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Nucleophilic Ring-Opening of Methyl 1-Nitrocyclopropanecarboxylates

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Nucleophilic Ring-Opening of Methyl 1-Nitrocyclopropanecarboxylates

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Prof. Richard Giasson, président-rapporteur

Prof. André B. Charette, directeur de recherche

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Résumé

Dans ce mémoire sont décrites deux méthodologies impliquant l'ouverture énantiospécifique des dérivés nitrocyclopropane esters par différents hétéronucléophiles azotés et oxygénés. Les conditions de réactions utilisées sont douces et les ouvertures procèdent avec rétention complète de l'excès énantiomérique des cyclopropanes énantioenrichis aux produits acycliques. Cette méthodologie a par la suite été utilisée pour la synthèse énantiosélective de produits pharmaceutiques actifs.

Le premier chapitre parcoure les précédents littéraires du sujet, incluant un résumé des différentes méthodes de cyclopropanation et plus précisément sur les méthodes de synthèse des 1-nitrocyclopropane esters développées dans le groupe de recherche. La fission du cyclopropane est ensuite abordée, incluant une revue des propriétés physiques de celui-ci, les différents types de cyclopropanes dits activés et leurs réactivités, l'énantiocontrôle des réactions d'ouverture ainsi que l'énantiosélectivité et l'éventail d'application des additions homoconjuguées des cyclopropanes.

Le second chapitre présente les résultats obtenus lors de l'ouverture de cycle des 1-nitrocylcopropane esters par des hétéronucléophiles azotés. Le développement, l'optimisation et les limitations des ouvertures thermiques de cycles sont discutés. Une méthode améliorée catalysée par un acide de Lewis et réalisée à température ambiante est élaborée et son application est explorée. Un mécanisme de réaction est ensuite proposé se basant principalement sur la stéréochimie des substrats transformés.

Le troisième chapitre démontre l'extension de la méthodologie aux hétéronucléophiles oxygénés. L'optimisation ainsi que l'applicabilité de la réaction sont élaborées. La configuration absolue du produit formé est aussi démontrée. De l'information mécanistique est obtenue à partir de la stéréochimie absolue et relative des produits finaux.

Le quatrième chapitre présente l'application de la méthodologie lors de la synthèse de produits pharmaceutiques actifs. Une synthèse énantiosélective rapide de l'inhibiteur

sérotonine/norépinéphrine (3*R*)-3-(1*H*-indol-1-yl)-*N*-méthyl-3-phénylpropan-1-amine et l'inhibiteur de la norépinéphrine commercial atomoxetine (Strattera^{TM}) on été accomplies en 5-6 étapes respectivement avec conservation complète de la stéréochimie et un rendement superier à 50%.

Mots-clés :

1-Nitrocyclopropane esters
Ouverture de cycle de cyclopropane
Nucléophiles aminés
Phénolates nucléophiles
Synthèses énantiosélective
Inhibiteurs sélectif de la recapture des monoamines

Abstract

This thesis describes the development of a methodology for the ring-opening of methyl 1-nitrocyclopropanecarboxylates with heteroatom nucleophiles under mild conditions and with complete transfer of the enantiomeric excess of the cyclopropane to the acyclic product. The methodology was applied to an enantioselective synthesis of small pharmaceutically active molecules.

The first chapter presents the literature background, including a brief overview of cyclopropanation methodologies and the synthesis of methyl 1-nitrocyclopropane carboxylates developed in this research group. Cyclopropane ring-fission is discussed in detail, covering the physical description of the cyclopropane, the types of activated cyclopropanes and their reactions, enantiocontrol of the ring-opening reactions and the stereochemistry and scope of homoconjugate addition to cyclopropanes.

The second chapter describes the results of the nucleophilic ring-opening of methyl 1-nitrocyclopropanecarboxylates with amine nucleophiles. Development, optimization and limitations of the ring-opening under thermal conditions with aniline derivatives are discussed. An improved methodology that utilizes Lewis acid catalysis at ambient temperature is presented, and the reaction scope is explored. A reaction mechanism is proposed, based on the examination of the stereochemistry of the transformation.

The third chapter presents the extension of the ring-opening methodology to phenol nucleophiles. Optimization and scope of the reaction are described, and determination of the absolute configuration of the products is presented. Mechanistic insight is given based on the determined absolute and relative configuration of the products.

The fourth chapter demonstrates the practical application of the developed methodologies to the synthesis of pharmaceutically active compounds. An expedient enantioselective synthesis of the dual serotonin/norepinephrine inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenyl-propan-1-amine and the commercial norepinephrine inhibitor atomoxetine

(Strattera™) was performed in 5-6 steps, with complete preservation of the optical purity from the cyclopropane and in >50% overall yield.

Keywords : Methyl 1-nitrocyclopropane carboxylates
Cyclopropane ring-opening
Amine nucleophiles
Phenolate nucleophiles
Enantioselective synthesis
Monoamine reuptake inhibitors

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List of abbreviations

Ac	acetyl
aliph.	aliphatic
aq.	aqueous
Ar	aryl
arom.	aromatic
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
ca	*circa,* approximately
cat.	catalytic
conc.	concentrated
COSY	correlation spectroscopy
d	day(s)
δ	chemical shift
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Et	ethyl
equiv	equivalent(s)
EWG	electron-withdrawing group
FTIR	Fourier transform infrared spectroscopy

h	hour(s)
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
J	coupling constant
LA	Lewis acid
LG	leaving group
Lit.	literature
M	molar, mol/L
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mp	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
Pr	propyl
quat.	quaternary
R_f	retention factor
rt	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
temp	temperature
tert, t	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
xs.	excess

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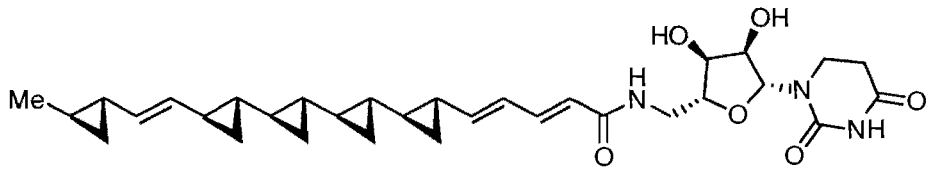
Chapter 1: The chemistry of cyclopropanes

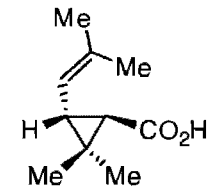
1.1 Introduction

Since their discovery in 1881 by Freund,[1] cyclopropanes have continued to inspire much theoretical and synthetic work. Indeed, their unusual physical and bonding properties, remarkable chemical versatility and the presence in a variety of natural products[2] make cyclopropanes particularly attractive subjects of research. Naturally occurring cyclopropanes often exhibit potent biological activity – for example, the pentacyclopropane nucleoside (-)-FR-900848 **1** is a powerful fungicide,[3] while *trans*-chrysanthemic acid **2** is a widely used insecticide[4] (Figure 1). Synthetic cyclopropane derivatives have also been employed in the pharmaceutical industry, where the three-membered structure is used to rigidify the molecular conformation of the drug, such as the monoamine reuptake inhibitor Milnacipran **3**, used to treat depression and other psychiatric disorders.[5]

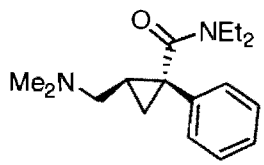
Figure 1: Natural products containing the cyclopropane structure[3,4,5]



(-)-FR-900848 **1**



trans-chrystanthemic acid **2**



Milnacipran **3**

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[1] Freund, A. *J. für Prakt. Chem.* **1881**, *26*, 625.

[2] (a) Djerassi, C.; Doss, G. A. *New J. Chem.* **1990**, *14*, 713; (b) Salaun, J. *Curr. Med. Chem.* **1995**, *2*, 511; (c) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1; (d) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251; (e) de Meijere, A. *Angew. Chem., Int. Ed.* **1979**, *18*, 809. (f) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20; (g) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229; (h) Suckling, C. J. *Angew. Chem., Int. Ed.* **1988**, *27*, 537.

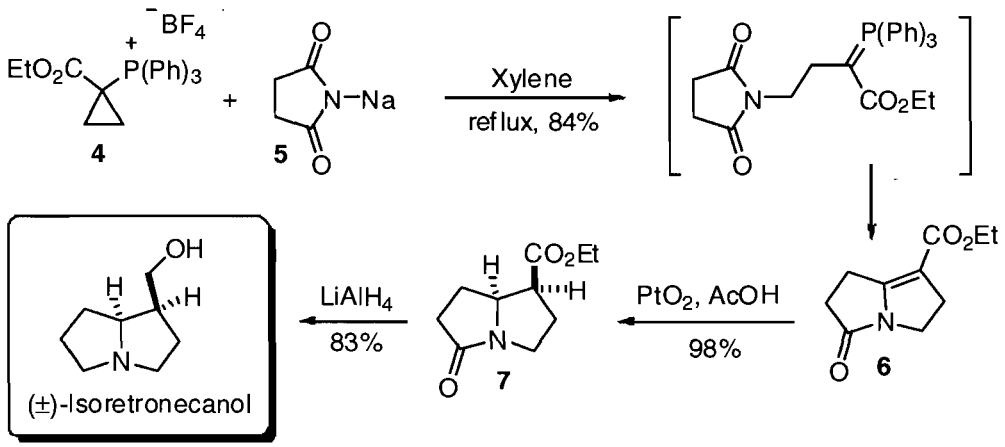
[3] Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiotics* **1990**, *18*, 748.

[4] Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 177.

[5] Moret C.; Charveron M.; Finberg J. P.; Couzinier J. P.; Briley, M. *Neuropharmacology* **1985**, *24*, 1211.

In addition to being part of synthetic targets, cyclopropane derivatives serve as versatile precursors in the construction of carbon skeletons through ring fission.[6] This seemingly simple transformation has been shown to generate an impressive level of complexity, and consequently used in the synthesis of a number of natural products. For example, Flitsch and Wernsman used the ring-opening of cyclopropylphosphonium **4** with sodium succinimide **5** followed by a tandem intramolecular Wittig reaction to rapidly access the backbone of the pyrrolizidine alkaloid isoretronecanol **6** (Scheme 1).[7] Diastereoselective hydrogenation of the double bond in **6** and reduction of the carbonyl groups in **7** furnished the natural product in only three overall steps.

Scheme 1: Synthesis of (±)-isoretronecanol [7]



The use of cyclopropanes as functional group equivalents has been exploited in numerous total syntheses. Danishefsky and colleagues, for example, used a hydroxyl-directed Simmons-Smith cyclopropanation of the glycal **8** to introduce a cyclopropane ring in the intermediate **9** in their route toward epothilone A (Scheme 2).[8] Oxidative solvolytic fragmentation of **9** with NIS in methanol followed by reductive deiodination allowed the

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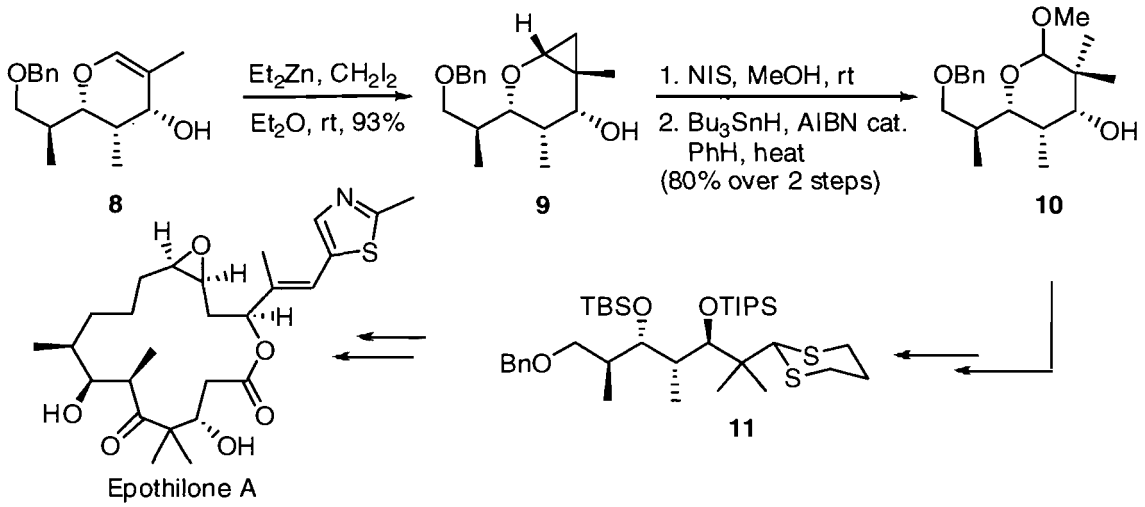
[6] For reviews, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66; (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151; (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165; (d) Burritt, A.; Coron, J. M.; Steel, P. J. *Trends Org. Chem.* **1993**, *4*, 517; (e) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603; (f); Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321; (g) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117

[7] Flitsch, W.; Wernsmann, P. *Tetrahedron Lett.* **1981**, *22*, 719.

installation of *gem*-dimethyl and acetal groups in the glycoside **10**. This glycoside was subsequently cleaved into a linear product **11** which was further extended to make up the backbone of Epothilone A.

Scheme 2: Cyclopropane as a functional group equivalent in the synthesis of Epothilone A[8]



Within the scope of ring-opening reactions, the cyclopropane's versatile chemical behaviour has been documented in virtually every reaction type, including polar,[6a-f] pericyclic,[6b-f] radical[6c] and transition metal-catalyzed processes.[6c,g] Importantly, the substituents on the cyclopropane can dictate ways in which the three-membered ring can be fragmented, and determine the charge distribution within the linear or ring-expanded products.[6c]

1.2 Cyclopropane synthesis

1.2.1 Overview of the main cyclopropanation methodologies

Given the value of cyclopropanes as synthetic building blocks, it is not surprising that an abundance of cyclopropanation methodologies have been developed over the past twelve decades.[1] Apart from photochemical approaches,[9] organotitanium-promoted reactions,[10]

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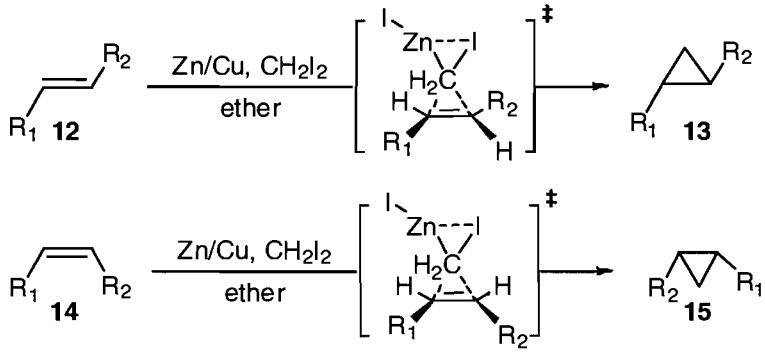
[8] Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073.

[9] See, for example: Wessig, P.; Mühling, O. *Angew. Chem. Int. Ed.* **2001**, *40*, 1064.

and nucleophilic addition/ring closure reactions,[11] a widely used class of cyclopropanation methodologies relies on the [2+1] cycloaddition of carbenoid species and alkenes. The earliest example of such carbenoid-based approach was developed by Simmons and Smith, who demonstrated that an iodomethylzinc carbenoid generated from the insertion of zinc into diiodomethane can cyclopropanate alkenes.[12] Mechanistic studies revealed that the stereospecific cyclopropanation of both *E* (**12**) and *Z* (**14**) alkenes occurs *via* a "butterfly" transition state structure to yield *trans*- and *cis*-disubstituted cyclopropanes **13** and **15**, respectively (Scheme 3).[12c]

Scheme 3: Simmons-Smith cyclopropanation[12]



Due to its excellent chemoselectivity and functional group tolerance, the Simmons-Smith cyclopropanation has been the subject of extensive research. Consequently, various modifications have been developed to include alternative methods for the preparation of the Simmons-Smith reagent,[13] other zinc carbenoid species[14] and metals,[15] and to perform the reaction asymmetrically.[11]

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[10] Kulinkovich, O. G.; De Meijere, A. *Chem. Rev.*, **2000**, *100*, 2789.

[11] Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.*, **2003**, *103*, 977.

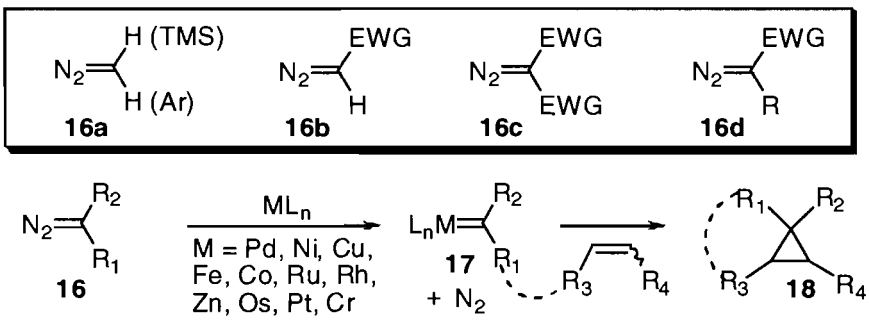
[12] (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323; (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**,*81*, 4256. (c) For a recent mechanistic study, see: Fang, W.-H.; Phillips, D. L.; Wang, D.-Q.; Li, Y.-L. *J. Org. Chem.* **2002**, *67*, 154.

[13] (a) Wittig, G.; Wingler, F. *Chem. Ber.* **1964**, *97*, 2146; (b) Wittig, G.; Wingler, F. *Justus Liebigs Ann. Chem.* **1961**, *650*, 18; (c) Wittig, G.; Jautelat, M. *Liebigs Ann. Chem.* **1967**, *702*, 24; (d) Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1962**, *650*, 1; (e) Wittig, G.; Schwarzenbach, K. *Angew. Chem.* **1959**, *71*, 652; (f) Goh, S. H.; Closs, L. E.; Closs, G. L. *J. Org. Chem.* **1969**, *34*, 25.

[14] (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353; (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53; (c) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974; (d) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669. (e) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539; (f) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.*

An alternative carbenoid-based cyclopropanation involves the decomposition of the diazo compounds **16** by a Lewis acidic transition metal. Diazo precursors bearing electron-withdrawing and donating groups (**16a-d**), as well as a multitude of metals have been used for this transformation (Scheme 4).[16] In all cases the carbenoid **17** is formed by an attack of the diazo precursor on the electrophilic metal center and driven by the irreversible loss of N_2. Cycloaddition of **17** with an *E* or *Z* alkene leads to the substituted cyclopropane **18**. If the carbenoid is generated on a side chain of the alkene (e.g. R_1 and R_3 in **17** are linked), an intramolecular cyclopropanation can occur, generating a bicyclic system with a variety of possible ring sizes.[16] Similarly to the halomethylmetal-mediated cyclopropanation, diazo decomposition has received extensive attention in terms of the mechanistic studies[17] and the development of the asymmetric versions of the reaction.[11]

Scheme 4: Cyclopropanation by decomposition of diazo compounds[16]



Most recently, progress in hypervalent iodine(III) chemistry has shown that iodonium ylides[18] can act as attractive alternatives to diazo compounds, which are generally unstable and potentially explosive upon heating or when handled neat.[19] Iodonium ylides can be prepared from the corresponding methylene precursors and hypervalent iodine reagents in

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1998, *39*, 8621; (g) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem.,Int. Ed.* **2000**, *39*, 4539.

[15] (a) Cintas, P. *Activated Metals in Organic Synthesis*; CRC Press: London, 1993. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525. (c) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942; (d) Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4412.

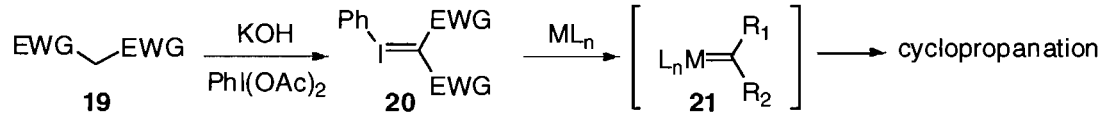
[16] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*. Wiley & Sons: New York, 1998.

[17] See; for example: Davies, H. M. L.; Antoulinakis, E. *Org. React.* **2001**, *57*, 1.

[18] (a) For the report of the first isolated iodonium ylide, see: Gudrienietse, E.; Nielands, O.; Vanag, G. *J. Gen. Chem. USSR* **1957**, *27*, 2772; (b) For a review, see: Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243.

the presence of a base, and are isolable. For example, phenyliodonium ylide **20** commonly used in cyclopropanation reactions is synthesized by treating acidic methylene precursors **19** with methanolic KOH and bis(acetoxy)benzene (Scheme 5).[20] If the methylene precursor contains sufficiently acidic protons (e.g. when flanked by at least one electron-withdrawing group),[21d] iodonium ylides can be generated *in situ* and decomposed by a transition metal to a carbenoid **21** in a convenient one-pot cyclopropanation.[21]

Scheme 5: Formation of isolatable phenyliodonium ylides[20]



1.2.2 Synthesis of racemic 1-nitro-1-carbonyl cyclopropanes

In our group, a continued interest in the synthesis of biologically relevant cyclopropane α-amino acids[22] has led to the development of several efficient methodologies to generate 1-nitro-1-carbonyl cyclopropanes.[23,25,26] Initial studies involving diazo decomposition demonstrated that when α-nitro-α-diazocarbonyl reagents were reacted with alkenes in the presence of catalytic $[Rh(OAc)_2]_2$, excellent *E/Z* diastereoselectivity could be achieved with sterically unencumbered carbonyl substituents.[23a] In particular, the reaction of methyl 2-diazo-2-nitroacetate **22** with styrene yielded the cyclopropane **(±)-23a** with a 91:9 *E/Z* ratio, whereby the diastereomers could be easily separated by flash chromatography (Scheme 6, major *E*-isomer shown).

---

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

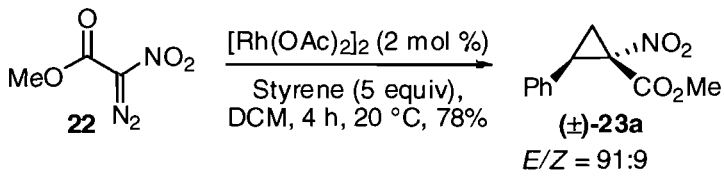
[20] Georgakopoulou, G.; Kalogiros, C.; Hadjiarapoglou, L. P. *Synlett* **2001**, 1843.

[21] (a) Müller, P.; Ghanem, A. *Synlett* **2003**, 1830; (b) Müller, P.; Ghanem, A. *Org. Lett.* **2004**, *6*, 4347; (c) Ghanem, A.; Aboul-Enein, H. Y.; Müller, P. *Chirality* **2005**, *17*, 44. (d) Bonge, H. T.; Hansen, T. *Synlett* **2007**, *1*, 55.

[22] Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538; (b) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

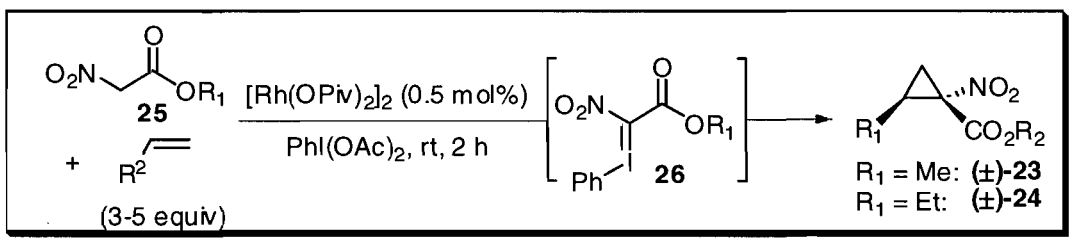
[23] (a) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, 85, 4468; (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327; (c) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262.

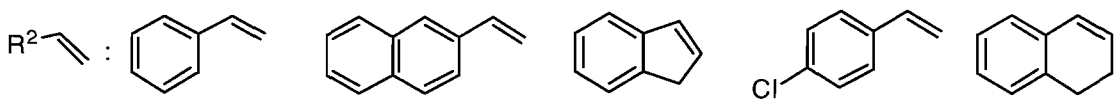
Scheme 6: Formation of (±)-**23a** by diazo decomposition[23a]



In an attempt to avoid the potentially dangerous α-nitro-α-diazocarbonyl reagents, an alternative Rh-catalyzed cyclopropanation involving *in situ*-generated phenyliodonium ylides **26** was subsequently developed (Scheme 7).[23b,c] In this reaction, $PhI(OAc)_2$ was used to form the hypervalent phenyliodonium intermediate **26** from methyl- or ethylnitroacetate **25**, which was decomposed by rhodium to perform the cyclopropanation. It was found that the reaction afforded the cyclopropane products (±)-**23** and (±)-**24** in good yield even in the absence of any base additives or a solvent.[23b]

Scheme 7: Racemic synthesis of cyclopropanes (±)-**23** and (±)-**24** and selected scope[23c]





R_1= Me: (±)-**23a**, 83%, *E/Z* = 98:2; R_1 = Et: (±)-**24a**, 84%, *E/Z* = 93:7

R_1 = Me: (±)-**23b**, 87%, *E/Z* = 95:5

R_1 = Me: (±)-**23c**, 91%, *E/Z* = 100:0; R_1 = Et, (±)-**24b**, 83%, *E/Z* = 97:3

R_1 = Me: (±)-**23d**, 80%, *E/Z* = 91:9

R_1 = Me: (±)-**23e**, 72%, *E/Z* = 97:3

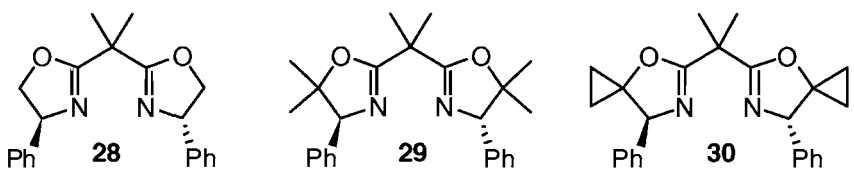
Optimization of the reaction conditions identified rhodium(II) pivaloate dimer as the most active catalyst which performed the reaction in 2-4 h. A less active but significantly less expensive rhodium(II) octanoate dimer catalyst performed the reaction in comparable

yields overnight, and was subsequently chosen in this work (Section 2.2).[24] The one-pot cyclopropanation procedure was shown to tolerate both electron-rich and electron-poor alkenes to afford a variety of methyl and ethyl 1-nitrocyclopropanecarboxylates **23a-e** and **24a-b** with generally > 90:10 *E/Z* selectivity and 72-87% yield (Scheme 7). The methodology was further extended to the synthesis of 1-nitro and 1-cyano-cyclopropylketones using the corresponding diazo or phenyliodonium precursors.[25] Initial studies towards the asymmetric version of this cyclopropanation employed the α-nitro-α-diazocarbonyl reagents and chiral rhodium carboxylates and amides, as well as chiral copper-bis(oxazoline) catalysts.[26] However, these attempts resulted in only modest asymmetric induction (ee ≤ 72%) and modest to good diastereoselectivity.

1.2.3 Synthesis of enantioenriched 1-methyl nitrocyclopropanecarboxylates

The problem of efficient enantiocontrol in the formation of 1-nitro-1-carbonyl cyclopropanes was overcome in our group by combining the use of *in situ* generated phenyliodonium ylides and a chiral Cu(I)-bis(oxazoline) catalyst system.[27a] The study was initiated by using iodosobenzene **27** as the hypervalent iodine(III) reagent, 3Å molecular sieves to scavenge water, and the commercially available bis(oxazoline) **28** as the ligand for the copper catalyst (Figure 2).

Figure 2: Bis(oxazoline) ligands used in the asymmetric cyclopropanation[27b]



A screen of additives, solvents and copper sources identified the optimal conditions which afforded the cyclopropane products **23** from ethyl nitroacetate **25** with > 90:10 *E/Z*

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[24] $[Rh(C_7H_{15}CO_2)_2]_2$ (rhodium octanoate dimer): $173/g; $[Rh(OPiv)_2]_2$ (rhodium pivaloate dimer): $709/g (Sigma-Aldrich, 2007-2008, price in $CAD)

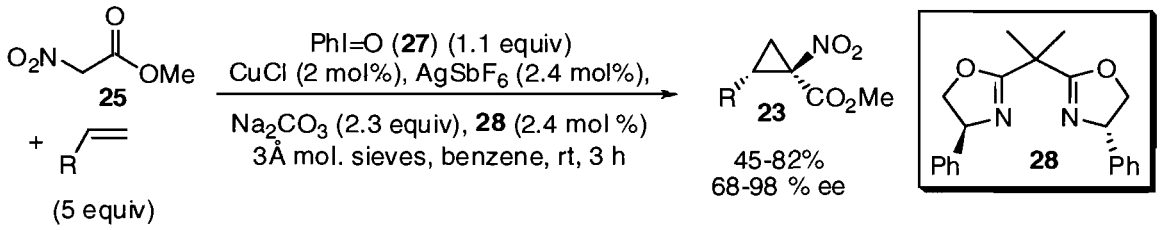
[25] Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313.

[26] Wurz, R. P.; Charette, A. B. *J. Mol. Cat. A: Chem.* **2003**, *196*, 83.

[27] (a) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (b) Moreau, B.; Alberico, D.; Charette, A. B. **2008** *Manuscript in preparation.*

diastereoselectivity and generally >90% enantiomeric excess (Scheme 8). The enantioselectivity could be further improved by using derivatives of the C_2-symmetric bis(oxazoline) ligand, including ligands **29** and **30** used in this work (Figure 2).[27b]

Scheme 8: Enantioselective synthesis of methyl 1-nitrocyclopropylcarboxylates **23**[27a]



1.3 Cyclopropane ring fission in organic synthesis

1.3.1 Introduction

Arranged into the smallest possible ring system, the C-C bonds of the cyclopropane are subject to a significant angular and torsional strain.[6c] It is therefore not surprising that the chemistry of cyclopropanes is characterized by a variety of thermodynamically favourable ring-opening reactions. However, the reactivity profile of cyclopropanes suggests that the three-membered unit is more stable than would be expected from its strained geometry. Indeed, the strain energy of a cyclopropane (27.5 kcal/mol)[28] is much lower than predicted by vibrational spectroscopy, which calculates the C-C-C bending force to result in a strain of 104 kcal/mol.[29] In fact, the strain energy of a cyclopropane is almost the same as that of a cyclobutane (26.5 kcal/mol), which possesses greater bond angles.[28] The same holds true for the energy of homolytic C-C cleavage for cyclopropane (61 kcal/mol) and cyclobutane (62.5 kcal/mol).[30] These characteristics point to unusual bonding interactions in the cyclopropane which deviate from a simple arrangement of three linear sp^3-hybridized bonds. A model by Coulson and Moffitt suggests a trigonal arrangement of three sp^3-

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[28] Cox, J. D.; Plicher. G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970.

[29] (a) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669; (b) Snyder, R. G.; Schactschneider, J. H. *Spectrochim. Acta* **1965**, *21*, 169.

[30] Benson, S. W. *Thermochemical Kinetics;* Wiley: New York, 1968.

hybridized "banana" bonds, which experience reduced orbital overlap due to an outward bend by approximately 22°.[31] This deviation from the optimal overlap is used to explain the angular strain and other physical characteristics of the cyclopropane. Another model pioneered by Walsh envisions the cyclopropane as a three-centered π-system, or an insertion of methylene into ethylene by a dative bond.[32] In this arrangement, every carbon is sp^2-hybridized, which is in good agreement with the cyclopropane's olefinic behaviour. A further concept proposes that the cyclic arrangement of the cyclopropane's 6 electrons is "σ-aromatic," implying some conjugation of σ-bonds and thus satisfying the rules of aromaticity.[29a] Such aromatic properties of the cyclopropane readily explain its unexpectedly low strain energy, as well as the upfield shift of its protons in ^{1}H NMR, which results from the ring current effects shielding the protons from the applied magnetic field.[6c]

Given such stability, the heterolytic ring fission of cyclopropanes can only be carried out under relatively mild conditions if the three-membered ring is activated by electron-withdrawing and/or electron-donating substituents.[6] These functional groups stabilize the polar process of ring cleavage through inductive and resonance effects, or chemically participate in the ring-opening reaction. Based on these modes of activation, the various approaches used to fragment the cyclopropane can be broadly divided into two classes. The first class includes the reactions of donor-acceptor cyclopropanes that bear a functionality with a *delocalizable lone pair* conjugated to the three-membered ring (the donor group) and one or more electron-withdrawing (acceptor) groups.[6b,e,f] The second class involves the reactions of the electrophilic cyclopropanes, which may be activated by *cation stabilizing* groups and electron-withdrawing acceptor groups in a 1,2-relationship.[6a] Although in both cases, the cyclopropane acts as a 1,3-dipolar synthon, the two reaction classes differ in the types of possible reactions, intermediates and primary products. Invoking the analogy to a double bond, the reactivity of the donor-acceptor cyclopropanes most closely resembles that of enol ethers, while electrophilic cyclopropanes are best compared to Michael acceptors.[6a]

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[31] Coulson, C. A.; Moffit, W. W. *J. Chem. Phys.* **1947**, *15*, 151.
[32] (a) Walsh, A. D. *Nature* **1947**, *159*, 165; (b) Snudgen, T. N. *Nature* **1947**, *160*, 367.

1.3.2 Donor-acceptor cyclopropanes

Though the definition of a donor-acceptor cyclopropane is somewhat inconsistent in the literature,[33] it is generally agreed that a donor group capable of delocalizing its lone pair into the three-membered carbocycle and acceptor groups capable of taking up the electrons from the C-C bond cleavage characterize this class of activated cyclopropanes.[34] The most reactive members of this class have the vicinal or 1,2-disubstituttion pattern shown in compound **31**, where both electron-donating and electron-withdrawing functionalities act in a synergistic manner (Figure 3). The typical donor groups are ether,[6b] amine[6e], and less commonly sulfide[6f] and trialkyl/aryl silyl methyl[6b] groups, which may be directly attached to the cyclopropane or conjugated through one or more double bond. The most common acceptor group is a carbonyl moiety; other electron withdrawing groups such as cyano, oxazolinyl, sulfonyl or phosphonyl groups are known but have found fewer synthetic applications.[6b] Delocalization of the donor group's lone pair into the cyclopropane which results in ring-opening can be induced by the "pulling" action of a Lewis or Brønsted acid reacting with the acceptor group or the "pushing" action of a nucleophile which breaks the R-X bond in **31** by an attack on the R-group. The simplest outcome of such a reaction is the protonolysis product **32**, which possesses a useful 1,4-dicarbonyl relationship when X = O (Figure 2). Alternatively, the carbanion resulting from the ring-opening reaction can be trapped with a different electrophile affording **33**, or undergo both electrophilic and nucleophilic attacks to give **34** (Figure 3). When the external electrophile and the nucleophile are part of the same molecule, formal [3+2] cycloaddition reactions may occur, giving rise to five-membered carbocycles **35** or heterocycles **36**.

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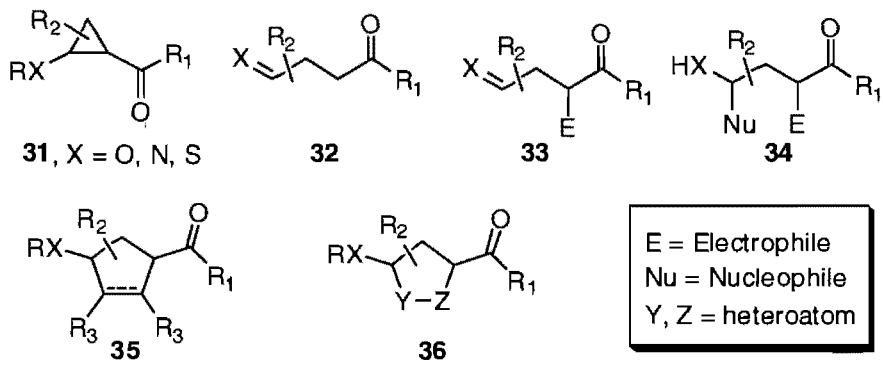
[33] Due to their common 1,3-dipolar character, some authors choose to call electrophilic cyclopropanes (which lack an oxygen, nitrogen or an equivalent substituent) "donor-acceptor" cyclopropanes. See, for example: (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014; (b) Lebold, T. P.; Carson, C. A.; Kerr, M. A. *Synlett* **2006**, *3*, 364.

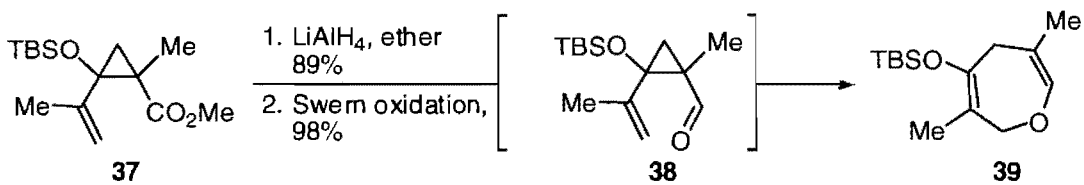
[34] For reviews up to 2005, see refs. **1c**, **e** and **f**; For a review up to 1988, see: Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73; For a recent example in natural product synthesis, see: (a) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631.

Figure 3: Donor-acceptor cyclopropanes and their common reaction products[6b]



While only five-membered cycles can be obtained by the intermolecular pericyclic reactions, intramolecular rearrangements of donor-acceptor cyclopropanes can give access to larger ring sizes. For example, the seven-membered 2,5-dihydrooxepine **39** was obtained by a [3,3] sigmatropic-type rearrangement of the donor-acceptor cyclopropane **38**, which itself was formed as an unstable intermediate from cyclopropane **37** (Scheme 9).[35]

Scheme 9: Intramolecular pericyclic rearrangement of donor-acceptor cyclopropane **37**[35]



In addition to the reactions with Brønsted or Lewis acids, electrophiles and nucleophiles (products **31-36**), donor-acceptor cyclopropanes can also participate in radical reactions and polymerizations, as well as a variety of sequential and multicomponent reactions.[6b] Such a broad reactivity profile renders itself particularly valuable to natural product synthesis; indeed, the ring-opening of donor-acceptor cyclopropanes has been exploited in the construction of carbohydrates, amino acids, peptides and alkaloids.[6b,e,f]

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[35] Hoffman, B.; Reissig, H.-U. *Synlett* **1993**, 27.

1.3.3 Electrophilic cyclopropanes

Electrophilic cyclopropanes are the oldest and most studied class of activated cyclopropanes: already in 1895, their electrophilic reactivity was recognized and explored.[36] Unlike the donor-acceptor cyclopropanes, they lack a substituent which can initiate ring-opening by the delocalization of its lone pair into the ring system. Instead, a sufficiently strong Lewis acid can ring-open an electrophilic cyclopropane of type **40** into a 1,3-zwitterionic intermediate **41** (Scheme 9). Such ring-opening is favoured by activating groups on the cyclopropane which effectively stabilize the positive and negative charges of the zwitterion.[37c] The typical cation-stabilizing substituents are the alkyl, aryl and vinyl groups which place the positive charge at the 2° or 3° alkyl, benzylic or allylic position. Most common anion-stabilizing substituents are the carbonyl, cyano, nitro, amide, sulfonyl and phosphonium groups, as well as their various combinations.[6a,38] Once formed, the zwitterionic intermediate **41** can undergo an intramolecular rearrangement into a neutral species[38,39b] or combine with a nucleophile through an S_N1 pathway to give the acyclic product **42** (Scheme 10).[6a,c,d] Importantly, whereas the donor-acceptor cyclopropanes require ring-cleavage for the development of an electrophilic center capable of combining with the nucleophile,[6b] electrophilic cyclopropanes can be ring-opened directly by a concerted S_N2 mechanism (Scheme 10).[39] This fact has important implications in the enantiocontrol of the ring-opening reactions and will be discussed in sections 1.3.4 and 1.4.1.

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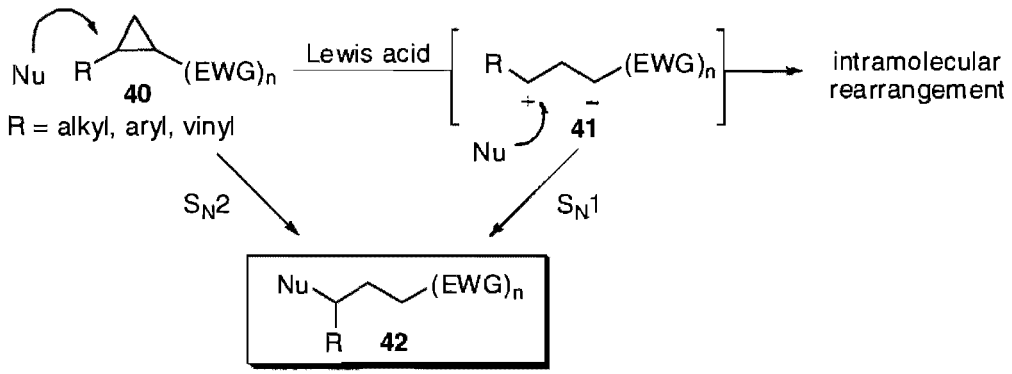
[36] Bone, W. A.; Perkin, W. H. *J. Chem. Soc.* **1895**, *108*, 67.

[37] For recent examples see: Formal homo-[3+2] cycloadditions: (a) Jackson, S. K.; Karadeolian, A.; Driega A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196; (b) Perreault, C.; Goudreau, S.; Zimmer, L.; Charette, A. B. *Org Lett.* **2008**, *10*, 689; (c) Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023; Formal [3+2] cycloaddition: (d) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014; (e) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057.

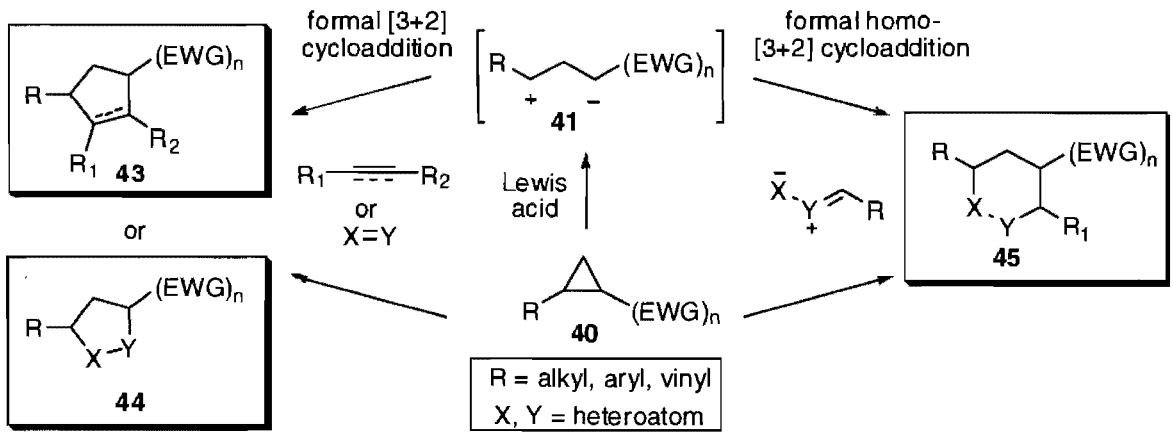
[38] For examples of the isomerization of nitrocyclopropanecarboxylates to isoxazoline *N*-oxides, see: (a) Bianchini, L.; Dell'Erba, C.; Gasparrini, F.; Novi, M.; Petrillo, G.; Sancassan, F.; Tavani, C. *Arkivoc* **2002**, 142; (b) Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tet. Lett.* **2006**, *47*, 647 (c) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 195; (d) Seebach, D.; Haener, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507; (e) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *21*, 7341.

Scheme 10: Reactions of electrophilic cyclopropanes leading to acyclic products[39]



In addition to generating acyclic products of type **42**, electrophilic cyclopropanes can also participate in formal [3+2] cycloadditions, either in the capacity of a 1,3-dipole to afford carbocycles **43** or heterocycles **44**,[37a-c] or in the capacity of a 1,3-dipolarophile to give cycles **45**[37d-e] (Scheme 11). Either formal cycloaddition may be initiated by an S_N2 or S_N1 process depending on the existence of the ring-opened intermediate **41**.

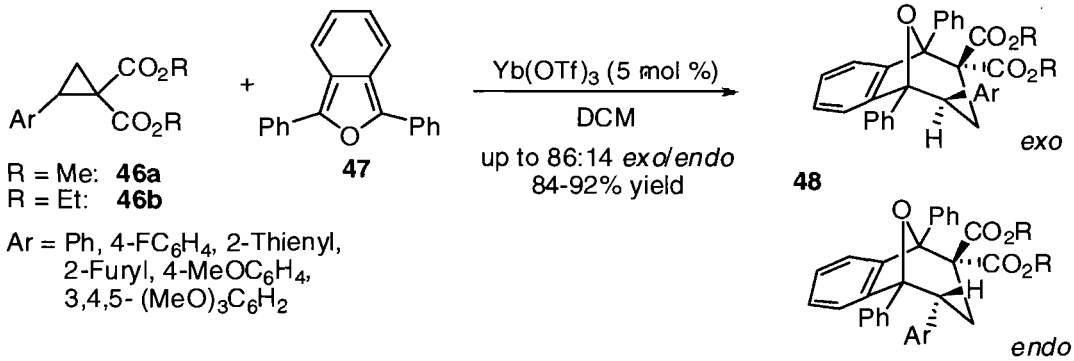
Scheme 11: Formal [2+3] cycloaddition reactions of electrophilic cyclopropanes[37]



[39] See, for example: (a) Danishefsky, S.; Rovnyak, G. *J. Chem. Soc. Chem. Comm.* **1972**, 821; (b) Yankee, E. W.; Spencer, B; Howe, N. E.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4220. This report also describes the isomerization of *gem*-cyanoestercyclopropane **65** into a substituted 2,3-dihydrofuran.

Most recently, Ivanova *et al.* demonstrated that electrophilic cyclopropanes **46** can also participate in [4+3] cycloadditions with 1,3-diphenylisobenzofuran **47**, affording substituted oxabicycles **48** as mixtures of *exo* and *endo* diastereomers (Scheme 12).[40]

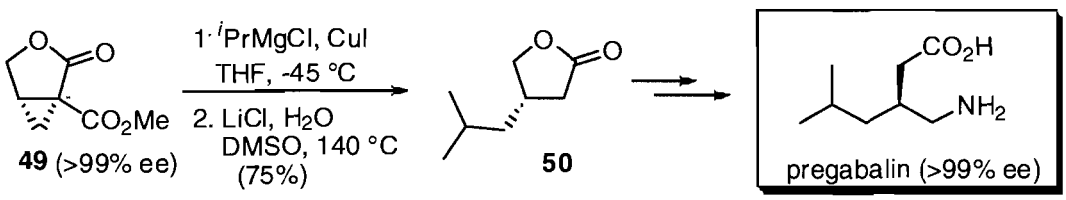
Scheme 12: [4+3] cycloaddition reaction of electrophilic cyclopropanes **46**[40]



1.3.4 Enantiocontrol in the cyclopropane ring-opening reactions

One of the valuable features of cyclopropanes in organic synthesis is the possibility of using a cyclopropanation – ring-opening sequence to effectively install a stereogenic center. Lee and colleagues, for example, used this strategy to access highly enantioenriched γ-butyrolactones with various aromatic or aliphatic substituents at the β-center.[41] Applying the methodology to the synthesis of an anticonvulsant drug pregabalin, they were able to introduce an isobutyl group in lactone **50** with > 99% ee by ring-opening the enantioenriched bicyclic lactone **49** with isopropyl cuprate (Scheme 13).

Scheme 13: Enantioselective synthesis of pregabalin by cyclopropane ring-opening[41]

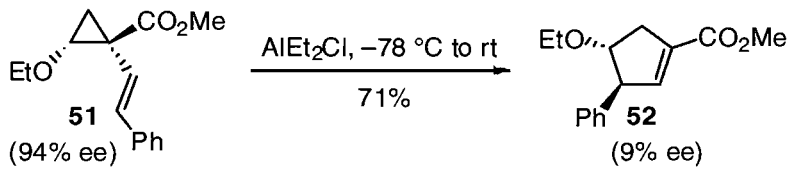


[40] Ivanova, O. A; Budynina, K. M.; Grishin, Y. K. Trushkov, I.V.; Verteletskii, P.V. *Angew. Chem. Int. Ed.* **2008**, *47*, 1107.

[41] Ok, T; Jeon, A.; Lee, J.; Lim, J. H.; Hong, C. S.; Lee, H.-S. *J. Org. Chem.* **2007**, *72*, 7390.

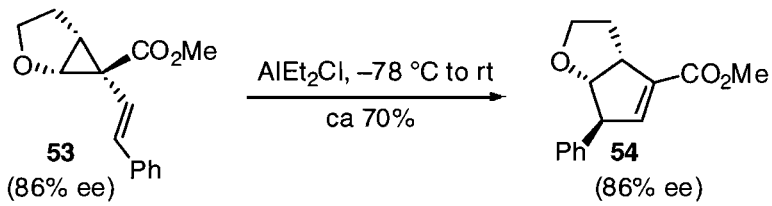
Effective enantiocontrol in the cyclopropane ring-opening reactions is not without challenges, however. In many reaction pathways, intermediacy of an ionic ring-opened form of the cyclopropane leads to the loss of chiral information. This is particularly true for donor-acceptor cyclopropanes which must undergo ring-opening before they can combine with a nucleophile.[6b] Thus, when Davies *et al.* treated the enantioenriched donor-acceptor cyclopropane **51** with a Lewis acid, the rearranged product **52** was obtained with almost complete loss of optical purity (Scheme 14).[42]

Scheme 14: Loss of enantiopurity in the ring-opening of donor-acceptor cyclopropanes[42]



Only by using the fused bicycle **53**, which presumably hinders the bond rotation of the ring-opened intermediate prior to ring closure, could the authors obtain the ring-expanded product **54** with full preservation of the enantiomeric excess (Scheme 15).[42]

Scheme 15: Ring expansion of cyclopropane **53** with the preservation of optical purity[42]



Electrophilic cyclopropanes may similarly lose optical activity by forming an achiral 1,3-zwitterionic intermediate **41** (Scheme 10) during the course of a reaction. Sibi and colleagues found this to be the case in their studies of Lewis-acid catalyzed formal homo-[3+2] cycloaddition reactions between nitrones **55** and activated cyclopropane diesters **56**.[43] Consequently, they used an external chiral source **57** and racemic cyclopropanes **(±)-56** to

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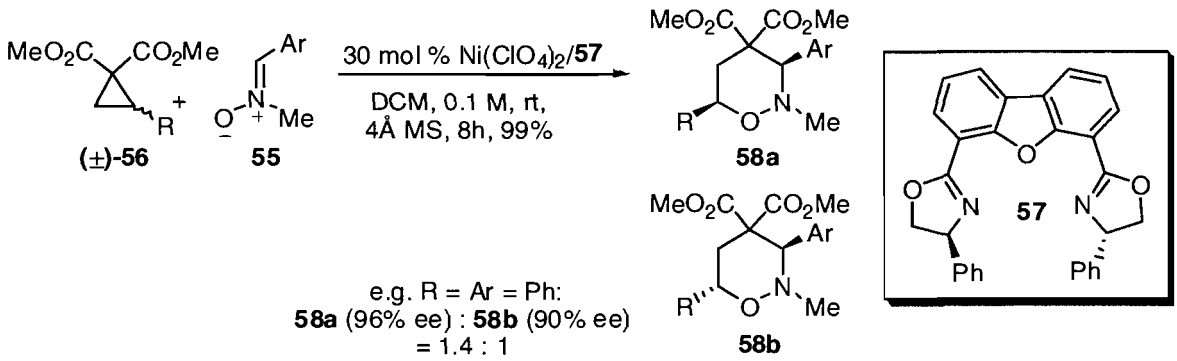
[42] Davies, H. M. L.; Kong, N.; Churchill, M. R. *J. Org. Chem.* **1998**, *63*, 6586.
[43] Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764.

attain high enantioselectivity in the formation of tetrahydro-1,2-oxazines **58**, albeit with low diastereoselectivity (Scheme 16).

Scheme 16: Chiral Lewis acid-catalyzed addition of nitrones to cyclopropane diesters[43]



Kerr and colleagues, who pioneered and extensively studied this formal cycloaddition, showed that the enantiomeric excess of the chiral cyclopropanes **56** could be preserved under their standard conditions of $Yb(OTf)_3$ catalysis, and used this transformation in the total synthesis of two natural products.[44] However, they also showed that the transfer of chirality from the cyclopropane to the cycloaddition product **58a** (exclusive diastereomer formed) was dependent on the reaction temperature and the nature of the cyclopropane substituent.[45] This suggested that under certain conditions, the Lewis acid-induced polarization of the cyclopropanediester **56** (transition state structure **59**) which catalyzes the cycloaddition, partially ring-opened the cyclopropane into a linear zwitterionic intermediate **60** causing loss of optical purity (Scheme 17).

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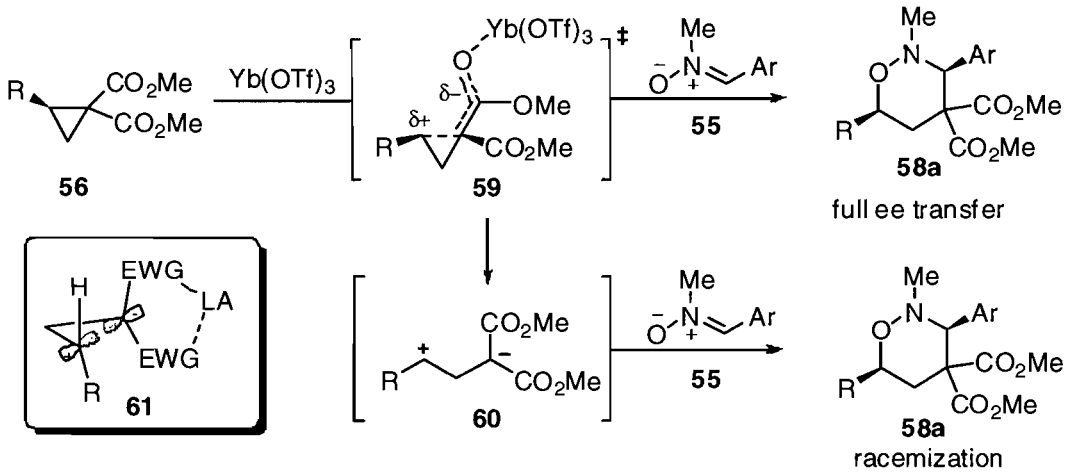
[44] (a) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560; (b) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953-955; (c) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465.

[45] Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597.

Scheme 17: Proposed mechanism of racemization of **58a**[45]



In general, a concerted S_N2 attack on the cyclopropane, without the intermediacy of a ring-opened ionic species, is required for the full transfer of chirality, although configurationally stable carbenium/carbanion pair **61** has been implicated in some ring-opening reactions with high fidelity of chirality transfer.[39b,46] The action of heat, halide ions, certain Lewis and protic acids have all been observed to cause the ring-opening of electrophilic cyclopropanes into achiral zwitterions of type **60**.[38] Careful optimization of these, and other parameters is therefore necessary for effective enantiocontrol.

