Enantioselective Diamination of Alkenes, Hydroamination of 1,3-Dienes, and the Development of NHC Palladium Complexes

Erica L. Ingalls

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Reading Committee:

Forrest E. Michael, Chair

Gojko Lalic

Andrew J. Boydston

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University of Washington

Abstract

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Erica Louise Wetter Ingalls

Chairperson of the Supervisory Committee:
Associate Professor Forrest E. Michael
Department of Chemistry

Nitrogen containing heterocylces make up a vast majority of biologically relevant small molecules. Using transition metal catalysts to directly synthesize functionalized amine heterocycles is a valuable and efficient tool in chemical synthesis. Herein, the development of two palladium-catalyzed transformations are described; the enantioselective diamination of unactivated alkenes and the hydroamination of 1,3-dienes. Also, the synthesis and application of NHC-pyridine palladium catalysts for the hydroamination of protected aminoalkenes is discussed.

An enantioselective Pd-catalyzed vicinal diamination of unactivated alkenes using *N*-fluorobenzenesulfonimide as both an oxidant and a source of nitrogen was achieved. Using either Ph-pybox or Ph-quinox ligands, this reaction produced differentially protected vicinal diamines in good yields and high enantioselectivities. Mechanistic experiments revealed that the high enantioselectivity arises from selective formation of only one of four possible diastereomeric aminopalladation products of the chiral Pd complex. This complex was shown to form through

anti-aminopalladation. Finally, the aminopalladation complex was characterized by X-ray crystallography.

A room temperature palladium-catalyzed hydroamination of amino-1,3-dienes was also developed. This transformation created homoallylic amines in high yields and high selectivity with intramolecular substrates. A variety of amine protecting groups and diene substitution patterns were tolerated. A palladium η^1-allyl complex was isolated and shown to be a viable intermediate, giving insight into the reaction mechanism.

Synthesis of tridentate and bidentate pyridine or quinoline NHC Pd catalysts have been developed. Applications for these tridentate CNC-Pd compounds include a room temperature palladium-catalyzed intramolecular hydroamination of aminoalkenes. This reaction gave high conversions of carbamate protected aminoalkenes. Several chiral CNC-Pd complexes were attempted, but no enantioenriched hydroamination products were obtained. Both achiral and chiral bidentate NC ligands were synthesized along with several Pd complexes.

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List of Abbreviations

Δ:	Heat
Å:	Ångstrom
Ac:	Acetyl
Ar:	Aryl
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn:	Benzyl
Boc:	*tert*-Butyloxycarbonyl
Cbz:	Carbobenzyloxy
CNC:	2,6-Bis(NHC)-pyridine
COD:	Cyclooctadiene
COSY:	Correlation spectroscopy
Cy:	Cyclohexyl
d:	Day
dba:	Dibenzylideneacetone
DIBAL:	Diisobutylaluminium hydride
DMSO:	Dimethyl sulfoxide
dr:	Diastereomeric ratio
E^+:	Electrophile
ee:	Enantiomeric excess
ESI MS:	Electrospray ionization mass spectrometry
EXSY:	Exchange spectroscopy

FTIR:	Fourier transform infrared spectroscopy
GC/MS:	Gas chromatography/mass spectrometry
h:	Hour
HPLC:	High Performance Liquid Chromatography
Hz:	Hertz
L:	Ligand
LAH:	Lithium Aluminum Hydride
LDA:	Lithium diisopropylamide
Mes:	Mesityl
MHz:	Megahertz
Moz:	*p*-Methoxybenzyl carbonyl
mp:	Melting point
Ms:	Mesyl
M:	Molar
ND:	Not determined
NFBS:	*N*-fluorobenzenesulfonimide
NHC:	*N*-Heterocyclic carbene
NMR:	Nuclear Magnetic Resonance

Abbreviations for NMR splitting:

s:	singlet
d:	doublet
t:	triplet
q:	quartet

quin:	quintet
m:	multiplet
br:	broad
NOESY:	Nuclear Overhauser effect spectroscopy
Ns:	4-Nitrobenzenesulfonyl
Nu:	Nucleophile
ORTEP:	The Oak Ridge Thermal Ellipsoid Plot
pg:	Protecting group
PNP:	2,6-Bis(diphenylphosphinomethyl)-pyridine
ppm:	Parts per million
rt:	Room temperature
TfO:	Trifluoromethanesulfonate
TEA:	Triethylamine
TEMPO:	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA:	Trifluoromethylcarboxylate
THF:	Tetrahydrofuran
TLC:	Thin layer chromatography
TMS:	Tetramethylsilane
Tol:	Toluene
Troc:	2,2,2-Trichlorethoxycarbonyl
Ts:	*p*-Toluenesulfonyl
TsCl:	*p*-Toluenesulfonylchloride

Acknowledgements

This thesis would not exist without the help and encouragement of many people. The expression of my gratitude to all of these professors, advisors, mentors, co-workers, friends and family will most likely be lacking. Yet, I am going to attempt to thank all of them.

Primarily, I would like to thank my advisor Forrest Michael. I can only hope that this thesis represents some of the many lessons he has taught (or attempted to teach) me in the past five years. I am extremely grateful to him for everything that I have learned about chemistry. Mostly, I am thankful for the way he has taught me to think and approach chemistry problems.

One of the very first lessons I learned in graduate school, was that it was hard. Fortunately, as I continued this work I encountered many people who made it much easier. One co-worker and friend who I would like to thank is Alicia McGhee. Not only was she available to help me in lab, but her presence from our first day meeting with Forrest through each exam and finally our defense made each everything better. I would like to acknowledge her amazing role in the following: snake bites, coincidental matching outfits, teaching 462, organizing division bbqs, and frozen yoghurt. I would also like to thank a few people who initially taught me how to work in the lab: Brian Cochran, Paul Sibbald, Helena Lovick, and Jessica Hoover were exceptional chemistry graduate student role models, and they really helped me a lot! I would also like to thank Carolyn Rosewall, James Liskin, Annie Vikart, Justin Pierson and Derek Whorton for their help in lab and for some amazingly funny lab experiences. I would also like to thank two special officemates, Megan Duda and Richard Vo. Megan not only classed up this joint, but she has influenced many aspects of my life such as organization, flowers, wine, and chemistry. I have to

thank Richard for working with me on many chemistry projects and for his enthusiasm for chemistry, board games, and life. Also for his and Justin's immense involvement and hard work on chapter 2 of this thesis. Thank you, Michael Lab! Beyond the Michael lab, I would like to thank my ever helpful peers: Richard Rucker, Kate Allen, Ben Van Kuiken, David Lao, Aaron Whittaker, Mycah Uehling, and Nick Cox.

Since in chemistry our knowledge builds on previously learned lessons. Thus, I need to thank my graduate school committee members and previous chemistry instructors. Thank you Gojko Lalic, James Mayer and AJ Boydston for sitting thtrough my exams and for passing me. Ronald Kay, Dwight Tshudy, Irv Levy, and Maureen Driscoll were all massively influential and exceptional mentor-teachers.

Lastly, I would like to thank my friends and family. I would like to thank my parents and sister for their encouragement, love and lessons of perseverance. Most importantly, I need to thank my husband, Peter Mark, for everything he has done in the past five years which is far too long to list. Thanks!

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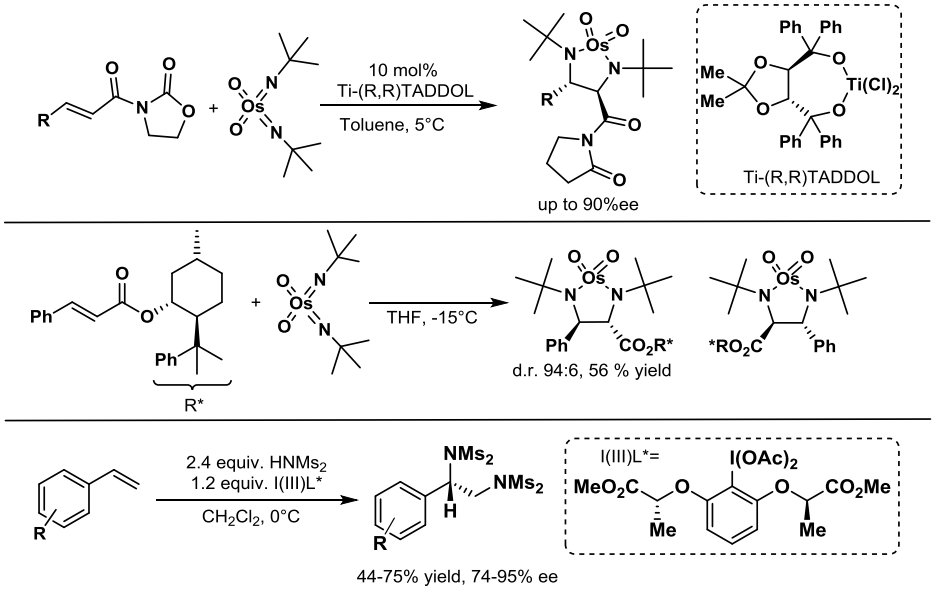
Chapter 1

Enantioselective Palladium-Catalyzed Diamination of Alkenes using *N*-fluorobenzenesulfonimide[1]

Section 1: Introduction

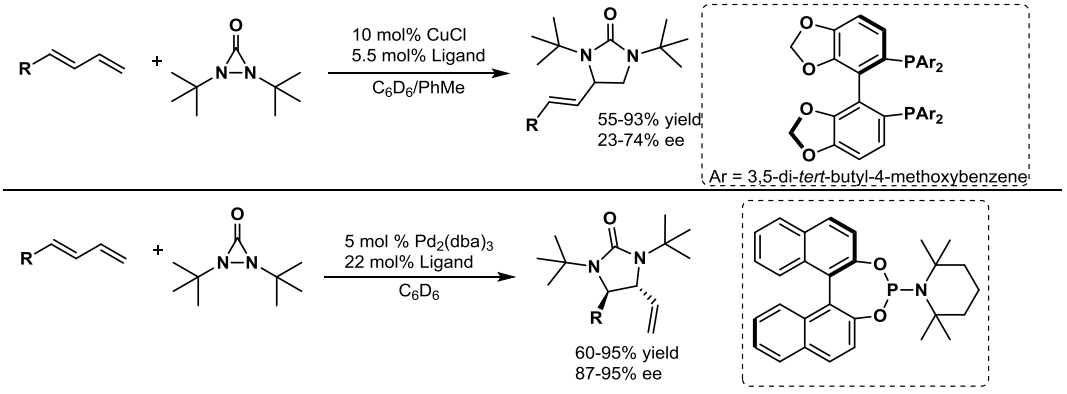
Chiral 1,2-diamines are important moieties found in biologically active compounds, organocatalysts, asymmetric ligands and auxiliaries.[2,3] Direct difunctionalization of unactivated alkenes constitutes a valuable and powerful method for creating such useful chiral diamine motifs. Despite the many uses of asymmetric 1,2-diamine scaffolds, efficient methods for their direct synthesis from alkenes are limited compared to conceptually similar dihydroxylation and aminohydroxylation transformations.[4] Though several transition metal catalyzed diamination reactions have been recently developed,[5] enantioselective variants are still rare. Notable examples include the intermolecular enantioselective diaminations reported by Muñiz[6,7] and Shi.[8]

Scheme 1.1. *Enantioselective Intermolecular Reactions Developed by Muñiz.*



Muñiz initially developed asymmetric diaminations of alkenes using bis(imido)osmium as the oxidant and nitrogen source, but these reactions suffered from a limited substrate scope and the requirement for stoichiometric amounts of expensive osmium which is difficult to remove.[6] More recently, Muñiz has developed a metal-free reaction using a chiral hypervalent iodine oxidant that functionalizes styrenes to give diamination products with very good yields and high enantioselectivity (Scheme 1.1).[7] Additionally, Shi has extensively studied palladium and copper catalyzed diaminations of dienes using chiral ligands with di-*tert*-butyldiaziridinone as the oxidant and nitrogen source (Scheme 1.2).[8]

Scheme 1.2. *Enantioselective Intermolecular Reactions Developed by Shi.*

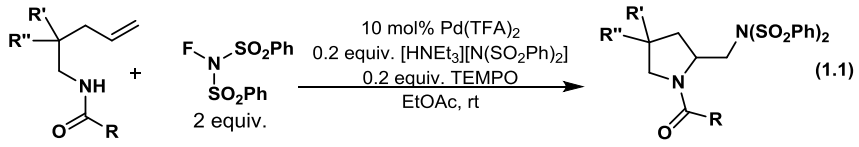


Though these methods provide high yields and enantioselectivities, there are still limitations in the scope of these transformations, particularly that they require stoichiometric amounts of osmium[6] or chiral iodine reagent,[7] or are limited to diene substrates.[8]

Recently, our lab disclosed a novel palladium-catalyzed diamination of alkenes using *N*-fluorobenzenesulfonimide (NFBS) as both an oxidant and a source of nitrogen.[9] This method

was useful for the generation of a variety of differentially protected cyclic 1,2-diamines (Scheme 1.3). Optimization studies showed that the addition of TEMPO[10] and $[HNEt_3][N(SO_2Ph)_2]$ increased the yield by preventing isomerization and trifluoracetate incorporation, respectively.

Scheme 1.3. *Pd-Catalyzed Diamination using NFBS.*



(1.1)

Deuterium labeling experiments[11] confirmed that the mechanism proceeds through a sequence of *anti*-aminopalladation, oxidative addition of NFBS, benzenesulfonimide anion dissociation, and then nucleophilic attack to form the s*yn*-diamination product (*Figure 1.1*). This chapter discusses the development, scope and mechanism of an enantioselective version of this NFBS diamination reaction.

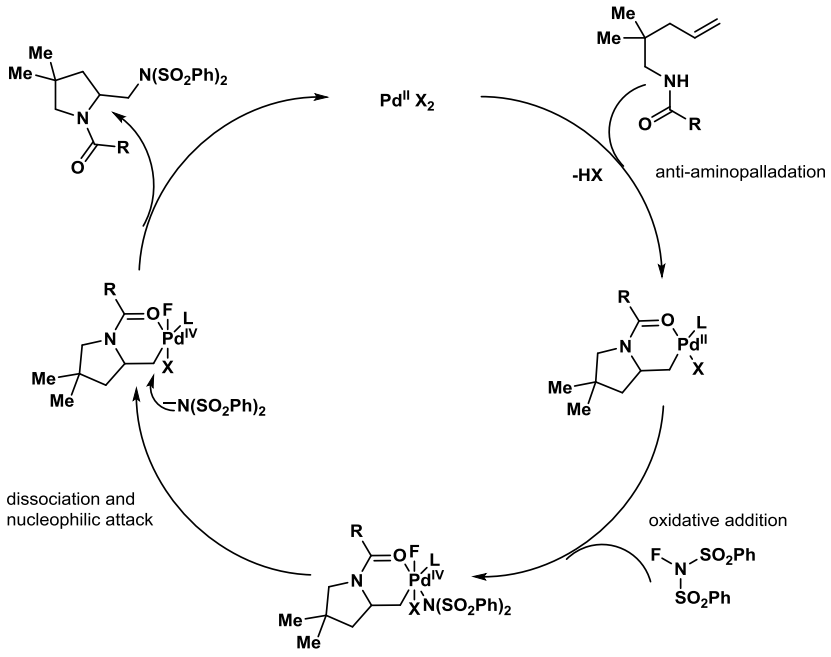


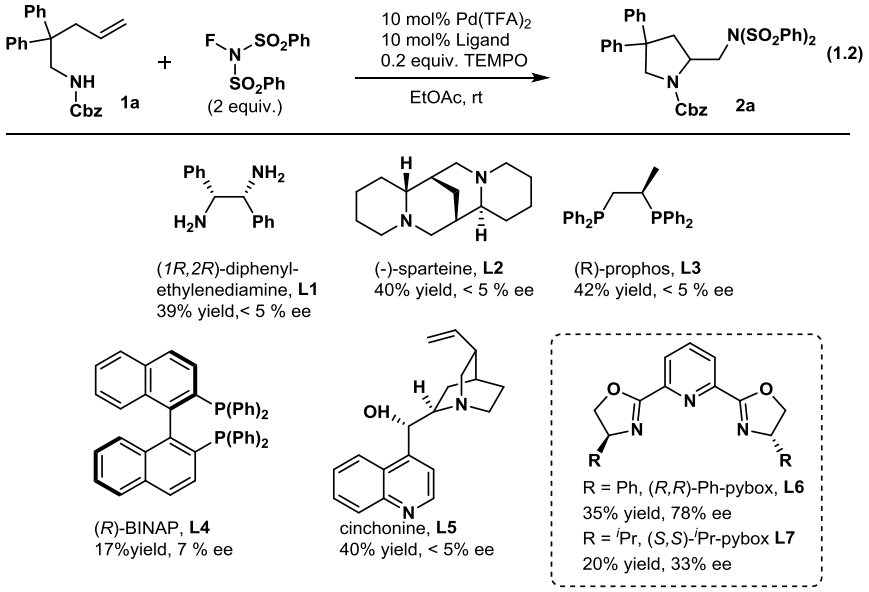
Figure 1.1. Catalytic Cycle of NFBS Diamination

Section 2. Results and Discussion

1.2.1 Initial results

Development of an enantioselective diamination reaction began with a screen of the chiral ligands depicted in Scheme 1.4 under standard diamination conditions using substrate **1a**. It was clear that only the pyridine bisoxazoline (pybox) ligands **L6**-**L7** gave diamination products with any significant enantiomeric excess (ee).

Scheme 1.4. *Chiral ligand screen.*



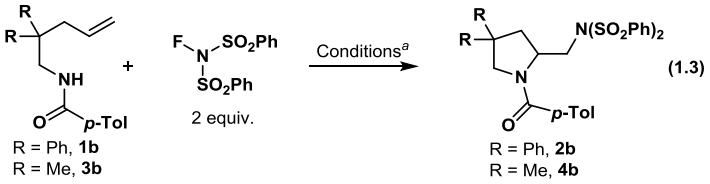
1.2.2 Development and Scope using Pybox Ligands

Using substrate **1b**, we were able to produce similar the results with **L6**, but with low reactivity (Table 1.1, entry 1). We found that refluxing the reaction in EtOAc increased the reactivity and selectivity of the catalyst (75% yield, 92% ee). With this new result, a screen of pybox ligands was conducted, and under optimized conditions **L6** proved to be the best ligand (Table 1.1, entries 2-6). It is interesting to note that an increase in the size of the group on the oxazoline (**L9**, **L10**) was not proportional to an increase in the ee, and thus the enantioselectivity is not simply sterically driven.

Although ligand **L6** gave a good yield of product **2b**, it (like all of these pybox ligands) resulted in a substantial decrease in catalyst reactivity. This drop in reactivity was increasingly

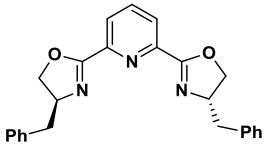
apparent when a substrate with decreased Thorpe-Ingold effects, **3b**, was used in the reaction with ligand **L6**. **3b** gave only 50% yield of the desired product (Table 1.1, entry 7).

Table 1.1. Optimization and Pybox Screen

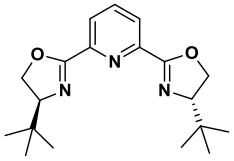


entry	Alkene	ligand	cond.[a]	% yield	% ee[b]
1	**1b**	**(*R*,*R*)-L6**	A	25	85
2	**1b**	**(*R*,*R*)-L6**	B	75	92
3	**1b**	**(*S*,*S*)-L7**	B	56	-32
4	**1b**	**(*S*,*S*)-L8**	B	62	-10
5	**1b**	**(*S*,*S*)-L9**	B	59	-20
6	**1b**	**(*S*,*S*)-L10**	B	60[c]	-62
7	**3b**	**(*R*,*R*)-L6**	B	50	80

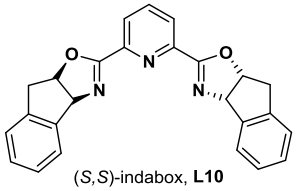
[a] Conditions A: 10 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, EtOAc, rt. Conditions B: 15 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, EtOAc, reflux. [b] Determined by chiral HPLC. [c] ^1H NMR yield versus internal standard, 1,3-dinitrobenzene.



(*S*,*S*)-Bn-pybox, **L8**



(*S*,*S*)-^{t}Bu-pybox, **L9**

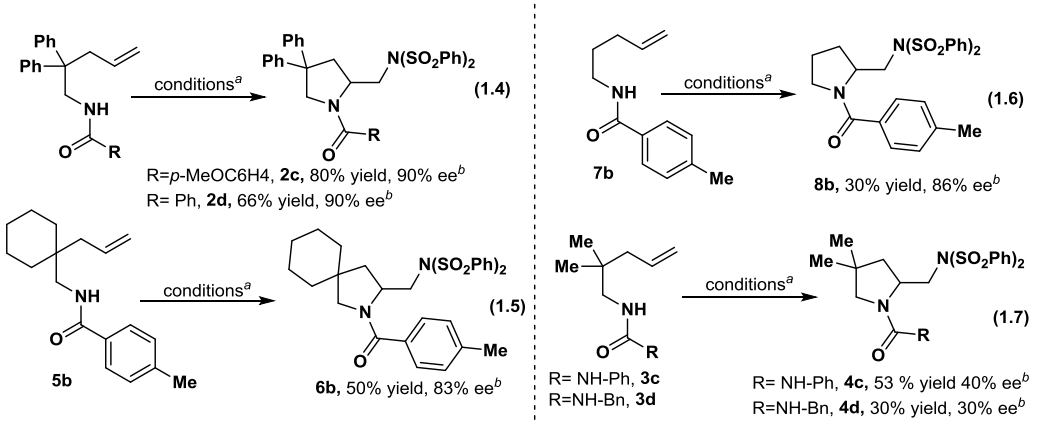


(*S*,*S*)-indabox, **L10**

Further exploration into the scope of this reaction revealed that substrates with Thorpe-Ingold effects gave high ee's and moderate yields, especially when compared to the low yields of the unsubstituted substrate **7b** (Scheme 1.5). While subsrates with other amine protecting groups such as ureas **3c** and **3d** were subjected to the reaction conditions, they resulted in low yields and enantioselectivities (Scheme 1.5, eq 1.7). Many other substrates were attempted but did not give

any desired diamination products, such as those with carbamate protecting groups and disubstituted alkenes.

