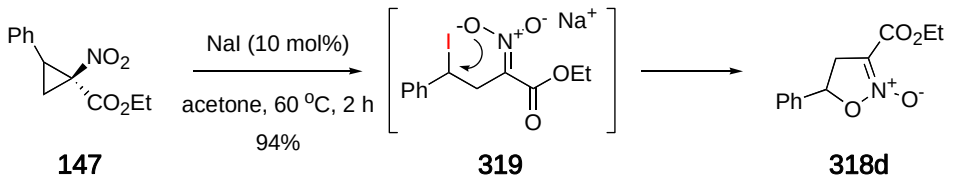
(51)

One disadvantage of this rearrangement was that it was limited to only certain aryl groups. For example, the nitro cyclopropanecarboxylates derived from styrene **147** or indene **162** were robust and never underwent rearrangements to the corresponding isoxazoline *N*-oxides. In light of the strategy envisioned for the synthesis of γ-lactams, the ability to expand the scope of this intramolecular rearrangement would enable diversification to other derivatives. Additionally, expanding the scope of this rearrangement could help overcome problems that may arise in later steps.

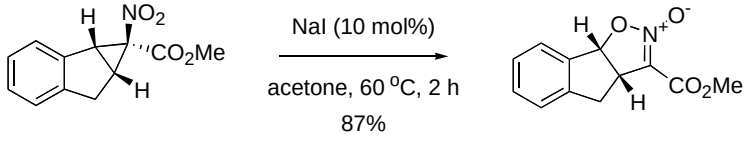
It has been previously demonstrated that intermolecular ring opening reactions with nitro cyclopropanecarboxylates could be promoted by a variety of nucleophiles (Chapter 7).[81d,236,240] However, a nucleophile that could also act as a good leaving group could enable intramolecular cyclization of the nitronate intermediate **319** following ring opening. In this manner, an appropriate nucleophile could be used to catalytically rearrange the nitro cyclopropanecarboxylates to the desired isoxazoline *N*-oxides **318** in a two-step process.

To test this hypothesis, ethyl 1-nitro-2-phenyl-cyclopropanecarboxylate (**147**) was treated with NaI (10 mol%) in refluxing acetone for 2 h. The desired isoxazoline *N*-oxide **318d** could then be recovered in 94% yield (Eq. 52). Unfortunately, when the same reaction was conducted in the presence of allyl iodide (2.0 equiv) and Na_2CO_3, no intermolecular trapping of the electrophile by the nitronate intermediate **319**

occurred.[301] The nitro cyclopropanecarboxylate derived from indene **162** was also found to afford the desired isoxazoline *N*-oxide **318e** in an excellent yield (87%) under the same reaction conditions (Eq. 53).



147 **319** **318d** (52)



162 **318e** (53)

In contrast, highly activated 1-nitro-1-ketocyclopropanes were found to undergo a different type of rearrangement on silica gel. The ketone is presumably more nucleophilic than the nitro group, resulting in an intramolecular trapping by the carbonyl (oxygen atom) instead of the nitronate (oxygen atom). The result of this intramolecular rearrangement is the formation of 3-nitro-dihydrofurans instead of isoxazoline *N*-oxides. Alonso and Morales have observed analogous rearrangements of 4-methoxy-phenylcyclopropyl ketones in a stereospecific manner on aluminum oxide to the corresponding 4,5-dihydrofurans.[302]

One illustrative example of this rearrangement with 1-nitro-1-ketocyclopropanes involves the cyclopropyl ketone derived from indene **320**. This cyclopropane was observed in the crude reaction mixture directly following the cyclopropanation reaction. However, when it was submitted to column chromatography on silica gel, it rearranged to the corresponding 3-nitro-dihydrofuran **321** in 44% isolated yield (Eq. 54).

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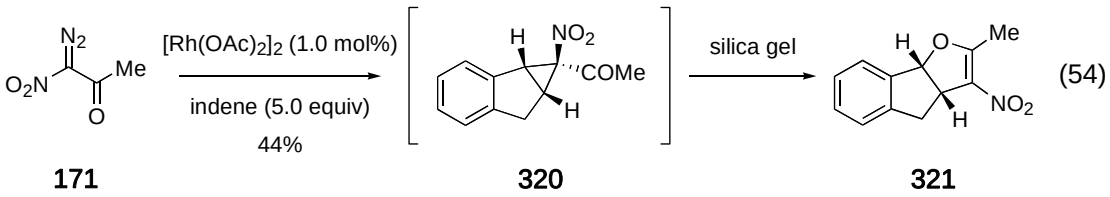
301. This would allow for the synthesis of α,α-disubstituted amino acids upon reduction of the nitro group and saponification of the ester.
302. Alonso, M. E.; Morales, A. *J. Org. Chem*. **1980**, *45*, 4530-4532.



171 **320** **321**

The outcome of this rearrangement was confirmed by X-ray crystallography of 2-methyl-3-nitro-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (**321**, Fig. 32). This compound crystallized in a monoclinic unit cell from EtOAc at -20 ^{o}C.[303]

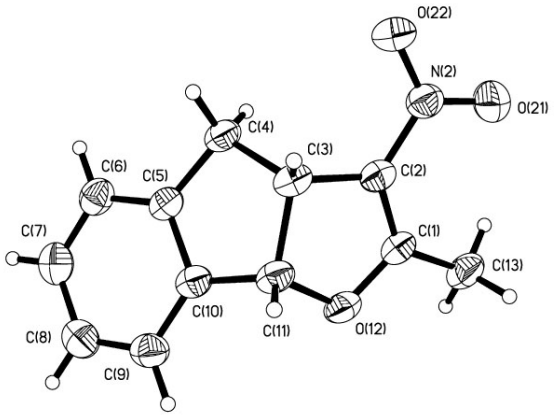


Figure 32. ORTEP representation of the crystal structure of 2-methyl-3-nitro-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (**321**).

8.3 Development of a tandem cyclopropane rearrangement 1,3-dipolar cycloaddition process

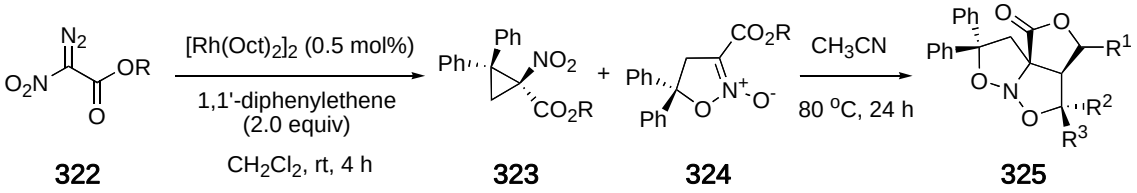
Previous research involving intramolecular cyclopropanations of α-nitro-α-diazocarboxylates (Chapter 3) demonstrated that they were best performed in refluxing CH_2Cl_2. This observation would suggest that cyclopropanation reactions would proceed in an intermolecular fashion in the presence of an additional olefin at room temperature. Therefore, application of this specific reactivity pattern led to the

303. See Appendix VI for the complete structural data concerning the crystal structure of 2-methyl-3-nitro-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (**321**).

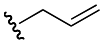
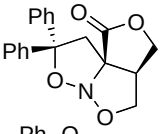
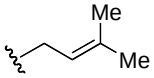
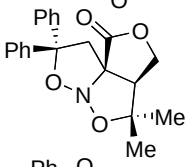
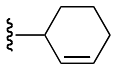
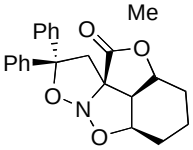
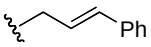
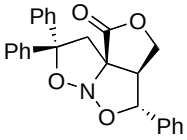
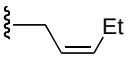
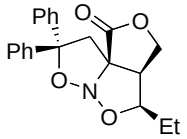
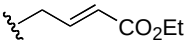
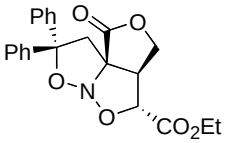
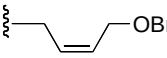
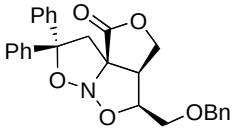
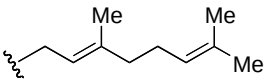
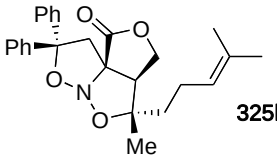
straightforward preparation of nitro cyclopropanecarboxylates containing unsaturated esters.

In order to test the feasibility of the 1,3-dipolar cycloaddition reactions, 1,1'-diphenylethene was used as a substrate. As expected, purification of these doubly activated cyclopropanes **323** on silica gel led to partial rearrangement to the corresponding isoxazoline *N*-oxides **324**. These substrates were then submitted to a variety of conditions in order to induce an intramolecular 1,3-dipolar cycloaddition reaction. The scope of this cycloaddition reaction was explored for a variety of olefin substitution patterns. Satisfyingly, it was found to occur with a considerable degree of efficiency in acetonitrile at 80 ^{o}C (Table 56).

Table 56. Scope of the intermolecular cyclopropanation reaction followed by a tandem cyclopropane rearrangement 1,3-dipolar cycloaddition.



322 **323** **324** **325**

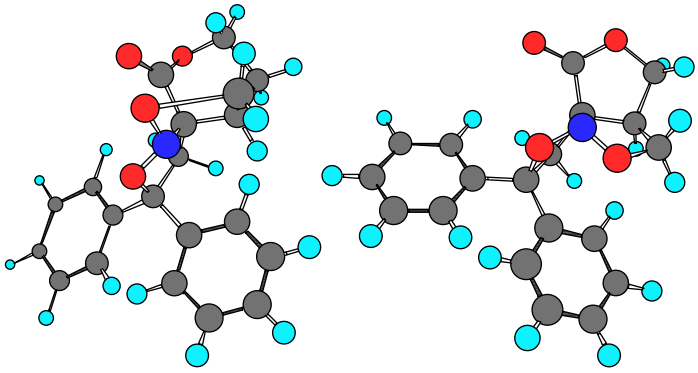
entry	R-group	yield of cyclopropane (%)[a]	product		yield (%)[b]
1		84		**325a**	66
2		87		**325b**	80
3		75		**325c**	57
4		96		**325d**	70
5		94		**325e**	80
6		85		**325f**	93
7		69		**325g**	67
8		84		**325h**	71

a) Combined isolated yields of cyclopropanes **323** and isoxazoline *N*-oxides **324**. b) Isolated yields of nitroso-acetals **325** after purification by column chromatography.

Initially, only the isoxazoline *N*-oxides **324** were submitted to the thermal conditions necessary for the 1,3-dipolar cycloaddition reactions. It was then realized that heating the doubly activated cyclopropanes **323** at 80 ^{o}C induced a spontaneous rearrangement to the isoxazoline *N*-oxides **324** followed by the desired 1,3-dipolar cycloaddition in an efficient manner.

The scope of the cyclopropanation and 1,3-dipolar cycloaddition reactions were explored upon preparation of a diverse series of substrates. The substrate bearing an allyl ester afforded the corresponding tricyclic nitrosoacetal **325a** in 66% isolated yield (Table 56, entry 1), whereas an improved yield was obtained for the 3-methyl-but-2-en-1-ol derivative, leading to nitrosoacetal **325b** in 80% yield (Table 56, entry 2). The nitro cyclopropanecarboxylate bearing an ester derived from the chiral racemic cyclohex-2-en-1-ol **323c** also underwent a reasonably efficient cycloaddition reaction affording the 5,5,5,6-tetracyclic nitrosoacetal **325c** in 57% isolated yield (Table 56, entry 3). For substrates bearing *cis* **324d** and *trans*-olefins **324e**, the stereochemical integrity of the olefins were conserved, as only the *syn*-diastereomer **325d** and *anti*-diastereomer **325e** (with respect to the lactone) were observed, respectively (Table 56, entries 4 and 5). The cyclopropane bearing an electron-poor allylic ester **323f**, derived from 4-hydroxy-but-2-enoic acid ethyl ester, also afforded nitrosoacetal **325f** in an excellent yield of 93% (Table 56, entry 6). Substrates bearing esters derived from *cis*-4-benzyloxy-but-2-en-1-ol **324g** and geraniol **324h** also afforded the desired nitrosoacetals **325g** and **325h**, respectively, in acceptable yields (Table 56, entries 7 and 8).

Unfortunately, attempts to extend the scope of the 1,3-dipolar cycloaddition to include esters derived from 2-substituted allylic alcohols, such as 2-methylallyl ester, were unsuccessful leading only to the recovery of the isoxazoline *N*-oxides. Substrates derived from homoallylic alcohols were also submitted to the thermal conditions used to induce the 1,3-dipolar cycloaddition. This would lead to formation of the 5,5,6-nitrosoacetal ring systems. However, when these substrates were submitted to the reaction conditions, only unreacted isoxazoline *N*-oxides could be recovered. This is presumably due to the ring strain imposed on the system by the presence of the 6-membered lactone ring (Fig. 33).



Carbon = grey, Oxygen = red, Nitrogen = blue

Figure 33. Chem3D Pro models of a 5,5,6-nitrosoacetal (left-handed structure) and the 5,5,5-nitrosoacetal **325a** (right-handed structure).

The retention of the stereochemical integrity of the olefin following the 1,3-dipolar cycloaddition reaction was confirmed by X-ray crystallography of 4-ethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*] pentalene-1-one (**325e**, Fig. 34). The 5,5,5-ring system forms a structure resembling a “chair” truncated by two phenyl rings.

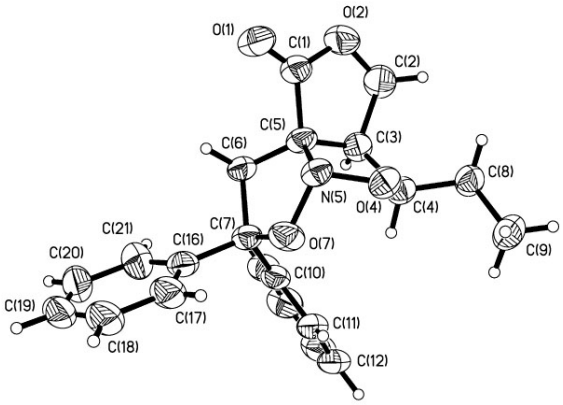


Figure 34. ORTEP representation of the crystal structure of 4-ethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalene-1-one (**325e**).[304]

8.4 Attempted reduction of the nitrosoacetal and γ-lactam formation

Reduction of the nitrosoacetals **312** was desired to complete the synthesis of the γ-lactam cores **311** according to the envisioned retrosynthetic strategy (Scheme 35). The nitrosoacetal bearing the ethyl ester **325f** was of particular interest since complete hydrogenolysis of its N-O bonds would presumably reveal a primary amine that would cyclize with the ester affording the desired γ-lactam. A variety of reduction conditions were tested including Raney-Ni,[296a,305] $FeCl_3$, 10% Pd/C, 20% $Pd(OH)_2$,[296b] 5% Rh/C, $TiCl_3$-H_2O/MeOH,[306] SmI_2,[307] Zn-HCl[308] and 5% Pt/C resulting in either recovery of the starting material or cleavage of a single N-O bond.

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304. See Appendix VII for the complete structural data concerning the crystal structure of 4-ethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*] pentalene-1-one (**325e**).

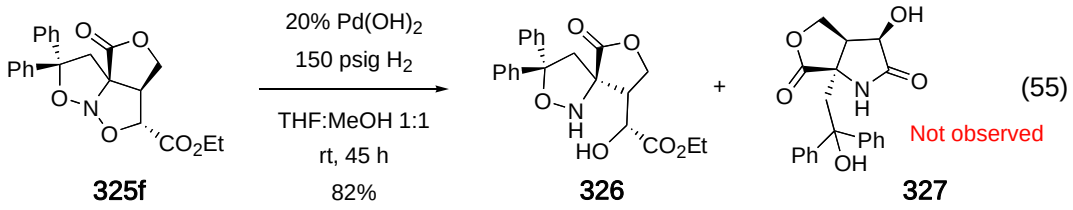
305.(a) Denmark, S. E.; Gomez, L. *Org. Lett*. **2001**, *3*, 2907-2910. (b) Denmark, S. E.; Cottell, J. J. *J. Org. Chem*. **2001**, *66*, 4276-4284. (c) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc*. **1990**, *112*, 311-315.

306. Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett*. **1985**, *26*, 4633-4636.

307. Westermann, B.; Walter, A.; Flörke, U.; Altenback, H.-J. *Org. Lett*. **2001**, *3*, 1375-1378.

308. Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett*. **1988**, *29*, 2973-2976.

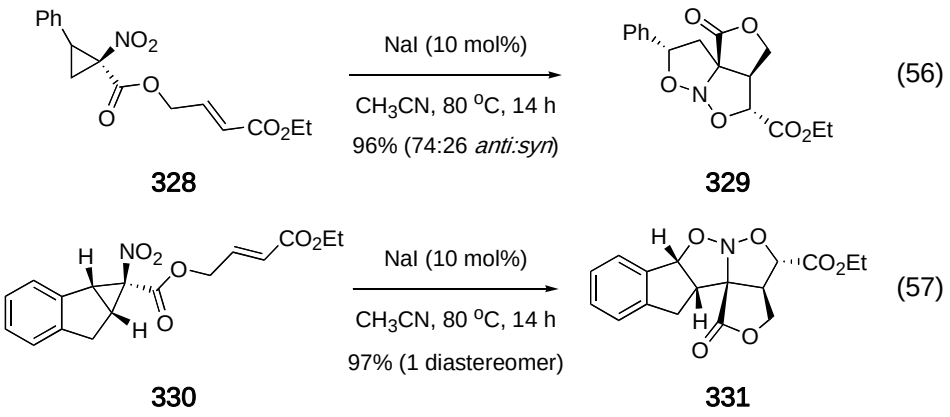
For example, 20% $Pd(OH)_2$[296b] (Pearlman's catalyst) gave the highest yields of the mono-cleaved product (**326**, Eq. 55).



325f **326** **327** (55)

Other researchers have reported difficulties in the reductive cleavage of similar N-O bonds,[309] noting that they were unexpectedly resistant to most traditional reagents for N-O bond reduction. In our case, the steric bulk associated with the diphenyl moiety probably serves to impede the hydrogenation of the remaining N-O bond. In light of this, the strategy used for the synthesis of isoxazoline *N*-oxides from styrene and indene derived cyclopropanes was applied. In these cases, the steric bulk would be reduced and presumably allow for a more facile reductive cleavage of the remaining N-O bond. Accordingly, a tandem intermolecular cyclopropane ring opening catalyzed by NaI followed by intramolecular ring closing led to isoxazoline *N*-oxide formation. Subsequently, 1,3-dipolar cycloaddition was used for the preparation of the desired nitrosoacetals. When the styrene-derived cyclopropane **328** was submitted to these conditions, an excellent yield of 96% could be obtained of the desired nitrosoacetal **329** in an 74:26 *anti:syn* ratio (Eq. 56). In a similar manner, the indene-derived cyclopropane **330** also underwent the efficient cascade reaction affording 97% of the desired pentacyclic nitrosoacetal **331** in 97% isolated yield as a single diastereomer (Eq. 57).

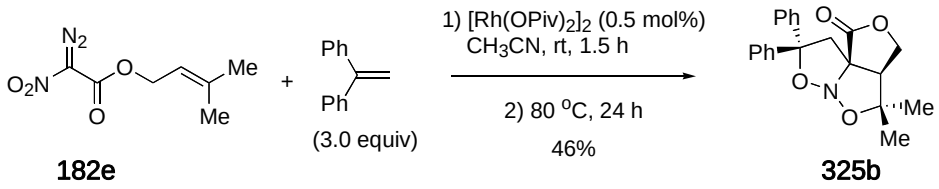
309. DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc*. **1983**, *105*, 1686-1688.



The nitrosoacetals **329** and **331** were again submitted to a variety of reduction conditions in an attempt to cleave both of the N-O bonds. Unfortunately, γ-lactam formation was again unsuccessful as only the N-O bond in α– to the ester moiety was cleaved. These results suggest that the electronic nature of this bond may also be playing an important role. Further attempts to affect the cleavage are ongoing and will hopefully be successful in the near future.

In the meantime, the conditions for the cascade reaction were further optimized. Since intermolecular cyclopropanation reactions with α-nitro-α-diazocarbonyl substrates are also compatible with solvents such as CH_3CN, a cascade involving a "one pot" cyclopropanation, intramolecular ring opening, 1,3-dipolar cycloaddition reaction sequence was also attempted. This sequence resulted in the formation of the desired nitrosoacetal **325b** in 46% yield for the three steps (Eq. 58).[310] Presumably, some byproduct results from competitive 1,3-dipolar cycloaddition reactions with the extra equivalents of the olefin (1,1'-diphenylethene). However, when only one equivalent of the olefin substrate was used, an isolated yield of only 38% was obtained. This "one pot" reaction was also found to be very sensitive to reaction solvent as benzene, acetone and 1,2-dichloroethane did not have sufficiently high dielectric constants to induce rearrangement of the cyclopropane into the desired isoxazoline *N*-oxide intermediate. In these cases, the corresponding cyclopropane was observed in the crude reaction mixtures.

310. This translates to an average of 77% yield for each step.



(58)

8.5 Conclusions

Unfortunately, the complete reduction of the nitrosoacetal **325f** was unsuccessful, thus the synthesis of the desired densely functionalized γ-lactam targets could not be accomplished. However, these preliminary results remain encouraging, suggesting that a cascade strategy should be feasible. Moreover, the application of nitro cyclopropanecarboxylates as synthons was demonstrated to be synthetically useful for the preparation of various isoxazoline *N*-oxides and 3-nitro-4,5-dihydrofurans.

1,3-dipolar cycloaddition reactions have maintained a place of prominence in the toolbox of a synthetic chemist and, as such, many catalytic asymmetric methodologies have been developed.[311] Therefore, it is conceivable that a catalytic asymmetric version of this reaction would allow for the synthesis of chiral nitrosoacetals. In the future, preparation of γ-lactams using this methodology could be realized upon development of an efficient method for N-O bond cleavage. Nonetheless, this cascade involving an intramolecular 1,3-dipolar cycloaddition does illustrate its utility for the expedient construction of structurally complex polycyclic molecules.

In conclusion, it has been demonstrated that nitro cyclopropanecarboxylates serve as useful synthons in organic chemistry. Hopefully, further research will expand on the usefulness of this synthon. Its only limitation is one's imagination. It is my hope that future researchers will continue developments in this delightful field of research.

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311. For a recent review see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863-909. For recent examples involving asymmetric catalysis see: (b) Viton, F.; Bernardinelli, G.; Kündig, P. E. *J. Am. Chem. Soc*. **2002**, *124*, 4968-4969. (c) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett*. **2002**, *4*, 2457-2460.

Experimental Section

General Notes

All glassware was dried for several hours in an oven and cooled in a dessicator before use. Reagents were handled with oven-dried syringes. Generally, solvents and reagents were purified prior to use. Several of the more often used solvents are listed:

Dichloromethane	dried on a GlassContour system (Irvine, CA).
Diethyl ether	dried on a GlassContour system (Irvine, CA).
Iso-propyl alcohol	used directly from the bottle.
Pyridine	distilled over CaH_2.
Tetrahydrofuran	dried on a GlassContour system (Irvine, CA).
Toluene	dried on a GlassContour system (Irvine, CA).
Triethylamine	distilled over CaH_2.
Triflic anhydride	distilled from P_2O_5, stored under an argon atmosphere.

Other reagents or solvents of reagent grade or better could be used as received in many cases. Reported yields refer to products isolated after purification by flash chromatography after complete removal of solvent by placing under high vacuum. Cyclopropanation reactions using iodobenzene diacetate, $PhI(OAc)_2$, as a reagent were routinely performed in flasks open to air while cyclopropanation reactions involving diazo compounds were performed under an argon atmosphere in anhydrous CH_2Cl_2 prepared by filtration through drying columns on a GlassContour system (Irvine, CA).

Analytical thin-layer chromatography (TLC) was performed on commercially available, precoated, fluorescence indicator impregnated, glass-backed silica gel plates (Merck 60 F_{254}) which were stored over Drierite© prior to use. Visualization of the chromatograms was achieved by UV absorbance, aqueous $KMnO_4$, aqueous cerium molybdate or ninhydrin (amino esters). Column chromatography was performed on 230-400 mesh silica gel (EM Science 60) according to standard

techniques.[312] Solvent compositions for the column chromatography are listed as volume/volume ratios. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One FTIR Spectrometer equipped with a Golden Gate Diamond ATR. Only the most important and relevant IR frequencies are reported. High-resolution mass spectra (HRMS) were obtained from the Centre régional de spectrométrie de masse de l'Université de Montréal on a MS50 Kratos and are reported as m/e. Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with AMX 300 Bruker (300 MHz), AV400 Bruker (400 MHz) or AMX R 400 Bruker (400 MHz) spectrometers. Chemical shifts of the ^{1}H NMR spectra are reported in parts per million (ppm) on the δ-scale from an internal standard of residual chloroform (7.27 ppm). Data is reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sex=sextet, sept=septet, m=multiplet and br=broad), coupling constant in hertz (Hz) and integration. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with AMX 300 Bruker (300 MHz), AV400 Bruker (400 MHz) or AMX R 400 Bruker (400 MHz) spectrometers. Chemical shifts are reported in delta (δ) units, parts per million (ppm), relative to the central line of the triplet at 77.23 ppm for deuteriochloroform ($CDCl_3$). ^{13}C NMR spectra were routinely run with broadband decoupling. Full assignment of chemical shifts was confirmed by DEPT experiments.

Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal. The samples were rigorously purified, recrystallized or distilled and submitted to high vacuum (< 0.2 mm Hg) for a minimum of two days prior to analysis. Single crystal X-ray diffraction analyses were taken by the Laboratoire de Diffraction des Rayon X de l'Université de Montréal using an Enraf-Nonius CAD-3 or CAD-4 instrument. Further details are provided in the appropriate appendices for the crystals in question.

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312. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

The enantioselectivities of asymmetric cyclopropanation reactions were determined using super-critical fluid chromatography on a Berger SFC Analytical instrument equipped with a diode array UV detector. Data is reported as follows: column type, eluent, flow rate and retention time (t_r). The mobile phase was super-critical carbon dioxide while the modifier was invariably methanol.

Nomenclature for the configuration of the cyclopropanes

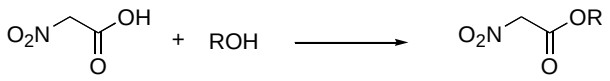
Over the course of writing this account, it was brought to my attention that the proper nomenclature for assigning cyclic cyclanes (eg. cyclopropanes) should not use *E-Z* descriptors to define their relative stereochemistry.[313] A preferable nomenclature (Cross and Klyne, 1976) uses the prefix *r*- and that the position of the other substituent(s) is/are marked relative to it and are to be denoted as *c*- (*cis*) or *t*- (*trans*). However, since *E-Z* descriptors have been almost exclusively used in describing the stereochemistry of the class of cyclopropanes described in this thesis by the scientific community, this nomenclature will be used for the sake of clarity and consistency to what has been previously published.

Experimental: Chapter 2

Nitro compounds **94**, **95** and **99** are commercially available from Aldrich Chemical Company. Compounds **71**, **97**, **98**, **121b** have been previously reported by O'Bannon and Dailey.[81c,d] Compounds **120b**, **120c**, **120f**, **120o**, have been previously reported by Mioskowski *et al*. Compound **120i** has been previously reported by Fenk.[314]

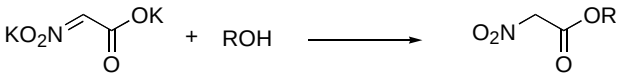
313. Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*, John Wiley & Sons: Toronto, **1993**, pg. 665-666.
314. Fenk, C. J. *Tetrahedron Lett*. **1999**, *40*, 7955-7959.

General procedure for the synthesis of the α-nitroesters.



123 **120**

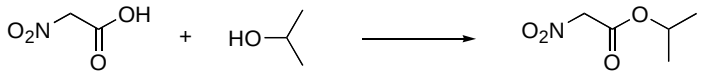
Method 1: DCC coupling of alcohols and nitroacetic acid (123). In a round-bottomed flask under an argon atmosphere to freshly prepared nitroacetic acid (**123**, 1.00 mmol) was added a solution of the desired alcohol (1.00 mmol, 1.0 equiv) in anhydrous THF (1.0 mL). The solution was cooled to 0 °C then a solution of 1,3-dicyclohexylcarbodiimide (DCC, 1.10 mmol, 1.1 equiv) in THF (1.0 mL) was added slowly *via* syringe. The reaction temperature was maintained at 0 °C, while the progress of the reaction was monitored by TLC. After complete consumption of the starting materials by TLC (2-8 h), the reaction mixture was filtered through a short silica gel plug washing with Et_2O. The crude reaction mixture was then purified by column chromatography on silica gel (eluent 5-20% EtOAc/Hexane) affording the desired α-nitroester (**120**). All of the α-nitroesters (**120**) described can be prepared using this method.



129 **120**

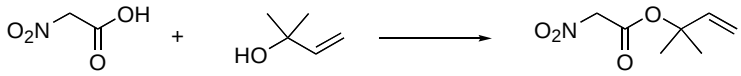
Method 2: Esterification of dipotassium nitroacetate (129).[101,105] Dipotassium nitroacetate (**129**, 3.00 g, 16.6 mmol) was ground with a mortar and pestal and treated with the desired anhydrous alcohol (300 mmol, 18.0 equiv). Anhydrous Et_2O (10 mL) was then added and the solution cooled to -25 ± 5 ^oC. The vigorously stirring solution was treated with concentrated sulfuric acid (5.52 g, 3.0 mL, 56.2 mmol, 3.4 equiv) by a slow dropwise addition *via* pipette over a 30 min period. The solution was allowed to warm slowly to room temperature stirring an additional 20 h before it was filtered through a cotton plug and concentrated under reduced pressure (rotary evaporator). The resulting crude oil was then extracted with benzene (2x50 mL), washed with

distilled water (2x50 mL) and saturated brine (1x50 mL) and dried over sodium sulfate. Concentration under reduced pressure afforded the analytically pure α-nitroester (**120**). Methyl and ethyl nitroacetate (**94**, **99**) can be prepared using this protocol.



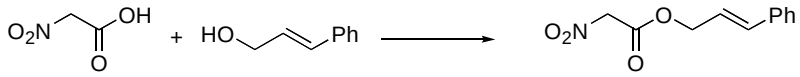
123 **120a**

***iso*-Propyl nitroacetate (120a).** Clear colorless oil (664 mg, 68%): R_f 0.83 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (sept, J = 6.3 Hz, 1H), 5.13 (s, 2H), 1.32 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 76.7, 71.8, 21.6; IR (film) 1748 (C=O), 1567, 1378, 1329 (NO_2) cm^{-1}.



123 **120d**

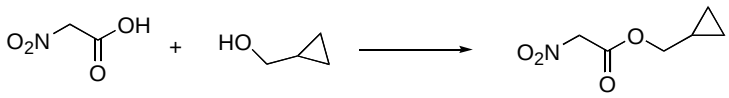
1,1-(Dimethyl)allyl nitroacetate (120d). Pale yellow oil (334 mg, 33%): R_f 0.55 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dd, J = 17.5, 10.9 Hz, 1H), 5.24 (d, J = 17.5 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 5.09 (s, 2H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 140.7, 114.6, 85.3, 77.2, 26.3; IR (film) 1751 (C=O), 1563, 1340 (NO_2), 1229, 1124 cm^{-1}; Elem. Anal. calcd for $C_7H_{11}NO_4$: C 48.55, H 6.40, N 8.09; found: C 48.55, H 6.47, N 8.31.



123 **120e**

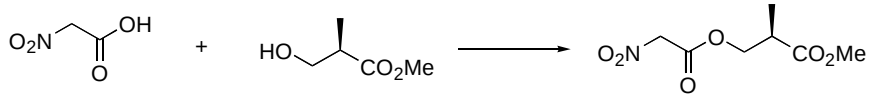
(*E*)-Cinnamyl nitroacetate (120e). Pale yellow oil (291 mg, 39%): R_f 0.30 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.42 (m, 5H), 6.72 (d, J = 15.9 Hz, 1H), 6.28 (dt, J = 15.8, 6.7 Hz, 1H), 5.21 (s, 2H), 4.92 (d, J = 6.7 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 161.9, 136.5, 135.8, 128.9, 128.8, 127.0, 121.2, 76.5, 67.8; IR (film) 1703 (C=O), 1547, 1328 (NO_2), 1199, 1025 cm^{-1}; LRMS (FAB) calcd for $C_{11}H_{11}NO_4$ $[M]^+$: 221.2 *m/z*, found: 221.1 *m/z*.



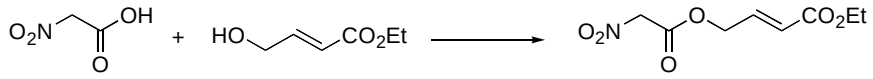
123 **120g**

Cyclopropylmethyl nitroacetate (120g). Clear colorless oil (177 mg, 84%): R_f 0.37 (30% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 2H), 4.10 (d, J = 7.5 Hz, 2H), 1.16-1.58 (m, 1H), 0.61-0.65 (m, 2H), 0.31-0.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 76.5, 72.2, 9.64, 3.62; IR (film) 1755 (C=O), 1567, 1354 (NO_2), 1217, 973 cm^{-1}; HRMS (EI^+) calcd for $C_6H_9NO_4$ $[M]^+$: 159.05316, found: 159.05265.



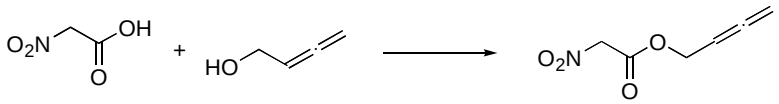
123 **120h**

Methyl (*R*)-2-methyl-3-[(2-nitroacetyl)oxy]propanoate (120h). Yellow oil (150 mg, 73%): R_f 0.67 (50% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 2H), 4.44 (dd, J = 10.9, 7.4 Hz, 1H), 4.35 (dd, J = 10.9, 5.5 Hz, 1H), 3.72 (s, 3H), 2.85-2.87 (m, 1H), 1.23 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 161.8, 76.2, 67.8, 52.2, 38.8, 13.7; IR (film) 1760, 1737 (C=O), 1567, 1340 (NO_2), 1204, 1005 cm^{-1}.



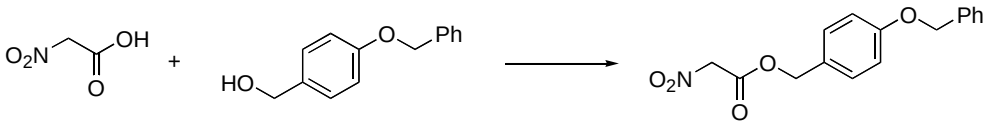
123 **120j**

4-Hydroxy-2-butenoic acid ethyl ester. Prepared according to the method reported by Kende and Fludzinski.[315] **4-Nitroacetoxy-but-2-enoic acid ethyl ester (120j).** White solid (319 mg, 57%): M.p. 39-41 ^{o}C; R_f 0.40 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dt, J = 15.8, 4.8 Hz, 1H), 5.95 (dt, J = 15.8, 1.9 Hz, 1H), 5.23 (s, 2H), 4.83 (dd, J = 4.8, 1.8 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 161.6, 139.0, 123.3, 76.0, 64.6, 60.7, 14.0; IR (solid) 1758, 1716 (C=O), 1563, 1311 (NO_2), 1278, 1182 cm^{-1}.



123 **120k**

Buta-2,3-dienyl nitroacetate (120k). Clear colorless oil (748 mg, 61%): R_f 0.41 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (qn, J = 6.8 Hz, 1H), 5.17 (s, 2H), 4.86-4.91 (m, 2H), 4.70-4.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 85.3, 77.3, 76.3, 64.8, -3.38; IR (film) 1958, 1758 (C=O), 1567, 1340 (NO_2), 1195, 824 cm^{-1}.

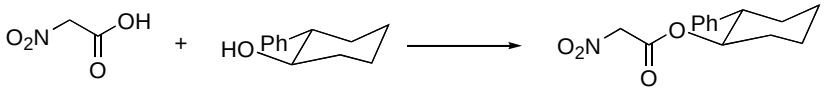


123 **120l**

4-(Benzyloxy)benzyl nitroacetate (120l). Yellow solid (594 mg, 70%): M.p. 87 ^{o}C; R_f 0.35 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.45 (m, 7H), 6.97-7.00 (m, 2H), 5.22 (s, 2H), 5.17 (s, 2H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 159.6, 136.8, 130.9, 128.9, 128.3, 127.7, 126.6, 115.3, 76.5, 70.3,

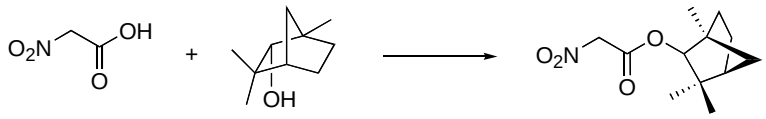
315. Kende, A. S.; Fludzinski, P. *Org. Synth*. **1986**, *64*, 104-107.

68.9; IR (solid) 1703 (C=O), 1547, 1328 (NO_2), 1199, 1024 cm^{-1}; HRMS (EI^+) calcd for $C_{16}H_{15}NO_5$ $[M]^+$: 301.09503, found: 301.09640.



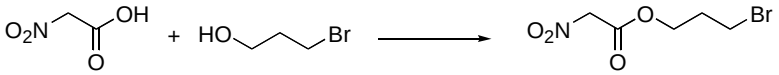
123 **120m**

(*1R*,2S)-2-Phenylcyclohexyl nitroacetate (120m).** Clear colorless oil (240 mg, 91%): R_f 0.18 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.32 (m, 5H), 5.06-5.12 (m, 1H), 4.84 (dd, J = 30.2, 14.3 Hz, 2H), 2.65-2.72 (m, 1H), 2.18-2.21 (m, 1H), 1.89-2.05 (m, 2H), 1.80-1.83 (m, 1H), 1.44-1.66 (m, 1H), 1.26-1.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 142.1, 128.6, 127.5, 126.9, 79.7, 76.1, 49.5, 33.4, 32.0, 25.6, 24.7; IR (film) 1749 (C=O), 1567, 1336 (NO_2), 1267, 1218, 1009, 701 cm^{-1}; HRMS (EI^+) calcd for $C_{14}H_{17}NO_4$ $[M]^+$: 263.11576, found: 263.11492.



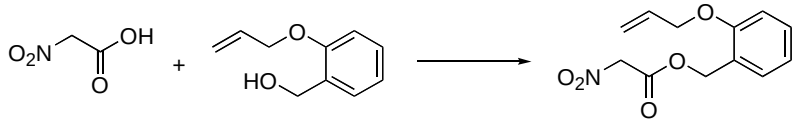
123 **120n**

(*1S,2S,4R*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl 2-nitroacetate (120n). Colorless oil (532 mg, 41%): R_f 0.62 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 2H), 4.51 (s, 1H), 1.44-1.77 (m, 6H), 1.22-1.25 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 89.8, 76.5, 48.6, 48.3, 41.4, 39.9, 29.7, 26.5, 25.8, 20.1, 19.4; IR (film) 1751 (C=O), 1565, 1339 (NO_2), 1267, 1220, 1032 cm^{-1}; HRMS (EI^+) calcd for $C_{12}H_{19}NO_4$ $[M]^+$: 241.13141, found: 241.13176.



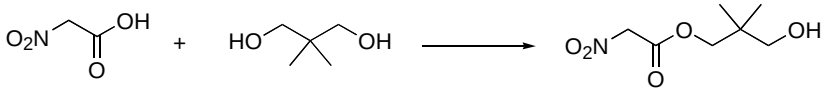
123 **120p**

3-Bromopropyl 2-nitroacetate (120p). Pale yellow oil (528 mg, 75%): R_f 0.24 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 2H), 4.43 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 2.24 (qn, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 76.3, 64.9, 31.3, 28.8; IR (film) 1755 (C=O), 1563, 1337 (NO_2), 1195, 1006, 689 cm^{-1}.



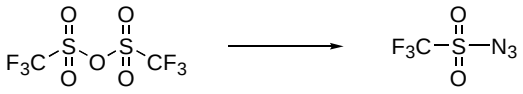
123 **120q**

2-Allyloxy-benzyl nitroacetate (120q). Pale yellow oil (670 mg, 46%): R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.36 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.00-6.08 (m, 1H), 5.42-5.43 (m, 0.5H), 5.38-5.39 (m, 2.5H), 5.28-5.32 (m, 1H), 5.18 (s, 2H), 4.57-4.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 157.0, 133.1, 130.7, 122.8, 120.9, 117.8, 112.1, 76.5, 69.1, 64.7; IR (film) 1755 (C=O), 1567, 1335 (NO_2), 1256, 998, 757 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{13}NO_5$ [M]$^+$: 251.07937, found: 251.07887.

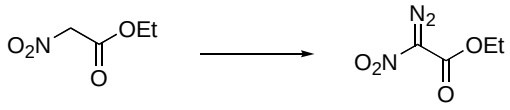


123 **120r**

3-Hydroxy-2,2-dimethyl-propyl nitroacetate (120r). Clear colorless oil (113 mg, 54%): R_f 0.54 (60% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (s, 2H), 4.06 (s, 2H), 3.31 (s, 2H), 2.47 (s(*br*), 1H), 0.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 76.4, 71.9, 68.0, 36.3, 21.3; IR (film) 3322 (OH), 1748 (C=O), 1560, 1337 (NO_2), 1219, 1192, 1047, 1002, 689 cm^{-1}.



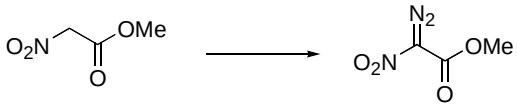
Preparation of trifluoromethanesulfonyl azide (triflyl azide) solution in hexane.[94] A solution of sodium azide (3.32 g, 51.1 mmol, 2.2 equiv) and tetra-*n*-butyl ammonium hydrogen sulfate (0.160 g, 0.471 mmol, 2.0 mol%) in distilled water (23 mL) was cooled in an ice bath. A solution of trifluoromethanesulfonyl anhydride (6.71 g, 2.0 mL, 23.8 mmol, 1.0 equiv) in hexane (22 mL) was then slowly added over 5 min. The resulting solution was allowed to stir for an additional hour at 0 ^{o}C. The reaction mixture was then transferred to a separatory funnel, the organic layer removed and the aqueous layer re-extracted with hexane (3-5 mL). The combined organic layers were dried over sodium hydroxide pellets and decanted into a graduated cylinder and stoppered with a septum. This solution of triflyl azide could be stored at -15 ^{o}C for months without a noticeable decrease in its effectiveness in diazo transfer reactions. The concentration of the azide solution was estimated based on the total volume of the solution and assuming a quantitative conversion based on the amount of triflic anhydride used.



99 **71**

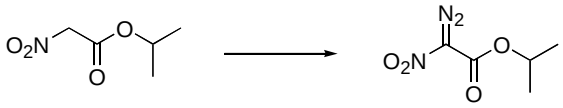
General procedure for the preparation of the α-nitro-α-diazocarbonyls. **CAUTION:** *Although we have not experienced any problems in the handling of these compounds (trifluoromethanesulfonyl azide (triflyl azide) and the α-nitro-α-diazocarbonyl derivatives), extreme care should be taken when manipulating them due to their explosive nature.* **Ethyl nitro diazoacetate (71).** To a solution of ethyl nitroacetate (**99**, 412 mg, 3.10 mmol, 1.0 equiv) in CH_3CN (4.0 mL) cooled in an ice bath was added a 0.85 M solution of trifluoromethanesulfonyl azide (4.0 mL, 3.41 mmol, 1.1 equiv) in hexane. Pyridine (0.50 mL, 6.19 mmol, 2.0 equiv) was then added dropwise over *ca*. 3 min. The reaction mixture was stirred for 14 h warming to

room temperature after which it was concentrated under reduced pressure (rotary evaporator). Purification of the crude residue by flash chromatography on silica gel ($CHCl_3$) afforded the title compound (**71**, 453 mg, 92%) as a bright yellow oil. All reported examples of α-nitro-α-diazocarbonyls were prepared in this manner invariably using silica gel and $CHCl_3$ as an eluent for their purification.



94 **97**

Methyl nitro diazoacetate (97). Pale yellow solid (641 mg, 90%): M.p. 55-57 °C; R_f 0.31 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 101.8 (CN_2), 53.4; IR (solid) 2153 (CN_2), 1727 (C=O), 1496, 1433 (NO_2), 1296, 1126, 745 cm^{-1}.



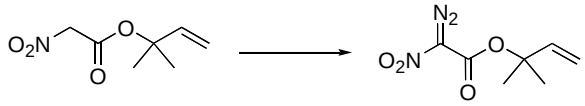
120a **121a**

***iso*-Propyl nitro diazoacetate (121a).** Yellow oil (163 mg, 86%): R_f 0.67 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (sept, J = 5.7 Hz, 1H), 1.30 (d, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 101.6 (CN_2), 71.7, 21.8; IR (film) 2150 (CN_2), 1738 (C=O), 1517, 1321 (NO_2), 1094, 909 cm^{-1}.

120c **121c**

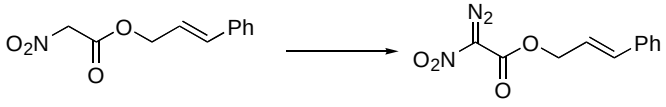
Allyl nitro diazoacetate (121c). Yellow oil (159 mg, 88%): R_f 0.61 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-6.00 (m, 1H), 5.34-5.44 (m, 2H), 4.79-4.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 130.6, 120.1, 101.6 (CN_2), 67.1; IR (film)

2147 (CN_2), 1746 (C=O), 1513, 1320 (NO_2), 1216, 1108, 942 cm^{-1}; HRMS (EI^+) calcd for $C_5H_6N_3O_4$ $[M+1]^+$: 172.03583, found: 172.03530.



