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Direct Functionalization of Heterocyclic and Non-Heterocyclic Arenes

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Résumé

L'application des métaux de transition à la fonctionnalisation directe a ouvert la voie à une nouvelle classe de réactions pour la formation de liens carbone-carbone. De par l'omniprésence des liaisons C–H, l'introduction de nouvelles fonctionnalités chimiques par voie directe et pré-activation minimale s'impose comme une stratégie de synthèse très attrayante. Ainsi, il est envisageable de préparer de manière rapide et efficace des supports complexes menant à des molécules complexes, qui pourraient être utiles dans divers domaines de la chimie.

L'objectif principal de la présente thèse vise la fonctionnalisation directe des arènes hétérocycliques et non hétérocycliques et, plus précisément, les techniques d'arylation. Dans un premier temps, nous allons aborder le thème de l'arylation directe tout en mettant l'accent sur les pyridines (Chapitre 1). Ces molécules sont à la base d'une multitude de composés biologiquement actifs et jouent un rôle important dans le domaine des sciences des matériaux, de l'agrochimie et de la synthèse des produits naturels. Dans un deuxième temps, nous discuterons de nos travaux sur l'arylation directe catalysé par un complex de palladium sur des ylures de *N*-iminopyridinium en soulignant la dérivatisation du sel de pyridinium après une phénylation sp^2 (Chapitre 2). L'étude de ce procédé nous a permis de mettre en lumière plusieurs découvertes importantes, que nous expliquerons en détails une à une : l'arylation benzylique directe lorsque des ylures *N*-iminopyridinium substituées avec un groupement alkyl à la position 2 sont utilisés comme partenaires dans la réaction; les allylations Tsuji-Trost catalysée par un complex de palladium; et l'alkylation directe et sans métal via une catalyse par transfert de phase.

Plusieurs défis restent à relever pour le développement de procédés directs utilisant des métaux de transition peu coûteux, d'autant plus que la synthèse par transformation directe des pyridines 2-alcényles, lesquelles sont pertinentes sur le plan pharmacologique, n'a pas encore été rapportée à ce jour. Avec cette problématique en tête, nous avons réussi à mettre au point une alcénylation directe catalysé par un complex de cuivre sur des ylures de

N-iminopyridinium. Nous discuterons également d'une nouvelle méthode pour la préparation des iodures de vinyle utilisés dans les couplages. Ces réactions sont non seulement remarquablement chimiosélectives, mais sont aussi applicables à plusieurs substrats (Chapitre 3). En optimisant ce procédé direct, nous avons découvert une façon unique de synthétiser les pyrazolo[1,5-*a*]pyridines 2-substituées (Chapitre 4). Le mécanisme global met en jeu une séquence tandem de fonctionnalisation-cyclisation directe et un procédé direct en cascade, qui n'avais jamais été rapporté. Cela simplifie ansi la synthèse autrement compliquée de ces substrats en y apportant une solution à un problème de longue date.

Dans les deux derniers chapitres, nous examinerons en détail les techniques d'arylation directe qui n'impliquent pas les partenaires de couplage hétérocycliques. Entre autres, au Chapitre 5, nous soulignerons notre découverte d'un *umpolung* dirigé et catalysé par un complexe de palladium du benzène et de quelques autres dérivés arènes. Il s'agit là du premier cas de fonctionnalisation directe dans laquelle le groupe directeur se trouve sur le partenaire halogène et il s'ajoute à la courte liste d'exemples connus dans la littérature rapportant une arylation directe du benzène. Finalement, au Chapitre 6, nous passerons en revue une nouvelle arylation directe catalysée au fer, qui se veut un procédé peu coûteux, durable et présentant une économie d'atomes. Nous discutons des substrats possibles ainsi des études mécanistiques réalisés.

Mots-clés : Ylures de *N*-iminopyridinium, arylation directe, vinylation, catalyse, palladium, cuivre, fer, groupement directeur.

Abstract

The application of transition metals towards direct functionalization processes has exposed an opportunistic new class of carbon-carbon bond forming reactions. Given the undeniable ubiquity of C–H bonds, the possibility of introducing functionality through direct means with minimal preactivation is an irresistible strategy in synthesis. As such one can envision rapidly and efficiently building up complex scaffolds towards complex molecules of interest in a plethora of chemical fields.

The focus of this thesis is on the direct functionalization of heterocyclic and non-heterocyclic arenes, focusing on arylation technologies. First, the topic of direct arylation will be introduced, with special emphasis being on pyridines (Chapter 1). These molecules comprise the backbone of a myriad of biologically active compounds, and are also relevant in material sciences, agrochemicals, and natural products synthesis. This will be followed by a discussion of work on the palladium-catalyzed direct arylation of *N*-iminopyridinium ylides with accent on the derivatization of the pyridinium following the sp^2 phenylation (Chapter 2). The exploration of this process led to the discovery of direct benzylic arylation when 2-alkyl *N*-iminopyridinium ylides are employed as reacting partners, in addition to palladium-catalyzed Tsuji-Trost allylations, and metal-free direct alkylation *via* phase transfer catalysis. All of these findings will be discussed in detail.

There remains a significant challenge in developing direct processes utilizing inexpensive transition metals. Furthermore, the synthesis of pharmacologically relevant 2-alkenyl pyridines through direct transformations had not yet been reported. We focused on these challenges and developed a copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides. A novel method to prepare the vinyl iodide coupling partners will also be discussed. The scopes of these reactions are quite large and remarkably chemoselective (Chapter 3). Through the optimization of this direct process we uncovered an unique means of synthesizing 2-substituted pyrazolo[1,5-*a*]pyridines (Chapter 4). The global process involved a tandem direct functionalization/cyclization sequence, and may be

the first account of a direct process used in a cascade. This work also solves an important problem, as the synthesis of these substrates through alternate means is not straightforward.

The last two chapters will detail direct arylation technologies that do not involve heterocyclic coupling partners. Chapter 5 will highlight our uncovering of a palladium-catalyzed, directed, *umpolung* arylation of benzene and other arene derivatives. This was the first account of a direct functionalization whereby the directing group is situated on the *pseudo* electrophile. Also, it adds to the few examples of direct benzene arylation exisiting in the literature. Finally, a discussion of an atom economical, inexpensive, sustainable iron-catalyzed direct arylation process will be presented with special emphasis on substrate scope and mechanistic investigations (Chapter 6).

Keywords : *N*-Iminopyridinium ylides, direct arylation, alkenylation, catalysis, palladium, copper, iron, directing group.

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List of Schemes

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List of Abbreviations

1°	primary
2°	secondary
3°	tertiary
Å	Angstrom
Ac	acetyl
acac	acetoacetate
AIBN	2,2′-azobis(2-methylpropionitrile)
aq.	aqueous
Ar	aryl
Atm	atmosphere
Boc	*t*-butyloxycarbonyl
Bn	benzyl
BQ	benzoquinone
Bu	butyl
Bz	benzoyl
c	*cyclo*
cat.	Catalyst
cm	centimeter
CMD	concerted metallation deprotonation
Cp	cyclopentadienyl
coe	cyclooctene
concn.	concentration
convn.	conversion
Cy	cyclohexyl
cyclen	1,4,7,10-tetraazacyclododecane
CyJohnPhos	(2-biphenyl)dicyclohexylphosphine
d	day

D	debye
DavePhos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DIBAL	diisobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMA	*N,N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMEDA	dimethylethyldiamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E	*entgegen*
E^+	electrophile
EBI	ethylenebis(indenyl)
EBTHI	ethylenebis(tetrahydroindenyl)
EDG	electron-donating group
ee	enantiomeric excess
elimn	elimination
Eq.	equation
equiv	equivalent
Et	ethyle
ES	electrospray

EWG	electron-withdrawing group
FES	Faculté d'étude supérieure
FT-IR	Fourier-transform infrared spectroscopy
g	gram
GC	gas chromatography
gem	geminal
h	hour
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
hυ	light
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
*i*Bu	*iso*-butyl
iMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant
kcal	kilocalorie
KIE	kinetic isotope effect
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LC	liquid chromatography
LRMS	low resolution mass spectroscopy
LUMO	Lowest Unoccupied Molecular Orbital
LT	leukotriene

M ..... metal

m ..... *meta*

Me ..... methyl

MHz ..... megahertz

min ..... minutes

mL ..... milliliter

mol ..... mole

mmol ..... millimole

MOP ..... 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl

mp ..... melting point

MS ..... molecular sieves

Napquin ..... naphthylquinone

NBS ..... *N*-bromosuccinimide

NHC ..... *N*-heterocyclic carbene

NMP ..... *N*-methylpyrrolidine

NMR ..... nuclear magnetic resonance

Nuc ..... nucleophile

o ..... *ortho*

OAc ..... acetate

ODNP 3,5-dinitrophenol

*o*Tol ..... *ortho* tolyl

p ..... *para*

PEPPSI ..... [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride

PhenDavePhos ..... 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

Ph ..... phenyl

PHOX ..... phosphinooxazoline
Piv ..... pivaloate
pKa ..... acid dissociation constant
ppb ..... parts per billion
ppm ..... parts per million
Prof. ..... Professor
psi ..... pounds per square inch
PTC ..... phase transfer catalysis
pyr. ..... Pyridine
quant. ..... quantitative
R^2 ..... coefficient de corrélation
R ..... *rectus*
R ..... substituent
R_f ..... retention factor
S ..... *sinister*
S_EAr ..... electrophilic aromatic substitution
sec ..... second
SFC ..... supercritical fluid chromatography
SM ..... starting material
S-NMDPP ..... (*S*)-(+)-meomenthyldiphenylphosphine
*t*Bu ..... *tert*-butyl
TC thiophene-2-carboxylate
Temp. ..... temperature
Tf ..... triflyl
TFA ..... trifluoroacetic acid
THF ..... tetrahydrofuran
TIPS ..... triisopropylsilyl
TLC ..... thin layer chromatography
TMS ..... trimethylsilyl

Tol	toluene
X	halogen
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	*zusammen*

To Melissa, Évangéline and Owen

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A pessimist sees the difficulty in every opportunity;
an optimist sees the opportunity in every difficulty.

-Winston Churchill

Chapter 1

Transition Metal Mediated Direct Functionalization of Pyridine Derivatives

1.1 Introduction

Six-membered nitrogen-containing heterocycles are privileged structures present in many aspects of the physical and biological sciences.[1] They are prevalent in nature, pharmacophores, as well as in supramolecular and organomaterials.[2] The importance of their biological activity is reflected in recent surveys of several pharmaceutical companies demonstrating that 88% of small molecules in the drug pipeline contain 6-membered aromatic heterocycles, and the majority of these are nitrogen based.[3,4,5] Given this reality, it is of no surprise that these motifs have garnered much interest from synthetic chemists and significant efforts have been put forth in the development of new and efficient reaction methodologies towards their structural elaboration (**Figure 1**).[1,2]

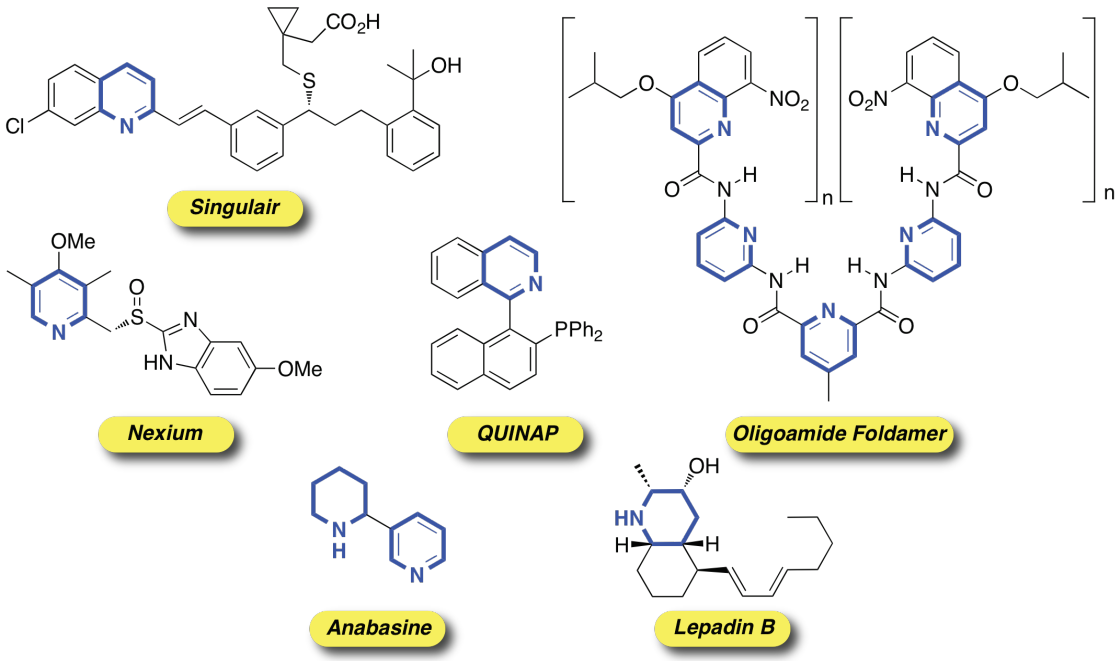


Figure 1. Examples of molecules bearing 6-membered azacycles.

The pyridine family is the simplest of the azines. The presence of the endocyclic nitrogen atom has several important implications for their properties and reactivity. The lone pair of this Lewis basic site is perpendicular to the π-system, and is essential for the binding motifs in many compounds. The electronegative nitrogen atom provides the heterocycle with a dipole of 2.22 D, giving access to unique macromolecular chemical reactivity.[1] The nitrogen lone pair brings additional anisotropy to the system, further increasing the electron deficiency at the 2- and 6- positions relative to the 3- and 5- positions.[1,2a] Given these actualities, pyridine is amenable to derivatization, giving potential access not only to pyridine products, but also to various dihydro- and tetrahydropyridines, as well as piperidines (**Figure 2**). Covering all facets of pyridine elaboration is not possible without writing an extensive review. As such, this chapter will focus on outlining past work of both 1) transition metal-mediated and catalyzed activation and 2) direct functionalization of activated pyridine derivatives, with later emphasis on direct arylation processes, as this aspect is most pertinent to this research.

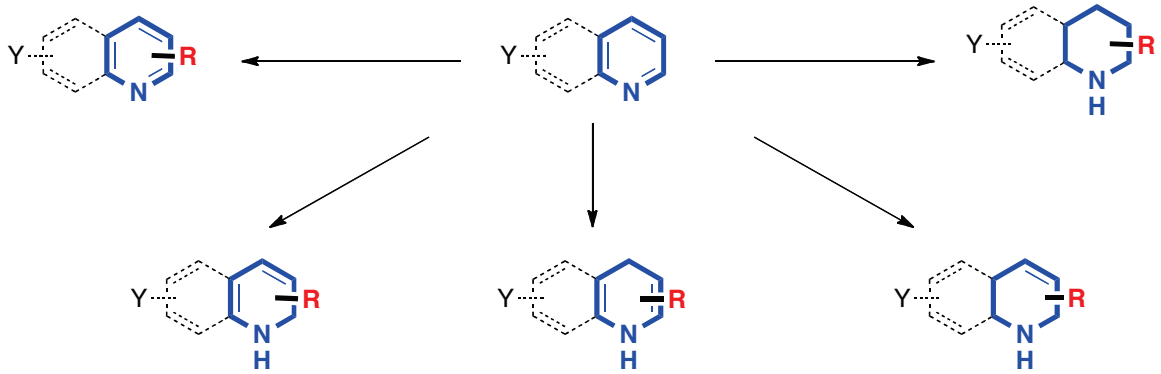


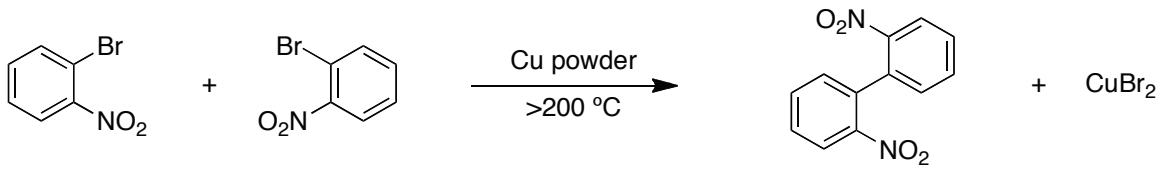
Figure 2. Various heterocycles accessed from pyridine.

1.2 A Brief Overview of Direct Arylation Reactions

The synthesis of biaryl compounds can be traced back to the Ullmann reaction first disclosed in 1901 (**Scheme 1**).[6,7] This reaction effectively couples two iodo or bromoarenes in the presence of copper salts at elevated reaction temperatures. Despite the

power of this transformation there are a few drawbacks to this reaction.[6,8] First the reaction is largely limited to the synthesis of symmetrical biaryl compounds. Heterocoupling is possible when one of the two halide partners is more electron-rich, though limited accounts of this type of coupling have been described.[8b] Secondly, in many cases an activated copper species is needed, potentially increasing the cost of the reaction. In conjunction, the majority of the cases reported use stoichiometric quantities of metal reagent, decreasing the overall economy of the process. Lastly, many cases require elevated reaction temperatures, leading to potential problems with functional group tolerance. Curiously, the exact mechanism of the reaction remains unknown.[8b,c]

Scheme 1. Original Ullmann reaction.

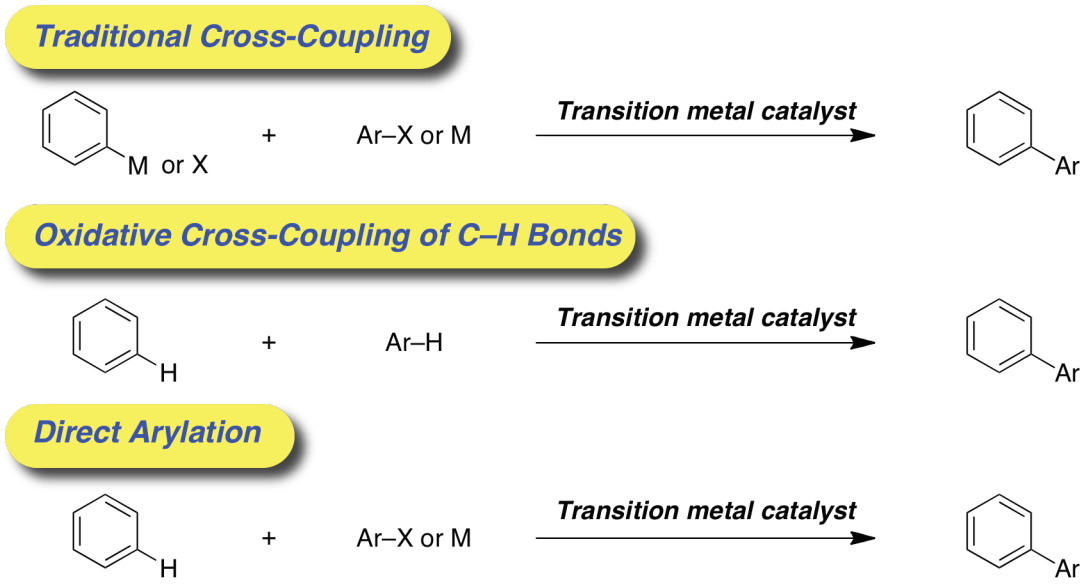


The development of several important cross-coupling reactions provided powerful tools for the preparation of biaryl scaffolds. These now traditional methods have dominated the way these compounds have been synthesized since the 1970s (**Scheme 2**).[6,8a,9] The first accounts of a nickel-catalyzed cross coupling between an aryl Grignard reagent and an aryl halide were reported independently in 1972 by Kumada and Corriu.[10] This was later developed into a palladium-catalyzed process and Stille found that the aryl magnesium species could be replaced with more stable aryl stannanes.[11] Suzuki and Miyaura found that non-toxic boronic acids and esters were viable pseudo-nucleophiles, followed later by a report of the application of organosilanes in the 1980s by Hiyama.[12] Given the plethora of available coupling partners available, it is no surprise that these procedures are the methods of choice in the synthesis of biaryl compounds. However, as with the Ullmann coupling, there are a few drawbacks to these reactions. The most important of these is the need for *both* a pseudo-nucleophile *and* a pseudo-electrophile to effect the coupling. This preactivation decreases the atom economy of the process as the

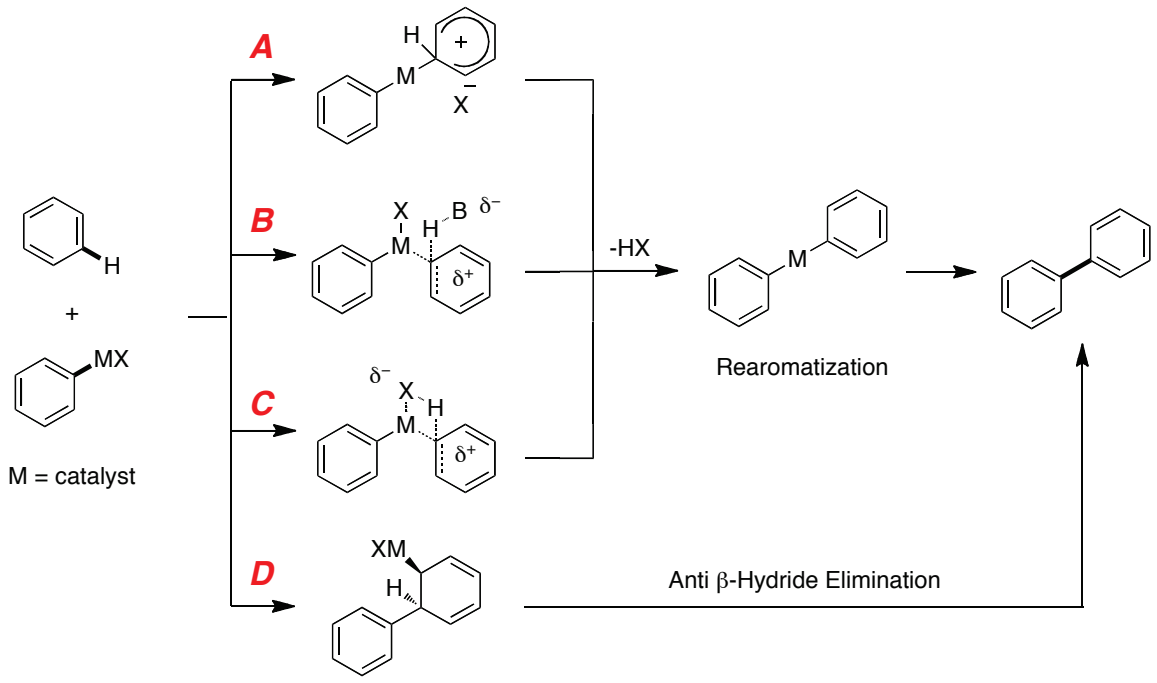
organometallic or organohalide species must first be synthesized, in addition to the generation of stoichiometric quantities of sometimes toxic salts during the transformation.

The activation of C–H bonds is a conspicuous challenge due to their high energy and relative inertness, and has received much attention in recent years.[13] The ideal coupling situation would involve the oxidative coupling of two C–H groups. Though stunning efforts have been made in this domain, there are issues with reactivity, and perhaps more importantly with selectivity.[13j,14] As a compromise, efforts over the past half-decade have been directed towards *direct* arylation reactions whereby one of the two preactivating groups is replaced by a simple C–H bond.[13] Clearly the challenge in such a reaction lies in breaking the strong sp^2 C–H bond in a chemoselective manner. This is illustrated by the fact that benzene homocoupling is disfavored by 3.4 kcal/mol.[13a] Despite this, numerous catalytic systems have been reported describing intra and intermolecular arylation reactions, as well as numerous other direct transformations.[13]

Scheme 2. Various modern methods for the synthesis of biaryl compounds.



Scheme 3. Various proposed mechanisms for direct arylation reactions.

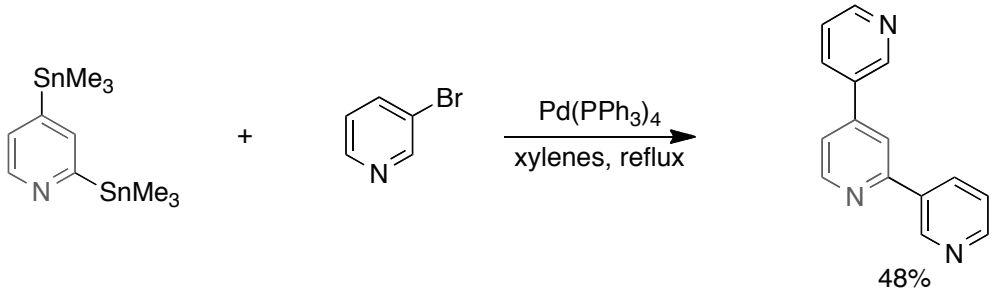


Though direct arylation reactions have been largely successful on arenes and electron-rich heteroarenes, electron-poor arenes such as pyridine have presented a significant challenge.[15] Several mechanisms for direct arylations have been proposed, each of which are difficult to apply to electron-poor species. The first is a S_EAr pathway (**Scheme 3**, path **A**). This route requires an electron-rich arene to attack the transition metal center, generating a Wheland intermediate. Rearomatization and reductive elimination then provides the biaryl product. This route would be difficult to obtain with pyridine adducts as the electron density is not sufficient to attack the metal center, and the resulting Wheland intermediate would be energetically not favored. Similarly, concerted S_E3 sequences have been reported (**Scheme 3**, path **B**), though such a mechanism would lead to a partial build up of positive charge in the arene, which again would be disfavored in electron-poor substrates. The same can be said for a σ–bond metathesis pathways (**Scheme 3**, path **C**). Heck-like mechanisms have been proposed, though are often not considered due to the unlikelihood of *anti* β-hydride elimination (**Scheme 3**, path **D**), and the high cost of isomerization to permit *syn* elimination. The last proposed addition

involved the oxidative addition into the aryl C–H bond. This is possible for certain but not all transition metals. Given these studies, it becomes clear the difficulties in performing the direct arylation, and other C–H activation, of pyridine.

Classical cross coupling at the 2-position of pyridine has also been problematic. Catalyst poisoning by the Lewis basic nitrogen must be considered, though can be overridden with the judicious choice of ligand.[16] 2-Halopyridines are viable pseudo-electrophiles, though their commercial availability is limited (as evidenced by their cost) and synthesis often non-selective.[2a] 2-Metallopyridines are largely limited to Stille cross coupling reactions, which present environmental challenges with regards to toxicity of tin reagents (**Scheme 4**).[15] Pyridines bearing a zinc or boronic acid at the 2-position are also viable pseudo-nucleophiles,[15] though their synthesis and stability are not trivial. Again this is reflected in their high cost. In light of these realities, the development of transition-metal catalyzed activation α to the nitrogen atom would provide not only an efficient route to synthesize more complex pyridine derivatives, but would also solve the two aforementioned outstanding problems in the elaboration of this azine.

Scheme 4. Example of Stille cross coupling on pyridine.[15e]



The following sections will outline progress made towards transition metal-mediated activation and functionalization of pyridyl C–H bonds with particular emphasis on processes involving *d*-block transition elements. The first section will outline some of the early work in the area, with the focus on early transition metals and their use to activate the pyridine ring followed by their insertion into the pyridyl C–H bond. Several

of these transformations, though requiring a stoichiometric amount of metal reagent, describe the first forays into C–H activation and functionalization. This section will be non-exhaustive, providing only a flavour of the work in the area. This will be followed by a description of the application of catalytic quantities of transition metal to the functionalization of pyridines leading into current direct arylation methodologies with late transition metals.

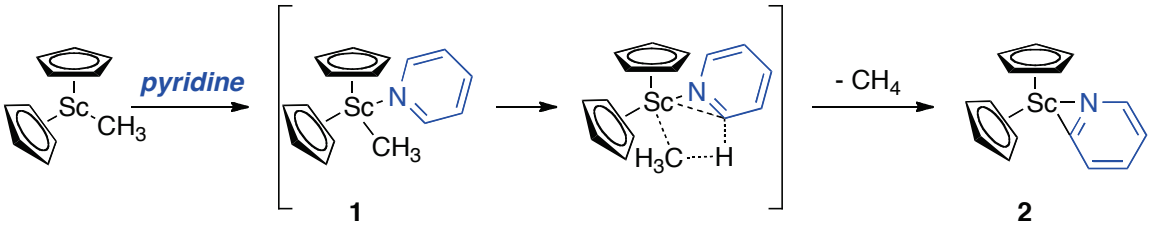
1.3 Transition Metal Activation of Pyridyl C–H Bonds

1.3.1. Initial Studies of Groups III, IV, and Other Metals to Form Pyridine-Metal Complexes

Observations in the early 1980s noted that sp^2 hybridized C–H bonds were deemed more reactive towards insertion than their sp^3 counterparts despite their increased bond strengths, due to the initial formation of a π-complex with the metal. However, accessing the C–H bonds of pyridine still proved problematic due to the electron-poor nature of the azine.[17] Consequently, by using a more electrophilic metal, it was reasoned that systems with increased reactivity could be employed to activate these elusive bonds.[17] This was exploited by Bercaw and co-workers as they applied derivatives of permethylscandocene prepared from $ScCl_3$ in C–H activation of various arenes, most notably the α-position of pyridine, through a metathecal pathway (**Scheme 3**, path **C**). While non-heterocyclic arenes formed η^1 complexes, pyridine provided an orthometallated C,N–η^2 compound as determined by X-ray crystallography (**Scheme 5**).[17] The C–H insertion first occurs with the scandium reagent coordinating with the Lewis basic nitrogen as a reaction between Cp^*_2ScMe and pyridine provided a $Cp^*_2ScMe(Pyr)$ complex **1** that was observable by ^1H NMR.[17] This quarternization of the nitrogen presumably activates the pyridine ring, further favoring the insertion into the C–H bond, liberating methane in the case of Cp^*_2ScMe. Complex **2** does not aggregate in solution due to the crowded coordination sphere of the scandium. As such, they were found to have poor affinity towards basic phosphine and aza reagents, due to the lack of access of the metal, thereby limiting their

application towards structural elaboration.[17] Various derivatives of Cp^*_2ScR were applied to confirm that the insertion does occur via a σ-bond metathesis pathway (**Scheme 5**). More recently DFT studies demonstrated that though the scandium does insert via σ-bond metathesis, this might not be the case for all Group III metals, as evidence points to ionic pathways being more favorable with later metals having larger ionic radii.[18]

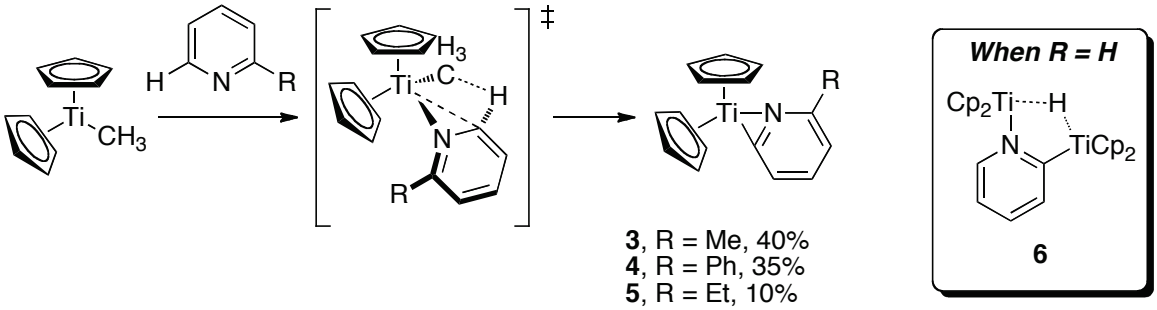
Scheme 5. Insertion of pyridine into Cp^*_2ScMe.



Titanium is the first element of the Group IV metals, and the first transition metal believed to be involved in a C–H insertion into the α-position pyridine. In 1978 Klei and Teuben described the insertion of Cp^*_2TiMe into 2-picoline to give C,N–η^2 titanocycles **3**, **4**, and **5** at the 6-position of the ring, isolated as purple crystals.[19] The Cp^*_2TiMe was prepared from Cp^*_2TiCl, which in turn arose from a reduction of $Cp^*_2TiCl_2$ by *i*PrMgCl. This was the first report of a 3-membered azametallocycle. The colour change during the reaction (due to the partly filled *d*-orbitals of the metal) suggested the complexation of the titanium with the pyridyl nitrogen, thereby generating a more reactive pyridinium species, and the insertion was observed *via* the evolution of methane.[20] Substitution at the 2-position was mandatory for the reaction to occur and a small substrate scope was explored (**Scheme 6**). The α-substitution is required to force the pyridine ring out of plane to force interaction with the π system and favour σ-bond metathesis (**Scheme 6**).[20] In 2005 it was found that unsubstituted pyridine does undergo C–H insertion with Cp^*_2TiCl, but instead forms the 'dimeric' compound **6** bearing two titanium atoms separated by a hydride bridge as inferred by X-ray crystallography.[21] This insertion was suggested to be

concerted in nature, avoiding the build-up of positive charge in the transition state. This complex though thermally stable, is extremely air sensitive.

Scheme 6. Insertion of pyridine into Cp^*_2TiMe.

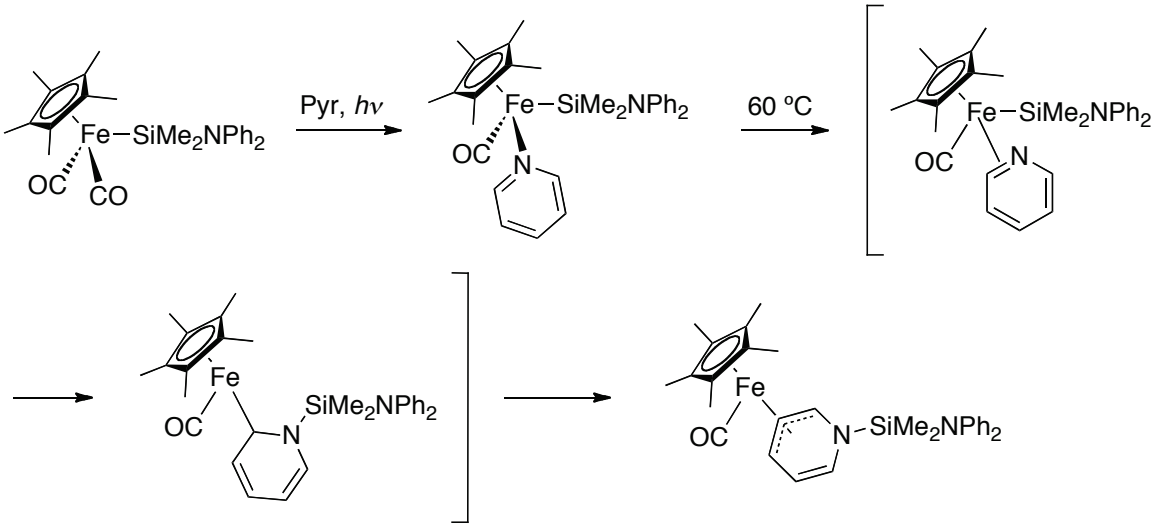


Other Group IV metals (Zr, Hf, Th) have also been demonstrated to insert α- to the nitrogen of pyridine. A common feature of these reagents is their increased electropositivity, permitting attack of electron poor arenes, such as pyridine, on the metal. Zirconium is perhaps most applied, in particular with the direct functionalization of pyridine, forming C,N–η^2 metallocycles (*vide infra*). Hafnium has been seldom reported.[22] Thorium, though in the same group exhibits unique properties in part to its large atomic radius, thus reactivity is often governed by sterics, and its access to 5f orbitals.[22] Unlike Ti, Zr, and Hf, it does not have a tendency to complex to sp^2 and *sp* hybridized systems. Despite this, where $(C_5Me_5)_2ZrMe_2$ and $(C_5Me_5)_2HfMe_2$ reagents show no ability to insert into the α C–H bond, $(C_5Me_5)_2ThMe_2$ readily inserts forming a C,N–η^2 metallocycle similar to that reported with Sc and Ti (**Scheme 5**, **Scheme 6**).[22] Additionally, the thorium reagent can also insert into the α-site of pyridine *N*-oxide, generating an η^1 organometallic species.[22] This metal has not been applied in the derivatization of pyridine.

Several late transition metals have been known to generate pyridinium-like complexes that permit functionalization of the heterocycle. For example, $Cp^*(CO)_2FeSiMe_2NPh_2$ will lead to silyl-metallation of pyridine (**Scheme 7**).[23,24] Irradiation complexes the pyridine to the iron reagent, simultaneously expelling carbon

monoxide. Heating to 60 ºC, initiated the hydrosilation of the activated Fe-Pyr complex through an η^1–σ–allyl intermediate, which following isomerization provided the observed η^3–(*C,C,C*) Fe-Pyr product.[23]

Scheme 7. Insertion of pyridine into $Cp^*(CO)_2FeSiMe_2NPh_2$.



Metals such as Ta, Cr, Mn, Re, Os, and U are known to activate pyridine and insert to give α-metalated C,N–η^2 complexes.[25,26,27] In most of these cases, the complexes were not used to further elaborate the azacycle. The following section will describe the use of stoichiometric quantities of Zr, Ti, Ru, and other reagents to activate and further functionalize the pyridine ring.

1.3.2. Application of Metal Complexes Towards Further Pyridine Activation and Functionalization

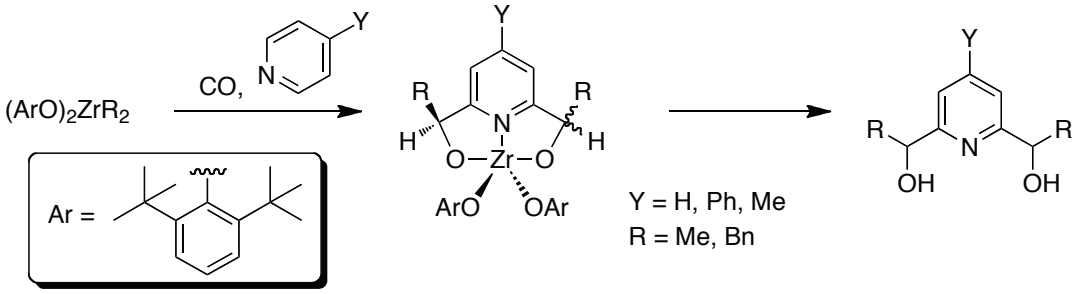
1.3.2.1 Zirconium-Mediated Functionalization

Zirconium was one of the earlier metals reported in the activation/functionalization of the pyridine ring (*vide supra*). This Group IV metal had long been known to be able to activate and insert into molecular hydrogen via a four-centered transition state following initial coordination of the H–H σ-bond.[29] It was reasoned that a similar metathecal

pathway should be possible for C–H bonds on molecules complexed to the metal centers.[28] The fact that such transformations would undergo a concerted σ-bond metathesis pathway would make it compatible with a myriad of insertion and β-hydride elimination chemistries, leading to the direct functionalization of molecules.[28] Furthermore, at the time this was the only way seen to perform such C–H activated transformations as conditions for similar reactions with late transition metal chemistry were not yet discovered. Such 18-electron complexes were made through the oxidative addition of the metal into the C–H bond, and the resulting compounds were resistant to insertion and β-hydride elimination chemistry.[28]

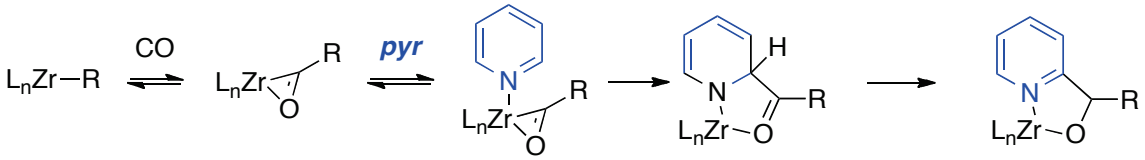
In the mid 1980s Rothwell and coworkers described the use of Zr(2,6-di-*tert*-butylphenoxide)$_2$Me$_2$ in the synthesis of α,α-disubsituted-2,6-pyridinedimethoxide compounds from pyridine and carbon monoxide (**Scheme 8**).[29] These products are an important class of ligands and have been applied as metalloenzyme models.[30] It was found that the methyl-group could be replaced with benzyl functionality without an appreciable drop in yields (50-75%).[30] The presence of groups at the 4-position appear to be required, and perhaps function as 'blocking groups' despite the fact that this position is outside the coordination sphere of the metal. Where bipyridine could be directly alkylated with a similar zirconium reagent,[31] carbon monoxide was determined to be essential. Though the role of 2,6-di-*tert*-butylphenoxide is unclear, it is also required and the steric hindrance of the ligand suggests a role as a non-transferable group. It is possible to liberate the bis-substituted pyridine product from the metal through hydrolysis and purification via elution on silica.

Scheme 8. Zr-Mediated synthesis of *bis*-hydroacylated pyridines.



The mechanism of the reaction was found to proceed through the migratory insertion of CO into the Zr-alkyl bond generating an η^2-complex. The pyridine then complexes to the zirconium and the COR proceeds to insert into the 2- and 6-positions of the heterocycles (**Scheme 9**). The N–Zr bond length is 0.18 Å shorter than expected, indicating a strong interaction and the likelihood of the pyridine ring being activated by the metal center.[29] The primary kinetic isotope effect was found to be 1, suggesting that the rate limiting step is the complexation of the pyridine ring and not the insertion into the C–H bond. The acyl group is thought to be carbene-like, and thus the electrophilicity on the carbon affects the reactivity (**Scheme 9**).[29,30] As only the disubstituted pyridine is observed, the formation of the C,N–η^2 complex observed with other Group III and IV metals is ruled out (**Scheme 6**), as steric congestion would inhibit reactions at the 6-position.[30] Addition of the 2,6-position exclusively and not the 4-position is a result of the acyl nucleophile addition to the pyridine within the coordination sphere of the metal.

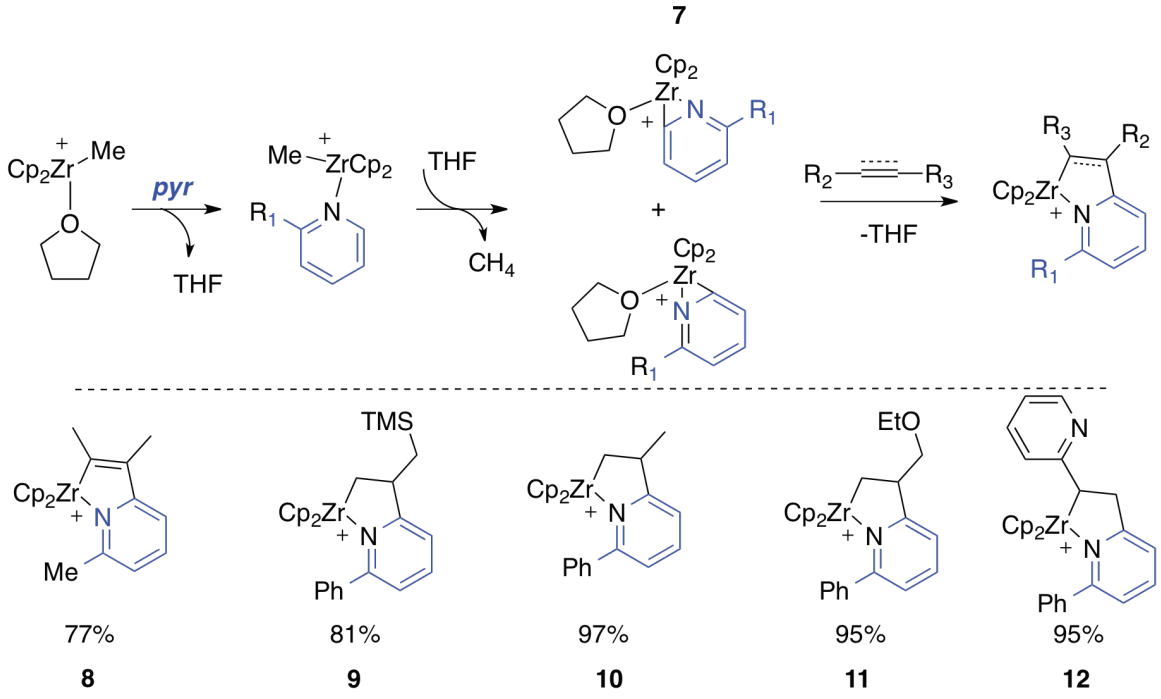
Scheme 9. Proposed mechanistic pathways for pyridine acylation.



The Jordan group has been active in applying cationic zirconium complexes in the functionalization of pyridine derivatives. The authors found that the highly Lewis acidic $Cp_2^*ZrMe(THF)$ could quickly complex and insert into 2-picoline (and derivatives)

generating a stable C,N–η^2 complex as a single isomer bearing a THF ligand while liberating methane.[32] This in turn was found to react with various unsaturated compounds *via* migratory insertion (**Scheme 10**). Tetrahydrofuran does not undergo C–H insertion as crystal structures show that steric considerations force the α C–H bonds out of plane relative to the LUMO of the zirconium center, precluding any reaction.[28] The lability of the Zr–O interaction is key to the reaction of pyridine, as when the insertion is attempted in THF no C,N–η^2 Zr-Pyr complex is noticed, presumably as pyridine cannot gain access the metal center. When bound, the pyridine is found to be perpendicular to the plane between the two cyclopentadiene ligands. This places the α-pyridine hydrogen atoms in the LUMO of the zirconium, and initiating a weak agostic interaction that is observable by ^{1}H NMR leading to the insertion.[28] Substitution at the 2-position of the pyridine ring is needed to help force this arrangement.

Scheme 10. Mechanism and scope of Zr-mediated functionalization of pyridine with unsaturated compounds.



The scope of the reaction is quite general, providing 5-membered azametallacycles in all cases. 2-Butyne (**Scheme 10**, (**8**)), ethylene, and propene are all viable reagents for insertion, in decreasing order of reactivity.[28] Addition of allyltrimethylsilane, propene, and allyl ethyl ether afforded 1,2-insertion products (compounds **9**-**11**).[33,34] This is the expected insertion product as the least encumbered metal complex is formed, and the δ^+ is stabilized by being on the more hindered carbon atom (**Figure 3**).[34] However, a reverse 2,1-insertion product is observed with vinyltrimethylsilane, styrene, and 2-vinyl pyridine (**12**). In these cases, electronic effects outweigh steric considerations. It is reasoned that in the case of vinyltrimethylsilane the silicon atom is able to simulatenously stabilize both the positive and negative charges built up in the polar transition state.[34] This was later confirmed through DFT calculations, showing that the 2,1-transition state is lower in energy.[35] Furthermore, the steric repulsion between the TMS group and the Cp groups is not as strong as initially thought, due to the longer C–Si bond.[34,35] The addition of alkenes to the Zr–Pyr complex is thermally reversible as was demonstrated through competition studies, though the addition of alkynes is not. 2-Substituted pyridines react faster than pyridine itself, though the products obtained from 2-methyl pyridine were significantly more soluble than 2-phenyl pyridine.[34] The 5-membered azametallocycle could be hydrolyzed to liberate the free pyridine through several ways. 2-Alkenyl pyridine could be prepared through β-hydride elimination. However, this was only possible in MeCN as the cyano nitrogen atom was effective in trapping the Zr–H species generated.[28] Hydrolysis in water provided 2-alkyl pyridines,[34] and alkynyl adducts were not susceptible to hydrolysis.

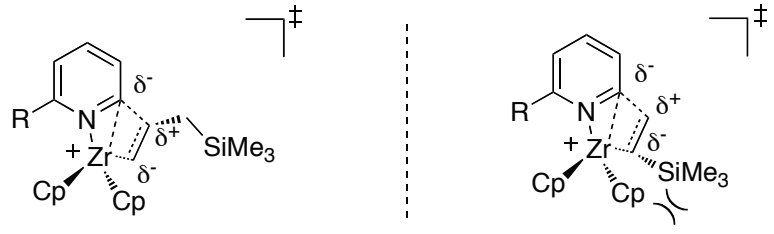
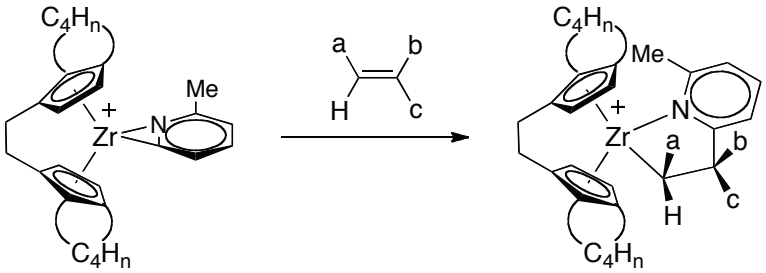


Figure 3. Site selectivity for the addition of allyl and vinyl silane to pyr-Zr complexes.

As can be seen in the scope of the reaction (**Scheme 10**, products **9**, **10**, **11**), it is possible to generate a stereogenic center. The use of chiral zirconium complexes bearing either ethylenebis(indenyl) (EBI) or ethylenebis(tetrahydroindenyl) (EBTHI) ligands permitted the elaboration of a stereoselective version of this reaction (**Table 1**).[36] Moderate to excellent diastereoselectivities were obtained with both ligands, though again 2-substitution was required on the pyridine ring. In the case of propene and 1-hexene, the major diastereomer obtained had the alkyl group pointing towards the Cp ring. The orientation is the result of the steric interaction of the 2-position of the pyridine ring with the other Cp unit, causing a 'tipping' of the pyridine ring.[37] In the case of vinyl silane and styrene, the Si and Ph group point away from the cyclopentadienyl ring, presumably due to π–π interactions. Low temperature studies indicate that the major diastereomer formed is the kinetic product, as heating leads to racemization and isomerization.[37]

Table 1. Selected scope for the diastereoselective addition of alkenes to Zr-activated pyridines.



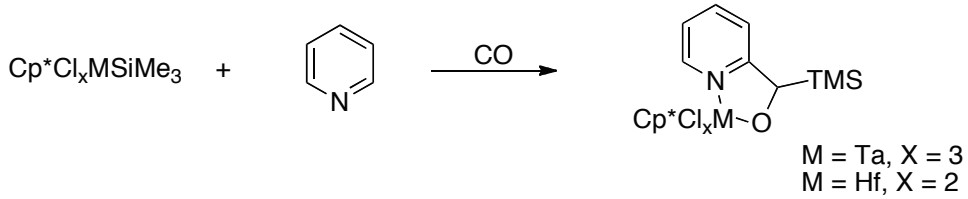
n = 4; EBI
n = 8; EBTHI

entry	ligand	a	b	c	de
1	EBI	H	H	Me	83
2	EBTHI	H	H	Me	64
3	EBI	H	H	Bu	83
4	EBTHI	Ph	H	H	>98
5	EBI	Ph	H	H	>98
6	EBTHI	Si	H	H	>98

1.3.2.2 Activation and Functionalization by Other Metals

In the late 1980s Tilley and co-workers demonstrated the ability of C,N–η^2 pyridine complexes of both halfnium[38] and tantalum[39] to undergo silaacylation reactions (**Scheme 11**). As was previously reported by Rothwell with zirconium,[30] the reactions first proceed by insertion of carbon monoxide into the M–Si bond, forming an η^2-complex.[38,39] Pyridine can then coordinate to this complex, activating the ring and permitting attack of the silicon atom to the 2-position. With both metals the reaction proceeds smoothly in the absence of any substitution on the pyridine ring. Unlike in Rothwell's study, only mono acylated products were reported.

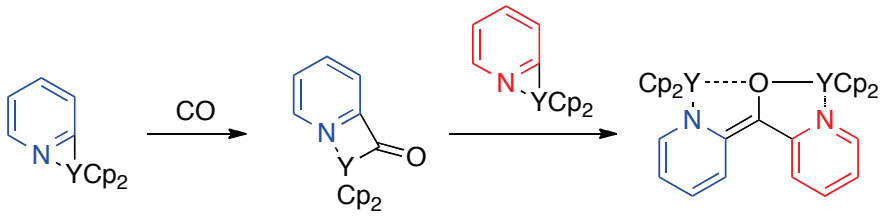
Scheme 11. Hydroacylation of pyridine by halfnium and tantalum.



Teuben described the cyclometallation of pyridine with $(Cp^*_2YH)_2$ to form C,N–η^2 Y–Pyr complexes, showing that Group III metals can also be used to derivatize pyridine (**Scheme 12**).[40] These complexes were determined to be quite robust, though reversibly bound with benzene at elevated temperatures. These Y-Pyr complexes were found to react with ethylene and propene to produce 2-alkyl pyridine adducts. In the case of propene, the 1,2-insertion product was observed. It should be noted that the rate of reaction with propene was much slower (4 d at 60 ºC vs 1 h at rt). This is reasoned to be the result of the steric saturation of the yttrium center, thereby the bigger the molecule, the more difficult it is to access.[40] Propyne and 2-butyne did not insert and only the alkynyl metal complex was observed. Curiously, 2-pentyne did successfully insert in 63% yield after two days at 75 ºC. This was reasoned to be the result of steric hindrance forcing insertion.[40] A unique feature of these complexes is their reaction with CO to prepare bi-metallic bis-pyridine

compounds (**Scheme 12**). In all these cases no attempts were reported to liberate the free pyridine ring.

Scheme 12. Yttrium-mediated carbonylation of pyridine to make *bis*-pyridyl adducts.



Finally, other metal complexes of titanium[19,20] and thorium[41] have been demonstrated to insert at the 2-position of the pyridine ring. However, these efforts will not be discussed due to limited scope and reactivity.

1.3.3. Catalytic Functionalization of Pyridine Derivatives

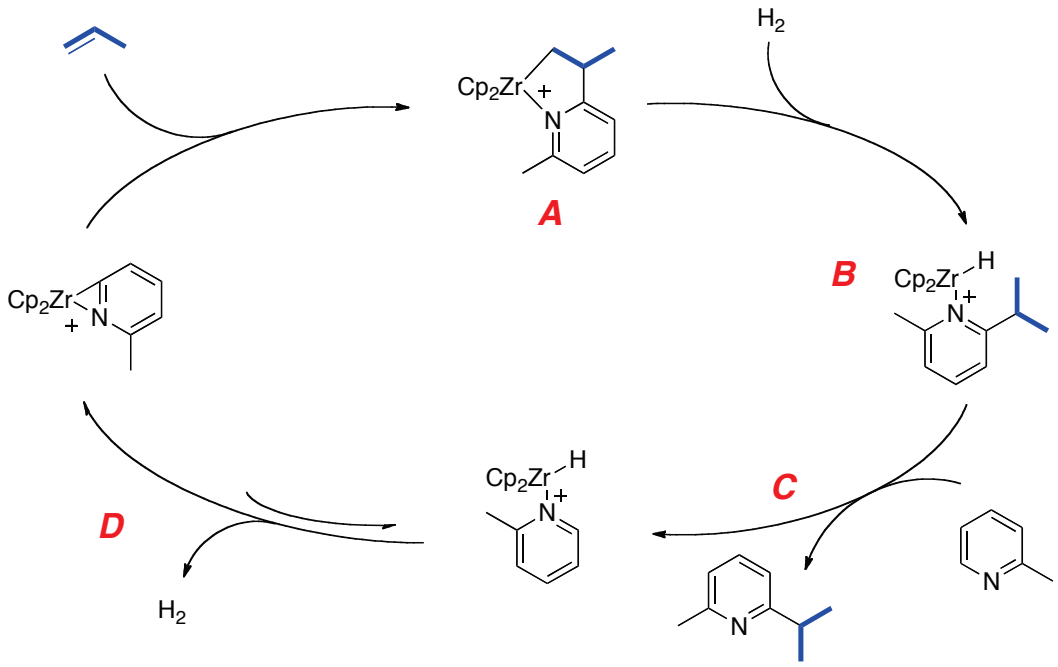
These methodologies were essential in providing the understanding required to minimize the pre-functionalization of the pyridine moiety necessary for structural elaboration. However, the use of a catalytic amount of transition metal is usually desired. Group III, lanthanide, actinide, as well as late transition metals tend to be costly, as are several of the ligands needed to induce their desired reactivity, several of which must be synthesized. Additionally, the reduced environmental impact and improved atom economy of catalytic quantities of transition metal is important to enable the use of a methodology on scale. This section will highlight progress and advances towards the catalytic application of both early and late transition metals in the direct alkylation and arylation of pyridine.

1.3.3.1 Direct Alkylation and Acylation of Pyridine

Jordan's first account of zirconium-mediated alkylation of 2-picoline was developed into a catalytic reaction.[32] Through the application of a catalytic quantity of H_2 (1 atm), 4 mol % of the complex **7** could be used to directly functionalize pyridine with

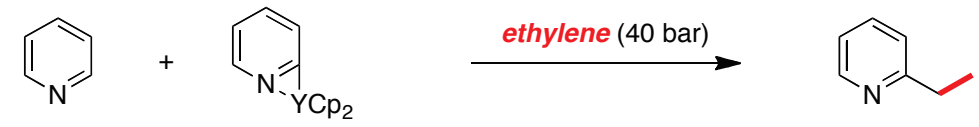
alkenes, providing 2-alkylpyridine derivatives. The catalytic cycle proceeds as follows (**Scheme 13**). First the C,N–η^2 complex undergoes migratory insertion into propene, giving a 5-membered azametallocycle (**A**). The C–Zr bond is then cleaved by the addition of H_2 (**B**). Isolating the metallocycle and submitting it to hydrogenation verified this cleavage.[32] Later, DFT calculations indicated that this was energetically favorable as it relieves steric strain, replacing a bulky alkyl group with a hydride.[35] The sterically encumbered 2-methyl-6-isopropyl pyridine is then displaced by a less hindered 2-picoline (**C**), liberating the intended product. Again, this was determined to be thermodynamically favored, and is likely driven by the tighter binding association of the 2-picoline due to decreased crowding of the complex. Insertion of the zirconium into the α-position of the pyridine simultaneously regenerates H_2 and the C,N–η^2 Zr–Pyr complex (**D**). Enantioenriched 2-alkylpyridine products were obtained using the chiral ligands described above in the catalytic Zr species. One example was provided, using 1-hexene (*R*)-2-Me, 6-(2-hexyl)pyridine was isolated with 58% ee (c.f. 64% de for the metallocycle prepared with the stoichiometric chiral reagent, **Table 1** entry 2).[36] Curiously, there have been few if any accounts of similar transformations since this disclosure. The scope of the reaction is largely unexplored, and the need for simpler catalytic systems remains.

Scheme 13. Catalytic cycle for the Zr-catalyzed direct alkylation of pyridine.



An analogous methodology using yttrium was also reported. However, in this case hydrogen was not required to effect the catalytic cycle.[40] The cycle is driven by the fact that Group III metals undergo more readily metathecal transformations due to their increased electrophilicity, and thus the yttrium azametallocycle can directly insert into another molecule of pyridine. It was found that 2-ethylpyridine could be prepared in 44% yield from pyridine, 3 mol % of complex **13** (**Scheme 14**) and 40 bar of ethylene.[40] Another advantage of the reaction is that substitution at the 2-position of the pyridine ring is not needed to drive the reaction, though this is offset by the high cost of the metal.

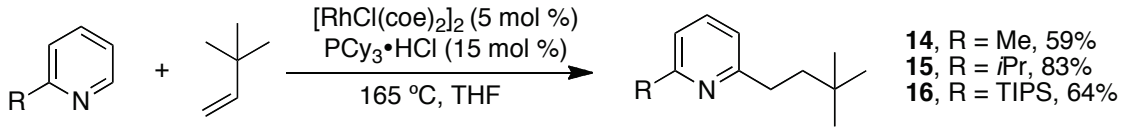
Scheme 14. Yttrium-catalyzed ethylation of pyridine.



More recently Ellman and Bergman reported a $[RhCl(coe)_2]_2$ catalyzed direct alkylation of 2-substituted pyridines with 3,3-dimethyl-1-butene in the presence of PCy_3 (**Scheme 15**).[42] This elegant approach is the first account of a late transition metal catalyzed direct alkylation of pyridine. Though an in-depth mechanistic investigation was not performed, the reaction presumably proceeds though the coordination of the Rh–phosphine complex to the Lewis basic nitrogen, activating the pyridine ring. The alkene may then coordinate to the complex, possibly generating a carbene-like species that can proximally insert into the 2-position of the pyridine ring.[42] The scope of the alkene was explored with only the quinoline series, which provided superior results to pyridines due to the decreased aromaticity of the heterocycle. However, 2-isopropyl and 2-triisopropylsilyl (TIPS) pyridine were found to be effective partners with moderate yield (products **14** and **15**).[42] The latter is of particular interest as the TIPS can serve as a blocking group (**16**), as demonstrated though its cleavage by HF. However, a drawback of

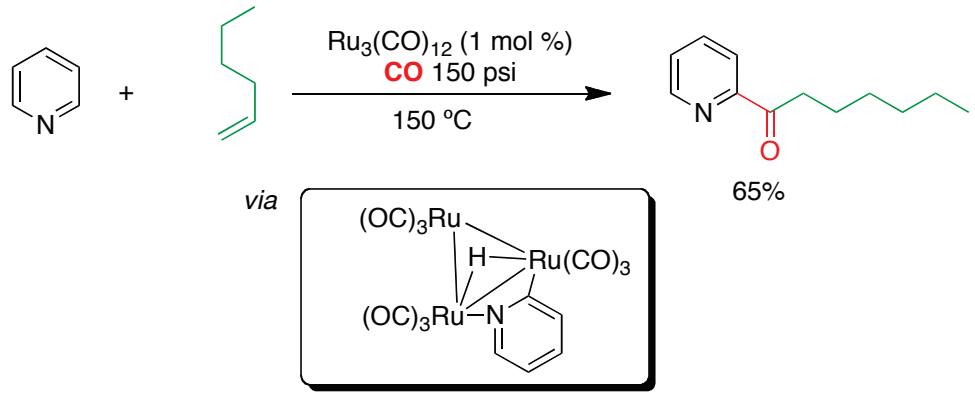
the reaction is the relative high catalyst loading, as well as reaction temperatures that exceed 160 ºC.

Scheme 15. Ellman's direct alkylation of pyridine.



Triruthenium dodecylcarbonyl was found to catalyze the direct acylation of pyridine in presence of terminal alkenes under a CO atmosphere (**Scheme 16**).[43] Carbon monoxide is essential as the photochemical direct alkyation of pyridine with $Ru_3(CO)_{12}$ was not observed. The metal activates the pyridine ring through a trinuclear cluster. The fact that the reaction was found to be first-order with regards to the catalyst and zero-order in CO led the authors to postulate that the reaction proceeds first through pyridine coordination and *ortho* insertion into the heterocycle.[43] Olefin coordination and insertion into the bridging hydride is followed by alkyl to acyl migratory insertion and reductive elimination. 2-Substitution on the ring was permitted, though electron-withdrawing groups on the heterocycle inhibited the reaction, presumably by decreasing the ability of the basic nitrogen to coordinate to the metal center. Finally, other systems bearing a pyridine ring (i.e. quinoline) are reactive, albeit less so than pyridine.[43] As with the rhodium-catalyzed direct alkylation, the reaction suffers from the drawback of elevated reaction temperatures.

Scheme 16. Ru-catalyzed direct acylation of pyridine.



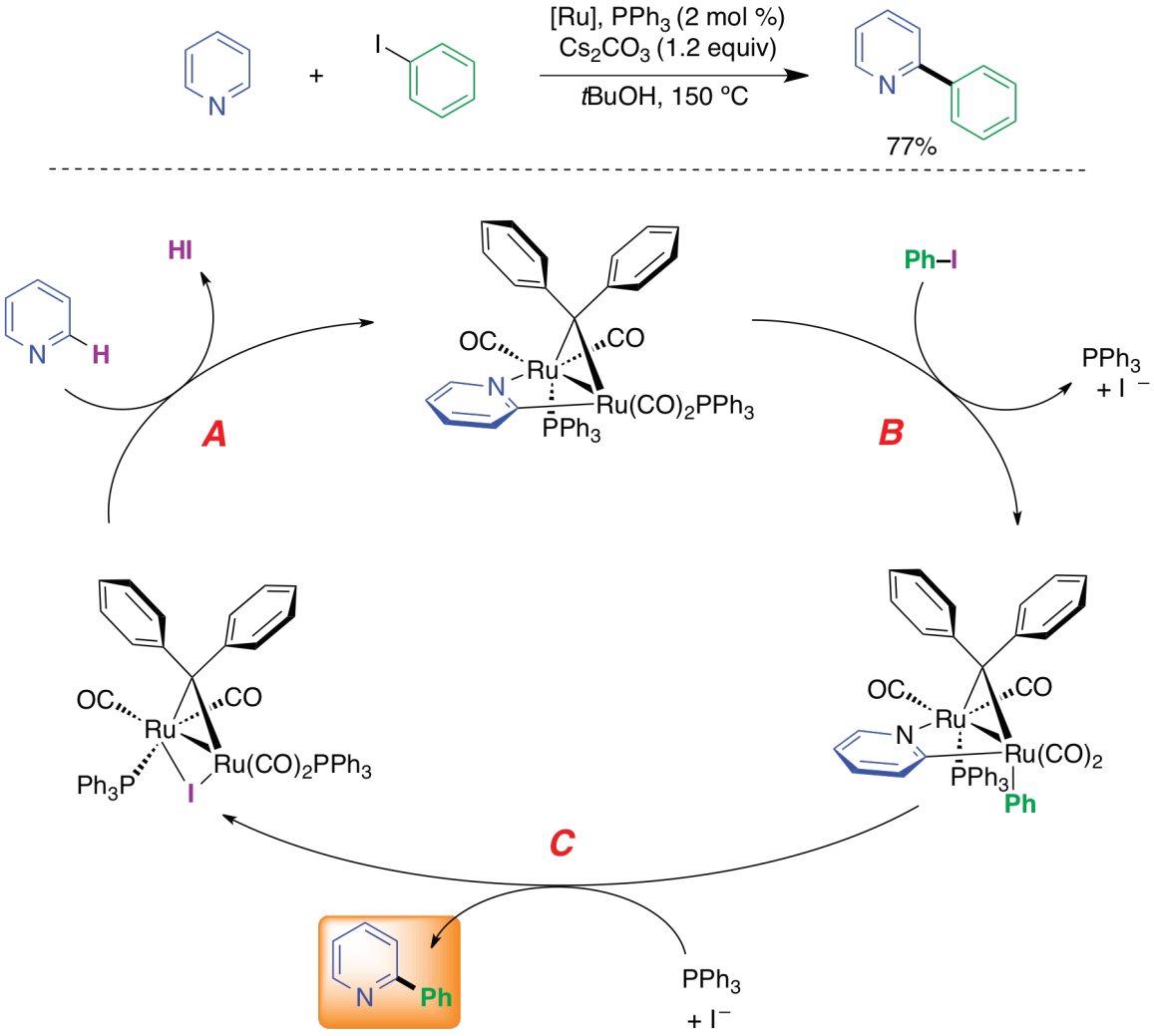
1.3.3.2 Late Transition Metal Catalyzed Direct Arylation of Pyridine Derivatives

Though there have been very recent advances in the synthesis and cross-coupling of 2-metallopyridine derivatives, as mentioned earlier, historically this approach to the synthesis of 2-arylpyridines has been problematic.[44,45] This is due to the lack of stability in these organometallic reagents, in particular pyridines with a boronic acid at the 2-position, which readily undergo proto-deborylation reactions. In the mid 2000s, the direct arylation of pyridine was viewed as a solution to the problem of cross-coupling of 2-pyridine. It can be argued that the work described in the previous section provided better understanding in the activation of pyridyl C–H bonds. This section will cover the progress and development in the area of direct arylation.

In 2005 Sames described the cross-coupling of pyridine with iodobenzene to give 2-aryl pyridines in the presence of a ruthenium catalyst.[46] Initial screening led to the discovery that the same $Ru_3(CO)_{12}$ used in the aforementioned direct acylation provided the desired product in 36% yield in presence of 1.2 equiv of Cs_2CO_3 in *t*BuOH (**Scheme 17**). Optimization led to the discovery that the inclusion of PPh_3 provided vastly improved yields (70%). Mechanistic investigations demonstrated that the phosphine likely disrupts the trinuclear complex formed upon oxidative insertion into pyridine, thereby giving a phosphido-bridged binuclear ruthenium complex though sequential C–H and C–P bond

cleavage (**Scheme 17**, **A**).[46] This complex could in turn oxidatively add into iodobenzene (**B**), providing the biaryl product after reductive elimination (**C**). The scope of the reaction was not explored.

Scheme 17. Sames' ruthenium-catalyzed arylation of pyridine

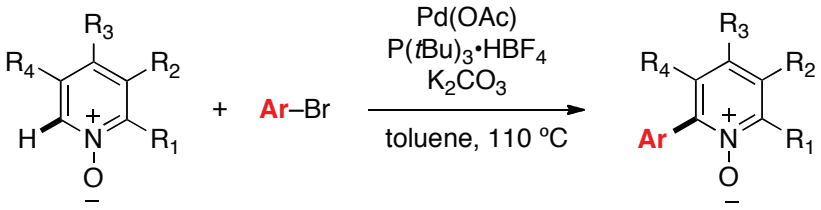


Aside from this ruthenium-catalyzed direct arylation of pyridine by Sames, there had been no reports of direct arylation reactions on pyridine and only more electron-rich arenes such as indoles and non-heterocyclic aromatic systems had been applied in these processes. It was thought that an S_EAr pathway was required for the arylation to proceed,

which an electron deficient arene should not be able to participate.[47] However, around the same time as Sames' disclosure, Fagnou reported the palladium-catalyzed direct arylation of pyridine *N*-oxides with aryl bromides.[47] An advantage of the *N*-oxide group was that it prevented nonproductive binding between the transition metal catalyst and the nitrogen lone pair (and poisoning the catalyst), thus favoring productive π-binding interaction with the arene ring.[16] The *N*-oxide functionality also helped to increase the electron density in the pyridine ring, while increasing the Brönsted acidity of the C–H bonds at the 2-position.[16] Because of the former, the use of a more expensive, electropositive early transition metal complex could be avoided. Finally, though the argument can be made that forming the pyridine *N*-oxide is a form of preactivation*,* their high stability, wide commercial availability, and ease of synthesis makes them an attractive alternative to 2-metallopyridines.

The initial conditions with aryl bromides used 4 equiv of the pyridine *N*-oxide in the presence of $Pd(OAc)_2$ (5 mol %), $P(t\text{Bu})_3\bullet HBF_4$ (15 mol %), K_2CO_3 (2 equiv) in toluene at 110 ºC.[47] The scope of the reaction tolerated hindered, electron-rich, and electron-poor substrates, though the latter provides slightly lower yields (**Table 2**). Though a large excess of the pyridine reagent was needed, it was reported that 95% of the unreacted material could be recovered. It was later discovered that by increasing the catalyst:ligand ratio from 1:3 to 1:1.2 and decreasing the base loading from 2 equiv to 1.5 equiv permitted the use of 2 equiv of the pyridine *N*-oxide while maintaining moderate yields.[48] Similar reaction conditions allowed the reaction to be scaled-up, being performed on a 50 mmol scale.[16]

Table 2. Selected scope for Fagnou's direct arylation of pyridine *N*-oxides.

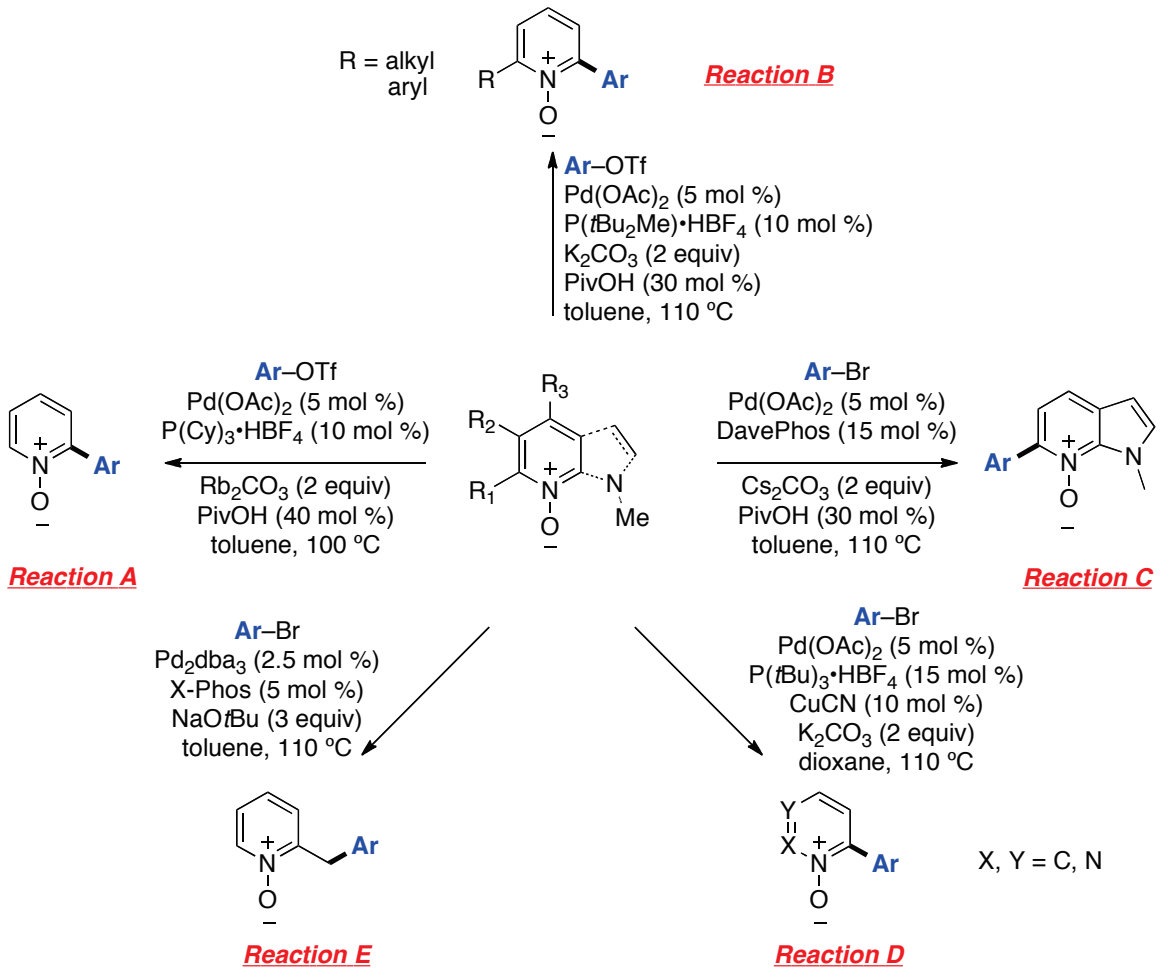


entry	Ar	R_1	R_2	R_3	R_4	yield (%)
1	4-MePh	H	H	H	H	91
2	3-MeOPh	H	H	H	H	97
3	4-CF_3Ph	H	H	H	H	76
4	4-MePh	Me	H	H	H	54
5	3,5-MePh	H	Ph	H	H	80[a]
6	3,5-MePh	H	H	H	F	78[a]

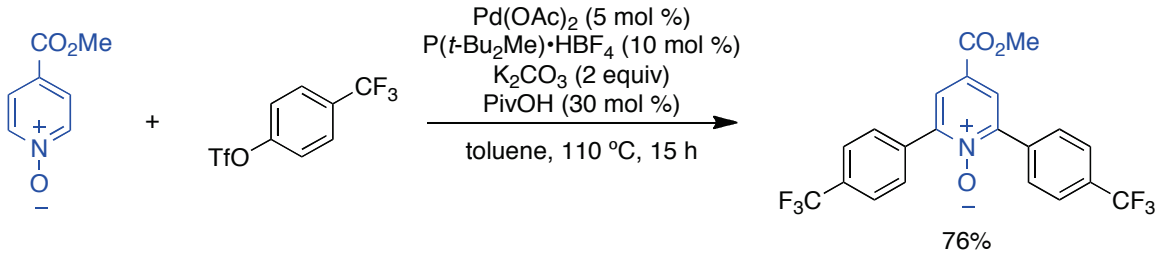
[a] Isolated yield of the major isomer.

The use of aryl triflates was explored (**Scheme 18**) due to their ease of synthesis from phenols, and thus has applications in the late stage synthesis of complex molecules.[49] Though aryl triflates are known to undergo oxidative insertion at comparable rates to aryl bromides,[8] in this instance they proved more reactive and had an increased propensity to form diarylated products (**Scheme 19**). As such, reaction conditions were re-optimized and two sets of conditions were reported (**Scheme 18**, Reactions **A** and **B**), one for unsubstituted pyridines and one for 2-substituted pyridine derivatives. The former required $Pd(OAc)_2$ (5 mol %), bulky PCy_3 (10 mol %), Rb_2CO_3 (2 equiv), and PivOH (40 mol %) as an additive.[49] The scope of the reaction was found to be general, though like the bromides electron-rich aryl triflates outperformed electron-poor substrates. Unlike with the aryl bromides, steric hindrance led to decreased reaction yields.

Scheme 18. Overview of various Pd-catalyzed arylations of pyridine *N*-oxide derivatives.



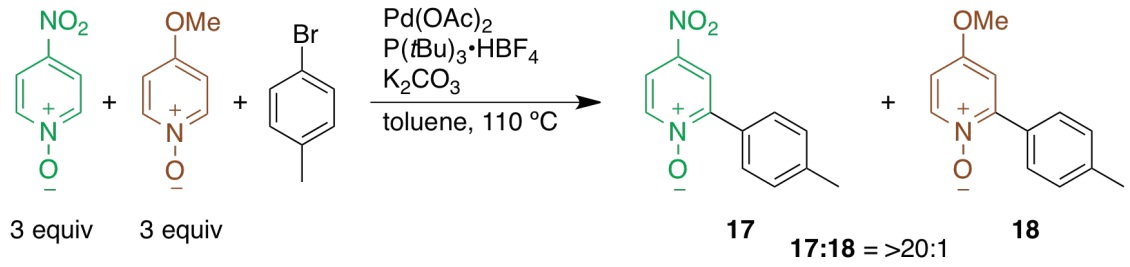
Scheme 19. Example of bis-arylation of pyridine *N*-oxides with aryl triflates.



With a wide variety of *pseudo* electrophiles tested, various pyridine derivatives were considered. Substitution on the pyridine ring was tolerated. As mentioned, in the case of aryl triflates, a separate set of conditions using $Pd(OAc)_2$ (5 mol %),

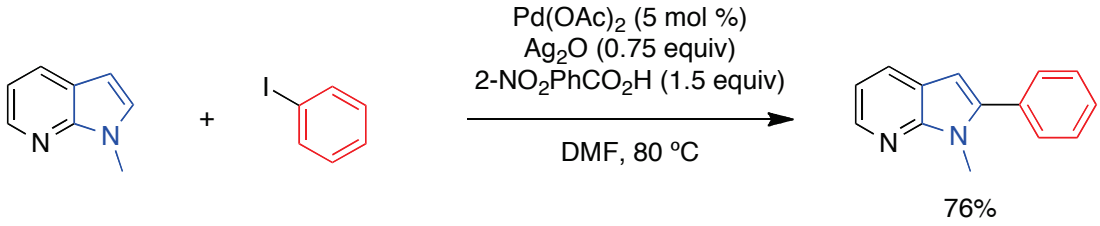
P(tBu$_2$Me)•HBF$_4$ (10 mol %), K$_2$CO$_3$ (2 equiv), and PivOH (30 mol %) were required for 2-substituted pyridines (**Scheme 18**, Reaction **B**).[49] It is reasoned that the bulkier substrate requires a less hindered ligand, facilitating the insertion of the transition metal into the C–H bond. In the case of aryl bromides, 2-substitution was tolerated under the standard reaction conditions, with the exception of a 2-methyl where decreased yields were noted. It was found that this is due to competing arylation at the benzylic site (**Scheme 18**, Reaction **E**).[48] Optimization led to the use of a stronger base (KOtBu) and X-Phos to provide excellent arylation of the sp^3 hybridized site, which in turn provided conditions for the site-selective arylation of the picoline (6– vs benzylic).[48] 3-Substituted pyridines provide unsymmetrical products (**Table 2**, entries 5, 6), with a mixture of 2- and 6- aryl products observed. When the 3-group was phenyl or ethyl ester, strong preference for the least hindered product was noted.[16] 3-Picoline *N*-oxide gave weak preference for the less hindered substrate, possibly due to competing weak agostic interactions. Other groups such as F, CN, and NO$_2$ gave strong preference for the more hindered product.[16] However, this phenomenon is not unknown with palladium-catalyzed processes, and may be the result of a combination of increased acidity and electrostatic interactions at reaction site. Competition studies between 4-nitropyridine *N*-oxide (**17**) and 4-methoxypyridine *N*-oxide (**18**) showed that electron poor heterocycles reacted much faster (**Scheme 20**).[47] This may be in part due to the increased Brönsted acidity at the reaction site of these substrates. Other heterocycles such as diazine *N*-oxides and quinolines *N*-oxides were also possible, but required either the inclusion CuCN as a catalytic additive, or less sterically demanding ligands (**Scheme 18**, Reaction **D**).[16,50]

Scheme 20. Competition studies in Fagnou's direct arylation of pyridine *N*-oxides.



N-Methyl 6- and 7-azaindole *N*-oxides readily undergo arylation with bromoarenes α- to the pyridyl nitrogen atom in moderate to excellent yields (**Scheme 18**, Reaction **C**).[51] The optimized conditions employed 5 mol % $Pd(OAc)_2$, 15 mol % DavePHOS, 30 mol % PivOH, 2 equiv Cs_2CO_3 in toluene at 110 ºC. By applying the Larrosa arylation conditions ($Pd(OAc)_2$, Ag_2O, 2-NO_2PhCO_2H) selective azole arylation with iodoarenes was also achieved (**Scheme 21**), thereby offering site selectivity for the arylation process.[51]

Scheme 21. Site-selective Larossa arylation of azaindoles.



The reaction has been postulated to proceed through a concerted metallation-deprotonation (CMD) sequence (**Figure 4**).[52] Not surprisingly an S_EAr pathway was calculated to have too high of an energy barrier due to the buildup of a positive charge on an already deficient species, as would oxidative insertion leading to Pd^{IV} intermediates.[53,54,55] A key feature to these reactions is the necessity for palladium acetate and in some cases pivalic acid. Both acetate and pivalate groups are known to be effective proton shuttle agents. The deprotonation step was determined to be the rate-determining step as the KIE was measured to be 4.7. The 6-membered transition state that is postulated to be active is also energetically favored. Finally, DFT calculations have shown that the activation energy for CMD metallation of the 2-position of pyridine *N*-oxide is ~3 kcal/mol lower than at the 3- and 4-positions, explaining the selectivity for that site (**Figure 4**).[52]

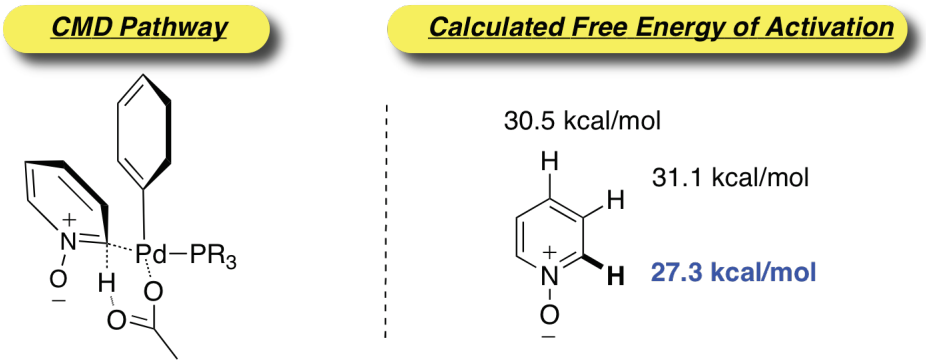
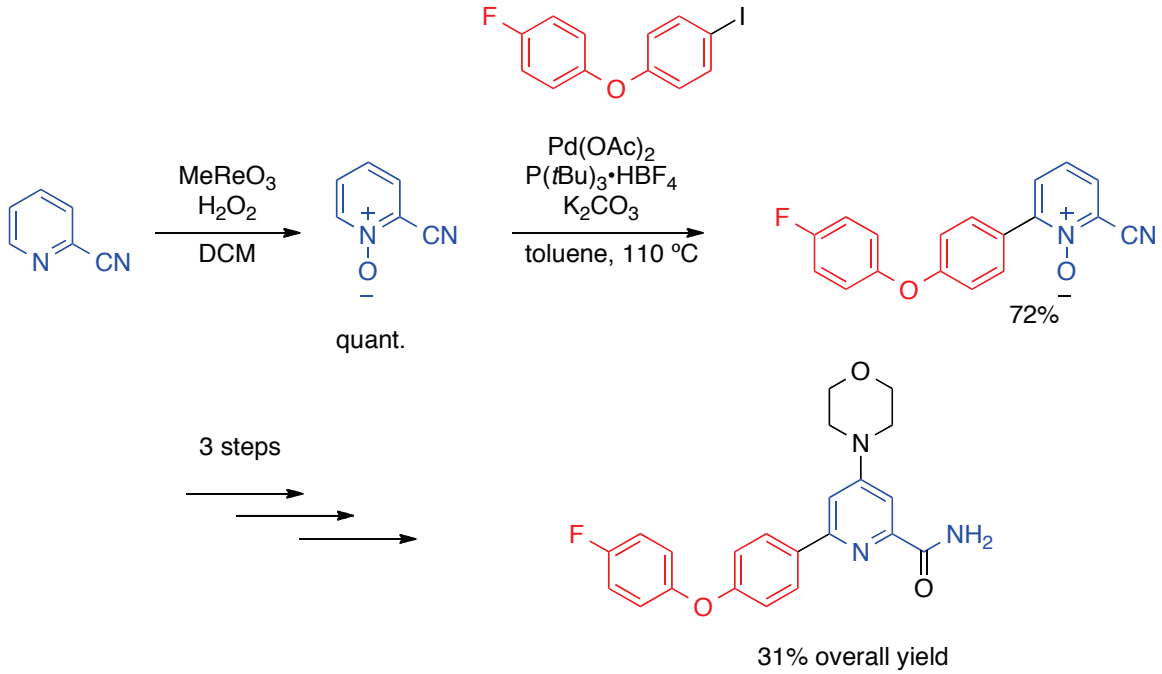


Figure 4. Mechanistic pathway for the Pd-catalyzed arylation of pyridine *N*-oxides.

An advantage of using pyridine *N*-oxides is the fact that the arylation products themselves are activated pyridinium species and are amenable to further reactions. Also, deprotection of the nitrogen to prepare the naked pyridine is possible under many reductive techniques.[16] Though large excess of the pyridinium were needed, it could be recovered. The application of aryl triflates in the bis-arylation of pyridine *N*-oxide provided a 2,6-bisarylated pyridine derivative that is a key intermediate in the preparation of a biologically active molecule known to exhibit antimalarial and antimicrobial activity.[49] This route employed three fewer steps than previously reported methodologies. The use of aryl iodides was also employed in the preparation of a sodium channel inhibitor in only five steps with 31% overall yield (**Scheme 22**).[16]

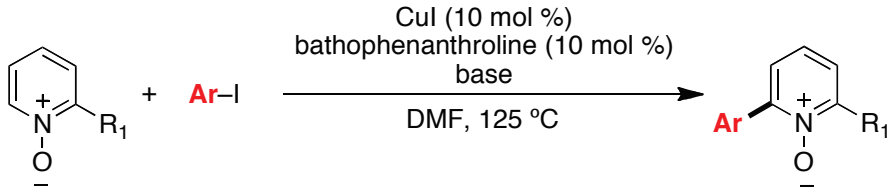
Scheme 22. Pyridine *N*-oxide arylation in the synthesis of a Na pump inhibitor.



Daugulis and co-workers have described the copper-catalyzed direct arylation of 2-phenylpyridine *N*-oxide with iodobenzene in 66% yield.[56] The obvious advantage of a Cu-catalyzed process over Pd, Rh, Ru, etc. is the low cost of the catalyst. The initial reaction conditions employed CuI (10 mol %), LiO*t*Bu (2 equiv), at 140 ºC in DMF. There were however a few issues with the reaction. First, it was determined that the copper catalyst was not stable at the required reaction temperature. The stability was improved through the inclusion of bathophenanthroline, which was found to stabilize the organocopper intermediates formed in the reaction.[57] Secondly, the use of KO*t*Bu led to regioselectivity issues, through the formation of benzyne. The regioselectivity issue was remedied through the use of weaker bases such as LiO*t*Bu and K_3PO_4.[57] When a stronger base was needed for less reactive substrates, the very hindered $KOCEt_3$ was determined to be effective, minimizing both substitution and benzyne formation. The scope of the reaction was explored, though lower yields were obtained relative to Fagnou's palladium-catalyzed method. 2-Picoline *N*-oxide gave decreased yield, likely due to the

aforementioned acidity of the benzylic group (**Table 3)**. For 2-iodopyridine, alkoxide bases could not be used due to the formation of 2-alkoxidepyridines.[57]

Table 3. Direct arylation of pyridine *N*-oxides with iodoarenes under copper catalysis.



entry	R_1	Ar	base	yield (%)
1	H	Ph	LiO*t*Bu	58
2	H	Pyr	K_3PO_4	41
3	Me	Ph	LiO*t*Bu	43
4	Ph	4-CF_3Ph	LiO*t*Bu	80
5	Ph	naphthyl	LiO*t*Bu	91

1.4. Conclusions and Research Goals.

C–H functionalization constitutes an exciting class of chemical reactions that is enjoying resurgence in the current literature. The direct functionalization of electron-deficient heterocycles, most notably pyridine, remains a synthetic challenge. This is substantiated by the fact that far more accounts of rich arenes continue to be reported in the literature. Though some elegant forays into the direct functionalization of pyridine were achieved in the mid 1980s through the early-to-mid 1990s, the majority of these accounts require stoichiometric quantities of expensive early group metals, or in the case of catalytic systems, the multi-step synthesis of the active catalytic species. Additionally, the substrate scope of these reactions have not yet been fully explored.

More recently, some research groups have begun to explore late-transition metal catalyzed process for the functionalization of pyridine. Again, though clever altering of

the electronic properties of pyridine have provided seemingly attractive tools towards solving this problem, the chemistry is largely limited to the use of large excesses of pyridine *N*-oxides. Furthermore there remains a deficiency in both the arylation of sp^3 hybridized groups, and the use of less expensive transition metals.

The goal of this thesis is to describe our work towards solving problems associated with the direct functionalization of pyridine and other arene derivatives. Chapter 2 will briefly describe our work on the direct arylation of *N*-iminopyridinium ylides and focus on our efforts towards the derivitization of the benzylic position of *N*-imino-2-picolinium ylides. Chapter 3 will describe our work on the use of copper catalysis in the synthesis of 2-alkenyl pyridines, which prior to this thesis was still a challenge in synthesis. Chapter 4 will describe the palladium-catalyzed addition of halostyrenes and alkynes to the 2-position of *N*-iminopyridinium ylides to access a pyrazolopyridine core. Finally, the last two chapters will highlight our work on the palladium and iron catalyzed direct arylation of non-heterocyclic arenes.

Chapter 2

Benzylic Functionalization of 2-Alkyl *N*-Iminopyridinium Ylides

2.1 Introduction

2-Alkyl pyridine derivatives are an important class of compounds often seen in a variety of pharmacophores (**Figure 5**). In particular, 6-membered azaheterocycles such as Concerta© and CGP 49823 bear a phenyl ring separated from the piperidine core by a single methylene group, and display important biological activity. Given that the piperidine motif can be accessed from pyridine (**Section 1.1**), a reasonable synthetic route to these compounds could be *via* the direct arylation of 2-alkyl pyridine derivatives.

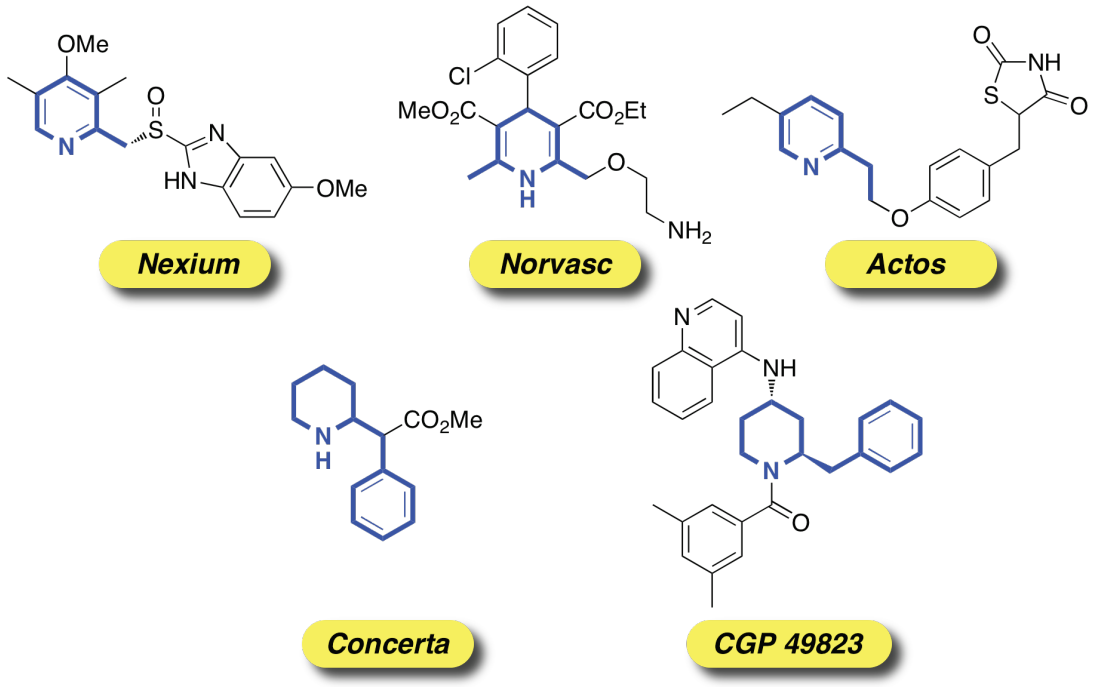
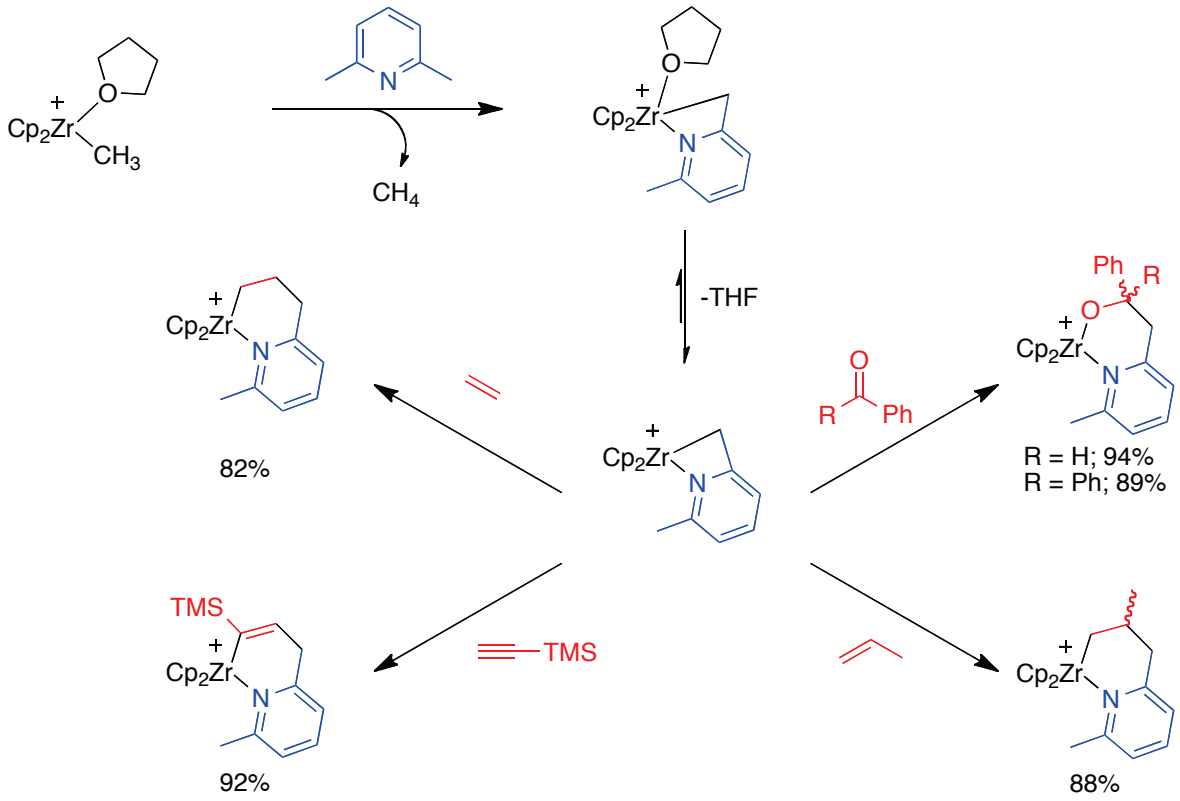


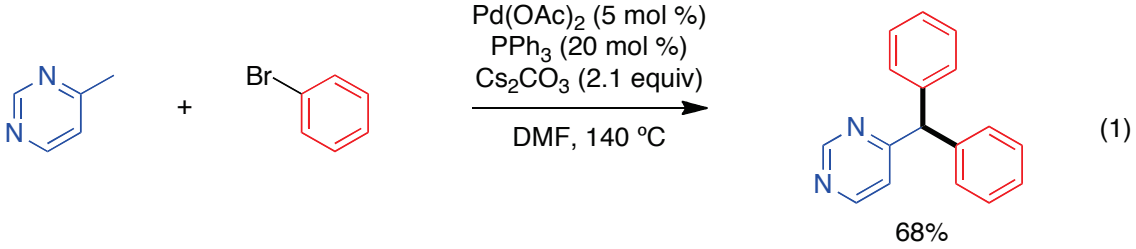
Figure 5. Various biologically active 2-alkyl pyridine and piperidine derivatives.