Scheme 1.5. *Substrate Scope using* ***L6.***



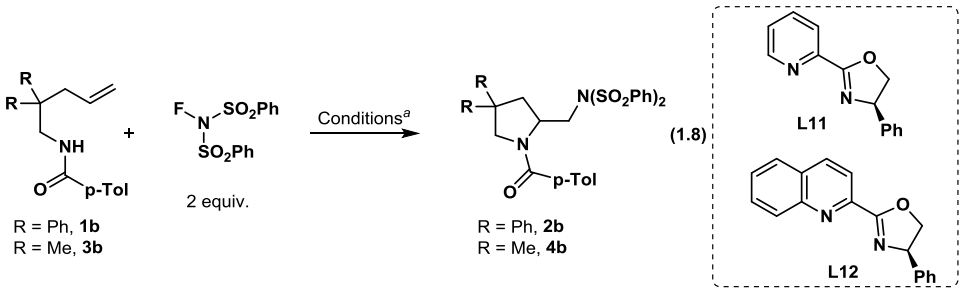
[a]Conditions: 15 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, 2 equiv. NFBS, Ethyl acetate, reflux. [b]determined by chiral HPLC.

1.2.3 Development and Scope using Bidentate Ligands

We reasoned that perhaps the tridentate ligands were donating too much electron density to the metal center and thereby slowing the rate of aminopalladation. If true, the use of a bidentate ligand should alleviate this problem. Additionally, similar bidentate oxazoline ligands have shown high enantioselectivities when used with Pd^{II} sources in other oxidative cyclizations.[12] The use of an analogous bidentate ligand, the pyridine oxazoline (pyrox) ligand (**L11**), gave diamination product **1b** in low yields and enantioselectivies with significant isomerization side products (Table 1.2, entry 1). Gratifyingly, the analogous quinoline oxazoline (quinox), **L12,** resulted in a much more active catalyst with only slightly diminished enantioselectivity. When these conditions were used with substrate **3b**, the yield increased while the ee was the same as the previous reaction with **L7** (entry 3). Additionally, the results were

identical at room temperature proving that this catalyst is more active than previously seen with the pybox ligand (entry 4).

Table 1.2. Chiral Ligand Screen and Optimization

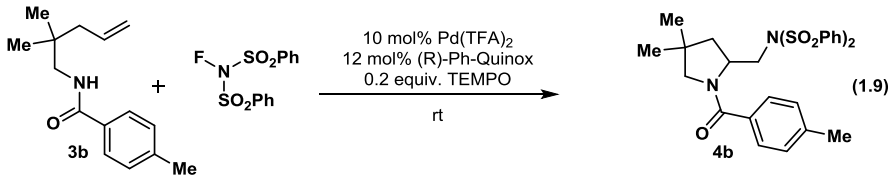


entry	alkene	ligand	cond.[a]	% yield	% ee[c]
1	**1b**	**(*R*)-L11**	A	42	36
2	**1b**	**(*R*)-L12**	A	70[b]	80
3	**3b**	**(*R*)-L12**	A	60[b]	80
4	**3b**	**(*R*)-L12**	B	60[b]	80

[a] Conditions A: 15 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, EtOAc, reflux. Conditions B: 12 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, Ethyl acetate, rt. [b] ^1H NMR yield versus internal standard, 1,3-dinitrobenzene. [c] Determined by chiral HPLC.

With such exciting results, a short optimization was conducted (Table 1.3). Several factors were found to be significant, namely the solvent, concentration, and number of equivalents of the oxidant. We found that halving the concentration of the reaction increased the ee significantly while not disturbing the yield (Table 1.3, entry 2). Reducing the amount of NFBS or slowly adding it also increased the ee slightly, but drastically lowered the yield (entries 3 – 5). We found the optimal conditions for both the yield and ee were at 0.1 M in 1,4-dioxane (Table 1.3, entry 10).

Table 1.3. **L12** Reaction Optimization.



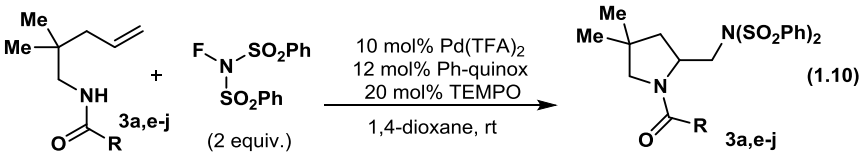
entry	Solvent	NFBS (equiv.)	concentration (M)	% yield[a]()[b]	% ee
1	EtOAc	2	0.2	60	80
2	EtOAc	2	0.1	60	92
3	EtOAc	1.5	0.1	50	93
4	EtOAc	1.0	0.1	40	94
5	EtOAc	2.0[c]	0.1	50	95
6	THF	2.0	0.1	60	91
7	MeCN	2.0	0.1	30	33
8	Ether	2.0	0.1	50	84
9	CH_2Cl_2	2.0	0.1	25	86
10	1,4-Dioxane	2.0	0.1	70 (66)	94

[a] ^{1}H NMR yield, using internal standard 1,3-dinitrobenzene. [b] isolated yield. [c] slow addition of NFBS over 2 hours.

Amide and carbamate protecting groups were tested under the optimized reaction conditions (Table 1.4). Both electron withdrawing and donating groups on the amide gave high enantioselectivities and similar yields to substrate **3b**. Carbamates (entries 5-7) also afforded high enantioselectivities, albeit with somewhat lower yields when compared to the amides.

Substrates with different substitution patterns were also subjected to the optimized conditions (Scheme 1.6). Products with geminal disubstitution on the backbone (**2f**, **6a**) could generally be made in good yields and high enantioselectivity. Monosubstituted substrate **7** also gave excellent enantioselectivity, however, the yield and diastereoselectivity were modest. Thus, the formation of the new stereocenter in the reaction with **L12** is independent of substrate stereochemistry.

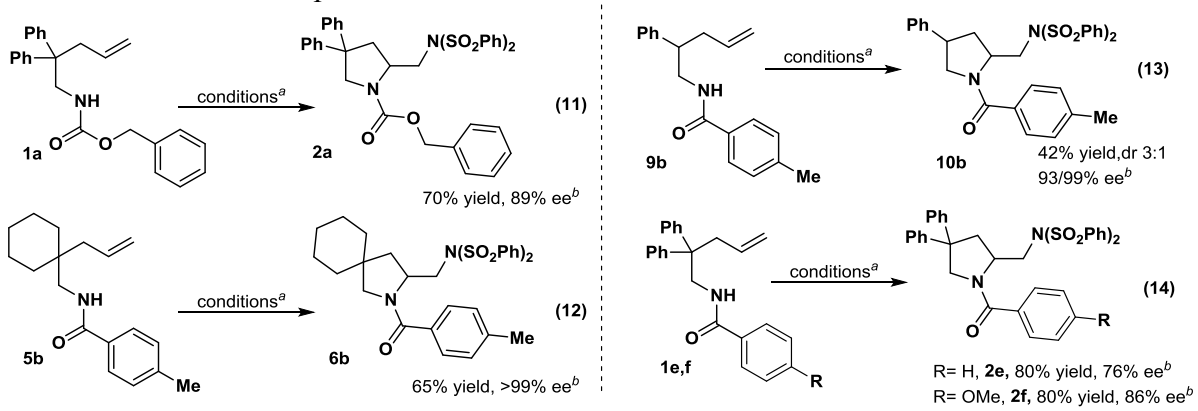
Table 1.4. Scope of Amine Protecting Group



entry	alkene	R	% yield	% ee[a]
1	**3e**	Ph	75	91
2	**3f**	*p*-$MeOC_6H_4$	71	96
3	**3g**	*p*-BrC_6H_4	70	94
4	**3h**	CH_3	71	91
5	**3a**	OBn	60	93
6	**3i**	O*t*-Bu	34	82
7	**3j**	OCH_2CCl_3	50	91

[a]determined by chiral HPLC

Scheme 1.6. *Substrate Scope with **L12**.*



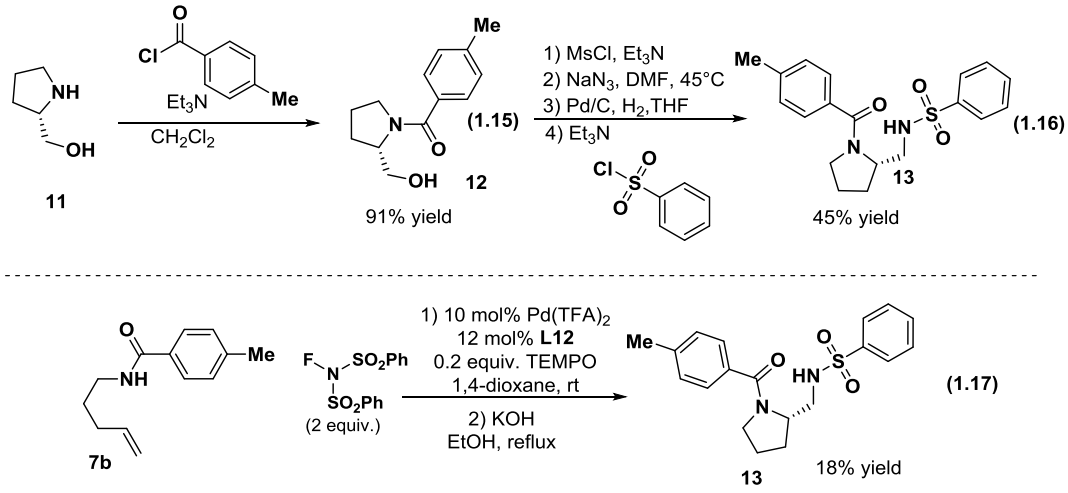
[a]Conditions: 12 mol% ligand, 10 mol% $Pd(TFA)_2$, 20 mol% TEMPO, 2 equiv. NFBS, 1,4-dioxane, rt. [b]determined by chiral HPLC.

1.2.4 Determination of Absolute Stereochemistry

The absolute configurations of the diamination products were determined by transforming (*S*)-(+)-2-hydroxylmethylpyrrolidine (**11**) into the diamination product **13**. Product

13 was compared to the partially deprotected diamination product (eq 1.17) using optical rotation and chiral HPLC to determine that the *S* product is given when using *R* conformation of **L12**.

Scheme 1.7. *Correlation of Absolute Stereochemistry.*



1.2.5 Mechanistic Studies

In our previous mechanistic work on the diamination reaction,[11] an intermediate alkylpalladium complex was isolated by trapping with a bipyridine ligand. In order to learn more about the origin of the enantioselectivity in this reaction, a **L12**Pd(TFA)$_2$ complex was generated by mixing Pd(TFA)$_2$ and ligand **L12**, which was then treated with substrate **3h** (Scheme 1.8).

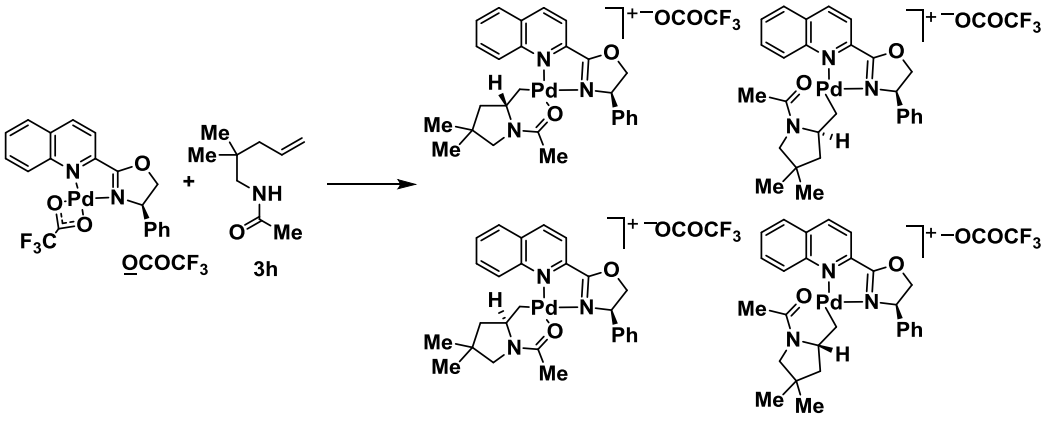
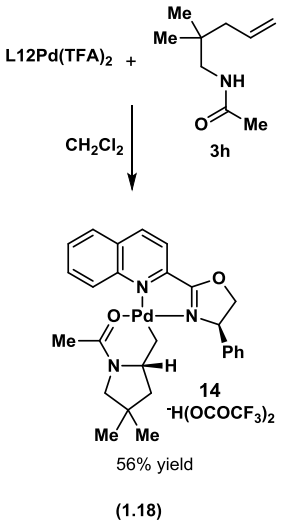


Figure 1.2. The four possible stereoisomers of the reaction between **L12**Pd(TFA)$_2$ and **3h**.

Scheme 1.8. *Formation of Alkylpalladium Intermediate.*



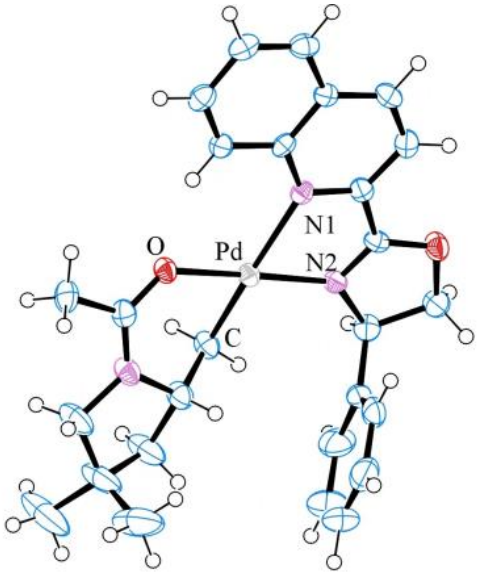


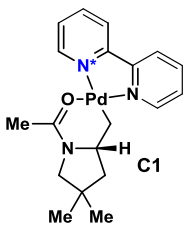
Figure 1.3. Crystal structure of (*R*)-Ph-quinox-Pd-alkyl complex **14**, complex counterion omitted for clarity. Bond distances (Å): Pd-C (1.998), Pd-O (2.039), Pd-N1 (2.233), Pd-N2 (2.021).

Remarkably, full conversion to only one of the four possible stereoisomeric products (*Figure 1.2*) was detected by ^{1}H NMR spectroscopy. It was determined that this complex was

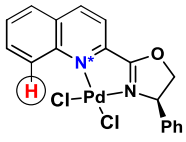
alkylpalladium complex **14**. Complex **14** was isolated in 56% yield, crystallized and analyzed by X-ray crystallography (*Figure 1.3*).

This structure shares several important features with our previously reported bipy-Pd-alkyl complex,[9] including the strong chelation of the amide carbonyl to the Pd center and the presence of the complex $H(OCOCF_3)_2$ counterion. The very large difference in Pd-N bond lengths (2.02 vs 2.23 Å) in this complex is noteworthy. Two factors could be responsible for this difference. First, the large difference in *trans* influence between O and C should result in some lengthening of the quinoline-Pd bond. Second, the quinoline-Pd bond should also be longer due to steric interference between the peri hydrogen of the quinoline and the ligand that is *cis* to the quinoline. Two existing X-ray crystal structures confirm that both factors are operative and that the latter factor is more important. In the bipy-Pd-alkyl complex, which should only be affected by the trans influence, the Pd-N bond trans to C is only 0.07 Å longer than the Pd-N bond trans to O (2.03 vs. 2.10 Å). In the (*t*-Bu-quinox)$PdCl_2$ complex reported by Yang[13], which should only display the effects of quinoline sterics, the quinoline-Pd bond is 0.15 Å longer than the oxazoline-Pd bond (2.16 vs. 2.01 Å). The 0.21 Å difference in bond lengths in complex **14** is very nearly the sum of those two factors (Table 1.5). The failure of the pyrox ligand **L11** to give high enantioselectivity (Table 1.2, entry 1), indicates that the steric effect of the quinoline plays a crucial role in determining stereoselectivity.

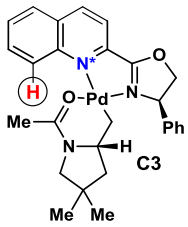
Table 1.5. Trans influence and steric effects on Pd-N bond distances



C1



C2



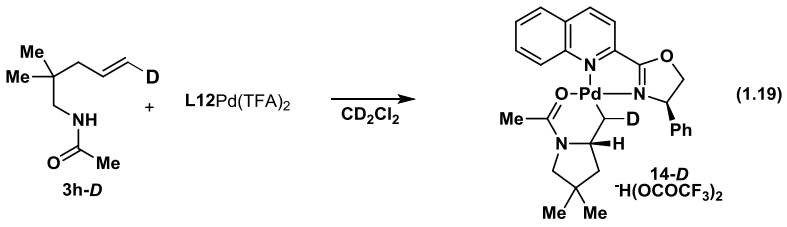
C3

Bond	C1[11]	C2[13]	C3
Pd-N*	2.10 Å	2.16 Å	2.23 Å
Pd-N	2.03 Å	2.01 Å	2.02 Å
Difference	0.07 Å	0.15 Å	0.21 Å

The peri hydrogen is circled and represented in red, while blue N* is the quinoline or N *trans* to the C.

Previously, the stereochemistry of the aminopalladation step in this reaction had been determined to be *trans* or *anti*. We presumed that the formation of **14** also proceeds through *anti*-aminopalladation, but mechanistic studies of palladium-catalyzed Wacker-type cyclizations with pyrox ligands have proved that the introduction of a ligand to the reaction can influence this step.[14] A ^{1}H NMR experiment of substrate **3h-*D*** with **L12**Pd(TFA)$_2$ in CD_2Cl_2 was conducted to determine the effect of a **L12** on the aminopalladation (Scheme 1.9).

Scheme 1.9. *Formation of Deuterated Alkylpalladium Intermediate,* **14-*D*.**



The reaction again formed one complex with the clear absence of a proton at 1.52 ppm. The large *geminal* coupling contant (J_{bc} = 8.5 Hz) was also absent, simplifying the proton at 2.12

ppm to a doublet. The remaining smaller *cis* vicinal coupling constant (J_{ab} = 2.5 Hz, *Figure 1.4*) is consistent with the assignment of *anti*-aminopalladation even in the presence of ligand **L12**. Therefore the formation of **14** also proceeds through *anti*-aminopalladation.

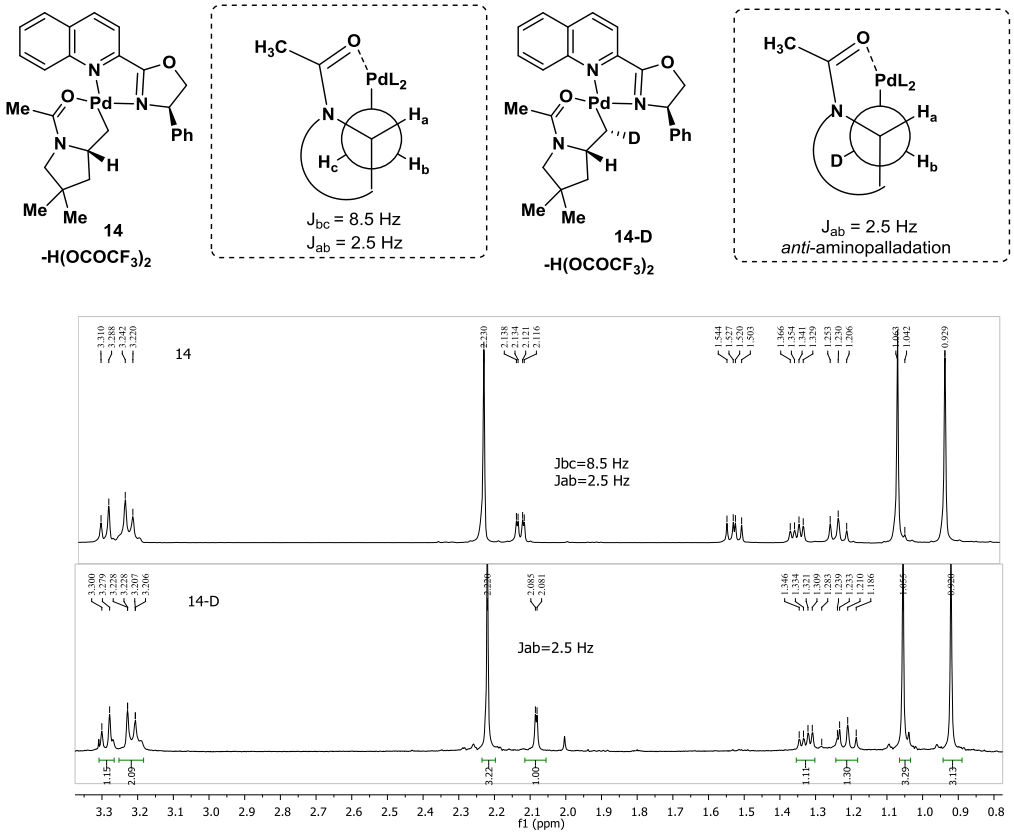
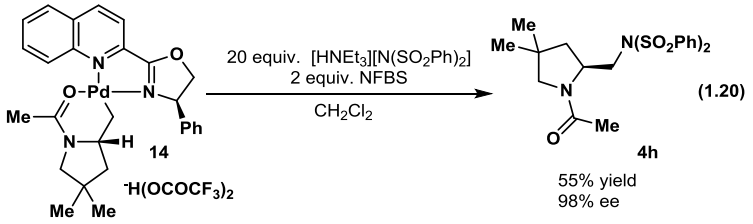


Figure 1.4. Newman projections and ^{1}H NMR spectra of **14** and **14-*D***,

To further establish the intermediacy of complex **14** in the catalytic diamination, **14** was treated with NFBS and triethylammonium benzenesulfonimide.[15] Under these conditions the diamination product was isolated in 55% yield and 98% ee, which is very nearly the same as the catalytic reaction affords. Furthermore, the major enantiomer produced in this reaction matches that observed in the catalytic reaction and its absolute configuration (*S*) was determined to be the

same as was observed in complex **14** (Scheme 1.7). This is consistent with aminopalladation serving as the enantiodetermining step of the catalytic cycle.

Scheme 1.10. *Amination of the Alkylpalladium Complex.*



Section 3. Conclusion

In conclusion, an enantioselective method for the diamination of alkenes to create a differentially protected diamination product has been developed. The palladium-catalyzed reaction provided products with moderate yields, and up to 99% ee using the (*R*)-Ph-quinox ligand. Isolation of a single stereoisomer of the intermediate alkylpalladium complex established that aminopalladation is the enantiodetermining step of this transformation.