1.4 Homoconjugate addition to electrophilic cyclopropanes

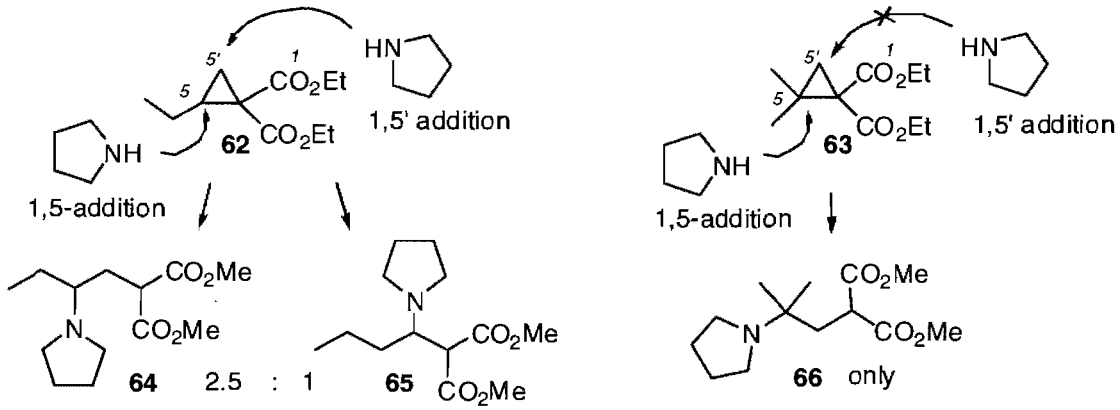
1.4.1 Regio- and stereochemistry of the nucleophilic addition

The close resemblance of electrophilic cyclopropanes to Michael acceptors has led to the formulation of homoconjugate (or 1,5) addition to describe their nucleophilic ring opening into acyclic products.[36] In unsymmetrical cyclopropanes, the bond which is most thermodynamically favoured for cleavage determines the regioselectivity of nucleophilic addition. Thus, cation-stabilizing substituents vicinal to the acceptor groups favour a 1,5-addition over 1,5'-addition (Scheme 18), presumably by conferring greater charge

[46] Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am Chem. Soc.* **2008**, In press: doi: 10.1021/ja8015928

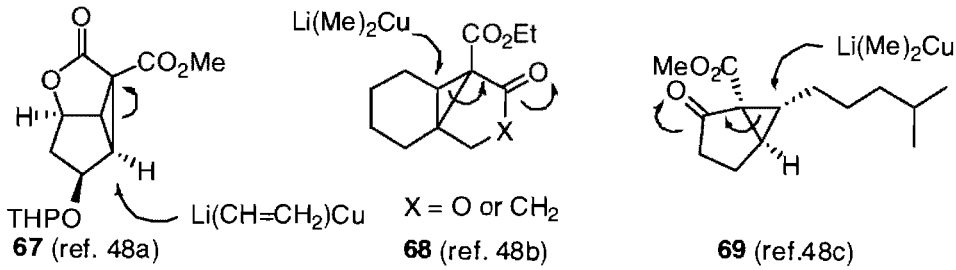
separation on the transition state of the ring-opening reaction.[6c] This trend can be observed, for example, in the nucleophilic addition of pyrrolidine to cyclopropanes **62** and **63** (Scheme 18).[47] Lesser alkyl substitution of **62** led to a 2.5 : 1 mixture of the 1,5-addition product **64** and 1,5'-addition product **65**. In contrast, the more substituted cyclopropane **63** underwent ring-opening exclusively *via* the 1,5-addition (product **66**) despite increased steric hindrance at C-5.

Scheme 18: The predominance of 1,5- vs. 1,5'-addition to electrophilic cyclopropanes[47]



When more than one cation-stabilizing group is present around the cyclopropane ring and/or when the cyclopropane is part of a ring system, the direction of the bond cleavage is more difficult to generalize. The observed regioselectivity in the ring-opening of **67**, **68** and **69**, respectively, has been rationalized on the basis of the best orbital overlap between the cleaved bond and *both* of the acceptor groups (Scheme 19).[48]

Scheme 19: Ring-opening of electrophilic cyclopropanes fused to ring systems[48]



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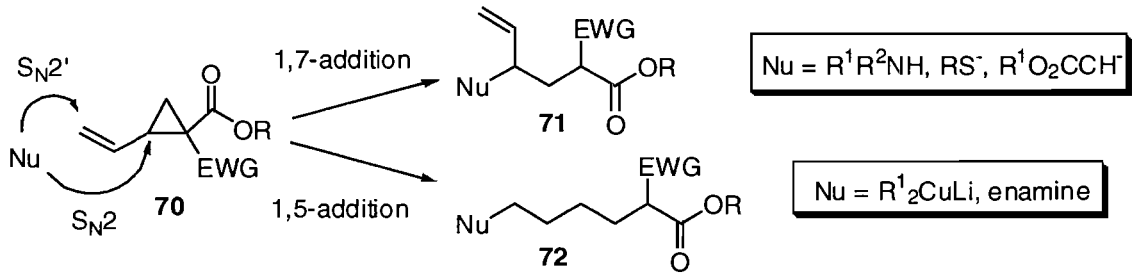
[47] Danishefsky, S.; Rovnyak, G. *J. Org. Chem.* **1975**, *40*, 114.

[48] (a) Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014; (b) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1975**, 526; (c) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3875.

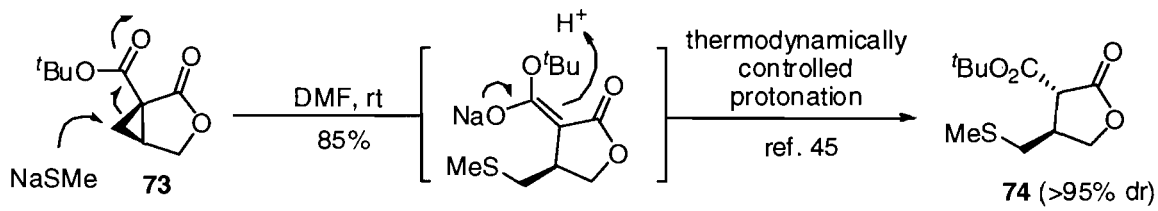
Vinyl-substituted cyclopropanes **70** are a unique class of electrophilic cyclopropanes which contain an alternative conjugated electrophilic site. Depending on the nucleophile, they may undergo a vinylogous 1,7-addition (S_N2') in competition with 1,5-addition (S_N2) (Scheme 20). It has been empirically determined that amine, thiolate and malonate nucleophiles favour the 1,5-addition (product **71**), while cuprates and enamines generally result in an exclusive 1,7-attack (product **72**).[6a]

Scheme 20: Vinylogous (1,7) vs. homo-Michael (1,5) addition to vinyl cyclopropanes[6a]



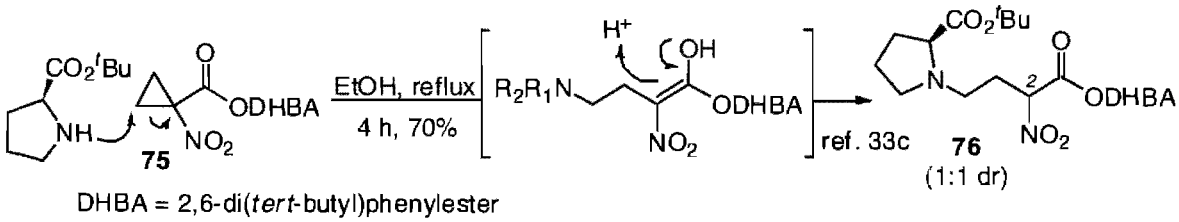
From the stereochemical standpoint, the nucleophilic opening of enantioenriched cyclopropanes by a S_N2 1,5-addition has been shown to result in clean inversion of configuration at the electrophilic carbon.[39,49] The stereochemical outcome of the electrophilic attack by the carbanion formed in the ring-opening is thermodynamically controlled. While bicyclic systems of type **73** tend to be diastereoselective in ring-opening to give a more thermodynamically stable product **74** (Scheme 21),[50] cyclopropanes of type **75** not constrained into a ring system typically give ring-opened products of type **76** as 1:1 diastereomeric mixtures at C-2 (Scheme 22).[38c-e]

Scheme 21: Diastereoselectivity of the cyclopropane ring-opening in polycyclic systems[50]



[49] Cristol, S. J.; Jarvis, B. B. *J. Am. Chem. Soc.* **1967**, *89*, 5885.
[50] Lee, C.-S.; Lee, K.-I.; Hamilton A. D. *Tetrahedron Lett.* **2001**, 211.

Scheme 22: Diastereoselectivity of cyclopropane ring-opening in monocyclic systems[38c]

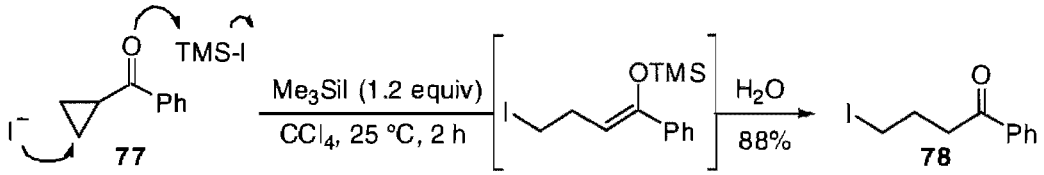


DHBA = 2,6-di(*tert*-butyl)phenylester

1.4.2 The scope of the nucleophilic ring-opening reactions

Within the wide scope of homoconjugate addition reactions to electrophilic cyclopropanes disclosed in the literature, there exist two distinct classes of reactions. The first class includes the reactions of weakly basic nucleophiles bound to strong conjugate Lewis acids. The hard acid initiates the formal nucleophilic addition by reacting with, and thus activating the acceptor substituent of the cyclopropane, while the soft base performs the nucleophilic attack. Examples of such reagents include trimethylsilyl halides, Me_3AlSPh and MeS-$SiMe_3$ where aluminum and silicon act as hard (oxygenophilic) acids and sulfur and iodine are the nucleophilic soft bases.[51] Because the cyclopropane undergoes a reversible electrophilic activation prior to the nucleophilic attack, even cyclopropanes bearing one acceptor group (e.g. **77**) can be ring-opened under mild conditions and in good yield, affording a linear product (e.g. **78**) after an aqueous workup (Scheme 23).[51]

Scheme 23: Addition of hard acid-soft base nucleophiles to electrophilic cyclopropanes[51]



The second class of reactions includes the strictly nucleophilic processes which do not involve a reversible chemical activation of the cyclopropane prior to the nucleophilic attack. Carbon-based nucleophiles such as enolates, as well as heteroatom nucleophiles including alcohols, amines, thiols, selenoates, hydride and halides, and organometallic

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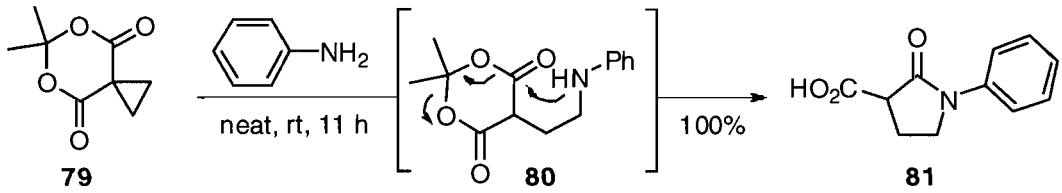
[51] Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2414.

reagents have been reported in this transformation.[6] This class of reactions usually requires more than one acceptor group on the cyclopropane to proceed under relatively mild conditions;[52] and is typically carried out under basic conditions and/or at elevated temperatures.[53] Exceptions are the ring-opening reactions with organometallic reagents which are performed at low temperatures,[54] and the opening of particularly strained cyclopropanes fused to ring systems, which may be activated by only one acceptor group.[6a] In cases where the attacking nucleophile contains more than one lone pair capable of a nucleophilic attack (such as a primary amine), it may further react with a cyclopropane substituent after the ring-opening, resulting in cyclization. For example, the intermediate **80** formed from the ring-opening of cyclopropane **79** with aniline was found to undergo spontaneous cyclization at room temperature to afford the lactam **81** in quantitative yield (Scheme 24).[52]

Scheme 24: Cyclization after nucleophilic ring-opening with dibasic nucleophiles[52]



Expanding the scope of 1,5-homoconjugate addition to new classes of cyclopropanes, while developing mild, efficient and enantioselective ring-opening methodologies represents a useful extension to the existing body of work. This thesis focused on the ring-opening reactions of electrophilic methyl 1-nitrocyclopropanecarboxylates **23** by homoconjugate addition of heteroatom nucleophiles. The following chapter presents the relevant literature background and the development of a method for the ring-opening of cyclopropanes **23** with amine nucleophiles.[55]

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[52] Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239.

[53] For typical conditions, see: (a) Stewart, J. M.; Westberg, H. H. *J. Org. Chem.* **1965**, *30*, 1951; (b) Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1981**, *46*, 4042; (c) O'Bannon P. E.; Dailey, W. P. *Tetrahedron* **1990**, *21*, 7341; (d) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561.

[54] See, for example: (a) Bambal, R.; Kemmitt, R. D. W. *J. Chem. Soc. Chem. Commun.* **1988**, 734; (b) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373.

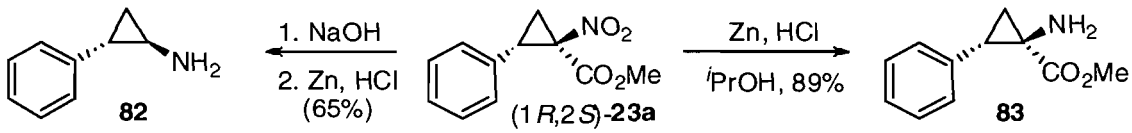
[55] Lifchits, O.; Charette, A. *Org. Lett.* **2008**, *10*, 2809.

Chapter 2: Ring-opening of methyl 1-nitrocyclopropanecarboxylates with amine nucleophiles

2.1 Introduction

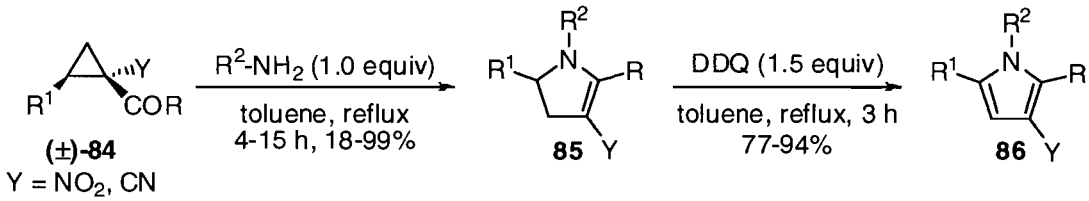
The efficient methodologies developed in our group to generate 1-nitrocyclopropanecarbonyls in both racemic and enantiomerically enriched forms (Sections 1.2.2 and 1.2.3) have been applied to the synthesis of several biologically relevant structures. Moreau and Charette[27a] used the 1-nitrocyclopropanecarboxylate (1*R*,2*S*)-**23a** to synthesize the monoaminooxidase inhibitor tranylcypromine **82** and cyclopropane α-amino ester **83**, an unnatural amino acid analogue used to create β-turns in protein structures[56] (Scheme 25).

Scheme 25: Derivatization of (1*R*,2*S*)-**23a** into biologically active compounds[27a]



Wurz and Charette similarly used racemic methyl and ethyl 1-nitrocyclopropylcarboxylates to synthesize cyclopropane α-amino acids and esters.[23c] Moreover, they demonstrated that the cyclopropyl ketone derivatives (±)-**84** could be ring-opened with amine nucleophiles to generate trisubstituted dihydropyrroles **85** and pyrroles **86** (Scheme 26).[25]

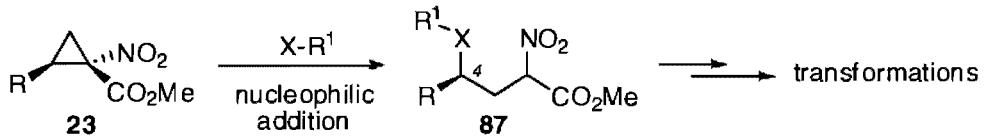
Scheme 26: Synthesis of substituted pyrroles from cyclopropyl ketones[25]



The goal of this work was to further extend the utility of methyl 1-nitrocyclopropanecarboxylates **23** by developing a procedure for their ring-opening with heteroatom nucleophiles (Scheme 27). The generated 1,3-bifunctional compounds **87** represent useful

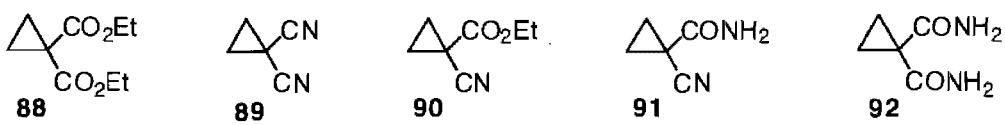
synthetic building blocks, where both the ester and the nitro groups could be subjected to a multitude of further chemical transformations. It was also envisioned that the transfer of the optical purity from the cyclopropane to C-4 of the ring-opened product would grant a practical access to highly enantioenriched heteroatom skeletons, whereby diversity could be readily generated by changing the nucleophile and/or the R-substituent of the cyclopropane. Due to their high reactivity and availability, amines were first chosen as the nucleophiles.

Scheme 27: Functionalization of 1-nitrocyclopropanecarboxylates envisioned in this work



A survey of the literature revealed that the nucleophilic addition of amines to electrophilic cyclopropanes almost invariably required elevated temperature and/or basic conditions. The earliest examples of this transformation were disclosed by Stewart and Westberg, who used the electrophilic cyclopropanes **88-92** (Figure 4) for ring-opening reactions with various nucleophiles.[53a] Addition of the secondary aliphatic amines at 78-102 °C was shown to afford the products in modest yield (~ 40%), while primary aliphatic amines did not undergo the desired addition even under highly forcing conditions. Instead, they preferentially reacted with the acceptor substituents of the cyclopropane.

Figure 4: Cyclopropanes used in the earliest examples of ring-opening with amines[53a]



Danishefsky and colleagues addressed this problem by using the spiroactivated vinylcyclopropane **93** which undergoes facile aminolysis with piperidine at ambient temperature to afford the ring-opened product **94** (Scheme 28, eq. 1).[57] Blanchard and Schneider used an alternative activation strategy, employing a stoichiometric Lewis acid

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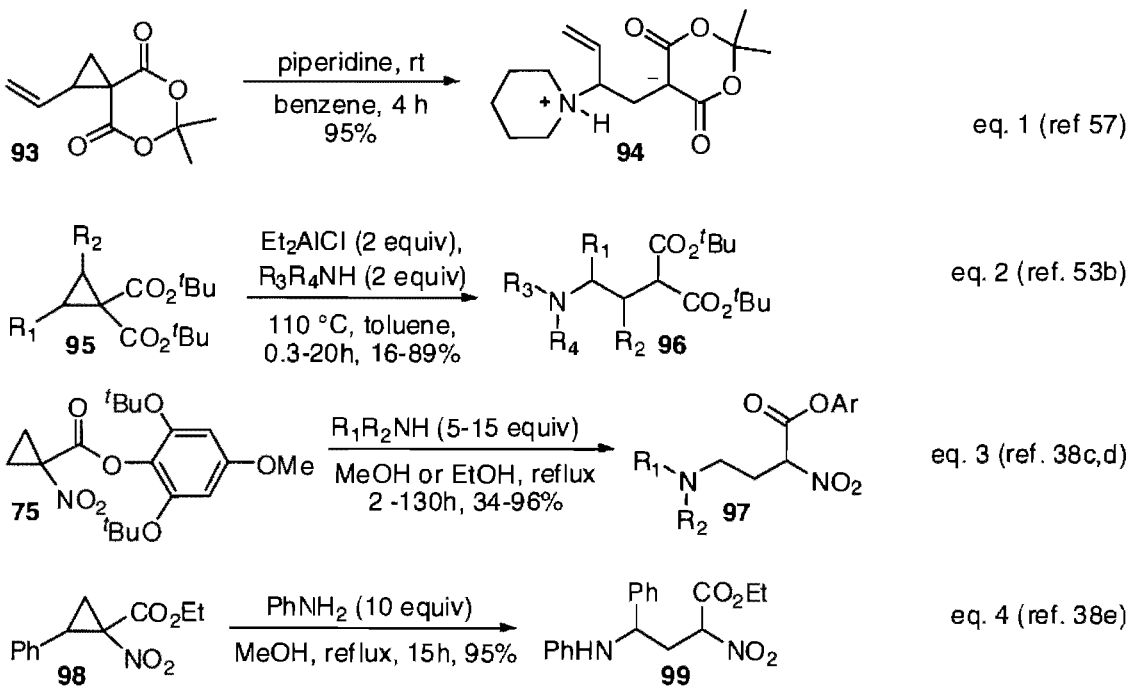
[56] Jimenez, A. I.; Cativiela, C.; Aubry, A.; Marraud, M. *J. Am. Chem. Soc.* **1998**, *120*, 9452.
[57] Danishefsky, S.; Singh, R. K. *J. Org. Chem.* **1975**, *40*, 3807.

$AlEt_2Cl$ to promote the nucleophilic addition of secondary aliphatic amines to 1,1-cyclopropanediesters **95** (Scheme 28, eq. 2).[53b] High reaction temperature (110 °C) was nevertheless required for efficient conversion to **96**. The same reaction temperature was also employed by Magolan and Kerr who used a lanthanide Lewis acid $Y(OTf)_3$ to catalyze the ring-opening of 1,1-cyclopropanediesters **56** (Scheme 16) with indoline.[53d] Nucleophilic ring-opening of more activated 1-nitrocyclopropanearboxylates with amines was first disclosed by Seebach and colleagues.[38c,d] In this report, cyclopropanes **75** were efficiently ring-opened with various aliphatic and aromatic amine nucleophiles to give adducts **97** by refluxing the reaction mixture in methanol or ethanol for 2-21 h (Scheme 28, eq. 3). O'Bannon and Dailey reported a similar transformation with racemic ethyl 1-nitro-2-phenylcyclopropyl-carboxylate **98** which was ring-opened with aniline in refluxing methanol to afford the adduct **99** in 95% yield (Scheme 28, eq. 4).[38e] Apart from the spiroactivated cyclopropanes **93**, the only other example of cyclopropane ring-opening with amines at ambient temperature and neutral conditions was reported with highly activated 2-unsubstituted 1,1-dinitrocyclopropanes.[38b]

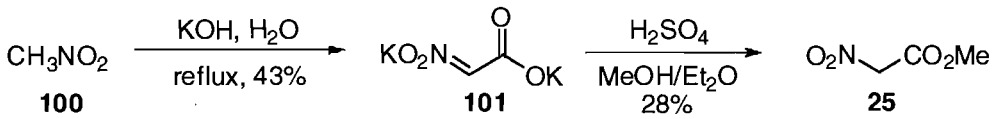
Scheme 28: Precedent for nucleophilic addition of amines to electrophilic cyclopropanes



2.2 Synthesis of the starting materials 23

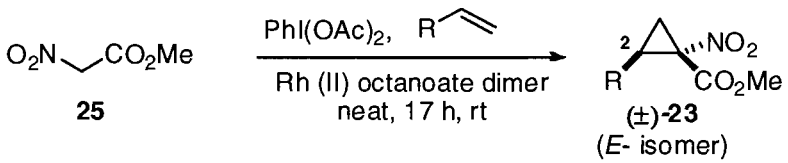
Racemic methyl 1-nitrocyclopropanecarboxylates **23** used for the ring-opening reactions were prepared following the method of Wurz and Charette.[23c] Although the carbenoid precursor methyl nitroacetate **25** is commercially available, its prohibitively high price[58] necessitated a two-step synthesis from nitromethane **100**.[59] Self-condensation of 2 mol of nitromethane in the presence of aqueous KOH furnished dipotassium nitroacetate **101** which was acidified and esterified with methanolic H_2SO_4 to give **25** (Scheme 29).

Scheme 29: Synthesis of methyl nitroacetate **25**



Using **25**, cyclopropanes **(±)-23** bearing various groups at C-2 were synthesized using rhodium octanoate dimer as the catalyst (Table 1). The major *E* diastereomer was separated from the minor Z diastereomer (dr > 90:10) by flash chromatography and used in all ring-opening reactions. Although both racemic diastereomers would afford the same product in a ring-opening reaction, the *E* isomer was used for consistency, since it is formed with higher enantioselectivity in the asymmetric cyclopropanation.[27a]

Table 1: Synthesis of racemic 1-nitrocyclopropylcarboxylates **(±)-23a,d,f**



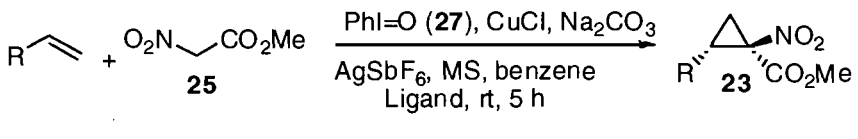
entry	R	product	yield (*E*),% [a]	yield (*Z*),%[a]
1	Ph	**(±)-23a**	63	-
2	*p*-Cl-Ph	**(±)-23d**	65	-
3	CH_2=CH	**(±)-23f**	28	11

[a] Isolated yield

[58] Methyl nitroacetate is commercially available at $99.40/1 g (Sigma-Aldrich, 2007-2008)
[59] Zen, S.; Koyama, M.; Koto, S. *Org. Synth.***1988**, *6*, 797.

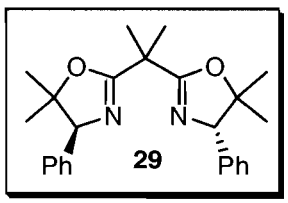
Enantioenriched cyclopropanes **23a** and **23g** were synthesized using the methodology of Moreau and Charette[27a] (Table 2). Despite the reported scalability of the reaction, the enantioenriched cyclopropanes were obtained in consistently poor yields on large scale (3-5 mmol). Attempts to improve the yield by using a water bath to control the reaction temperature and by using different sources of the CuCl and $AgSbF_6$ met with only limited success.

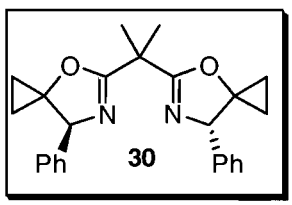
Table 2: Synthesis of enantioenriched 1-nitrocyclopropylcarboxylates **23a** and **23g**



entry	R	ligand	product	yield,% [a]	ee,%
1	Ph	**29**	(1*R*,2*S*)-**23a**	14[c], 24[b,c]	90
2	Ph	***ent*-29**	(1*S*,2*R*)-**23a**	14[c]	92
3	Ph	**30**	(1*R*,2*S*)-**23a**	54	93
4	1-naphthyl	**30**	(1*R*,2*S*)-**23g**	12[c]	92

[a] Isolated yield of the *trans*-diastereomer [b] water bath used to control the reaction temperature [c] Reaction performed on 3-5 mmol scale



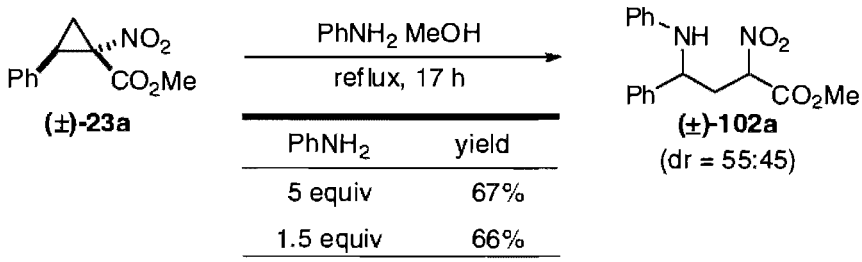


2.3 Ring-opening of cyclopropanes 23 under thermal conditions

2.3.1 Optimization of solvent and temperature

The nucleophilic ring-opening of methyl 1-nitrocyclopropylcarboxylates **23** was first tested under thermal conditions. Since aniline was shown by O'Bannon and Dailey to efficiently ring-open ethyl 1-nitro-2-phenylcyclopropylcarboxylate **98** (Scheme 28),[38e] it was chosen as the nucleophile for optimization studies. Reaction of **(±)-23a** with a five-fold excess of aniline in refluxing methanol afforded the desired ring-opened product **(±)-102a** as a 55:45 mixture of diastereomers with complete conversion and 67% yield (Scheme 30). Lowering the aniline loading to 1.5 equiv did not decrease the efficiency of the reaction, affording the product in 66% yield.

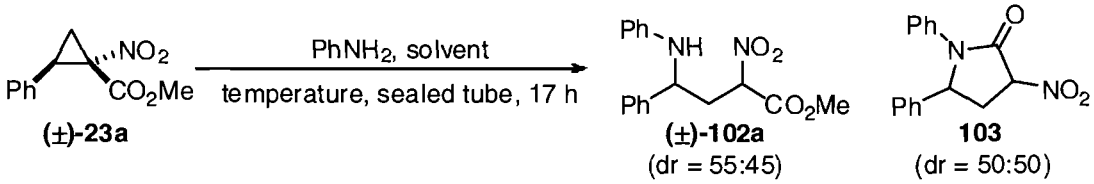
Scheme 30: Optimization of aniline loading in the ring-opening of **(±)-23a**



$PhNH_2$	yield
5 equiv	67%
1.5 equiv	66%

The reaction could also be performed in a sealed tube at 80 °C which gave the product in a slightly improved yield (74%, Table 3, entry 1). Although complete conversion was observed in all cases, the presence of side products necessitated optimization of the solvent and temperature. Different solvents were tested in a sealed tube slightly above their refluxing temperatures (Table 3, all yields determined by ^{1}H NMR). Performing the reaction in low boiling solvents dichloromethane (entry 2) and diethyl ether (entry 3) led to low conversion and yield of the desired product, although no side products were observed. The lowered yield was probably due to an insufficient amount of thermal energy required to weaken the cyclopropane's C-C bond for nucleophilic ring-opening. Dimethylformamide solvent (entry 4) afforded a complex mixture with only traces of the desired product, presumably by participating in the reaction. The reaction in toluene (entry 5) proceeded to full conversion but the desired adduct was obtained in only 38% yield due to the formation of side products including lactam **103** (50:50 dr). An increase in the aniline loading to 3 equiv (entry 6) did not improve yield of the desired product. Performing the reaction in THF (entry 7) led to a clean formation of **(±)-102a** but with incomplete conversion, which could not be improved with increased loading of aniline (entry 8). The best results were obtained by performing the reaction in acetonitrile at 90 °C (entry 10) which afforded **(±)-102a** without any side products and in 88% yield. Essentially the same yield (89%) was obtained when 3 equiv of aniline were used (entry 11), suggesting that a slight excess of nucleophile was sufficient. These results are in accord with the findings of Budynina *et al.* who studied the ring-opening of 1,1-dinitrocyclopropane with various nucleophiles and similarly found acetonitrile to be the optimal solvent.[38b]

Table 3: Optimization of solvent and temperature in the thermal ring-opening of **(±)-23a**



(±)-23a **(±)-102a** (dr = 55:45) **103** (dr = 50:50)

entry	solvent	temp, °C	equiv $PhNH_2$	yield,**(±)-102a** %[a]	notes
1	MeOH	80	1.5	74	minor side products
2	CH_2Cl_2	50	1.5	42	no side products; incomplete conversion
3	Et_2O	50	1.5	32	no side products; incomplete conversion
4	DMF	120	1.5	trace	complex mixture
5	Toluene	120	1.5	38	incomplete conversion; side product **103**
6	Toluene	120	3	31	complete conversion, side product **103**
7	THF	80	1.5	58	no side products; incomplete conversion
8	THF	80	3	68	no side products; incomplete conversoin
9	MeCN	90	1.5	88	clean; complete converson
10	MeCN	90	3	89	clean; complete conversion

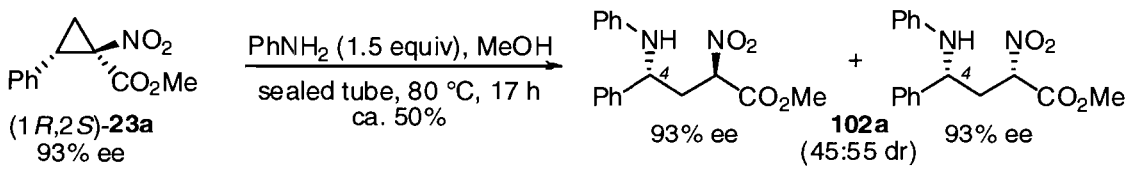
[a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

2.3.2 Preservation of the enantiomeric excess

To test whether the enantiomeric excess of the cyclopropane could be transferred to the acyclic product under thermal conditions, the ring-opening reaction was performed under unoptimized conditions on the enantioenriched cyclopropane (1*R*,2*S*)-**23a** (Scheme 31). Loss of chiral information is possible if the action of heat results in the ring-opening of cyclopropanes into achiral 1,3-zwitterionic intermediate which reacts with the nucleophile by an S_N1 pathway or re-forms the cyclopropane racemically (Section 1.3.4).[6a,45] The ring-

opening of (1*R*,2*S*)-**23a** (93% ee), however, led to complete preservation of the enantiomeric excess at C-4 in **102a** in both diastereomers (Scheme 31).

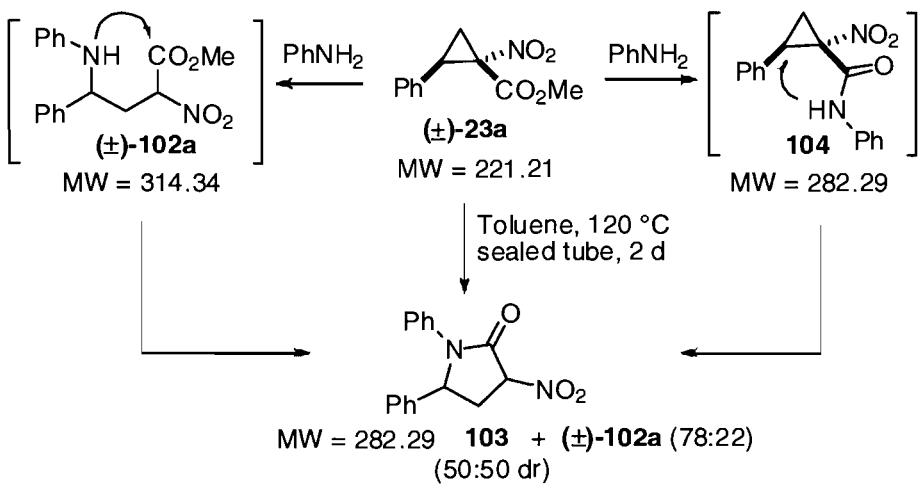
Scheme 31: Preservation of optical purity in the thermal ring-opening of (1*R*,2*S*)-**23a**



2.3.3 Lactamization of the ring-opened product (±)-102a

The formation of the side product **103** (50:50 dr) in the ring-opening reaction of (±)-**23a** with aniline (Table 3, entries 5-6) was briefly explored. This γ-lactam was only observed at temperatures above 120 °C, and is presumably formed by the self-condensation of the ring-opened product (±)-**102a**. Alternatively, the mechanism could involve an initial amidation of the cyclopropane to give **104**, followed by an intramolecular cyclopropane ring-opening (Scheme 32).

Scheme 32: Possible mechanisms for the formation of the side product **103**



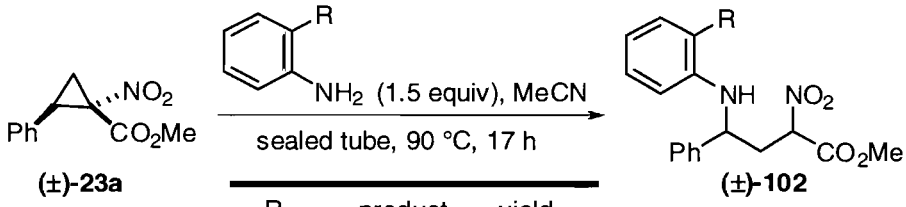
Carrying out the reaction of (±)-**23a** and aniline in toluene at 120 °C afforded an inseparable 78:22 mixture of **103**:(±)-**102a** after 48 h (Scheme 30). TLC and mass spectrometry control over time showed the presence of (±)-**102a** before any formation of the γ-lactam **103**, while the presence of an intermediate **104** was not observed by TLC.

These observations support lactamization occurring after the ring opening. In an effort to encourage lactamization, the reaction was carried out in the presence of 4Å molecular sieves to scavenge methanol formed in the condensation; however, only a complex mixture was obtained.

2.3.4 Addition of a hindered aniline

Carrying out the thermal ring-opening of **(±)-23a** with aniline under the optimized conditions cleanly afforded the addition product **(±)-102a** in 86% isolated yield. However, when a more sterically hindered *o*-bromoaniline was used, the desired product **(±)-102b** was obtained in a disappointing 37% conversion and 15% yield after 17 h (Scheme 33).

Scheme 33: Addition of a hindered aniline to **(±)-23a** under thermal conditions



R	product	yield
H	**(±)-102a**	86%
Br	**(±)-102b**	15%

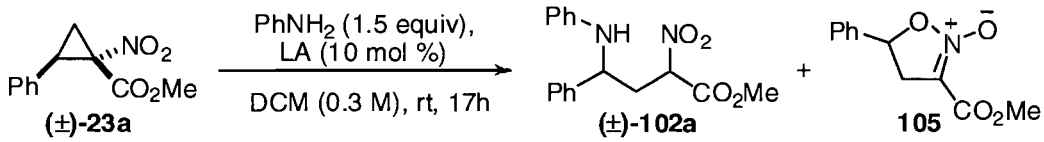
While the use of higher temperature and/or a base catalyst could potentially solve the problem of poor reactivity with hindered nucleophiles, harsh reaction conditions would diminish the synthetic utility of the transformation. Instead, a Lewis acid-catalyzed version of the reaction was envisioned, which could sufficiently activate the cyclopropane toward a nucleophilic attack. Lewis acid-catalyzed nucleophilic ring-opening of cyclopropanes **23** at ambient temperature would serve as a very mild extension to the existing thermal methodologies.

2.4 Lewis acid-catalyzed ring-opening of cyclopropanes 23

2.4.1 Lewis acid screening

Kerr and colleagues have shown that the bidentate Lewis acid $Yb(OTf)_3$ efficiently activates 1,1-cyclopropanediesters toward [3+2] cycloadditions[33b,37a,c,44a,b,45] and homo-conjugate addition by indoline,[53d] presumably by coordinating to both of the carbonyl groups of the cyclopropane. Since cyclopropanes **23** similarly contain two Lewis basic acceptor groups, $Yb(OTf)_3$ as well as triflate salts of other group III metals were tested as catalysts in the nucleophilic ring-opening of **(±)-23a** at ambient temperature (Table 4). As a control, the reaction was also performed in the absence of a Lewis acid under otherwise identical conditions. Anhydrous dichloromethane solvent and an atmosphere of argon were initially employed. When no Lewis acid was present (Table 4, entry 1), the reaction afforded the ring-opened product with 35% conversion after 17 h and no side products. Using 10 mol % of $Yb(OTf)_3$, **(±)-102a** was obtained with a similar conversion of 31% (entry 2), suggesting a lack of catalysis. The reaction with 10 mol % $Y(OTf)_3$ (entry 3) gave **(±)-102a** with a slightly better conversion (44%) in addition to 6% of a novel side product **105**. The presence of catalytic $Sc(OTf)_3$ (entry 4) resulted in an exclusive formation of **105** with full consumption of the starting cyclopropane.

Table 4: Screen of the Group III metal Lewis acids in the catalytic ring-opening of **(±)-23a**



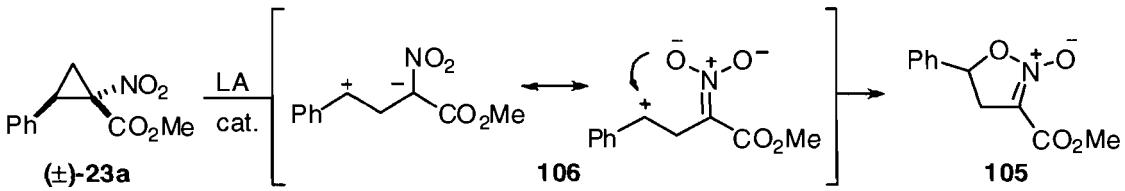
entry	Lewis acid	(±)-23a, %	(±)-102a, %	105, %[a]
1	none	65	35	0
2	$Yb(OTf)_3$	69	31	0
3	$Y(OTf)_3$	50	44	6
4	$Sc(OTf)_3$	0	0	100

[a] Determined by ^1H NMR of the crude reaction mixture

The isoxazoline *N*-oxide **105** is presumably formed by the Lewis acid-catalyzed ring-opening of **(±)-23a** into a zwitterionic intermediate **106** which cyclizes by the attack of the

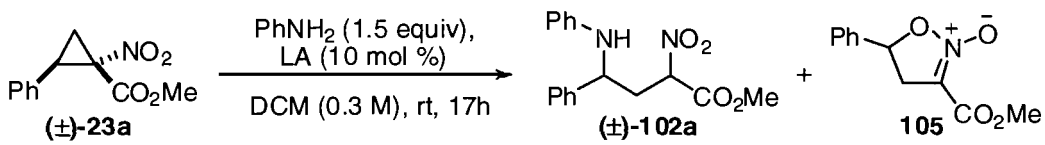
oxygen in the nitro group on the carbocation (Scheme 32).[38]

Scheme 34: Proposed mechanism for the formation of rearrangement product **105** [38]



The undesired formation of **105** was nevertheless encouraging, since it suggested that the scissile bond of **(±)-23a** was amenable to Lewis acid activation. It was reasoned that the formation of the ring-opened product **102** could be favoured over rearrangement into **105** by adjusting the relative activating strength of the Lewis acid. A further screen of common Lewis acids with different activating strengths[37b,c] and coordination number was consequently performed (Table 5).

Table 5: Further screen of Lewis acids in the catalytic the ring-opening of **(±)-23a**



entry	Lewis acid	**(±)-23a**,%	**(±)-102a**, %	**105**, %[a]
1	$SnCl_4$	0	0	100
2	$AlCl_3$	13	21	66
3	$BF_3 \cdot Et_2O$	40	38	22
4	$ZnCl_2$	60	40	0
5	$Ti(O^iPr)_4$	65	35	0
6	none	65	35	0
7	$Cu(OTf)_2$	45	48	7
8	$Ni(ClO_4)_2 \cdot 6H_2O$	10	87	3

[a] Determined by ^1H NMR of the crude reaction mixture

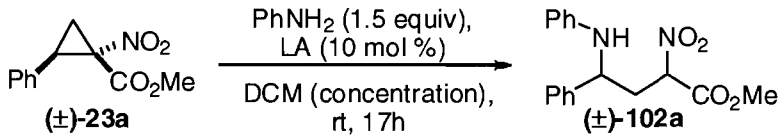
The bidentate Lewis acid $SnCl_4$ (Table 5, entry 1) proved to be highly activating, causing a complete rearrangement of the cyclopropane into isoxazoline *N*-oxide **105**. A slightly less activating bidentate $AlCl_3$ (entry 2) afforded 66% of the rearrangement product **105**, in

addition to 21% of the desired adduct **(±)-102a**. Monodentate $BF_3{\cdot}Et_2O$ (entry 3) gave the desired product **(±)-102a** with an improved 38% conversion, but with a significant amount of the rearrangement product **105**. In contrast, weakly activating bidentate Lewis acids zinc chloride (entry 5) and titanium tetraisopropoxide (entry 6) gave only the ring-opened adduct **(±)-102a** with low conversion which was similar to an uncatalyzed reaction (entry 7). $Cu(OTf)_3$ catalysis (entry 8) gave the desired product with 48% conversion along with 7% of the rearrangement product **105**. The optimal Lewis acid was found to be $Ni(ClO_4)_2{\cdot}6H_2O$ (entry 9), which afforded the desired addition product with 87% conversion along with 3% of the isoxazoline *N*-oxide **105**.

2.4.2 Optimization of reaction conditions

While repeating the reaction with catalytic $Y(OTf)_3$ on a small scale and under a non-static atmosphere of argon, it was noticed that the results varied between different trials. The lack of reproducibility was attributed to the loss of volatile dichloromethane solvent, leading to significant changes in the reaction concentration. Consequently, the reaction was tested under different concentrations alongside a control reaction with no Lewis acid (Table 6). In order to ensure that no solvent loss occurred, the reactions were performed in microwave vials sealed with a Teflon cap.

Table 6: The effect of reaction concentration in the catalytic the ring-opening of **(±)-23a**



(±)-23a **(±)-102a**

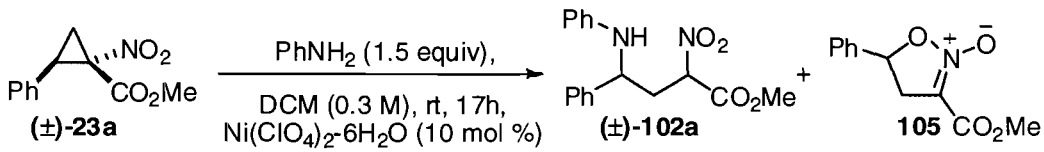
entry	Lewis acid	concentration, M	Conversion, %[a]
1	none	0.75	6
2	none	2.3	26
3	$Y(OTf)_3$	0.2	26
4	$Y(OTf)_3$	0.75	39
5	$Y(OTf)_3$	2.3	81
6	$Ni(ClO_4)_2{\cdot}6H_2O$	2.3	94

[a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard

The positive effect of the concentration was observed for both catalyzed and non-catalyzed reactions. In the absence of a Lewis acid, the nucleophilic ring-opening of **(±)-23a** afforded the product **(±)-102a** with only 6% conversion at 0.75 M (entry 1), but with 26% conversion at 2.3 M (entry 2). The same held true for $Y(OTf)_3$-catalyzed reaction which afforded the product with 26% conversion at 0.25 M (entry 3), 44% conversion at 0.75 M (entry 4) and 81% conversion at 2.3 M (entry 5). When the optimal reaction concentration of 2.3 M was used with the best Lewis acid $Ni(ClO_4)_2 \cdot 6H_2O$ (Table 5), the desired product **(±)-102a** was obtained cleanly with 94% conversion and none of the rearranged product **105** (Table 6, entry 6).

Perrault *et al.* who employed $Ni(ClO_4)_2 \cdot 6H_2O$ for homo-[3+2] cycloaddition between *N*-iminoquinolinium ylides and 1,1-cyclopropanediesters found that 3Å molecular sieves (MS) in the reaction mixture gave superior results.[37b] Surprisingly, the addition of 3Å MS to the optimized reaction conditions changed the nature of the Lewis acid dramatically (Table 7). Only the rearrangement product **105** was obtained after 1 h in the absence of aniline (entry 2), and a sluggish conversion to **(±)-102a** was observed in the presence of aniline (entry 3).

Table 7: The effect of 3Å molecular sieves in the optimized reaction conditions



entry	Additive	$PhNH_2$, equiv	**(±)-23a**,%	**(±)-102a**, %	**105**, %[a]
1	none	1.5	6	94	0
2	3Å mol. sieves	0	0	0	100[b]
3	3Å mol. sieves	1.5	45	55	0

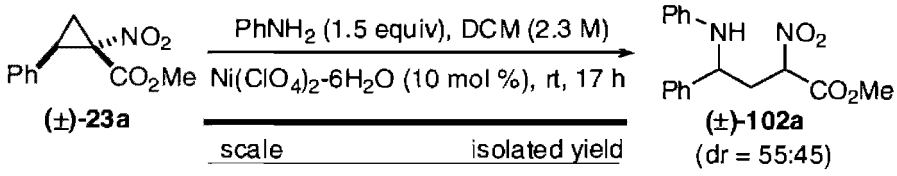
[a] Determined by ^1H NMR of the crude reaction mixture
[b] Reaction time 1 h

To determine whether molecular sieves themselves could catalyze cyclopropane ring-opening, **(±)-23a** was stirred with 3Å MS alone, and with 3Å MS in the presence of 60 mol % of water. In both cases, however, only unchanged starting material was recovered after 48 h. The results in Table 7 suggest that the molecular sieves may remove one or more

aqua ligands from the Ni-metal center, creating a Lewis acid with different catalytic properties. Aniline could further act as a ligand, thus changing the nature of $Ni(ClO_4)_2$ as a catalyst, as well as reducing its own reactivity toward cyclopropane ring-opening.

Using the optimized reaction conditions, the Lewis acid-catalyzed addition of aniline to (±)-**23a** at ambient temperature was performed on 50 mg and 0.2 g scale under non-anhydrous conditions and an atmosphere of air (Scheme 35). Both reactions cleanly afforded the desired product (±)-**102a** in good isolated yield (81-82%).

Scheme 35: Lewis acid-catalyzed addition of aniline to (±)-**23a** under optimized conditions



scale	isolated yield
0.2 mmol (50 mg)	82%
1 mmol (0.2 g)	81%

2.4.3 Reaction scope: addition of aromatic amines

With the optimal conditions in hand, the substrate scope was examined, first using various aromatic amines **107** (Table 8). The reaction with aniline was repeated on an enantioenriched cyclopropane (1*R*,2*S*)-**23a** (92% ee) to determine if the cyclopropane's enantiomeric excess could be efficiently transferred to the acyclic product under Lewis acid catalysis. Indeed, the desired product **102a** was obtained in 82% yield and with complete preservation of the cyclopropane's enantiomeric excess at C-4 (Table 8, entry 1). Gratifyingly, the reaction of (±)-**23a** with the sterically hindered *o*-bromoaniline worked equally well, affording the ring-opened product in 83% yield (entry 2). Secondary aromatic amines (entries 6, 9) gave the ring-opened product in good to excellent yields, as did electron-rich (entry 7) and halogen-substituted (entries 2, 4) aniline derivatives. As expected, the electron-poor *p*-nitroaniline **107g** (entry 8) resulted in a slower reaction, but full conversion was achieved after 48 h, with an excellent isolated yield. Boc-protected amine **107d** was found to be stable to the reaction conditions, allowing for the introduction of a second amine functionality (entry 5), which could potentially be deprotected and

further derivatized. Varying the substituents at the 2-position of the cyclopropane to a naphthyl (entry 3), *p*-chlorobenzyl, indenyl and vinyl groups (entries 10,11,12) also gave the addition products in good yields. In all cases, the reactions proceeded with complete regioselectivity: only addition at the benzylic or allylic position (1,5-attack) was observed with all cyclopropane substrates. No 1,7-vinylogous addition products were detected in the ring-opening of **(±)-23f** with aniline (entry 12).

Table 8: Scope of the nucleophilic ring-opening of cyclopropanes **23** with aromatic amines

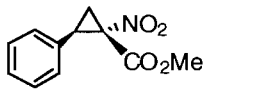
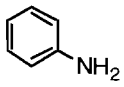
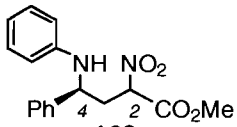
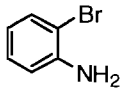
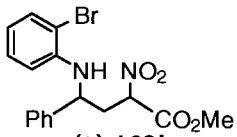
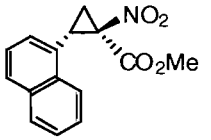
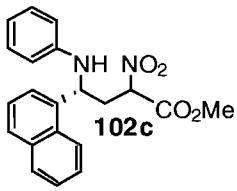
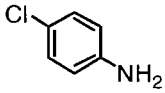
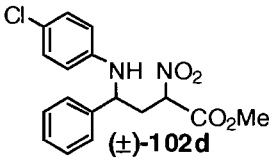
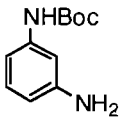
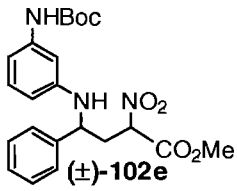
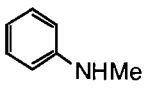
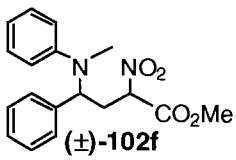
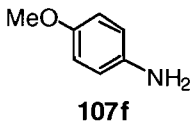
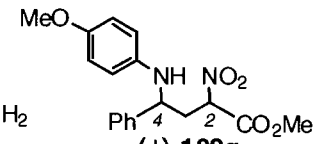
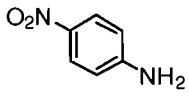
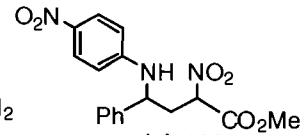
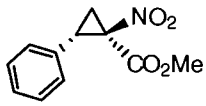
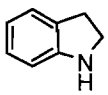
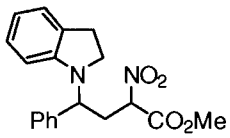
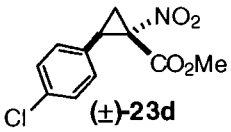
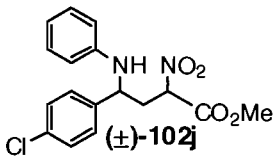
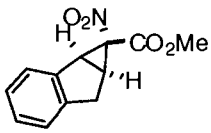
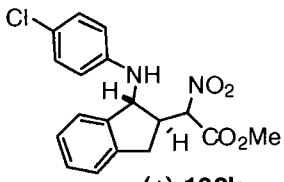
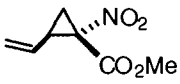
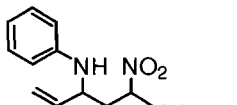
entry	cyclopropane (ee,%)	amine	product	yield,%[a,b]	ee,%[c]	dr
1	 (1*S*,2*R*)-**23a** (92)	 **107a**	 **102a**	82	92	55:45
2	**(±)-23a**	 **107b**	 **(±)-102b**	83	-	50:50
3	 (1*R*,2*S*)-**23g** (92)	**107a**	 **102c**	73	92	55:45
4	**(±)-23a**	 **107c**	 **(±)-102d**	86	-	50:50
5	**(±)-23a**	 **107d**	 **(±)-102e**	66	-	50:50
6	**(±)-23a**	 **107e**	 **(±)-102f**	80	-	55:45

Table 8: Scope of the nucleophilic ring-opening of 23 with aromatic amines (cont'd)

entry	cyclopropane (ee,%)	amine	product	yield,%[a,b]	ee,%[c]	dr
7	**(±)-23a**	 **107f**	 **(±)-102g**	71	-	50:50
8	**(±)-23a**	 **107g**	 **(±)-102h**	92[d]	-	50:50
9	 (1*R*,2*S*)-**23a** (90)	 **107h**	 **102i**	94	90	55:45
10	 **(±)-23d**	**107a**	 **(±)-102j**	74	-	50:50
11	 **(±)-23c**	**107c**	 **(±)-102k**	78	-	70:30
12	 **(±)-23f**	**107a**	 **(±)-102l**	76	-	50:50

[a] Reaction conditions: **23** (1 equiv), **107** (1.5 equiv), $Ni(ClO_4)\cdot 6H_2O$ (10 mol %), DCM (2.3 M), rt, 17 h. [b] Yield of isolated product. [c] Determined by SFC with a chiral stationary phase [d] Reaction time 48 h.