The direct functionalization of sp^3 hybridized C–H bonds has received increased attention in recent years.[58] However, the arylation of benzylic sites of alkyl substituted pyridine and other aromatic azine derivatives have not been well addressed. In the early 1990s Jordan reported the first example of a transition metal-catalyzed direct functionalization of picolines.[59] This elegant account described the insertion of a $Cp^*_2ZrMe•THF$ complex into the benzylic site of 2,6-lutidine (**Scheme 23**). The dissociation of the tetrahydrofuran ligand allows for coordination and insertion of various unsaturated systems to provide the 2,1-insertion products in good to excellent yields. They later reported that the resulting 6-membered azametallocycle Zr–N complex can be broken upon hydrolysis in water and that the pyridine scope can be expanded to include 2,6-diethylpyridine.[60] The relief of ring strain drives the reaction as the 4-membered azametallocycle is converted into a less constrained 6-membered ring.

Scheme 23. Jordan's direct functionalization of pyridyl benzylic sites.



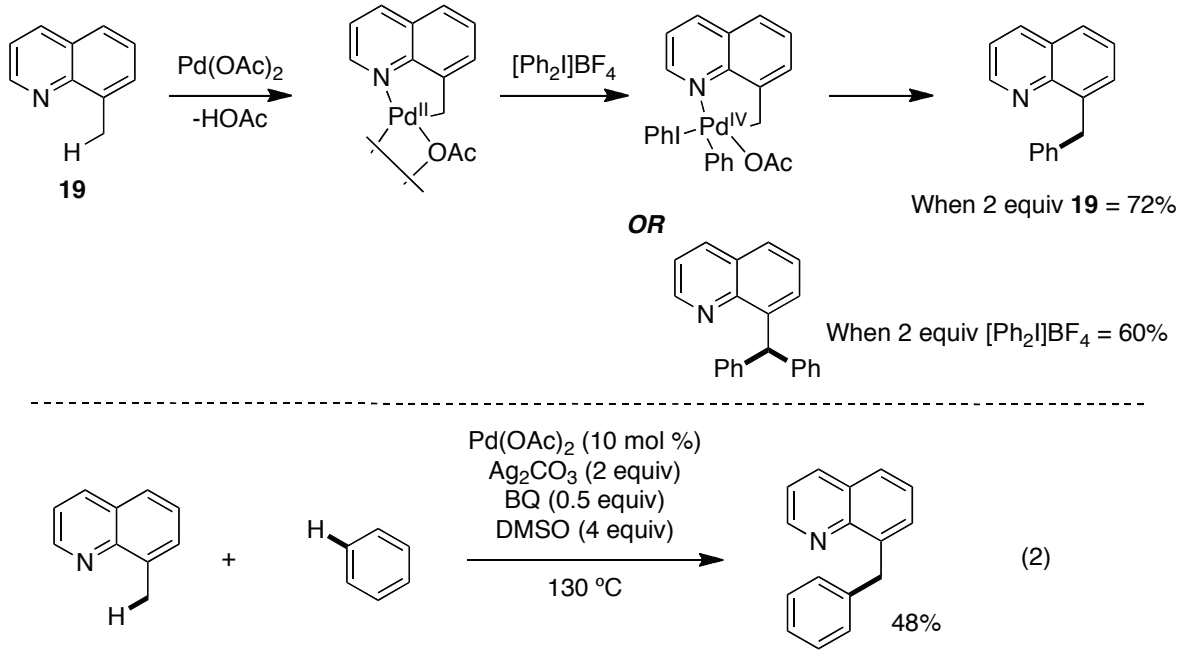
The first benzylic arylation of azaheterocycles was reported by Miura in 1997.[85] During their studies of the arylation of electron poor arenes, they found that 4-methylpyrimidine could be readily arylated in the presence of $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 in DMF. The reaction provides only the bis-arylated product in 68% yield (Eq. 1). Given the high solubility of the Cs_2CO_3 in DMF the reaction is proposed to occur through the deprotonation of the benzylic methylene carbon atom. The formation of the bis-arylated product can be reasoned by the increased acidity of the benzylic protons following the first arylation, facilitating a second deprotonation event.



(1)

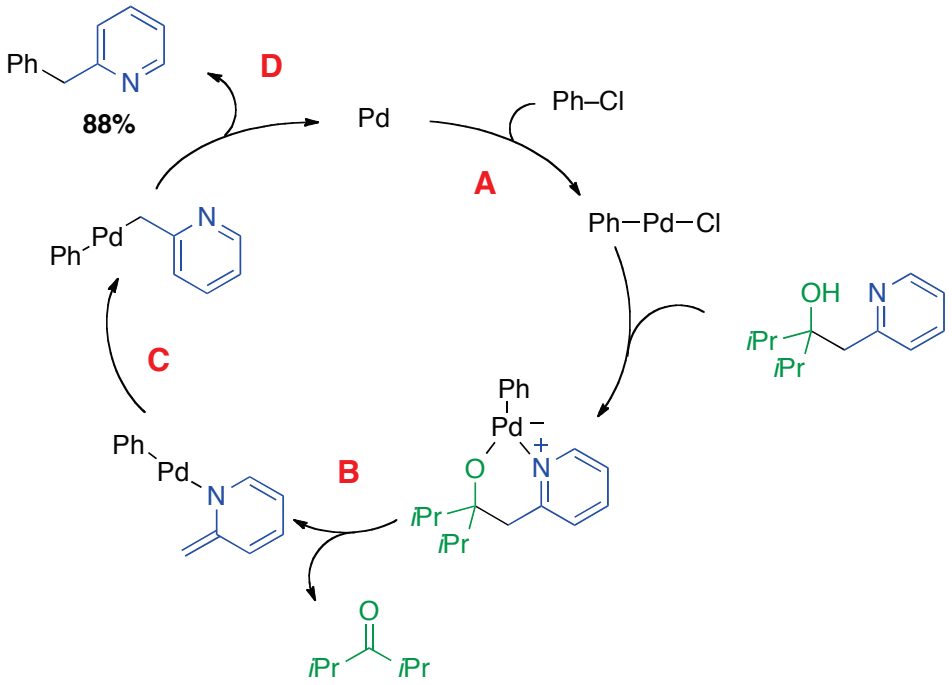
In 2005 Sanford described the arylation of 8-methylquinoline (**19**) with aryl iodonium salts.[61] Though the alkyl group of interest is not directly linked to the pyridine ring, this is still an excellent example displaying the potential of benzylic arylation reactions. The reaction was thought to proceed by an oxidative insertion process where the palladium acetate first inserts into the benzylic C–H bond (**Scheme 24**). This process is likely directed, and stabilized by the Lewis basic quinoline nitrogen atom, and the resulting Pd^{II} species then oxidatively adds into the phenyl iodonium salt. Reductive elimination of the Pd^{IV} species gives the desired product. A useful feature of this reaction is the ability to control mono *vs* di-arylation by altering the stoichiometry of the reaction.[61] Two years later the process was improved to a palladium-catalyzed oxidative cross coupling with benzene in the presence of benzoquinone and Ag_2CO_3 (Eq. 2).[62] This advancement eliminates the need for prefunctionalization of the coupling partners, affording a highly economical methodology.

Scheme 24. Pd-catalyzed oxidative benzylic arylation of 8-methylquinoline.

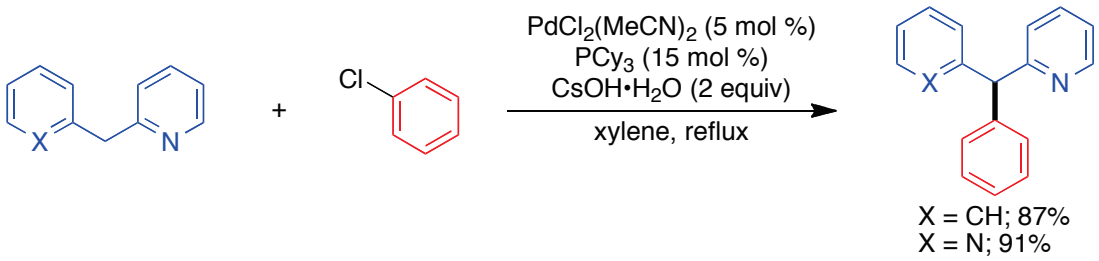


Yorimitsu and Oshima were the first to describe a benzylic arylation of 2-alkyl pyridines through the chelate-assisted retroaldol-type reaction of 2-pyridyl alcohols (**Scheme 25**).[63] The reaction proceeds first through the oxidative addition into an aryl halide (step **A**). The pyridyl nitrogen and the hydroxyl group then chelate the resulting Pd^{II} species (**B**). This promotes cleavage of the Csp^3–Csp^3 bond, irreversibly liberating pivalone (**B**). Migration of the palladium on the pyridyl amide (**C**) and reductive elimination generates the 2-benzylpyridine (**D**). Aryl chlorides are viable cross coupling partners in the presence of PCy_3, though PPh_3 can be used with aryl iodides without sacrificing yields.[63] The reaction was demonstrated to indeed proceed through the aformentioned double chelation, as when the pyridine moiety is replaced with benzene, or if the aliphatic alcohol was placed at the 4-position of the heterocycle, none of the desired product was observed. Though a wide range of substrates are reported giving products in moderate to excellent yields, the reaction suffers from the drawback of poor atom economy and the need of reaction temperatures in excess of 150 ºC.

Scheme 25. Proposed catalytic cycle for the benzylic arylation of 2-alkyl pyridines through chelation assisted cleavage of Csp^3–Csp^3 bonds.



Shortly after this account they also reported the benzylic arylation of 2-benzylpyridines (Eq. 3).[64] The reaction relies on the deprotonation of the benzylic site by cesium hydroxide followed by a presumed cesium/palladium transmetallation to afford the product following reductive elimination. This process relies on the methylene site being doubly arylated, as the acidity of the protons is otherwise not sufficient for the reaction to occur, and thus the only products that can be obtained are triarylmethanes.[64] Another problem is again the elevated reaction temperatures needed for the process.



(3)

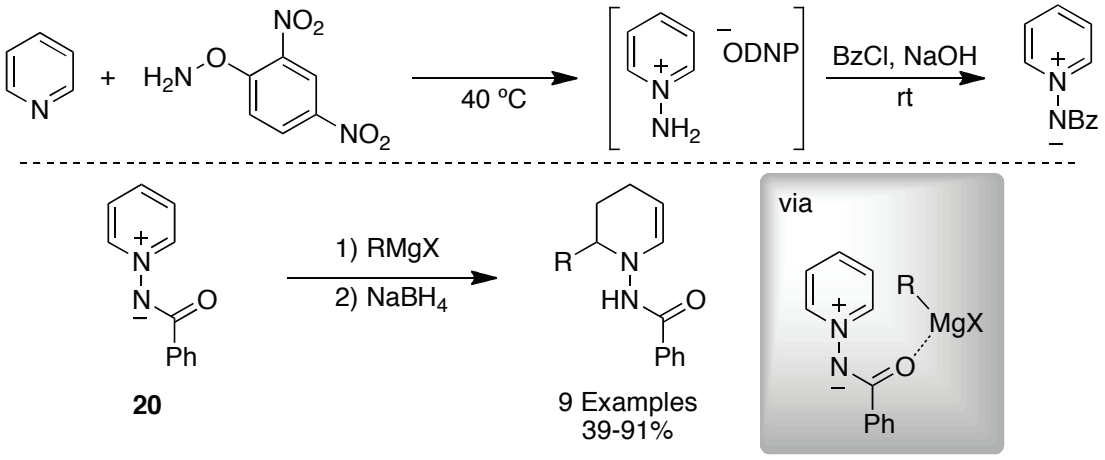
Our group's foray into the benzylic arylation of 2-alkyl *N*-iminopyridinium ylides begins with our work on the direct sp^2-arylation of the 2-position of these pyridiniums. The following section will describe the work in the area performed by Alexandre Larivée, as well as some work performed following his graduation. This will lead into the main topic of this chapter.

2.2 Direct sp^2-Arylation of *N*-Iminopyridinium Ylides

2.2.1 Introduction

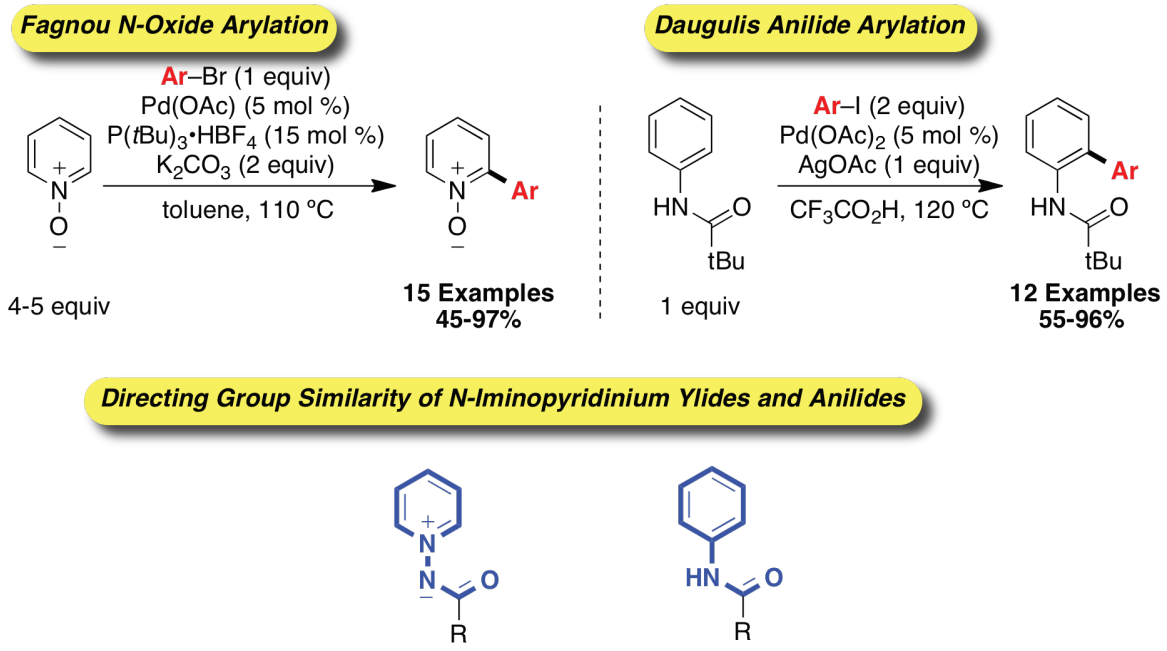
Over the past decade the Charette group has exploited the use of *N*-iminopyridinium ylides in the elaboration of pyridine structures.[65] These reagents are readily prepared in a 2-step/one-pot process where pyridine is reacted with *O*-(2,4-dinitrophenyl)hydroxylamine followed by benzoyl chloride in presence of aq. NaOH.[66] These pyridinium compounds have been effective in undergoing attack by Grignard reagents to give a variety 2-alkyl tetrahydropyridine (**Scheme 26**). The presence of the *N*-imino moiety plays a dual role in both activating the pyridine and directing the delivery of the organomagnesium nucleophile.

Scheme 26. Directed addition of Grignard reagents to *N*-iminopyridinium ylides.



As mentioned in the introductory chapter, in 2005 the Fagnou group reported the palladium-catalyzed direct arylation of pyridine *N*-oxides with various aryl bromides (**Scheme 27**).[47] This was a breakthrough for the arylation of pyridines, and demonstrated the power of pyridinium species in such transformations. An important drawback however was this need for a large excess of the *N*-oxide partner. Almost simultaneously, Daugulis disclosed the *ortho* arylation of various protected anilines with aryl iodides (**Scheme 27**).[67,68] A key feature of this process is the directing ability of the Lewis basic *N*-Piv group.[69] Unlike the arylation of pyridine *N*-oxides, an excess of the halide partner was necessary for good reaction yields. Given the ability of pyridinium species to undergo the desired C–H phenylation, and the similarity of the *N*-imino group to the anilide group, we reasoned that these *N*-iminopyridinium ylides would not only be suitable for such processes, but may also be able to do so without large excess of either coupling partner. The next section will highlight our work in the area disclosing novel reactivity of these ylides.[70]

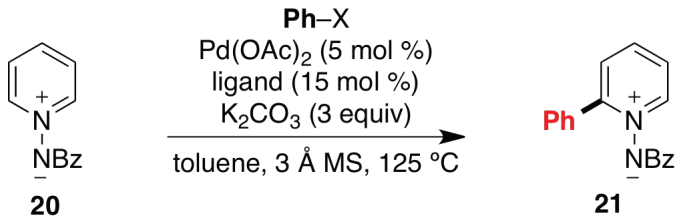
Scheme 27. Comparison of pyridinium and anilide arylation.



2.2.2 Reaction Optimization, Scope, and Application

Alexandre Larivée explored the optimization and scope of the reaction. A selected optimization is provided in **Table 4**.[70] A series of palladium catalysts were screened and $Pd(OAc)_2$ was proven to be most effective. A range of phosphine and amine ligands were studied and $P(t\text{Bu})_3$ proved superior (entry 1), suggesting the need for a bulky, monodentate, electron-rich phosphine to effect the intended transformation. Curiously, the air-stable BF_4 salt of the ligand provided decreased yields (entry 2). The pre-made palladium-phosphine complex gave slightly better results (entry 3), but the increased cost of the reagent did not justify its use.[70] The process is sensitive to the loading of the ylide (entries 4 to 6), with 1.5 equiv proving optimal. Diluting the reaction had minimal impact (entries 7, 8). Slightly higher yields were obtained with molecular sieves present, though the presence of water in the reaction vessel did not severely impair the transformation (entries 9, 10). Aryl bromides were chosen due to their wider availability and lower cost.

Table 4. Selected optimization for the direct sp^2 arylation of *N*-iminopyridinium ylides.



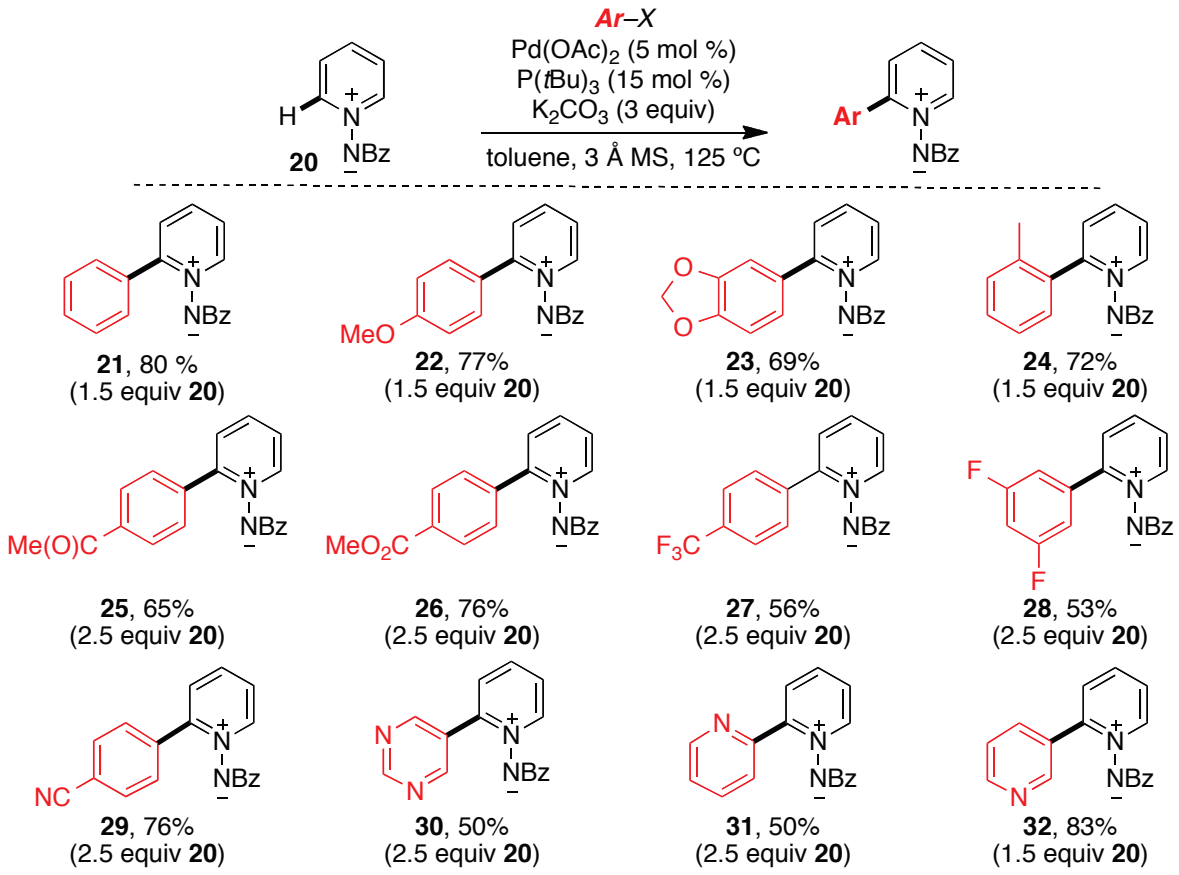
entry	ligand	X	equiv of ylide	conc. (M)	temp. (°C)	yield (%)[a]
1	tBu$_3$P	Br	1.5	0.30	125	87
2	tBu$_3$P•HBF$_4$	Br	1.5	0.30	125	55
3	Pd(tBu$_3$P)$_2$[b]	Br	1.5	0.30	125	90
4	tBu$_3$P	Br	1.5	0.30	110	66
5	tBu$_3$P	Br	1.3	0.30	125	64
6	tBu$_3$P	Br	1.0	0.30	125	36
7	tBu$_3$P	Br	1.5	0.10	125	82
8	tBu$_3$P	Br	1.5	0.050	125	73
9[c]	tBu$_3$P	Br	1.5	0.30	125	81
10[d]	tBu$_3$P	Br	1.5	0.30	125	83
11	tBu$_3$P	I	1.5	0.30	125	95
12	tBu$_3$P	Cl	1.5	0.30	125	42

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] 5 mol % of Pd(PtBu$_3$)$_2$ was used instead of Pd(OAc)$_2$/ligand. [c] Run without 3 Å mol. sieves. [d] Run without 3 Å mol. sieves and in presence of 5 equiv of H_2O.

The scope of the reaction was then investigated using various aryl bromide coupling partners (**Scheme 28**).[70] Under the optimized reaction conditions of **20** (1.5 equiv), Pd(OAc)$_2$ (5 mol %), P(tBu)$_3$ (15 mol %), K_2CO_3 (3 equiv), 3Å mol. sieves, toluene at 125 °C using bromobenzene (1 equiv), the 2-phenyl-*N*-iminopyridinium ylide **21** was obtained in 80% isolated yield. Electron-rich and more encumbered substrates provided the products in good yield (**22-24**). Electron-poor aryl bromides arylated with moderate to good results (**25-29**), though an additional equivalent of ylide **20** was needed to promote the transformation.[70] Enolizable centers were tolerated (**25**), highlighting the mild reaction conditions. Of note was the ability of heterocyclic aryl bromides to affect the arylation (**30-**

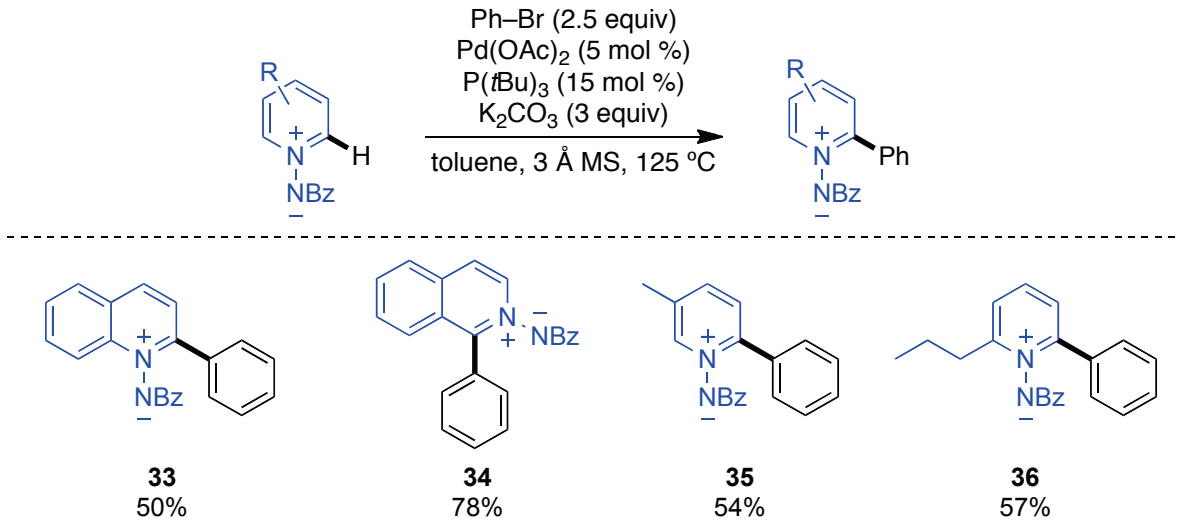
32). Again an extra equivalent of **20** was needed, except with 3-bromopyridine where the original conditions were sufficient to give the biaryl in 83% yield.

Scheme 28. Scope of the aryl bromide in the arylation of ylide **20**.

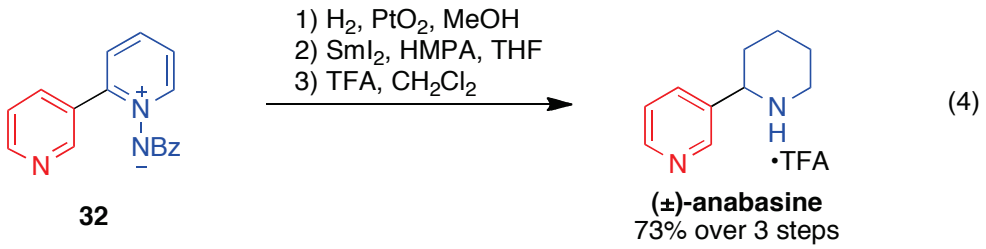


Cognizant that many pyridines are available already bearing substitution, Dr. Larivée next considered the scope of the pyridinium ylide. For the most part, the substrates provided poorer yields and an excess of bromobenzene was required, giving the 2-phenyl azines in moderate yields (**33**, **35**, **36**).[70] An exception was noted with isoquinoline **34** where 1.5 equiv of the pyridinium and 1 equiv of the Ph–Br could be used with the arylation proceeding in good yield. Furthermore, the reaction proceeded giving the product as a single regioisomer. A similar result was noted with the 3-methyl-*N*-iminopyridinium ylide, with the arylation occurring on the least hindered position (**35**).[70]

Scheme 29. Scope of the pyridinium ylide.



The synthetic potential of this methodology was demonstrated though the synthesis of (±)-anabasine (Eq. 4). It was reasoned that this natural product could be obtained from the chemoselective hydrogenation of ylide **32**.[70] Indeed this was the case, as only the activated pyridine moiety was reduced under standard conditions affording the racemic natural product.



(4)

2.2.3 Further Investigations

A few concerns of the reaction were raised following Dr. Larivée's departure from the Charette group. Among these included the possibility of synthesizing 2,6-diarylated pyridinium ylides, as well as cleavage of the ylide *N–N* bond to give access to the free arylated pyridine. Several trials were made to form the diarylated product from the 2-

phenyl-*N*-iminopyridinium ylide, however they were unsuccessful, providing <5% of the desired product. Attempts included using excesses of both coupling partners, increased catalyst loadings, and temperature variation. We believe that the reaction was not successful due to the conformation of the directing group following the arylation (**Figure 6**).[71] As can be seen in the crystal structure of the non-arylated ylide **A** the *N*–carbonyl moiety is approximately in plane with the heterocycle, allowing for conjugation and positioning the Lewis basic group to direct the palladium catalyst following complexation of the metal. However, following arylation, the activating/directing group is twisted to be perpendicular to the plane of the heterocycle (crystal structure **B**). This is likely due to a combination of steric and π–π interactions between the 2-phenyl and benzoyl rings. Consequently, the *N*-imino group is no longer in position to direct palladium towards the 6-position, possibly precluding any further reaction from occurring.

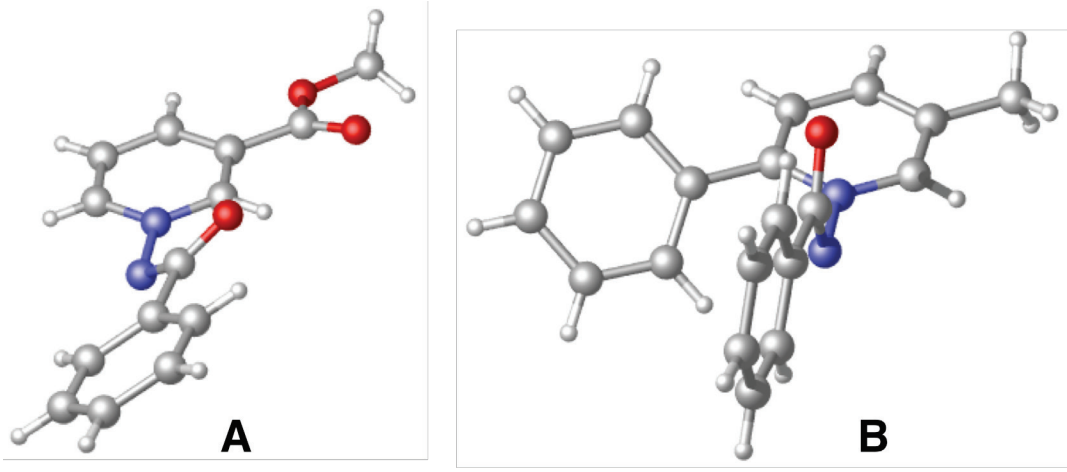
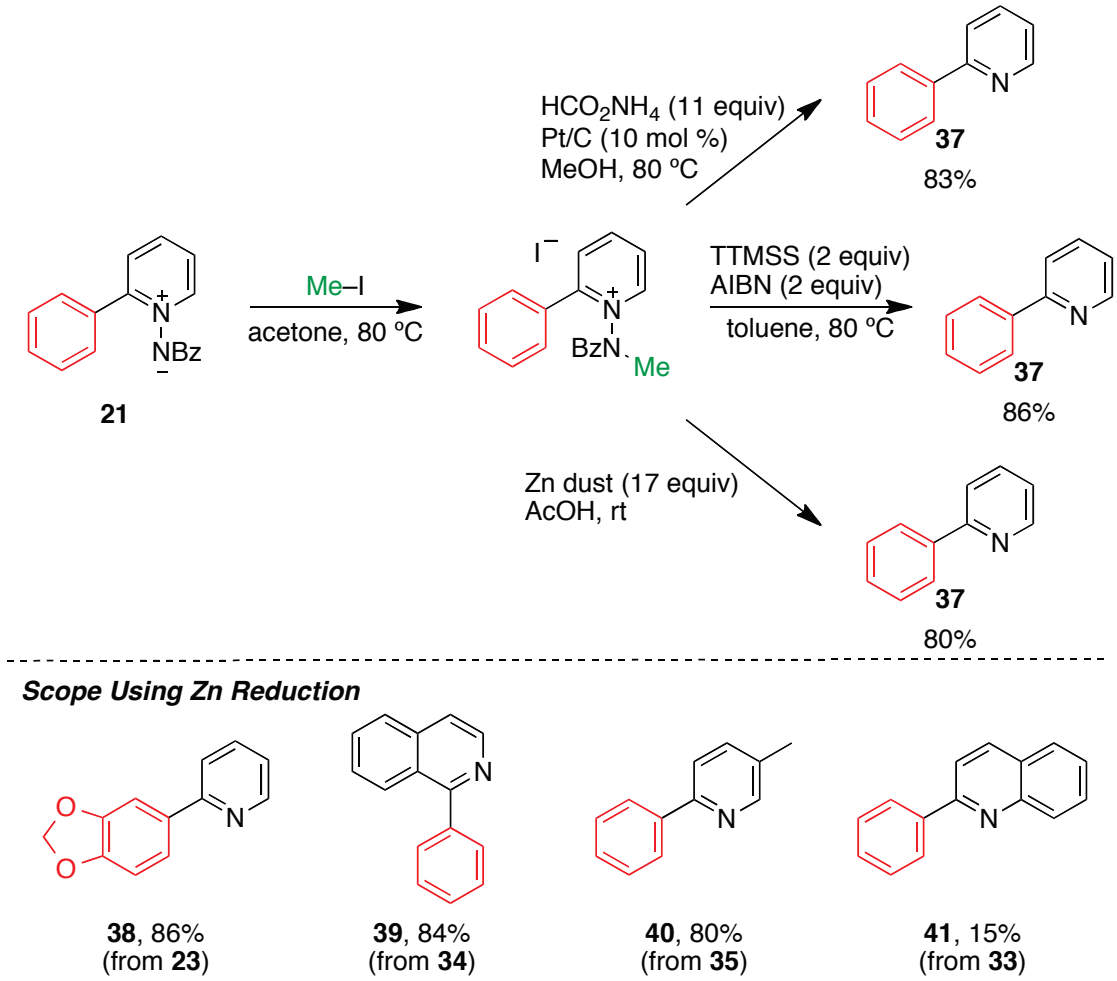


Figure 6. Comparison of crystal structures before (**A)** and after (**B**) arylation.

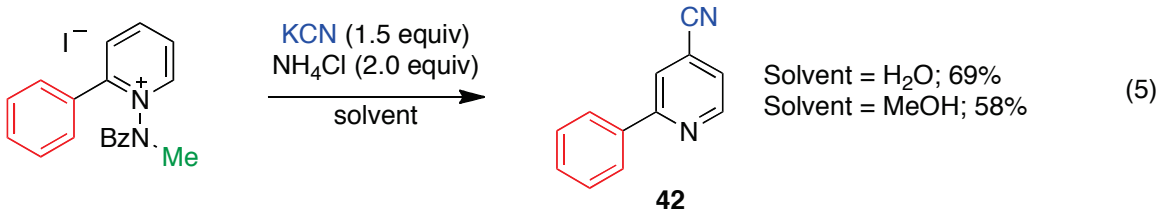
Efforts to cleave the *N*–*N* bond of the biaryl were more fruitful. Initial attempts were made with SmI_2 due to our success applying this reagent in the cleavage of this bond in other substrates, though the reagent proved ineffective in this case.[70] Alvarez-Builla reported several accounts of methylating the nitrogen atom of similar ylides and performing

a range of reductive transformations on the corresponding pyridinium salt and cleaving the *N–N* bond.[72,73] The ylide methylation proceeded smoothly employing iodomethane in acetone at reflux overnight (**Scheme 30**). The resulting pyridinium salt was then subjected to several hydride sources (Et_3SiH, LAH, $NaBH_3CN$), though no conversion of the starting material was observed. In Alvarez-Builla's accounts, they described the use of HCO_2NH_4 as a hydride source in the presence of Pt/C as being effective for the cleavage of the *N–N* bonds of pyridinium salts.[72] These conditions proved effective in providing the 2-phenylpyridine. Other reported conditions were also attempted in order to provide a variety of possible conditions and thus give flexibility towards functional group tolerance. Radical cleavage by tristrimethylsilyl silane and AIBN proved equally effective,[73] as was zinc dust in acetic acid.[73] Given the latter could be performed at room temperature the scope of the *N–N* cleavage was then considered. Ylides **23**, **34**, and **35** all provided the 2-phenyl heterocycles in good yields over the two steps (**Scheme 30**). 2-Phenyl quinolinium ylide **33** gave poor yields, though this is believed to be related to the poor stability of the compound, and other reduction methods were not attempted, as they required elevated reaction temperatures.

Scheme 30. Efforts towards cleaving *N*–*N* bond.



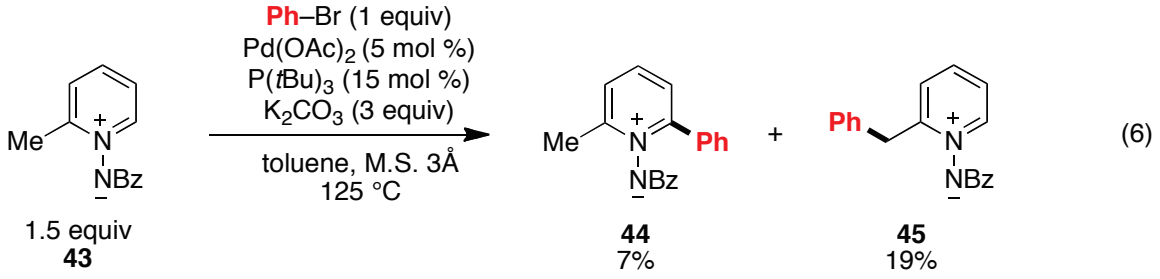
In 1975 Sainsbury and co-workers described the addition of KCN in presence of NH_4Cl to 1-(*N*-methylacetamide)pyridinium salts en route to the synthesis of 4-cyanopyridine derivatives.[74] To date that process had not been applied to the benzoyl salts, and given the similarities between the two pyridinium species it was reasoned that the reaction should proceed. Indeed this was determined to be true as 2-phenyl-4-cyanopyridine **42** was obtained in 69% yield when water was used as the reaction medium (Eq. 5). Given the incomplete solubility of the salts in water, methanol and methanol/water mixtures were attempted to improve solubility, though this proved to be detrimental to the yield of the reaction.



2.3 Direct Benzylic Arylation of 2-Alkyl *N*-Iminopyridinium Ylides

2.3.1 Reaction Optimization and Scope

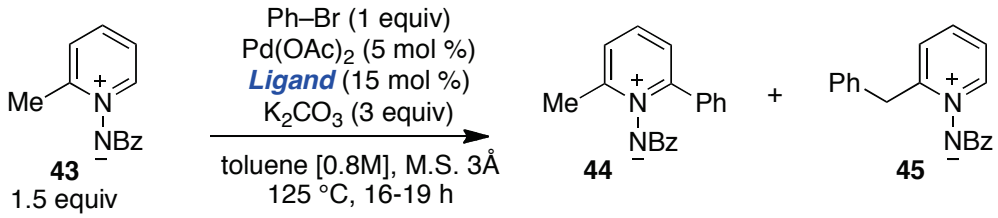
During the course of our direct arylation studies, it was noted that the 2-picolonium ylide **43** gave a marked decrease in the yield for the expected product **44** (Eq. 6). Investigation of this found that the arylation of the benzylic position was indeed preferred, giving product **45**. Not only did these results add to one of the few examples of direct arylation of sp^3-sites, they provided for facile access to these privileged motifs. Excited by this we pursued the optimization of the reaction conditions.[75]

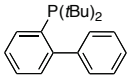
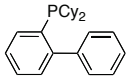
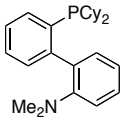
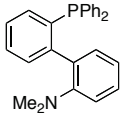


Several *N*-heterocyclic carbene (NHC) complexes failed to provide any conversion to the desired product (**Table 5**, entries 1-3), though bulky, monodentate, electron-rich phosphines generally provided encouraging results. Tricyclohexylphosphine only provided 7% of the desired product (entry 4), though (2-biphenyl)di-*tert*-butylphosphine, PMe(tBu)$_2$ and CyJohnPhos proved superior to P(tBu)$_3$ (entries 5-8). Interestingly PPh$_3$ provided the desired product in good yield (entry 9) while DavePhos and PhenDavePhos proved to be

the best (entries 10 and 11).[75] However, given the similar yields, low cost, and wide availability of PPh_3, this was chosen as the ligand for the remainder of the optimization.

Table 5. Ligand screening for the direct benzylic arylation of *N*-iminopyrdinium ylides.



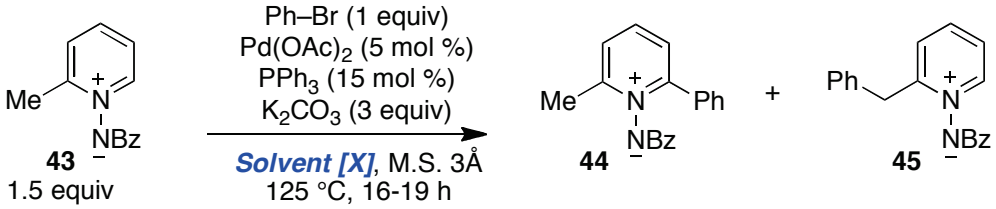
entry	ligand	yield **44** (%)[a]	yield **45** (%)[a]
1	PEPPSI[b,c]	<5	<5
2	$(IMes)_2PdCl_2$[b,c]	<5	<5
3	IMes•HCl[c]	<5	<5
4	PCy_3	<5	7
5	$P(t\text{Bu})_3$	7	19
6		<5	20
7	$PMe(t\text{Bu})_2$	8	33
8		<5	33
9	PPh_3	<5	40
10		<5	83
11		<5	42

[a] Yields are measured by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] $Pd(OAc)_2$ not added. [c] Cs_2CO_3 used in place of K_2CO_3.

We next considered the reaction concentration and solvent. The transformation appeared insensitive to the concentration (entries 1-3) and 0.80 M was chosen for ease of the reaction set-up. Dimethylformamide (DMF) as the solvent provided the best results as

other solvents gave slightly lower yields.[75] This may be due to the increased solubility of the base, facilitating deprotonation and enabling the reaction to proceed. Furthermore, formation of **44** was not observed in any case.

Table 6. Solvent optimization for benzylic arylation of *N*-iminopyridinium ylides.



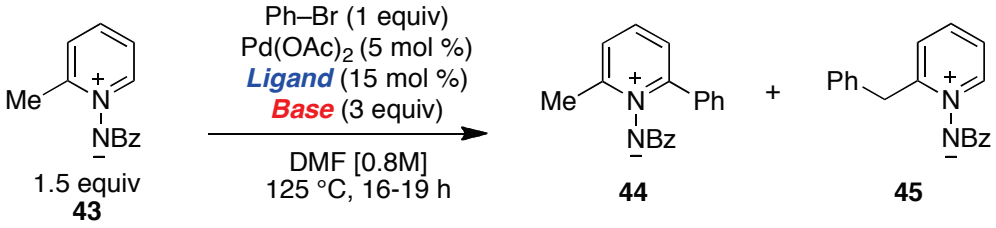
entry	solvent (conc.)	yield **44** (%)[a]	yield **45** (%)[a]
1	toluene (0.40 M)	<5	27
2	toluene (1.5 M)	<5	27
3	toluene (0.80 M)	<5	24
4	DMA (0.80 M)	<5	16
5	MeCN (0.80 M)	<5	17
6	1,4-dioxane (0.80 M)	<5	21
7	DME (0.80 M)	<5	22
8	DMF (0.80 M)	<5	31

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

A survey of bases showed that only alkali carbonates were viable in effectuating the arylation (**Table 7**). Silver carbonate, NaHMDS, KO*t*Bu, and CuOAc were effective in consuming the ylide starting material (entries 1-4), though the resulting side-products could not be identified. Sodium acetate was ineffective (entry 5). An encouraging result was obtained when employing Cs_2CO_3 as the yield was increased to 63% (entry 7). This is likely attributed to the 'Cesium Effect' whereby the large ionic radius and high polarizability allows for easy solvation and formation of naked ions in highly polar solvents such as DMF.[76] These properties give this reagent a basicity much greater than K_2CO_3,

while remaining considerably milder than strong bases such as the *tert*-butoxides.[76] Replacing PPh_3 with DavePhos (12 mol %) increased the yield by 21% and it was found that 1.1 equiv of the ylide relative to the aryl bromide was tolerated (entry 8).[75]

Table 7. Base screening for the direct benzylic arylation of *N*-iminopyridinium ylides.

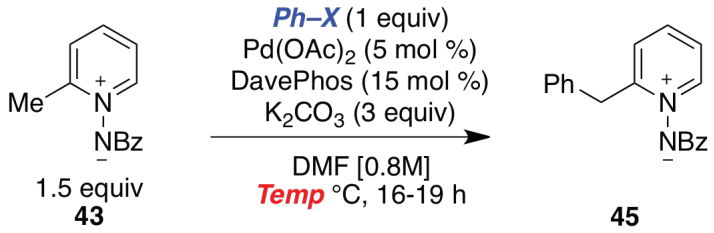


entry	base	ligand	yield **44** (%)[a]	yield **45** (%)[a]
1	Ag_2CO_3	PPh_3	<5	<5
2	NaHMDS	PPh_3	<5	<5
3	KO*t*Bu	PPh_3	<5	<5
4	CuOAc	PPh_3	<5	<5
5	NaOAc	PPh_3	<5	<5
6	K_2CO_3	PPh_3	<5	31
7	Cs_2CO_3	PPh_3	<5	63
8[b]	Cs_2CO_3	DavePhos	10	84

[a] Yields are measured by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] 1.1 equiv of **43** and 12 mol % of DavePhos used.

Bromobenzene and chlorobenzene were both effective coupling partners at 125 ºC giving the benzyl arylated products in 84% and 88% ^{1}H NMR yield respectively (**Figure 7**).[75] Milder conditions were sought and the reaction temperature could be lowered to 70 ºC for aryl clorides while still maintaining 86% yield while the typically more reactive bromobenzene gave poorer results (66%). The reaction was not reproducible with iodobenzene and none of the phenyl halides were reactive at room temperature. The increased reactivity towards aryl chlorides can be attributed to the application of DavePhos, which is well known to be able to oxidatively add into aryl chloride bonds.[77] Coupling

reactions using aryl chlorides has received much recent interest due to the wide availability and low cost of the reagents.



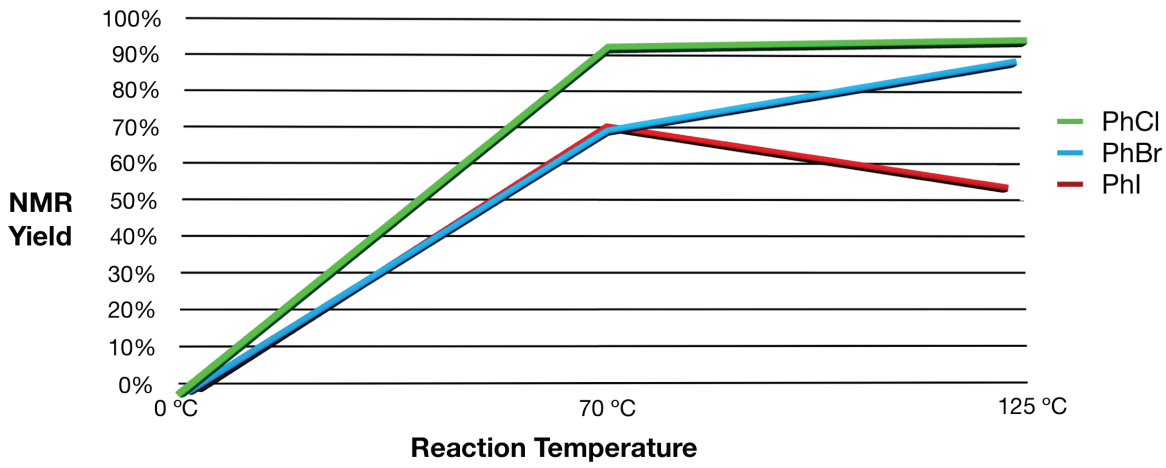


Figure 7. Comparison of phenyl halides at various reaction temperatures.

Finally we studied the conversion of the ylide to arylated product as a function of time (**Figure 8**). This was achieved by analyzing aliquots of the reaction mixture by ^{1}H NMR at designated time intervals. The reaction was deemed essentially complete after 8 h, though it was decided to leave it overnight for ease and efficiency.[75]

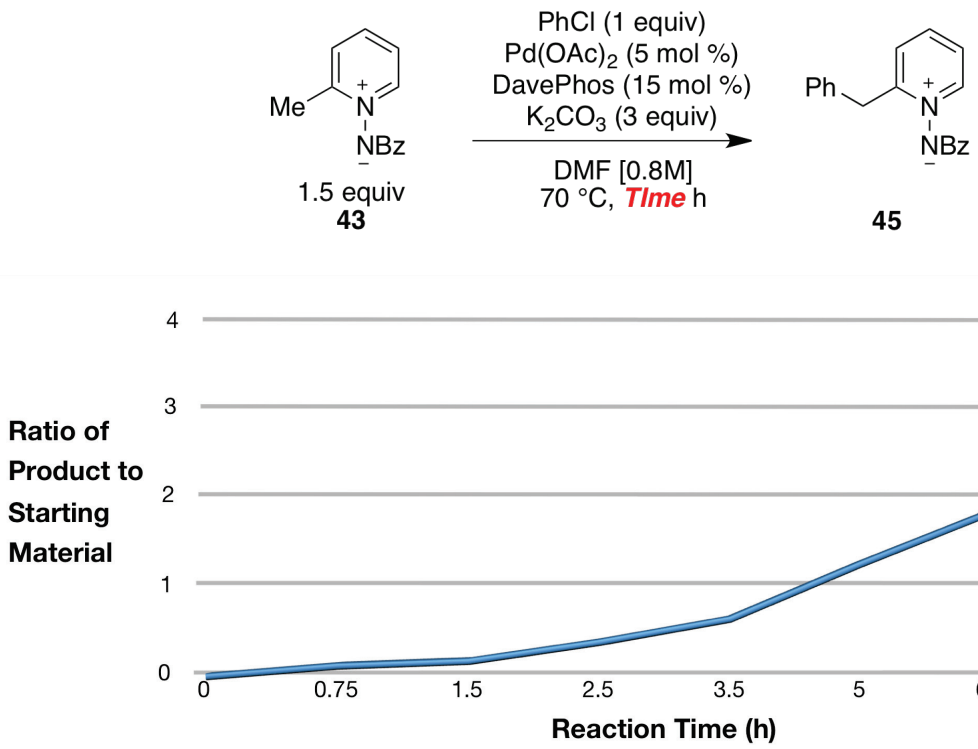
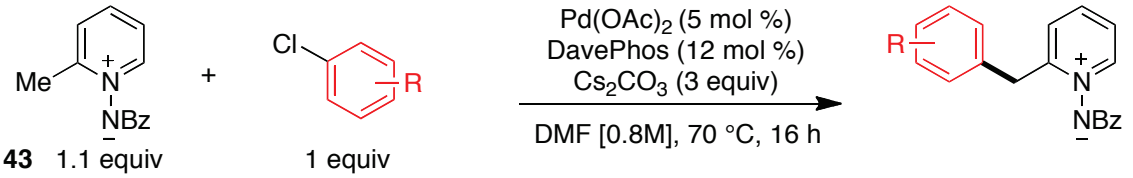
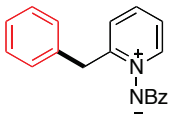
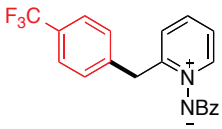
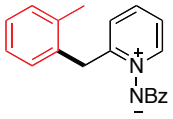
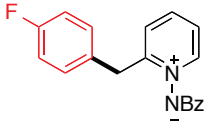
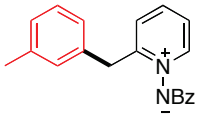
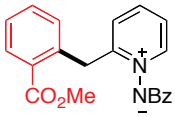
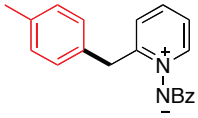
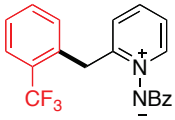
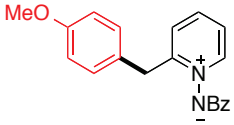
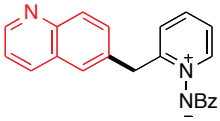
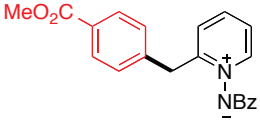
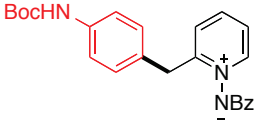
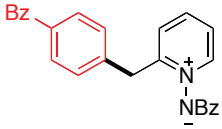


Figure 8. Ratio of product to starting material as a function of time.

Under the optimized conditions we eagerly pursued the scope of the reaction.[75] As seen in **Table 8**, chlorobenzene afforded the desired benzyl arylated product in 86% yield. As evidenced by 2-chlorotoluene (entry 2), steric encumbrance did not hinder the reaction and a range of electron-rich substrates are tolerated (entries 2-5). Most electron-poor substrates reacted with moderate to good yields (entries 6-12), though reagents bearing electron-poor substrates *ortho* to the halide tended to couple less effectively (entries 10 and 11). 6-Chloroquinoline gave poor yields and may be the result of catalyst poisoning by the reagent. Functional group tolerance is broad, permitting ethers, esters, ketones and Boc-protected amines (entry 13). However, free alcohols and amines, as well as nitro and ketone groups bearing enolizable centers remain a challenge. It should be noted that in cases where lower yields are noted the results are attributed to unreacted starting material and not side reactions.[75] As a result, these materials may be recuperated and reused in further transformations.

Table 8. Reaction scope of the aryl chlorides for the sp^3 arylation of **43**.



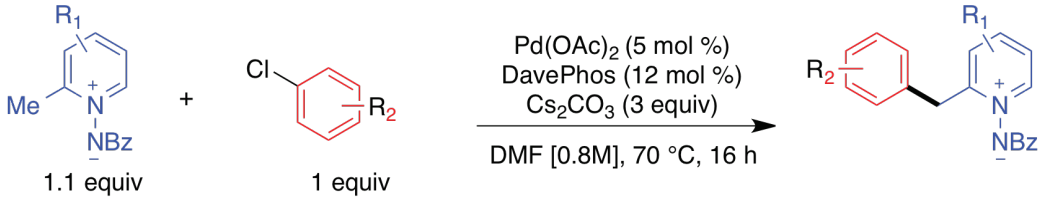
entry	product		yield (%)[a]	entry	product		yield (%)[a]
1		**45**	86	8		**52**	64
2		**46**	93	9		**53**	94
3		**47**	76	10		**54**	43
4		**48**	72	11		**55**	11
5		**49**	69	12		**56**	19
6		**50**	72	13		**57**	48
7		**51**	71				

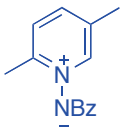
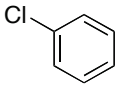
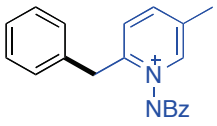
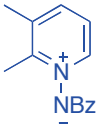
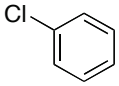
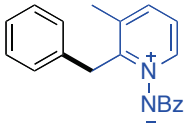
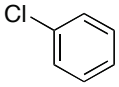
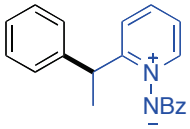
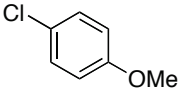
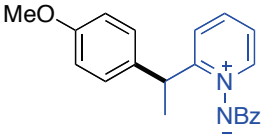
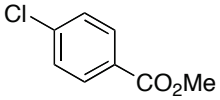
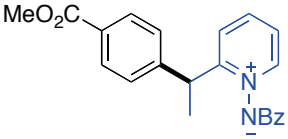
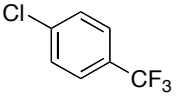
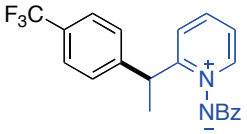
[a] Yield of isolated product.

The reaction conditions were readily transposable to other pyridinium species (**Table 9**).[75] The 2,5- and 2,3-dimethyl ylides reacted exclusively at the expected 2-position

(entries 1 and 2). Interestingly, though electronically equivalent, the more hindered substrate provided the arylated product in higher yield. 2-Ethyl-*N*-iminopyridinium ylide also reacted exclusively at the benzylic site. No side-products from potential β-hydide elimination were observed, and aryl chlorides with electron-rich and poor substituents were tolerated (entries 3-6).

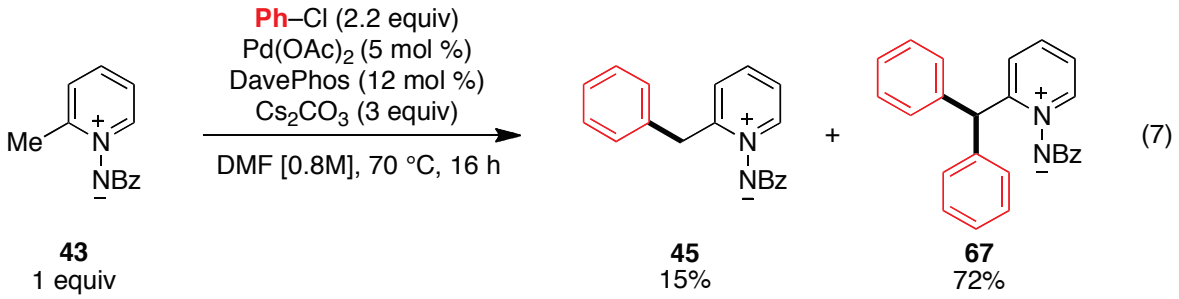
Table 9. Effect of the ylide in the benzylic arylation reaction.



entry	ylide		aryl chloride	product		yield (%)[a]
1		**58**			**61**	43
2		**59**			**62**	92
3		**60**			**63**	86
4		**60**			**64**	79
5		**60**			**65**	53
6		**60**			**66**	69

[a] Yield of isolated product.

It is noteworthy that the double arylation of the benzylic site was formed in a non-reproducible manner in most of these reactions. This side product was easily removed *via* column chromatography.[75] Cognizant of this, we subjected the ylide to the reaction conditions in presence of an excess of chlorobenzene (Eq. 7). This furnished the di-sp^3-arylated product in 72% yield.[75]



43
1 equiv

45
15%

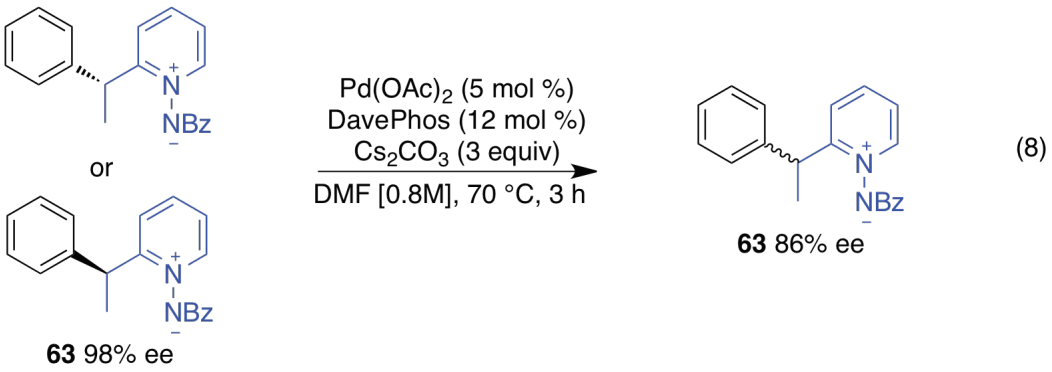
67
72%

2.3.2 Asymmetric Benzylic Arylation of 2-Ethyl-*N*-Iminopyridinium Ylides.

Given the formation of a stereogenic center in products **63**-**66**, we became interested in the possibility of performing the arylation in an asymmetric fashion. A survey of the literature at the time confirmed that this indeed has not yet been reported and further convinced us to investigate the reaction.[78]

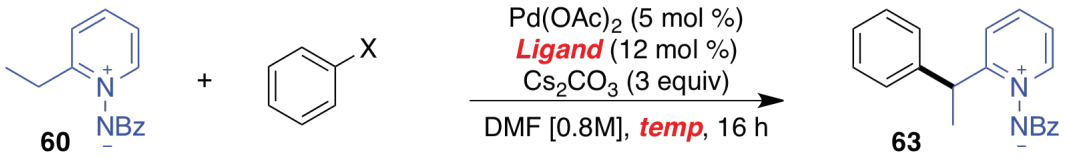
Given the results published by Oshima describing the high acidity of 2-benzyl pyridines (Eq. 3), we were concerned about epimerization of the product under the reaction conditions. Consequently racemic **63** was separated by SFC and the individual enantiomers were submitted to the reaction conditions for 3 h (Eq. 8). Analysis of the resulting ylides demonstrated only 13% ee erosion, suggesting that if the reaction time is kept relatively short, an asymmetric process should be viable. Bearing this in mind several chiral ligands were screened with the focus being on finding a chiral ligand with similar reactivity to DavePhos. Bisoxazoline ligands were inoperative under both palladium and nickel

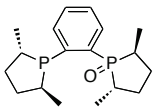
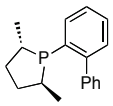
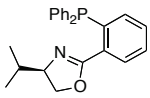
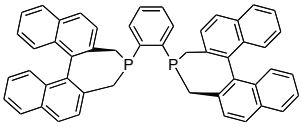
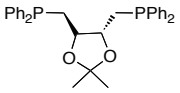
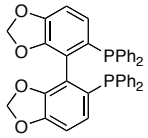
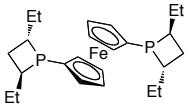
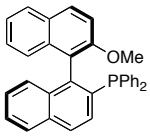
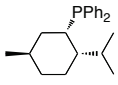
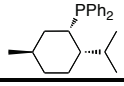
catalysis. MeDuPhos monoxide and PHOX derivatives were unsuccessful at converting the starting materials (**Table 10**, entries 1 and 2). In light of this, the reaction temperature was increased to 110 ºC and bromobenzene was used in place of chlorobenzene in an effort to facilitate the oxidative addition. While BinaPhane did not give the arylated product (entry 3), other bidentate phosphines such as DIOP, SegPhos, and Ferrotane did give some of the arylated product (entries 4-7). Not surprisingly, due to its similarity to DavePhos, MOP gave improved yields (entry 8). The best conversions were found with *S*-NMDPP as yields of 81% were obtained for reactions left for 16 h (entry 9). However, only 10% ee was observed, and even leaving the reaction for 1 h gave the product in 8% yield also with 10% ee, suggesting that ee erosion by the reaction conditions is not an issue (entry 10). To this point results suggested that the transformation with this system would persist to be problematic without a complete design of the catalyst-ligand match. Given advances in other research projects, this research was not pursued further.



(8)

Table 10. Ligand screening for the asymmetric arylation of *N*-iminopyridinium ylides.



entry	ligand	X	temp. (°C)	ee (%)[a]	yield (%)[b]
1		Cl	70	n/a	<5
2		Br	110	n/a	<5
3		Br	110	n/a	<5
4		Br	110	n/a	<5
5		Br	110	n/a	15
6		Br	110	n/a	21
7		Br	110	n/a	22
8		Br	110	0	33
9		Br	70	10	81
10[c]		Br	70	10	8

[a] ee determined via SFC using a Chiralpak AD-H 25 cm column. [b] Yields are measured by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] Reaction time of 3 h.

2.3.3 Proposed Catalytic Cycle

Córdova demonstrated that enamines are suitable nucleophiles in palladium catalysis.[79,80] This was shown through the palladium-catalyzed intramolecular addition of enamines to unsaturated systems. Though a delocalized aromatic system, one can see the possible similarities between imines and the pyridinium system. Deprotonation of the methylene site would lower the energy of the endocyclic nitrogen atom, and the negative charge on the adjacent nitrogen can be delocalized into the more electronegative oxygen atom (**Figure 9**). Furthermore, with an alkyl substituent at the 2-position, one can consider the possibility of forming an enamine-like intermediate under basic conditions. As such, given the elimination of the positive charge on nitrogen atom, a weak base should be able to enable the desired deprotonation of the benzylic site.

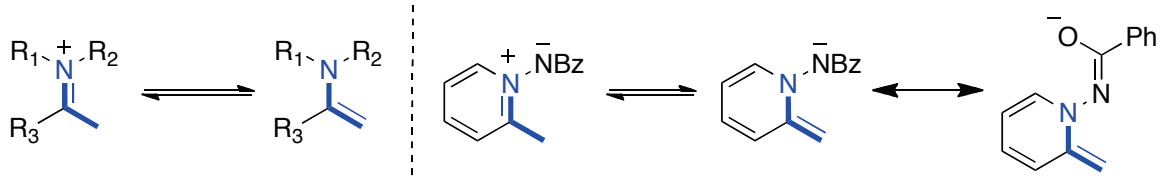
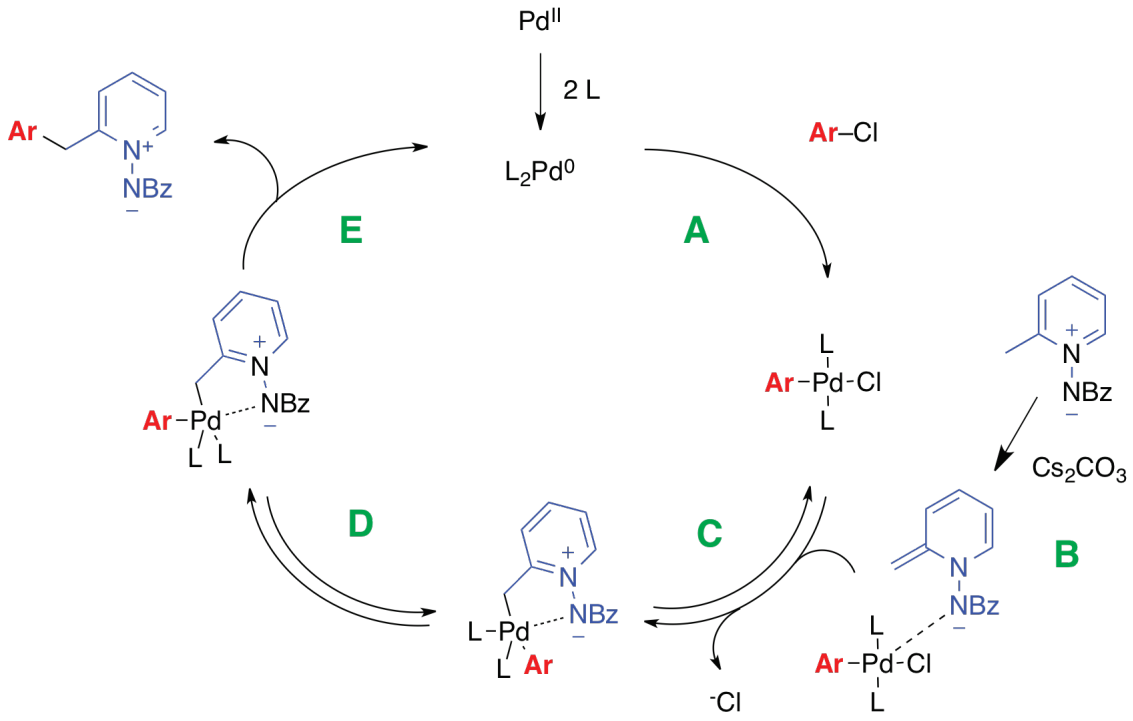


Figure 9. Comparison of enamines to 2-alkyl *N*-iminopyridinium ylides.

The reaction mechanism is believed to proceed as follows (**Scheme 31**). Following reduction of Pd^{II} to Pd^{0} by the phosphine ligand, the catalyst undergoes oxidative addition into the aryl chloride (**A**). Simultaneously the 2-alkyl pyridinium ylide is deprotonated and converted into an enamine-like species (**B**). Presumably there is an excess of this carbon nucleophile in solution as the Cs_2CO_3 is largely soluble under the reaction conditions. The Lewis basic *N*-imino group then coordinates the palladium catalyst bearing the aryl coupling partner and direct carbopalladation (**C**) takes place. *Cis*/*trans* isomerization (**D**) followed by reductive elimination (**E**) then provides the arylated product whilst regenerating the active Pd^{0} catalyst.

Scheme 31. Proposed catalytic cycle for the benzylic arylation of *N*-iminopyridinium ylides.

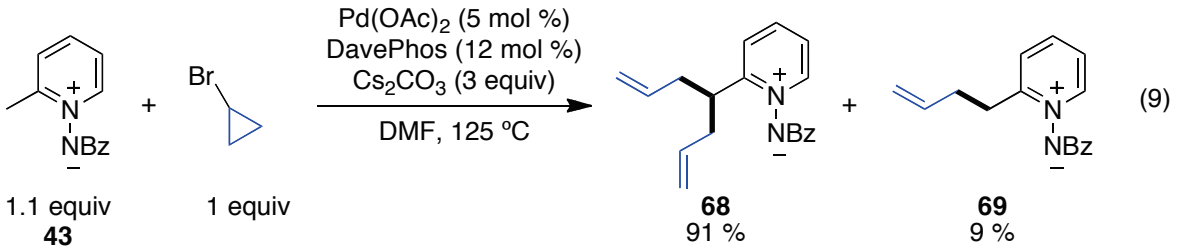


2.4 Direct Allylation of 2-Alkyl *N*-Iminopyridinium Ylides

2.4.1 Origins

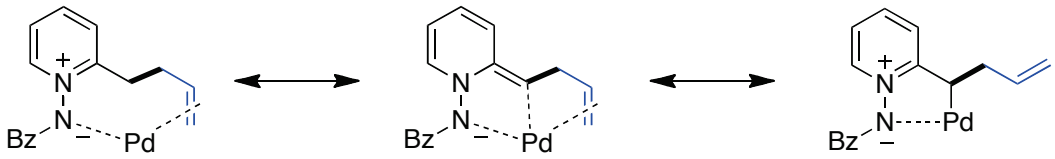
Given the ability of cyclopropanes to undergo cross coupling reactions, in addition to our group's interest in cyclopropane chemistry and our expertise on activated pyridinium species, it seemed reasonable to use a halocyclopropane as a coupling partner in the direct functionalization of 2-methyl-*N*-iminopyridinium ylides. As we disclosed accounts for the synthesis of iodocyclopropane derivatives these substrates were tested first under the optimal reaction conditions for the direct arylation.[81] However, none of the desired product was observed. Given the absence of cyclopropane in the crude reaction mixture we became concerned about the stability of these reagents at elevated reaction temperatures.

Consequently, we attempted bromocyclopropane as a coupling partner, hoping that the reagent would be less susceptible to degradation under the reaction conditions. To our delight the starting material was completely consumed, however the observed product was the bis-allylated ylide **68** (Eq. 9). These products are interesting due to the wide potential of coupling partners, leading to the potential synthesis of a library of interesting and synthetically useful compounds.



Given that halocyclopropanes have been reported to ring open to π-allyl intermediates in the presence of palladium,[82] we reasoned that the electrophilic Pd-π-allyl species could be attacked by the deprotonated pyridinium ylide. The net process would be akin to a Tsuji-Trost allylation reaction.[83] Though heteroatoms are often employed as the nucleophiles, several accounts of carbon nucleophiles, often in the form of enolates, have been described.[83] This fact allows us to propose a potential reaction cycle as follows. Palladium is reduced to Pd^0 and can form the desired π-allyl intermediate. As with the aforementioned arylation (**Scheme 31**), the pyridinium is deprotonated under the basic conditions and the Lewis basic site directs carbopalladation. Reductive elimination provides the product while regenerating the active catalyst. The explanation of double allylation may be the result of coordination of the palladium to both the *N*-iminobenzoyl group and the π-orbitals of the alkene following the first allylation. This 'sandwhiching effect' places the catalyst near the benzylic site, and thus in position for a second carbopalladation (**Scheme 32**).

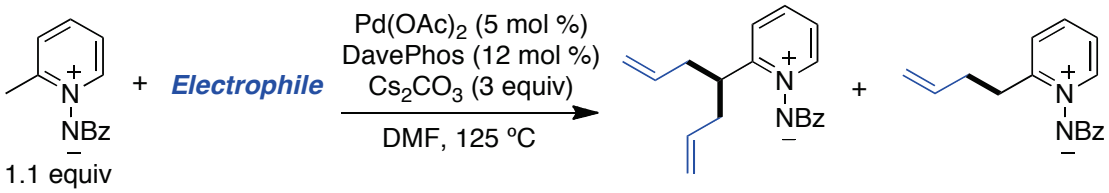
Scheme 32. Possible explanation for the double allylation.

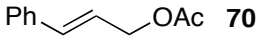
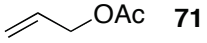


2.4.2 Optimization

The reaction optimization commenced with an effort to find a suitable electrophile as a coupling partner (**Table 11**). While allyl bromide was extremely effective in promoting the reaction, it provided primarily the bisallylated product (entry 1). Efforts to control mono- and di-allylation through excess of either coupling reagent proved detrimental to the reaction. Cinamyl acetate proved more reactive than allyl acetate (entries 2, 3), and a preformed Pd-allyl complex when used in stoichiometric quantity was also operative (entry 4), confirming that this is the likely intermediate in the coupling reaction. Though it provided lower conversion, allyl acetate was chosen to proceed due to its improved selectivity towards mono-allylation, ease of preparation, and the overall green nature of the reagent. It should be noted that allyl alcohol is also a viable partner. Both Tamaru[84] and Nomura[85] demonstrated that Lewis acids can be used to activate allyl alcohols towards Tsuji-Trost processes. A single test did show that Et_3B was effective in activating alcohol in the allylation of the ylide, giving a ratio of 1:1.5:4.9 for **69**:**68**:**43**, however the yields of the reaction were not determined.

Table 11. Pseudoelectrophile screening for the allylation of *N*-iminopyridinium ylides.

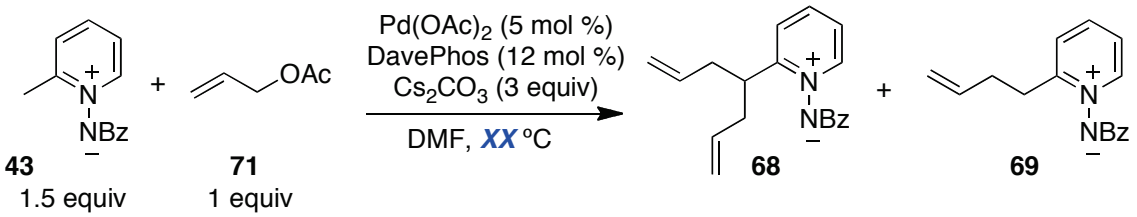


entry	electrophile	yield **68** (%)[a]	yield **69** (%)[a]
1	Allyl Bromide	10	51
2	 **70**	67	17
3	 **71**	39	15
4[b]	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	50	27

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] 1 equiv of the allyl Pd and 1 equiv of DavePhos used.

With a suitable electrophile in hand we first elected to perform a preliminarly screening of reaction temperatures (**Table 12**). The yield increased with decreasing reaction temperature. This may speak towards the stability of the reaction intermediates and was considered an advantage due to potential functional group tolerance and may make the methodology amenable to future asymmetric allylations. Some conversion was noted at room temperature (entry 1), however 40 ºC provided the best results and was used for further optimization (entry 2).

Table 12. Temperature screening for the allylation of *N*-iminopyridinium ylides.

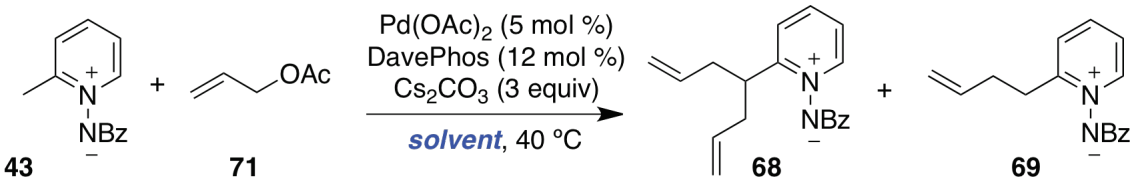


entry	temperature (°C)	yield **68** (%)[a]	yield **69** (%)[a]
1	22	<5	9
2	40	52	33
3	60	35	28
4	80	18	41
5	120	15	35

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Solvent verification noted that ethereal solvents generally provided the best results (**Table 13**). Polar solvents appeared to be necessary (entries 4-7), and this may be due to the increased solubility of the Cs_2CO_3. Though DME provided the highest yield (entry 7) with a combined yield of the two products at 90%, 1,4-dioxane was chosen to proceed as the best selectivity towards monoallylation was observed (entry 3).

Table 13. Optimization of solvents for the allylation of *N*-iminopyridinium ylides.

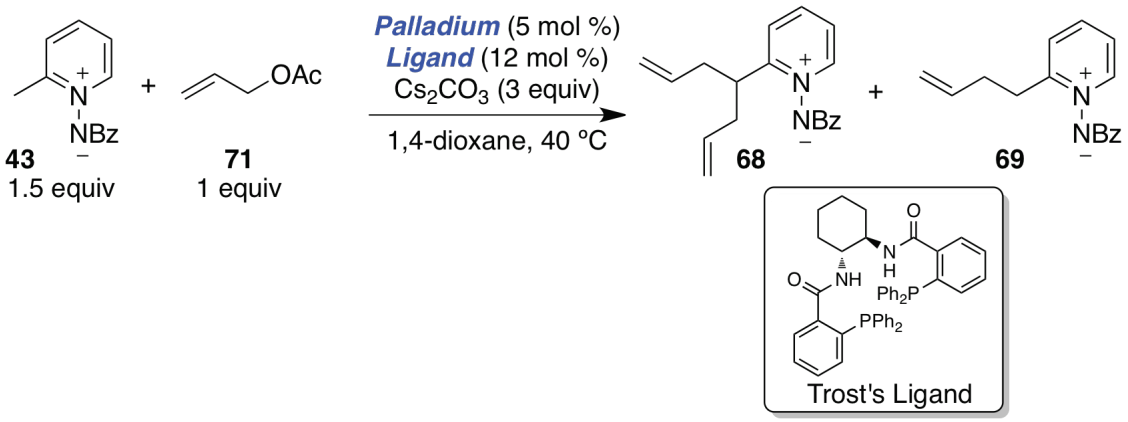


entry	solvent	yield **68** (%)[a]	yield **69** (%)[a]
1	DCM	14	22
2	toluene	12	26
3	1,4-dioxane	11	28
4	DCE	35	37
5	DMF	52	33
6	THF	40	45
7	DME	55	35

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

PEPPSI was unable to catalyze the reaction, suggesting that NHC ligands may not be compatible. Palladium chloride, $Pd(PPh_3)_4$, and PdI_2 all gave low conversion while $Pd(dba)_2$, $Pd(OAc)_2$, and $PdCl_2(NCPh)_2$ provided similar results. $Pd(TFA)_2$ presented an improvement in the yield, and performing the reaction in THF gave not only good yields, but also improved selectivity. A small ligand screen demonstrated that PCy_3 in dioxane also gave good yield, albeit with poor selectivity, while P(*t*Bu)$_3$ and 'Trost's Ligand' were non operative.

Table 14. Screening of palladium and ligand sources for the allylation of *N*-iminopyridinium ylides.

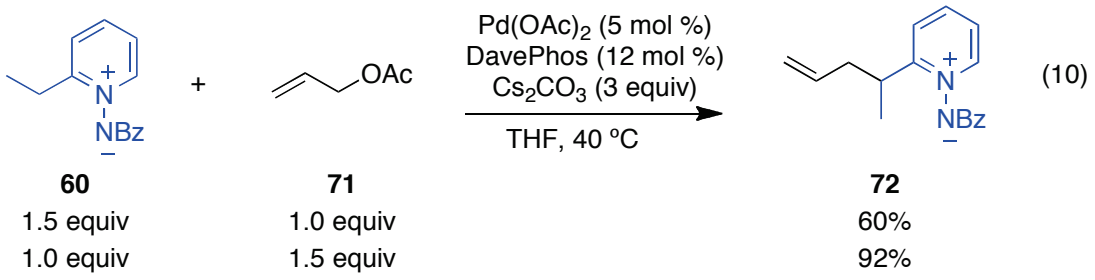


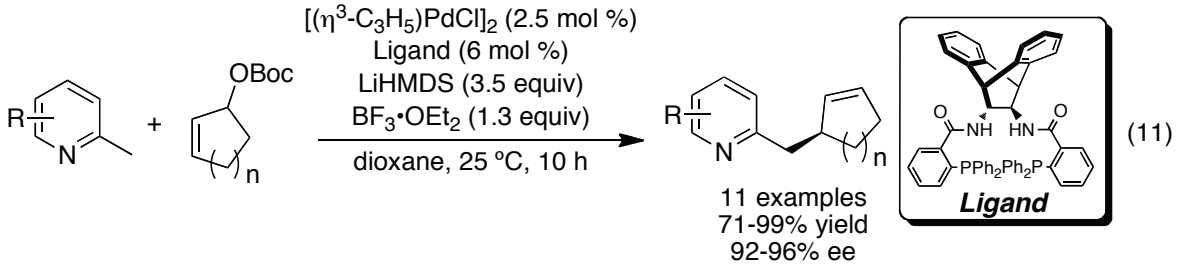
entry	palladium	ligand	yield **68** (%)[a]	yield **69** (%)[a]
1	PEPPSI	DavePhos	<5	<5
2	$PdCl_2$	DavePhos	<5	12
3	$Pd(PPh_3)_4$	DavePhos	<5	16
4	PdI_2	DavePhos	7	12
5	$Pd(dba)_2$	DavePhos	12	26
6	$Pd(OAc)_2$	DavePhos	11	28
7	$PdCl_2(NCPh)_2$	DavePhos	12	28
8	$Pd(TFA)_2$	DavePhos	14	30
9[b]	$Pd(TFA)_2$	DavePhos	18	52
10	$Pd(TFA)_2$	PCy_2	46	38
11	$Pd(TFA)_2$	$P(t\text{Bu})_3$	<5	<5
12	$Pd(TFA)_2$	Trost's Ligand	<5	<5

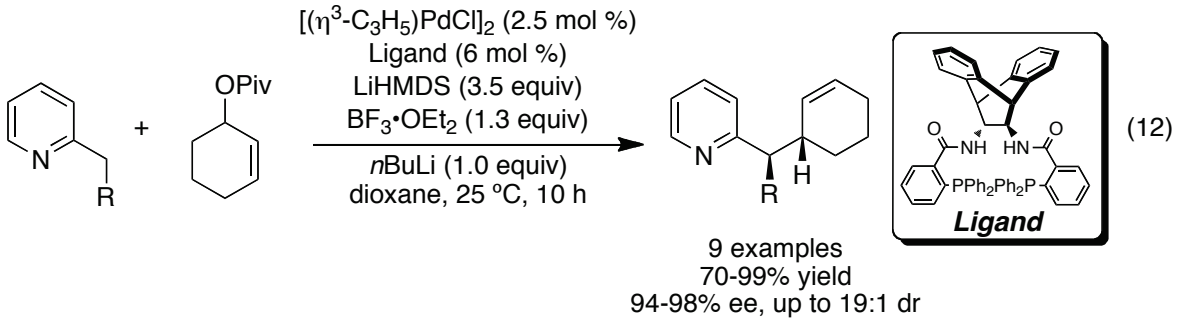
[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Reaction performed in THF.

Finally, a study of the base loading showed that 2 equiv of Cs_2CO_3 was optimal in terms of providing the allylated product with 95% ^{1}H NMR yield, albeit as a 1:1 mixture of the mono- and di-allylated products. No other base was attempted in the reaction.

Given that the 2-ethyl-*N*-iminopyridinium ylide **60** did not give any bis-arylated product, we tested this substrate to see whether monoallylation could be obtained. Indeed this was the only product observed in 60% yield (Eq. 10). Using a slight excess of the acetate provided the allylated pyridinium in 92% yield by ^{1}H NMR. However, at the time of these investigations, Trost disclosed a similar allylation methodology using BF_3•OEt_2 to activate 2-alkyl pyridines towards asymmetric benzylic allylation reactions.[86,87] These reactions were reported to proceed in good yield and high ee (Eqs 11, 12). As a result, given success we were having in other projects (*vide infra*), we chose not to concentrate our efforts on this avenue.



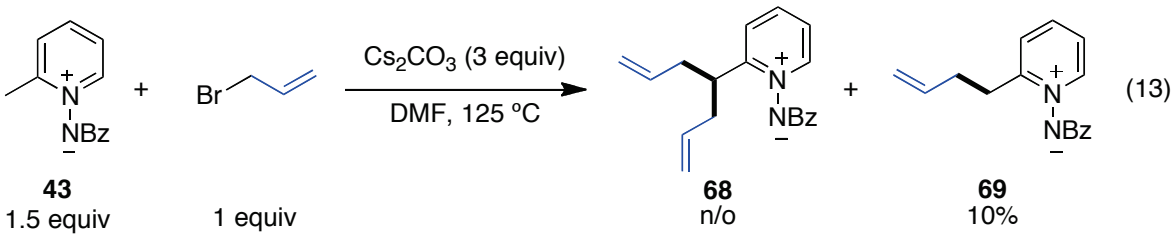




2.5 Alkylation of 2-Alkyl Pyridinium Ylides Through Phase Transfer Catalysis

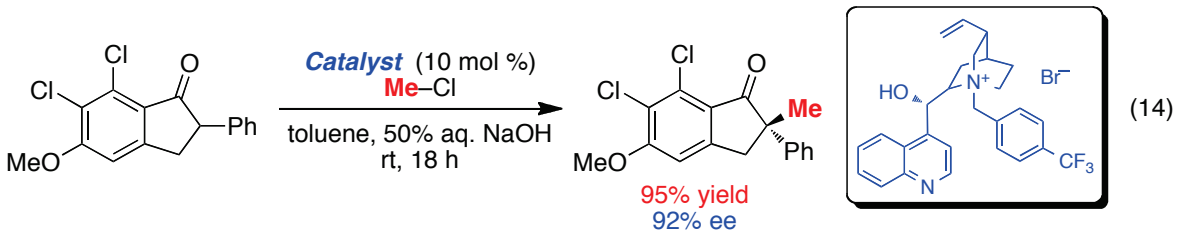
2.5.1 Origins

During the course of the optimization of the allylation reaction, it was noted that at elevated temperatures the 2-methyl pyridinium ylide could be allylated in absence of the palladium catalyst (Eq. 13). It was reasoned that the cesium carbonate is soluble in the DMF at these temperatures, increasing the likelihood of deprotonation. The elevated reaction temperature also provides additional energy to aid in promoting addition onto an electrophile.



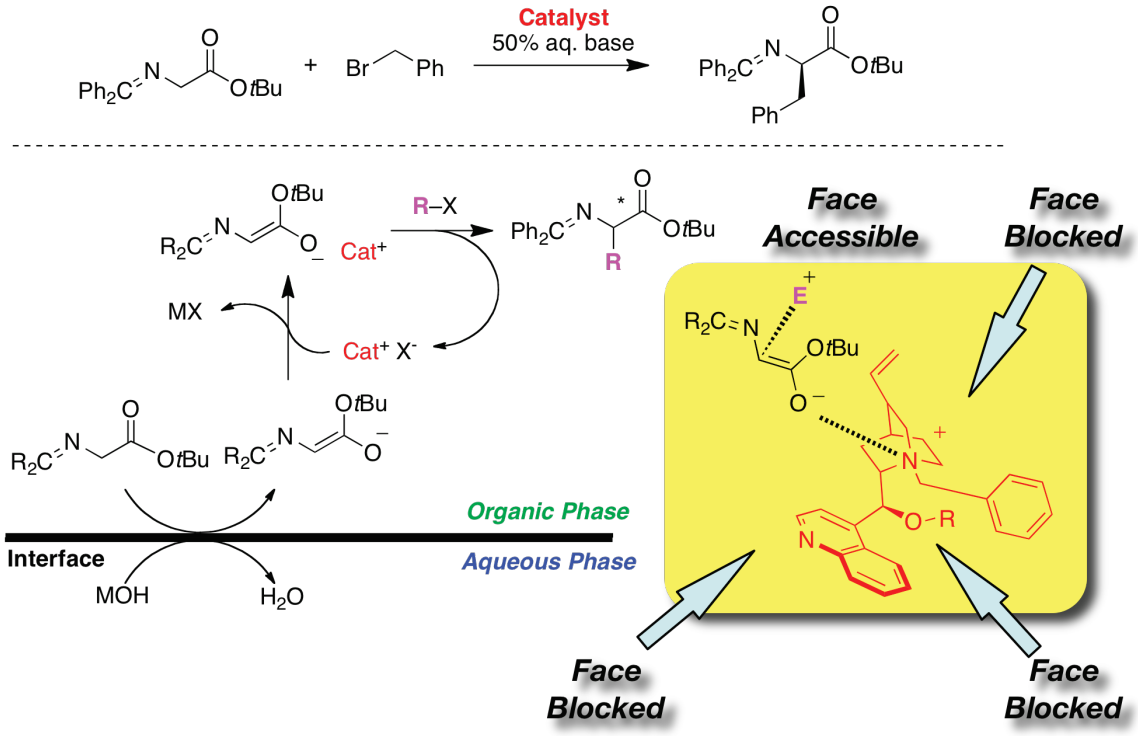
Starks introduced phase transfer catalysis in the 1970s as a tool to effect the alkylation of various carbon nucleophiles.[88] This methodology permits the reaction between reagents in biphasic solutions. As such, relatively benign bases in aqueous solutions can be applied in these transformations, affording a cheaper, greener process. In the 1980s the Merck group applied the use of quartenary ammonium salts derived from readily available, inexpensive cinchona alkaloids in the asymmetric alkylation of indanone derivatives (Eq. 14).[89] Following this report a plethora of ammonium salt catalysts were disclosed. Though various carbon nucleophiles have been described, this methodology has been largely employed towards the synthesis of chiral, non-natural amino acid derivatives through the α-alkylation of glycine Schiff base derivatives.[90] The overall process is believed to proceed as follows.[91] At the interface of the aqueous and organic layers, the nucleophile is deprotonated by the base (**Scheme 33**). The deprotonated base forms an anionic complex

with the quartenary ammonium salt. This complex then reacts with a suitable electrophile, providing the alkylated product with a high-level of stereoselectivity. This selectivity is governed by the facial blocking of the nucleophile with only one site being open for the anionic coordination, and the subsequent approach of the electrophile (**Scheme 33**). Furthermore, in order to ensure reaction selectivity, formation of the anionic complex between the nucleophile and the ammonium salt must be faster than the reaction between the uncomplexed nucleophile and the electrophile, as the latter would lead to the formation of a racemic product.[91]



(14)

Scheme 33. Mechanism for the asymmetric alkylation of Schiff base glycine derivatives.



Given the ionic nature of the pyridinium ylides, and the fact that they are able to undergo alkylation by simple deprotonation, we elected to pursue the asymmetric alkylation of these ylides in presence of cinchona-based phase transfer catalysts. The following section will describe our initial work in this area.

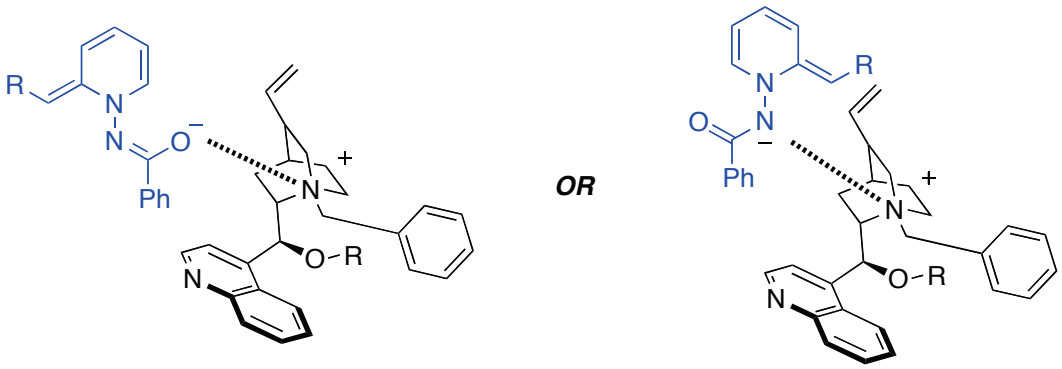
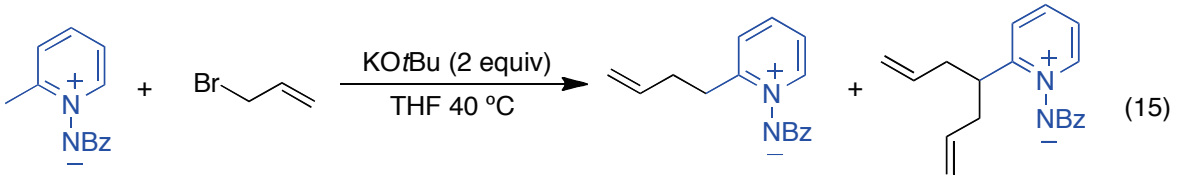
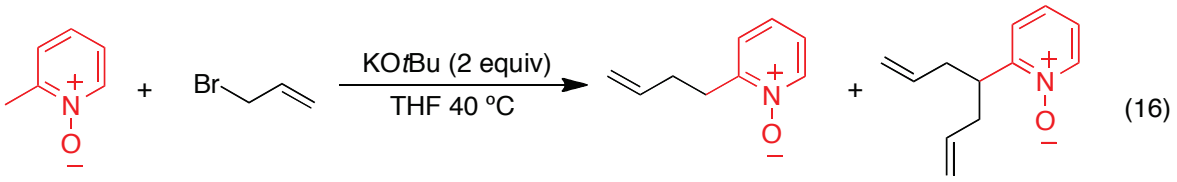


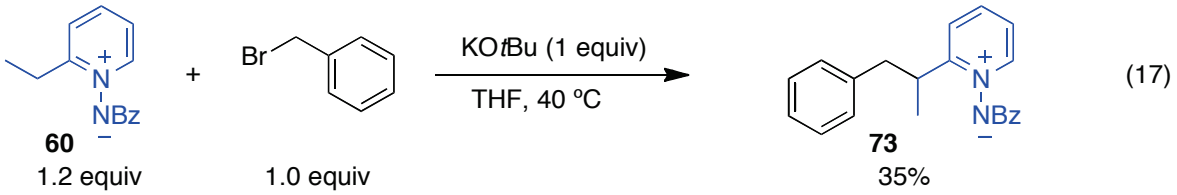
Figure 10. Proposed model for the coordination of the pyridinium to the PTC.

2.5.2 Reaction Optimization

The first task was to determine whether the metal-free alkylation could be achieved under milder reaction conditions. In order to verify this, KO*t*Bu was chosen as a base due to its solubility in polar organic solvents, in addition to its high basicity. Gratifyingly the reaction between the 2-picolonium ylide and allyl bromide proceeded with full conversion of the electrophile, giving a 1:1 mixture of the mono- and bisallylated products (reaction followed by ^{1}H NMR, Eq 15). It is noteworthy that the 2-methyl pyridine *N*-oxide was less effective, giving only 52% conversion (Eq. 16) and 2-picoline proved unreactive. Given that benzyl bromide is a common electrophile in the alkylation of glycine Schiff base derivatives, we tested this electrophile with ylide **60**. The desired product was isolated in 35% yield (Eq. 17).