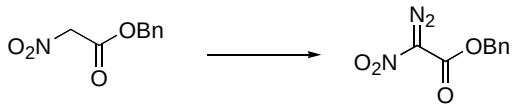
120d **121d**

1,1-(Dimethyl)allyl 2-nitro diazoacetate (121d). Yellow oil (89 mg, 73%): R_f 0.61 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (dd, J = 17.4, 10.9 Hz, 1H), 5.29 (d, J = 17.4 Hz, 1H), 5.19 (d, J = 10.9 Hz, 1H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 140.8, 114.8, 86.1, 26.6; IR (film) 2143 (CN_2), 1744 (C=O), 1515, 1321 (NO_2), 1218, 1103 cm^{-1}; HRMS (EI^+) calcd for $C_7H_9N_3O_4$ $[M]^+$: 199.05931, found: 199.05898.



120e **121e**

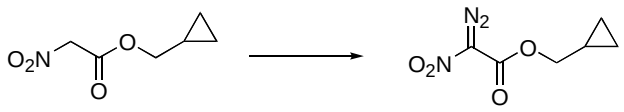
(*E*)-Cinnamyl nitro diazoacetate (121e). Yellow crystalline solid (130 mg, 81%): M.p. 62-63 ^oC; R_f 0.78 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.44 (m, 5H), 6.75 (d, J = 15.9 Hz, 1H), 6.30 (dt, J = 15.8, 6.7 Hz, 1H), 4.99 (d, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.8, 135.7, 128.9, 128.8, 127.0, 121.3, 67.6; IR (film) 2145 (CN_2), 1738, 1699 (C=O), 1515, 1316 (NO_2), 1108, 970, 743 cm^{-1}.



120f **121f**

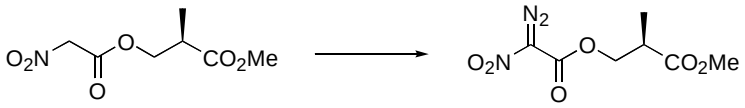
Benzyl nitro diazoacetate (121f). Yellow oil (98 mg, 96%): R_f 0.43 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (br, 5H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 134.3, 129.3, 129.0, 128.9, 101.8 (CN_2), 68.5; IR (film) 2149 (CN_2), 1746

(C=O), 1520, 1288 (NO_2), 1216, 1107, 743 cm^{-1}; HRMS (EI^+) calcd for $C_9H_7N_3O_4$ $[M]^+$: 221.04366, found: 221.04387; Elem. Anal. calcd for $C_9H_7N_3O_4$: C 48.87, H 3.19; found: C 48.87, H 3.19.



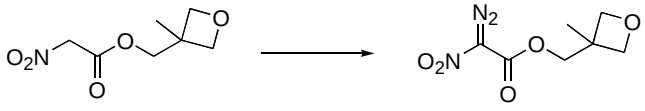
120g **121g**

Cyclopropylmethyl nitro diazoacetate (121g). Yellow oil (84 mg, 72%): R_f 0.59 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, J = 7.4 Hz, 2H), 1.17-1.24 (m, 1H), 0.61-0.66 (m, 2H), 0.34-0.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 101.6 (CN_2), 71.8, 9.8, 3.6; IR (film) 2149 (CN_2), 1743, 1697 (C=O), 1521, 1321 (NO_2), 1219, 1112, 947 cm^{-1}.



120h **121h**

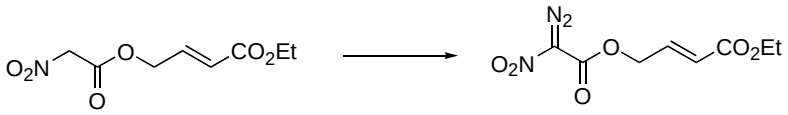
Methyl (*R*)-3-[(2-nitro-2-diazoacetyl)oxy]-2-methylpropanoate (121h). Yellow oil (84 mg, 68%): R_f 0.26 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.94-4.47 (m, 2H), 3.72 (s, 3H), 2.86-2.92 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 155.1, 101.7 (CN_2), 67.4, 52.2, 38.9, 13.6; IR (film) 2152 (CN_2), 1741 (C=O), 1520, 1294 (NO_2), 1216, 1118 cm^{-1}; HRMS (FAB) calcd for $C_7H_{10}N_3O_6$ $[M+1]^+$: 232.05696, found: 232.05580.



120i **121i**

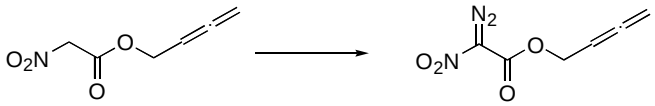
(3-Methyloxetan-3-yl)methyl nitro diazoacetate (121i). Yellow oil (114 mg, 87%): R_f 0.12 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 1H), 4.44 (s,

1H), 4.39 (s, 2H), 4.37 (s, 2H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 102.0 (CN_2), 79.2, 70.7, 39.3, 20.9; IR (film) 2150 (CN_2), 1746, 1703 (C=O), 1520 1323 (NO_2), 1220, 1114, 979 cm^{-1}.



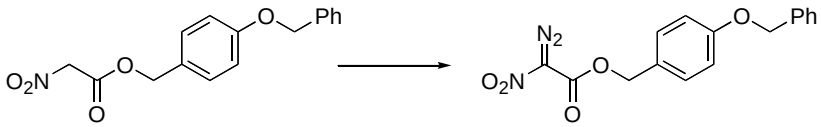
120j **121j**

4-(But-2-enoic acid ethyl ester)-2-nitro diazoacetate (121j). Yellow solid (312 mg, 81%): M.p. 40-42 ^{o}C; R_f 0.56 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, J = 15.8, 4.9 Hz, 1H), 5.95 (dt, J = 15.8, 1.9 Hz, 1H), 4.97 (dd, J = 4.9, 1.9 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 154.9, 139.0, 123.5, 101.9 (CN_2), 64.4, 60.7, 14.1; IR (solid) 2149 (CN_2), 1750, 1717 (C=O), 1519, 1320 (NO_2), 1118 cm^{-1}.



120k **121k**

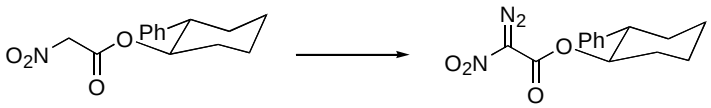
Buta-2,3-dienyl nitro diazoacetate (121k). Yellow oil (351 mg, 91%): R_f 0.46 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (qn, J = 6.8 Hz, 1H), 4.89-4.93 (m, 2H), 4.79-4.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 85.3, 77.2, 64.3, -3.50; IR (film) 2150 (CN_2), 1751 (C=O), 1522, 1327 (NO_2), 1106 cm^{-1}.



120l **121l**

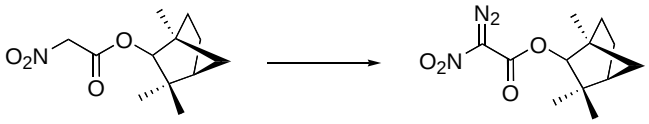
4-(Benzyloxy)benzyl nitro diazoacetate (121l). Yellow crystalline solid (93 mg, 85%): M.p. 89-90 ^{o}C; R_f 0.58 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.47 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 5.30 (s, 2H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 159.6, 155.4, 136.8, 130.9, 128.8, 128.2, 127.6, 126.7, 115.2, 70.2, 68.4; IR (solid) 2146 (CN_2), 1745, 1694 (C=O), 1514, 1319 (NO_2), 1217, 1101 cm^{-1}; HRMS (FAB^+) calcd for $C_{16}H_{13}N_3O_5$ $[M]^+$: 327.08551, found: 327.08694.



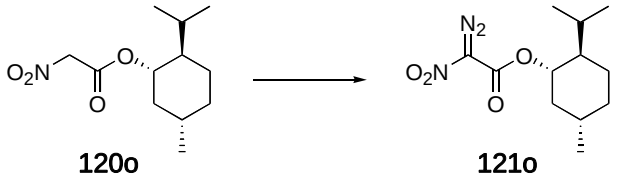
120m **121m**

(*1R*,2S)-2-Phenylcyclohexyl nitro diazoacetate (121m).** Yellow oil (298 mg, 61%): R_f 0.62 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H), 5.06-5.12 (m, 1H), 2.68-2.75 (m, 1H), 2.26-2.30 (m, 1H), 1.91-2.01 (m, 2H), 1.80-1.84 (m, 1H), 1.58-1.68 (m, 1H), 1.57-1.50 (m, 2H), 1.26-1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 142.3, 128.8, 127.5, 127.1, 101.1 (CN_2), 80.2, 49.9, 33.5, 32.5, 25.7, 24.8; IR (film) 2145 (CN_2), 1743, 1696 (C=O), 1520, 1324 (NO_2), 1219, 1112, 757 cm^{-1}.



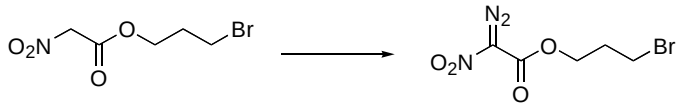
120n **121n**

(*1S,2S,4R*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl nitro diazoacetate (121n). Yellow solid (179 mg, 96%): M.p. 46 °C; R_f 0.82 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, J = 1.9 Hz, 1H), 1.79-1.60 (m, 4H), 1.55-1.45 (m, 1H), 1.23-1.27 (m, 1H), 1.15-1.17 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 101.8 (CN_2), 89.8, 48.6, 48.2, 41.3, 39.8, 29.6, 26.6, 25.8, 20.3, 19.4; IR (solid) 2145 (CN_2), 1748, 1698 (C=O), 1522, 1323 (NO_2), 1221, 1117, 742 cm^{-1}.



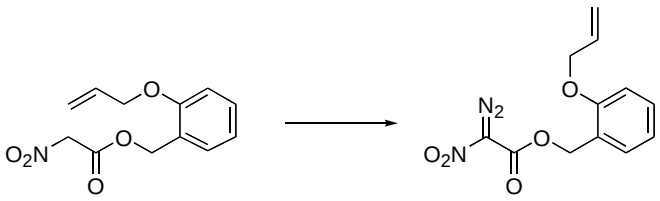
120o **121o**

(*1R,2S,5R*)-Menthyl nitro diazoacetate (121o). Pale yellow solid (734 mg, 99%): M.p. 43-45 ^{o}C; R_f 0.62 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90-4.96 (m, 1H), 2.07-2.11 (m, 1H), 1.81-1.86 (m, 1H), 1.70-1.76 (m, 2H), 1.44-1.58 (m, 2H), 1.05-1.14 (m, 2H), 0.84-1.00 (m, 7H), 0.79 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 101.6 (CN_2), 78.1, 47.1, 41.0, 34.1, 31.6, 26.6, 23.6, 22.1, 20.8, 16.5; IR (solid) 2145 (CN_2), 1739, 1694 (C=O), 1525, 1317 (NO_2), 1220, 1114, 950 cm^{-1}; Elem. Anal. calcd for $C_{12}H_{19}N_3O_4$: C 53.52, H 7.11; found: C 53.52, H 7.38.



120p **121p**

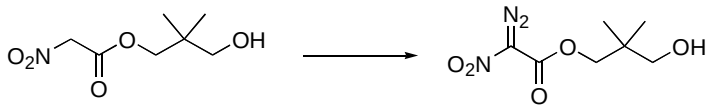
3-Bromopropyl nitro diazoacetate (121p). Yellow oil (170 mg, 83%): R_f 0.27 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 6.3 Hz, 2H), 2.24 (qn, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 101.8 (CN_2), 64.7, 31.3, 29.0; IR (film) 2148 (CN_2), 1746 (C=O), 1515, 1322 (NO_2), 1218, 1115 cm^{-1}.



120q **121q**

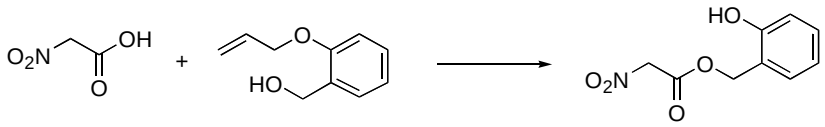
2-Allyloxy-benzyl nitro diazoacetate (121q). Yellow oil (119 mg, 99%): R_f 0.52 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.36 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 5.99-6.09 (m, 1H), 5.38-5.44 (m, 3H), 5.28-5.31 (m, 1H),

4.57-4.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 155.4, 133.1, 130.8, 130.7, 122.9, 120.9, 117.7, 112.0, 69.0, 64.4; IR (film) 2143 (CN_2), 1740 (C=O), 1515, 1317 (NO_2), 1215, 1102 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{11}N_3O_5$ [M]$^+$: 277.06987, found: 277.06949.



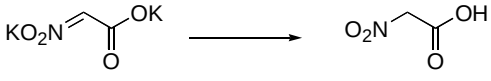
120r **121r**

3-Hydroxy-2,2-dimethyl-propyl nitro diazoacetate (121r). Pale yellow oil (95 mg, 75%): R_f 0.48 (60% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 2H), 3.42 (s, 2H), 1.78 (s(*br*), 1H), 0.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 72.2, 68.3, 36.4, 21.4; IR (film) 3406 (OH), 2145 (CN_2), 1741 (C=O), 1514, 1317 (NO_2), 1218, 1117 cm^{-1}; HRMS (EI$^+$) calcd for $C_7H_{11}N_3O_5$ [M+1]$^+$: 218.07770, found: 218.07852.



123 **122**

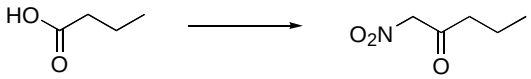
2-Hydroxybenzyl nitroacetate (122). Clear colorless oil (294 mg, 75%): R_f 0.20 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.33 (m, 1H), 7.10-7.14 (m, 1H), 6.88-6.98 (m, 2H), 5.32 (d, J = 10.4 Hz, 1H), 5.22 (d, J = 8.7 Hz, 2H); IR (film) 3454 (OH), 1751 (C=O), 1563, 1336 (NO_2), 1210 cm^{-1}.



129 **123**

Synthesis of nitroacetic acid (123). Dipotassium nitroacetate (**129**) (3.00 g, 16.6 mmol) was treated with ice-cold water (10 mL) in a 250 mL round-bottomed flask.

The resulting orange solution was then treated with a solution of L-tartaric acid (21.43 g, 142.8 mmol, 8.6 equiv) in water (40 mL) over 15 min while maintaining the temperature between -5 °C and -15 °C (dry ice, EtOH bath). The mixture was then filtered and extracted with ice-cold Et_2O (5x30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure (rotary evaporator) to afford a yellow oil. Further evaporation of residual solvent under high vacuum afforded nitroacetic acid (**123**) as a pale yellow crystalline solid (1.39 g, 80%): M.p. 84-85 ^{o}C; R_f 0.85 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s(*br*), 1H), 5.24 (s, 2H); IR (solid) 3400-2600 (OH), 1721 (C=O), 1551, 1388 (NO_2), 1224, 1189, 853 cm^{-1}.

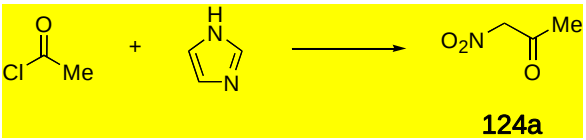


124

General procedure for the synthesis of the α-nitroketones (1-nitro-pentan-2-one, 124e). Compounds **124a** and **124g**[316] and have been previously reported. In a round-bottomed flask under an argon atmosphere carbonyl diimidazole (CDI, 649 mg, 4.0 mmol) was added dropwise to a solution of butyric acid (352 mg, 4.0 mmol, 1.0 equiv) dissolved in THF (8.0 mL). The reaction mixture was then heated to 70 ^{o}C in an oil bath for 1.0 h. In another flask a solution of potassium *tert*-butoxide (539 mg, 4.8 mmol) in THF (8.0 mL) was treated with nitromethane (1.0 mL, 4.84 mmol, 1.01 equiv). After stirring for 1 h, this suspension was treated with the imidazolide solution. The combined mixture was refluxed for 16 h then carefully quenched with water (10 mL) and washed with ether (3x40 mL). The aqueous phase was slowly acidified with 10% aqueous hydrochloric acid until pH 3 and extracted with EtOAc (3x25 mL). The organic phases were combined, dried over magnesium sulfate and evaporated under reduced pressure affording a crude oil. 1-Nitro-pentan-2-one (**124e**) was then purified by flash chromatography on silica gel (15% EtOAc/Hexane) affording the pure product as a pale yellow solid (418 mg, 80%): M.p. 28-30 ^{o}C; R_f

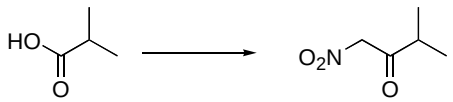
316. Yuasa, Y. *Synth. Commun*. **1998**, *28*, 395-401.

0.39 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (s, 2H), 2.53 (t, J = 7.2 Hz, 2H), 1.68 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 83.4, 42.4, 16.9, 13.6; IR (film) 1734 (C=O), 1558, 1384 (NO_2), 1188, 1125, 1057 cm^{-1}; HRMS (EI^{+}) calcd for $C_5H_9NO_3$ $[M]^{+}$: 131.05824, found: 131.05820.



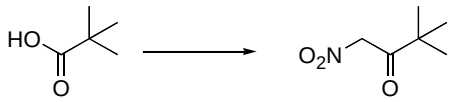
124a

1-Nitropropan-2-one (124a). Yellow crystalline solid (1.54 g, 81%): M.p. 48 °C; R_f 0.32 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 83.9, 27.6; IR (solid) 1732 (C=O), 1544, 1414, 1386 (NO_2), 1198 cm^{-1}.



124b

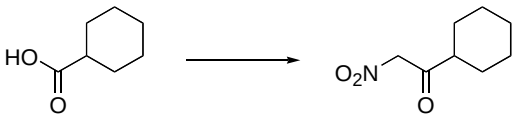
3-Methyl-1-nitrobutan-2-one (124b). Clear colorless oil (1.26 g, 59%): R_f 0.10 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 2H), 2.72 (sept, J = 6.9 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 81.9, 39.8, 17.9; IR (film) 1732 (C=O), 1560, 1385 (NO_2), 1046 cm^{-1}; HRMS (EI^{+}) calcd for $C_5H_9NO_3$ $[M]^{+}$: 131.05824, found: 131.05819.



124c

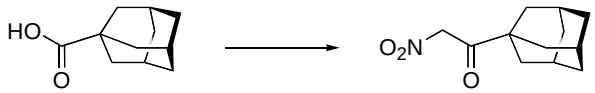
Nitromethyl *tert*-butyl ketone (124c). Pale yellow oil (1.87 g, 72%): R_f 0.35 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 2H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 80.2, 44.3, 26.0; IR (film) 1732 (C=O), 1567, 1383

(NO_2), 1319, 1063, 1016 cm^{-1}; HRMS (EI^+) calcd for $C_6H_{11}NO_3$ $[M]^+$: 145.07389, found: 145.07427.



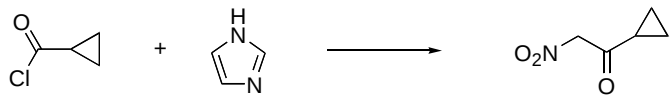
124d

Nitromethyl cyclohexyl ketone (124d). Clear colorless semi-solid (3.41 g, 89%): R_f 0.42 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 2H), 2.42-2.51 (m, 1H), 2.28-2.37 (m, 2H), 1.69-1.95 (m, 4H), 1.15-1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 82.1, 49.2, 43.0, 29.0, 25.9, 25.5, 25.4; IR (film) 1724 (C=O), 1541, 1392 (NO_2), 1201, 1002, 680 cm^{-1}.



124f

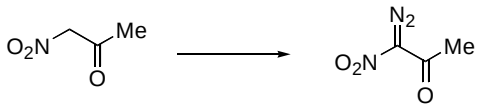
Nitromethyl 1-adamantyl ketone (124f). White platelets (4.25 g, 86%): M.p. 82 ^oC; R_f 0.73 (30% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (s, 2H), 2.11 (s(*br*), 4H), 1.86 (s, 6H), 1.81 (s, 3H), 1.69-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 80.1, 46.7, 38.9, 37.9, 36.4, 36.3, 27.9, 27.8; IR (solid) 1703 (C=O), 1547, 1328 (NO_2), 1199, 1025 cm^{-1}; HRMS (EI^+) calcd for $C_{12}H_{17}NO_3$ $[M]^+$: 223.12084, found: 223.12059; Elem. Anal. calcd for $C_{12}H_{17}NO_3$: C 64.55, H 7.67, N 6.27; found: C 64.78, H 7.87, N 6.11.



124h

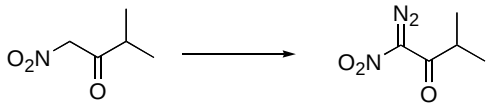
1-Cyclopropyl-2-nitro-ethanone (124h). White solid (2.20 mg, 74%): M.p. 73-75 ^oC; R_f 0.15 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (s, 2H), 1.93-

1.98 (m, 1H), 1.24-1.28 (m, 2H), 1.10-1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 83.9, 19.2, 13.1; IR (solid) 1711 (C=O), 1553, 1377 (NO_2), 1300, 1068 cm^{-1}; HRMS (EI$^+$): calcd for $C_5H_7NO_3$ $[M+1]^+$: 129.04259, found: 129.04283; Elem. Anal. calcd for $C_5H_7NO_3$: C 46.51, H 5.46, N 10.85; found: C 46.39, H 5.53, N 10.89.



124a **125a**

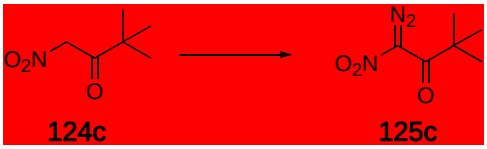
General procedure for the preparation of α-nitro-α-diazomethyl ketones (1-nitro-1-diazopropan-2-one, 125a). To a solution of 1-nitro-propan-2-one (**124a**, 140 mg, 1.36 mmol) in CH_3CN (2.0 mL) was added a 0.90M solution of trifluoro-methanesulfonyl azide (1.70 mL, 1.49 mmol, 1.1 equiv) in hexane. The reaction mixture was cooled to 0 ^{o}C then pyridine (0.22 mL, 2.72 mmol, 2.0 equiv) was added slowly dropwise. The reaction mixture was stirred for 14 h while slowly warming to room temperature. It was then concentrated under reduced pressure (rotary evaporator) affording a bright yellow residue. Purification of the crude residue by flash chromatography on silica gel ($CHCl_3$) afforded the title compound as a pale yellow solid (146 mg, 83%): M.p. 42 ^{o}C; R_f 0.41 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 112.6 (CN_2), 29.2; IR (solid) 2163 (CN_2), 1656 (C=O), 1497, 1276 (NO_2), 959 cm^{-1}; Note: this product readily sublimes if left under high vacuum for extended periods of time.



124b **125b**

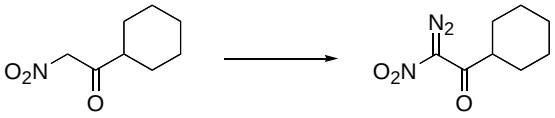
1-Nitro-3-methyl-1-diazobutan-2-one (125b). Yellow oil (259 mg, 93%): R_f 0.73 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (sept, J = 6.8 Hz, 1H), 1.20 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 37.8, 18.2; IR (film) 2170, 2136

(CN_2), 1666 (C=O), 1513, 1313 (NO_2), 1227, 989 cm^{-1}; HRMS (EI^+) calcd for $C_5H_7N_3O_3$ $[M]^+$: 157.04874, found: 157.04927.



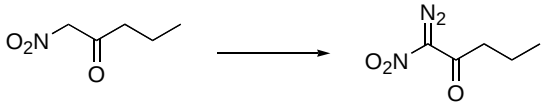
124c **125c**

1-Nitro-3,3-dimethyl-1-diazobutan-2-one (125c). Yellow oil (209 mg, 80%): R_f 0.77 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 44.8, 25.7; IR (film) 2165 (CN_2), 1648 (C=O), 1517, 1301 (NO_2), 1195, 963 cm^{-1}.



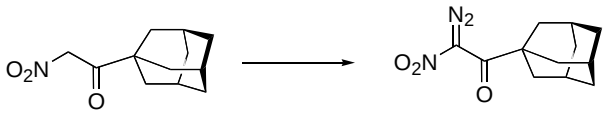
124d **125d**

Nitro-diazomethyl cyclohexyl ketone (125d). White solid (258 mg, 78%): M.p. 62 ^oC; R_f 0.69 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.38-3.44 (m, 1H), 1.82-1.89 (m, 4H), 1.71-1.76 (m, 1H), 1.35-1.49 (m, 4H), 1.22-1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 112.1 (CN_2), 47.3, 28.4, 25.8, 25.6; IR (solid) 2174 (CN_2), 1651 (C=O), 1532, 1312 (NO_2), 979 cm^{-1}.



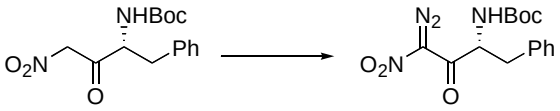
124e **125e**

1-Nitro-1-diazopentan-2-one (125e). Pale yellow solid (112 mg, 81%): M.p. 36-37 ^oC; R_f 0.60 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.96 (t, J = 7.3 Hz, 2H), 1.69 (sex, J = 7.3 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 112.3 (CN_2), 42.8, 17.2, 13.7; IR (solid) 2150 (CN_2), 1664 (C=O), 1498, 1310 (NO_2), 1015, 735 cm^{-1}.



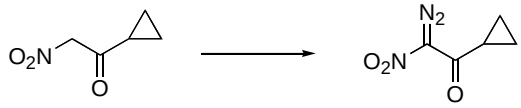
124f **125f**

1-(Adamant-1-yl)-2-nitro-2-diazoethanone (125f). Yellow solid (139 mg, 93%): M.p. 64-65 ^{o}C; R_f 0.84 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s(*br*), 3H), 2.03 (s(*br*), 6H), 1.77 (s(*br*), 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 115.0 (CN_2), 47.7, 36.6, 36.4, 28.1; IR (solid) 2164 (CN_2), 1638 (C=O), 1495, 1268 (NO_2), 1152, 989, 791 cm^{-1}.



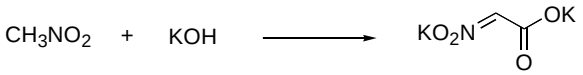
124g **125g**

***tert*-Butyl *N*-(3-nitro-1-benzyl-3-diazo-2-oxopropyl) carbamate (125g).** Pale yellow solid (114 mg, 80%): M.p. 128 ^{o}C (dec.); R_f 0.43 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.36 (m, 5H), 5.54-5.59 (m, 1H), 5.04 (d, J = 8.3 Hz, 1H), 3.19-3.24 (m, 1H), 2.75-2.81 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 155.3, 135.3, 129.5, 129.0, 127.6, 113.3, 80.7, 58.0, 37.7, 28.4; IR (solid) 3340 (NH), 2131 (CN_2), 1699, 1684 (C=O), 1510, 1309 (NO_2), 1162, 979, 708 cm^{-1}.



124h **125h**

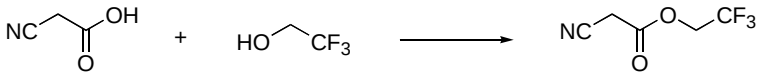
1-Cyclopropyl-2-nitro-2-diazo-ethanone (125h). Pale yellow solid (273 mg, 80%): M.p. 54-55 ^{o}C; R_f 0.67 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13-3.19 (m, 1H), 1.30-1.34 (m, 2H), 1.16-1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 18.8, 13.5; IR (solid) 2151 (CN_2), 1644 (C=O), 1512, 1306 (NO_2), 1036, 998 cm^{-1}; HRMS (EI^{+}) calcd for $C_5H_5N_3O_3$ $[M+1]^{+}$: 156.0332, found: 156.0396.



129

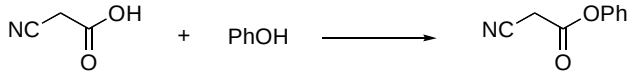
Synthesis of dipotassium nitroacetate (129). In a two-necked round-bottomed flask equipped with a condenser, to a solution of potassium hydroxide (44.8 g, 798 mmol) in water (22.5 mL) at 70 °C was added slowly dropwise nitromethane (10.8 mL, 12.2 g, 200 mmol) *via* syringe. After completion of the addition, the stirring was stopped and the temperature of the oil bath increased to 160 °C and heated for 1 h. The resulting peach colored solid was then allowed to cool to room temperature, filtered through a sintered glass frit and washed with methanol (3x75 mL). The free-flowing peach colored powder was then dried under vacuum overnight (15.3 g, 84%); M.p. 240 °C (dec.) (lit. 262 °C (dec.).

General procedure for the synthesis of α-cyanomethyl esters (132b-h). Ethyl cyanoacetate (**132a**) is commercially available and compound **132c**[118b] has been previously reported. The α-cyanoesters substrates were prepared according to the method reported by Nahmany and Melman involving the DCC coupling of cyanoacetic acid and the desired alcohol.[118a]



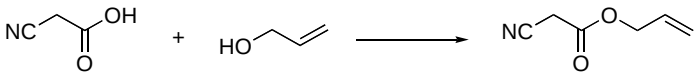
132b

2,2,2-Trifluoroethyl cyano-acetic acid ester (132b). Yellow oil (1.88 g, 75%): R_f 0.27 (20% EtOAc/Hexane); ^{19}F NMR (400 MHz, $CDCl_3$) δ -76.7 (t, J = 7.9 Hz, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (q, J = 8.2 Hz, 2H), 3.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 122.5 (q, J = 277.2 Hz, 1C), 112.4, 61.9 (q, J = 37.4 Hz, 1C), 24.5; IR (film) 2214 (CN), 1768 (C=O), 1281, 1156, 1050 cm^{-1}.



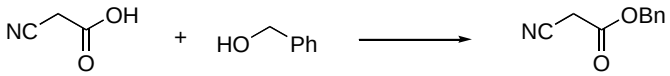
132c

Phenyl cyano-acetic acid ester (132c). White solid (1.41 g, 39%): M.p. 40-41 ^{o}C; R_f 0.27 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.41 (m, 2H), 7.12-7.14 (m, 1H), 7.12 (d, J = 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 149.9, 129.6, 126.6, 121.0, 113.2, 24.8; IR (film) 2261 (CN), 1760 (C=O), 1593, 1490, 1257, 1222, 926 cm^{-1}; Elem. Anal. calcd for $C_9H_7NO_2$: C 67.07, H 4.38, N 8.69; found: C 67.07, H 4.38, N 8.83.



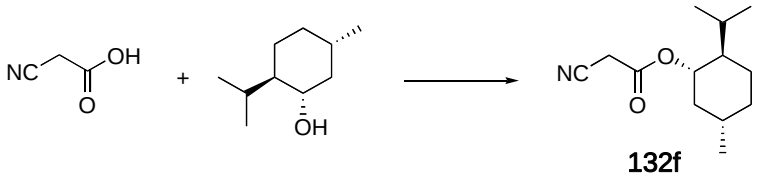
132d

Allyl cyano-acetic acid ester (132d). Pale yellow oil (3.99 g, 93%): R_f 0.29 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.91 (m, 1H), 5.24-5.35 (m, 2H), 4.64 (d, J = 5.8 Hz, 2H), 3.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 130.8, 119.6, 113.2, 67.2, 24.7; IR (film) 2263 (CN), 1744 (C=O), 1332, 1184, 991 cm^{-1}.



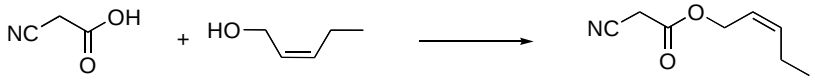
132e

Benzyl cyano-acetic acid ester (132e). Clear colorless oil (189 mg, 92%): R_f 0.53 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 5.23 (s, 2H), 3.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 134.5, 129.1, 128.9, 128.8, 113.1, 68.7, 24.9; IR (solid) 2162 (CN), 1751 (C=O), 1336, 1177 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{10}H_9NO_2$ [M-H]$^{-}$: 174.2 *m/z*, found: 174.1 *m/z*.



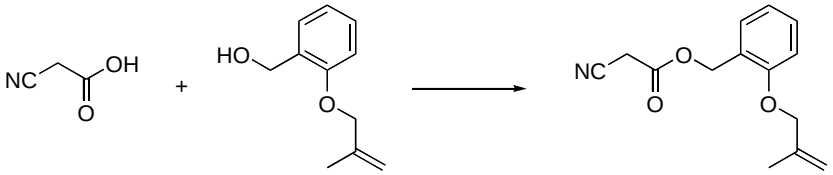
132f

(*1R, 2S, 5R*)-Menthyl cyano-acetic acid ester (132f). White solid (1.19 g, 83%): M.p. 78-79 ^{o}C; R_f 0.60 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (dt, J = 10.9, 4.5 Hz, 1H), 3.44 (s, 2H), 1.99-2.03 (m, 1H), 1.82-1.88 (m, 1H), 1.60-1.73 (m, 2H), 1.40-1.50 (m, 2H), 1.03-1.11 (m, 2H), 0.89-0.93 (m, 7H), 0.77 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 113.3, 77.7, 46.9, 40.7, 34.2, 31.6, 26.5, 25.2, 23.5, 22.1, 20.9, 16.4; IR (film) 2263 (CN), 1736, 1337, 1193 cm^{-1}; Elem. Anal. calc. for $C_{13}H_{21}NO_2$: C 69.92, H 9.48, N 6.27; found: C 70.03, H 9.81, N 6.41.



132g

(*Z*)-Cyano-acetic acid but-1-enyl ester (132g). Clear colorless oil (1.18 g, 95%): R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61-5.70 (m, 1H), 5.41-5.49 (m, 1H), 4.70 (d, J = 7.0 Hz, 2H), 3.45 (s, 2H), 2.09 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 138.5, 121.2, 113.3, 62.4, 24.8, 20.9, 14.0; IR (film) 2266 (CN), 1748 (C=O), 1266, 1184 cm^{-1}; LRMS (APCI, Neg) calcd for $C_8H_{11}NO_2$ [M-1]$^{-}$: 152.2 *m/z*, found: 152.2 *m/z*.

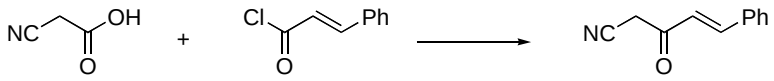


132h

Cyano-acetic acid-2-(2-methyl-allyloxy)-benzyl ester (132h). Clear colorless oil (1.05 g, 94%): R_f 0.43 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-

7.36 (m, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 5.32 (s, 2H), 5.09 (s, 1H), 5.01 (s, 1H), 4.48 (s, 2H), 3.47 (s, 2H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 156.9, 140.7, 130.5, 130.4, 123.0, 120.7, 113.2, 112.83, 112.79, 111.9, 71.8, 64.4, 24.8, 19.5; IR (film) 2263 (CN), 1746 (CO), 1495, 1244, 1177 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{14}H_{15}NO_3$ $[M-1]^+$: 244.3 *m/z*, found: 244.2 *m/z*.

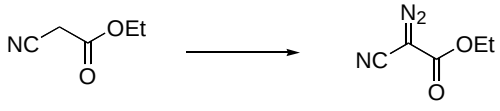
General procedure for the synthesis of α-cyanomethyl ketones (132i-j). Benzoylacetonitrile (**132i**) is commercially available while α-cyanomethyl ketone **132j** was prepared from cyanoacetic acid and the desired acid chloride according to Chen and Sieburth.[117b]



132j

Cyanomethyl (*E*)-cinnamyl ketone (132j). Pale yellow solid (470 mg, 51%): M.p. 76-77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.45-7.47 (m, 2H), 6.88 (s, 1H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 146.8, 133.6, 131.9, 129.4, 129.1, 122.5, 114.2, 31.1; IR (film) 2258 (CN), 1671 (C=O), 1329, 1179, 924 cm^{-1}.

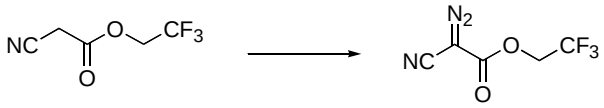
Caution: *Although we have not experienced any problems in the handling of these compounds (triflyl azide and the α-cyano-α-diazocarbonyl compounds), extreme care should be taken when manipulating them due to their explosive nature.*



132a **133a**

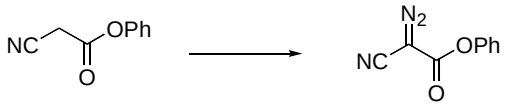
General procedure for the preparation of α-cyano-α-diazocarbonyls (Ethyl cyano diazoacetate, 133a). To a stirred solution of ethyl cyanoacetate (**132a**, 100

mg, 0.88 mmol) in CH_3CN (2.0 mL) cooled in an ice bath at 0 ^oC was added triflyl azide (1.6 mL, 0.85M in hexane, 1.5 equiv). Pyridine (0.14 mL, 1.76 mmol, 2.0 equiv) was then added slowly dropwise. The reaction mixture was stirred for 14 h warming slowly to room temperature then concentrated under reduced pressure (rotary evaporator). All diazo compounds of this type were prepared using the exact same procedure. Purification of the crude residue by flash chromatography on silica gel ($CHCl_3$) afforded ethyl cyano diazoacetate (**133a**) as a slightly volatile yellow oil (97 mg, 79%): R_f 0.46 ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.33 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 107.5, 76.8, 63.6, 14.4; IR (film) 2230 (CN), 2132 (CN_2), 1715 (C=O), 1294, 1246, 1135 cm^{-1}.



132b **133b**

2,2,2-Trifluoroethyl cyano diazoacetate (133b). Yellow oil (116 mg, 81%): R_f 0.51 ($CHCl_3$); ^{19}F NMR (400 MHz, $CDCl_3$) δ -76.7 (t, J = 7.9 Hz, 3F); ^1H NMR (400 MHz, $CDCl_3$) δ 4.61-4.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 122.4 (q, J = 277.5 Hz, 1C), 106.4, 61.8 (q, J = 37.6 Hz, 1C), 51.9 (CN_2); IR (film) 2234 (CN), 2141 (CN_2), 1729 (C=O), 1417, 1323, 1172, 1127, 971 cm^{-1}; HRMS (EI^+) calcd for $C_5H_2F_3N_3O_2$ $[M]^+$: 193.00991, found: 193.00960.



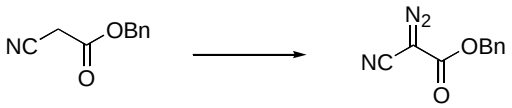
132c **133c**

Phenyl cyano diazoacetate (133c). Clear yellow solid (108 mg, 93%): M.p. 70-71 ^oC; R_f 0.36 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.43 (m, 2H), 7.27-7.31 (m, 1H), 7.16-7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.9, 129.7, 126.8, 121.2, 107.0, 52.0 (CN_2); IR (solid) 2231 (CN), 2140 (CN_2), 1731 (C=O), 1493,

1325, 1301, 1191, 1088 cm^{-1}; Elem. Anal. calcd for $C_9H_5N_3O_2$: C 57.76, H 2.69, N 22.45; found: C 57.63, H 2.58, N 22.50.

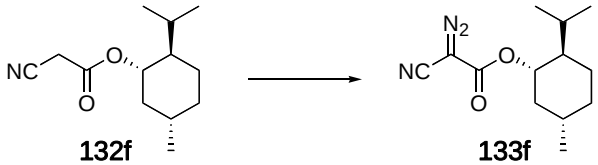
132d **133d**

Allyl cyano diazoacetate (133d). Yellow oil (91 mg, 86%): R_f 0.49 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.85-5.94 (m, 1H), 5.27-5.38 (m, 2H), 4.74 (dt, J = 5.9, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 130.8, 119.9, 107.3, 67.6; IR (film) 2230 (CN), 2134 (CN_2), 1717 (C=O), 1368, 1133 cm^{-1}.



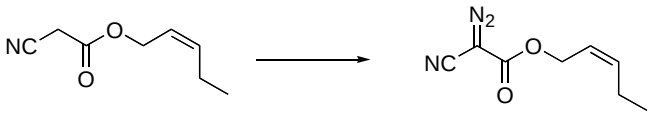
132e **133e**

Benzyl cyano diazoacetate (133e). Pale pink solid (99 mg, 86%): M.p. 37-38 ^oC; R_f 0.41 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.5, 129.0, 128.8, 128.6, 107.3, 68.7; IR (solid) 2231 (CN), 2135 (CN_2), 1706 (C=O), 1379, 1316, 1116 cm^{-1}.



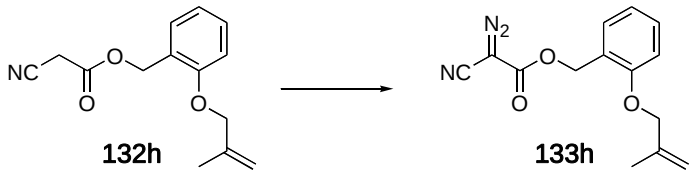
132f **133f**

(*1R*,2*S*,5*R*)-Menthyl cyano diazoacetate (133f). Yellow oil (102 mg, 71%): $[\alpha]_D$ -92.9 ^{o} (*c* 0.62, $CHCl_3$); R_f 0.59 ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.80-4.87 (m, 1H), 2.01-2.04 (m, 1H), 1.81-1.85 (m, 1H), 1.67-1.72 (m, 2H), 1.42-1.51 (m, 2H), 1.04-1.12 (m, 2H), 0.83-0.92 (m, 7H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 107.6, 78.4, 47.0, 41.0, 34.1, 31.6, 26.6, 23.7, 22.1, 20.8, 16.6; IR (film) 2229 (CN), 2130 (CN_2), 1706 (C=O), 1456, 1240, 1127, 950, 737 cm^{-1}.



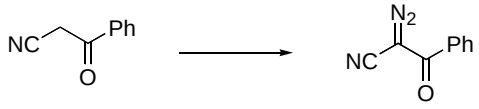
132g **133g**

(*Z*)-Pent-2-enyl cyano diazoacetate (133g). Yellow oil (392 mg, 84%): R_f 0.55 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62-5.71 (m, 1H), 5.41-5.49 (m, 1H), 4.76 (d, *J* = 6.7 Hz, 2H), 2.06-2.11 (m, 2H), 0.93-0.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 138.6, 121.2, 107.4, 62.6, 20.8, 13.9; IR (film) 2229 (CN), 2132 (CN_2), 1713 (C=O), 1265, 1124, 918 cm^{-1}.



132h **133h**

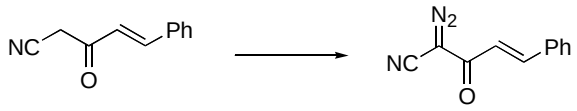
2-(2-Methyl-allyloxy)-benzyl cyano diazoacetate (133h). Yellow oil (382 mg, 91%): R_f 0.40 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.35 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.39 (s, 2H), 5.09 (s, 1H), 5.01 (s, 1H), 4.48 (s, 2H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 157.0, 140.7, 130.5, 123.0, 120.7, 112.8, 111.9, 107.4, 71.9, 64.7, 19.5; IR (film) 2229 (CN), 2131 (CN_2), 1717 (CO), 1495, 1243, 1126 cm^{-1}; Elem. Anal. calcd for $C_{14}H_{13}N_3O_3$: C 61.99, H 4.83, N 15.49; found: C 62.02, H 5.03, N 15.38.



132i **133i**

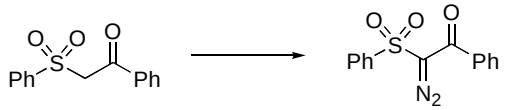
Cyanodiazomethyl phenyl ketone (133i). Yellow solid (112 mg, 94%): M.p. 39-40 ^{o}C; R_f 0.49 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.89 (m, 2H), 7.60-7.64 (m,

1H), 7.48-7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 134.7, 134.0, 129.0, 128.2, 109.4; IR (solid) 2223 (CN), 2134 (CN_2), 1646 (C=O), 1281, 1247, 633 cm^{-1}.



132j **133j**

Cyanodiazomethyl (*E*)-cinnamyl ketone (133j). Pale pink solid (120 mg, 99%): M.p. 108-109 °C; R_f 0.41 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 15.5 Hz, 1H), 7.58-7.60 (m, 2H), 7.39-7.44 (m, 3H), 6.98 (d, J = 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 145.5, 133.6, 131.6, 129.2, 129.1, 118.7, 108.7, 59.0 (CN_2); IR (solid) 2224 (CN), 2143 (CN_2), 1649 (C=O), 1592, 1339, 1197 cm^{-1}; Elem. Anal. calcd for $C_{11}H_7N_3O$: C 67.00, H 3.58, N 21.31; found: C 66.91, H 3.53, N 21.13.



134 **135**

2-(Phenyl-sulfonyl) diazoacetophenone (135). Pale yellow solid (174 mg, 98%): M.p. 114-115 °C; R_f 0.57 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.07 (m, 2H), 7.61-7.66 (m, 1H), 7.51-7.56 (m, 5H), 7.38-7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 141.4, 135.8, 134.3, 133.2, 129.2, 129.0, 128.2, 127.5, 83.3 (CN_2); IR (solid) 2114 (CN_2), 1633 (C=O), 1449, 1328, 1143 cm^{-1}; Elem. Anal. calcd for $C_{14}H_{10}N_2SO_3$: C 58.73, H 3.52, N 9.78; found: C 58.40, H 3.38, N 9.93.

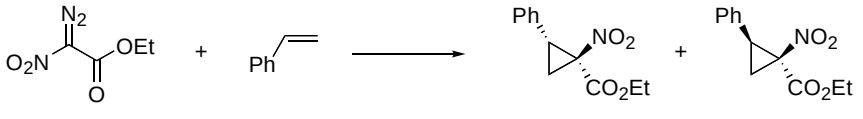
General procedure for diazo transfer reactions employing NaH as a base. NaH was rinsed with hexane (2x10 mL) and suspended in anhydrous Et_2O (2.5 mL) while cooling to 0 °C. Benzyl cyanoacetate (**132e**, 100 mg, 0.57 mmol) in Et_2O (2.5 mL) was then added slowly dropwise to the NaH suspension, stirred 15 min at 0 °C, then 1 h at room temperature. The resulting suspension was then cooled to 0 °C and triflyl

azide (1.0 mL, 0.85 M in hexane, 1.5 equiv) was added slowly dropwise. The reaction mixture was allowed to stir for 14 h, warming to room temperature, then filtered and concentrated under reduced pressure (rotary evaporator). Purification was achieved as above.