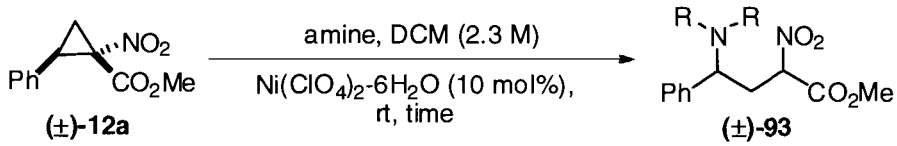
A mixture of diastereomers at C-2 was obtained with all substrates, in approximately 1:1 ratio, except for the product **(±)-102k** (70:30 dr, entry 11). When enantioenriched cyclopropanes were used as starting materials (entries 1, 3, 9), the reactions proceeded with a complete preservation of the enantiomeric excess at C-4. Upon crystallization,

102a underwent a self-catalyzed enrichment of the diastereomeric ratio at C-2 to 85:15 as indicated by ^{1}H NMR analysis of a freshly prepared solution of the crystallized solid in $CDCl_3$. When left in solution at room temperature, however, **102a** re-equilibrated to 51:49 dr within several hours. This suggests that the inseparable diastereomers of **102** probably interconvert under neutral conditions.

2.4.4 Reaction scope: addition of aliphatic amines

The nucleophilic addition of aliphatic amines to **(±)-23a** was next tested under the optimized reaction conditions. Despite being more nucleophilic than aniline derivatives, aliphatic amines were found to be significantly less reactive, presumably due to a strong complexation of $Ni(ClO_4)_2{\cdot}6H_2O$ to the Lewis basic nitrogen. This complexation was evident by the change in the colour of the reaction mixture and by the complete dissolution of catalytic $Ni(ClO_4)_2{\cdot}6H_2O$ which is otherwise only sparingly soluble in dichloromethane. Table 9 shows the results for the ring-opening reactions of several aliphatic amines and their optimization. As a control, a reaction with aniline using the same source of $Ni(ClO_4)_2{\cdot}6H_2O$ was performed, which afforded the product with the expected 92% yield (entry 1). Sterically hindered diisopropylamine failed to give the desired product under the standard conditions (entry 2) and with higher amine loading and longer reaction times (entries 3,4). Addition of diethyl amine gave <10% of the desired product **(±)-102n** with 1.5 equiv of the nucleophile after 17 h (entry 5), but afforded **(±)-102n** in good yield (76%) using a higher amine loading and longer reaction time (entry 6). More nucleophilic piperidine gave the product **(±)-102o** with incomplete conversion and a 30% yield under the standard conditions (entry 7), but in synthetically useful 63% yield with longer reaction time (entry 8). Reaction with pyrrolidine yielded only 45% of the desired product under the optimized conditions (entry 9). Increasing the reaction time led to better conversion, but a partially inseparable impurity was concomitantly formed, giving the impure product **(±)-102p** in approximately 63% yield (entry 10). However, clean formation of **(±)-102p** in 90% yield could be achieved by increasing the amine loading and using a shorter reaction time (entry 11).

Table 9: Scope of the nucleophilic ring-opening of **(±)-23a** with aliphatic amines

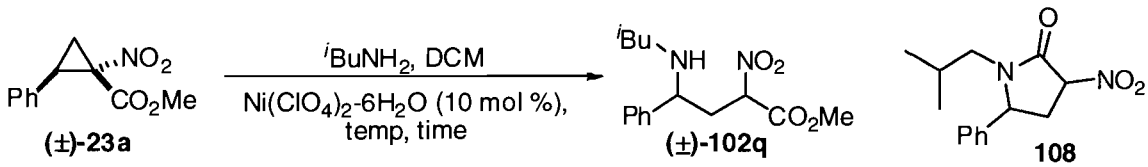


(±)-12a **(±)-93**

entry	amine	equiv	time,h	product	Yield, %	entry	amine	equiv	time,h	product	Yield, %
1	$PhNH_2$	1.5	17	**(±)-93a**	92	7	piperidine	1.5	17	**(±)-93o**	30
2	$^iPr_2NH$	1.1	17	**(±)-93m**	0	8	piperidine	1.5	48	**(±)-93o**	63
3	$^iPr_2NH$	2.1	17	**(±)-93m**	0	9	pyrrolidine	1.5	17	**(±)-93p**	45
4	$^iPr_2NH$	2.1	24	**(±)-93m**	0	10	pyrrolidine	1.5	72	**(±)-93p**	~63
5	Et_2NH	1.5	17	**(±)-93n**	<10%	11	pyrrolidine	2.1	24	**(±)-93p**	90
6	Et_2NH	2.1	30	**(±)-93n**	76						

Addition of the primary isobutylamine using various reaction times, amine loadings and reaction temperatures (Table 10, entries 1-7) only led to complex mixtures with <10% of the desired product **(±)-102q** and multiple side products including lactam **108**. Using 10 equiv of $^iBuNH_2$ and 1 equiv of $Ni(ClO_4)_2 \cdot 6H_2O$, **108** could be isolated in 43% yield (entry 6).

Table 10: Addition of isobutylamine to **(±)-23a**



(±)-23a **(±)-102q** **108**

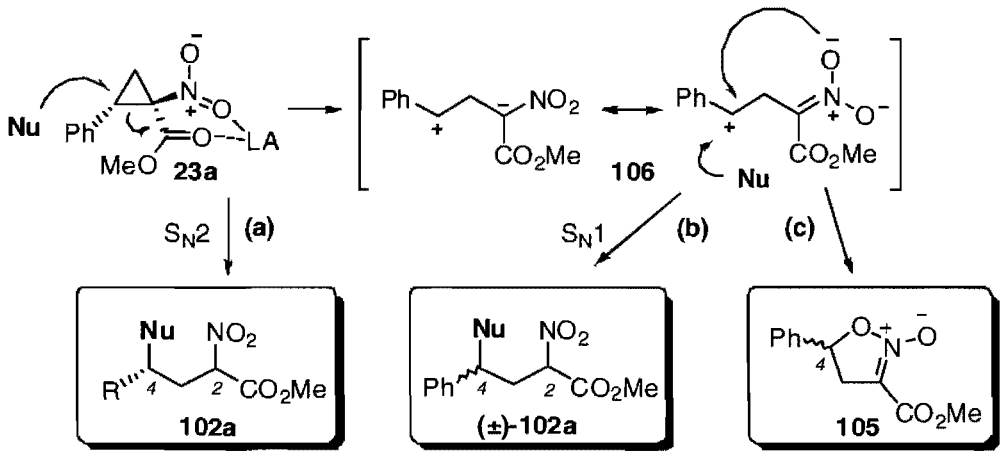
entry	equiv $^iBuNH_2$	time, h	temp, °C	conc, M	Yield **(±)-102q**,%	entry	equiv $^iBuNH_2$	time, h	temp, °C	conc, M	Yield **(±)-102q**, %
1	1.5	17	rt	2.3	trace	5	2	17	rt	0.45	<10 + **108**[a]
2	1.5	72	rt	2.3	<10 + **108**	6	5	17	rt	0.45	<10 + **108**[a]
3	2.1	24	rt	2.3	<10 + **108**	7	7	17	rt	0.45	<10 + **108**[a]
4	2.1	17	60	2.3	<10	8	10	17	rt	0.45	43 (**108**)[a]

[a] 1 equiv of $Ni(ClO_4)_2 \cdot 6H_2O$ used

2.4.5 Mechanistic insight

Based on the observed products, three mechanistic pathways can be envisioned for the Lewis acid-catalyzed ring-opening of the cyclopropanes **23**. Depending on the strength of the Lewis acid activation, the scissile C-C bond of the cyclopropane may be activated toward a S_N2 attack[39a] (Scheme 36, pathway a) or cleaved into a zwitterionic intermediate **106**, which can combine with a nucleophile by an S_N1 process (pathway b) or rearrange into **105** (pathway c).

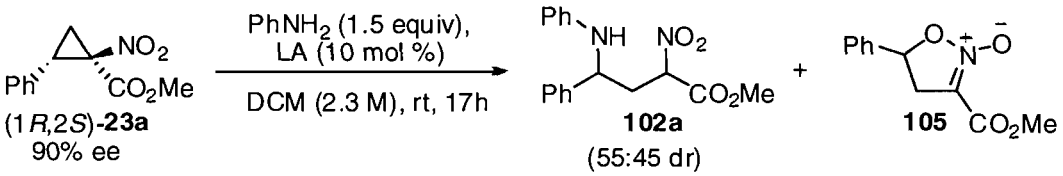
Scheme 36: Possible mechanisms of (bidentate) Lewis acid-catalyzed ring-opening of **23**



While pathway (a) should result in full transfer of the enantiomeric excess from the cyclopropane to the acyclic product **102** at C-4, pathways (b) and (c) would be expected to result in racemization at this center. To test this hypothesis, the enantioenriched cyclopropane (1*R*,2*S*)-**23a** was subjected to the ring-opening reactions with several Lewis acids of varying strength, and the enantiomeric excess of the products **102a** and **105** was measured (Table 11). In the absence of a Lewis acid (entry 1), the nucleophilic addition product **102a** was obtained with 26% conversion and a full preservation of the cyclopropane's enantiomeric excess (90% ee). The fidelity of ee transfer and the absence of any rearrangement product **105** suggest that the uncatalyzed reaction proceeds exclusively by pathway (a). In contrast, the only rearrangement product **105** obtained from the $SnCl_4$-catalyzed reaction was nearly racemic (10% ee, entry 2). Presumably, a strongly activating Lewis acid catalyzes the ring-opening of (1*R*,2*S*)-**23a** into the achiral intermediate **106**

which experiences significant bond rotation before cyclizing to form **105**. When the less activating $AlCl_3$ was used as a Lewis acid (entry 3), the rearranged product **105** was obtained with 64% conversion and a similar loss of optical purity (20% ee). Interestingly, the concurrently formed addition product **102a** was obtained with 23% conversion and no loss of the enantiomeric excess (90% ee), ruling out pathway (b). Instead, the low conversion to **102a** suggests that it was formed by an uncatalyzed process. Presumably, the intramolecular cyclization of the zwitterion **106** into isoxazoline *N*-oxide **105** (pathway c) occurs significantly faster than an S_N1 reaction with a nucleophile (pathway b), so that the only way by which **102a** can form is through an uncatalyzed S_N2 attack on (1*R*,2*S*)-**23a**. Reaction with catalytic $Ni(ClO_4)_2{\cdot}6H_2O$ (entry 4) afforded only **102a** with excellent conversion and full preservation of the cyclopropane's optical activity. This suggests that $Ni(ClO_4)_2{\cdot}6H_2O$ catalyzes an S_N2 nucleophilic ring-opening (pathway a) by polarizing, but not cleaving, the cyclopropane's scissile bond.

Table 11: Transfer of optical purity from cyclopropane **23a** to products **102a** and **105**



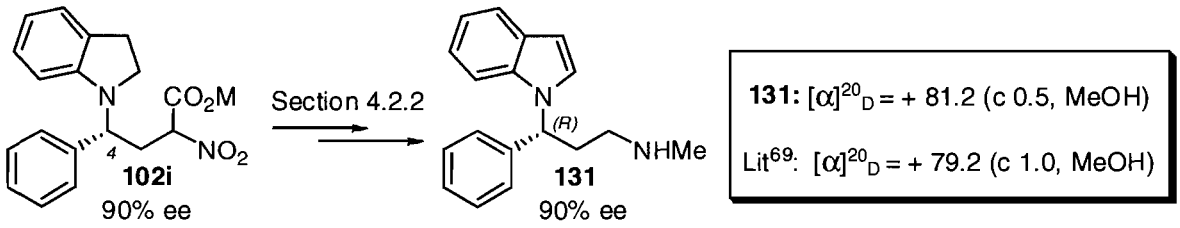
entry	Lewis acid	(±)-**23a**,% recovered	**102a**, % conv.[a]	ee[b]	**105**, %[a] conv.[a]	ee[b]
1	none	73	26	90	0	-
2	$SnCl_4$	0	0	-	100	10
3	$AlCl_3$	13	23	90	64	20
4	$Ni(ClO_4)_2$-$6H_2O$	0	94	90	0	-

[a] Determined by ^1H NMR of the crude reaction mixture [b] Determined by SFC with a chiral stationary phase

As a further proof of this mechanism, the expected stereoselective inversion of the absolute configuration at C-4 was proven by converting **102i** (90% ee) to a known compound **131** (90% ee) and comparing its optical rotation to the literature value[70] (Scheme 37, Section

4.2.2). The positive sign of the optical rotation confirmed the (*R*)-configuration of **131** and hence the (*R*)-configuration of **102i** at C-4, which is in accord with an S_N2 mechanism.

Scheme 37: Determination of the absolute configuration of **102i**

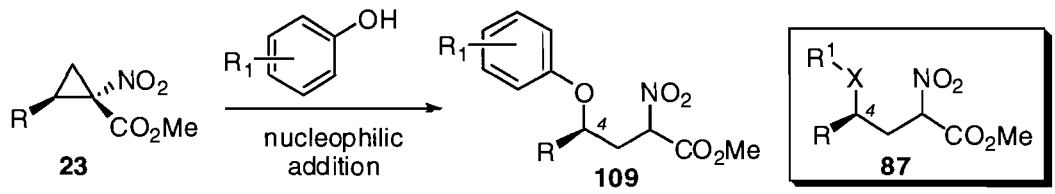


Chapter 3: Ring-opening of 1-methyl nitrocyclopropane-carboxylates with phenol derivatives

3.1 Introduction

The diversity of the heterocyclic skeletons **87** generated from the ring-opening of cyclopropanes **23** can be readily expanded by using different types of nucleophiles. Like aniline derivatives, aromatic alcohols are a useful class of reagents due to their wide availability and good nucleophilicity as phenolate anions. Ring-opening of cyclopropanes **23** with phenol derivatives would result in the formation of substituted ethers of type **109** (Scheme 38).[60] This transformation was also envisioned to proceed with complete transfer of the optical purity from the cyclopropane to C-4 of the ring-opened product **109**.

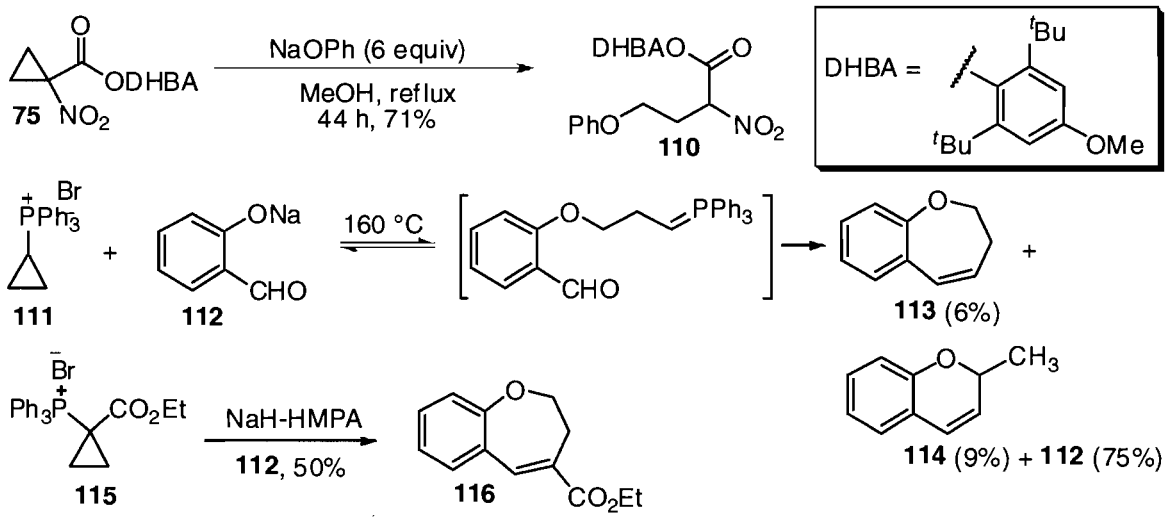
Scheme 38: The envisioned ring-opening of **23** with phenol derivatives



[60] Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**. *In press.*

Although the addition of aliphatic alcohols to electrophilic cyclopropanes to generate alkoxybutanoates (e.g. **117**, **118**, Scheme 40) is well precedented,[6a,39b,d,39e,b] only a few reports in the literature disclose the nucleophilic ring-opening with phenol derivatives. Seebach *et al.* showed that sodium phenoxide can ring-open cyclopropane **75** in refluxing methanol, giving the desired addition product **110** in 71% yield after 44 h (Scheme 39).[38d] Schweizer and colleagues[61] reported a ring-opening of cyclopropylphosphonium **111** with sodium 2-formylphenolate **112** which was followed by a tandem Wittig olefination (Scheme 39). A mixture of the cycloalkenylation products **113** and **114** was obtained in a very modest yield, likely due to the difficulty of ring-opening a monoactivated cyclopropane.[62] Fuchs improved this procedure by using a diactivated cyclopropane **115** which underwent facile ring-opening by 2-formylphenolate **103** before cyclizing *via* a Wittig reaction to give **116** in 50% yield (Scheme 39).[62]

Scheme 39: Addition of phenol derivatives to electrophilic cyclopropanes[38d,61,62]



Addition of alcohols to 1-nitrocyclopropanecarboxylates **75** and **98** was demonstrated by Seebach[38d] and Dailey,[38e] who used sodium methoxide and methanol, respectively, to obtain the corresponding ethers **117** and **118** in excellent yields although with somewhat lengthy reaction times (Scheme 40).

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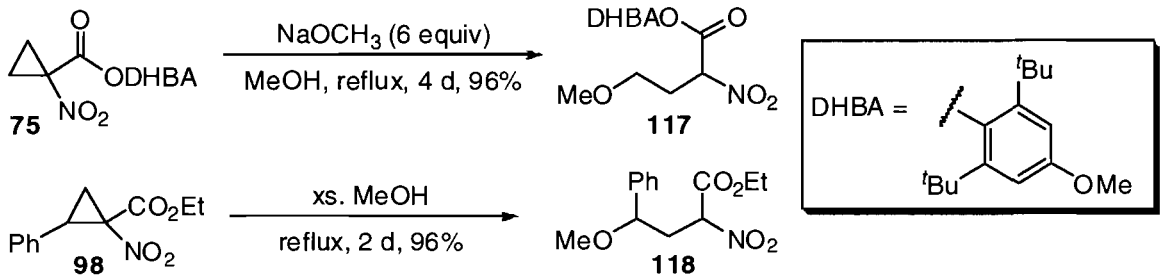
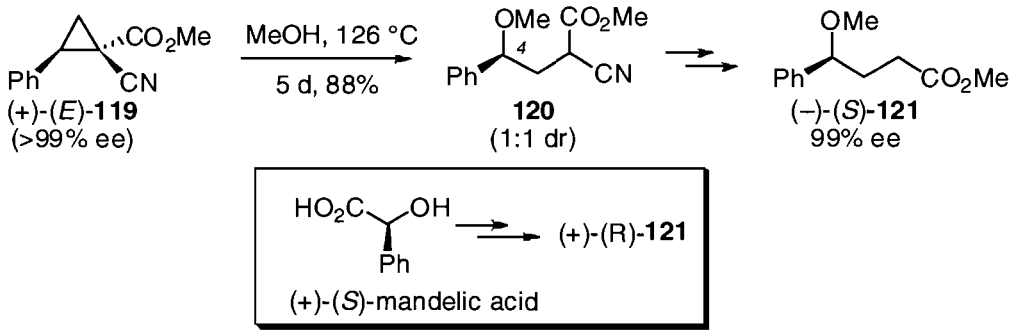
[61] Schweizer, E. E.; Berniger, C. J.; Thompson, J. G. *J. Org. Chem.* **1968**, *33*, 336.

Scheme 40: Methanolysis of 1-nitrocyclopropylcarboxylates[38d,e]



Cram and colleagues showed that methanolysis of the cyclopropane (+)-(*E*)-**119** under neutral conditions at 126 °C afforded the ring-opened product **120** with essentially no loss of enantiopurity and a complete inversion of stereochemistry at C-4 (Scheme 39).[39b] This was proven by converting the diastereomeric mixture **120** to the ester (–)-(*S*)-**121** and comparing its optical rotation to the same derivative prepared from (*S*)-mandelic acid.

Scheme 41: Stereochemistry of the ring-opening of (+)-(*E*)-**119** with methanol[39b]



3.2 Initial studies and optimization

3.2.1 Optimization of the reaction conditions

Phenol was first tested in the ring-opening reaction of racemic cyclopropane (±)-**23a** under thermal conditions. Following Seebach's procedure,[38d] methanol was used as a solvent at 80 °C. Potassium and cesium carbonate were chosen as mild bases to deprotonate phenol for the nucleophilic attack. Different numbers of equivalents of the base and phenol were

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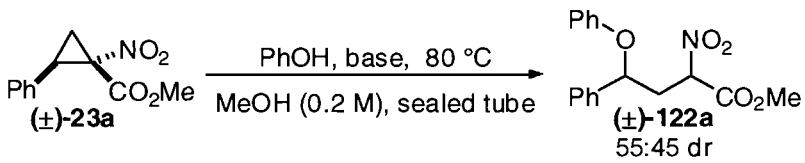
[62] Fuchs, P. L. *J. Am. Chem. Soc.* **1974**, *96*, 1607.

screened, keeping the reaction concentration at 0.2 M with respect to **(±)-23a** (Table 12, all yields determined by ^{1}H NMR). A six-fold excess of both the base and the phenol used by Seebach[38d] gave modest yields of the desired product **(±)-122a** with both K_2CO_3 (entry 1) and Cs_2CO_3 (entry 2). Keeping the base and the phenol approximately equimolar but reducing their loading to 3 equiv resulted in an improved yield with either K_2CO_3 (entry 3) or Cs_2CO_3 (entry 4). Further reduction of the base and phenol loading with either base (entries 4 and 5) caused a decrease of yield due to incomplete conversion. In all cases **(±)-122a** was obtained as an inseparable 55:45 mixture of two diastereomers.

Table 12: Optimization of base and phenol loading in the ring-opening of **(±)-23a**

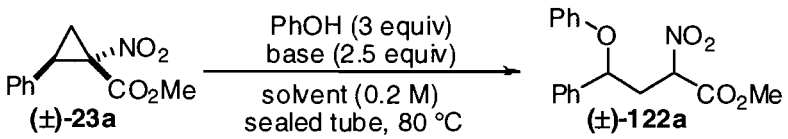


entry	PhOH, equiv	base	base equiv	yield,%[a]
1	6	K_2CO_3	5.8	51
2	6	Cs_2CO_3	5.8	69
3	3	K_2CO_3	2.5	78
4	3	Cs_2CO_3	2.5	73
5	1.5	K_2CO_3	1.3	43
6	1.5	Cs_2CO_3	1.3	38

[a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Using the optimal base and phenol loading, the reaction was next tested in a non-alcoholic solvent THF to prevent the possible competitive addition of methanol (Table 13, all yields determined by ^{1}H NMR). Compared to methanol (entry 1), the reaction with potassium carbonate in THF (entry 2) resulted in < 10% of the desired product and mostly unchanged starting material. Using cesium carbonate in THF (entry 3), on the other hand, afforded **(±)-122a** with an improved yield compared to methanol (entry 4). Subsequently, cesium carbonate was used for further optimization.

Table 13: Optimization of the base in the ring-opening of **(±)-23a** with phenol

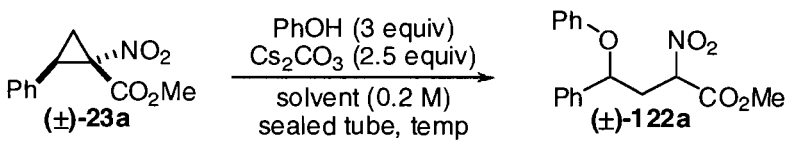


entry	base	solvent	yield,%[a]
1	K_2CO_3	MeOH	78
2	K_2CO_3	THF	<10
3	Cs_2CO_3	MeOH	73
4	Cs_2CO_3	THF	88

[a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

A screen of high boiling solvents at their reflux temperatures was performed (Table 14, all yields determined by ^{1}H NMR). However, at temperatures above 80 °C, neither polar solvents (entries 2,4,5) nor non-polar solvent (entry 3) proved superior to THF.

Table 14: Screen of solvents in the ring-opening of **(±)-23a** with phenol

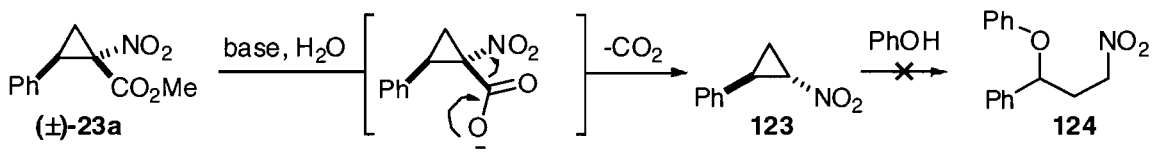


entry	solvent	temp, °C	yield,%[a]
1	THF	80	88
2	DMF	120	66
3	toluene	120	60
4	DME	90	71
5	MeCN	90	75

[a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

A common side product observed in most of the optimization reactions was the decarboxylated cyclopropane **123** (Scheme 42). The ring-opened product **124** was not detected in the crude reaction mixture, suggesting that **123** itself is not sufficiently activated for a nucleophilic attack.

Scheme 42: Formation of side product **123** in the ring-opening of **(±)-23a** with phenol



Wurz and Charette have shown that cyclopropanes **23** undergo facile decarboxylation if the ester group is hydrolyzed to a carboxylate anion.[23] It was therefore reasoned that the formation of the side product **123** can be prevented by maintaining anhydrous conditions and lowering the temperature to prevent ester hydrolysis. Indeed, by performing the reaction at 65 °C and using dried cesium carbonate, anhydrous THF and an atmosphere of argon, the formation of **123** was minimized, giving the desired product **(±)-122a** in isolated 75% yield.

3.2.2 Optimization of the workup

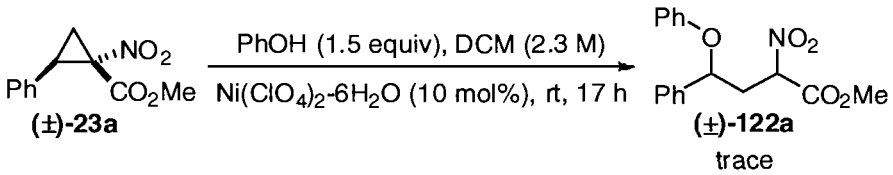
^{1}H NMR analysis of the crude reaction between phenol and **(±)-23a** under the optimized conditions (THF, 65 °C, 2.5 equiv of Cs_2CO_3 and 3 equiv PhOH) showed clean formation of the desired product **(±)-122a** with only traces of impurities. However, chromatographic separation of the excess phenol from **(±)-122a** proved difficult with all solvent systems examined, leading to a reduced isolated yield. An acid-base extraction was consequently employed to remove phenol. Due to similar pKa values of the phenolic proton and the acidic proton at C-2 in **(±)-122a**, it was necessary to achieve a pH at which only phenol would be deprotonated. A screen of different bases and concentrations identified 0.1 N NaOH as the optimal agent for the extraction of phenol into the aqueous phase. Using this workup followed by flash chromatography (10% EtOAc/Hexane), **(±)-122a** could be isolated completely free of excess phenol and in spectroscopically pure form.

3.2.3 Attempt toward Lewis acid-catalyzed ring-opening of (±)-23a with phenol

The Lewis acid-catalyzed addition of phenol to **(±)-23a** was attempted using the conditions optimized for aniline nucleophiles (Scheme 43). However, only traces of the ring-opened product were detected after 17 h. The lack of reactivity is probably due to the lower

nucleophilicity of phenol compared to amine substrates, which makes elevated temperature and basic conditions necessary for efficient ring-opening. Optimization of this reaction was not pursued.

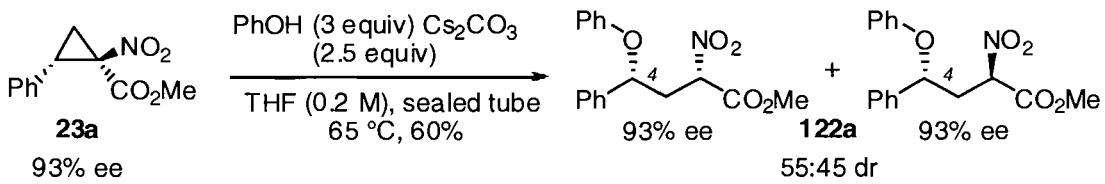
Scheme 43: Attempted Lewis acid-catalyzed ring-opening of (±)-**23a** with phenol



3.2.4 Preservation of the enantiomeric excess

To establish whether the enantiomeric excess of the cyclopropanes could be efficiently transferred to the ring-opened product, the reaction with phenol was performed on the enantioenriched cyclopropane (1*R*,2*S*)-**23a** (93% ee) under unoptimized conditions (Scheme 44). Gratifyingly, both diastereomers of **122a** were obtained without any loss of optical purity at C-4.

Scheme 44: Preservation of the enantiomeric excess in the ring-opening of **23a** with phenol

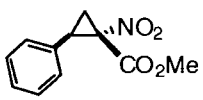
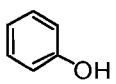
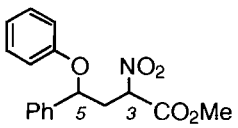
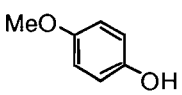
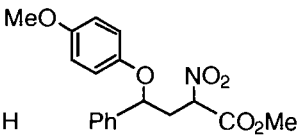
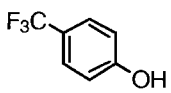
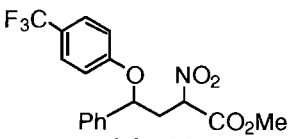
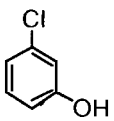
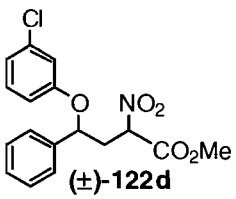
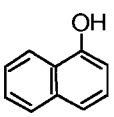
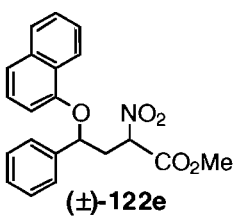


3.3 Reaction scope

With the optimal conditions in hand, the scope of the ring-opening reaction was examined, first employing the racemic cyclopropanes (±)-**23a,c,d,g** (Section 2.2) and various aromatic alcohols **125** (Table 15). Phenol derivatives substituted with both electron-donating (entry 2) and electron-withdrawing (entry 3) substituents were well tolerated. Slightly lower yields were obtained with *m*-chlorophenol (entry 4) and with the bulkier 1-naphthol (entry 5). Phenol bearing a Boc-protected amine group (entry 6) afforded the desired product in good yield, allowing for the introduction of an amine functionality which could be

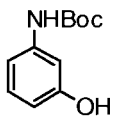
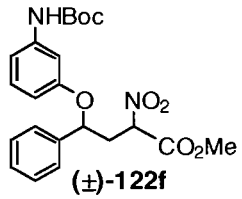
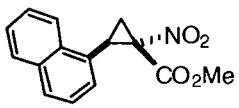
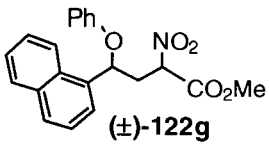
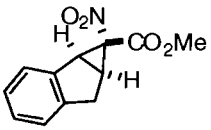
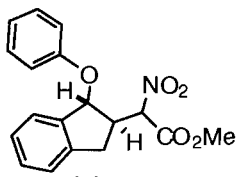
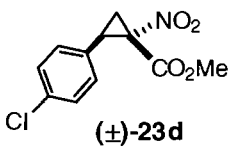
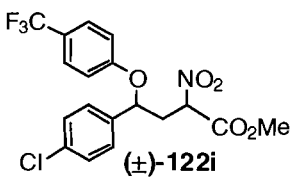
potentially deprotected and further derivatized. Varying the 2-substituents on the electrophilic cyclopropane to more sterically encumbered naphthyl (entry 7) and indenyl (entry 8) groups resulted in slightly lower but synthetically useful yields. The presence of substituents on both the nucleophile and the electrophile (entry 9) was unproblematic, and the desired functionalized product was obtained in a good yield. Scaling up of the reaction also proved straightforward: nucleophilic addition of the *p*-(trifluoromethyl)phenol (entry 3) on a 1-g scale under reflux cleanly afforded 1.5 g of **(±)-122c**.

Table 15: Scope of the nucleophilic ring-opening of **(±)-23** with aromatic alcohols

entry	cyclopropane	alcohol	product	yield,%[a,b]	dr
1	 **(±)-23a**	 **125a**	 **(±)-122a**	75	55:45
2	**(±)-23a**	 **125b**	 **(±)-122b**	68	55:45
3	**(±)-23a**	 **125c**	 **(±)-122c**	84	50:50
4	**(±)-23a**	 **125d**	 **(±)-122d**	57	50:50
5	**(±)-23a**	 **125e**	 **(±)-122e**	53	50:50

[a] Reaction conditions: **(±)-23** (1 equiv), **125** (3 equiv), Cs_2CO_3 (2.5 equiv), THF, 65 °C, 12 h. [b] Yield of isolated product.

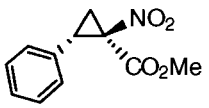
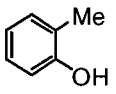
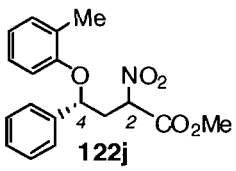
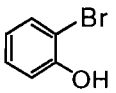
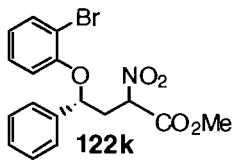
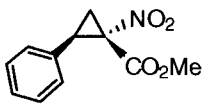
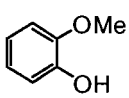
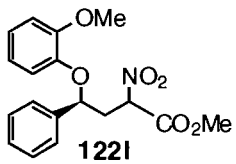
Table 15 (cont'd): Scope of the ring-opening of (±)-**23** with aromatic alcohols

entry	cyclopropane	alcohol	product	yield,%[a,b]	dr
6	(±)-**23a**	 **125f**	 (±)-**122f**	72	50:50
7	 (±)-**23g**	**125a**	 (±)-**122g**	58	55:45
8	 (±)-**23c**	**125a**	 (±)-**122h**	59	55:45
9	 (±)-**23d**	**125c**	 (±)-**122i**	57	50:50

[a] Reaction conditions: (±)-**23** (1 equiv), **125** (3 equiv), Cs_2CO_3 (2.5 equiv), THF, 65 °C, 12 h. [b] Yield of isolated product.

The ring opening of enantioenriched cyclopropanes was explored next as a method to access nonracemic adducts. Ring opening of (1*R*,2*S*)-**23a** (90% ee) with *o*-cresol afforded the product **122j** in 76% yield and with complete preservation of the cyclopropane's enantiomeric excess at C-4 (Table 16, entry 1). Similarly, the addition of *o*-bromophenol to **125h** (entry 2) afforded the adduct **122k** in 74% yield and with 90% ee of both diastereomers. Ring-opening of (1*S*,2*R*)-**23a** (95% ee) with *o*-methoxyphenol **125h** (entry 3) gave **122l** in a 78% yield and with 95% ee.

Table 16: Scope of the nucleophilic ring-opening of **23** with aromatic alcohols

entry	cyclopropane (ee,%)	alcohol	product	yield,%[a,b]	ee,%[c]	dr
1	 (1*R*,2*S*)-**23a** (90)	 **125g**	 **122j**	76	90	50:50
2	(1*R*,2*S*)-**23a** (90)	 **125h**	 **122k**	74	90	60:40
3	 (1*S*,2*R*)-**23a** (90)	 **125i**	 **122l**	78	95	70:30

[a] Reaction conditions: **23a** (1 equiv), **125** (3 equiv), Cs_2CO_3 (2.5 equiv), THF, 65 °C, 12 h. [b] Yield of isolated product. [c] Determined by SFC using a chiral stationary phase.

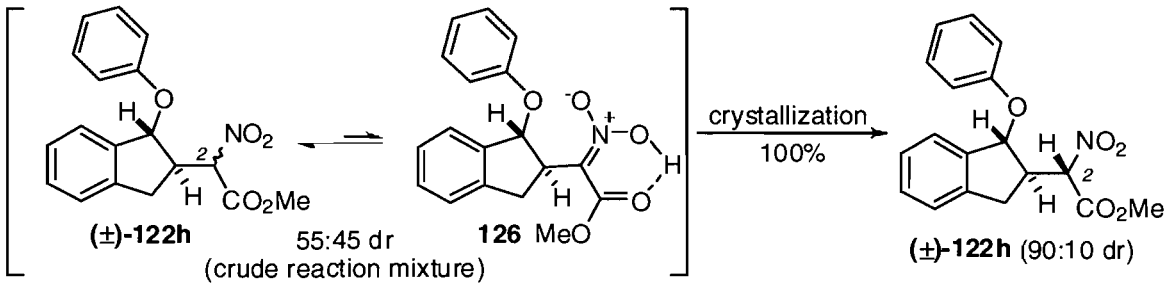
In all cases the adducts were isolated as mixtures of diastereomers at C-2 in approximately 1:1 ratio except for **122k** (60:40 dr, entry 2) and **122l** (70:30 dr, entry 3). It was found that some ring-opened products could be purified without the aqueous workup by flash chromatography eluting with 100% benzene, which led to improved isolated yields (see Chapter 6 for experimental details).

3.4 Configuration of the ring-opened products 122

^{1}H NMR analysis of a freshly prepared solution of the crystalline **(±)-122h** showed an enrichment of the diastereomeric ratio from 55:45 (crude reaction) to 90:10 at C-2 (Scheme 45). When left in solution at room temperature, however, **(±)-122h** epimerized to 80:20 dr after 1 h, 70:30 dr after 2 h and to 55:45 dr after 16 h. Subsequent crystallization reproducibly led to diastereomeric enrichment at C-2 to 90:10 dr. Presumably, the acidity of the proton at C-2 allows for facile interconversion of this chiral center *via* a conjugated

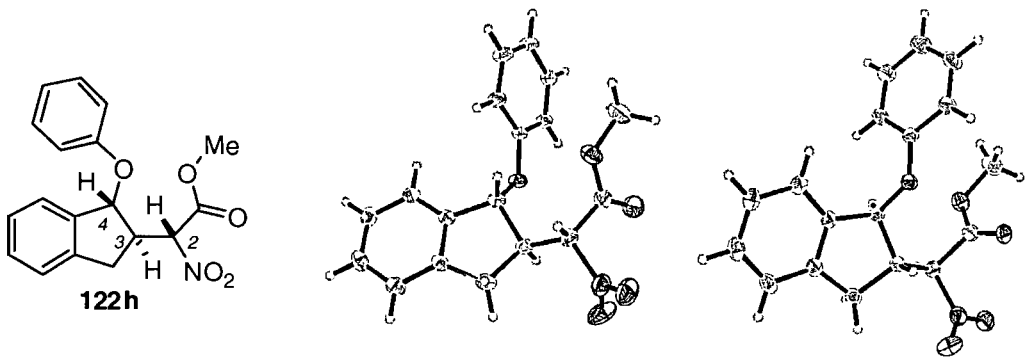
aci-nitro tautomer[63] **126** (Scheme 45). Because no mother liquor was present after crystallization, and the ^{1}H NMR analysis was performed by dissolving the entire sample, enrichment by partial crystallization of one diastereomer is ruled out. Instead, the enrichment probably occurs by a "thermodynamic resolution," whereby the mixture equilibrates to one diastereomer which is thermodynamically preferred in the solid state by an intermolecular proton transfer. Epimerization of **(±)-122h** in neutral solution to the original 55:45 dr suggests that, in general, the inseparable diastereomers of **122** are interconvertible by self-catalysis due to high acidity at C-2.

Scheme 45: Self-catalyzed diastereomeric enrichment of **(±)-122h**



Slow recrystallization by vapour diffusion of hexane into the benzene solution of **(±)-122h** afforded colourless needles which were suitable for single-crystal X-ray diffraction analysis. The asymmetric unit of the crystal structure was found to contain a single diastereomer and both enantiomers of **(±)-122h** (Figure 5). The *trans* relationship at C-3 and C-4 confirmed that the cyclopropane ring-opening occurs with an S_N2 inversion at C-4.

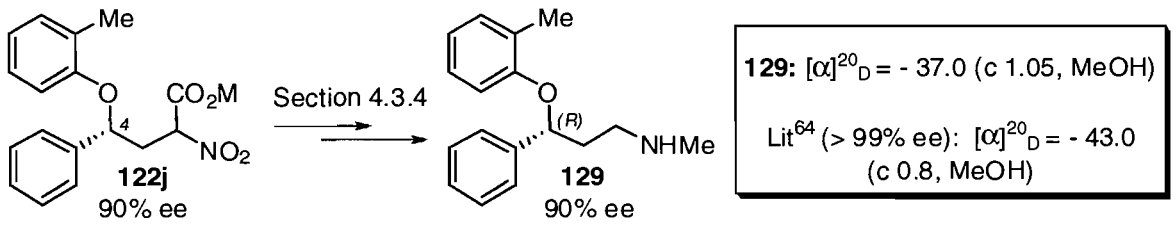
Figure 5: ORTEP representation of the asymmetric unit of **(±)-122h**



[63] Hantzsch, A.; Voigt, K. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 85.

To establish the absolute configuration of the enantioenriched ring-opened products, **122j** (90% ee) was converted to a known compound **129** (Section 4.3.4). Comparison of the optical rotation of **129** with the literature value[64] confirmed the absolute configuration and provided additional proof for an S_N2 inversion at C-4 (Scheme 46).

Scheme 46: Determination of the absolute configuration of **122j**



Chapter 4: Application of the ring-opening methodology in synthesis

4.1 Introduction

The developed methodology for the ring-opening of cyclopropanes **23** (Section 2.2) with amine and phenol nucleophiles was next applied to the enantioselective synthesis of biologically relevant targets.[55,60] The 1,3-bifunctional motif generated in the reaction is present in the core of a variety of small molecules with biological or pharmaceutical activity.[65] In particular, both the 3-aryl-3-aminopropane skeleton of **102** (Chapter 2) and the 3-aryl-3-phenoxypropane skeleton of **122** (Chapter 3) are contained in the structure of monoamine reuptake inhibitors, which are used in the pharmacological therapy of major psychiatric disorders.[66] These inhibitors mimic the biogenic amine neurotransmitters serotonin, norepinephrine and dopamine (Figure 6) and block their reuptake from the

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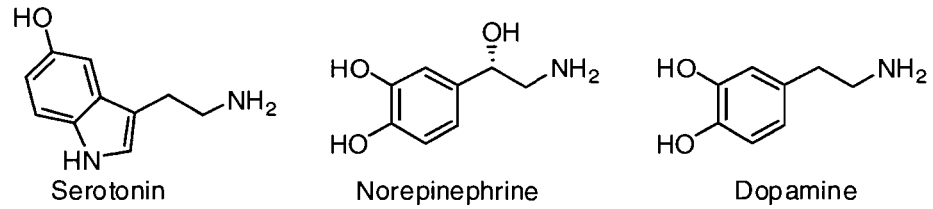
[64] Kamal, A.; Khanna, G.B.R., Ramu R. *Tetrahedron Asym.* **2002**, *13*, 2039.

[65] See, for example: (a) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Biosc. Biotech Biochem.* **1995**, *59*, 2091; (b) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto. K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331; (c) Bose, G.; Langer, P. *Tetrahedron Lett.* **2004**, *45*, 3861.

[66] Walter, M. W. *Drug Dev. Res.* **2005**, *65*, 97.

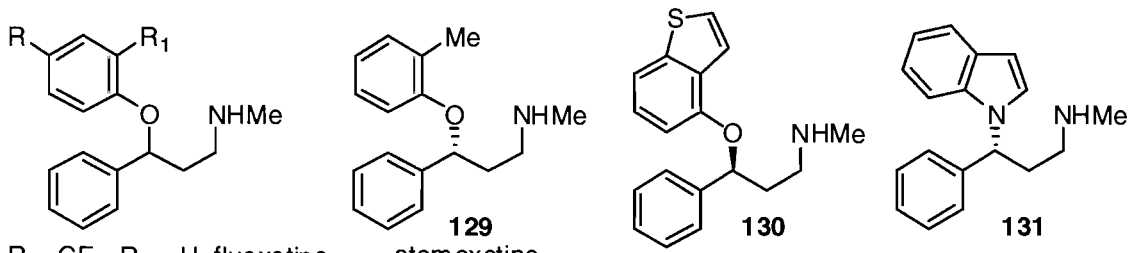
synapse. Increased extracellular levels of the neurotransmitters cause a cascade of the intracellular neurochemical changes in the central nervous system which lead to the desired therapeutic effect.[66]

Figure 6: Biogenic amine neurotransmitters



Several of the monomamine reuptake inhibitors containing the 3-aryl-3-phenoxypropanamine core structure are in wide clinical use, including fluoxetine (Prozac™) **127** and atomoxetine (Strattera™) **129** which annually generate $0.4 and $0.6 billion in sales, respectively[67] (Figure 7). Related structures such as nisoxetine **128**[68] and dual serotonin/norepinephrine inhibitor **130**[69] are used in biochemical research or are under investigation for clinical use. Recently, a potent dual serotonin/norepinephrine inhibitor **131** which contains a 3-aryl-3-indolylpropanamine in its core structure was identified.[70]

Figure 7: Serotonin and norepinephrine reuptake inhibitors[66,70,70]



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[67] Top 200 brand and generic drugs by retail dollars in 2002. *Drug Topics* **2003**, *7:53*, 57.

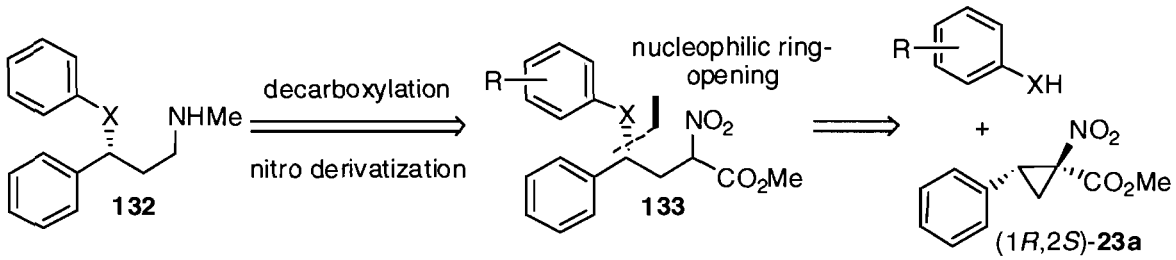
[68] Graham, D.; Langer, S. Z. *Life Sci.* **1992**, *51*, 631.

[69] Boot, J. R.; Brace,G.; Delatour, C. L.; Dezutter N.; Fairhurst J.; Findlay J.; Gallgher, P. T.; Hoes, I.; Mahadevan, S.; Mitchell, S. N.; Rathmell, R. E.; Richards, S. J.; Simmonds, R. G.; Wallace, L.; Whatton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5395.

[70] Mahaney, P. E.; Vu, A. T.; McComas, C. C.; Zhang, P.; Nogle, L. M.; Watts, W. L.; Sarkahian, A.; Leventhal, L.; Sullivan, N. R.; Uveges, A. J.; Trybulski, E. J. *Bioorg. Med. Chem.* **2006**, *14*, 8455.

All of the neurotransmitters shown in Figure 7 can be in principle accessed by the cyclopropane ring-opening methodology. Enantioselective ring-opening of (1*R*,2*S*)-**23a** with an amine or phenol nucleophile would give the required skeleton **133**, which can be converted to the target **132** by cleavage of the ester group and derivatization of the nitro group (Scheme 47).

Scheme 47: Retrosynthesis of monoamine reuptake inhibitors



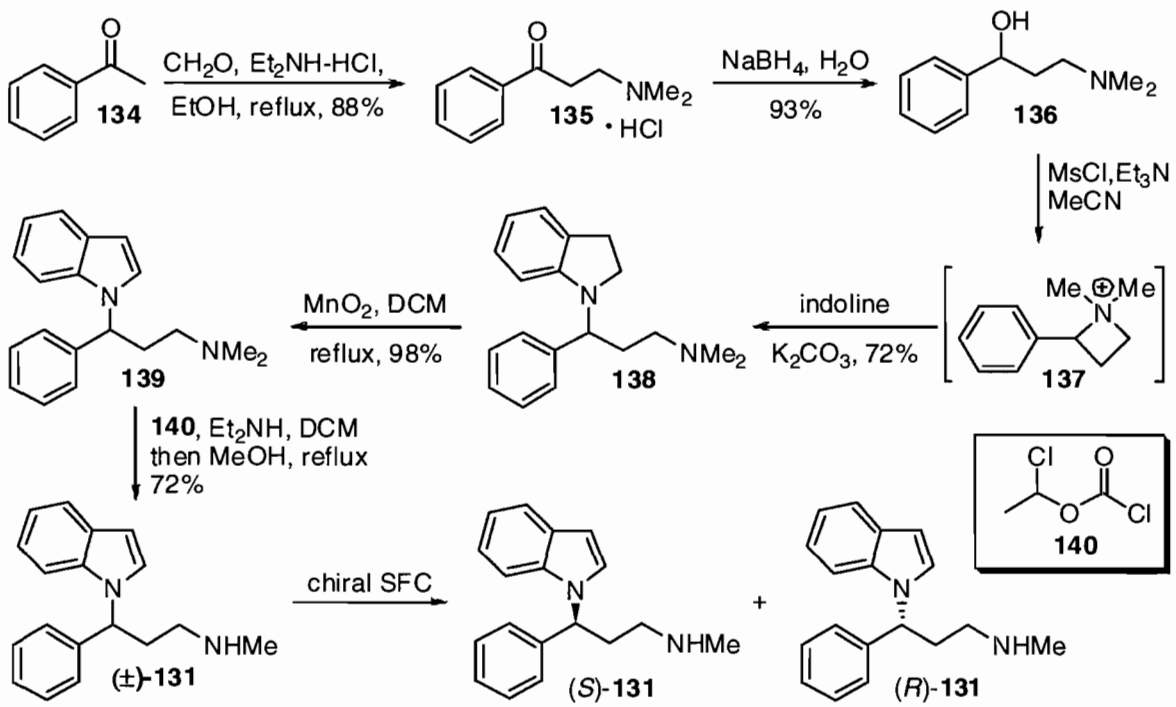
4.2 Synthesis of the monoamine reuptake inhibitors 131 and (±)-139

4.2.1 Previous synthesis

The racemic synthesis of **131** as well as several of its fluorine-substituted derivatives has been reported by Mahaney *et al.* who identified and studied the biological activity of these novel inhibitors.[70] Biological assays of chromatographically separated enantiomers showed that the *S*-isomer was significantly more potent that the racemic mixture or the *R*-enantiomer for 4-, and 6-fluoroindole derivatives of **131**, highlighting the value of an enantioselective synthesis for this class of compounds. Synthesis of **(±)-131** by Mahaney *et al.* was accomplished in 6 steps and 41% overall yield (for both enantiomers) from acetophenone **134** (Scheme 48). A Mannich reaction of **134** formed the required carbon skeleton **135**, which was reduced to form the alcohol **136**. Mesylation of the alcohol and treatment of the reaction mixture with indoline afforded **138**, presumably *via* a regioselective ring-opening of azetidinium ion **137** formed *in situ*. Oxidation of the indoline to indole **139** followed by demethylation with **140** afforded **(±)-131** which was separated into its enantiomers by preparative chiral SFC. Structure-activity relationship analyses

performed on the synthetic intermediates also identified **139** as an active though less potent inhibitor.

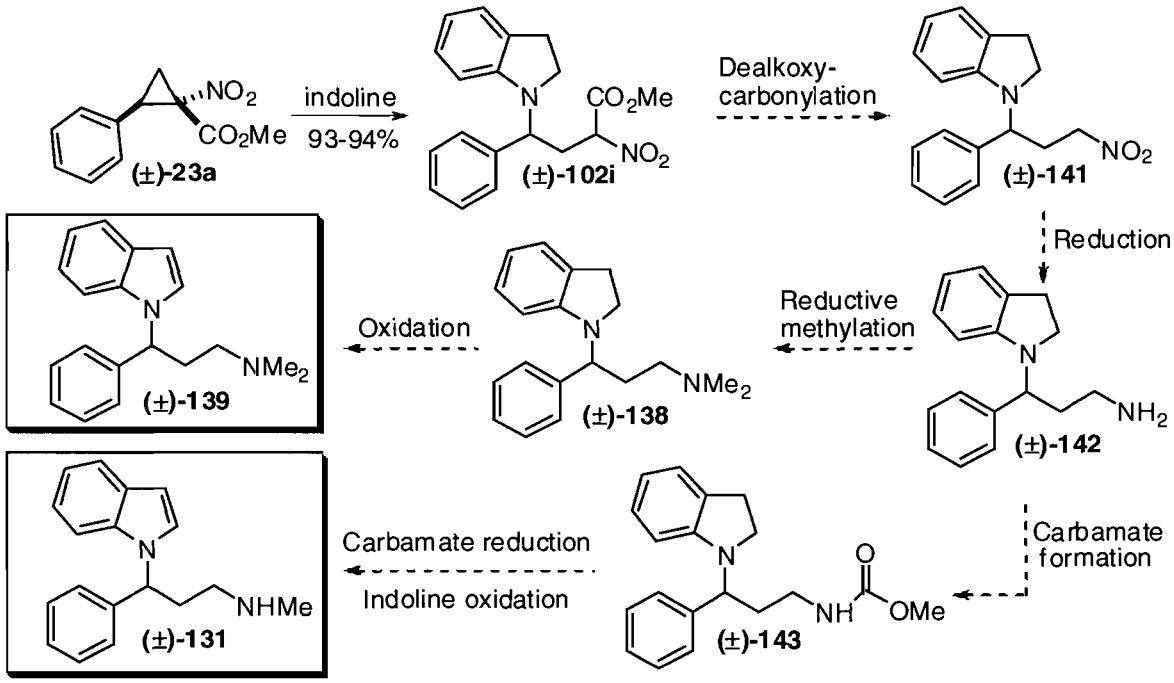
Scheme 48: Racemic synthesis of **(±)-131** by Mahaney *et al.*[70]



4.2.1 Racemic synthesis of (±)-131 and (±)-139 *via* the ring-opening of (±)-23a

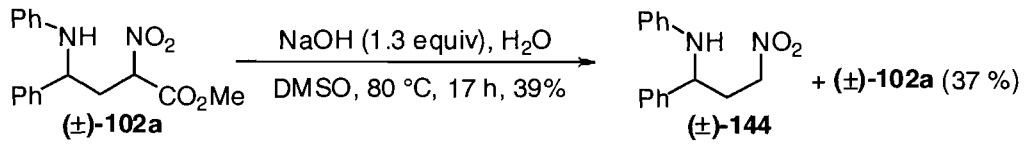
The synthesis of **131** and its dimethyl analogue **(±)-139** *via* the ring-opening of cyclopropane **23a** was first tested on racemic substrates. Scheme 49 shows the planned synthetic route. The first step employs the developed Lewis acid-catalyzed nucleophilic ring-opening of **(±)-23a** with indoline, which was shown to afford the adduct **102i** in 93-94% yield (Section 2.4.3). Removal of the ester group (demethoxycarbonylation) would furnish the nitropropyl intermediate **(±)-141**, which would be reduced to a primary amine **(±)-142**. Reductive methylation of **(±)-142** to the dimethyl intermediate **(±)-138** followed by the oxidation of indoline would afford the neurotransmitter reuptake inhibitor **(±)-139**. Alternatively, **(±)-142** would be converted to a carbamate **(±)-143** which, upon reduction and indoline oxidation would give the inhibitor **(±)-131**.