Section 4. Experimental

General Procedures and Materials

All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise indicated. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass Spectroscopy on a Bruker Esquire 1100 Liquid Chromatograph - Ion Trap

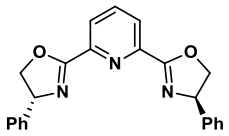
Mass Spectrometer or a JEOL HX-110. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker DPX-200, AV-300, AV-301, DRX-499, or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm) or CH_2Cl_2 (5.30 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.0 ppm). Melting points were taken on MEL-TEMP melting point apparatus and are uncorrected. Chiral HPLC analysis was performed on a Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 254 nm; column, DAICEL CHIRALPAK AD-H or CHIRALPAK OD-H; mobile phase, 2-propanol/hexanes. Optical rotations were taken with a Na lamp Jasco DIP-370 digital polarimeter using a Jasco 1 mL polarimeter cell.

Tetrahydrofuran, diethyl ether, dichloromethane, and acetonitrile were degassed and dried by passing through a column of neutral alumina. 3Å molecular sieves were activated under vacuum at 200 °C for 14 h and stored in an oven at 120 °C. Deuterated solvents, $CDCl_3$ and CD_2Cl_2 were obtained from Cambridge Isotope Laboratories, Inc. unless otherwise stated and stored over activated 3Å molecular sieves. Ethyl acetate and 1,4-dioxane was obtained from EMD or Sigma Aldrich and degassed with nitrogen and stored over activated 3Å molecular sieves. Palladium trifluoroacetate was obtained from Strem Chemicals and was used without further purification. *N*-Fluorobenzenesulfonimide was obtained from Synquest labs and used without further purification. 99% (*S*)-(+)-2-Pyrrolidinemethanol (**11**) and 2,6-Bis[4'-(*S*)-isopropyloxazolin-2'-yl]pyridine (**L7**) were obtained from Sigma-Aldrich and used without

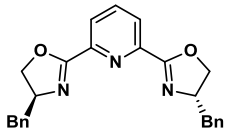
further purification. *(1R), (2R)*-diphenylethylenediamine (**L1**), (-)-Sparteine (**L2**), *(R)*-Prophos (**L3**), *(R)-(+)*-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (**L5**), and Cinchonine (**L5**) were obtained from commercial sources and used without further purification.

1.4.1 Synthesis of Ligands

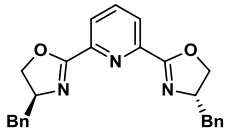
2,6-Bis[4'-(*R*)-phenyloxazolin-2'-yl]pyridine (**L6**), **2,6-Bis[4'-(*S*)-benzyloxazolin-2'-yl]pyridine** (**L8**), **2,6-Bis[4'-(*S*)- *tert*-butyloxazolin-2'-yl]pyridine** (**L9**), **[3a*S*-[2(3'a*R**, 8' a*S**), 3aα, 8aα]]-2,2'-(2,6-pyridinediyl)bis-[3a, 8a-dihydro-8H-indeno[1,2-d]oxazole] (L10)**, **(*R*)-4-phenyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (L11)** **(4'*R*)-2-(4', 5'-dihydro-4'-phenyl-2'-oxazolyl)quinoline** (**L12**), and were all synthesized from previously reported literature procedures.[16, 18, 19, 20]



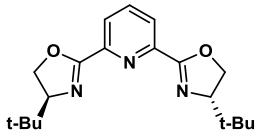
2,6-Bis[4'-(*R*)-phenyloxazolin-2'-yl]pyridine, (**L6**). Spectral data matches literature values.[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 7.8 Hz, 2H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.38–7.28 (m, 10H), 5.46 (dd, *J* = 8.3 Hz, 10.3 Hz, 2H), 4.92 (dd, *J* = 8.3 Hz, 10.3 Hz), 4.42 (t, *J* = 8.3 Hz, 2H).



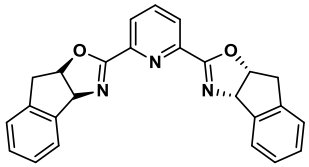
2,6-Bis[4'-(*S*)-benzyloxazolin-2'-yl]pyridine, (**L8**). Spectral data matches literature values.[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.1 Hz, 2H), 7.89 (t, *J* = 8.1 Hz, 1H), 7.34 – 7.23 (m, 10H), 4.65 (tdd, *J* = 9.3, 7.5, 5.1 Hz, 2H), 4.46 (dd, *J* = 9.3, 8.7 Hz, 2H), 4.25 (dd, *J* = 8.7, 7.5 Hz, 2H), 3.27 (dd, *J* = 13.8, 5.1 Hz, 2H), 2.79 (dd, *J* = 13.8, *J* = 9.3 Hz, 2H).



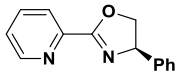
2,6-Bis[4'-(*S*)-benzyloxazolin-2'-yl]pyridine, (**L8**). Spectral data matches literature values.[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.1 Hz, 2H), 7.89 (t, *J* = 8.1 Hz, 1H), 7.34 – 7.23 (m, 10H), 4.65 (tdd, *J* = 9.3, 7.5, 5.1 Hz, 2H), 4.46 (dd, *J* = 9.3, 8.7 Hz, 2H) 4.25 (dd, *J* = 8.7, 7.5 Hz, 2H), 4.27 (dd, *J* = 13.8, 5.1 Hz, 2H), 2.79 (dd, *J* = 13.8, *J* = 9.3 Hz, 2H).



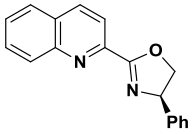
2,6-Bis[4'-(*S*)-*tert*-butyloxazolin-2'-yl]pyridine, (**L9**). Spectral data matches literature values.[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.8 Hz, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 4.47 (dd, *J* = 8.8 Hz, 10.3 Hz, 2H), 4.32 (dd, *J* = 8.8, 10.3 Hz, 2H), 4.11 (t, *J* = 8.8 Hz, 2H), 0.96 (s, 18H).



[3a*S*-[2(3'a*R, 8' a*S**), 3aα, 8aα]]-2,2'-(2,6-Pyridinediyl)bis-[3a, 8a-dihydro-8H-indeno[1,2-d]oxazole] (L10).** Spectral data matches literature values.[18] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.1 Hz, 2H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.57 – 7.54 (m, 6H), 5.78 (d, *J* = 7.8 Hz, 2H), 5.60 (dt, *J* = 8.1, 4.2 Hz, 2H), 3.49 (d, *J* = 4.2 Hz, 4H).



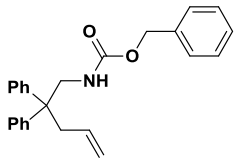
2-(4'-(*R*)-phenyloxazolin-2'-yl)pyridine (L11). Spectral data matches literature values.[19] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (ddd, *J* = 4.8 Hz, 1.7 Hz, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.9 Hz, 1.0 Hz, 1H), 7.80 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.42 (ddd, *J* = 7.6 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.44 – 7.29 (m, 5H), 5.46 (dd, *J* = 10.2 Hz, 8.6 Hz, 1H), 4.9 (dd, *J* = 10.2 Hz, 8.5 Hz, 1H), 4.39 (t, *J* = 8.5 Hz, 1H).



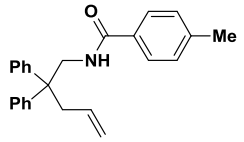
2-(4'-(*R*)-phenyloxazolin-2'-yl)quinoline (**L12**). Spectral data matches literature values.[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 – 8.25 (m, 3H), 7.80 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.77 (ddd, *J* = 8.2, 1.6, 0.7 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.40 – 7.26 (m, 5H), 5.52 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.99 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.48 (t, *J* = 8.6 Hz, 1H).

1.4.2 Synthesis of Aminoalkenes and Protected Substrates

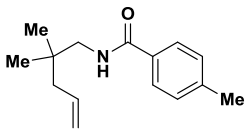
_N_-(2,2-diphenylpent-4-enyl)-4-methylbenzamide (1b), _N_-(2,2-dimethylpent-4-enyl)-4-methylbenzamide (3b), _N_-(2,2-dimethylpent-4-enyl)benzamide (3b), _N_-(2,2-dimethylpent-4-enyl)-4-methoxybenzamide (3c), 4-bromo-_N_-(2,2-dimethylpent-4-enyl)benzamide (3e), _N_-(2,2-dimethylpent-4-enyl)acetamide (3h), benzyl 2,2-dimethylpent-4-enylcarbamate (3a), *tert*-butyl 2,2-dimethylpent-4-enylcarbamate (3i), benzyl 2,2-diphenylpent-4-enylcarbamate (1a), 4-methyl-_N_-pent-4-enyl-benzamide (7b), _N_-((1-allylcyclohexyl)methyl)-4-methylbenzamide (5b), and **_N_-(2-phenylpent-4-enyl) 4-methylbenzamide (9b)** were synthesized according to literature procedures.[9,11,22,23,21]



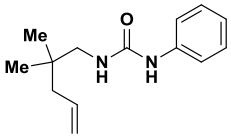
Benzyl 2,2-diphenylpent-4-enylcarbamate (1a). Spectral data matches literature values.[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.20 (m, 15H), 5.70 – 5.40 (m, 1H), 5.20 – 5.00 (m, 4H), 4.50 – 4.20 (m, 1H), 4.01 (d, J = 5.8 Hz, 2H), 2.95 (d, J = 6.8 Hz, 2H).



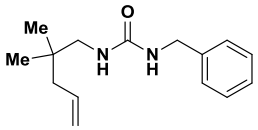
***N*-(2,2-Diphenylpent-4-enyl)-4-methylbenzamide (1b).** Spectral data matches literature values.[22] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 4H), 7.28 – 7.23 (m, 6H), 7.15 (d, *J* = 7.7 Hz, 2H), 5.64 (br, 1H), 5.60 – 5.40 (m, 1H), 5.05 – 4.95 (m, 2H), 4.14 (d, *J* = 5.5 Hz, 2H), 2.92 (d, *J* = 6.8 Hz, 2H), 2.35 (s, 3H).



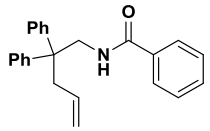
***N*-(2,2-dimethylpent-4-enyl)-4-methylbenzamide (3b).** Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.16 (br, 1H) 5.96 (m, 1H), 5.09 (s, 1H), 5.07 (d, *J* = 6.0 Hz, 1H), 3.30 (d, *J* = 6.3 Hz, 2H), 2.40 (s, 3H), 2.06 (d, *J* = 7.2 Hz, 2H), 0.96 (s, 6H).



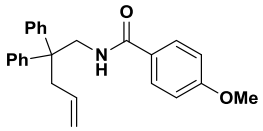
1-(2,2-dimethylpent-4-enyl)-3-phenylurea (3c). Spectral data matches literature values.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (br, 1H), 7.40 – 7.20 (m, 4H), 7.03 (br, 1H), 5.89 (br, 1H), 5.80 – 5.70 (m, 1H), 5.10 – 4.90 (m, 2H), 3.07 (br, 2H), 1.95 (br, 2H), 0.86 (s, 3H).



1-Benzyl-3-(2,2-dimethylpent-4-enyl)urea (3d). Spectral data matches literature values.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.25 (m, 5H), 5.78 (ddt, *J* = 17.7, 10.3, 7.5 Hz, 1H), 5.05 – 4.90 (m, 2H), 4.73 (br, 1H), 4.43 (br, 1H), 4.35 (d, *J* = 5.8 Hz, 2H), 3.00 (d, *J* = 6.3 Hz, 2H), 1.91 (d, *J* = 7.5 Hz, 2H), 0.84 (s, 6H).

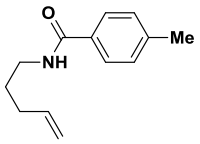


***N*-(2,2-Diphenylpent-4-enyl)benzamide (1e).** Spectral data matches literature values. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.25 (m, 15H), 5.68 (br, 1H), 5.55 – 5.41 (m, 1H), 5.02 (d, *J* = 5.7 Hz, 1H), 4.98 (s, 1H), 4.15 (d, *J* = 5.7 Hz, 1H), 2.93 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 145.2, 134.6, 133.6, 131.1, 128.4, 128.0, 126.7, 118.8, 50.6, 46.3, 42.3.

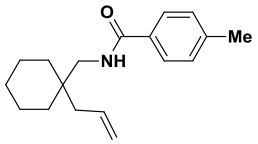


***N*-(2,2-Diphenylpenta-4-enyl)-4-methoxybenzamide** (**1f**). To a solution of 2,2-diphenylpentamine HCl salt (0.41 g, 1.5 mmol) in CH_2Cl_2 (10 mL), 4-methoxybenzoyl chloride

(0.51 g, 3.0 mmol) and triethylamine (0.52 g, 3.75 mmol) were added. The misture was allowed to stir for 2 days. The reaction was diluted with CH_2Cl_2 and washed with 1 M HCl (2x, 20 mL), 1 M NaOH (2x, 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (10:90 EtOAc/hexanes) to a white solid (0.32 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.7Hz, 2H), 7.36 – 7.23 (m, 10H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.58 (br s, 1H), 5.53 – 5.39 (m, 1H), 5.01 (d, *J* = 4.8 Hz, 1H), 4.96 (s, 1H), 4.13 (d, *J* = 5.7 Hz, 2H), 3.81 (s, 3H), 2.91 (d, *J* = 6.9 Hz, 2H).

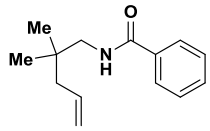


4-Methyl-*N*-pent-4-enyl-benzamide (7b). Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.10 (br, 1H) 5.82 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.10 – 4.98 (m, 2H), 3.47 (q, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 2.16 (q, *J* = 7.0 Hz, 2H), 1.73 (quin, *J* = 7.5 Hz, 2H).

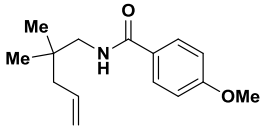


***N*-((1-Allylcyclohexyl)methyl)-4-methylbenzamide (5b).** Spectral data matches literature values.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.18

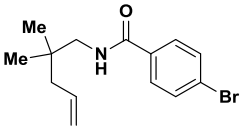
(br s, 1H), 6.00 – 5.90 (m, 1H), 5.20–5.10 (m, 2H), 3.42 (d, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.15 (d, *J* = 7.4 Hz, 2H), 1.60 – 1.37 (m, 10H).



***N*-(2,2-Dimethylpent-4-enyl)benzamide (3e).** Spectral data matches literature values.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 6.20 (br, 1H), 6.0–5.8 (m, 1H), 5.2–5.0 (m, 2H), 3.32 (d, *J* = 6.3 Hz, 2H), 2.07 (d, *J* = 7.4 Hz, 2H), 0.97 (s, 6H).

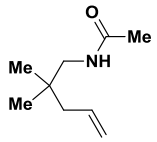


***N*-(2,2-Dimethylpent-4-enyl)-4-methoxybenzamide (3f).** Spectral data matches literature values.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.16 (br, 1H), 5.89 (ddt, *J* = 17.9, 10.5, 7.5 Hz, 1H), 5.20 – 5.00 (m, 2H), 3.85 (s, 3H), 3.30 (d, *J* = 6.4 Hz, 2H), 2.06 (d, *J* = 7.5 Hz, 2H), 0.96 (s, 6H).

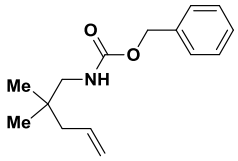


4-Bromo-*N*-(2,2-dimethylpent-4-enyl)benzamide (3g). Spectral data matches literature values.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 6.17

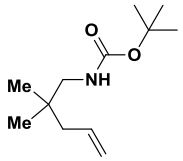
(br s, 1H), 6.00 – 5.80 (m, 1H), 5.20–5.00 (m, 2H), 3.31 (d, *J* = 6.4 Hz, 2H), 2.06 (d, *J* = 7.5 Hz, 2H), 0.97 (s, 3H).



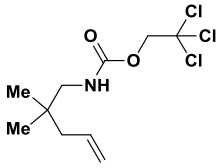
***N*-(2,2-dimethylpent-4-enyl)acetamide (3h).** Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.7, 10.2, 7.2 Hz, 1H), 5.46 (br, 1H), 5.08 – 5.01 (m, 2H), 3.09 (d, *J* = 6.3 Hz, 2H), 2.01 (s, 3H), 2.00 – 1.96 (m, 2H), 0.89 (s, 6H).



Benzyl 2,2-dimethylpent-4-enylcarbamate (3a). Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 5H), 5.88 – 5.74 (m, 1H), 5.11 (s, 2H), 5.07 – 5.00 (m, 2H), 4.78 (br s, 1 H), 3.04 (d, *J* = 6.6 Hz, 2H), 1.98 (d, *J* = 7.2 Hz, 2H), 0.89 (s, 6H).

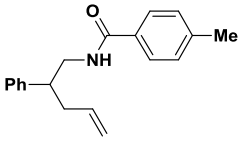


***tert*-Butyl 2,2-dimethylpent-4-enylcarbamate (3i).** Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 – 5.70 (m, 1H), 5.10 – 4.90 (m, 2H), 4.55 (br, 1H), 2.95 (d, *J* = 6.6 Hz, 2H), 1.96 (d, *J* = 7.5 Hz, 2H), 1.43 (s, 9H), 0.87 (s, 6H).



2,2,2-Trichloroethyl 2,2-dimethylpent-4-enylcarbamate (3j). To a solution of pent-4-en-1-amine (0.40 g, 3.53 mmol) and triethylamine (0.54 mL, 3.89 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise 2,2,2-trichloroethylchlorofomate (0.54 mL, 3.89 mmol). The mixture was stirred for 2 h, and then was quenched by the addition of 1M HCl. The layers were separated and the organic layer was washed with 1M NaOH and dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by chromatography (10% EtOAc/Hex) to afford a colorless oil (820 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.6, 10.2, 7.5 Hz, 1H), 5.08 – 5.03 (m, 2H), 5.0 (br s, 1H), 4.74 (s, 2H), 3.07 (d, *J* = 6.6 Hz, 2H), 1.99 (d, *J* = 7.5 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 134.5, 117.8, 95.7, 74.5, 51.0, 44.2, 34.8, 24.7. FTIR ($CDCl_3$, cm^{-1}): 3455, 3342, 3076, 2962, 2875, 1721, 1638, 1534, 1472,

1431, 1389, 1363, 1239, 1145, 1062, 1036, 990, 912, 881, 818, 767, 725. MS (ESI, m/z): [($^{35/37}$Cl)M+H]. 288.1 (100), 290 (96), 292 (30).



***N*-(2-phenylpent-4-enyl) 4-methylbenzamide (9a).** Spectral data matches literature values.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.22 (m, 5H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.91 (br, 1H), 5.80-5.65 (m, 1H), 5.04 (d, *J* =17.1 Hz, 1H), 4.98 (d, *J* =10.5 Hz, 1H), 4.00 (ddd, *J* = 5.7, 6.9, 13.2 Hz, 1H), 3.43 (ddd, *J* = 4.6, 9.3, 13.5 Hz, 1H), 3.04 (dt, *J* = 14.7, 7.5 Hz, 1H), 2.60-2.45 (m, 2H), 2.39 (s, 3H).

1.4.3 Synthesis and Characterization of Diamination Products

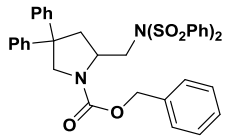
All racemic diamination products were synthesized according to literature procedures or modified literature procedures.[9]

General Procedures for Enantioselective Diaminations:

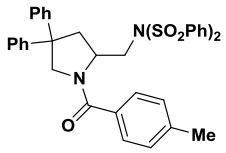
Method A: Palladium(II) trifluoroacetate (6.6 mg, 0.02 mmol), and ligand (0.03 mmol) were dissolved in EtOAc (1 mL) and allowed to stir for 10 min. TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (6.3 mg, 0.04 mmol), *N*-fluorobenzenesulfonimide (0.126 g, 0.40 mmol), and the aminoalkene (0.20 mmol) were added and the reaction mixture was refluxed for 12–18 h. The reaction was then diluted with CH_2Cl_2, washed with water (1 x 20 mL), and 1 M

NaOH (2 x 20 mL). The organic layer was dried with $MgSO_4$, then concentrated under reduced pressure and purified by column chromatography with EtOAc/hexanes.

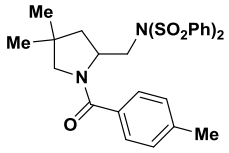
Method B: Palladium(II) trifluoroacetate (6.6 mg, 0.02 mmol) and (*R*)-Ph-Quinox (6.6 mg, 0.024 mmol), were dissolved in 1,4-dioxane (2 mL) and allowed to stir for 10 min. TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (6.3 mg, 0.04 mmol), *N*-fluorobenzenesulfonimide (0.126 g, 0.40 mmol), and the aminoalkene (0.20 mmol) were all added at once and the reaction mixture and the reaction mixture stirred for 3–24 h. The reaction was then concentrated under reduced pressure and purified by column chromatography with EtOAc/hexanes.



Benzyl-4,4-diphenyl-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methyl)pyrrolidine-1-carboxylate (2a). Spectral data matches literature values.[9] Method B, white solid, 0.093 g, 70% yield, 89% ee. $[\alpha]_D^{20}$ = -70.3 (*c* = 0.85, CH_2Cl_2)**.** HPLC: DAICEL CHIRALPAK OD-H, hexanes/2-propanol = 50:50, flow 0.5 mL/min, detection at 254 nm, r_t = 16.5 min, 49.4 min. ^{1}H NMR (500 MHz, $CDCl_3$ observed as a 1:1 mixture of rotamers): δ 8.00 – 7.80 (m, 4H), 7.59 (br, 2H), 7.50 – 7.40 (m, 6H), 7.30 – 7.10 (m, 9H), 7.09 (br, 2H), 7.00 (br, 2H), 5.40 – 5.20 (m, 1H), 5.12 (d, *J* = 11.4 Hz, 0.5H), 5.03 (d, *J* = 11.8 Hz, 0.5H), 4.73 (d, *J* = 10.3 Hz, 0.5H), 4.57 (d, *J* = 10.1 Hz, 0.5H), 4.50 (d, *J* = 13.6 Hz, 0.5H), 4.30 (d, *J* = 11.6 Hz, 0.5H), 3.99 (br s, 0.5H), 3.90 – 3.80 (m, 1H), 3.50 – 3.30 (m, 1H), 2.70 – 2.60 (m, 1H), 2.50 – 2.40 (m, 1H).