Experimental: Chapter 3

General cyclopropanation procedure. In an oven-dried round-bottomed flask was added the appropriate Rh(II) catalyst (2.0 mol%) followed by freshly distilled olefin (5.0 equiv based on diazo). In another flask the α-nitro-α-diazocarbonyl (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 to afford a 1.0M solution and added slowly dropwise to the solution containing the catalyst and olefin *via* syringe ensuring a controlled rate of nitrogen evolution. The solution was then allowed to stir an additional 2-4 h, concentrated under reduced pressure (rotary evaporator). The crude residue was purified by column chromatography on silica gel, first eluting with hexane (100%) then with 3-10% EtOAc/Hexane to afford the desired cyclopropanes.

Catalysts. $[Rh(Cap)_2]_2$, $[Rh(OAc)_2]_2$ and $[Rh(OPiv)_2]_2$ are commercially available and were purchased from Aldrich Chemical Company, while $[Rh(CF_3CO_2)_2]_2$, $[Rh(Oct)_2]_2$ and Cu(I)OTf as $[CF_3SO_3Cu]_2 \bullet C_6H_5Me$ were purchased from Strem Chemicals. $[Rh(Ph_3CCO_2)_2]_2$ was prepared according to the method of Callot *et al*., and $[Rh(1\text{-Adaman})_2]_2$ was prepared according to the method of Nelson.[317]

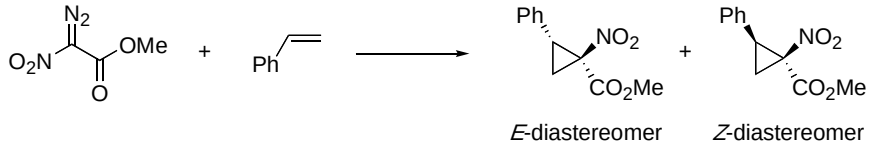


E-diastereomer *Z*-diastereomer

71 **147**

317. Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, R. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett*. **2000**, *41*, 1877-1881.

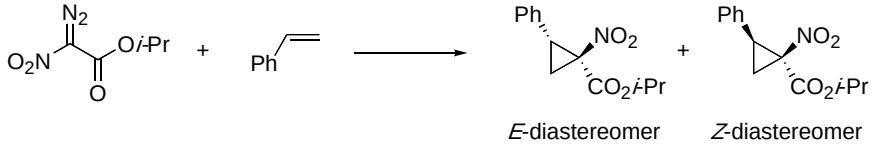
Ethyl-1-nitro-2-phenyl-cyclopropanecarboxylate (147). Clear colorless oil: **Ethyl *E*-1-nitro-2-phenyl-cyclopropanecarboxylate (147).** R_f 0.61 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 3H), 7.21-7.23 (m, 2H), 3.95-4.00 (m, 2H), 3.78 (t, *J* = 9.9 Hz, 1H), 2.46 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.21 (dd, *J* = 10.7, 6.6 Hz, 1H) 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 132.2, 128.7, 128.5, 71.9, 62.7, 34.3, 20.9, 13.7; IR (film) 1743 (C=O), 1543, 1352 (NO_2), 1213, 1146, 1022 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{13}NO_4$ [M]$^+$: 235.08446, found: 235.08520; **Ethyl *Z*-1-nitro-2-phenyl-cyclopropanecarboxylate (147).** R_f 0.54 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.34 (m, 3H), 7.21-7.26 (m, 2H), 4.33-4.39 (m, 2H), 3.48 (t, *J* = 9.5 Hz, 1H), 2.68 (dd, *J* = 9.2, 6.9 Hz, 1H), 2.03 (dd, *J* = 9.9, 6.9 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 131.6, 128.9, 128.7, 128.5, 77.5, 63.5, 33.9, 20.2, 14.2; IR (film) 1740 (C=O), 1538, 1377 (NO_2), 1293, 1147 cm^{-1}; Elem. Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27, H 5.57, N 5.95; found: C 61.02, H 5.83, N 5.97.



97 **150a**

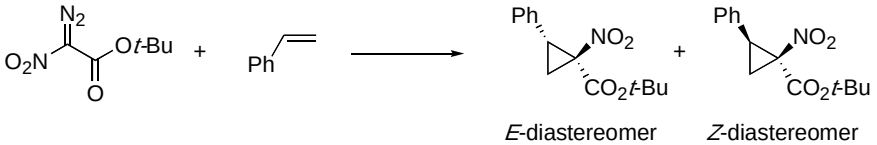
Methyl-1-nitro-2-phenyl-cyclopropanecarboxylate (150a). Clear colorless oil: **Methyl *E*-1-nitro-2-phenyl-cyclopropanecarboxylate (150a).** R_f 0.76 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 3H), 7.20-7.22 (m, 2H), 3.78 (t, *J* = 9.3 Hz, 1H), 3.51 (s, 3H), 2.46 (dd, *J* = 9.2, 6.6, Hz, 1H), 2.24 (dd, *J* = 10.8, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 132.2, 128.7, 128.6, 128.5, 71.9, 53.3, 34.4, 21.1; IR (film) 1747 (C=O), 1539, 1347 (NO_2), 1219, 1146 cm^{-1}; HRMS (EI$^+$) calcd for $C_{11}H_{11}NO_4$ [M]$^+$: 221.06881, found: 221.06937; **Methyl *Z*-1-nitro-2-phenyl-cyclopropanecarboxylate (150a)**. Pale yellow solid: M.p. 35-37 ^{o}C; R_f 0.64 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.34 (m, 3H), 7.21-7.23 (m, 2H), 3.90 (s, 3H), 3.49 (t, *J* = 9.3 Hz, 1H), 2.69 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.05 (dd, *J* = 9.9, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 131.5,

128.93, 128.89, 128.5, 76.9, 54.0, 34.1, 20.3; IR (solid) 1747 (C=O), 1536, 1441 (NO_2), 1300, 1155 cm^{-1}; Elem. Anal. calcd for $C_{11}H_{11}NO_4$: C 59.73, H 5.01, N 6.33; found: C 59.83, H 5.19, N 6.33.



121a **150b**

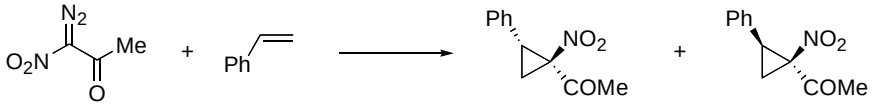
***iso*-Propyl-1-nitro-2-phenylcyclopropanecarboxylate (150b).** Clear colorless oil: IR (film) (E/Z mix) 1734 (C=O), 1540, 1351 (NO_2), 1100 cm^{-1}; ***iso*-Propyl *E*-1-nitro-2-phenylcyclopropanecarboxylate (150b).** R_f 0.73 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.33 (m, 5H), 4.81 (sept, J = 6.3 Hz, 1H), 3.76 (t, J = 9.7 Hz, 1H), 2.44 (dd, J = 9.1, 6.6 Hz, 1H), 2.18 (dd, J = 10.7, 6.6 Hz, 1H), 1.02 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 132.3, 128.7, 128.6, 128.4, 72.0, 70.8, 34.1, 21.21, 21.15, 20.6; IR (film) 1739 (C=O), 1545, 1352 (NO_2), 1217, 1104, 913 cm^{-1}; HRMS (EI^+) calcd for $C_{13}H_{15}NO_4$ $[M]^+$: 249.10011, found: 249.10065; ***iso*-Propyl *Z*-1-nitro-2-phenylcyclopropane carboxylate (150b).** R_f 0.63 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.37 (m, 5H), 5.20 (sept, J = 6.3 Hz, 1H), 3.46 (dd, J = 9.8, 9.3 Hz, 1H), 2.44 (dd, J = 9.1, 6.6 Hz, 1H), 2.00 (dd, J = 9.9, 6.9 Hz, 1H), 1.33 (dd, J = 6.3, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 131.7, 128.9, 128.8, 128.5, 73.0 71.7, 33.6, 21.8, 21.7, 20.7.



121b **150c**

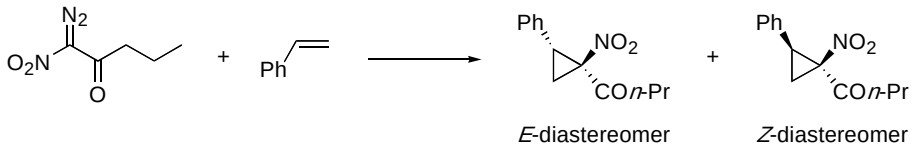
***tert*-Butyl-1-nitro-2-phenylcyclopropanecarboxylate (150c).** Pale yellow solid: IR (solid) (E/Z mix) 1735 (C=O), 1545, 1370 (NO_2), 1145, 911 cm^{-1}; ***tert*-Butyl *E*-1-nitro-2-phenylcyclopropanecarboxylate (150c).** M.p. 81-82 ^{o}C; R_f 0.43 (20%

EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.34 (m, 5H), 3.73 (t, *J* = 9.8 Hz, 1H), 2.39 (dd, *J* = 9.0, 6.6 Hz, 1H), 2.13 (dd, *J* = 10.7, 6.6 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 132.4, 128.9, 128.6, 128.3, 83.9, 72.6, 33.8, 27.5, 20.4; IR (solid) 1715 (C=O), 1541, 1347 (NO_2), 1244, 1141 cm^{-1}; HRMS (EI$^+$) calcd for $C_{14}H_{17}NO_4$ [M]$^+$: 263.11576, found: 263.11484; ***tert*-Butyl *Z*-1-nitro-2-phenyl cyclopropanecarboxylate (150c).** R_f 0.40 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.34 (m, 5H), 3.40 (t, *J* = 9.5 Hz, 1H), 2.60 (dd, *J* = 9.1, 6.9 Hz, 1H), 1.95 (dd, *J* = 9.8, 6.9 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 131.9, 128.8, 128.7, 128.5, 84.9, 73.5, 33.2, 28.1, 19.8.



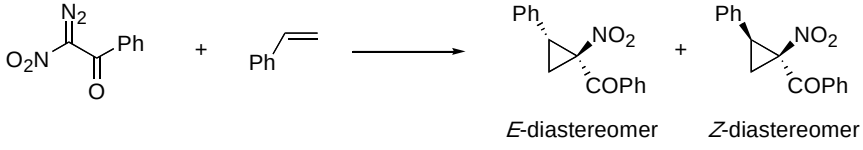
125a **150d**

1-Nitro-2-phenylcyclopropane-methyl ketone (150d). White solid (159 mg, 77%): ***E*-1-Nitro-2-phenylcyclopropane-methylketone (150d).** M.p. 67-69 ^{o}C; R_f 0.73 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.32 (m, 3H), 7.13-7.15 (m, 2H), 3.82 (t, *J* = 9.9 Hz, 1H), 2.58 (dd, *J* = 9.0, 6.4 Hz, 1H), 2.21 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ı□ □̃7, 131.3, 129.0, 128.6, 128.5, 77.1, 37.2, 29.1, 20.3; IR (solid) 1707 (C=O), 1528, 1351 (NO_2), 1127 cm^{-1}; HRMS (EI$^+$) calcd for $C_{11}H_{11}NO_3$ [M]$^+$: 205.07389, found: 205.07440; ***Z*-1-Nitro-2-phenylcyclopropane-methyl ketone (150d).** R_f 0.54 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.34 (m, 3H), 7.19-7.21 (m, 2H), 3.56 (t, *J* = 9.5 Hz, 1H), 2.73 (dd, *J* = 9.3, 6.5 Hz, 1H), 2.52 (s, 3H), 2.02 (dd, *J* = 9.8, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 131.6, 128.9, 128.87, 128.7, 84.3, 36.9, 27.8, 22.8; IR (solid) 1707 (C=O), 1533, 1357 (NO_2), 1267, 1231, 1136 cm^{-1}; Elem. Anal. calcd for $C_{11}H_{11}NO_3$: C 64.38, H 5.40, N 6.83; found: C 64.16, H 5.45, N 6.70.



125e **150e**

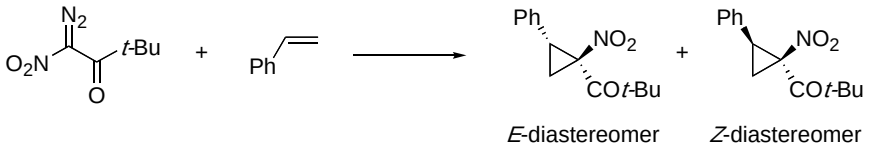
1-Nitro-2-phenylcyclopropane-*n*-propyl ketone (150e). Clear colorless oil (113 mg, 74%): ***E*-1-nitro-2-phenylcyclopropane-*n*-propylketone (150e).** R_f 0.63 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.33 (m, 3H), 7.12-7.14 (m, 2H), 3.81 (t, *J* = 9.9 Hz, 1H), 2.68 (dd, *J* = 6.4, 4.4 Hz, 1H), 2.17 (dd, *J* = 10.6, 6.4 Hz, 1H), 1.35-1.39 (m, 2H), 1.12-1.20 (m, 2H), 0.62 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ı□6.3, 131.4, 128.9, 128.6, 77.1, 43.5, 36.7, 20.1, 17.0, 13.4; IR (film) (E/Z mix) 1716 (C=O), 1535, 1349 (NO_2), 698 cm^{-1}; HRMS (EI$^+$) calcd for $C_{13}H_{15}NO_3$ $[M]^+$: 233.10519, found: 233.10524; ***Z*-1-nitro-2-phenylcyclopropane-*n*-propyl ketone (150e).** R_f 0.63 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.33 (m, 3H), 7.19-7.21 (m, 2H), 3.56 (t, *J* = 9.5 Hz, 1H), 2.90-3.05 (m, 1H), 2.75-2.83 (m, 2H), 1.89-1.98 (m, 2H), 1.65-1.75 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 131.8, 129.2, 128.8, 128.7, 80.1, 41.6, 36.1, 22.5, 17.5, 13.7.



98 **150f**

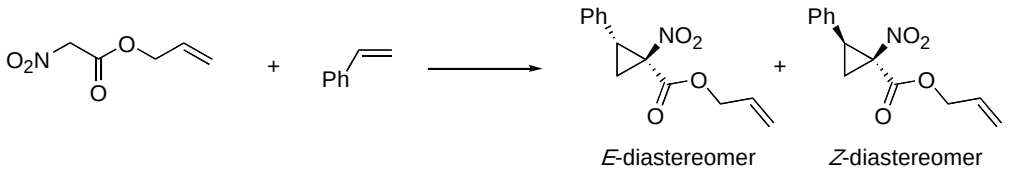
1-Nitro-2-phenylcyclopropane-acetophenone (150f). Pale yellow solid: ***E*-1-Nitro-2-phenylcyclopropane-acetophenone (150f).** R_f 0.56 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.62-7.68 (m, 1H), 7.45-7.52 (m, 2H), 7.10-7.35 (m, 5H), 4.09 (t, *J* = 9.4 Hz, 1H), 2.71 (dd, *J* = 9.2, 6.5 Hz, 1H), 2.30 (dd, *J* = 10.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ □□ı, 135.3, 133.9, 131.5, 129.1, 128.8, 128.6, 128.4, 128.1, 74.7, 36.4, 20.5; IR (solid) 1703 (C=O), 1547, 1329 (NO_2), 1199, 1025, 651 cm^{-1}; ***Z*-1-Nitro-2-phenylcyclopropane-acetophenone (150f).** M.p. 123-125 ^{o}C; R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.89-7.91 (m, 2H), 7.60-7.64 (m, 1H), 7.48-7.58 (m, 2H), 7.28-7.44 (m, 5H), 3.87 (t, J = 9.6 Hz, 1H), 3.04 (dd, J = 9.4, 6.6 Hz, 1H), 1.99 (dd, J = 9.8, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 135.1, 134.2, 131.6, 129.2, 129.1, 128.8, 128.3, 128.7, 76.9, 32.5, 21.6; IR (solid) 1683 (C=O), 1526, 1347 (NO_2), 1174, 658 cm^{-1}; HRMS (EI$^+$) calcd for $C_{16}H_{13}NO_3$ [M]$^+$: 267.08954, found: 267.08906; Elem. Anal. calcd for $C_{16}H_{13}NO_3$: C 71.90, H 4.90, N 5.24; found: C 72.01, H 4.89, N 5.26.



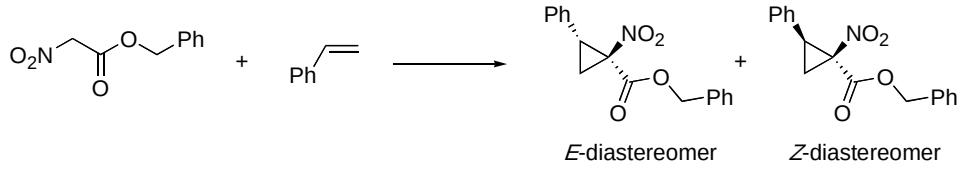
125c **150g**

1-Nitro-2-phenylcyclopropane-*tert*-butylketone (150g). White solid (147 mg, 55%): M.p. 48-50 ^{o}C; R_f 0.80 (20% EtOAc/Hexane); IR (solid) (E/Z mix) 1705 (C=O), 1539, 1352 (NO_2), 911, 735 cm^{-1}; ***E*-1-Nitro-2-phenyl cyclopropane-*tert*-butylketone (150g).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 4H), 7.09-7.12 (m, 1H), 3.86 (t, J = 9.3 Hz, 1H), 2.54 (dd, J = 9.2, 6.5 Hz, 1H), 1.98 (dd, J = 10.7, 6.5 Hz, 1H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 131.7, 128.9, 128.6, 128.5, 76.6, 44.9, 34.8, 27.2, 20.2; ***Z*-1-Nitro-2-phenylcyclopropane-*tert*-butylketone (150g).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.39 (m, 4H), 7.09-7.12 (m, 1H), 3.55 (t, J = 9.6 Hz, 1H), 2.76 (dd, J = 9.4, 6.8 Hz, 1H), 1.71(dd, J = 9.8, 6.8 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 131.8, 129.0, 128.7, 128.5, 76.7, 46.2, 31.7, 28.2, 20.2; IR (film) 1705 (C=O), 1533, 1348 (NO_2), 1234, 1015, 882 cm^{-1}; HRMS (EI$^+$) calcd for $C_{14}H_{17}NO_3$ [M]$^+$: 247.12084, found: 247.12170; Elem. Anal. calcd for $C_{14}H_{17}NO_3$: C 68.00, H 6.93, N 5.66; found: C 68.27, H 7.06, N 5.70.



120c 150h

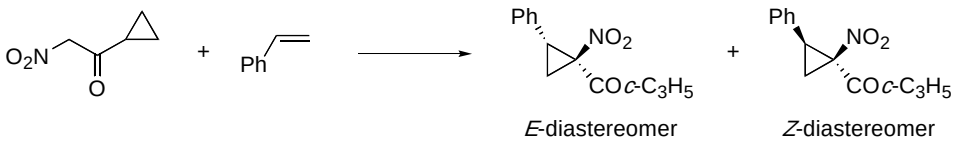
Allyl-1-nitro-2-phenylcyclopropanecarboxylate (150h). Clear colorless oil (86 mg, 71%): **Allyl *E*-1-nitro-2-phenylcyclopropanecarboxylate (150h)**. R_f 0.58 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.32 (m, 3H), 7.21-7.22 (m, 2H), 5.43-5.52 (m, 1H), 5.07-5.12 (m, 2H), 4.38-4.39 (m, 2H), 3.76-3.81 (m, 1H), 2.45-2.49 (m, 1H), 2.20-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 132.1, 130.7, 128.7, 128.66, 128.64, 128.4, 119.3, 71.9, 67.1, 34.3, 20.9; IR (film) 1742 (C=O), 1541, 1350, 1331 (NO_2), 1143, 698 cm^{-1}; **Allyl *Z*-1-nitro-2-phenylcyclopropanecarboxylate (150h)**. R_f 0.46 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.34 (m, 3H), 7.22-7.27 (m, 2H) 5.91-5.98 (m, 1H), 5.36 (ddd, J = 30.0, 16.5, 1.2 Hz, 2H), 4.77-4.84 (m, 2H), 3.51 (t, J = 9.5 Hz, 1H), 2.71 (dd, J = 9.2, 7.0 Hz, 1H), 2.06 (dd, J = 9.9, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 131.5, 130.9, 128.92, 128.88, 128.6, 119.8, 75.8, 72.7, 67.6, 34.1, 20.3; IR (film) 1740 (C=O), 1544, 1283 (NO_2), 1152 cm^{-1}.



120f 150i

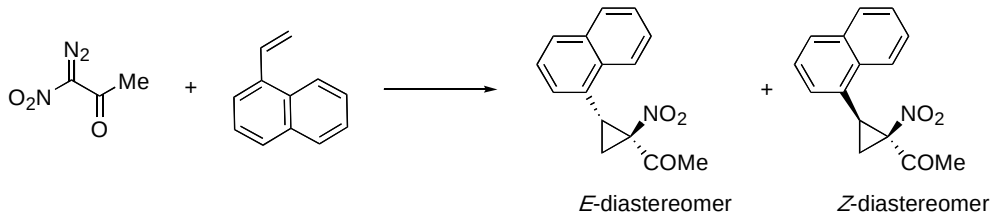
Benzyl 1-nitro-2-phenylcyclopropanecarboxylate (150i). (106 mg, 83%): **Benzyl *E*-1-nitro-2-phenylcyclopropanecarboxylate (150i).** White crystalline solid: M.p. 49-50 ^{o}C; R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.34 (m, 6H), 7.17-7.21 (m, 2H), 7.00-7.04 (m, 2H), 4.94 (dd, J = 21.7, 12.1 Hz, 1H), 3.80 (t, J = 10.0 Hz, 1H), 2.48 (dd, J = 9.2, 6.6 Hz, 1H), 2.23 (dd, J = 10.8, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 134.4, 132.0, 128.7, 128.64, 128.60, 128.54, 128.47, 128.45, 71.9, 68.4, 34.4, 21.1; IR (solid) 1744 (C=O), 1543, 1351 (NO_2), 1148 cm^{-1};

Benzyl *Z*-1-nitro-2-phenylcyclopropanecarboxylate (150i). White crystalline solid: M.p. 88-90 ^{o}C; R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.39 (m, 4H), 7.30-7.34 (m, 4H), 7.21-7.27 (m, 2H), 5.33 (dd, *J* = 17.4, 12.3 Hz, 2H), 3.51 (t, *J* = 9.6 Hz, 1H), 2.70 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.05 (dd, *J* = 9.9, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 134.6, 131.5, 129.0, 128.92, 128.89, 128.6, 128.4, 72.8, 68.8, 34.1, 20.4; IR (solid) 1739 (C=O), 1532, 1355, 1298 (NO_2), 1160, 695 cm^{-1}; Elem. Anal. calcd for $C_{17}H_{15}NO_4$: C 68.68, H 5.09, N 4.71; found: C 68.39, H 5.18, N 4.72.



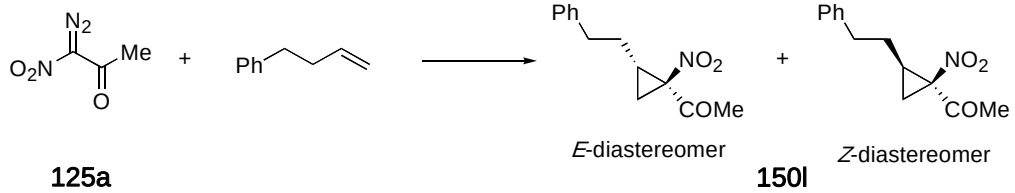
150j

Cyclopropyl-(1-nitro-2-phenyl-cyclopropyl)-methanone (150j). (115 mg, 72%): ***E*-Cyclopropyl-(1-nitro-2-phenyl-cyclopropyl)-methanone (150j).** Pale yellow crystalline solid: M.p. 69-70 ^{o}C; R_f 0.65 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.31 (m, 3H), 7.11-7.17 (m, 2H), 3.86 (t, *J* = 9.9 Hz, 1H), 2.58 (dd, *J* = 9.3, 6.3 Hz, 1H), 2.22 (dd, *J* = 10.6, 6.3 Hz, 1H), 1.99-2.07 (m, 1H), 1.08-1.16 (m, 1H), 0.89-0.99 (m, 1H), 0.40-0.49 (m, 1H), 0.09-0.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 131.9, 128.7, 128.7, 128.4, 37.0, 21.9, 20.1, 13.6, 11.8; IR (solid) 1697 (C=O), 1526, 1345 (NO_2), 1057, 694 cm^{-1}; HRMS (EI^{+}) calcd for $C_{13}H_{13}NO_3$: $[M]^{+}$ 231.08954, found: 231.08956; ***Z*-Cyclopropyl-(1-nitro-2-phenyl-cyclopropyl)-methanone (150j).** White semi-solid: R_f 0.62 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.33 (m, 5H), 3.61 (t, *J* = 9.5 Hz, 1H), 2.75 (dd, *J* = 9.3, 6.5 Hz, 1H), 1.93-2.07 (m, 2H), 1.21-1.32 (m, 1H), 0.90-0.99 (m, 1H), 0.40-0.49 (m, 1H), 0.09-0.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 131.8, 128.8, 128.5, 76.7, 35.6, 22.6, 18.7, 13.5; IR (film) (E/Z mix) 1696 (C=O), 1529, 1392, 1346 (NO_2), 1057 cm^{-1}; Elem. Anal. calcd for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06; found: C 67.19, H 5.65, N 6.00.



125a **150k**

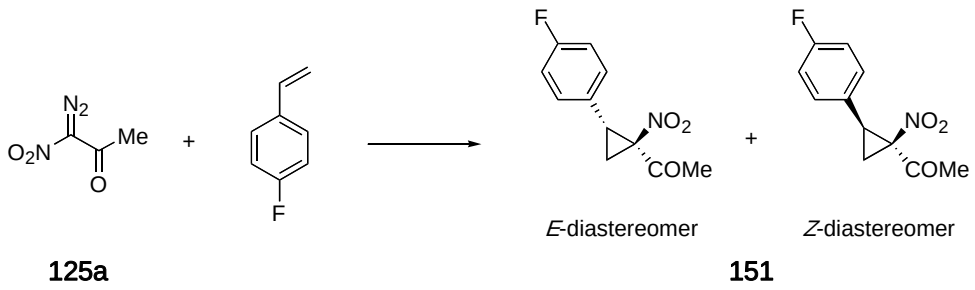
1-(2-Naphthalen-1-yl-1-nitro-cyclopropyl)-ethanone (150k). (155 mg, 52%): ***E*-1-(2-Naphthalen-1-yl-1-nitro-cyclopropyl)-ethanone (150k).** White crystalline solid: M.p. 118-120 ^{o}C; R_f 0.68 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.84 (m, 3H), 7.58 (s, 1H), 7.50-7.52 (m, 2H), 7.28 (d, J = 8.5 Hz, 1H), 3.98 (t, J = 10.0 Hz, 1H), 2.73 (dd, J = 9.3, 6.4 Hz, 1H), 2.29 (dd, J = 10.5, 6.4 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 133.2, 133.1, 128.7, 128.1, 127.8, 127.7, 126.84, 126.79, 126.1, 77.2, 37.4, 29.1, 20.5; IR (solid) 1708 (C=O), 1529, 1348 (NO_2), 823, 759 cm^{-1}; HRMS (EI^{+}) calcd for $C_{15}H_{13}NO_3$ $[M]^{+}$: 255.08954, found: 255.08931; ***Z*-1-(2-Naphthalen-1-yl-1-nitro-cyclopropyl)-ethanone (150k).** Clear colorless oil: R_f 0.56 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.93 (m, 3H), 7.67 (s, 1H), 7.42-7.57 (m, 2H), 7.27-7.33 (m, 1H), 3.68-3.77 (m, 1H), 2.87 (dd, J = 9.3, 6.4 Hz, 1H), 2.10 (dd, J = 9.4, 6.1 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 133.2, 136.4, 128.1, 127.91, 127.86, 127.0, 126.8, 126.7, 126.3, 84.5, 37.1, 36.5, 27.8, 22.9, 15.6; Elem. Anal. calcd for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49; found: C 70.17, H 5.33, N 5.15.



125a **150l**

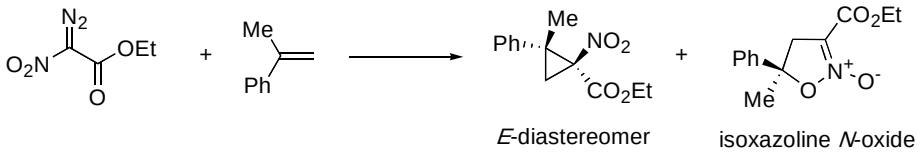
1-(1-Nitro-2-phenethyl-cyclopropyl)-ethanone (150l). Clear colorless oil (81 mg, 36%): ***E*-1-(1-nitro-2-phenethyl-cyclopropyl)-ethanone (150l).** R_f 0.52 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.32 (m, 2H), 7.22-7.24 (m, 1H), 7.14-7.16 (m, 2H), 2.43-2.72 (m, 4H), 2.38 (s, 3H), 1.83 (d, J = 9.9 Hz, 1H),

1.76-1.77 (m, 1H), 1.59-1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 140.4, 128.8, 128.64, 128.57, 76.1, 35.2, 33.8, 29.2, 28.5, 23.7; IR (film) 1713 (C=O), 1538, 1355 (NO_2), 1134, 701 cm^{-1}; Elem. Anal. calcd for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.00; found: C 66.87, H 6.49, N 5.99; ***Z*-1-(1-nitro-2-phenethyl-cyclopropyl)-ethanone (150l).** R_f 0.41 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.31 (m, 2H), 7.21-7.22 (m, 1H), 7.14-7.16 (m, 2H), 2.73-2.75 (m, 2H), 2.43 (s, 3H), 1.87-1.91 (m, 1H), 1.89 (dd, *J* = 8.9, 5.9 Hz, 1H), 1.70-1.83 (m, 1H), 1.66 (dd, *J* = 9.7, 6.0 Hz, 1H), 1.57-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 140.6, 128.8, 128.6, 126.5, 79.0, 34.5, 31.8, 29.9, 27.3, 25.1; IR (film) 1709 (C=O), 1532, 1360 (NO_2), 1142, 1033, 700 cm^{-1}.



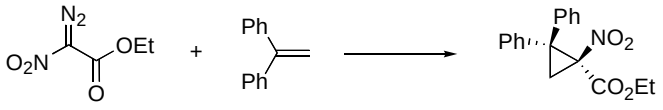
1-[1-Nitro-(2-(4-fluorophenyl)-cyclopropyl]-ethanone (151). (405 mg, 63%): ***E*-1-[1-Nitro-(2-(4-fluorophenyl)-cyclopropyl]-ethanone (151).** White crystalline solid: M.p. 70 ^{o}C; R_f 0.34 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.14 (m, 2H), 6.99-7.04 (m, 2H), 3.80 (t, *J* = 10.0 Hz, 1H), 2.55 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.22 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 162.8 (d, *J* = 248.3 Hz, 1C), 130.4, 130.3, 116.2, 115.9, 77.4, 36.6, 29.2, 20.6; IR (solid) 1716 (C=O), 1513, 1347 (NO_2), 1224, 842 cm^{-1}; HRMS (EI$^+$) calcd for $C_{11}H_{10}NO_3F$ $[M]^+$: 223.06447, found: 223.06525; ***Z*-1-[1-Nitro-(2-(4-fluorophenyl)-cyclopropyl]-ethanone (151).** Clear colorless oil: R_f 0.21 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.20 (m, 2H), 6.99-7.03 (m, 2H), 3.53 (t, *J* = 9.6 Hz, 1H), 2.68 (dd, *J* = 9.3, 6.5 Hz, 1H), 2.51 (s, 3H), 2.01 (dd, *J* = 9.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 163.1 (d, *J* = 248.2 Hz, 1C), 130.6, 130.5, 116.1, 115.8, 36.0, 27.8, 22.9; IR (film) 1710 (C=O), 1537, 1514, 1360 (NO_2), 1228 cm^{-1};

Elem. Anal. calcd for $C_{11}H_{10}NO_3F$: C 59.19, H 4.52, N 6.28; found: C 59.32, H 4.47, N 6.30.



71 **161a**

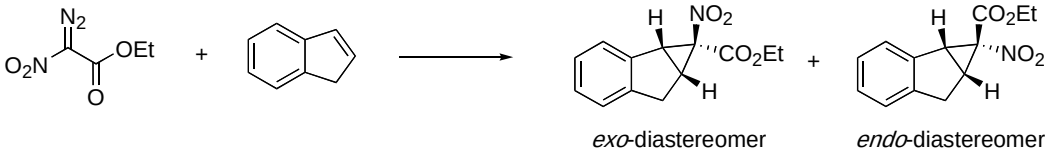
Ethyl 1-nitro-2-phenyl-2-methyl-cyclopropanecarboxylate (161a). White solid in a 72:28 product ratio cyclopropane:isoxazoline *N*-oxide after chromatography (119 mg, 95%): **Ethyl 1-nitro-(*trans*-2-phenyl)-(*cis*-2-methyl)-cyclopropanecarboxylate (161a).** (Ph is *trans* to NO_2): M.p. 54-55 ^oC; R_f 0.56 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 5H), 3.89-3.95 (m, 2H), 2.42 (d, J = 6.8 Hz, 1H), 2.15 (d, J = 6.8 Hz, 1H), 1.54 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 139.3, 128.8, 128.0, 127.9, 76.4, 62.7, 39.4, 26.5, 25.1, 13.7; IR (film) 1736 (C=O), 1543, 1369 (NO_2), 1307, 1235, 1138 cm^{-1}; HRMS (EI^+) calcd for $C_{13}H_{15}NO_4$ $[M+1]^+$: 250.10793, found: 250.10682; **5-methyl-2-oxy-5-phenyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (161a).** R_f 0.26 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H), 4.29 (q, J = 7.2 Hz, 2H), 3.57 (m, 2H), 1.82 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 143.1, 129.1, 128.4, 124.3, 109.1, 82.9, 62.0, 44.5, 28.3, 14.4; IR (film) 1723 (C=O), 1606, 1253 (NO), 1020, 726 cm^{-1}.



71 **161b**

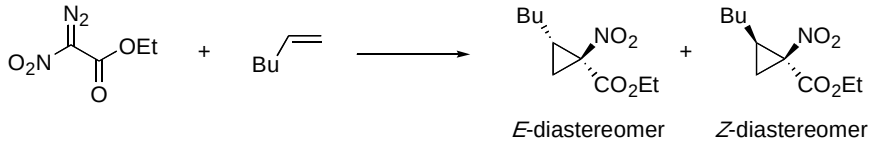
Ethyl 1-nitro-2,2'-diphenylcyclopropanecarboxylate (161b). Observed in the crude reaction mixture (104 mg, 97%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.45 (m, 10H), 3.98-4.08 (m, 2H), 3.01 (d, J = 6.9 Hz, 1H), 2.67 (d, J = 6.9 Hz, 1H), 0.98 (t, J = 7.2 Hz, 3H); **2-oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester**

(161b). Isolated following chromatography on silica gel as a pale yellow solid: M.p. 101-103 ^{o}C; R_f 0.35 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.45 (m, 10H), 4.30 (dq, J = 7.1, 0.6 Hz, 2H), 4.04 (s, 2H), 1.33 (dt, J = 7.1, 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.6, 129.0, 128.7, 125.9, 109.0, 86.0, 62.2, 43.8, 14.4; IR (solid) 1731 (C=O), 1620 (NO), 1232, 1182, 1023, 913 cm^{-1}; HRMS (EI^{+}) calcd for $C_{18}H_{17}NO_4$ $[M+1]^{+}$: 312.12358, found: 312.12391; Elem. Anal. calcd for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found: C 69.63, H 5.53, N 4.37.



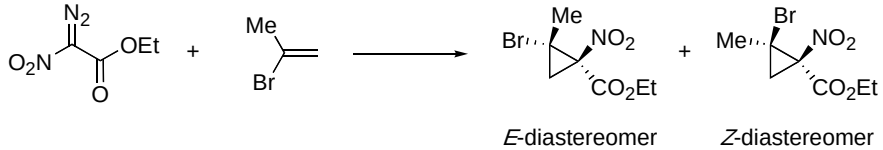
71 **161c**

Ethyl-1-nitro-2,3-indenecyclopropanecarboxylate (161c). White solid (117 mg, 85%): **Ethyl *exo*-1-nitro-2,3-indenecyclopropanecarboxylate (161c).** M.p. 57-58 ^{o}C; R_f 0.73 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.44 (m, 1H), 7.15-7.26 (m, 3H), 3.85-3.92 (m, 2H), 3.82 (d, J = 7.4 Hz, 1H), 3.49 (d, J = 18.0 Hz, 1H), 3.40 (dd, J = 18.0, 6.1 Hz, 1H), 3.12 (ddd, J = 7.3, 6.2, 0.9 Hz, 1H) 0.82 (dt, J = 7.1, 0.26 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 142.0, 137.9, 128.3, 127.5, 126.0, 125.1, 72.9, 62.3, 42.0, 34.4, 13.5; IR (film) 1739 (C=O), 1539, 1338 (NO_2), 1181, 912, 728 cm^{-1}; HRMS (EI^{+}) calcd for $C_{13}H_{13}NO_4$ $[M]^{+}$: 247.08446, found: 247.08439; Elem. Anal. calcd for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.67; found: C 63.11, H 5.30, N 5.65; **Ethyl *endo*-1-nitro-2,3-indenecyclopropanecarboxylate.** R_f 0.59 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.49 (m, 4H), 4.33 (q, J = 7.2 Hz, 2H), 2.94 (dt, J = 7.1, 1.6 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H).



71 **161d**

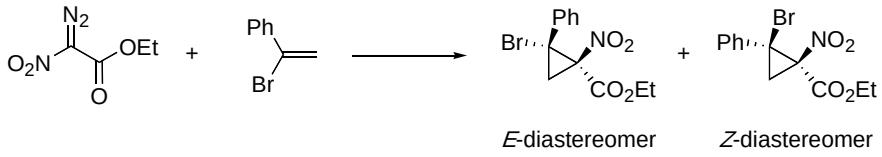
Ethyl-1-nitro-2-butylcyclopropanecarboxylate (161d). Clear colorless oil (38 mg, 40%): IR (film) (E/Z mix) 1742 (C=O), 1545, 1357 (NO_2), 1211, 1150 cm^{-1}; **Ethyl *E*-1-nitro-2-butylcyclopropanecarboxylate (161d).** R_f 0.84 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (q, J = 7.2 Hz, 2H), 2.37-2.44 (m, 2H), 1.81-1.88 (m, 2H), 1.63-1.70 (m, 2H), 1.14-1.53 (m, 10H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 70.7, 62.9, 30.6, 28.1, 27.7, 23.3, 22.6, 22.3, 14.2; **Ethyl *Z*-1-nitro-2-butylcyclopropanecarboxylate (161d).** R_f 0.84 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (m, 2H), 2.08-2.14 (m, 2H), 1.14-1.53 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 71.7, 63.1, 30.8, 29.5, 23.3, 22.4, 22.3, 14.1, 14.0; HRMS (EI^+) calcd for $C_{10}H_{17}NO_4$ $[M+1]^+$: 216.12358, found: 216.12320; Elem. Anal. calcd for $C_{10}H_{17}NO_4$: C 55.80, H 7.96, N 6.51; found: C 55.79, H 8.08, N 6.41.



71 **161e**

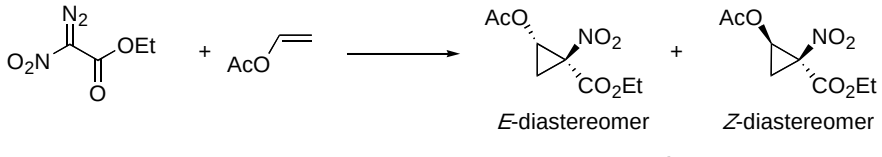
Ethyl-1-nitro-2-bromo-2-methylcyclopropanecarboxylate (161e). Clear colorless oil (62 mg, 50%): IR (film) (E/Z mix) 1745 (C=O), 1552, 1352 (NO_2), 1255, 1113, 1014 cm^{-1}; **Ethyl *E*-1-nitro-2-bromo-2-methylcyclopropanecarboxylate (161e).** R_f 0.65 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (q, J = 7.1 Hz, 2H), 2.37 (d, J = 8.6 Hz, 1H), 2.21 (d, J = 8.6 Hz, 1H), 1.94 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 74.5, 63.9, 34.4, 30.6, 27.0, 14.2; **Ethyl *Z*-1-nitro-2-bromo-2-methylcyclopropanecarboxylate (161e).** R_f 0.52 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.30 (q, J = 7.1 Hz, 2H), 2.49 (d, J =

8.7 Hz, 1H), 2.12 (d, J = 8.7 Hz, 1H), 2.06 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 76.9, 63.8, 36.2, 31.4, 24.9, 14.1; Elem. Anal. calcd for $C_7H_{10}NO_4Br$: C 33.35, H 4.00, N 5.56; found: C 33.39, H 4.04, N 5.48.



71 **161f**

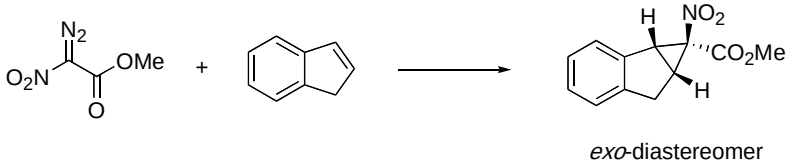
Ethyl-1-nitro-2-bromo-2-phenylcyclopropanecarboxylate (161f). Pale yellow solid (160 mg, 77%): **Ethyl *E*-1-nitro-2-bromo-2-phenylcyclopropanecarboxylate (161f).** Clear colorless oil: R_f 0.39 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.48 (m, 2H), 7.34-7.39 (m, 3H), 4.48 (q, J = 7.2 Hz, 2H), 3.03 (d, J = 8.8 Hz, 1H), 2.59 (d, J = 8.7 Hz, 1H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 134.2, 130.0, 129.1, 128.8, 74.5, 63.9, 39.7, 28.9, 14.2; IR (film) 1746 (C=O), 1554, 1341 (NO_2), 1266, 1134, 1021 cm^{-1}; **Ethyl *Z*-1-nitro-2-bromo-2-phenylcyclopropanecarboxylate (161f).** Yellow solid: M.p. 79-80 ^{o}C; R_f 0.26 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.46 (m, 2H), 7.35-7.37 (m, 3H), 3.95-3.99 (m, 2H), 2.83 (d, J = 8.7 Hz, 1H), 2.75 (d, J = 8.7 Hz, 1H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 137.2, 129.6, 129.0, 128.6, 75.1, 63.5, 39.4, 29.5, 13.6; IR (solid) 1732 (C=O), 1548, 1361 (NO_2), 1290, 1132 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{12}NO_4Br$ [M]$^+$: 312.99497, found: 312.99554.



71 **161g**

Ethyl-2-acetoxy-1-nitro-cyclopropanecarboxylate (161g). Clear colorless oil (60 mg, 51%): IR (film) (E/Z mix) 1770, 1749 (C=O), 1552, 1374 (NO_2), 1226 cm^{-1}; **Ethyl *E*-2-acetoxy-1-nitro-cyclopropanecarboxylate (161g).** R_f 0.26 (20%

EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (t, *J* = 6.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.30 (d, *J* = 6.9 Hz, 2H), 2.05 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 160.9, 63.6, 63.4, 57.0, 22.1, 20.4, 14.1; **Ethyl *Z*-2-acetoxy-1-nitro-cyclopropanecarboxylate (161g).** R_f 0.26 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (t, *J* = 5.9 Hz, 1H), 4.25-4.33 (m, 2H), 2.41 (dd, *J* = 8.6, 5.9 Hz, 1H), 2.00-2.06 (m, 1H), 1.29-1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 140.2, 68.6, 63.6, 57.0, 55.4, 20.8, 20.5; HRMS (EI^+) calcd for $C_8H_{11}NO_6$ $[M]^+$: 217.05864, found: 217.05964.



exo-diastereomer

97 **162**

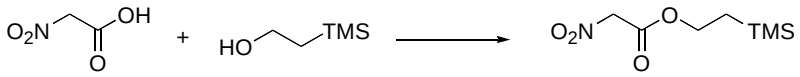
Methyl *exo*-1-nitro-2,3-indenecyclopropanecarboxylate (162). White crystalline solid (170 mg, 91%): M.p. 80-82 °C; R_f 0.51 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.45 (m, 1H), 7.16-7.25 (m, 3H), 3.84 (d, *J* = 7.4 Hz, 1H), 3.37-3.47 (m, 2H), 3.41 (s, 3H), 3.11-3.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 141.8, 137.7, 128.3, 127.6, 125.9, 125.0, 72.9, 53.0, 42.0, 34.44, 34.36; IR (solid) 1747 (C=O), 1543, 1346, 1329 (NO_2), 1211, 786 cm^{-1}; HRMS (EI^+) calcd for $C_{12}H_{11}NO_4$ $[M]^+$: 233.06881, found: 233.06901; Elem. Anal. calcd for $C_{12}H_{11}NO_4$: C 61.80, H 4.75, N 6.01; found: C 61.90, H 4.73, N 6.02.

Rh(II) carboxylate catalyzed enantioselective cyclopropanation reactions. The synthesis of amino acid derived ligands was accomplished by treating the desired amino acids with commercially available anhydrides in DMF at 100 °C according to the method reported by Hoshino and Yamamoto.[318] Catalysts **61** and **62** are commercially available from the Aldrich Chemical Company while catalysts **167a-d, 167i** were prepared according to the method of Callot and Metz. Catalysts **167e-g,**

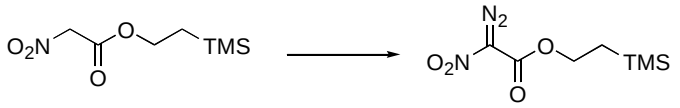
318. Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc*. **2000**, *122*, 10452-10453.