Scheme 49: Planned synthesis of (±)-**139** and (±)-**131** *via* the ring-opening of (±)-**23a**



Demethoxycarbonylation was first tested on the simple ring-opened product (±)-**102a** using conditions developed by Wurz and Charette to remove the ester group from cyclopropanes **23**.[23] In this procedure, the ester is saponified with aqueous NaOH in DMSO at 80 °C to form a carboxylate which readily eliminates as CO_2 under thermal conditions due to a highly electron-withdrawing nitro group in the α-position. However, these conditions proved inefficient with the substrate (±)-**102a**, affording the desired product (±)-**144** in only 39% yield along with 37% of the recovered starting material (Scheme 50).

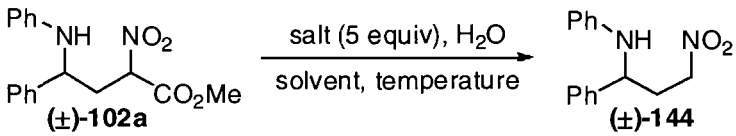
Scheme 50: Dealkoxycarbonylation of (±)-**102a** by saponification



As an alternative procedure, demethoxycarbonylation of (±)-**102a** was tried using the Krapcho reaction.[71] In this transformation, a nucleophilic anion (typically a halide) of an

alkaline salt in a polar aprotic solvent fragments the ester group by the nucleophilic displacement of the ester's alkyl group. Various salts and solvents have been employed in this reaction;[71b] in particular, elimination of an ester α to a nitro group has been performed with NaCl in DMSO[71a] and NaI in DMF.[71b] However, neither of these conditions afforded the desired product **(±)-144** in acceptable yields due to a significant formation of side products (Scheme 51).

Scheme 51: Krapcho demethoxycarbonylation of **(±)-102a**



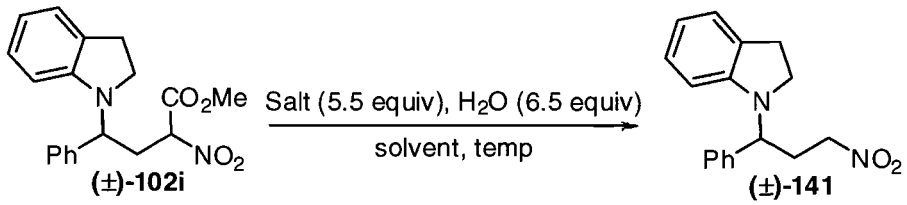
(±)-102a **(±)-144**

salt	solvent	temperature	yield
NaCl	DMSO	140 °C	37%
NaI	DMF	150 °C	22%

The Krapcho decarboxylation with NaCl in DMSO at different temperatures was next tested on the indoline adduct **(±)-102i** (Table 17). Performing the reaction in an oil bath for 2 h afforded the desired product **(±)-141** in only 40% yield (entry 1). Microwave irradiation of the reaction mixture at 150 °C for 5 min led to about 50% conversion of the starting material (entry 2). Increasing the temperature to 250 °C (entry 3) resulted in decomposition of the starting material and the solvent DMSO with evolution of dimethyl sulfide. The best results were obtained by performing the reaction at 150 °C for 10 min in the microwave, which gave the desired product **(±)-141** in 61% yield (entry 4). Using this reaction temperature and time, the reaction was tested in DMF (entry 5) and in DMSO with NaI (entry 6). However, neither set of conditions proved superior to entry 4.

[71] (a) Krapcho, A. P.; Jahngen, E. G. E.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1967,** 215; (b) Krapcho, A. P. *Arkivoc* **2007** (iii), 1.

Table 17: Krapcho demethoxycarbonylation of **(±)-102i**

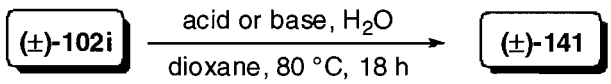


entry	heating method	salt	temp, °C	time	solvent	yield,%
1	oil bath	NaCl	140	2 h	DMSO	39.7[a]
2	microwave	NaCl	150	5 min	DMSO	- (50% conv)
3	microwave	NaCl	250	5 min	DMSO	decomposition
4	microwave	NaCl	150	10 min	DMSO	60.7[a]
5	microwave	NaCl	150	10 min	DMF	<22
6	microwave	NaI	150	10 min	DMSO	14

[a] No aqueous workup; crude reaction purified by column chromatography directly.

The unsatisfactory yields obtained with the Krapcho reaction prompted to test the demethoxycarbonylation of **(±)-102i** by ester hydrolysis under modified conditions (Table 18). Instead of DMSO, dioxane was used to facilitate the extraction of the product in the aqueous workup, since it can be partitioned into the organic layer with the product. While acidic hydrolysis using excess 3 M HCl in dioxane yielded a complex mixture of products (entry 1), saponification of the ester group in **(±)-102i** with NaOH in dioxane at 80 °C led to a clean formation of the desired product **(±)-141** in 82% yield (entry 2). A slightly better yield (84%) was obtained with LiOH (entry 3).

Table 18: Decarboxylation of **(±)-102i** by ester hydrolysis

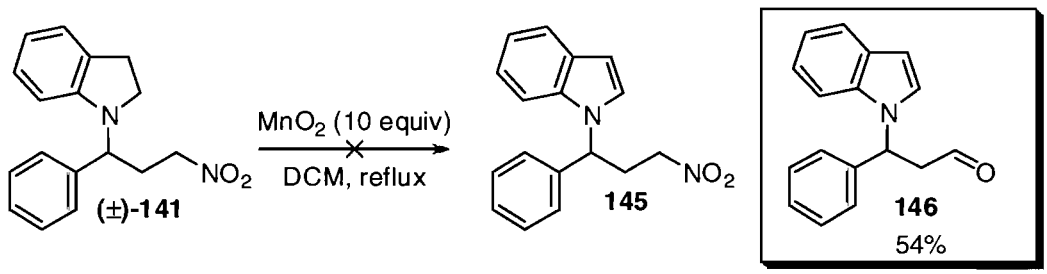


entry	acid/base	equiv	yield, %
1	HCl, 3M	57	complex mixture
2	NaOH	1.5	82
3	LiOH	1.5	84

Using the optimal conditions (1.5 equiv LiOH, dioxane/H_2O, 80 °C), the decarboxylation was performed on a larger (0.5 g) scale. Though the reaction time was longer (48 h), the desired product **(±)-141** was obtained cleanly in 89% isolated yield.

At this stage, oxidation of the indoline moiety in **(±)-141** to indole with MnO_2 was attempted. However, instead of the expected 1-(3-nitro-1-phenylpropyl)-1*H*-indole **145**, a Nef product **146** was obtained in 54% yield (Scheme 52). Although the Nef reaction is known to convert nitro groups to aldehydes with $KMnO_4$,[72] and oximes to aldehydes with MnO_2,[73] no precedent of direct conversion of the nitro group to aldehydes with MnO_2 could be found in the literature.

Scheme 52: Unexpected Nef reaction of **(±)-141** with MnO_2



It was decided to pursue the indoline oxidation at a later stage, and perform the necessary derivatization of the nitro group first. Reduction of **(±)-141** to a primary amine **(±)-142** was first tried using palladium-catalyzed hydrogenation at atmospheric pressure (Table 19, entry 1). However, only a complex mixture of products was obtained. Employing 2 equivalents of $LiAlH_4$ in ether (entry 2), complete consumption of the starting material was observed after 30 min, but the desired product was isolated in only 22% yield due to a significant formation of reduction intermediate oxime **147** which was partly inseparable by chromatography. Increasing the reaction time to 17 h (entry 3) led to a 1:1 mixture of **(±)-142** and **147**. Using a 3-fold excess of $LiAlH_4$ in ether (entry 4) led to a clean reduction overnight affording the product in quantitative yield on both 80 mg and 0.5-g scale.

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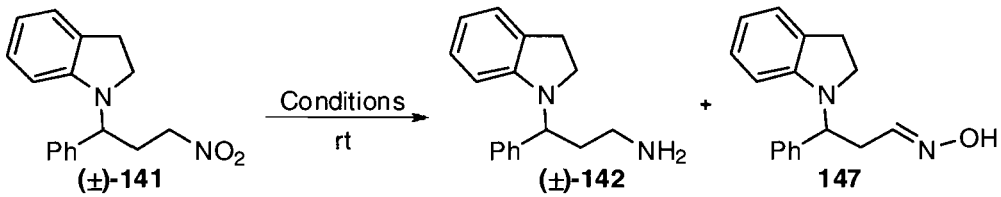
[72] Noland, W. W. *Chem. Rev.* **1955**, *55*, 137.
[73] Shinada, T.; Yoshihara, K. *Tetrahedron Lett.* **1995**, *36*, 6701.

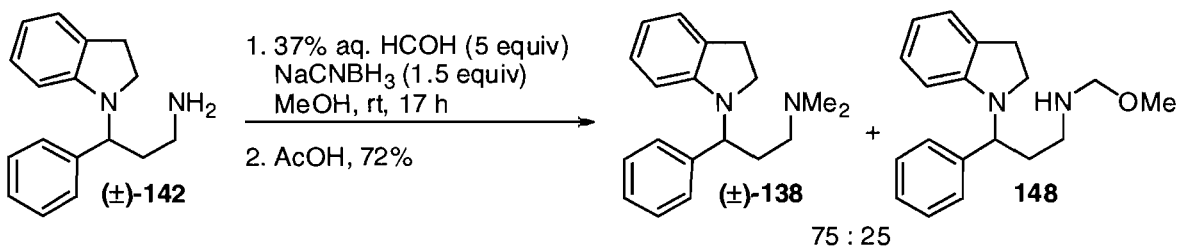
Table 19: Reduction of **(±)-141** to primary amine **(±)-142**



entry	reductant	equiv	solvent	time, h	yield (±)-142
1	H_2, Pd/C	xs.	EtOH	17	complex mixture
2	$LiAlH_4$	2	Et_2O	0.5	22% + **147**
3	$LiAlH_4$	2	Et_2O	17	50% + **147** (50%)
4	$LiAlH_4$	3	Et_2O	17	quant.

Reductive methylation of **(±)-142** to the dimethyl intermediate **(±)-138** was performed using aqueous formaldehyde and sodium cyanoborohydride in methanol, followed by an acidic workup (Scheme 53).[74] The desired product **(±)-138** was obtained as a 75:25 mixture with an unreactive aminal side product **148**. After some optimization of the conditions for the chromatographic purification, **(±)-138** could be cleanly isolated in 72% yield.

Scheme 53: Synthesis of **(±)-138** by reductive methylation of **(±)-142**



Oxidation of the indoline moiety in **(±)-138** to indole using excess MnO_2 proceeded smoothly giving the desired neurotransmitter reuptake inhibitor **(±)-139** in a quantitative yield (Scheme 54).

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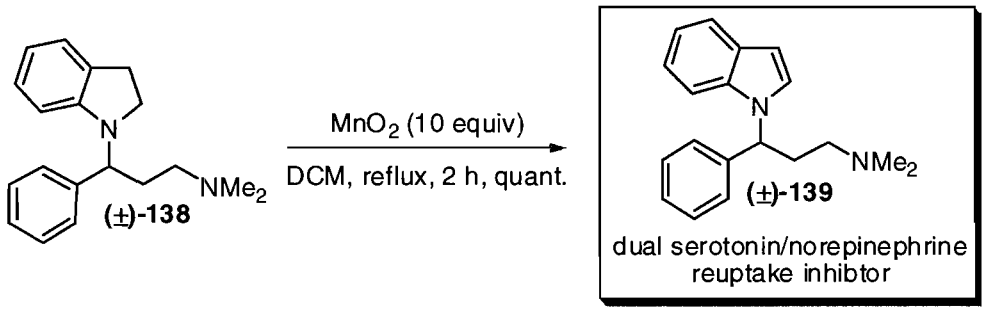
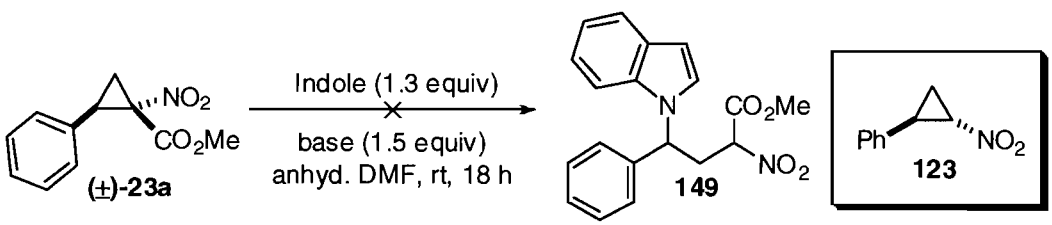
[74] Sikazwe, D.; Bondarev, M. L.; Dukat, M.; Rangisetty, J. B.; Roth, B. L.; Glennon, R. A. *J. Med. Chem.* **2006**, *49*, 5217.

Scheme 54: Synthesis of (±)-**139** by oxidation of the indole moiety in (±)-**138**



The racemic synthesis of (±)-**139** using optimized conditions was accomplished in 5 steps and a 60% overall yield from the cyclopropane (±)-**23a**. In this route, introduction of the indole moiety required the initial nucleophilic ring-opening by indoline followed by the oxidative aromatization of the indoline group to indole. In order to reduce the number of steps, direct ring-opening of (±)-**23a** by indole was attempted. Since the C-3 of unsubstituted indoles is more nucleophilic than the nitrogen under neutral conditions, deprotonation of the indole with a base was required for the desired chemoselectivity of the attack. Using various bases, the desired ring-opening could not be achieved (Table 20). Instead of the indole adduct **149**, only the decarboxylated cyclopropane **123**[27a] was obtained with complete conversion of the starting material, presumably by basic ester saponification and loss of CO_2.

Table 20: Attempts toward the ring-opening of (±)-**23a** by indole

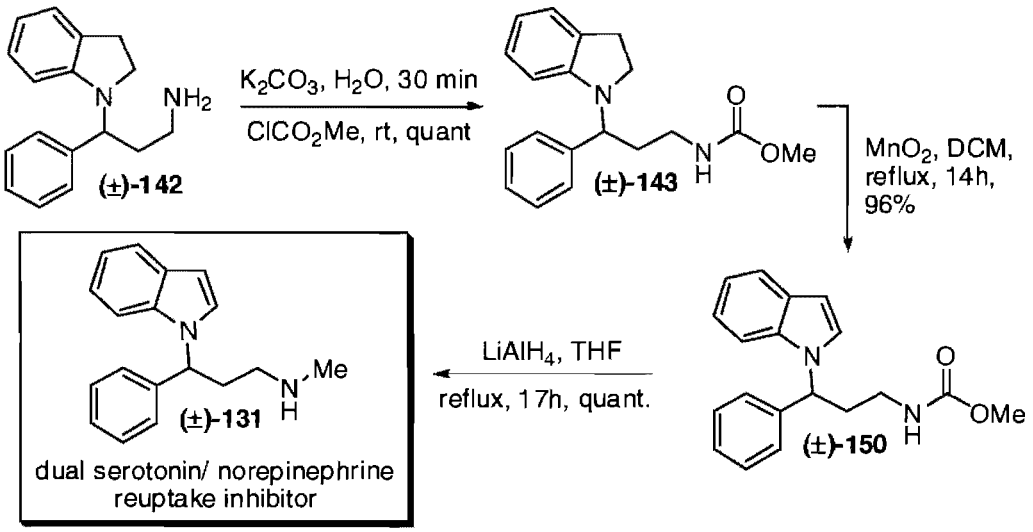


entry	base	**149**, % conv[a]	**123**, % conv[a]
1	NaH	4	96
2	KOH	0	100
3	KO^{t}Bu	0	100

[a] Determined by ^{1}H NMR of the crude reaction mixture

The synthesis of the related monomethylated neurotransmitter reuptake inhibitor (±)-**131** was accomplished in three steps from the common intermediate (±)-**142** (Scheme 55). Conversion of (±)-**142** to the carbamate (±)-**143** was unproblematic and gave the desired product quantitatively. Oxidation of the indoline moiety with excess MnO_2 afforded indole (±)-**150** in 96% yield, which was reduced using $LiAlH_4$ in quantitative yield. Overall, the target molecule (±)-**131** was obtained in 80% yield over 6 steps from cyclopropane (±)-**23a**.

Scheme 55: Synthesis of (±)-**131** from the common intermediate (±)-**142**

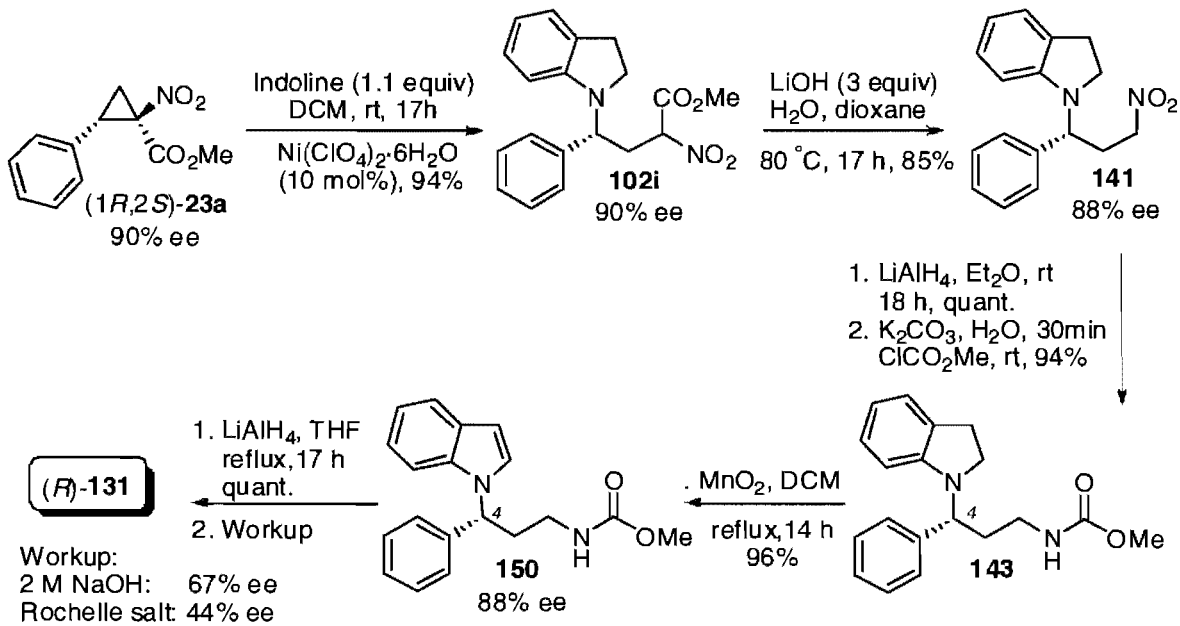


4.2.2 Enantioselective synthesis of (*R*)-131 *via* the ring-opening of (1*S*,2*R*)-23a

The enantioselective synthesis of (*R*)-**131** was performed using the same route as with the racemic substrates (Scheme 56). Nucleophilic ring-opening of (1*S*,2*R*)-**23a** (90% ee) with indole gave the addition product **102i** in 94% yield and with 90% ee. To reduce the reaction time, demethoxycarbonylation of **102i** on a 0.3g-scale was performed with a larger excess of LiOH (3 equiv). Although the product **141** was obtained after a shorter reaction time (17h) in 85% yield, slight erosion of ee to 88% was observed. Subsequent nitro reduction, carbamate formation and indoline oxidation afforded the product **150** in 90% yield over 3 steps and without any further loss of the optical purity. When the carbamate **150** was reduced to the desired product (*R*)-**131** with $LiAlH_4$, however, significant racemization to

67% ee was observed. To determine if the racemization occurred in the aqueous workup, which involved the precipitation of aluminum hydroxide with 2 M NaOH, the reaction was repeated and quenched with Rochelle salt (pH 7). However, significant racemization of the product (*R*)-**131** to 44% ee still took place. In an effort to discourage racemization, the reaction was repeated at room temperature; however, only minimal conversion to the desired product was observed after 3 d.

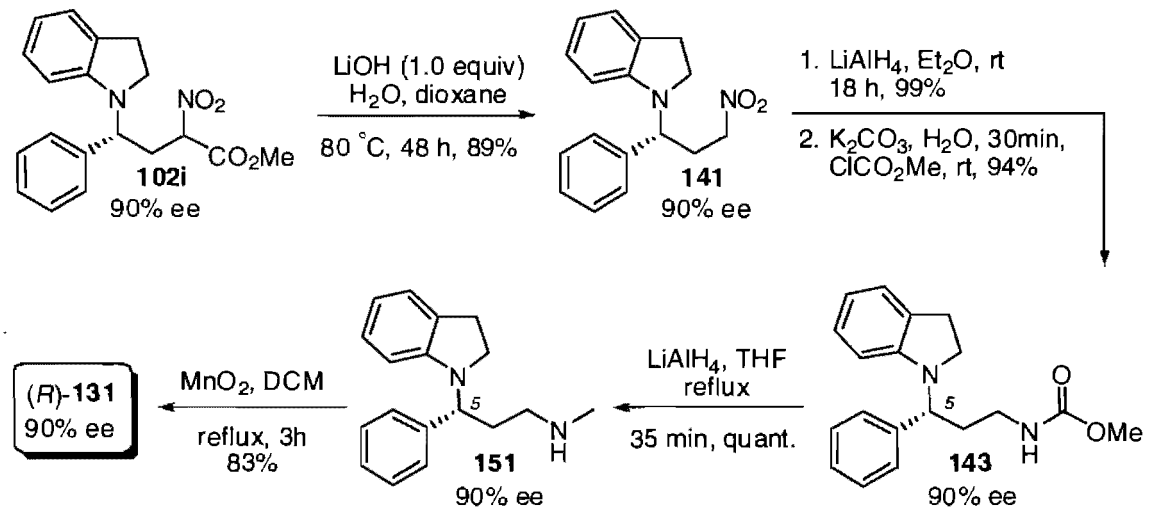
Scheme 56: First route toward the enantioselective synthesis of (*R*)-**131**



Presumably, the acidity of the C-4 proton in **150** which is flanked by inductively withdrawing indole and carbanion-stabilizing phenyl group promoted the racemization of **150** and/or (*R*)-**131** under the basic conditions of $LiAlH_4$ reduction. Based on this assumption, it was expected that the racemization could be diminished by reversing the last two steps of the synthesis. Submitting carbamate **143** which contains a less acidic proton at C-4 to the $LiAlH_4$ reduction would yield the indoline **151**, which could then be oxidized to (*R*)-**131** under mild neutral conditions with MnO_2 (Scheme 57). The revised synthesis was performed starting from **102i**. Using only 1.0 equiv of LiOH to demethoxycarbonylate **102i**, the desired product **141** was obtained in 89% yield and without any loss of optical purity after 48 h. Reduction of the nitro group and carbamate formation afforded **143** in

93% yield over two steps and with 90% ee. As was hoped, the reduction of **143** to the monomethylated amine **151** with $LiAlH_4$ proceeded without racemization and in excellent yield. Oxidation of the indoline moiety in **151** afforded (*R*)-**131** in 83% yield and with 90% ee. Overall, the synthesis proceeded with complete preservation of the enantiomeric excess from the starting cyclopropane (1*S*,2*R*)-**23a** and in 65% yield over 6 steps.

Scheme 57: Revised route toward the enantioselective synthesis of (*R*)-**131**



By varying the substituents on the cyclopropane and the indole reagents which have been shown to impart different biological activity,[70] various enantioenriched derivatives of the inhibitor could in principle be easily accessed.

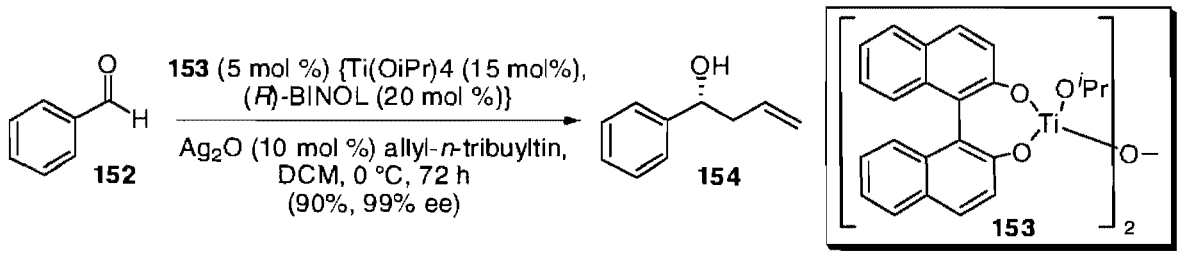
4.3 Synthesis of the monoamine reuptake inhibitors 127 and 129

4.3.1 Previous synthetic approaches

Due to their high activity and selectivity as norepinephrine and serotonin reuptake inhibitors, atomoxetine **129** and fluoxetine **127**, respectively, (Section 4.1) have gained considerable attention as synthetic targets. Appropriately, a multitude of racemic and enantioselective approaches have been disclosed in the literature since late 1980's. Though fluoxetine **127** (Prozac^{TM}, Eli Lilly Co.) is sold racemically, its (*R*)-enantiomer has been shown to be more active in treating depression, while the (*S*)-enantiomer was demonstrated

to be useful in treating migraines.[75] Most of the reported enantioselective syntheses employ (kinetic) enzymatic resolution of benzylic alcohols or enzymatic reduction of ketones and β-ketoesters to establish the chiral center in both **127**[76,77d,e] and **129**.[77] The most common chemical approaches include asymmetric epoxidation,[78] asymmetric reductions[79] and transition metal-catalyzed reactions.[80] For example, de Fatima *et al.* recently reported the enantioselective synthesis of (*R*)-fluoxetine (*R*)-**127** (99% ee) *via* a catalytic asymmetric allylation of benzaldehyde with Maruoka's catalyst **153** (Scheme 58).[80e] The key step of allylation of benzaldehyde **152** with allyltri-*n*-butyltin and *in situ*-generated catalyst **153** gave the desired allyl alcohol **154** in 90% yield and with 99% ee.

Scheme 58: Key step in the synthesis of fluoxetine (*R*)-**127** by de Fatima *et al.* [80e]



Oxidative cleavage of the double bond of **154** and reduction furnished the diol **155**. The primary alcohol was mesylated and displaced with methylamine to give **156** (Scheme 59).

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[75] Adly C.; Straumanis J.; Chesson A *Headache* **1992**, *32*, 101.

[76] (a) Quiros, M.; Rebolledo, F.; Liz, R.; Gotor, V. *Tetrahedron Asym.* **1997**, *8*, 3035; (b) Master, H. E.; Newadkar, R. V.; Rane, R. A.; Kumar, A. *Tetrahedron Lett.* **1996**, *37*, 9253; (c) Chenevert, R.; Fortier, G.; Rhild, R. B. *Tetrahedron* **1992**, *48*, 6769; (d) Schneider, M. P.; Goergens, U. *Tetrahedron Asym.* **1992**, *3*, 525; (e) Kumar, A.; Ner, D. H.; Dike, S. Y. *Indian J. Chem.* **1992**, *31B*, 803. (f) Chenevert, R.; Fortier, G. *Chem. Lett.* **1991**, 1603; (g) Fronza, G.; Fuganti, C.; Grasselli, P.; Mele, A. *J. Org. Chem.* **1991**, *56*, 6019.

[77] (a) Xu, C.-F.; Yuan, C.-Y. *Chin. J. Chem.* **2004**, *22*, 775; (b) Xu, C.-F.; Yuan, C.-Y. *Tetrahedron* **2005**, *61*, 2169; (c) Liu, H.L.; Hoff, B. H.; Anthonsen, T. *Perkin 1* **2000**, *11*, 1767; (d) Bracher, F.; Litz, T.; *Bioorg. Med. Chem.* **1996**, *4*, 877; (e) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, 32, 1901.

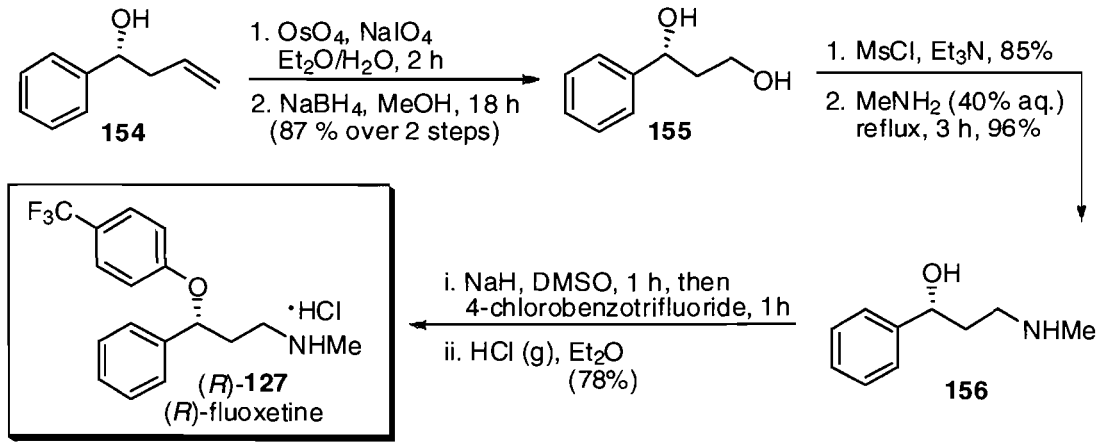
[78] (a) Gao, Y.; Sharpless, K.B. *J. Org. Chem.*, **1988**, *53*, 4081; (b) Mitchell, D.; Koenig, T. *Synth. Commun.***1995**, *25* 1231.

[79] (a) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207; (b) Sakuraba, S.; Achiwa, K. *Synlett* **1991**, 689; (c) Devocelle, M.; Agbossou, F.; Mortreux, A. *Synlett* **1997**, 1306; (d) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916; (e) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919.

[80] (a) Trost, B. M.; Fraisee, P. L.; Ball, Z. T. *Angew.Chem., Int. Ed.* **2002**, *41*, 1059; (b) Devine, P. N.; Heid, R. M.; Tschaen Jr., D. M. *Tetrahedron* **1997**, *53*, 6739; (d) Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S.; *Tetrahedron* **2001**, *57*, 9925; (e) de Fatima, A.; Lapis, A. A. M.; Pilli, R. A. *J. Braz. Chem Soc.* **2005**, *16*, 495.

Etherification with 4-chlorobenzotrifluoride and acidification afforded the HCl salt of (*R*)-fluoxetine (*R*)-**127** in a total of six steps and 50% overall yield.

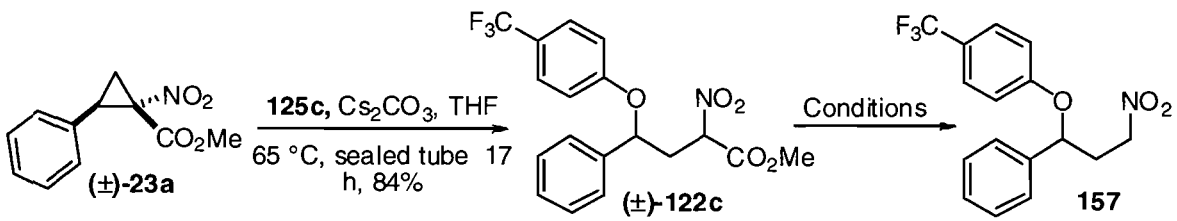
Scheme 59: Synthesis of (*R*)-fluoxetine (*R*)-**127** by de Fatima *et al.* starting from **154**[80e]

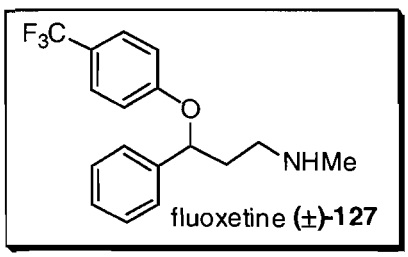


4.3.2 Attempts toward the synthesis of (±)-127 *via* the ring-opening of (±)-23a

The planned synthesis of (±)-**127** *via* the nucleophilic ring-opening of (±)-**23a** followed the same general strategy used in the synthesis of (*R*)-**131** (Scheme 55). Ring-opening of (±)-**23a** with 4-(trifluoromethyl)phenol **125c** on a 1-g scale afforded the required skeleton (±)-**122c** in 84% (Scheme 60).

Scheme 60: Attempts toward the synthesis of (±)-**127**

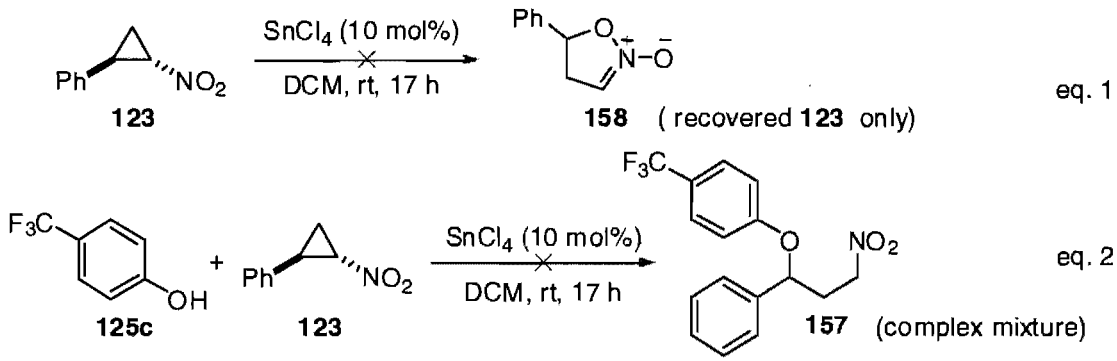




conditions	conversion	yield
LiOH (4 eqv), H_2O, dioxane, 80 °C, 17 h	100%	26%
NaCl, DMSO, H_2O, 2 d 140 °C, sealed tube	<5%	-

However, the demethoxycarbonylation of (±)-**122c** under the optimized conditions afforded the desired nitropropyl intermediate **157** in only 26% yield due to a significant formation of side products (Scheme 60). The high acidity of **125c** and therefore its high stability as a phenolate anion probably made it a good leaving group, which was displaced by water under the aqueous basic conditions used. The Krapcho reaction using NaCl and DMSO at 150 °C proved to be extremely slow and afforded < 5 % of the desired product **157** after 48 h. Given the difficulty of the decarboxylation, it was attempted to ring-open the monoactivated cyclopropane **123** with 4-(trifluoromethyl)phenol **125c** directly using the Lewis acid $SnCl_4$ (Scheme 61). This Lewis acid was shown to be highly activating toward ring-opening with the cyclopropane (±)-**23a**, catalyzing its ring expansion into isoxazoline *N*-oxide **105** (Section 2.4.1). However, when **123** was treated with 10 mol % $SnCl_4$ in the absence of a nucleophile, no ring-expansion product **158** was observed, and only the starting material was recovered, suggesting that the additional activation of an ester group is required for the ring-opening (Scheme 61, eq. 1). In the presence of 4-(trifluoromethyl)-phenol, the starting material **123** was completely consumed, but only a complex mixture was obtained with none of the desired product **157** (Scheme 61, eq. 2). Presumably, the reaction of **125c** with $SnCl_4$ to form a tin alkoxide species led to the undesired side reactions.

Scheme 61: Attempts toward the ring-opening of **123** with 4-(trifluoromethyl)phenol



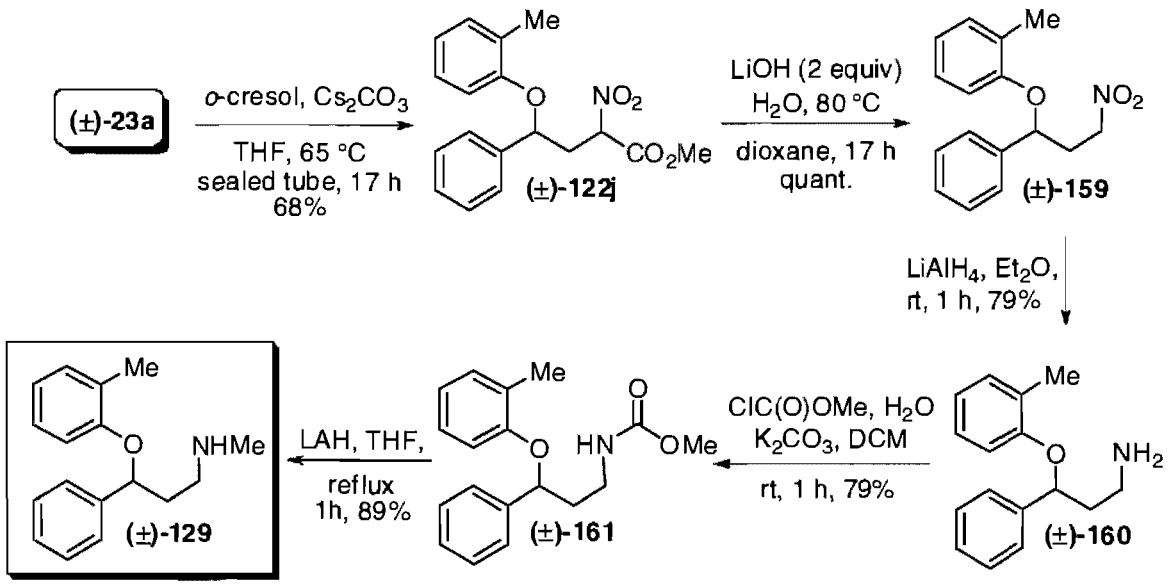
Given the difficulty in the demethoxycarbonylation of (±)-**122c** and the necessity of the ester group in the cyclopropane ring-opening reactions, the synthesis of (±)-**127** was not pursued further. Instead, the attention was turned to the synthesis of atomoxetine **129**.

4.3.3 Racemic synthesis of (±)-129

The racemic monoamine reuptake inhibitor atomoxetine **(±)-129** was synthesized in five steps from the cyclopropane **(±)-23a** (Scheme 62). Ring-opening of **(±)-23a** with *o*-cresol on a 1-g scale afforded the desired adduct **(±)-122j** in 68% yield. The demethoxycarbonylation of **(±)-122j** with 2.0 equiv LiOH proved to be unproblematic and the desired nitropropyl intermediate **(±)-159** was obtained in quantitative yield and in essentially pure form after an aqueous extraction. The ease of demethoxycarbonylation of **(±)-122j** compared to **(±)-122c** can probably be explained by the significantly lower lability of the 2-methylphenyl group, whose inductively donating methyl group reduces the stability of the phenolate anion and sterically hinders its displacement by water.

Reduction of the crude product **(±)-159** with $LiAlH_4$ afforded the primary amine **(±)-160** in 79% yield. Monomethylation of the amine was carried out *via* the carbamate intermediate **(±)-161**, which was smoothly reduced with $LiAlH_4$ to furnish the target molecule **(±)-129** in an overall 42% yield over 5 steps.

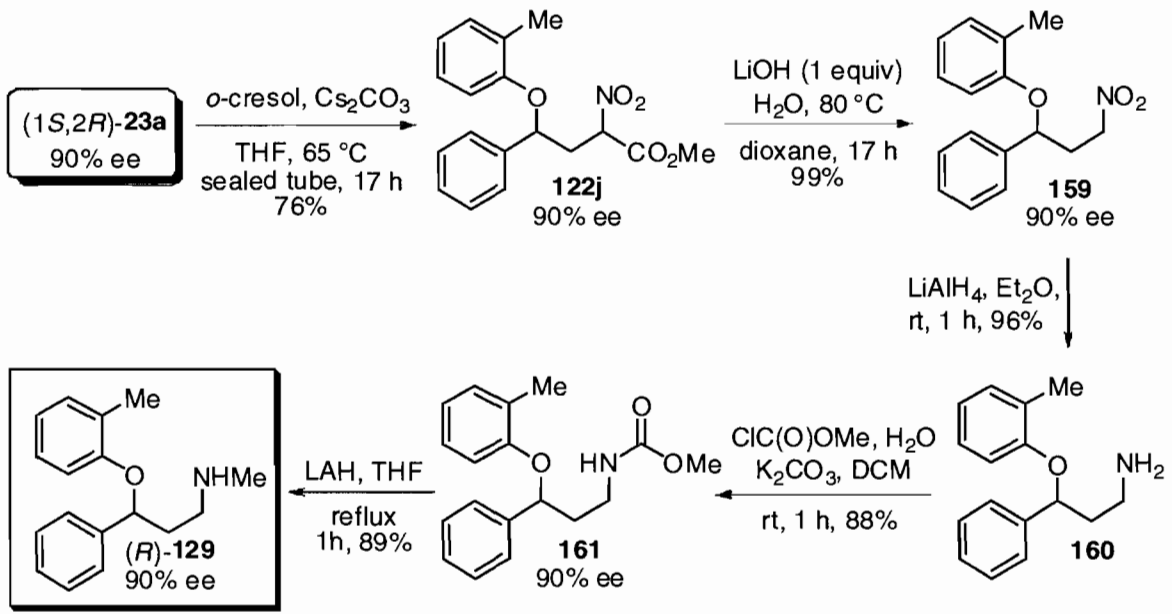
Scheme 62: Racemic synthesis of atomoxetine **(±)-129**



4.3.4 Enantioselective synthesis of (*R*)-129

The enantioselective synthesis of (*R*)-**129** was carried out using the cyclopropane (1*S*,2*R*)-**23a** (Scheme 63). Ring-opening of (1*S*,2*R*)-**23a** (90% ee) with *o*-cresol afforded the desired adduct **122j** in 76% yield and with 90% ee. Demethoxycarbonylation was performed with 1.0 equiv LiOH to avoid possible racemization and gave the nitropropyl intermediate **159** with 90% ee and 99% yield following chromatographic purification. Reduction of the purified **159** with $LiAlH_4$ gave the primary amine product **160** in an improved 96% yield. Carbamate formation afforded **161** in 88% yield, which was reduced to the target molecule (*R*)-**129** in 89% yield and with no loss of optical purity. Overall, the synthesis was carried out with complete preservation of the enantiomeric excess from the cyclopropane (1*S*,2*R*)-**23a** (90% ee) and in 56% yield over 5 steps.

Scheme 63: Enantioselective synthesis of atomoxetine (*R*)-**129**

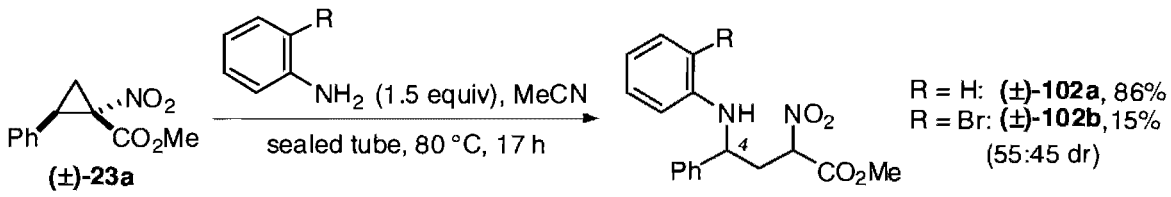


5 Conclusions and future work

5.1 Summary and conclusions

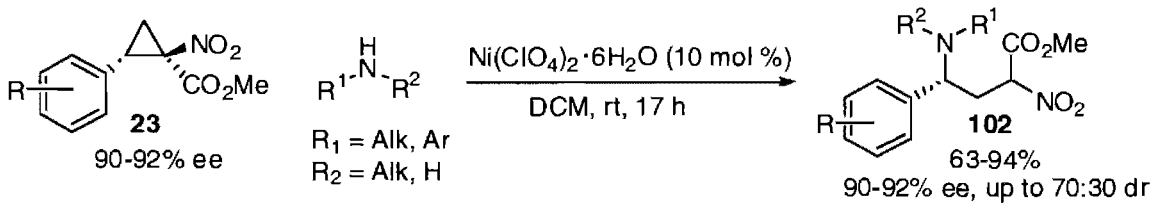
Ring-opening of methyl 1-nitrocyclopropanecarboxylates **23** with diverse amine nucleophiles has been developed. Under the optimized thermal conditions, cyclopropane **(±)-23a** was shown to undergo efficient ring-opening by aniline to afford the acyclic product **(±)-102a** in 86% yield (Scheme 64). Complete preservation of the optical purity at C-4 was observed when the enantioenriched cyclopropane (1*R*,2*S*)-**23** was used. However, the reaction was found to be sensitive to steric hindrance, since ring-opening of **(±)-23a** with *o*-bromoaniline under the optimized conditions gave the desired product **(±)-102b** in a disappointing 15% yield.

Scheme 64: Addition of aniline derivatives to **(±)-23a** under optimized thermal conditions



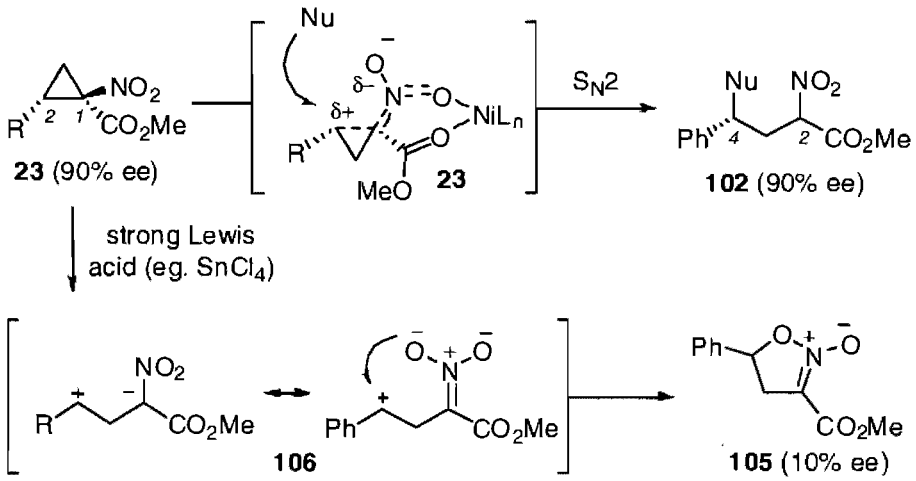
It was found that Lewis acidic catalysis can circumvent this problem by activating the scissile bond of the cyclopropane toward efficient nucleophilic ring-opening at ambient temperature. Optimization of reaction conditions identified $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %) as the most effective Lewis acid. A variety of electron-rich and electron-poor aniline derivatives with different degrees of steric hindrance, as well as several secondary aliphatic amines were shown to ring-open cyclopropanes **23** in good yield (63-94%) and with complete 1,5-regioselectivity (Scheme 65).

Scheme 65: Lewis acid-catalyzed ring-opening of **23** by amine nucleophiles



Full transfer of the enantiomeric excess and an inversion of the absolute configuration was observed in the ring-opened products **102** at C-4. The absolute configuration was proven by derivatizing the adduct **102i** to a pharmaceutically active compound (*R*)-**131** and comparing the value of optical rotation to that disclosed in the literature (Scheme 68).[70] The fidelity of the ee transfer and the inversion of the absolute configuration at C-4 support a mechanism in which the coordination of the bidentate Lewis acid to the cyclopropane acceptor groups polarizes the scissile bond of the three-membered ring without cleaving it into an achiral zwitterionic intermediate **106** (Scheme 66). Charge separation along C1-C2 in **23** is rationalized to catalyze the regioselective attack by amine nucleophiles *via* an S_N2 process. The existence of the zwitterionic **106** with more strongly activating Lewis acids such as $SnCl_4$ was established by isolating the rearrangement product **105** which was found to be nearly racemic.

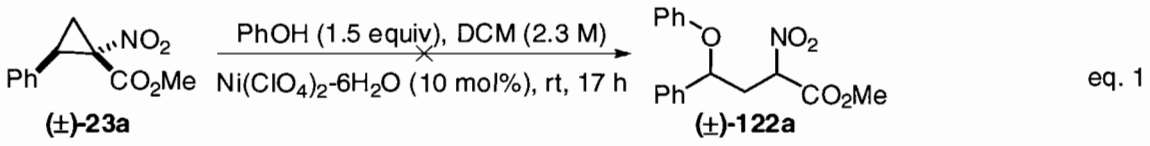
Scheme 66: Proposed mechanism of the nucleophilic ring-opening of **23**

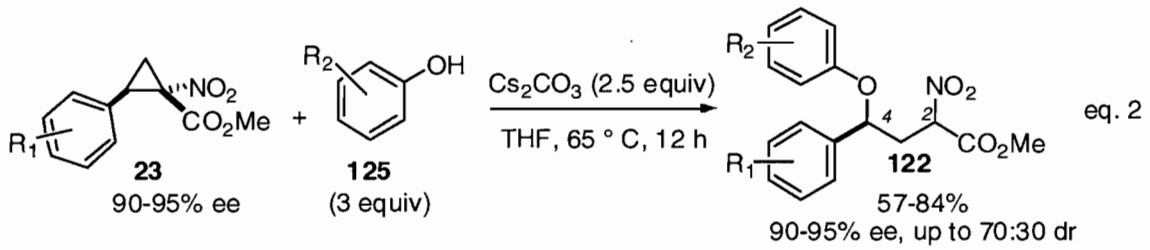


The nucleophilic ring-opening methodology was extended to phenol nucleophiles. Though Lewis acidic catalysis failed to activate (±)-**23a** toward a nucleophilic attack by phenol (Scheme 67, eq. 1), cesium phenolates under thermal conditions were found to cleanly afford the ring-opened products **122** (Scheme 67, eq. 2). The reaction was shown to tolerate a variety of substituents on both the aromatic alcohol **125** and the cyclopropane **23**, and afford the products **122** in good yield (53-84%). Full preservation of the enantiomeric excess and an inversion of the absolute configuration at C-4 of **122** was observed when

enantioenriched cyclopropanes were used. This was proven by derivatizing the enantioenriched adduct **122j** to the pharmaceutical (*R*)-**129** and comparing its optical rotation with the literature value.[64] Further evidence was obtained from an X-ray crystallographic analysis of the indenyl derivative (±)-**122h**, whose relative configuration confirmed the S_N2 inversion at C-4. Complete 1,5-regiochemistry of nucleophilic addition was observed in all reactions.

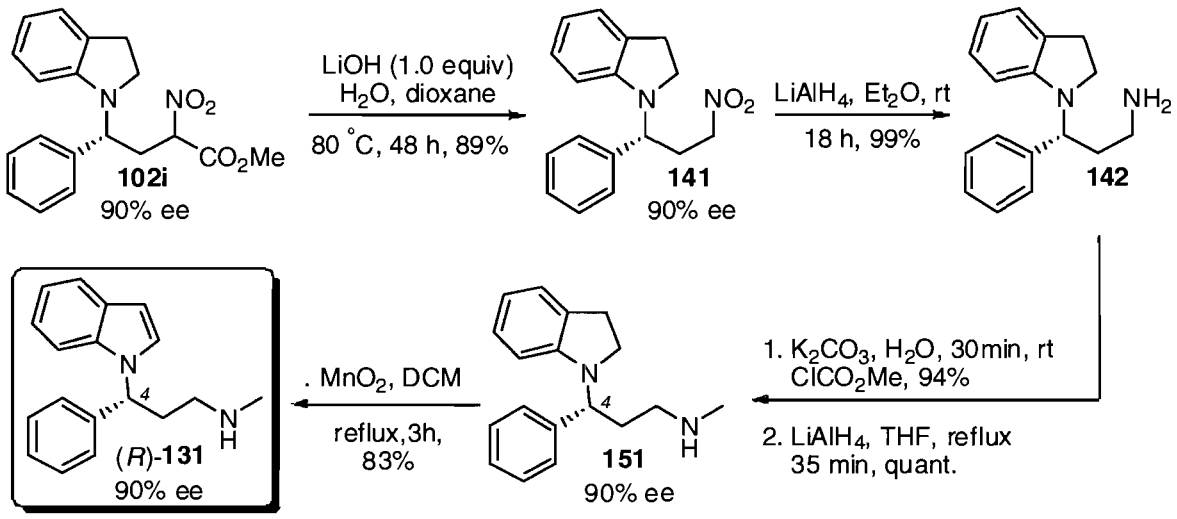
Scheme 67: Ring-opening of **23** with cesium phenolates





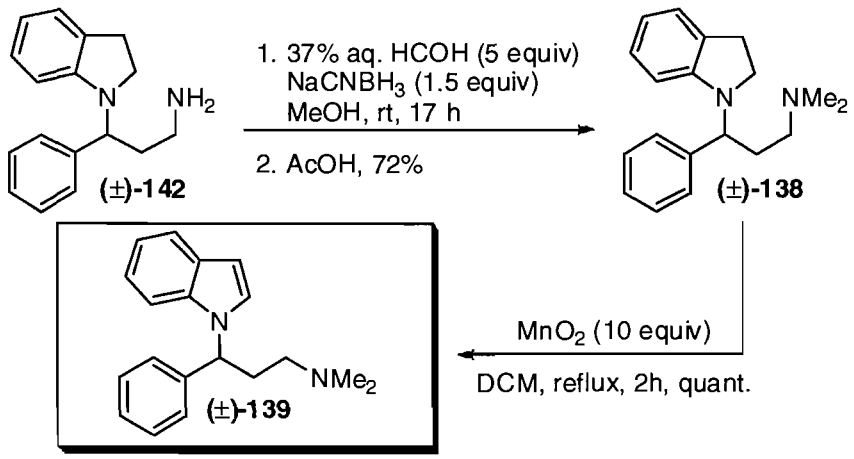
The ring-opening methodologies were applied to the enantioselective syntheses of the dual serotonin/norepinephrine reuptake inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenyl-propan-1-amine (*R*)-**131**[70] and the norepinephrine reuptake inhibitor atomoxetine (Strattera™) (*R*)-**129**.[66] In addition, a racemic dimethylated derivative of (*R*)-**131**, (±)-**139**[70] was synthesized. The inhibitor (*R*)-**131** was synthesized in 69% yield and with 90% ee over 6 steps starting from the enantioenriched ring-opened product **102i** (Scheme 68). Demethoxycarbonylation of **102i** by saponification with aqueous LiOH afforded the nitropropyl intermediate **141**. The nitro group was reduced to the the primary amine **142** and converted to the monomethyl derivative **151** in two steps. Oxidation of the indoline functionality to indole in **151** afforded the target molecule (*R*)-**131**. Using this optimized route, complete transfer of the optical activity from the cyclopropane to the final product was achieved. By varying substituents on indoline and the cyclopropane at C-2, different enantioenriched derivatives of the inhibitor could in principle be easily accessed, which have been shown to display different biological activities.[70]

Scheme 68: Enantioselective synthesis of (*R*)-**131**



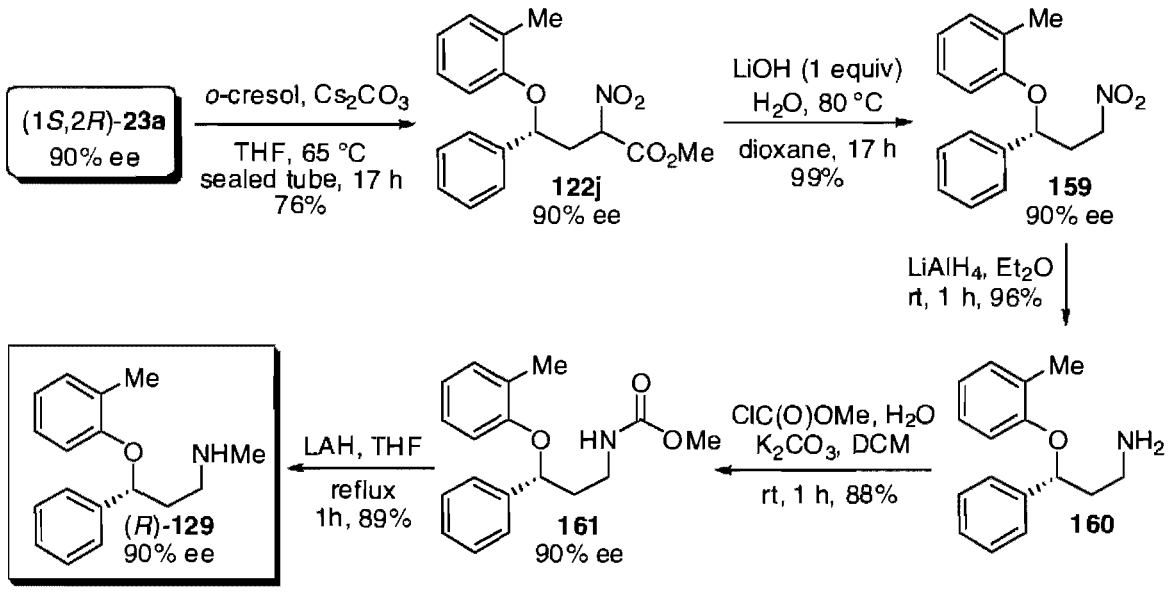
The dimethylated derivative of the dual serotonin/norepinephrine inhibitor, **(±)-139** was synthesized from the racemic common intermediate **(±)-142**. Reductive methylation afforded the diamine **(±)-138** wich was converted to the target molecule **(±)-139** by oxidation of the indoline group with MnO_2 (Scheme 69).