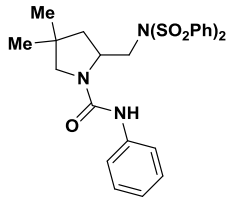


***N*-((1-(4-Methylbenzoyl)-4,4-diphenylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (2b).** Spectral data matches literature values.[9] Method A, *(S,S)*-Ph-pybox, white solid, 0.098 g, 75% yield, 92 % ee, $[\alpha]_D^{23}$= 7.3 (c = 0.24, CH_2Cl_2). Method B, white solid, 0.106 g, 82% yield, 80% ee, $[\alpha]_D^{23}$= -61.8 (c = 0.158, CH_2Cl_2) HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (50:50), flow 0.5 mL/min, detection at 254 nm, r_t = 19.0 min (major), 55.6min (minor). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 4H), 7.60 (t, *J* = 7.1 Hz, 2H), 7.52 – 7.42 (m, 6H), 7.30 – 7.10 (m, 8H), 7.04 (d, *J* = 7.3 Hz, 2H), 6.91 (d, *J* = 7.3 Hz, 2H), 4.51 (dd, *J* = 4.0, 14.8 Hz, 1H), 4.40 – 4.30 (m, 2H), 4.04 (dd, *J* = 8.3, 14.8 Hz, 1H), 3.84 (d, *J* = 11.2 Hz, 1H), 2.81 (t, *J* = 11.7 Hz, 1H), 2.60 (dd, *J* = 5.7, 11.7 Hz, 1H), 2.41 (s, 3H).

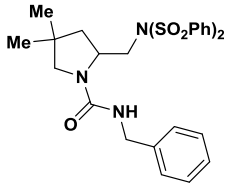


***N*-((4,4-Dimethyl-1-(4-methylbenzoyl)pyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl) benzenesulfonamide (4b).** Spectral data matches literature values.[9] Method A, white solid, 0.054 g, 50% yield, 80 % ee. Method B, white solid, 0.071 g, 66% yield, 93% ee. $[\alpha]_D^{23}$ = -

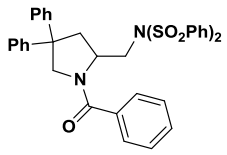
39.4 (*c* = 0.27, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5 mL/min, detection at 254 nm, r_t = 24.5 min, 41.5 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.60 – 7.30 (m, 9H), 4.80 – 4.60 (m, 1H), 4.36 (dd, *J* = 4.6, 15.0 Hz, 1H), 3.96 (dd, *J* = 8.6, 15.0 Hz, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 3.12 (d, *J* = 10.4 Hz, 1H), 1.88 (t, *J* = 11.4 Hz, 1H), 1.73 (dd, *J* = 7.4, 12.5 Hz, 1H), 1.05 (s, 3H), 0.88 (s, 3H).



***N*-phenyl-4,4-dimethyl-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methyl)pyrrolidine-1-carboxamide (4c**). Spectral data matches literature values.[9] Method A, *(S,S)*-Ph-pybox, white solid, 0.056 g, 53% yield, 40% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.9Hz, 4H), 7.66 (t, *J* = 7.4 Hz, 2H),7.60 – 7.40 (m, 6H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.07 (br, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.13 (dd, *J* = 3.2, 14.9 Hz, 1H), 3.72 (dd, *J* = 9.4, 14.9 Hz, 1H), 3.60 (d, *J* = 10.4 Hz, 1H), 3.11 (d, *J* = 10.5 Hz, 1H), 1.87 (dd, *J* = 7.0, 12.9 Hz, 1H), 1.82 (dd, *J* = 7.8, 12.7 Hz, 1H), 1.16 (s, 3H), 1.00 (s, 3H). HPLC, DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (75:25), flow 0.5 mL/min, detection at 254 nm, r_t = 38.3 min, 42.8 min.

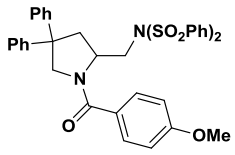


***N*-benzyl-4,4-dimethyl-2-((*N*- (phenylsulfonyl) phenylsulfonamido)methyl)pyrrolidine-1-carboxamide (4d).** Spectral data matches literature values.[9] Method A, (*S,S*)-Ph-pybox, white solid, 0.033 g, 30% yield, 30% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.9 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.70 (t, *J* = 7.7 Hz, 4H), 7.40 – 7.20 (m, 5H), 5.29 (br, 1H), 4.44 (dd, *J* = 5.6, 14.6 Hz, 1H), 4.39 (dd, *J* = 5.5, 14.8 Hz, 1H), 4.30 – 4.10 (m, 1H), 4.09 (d, *J* = 14.6 Hz, 1H), 3.72 (dd, *J* = 9.5, 14.8 Hz, 1H), 3.41 (d, *J* = 9.5 Hz, 1H), 2.98 (d, *J* = 10.1 Hz, 1H), 1.77 (dd, *J* = 7.5, 12.7 Hz, 1H), 1.66 (dd, *J* = 7.6, 12.5 Hz, 1H), 1.09 (s, 3H), 0.93 (s, 3H). HPLC, DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (75:25), flow 0.5 mL/min, detection at 254 nm, r_t = 15.1 min, 64.7 min.

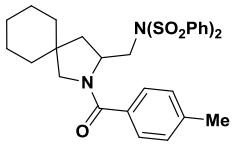


***N*-((1-benzoyl)-4,4-diphenylpyrrolidin-2-yl)methyl)-*N*- (phenylsulfonyl)benzenesulfonamide (2e).** Method A, *(S,S)*-Ph-pybox, white solid, 0.084g, 66% yield, 90 % ee. Method B, white solid, 0.102 g, 80 % yield, 76 % ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 10.2 Hz, 4H), 7.64 – 7.44 (m, 11H), 7.24 – 7.17 (m, 6H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 4.50 (dd, *J* = 15.0, 4.5 Hz, 1H), 4.41 – 4.31 (m, 2H), 4.07 (dd, *J* = 14.7, 7.8 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 2.74 (t, *J* = 12.3 Hz, 1H), 2.61 (ddd, *J* = 12.3, 6.6, 1.2 Hz, 1H). HPLC, DAICEL

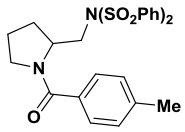
CHIRALPAK AD-H, hexanes/2-propanol = (45:55), flow 0.5 mL/min, detection at 254 nm, r_t = 21.4 min, 44.1 min.



***N*-((1-(4-methoxybenzoyl)-4,4-diphenylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (2f).** Method A, *(S,S)*-Ph-pybox, white solid, 0.106 g, 80 % yield, 90 % ee. Method B, white solid, 0.106 g, 80 % yield, 90 % ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.5 Hz, 4H), 7.64 – 7.58 (m, 4H), 7.49 – 7.43 (m, 4H) 7.25 – 7.18 (m, 6H), 7.07 (d, *J* = 6.9 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 6.3 Hz, 2H), 4.49 (dd, *J* = 14.7 Hz, 4.5 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.31 (m, 1H), 4.01 (dd, *J* = 14.7, 8.1 Hz, 1H), 3.87 – 3.82 (m, 4H), 2.81 (t, *J* = 12.0 Hz, 1H) 2.60 – 2.53 (m, 1H). HPLC, DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (50:50), flow 0.5 mL/min, detection at 254 nm, r_t = 25.1 min, 100.0 min.

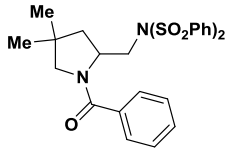


***N*-((2-(4-Methylbenzoyl)-2-azaspiro[4.5]decane-3-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (6b).** Spectral data matches literature values.[9] Method A, *(S,S)*-Ph-pybox, white solid, 0.060 g, 53 % yield, 83 % ee. Method B, white solid, 0.074 g, 65 % yield, 99 % ee. $[\alpha]_D^{20}$ = -42.1 (*c* = 0.10, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 50:50, flow 0.5 mL/min, detection at 254 nm, r_t = 17.7 min (major), 26.6 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.7 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 4H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.6, 2H), 4.75 – 4.60 (m, 1H), 4.34 (dd, *J* = 4.4, 14.8 Hz,1H), 3.92 (dd, *J* = 8.8, 14.7 Hz, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 3.22 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H), 1.87 (dd, *J* = 7.4, 12.0 Hz, 1H), 1.68 (t, *J* = 11.4 Hz, 1H), 1.50 – 1.10 (m, 10H).

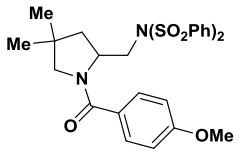


***N*-((1-(4-methylbenzoyl)pyrrolidin-2-yl)methyl)-*N*- (phenylsulfonyl)benzenesulfonamide (8b).** Method A, *(S,S)*-Ph-pybox, white solid , 0.030 g, 30 % yield, 86 % ee. $[\alpha]_D^{20}$ = -2.5 (*c* = 0.08, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (50:50), flow 0.5 mL/min, detection at 254 nm, r_t = 17.8 min (major), 38.0 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 3H), 7.69 (t, *J* = 7.5 Hz, 3H), 7.50 (t, *J* = 7.5 Hz, 4H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 4.72 (br, 1H), 3.85 (dd, *J* = 9.3 Hz, 1H), 3.85 (dd, *J* = 9.3

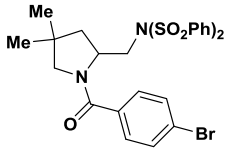
Hz, 17.1, 1H), 3.69 (m, 1H), 3.58 – 3.43, (m, 2H), 2.38 (s, 3H), 2.0 – 1.94 (m, 2H), 1.73 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 140.3, 138.7, 133.9, 129.0, 128.4, 128.6, 127.4, 56.6, 50.6, 49.2, 28.1, 24.8, 21.4. MS (ESI, m/z): 499 [M+H], 521 [M+Na], 537 [M+K].



***N*-((1-Benzoyl-4,4-dimethylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (4e).** Spectral data matches literature values.[9] Method B, white solid, 0.077 g, 75 % yield, 91 % ee. $[\alpha]_D^{20}$ = -4.7 (*c* = 0.062, CH_2Cl_2). HPLC, DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5 mL/min, detection at 254 nm, r_t = 21.5 min (major), 39.3 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8Hz,4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.60 – 7.30 (m, 9H), 4.80 – 4.60 (m, 1H), 4.36 (dd, *J* = 4.6, 15.0 Hz, 1H), 3.96 (dd, *J* = 8.6, 15.0 Hz, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 3.12 (d, *J* = 10.4 Hz, 1H), 1.88 (t, *J* = 11.4 Hz, 1H), 1.73 (dd, *J* = 7.4, 12.5 Hz, 1H), 1.05 (s, 3H), 0.88 (s, 3H).

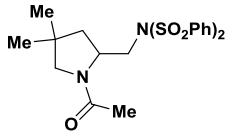


***N*-((1-(4-Methoxybenzoyl)-4,4-dimethylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (4f)**. Spectral data matches literature values.[9] Method B, white solid, 0.077 g, 71 % yield, 96 % ee. $[\alpha]_D^{23}$ = -35.4 (*c* = 0.65, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5mL/min, detection at 254 nm, r_t = 32.4 min (major), 40.53 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.7 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.51 (dd, *J* = 16.4, 8.3 Hz, 6H), (d, *J* = 8.4 Hz, 2H), 4.80 – 4.65 (m, 1H), 4.35 (dd, *J* = 14.8, 4.2 Hz, 1H), 3.93 (dd, *J* = 14.9, 8.7 Hz, 1H), 3.84 (s, 3H), 3.36 (d, *J* = 10.2 Hz, 1H), 3.19 (d, *J* = 10.2 Hz, 1H), 1.87 (t, *J* = 11.4 Hz, 1H), 1.69 (dd, *J* = 12.1, 7.3 Hz, 1H), 1.05 (s, 3H), 0.85 (s, 3H).

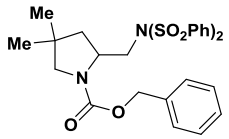


***N*-((1-(4-Bromobenzoyl)-4,4-dimethylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (4g).** Spectral data matches literature values.[9] Method B, white solid, 0.083 g, 70 % yield, 94 % ee. $[\alpha]_D^{20}$ = -42.0 (*c* = 0.1, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 50:50, flow 0.5mL/min, detection at 254 nm, r_t = 18.0 min (major), 43.6 (minor) min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.9 Hz, 4H),

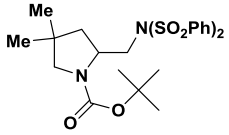
7.63 (t, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 4H), 7.43 (d, *J* = 8.2 Hz, 2H), 4.80 – 4.60 (m, 1H), 4.31 (dd, *J* = 4.6, 15.0 Hz, 1H), 3.97 (dd, *J* = 8.2, 15.0 Hz, 1H), 3.31 (d, *J* = 10.4 Hz, 1H), 3.09 (d, *J* = 10.3 Hz, 1H), 1.88 (t, *J* = 11.5 Hz, 1H), 1.73 (dd, *J* = 7.3, 12.3 Hz, 1H), 1.05 (s, 3H), 0.86 (s, 3H).



***N*-((1-Acetyl-4,4-dimethylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (4h).** Spectral data matches literature values.[11] Method B, white solid, 0.065 g, 72 % yield, 91 % ee. $[\alpha]_D^{20}$ = -15.1 (c = 0.12, EtOAc). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5mL/min, detection at 254 nm, r_t = 29.5 min (minor), 36.4 min (major). ^{1}H NMR (500 MHz, $CDCl_3$, 5:1 mixture of rotamers observed): δ 8.02 (d, *J* = 7.5 Hz, 4H, minor), 7.91 (d, *J* = 7.5 Hz, 4H, major), 7.70 (t, *J* = 7.5 Hz, 2H, minor), 7.64 (t, *J* = 7.5 Hz, 2H, major), 7.59 (t, *J* = 7.5 Hz, 4H, major), 7.51 (t, *J* = 7.5 Hz, 4H, major), 4.50–4.40 (m, 1H, major), 4.40 (dd, *J* = 4.0, 15.0 Hz, 1H, major), 4.40 – 4.30 (m, 1H, minor), 3.90 (dd, *J* = 4.0, 13.5 Hz, 1H, minor), 3.90 – 3.80 (m, 1H, minor), 3.78 (dd, *J* = 9.5, 15.0 Hz, 1H, major), 3.63 (dd, *J* = 9.5, 13.5 Hz, 1H, minor), 3.18 (d, *J* = 10.5 Hz, 1H, major), 3.15 (d, *J* = 10.5 Hz, 1H, major), 2.87 (d, *J* = 11.5 Hz, 1H, minor), 2.11 (s, 3H, minor), 2.02 (s, 3H, major), 1.83 (dd, *J* = 10.0, 12.0 Hz, 1H, major), 1.90 – 1.70 (m, 1H, minor), 1.68 (dd, *J* = 7.5, 12.0 Hz, 1H, major), 1.70 – 1.60 (m, 1H, minor), 1.10 (s, 3H, both), 0.95 (s, 3H, major), 0.90 (s, 3H, minor).

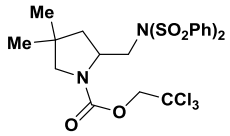


Benzyl 4,4-dimethyl-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methyl)pyrrolidine-1-carboxylate (4a). Spectral data matches literature values.[9] Method B, white solid, 0.081 g, 60 % yield, 93 % ee. $[\alpha]_D^{20}$ = -26.1 (*c* = 0.21, CH_2Cl_2)**.** HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5 mL/min, detection at 254 nm, r_t = 46.4 min, 71.5 min. ^{1}H NMR (500 MHz, $CDCl_3$, observed as a 5:4 mixture of rotamers): δ 7.97 (d, *J* = 7.4 Hz, 4H, major), 7.89 (d, *J* = 7.1 Hz, 4H, minor), 7.70 – 7.60 (m, 2H, both), 7.60 – 7.40 (m, 4H, both), 7.40 – 7.30 (m, 5H, both), 5.30 – 5.00 (m, 2H, both), 4.40 – 4.30 (m, 1H, minor), 4.30 – 4.20 (m, 2H, major), 4.20 – 4.10 (m, 1H, minor), 3.83 (dd, *J* = 9.3, 13.9 Hz, 1H, major), 3.72 (dd, *J* = 9.8, 13.5 Hz, 1H, minor), 3.46 (d, *J* = 10.6 Hz, 1H, minor), 3.33 (d, *J* = 10.5 Hz, 1H, major), 2.90 – 2.80 (m, 1H, both), 1.80 – 1.70 (m, 1H, both), 1.57 (dd, *J* = 7.3, 11.8 Hz, 1H, major), 1.47 (dd, *J* = 7.4, 11.6 Hz, 1H, minor), 1.03 (s, 6H, minor), 0.90 – 0.80 (m, 6H, major).



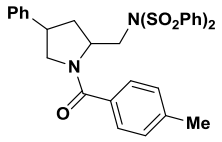
***tert*-Butyl 4,4-dimethyl-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methyl)pyrrolidine-1-carboxylate (4i).** Spectral data matches literature values.[9] Method B, white solid, 0.035 g, 34 % yield, 82 % ee. $[\alpha]_D^{20}$ = -31.5 (*c* = 0.12, CH_2Cl_2)**.** HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 90:10, flow 1.0 mL/min, detection at 254 nm, r_t = 9.2 min, 17.3 min. ^{1}H

NMR (500 MHz, $CDCl_3$, observed as a 1:1 mixture of rotamers): δ 8.10 – 7.90 (m, 4H, both), 7.88 (t, *J* = 7.1 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 2H), 7.70 – 7.50 (m, 4H, both), 4.40 – 4.10 (m, 2H, both), 3.80 – 3.60 (m, 1H, both), 3.40 – 3.30 (m, 1H), 3.30 – 3.20 (m, 1H), 2.80 – 2.70 (m, 1H, both), 1.69 (dd, *J* = 8.8, 12.6 Hz, 1H, both), 1.60 – 1.40 (m, 1H, both), 1.48 (s, 9H, both).



2,2,2-Trichloroethyl-4,4-dimethyl-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methyl)pyrrolidine-1-carboxylate (4j). Method B, white solid, 0.059 g, 50 % yield, 91 % ee. $[\alpha]_D^{20}$ = -26.6 (*c* = 0.20, CH_2Cl_2)**.** ^{1}H NMR (500 MHz, $CDCl_3$, observed as a 3:2 mixture of rotamers): 8.00 – 7.97 (m, 4H, both), 7.67 – 7.63 (m, 2H, both), 7.56 – 7.51 (m, 4H, both), 4.88 (d, *J* = 12.0 Hz, 1H, major), 4.86 (d, *J* = 12.0 Hz, 1H, minor), 4.69 (d, *J* = 12.0 Hz, 1H, minor), 4.60 (d, *J* = 12.0 Hz, 1H, major), 4.42 – 4.29 (m, 2H, both), 3.83 (dd, *J* = 15.0 Hz, 9.5 Hz, 1H, major), 3.77 (dd, *J* = 15.0 Hz, 9.5 Hz, 1H, minor), 3.47 (d, *J* = 14.5 Hz, 1H, minor), 3.43 (d, *J* = 14.5 Hz, 1H, major), 2.98 (d, *J* = 11.0 Hz, 1H, major), 2.89 (d, *J* = 11.0 Hz, 1H, minor), 1.77 (dd, *J* = 12.5 Hz, 9.5 Hz, 1H, major), 1.69 (dd, *J* = 12.5 Hz, 9.5 Hz, 1H, minor), 1.63 (dd, *J* = 13.0 Hz, 7.0 Hz, 1H, major), 1.42 (dd, *J* = 12.0 Hz, 7.0 Hz, 1H, minor), 1.07 (s, 3H, major), 1.02 (s, 3H, minor), 0.93 (s, 3H, major), 0.88 (s, 3H, minor). ^{13}C NMR (125 MHz, $CDCl_3$, observed as a 3:2 mixture of rotamers): δ 153.7 (major), 153.5 (minor), 139.5 (minor), 139.1 (major), 134.0 (minor), 133.9 (major), 129.1 (minor), 129.0

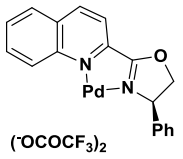
(major), 128.5 (major), 128.3 (minor), 95.7 (major), 95.6 (minor), 74.7 (both), 59.7 (minor), 59.5 (major), 56.9(minor), 55.9 (major), 52.0 (minor), 50.5 (major), 43.0 (minor), 42.9 (major), 37.5 (major), 37.1 (minor), 26.0 (major), 25.8 (minor), 25.7(major), 25.5 (minor). FTIR (CH_2Cl_2, cm^{-1}): 3068, 2959, 2874, 1716, 1585, 1559, 1522, 1479, 1449, 1436, 1412, 1378, 1355, 1315, 1288, 1224, 1170, 1121, 1086, 1063, 1044. HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 95:5, flow 1.0 mL/min, detection at 254 nm, r_t = 31.4 min, 33.4 min. MS (ESI, m/z): [($^{35/37}$Cl) M+H] 583(90), 585 (100), 587(40), [($^{35/37}$Cl) M+Na] 605 (90), 607(100), 609 (40) [($^{35/37}$Cl)M+K] 623 (100), 621 (90), 625(40). HRMS calculated for $C_{22}H_{26}Cl_3N_2O_6S_2$ 585.0273 found 585.0246 (M+H). m.p. 125 °C.



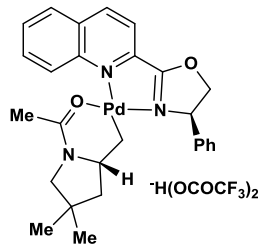
***N*-((1-(4-methylbenzoyl)-4-phenylpyrrolidin-2-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (10a).** Spectral data matches literature values.[9] Method B, white solid, 0.048 g, 42 % yield, 93 % ee (major), 99% ee (minor). $[\alpha]_D^{20}$ = -20.7 (*c* = 0.059, CH_2Cl_2). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 50:50, flow 0.5mL/min, detection at 254 nm, r_t = 19.3 min, 42.9 min, 25.4 min, 85.6 min. ^{1}H NMR (300 MHz, $CDCl_3$, isolated as a 3:1 mixture of diastereomers): δ 8.00 – 7.80 (m, 4H, both), 7.61 (t, *J* = 7.4 Hz, 2H, major), 7.70 – 7.50 (m, 2H, minor), 7.60 – 7.30 (m, 6H, both), 7.40 – 7.00 (m, 7H, both), 4.83 (br s, 1H, both), 4.44 (dd, *J* = 4.4, 15.0 Hz, 1H, major), 4.33 (dd, *J* = 3.7, 14.9 Hz, 1H, minor), 4.06 (dd, *J* = 8.6, 15.2 Hz, 1H, major), 3.94 (dd, *J* = 6.5, 16.0 Hz, 1H, minor), 3.83 (dd, *J* = 7.8,

9.8 Hz, major), 3.56 (t, *J* = 10.9 Hz, 1H, major), 3.60 – 3.50 (m, 1H, minor), 3.44 (t, *J* = 8.7 Hz, 1H, minor), 3.30 – 3.10 (m, 1H, major), 2.60 – 2.20 (m, 5H, both).