In collaboration with a summer intern (Guillaume Poutiers), we next considered performing the reaction under phase transfer catalysis (PTC) conditions. A series of known

(-)-cinchonidine-based catalysts were synthesized using standard conditions (**Figure 11**).[92,93,94] Control reactions in absence of any catalyst provided little or no conversion in presence of common hydroxide bases (**Table 15**, entries 1-4). These bases were then used in presence of the four first catalysts prepared (**74-77**). Toluene was chosen as the solvent as it is commonly used in such reactions.[91] Also habitually reported in these reactions is a large excess of the benzyl bromide in order to help promote the reaction. Low to moderate yields for the benzylated pyridinium were obtained. Generally, NaOH (entries 6, 10, 13, 16) and KOH (entries 7, 11, 14, 17) were superior to LiOH (entries 5, 9) and CsOH (entries 8, 12, 15, 18). Though a degree of enantioselectivity was found to be low, it was sufficiently high to encourage us to proceed with screening. Catalyst **75** in presence of NaOH was selected for further testing as it provided the desired product in 62% yield and 21% ee.

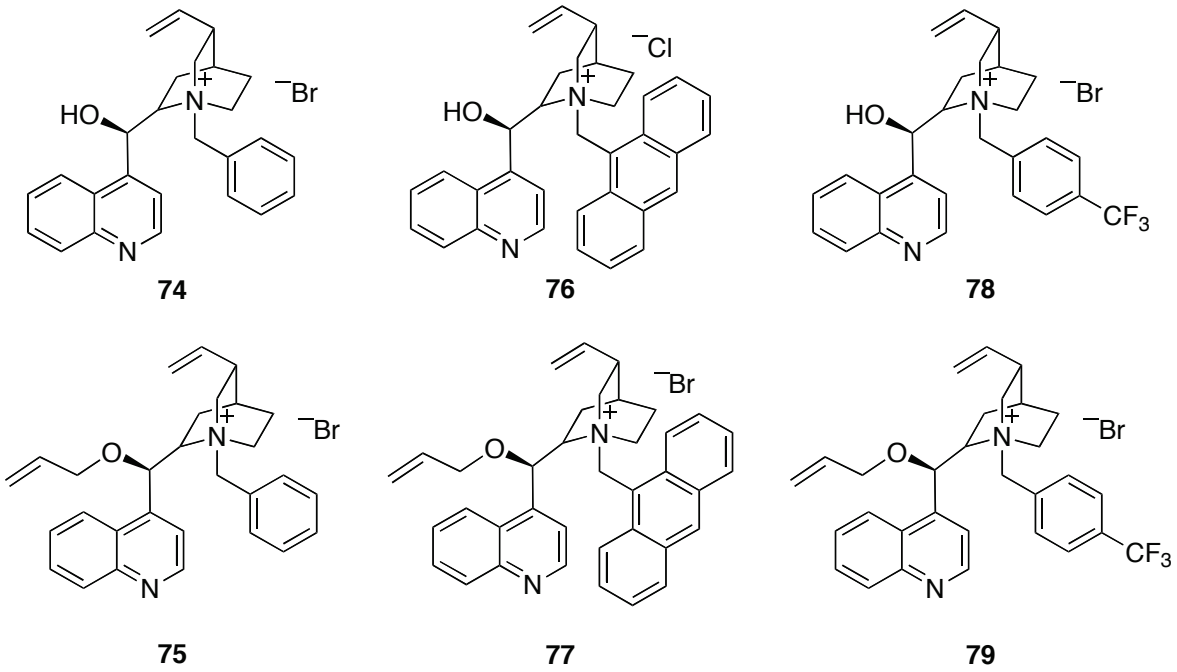
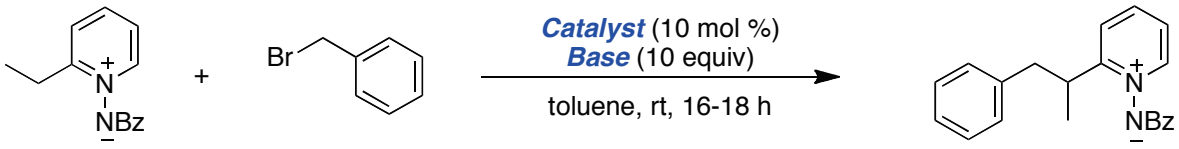


Figure 11. Phase transfer catalysts prepared.

Table 15. Base optimization for the PTC catalyzed alkylation of *N*-iminopyridinium ylides.



60
1 equiv

5 equiv

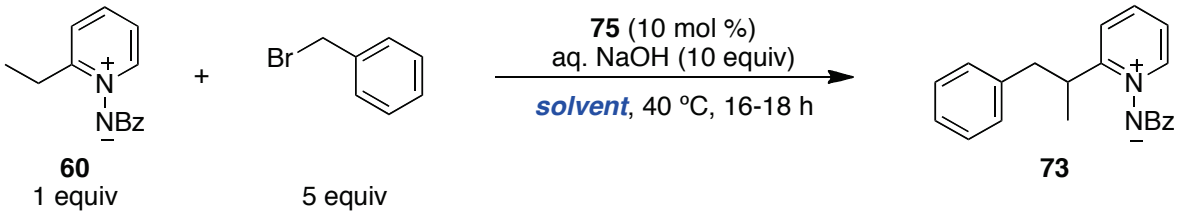
73

entry	catalyst	base	yield (%)[a]	ee (%)[b]
1	-	LiOH	0	-
2	-	NaOH	6	-
3	-	KOH	1	-
4	-	CsOH	3	-
5	**74**	LiOH	0	-
6	**74**	NaOH	57	20
7	**74**	KOH	35	27
8	**74**	CsOH	15	-
9	**75**	LiOH	20	19
10	**75**	NaOH	62	21
11	**75**	KOH	40	19
12	**75**	CsOH	7	18
13	**76**	NaOH	32	14
14	**76**	KOH	19	14
15	**76**	CsOH	5	9
16	**77**	NaOH	17	8
17	**77**	KOH	23	25
18	**77**	CsOH	3	-

[a] Isolated yield. [b] ee determined via SFC using a Chiralpak AD-H 25 cm column.

Toluene proved to be the most effective solvent with catalyst **75** (**Table 16**). Non-aromatic solvents not only gave lower yields, but also had a detrimental effect on the selectivity, suggesting a possible role of π-stacking in the transition state. Chlorinated solvents gave the poorest results (entries 8, 9). When benzene was used in place of toluene, the enantioselectivites were consistent while decreasing the yield of the target compound.

Table 16. Solvent screen for the PTC catalyzed alkylation of *N*-iminopyridinium ylides.

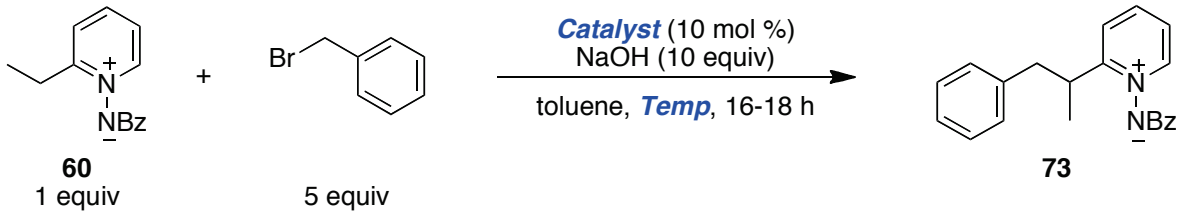


entry	solvent	yield (%)[a]	ee (%)[b]
1	toluene	62	21
2	benzene	29	23
3	DME	43	6
4	ethyl ether	33	11
5	1,4-dioxane	19	7
6	hexanes	27	2
8	DCM	8	2
9	DCE	10	2

[a] Isolated yield. [b] ee determined via SFC using a Chiralpak AD-H 25 cm column.

Lastly we considered the temperature of the reaction and effect of electronics on the PTC. Cognizant that lower temperatures often lead to improved selectivity,[91] we attempted the reaction at 0 ºC, –10 ºC, and –30 ºC. Though the enantioselectivity marginally improved, the product yield dramatically decreased as a function of temperature. Consequently we chose to perform the reaction at room temperature. A small screening of further catalysts found that an electron-withdrawing benzylic group on the amine of the catalyst increased the ee's while slightly decreasing the yield.

Table 17. Temperature and further catalyst screening for the PTC catalyzed alkylation of *N*-iminopyridinium ylides.

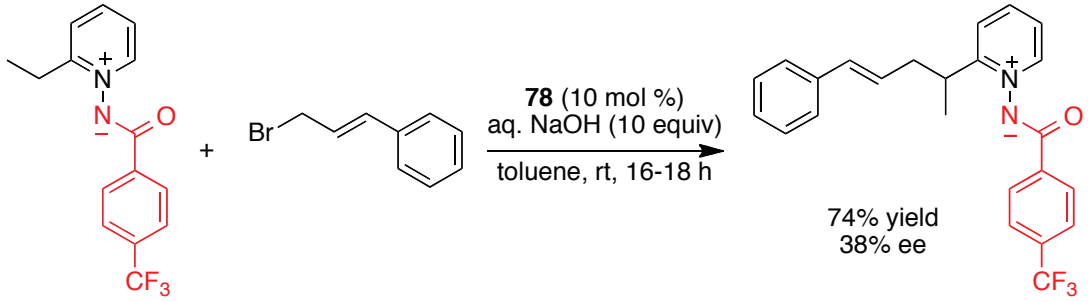


60 1 equiv — 5 equiv — **73**

entry	temperature (°C)	catalyst	yield (%)[a]	ee (%)[b]
1	–30	**75**	9	7
2	–10	**75**	12	27
3	0	**75**	33	22
4	20	**75**	62	21
5	20	**78**	46	30
6	20	**79**	19	14

[a] Isolated yield. [b] ee determined via SFC using a Chiralpak AD-H 25 cm column.

Again, due to progress in later projects, this work was temporarily placed on the side. Recently it has been revived by a current Ph.D. student (Daniela Sustac-Roman), and she has demonstrated that interesting results can be achieved by altering the electronics of the pyridinium ylide (Eq 18). By increasing the electron deficiency of the ylide improved yields and enantioselectivities are observed. The improved yield may be a consequence of the increased acidity of the methylene protons. The improved selectivites are currently under investigation.



(18)

2.6 Summary

In summary were had developed a range of efficient direct methodologies for the elaboration of the pyridine motif. Through the activation of the heterocycle with an *N*-iminobenzoyl group was effected a directed arylation at the 2-position of the pyridine ring. Using this methodology we performed a chemoselective reduction in the synthesis of (±)-anabasine. The 2,6-diarylation however was not achieved, and this is thought to be due to the unfavourable orientation of the directing group following the first transformation. We also demonstrated that the *N*-*N* bond could be easily cleaved in high yield following arylation.

Next we explored the direct benzylic arylation of 2-alkyl *N*-iminopyridinium ylides. Reaction optimization determined that relatively mild temperatures could be employed and a range of aryl chlorides were effective coupling partners. This is of note due to the large commercial availability of these compounds at relatively low cost. The reaction mechanism is believed to proceed through an enamine-like intermediate. While the asymmetric arylation for now seems unlikely without the design of new phosphine ligands, the palladium-catalyzed allylation of this site was discovered. The reaction proceeds at even milder conditions than the arylation and the process is largely optimized.

Lastly, phase transfer catalysis is a viable method to perform metal-free alkylation of 2-alkyl *N*-iminopyridinium ylides. Preliminary results show that cinchonidine-based catalysts can afford the alkylated product in high yields with moderate enantioselectivities.

Chapter 3
Copper-Catalyzed Direct Alkenylation of *N*-Iminopyridinium Ylides

3.1 Introduction

3.1.1 Overview and Conventional Methods of 2-Alkenyl Pyridine Synthesis

Derivatives of 2-alkenyl pyridine are relevant pharmacophores and are an important class of transition metal ligands (**Figure 12**). For example, Singulair© by Merck is a leukotriene receptor antagonist used in the treatment of respiratory ailments and has generated $2.9B in sales in 2008.[95] CGS23113 has been reported to be a potent LTB_4 inhibitor displaying interesting anti-inflammatory properties.[96] The natural product lobelane is a known psychostimulant bearing a piperidine core that can be accessed from pyridine.[97] Other alkenyl pyridines of medicinal interest are metabotropic glutamate antagonists[98] and 5-HT_{2A} ligands that can be used to treat insomnia.[99] As mentioned, these compounds also find applications as ligands for iron and other transition metals, generating precursors that are amenable to C–H insertion processes (**Figure 12**).[100,101] Though this list of utilization is not complete, it does highlight that the 2-phenylethenylpyridine core is a recurring theme in various chemical fields, particularly in medicinal chemistry. Consequently, there has been interest in developing effective methods for their synthesis.

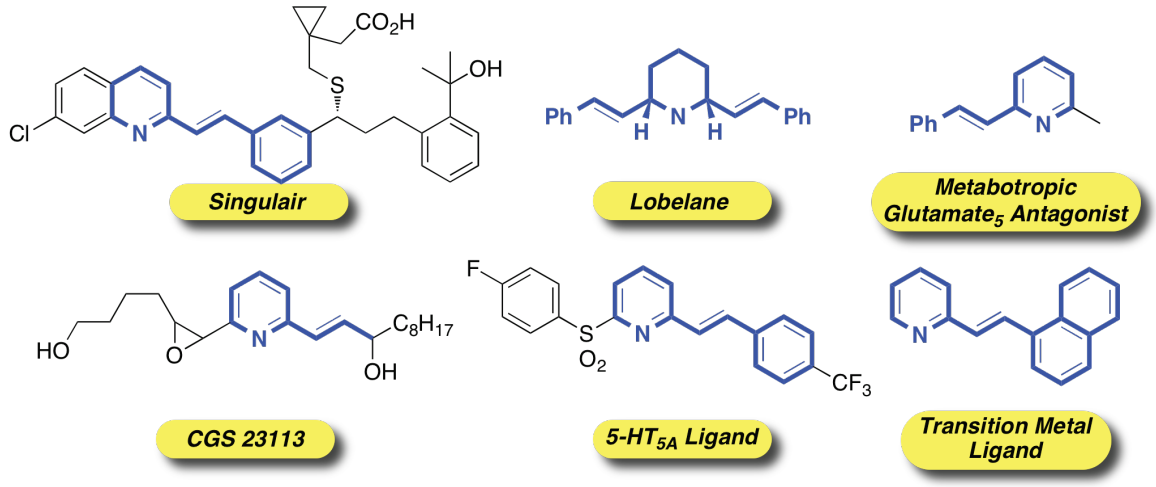
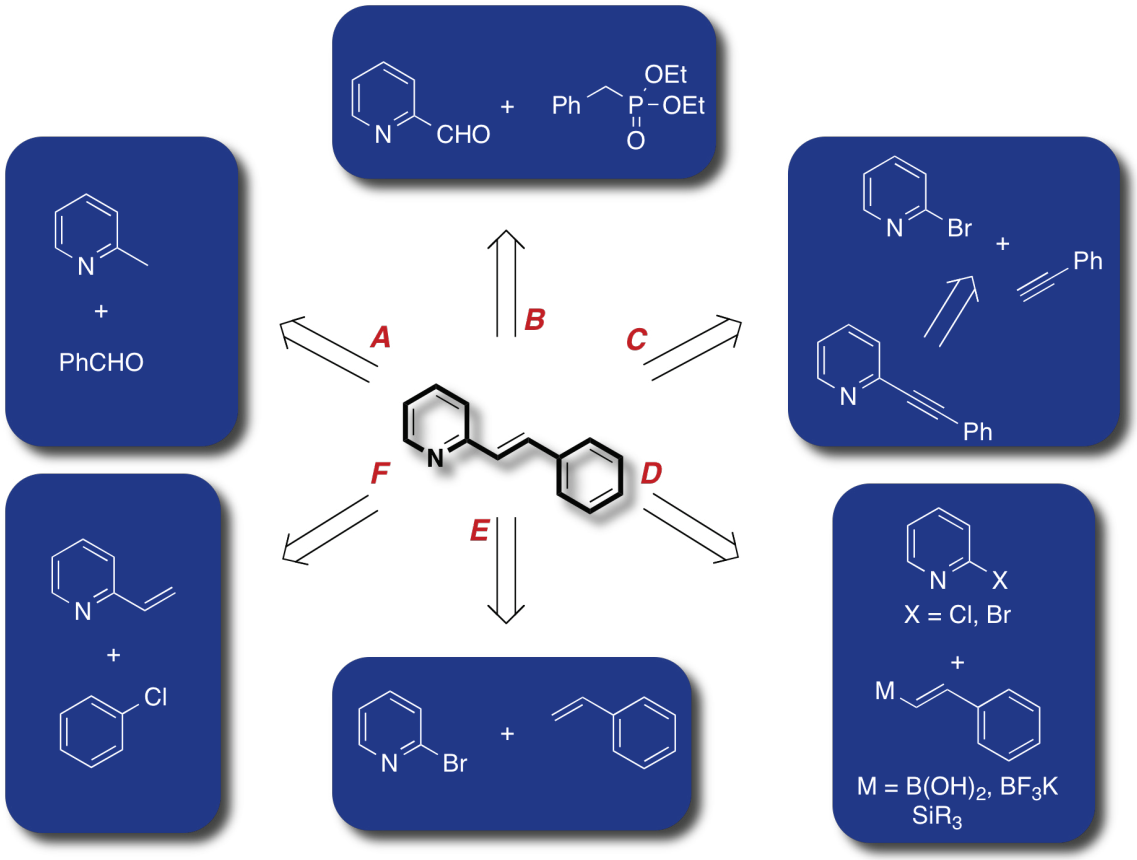


Figure 12. Various 2-alkenyl pyridine derivatives.

Despite their importance, there are relatively few conventional tools available for the synthesis of these privileged compounds (**Scheme 34**). Perhaps the oldest method is through the condensation of 2-picoline with benzaldehyde under strongly basic conditions (route **A**).[100,102] Though this is a reliable method featuring economical materials, the harsh reaction conditions that often involve refluxing in DMSO or acetic anhydride suggest potential functional group incompatibilites. Azzena has described a Horner-Wadsworth-Emmons alkenylation between picolinaldehyde and a prepared aryl phosphonate, though the substrate scope is limited, affording the desired product in moderate yields (route **B**).[103] Other methods rely on expensive late transition metal catalysis. One such account details a Sonogoshira coupling between phenylacetylene and a 2-halopyridine, followed by reduction of the 2-alkynylpyridine to the 2-phenylethenylpyridine (route **C**).[104] This technology depends on the availability of aryl acetylenes and one must consider the cost of various 2-halopyridine derivatives. Molander and others have delineated a Suzuki cross coupling method between 2-bromo and 2-chloropyridines and various vinylboronic acids (route **D**).[105] Though this coupling is very efficient, as mentioned in the previous chapter, it suffers from the drawback in that both partners must be preactivated, initiating potential lengthy syntheses or high costs and invoking large quantities of waste. Finally, Heck-type

coupling between 2-vinyl pyridine and aryl chlorides can give the desired product in moderate yields (route **F**).[106] Although the inverse of this process has also been uncovered, yields remain low (route **E**).[107,108]

Scheme 34. Common ways to synthesize 2-alkenylpyridines.

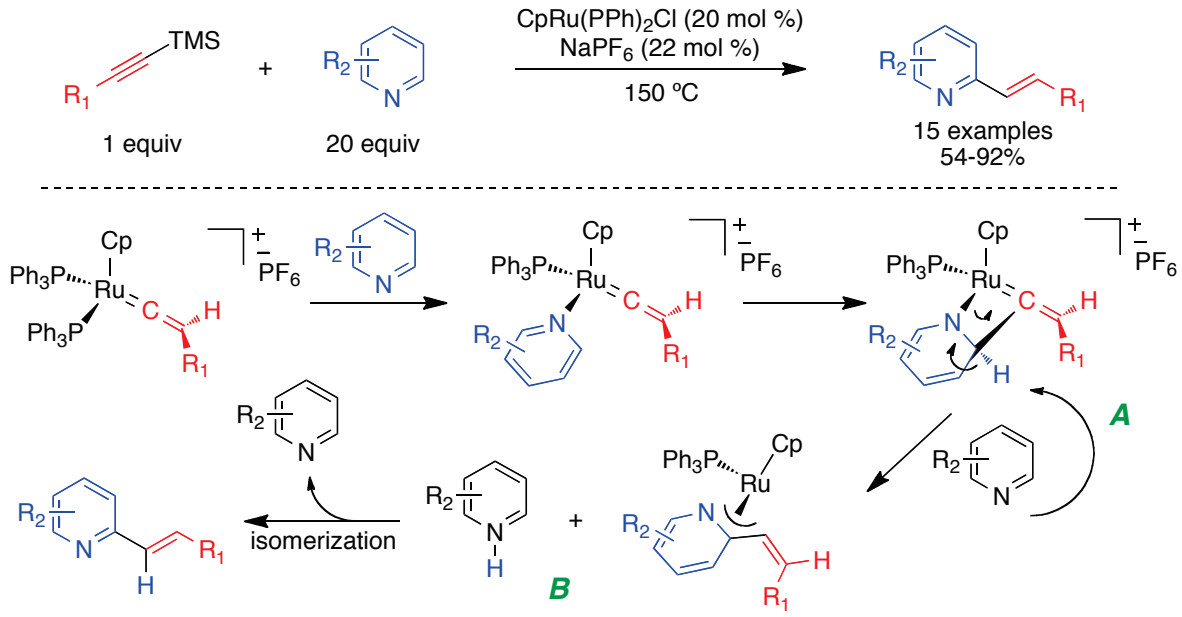


All these reports have positive aspects, however important drawbacks include potential functional group sensitivity, high cost of starting materials, and multistep syntheses of the required starting materials. As such, a more modern route would utilize an economical *direct* approach whereby the α C–H bond of the pyridine would be amenable to the addition of an alkene.

3.1.2 Direct Alkenylation of Pyridine

In contrast to the arylation methodologies described in the previous chapter, the *direct alkenylation* of arenes has received little attention.[109] Moreover, there are scant reports on the vinylation of heterocycles.[110] Of these disclosures, the limited application of pyridine-based heterocycles has received the most attention. Murakami reported the first example of a direct alkenylation with the ruthenium-catalyzed addition of vinylidene complexes to pyridine.[111] The reaction is proposed to proceed as follows (**Scheme 35**). First the cationic ruthenium vinylidine complex generated from aryl trimethyl silyl acetylenes and $CpRu(PPh_3)_2Cl$ undergoes a [2+2] heterocycloaddition with the pyridine to form a 4-membered ruthenacycle complex **A**. Deprotonation of the β-hydrogen atom (**B**) followed by protonolysis gives the observed 2-alkenyl pyridine in moderate to excellent yield.[111] Though this sequence should afford the *cis* alkene, only the *trans* double bond is observed. This was explained by the thermodynamic isomerization of the alkene under the reaction conditions.[111] A possible criticism of the reaction is the limited substrate scope devoid of functionality, and the need of highly elevated reaction temperatures to provide the products in a timely fashion. Nevertheless, this process laid the groundwork for future late transition metal-catalyzed direct alkenylations of pyridine.

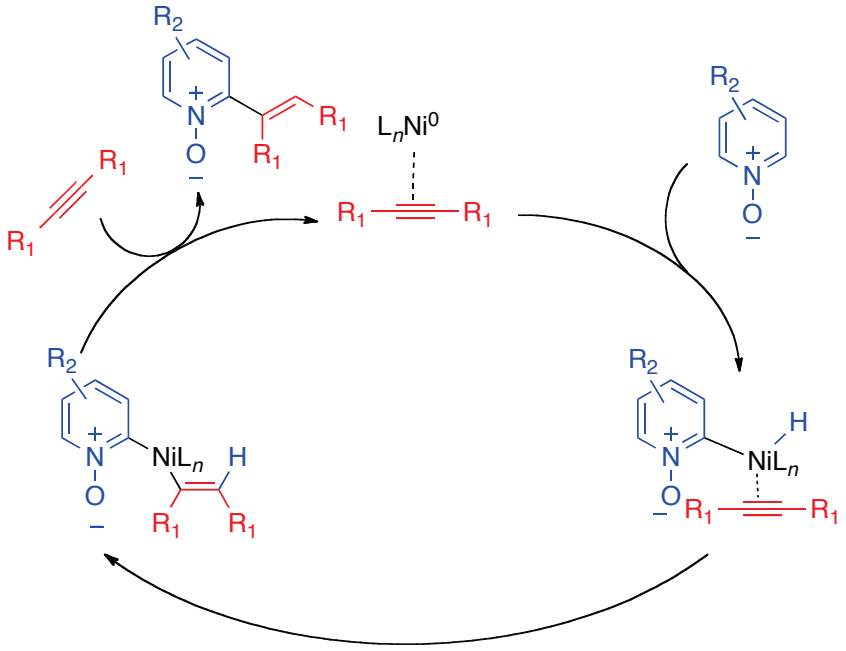
Scheme 35. Murakami's Ru-catalyzed vinylation of pyridine.



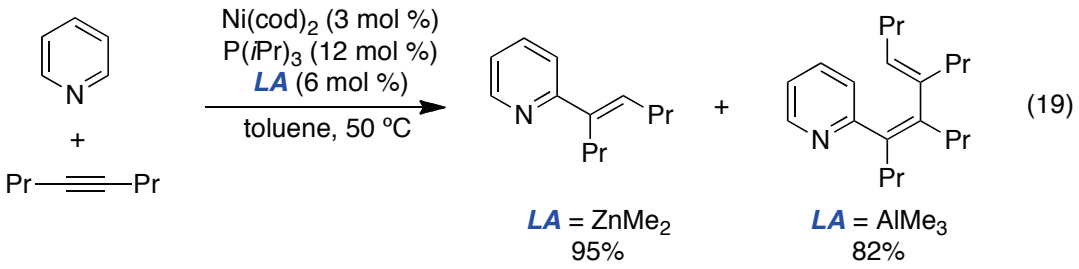
No examples of direct vinylation were reported for the following five years until Hiyama disclosed a Ni-catalyzed hydroalkynylation of pyridines (**Scheme 36**).[112] Prior to this account they had demonstrated that 5-membered electron-rich heterocycles undergo a Ni-catalyzed Fujiwara-type coupling of alkynes in presence of PCy_3 in the synthesis of alkenyl heterocycles. Though pyridine itself was unreactive, they were able to take advantage of the reactivity of pyridine *N*-oxide and effect the addition of alkynes, synthesizing 2-alkenyl pyridines *N*-oxides with high selectivity at low temperature.[112] A range of symmetrical alkynes was tolerated, however no functional groups were included in the scope. Unsymmetrical alkynes bearing groups whereby one is more bulky than the other can be added with complete regioselectivity. Terminal alkynes do not couple, presumably due to the rapid oligomerization, revealing another limitation.[112] Substitution on the *N*-oxide ring is tolerated, but reactions of pyridines bearing electron-withdrawing groups (Cl, Br, NO_2) were said to be sluggish. The mechanism of the reaction is postulated to proceed first through coordination of the nickel to the alkyne. This nickel species then undergoes

oxidative insertion into the pyridinium giving the pyridyl-nickel hydride. Hydronickelation and reductive elimination then gives the 2-alkenyl pyridine *N*-oxide (**Scheme 36**).[112]

Scheme 36. Proposed mechanism for Hiyama's hydroalkynylation of pyridine *N*-oxide.

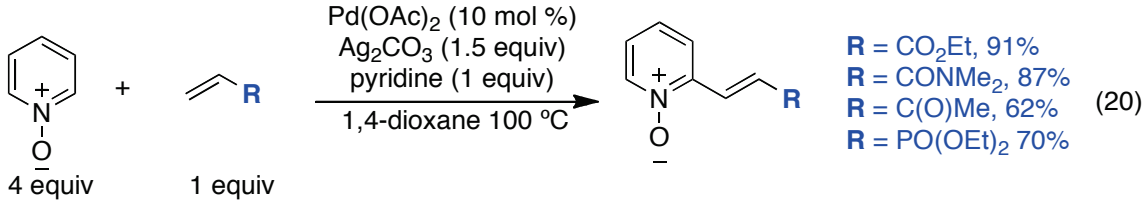


A year later they improved the methodology through the catalytic activation of the pyridine ring.[113] This was attained *via* the addition of a mild Lewis acid (Eq. 19). The inclusion of 6 mol % of $ZnMe_2$, $ZnPh_2$, or $AlMe_3$ was sufficient to generate 2-alkenyl pyridines. Excess of pyridine was needed to avoid 2,6-dialkenylation. The use of a mild Lewis acid was likely needed to enable reversible complexation to the pyridyl nitrogen atom. The zinc Lewis acids provided the mono-alkenylated products whereas the aluminium gave the bis-adduct.[113] Unsurprisingly, based on their results with the *N*-oxide, electron-poor pyridines gave lower yields than electron-rich pyridines. The catalytic cycle is postulated to be similar to the one proposed for the hydroalkynylation of pyridine *N*-oxides.[113]



(19)

Chang described the oxidative addition of alkenes to pyridine *N*-oxides.[114] Pyridine *N*-oxide in presence of $Pd(OAc)_2$, Ag_2CO_3, a pyridine additive, in 1,4-dioxane at 100 ºC gives the 2-alkenylated pyridines in moderate to excellent yields (Eq. 20). The scope of the reaction is largely limited to Heck-acceptors, perhaps giving insight into the reaction mechanism. The *N*-oxide bound palladium complex was synthesized and was found to be inactive in the reaction.[114] This corroborated the fact that the *N*-oxide group does not play a role in directing the reaction, and that the site selectivity is likely due solely to electronic activation, as reported by Fagnou and Gorelsky.[52] The role of the pyridine additive is not fully understood, but given its replacement with K_2CO_3 leads to only a modest drop in yield suggesting it acts as a weak base. Finally, arylation with benzene is also possible under the same reaction conditions, giving the 2-phenyl pyridine *N*-oxides in moderate to good yield.[114] A year later Wu reported a similar version of this alkenylation with quinoline *N*-oxides without the inclusion of an external oxidant.[115]

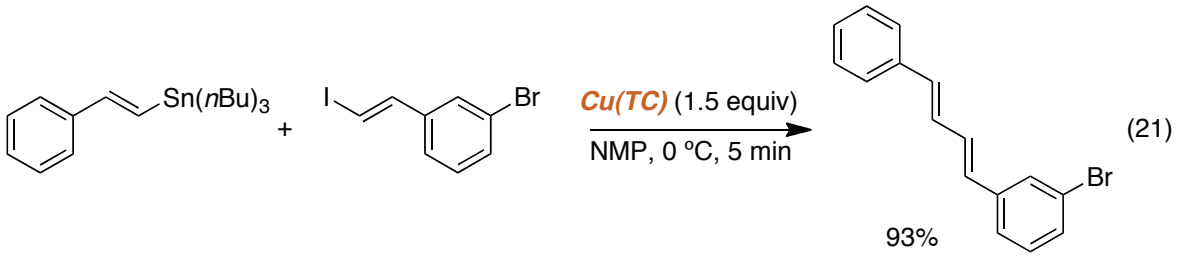


(20)

3.1.3 Copper-Catalyzed Direct Functionalization

The well-known Ullmann reaction is the first transition metal-mediated process for the synthesis of bi-aryl compounds (*vide supra*).[6] However, due to limitations in the

preparation of unsymmetrical compounds, the elevated temperatures typically required, and the advent of palladium as well as nickel-catalyzed cross coupling chemistry, the catalytic application of copper catalysts have been largely put on the wayside. This is despite their typical high stability, low cost, and low toxicity relative to palladium and nickel.[8a] In the mid-1990's Liebeskind divulged a copper-mediated Stille-type cross coupling reaction (Eq. 21).[116] The reaction could be employed at low temperature, providing an inexpensive and highly active catalytic system. This work laid the foundation for work towards replacement of expensive metal catalysts, and copper has been since applied in various other cross coupling reactions,[117] amination reactions (even bearing ppb levels of copper),[118,119,120] and has been applied in the synthesis of various heterocycles.[121] Though progress has been made in the application of copper catalysts in more traditional processes, it can be argued that the use of this reagent still lags behind less sustainable palladium and nickel systems.

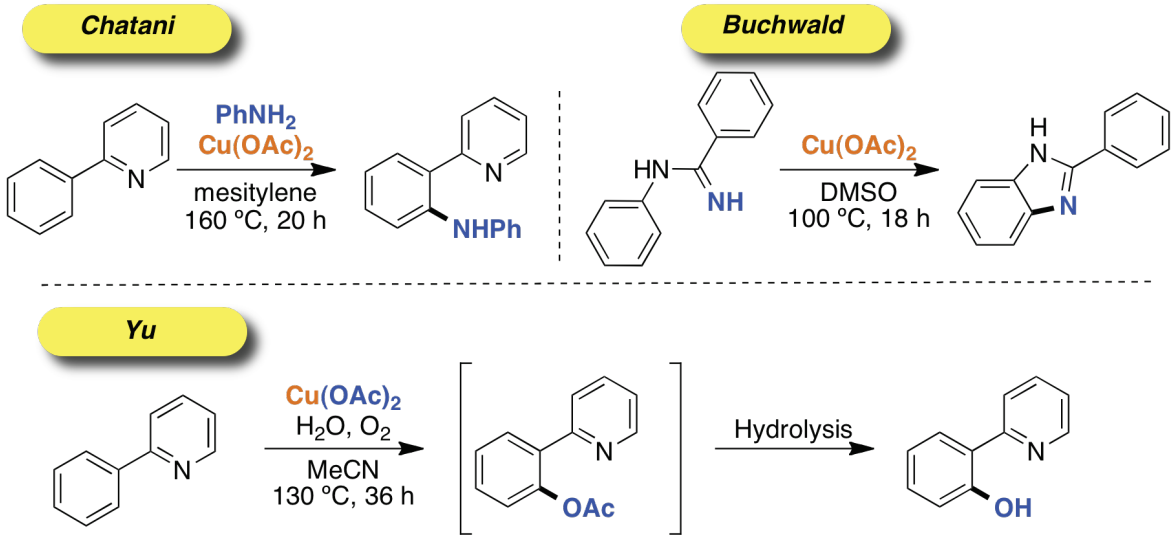


(21)

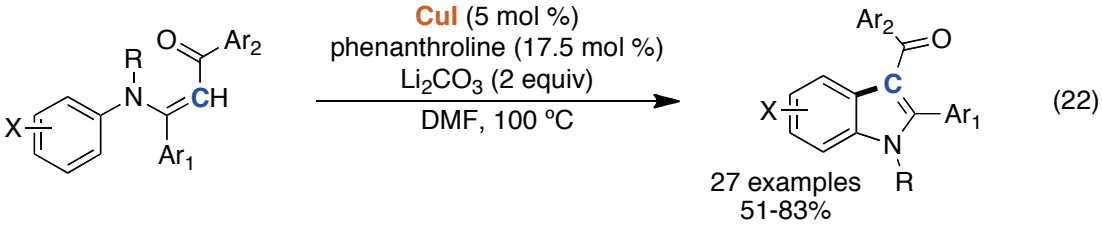
Perhaps due to the increased familiarity of the metal as a result of cross coupling technology, palladium has dominated the domain of C–H functionalization chemistry.[8c,13] Consequently, less costly copper and iron catalytic systems are seldom reported. A summary of copper applications can be seen below. Perhaps one of the first examples of aromatic C–H derivation is the directed *ortho*-amination of 2-phenylpyridines by Chatani (**Scheme 37**).[122] The reaction employs inexpensive $Cu(OAc)_2$, though necessitates refluxing in mesitylene and the reported functional group scope is limited. Two years later Buchwald reported an intramolecular amination with amidines to form a range of benzimidoles using the same copper source, though this time as a catalyst (**Scheme 37**).[123] The reaction was performed at 100 ºC, required an O_2 atmosphere, and delineated a large

substrate scope. Similar to amination reactions, Yu applied conditions employing stoichiometric copper in the directed oxygenation of 2-phenylpyridine (**Scheme 37**).[124]

Scheme 37. Copper-catalyzed direct amination and hydroxylation reactions.



Cacchi described an interesting C–C bond formation process through the synthesis of multisubstituted indole skeletons from *N*-aryl enaminones.[125,126] The reaction engaged a CuI/phenanthroline catalytic system, in presence of Li_2CO_3 in DMF at 100 ºC (Eq. 22).

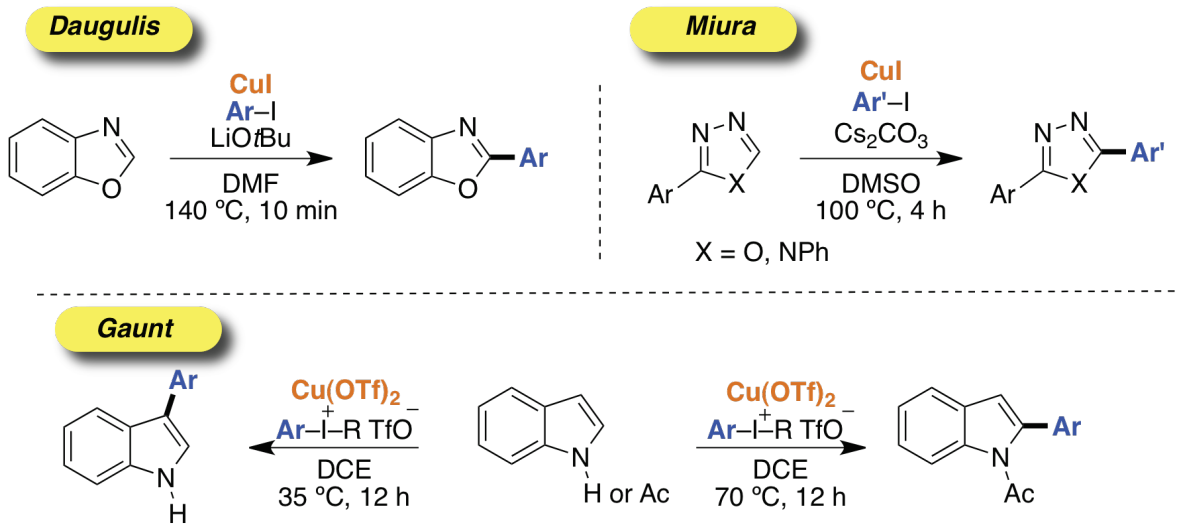


(22)

More pertinent to our research interests are copper-catalyzed direct arylation reactions. Electron-rich heterocycles have been most used in these methodologies. In 2007 Daugulis detailed a CuI catalyzed arylation of benzoxazole derivatived with aryl iodides (**Scheme 38**).[57] Both KO*t*Bu and LiO*t*Bu could be applied as bases, with the former initiating a likely benzyne intermediate during the course of the reaction. This reaction was

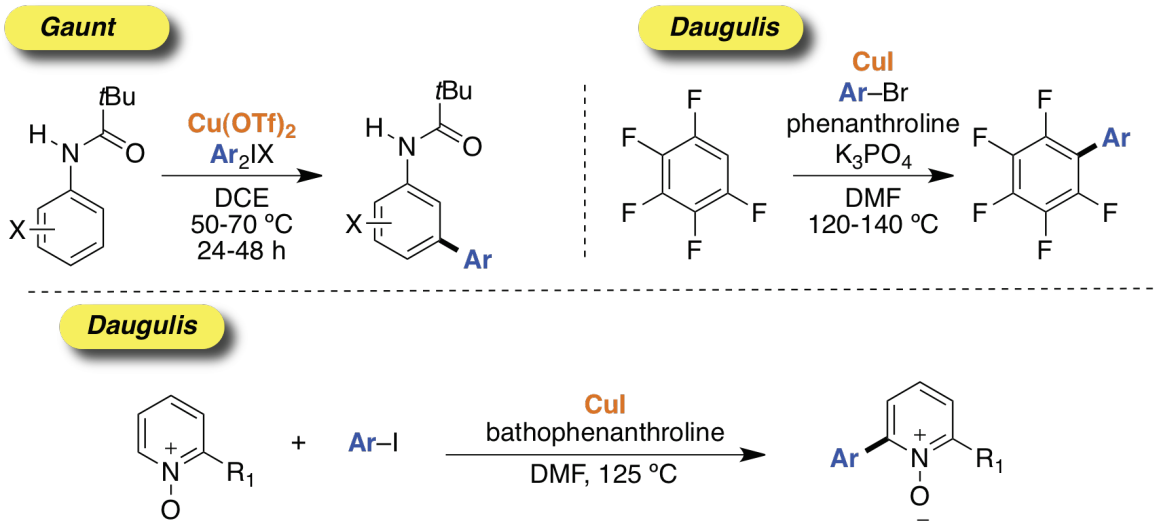
used by You in the arylation of caffeine en route to the synthesis of fluorescent probes.[127] Not surprisingly, as reported by Miura, 1,3,4-oxadiazoles and 1,2,4-triazoles couple with aryl iodides effectively, though PPh_3 is needed in addition to the copper catalyst (**Scheme 38**).[128] Gaunt communicated an elegant arylation of indoles with aryl iodonium salts in presence of a catalytic amount of $Cu(OTf)_2$ (**Scheme 38**).[129] They displayed exceptional control of the arylation of the *C2* and *C3* sites by tuning the substitution of the endocylic nitrogen atom.

Scheme 38. Copper-catalyzed direct arylation reaction with electron-rich arenes.

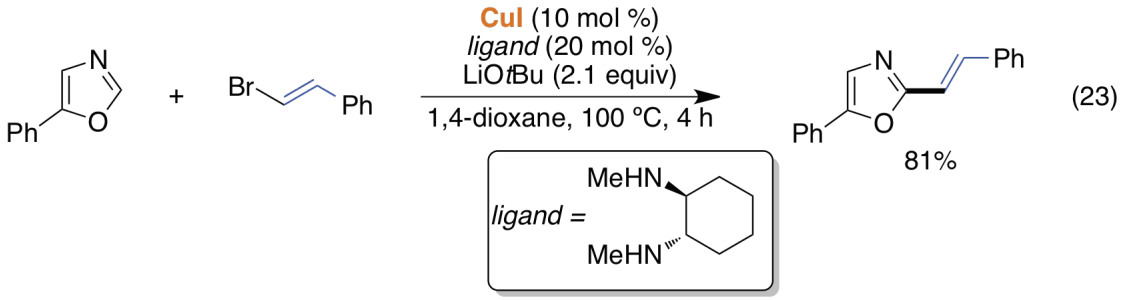


Gaunt followed this account with the first example of a *meta*-selective direct arylation.[130] Anilides could be arylated *meta* to the functional group by aryl iodononium salts under copper catalysis (**Scheme 39**). Not only does this go against electrophilic aromatic substitution as the anilide group is *ortho*- and *para*-directing, similar *palladium*-catalyzed C–H arylation occurs *ortho* to the group presumably due to directing effects.[58] Daugulis reported the arylation of perfluoroarenes under mildly basic conditions (**Scheme 39**).[131] Germane to the topic at hand, he also uncovered the copper-catalyzed direct arylation of pyridine *N*-oxides.[57] The reaction is believed to proceed primarily due to the relative high acidity of the α-protons of the pyridinium ring (**Section 1.3.3**).

Scheme 39. Copper-catalyzed direct arylation of electron-poor arenes.



Piguel exposed the only example of a direct alkenylation in 2008 (Eq. 23).[132,133] They established that oxazoles could be alkenylated by vinyl chlorides, bromides, and iodides in presence of a catalytic system composed of CuI and trans-*N,N'*-dimethylcyclohexane-1,2-diamine. As with Daugulis, LiO*t*Bu was employed as a base. The scope of the reaction tolerated a wide range of functionalities, giving the products in good to excellent yields.



3.1.4 Research Goals

Given the above summary, there remains a challenge in synthesizing 2-alkenyl pyridines in an efficient fashion, bearing serviceable functionality, and using inexpensive,

non-toxic catalysts. Furthermore, there are few copper-catalyzed direct functionalization reactions relative to more expensive metals, and only a single example of a copper-catalyzed direct alkenylation. This example is on an electron-rich arene, and no electron-poor species have been published at the start of this work. The following sections will describe our work on the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides. We will first start with the description of a novel method to make a range of alkenyl halides. This will be followed by the optimization of the alkenylation, and the application of these newly prepared halides in the derivitization of *N*-iminopyridinium ylides.

3.2 Stereoselective Synthesis of (*E*)-β-Aryl Vinyl Iodides

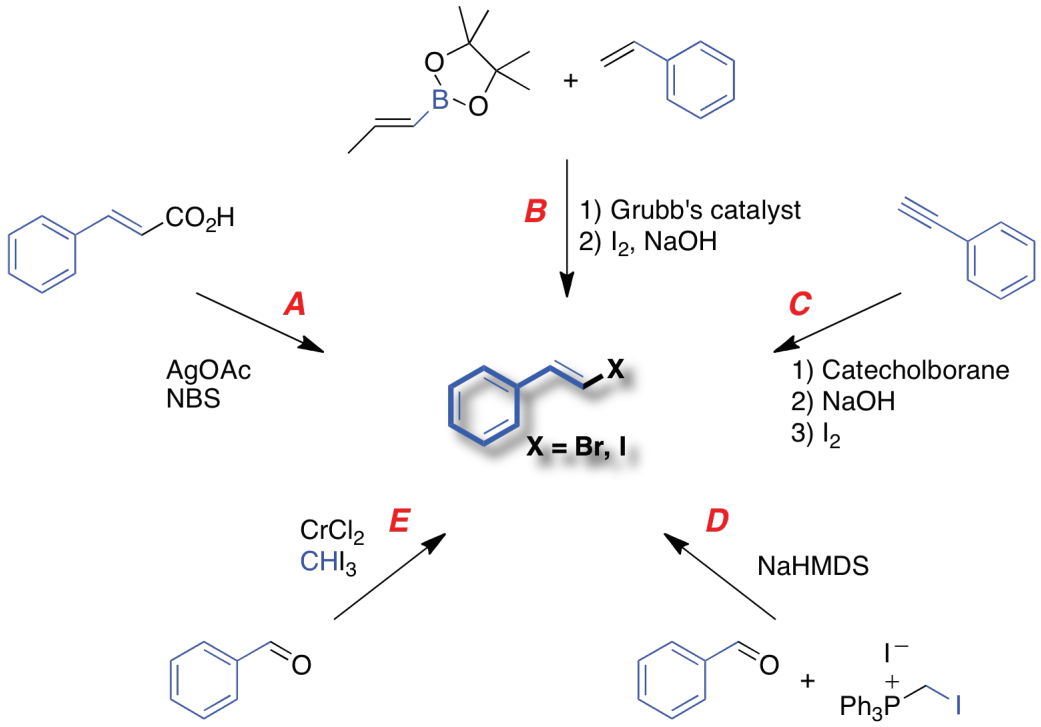
3.2.1 Introduction

Over the past four decades aryl and vinyl halides have become increasingly important reagents due to the advent of cross coupling and, more recently, C–H functionalization reactions. These methods have permanently facilitated, and thus altered the way we construct carbon skeletons. Whilst aryl halides are widely commercially available, the corresponding stereochemically pure vinyl halides are much less so, as is reflected in their high cost. Ergo, there has been much interest in developing systematic methods for the synthesis of these compounds. In particular, (*E*)-β-aryl vinyl halides are attractive materials as vinyl aryls are present in several compounds bearing biological and medicinal activity.[132,134]

Several methods have been disclosed for the preparation of these compounds (**Scheme 40**). However, these techniques are largely inefficient, necessitating the formation of the requisite alkene precursor followed by installation of the desired halide. One method to form these useful reagents is *via* the Hunsdiecker reaction whereby cinnamic acid derivatives are decarboxylated and quenched with a halide (route **A**).[135] A drawback of this is the need for expensive pure and scrupulously dry silver salts, though this can replaced by

thalium or mercury salts leading to increased toxicity. Cross-metathesis with a vinyl boronate (route **B**),[136] or reduction of an alkyne followed by the appropriate electrophile quench (route **C**) is also a means to prepare (*E*)-β-aryl vinyl halides,[137] though these routes suffer from multistep syntheses and potential high cost of reagents. Homologative methods include the Wittig (route **D**)[138] and Takai[139] olefination processes (route **E**). These are often high yielding, the former tends to provide only moderate selectivity, and the latter often requires large excesses of toxic Cr salts, decreasing the appeal of the method.

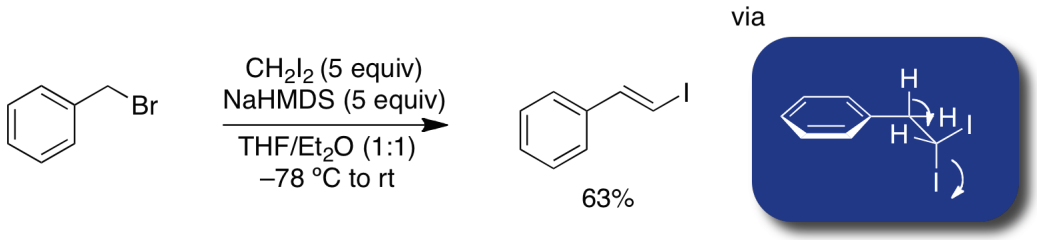
Scheme 40. Various means of preparing β-aryl halides.



During the course of his work in the synthesis of *gem*-diiodoalkanes through the alkylation of diiodomethane with alkyl bromides or iodides,[140] a former post-doctoral researcher (Dr. James Bull), noted that during the alkylation of $NaCHI_2$ with benzyl bromide the diiodide produced tended to undergo elimination to give (*E*)-β-phenyl vinyl iodide (**Scheme 41**). Given that the elimination product could be obtained in high yield

through a one-pot homologation/elimination, and benzyl bromide derivatives are widely available, this was envisioned as a solution to some of the aforementioned challenges typically encountered in the synthesis of these reagents. The following section will outline work conducted towards the optimization and exploration of the reaction.

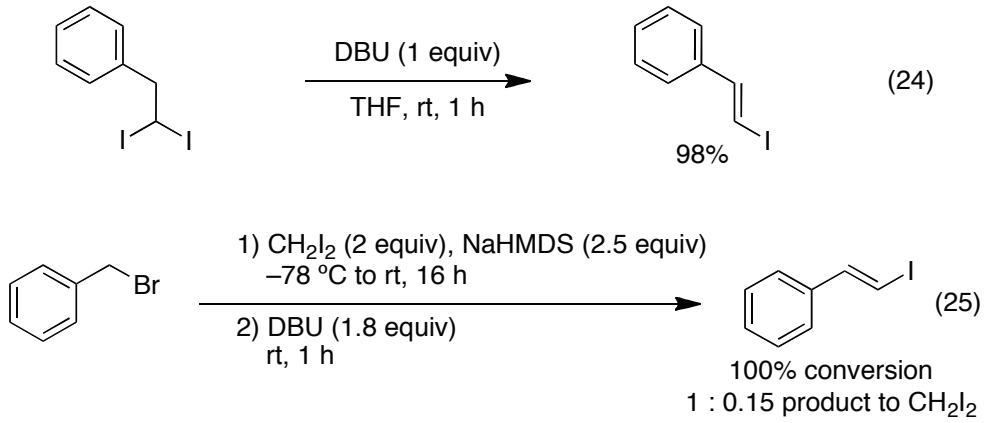
Scheme 41. Synthesis of (*E*)-β-aryl vinyl iodide from benzyl bromide.



3.2.2 Optimization and Scope

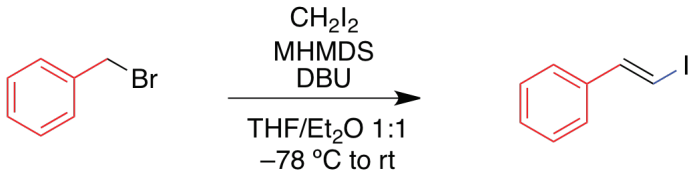
*3.2.2.1 Synthesis of (*E*)-β-Aryl Vinyl Iodides*

The conditions above (**Scheme 41**) used 5 equiv of $NaCHI_2$ propared from diiodomethane and CH_2I_2 as required in the alkylation with alkyl iodides. We felt optimistic that it would be possible to reduce the excess reagents to provide a more efficient reaction while increasing the yield. However, initial studies with reduced equivalents showed that the loading could be reduced maintaining complete conversion of the benzyl bromide. However, complete elimination was not always obtained, leaving the diiodide, which caused problems with purification. Separately we found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was effective in driving the elimination of the diodide in quantitative yield (Eq. 24). An exploratory run determined that the DBU could be added to the reaction mixture following the alkylation to afford only the styryl iodide (Eq. 25), However, residual diiodomethane proved difficult to separate from the product. With this knowledge in hand, Dr. Bull proceeded with the optimization for the vinyl iodides.[141]



Previously the synthesis of the *gem*-diiodoalkane derived from benzyl bromide was achieved by using LiHMDS in a 1:1 ratio with CH_2I_2 with minimal elimination to the vinyliodide (**Table 18**, entry 1).[140] As evidenced by **Scheme 41**, the application of the more reactive sodium anion favours the stereoselective elimination to the desired product.[141] Investigating the equivalents of base and diiodomethane (entries 2-4) determined that full conversion with 73% elimination could be obtained with 3 equiv NaHMDS and 1.5 equiv CH_2I_2, while destroying any residual inseparable diiodomethane in the reaction mixture. As expected, the addition of DBU eliminated the remaining *gem*-diiodide, giving the (*E*)-β-phenyl vinyl iodide exclusively in a 99:1 *E*/*Z* ratio (entry 5). This is due to the minimization of unfavourable steric interactions during the elimination (**Scheme 41**).[141] Increasing the reaction concentration (entries 6-8) gave higher levels of elimination, though 0.2 M was chosen for sake of reproducibility. Additionally, the reaction times could be shortened dramatically under these conditions (entry 9). Finally, the DBU was included to ensure complete elimination across a range of substrates (entry 10, **Method A**). Also, for more sensitive substrates a new set of conditions employing LiHMDS followed by addition of DBU was developed (entry 11, **Method B**).[141] As expected, based on the result in entry 1, the involvement of DBU was essential for the elimination to proceed.

Table 18. Selected optimization for the synthesis of (*E*)-β-aryl vinyl iodides from benzyl bromide.



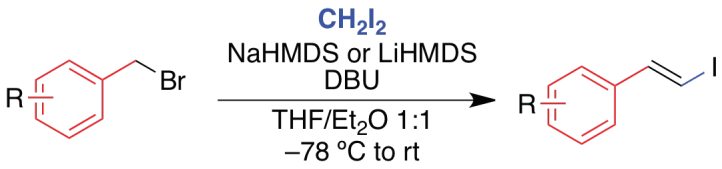
entry	equiv NaHMDS	equiv CH_2I_2	conditions[a]	concn (M)[b]	convn (%)[c]	elimn (%)[d]
1	2.0[e] (LiHMDS)	2.0	–78 °C to rt over 16 h	0.05	100	5
2	2.0	2.0	–78 °C to rt over 16 h	0.05	97	16
3	2.0	1.0	–78 °C to rt over 16 h	0.05	91	71
4	3.0	1.5	–78 °C to rt over 16 h	0.05	100	73
5	3.0	1.5	–78 °C to rt over 16 h then DBU 1 h[f]	0.05	100	100
6	3.0	1.5	–78 °C to rt over 16 h	0.1	100	94
7	3.0	1.5	–78 °C to rt over 16 h	0.2	100	99
8	3.0	1.5	–78 °C to rt over 16 h	0.3	100	100
9[b]	3.0	1.5	–78 °C 1.5 h, to rt 1 h	0.2	100	87
10[g]	3.0	1.5	–78 °C 1.5 h, to rt 30 min then DBU 1 h	0.2	100	100
11[h]	2.0[e] (LiHMDS)	2.0	–78 °C to rt over 16 h, then DBU 1 h[i]	0.2	100	100

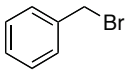
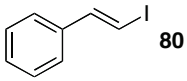
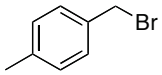
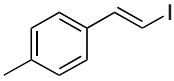
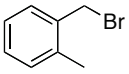
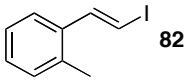
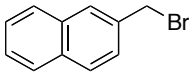
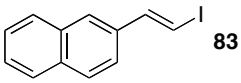
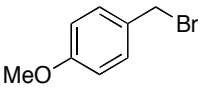
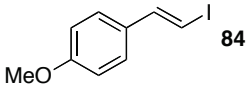
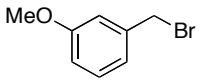
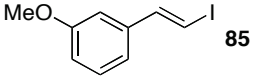
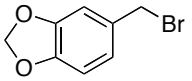
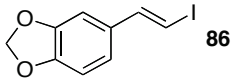
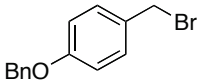
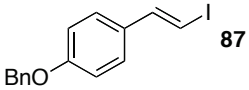
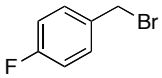
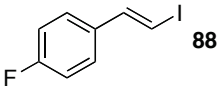
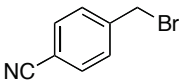
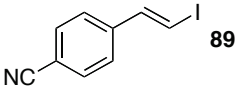
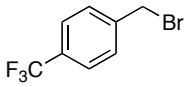
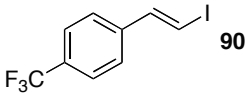
[a] Reaction performed on a 1 mmol scale. [b] Concentration of BnBr in solution. [c] Determined by analysis of the crude mixture by ^{1}H NMR. [d] Percentage of the *gem*-diiodide that underwent elimination to the vinyl iodide. [e] LiHMDS used in place of NaHMDS. [f] One equivalent of DBU used. [g] Method A. [h] Method B. [i] Two equivalents of DBU used.

With the two sets of optimized conditions in hand (**Table 18**, entries 10, 11) we explored the scope of the reaction.[141] Alkyl-substituted and naphtyl derived benzyl bromides provided the corresponding styryl iodides in good to excellent yields with near complete *E*-selectivity (**Table 19**, entries 1-5). As seen by entry 1, Method A (**Table 18** entry 10) provided superior results with shorter reaction times and thus were our conditions

of choice.[141] Electron-rich arenes were well tolerated, (entries 6-9) though a slight excess of DBU was needed to complete the elimination, and the milder conditions employing LiHMDS were needed for 4-OBn benzyl bromide (entry 9). Electron-poor substrates fared less well (entries 10-12), with the milder reaction conditions needed to obtain synthetically useful quantities of the desired products (Method B, **Table 18** entry 11).[141] In all cases very good *E*-selectivity was obtained.

Table 19. Synthesis of (*E*)-β-aryl vinyl iodides.

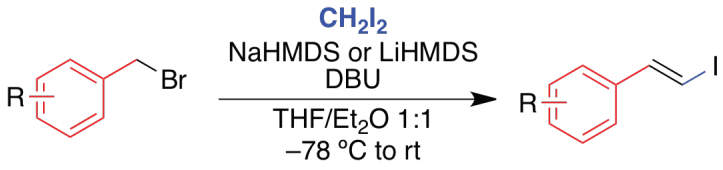


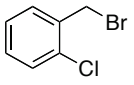
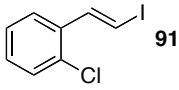
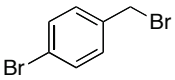
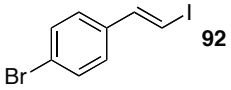
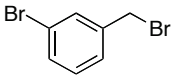
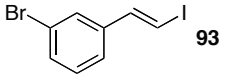
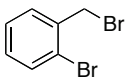
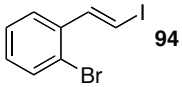
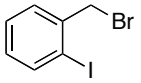
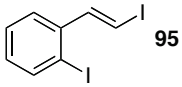
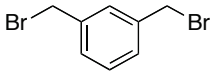
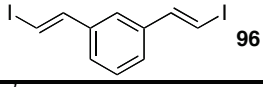
entry [a]	BnBr derivative	method [b]	product	yield (%) [c]	*E*/*Z* [d]
1		A	 **80**	92	98:2
2		B		82	97:3
3		A	 **81**	93	99:1
4		A	 **82**	90	99:1
5		A	 **83**	70	98:2
6		A[f]	 **84**	92	97:3
7		A[f]	 **85**	95	99:1
8		A[f]	 **86**	93	99:1
9		B[g]	 **87**	76	99:1
10		A	 **88**	85	98:2
11		B	 **89**	51	99:1
12		B	 **90**	63	99:1

[a] Reactions performed on 4.0 mmol scale. [b] Method A: CH_2I_2 (1.5 equiv), NaHMDS (3.0 equiv), 0.2 M, –78 ºC (1.5 h) to rt (30 min), then DBU (1 equiv for 1 h). Method B: CH_2I_2 (2.0 equiv), LiHMDS (2.0 equiv), 0.2 M, –78 ºC to rt (16 h), then DBU (2 equiv for 1 h). [c] Yield of the isolated product. [d] Ratio determined by ^{1}H NMR spectroscopy. [f] Used 1.5 equiv DBU. [g] Used 3.0 equiv DBU.

We became interested in the synthesis of lynchpin fragments whereby halides would also be present on the arene ring. As such, cross coupling partners could be made to couple different groups selectively at different sites.[141] (*E*)-β-aryl vinyl iodides with chlorine (**Table 20**, entry 1), bromine (entries 2-7), or iodine (entry 8) on the aromatic ring were prepared in moderate to very good yields. In these cases, these reactions benefited from the conditions with LiHMDS, though for most cases either method provided acceptable yields. Finally, the bis-vinyl iodide **96** could be readily prepared with excellent selectivity from α,α'-dibromo-*m*-xylene (entry 9).

Table 20. Synthesis of vinyl iodide lynchpins.



entry [a]	BnBr derivative	method [b]	product	yield (%) [c]	*E*/*Z* [d]
1		A	 **91**	78	98:2
2		A	 **92**	43	99:1
3		B		87	99:1
4		A	 **93**	62	99:1
5		B		87	98:2
6		A	 **94**	4	99:1
7		B		88	98:2
8		B	 **95**	73	99:1
9[e]		A	 **96**	73	97:3 (EE/EZ)

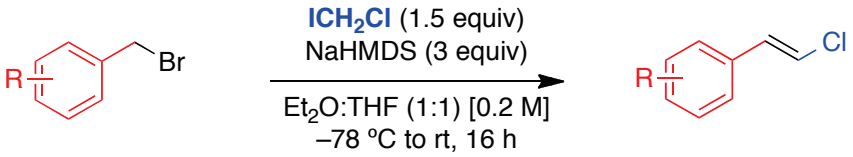
[a] Reactions performed on 4.0 mmol scale. [b] Method A: CH_2I_2 (1.5 equiv), NaHMDS (3.0 equiv), 0.2 M, –78 ºC (1.5 h) to rt (30 min), then DBU (1 equiv for 1 h). Method B: CH_2I_2 (2.0 equiv), LiHMDS (2.0 equiv), 0.2 M, –78 ºC to rt (16 h), then DBU (2 equiv for 1 h). [c] Yield of the isolated product. [d] Ratio determined by ^{1}H NMR spectroscopy. [e] Same procedure as Method A, though the quantities of NaHMDS, CH_2I_2, and DBU are doubled.

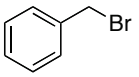
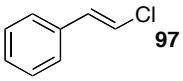
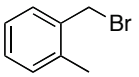
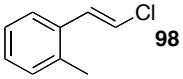
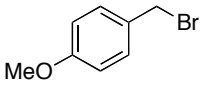
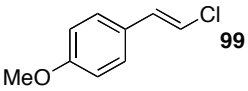
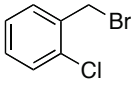
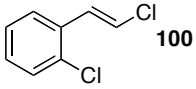
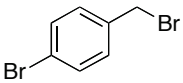
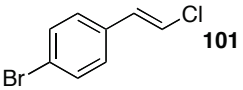
The above reactions were performed on a 4 mmol scale. Given the potential application of the methodology in large-scale processes we proceeded to investigate the scale up of the reaction. Indeed it was found that the reaction could be performed with 30 mmol of benzyl bromide, giving 6.0 g of (*E*)-(2-iodovinyl)benzene.[142] Little optimization was needed as the stoichiometry of the reagents could be maintained from method A. The main difference required was extended reaction times with warming from –78 ºC to rt over 16 h to ensure complete consumption of the reagents.[142]

*3.2.2.2 Synthesis of (*E*)-β-Aryl Vinyl Chlorides and Bromides*

Dr. Bull applied this strategy towards the synthesis of vinyl chlorides and bromides.[141] Gratifyingly, deprotonating ICH_2Cl with NaHMDS prior to the addition of benzyl bromide provided the vinyl chloride in moderate to very good yields with excellent selectivity (**Table 21**). Relative to the synthesis of vinyl iodides, extended reaction times were needed to ensure complete consumption of the benzyl bromide. However, the addition of DBU was not needed, as complete elimination was achieved in all cases.[141] Importantly, when NaHMDS was used, only the vinyl chloride was noted, as the elimination of HCl from the 1,1-chloroiodoalkane intermediate was not observed. The scope was general, and again LiHMDS could be used on more sensitive substrates to afford the desired products with improved yields (entries 2, 7).[141]

Table 21. Synthesis of (*E*)-β-aryl vinyl chlorides.

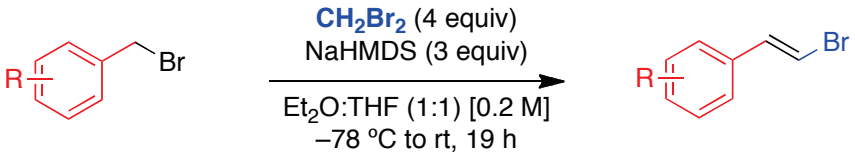


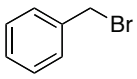
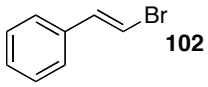
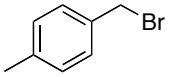
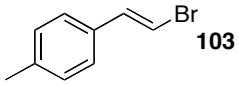
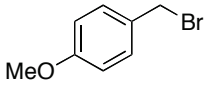
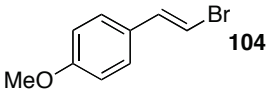
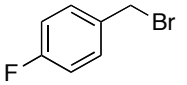
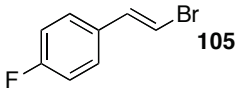
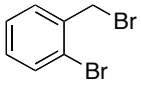
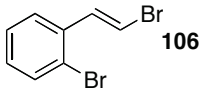
entry [a]	BnBr derivative	product	yield (%)[b]	*E*/*Z*[c]
1		 **97**	89	97:3
2[d]			90	97:3
3		 **98**	85	97:3
4		 **99**	88	96:4
5		 **100**	55	>99:1
6		 **101**	69	>99:1
7[d]			80	94:6[e]

[a] Reactions performed on 1.0 mmol scale. [b] Yield of the isolated product. [c] Ratio determined by ^{1}H NMR spectroscopy. [d] Used LiHMDS under otherwise identical conditions. [e] 2% vinyl iodide present.

Widening the breadth to the synthesis of vinyl bromides required modification of the reaction conditions to be successful as CH_2Br_2 proved more problematic than CH_2I_2. In many cases, byproducts were observed, including the formation of the alkyne from double elimination.[141] These were minimized by using an excess of the dibromomethane relative to the alkali base, consequently reducing the basicity of the reaction. As with the vinyl chlorides, the inclusion of an additional base was not needed as none of the *gem*-dibromide intermediate was observed.[141] The substrate scope was general, with electron-rich (**Table 22**, entries 1-3), electron-poor (entry 4), and functionalized arenes (entry 5) being tolerated.

Table 22. Synthesis of (*E*)-β-aryl vinyl bromides.



entry [a]	BnBr derivative	product	yield (%)[b]	*E*/*Z*[c]
1		 **102**	92	98:2
2		 **103**	82	97:3
3		 **104**	93	99:1
4		 **105**	90	99:1
5		 **106**	63	99:1

[a] Reactions performed on 1.0 mmol scale [c] Yield of the isolated product. [d] Ratio determined by ^{1}H NMR spectroscopy.

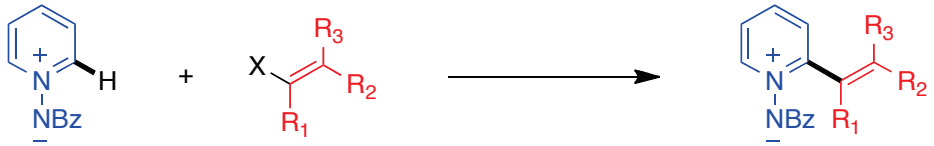
3.3 Direct Alkenylation of *N*-Iminopyridinium Ylides

3.3.1 Reaction Optimization

Our approach to the direct synthesis of 2-alkenyl pyridine derivatives was through the coupling of vinyl halides at the 2-position of the *N*-iminopyridinium ylides (**Scheme 42**). To date there had been no examples of such alkenylations of electron-deficient heterocycles. We believed that this might provide a potential solution to some of the aforementioned challenges in the synthesis of these relevant molecules (*vide supra*, **Section 3.1**) as we have documented the facile synthesis of ylides[66] and applied them in various reactions.[65,70,75] Furthermore, these ylides not only generate activated pyridinium species that are amenable to a myriad of transformations, they also demonstrate a powerful

directing group capability, and this should favour metal-mediated transformations at the 2-position.[65,70,75] Now equipped with a veritable library of potential vinyl halide coupling partners,[141,142] and with the aforementioned experience in the direct functionalization of these ylides, we embarked on the optimization and exploration of this reaction.

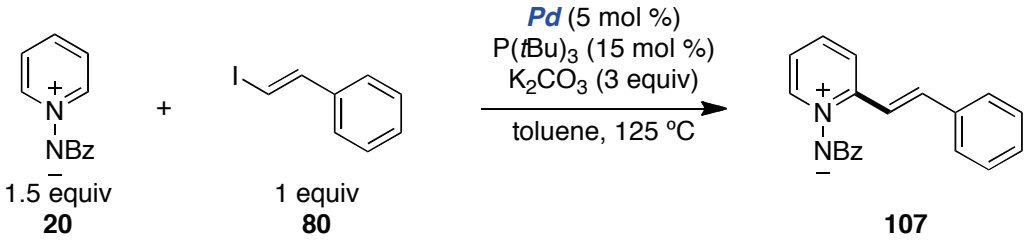
Scheme 42. Proposed direct alkenylation of *N*-iminopyridinium ylides.



3.3.1.1 Initial Attempts under Palladium Catalysis

Based on our antecedent work on the direct sp^2 arylation, we first elected to try the reaction under palladium catalysis as it deemed to be a logical extension of the process.[70] Starting with our optimized arylation conditions (**Table 23**), and as aryl iodides were viable coupling partners in the direct arylation reaction, we chose styryl iodide **80** as our model coupling partner. This was to ensure that the oxidative addition into the vinyl-halide bond by the catalyst would not be a limiting factor (entry 1). This was verified to be the most reactive of the halides, as the vinyl bromide and chloride provided inferior yields (entries 2, 3). A screening of $Pd(TFA)_2$ gave similar results to $Pd(OAc)_2$ (entry 4), and these were superior to all other palladium sources tested (entries 5-8), though $Pd(dba)_2$ did give moderate results (entry 5). Palladium/ligand complexes were largely ineffective (entries 9-12), and Pd-NHC complexes failed to provide any conversion (entries 13, 14).

Table 23. Screening of palladium catalysts in the direct alkenylation of *N*-iminopyridinium ylides.



entry	Pd source	yield (%)[a]	entry	Pd source	yield (%)[a]
1	$Pd(OAc)_2$	55	8	$PdCl_2(NCPh)_2$	0
2	$Pd(OAc)_2$[b]	23	9	$Pd(tBu_3P)_2$[d]	11
3	$Pd(OAc)_2$[c]	20	10	$Pd(PPh_3)_4$[d]	10
4	$Pd(TFA)_2$	58	11	$(PPh_3)_2Pd(OAc)_2$[d]	9
5	$Pd(dba)_2$	45	12	PCy_2PdCl_2[d]	<5
6	PdI_2	34	13	Pd(*i*Mes)•Napquin[d]	<5
7	$PdBr_2$	14	14	PEPPSI[d]	<5

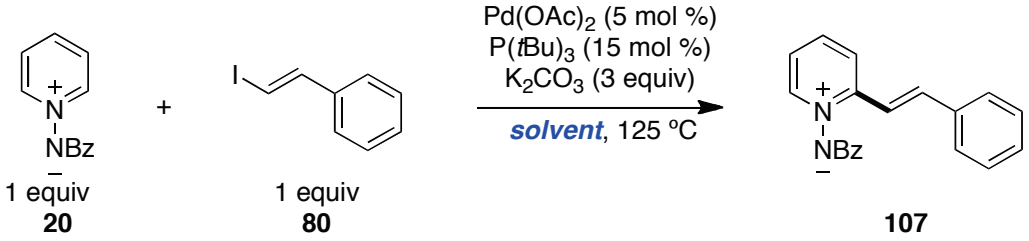
[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] (*E*)-β-phenyl vinyl bromide **102** in place of **80**. [c] (*E*)-β-phenyl vinyl chloride **97** in place of **80**.[d] P(*t*Bu)$_3$ was not included into the reaction mixture.

Ligand screening was not fruitful as out of 14 phosphines tested only P(*t*Bu)$_3$ (**Table 23**, entry 1) and P(*o*Tol)$_3$ (17% by ^{1}H NMR) provided any product whatsoever. The vinylation proceeded best when a 1:1 ratio of ylide to iodide was placed in the reaction mixture, as excesses of either starting material led to decreased yields. Temperature screening determined that an elevated reaction temperature of 125 ºC was needed for the reaction to proceed. Increasing the reaction temperature above this point was not beneficial, and conversions decreased below this point, and little conversion noted under 100 ºC.

Given that the conditions to this point remained largely unchanged, we proceeded with a screening of solvents (**Table 24**). It was found that non-heterocyclic aromatic and ethereal solvents to be best for the C–H transformation. Pyridine, DCE, and NMP were ineffective (entries 1-3) while DMA and DMF as the reaction medium provided poorer

reactivity (entries 4, 5), despite the improved homogeneity of the reaction mixture. Xylenes, DME, and 1,4-dioxane gave improved yields (entries 6-8), with toluene and THF giving the best conversions (entries 9, 10). Despite its relative high volatility, THF was chosen as the solvent for the remainder of the optimization.

Table 24. Solvent screening for the Pd-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



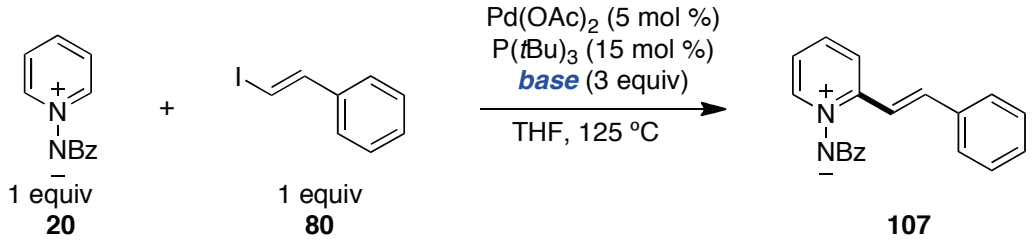
entry	solvent	yield (%)[a]
1	pyridine	<5
2	dichloroethane	<5
3	*N*-methylpyrrolidinone	<5
4	dimethylacetamide	15
5	dimethylformamide	19
6	xylenes	32
7	dimethoxyethane	43
8	1,4-dioxane	49
9	toluene	55
10	THF	59

[a] Yields are measured by ^{1}H NMR spectropscopy using 1,3,5-trimethoxybenzene as the internal standard.

Exploring the range of bases proved unproductive (**Table 25**). Potassium carbonate proved to be the optimal base, though phosphate and other carbonate bases were mildly compatible. Of note is the absence of any reactivity when employing stronger bases such as NaO*t*Bu, KO*t*Bu, and KH. Not only was there no conversion towards the alkenylated

pyridinium, in these cases the ylide starting material was completely destroyed, with only degradation products noted by ^{1}H NMR spectroscopy.

Table 25. Base screening for the Pd-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



entry	base	yield (%)[a]
1	K_2CO_3	59
2	K_3PO_4	45
3	Cs_2CO_3	17
4	$KHCO_3$	7
5	Na_2CO_3	<5

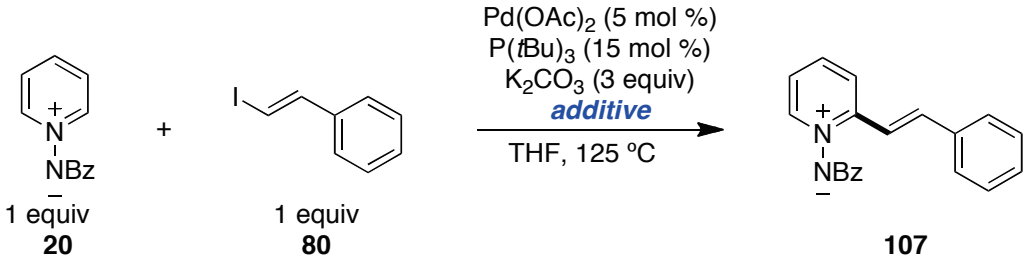
[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

3.3.1.2 Optimization under Copper Catalysis

As the standard reaction parameters failed to lead to significant improvement in yield, we next considered the application of various additives to assist the reaction (**Table 26**). Lithium chloride was added to assist in oxidative addition (entry 2),[8a] though this appeared to completely halt any reaction with only unreacted starting material being observed in the crude ^{1}H NMR spectrum. Fagnou reported much success administering pivalic acid to facilitate concerted metallation/deprotonation (CMD) sequences,[52,58a,i] though this proved detrimental to our efforts (entry 3). Inclusion of water to increase the solubility of the base led to decreased yields (entry 4), as did molecular sieves (entry 5). The latter is likely due to an inhibition of the agitation of the reaction mixture. Benzoquinone was ineffective (entry 6).[13] Interestingly, adding DMSO was beneficial

providing the desired product in 60% yield (entry 7). This is known to inhibit aggregation of Pd^0 intermediates, improving the turnover of the catalyst.[62,143] Copper (I) bromide was incorporated into the mixture as copper has been used to mask Lewis basic sites in other catalytic systems involving nitrogenous heterocycles, further activating the ring towards direct arylation processes.[50] This proved particularly effective in our catalytic system with a yield of 63% being observed along with evidence for the formation of the 2,6-divinylated *N*-iminopyridinium ylide.[144]

Table 26. Addition of additives to the direct alkenylation of *N*-iminopyridinium ylides



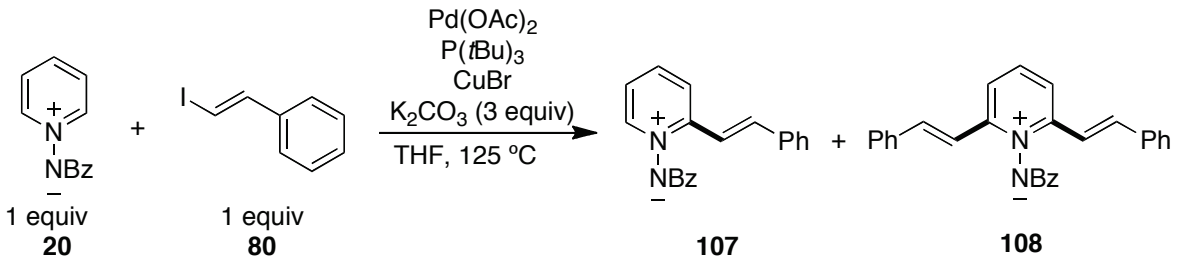
entry	additive	equiv	yield (%)[a]
1	none	n/a	54
2	LiCl	3.0	<5
3	PivOH	0.4	24
4	H_2O	10 vol %	16
5	MS 3Å	1:1 with **20**	35
6	benzoquinone	1.5	30
7	DMSO	10 vol %	60
8	CuBr	0.5	63[b]

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Evidence of 2,6-diarylation in crude reaction mixture by LCMS and ^{1}H NMR spectroscopy.

We were curious as to the role of the copper additive (**Table 27**). The inclusion of 10 mol % CuBr, while giving comparable yields towards the mono-alkenylated product as the Cu-free reaction (entry 2), led to overall superior conversions due to the presence of a significant amount of 2,6-disubsituted pyridinium ylide. Increasing the copper loading to

0.5 equiv did lead to increased amounts of the mono-alkenylated product (entry 3), and supplementing with an additional 0.5 equiv did not improve conversions (entry 4). In light of these results we postulated that copper alone may be promoting the reaction.[144] Gratifyingly, removing palladium in presence of 50 mol % CuBr provided the same result with or without palladium was present (entries 5, 6), and superior results to palladium catalysis, suggesting that copper may indeed be a more reactive catalyst. Decreasing the copper loading to 10 mol % still provided the desired product in 37% yield, clearly demonstrating a copper-catalyzed transformation (entry 7).[144]

Table 27. Investigation of the role of the copper additive.



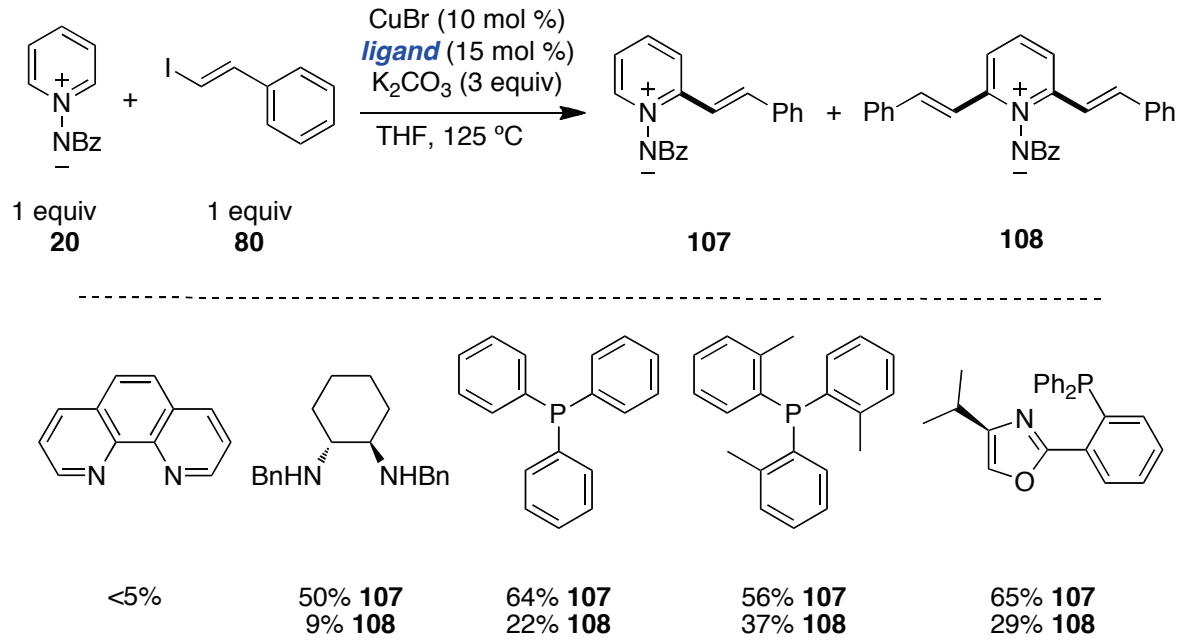
entry	$Pd(OAc)_2$ (mol %)	CuBr (equiv)	$P(tBu)_3$ (mol %)	yield **107** (%)[a]	yield **108** (%)[a]	total convn **80** (%)
1	5	0	15	55	<5	55
2	5	0.1	15	53	27	80
3	5	0.5	15	64	22	86
4	5	1.0	15	61	25	86
5	0	0.5	15	62	18	80
6	0	0.5	50	63	20	83
7	0	0.1	15	37	<5	37

[a] Yields are measured by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Due to the low cost, wide abundance, low toxicity, and few accounts of copper catalyzed direct C–H functionalization reactions we proceeded with the optimization of the vinylation with this metal. A small examination of potential ligands indicated that PHOX and triphenylphosphine derivatives might be optimal (**Scheme 44**). However, upon

exploring the effect of the ligand to catalyst ratio it was discovered that acceptable conversions could be obtained in absence of an external ligand (**Figure 13**).[144] This is postulated to be due to the presence of the *N*-iminobenzoyl moiety that can serve as an intramolecular ligand.

Scheme 44. Ligand investigation for the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



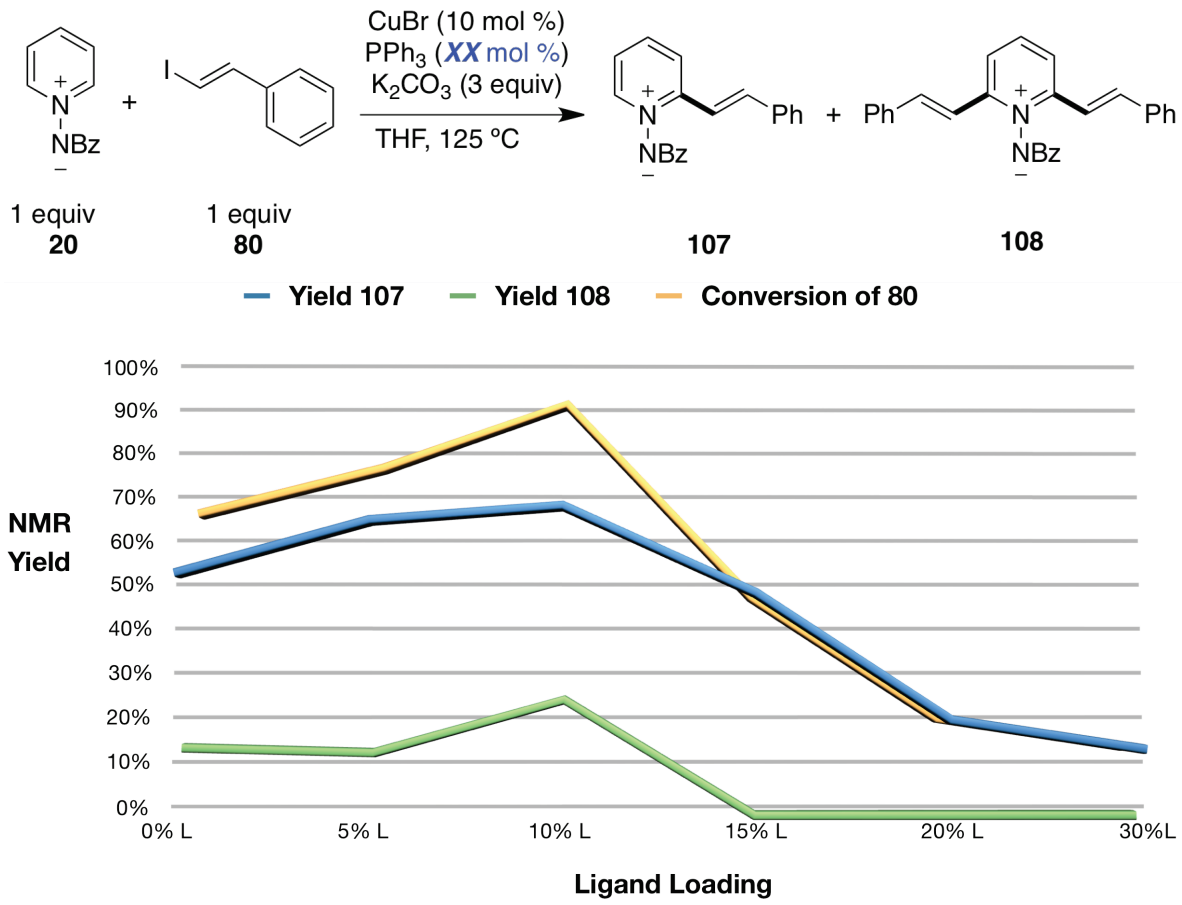
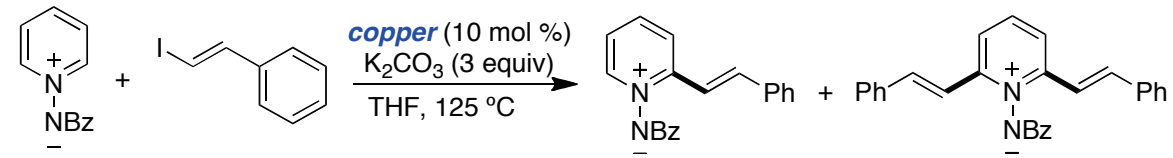


Figure 13. Dependancy of PPh_3 loading on the direct alkenylation of the pyridinium ylides.

Motivated by these results we proceeded with the optimization in the absence of an external ligand. The alkenylation was largely insensitive to the source and oxidation state of the copper (**Table 28**).[144] Both CuBr and $CuBr_2$ gave similar conversions (entries 1,2), though $CuBr_2$ displayed improved selectivity towards the monoalkenylation. Other comparable sources included CuI, CuCl, Cu(OAc), $Cu(OAc)_2$, and CuOTf•Tol (entries 3-7). Even copper dust proved quite reactive (entries 8, 9). As a test of the generality of the process, a copper reaction vessel was fabricated and used in the transformation (**Figure 14**) with the direct functionalization occurring without the inclusion of an additional source of copper. The reaction could be promoted by a penny, even though there is a relatively small amount of copper in the plating of the coin.[144] Only copper oxides gave decreased yields

(entries 10, 11), with Cu_2O providing the product in 55% yield and CuO giving no conversion whatsoever. Of note is the relative low cost of all these potential catalysts. Where $Pd(OAc)_2$ costs ~25 000$/mol, the cost of these salts is largely under 100$/mol, providing an inexpensive technology in the synthesis of these compounds.[145] Ultimately $CuBr_2$ was chosen as the catalyst of choice due to its improved selectivity and known stability.

Table 28. Screening of copper catalysts.

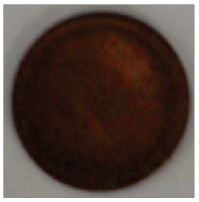


entry	copper source	cost/mol	yield **107** (%)[a]	yield **108** (%)[a]	total convn **80** (%)
1	CuBr	71$	51	32	83
2	$CuBr_2$	112$	61	19	80
3	CuI	49$	61	21	82
4	CuCl	12$	60	26	86
5	Cu(OAc)	1054$	54	26	80
6	$Cu(OAc)_2$	303$	53	23	76
7	CuOTf•Tol	1479$	53	32	85
8[b]	Cu dust (98%)	20$	82	n/a	82
9[b]	Cu dust (99.999%)	736$	88	n/a	88
10[b]	Cu_2O	11$	55	n/a	55
11[b]	CuO	14$	<5	n/a	<5

[a] Yields are measured by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Reaction performed with 1.5 equiv of **20**, 2 equiv of K_2CO_3, in chlorobenzene.

Copper Reaction Vessel ***Penny as a Copper Source***

before



after

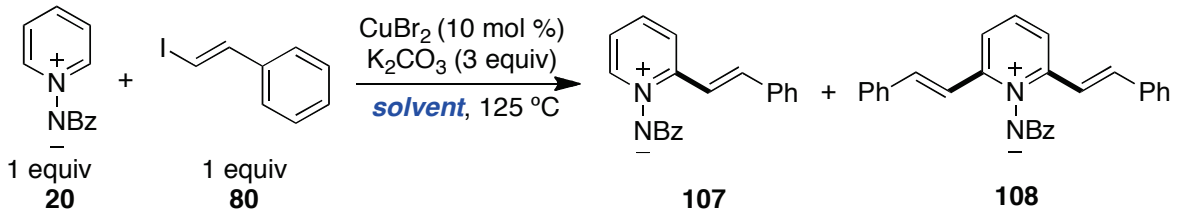
83% yield **107**
(1.5 equiv **20**, 1.0 equiv **80**
2 equiv K_2CO_3, PhCl, 125 ºC, 16 h)

77% yield **107**
(1.5 equiv **20**, 1.0 equiv **80**
2 equiv K_2CO_3, PhCl, 125 ºC, 16 h)

Figure 14. Alternate sources of copper employed.

Aromatic and ethereal solvents provided the best results (**Table 29**).[144] While DMPU, DCE, DMSO, MeCN, and DMF gave low to moderate yields (entries 1-5), THF, dioxane, DME, xylenes, toluene, and chlorobenzene provided very good overall conversions (entries 6-11). Chlorobenzene was chosen as the optimal solvent due to its low volatility, though less expensive toluene could be used in place with nearly identical results.

Table 29. Solvent screen for the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



entry	solvent	yield **107** (%)[a]	yield **108** (%)[a]	total convn **80** (%)
1	DMPU	19	<5	19
2	DCE	22	<5	22
3	DMSO	38	<5	38
4	MeCN	39	<5	39
5	DMF	40	<5	40
6	THF	59	11	70
7	dioxane	64	22	86
8	DME	65	22	87
9	xylenes	60	24	84
10	PhMe	68	20	88
11	PhCl	67	22	89

[a] Yields are measured by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Though PhCl gave excellent overall conversion (89%), it provided less than ideal selectivity with the 2-vinyl ylide obtained in 67% yield. As a result we reasoned that it should be possible to suppress the unwanted 2,6-bisalkenylated product by applying an excess of the pyridinium ylide (**Figure 15**). Indeed it was found that only a 1.5 fold excess of the ylide relative to the styryl iodide was needed to statistically contain the double functionalization, giving 85% yield of the desired product.[144] Though slightly improved yields were noted with further increases of the ylide loading, these were not deemed

significant enough to warrant the application of large excesses of the starting material.

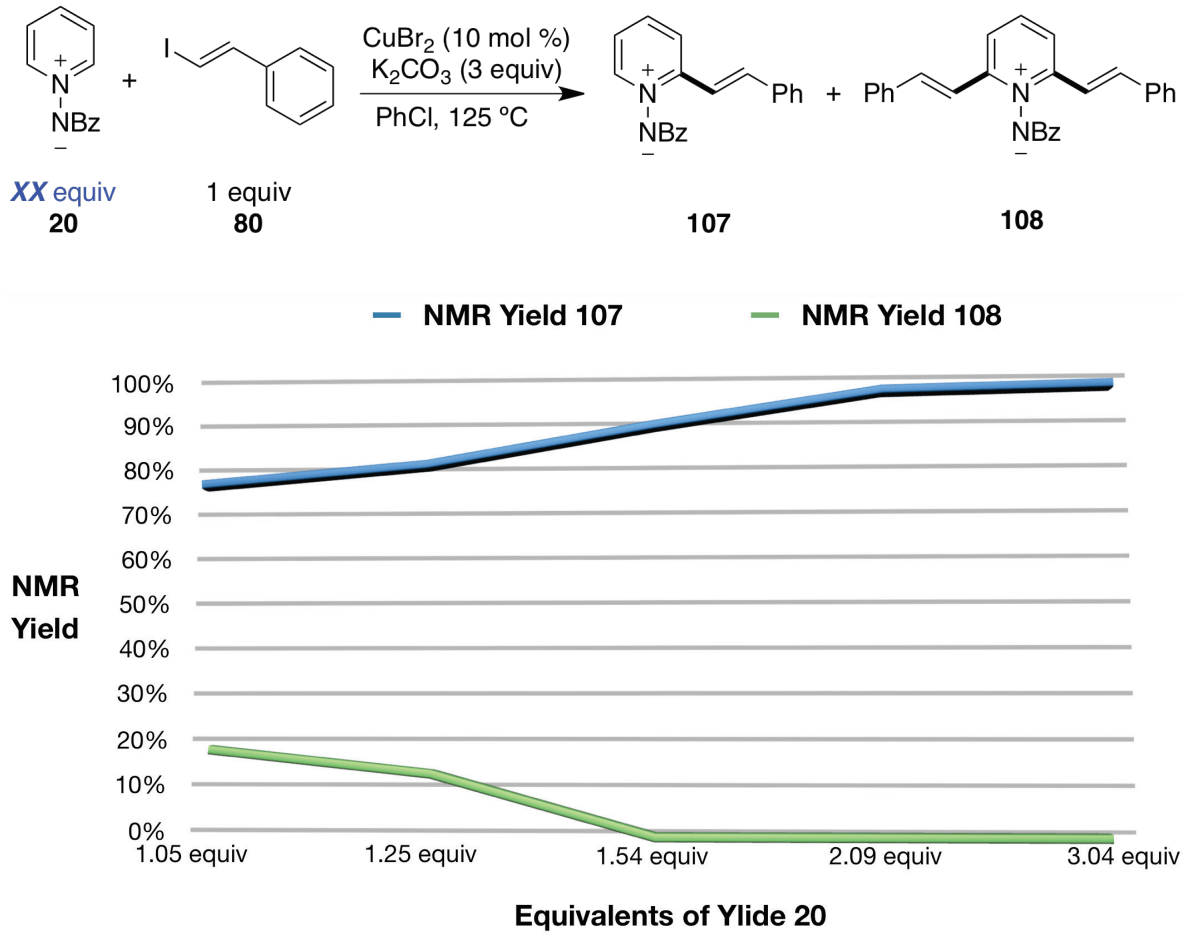
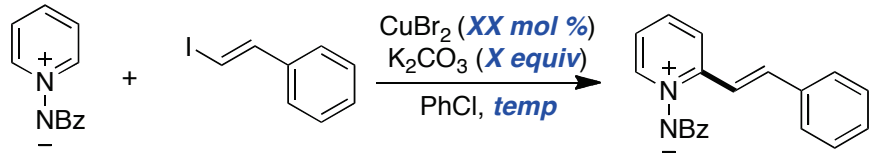


Figure 15. Suppression of the bis-vinylation.