Scheme 69: Synthesis of **(±)-139** from the common intermediate **(±)-142**



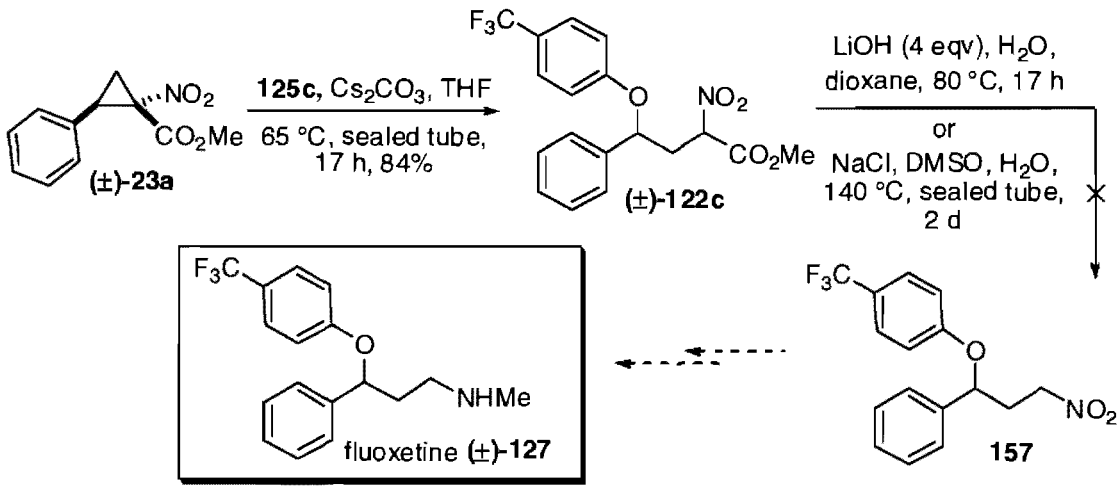
Atomoxetine (*R*)-**129** was synthesized *via* a similar route using the ring-opening of (1*S*,2*R*)-**23a** (90% ee) by *o*-cresol in the first step (Scheme 70). The 5-step synthesis afforded the desired product in 56% overall yield and 90% ee.

Scheme 70: Enantioselective synthesis of atomoxetine (*R*)-**129**



Attempts toward the synthesis of serotonin reuptake inhbitor fluoxetine (Prozac™) **127** [66] using the above routes were not successful, due to the lability of the 4-(trifluoromethyl)-phenoxy group of (±)-**122c** under the attempted decarboxylation conditions (Scheme 71).

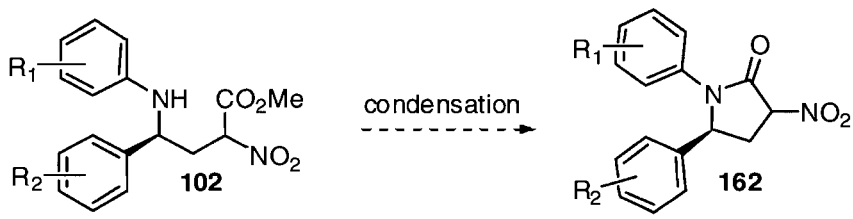
Scheme 71: Attempts toward the synthesis of (±)-**127**



5.2 Future work

The *gem*-nitroester group contained in the ring-opened products **102** and **122** provides a useful handle for further derivatization. Thus, a variety of synthetic targets containing a chiral benzylic or allylic amine or ether can in principle be accessed. For example, self-condensation of **102** could generate substituted chiral γ-lactams of type **162**, which make up the core of numerous natural products[81] and therapeutic agents (Scheme 72).[82]

Scheme 72: Generation of chiral γ-lactams **162** derived from self-condensation of **102**



The cholesterol absorption inhibitor **164**[83] is an example of a biologically active γ-lactam that could potentially be accessed using the developed ring-opening methodology. Nucleophilic addition of 4-chloroaniline to the known cyclopropane **23h**[27a] would afford the adduct **102r**. Self-condensation of **102r** followed by radical denitration would give the chiral γ-lactam **163** which has been shown to undergo substrate-controlled diastereoselective alkylation[83] to afford the target molecule **164** (Scheme 73).

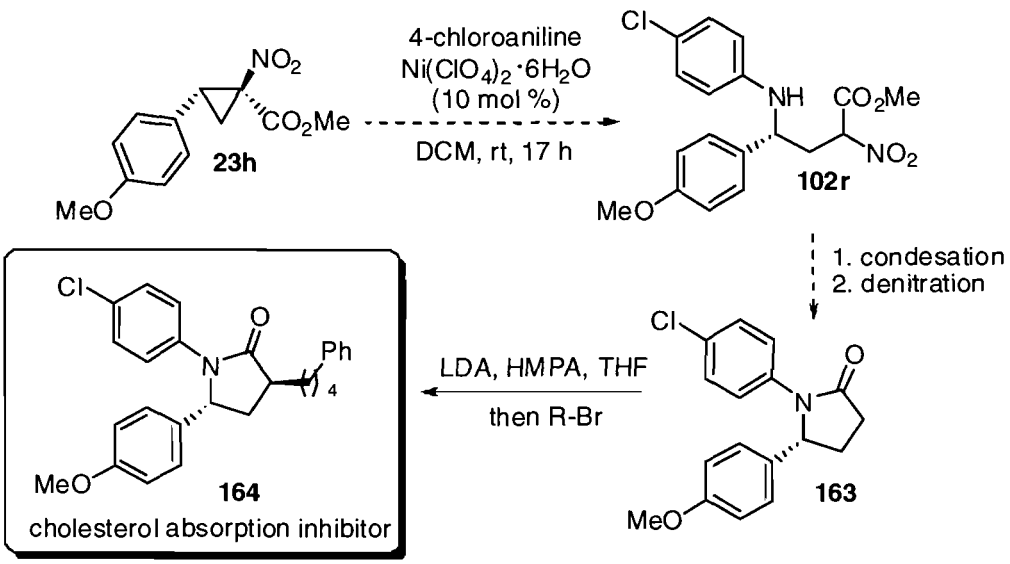
---

[81] For examples, see: (a) Grohmann, M.; Buck, S.; Schäffler, L.; Maas, G. *Adv. Synth. Catal.* **2006**, *348*, 2203; (b) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113; (c) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117; (d) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**,*42*, 355; (e) Barrett, A. G. M.; Head, J.; Smith, L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005.

[82] For examples, see: (a) *Drug Therapeutics Bull.* **2002**, *40*, 30; (b) Sherrill, R. G.; Andrews, C. W.; Bock, W. J.; Davis-Ward, R. G.; Furfine, E. S.; Hazen, R. J.; Rutkowske, R. D.; Spaltenstein, A.; Wright, L. L. *Biorg. Med. Chem. Lett.* **2005**, *15*, 81. (c) Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Biorg. Med. Chem. Lett.* **2004**, *14*, 5689. (d) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. *Biorg. Med. Chem. Lett.* **2004**, *14*, 5685.

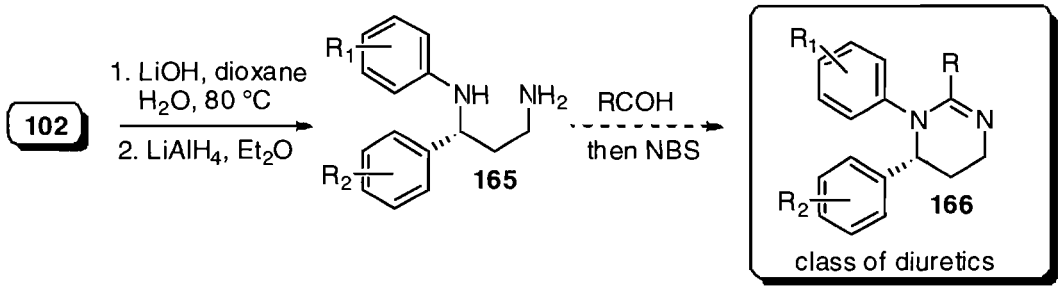
[83] Dugar, S.; Kirkup, M. P.; Clader, J. W.; Lin, S.-I.; Rizvi, R.; Snow, M. E.; Davis Jr., H. R.; McCombie, S. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2947.

Scheme 73: Potential application of γ-lactams **162** derived from condensation of **102**



Chiral diamines **165** derived from demethoxycarbonylation and reduction of **102** represent another useful class of substrates as metal ligands in asymmetric reactions or as pharmaceutical precursors. For example, one-pot condensation of **165** with aldehydes followed by *in situ* oxidation with NBS[84] could furnish a class of diuretics **166** (Scheme 74).[85]

Scheme 74: Potential application of diamines **165** derived from **102**



A variety of transition metal-catalyzed annulation reactions can be envisioned with the ring-opened products **102** and **122**. The presence of the *gem*-nitroester group, for example,

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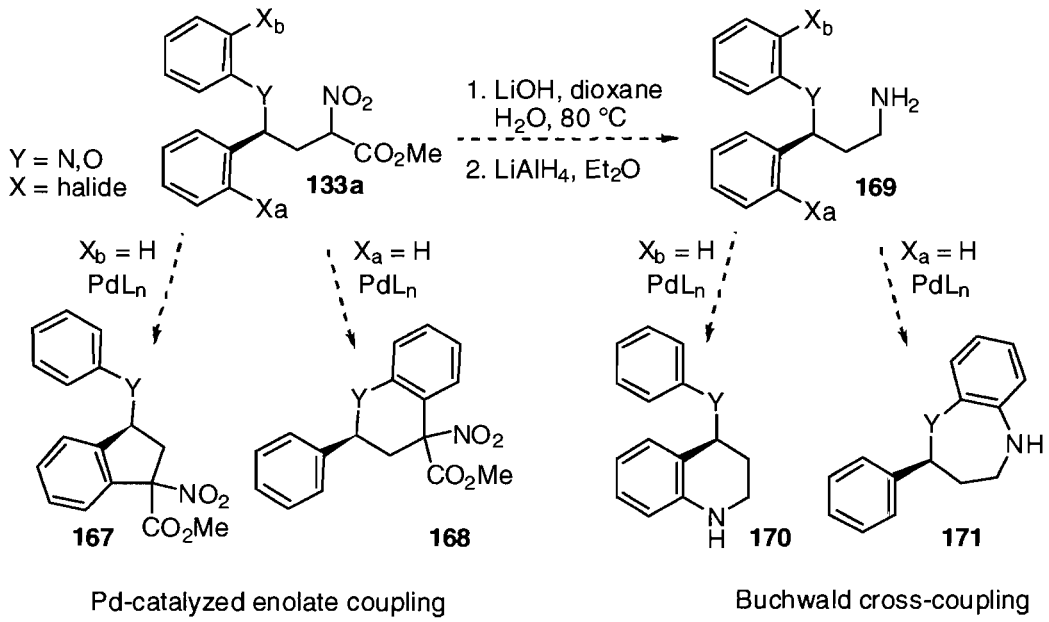
[84] Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638.
[85] Gauthier, J. A.; Jirkovsky, I. US Patent No. 4379926, 1983.

makes the general structure **133a** a suitable substrate for Pd-catalyzed enolate coupling.[86] Intramolecular cross-coupling of **133a** with X_a would afford chiral indane **167**, while cross-coupling with X_b would yield the chiral heterocycle **169** (Scheme 75). Alternatively, the amines **169** derived from demethoxycarbonylation and reduction of **133a** could undergo Pd-catalyzed Buchwald-Hartwig cross-coupling with X_a or X_b to give heterocycles **170** and **171**, respectively.

Scheme 75: Possible Pd-catalyzed annulation reactions of the general structure **124**



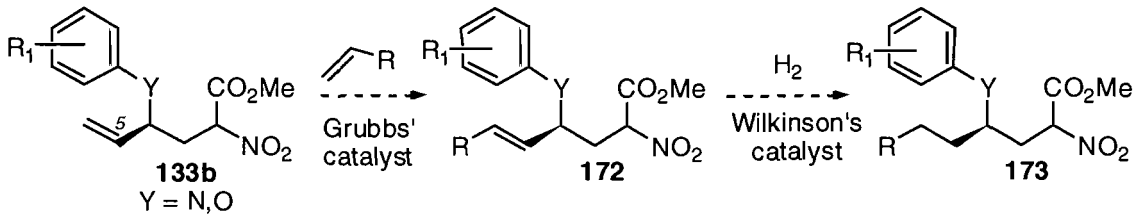
Derivatization of **102** and **122** at C-5 is also conceivable. While the cyclopropanation methodology is limited to aryl or vinyl substituents at the electrophilic carbon of **23**, alkyl-substituted products **173** can in principle be accessed from the vinyl-substituted ring-opened intermediates **133b**. Cross-metathesis of **133b** with an olefin using Grubbs catalyst would afford the alkene **172** which could be chemoselectively reduced with the Wilkinson's catalyst[87] to the saturated products **173** (Scheme 76).

---

[86] Beare, N.A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.

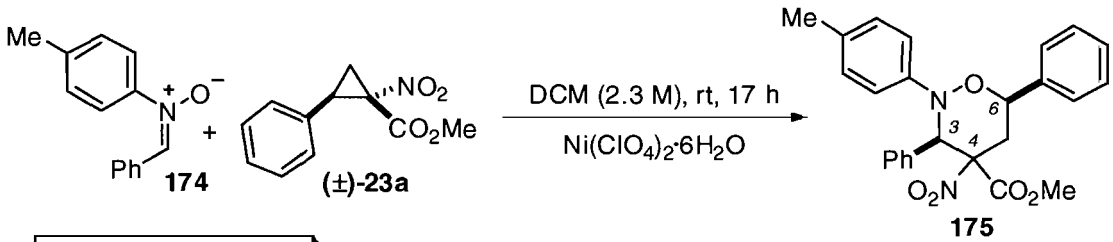
[87] Burgess, K.; Van der Donk, W. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 2, pp 1253-1261.

Scheme 76: Introducing alkyl substituents at C-5 of ring-opened products **133a**



The cyclopropanes **23** can be employed in the homo-[3+2] cycloaddition reactions with nitrones.[37c] Initial experiments using 10 mol % $Ni(ClO_4)_2 \cdot 6H_2O$ showed that the reaction between nitrone **174** and **(±)-23a** at room temperature affords the cycloaddition product **175** in an unoptimized 57% yield as a 60:40 mixture of diastereomers at C-4, whereas an uncatalyzed reaction gives <4% of the desired product (Scheme 77). The ring-expansion product isoxazoline N-oxide **105** was not observed in either reaction. In accord with Kerr's findings[37c] the phenyl substituents at C-3 and C-6 in **175** were obtained in an exclusively *cis*-relationship.

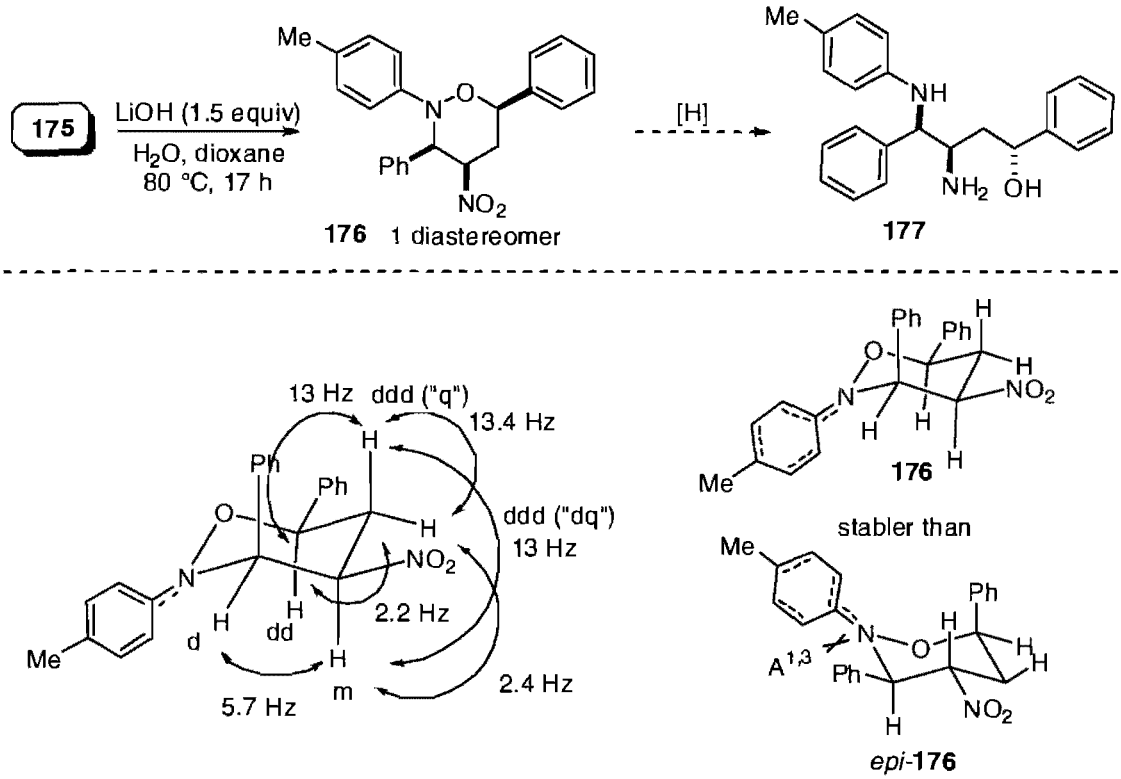
Scheme 77: Homo-[3+2] cycloaddition between **(±)-23a** and **174**



$Ni(ClO_4)_2 \cdot 6H_2O$	yield of **175**	dr
10 mol %	57%	60:40
none	< 4%	-

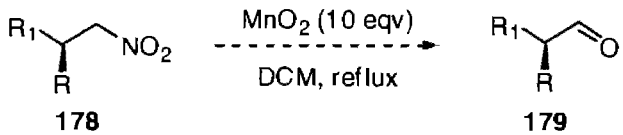
Furthermore, decarboxylation of **175** with LiOH in dioxane at 80 °C furnished a single diastereomer **176**, whose relative configuration was elucidated from the coupling constants and splitting patterns in ^{1}H NMR, and can be rationalized by the minimization of the pseudo-allylic $A^{1,3}$ strain (Scheme 78). The potential of this methodology lies in the facile synthesis of chiral diaminoalcohols **177** *via* the reduction of the nitro group and the N-O bond in **176**.

Scheme 78: Application of the homo-[3+2] cycloaddition between (±)-**23a** and **174**



The capacity of the unexpected Nef-type reaction observed Section 4.2.1 (Scheme 52) could be further explored as a valuable method for converting nitro groups in compounds of type **178** to aldehyde moieties (product **179**) under the mild conditions of MnO_2 oxidation (Scheme 79).

Scheme 79: Nef-type reaction with MnO_2



Compared to the existing methodologies which employ oxidizing reagents,[88] the use of MnO_2 would avoid many compatibility issues. For example, numerous Nef reagents are generally incompatible with double and triple bonds (Oxone™, $KMnO_4$, mCPBA, O_3,

[88] Ono, N. *The nitro group in organic synthesis.* Wiley & Sons: New York, 2001; p. 159-167.

H_2O_2, dimethyldioxirane, MoO_5-pyridine-HMPA complex, $^tBuOOH/VO(acac)_2$), and/or with non-tertiary alcohols (ceric ammonium nitrate, tetrapropylammonium perruthenate, *m*-iodoxbenzoic acid and sodium chlorite); those Nef reagents compatible with an unsaturated bond can over-oxidize the nitro group to a carboxylic acid (e.g. $NaNO_2$/AcOH). The classical Nef conditions employing an acid[89] and some reductive methods such as the treatment with $TiCl_3$[88] are also incompatible with acid-sensitive substrates and racemization-prone aldehyde products bearing a chiral group in the α-position. The neutral pH of MnO_2 oxidation should in principle avoid racemization at the acidic α-carbon of aldehydes, allowing for the conversion of the readily available chiral β-substituted nitro compounds **178**[90] into α-substituted aldehydes **179** without any loss of the enantiomeric excess (Scheme 79). Moreover, MnO_2 is compatible with a variety of functional groups, including double and triple bonds and non-allylic or benzylic alcohols.[91] Reaction of excess MnO_2 with secondary nitro groups, although not yet tried, is expected to provide a useful method of generating ketones.

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[89] Pinnick, H. W. In *Organic Reactions* (Chapter 3), ed. L. A. Paquette. John Wiley: New York, 1990.

[90] Chiral β-substituted nitro compounds can be prepared with high enantioselectivity by a number of methods, including nitroaldol (Henry) reactions (see ref. 88 for a review) and asymmetric Michael addition and reduction of nitroalkanes (for a recent review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**,1877

[91] Cahiez, G.; Alami, M.; Taylor, R. J. K.; Reid, M.; Foot, J. S.; Fader, L. "Manganese Dioxide" in Encyclopedia of Reagents for Organic Synthesis (Ed: L. Paquette) 2007, John Wiley & Sons, New York. DOI: 10.1002/047084289.

6 Experimental

6.1 General information

All non-aqueous reactions were run under an inert atmosphere of argon with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[92] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by natural fluorescence or fluorescence quenching at 254 nm UV light and/or aqueous cerium molybdate, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) and the indicated solvent system according to standard technique. Melting points were obtained on a Büchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^{1}H, ^{13}C, DEPT 135, COSY, HMQC) were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400, or DMX 700 spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, m_c = centered multiplet and br = broad), coupling constant in Hz, integration, and assignment. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.00 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using COSY, HMQC and DEPT 135 experiments.

Where inseparable and/or interconvertible mixtures of diastereomers were obtained, the spectra are reported as observed; where chemical shifts are coincidental, they are reported with an integration of 1 H (assignment *X-H*); where diastereomers display separate

chemical shifts, integrations (and assignments) are reported as 1 H^{d1} (assignment *X-H*^{d1}) and 1 H^{d2} (assignment *X-H*^{d2}) for the first and second diastereomer, respectively. The two diastereomers were arbitrarily assigned as d_1 and d_2 with the following relationship to their chemical shifts:

d_1 = more deshielded diastereomer

d_2 = less deshielded diastereomer

Diastereotopic protons with separate chemical shifts are reported as H_a and H_b; diastereotopic carbons with separate chemical shifts are reported as C_a and C_b. Quaternary carbons identified by DEPT 135 experiments are reported as C_{quat}.

Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm and 20 °C. Data are reported as follows: $[\alpha]_\lambda^{temp}$, concentration (c in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Analytical supercritical fluid chromatography (SFC) was performed on a Thar Technologies SD-AMDS SFC system equipped with a diode array UV detector recording at 210 nm. Data are reported as follows: (column type, eluent, flow rate, pressure, column temperature: retention time (t_r)).

6.2 Reagents

Unless otherwise stated, commercial reagents were obtained from commercial sources (Sigma-Aldrich, Alfa Aesar or Strem) and used without purification. Anhydrous solvents were obtained either by filtration through drying columns (THF, diethyl ether, CH_2Cl_2, benzene, toluene, hexane) on a GlassContour system (Irvine, CA) or by distillation over calcium hydride (Et_3N, pyridine, diisopropylamine). Molecular sieves were dried at 120 °C for 16 hours and stored in a dessicator. Air-sensitive compounds (CuCl, $AgSbF_6$, bisoxazoline ligands **12**, **13**) were stored and handled in a glovebox under an atmosphere of argon. $Ni(ClO_4)_2 \cdot 6H_2O$ was stored in a dessicator due to its high hygroscopicity.

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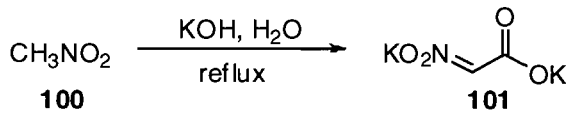
[92] Shriver, D.F.; Drezdzon, M.A. *The manipulation of air-sensitive compounds*; 2nd Edition; Wiley: New York, 1986.

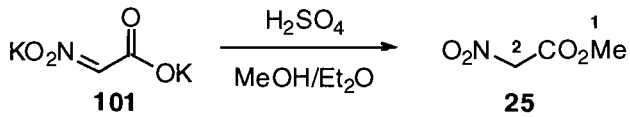
6.3 Synthesis of the cyclopropanes 23

6.3.1 Synthesis of the starting materials 101, 25 and 27



100 101

Dipotassium nitroacetate (101, IZ-01-001).[93] To a three-necked 500 mL flask equipped with a reflux condenser was added KOH (110 g, 1.96 mol, 8 equiv). Water (75 mL) was added slowly maintaining the exotherm, until all the solid was dissolved, and the flask was cooled to room temperature. Nitromethane **100** (27 mL, 0.49 mol, 2 equiv) was added dropwise (solution turns dark brown), and the reaction mixture was stirred at reflux for 1.5 h. After cooling to room temperature, methanol (75 mL) was added; the mixture was cooled to 0 °C for 15 min and filtered, washing with methanol. The resulting light orange solid was dried under vacuum overnight and used without further purification (19.2 g, 0.11 mol, 43%).



101 25

Methyl nitroacetate (25, OL-01-213).[94] In a 500 mL round bottom flask, dipotassium nitroacetate **101** (25.6 g, 0.14 mol, 1 equiv) was dissolved in diethyl ether (160 mL) and methanol (103 mL). The solution was cooled to 0 °C and conc. H_2SO_4 (18 M, 28 mL, 0.49 mol, 3.5 equiv) was added dropwise. The reaction was warmed up to rt and stirred for 4 h. The crude reaction mixture was filtered through Celite, washing with diethyl ether, evaporated under reduced pressure and dissolved in benzene (100 mL). This solution was partitioned between benzene and water, washed with sat. aq. NaCl, dried over Na_2SO_4 and evaporated. The product may be used without further purification or purified by flash chromatography eluting with 100% diethyl ether, and must be refrigerated for storage due

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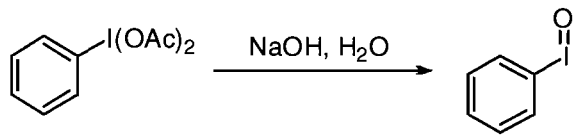
[93] Sutor, D. J.; Llewelyn, F. J.; Maslen, H. C. *Acta Cryst* **1945,** *7*, 145.

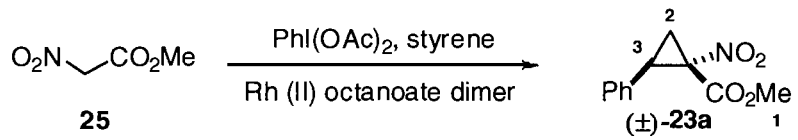
to its instability. Pale yellow oil (4.62 g, 38.8 mmol, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H *1-H*), 5.18 (s, 2H, *2-H*), d = 1.294 g/mL.



27

Phenyliodane oxide (iodosobenzene) (27, OL-01-255).[95] To a solution of NaOH (11.2 g, 0.28 mol, 4.5 equiv) in water (90 mL) was added $PhI(OAc)_2$ (20.0 g, 0.06 mol, 1 equiv). The mixture was stirred for 1 h at rt and 100 mL of water were added. The precipitate was filtered through a Büchner funnel, washing with water and then with chloroform and dried under vacuum overnight, affording a yellow flaky solid, which was used without further purification.

6.3.2 Synthesis of racemic and enantioenriched cyclopropanes 23



25 **(±)-23a**

Methyl 1-nitro-2-phenylcyclopropanecarboxylate ((±)-23a, OL-01-136). In a 100 mL round bottom flask wrapped in Al foil, Rh (II) octanoate dimer (114.5 mg, 0.15 mmol, 0.5 mol %) was combined with methyl nitroester **25** (2.7 mL, 29.4 mmol, 1 equiv), styrene (16.8 mL, 147 mmol, 5 equiv) and $PhI(OAc)_2$ (10.4 g, 32.3 mmol, 1.1 equiv). The reaction was stirred neat overnight at rt, whereby an exotherm was observed and the colour of the reaction mixture changed from the original green to grey. The crude reaction mixture was purified directly by flash chromatography, eluting with a gradient of 0% to 10% EtOAc in hexanes, affording a white crystalline solid (4.09 g, 18.5 mmol, 63%). R_f = 0.28 (10% EtOAc/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, *Ph-H*), 3.78 (t,

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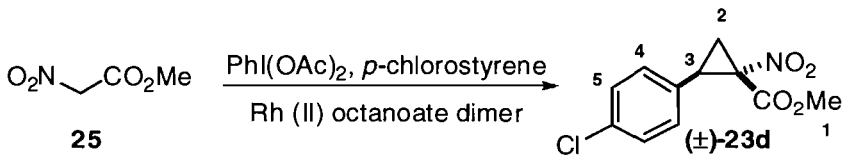
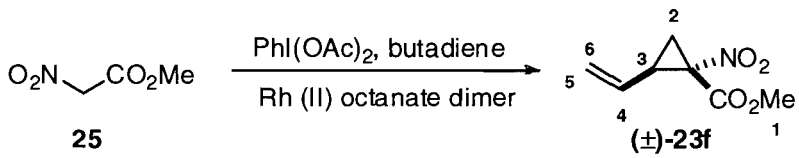
[94] Zen, S.; Koyama, M.; Koto, S. *Org. Synth.***1988**, *6*, 797. Methyl nitroacetate is also commercially available at $99.40/1 g (Sigma-Aldrich, 2007-2008)

[95] Saltzman, H.; Sharefkin, J. G. *Org. Synth.***1973** Coll Vol. 5, 658; **1963** Vol 43, 60.

$^3J_{3,2}$ = 10.3 Hz, *3-H*), 3.52 (s, 3H, *1-H*), 2.47 (dd, $^3J_{3,2}$ = 9.5 Hz, $^2J_{2a,2b}$ = 6.6 Hz, *2-H$_a$*), 2.23 (dd, $^3J_{3,2}$ = 10.5 Hz, $^2J_{2a,2b}$ = 6.6 Hz, *2-H$_b$*). Spectroscopic data are in full agreement with the literature values.[96]



Methyl 2-(4-chlorophenyl)-1-nitrocyclopropanecarboxylate ((±)-23d, OL-01-194). In a 25 mL round bottom flask wrapped in Al foil, Rh (II) octanoate dimer (32.7 mg, 0.42 mmol, 5 mol %) was combined with 4-chlorostyrene (5.8 g, 42.0 mmol, 5 equiv), methyl nitroester **25** (1.00 g, 8.40 mmol, 1 equiv) and PhI(OAc)$_2$ (2.98 g, 9.24 mmol, 1.1 equiv). The reaction was stirred neat overnight at rt and purified directly by flash chromatography eluting with a gradient of 0% to 20% EtOAc in hexanes. White solid (1.39 g, 5.4 mmol, 65%). R_f = 0.73 (30% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H, *5-H*), 7.18-7.16 (m, 2H, *4-H*), 3.75 (t, $^3J_{3,2}$ = 9.8 Hz, *3-H*), 3.56 (s, 3H, *1-H*), 2.43 (dd, $^3J_{3,2a}$ = 9.2 Hz, $^2J_{2a,2b}$ = 6.7 Hz, *2-H$_a$*), 2.25 (dd, $^3J_{3,2b}$ = 10.9 Hz, $^2J_{2a,2b}$ = 6.9 Hz, *2-H$_b$*). Spectroscopic data are in full agreement with the literature values.[96]



Methyl 1-nitro-2-vinylcyclopropanecarboxylate[3] ((±)-23f, OL-01-217). To a 100 mL 3-neck flask equipped with a cold finger (dry ice/acetone) and a needle outlet (against pressure buildup) was added benzene at 0 °C. Butadiene (2.3 g, 42.0 mmol, 5 equiv) was added by bubbling the gas into benzene and periodically weighing the tared flask. Once the appropriate amount of butadiene was dissolved in benzene, Na_2CO_3 (2.05 g, 19.3 mmol, 2.3 equiv), PhI(OAc)$_2$ (2.98 g, 9.20 mmol, 1.1 equiv) and water (20 mL) were added, followed by methyl nitroacetate **25** (1.00 g, 8.40 mmol, 1 equiv) and the reaction was stirred at rt

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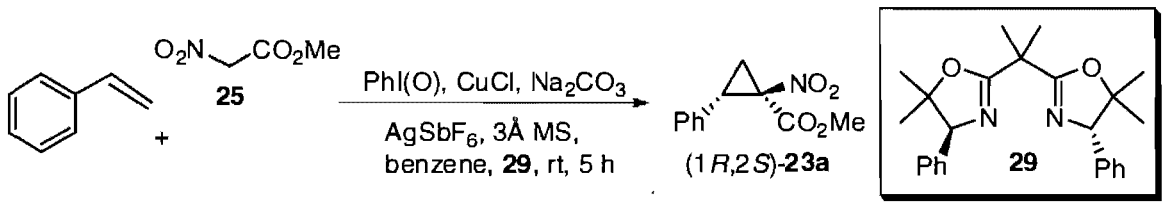
[96] Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262.

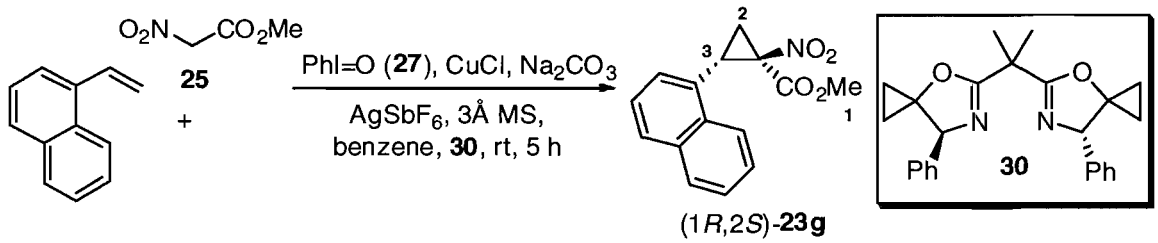
overnight. The crude reaction mixture was evaporated under reduced pressure and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (10 mL) three times and the combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography eluting with 15% EtOAc in hexanes afforded the desired *trans*-product **(±)-23f** (406.7 mg, 2.4 mmol, 28%) and the *cis*-diastereomer (157.1 mg, 0.92 mmol, 11%), both as yellow oils. **(±)-23f**: R_f = 0.62 (20% EtOAc/ Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) for **(±)-23f**: δ 5.47-5.56 (ddd, $^3J_{4,3}$ = 7.6 Hz, $^3J_{4,5\text{-}Z}$ = 10.2 Hz, $^3J_{4,6\text{-}E}$ = 17.3 Hz, 1H, *4-H*), 5.39 (dd, $^3J_{6,4\text{-}E}$ = 17.3 Hz, $^3J_{6,5}$ = 0.7 Hz, 1H, *6-H*), 5.29 (dd, $^3J_{5,4\text{-}Z}$ = 17.3 Hz, $^3J_{6,5}$ = 0.7 Hz, 1H, *5-H*), 3.87 (s, 3H, *1-H*), 3.16 (m_c, 1H, *3-H*), 2.08 (dd, $^3J_{3,2a}$ = 10.4 Hz, $J_{2a,2b}$ = 6.6 Hz, *2-H*$_a$), 2.01 (dd, $^3J_{3,2b}$ = 8.9 Hz, $J_{2a,2b}$ = 6.6 Hz, *2-H*$_b$). Spectroscopic data are in full agreement with the literature values.[96]



Methyl (1*R*,2*S*)-1-nitro-2-phenylcyclopropanecarboxylate ((1*R*,2*S*)-23a, OL-01-164). In a glovebox, a flame-dried 100 mL round bottom flask equipped with a magnetic stirbar was charged with CuCl (10.0 mg, 0.1 mmol, 0.02 equiv), $AgSbF_6$ (41.0 mg, 0.12 mmol, 0.024 equiv) and the bisoxazoline ligand **30** (47.0 mg, 0.12 mmol, 0.024 equiv). The flask was removed from the glovebox and wrapped in aluminum foil. Benzene (50 mL) was added and mixture was stirred for 1 hour. After this time, styrene (2.9 mL, 25.0 mmol, 5 equiv) was added. In a separate vial were added 3Å molecular sieves (1.2 g), Na_2CO_3 (1.22 g, 11.5 mmol, 2.3 equiv) and iodosobenzene **27** (1.21 g, 5.5 mmol, 1.1 equiv). The vial was purged with argon for 10 min and the mixture was quickly added in one portion to the main reaction vessel, followed by methyl nitroacetate **25** (600 mg, 5.0 mmol, 1 equiv). The reaction was stirred fro 3 h at rt with exclusion of light, quenched with water (20 mL) and partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (10 mL) three times, and the combined organic layers were washed with sat. aq.

NaCl, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography eluting with 10% EtOAc in hexanes afforded the desired product (1*R*,2*S*)-**23g** as a pale yellow oil (154.8 mg, 0.70 mmol, 14%, 90% ee). Spectroscopic data are identical to **(±)-23a** and the literature values.[97]

SFC (Chiralcel OJ-H, 1% ^{i}PrOH, 3 mL/min, 150 bar, 40 °C) t_r 3.9 min (minor enantiomer), t_r 4.4 min (major enantiomer).



Methyl (1*R*,2*S*)-2-(1-naphthyl)-1-nitrocyclopropanecarboxylate ((1*R*,2*S*)-23g, OL-01-164). In a glovebox, a flame-dried 100 mL round bottom flask was charged with CuCl (5.94 mg, 0.06 mmol, 0.02 equiv), $AgSbF_6$ (24.7 mg, 0.072 mmol, 0.024 equiv) and the bisoxazoline ligand **30** (27.8 mg, 0.072 mmol, 0.024 equiv). The flask was removed from the glovebox and wrapped in aluminum foil. Benzene (30 mL) was added and mixture was stirred for 1 h. After this time, 1-vinylnaphthalene (1.56 g, 14.97 mmol, 5 equiv) was added. In a separate vial were added 3Å molecular sieves (1 g), Na_2CO_3 (731 mg, 6.90 mmol, 2.3 equiv) and iodosobenzene **27** (1.06 g, 3.3 mmol, 1.1 equiv). The vial was purged with argon for 10 min and the mixture was quickly added in one portion to the main reaction vessel, followed by methyl nitroacetate **25** (357 mg, 3.00 mmol, 1 equiv). The reaction was stirred fro 3 h at rt with exclusion of light, quenched with water (20 mL) and partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (10 mL) three times, and the combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography eluting with 10% EtOAc in hexanes afforded the desired product (1*R*,2*S*)-**23g** as a pale

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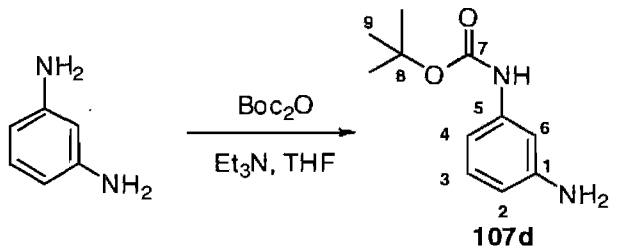
[97] Moreau, B.; Charette, A.B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.

yellow oil (75.5 mg, 0.28 mmol, 12%, 92% ee). R_f = 0.30 (10% EtOAc/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (m_c, 1H, *Arom-H*), 7.84 (m_c, 2H, *Arom-H*), 7.62-7.49 (m, 2H, *Arom-H*), 7.43-7.33 (m, 2H, *Arom-H*), 3.99 (m, 1H, *3-H*), 3.98 (s, 3H, *1-H*), 2.95 (dd, $^3J_{3,2a}$ = 9.5 Hz, $^2J_{2a,2b}$ = 6.9 Hz, *2-H$_a$*), 2.14 (dd, $^3J_{3,2b}$ = 9.9 Hz, $^2J_{2a,2b}$ = 6.9 Hz, *2-H$_b$*). Spectroscopic data are in full agreement with the literature values.[97]

SFC (Chiralcel OD, 0.8% MeOH, 1 mL/min, 200 bar, 40 °C) t_r 16.9 min (major enantiomer), t_r 23.6 min (minor enantiomer).

6.4 Ring-opening of methyl 1-nitrocyclopropanecarboxylates 23 with amine nucleophiles

6.4.1 Synthesis of the starting material 107d

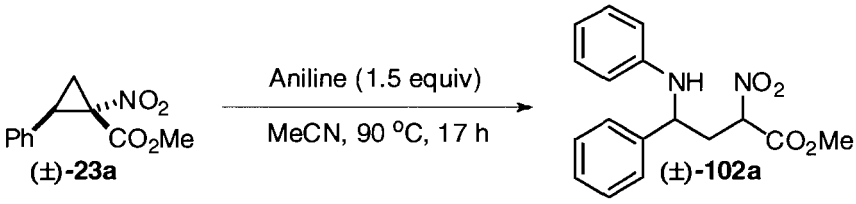


107d

***Tert*-butyl 3-aminophenylcarbamate (107d, OL-01-189).** In a 250 mL flame-dried round bottom flask was added benzene 1,3-diamine (1.00 g, 9.3 mmol, 1 equiv), freshly distilled triethylamine (1.3 mL, 9.5 mmol, 1.02 equiv) and anhydrous THF (50 mL). To this mixture under an atmosphere of argon was added di-*tert*-butyl-dicarbonate (2.02 g, 9.3 mmol, 1 equiv) and the reaction was stirred at rt for 12 h. After evaporating the crude reaction mixture under reduced pressure, the off-white solid residue was redissolved in dichloromethane, washed with 1 M NaOH (10 mL), sat. aq. NaCl (10 mL) and water (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography eluting with 30% EtOAc/Hexane afforded the spectroscopically pure product as a white crystalline solid (1.23 g, 5.9 mmol, 63%, lit.[98] 84%); mp 105-106 °C (lit.[1]: 109-110 °C); R_f = 0.28 (30% EtOAc/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-7.02 (m, 1H, *3-H*), 6.97 (br. s, 1H, *6-H*), 6.55 (d, $^3J_{4,3}$ = 8.5 Hz, 1H, *4-H*), 6.47 (br. s, 1H, C_5-N-*H*), 6.36 (d,

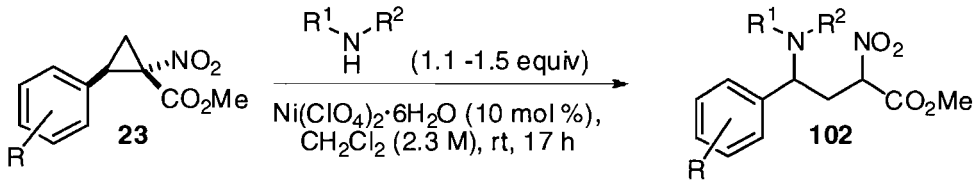
$^3J_{2,3}$ = 8.5 Hz, 1H, *2-H*), 3.68 (br. s, 2H, C_1-N-*H*), 1.52 (s, 9H, *9-H*); Spectroscopic data are in full agreement with the literature values.[98]

6.4.2 Nucleophilic ring opening of (±)-23a with aniline under optimized thermal conditions



Methyl 4-anilino-2-nitro-4-phenylbutanoate ((±)-102a, OL-01-142). In a 2-mL microwave vial containing a magnetic stirbar, cyclopropane **(±)-23a** (100 mg, 0.45 mmol, 1 equiv) was dissolved in acetonitrile (1.5 mL), and aniline (58 μL, 0.68 mmol, 1.5 equiv) was added. The vial was sealed with a Teflon-lined cap and the reaction mixture stirred at 90 °C for 17 h. The crude reaction mixture was cooled to room temperature, evaporated under reduced pressure and purified by flash chromatography, eluting with 25% EtOAc in hexanes to afford pure **(±)-102a** as a yellow crystalline solid (122.0 mg, 0.39 mmol, 86%).

6.4.3 Lewis acid-catalyzed ring opening of 23 with amine nucleophiles



General procedure: In a 2-mL microwave vial containing a magnetic stirbar, cyclopropane **23** (0.23 mmol, 1 equiv) was mixed with the appropriate amine (0.34 mmol, 1.5 equiv), and dichloromethane (100 μL) was added, followed by $Ni(ClO_4)_2 \cdot 6H_2O$ (8.3 mg, 0.023 mmol, 0.1 equiv). The vial was sealed with a Teflon-lined cap to prevent

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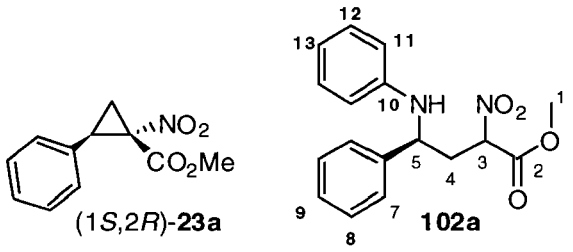
[98] Sauer, M.; Yeung, C.; Chong, J. H.; Patrick, B.O.; MacLachlan, M. J. *J. Org. Chem.* **2006**, *71*, 775.

solvent evaporation (a regular septum is sufficient on a larger scale), and the reaction mixture was stirred at room temperature for 17 h. The crude reaction mixture was evaporated under reduced pressure and purified by flash chromatography. In cases where the remaining excess aniline derivative was difficult to separate by flash chromatography, it was removed by the following aqueous workup prior to chromatographic purification: the organic layer was washed twice with 3 M HCl and the combined acidified aqueous layers were extracted with diethyl ether twice. Combined organic layers were then neutralized with sat. aq. $NaHCO_3$, washed with sat. aq. NaCl, dried over Na_2SO_4 and evaporated under reduced pressure.

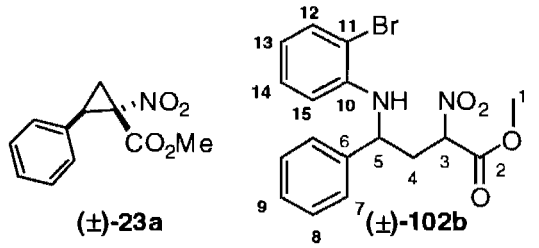


Methyl (4*S*)-4-anilino-2-nitro-4-phenylbutanoate (102a, rac: OL-01-168; ent: OL-01-129). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane (1*S*,2*R*)-**23a** (50.0 mg, 0.23 mmol, 1 equiv, 92% ee) and aniline (29.2 μL, 0.34 mmol, 1.5 equiv), and purified by the aqueous workup described above, followed by flash chromatography, eluting with 30% EtOAc in hexanes, to afford spectroscopically pure **102a** as a crystalline yellow solid (58.2 mg, 0.18 mmol, 82%, 55:45 dr, 92% ee). mp 64-67 °C; R_f = 0.44 (d_1), 0.50 (d_2) (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.42-7.25 (m, 5H, *7,8,9-H*), 7.17-7.10 (m, 2H, *12-H*), 6.72 (t, $^3J_{13,12}$ = 7.4 Hz, 1H, *13-H*), 6.60-6.56 (m, 2H, *11-H*), 5.47 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 8.8 Hz, 1H^{d1}, *3-H^{d1}*), 5.15 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 8.6 Hz, 1H^{d2}, *3-H^{d2}*), 4.57-4.50 (m, 1H, *5-H*), 4.10 (br. s, 1H, N-*H*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.81 (s, 3H^{d2}, *1-H^{d2}*), 2.94-2.80 (m, 1H, *4-H$_a$*), 2.67-2.55 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.2 (C-2^{d1}), 164.8 (C-2^{d2}), 146.2 (C_{quat}-10), 141.2 (C_{quat}-6^{d1}), 140.8 (C_{quat}-6^{d2}), 129.27 (C-12^{d1}), 129.25 (C-12^{d2}), 129.18 (C-8^{d1}), 129.0 (C-8^{d2}), 128.1 (C-9^{d1}), 127.9 (C-9^{d2}), 126.3 (C-7^{d1}), 126.0 (C-7^{d2}), 118.6 (C-13^{d1}), 118.4 (C-13^{d2}), 114.0 (C-11^{d1}),

113.7 (C-11^{d2}), 85.5 (C-3^{d1}), 85.3 (C-3^{d2}), 55.2 (C-5^{d1}), 54.6 (C-5^{d2}), 53.8 (C-1^{d1}), 53.7 (C-1^{d2}), 38.6 (C-4^{d1}), 37.9 (C-4^{d2}); FTIR (neat) 3399, 3028, 2957, 2247, 1750, 1601, 1559, 1504, 1372, 907, 729 cm^{-1}; HRMS Calcd for $C_{17}H_{19}N_2O_4$ $(M+H)^+$: 315.1339. Found 315.1337.

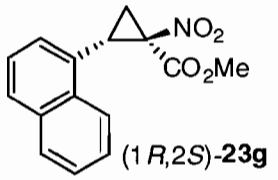
SFC (Chiralcel AD-H, 10% MeOH, 2.5 mL/min, 200 bar, 25 °C) t_r 5.2 min (minor enantiomer, minor diastereomer), t_r 6.3 min (minor enantiomer, major diastereomer), t_r 6.7 min (major enantiomer, minor diastereomer), t_r 11.7 min (major enantiomer, major diastereomer).

Note: upon crystallization, **102a** undergoes a self-catalyzed enrichment of the diastereomeric ratio at C-3 to 85:15 as indicated by ^1H NMR analysis of a freshly prepared solution of the crystallized solid in $CDCl_3$. When left in solution at room temperature, however, **102a** re-equilibrates to 51:49 dr within several hours.

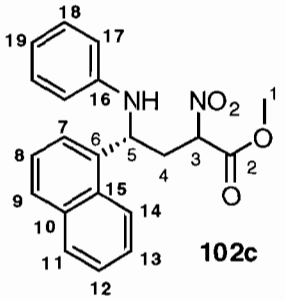


Methyl 4-[(2-bromophenyl)amino]-2-nitro-4-phenylbutanoate ((±)-102b, OL-01-179). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and 2-bromoaniline (58.3 mg, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 7% EtOAc in hexanes, to afford spectroscopically pure (±)-**102b** as a yellow oil (73.8 mg, 0.19 mmol, 83%, 50:50 dr). R_f = 0.76 (30% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.45-7.26 (m, 6H, *7,8,9,15-H*), 7.09-7.02 (m, 1H, *12-H*), 6.58 (m_c, 1H, *14-H*), 6.50 (ddd, $^3J_{13,14}$ = 8.3 Hz, $^3J_{13,12}$ = 13.0 Hz, $^4J_{13,15}$ = 1.4 Hz, 1H, *13-H*), 5.46 (dd, $^3J_{3,4a}$ = 5.2 Hz, $^3J_{3,4b}$ = 8.6 Hz, $1H^{d1}$, *3-H*^{d1}), 5.12 (dd, $^3J_{3,4a}$ = 4.9 Hz, $^3J_{3,4b}$ = 8.9 Hz, $1H^{d2}$,

3-H^{d2}), 4.75 (m, 1H, N-*H*), 4.63-4.52 (m, 1H, *5-H*), 3.87 (s, 3H^{d1}, *1-H*^{d1}), 3.82 (s, 3H^{d2}, *1-H*^{d2}), 3.01-2.84 (m, 1H, *4-H*$_a$), 2.72-2.61 (m, 1H, *4-H*$_b$); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.0 (C-2^{d1}), 164.7 (C-2^{d2}), 143.08 (C_{quat}-10^{d1}), 143.03 (C_{quat}-10^{d2}), 140.6 (C_{quat}-6^{d1}), 140.1 (C_{quat}-6^{d2}), 132.45 (C-15^{d1}), 132.43 (C-15^{d2}), 129.3 (C-8^{d1}), 129.1 (C-8^{d2}), 128.5 (C-12^{d1}), 128.4 (C-12^{d2}), 128.3 (C-9^{d1}), 128.0 (C-9^{d2}), 126.3 (C-7^{d1}), 125.9 (C-7^{d2}), 119.1 (C-14^{d1}), 118.9 (C-14^{d2}), 113.0 (C-13^{d1}), 112.7 (C-13^{d2}), 110.5 (C_{quat}-11^{d1}), 110.3 (C_{quat}-11^{d2}), 85.31 (C-3^{d1}), 85.29 (C-3^{d2}), 55.1 (C-5^{d1}), 54.7 (C-5^{d2}), 53.9 (C-1^{d1}), 53.8 (C-1^{d2}), 38.7 (C-4^{d1}), 38.0 (C-4^{d2}); FTIR (neat) 3393, 2954, 1750, 1595, 1558, 1453, 1268, 1019, 908, 741 cm^{-1}; HRMS Calcd for $C_{17}H_{18}N_2O_4$ $(M+H)^+$: 393.0444. Found 393.0449.