167j were prepared according to Tsutsui *et al*. and catalyst **167h** was prepared according to Moody *et al*. Catalyst **167k** has been previously reported by Müller *et al*.[144,226] while azetidine-derived catalysts **163a-d** were prepared according to Doyle *et al*. Catalyst **169** was prepared according to Pirrung and Zhang[152a] and *ortho*-metallated phosphine-derived catalysts **170a-b** were prepared according to Taber and Malcolm.[153a]

Enantiomeric excesses were determined on the mixture of *E*- and *Z*-diastereomers using super-critical fluid chromatography (SFC) by Berger Analytical Instruments on chiral stationary phase. Cyclopropane **150a**: (Chiracel OJ, 2.0% MeOH in supercritical CO_2, 2.0 mL/min: *E*-**150a** t_r, 4.5 min, *E*-**150a** t_r 5.0 min, *Z*-**150a** t_r, 7.9 min, *Z*-**150a** t_r 19.6 min).

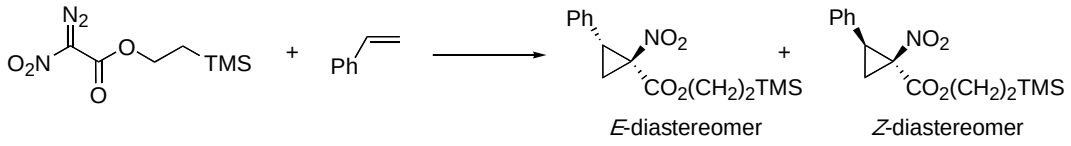


2-Trimethylsilanyl-ethyl nitroacetate. Clear colorless oil (1.02 g, 74%): R_f 0.57 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 2H), 4.34-4.38 (m, 2H), 1.04-1.08 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 76.7, 66.1, 17.5, -1.39; IR (film) 1747 (C=O), 1567, 1335 (NO_2), 1178, 837 cm^{-1}; HRMS (EI$^+$) calcd for $C_7H_{15}NO_4Si$ $[M]^+$: 205.07704, found: 205.07747; Elem. Anal. calcd for $C_7H_{15}NO_4Si$: C 40.96, H 7.36, N 6.82; found: C 40.99, H 7.37, N 6.85.



171

2-Trimethylsilanylethyl nitro diazoacetate (171). Yellow oil (126 mg, 86%): R_f 0.67 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41-4.47 (m, 2H), 1.07-1.13 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 66.0, 53.5, 17.8, -1.4; IR (film) 2144 (CN_2), 1747, 1698 (C=O), 1521, 1319 (NO_2), 1222, 1107, 838, 744 cm^{-1}.



171 **172**

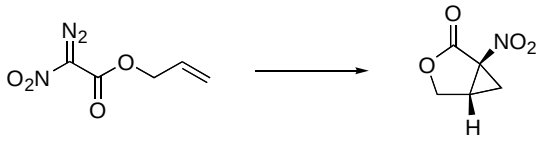
2-Trimethylsilanyl-ethyl-1-nitro-2-phenyl-cyclopropanecarboxylate (172). White solid (86 mg, 89%): M.p. 40-41 ^{o}C; **2-Trimethylsilanyl-ethyl-*E*-1-nitro-2-phenyl-cyclopropanecarboxylate (172**). R_f 0.71 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 3H), 7.20-7.23 (m, 2H), 3.95-3.98 (m, 2H), 3.76 (t, J = 9.4 Hz, 1H), 2.44 (dd, J = 9.1, 6.7, Hz, 1H), 2.19 (dd, J = 10.7, 6.6 Hz, 1H), 0.58-0.65 (m, 2H), -0.05 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 132.3, 128.7, 128.6, 128.4, 72.0, 65.2, 34.1, 20.8, 17.0, -1.54; IR (solid) 1742 (C=O), 1546, 1352 (NO_2), 1251, 1151; HRMS (EI^{+}) calcd for $C_{15}H_{21}NO_4Si$ $[M]^{+}$: 307.12399, found: 307.12355; **2-Trimethylsilanyl-ethyl-*Z*-1-nitro-2-phenyl-cyclopropanecarboxylate (172**). Clear colorless oil: R_f 0.70 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 3H), 7.20-7.23 (m, 2H), 4.36-4.42 (m, 2H), 3.46 (t, J = 9.6 Hz, 1H), 2.66 (dd, J = 9.2, 6.9 Hz, 1H), 2.01 (dd, J = 9.9, 6.9 Hz, 1H), 1.06-1.12 (m, 2H), 0.07 (m, 9H).

General procedure for the Cu-catalyzed intermolecular cyclopropanation of styrene with α-nitro-α-diazocarbonyls. To the copper source (5.0 mol%) was added the desired ligand (5.05 mol%) in the glove-box followed by the addition of anhydrous degassed CH_2Cl_2 (0.1 M). The resulting green solution was stirred for 1 h at room temperature then was treated with anhydrous degassed styrene under an argon atmosphere and heated with a reflux condenser to 50 ^{o}C. At this point, the additives necessary for activation of the catalyst were introduced. Directly following catalyst activation, methyl nitro diazoacetate (**97**) was added in anhydrous degassed CH_2Cl_2 (0.5M) *via* syringe pump over 2 h. The solution was allowed to stir an additional 6 h at 50 ^{o}C before it was filtered through a short pad of silica gel and concentrated under reduced pressure (rotary evaporator). The desired cyclopropane

150a was then purified by column chromatography on silica gel eluting first with hexane (100%) then with 3-5% EtOAc/Hexane affording the pure cyclopropane **150a**.

Rh(II) Catalyzed Intramolecular Cyclopropanations

General procedure for the Rh-catalyzed intramolecular cyclopropanations. In an oven dried round-bottomed flask was added the required amount of catalyst (0.5 mol%) followed by anhydrous CH_2Cl_2 (0.7 mL). The flask was fitted with a reflux condenser and the solution containing the catalyst was heated to 50 ^oC. A solution containing the desired diazo compound in CH_2Cl_2 (0.5M) was then added slowly dropwise *via* syringe pump over a 2-4 h period. The solution was allowed to stir an additional 30 min at 50 ^oC, cooled to room temperature and the solvent removed under reduced pressure (rotary evaporator). The resulting cyclopropyl lactones were then purified by column chromatography on silica gel using 15-30% EtOAc/Hexane as an eluent.

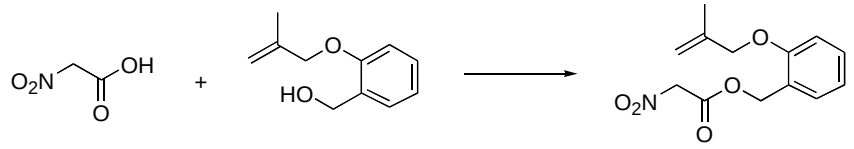


71 **176**

1-Nitro-3-oxa-bicyclo[3.1.0]hexan-2-one (176). White semi-solid (13 mg, 25%): R_f 0.50 (60% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.51-4.55 (m, 1H), 4.21 (d, J = 9.9 Hz, 1H), 3.24-3.29 (m, 1H), 2.73-2.77 (m, 1H), 1.71-1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 67.0, 30.2, 22.4; IR (solid) 1784 (C=O), 1541, 1376, 1345 (NO_2), 1114, 989 cm^{-1}.

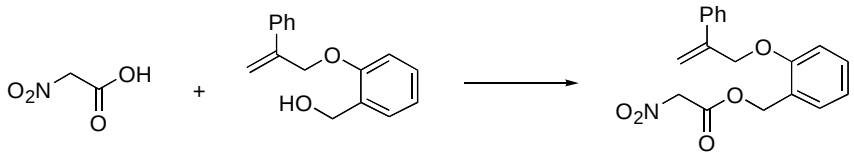
Preparation of 2-alloxy benzyl alcohol derivatives (178). Compounds **178a-c** have been previously reported by Lachapelle and St. Jacques.

Preparation of 2-alloxy benzyl nitroacetate derivatives (179). Compounds **179b-c** were prepared according to the method reported by Mioskowski *et al*.



123 **179b**

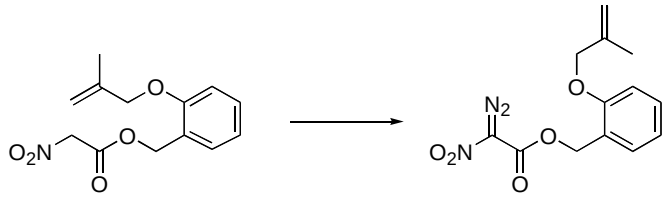
2-(2-Methyl-allyloxy)-benzyl nitroacetate (179b). Clear colorless oil (852 mg, 85%): R_f 0.53 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.37 (m, 2H), 6.96-7.00 (m, 1H), 6.92 (d, J = 8.5 Hz, 1H), 5.38 (s, 2H), 5.16 (s, 2H), 5.11 (s, 1H), 5.03 (s, 1H), 4.49 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.0, 156.9, 140.6, 130.6, 122.6, 120.7, 112.7, 111.8, 76.3, 71.7, 64.5, 19.4; IR (film)1758 (C=O), 1567, 1334 (NO_2), 902 cm^{-1}; HRMS (MAB) calcd for $C_{13}H_{15}NO_5$ $[M]^+$: 265.09502, found: 265.09526.



123 **179c**

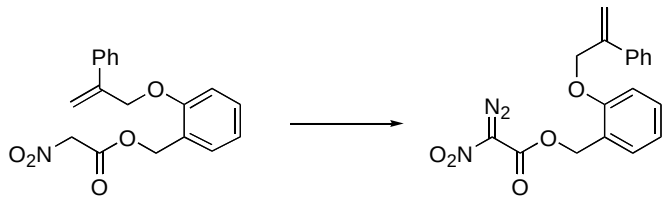
2-(2-Phenyl-allyloxy)-benzyl nitroacetate (179c). Clear colorless oil (242 mg, 64%): R_f 0.46 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.50 (m, 2H), 7.32-7.42 (m, 5H), 6.99-7.02 (m, 2H), 5.64 (s, 1H), 5.47 (s, 1H), 5.28 (s, 2H), 5.01 (s, 2H), 4.97 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.9, 156.9, 143.0, 138.3, 130.8, 130.7, 128.7, 128.3, 126.2, 122.9, 121.0, 115.2, 112.1, 76.2, 70.0, 64.7; IR (film) 1755 (C=O), 1563,1494, 1334 (NO_2), 1251, 1205, 910 cm^{-1}; HRMS (MAB) calcd for $C_{18}H_{17}NO_5$ $[M]^+$: 327.11067, found: 327.11080.

Preparation of α-nitro-α-diazocarbonyls (121q, 180b-c). Prepared according to the standard diazo transfer procedure used for α-nitro-α-diazocarbonyls **121**. Purification was performed by column chromatography on silica gel using $CHCl_3$ as an eluent.



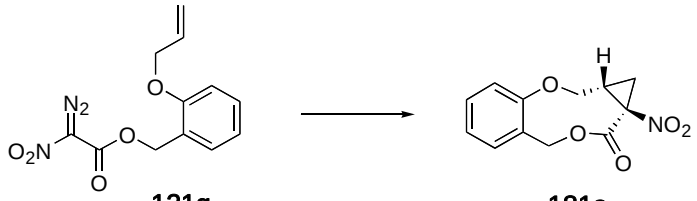
179b **180b**

(2-Methyl-allyloxy)-benzyl-nitro-diazoacetate (180b). Pale yellow solid (276 mg, 95%): M.p. 50-52 ^{o}C; R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 2H), 6.93-6.97 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.42 (s, 2H), 5.09 (s, 1H), 5.00 (s, 1H), 4.46 (s, 2H), 1.83 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.0, 155.2, 140.5, 130.7, 130.5, 122.6, 120.6, 112.6, 111.7, 71.6, 64.1, 19.3; IR (solid) 2146 (CN_2), 1748 (C=O), 1521, 1322 (NO_2), 1102, 900 cm^{-1}; HRMS (MAB) calcd for $C_{13}H_{13}N_3O_5$ $[M]^+$: 291.08552, found: 291.08556.



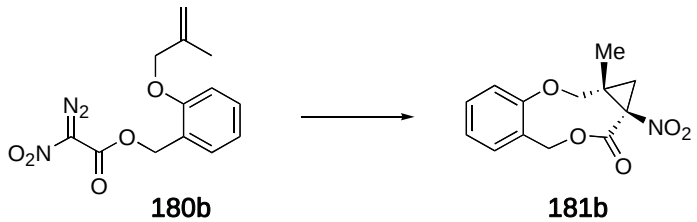
179c **180c**

2-(2-Phenyl-allyloxy)-benzyl-nitro-diazoacetate (180c). White fluffy solid (404 mg, 96%): M.p. 89-91 ^{o}C; R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.48 (m, 2H), 7.31-7.40 (m, 5H), 6.97-7.02 (m, 2H), 5.62 (s, 1H), 5.46 (s, 1H), 5.33 (s, 2H), 4.96 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.0, 155.1, 143.0, 138.2, 131.0, 130.8, 128.6, 128.2, 126.1, 122.9, 121.0, 115.2, 112.0, 69.9, 64.3; IR (solid) 2143 (CN_2), 1744 (C=O), 1518,1495, 1319 (NO_2), 1217, 1102, 914 cm^{-1}.



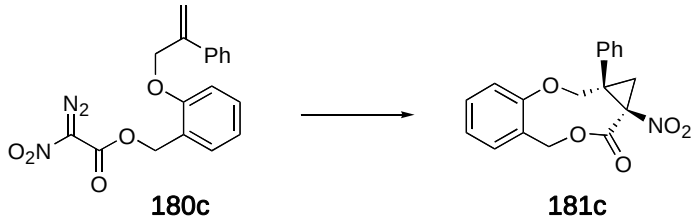
121q **181a**

6-Nitro-2,8-dioxa-tricyclo[8.4.0.0^{4,6}]tetradeca-1(10),11,13-trien-7-one (181a). White solid (23 mg, 33%): M.p. 110-113 ^{o}C; R_f 0.35 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.21 (m, 1H), 7.06-7.12 (m, 2H), 6.98 (d, J = 7.9 Hz, 1H), 5.89 (d, J = 14.1 Hz, 1H), 5.30 (d, J = 14.1 Hz, 1H), 4.39-4.43 (m, 1H), 4.27-4.31 (m, 1H), 2.64-2.73 (m, 1H), 2.12-2.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 158.1, 129.4, 128.1, 126.4, 124.8, 122.4, 70.1, 66.8, 30.4, 20.1; IR (solid) 1751 (C=O), 1542, 1351, 1331 (NO_2), 1196, 1133; HRMS (MAB) calcd for $C_{12}H_{11}NO_5$ $[M]^+$: 249.06372, found: 249.06419; Enantiomeric excess determined by SFC: Chiracel OJ column, Modifier: 1.4% MeOH, Flow: 1.4 mL/min.



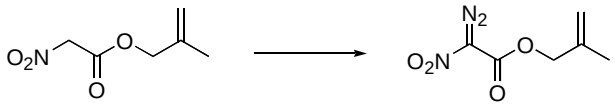
180b **181b**

4-Methyl-6-nitro-2,8-dioxa-tricyclo[8.4.0.0^{4,6}]tetradeca-1(10),11,13-trien-7-one (181b). White solid (100 mg, 58%): M.p. 95-98 ^{o}C; R_f 0.26 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.24 (m, 1H), 7.09-7.11 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.03 (d, J = 14.3 Hz, 1H), 5.20 (d, J = 14.3 Hz, 1H), 4.24 (d, J = 10.3 Hz, 1H), 4.04 (d, J = 10.3 Hz, 1H), 2.23 (d, J = 6.9 Hz, 1H), 2.16 (d, J = 6.9 Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.6, 157.5, 129.2, 127.8, 126.7, 125.2, 123.4, 76.2, 73.4, 66.3, 35.2, 23.2, 15.0; IR (solid) 1750 (C=O), 1542,1347 (NO_2), 1215, 1123; HRMS (MAB) calcd for $C_{13}H_{13}NO_5$ $[M]^+$: 263.07937, found: 263.07930; Enantiomeric excess determined by SFC: Column: Regis Whelk O, Modifier: 1.5% MeOH, Flow: 1.5 mL/min.



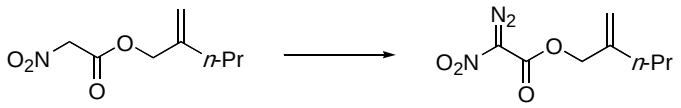
180c **181c**

6-Nitro-4-phenyl-2,8-dioxa-tricyclo[8.4.0.0^{4,6}]tetradeca-1(10),11,13-trien-7-one (181c). White crystalline solid (82 mg, 66%): M.p. 172 ^{o}C; R_f 0.49 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.37 (m, 5H), 7.20-7.27 (m, 1H), 7.13-7.16 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 14.4 Hz, 1H), 5.17 (d, *J* = 14.4 Hz, 1H), 4.40 (d, *J* = 10.5 Hz, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 2.76 (d, *J* = 6.9 Hz, 1H), 2.55 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 157.2, 133.5, 129.3, 129.2, 129.1, 128.8, 127.8, 126.7, 125.4, 123.6, 76.3, 73.0, 66.3, 44.2, 20.8; IR (solid) 1742 (C=O), 1538, 1343 (NO_2), 1129, 995 cm^{-1}; Elem. Anal. calcd for $C_{18}H_{15}NO_5$: C 66.46, H 4.65, N 4.31; found: C 66.68, H 4.75, N 4.31; Enantiomeric excess determined by SFC: Regis Whelk O column, Modifier: 6.0% MeOH, Flow: 2.0 mL/min. The relative stereochemistry was confirmed by X-ray crystallography.



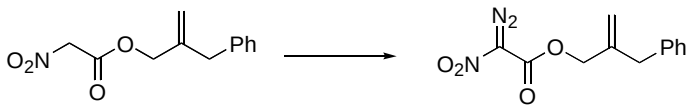
182a

2-Methyl allyl-nitroacetate. Clear colorless oil (663 mg, 71%): R_f 0.39 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 2H), 4.99-5.01 (m, 2H), 4.67 (s, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 138.4, 115.0, 76.9, 70.3, 19.5; IR (film) 1751 (C=O), 1560, 1335 (NO_2), 1189 cm^{-1}; **2-Methyl allyl-nitro-diazoacetate (182a)**. Yellow oil (520 mg, 95%): R_f 0.50 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, *J* = 5.8 Hz, 2H), 4.73 (s, 2H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.4, 114.8, 101.5 (CN_2), 69.9, 19.4; IR (film) 2150 (CN_2), 1751 (C=O), 1523, 1323 (NO_2), 1218, 1114 cm^{-1}.



182c

The necessary allylic alcohol was prepared according to the method reported by Duboudin and Jousseaume involving treatment of propargyl alcohol with PrMgBr in the presence of CuI (10 mol%).[319] **2-Propyl-allyl nitroacetate.** Clear colorless oil (534 mg, 72%): R_f 0.42 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 2H), 5.02 (d, J = 17.2 Hz, 2H), 4.67 (s, 2H), 2.02 (t, J = 7.6 Hz, 2H), 1.40-1.52 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 142.4, 114.1, 76.4, 69.4, 35.2, 20.7, 13.8; IR (film) 1760 (C=O), 1569, 1336 (NO_2), 1196 cm^{-1}; **2-Propyl-allyl-nitro-diazoacetate (182c).** Clear colorless oil (349 mg, 95%): R_f 0.68 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J = 19.6 Hz, 2H), 4.73 (s, 2H), 2.03 (t, J = 7.6 Hz, 2H), 1.40-1.53 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 142.4, 114.1, 69.0, 35.2, 20.7, 13.8; IR (film) 2145 (CN_2), 1748 (C=O), 1521, 1320 (NO_2), 1217, 1112 cm^{-1}.

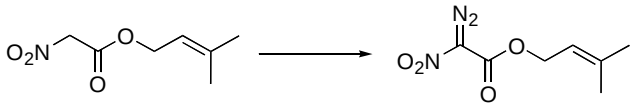


182d

The necessary allylic alcohol was prepared according to the method reported by Duboudin and Jousseaume involving treatment of propargyl alcohol with BnMgBr in the presence of CuI (10 mol%). **2-Benzyl-allyl nitroacetate.** Clear colorless oil (478 mg, 58%): R_f 0.41 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.35 (m, 2H), 7.24-7.27 (m, 1H), 7.19-7.23 (m, 2H), 5.19 (s, 1H), 5.10 (s, 1H), 5.07 (s, 2H), 4.67 (s, 2H), 3.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 141.7, 138.2, 129.0, 128.8, 126.8, 116.6, 76.2, 68.9, 40.3; IR (film) 1759 (C=O), 1567, 1334 (NO_2), 1197 cm^{-1}; **2-Benzyl-allyl-nitro-diazoacetate (182d).** Clear colorless oil (285 mg,

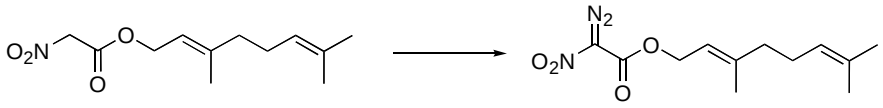
319. Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1-11.

91%): R_f 0.61 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.40 (m, 5H), 5.24 (s, 1H), 5.14 (s, 1H), 4.75 (s, 2H), 3.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 141.6, 138.2, 128.8, 128.6, 126.7, 116.9, 68.6, 40.4; IR (film) 2145 (CN_2), 1748 (C=O), 1520, 1319 (NO_2), 1217, 1108 cm^{-1}.



182e

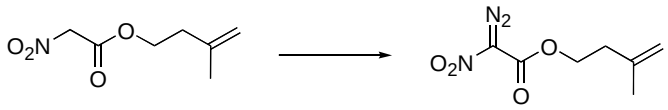
3-Methyl-but-2-enyl nitroacetate. Clear colorless oil (559 mg, 80%): R_f 0.56 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31-5.36 (m, 1H), 5.15 (s, 3H), 4.73 (d, J = 7.5 Hz, 2H), 1.76 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 141.7, 117.0, 76.5, 64.0, 25.9, 18.2; IR (film) 1749 (C=O), 1563, 1377 (NO_2), 1194 cm^{-1}; **3-Methyl-but-2-enyl-nitro-diazoacetate (182e)**. Yellow oil (254 mg, 96%): R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.38 (m, 1H), 4.81 (d, J = 7.5 Hz, 2H), 1.76 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 141.9, 117.2, 63.8, 26.0, 18.3; IR (film) 2145 (CN_2), 1745 (C=O), 1521, 1319 (NO_2), 1218, 1103 cm^{-1}.



182f

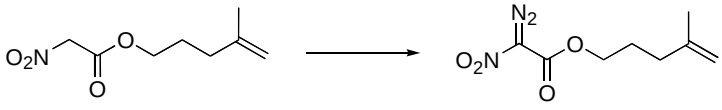
3,7-Dimethyl-octa-2,6-dienyl nitroacetate. Clear colorless oil (612 mg, 74%): R_f 0.69 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.35 (m, 1H), 5.16 (s, 2H), 5.06-5.07 (m, 1H), 4.77 (d, J = 7.4 Hz, 2H), 2.04-2.11 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 145.0, 132.3, 123.6, 116.7, 76.5, 64.1, 39.7, 26.3, 25.9, 17.9, 16.7; IR (film) 1754 (C=O), 1567, 1377 (NO_2), 1197 cm^{-1}; **3,7-dimethyl-octa-2,6-dienyl-nitro-diazoacetate (182f)**. Pale yellow crystalline solid (288 mg, 92%): M.p. 28-29 ^{o}C; R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.38 (m, 1H), 5.03-5.07 (m,

1H), 4.84 (d, *J* = 7.4 Hz, 2H), 2.03-2.11 (m, 4H), 1.74 (s, 3H). 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 145.1, 132.2, 123.6, 116.9, 63.8, 39.7, 26.3, 25.9, 17.9, 16.7; IR (solid) 2143 (CN_2), 1747 (C=O), 1523, 1319 (NO_2), 1219, 1105 cm^{-1}.



182g

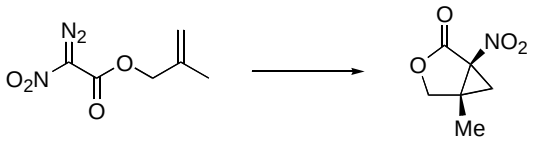
3-Methyl-but-3-enyl nitroacetate. Clear colorless oil (167 mg, 71%): R_f 0.37 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 2H), 4.84 (s, 1H), 4.74 (s, 1H), 4.38 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 6.8 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 140.8, 113.2, 76.4, 65.3, 36.5, 22.5; IR (film) 1755 (C=O), 1567, 1339 (NO_2), 1200 cm^{-1}; **3-Methyl-but-3-enyl-nitro-diazoacetate (182g)**. Yellow oil (257 mg, 95%): R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.76 (s, 1H), 4.46 (t, *J* = 6.7 Hz, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 140.8, 113.3, 64.9, 36.8, 22.4; IR (film) 2145 (CN_2), 1750 (C=O), 1519, 1323 (NO_2), 1219, 1116 cm^{-1}.



182h

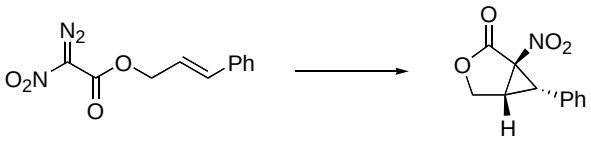
4-Methyl-pent-4-en-1-ol was prepared according to Ley *et al*. **4-Methyl-pent-4-enyl nitroacetate.** Clear colorless oil (234 mg, 67%): R_f 0.60 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 2H), 4.75 (s, 1H), 4.69 (s, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 2.07 (t, *J* = 7.4 Hz, 2H), 1.80-1.87 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 144.1, 111.0, 76.4, 66.9, 33.8, 26.2, 22.4; IR (film) 1757 (C=O), 1568, 1339 (NO_2), 1215 cm^{-1}; **4-Methyl-pent-4-enyl-nitro-diazoacetate (182h).** Yellow oil (229 mg, 87%): R_f 0.52 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.68 (s, 1H), 4.32 (t, *J* = 6.6 Hz, 2H), 2.08 (t, *J* = 7.5

Hz, 2H), 1.82-1.89 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 144.1, 111.0, 66.6, 33.8, 26.3, 22.3; IR (film) 2146 (CN_2), 1748 (C=O), 1521, 1322 (NO_2), 1219, 1118 cm^{-1}.



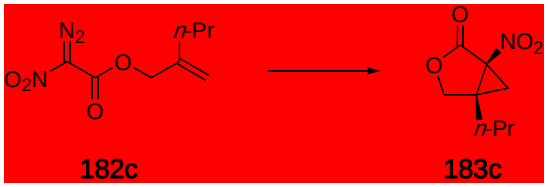
182a **183a**

5-Methyl-1-nitro-3-oxa-bicyclo[3.1.0]hexan-2-one (183a). White crystalline solid (67 mg, 82%): M.p. 92-94 ^{o}C; R_f 0.39 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (s, 2H), 2.60 (d, J = 6.4 Hz, 1H), 1.78 (d, J = 6.4 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 72.0, 68.3, 38.1, 26.1, 13.7; IR (solid) 1786 (C=O), 1531, 1364 (NO_2), 1215, 1102, 1004 cm^{-1}; Elem. Anal. calcd for $C_6H_7NO_4$: C 45.86, H 4.49, N 8.91, found: C 45.72, H 4.60, N 8.79; Enantiomeric excess determined by SFC: Column: Chiracel OD, Modifier: 1.5% MeOH, Flow: 1.5 mL/min.



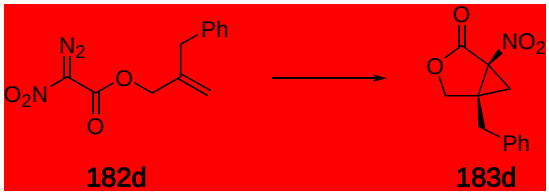
121e **183b**

1-Nitro-6-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (183b). Pale yellow solid (32 mg, 36%): M.p. 105-108 ^{o}C; R_f 0.45 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.40 (m, 3H), 7.25-7.30 (m, 2H), 4.67 (dd, J = 9.7, 5.0 Hz, 1Hz), 4.38 (d, J = 9.7 Hz, 1H), 3.76 (t, J = 5.3 Hz, 1H), 3.21 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 129.6, 129.3, 128.7, 128.6, 69.9, 67.3, 39.2, 28.6; IR (solid) 1783, 1771 (C=O), 1534, 1372 (NO_2), 1258, 1179 cm^{-1}; HRMS (MAB) calcd for $C_{11}H_9NO_4$ $[M+1]^+$: 220.06098, found: 220.06234.



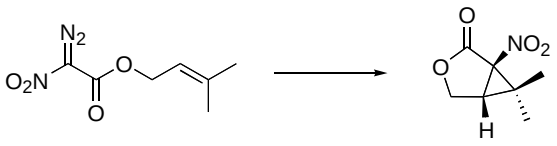
182c 183c

1-Nitro-5-propyl-3-oxa-bicyclo[3.1.0]hexan-2-one (183c). Pale yellow oil (31 mg, 39%): R_f 0.32 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (d, J = 9.7 Hz, 1H), 4.23 (d, J = 9.7 Hz, 1H), 2.60 (d, J = 6.4 Hz, 1H), 1.41-1.90 (m, 4H), 1.76 (d, J = 5.5 Hz, 1H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 71.2, 71.1, 41.8, 30.5, 25.6, 19.8, 14.0; IR (film) 1787 (C=O), 1537, 1358 (NO_2), 1093, 1009 cm^{-1}.



182d 183d

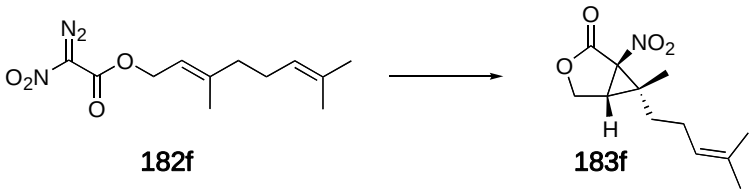
5-Benzyl-1-nitro-3-oxa-bicyclo[3.1.0]hexan-2-one (183d). White solid (33 mg, 37%): M.p. 83-84 ^{o}C; R_f 0.25 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.39 (m, 3H), 7.14-7.17 (m, 2H), 4.31 (d, J = 9.8 Hz, 1H), 4.08 (d, J = 9.8 Hz, 1H), 3.17 (d, J = 14.9 Hz, 1H), 3.06 (d, J = 14.9 Hz, 1H), 2.85 (d, J = 6.4 Hz, 1H), 1.85 (d, J = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 134.8, 129.5, 128.8, 128.0, 70.7, 42.1, 34.7, 25.7; IR (solid) 1794 (C=O), 1538, 1354 (NO_2), 1108, 1011 cm^{-1}.



182e 183e

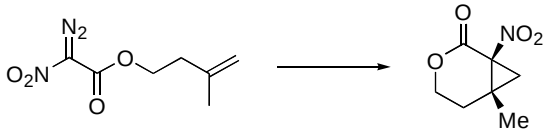
6,6-Dimethyl-1-nitro-3-oxa-bicyclo[3.1.0]hexan-2-one (183e). Pale yellow oil (13 mg, 50%): R_f 0.35 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J =

10.3, 5.5 Hz, 1Hz), 4.16 (d, *J* = 10.3 Hz, 1H), 3.04 (d, *J* = 5.4 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 75.0, 64.9, 35.8, 33.5, 20.4, 15.3; IR (film) 1783 (C=O), 1541, 1355 (NO_2), 1189, 1060 cm^{-1}.



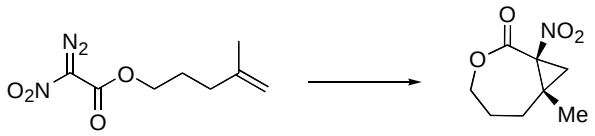
182f **183f**

6-Methyl-6-(4-methyl-pent-3-enyl)-1-nitro-3-oxa-bicyclo[3.1.0]hexan-2-one (183f). Yellow oil (21 mg, 30%): R_f 0.42 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99-5.03 (m, 1H), 4.58 (dd, *J* = 10.3, 5.5 Hz, 1H), 4.13 (d, *J* = 10.3 Hz, 1H), 3.03 (d, *J* = 5.2 Hz, 1H), 2.10-2.14 (m, 2H), 1.61-1.71 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.36-1.47 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 133.7, 122.1, 75.2, 64.8, 37.1, 35.2, 34.0, 25.9, 24.5, 17.8, 12.5; IR (film) 1785 (C=O), 1541, 1353 (NO_2), 1181, 1088 cm^{-1}.



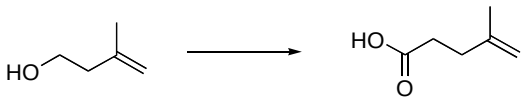
182g **183g**

6-Methyl-1-nitro-3-oxa-bicyclo[4.1.0]heptan-2-one (183g). Pale yellow solid (59 mg, 80%): M.p. 74-76 ^{o}C; R_f 0.11 (40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (ddd, *J* = 7.4, 5.8, 1.6 Hz, 1H), (dt, *J* = 12.8, 3.5 Hz, 1H), 2.26 (ddd, *J* = 13.1, 8.8, 5.8 Hz, 1H), 2.16 (s, 2H), 2.02 (ddd, *J* = 15.4, 3.5, 1.6 Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 71.6, 65.6, 30.7, 27.0, 21.5, 19.0; IR (solid) 1721 (C=O), 1544, 1303 (NO_2), 1218, 1122 cm^{-1}; HRMS (MAB) calcd for $C_7H_9NO_4$ $[M+1]^+$: 172.06098, found: 172.06187; Elem. Anal. calcd for $C_7H_9NO_4$: C 49.12, H 5.30, N 8.18; found: C 49.11, H 5.33, N 7.99.



182h **183h**

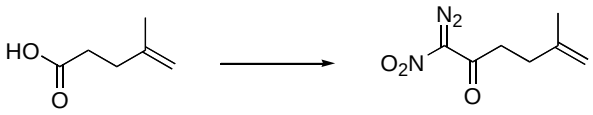
7-Methyl-1-nitro-3-oxa-bicyclo[5.1.0]octan-2-one (183h). White crystalline solid (60 mg, 95%): M.p. 136-137 ^{o}C; R_f 0.39 (40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39-4.43 (m, 2H), 2.24-2.30 (m, 1H), 2.26 (d, J = 7.0 Hz, 1H), 2.00-2.11 (m, 1H), 1.83-1.93 (m, 1H), 1.53 (d, J = 7.0 Hz, 1H), 1.32 (s, 3H), 0.99-1.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 73.0, 65.6, 32.2, 28.8, 23.0, 14.4; IR (solid) 1736 (C=O), 1532, 1341 (NO_2), 1255, 1110 cm^{-1}.



184 **185**

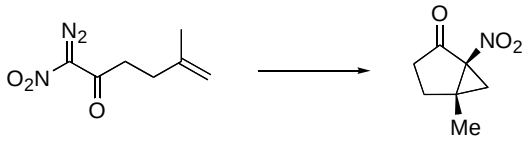
Commercially available 3-methyl-but-3-en-1-ol (**184**) was brominated using NBS and PPh_3 according to the method reported by Berkowitz and Wu.[320] The bromide was then treated with KCN (4.0 equiv) in DMSO at 70 ^{o}C for 2 h then hydrolyzed with NaOH (10.0 equiv) in DMSO:H_2O 1:1 for 8 h at 70 ^{o}C. **4-Methyl-pent-4-enoic acid (185)**. Yellow oil (581 mg, 21% for 3 steps): R_f 0.81 (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.87 (s(*br*), 1H), 4.75 (s, 1H), 4.70 (s, 1H), 2.48-2.54 (m, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 143.9, 110.7, 32.7, 32.4, 22.7; IR (film) 3079 (OH), 1716 (C=O), 1445 cm^{-1}.

320. Berkowitz, W. F.; Wu, Y. *J. Org. Chem*. **1997**, *62*, 1536-1539.



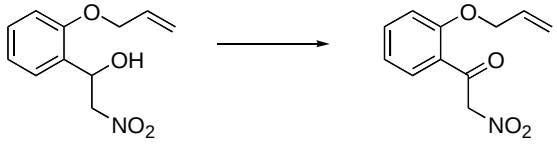
185 186

5-Methyl-1-nitro-1-diazo-hex-5-en-2-one (186). Yellow solid (290 mg, 47% for 2 steps): R_f 0.59 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.68 (s, 1H), 3.12 (t, J = 7.6 Hz, 2H), 2.34 (t, J = 7.6 Hz, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 143.6, 110.9, 39.1, 31.2, 22.5; IR (solid) 2142 (CN_2), 1662, 1649 (C=O), 1493, 1315, 1294 (NO_2), 880 cm^{-1}.



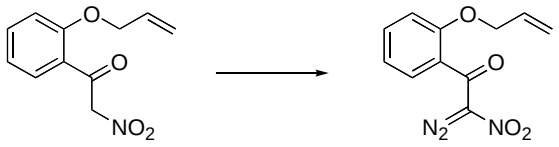
186 187

5-Methyl-1-nitro-bicyclo[3.1.0]hexan-2-one (187). Pale yellow solid (81 mg, 85%): M.p. 32-33 ^{o}C; R_f 0.13 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (d, J = 6.3 Hz, 1H), 2.39-2.45 (m, 1H), 2.24-2.34 (m, 1H), 2.11-2.16 (m, 2H), 1.81 (d, J = 6.5 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 42.7, 33.5, 28.0, 26.7, 17.5; IR (solid) 1748 (C=O), 1528, 1358 (NO_2), 1036 cm^{-1}.



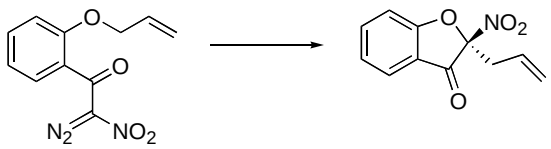
189 190

1-(2-Allyloxy-phenyl)-2-nitro-ethanone (190). White solid (175 mg, 93%): M.p. 53-54 ^{o}C; R_f 0.21 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.9 Hz, 1H), 7.55-7.61 (m, 1H), 7.10 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.03-6.16 (m, 1H), 5.81 (s, 2H), 5.39-5.49 (m, 2H), 4.69 (d, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 158.8, 136.4, 131.8, 123.8, 121.8, 120.3, 113.0, 85.6, 77.4, 70.1; IR (solid) 1672 (C=O), 1561, 1482 (NO_2), 1290, 988 cm^{-1}.



190 **191**

1-(2-Allyloxy-phenyl)-2-nitro-2-diazo-ethanone (191). Yellow oil (128 mg, 72%): R_f 0.54 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.54 (m, 2H), 7.05-7.10 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.90-6.02 (m, 1H), 5.28-5.40 (m, 2H), 4.55 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 156.9, 134.4, 132.3, 130.0, 126.0, 121.5, 118.8, 112.4, 69.9; IR (film) 2148 (CN_2), 1635 (C=O), 1517, 1310 (NO_2), 995, 934 cm^{-1}.



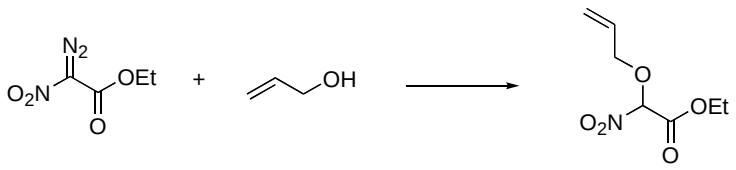
191 **192**

2-Allyl-2-nitro-benzofuran-3-one (192). Yellow oil (28 mg, 52%): R_f 0.22 (5.0% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.80 (m, 2H), 7.32-7.35 (m, 1H), 7.26-7.29 (m, 2H), 5.22-5.38 (m, 2H), 3.37 (dd, J = 14.6, 7.0 Hz, 1H), 3.18 (dd, J = 14.6, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 171.6, 140.0, 127.0, 126.1, 124.7, 123.1, 118.0, 113.8, 111.3, 37.1; IR (film) 1742 (C=O), 1615, 1564 (NO_2), 1463, 1299 cm^{-1}.

Experimental: Chapter 4

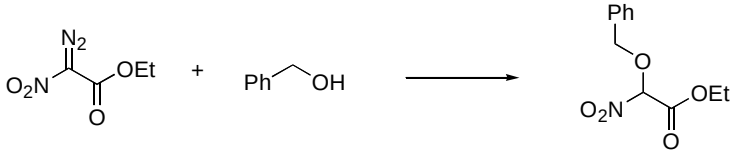
General procedure for O-H insertion reactions involving α-nitro-α-diazocarbonyls. To a mixture of $[Rh(OAc)_2]_2$ (8.8 mg, 0.025 mmol, 5.0 mol%) and the desired alcohol (2.5 mmol, 5.0 equiv) under argon was added slowly dropwise a solution of the α-nitro-α-diazoester (0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.50 mL). The reaction mixture was then stirred at room temperature for 2-4 h followed by concentration under reduced pressure (rotary evaporator). The crude residue was then

purified by column chromatography on silica gel eluting with 5% EtOAc/Hexane to afford the pure α-alkoxy-α-nitrocarbonyl compounds.



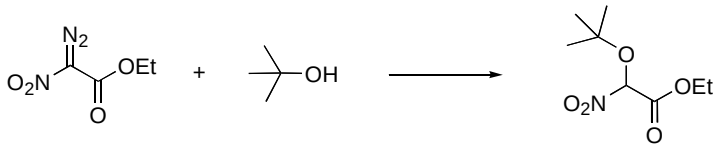
71 **195a**

Ethyl allyloxy-nitroacetate (195a). Clear colorless oil (74 mg, 84%): R_f 0.50 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.98 (m, 1H), 5.60 (s, 1H), 5.38-5.44 (m, 2H), 4.48-4.53 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.21-4.26 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 131.0, 121.8, 103.3, 73.9, 63.8, 14.0; IR (film) 1760 (C=O), 1575, 1339 (NO_2), 1267, 1207, 1025, 854 cm^{-1}.



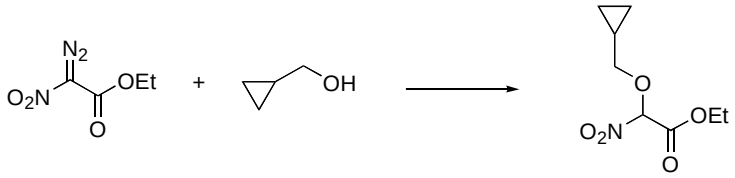
71 **195b**

Ethyl benzyloxy-nitroacetate (195b). Clear colorless oil (97 mg, 99%): R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.42 (m, 5H), 5.59 (s, 1H), 5.06 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 134.0, 129.4, 129.1, 129.0, 103.2, 74.6, 63.8, 14.0; IR (film) 1760 (C=O), 1575, 1340 (NO_2), 1210, 1166, 1027 cm^{-1}; Elem. Anal. calcd for $C_{11}H_{13}NO_5$: C 55.23, H 5.48, N 5.86; found: C 55.25, H 5.52, N 5.88.



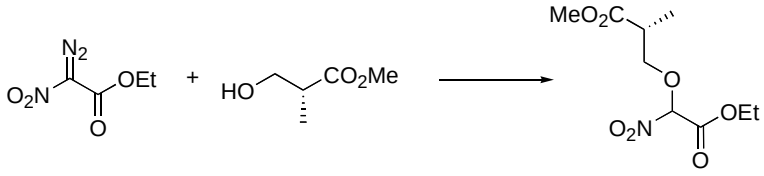
71 **195c**

Ethyl *tert*-butoxy-nitroacetate (195c). Clear colorless oil (38 mg, 45%): R_f 0.50 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.29 (dq, J = 7.2, 1.3 Hz, 2H), 1.32 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 100.0, 81.6, 63.6, 27.5, 14.0; IR (film) 1760 (C=O), 1575, 1374 (NO_2), 1207, 1147, 1022, 737 cm^{-1}.



71 **195d**

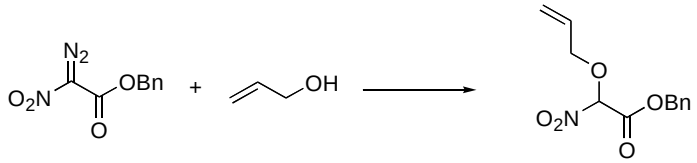
Ethyl cyclopropylmethoxy-nitroacetate (195d). Clear colorless oil (83 mg, 87%): R_f 0.31 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.65-3.70 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.15-1.19 (m, 1H), 0.62-0.68 (m, 2H), 0.28-0.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 104.2, 78.3, 63.8, 14.0, 9.8, 3.9, 3.3; IR (film) 1760 (C=O), 1574, 1361 (NO_2), 1299, 1199, 1028, 988, 854 cm^{-1}.



71 **195e**

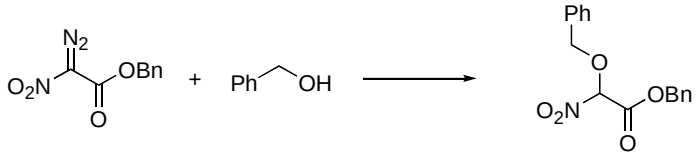
3-(Ethoxycarbonyl-nitro-methoxy)-2*R*-methyl-propionic acid methyl ester (195e). Clear colorless oil as *ca*. 1:1 mix of diastereomers (125 mg, 74%): R_f 0.30 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.629 (s, 1H), 5.624 (s, 1H),

4.32-4.36 (m, 2H), 4.16-4.21 (m, 0.5H), 4.02-4.06 (m, 0.5H), 3.87-3.99 (m, 1H), 3.74 (s, 3H), 2.87-2.98 (m, 1H), 1.338 (t, J = 7.1 Hz, 3H), 1.344 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 173.9, 161.5, 161.4, 105.0, 104.7, 74.9, 74.7, 68.74, 68.70, 52.2, 40.0, 39.8, 14.0, 13.8; IR (film) 1742 (C=O), 1576, 1463, 1378 (NO_2), 1207, 1023 cm^{-1}.