Owing to the low cost and high efficiency of K_2CO_3, we elected to continue with this base (**Table 30**, entries 1-5).[144] It was found that the loading of K_2CO_3 could be decreased from 3.0 equiv to 1.5 equiv without significant decrease in yield (entries 1-3). However, 2 equiv was chosen for sake of reproducibility (entry 2). The reaction remained effective with copper loadings as low as 2.5 mol %, though 10 mol % was chosen again for the repeatability of the reaction (**Table 30**, entries 6-9). The optimal temperature was discovered to indeed be 125 ºC, as lower temperatures decreased yields, (**Table 1**, entries

10-13). Lastly, though mostly complete through 5 h, the reaction was run overnight to maximize reaction yields (**Figure 16**).[144]

Table 30. Base and catalyst loading in the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



1.5 equiv **20** + 1 equiv **80** → **107**

entry	K_2CO_3 equiv	$CuBr_2$ loading (mol %)	temperature (ºC)	yield **107** (%)[a]
1	3.0	10	125	84
2	2.0	10	125	83
3	1.5	10	125	80
4	1.0	10	125	46
5	0	10	125	<5
6	2.0	10	125	84
7	2.0	5.0	125	82
8	2.0	2.5	125	74
9	2.0	0	125	<5
10	2.0	10	125	84
11	2.0	10	115	82
12	2.0	10	105	72
13	2.0	10	90	31

[a] Yields are measured by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

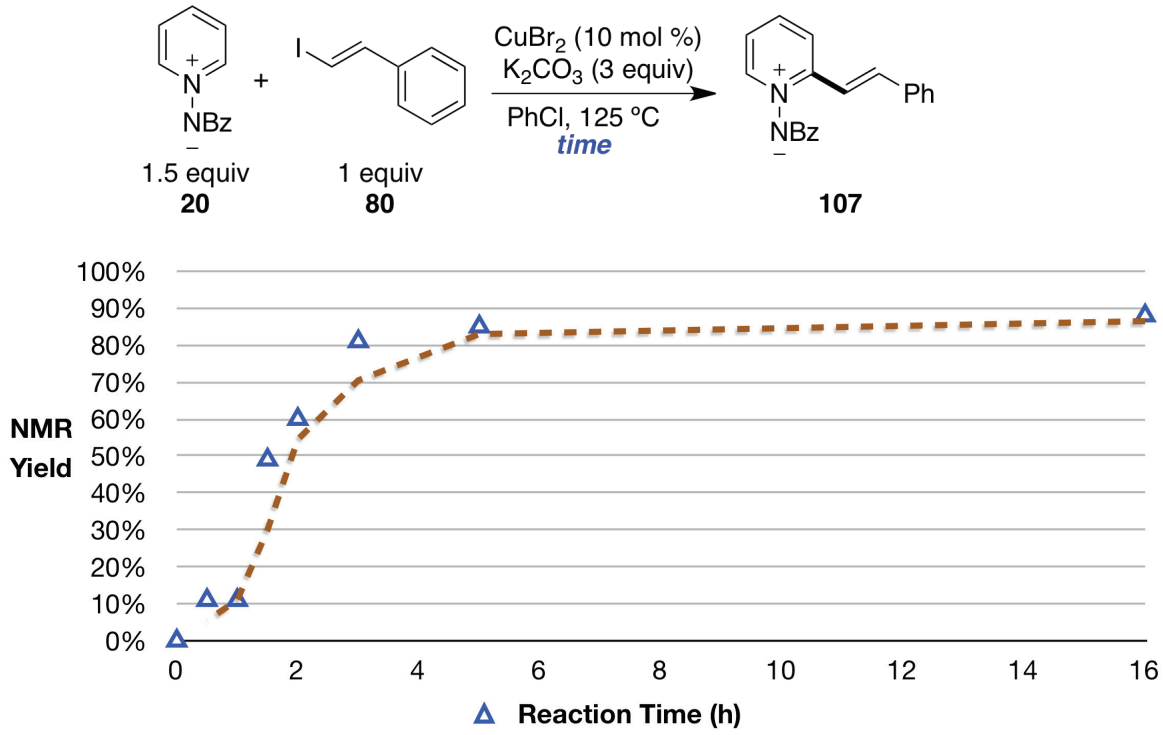


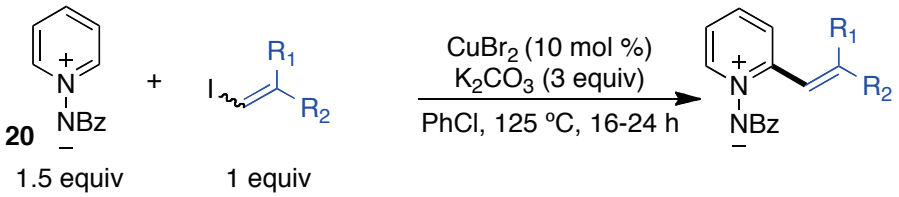
Figure 16. Reaction yield vs time for the direct alkenylation of *N*-iminopyridinium ylides.

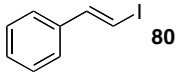
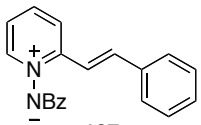
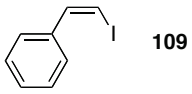
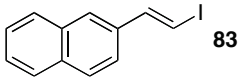
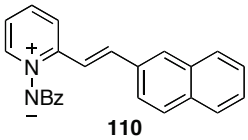
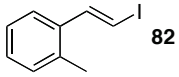
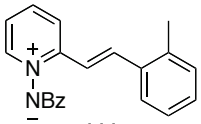
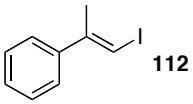
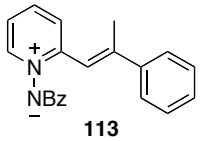
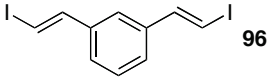
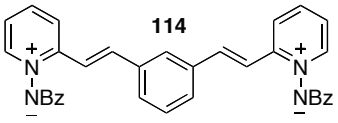
3.3.2 Scope for the Direct Alkenylation of *N*-Iminopyridinium Ylides

With the optimal conditions consisting of the ylide **20** (1.5 equiv), vinyl iodide (1.0 equiv), $CuBr_2$ (10 mol %), K_2CO_3 (2 equiv), in chlorobenzene at 125 ºC for 16 h we studied the breadth of the transformation. The scope of the copper-catalyzed reaction was found to be quite general.[144] Unsubstituted arenes present on the double bond reacted well, with *E*-iodides proving more reactive than *cis*-electrophile (**Table 31**, entries 1-3). This is thought to be due to steric congestion, as the electronics between the two substrates are very similar. Curiously, only the *E*-product was recovered, suggesting isomerization to the more thermodynamically favoured conformation. Furthermore, the unreacted ylide could be readily recovered (entry 1). Substitution at the 2-position of the arene has little impact (entry 4), though a methyl group on the alkene where it is less removed from the reaction

site provides the intended product in moderate yield (entry 5). The bis(vinyl iodide) **96** also converted to give the dipyridinium adduct in synthetically useful yields (entry 6).[144]

Table 31. Scope of various 2-aryl alkenes bearing electron-neutral groups.



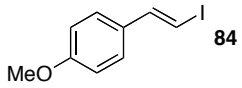
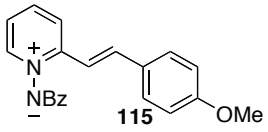
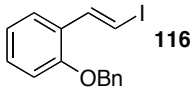
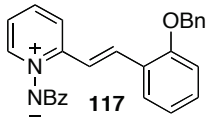
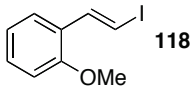
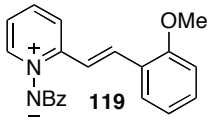
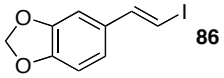
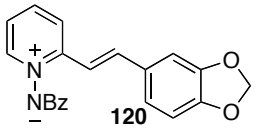
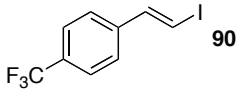
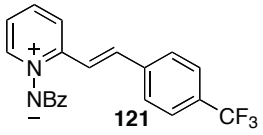
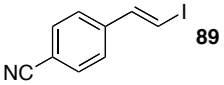
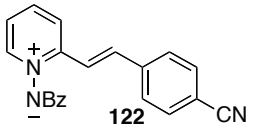
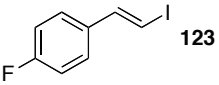
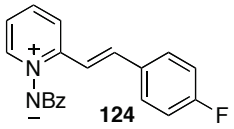
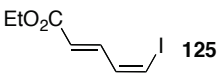
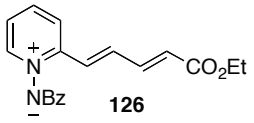
entry	alkenyl iodide	product	yield (%)[a]
1	 **80**		81 (93)[b]
2	 **109**	**107**	71
3	 **83**	 **110**	81
4	 **82**	 **111**	78
5	 **112**	 **113**	48
6[c]	 **96**	 **114**	63

[a] Yield of isolated product. [b] Yield based on recovered starting material. [c] Used 3.1 equiv of ylide **20**.

The reaction was determined to be insensitive to the electronics of the arene component on the alkene (**Table 32**).[144] More electron-rich substrates provided products in good to excellent yield (entries 1-4), with more hindered 2-substitution on the phenyl ring

being a non-factor (entries 2, 3). Substrates marked with electron-withdrawing functionality displayed similar reactivity (entries 5-7), furnishing the 2-alkenyl substituted ylides in very good yields. Diene **125** bearing a distal ester functionality coupled in 41% yield (entry 8).

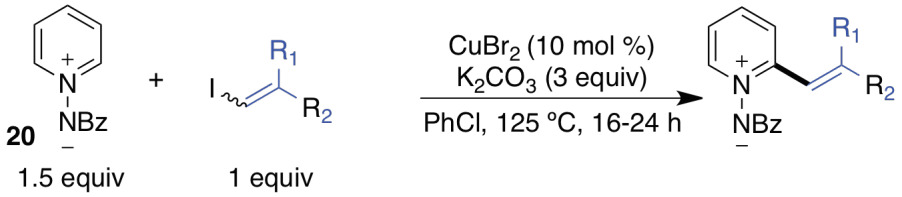
Table 32. Scope of electron-rich and poor alkenes.

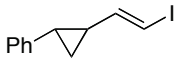
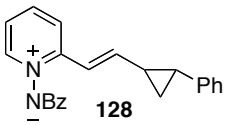
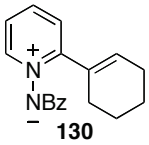
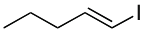
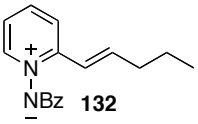
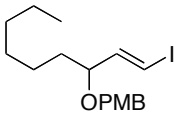
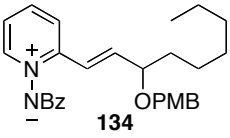
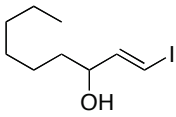
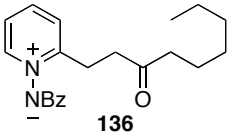
entry	alkenyl iodide	product	yield (%)[a]
1	 **84**	 **115**	87
2	 **116**	 **117**	71
3	 **118**	 **119**	93
4	 **86**	 **120**	75
5	 **90**	 **121**	71
6	 **89**	 **122**	89
7	 **123**	 **124**	83
8	 **125**	 **126**	41

[a] Reaction conditions: Ylide **20** (1.5 equiv), iodide (1.0 equiv), $CuBr_2$ (10 mol %), K_2CO_3 (2 equiv), PhCl [0.2 M], 125 ºC, 16-24 h. [b] Yield of isolated product.

Reactivity with iodoalkenes possessing sp^3 substitution proved to be substrate dependant (**Table 33**).[144] Alkenes containing a cyclopropyl moiety proceeded with moderate conversion (entry 1). While 1-iodocyclohexene reacted giving the product in 52% yield (entry 2), 1-iodopentene proved much less reactive (entry 3). Several other substrates were attempted (**Figure 17**), each giving little or no product. When the protected vinyl iodide **133** was used the desired pyridinium was obtained in 30% yield (entry 4). This could be useful in the synthesis of bioactive compounds (**Figure 12**). When the unprotected allylic alcohol is used the resulting ketone is formed from an *in situ* allylic isomerization (entry 5). Though such oxidations are known with other late-transition metals, to the best of our knowledge, this is the first such example performed in presence of copper.

Table 33. Scope of alkyl substituted alkenyl iodides.



entry	alkenyl iodide	product	yield (%)[a]
1	 **127**	 **128**	53
2	 **129**	 **130**	52
3	 **131**	 **132**	15
4	 **133**	 **134**	30
5	 **135**	 **136**	22

[a] Yield of isolated product.

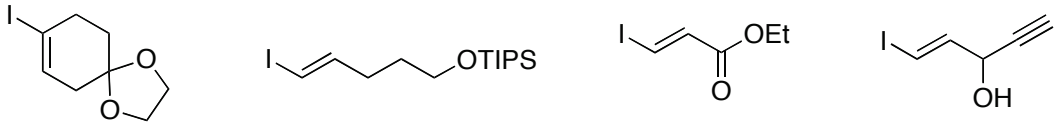
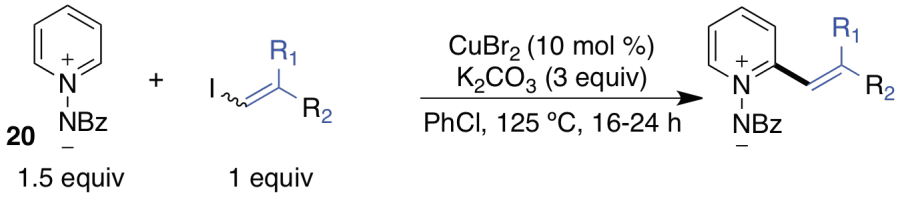


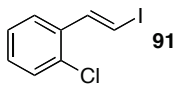
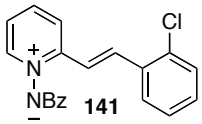
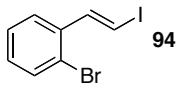
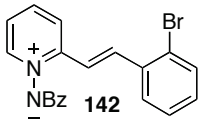
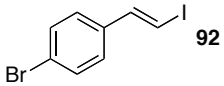
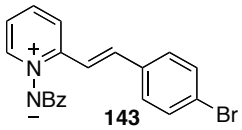
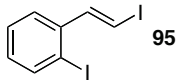
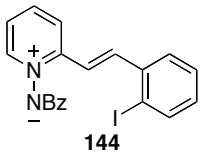
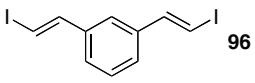
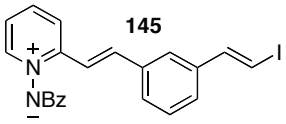
Figure 17. Examples of non-productive alkenyl iodides.

Perhaps the most striking feature of the reaction is its chemoselectivity (**Table 34**).[144] Halogen substituents (Cl, Br, I) on the phenyl ring were tolerated (entries 1-4), with

the coupling occurring selectively on the alkenyl iodide in moderate to good yields, and no arylated products were observed. These compounds are of particular usefulness as they contain reactive handles that could be used as a scaffold for the synthesis of more complex molecules. The bis(vinyl iodide) can be selectively reacted at one site under unmodified reaction conditions, leaving an iodoalkene present in the final product (entry 5).[144]

Table 34. Chemoselectivity of the direct alkenylation.



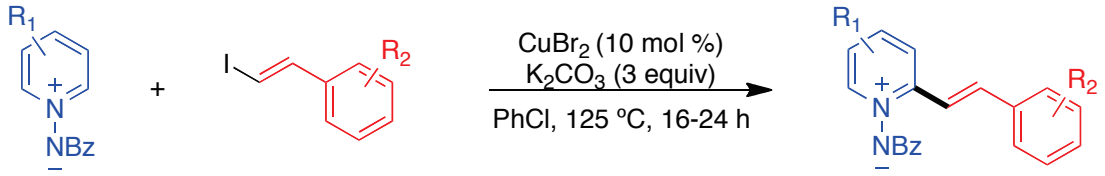
entry	alkenyl iodide	product	yield (%)[a]
1	 **91**	 **141**	74
2	 **94**	 **142**	65
3	 **92**	 **143**	74
4	 **95**	 **144**	47
5	 **96**	 **145**	41

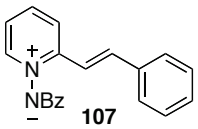
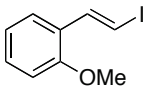
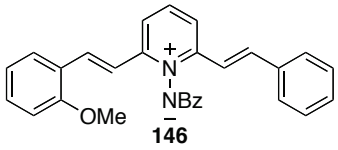
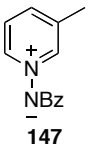
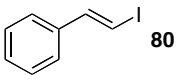
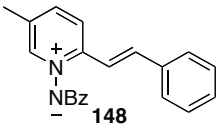
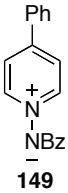
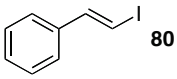
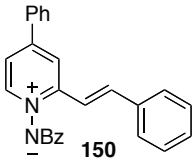
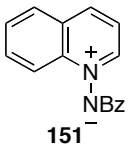
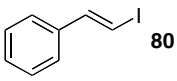
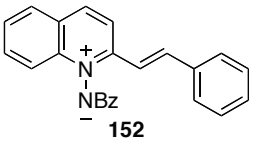
[a] Yield of isolated product.

Again cognizant that pyridine derivatives may be desired coupling partners, we next explored the scope of various pyridinium ylides (**Table 35**).[144] Subsitution at the 2-, 3-, and

4-positions of the pyridinium ring was tolerated (entres 1-3). Unsymmetrical 2-, 6-bisvinylated ylides can be prepared when starting with a pyridinium species already alkenylated at the 2-site. In the case of 3-methyl pyridine, the C–H functionalization occurs exclusively at the less hindered 6-position. The 2-alkenylated quinolonium ylide was isolated with moderate yield, demonstrating that other 6-membered azaheterocycles are viable coupling partners.

Table 35. Scope of the pyridinium ylide in the direct alkenylation reaction.

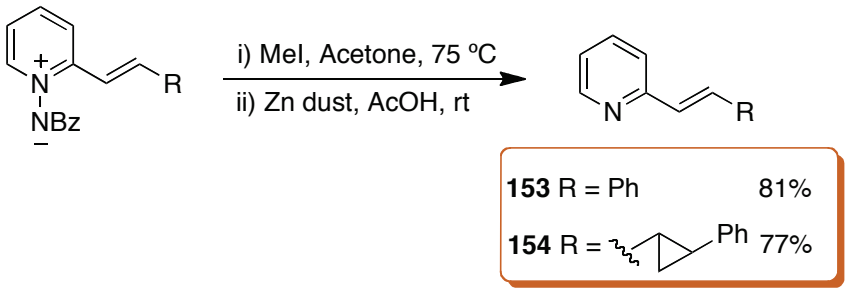


entry	ylide	alkenyl iodide	product	yield (%)[a]
1	 **107**	 **118**	 **146**	74
2	 **147**	 **80**	 **148**	65
3	 **149**	 **80**	 **150**	74
4	 **151**	 **80**	 **152**	41

[a] Yield of isolated product.

In our previous arylation account we were successful in cleaving the *N-N* bond through various reductive techniques.[70] It is noteworthy that it is possible to transpose this

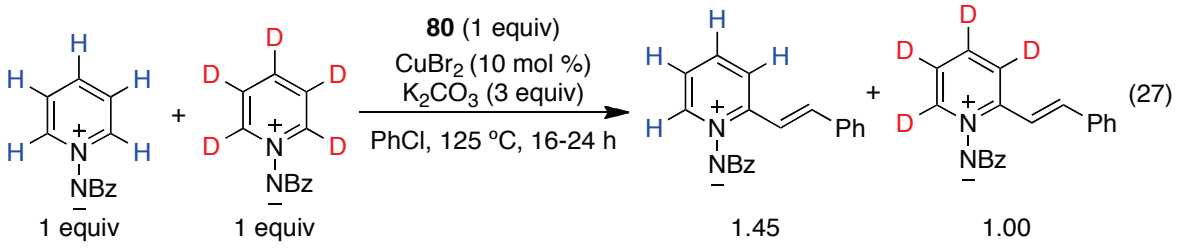
to these newly formed substrates leaving the valuable double bond intact. The *N-N* scission occurs in good yields over the two steps in presence of zinc dust and acetic acid (Eq. 26).[144]



(26)

3.3.3 Mechanistic Investigations

To gain some mechanistic insight into the pathway of the reaction we performed isotopic studies. A primary isotope effect value of 1.45 was obtained through a competition study (Eq. 27). [146,147,144] This low value indicates that the transition state is either product-like or reactant-like in that the hydrogen atom is either close to the base of the starting materical respectively. Also, as varying the isotope typically has little effect on reactivity and only on the rate of the reaction, the value implies that there is little difference between the presence of H or D, and thus the bond breaking is likely not the rate limiting step.[147] it also suggests that the reaction does not proceed through a radical pathway as this class of arylation typically gives a KIE value of 1.0.

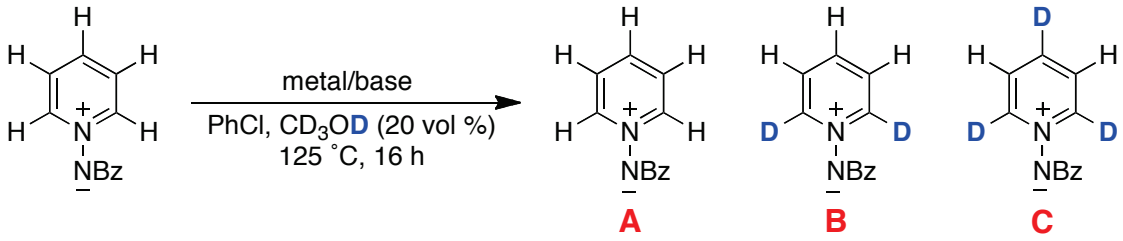


(27)

We were curious as to the directing group ability of the *N*-iminobenzoyl moiety. We performed the alkenylation reaction in presence of 20 vol % MeOH and still obtained 80% yield of the desired product. As such we hypothesized that the inclusion of this proton (or

deuterium) source does not adversely affect or alter the reaction. Consequently, we embarked on a labeling study (**Table 36**).[144] Mixing ylide **20** in PhCl with 20 vol % CD_3OD at 125 ºC for 16 h failed to provide any deuterium incorporation into the pyridinium (entry 1). Performing the same process in presence of K_2CO_3 gave equal 90% D incorporation at the 2, 4, and 6 positions (entry 3). This was expected as these are known to be the most labile protons in similar pyridinium species.[1] The inclusion of $CuBr_2$, in absence of any base, still gave deuterium incorporation at the 2- and 6-sites of the pyridinium exclusively (entry 3), suggesting that the copper readily inserts in a directed fashion without the aid of the base.[144] The exact level of incorporation could not be determined due to peak broadening in the ^1H NMR spectrum, implying that a stable cupracycle may be formed, though efforts to crystallize this were unsuccessful. Curiously, under the complete reaction conditions with both $CuBr_2$ and K_2CO_3, again selective deuterium incorporation at the 2- and 6- site were noted, with no deuterium present at the 4-site, this despite the large excess of carbonate relative to the copper catalyst (entry 4). Furthermore, unlike when $CuBr_2$ was used in absence of base, the level of deuterium could be determined, implying the possible presence of a different catalytic reagent.

Table 36. Deuterium labelling study in the direct alkenylation of *N*-iminopyridinium ylides.



entry	metal/base	% D incorporation[a]	LCMS [*M* + 1]	product
1	none	0	199.2	A
2	$CuBr_2$ (10 mol %)	n/a	201.2	B
3[b]	K_2CO_3 (2 equiv)	90	202.2	C
4	$CuBr_2$ (10 mol %), K_2CO_3 (2 equiv)	92	201.2	B

[a] Incorporation determined by ^1H NMR. [b] Equal D incorporation in 2,4,6-positions.

These results led us to propose the following catalytic cycle (**Figure 18**).[144] Given that a wide range of active catalysts were equally operative (**Table 28**, **Figure 14**), and the result obtained in the previous table (

Table 36, entry 4), it is believed that a single active copper species is responsible for the alkenylation. An additional note is the fact that the reaction works in presence of Cu^0, Cu^I, and Cu^{II} salts, also giving weight to this hypothesis. We believe that the active copper species is a Cu^I intermediate. Copper (II) can be reduced to copper (I) via the pyridinium ylide (**Figure 18**, **A**), as this is known with various nitrogen nucleophiles, or through known disproportionation to Cu^I/Cu^{III}. [129,148] The fact that this occurs would also explain the lag in reaction observed in the first hour of the transformation (**Figure 16**). Additionally, the characteristic red-brown colour of copper (I) salts is observed following the reaction, suggesting its formation.[149] In the case of copper (0), the ylide can add into the copper, generating a copper (II) intermediate that is again converted to the active copper (I) catalyst.[150] Once the Cu^I reagent is available it may undergo a known ligand exchange with K_2CO_3 (**B**) to generate $CuCO_3$ that can undergo a possible directed CMD insertion into the 2-position of the pyridinium ring (**C**).[151,152] As noted, the carbonate, though not needed to effect the insertion, is required for the reaction to proceed and may ultimately act in controlling the pH of the reaction through the formation of potassium bicarbonate. The metallated pyridinium can oxidatively add into the alkenyl iodide (**D**),[153] forming a high energy Cu^{III} intermediate that undergoes rapid reductive elimination to liberate the product (**E**) and CuI, that then reinserts into the catalytic cycle.[144]

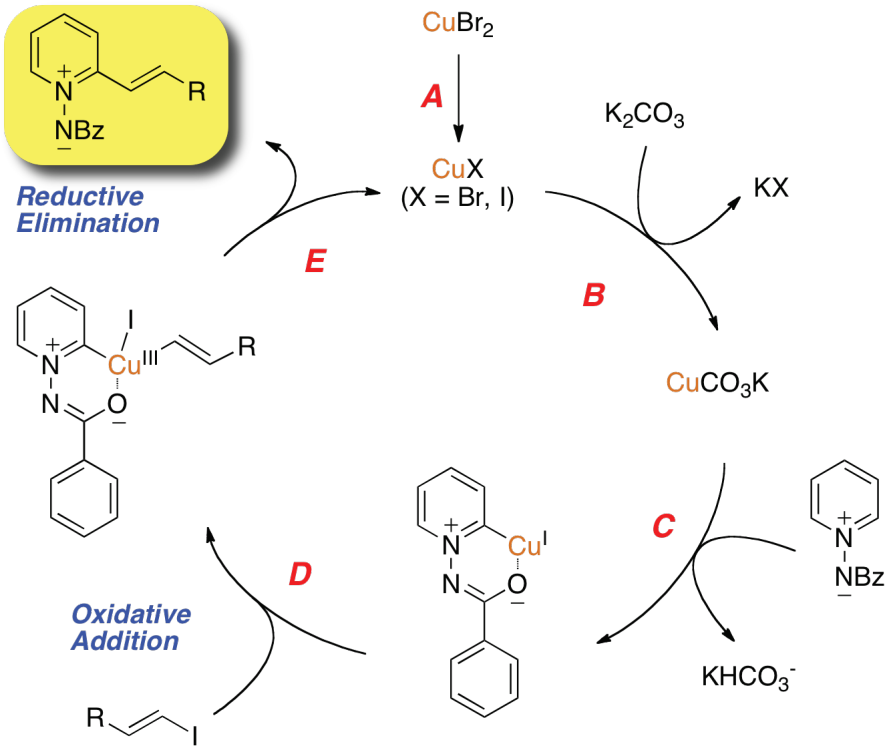


Figure 18. Proposed catalytic cycle for the direct alkenylation of *N*-iminopyridinium ylides.

3.4 Summary

In summary we have presented solutions to three problems present in organic synthesis. Firstly, we developed a high yielding, extremely selective synthesis of (*E*)-β-aryl vinyl iodides, with a large scope tolerating a breadth of functional groups. This method is advantageous as it avoids multistep syntheses by using readily available benzyl bromides, it does not employ expensive or toxic metal reagents, and offers facile reaction work-up.

These reagents were then employed in the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides. This provides a relatively general and facile method to access 2-alkenyl pyridines with moderate to excellent yields. Previous reported methods, though

efficient, suffer from harsh reaction conditions and poor functional group tolerance. In addition to supplying a new method for the synthesis of these compounds, we discovered that the reaction can be indeed be copper-catalyzed, adding to the few known examples of copper-catalyzed direct functionalizations, and the first copper-catalyzed direct alkenylation of electron-poor arenes.

Chapter 4
Synthesis of 2-Substituted Pyrazolo[1,5-*a*]pyridines

4.1 Introduction

Pyrazolopyridines (**Figure 20**) are an important class of nitrogen-containing compounds and are often employed as the backbone of pharmacologically active molecules. They are applied as indole isosteres due to their relatively high metabolic stability. Notably, pyrazolo[1,5-*a*]pyridines (**Figure 21**), specifically when substituted in the 2-position, are known for their ability to act as dopamine D3 agonists and antagonists, and are used in the treatment of various psychostimulant addictions.[154] Indeed the D3 receptor controls dopamine synthesis, release, neuronal firing and is linked to the pathophysiology of Parkinson's disease as well as schizophrenia.[154] Other applications of pyrazolo[1,5-a]pyridines include adenosine A1 receptor antagonists with potent diuretic activity as well as in the treatment of cardiac arrhythmias and for the diagnosis of ischemic heart diseases.[155] Finally, certain pyrazolo[1,5-*a*]pyridine derivates have also been found to have superior reactivity than Acyclovir and its prodrug Valacyclovir as antiherpetic agents.[155]

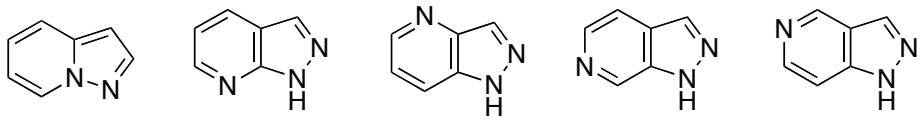


Figure 20. Various pyrazolopyridine analogues.

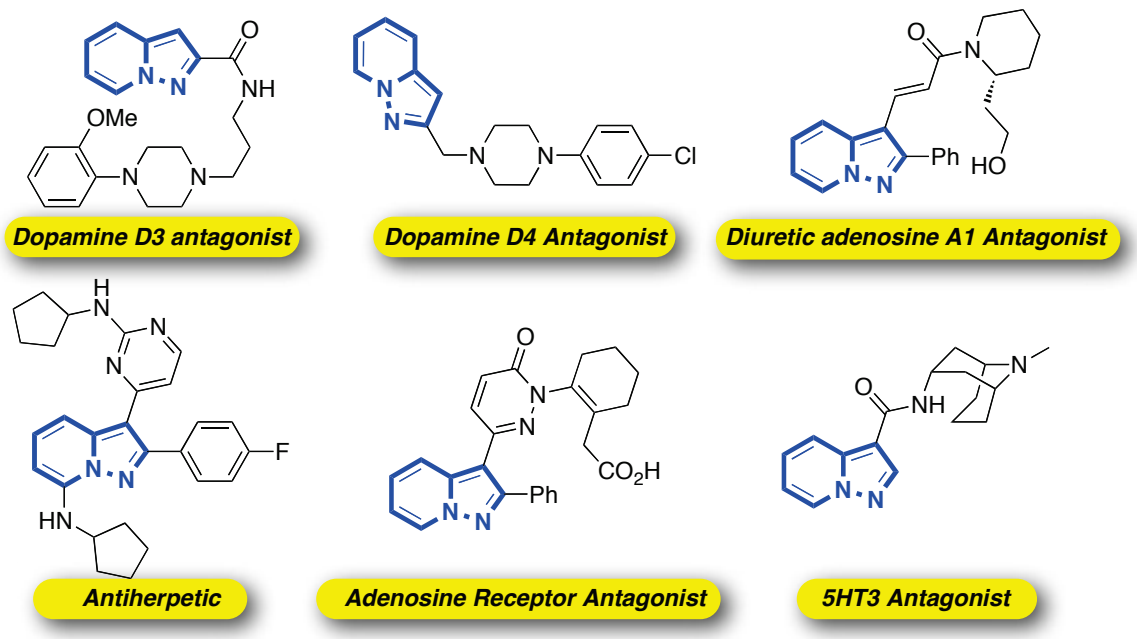
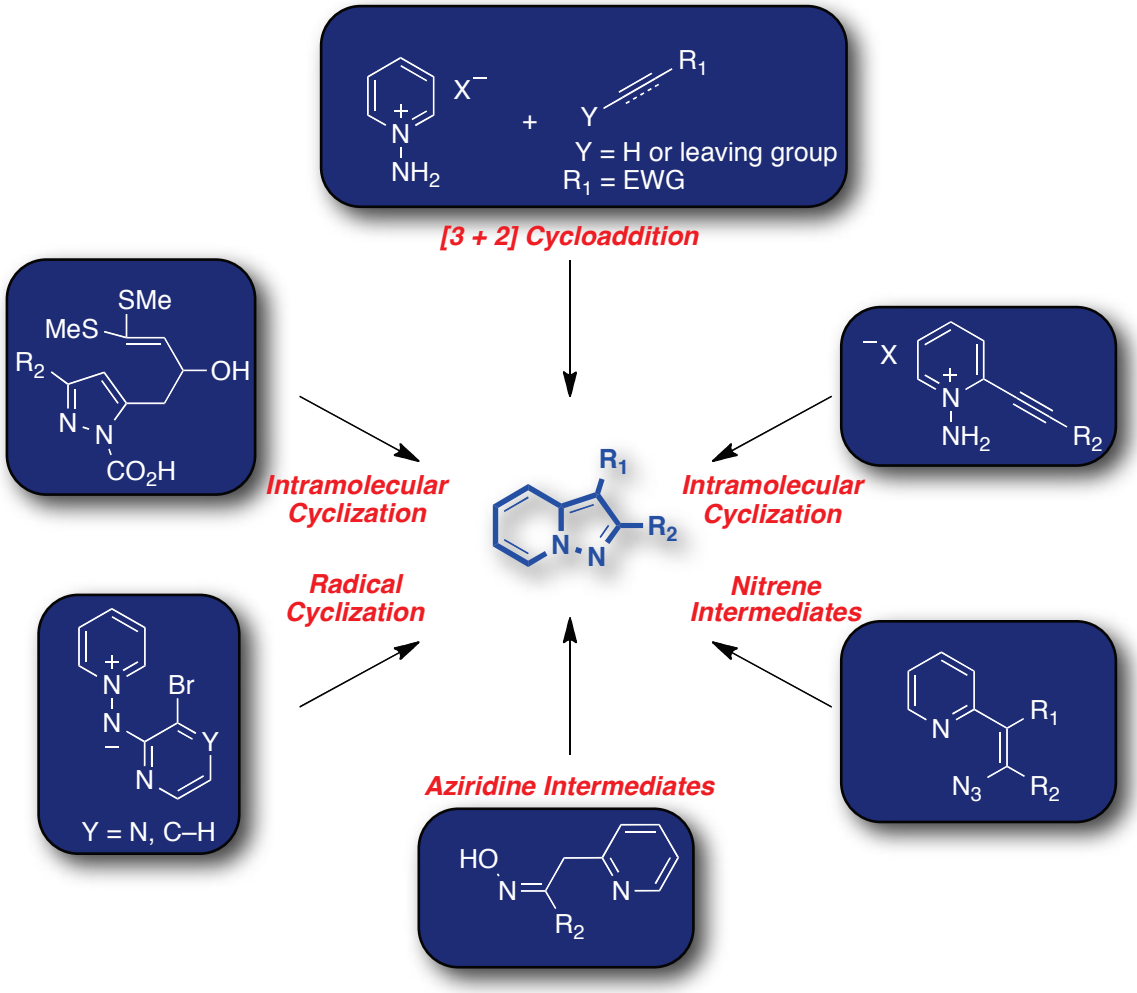


Figure 21. Various biologically active pyrazolo[1,5-*a*]pyridine derivatives.

Despite their clear importance, the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines (from here on generalized as pyrazolopyridines) remains a challenge. The most reported and perhaps reliable method involves a [3+2] cycloaddition onto an *N*-amino pyridinium salt (**Scheme 45**).[156] Though 2-substitution is possible, typically 2-, 3-disubstituted or 3-substituted pyrazolopyridines are observed. Additional limitations of this process include the need for an electron-withdrawing group on the dipolarophile, and the moderate yields of the products.[156] 2-Substituents on the heterocyclic system are possible through various intramolecular cyclizations, including displacements,[157] radical additions,[158] nitrenes,[159] and *via* rearrangements of pyridine derivatives bearing aziridine intermediates (**Scheme 45**).[156b,160] Several of these transformations have been reported with good yield, though several synthetic steps are often required to build-up these building blocks, hampering the efficiency of the preparation of these compounds.

Scheme 45. Various methods for the synthesis of pyrazolopyridines.

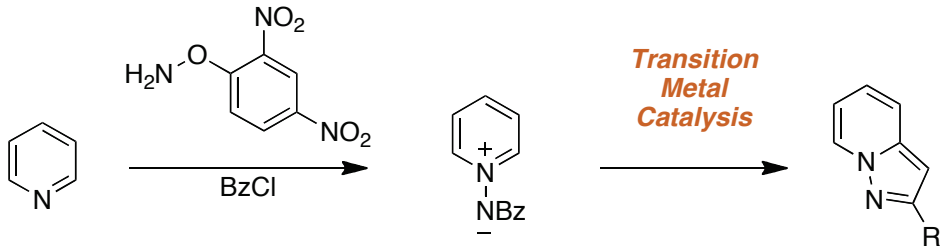


4.1.1 Research Goals

One way to improve the convergence of these reactions is through the use of cascade processes. Modern synthetic methodology emphasizes molecular complexity while minimizing the requisit number of synthetic steps. As such, cascade, or tandem, processes in which several bonds can be made/broken in a single reaction vessel have garnered much attention.[161] These domino sequences are often atom economical, and save considerable resources in both time and cost by limiting the number of operations

required to reach a specific target. An ideal scenario would also involve *direct* transformations in the cascade, further improving the overall economy of the process. While several applications of *N*-iminopyridinum ylides have been presented in this dissertation, until recently they have not been applied in tandem reactions. The following sections will describe the efficient synthesis of 2-substituted pyrazolopyridines from these pyridinium ylides through a direct functionalization/cyclization reaction involving various vinyl halides and alkynes. This is thought to be the first example of a direct functionalization/cyclization sequence. The total reaction sequence is two-steps from pyridine (**Scheme 45**), and the wide availability of coupling partners allows for the facile build-up of a library of medicinally relevant compounds.[162]

Scheme 45. Facile two-step synthesis of pyrazolo[1,5-*a*]pyridines from pyridine.



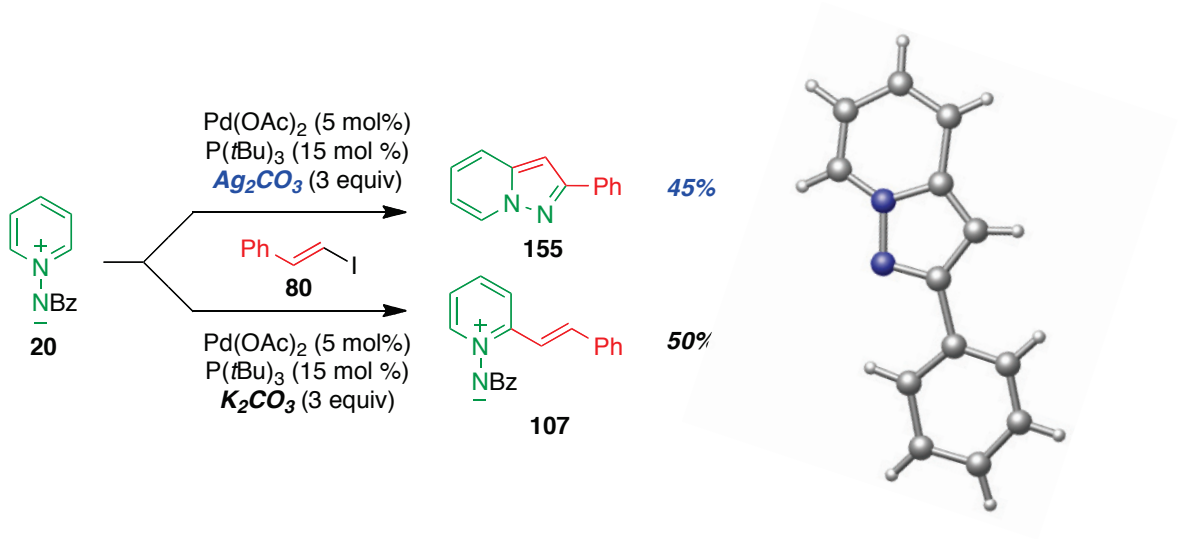
4.2 Results and Discussion

4.2.1 Reaction Optimization

During the work towards developing a palladium-catalyzed direct alkenylation reaction on *N*-iminopyridinium ylides,[144] we found that substituting K_2CO_3 with Ag_2CO_3 as the base led to the formation of 2-phenylpyrazolopyridine **155** (**Scheme 46**), as confirmed by x-ray crystallography. In the crude reaction mixture, no uncyclized product **107** was observed, and only the unreacted ylide **20** along with **80** and benzoic acid were present.[162] The initial explanation for this result was a palladium-catalyzed direct alkenylation followed by a silver-mediated cyclization process. The benzoic acid

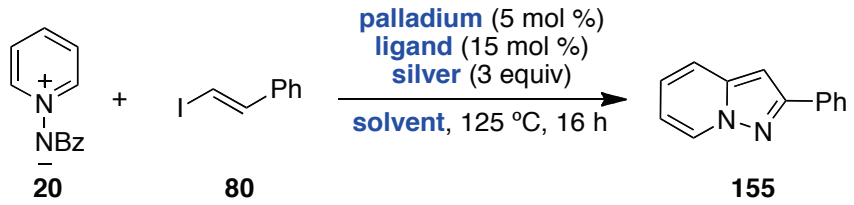
generated was presumably formed from the cleavage of the benzoyl moiety of the ylide. Mindful of the biological relevance of these compounds, in addition to the lengthy syntheses typically associated with them, we embarked on the optimization of this transformation.

Scheme 46. Initial synthesis and x-ray structure of pyrazolo[1,5-*a*]pyridine **155**.



Angélique Fortier, a current M.Sc. student, largely performed the optimization (**Table 37**).[162] A screening of silver salts determined that a carbonate/acetate motif was necessary to promote the reaction (entries 1-4), with silver benzoate being optimal (entry 4). Although $Pd(OAc)_2$ displayed similar reactivity, $PdBr_2$ proved to be superior to other palladium catalysts (entries 4-6). The process was relatively insensitive to the phosphine ligand employed, though $P(4\text{-MeOPh})_3$ did provide the best yields (entries 6-9). Etheral solvents were validated to be the best reaction media, with 1,4-dioxane chosen due to its relatively low volatility (entries 10-13), and a slight increase of the loading of ylide **20** gave the optimal reaction conditions (entry 14).[162] Ms. Fortier also considered other conditions such as reaction time and temperature, though it was discovered that decreasing time or lowering the heat available to the system proved deleterious.

Table 37. Selected optimization for the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines.



20 **80** **155**

entry	palladium	ligand	silver	solvent	yield (%)[a]
1	$Pd(OAc)_2$	$P(tBu)_3$	AgOTf	PhMe	<5
2	$Pd(OAc)_2$	$P(tBu)_3$	AgOAc	PhMe	13
3	$Pd(OAc)_2$	$P(tBu)_3$	Ag_2CO_3	PhMe	45
4	$Pd(OAc)_2$	$P(tBu)_3$	AgOBz	PhMe	50
5	$Pd_2(dba)_3$	$P(tBu)_3$	AgOBz	PhMe	31
6	$PdBr_2$	$P(tBu)_3$	AgOBz	PhMe	52
7	$PdBr_2$	PPh_3	AgOBz	PhMe	59
8	$PdBr_2$	$P(2\text{-}MePh)_3$	AgOBz	PhMe	60
9	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	PhMe	63
10	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	DMF	46
11	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	THF	64
12[b]	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	DME	63
13	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	1,4-dioxane	69
14[c]	$PdBr_2$	$P(4\text{-}MeOPh)_3$	AgOBz	1,4-dioxane	80

[a] Yield was determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] 1 equiv of **20** was used. [c] 2 equiv of **20** was used.

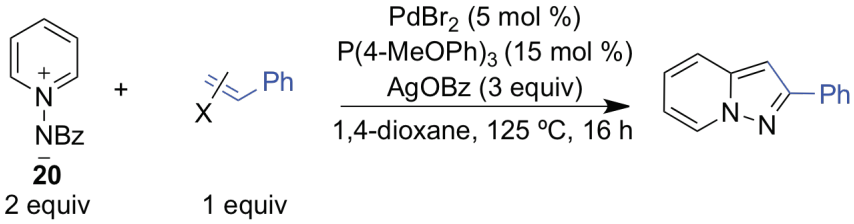
4.2.2 Scope of the Reaction

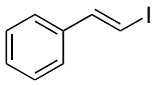
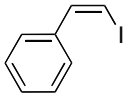
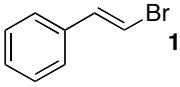
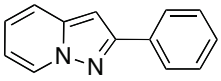
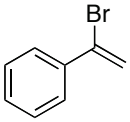
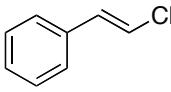
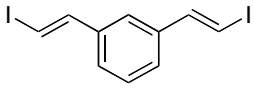
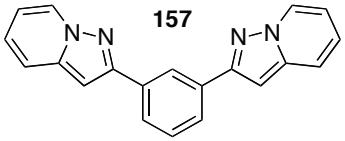
4.2.2.1 Vinyl Halides

With these conditions in hand we next explored the scope of the halide coupling partner. Given the plethora of vinyl halides already prepared,[141] and due to the medicinal interest of 2-phenyl pyrazolopyridines (**Figure 21**), we first considered these

pseudo-electrophiles. (**Table 38**). Both *E* and *Z* substituted styryl iodides provided the desired 2-phenyl pyrazolopyridine, though improved yields were noted for the *E*-alkene (entries 1, 2).[162] Styryl bromides were equally efficient (entries 3, 4), though chlorides proved unreactive with only starting material observed in the crude reaction mixture (entry 5).[163] The curious result obtained in entry 4 will be discussed further in Section 4.2.2.2**.** When the *bis*(vinyl) iodide **96** was employed, the *bis*-pyrazolopyridine was isolated in 40% yield (entry 8).

Table 38. Scope of unsubstituted styryl halides.

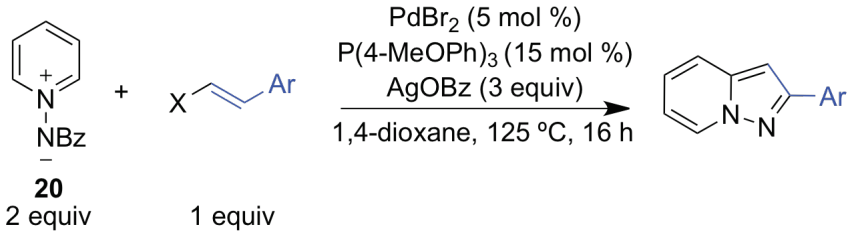


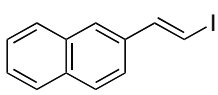
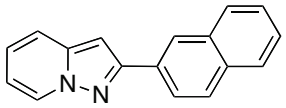
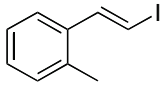
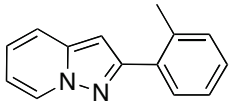
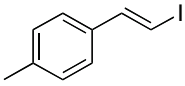
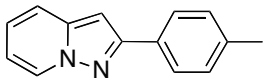
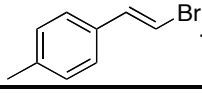
entry	alkenyl halide	product	yield (%)[a]
1	 **80**		78
2	 **109**		64
3	 **102**	 **155**	80
4	 **156**		58
5	 **97**		n/r
6[b]	 **96**	 **157**	40

[a] Yield of isolated product. [b] 4 equiv of **20** was used in the reaction.

We next considered electron-neutral substitution on the arene ring of the vinyl iodide (**Table 39**).[162,163] Napthalene was tolerated, though the product was obtained in moderate yield (entry 1). Methyl groups at the 2- and 4- positions were well endured (entries 2, 3), though with a slight negative effect in the former, presumably due to increased steric conjestion. As seen in the previous table, vinyl iodides and bromides displayed similar reactivity (entry 4).

Table 39. Study of electron-neutral substitution on the styryl halide arene ring.

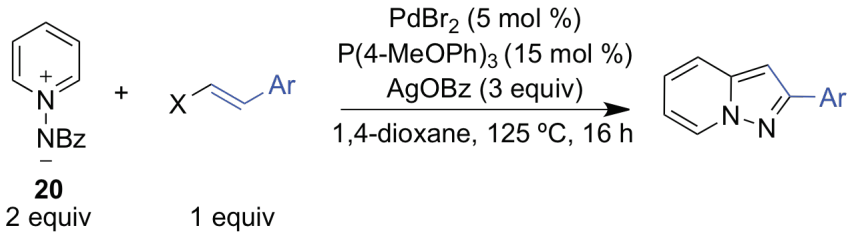


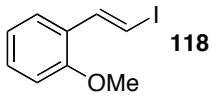
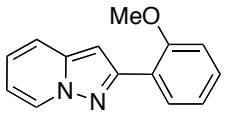
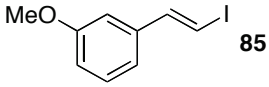
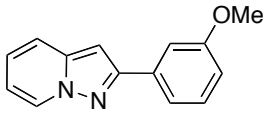
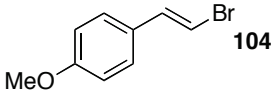
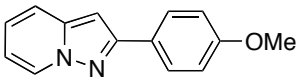
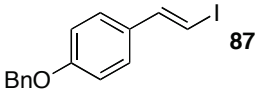
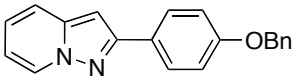
entry	alkenyl halide	product	yield (%)[a]
1	 **83**	 **158**	61
2	 **82**	 **159**	70
3	 **81**	 **160**	79
4	 **103**		76

[a] Yield of isolated product.

Electron-donating groups at the 2-, 3-, and 4-positions were operative in providing the product (**Table 40**). Interestingly benzyl ethers appeared more reactive than the 4-methoxy analogue.[162] Again, styryl bromides were equally reactive (entry 3).[163]

Table 40. Scope of electron-rich styryl halides.

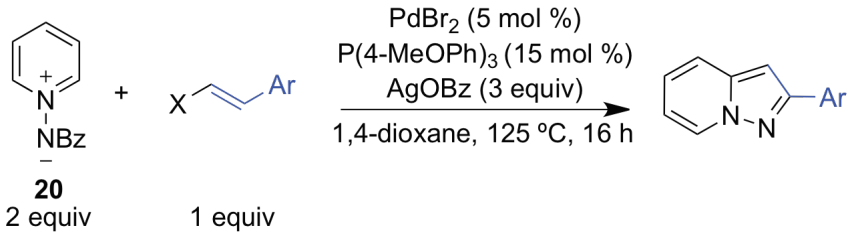


entry	alkenyl halide		product		yield (%)[a]
1		**118**		**161**	70
2		**85**		**162**	65
3		**104**		**163**	63
4		**87**		**164**	87

[a] Yield of isolated product.

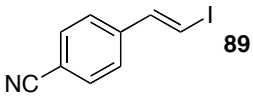
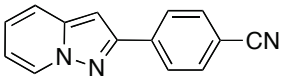
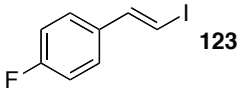
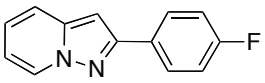
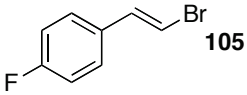
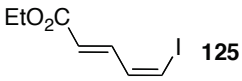
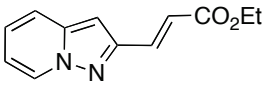
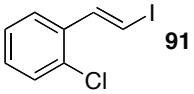
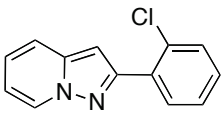
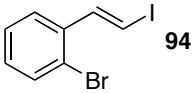
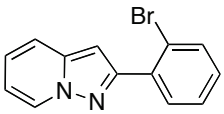
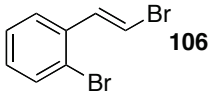
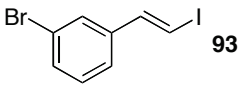
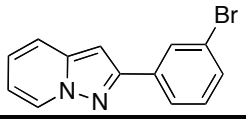
Next the effects of electron-poor arenes on the vinyl halide were explored.[162,163] Generally moderate to good yields were obtained (**Table 41**, entries 1, 3), and though not an arene, the diene **125** bearing a distal ester also reacted with synthetically useful results (entry 4). As noted in the previous chapter with the copper-catalyzed alkenylation, excellent chemoselectivity was observed with substrates containing halides on the aryl component (entries 5-8). With aryl chlorides and bromides no evidence of direct arylation was noted, with the 2-substituted pyrazolopyridine being the only outcome observed. Aryl iodides, however, yielded complex mixtures where the reaction byproducts could not be identified. This possibility was expected due to the large excess of silver salts required for the reaction to proceed.

Table 41. Scope of electron-poor and haloarenes in the synthesis of 2-substituted pyrazolopyridines.



20
2 equiv

1 equiv

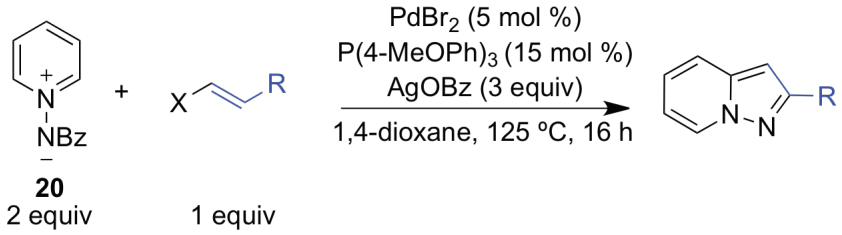
entry	alkenyl halide	product	yield (%)[a]
1	 **89**	 **165**	61
2	 **123**	 **166**	86
3	 **105**		79
4	 **125**	 **167**	49
5	 **91**	 **168**	63
6	 **94**	 **169**	70
7	 **106**		60
8	 **93**	 **170**	60

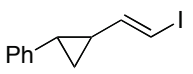
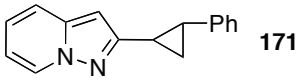
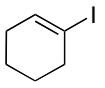
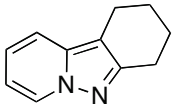
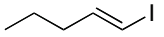
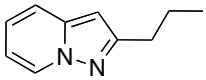
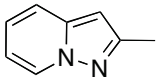
[a] Yield of isolated product.

As with the copper-catalyzed alkenylation, alkyl substitution on the double bond was a limiting factor in the process (**Table 42**).[162] Only vinyl iodide **127** bearing a cyclopropane provided satisfactory results (entry 1). Where the 1-iodocyclohexene **129**

was effective in the alkenylation, it failed to react in a productive fashion towards the pyrazolopyridine, with the crude reaction mixture displaying only starting material (entry 2). Iodide **131** proved completely unreactive (entry 3), as were various vinyl bromides bearing alkanes, such as *cis*-1-bromo propene (entry 4).

Table 42. Scope of vinyl halides bearing alkanes in the synthesis of 2-substituted pyrazolopyridines.



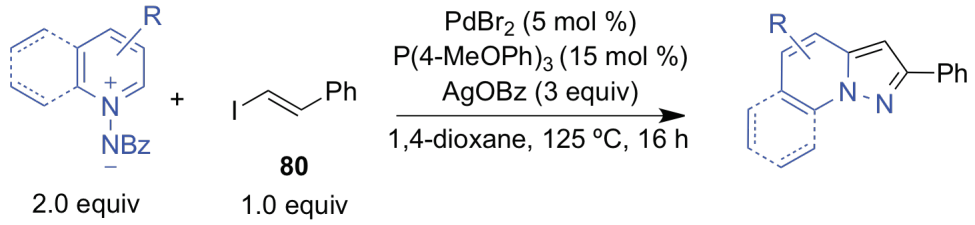
entry	alkenyl halide	product	yield (%)[a]
1	 **127**	 **171**	62
2	 **129**		<5
3	 **131**		<5
4			<5

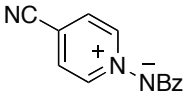
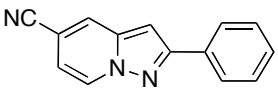
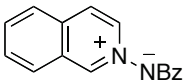
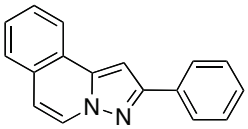
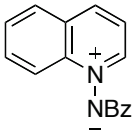
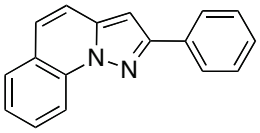
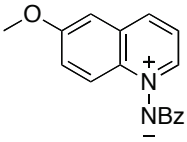
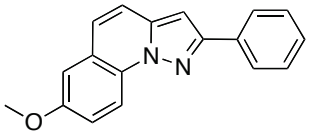
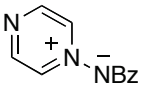
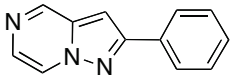
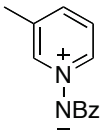
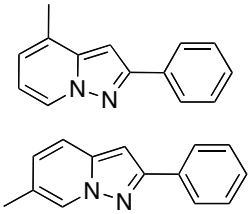
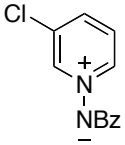
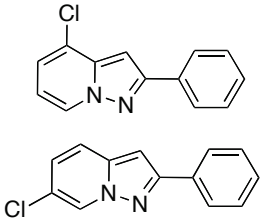
[a] Yield of isolated product.

Having exhausted many of the possibilities with regards to the halide coupling partner, we next considered the scope of the pyridinium ylide (**Table 43**).[162] A nitrile at the 4-position of the heterocyclic ring had little effect on the reaction (entry 1). Both the isoquinolonium and quinolonium ylides were viable partners (entries 2, 3), with the latter giving the pyrazolopyridine derivative in excellent yield. When the ylide derived from 6-methoxyquinoline was employed the yield decreased to 69% (entry 4), suggesting a possible effect of acidity at the 2-position of the ring in the transformation.

The pyrazine ylide **179** reacted, also furnishing the desired product in 69% yield (entry 5). Finally, 3-substituted pyridines reacted in good yields, with the least hindered product being the major product in both cases (entries 6, 7).

Table 43. Scope of the ylide in the synthesis of pyrazolopyridines from vinyl halides.



entry[a]	ylide		product		yield (%)[b]
1		**172**		**173**	62
2		**174**		**175**	60
3		**151**		**176**	90
4		**177**		**178**	69
5		**179**		**180**	69
6		**147**		**181**	77
7		**182**		**183**	90

[a] Yield of isolated product.

4.2.2.2 Alkyne Coupling Partners

We were puzzled by the result obtained with α-bromostyrene **156** (**Table 38**, entry 4), as the expected product was the 3-substituted pyrazolo[1,5-*a*]pyridine (**Scheme 47**). It was reasoned that the observed 2-substitution might result from first elimination of the alkene forming phenylacetylene, and that this may indeed be the reactive species in all the above cases.[163] To test this hypothesis, phenylacetylene was employed as the coupling partner under the reaction conditions and we were elated to find that the 2-phenyl pyrazolopyridine was isolated in 56% yield. Encouraged by this we embarked on a small reaction optimization with the goal of obtaining comparable reaction yields to those obtained with the styryl iodides and bromides. A short optimization sequence determined that the presence of the palladium catalyst, phosphine ligand, and silver source were essential to effect the transformation. Furthermore, the yields could be easily improved to 76% by adding an extra equivalent of both the ylide and silver salt (**Table 44**, entries 1-6). Though it can be argued that this decreases the efficiency of the reaction, the majority of the unreacted ylide could be recovered, giving a yield based on recoverd ylide starting material of 95% (entry 6).

Scheme 47. Proposed intermediate in the synthesis of 2-substituted pyrazolopyridines.

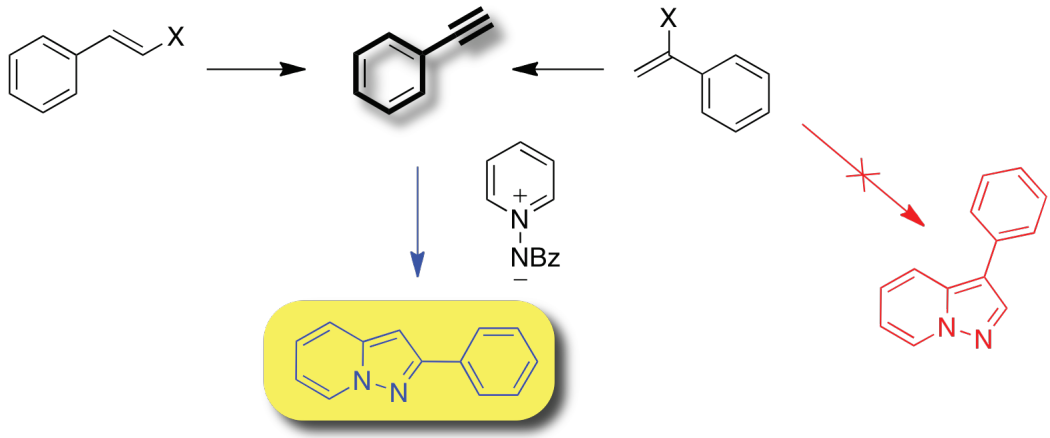
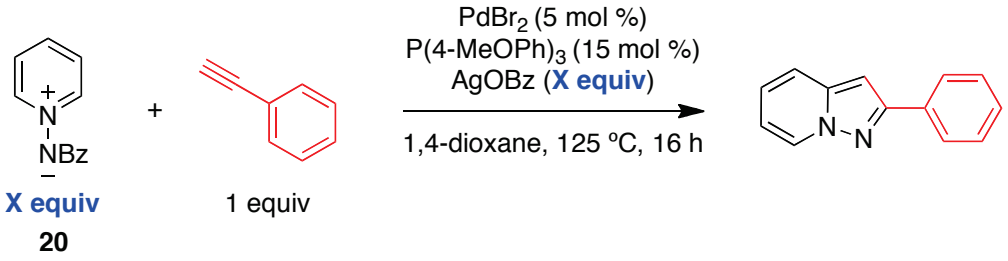


Table 44. Optimization for the sythesis of 2-pyrazolopyridines from phenylacetylene.

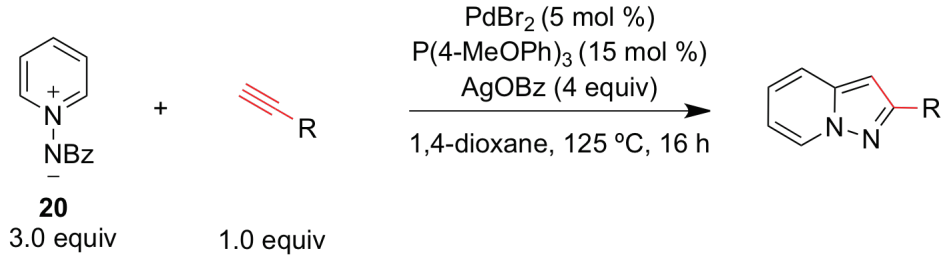


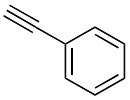
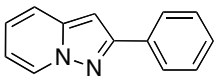
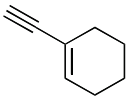
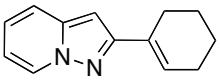
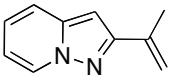
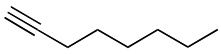
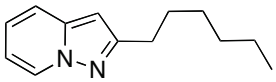
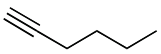
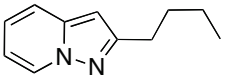
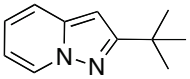
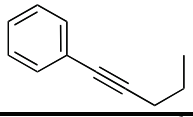
entry	equiv ylide	equiv AgOBz	yield (%)[a]
1	2	3	62
2	1	3	46
3	2	2	33
4	3	2	36
5	2	4	65
6	3	4	76[b] (95)[c]

[a] Yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Yield of isolated product. [c] Yield based on recovered ylide starting material.

With the slightly modified reaction conditions we explored the scope of the reaction with alkyne coupling partners.[163] Given the large scope obtained with (*E*)-β-aryl vinyl halides, and the fact that phenyl acetylene (**Table 45**, entry 1) gave nearly identical result to the styryl iodide **80** (76% vs 78%), we elected to pursue the scope of other substrates. 1-Ethynylcyclohexene reacted to give the desired pyrazolopyridine in 85% yield (entry 2), while the analogous 2-methyl-1-buten-3-yne only reacted in 29% (entry 3). Of note were 1-octyne, 1-hexyne, and 3,3-dimethyl-1-butyne, which reacted giving the 2-alkyl pyrazolopyridines in moderate to good yields (entries 4-6). This result demonstrated the complimentarity of these alkynes, as alkyl substituted vinyl halides proved largely incompatible. Internal alkynes were a limitation of the reaction displaying no reactivity (entry 7).

Table 45. Scope of alkynes in the synthesis of 2-substituted pyrazolopyridines.

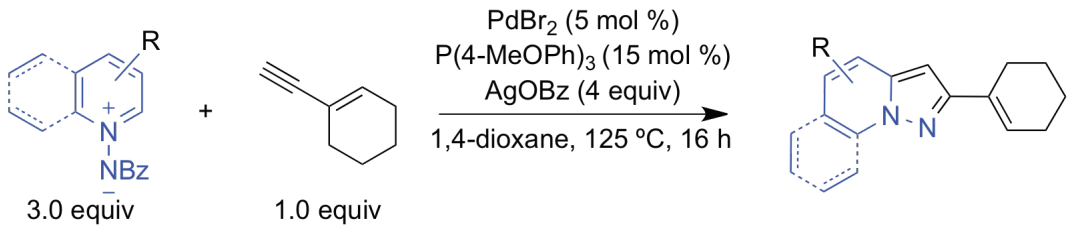


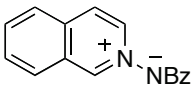
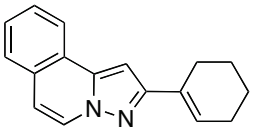
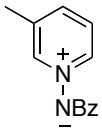
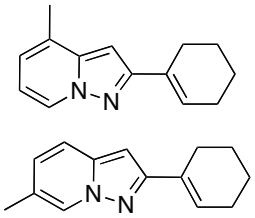
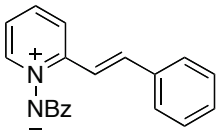
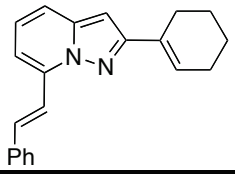
entry	alkyne	product		yield (%)[a]
1			**155**	76 (95)[b]
2			**184**	85
3			**185**	29
4			**186**	50
5			**187**	55
6			**188**	64
7				<5%

[a] Yield of isolated product. [b] Yield based on recovered starting material.

Finally we considered the scope of the ylide (**Table 46**). Though these results are preliminary, the isoquinolinium ylide reacted well, affording the product in 72% yield (entry 1). As with the iodo styrene, substitution at the 3-position gave the product in 64% yield, with an inseparable 3:1 mixture favouring the least hindered adduct (entry 2). The 2-alkenyl ylide reacted in only 21% (entry 3).

Table 46. Scope of the pyridinium in the synthesis of 2-subsituted pyrazolopyridines from alkynes.



entry	ylide		product		yield (%)[a]
1		**174**		**188**	71
2		**147**		**189**	64
3		**107**		**190**	21

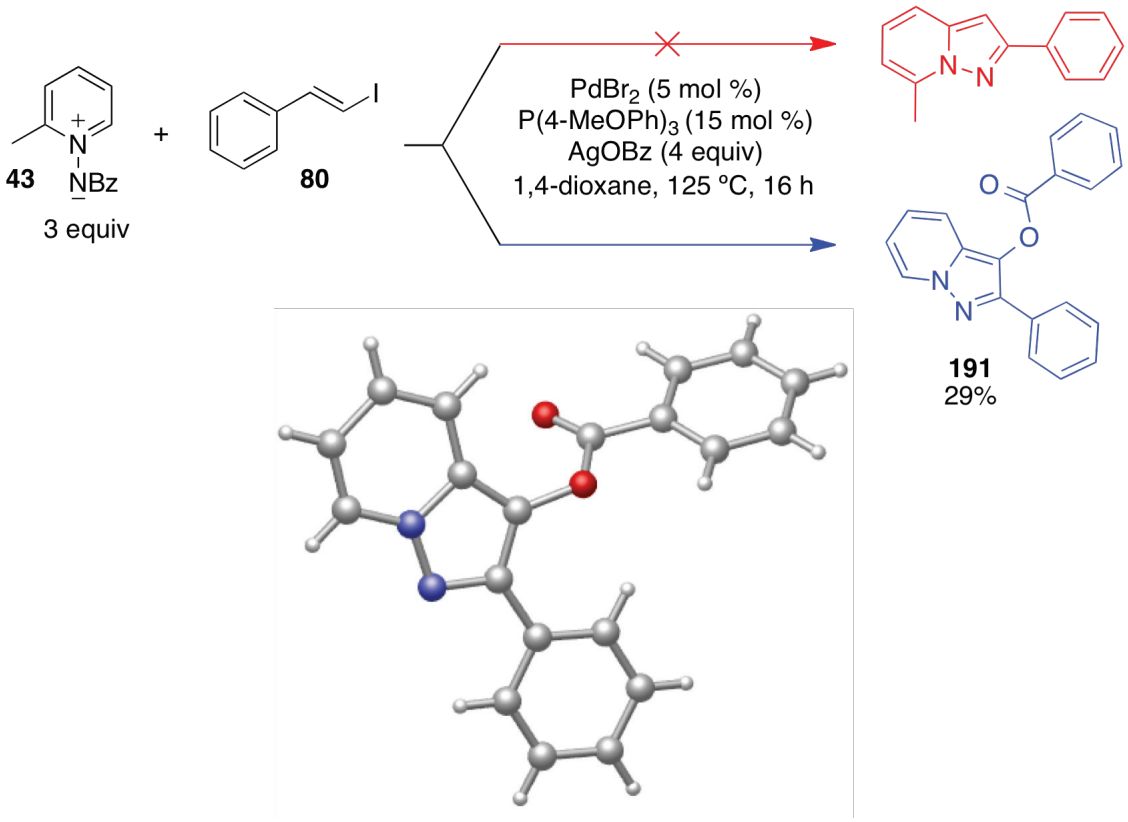
[a] Yield of isolated product.

4.2.2.4 2-Methyl N*-Iminopyridinium Ylides*

When the 2-picolonium ylide was applied in the reaction the anticipated methylated pyrazolopyridine was not observed. Instead the 2-phenyl, 3-acetyl pyazolopyridine was isolated in 29% yield (**Scheme 48**). The structure of the product was confirmed through X-ray crystallography. Additionally **191** was obtained without employing styryl iodide **80**, though the palladium catalyst and silver benzoate were needed to effect the transformation.[163] A complete optimization of this was not pursued

due to insufficient time, though it was found that replacing AgOBz with AgOAc did improve reaction yields to 49% (Eq. 28).

Scheme 48. Product obtained from 2-methyl *N*-iminopyrididinium ylide **43**.

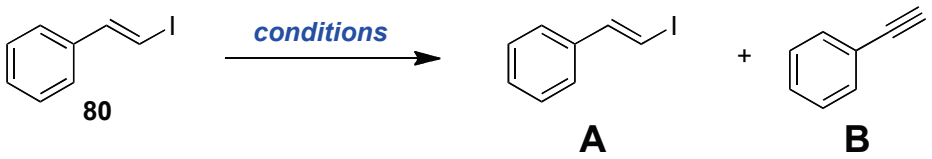


4.2.3 Mechanistic Investigations

As with the other direct functionalizations presented to date, we performed some mechanistic investigations to gain insight into the transformation.[163] As suggested *vide*

supra we believed that the active coupling partner in all cases was indeed the alkyne. A series of control experients were performed whereby the styryl iodide **80** was subjected to varients of the reaction conditions without the presence of the ylide (**Table 47**). In the presence of the palladium catalyst and phosphine ligand the iodide was recovered in 84% yield, with the balance appearing to be from degradation products (entry 1). In the presence of AgOBz alone, it was recovered in 73% yield, though there was some evidence for the elimination to the alkyne (entry 2). This suggests, though while halophilic, the silver source alone was not enough to dehalogenate the material. Finally, when the complete reaction conditions are employed, the iodide is completely consumed towards phenyl acetylene (entry 3). As evidenced by both ^{1}H and ^{13}C NMR, the resulting product was found to be the silver acetylide.

Table 47. Control studies for the fate of the alkenyl iodide.

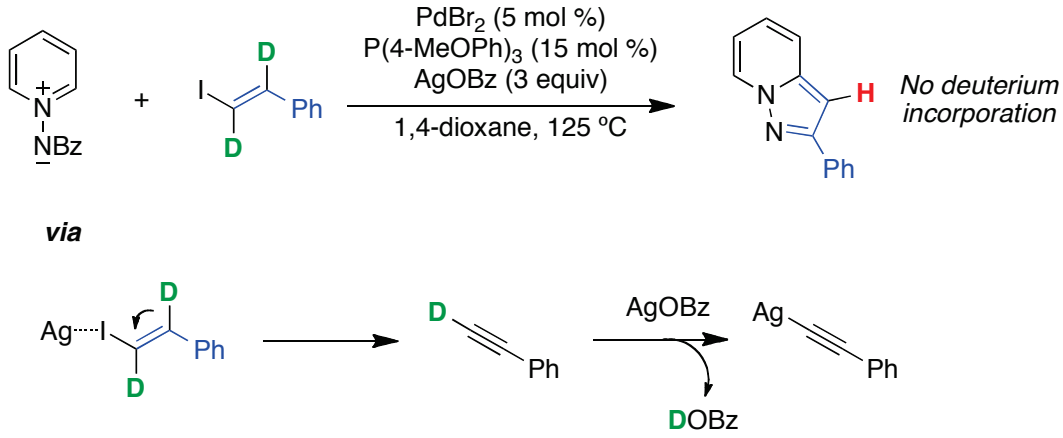


entry	conditions	product (%)[a]
1	iodide **80** (1 equiv), $PdBr_2$ (5 mol %), $P(4\text{-}MeOPh)_3$ (15 mol %), 1,4-dioxane [0.2 M], 125 ºC, 16 h	**A** (84)
2	iodide **80** (1 equiv), AgOBz (4 equiv), dioxane [0.2 M], 125 ºC, 16 h	**A** (73)
3	iodide **80** (1 equiv), $PdBr_2$ (5 mol %), $P(4\text{-}MeOPh)_3$ (15 mol %), AgOBz (4 equiv), 1,4-dioxane [0.2 M], 125 ºC, 16 h	**B** (>95)

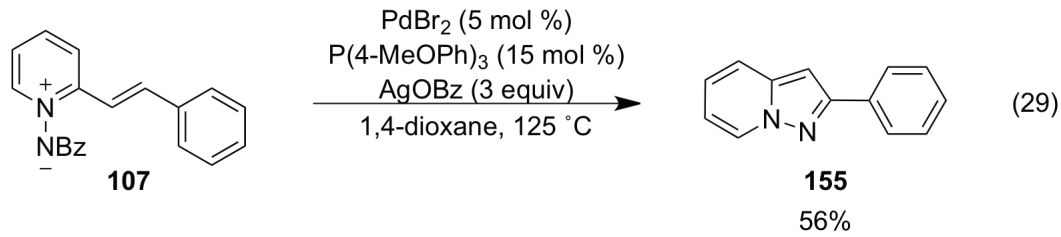
[a] Yields of isolated product.

Confirming that the alkyne can indeed be formed *in situ* we performed a labeling study to understand how the alkyne may couple to the pyridinium (**Scheme 49**).[163] The deuterated vinyl iodide was synthesized and employed in the reaction conditions. No deuterium was found in the final product, confirming the possible presence of the silver acetylide.

Scheme 49. Labelling study in the synthesis of 2-substituted pyrazolopyridines from vinyl iodides.



The low yield obtained for product **190** (**Table 46**, entry 3) partly results from the intramolecular cyclization of the alkene to give the 2-phenyl pyrazolopyridine **155** in 14% yield. As such we performed a series of control experiments akin to those of the styryl iodide. In the presence of the palladium or silver alone no cyclization was observed with only the 2-alkenyl pyridinium ylide recovered.[162] However, under the complete reaction conditions the 2-phenyl pyrazolo[1,5-*a*]pyridine could be isolated in 56% yield (Eq. 29),[164] suggesting that a tandem coupling cyclization pathway and not a [3+2] cycloaddition pathway was operative.

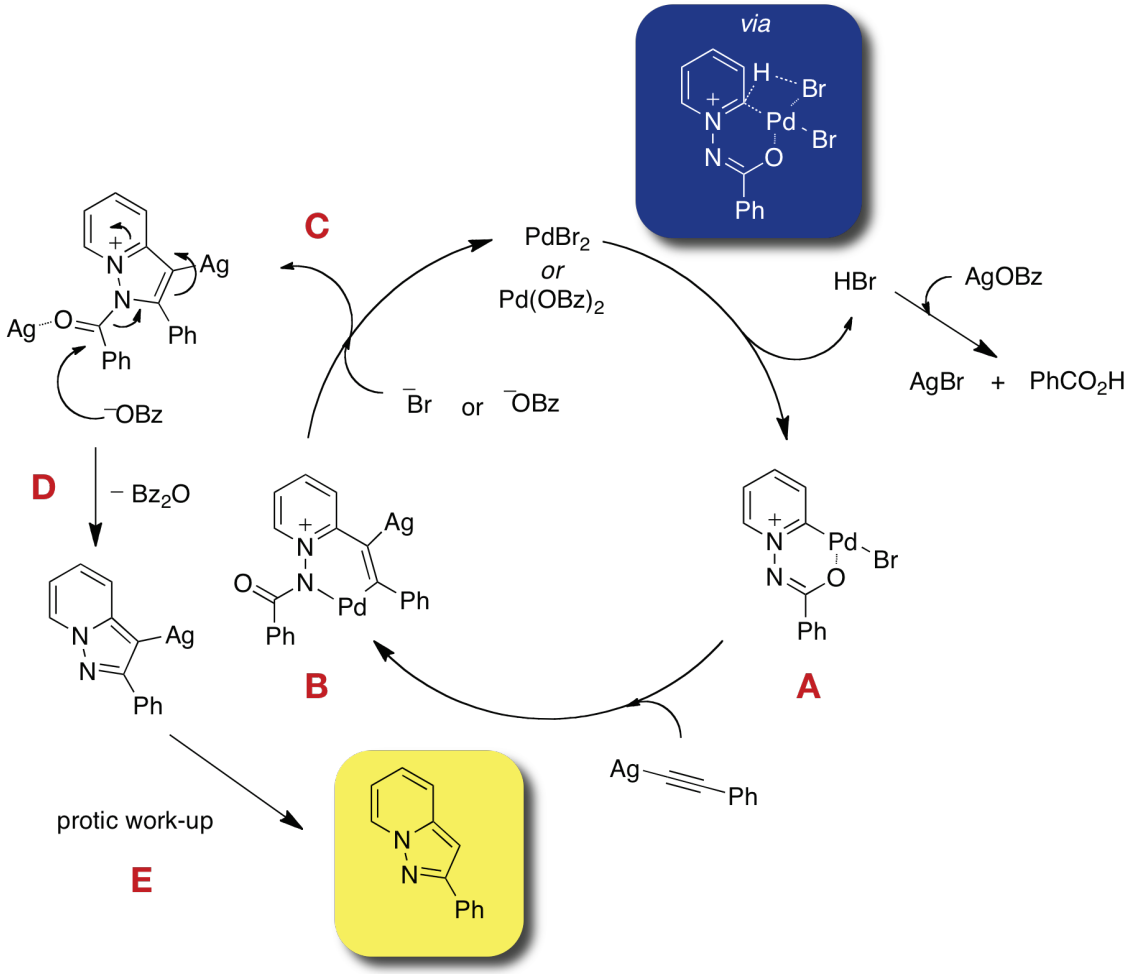


Finally, primary isotope values of 1.7 and 1.5 were noted when **80** and phenyl acetylene were used as coupling partners respectively.[163] As with what was observed in the Cu-catalyzed alkenylation, this suggests that the hydrogen atom lies either near the ylide or near the base in the transition state, making the state either reactant-like or

product-like. In addition, their similar value suggest that analogous reaction pathway is likely.

With this information in hand the following catalytic cycle is proposed. First, palladium undergoes directed insertion into the 2-position of the pyridinium ring (**Scheme 50**, **A**). This may happen *via* σ-bond metathesis, generating HBr that can be buffered by the excess benzoate. The palladated ylide then can add into the silver acetylide giving the metallocycle **B**. This is analogous to Fujiwara-type alkynylation reactions.[165] The role of the silver may be to activate the triple bond,[164] and the fact that this species is needed may explain why internal alkynes are not viable partners. It is possible that vinyl iodides bearing alkyl groups were non-operative as the elimination to the alkyne is more difficult for these substrates. When it was demonstrated that the uncyclized 2-vinyl ylide could undergo the cyclization, similar Pd-complexes had been reported, as has Pd-catalyzed conjugate addition of amines.[166] Reductive elimination (**C**) then gives the cyclic intermediate that rearomatizes through the expulsion of the benzoyl moiety (**D**). This may be assisted by silver acting as a Lewis acid. Protonolysis of the C–Ag bond at *C3* upon work up gives the observed product, explaining the lack or deuterium incorporation in the labeling studies (**E**).

Scheme 50. Proposed catalytic cycle for the synthesis of 2-substituted pyrazolopyridines.



4.3 Summary

In summary we have presented a novel, facile method for the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines in two steps from pyridine. Previous methods to prepare these compounds either require multi-step syntheses, or cannot avoid possible undesired substitution on the 3-position of the product that would require further

sequences for its removal. We solved these problems by developing an efficient cascade direct functionalization/cyclization process. As the two steps occur in tandem, the reaction can be said to be economical, and excess substrates employed can be recovered and reused. The scope of potential coupling partners tolerates a range of pyridinium species in conjunction with complimentary vinyl iodides, bromides, and alkynes. The flexibility of the reaction is likely due to the presence of a single reactive species, allowing chemists a wide choice of possible reagents in the preparation of these biologically relevant compounds.

Chapter 5
Palladium-Catalyzed *Umpolung* Direct Arylation Reactions

5.1 Introduction

The previous four chapters have been focused on direct transformations of electron-deficient arenes, covering arylation, alkenylation, and alkynylation/cyclization processes. Though this has been the primary focus of this doctoral research, we have also considered solving quandaries with non-heterocyclic arenes. As alluded in Chapter 1, the biaryl motif is a privileged structure (**Figure 22**), present in many facets of chemistry and biology. This motif is part of the scaffold of many pharmaceutically active reagents, natural products, agrochemicals, dyes, as well as in supramolecular and organomaterial sciences.[2e,f, 5, 6,167] Direct arylation reactions have provided a solution to some of the problems associated with cross coupling chemistry that has dominated the means of the synthesis of these compounds.[8,9,13] This technology has achieved this by eliminating one of the two (if not both) of the preactivated handles needed on the coupling partners.

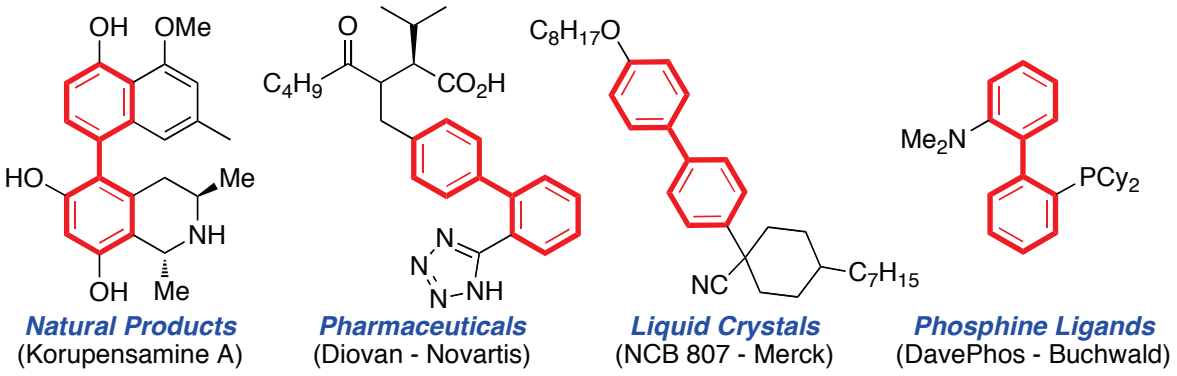
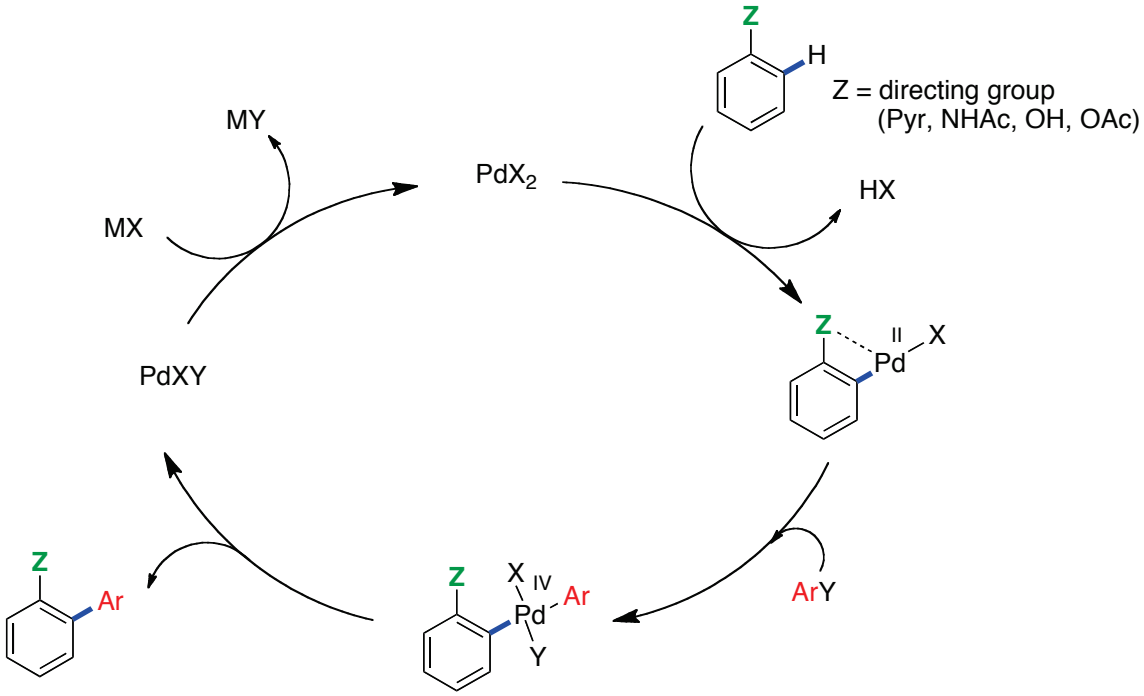


Figure 22. Selected examples of the biaryl motif.

Of the direct arylations described, the most dominant class of reactions involves the use of a directing group to facilitate the addition of a transition metal, typically palladium,

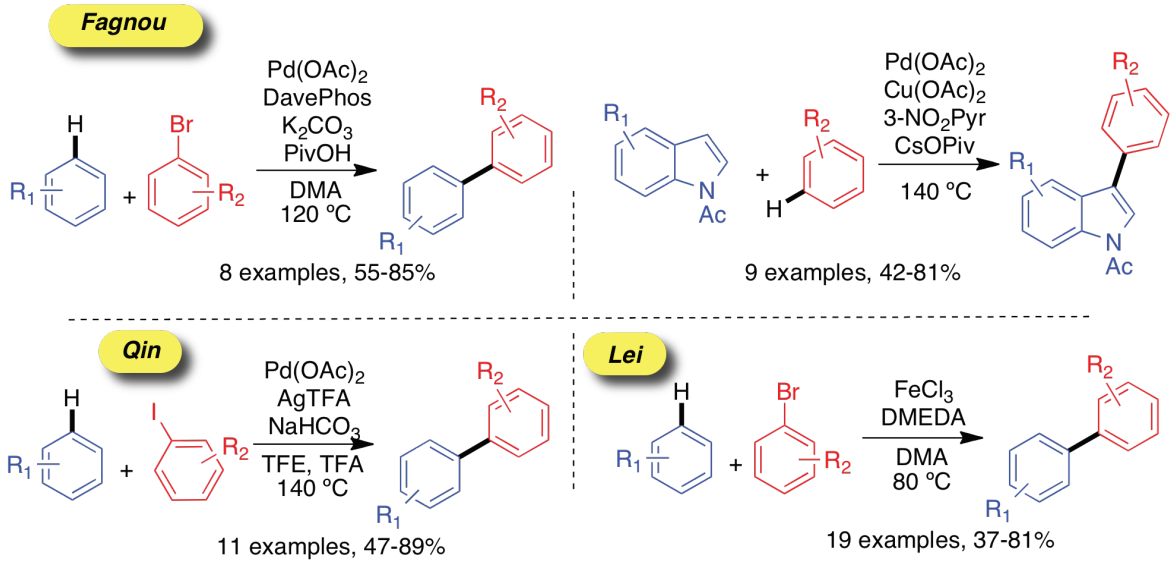
into the C–H bond. There are too many examples to enumerate here, but a common theme outlines that the resulting metallocycle then oxidatively adds into an aryl halide to generate a high-energy species that quickly reductively eliminates to afford the desired product (**Scheme 53**).[14c,168] There have been a plethora of accounts, describing various directing groups and coupling partners, covering a wide range of potential substrates. However, the *umpolung* version of this process, until recently, had not been described. This approach would rely on a directing group facilitating oxidative addition into an *ortho* C–X bond where X is a suitable leaving group. The stabilized metallocycle could then be used in a direct arylation reaction with an unactivated arene. The advantage of this method is that the aryl halide can be readily prepared from inexpensive starting materials by directed orthometallation chemistry.[169] Also, the arene undergoing C–H substitution can be used not only as a reactive species, but also as a solvent and separated and reused for further reactions.

Scheme 53. General catalytic-cycle for traditional directed direct arylation reactions.



There have been very few examples of the direct arylation of benzene (**Scheme 54**). In 2006 Fagnou reported the palladium-catalyzed arylation of benzene with aryl bromides.[53] This elegant account can be considered a seminal paper in directing group-free arylation methodologies, though suffers from several drawback such as limited substrate scope, mostly moderate yields, and the inclusion of several reagents/additives into the reaction mixture, complicating the reaction set-up. Subsequently they disclosed a direct C–H / C–H coupling of benzene with indoles.[14a] Albeit remarkably atom economical and a vital precedent, again limited substrate scope and the inclusion of multiple items into the reaction mixture can be considered as a drawback. Qin described the arylation of benzene with iodoarenes, though an excess of silver salts and trifluoroethanol were needed, while reporting limited scope.[170] Finally Lei disclosed an iron-catalyzed arylation of benzene in 2010, though this will be discussed further in the following chapter.[171]

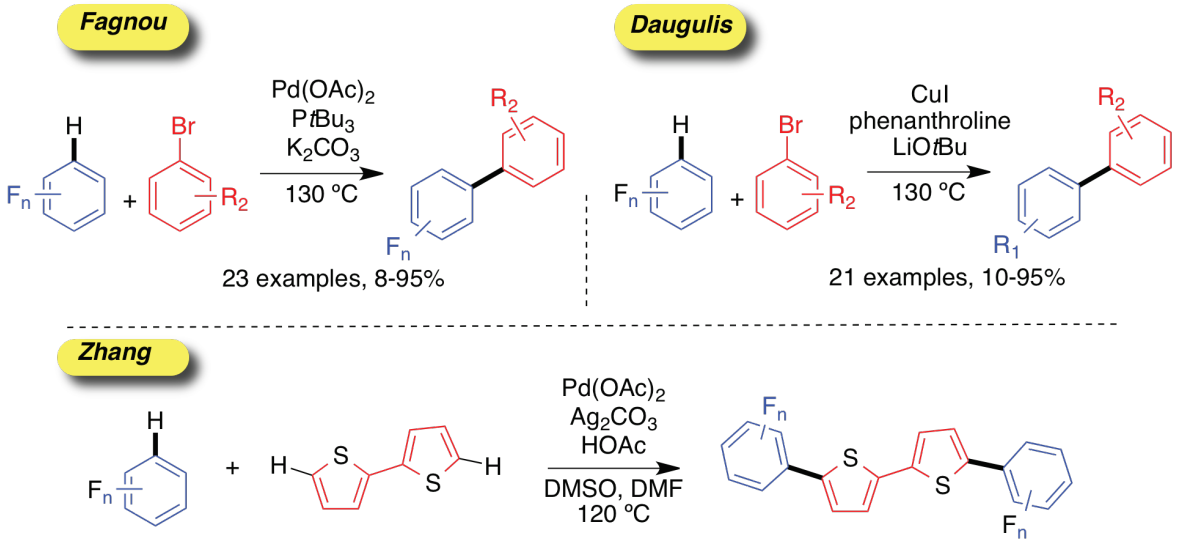
Scheme 54. Few known examples of the direct arylation of benzene.



More often, the arylation of benzene derivatives occurs with electron-poor arenes, namely perfluoroarenes (**Scheme 55**). Studies have elucidated that this is a consequence of the increased acidity of the reactive C–H bonds, as well as the coordinative properties of

the fluorine atom. Again Fagnou was among the pioneers in this area, publishing two accounts and using these substrates to help elucidate the often cited 'concerted metallation-deprotonation' pathway for arylation.[54,172] Daugulis has also disclosed a few accounts applying copper catalysis.[57,131] This reaction is believed to pass through a simple deprotonation and metallation of the arene, explaining the need for more electron-poor substrates. When very strong bases are employed, benzyne intermediates have been proposed. Recently Zhang uncovered an oxidative C–H / C–H coupling between electron-rich thiophenes and perfluoroarenes.[173] The role of Ag_2CO_3 in this account is thought to be that of an oxidant, regenerating the active Pd^{II} catalyst. They also applied this process to Heck-like reactions whereby the perfluoroarene was added across an alkene.[174]

Scheme 55. Application of electron-deficient non-heterocyclic arenes in direct arylation reactions.