1.4.4 Synthesis of Metal Complexes

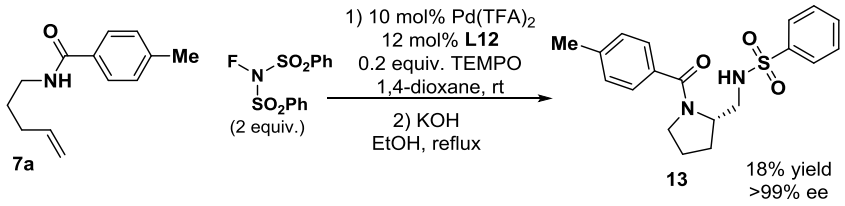


[(Ph-Quinox)Pd][(˙CO_2CF_3)$_2$] (L12 Pd(TFA)$_2$**).** Pd(TFA)$_2$ (0.166 g, 0.5 mmol) and Ph-Quinox (**L12)** (0.137g, 0.5 mmol) were dissolved in 10 mL of THF. The mixture was stirred for 30 min and then the solvent was removed under reduced pressure. The remaining orange solid was dissolved in CH_2Cl_2 and filtered through a Celite plug and then concentrated under reduced pressure to give an orange solid (0.30 g, 99 % yield) $[\alpha]_D^{23}$ = -9.9 (c = 0.535, CH_2Cl_2). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 9.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.86 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.80 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.45 – 7.29 (m, 3H), 7.29 – 7.26 (m, 2H), 5.42 (dd, *J* = 10.5, 8.0 Hz, 1H), 5.32 (dd, *J* = 10.5, 8.0 Hz, 1H), 4.77 (t, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 162.5 (q, *J* = 40.0 Hz), 148.8, 144.7, 142.9, 136.4, 134.2, 131.2, 130.9, 129.6, 129.5, 128.5, 126.6, 126.4, 120.1, 113.4 (q, *J* = 308 Hz), 79.5, 66.9. FTIR (CH_2Cl_2, cm^{-1}): 3456, 1704, 1591, 1523, 1488, 1423, 1402, 1193, 1141.



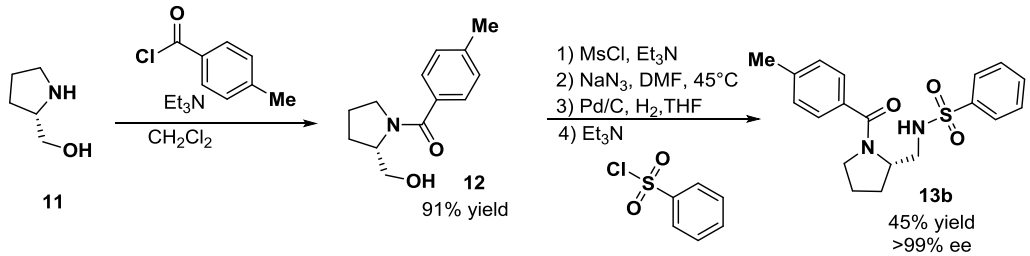
Palladium Ph-Quinox alkyl complex (14). To a flame dried flask charged with nitrogen, **L12**Pd(TFA)$_2$ (0.152 g, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL). Then a solution of *N*-(2,2-dimethylpent-4-enyl)acetamide (**3a**) (0.039 g, 0.25 mmol) in CH_2Cl_2 (0.25 mL) was added and stirred until the solution turned yellow. The mixture was concentrated under vacuum, and 20 mL of diethyl ether was added. The solution was cooled to -5 ^{o}C and allowed to stir for 1 h, at which point light yellow microcrystals formed. The precipitate was isolated by filtration, yielding 0.106 g, 55 % yield. Diffusion by layering with CH_2Cl_2 and diethyl ether gave yellow needles suitable for X-ray analysis. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.91 (d, *J* = 8.5 Hz, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.92 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.83 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.47 (m, 3H), 7.36 (d, *J* = 7.0 Hz, 2H), 5.43 (dd, *J* = 10.5, 6.5 Hz, 1H), 5.32 (dd, *J* = 10.5, 9.0 Hz, 1H), 4.76 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.30 (d, *J* = 10.5 Hz, 1H), 3.24 – 3.22 (m, 2H), 2.23 (s, 3H), 2.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 1.52 (dd, *J* = 11.5, 8.5 Hz, 1H), 1.35 (dd, *J* = 12.5, 6.0 Hz, 1H), 1.23 (t, 11.5 Hz, 1H), 1.06 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 170.6, 160.3 (q, *J* = 39 Hz), 148.1, 142.6, 140.8, 139.2, 132.6, 131.2, 130.1, 129.3, 128.9, 128.3, 127.8, 126.7, 120.0, 116.3 (q, *J* = 309 Hz), 79.6, 66.8, 62.4, 56.8, 45.3, 37.8, 26.4, 26.3, 22.2, 18.4. FTIR (CH_2Cl_2, cm^{-1}): 3436, 2962, 1738, 1689, 1642, 1581, 1513, 1481, 1409, 1199, 1126.

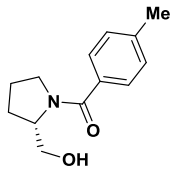
1.4.5 Correlation of Absolute Stereochemistry



***N*-((1-(4-Methylbenzoyl)pyrrolidin-2-yl)methyl)benzenesulfonamide (13).** Palladium(II) trifluoroacetate (36.5 mg, 0.11 mmol) and (*R*)-Ph-quinox (31.2 mg, 0.132 mmol), were dissolved in 1,4-dioxane (11 mL) and allowed to stir for ten min. TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (34.4 mg, 0.22 mmol), *N*-fluorobenzenesulfonimide (0.693g, 2.2 mmol), and **7a** (1.1 mmol) were added and the reaction mixture was stirred overnight. The mixture was then concentrated under reduced pressure and ran through an EtOAc silica plug. The crude diamination product was then dissolved in a 1M ethanolic KOH solution (5 mL), which was refluxed overnight. The solution was then made acidic with dilute aq. HCl and extracted with CH_2Cl_2 (3 x 10mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/Hexanes) to give a white solid, 0.068 g, 18 % yield, >99 % ee. $[\alpha]_D^{20}$ = -36.3 (*c* = 0.075, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.38 (br s, 1H), 4.29 – 4.27 (m, 1H), 3.46 – 3.40 (m, 2H), 3.33 (ddd, *J* = 10.0, 6.5, 3.5 Hz, 1H), 3.08 (ddd, *J* = 11.5, 7.0, 4.0 Hz, 1H), 2.38 (s, 3H), 2.14 – 2.11 (m, 1H), 1.86 – 1.82 (m, 1H), 1.77 – 1.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 140.7, 140.1, 133.3, 132.4, 129.0, 128.9, 127.3,

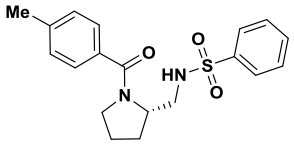
126.9, 57.3, 50.9, 47.9, 29.4, 24.9, 21.4. FTIR ($CHCl_3$, cm^{-1}): 3167, 2972, 2877, 1726, 1685, 1608, 1566, 1514, 1445, 1426, 1328, 1205, 1160, 1093. m.p. 151°C MS (ESI, m/z): 359.3 [M+H], 381.2 [M+Na], 397.2 [M+K]. HRMS calculated for $C_{19}H_{23}N_2O_3S$, 359.1429 found 359.1430 (M+H). HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5mL/min, detection at 254 nm, r_t = 22.3 min (minor), 27.3 min (major).





(*S*)-1-(4-Methylbenzoyl)-2-(hydroxymethyl)pyrrolidine (12). A solution of (*S*)-(+)-2-pyrrolidinemethanol (**11**) (0.49 mL, 5.0 mmol) and triethylamine (0.70 mL, 5.0 mmol) in CH_2Cl_2 (20 mL) was cooled to -10 °C under N_2. After dropwise addition of *p*-toluoyl chloride (0.75 mL, 5.0 mmol) the mixture was stirred for 4 h. The mixture was diluted with dichloromethane (20 mL) and was washed with 10% citric acid (20 mL), sat. $NaHCO_3$ (20 mL), and sat. NaCl (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by chromatography (75% EtOAc/Hex to 100% EtOAc)

to afford a colorless oil (1.09 g, 91 % yield). $[\alpha]_D^{20}$ = -98.5 (*c* = 0.14, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.03 (br s, 1H), 4.40 – 4.38 (m, 1H), 3.77 (d, *J* = 11.0 Hz, 1H), 3.71 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.54 – 3.43 (m, 2H), 2.36 (s, 3H), 2.16 – 2.13 (m, 1H), 1.86 – 1.83 (m, 1H), 1.76 – 1.67 (m, 1H), 1.65 – 1.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 140.4, 133.7, 128.9, 127.2, 67.4, 61.5, 51.2, 28.6, 25.1, 21.4. FTIR ($CHCl_3$, cm^{-1}): 3398, 2968, 2875, 1617, 1570, 1555, 1513, 1420, 1340, 1287, 1230, 1182, 1145, 1110, 1087, 1051, 1020. MS (ESI, m/z): 220.1 [M+H], 242.0 [M+Na], 258.0 [M+K]. HRMS calculated for $C_{13}H_{18}NO_2$ 220.1338 found 220.1340 (M+H).



(*S*)-*N*-((1-(4-methylbenzoyl)pyrrolidin-2-yl)methyl)benzenesulfonamide (13b). A solution of **12** (0.110 g, 0.5 mmol) and triethylamine (0.30 mL, 2.0 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C under N_2. After dropwise addition of methanesulfonyl chloride (57 μL, 0.75 mmol) the mixture was stirred over 12 h. Water was added (5 mL) and the mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and used without further purification.

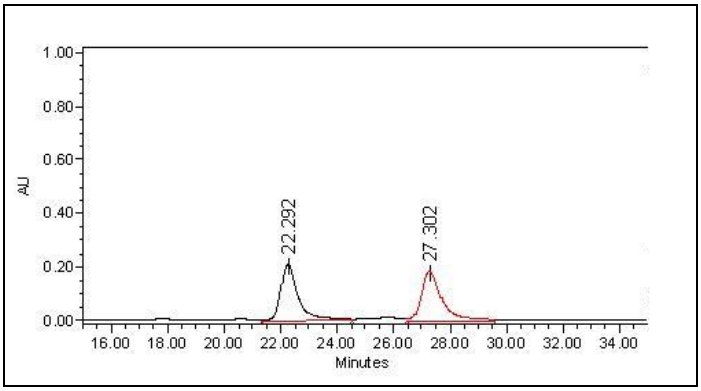
The resulting crude mixture was dissolved in DMF (2 mL) under N_2 and sodium azide (0.165 g, 2.5 mmol) was added. The solution was heated to 45 °C and stirred for 22 h. The mixture was cooled to room temperature and diluted with diethyl ether (15 mL). 2% (w/v)

aqueous $NaHCO_3$ was added and the organic layer was collected. The aqueous layer was then extracted with diethyl ether (2 x 15 mL). The organic layers were combined and washed with water (2 x 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude azide was passed through a plug of silica gel (EtOAc/hexanes), concentrated, and used without further purification. The crude azide was dissolved in THF (5 mL) and Pd/C (50 mg) was added. The flask was flushed with H_2 and then stirred under 1 atm of H_2 for 4 h. The mixture was filtered through a Celite plug, concentrated under reduced pressure, and used without further purification.

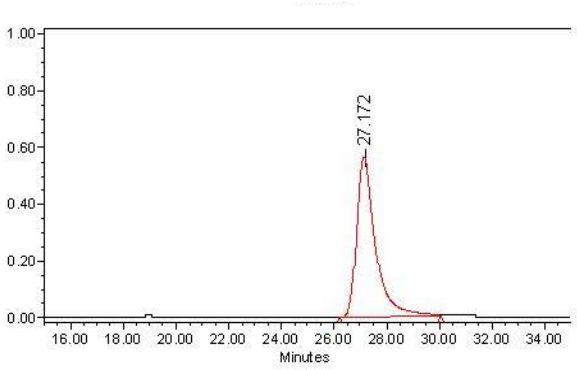
The crude residue was then dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C under N_2. Addition of triethylamine (0.10 mL, 0.7 mmol) was followed by dropwise addition of benzenesulfonyl chloride (40 μL, 0.3 mmol). The mixture was allowed to warm to room temperature and stir for 18 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with 1M HCl (15 mL). The organic layer was separated and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by chromatography (30:70, EtOAc:hexanes to 50:50, EtOAc:hexanes) to afford a white solid (0.077 g, 43 % yield). $[\alpha]_D^{20}$ = -41.9 (*c* = 0.075, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.38 (br s, 1H), 4.29 – 4.27 (m, 1H), 3.46 – 3.40 (m, 2H), 3.33 (ddd, *J*= 10.0 Hz, 6.5 Hz, 3.5 Hz, 1H), 3.08 (ddd, *J* = 11.5 Hz, 7.0 Hz, 4.0 Hz, 1H), 2.38 (s, 3H), 2.14 – 2.11 (m, 1H), 1.86 – 1.82 (m, 1H), 1.77 – 1.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 140.7, 140.1, 133.3, 132.4, 129.0, 128.9, 127.3, 126.9, 57.3, 50.9, 47.9, 29.4, 24.9, 21.4. FTIR ($CDCl_3$, cm^{-1}): 3167, 2972, 2877, 1726, 1685, 1608, 1566, 1514, 1445, 1426, 1328, 1205, 1160, 1093. m.p.

151°C MS (ESI, m/z): 359.3 [M+H], 381.2 [M+Na], 397.2 [M+K]. HRMS calculated for $C_{19}H_{23}N_2O_3S$, 359.1429 found 359.1430 (M+H).HPLC: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = 75:25, flow 0.5 mL/min, detection at 254 nm, r_t = 22.3 min (minor), 27.3 min (major).

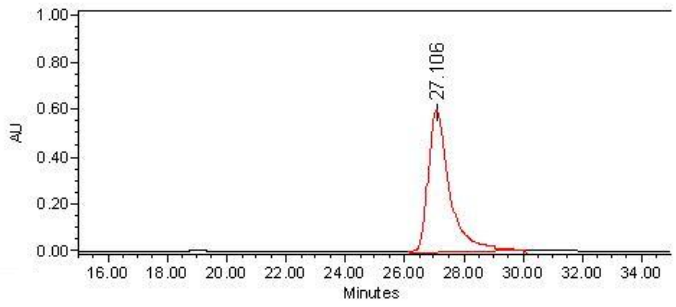
Racemic Trace: DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (75:25), flow 0.5 mL/min, detection at 254 nm, r_t=22.3 min., 27.3 min.



Trace of Diamination Product (**13**): DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (75:25), flow 0.5 mL/min, detection at 254 nm



HPLC trace for compound (**13 b**): DAICEL CHIRALPAK AD-H, hexanes/2-propanol = (75:25), flow 0.5 mL/min, detection at 254 nm



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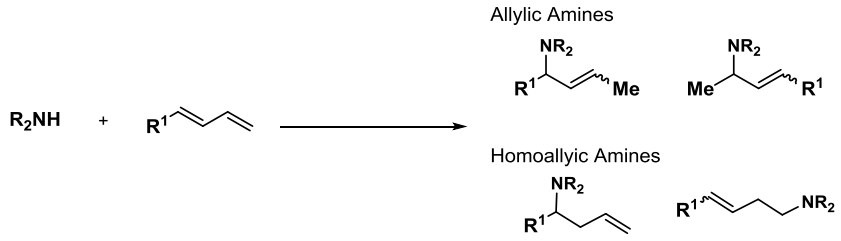
Chapter 2

Palladium-Catalyzed Hydroamination of 1,3-dienes[1]

Section 1. Introduction

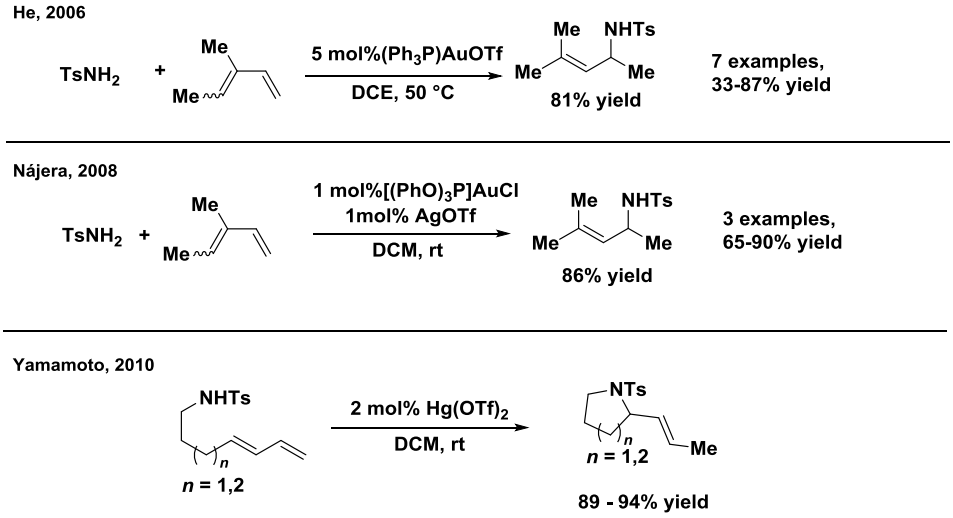
Nitrogen heterocycles are key features of many natural products and industrially relevant pharmaceuticals.[2] As a result, many methods for the construction of these core structures have been developed. In particular, the hydroamination of unsaturated hydrocarbons has arisen as a general and useful method for generating new carbon-nitrogen bonds in heterocycles due to its atom economy and mild reaction conditions.[3] Numerous transition metal and Brønsted acid hydroamination catalysts have been discovered.

Scheme 2.1 *Possible Regioisomers arising from Hydroaminations of 1,3-dienes*



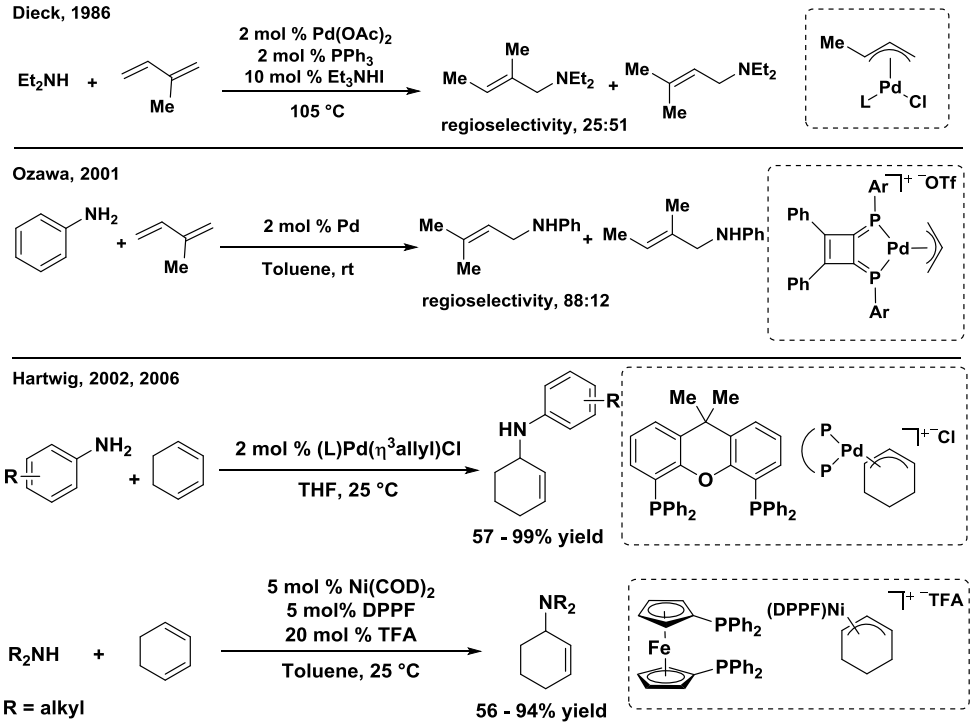
The hydroamination of 1,3-dienes is a useful transformation because the resulting aminoalkenes possess a handle for further functionalization. A major challenge for diene hydroamination catalysts is controlled formation of one of the several possible regioisomeric products (Scheme 2.1). In practice, the vast majority of reported diene hydroamination reactions are selective for the formation of allylic amine products (Scheme 2.2).[4]

Scheme 2.2 *Hydroaminations that produce allylic amine products*



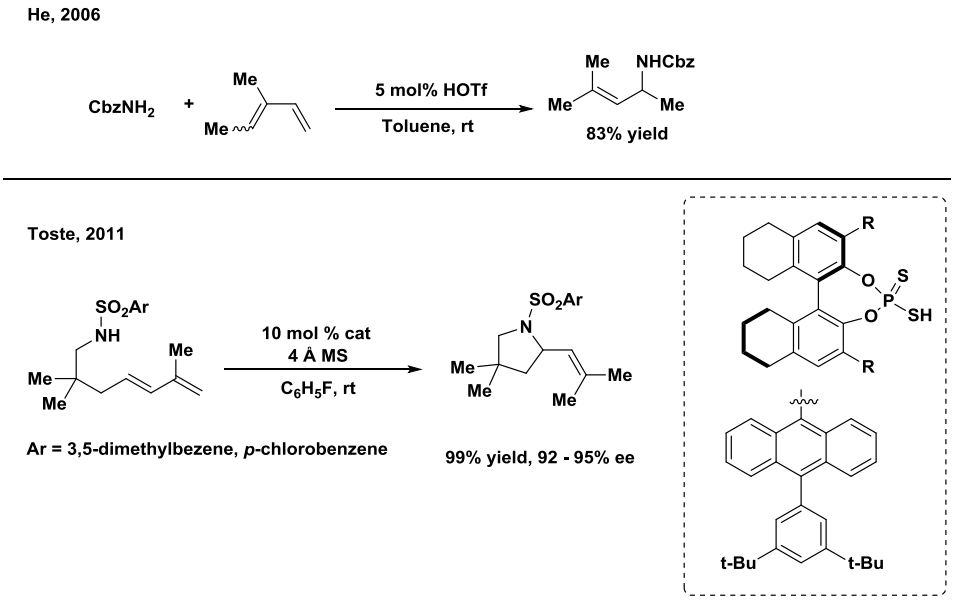
In particular, known hydroamination reactions catalyzed by Ni and Pd give exclusively allylic amines, due to the intermediacy of a η^3-allyl complex (Scheme 2.3).[5]

Scheme 2.3 *Ni and Pd η^3-allyl complexes give allylic amines*



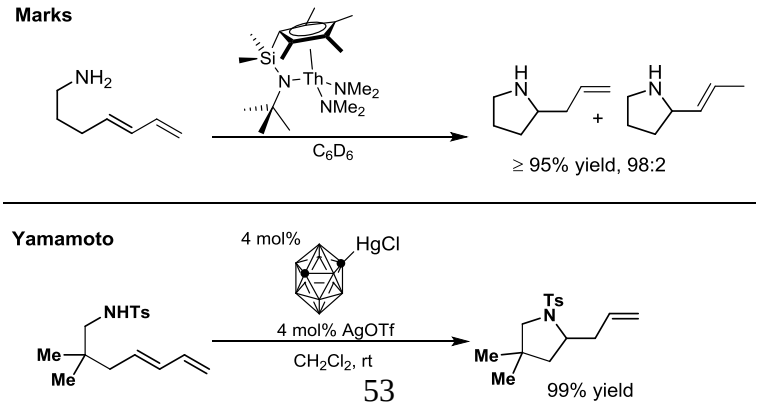
Similarly, Brønsted acid catalyzed hydroamination reactions also generate allylic amine products, as predicted by the stability of the intermediate allyl cation (Scheme 2.4).[6]

Scheme 2.4 *Brønsted acid catalyzed hydroaminations*



In contrast, the formation of homoallylic amine products in hydroamination reactions is a more challenging task. A few hydroamination catalysts have been reported to give mixtures of allylic and homoallylic amine products[7] but only two reports of hydroamination catalysts that selectively give homoallylic amines have been published (Scheme 2.5).