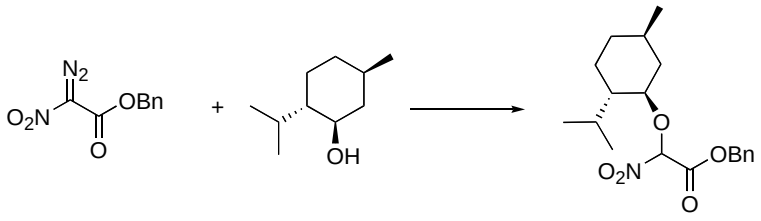
121f **195f**

Benzyl allyloxy-nitroacetate (195f). Clear colorless oil (92 mg, 92%): R_f 0.57 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.41 (m, 5H), 5.87-5.97 (m, 1H), 5.64 (s, 1H), 5.37-5.42 (m, 2H), 5.29 (s, 2H), 4.48-4.53 (m, 1H), 4.21-4.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 134.1, 130.9, 129.1, 128.9, 128.6, 121.7, 103.1, 73.9, 69.1; IR (film) 1760 (C=O), 1573, 1338 (NO_2), 1271, 1176, 991 cm^{-1}.



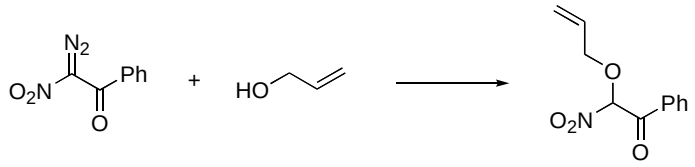
121f **195g**

Benzyl benzyloxy-nitroacetate (195g). Clear colorless oil (101 mg, 84%): R_f 0.34 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.41 (m, 10H), 5.62 (s, 1H), 5.26 (s, 2H), 5.06 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 134.1, 134.0, 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 103.2, 74.7, 69.0; IR (film) 1761 (C=O), 1574, 1340 (NO_2), 1280, 1168, 1010 cm^{-1}.



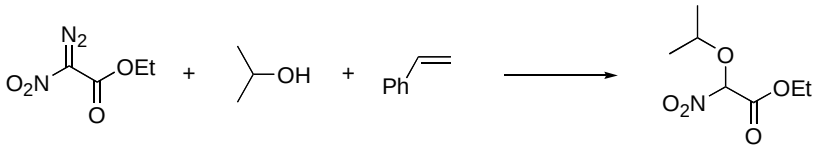
121f **195h**

Benzyl menthyloxy-nitroacetate (195h). Clear colorless oil as *ca*. 55:45 mix of diastereomers (110 mg, 79%): M.p. 40-42 ^{o}C; R_f 0.79 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.41 (m, 10H), 5.78 (s, 1H), 5.64 (s, 1H), 5.22-5.32 (m, 4H), 3.50-3.58 (m, 2H), 2.43-2.47 (m, 1H), 1.90-2.12 (m, 4H), 1.60-1.72 (m, 6H), 1.26-1.49 (m, 6H), 1.00-1.14 (m, 2H), 0.85-0.94 (m, 20H), 0.86 (d, J = 7.0 Hz, 6H), 0.77 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.31, 162.26, 134.3, 134.2, 129.1, 129.0, 128.9, 128.7, 128.5, 105.4, 102.0, 87.3, 82.4, 69.0, 68.8, 48.1, 47.8, 40.5, 40.4, 39.3, 34.1, 34.0, 31.8, 31.6, 25.5, 25.4, 23.1, 23.0, 22.3, 22.2, 21.2, 20.9, 16.0, 15.9; IR (film) 1745 (C=O), 1571, 1456 (NO_2), 1170, 743 cm^{-1}; Elem. Anal. calcd for $C_{19}H_{27}NO_5$: C 65.31, H 7.79, N 4.01; found: C 65.61, H 8.05, N 3.95.



98 **196**

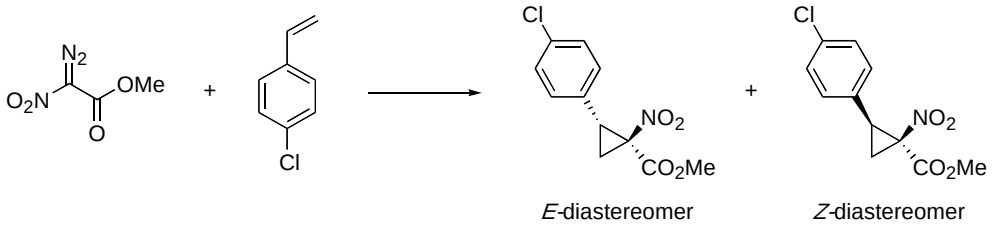
2-Allyloxy-2-nitro-1-phenyl-ethanone (196). Pale yellow oil (86 mg, 78%): R_f 0.31 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.99 (m, 2H), 7.63-7.67 (m, 1H), 7.48-7.52 (m, 2H), 6.20 (s, 1H), 5.94-6.04 (m, 1H), 5.40-5.45 (m, 2H), 4.58-4.63 (m, 1H), 4.33-4.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 135.1, 132.6, 131.0, 129.7, 129.2, 121.9, 106.4, 74.3; IR (film) 1700 (C=O), 1574, 1451, 1325 (NO_2), 1223, 1172, 984 cm^{-1}; Elem. Anal. calcd for $C_{11}H_{11}NO_4$: C 59.73, H 5.01, N 6.33; found: C 59.45, H 4.99, N 5.70.



71 **195i**

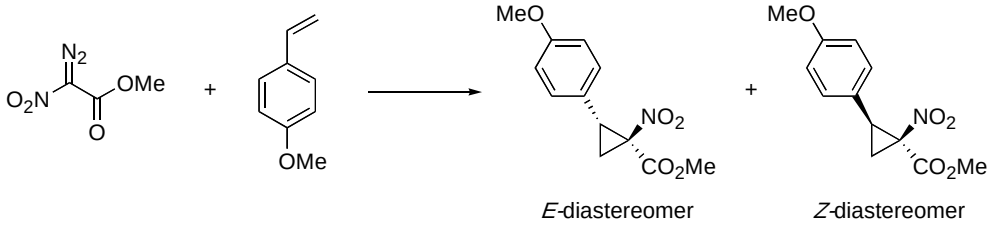
Ethyl *iso*-propyloxy-nitroacetate (195i). Clear, volatile colorless oil (413 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.99 (sept, *J* = 7.1 Hz, 1H), 1.25-1.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 103.8, 76.9, 64.0, 22.7, 21.6, 14.3; IR (film) 1761 (C=O), 1575, 1375 (NO_2), 1199, 1107, 1024, 929, 849 cm^{-1}.

Typical procedure for cyclopropanation of olefins with α-nitro-α-diazocarbonyls in aqueous media. Methyl nitro diazoacetate (**97**, 80.0 mg, 0.55 mmol) was dissolved in water (4.0 mL) using magnetic agitation and heating in a warm water bath (*ca.* 45 ^{o}C). In another 25 mL round-bottomed flask $[Rh(OPiv)_2]_2$ (1.7 mg, 2.76 x 10^{-3} mmol, 0.5 mol%) was treated with distilled styrene (115 mg, 1.10 mmol, 2.0 equiv) and water (0.5 mL). The aqueous solution containing diazo **97** was then added slowly dropwise *via* pipette to the olefin/catalyst solution over 20 min. The rapidly stirring suspension of purple beads was found to release N_2 bubbles upon addition of the diazo compound. The stirring was continued for another 2 h then extracted with EtOAc (2x5 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The crude reaction mixture was then purified by flash chromatography on silica gel first eluting with hexane (100%) then with 3-5% EtOAc/Hexane affording the desired cyclopropane (**150a**, 91%, 110 mg).



97 **197a**

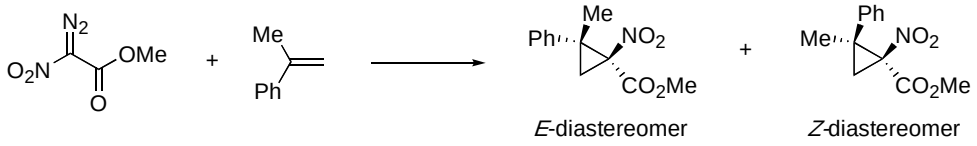
Methyl-1-nitro-2-(4-chlorophenyl)-cyclopropanecarboxylate (197a). (151 mg, 87%): **Methyl *E*-1-nitro-2-(4-chlorophenyl)-cyclopropanecarboxylate (197a)**. White solid: M.p. 33-35 ^{o}C; R_f 0.57 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 3.71 (t, J = 9.9 Hz, 1H), 3.55 (s, 3H), 2.40 (dd, J = 9.1, 6.8 Hz, 1H), 2.22 (dd, J = 10.7, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 134.4, 130.8, 129.9, 128.9, 71.7, 53.5, 33.5, 21.0; IR (solid) 1746 (C=O), 1546, 1347 (NO_2), 1220, 1094, 1016, 837 cm^{-1}; HRMS (EI^{+}) calcd for $C_{11}H_{10}NO_4Cl$ $[M]^{+}$: 255.02984, found: 255.02976; **Methyl *Z*-1-nitro-2-(4-chlorophenyl)-cyclopropanecarboxylate (197a).** Clear colorless oil; R_f 0.30 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 6.5 Hz, 2H), 7.15 (d, J = 6.5 Hz, 2H), 3.90 (s, 3H), 3.45 (t, J = 9.5 Hz, 1H), 2.65 (dd, J = 9.1, 7.1 Hz, 1H), 2.05 (dd, J = 9.9, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 135.0, 130.0, 129.9, 129.2, 72.5, 54.1, 33.2, 20.3; IR (film) 1745 (C=O), 1544, 1296 (NO_2), 1154, 842 cm^{-1}; Elem. Anal. calcd for $C_{11}H_{10}NO_4Cl$: C 51.68, H 3.94, N 5.48; found: C 51.51, H 3.91, N 5.49.



97 **197b**

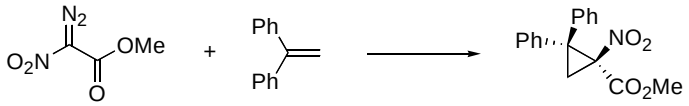
Methyl 1-nitro-2-(4-methoxyphenyl)cyclopropanecarboxylate (197b). This compound rearranges to 5-(4-methoxyphenyl)-2-oxy-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester (**318a**) on silica gel (94 mg, 82%): ***E*-Methyl 1-nitro-2-**

(4-methoxyphenyl)cyclopropanecarboxylate (197b). Observed in the crude reaction mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.73 (t, *J* = 9.9 Hz, 1H), 3.54 (s, 3H), 2.42 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.21 (dd, *J* = 10.8, 6.6 Hz, 1H); ***Z*-Methyl 1-nitro-2-(4-methoxyphenyl) cyclopropanecarboxylate (197b).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.45 (t, *J* = 9.6 Hz, 1H) 2.65 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.03 (dd, *J* = 9.9, 6.9 Hz, 1H).



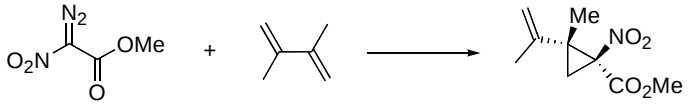
97 **197c**

Methyl 1-nitro-(*trans*-2-phenyl)-(*cis*-2-methyl)-cyclopropanecarboxylate (197c). Clear colorless oil (130 mg, 80%): R_f 0.60 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 5H), 3.49 (s, 3H), 2.42 (d, *J* = 6.8 Hz, 1H), 2.17 (d, *J* = 6.8 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 139.0, 128.8, 127.9, 127.8, 76.2, 53.2, 39.4, 26.7, 24.9; IR (film) 1745 (C=O), 1544, 1363, 1313 (NO_2), 1236, 1141 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{13}NO_4$ [M+1]: 236.09228, found: 236.09174; Elem. Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27, H 5.57, N 5.95; found: C 61.00, H 5.55, N 5.91; On acidic silica gel (EM Science) the cyclopropane partially rearranges to **5-phenyl-5-methyl-2-oxy-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester**. Clear colorless oil: R_f 0.24 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.44 (m, 5H), 3.83 (s, 3H), 3.57 (dd, *J* = 28.0, 16.7 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 143.0, 129.1, 128.4, 124.3, 109.0, 83.1, 52.8, 44.4, 28.2; IR (film) 1739, 1704 (C=O), 1621 (NO), 1445, 1256 cm^{-1}.



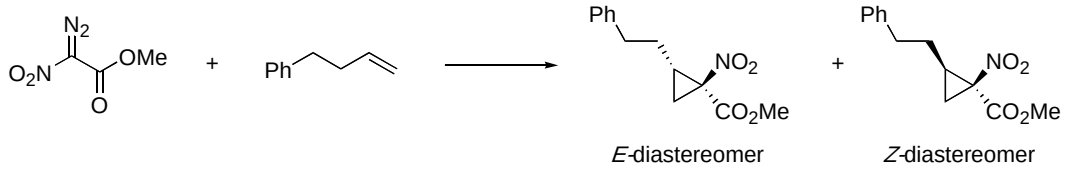
97 **197d**

Methyl 1-nitro-2,2'-diphenylcyclopropanecarboxylate (197d). Observed in the crude reaction mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.47 (m, 10H), 3.60 (s, 3H), 3.04 (d, *J* = 6.9 Hz, 1H), 2.67 (d, *J* = 6.9 Hz, 1H); On silica gel the cyclopropane rearranges to **5,5-diphenyl-2-oxy-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester.** White crystalline solid (120 mg, 63%): M.p. 116-117 ^{o}C; R_f 0.28 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.45 (m, 10H), 4.05 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 141.5, 129.0, 128.7, 125.9, 109.0, 86.2, 52.9, 43.7; IR (solid) 1700 (C=O), 1631 (NO), 1441, 1239 cm^{-1}; HRMS (EI^{+}) calcd for $C_{17}H_{15}NO_4$ $[M]^{+}$: 297.10011, found: 297.09999; Elem. Anal. calcd for $C_{17}H_{15}NO_4$: C 68.68, H 5.09, N 4.71; found: C 68.59, H 5.05, N 4.62.



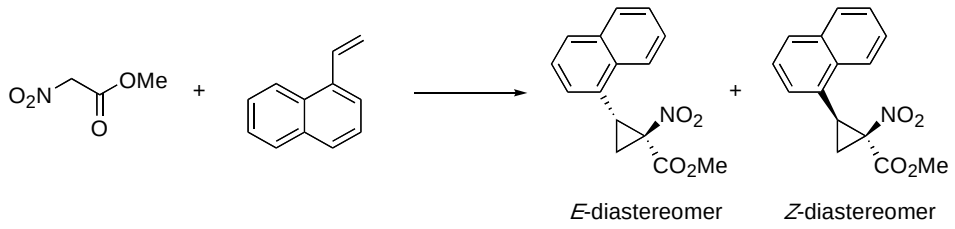
97 **197e**

Methyl *E*-1-nitro-2-isopropenyl-2-methylcyclopropanecarboxylate (197e). Clear colorless oil (92 mg, 31%): R_f 0.61 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, *J* = 18.2 Hz, 2H), 3.75 (s, 3H), 2.12 (d, *J* = 6.7 Hz, 1H), 1.96 (d, *J* = 6.7 Hz, 1H), 1.75 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 142.2, 114.7, 75.6, 53.4, 40.6, 27.5, 21.4, 20.1; IR (film) 1746 (C=O), 1545, 1438, 1360 (NO_2), 1312, 1124, 900 cm^{-1}; HRMS (EI^{+}) calcd for $C_9H_{13}NO_4$ $[M+1]^{+}$: 200.09228, found: 200.09209.



97 **197f**

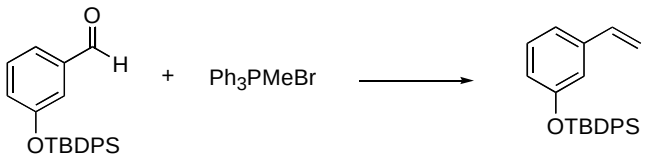
Methyl 1-nitro-2-(2-phenethyl)cyclopropanecarboxylate (197f). (82 mg, 70%): **Methyl *E*-1-nitro-2-(2-phenethyl)cyclopropanecarboxylate (197f).** Clear colorless oil: R_f 0.42 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.32 (m, 5H), 3.86 (s, 3H), 2.72-2.77 (m, 2H), 2.39-2.53 (m, 1H), 1.83-1.91 (m, 2H), 1.63-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 140.6, 128.8, 128.6, 126.5, 70.5, 53.7, 34.9, 30.2, 30.0, 23.3; IR (film) 1745 (C=O), 1544, 1354 (NO_2), 1219, 1149 cm^{-1}; Elem. Anal. calcd for $C_{13}H_{15}NO_4$: C 62.64, H 6.07, N 5.62; found: C 62.49, H 6.09, N 5.60; **Methyl *Z*-1-nitro-2-(2-phenethyl)cyclopropanecarboxylate (197f).** Clear colorless oil: R_f 0.36 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H), 3.83 (s, 3H), 2.75-2.81 (m, 2H), 2.12-2.17 (m, 1H), 1.80-1.83 (m, 2H), 1.68-1.72 (m, 1H), 1.52-1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.6, 128.8, 128.6, 126.5, 71.4, 53.8, 34.6, 30.4, 29.0, 22.5; IR (film) 1745 (C=O), 1543, 1439, 1304 (NO_2), 1156 cm^{-1}; HRMS (EI$^+$) calcd for $C_{13}H_{15}NO_4$ $[M]^+$: 249.10015, found: 249.10069.



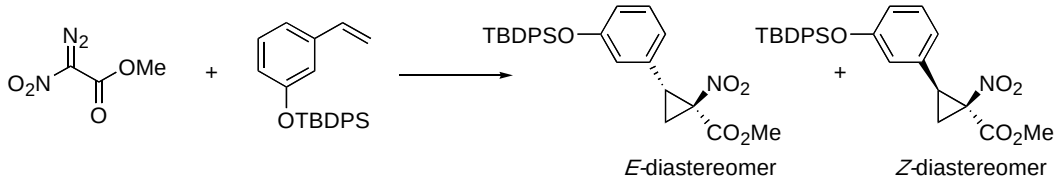
94 **197g**

Methyl 2-(1-naphthyl)-1-nitrocyclopropanecarboxylate (197g). (537 mg, 87%): **Methyl *E*-2-(1-naphthyl)-1-nitrocyclopropanecarboxylate (197g).** White crystalline solid: M.p. 85-86 ^{o}C; R_f 0.61 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.2, 0.9 Hz, 1H), 7.83-7.90 (m, 2H), 7.52-7.63 (m, 2H), 7.44 (t, J = 7.7 Hz, 1H), 7.30 (dd, J = 7.1, 1.0 Hz, 1H), 4.17 (t, J = 9.9 Hz, 1H), 3.23 (s,

3H), 2.68 (dd, *J* = 9.2, 6.5 Hz, 1H), 2.35 (dd, *J* = 10.6, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 133.5, 132.6, 129.2, 128.7, 128.4, 126.9, 126.4, 126.0, 125.1, 123.8, 71.9, 53.0, 32.4, 20.7; IR (solid) 1743 (C=O), 1539, 1347, 1334 (NO_2), 1212, 1141 cm^{-1}; Elem. Anal. calcd for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16; found: C 66.40, H 4.90, N 5.18; **Methyl *Z*-2-(1-naphthyl)-1-nitrocyclopropanecarboxylate (197g).** White crystalline solid: M.p. 110-111 ^{o}C; R_f 0.45 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 8.3 Hz, 2H), 7.50-7.62 (m, 2H), 7.34-7.44 (m, 2H), 3.97-4.03 (m, 1H), 3.99 (s, 3H), 2.96 (dd, *J* = 9.4, 6.8 Hz, 1H), 2.14 (dd, *J* = Hz, 9.9, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 133.8, 132.7, 129.8, 128.9, 127.4, 127.1, 126.5, 126.2, 125.2, 123.7, 72.3, 54.2, 32.2, 19.9; IR (solid) 1741 (C=O), 1541, 1299 (NO_2), 1055 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{15}H_{13}NO_4$ $[M+H]^+$: 272.3 *m/z*, found: 272.1 *m/z*.

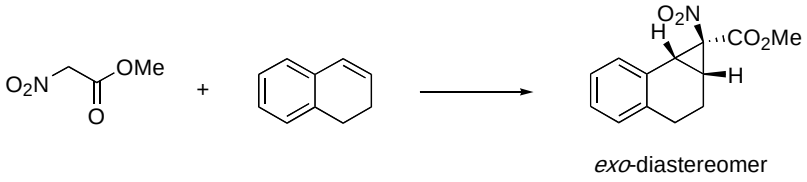


3-[(*tert*-Butyldiphenylsilyl)oxy]phenyl-styrene (precursor to 197h). Viscous colorless oil (870 mg, 72%): R_f 0.46 (Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.86 (m, 4H), 7.41-7.53 (m, 6H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.97-7.01 (m, 2H), 6.72-6.76 (m, 1H), 6.63 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.60 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 139.0, 136.8, 135.7, 133.1, 130.1, 129.4, 128.0, 119.5, 119.4, 117.5, 114.0, 26.8, 19.7; IR (film) 1578, 1485, 1429, 1279, 1112, 965 cm^{-1}; HRMS (EI^+) calcd for $C_{24}H_{26}SiO$ $[M]^+$: 358.17529, found: 358.17398.



97 **197h**

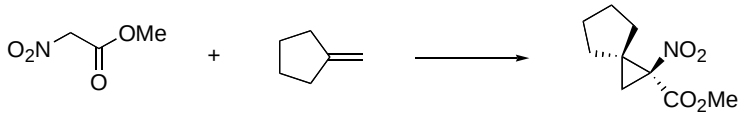
Methyl 2-(3-{[*tert*-butyldiphenyl)silyl]oxy}phenyl)-1-nitrocyclopropane carboxylate (197h). (356 mg, 92%): **Methyl *E*-2-(3-{[*tert*-butyldiphenyl)silyl]oxy} phenyl)-1-nitrocyclopropanecarboxylate (197h).** Viscous, colorless oil: R_f 0.83 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.3 Hz, 4H), 7.39-7.50 (m, 6H), 7.03 (t, *J* = 8.3 Hz, 1H), 6.69-6.76 (m, 3H), 3.64 (t, *J* = 9.9 Hz, 1H), 3.48 (s, 3H), 2.23 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.11 (dd, *J* = 10.7, 6.6 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 155.9, 135.7, 133.6, 132.9, 130.2, 129.4, 128.0, 121.2, 120.0, 119.8, 71.8, 53.1, 34.0, 26.7, 21.0, 19.6; IR (film) 1748 (C=O), 1545, 1350 (NO_2), 1114 cm^{-1}; **Methyl *Z*-2-(3-{[*tert*-butyldiphenyl)silyl]oxy}phenyl) -1-nitrocyclopropanecarboxylate (197h).** Viscous, colorless oil: R_f 0.62 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.73 (m, 4H), 7.37-7.47 (m, 6H), 7.01 (t, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.65-6.67 (m, 2H), 3.88 (s, 3H), 3.34 (t, *J* = 9.5 Hz, 1H), 2.42 (dd, *J* = 9.2, 6.9 Hz, 1H), 1.91 (dd, *J* = 9.9, 6.9 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.0, 135.7, 132.93, 132.88, 132.76, 130.1, 129.7, 128.0, 121.3, 120.2, 120.1, 72.5, 53.9, 33.8, 26.7, 20.2, 19.7; IR (film) 1744 (C=O), 1546, 1428, 1283 (NO_2), 1153, 1113 cm^{-1}.



94 **197i**

***exo*-Methyl 1-nitro-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (197i).** (200 mg, 84%): ***exo*-Methyl 1-nitro-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (197i).** White crystalline solid: M.p. 73-

74 °C; R_f 0.57 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.39 (m, 1H), 7.20-7.26 (m, 2H), 7.05-7.08 (m, 1H), 3.66 (s, 3H), 3.35 (d, J = 10.6 Hz, 1H), 2.91-2.96 (m, 1H), 2.72-2.77 (m, 1H), 2.31-2.40 (m, 2H), 2.08-2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 134.6, 130.8, 128.75, 128.69, 128.1, 126.8, 73.2, 53.5, 32.7, 30.1, 25.2, 17.1; IR (solid) 1744 (C=O), 1538, 1336 (NO_2), 1202, 1169 cm^{-1}; Elem. Anal. calcd for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.67; found: C 63.00, H 5.37, N 5.67.



94 **197j**

1-Nitro-spiro[2.4]heptane-1-carboxylic acid methyl ester (197j). Slightly volatile, clear colorless oil (111 mg, 73%): R_f 0.57 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 2.05 (d, J = 6.4 Hz, 1H), 1.96-2.02 (m, 1H), 1.78 (d, J = 6.4 Hz, 1H), 1.56-1.75 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 74.7, 53.3, 41.7, 33.7, 32.3, 29.2, 26.2, 25.8; IR (film) 1742 (C=O), 1542, 1438, 1365 (NO_2), 1122 cm^{-1}.

Typical procedure for cyclopropanation of olefins with ethyl diazoacetate (101) in aqueous media. Ethyl diazoacetate (**101**, 100 mg, 0.88 mmol) was dissolved in water (5.0 mL) using magnetic agitation. In another 25 mL round-bottomed flask $[Rh(Oct)_2]_2$ (3.4 mg, 4.38 x 10^{-3} mmol, 0.5 mol%) was treated with distilled styrene (182 mg, 1.75 mmol, 2.0 equiv) and water (0.5 mL). The solution containing diazo **101** was then added slowly dropwise *via* pipette to the olefin/catalyst solution over 50 min. The rapidly stirring suspension of green beads was found to release N_2 bubbles upon addition of the diazo compound. The stirring was continued for an additional 2 h then extracted with EtOAc (2x5 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The crude reaction mixture was then purified by flash chromatography on silica gel first eluting

with hexane (100%) then 1.5-2.5% EtOAc/Hexane to afford the pure cyclopropane (**198a**, 72%, 120 mg).

The characterization data for cyclopropanes **198a-h** have been previously reported in the literature.

Determination of enantiomeric excess of cyclopropanes 198.

2-Phenyl-cyclopropane carboxylic acid ethyl ester (198a). Cyclopropanation reaction catalyzed by Ru(II)-pybox (**205**): Enantiomeric excess (90% *trans*) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9 mL/min: (1*S*,2*S*) *trans*-**198a** t_r, 8.2 min, (1*R*,2*R*) *trans*-**198a** t_r 9.1 min). $[\alpha]_D$ -281^o (*c* 1.47, $CHCl_3$). Assignment of absolute stereochemistry was made by comparison with literature values. Cyclopropanation catalyzed by Co(II)-salen **206**: Enantiomeric excess (47% *trans*) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9 mL/min: (1*S*,2*S*) *trans*-**198a** t_r, 8.2 min, (1*R*,2*R*) *trans*-**198a** t_r 9.1 min). $[\alpha]_D$ +162^o (*c* 0.35, $CHCl_3$).

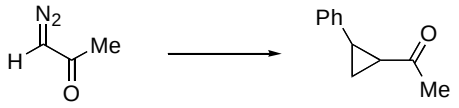
2-(4-Chlorophenyl)-cyclopropane carboxylic acid ethyl ester (198b). Cyclopropanation catalyzed by Ru(II)-pybox **205**: Enantiomeric excess (83% *trans*) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9 mL/min: (1*S*,2*S*) *trans*-**198b** t_r, 9.6 min, (1*R*,2*R*) *trans*-**198b** t_r 10.7 min). $[\alpha]_D$ -252^o (*c* 0.83, $CHCl_3$). Cyclopropanation catalyzed by Co(II)-salen **206**: Enantiomeric excess (47% *trans*) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9 mL/min: (1*S*,2*S*) *trans*-**198b** t_r, 10.6 min, (1*R*,2*R*) *trans*-**198b** t_r 11.7 min). $[\alpha]_D$ +153^o (*c* 0.96, $CHCl_3$).

2-(4-Methoxyphenyl)-cyclopropane carboxylic acid ethyl ester 198g. Cyclopropanation catalyzed by Ru(II)-pybox **205**: Enantiomeric excess (87% *trans*) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9

mL/min: (1*S*,2*S*) *trans*-**198g** t_r, 14.1 min, (1*R*,2*R*) *trans*-**198g** t_r 15.7 min). $[\alpha]_D$ -250° (*c* 0.58, $CHCl_3$).

2,2'-Diphenyl-cyclopropane carboxylic acid ethyl ester 198h. Cyclopropanation catalyzed by Ru(II)-pybox **205**: Enantiomeric excess (86%) was determined by SFC analysis (Whelk O, 0.9% MeOH in supercritical CO_2, 0.9 mL/min: (*R*)-**198h** t_r, 17.5 min, (*S*)-**198h** t_r 19.8 min). $[\alpha]_D$ -158° (*c* 0.97, $CHCl_3$).

1-Diazo-propan-2-one (**199**) was prepared according to a previously described procedure.



199 **200**

1-(2-Phenyl-cyclopropyl)-ethanone (200). (94 mg, 50%): ***trans*-1-(2-Phenyl-cyclopropyl)-ethanone (200).** Clear colorless oil: R_f 0.25 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.32 (m, 2H), 7.22-7.24 (m, 1H), 7.11 (d, *J* = 7.0 Hz, 1H), 2.50-2.58 (m, 1H), 2.32 (s, 3H), 2.22-2.24 (m, 1H), 1.67-1.70 (m, 1H), 1.38-1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 140.4, 128.6, 126.7, 126.1, 33.0, 31.0, 29.2, 19.3; IR (film) 1698 (C=O), 1398, 1187 cm^{-1}; ***cis*-1-(2-Phenyl-cyclopropyl)-ethanone (200).** Clear colorless oil: R_f 0.17 (10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.29 (m, 5H), 2.68-2.72 (m, 1H), 2.43-2.45 (m, 1H), 2.03 (s, 3H), 1.83-1.87 (m, 1H), 1.29-1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 136.2, 129.3, 128.2, 126.9, 31.4, 30.4, 28.4, 11.8; IR (film) 1698 (C=O), 1387, 1170 cm^{-1}; HRMS (EI^+) calcd for $C_{11}H_{12}O$ $[M]^+$: 160.08882, found: 160.08814.

Enantioselective cyclopropanation of olefins with EDA (101) in aqueous media.

Materials. Ru(II)-pybox ethylene complex **205** was prepared according to the method reported by Totleben *et al*. while Co(II)-salen complex **206** was prepared according to the method reported by Fukuda and Katsuki.[321]

Typical procedure for the Ru(II)-pybox 205 catalyzed cyclopropanation of olefins with ethyl diazoacetate (101) in water. Styrene (456 mg, 0.5 mL, 5.0 equiv) was added to a 10 mL round-bottomed flask containing the Ru(II)-pybox catalyst (**205**, 4.4 mg, 8.8 x 10^{-3}mmol, 1.0 mol%) followed by distilled water (0.5 mL). This was followed by the slow dropwise addition of ethyl diazoacetate (**101**, 100 mg, 0.88 mmol, 1.0 equiv) dissolved in distilled water (5.0 mL, 0.18M) over 2 h. The dark red biphasic solution was allowed to stir an additional 4 h before it was treated with brine (5.0 mL) and extracted with EtOAc (3x5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The crude cyclopropane was chromatographed on silica gel washing first with hexane, then eluting with 2% EtOAc/Hexane affording the pure cyclopropane as a clear colorless oil (**198a**, 77 mg, 0.40 mmol, 46%).

Typical procedure for the Co(II)-salen 206 catalyzed cyclopropanation of olefins with ethyl diazoacetate (101) in water. Under an argon atmosphere, styrene (268 mg, 0.29 mL, 5.0 equiv) was added to a 10 mL round-bottomed flask containing the Co(II)-salen catalyst (**206**) (15.4 mg, 2.6 x 10^{-2}mmol, 5.0 mol%) followed by *N*-methylimidazole (4.2 mg, 4.1 x 10^{-3}mL, 10 mol%) affording a dark orange solution. Ethyl diazoacetate (**101**, 59 mg, 0.51 mmol, 1.0 equiv) dissolved in argon purged water (3.0 mL, 0.18M) was then added in one portion. The biphasic orange/yellow solution was allowed to stir for 24 h then treated with brine (5.0 mL) and extracted with EtOAc (3x5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The crude cyclopropane was chromatographed

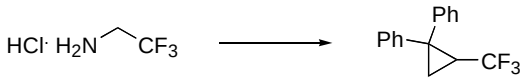
321. Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201-7208.

on silica gel washing first with hexane then eluting with 2% EtOAc/Hexane affording the pure cyclopropane as a clear colorless oil (**198a**, 78 mg, 0.41 mmol, 80%).

Typical procedure for Rh(II) carboxylate catalyzed cyclopropanation of olefins using ethyl diazoacetate (101) generated *in situ*. To a 25 mL round-bottomed flask containing $[Rh(Oct)_2]_2$ (5.5 mg, 7.1 x 10^{-3} mmol, 0.5 mol%) and styrene (298 mg, 2.9 mmol, 2.0 equiv) was added glycine ethyl ester hydrochloride (**211**, 200 mg, 1.5 mmol, 1.0 equiv) and sodium acetate buffer (7.0 mg, 6.0 mol%) in distilled water (2.0 mL). The solution was cooled in an ice bath to 0 ^oC and a solution of $NaNO_2$ (115 mg, 1.7 mmol, 1.16 equiv) in water (2.0 mL) was added in one portion followed by two drops of a 10% sulfuric acid solution. The reaction mixture was then stirred 14 h while warming slowly to room temperature. It was treated with brine (5.0 mL) and extracted with EtOAc (3x5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The residue was purified on silica gel washing first with hexane then eluting with 2% EtOAc/Hexane affording the pure cyclopropane as a clear colorless oil (**198a**, 165 mg, 0.87 mmol, 66%).

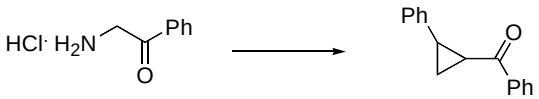
Typical procedure for Rh(II) carboxylate catalyzed cyclopropanation of olefins using ethyl diazoacetate (101) generated *in situ*: (sodium borate buffer and phosphoric acid). To a 25 mL round-bottomed flask containing $[Rh(Oct)_2]_2$ (5.5 mg, 7.1 x 10^{-3} mmol, 0.5 mol%) and styrene (298 mg, 2.9 mmol, 2.0 equiv) was added glycine ethyl ester hydrochloride (**211**, 200 mg, 1.5 mmol, 1.0 equiv) and sodium borate ($Na_2B_4O_7{\cdot}10H_2O$) buffer (45 mg, 0.12 mmol, 8.0 mol%) in distilled water (2.0 mL). The solution was cooled in an ice bath to 0 ^oC and a solution of $NaNO_2$ (115 mg, 1.7 mmol, 1.16 equiv) in water (2.0 mL) was added in one portion followed by a 2.0% H_3PO_4 solution (2.0 mL) added slowly over 15-20 min. The reaction mixture was then stirred 14 h while warming slowly to room temperature. It was treated brine (5.0 mL) and extracted with EtOAc (3x5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (rotary evaporator). The residue was purified on silica gel washing first with hexane then eluting with 2% EtOAc/Hexane affording the pure cyclopropane as a clear colorless oil (180 mg, 0.95 mmol, 68%).

Using 3.0 equiv of styrene 70% yield (*t/c* 1.6) and with 1.0 equiv of styrene 51% yield (*t/c* 1.5) of the pure cyclopropane was obtained.



213 **214**

[1-Phenyl-2-(trifluoromethyl)cyclopropyl]benzene (214). The procedure developed for the *in situ* generation of EDA (**101**) was repeated replacing glycine ethyl ester hydrochloride (**211**) with commercially available 2,2,2-trifluoro-ethylamine hydrochloride (**213**). Pale yellow oil (78 mg, >52%): R_f 0.17 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.88 (m, 1H), 7.61-7.65 (m, 1H), 7.49-7.55 (m, 2H), 7.06-7.45 (m, 6H), 2.36-2.45 (m, 1H), 1.93-1.96 (m, 1H), 1.55-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6, 130.2, 129.8, 128.8, 128.6, 128.5, 128.0, 127.3, 127.0, 36.1, 26.9 (q, J = 35.8 Hz, 1C), 15.7; IR (film) 1659, 1410, 1275, 1123, 697 cm^{-1}.

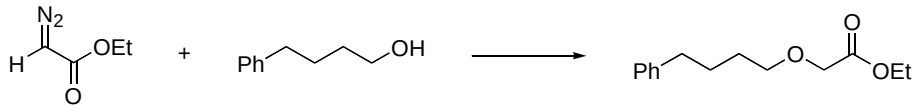


215 **216**

α-Aminoacetophenone hydrochloride (215). Prepared according to Abdalla and Sowell[322] (13.1 g, 70%): M.p. 183 °C (lit. 186.5 °C); The procedure developed for the *in situ* generation of EDA (**101**) was repeated replacing glycine ethyl ester hydrochloride (**211**) with α-aminoacetophenone hydrochloride **(215)**. **Phenyl-(2-phenyl-cyclopropyl)-methanone (216).** (74 mg, 28%): ***trans*-Phenyl-(2-phenyl-cyclopropyl)-methanone (216).** White paste: R_f 0.31 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-8.04 (m, 2H), 7.46-7.73 (m, 1H), 7.32-7.36 (m, 2H), 7.28-7.32 (m, 2H), 7.19-7.27 (m, 3H), 2.91-2.95 (m, 1H), 2.70-2.75 (m, 1H), 1.93-1.98 (m, 1H), 1.57-1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 140.7, 133.1, 129.6, 129.3, 128.8, 128.3, 126.8, 126.4, 30.2, 29.5, 19.5; IR (film) 1661 (C=O),

322. Abdalla, G. M.; Sowell, J. W. Sr. *J. Heterocyclic Chem*. **1987**, *24*, 297-301.

1447, 1398, 1342, 1221, 987 cm^{-1}; ***cis*-Phenyl-(2-phenyl-cyclopropyl)-methanone (216).** White paste: R_f 0.28 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-8.04 (m, 2H), 7.15-7.73 (m, 8H), 3.10-3.19 (m, 1H), 2.16-2.25 (m, 1H), 1.46-1.53 (m, 1H), 0.86-0.97 (m, 1H).



101 **217**

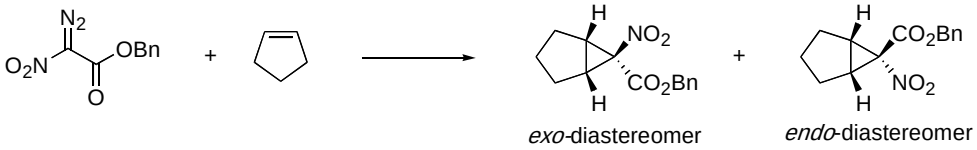
(4-Phenyl-butoxy)-acetic acid ethyl ester (217). Clear colorless oil (74 mg, 45%): R_f 0.58 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.30 (m, 2H), 7.16-7.20 (m, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 3.55 (t, J = 6.2 Hz, 2H), 2.66 (t, J = 7.4 Hz, 2H), 1.65-1.75 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 142.4, 128.5, 128.4, 125.8, 71.8, 68.5, 60.9, 35.7, 29.3, 27.9, 14.3; IR (film) 1752, 1733 (C=O), 1200, 1136 cm^{-1}; HRMS (EI^+) calcd for $C_{14}H_{20}O_3$ $[M]^+$: 236.14125, found: 236.14155.

Experimental: Chapter 5

Typical procedure for the Rh(II) carboxylate catalyzed cyclopropanations of olefins with α-nitro-α-diazoesters. Styrene (160 mg, 1.54 mmol, 0.18 mL, 2.0 equiv) was added to a 10 mL round-bottomed flask containing the required amount of $[Rh(Oct)_2]_2$ catalyst (2.7 mg, 3.5 x 10^{-3} mmol, 0.5 mol%). Methyl nitro diazoacetate (**97**, 111 mg, 0.77 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.77 mL, 1.0 M) and added slowly dropwise to the olefin/catalyst solution allowing for a controlled rate of N_2 evolution (over *ca*. 15-20 min). CH_2Cl_2 (0.5 mL) was then used to rinse the flask containing the diazo compound to ensure complete transfer of material. The reaction was allowed to stir 2-4 h, then concentrated under reduced pressure. The diastereoselectivity of the cyclopropanation reaction was determined by ^1H NMR of the crude reaction mixture. Purification by chromatography on silica gel, first eluting with hexane (to remove excess olefin) then 5% EtOAc/Hexane afforded

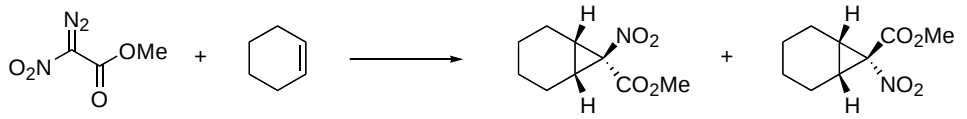
150a as a clear colorless oil (152 mg, 90%) in a 93:7 *E:Z* ratio. Separation of the diastereomers is possible using a less polar eluent (3% EtOAc/Hexane).

Typical procedure for the *in situ* Rh(II) carboxylate catalyzed cyclopropanations of olefins with α-nitrocarbonyls and $PhI(OAc)_2$. Styrene (587 mg, 5.64 mmol, 0.65 mL, 5.0 equiv) was added to a 25 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (3.4 mg, 5.6 x 10^{-3}mmol, 0.5 mol%) and methyl nitroacetate (**94**, 135 mg, 1.13 mmol, 1.0 equiv). Commercially available iodobenzene diacetate (400 mg, 1.24 mmol, 1.1 equiv) was then added in one portion and the mixture allowed to stir for 2 h open to air. The crude reaction mixture was then chromatographed directly on silica gel, first eluting with hexane (to remove excess olefin), then with 5% EtOAc/Hexane affording **147** as a clear colorless oil (223 mg, 84%) in a 92:8 *E:Z* ratio.



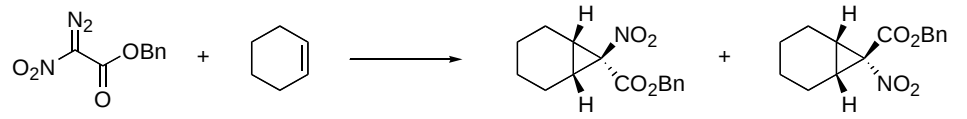
97 **227a**

Benzyl 6-nitrobicyclo[3.1.0]hexane-6-carboxylate (227a). White waxy solid (200 mg, 81%): ***exo*-Benzyl 6-nitrobicyclo[3.1.0]heptane-6-carboxylate (227a).** R_f 0.64 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.43 (m, 5H), 5.29 (s, 2H), 2.61-2.63 (m, 2H), 1.94-2.17 (m, 4H), 1.58-1.68 (m, 1H), 0.74-0.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 134.6, 128.9, 128.8, 72.4, 68.5, 37.9, 27.0, 21.4; ***endo*-Benzyl 6-nitrobicyclo[3.1.0]hexane-6-carboxylate (227a).** R_f 0.68 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.43 (m, 5H), 5.22 (s, 2H), 2.44-2.46 (m, 2H), 1.94-2.17 (m, 4H), 1.68-1.81 (m, 1H), 0.82-0.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.7, 128.9, 128.5, 128.2, 75.0, 68.3, 37.5, 27.3, 21.7; IR (solid) (*exo/endo* mix) 1733 (C=O), 1535, 1315 (NO_2), 1169 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{14}H_{15}NO_4$ $[M-H]^-$: 260.3 *m/z*, found: 260.1 *m/z*.



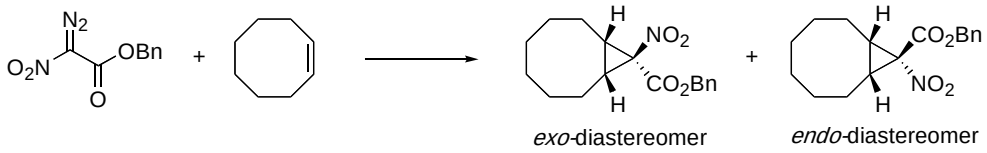
97 **227b**

Methyl 7-nitrobicyclo[4.1.0]heptane-7-carboxylate (227b). White semi-solid (124 mg, 55%): ***exo*-Methyl 7-nitrobicyclo[4.1.0]heptane-7-carboxylate (227b).** R_f 0.63 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 2.29-2.33 (m, 2H), 1.86-1.92 (m, 4H), 1.12-1.30 (m, 2H), 0.95-1.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 72.1, 53.2, 28.7, 20.2, 19.2; ***endo*-Methyl 7-nitrobicyclo[4.1.0] heptane-7-carboxylate (227b).** R_f 0.63 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 2.25-2.30 (m, 2H), 1.97-2.05 (m, 4H), 1.12-1.30 (m, 2H), 0.95-1.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 72.5, 53.6, 26.7, 20.0, 19.1; IR (film) (*exo/endo* mix) 1740 (C=O), 1535, 1332 (NO_2), 1207, 1166, 1113 cm^{-1}.