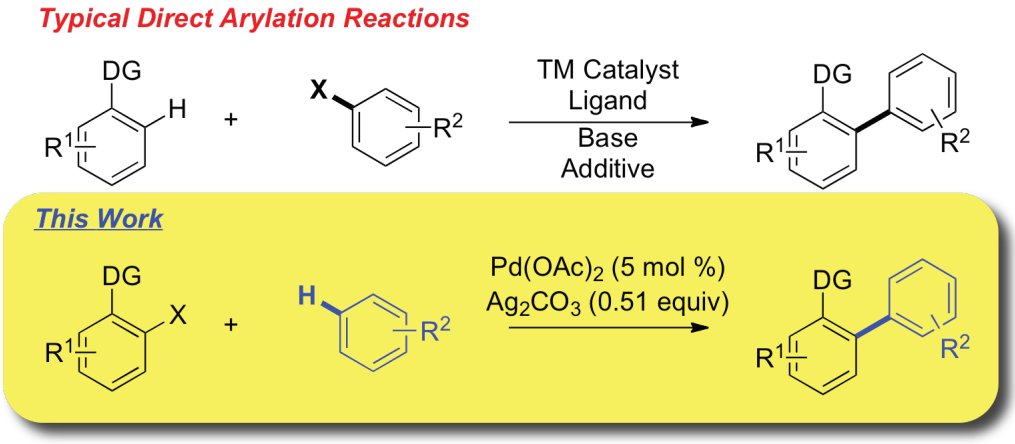


5.1.1 Research Goals

The remainder of this chapter will discuss the work on a facile, high-yielding, palladium-catalyzed direct arylation reaction between an aryl halide bearing an *ortho*-directing group and an unactivated arene. This displays opposite reactivity to what has been

typically reported in such transformations and adds to the few examples of the direct arylation of benzene derivatives. As will be described, the procedure nessitates only a catalytic amount of palladium in absence of a phosphine ligand and a substoichiometric amount of silver carbonate.[175]

Scheme 56. Proposed direct arylation reaction.

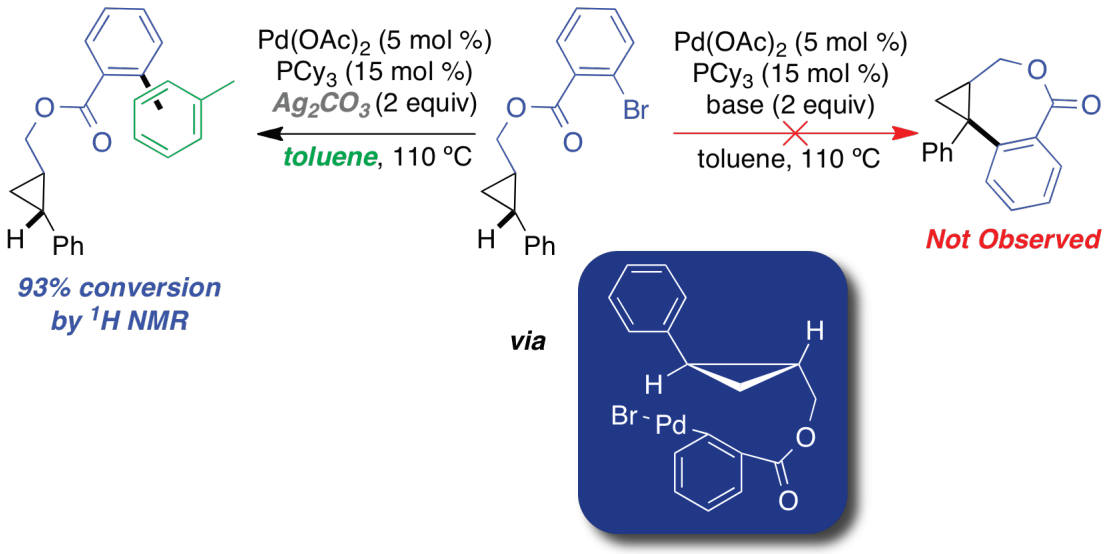


5.2 Results and Discussion

5.2.1 Reaction Optimization

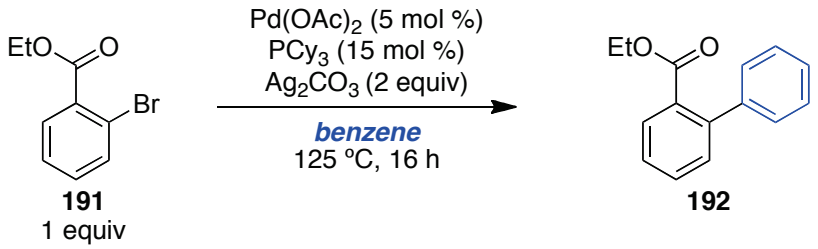
The origins of this project stemmed through attempts of intramolecular cyclopropane arylation. It was reasoned that the cyclopropane in **Scheme 57** would be ideally configured to undergo C–H arylation, being additionally activated considering it is also at the benzylic site. Several efforts were made to effect the transformation with little success. However, when applying Ag_2CO_3 as the base 93% of the starting material was consumed. Further analysis determined that the observed product was the result of the toluene solvent coupling with the aryl bromide.

Scheme 57. Discovery of the palladium-catalyzed *umpolung* arylation.



We postulated early that the cyclopropane moiety of the molecule might simply be acting as an exotic ester, directing the catalyst towards oxidative addition. To verify this, ethyl 2-bromobenzoate **191** was prepared and subjected to the reaction conditions, this time using benzene as the reaction medium (**Table 48**). We were delighted to observe the desired biaryl in 93% yield using 100 equiv of benzene (entry 1). Also, reproducibility could be improved by increasing the temperature to 125 ºC (entry 2). Conscious of the literature precedent detailing few examples of benzene arylation processes, in addition to the fact that directing groups had not yet been employed in this fashion, we embarked on a preliminary optimization of the reaction. We found that excellent conversions were obtained with as little as 30 equiv of the reagent/solvent (entries 3, 4). Good conversions were obtained with lower amounts, though the reaction was less clean, yielding complex mixtures (entry 5). This however could be improved through the use of a co-solvent (entry 6). For sake of simplicity, we elected to use 100 equiv of the arene as the solvent.

Table 48. Initial *umpolung* arylation optimization with ethyl 2-bromobenzoate.

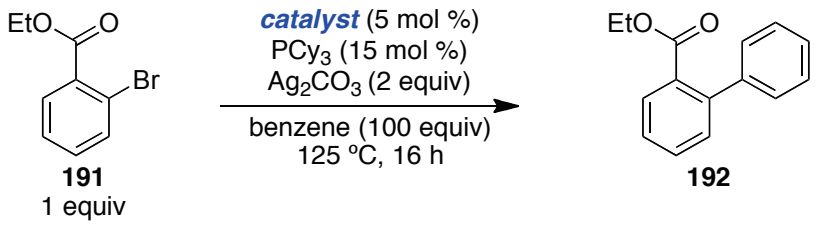


entry	solvent	equiv C_6H_6	yield **192** (%)[a]
1[b]	benzene	100	92
2	benzene	100	93
3	benzene	120	98
4	benzene	30	93
5	benzene	15	66
6	10% benzene in 1,4-dioxane	20	73

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Reaction performed at 110 °C

A former M.Sc. student (Fredéric Vallée) assisted with the screening of palladium and ligand sources. As anticipated, the reaction did not proceed in absence of the catalyst (**Table 49**, entry 1). We quickly determined that $Pd(OAc)_2$ was by far the most reactive catalyst (entries 2-6). Nickel (entries 7, 8), copper (entries 9, 10), and iron catalysts (entries 11, 12) were not effective in providing the biaryl compound.

Table 49. Screening of catalysts in the palladium-catalyzed direct arylation of benzene.

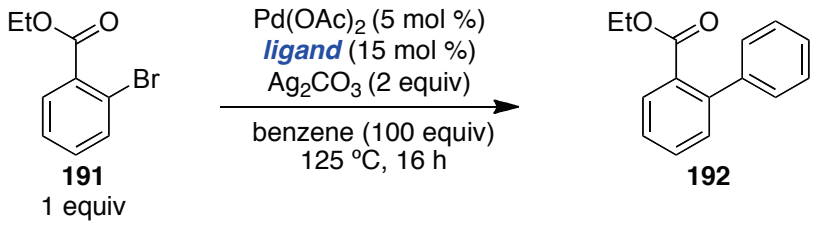


entry	catalyst	yield **192** (%)[a]	entry	catalyst	yield **192** (%)[a]
1	none	<5	7[b]	$Ni(COD)_2$	<5
2	$Pd(OAc)_2$	92	8	$Ni(COD)_2$	<5
3	PdI_2	7	9	CuI	<5
4	$Pd_2(dba)_3$	6	10	$CuBr_2$	<5
5	$Pd(PPh_3)_4$	<5	11[b]	$Fe(acac)_3$	<5
6	PEPPSI	<5	12	$Fe(acac)_3$	<5

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Reaction performed in absence of a ligand.

Ligand screening found little sensitivity towards the phosphine additive, tolerating both mono (**Table 50**, entries 1-3) and bidentate species (entries 4-6), with all reagents attempted providing yields in excess of 80%. We were elated to discover that the best conditions observed involved the absence of any ligand (entry 7), giving a more economical reaction in terms of both cost and time. Furthermore, inert atmosphere was not required, with the arylation performing equally well in the presence of air, bestowing the product in 97% yield (entry 8).

Table 50. Screening of ligands in the palladium-catalyzed direct arylation of benzene.

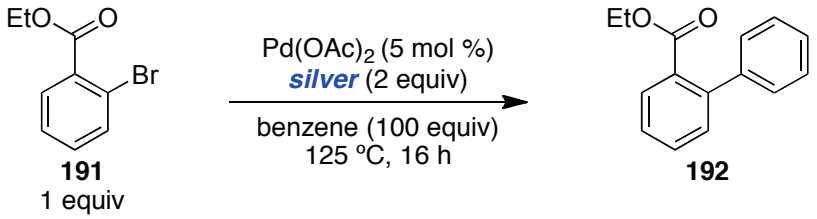


entry	ligand	yield **192** (%)[a]	entry	ligand	yield **192** (%)[a]
1	PCy_3	92	5	BINAP	91
2	PPh_3	87	6	MeDuPhos monoxide	95
3	DavePhos	84	7	none	97
4	DIOP	80	8[b]	none	97

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Performed in presence of air.

Though it could be argued that optimal conditions were in hand, we studied the silver reagent in order to gain a better understanding of the process. A small screening determined that carbonate/acetate motif was again essential for the reaction, with Ag_2CO_3 proving to be most favourable (**Table 51**). An investigation of the loading gave particularly interesting results denoting complete linearity (**Figure 23**). Only 0.51 equiv of Ag_2CO_3 was need to effect 98% conversion to the biphenyl, and 0.25 equiv have 53 %, and 0.11 equiv yielded 21%. Consequently, 0.51 equiv was chosen as the loading. While substoichiometric in quantity, for every mole of the reagent there are two moles of silver, demonstrating an efficient methodology whereby all the silver included in the reaction goes towards the formation of the desired biaryl.

Table 51. Silver screening for the optimization of the palladium-catalyzed *umpolung* arylation of benzene.



entry	silver	yield **192** (%)[a]	entry	silver	yield **192** (%)[a]
1	Ag_2CO_3	98	4	$AgNO_2$	<5
2	AgOAc	71	5	none	<5
3	AgO	<5			

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Performed in presence of air.

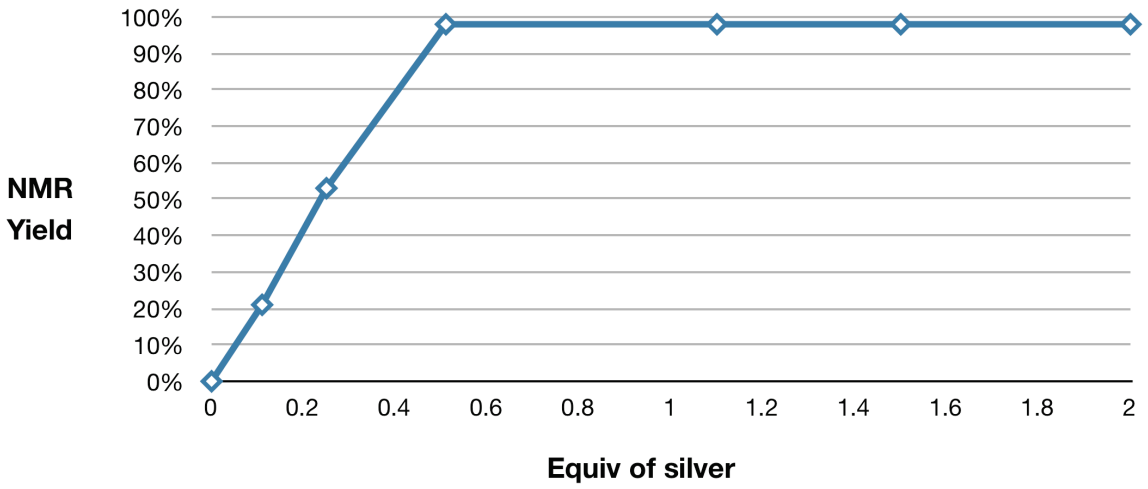
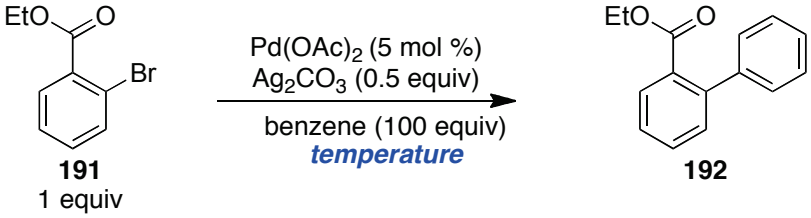


Figure 23. Dependancy of yield on silver loading.

Finally, we re-verified the reaction temperature only to determine that the optimal conditions were indeed 125 ºC, with yields tumbling rapidly below 110 ºC (**Table 52**). An investigation of the reaction time demonstrated that 8 h was needed to obtain 90%

conversion to the product (**Figure 24**), though 16 h was chosen for ease of set-up and work-up, in addition to maximize conversions.

Table 52. Effect of temperature on the palladium-catalyzed direct *umpolung* arylation of benzene.



entry	reaction temperature (ºC)	yield **192** (%)[a]
1	125	98
2	110	78
3	100	37
4	90	25
5	80	15
6	60	<5

[a] Yields are measured by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

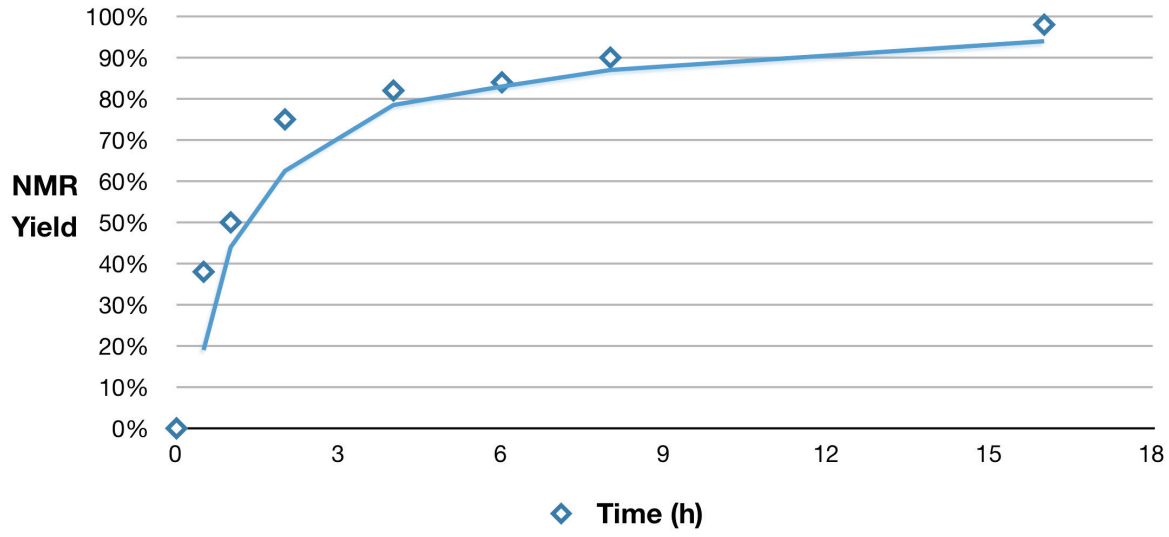
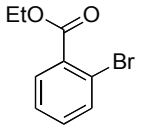
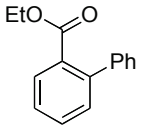
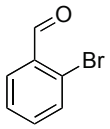
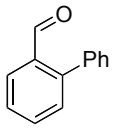
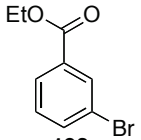
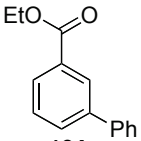
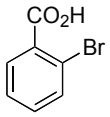
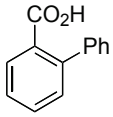
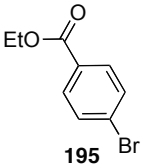
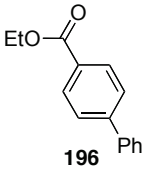
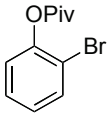
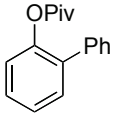
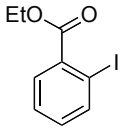
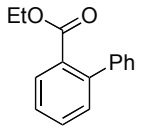
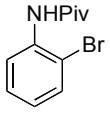
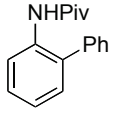
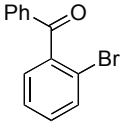
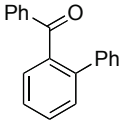
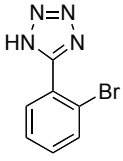
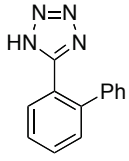
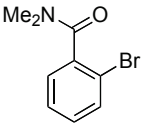
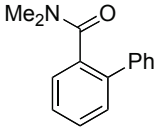
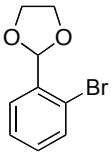
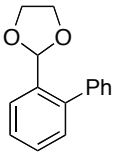
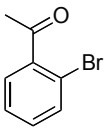
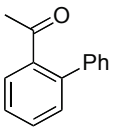
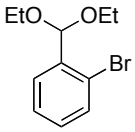
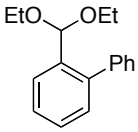


Figure 24. Conversion vs time for the palladium-catalyzed direct arylation of benzene.

5.2.2 Scope of the Reaction

With the optimized conditions in hand the scope of the directing group was explored with Melanie Lorion, a summer intern student (**Table 53**).[175] The presence of the coordinating functionality *ortho* to the halide is essential, as *meta* and *para* substituted halides provided poor conversion to the product (entries 1-3). Aryl iodides were equally reactive (entry 4), though 2-chloroethylbenzoate was unresponsive. This was expected, as typically electron-rich phosphines are needed to assist palladium in the oxidative addition into the C–Cl bond. A notable trend is improved yields as the Lewis basicity of the directing group is increased.[175] Consequently phenyl ketone (entry 5) is more responsive than esters (entries 1, 4), and amides are also very reactive (entry 6). 2'-Bromoacetophenone reacts in moderate yield despite the presence of an enolizable center (entry 7). 2-Bromobenzaldehyde reacts in good yield (entry 8). 2-Bromobenzoic acid gave full conversion though the desired product was only isolated in 42% yield (entry 9). This was thought to be the result of decarboxylation of the product under the reaction conditions, and the resulting biphenyl was removed during purification. This could not be verified however as biphenyl resulting from homocoupling of benzene was always observed, albeit in a non-reproducible manner.[175] Thus differentiating the biphenyl from decarboxylation of the naturally occurring by-product was not possible. Pivalate protected 2-bromophenol and 2-bromoaniline gave products in 25% and 33% respectively (entries 10, 11). In both cases the halide was completely consumed, and the balance of the material in the reaction was a complex mixture. This poorer reactivity is believed to be the result of the formation of a six-membered palladacycle intermediate, as opposed to a more kinetically favoured 5-membered cycle, as the Lewis basicity of the *O*- and *N*-Piv groups are comparable to those of the ester and aldehyde respectively.[175] Other directing groups such as tetrazole, and both cyclic and acyclic acetals were not suitable (entries 12-14).

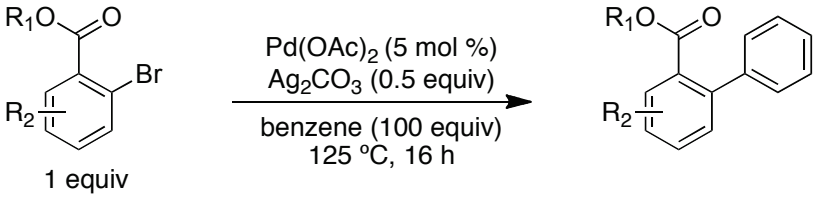
Table 53. Scope of the directing group in the palladium-catalyzed direct *umpolung* arylation of benzene.

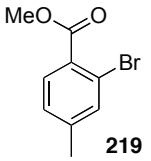
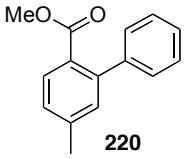
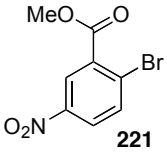
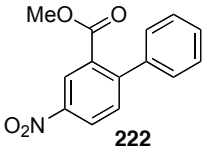
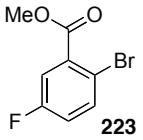
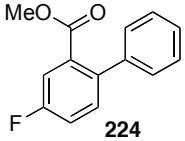
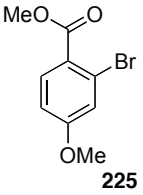
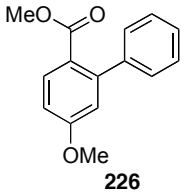
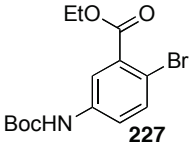
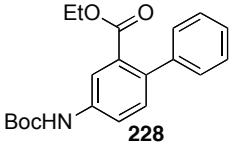
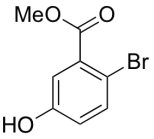
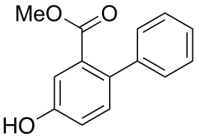
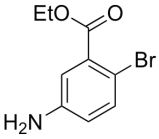
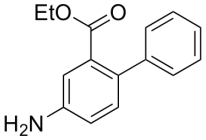
entry[a]	aryl bromide	product	yield (%)[b]	entry[a]	aryl bromide	product	yield (%) [b]
1	 **191**	 **192**	88	8	 **205**	 **206**	74
2	 **193**	 **194**	<5	9	 **207**	 **208**	42
3	 **195**	 **196**	<5	10	 **209**	 **210**	25
4	 **197**	 **198**	81	11	 **211**	 **212**	33
5	 **199**	 **200**	94	12	 **213**	 **214**	<5
6	 **201**	 **202**	87	13	 **215**	 **216**	<5
7	 **203**	 **204**	51	14	 **217**	 **218**	<5

[a] Reaction conditions: aryl halide (1 equiv), benzene (100 equiv), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.51 equiv), 125 ºC, 16–20 h. [b] Yield of the isolated product.

We next considered the functional group tolerance of the halide partner (**Table 54**).[175] Methyl and ethyl ester functional groups were chosen as the directing component due to their combination of reactivity and flexibility towards potential further structural elaboration. A methyl group *meta* to the bromine atom was well tolerated, giving the biaryl product in 82% yield (entry 1). Conversely, when the methyl is *ortho* only 25% conversion was noted, indicating sensitivity of the system towards steric hindrance. Electron-poor substrates (entries 2, 3), even those bearing a potentially troublesome nitro group performed well (94% yield),[8a] presumably by futher facilitating oxidative addition of the catalyst. Likewise electron-rich species such as protected hydroxyl and amino moieties provided products in moderate yields (entries 4, 5).[175] These functional groups absolutely required masking, as the presence of free OH or NH_2 in the haloarene was found to be deleterious to the reaction (entries 6, 7).

Table 54. Functional group tolerance on the aryl bromide in the direct *umpolung* arylation.

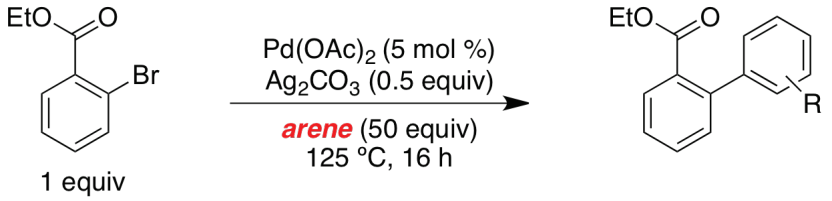


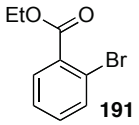
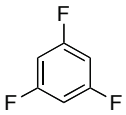
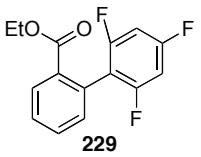
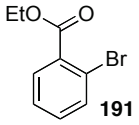
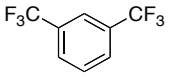
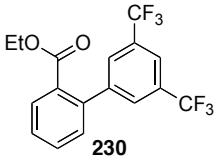
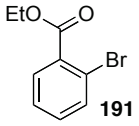
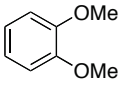
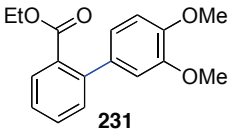
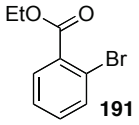
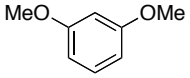
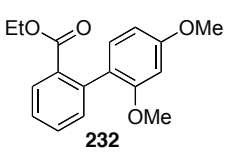
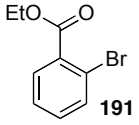
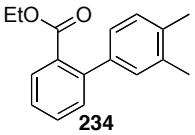
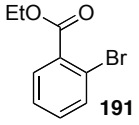
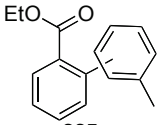
entry	aryl bromide	product	yield (%)[a]
1	 **219**	 **220**	82
2	 **221**	 **222**	94
3	 **223**	 **224**	89
4	 **225**	 **226**	48
5	 **227**	 **228**	47
6			<5
7			<5

[a] Yield of the isolated product.

Given the few reported examples of substituted arenes, we next scrutinized the scope of the C–H coupling partner (**Table 55**).[175] Where 100 equivalents of benzene was used in the previous reactions for a cleaner process, it was found that 50 equivalents of high-boiling reagents was sufficient to effect the desired transformation with acceptable results. 1,3,5-Trifluorobenzene reacted in good yield (entry 1). The result obtained was comparable to those noted with benzene, suggesting that the role of fluorine interacting with the catalyst while simultaneously increasing Brønsted acidity is not a major factor in the arylation.[176] Interestingly 1,3-bis(trifluoromethyl)benzene reacted poorly, possibly due to poor π-complexation with the palladium catalyst (entry 2). Again electron-donating species afforded the products in moderate yields (entries 3, 4). Substrates providing lower yields are the result of incomplete consumption of the bromide starting material. Efforts to improve this through additional heating or increased Ag_2CO_3 loading were unsuccessful. A striking feature is the regioselectivity of the process as in many cases where multiple products were possible, only one regioisomer was observed (entries 2, 3, 5). Entries that can provide three isomers also give only two. This coincides with the previous observation of steric sensitivity.[175]

Table 55. Scope of the arene component in the palladium-catalyzed arylation of arenes.



entry	aryl bromide	arene	product	yield (%)[a]
1	 **191**		 **229**	80
2[b]	 **191**		 **230**	27
3[b]	 **191**		 **231**	43
4	 **191**		 **232** **233**	48[c]
5	 **191**		 **234**	77
6	 **191**		 **235** **0:1:1 *o:m:p***	88

[a] Yield of the isolated product. [b] 1 equiv of Ag_2CO_3 employed. [c] Yield of the combined products. **232** was isolated in 30% yield and **233** in 18% yield.

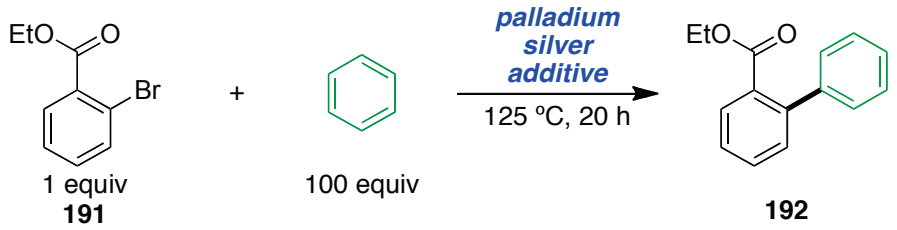
5.2.3 Mechanistic Investigations

Several facets of this transformation were particularly intriguing. Perhaps the most interesting parameter was the nature of the palladium catalyst. Given the absence of a phosphine ligand, no species were present in the reaction mixture to reduce the palladium (II) species to the expected palladium (0), suggesting that a Pd^{0}/Pd^{II} manifold was not operative. There have been accounts of electron-rich alkenes donating π-electrons to palladium, effectively reducing the metal.[177] However, no accounts of arenes have been described to do this, and though one can argue of its feasibility given the arene is in 2000-fold excess with regards to the catalyst, the poor reactivity of electron-donating substrates (**Table 55**, entries 3, 4) suggests this hypothesis to be doubtful.

To elucidate the mechanistic pathway we performed a series of control experiments.[175] Based on initial results during the reaction optimization, a palladium (II) catalyst appeared to be vital for the reaction to proceed. This was confirmed through the application of $Pd_2(dba)_3$ under the optimal conditions as the reaction was ineffective both with and without the presence of a phosphine ligand (**Table 56**, entries 2, 3). Interestingly, most of the reactivity could be restored though the addition of KOAc in a 2:1 ratio with $Pd_2(dba)_3$, demonstrating the importance of the acetate unit (entry 4). As mentioned earlier in this dissertation, this motif is a vital proton shuttle in metallation/deprotonation sequences.[52,55,178,179] Bearing this in mind we tested $Pd(TFA)_2$, as the TFA moiety should be a less effective shuttle, and indeed the reaction proceeded in only 51% yield (entry 5). Again, much reactivity was recovered through the addition of KOAc (entry 6). To see if acetate in absence of carbonate was sufficient we re-attempted AgOAc under the best conditions and obtained only 50% yield (entry 7). The inclusion of K_2CO_3 as an external carbonate source increased the conversion by 15% (entry 8), implying that the carbonate may play a role in the regulation of the pH of the reaction mixture, and is not necessarily involved in the deprotonation. Lastly, a large primary isotope effect of 5.4 was observed. This indicates that the hydrogen atom in the activated complex is almost equally shared

between the base and the arene. Also, the large value demonstrates the protium reacts fasters than deuterium, and as their chemical reactivity is the same, implies that the C–H breaking event may be rate-determining, though this cannot be determines absolutely without further kinetic studies.[147,175]

Table 56. Role of the reagents in the palladium-catalyzed benzene arylation.



1 equiv **191** | 100 equiv | **192**

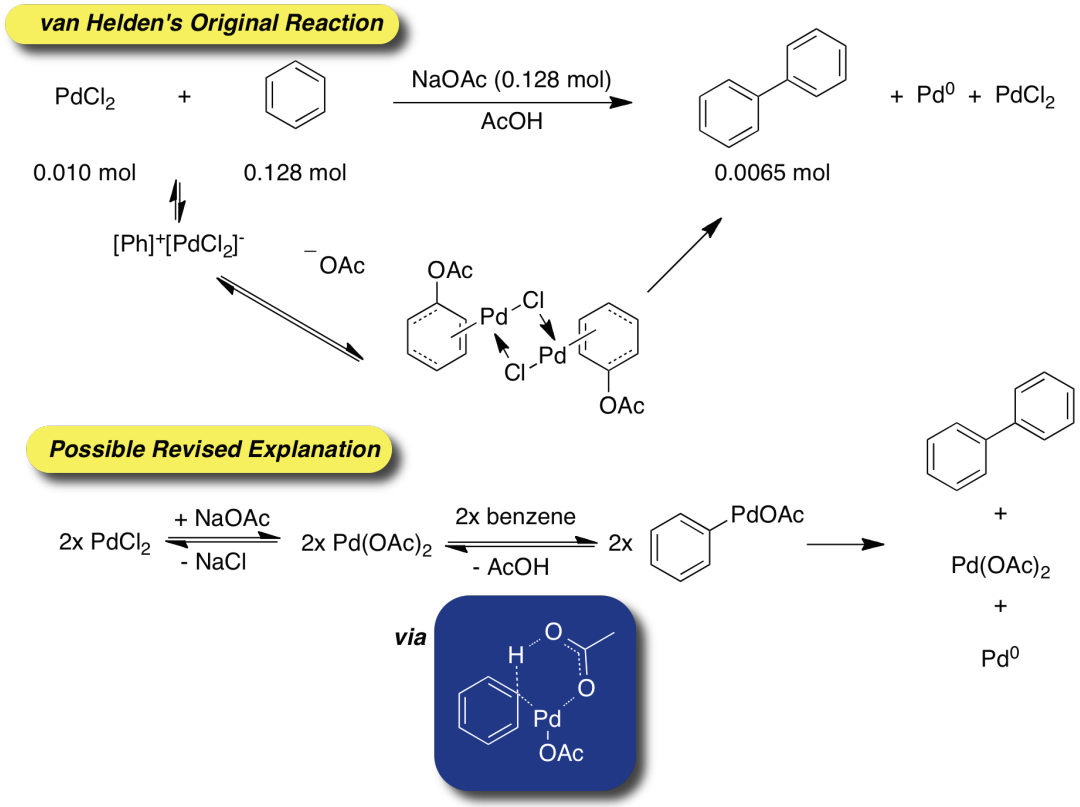
entry[a]	Pd source	silver source	additive	yield (%)[a]
1	$Pd(OAc)_2$ [b]	Ag_2CO_3 [d]	none	90
2	$Pd_2(dba)_3$	Ag_2CO_3 [d]	none	<5
3	$Pd_2(dba)_3$ [c]	Ag_2CO_3 [d]	PCy_3 (7.5 mol %)	<5
4	$Pd_2(dba)_3$ [c]	Ag_2CO_3 [d]	KOAc (10 mol %)	76
5	$Pd(TFA)_2$ [b]	Ag_2CO_3 [d]	none	51
6	$Pd(TFA)_2$ [b]	Ag_2CO_3 [d]	KOAc (10 mol %)	73
7	$Pd(OAc)_2$ [b]	AgOAc [e]	none	50
8	$Pd(OAc)_2$ [b]	AgOAc [e]	K_2CO_3 (0.51 equiv)	65

[a]Yields are measured by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] 5 mol % of catalyst employed. [c] 2.5 mol % of catalyst employed. [d] 0.51 equiv employed. [e] 1 equiv employed.

In 1965 van Helden described a $PdCl_2$-mediated homocoupling of benzene in presence of a large excess of NaOAc and acetic acid (**Scheme 58**).[180] The reaction is believed to proceed by a σ–π coordination between the palladium and benzene, followed byrapid attack of the acetate ion to generate C_6H_6 •$PdCl_2$ Wheland pair, dimerization of the system and disproportionation to give biphenyl, $PdCl_2$ and Pd^0.[180] Kinetic studies disclosed that the initial coordination is reversible and rate determining. Though $PdCl_2$ is regenerated, Pd^0 nanoparticles quickly agglomerate, precipitate, and become inactive. More recently,

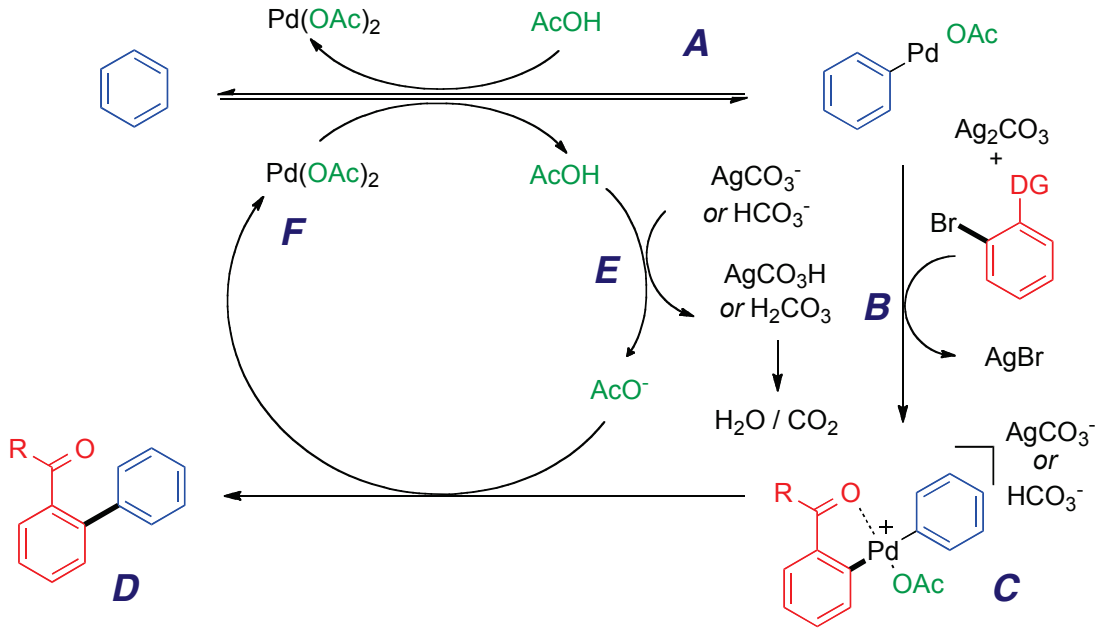
Sasson rendered the process catalytic through the inclusion of chlorobenzene, which can trap the palladium (0) generated, and through disproportionation fully convert the palladium to the supposed active form, $PdCl_2$.[181] Given knowledge recently gained by Fagnou and Echavarren, and the suspicious requirement of large amount of acetate in solution,[52,55,178] it is not unreasonable to propose an alternate pathway to van Helden's reaction (**Scheme 58**). It is conceivable that the metal undergoes ligand exchange to generate $Pd(OAc)_2$ *in situ*. This is the species that then coordinates to the arene, and inserts into the C–H bond through a CMD pathway. Given the excess of acetic acid in solution, this process is reversible. Disproportionation with another palladated species then affords $Pd(OAc)_2$ and $PdPh_2$, which following reductive elimination gives the corresponding biphenyl and palladium black.

Scheme 58. Palladium-mediated homocoupling of benzene as reported by van Helden.



Based on our own studies and the aforementioned precedent, we propose the following catalytic cycle (**Scheme 59**).[175] As with van Helden, we believe the palladium reversibly adds into the aromatic ring, albeit through a CMD mechanism (**A**). The phenylated palladium is then quickly trapped by the Lewis basic group of the halide partner and undergoes a silver-assisted oxidative addition (**B**). Due to the generation of AgBr, the formation of a highly activated cationic palladium (IV) species occurs that is stabilized by the directing group (**C**).[182] This intermediate reductively eliminates to give the corresponding biaryl (**D**). Simultaneously the acetic acid generated in the carbopalladation step is deprotonated by the carbonate (**E**) and religates to the palladium, regenerating the active palladium catalyst (**F**). We believe this cycle explains the need for only one equivalent of silver atoms, the need for acetate, and the possible role of carbonate in regulating the reaction. This pathway also accounts to the aforementioned formation of trace quantities of biphenyl, as if the phenylated palladium is not trapped it may proceed through the disproportionation and continue through the non-productive pathway similar to what was previously reported.[180,181] Free hydroxyl and amine groups may not be operative due to potential complexation with the palladium catalyst or silver reagent, and may alter the pH balance of the reaction.

Scheme 59. Proposed catalytic cycle.



5.3 Summary

We have disclosed an efficient palladium-catalyzed direct arylation reaction performed in absence of an external base and requires only substoichiometric amounts of silver carbonate. This work describes a directed arylation process that is opposite to what has been typically reported to date, in that the directing group is *ortho* to the halide. This is advantageous, permiting the facile synthesis or a wide array of starting materials, and enables the use of inexpensive benzene (or other arenes) as both reaction medium and feedstock. Though a large excess of benzene is applied, it can be recovered and reused in future transformations, and preliminary work during the optimization phase indicated that a decrease in loading is viable. This work adds to the few examples of known arylation of unactivated arenes, and experiments performed allowed for the proposal of a viable reaction mechanism.

Chapter 6
Iron-Catalyzed Direct Arylation through an Aryl Radical Transfer Pathway

6.1 Introduction

6.1.1 Iron

Iron is the most abundant element on Earth, forming much of the planet's core. This element is the fifth most common, and it is the second most present metal in the planet's crust.[183] It is a paramagnetic metal of the Group VIII family. One of the key features of this element is its existence over a wide range of oxidation states as Fe^{-II}, Fe^{0}, Fe^{I}, Fe^{II}, Fe^{III}, Fe^{IV}, Fe^{V}, and Fe^{VI} species have been reported.[183] Moreover it possesses a multitude of possible geometries, varying the coordination sphere of the metal, and making it amenable for a myriad of chemical transformations. Iron can exist as high or low spin complexes that are tunable by ligands, and permiting a degree of control over reactivity. Nature has taken advantage of this abundance and of its oxidative/reductive potential, as it is a key component of the heme group of hemoglobin, present in many enzymatic cofactors, and functional in other cellular mechanisms.[184]

6.1.2 Iron in Catalysis

Given its abundance, several iron catalysts are available at low cost. As seen in **Table 57**, the price of iron reagents is often lower than more traditional palladium, rhodium, and iridium species. However, despite this economy, in addition to their low toxicity and applicability towards sustainable practices, the use of iron catalytic species remains largely unexplored.[185] Perhaps the first example of its use in coupling reactions was disclosed by Kochi in the early 1970s.[186] He described a Kumada-type cross coupling employing $FeCl_3$ (**Scheme 58**). In this process, some of the Grignard reagent is sacrificed

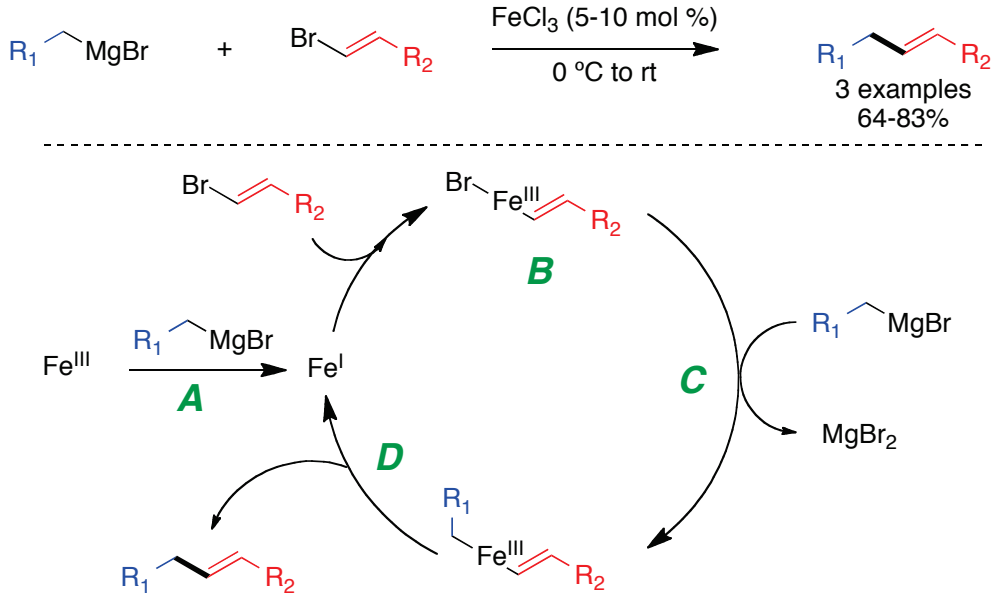
to generate an iron (I) intermediate (**A**) that can oxidatively add into the carbon-halide bond (**B**) of the pseudo-electrophile. Transmetallation of the resulting iron (III) with another equivalent of organomagnesium species (**C**), followed by reductive elimination affords the desired product (**D**) while liberating Fe (I), that is free to re-enter the catalytic cycle.[186]

Table 57. Cost of various transition metal reagents per mole.[a]

catalyst	cost ($)	catalyst	cost ($)
$FeCl_3$	***3.24***	***$Fe(acac)_3$***	***229.57***
CuCl	6.93	***$FeCl_2$***	***292.79***
$CuCl_2$	10.76	***$Fe(OAc)_2$***	***825.25***
$ZnCl_2$	15.00	$PdCl_2$	4610.32
$FeCl_2{\bullet}4H_2O$	***15.91***	$Pd(OAc)_2$	8281.94
$NiCl_2$	46.65	AuCl	15 944.01
$CoCl_2$	67.51	$RhCl_3$	22 808.90
$CrCl_5$	99.76	$IrCl_3$	23 288.46
$RuCl_3$	207.43		

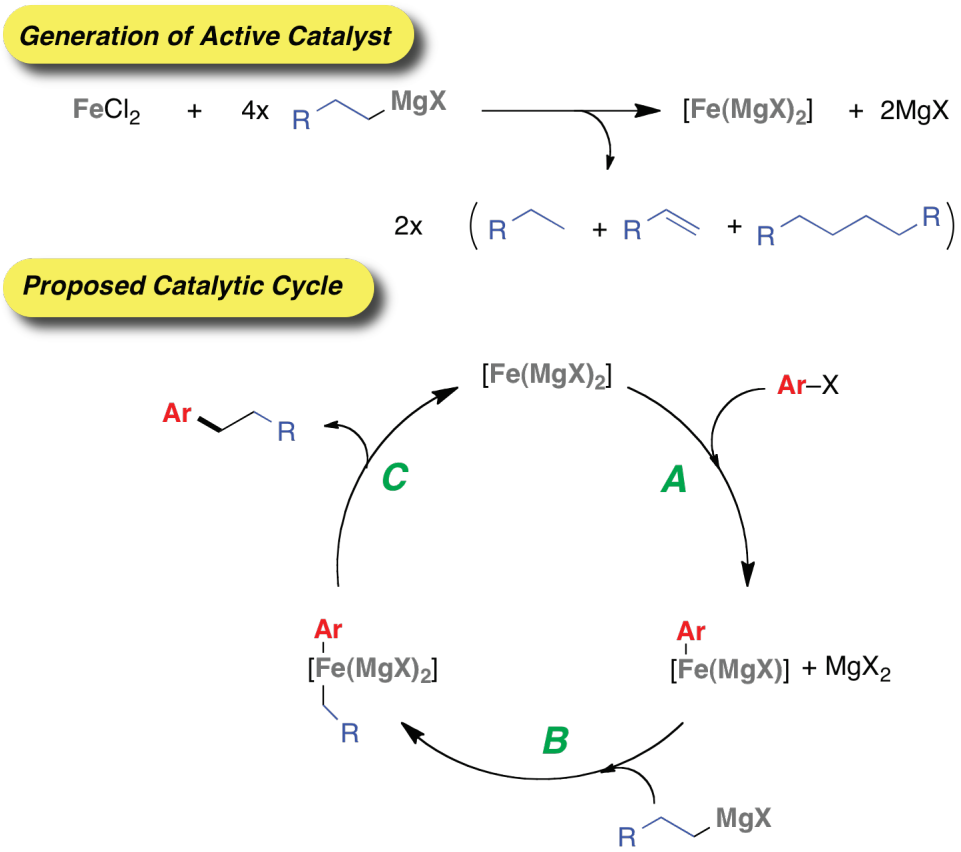
[a] Prices obtained from Strem Chemicals November 21 2010.

Scheme 58. Kochi's iron-catalyzed cross coupling reaction.



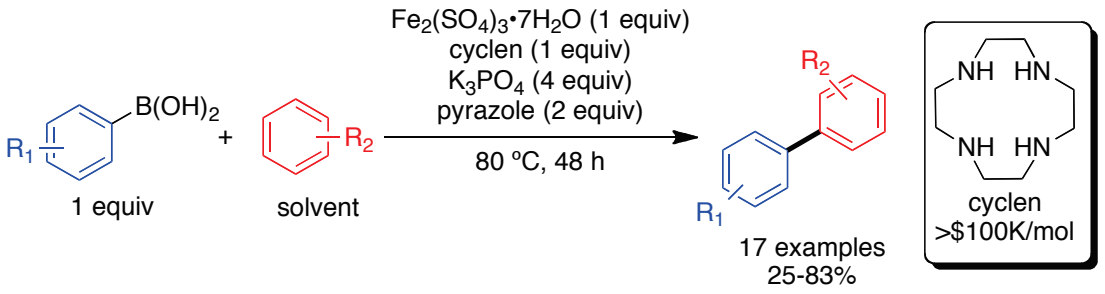
In the early 2000s Fürstner and co-workers revisited this chemistry reporting an iron-catalyzed cross coupling reaction with more nucleophilic Fe^{-II} complexes.[187] Again, the coupling is between Grignard reagents and aryl halides in the presence of a catalytic amount of $FeCl_2$. The proposed mechanism suggests that the catalyst reacts with 4 equiv of Grignard reagent to generate the active catalyst, MgX_2 salts, and a variety of unproductive carbon chains (**Scheme 59**).[187] The catalyst then undergoes oxidative addition (**A**) into an aryl halide bond, and following transmetallation (**B**) / reductive elimination (**C**) the desired product is obtained.

Scheme 59. Fürstner's iron-catalyzed cross coupling reaction.



Needless to say, the application of a direct process minimizing activated partners is more desired, however, until very recently, little or no examples of direct functionalization

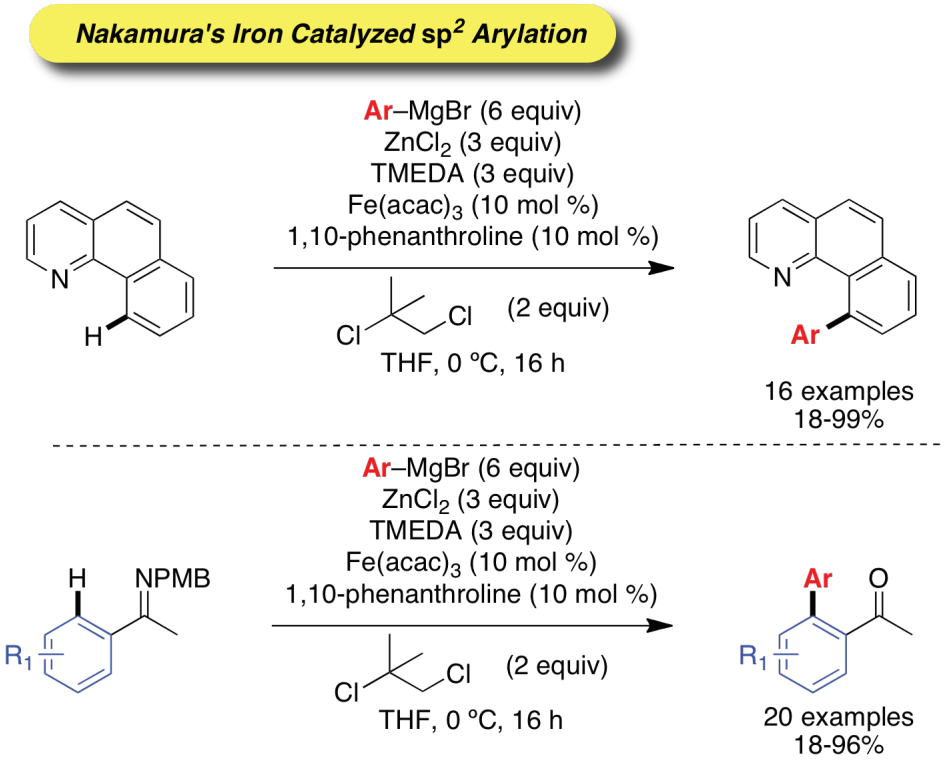
processes, and more specifically arylation reactions, have been explored.[188] Yu disclosed the first example of an iron-mediated direct arylation in 2008 whereby an aryl boronic acid is coupled to benzene.[189] The active metal species is a $Fe_2(SO_4)_3$•$7H_2O$ / cyclen complex that it used in stoichiometric quantities. The scope is general with regards to the arene and the boronic acid, tolerating an array of coupling partners (Eq. 30). The only limitation was that of *ortho* substitution with regards to the aryl boronic acid, as these substrates proved unreactive as a result of steric sensitivity.[189] Another drawback is the use of cyclen due to its highly prohibitive cost (Eq. 30). For now, the role of the pyrazole additive remains unknown. The high kinetic isotope effect and the fact that radical scavengers do not inhibit the transformation precludes a radical pathway, though the exact mechanism of the process was not elucidated.



(30)

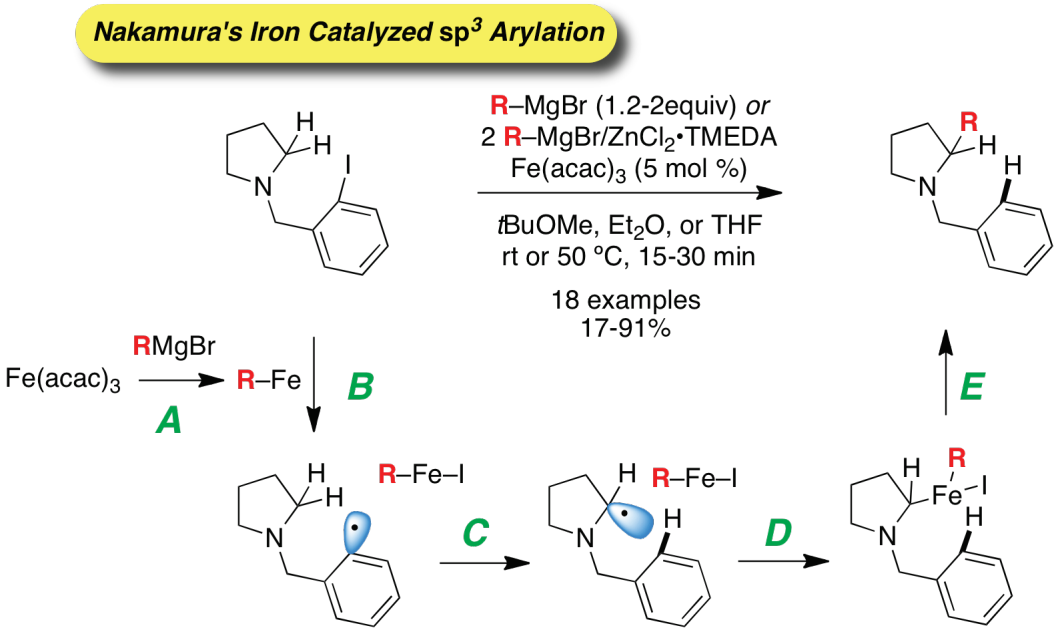
More pertinent to this research is the work published by Nakamura. In 2008 he disclosed a directed arylation of aryl magnesium bromides into sp^2-hybridized C–H bonds catalyzed by a $Fe(acac)_3$ / 1,10-phenanthroline system.[190] This elegant approach was achieved under extremely mild conditions, permitting a large substrate scope. Later the directing group was improved from pyridine to an imine, allowing greater flexibility towards further structural elaboration.[191] The scope in both processes is extensive, supporting a myriad of functional groups (**Scheme 60**). Drawbacks however include the addition of 3 equiv of $ZnCl_2$ / TMEDA, and the need for 2 equiv of 1,2-dichloro-2-methylpropane, which can no longer be purchased form Sigma Aldrich nor Alfa Aesar.

Scheme 60. Nakamura's iron-catalyzed directed sp^2 arylation.

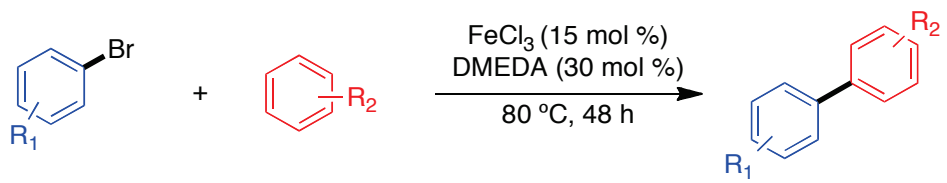


In 2010 Nakamura also described an iron-catalyzed arylation of sp^3-hybridized C–H bonds.[192] As seen in **Scheme 61**, though not described, it is reasonable to assume that the Fe^I species is sacrificially generated by some of the Grignard reagent (**A**).[186] The reaction then proceeds through the generation of a proximal aryl radical (**B**) that can be transferred to the alkane *via* 1,5-hydrogen radical shift (**C**). The newly formed radical is stabilized by the adjacent nitrogen atom, and is trapped by the iron catalyst (**D**) (**Scheme 61**). Transmetallation and reductive elimination affords the corresponding product (**E**). A range of aryl, vinyl and even alkyl Grignard reagents were viable coupling partners.[192]

Scheme 61. Nakamura's iron-catalyzed sp^3 arylation.



Around the same time as the disclosure of the work in this chapter, Lei published an iron-catalyzed arylation of arene derivatives with an array of aryl bromides.[171] The radical process employs DMEDA as the ligand and LiHMDS as the base (Eq. 31). A range of coupling partners was operative, though sensitivity towards electron-poor and sterically encumbered substrates was noted. Also, though relatively mild with regards to the reaction temperature, extended reaction times are required. Interestingly, aryl chlorides also displayed modest reactivity, though selectivity towards bromides was demonstrated in substrates bearing both chlorine and bromine atoms. The mechanism of arylation is not clear, as there is no evidence of a benzyne intermediate, and the observed KIE of 1.7 is too high for a radical process.[147]



(31)

6.1.3 Proposed Research

Though several methods of arylation have been presented in this dissertation (**Figure 24**), with several of these technologies providing improvements over classical techniques, there still remains several unsolved challenges. Perhaps one of the biggest quandaries lies in developing inexpensive, sustainable catalytic systems. Though some progress has been made employing iron reagents, the most common drawbacks include the need for directing groups, in addition to large excesses of zinc salts and other additives. The remainder of this chapter will focus on our work towards the development of a high-yielding, efficient iron-catalyzed direct arylation sequence without the addition of stoichiometric amount of metal additives or other reagents, while circumventing the need for a directing group.[193]

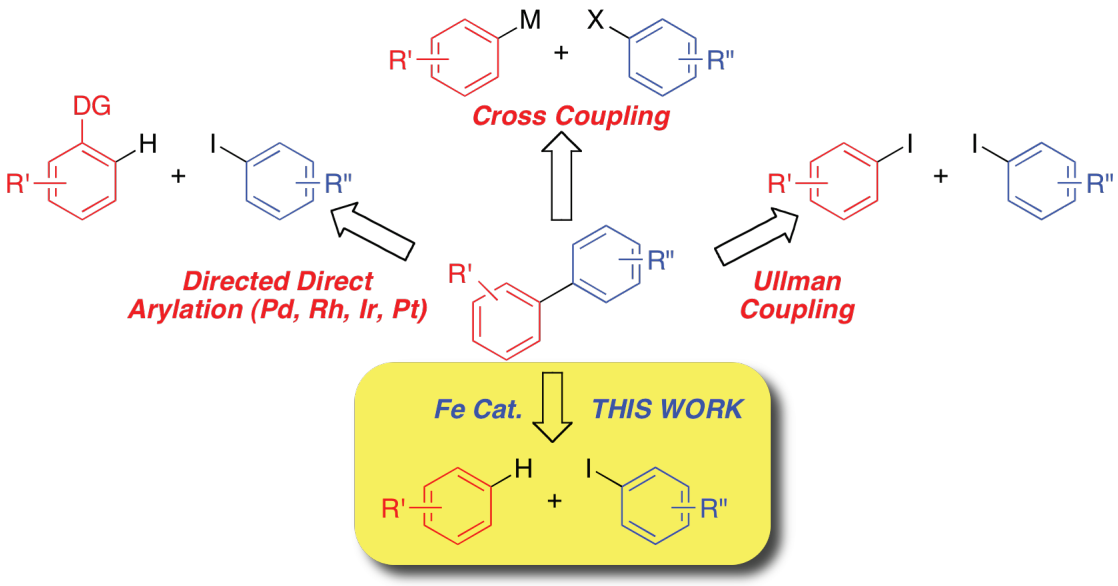


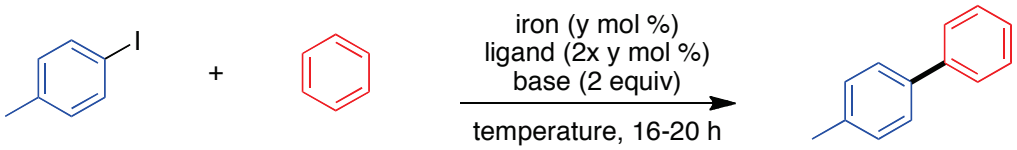
Figure 24. Various ways to synthesize the biaryl motif.

6.2 Results and Discussion

6.2.1 Reaction Optimization

During the course of the optimization of the palladium-catalyzed umpolung direct arylation discussed *vide supra* Frédéric Vallée considered employing a more sustainable catalytic system to effect the biaryl formation. Though we showed that a reaction incorporating $Fe(acac)_3$, PCy_3, and Ag_2CO_3 failed to provide any of the desired product (**Section 5.2.1** and **Table 58** entry 1), we quickly recognized that such phosphines have not been reported with iron catalysts for arylations, and we could not rule out a possible detrimental role of the Ag_2CO_3, which is a known oxidant. Aware of other arylation precedents using phenanthroline-based ligands we were pleased to observe 28% yield by GC/MS when replacing the phosphine with bathophenanthroline (entry 2). Mr. Vallée proceeded with the reaction optimization.[193] It was found that substituting the aryl bromide with an aryl iodide quickly improved yields (entry 3). A sampling of catalysts determined that $Fe(OAc)_2$ was most reactive (entries 4-6). Verification of ligands confirmed the use of bathophenanthroline as the reagent of choice, though unsurprisingly 1,10-phenanthroline also provided encouraging yields (entries 7-12). Potassium *tert*-butoxide was the optimal base with KHMDS displaying only slightly lower reactivity (entries 13-15). Interestingly catalyst loading as low as 0.5 mol % still provided 76% conversion at 125 ºC (entry 16), though 5 mol % was chosen for ease of set-up (entry 17). We were pleased to see that the yield improved at 80 ºC, increasing the energetic economy of the process, and moderate yields could be achieved as low as 40 ºC (entries 18-20). Finally the arylation did not proceed in absence of the iron reagent, nor the ligand (entries 21-22). It should be noted that the reaction proceeded most smoothly when the iron, ligand, and base were stirred in benzene for 20 min prior to the addition of the aryl iodide.[193]

Table 58. Selected optimization for the direct arylation of benzene with 4-iodotoluene.



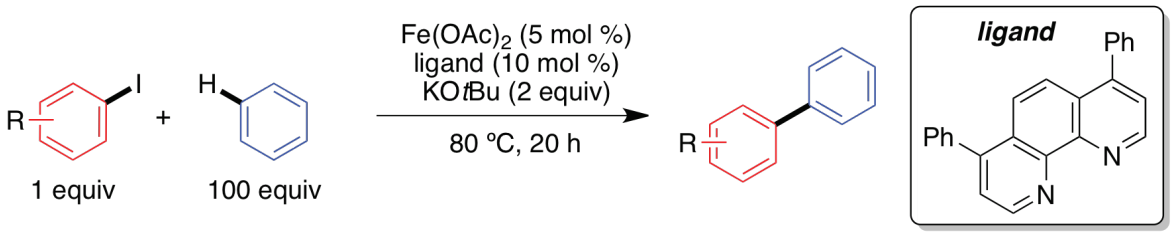
entry	iron	ligand	Fe (mol %)	base	temp. (ºC)	yield (%)[a]
1	$Fe(acac)_3$	PCy_3[b]	5	Ag_2CO_3	125	<5
2	$Fe(acac)_3$	bathophenanthroline	8	KO*t*Bu	125	28
3	$Fe(acac)_3$	bathophenanthroline	8	KO*t*Bu	125	68
4	$FeCl_3$	bathophenanthroline	8	KO*t*Bu	125	21
5	Fe(phthalo-cyanine)	none	8	KO*t*Bu	125	37
6	$Fe(OAc)_2$	bathophenanthroline	8	KO*t*Bu	125	70
7	$Fe(OAc)_2$	none	8	KO*t*Bu	125	22
8	$Fe(OAc)_2$	P(*t*Bu)$_3$	8	KO*t*Bu	125	20
9	$Fe(OAc)_2$	DavePhos	8	KO*t*Bu	125	32
10	$Fe(OAc)_2$	TMEDA	8	KO*t*Bu	125	35
11	$Fe(OAc)_2$	bipyridine	8	KO*t*Bu	125	35
12	$Fe(OAc)_2$	1,10-phenanthroline	8	KO*t*Bu	125	59
13	$Fe(OAc)_2$	bathophenanthroline	8	none	125	2
14	$Fe(OAc)_2$	bathophenanthroline	8	NaOMe	125	12
15	$Fe(OAc)_2$	bathophenanthroline	8	KHMDS	125	75
16	$Fe(OAc)_2$	bathophenanthroline	0.5	KO*t*Bu	125	76
17	$Fe(OAc)_2$	bathophenanthroline	5	KO*t*Bu	125	87
18	$Fe(OAc)_2$	bathophenanthroline	5	KO*t*Bu	40	45
19	$Fe(OAc)_2$	bathophenanthroline	5	KO*t*Bu	60	69
20	$Fe(OAc)_2$	bathophenanthroline	5	KO*t*Bu	80	91
21	none	none	n/a	KO*t*Bu	80	0
22	none	bathophenanthroline	10	KO*t*Bu	80	0

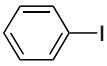
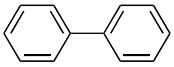
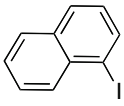
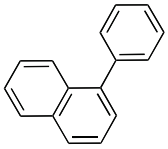
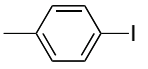
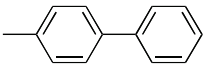
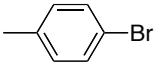
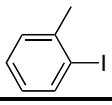
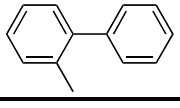
[a]Yields are measured by GC/MS using 1,3,5-trimethylbenzene as the internal standard. [b] 15 mol % of ligand employed and PhBr used in place of PhI.

6.2.2 Scope of the Reaction

Elated as we optimized conditions that minimized the need for stoichiometric additives and did not require a directing group, we next investigated the scope of the reaction. Gratifyingly, the arylation proved quite general. Electron-neutral iodobenzene, iodonaphthalene, 4-iodotoluene, and even 4-bromotoluene reacted in moderate to very good yields (**Table 59**, entries 1-4). Unlike what was observed with the aforementioned palladium-catalyzed arylation, steric hinderance was a non-issue, as 2-iodotoluene provided the product in 80% yield, though more elevated reaction temperatures were needed.[193]

Table 59. Scope of electron-neutral iodides in the Fe-catalyzed direct arylation of benzene.



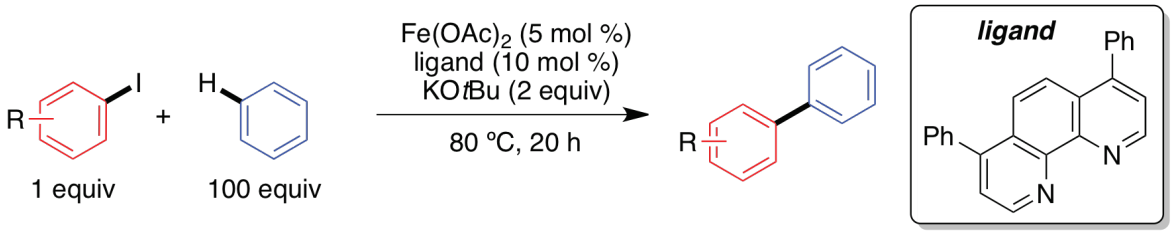
entry	aryl halide	product		yield (%)[a]
1			**236**	89
2			**237**	60
3			**238**	86
4				46
5[b]			**239**	80

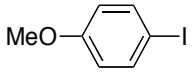
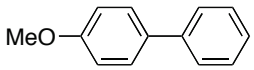
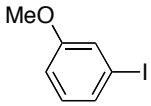
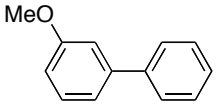
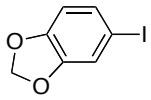
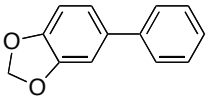
[a]Yield of the isolated product. [b] Reaction performed at 125 °C.

Electron-rich iodides proved to be amongst the most reactive substrates. Ethers located at the *para* and *meta* positions arylated in good to excellent yields (**Table 60**,

entries 1-4). We exploited this trend, stirring 4-iodoanisole in the reaction conditions at room temperature over 60 h (entry 2). We were pleased to isolate the desired biaryl in 51% yield.[193]

Table 60. Scope of electron-rich arenes in the iron-catalyzed direct arylation of benzene.

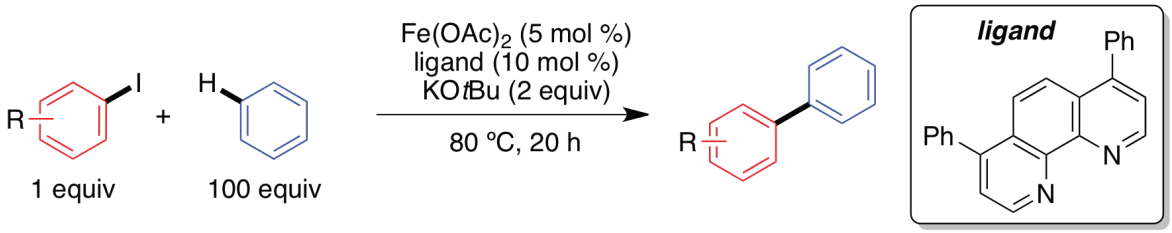


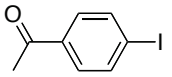
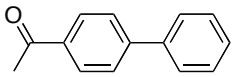
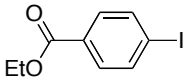
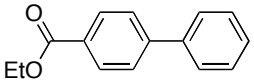
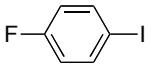
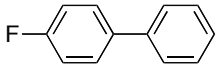
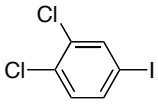
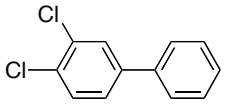
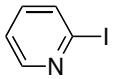
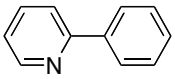
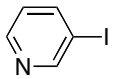
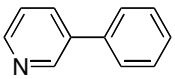
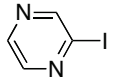
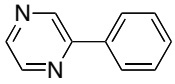
entry	aryl iodide	product		yield (%)[a]
1			**240**	93
2[b]				51
3			**241**	88
4			**242**	72

[a]Yield of the isolated product. [b]Reaction performed at rt for 60 h.

Though operative, electron-poor species fared less well in the arylation, largely providing biaryls in moderate yields (**Table 61**). Of note however is the tolerance towards enolizable centres and as well as esters (entries 1, 2) despite the presence of a harsh base. Chemoselectivity was noted, with fluorine and chlorine atoms remaining untouched (entries 3, 4). The balance of the product in the reaction mixture was unreacted staring material. Electron-poor heterocyclic iodoarenes functioned well, with 2- and 3-iodopyridine being operative, as well as 2-iodopyrazine (entries 5-7), giving potential access to a range of medicinally relevant compounds.[70, 193]

Table 61. Scope of electron-poor iodides in the iron-catalyzed direct arylation of benzene.



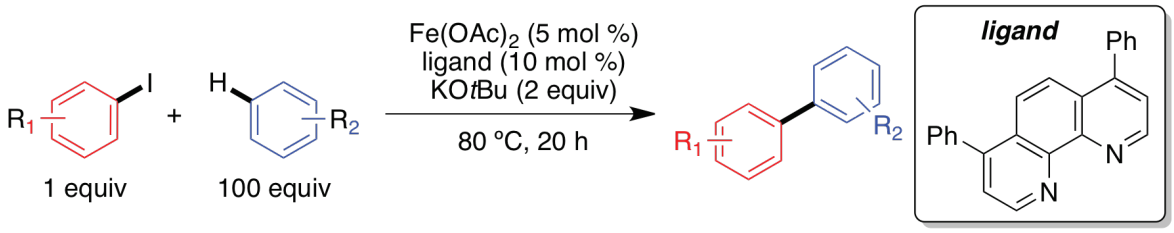
entry	aryl iodide	product		yield (%)[a]
1[b]			**243**	69
2			**244**	40
3			**245**	86
4			**246**	53
5			**247**	85
6			**248**	85
7			**249**	79

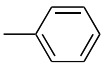
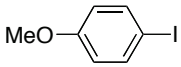
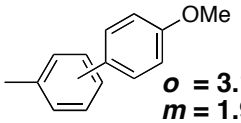
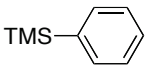
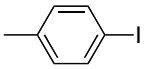
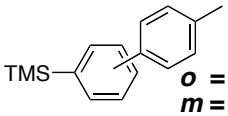
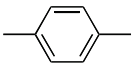
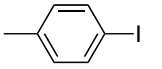
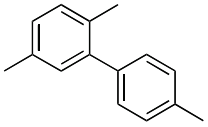
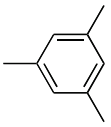
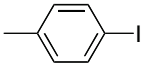
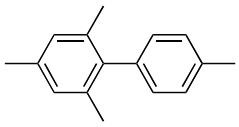
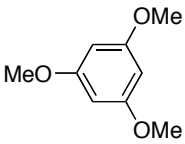
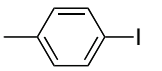
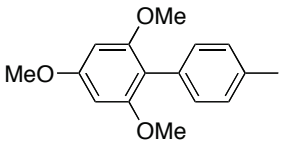
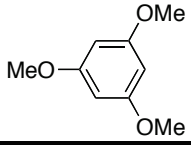
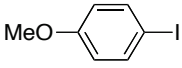
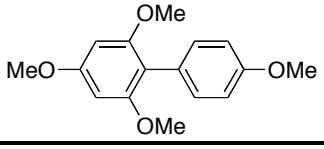
[a] Yield of the isolated product. [b]Reaction performed at 90 °C.

Next we considered the scope of various arene derivatives. Substituted arenes coupled with aryl iodides to afford the corresponding biaryl products in moderate to good yields (**Table 62**). Toluene coupled with 4-iodoanisole with moderate results, affording a mixture of regioisomers favouring the more hindered *ortho* substituted product (entry 1). This is in contrast to PhTMS which favoured the *para* adduct (entry 2). The poor yield of this substrate is possibly due to desilylation, leading to complex mixtures. A striking feature is the robustness of the method towards hindered arenes such as *p*-xylene,

mesitylene, and trimethoxybenzene, while all reacted in moderate to good yields (entries 3-6).[193]

Table 62. Scope of the arene partner in the iron-catalyzed direct arylation reaction.

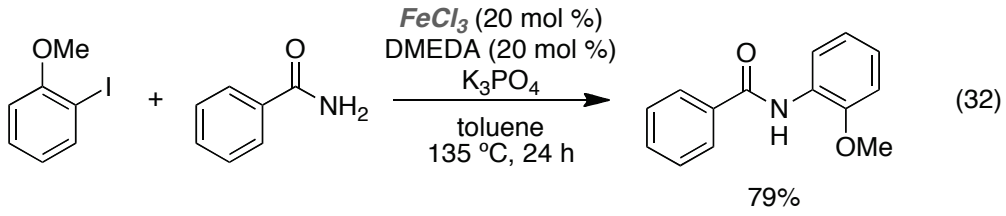


entry	arene	aryl halide	product		yield (%)[a]
1			 **o = 3.1 m = 1.9 p = 1.0**	**250**	50[b]
2			 **o = 3.3 m = 7.1 p = 1.0**	**251**	28[b]
3				**252**	81
4				**253**	63
5				**254**	54
6				**255**	41

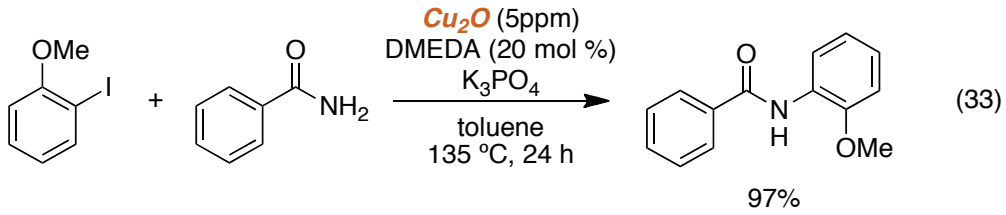
[a] Yield of the isolated product. [b] Yield determined as a mixture of isomers.

6.2.3 Possible Role of Contaminants

Recently Buchwald and Bolm investigated the role of metal impurities in iron-catalyzed amination and amidation reactions.[194] Bolm discovered that the source of the purity of the $FeCl_3$ catalyst had significant impact on the yield. For example, they reported the $FeCl_3$-catalyzed coupling between 2-iodoanisole and an aromatic amide in 79% when using a catalyst of 98% purity (Eq. 32), and no conversion when using catalysts of 99.995% purity. They subsequently found that the same reaction proceed in 97% yield when the iron is substituted with 5ppm Cu_2O, indicating that the presence of copper impurities may in fact may be promoting the transformation (Eq. 33). Further evidence for this was determined in absence of the ligand, where a modest 34% yield of product was obtained when using 5ppm Cu_2O alone.[194]



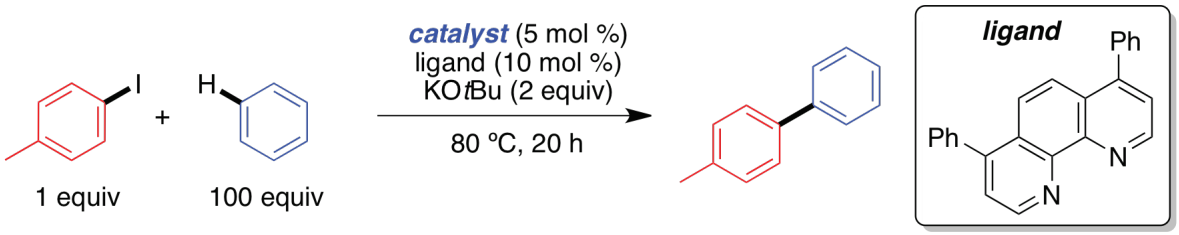
(32)



(33)

Conscious of this we investigated whether a catalytic amount of copper could influence the outcome of the reaction.[193] The purity of iron does not seem to play a significant role in the reaction (**Table 63**, entries 1, 2), in fact superior results were obtained with the high purity catalyst. Both copper (I) and (II) acetate were ineffective in initiating the arylation (entries 3, 4), and when used in conjunction with $Fe(OAc)_2$ lower yields were obtained (entries 5, 6). Consequently, it reasonable to assume that the process is indeed iron-catalyzed.[193]

Table 63. Direct arylation in presence of iron and copper catalysts.

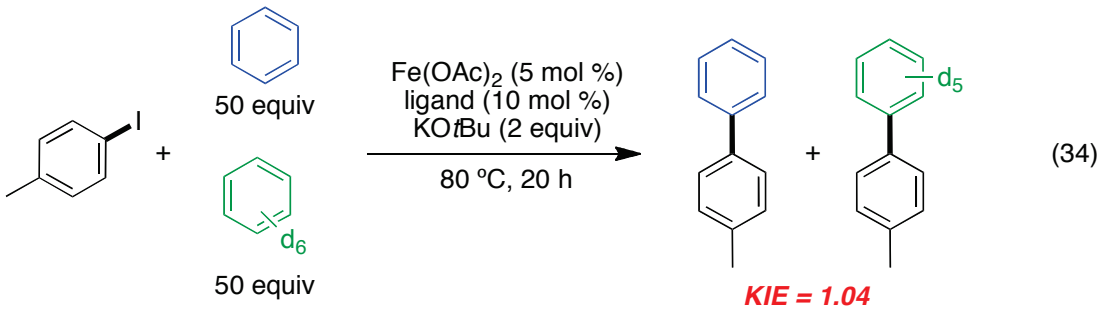


entry	catalyst	purity (%)	source	yield (%)[a]
1	$Fe(OAc)_2$	99.995	Aldrich	98 (87)[b]
2	$Fe(OAc)_2$	97	Strem	91
3	Cu(OAc)	99	Strem	6
4	$Cu(OAc)_2$	97	Strem	9
5	$Fe(OAc)_2$ + Cu(OAc)	99.995 + 99	Aldrich/Strem	57
6	$Fe(OAc)_2$ + $Cu(OAc)_2$	99.995 + 97	Aldrich/Strem	48

[a] Yield determined by GCMSanalysis using 1,3,5-trimethylbenzene as an internal standard.
[b] Yield of isolated product.

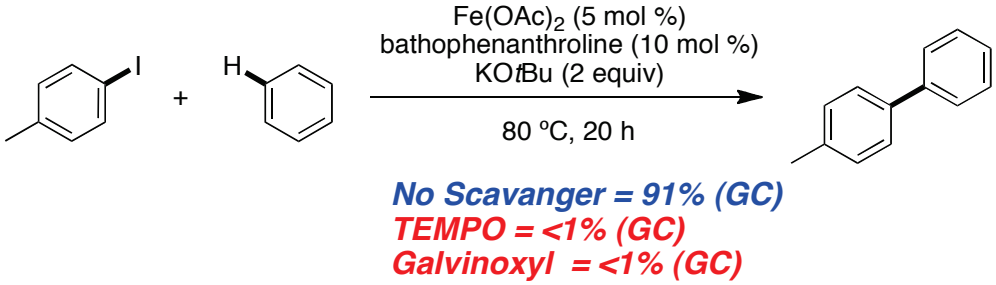
6.2.4 Mechanistic Investigations

A kinetic isotope experiment was performed in order to gain some understanding of the reaction (Eq. 34).[193] Curiously, an isotopic value of 1.04 was obtained. This was surprising given our past experience with direct processes, and quickly prompted us to consider a radical pathway. Radical arylations are known to exhibit such low values, as the rate-limiting step is often the formation of the radical species.[147,195] Furthermore, radical-mediated arylation often favours the formation of more hindered *ortho* substituted products as we observed with toluene (**Table 62**, entry 1).[147] This is in order to form a tertiary radical intermediate stabilized through hyperconjugation. This potential mechanism was further confirmed through the inclusion of an equivalent of galvinoxyl or TEMPO, known radical scavengers that effectively suppressed the arylation (**Scheme 62**).[196]



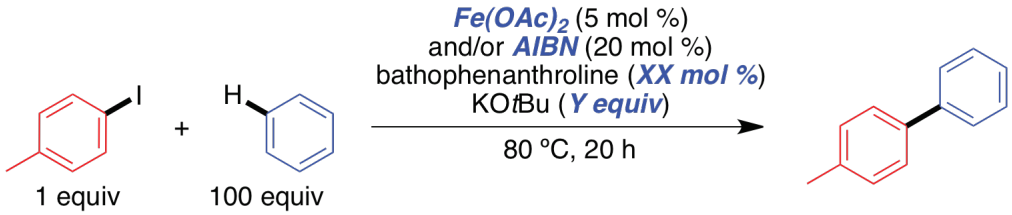
(34)

Scheme 62. Effect of radical inhibitors in the iron-catalyzed arylation.



Other experiments performed suggested that KO*t*Bu is not the source of radical, as had been reported in an elegant account by Itami (**Table 64**, entry 2).[193] The presence of 20 mol % AIBN gave 17% of the desired product (entry 3), indicating a stoichiometric role of the radical initiator, and suggesting a possible metal-free process. Though the base likely is not involved in the formation of a radical intermediate, its presence is needed, as no arylated product was observed employing $Fe(OAc)_2$ and AIBN alone.[193]

Table 64. Direct arylation in presence of iron and AIBN.

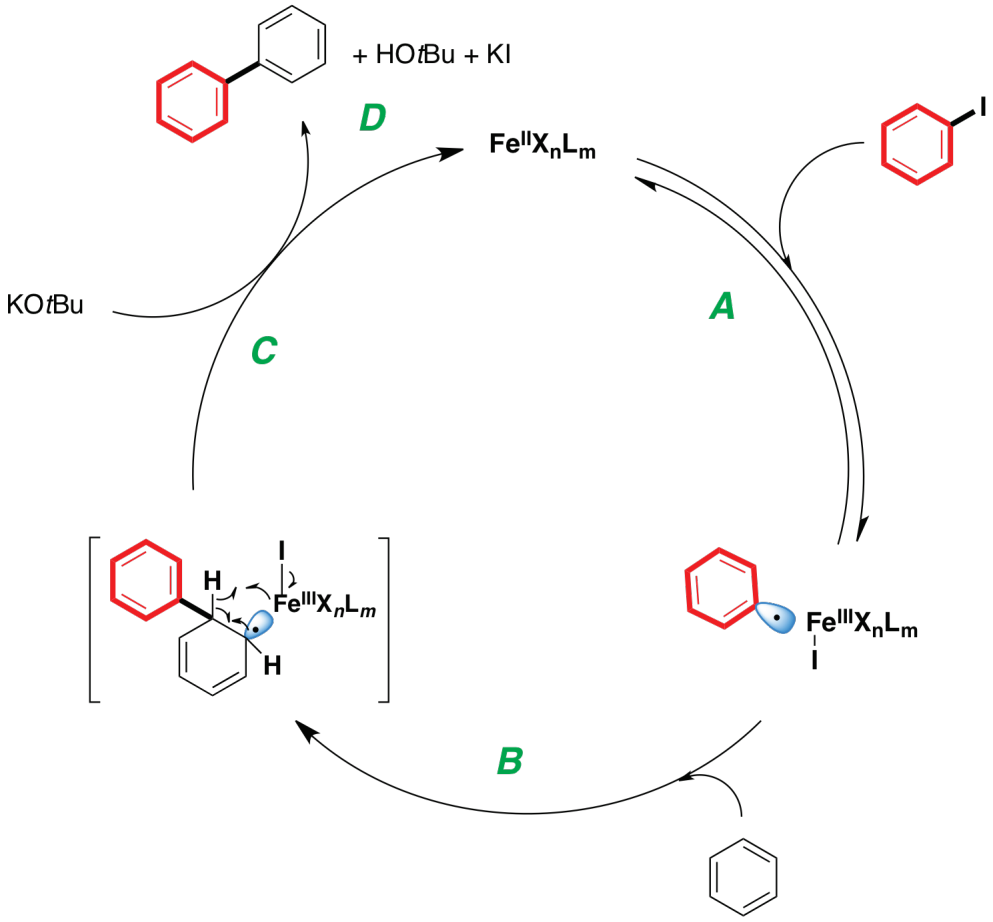


entry	catalyst	ligand loading (mol %)	KO*t*Bu loading	yield (%)[a]
1	$Fe(OAc)_2$	10	2 equiv	91
2	none	10	2 equiv	<1
3	AIBN	none	2 equiv	17
4	$Fe(OAc)_2$ + AIBN	10	none	<1

[a]Yield determined by GCMS analysis using 1,3,5-trimethylbenzene as an internal standard.

Given these results, we believe that the reaction proceeds through a mechanistic pathway akin to a metal-catalyzed living radical polymerization (**Scheme 63**).[197] The first step of the process involved activation of the C–I bond by a one-electron oxidation of the metal center. This reversibly forms the initiating radical species (in this case an arene) that is associated to an oxidized metallo-intermediate (**A**). This radical intermediate is then transformed into the desired biaryl product by addition onto the unactivated arene that is possibly pre-coordinated to the iron catalyst (**B**). Proximal abstraction of the iodine permits rearomatization while regenerating the active iron (II) catalyst (**C**). At this stage the radical is no longer bound to the iron reagent, but instead the duo forms a tight pair.[197] This generates HI that can be quenched by the presence of KO*t*Bu, though we cannot for the time being rule-out another possible role for the base (**D**). As in metal-catalyzed polymerization pathways the reaction relies on creating a dynamic equilibrium between a low concentration of the propagating species, and a large amount of dormant species that cannot propagate. Consequently, side-reactions are minimized, and the coupling process is efficient. Furthermore, such a mechanism would explain the increased effectiveness of electron-rich iodides, as radical intermediates would be better stabilized.

Scheme 63. Proposed catalytic cycle for the iron-catalyzed direct arylation of arenes.



6.3 Summary

We demonstrated that the ecofriendly and relatively inexpensive catalytic system comprising of $Fe(OAc)_2$ and bathophenanthroline is highly effective in catalyzing direct arylation reactions between aryl iodides and a variety of unactivated arenes. This work adds to the few examples of iron-catalyzed arylation processes and solves previous limitations that necessitate directing groups and large excesses of a myriad of additives. Mechanistic investigations confirmed that the reaction is indeed iron-catalyzed and proceeds through a radical pathway. This process constitutes a powerful and practical direct technology under mild conditions and will be of interest across a range of chemical sciences.

Chapter 7
Conclusions and Future Considerations

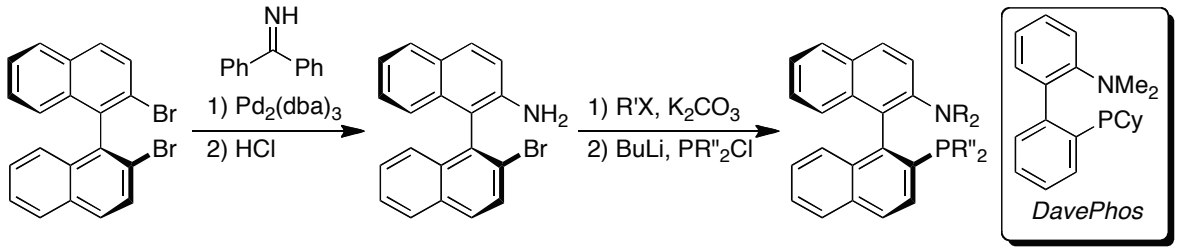
7.1 Direct Benzylic Functionalization of *N*-Iminopyridinium Ylide Derivatives

7.1.1 Arylation

As mentioned early in this thesis, the direct functionalization of C–H bonds has presented a new opportunistic means of synthesis of carbon-carbon bonds. Our foray into this work began with the palladium-catalyzed direct arylation at the 2-position of *N*-iminopyridinium ylides with a range of aryl bromides. While we demonstrated that 2,6-diarylation might not be feasible, we applied four methodologies to cleave the *N*-*N* bond of the ylide, liberating the free pyridine.

This work was the genesis of the direct benzylic arylation of 2-alkyl *N*-iminopyridinium ylides. In short, we developed a new method for sp^3 arylation, which up to the time of its disclosure, had been seldom reported. The reaction is performed at a relatively mild 70 ºC and utilizes aryl chloride coupling partners. The latter is particularly attractive due to their low cost and wide commercial availability. While attempts of asymmetric arylation gave low selectivities, part of the problem may lie in the choice of ligand. An alternate possible route would be through the synthesis of BINAP variants of DavePhos (**Scheme 64**), and exploring their reactivity/selectivity. Buchwald has successfully employed these ligands in enantioselective enolate arylation processes.[198]

Scheme 64. Known synthesis of BINAP variants of DavePhos.



7.1.2 Allylation

We have exploited the nucleophilicity of the *N*-iminopyridinium ylide in a Tsuji-Trost allylation reaction. Though selectivity towards bis-allylation is readily achieved, selectivity towards mono allylation remains a challenge. However, judicious screening of catalyst/ligand has determined that 3:1 ratio of mono to di-allylation is possible, and other parameters remain to be tested. Furthermore, in the case of 2-ethyl pyridinium ylides, only mono addition is observed with excellent yields, presenting avenues for asymmetric transformations. The reaction tolerates allyl acetate, bromide, and cyclopropyl bromide electrophiles.

7.1.3 Alkylation Under Phase Transfer Catalysis

We have demonstrated that, in presence of a strong base, metal-free functionalization of *N*-iminopyridinium ylides is possible. We exploited the use of cinchonidine-based chiral phase transfer catalysts in an effort to effect a green asymmetric alkylation reaction. To date we have a process that through the modification of the ylide electronics, gives a good yields and moderate selectivity. It may be possible to bias the selectivity through the inclusion of functional groups at the 3-position of the pyridinium ylide, favouring the formation of the *Z*-enamine (**Figure 25**).

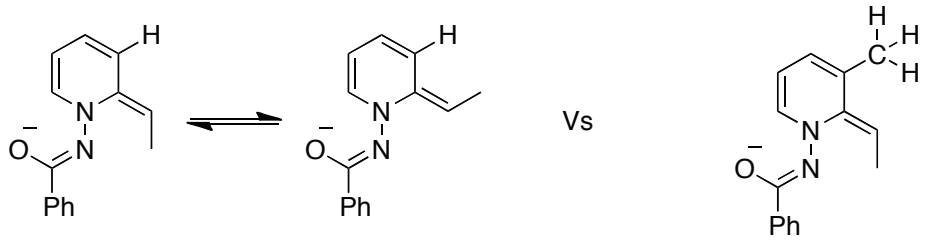


Figure 25. Comparison of enamine-like intermediates.

7.2 Copper-Catalyzed Direct Alkenylation Reactions

Through this work we uncovered a highly flexible copper-catalyzed direct alkenylation reaction. The process tolerates a large scope of styryl iodides and can employ virtually any copper (0), copper (I), or copper (II) source as the catalyst. This methodology permits access to biologically relevant 2-alkenyl pyridines. Mechanistic work performed indicates that the *N*-imino moiety plays a vital role in directing the copper catalyst to the 2-position of the heterocyclic ring. Also, a new method detailing the synthesis of vinyl iodides was discussed, providing a library of compounds for the alkenylation substrate scope. This methodology was also found to be readily scalable.

The reactivity of these alkenylated pyridinium compounds remains unexplored. One could easily envisage applying them to conjugate addition, Heck, and Diels-Alder reactions. Also, in the case of substituted alkenes, asymmetric hydrogenations could be performed, giving chiral 2-alkyl pyridines (**Figure 26**).

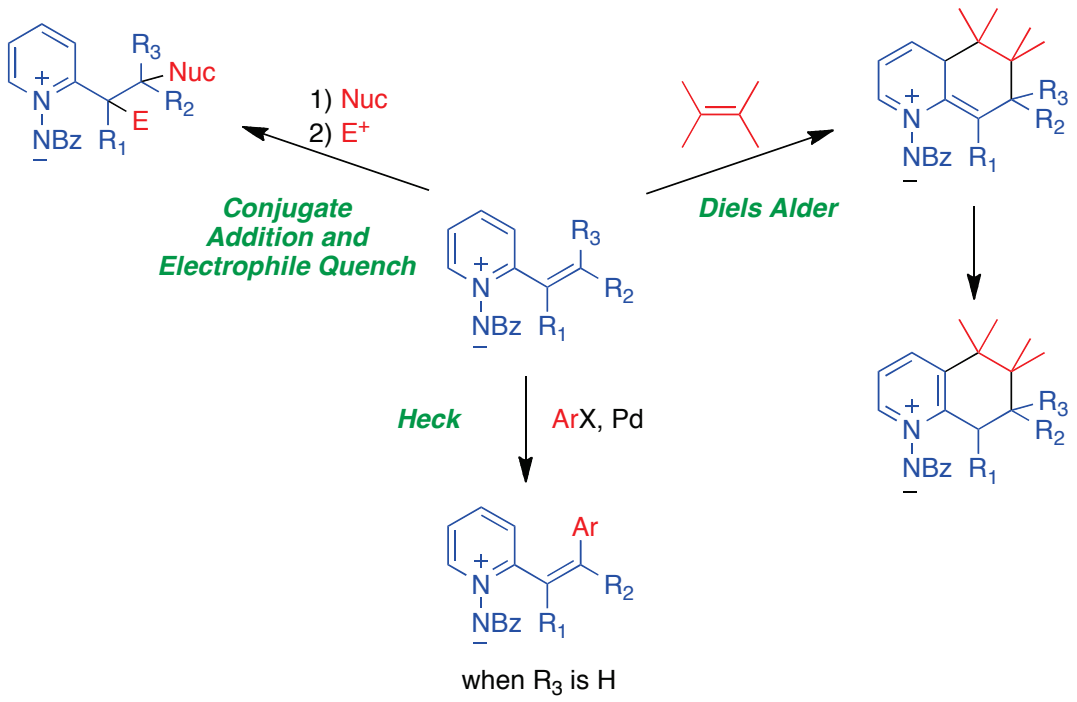
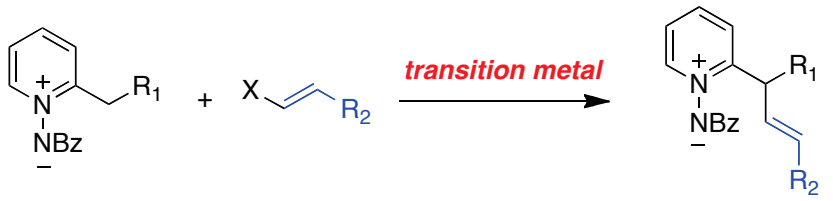


Figure 26. Proposed reactions on 2-alkenyl *N*-iminopyridinium ylides.