Scheme 2.5 *Previous hydroaminations that give homoallylic amines*



Marks has reported a Th catalyst that gives high selectivity for two substrates lacking substitution on the diene, but a third substituted diene substrate gives poor selectivity.[8b] Yamamoto has discovered a carboranyl Hg catalyst that affords exclusively homoallylic amines for a range of sulfonamidodiene substrates.[9] In this case, no substrates with substitution on the diene moiety were reported.

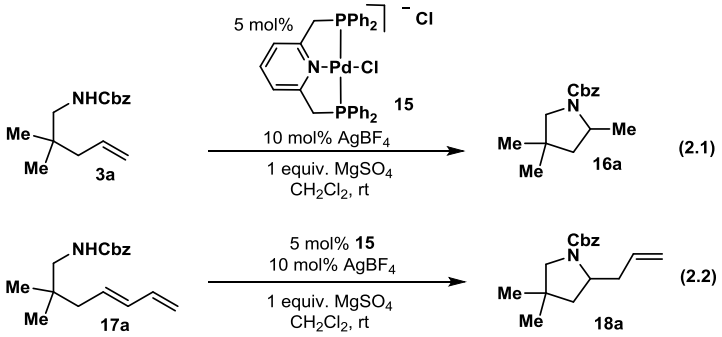
This chapter focuses on a Pd catalyst for the hydroamination of dienes that gives exclusively homoallylic amine products for a variety of diene substitution patterns in excellent yields.

Section 2. Results and discussion

2.2.1 Initial Results

Previously, our lab reported a mild Pd-catalyzed intramolecular hydroamination of aminoalkenes that generated pyrrolidine, piperidine, and piperazine scaffolds (Scheme 2.6, eq 2.1).[10] We hypothesized that the same Pd catalyst should also catalyze the hydroamination of dienes by a similar mechanism, and, by virtue of the increased reactivity of dienes, tolerate a greater range of substitution. Initial studies began by subjecting protected aminodiene **17a** to the previously reported hydroamination conditions (Scheme 2.6, eq 2.2).[11]

Scheme 2.6 *Pd-catalyzed Intramolecular Hydroaminations*

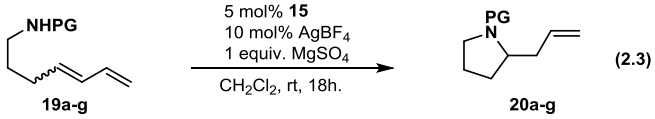


Encouragingly, this afforded a single isomer of the cyclization product in excellent yield. This isomer was identified as the homoallylic amine product **18a**, arising from 5-*exo* 1,2-addition.

2.2.2 Substrate Scope

Exposure of a substrate without geminal backbone substitution to these conditions gave the product in equally high yields and regioselectivity (Table 2.1, entry 1), establishing that this hydroamination catalyst is active even with substrates lacking Thorpe-Ingold effects.

Table 2.1 Protecting Group Scope



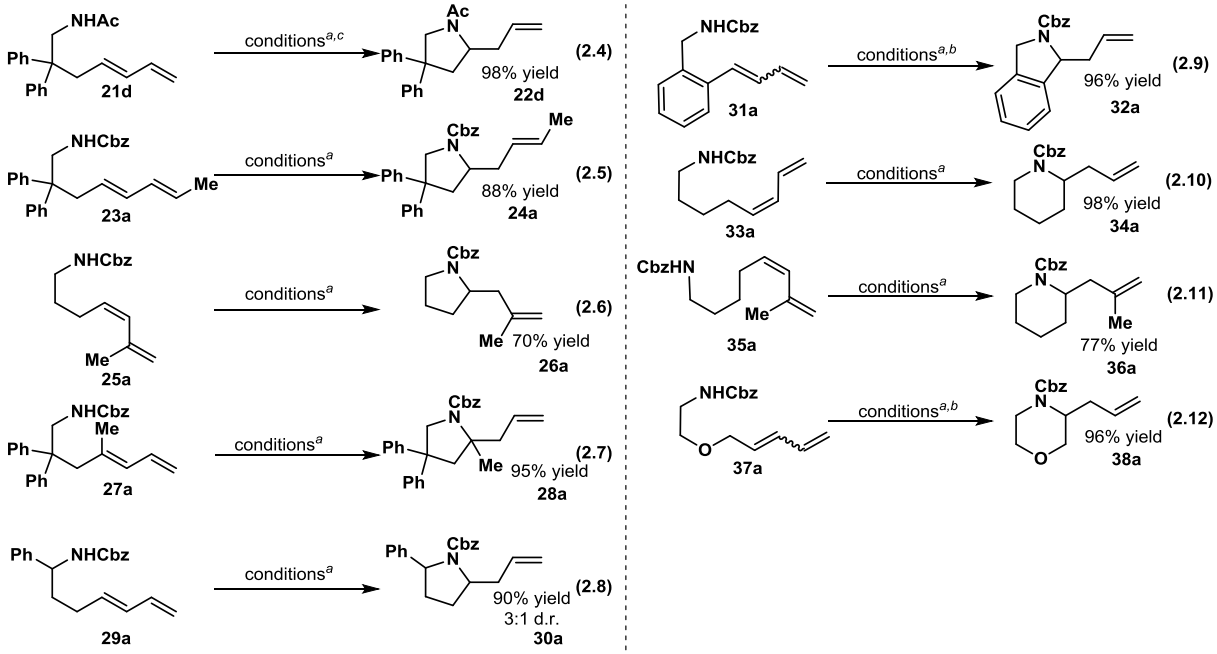
Entry	PG[a]	Product	% yield
1	Cbz (**19a**)	**20a**	>99,(95%)[b]
2	Boc (**19b**)	**20b**	76
3	*p*-Toluoyl (**19c**)	**20c**	86
4	Ac (**19d**)	**20d**	>99
5	Ts (**19e**)	**20e**	73
6	4-Ns (**19f**)	**20f**	97
7	SES (**19g**)	**20g**	73

[a] see Section 4 for *E*/*Z* ratios, [b] conducted on 1.8 mmol scale.

This reaction can be applied to substrates bearing a wide array of amine protecting groups (Table 2.1). Importantly, the synthetically useful protecting groups Cbz (**19a**) and Boc (**19b**) successfully gave hydroamination products, making this the only catalytic system that gives homoallylic amines with these protecting groups. Amides also cyclized in good to excellent yields (**19c-d**). Even sulfonamide protected amines (**19e-19g**) underwent hydroamination under standard conditions, which is somewhat surprising given the previous failure of catalyst **15** to react with sulfonamidoalkenes.[10]

The effect of diene substitution pattern on the regioselectivity of intramolecular hydroamination has not been extensively explored, so we prepared substituted diene substrates **23a**, **25a** and **27a**, bearing substitution at the 4, 3, and 1 positions of the diene, respectively. All three substrates cleanly underwent hydroamination, affording high yields of the allylpyrrolidine products (Scheme 2, eqs 2.5-2.7). The excellent yield of **28a** shows that this method can be used to construct sterically hindered tetrasubstituted carbon centers. Other backbone substitution patterns and lengths were also tolerated, affording isoindoline (**32a**), piperidine (**34a**) and morpholine (**38a**) heterocycles in >95% yield (eqs 2.9-2.12). Excellent regioselectivity (>20:1) was obtained in all cases.

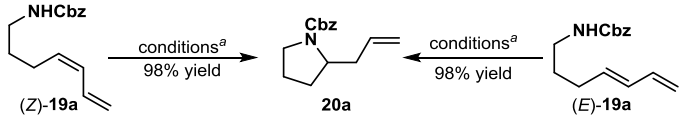
Scheme 2.7 *Hydroaminations of other substrates*



[a] 5 mol% **15**, 10 mol% $AgBF_4$, 1 equiv. $MgSO_4$, CH_2Cl_2, rt, 18 h. [b] see Section 4 for *E*/*Z* ratios. [c] same yield on both 0.2 and 2.0 mmol scale.

Though it is clear from that both *E* and *Z* alkenes are capable of undergoing hydroamination, we tested whether the initial stereochemistry had any influence on the hydroamination reactivity. Hydroamination of *E*-**19a** and *Z*-**19a** gave the same product in identical 98% yields, illustrating that alkene stereochemistry has little effect on the outcome of hydroamination (Scheme 2.8).

Scheme 2.8 *Hydroaminations of E and Z Dienes*

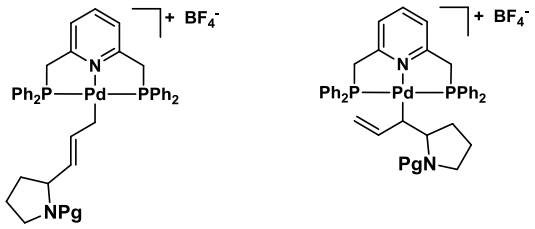


[a] 5 mol% **15**, 10 mol% $AgBF_4$, 1 equiv. $MgSO_4$, CH_2Cl_2, rt, 18h.

2.2.3 Hydroamination Mechanistic Studies

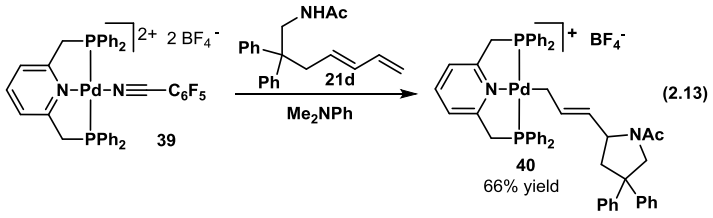
Understanding the high selectivity for formation of homoallylic amines in this system requires consideration of the possible mechanisms and key Pd-alkyl intermediates arising from aminopalladation of the diene.[10c] The use of the tightly bound tridentate ligand (PNP) allows the Pd catalyst only one open coordination site for catalysis, which hinders β-hydride elimation. The possible key η^1 intermediates are shown in *Figure 2.1*.

Figure 2.1 Possible η^1 allyl intermediates



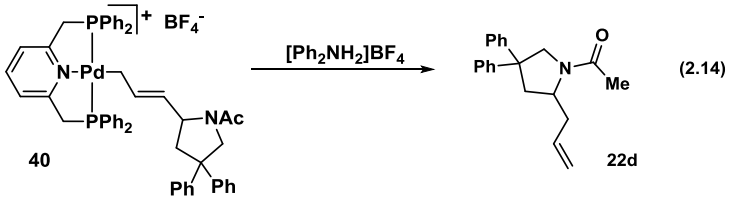
To investigate these intermediates, a stoichiometric reaction of the Pd complex with substrate **21d** was performed in the presence of various bases. *N,N*-Dimethylaniline proved to be an appropriately strong and bulky base to allow the allyl intermediate **40** to be isolated as a yellow solid in 66% yield (Scheme 2.9). NMR spectroscopy confirmed that the allyl group was bound to the distal terminus of the former diene moiety. Similar pincer-ligated Pd allyl complexes have been shown to be preferentially η^1.[12]

Scheme 2.9. *Formation of η^1-allyl Pd complex*



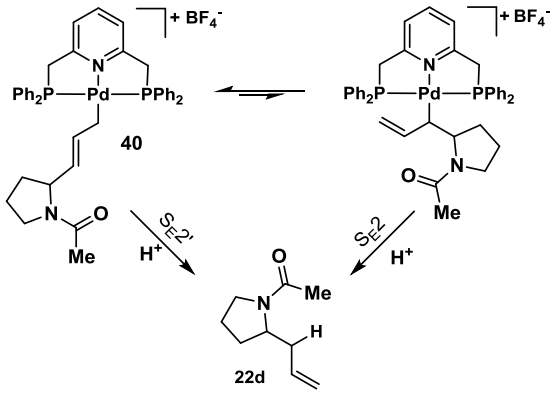
When complex **40** was treated with a Brønsted acid, hydroamination product **22d** was obtained, which was consistent with the intermediacy of this complex in the catalytic reaction.

Scheme 2.10. *Protonolysis of η^1-allyl Pd complex*



It appears that the regioselectivity observed in this hydroamination reaction arises from (i) initial 1,4-aminopalladation to form the less substituted η^1-allyl complex **40**, followed by (ii) regioselective S_E2' protonation of the Pd allyl complex. Although, since similar complexes to the two regioisomeric η^1-allyl complexes (*Figure 2.1*) are known to interconvert rapidly at room temperature,[12] we cannot rule out S_E2 protonation of the unobserved allyl isomer (Scheme 2.11).

Scheme 2.11. *Possible mechanisms for Protonolysis*



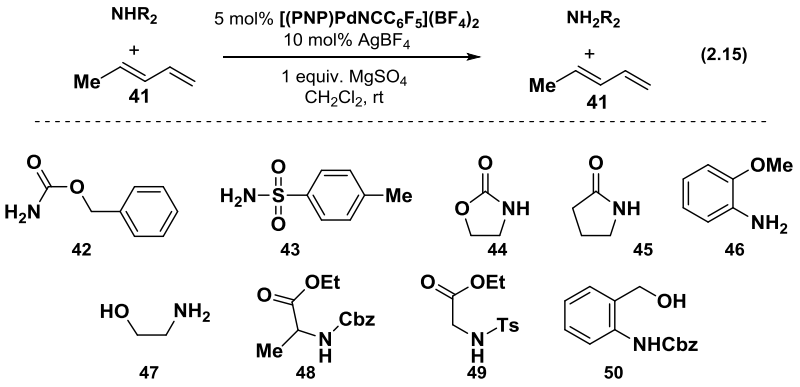
2.2.4 Intermolecular attempts and Urea substrates

The discovery that homoallylic amines could be exclusively generated from aminodienes increased the generality of **15** as a hydroamination catalyst, but limitations in this sytem still exist. The development of an intermolecular reaction which also only produces homoallylic amines would be a key advancement for this catalyst. Intermolecular hydroaminations of alkenes using **15** have been unsuccessful, possibly due to the high enthalpic and entropic barriers inherent in this reaction.[13] We reasoned that our observation of the higher reactivity of dienes in this system might be able to overcome these previous shortcomings.

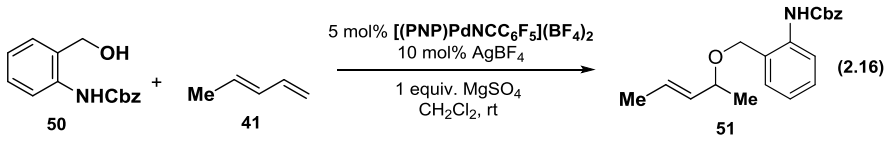
Studies towards the development of an intermolecular reaction began by combining 1,3-pentadiene and a variety of amine sources under the standard hydroamination conditions. Nitrogen sources **42** – **45** were choosen based on their similarity to amines that were successful in the previous intramolecular reaction. Other substrates were chosen due to the proximity of a hydrogen bonding functional group which could facilitate protonolysis, such as an alcohol or

carbonyl, **46** – **50**. Unfortunately, all of the amines, carbamates, amides, and anilines we subjected to this reaction did not result in hydroamination products (Scheme 2.9). Rather, almost all of these reactions resulted in the recovery of the initial diene and amine starting materials. The lone exception was with **50**, where a new product was observed. Characterization revealed it to be the Markovnikov product of the addition of the alcohol to the diene, which is most likely acid-catalyzed rather than Pd-catalyzed (Scheme 2.13).

Scheme 2.12. *Attempts toward Intermolecular 1,3-diene Hydroaminations*



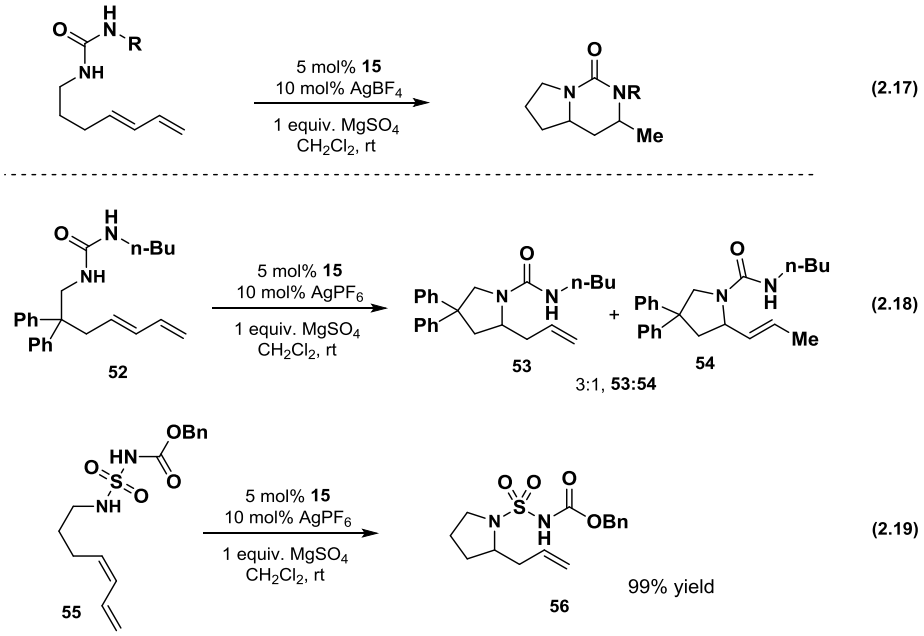
Scheme 2.13. *Reactivity of **50***



Another feature of this hydroamination is the fact that an alkene moiety remains after hydroamination. It is possible that this group could be further functionalized in a second hydroamination reaction. Urea protecting groups were highly reactive in the hydroamination of

alkenes, and we assumed that a urea protected amino-1,3-diene would rapidly undergo hydroamination as well. The resulting first hydroamination product would then be positioned to undergo a second hydroamination producing a 1,3-diamine in a bicyclic system (Scheme 2.14, eq 2.17). To test this double hydroamination, *n*-butyl urea derived diene **52** was synthesized. Using standard conditions, we found that this reaction gave a 3:1 mixture of homoallyic and allylic amines from an initial hydroamination reaction. The allylic amine product (**54**) may simply arise from isomerization of the homoallylic amine product under the long reaction times. We considered that the second hydroamination of this substrate lacks an external carbonyl group that appeared to be necessary in all previous hydroaminations catalyzed by **15**. Knowing that the hydroamination of 1,3-dienes tolerated sulfonyl protecting groups, we constructed a substrate consisting of a sulfonyl benzyl carbamate protecting group which includes a second external carbonyl from the carbamate. Once again, when substrate **55** was subjected to the reaction conditions, it smoothly produced the initial hydroamination product, homoallylic amine **56**, in quantitative yields.

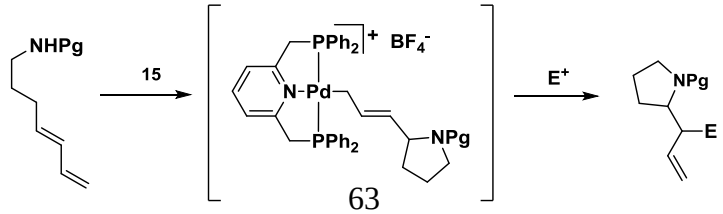
Scheme 2.14. *Double hydroamination attempts with urea substrates*



2.2.5 Alternate Electrophile attempts

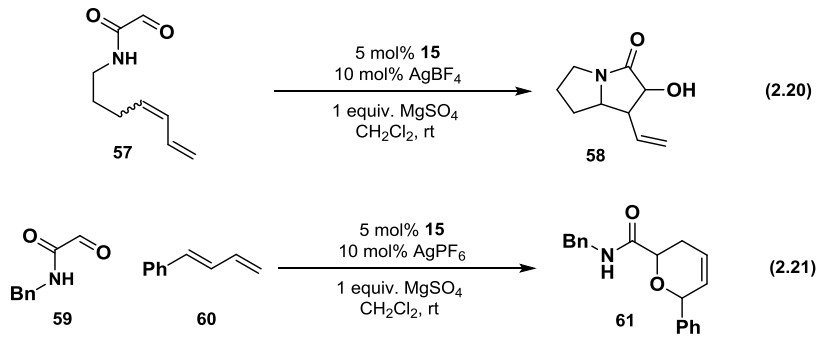
Since the key step of this reaction is protonation of Pd-allyl intermediate (**40**), it appears that **40** is a rare example of a nucleophilic Pd-allyl complex. Recent literature examples of nucleophillic allyl additions to aldehydes and imines have been accomplished using palladium catalysts with similar pincer ligands.[14] Noting the success of these reactions, we hoped to intercept the presumed η^1-allyl intermediate with an electrophile other than a proton (*Figure 2.2*).

Figure 2.2 Alternative Electrophiles



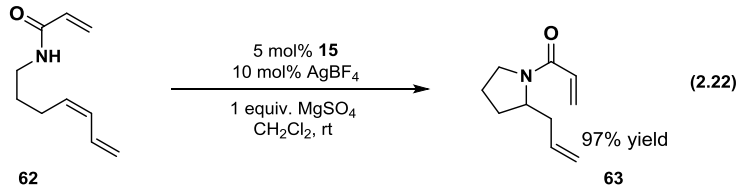
Initial work in this area has been accomplished in our lab by incorporating an intramolecular aldehyde into the substrate through the synthesis of a glyoxamide substrate, **57**.[15] Yields up to 50% of a mixture of diasteromers have been achieved. We attempted to extend this reaction to an intramolecular substrate, using 4-phenyl-1,3-butadiene and benzyl glyoxamide. When these substrates were subjected to the reaction conditions, a hetero Diels-Alder product was produced instead. Two diastereomers were isolated and characterized by ^{1}H NMR spectroscopy and COSY. Similar reactivity has been documented in the literature using Lewis Acid catalysts.[16]

Scheme 2.15. *Towards Developing an Intermolecular Tandem Hydroamination-allylation*



Knowing that this η^1-allyl intermediate has been intercepted with an intramolecular electrophile, we considered other possible tethered electrophiles. A substrate that incorporates a Michael acceptor in the protecting group was synthesized. When substrate **62** was subjected to standard hydroamination conditions it converted solely to the hydroamination product, which was isolated in 97% yield (Scheme 2.12).