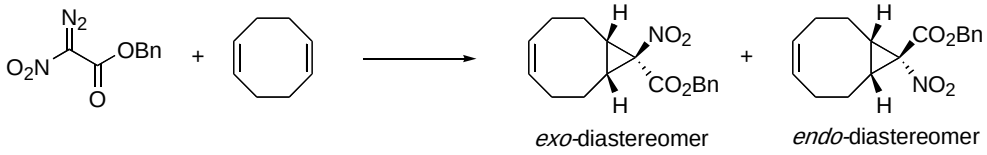
97 **227c**

Benzyl 7-nitrobicyclo[4.1.0]heptane-7-carboxylate (227c). Clear colorless oil (137 mg, 39%): ***exo*-Benzyl 7-nitrobicyclo[4.1.0]heptane-7-carboxylate (227c).** R_f 0.46 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.45 (m, 5H), 5.33 (s, 2H), 2.35-2.39 (m, 2H), 1.91-1.96 (m, 4H), 1.06-1.34 (m, 2H), 0.92-1.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 134.6, 128.9, 128.8, 128.7, 72.1, 68.4, 28.7, 20.2, 19.1; ***endo*-Benzyl 7-nitrobicyclo[4.1.0]heptane-7-carboxylate (227c).** R_f 0.46 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.45 (m, 5H), 5.22 (s, 2H), 2.38-2.42 (m, 2H), 2.00-2.11 (m, 4H), 1.06-1.34 (m, 2H), 0.92-1.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 134.7, 128.9, 128.7, 128.1, 73.1, 68.3, 26.8, 20.1, 19.1; IR (film) (*exo/endo* mix) 1739 (C=O), 1538, 1337 (NO_2), 1167, 1111 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{15}H_{17}NO_4$ $[M-H]^-$: 274.3 *m/z*, found: 274.1 *m/z*.



97 **227d**

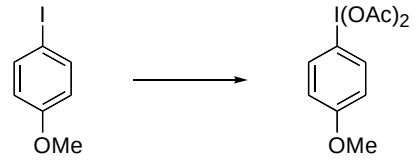
Benzyl 9-nitrobicyclo[6.1.0]nonane-9-carboxylate (227d). White, waxy solid (187 mg, 66%): M.p. 49-55 ^{o}C. ***exo*-Benzyl 9-nitrobicyclo[6.1.0]nonane-9-carboxylate (227d).** R_f 0.44 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.41 (m, 5H), 5.29 (s, 2H), 2.08-2.26 (m, 4H), 1.57-1.71 (m, 4H), 1.34-1.51 (m, 4H), 1.11-1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 134.9, 128.72, 128.67, 128.5, 72.3, 68.1, 34.1, 28.2, 26.1, 22.8; ***endo*-Benzyl 9-nitrobicyclo[6.1.0]nonane-9-carboxylate (227d).** R_f 0.44 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.41 (m, 5H), 5.24 (s, 2H), 2.08-2.14 (m, 4H), 1.90-1.93 (m, 4H), 1.57-1.71 (m, 4H), 1.11-1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 134.7, 128.7, 128.5, 128.1, 73.6, 68.1, 32.1, 26.2, 23.0; IR (solid) (*exo/endo* mix) 1745 (C=O), 1531, 1350 (NO_2), 1164 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{17}H_{21}NO_4$ $[M-H]^-$: 302.4 *m/z*, found: 302.1 *m/z*.



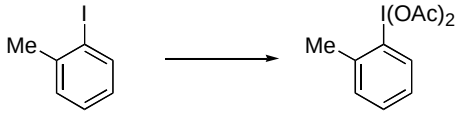
97 **227e**

Benzyl 9-nitrobicyclo[6.1.0]non-4-ene-9-carboxylate (227e). Viscous, colorless oil (210 mg, 71%): ***exo*-Benzyl 9-nitrobicyclo[6.1.0]non-4-ene-9-carboxylate (227e).** R_f 0.46 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 5.60-5.67 (m, 2H), 5.30 (s, 2H), 2.31-2.44 (m, 4H), 2.03-2.19 (m, 4H), 1.88-1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 134.8, 129.2, 128.8, 128.6, 128.2, 72.4, 68.1, 33.9, 26.2, 23.8; ***endo*-Benzyl 9-nitrobicyclo[6.1.0]non-4-ene-9-carboxylate (227e).** R_f 0.39 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 5.60-5.67 (m, 2H), 5.24 (s, 2H), 2.31-2.44 (m, 4H), 2.03-2.19 (m, 4H), 1.65-1.79

(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 134.7, 129.2, 128.8, 128.6, 128.2, 73.5, 32.1, 26.4, 24.1; IR (film) (*exo/endo* mix) 1738 (C=O), 1539, 1344 (NO_2), 1175, 1129 cm^{-1}; LRMS (APCI, Neg) calcd for $C_{17}H_{19}NO_4$ [M-H]$^-$: 300.3 *m/z*, found: 300.1 *m/z*.

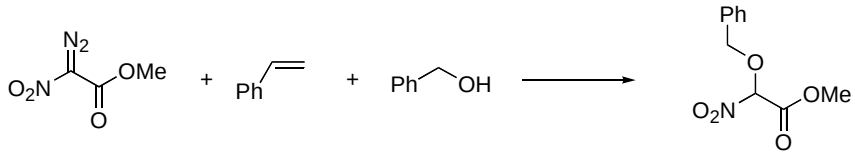


Bis(acetoxy)-4-methoxy-iodobenzene. Prepared according to McKillop and Kemp. White crystalline solid (2.18 g, 59%): M.p. 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.0, 2.2 Hz, 2H), 6.97 (dd, *J* = 7.0, 2.1 Hz, 2H), 3.86 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 162.4, 137.3, 116.8, 111.8, 55.8, 20.6; IR (solid) 1645 (C=O), 1492, 1251, 1008, 665 cm^{-1}.



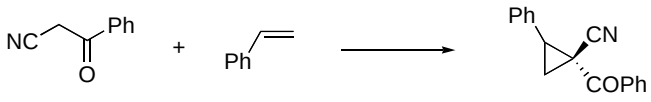
Bis(acetoxy)-2-methyl-iodobenzene. Prepared according to McKillop and Kemp. White crystalline solid (2.42 g, 72%): M.p. 134-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.22 (m, 1H), 7.51-7.52 (m, 2H), 7.24-7.28 (m, 2H), 2.72 (s, 3H), 1.99 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 140.9, 137.4, 132.9, 131.0, 128.6, 127.6, 25.8, 20.5; IR (solid) 1641 (C=O), 1274 cm^{-1}.

Bis(trifluoroacetoxy)iodobenzene. White crystalline solid (4.31 g, 66%): M.p. 117-119 °C. Prepared according to the method of Merkushev *et al*. upon treatment of bis(acetoxy)iodobenzene with trifluoroacetic acid at 50 °C for 1.5 h.[221]



97 **236**

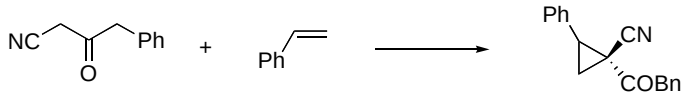
Methyl benzyloxy-nitroacetate (236). Clear colorless oil (57 mg, 33%): R_f 0.38 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s(*br*), 5H), 5.61 (s, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 133.9, 129.5, 129.1, 129.0, 103.0, 74.7, 54.1; IR (film) 1759 (C=O), 1568, 1440, 1341 (NO_2), 1215, 1161, 1025, 743, 698 cm^{-1}; HRMS (EI$^+$) calcd for $C_{10}H_{11}NO_5$ $[M]^+$: 225.06372, found: 225.06473.



132i **237a**

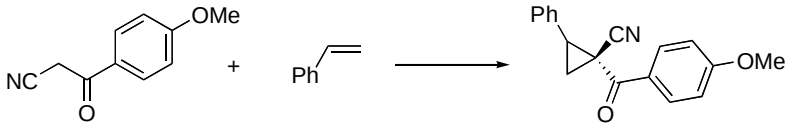
Typical procedure for the *in situ* Rh(II) carboxylate catalyzed cyclopropanations of olefins with α-cyanomethyl ketones and PhI(OAc)$_2$. Styrene (373 mg, 3.58 mmol, 0.41 mL, 5.0 equiv) was added to a 25 mL round-bottomed flask containing the required amount of $[Rh(Oct)_2]_2$ catalyst (2.8 mg, 3.58 x 10^{-3}mmol, 0.5 mol%), benzoyl acetonitrile (**132i**, 104 mg, 0.72 mmol, 1.0 equiv), anhydrous Na_2CO_3 (175 mg, 1.65 mmol, 2.3 equiv), 4 Å MS (105 mg) and iodobenzene diacetate (254 mg, 0.79 mmol, 1.1 equiv). Anhydrous CH_2Cl_2 (0.72 mL) was then added and the suspension was allowed to stir for 5 h at room temperature under an argon atmosphere. The crude reaction mixture was then filtered through a cotton plug and chromatographed on silica gel, first eluting with hexane (to remove excess olefin) then with 4-8% EtOAc/Hexane affording **1-Benzoyl-2-phenyl-cyclopropane carbonitrile (237a).** Pale yellow solid (128 mg, 72%): M.p. 79-80 ^{o}C (E/Z mix); ***E*-1-Benzoyl-2-phenyl-cyclopropanecarbonitrile (237a).** R_f 0.38 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.99 (m, 2H), 7.26-7.65 (m, 8H), 3.16 (t, *J* = 8.6 Hz, 1H), 2.56 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.23 (dd, *J* = 8.3, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 135.7, 133.9, 133.3, 129.1, 129.0, 128.9,

128.4, 118.8, 38.2, 28.9, 22.6; IR (film) 2237 (CN), 1681 (C=O), 1269, 1009, 696 cm^{-1}; ***Z*-1-Benzoyl-2-phenyl-cyclopropanecarbonitrile (237a).** R_f 0.38 (20% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-8.01 (m, 2H), 7.36-7.65 (m, 5H) 7.16-7.26 (m, 3H), 3.56 (t, *J* = 9.0 Hz, 1H), 2.81 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.06 (dd, *J* = 9.3, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 135.7, 133.9, 133.3, 129.1, 129.0, 128.9, 128.4, 120.7, 38.8, 26.3, 18.0; IR (film) (E/Z mix) 2238 (CN), 1671 (C=O), 1271, 1010, 740, 693 cm^{-1}.



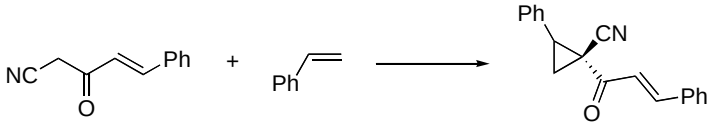
132k **237b**

3-Oxo-4-phenyl-butyronitrile (132k). Prepared according to Chen and Sieburth.[117b] Orange solid (1.46 g, 82%): M.p. 29 °C; R_f 0.11 (20% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.40 (m, 3H), 7.19-7.26 (m, 2H), 3.83 (s, 2H), 3.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 132.2, 129.6, 129.2, 127.9, 114.0, 49.1, 31.4; IR (film) 2259 (CN), 1733 (C=O), 1498, 1455, 1060 cm^{-1}; **2-Phenyl-1-phenylacetyl-cyclopropanecarbonitrile (237b).** An inseparable mixture of diastereomers as a pale yellow solid (94 mg, 57%): M.p. 44-46 °C; R_f 0.52 (20% EtOAc/Hexane); ***E*-2-Phenyl-1-phenylacetyl-cyclopropanecarbonitrile (237b).** ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.43 (m, 6H), 7.20-7.29 (m, 2H), 7.09-7.20 (m, 2H), 4.27 (d, *J* = 15.4 Hz, 1H), 4.19 (d, *J* = 15.4 Hz, 1H), 3.04 (t, *J* = 8.6 Hz, 1H), 2.26 (dd, *J* = 9.1, 5.0 Hz, 1H), 2.11 (dd, *J* = 8.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 133.1, 132.3, 130.0, 129.0, 128.8, 128.7, 128.3, 127.6, 118.4, 48.4, 39.3, 29.9, 24.3; ***Z*-2-Phenyl-1-phenylacetyl-cyclopropanecarbonitrile (237b).** ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.43 (m, 6H), 6.98-7.00 (m, 2H), 6.94-6.96 (m, 2H), 4.02 (d, *J* = 15.1 Hz, 1H), 3.93 (d, *J* = 15.2 Hz, 1H), 3.30 (t, *J* = 9.2 Hz, 1H), 2.54 (dd, *J* = 9.1, 5.5 Hz, 1H), 1.99 (dd, *J* = 9.4, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 131.5, 130.9, 129.8, 129.4, 128.7, 128.2, 127.4, 120.8, 48.7, 40.5, 27.5, 20.0; IR (solid) (E/Z mix) 2235 (CN), 1706 (C=O), 1496, 1454, 1070 cm^{-1}.



132l **237c**

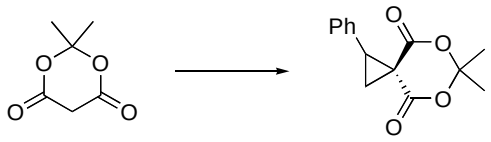
3-(4-Methoxyphenyl)-3-oxo-propionitrile (132l). Prepared according to Chen and Sieburth. White crystalline solid (443 mg, 42%): M.p. 117-118 ^{o}C; R_f 0.09 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 8.9 Hz, 1H), 4.04 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 164.9, 131.1, 127.4, 114.5, 114.3, 55.9, 29.2; IR (solid) 2258 (CN), 1686 (C=O), 1596, 1224, 1171, 1011, 848, 814 cm^{-1}; **1-(4-Methoxy-benzoyl)-2-phenyl-cyclopropane carbonitrile (237c).** An inseparable mixture of diastereomers as a clear viscous oil (106 mg, 63%): ***E*-1-(4-Methoxy-benzoyl)-2-phenyl-cyclopropanecarbonitrile (237c).** R_f 0.44 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 9.0 Hz, 2H), 7.34-7.47 (m, 5H), 6.98 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.11 (t, J = 8.7 Hz, 1H), 2.52 (dd, J = 9.1, 5.3 Hz, 1H), 2.17 (dd, J = 8.3, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 164.2, 133.5, 131.6, 131.5, 129.0, 128.7, 128.3, 114.1, 55.7, 37.1, 28.3, 21.8; ***Z*-1-(4-Methoxy-benzoyl)-2-phenyl-cyclopropanecarbonitrile (237c).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 2H), 7.34-7.47 (m, 3H), 7.15-7.20 (m, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 3.48 (t, J = 8.9 Hz, 1H), 2.77 (dd, J = 8.6, 5.8 Hz, 1H), 2.00 (dd, J = 9.3, 5.8 Hz, 1H); IR (film) (E/Z mix) 2236 (CN), 1668 (C=O), 1598, 1255, 1167 cm^{-1}.



132j **237d**

2-Phenyl-1-(3-phenyl-acryloyl)-cyclopropanecarbonitrile (237d). An inseparable mixture of diastereomers as a pale yellow oil (88 mg, 65%): ***E*-2-Phenyl-1-(3-phenyl-acryloyl)-cyclopropanecarbonitrile (237d).** R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 15.5 Hz, 1H), 7.15-7.68 (m, 11H), 3.27 (t,

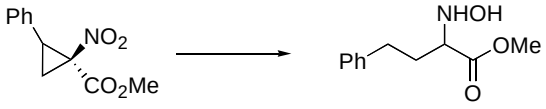
J = 8.8 Hz, 1H), 2.37 (dd, *J* = 9.1, 4.9 Hz, 1H), 2.20 (dd, *J* = 8.4, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 146.1, 133.9, 133.6, 131.5, 129.2, 129.1, 129.0, 128.9, 128.4, 121.6, 120.6, 38.9, 30.7, 24.9; ***Z*-2-Phenyl-1-(3-phenyl-acryloyl)-cyclopropanecarbonitrile (237d).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.68 (m, 12H), 3.47 (t, *J* = 9.2 Hz, 1H), 2.65 (dd, *J* = 8.9, 5.3 Hz, 1H), 2.06 (dd, *J* = 9.3, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 145.7, 133.9, 131.7, 131.3, 129.6, 129.2, 128.9, 128.7, 128.4, 121.0, 40.2, 27.7, 20.1; IR (film) (E/Z mix) 2232 (CN), 1677 (C=O), 1603, 1449, 1331, 1076, 975 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{19}H_{15}NO$ $[M+H]^+$: 274.3 *m/z*, found: 274.2 *m/z*.



238 **239**

6,6-Dimethyl-1-phenyl-5,7-dioxa-spiro[2.5]octane-4,8-dione (239). White crystalline solid (108 mg, 59%): M.p. 120-121 ^{o}C; R_f 0.32 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s(*br*), 5H), 3.44 (t, *J* = 9.4 Hz, 1H), 2.68 (dd, *J* = 9.3, 4.8 Hz, 1H), 2.53 (dd, *J* = 9.5, 4.8 Hz, 1H), 1.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 163.6, 131.2, 129.6, 128.8, 128.5, 105.0, 44.6, 33.2, 28.0, 27.7, 23.0; IR (solid) 1760, 1730 (C=O), 1327, 1289, 959 cm^{-1}.

Experimental: Chapter 6

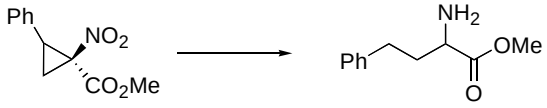


150a **249**

Typical reduction procedure involving Pd/C. In a 25 mL round-bottomed flask was added cyclopropane **150a** (84 mg, 0.38 mmol, 1.0 equiv) followed by anhydrous THF (2.2 mL) and anhydrous MeOH (2.2 mL). 10% Pd/C was then added (26 mg)

followed by NH_4CO_2H (238 mg, 3.78 mmol, 10.0 equiv). The reaction was allowed to stir for 25 min then filtered through a short celite plug washing with Et_2O. The solvent was removed under reduced pressure (rotary evaporator) and the crude residue purified by column chromatography eluting with 30% EtOAc/Hexane. **2-Hydroxyamino-4-phenyl-butyric acid methyl ester (249).** White solid (57 mg, 79%): M.p. 82-83 ^oC; R_f 0.13 (30% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.31 (m, 2H), 7.18-7.22 (m, 3H), 6.35 (s(*br*), 1H), 5.68 (s(*br*), 1H), 3.77 (s, 3H), 3.67 (dd, J = 7.4, 6.5 Hz, 1H), 2.66-2.73 (m, 2H), 1.89-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 140.9, 128.7, 128.6, 126.4, 64.7, 52.3, 32.2, 31.0; IR (solid) 3276 (NH), 3167 (OH), 1746 (C=O), 1453, 1198, 1174 cm^{-1}; HRMS (EI^+) calcd for $C_{11}H_{15}NO_3$ $[M]^+$: 209.10519, found: 209.10571; Elem. Anal. calcd for $C_{11}H_{15}NO_3$: C 63.14, H 7.23, N 6.69; found: C 62.98, H 7.67, N 6.61.

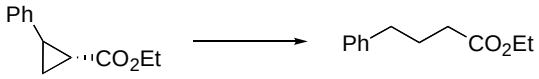
General procedure for Pd-catalyzed reductions using high pressures of hydrogen. In a 20 mL stainless steel bomb was added the desired cyclopropane followed by anhydrous MeOH (0.15M). 20% $Pd(OH)_2/C$ was then added (10 mol%) and the bomb sealed. The internal atmosphere was purged with hydrogen (5x100 psig) and left under 100 psig of hydrogen with vigorous stirring at room temperature for 24 h. The pressure was then released and the reaction mixture filtered through a short plug of celite washing with MeOH. The solvent was removed under reduced pressure (rotary evaporator) and the crude residue purified by column chromatography using a gradient of 30-100% EtOAc/Hexane.



150a **250**

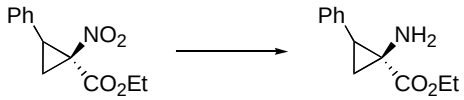
2-Amino-4-phenyl-butyric acid methyl ester (250). White solid (52 mg, 74%): M.p. 54-56 ^oC; R_f 0.18 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.30 (m, 2H), 7.13-7.21 (m, 3H), 3.71 (s, 3H), 3.46 (dd, J = 7.9, 5.2 Hz, 1H), 2.67-2.79 (m, 2H), 2.03-2.12 (m, 1H), 1.81-1.90 (m, 1H), 1.55 (s(*br*), 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 176.0, 141.2, 128.6, 128.5, 126.1, 53.8, 52.2, 36.1, 31.9; IR (solid) 3381 (NH), 1734 (C=O), 1455, 1436, 1197, 1174 cm^{-1}; HRMS (EI^+) calcd for $C_{11}H_{15}NO_2$ $[M]^+$: 193.11028, found: 193.11003.



198a **251**

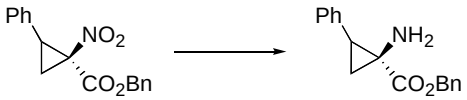
4-Phenyl-butyric acid ethyl ester (251). Clear colorless oil (69 mg, 81%): R_f 0.41 (2.5% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.32 (m, 2H), 7.18-7.28 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.97 (pent, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 141.7, 128.7, 128.6, 126.2, 60.5, 35.3, 33.9, 26.8, 14.4; IR (film) 1733 (C=O), 1454, 1374, 1180, 1032 cm^{-1}.



147 **252a**

Typical reduction procedure Ethyl-2-phenyl-1-nitrocyclopropanecarboxylate 147. Cyclopropane **147** (104 mg, 0.44 mmol) was dissolved in 8.8 mL of 2-propanol (0.05M) and treated with 1N HCl (4.4 mL, 10 equiv). Zinc dust (578 mg, 8.80 mmol, 20 equiv) was then added in small portions over 10-15 min and the solution allowed to stir for 2 h at room temperature. The suspension was quenched by addition of a saturated solution of $NaHCO_3$ (*ca*. 10 mL), stirred 15 min and filtered through a small plug of celite washing with EtOAc (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (2x10 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was then chromatographed on silica gel pre-treated with 1:5:19 Et_3N:EtOAc:Hexane (100 mL), rinsed with 20% EtOAc/Hexane (200 mL) and eluted with a gradient of 20-80% EtOAc/Hexane. The *E*- and *Z*-diastereomers were easily

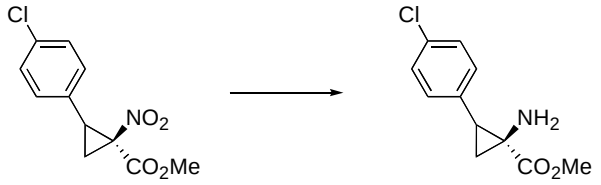
separated and the appropriate fractions combined (ninhydrin used as a developer) affording the corresponding amino esters (70 mg, 77%). **Ethyl *E*-1-amino-2-phenyl-1-cyclopropanecarboxylate (252a).** Pale yellow oil: R_f 0.16 (60% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.27 (m, 5H), 3.68-3.83 (m, 2H), 2.66 (t, *J* = 8.7 Hz, 1H), 2.20 (s(*br*), 2H), 1.99 (dd, *J* = 7.9, 5.0 Hz, 1H), 1.45 (dd, *J* = 9.5, 5.0 Hz, 1H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.9, 129.4, 128.1, 126.7, 60.8, 43.2, 36.4, 20.0, 13.8; IR (film) 3374 (NH), 1713 (C=O), 1144 cm^{-1}; **Ethyl *Z*-1-amino-2-phenyl-1-cyclopropanecarboxylate (252a).** Pale yellow oil: R_f 0.57 (80% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.35 (m, 2H), 7.23-7.27 (m, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.82 (t, *J* = 9.5 Hz, 1H), 1.84 (dd, *J* = 9.6, 4.9 Hz, 1H), 1.56 (s(*br*), 2H), 1.44 (dd, *J* = 7.6, 4.9 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 136.0, 129.4, 128.3, 127.0, 61.5, 41.3, 33.2, 22.1, 14.5; IR (film) 3384 (NH), 1717 (C=O), 1262, 1148, 834 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{12}H_{15}NO_2$ $[M+H]^+$: 206.3 *m/z*, found: 206.1 *m/z*.



150i **252b**

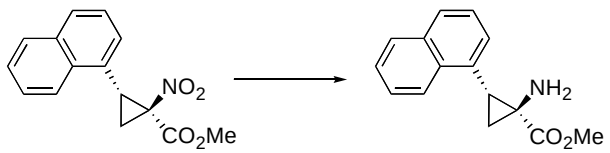
Benzyl 1-amino-2-phenyl-1-cyclopropanecarboxylate (252b). The *E*- and *Z*-isomers were easily separated (145 mg, 75%): **Benzyl *E*-1-amino-2-phenyl-1-cyclopropanecarboxylate (252b).** Clear colorless oil: R_f 0.42 (60% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.28 (m, 8H), 6.94-6.96 (m, 2H), 4.91 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 2.70-2.74 (m, 1H), 2.26 (s(*br*), 2H), 2.01-2.04 (m, 1H), 1.48-1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 136.5, 135.5, 129.3, 128.9, 128.4, 128.3, 128.1, 126.8, 66.7, 43.3, 36.5, 20.3; IR (film) 3373 (NH), 1714 (C=O), 1142, 697 cm^{-1}; **Benzyl *Z*-1-amino-2-phenyl-1-cyclopropane carboxylate (252b).** Clear colorless oil: R_f 0.85 (60% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.41 (m, 7H), 7.27-7.28 (m, 3H), 5.23 (s, 2H), 2.89 (t, *J* = 8.7 Hz, 1H), 1.89-1.93 (m, 1H), 1.65 (s(*br*), 2H), 1.48-1.51 (m, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 175.4, 136.0, 135.8, 129.3, 128.8, 128.5, 128.3, 128.2, 127.0, 67.2, 41.3, 33.4, 22.3; IR (film) 3385 (NH), 1718 (C=O), 1259, 1145 cm^{-1}.



197a **252c**

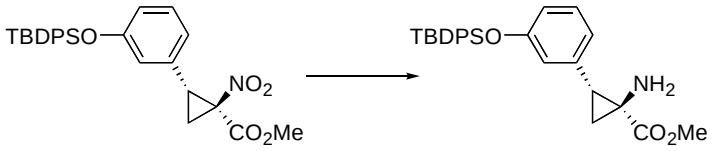
Methyl 1-amino-2-(4-chlorophenyl)-1-cyclopropanecarboxylate (252c). The *E*- and *Z*-isomers were easily separated (92 mg, 76%): **Methyl *E*-1-amino-2-(4-chlorophenyl)-1-cyclopropanecarboxylate (252c).** Pale yellow wax: M.p. 33-34 ^oC; R_f 0.14 (50% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 3.34 (s, 3H), 2.59 (t, J = 8.5 Hz, 1H), 2.19 (s(*br*), 2H), 1.94 (dd, J = 7.9, 5.1 Hz, 1H), 1.46 (dd, J = 9.4, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 135.1, 132.5, 130.5, 128.2, 51.8, 43.5, 35.8, 20.3; IR (solid) 3383 (NH), 1711 (C=O), 1284, 1182, 1132, 841 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{11}H_{12}NO_2Cl$ $[M+H]^+$: 226.7 *m/z*, found: 225.9, 227.9 *m/z*; **Methyl *Z*-1-amino-2-(4-chlorophenyl)-1-cyclopropanecarboxylate (252c).** Pale yellow oil: R_f 0.36 (50% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 3.76 (s, 3H), 2.77 (t, J = 7.6 Hz, 1H), 1.84 (dd, J = 9.6, 5.0 Hz, 1H), 1.56 (s(*br*), 2H), 1.40 (dd, J = 7.6, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 134.5, 132.8, 130.7, 128.4, 52.7, 41.3, 32.7, 22.4; IR (film) 3385 (NH), 1718 (C=O), 1496, 1436, 1265, 1148, 834 cm^{-1}.



197g **252d**

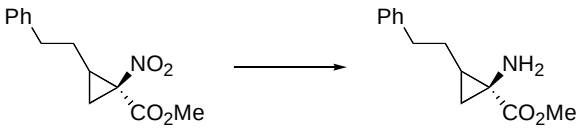
Methyl *E*-1-amino-2-(1-naphthyl)-1-cyclopropanecarboxylate (252d). Pale yellow solid (88 mg, 76%): M.p. 63-65 ^oC; R_f 0.18 (50% EtOAc/Hexane); ^1H NMR (300

MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.35-7.56 (m, 4H), 3.05 (s, 3H), 2.99 (t, *J* = 8.6 Hz, 1H), 2.44 (s(*br*), 2H), 2.15 (dd, *J* = 7.9, 4.9 Hz, 1H), 1.67 (dd, *J* = 9.3, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 133.5, 133.3, 133.2, 128.7, 127.5, 126.6, 126.2, 125.7, 125.4, 124.0, 51.6, 43.1, 35.0, 20.7; IR (solid) 3384, 3325 (NH), 1712 (C=O), 1321, 1055, 1033 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.3 *m/z*, found: 242.1 *m/z*; Elem. Anal. calcd for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81; found: C 74.56, H 6.40, N 5.76.



197h **252e**

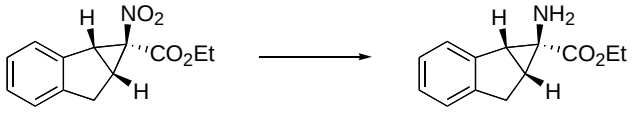
Methyl *E*-1-amino-2-[3-{[*tert*-butyl(diphenyl)silyl]oxy}phenyl) cyclopropane carboxylate (252e). Clear colorless oil (106 mg, 74%): R_f 0.13 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.73 (m, 4H), 7.33-7.43 (m, 6H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.67-6.71 (m, 2H), 6.53-6.57 (m, 1H), 3.23 (s, 3H), 2.50 (t, *J* = 8.7 Hz, 1H), 2.14 (s(*br*), 2H), 1.77 (dd, *J* = 7.9, 5.0 Hz, 1H), 1.34 (dd, *J* = 9.5, 5.0 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 155.3, 138.0, 135.7, 133.1, 130.0, 128.6, 127.9, 121.9, 120.7, 118.1, 51.5, 43.2, 36.1, 26.7, 20.0, 19.6; IR (film) 3380 (NH), 1720 (C=O), 1429, 1195, 702 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{27}H_{31}NO_3Si$ $[M+H]^+$: 446.6 *m/z*, found: 446.1 *m/z*.



197f **252f**

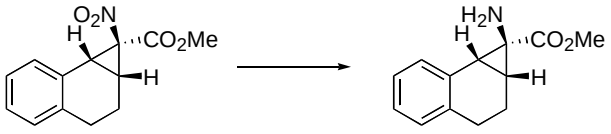
Methyl 1-amino-2-phenethyl-cyclopropanecarboxylate (252f). The *E*- and *Z*-isomers were easily separated (104 mg, 93%): **Methyl *E*-1-amino-2-phenethyl-cyclopropanecarboxylate (252f).** Pale yellow oil: R_f 0.14 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.30 (m, 2H), 7.14-7.20 (m, 3H), 3.67 (s, 3H), 2.53-

2.73 (m, 2H), 1.95 (s(*br*), 2H), 1.72-1.92 (m, 2H), 1.30-1.40 (m, 1H), 1.20-1.26 (m, 1H), 1.08-1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 142.0, 128.7, 128.5, 126.0, 52.2, 40.4, 36.0, 32.4, 29.4, 23.2; IR (film) 3382 (NH), 1720 (C=O), 1436, 1312, 1153, 833 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{17}NO_2$ $[M+H]^+$: 220.3 *m/z*, found: 220.1 *m/z*; **Methyl *Z*-1-amino-2-phenethyl-cyclopropanecarboxylate (252f).** Pale yellow oil: R_f 0.37 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.30 (m, 2H), 7.16-7.21 (m, 3H), 3.66 (s, 3H), 2.62-2.81 (m, 2H), 1.78-1.97 (m, 2H), 1.50 (s(*br*), 2H), 1.38-1.55 (m, 2H), 0.63 (dd, *J* = 7.0, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 142.2, 128.8, 128.5, 126.0, 52.3, 39.4, 36.1, 29.6, 28.7, 23.4; IR (film) 3382 (NH), 1718 (C=O), 1436, 1195, 1149, 827 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{17}NO_2$ $[M+H]^+$: 220.3 *m/z*, found: 220.1 *m/z*.



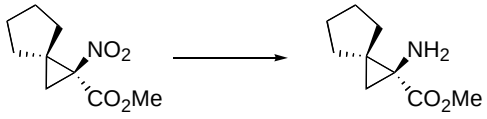
161c **252g**

***exo*-Ethyl 1-amino-1,1a,6,6a-tetrahydro-cyclopropa[*a*]-indene-1-carboxylate (252g).** Clear colorless oil (156 mg, 79%): R_f 0.20 (60% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.30 (m, 1H), 7.09-7.10 (m, 3H), 3.74-3.85 (m, 2H), 3.17-3.36 (m, 2H), 2.87 (dd, *J* = 6.8, 1.1 Hz, 1H), 2.26 (dt, *J* = 6.8, 1.3 Hz, 1H), 2.12 (s(*br*), 2H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 145.2, 140.2, 126.6, 126.2, 124.9, 124.1, 60.5, 44.8, 41.7, 33.5, 32.9, 13.8; IR (film) 3375 (NH), 1724 (C=O), 1304, 1132 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.3 *m/z*, found: 218.1 *m/z*.



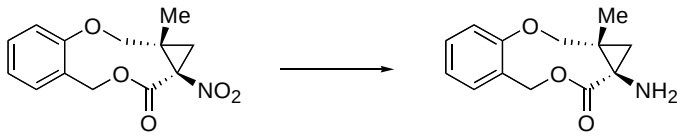
197i **252h**

***exo*-Methyl 1-amino-1,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]-naphthalene-1-carboxylate (252h).** Clear colorless oil (99 mg, 86%): R_f 0.23 (60% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.22 (m, 1H), 7.04-7.14 (m, 3H), 3.45 (s, 3H), 2.71-2.79 (m, 1H), 2.45-2.50 (m, 1H), 2.45 (d, *J* = 9.4 Hz, 1H), 1.96-2.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 138.1, 132.5, 129.9, 128.0, 126.5, 126.1, 51.8, 46.8, 31.5, 29.0, 27.9, 18.8; IR (film) 3374 (NH), 1725 (C=O), 1433, 1311, 1190, 1136, 744 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.3 *m/z*, found: 218.1 *m/z*.



197j **252i**

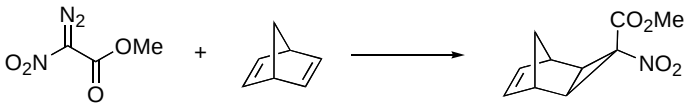
Methy 1-aminospiro[2.4]heptane-1-carboxylate (252i). Clear colorless oil (98 mg, 54%): R_f 0.16 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 1.96-2.05 (m, 2H), 1.84 (s(*br*), 2H), 1.58-1.79 (m, 5H), 1.53 (d, *J* = 4.5 Hz, 1H), 0.88 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 51.8, 43.5, 38.7, 32.5, 32.0, 29.6, 26.9, 26.3; IR (film) 3381 (NH), 1716 (C=O), 1287, 1197, 1132 cm^{-1}; LRMS (APCI, Pos) calcd for $C_9H_{15}NO_2$ $[M+H]^+$: 170.2 *m/z*, found: 170.1 *m/z*.



181b **252j**

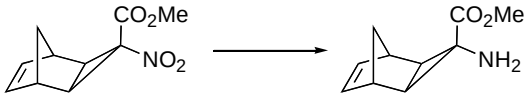
1a-Methyl-10a-nitro-1,1a,2,10a-tetrahydro-8*H*,10*H* benzo[*b*]cyclopropa-[*g*][1,5]-dioxonin-10-one (252j). White solid (68 mg, 70%): M.p. 67-68 ^{o}C; R_f 0.44 (50%

EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.22 (m, 1H), 7.06-7.08 (m, 2H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 14.3 Hz, 1H), 4.78 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 10.1 Hz, 1H), 3.73 (d, *J* = 10.1 Hz, 1H), 1.98 (s(*br*), 2H), 1.84 (d, *J* = 4.9 Hz, 1H), 1.51 (s, 3H), 1.04 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 158.6, 128.8, 127.8, 127.6, 124.4, 123.6, 84.3, 65.8, 43.3, 33.5, 29.6, 19.1; IR (solid) 3377 (NH), 1717 (C=O), 1490, 1211, 1099, 769 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{15}NO_3$ $[M+H]^+$: 234.3 *m/z*, found: 234.1 *m/z*; Elem. Anal. calcd for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.00; found: C 66.68, H 6.77, N 5.84.



97

Methyl 3-nitro-tricyclo[3.2.1.0]oct-6-ene-3-carboxylate. Clear colorless oil (69 mg, 42%): R_f 0.56 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 2H), 3.87 (s, 3H), 3.28 (s, 2H), 2.38 (s, 2H), 1.17 (d, *J* = 11.0 Hz, 1H), 0.90 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 83.5, 53.8, 43.3, 42.7, 41.1.

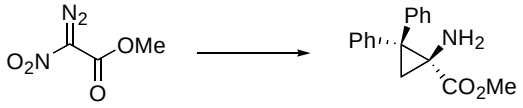


252k

Methyl 3-amino-tricyclo[3.2.1.0]oct-6-ene-3-carboxylate (252k). Clear colorless oil (47 mg, 80%): R_f 0.16 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 2H), 3.72 (s, 3H), 3.00 (s, 2H), 1.88 (s(*br*), 2H), 1.34 (s, 2H), 0.96 (d, *J* = 10.5 Hz, 1H), 0.79 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 141.7, 57.0, 52.5, 42.0, 40.9, 38.2; IR (film) 3370 (NH), 1728 (C=O), 1436, 1311 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{10}H_{13}NO_2$ $[M+H]^+$: 180.2 *m/z*, found: 180.1 *m/z*.

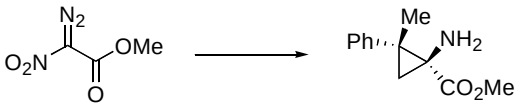
"One pot" cyclopropanation reduction procedure for the preparation of sensitive cyclopropanes 252l and 252m. $[Rh(Oct)_2]_2$ (4.5 mg, 0.5 mol%) was added

to a 100 mL round-bottomed flask followed by 1,1'-diphenylethene (415 mg, 2.30 mmol, 2.0 equiv). Methyl nitro diazoacetate (**97**, 167 mg, 1.15 mmol, 1.0 equiv) was then added slowly dropwise as a solution in CH_2Cl_2 (1.2 mL, 1.0M) to the catalyst/olefin mixture over 20 min. The solution was allowed to stir at room temperature for 4 h then the solvent was removed under reduced pressure (rotary evaporator). The crude residue was treated with 2-propanol (23 mL, 0.05M) and 1N HCl (11.5 mL, 10 equiv) was added. Zinc dust (1.50 g, 23.0 mmol, 20 equiv) was added in small portions over 10-15 min and the resulting suspension was allowed to stir an additional 2 h. It was quenched by the addition of a saturated solution of $NaHCO_3$ (*ca*. 15 mL) and allowed to stir 15 min. The suspension was filtered through a small celite plug, washing with EtOAc (25 mL). After separation of the organic phase, the aqueous phase was re-extracted with CH_2Cl_2 (2x15 mL), the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure (rotary evaporator). Purification of the crude residue by chromatography on silica gel pre-treated with 1:5:19 Et_3N:EtOAc:Hexane (100 mL) followed by rinsing with 20% EtOAc/Hexane (200 mL) was achieved by eluting with a gradient of 10-40% EtOAc/Hexane affording pure **252l** (174 mg, 57%). The same procedure was repeated for cyclopropane amino ester **252m.**



97 **252l**

Methyl 1-amino-2,2-diphenyl-1-cyclopropanecarboxylate (252l). Pale yellow oil (174 mg, 57%): R_f 0.35 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.47 (m, 10H), 3.36 (s, 3H), 2.41 (d, J = 5.4 Hz, 1H), 1.80 (s(*br*), 2H), 1.76 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 142.6, 140.8, 129.5, 128.9, 128.8, 128.5, 127.1, 126.8, 51.9, 46.2, 46.1, 25.7; IR (film) 3383 (NH), 1717 (C=O), 1494, 1447, 1202, 706 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{17}H_{17}NO_2$ $[M+H]^+$: 268.3 *m/z*, found: 267.9 *m/z*.

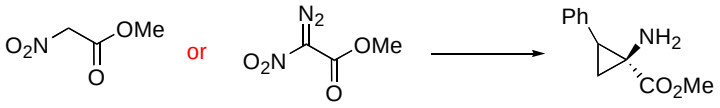


97 **252m**

Methyl 1-amino-(*cis*-2-methyl)-(*trans*-2-phenyl)-1-cyclopropanecarboxylate (252m). Pale yellow oil (200 mg, 62%): R_f 0.18 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.27 (m, 5H), 3.16 (m, 3H), 2.08 (d, *J* = 5.0 Hz, 1H), 1.99 (s(*br*), 2H), 1.57 (s, 3H), 1.04 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.7, 128.7, 128.67, 128.2, 128.1, 126.3, 51.3, 45.5, 36.9, 26.5, 25.5, 22.8; IR (film) 3379 (NH), 1722 (C=O), 1440, 1197 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{12}H_{15}NO_2$ $[M+H]^+$: 206.3 *m/z*, found: 206.1 *m/z*.

"One pot" cyclopropanation reduction procedure for Rh(II) carboxylate catalyzed cyclopropanation of styrene with methyl nitro diazoacetate (97) in water. Styrene (158 mg, 0.17 mL, 2.0 equiv) was added to a 100 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (2.3 mg, 3.8 x 10^{-3} mmol, 0.5 mol%) and distilled water (0.5 mL). Methyl nitro diazoacetate (**97**, 110 mg, 0.76 mmol, 1.0 equiv) was dissolved in hot water (4.0 mL, at 40 ^{o}C), cooled and added slowly dropwise to the aqueous catalyst/styrene mixture over 30 min. After stirring an additional 2 h, the reaction mixture was diluted with *i*-PrOH (15 mL, 0.05 M) and treated with 1N HCl (7.6 mL, 10 equiv). Zinc dust (987 mg, 15.1 mmol, 20 equiv) was added to the solution over 10-15 min in small portions and the resulting suspension was allowed to stir an additional 2 h. It was quenched by the addition of a saturated solution of $NaHCO_3$ (*ca*. 15 mL) and stirred an additional 15 min. The suspension was filtered through a small celite plug washing with EtOAc (25 mL). After separation of the organic phase, the aqueous phase was re-extracted with CH_2Cl_2 (2x15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure (rotary evaporator). Purification of the crude residue by chromatography on silica gel pre-treated with 1:5:19 Et_3N:EtOAc:Hexane (100 mL), rinsing with 20% EtOAc/Hexane (200 mL) and eluting with a gradient of 20-80% EtOAc/Hexane afforded pure **252n** (96 mg, 66%, 71:29 *E:Z*).

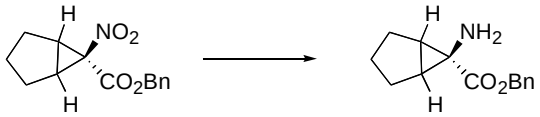
"One pot" cyclopropanation reduction procedure for Rh(II) carboxylate catalyzed cyclopropanation of styrene with methyl nitroacetate (94) and $PhI(OAc)_2$. Styrene (525 mg, 0.58 mL, 5.0 equiv) was added to a 100 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (3.1 mg, 5.0 x 10^{-3} mmol, 0.5 mol%) and methyl nitroacetate (**94**, 120 mg, 1.01 mmol, 1.0 equiv). $PhI(OAc)_2$ was then added (357 mg, 1.11 mmol, 1.1 equiv) in one portion and the mixture allowed to stir 2.5 h. The reaction mixture was then concentrated under reduced pressure to remove iodobenzene and excess olefin. The crude residue was suspended in 2-propanol (20 mL, 0.05M) and treated with 1N HCl (10.1 mL, 10 equiv). Zinc dust (1.32 g, 20.2 mmol, 20 equiv) was then added in small portions over 10-15 min and the solution allowed to stir for 2 h at room temperature. The suspension was quenched by addition of a saturated solution of $NaHCO_3$ (*ca*. 15 mL), stirred 15 min and filtered through a small plug of celite washing with EtOAc (25 mL). The aqueous phase was further extracted with CH_2Cl_2 (2x15 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure (rotary evaporator). The crude product was then chromatographed on silica gel pre-treated with 1:5:19 Et_3N:EtOAc:Hexane (100 mL), rinsing with 20% EtOAc/Hexane (200 mL) and eluting with a gradient of EtOAc/Hexane 20-80%. The *E*- and *Z*-diastereomers were easily separated and the appropriate fractions combined (ninhydrin used as a developer) affording the corresponding amino esters **252n** (125 mg, 65%, 65:35 *E:Z*).



94 **97** **252n**

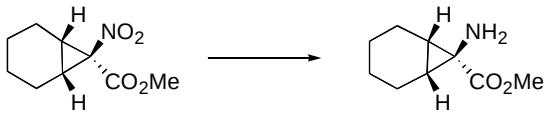
Methyl 1-amino-2-phenyl-1-cyclopropanecarboxylate (252n). The *E*- and *Z*-isomers were easily separated (108 mg, 66%). **Methyl *E*-1-amino-2-phenyl-1-cyclopropanecarboxylate (252n).** White solid: M.p. 34 ^oC; R_f 0.18 (80% EtOAc/ Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.28 (m, 5H), 3.29 (s, 3H), 2.66 (t, J = 8.7 Hz, 1H), 2.20 (s(*br*), 2H), 1.99 (dd, J = 7.9, 5.0 Hz, 1H), 1.46 (dd, J = 9.5, 5.0 Hz,

1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 136.6, 129.2, 128.1, 126.8, 51.7, 43.5, 36.5, 20.2; IR (solid) 3375 (NH), 1718 (C=O), 1315, 1206, 1146, 698 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{11}H_{13}NO_2$ $[M+H]^+$: 192.2 *m/z*, found: 192.1 *m/z*; Elem. Anal. calcd for $C_{11}H_{13}NO_2$: C 69.09, H 6.85, N 7.32; found: C 68.82, H 7.16, N 7.11; **Methyl *Z*-1-amino-2-phenyl-1-cyclopropanecarboxylate (252n).** Pale yellow oil: R_f 0.52 (80% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.36 (m, 2H), 7.24-7.27 (m, 3H), 3.77 (s, 3H), 2.84 (t, *J* = 7.7 Hz, 1H), 1.85 (dd, *J* = 9.6, 4.9 Hz, 1H), 1.56 (s(*br*), 2H), 1.45 (dd, *J* = 7.6, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 135.8, 129.4, 128.4, 127.0, 52.6, 41.2, 33.4, 22.2; IR (film) 3388 (NH), 1718 (C=O), 1264, 1148 cm^{-1}.