Other potential processes include a direct benzylic alkenylation transformation (Eq. 34). Similar to the analogous direct arylation, the direct vinylation of sp^3 centers remains relatively unknown. This may be possible under either (or both) copper or palladium catalysis. Also, the copper-catalyzed arylation of these ylides is only in the early stages of exploration.



(34)

7.3 Synthesis of 2-Substituted Pyrazolo[1,5-*a*]pyridines

Herein we described the efficient synthesis of 2-substituted pyrazolopyridines in 2-steps from pyridine. Previous reports detailing the synthesis of these medicinally relevant

compounds require either multi-step syntheses, or cannot avoid substitution at the 3-position. The reaction may be the first such example of a tandem direct functionalization cyclization sequence, tolerating a myriad of vinyl iodide and vinyl bromide coupling partners. Mechanistic investigations quickly suggested that the reactive intermediate was indeed an alkyne and, consequently, we ascertained that these unsaturated compounds are indeed viable coupling partners.

Concurrently we found that the presence of a methyl group at the 2-position of the pyridinium led to an intramolecular cyclization giving the 2,3-disusbtituted pyrazolopyridine. Yields can be improved by increasing the nucleophilicity of the ligand on silver. It remains to be seen if using more electron-withdrawing groups on the ylide moiety can positively influence the acidity of the benzylic protons, further improving reactivity.

7.4 Palladium-Catalyzed Umpolung Direct Arylation

We disclosed a novel palladium-catalyzed arylation that proceeds in absence of an external ligand or base, necessitating only a substoichiometric quantity of silver carbonate. The reaction displays inverse reactivity to what is typically observed with direct arylation reactions, whereby the directing group is *ortho* to the halide functionality. The process is also one of the few that describes the arylation of benzene and other unactivated arenes, which are used both as material feedstock and the reaction medium. It can be recovered and recycled towards other reactions. The presence of acetate was clearly demonstrated to be necessary, suggesting a concerted metallation deprotonation pathway. The mechanism is postulated to proceed through a cationic palladium (IV) species whereby the high-energy palladium generated is stabilized by the presence of the directing group. The substrate scope with regards to the halide and arene was deemed to be forgiving, giving the products in moderate to very good yields.

7.5 Iron-Catalyzed Direct Arylation Through Radical Intermediates.

Though the discovery of direct arylation reactions has led to a more efficient means of the synthesis of biaryl motifs, traditionally they rely on expensive, non-sustainable rare-earth elements as catalysts. A more desirable route would utilize inexpensive and abundant iron reagents. Though elegant accounts for this exist, they often require the inclusion of a large excess of metal and/or non-metal additives, in addition to a directing group decreasing the efficiency of the transformation. With this work we developed an iron-catalyzed arylation that proceeds under mild reaction temperatures, without the insertion of stoichiometric additives, or necessitating a directing group. The scope is widely general and the technology can be applied at room temperature with electron-rich substrates. Mechanistic investigations elucidated a radical pathway analogous to living radical polymerizations.

A logical extension of this would be to couple the styryl iodides prepared in Chapter 3 (Eq. 35). The resulting stilbenes would be of potential interest to materials and supramolecular chemists. Preliminary studies have demonstrated that with slight modification of reaction conditions this should indeed be possible.

(35)

7.6 Final Thoughts

At the beginning of this doctoral research the study of direct reactions was still a relatively new area of chemistry. Though far from a mature science, it has been quite astonishing to witness first hand the incredibly rapid growth of the field. Several new transformations can be seen every day in the literature and, given the importance and attractiveness of these methods, one can only assume that this will continue to be an

upward trend. It has been a great pleasure to have added a few pieces to the toolbox of direct transformations, and hope that this work will have an important impact on the synthesis of heterocyclic and non-heterocyclic arenes. More importantly, it has been gratifying to open the door for others to continue various avenues of this work. Undoubtedly this chemistry will continue to advance, and change the way we approach the synthesis of carbon-carbon bonds.

Experimental Section

All reactions requiring anhydrous conditions were performed using standard techniques under an argon atmosphere in glassware that was dried either for a minimum of 8 h at 120 ºC in an oven, or by flame with cooling under a flow of argon. [199] All of the chemical products were of reagent or technical grade and were purchased from Sigma Aldrich Chemical Company, Strem Chemicals, Alfa Aesar, Oakwood Products, or Acros Organics. Purification of these products was left to the chemist's discretion, and if need be, was performed under standard techniques.[200] Solvents used were of ACS or HPLC grade and were obtained from VWR or Anachemia. Anhydrous solvents were dried and deoxygenated with drying columns on a GlassContour system (Irvine CA). the reported yields represent the yields of products isolated following either distillation, flash chromatography, preparative TLC, HPLC, or recrystallization.

Thin layer chromatography (TLC) was performed on glass-backed silica plates (Merck GF-UV254, 0.25 mm, or SiliCycle TLG-R10011B, 0.25 mm) and contained a fluorescence indicator. Following elution, the products were visualized with the following methods or stains: UV lamp, CAM solution (aqueous ammonium molybdate and cerium sulfate), aqueous $KMnO_4$ solution, aqueous PMA (phosphomolybdinamic acid), *p*-anisaldehyde in 95% ethanol, or a solution of vanillin in 85% ethanol. Flash chromatography was performed as per the method developed by Still[201] using either Merck 9385 or Silicycle R10030B (40-60 μm; 230-240 mesh) silica gel. Preparative High Performance Liquid Chromatography was performed on an Agilent 1100 Series LC system equipped with simultaneous diode array UV detection. Data are reported as follows: (column type, eluent, flow rate: retention time (tr)).

Nuclear Magnetic Resonance spectra (^1H, ^{13}C, and ^{19}F) were taken on the following instruments using BBO, QNP, or DUAL probes: Bruker AMX-300 (300 MHz and 75 MHz), Bruker ARX-400 (400 MHz and 100 MHz), AV-400 (400 MHz, 100 MHz), AV-300 (300 MHz, 75 MHz, 282 MHz (^{19}F)). Chemical shifts for 1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the

internal standard (chloroform, d = 7.27 ppm).[202] Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, qn = quintet, sext = sextet, h = heptet, o = octet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per using the solvent resonance as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. When need be, COSY, HMQY, HMBC, NOESY, and DEPT135 experiments were performed.

Analytical supercritical fluid chromatography was performed with a Berger SFC fashioned with a UV diode detector. Data are reported as follows: (column type, eluent, retention time (tr)). Low-resolution mass sprectra were performed either on a GC/MS Agilent 6890 Series GC system equipped with an Agilent 5973 Network-G2578A Standard Turbo EI MSD and/or on an Agilent 1100 Series LC/MSD system equipped with an APCI mass detector with simultaneous diode array UV detection.

Melting points were obtained on a Thomas Hoover apparatus and are not corrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR with the important vibrations being reported in cm^{-1}. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal Under either EI, ES, FAB, MAB, or APCI ionization modes. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal. X-ray structures were obtained though Laboratoire de diffraction des rayons-X de l'Université de Montréal using an Enraf-Nonius CAD-3 or CAD-4 apparatus.

Experimental protocols and characterization data for new compounds and selected known compounds presented in this thesis are described in the following Annex, as are data obtained from x-ray analysis.

Bibliography

(1) Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications, 2nd Edition; Wiley-VCH: Weinheim, 2003.

(2) For selected reviews see : (a) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007,** *36*, 1161. (b) Youssif, S. *ARKIVOC* **2001**, 242. (c) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007,** *36*, 1036. (d) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007,** *36*, 1095. (e) Lehn, J.-M. *Science* **2002,** *295*, 2400. (f) Lehn, J.-M. *Proc. Nat. Acad. Sci. U.S.A*. **2002**, *99*, 4763.

(3) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005,** *9*, 253.

(4) Carey, J. S.; Laffan, L.; Thompson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006,** *4*, 2337.

(5) Laird, T. *Org. Process Res. Dev.* **2006,** *10*, 851.

(6) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102*, 1359.

(7) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901,** *34*, 2174.

(8) For reaction overview see: (a) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley and sons, 2004. (b) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Academic Press, 2005. (c) *Modern Arylation Methods*; Ackermann, L. *Ed.*; Wiley-VCH: Weinheim, 2009.

(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95*, 2457.

(10) (a) Stanforth, S. P. *Tetrahedron* **1998,** *54*, 263. (b) Corriu, R. J. P. *J. Organomet. Chem.* **2002,** *653*, 20.

(11) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004,** *43*, 4704.

(12) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008,** *41*, 1486.

(13) For selected reviews see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007,** *107*, 174. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Miura, M.; Satoh, T. *Topics in Organometallic Chemistry* **2005,** *14*, 55. (d) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007,** *40*, 35. (e) Ellman, J. *Science* **2007,** *316*, 1131. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62*, 2439. (g) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009,** *48*, 9792. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110*, 1147. (i) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (j) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009,** *38*, 2447. (k) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (l) Ackermann, L. *Top. Organomet. Chem.* **2007**, 35.

(14) For selected examples see: (a) Stuart, D. R.; Fagnou, K. *Science* **2007,** *316*, 1172. (b) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010,** *1*, 331. (c) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010,** *132*, 5837.

(15) For reviews for the direct arylation of heterocycles see: (a) Satoh, T.; Miura, M. *Chem. Lett.* **2007,** *36*, 200. (b) Miura (c) Seregin, I. Y.; Gevorgyan, V. *Chem. Soc. Rev.* **2007,** *36*, 1173. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009,** *110*, 624. (e) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007,** *36*, 1058. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2009,** *65*, 10269.

(16) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009,** *131*, 3291.

(17) Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarsiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987,** *109*, 203.

(18) Barros, N.; Eisenstein, O.; Maron, L. *Dalton Trans.* **2006**, 3052.

(19) Klei, B.; Teuben, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 659.

(20) Klei, E.; Teuben, J. H. *J. Organomet. Chem.* **1981,** *214*, 53.

(21) Piglosiewicz, I. M.; Kraft, S.; Beckhause, R.; Haase, D.; Saak, W. *Eur. J. Inorg. Chem.* **2005**, 938.

(22) Jantunen, K. C.; Scott, B. L.; Kiplinger, J. L. *J. Alloys Compd.* **2007,** *444-445*, 363.

(23) Iwata, M.; Okazaki, M.; Tobita, H. *Chem. Commun.* **2003**, 2744.

(24) Iwata, M.; Okazaki, M.; Tobita, H. *Organometallics* **2006,** *25*, 6115.

(25) Dyker, G. *Angew. Chem., Int. Ed.*, **1999**, *38*, 1698.

(26) Durfee, L. D.; Rothwell, I. P. *Chem. Rev.* **1988,** *88*, 1059.

(27) Sadimenko, A. P. *Adv. Heterocycl. Chem.* **2005,** *88*, 111.

(28) Jordan, R. F.; Taylor, D. F.; Baenziger, N. C. *Organometallics* **1990,** *9*, 1546.

(29) Fanwick, P. E.; Kobriger, L. M.; McMullen, A. K.; Rothwell, I. P. *J. Am. Chem. Soc.* **1986,** *108*, 8095.

(30) Zambrano, C. H.; McMullen, A. K.; Kobriger, L. M.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1990,** *112*, 6565.

(31) Kobriger, L. M.; McMullen, A. K.; Fanwick, P. E.; Rothwell, I. P. *Polyhedron* **1989,** *8*, 77.

(32) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989,** *111*, 778.

(33) Guram, A. S.; Jordan, R. F. *Organometallics* **1990,** *9*, 2190.

(34) Guram, A. S.; Jordan, R. F. *Organometallics* **1991,** *10*, 3470.

(35) Bi, S.; Lin, Z.; Jordan, R. F. *Organometallics* **2004,** *23*, 4882.

(36) Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994,** *116*, 4491.

(37) Dagorne, S.; Rodewald, S.; Jordan, R. F. *Organometallics* **1997,** *16*, 5541.

(38) Arnold, J.; Woo, H. G.; Tilley, T. D.; Rheingold, A. L.; Geib, S. J. *Organometallics* **1988,** *7*, 2045.

(39) Arnold, J.; Tilley, T. D.; Rheingold, A. L.; Geib, S. J.; Arif, A. M. *J. Am. Chem. Soc.* **1989,** *111*, 149.

(40) Deelman, B.-J.; Stevels, W. M.; Teuben, J. H.; Lakin, M. T.; Spek, A. L. *Organometallics* **1994,** *13*, 3881.

(41) Erker, G.; Muehlenbernd, T.; Benn, R.; Rufinska, A. *Organometallics* **1986,** *5*, 402.

(42) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007,** *129*, 5332.

(43) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992,** *114*, 5888.

(44) Billinsley, K. L.; Buchwald, S. *Angew. Chem., Int. Ed.* **2008,** *47*, 4695.

(45) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.--Eur. J.* **2010,** *16*, 3300.

(46) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005,** *127*, 3648.

(47) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005,** *127*, 18020.

(48) Campeau, L. C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130*, 3266.

(49) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009,** *65*, 4977.

(50) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006,** *45*, 7781.

(51) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009,** *11*, 1357.

(52) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130*, 10848.

(53) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128*, 16496.

(54) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128*, 8754.

(55) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006,** *128*, 1066.

(56) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007,** *129*, 12404.

(57) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130*, 15185.

(58) For selected examples see: (a) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007,** *129*, 14570. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007,** *129*, 3510. (c) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006,** *128*, 14220. (d) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128*, 12634. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006,** *128*, 9048. (f) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005,** *127*, 13154. (g) Campos, K. R. *Chem. Soc. Rev.* **2007,** *36*, 1069. (h) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.--Eur. J.* **2010,** *16*, 2654. (i) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010** *132*, 10692. (j) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706.

(59) Guram, A. S.; Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1991,** *113*, 1833.

(60) Guram, A. S.; Swenson, D. G.; Jordan, R. F. *J. Am. Chem. Soc.* **1992,** *114*, 8991.

(61) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005,** *127*, 7330.

(62) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007,** *129*, 11904.

(63) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007,** *46*, 2643.

(64) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007,** *9*, 2373.

(65) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2003,** *125*, 6360.

(66) Legault, C. Y.; Charette, A. B. *J. Org. Chem.* **2003,** *68*, 7119.

(67) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005,** *44*, 4046.

(68) The first example of palladium undergoing *ortho* arylation in anilides was described here: Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984,** *106*, 5759.

(69) For discussion on directing group effects see: Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008,** *130*, 13285.

(70) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008,** *130*, 52.

(71) X-Ray data was obtained from the following theses: (a) Legault, C. Y., Ph.D. Thesis, Université de Montréal, 2005. (b) Larivée, A., Ph.D. Thesis, Université de Montréal, 2007.

(72) Martinez-Barrasa, V.; Delgado, F.; Burgos, C.; Garcia-Navio, J. L.; Izquiero, M. L.; Alvarez-Builla, J. *Tetrahedron* **2000,** *56*, 2481.

(73) Sanchez, A.; Nunez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006,** *47*, 8343.

(74) (a) Sainsbury, M.; Webb, B.; Schinazi, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 289. (b) Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Vice, S.; S., M.; Cox, K.; Strizki, J.; Baroudy, B. M. *Bioorg. Med. Chem. Lett.* **2003,** *13*, 709.

(75) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008,** *10*, 1641.

(76) Galli, C. *Org. Prep. Proced. Int.* **1992,** *24*, 287.

(77) For review see: Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008,** *41*, 1461.

(78) For examples see: (a) Shi, B.-F.; Maugel, N.; zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008,** *47*, 4882. (b) Giri, R.; Shi, B.-F.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009,** *38*, 3242. (c) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005,** *44*, 2112.

(79) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006,** *45*, 1952.

(80) Zhao, G.-L.; Ullah, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Córdova, A. *Chem.--Eur. J.* **2010,** *16*, 1585.

(81) (a) Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009,** *131*, 15624. (b) Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem.--Eur. J.* **2009,** *15*, 11829.

(82) He, Z.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 5829.

(83) For selected reviews see: (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987,** *20*, 140. (b) Trost, B. M. *Acc. Chem. Res.* **1980,** *13*, 385. (c) Trost, B. M. *Acc. Chem. Res.* **1996,** *29*, 355. (d) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006,** *39*,

747. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996,** *96*, 395. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003,** *103*, 2921.

(84) (a) Kimura, M.; Mukai, R.; Tanigawa, N.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2003,** *59*, 7767. (b) Kimura, M.; Fukushima, M.; Tamaru, Y. *Heterocycles* **2006,** *67*, 535.

(85) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997,** *62*, 4877.

(86) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008,** *130*, 14092.

(87) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009,** *131*, 12056.

(88) Starks, C. M. *J. Am. Chem. Soc.* **1971,** *93*, 195.

(89) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984,** *106*, 446.

(90) For selected examples see: (a) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, T. *Tetrahedron Lett.* **2000,** *41*, 8339. (b) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, T. *Angew. Chem., Int. Ed.* **2002,** *41*, 4542.

(91) For selected reviews see: (a) Jew, S.-s.; Park, H.-g. *Chem. Commun.* **2009**, 7090. (b) Maruoka, K. *Org. Process Res. Dev.* **2008,** *12*, 679. (c) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007,** *46*, 4222. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003,** *103*, 3013. (e) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007,** *107*, 5656.

(92) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997,** *119*, 12414.

(93) Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; rosa, A. M.; Gomes, M. J. J.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* **2001,** *12*, 3349.

(94) Arai, S.; Tsuge, H.; Oku, M.; Miuara, M.; Shiori, T. *Tetrahedron* **2002,** *58*, 1623.

(95) "Top 200 Brand-Name Retail Drugs by Retail Dollars 2008." *Compiled by Njardarson Group, Cornell University*.

(96) Jackson, R. H.; Morrissey, M. M.; Stills, M. A.; Jarvis, M. F. *J. Pharmacol. Exp. Ther.* **1992,** *262*, 80.

(97) Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Zhu, J.; Jones, M. D.; Crooks, P. A. *Bioorg. Med. Chem.* **2005,** *13*, 3899.

(98) Wang, S.-J.; Sihra, T. S. *J. Pharmacol. Exp. Ther.* **2004,** *309*, 951.

(99) Wilson, K. J.; van Niel, M. B.; Cooper, L.; Bloomfield, D.; O'Connor, D.; Fish, L. R.; MacLeod, A. M. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 2643.

(100) Shi, X.-F.; Xing, Z.-Y.; Zhang, W.-Q. *Inorg. Chim. Acta* **2006,** *359*, 603.

(101) Klein, H.-F.; Camedanli, S.; Beck, R.; Florke, U. *Chem. Commun.* **2004**, 381.

(102) Loeffler, G. *Chem. Ber.* **1907,** *40*, 1342.

(103) Azzena, U.; Dettori, G.; Lubinu, C.; Mannu, A.; Pisano, L. *Tetrahedron* **2005,** *61*, 8663.

(104) Luo, F.; Pan, C.; Wang, W.; Ye, Z.; Chang, J. *Tetrahedron* **2010,** *66*, 1399.

(105) For selected examples see: (a) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002,** *67*, 8424. (b) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002,** *4*, 107. (c) Navarro,

O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.--Eur. J.* **2006,** *12*, 5142. (d) Wang, Z.; Pitteloud, J.-P.; Montes, L.; Rapp, M.; Derane, D.; Wnuk, S. F. *Tetrahedron* **2008,** *64*, 5322.

(106) Li, M.; Hua, R. *Appl. Organomet. Chem.* **2008,** *22*, 397.

(107) Sakamoto, T.; Arakida, H.; Edo, K.; Yamanaka, H. *Chem. Pharm. Bull.* **1982,** *30*, 3647.

(108) Cui, X.; Zhou, Y.; Wang, N.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007,** *48*, 163.

(109) For examples with non-heterocyclic arenes see: (a) Yamaguchi, M. *Pure Appl. Chem.* **1998,** *70*, 1091. (b) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008,** *10*, 5309. (c) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009,** *131*, 5072. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010,** *132*, 3680.

(110) For a single example onto oxazoles giving alkynyl products see: Pacheco Berciano, B.; Lebrequier, S.; Besselievre, F.; Piguel, S. *Org. Lett.* **2010,** *12*, 4038.

(111) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003,** *125*, 4720.

(112) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007,** *46*, 8872.

(113) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008,** *130*, 2448.

(114) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008,** *130*, 9254.

(115) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009,** *131*, 13888.

(116) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996,** *118*, 2748.

(117) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008,** *108*, 3034.

(118) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005,** *70*, 8107.

(119) Larsson, P. F.; Correa, A.; Carril, M.; Norrby, P. O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009,** *48*, 5691.

(120) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003,** *42*, 5400.

(121) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008,** *108*, 3395.

(122) Uemura, S.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006,** *35*, 842.

(123) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008,** *47*, 1932.

(124) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128*, 6790.

(125) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009,** *48*, 8078.

(126) For another example of copper-catalyzed oxidative coupling of C–C bonds see: Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008,** *73*, 7822.

(127) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem.* **2009,** *121*, 3346.

(128) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009,** *11*, 3072.

(129) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008,** *130*, 8172.

(130) Phipps, R. J.; Gaunt, M. J. *Science* **2009,** *323*, 1593.

(131) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130*, 1128.

(132) Besselie, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008,** *10*, 4029.

(133) For similar direct alkynylation see: Besselievre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009,** *48*, 9553.

(134) Kabir, M. S.; Van Linn, M. L.; Monte, A.; Cook, J. M. *Org. Lett.* **2008,** *10*, 3363.

(135) For recent examples see: (a) Das, J. P.; Roy, S. *J. Org. Chem.* **2002,** *67*, 7861. (b) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005,** *61*, 637. (c) You, H.-W.; Lee, K. J. *Synlett* **2001**, 105. (d) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, 1319.

(136) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003,** *68*, 6031.

(137) Brown, H.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989,** *54*, 6075.

(138) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989,** *30*, 2173.

(139) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986,** *108*, 7408. (b) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268.

(140) Bull, J. A.; Charette, A. B. *J. Org. Chem.* **2008,** *73*, 8097.

(141) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008,** *10*, 5485.

(142) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Synth.* **2010,** *87*, 170.

(143) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006,** *128*, 4348.

(144) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010,** *49*, 1115.

(145) Prices retrieved from Strem chemicals Oct. 28, 2010.

(146) For examples of radical arylations through copper see: Sainsbury, M. *Tetrahedron* **1980,** *36*, 3327.

(147) For discussion on isotope effects and means to determine them by either competition or kinetic studies see: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: Sausalito, 2005.

(148) For various examples see: (a) Shirafugi, T.; Yamamoto, Y.; Nozaki, H. *Tetrahedron* **1971,** *27*, 5353. (b) Fritschi, H.; Leutenegger, U.; Sigmann, K.; Pfaltz, A. *Helv. Chim. Acta* **1988,** *71*, 1541. (c) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988,** *71*, 1553. (d) Brown, D. B.; Donner, J. A.; Hall, J. W.; Wilson, S. R.; Wilson, R. B.; Hodgson, D. J.; Hatfield, W. E. *Inorg. Chem.* **1979,** *18*, 2635. (e) Tuong, T. d.; Hida, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 676. (f) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973,** *95*, 3300.

(149) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem.* **2005,** *117*, 615.

(150) For examples of converting Cu^0 to Cu^I see: (a) Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* **1972,** *94*, 4363. (b) Lewin, A. H.; Zovko, M. j.; Rosewater, W. H.; Cohen, T. *Chem. Commun.* **1967**, 80. (c) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970,** *92*, 3189.

(151) For direct copper reactions see: Breit, B.; Schmidt, Y. *Chem. Rev.* **2008,** *108*, 2928.

(152) For carbonate/halogen exchange on copper see: Weingarten, H. *J. Org. Chem.* **1964,** *29*, 3624.

(153) For review of copper insertion into aryl halogen bonds see: Lindley, J. *Tetrahedron* **1984,** *40*, 1433.

(154) (a) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 2377. (b) Hansen, J. B.; Weis, J.; Suzdak, P. D.; Eskesen, K. *Bioorg. Med. Chem. Lett.* **1994,** *4*, 695. (c) Bettinetti, L.; Schlotter, K.; Hubner, H.; Gmeiner, P. *J. Med. Chem.* **2002,** *45*, 4594.

(155) (a) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Samano, V. A.; Ray, J. A.; Freeman, G. A.; Boyd Jr, F. L.; Sexton, C. J.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2005,** *13*, 2397. (b) Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Kinoshita, T.; Tenda, Y.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 1979. (c) Akahane, A.; Katayama, H.; Mitsunaga, T.; Kato, T.; Kinoshita, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *J. Med. Chem.* **1999,** *42*, 779.

(156) For examples see: (a) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 97. (b) Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M.; Harris, P. A.; Chamberlain, S. D.; Peel, M. R. *Org. Lett.* **2005,** *7*, 4753. (c) Yu, X.; Ye, S.; Wu, J. *Adv. Synth. Catal.* **2010,** *352*, 2050. (d) Chen, Z.; Su, M.; Yu, X.; Wu, J. *Org. Biomol. Chem.* **2009,** *7*, 4641. (e) Johnston, K. A.; Allcock, R. W.; Jiang, Z.; Collier, I. D.; Blakli, H.; Rosair, G. M.; Bailey, P. d.; Morgan, K. M.; Kohno, Y.; Adams, D. R. *Org. Biomol. Chem.* **2008,** *6*, 175. (f) Harju, K.; Kylanlahti, I.; Paananen, T.; Polamo, M.; Nielsen, J.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2006,** *8*, 344. (g) Patnaik, S.; Dietz, H. C.; Zheng, W.; Austin, C.; Marugan, J. J. *J. Org. Chem.* **2009,** *74*, 8870. (h) Miki, Y.; Tasaka, J.; Uemura, K.; Miyazeki, K.; Yamada, J. *Heterocycles* **1996,** *43*, 2249. (i) Chen, Z.; Wu, J. *Org. Lett.* **2010,** *12*, 4856.

(157) (a) Tsuchiya, T.; Sashida, H. *J. Chem. Soc., Chem. Commun.* **1980**, 1109. (b) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010,** *49*, 2743. (c) Kishore, K.; Reddy, K. R.; Suresh, J. R.; Ila, H.; Junjappa, H. *Tetrahedron* **1999,** *55*, 7645. (d) Gilligan, P. J.; Clarke, T.; He, L.; Lelas, S.; Li, Y.-W.; Heman, K.; Fitzgerald, L.; Miller, K.; Zhang, G.; Marshall, A.; Krause, C.; McElroy, J. F.; Ward, K.; Zeller, K.; Wong, H.; Bai, S.; Saye, J.; Grossman, S.; Zaczek, R.; Arneric, S. P.; Hartig, P.; Robertson, D.; Trainor, G. *J. Med. Chem.* **2009,** *52*, 3084.

(158) (a) Abet, V.; Nunez, A.; Mendicuti, F.; Burgos, C.; Alvarez-Builla, J. *J. Org. Chem.* **2008,** *73*, 8800. (b) Nunez, A.; de Viedma, A. G.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002,** *2002*, 1093.

(159) Csanyi, D.; Hajos, G.; Riedl, Z.; Timari, G.; Bajor, Z. n.; Cochard, F.; Sapi, J.; Laronze, J.-Y. *Bioorg. Med. Chem. Lett.* **2000,** *10*, 1767.

(160) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L.; Peel, M. R. *Tetrahedron* **2003,** *59*, 9001.

(161) (a) Tietze, L. F. *Chem. Rev.* **1996,** *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996,** *96*, 195. (c) Touree, B. B.; Hall, D. G. *Chem. Rev.* **2009,** *109*, 4439.

(162) Mousseau, J. J.; Fortier, A.; Charette, A. B. *Org. Lett.* **2010,** *12*, 516.

(163) Mousseau, J. J.; Fortier, A.; Bull, J. A.; Ladd, C.; Charette A. B. *Unpublished Results – Manuscript in Preaparation.*

(164) For the use of silver in the synthesis of heterocycles see: (a) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2008,** *108*, 3174. (b) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008,** *108*, 3149. (c) Yoshikawa, T.; Shindo, M. *Org. Lett.* **2009,** *11*, 5378. (d) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009,** *74*, 2893.

(165) For Fujiwara coupling reactions see: (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001,** *34*, 633. (b) Kitamura, T. *Eur. J. Org. Chem.* **2009,** *2009*, 1111.

(166) For examples see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007,** *107*, 5318. (b) Phua, P. H.; de Vries, J. G.; Hii, K. K. *Adv. Synth. Catal.* **2005,** *347*, 1775. (c) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004,** *6*, 1861.

(167) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998,** *37*, 2704.

(168) For selected recent examples: (a) Ackermann, L.; Born, R.; Alvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007,** *46*, 6364. (b) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009,** *48*, 8935. (c) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007,** *129*, 6066. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009,** *131*, 9651. (f) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009,** *131*, 11234. (g) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010,** *132*, 468. (h) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010,** *132*, 4978. (i) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009,** *42*, 1074. (j) Shabashov, D.; Maldonado, J. R. M.; Daugulis, O. J. Org. Chem. 2008, 73, 7818.

(169) Snieckus, V. *Chem. Rev.* **1990,** *90*, 879.

(170) Qin, C.; Lu, W. *J. Org. Chem.* **2008,** *73*, 7424.

(171) Liu, W.; Cao, H.; Lei, A. *Angew. Chem., Int. Ed.* **2010,** *49*, 2004.

(172) René, O.; Fagnou, K. *Org. Lett.* **2010,** *12*, 2116.

(173) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010,** *132*, 12850.

(174) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010,** *132*, 4506.

(175) Mousseau, J. J.; Vallée, F.; Lorion, M. M.; Charette, A. B. *J. Am. Chem. Soc.* **2010,** *132*, 14412.

(176) Schlosser, M.; Marzi, E. *Chem.–Eur. J.* **2005,** *11*, 3449.

(177) For examples see: (a) Beller, M.; Fishcer, H.; Kühlein, K. *Tetrahedron Lett.* **1994,** *35*, 8773. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969,** *91*, 7166. (c) Yong, W.; Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1991**, 967. (d) Taccardi, N.; Paolillo, R.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Räisänen, M.; Repo, T. *Eur. J. Inorg. Chem.* **2007**, 4645.

(178) Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006,** *128*, 5033.

(179) For recent discussions see: (a) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010,** *132*, 10692. (b) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010,** *132*, 10706.

(180) van Helden, R.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1965,** *84*, 1263.

(181) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *J. Org. Chem.* **2000,** *65*, 3107.

(182) For examples of cationic palladium (IV) species see: (a) Campora, J.; Palma, P.; del Rio, D.; Carmona, E. *Organometallics* **2003,** *22*, 3345. (b) Campora, J.; Palma, P.; del Rio, D.; Lopez, J. A.; Alvarez, E. *Organometallics* **2005,** *24*, 3624.

(183) Rayner-Canham, G. *Descriptive Inorganic Chemistry*, 2nd ed.; W. H. Freeman: New York, 2000.

(184) Stryer, L. *Biochemistry*, 4th ed.; W. H. Freeman: New York, 1995.

(185) For an overview of iron-catalyzed reactions see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (c) Iron Catalysis in Organic Chemistry: Reactions and Applications (Ed.: B. Plietker), Wiley-VCH, Weinheim, 2008. (d) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res*. **2008**, *41*, 1500. (f) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730.

(186) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971,** *93*, 1487. (b) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976,** *41*, 502. (c) Kochi, J. K. *J. Organomet. Chem.* **2002,** *653*, 11.

(187) (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002,** *41*, 609. (b) Fürstner, A.; Leitner, A.; Mandez, M.; Krause, H. *J. Am. Chem. Soc.* **2002,** *124*, 13856. (c) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004,** *69*, 3943.

(188) For an overview of iron-catalyzed C–H transformations see: Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2010**, *ASAP* DOI:10.1021/cr100198w.

(189) Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem., Int. Ed.* **2008,** *47*, 8897.

(190) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008,** *130*, 5858.

(191) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009,** *48*, 2925.

(192) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010,** *132*, 5568.

(193) Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010,** *132*, 1514.

(194) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009,** *48*, 5586.

(195) For recent direct arylations proceeding through radical pathways see: (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008,** *10*, 4673. (b) Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010,** *132*, 15537. (c) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, ASAP DOI: 10.1021/ja103050x. (d) Dichiarante, V.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2007,** *46*, 6495. (e) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nature Chem.* **2010**, *2*, 1044.

(196) For arylation by TEMPO see: Kirchberg, S.; Volger, T.; Studer, A. *Synlett* **2008**, 2841.

(197) For discussion on living radical polymerization processes see: (a) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001,** *101*, 2921. (b) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001,** *101*, 3689. (c) Xue, Z.; Linh, N. T. B.; Noh, S. K.; Lyoo, W. S. *Angew. Chem., Int. Ed.* **2008,** *47*, 6426.

(198) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001,** *3*, 1897.

(199) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Ed.; Wiley: New York, 1986.

(200) Amarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th Ed.; Butterworth-Heinemann: Oxford, 1996.

(201) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(202) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

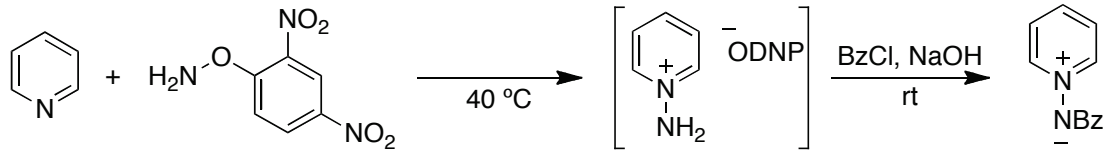
Annexes

Annex 1 : Experimental Section

Experimental Section of Chapter 2

Direct sp^2 Arylation and* N-N-*Cleavage

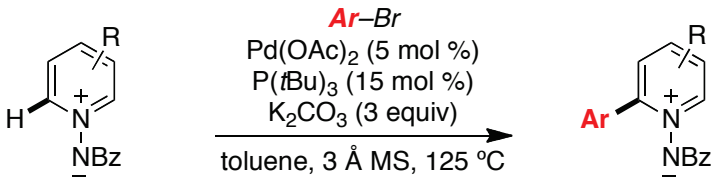
General Procedure for the Synthesis of N-Iminopyridinium Ylides[1]



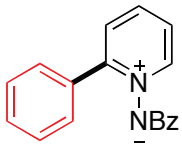
Pyridine (0.100 mL, 1.24 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (272 mg, 1.36 mmol) were added to H_2O/THF (1:1 mixture, 1.0 mL). The reaction flask was sealed with a septum, and the resulting suspension was stirred at 40 °C for 16 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5 N, 6 mL) at room temperature, stirred for 5 min, and then benzoyl chloride (0.215 mL, 1.84 mmol) was added in one portion. After 5 h, the reaction was diluted with H_2O (5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with NaOH (2.5 N, 5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording the *N*-iminobenzoylpyridinium ylide as a beige solid (236 mg, 96% yield). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.9 Hz, 2H), 8.16 (d, J = 5.7 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.0 Hz, 2H), 7.48- 7.37 (m, 3H).

[1] All ylides were previously reported, see: Legault, C. Y.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7119.

General Procedure for the Formation of 2-Aryl-*N*-Iminopyridinium Ylides Derived from *N*-Iminopyridinium ylides[2]



The desired *N*-iminobenzoylpyridinium ylide (0.52 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.02 mmol, 5 mol %), tBu_3P (0.05 mmol, 15 mol %), anhydrous powdered K_2CO_3 (1.09 mmol, 3 equiv) and 3 Å molecular sieves (105.7 mg) were charged with a stir bar in a Schlenk flask inside a glovebox. Toluene (1.2 mL, 0.3 M) was added and the suspension was stirred vigorously at rt for 5 min. Then, ArBr (2) (0.35 mmol, 1 equiv) was added and the vigorously stirred reaction mixture was heated to 125 °C in an oil bath. After 16-20 h of reaction the suspension was chilled to rt, filtered on a short pad of silica (washing with 15% methanol in dichloromethane) and the filtrate was concentrated under reduced pressure. Preparative High Performance Liquid Chromatography afforded the pure compound.

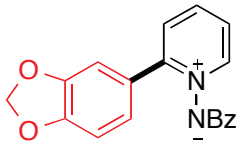


21

2-Phenyl-*N*-benzoyliminopyridinium ylide (21).[2] Prepared according to the general procedure (page IV). The title compound was purified by reverse phase preparative High Performance Liquid Chromatography (ZORBAX Eclipse XDB-C8, 2% to 60% MeCN in H_2O over 10 min, 20 mL/min: t_r = 7.77 min) afforded **21** as a pale yellow solid (76.1 mg, 80%). R_f = 0.42 (methanol/hexanes/dichloromethane, 15/25/60). mp: 96-100 ºC. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.73 (dd, J = 6.4, 0.9 Hz, 1H), 7.99 (td, J = 7.7, 1.4 Hz, 1H), 7.94 (dd, J = 8.1, 1.4 Hz, 2H), 7.75 (dd, 8.0, 1.3 Hz, 1H), 7.68-7.62 (m, 3H), 7.48-7.30 (m, 6H). ^{13}C

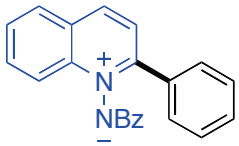
[2] Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008,** *130*, 52.

NMR ($CDCl_3$, 100 MHz) δ 170.4, 153.1, 146.0, 137.2, 136.8, 132.0, 130.0, 129.5, 129.0, 128.0, 127.9, 127.6, 127.4. FTIR (neat) 3060, 1591, 1549, 1478, 1332, 764, 712, 697 cm^{-1}. LRMS (APCI) Calcd for $C_{18}H_{15}N_2O$ $(M + H)^+$: 274.11. Found: 275.2.



23

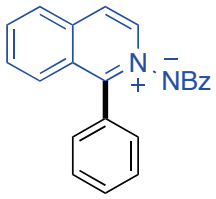
2-(1,3-Dibenzodioxol-5-yl)-*N*-benzoyliminopyridinium ylide (23).[2] Prepared according to the general procedure (page IV). The title compound was purified by reverse phase preparative High Performance Liquid Chromatography (ZORBAX Eclipse XDB-C8, 2% to 60% MeCN in H_2O over 10 min, 20 mL/min: t_r = 7.85 min) afforded **3c** as a white foam (54.7 mg, 69%). R_f = 0.40 (methanol/hexanes/dichloromethane, 15/25/60). mp: 165-167 ºC. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.63 (dd, J = 6.4, 1.1 Hz, 1H), 8.00-7.91 (m, 3H), 7.69 (dd, J = 8.0, 1.4 Hz, 1H), 7.58 (ddd, J = 7.4, 6.4, 1.7 Hz, 1H), 7.41-7.31 (m, 3H), 7.20 (d, J = 1.8 Hz, 1H), 7.15 (dd, J = 8.2, 1.8 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.98 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 153.3, 149.6, 147.7, 146.4, 137.9, 137.2, 130.1, 128.5, 128.2, 128.0, 125.9, 124.5, 124.2, 109.9, 108.4, 101.8. FTIR (neat) 3061, 2973, 2844, 1611, 1590, 1544, 1473, 1340, 1230, 1033, 714 cm^{-1}. LRMS (APCI) Calcd for $C_{19}H_{15}N_2O_3$ $(M + H)^+$: 318.10. Found: 319.2.



33

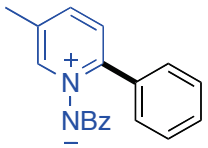
2-Phenyl-*N*-benzoyliminoquinolinium ylide (33).[2] The title compound **33** was prepared according to the general procedure described above (page IV), except that 2.5 equiv of bromobenzene was used instead of 1.0 equiv, 1.0 equiv of the ylide was used instead of 1.5 equiv and the concentration used was 1.0 M instead of 0.3 M. The title compound was purified by reverse phase preparative High Performance Liquid Chromatography (ZORBAX Eclipse XDB-C8, 40% to 20% MeCN in H_2O over 15 min, 20 mL/min: t_r = 4.05 min) afforded **33** as a yellow solid (48.9 mg, 50%). R_f = 0.48

(methanol/hexanes/dichloromethane, 5/30/65). mp: 85-89 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (d, J = 8.6 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 8.07-7.97 (m, 3H), 7.92 (ddd, J = 8.7, 7.1, 1.6 Hz, 1H), 7.85-7.73 (m, 4H), 7.47-7.32 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 155.6, 140.6, 139.1, 137.5, 134.2, 134.0, 130.6, 130.0, 129.4, 129.3, 129.1, 128.8, 128.5, 128.3, 128.0, 124.2, 121.6;.FTIR (neat) 3059, 1593, 1548, 1342, 1295, 903, 712 cm^{-1}. LRMS (APCI) Calcd for $C_{22}H_{17}N_2O$ $(M + H)^+$: 325.13. Found: 325.2.



34

1-Phenyl-*N*-benzoyliminoisoquinolinium ylide (34).[2] Prepared according to the general procedure (page IV). The title compound was purified by preparative thin liquid chromatography (5% MeOH/30% hexane/CH_2Cl_2) afforded **34** as a beige solid (46.7 mg, 78%). R_f = 0.30 (methanol/hexanes/dichloromethane, 5/30/65). mp: 232-235 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (d, J = 6.8 Hz, 1H), 8.07-8.01 (m, 2H), 7.92 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.84-7.80 (m, 3H), 7.70 (ddd, J = 8.2, 7.1, 1.3 Hz, 1H), 7.60-7.52 (m, 5H), 7.37-7.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 155.4, 138.7, 137.7, 135.4, 133.3, 130.6, 130.3, 129.8, 129.4, 129.3, 128.8, 128.5, 128.1, 127.8, 127.3, 123.6. FTIR (neat) 3061, 1591, 1548, 1514, 1493, 1448, 1330, 1295, 1146, 907, 764, 712, 714, 701 cm^{-1}. LRMS (APCI) Calcd for $C_{22}H_{17}N_2O$ $(M + H)^+$: 325.13. Found: 325.2.

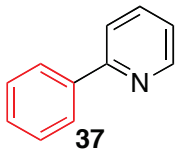


35

5-Methyl-2-phenyl-*N*-benzoyliminopyridinium ylide (35).[2] The title compound **35** was prepared according to the general procedure described above (page IV), except that 2.5 equiv of bromobenzene was used instead of 1.0 equiv, 1.0 equiv of the ylide was used instead of 1.5 equiv and the concentration used was 1.0 M instead of 0.3 M. The title

compound was purified by preparative Thin Liquid Chromatography (methanol/hexanes/dichloromethane, 15/25/60) afforded **35** as beige needle like crystals (35.6 mg, 54%). R_f = 0.31 (methanol/hexanes/dichloromethane, 10/25/65). mp: 189-192 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (s, 1H), 7.94 (dd, J = 8.5, 1.6 Hz, 2H), 7.79 (dd, J = 8.3, 1.3 Hz, 1H), 7.65-7.60 (m, 3H), 7.46-7.28 (m, 6H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 151.0, 145.9, 139.1, 137.3, 135.6, 132.4, 130.3, 130.0, 129.5, 128.3, 128.1, 127.9 (2), 18.4. FTIR (neat) 3059, 1591, 1547, 1487, 1335, 1295, 710 cm^{-1}. LRMS (APCI) Calcd for $C_{19}H_{17}N_2O$ $(M + H)^+$: 288.13. Found: 289.2.

Methods for the Reductive Cleavage of the *N*-*N* Bond[2]



37

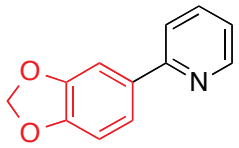
2-Phenylpyridine (37)

Method A. A Schlenk flask equipped with a stir bar was charged with compound **21** (146.0 mg, 0.532 mmol, 1.0 equiv) and purged with argon. Acetone (4.1 mL) followed by iodomethane (0.25 mL, 4.0 mmol, 7.5 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a beige powder. To this solid was added zinc dust (<10 micron, 610.0 mg, 9.3 mmol, 17.6 equiv), acetic acid (3.2 mL), and the mixture was stirred at room temperature for 16 h. The mixture was filtered through celite, concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (65.0 mg, 80% yield). R_f = 0.58 (ethyl acetate/hexane, 1/4). Spectrum matches reagent available through Sigma-Aldrich. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.71 (d, J = 7.1 Hz, 1H), 8.01 (m, 2H), 7.71-7.80 (m, 2H), 7.40-7.52 (m, 3H), 7.22-7.27 (m, 1H).

Method B. A Schlenk flask equipped with a stir bar was charged with compound **21** (168.2 mg, 0.613 mmol, 1.0 eq.) and purged with argon. Acetone (4.1 mL) followed by iodomethane (0.250 mL, 4.0 mmol, 6.5 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a beige powder.

To this powder was added Pt/C (70 mg), ammonium formate (411.0 mg, 6.5 mmol, 11.0 equiv) and the flask was purged with argon. Dry methanol was added (2.5 mL) and the suspension was heated to 75 ºC with stirring for 16 h. The mixture was filtered through celite, concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (80.0 mg, 83% yield). R_f = 0.58 (ethyl acetate/hexane, 1/4). Spectrum matches reagent available through Sigma-Aldrich. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.71 (d, J = 7.1 Hz, 1H), 8.01 (m, 2H), 7.71-7.80 (m, 2H), 7.40-7.52 (m, 3H), 7.22-7.27 (m, 1H).

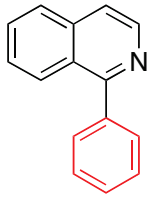
Method C. A Schlenk flask equipped with stir bar was charged with compound **21** (109.0 mg, 0.400 mmol, 1.0 equiv) and purged with argon. Acetone (2.5 mL) followed by iodomethane (0.170 mL, 2.7 mmol, 6.8 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a beige powder. The solid was placed in a round bottom flask with a stir bar, suspended in toluene (2.0 mL), and purged with argon. Tris(trimethylsilyl)silane (0.234 mL, 0.76 mmol, 2.0 equiv) and AIBN (0.125 mg, 0.76 mmol, 2 equiv) were dissolved in toluene (10 mL) and added to the above prepared suspension via a drop funnel over 30 min at 85 ºC. Following addition, the mixture was left to stir at this temperature for 16 h. The resulting solution was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (50.1 mg, 85% yield). R_f = 0.58 (ethyl acetate/hexane, 1/4). Spectrum matches reagent available through Sigma-Aldrich. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.71 (d, J = 7.1 Hz, 1H), 8.01 (m, 2H), 7.71-7.80 (m, 2H), 7.40-7.52 (m, 3H), 7.22-7.27 (m, 1H).



38

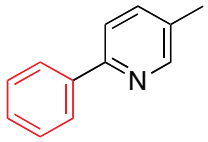
2-(Benzo[d][1,3]dioxol-5-yl)pyridine (38). Method A was used to prepare the title compound (page VII). The resulting product was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (31.2 mg, 86 % yield). R_f = 0.42 (ethyl acetate/hexane, 1/4). The observed characterization data (^{1}H) was consistent

with that previously reported in the literature.[3] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.64 (d, J = 4.8 Hz, 1H), 7.72 (t, J = 5.5 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.47-7.55 (m, 2H), 7.16-7.23 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.02 (s, 2H).



39

1-Phenylisoquinoline (39). Method A was used to prepare the title compound (page VII). The resulting product was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (5.1 mg 80% yield). R_f = 0.33 (ethyl acetate/hexane, 1/4). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[4] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.63 (d, J = 5.8 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.65-7.74 (m, 4H), 7.50-7.58 (m, 4H).



40

5-Methyl-2-phenylpyridine (40). Method A was used to prepare the title compound (page VII). The resulting product was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (15.1 mg, 84% yield). R_f = 0.76 (ethyl acetate/hexane, 1/4). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[5] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.54 (s, 1H), 7.98 (d,

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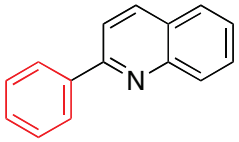
[3] Dipannita, K.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

[4] Korn, T. S.; Schade, M. A.; Cheemala, M. N.; Wirth, S.; Guevara, S. A.; Cahiez, G.; Knochel, P. *Synthesis* **2006**, *21*, 3547.

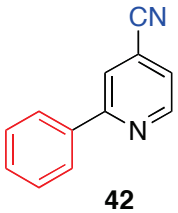
[5] Francis, R. F.; Crews, C. D.; Scott, B. S. *J. Org. Chem.* **1978**, *43*, 3227.

J = 7.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.56 (dd, J = 8.1, 2.3 Hz, 1H) 7.48 (t, J = 8.2 Hz, 2H), 7.38-7.43 (m, 1H), 2.38 (s, 3H).



41

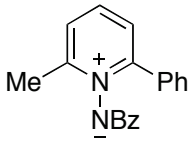
1-Phenylquinoline (41). Method A was used to prepare the title compound starting from 0.213 mmol of the ylide (page VII). The resulting product was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1/4) to give a clear liquid (6.7 mg 15% yield). R_f= 0.67 (ethyl acetate/hexane, 1/4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.24 (d, J = 8.6 Hz, 1H), 8.20-8.16 (m, 2H), 7.90-7.88 (m, 1H), 7.85-7.83 (m, 1H), 7.76-7.72 (m, 1H), 7.57-7.52 (m, 3H), 7.49-7.43 (m, 2H). Spectrum matches reagent available through Sigma-Aldrich.



42

2-Phenyl-4-Cyanopyridine (42) A Schlenk flask equipped with stir bar was charged with compound **21** (109.0 mg, 0.400 mmol, 1.0 equiv) and purged with argon. Acetone (2.5 mL) followed by iodomethane (0.170 mL, 2.7 mmol, 6.8 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a beige powder. Of this powder 73.0 mg (0.175 mmol, 1 equiv) was added to a test tube with a stir bar. Water (0.2 mL) was added followed by NH_4Cl (20.0 mg, 0.37 mmol, 2.1 equiv) and KCN (15.0 mg, 0.230 mmol, 1.5 equiv). After stirring for 4 h at rt, MeOH (2 mL), and water (2 mL) were added. The product was extracted with dichloromethane, concentrated and purified by column chromatography to give a beige oil (21.8 mg, 69% yield). R_f= 0.73 (ethyl acetate/hexane, 1/4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89-8.86 (m, 1H), 8.03-7.99 (m, 2H), 7.97-7.95 (m, 1H), 7.55-7.50 (m, 3H), 7.46 (dd, J = 6.4, 1.8 Hz, 1H); ^{13}C NMR

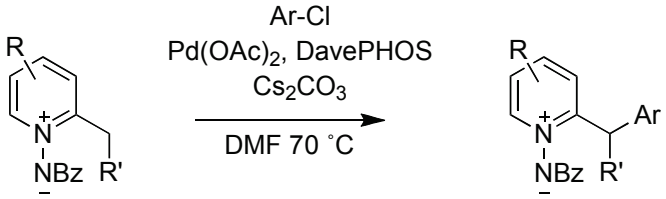
($CDCl_3$, 100 MHz) δ 158.8, 150.7, 137.3, 130.3, 129.1, 127.0, 123.2, 122.1, 121.2, 116.7. Spectrum matches literature values.[6]



44

Direct Benzylic Functionalization of* N-*Iminopyridinium Ylides

6-Methyl-2-phenyl-*N*-benzoyliminopyridinium ylide (44). The title compound **44** was prepared according to the general arylation procedure described above, except that 2.5 equiv of Ph–Br were used instead of 1.0 equiv, 1.0 equiv of **43** was used instead of 1.5 equiv and the concentration used was 1.0 M instead of 0.3 M. Reverse phase preparative High Performance Liquid Chromatography (ZORBAX Eclipse XDB-C8, 2% to 72% MeCN in H_2O over 12 min, 20 mL/min: t_r = 7.98 min) afforded **43** as a yellow solid (23.6 mg, 7%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (t, J = 7.6 Hz, 1H), 7.84 (dd, J = 8.4, 1.7 Hz, 2H), 7.66-7.55 (m, 4H), 7.42-7.26 (m, 6H), 2.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 155.7, 155.4, 137.8, 137.6, 133.7, 130.1, 129.7, 128.9, 128.3, 128.1, 127.9, 126.9, 126.4, 20.3. FTIR (neat) 3060, 1592, 1551, 1478, 1348, 718 cm^{-1}. LRMS (APCI) Calcd for $C_{19}H_{17}N_2O$ $(M + H)^+$: 289.13. Found: 289.2.

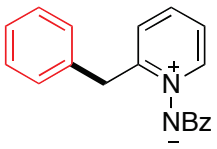


General procedure for the benzylic aryaltion of 2-substituted-*N*-benzoyliminopyridinium ylides.[7] 2-Alkyl *N*-benzoyliminopyridinium ylide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), DavePHOS (12 mol %), anhydrous powdered Cs_2CO_3 (3 equiv) were added with a stir bar in a 2 mL microwave vial inside a glovebox and sealed with teflon

[6] Guchlait, S. K; Kashyap, M.; Saraf, S. *Synthesis* **2010**, *7*, 1166.

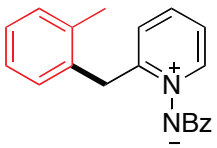
[7] Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008,** *10*, 1641.

lined cap. A 1.6 M solution of Ar–Cl (1 equiv) in dry, degassed *N,N*-dimethylformamide (DMF) was added *via* syringe and then diluted with an equal volume of DMF to bring the reaction concentration to 0.8 M. The mixture was heated to 70 °C in an oil bath. After 16-20 h of reaction the suspension was cooled to rt, filtered on a short pad of silica (washing with methanol/dichloromethane, 15/85) and the filtrate was concentrated under reduced pressure. The crude mixture was purified using flash chromatography using a gradient of 20/10/70 toluene/methanol/ethyl acetate to 10/90 methanol in ethyl acetate to give the pure product.



45

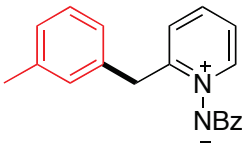
2-Benzyl-*N*-benzoyliminopyridinium ylide (45).[7] The title compound **45** was prepared according to the general procedure described above (page XI) as a yellow oil (163.4 mg, 86%). R_f = 0.31 (toluene/methanol/ethyl acetate, 1/1/8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 6.3, 1.1 Hz, 1H), 8.24-8.19 (m, 2H), 7.77 (td, J = 7.8, 1.4 Hz 1H), 7.52-7.48 (m, 1H), 7.47-7.23 (m, 9H), 4.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 156.2, 145.1, 137.2, 137.1, 135.1, 130.1, 129.8, 129.1, 128.0, 127.0, 127.5, 126.7, 123.4, 37.6. FTIR (neat) 3151, 2981, 1592, 1551, 1333, 1055, 713 cm^{-1}. HRMS Calcd for $C_{19}H_{17}N_2O$ $(M + H)^+$: 289.13354. Found: 289.13380.



46

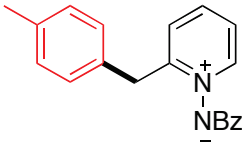
2-(2-Methylbenzyl)-*N*-benzoyliminopyridinium ylide (46).[7] The title compound **46** was prepared according to the general procedure described above (page XI) as a pale yellow solid (172.8 mg, 93%). R_f = 0.30 (toluene/methanol/ethyl acetate, 1/1/8. mp: 106-109 ºC. ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.70 (d, J = 6.1 Hz, 1H), 8.20 (m, 2H), 7.73 (t, J = 7.9 Hz 1H), 7.49 (t, J = 6.4 Hz, 1H), 7.40 (m, 3H), 7.24-7.14 (m, 4H), 7.03 (d, J = 7.9 Hz 1H), 4.42 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$,) δ 170.0, 155.8, 145.1, 137.2, 137.2, 137.1, 133.5, 130.9, 130.8, 130.1, 128.0, 128.0, 127.8, 126.8, 125.9, 123.3, 35.6, 19. 4.

FTIR (neat) 3062, 1594, 1555, 1489, 1332, 1177, 713 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.14902.



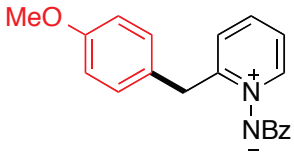
47

2-(3-Methylbenzyl)-*N*-benzoyliminopyridinium ylide (47).[7] The title compound **47** was prepared according to the general procedure described above (page XI) as a yellow oil (148.3 mg, 76%). R_f = 0.30 (toluene/methanol/ethyl acetate, 1/1/8). ^1H NMR (300 MHz, DMSO) δ 8.68 (dd, J = 6.3, 1.1 Hz, 1H), 8.24-8.19 (m, 2H), 7.77 (dt, J = 7.8, 1.4 Hz 1H), 7.52-7.48 (m, 1H), 7.47-7.23 (m, 9H), 4.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 156.2, 145.1, 137.2, 137.1, 135.1, 130.1, 129.8, 129.1, 128.0, 127.0, 127.5, 126.7, 123.4, 37.6. FTIR (neat) 3061, 1593, 1553, 1489, 1330, 1177, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.14987.



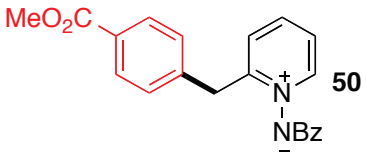
48

2-(4-Methylbenzyl)-*N*-benzoyliminopyridinium ylide (48).[7] The title compound **48** was prepared according to the general procedure described above (page XI) as a pale yellow solid (137.8 mg, 72%). R_f = 0.32 (toluene/methanol/ethyl acetate, 1/1/8). mp: 118-120 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J = 6.3, 1.1 Hz, 1H), 8.22 (m, 2H), 7.74 (td, J = 7.8, 1.2 Hz 1H), 7.49-7.40 (m, 4H), 7.24 (m, 1H), 7.15 (m, 4H), 4.40 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 156.4, 144.9, 137.0, 132.0, 130.0, 129.69, 129.66 127.9, 127.7, 126.6, 123.2, 37.2, 21.0. FTIR (neat) 3024, 2922, 1593, 1553, 1489, 1330, 1177, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.15024.



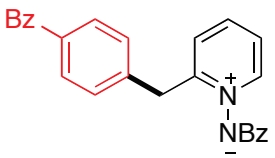
49

2-(4-Methoxybenzyl)-*N*-benzoyliminopyridinium ylide (49).[7] The title compound **49** was prepared according to the general procedure described above (page XI) as a yellow/brown oil (164.7 mg, 69%). R_f = 0.31 (toluene/methanol/ethyl acetate, 1/1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, *J*= 6.3, 0.9 Hz, 1H), 8.18 (dt, *J* = 4.8, 2.4 Hz, 2H), 7.73 (td, *J* = 7.8, 1.1 Hz, 1H), 7.48-7.37 (m, 4H), 7.24-7.13 (m, 3H), 6.87-6.84 (m, 2H), 4.34 (s, 2H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 158.9, 156.6, 144.9, 137.2, 137.1, 130.9, 130.0, 128., 127.8, 126.9, 126.6, 123.3, 114.4, 55.2, 36.7. FTIR (neat) 3061, 2934, 2835, 1593, 1552, 1551, 1489, 1331, 1247, 1177, 1032, 714 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O_2$ $(M + H)^+$: 319.14410. Found: 319.14305.



50

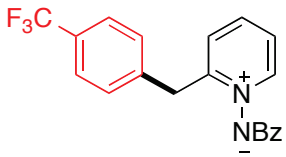
2-[(4-Methoxycarbonyl)benzyl]-*N*-benzoyliminopyridinium ylide (50).[7] The title compound **50** was prepared according to the general procedure described above (page XI), as a brown solid (136.2 mg, 73%). R_f = 0.25 (toluene/methanol/ethyl acetate, 1/1/8). mp: 64-67 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 6.3, 1.0 Hz, 1H), 8.18-8.15 (m, 2H), 8.03-7.99 (m, 2H), 7.80 (td, *J* = 7.8, 1.4 Hz, 1H), 7.56-7.51 (m, 1H), 7.45-7.39 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.28-7.25 (m, 1H), 4.49 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 166.6, 155.0, 145.3, 140.4, 137.4, 136.8, 130.22, 130.15, 129.7, 129.3, 127.9, 127.8, 126.7, 123.8, 52.1, 37.6. FTIR (neat) 3152, 2981, 1717, 1592, 1553, 1331, 1281, 1111, 1033, 713 cm^{-1}. HRMS Calcd for $C_{21}H_{20}N_2O_3$ $(M + H)^+$: 347.13929. Found: 347.13927.



51

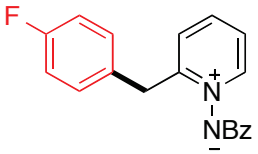
2-(4-Benzoylbenzyl)-*N*-benzoyliminopyridinium ylide (51).[7] The title compound **51** was prepared according to the general procedure described above (page XI) as a light brown oil

(170.1 mg, 71%). R_f = 0.29 (toluene/methanol/ethyl acetate, 1/1/8). ^{1}H NMR (300 MHz, DMSO) δ 8.77 (d, J = 5.8 Hz, 1H), 8.13 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 6.7 Hz), 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1 H), 7.71-7.58 (m, 5H), 7.58-7.49 (m, 2H), 7.49-7.33 (m, 5H), 4.46 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ 196.6, 169.2, 154.6, 147.0, 142.8, 139.8, 139.0, 138.3, 136.7, 133.9, 131.2, 130.9, 130.8, 130.6, 129.8, 129.2, 129.0, 128.9, 125.9, 38.14. FTIR (neat) 3060, 1655, 1594, 1555, 1490, 1446, 1319, 1278, 1177, 701 cm^{-1}. HRMS Calcd for $C_{26}H_{21}N_2O_2$ $(M + H)^+$: 393.15975. Found: 393.16014.



52

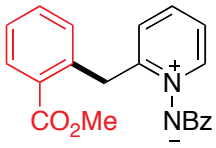
2-(4-Trifluoromethylbenzyl)-*N*-benzoyliminopyridinium ylide (52).[7] The title compound **52** was prepared according to the general procedure described above (page XI) as a yellow oil (132.8 mg, 64%). R_f = 0.31 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 6.3, 1.0 Hz ,1H), 8.17 (dd, J = 7.8, 1.7 Hz, 2H), 7.80 (td, J = 7.8, 1.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.55-7.51 (m, 1H), 7.44-7.37 (m, 5H), 7.27 (d, J = 8.1 Hz, 1H), 4.49 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 154.7, 145.4, 139.4, 137.3, 136.9, 130.1, 130.0, 129.7 (q, 32.1 Hz), 127.9, 127.8, 126.7, 125.9, 124.6 (q, J = 271.8 Hz), 123.8, 37.4. FTIR (neat) 3064, 1593, 1554, 1490, 1323, 1163, 1120, 1066, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{17}F_3N_2O$ $(M + H)^+$: 357.12092. Found: 357.12227.



53

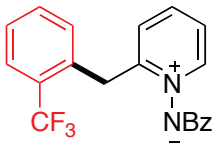
2-(4-Fluorobenzyl)-*N*-benzoyliminopyridinium ylide (53).[7] The title compound **53** was prepared according to the general procedure described above (page XI) as a pale yellow oil (172.0 mg, 94%). R_f = 0.55 (toluene/methanol/ethyl acetate, 1/1/8).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (dd, J = 6.3, 1.1 Hz, 1H), 8.20-8.17 (m, 2H), 7.80 (td, J = 7.8, 1.4 Hz, 1H),

7.53-7.48 (m, 1H), 7.45-7.38 (m, 3H), 7.27-7.20 (m, 3H), 7.06-7.00 (m, 2H), 4.40 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.1 (d, J = 246.5 Hz) 155.8, 145.1, 137.4, 136.9, 131.4, 131.3, 130.8, 130.7, 130.1, 127.9, 127.8, 126.6, 123.6, 15.9 (d, J = 21.5 Hz), 36.8. FTIR (neat) 3062, 2924, 1592, 1551, 1508, 1489, 1328, 1220, 1158, 712 cm^{-1}. HRMS Calcd for $C_{19}H_{16}FN_2O$ $(M + H)^+$: 307.12412. Found: 307.12379.



54

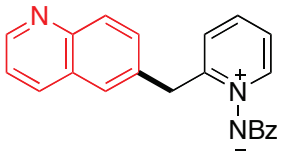
2-[(2-Methoxycarbonyl)benzyl]-*N*-benzoyliminopyridinium ylide (54).[7] The title compound **54** was prepared according to the general procedure described above (page XI), as a brown oil (83.5 mg, 43%). R_f = 0.68 (toluene/methanol/ethyl acetate, 1/1.5/7.5). ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.69 (d, J = 5.6 Hz, 1H), 8.25-8.21 (m, 2H), 8.05 (dd, J = 7.8, 1.4 Hz, 1H), 7.72 (dt, J = 7.6, 1.0 Hz, 1H), 7.56-7.36 (m, 7H), 7.09 (d, J = 8.0 Hz, 1H), 4.78 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$,) δ 169.9, 166.9, 156.4, 144.7, 137.1, 137.0, 136.7, 132.9, 132.8, 131.5, 130.0, 129.9, 128.1, 127.8, 127.7, 126.0, 123.0, 52.2, 36.8. FTIR (neat) 3063, 2950, 1716, 1593, 1552, 1490, 1330, 1268, 1080, 712 cm^{-1}. HRMS Calcd for $C_{21}H_{20}N_2O_3$ $(M + H)^+$: 347.13929. Found: 347.13917.



55

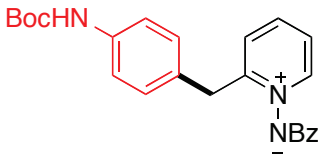
2-(2-Trifluoromethylbenzyl)-*N*-benzoyliminopyridinium ylide (55). The title compound **55** was prepared according to the general procedure described above (page XI) as a yellow oil (21.7 mg, 11%). R_f = 0.41 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.00 (dd, J = 6.4, 1.0 Hz, 1H), 8.18-8.14 (m, 2H), 7.98 (d, J = 7.8 Hz, 1H), 7.83 (td, J = 7.8, 1.4 Hz, 1H), 7.72-7.70 (m, 2H), 7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.55-7.39 (m, 5H), 7.15 (dd, J = 8.0, 1.6 Hz, 1H), 6.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6,

141.5 (q, J = 283.4 Hz), 138.5, 137.5, 133.4, 131.4, 129.7, 129.6, 128.8, 128.6, 127.1 (q, J = 5.7 Hz), 126.6, 126.5, 125.6, 122.9, 78.1, 68.2. FTIR (neat) 3070, 1592, 1547, 1489, 1310, 1155, 1124, 1037, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{15}F_3N_2O$ $(M + H)^+$: 357.11365. Found: 357.11929.



56

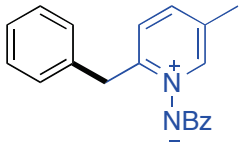
2-(6-Quinoline)benzyl)-*N*-benzoyliminopyridinium ylide (56). The title compound **56** was prepared according to the general procedure described above (page XI) as a yellow oil (40.5 mg, 19%). R_f = 0.27 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^1H NMR (400 MHz, $CDCl_3$) δ 8.93-8.90 (m, 1H), 8.71-8.69 (m, 1H), 8.21-8.18 (m, 2H), 8.11-8.07 (m, 2H), 7.83-7.79 (m, 1H), 7.73 (s, 1H), 7.61-7.53 (m, 2H), 7.47-7.39 (m, 4H), 7.32-7.30 (m, 1H), 4.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.6, 140.6, 139.1, 137.5, 134.2, 134.0, 130.6, 130.0, 129.4, 129.3, 129.1, 128.8, 128.5, 128.3, 128.0, 124.2, 121.6. FTIR (neat) 3062, 1591, 1552, 1333, 1281, 913, 712 cm^{-1}; LRMS (APCI) Calcd for $C_{22}H_{17}N_3O$ $(M + H)^+$: 340.14. Found: 340.2.



57

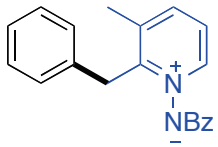
2-(4-(*tert*-Butoxycarbonylamino)benzyl)-*N*-benzoyliminopyridinium ylide (57). The title compound **57** was prepared according to the general procedure described above a (page XI) s a brown solid (90.6 mg, 48%). R_f = 0.61 (toluene/methanol/ethyl acetate, 1/1.5/7.5). mp = 171-174 ºC ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (dd, J = 6.3, 1.0 Hz, 1H), 8.24-8.20 (m, 2H), 7.73 (td, J = 7.8, 1.3 Hz, 1H), 7.49-7.33 (m, 6H), 7.20 (dd, J = 8.0, 1.2 Hz, 1H), 7.11 (t, J = 9.8 Hz, 3H), 4.36 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$)

δ 170.0, 156.4, 152.8, 144.9, 137.9, 137.3, 137.00, 130.3, 130.1, 129.1, 128.0, 127.8, 126.6, 123.3, 119.1, 80.4, 36.9, 28.2. FTIR (neat) 3236, 2977, 2929, 1716, 1593, 1530, 1342, 1240, 1158, 713 cm^{-1}. HRMS Calcd for $C_{24}H_{26}N_3O_3$ $(M + H)^+$: 404.19687. Found: 404.19727.



61

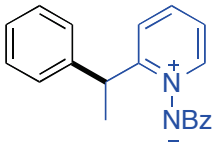
2-Benzyl-5-methyl-*N*-benzoyliminopyridinium ylide (61).[7] The title compound **61** was prepared according to the general procedure described above (page XI) as a yellow oil (76.1 mg, 43%). R_f = 0.58 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.18 (m, 2H), 7.56 (d, J = 8.2 Hz, 1H), 7.41-7.21 (m, 8H), 7.10 (d, J = 8.2 Hz, 1H), 4.36 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 153.3, 144.5, 138.4, 137.1, 135.4, 134.3, 130.0, 129.8, 129.0, 128.0, 127.8, 127.3, 126.1, 37.1, 18.2. FTIR (neat) 3058, 2910, 2846, 1591, 1536, 1509, 1344, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.14939.



62

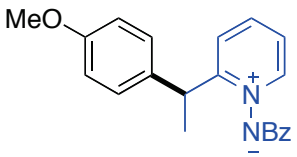
2-Benzyl-3-methyl-*N*-benzoyliminopyridinium ylide (62).[7] The title compound **62** was prepared according to the general procedure described above (page XI) as a yellow solid (149.3 mg, 92%). R_f = 0.58 (toluene/methanol/ethyl acetate, 1/1.2/7.8). mp = 123-127 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 6.2 Hz 1H), 8.17-8.14 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.45-7.34 (m, 4H), 7.29-7.19 (m, 5H), 4.55 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 153.6, 143.4, 138.9, 137.1, 137.0, 135.3, 129.8, 128.7, 128.4, 127.9, 127.6, 126.8, 122.9, 34.5, 19.3. FTIR (neat) 3026, 2966, 1592, 1551, 1476, 1326,

1170, 1027, 713, 697 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.14868.1



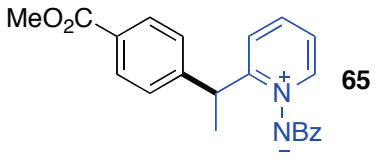
63

2-(1-Phenylethyl)-*N*-benzoyliminopyridinium ylide (63).[7] The title compound **63** was prepared according to the general procedure described above (page XI) as a yellow oil (105.5 mg, 86%). Enantiomeric excess (10 % ee) as determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 15% MeOH, 2 mL/min, 26.7 °C, 151 psi, t_r (minor) 19.3 min, t_r (major) 26.0 min);R_f = 0.60 (toluene/methanol/ethyl acetate, 1/1.5/7.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J = 6.4, 1.0 Hz, 1H), 8.22-8.19 (m, 2H), 7.81 (td, J = 7.8, 1.4 Hz, 1H), 7.50-7.41 (m, 5H), 7.35-7.24 (m, 5H), 5.25 (q, J = 7.2 Hz, 1H), 1.70 Hz (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 160.1, 145.6, 141.1, 137.3, 137.1, 123.0, 128.7, 128.0, 127.9, 127.7, 127.2, 125.5, 123.1, 39.6, 19.0. FTIR (neat) 3060, 2972, 2933, 1592, 1550, 1488, 1327, 1176, 712, 700 cm^{-1}. HRMS Calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$: 303.14918. Found: 303.14838.



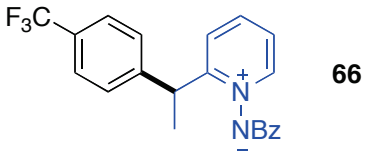
64

2-(1-(4-Methoxyphenyl)ethyl)-*N*-benzoyliminopyridinium ylide (64).[7] The title compound **64** was prepared according to the general procedure described above (page XI) as a yellow oil (110.1 mg, 79%). R_f = 0.26 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, J = 6.4, 1.1 Hz, 1H), 8.21 (m, 2H), 7.81 (td, J = 7.8, 1.4 Hz, 1H), 7.50-7.40 (m, 5H), 7.24 (m , 2H), 6.90-6.85 (m, 2H), 5.18 (q, J = 7.2 Hz, 1H), 3.79 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 161.6, 159.6, 146.5, 138.15 134.0, 130.9, 129.9, 128.9, 128.7, 126.3, 123.9, 115.0, 56.1, 39.7, 20.0. FTIR (neat) 2971, 2835, 1593, 1555, 1511, 1487, 1329, 1248, 1178, 1032, 713 cm^{-1}. HRMS Calcd for $C_{21}H_{20}N_2O_2$ $(M + H)^+$: 333.15975. Found: 333.16085.



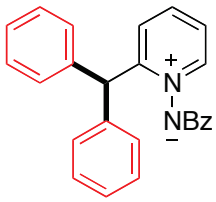
65

2-(1-(4-Methoxycarbonyl)-*N*-benzoyliminopyridinium ylide (65).[7] The title compound **65** was prepared according to the general procedure described above (page XI), as a yellow oil (82.0 mg, 53%). R_f = 0.26 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 6.2 Hz, 1H), 8.14 (dd, J = 7.7, 1.6 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H), 7.88-7.84 (m, 1H), 7.54-7.39 (m, 5H), 7.35 (d, J = 8.3 Hz, 2H), 5.22 (q, J = 7.2 Hz, 1H), 3.89 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.7, 159.1, 146.2, 145.9, 137.3, 136.9, 130.1, 130.0, 129.1, 128.0, 127.9, 127.80, 125.3, 123.52, 52.1, 39.3, 19.1. FTIR (neat) 3063, 1717, 1593, 1552, 1329, 1282, 1111, 714 cm^{-1}. HRMS Calcd for $C_{22}H_{21}N_2O_3$ $(M + H)^+$: 361.15467. Found: 361.15415.



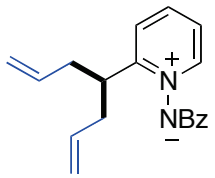
66

2-(1-(4-(Trifluoromethyl)phenyl)ethyl)-N-benzoyliminopyridinium ylide (66).[7] The title compound **66** was prepared according to the general procedure described above (page XI), as a yellow oil (82.0 mg, 53 %). Rf = 0.27 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (dd, J = 6.3, 1.0 Hz, 1H), 8.16-8.12 (m, 2H), 7.89 (td, J = 7.9, 1.4 Hz, 1H), 7.58-7.38 (m, 9H), 5.23 (q, J = 7.2 Hz, 1H), 1.72 (d, J = 7.2 Hz, 3H). ±C NMR (75 MHz, $CDCl_3$) δ 170.7, 159.7, 146.9, 146.1, 138.3, 137.8, 131.0, 130.2 (q, J = 32.4 Hz), 129.1, 128.86, 128.7, 126.5, 126.1, 124.5, 121.1 (q, J = 272.0 Hz), 40.6, 20.2. FTIR (neat) 3062, 2974, 1593, 1552, 1488, 1321, 1162, 1112, 1067, 844, 711 cm^{-1}. HRMS Calcd for $C_{21}H_{18}F_3N_2O$ (M + H)+: 371.13657. Found: 371.13741.



67

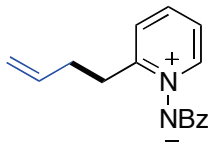
2-Benzhydryl-*N*-benzoyliminopyridinium ylide (67).[7] The title compound **67** was prepared according to the general procedure described above (page XI), except that 2.2 equiv of chlorobenzene were used. Product **3r** was isolated as a beige oil (129.2 mg, 72 %). R_f = 0.42 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.76-8.74 (m, 1H), 7.98 (dd, J = 7.9, 1.6 Hz, 2H), 7.77 (td, J = 7.8, 1.0 Hz, 1H), 7.52-7.47 (m, 1H), 7.37-7.21 (m, 10H), 7.10-7.07 (m, 4H), 6.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 157.5, 145.8, 139.1, 137.1, 136.5, 129.9, 129.2, 128.7, 127.9, 127.6, 127.6, 127.3, 123.5, 52.1. FTIR (neat) 3061, 1593, 1555, 1487, 1326, 1177, 700 cm^{-1}. HRMS Calcd for $C_{25}H_{21}N_2O$ $(M + H)^+$: 365.16484. Found: 365.16503.



68

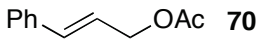
2-(hepta-1,6-dien-4-yl)-*N*-benzoyliminopyridinium ylide (67). To a mircowave vial charged with a stir bar was added 2-methyl *N*-iminopyridinium ylde **43** (46.2 mg, 0.218 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), DavePhos (9.4 mg, 12 mol %), and Cs_2CO_3 (193.0 mg, 1.00 mmol, 3.0 equiv) in a dry-box. The vial was crimped shut and THF (0.424 mL), followed by allyl bromide (0.124 mL, 0.198 mmol, 1.0 equiv). The mixture was stirred at 40 ºC for 16 h, after which it was filtered on a pad of silica gel (9/1 DCM/MeOH eluent) and concentrated. Purified by flash chromatography (9/1 DCM/MeOH) yielded the major product as a light brown oil (14.5 mg, 50%). R_f = 0.32 (methanol/DCM, 1/9) ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.72-8.70 (m, 1H), 8.23-8.20 (m, 2H), 7.87 (td, J = 7.9, 1.4 Hz, 1H), 7.53-7.40 (m, 5H), 5.73-5.63 (m, 2H), 5.05-4.99 (m, 4H), 4.12-4.06 (m, 1H), 2.57-2.47 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 157.5, 145.8, 139.1, 137.1, 136.5, 129.9, 129.2, 128.7, 127.9, 127.6, 127.6, 127.3, 123.5, 52.1. FTIR (neat) 3061, 2980, 1592,

1552, 1486, 1328, 1294, 1177, 1055, 1033 cm^{-1}. LRMS (APCI) Calcd for $C_{19}H_{21}N_2O$ $(M + H)^+$: 293.11. Found: 293.2.



69

2-(but-3-enyl)-*N*-benzoyliminopyridinium ylide (69). Same reaction as for **68** and the product is isolated as the minor product as a beige oil (4.5 mg, 11 %). R_f = 0.22 (toluene/methanol/ethyl acetate, 1/1.2/7.8). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.69-8.67 (m, 1H), 8.21-8.18 (m, 2H), 7.88 (t, J = 7.7 Hz 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.58-7.51 (m, 1H), 7.47-7.40 (m, 3H), 5.87-5.77 (m, 1H), 5.10-5.01 (m, 2H), 3.20 (t, J = 7.5 Hz, 2H), 2.58 (q, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 157.5, 145.8, 139.1, 137.1, 136.5, 129.9, 129.2, 128.7, 127.9, 127.6, 127.6, 127.3, 123.5, 52.1. FTIR (neat) 3060, 2980, 1582, 1554, 1486, 1328, 1294, 1187, 1045, 1031 cm^{-1} LRMS (APCI) Calcd for $C_{16}H_{17}N_2O$ $(M + H)^+$: 253.11. Found: 253.2.



70

Cinnamyl Acetate (70).[8] To a round-bottomed flask charged with a stir bar was was added cinnamyl alcohol (1.34 g, 10.0 mmol, 1 equiv), acetic anhydride (1.89 mL, 20 mmol, 2 equiv), DMAP (0.122 g, 10 mol %) and pyridine. The solution was left to stir at room temperature for 18 h, after which water (10 mL) then saturated aq. $NaHCO_3$ (50 mL). The mixture was extracted 3x with ethyl ether, and the organic phase was washed with $CuSO_4$ solution until no longer purple. Washed with 2x30 mL water and concentrated to afford the pure product as a clear oil (1.78 g, 99%). Spectrum matches reagent available through Sigma-Aldrich. R_f = 0.85 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.29-7.25 (m, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.30 (dt, J = 15.9, 6.5 Hz, 1H), 4.74 (dd, J = 6.5, 1.3 Hz, 2H), 2.11 (s, 3H).

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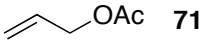
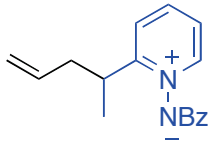
[8] Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc. Perkin 1* **1988**, 2509.



71

Allyl Acetate (71).[9] To a round-bottomed flask charged with a stir bar was was added allyl alcohol (1.40 mL, 20.0 mmol, 1 equiv) and acetyl chloride (1.8 mL, 22.0 mmol, 1.14 equiv). The solution was cooled on an ice bath, afterwhich zinc oxide (0.170g, 2.1 mmol, 8 mol %) was added portion-wise. Following the evolution of gas and additional 0.5 mL of allyl alcohol and acetyl chloride were added and the mixture was let to stir for 1 h. The reaction mixtre was then diluted in DCM, washed with saturated aq. $NaHCO_3$, dired on sodium sulfate to give the product as a clear oil (1.818 g, 65%). Spectrum matches reagent available through Sigma-Aldrich. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.85 (m, 1H), 5.33-5.27 (m, 1H), 5.22 (ddt, J = 10.4, 2.1, 1.0 Hz, 1H), 4.55 (dt, J = 5.7, 1.4 Hz, 2H), 2.07 (s, 3H).

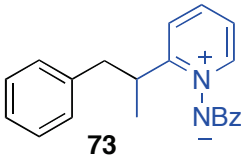


72

2-(2-(pent-4-en-2-yl)-*N*-benzoyliminopyridinium ylide (72). To a mircowave vial charged with a stir bar was added 2-ethyl *N*-iminopyridinium ylde **60** (84.0 mg, 0.373 mmol, 1.1 equiv), $Pd(OAc)_2$ (3.8 mg, 5 mol %), DavePhos (16.0 mg, 12 mol %), and Cs_2CO_3 (331.0 mg, 1.00 mmol, 3 equiv) in a dry-box. The vial was crimped shut and THF (0.424 mL), followed by allyl acetate **71** (0.037 mL, 0.339 mmol, 1.0 equiv). The mixture was stirred at 40 ºC for 16 h, after which it was filtered on a pad of silica gel (methanol/dichloromethane, 1/9 eluent) and concentrated. Purified by flash chromatography (methanol/dichloromethane, 1/9) yielded the product as a light brown oil (54.0 mg, 60%). R_f = 0.32 (methanol/dichloromethane, 1/9). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.68-8.67 (m, 1H), 8.23-8.20 (m, 2H), 7.92 (td, J = 7.8, 1.3 Hz, 1H), 7.61 (dd, J = 8.1, 1.4 Hz, 1H), 7.54-7.51 (m, 1H), 7.48-7.42 (m, 3H), 5.79-5.69 (m, 1H), 5.07 (dd, J = 4.3, 2.8, 1H), 5.03 (s, 1H), 4.03-3.98 (m, 1H), 2.63-2.56 (m, 1H), 2.42-2.34 (m, 1H), 1.35 (d, J = 7.0 Hz 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 157.5, 145.8, 139.1, 137.1, 136.5, 129.9,

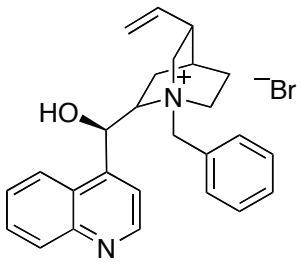
[9] Tamaddar, F.; Amrollahi, M. A.; Sharafat, L. *Tetrahedron Lett.* **2005**, *46*, 7841.

129.2, 128.7, 127.9, 127.6, 127.6, 127.3, 123.5, 52.1. FTIR (neat) 3061, 2982, 1582, 1554, 1486, 1325, 1294, 1187, 1041, 1030 cm^{-1}. LRMS (APCI) Calcd for $C_{17}H_{19}N_2O$ $(M + H)^+$: 267.14. Found: 267.2.



73

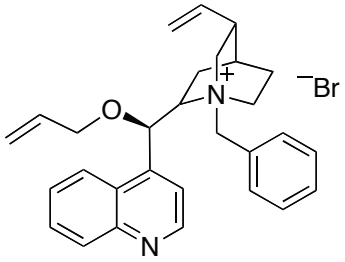
2-(1-phenylpropan-2-y)-*N*-benzoyliminopyridinium ylide (73). To a round-bottom flask equipped with a stirred bar was added 2-ethyl-*N*-benzoyliminopyridinium ylide (0.22 mmol, 1 equiv), followed successively by benzyl bromide (0.14 mL, 1.16 mmol, 5 rquiv), PTC (0.022 mmol, 10 mol %)), 2 mL of toluene, and 10% aqueous NaOH (0.19 mL, 2.33 mmol). The mixture was stirred at room temperature for 16 h. During this period, the solution turned orange brown. Purification by flash chromatography (methanol/DCM 5/95) afforded the product as a beige oil. Enantiomeric excess were determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 20% MeOH, 2 mL/min, 40 °C, 15 psi, t_r (minor) 25.3 min, t_r (major) 31.1 min). R_f = 0.59 (methanol/chloroform, 1/9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, J = 7.2, 1.2 Hz, 1H), 8.27 (m, 2H), 7.86 (td, J = 7.8, 1.2 Hz, 1H), 7.49 (m, 5H),7.19 (m, 3H), 7.10 (m, 2H), 4.21 (m, 1H), 3.22 (dd, J = 13.3, 4.7 Hz, 1H), 2.76 (dd, J = 13.3, 9.0 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.18, 160.29, 146.24, 138.49, 137.37, 137.33, 130.27, 129.47, 128.45, 128.21, 128.01, 126.58, 124.59, 123.22, 41.08, 36.03, 17.73. FTIR (neat) 3386, 3026, 2971, 1593, 1551, 1491, 1332, 1176, 713. HRMS Calcd for $C_{21}H_{20}N_2O$ $(M + H)^+$: 317.1648. Found: 317. 1655.



74

***N*-Benzylcinchonidinium bromide (74).** To a suspension of cinchonidine (2.50 g, 8.5 mmol) in toluene (40 mL) was added benzyl bromide (1.52 g, 8.9 mmol, 1.1 equiv), and the mixture was stirred at reflux for 2 h. The solution was cooled to 23 °C, poured onto 200 mL

of diethyl ether and filtered. The solid was collected to obtain the desired product as a light pink solid (3.17 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 4.8 Hz, 1H), 8.22 (dd, J = 7.8, 2.1 Hz, 1H), 7.86 (d, J = 4.5 Hz, 1H), 7.73 (m, 1H), 7.67 (d, J = 6.9 Hz, 2H), 7.20 (m, 5H), 6.66 (d, J = 6.0 Hz, 1H), 6.53 (m, 1H), 5.90 (d, J = 5.7 Hz, 1H), 5.53 (d, J = 12 Hz, 1H), 5.43 (m, 1H), 5.26 (d, J = 8.1 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.62 (m, 1H), 4.14 (t, 1H), 3.90 (d, J = 12.9, 1H), 3.12 (m, 2H), 2.48 (m, 2H), 2.08 (t, J =11 Hz, 1H), 1.88 (m, 2H), 1.59 (m, 1H), 1.06 (m, 1H) ppm. LC/MS : 385.3. Spectrum matches literature values.[10]



75

***O*-(9)-Allyl- *N*-benzylcinchonidinium bromide (75).** To a suspension of **74** (0.739 g, 1.92 mmol, 1.0 equiv) in 10 mL of CH_2Cl_2 was added allyl bromide (0.5mL, 5.77 mmol, 5.7 equiv) and 2.5 mL of 50% aqueous KOH (24.4 mmol). The resulting mixture was stirred vigorously at 23 °C for 4 h, during which time all of the solid was dissolved. The mixture was diluted with 20 mL of water and was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was collected to obtain the desired product as a light pink solid (0.792 g, 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 3.6 Hz, 1H), 8.91 (d, J = 4.5 Hz 1H), 8.16 (d, J = 6.3 Hz, 1H), 7.94 (m, 3H), 7.83 (m, 1H), 7.52 (m, 3H), 7.31 (m, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.11 (m, 2H), 5.76 (m, 1H), 5.44 (m, 2H), 5.40 (m, 1H), 5.21 (m, 1H), 5.06 (m, 1H), 4.57 (m, 1H), 4.25 (m, 2H), 4.01 (m, 1H), 3.42 (m, 2H), 3.24 (t, 1H), 2.61 (m, 1H), 2.11 (m, 4H), 1.80 (m, 1H), 1.44 (m, 1H) ppm. LC/MS: 425.3. Spectrum matches literature values.[11]

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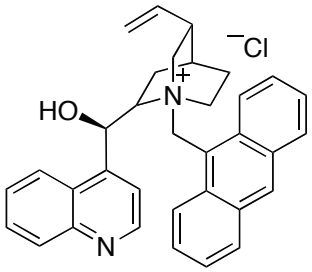
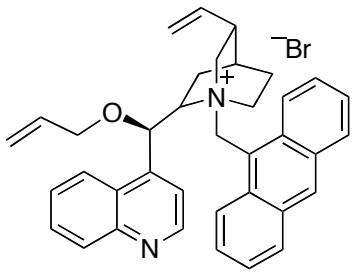
[10] Corey, E. J..; Xu, F.; Noe, C. M. *J. Am. Chem. Soc.* **1997**, 119, 12414.

[11] Fowelin, C.; Schüpbach, B.; Terfort, A. *Eur. J. Org. Chem.* **2007**, 1013.



76

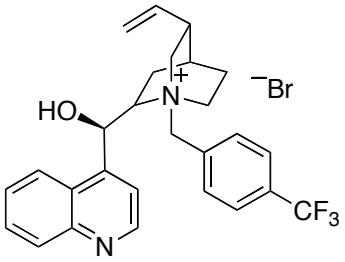
***N*-9-Anthracenylmethylcinchonidinium chloride (76)**. To a suspension of cinchonidine (2.50 g, 8.5 mmol) in toluene (40 mL) was added 9-chloromthylanthracene (2.01 g, 8.9 mmol, 1.1 equiv), and the mixture was stirred at reflux for 2 h. The solution was cooled to 23 °C, poured onto 200 mL of diethyl ether and filtered. The solid was collected to obtain the desired product as a yellow solid (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, J = 9.0 Hz, 1H), 8.83 (m, 2H), 8.74 (d, J = 9.0 Hz, 1H), 8.19 (d, J = 5.4 Hz, 1H), 8.02 (m, 1H), 7.63 (m, 3H), 7.41 (m, 1H), 7.22 (m, 6H), 7.07 (m, 2H), 6.74 (m, 2H), 5.43 (m, 1H), 5.24 (m, 1H), 4.90 (d, J = 9.6 Hz, 1H), 4.72 (m, 2H), 4.03 (d, J = 12.6 Hz, 1H), 2.58 (t, J =9.7 Hz, 1H), 2.43 (td, 1H), 2.13 (m, 1H), 1.80 (m, 2H), 1.72 (m, 2H), 1.12 (m, 2H) ppm. LC/MS: 485.2. Spectrum matches literature values.[11]



77

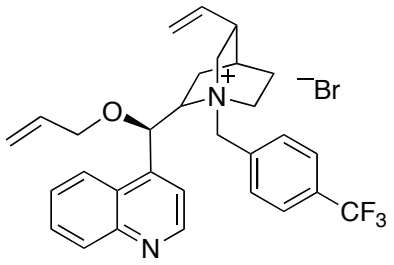
***O*-(9)-Allyl-*N*-9-Anthracenylmethylcinchonidinium bromide (77)**. To a suspension of **76** (0.931 g, 1.92 mmol, 1.0 equiv) in 10 mL of CH_2Cl_2 was added allyl bromide (0.5mL, 5.77 mmol, 5.7 equiv) and 2.5 mL of 50% aqueous KOH (24.4 mmol). The resulting mixture was stirred vigorously at 23 °C for 4 h, during which time all of the solid was dissolved. The mixture was diluted with 20 mL of water and was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was collected to obtain the desired product as a light yellow solid (0.897 g, 89% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 9.06 (d, J = 9.0 Hz,

1H), 8.71 (m, 2H), 8.61 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 4.4 Hz, 1H), 7.96 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H),7.60 (m, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.38 (m, 1H), 7.24 (m, 4H), 7.20 (m, 2H), 6.83 (d, *J* = 13.5 Hz, 1H), 6.67 (d, *J* = 13.6 Hz, 1H), 5.42 (m, 1H), 5.25 (dd, *J* = 17.3, 1.0 Hz, 1H), 4.90 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.62 (m, 2H), 3.93 (bd, *J* =12.9 Hz, 1H), 2.56 (dd, *J* = 12.8, 10.7 Hz, 1H), 2.35 (app. , *J* = 11.1 Hz, 1H), 2.12 (bs, 1H), 1.90 (m, 2H), 1.72 (bs, 1H), 1.18 (m, 1H), 1.06 (m, 1H) ppm; LC/MS: 525.2.



78

***N*-4-(trifluoromethyl)benzylcinchonidinium bromide (78).** To a suspension of cinchonidine (2.50 g, 8.5 mmol) in toluene (40 mL) was added 4-(trifluoromethyl)benzyl bromide (2.13 g, 8.9 mmol, 1.1 equiv), and the mixture was stirred at reflux for 2 h. The solution was cooled to 23 °C, poured onto 200 mL of diethyl ether and filtered. The solid was collected to obtain the desired product as a light purple solid (3.85 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, *J* = 5.4 Hz, 1H), 8.12 (m, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 4.5 Hz, 1H), 7.58 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.06 (m, 2H), 6.53 (m, 2H), 6.23 (d, *J* = 11.7 Hz, 1H), 5.63 (d, *J* = 11.7 Hz, 1H), 5.36 (m, 2H), 4.92 (dd, 1H), 4.68 (dd, 1H), 4.17 (td, 1H), 3.92 (q, 1H), 2.96 (m, 2H), 2.49 (m, 1H), 2.09 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.02 (m, 1H) ppm. LC/MS: 453.2. Spectrum matches literature values.[12]



79

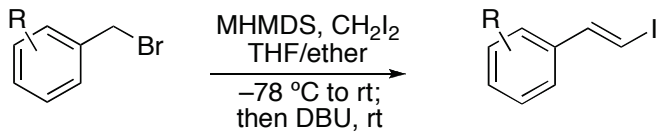
***O*-(9)-Allyl-*N*-4-(trifluoromethyl)benzylcinchonidinium bromide (79).** To a suspension of **78** (0.870 g, 1.92 mmol, 1.0 equiv) in 10 mL of CH_2Cl_2 was added allyl bromide (0.5mL, 5.77 mmol, 5.7 equiv) and 2.5 mL of 50% aqueous KOH (24.4 mmol). The resulting mixture was stirred vigorously at 23 °C for 4 h, during which time all of the solid was dissolved. The mixture was diluted with 20 mL of water and was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was collected to obtain the desired product as a light yellow solid (0.946 g, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, J = 4.5 Hz, 1H), 8.91 (d, J = 8.4 Hz 1H), 8.15 (d, J = 8.4 Hz, 3H), 7.96 (m, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 11.7 Hz, 1H), 6.11 (m, 2H), 5.72 (m, 1H), 5.42 (m, 1H), 5.17 (m, 2H), 5.07 (m, 1H), 5.04 (m, 1H), 4.81 (m, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.39 (m, 1H), 4.30 (m, 1H), 4.02 (m, 1H), 3.33 (td, J = 11.9, 3.0 Hz, 1H), 3.14 (t, J = 11.4 Hz, 1H), 2.63 (m, 1H), 2.14 (m, 3H), 1.82 (m, 1H), 1.44 (m, 1H) ppm. LC/MS: 493.2. Spectrum matches literature values.[13]

[12] Corey, E. J..; Xu, F.; Noe, C. M. *J. Am. Chem. Soc.* **1997**, 119, 12414.