(1*R*,2*S*)-**23g**

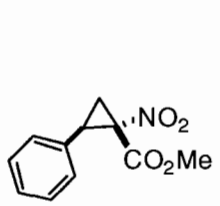


102c

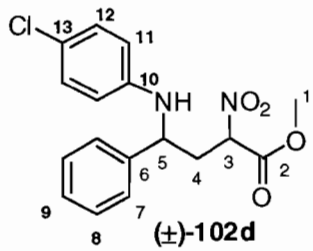
Methyl (4*R*)-4-anilino-4-(1-naphthyl)-2-nitrobutanoate (102c, OL-01-185). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane (1*R*,2*S*)-**23g** (50.0 mg, 0.18 mmol, 1 equiv, 92% ee) and aniline (23.8 μL, 0.28 mmol, 1.5 equiv), and purified by the aqueous workup described above, followed by flash chromatography, eluting with a gradient of 15% to 30% EtOAc in hexanes, to afford spectroscopically pure **102c** as an off-white foam (49.3 mg, 0.13 mmol, 73%, 55:45 dr, 92% ee). R_f = 0.59 (d_1), 0.69 (d_2) (10% EtOAc/Toluene); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 8.24 (d, $^3J_{14,13}$ = 8.3 Hz, 1H^{d1}, *14-H*^{d1}), 8.19 (d, $^3J_{14,13}$ = 7.9 Hz, 1H^{d2}, *14-H*^{d2}), 7.94 (d, $^3J_{11,12}$ = 8.2 Hz, 1H, *11-H*), 7.82 (d, $^3J_{7,8}$ = 6.8 Hz, 1H^{d1}, *7-H*^{d1}), 7.80 (d, $^3J_{7,8}$ = 6.3 Hz, 1H^{d2}, *7-H*^{d2}), 7.69-7.39 (m, 4H, *8,9,12,13-H*), 7.14-7.06 (m, 2H, *18-H*), 6.74-6.68 (m, 1H, *19-H*), 6.61-6.55 (m, 2H, *17-H*), 5.69 (dd, $^3J_{3,4a}$ = 4.2 Hz, $^3J_{3,4b}$ = 9.4 Hz, 1H^{d1}, *3-H*^{d1}), 5.50-5.36 (m, 1H + 1H^{d2}, *5-H* + *3-H*^{d2}), 4.29 (br. s, 1H, N-*H*), 3.87 (s, 3H^{d1}, *1-H*^{d1}), 3.81 (s, 3H^{d2}, *1-H*^{d2}), 3.16-3.06 (m, 1H^{d1}, *4-H*$_b^{d1}$), 3.04-2.95 (m, 1H^{d2}, *4-H*$_b^{d2}$), 2.83-2.73 (m, 1H^{d1}, *4-H*$_a^{d1}$), 2.58-2.48 (m, 1H^{d2}, *4-H*$_a^{d2}$); ^{13}C NMR (75

MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.3 (C-2^{d1}), 165.0 (C-2^{d2}), 146.1 (C_{quat}-16^{d1}), 146.0 (C_{quat}-16^{d2}), 136.4 (C_{quat}-6^{d1}), 136.2 (C_{quat}-6^{d2}), 134.12 (C_{quat}-10^{d1}), 134.06 (C_{quat}-10^{d2}), 130.8 (C_{quat}-15^{d1}), 130.6 (C_{quat}-15^{d2}), 129.32 (C-18^{d1}), 129.30 (C-18^{d2}), 129.28 (C-11^{d1}), 129.25 (C-11^{d2}), 128.6 (C-7^{d1}), 128.4 (C-7^{d2}), 126.9, 126.0, 125.6, 122.7 (C-8^{d1}, 9^{d1}, 12^{d1}, 13^{d1}), 126.9, 125.9, 125.5, 122.3 (C-8^{d2}, 9^{d2}, 12^{d2}, 13^{d2}), 122.1 (C-14^{d1}), 121.9 (C-14^{d2}), 118.6 (C-19^{d1}), 118.4 (C-19^{d2}), 113.8 (C-17^{d1}), 113.6 (C-17^{d2}), 85.5 (C-3^{d1}), 85.3 (C-3^{d2}), 53.81 (C-1^{d1}), 53.78 (C-1^{d2}), 50.8 (C-5^{d1}), 50.3 (C-5^{d2}), 37.7 (C-4^{d1}), 37.3 (C-4^{d2}); FTIR (neat) 3393, 3052, 2956, 1752, 1601, 1504, 1436, 1255, 778 cm^{-1}; HRMS Calcd for $C_{21}H_{21}N_2O_4$ $(M+H)^+$: 365.1496. Found 365.1494.

SFC (Chiralcel AD-H, 5% MeOH, 5 mL/min, 150 bar, 25 °C) t_r 5.3 min (minor enantiomer, minor diastereomer), t_r 6.3 min (major enantiomer, minor diastereomer), t_r 6.7 min (major enantiomer, major diastereomer), t_r 8.7 min (minor enantiomer, major diastereomer).



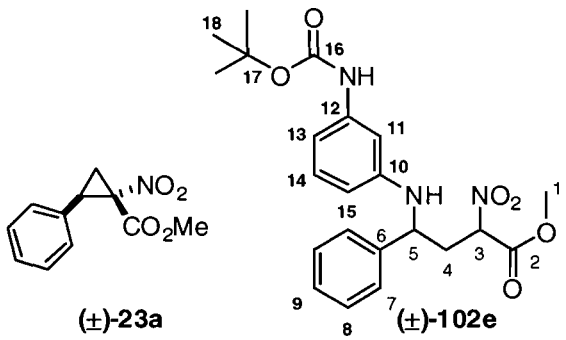
(±)-23a



(±)-102d

Methyl 4-[(4-chlorophenyl)amino]-2-nitro-4-phenylbutanoate ((±)-102d, OL-01-186). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and 4-chloroaniline (43.2, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 10% EtOAc in hexanes, to afford spectroscopically pure (±)-**102d** as a yellow oil (67.9 mg, 0.19 mmol, 86%, 50:50 dr). R_f = 0.52 (d_1), 0.59 (d_2) (10% EtOAc/Toluene); ^1H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.42-7.26 (m, 5H, *7,8,9-H*), 7.07 (m_c, 2H, *12-H*), 6.50 (m_c, 2H, *11-H*), 5.45 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 8.7 Hz, 1H^{d1}, *3-H^{d1}*), 5.14 (dd, $^3J_{3,4a}$ = 5.0 Hz, $^3J_{3,4b}$ = 8.8 Hz, 1H^{d2}, *3-H^{d2}*), 4.47 (m_c, 1H, *5-H*), 4.12 (br. s, 1H, N-*H*), 3.83 (s, 3H^{d1}, *1-H^{d1}*), 3.80 (s, 3H^{d2}, *1-H^{d2}*), 2.92-2.79 (m, 1H, *4-H$_a$*), 2.66-2.54 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.1 (C-2^{d1}), 164.7 (C-2^{d2}), 144.8

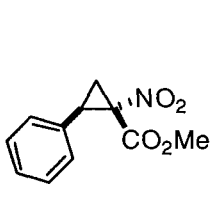
(C_{quat}-10^{d1}), 144.7 (C_{quat}-10^{d2}), 140.7 (C_{quat}-6^{d1}), 140.3 (C_{quat}-6^{d2}), 129.2 (C-8^{d1}), 129.08 (C-8^{d2}), 129.07 (C-12^{d1}), 129.05 (C-12^{d2}), 128.3 (C-9^{d1}), 128.0 (C-9^{d2}), 126.2 (C-7^{d1}), 125.9 (C-7^{d2}), 123.1 (C_{quat}-13^{d1}), 123.0 (C_{quat}-13^{d2}), 115.1 (C-11^{d1}), 114.8 (C-11^{d2}), 85.4 (C-3^{d1}), 85.2 (C-3^{d2}), 55.3 (C-5^{d1}), 54.7 (C-5^{d2}), 53.80 (C-1^{d1}), 53.79 (C-1^{d2}), 38.4 (C-4^{d1}), 37.8 (C-4^{d2}); FTIR (neat) 3400, 3029, 1749, 1598, 1559, 1495, 1254, 908, 731 cm^{-1}; HRMS Calcd for $C_{17}H_{18}N_2O_4Cl$ $(M+H)^+$: 349.0950. Found 349.0948.



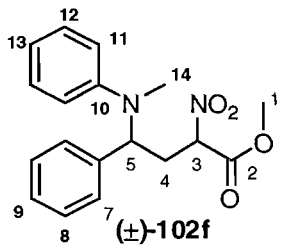
(±)-23a (±)-102e

Methyl 4-({3-[(*tert*-butoxycarbonyl)amino]phenyl}amino)-2-nitro-4-phenyl-butanoate ((±)-102e, OL-01-196). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and *tert*-butyl 3-aminophenylcarbamate **107d** (70.6 mg, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 20% EtOAc in hexanes, to afford spectroscopically pure (±)-**102e** as a crystalline yellow solid (64.2 mg, 0.15 mmol, 66%, 50:50 dr). mp 112-114 °C; R_f = 0.53 (30% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.23 (m, 5H, *7,8,9-H*), 7.00 (m_c, 1H, *14-H*), 6.87 (br. s, 1H^{d1}, *11-H^{d1}*), 6.83 (br. s, 1H^{d2}, *11-H^{d2}*), 6.60-6.53 (m, 1H, *13-H*), 6.40 (br. s, 1H, C_{12}-N-*H*), 6.22 (m_c, 1H, *15-H*), 5.44 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 9.0 Hz, 1H^{d1}, *3-H^{d1}*), 5.12 (dd, $^3J_{3,4a}$ = 5.3 Hz, $^3J_{3,4b}$ = 8.8 Hz, 1H^{d2}, *3-H^{d2}*), 4.51-4.47 (m, 1H, *5-H*), 4.12 (br. s, 1H, C_5-N-*H*), 3.83 (s, 3H^{d1}, *1-H^{d1}*), 3.80 (s, 3H^{d2}, *1-H^{d2}*), 2.89-2.77 (m, 1H, *4-H$_b$*), 2.63-2.48 (m, 1H, *4-H$_a$*), 1.50 (s, 9H, *18-H*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.2 (C-2^{d1}), 164.8 (C-2^{d2}), 152.6 (C_{quat}-16), 147.03 (C_{quat}-10^{d1}), 147.02 (C_{quat}-10^{d2}), 141.1 (C_{quat}-61^{d}), 140.7 (C_{quat}-6^{d2}), 139.3 (C_{quat}-12), 129.76 (C-14^{d1}), 129.74 (C-14^{d2}), 129.1 (C-8^{d1}), 129.0 (C-8^{d2}), 128.1 (C-9^{d1}), 127.8 (C-9^{d2}), 126.3 (C-7^{d1}), 125.9 (C-7^{d2}), 108.6

(C-13^{d1}), 108.5 (C-13^{d2}), 108.1 (C-15^{d1}), 108.0 (C-15^{d2}), 104.3 (C-11^{d1}), 104.0 (C-11^{d2}), 85.4 (C-3^{d1}), 85.3 (C-3^{d2}), 80.3 (C_{quat}-17), 55.0 (C-5^{d1}), 54.3 (C-5^{d2}), 53.8 (C-1^{d1}), 53.7 (C-1^{d2}), 38.0 (C-4^{d1}), 37.8 (C-4^{d2}), 28.3 (C-18); FTIR (neat) 3385, 2977, 1751, 1707, 1559, 1526, 1479, 1231, 908, 729.cm^{-1}; HRMS Calcd for $C_{22}H_{28}N_3O_6$ $(M+H)^+$: 430.1973. Found 430.1980.

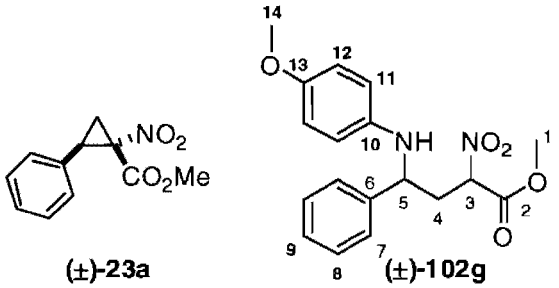


(±)-23a



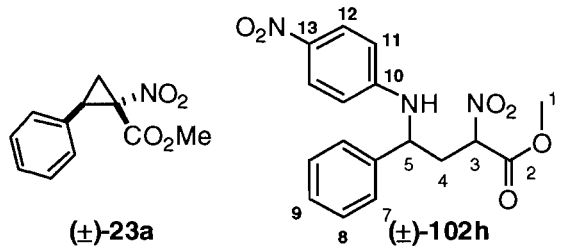
(±)-102f

Methyl 4-[methyl(phenyl)amino]-2-nitro-4-phenylbutanoate ((±)-102f OL-01-188). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and *N*-methylaniline (36.7 μL, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 100% toluene, to afford spectroscopically pure **(±)-102f** as a yellow oil (59.2 mg, 0.18 mmol, 80%, 55:45 dr). R_f = 0.81 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.16 (m, 7H, *7,8,9,12-H*), 6.88-6.81 (m, 3H, *11,13-H*), 5.45 (dd, $^3J_{3,4a}$ = 4.2 Hz, $^3J_{3,4b}$ = 9.5 Hz, 1H^{d1}, *3-H^{d1}*), 5.29-5.20 (m, 1H^{d2} + 1H^{d1}, *5-H^{d1}* + *3-H^{d2}*), 5.10 (dd, $^3J_{5,4a}$ = 4.6 Hz, $^3J_{5,4a}$ = 11.5 Hz, 1H^{d2}, *5-H^{d2}*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.80 (s, 3H^{d2}, *1-H^{d2}*), 3.11-2.91 (m, 2H, *4-H*), 2.62 (s, 3H^{d1}, *14-H^{d1}*), 2.60 (s, 3H^{d2}, *14-H^{d2}*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.3 (C-2^{d1}), 164.9 (C-2^{d2}), 150.1 (C_{quat}-10^{d1}), 150.0 (C_{quat}-10^{d2}), 138.0 (C_{quat}-6^{d1}), 137.8 (C_{quat}-6^{d2}), 129.4 (C-8^{d1}), 129.3 (C-8^{d2}), 128.6 (C-12^{d1}), 128.5 (C-12^{d2}), 127.84 (C-9^{d1}), 127.77 (C-9^{d2}), 126.9 (C-7^{d1}), 126.8 (C-7^{d2}), 118.6 (C-13^{d1}), 118.4 (C-13^{d2}), 114.6 (C-11^{d1}), 114.3 (C-11^{d2}), 85.6 (C-3^{d1}), 85.4 (C-3^{d2}), 59.05 (C-5^{d1}), 59.03 (C-5^{d2}), 53.7 (C-1^{d1}), 53.6 (C-1^{d2}), 32.2 (C-4^{d1}), 32.0 (C-4^{d2}), 31.81 (C-14^{d1}), 31.78 (C-14^{d2}); FTIR (neat) 2955, 1750, 1596, 1558, 1372, 1266, 1108, 991, 750, 697 cm^{-1}; HRMS Calcd for $C_{18}H_{21}N_2O_4$ $(M+H)^+$: 329.1496. Found 329.1497.



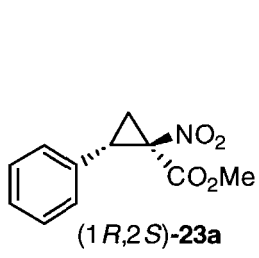
(±)-23a (±)-102g

Methyl 4-[(4-methoxyphenyl)amino]-2-nitro-4-phenylbutanoate ((±)-102g, OL-01-192). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and *p*-methoxyaniline (41.7 mg, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 30% EtOAc in hexanes, to afford spectroscopically pure **(±)-102g** as a dark yellow oil (55.0 mg, 0.16 mmol, 71%, 50:50 dr). R_f = 0.47 (d_1), 0.52 (d_2) (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.40-7.23 (m, 5H, *7,8,9-H*), 6.73-6.69 (m, 2H, *12-H*), 6.55-6.51 (m, 2H, *11-H*), 5.52 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 8.8 Hz, 1H^{d1}, *3-H^{d1}*), 5.17 (dd, $^3J_{3,4a}$ = 5.0 Hz, $^3J_{3,4b}$ = 8.6 Hz, 1H^{d2}, *3-H^{d2}*), 4.46-4.40 (m, 1H, *5-H*), 3.83 (s, 3H^{d1}, *1-H^{d2}*), 3.81 (s, 3H^{d2}, *1-H^{d1}*), 3.78 (br. s, 1H, N-*H*), 3.71 (s, 3H^{d1}, *14-H^{d1}*), 3.70 (s, 3H^{d2}, *14-H^{d2}*), 2.91-2.77 (m, 1H, *4-H$_a$*), 2.64-2.51 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.3 (C-2^{d1}), 164.9 (C-2^{d2}), 152.8 (C_{quat}-13^{d1}), 152.7 (C_{quat}-13^{d2}), 141.4 (C_{quat}-10^{d1}), 141.0 (C_{quat}-10^{d2}), 140.2 (C_{quat}-6^{d1}), 140.1 (C_{quat}-6^{d2}), 129.1 (C-8^{d1}), 129.0 (C-8^{d2}), 128.0 (C-9^{d1}), 127.8 (C-9^{d2}), 126.3 (C-7^{d1}), 126.0 (C-7^{d2}), 115.7 (C-11^{d1}), 115.3 (C-11^{d2}), 114.7 (C-12), 85.6 (C-3^{d1}), 85.4 (C-3^{d2}), 56.1 (C-5^{d1}), 55.7 (C-5^{d2}), 55.59 (C-14^{d1}), 55.56 (C-14^{d2}), 53.7 (C-1), 38.6 (C-4^{d1}), 38.0 (C-4^{d2}); FTIR (neat) 3372, 2956, 1750, 1708, 1557, 1439, 1357, 1237, 822, 735 cm^{-1}; HRMS Calcd for $C_{18}H_{21}N_2O_5$ $(M+H)^+$: 355.1445. Found 345.1443.

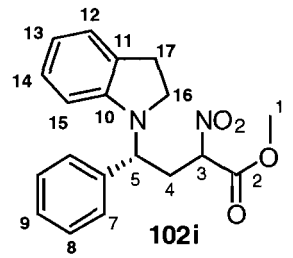


(±)-23a (±)-102h

Methyl 2-nitro-4-[(4-nitrophenyl)amino]-4-phenylbutanoate ((±)-102h, OL-01-198). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and *p*-nitroaniline (41.7 mg, 0.34 mmol, 1.5 equiv). To achieve full conversion, the reaction mixture was stirred for 48h before being evaporated under reduced pressure. The crude mixture was purified by flash chromatography, eluting with 5% EtOAc in toluene, to afford spectroscopically pure **(±)-102h** as a bright yellow viscous oil (74.9 mg, 0.21 mmol, 92%, 50:50 dr). R_f = 0.41 (5% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 8.49 (d, $^3J_{NH,5}$ = 6.1 Hz, 1H^{d1}, N-*H*^{d1}), 8.43 (d, $^3J_{NH,5}$ = 7.8 Hz, 1H^{d2}, N-*H*^{d2}), 8.20 (dd, $^3J_{12b,11}$ = 8.7 Hz, $^4J_{12a,12b}$ = 1.5 Hz, 1H^{d1}, *12-H*$_b^{d1}$), 8.18 (dd, $^3J_{12a,11}$ = 8.6 Hz, $^4J_{12a,12b}$ = 1.5 Hz, 1H^{d1}, *12-H*$_a^{d1}$), 7.45-7.31 (m, 5H + 2H^{d2}, *7,8,9-H + 12-H*^{d2}), 6.77-6.67 (m, 2H, *11-H*), 5.40 (dd, $^3J_{3,4a}$ = 4.7 Hz, $^3J_{3,4b}$ = 9.3 Hz, 1H^{d1}, *3-H*^{d1}), 5.01 (dd, $^3J_{3,4a}$ = 4.4 Hz, $^3J_{3,4b}$ = 9.8 Hz, 1H^{d2}, *3-H*^{d2}), 4.74-4.61 (m, 1H, *5-H*), 3.87 (s, 3H^{d1}, *1-H*^{d1}), 3.81 (s, 3H^{d2}, *1-H*^{d2}), 3.11-2.88 (m, 1H, *4-H*$_a$), 2.77-2.61 (m, 1H, *4-H*$_b$); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.5 (C-2^{d1}), 164.3 (C-2^{d2}), 143.8 (C$_{quat}$-10^{d1}), 143.6 (C$_{quat}$-10^{d2}), 139.8 (C$_{quat}$-6^{d1}), 139.1 (C$_{quat}$-6^{d2}), 136.4 (C$_b$-12^{d1}), 136.3 (C$_a$-12^{d1}), 133.0 (C$_{quat}$-13^{d1}), 132.8 (C$_{quat}$-13^{d1}), 129.6 (C-8^{d1}), 129.4 (C-8^{d2}), 128.8 (C-9^{d1}), 128.4 (C-9^{d2}), 126.8 (C-12^{d2}), 126.4 (C-7^{d1}), 125.9 (C-7^{d2}), 116.8 (C$_a$-11^{d1}), 116.6 (C$_b$-11^{d1}), 114.8 (C$_a$-11^{d2}), 114.5 (C$_b$-11^{d2}), 85.0 (C-3^{d1}), 84.9 (C-3^{d2}), 54.4 (C-5^{d1}), 54.1 (C-5^{d2}), 54.0 (C-1^{d1}), 53.9 (C-1^{d2}), 38.7 (C-4^{d1}), 37.7 (C-4^{d2}); FTIR (neat) 3362, 2957, 1752, 1561, 1501, 1417, 1350, 1235, 1039, 910, 742 cm^{-1}; HRMS Calcd for $C_{17}H_{17}N_3O_6Na$ (M+Na)$^+$: 382.1010. Found 382.1006.



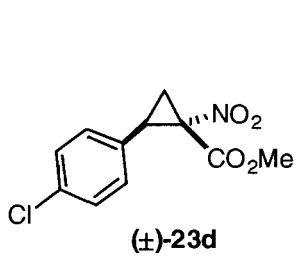
(1*R*,2*S*)-**23a**



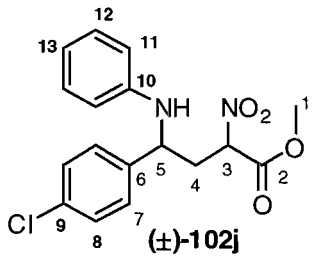
102i

Methyl (4*R*)-4-(2,3-dihydro-1*H*-indol-1-yl)-2-nitro-4-phenylbutanoate (102i, rac: OL-01-195, ent: OL-02-014). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane (1*R*,2*S*)-**23a** (50.0 mg, 0.23 mmol, 1 equiv, 90% ee) and indoline (38 μL, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 20% EtOAc in hexanes, to afford spectroscopically pure **102i** as a beige solid (72.3 mg, 0.21 mmol, 94%, 55:45 dr, 90% ee). mp 82-85 °C, R_f = 0.76 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.25 (m, 5H, *7,8,9-H*), 7.12-7.04 (m, 2H, *12,14-H*), 6.69-6.58 (m, 2H, *13,15-H*), 5.50 (dd, $^3J_{3,4a}$ = 5.1 Hz, $^3J_{3,4b}$ = 8.9 Hz, 1H^{d1}, *3-H^{d1}*), 5.26 (dd, $^3J_{3,4a}$ = 6.3 Hz, $^3J_{3,4b}$ = 7.3 Hz, 1H^{d2}, *3-H^{d2}*), 4.90 (dd, $^3J_{5,4a}$ = 6.4 Hz, $^3J_{5,4b}$ = 9.2 Hz, 1H^{d1}, *5-H^{d1}*), 4.83 (dd, $^3J_{5,4a}$ = 4.7 Hz, $^3J_{5,4b}$ = 11.0 Hz, 1H^{d2}, *5-H^{d2}*), 3.80 (s, 3H^{d1}, *1-H^{d1}*), 3.79 (s, 3H^{d2}, *1-H^{d2}*), 3.44-3.35 (m, 1H, *4-H$_a$*), 3.12-2.80 (m, 5H, *16,17-H, 4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.3 (C-2^{d1}), 164.9 (C-2^{d2}), 150.6 (C$_{quat}$-10^{d1}), 150.5 (C$_{quat}$-10^{d2}), 137.2 (C$_{quat}$-6^{d1}), 137.1 (C$_{quat}$-6^{d2}), 129.7 (C$_{quat}$-11^{d1}), 129.5 (C$_{quat}$-11^{d2}), 128.8 (C-8^{d1}), 128.6 (C-8^{d2}), 128.1 (C-9^{d1}), 128.0 (C-9^{d2}), 127.7 (C-7^{d1}), 127.5 (C-7^{d2}), 127.4 (C-12^{d1}), 127.3 (C-12^{d2}), 124.8 (C-14^{d1}), 124.7 (C-14^{d2}), 117.94 (C-13^{d1}), 117.91 (C-13^{d2}), 107.1 (C-15^{d1}), 107.0 (C-15^{d2}), 85.60 (C-3^{d1}), 85.58 (C-3^{d2}), 55.7 (C-5^{d1}), 55.0 (C-5^{d2}), 53.62 (C-1^{d1}), 53.58 (C-1^{d2}), 46.7 (C-4^{d1}), 46.2 (C-4^{d2}), 32.2 (C-16^{d1}), 31.8 (C-16^{d2}), 28.0 (C-17); FTIR (neat) 3029, 2955, 2849, 1750, 1605, 1558, 1485, 1436, 1328, 1254, 1002, 873, 745 cm^{-1}; HRMS Calcd for $C_{19}H_{21}N_2O_4$ (M+H)$^+$: 341.1496. Found 341.1499.

SFC (Chiralcel OJ-H, 10% ^{i}PrOH, 2 mL/min, 150 bar, 25 °C) t_r 10.9 min (minor enantiomer, minor diastereomer), t_r 15.0 min (minor enantiomer, major diastereomer), t_r 18.6 min (major enantiomer, minor diastereomer), t_r 21.6 min (major enantiomer, major diastereomer).

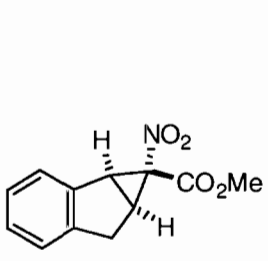


(±)-23d

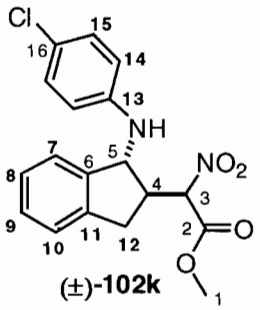


(±)-102j

Methyl 4-anilino-4-(4-chlorophenyl)-2-nitrobutanoate ((±)-102j, OL-01-201). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23d** (57.8 mg, 0.23 mmol, 1 equiv) and aniline (29.2 μL, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 100% toluene, to afford spectroscopically pure **(±)-102j** as a yellow oil (58.6 mg, 0.17 mmol, 74%, 50:50 dr). R_f = 0.43 (toluene); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.36-7.24 (m, 4H, *7,8-H*), 7.13 (m_c, 2H, *12-H*), 6.74 (t, $^3J_{13,12}$ = 7.3 Hz, 1H^{d1}, *13-H^{d1}*), 6.73 (t, $^3J_{13,12}$ = 7.3 Hz, 1H^{d2}, *13-H^{d2}*), 6.54 (m_c, 2H, *11-H*), 5.46 (dd, $^3J_{3,4a}$ = 4.9 Hz, $^3J_{3,4b}$ = 8.9 Hz, 1H^{d1}, *3-H^{d1}*), 5.16 (dd, $^3J_{3,4a}$ = 5.3 Hz, $^3J_{3,4b}$ = 8.3 Hz, 1H^{d2}, *3-H^{d2}*), 4.54-4.49 (m, 1H, *5-H*), 4.04 (br. s, 1H, N-*H*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.82 (s, 3H^{d2}, *1-H^{d2}*), 2.88-2.77 (m, 1H, *4-H$_a$*), 2.65-2.50 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.1 (C-2^{d1}), 164.7 (C-2^{d2}), 145.86 (C_{quat}-10^{d1}), 145.84 (C_{quat}-10^{d2}), 139.8 (C_{quat}-6^{d1}), 139.5 (C_{quat}-6^{d2}), 133.8 (C_{quat}-9^{d1}), 133.6 (C_{quat}-9^{d2}), 129.34 (C-12^{d1}), 129.32 (C-12^{d2}), 129.29 (C-8^{d1}), 129.19 (C-8^{d2}), 127.7 (C-7^{d1}), 127.4 (C-7^{d2}), 118.8 (C-13^{d1}), 118.7 (C-13^{d2}), 114.0 (C-11^{d1}), 113.8 (C-11^{d2}), 85.3 (C-3^{d1}), 85.2 (C-3^{d2}), 54.6 (C-5^{d1}), 54.1 (C-5^{d2}), 53.86 (C-1^{d1}), 53.84 (C-1^{d2}), 38.5 (C-4^{d1}), 38.0 (C-4^{d2}); FTIR (neat) 3394 (br), 2957, 1750, 1601, 1559, 1490, 1436, 1372, 1313, 1265, 1179, 1090, 826, 752, 692 cm^{-1}; HRMS Calcd for $C_{17}H_{18}N_2O_4Cl$ $(M+H)^+$: 349.0950. Found 349.0954.

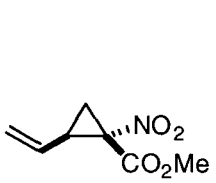


(±)-23c

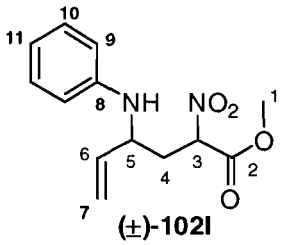


(±)-102k

Methyl {1-[(4-chlorophenyl)amino]-2,3-dihydro-1*H*-inden-2-yl}(nitro)acetate ((±)-102k, OL-01-209). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23c** (52.7 mg, 0.23 mmol, 1 equiv) and *p*-chloroaniline (43.2 mg, 0.34 mmol, 1.5 equiv), and purified by flash chromatography, eluting with 100% toluene, to afford the spectroscopically pure **(±)-102k** as an orange solid (60.3 mg, 0.18 mmol, 78%, 70:30 dr). mp 111-113 °C; R_f = 0.43 (toluene); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.31-7.15 (m, 6H, *7,8,9,10,15-H*), 6.71-6.64 (m, 2H, *14-H*), 5.47 (d, $^3J_{3,4}$ = 5.7 Hz, 1H^{d1}, *3-H^{d1}*), 5.39 (d, $^3J_{3,4}$ = 8.7 Hz, 1H^{d2}, *3-H^{d2}*), 5.26 (t, $^3J_{5,4}$ = 9.1 Hz, $^3J_{5,NH}$ = 9.1 Hz, 1H^{d1}, *5-H^{d1}*), 5.04 (t, $^3J_{5,4}$ = 9.1 Hz, $^3J_{5,NH}$ = 9.1 Hz, 1H^{d2}, *5-H^{d2}*), 3.91 (br. s, 1H^{d1}, N-*H^{d1}*), 3.88 (br. s, 1H^{d2}, N-*H^{d2}*), 3.81 (s, 3H^{d1}, *1-H^{d1}*), 3.64 (s, 3H^{d2}, *1-H^{d2}*), 3.40-3.30 (m, 1H, *12-H$_a$*), 3.25-3.10 (m, 1H, *4-H*), 2.93-2.84 (m, 1H, *12-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.4 (C-2^{d1}), 164.2 (C-2^{d2}), 145.7 (C$_{quat}$-13^{d1}), 145.6 (C$_{quat}$-13^{d2}), 142.5 (C$_{quat}$-11^{d1}), 142.4 (C$_{quat}$-11^{d2}), 139.4 (C$_{quat}$-6^{d1}), 139.2 (C$_{quat}$-6^{d2}), 129.41, 128.54, 127.4, 125.05, 124.0 (C-7^{d1}, 8^{d1}, 9^{d1}, 10^{d1}, 15^{d1}), 129.37, 128.52, 127.4, 125.02, 123.8 (C-7^{d2}, 8^{d2}, 9^{d2}, 10^{d2}, 15^{d2}), 123.1 (C-16^{d1}), 123.0 (C-16^{d2}), 114.5 (C-14^{d1}), 114.4 (C-14^{d2}), 89.6 (C-3^{d1}), 88.1 (C-3^{d2}), 60.5 (C-5^{d1}), 59.6 (C-5^{d2}), 53.6 (C-1), 43.4 (C-4), 33.9 (C-12^{d1}), 32.7 (C-12^{d2}); FTIR (neat) 3392, 2955, 1751, 1598, 1501, 1459, 1293, 1179, 1004, 910, 817, 750 cm^{-1}; HRMS Calcd for $C_{18}H_{18}N_2O_4Cl$ $(M+H)^+$: 361.0950. Found 361.0945.

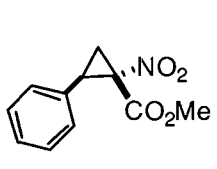


(±)-23f

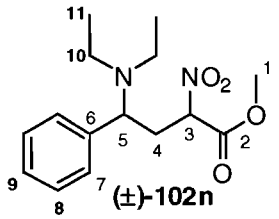


(±)-102l

Methyl 4-anilino-2-nitrohex-5-enoate ((±)-102l, OL-01-219). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23f** (39.0 mg, 0.23 mmol, 1 equiv) and aniline (29.2 μL, 0.34 mmol, 1.5 equiv). The crude reaction mixture was washed twice with 3 M HCl and the combined acidified aqueous layers were washed with dichloromethane twice. Combined organic layers were then neutralized with sat. aq. $NaHCO_3$, washed with sat. aq. NaCl and dried over Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by flash chromatography, eluting with 30% EtOAc in hexanes, to afford spectroscopically pure **((±)-102l** as a yellow oil (40.0 mg, 0.15 mmol, 67%, 50:50 dr). R_f = 0.36 (15% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.18 (m_c, 2H, *10-H*), 6.76 (t, $^3J_{11,10}$ = 7.3 Hz, 1H, *11-H*), 6.62 (m_c, 2H, *9-H*), 5.83-5.70 (m, 1H, *6-H*), 5.47 (dd, $^3J_{3,4a}$ = 4.9 Hz, $^3J_{3,4b}$ = 8.8 Hz, 1H^{d1}, *3-H^{d1}*), 5.33 (dd, $^3J_{3,4a}$ = 5.4 Hz, $^3J_{3,4b}$ = 8.3 Hz, 1H^{d2}, *3-H^{d2}*), 5.31-5.18 (m, 2H, *7-H*), 4.02 (m_c, 1H, *5-H*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.83 (s, 3H^{d2}, *1-H^{d2}*), 3.56 (br. s, 1H, N-*H*), 2.74-2.59 (m, 1H, *4-H$_a$*), 2.49-2.31 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.2 (C-2^{d1}), 165.0 (C-2^{d2}), 146.4 (C_{quat}-8^{d1}), 146.3 (C_{quat}-8^{d2}), 137.4 (C-6^{d1}), 137.2 (C-6^{d2}), 129.34 (C-10^{d1}), 129.32 (C-10^{d2}), 118.7 (C-11^{d1}), 118.6 (C-11^{d2}), 117.8 (C-7^{d1}), 116.8 (C-7^{d2}), 114.1 (C-9^{d1}), 113.8 (C-9^{d2}), 85.2 (C-3^{d1}), 85.1 (C-3^{d2}), 53.7 (C-1), 53.3 (C-5^{d1}), 52.8 (C-5^{d2}), 35.8 (C-4^{d1}), 35.4 (C-4^{d2}); FTIR (neat) 3384, 2957, 1749, 1601, 1557, 1498, 1360, 1310, 1217, 992, 751 cm^{-1}; HRMS Calcd for $C_{13}H_{17}N_2O_4$ $(M+H)^+$: 265.1183. Found 265.1174.

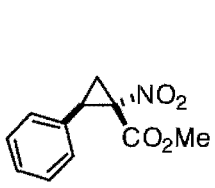


(±)-23a

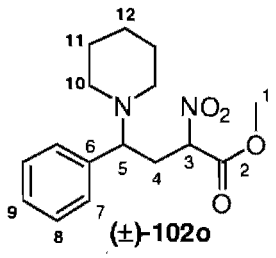


(±)-102n

Methyl 2-nitro-4-phenyl-4-pyrrolidin-1-ylbutanoate ((±)-**102n, OL-02-055**). In a 2-mL microwave vial containing a magnetic stirbar, cyclopropane (±)-**23a** (50 mg, 0.23 mmol, 1 equiv) was mixed with diethylamine (49 μL, 0.48 mmol, 2.1 equiv), and dichloromethane (100 μL) was added, followed by $Ni(ClO_4)_2 \cdot 6H_2O$ (8.3 mg, 0.023 mmol, 0.1 equiv.) The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at room temperature for 24 h. The crude reaction was evaporated under reduced pressure and purified by flash chromatography, eluting with 5% MeOH in dichloromethane, affording spectroscopically pure (±)-**102n** as a pale yellow oil (50.3 mg, 0.17 mmol, 76%, 50:50 dr). R_f = 0.38 (5% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.38-7.17 (m, 5H, *7,8,9-H*), 5.74 (br. s, 1H^{d1}, 3-H^{d1}), 5.21 (br. s, 1H^{d2}, *3-*H^{d2}), 3.77-3.86 (m, 4H, *1-H* + *5-H*), 3.09-2.98 (m_c, 1H^{d1}, *4-*H_a^{d1}), 2.83 (m_c, 1H^{d2}, *4-*H_a^{d2}), 2.69-2.42 (m, 3H, *4-*H_b + *10-H*), 2.25-2.04 (m, 2H, *10-H*), 1.04-0.99 (m, 6H, *11-H*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 166.1 (C-2^{d1}), 165.1 (C-2^{d2}), 138.1 (C_{quat}-6^{d1}), 137.1 (C_{quat}-6^{d2}), 128.4 (C-8), 128.3 (C-7^{d1}), 128.1 (C-7^{d2}), 127.6 (C-9), 86.5 (C-3^{d1}), 86.0 (C-3^{d2}), 60.6 (C-5^{d1}), 58.9 (C-5^{d2}), 53.4 (C-1), 43.1 (C-10^{d1}), 43.0 (C-10^{d2}), 33.2 (C-4^{d1}), 32.6 (C-4^{d2}), 13.7 (C-11^{d1}), 12.9 (C-11^{d2}); FTIR (neat) 2969, 2821, 1751, 1558, 1452, 1375, 1252, 1199, 769, 702 cm^{-1}; HRMS Calcd for $C_{15}H_{23}N_2O_4$ $(M+H)^+$: 295.1652. Found 295.1651.

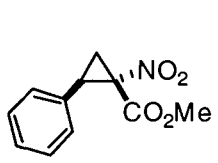


(±)-23a

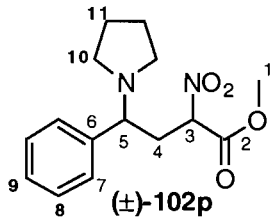


(±)-102o

Methyl 2-nitro-4-phenyl-4-pyrrolidin-1-ylbutanoate ((±)-102o, OL-02-033). In a 2-mL microwave vial containing a magnetic stirbar, cyclopropane (±)-**23** (100 mg, 0.45 mmol, 1 equiv) was mixed with the piperidine (67 μL, 0.68 mmol, 1.5 equiv), and dichloromethane (200 μL) was added, followed by $Ni(ClO_4)_2 \cdot 6H_2O$ (8.3 mg, 0.023 mmol, 0.1 equiv.) The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at room temperature for 48 h. The crude reaction was evaporated under reduced pressure and purified by flash chromatography, eluting with 5% MeOH in dichloromethane, affording spectroscopically pure (±)-**102o** as a beige crystalline solid (87.3 mg, 0.28 mmol, 63%, 50:50 dr). mp 68-71 °C; R_f = 0.20 (5% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.31 (m, 3H, *7,9-H*), 7.16 (m_c, 2H, *8-H*), 5.67 (m_c, $1H^{d1}$, 3-H^{d1}); 5.22 (dd, $^3J_{3,4a}$ = 5.6 Hz, $^3J_{3,4b}$ = 8.3 Hz, $1H^{d2}$, *3-*H^{d2}), 3.87 (s, $3H^{d1}$, *1-*H^{d1}), 3.81 (s, $3H^{d2}$, *1-*H^{d2}), 3.58-3.52 (m, 1H, *5-H*), 3.15-3.04 (m, $1H^{d1}$, *4-*H_a^{d1}), 2.94 (m_c, $1H^{d2}$, *4-*H_a^{d2}), 2.56-2.38 (m, $4H^{d1}$ + 1H, *10-*H^{d1}+ *4-*H_b), 2.15 (m_c, $4H^{d2}$, *10-*H^{d2}), 1.50 (m_c, 4H, *11-H*), 1.33-1.27 (m, 2H, *12-H*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.9 (C-2^{d1}), 165.4 (C-2^{d2}), 136.4 (C_{quat}-6^{d1}), 135.7 (C_{quat}-6^{d2}), 128.5 (C-8^{d1}), 128.2 (C-8^{d2}), 128.0 (C-7^{d1}), 127.8 (C-7^{d2}), 127.7 (C-9), 86.8 (C-3^{d1}), 86.1 (C-3^{d2}), 67.2 (C-5^{d1}), 63.5 (C-5^{d2}), 53.5 (C-1), 50.8 (C-10^{d1}), 50.3 (C-10^{d2}), 32.5 (C-4^{d1}), 32.0 (C-4^{d2}), 26.3 (C-11^{d1}), 26.0 (C-11^{d2}), 24.4 (C-12); FTIR (neat) 3029, 2933, 2806, 1751, 1558, 1436, 1371, 1160, 1100, 871, 702 cm^{-1}; HRMS Calcd for $C_{16}H_{23}N_2O_4$ $(M+H)^+$: 307.1652. Found 307.1654.



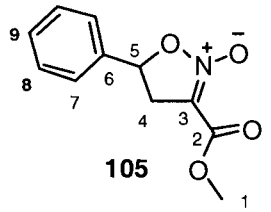
(±)-23a



(±)-102p

Methyl 2-nitro-4-phenyl-4-pyrrolidin-1-ylbutanoate ((±)-102p, OL-02-051). The title compound was prepared by the Lewis acid-catalyzed procedure described above using cyclopropane **(±)-23a** (50.0 mg, 0.23 mmol, 1 equiv) and pyrrolidine (39.5 μL, 0.48 mmol, 2.1 equiv), stirring the reaction mixture for 48 hours. It was purified by flash chromatography, eluting with 5% MeOH in dichloromethane, to afford spectroscopically pure **(±)-102p** as a yellow oil (60.5 mg, 0.21 mmol, 90%, 60:40 dr). R_f = 0.30 (5% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.40-7.22 (m, 5H, *7,8,9-H*), 5.22 (m_c, 1H^{d1}, 3-H^{d1}), 4.83 (dd, $^3J_{3,4a}$ = 3.4 Hz, $^3J_{3,4b}$ = 11.0 Hz, 1H^{d2}, 3-H^{d2}), 3.82 (s, 3H^{d1}, *1*-H^{d1}), 3.76 (s, 3H^{d2}, *1*-H^{d2}), 3.50 (m_c, 1H^{d1}, *5*-H^{d1}), 3.19 (dd, $^3J_{5,4a}$ = 4.6 Hz, $^3J_{5,4b}$ = 10.0 Hz, 1H^{d2}, 5-H^{d2}), 3.06 (m_c, 1H^{d1}, *4*-H_b^{d1}), 2.92 (m_c, 1H^{d2}, *4*-H_b^{d2}), 2.68-2.35 (m, 5H, *10-H* + *4*-H_a), 1.79-1.66 (m, 4H, *11-H*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.2 (C-2^{d1}), 165.1 (C-2^{d2}), 139.7 (C_{quat}-6^{d1}), 138.0 (C_{quat}-6^{d2}), 128.7 (C-8^{d1}), 128.4 (C-7^{d1}), 128.3 (C-8^{d2}), 128.1 (C-7^{d2}), 127.9 (C-9), 85.9 (C-3^{d1}), 85.6 (C-3^{d2}), 66.0 (C-5^{d1}), 63.9 (C-5^{d2}), 53.5 (C-1^{d1}), 53.4 (C-1^{d2}), 52.1 (C-10^{d1}), 50.2 (C-10^{d2}), 36.0 (C-4^{d1}), 35.0(C-4^{d2}), 23.2 (C-11^{d1}), 23.0 (C-11^{d2}); FTIR (neat) 2959, 2795, 1754, 1561, 1454, 1436, 1262, 1210, 1135, 884, 704 cm^{-1}; HRMS Calcd for $C_{15}H_{21}N_2O_4$ $(M+H)^+$: 293.1496. Found 293.1498.

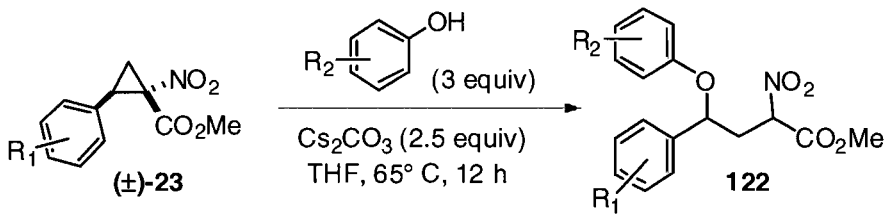
6.4.4 Characterization data for the isoxazoline-*N*-oxide 105



Methyl 5-phenyl-4,5-dihydroisoxazole-3-carboxylate 2-oxide (105, ent : OL-02-039; OL-02-042). Beige solid; mp 89-91 °C; R_f = 0.35 (30% EtOAC/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.36 (m, 5H, *7,8,9-H*), 5.73 (dd, $^3J_{5,4b}$ = 7.8 Hz, $^3J_{5,4a}$ = 9.6 Hz, 1H, *5-H*), 3.87 (s, 3H, *1-H*), 3.81 (dd, $^2J_{4a,4b}$ = 16.9 Hz, $^3J_{4a,5}$ = 9.6 Hz, 1H, *4-H$_a$*); 3.44 (dd, $^2J_{4a,4b}$ = 16.9 Hz, $^3J_{4b,5}$ = 7.8 Hz, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C-2), 137.6 (C_{quat}-6), 129.1 (C-9), 129.0 (C-8), 125.7 (C-7), 107.7 (C-3), 76.8 (C_{quat}-3), 52.6 (C-1), 38.3 (C-4); FTIR (neat) 2952, 1733, 1702, 1614, 1438, 1241, 1197, 977, 746, 700 cm^{-1}; HRMS Calcd for $C_{11}H_{11}NO_4Na$ $(M+Na)^+$: 244.0580. Found 244.0575.

SFC (Chiralcel AD-H, 5% MeOH, 2 mL/min, 200 bar, 25 °C): t_r 14.8 min (major enantiomer), t_r 19.2 min (minor enantiomer).

6.5 Nucleophilic ring-opening of 23 with phenol derivatives



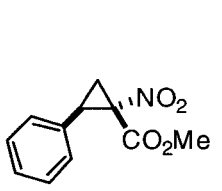
6.5.1 General procedure for the ring opening of 23 with phenol derivatives

In an oven-dried 2-mL microwave vial, cyclopropane (±)-**23** (0.45 mmol, 1 equiv) was combined with the appropriate phenol derivative (1.36 mmol, 3 equiv), anhydrous Cs_2CO_3 (0.32 g, 1.13 mmol, 2.5 equiv) and anhydrous tetrahydrofuran (2 mL). The vial was sealed with a Teflon cap and the reaction mixture was stirred at 65 °C in an oil bath for 12 h,

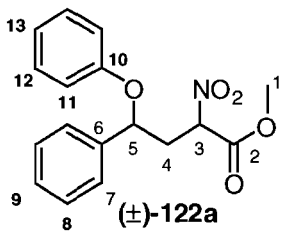
quenched with sat. aq. NH_4Cl (5 mL) and partitioned. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography eluting with 100% benzene afforded the spectroscopically pure product (**method A**). In the cases where the remaining excess of the phenol derivative was difficult to separate by flash chromatography, it was removed by the following aqueous workup (**method B**): the reaction was quenched with sat. aq. NH_4Cl (5 mL) and partitioned. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with 0.1 M NaOH three times, dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography eluting with 10-20% EtOAc/Hexane afforded the spectroscopically pure product.

On large scale, the reaction was performed in a round-bottom flask equipped with a reflux condenser and heated at reflux in an oil bath for 12 h.

6.5.2 Specific experimental procedures for the ring-opening of 23 with phenol derivatives



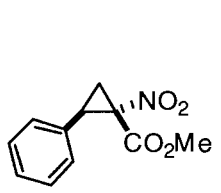
(±)-23a



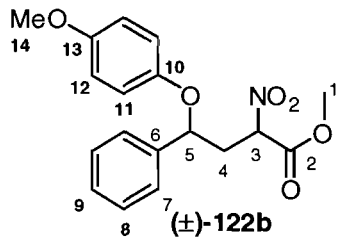
(±)-122a

Methyl 2-nitro-4-phenoxy-4-phenylbutanoate ((±)-122a, IZ-01-084). The title compound was prepared by the procedure described above using cyclopropane **(±)-23a** (100.0 mg, 0.45 mmol, 1 equiv) and phenol (127.6 mg, 1.36 mmol, 3 equiv) and purified by method A, to afford the pure product **(±)-122a** as a pale yellow oil (106.9 mg, 0.34 mmol, 75%, 55:45 dr). R_f = 0.67 (25% EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.30 (m, 5H, *7,8,9-H*), 7.17 (m_c, 2H, *12-H*), 6.91 (t,

$^3J_{13,12}$ = 7.3 Hz, 1H, *13-H*), 6.81-6.79 (m, 2H, *11-H*), 5.63 (dd, $^3J_{5,4a}$ = 3.7 Hz, $^3J_{5,4b}$ = 10.5 Hz, 1H^{d1}, *5-H^{d1}*), 5.36 (t, $^3J_{3,4b/4a}$ = 6.6 Hz, 1H^{d2}, *5-H^{d2}*), 5.31 (dd, $^3J_{3,4a}$ = 4.4 Hz, $^3J_{3,4b}$ = 9.0 Hz, 1H^{d1}, *3-H^{d1}*), 5.17 (dd, $^3J_{3,4a}$ = 3.0 Hz, $^3J_{3,4b}$ = 9.9 Hz, 1H^{d2}, *3-H^{d2}*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.83 (s, 3H^{d2}, *1-H^{d2}*), 3.01-2.84 (m, 1H, *4-H$_a$*), 2.78-2.70 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.9 (C-2^{d1}), 164.7 (C-2^{d2}), 157.14 (C$_{quat}$-10^{d1}), 157.12 (C$_{quat}$-10^{d2}), 139.5 (C$_{quat}$-6^{d1}), 139.4 (C$_{quat}$-6^{d2}), 129.41 (C-12^{d1}), 129.32 (C-12^{d2}), 129.02 (C-8^{d1}), 128.97 (C-8^{d2}), 128.4 (C-9^{d1}), 128.3 (C-9^{d2}), 125.8 (C-7^{d1}), 125.7 (C-7^{d2}), 121.6 (C-13^{d1}), 121.4 (C-13^{d2}), 115.9 (C-11^{d1}), 115.7 (C-11^{d2}), 84.9 (C-3^{d1}), 84.7 (C-3^{d2}), 76.5 (C-5^{d1}), 75.7 (C-5^{d2}), 53.71 (C-1^{d1}), 53.70 (C-1^{d2}), 39.1 (C-4^{d1}), 38.9 (C-4^{d2}); FTIR (neat) 3710, 3681, 2957, 1753, 1559, 1588, 1494,1227, 1054, 1033, 909 cm^{-1}; HRMS Calcd for $C_{17}H_{16}NO_5$ $(M-H)^-$: 314.1034. Found 314.1034.



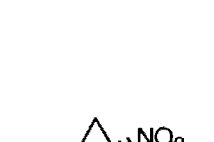
(±)-23a



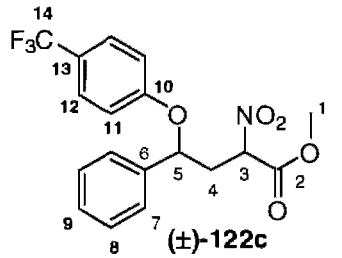
(±)-122b

Methyl 4-(4-methoxyphenoxy)-2-nitro-4-phenylbutanoate ((±)-122b, IZ-01-064). The title compound was prepared by the procedure described above using cyclopropane **(±)-23a** (100.0 mg, 0.45 mmol, 1 equiv) and 4-methoxyphenol (168.3 mg, 1.36 mmol, 3 equiv) and purified by method B (column chromatography: 10% EtOAc/Hexane) to afford the spectroscopically pure **(±)-122b** as a brown oil (106.1 mg, 0.31 mmol, 68%, 55:45 dr). R_f = 0.51 (25% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.38-7.26 (m, 5H, *7,8,9-H*), 6.72 (m$_c$, 4H, *11,12-H*), 5.66 (dd, $^3J_{5,4a}$ = 3.8 Hz, $^3J_{6,4b}$ =10.5 Hz, 1H^{d1}, *5-H^{d1}*), 5.37 (m$_c$, 1H^{d2}, *5-H^{d2}*), 5.19 (dd, $^3J_{3,4a}$ = 4.4 Hz, $^3J_{3,4b}$ = 9.2 Hz, 1H^{d1}, *3-H^{d1}*), 5.04 (dd, $^3J_{3,4a}$ = 3.1 Hz, $^3J_{3,4b}$ = 10.0 Hz, 1H^{d2}, *3-H^{d2}*), 3.83 (s, 3H^{d1}, *1-H^{d1}*), 3.82 (s, 3H^{d2}, 3H^{d1}), 3.704 (s, 3H^{d1}, *14-H^{d1}*), 3.701 (s, 3H^{d2}, *14-H^{d2}*), 2.99-2.80 (m, 1H, *4-H$_a$*), 2.75-2.68 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2

diastereomers) δ 164.9 (C-2^{d1}), 164.7 (C-2^{d2}), 154.3 (C_{quat}-13^{d1}), 154.2 (C_{quat}-13^{d2}), 151.2 (C_{quat}-10^{d1}), 151.1 (C_{quat}-10^{d2}), 139.7 (C_{quat}-6^{d1}), 139.6 (C_{quat}-6^{d2}), 128.9 (C-8^{d1}), 128.8 (C-8^{d2}), 128.3 (C-9^{d1}), 128.2 (C-9^{d2}), 125.85 (C-7^{d1}), 125.77 (C-7^{d2}), 117.1 (C-11^{d1}), 116.8 (C-11^{d2}), 114.41 (C-12^{d1}), 114.39 (C-12^{d2}), 85.0 (C-3^{d1}), 84.7 (C-3^{d2}), 77.4 (C-5^{d1}), 76.7 (C-5^{d2}), 55.38 (C-14^{d1}), 55.36 (C-14^{d2}), 53.54 (C-1^{d1}), 53.53 (C-1^{d2}), 38.9 (C-4^{d1}), 38.7 (C-4^{d2}); FTIR (neat) 2951, 2051, 1754, 1562, 1454, 1439, 1099, 825, 733 cm^{-1}; HRMS Calcd for $C_{18}H_{18}NO_6$ $(M-H)^-$: 344.1140. Found 344.1137.