Scheme 2.16. *Attempts at Intramolecular Michael Addition*



Section 3. Conclusion

In conclusion, a room temperature palladium catalyzed hydroamination of amino-1,3-dienes has been developed resulting in the formation of useful olefinic nitrogen heterocycles. This reaction occurred in high yields and high selectivity for the formation of homoallylic amines with intramolecular substrates. A wide variety of amine protecting groups could be employed and various diene substitution patterns were tolerated. A palladium η^1-allyl complex was isolated and shown to be a viable intermediate, giving insight into the reaction mechanism. Development of an intermolecular reaction, tandem double reaction with a urea protecting groups, and extension to alternative electrophiles were attempted.

Section 4. Experimental

1.1 General Procedures

All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise indicated. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass Spectroscopy on a Bruker Esquire 1100 Liquid Chromatograph Ion Trap Mass Spectrometer, Bruker Esquire with DART Ion Trap Mass Spectrometer, or a Hewlett

Packard 5971A Gas Chromatograph Mass Spectrometer. Column chromatography was performed using silica gel (Sorbent Technologies, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499, or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm) or CH_2Cl_2 (5.32 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.0 ppm). Melting points were taken on MEL-TEMP melting point apparatus and are uncorrected.

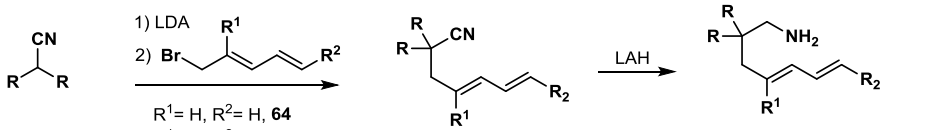
1.2 Materials

Tetrahydrofuran, diethyl ether, dichloromethane, and acetonitrile were degassed and dried by passing through a column of neutral alumina. 3Å molecular sieves were activated under vacuum at 200 °C for 14 h and stored in an oven at 120 °C. Toluene was degassed with nitrogen and dried by passing through a column of neutral alumina and a column of Q5 reactant. 3 Å and 4 Å molecular sieves were powdered and activated under vacuum at ~ 200 °C for 14 h and stored in a glove box or in an oven at 150°C. Deuterated solvents, $CDCl_3$ and CD_2Cl_2 were obtained from Cambridge Isotope Laboratories, Inc. unless otherwise stated and stored over activated 3Å molecular sieves. Palladium chloride and silver tetrafluoroborate were purchased from Strem Chemicals and used without further purification. Anhydrous magnesium sulfate, benzyl chloroformate, di-*tert*-butyldicarboxylate, *p*-toluoyl chloride, acetic anhydride, *p*-toluenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 2-(trimethylsilyl)ethanesulfonyl

chloride, and (4-bromobutyl)triphenylphosphonium bromide were purchased from Aldrich and used without further purification. 1,3-pentadiene was purchased and distilled prior to use.

1.3 Substrates synthesis

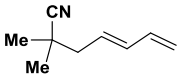
1.3.1 Synthesis of backbone-substituted aminodienes



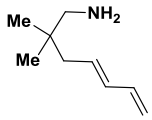
R= Me, R^1= H, R^2= H, **67**
R= Ph, R^1= H, R^2= H, **68**
R= Ph, R^1= H, R^2= Me, **69**
R= Ph, R^1 = Me, R^2= H, **70**

R= Me, R^1= H, R^2= H, **71**
R= Ph, R^1= H, R^2= H, **72**
R= Ph, R^1= H, R^2= Me, **73**
R= Ph, R^1= Me, R^2= H, **74**

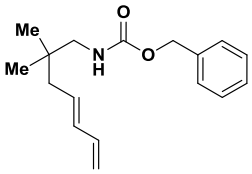
Dienyl bromides (**64**) and (**65**) were synthesized in a fashion analogous to previously reported methods.[17] Spectral data matches literature data for dienyl bromide (**66**).[18]



(*E*)-2,2-Dimethylhepta-4,6-dienenitrile (67). Synthesized according to a literature procedure.[6a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (dt, *J* = 16.8, 10.2 Hz, 1H), 6.16 (dd, *J* = 15.0, 10.2 Hz, 1H), 5.74 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 2.31 (d, *J* = 7.5 Hz, 2H), 1.34 (s, 6H).

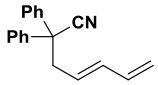


(*E*)-2,2-Dimethylhepta-4,6-dien-1-amine (71). Synthesized according to a literature procedure.[6a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.06 (dd, *J* = 15.1, 10.3 Hz, 1H) 5.70 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.10 (d, *J* = 16.7 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 2.45 (s, 2H), 2.00 (d, *J* = 7.5 Hz , 2H), 1.38 (br s, 2H), 0.86 (s, 6H).

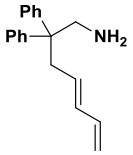


(*E*)-Benzyl 2,2-dimethylhepta-4,6-dienylcarbamate (17a). To a reaction flask was added (*E*)-2,2-dimethylhepta-4,6-dien-1-amine (**71**) (0.142 g, 0.8 mmol), CH_2Cl_2 (2 mL), triethylamine (0.28 mL, 2.0 mmol) and placed under a nitrogen atmosphere. The mixture was cooled to 0 °C and allowed to stir for one hour. To the mixture was added benzyl chloroformate (0.14 mL, 1.0 mmol) dropwise over a period of 5 minutes. The reaction was allowed to slowly warm to room temperature and stir overnight. The reaction quenched with water (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 2 mL) and combined organic layers were dried over $MgSO_4$, filtered and condensed. Purification by flash chromatography (10:1 Hex:EtOAc) afforded a colorless oil (0.056 g, 25% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.05 (m, 5H), 6.31 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.04 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.69 (dt, *J* = 15.2, 7.6 Hz, 1H), 5.10 (d, *J* = 16.5 Hz, 1H), 5.09 (s, 2H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.83 (br s,

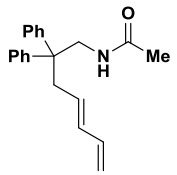
1H), 3.02 (d, J = 6.5 Hz, 2H), 1.99 (d, J = 7.7 Hz, 2H), 0.87 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 136.9, 136.6, 133.8, 130.7, 128.5, 128.1, 115.4, 66.6, 50.8, 42.9, 35.2, 24.7. ESI MS: 296.6 $[M+Na]^+$. FTIR ($CDCl_3$, cm^{-1}): 3434, 3341, 3085, 3032, 3008, 2960, 1701, 1534, 1468, 1454, 1244, 1139, 1071, 1039, 1028, 1004, 899.



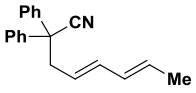
(*E*)-2,2-Diphenylhepta-4,6-dienenitrile (68). Synthesized according to a modified literature procedure.[19] Spectral data matches literature values.[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 – 7.27 (m, 10H), 6.30–6.13 (m, 2H), 5.57 (dt, J = 15.6, 7.2 Hz, 1H), 5.14 (d, J = 17.1 Hz, 2H), 5.03 (d, J = 10.5 Hz, 2H), 3.16 (d, J = 7.5 Hz, 2H).



(*E*)-2,2-Diphenylhepta-4,6-dien-1-amine (72). Synthesized according to literature procedure.[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.11 (m, 10H), 6.25–5.98 (m, 2H), 5.26 (dt, J = 14.6, 7.3 Hz, 1H), 5.05 (d, J = 15.1 Hz, 1H), 4.93 (d, J = 8.6 Hz, 1H), 3.31 (s, 2H), 2.95 (d, J = 7.4 Hz, 2H), 1.21 (br s, 2H).

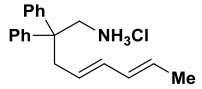


(*E*)-*N*-(2,2-Diphenylhepta-4,6-dienyl)acetamide (21d). To a reaction flask was added acetic anhydride (0.11mL, 1.2 mmol), and CH_2Cl_2 (1 mL). (*4E,6E*)-2,2-diphenylhepta-4,6-dien-1-amine (0.263 g, 1.0 mmol) was added dropwise at room temperature and the reaction was allowed to stir for 5 hours. Reaction was diluted with CH_2Cl_2 (5 mL) quenched with 1M NaOH (5 mL) and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (3:1 Hex: EtOAc) afforded the title compound as a colorless oil (0.250 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.17 (m, 10H), 6.14 (dt, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.93 (dd, *J* = 15.0 Hz, 10.0 Hz, 1H), 5.31 (dt, *J* = 15.0 Hz, 7.5 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 4.97 (br s, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 3.94 (d, *J* = 6.0 Hz, 2H), 2.87 (d, *J* = 7.5 Hz, 2H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 145.0, 136.7, 134.6, 129.4, 128.3, 128.27, 127.9, 126.5, 115.7, 50.5, 46.2, 40.9, 23.3. GC/MS(EI, m/z): 305(2)$[M]^+$, 264(60)$[M\text{-allyl}]^+$, 222(100). FTIR ($CDCl_3$, cm^{-1}): 3310, 3086, 3057, 2924, 1653, 1648, 1545, 1496, 1444, 1374, 1284, 1006, 906, 699.



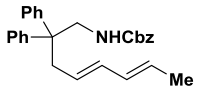
(*4E,6E*)-2,2-Diphenylocta-4,6-dienenitrile (69). Under an atmosphere of N_2, a suspension of sodium hydride (60% dispersion in oil, 9.63 mmol, 0.324 g) was dissolved in DMF (35 mL, 0.25

M) and cooled to 0 °C. Diphenylacetonitrile (8.76 mmol, 1.69 mg) was added and once hydrogen evolution stopped, dienyl bromide **(65)** was added dropwise. The mixture was slowly warmed to room temperature and allowed to stir overnight after which it was quenched with sat. ammonium chloride (50 mL) and extracted with ether (3 x 75 mL). The combined organic layers were washed with a 10% LiCl solution (2 x 50mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure affording a yellow oil that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.18 (m, 10H), 6.13 (d, *J* = 14.9, 10.9 Hz, 1H), 6.01 – 5.88 (m, 1H), 5.76–5.53 (m, 1H), 5.40 (dt, *J* = 14.6, 7.2 Hz, 1H), 3.13 (d, *J* = 7.2 Hz, 2H), 1.71 (d, *J* = 5.9 Hz, 3H).

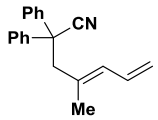


(*4E,6E*)-2,2-Diphenylocta-4,6-dien-1-amine HCl Salt (73). To a flame dried reaction flask under N_2, a suspension of lithium aluminum hydride (18 mmol, 0.702 g, 2 equiv.) in ether (25 mL) was cooled 0 °C. A solution of **53** (9 mmol, 2.5 g) in ether (5 mL) was added dropwise and the mixture was allowed to slowly warm to room temperature and stir overnight. The mixture was cooled to 0 °C and was quenched by the slow addition of 1M NaOH (~5mL), then filtered through a pad of celite. The filtrate was dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield the amine as a colorless oil. The amine was then acidified with 2M HCl in Ether. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 10H), 6.30 (dd, *J* = 15.3, 10.2 Hz, 1H),

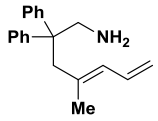
5.88 (dd, *J* = 14.4, 10.5 Hz, 1H), 5.67 – 5.56 (m, 1H), 5.05 – 4.95 (m, 1H), 3.55 – 3.51 (m, 2H), 3.10 (d, *J* = 6.9 Hz, 2H), 1.70 (br s, 3H) 1.69 (d, *J* = 6.6 Hz, 3H).



Benzyl (*4E*,*6E*)-2,2-diphenylocta-4,6-dienylcarbamate (23a): Under an atmosphere of nitrogen, dienylamine HCl salt **73** (0.314 g, 1.0 mmol) and triethylamine (0.44 mL, 3.0mmol) were dissolved in CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and benzyl chloroformate (0.30 mL, 2.0 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to stir for 5 hours. The reaction quenched with water at 0 °C and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and combined organic layers were washed with 0.5 M citric acid and sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and condensed under reduced pressure. Purification by flash chromatography (8:1 Hex: EtOAc) afforded the product as a clear oil (0.312 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.17 (m, 15H), 5.93 – 5.89 (m, 2H), 5.57 – 5.52 (m, 1H), 5.20 – 5.06 (m, 3H), 4.38 (br s, 1H), 3.93 (d, *J* = 6.0 Hz, 2H), 2.88 (d, *J* = 6.3 Hz, 2H), 1.70 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$):156.2, 145.2, 136.5, 134.1, 131.4, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 126.4, 125.9, 66.7, 50.6, 47.8, 40.7, 18.0. ESI MS: 412 $[M]^+$. FTIR ($CDCl_3$, cm^{-1}): 3433, 3059, 3029, 2932, 1717, 1515, 1496, 1445, 1224, 992, 911, 755, 734, 699.

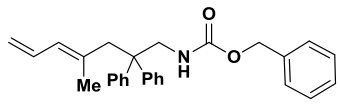


(*E*)-4-Methyl-2,2-diphenylhepta-4,6-dienenitrile (70). Under an atmosphere of N_2 a suspension of sodium hydride (60% dispersion in oil, 3.12 mmol) was dissolved in dimethylformamide (11 mL, 0.26 M). The mixture was cooled to 0 °C, diphenylacetonitrile (2.84 mmol, 0.55 g) was added and once hydrogen evolution stopped, dienyl bromide (**66)** was added dropwise. The reaction was slowly warmed to room temperature and allowed to stir overnight. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with ether (3 x 10 mL). The combined organic layers were washed with a 10% LiCl solution (2 x 10 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (15:1 Hex: EtOAc) afforded the product as colorless oil (0.62 g, 2.27 mmol, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.22 (m, 10H), 6.45 (dt, *J* = 16.3, 10.3 Hz, 1H), 5.80 (d, *J* = 11.1 Hz, 1H), 5.12 – 4.96 (m, 2H), 3.15 (s, 2H), 1.50 (s, 3H).



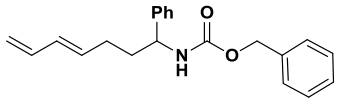
***(E)*-4-Methyl-2,2-diphenylhepta-4,6-dien-1-amine (74).** Under an atmosphere of N_2, a suspension of lithium aluminum hydride (4.6 mmol, 0.172 g) in ether (5 mL) was cooled to 0 °C. A solution of dienenitrile (**70**) (2.27 mmol, 0.62 g) in ether (2 mL) was added dropwise. The reaction was allowed to slowly warm to room temperature and stir until the nitrile was consumed

(TLC). The reaction was cooled to 0 °C and was quenched by the slow addition of 1M NaOH (~1 mL) and was allowed to stir an additional 30 minutes then filtered through a pad of celite. The filtrate was dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield the corresponding amine as a clear oil, which was used without further purification (0.595 g, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.17 (m, 10H), 6.48 (dt, *J* = 10.5, 16.8 Hz, 1H), 5.76 (d, *J* = 11.1 Hz, 1H), 5.08 – 4.97 (m, 2H), 3.36 (s, 2H), 2.97 (s, 2H), 1.08 (s, 3H), 0.87 (s, 2H).

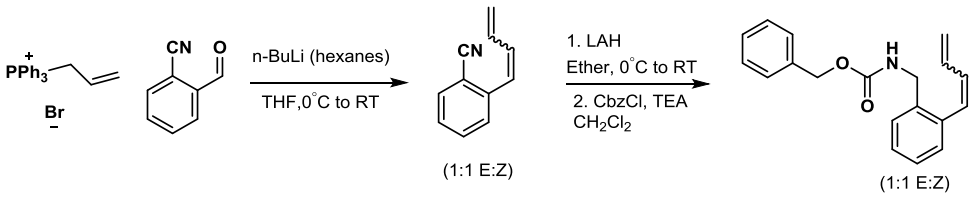


(*E*)-Benzyl 4-methyl-2,2-diphenylhepta-4,6-dienylcarbamate (27a). To a reaction flask was added **74** (0.595 g, 2.1mmol), CH_2Cl_2 (21 mL), triethylamine (0.36 mL, 2.6 mmol) and placed under a nitrogen atmosphere. The mixture was cooled to 0 °C and to the mixture was added benzyl chloroformate (0.34 mL, 2.4 mmol) dropwise over a period of 5 minutes. The reaction was allowed to slowly warm to room temperature and stir overnight. The reaction was quenched with 0.5 M citric acid (10 mL) and the layers were separated. The aqueous layer was extracted with ether (2 x 10 mL) and combined organic layers were washed with, saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered and condensed. Purification by flash chromatography (12:1–hexanes:EtOAc) afforded the product as a white solid (0.560 g, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.08 (m, 15H), 6.35 (dt, *J* = 17.0, 10.5 Hz, 1H), 5.63 (d, *J* = 11.0 Hz, 1H), 4.96 (s, 2H), 4.94 (m, 1H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.22 (s, 1H), 3.88 (d, *J* = 5.5 Hz, 2H), 2.81 (s, 2H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 145.5, 136.4, 132.8, 131.0, 128.3,

128.1, 128.0, 127.9, 126.4, 155.8, 66.49, 50.3, 47.0, 46.9, 18.2. ESI MS: 412 $[M+H]^+$, 429 $[M+NH_4]^+$. FTIR (CH_2Cl_2, cm^{-1}): 3433, 3086, 3060, 3032, 2924, 2855, 1725, 1642, 1597, 1505, 1554, 1444, 1366, 1221, 907, 756, 737, 699.



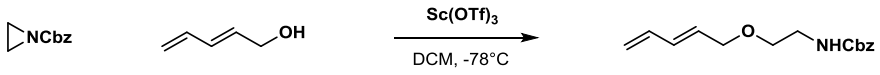
(*E*)-Benzyl 1-phenylhepta-4,6-dienylcarbamate (29a). (*E*)-1-phenylhepta-4,6-dien-1-amine[9] (0.599 g, 0.32 mmol), CH_2Cl_2 (2.0 mL), and triethylamine (0.053 mL, 0.38 mmol) were added to a reaction flask and placed under a nitrogen atmosphere. The mixture was cooled to 0 °C, and benzyl chloroformate (0.050 mL, 0.35 mmol) was added dropwise to the mixture. The reaction was allowed to slowly warm to room temperature and stir overnight. The reaction quenched with 0.5M citric acid (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography afforded the product as a colorless oil (0.050 g, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.08 (m, 10H), 6.28 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.01 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.66 (dt, *J* = 15.0, 6.6 Hz, 1H), 5.17 – 5.00 (m, 4H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.73 – 4.66 (m, 1H), 2.16 – 1.97 (m, 2H), 1.94 – 1.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 136.9, 136.3, 133.5, 131.7, 128.6, 128.4, 128.1, 127.4, 126.3, 115.3, 66.7, 55.0, 36.0, 29.1. ESI MS: 321.9 $[M+H]^+$, 338.9 $[M+NH_4]^+$. FTIR ($CDCl_3$, cm^{-1}): 3321, 3073, 3031, 2934, 2855, 1950, 1877, 1805, 1696, 1602, 1530, 1454, 1339, 1248, 1129, 1045, 1005, 951, 900, 752, 697.



Benzyl 2-(buta-1,3-dienyl)benzylcarbamate (31a). To a suspension of allyltriphenylphosphonium bromide[21] in 40 mL of THF was cooled to 0 °C and *n*-BuLi in hexanes (2M) was added dropwise. The mixture was allowed to stir for 30 min. Then a solution of 2-cyanobenzaldehyde in 10 mL of THF was added dropwise and the mixture was stirred for an additional hour at 0 °C, then warmed to room temperature and let stir for one more hour. A saturated solution of NH_4Cl (50 mL) was added and the mixture was extracted with ether (3 x 100 mL). The combined organic phases were washed and brine (100 mL) dried over $MgSO_4$, and the solvents were removed to give the crude product. The product was purified using column chromatography to yield a clear oil (0.250 g, 20% yield).

To a vacuum dried flask under N_2, lithium aluminum hydride (0.049 g, 1.33 mmol) was added to the flask followed by 5 mL of ether. The mixture was cooled to 0 °C, and the crude dienylnitrile (0.201 g, 1.3 mmol) was dissolved in 5 mL of ether and added dropwise over 10 min. The mixture was allowed to stir at room temperature overnight. The mixture was then quenched with 1 mL of 1 M NaOH, diluted with ether, filtered through a pad of celite and concentrated to afford a white solid as the crude product. The crude product was used without further purification.

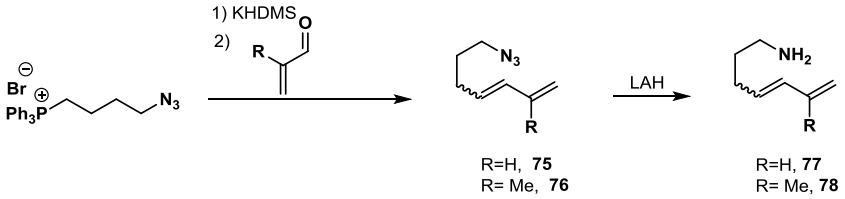
To a flame dried flask, the crude dienamine was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C. Triethylamine (0.52 mL, 3.9 mmol) was then added to the mixture which was allowed to stir at 0°C for 10 min. Benzylchloroformate (0.55 mL, 3.9 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature and stir overnight. The mixture was diluted with CH_2Cl_2 and washed with 1 M HCl (2 x 20 mL) and sat. $NaHCO_3$ (1 x 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (15:85, EtOAc:hexanes) and a clear oil was obtained (0.205 g, 26% yield). ^{1}H NMR (500 MHz, $CDCl_3$, isolated as a 1:1 mixture of *E/Z* isomers): 7.45 (d, *J* = 7.5 Hz, 1H), 7.28 – 7.14 (m, 17H, both), 6.71 (d, *J* = 16.0 Hz, 1H), 6.35 (dd, *J* = 15.5, 10.0 Hz, 1H), 6.78 – 6.43 (m, 2H, both), 6.26 (t, *J* = 11.0 Hz, 1H), 5.27 (dd, *J* = 16.5, 4.0 Hz, 2H, both), 5.12 (t, *J* = 10.5 Hz, 2H, both), 5.04 (t, *J* = 6.5 Hz, 4H, both), 4.89 (br s, 1H), 4.84 (br s, 1H), 4.38 (d, *J* = 5.5 Hz, 2H), 4.29 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 156.2, 156.0, 137.2, 136.5, 136.4, 136.2, 136.0, 135.9, 135.1, 133.0, 132.3, 132.2, 130.2, 128.5, 128.48, 128.1, 127.8, 127.6, 127.3, 125.9, 119.8, 118.3, 66.8, 66.77, 43.1. GC/MS (EI, m/z): 293(1) $[M]^+$, 202(4), 158(20), 91(100). FTIR ($CDCl_3$, cm^{-1}): 3335, 3085, 362, 3028, 2058, 2934, 2887, 1703, 1520, 1454, 1249, 1131, 1003, 753, 697.