[13] Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, 58, 1623.

Experimental Section of Chapter 3

Synthesis of (*E*)-β-Aryl Vinyl Iodides from Benzyl Bromides and CH_2I_2



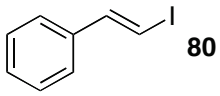
Method A:

A solution of CH_2I_2 (483 mL, 6.0 mmol) in THF (1.5 mL) was added dropwise to a solution of NaHMDS (2.20 g, 12.0 mmol) in THF (8 mL) and ether (8 mL) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (4.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 90 min then removed from the cold bath to warm to rt. After 30 min, DBU (597 mL, 4.0 mmol) was added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of celite/silica (approximately 3 cm celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the pure vinyl iodide.

Method B:

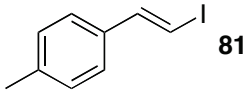
A solution of CH_2I_2 (644 mL, 8.0 mmol) in THF (1.9 mL) was added dropwise to a solution of LiHMDS (1.34 g, 8.0 mmol) in THF (8 mL) and ether (8 mL) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (4.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at –78 ºC allowing to warm to rt slowly over 16 h. After this time DBU (1.19 mL, 8.0 mmol) was

added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of celite/silica (approximately 3 cm celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl iodide. Where necessary, residual CH_2I_2 following flash chromatography was removed under high vacuum.



80

(*E*)-(2-Iodovinyl)benzene (80). Prepared according to the general procedure (Method A, page XXX) starting from benzyl bromide (684 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **80** as a yellow oil (849 mg, 92%, 98:2 E:Z). The observed characterization data (1H, 13C) was consistent with that previously reported in the literature.[14] R_f = 0.65 (hexanes, 100%). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.44 (d, J = 14.9 Hz, 1H), 7.38-7.27 (m, 5H), 6.84 (dd, J = 14.9, 1.8 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) δ 145.0, 137.6, 128.7, 128.4, 126.0, 76.7. FTIR (neat) 3059, 3021, 1595, 1494, 1444, 1210, 1169, 1070, 945, 726, 688 cm^{-1}.



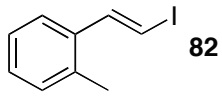
81

(*E*)-1-(2-Iodovinyl)-4-methylbenzene (81). Prepared according to the general procedure (Method A, page XXX) starting from 4-methylbenzyl bromide (740 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **81** as an off-white solid (906 mg, 93%, 99:1 *E*:*Z*). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[15] R_f = 0.54 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 14.9 Hz, 1H), 7.21-7.13 (m, 4H), 6.75 (d, *J* = 14.9

[14] Lee, G. C. M.; Tobias, B.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 9330.

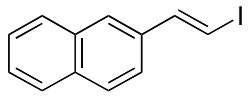
[15] Shastin, A. V.; Korotchenko, V. N.; Varseev, G. N.; Nenaidenko, V. G.; Balenkova, E. S. *Russ. J. Org. Chem.* **2003**, *39*, 403.

Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.2, 134.9, 129.3, 125.8, 75.4, 21.3. FTIR (neat) 3053, 3029, 2915, 2859, 1608, 1591, 1561, 1509, 1379, 1280, 1189, 1172, 958, 939, 827, 765 cm^{-1}.



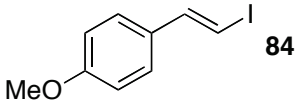
82

(*E*)-1-(2-Iodovinyl)-2-methylbenzene (82) Prepared according to the general procedure (Method A, page XXX) starting from 2-methylbenzyl bromide (740 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **82** as an off-white solid (879 mg, 90%, 99:1 *E*:*Z*). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[14] R_f = 0.63 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 14.7 Hz, 1H), 7.32-7.11 (m, 4H), 6.68 (d, J = 14.7 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.9, 134.7, 130.3, 128.2, 126.2, 125.6, 77.7, 19.7. FTIR (neat) 3055, 3017, 2921, 1587, 1562, 1479, 1457, 1379, 1280, 1190, 1176, 947, 740 cm^{-1}.



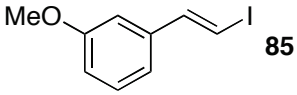
83

(*E*)-2-(2-Iodovinyl)naphthalene (83). Prepared according to the general procedure (Method A, page XXX) starting from 2- (bromomethyl)napthylene (884 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **83** as a yellow solid (782 mg, 70%, 98:2 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[14] R_f = 0.53 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.75 (m, 3H), 7.65 (s, 1H), 7.56 (d, J = 14.9 Hz, 1H), 7.46 (m, 3H), 6.94 (d, J = 14.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 135.0, 133.3, 133.1, 128.4, 128.2, 127.7, 126.6, 126.4, 126.2, 122.7, 77.0. FTIR (neat) 3049, 1599, 1585, 1507, 1433, 1293, 1274, 1216, 1181, 1152, 952, 828, 781, 765, 735 cm^{-1}.



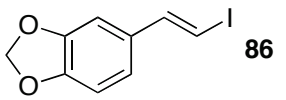
84

(*E*)-1-(2-Iodovinyl)-4-methoxybenzene (84) Prepared according to a modification of the general procedure (Method A, page XXX) on a 1 mmol scale starting from 4-methoxybenzyl bromide (220 mg, 1.1 mmol) and employing excess DBU (240 μL, 1.5 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded vinyl iodide **84** as a white solid (265 mg, 92%, 97:3 *E*:*Z*). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[14] R_f = 0.71 (ether/hexanes, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 14.9 Hz, 1H), 7.26-7.23 (m, 2H), 6.88-6.85 (m, 2H), 6.64 (d, J = 14.9 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 144.3, 130.7, 127.2, 114.0, 73.6, 55.3. IR (neat) 3055, 3005, 2965, 2933, 2838, 1602, 1509, 1460, 1250, 1177, 1028, 948, 840, 770 cm^{-1}.



85

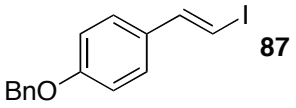
(*E*)-1-(2-Iodovinyl)-3-methoxybenzene (85). Prepared according to a modification of the general procedure (Method A, page XXX) starting from 3-methoxybenzyl bromide (834 mg, 4.1 mmol) and employing excess DBU (900 μL, 6.0 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded vinyl iodide **85** as a yellow oil (1.038 g, 95%, 99:1 *E*:*Z*). R_f = 0.70 (ether/hexanes, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 14.9 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 6.93-6.85 (m, 4H), 3.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 144.7, 138.8, 129.6, 118.5, 113.9, 111.2, 77. 1, 55.2. FTIR (neat) 3057, 2999, 2936, 2832, 1596, 1572, 1490, 1463, 1428, 1313, 1284, 1261, 1152, 1048, 944, 757, 684 cm^{-1}. HRMS Calcd for C_9H_9IO $[M + H]^+$: 259.9693 Found: 259.9691.[16]



86

[16] Compound previously reported: Furstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286.

(*E*)-5-(2-Iodovinyl)benzo[d][1,3]dioxole (86). Prepared according to a modification of the general procedure (Method A, page XXX) starting from 3,4-(methylenedioxy)benzyl bromide[17] (860 mg, 4.0 mmol) and employing excess DBU (896 μL, 6.0 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded vinyl iodide **86** as a white solid (1.02 g, 93%, 99:1 *E*:*Z*). R_f = 0.42 (ether/hexanes, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 14.9 Hz, 1H), 6.81 (m, 1H), 6.74 (m, 2H), 6.62 (dd, J = 14.8, 0.1 Hz, 1H), 5.96 (d, J = 0.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.8, 144.3, 132.2, 120.9, 108.3, 105.2, 101.3, 74.1. FTIR (neat) 3058, 2890, 2777, 1499, 1487, 1444, 1350, 1247, 1171, 1037, 943, 928, 762 cm^{-1}. HRMS Calcd for $C_9H_7IO_2$ $[M + H]^+$: 273.9485 Found: 273.9491.[18]



87

(*E*)-1-(2-Iodovinyl)-4-benzyloxybenzene (87) Prepared according to a modification of the general procedure (Method B, page XXX) starting from 1-(benzyloxy)-4-(bromomethyl)benzene[19] (1.11g mg, 4.0 mmol) and employing excess DBU (1.8 mL, 12.0 mmol). Purification by flash chromatography (ether/hexanes, 1/99) afforded vinyl iodide **87** as an off-white solid (1.02 g, 76%, 99:1 *E*:*Z*). R_f = 0.18 (ether/hexanes, 1/99). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 6H), 7.24-7.19 (m, 2H), 6.94-6.90 (m, 2H), 6.62 (d, J = 14.9 Hz, 1H), 5.05 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 144.2, 136.6, 130.9, 128.6, 128.0, 127.44, 127.26, 115.0, 73.8, 70.0. FTIR (neat) 3054, 2932, 2868, 1600, 1508, 1467, 1454, 1377, 1281, 1250, 1181, 999, 947, 836, 768, 747, 735, 701 cm^{-1}. HRMS Calcd for $C_{15}H_{13}IOAg$ $[M + Ag]^+$: 442.9057 Found: 442.9063.

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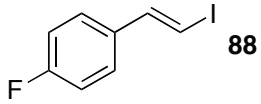
[17] Prepared according to previously reported procedure: Imperio, D.; Pirali, T.; Galli, U.; Pagliai, F.; Cafici, L.; Luigi Canonico, P.; Sorba, G.; Genazzani, A. A.; Cesare Tron, G. *Bioorg. Med. Chem.* **2007**, *15*, 6748.

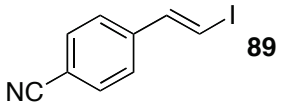
[18] Compound previously reported: Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369.

[19] Prepared from 4-benzyloxybenzyl alcohol by a previously reported procedure: Albert, S.; Soret, A.; Blanco, L.; Deloisy, S. *Tetrahedron* **2007**, *63*, 2888.



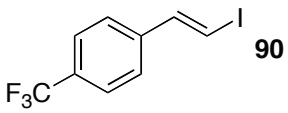
88

(*E*)-1-Fluoro-4-(2-iodovinyl)benzene (88). Prepared according to the general procedure (Method A, page XXX) starting from 4-fluorobenzyl bromide (756 mg, 4.0 mmol). Purification by flash chromatography (100% hexane) afforded vinyl iodide **88** as a yellow solid (843 mg, 85%, 98:2 *E*:*Z*).R_f = 0.66 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 14.9 Hz, 1H), 7.27-7.22 (m, 2H), 7.02-6.95 (m, 2H), 6.73 (dd, J = 14.9, 0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J = 249 Hz), 143.7, 133.9 (d, J = 3 Hz), 127.6 (d, J = 8 Hz), 115.7 (d, J = 22 Hz), 76.1 (d, 2.5 Hz). FTIR (neat) 3056, 1598, 1578, 1505, 1230, 1172, 1157, 949, 837, 769 cm^{-1}. HRMS Calcd for C_8H_6FI $[M]^+$: 247.9493 Found: 247.9493.



89

(*E*)-4-(2-Iodovinyl)benzonitrile (89) Prepared according to the general procedure (Method B, page XXX) starting from 4-(bromomethyl)benzonitrile 756 mg, 4.0 mmol). Purification by flash chromatography (ether/hexanes 1/9) afforded vinyl iodide **89** as a pale yellow solid (843 mg, 51%, 99:1 *E*:*Z*). R_f = 0.34 (ether/hexanes 1/9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2H), 7.40 (d, J = 15.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.06 (d, J = 15.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 141.4, 132.5, 126.3, 118.5, 111.5, 81.7. FTIR (neat) 3242, 3048, 2221, 1601, 1407, 1173, 937, 840, 771 cm^{-1}. HRMS Calcd for C_9H_6INAg $[M + Ag]^+$: 361.8590 Found: 361.8596.[20]

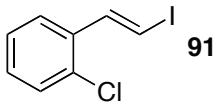


90

(*E*)-1-(2-Iodovinyl)-4-(trifluoromethyl)benzene (90) Prepared according to the general procedure (Method B, page XXX) starting from 4-(trifluoromethyl)benzyl bromide (956

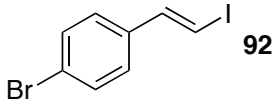
[20] Compound previously reported: Furstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009.

mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **90** as a yellow solid (750 mg, 63%, 99:1 *E*:*Z*). R_f = 0.39 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 15.0 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 15.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.7 (q, J = 1 Hz), 130.1 (q, J = 33 Hz), 126.1, 125.7 (q, J = 4 Hz), 124.0 (q, J = 274 Hz), 118.6. IR (neat) 3055, 1614, 1409, 1322, 1160, 1106, 1066, 940, 844, 776 cm^{-1}.[21]



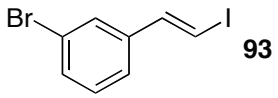
91

(*E*)-1-Chloro-2-(2-iodovinyl)benzene (91). Prepared according to the general procedure (Method A, page XXX) starting from 2-chlorobenzyl bromide (823 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **91** as a yellow oil (816 mg, 78%, 98:2 *E*:*Z*). R_f = 0.75 (hexanes, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 14.9 Hz, 1H), 7.42-7.33 (m, 2H), 7.26-7.21 (m, 2H), 6.90 (d, J = 14.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 135.6, 132.0, 129.9, 129.2, 126.9, 126.7, 79.6. FTIR (neat) 3057, 1590, 1466, 1438, 1274, 1180, 1121, 1051, 946, 747 cm^{-1}. HRMS Calcd for $C_8H_6ClI_2$ $[M]^+$: 263.9197 Found: 263.9200.



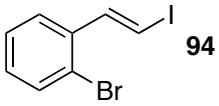
92

(*E*)-1-Bromo-4-(2-iodovinyl)benzene (92) Prepared according to the general procedure, (Method B, page XXX) starting from 4-bromobenzyl bromide (1.0 g, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **92** as an off-white solid (1.07 g, 87%, 99:1 *E*:*Z*). R_f = 0.74 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.34 (d, J = 14.9 Hz, 1H), 7.15-7.12 (m, 2H), 6.84 (d, J = 14.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 136.5, 131.8, 127.4, 122.3, 77.6. FTIR (neat) 3044, 1582, 1483, 1394, 1169, 1072, 1007, 959, 941, 832, 766, 708 cm^{-1}. HRMS Calcd for C_8H_6BrI $[M]^+$: 307.8692 Found: 307.8700.



93

(*E*)-1-Bromo-3-(2-iodovinyl)benzene (93) Prepared according to the general procedure, (Method B, page XXX) starting from 3-bromobenzyl bromide (1.0 g, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **93** as a yellow oil (1.08 g, 87%, 98:2 *E*:*Z*). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[22] R_f = 0.56 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.33 (d, J = 14.9 Hz, 1H), 7.20-7.14 (m, 2H), 6.87 (d, J = 14.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 139.4, 131.1, 130.1, 128.8, 124.5, 122.8, 78.7. FTIR (neat) 3056, 1590, 1557, 1474, 1209, 1071, 942, 755 cm^{-1}.



94

(*E*)-1-Bromo-2-(2-iodovinyl)benzene (94) Prepared according to the general procedure, (Method B, page XXX) starting from 2-bromobenzyl bromide (1.0 g, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **94** as a yellow oil (1.09 g, 87%, 98:2 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[15] R_f = 0.48 (hexanes, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 14.8 Hz, 1H), 7.55 (dd, J = 7.9, 1.3 Hz, 1H), 7.40 (dd, J = 7.9, 1.7 Hz, 1H), 7.30-7.26 (m, 1H), 7.16 (td, J = 7.7, 1.7 Hz, 1H), 6.86 (d, J = 14.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.5, 132.9, 129.5, 127.6, 127.0, 122.3, 79.9. FTIR (neat) 3056, 1587, 1461, 1434, 1180, 1027, 945, 938, 743 cm^{-1}.

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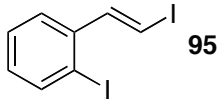
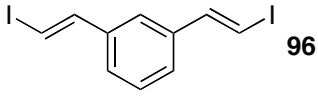
[21] Compound previously reported: Shimizu, M.; Shimono, K.; Schelper, M.; Hiyama, T. *Synlett* **2007**, 1969.

[22] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.



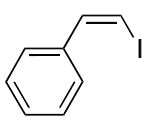
95

(*E*)-1-Iodo-2-(2-iodovinyl)benzene (95) Prepared according to the general procedure (Method B, page XXX) on a 1 mmol scale, starting from 2-iodobenzyl bromide (297 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **95** as a yellow oil (260 g, 73%, 99:1 *E*:*Z*).R_f = 0.57 (hexanes, 100%). ^{1}H NMR (300 MHz $CDCl_3$) δ 7.82 (dd, J = 7.9, 1.2 Hz, 1H), 7.60 (d, J = 14.7 Hz, 1H), 7.37-7.28 (m, 2H), 7.01-6.95 (m, 1H), 6.78 (d, J = 14.7 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 148.4, 141.1, 139.5, 129.7, 128.5, 126.7, 98.0, 80.0. FTIR (neat) 3053, 1584, 1456, 1429, 1323, 1177, 1015, 1007, 935, 742 cm^{-1}. HRMS Calcd for $C_8H_7I_2$ $[M]^+$: 356.8632 Found: 356.8647.



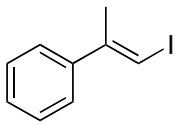
96

1,3-bis((*E*)-2-Iodovinyl)benzene (96) A solution of CH_2I_2 (483 μL, 6.0 mmol) in THF (1.5 mL) was added dropwise to a solution of NaHMDS (2.20 g, 12.0 mmol) in THF (8 mL) and ether (8 mL) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of α,α'-dibromo-m-xylene (528 mg, 2.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 90 min then removed from the cold bath to warm to rt. After 30 min, DBU (597 μL, 4.0 mmol) was added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of celite/silica (approximately 3 cm celite over 3 cm silica) and the solvent removed under reduced pressure. Purification by flash chromatography (hexanes, 100%) afforded vinyl iodide **96** as a pale yellow solid (560 mg, 73%, 97:3 *EE*:*EZ*). R_f = 0.44 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 14.9 Hz, 2H), 7.26-7.17 (m, 4H), 6.84 (d, J = 14.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 138.1, 129.1, 125.8, 123.6, 77.6. FTIR (neat) 3046, 1598, 1584, 1569, 1481, 1172, 945, 752 cm^{-1}. HRMS Calcd for $C_{10}H_8I_2$ $[M]^+$: 381.8710 Found: 381.8707.



109

(*Z*)-1-Iodo-2-phenylethene (109) Prepared according to literature procedure.[23] Iodomethylenetriphenylphosphorane (0.550 g, 1.0 mmol, 1.2 equiv) was added to a flame-dried flask with stir bar. The flask was sealed with a septum, purged with argon, and suspended in THF (2.3 mL). NaHMDS (1 mL of a 1 M solution) was added slowly and the resulting solution was cooled to -60 ºC. HMPA (0.3 mL) was added and the solution was cooled further to -78 ºC. Benzaldehyde (0.082 mL, 0.8 mmol, 1 equiv) was added and the mixture was stirred at -78 ºC for 1 min, and then allowed to warm to rt over 35 min. Ethyl ether (20 mL) was added, and the mixture was filtered over a pad of Celite. Purification by column chromatography yielded **109** as a yellow liquid (0.132 g, 72%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[24] R_f = 0.72 (100% hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.60 (m, 2H), 7.39-7.34 (m, 3H), 7.30 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H).



112

(*E*)-(1-Iodoprop-1-en-2-yl)benzene (112)[25] $AlMe_3$ (1.44 g, 20 mmol, 2 equiv) was added dropwise to a solution of Cp_2ZrCl_2 (2.92 g, 10 mmol, 1 equiv) in DCE (25 mL) to give a yellow solution. Phenylacetylene (1.02 g, 10 mmol, 1 equiv) was then added and the reaction mixture was left to stir for 16 h. The reaction mixture was then cooled to 0 ºC and I_2 (3.04 g, 12 mmol, 1.2 equiv) in THF (15 mL) was added via syringe over 3 min. After 2 h the resulting dark solution faded and the reaction mixture was quenched with H_2O/ether (1:1, 50 mL). The organic layer was separated, washed with $Na_2S_2O_3$, dried with $MgSO_4$, concentrated and purified by flash chromatography (hexanes, 100%) to afford **112** as a single isomer (1.86 g, 76%). R_f = 0.70 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.42-6.57 (q, J = 1.5 Hz, 1 H), 2.29 (d, J = 1.5 Hz, 3H).

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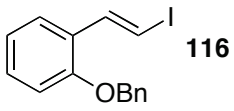
[23] Stork, G.; Kang, Z. *Tetrahedron Lett.* **1989**, 2173.

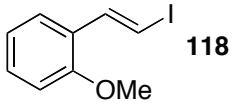
[24] Carpita, A.; Ribecai, A.; Rossi, R.; Stabile, P. *Tetrahedron* **2002**, *58*, 3673.

[25] Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.



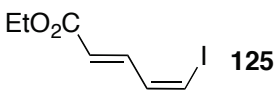
116

(*E*)-1-(2-Iodovinyl)-2-benzyloxybenzene (116) Prepared according to a modification of the general procedure (Method B, page XXX) on a 1.3 mmol scale starting from 2-benzyloxybenzyl bromide (360 mg, 1.3 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded the vinyl iodide **116** as a white solid (315 mg, 72%, 98:2 *E*:*Z*). R_f = 0.68 (ether/hexanes, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 14.9 Hz, 1H), 7.48 (m, 4H), 7.42 (m, 1H), 7.36 (dd, J = 9.3, 1.7 Hz, 1H), 7.29 (td, J = 8.2, 1.7 Hz, 1H), 7.01-6.96 (m, 3H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 140.4, 132.9, 129.3, 128.6, 128.0, 127.6, 127.2, 126.8, 121.0, 112.5, 78.3, 70.3. FTIR (neat) 3031, 2923, 2859, 1596, 1483, 1449, 1241, 1102, 1033, 1012, 949, 735 cm^{-1}. HRMS Calcd for $C_{15}H_{13}IO$ $(M + Na)^+$: 358.98931. Found: 358.99033.



118

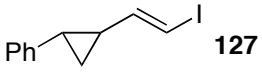
(*E*)-1-(2-Iodovinyl)-2-methoxybenzene (118). Prepared according to the general procedure (Method B, page XXX) starting from 2-methoxybenzyl bromide (804 mg, 4.0 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded vinyl iodide **118** as a yellow oil (784 mg, 75%, 98:2 *E*:*Z*). R_f = 0.68 (ether/hexanes, 5/95). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 14.9 Hz, 1H), 7.29 (t, J = 7.7 Hz, 2H), 6.97-6.88 (m, 3H), 3.88 (s, 3H).



125

[26] Graven, A.; Jorgensen, K. A.; Dahl, S.; Stanczak, A. *J. Org. Chem.* **1994**, *59*, 3543.

Ethyl-(2*E*, 4*Z*)-5-iodopenta-2,4-dienoate (125) To a solution of ethyl (*Z*)-β-iodoacrylate[27] (5.0 mL, 39 mmol, 1 equiv) in DCM (90 mL) at -78 ºC was added DIBAL (43 mmol, 1.1 equiv) over 10 min. After stirring for 5 min the reaction was quenched with MeOH (7.0 mL), followed by sodium potassium tartrate (200 mL). Following warming to room temperature Et_2O (100 mL) was added, stirred for 1 h, then further diluted with ether and water (50 mL). The organic layer was separated and he aqueous phase was extracted with Et_2O (4x 80 mL). The combined organic extracts with washed with brine, dried with K_2CO_3 and concentrated to give the crude aldehyde. Separately trimethyl phosphonoacetate (8.20 mL, 41 mmol, 1.1 equiv) in THF (80 mL) was cooled to -78 ºC. To this solution was added *n*-BuLi (1.7M in hexanes, 41 mmol, 1.1 equiv) and the solution was stirred for 30 min. The previously prepared aldehyde in THF (40 mL) was then canulated in. The reaction mixture was allowed to warm to rt over 2 h, and then stirred at rt for 1 h after which ether/water (50/50, 100 mL) was added. The organic layer was separated and the aqueous phase was extracted 4x with Et_2O. The combined organic extracts were washed with brine, dried with Mg_2SO_4, concentrated, and purified via column chromatography (ethyl acetate/petroleum ether, 5/95) to give **125** as a yellow liquid. The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[28] R_f = 0.41 (ethyl acetate/petroleum ether, 1/9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (ddd, J = 15.2, 10.3, 0.9 Hz, 1H), 6.90 (ddd, J = 11.2, 7.7, 0.8 Hz, 1H), 6.82 (ddd, J = 7.9, 0.8, 0.8 Hz, 1H), 6.10 (ddd, J = 15.2, 0.7, 0.7 Hz, 1H), 4.23 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).



127

(*E*)-(2-(2-Iodovinyl)cyclopropyl)benzene (127) A stirred solution of DME (7.7 mL, 74.5 mmol, 2 equiv) in CH_2Cl_2 (170 mL) was cooled to –15 ºC. $ZnEt_2$ (7.6 mL, 74.5 mmol, 2 equiv) was added dropwise while maintaining the temperature of the solution below –14 ºC. Diiodomethane (12.0 mL, 149.0 mmol, 4 equiv) was added dropwise, maintaining the reaction temperature below –6 ºC. After stirring for 10 min a solution of cinnamyl alcohol

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[27] Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1997**, *74*, 194.

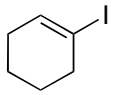
[28] Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666.

(5.0 g, 37.3 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added dropwise, keeping the reaction temperature below –5 ºC. The reaction was left to stir and warm to room temperature over 16 h after which saturated NH_4Cl solution (50 mL) was added followed by aqueous HCl (10%, 100 mL). The mixture was diluted with Et_2O (300 mL), then the organic layer was separated, washed with Na_2SO_3, $NaHCO_3$, and saturated NaCl solutions, dried over $MgSO_4$ and concentrated. The crude cyclopropane was purified with column chromatography (30% EtOAc/Hexane). To remove unreacted cinnamyl alcohol, the flashed product was dissolved in actone/water (1:1, 184 mL), then NMO (6.5 g, 55 mmol, 1.5 equiv) and OsO_4 (0.061M in *t*BuOH, 15 mL, 2.5 mol %) were added. The reaction was stirred in the dark for 16h then diluted with Et_2O and washed with Na_2SO_3 (100 mL). The organic layer was removed and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with $NaHCO_3$ (100 mL) and brine, dried over $MgSO_4$ and purified by column chromatography (ethyl acetate/hexanes, 3/7) to give *trans*-2-phenylcyclopropylmethanol (3.85 g, 26 mmol, 70%).

PCC (1.02 g, 4.8 mmol, 1.1 equiv) was added to a solution of *trans*-2-phenylcyclopropylmethanol (0.630 g, 4.2 mmol, 1 equiv) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 14 h, then filtered through a pad of silica and celite (ethyl acetate/hexanes, 3/7) to afford the cyclopropyl aldehyde (0.513 g, 3.6 mmol, 88%).

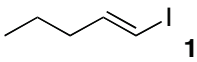
$CrCl_2$ (3.10 g, 25.2 mmol, 7 equiv) was dissolved in THF (20 mL) and the mixture cooled to 0 ºC. The previously prepared cyclopropyl aldehyde (0.513 g, 3.6 mmol, 1 equiv) was diluted in THF (15 mL) and iodoform (2.83 g, 7.2 mmol, 2 equiv) was dissolved in this solution. The resulting solution was added to the $CrCl_2$ solution at 0 ºC via syringe and the mixture was left to stir for 3 h. Water (100 ml) was added and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried with Na_2SO_4, concentrated, and purified by column chromatography (hexanes, 100%) to afford the title compound **127** as a colourless oil (0.608 g, 61%, 7.5:1 *E*:*Z*). R_f = 0.55 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 6.20 (dd, J = 14.4, 8.8 Hz, 1H), 6.04 (d, J = 14.4 Hz, 1H), 2.03 (m, 1H), 1.74 (m, 1H), 1.29 (m, 1H), 1.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 141.3, 128.4, 125.9, 125.7, 71.8, 29.5, 24.7, 16.1.

FTIR (neat) 3025, 1604, 1495, 1458, 1277, 1199, 1180, 1127, 1073, 942 cm^{-1}. GCMS Calcd for $C_{11}H_{11}I$: 269.99. Found: 270.



129

1-Iodocyclohexene (129) Cyclohexanone (5.2 mL, 50 mmol, 1 equiv) was added dropwise over 5-10 min to hydrazine monohydrate (15 mL, 310 mmol, 6 equiv) while stirring vigorously. A white precipitate formed and the reaction mixture was refluxed at 150 ºC for 2 h. The mixture was cooled to room temperature, then CH_2Cl_2 (100 mL) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried with Na_2SO_4 and concentrated to give the crude hydrazone. Tetramethylguanidine (37 mL, 300 mmol, 6 equiv) in THF (55 mL) was added to iodine (14 g, 300 mmol, 6 equiv) in THF (80 mL). The resulting solution was cannulated onto the crude hydrazone (2.8 g) in THF (25 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature overnight and then refluxed for 2 h at 85 ºC and then cooled to room temperature. The organic layer was washed with aqueous HCl (1M, 100 mL) and saturated NaCl solution. The aqueous layer was extracted with Et_2O (2 x 100 mL), dried with $MgSO_4$, concentrated, and purified via column chromatography (hexanes, 100%) to give **129** as a colorless oil (0.970 g, 20% over two steps). The observed characterization data (^1H) was consistent with that previously reported in the literature.[29] R_f = 0.8 (hexanes, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (m, 1H), 2.51 (m, 2H), 2.10 (m, 2H), 1.60-1.70 (m, 4H).

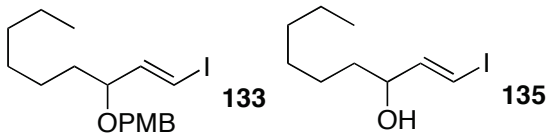


131

1-Iodopentene (131). To a flame-dried round-bottomed-flask was added pentyl (4.2 mL, 42.6 mmol, 1.0 equiv), and hexanes (50 mL). The solution was cooled to –78 ºC afterwhich DIBAL (9.5 mL, 53.3 mmol, 1.3 equiv) was added over 30 min. The reaction temperature

[29] Jarho, E. M.; Venalainen, J. I.; Poutiainen, S.; Leskinen, H.; Vepsalainen, J.; Christiaans, J. A. M.; Forsberg, M. M.; Mannisto, P. T.; Wallen, E. A. A. *Bioorg. Med. Chem.* **2007**, *15*, 2024.

was warmed to rt overnight and then cooled to –78 ºC. Iodine (13.8 g, 54.3 mmol, 1.3 equiv) was dissolved in THF (50 mL) and added *via* syringe. The solution was left to stir at –78 ºC for 30 min and then left to stir at rt for 1 h. The solution was poured onto 100 mL of iced 1M HCl and an additional 100 mL 1M HCl was added. The organic layer was separated and the aqueous phase was extracted with 3 x 100 mL pf pentane. The organic layers were combined, washed with 2x100 mL sat. $NaHCO_3$ solution, 2x100 mL sat. $Na_2S_2O_3$ solution, and 2x100 mL sat. NaCl solution, then dried with $MgSO_4$. Filtration on silca and concentration *in vacuo* afforded **131** as a clear liquid (1.9235 g, 25%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[30] R_f = 0.81 (hexanes, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, J = 14.5, 1.5 Hz, 1H), 5.96 (dt, J = 14.5, 1.5 Hz, 2H), 2.03 (m, 2H), 1.43 (s, J = 7.5 Hz, 2H), 0.91 (t, J = 7.5 Hz, 3H).



(*E*)-1-((1-Iodonon-1-en-3-yloxy)methyl)-4-methoxybenzene (133), (*E*)-1-iodonon-1-en-3-ol (135) A solution of ethyl (*Z*)-β-iodoacrylate[31] (1.13 g, 5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was cooled to –78 ºC with an acetone/liquid nitrogen bath. DIBAL-H (neat, 0.890 mL, 5 mmol, 1 equiv) was added via syringe and the internal temperature was not allowed to increase above –75 ºC. The solution was allowed to warm to 0 ºC over 1.5 h and then cooled to –20 ºC. Hexylmagnesium bromide (2.0 M in ether, 2.75 mL, 5.3 mmol, 1.1 equiv) was then added and the reaction was warmed to room temperature over 1.5 h after which ethyl ether (50 mL) and aqueous HCl (1M, 50 mL) were added. The mixture was extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$, concentrated and the crude allylic alcohol was purified via column chromatography (ethyl acetate/hexanes, 15/85) to give (*E*)-1-iodonon-1-en-3-ol (**135**) as a white solid (0.610g, 46%)

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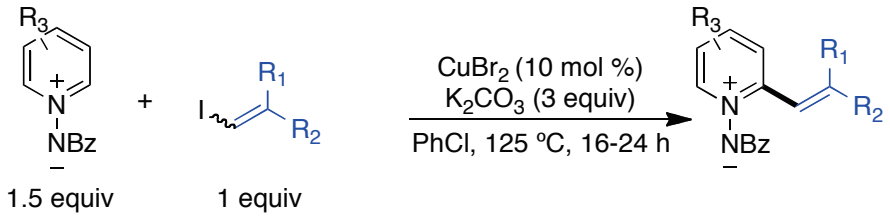
[30] Barrett, A. G. M.; Bennett, A. J.; Menzer, S.; Smith, M. L.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 162.

[31] Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1997**, *74*, 194.

The allylic alcohol (0.300 g, 1.1 mmol, 1 equiv) was dissolved in THF (6 mL) and the solution was cooled to 0 ºC. NaH (0.304 g, 60% in mineral oil) was added. The mixture was left to stir for 20 min and PMBBr (0.175 mL, 1.2 mmol, 1.1 equiv) was added. The reaction mixture was left to warm to room temperature overnight after which Et_2O (50 mL) was added and resulting mixture was washed with aqueous HCl (1M, 100 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4, concentrated and purified by column chromatography (ethyl acetate/hexanes, 15/85) to give **133** as a yellow oil (0.321 g, 78%). R*f* 0.61 (ethyl acetate/hexanes, 15/85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.49 (dd, J = 14.5, 7.8 Hz, 1H), 6.30 (d, J = 14.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.30 (d, J = 11.5 Hz, 1H), 3.82 (s, 3H), 3.73 (q, J = 6.7 Hz, 1H), 1.63 (m, 1H), 1.58 (m, 1H), 1.28 (m, 8H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 146.9, 129.9, 129.0, 113.4, 80.8, 77.5, 69.8, 54.9, 34.6, 31.8, 28.8, 24.8, 22.3, 13.8. FTIR (neat) 2926, 2855, 1611, 1512, 1246, 1172, 1082, 1037, 949, 821 cm^{-1}. HRMS Calcd for $C_{17}H_{25}IO_2$ $(M + Na)^+$: 411.07914. Found 411.08048.

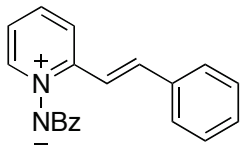
Synthesis and Characterization of 2-Vinyl Pyridinium Ylides



General Procedure

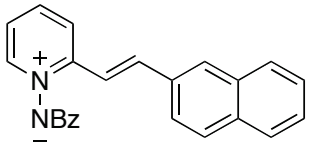
To a microwave vial with a stir bar was added the *N*-iminopyridinium ylide (0.6 mmol, 1.5 equiv), $CuBr_2$ (0.04 mmol, 10 mol %), and crushed dry K_2CO_3 (0.8 mmol, 2 equiv). The vial was then sealed with a septum and purged with argon for 5 min. To a separate vial was added the vinyl iodide (0.4 mmol, 1 equiv). The iodide was diluted in chlorobenzene (0.5 mL) and added to the reaction vessel via syringe. The vial and syringe were then rinsed three times with chlorobenzene (0.5 mL) bringing the total reaction volume to 2 mL. The reaction was stirred vigorously for 16 h at 125 ºC. Following cooling,

2 mL of CH_2Cl_2/MeOH (9:1) was added, and the solution was filtered though a silica/Celite pad. The pad was then rinsed with 15 mL of CH_2Cl_2/MeOH (9:1). The combined solution was concentrated and the crude mixture was purified via column chromatography to afford the vinylated pyridinium products.



107

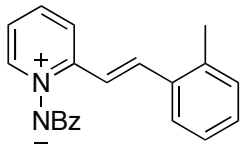
2-(*E*)-Styryl-*N*-benzoyliminopyridinium ylide (107) The title compound **109** was prepared according to the general procedure described above (page XLV) using vinyl iodide **80** or **109**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (98.2 mg, 81%). 47.8 mg of the unreacted ylide was also recovered. R_f = 0.26 (methanol/dichloromethane, 5/95). mp: 199-201 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.9 Hz, 1H), 8.25 (d, J = 7.0 H, 2H), 7.99 (d, J = 8.2 Hz, 1H), 7.85 (t, J = 8.2 H, 1H), 7.78 (d, J = 16.6 Hz, 1H), 7.52-7.41 (m, 7H), 7.36-7.34 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 146.2, 140.3, 137.7, 136.0, 131.0, 130.9, 129.8, 129.3, 129.0, 128.8, 128.7, 128.4, 124.1, 124.0, 119.4. FTIR (neat) 3054, 1612, 1590, 1552, 1483, 1325, 1289, 1173, 1066, 965 cm^{-1}. HRMS Calcd for $C_{20}H_{17}N_2O$ $(M + H)^+$: 301.13354. Found: 301.13502.



110

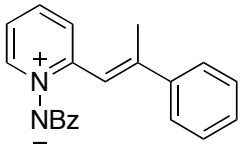
2-(*E*)-(2-(Naphthalen-2-yl)vinyl)-*N*-benzoyliminopyridinium ylide (110) The title compound **110** was prepared according to the general procedure described above (page XLV) using vinyl iodide **83**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a yellow/brown oil (113.2 mg, 81%). R_f = 0.35 (methanol/dichloromethane, 1/9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 6.3 Hz, 1H), 8.31 (m, 2H), 8.03 (dd, J = 8.3, 1.2 Hz, 1H), 7.88-7.68 (m, 6H), 7.61-7.56 (m, 2H), 7.51-7.45 (m, 5H), 7.43-7.40 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 146.1, 140.6, 138.2,

137.7, 134.9, 134.0, 133.5, 131.1, 130.6, 129.6, 129.4, 129.2, 129.0, 128.9, 128.8, 128.6, 128.0, 127.5, 124.0, 123.9, 119.2. FTIR (neat) 3056, 1609, 1591, 1550, 1497, 1326, 1293, 1175, 1066, 962 cm^{-1}. HRMS Calcd for $C_{24}H_{19}N_2O$ $(M + H)^+$: 351.14919. Found: 351.15033.



111

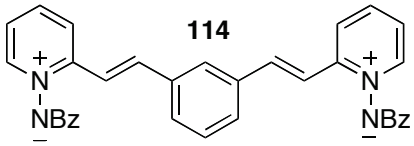
2-(*E*)-(2-Methylstyryl)-*N*-benzoyliminopyridinium ylide (111). The title compound **111** was prepared according to the general procedure described above (page XLV) using vinyl iodide **82**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (97.6 mg, 78%). R_f = 0.36 (methanol/dichloromethane, 1/9). mp: 182-184 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 6.2 Hz, 1H), 8.24 (m, 2H), 8.05 (d, J = 8.2, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.70 (s, 2H), 7.57 (d, J = 7.6 Hz, 1H), 7.50-7.42 (m, 5H), 7.26-7.17 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 146.2, 138.1, 137.9, 137.7, 135.1, 131.6, 130.9, 130.7, 128.9, 128.7, 127.5, 127.4, 127.1, 124.2, 124.1, 120.7, 78.2, 20.8. FTIR (neat) 3060, 1592, 1552, 1492, 1331, 1294, 1176, 910 cm^{-1}. HRMS Calcd for $C_{21}H_{19}N_2O$ $(M + H)^+$: 315.14919. Found: 315.15057.



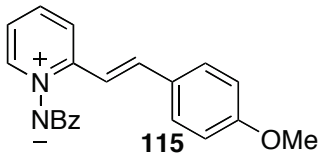
113

2-(*E*)-(2-Phenylprop-1-enyl)-*N*-benzoyliminopyridinium ylide (113) The title compound **113** was prepared according to the general procedure described above (page XLV) using vinyl iodide **112**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a brown solid (61.0 mg, 48%). R_f = 0.55 (methanol/dichloromethane, 1/9). mp: 155-157 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, J = 6.4, 0.9 Hz, 1H), 8.21-8.18 (m, 2H), 7.92 (t, J = 7.8 Hz, 1H), 7.77 (dd, J = 7.8, 1.6 Hz, 1H), 7.56-7.30 (m, 9H), 7.13 (d, J = 0.5 Hz, 1H), 2.35 (d, J = 0.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.9, 146.3,

146.2, 142.4, 138.2, 137.2, 130.9, 129.6, 129.4, 128.9, 128.7, 128.6, 127.1, 124.1, 119.8, 19.1. FTIR (neat) 3061, 2981, 1612, 1592, 1554, 1486, 1328, 1294, 1177, 1055, 1033 cm^{-1}. HRMS Calcd for $C_{21}H_{19}N_2O$ $(M + H)^+$: 315.14919. Found. 315.15044.

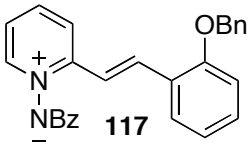


(2,2'-(1*E*,1'*E*)-2,2'-(1,3-Phenylene)bis(ethene-2,1-diyl)bis(pyridinium-2,1-diyl))bis(benzoylamide) (114) The title compound **114** was prepared according to the a modification of the general procedure described above (page XLV) using 3 equiv of ylide **20** and bis-vinyl iodide **96**, and purified by column chromatography (gradient 5/5/90 Et_3N/MeOH/DCM to 5/95 MeOH/DCM) as a cream colored solid (63.6 mg, 63%). R_f = 0.26 (methanol/dichloromethane, 5/95). mp: 199-201 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 5.8 Hz, 2H), 8.27 (m, 4H), 7.97 (d, J = 8.1 Hz, 2H), 7.81 (t, J = 7.6 Hz, 2H), 7.67 (d, J = 16.6 Hz, 2H), 7.48-7.41 (m, 11H), 7.35 (d, J = 16.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 150.5, 145.0, 138.4, 136.8, 136.6, 135.5, 129.9, 129.4, 129.3, 128.2, 128.1, 127.8, 127.6, 123.2, 119.1. FTIR (neat) 3060, 1612, 1591, 1545, 1489, 1336, 1294, 1176, 1066 cm^{-1}. HRMS Calcd for $C_{34}H_{27}N_4O_2$ $(M + H)^+$: 523.21285. Found. 523.21476.



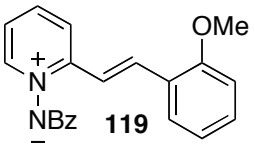
2-(*E*)-(4-Methoxystyryl)-*N*-benzoyliminopyridinium ylide (115) The title compound **115** was prepared according to the general procedure described above (page XLV) using vinyl iodide **84**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (95.2 mg, 78%). R_f = 0.26 (methanol/dichloromethane, 5/95). mp: 201-202 ºC. ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 5.6 Hz, 1H), 8.27 (m, 2H), 7.97 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 16.6 Hz, 1H), 7.48-7.83 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H) ^{13}C NMR (75

MHz, $CDCl_3$) δ 162.1, 152.2, 145.9, 140.1, 137.6, 131.6, 130.9, 130.4, 128.9, 128.8, 128.7, 123.6, 123.4, 116.8, 115.2, 114.9, 56.2. FTIR (neat) 3060, 2930, 2831, 1610, 1591, 1547, 1327, 1245, 1024, 910 cm^{-1}. HRMS Calcd for $C_{21}H_{19}N_2O_2$ $(M + H)^+$: 331.14410. Found: 331.14416.



117

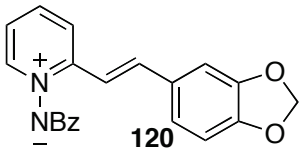
2-(*E*)-(2-(Benzyloxy)styryl)-*N*-benzoyliminopyridinium ylide (117) The title compound **117** was prepared according to the general procedure described above (page XLV) using vinyl iodide **116**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (115.0 mg, 71%). R_f = 0.48 (methanol/dichloromethane, 5/95). mp: 186-187 ºC. ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 6.1 Hz, 1H), 8.24 (m, 2H), 7.95 (d, J = 8.2 Hz, 1H), 7.87 (s, 2H), 7.81 (t, J = 7.9 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.45-7.25 (m, 10H), 6.95 (m, 2H), 5.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 152.4, 146.0, 138.1, 137.6, 137.5, 135.2, 130.9, 129.6, 129.3, 128.95, 128.93, 128.8, 128.7, 128.1, 125.5, 124.0, 123.8, 122.1, 119.6, 113.6, 71.3. FTIR (neat) 3062, 1610, 1593, 1553, 1492, 1452, 1331, 1235, 1000 cm^{-1}. HRMS Calcd for $C_{27}H_{23}N_2O_2$ $(M + H)^+$: 407.17540. Found: 407.17545.



119

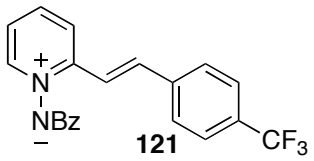
2-(*E*)-(2-Methoxystyryl)-*N*-benzoyliminopyridinium ylide (119) The title compound **119** was prepared according to the general procedure described above (page XLV) using vinyl iodide **118**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a brown solid (130.1 mg, 93%). R_f = 0.45 (methanol/dichloromethane, 5/95). mp: 102-104 ºC. ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 6.3 Hz, 1H), 8.26 (m, 2H), 8.02 (dd, J = 8.3, 1.4 Hz, 1H), 7.90-7.76 (m, 3H), 7.52 (dd, J = 7.7, 1.6 Hz, 1H), 7.46-7.38 (m, 4H), 7.3 (t, J = 7.7 Hz, 1H), 6.95-6.85 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 152.5,

145.9, 138.2, 137.2, 135.6, 132.2, 130.9, 129.3, 129.0, 128.7, 125.0, 123.9, 123.7, 121.7, 120.0, 111.9, 56.3. FTIR (neat) 3060, 2938, 2836, 1591, 1547, 1481, 1329, 1243, 1176, 1024, 911 cm^{-1}. HRMS Calcd for $C_{21}H_{19}N_2O_2$ $(M + H)^+$: 331.14410. Found: 331.14393.



120

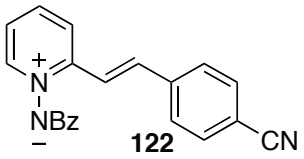
2-(*E*)-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-*N*-benzoyliminopyridinium ylide (120) The title compound **120** was prepared according to the general procedure described above (page XLV) using vinyl iodide **86**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a beige oil (102.9 mg, 75%). R_f = 0.25 (methanol/dichloromethane, 5/95). mp: 199-201 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 5.9 Hz, 1H), 8.21 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 16.5 Hz, 1H), 7.43-7.27 (m, 5H), 6.95-6.90 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 5.93 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 149.3, 148.2, 145.1, 139.1, 137.2, 136.6, 130.0, 129.6, 127.9, 127.8, 124.1, 122.7, 122.6, 116.3, 108.4, 106.2, 101.5, 77.2. FTIR (neat) 3062, 2981, 2894, 1591, 1549, 1489, 1445, 1328, 1235, 1034, 910 cm^{-1}. HRMS Calcd for $C_{21}H_{17}N_2O_3$ $(M + H)^+$: 345.12337. Found. 345.12483.



121

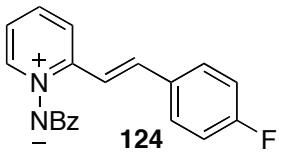
2-(*E*)-(4-(Trifluoromethyl)styryl)-*N*-benzoyliminopyridinium ylide (121). The title compound **121** was prepared according to the general procedure described above (page XLV) using vinyl iodide **90**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a beige solid (103.9 mg, 71%). R_f = 0.26 (methanol/dichloromethane, 5/95). mp: 166-168 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 6.4 Hz, 1H), 8.24 (m, 2H), 8.03 (dd, J = 8.2, 1.6 Hz, 1H), 7.95-7.84 (m, 2H), 7.62 (s, 4H), 7.55 (m, 1H), 7.49-7.42 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 150.2, 145.2,

138.3, 137.3, 136.8, 131.2 (q, J = 32.1 Hz), 127.9, 127.8, 127.7, 125.7, 125.6, 124.1 (q, J = 271.9 Hz), 123.7, 123.4, 120.9 FTIR (neat) 3062, 1592, 1549, 1488, 1319, 1294, 1165, 1117, 1066, 1016, 910 cm^{-1}. HRMS Calcd for $C_{21}H_{16}F_3N_2O$ $(M + H)^+$: 369.12092. Found: 369.12252.



122

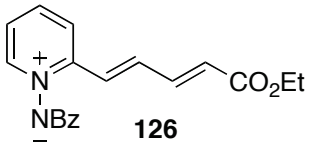
2-(*E*)-(4-Cyanostyryl)-*N*-benzoyliminopyridinium ylide (122). The title compound **122** was prepared according to the general procedure described above (page XLV) using vinyl iodide **89**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a beige solid (117.1 mg, 89%). R_f = 0.29 (methanol/dichloromethane, 5/95). mp: 194-195 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 6.4 Hz, 1H), 8.23 (m, 2H), 8.01 (dd, J = 8.2, 1.5 Hz, 1H), 7.92-7.81 (m, 2H), 7.63-7.52 (m, 5H), 7.48-7.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 146.4, 140.2, 138.7, 137.84, 137.81, 137.5, 133.5, 131.2, 129.0, 128.9, 128.8, 125.1, 124.5, 123.0, 119.3, 113.8. FTIR (neat) 3063, 2225, 1592, 1554, 1487, 1330, 1293, 1175, 1066, 1024, 911 cm^{-1}. HRMS Calcd for $C_{21}H_{16}N_3O$ $(M + H)^+$: 326.12879. Found: 326.12983.



124

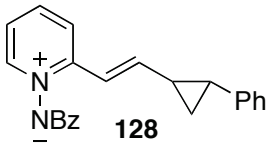
2-(*E*)-(4-Fluorostyryl)-*N*-benzoyliminopyridinium ylide (124). The title compound **124** was prepared according to the general procedure described above (page XLV) using vinyl iodide **88** (**123**), and purified by column chromatography (methanol/dichloromethane, 5/95) as a yellow oil (109.1 mg, 83%). R_f = 0.36 (methanol/dichloromethane, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 6.2 Hz, 1H), 8.25 (d, J = 6.2 Hz, 2H), 7.98 (d, J = 8.2 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 7.67 (d, J = 16.6 Hz, 1H), 7.48-7.37 (m, 7H), 7.02 (t, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (d, J = 251 Hz), 151.7, 146.0, 139.1, 137.9, 132.2 (d, J = 3.4 Hz), 131.1, 130.6, 130.5, 128.9, 128.8, 128.7, 124.1, 124.0, 119.0,

116.9 (d, J = 22.1 Hz). FTIR (neat) 3060, 1591, 1547, 1508, 1487, 1329, 1293, 1227, 1158, 1067, 967 cm^{-1}. HRMS Calcd for $C_{20}H_{16}HN_2O$ $(M + 1)^+$: 319.12412. Found: 319.12392.



126

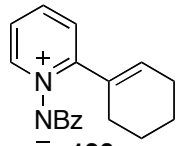
Ethyl-(2*E*, 4*E*)-5-[*N*-benzoyliminopyridinium ylide]-penta-2,4-dienoate (126). The title compound **126** was prepared according to the general procedure described above (page XLV) using vinyl iodide **125**. The title compound **126** was purified by preparatory thin layer chromatography (methanol/dichloromethane, 5/95) as a brown-colored oil (52.1 mg, 41%). R_f = 0.28 (methanol/dichloromethane, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 6.4 Hz, 1H), 8.22 (dd, J = 7.6, 2.0 Hz, 2H), 7.97-7.88 (m, 2H), 7.59-7.55 (m, 2H), 7.47-7.40 (m, 4H), 7.17 (dd, J = 15.2, 4.4 Hz, 2H), 6.15 (d, J = 15.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 1.32 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 165.8, 149.4, 145.4, 142.0, 136.8, 136.6, 135.6, 130.2, 128.7, 128.0, 127.8, 126.9, 124.3, 60.8, 14.1. FTIR (neat) 3406, 3061, 2981, 1707, 1591, 1548, 1488, 1444, 1331, 1175, 1026, 713 cm^{-1}. HRMS Calcd for $C_{20}H_{17}N_2O$ $(M + H)^+$: 323.13902. Found: 323.13893.



128

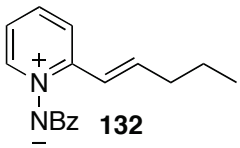
2-(*E*)-(2-(2-Phenylcyclopropyl)vinyl)-*N*-benzoyliminopyridinium ylide (128). The title compound **128** was prepared according to the general procedure described above (page XLV) using vinyl iodide **127**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a light brown solid (72.0 mg, 53%). R_f = 0.41 (methanol/dichloromethane, 5/95). mp: 179 ºC ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 6.2 Hz, 1H), 8.25 (m, 2H), 7.83-7.76 (m, 2H), 7.45-7.37 (m, 4H), 7.27 (t, J = 7.6 Hz, 2H), 7.22-7.17 (m, 2H), 7.04 (d, J = 7.2 Hz, 2H), 6.37 (m, 1H), 2.18 (m, 1H), 1.94 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 151.7, 147.6, 145.7, 141.4, 138.0, 137.8, 131.0, 129.3. 128.9, 128.7, 127.0, 126.6, 123.6, 123.5, 119.5, 29.4, 28.2,

19.2. FTIR (neat) 3061, 1632, 1593, 1553, 1490, 1330, 1175, 713 cm^{-1}. HRMS Calcd for $C_{23}H_{21}N_2O$ $(M + H)^+$: 341.16484. Found: 341.16601.



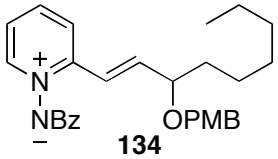
130

2-(*E*)-Cyclohexenyl-*N*-benzoyliminopyridinium ylide (130). The title compound **130** was prepared according to the general procedure described above (page XLV) using vinyl iodide **129**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a pale yellow oil (58.9 mg, 52%). R_f = 0.33 (methanol/dichloromethane, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 6.2 Hz, 1H), 8.16 (m, 2H), 7.85 (t, J = 7.5 Hz, 1H), 7.54 (m, 2H), 7.41 (m, 3H), 6.06 (m, 1H), 2.46 (m, 2H), 2.21 (m, 2H), 1.67 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 156.9, 146.7, 138.3, 134.5, 134.1, 130.7, 128.9, 128.6, 128.1, 124.6, 78.1, 27.6, 26.4, 23.1, 22.4. FTIR (neat) 3061, 2980, 1592, 1552, 1486, 1328, 1294, 1177, 1055, 1033 cm^{-1}. HRMS Calcd for $C_{18}H_{19}N_2O$ $(M + H)^+$: 279.14919. Found: 279.14885.



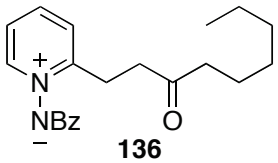
132

2-(*E*)-Pentenyl-*N*-benzoyliminopyridinium ylide (132). The title compound **132** was prepared according to the general procedure described above (page XLV) using vinyl iodide **131**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a pale yellow oil (12.0 mg, 15%). R_f = 0.39 (methanol/dichloromethane, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56-8.54 (m, 1H), 8.23-8.20 (m, 2H), 7.85 (d, J = 4.0 Hz, 2H), 7.44 (m, 4H), 7.15-7.09 (m, 1H), 6.70 (dt, J = 16.0, 6.9 Hz, 1H), 2.31 (q, J = 7.3 Hz, 2H), 1.53 (q, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 145.9, 144.6, 138.1, 137.6, 130.8, 128.9, 128.6, 124.3, 124.0, 123.9, 122.3, 36.3, 22.0, 14.5. FTIR (neat) 3062, 2983, 1592, 1542, 1486, 1326, 1290, 1187, 1065, 1033 cm^{-1}. LRMS (APCI) Calcd for $C_{17}H_{19}N_2O$ $(M + H)^+$: 267.14. Found: 267.2.



134

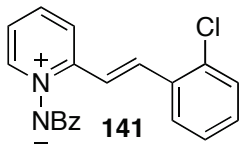
2-(*E*)-(3-(4-methoxybenzyloxy)non-1-enyl)-*N*-benzoyliminopyridinium ylide (134). The title compound **134** was prepared according to the general procedure described above (page XLV) using vinyl iodide **133**, and purified by preparative HPLC (ZORBAX Eclipse XDB-C8, 2% to 98% MeCN in H_2O over 10 min, 20 mL/min: t_r = 9.75 min) as a colourless oil (41.0 mg, 30%). R_f = 0.41 (methanol/dichloromethane, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 6.1 Hz, 1H), 8.21 (m, 2H), 7.86 (m, 2H), 7.53 (dt, J = 6.7, 2.2 Hz, 1H), 7.45 (m, 3H), 7.27 (d, J = 16.3 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.56-6.58 (m, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.32 (d, J = 11.6 Hz, 1H), 3.94 (q, J = 6.2 Hz, 1H), 3.76 (s, 3H), 1.68 (m, 1H), 1.56 (m, 1H), 1.24 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 160.0, 151.5, 146.1, 143.6, 138.0, 137.7, 130.9, 130.4, 129.0, 128.7, 124.6, 123.6, 118.3, 114.6, 79.2, 78.1, 71.3, 56.1, 36.2, 32.6, 30.0, 26.1, 23.4, 14.9. FTIR (neat) 3061, 2927 2856, 1612, 1593, 1512, 1331, 1295, 1247, 1176, 1034, 713 cm^{-1}. HRMS Calcd for $C_{29}H_{35}N_2O_3$ $(M + 1)^+$: 459.26422. Found: 459.26289.



136

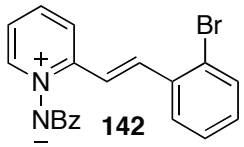
2-(*E*)-(3-oxononyl)-*N*-benzoyliminopyridinium ylide (136). The title compound **136** was prepared according to the general procedure described above (page XLV) using vinyl iodide **135**, and purified by preparative HPLC (ZORBAX Eclipse XDB-C8, 2% to 98% MeCN in H_2O over 10 min, 20 mL/min: t_r = 9.65 min) as a colourless oil (18.0 mg, 22%). R_f = 0.41 (methanol/dichloromethane, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69-8.66 (m, 1H), 8.21-8.18 (m, 2H), 7.88-7.83 (m, 1H), 7.78-7.75 (m, 1H), 7.56-7.51 (m, 1H), 7.47-7.44 (m, 3H), 3.34 (t, J = 6.6 Hz, 2H), 2.99 (t, J = 6.5 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.53-1.44 (m, 2H), 1.26-1.17 (m, 6H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 190.1, 171.2, 145.6, 145.6, 139.1, 137.2, 130.2, 129.0, 128.6, 124.2, 122.0, 36.4, 36.2, 32.6, 30.0, 29.2, 26.1, 23.4, 14.9. FTIR (neat) 3065, 2925 2876, 1702, 1593, 1515, 1321, 1275, 1247, 1177, 1033, 712 cm^{-1}. LRMS (APCI) Calcd for $C_{21}H_{27}N_2O_2$ $(M + 1)^+$: 339.20. Found: 339.2.



141

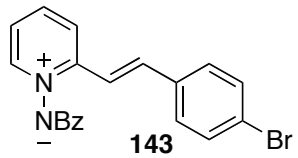
2-(*E*)-(2-Chlorostyryl)-*N*-benzoyliminopyridinium ylide (141). The title compound **141** was prepared according to the general procedure described above (page XLV) using vinyl iodide **91**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (98.9 mg, 74%). R_f = 0.63 (methanol/dichloromethane, 1/9). mp: 202-204 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 6.1 Hz, 1H), 8.26 (m, 2H), 8.06 (dd, J = 8.2, 1.4 Hz, 1H), 7.94-7.75 (m, 3H), 7.67 (m, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.46-7.39 (m, 4H), 7.31-7.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 146.3, 138.0, 137.8, 135.7, 135.4, 134.1, 131.7, 131.0, 130.9, 128.9, 128.8, 128.4, 128.2, 128.0, 124.6, 124.4, 121.9. FTIR (neat) 3055, 1590, 1554, 1485, 1444, 1324, 1289, 1171, 1050, 967, 910, 719 cm^{-1}. HRMS Calcd for $C_{20}H_{16}ClN_2O$ $(M + H)^+$: 335.09457. Found. 335.09611.



142

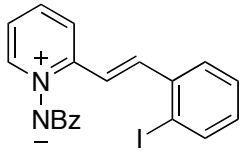
2-(*E*)-(2-Bromostyryl)-*N*-benzoyliminopyridinium ylide (142). The title compound **142** was prepared according to the general procedure described above (page XLV) using vinyl iodide **94**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a brown oil (102.7 mg, 65%). R_f = 0.28 (methanol/dichloromethane, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (dd, J = 5.4, 0.9 Hz, 1H), 8.25 (m, 2H), 8.10 (dd, J = 8.3, 1.5 Hz, 1H), 7.95 (t, J = 8.5 Hz, 1H), 7.88-7.59 (m, 4H), 7.54 (m, 1H), 7.47 (m, 3H), 7.32 (dt, J = 7.4, 0.9 Hz, 1H), 7.21 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 150.4, 145.3, 137.4, 137.0, 136.8, 134.8, 133.1, 131.8, 130.9, 130.0, 128.4, 128.0, 127.7, 127.3, 125.0, 123.6,

121.1. FTIR (neat) 3061, 1673, 1592, 1550, 1490, 1332, 1295, 1176, 1025, 713 cm^{-1}. HRMS Calcd for $C_{20}H_{16}BrN_2O$ $(M + H)^+$: 379.04405. Found. 379.04352.



143

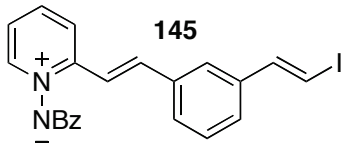
2-(*E*)-(4-Bromostyryl)-*N*-benzoyliminopyridinium ylide (143). The title compound **143** was prepared according to the general procedure described above (page XLV) using vinyl iodide **92**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a beige solid (112.0 mg, 74%). R_f = 0.28 (methanol/dichloromethane, 5/95). mp: 204 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 6.3 Hz, 1H), 8.24, (d, J = 7.5 Hz, 2H), 7.99 (d, J = 7.5 Hz, 1H), 7.87 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 16.6 Hz, 1H), 7.51-7.46 (m, 6H), 7.38-7.34 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 151.6, 146.3, 138.9, 137.9, 137.8, 134.9, 133.0, 131.1, 130.1, 129.0, 128.8, 125.1, 124.4, 12.1, 120.0. FTIR (neat) 3056, 1612, 1594, 1490, 1333, 1294, 1179, 1070, 1007, 711 cm^{-1}. HRMS Calcd for $C_{20}H_{16}BrN_2O$ $(M + H)^+$: 379.04405. Found. 379.04544.



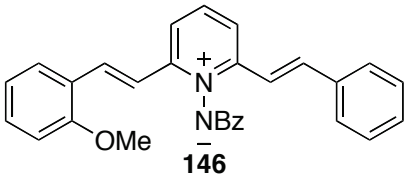
144

2-(*E*)-(2-Iodostyryl)-*N*-benzoyliminopyridinium ylide (144). The title compound **144** was prepared according to the general procedure described above (page XLV) using vinyl iodide **95**, and purified by column chromatography (methanol/dichloromethane, 5/95) as a cream colored solid (80.1 mg, 47%). R_f = 0.37 (methanol/dichloromethane, 5/95). mp: 199-201 ºC ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 6.4 Hz, 1H), 8.24 (m, 2H), 8.07 (dd, J = 8.2, 1.5 Hz, 1H), 7.94 (dt, J = 7.9, 1.3 Hz, 1H), 7.88 (dd, J = 7.9, 1.3 Hz, 1H), 7.68 (s, 2H), 7.61 (dd, J = 9.5, 1.6 Hz, 1H), 7.53 (dt, J = 7.9, 1.3 Hz, 1H), 7.45 (m, 3H), 7.34 (dt, J = 7.6, 1.2 Hz, 1H), 7.04 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 150.3, 145.3, 142.3, 139.7, 138.0, 137.0, 136.8, 130.9, 130.0, 128.7, 128.0, 127.8, 127.4, 123.6, 123.5, 121.3,

101.1. FTIR (neat) 3057, 2922, 1592, 1552, 1488, 1327, 1293, 1175, 1012, 712 cm^{-1}. HRMS Calcd for $C_{20}H_{16}IN_2O$ $(M + H)^+$: 427.03018. Found: 427.03195.



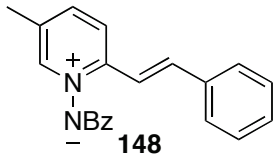
2-(*E*)-(3-((*E*)-2-Iodovinyl)styryl)-*N*-benzoyliminopyridinium ylide (145). The title compound **145** was prepared according to the general procedure described above (page XLV) using bis-vinyl iodide **96**, and purified by column chromatography methanol/dichloromethane, 5/95) as a cream colored solid (95.2 mg, 78%). R_f = 0.26 (methanol/dichloromethane, 5/95). mp: 200-201 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 5.8 Hz, 1H), 8.27 (m, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 16.6 Hz, 1H), 7.51-7.25 (m, 10H), 6.83 (d, J = 15.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 150.5, 144.9, 143.7, 138.5, 137.9, 136.7, 136.6, 135.3, 130.0, 128.9, 127.7, 127.6, 127.0, 126.9, 125.3, 123.1, 123.0, 118.9, 77.8. FTIR (neat) 3053, 1612, 1590, 1545, 1489, 1332, 1293, 1176, 1066, 947, 762, 709 cm^{-1}. HRMS Calcd for $C_{22}H_{18}IN_2O$ $(M + H)^+$: 453.04583. Found: 453.04716.



146

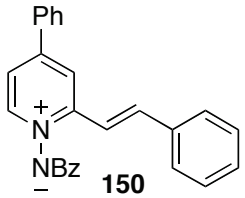
2-(*E*)-2-methoxystyryl-6-(*E*)-styryl-*N*-benzoyliminopyridinium ylide (146). The title compound **146** was prepared according to a modification of the general procedure described above (page XLV) using 0.267 mmol of vinyl iodide **118** and ylide **107**. The title compound **146** was purified by column chromatography (methanol/dichloromethane, 5/95) as a yellow solid (73.2 mg, 64%). R_f = 0.55 (methanol/dichloromethane, 5/95). mp: >220 ºC ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.86-7.62 (m, 6H), 7.48 (m, 6H), 7.38-7.27 (m, 5H), 6.87 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 153.6, 152.8, 139.6, 138.1, 137.3, 136.3, 135.5, 131.8, 130.8, 129.7, 129.6, 129.1, 128.8, 128.6, 125.2, 122.1, 121.9, 121.6, 120.9, 120.6, 111.8, 56.1. FTIR (neat) 3058, 2939, 1592, 1556, 1479,

1330, 1246, 1207, 1173, 1025 cm^{-1}. HRMS Calcd for $C_{26}H_{24}N_2O_2$ $(M + H)^+$: 433.19105. Found: 433.19181.



148

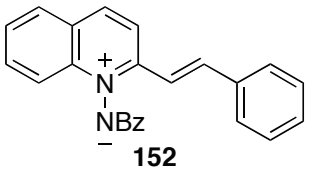
5-Methyl-2-(*E*)-styryl-*N*-benzoyliminopyridinium ylide (148). The title compound **148** was prepared according to the general procedure described above (page XLV) using vinyl iodide **80** and ylide **147**. The title compound **148** was purified by column chromatography (methanol/dichloromethane, 5/95) as a brown colored oil (89.3 mg, 72%). R_f = 0.48 (5 methanol/dichloromethane, 5/95). ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.25 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 16.6 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.32 (m, 9H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 145.4, 139.2, 139.0, 138.2, 136.2, 135.2, 130.9, 130.7, 129.7, 128.9, 128.7, 128.6, 123.5, 119.3, 19.1 FTIR (neat) 3055, 2990, 1592, 1551, 1507, 1328, 1262, 1210, 1171, 1067 cm^{-1}. HRMS Calcd for $C_{21}H_{18}N_2O$ $(M + H)^+$: 315.14919. Found: 315.14930.



150

4-Phenyl-2-(*E*)-styryl-*N*-benzoyliminopyridinium ylide (150). The title compound **150** was prepared according to the general procedure described above using (page XLV) vinyl iodide **80** and ylide **149**. The title compound **150** was purified by column chromatography (methanol/dichloromethane, 5/95) as a pale yellow solid (113.4 mg, 76%). R_f = 0.58 (methanol/dichloromethane, 5/95). m.p.: >220 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 6.7 Hz, 1H), 8.28 (m, 2H), 8.17 (s, 1H), 7.86 (d, J = 16.6 Hz, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 7.67-7.39 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 152.1, 151.6, 150.4, 149.2, 146.1, 145.5, 140.0, 139.1, 138.3, 136.1, 131.5, 131.2, 130.9, 130.5, 129.9, 120.0, 128.7, 128.1, 126.5, 122.9, 122.5, 121.9, 121.3, 119.8. FTIR (neat) 3055, 1589, 1537, 1476,

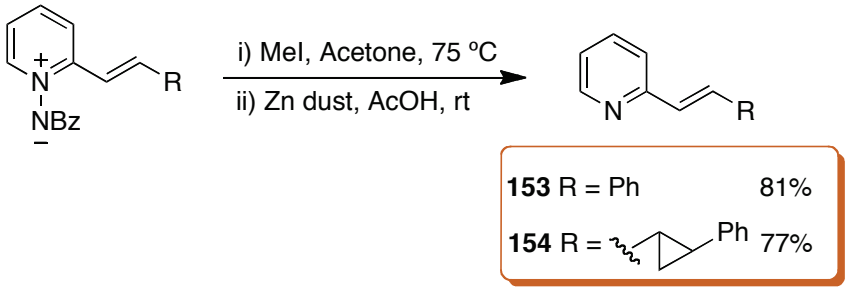
1332, 1297, 1175, 1067 cm^{-1}. LRMS Calcd for $C_{26}H_{20}N_2O$ $(M + H)^+$: 377.16484. Found: 377.16524.



152

2-(*E*)-Styryl-*N*-benzoyliminopyridinium ylide (152). The title compound **152** was prepared according to the general procedure described above (page XLV) using vinyl iodide **2a** and ylide **151**, except that CuBr was used in place of $CuBr_2$. The title compound **152** was purified by preparatory thin layer chromatography (methanol/dichloromethane, 5/95) as a pale green solid (68.0 mg, 49%). R_f = 0.28 (methanol/dichloromethane, 5/95). m.p. >220 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 8.9 Hz, 1H), 8.36 (m, 3H), 8.09 (d, J = 8.9 Hz, 1H), 7.95-7.82 (m, 3H), 7.71-7.65 (m, 2H), 7.56-7.49 (m, 5H), 7.37-7.35 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 153.0, 143.2, 141.1, 138.5, 137.9, 136.0, 134.4, 131.3, 131.0, 129.8, 129.5, 129.4, 129.23, 129.19, 129.1, 128.8, 121.8, 120.7, 119.7. FTIR (neat) 3348, 3059, 1592, 1557, 1519, 1334, 1211, 1149, 1001, 743 cm^{-1}. HRMS Calcd for $C_{24}H_{19}N_2O$ $(M + H)^+$: 351.16919. Found: 351.14901.

***N-N* Bond Cleavage**



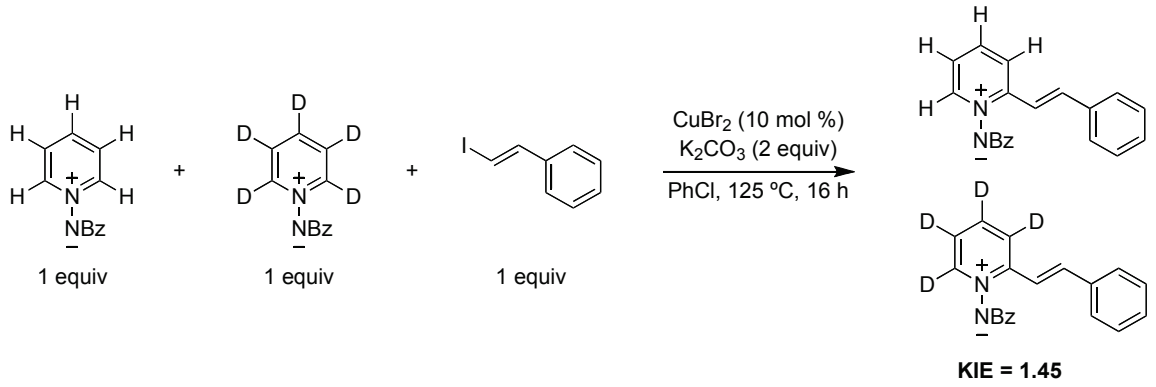
2-Styrylpyridine (153). A Schlenk flask equipped with a stir bar was charged with compound **107** (53.0 mg, 0.177 mmol, 1.0 equiv) and purged with argon. Acetone (1.0 mL) followed by iodomethane (0.10 mL, 1.6 mmol, 9.0 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a

beige powder. To this solid was added zinc dust (<10 micron, 174.0 mg, 2.7 mmol, 15.0 equiv), acetic acid (1.5 mL), and the mixture was stirred at room temperature for 16 h. The mixture was filtered through celite, concentrated and purified by flash chromatography (ethyl acetate/hexanes, 35/65) to give **153** as a white solid (26.0 mg, 81%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[32] R_f = 0.41 (ethyl acetate/hexanes, 35/65); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.64 (d, J = 6.4 Hz, 1H), 7.71-7.60 (m, 4H), 7.43-7.39 (m, 3H), 7.33 (t, J = 7.2 Hz, 1H), 7.22-7.16 (m, 2H).

2-(*E*)-(2-(2-Phenylcyclopropyl)vinyl)-pyridine (154). A Schlenk flask equipped with a stir bar was charged with compound **128** (41.0 mg, 0.120 mmol, 1.0 equiv) and purged with argon. Acetone (0.8 mL) followed by iodomethane (0.072 mL, 1.12 mmol, 9.4 equiv) was added via syringe and the mixture was heated to 75 ºC with stirring for 16 h. The solvent was evaporated to give a beige powder. To this solid was added zinc dust (<10 micron, 118.0 mg, 1.8 mmol, 15.0 eq.), acetic acid (1.2 mL), and the mixture was stirred at room temperature for 16 h. The mixture was filtered through celite, concentrated and purified by flash chromatography (ethyl acetate/hexanes, 1/4) to give a clear liquid (20.4 mg, 77%). R_f = 0.48 (ethyl acetate/hexanes, 35/65); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.32-7.27 (m, 2H), 7.20 (t, J = 8.0 Hz, 2H), 7.14-7.09 (m, 3H), 6.58 (d, J = 15.2 Hz, 1H), 6.49 (m, 1H), 2.18 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H), 1.34 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 149.1, 141.5, 137.6, 136.1, 128.0, 127.5, 125.44, 125.42, 121.1, 120.8, 27.2, 25.8, 17.0. FTIR (neat) 3002, 1646, 1584, 1469, 1431, 966 cm^{-1}. HRMS Calcd for $C_{20}H_{17}N_2O$ $(M + H)^+$: 222.12794. Found: 222.12773.

[32] Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.

Kinetic Isotope Experiments



To a microwave vial with a stir bar was added the *N*-iminopyridinium ylide **20** (0.4 mmol, 1.0 equiv), *N*-iminopyridinium ylide d_5[33] (0.4 mmol, 1.0 equiv), $CuBr_2$ (0.04 mmol, 10 mol %), and crushed dry K_2CO_3 (0.8 mmol, 2 equiv). The vial was then sealed with a septum and purged with argon for 5 min. To a separate vial was added the vinyl iodide **80** (0.4 mmol, 1 equiv). The iodide was diluted in chlorobenzene (0.5 mL) and added to the reaction vessel via syringe. The vial and syringe were then rinsed three times with chlorobenzene (0.5 mL) bringing the total reaction volume to 2 mL. The reaction was stirred vigorously for 16 h at 125 ºC. Following cooling, 2 mL of CH_2Cl_2/MeOH (9:1) was added, and the solution was filtered though a silica/Celite pad. The pad was then rinsed with 15 mL of CH_2Cl_2/MeOH (9:1). The combined solution was concentrated and the crude mixture was purified via column chromatography (5% MeOH/DCM) to afford the vinylated pyridinium.

The kinetic isotope was determined through integration of the proton at the C6 position of the pyridinium ring and the d1 of the ^{1}H NMR pulse sequence was set at 10 s to ensure maximum relaxation.[34]

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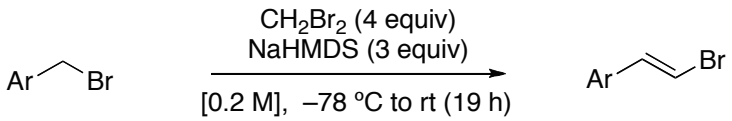
[33] For synthesis of the deuterated ylide same procedure used for **1** was applied with the exception that pyridine-*d*5 and D_2O were used.

[34] KIE determined as follows (0.592/0.408 = 1.45).

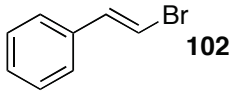
Experimental Section of Chapter 4

Sythesis and Characterization of Vinyl Bromides



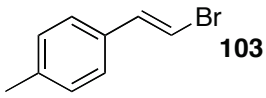
General Method

Dibromomethane (281 μL, 4 mmol) was added dropwise to a solution of NaHMDS (550 mg, 3.0 mmol) in THF (2 mL) and ether (2 mL) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (1.0 mmol) in THF (1 mL) was added dropwise. The reaction mixture was maintained at –78 ºC for at least 3 h then continued stirred at –78 ºC allowing to warm to rt slowly over 16 h. Ether (50 mL) was added then the mixture was filtered through a plug of celite/silica (approximately 3 cm celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl bromide. These compounds were all prepared by Dr. James Bull.



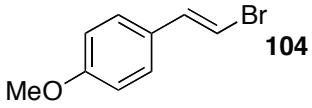
102

(*E*)-(2-Bromovinyl)benzene (102). Prepared according to the general procedure (page LXII) for vinyl bromides starting from benzyl bromide (171 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl bromide **102** as a colourless oil (127 mg, 69%, 99:1 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[35] R_f = 0.60 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 7.12 (d, J = 14.0 Hz, 1H), 6.78 (d, J = 14.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.9, 128.8, 128.2, 126.1, 106.5. FTIR (neat) 3074, 3024, 1607, 1496, 1445, 1221, 939, 730 cm^{-1}.



103

(*E*)-1-(2-Bromovinyl)-4-methylbenzene (103). Prepared according to the general procedure (page LXII) for vinyl bromides starting from 4-methylbenzyl bromide (186 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl bromide **103** as a white solid (179 mg, 91%, >99:1 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[35] R_f = 0.59 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.12 (m, 4H), 7.08 (d, J = 14.0 Hz, 1H), 6.71 (d, J = 14.0 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 136.9, 133.1, 129.4, 125.9, 105.4, 21.2. FTIR (neat) 3070, 2914, 1602, 1509, 1226, 1194, 949, 936, 907, 825, 769, 725 cm^{-1}.

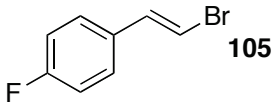


104

(*E*)-1-(2-Bromovinyl)-4-methoxybenzene (104). Prepared according to the general procedure (page LXII) for vinyl bromides starting from 4-methoxybenzyl bromide (201 mg, 1.0 mmol). Purification by flash chromatography (ether/hexanes, 5/95) afforded vinyl

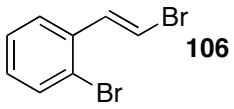
[35] Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron*, **2002**, *58*, 1491.

bromide **104** as a white solid (153 mg, 72%, >99:1 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[35] R_f = 0.46 (ether/hexanes, 5/95). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.02 (d, J = 13.9 Hz, 1H), 6.85-6.82 (m, 2H), 6.59 (d, J = 13.9 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 136.4, 128.6, 127.2, 114.1, 103.9, 55.2. FTIR (neat) 3067, 2956, 2932, 2837, 1605, 1510, 1460, 1304, 1254, 1177, 1028, 950, 836, 776 cm^{-1}.



105

(*E*)-1-Fluoro-4-(2-bromovinyl)benzene (105). Prepared according to the general procedure (page LXII) for vinyl bromides starting from 4-fluorobenzyl bromide (189 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl bromide **105** as a colourless oil (159 mg, 79%, >99:1 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[36] R_f = 0.53 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.07-6.97 (m, 3H), 6.67 (dd, J = 14.0, 0.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, J = 248 Hz), 136.0, 132.1 (d, J = 3 Hz), 127.7 (d, J = 8 Hz), 115.8 (d, J = 22 Hz), 106.9 (d, 2.5 Hz). FTIR (neat) 3056, 1590, 1557, 1474, 1421, 1209, 1071, 942, 755 cm^{-1}.



106

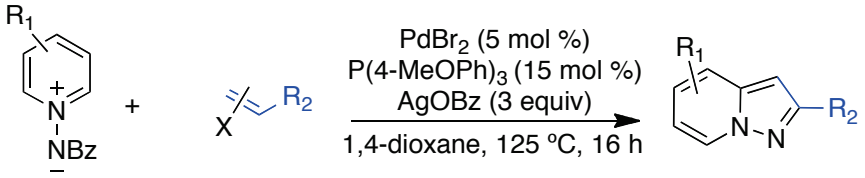
(*E*)-1-Bromo-2-(2-bromovinyl)benzene (106). Prepared according to the general procedure (page LXII) for vinyl bromides starting from 2-bromobenzyl bromide (250 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded vinyl bromide **106** as a colourless oil (175 mg, 67%, >99:1 *E*:*Z*). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[37] R_f = 0.56 (hexanes, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 1H), 7.42 (d, J = 13.9 Hz, 1H), 7.38-

[36] Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis*, **2005**, 1319-1325.

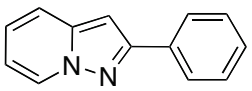
[37] Horibe, H.; Fukuda, Y.; Kondo, K.; Okuno, H.; Murakamia, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701–10709.

7.35 (m, 1H), 7.28-7.23 (m, 1H), 7.16-7.11 (m, 1H), 6.74 (d, J = 13.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 135.9, 133.1, 129.6, 127.6, 127.1, 122.7, 109.2. FTIR (neat) 3069, 1603, 1463, 1435, 1219, 1020, 931, 740 cm^{-1}.

Synthesis of 2-Substituted Pyrazolopyridines from Vinyl Halides



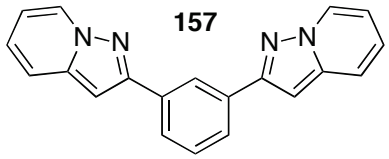
General procedure for the synthesis of 2-substituted-pyrazolo[1,5-a]pyridines. To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide (1.0 mmol, 2 equiv). In a glove box was added *para*-tris-methoxyphenylphosphine (0.15 equiv), palladium bromide (0.05 equiv), and silver benzoate (1.5 mmol, 3 equiv). The microwave vial was crimped shut. The alkenyl iodide derivative (0.5 mmol, 1 equiv) was diluted in 0.5 mL 1,4-dioxane and added via syringe. The syringe was rinsed three times with 0.5 mL dioxane to reach a final volume of 2 mL. The solution was heated to 125 ºC with fast stirring. Within five minutes a colour change was observed. The mixture was stirred for 16 h. The solution was cooled to room temperature. Dichloromethane was added and the precipitate was filtered on cotton plug and washed with dichloromethane. Saturated sodium bicarbonate was added and the organic phase was extracted with dichloromethane. The solution was dried with sodium sulfate and concentrated under reduced pressure and purified via column chromatography to afford the title compounds.



155

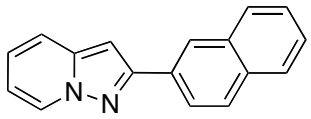
2-Phenylpyrazolo[1,5-a]pyridine (155). The title compound **155** was prepared as per the general procedure (page XLV) using 0.5 mmol of (*E*)-(2-iodovinyl)benzene. The product was purified by column chromatography (hexane/dichloromethane, 5/95) to give a light yellow powder (75.3 mg, 78%). R_f = 0.79 (dichloromethane, 100%). mp: 110-113 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.54-7.34 (m,

1H), 7.08 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.73 (t, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.5, 134.2, 129.4, 129.2, 124.2, 118.7, 112.7, 94.4. FTIR (neat) 3086, 1630, 1508, 1467, 1327, 763, 688 cm^{-1}; HRMS Calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.09167. Found: 195.09088.



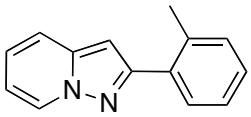
157

1,3-Di(pyrazolo[1,5-a]pyridin-2-yl)benzene (157). The title compound **157** was prepared as per the general procedure (page XLV) using 0.244 mmol of **96**. The product was purified by column chromatography (toluene/ethylacetate, 6/4) to give a light yellow oil in (75.3 mg, 40%). R_f = 0.80 (toluene/ethylacetate, 6/4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.57 (m, 1H), 8.54 (dd, J = 7.0, 1.0 Hz 2H), 8.00 (dd, J = 7.7, 1.7 Hz 2H), 7.59-7.54 (m, 3H), 7.15-7.11 (m, 2H), 6.93-6.92 (s, 2H), 6.79-6.75 (dt, J = 6.9, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 141.2, 133.4, 128.9, 128.2, 126.1, 124.3, 123.0, 117.6, 111.4, 93.6; FTIR (neat) 3077, 2975, 1634, 1520, 1459, 1329, 1256, 770 cm^{-1}. HRMS Calcd for $C_{20}H_{15}N_4$ $[M+H]^+$: 311.12912. Found: 311.12912.



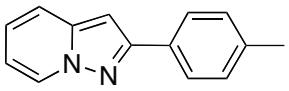
158

2-(Naphthalen-2-yl)pyrazolo[1,5-a]pyridine (158). The title compound **158** was prepared as per the general procedure (page XLV) using 0.5 mmol of **83**. The product was purified by column chromatography (hexane/dichloromethane, 1:1) to give a light yellow/orange powder (75.6 mg, 61%). R_f = 0.79 (dichloromethane, 100%). mp: 61 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.0 Hz, 1H), 8.49 (s, 1H), 8.13 (dd, J = 8.5, 1.4 Hz, 1H), 7.95 (dd, J = 8.8, 3.6 Hz, 2H), 7.90-7.87 (m, 1H), 7.55-7.48 (m, 3H), 7.09 (m, 1H), 6.93 (s, 1H), 6.75 (t, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.5, 134.2, 129.4, 129.2, 124.2, 118.7, 112.7, 94.4. FTIR (neat) 3104, 3051, 2918, 1632, 1506, 1497, 1327, 1254, 1141, 827, 777 cm^{-1}. HRMS Calcd for $C_{17}H_{13}N_2$ $[M+H]^+$: 245.10732. Found: 245.10732.



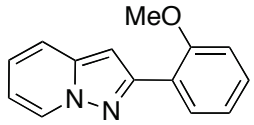
159

2-(2-methylphenyl)pyrazolo[1,5-a]pyridine (159). The title compound **159** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-(2-iodovinyl)-2-methylbenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a light beige powder (73.3 mg, 70%). R_f = 0.27 (dichloromethane, 100%). mp: 59-63 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.52 (d, J = 6.9 Hz, 1H), 7.75-7.67 (m, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.30 (s, 3H), 7.12 (t, J = 6.8 Hz 1H), 6.65 (s, 1H); 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.9, 141.8, 137.4, 134.0, 131.8, 130.8, 129.3, 129.2, 126.8, 124.3, 118.7, 112.4, 97.8, 22.2. IR (neat) 1720, 1631, 1507, 1459, 1328, 1250, 748, 759, 724 cm^{-1}. HRMS Calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.10732. Found: 209.10685.



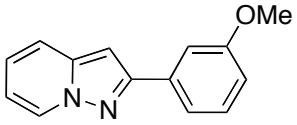
160

2-(4-methylphenyl)pyrazolo[1,5-a]pyridine (160). The title compound **160** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-(2-iodovinyl)-4-methylbenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a light beige powder in (82.5 mg, 79%). R_f = 0.23 (hexane/dichloromethane, 10/90). mp: 117-118 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (d J = 6.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 9.3 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 8.0 Hz 1H), 6.77 (s, 1H), 6.72 (t, J = 6.9 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.5, 142.6, 139.4, 131.4, 130.3, 129.2, 127.8, 124.4, 118.5, 112.2, 94.7, 22.3. FTIR (neat) 1632, 1513, 1472, 1424, 1328, 1250, 827, 774, 744 cm^{-1}. HRMS Calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.10732. Found: 209.10644.



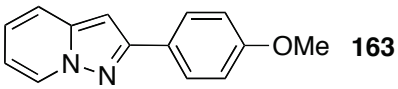
161

2-(2-Methoxyphenyl)pyrazolo[1,5-a]pyridine (161). The title compound **161** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-(2-iodovinyl)-2-methoxybenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a light beige powder in (78.9 mg, 70%). R_f = 0.27 (hexane/dichloromethane, 10/90). mp: 55 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.0 Hz, 1H), 8.11 (dd, J = 7.7, 1.5 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.40-7.34 (m, 1H), 7.12-7.03 (m, 4H), 6.72 (t, J = 6.8 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 146.8, 130.5,5, 130.46, 130.41, 129.2, 124.1, 122.6, 121.8, 118.9, 112.6, 112.2, 99.0, 56.4; FTIR (neat) 3005, 2934, 1633, 1582, 1519, 1478, 1328, 1272, 11244, 1024, 753 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$: 225.1022. Found: 225.1015.



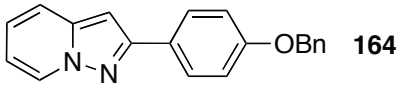
162

2-(3-Methoxyphenyl)pyrazolo[1,5-a]pyridine (162). The title compound **162** was prepared as per the general procedure using 0.5 mmol of (*E*)-1-(2-iodovinyl)-3-methoxybenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a yellow powder (73.4 mg, 65%). R_f = 0.23 (dichloromethane, 100%). mp: 43-45 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 6.9 Hz, 1H), 7.58-7.52 (m, 2H), 7.49 (d, J = 9.0 Hz, 1H), 7.36 (t, J = 8.3 Hz, 1H), 7.06 (t, J = 6.9 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H); 6.79 (s, 1H), 6.71 (t, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 154.2, 142.3, 135.6, 130.6, 129.4, 123.7, 119.9, 118.7, 115.1, 112.6, 112.4, 94.8, 56.0. FTIR (neat) 2833, 1603, 1583, 1520, 1470, 1245, 1158, 1041, 768, 737 cm^{-1}. HRMS Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$: 225.10224. Found: 225.10151.



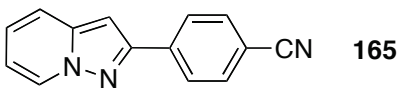
163

2-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (163). The title compound **163** was prepared as per the general procedure using 0.5 mmol of (*E*)-1-(2-iodovinyl)-4-methoxybenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a yellow powder (72.4 mg, 63%). R_f = 0.23 (dichloromethane, 100%). mp: 100-101 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 6.9 Hz, 1H), 7.93-7.88 (m, 2H), 7.47 (d, J = 8.9 Hz, 1H), 7.09-6.97 (m, 3H), 6.72-6.67 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 154.3, 142.5, 129.3, 128.6, 126.8, 124.2, 118.5, 115.0, 112.2, 93.9, 56.2. FTIR (neat) 3076, 2954, 1631, 1613, 1514, 1463, 1243, 1178, 1028, 842, 771 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$: 225.10224. Found: 225.10223.



164

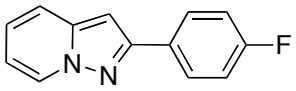
2-[4-(benzyloxy)phenyl]pyrazolo[1,5-a]pyridine (164). The title compound **164** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-(2-iodovinyl)-4-benzyloxybenzene. The product was purified by column chromatography (dichloromethane, 100%) to give a light yellow powder (131 mg, 87%). R_f = 0.24 (dichloromethane, 100%). mp: 164-165 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.9 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.50-7.31 (m, 6H), 7.10-7.04 (m, 3H), 6.73-6.67 (m, 2H), 5.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 154.4, 142.5, 137.9, 129.5, 129.3, 128.8, 128.6, 128.4, 127.1, 124.3, 118.6, 115.9, 112.2, 93.9, 71.0. FTIR (neat) 3031, 1612, 1451, 1250, 1176, 1043, 836, 777, 725 cm^{-1}. HRMS Calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.13354. Found: 301.13310.



165

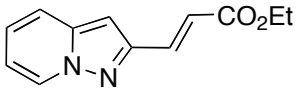
4-Pyrazolo[1,5-a]pyridin-2-ylbenzonitrile (165). As per general procedure (page LXV) using 0.5 mmol of (*E*)-4-(2-iodovinyl)benzonitrile. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a yellow powder (67 mg, 61%). R_f = 0.63 (dichloromethane, 100%). mp: 214-216 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46

(d, J = 6.9 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.84 (s, 1H), 6.80 (t, J = 6.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.7, 138.7, 133.2, 129.6, 127.7, 124.6, 119.9, 119.1, 113.4, 112.5, 95.3. FTIR (neat) 3032, 2223, 1632, 1603, 1505, 1427, 842, 778, 753 cm^{-1}. HRMS Calcd for $C_{14}H_{10}N_3$ $[M+H]^+$: 220.08692. Found: 220.08626.



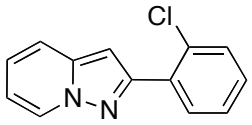
166

2-(4-Fluorophenyl)pyrazolo[1,5-a]pyridine (166). The title compound **166** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-fluoro-4-(2-iodovinyl)benzene. The product was purified by column chromatography (hexane/dichloromethane, 5/95) to give a beige powder (96.4 mg, 86%). R_f = 0.79 (dichloromethane, 100%). mp: 145-147 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 6.3 Hz, 1H), 7.95-7.90 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.18-7.02 (m, 3H), 6.75-6.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, J = 247.2 Hz), 153.5, 142.5, 130.3 (d, J = 3.3 Hz), 129.3, 129.0 (d, J = 9.1 Hz), 124.4, 118.7, 116.5 (d, J = 21.7 Hz), 112.6, 94.3. FTIR (neat) 1630, 1599, 1512, 1473, 1429, 1213, 836, 772, 745 cm^{-1}. HRMS Calcd for $C_{13}H_{10}FN_2$ $[M+H]^+$: 213.08225. Found: 213.08138.



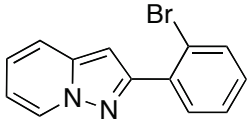
167

(*E*)-Ethyl-2-(pyrazolo[1,5-a]pyridin-2-yl)acrylate (167). The title compound **167** was prepared as per the general procedure using 0.4 mmol of the ethyl-(2*E*, 4*Z*)-5-iodopenta-2,4-dienoate. The product was purified by column chromatography (hexane/dichloromethane, 10/90) to give a light brown oil (42.1 mg, 49% yield). R_f = 0.26 (dichlomethane/hexanes, 95/5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, J = 7.1 Hz, 1H), 7.79 (d, J = 16.1 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 7.0 Hz, 1H), 6.78 (t, J = 6.9 Hz, 1H), 6.67 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 150.3, 142.1, 137.2, 129.3, 124.6, 122.1, 119.2, 113.7, 97.4, 61.4, 15.1; FTIR (neat) 2980, 1711, 1650, 1634, 1299, 1269, 1173, 1034, 979 cm^{-1}; HRMS Calcd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.09715, found: 217.09671.