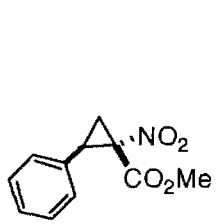
(±)-23a



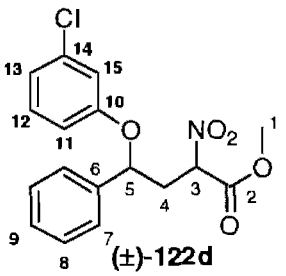
(±)-122c

Methyl 2-nitro-4-phenyl-4-[4-(trifluoromethyl)phenoxy]butanoate ((±)-122c, OL-01-275). The title compound was prepared by the procedure described above using cyclopropane **(±)-23a** (1.00 g, 4.5 mmol, 1 equiv) and 4-(trifluoromethyl)-phenol (2.20 g, 13.6 mmol, 3 equiv) using a round bottom flask equipped with a reflux condenser and heating the reaction mixture at reflux for 12 h. The crude product was purified by method A to afford the spectroscopically pure **(±)-122c** as a yellow oil (1.45 g, 3.78 mmol, 84%, 50:50 dr). R_f = 0.56 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.46-7.30 (m, 7H, *7,8,9,12-H*), 6.87 (d, $^3J_{11,12}$ = 8.8 Hz, 2H, *11-H*), 5.58 (dd, $^3J_{5,4a}$ = 3.9 Hz, $^3J_{5,4b}$ = 10.3 Hz, 1H^{d1}, *5-H^{d1}*), 5.37-5.30 (m, 1H^{d2} + 1H^{d1}, *3-H^{d1}* + *5-H^{d2}*), 5.23 (dd, $^3J_{3,4a}$ = 3.4 Hz, $^3J_{3,4b}$ = 9.7 Hz, 1H^{d2}, *3-H^{d2}*), 3.85 (s, 3H^{d1}, *1-H^{d1}*), 3.84 (s, 3H^{d2}, *1-H^{d2}*), 3.05-2.85 (m, 1H, *4-H$_a$*), 2.81-2.71 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.7 (C-2^{d1}), 164.6 (C-2^{d2}), 159.5 (C_{quat}-10^{d1}), 159.4 (C_{quat}-10^{d2}), 138.6 (C_{quat}-6^{d1}), 138.5 (C_{quat}-6^{d2}), 129.24 (C-8^{d1}), 129.20 (C-8^{d2}), 128.8 (C-9^{d1}), 128.7 (C-9^{d2}), 126.9 (q, $^4J_{C,F}$ = 2.2 Hz, C-12), 125.7 (C-7^{d2}), 125.6 (C-7^{d2}), 123.7 (q, $^3J_{C,F}$ = 32.9 Hz, C_{quat}-13), 124.1 (q, $^2J_{C,F}$ = 271.0 Hz, C-14), 115.7 (C-11^{d1}), 115.6 (C-11^{d2}), 84.8 (C-3^{d1}), 84.5 (C-3^{d2}), 76.97 (C-5^{d1}), 75.9 (C-5^{d2}), 53.8

(C-1), 38.9 (C-4^{d1}), 38.7 (C-4^{d2}); FTIR (neat) 3709, 2966, 1754, 1614, 1562, 1516, 1161, 836, 701 cm^{-1}; HRMS Calcd for $C_{18}H_{16}NO_5F_3Na$ $(M+Na)^+$: 406.0873. Found 406.0868.

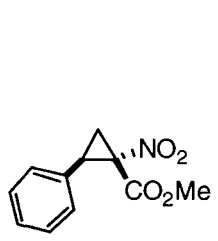


(±)-23a

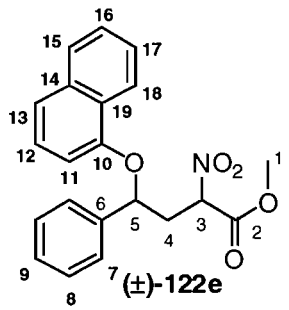


(±)-122d

Methyl 4-(3-chlorophenoxy)-2-nitro-4-phenylbutanoate ((±)-122d, IZ-01-076). The title compound was prepared by the procedure described above using cyclopropane **(±)-23a** (100.0 mg, 0.45 mmol, 1 equiv) and 3-chlorophenol (174.3 mg, 1.36 mmol, 3 equiv) and purified by method A to afford the pure product as a yellow oil (90.2 mg, 0.26 mmol, 57%, 50:50 dr). R_f = 0.67 (25% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.42-7.29 (m, 5H, *7,8,9-H*), 7.12-7.06 (m, 1H, *12-H*), 6.91-6.87 (m, 1H, *15-H*), 6.83-6.81 (m, 1H, *13-H*), 6.69-6.64 (m, 1H, *11-H*), 5.57 (dd, $^3J_{5,4a}$ = 3.7 Hz, $^3J_{5,4b}$ = 10.3 Hz, 1H^{d1}, *5-H^{d1}*), 5.32 (m_c, 1H^{d2}, *5-H^{d2}*), 5.28 (dd, $^3J_{3,4a}$ = 4.3 Hz, $^3J_{3,4b}$ = 8.9 Hz, 1H^{d1}, *3-H^{d1}*), 5.15 (dd, $^3J_{3,4a}$ = 3.2 Hz, $^3J_{3,4b}$ = 9.8 Hz, 1H^{d2}, *3-H^{d2}*), 3.844 (s, 3H^{d1}, *1-H^{d1}*), 3.836 (s, 3H^{d2}, *1-H^{d2}*), 3.01-2.82 (m, 1H, *4-H$_a$*), 2.77-2.67 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.8 (C-2^{d1}), 164.6 (C-2^{d2}), 157.80 (C_{quat}-10^{d1}), 157.76 (C_{quat}-10^{d2}), 138.8 (C_{quat}-6^{d1}), 138.7 (C_{quat}-6^{d2}), 134.79 (C_{quat}-14^{d1}), 134.77 (C_{quat}-14^{d2}), 130.21 (C-12^{d1}), 130.20 (C-12^{d2}), 129.2 (C-8^{d1}), 129.1 (C-8^{d2}), 128.7 (C-9^{d1}), 128.6 (C-9^{d2}), 125.7 (C-7^{d1}), 125.6 (C-7^{d2}), 121.9 (C-13^{d1}), 121.7 (C-13^{d2}), 116.6 (C-15^{d1}), 116.4 (C-15^{d2}), 113.94 (C-11^{d1}), 113.91 (C-11^{d2}), 84.8 (C-3^{d1}), 84.6 (C-3^{d2}), 76.0 (C-5), 53.8 (C-1), 39.0 (C-4^{d1}), 38.7 (C-4^{d2}); FTIR (neat) 3681, 1755, 1592, 1563, 1454, 1226, 1055, 764, 630 cm^{-1}; HRMS Calcd for $C_{17}H_{16}ClNO_5Na$ $(M+Na)^+$: 372.0609. Found 372.0592.

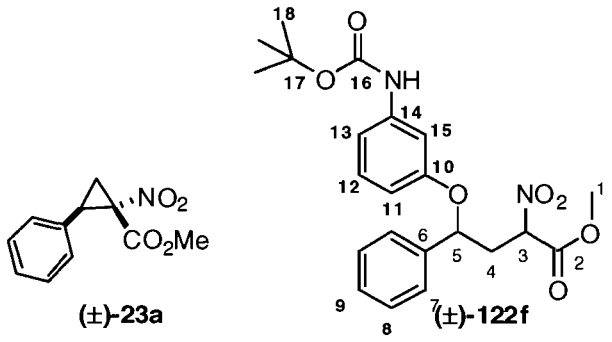


(±)-23a



(±)-122e

Methyl 4-(1-naphthyloxy)-2-nitro-4-phenylbutanoate ((±)-**122e, IZ-01-071**). The title compound was prepared by the procedure described above using cyclopropane (±)-**23a** (100.0 mg, 0.45 mmol, 1 equiv) and 1-naphthol (195.5 mg, 1.36 mmol, 3 equiv) and purified by method A to afford the spectroscopically pure (±)-**122e** as a brown oil (87.5 mg, 0.24 mmol, 53%, 50:50 dr). R_f = 0.58 (25% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 8.35 (m_c, 1H, *18-H*), 7.83-7.80 (m, 1H, *Arom-H*), 7.59-7.52 (m, 2H, *Arom-H*), 7.46-7.29 (m, 6H, *Arom-H*), 7.22-7.17 (m, 1H, *Naph-H*), 6.61 (d, $^3J_{11,12}$ = 7.8 Hz, 1H^{d1}, *11-H^{d1}*), 6.57 (d, $^3J_{11,12}$ = 7.9 Hz, 1H^{d2}, *11-H^{d2}*), 5.67 (dd, $^3J_{5,4a}$ = 3.7 Hz, $^3J_{6,4b}$ =10.0 Hz, 1H^{d1}, *5-H^{d1}*), 5.58 (dd, $^3J_{5,4a}$ = 3.9 Hz, $^3J_{6,4b}$ =8.6 Hz, 1H^{d2}, *5-H^{d2}*), 5.48 (dd, $^3J_{3,4a}$ = 3.6 Hz, $^3J_{3,4b}$ = 9.5 Hz, 1H^{d1}, *3-H^{d1}*), 5.44 (m_c, 1H^{d2}, *3-H^{d2}*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.78 (s, 3H^{d2}, *1-H^{d2}*), 3.21-3.13 (m, 1H^{d1}, *4-H$_a^{d1}$*), 3.08-3.01 (m, 1H^{d2}, *4-H$_a^{d2}$*), 2.98-2.68 (m, 1H, *4-H$_b$*); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.9 (C-2^{d1}), 164.7 (C-2^{d2}), 152.33 (C_{quat}-10^{d1}), 152.29 (C_{quat}-10^{d2}), 139.12 (C_{quat}-6^{d1}), 139.09 (C_{quat}-6^{d2}), 127.6 (C-16^{d1}), 127.5 (C-16^{d2}), 126.5 (C-15^{d1}), 126.4 (C-15^{d2}), 125.62 (C-17), 125.56 (C_{quat}-19), 125.54 (C-12), 125.52 (C-7^{d1}), 125.47 (C-7^{d2}), 121.7 (C-18^{d1}), 121.6 (C-18^{d2}), 120.9 (C-13^{d1}), 120.8 (C-13^{d2}), 106.8 (C-11^{d1}), 106.7 (C-11^{d2}), 85.0 (C-3^{d1}), 84.7 (C-3^{d2}), 76.4 (C-5^{d1}), 75.5 (C-5^{d2}), 53.74 (C-1^{d1}), 53.70 (C-1^{d2}), 39.1 (C-4^{d1}), 38.9 (C-4^{d2}); FTIR (neat) 3708, 3681, 2865, 1752, 1508, 1437, 1264, 1057, 910, 771, 700 cm^{-1}; HRMS Calcd for $C_{21}H_{19}NO_5Na$ $(M+Na)^+$: 388.1155. Found 388.1143.



Methyl 4-{3-[(*tert*-butoxycarbonyl)amino]phenoxy}-2-nitro-4-phenylbutanoate ((±)-122f, OL-02-073). The title compound was prepared by the procedure described above using cyclopropane **(±)-23a** (100.0 mg, 0.45 mmol, 1 equiv) and *tert*-butyl 3-hydroxyphenylcarbamate[99] (283.7 mg, 1.36 mmol, 3 equiv) and purified by method A to afford the spectroscopically pure **(±)-122f** as a pale yellow oil (139.4 mg, 0.32 mmol, 72%, 50:50 dr). R_f = 0.52 (25% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.37-7.28 (m, 5H, *7,8,9-H*), 7.08-7.02 (m, 1H^{d1} + 1H, *15-H^{d1}* + *12-H*), 6.97 (s, 1H^{d2}, *15-H^{d2}*), 6.88-6.81 (m, 1H, *13-H*), 6.41 (m$_c$, 2H, *11-H* + N-*H*), 5.60 (dd, $^3J_{5,4a}$ = 3.7 Hz, $^3J_{5,4b}$ = 10.5 Hz, 1H^{d1}, *5-H^{d1}*), 5.34 (m$_c$, 1H^{d2}, *5-H^{d2}*), 5.29 (dd, $^3J_{3,4a}$ = 4.1 Hz, $^3J_{3,4b}$ = 9.0 Hz, 1H^{d1}, *3-H^{d1}*), 5.16 (dd, $^3J_{3,4a}$ = 3.1 Hz, $^3J_{3,4b}$ = 10.4 Hz, 1H^{d2}, *3-H^{d2}*), 3.84 (s, 3H^{d1}, *1-H^{d1}*), 3.83 (s, 3H^{d2}, *1-H^{d2}*), 2.97-2.81 (m, 1H, *4-H$_a$*), 2.76-2.66 (m, 1H, *4-H$_b$*), 1.51 (s, 9H, *18-H*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.9 (C-2^{d1}), 164.7 (C-2^{d2}), 157.7 (C$_{quat}$-10), 152.4 (C-16^{d1}), 139.6 (C$_{quat}$-6^{d1}), 139.5 (C$_{quat}$-6^{d2}), 139.4 (C$_{quat}$-14^{d1}), 139.3 (C$_{quat}$-14^{d2}), 129.62 (C-12^{d1}), 129.61 (C-12^{d2}), 128.96 (C-8^{d1}), 128.93 (C-8^{d2}), 128.4 (C-9^{d1}), 128.3 (C-9^{d2}), 125.8 (C-7^{d1}), 125.7 (C-7^{d2}), 111.6 (C-15), 109.8 (C-11^{d1}), 109.7 (C-11^{d2}), 106.5 (C-13^{d1}), 106.4 (C-13^{d2}), 84.8 (C-3^{d1}), 84.6 (C-3^{d2}), 80.5 (C$_{quat}$-17), 76.4 (C-5^{d1}), 75.5 (C-5^{d2}), 53.70 (C-1^{d1}), 53.68 (C-1^{d2}), 39.1 (C-4^{d1}), 38.7 (C-4^{d2}), 28.2 (C-18); FTIR (neat) 3387, 2978, 1753, 1708, 1561, 1525, 1476, 1366, 1152, 1050, 732 cm^{-1}; HRMS Calcd for $C_{22}H_{27}N_2O_7$ (M+H)$^+$: 431.1813. Found 431.1809.

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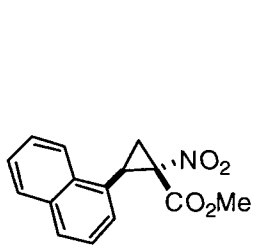
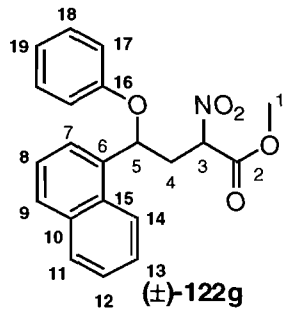
[99] Chankeshwara, S.V.; Chakraborti, A.K. *Tetrahedron Lett.* **2006**, *47*, 1087.

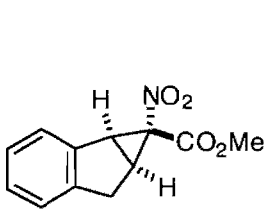


(±)-23g

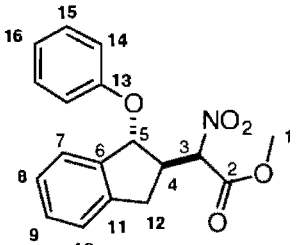


(±)-122g

Methyl 4-(1-naphthyl)-2-nitro-4-phenoxybutanoate ((±)-**122g, IZ-01-077**). The title compound was prepared by the procedure described above using cyclopropane (±)-**23g** (100.0 mg, 0.37 mmol, 1 equiv) and phenol (104.1 mg, 1.11 mmol, 3 equiv) and purified by method A to afford the pure product ((±)-**122g** as a pale yellow oil (78.6 mg, 0.21 mmol, 58%, 55:45 dr). R_f = 0.64 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 8.26 (d, $^3J_{14,13}$ = 8.3 Hz, 1H^{d1}, *14-H^{d1}*), 8.16 (d, $^3J_{14,13}$ = 8.3 Hz, 1H^{d2}, *14-H^{d2}*), 7.94 (d, $^3J_{11,12}$ = 8.1 Hz, 1H, *11-H*), 7.83 (d, $^3J_{9,8}$ = 8.3 Hz, 1H, *9-H*), 7.69-7.56 (m, 3H, *8,12,13-H*), 7.43 (m$_c$, 1H, *7-H*), 7.15 (m$_c$, 2H, *18-H*), 6.89 (t, $^3J_{19,18}$ = 7.3 Hz, 1H, *19-H*), 6.79-6.76 (m, 2H, *17-H*), 6.11 (dd, $^3J_{5,4a}$ = 3.6 Hz, $^3J_{5,4b}$ = 9.5 Hz, 1H^{d1}, *5-H^{d1}*), 5.93 (dd, $^3J_{5,4a}$ = 2.2 Hz, $^3J_{5,4b}$ = 10.5 Hz, 1H^{d2}, *5-H^{d2}*), 5.81 (dd, $^3J_{3,4a}$ = 2.9 Hz, $^3J_{3,4b}$ = 11.0 Hz, 1H^{d1}, *3-H^{d1}*), 5.58 (m$_c$, 1H^{d2}, *3-H^{d2}*), 3.88 (s, 3H^{d1}, *1-H^{d1}*), 3.83 (s, 3H^{d2}, *1-H^{d2}*), 3.16-3.09 (m, 1H^{d1}, *4-H$_a^{d1}$*), 3.06-2.93 (m, 1H^{d2} + 1H^{d1}, *4-H$_a^{d2}$* + *4-H$_b^{d1}$*), 2.81-2.74 (m, 1H^{d2}, *4-H$_b^{d2}$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.0 (C-2^{d1}), 164.9 (C-2^{d2}), 157.07 (C$_{quat}$-16^{d1}), 157.04 (C$_{quat}$-16^{d2}), 134.81 (C$_{quat}$-10^{d1}), 134.76 (C$_{quat}$-10^{d2}), 133.92 (C$_{quat}$-6^{d1}), 133.88 (C$_{quat}$-6^{d2}), 129.7 (C$_{quat}$-15^{d1}), 129.6 (C$_{quat}$-15^{d2}), 129.45 (C-18^{d1}), 129.43 (C-18^{d2}), 129.3 (C-7^{d1}), 129.2 (C-7^{d2}), 128.9 (C-8^{d1}), 128.8 (C-8^{d2}), 127.0 (C-14^{d1}), 126.9 (C-14^{d2}), 126.01 (C-11^{d1}), 125.97 (C-11^{d2}), 125.7 (C-9^{d1}), 125.6 (C-9^{d2}), 123.6 (C-13^{d1}), 123.3 (C-13^{d2}), 122.1 (C-12^{d1}), 121.9 (C-12^{d2}), 121.5 (C-19^{d1}), 121.4 (C-19^{d2}), 115.5 (C-17^{d1}), 115.4 (C-17^{d2}), 84.9 (C-3^{d1}), 84.7 (C-3^{d2}), 73.7 (C-5^{d1}), 72.6 (C-5^{d2}), 53.8 (C-1^{d1}), 53.7 (C-1^{d2}), 38.0 (C-4^{d1}), 37.9 (C-4^{d2}); FTIR (neat) 3042, 1752, 1597, 1559, 1493, 1367, 1225, 1067, 909, 732, 630 cm^{-1}; HRMS Calcd for $C_{21}H_{19}NO_5Na$ $(M+Na)^+$: 388.1155. Found 388.1153.



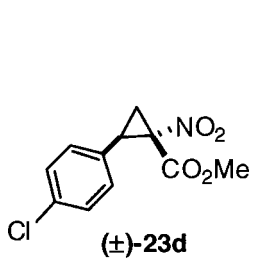
(±)-23c



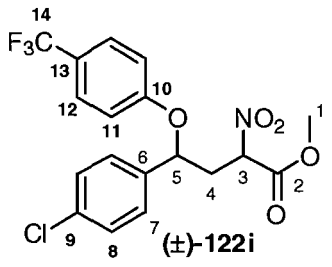
(±)-122h

Methyl nitro(1-phenoxy-2,3-dihydro-1*H*-inden-2-yl)acetate ((±)-122h, OL-02-075, IZ-01-078). The title compound was prepared by the procedure described above using cyclopropane **(±)-23c** (100.0 mg, 0.43 mmol, 1 equiv) and phenol (121.1 mg, 1.29 mmol, 3 equiv). The conversion was monitored by TLC using 10% EtOAc/Hex as an eluent. The crude reaction mixture was purified by method A to afford the spectroscopically pure **(±)-122h** as a yellow solid (67.4 mg, 0.25 mmol, 59%, 55:45 dr). mp 92-93 °C; R_f = 0.64 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.39-7.17 (m, 6H, *7,8,9,10,15-H*), 7.08-7.02 (m, 3H, *14,16-H*), 6.04 (d, $^3J_{5,4}$ = 6.4 Hz, 1H^{d1}, *5-H^{d1}*), 5.89 (d, $^3J_{5,4}$ = 7.3 Hz, 1H^{d2}, *5-H^{d2}*), 5.43 (d, $^3J_{3,4}$ = 5.7 Hz, 1H^{d1}, *3-H^{d1}*), 5.36 (d, $^3J_{3,4}$ = 8.5 Hz, 1H^{d2}, *3-H^{d2}*), 3.74 (s, 3H^{d1}, *1-H^{d1}*), 3.60 (s, 3H^{d2}, *1-H^{d2}*), 3.61-3.47 (m, 1H, *4-H*), 3.43 (dd, $^3J_{12a,4}$ = 8.0 Hz, $^2J_{12a,12b}$ = 15.7 Hz, 1H, *12-H$_a$*), 2.91 (dd, $^3J_{12b,4}$ = 8.5 Hz, $^2J_{12a,12b}$ = 15.7 Hz, 1H, *12-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.1 (C-2), 158.2 (C$_{quat}$-13), 140.4 (C$_{quat}$-11), 139.8 (C$_{quat}$-6), 129.7 (C-15), 129.15 (C-7^{d1}), 129.13 (C-7^{d2}), 127.3 (C-8), 125.03 (C-9^{d1}), 125.02 (C-9^{d2}), 124.8 (C-10^{d1}), 124.6 (C-10^{d2}), 121.8 (C-16^{d1}), 121.7 (C-16^{d2}), 115.9 (C-14^{d1}), 115.6 (C-14^{d2}), 89.0 (C-3^{d1}), 87.8 (C-3^{d2}), 82.1 (C-5^{d1}), 81.0 (C-5^{d2}), 53.53 (C-1^{d1}), 53.48 (C-1^{d2}), 47.65 (C-4^{d1}), 47.62 (C-4^{d2}), 33.6 (C-12^{d1}), 32.6 (C-12^{d2}); FTIR (neat) 3708, 3681, 2952, 1752, 1595, 1559, 1437, 1301, 1033, 750; HRMS Calcd for $C_{18}H_{17}NO_5Na$ $(M+Na)^+$: 350.0999. Found 350.0988.

Note: upon crystallization, **(±)-122h** undergoes a self-catalyzed enrichment of the diastereomeric ratio at C-3 to 90:10 as indicated by ^{1}H NMR analysis of a freshly prepared solution of the crystallized solid in $CDCl_3$. When left in solution at room temperature, however, **(±)-122h** re-equilibrates to 55:45 dr within several hours.

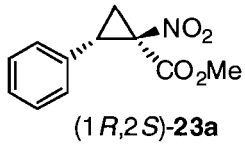


(±)-23d

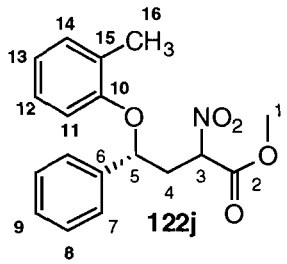


(±)-122i

Methyl 4-(4-chlorophenyl)-2-nitro-4-[4-(trifluoromethyl)phenoxy]butanoate ((±)-122i, IZ-01-079). The title compound was prepared by the procedure described above using cyclopropane **((±)-23d** (100.0 mg, 0.39 mmol, 1 equiv) and 4-(trifluoromethyl)phenol (190.2 mg, 1.17 mmol, 3 equiv) and purified by method A to afford the spectroscopically pure **(±)-122i** as a yellow oil (121.6 mg, 0.29 mmol, 74%, 50:50 dr). $R_f = 0.65$ (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.47 (d, $^3J_{12,11}$ = 8.8 Hz, 2H, *12-H*), 7.40-7.23 (m, 4H, *7,8,9-H*), 6.86 (d, $^3J_{11,12}$ = 8.8 Hz, 2H, *11-H*), 5.58 (dd, $^3J_{5,4a}$ = 3.6 Hz, $^3J_{5,4b}$ = 10.5 Hz, 1H^{d1}, *5-H^{d1}*), 5.38-5.32 (m, 1H^{d1} + 1H^{d2}, *3-H^{d1}+5-H^{d2}*), 5.23 (dd, $^3J_{3,4a}$ = 3.1 Hz, $^3J_{3,4b}$=10.0 Hz, 1H^{d2}, *3-H^{d2}*), 3.87 (s, 3H^{d1}, *1-H^{d1}*), 3.85 (s, 3H^{d2}, *1-H^{d2}*), 3.01-2.84 (m, 1H, *4-H$_a$*), 2.78-2.70 (m, 1H, *4-H$_b$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.6 (C-2^{d1}), 164.5 (C-2^{d2}), 159.2 (C_{quat}-10), 137.13 (C_{quat}-6^{d1}), 137.08 (C_{quat}-6^{d2}), 134.7 (C-9^{d1}), 134.6 (C-9^{d2}), 129.5 (C-8^{d1}), 129.4 (C-8^{d2}), 127.1 (C-7^{d2}), 127.0 (C-7^{d2}), 126.99 (q, $^4J_{C,F}$ = 1.9 Hz, C-12), 124.1 (q, $^3J_{C,F}$ = 32.8 Hz, C_{quat}-13), 124.0 (q, $^2J_{C,F}$ = 271.3 Hz, C-14), 115.8 (C-11^{d1}), 115.6 (C-11^{d2}), 84.7 (C-3^{d1}), 84.3 (C-3^{d2}), 76.3 (C-5^{d1}), 75.3 (C-5^{d2}), 53.9 (C-1), 38.8 (C-4^{d1}), 38.6 (C-4^{d2}); FTIR (neat) 3708, 2966, 2342, 1755, 1615, 1562, 1516,1324, 1032, 908, 732, 632 cm^{-1}; HRMS Calcd for $C_{18}H_{14}ClF_3NO_5$ $(M-H)^-$: 416.0518. Found 416.0517.



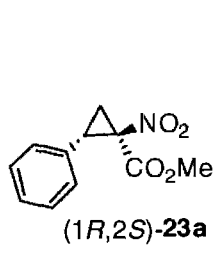
(1*R*,2*S*)-**23a**



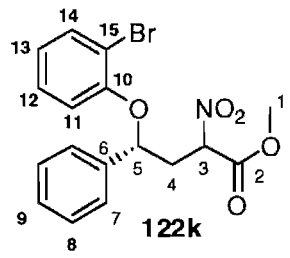
122j

Methyl (4*R*)-4-(2-methylphenoxy)-2-nitro-4-phenylbutanoate (122j, rac: OL-02-005, ent: OL-02-020). The title compound was prepared by the procedure described above using cyclopropane (1*R*,2*S*)-**23a** (100.0 mg, 0.45 mmol, 1 equiv, 90% ee) and *o*-cresol (146.6 mg, 1.36 mmol, 3 equiv) and purified by method A to afford the pure product as a pale yellow solid (112.4 mg, 0.34 mmol, 76%, 50:50 dr, 90% ee). mp 83-90 °C; $R_f = 0.69$ (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.41-7.28 (m, 5H, *7,8,9-H*), 7.13 (d, $^3J_{14,13}$ = 7.3 Hz, 1H, *14-H*), 6.99-6.92 (m, 1H, *12-H*), 6.84-6.79 (m, 1H, *13-H*), 6.57 (d, $^3J_{11,12}$ = 7.6 Hz, 1H^{d1}, *11-H*^{d1}), 6.52 (d, $^3J_{11,12}$ = 7.3 Hz, 1H^{d2}, *11-H*^{d2}), 5.59 (dd, $^3J_{5,4a}$ = 3.5 Hz, $^3J_{5,4b}$ =10.5 Hz, 1H^{d1}, *5-H*^{d1}), 5.37-5.31 (m, 1H^{d2} + 1H^{d1}, *3-H*^{d1} + *5-H*^{d2}), 5.25 (dd, $^3J_{3,4a}$ = 3.2 Hz, $^3J_{3,4b}$ = 9.3 Hz, 1H^{d1}, *3-H*^{d1}), 3.83 (s, 3H^{d1}, *1-H*^{d1}), 3.81 (s, 3H^{d2}, *1-H*^{d2}), 3.08-2.90 (m, 1H, *4-H*$_a$), 2.81-2.71 (m, 1H, *4-H*$_b$), 2.32 (s, 3H^{d1}, *16-H*^{d1}), 2.30 (s, 3H^{d2}, *16-H*^{d2}); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.0 (C-2^{d1}), 164.7 (C-2^{d2}), 155.0 (C$_{quat}$-10^{d1}), 154.9 (C$_{quat}$-10^{d2}), 139.5 (C$_{quat}$-6^{d1}), 139.4 (C$_{quat}$-6^{d2}), 130.9 (C-14^{d1}), 130.8 (C-14^{d2}), 129.02 (C-8^{d1}), 129.00 (C-8^{d2}), 128.4 (C-9^{d1}), 128.3 (C-9^{d2}), 127.1 (C$_{quat}$-15^{d1}), 126.9 (C$_{quat}$-15^{d2}), 126.6 (C-12^{d1}), 126.5 (C-12^{d2}), 125.8 (C-7^{d1}), 125.6 (C-7^{d2}), 121.0 (C-13^{d1}), 120.9 (C-13^{d2}), 112.6 (C-11^{d1}), 112.4 (C-11^{d2}), 85.1 (C-3^{d1}), 84.6 (C-3^{d2}), 76.1 (C-5^{d1}), 75.2 (C-5^{d2}), 53.73 (C-1^{d1}), 53.72 (C-1^{d2}), 39.1 (C-4^{d1}), 38.9 (C-4^{d2}), 16.4 (C-16^{d1}), 16.3 (C-16^{d2}); FTIR (neat) 3708, 3680, 2951, 2844, 1754, 1561,1454, 1235, 1053, 1121, 750, 701 cm^{-1}; HRMS Calcd for $C_{18}H_{18}NO_5$ $(M-H)^-$: 328.1191. Found 328.1195.

SFC (Chiralcel OD-H, 3% MeOH, 2 mL/min, 200 bar, 30 °C) t_r 5.7 min (minor enantiomer, d_1), t_r 6.4 min (minor enantiomer, d_2), t_r 7.0 min (major enantiomer, d_2), t_r 8.5 min (major enantiomer, d_1).



(1*R*,2*S*)-**23a**

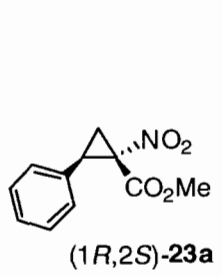


122k

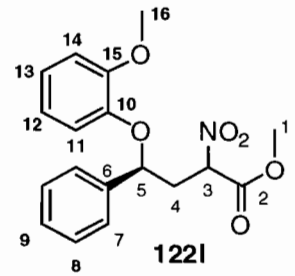
Methyl (4*R*)-4-(2-bromophenoxy)-2-nitro-4-phenylbutanoate (122k, rac: IZ-01-072, ent: OL-02-074). The title compound was prepared by the procedure described above using cyclopropane (1*R*,2*S*)-**23a** (54.0 mg, 0.24 mmol, 1 equiv, 90% ee) and *o*-bromophenol (85 μL, 0.73 mmol, 3 equiv) in a sealed tube, and purified by method B (flash chromatography: 20% EtOAc/Hexane) to afford the pure product as a pale yellow oil (71.4 mg, 0.18 mmol, 74%, 60:40 dr, 90% ee). R_f = 0.63 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.52 (dd, $^3J_{14,13}$ = 7.9 Hz, $^4J_{14,12}$ = 1.6 Hz, 1H, *14-H*), 7.40-7.29 (m, 5H, *7,8,9-H*), 7.09-7.01 (m, 1H, *12-H*), 6.79 (m_c, 1H, *13-H*), 6.65 (dd, $^3J_{11,12}$ = 8.3 Hz, $^4J_{11,13}$ = 1.4 Hz, 1H^{d1}, *11-H*^{d1}), 6.58 (dd, $^3J_{11,12}$ = 8.3 Hz, $^4J_{11,13}$ = 1.3 Hz, 1H^{d2}, *11-H*^{d2}), 5.84 (dd, $^3J_{5,4a}$ = 3.5 Hz, $^3J_{5,4b}$ = 10.5 Hz, 1H^{d1}, *5-H*^{d1}), 5.49 (m_c, 1H^{d2}, *5-H*^{d2}), 5.36 (dd, $^3J_{3,4a}$ = 4.8 Hz, $^3J_{3,4b}$ = 9.0 Hz, 1H^{d1}, *3-H*^{d1}), 5.19 (dd, $^3J_{3,4a}$ = 3.5 Hz, $^3J_{3,4b}$ = 9.8 Hz, 1H^{d2}, *3-H*^{d2}), 3.85 (s, 3H^{d1}, *1-H*^{d1}), 3.82 (s, 3H^{d2}, *1-H*^{d2}), 3.08-2.92 (m, 1H^{d1}, *4-H*$_a^{d1}$), 2.90-2.74 (m, 1H + 1H^{d2}, *4-H*$_b$ + *4-H*$_b^{d2}$); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 164.9 (C-2^{d1}), 164.7 (C-2^{d2}), 153.39 (C_{quat}-10^{d1}), 153.36 (C_{quat}-10^{d2}), 139.0 (C_{quat}-6^{d1}), 138.6 (C_{quat}-6^{d2}), 133.43 (C-14^{d1}), 133.39 (C-14^{d2}), 129.12 (C-8^{d1}), 129.10 (C-8^{d2}), 128.7 (C-9^{d1}), 128.6 (C-9^{d2}), 128.3 (C-12^{d1}), 128.2 (C-12^{d2}), 125.9 (C-7^{d1}), 125.6 (C-7^{d2}), 122.7 (C-13^{d1}), 122.6 (C-13^{d2}), 115.1 (C-11^{d1}), 115.0 (C-11^{d2}), 112.7 (C_{quat}-15^{d1}), 112.6 (C_{quat}-15^{d2}), 84.6 (C-3^{d1}), 84.5 (C-3^{d2}), 77.3 (C-5^{d1}), 76.9 (C-5^{d2}), 53.8 (C-1^{d1}), 53.7 (C-1^{d2}), 39.2 (C-4^{d1}), 38.7 (C-4^{d2}); FTIR (neat) 3707, 3680, 2844, 1754, 1562, 1442, 1241, 1032, 1016, 749 cm^{-1}; HRMS Calcd for $C_{17}H_{15}NO_5Br$ $(M-H)^-$: 392.0128. Found 392.0132.

SFC (Chiralcel AS-H, 5% ^{i}PrOH, 2 mL/min, 200 bar, 35 °C) t_r 3.8 min (minor enantiomer, major diastereomer), t_r 4.2 min (major enantiomer, major diastereomer), t_r 4.7

min (minor enantiomer, minor diastereomer), t_r 5.2 min (major enantiomer, minor diastereomer).



(1*R*,2*S*)-**23a**



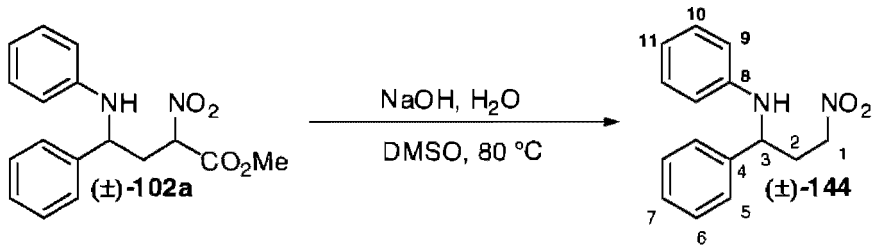
122l

Methyl (4*S*)-4-(2-methoxyphenoxy)-2-nitro-4-phenylbutanoate (122l, rac: IZ-01-975, ent: OL-02-076). The title compound was prepared by the procedure described above using cyclopropane (1*S*,2*R*)-**23a** (87.2 mg, 0.39 mmol, 1 equiv, 95% ee) and 2-methoxyphenol (130 μL, 1.18 mmol, 3 equiv) and purified by method B (flash chromatography: 20% EtOAc/Hexane) to afford the pure product as a pale yellow oil (106.3 mg, 0.31 mmol, 78%, 70:30 dr, 95% ee). R_f = 0.56 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 7.42-7.28 (m, 5H, *7,8,9-H*), 6.97-6.86 (m, 2H, *12,13-H*), 6.73-6.59 (m, 2H, *11,14-H*), 6.03 (dd, $^3J_{5,4a}$ = 3.6 Hz, $^3J_{5,4b}$ =10.3 Hz, 1H^{d1}, *5-H^{d1}*), 5.60 (dd, $^3J_{5,4a}$ = 6.2 Hz, $^3J_{5,4b}$ =7.4 Hz, 1H^{d2}, *5-H^{d2}*), 5.17 (dd, $^3J_{3,4a}$ = 4.6 Hz, $^3J_{3,4b}$ = 9.5 Hz, 1H^{d1}, *3-H^{d1}*), 5.01 (dd, $^3J_{3,4a}$ = 3.2 Hz, $^3J_{3,4b}$ = 10.0 Hz, 1H^{d2}, *3-H^{d2}*), 3.87 (s, 3H^{d1}, *16-H^{d1}*), 3.85 (s, 3H^{d2}, *16-H^{d2}*), 3.848 (s, 3H^{d1}, *1-H^{d1}*), 3.841 (s, 3H^{d2}, *1-H^{d2}*), 3.06-2.96 (m, 1H^{d1}, *4-H$_a^{d1}$*), 2.86-2.68 (m, 1H^{d2} + 1H, *4-H$_b$* + *4-H$_a^{d2}$*); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.6 (C-2^{d1}), 165.0 (C-2^{d2}), 151.0 (C$_{quat}$-10^{d1}), 150.6 (C$_{quat}$-10^{d2}), 146.7 (C$_{quat}$-15^{d1}), 146.4 (C$_{quat}$-15^{d2}), 140.1 (C$_{quat}$-6^{d1}), 139.7 (C$_{quat}$-6^{d2}), 128.8 (C-8^{d1}), 128.7 (C-8^{d2}), 128.4 (C-9^{d1}), 128.3 (C-9^{d2}), 126.3 (C-7^{d1}), 126.2 (C-7^{d2}), 123.6 (C-12^{d1}), 122.9 (C-12^{d2}), 120.6 (C-13^{d1}), 120.5 (C-13^{d2}), 119.9 (C-14^{d1}), 118.2 (C-14^{d2}), 112.1 (C-11^{d1}), 111.9 (C-11^{d2}), 84.8 (C-3^{d1}), 84.6 (C-3^{d2}), 78.9 (C-5^{d1}), 78.8 (C-5^{d2}), 55.7 (C-16^{d1}), 55.4 (C-16^{d2}), 53.60 (C-1^{d1}), 53.56 (C-1^{d2}), 39.1 (C-4^{d1}), 38.8 (C-4^{d2}); FTIR (neat) 3709, 2966, 2844, 1754, 1559, 1454, 1254, 1032, 746, 630 cm^{-1}; HRMS Calcd for $C_{18}H_{18}NO_6(M\text{-}H)^-$: 344.1140. Found 344.1140.

SFC (Chiralcel OJ-H, 5% ^{i}PrOH, 3 mL/min, 200 bar, 35 °C) t_r 3.3 min (major enantiomer, major diastereomer), t_r 3.7 (minor enantiomer, major diastereomer), t_r 5.1 (minor enantiomer, minor diastereomer), t_r 5.5 min (major enantiomer, minor diastereomer).

6.6 Synthesis of the norepinephrine and serotonin reuptake inhibitors (*R*)-131, (±)-139, and atomoxetine 129

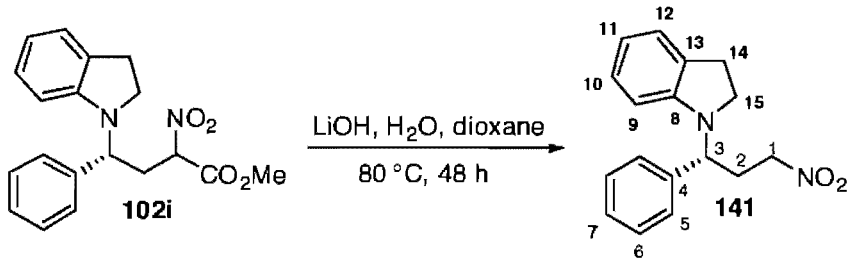
6.6.1 Demethoxycarbonylation of (±)-102a



Methyl 4-anilino-2-nitro-4-phenylbutanoate ((±)-144, OL-01-148). In a 25 mL round bottom flask, **(±)-102a** (118.3 mg, 0.38 mmol, 1 equiv) was dissolved in DMSO (2.4 mL) and water (1.2 mL). NaOH (19.5 mg, 0.49 mmol, 1.3 equiv) was added and the reaction was stirred at 80 °C for 12 hours. After cooling to rt, the reaction was quenched with sat. aq. NH_4Cl (2 mL) and partitioned between water and diethyl ether. The aqueous phase was washed with diethyl ether (10 mL) three times and the organic phase was washed with water (3 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography eluting with 15% EtOAc in hexanes afforded the product **(±)-144** as a yellow solid (37.4 mg, 0.15 mmol, 39%) and the recovered starting material **(±)-102a** (44.1 mg, 0.14 mmol, 37%). mp 76-78 °C; R_f = 0.36 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H, *5,6,7-H*), 7.13 (dd, $^3J_{10,11}$ = 7.3 Hz, $^3J_{10,9}$ = 7.6 Hz, 2H, *10-H*), 6.71 (t, $^3J_{11,10}$ = 7.3 Hz, 1H, *11-H*), 6.58 (d, $^3J_{9,10}$ = 7.6 Hz, 1H, *9-H*), 4.56-4.39 (m, 3H, *1-H* + *3-H*), 4.05 (br. s, 1H, N-*H*), 2.63-2.41 (m, 2H, *2-H*); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 146.5 (C_{quat}-8), 141.5 (C_{quat}-4), 129.2 (C-10), 129.0 (C-6), 127.9 (C-7), 126.2 (C-5), 118.2 (C-11), 113.7 (C-9), 72.6 (C-1), 55.5 (C-3), 35.1 (C-2); FTIR (neat) 3401, 3026, 2924, 1729, 1600 1546, 1504, 1314, 1180, 1028, 872 cm^{-1}; HRMS Calcd for $C_{15}H_{17}N_2O_2$ $(M+H)^+$: 257.1284. Found 257.1286.

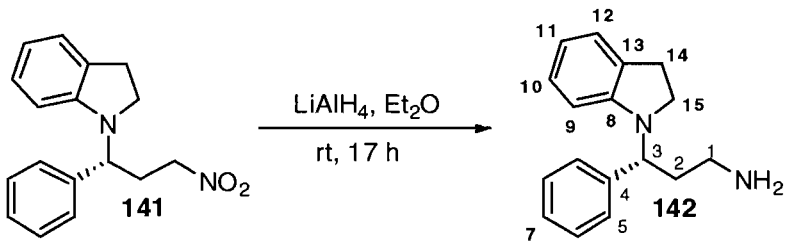
6.6.2 Synthesis of (*R*)-131



1-[(1*R*)-3-nitro-1-phenylpropyl]indoline (141, rac: OL-01-228, ent: OL-01-288). To a solution of **102i** (500 mg, 1.5 mmol, 1 equiv, 90% ee) in dioxane (10 mL) and water (5 mL) was added LiOH (53 mg, 2.2 mmol, 1.5 equiv), and the reaction mixture was stirred at 80 °C for 48 h, after which all of the starting material was consumed. The crude reaction mixture was cooled to room temperature, neutralized with 1 M HCl and partitioned with EtOAc. The aqueous phase was extracted with EtOAc three times, and the combined organic phases were washed with sat. aq. NaCl and dried over Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by flash chromatography, eluting with 20% EtOAc in hexanes, affording spectroscopically pure **141** as a crystalline yellow solid (369.5 mg, 1.31 mmol, 89%, 90% ee). $[\alpha]_D^{20}$: + 150.8 (*c* 0.455, MeOH); mp 69-71 °C; R_f = 0.76 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H, *5,6,7-H*), 7.06 (m_c, 2H, *10,12-H*), 6.64 (ddd, $^3J_{11,12}$ = 7.6 Hz, $^3J_{11,10}$ = 7.3 Hz, $^4J_{11,9}$ = 0.9 Hz, 1H, *11-H*), 6.56 (d, $^3J_{9,10}$ = 8.1 Hz, 1H, *9-H*), 4.82 (dd, $^3J_{3,2a}$ = 5.9 Hz, $^3J_{3,2b}$ = 9.6 Hz, 1H, *3-H*), 4.62-4.46 (m, 2H, *1-H*), 3.45-3.37 (m, 1H, *15-H$_a$*), 3.20-3.11 (m, 1H, *15-H$_b$*), 3.02-2.88 (m, 2H, *14-H*), 2.84-2.61 (m, 2H, *2-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8 (C_{quat}-8), 138.0 (C_{quat}-4), 129.6 (C_{quat}-13), 128.7

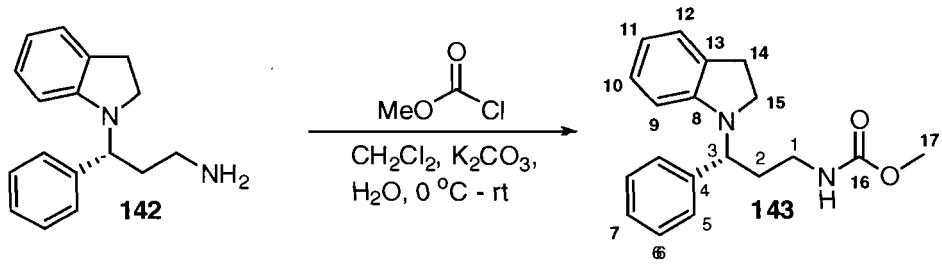
(C-6), 127.9 (C-7), 127.6 (C-5), 127.4 (C-10), 124.7 (C-12), 117.6 (C-11), 106.8 (C-9), 73.0 (C-1), 56.0 (C-3), 46.7 (C-15), 28.9 (C-2), 28.1 (C-14); FTIR (neat) 3027, 2925, 2848, 1604, 1546, 1381, 1255, 1024, 919, 873, 744 cm^{-1}; HRMS Calcd for $C_{17}H_{19}N_2O_2$ $(M+H)^+$: 283.1441. Found 283.1434.

SFC (Chiralcel OD-H, 20% MeOH, 4 mL/min, 100 bar, 25 °C) t_r 5.8 min (minor enantiomer), t_r 15.5 min (major enantiomer).

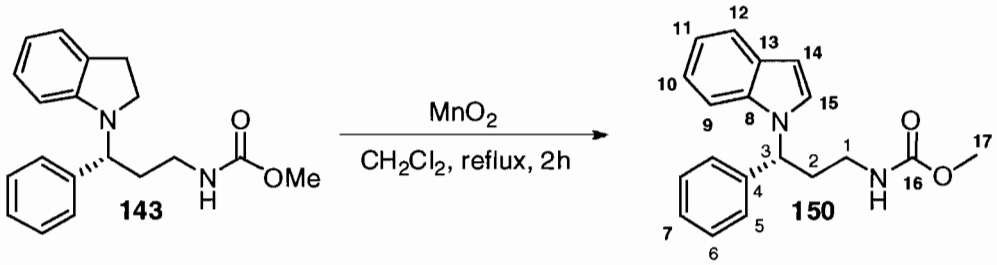


(3*R*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropylamine (142, rac : OL-01-276 ent : OL-01-289). In a flame-dried 25 mL round bottom flask, **141** (200 mg, 0.71 mmol, 1 equiv) was dissolved in anhydrous diethyl ether (6 mL) under an atmosphere of argon. $LiAlH_4$ (107 mg, 2.8 mmol, 4 equiv) was added quickly in one portion at 0 °C. When the exotherm ceased, the reaction mixture was warmed up to room temperature and stirred overnight. The crude reaction mixture was quenched with several drops of H_2O at 0 °C, and several drops of 2M NaOH were added so that a thick white precipitate of aluminum hydroxide formed. This suspension was filtered through a pad of Celite washing with diethyl ether, yielding a clear yellowish solution, which was evaporated under reduced pressure to afford spectroscopically pure **142** (177 mg, 0.70 mmol, 99%, 90% ee) which was used without further purification. $[\alpha]_D^{20}$: + 155.4 (*c* 0.975, MeOH); R_f = 0.15 (20% MeOH in dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H, *5,6,7-H*), 7.07-7.02 (m, 2H, *10,12-H*), 6.61–6.53 (m, 2H, *9,11-H*), 4.79 (dd, $^3J_{3,2a}$ = 7.1 Hz, $^3J_{3,2b}$ = 7.9 Hz, *3-H*), 3.49 (m_c, 1H, *15-H$_a$*), 3.28 (m_c, 1H, *15-H$_b$*), 3.04-2.88 (m, 2H, *14-H*), 2.83 (t, $^3J_{1,2}$ = 7.2 Hz, 2H, *1-H*), 2.28-2.02 (m, 2H, *2-H*), 1.29 (br. s, 2H, N-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4 (C_{quat}-8), 140.2 (C_{quat}-4), 129.5 (C_{quat}-13), 128.3 (C-6), 127.7

(C-5), 127.2 (C-7), 127.1 (C-10), 124.5 (C-12), 116.6 (C-11), 106.3 (C-9), 53.4 (C-3), 46.8 (C-15), 39.7 (C-1), 35.0 (C-2), 28.1 (C-14); FTIR (neat) 3025, 2924, 2847, 1605, 1487, 1329, 1258, 1157, 837, 742, 631 cm^{-1}; HRMS Calcd for $C_{17}H_{21}N_2$ $(M+H)^+$: 253.1699. Found 253.1697.

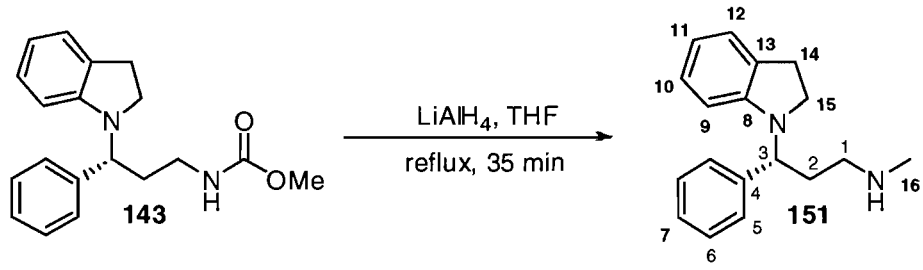


Methyl (3*R*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropylcarbamate (143, rac: OL-01-252, ent: OL-01-290). To a solution of **142** (165 mg, 0.65 mmol, 1 equiv) in dichloromethane (5 mL) was added methyl chloroformate (61 µL, 0.78 mmol, 1.2 equiv). The solution was cooled to 0 °C and K_2CO_3 (362 mg, 2.6 mmol, 4 equiv) and H_2O (5 mL) were added. The reaction was warmed to room temperature and stirred for 30 min. Water (5 mL) was added and the reaction mixture was extracted with dichloromethane three times, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography, eluting with 30% EtOAc in hexanes, afforded the spectroscopically pure **143** as a colourless oil (191.0 mg, 0.61 mmol, 94%, 90% ee). $[\alpha]_D^{20}$: + 117.0 (*c* 0.675, MeOH); R_f = 0.33 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H, *5,6,7-H*), 7.10-7.06 (m, 2H, *10,12-H*), 6.63 (dd, $^3J_{11,12}$ = 7.2 Hz, $^3J_{11,10}$ = 7.2 Hz, 1H, *11-H*), 6.56 (d, $^3J_{9,10}$ = 8.0 Hz, 1H, *9-H*), 4.97 (br. s, 1H, N-*H*), 4.75 (t, $^3J_{3,2}$ = 7.1 Hz, 1H, *3-H*), 3.70 (s, 3H, *17-H*), 3.53-3.47 (m, 1H, *15-H$_a$*), 3.40-3.23 (m, 2H, *15-H$_b$*), 3.04-2.89 (m, 2H, *1-H*), 2.26 (m_c, 2H, *2-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (C-16), 150.2 (C_{quat}-8), 138.5 (C_{quat}-4), 128.5 (C_{quat}-13), 127.3 (C-6), 126.6 (C-5), 126.3 (C-10), 126.2 (C-7), 123.6 (C-12), 115.9 (C-11), 105.4 (C-9), 55.4 (C-3), 51.0 (C-17), 45.6 (C-15), 37.9 (C-1), 30.3 (C-2), 27.0 (C-14); FTIR (neat) 3030, 3026, 2946, 1698, 1604, 1519, 1452, 1188, 1023, 918, 741 cm^{-1}; HRMS Calcd for $C_{19}H_{23}N_2O_2$ $(M+H)^+$: 311.1754. Found 311.1747.