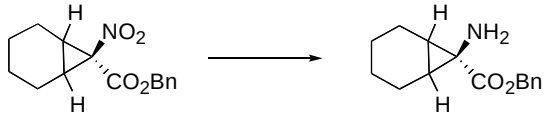
227a **253a**

Benzyl 6-aminobicyclo[3.1.0]hexane-6-carboxylate (253a). The *exo*- and *endo*-isomers were easily separated (117 mg, 88%): ***exo*-Benzyl 6-aminobicyclo[3.1.0]hexane-6-carboxylate (253a).** Clear colorless oil; R_f 0.42 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 5.13 (s, 2H), 1.98 (s(*br*), 2H), 1.75-1.94 (m, 4H), 1.57-1.71 (m, 3H), 1.08-1.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 135.9, 128.7, 128.6, 128.5, 66.7, 43.5, 35.3, 26.2, 24.6; IR (film) 3374 (NH), 1722 (C=O), 1456, 1300, 1129, 1018, 699 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{14}H_{17}NO_2$ $[M+H]^+$: 232.3 *m/z*, found: 232.1 *m/z*; ***endo*-Benzyl 6-aminobicyclo[3.1.0]heptane-6-carboxylate (253a).** Pale yellow wax: M.p. 53-54 ^{o}C; R_f 0.96 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.39 (m, 5H), 5.10 (s, 2H), 1.79-2.05 (m, 5H), 1.67-1.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 136.3, 128.8, 128.4, 128.2, 66.9, 43.1, 35.2, 26.4, 25.7; IR (solid) 3386 (NH), 1700 (C=O), 1304, 1244, 1222, 1117, 730 cm^{-1}.



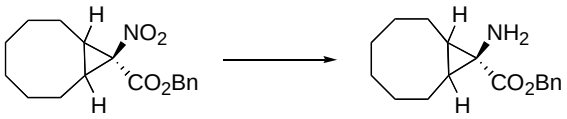
227b **253b**

***exo*-Methyl 7-aminobicyclo[4.1.0]heptane-7-carboxylate (253b).** Pale yellow oil (63 mg, 74%): R_f 0.23 (60% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 1.97 (s(*br*), 2H), 1.77-1.90 (m, 2H), 1.53-1.63 (m, 2H), 1.32-1.39 (m, 2H), 1.15-1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 51.7, 42.8, 26.5, 21.0, 18.7; IR (film) 3377 (NH), 1723 (C=O), 1435, 1318, 1164, 1101, 835 cm^{-1}; LRMS (APCI, Pos) calcd for $C_9H_{15}NO_2$ $[M+H]^+$: 170.2 *m/z*, found: 170.1 *m/z*.



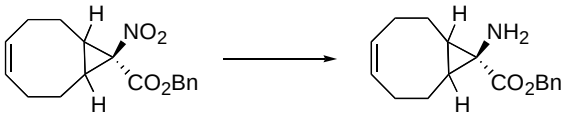
227c **253c**

Benzyl 7-aminobicyclo[4.1.0]heptane-7-carboxylate (253c). Pale yellow oil as a separable mixture of *exo*- and *endo*-isomers (82 mg, 87%): ***exo*-Benzyl 7-aminobicyclo[4.1.0]heptane-7-carboxylate (253c).** R_f 0.39 (40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.40 (m, 5H), 5.16 (s, 2H), 2.06 (s(*br*), 2H), 1.80-1.89 (m, 2H), 1.60-1.67 (m, 2H), 1.37-1.40 (m, 2H), 1.15-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 136.1, 128.7, 128.6, 128.4, 66.5, 42.6, 26.4, 20.9, 18.7; IR (film) 3374 (NH), 1722 (C=O), 1456, 1309, 1161, 1098 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{15}H_{19}NO_2$ $[M+H]^+$: 246.3 *m/z*, found: 246.1 *m/z*; ***endo*-Benzyl 7-aminobicyclo[4.1.0]heptane-7-carboxylate (253c).** R_f 0.99 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.40 (m, 5H), 5.08 (s, 2H), 1.71-1.89 (m, 4H), 1.64-1.69 (m, 2H), 1.48-1.62 (m, 2H), 1.37-1.48 (m, 2H), 1.19-1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 136.3, 128.8, 128.4, 128.3, 66.8, 40.7, 24.1, 21.8, 18.3; IR (film) 3384 (NH), 1710 (C=O), 1456, 1240, 1161, 1133, 697 cm^{-1}.



227d **253d**

Benzyl 9-aminobicyclo[6.1.0]nonane-9-carboxylate (253d). Clear viscous oil as a separable mixture of *exo*- and *endo*-isomers (146 mg, >99%): ***exo*-Benzyl 9-aminobicyclo[6.1.0]nonane-9-carboxylate (253d).** R_f 0.46 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 5.14 (s, 2H), 2.14 (s(*br*), 2H), 1.58-1.76 (m, 8H), 1.29-1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 136.3, 128.7, 128.3, 66.5, 41.8, 35.4, 29.1, 26.4, 21.4; IR (film) 3386 (NH), 1710 (C=O), 1454, 1298, 1142, 1104, 696 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.4 *m/z*, found: 274.1 *m/z*; ***endo*-Benzyl 9-nitrobicyclo[6.1.0]nonane-9-carboxylate (253d).** R_f 0.83 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.41 (m, 5H), 5.12 (s, 2H), 1.63-1.72 (m, 10H), 1.26-1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 136.3, 128.7, 128.4, 128.3, 66.9, 40.8, 30.8, 28.8, 26.6, 21.2; IR (film) 3382 (NH), 1713 (C=O), 1455, 1250, 1165 cm^{-1}.

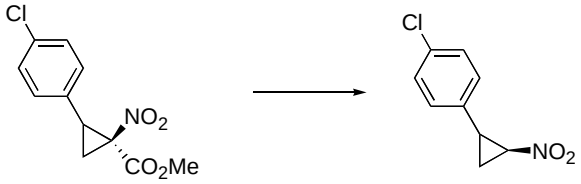


227e **253e**

Benzyl 9-aminobicyclo[6.1.0]non-4-ene-9-carboxylate (253e). Clear viscous oil as a separable mixture of *exo*- and *endo*-isomers (145 mg, 94%): ***exo*-Benzyl 9-aminobicyclo[6.1.0]non-4-ene-9-carboxylate (253e).** R_f 0.31 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5H), 5.52-5.62 (m, 2H), 5.16 (s, 2H), 2.41-2.49 (m, 2H), 2.06-2.18 (m, 4H), 1.93-2.04 (m, 2H), 1.81-1.90 (m, 2H), 1.46-1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 136.1, 129.3, 128.6, 128.4, 66.5, 42.3, 35.1, 26.9, 23.1; IR (film) 3377 (NH), 1713 (C=O), 1306, 1252, 1166, 1107 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{17}H_{21}NO_2$ $[M+H]^+$: 272.4 *m/z*, found: 272.1 *m/z*; ***endo*-Benzyl 9-aminobicyclo[6.1.0]non-4-ene-9-carboxylate (253e).** R_f 0.81 (40%

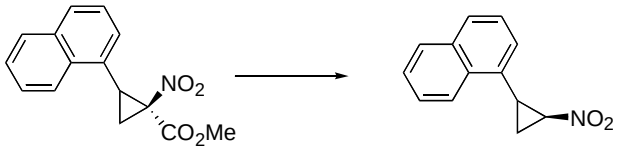
EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5H), 5.60-5.67 (m, 2H), 5.10 (s, 2H), 2.39-2.49 (m, 2H), 2.03-2.14 (m, 2H), 1.84-2.02 (m, 4H), 1.26-1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 136.2, 129.5, 128.7, 128.4, 66.8, 40.0, 30.4, 27.0, 22.9; IR (film) 3379 (NH), 1711 (C=O), 1260, 1178, 1033 cm^{-1}.

Procedure for the dehalogenation and reduction of bromo cyclopropane 161f. The standard reduction procedure was followed except the reaction was conducted in MeOH.



197a **277c**

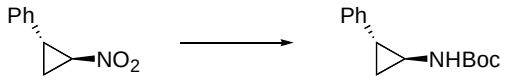
Typical procedure for the synthesis of nitrocyclopropanes. Compound **277a** has been previously reported. Cyclopropane **197a** was treated with DMSO (7.0 mL) and NaOH (62.6 mg, 1.57 mmol, 1.0 equiv) dissolved in distilled water (2.5 mL). The reaction mixture was heated to 80 ^{o}C for 2 h then quenched with a saturated solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (2x20 mL), washed with distilled water (3x25 mL), brine (1x25 mL) and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure (rotary evaporator) afforded the crude nitrocyclopropane **277c**. It was purified by column chromatography on silica gel using a gradient 4-10% EtOAc/Hexane allowing separation of the *trans*- and *cis*-diastereomers of **277c** (83:17 *trans:cis*): ***trans*-1-Chloro-4-(2-nitrocyclopropyl)benzene (277c).** Clear colorless oil (301 mg, 96%): R_f 0.53 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.37-4.40 (m, 1H), 3.08-3.13 (m, 1H), 2.22-2.27 (m, 1H), 1.63-1.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 133.7, 129.1, 128.2, 61.6, 28.8, 18.8; IR (film) 1539, 1496, 1364 (NO_2), 1093, 1012, 814 cm^{-1}; HRMS (EI^{+}) calcd for $C_9H_8NO_2Cl$ [M]$^{+}$: 197.02436, found: 197.02477.



197g **277b**

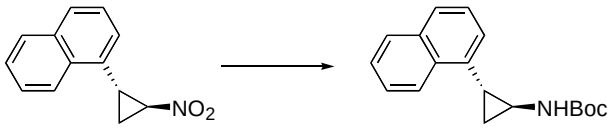
***trans*-1-(2-nitrocyclopropyl)naphthalene (277b).** Pale yellow solid (193 mg, 79%): M.p. 35-36 ^{o}C; R_f 0.55 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.5, 0.6 Hz, 1H), 7.91 (dd, J = 7.0, 2.0 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.49-7.64 (m, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.1 Hz, 1H), 4.41-4.46 (m, 1H), 3.57-3.64 (m, 1H), 2.34-2.41 (m, 1H), 1.78-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 132.5, 132.0, 128.9, 128.8, 127.0, 126.4, 125.3, 124.7, 123.5, 60.9, 27.7, 17.9; IR (solid) 1534, 1356 (NO_2), 775 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_{11}NO_2$ $[M+H]^+$: 214.2 *m/z*, found: 214.1 *m/z*.

General procedure for the synthesis of Boc-protected *trans*-aminocyclopropanes. The standard reduction procedure was followed as previously described. The crude residue was dissolved in anhydrous THF and treated with freshly distilled Et_3N (1.0 equiv) while cooling in an ice bath. Boc_2O (1.1 equiv) was added in one portion and the solution was allowed to stir in an ice bath for an additional 10 min. It was then removed from the ice bath and allowed to stir at room temperature overnight. The reaction mixture was concentrated and the residue dissolved in EtOAc (20 mL). The solution was washed with 10% citric acid (2x15 mL) and brine (1x25 mL) then dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure (rotary evaporator) and purification by column chromatography on silica gel using a gradient of 5-15% EtOAc/Hexane afforded the pure Boc-protected cyclopropanes.



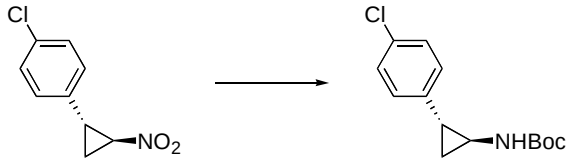
277a **278a**

***trans-tert*-Butyl 2-phenylcyclopropanecarbamate (278a).** White crystalline solid (140 mg, 60%): M.p. 69-72 ^{o}C; R_f 0.38 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.29 (m, 2H), 7.13-7.19 (m, 3H), 5.01 (s(*br*), 1H), 2.74 (s(*br*), 1H), 2.02-2.07 (m(*br*), 1H), 1.48 (s, 9H), 1.14-1.20 (m(*br*), 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5(*br*), 140.9, 128.4, 126.6, 126.1, 79.6(*br*), 32.6(*br*), 28.5, 25.1(*br*), 16.4; IR (solid) 3363 (NH), 1683 (C=O), 1509, 1163 cm^{-1}; HRMS (MAB) calcd for $C_{14}H_{19}NO_2$ $[M]^+$: 233.14158, found: 233.14123; Elem. Anal. calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00; found: C 71.71, H 8.42, N 5.92.



277b **278b**

***trans-tert*-Butyl 2-(1-naphthyl)cyclopropanecarbamate (278b).** Yellow oil (297 mg, 66%): R_f 0.34 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.72-7.74 (m, 1H), 7.49-7.58 (m, 2H), 7.37-7.41 (m, 2H), 4.98 (s(*br*), 1H), 2.96-2.98 (m, 1H), 2.44-2.49 (m, 1H), 1.50 (s, 9H), 1.19-1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7(*br*), 136.4, 133.8, 133.2, 128.7, 127.3, 126.1, 125.9, 125.7, 124.8, 124.4, 79.9(*br*), 31.0(*br*), 28.6, 23.0(*br*), 15.4; IR (film) 3330 (NH), 1693 (C=O), 1509, 1365, 1249, 1161, 775 cm^{-1}; HRMS (MAB) calcd for $C_{18}H_{21}NO_2$ $[M]^+$: 283.15723, found: 283.15688; Elem. Anal. calcd for $C_{18}H_{21}NO_2$: C 76.29, H 7.47, N 4.94; found: C 76.00, H 7.87, N 4.72.

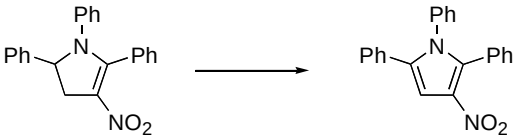


277c **278c**

***trans-tert*-Butyl 2-(4-chlorophenyl)cyclopropylcarbamate (278c).** White crystalline solid (223 mg, 67%): M.p. 122-123 ^{o}C; R_f 0.48 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.8 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 4.90 (s(*br*), 1H), 2.66 (s(*br*), 1H), 1.99-2.03 (m(*br*), 1H), 1.45 (s, 9H), 1.10-1.14 (m(*br*), 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5(*br*), 139.4, 131.8, 128.5, 128.1, 79.8(*br*), 32.6(*br*), 28.6, 24.8(*br*), 16.3; IR (solid) 3359 (NH), 1679 (C=O), 1505, 1496, 1251, 1156 cm^{-1}; HRMS (MAB) calcd for $C_{14}H_{18}NO_2Cl$ $[M]^+$: 267.10261, found: 267.10240.

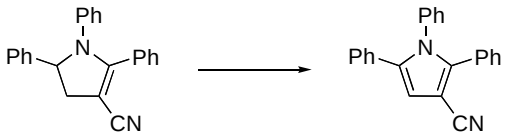
Experimental: Chapter 7

General procedure for the oxidation of dihydropyrroles to pyrroles using DDQ. In a 50 mL round-bottomed flask the dihydropyrrole **293** or **297** was treated with toluene (0.020M). DDQ was then added in one portion to the reaction mixture and the flask fitted with a reflux condenser under an argon atmosphere. The reaction mixture was heated to 140 ^{o}C in an oil bath for 3 h, cooled to room temperature and diluted with Et_2O (20 mL). The reaction mixture was then treated with a saturated solution of Na_2CO_3 in water (*ca*. 15 mL) and stirred for 20 min. After further treatment with brine (15 mL), the organic layer was removed. The organic layer was then washed with a saturated solution of Na_2CO_3 in water (2x15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure (rotary evaporator). The crude residue can then be recrystallized (EtOAc/Hexane) or purified by column chromatography on silica gel using 5-20% EtOAc/Hexane as an eluent.



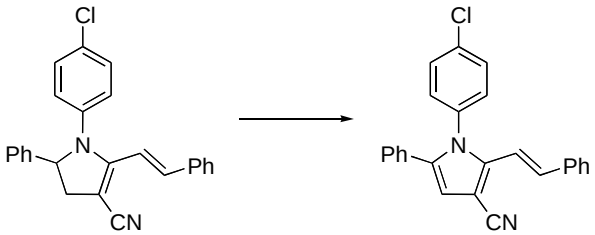
293c **292a**

3-Nitro-1,2,5-triphenyl-1*H*-pyrrole (292a). Yellow solid (63 mg, 77%): M.p. 166 ^{o}C; R_f 0.40 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.30 (m, 14H), 7.08-7.12 (m, 2H), 6.93-6.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 135.2, 134.4, 131.2, 131.0, 129.5, 129.04, 129.01, 128.94, 128.88, 128.54, 128.45, 128.0, 127.9, 106.0; IR (solid) 1492, 1396, 1319 (NO_2) cm^{-1}; LRMS (APCI, Pos) calcd for $C_{22}H_{16}N_2O_2$ $[M+H]^+$: 341.4 *m/z*, found: 341.1 *m/z*.



297c **292b**

1,2,5-Triphenyl-1*H*-pyrrole-3-carbonitrile (292b). White solid (149 mg, 94%): M.p. 217-218 ^{o}C; R_f 0.44 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.31 (m, 11H), 7.03-7.09 (m, 2H), 6.95-6.99 (m, 2H), 6.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 137.5, 136.3, 131.4, 129.9, 129.6, 129.25, 129.16, 128.8, 128.6, 128.52, 128.48, 128.4, 127.7, 117.4, 112.3, 112.2, 93.7, 77.7; IR (solid) 2228 (CN), 1494, 1190 cm^{-1}.

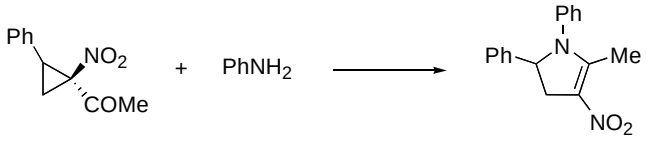


297a **292c**

1-(4-Chlorophenyl)-5-phenyl-2-styryl-1*H*-pyrrole-3-carbonitrile (292c). Pale yellow solid (136 mg, 91%): M.p. 197-198 ^{o}C; R_f 0.44 (10% EtOAc/Hexane); ^{1}H

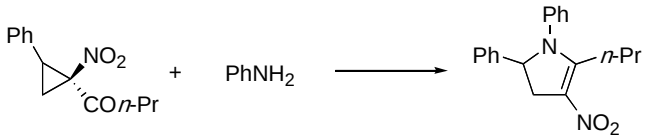
NMR (300 MHz, $CDCl_3$) δ 7.03-7.54 (m, 15H), 6.69 (s, 1H), 6.60 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 136.6, 136.3, 135.6, 135.2, 133.0, 130.8, 130.2, 129.9, 128.9, 128.7, 128.6, 128.0, 126.9, 117.6, 115.0, 113.3, 113.2, 91.3; IR (solid) 2116 (CN), 1493, 1093, 960, 839 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{25}H_{17}N_2Cl$ $[M+H]^+$: 381.9 *m/z*, found: 381.1 *m/z*.

General procedure for the synthesis of dihydro-1*H*-pyrroles. The cyclopropane (0.30 mmol) was treated with anhydrous toluene (1.0 mL) under an argon atmosphere in a 10 mL round-bottomed flask and the desired amine (0.30 mmol) was added. The reaction vessel was fitted with a reflux condenser and heated to 140 ^oC resulting in a vigorous reflux of the toluene. After 1-10 h, the reaction was allowed to cool and the bright yellow residue was purified on silica gel using 5-20% EtOAc/Hexane as an eluent.



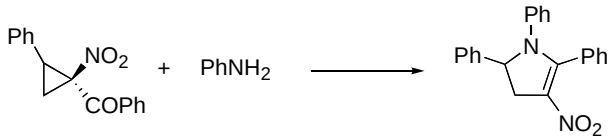
150d **293a**

5-Methy-4-nitro-1,2-diphenyl-2,3-dihydro-1*H*-pyrrole (293a). Yellow solid (34 mg, 91%): M.p. 134-135 ^oC; R_f 0.53 (50% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.31 (m, 8H), 6.90-6.93 (m, 2H), 5.17 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.77 (dd, *J* = 15.5, 11.7 Hz, 1H), 3.30 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 140.0, 138.3, 129.7, 129.2, 128.8, 128.4, 127.3, 127.0, 123.3, 69.4, 36.8, 15.7; IR (solid) 1557, 1379, 1362 (NO_2), 1262, 1170 cm^{-1}; HRMS (EI^+) calcd for $C_{17}H_{16}N_2O_2$ $[M]^+$: 280.12118, found: 280.12085; Elem. Anal. calcd for $C_{17}H_{16}N_2O_2$: C 72.84, H 5.75, N 9.99; found: C 72.69, H 5.86, N 9.86.



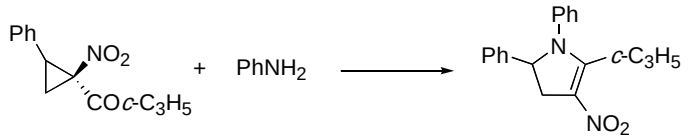
150e 293b

4-Nitro-1,2-diphenyl-5-propyl-2,3-dihydro-1*H*-pyrrole (293b). Yellow solid (86 mg, 78%): M.p. 155-156 ^{o}C; R_f 0.12 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.29 (m, 6H), 7.18-7.20 (m, 2H), 6.91-6.92 (m, 2H), 5.08 (dd, J = 11.7, 7.1 Hz, 1H), 3.76 (dd, J = 15.5, 11.8 Hz, 1H), 3.30 (dd, J = 15.6, 7.1 Hz, 1H), 2.80-2.87 (m, 1H), 2.59-2.66 (m, 1H), 1.58-1.69 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 140.1, 138.2, 129.7, 129.1, 128.8, 128.7, 127.3, 122.3, 69.6, 36.8, 29.5, 21.1, 14.4; IR (solid) 1529, 1505, 1399 (NO_2), 1360, 1265 cm^{-1}; HRMS (EI$^+$) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$: 308.15248, found: 308.15284; Elem. Anal. calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found: C 73.62, H 6.63, N 8.97.



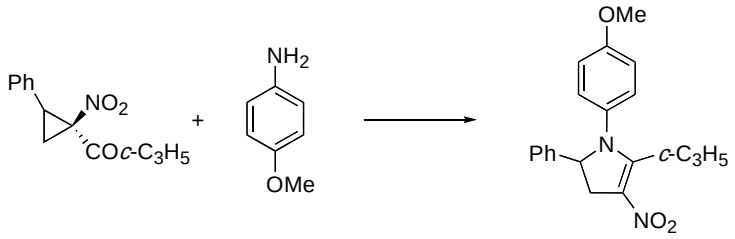
150f 293c

4-Nitro-1,2,5-triphenyl-2,3-dihydro-1*H*-pyrrole (293c). Yellow solid (96 mg, 91%): M.p. 185-187 ^{o}C; R_f 0.28 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.41 (m, 10H), 6.97-7.04 (m, 3H), 6.63-6.66 (m, 2H), 5.25 (dd, J = 11.8, 6.6 Hz, 1H), 3.98 (dd, J = 15.6, 11.8 Hz, 1H), 3.41 (dd, J = 15.6, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 141.2, 140.1, 130.4, 129.9, 129.4, 129.3, 129.0, 128.8, 128.3, 127.0, 126.7, 123.4, 69.0, 38.3; IR (solid) 1561, 1490, 1365, 1346 (NO_2), 1259 cm^{-1}; HRMS (EI$^+$) calcd for $C_{22}H_{18}N_2O_2$ $[M]^+$: 342.13683, found: 342.13666; Elem. Anal. calcd for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18; found: C 77.30, H 5.51, N 8.02.



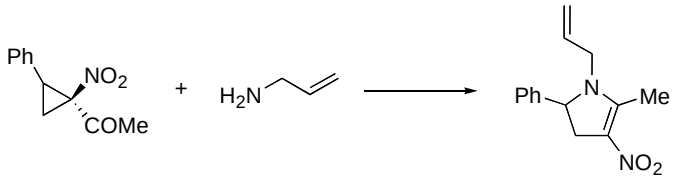
150j **293d**

5-Cyclopropyl-4-nitro-1,2-diphenyl-2,3-dihydro-1*H*-pyrrole (293d). Yellow oil (93 mg, 79%): R_f 0.38 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-7.36 (m, 8H), 6.92-6.98 (m, 2H), 5.03 (dd, *J* = 11.7, 6.2 Hz, 1H), 3.76 (dd, *J* = 15.5, 11.7 Hz, 1H), 3.20 (dd, *J* = 15.5, 6.2 Hz, 1H), 2.18-2.25 (m, 1H), 1.00-1.06 (m, 1H), 0.87-0.95 (m, 1H), 0.62-0.70; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 140.9, 140.1, 129.2, 129.1, 128.5, 127.4, 126.8, 125.8, 125.4, 68.9, 37.3, 11.5, 10.6, 9.8; IR (film) 1558, 1407, 1371, 1339 (NO_2), 1256 cm^{-1}; HRMS (EI$^+$) calcd for $C_{19}H_{18}N_2O_2$ $[M]^+$: 306.13683, found: 306.13666.



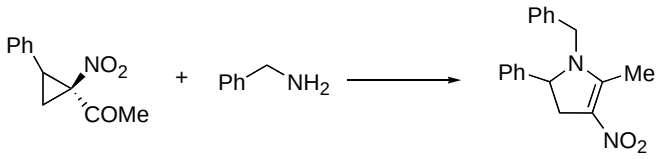
150j **293e**

5-Cyclopropyl-1-(4-methoxyphenyl)-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (293e). Yellow solid (209 mg, 97%): R_f 0.32 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.31 (m, 3H), 7.14-7.17 (m, 2H), 6.79-6.83 (m, 2H), 6.69-6.73 (m, 2H), 4.94 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.67-3.80 (m, 1H), 3.71 (s, 3H), 3.20 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.17-2.26 (m, 1H), 0.85-1.02 (m, 2H), 0.67-0.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 158.7, 140.7, 132.5, 129.0, 128.6, 127.6, 127.0, 124.4, 114.3, 69.4, 55.4, 37.0, 11.3, 10.1, 9.6; IR (solid) 1511, 1368, 1336 (NO_2), 1232, 1161 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{20}H_{20}N_2O_3$ $[M+H]^+$: 337.4 *m/z*, found: 337.2 *m/z*.



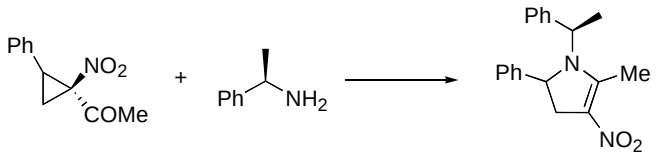
150d **293f**

1-Allyl-5-methyl-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (293f). Yellow oil (16 mg, 48%): R_f 0.05 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.42 (m, 3H), 7.23-7.26 (m, 2H), 5.57-5.64 (m, 1H), 5.26 (d, J = 9.7 Hz, 1H), 5.10 (d, J = 17.1 Hz, 1H), 4.82 (dd, J = 11.7, 7.2 Hz, 1H), 3.90-3.95 (m, 1H), 3.61-3.65 (m, 1H), 3.46-3.53 (m, 1H), 3.12-3.18 (m, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 139.7, 130.8, 129.5, 129.1, 127.3, 118.9, 65.5, 47.4, 36.7, 13.9; IR (film) 1547, 1382 (NO_2), 1249, 1164 cm^{-1}; HRMS (EI$^+$): $[M-2]^+$ $C_{14}H_{16}N_2O_2$: 242.10553, found: 242.10601.



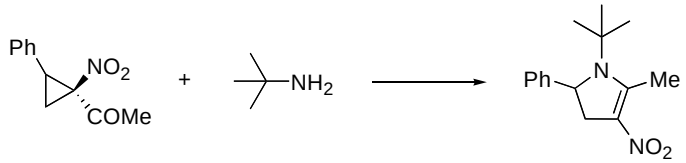
150d **293g**

1-Benzyl-5-methyl-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (293g). Yellow oil (39 mg, 35%): R_f 0.32 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.42 (m, 6H), 7.18-7.21 (m, 2H), 7.03-7.05 (m, 2H), 4.71 (dd, J = 11.8, 6.9 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 3.97 (d, J = 16.2 Hz, 1H), 3.58 (dd, J = 15.6, 11.8 Hz, 1H), 3.14 (dd, J = 15.6, 6.9 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 139.5, 134.5, 129.5, 129.4, 129.1, 128.5, 127.2, 65.0, 48.3, 36.5, 14.2; IR (film) 1549, 1379, 1345 (NO_2), 1241, 1164 cm^{-1}; HRMS (EI$^+$): $[M-2]^+$ $C_{18}H_{18}N_2O_2$: 292.12118, found: 292.12139.



150d **293h**

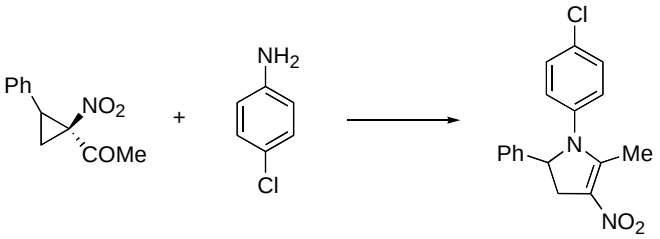
5-Methyl-4-nitro-2-phenyl-1-(1-*R*-phenyl-ethyl)-2,3-1*H*-pyrrole (293h). Yellow oil as a mixture of diastereomers (70 mg, 84%): **1st diastereomer.** R_f 0.29 (40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.42 (m, 6H), 7.17-6.97 (m, 4H), 4.97-5.02 (m, 1H), 4.59 (dd, *J* = 11.7, 5.4 Hz, 1H), 3.55 (dd, *J* = 15.5, 11.7 Hz, 1H), 3.04 (dd, *J* = 15.5, 5.3 Hz, 1H), 2.67 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 142.0, 138.8, 129.3, 129.2, 128.9, 128.6, 127.0, 126.9, 63.7, 55.6, 37.5, 19.0, 14.7; IR (film) 1549, 1375, 1350 (NO_2), 1258, 1167 cm^{-1}; HRMS (EI$^+$): $[M-2]^+$ $C_{19}H_{20}N_2O_2$: 306.13683, found: 306.13616; **2nd diastereomer.** R_f 0.24 (40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.39 (m, 10H), 4.92-4.97 (m, 1H), 4.71-4.73 (m, 1H), 3.68 (dd, *J* = 11.8, 3.7 Hz, 1H), 3.17 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.52 (s, 3H), 1.55 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 140.5, 138.8, 129.3, 129.2, 129.0, 128.8, 127.4, 126.3, 67.7, 56.1, 37.2, 19.0, 15.7; IR (film) (mix of diastereomers) 1542, 1374, 1347 (NO_2), 1248, 1151 cm^{-1}.



150d **293i**

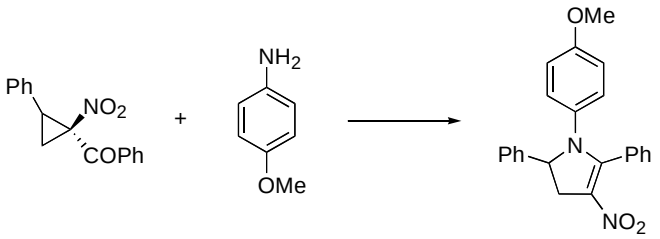
1-*tert*-Butyl-5-methyl-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (293i). Dark orange oil (78 mg, 47%): R_f 0.12 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.30 (m, 3H), 7.11-7.14 (m, 2H), 5.03-5.07 (m, 1H), 3.44-3.53 (m, 1H), 2.89 (s, 3H), 2.75-2.81 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 142.8, 129.3, 128.2, 125.2, 121.8, 64.9, 58.5, 37.4, 30.6, 17.6; IR (film) 1527, 1348 (NO_2),

1262, 1163, 999 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{15}H_{20}N_2O_2$ $[M+H]^+$: 261.3 *m/z*, found: 261.1 *m/z*.



150d **293j**

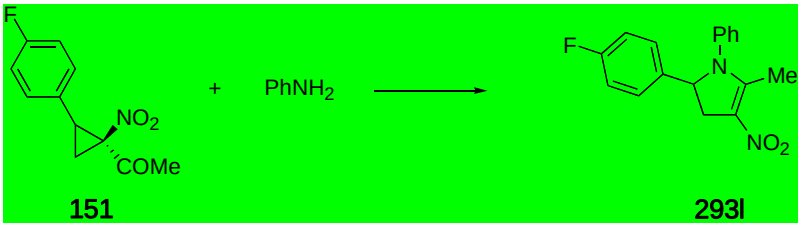
1-(4-Chlorophenyl)-5-methyl-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (293j). Yellow crystalline solid (81 mg, 95%): M.p. 153-154 ^oC; R_f 0.28 (30% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.33 (m, 7H), 6.85-6.90 (m, 2H), 5.13 (dd, *J* = 11.6, 7.3 Hz, 1H), 3.70-3.80 (m, 1H), 3.24-3.32 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 139.8, 136.9, 134.1, 130.0, 129.3, 129.0, 128.3, 127.3, 123.7, 69.3, 36.8, 15.6; IR (solid) 1552, 1497, 1346 (NO_2), 1243, 1166 cm^{-1}; HRMS (EI^+) calcd for $C_{17}H_{15}N_2O_2Cl$ $[M]^+$: 314.08221, found: 314.08180; Elem. Anal. calcd for $C_{17}H_{15}N_2O_2Cl$: C 64.87, H 4.80, N 8.90; found: C 65.01, H 4.77, N 8.81.



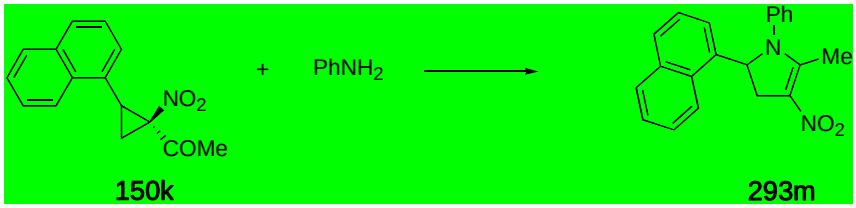
150f **293k**

1-(4-Methoxyphenyl)-4-nitro-2,5-diphenyl-2,3-dihydro-1*H*-pyrrole (293k). Yellow crystalline solid (96 mg, 96%): M.p. 60-78 ^oC; R_f 0.41 (40% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 10H), 6.56-6.61 (m, 2H), 6.48-6.53 (m, 2H), 5.17 (dd, *J* = 11.9, 7.0 Hz, 1H), 3.95 (dd, *J* = 15.6, 11.9 Hz, 1H), 3.62 (s, 3H), 3.43 (dd, *J* = 15.6, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 158.1, 141.0, 132.6, 130.1, 129.7, 129.4, 129.3, 128.7, 128.2, 127.9, 127.2, 122.6, 114.1, 69.4,

55.3, 37.9; IR (solid) 1511, 1343 (NO_2), 1236, 1125 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{23}H_{20}N_2O_3$ $[M+H]^+$: 373.4 *m/z*, found: 373.1 *m/z*.

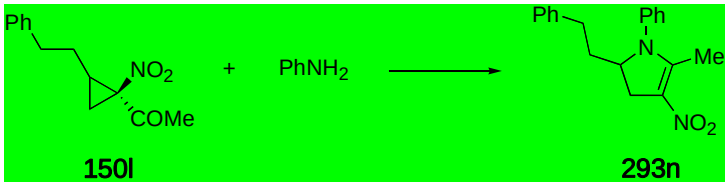


5-Methyl-4-nitro-1-phenyl-2-(4-fluorophenyl)-2,3-dihydro-1*H*-pyrrole (293l). Yellow glace (75 mg, 99%): M.p. 43-45 ^oC; R_f 0.09 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.33 (m, 5H), 6.90-7.01 (m, 4H), 5.17 (dd, *J* = 11.7, 7.2 Hz, 1H), 3.76 (dd, *J* = 15.5, 11.7 Hz, 1H), 3.27 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, *J* = 248.0 Hz, 1C), 138.1, 135.8, 129.8, 129.2, 129.1, 128.6, 127.1, 116.3, 116.1, 76.4, 68.9, 36.8, 15.8; IR (film) 1551, 1509, 1356 (NO_2), 1251, 1222, 1152 cm^{-1}; HRMS (EI^+) calcd for $C_{17}H_{15}N_2O_2F$ $[M]^+$: 298.11176, found: 298.11112.

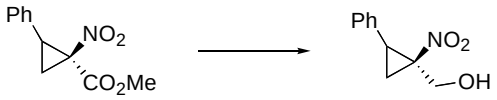


5-Methyl-2-naphthalen-1-yl-4-nitro-1-phenyl-2,3-dihydro-1*H*-pyrrole (293m). Yellow crystalline solid (49 mg, 84%): M.p. 175 ^oC; R_f 0.13 (50% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.85 (m, 2H), 7.74-7.76 (m, 1H), 7.58 (s, 1H), 7.46-7.51 (m, 2H), 7.41-7.44 (m, 1H), 7.18-7.28 (m, 3H), 6.92-6.95 (m, 2H), 5.34 (dd, *J* = 11.7, 7.0 Hz, 1H), 3.84 (dd, *J* = 15.6, 11.7 Hz, 1H), 3.38 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 138.3, 137.2, 133.4, 133.2, 129.8, 129.6, 128.4, 128.1, 128.0, 127.0, 126.8, 126.8, 124.1, 69.6, 36.8, 15.8; IR (solid) 1548, 1393, 1346 (NO_2), 1242, 1019 cm^{-1}; HRMS (EI^+) calcd for

$C_{21}H_{18}N_2O_2$ $[M]^+$: 330.13683, found: 330.13655; Elem. Anal. calcd for $C_{21}H_{18}N_2O_2$: C 76.34, H 5.49, N 8.48; found: C 76.33, H 5.56, N 8.48.

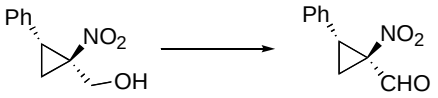


5-Methyl-4-nitro-2-phenethyl-1-phenyl-2,3-dihydro-1*H*-pyrrole (293n). Yellow oil (11 mg, 18%): R_f 0.08 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.49 (m, 3H), 7.18-7.27 (m, 3H), 7.04-7.11 (m, 4H), 4.28-4.30 (m, 1H), 3.47 (dd, J = 14.5, 11.1 Hz, 1H), 3.10 (d, J = 15.1, 7.2 Hz, 1H), 2.67-2.70 (m, 1H), 2.53-2.57 (m, 1H), 2.37 (s, 3H), 1.88-1.92 (m, 1H), 1.76-1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 140.5, 137.7, 130.1, 128.8, 128.4, 127.1, 126.5, 123.7, 64.6, 35.4, 32.8, 30.9, 15.6; IR (film) 1552, 1357 (NO_2), 1258, 1168 cm^{-1}; HRMS (EI$^+$) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$: 308.15248, found: 308.15229.



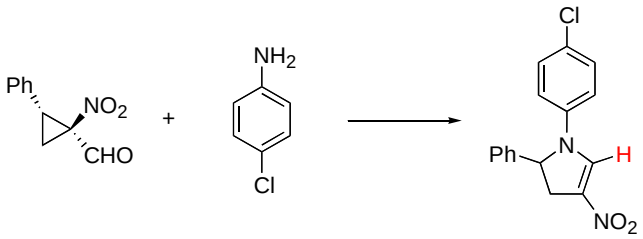
(1-Nitro-2-phenyl-cyclopropyl)-methanol (294). Prepared according to O'Bannon and Dailey[81d] (43 mg, 87%): ***E*-(1-Nitro-2-phenyl-cyclopropyl)-methanol (294).** White solid: M.p. 50-52 °C; R_f 0.21 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.39 (m, 5H), 3.98 (d, J = 13.9 Hz, 1H), 3.64 (d, J = 13.9 Hz, 1H), 3.56 (t, J = 9.3 Hz, 1H), 2.31 (dd, J = 10.3, 6.2 Hz, 1H), 1.85 (dd, J = 8.4, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 129.03, 128.98, 128.4, 70.6, 60.8, 34.8, 20.6; IR (film) 1537, 1351 (NO_2), 1043 cm^{-1}; ***Z*-(1-Nitro-2-phenyl-cyclopropyl)-methanol (294).** White solid: M.p. 38-39 °C; R_f 0.11 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 5H), 4.36 (d, J = 13.3 Hz, 1H), 3.96 (d, J = 13.4 Hz, 1H), 2.99 (t, J = 9.3 Hz, 1H), 2.64 (dd, J = 8.9, 6.7 Hz, 1H), 2.05 (s(*br*), 1H), 1.71

(dd, J = 9.5, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 129.3, 128.7, 128.3, 76.5, 72.7, 65.2, 33.5, 19.2; IR (film) 1529, 1350 (NO_2), 1036 cm^{-1}.



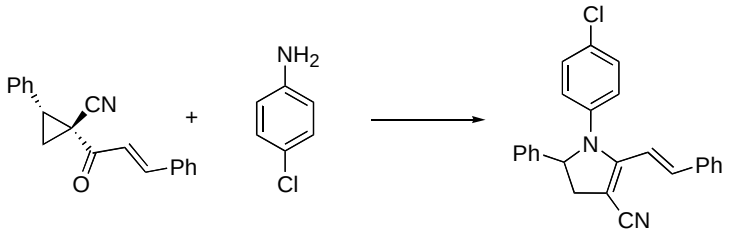
294 **295**

***E*-1-Nitro-2-phenylcyclopropanecarbaldehyde (295).** The oxidation was performed in refluxing EtOAc using IBX (3.0 equiv) as an oxidant according to More and Finney. White crystalline solid (27 mg, 54%): M.p. 80-81 ^{o}C; R_f 0.53 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.22-7.36 (m, 5H), 3.92 (t, J = 10.3 Hz, 1H), 2.60-2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 130.5, 129.6, 128.9, 128.7, 44.3, 22.9; IR (solid) 1713 (C=O), 1535, 1367, 1344 (NO_2) cm^{-1}.



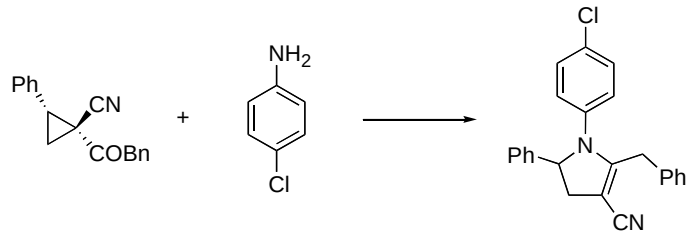
295 **296**

1-(4-Chlorophenyl)-4-nitro-2-phenyl-2,3-dihydro-1*H*-pyrrole (296). Yellow oil (33 mg, 79%): R_f 0.41 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.33-7.39 (m, 3H), 7.20-7.32 (m, 4H), 6.88-6.90 (m, 2H), 5.56 (dd, J = 11.9, 5.7 Hz, 1H), 3.80-3.87 (m, 1H), 3.12-3.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.8, 137.9, 130.0, 129.8, 128.9, 125.7, 118.2, 67.1, 37.6; IR (film) 1571, 1367 (NO_2), 1276, 1212 cm^{-1}.



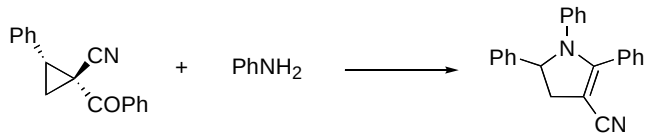
237d **297a**

1-(4-Chlorophenyl)-5-phenyl-2-styryl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (297a). Yellow solid (66 mg, 82%): M.p. 72-73 ^{o}C; R_f 0.37 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.43 (m, 10H), 7.13-7.18 (m, 2H), 6.80-6.85 (m, 2H), 6.63 (d, *J* = 16.5 Hz, 1H), 4.99 (dd, *J* = 11.1, 7.0 Hz, 1H), 3.52 (dd, *J* = 15.5, 11.1 Hz, 1H), 2.81 (dd, *J* = 15.4, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 142.4, 141.6, 138.7, 135.5, 130.5, 129.7, 129.4, 129.3, 129.1, 128.4, 127.5, 126.6, 125.0, 119.6, 116.0, 81.1, 70.6, 39.4; IR (solid) 2184 (CN), 1490, 1386, 827, 751, 692 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{25}H_{19}N_2Cl$ $[M+H]^+$: 383.9 *m/z*, found: 383.1 *m/z*.



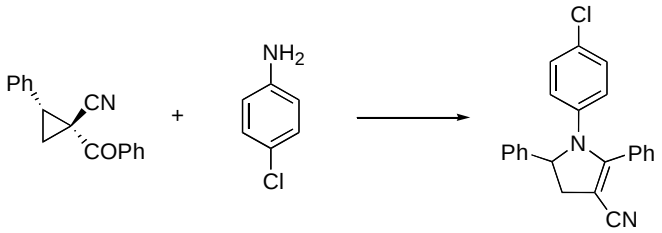
237b **297b**

2-Benzyl-1-(4-chlorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (297b). Pale yellow oil (121 mg, 91%): R_f 0.40 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.27 (m, 6H), 7.08-7.15 (m, 4H), 6.97-7.00 (m, 2H), 6.63-6.68 (m, 2H), 4.98 (dd, *J* = 11.4, 9.3 Hz, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.63 (d, *J* = 15.0 Hz, 1H), 3.39 (dd, *J* = 12.3, 11.4 Hz, 1H), 2.85 (dd, *J* = 14.6, 10.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 141.5, 139.7, 135.9, 132.4, 129.4, 129.0, 128.7, 128.6, 128.3, 128.1, 127.2, 127.1, 119.8, 79.7, 70.8, 38.4, 33.3; IR (film) 2187 (CN), 1593, 1493, 1422, 1188, 824, 724, 696 cm^{-1}.