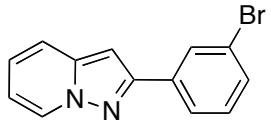
168

2-(2-Chlorophenyl)pyrazolo[1,5-a]pyridine (168). The title compound **168** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-chloro-2-(2-iodovinyl)benzene. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a yellow powder (72.4 mg, 63%). R_f = 0.79 (dichloromethane, 100%). mp: 45-47 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 6.9 Hz, 1H), 7.58-7.49 (m, 2H), 7.39-7.27 (m, 2H), 7.11 (t, J = 7.8 Hz 1H), 7.04 (s, 1H); 6.76 (t, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 141.5, 133.6, 133.1, 132.3, 131.2, 130.2, 129.3, 127.8, 124.2, 119.1, 112.9, 99.0. FTIR (neat) 3031, 1634, 1518, 1462, 1333, 1048, 775, 740, 724 cm^{-1}. HRMS Calcd for $C_{13}H_{10}ClN_2$ $[M+H]^+$: 229.0527. Found: 229.05273.



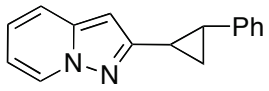
169

2-(2-Bromophenyl)pyrazolo[1,5-a]pyridine (169). The title compound **169** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-bromo-2-(2-iodovinyl)benzene. The product was purified by column chromatography (dichloromethane, 100%) to give a yellow-brown powder (96.0 mg, 70%). R_f = 0.39 (dichlomethane/hexanes, 9/1). mp: 45-46 ºC. ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.51 (d, J = 6.9 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.78 (t, J = 6.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 141.5, 135.4, 134.5, 132.7, 130.5, 129.3, 128.3, 124.2, 123.3, 119.0, 112.8, 98.8. FTIR (neat) 3055, 1633, 1519, 1458, 1330, 1024, 755, 737, 726 cm^{-1}. HRMS Calcd for $C_{13}H_{10}BrN_2$ $[M+H]^+$: 273.00219. Found: 273.00219.



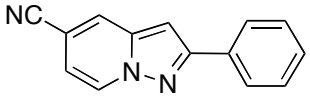
170

2-(2-Bromophenyl)pyrazolo[1,5-a]pyridine (170). The title compound **170** was prepared as per the general procedure (page LXV) using 0.5 mmol of (*E*)-1-bromo-3-(2-iodovinyl)benzene. The product was purified by column chromatography (hexanes/ethyl acetate (1:1) to give a yellow-brown powder (81.5 mg, 60%). R_f = 0.63 (dichlomethane/hexanes, 9/1). mp: 126 ºC. ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.46 (d, J = 7.0 Hz, 1H), 8.14 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.52-7.48 (m, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.76-6.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 142.5, 136.2, 132.1, 131.1, 130.2, 129.3, 125.8, 124.5, 123.8, 118.9, 113.0, 94.8. FTIR (neat) 3045, 1633, 1519, 1465, 1330, 1068, 772, cm^{-1}. HRMS Calcd for $C_{13}H_{10}BrN_2$ $[M+H]^+$: 273.00219. Found: 273.00234.



171

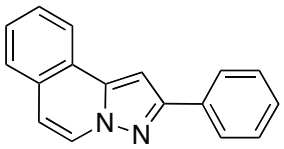
2-(2-Phenylcyclopropyl)pyrazolo[1,5-a]pyridine (171). The title compound **171** was prepared as per the general procedure (page LXV) using 0.5 mmol of the iodocyclopropane **127**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a light brown powder (73 mg, 62%). R_f = 0.26 (dichlomethane/hexanes, 95/5). mp: 53-55 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.371 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.34-7.29 (m, 2H), 7.22-7.17 (m, 3H), 7.04 (t, J = 7.8 Hz, 1H), 6.65 (t, J = 6.9 Hz, 1H), 6.28 (s, 1H), 2.49-2.36 (m, 2H), 1.69-1.62 (m, 1H), 1.55-1.48 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 143.0, 142.0, 129.2, 129.0, 126.7, 126.6, 124.1, 118.1, 111.7, 94.4, 28.4, 22.6, 19.3. FTIR (neat) 3027, 1724, 1632, 1520, 1493, 745, 695 cm^{-1}. HRMS Calcd for $C_{16}H_{15}N_2$ $[M+H]^+$: 235.12297. Found: 235.12373.



173

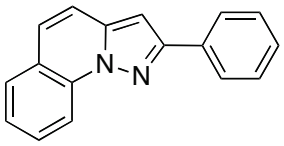
2-Phenylpyrazolo[1,5-a]pyridine-5-carbonitrile (173). The title compound **173** was prepared as per the general procedure (page LXV) using 1.0 mmols of 4-cyano-*N*-

benzoyliminopyridinium ylide **173**. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a yellow powder (67.4 mg, 62%). R_f = 0.76 (dichloromethane, 100%). mp: 186-189 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.2 Hz, 1H), 7.96-7.92 (m, 3H), 7.50-7.38 (m, 3H), 7.69 (s, 1H), 6.83 (d, J = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 140.8, 132.7, 130.2, 130.1, 129.8, 127.5, 125.3, 118.4, 112.5, 107.7, 97.7. FTIR (neat) 3048, 2229, 1523, 1476, 1455, 1431, 1258, 898, 753, 718, 680 cm^{-1}. HRMS Calcd for $C_{14}H_{10}N_3$ $[M+H]^+$: 220.08692. Found: 220.08705.



175

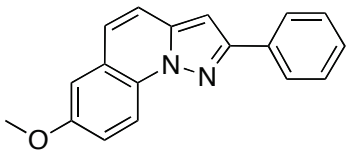
2-Phenylpyrazolo[1,5-a]isoquinoline (175). The title compound **175** was prepared as per the general procedure (page LXV) using 1.0 mmol of *N*-benzoyliminoisoquinolinium ylide **174**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a beige powder (73.7 mg, 60%). R_f = 0.84 (dichloromethane, 100%); mp: 115-117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 6.9 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 6.3 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.62-7.47 (m, 4H), 7.44-7.37 (m, 1H), 7.29 (s, 1H), 6.98 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 140.7, 134.0, 129.7, 129.2, 128.8, 128.5, 128.1, 127.2, 125.3, 124.6, 113.0, 95.4. FTIR (neat) 1537, 1460, 1360, 792, 756, 695 cm^{-1}. HRMS Calcd for $C_{17}H_{13}N_2$ $[M+H]^+$: 245.10732. Found: 245.1067.



176

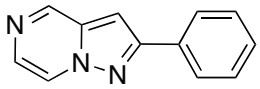
2-(1-(4-Methoxyphenyl)ethyl)-*N*-benzoyliminopyridinium ylide (176). The title compound **176** was prepared as per the general procedure (page LXV) using 1.0 mmol of *N*-benzoyliminoquinolinium ylide **151**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a yellow powder (110.2 mg, 90%). R_f = 0.81 (dichlomethane, 100%). mp: 92-95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.75 (m, 2H), 7.52-7.37 (m, 1H), 6.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 140.4, 135.8, 134.4, 130.2, 129.6, 129.2, 129.1, 125.5,

124.0, 117.5, 116.4, 97.6. FTIR (neat) 1732, 1603, 1454, 1392, 1812, 753, 743, 690, 679 cm^{-1}; HRMS Calcd for $C_{17}H_{13}N_2$ $[M+H]^+$: 245.10732. Found: 245.10727.



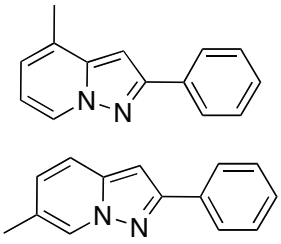
178

7-Methoxy-2-phenylpyrazolo[1,5-a]quinoline (178). The title compound **178** was prepared as per the general procedure (page LXV) using 0.3244 mmol of *N*-benzoyliminoquinolinium ylide **177**. The product was purified by column chromatography (dichloromethane/hexanes, 1:1) to give a yellow powder (30.3 mg, 69%). R_f = 0.65 (dichloromethane/hexanes, 1:1). mp: 115 ºC;=. ^{1}H NMR (300 MHz, $CDCl_3$):= δ8.61 (d, J = 9.1 Hz, 1H), 8.06 (d, J = 7.7 Hz, 2H), 7.45 (m, 3H), 7.35-7.27 (m, 3H), 7.15 (m, 1H), 6.88 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 152.4, 141.8, 138.1, 135.1, 134.4, 130.0, 129.8, 129.1, 127.3, 124.3, 118.1, 115.9, 98.2, 55.4. FTIR (neat) 3372, 2935, 1728, 1619, 1563, 1482, 1456, 1247, 1167, 1043, 760 cm^{-1}. HRMS Calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.11789. Found: 275.11824.



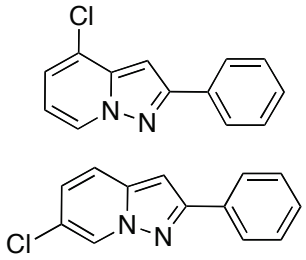
180

2-Phenylpyrazolo[1,5-a]pyrazine (180). The title compound **180** was prepared as per the general procedure (page LXV) using 0.5 mmol of *N*-benzoyliminopyrazonium ylide **179**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a white powder (81.5 mg, 60%). R_f = 0.63 (dichloromethane/hexanes, 1:1). mp: 142 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.98 (d, J = 7.4 Hz, 2H), 7.86 (d, J = 4.7 Hz, 1H), 7.51-7.39 (m, 3H), 7.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 145.3, 138.0, 133.0, 130.1, 129.9, 129.8, 129.4, 128.2, 127.5, 122.5, 96.1. FTIR (neat) 3127, 3020, 1527, 1469, 1421, 1331, 1233, 1080 cm^{-1}. HRMS Calcd for $C_{12}H_{10}N_3$ $[M+H]^+$: 196.08692. Found: 196.08726.



181

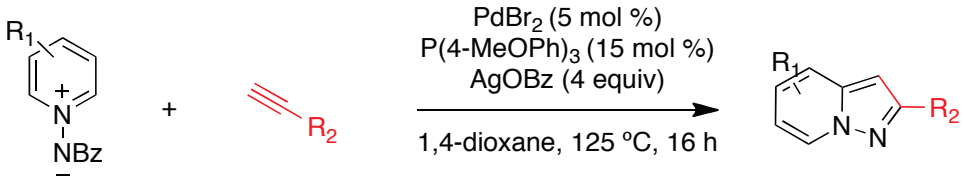
3/6-methyl-2-phenylpyrazolo[1,5-a]pyridine (181). The title compound **181** was prepared as per the general procedure using 1.0 mmol of 3-methyl-*N*-benzoyliminopyridinium ylide **147**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a beige powder (45 mg, 77%). R_f = 0.43 (dichlomethane, 100%); mp: 121-129 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 7.52-7.34 (m, 4H), 6.94 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 143.7, 141.2, 134.4, 129.6, 129.0, 127.4, 123.2, 122.4, 118.0, 112.7, 94.1, 93.5, 18.8. FTIR (neat) 1507, 1438, 1318, 1027, 809, 761, 691 cm^{-1}. HRMS Calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.10732. Found: 209.10685.



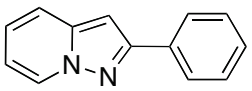
183

3/6-chloro-2-phenylpyrazolo[1,5-a]pyridine (183). The title compound **183** was prepared as per the general procedure using 1.0 mmol of 3-chloro-*N*-benzoyliminopyridinium ylide **182**. The product was purified by column chromatography (hexanes/dichloromethane, 10/90) to give a beige powder (45 mg, 77%). R_f = 0.43 (dichlomethane, 100%). mp: 121-129 ºC. ^{1}H NMR (300 MHz, $CDCl_3$). δ 9.42 (m, , 1H), 9.22-9.20 (m, 2H), 8.15 (m, J, 4H), 8.10-8.04 (m, 7H), 7.70-7.65 (m, 3H), 7.58-7.46 (m, 18H), 7.08-6.99 (m, 6H). ^{13}C NMR (major, 75 MHz, $CDCl_3$) δ 154.7, 141.6, 133.5, 129.7, 127.9, 127.4, 124.6, 123.4, 111.9, 94.9. FTIR (neat) 3141, 3069, 3030, 1630, 1533, 1513, 1464, 1314, 1181, 955, 745 cm^{-1}. HRMS Calcd for $C_{13}H_{10}ClN_2$ $[M+H]^+$: 229.05270. Found: 229.05282.

Synthesis of 2-Substituted Pyrazolopyridines from Alkynes

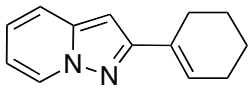


General procedure for the synthesis of 2-substituted-pyrazolo[1,5-a]pyridines. To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide (1.5 mmol, 3 equiv). In a glove box was added *para*-tris-methoxyphenylphosphine (0.15 equiv), palladium bromide (0.05 equiv), and silver benzoate (2.0 mmol, 4 equiv). The microwave vial was crimped shut. The alkyne derivative (0.5 mmol, 1 equiv) was diluted in 0.5 mL 1,4-dioxane and added via syringe. The syringe was rinsed three times with 0.5 mL dioxane to reach a final volume of 2 mL. The solution was heated to 125 ºC with fast stirring. Within five minutes a colour change was observed. The mixture was stirred for 16 h. The solution was cooled to room temperature. Dichloromethane was added and the precipitate was filtered on cotton plug and washed with dichloromethane. Saturated sodium bicarbonate was added and the organic phase was extracted with dichloromethane. The solution was dried with sodium sulfate and concentrated under reduced pressure and purified via column chromatography to afford the title compounds.



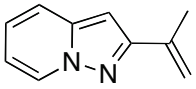
155

2-Phenylpyrazolo[1,5-a]pyridine (155). The title compound **155** was prepared as per the general procedure (page LXXVI) using 0.5 mmol of phenyl acetylene. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a light yellow powder (73.7 mg, 76%). R_f = 0.79 (dichloromethane, 100%). mp: 110-113 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.54-7.34 (m, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.73 (t, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.5, 134.2, 129.4, 129.2, 124.2, 118.7, 112.7, 94.4. FTIR (neat) 3086, 1630, 1508, 1467, 1327, 763, 688 cm^{-1}. HRMS Calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.09167. Found: 195.09088.



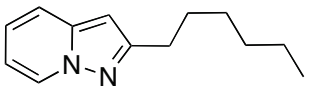
184

2-Cyclohexenylpyrazolo[1,5-a]pyridine (184). The title compound **155** was prepared as per the general procedure (page LXXVI) using 0.5 mmol of the alkyne. The product was purified by column chromatography (dichloromethane/hexanes, 1/1) to give a light brown powder (84.2 mg, 85%). R_f = 0.43 (dichloromethane/hexanes, 1/1); mp: 44-45 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, J =7.0 Hz, 1H), 7.42 (d, J = 9 Hz, 1H), 7.00-6.95 (m, 1H), 6.63-6.52 (m, 2H), 6.44 (s, 1H), 2.52-2.60 (m, 2H), 2.21-2.20 (m, 2H), 1.81-1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 140.9, 130.2, 128.2, 126.6, 122.9, 117.4, 110.9, 92.4, 26.1, 25.5, 22.6, 22.1; FTIR (neat) 3075, 2922, 2854, 1629, 1516, 1488, 1327, 1252, 1138, 918, 767 cm^{-1}; HRMS Calcd for $C_{13}H_{15}N_2$ $[M+H]^+$: 199.12297. Found: 199.12269.



185

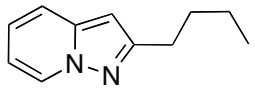
2-(Prop-1-en-2-yl)pyrazolo[1,5-a]pyridine (185). The title compound **185** was prepared as per the general procedure (page LXXVI) using 0.5 mmol of the alkyne. The product was purified by column chromatography (hexanes/dichloromethane, 3/7) to give a light brown oil (22.7 mg, 29%). R_f = 0.63 (hexanes/dichloromethane, 3/7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 7.0, 0.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.08-7.04 (m, 1H), 6.70 (td, J = 6.9, 1.2 Hz, 1H), 6.59 (s, 1H), 5.78 (s, 1H), 5.23 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 141.9, 137.7, 129.2, 124.1, 118.6, 114.7, 112.3, 94.5, 21.4. FTIR (neat) 3085, 2972, 2921, 1631, 1518, 1245, 1055, 1033, 1014, 893, 777, 752, 734 cm^{-1}. HRMS Calcd for $C_{10}H_{11}N_2$ $[M+H]^+$: 159.09167. Found: 159.09142.



186

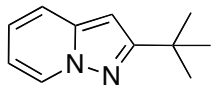
2-Hexylpyrazolo[1,5-a]pyridine (186). The title compound **186** was prepared as per the general procedure (page LXXVI) using 0.390 mmol of the alkyne. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a light brown oil (39.3 mg, 50%). R_f = 0.73 (dichloromethane, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 6.65 (t, J = 6.9

Hz, 1H), 6.29 (s, 1H), 2.82 (m, 2H), 1.74 (q, J = 7.6 Hz, 2H), 1.41-1.31 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 141.8, 129.0, 123.9, 118.2, 111.5, 95.9, 32.5, 30.6, 30.0, 29.5, 23.5, 14.9. FTIR (neat) 3081, 2925, 2855, 1634, 1520, 1488, 1328, 1253, 1142, 1021, 765 cm^{-1}. HRMS Calcd for $C_{13}H_{19}N_2$ $[M+H]^+$: 203.15428. Found: 203.15410.



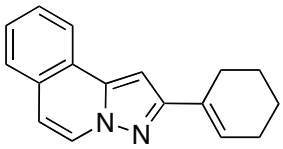
187

2-Butylpyrazolo[1,5-a]pyridine (187). The title compound **187** was prepared as per the general procedure (page LXXVI) using 0.366 mmol of the alkyne. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a light brown oil (34.9 mg, 55%). R_f = 0.69 (dichloromethane, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 1H), 7.41 (dd, J = 8.9, 0.8 Hz, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.65 (t, J = 6.9 Hz, 1H), 6.29 (s, 1H), 2.83 (t, J = 7.7 Hz, 2H), 1.75 (quintet, J = 7.5 Hz, 2H), 1.43 (sextet, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 141.8, 129.0, 123.9, 118.2, 111.5, 95.9, 32.8, 29.1, 23.4, 14.8. FTIR (neat) 3072, 2955, 2859, 1635, 1520, 1474, 1329, 1254, 1238, 1144, 1023, 767 cm^{-1}. HRMS Calcd for $C_{11}H_{15}N_2$ $[M+H]^+$: 175.12297. Found: 175.12282.



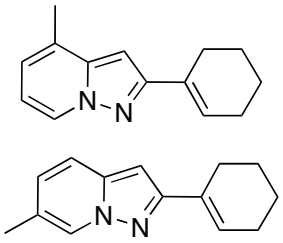
188

2-tert-Butylpyrazolo[1,5-a]pyridine (188). The title compound **187** was prepared as per the general procedure (page LXXVI) using 0.5 mmol of the alkyne. The product was purified by column chromatography (hexanes/dichloromethane, 5/95) to give a light brown oil (55.3 mg, 64%). R_f = 0.75 (dichloromethane, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.04-7.00 (m, 1H), 6.65 (t, J = 6.8, Hz, 1H), 6.35 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 140.4, 128.0, 122.5, 117.1, 110.3, 92.5, 32.0, 30.4. FTIR (neat) 3078, 2958, 2864, 1632, 1519, 1492, 1327, 1236, 770 cm^{-1}. HRMS Calcd for $C_{11}H_{15}N_2$ $[M+H]^+$: 175.12297. Found: 175.12277.



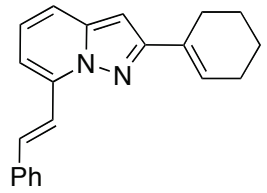
188

2-Cyclohexenylpyrazolo[5,1-a]isoquinoline (188). The title compound **188** was prepared as per the general procedure (page LXXVI) using ylide **174** and 0.25 mmol of the alkyne. The product was purified by column chromatography (dichloromethane, 100%) to give a yellow powder (44.5 mg, 72%). R_f = 0.83 (dichloromethane, 100%). mp: 87-88 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.4 Hz, 1H), 8.08-8.06 (m, 1H), 7.71-7.68 (m, 1H), 7.55 (m, , 2H), 7.01 (s, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.60 (m, 1H), 2.63-2.59 (m, 2H), 2.32-2.26 (m, 2H), 1.88-1.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.9, 131.2, 129.7, 128.6, 128.3, 128.0, 127.4, 127.2, 125.3, 124.5, 112.2, 94.3, 27.0, 26.5, 23.5, 23.1. FTIR (neat) 2924, 2856, 1634, 1537, 1477, 1368, 1054, 1033, 787, 754 cm^{-1}. HRMS Calcd for $C_{17}H_{17}N_2$ $[M+H]^+$: 249.13862. Found: 249.13856.



189

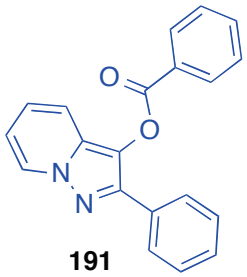
2-cyclohexenyl-6 and 4-methylpyrazolo[1,5-a]pyridine (189). The title compound **189** was prepared as per the general procedure (page LXXVI) using ylide **147** and 0.25 mmol of the alkyne. The product was purified by column chromatography as an inseparable 4:1 mixture towards the least hindered product (dichloromethane, 100%) to give a yellow powder (44.5 mg, 72%). R_f = 0.83 (dichloromethane, 100%). mp: 46-47 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28-8.25 (m), 8.20 (s, 1H), 7.33 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 6.59-6.55 (m, 1H), 6.44 (m, 1H), 3.71 (s, 1H), 2.56-2.51 (m, 3H), 2.43 (s, 1H), 2.30-2.21 (m, 6H), 1.84-1.66 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 155.8, 142.9, 140.4, 131.3, 128.1, 127.3, 127.1, 127.0, 126.9, 126.8, 122.7, 121.6, 117.1, 112.0, 92.9, 92.2, 67.9, 54.3, 27.1, 26.5, 23.0, 23.1, 19.1, 18.9. FTIR (neat) 2922, 1642, 1517, 1485, 1435, 1319, 1261, 1054, 1033, 797 cm^{-1}. HRMS Calcd for $C_{14}H_{17}N_2$ $[M+H]^+$: 213.13862. Found: 213.13841.



190

(*E*)-2-Cyclohexenyl-7-styrylpyrazolo[1,5-a]pyridine (190). The title compound **189** was prepared as per the general procedure (page LXXVI) using ylide **107** and 0.25 mmol of the alkyne. The product was purified by column chromatography (dichloromethane, 100%) to give a yellow powder (13.9 mg, 21%). R_f = 0.73 (dichloromethane, 100%). mp: 95-98 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.64-7.60 (m, 2H), 7.41-7.36 (m, 3H), 7.33-7.27 (m, 1H), 7.08-7.03 (m, 1H), 6.97-6.94 (m, 1H), 6.68-6.63 (m, 1H), 6.53 (s, 1H), 2.63-2.56 (m, 2H), 2.30-2.22 (m, 2H), 1.84-1.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 141.8, 137.3, 136.9, 133.9, 130.5, 128.6, 128.3, 127.1, 126.4, 122.7, 120.1, 115.9, 109.3, 92.8, 26.1, 25.6, 22.6, 22.2. FTIR (neat) 3057, 2924, 1632, 1522, 1448, 1305, 1260, 1080, 965, 782, 717 cm^{-1}. HRMS Calcd for $C_{21}H_{21}N_2$ $[M+H]^+$: 301.16993. Found: 301.16961.

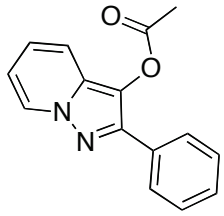
Synthesis of 2,3-Disubstituted Pyrazolopyridines



191

2-Phenylpyrazolo[1,5-a]pyridin-3-yl benzoate (191). To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide **43** (0.279 mmol, 1 equiv). In a glove box was added *para*-tris-methoxyphenylphosphine (0.15 equiv), palladium bromide (0.05 equiv), and silver benzoate (1.15 mmol, 4 equiv). The microwave vial was crimped shut. 1,4-Dioxane was added via syringe. The solution was heated to 125 ºC with fast stirring. Within five minutes a colour change was observed. The mixture was stirred for 16 h. The solution was cooled to room temperature. Dichloromethane was added and the precipitate was filtered on cotton plug and washed with dichloromethane. Saturated sodium bicarbonate was added and the organic phase was extracted with dichloromethane. The solution was dried with sodium sulfate and concentrated under reduced pressure and

purified via column chromatography (dichloromethane/methanol, 9/1) to afford the title compound **191**. (30.0 mg, 34%). R_f = 0.23 (dichloromethane, 100%). mp: 86-88 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 7.0 Hz, 1H), 8.31 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 7.7 Hz, 2H), 7.73-7.68 (m, 1H), 7.58 (t, J = 7.7 Hz, 2H), 7.46-7.34 (m, 4H), 7.12 (m, , 1H), 6.79 (t, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 144.4, 134.8, 134.2, 132.4, 131.3, 129.7, 129.6, 129.5, 129.4, 128.2, 124.0, 122.9, 117.3, 113.0; FTIR (neat) 3062, 1741, 1474, 1348, 1255, 1237, 1202, 1087, 1049, 1022, 741 cm^{-1}. HRMS Calcd for $C_{20}H_{15}N_2O_2$ $[M+H]^+$: 315.11280. Found: 315.11307.

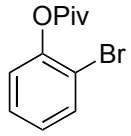


2-Phenylpyrazolo[1,5-a]pyridin-3-yl acetate. To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide **43** (0.50 mmol, 1 equiv). In a glove box was added *para*-tris-methoxyphenylphosphine (0.15 equiv), palladium bromide (0.05 equiv), and silver acetate (2.0 mmol, 4 equiv). The microwave vial was crimped shut. 1,4-Dioxane was added via syringe. The solution was heated to 125 ºC with fast stirring. Within five minutes a colour change was observed. The mixture was stirred for 16 h. The solution was cooled to room temperature. Dichloromethane was added and the precipitate was filtered on cotton plug and washed with dichloromethane. Saturated sodium bicarbonate was added and the organic phase was extracted with dichloromethane. The solution was dried with sodium sulfate and concentrated under reduced pressure and purified via column chromatography (acetone/chloroform, 5/95) to afford the title compound. (62.1 mg, 49%). R_f = 0.83 (acetone/chloroform, 5/95). mp: 64-66 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 1H), 7.95-7.92 (m, 2H), 7.51-7.45 (m, 2H), 7.43-7.37 (m, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.10 (m, 1H), 6.75 (td, J = 6.9, 1.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 144.2, 134.2, 132.4, 129.5, 129.4, 129.3, 128.2, 123.9, 122.9, 117.0, 112.9, 21.6. FTIR (neat) 3041, 2932, 1762, 1638, 1472, 1432, 1368, 1348, 1190, 1077, 740, 695 cm^{-1}. HRMS Calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$: 253.09715. Found: 253.09712.

Experimental Section of Chapter 5

Synthesis of Starting Material

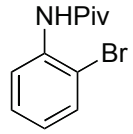
Starting materials not listed below were obtained commercially and the reagents were used without further purification.



209

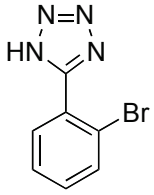
2-Bromophenyl pivalate (209) To a flame-dried flask was added 2-bromophenol (0.35 mL, 3.0 mmol), CH_2Cl_2 (5 mL), and Et_3N (0.84 mL, 6.0 mmol). The resulting solution was cooled to 0 ºC after which PivCl (0.37 mL, 3.0 mmol) was added dropwise. The solution was stirred at this temperature for 30 min and then at rt for three days. The reaction mixture was washed with 20 mL of saturated $NaHCO_3$ solution followed by 20 mL water, dried over $MgSO_4$ and concentrated. Purification by column chromatography (ethyl acetate/hexanes, 4/6) afforded **209** as a while oil (0.57 g, 65%). R_f = 0.81 (ethyl acetate/hexanes, 4/6). The observed characterization data (^1H) was consistent with that

previously reported in the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (d, J = 8.4 Hz, 1H), 7.33-7.28 (t, J = 8.2 Hz, 1H), 7.11-7.06 (t, J = 8.6 Hz, 2H), 1.38 (s, 9H).



211

***N*-(2-bromophenyl)pivalamide (211)** To a round-bottomed flask equipped with a stir bar was added 2-bromoaniline (0.53 g, 4.4. mmol), Na_2CO_3 (0.93 g, 8.8 mmol), CH_2Cl_2 (10 mL), and water (10 mL). The mixture was stirred at rt until all the reagents dissolved and then refluxed for 3 h. The mixture was then diluted with CH_2Cl_2, washed with 10% aq. NaOH, water, and then dried over Na_2SO_4. Purification by column chromatography (ether/hexanes, 1/9) afforded the product as a cream coloured oil (0.906 g, 80%). R_f = 0.40 (ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.3, 1.5 Hz, 1H), 8.04 (bs, 1H), 7.55 (dd, J = 8.0, 1.4 Hz, 1H), 7.33 (t, J = 8.7 Hz, 1H), 6.99 (dt, J = 8.0, 1.6 Hz, 1H), 1.38 (s, 9H).



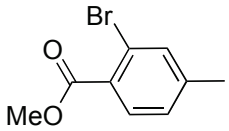
213

2-Bromo-1-trazolobenzene (213). To a round-bottomed flasked equipped with a stir bar and reflux condenser was added 1-bromo-2-cyanobenzene (0.465 g, 2.5 mol, 1 equiv), $TMSN_3$ (0.660 mL, 5 mmol, 2 equiv), Bu_2SnO (0.065g, 10 mol %), and toluene (5 mL). the mixture was refluxed for 38 h. The crude reaction mixture was added to water, and then extracted with 3x 40 mL ether. The title compound was obtained following column

[38] Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322.

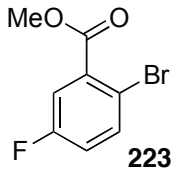
[39] Matsuhira, T.; Yamamoto, H.; Okamura, T.-a.; Ueyama, N. *Org. Biomol. Chem.* **2008**, *6*, 1926.

chromatography (ether/hexanes, 1/1 as a white solid (0.360 g, 64%). (^{1}H) was consistent with that previously reported in the literature.[40] ^{1}H NMR (300 MHz, CD_3OD) δ 7.84 (dd, J = 6.0, 1.1 Hz, 1H), 7.70 (dd, J = 7.0, 2.0 Hz, 1H), 7.48-7.60 (m, 2H).



219

Methyl 2-bromo-4-methylbenzoate (219). To a round-bottomed flask with stir bar was added 2-bromo-4-methylbenzoic acid (0.500 g, 2.3 mmol), CH_3OH (9 mL) and 5 drops of H_2SO_4. The flask was fitted with a reflux condenser and heated to 70 ºC for 12 h. The reaction mixture was diluted in EtOAc, washed with water, sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated to give the product as a white solid (0.42 g, 80%). R_f = 0.40 (ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.07 (dd, J = 7.9, 0.5 Hz, 1H), 3.84 (s, 3H), 2.28 (s, 3H).



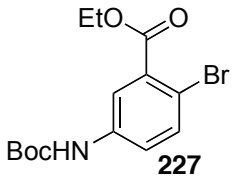
223

Methyl 2-bromo-5-fluorobenzoate (223). To a round-bottomed flask with stir bar was added 2-bromo-4-methylbenzoic acid (0.500 g, 2.3 mmol), CH_3OH (9 mL) and 5 drops of H_2SO_4. The flask was fitted with a reflux condenser and heated to 70 ºC for 12 h. The reaction mixture was diluted in EtOAc, washed with water, sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated to give the product as a white solid (0.335 g, 63%). R_f = 0.40 (ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that

[40] Wittenberger, S. J.; Sonner, B. G. *J. Org. Chem*. **1993**, *58*, 4139.

[41] Chang, D.-J.; Yoon, E.-Y.; Lee, G.-B.; Kim, S.-O.; Kim, Y.-M.; Jung, J.-W.; An, H.; Suh, Y.-G. *Biorg. Med. Chem. Lett.* **2009**, *19*, 4416.

previously reported in the literature.[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.8, 5.1 Hz, 1H), 7.46 (dd, J = 8.8, 3.1 Hz, 1H), 7.05-6.98 (m, 1H), 3.88 (s, 3H).



227

Ethyl 2-bromo-5-(*tert*-butoxycarbonylamino)benzoate (227). To a round-bottomed flask equipped with stir bar was added ethyl 2-bromo-5-aminobenzoate (0.500 g, 2.0 mmol), Et_3N (0.42 mL, 4.8 mmol), and THF (5 mL). Then $(Boc)_2O$ (1.05 g, 4.8 mmol) was added and the mixture was refluxed for 2 h, followed by stirring at rt for 2 h. The mixture was diluted in EtOAc, washed with sat. $NaHCO_3$, H_2O, and dried over Na_2SO_4. Purification by column chromatography (ethyl acetate/hexanes, 1/1) afforded the product as a beige oil (0.41g, 60%). R_f = 0.31 (ethyl acetate/hexanes, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.44-7.36 (m, 2H), 7.22 (d, J = 6.1 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.43 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 128.7, 126.9, 126.7. FTIR (neat) 3342, 2980, 1700, 1521, 1391, 1367, 1226, 1151, 1108, 1055, 1031, 736 cm^{-1}. LRMS Calcd for $C_{14}H_{18}BrNO_4$ M^+: 344.20. Found: 344.

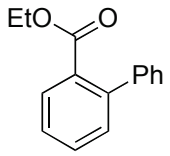
Arylation Products

General Arylation Procedure.

To a microwave vial equipped with a stir bar was added $Pd(OAc)_2$ (5.4 mg, 5 mol %), and Ag_2CO_3 (71 mg, 0.51 equiv). The aryl halide was weighed into a separate vial (0.5 mmol, 1 equiv). The halide was dissolved/mixed in ¼ the amount of arene coupling partner and added to the reaction vessel via syringe. The vial ws then rinsed 3x ¼ the volume of the arene to reach the total reaction volume. The microwave vial was sealed with Teflon cap and stirred at 125 ºC for 16 h. Upon cooling, the reaction was filtered through a silica plug

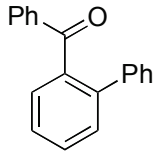
[42] Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **2005**, *70*, 4354.

(ether/hexanes, 1/1). The combined solution was concentrated and the crude mixture was purified via column chromatography to afford the biphenyl products.



192

Ethyl biphenyl-2-carboxylate (2a). The title compound **192** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 1/9) as a clear oil (99.7 mg, 88%). R_f = 0.37 (ethyl acetate/hexanes, 1/9). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.47-7.34 (m, 7H), 4.15 (q, J = 7.1 Hz, 2H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 142.1, 141.2, 131.0, 130.8, 130.2, 129.4, 128.0, 127.6, 126.81, 126.80, 60.6, 13.3. LRMS Calcd for $C_{15}H_{14}O_2$ M^+: 226.27. Found: 226.



200

Biphenyl-2-yl(phenyl)methanone (200). The title compound **200** was prepared according to the general procedure described above (page LXXXV) using (2-bromophenyl)(phenyl)methanone **199** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 1/9) as a clear oil (122.0 mg, 94%). R_f = 0.41 (ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.68 (m, 2H), 7.61 (td, J = 7.4, 1.5 Hz, 1H), 7.57-7.47 (m, 3H), 7.46-7.41 (m, 1H), 7.32-7.28 (m, 4H), 7.25-7.16 (m, 3H). LRMS Calcd for $C_{19}H_{14}O$ M^+: 258.31 Found: 258.

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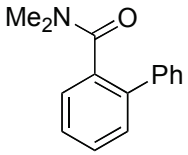
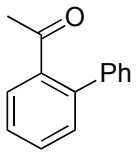
[43] Liu, Q.; Lau, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201.



202

***N*,*N*-Dimethylbiphenyl-2-carboxamide (202).** The title compound **202** was prepared according to the general procedure described above (page LXXXV) using 2-bromo-*N*,*N*-dimethylbenzamide **201** with benzene (100 equiv), and purified by column chromatography (ethyl acetate/benzene, 3/7) as a clear oil (98.0 mg, 87%). R_f = 0.34 (ethyl acetate/hexanes, 1/1). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.29 (m, 9H), 2.81 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 139.9, 138.6, 135.7, 132.6, 129.3, 128.4, 128.3, 127.6, 127.5, 127.3, 37.9, 34.5; LRMS Calcd for $C_{15}H_{15}NO$ M^+: 225.12. Found: 225.

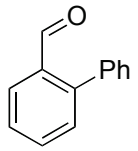


204

1-(Biphenyl-2-yl)ethanone (204). The title compound **204** was prepared according to the general procedure described above (page LXXXV) using (2-bromophenyl)ethanone **203** with benzene (100 equiv), and purified by column chromatography (ethyl acetate/benzene, 1/9) as a clear oil (49.8 mg, 51%). R_f = 0.72 (ethyl acetate/benzene, 1/9). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.52 (m, 2H), 7.48-7.36 (m, 7H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 140.6, 140.4, 140.2, 130.4, 129.9, 128.5, 128.3, 127.54, 127.51, 127.1, 30.1. LRMS Calcd for $C_{14}H_{12}O$ M^+: 196.24 Found: 196.

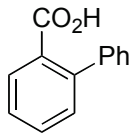
[44] Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, *6*, 4395.

[45] Zeng, F.; Yu, Z. *J. Org. Chem.*, **2006**, *71*, 5274.



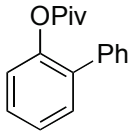
206

Biphenyl-2-carbaldehyde (206). The title compound **206** was prepared according to the general procedure described above (page LXXXV) using 2-bromobenzaldehyde **205** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 1/4) as a while solid (67.0 mg, 74%). R_f = 0.42 (ether/hexanes, 1/4). The observed characterization data (^{1}H, ^{13}C) was consistent with commercially available biphenyl-2-carboxylic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.07-8.04 (d, J = 8.6 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.54-7.40 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 146.8, 138.6, 134.6, 134.4, 131.6, 131.0, 129.3, 129.0, 128.6, 128.4. LRMS Calcd for $C_{13}H_{10}O$ M^+: 182.22. Found: 182.



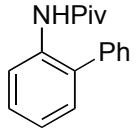
208

Biphenyl-2-carboxylic acid (2g). The title compound **208** was prepared according to the general procedure described above (page LXXXV) using 2-bromobenzoic **207** with benzene (100 equiv), and purified by column chromatography (methanol/dichloromethane, 1/4) as a while solid (41.2 mg, 42%). R_f = 0.82 (methanol/dichloromethane, 1/4). The observed characterization data (^{1}H, ^{13}C) was consistent with commercially available biphenyl-2-carboxylic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 1H), 7.60-7.55 (m, 1H), 7.46-7.36 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 143.2, 140.9, 132.0, 131.1, 130.6, 129.2, 128.3, 128.0, 127.2, 127.1. LRMS Calcd for $C_{13}H_{12}O_2$ M^+: 198.22. Found: 198.



210

Biphenyl-2-yl pivalate (210) The title compound **210** was prepared according to the general procedure described above (page LXXXV) using 2-bromophenyl pivalate **209** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 2/5) as a viscous beige oil (32.0 mg, 25%). R_f = 0.84 (ether/hexanes, 2/5). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 7.38-7.32 (m, 2H), 7.28 (s, 2H), 7.12-7.10 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 175.9, 148.3, 148.0, 137.4, 135.1, 133.2, 130.7, 129.1, 128.6, 128.3, 127.9, 127.3, 127.0, 125.9, 123.6, 122.6, 116.1, 39.2, 38.7, 27.1, 26.9. LRMS Calcd for $C_{17}H_{18}O_2$ M^+: 254.32. Found: 254.



212

***N*-(biphenyl-2-yl)pivalamide (212).** The title compound **212** was prepared according to the general procedure described above (page LXXXV) using *N*-(2-bromophenyl)pivalamide **211** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 1/3) as a viscous beige oil (41.2 mg, 33%). R_f = 0.48 (ether/hexanes, 1/3). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.3 Hz 1H), 7.50-7.32 (m, 7H), 7.24-7.21 (m, 1H), 7.15 (dt, J = 7.3, 1.2 Hz, 1H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 138.0, 135.0, 132.0, 129.6, 129.2, 128.9, 128.4, 127.9, 123.8, 120.7, 39.7, 27.3. LRMS Calcd for $C_{17}H_{19}NO$ M^+: 253.34. Found: 253.

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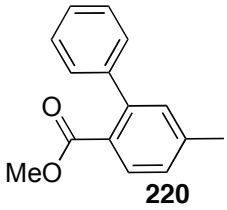
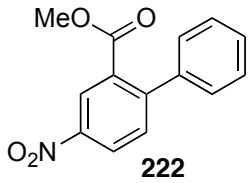
[46] Tomomichi, I.; Mako, O.; Toshiaki, I. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3621.

[47] Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.



220

Methyl 5-methylbiphenyl-2-carboxylate (220). The title compound **220** was prepared according to the general procedure described above (page LXXXV) using methyl 2-bromo-4-methylbenzoate **219** with benzene (100 equiv), and purified by column chromatography (ethyl acetate/benzene, 1/9) as a beige oil (93.0 mg, 82%). R_f = 0.38 (ethyl acetate/benzene, 1/9). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.9 Hz, 1H), 7.46-7.34 (m, 5H), 7.28-7.23 (m, 2H), 3.67 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.7, 142.6, 142.5, 132.5, 131.0, 129.2, 128.8, 128.7, 128.6, 128.0, 52.6, 22.3. LRMS Calcd for $C_{15}H_{14}O_2$ M^+: 226.67. Found: 226.



222

Methyl 4-nitrobiphenyl-2-carboxylate (222). The title compound **222** was prepared according to the general procedure described above (page LXXXV) using methyl 2-bromo-5-nitrobenzoate **221** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 3/7) as a beige solid (122.0 mg, 94%). R_f = 0.38 (ether/hexanes, 3/7). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 8.5, 2.5 Hz 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.48-7.45 (m, 3H), 7.35-7.32 (m, 2H), 3.73 (s, 3H). LRMS Calcd for $C_{14}H_{11}NO_4$ M^+: 257.24. Found: 257.

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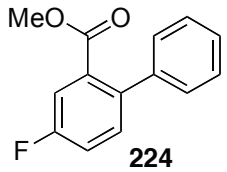
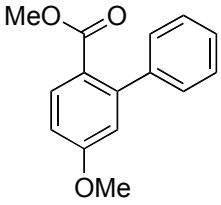
[48] Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

[49] Deng, C.-L.; Guo, S.-M.; Xie, Y.-X.; Li, J.-H. *Eur. J. Org. Chem.* **2007**, 1457.



224

Methyl 4-fluorobiphenyl-2-carboxylate (224). The title compound **224** was prepared according to the general procedure described above (page LXXXV) using methyl 2-bromo-5-fluorobenzoate **223** with benzene (100 equiv), and purified by column chromatography (ether/hexanes, 1/4) as a beige solid (102.3 mg, 89%). R_f = 0.69 (ether/hexanes, 1/4). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[50] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 9.0, 2.7 Hz, 1H), 7.45-7.36 (m, 4H), 7.32-7.23 (m, 3H), 3.68 (s, 3H). LRMS Calcd for $C_{14}H_{11}FO_2$ M^+: 230.23. Found: 230.

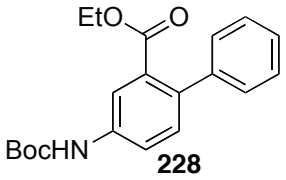


226

Methyl 5-methoxybiphenyl-2-carboxylate (226). The title compound **226** was prepared according to the general procedure described above (page LXXXV) using methyl 2-bromo-4-methoxybenzoate **225** with benzene (100 equiv), and purified by column chromatography (80% DCM in hexanes) as a beige oil (57.6 mg, 48%). R_f = 0.35 (80% DCM in hexanes). The observed characterization data (^{1}H, ^{13}C) was consistent with that previously reported in the literature.[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 7H), 7.11-7.08 (m, 1H), 3.90 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 159.4, 141.9, 135.8, 132.7, 132.6, 129.2, 128.8, 127.7, 118.4, 115.2, 56.4, 52.9. LRMS Calcd for $C_{15}H_{14}O_3$ M^+: 242.27. Found: 242.

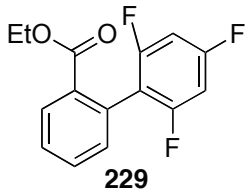
[50] Eli Lilly Patent WO2005/20975 A1, 2005.

[51] Kotnis, A. S. *Tetrahedron Lett.* **1990**, *31*, 481.



228

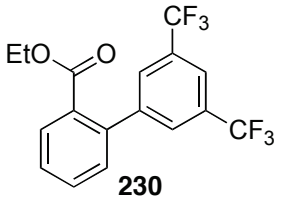
Ethyl 4-(*tert*-butoxycarbonylamino)biphenyl-2-carboxylate (228). The title compound **228** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromo-5-(*tert*-butoxycarbonylamino)benzoate **227** with benzene (100 equiv), and purified by column chromatography (ethyl acetate/hexanes, 1/1) as a beige oil (59.1 mg, 47%). R_f = 0.33 (ethyl acetate/hexanes, 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.66 (m, 2H), 7.41-7.30 (m, 6H), 6.69 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.56 (s, 9H) 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 152.3, 140.7, 137.2, 136.6, 131.4, 131.0, 128.1, 127.6, 126.6, 120.7, 119.1, 80.6, 60.7, 28.0, 13.3. FTIR (neat) 3342, 2979, 2300, 1699, 1586, 1521, 1366, 1308, 1226, 1152, 756 cm^{-1}. LRMS Calcd for $C_{20}H_{23}NO_4$ M^+: 341.40. Found: 341.



229

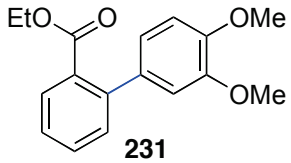
Ethyl 2',4',6'-trifluorobiphenyl-2-carboxylate (229). The title compound **229** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with 1,3,5-trifluorobenzene (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 5/95) as a beige solid (112.0 mg, 80%). R_f = 0.31 (ethyl acetate/benzene, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 6.8 Hz 1H), 7.62 (t, J = 7.6 Hz 1H), 7.54 (t, J = 6.8 Hz 1H), 7.36 (d, J = 7.65 Hz, 1H), 6.77 (t, J = 7.6 Hz, 2H), 4.22 (q, J = 7.4 Hz, 2H), 1.21 (t, J = 7.4 Hz, 3H). LRMS Calcd for $C_{15}H_{11}F_3O_2$ M^+: 280.24. Found: 280.

[52] Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.



230

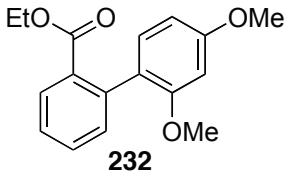
Ethyl 3',5'-bis(trifluoromethyl)biphenyl-2-carboxylate (230). The title compound **230** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with 1,3-(bis)trifluoromethylbenzene (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 5/95) as a beige oil (49.0 mg, 27%). R_f = 0.34 (ethyl acetate/benzene, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz 1H), 7.91 (s, 1H), 7.79 (s, 2H), 7.63 (dt, J = 7.6 Hz, 1.1, 1H), 7.55 (dt, J = 7.6 Hz, 1.1, 1H), 7.37 (d, J = 7.6 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.2, 140.1, 132.3, 131.8, 131.5, 131.1, 131.0, 129.2, 129.1, 123.8 (q, J = 272.7 Hz), 121.3 (m, 3.9 Hz), 61.6, 14.0. FTIR (neat) 2986, 1720, 1379, 1274, 1172, 1126, 1057, 899, 763, 706 cm^{-1}. LRMS Calcd for $C_{17}H_{12}F_6O_2$ M^+: 362.27. Found: 362.



231

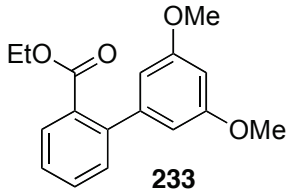
Ethyl 3',4'-dimethoxybiphenyl-2-carboxylate (231). The title compound **231** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with 1,2-anisole (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 15/85) as a beige oil (59.0 mg, 43%). R_f = 0.34 (ethyl acetate/benzene, 15/85). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[53] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.4 Hz, 1H), 7.53 (t, J = 6.3 Hz, 1H), 7.41 (t, J = 6.3 Hz, 2H), 6.94-6.88 (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H). LRMS Calcd for $C_{17}H_{18}O_4$ M^+: 286.32. Found: 286.

[53] Pfizer Inc. US6194439 B1 2001.



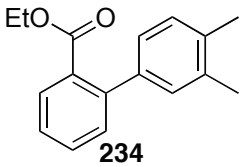
232

Ethyl 2',4'-dimethoxybiphenyl-2-carboxylate (232). The title compound **232** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with 1,3-anisole (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 15/85) as a beige oil (42 mg, 30%). R_f = 0.23 (ethyl acetate/benzene, 15/85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 7.56-7.52 (m, 1H), 7.41-7.37 (m, 1H), 7.33 (dd, J = 7.6, 0.6 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 6.59 (dd, J = 8.3, 2.3 Hz, 1H), 6.51 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 1.11 (t, J = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.9, 157.5, 138.9, 132.5, 131.79, 131.77, 130.7, 129.8, 127.2, 124.0, 104.6, 98.6, 61.0, 55.8, 55.6, 14.4. FTIR (neat) 2937, 2836, 1713, 1610, 1438, 1281, 1254, 1206, 1157, 1032, 764 cm^{-1}. LRMS Calcd for $C_{17}H_{18}O_4$ M^+: 286.32. Found: 286.



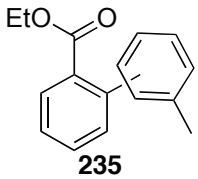
233

Ethyl 3',5'-dimethoxybiphenyl-2-carboxylate (233). The title compound **233** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with 1,3-anisole (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 15/85) as a beige oil (25 mg, 18%). R_f = 0.34 (ethyl acetate/benzene, 15/85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.6, 0.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.45-7.40 (m, 2H), 6.50 (s, 3H), 4.16 (q, J = 7.1 Hz, 2H), 3.82 (s, 6H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 160.8, 143.9, 142.5, 132.0, 131.4, 130.7, 129.9, 127.7, 107.0, 99.9, 61.4, 55.8, 14.2. FTIR (neat) 2937, 2837, 1714, 1591, 1456, 1420, 1287, 1255, 1203, 1126, 1064, 763 cm^{-1}. LRMS Calcd for $C_{17}H_{18}O_4$ M^+: 286.32. Found: 286.



234

Ethyl 3',4'-dimethylbiphenyl-2-carboxylate (234). The title compound **234** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **191** with *o*-xylene (50 equiv), and purified by column chromatography (ethyl acetate/benzene, 5/95) as a beige oil (98.8 mg, 77%). R_f = 0.28 (ethyl acetate/benzene, 5/95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 1H), 7.54 (td, J = 7.5, 1.2 Hz, 1H), 7.48-7.40 (m, 2H), 7.21-7.10 (m, 3H), 4.18 (q, J = 7.1 Hz, 2H), 2.35 (s, 6H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.3, 138.8, 136.0, 135.4, 131.3, 130.9, 130.5, 129.5, 129.4, 129.2, 126.7, 125.7, 60.8, 19.7, 19.4, 13.7. FTIR (neat) 2977, 2937, 1712, 1445, 1288, 1275, 1123, 1086, 1053, 762 cm^{-1}. LRMS Calcd for $C_{17}H_{18}O_2$ M^+: 254.32. Found: 254.



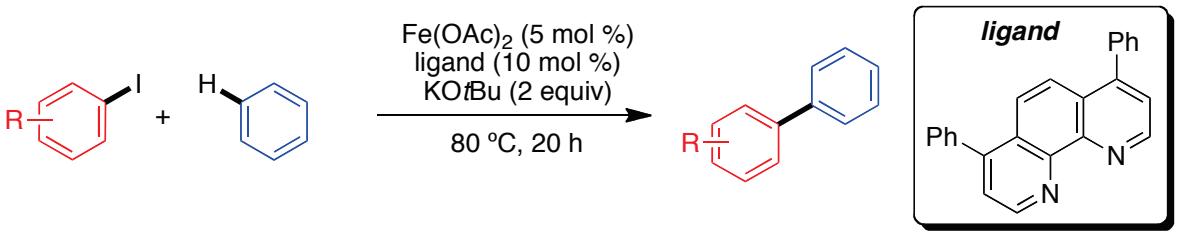
235
0:1:1 *o:m:p*

Ethyl tolylbiphenyl-2-carboxylate (235). The title compound **235** was prepared according to the general procedure described above (page LXXXV) using ethyl 2-bromobenzoate **1a** with toluene (100 equiv), and purified by column chromatography (ethyl acetate/benzene, 15/85) as a beige oil (104.2 mg, 88%). R_f = 0.33 (ethyl acetate/benzene, 15/85). Products determined based on known literature results.[54]

[54] Eli Lilly WO2004/052848 A1 2004.

Experimental Section of Chapter 6

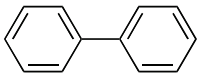
Experimental Procedures and Characterization Data



General procedure for the synthesis of biaryl products

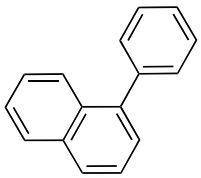
In a drybox under argon atmosphere, to a flame dried microwave vial equipped with a stir bar, was added the $Fe(OAc)_2$ (0.025 mmol, 5 mol %), bathophenanthroline (0.05 mmol, 10 mol %), and crushed dry KO*t*Bu (1.0 mmol, 2 equiv). The vial was then sealed with a septum. To a separate flame dried vial was added the aryl iodide (0.5 mmol, 1 equiv). The vial was subsequently sealed with a septum and purged with argon. The iodide was diluted in the corresponding dried arene (12.5 mmol, 25 equiv) and added to the reaction vessel via syringe. The vial and syringe were then rinsed with the arene (3 x 12.5 mmol, 25 equiv), bringing the total amount of arene added to 100 equiv. The reaction was stirred vigorously at room temperature for 20 min and then at 80 ºC for 20 h. Following cooling, 2 mL of dichloromethane/hexanes (1:1) was added, and the solution was filtered though a silica pad. The pad was then rinsed with 15 mL of dichloromethane/hexanes (1:1). The combined

solution was concentrated and the crude mixture was purified via column chromatography to afford the biphenyl products.



236

Biphenyl (236). The title compound **236** was prepared according to the general procedure described above (page XCVI) using iodobenzene with benzene, and purified by column chromatography (hexanes, 100%) as a white solid (75 mg, 89%). R_f = 0.37 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[55,56] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.50 (m, 4H), 7.47 (t, J = 7.6 Hz, 4H), 7.43-7.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 128.7, 126.9, 126.7. LRMS Calcd for $C_{12}H_{10}$ M^+: 154.08. Found: 154.



237

1-Phenylnaphthalene (237). The title compound **237** was prepared according to the general procedure described above (page XCVI) using 1-iodonapthalene with benzene, and purified by preparative HPLC (ZORBAX Eclipse XDB-C18, 50:50 MeOH:H_2O over 20 min at 20 mL/min, go to 90:10 MeOH:H_2O over 4 min at 30 mL/min *rt* = 26.50 min) as a colourless oil (61.7 mg, 60%). R_f = 0.31 (100% hexanes). The observed characterization data (^{1}H) was consistent with that previously reported in the literature. [57, 58, 59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, J = 6.3 Hz, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.60-7.54 (m, 6H),

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[55] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc*. **2006**, *128*, 16496.

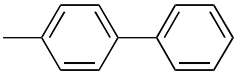
[56] S. Proch, R. Kempe, *Angew. Chem. Int. Ed.* **2007**, *46*, 3135; *Angew. Chem.* **2007**, *119*, 3196.

[57] M. Kuriyama, R. Shimazawa, R. Shirai, *Tetrahedron* **2007**, *63*, 9393.

[58] P. D. Stevens, J. Fan, H. M. R. Gardimalla, M. Yen, Y. Gao, *Org. Lett.* **2005**, *7*, 2085.

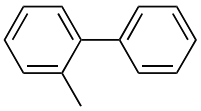
[59] A. C. Spivey, C.-C. Tseng, J. P. Hannah, C. J. G. Gripton, P. de Fraine, N. J. Parr, Scicinski, J. J. *Chem. Commun.* **2007**, 2926.

7.53-7.45 (m, 3H).[13]C NMR (75 MHz, $CDCl_3$) δ 141.7, 141.2, 134.7, 132.5, 131.0, 129.2, 128.6, 128.1, 127.8, 127.0, 126.7, 126.3. LRMS Calcd for $C_{16}H_{12}$ M^+: 204.08. Found: 204.



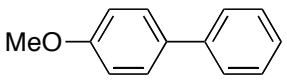
238

4-Methylbiphenyl (238). The title compound **238** was prepared according to the general procedure described above (page XCVI) using 4-iodotoluene with benzene, and purified by column chromatography (hexanes, 100%) as a white solid (75.3 mg, 86%). R_f = 0.45 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[57, 58, 60, 61] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 6.7 Hz, 2H), 7.59 (d, J = 8.3 Hz 2H), 7.51 (t, J = 7.9, 2H), 7.43-7.36 (m, 1H), 7.33 (d, J = 7.9 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 138.7, 137.3, 129.8, 129.1, 127.3, 21.3. LRMS Calcd for $C_{13}H_{12}$ M^+: 168.09. Found: 168.



239

2-Methylbiphenyl (239). The title compound **239** was prepared according to the general procedure described above (page XCVI) using 2-iodotoluene with benzene, and purified by preparative HPLC (ZORBAX Eclipse XDB-C18, 50:50 MeOH: H_2O over 20 min at 20 mL/min, go to 90:10 MeOH:H_2O over 4 min at 30 mL/min *rt* = 25.60 min) as a colorless oil (69.8 mg, 80%). R_f = 0.41 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[57, 58, 60] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 7.7 Hz, 2H), 7.39-7.30 (m, 3H), 7.22-7.27 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.32, 142.26, 135.7, 130.7, 130.1, 129.6, 128.5, 127.6, 127.2, 126.1, 20.1. LRMS Calcd for $C_{13}H_{12}$ M^+: 168.09. Found: 168.

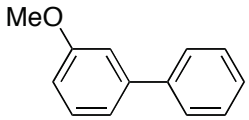


240

[60] K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2005**, *7*, 2229.

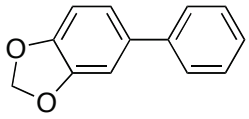
[61] L. Zhang, J. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 12250.

4-Methoxybiphenyl (240). The title compound **240** was prepared according to the general procedure described above (page XCVI) using 4-iodoanisole with benzene, and purified by column chromatography (hexanes, 100%) as a white solid (89.2 mg, 93%). R_f = 0.14 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[57, 58, 60, 61] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (t, J = 7.6 Hz, 4H), 7.48 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 6.9 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 141.2, 134.1, 129.1, 128.5, 127.1, 127.0, 114.5, 55.7. LRMS Calcd for $C_{13}H_{12}O$ M^+: 184.09. Found: 184.



241

3-Methoxybiphenyl (241). The title compound **241** was prepared according to the general procedure described above (page XCVI) using 3-iodoanisole with benzene, and purified by column chromatography (hexanes, 100%) as a colorless oil (83.8 mg, 88%). R_f = 0.14 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[55, 60] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.40 (m, 2H), 7.25-7.15 (m, 2H), 6.94 (dd, J = 8.2, 2.5 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 143.1, 141.4, 130.0, 129.0, 127.7, 127.5, 120.0, 113.2, 113.8, 55.6. LRMS Calcd for $C_{13}H_{12}O$ M^+: 184.09. Found: 184.

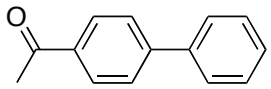


242

1-Phenyl-3,4-methylenedioxybenzene (242). The title compound **242** was prepared according to the general procedure described above (page XCVI) using 1-iodo-3,4-methylenedioxybenzene with benzene, and purified by column chromatography (hexanes/ ether, 9/1) as a cream colored solid (74.8 mg, 72%). R_f = 0.15 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[62] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H),7.44 (t, J = 7.7 Hz, 2H),

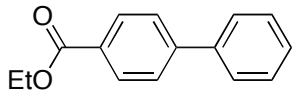
[62] C. M. So, H. W. Lee, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2009**, *11*, 371.

7.38-7.31 (m, 1H), 7.10 (d, J = 7.7 Hz, 2H), 6.92 (d, J = 7.7 Hz, 1H), 6.02 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.0, 141.8, 136.5, 129.7, 127.79, 127.76, 121.5, 109.5, 108.6, 102.0. LRMS Calcd for $C_{13}H_{10}O_2$ M^+: 198.07. Found: 198.



243

4-Acetyl-biphenyl (243). The title compound **243** was prepared according to the general procedure described above (page XCVI) using 4'-iodoacetophenone with benzene, and purified by column chromatography (hexanes, 100% to hexanes/ether, 80/20) as a cream colored solid (64.5 mg, 69%). R_f = 0.32 (hexanes/ether, 80/20). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[63] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.51-7.40 (m, 3H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 146.3, 140.3, 136.2, 129.3, 129.2, 128.5, 127.6, 127.5, 27.0; LRMS Calcd for $C_{14}H_{12}O$ M^+: 196.07. Found: 196.



244

Ethyl 4-phenylbenzoate (244). The title compound **244** was prepared according to the general procedure described above (page XCVI) using ethyl 4-iodobenzoate with benzene, and purified by column chromatography (hexanes/ether, 9:1) as yellow solid (47.6 mg, 40%). R_f = 0.34 (hexanes/ether, 9:1). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[64, 65, 66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.3 Hz, 2H), 7.72-7.60 (m, 4H), 7.48 (t, J = 7.4 Hz, 2H), 7.41 (t, J =

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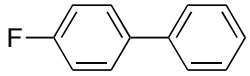
[63] A. R. Hajipour, S. E. Mallakpour, I. M. Baltork, H. Adibi, *Syn. Commun.*, **2001**, *31*, 1625.

[64] K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2005**, *7*, 2229.

[65] L. Zhang, J. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 12250.

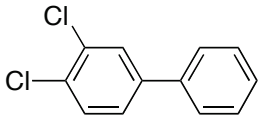
[66] K. Inamoto, J. Kuroda, K. Hiroya, Y. Noda, M. Watanabe, T. Sakamoto, *Organometallics* **2006**, *25*, 3095.

C
7.5 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.6 Hz 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 146.1, 140.5, 130.4, 129.5, 129.2, 128.4, 127.6, 127.3, 61.3, 14.7. LRMS Calcd for $C_{15}H_{14}O_2$ M^+: 226.1. Found: 226.



245

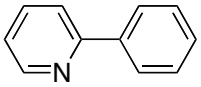
4-Fluorobiphenyl (245). The title compound **245** was prepared according to the general procedure described above (page XCVI) using 1-fluoro-4-iodobenzene with benzene, and purified by column chromatography (hexanes, 100%) as a white solid (81.8 mg, 86%). R_f = 0.42 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[67] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.56 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.40 (m, 1H), 7.18 (t, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.1, 140.6, 137.7, 137.6, 129.1 (t, J = 8.0 Hz), 127.4 (d, J = 18.8 Hz), 115.9 (d, J = 22.2 Hz).



246

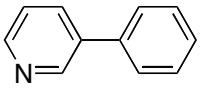
3,4-Dichlorobiphenyl (246). The title compound **246** was prepared according to the general procedure described above (page XCVI) using 3,4-dichloroiodobenzene with benzene, and purified by column chromatography (hexanes, 100%), (59.6 mg, 53%). R_f = 0.53 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[65] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.60-7.38 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 139.1, 133.2, 131.7, 131.0, 129.32, 129.27, 128.4, 127.3, 126.7; LRMS Calcd for $C_{12}H_8Cl_2$ M^+: 223.1. Found: 223.

[67] J. Lemo, K. Heuze, D. Astruc, *Org. Lett.*, **2005**, *7*, 2253.



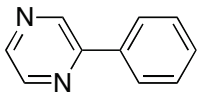
247

2-Phenylpyridine (247). The title compound **247** was prepared according to the general procedure described above (page XCVI) using 2-iodopyridine with benzene, and purified by column chromatography (dichloromethane/ether, 80/20) as colorless oil (75.4 mg, 85%). R_f = 0.50 (dichloromethane/ether, 90/10). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (td, J = 4.9, 1.5 Hz 1H), 8.02 (dd, J = 7.2, 1.5 Hz 2H), 7.78-7.72 (m, 2H), 7.49-7.43 (m, 3H), 7.26-7.20 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 150.6, 140.3, 137.6, 129.9, 129.7, 127.8, 123.0, 121.5. LRMS Calcd for $C_{11}H_9N$ M^+: 155.07. Found: 155.



248

3-Phenylpyridine (248). The title compound **248** was prepared according to the general procedure described above (page XCVI) using 3-iodopyridine with benzene, and purified by column chromatography (dichloromethane/ether, 80/20) as yellow oil (68.8 mg, 85%). R_f = 0.20 (dichloromethane/ether, 90/10). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[57, 60, 68] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.60 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.51-7.45 (m, 2H), 7.44-7.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 148.7, 138.1, 136.9, 134.7, 129.4, 128.4, 127.5, 123.9. LRMS Calcd for $C_{11}H_9N$ M^+: 155.07. Found: 155.

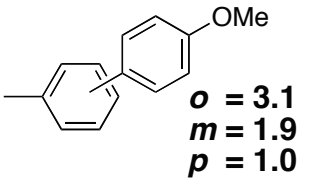


249

2-Phenylpyrazine (249). The title compound **249** was prepared according to the general procedure described above (page XCVI) using iodopyrazine with benzene, and purified by column chromatography (dichloromethane/ether, 80/20) as a cream solid (59.0 mg, 79%). R_f = 0.34 (dichloromethane/ether, 90/10). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[68] ^{1}H NMR (400 MHz, $CDCl_3$) δ

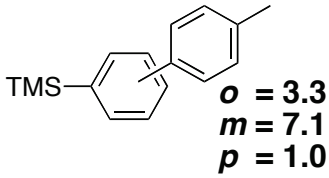
[68] A. Núñez, A. Sánchez, C. Burgos, J. A-Builla *Tetrahedron* **2004**, *60*, 6217.

9.05 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.04-8.01 (m, 2H), 7.56-7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 144.5, 143.3, 142.6, 136.7, 130.3, 129.4, 127.3. LRMS Calcd for $C_{10}H_8N_2$ M^+: 156.07. Found: 156 (M+).



250

Mixture of 4'-methoxy-2-methylbiphenyl, 4'-methoxy-3-methylbiphenyl, 4'-methoxy-2-methylbiphenyl (250). The title compound **250** was prepared according to the general procedure described above (page XCVI) using 4-iodoanisole with toluene, and purified by column chromatography (5% ethyl ether/hexanes) as colorless oil (49.5 mg, 50%). R_f = 0.40 (ethyl ether/hexanes, 5/95). HRMS Calcd for $C_{14}H_{14}O$ M^+: 198.10392. Found: 198.10394 (M+).



251

Mixture of Trimethyl(4'-methylbiphenyl-4-yl)silane, Trimethyl(4'-methylbiphenyl-3-yl)silane, Trimethyl(4'-methylbiphenyl-2-yl)silane (251). The title compound **251** was prepared according to the general procedure described above (page XCVI) using 4-iodotoluene with phenyltrimethylsilane, and purified by column chromatography (hexanes, 100%) as colorless oil (26.3 mg, 28%). R_f = 0.20 (hexanes, 100%). Trimethyl(4'-methylbiphenyl-4-yl)silane: trimethyl(4'-methylbiphenyl-3-yl)silane: trimethyl(4'-methylbiphenyl-2-yl)silane = 2.0: 1.4: 1.0, The ratio of the regioisomers was determined by ^{1}H NMR.[69,70] HRMS Calcd for $C_{14}H_{14}O$ M^+: 240.13288. Found: 240.13299 (M+).

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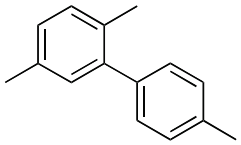
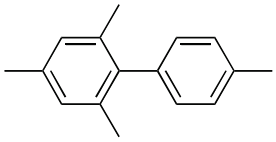
[69] Kaufmann, D. *Chem. Ber.* **1987**, *120*, 901. (*o*- and *p*- compounds)

[70] Ogawa. S.; Tajiri. Y.; Furukawa. N. *Bull. Chem. Soc. Jnp.* **1991**, *64*, 3182. (*m*-compound)



252

2,4',5-Trimethyl biphenyl (252). The title compound **252** was prepared according to the general procedure described above (page XCVI) using 4-iodotoluene with *p*-xylene, and purified by column chromatography (hexanes, 100%) as colorless oil (76.3 mg, 81%). R_f = 0.48 (hexanes, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 4H), 7.18, (d, J = 7.9 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H), 2.26 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 139.5, 136.6, 135.5, 132.6, 131.0, 130.6, 129.1, 128.1, 127.8, 126.7 21.5, 21.3, 20.4; LRMS Calcd for $C_{15}H_{16}$ M^+: 196.13. Found: 196 (M+).



253

2,4,4',6-Tetramethylbiphenyl (253). The title compound **253** was prepared according to the general procedure described above (page XCVI) using 4-iodotoluene with mesitylene, and purified by column chromatography (pentane, 100%) as colorless oil (64.0 mg, 63%). R_f = 0.24 (pentane, 100%). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[72] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.7 Hz, 2H), 7.04, (d, J = 7.7 Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 2.02 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 138.3, 136.8, 136.5, 136.3, 129.5, 129.4, 128.4, 21.6, 21.4, 20.1. LRMS Calcd for $C_{16}H_{18}$ M^+: 210.14. Found: 210 (M+).

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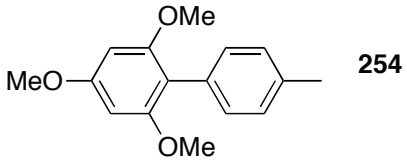
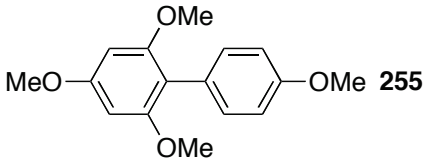
[71] Warner, K. F.; Bachrach, A.; Rehman, A.-u; Schnatter, W. F. K.; Mitra, A.; Shimanskas, C. *J. Chem. Research (S)*, **1998**, 814.

[72] Limmert, M. E.; Roy, A. H; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.



254

2,4,6-trimethoxy-4'-methylbiphenyl (254). The title compound **254** was prepared according to the general procedure described above (page XCVI) using 4-iodotoluene with 1,3,5-trimethoxybenzene, and purified by column chromatography (ethyl ether/hexanes, 1/9) as colorless oil (34.0 mg, 54%). R_f = 0.38 (ethyl ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[73] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 4H), 6.24, (s, 2H), 3.88 (s, 3H), 3.74 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 158.7, 136.4, 131.35, 131.29, 112.7, 91.2, 56.2, 55.7, 21.7. LRMS Calcd for $C_{16}H_{18}O_3$ M^+: 258.13. Found: 258 (M+).



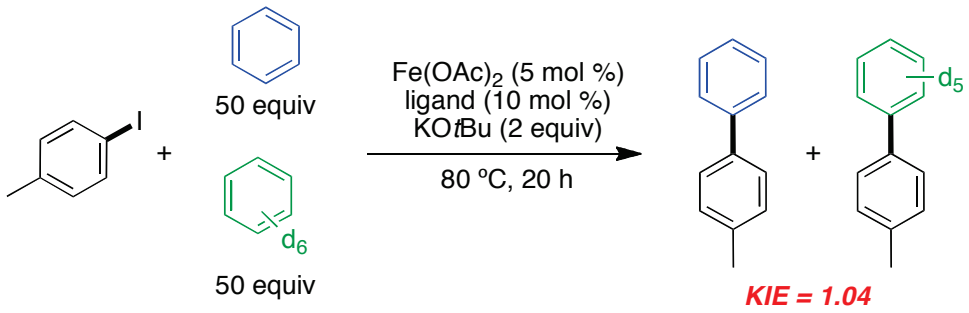
255

2,4,4',6-tetramethoxybiphenyl (255). The title compound **255** was prepared according to the general procedure described above (page XCVI) using 4-iodoanisole with 1,3,5-trimethoxybenzene, and purified by column chromatography (ethyl ether/hexanes, 1/9) as colorless oil (28.3 mg, 54%). R_f = 0.28 (ethyl ether/hexanes, 1/9). The observed characterization data (^{1}H) was consistent with that previously reported in the literature.[74] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.9 Hz, 2H), 7.26, (d, J = 8.9 Hz, 2H), 6.24 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 158.7, 132.5, 126.5, 113.6, 112.3, 91.2, 56.2, 55.7, 55.4. LRMS Calcd for $C_{16}H_{18}O_4$ M^+: 274.12. Found: 274 (M+).

[73] Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607.

[74] Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.*, **2007**, *7*, 1781.

Kinetic Isotope Experiments[75]

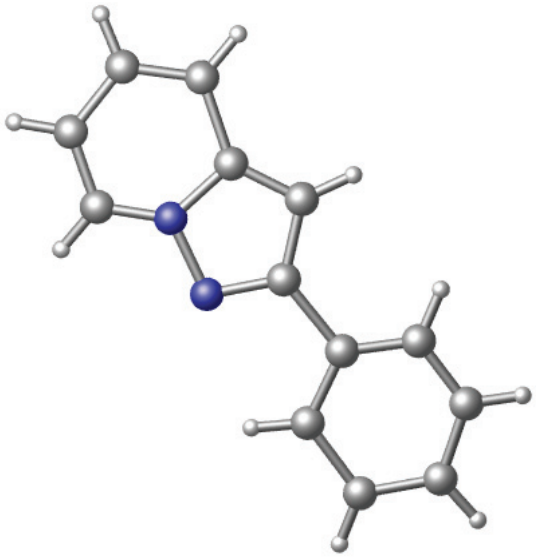


KIE study using benzene as the reagent. The reaction was performed with a modification of the general procedure using a 1:1 mixture of benzene and benzene-*d*6 (50 mmol each). The crude mixture was purified via column chromatography to afford the biphenyl product. The kinetic isotope was determined through integration of the proton at the C2 position of the benzene ring and the d1 of the ^{1}H NMR pulse sequence was set at 10 s to ensure maximum relaxation.[76] The protons of the C2 of the tolyl ring were chosen as calibration.

[75] For similar study see: Campeau, L. C.; Rousseaux, S.; Fagnou, K., *J. Am. Chem. Soc.* **2005,** *127*, 18020.

[76] KIE determined as follows: 1.02/0.98 = 1.04.

Annex 2 : Crystal and Molecular Structure of molecule 155



Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C13 H10 N2 COMPOUND (cha197)

Equipe Charette

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C.P. 6128, Succ. Centre-Ville, Montréal, Québec, H3C 3J7 (Canada)

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 C13 H10 N2.

Identification code	cha197
Empirical formula	C13 H10 N2
Formula weight	194.23
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	Pna21
Unit cell dimensions	a = 15.86(3) Å $\alpha = 90^\circ$ b = 10.73(2) Å $\beta = 90^\circ$ c = 5.8704(12) Å $\gamma = 90^\circ$
Volume	999.0(4)Å^3
Z	4
Density (calculated)	1.291 g/cm^3
Absorption coefficient	0.609 mm^{-1}
F(000)	408
Crystal size	0.12 x 0.03 x 0.03 mm
Theta range for data collection	4.98 to 67.62°
Index ranges	$-18 \leq h \leq 18$, $-11 \leq k \leq 12$, $-6 \leq \ell \leq 4$
Reflections collected	15715
Independent reflections	980 [R_{int} = 0.099]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9819 and 0.4709
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	980 / 91 / 136
Goodness-of-fit on F^2	1.574
Final R indices [I>2sigma(I)]	R_1 = 0.1200, wR_2 = 0.3536
R indices (all data)	R_1 = 0.1578, wR_2 = 0.3807
Largest diff. peak and hole	0.808 and -0.296 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C13 H10 N2.

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

	x	y	z	U_{eq}
N(1)	6868(5)	4961(7)	10745(19)	63(2)
N(2)	6297(6)	5968(8)	11008(19)	78(3)
C(1)	5881(5)	5982(8)	9072(18)	49(2)
C(2)	6149(8)	5081(8)	7520(20)	73(3)
C(3)	6755(6)	4481(10)	8600(20)	64(3)
C(4)	7336(6)	3388(9)	8030(20)	66(3)
C(5)	7879(6)	3052(9)	9662(19)	55(2)
C(6)	7898(7)	3681(9)	11750(20)	69(3)
C(7)	7397(7)	4658(9)	12220(20)	71(3)
C(11)	5209(6)	7031(9)	8750(20)	63(3)
C(12)	5119(6)	7860(12)	10520(20)	80(4)
C(13)	4479(6)	8872(10)	10320(20)	69(3)
C(14)	4035(6)	8886(10)	8310(20)	65(3)
C(15)	4198(6)	7996(9)	6690(20)	70(3)
C(16)	4783(7)	7114(10)	6880(30)	79(3)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C13 H10 N2.

	x	y	z	U_{eq}
H(2)	5943	4934	6022	87
H(4)	7314	2972	6606	79
H(5)	8256	2379	9399	66
H(6)	8281	3404	12890	83
H(7)	7443	5099	13621	85
H(12)	5458	7788	11848	96
H(13)	4386	9464	11495	83
H(14)	3620	9507	8041	78
H(15)	3869	8011	5336	84
H(16)	4886	6554	5654	95

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C13 H10 N2.

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
N(1)	62(4)	52(4)	75(5)	-10(4)	11(5)	8(4)
N(2)	90(5)	78(5)	66(6)	-3(5)	7(5)	-16(5)
C(1)	53(4)	46(4)	48(5)	-5(4)	-3(4)	-13(4)
C(2)	80(6)	66(5)	72(6)	-10(5)	0(6)	-13(5)
C(3)	44(4)	72(5)	78(6)	36(6)	-14(5)	-5(4)
C(4)	60(5)	65(5)	72(7)	-4(5)	8(5)	-10(4)
C(5)	54(4)	49(5)	61(6)	-3(4)	-2(5)	9(4)
C(6)	68(5)	60(5)	79(7)	0(5)	8(5)	0(5)
C(7)	74(6)	59(5)	80(6)	-6(5)	-5(6)	10(5)
C(11)	54(5)	51(5)	84(7)	-8(5)	11(5)	-5(4)
C(12)	61(5)	108(7)	71(7)	45(6)	-23(5)	-24(5)
C(13)	67(5)	67(5)	75(7)	1(5)	1(5)	8(5)
C(14)	49(4)	67(5)	78(7)	2(5)	-7(5)	1(4)
C(15)	60(5)	65(5)	86(7)	-6(5)	-10(6)	0(5)
C(16)	83(6)	64(6)	91(7)	-8(6)	-3(6)	8(5)

Table 5. Bond lengths [Å] and angles [°] for C13 H10 N2

N(1)-C(7)	1.250(15)	N(2)-C(1)-C(2)	113.9(9)
N(1)-C(3)	1.374(17)	N(2)-C(1)-C(11)	117.2(9)
N(1)-N(2)	1.418(13)	C(2)-C(1)-C(11)	128.8(1)
N(2)-C(1)	1.315(15)	C(3)-C(2)-C(1)	104.2(12)
C(1)-C(2)	1.396(15)	C(2)-C(3)-N(1)	110.7(11)
C(1)-C(11)	1.562(13)	C(2)-C(3)-C(4)	135.2(12)
C(2)-C(3)	1.319(15)	N(1)-C(3)-C(4)	114.0(8)
C(3)-C(4)	1.528(14)	C(5)-C(4)-C(3)	116.2(1)
C(4)-C(5)	1.336(15)	C(4)-C(5)-C(6)	120.7(9)
C(5)-C(6)	1.402(18)	C(7)-C(6)-C(5)	122.9(12)
C(6)-C(7)	1.344(15)	N(1)-C(7)-C(6)	117.2(13)
C(11)-C(16)	1.292(19)	C(16)-C(11)-C(12)	122.9(1)
C(11)-C(12)	1.377(17)	C(16)-C(11)-C(1)	120.7(1)
C(12)-C(13)	1.491(16)	C(12)-C(11)-C(1)	116.3(1)
C(13)-C(14)	1.375(18)	C(11)-C(12)-C(13)	118.8(1)
C(14)-C(15)	1.371(16)	C(14)-C(13)-C(12)	115.1(11)
C(15)-C(16)	1.330(13)	C(15)-C(14)-C(13)	119.4(9)
		C(16)-C(15)-C(14)	124.7(12)
C(7)-N(1)-C(3)	128.9(9)	C(11)-C(16)-C(15)	119(12)
C(7)-N(1)-N(2)	123.4(11)		
C(3)-N(1)-N(2)	107.6(9)		
C(1)-N(2)-N(1)	103.6(9)		

Table 6. Torsion angles [°] for C13 H10 N2.

C(7)-N(1)-N(2)-C(1)	178.3(1)	N(2)-N(1)-C(7)-C(6)	179.8(1)
C(3)-N(1)-N(2)-C(1)	1.9(1)	C(5)-C(6)-C(7)-N(1)	3.6(17)
N(1)-N(2)-C(1)-C(2)	-1.7(11)	N(2)-C(1)-C(11)-C(16)	179.1(11)
N(1)-N(2)-C(1)-C(11)	-177.9(7)	C(2)-C(1)-C(11)-C(16)	3.5(16)
N(2)-C(1)-C(2)-C(3)	0.8(12)	N(2)-C(1)-C(11)-C(12)	0.7(12)
C(11)-C(1)-C(2)-C(3)	176.5(9)	C(2)-C(1)-C(11)-C(12)	-174.8(1)
C(1)-C(2)-C(3)-N(1)	0.5(11)	C(16)-C(11)-C(12)-C(13)	2.4(16)
C(1)-C(2)-C(3)-C(4)	179.5(1)	C(1)-C(11)-C(12)-C(13)	-179.3(8)
C(7)-N(1)-C(3)-C(2)	-177.6(11)	C(11)-C(12)-C(13)-C(14)	-0.7(14)
N(2)-N(1)-C(3)-C(2)	-1.5(11)	C(12)-C(13)-C(14)-C(15)	0.6(14)
C(7)-N(1)-C(3)-C(4)	3.1(15)	C(13)-C(14)-C(15)-C(16)	-2.1(17)
N(2)-N(1)-C(3)-C(4)	179.3(7)	C(12)-C(11)-C(16)-C(15)	-3.8(18)
C(2)-C(3)-C(4)-C(5)	-179.6(11)	C(1)-C(11)-C(16)-C(15)	178.0(9)
N(1)-C(3)-C(4)-C(5)	-0.7(12)	C(14)-C(15)-C(16)-C(11)	3.7(18)
C(3)-C(4)-C(5)-C(6)	0.1(14)		
C(4)-C(5)-C(6)-C(7)	-1.6(17)		
C(3)-N(1)-C(7)-C(6)	-4.6(17)		

ORTEP view of the C13 H10 N2 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

REFERENCES

Flack, H.D. (1983). Acta Cryst. A39, 876-881.

Flack, H.D. and Schwarzenbach, D. (1988). Acta Cryst. A44, 499-506.

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.

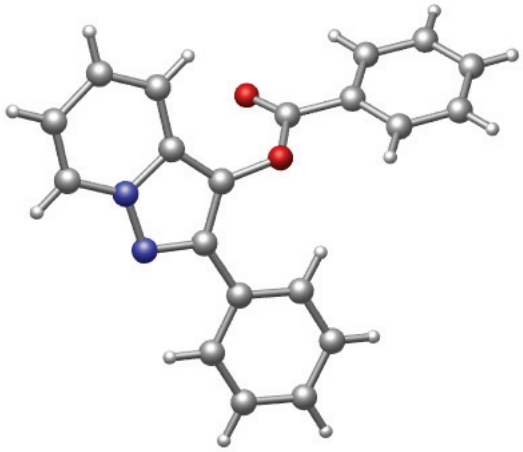
APEX2 (2009) ; Bruker Molecular Analysis Research Tool. Bruker AXS Inc., Madison, WI 53719-1173.

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 (2008) Version 2008/2; X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.

Annex 3 : Crystal and Molecular Structure of 2-Phenylpyrazolo[1,5-a]pyridin-3-yl acetate.



Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C20 H14 N2 O2 COMPOUND (cha195)

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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 C20 H14 N2 O2.

Identification code	cha195
Empirical formula	C20 H14 N2 O2
Formula weight	314.33
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 3.9864(3) Å $\alpha = 90^\circ$ b = 21.6026(15) Å $\beta = 93.004(5)^\circ$ c = 17.7499(14) Å $\gamma = 90^\circ$
Volume	1526.5(2)Å^3
Z	4
Density (calculated)	1.368 g/cm^3
Absorption coefficient	0.724 mm^{-1}
F(000)	656
Crystal size	0.15 x 0.05 x 0.03 mm
Theta range for data collection	3.22 to 67.39°
Index ranges	$-3 \leq h \leq 4$, $-25 \leq k \leq 25$, $-21 \leq \ell \leq 21$
Reflections collected	23109
Independent reflections	2728 [R_{int} = 0.064]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9785 and 0.6860
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2728 / 0 / 217
Goodness-of-fit on F^2	1.098
Final R indices [I>2sigma(I)]	R_1 = 0.0586, wR_2 = 0.1396
R indices (all data)	R_1 = 0.0724, wR_2 = 0.1519
Largest diff. peak and hole	0.275 and -0.412 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C20 H14 N2 O2.

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

	x	y	z	U_{eq}
N(1)	2175(4)	5980(1)	4899(1)	38(1)
N(2)	4015(4)	5861(1)	5543(1)	40(1)
C(3)	4008(5)	6400(1)	5941(1)	38(1)
C(4)	2139(5)	6846(1)	5528(1)	38(1)
C(5)	950(5)	6583(1)	4859(1)	38(1)
C(6)	-1016(5)	6762(1)	4215(1)	42(1)
C(7)	-1694(5)	6342(1)	3656(1)	46(1)
C(8)	-418(5)	5727(1)	3728(1)	46(1)
C(9)	1479(5)	5555(1)	4343(1)	43(1)
O(10)	1352(4)	7437(1)	5786(1)	41(1)
C(11)	2491(5)	7934(1)	5400(1)	39(1)
O(11)	4019(4)	7892(1)	4843(1)	53(1)
C(12)	1611(5)	8522(1)	5778(1)	39(1)
C(13)	20(5)	8535(1)	6453(1)	44(1)
C(14)	-670(6)	9098(1)	6791(1)	51(1)
C(15)	269(6)	9645(1)	6447(2)	56(1)
C(16)	1858(6)	9631(1)	5781(2)	54(1)
C(17)	2531(5)	9075(1)	5435(1)	47(1)
C(18)	5746(5)	6435(1)	6685(1)	39(1)
C(19)	7465(6)	5918(1)	6980(1)	46(1)
C(20)	9075(6)	5934(1)	7682(1)	51(1)
C(21)	9036(6)	6463(1)	8122(1)	51(1)
C(22)	7331(6)	6980(1)	7837(1)	52(1)
C(23)	5737(6)	6969(1)	7131(1)	45(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C20 H14 N2 O2.

	x	y	z	U_{eq}
H(6)	-1864	7172	4170	50
H(7)	-3017	6459	3219	55
H(8)	-913	5436	3337	55
H(9)	2320	5144	4388	51
H(13)	-600	8159	6685	53
H(14)	-1772	9109	7253	62
H(15)	-195	10031	6675	67
H(16)	2505	10008	5555	64
H(17)	3606	9068	4970	57
H(19)	7520	5549	6689	55
H(20)	10234	5577	7868	62
H(21)	10150	6472	8609	61
H(22)	7267	7346	8132	62
H(23)	4612	7329	6943	54

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C20 H14 N2 O2.

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
N(1)	52(1)	17(1)	47(1)	-1(1)	8(1)	0(1)
N(2)	55(1)	19(1)	46(1)	0(1)	7(1)	0(1)
C(3)	51(1)	19(1)	47(1)	0(1)	13(1)	-1(1)
C(4)	53(1)	15(1)	47(1)	-2(1)	11(1)	1(1)
C(5)	50(1)	16(1)	49(1)	0(1)	12(1)	1(1)
C(6)	54(1)	23(1)	49(1)	1(1)	8(1)	2(1)
C(7)	54(1)	35(1)	50(1)	-1(1)	5(1)	3(1)
C(8)	57(1)	28(1)	54(1)	-8(1)	8(1)	-4(1)
C(9)	56(1)	20(1)	53(1)	-6(1)	10(1)	-1(1)
O(10)	59(1)	15(1)	49(1)	-1(1)	12(1)	3(1)
C(11)	53(1)	20(1)	43(1)	2(1)	4(1)	1(1)
O(11)	81(1)	24(1)	55(1)	0(1)	23(1)	0(1)
C(12)	49(1)	21(1)	45(1)	-1(1)	-4(1)	3(1)
C(13)	54(1)	29(1)	49(1)	-4(1)	-1(1)	6(1)
C(14)	55(1)	40(1)	58(1)	-15(1)	-3(1)	11(1)
C(15)	56(1)	28(1)	81(2)	-18(1)	-13(1)	9(1)
C(16)	59(1)	20(1)	81(2)	-2(1)	-6(1)	0(1)
C(17)	56(1)	23(1)	62(1)	3(1)	0(1)	1(1)
C(18)	50(1)	22(1)	46(1)	3(1)	11(1)	-1(1)
C(19)	58(1)	27(1)	52(1)	1(1)	8(1)	2(1)
C(20)	60(1)	38(1)	57(1)	10(1)	6(1)	4(1)
C(21)	55(1)	49(1)	48(1)	4(1)	4(1)	-4(1)
C(22)	65(1)	39(1)	53(1)	-7(1)	9(1)	-2(1)
C(23)	58(1)	27(1)	51(1)	-1(1)	8(1)	0(1)

Table 5. Bond lengths [Å] and angles [°] for C20 H14 N2 O2

N(1)-N(2)	1.350(2)	C(4)-C(3)-C(18)	130.67(16)
N(1)-C(9)	1.366(2)	C(5)-C(4)-O(10)	125.83(17)
N(1)-C(5)	1.393(2)	C(5)-C(4)-C(3)	108.55(16)
N(2)-C(3)	1.361(2)	O(10)-C(4)-C(3)	125.35(18)
C(3)-C(4)	1.402(3)	C(4)-C(5)-N(1)	103.71(17)
C(3)-C(18)	1.460(3)	C(4)-C(5)-C(6)	137.77(17)
C(4)-C(5)	1.377(3)	N(1)-C(5)-C(6)	118.52(17)
C(4)-O(10)	1.399(2)	C(7)-C(6)-C(5)	119.41(18)
C(5)-C(6)	1.406(3)	C(6)-C(7)-C(8)	120.0(2)
C(6)-C(7)	1.360(3)	C(9)-C(8)-C(7)	120.9(2)
C(7)-C(8)	1.425(3)	C(8)-C(9)-N(1)	118.93(18)
C(8)-C(9)	1.347(3)	C(11)-O(10)-C(4)	117.94(15)
O(10)-C(11)	1.363(2)	O(11)-C(11)-O(10)	123.69(16)
C(11)-O(11)	1.192(2)	O(11)-C(11)-C(12)	125.57(17)
C(11)-C(12)	1.487(3)	O(10)-C(11)-C(12)	110.74(16)
C(12)-C(13)	1.385(3)	C(13)-C(12)-C(17)	120.15(18)
C(12)-C(17)	1.397(3)	C(13)-C(12)-C(11)	122.43(17)
C(13)-C(14)	1.390(3)	C(17)-C(12)-C(11)	117.40(18)
C(14)-C(15)	1.390(3)	C(12)-C(13)-C(14)	120.1(2)
C(15)-C(16)	1.370(4)	C(13)-C(14)-C(15)	119.3(2)
C(16)-C(17)	1.383(3)	C(16)-C(15)-C(14)	120.52(19)
C(18)-C(19)	1.397(3)	C(15)-C(16)-C(17)	120.7(2)
C(18)-C(23)	1.399(3)	C(16)-C(17)-C(12)	119.2(2)
C(19)-C(20)	1.372(3)	C(19)-C(18)-C(23)	117.5(2)
C(20)-C(21)	1.385(3)	C(19)-C(18)-C(3)	119.83(17)
C(21)-C(22)	1.390(3)	C(23)-C(18)-C(3)	122.61(18)
C(22)-C(23)	1.375(3)	C(20)-C(19)-C(18)	121.2(2)
		C(19)-C(20)-C(21)	121.0(2)
N(2)-N(1)-C(9)	124.48(15)	C(20)-C(21)-C(22)	118.5(2)
N(2)-N(1)-C(5)	113.22(15)	C(23)-C(22)-C(21)	120.8(2)
C(9)-N(1)-C(5)	122.29(18)	C(22)-C(23)-C(18)	121.1(2)
N(1)-N(2)-C(3)	105.18(15)		
N(2)-C(3)-C(4)	109.35(18)		
N(2)-C(3)-C(18)	119.97(17)		

Table 6. Torsion angles [°] for C20 H14 N2 O2.

C(9)-N(1)-N(2)-C(3)	-178.44(17)	O(11)-C(11)-C(12)-C(13)	-175.6(2)
C(5)-N(1)-N(2)-C(3)	0.1(2)	O(10)-C(11)-C(12)-C(13)	3.4(3)
N(1)-N(2)-C(3)-C(4)	-0.1(2)	O(11)-C(11)-C(12)-C(17)	2.8(3)
N(1)-N(2)-C(3)-C(18)	179.00(16)	O(10)-C(11)-C(12)-C(17)	-178.21(17)
N(2)-C(3)-C(4)-C(5)	0.0(2)	C(17)-C(12)-C(13)-C(14)	0.1(3)
C(18)-C(3)-C(4)-C(5)	-178.89(19)	C(11)-C(12)-C(13)-C(14)	178.40(19)
N(2)-C(3)-C(4)-O(10)	174.35(17)	C(12)-C(13)-C(14)-C(15)	-0.3(3)
C(18)-C(3)-C(4)-O(10)	-4.6(3)	C(13)-C(14)-C(15)-C(16)	0.0(3)
O(10)-C(4)-C(5)-N(1)	-174.27(17)	C(14)-C(15)-C(16)-C(17)	0.6(4)
C(3)-C(4)-C(5)-N(1)	0.0(2)	C(15)-C(16)-C(17)-C(12)	-0.9(3)
O(10)-C(4)-C(5)-C(6)	5.4(4)	C(13)-C(12)-C(17)-C(16)	0.5(3)
C(3)-C(4)-C(5)-C(6)	179.7(2)	C(11)-C(12)-C(17)-C(16)	-177.88(19)
N(2)-N(1)-C(5)-C(4)	0.0(2)	N(2)-C(3)-C(18)-C(19)	1.2(3)
C(9)-N(1)-C(5)-C(4)	178.50(17)	C(4)-C(3)-C(18)-C(19)	-180.0(2)
N(2)-N(1)-C(5)-C(6)	-179.78(16)	N(2)-C(3)-C(18)-C(23)	-177.89(18)
C(9)-N(1)-C(5)-C(6)	-1.2(3)	C(4)-C(3)-C(18)-C(23)	1.0(3)
C(4)-C(5)-C(6)-C(7)	-178.9(2)	C(23)-C(18)-C(19)-C(20)	0.2(3)
N(1)-C(5)-C(6)-C(7)	0.7(3)	C(3)-C(18)-C(19)-C(20)	-178.93(19)
C(5)-C(6)-C(7)-C(8)	0.1(3)	C(18)-C(19)-C(20)-C(21)	0.2(3)
C(6)-C(7)-C(8)-C(9)	-0.4(3)	C(19)-C(20)-C(21)-C(22)	-0.1(3)
C(7)-C(8)-C(9)-N(1)	-0.1(3)	C(20)-C(21)-C(22)-C(23)	-0.4(3)
N(2)-N(1)-C(9)-C(8)	179.33(18)	C(21)-C(22)-C(23)-C(18)	0.9(3)
C(5)-N(1)-C(9)-C(8)	0.9(3)	C(19)-C(18)-C(23)-C(22)	-0.7(3)
C(5)-C(4)-O(10)-C(11)	-67.5(3)	C(3)-C(18)-C(23)-C(22)	178.36(19)
C(3)-C(4)-O(10)-C(11)	119.2(2)		
C(4)-O(10)-C(11)-O(11)	2.6(3)		
C(4)-O(10)-C(11)-C(12)	-176.49(16)		

ORTEP view of the C20 H14 N2 O2 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

REFERENCES

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

Sheldrick, G.M. (2008). 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 (2009) ; 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 (2008) Version 2008/2; X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.