Methyl (3*R*)-3-(1*H*-indol-1-yl)-3-phenylpropylcarbamate (150, rac: OL-01-253, ent: OL-01-269) To a solution of **143** (362 mg, 0.65 mmol, 1 equiv, 88% ee) in dichloromethane (10 mL) was added MnO_2 (568 mg, 6.5 mmol, 10 equiv) and the reaction was stirred at reflux for 2 h. The reaction mixture was filtered through a pad of Celite, washing with dichloromethane, and evaporated under reduced pressure to afford the spectroscopically pure product **150** as a beige foam (193.6 mg, 0.63 mmol, 96%, 88% ee). $[\alpha]_D^{20}$: + 59.4 (*c* 0.98, MeOH); R_f = 0.35 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, $^3J_{12,11}$ = 7.6 Hz, 1H, *12-H*), 7.35-7.11 (m, 9H, *5,6,7,9,10,11, 15-H*), 6.64 (d, $^3J_{14,15}$ = 3.2 Hz, 1H, *14-H*), 5.59 (dd, $^3J_{3,2a}$ = 6.8 Hz, $^3J_{3,2b}$ = 8.4 Hz, 1H, *3-H*), 4.92, 4.97 (br. s, 1H, N-*H*, 2 rotamers), 3.67 (s, 3H, *17-H*), 3.25-3.18, 3.12-3.03 (m, 2H, *1-H*, 2 rotamers), 2.56 (m_c, 2H, *2-H*); ^{13}C NMR (75 MHz, $CDCl_3$), δ 156.0 (C-18), 139.7 (C_{quat}-4), 135.1 (C_{quat}-8), 127.7 (C-6), 127.6 (C_{quat}-13), 126.6 (C-7), 125.2 (C-5), 123.8 (C-15), 120.7 (C-11), 120.0 (C-12), 118.6 (C-10), 108.6 (C-9), 101.2 (C-14), 55.9 (C-3), 51.0 (C-17), 37.4 (C-1), 33.9 (C-2); FTIR (neat) 3032, 3029, 2947, 1699, 1458, 1305, 1259, 1191, 1013, 740cm^{-1}; HRMS Calcd for $C_{19}H_{21}N_2O_2$ $(M+H)^+$: 309.1598. Found 309.1608.

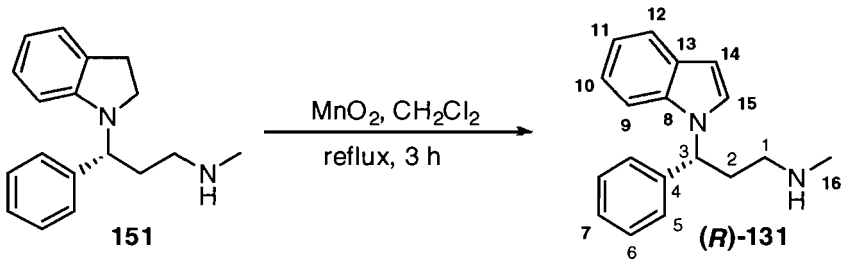
SFC (Chiralcel OD-H, 20% MeOH, 4 mL/min, 100 bar, 25 °C) t_r 8.7 min (minor enantiomer), t_r 11.8 min (major enantiomer).



(3*R*)-3-(2,3-dihydro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (151, rac: OL-01-281, ent: OL-02-018). In a flame-dried 25 mL round bottom flask, **143** (57.5 mg, 0.18 mmol, 1 equiv) was dissolved in anhydrous tetrahydrofuran (3 mL) under an atmosphere of argon and cooled to 0 °C. $LiAlH_4$ (28.1 mg, 0.74 mmol, 4 equiv) was added quickly in one portion. When the exotherm ceased, the reaction was warmed up to room temperature, and then stirred at reflux for 35 min, after which all of the starting material was consumed. The crude reaction mixture was quenched with several drops of H_2O at 0 °C, and several drops of 2 M NaOH were added so that a thick white precipitate of aluminum hydroxide formed. This suspension was filtered through a pad of Celite washing with diethyl ether, yielding a clear yellowish solution, which was evaporated under reduced pressure to afford pure **151** (49.2 mg, 0.18 mmol, quant., 90% ee) which was used without further purification. If desired, the product can be further purified by flash chromatography, eluting with 20% MeOH in dichloromethane or by filtration through a silica plug eluting with MeOH. $[\alpha]_D^{20}$: + 149.7 (*c* 0.625, MeOH); R_f = 0.10 (methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H, *5,6,7-H*), 7.07-7.02 (m, 2H, *10,12-H*), 6.61-6.53 (m, 2H, *9,11-H*), 5.77 (t, $^3J_{3,2}$ = 7.3 Hz, 1H, *3-H*), 3.49 (m_c, 1H, *15-H$_a$*), 3.25 (m_c, 1H, *15-H$_b$*), 3.02-2.84 (m, 2H, *14-H*), 2.70 (m_c, 2H, *1-H*), 2.44 (s, 3H, *16-H*), 2.31-2.11 (m, 2H, *2-H*), 1.81 (br. s, 1H, N-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4 (C_{quat}-8), 140.1 (C_{quat}-4), 129.5 (C_{quat}-13), 128.3 (C-6), 127.7 (C-5), 127.2 (C-7), 127.1(C-10), 124.4 (C-12), 116.6 (C-11), 106.4 (C-9), 56.9 (C-3), 49.5 (C-1), 46.8 (C-15), 36.5 (C-16), 31.4 (C-2), 28.1 (C-14); FTIR (neat) 3026, 2930, 2793, 1605, 1472, 1328,

1263, 1157, 1024, 735 cm^{-1}; HRMS Calcd for $C_{18}H_{23}N_2$ $(M+H)^+$: 267.1856. Found 267.1854. Spectroscopic data are in full agreement with the literature values.[100]

SFC (Chiralcel OD-H, 20% [MeOH + 0.2% NEt_3], 2 mL/min, 100 bar, 40 °C) t_r 6.4 min (minor enantiomer), t_r 8.0 min (major enantiomer).



(3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine ((*R*)-131, rac: OL-01-254, ent: OL-02-019). To a solution of **151** (49 mg, 0.18 mmol, 1 equiv) in dichloromethane (3 mL) was added MnO_2 (161 mg, 1.8 mmol, 10 equiv) and the reaction mixture was stirred at reflux for 3 h, after which all of the starting material was consumed. The crude reaction mixture was filtered through a pad of Celite, washing with dichloromethane, evaporated under reduced pressure and purified by flash chromatography eluting with 20% MeOH in dichloromethane, affording spectroscopically pure (*R*)-**131** as a pale yellow oil (40.3 mg, 0.15 mmol, 83%, 90% ee). $[\alpha]_D^{20}$: + 81.2 (*c* 0.50, MeOH); Lit.[4]: $[\alpha]^{25}_D$ = + 79.2 (*c* 1.0, MeOH); R_f = 0.13 (20% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, ^3J = 7.6 Hz, 1H, *12-H*), 7.37 (d, $^3J_{15,14}$ = 3.2 Hz, 1H, *15-H*), 7.40-7.24 (m, 6H, *5,6,7,9-H*), 7.20 (ddd, $^3J_{11,10}$ = 7.1 Hz, $^3J_{11,12}$ = 7.0 Hz, $^4J_{11,9}$ = 1.1 Hz, 1H, *11-H*), 7.14 (ddd, $^3J_{10,11}$ = 7.9 Hz, $^3J_{10,9}$ = 7.0 Hz, $^4J_{10,12}$ = 1.1 Hz, 1H, *10-H*), 6.63 (d, $^3J_{14,15}$ = 3.2 Hz, 1H, *14-H*), 5.71 (dd, $^3J_{3,2a}$ = 6.4 Hz, $^3J_{3,2b}$ = 8.6 Hz, 1H, *3-H*), 2.63-2.45 (m, 4H, *1,2-H*), 2.42 (s, 3H, *16-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3 (C_{quat}-4), 136.3 (C_{quat}-8), 128.6 (C-6), 128.5 (C_{quat}-13), 127.5 (C-7), 126.2 (C-5), 124.9 (C-15), 121.4 (C-11), 120.8 (C-12), 119.5 (C-10), 109.9 (C-9), 101.8 (C-14), 57.2 (C-3), 48.7 (C-1), 36.4 (C-16), 35.3 (C-2); FTIR

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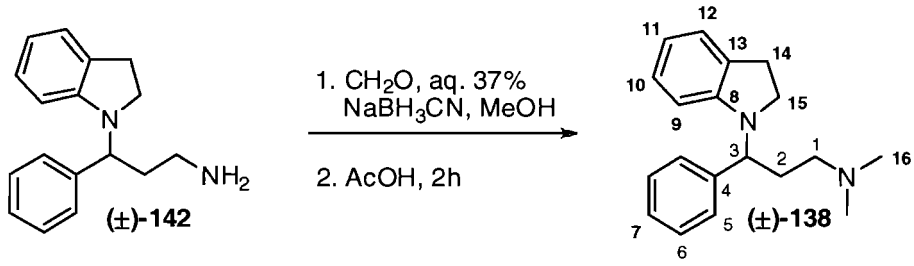
[100] Mahaney, P. E. *et al. Bioorg. Med. Chem.* **2006**, *14*, 8455.

(neat) 3028, 2932, 1609, 1509, 1474, 1308, 1212, 1013, 738 cm^{-1}; HRMS Calcd for $C_{18}H_{21}N_2$ $(M+H)^+$: 265.1699. Found 265.1704. Spectroscopic data are in full agreement with the literature values.[100]

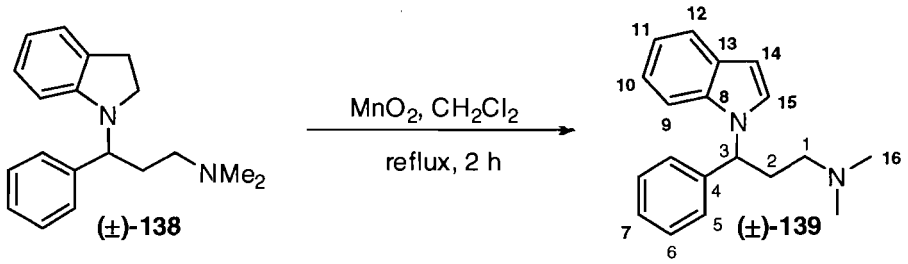
SFC (Chiralcel OD-H, 20% [MeOH + 0.2% NEt_3], 2 mL/min, 100 bar, 35 °C) t_r 7.1 min (minor enantiomer), t_r 12.9 min (major enantiomer).

6.6.3 Synthesis of (±)-139



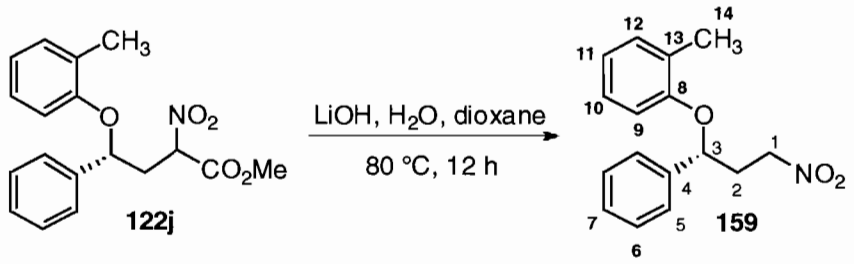
***N*-[3-(2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropyl]-*N*,*N*-dimethylamine[7] ((±)-138, OL-01-242).** To a solution of **(±)-142** (295 mg, 1.17 mmol, 1 equiv) in MeOH (6 mL) was added 37% aq. formaldehyde (483 mg, 5.95 mmol, 5 equiv) at room temperature, upon which a white suspension formed which dissolved under 1 min. $NaCNBH_3$ (120 mg, 1.90 mmol, 1.6 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. Several drops of glacial acetic acid were added (with gas evolution) and the reaction mixture was stirred for additional 2 hours. The reaction mixture was basified to pH 9 with 2 M NaOH and extracted with dichloromethane three times. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography, eluting with 20% MeOH in dichloromethane, afforded spectroscopically pure **(±)-138** as a colourless oil (234.9 mg, 0.84 mmol, 72%). R_f = 0.43 (20% MeOH in dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H, *5,6,7-H*), 7.06-7.02 (m, 2H, *10,12-H*), 6.61-6.53 (m, 2H, *9,11-H*), 4.74 (m_c, 1H, *3-H*), 3.50 (m_c, 1H, *15-H$_a$*), 3.44 (m_c, 1H, *15-H$_b$*), 3.03-2.85 (m, 2H, *14-H*), 2.56-2.37 (m, 2H, *1-H*), 2.32 (s, 6H, *16-H*), 2.30-2.14 (m, 2H, *2-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3

(C_{quat}-8), 139.9 (C_{quat}-4), 129.5 (C_{quat}-13), 128.3 (C-6), 127.4 (C-5), 127.22 (C-7), 127.20 (C-10), 124.5 (C-12), 116.6 (C-11), 106.4 (C-9), 56.9 (C-1), 56.8 (C-3), 46.7 (C-15), 45.3 (C-16), 29.1 (C-2), 28.1 (C-14); FTIR (neat) 3026, 2943, 2854, 2764, 1605, 1487, 1388, 1304, 1024, 738, 629 cm^{-1}; HRMS Calcd for $C_{19}H_{25}N_2$ $(M+H)^+$: 281.2012. Found 281.2000. Spectroscopic data are in full agreement with the literature values. [100]



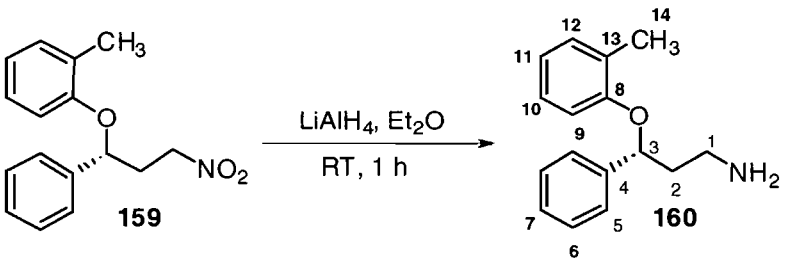
3-(1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine ((±)-139, OL-01-243). To a solution of **(±)-138** (234.9 mg, 0.84 mmol, 1 equiv) in dichloromethane (18 mL) was added MnO_2 (727 mg, 8.4 mmol, 10 equiv) and the reaction mixture was stirred at reflux for 2 hours. The reaction mixture was filtered through a pad of Celite washing with dichloromethane and evaporated under reduced pressure to afford spectroscopically pure **(±)-139** as a colourless oil (233.8 mg, 0.84 mmol, quant.). R_f = 0.33 (20% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, ^3J = 7.8 Hz, 1H, *12-H*), 7.43-7.13 (m, 9H, *5,6,7,9,10,11,15-H*), 6.65 (d, $^3J_{14,15}$ = 3.2 Hz, 1H, *14-H*), 5.72 (dd, $^3J_{3,2a}$ = 6.3 Hz, $^3J_{3,2b}$ = 8.7 Hz, 1H, *3-H*), 2.56-2.37 (m, 2H, *1-H*), 2.33-2.27 (m, 2H, *2-H*), 2.27 (s, 6H, *16-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4 (C_{quat}-4), 136.3 (C_{quat}-8), 128.6 (C-6), 128.5 (C_{quat}-13), 127.4 (C-7), 126.3 (C-5), 124.9 (C-15), 121.4 (C-11), 120.8 (C-12), 119.4 (C-10), 110.0 (C-9), 101.8 (C-14), 57.2 (C-3), 56.2 (C-1), 45.5 (C-16), 33.3 (C-2); FTIR (neat) 3030, 2944, 2860, 2768, 1510, 1407, 1213, 906, 727, 648 cm^{-1}; HRMS Calcd for $C_{19}H_{23}N_2$ $(M+H)^+$: 279.1856. Found 279.1862. Spectroscopical data are in full agreement with the literature values. [100]

6.6.3 Synthesis of atomoxetine (*R*)-129

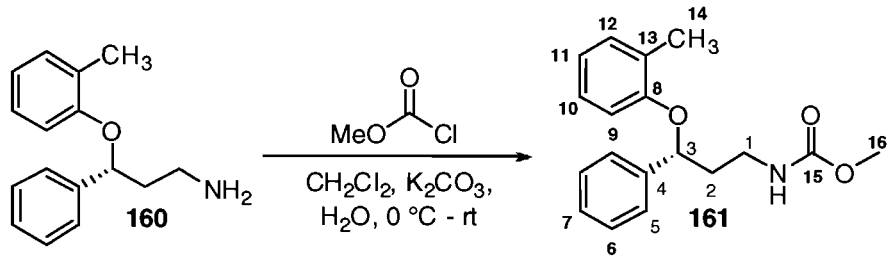


2-Methylphenyl (1*R*)-3-nitro-1-phenylpropyl ether (159, rac: OL-02-003, ent: OL-02-021). To a solution of **122j** (50 mg, 0.15 mmol, 1 equiv, 90% ee) in dioxane (1 mL) and water (0.5 mL) was added LiOH (3.6 mg, 0.152 mmol, 1 equiv), and the reaction mixture was stirred at 80 °C for 12 h. The crude reaction mixture was cooled to room temperature, neutralized with sat. aq. NH_4Cl and partitioned between water and diethyl ether. The aqueous phase was extracted with diethyl ether (10 mL) three times, and the combined organic phases were washed with sat. aq. NaCl and dried over Na_2SO_4. Evaporating the solvent under reduced pressure afforded an essentially spectroscopically pure product (43.0 mg, 0.15 mmol, quant) as a yellowish oil. Trace impurities were removed by flash chromatography, eluting with 15% EtOAc in hexanes, to afford **159** as a colourless oil (40.9 mg, 0.15 mmol, 99%, 90% ee). $[\alpha]_D^{20}$: – 12.5 (c 0.92, MeOH); R_f = 0.54 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H, *5,6,7-H*), 7.06 (d, $^3J_{12,11}$ = 7.9 Hz, 1H, *12-H*), 6.98 (dd, $^3J_{10,9}$ = 8.3 Hz, $^3J_{10,11}$ = 7.8 Hz, 1H, *10-H*), 6.83 (dd, $^3J_{11,10}$ = 7.5 Hz, $^3J_{11,12}$ = 7.9 Hz, 1H, *11-H*), 6.58 (d, 1H, $^3J_{9,10}$ = 8.3 Hz, *9-H*), 5.35 (t, $^3J_{3,2}$ = 6.3 Hz, 1H, *3-H*), 4.70 (dt, $^3J_{1a,1b}$ = 13.7 Hz, $^3J_{1,2}$ = 6.8 Hz, 1H, *1-H$_a$*), 4.54 (dt, $^3J_{1a,1b}$ = 13.7 Hz, $^3J_{1,2}$ = 6.8 Hz, 1H, *1-H$_b$*), 2.66 (dt, $^3J_{2,3}$ = 6.3 Hz, $^3J_{2,1}$ = 6.8 Hz, 2H, *2-H*), 2.34 (s, 3H, *14-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (C_{quat}-8), 139.9 (C_{quat}-4), 130.8 (C-12), 128.9 (C-6), 128.2 (C-7), 126.9 (C_{quat}-13), 126.6 (C-10), 125.6 (C-5), 120.8 (C-11), 112.5 (C-9), 76.1 (C-3), 71.9 (C-1), 35.8 (C-2), 16.4 (C-14); FTIR (neat) 3029, 2916, 1601, 1589, 1551,1382, 1236, 1121, 750, 701 cm^{-1}; HRMS Calcd for $C_{16}H_{17}NO_3Na$ $(M+Na)^+$: 294.1101. Found 294.1089.

SFC (Chiralcel OD-H, 5% MeOH, 3 mL/min, 200 bar, 30 °C) t_r 5.0 min (minor enantiomer), t_r 10.9 min (major enantiomer).

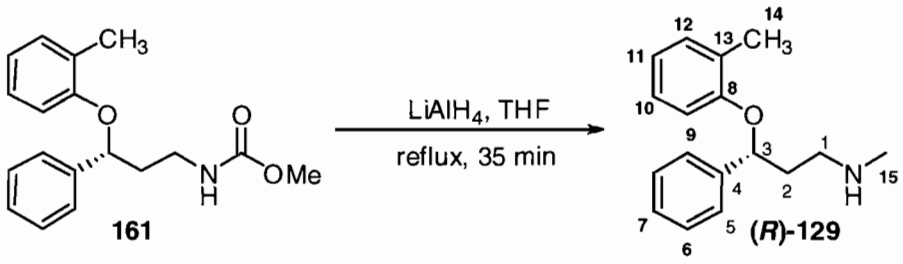


(3*R*)-3-(2-methylphenoxy)-3-phenylpropylamine (160, rac: OL-02-008, ent: OL-02-023). In a flame-dried 25 mL round bottom flask, **159** (128.5 mg, 0.47 mmol, 1 equiv, 90% ee) was dissolved in anhydrous diethyl ether (6 mL) under an atmosphere of argon. $LiAlH_4$ (72 mg, 1.9 mmol, 4 equiv) was added quickly in one portion at 0 °C. When the exotherm ceased, the reaction mixture was warmed up to room temperature and stirred for one hour. The crude reaction mixture was quenched with several drops of H_2O at 0 °C, and several drops of 2 M NaOH were added so that a thick white precipitate of aluminum hydroxide formed. This suspension was filtered through a pad of Celite washing with diethyl ether. The resulting clear colourless solution was evaporated under reduced pressure to afford spectroscopically pure **160** (109.5 mg, 0.45 mmol, 96%) as a colourless oil, which was used without further purification. $[\alpha]_D^{20}$: – 39.4 (c 1.0, MeOH); R_f = 0.27 (20% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H, *5,6,7-H*), 7.14 (d, $^3J_{12,11}$ = 8.0 Hz, 1H, *12-H*), 6.98 (dd, $^3J_{10,9}$ = 8.1 Hz, $^3J_{10,11}$ = 7.1 Hz, 1H, *10-H*), 6.79 (dd, $^3J_{11,10}$ = 7.1 Hz, $^3J_{11,12}$ = 8.0 Hz, 1H, *11-H*), 6.63 (d, 1H, $^3J_{9,10}$ = 8.1 Hz, *9-H*), 5.30 (d, $^3J_{3,2a}$ = 4.4 Hz, $^3J_{3,2b}$ = 8.3 Hz, 1H, *3-H*), 2.93 (t, $^3J_{1,2}$ = 6.8 Hz, 2H, *1-H*), 2.35 (s, 3H, *14-H*), 2.25-2.13 (m, 1H, *2-H$_a$*), 2.05-1.94 (m, 1H, *2-H$_b$*), 1.24 (br. s, 2H, N-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (C_{quat}-8), 142.1 (C_{quat}-4), 130.6 (C-12), 128.5 (C-6), 127.4 (C-7), 126.9 (C_{quat}-13), 126.5 (C-10), 125.7 (C-5), 120.1 (C-11), 112.6 (C-9), 77.7 (C-3), 42.6 (C-2), 38.8 (C-1), 16.5 (C-14); FTIR (neat) 3026, 2921, 1600, 1491, 1306, 1492, 1237, 1119, 816, 748, 701 cm^{-1}; HRMS Calcd for $C_{16}H_{20}NO$ $(M+H)^+$: 242.1539. Found 242.1533.



Methyl (3*R*)-3-(2-methylphenoxy)-3-phenylpropylcarbamate (161, rac: OL-01-011, ent: OL-01-024). To a solution of **160** (94.5 mg, 0.39 mmol, 1 equiv, 90% ee) in dichloromethane (4 mL) was added methyl chloroformate (36.4 µL, 0.47 mmol, 1.2 equiv). The solution was cooled to 0 °C and K_2CO_3 (216 mg, 1.6 mmol, 4 equiv) and H_2O (4 mL) were added. The reaction was warmed up to room temperature and stirred for 1 hour. Water (5 mL) was added and the reaction mixture was extracted with dichloromethane (10 mL) three times, dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography, eluting with 20% EtOAc in hexanes, afforded the spectroscopically pure **161** as a colourless oil (100.4 mg, 0.33 mmol, 88%, 90% ee). $[\alpha]_D^{20}$: – 40.8 (c 0.675, MeOH); R_f = 0.26 (20% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, *5,6,7-H*), 7.15 (d, $^3J_{12,11}$ = 8.1 Hz, 1H, *12-H*), 6.98 (dd, $^3J_{10,9}$ = 8.1 Hz, $^3J_{10,11}$ = 7.2 Hz, 1H, *10-H*), 6.81 (dd, $^3J_{11,10}$ = 7.2 Hz, $^3J_{11,12}$ = 8.1 Hz, 1H, *11-H*), 6.60 (d, $^3J_{9,10}$ = 8.1 Hz, 1H, *9-H*), 5.27 (dd, $^3J_{3,2a}$ = 5.6 Hz, $^3J_{3,2b}$ = 6.8 Hz, 1H, *3-H*), 5.07 (br. s, 1H, N-*H*), 3.67 (s, 3H, *16-H*), 4.46-4.37 (m, 2H, *1-H*), 2.37 (s, 3H, *14-H*), 2.21-2.14 (m, 2H, *2-H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0 (C-15), 155.6 (C_{quat}-8), 141.2 (C_{quat}-4), 130.7 (C-12), 128.7 (C-6), 127.6 (C-7), 126.8 (C_{quat}-13), 126.6 (C-10), 125.6 (C-5), 120.4 (C-11), 112.6 (C-9), 77.9 (C-3), 52.0 (C-16), 38.6 (C-2), 38.1 (C-1), 16.6 (C-14); FTIR (neat) 3334, 2949, 1703, 1589, 1517, 1264, 1234, 1120, 748, 609 cm^{-1}; HRMS Calcd for $C_{18}H_{21}NO_3Na$ $(M+Na)^+$: 322.1414. Found 322.1410.

SFC (Chiralcel OD-H, 20% MeOH, 3 mL/min, 150 bar, 30 °C) t_r 3.4 min (minor enantiomer), t_r 4.1 min (major enantiomer).



(3*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine (Atomoxetine, Strattera™) ((*R*)-129, rac: OL-02-012, ent: OL-02-025). In a flame-dried 25 mL round bottom flask equipped with a magnetic stirbar and a reflux condenser, **161** (81.0 mg, 0.27 mmol, 1 equiv, 90% ee) was dissolved in anhydrous tetrahydrofuran (5 mL) under an atmosphere of argon and cooled to 0 °C. $LiAlH_4$ (47.0 mg, 1.1 mmol, 4 equiv) was added quickly in one portion. When the exotherm ceased, the reaction was warmed up to room temperature, and stirred at reflux for 1 hour. The crude reaction mixture was quenched with several drops of H_2O at 0 °C, and several drops of 2 M NaOH were added so that a thick white precipitate of aluminum hydroxide formed. This suspension was filtered through a pad of Celite washing with diethyl ether yielding a clear yellowish solution, which was evaporated under reduced pressure. Purification by flash chromatography eluting with a gradient 5% to 20% MeOH in dichloromethane afforded the spectroscopically pure **(*R*)-129** as a colourless oil (61.5 mg, 0.24 mmol, 89%, 90% ee). $[\alpha]_D^{20}$: – 37.0 (c 1.05, MeOH), Lit.[101]: $[\alpha]_D^{30}$ = – 43.0 (c 0.8, MeOH, ee > 99%); R_f = 0.16 (20% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H, *5,6,7-H*), 7.13 (d, $^3J_{12,11}$ = 7.6 Hz, 1H, *12-H*), 6.97 (ddd, $^3J_{10,9}$ = 8.5 Hz, $^3J_{10,11}$ = 7.2 Hz, $^4J_{10,12}$ = 1.7 Hz, 1H, *10-H*), 6.79 (ddd, $^3J_{11,10}$ = 7.2 Hz, $^3J_{11,12}$ = 7.6 Hz, $^4J_{11,9}$ = 0.9 Hz, 1H, *11-H*), 6.62 (d, $^3J_{9,10}$ = 8.3 Hz, 1H, *9-H*), 5.28 (dd, $^3J_{3,2a}$ = 4.6 Hz, $^3J_{3,2b}$ = 8.3 Hz, 1H, *3-H*), 2.82 (m_c, 2H, *1-H*), 2.46 (s, 3H, *15-H*), 2.33 (s, 3H, *14-H*), 2.30-2.18 (m, 1H, *2-H$_a$*), 2.13-2.02 (m, 1H, *2-H$_b$*), 1.75 (br. s, 1H, N-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C_{quat}-8), 141.9 (C_{quat}-4), 130.6 (C-12), 128.6 (C-6), 127.4 (C-7), 126.9 (C_{quat}-13), 126.5 (C-10), 125.7 (C-5), 120.2 (C-11), 112.7 (C-9), 77.9 (C-3), 48.3 (C-1), 38.5 (C-2), 36.2 (C-15), 16.6 (C-14); FTIR

[101] Kamal, A.; Khanna, G.B.R., Ramu R. *Tetrahedron Asym.* **2002**, *13*, 2039.

(neat) 3027, 2924, 2791, 1601, 1589, 1491, 1305, 1237, 1119, 748, 700 cm^{-1}; HRMS Calcd for $C_{17}H_{22}NO$ $(M+H)^+$: 256.1696. Found 256.1688. Spectroscopic data are in full agreement with the literature values.[101]

Appendix I

Crystal structure of (±)-122h

Equipe Charette
Département de chimie, Université de Montréal,
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Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Francine Bélanger.

Table 1. Crystal data and structure refinement for $C_{18}H_{17}NO_5$.

Identification code	cha174	
Empirical formula	$C_{18}H_{17}NO_5$	
Formula weight	327.33	
Temperature	150K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 9.7146(10) Å	α = 90 °
	b = 11.0069(11	β = 96.608 (6) °
	c = 30.585(3)	γ = 90 °
Volume	3248.6(6)Å^3	
Z value	8	
Density (calculated)	1.339 g/cm^3	
Absorption coefficient	0.818 mm^{-1}	
F(000)	1376	
Crystal size	0.22 x 0.05 x 0.03 mm	

Theta range for data collection	2.91 to 67.82 °
Index ranges	$-10 \leq h$ -11, $-13 \leq k \leq 13$, $-36 \leq l \leq 36$
Reflections collected	52485
Independent reflections	5510 [$R_{int} = 0.147$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9758 and 0.7766
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5510 / 0 / 435
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	$R_1 = 0.0438$, $wR_2 = 0.0647$
R indices (all data)	$R_1 = 0.1090$, $wR_2 = 0.0725$
Largest diff. peak and hole	0.183 and -0.185 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C_{18} $H_{17}NO_5$.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
O(11)	2234(2)	3638(1)	3875(1)	35(1)
O(17)	3108(2)	2119(2)	3055(1)	48(1)
O(18)	844(2)	2612(2)	2991(1)	50(1)
C(11)	1358(3)	2732(2)	4035(1)	33(1)
C(12)	1944(3)	1467(2)	3954(1)	36(1)
C(13)	1395(3)	668(2)	4313(1)	41(1)
C(14)	1329(3)	1572(2)	4684(1)	37(1)
C(15)	1273(3)	1356(2)	5128(1)	45(1)
C(16)	1250(3)	2340(3)	5410(1)	50(1)
C(17)	1290(3)	3520(3)	5255(1)	44(1)
C(18)	1317(3)	3736(2)	4807(1)	37(1)
C(19)	1342(3)	2755(2)	4529(1)	33(1)
C(110)	1656(3)	4723(2)	3726(1)	34(1)
C(111)	297(3)	5074(2)	3754(1)	39(1)
C(112)	-166(3)	6176(2)	3578(1)	48(1)
C(113)	702(3)	6950(2)	3384(1)	53(1)

C(114)	2057(3)	6594(2)	3358(1)	54(1)
C(115)	2535(3)	5496(2)	3527(1)	42(1)
C(116)	1564(3)	1051(2)	3484(1)	38(1)
C(117)	1953(4)	1981(2)	3146(1)	43(1)
C(118)	1078(3)	3558(3)	2671(1)	66(1)
O(116)	3128(2)	-573(2)	3669(1)	67(1)
O(117)	2051(2)	-499(2)	3005(1)	64(1)
N(116)	2324(3)	-106(2)	3380(1)	50(1)
O(21)	2708(2)	8230(1)	868(1)	38(1)
O(27)	2261(2)	5157(2)	1105(1)	68(1)
O(28)	4387(2)	5797(2)	992(1)	54(1)
C(21)	3643(3)	8407(2)	1254(1)	35(1)
C(22)	3103(3)	7686(2)	1634(1)	37(1)
C(23)	3558(3)	8425(2)	2049(1)	45(1)
C(24)	3673(3)	9701(2)	1876(1)	36(1)
C(25)	3764(3)	10792(2)	2108(1)	46(1)
C(26)	3899(3)	11870(2)	1877(1)	48(1)
C(27)	3917(3)	11850(2)	1426(1)	46(1)
C(28)	3822(3)	10766(2)	1196(1)	39(1)
C(29)	3703(3)	9695(2)	1426(1)	32(1)
C(210)	3187(3)	8179(2)	455(1)	34(1)
C(211)	4542(3)	8445(2)	383(1)	42(1)
C(212)	4876(3)	8324(2)	-46(1)	50(1)
C(213)	3926(3)	7977(2)	-388(1)	45(1)
C(214)	2566(3)	7744(2)	-307(1)	40(1)
C(215)	2223(3)	7841(2)	119(1)	37(1)
C(216)	3623(3)	6380(2)	1654(1)	42(1)
C(217)	3295(3)	5701(2)	1217(1)	47(1)
C(218)	4303(3)	5192(3)	568(1)	66(1)
O(216)	3636(2)	4828(2)	2169(1)	70(1)
O(217)	1778(2)	5881(2)	2058(1)	79(1)
N(216)	2959(3)	5645(2)	1990(1)	52(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for $C_{18}H_{17}NO_5$.

	x	y	z	U_{eq}
H(11)	393	2807	3883	40
H(12)	2977	1506	4013	43
H(13A)	467	332	4211	49
H(13B)	2039	-7	4403	49
H(15)	1251	548	5237	53
H(16)	1207	2203	5715	60

H(17)	1298	4184	5453	53
H(18)	1318	4542	4696	44
H(111)	-309	4562	3893	47
H(112)	-1104	6406	3590	58
H(113)	376	7714	3270	64
H(114)	2663	7114	3223	65
H(115)	3468	5263	3508	51
H(116)	543	899	3434	46
H(11A)	1841	4084	2794	99
H(11B)	234	4044	2606	99
H(11C)	1316	3179	2400	99
H(21)	4591	8121	1206	42
H(22)	2067	7675	1585	44
H(23A)	2860	8378	2260	54
H(23B)	4461	8136	2195	54
H(25)	3735	10802	2417	55
H(26)	3979	12622	2030	58
H(27)	3995	12591	1272	56
H(28)	3837	10756	886	46
H(211)	5212	8698	616	50
H(212)	5798	8488	-104	60
H(213)	4188	7896	-676	54
H(214)	1884	7523	-541	48
H(215)	1303	7668	177	45
H(216)	4649	6383	1736	50
H(21A)	4005	4349	599	99
H(21B)	5216	5203	461	99
H(21C)	3632	5616	357	99

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for $C_{18}H_{17}NO_5$.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}$

	U11	U22	U33	U23	U13	U12
O(11)	28(1)	32(1)	46(1)	5(1)	10(1)	-1(1)
O(17)	44(1)	49(1)	55(1)	1(1)	21(1)	-4(1)
O(18)	46(2)	59(1)	45(1)	6(1)	3(1)	-3(1)
C(11)	28(2)	32(1)	42(2)	2(1)	10(1)	-4(1)
C(12)	32(2)	36(2)	41(2)	3(1)	10(1)	0(1)
C(13)	37(2)	39(2)	49(2)	9(1)	11(2)	1(1)
C(14)	23(2)	48(2)	41(2)	4(1)	6(1)	1(1)
C(15)	33(2)	55(2)	46(2)	15(2)	10(2)	0(2)

C(16)	36(2)	78(2)	38(2)	6(2)	7(2)	2(2)
C(17)	28(2)	63(2)	40(2)	-7(1)	4(2)	2(2)
C(18)	20(2)	47(2)	43(2)	1(1)	3(1)	5(1)
C(19)	20(2)	43(2)	37(2)	3(1)	6(1)	1(1)
C(110)	33(2)	32(2)	38(2)	0(1)	5(1)	0(1)
C(111)	33(2)	41(2)	44(2)	5(1)	9(2)	-2(1)
C(112)	35(2)	48(2)	62(2)	7(2)	7(2)	7(2)
C(113)	45(2)	48(2)	67(2)	13(2)	2(2)	3(2)
C(114)	46(2)	48(2)	70(2)	14(2)	16(2)	-9(2)
C(115)	27(2)	44(2)	57(2)	6(1)	9(2)	-5(1)
C(116)	35(2)	37(2)	46(2)	-2(1)	13(2)	-3(1)
C(117)	54(3)	38(2)	35(2)	-5(1)	6(2)	-3(2)
C(118)	80(3)	67(2)	49(2)	17(2)	-1(2)	1(2)
O(116)	67(2)	53(1)	80(2)	-14(1)	-3(2)	13(1)
O(117)	96(2)	50(1)	49(1)	-11(1)	23(1)	-8(1)
N(116)	60(2)	39(1)	55(2)	-6(1)	21(2)	-14(1)
O(21)	28(1)	56(1)	32(1)	-6(1)	8(1)	-1(1)
O(27)	58(2)	76(2)	69(2)	-16(1)	10(1)	-27(1)
O(28)	49(2)	58(1)	57(1)	-16(1)	14(1)	5(1)
C(21)	26(2)	46(2)	35(2)	-2(1)	6(2)	5(1)
C(22)	32(2)	41(2)	40(2)	0(1)	12(1)	3(1)
C(23)	48(2)	53(2)	35(2)	0(1)	10(2)	6(2)
C(24)	30(2)	42(2)	37(2)	-6(1)	4(1)	5(1)
C(25)	41(2)	53(2)	44(2)	-8(1)	3(2)	8(2)
C(26)	41(2)	44(2)	59(2)	-14(2)	0(2)	4(1)
C(27)	40(2)	36(2)	65(2)	3(1)	10(2)	3(1)
C(28)	28(2)	47(2)	42(2)	2(1)	8(1)	4(1)
C(29)	22(2)	40(2)	36(2)	-5(1)	3(1)	2(1)
C(210)	34(2)	37(2)	34(2)	-2(1)	13(2)	1(1)
C(211)	34(2)	55(2)	39(2)	-5(1)	7(2)	-8(1)
C(212)	36(2)	72(2)	45(2)	1(2)	14(2)	-7(2)
C(213)	39(2)	64(2)	34(2)	-2(1)	13(2)	-1(2)
C(214)	35(2)	48(2)	37(2)	-3(1)	1(2)	-3(1)
C(215)	26(2)	47(2)	39(2)	-4(1)	9(2)	-2(1)
C(216)	36(2)	42(2)	49(2)	2(1)	14(2)	-2(1)
C(217)	46(3)	41(2)	54(2)	-2(2)	12(2)	1(2)
C(218)	67(3)	71(2)	61(2)	-24(2)	12(2)	1(2)
O(216)	73(2)	49(1)	87(2)	19(1)	11(1)	6(1)
O(217)	51(2)	96(2)	97(2)	39(1)	34(2)	11(1)
N(216)	58(2)	39(1)	61(2)	8(1)	13(2)	2(1)

Table 5. Bond lengths [Å] and angles [°] for $C_{18}\ H_{17}\ NO_5$

O(11)-C(110)	1.375(3)
O(11)-C(11)	1.434(2)
O(17)-C(117)	1.195(3)
O(18)-C(117)	1.323(3)
O(18)-C(118)	1.465(3)
C(11)-C(19)	1.512(3)
C(11)-C(12)	1.535(3)
C(12)-C(116)	1.512(3)
C(12)-C(13)	1.549(3)
C(13)-C(14)	1.518(3)
C(14)-C(15)	1.385(3)
C(14)-C(19)	1.387(3)
C(15)-C(16)	1.387(3)
C(16)-C(17)	1.386(3)
C(17)-C(18)	1.393(3)
C(18)-C(19)	1.376(3)
C(110)-C(111)	1.388(3)
C(110)-C(115)	1.394(3)
C(111)-C(112)	1.381(3)
C(112)-C(113)	1.380(3)
C(113)-C(114)	1.384(4)
C(114)-C(115)	1.373(3)
C(116)-N(116)	1.524(3)
C(116)-C(117)	1.535(3)
O(116)-N(116)	1.221(3)
O(117)-N(116)	1.228(3)
O(21)-C(210)	1.397(2)
O(21)-C(21)	1.418(3)
O(27)-C(217)	1.185(3)
O(28)-C(217)	1.334(3)
O(28)-C(218)	1.453(3)
C(21)-C(29)	1.512(3)
C(21)-C(22)	1.547(3)
C(22)-C(216)	1.523(3)
C(22)-C(23)	1.531(3)
C(23)-C(24)	1.509(3)
C(24)-C(29)	1.380(3)
C(24)-C(25)	1.391(3)
C(25)-C(26)	1.395(3)
C(26)-C(27)	1.381(4)
C(27)-C(28)	1.383(3)
C(28)-C(29)	1.385(3)
C(210)-C(215)	1.361(4)
C(210)-C(211)	1.390(3)
C(211)-C(212)	1.395(3)

C(15)-C(14)-C(13)	129.1(2)
C(19)-C(14)-C(13)	110.8(2)
C(14)-C(15)-C(16)	118.7(2)
C(17)-C(16)-C(15)	121.0(2)
C(16)-C(17)-C(18)	120.2(2)
C(19)-C(18)-C(17)	118.5(2)
C(18)-C(19)-C(14)	121.5(2)
C(18)-C(19)-C(11)	129.3(2)
C(14)-C(19)-C(11)	109.2(2)
O(11)-C(110)-C(111)	125.2(2)
O(11)-C(110)-C(115)	115.3(2)
C(111)-C(110)-C(115)	119.5(2)
C(112)-C(111)-C(110)	119.3(2)
C(113)-C(112)-C(111)	121.5(3)
C(112)-C(113)-C(114)	118.8(3)
C(115)-C(114)-C(113)	120.7(2)
C(114)-C(115)-C(110)	120.2(3)
C(12)-C(116)-N(116)	112.4(2)
C(12)-C(116)-C(117)	112.7(2)
N(116)-C(116)-C(117)	104.73(19)
O(17)-C(117)-O(18)	126.8(2)
O(17)-C(117)-C(116)	123.4(3)
O(18)-C(117)-C(116)	109.7(2)
O(116)-N(116)-O(117)	125.3(2)
O(116)-N(116)-C(116)	119.1(2)
O(117)-N(116)-C(116)	115.6(3)
C(210)-O(21)-C(21)	120.65(19)
C(217)-O(28)-C(218)	117.3(2)
O(21)-C(21)-C(29)	114.5(2)
O(21)-C(21)-C(22)	108.3(2)
C(29)-C(21)-C(22)	102.85(18)
C(216)-C(22)-C(23)	113.9(2)
C(216)-C(22)-C(21)	112.03(18)
C(23)-C(22)-C(21)	105.1(2)
C(24)-C(23)-C(22)	103.3(2)
C(29)-C(24)-C(25)	120.2(2)
C(29)-C(24)-C(23)	110.8(2)
C(25)-C(24)-C(23)	128.9(2)
C(24)-C(25)-C(26)	118.8(2)
C(27)-C(26)-C(25)	120.2(2)
C(26)-C(27)-C(28)	120.9(2)
C(27)-C(28)-C(29)	118.7(2)
C(24)-C(29)-C(28)	121.1(2)
C(24)-C(29)-C(21)	110.3(2)
C(28)-C(29)-C(21)	128.6(2)

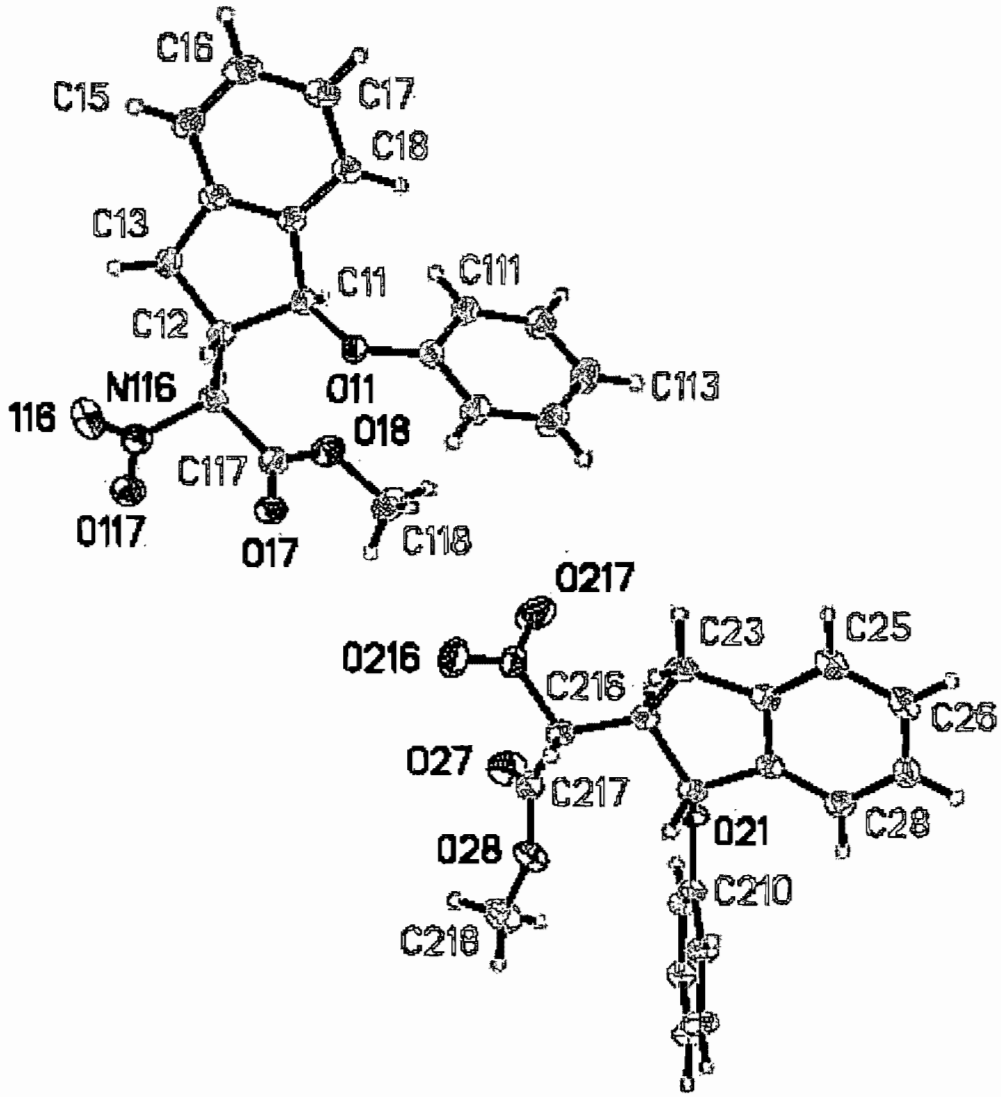
C(212)-C(213)	1.365(4)	C(215)-C(210)-C(211)	121.3(2)
C(213)-C(214)	1.396(3)	C(215)-C(210)-O(21)	115.0(2)
C(214)-C(215)	1.385(3)	C(211)-C(210)-O(21)	123.7(3)
C(216)-N(216)	1.511(3)	C(210)-C(211)-C(212)	117.1(3)
C(216)-C(217)	1.530(4)	C(213)-C(212)-C(211)	122.5(3)
O(216)-N(216)	1.207(3)	C(212)-C(213)-C(214)	119.1(2)
O(217)-N(216)	1.216(3)	C(215)-C(214)-C(213)	119.1(3)
C(110)-O(11)-C(11)	118.79(19)	C(210)-C(215)-C(214)	120.8(2)
C(117)-O(18)-C(118)	115.4(2)	N(216)-C(216)-C(22)	111.53(19)
O(11)-C(11)-C(19)	113.9(2)	N(216)-C(216)-C(217)	105.7(2)
O(11)-C(11)-C(12)	109.27(17)	C(22)-C(216)-C(217)	113.0(2)
C(19)-C(11)-C(12)	102.86(19)	O(27)-C(217)-O(28)	126.1(3)
C(116)-C(12)-C(11)	112.0(2)	O(27)-C(217)-C(216)	125.7(2)
C(116)-C(12)-C(13)	115.8(2)	O(28)-C(217)-C(216)	108.2(3)
C(11)-C(12)-C(13)	103.69(17)	O(216)-N(216)-O(217)	123.9(2)
C(14)-C(13)-C(12)	101.86(19)	O(216)-N(216)-C(216)	117.0(2)
C(15)-C(14)-C(19)	120.1(2)	O(217)-N(216)-C(216)	119.1(2)

Table 6. Torsion angles [°] for $C_{18}H_{17}NO_5$.

C(110)-O(11)-C(11)-C(19)	-95.0(3)	C(210)-O(21)-C(21)-C(29)	100.1(2)
C(110)-O(11)-C(11)-C(12)	150.6(2)	C(210)-O(21)-C(21)-C(22)	-145.79(19)
O(11)-C(11)-C(12)-C(116)	-80.2(3)	O(21)-C(21)-C(22)-C(216)	87.6(3)
C(19)-C(11)-C(12)-C(116)	158.4(2)	C(29)-C(21)-C(22)-C(216)	-150.8(2)
O(11)-C(11)-C(12)-C(13)	154.3(2)	O(21)-C(21)-C(22)-C(23)	-148.2(2)
C(19)-C(11)-C(12)-C(13)	32.9(3)	C(29)-C(21)-C(22)-C(23)	-26.6(3)
C(116)-C(12)-C(13)-C(14)	-154.3(2)	C(216)-C(22)-C(23)-C(24)	149.0(2)
C(11)-C(12)-C(13)-C(14)	-31.3(3)	C(21)-C(22)-C(23)-C(24)	26.0(3)
C(12)-C(13)-C(14)-C(15)	-161.0(3)	C(22)-C(23)-C(24)-C(29)	-15.9(3)
C(12)-C(13)-C(14)-C(19)	18.5(3)	C(22)-C(23)-C(24)-C(25)	165.1(3)
C(19)-C(14)-C(15)-C(16)	-0.9(4)	C(29)-C(24)-C(25)-C(26)	-0.6(4)
C(13)-C(14)-C(15)-C(16)	178.6(3)	C(23)-C(24)-C(25)-C(26)	178.3(3)
C(14)-C(15)-C(16)-C(17)	-0.4(4)	C(24)-C(25)-C(26)-C(27)	1.1(4)
C(15)-C(16)-C(17)-C(18)	1.7(4)	C(25)-C(26)-C(27)-C(28)	-0.9(5)
C(16)-C(17)-C(18)-C(19)	-1.8(4)	C(26)-C(27)-C(28)-C(29)	0.2(4)
C(17)-C(18)-C(19)-C(14)	0.6(4)	C(25)-C(24)-C(29)-C(28)	-0.1(4)
C(17)-C(18)-C(19)-C(11)	179.2(3)	C(23)-C(24)-C(29)-C(28)	-179.2(2)
C(15)-C(14)-C(19)-C(18)	0.8(4)	C(25)-C(24)-C(29)-C(21)	177.9(2)
C(13)-C(14)-C(19)-C(18)	-178.8(2)	C(23)-C(24)-C(29)-C(21)	-1.2(3)
C(15)-C(14)-C(19)-C(11)	-178.1(2)	C(27)-C(28)-C(29)-C(24)	0.3(4)
C(13)-C(14)-C(19)-C(11)	2.3(3)	C(27)-C(28)-C(29)-C(21)	-177.3(3)
O(11)-C(11)-C(19)-C(18)	40.7(4)	O(21)-C(21)-C(29)-C(24)	134.8(2)
C(12)-C(11)-C(19)-C(18)	158.8(3)	C(22)-C(21)-C(29)-C(24)	17.6(3)

O(11)-C(11)-C(19)-C(14) -140.5(2)
C(12)-C(11)-C(19)-C(14) -22.4(3)
C(11)-O(11)-C(110)-C(111) 6.3(4)
C(11)-O(11)-C(110)-C(115-172.6(2)
O(11)-C(110)-C(111)-C(11-177.8(2)
C(115)-C(110)-C(111)-C(112)1.1(4)
C(110)-C(111)-C(112)-C(113-1.7(4)
C(111)-C(112)-C(113)-C(114)1.5(4)
C(112)-C(113)-C(114)-C(115-0.8(5)
C(113)-C(114)-C(115)-C(110)0.2(4)
O(11)-C(110)-C(115)-C(114178.6(3)
C(111)-C(110)-C(115)-C(114-0.4(4)
C(11)-C(12)-C(116)-N(116)170.94(18)
C(13)-C(12)-C(116)-N(116)-70.5(3)
C(11)-C(12)-C(116)-C(117) 52.8(3)
C(13)-C(12)-C(116)-C(117)171.4(2)
C(118)-O(18)-C(117)-O(17) 1.2(4)
C(118)-O(18)-C(117)-C(116178.6(2)
C(12)-C(116)-C(117)-O(17) 77.7(3)
N(116)-C(116)-C(117)-O(17-44.8(3)
C(12)-C(116)-C(117)-O(18)-99.8(3)
N(116)-C(116)-C(117)-O(18137.7(2)
C(12)-C(116)-N(116)-O(116) 0.1(3)
C(117)-C(116)-N(116)-O(11122.8(3)
C(12)-C(116)-N(116)-O(117179.3(2)
C(117)-C(116)-N(116)-O(11-57.9(3)
O(21)-C(21)-C(29)-C(28) -47.4(3)
C(22)-C(21)-C(29)-C(28) -164.6(3)
C(21)-O(21)-C(210)-C(215)171.4(2)
C(21)-O(21)-C(210)-C(211) -8.4(3)
C(215)-C(210)-C(211)-C(212-1.3(4)
O(21)-C(210)-C(211)-C(212178.4(2)
C(210)-C(211)-C(212)-C(213)0.9(4)
C(211)-C(212)-C(213)-C(214)0.6(4)
C(212)-C(213)-C(214)-C(215-1.6(4)
C(211)-C(210)-C(215)-C(214)0.3(4)
O(21)-C(210)-C(215)-C(21-179.5(2)
C(213)-C(214)-C(215)-C(210)1.2(4)
C(23)-C(22)-C(216)-N(216) 67.5(3)
C(21)-C(22)-C(216)-N(216-173.4(2)
C(23)-C(22)-C(216)-C(217-173.6(2)
C(21)-C(22)-C(216)-C(217)-54.5(3)
C(218)-O(28)-C(217)-O(27) 0.6(4)
C(218)-O(28)-C(217)-C(216178.9(2)
N(216)-C(216)-C(217)-O(27)34.5(4)
C(22)-C(216)-C(217)-O(27)-87.8(3)
N(216)-C(216)-C(217)-O(2-143.7(2)
C(22)-C(216)-C(217)-O(28) 94.0(3)
C(22)-C(216)-N(216)-O(21-149.7(3)
C(217)-C(216)-N(216)-O(21687.1(3)
C(22)-C(216)-N(216)-O(217)32.2(4)
C(217)-C(216)-N(216)-O(21-91.0(3)

ORTEP view of the $C_{18}H_{17}NO_5$ compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.



Appendix I References

SAINT (2006) Release 7.34A; Integration Software for Single Crystal Data. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (1996). SADABS, Bruker Area Detector Absorption Corrections. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

SHELXTL (2001) version 6.12; Bruker Analytical X-ray Systems Inc., Madison, WI 53719-1173.

APEX2 (2006) version 2.1-0; Bruker Molecular Analysis Research Tool. Bruker AXS Inc., Madison, WI 53719-1173.

Spek, A.L. (2008). PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Maris, T. (2004). UdMX, University of Montréal, Montréal, QC, Canada.

XPREP (2005) Version 2005/2; X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.