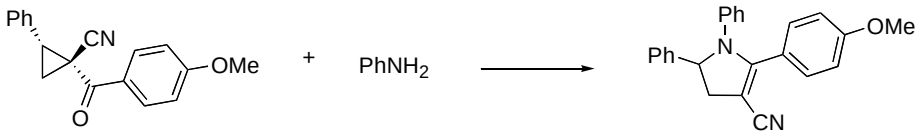
237a **297c**

1,2,5-Triphenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (297c). Pale yellow solid (127 mg, 97%): M.p. 126-127 °C; R_f 0.68 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.62 (m, 2H), 7.34-7.46 (m, 8H), 7.01-7.06 (m, 2H), 6.91-6.96 (m, 1H), 6.62-6.65 (m, 2H), 5.12 (d, *J* = 11.3, 5.6 Hz, 1H), 3.67 (dd, *J* = 15.0, 11.3 Hz, 1H), 2.84 (dd, *J* = 15.0, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 143.4, 143.2, 130.3, 129.9, 129.3, 128.8, 128.7, 128.6, 128.2, 126.1, 124.2, 123.1, 119.7, 81.2, 70.2, 39.6; IR (solid) 2177 (CN), 1661, 1581, 1560, 1493, 1417, 1271 cm^{-1}.



237a **297d**

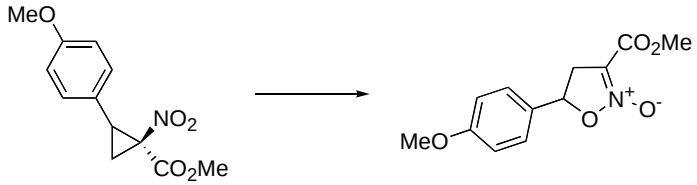
1-(4-Chlorophenyl)-2,5-diphenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (297d). White powder (138 mg, 99%): M.p. 178-179 °C; R_f 0.46 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.57 (m, 2H), 7.34-7.47 (m, 8H), 6.92-7.00 (m, 2H), 6.47-6.55 (m, 2H), 5.08 (d, *J* = 11.3, 5.8 Hz, 1H), 3.65 (dd, *J* = 15.1, 11.3 Hz, 1H), 2.83 (dd, *J* = 15.1, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 143.0, 141.8, 130.5, 129.6, 129.5, 129.4, 129.0, 128.8, 128.6, 128.3, 126.1, 124.3, 119.4, 82.1, 70.2, 39.6; IR (solid) 2177 (CN), 1563, 1492, 1423, 1091 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{23}H_{17}N_2Cl$ $[M+H]^+$: 357.9 *m/z*, found: 357.2 *m/z*.



237c **297e**

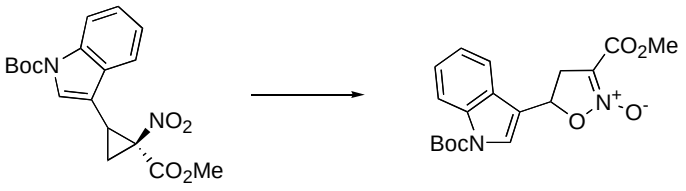
2-(4-Methoxy-phenyl)-1,5-diphenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (297e). White crystalline solid (156 mg, 77%): M.p. 97-98 ^{o}C; R_f 0.32 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 9.0 Hz, 2H), 7.33-7.45 (m, 5H), 7.00-7.06 (m, 2H), 6.85-6.95 (m, 3H), 6.60 (d, J = 8.5 Hz, 2H), 5.06 (dd, J = 11.1, 5.3 Hz, 1H), 3.82 (s, 3H), 3.63 (dd, J = 14.9, 11.2 Hz, 1H), 2.78 (dd, J = 14.9, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.0, 143.7, 130.3, 129.3, 128.8, 128.2, 126.2, 124.1, 123.2, 122.2, 120.2, 114.3, 80.0, 70.3, 55.5, 39.5; IR (solid) 2188 (CN), 1593, 1510, 1497, 1389, 1254, 1177, 1029 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{24}H_{20}N_2O$ $[M+H]^+$: 353.4 *m/z*, found: 353.2 *m/z*.

Experimental: Chapter 8



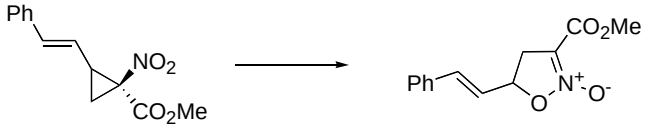
197b **318a**

5-(4-Methoxyphenyl)-2-oxy-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester (318a). White platelets (146 mg, 91%): M.p. 117-118 ^{o}C; R_f 0.19 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.66 (t, J = 8.7 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.71 (dd, J = 16.9, 9.5 Hz, 1H), 3.42 (dd, J = 16.9, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.6, 129.3, 127.7, 114.5, 108.3, 77.3, 55.5, 52.8, 38.2; IR (solid) 1736 (C=O), 1611, 1512, 1233 (NO) cm^{-1}; HRMS (EI^+) calcd for $C_{12}H_{13}NO_5$ $[M]^+$: 251.07937, found: 251.08022; Elem. Anal. calcd for $C_{12}H_{13}NO_5$: C 57.37, H 5.22, N 5.58; found: C 57.27, H 5.19, N 5.53.



316a **318b**

3-(3-Methoxycarbonyl-2-oxy-4,5-dihydro-isoxazol-5-yl)-indole-1-carboxylic acid *tert*-butyl ester (318b). Viscous pale yellow oil (176 mg, 93%): R_f 0.47 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.51 (d, J = 7.5 Hz, 1H) 7.35 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 5.95 (t, J = 9.0 Hz, 1H), 3.85 (s, 3H), 3.72-3.82 (m, 1H), 3.56-3.64 (m, 1H), 1.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 149.3, 136.0, 127.4, 125.2, 124.0, 123.1, 119.2, 116.8, 115.7, 108.2, 84.5, 71.7, 52.7, 36.0, 28.1; IR (film) 1732 (C=O), 1614 (NO), 1451, 1370, 1238, 1149, 1091 cm^{-1}.

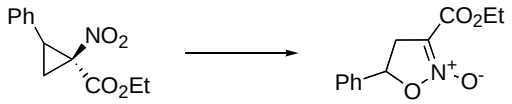


316b **318c**

2-Oxy-5-styryl-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester (318c). White crystalline solid (94 mg, 54%): M.p. 81 ^{o}C; R_f 0.31 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.41 (m, 5H), 6.73 (d, J = 15.8 Hz, 1H), 6.23 (dd, J = 15.8, 7.3 Hz, 1H), 5.28-5.35 (m, 1H), 3.85 (s, 3H), 3.59 (dd, J = 16.8, 9.4 Hz, 1H), 3.27 (dd, J = 16.8, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 135.3, 135.2, 128.8, 127.0, 124.0, 108.1, 76.8, 52.7, 36.5; IR (solid) 1736 (C=O), 1615 (NO), 1440, 1243 cm^{-1}.

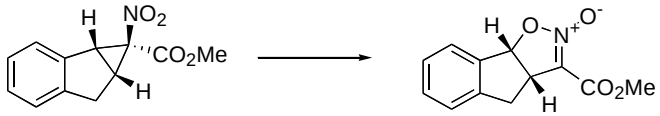
General procedure for the NaI catalyzed rearrangement of cyclopropanes to isoxazoline *N*-oxides. To an oven-dried 25 mL round-bottomed flask was added the desired cyclopropane and NaI (10 mol%). Acetone (0.5M) was added and the flask was fitted with a reflux condenser and heated to 60 ^{o}C for 2 h. The reaction was

allowed to cool, the solvent removed under reduced pressure and the resulting residue purified by column chromatography on silica gel using a gradient of 5-30% EtOAc/Hexane as the eluent.



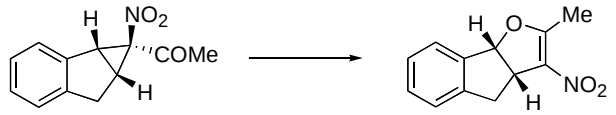
147 **318d**

2-Oxy-5-phenyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (318d). Clear colorless oil (78 mg, 94%): R_f 0.21 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s(*br*), 5H), 5.70 (t, *J* = 8.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.78 (dd, *J* = 16.9, 9.7 Hz, 1H), 3.40 (dd, *J* = 16.9, 7.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 137.9, 129.2, 129.1, 125.8, 107.9, 76.8, 61.9, 38.5, 14.2; IR (film) 1732 (C=O), 1615 (NO), 1240, 1176 cm^{-1}.



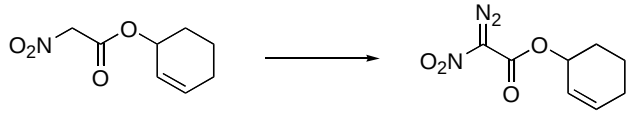
162 **318e**

2-Oxy-4,8b-dihydro-3a*H*-indeno[2,1-*d*]isoxazole-3-carboxylic acid methyl ester (318e). White crystalline solid (99 mg, 87%): M.p. 119-120 ^{o}C; R_f 0.12 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.44 (m, 4H), 6.04 (d, *J* = 9.0 Hz, 1H), 4.44-4.50 (m, 1H), 3.85 (s, 3H), 3.29-3.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 141.5, 138.1, 130.4, 127.8, 126.2, 125.3, 111.5, 82.8, 52.6, 46.3, 37.0; IR (solid) 1730 (C=O), 1598 (NO), 1436, 1236, 737 cm^{-1}.



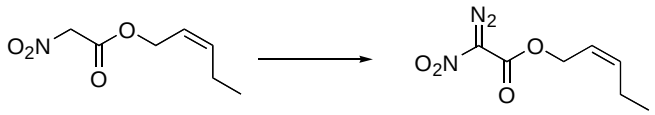
320 321

2-Methyl-3-nitro-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (321). Pale yellow crystalline solid (34 mg, 44%): R_f 0.66 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.50 (m, 1H), 7.37-7.41 (m, 1H), 7.26-7.34 (m, 2H), 6.18 (d, J = 9.1 Hz, 1H), 4.32-4.37 (m, 1H), 3.41-3.47 (m, 1H), 3.29-3.34 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 142.9, 138.8, 131.1, 130.6, 127.7, 126.0, 125.8, 91.4, 43.8, 37.7, 16.0; IR (solid) 1615, 1452, 1357 (NO_2), 1227 cm^{-1}.



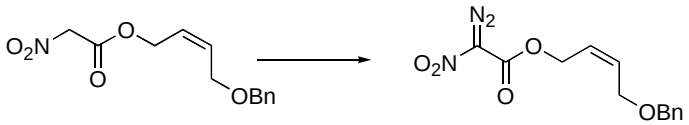
322c

Cyclohex-2-enyl nitroacetate. Clear colorless oil (454 mg, 81%): R_f 0.59 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01-6.05 (m, 1H), 5.70-5.75 (m, 1H), 5.39-5.40 (m, 1H), 5.15 (s, 2H), 2.02-2.09 (m, 2H), 1.71-1.90 (m, 2H), 1.65-1.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 134.7, 124.0, 76.7, 71.7, 28.0, 24.9, 18.5; IR (film) 1752 (C=O), 1574, 1343 (NO_2), 1219, 1033 cm^{-1}; **Cyclohex-2-enyl-nitro-diazoacetate (322c).** Clear yellow oil (367 mg, 96%): R_f 0.56 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01-6.08 (m, 1H), 5.72-5.78 (m, 1H), 5.45-5.50 (m, 1H), 2.01-2.18 (m, 2H), 1.77-2.00 (m, 2H), 1.60-1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 134.9, 124.2, 71.6, 28.3, 24.9, 18.6; IR (film) 2149 (CN_2), 1742 (C=O), 1522, 1318 (NO_2), 1219, 1112 cm^{-1}.



322e

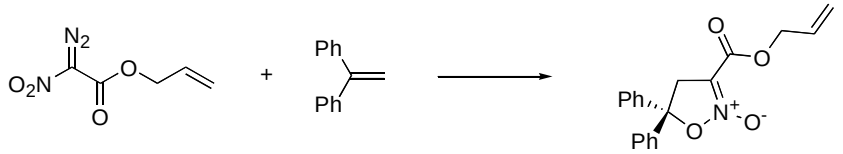
(*Z*)-Pent-2-enyl nitroacetate. Clear colorless oil (408 mg, 79%): R_f 0.58 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69-5.76 (m, 1H), 5.46-5.52 (m, 1H), 5.17 (s, 2H), 4.79 (dd, *J* = 7.1, 0.5 Hz, 2H), 2.09-2.17 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 139.1, 121.0, 76.4, 62.8, 21.0, 14.1; IR (film) 1754 (C=O), 1567, 1363, 1333 (NO_2), 1204 cm^{-1}; **(*Z*)-Pent-2-enyl nitro diazoacetate (322e).** Clear yellow oil (325 mg, 96%): R_f 0.58 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63-5.72 (m, 1H), 5.40-5.50 (m, 1H), 4.80 (dd, *J* = 7.1, 0.6 Hz, 2H), 2.04-2.15 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 139.0, 121.0, 62.2, 20.9, 13.9; IR (film) 2149 (CN_2), 1751 (C=O), 1524, 1324 (NO_2), 1218, 1108 cm^{-1}.



322g

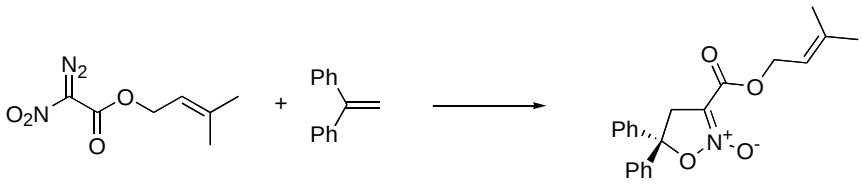
4-Benzyloxy-but-2-enyl nitroacetate. Clear colorless oil (780 mg, 70%): R_f 0.21 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.42 (m, 5H), 5.86-5.94 (m, 1H), 5.67-5.74 (m, 1H), 5.14 (s, 2H), 4.83 (d, *J* = 6.9 Hz, 2H), 4.53 (s, 2H), 4.14 (d, *J* = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 137.9, 132.6, 128.6, 127.9, 124.8, 76.2, 72.6, 65.7, 62.7; IR (film) 1757 (C=O), 1567, 1365 (NO_2), 1202 cm^{-1}; **4-Benzyloxy-but-2-enyl nitro diazoacetate (322g).** Yellow oil (221 mg, 88%): R_f 0.39 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.42 (m, 5H), 5.87-5.94 (m, 1H), 5.68-5.75 (m, 1H), 4.89 (d, *J* = 5.7 Hz, 2H), 4.53 (s, 2H), 4.15 (d, *J* = 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 137.9, 132.7, 128.5, 127.82, 127.80, 124.9, 72.7, 72.6, 65.7, 62.4; IR (film) 2149 (CN_2), 1749 (C=O), 1521, 1322 (NO_2), 1107 cm^{-1}.

General procedure for the preparation of isoxazoline *N*-oxides 324 *via* cyclopropanation of 1,1'-diphenylethene. In a 25 mL round-bottomed flask was added $[Rh(Oct)_2]_2$ (0.5 mol%) followed by 1,1'-diphenylethene (3.0 equiv). The desired diazo compound **322** was then added slowly dropwise over 30 min as a solution in anhydrous CH_2Cl_2 (1.0M). The reaction mixture was then allowed to stir an additional 4 h at room temperature. The solvent was then removed under reduced pressure (rotary evaporator) and the crude residue was chromatographed on silica gel using 3-10% EtOAc/Hexane as an eluent. Chromatography induced the cyclopropane rearrangement to the desired isoxazoline *N*-oxide **324**. In several cases, the corresponding cyclopropanes **323** could also be isolated. These compounds can also be submitted to the reaction conditions necessary for the 1,3-dipolar cycloaddition.



121c **324a**

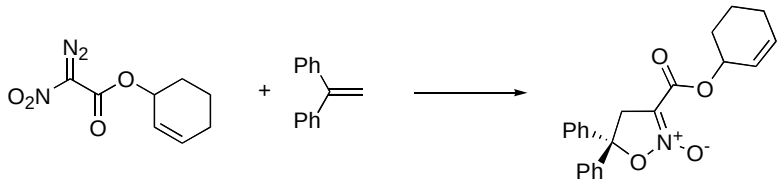
2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid allyl ester (324a). Clear colorless oil (182 mg, 84%): R_f 0.43 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.46 (m, 10H), 5.90-6.03 (m, 1H), 5.41 (d, J = 17.2 Hz, 1H), 5.31 (d, J = 10.4 Hz, 1H), 4.74 (dd, J = 5.8, 1.2 Hz, 2H), 4.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 141.5, 131.2, 128.9, 128.7, 125.8, 119.4, 108.8, 86.1, 66.5, 43.6; IR (film) 1735, 1699 (C=O), 1621 (NO), 1449, 1235 cm^{-1}.



322b **324b**

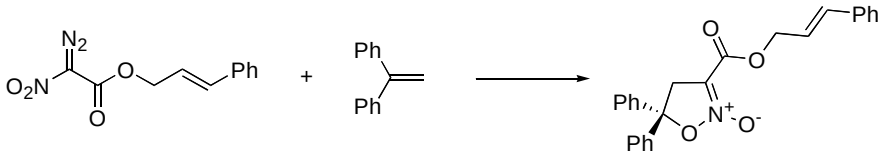
2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid 3-methyl-but-2-enyl ester (324b). Pale yellow oil (268 mg, 87%): R_f 0.58 (20% EtOAc/Hexane); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.25-7.50 (m, 10H), 5.27-5.39 (m, 1H), 4.73 (d, J = 7.3 Hz, 2H), 4.03 (s, 2H), 1.76 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 141.5, 140.3, 128.8, 128.5, 125.7, 117.8, 108.9, 85.8, 62.8, 43.7, 25.9, 18.2; IR (film) 1731, 1698 (C=O), 1620 (NO), 1232, 1167 cm^{-1}; HRMS (EI^+) $C_{21}H_{21}NO_4$ $[M]^+$: 351.14706, found: 351.14806.



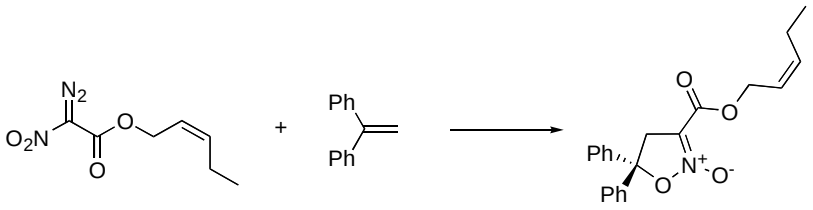
322c **324c**

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid cyclohex-2-enyl ester (324c). Clear colorless oil (206 mg, 75%): R_f 0.42 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.51 (m, 10H), 5.97-6.02 (m, 1H), 5.72-5.76 (m, 1H), 5.39-5.40 (m, 1H), 4.03 (s, 2H), 1.60-2.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 141.7, 133.9, 128.9, 128.6, 125.9, 125.0, 109.0, 85.8, 70.1, 43.9, 28.3, 25.0, 18.9; IR (film) 1728, 1694 (C=O), 1622 (NO), 1234, 910 cm^{-1}.



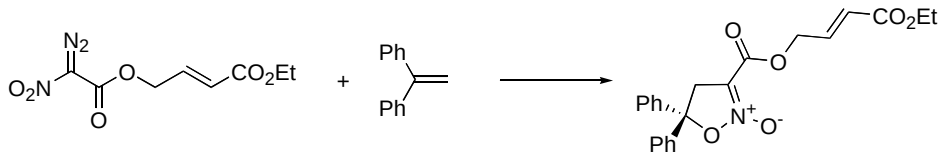
121e **324d**

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid 3-phenyl-allyl ester (324d). Pale yellow oil (302 mg, 96%): R_f 0.33 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.54 (m, 15H), 6.73 (d, J = 15.9 Hz, 1H), 6.33 (dt, J = 15.9, 6.6 Hz, 1H), 4.90 (d, J = 6.6 Hz, 2H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 141.4, 135.9, 135.5, 128.8, 128.7, 128.6, 128.4, 126.8, 125.7, 122.1, 108.8, 86.0, 66.4, 43.6; IR (film) 1732, 1698 (C=O), 1617 (NO), 1448, 1233, 1166 cm^{-1}.



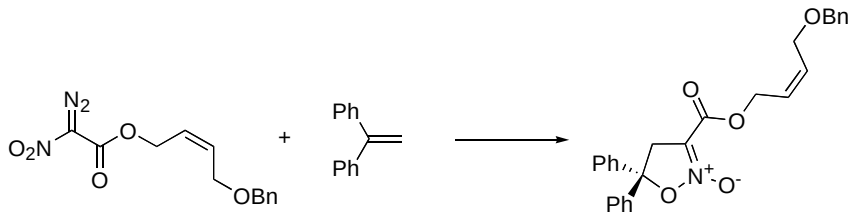
322e **324e**

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid pent-2-enyl ester (324e). Clear colorless oil (229 mg, 94%): R_f 0.64 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.46 (m, 10H), 5.65-5.73 (m, 1H), 5.47-5.57 (m, 1H), 4.79 (d, J = 6.9 Hz, 2H), 4.04 (s, 2H), 2.09-2.19 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 141.6, 138.2, 128.9, 128.6, 125.8, 121.9, 108.8, 86.0, 61.7, 43.7, 21.1, 14.2; IR (film) 1736, 1699 (C=O), 1626 (NO), 1450, 1236, 1170 cm^{-1}.



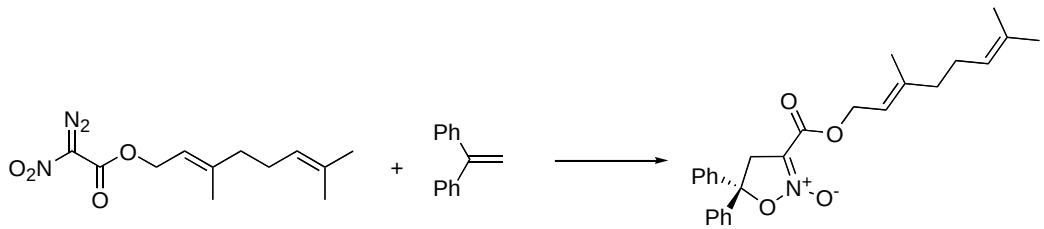
121j **324f**

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid 3-ethoxy carbonyl-allyl ester (324f). Pale yellow solid (281 mg, 85%): M.p. 115-117 ^{o}C; R_f 0.37 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.45 (m, 10H), 6.93 (dt, J = 15.7, 4.6 Hz, 1H), 6.09 (dt, J = 15.7, 1.8 Hz, 1H), 4.86 (dd, J = 4.6, 1.8 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 158.3, 141.3, 139.8, 128.9, 128.7, 125.8, 123.2, 108.5, 86.2, 63.7, 60.8, 43.4, 14.3; IR (solid) 1738, 1714 (C=O), 1620 (NO), 1268, 1233, 1166 cm^{-1}.



322g 324g

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid 4-benzyloxy-but-2-enyl ester (324g). Pale yellow oil (116 mg, 69%): R_f 0.27 (20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.52 (m, 15H), 5.86-5.91 (m, 1H), 5.71-5.77 (m, 1H), 4.81 (d, J = 6.7 Hz, 2H), 4.54 (s, 2H), 4.16 (d, J = 4.9 Hz, 2H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 141.4, 138.0, 132.0, 128.9, 128.63, 128.56, 127.91, 127.87, 125.8, 125.7, 108.7, 86.0, 72.6, 65.8, 61.6, 43.6; IR (film) 1734, 1699 (C=O), 1622 (NO), 1449, 1235 cm^{-1}.

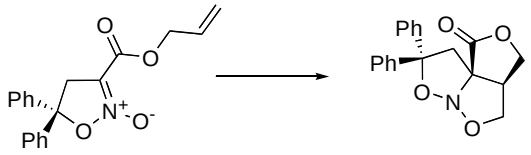


322h 324h

2-Oxy-5,5-diphenyl-4,5-dihydro-isoxazole-3-carboxylic acid 3,7-dimethyl-octa-2,6-dienyl ester (324h). White solid (127 mg, 84%): M.p. 41-43 ^{o}C; R_f 0.40 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.47 (m, 10H), 5.35-5.40 (m, 1H), 5.05-5.10 (m, 1H), 4.76 (d, J = 7.2 Hz, 2H), 4.04 (s, 2H), 2.02-2.12 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 143.5, 141.6, 132.0, 128.9, 128.6, 125.8, 123.8, 117.6, 108.9, 85.9, 62.9, 43.8, 39.7, 26.3, 25.8, 17.8, 16.7; IR (solid) 1734, 1698 (C=O), 1625 (NO), 1449, 1235, 1168 cm^{-1}.

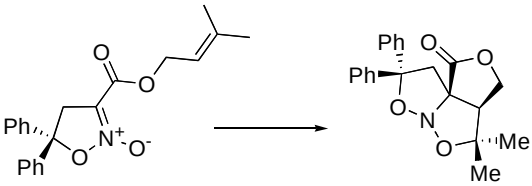
General procedure for the preparation of nitrosoacetals 325 *via* a 1,3-dipolar cycloaddition reaction. In a 50 mL round-bottomed flask was added the desired isoxazoline *N*-oxide **324** followed by anhydrous CH_3CN (0.1-0.5M) under an argon

atmosphere. The flask was fitted with a reflux condenser and heated to 80 °C for 24 h. After cooling the reaction mixture, the solvent was removed under reduced pressure (vacuum line) and the crude residue was chromatographed on silica gel. 20-100% EtOAc/Hexane was used as the eluent affording the desired nitrosoacetals **325**.



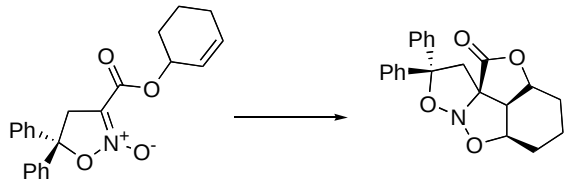
324a **325a**

7,7-Diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalen-1-one (325a). White fibrous solid (84 mg, 66%): M.p. 163-164 °C; R_f 0.60 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.49 (m, 10H), 4.48 (t, J = 9.3 Hz, 1H), 4.01-4.09 (m, 3H), 3.57 (d, J = 13.6 Hz, 1H), 3.43 (d, J = 13.6 Hz, 1H), 2.98-3.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 145.0, 142.9, 128.8, 128.5, 128.1, 127.7, 126.13, 126.06, 89.3, 84.0, 76.8, 71.0, 47.6, 46.5; IR (solid) 1768 (C=O), 1392, 1222 cm^{-1}; HRMS (MAB) calcd for $C_{19}H_{17}NO_4$ $[M]^+$: 323.11576, found: 323.11538.



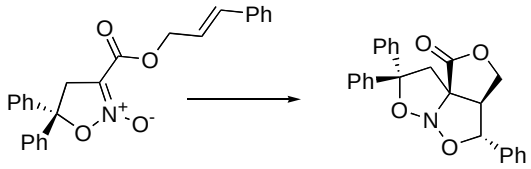
324b **325b**

4,4-Dimethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalen-1-one (325b). White crystalline solid (79 mg, 80%): M.p. 181-183 °C; R_f 0.29 (40% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.54 (m, 10H), 4.26-4.36 (m, 2H), 3.50 (d, J = 13.1 Hz, 1H), 3.29 (d, J = 13.1 Hz, 1H), 2.87-2.89 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 145.1, 143.6, 128.5, 128.4, 127.7, 127.6, 126.3, 126.0, 90.2, 88.8, 85.3, 66.5, 55.2, 47.5, 29.1, 23.2; IR (solid) 1771 (C=O), 1446, 1046, 976 cm^{-1}.



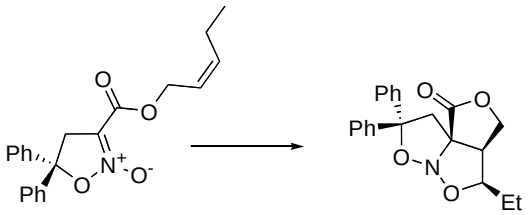
324c **325c**

2,2-Diphenyloctahydro[1]benzofuro[3',4':3,4,5]isoxazolo[2,3-*b*]isoxazol-4-one (325c). White solid (100 mg, 57%): M.p. 219-220 ^{o}C; R_f 0.59 (60% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.49 (m, 10H), 4.73-4.75 (m, 1H), 4.60-4.63 (m, 1H), 3.54 (s, 2H), 2.58 (t, J = 7.5 Hz, 1H), 2.05-2.24 (m, 2H), 1.24-1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 146.1, 143.4, 143.1, 128.9, 128.8, 128.53, 128.50, 127.9, 127.5, 125.9, 125.8, 125.7, 87.6, 87.3, 80.5, 74.0, 47.3, 43.9, 27.6, 24.8, 12.4; IR (solid) 1776 (C=O), 1451, 1057, 1033 cm^{-1}; HRMS (MAB) calcd for $C_{22}H_{21}NO_4$ $[M]^+$: 363.14706, found: 363.14671.



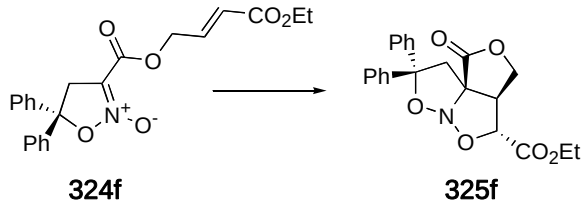
324d **325d**

4,7,7-Triphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalene-1-one (325d). White crystalline solid (94 mg, 70%): M.p. 227-228 ^{o}C; R_f 0.23 (CH_2Cl_2); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.31-8.35 (m, 2H), 8.10-8.16 (m, 3H), 8.03-8.07 (m, 6H), 7.86-8.02 (m, 2H), 7.21-7.24 (m, 2H), 5.34 (d, J = 8.4 Hz, 1H), 5.08-5.14 (m, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.34 (d, J = 13.3 Hz, 1H), 3.88 (d, J = 13.3 Hz, 1H), 3.80-3.86 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 175.1, 144.5, 143.8, 135.8, 129.4, 129.1, 129.0, 128.3, 128.2, 127.2, 126.6, 96.9, 85.6, 84.7, 67.9, 55.4, 47.3; IR (solid) 1785 (C=O), 1387, 1186, 1040 cm^{-1}.



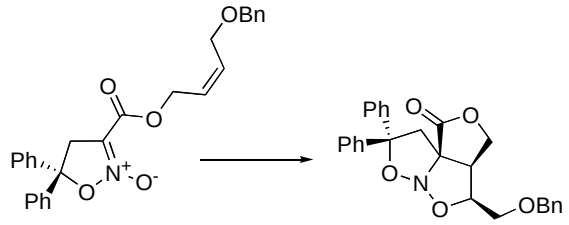
324e **325e**

4-Ethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalene-1-one (325e). White solid (126 mg, 80%): M.p. 147-148 ^{o}C; R_f 0.20 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.51 (m, 10H), 4.12-4.31 (m, 3H), 3.61 (d, J = 13.4 Hz, 1H), 3.30 (d, J = 13.4 Hz, 1H), 2.95-3.00 (m, 1H), 1.65-1.76 (m, 1H), 1.44-1.57 (m, 1H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 144.8, 143.2, 128.6, 128.3, 127.9, 127.5, 126.13, 126.10, 89.4, 86.0, 84.0, 64.9, 49.0, 47.7, 20.9, 11.1; IR (solid) 1779 (C=O), 1449, 1228, 1028, 910 cm^{-1}; HRMS (MAB) calcd for $C_{21}H_{21}NO_4$ $[M]^+$: 351.14706, found: 351.14830; Elem. Anal. calcd for $C_{21}H_{21}NO_4$: C 71.78, H 6.02, N 3.99; found: C 71.85, H 6.18, N 3.88.



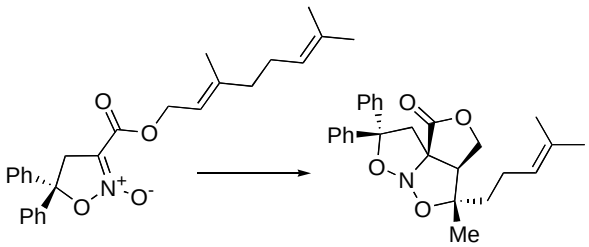
324f **325f**

1-Oxo-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalene-4-carboxylic acid ethyl ester (325f). White solid (113 mg, 93%): M.p. 164-165 ^{o}C; R_f 0.12 (1.0% EtOAc/CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57 (d, J = 7.4 Hz, 2H), 7.26-7.39 (m, 8H), 4.92 (d, J = 1.7 Hz, 1H), 4.61 (t, J = 9.2 Hz, 1H), 4.21-4.26 (m, 1H), 3.94-4.13 (m, 2H), 3.85-3.89 (m, 1H), 3.60 (d, J = 13.1 Hz, 1H), 3.45 (d, J = 13.1 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 172.8, 168.8, 145.4, 143.5, 128.84, 128.75, 128.1, 127.8, 126.0, 125.8, 89.4, 87.6, 84.9, 70.9, 62.6, 49.0, 47.5, 14.2; IR (solid) 1773, 1738 (C=O), 1448, 1391, 1218 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{22}H_{21}NO_6$ $[M+1]^+$: 396.14471, found: 396.14590.



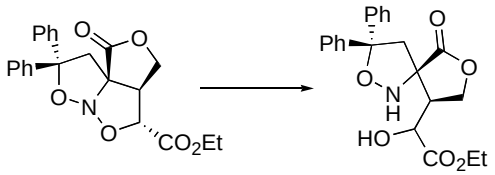
324g **325g**

4-Benzyloxymethyl-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*] pentalene-1-one (325g). White powdery solid (21 mg, 67%): M.p. 144-145 ^{o}C; R_f 0.23 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.51 (m, 15H), 4.53-4.60 (m, 1H), 4.45 (dd, *J* = 11.9, 5.0 Hz, 2H), 4.18-4.35 (m, 2H), 3.70 (dd, *J* = 5.4, 4.9 Hz, 1H), 3.60 (d, *J* = 13.3 Hz, 1H), 3.55 (d, *J* = 7.5, 3.2 Hz, 1H), 3.33 (d, *J* = 13.4 Hz, 1H), 3.07-3.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 144.7, 143.1, 137.3, 128.77, 128.75, 128.5, 128.3, 128.1, 128.0, 127.7, 126.2, 126.1, 89.6, 84.0, 82.7, 73.8, 66.2, 65.4, 49.0, 47.8; IR (solid) 1780 (C=O), 1449, 1228, 1110 cm^{-1}.



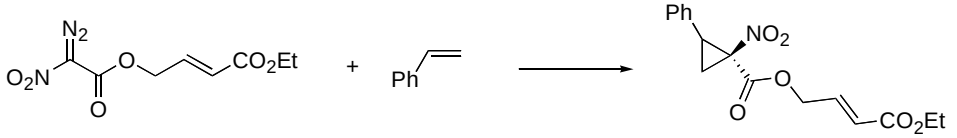
324h **325h**

4-Methyl-4-(4-methyl-pent-3-enyl)-7,7-diphenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalen-1-one (325h). White solid (25 mg, 71%): M.p. 142-143; R_f 0.23 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.51 (m, 2H), 7.18-7.42 (m, 8H), 4.80-4.85 (m, 1H), 4.25-4.36 (m, 2H), 3.50 (d, *J* = 13.1 Hz, 1H), 3.26 (d, *J* = 13.1 Hz, 1H), 2.88 (dd, *J* = 6.3, 1.8 Hz, 1H), 1.83-1.95 (m, 1H), 1.69 -1.76 (m, 1H), 1.65 (s, 3H), 1.52 (s, 3H), 1.42-1.50 (m, 1H), 1.28-1.36 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 145.1, 143.6, 132.3, 128.5, 128.3, 127.7, 127.6, 126.4, 126.1, 123.4, 91.2, 90.0, 85.0, 66.6, 54.7, 47.7, 41.5, 25.8, 23.1, 20.2, 17.9; IR (solid) 1772 (C=O), 1448, 1179 cm^{-1}.



325f **326**

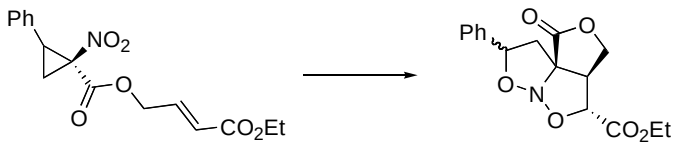
Typical procedure for the reductive cleavage of N-O bonds of nitrosoacetals. In a 20 mL stainless steel bomb nitrosoacetal **325f** (49 mg, 0.12 mmol) was dissolved in wet THF (1.5 mL) and MeOH (1.5 mL). 20% $Pd(OH)_2/C$ (18 mg) was then added and the bomb sealed and purged with hydrogen (5x150 psig). The bomb was then charged with 150 psig of hydrogen and stirred vigorously for 45 h at room temperature. The pressure in the bomb was released and the black solution was filtered through a small celite plug washing with THF and the solvent removed under reduced pressure (rotary evaporator). The resulting crude residue was purified by column chromatography on silica eluting with a gradient of 10-50% EtOAc/Hexane affording ester **326** as a white glace. **Hydroxy-(6-oxo-3,3-diphenyl-2,7-dioxa-1-aza-spiro[4.4]non-9-yl)-acetic acid ethyl ester (326).** White glace (40 mg, 82%): M.p. 53-57 ^{o}C; R_f 0.39 (50% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.52 (m, 2H), 7.21-7.42 (m, 8H), 5.90 (s(*br*), 1H) 4.40-4.49 (m, 2H), 4.32-4.39 (m, 2H), 4.20-4.31 (m, 1H), 3.54 (d, J = 12.9 Hz, 1H), 3.08-3.11 (m, 1H), 2.93 (d, J = 12.9 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 172.7, 143.5, 141.7, 129.0, 128.5, 128.3, 127.8, 126.7, 126.2, 93.5, 71.5, 68.9, 68.5, 62.5, 53.8, 48.8, 14.2; IR (solid) 3497 (OH/NH), 1777, 1734 (C=O), 1245 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{22}H_{23}NO_6$ $[M+H]^+$: 398.4 *m/z*, found: 398.1 *m/z*.



121j **328**

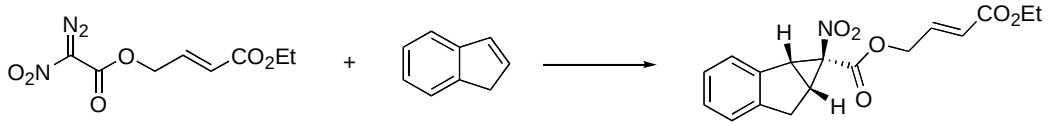
***E*-1-Nitro-2-phenyl-cyclopropanecarboxylic acid 3-ethoxycarbonyl-allyl ester (328).** Prepared according to the standard cyclopropanation procedure (catalyst: $[Rh(Oct)_2]_2$). Clear colorless oil (191 mg, 88%): R_f 0.32 (20% EtOAc/Hexane); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.26-7.33 (m, 3H), 7.17-7.22 (m, 2H), 6.51 (dt, *J* = 15.8, 4.9 Hz, 1H), 5.72 (dt, *J* = 15.8, 1.9 Hz, 1H), 4.51-4.53 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.80 (t, *J* = 10.0 Hz, 1H), 2.47 (dd, *J* = 9.2, 6.7 Hz, 1H), 2.25 (dd, *J* = 10.8, 6.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 161.6, 139.2, 131.8, 128.7, 128.6, 128.4, 123.1, 71.7, 64.4, 60.7, 34.5, 21.0, 14.3; IR (film) 1750, 1722 (C=O), 1547, 1350 (NO_2), 1185 cm^{-1}.



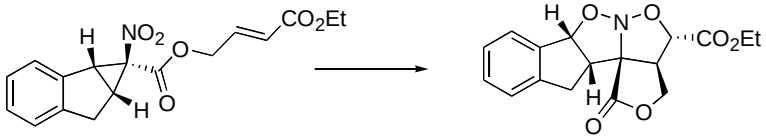
328 **329**

1-Oxo-7-phenyl-tetrahydro-2,5,6-trioxa-5a-aza-cyclopenta[*c*]pentalene-4-carboxylic acid ethyl ester (329). The cyclopropane was heated in CH_3CN (1.0M) with NaI (10 mol%) for 14 h at 80 ^oC. White fluffy solid in a 74:26 *anti:syn* ratio (101 mg, 96%): M.p. 150-153 ^oC; R_f 0.18 (40% EtOAc/Hexane); **Major diastereomer.** ^{1}H NMR (300 MHz, acetone d^6) δ 7.36-7.52 (m, 5H), 5.58-5.67 (m, 1H), 4.99 (d, *J* = 3.3 Hz, 1H), 4.78-4.85 (m, 1H), 4.47-4.52 (m, 1H), 4.16-4.32 (m, 2H), 3.17-3.24 (m, 1H), 2.65-2.79 (m, 1H) 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 169.7, 139.5, 129.5, 129.4, 127.7, 85.0, 84.6, 84.3, 70.8, 62.4, 50.1, 43.5, 14.4; **Minor diastereomer.** ^{1}H NMR (300 MHz, acetone d^6) δ 7.36-7.52 (m, 5H), 5.37 (d, *J* = 0.93 Hz, 1H), 4.99-5.11 (m, 1H), 4.39-4.43 (m, 1H), 4.16-4.32 (m, 2H), 2.95-3.08 (m, 1H), 2.65-2.79 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 170.4, 138.0, 129.5, 129.4, 127.9, 90.4, 85.3, 79.1, 71.6, 62.2, 49.3, 44.2, 14.4; IR (solid) 1768, 1737 (C=O), 1389, 1208, 1036 cm^{-1}; HRMS (EI^+) calcd for $C_{16}H_{17}NO_6$ $[M]^+$: 319.10559, found: 319.10461.



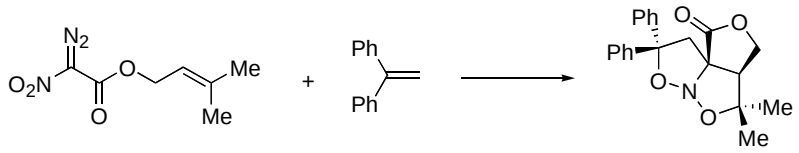
121j 330

***exo*-1-Nitro-1,1a,6,6a-tetrahydro-cyclopropa[*a*]indene-1-carboxylic acid 3-ethoxy carbonyl-allyl ester (330).** Prepared according to the standard cyclopropanation procedure (catalyst: $[Rh(Oct)_2]_2$). White crystalline solid (230 mg, 78%): M.p. 83-84 ^oC; R_f 0.36 (20% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.45 (m, 1H), 7.14-7.26 (m, 3H), 6.41 (dt, J = 15.8, 5.0 Hz, 1H), 5.68 (dt, J = 15.8, 1.8 Hz, 1H), 4.44 (dd, J = 5.0, 1.8 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 7.4 Hz, 1H), 3.37-3.49 (m, 2H), 3.12-3.16 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 160.0, 141.7, 139.3, 137.4, 128.6, 127.7, 125.9, 125.1, 123.2, 72.8, 64.1, 60.7, 42.1, 34.4, 34.3, 14.3; IR (solid) 1745, 1707 (C=O), 1534, 1309 (NO_2), 1151 cm^{-1}.



330 331

Ethyl-1-oxo-3a,4,12,12a-tetrahydro-3*H*,7a*H*-furo[3,4-*c*]indeno[2',1':4,5]isoxazolo [2,3-*b*]isoxazole-4-carboxylate (331). The cyclopropane was heated in CH_3CN (1.0 M) with NaI (10 mol%) for 14 h at 80 ^oC. White solid (108 mg, 97%): R_f 0.54 (60% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.38 (m, 4H), 5.77 (d, J = 6.7 Hz, 1H), 4.77-4.82 (m, 1H), 4.68 (dd, J = 10.1, 7.5 Hz, 1H), 4.25-4.44 (m, 3H), 3.84-3.95 (m, 2H), 3.66-3.74 (m, 1H), 3.30 (dd, J = 17.2, 9.3 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.6, 143.3, 138.7, 130.1, 127.3, 125.8, 125.0, 87.8, 87.6, 86.0, 69.6, 62.6, 50.3, 49.3, 32.5, 14.2; IR (solid) 1766, 1732 (C=O), 1217, 999, 750 cm^{-1}.



182e **325b**

"One pot" procedure for cyclopropanation, ring opening, 1,3-dipolar cycloaddition reaction. In a 25 mL round-bottomed flask was added $[Rh(OPiv)_2]_2$ (2.1 mg, 3.49 x 10^{-3} mmol, 0.5 mol%) and 1,1'-diphenylethene (377 mg, 2.09 mmol, 3.0 equiv). To this mixture of catalyst and olefin the diazo compound (**322b**, 139 mg, 0.70 mmol, 1.0 equiv) was added slowly dropwise as a solution in anhydrous anhydrous CH_3CN (1.5 mL, 0.5M) over 30 min. The reaction mixture was allowed to stir for 2.5 h at room temperature then the reaction vessel was fitted with a reflux condenser and heated to 80 ^oC for 24 h. After cooling the reaction mixture, the solvent was removed under reduced pressure (vacuum line) and the crude residue was chromatographed on silica gel. 5-35% EtOAc/Hexane was used as the eluent affording the desired nitrosoacetal **325b** as a white crystalline solid (113 mg, 46% over 3 steps).

Appendix I

Data for the crystal structure of
methyl nitro diazoacetate (**97**).

Appendix II

Data for the crystal structure of
(*E*)-1-[2-(4-fluorophenyl)-1-nitrocyclopropyl] ethanone (**151**).

Appendix III

Data for the crystal structure of
exo-1,1a,6,6a-tetrahydro-1-nitrocyclopropa[*a*]indene-1-carboxylate (**162**).

Appendix IV

Data for the crystal structure of
10a-nitro-1a-phenyl-1,1a,2,10a-tetrahydro-8*H*,10*H*
benzo[*b*]cyclopropa[*g*][1,5]dioxonin-10-one (**181c**).

Appendix V

Data for the crystal structure of
4-nitro-1,2-diphenyl-5-propyl-2,3-dihydro-1*H*-pyrrole (**293b**).

Appendix VI

Data for the crystal structure of
2-methyl-3-nitro-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (**321**).