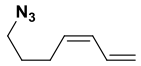


(*E*)-Benzyl-2-(penta-2,4-dienyloxy)ethylcarbamate (37a). A solution of benzylaziridine-1-carboxylate[22] (354.4 mg, 2.0 mmol) and (*E*)-penta-2,4-dien-1-ol[23] (336.5 mg, 4.0 mmol) in

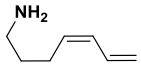
CH_2Cl_2 (5.0 ml) was cooled to -78 °C and quickly followed by addition of $Sc(OTf)_3$ (98.4 mg, 0.2 mmol). The mixture stirred at -78 °C for 2 hours. The mixture was warmed to room temperature and quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product was purified by chromatography (70:30–hexanes:EtOAc) to give product as a yellow oil (421.0 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): Isolated as a mixture of olefin isomers *E*/*Z* = (9:1) δ 7.38 – 7.29 (m, 10H, both), 6.64 – 6.53 (dt, J = 16.7, 10.6 Hz, 1H, minor), 6.33 (dt, J = 16.8, 10.2 Hz, 1H, major), 6.23 (dd, J = 15.0, 10.6 Hz, 1H, major), 6.14 (t, J = 11.2 Hz, 1H, minor), 5.74 (dt, J = 15.0, 6.0 Hz, 1H, major), 5.54 (dt, J = 10.5, 7.0 Hz, 1H, minor), 5.21 (d, J = 16.7 Hz, 1H, major), 5.18 (br s, 2H, both), 5.14 – 5.06 (m, 3H, both), 4.15 (d, J = 6.7 Hz, 2H, minor), 4.01 (d, J = 5.9 Hz, 2H, major), 3.61 (t, J = 5.3 Hz, 2H, minor), 3.50 (t, J = 4.9 Hz, 2H, major), 3.39 (q, J = 5.1 Hz, 4H, both). ^{13}C NMR (125 MHz, $CDCl_3$): 156.4 (both), 136.5 (both), 136.1 (major), 133.4 (major), 132.2 (minor), 131.4 (minor), 129.5 (both), 128.5 (both), 128.1 (both), 119.5 (minor), 117.9 (major), 71.1 (both), 68.9 (both), 66.6 (both), 40.9 (both). ESI MS: 261.9 $[M+H]^+$. FTIR ($CDCl_3$, cm^{-1}): 3425, 3336, 3087, 3065, 3034, 2937, 2863, 1953, 1812, 1716, 1699, 1603, 1538, 1519, 1455, 1406, 1353, 1330, 1254, 1147, 1115, 1063, 1007, 955, 908, 823, 776, 753, 737, 698.

1.3.2 Synthesis of backbone-unsubstituted aminodienes

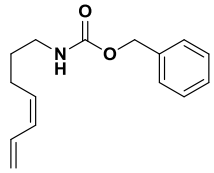




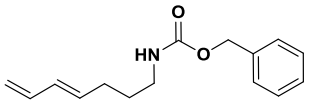
(*Z*)-7-Azidohepta-1,3-diene (75) Synthesized according to a literature procedure.[24] NMR (300 MHz, $CDCl_3$): δ 6.62 (dt, *J* = 17.0 10.3 Hz, 1H), 6.06 (t, *J* = 10.9 Hz, 1H), 5.41 (dt, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.69 (quint., *J* =7.3 Hz, 2H).



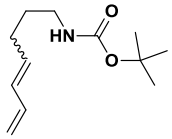
(*Z*)-Hepta-4,6-dien-1-amine (77). Synthesized according to a literature procedure.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (dt, *J* = 17.1, 10.5 Hz , 1H), 6.01 (t, *J* = 11.0 Hz, 1H), 5.45 (dt, *J* = 10.5, 8.1 Hz, 1H), 5.19 (d, *J* = 17.0 Hz , 1H), 5.09 (d, *J* = 10.2 Hz , 1H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.24 (q, *J* = 6.6 Hz, 2H), 1.54 (quint., *J* = 7.5 Hz, 2H), 1.40 (br s, 2H).



(*Z*)-Benzyl hepta-4,6-dienylcarbamate ((*Z*)-19a). Under a nitrogen atmosphere hepta-4,6-dien-1-amine (**77**) (0.129 g, 1.2 mmol) was dissolved in CH_2Cl_2 (11 mL) and triethylamine (0.19 mL, 1.4 mmol). The mixture was cooled to 0 °C, benzyl chloroformate (0.14 mL, 1.0 mmol) was added dropwise over the period of 10 minutes after which it was allowed to warm to room temperature and stir overnight. The mixture was quenched with 0.5 M citric acid (4 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 10 mL) and combined organic layers were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and condensed under reduced pressure. Purification by flash chromatography (90:10, hexanes:EtOAc) afforded the product as a colorless oil (0.182 g, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 5H), 6.61 (dt, *J* = 16.5, 10.5 Hz, 1H), 6.03 (t, *J* = 10.5 Hz, 1H), 5.45 (dt, *J* = 10.0, 7.5 Hz, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 5.12–5.10 (m, 3H), 4.89 (br s, 1H), 3.21 (q, *J* = 6.5 Hz, 2H), 2.22 (q, *J* = 7.5 Hz, 2H), 1.61 (quint., *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 136.6, 131.8, 131.2, 130.0, 128.5, 128.1, 117.3, 66.6, 40.1, 29.7, 24.9. GC/MS (EI, m/z): 245(1) $[M]^+$, 184(8), 93(27), 91(100). FTIR (CH_2Cl_2, cm^{-1}): 3332, 3030, 3007, 2936, 1699, 1535, 1252, 1134, 999, 906, 736, 697.

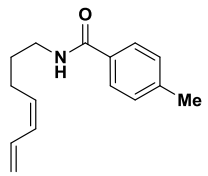


(*E*)-Benzyl hepta-4,6-dienylcarbamate((*E*)-(19a). Under a nitrogen atmosphere (*E*)-hepta-4,6-dien-1-amine[8a] (0.072 g, 0.65 mmol) was dissolved in CH_2Cl_2 (5 mL) and triethylamine (0.266 mL, 1.95 mmol). The mixture was cooled to 0 °C, benzyl chloroformate (0.14 mL, 1.95 mmol) was added dropwise over the period of 10 minutes after which it was allowed to warm to room temperature and stir overnight. The mixture was diluted with CH_2Cl_2 (1 x 20mL), and washed with 1M HCl (1 x 20 mL) and sat. $NaHCO_3$ (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and condensed under reduced pressure. Purification by flash chromatography (20:1, hexanes:EtOAc) afforded the product as a colorless oil (0.100 g, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 5H), 6.61 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.06 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.68 (dd, *J* = 14.7, 7.2 Hz, 1H), 5.21 – 5.07 (m, 4H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.73 (br s, 1H), 3.21 (q, *J* = 6.5 Hz, 2H), 2.22 (q, *J* = 7.2 Hz, 2H), 1.66 – 1.57(m, 2H).



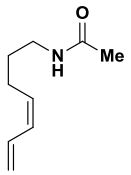
***Tert*-butyl hepta-4,6-dienylcarbamate (19b).** Under an atmosphere of nitrogen, hepta-4,6-dien-1-amine (**77**) (0.129 g, 1.2 mmol) was dissolved in CH_2Cl_2 (4 mL). To the solution was added a mixture of di-*tert*-butyl dicarbonate (0.252 mg, 1.2 mmol) in CH_2Cl_2 (0.5 mL) and the reaction was allowed to stir at room temperature overnight. The mixture was concentrated and the

remaining oil was purified by flash chromatography (10:1, hexanes:EtOAc). To afford the product as a colorless oil (0.146 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): Isolated as a mixture of olefin isomers *Z*/*E* = (3:1) δ 6.60 (dt, *J* = 17.0, 10.5 Hz, 1H, major), 6.29 (dt, *J* = 17.0, 10.5, 1H, minor), 6.06 (dd, *J* = 15.0, 10.5 Hz, 1H, minor), 6.02 (t, *J* = 10.5 Hz 1H, major), 5.68 (dt, *J* = 15.0, 7.0, 1H, minor), 5.42 (dd, *J* = 18.0, 8.0 Hz, 1H, major), 5.19 (d, *J* = 16.5 Hz, 1H, major), 5.10 (d, *J* = 10.0 Hz, 1H, major), 5.09 (d, *J* = 17.5 Hz, 1H, minor), 4.96 (d, *J* = 10.0 Hz, 1H, minor), 4.71 (br s, 2H, both), 3.12 (d, *J* = 5.5 Hz, 4H, both), 2.22 (q, *J* = 7.5 Hz, 2H, major), 2.12 (q, *J* = 7.5 Hz, 2H, minor), 1.57 (quint, *J* = 7.5 Hz, 4H, both), 1.44 (s, 18H, both). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9 (both), 28.4 (both), 29.9 (both), 40.1 (both), 79.1 (both), 115.2(minor), 117.4 (major), 129.9 (major), 131.4 (major), 131.6(minor), 131.9(major), 134.0(minor), 137.0(minor), 156.0(both). GC/MS (EI, m/z): 211(1)$[M]^+$, 155(16), 57(100). FTIR ($CDCl_3$, cm^{-1}): 3349, 3083, 3006, 2977, 2930, 1700, 1507, 1365, 1270, 1251, 1173, 999, 902, 783.



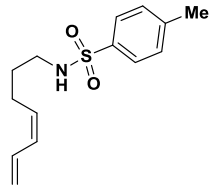
***(Z)-N*-(Hepta-4,6-dienyl)-4-methylbenzamide (19c).** Under an atmosphere of nitrogen, hepta-4,6-dien-1-amine (**77**) (0.129 g, 1.2 mmol) and triethylamine (0.18 mL, 1.3 mmol) were dissolved in CH_2Cl_2 (4 mL). The mixture was cooled to 0 °C and *p*-toluoyl chloride (0.168 mL, 1.3 mmol) was added dropwise and then was allowed to warm up to room temperature and stir overnight. The mixture was quenched with 1M HCl and the layers were separated. The aqueous

later was extracted once with ether and the combined organic layers were dried over $MgSO_4$, filtered and condensed under reduced pressure. Purification by flash chromatography (80:20, hexanes:EtOAc) afforded the product as a white solid (0.201g, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.62 (dt, *J* = 17.0, 10.5 Hz, 1H), 6.25 (br s, 1H), 6.04 (t, *J* = 10.5 Hz, 1H), 5.46 (dd, *J* = 18.0, 8.0 Hz, 1H), 5.21 (d, *J* = 16.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 3.46 (q, *J* = 6.5 Hz, 2H), 2.38 (s, 3H), 2.29 (q, *J* = 7.0 Hz, 2H), 1.72 (quint., *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 141.7, 131.8, 131.4, 123.0, 129.1, 126.8, 117.6, 39.6, 29.4, 25.2, 21.4. ESI MS: 230[M+H$^+$], 252 [M+Na$^+$], 481[2M+Na$^+$]. FTIR ($CDCl_3$, cm^{-1}): 3318, 3084, 3028, 3007, 2926, 2864, 1634, 1553, 1538, 1505, 1435, 1306, 1189, 1000, 966, 903, 838, 753. mp: 45 °C



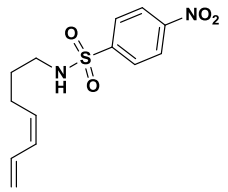
(*Z*)-*N*-(Hepta-4,6-dienyl)acetamide (19d). Under an atmosphere of nitrogen, acetic anhydride (0.57 mL, 6.0 mmol) was dissolved in CH_2Cl_2 (5 mL). Hepta-4,6-dien-1-amine (**77**) (0.555 g, 5.0 mmol) was added dropwise at room temperature and the reaction was allowed to stir for 5 hours. The mixture was quenched with 1M NaOH (5 mL) and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by

flash chromatography (50:50, hexanes:EtOAc) afforded the product as a colorless oil (0.625 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (dt, *J* = 17.0, 11.0 Hz, 1H), 6.03 (t, *J* = 11.0 Hz, 1H), 5.48 (br s, 1H), 5.42 (dd, 18.0, 8.0 Hz, 1H), 5.20 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 3.26 (q, 7.0 Hz, 2H), 2.23 (q, 7.0 Hz, 2H), 1.96 (s, 3H), 1.60 (quint., *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 131.8, 131.3, 130.0, 117.6, 29.4, 25.1, 23.4. GC/MS (EI, m/z): 153(3)$[M]^+$, 94(77), 79(100). FTIR ($CDCl_3$, cm^{-1}): 3289, 3084, 3008, 2930, 2862, 1653, 1560, 1560, 1555, 1437, 1369, 1292, 1197, 1157, 1103, 1039, 998, 904.



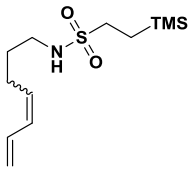
(*Z*)-*N*-(Hepta-4,6-dienyl)-4-methylbenzenesulfonamide (19e). Under an atmosphere of nitrogen, hepta-4,6-dien-1-amine (**77**) (0.111 g, 1.0 mmol) and triethylamine (0.35mL, 2.5mmol) were dissolved in CH_2Cl_2 (5 mL). The reaction was cooled to 0 °C and *p*-toluenesulfonyl chloride (0.210 g, 1.1 mmol) was added. The mixture was warmed to room temperature and stirred an additional 30 minutes. It was then quenched with 0.1M citric acid (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 5 mL) and the combined organic layers were washed with 1M NaOH (5 mL), brine (5 mL) dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (6:1, hexanes:EtOAc) afforded the compound as a colorless oil (0.109 g, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.52 (dtd, *J* = 17.0, 10.5, 1.0 Hz, 1H), 5.97 (t, *J* = 10.5 Hz, 1H) 5.31 (dd, *J* = 18.0, 8.0 Hz, 1H), 5.17 (d, *J* = 11.5 Hz, 1H) 5.08 (d, *J* = 10.0 Hz, 1H), 4.88

(br d, J = 19.0, 2H), 2.93 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.16 (q, J = 7.5 Hz, 2H), 1.55 (quint., J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 136.7, 131.8, 130.7, 130.2, 129.7, 127.0, 117.6, 42.7, 29.4, 24.7, 21.5. GC/MS (EI, m/z): 265(2) $[M]^+$, 184(57), 155(81), 91(100), 41(18). FTIR (CH_2Cl_2, cm^{-1}): 3281, 3007, 2937, 2867, 1598, 1494, 1434, 1324, 1305, 1289, 1160, 1095, 999, 951, 903, 814, 707, 667.



(*Z*)-*N*-(Hepta-4,6-dienyl)-4-nitrobenzenesulfonamide (19f). Under an atmosphere of nitrogen, hepta-4,6-dien-1-amine (0.111 g, 1.0 mmol) was added to a reaction flask followed by triethylamine (0.28 mL, 2.0 mmol) and CH_2Cl_2 (2 mL). The reaction was cooled to 0 °C and 4-nitrobenzenesulfonyl chloride (0.221g, 1.0 mmol) was added. The reaction was warmed to room temperature and stirred an additional 24 hours. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with 1M HCl (2 x 5 mL). The organic layer was then dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (80:20, hexanes:EtOAc) afforded the product as a white solid (0.202 g, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 6.47 (dt, J = 17.0, 11.0 Hz, 1H), 5.94 (t, J = 11.0 Hz, 1H), 5.41 (t, J = 6.0 Hz, 1H), 5.31-5.26 (m, 1H), 5.13 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 11.0 Hz, 1H), 2.98 (q, J = 6.5 Hz, 2H), 2.15 (q, J = 7.5 Hz, 2H), 1.56 (quint., J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz,

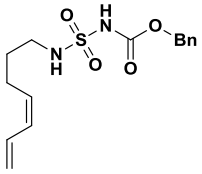
$CDCl_3$): δ 24.8, 29.6, 43.1, 118.1, 124.7, 128.6, 130.6, 130.7, 131.9, 146.0, 150.3. GC/MS (EI, m/z): 296(5) $[M]^+$, 215(82), 122(75), 94(80), 79(100), 41(44). FTIR ($CDCl_3$, cm^{-1}): 3295, 3105, 2940, 2868, 1530, 1350, 1311, 1165, 1093, 855, 746, 736, 686, 611. mp: 78 °C



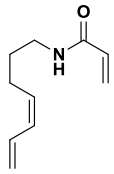
***N*-(Hepta-4,6-dienyl)-2-(trimethylsilyl)ethanesulfonamide (19g).** Hepta-4,6-dien-1-amine (0.111 g, 1.0 mmol) was added to a reaction flask followed by triethylamine (0.28 mL, 2.0 mmol) and CH_2Cl_2 (2 mL). The reaction was cooled to 0 °C and 2-(trimethylsilyl)ethanesulfonyl chloride (0.189 g, 1.0 mmol) was added. The reaction was warmed to room temperature and stirred an additional 24 hrs. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with 1M HCl (2 x 5 mL). The organic layer was then dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (80:20, hexanes:EtOAc) to afford the title compound as a pale yellow oil (0.109 g, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$): Isolated as a mixture of olefin isomers *Z*/*E* = (10:1) δ 6.61 (dtd, *J* = 17.0, 10.5, 1.0 Hz, 1H, major), 6.29 (dt, *J* = 17.0, 10.0 Hz, 1H, minor), 6.05 (t, *J* = 11.0 Hz, 2H, both), 5.66 (dt, *J* = 15.0, 7.0 Hz, 1H, minor), 5.41 (dt, *J* = 10.0, 8.0 Hz, 1H, major), 5.22 (d, *J* = 17.0 Hz, 1H, major), 5.13 (d, *J* = 10.5 Hz, 1H, major), 5.11 (d, *J* = 13.0 Hz, 1 H minor), 5.00 (d, *J* = 11.0 Hz, 1H, minor), 4.23 (br s, 2H, both), 3.11 (q, *J* = 7.0 Hz, 4H, both), 2.94 – 2.90 (m, 4H, both), 2.27 (dq, *J* = 7.5, 1.0 Hz, 4H, both),

1.67 (quint., J = 7.5 Hz, 4H, both), 1.02 – 0.98 (m, 4H, both), 0.05 (s, 18 H, both). ^{13}C NMR (125 MHz, $CDCl_3$): 136.8 (minor), 133.1(minor), 132.1(minor), 131.7(major), 130.6 (major), 130.4 (major), 1178.0 (major), 115.7 (minor), 48.7 (both), 42.8 (major), 30.2 (major), 29.8 (minor), 29.4 (minor), 24.7 (both), 10.6 (both), -2.0 (both). ESI MS: 293 $[M+NH_4]^+$, 568 $[2M+NH_4]^+$. FTIR (CH_2Cl_2, cm^{-1}): 3285, 3084, 3009, 2952, 2897, 1433, 1321, 1283, 1263, 1251, 1169, 1143, 860, 842, 758, 699.

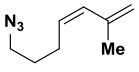
***(Z)-N*-(Hepta-4,6-dienyl)-*N'*-(benzyloxycarbonyl)sulfamide (55).** Hepta-4,6-dien-1-amine (**77**) (0.111 g, 1.0 mmol) was added to a reaction flask followed by triethylamine (0.28 mL, 2.0 mmol) and CH_2Cl_2 (2 mL). The reaction was cooled to 0 °C and benzyloxycarbonylaminosulfonyl chloride[25] (0.189 g, 1.0 mmol) in 2 mL of dichloromethane was added. The reaction was warmed to room temperature and stirred an additional 24 hrs. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with 1M HCl (2 x 5 mL). The organic



layer was then dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (100% CH_2Cl_2) to afford the title compound as a white solid (0.120 g, 7% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.33 (br s, 5H), 6.58 (dt, J = 16.8, 10.5 Hz, 1H), 6.02 (t, J = 10.8 Hz, 1H), 5.37 – 5.29 (m, 2H), 5.23 – 5.10 (m, 4H), 3.04 (q, J = 7.0 Hz, 2H) 2.24 – 2.19 (m, 2H), 1.65 – 1.56 (m, 2H).

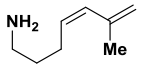


***(Z)-N*-(Hepta-4,6-dienyl)-acrylamide (62).** Hepta-4,6-dien-1-amine (**77**) (0.43 g, 3.45 mmol) was added to a reaction flask followed by triethylamine (0.7 mL, 6.9 mmol) and CH_2Cl_2 (10 mL). The reaction was cooled to 0 °C and acryloyl chloride (0.34 g, 3.8 mmol) was added. The reaction was warmed to room temperature and stirred an additional 24 hrs. The reaction was diluted with CH_2Cl_2 (50 mL) and washed with 1M HCl (1 x 25 mL) and 1 M NaOH (1 x 25 mL). The organic layer was then dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (90:10, hexanes:EtOAc) to afford the title compound as a colorless oil (0.354 g, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (dt, *J* = 16.5, 11 Hz, 1H), 6.27 (d, *J* = 17.0 Hz, 1H), 6.10 – 6.01 (m, 2H), 5.63 (d, *J* = 10.0 Hz, 2H), 5.47–5.41(m, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 3.36 (q, *J* = 7.0 Hz, 2H), 2.25 (q, *J* = 7.5 Hz, 2H) 1.69 – 1.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 131.8, 131.2, 130.9, 130.5, 126.3, 117.6, 39.2, 29.3, 25.1.



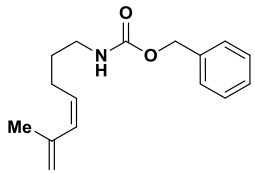
(*Z*)-7-Azido-2-methylhepta-1,3-diene (76). To a flame dried reaction flask was added (4-azidobutyl)triphenylphosphonium bromide (2.20 g, 5 mmol), and THF (5 mL). The reaction mixture was cooled to -78 °C and KHMDS (20% w/w in THF, 5.5 mL, 5 mmol) was added. The

reaction was allowed to stir at this temperature for 1 hour and then aldehyde was added (0.412 mL, 5 mmol) dropwise. The reaction was stirred for another hour and was then warmed to room temperature and quenched with water (5 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered and condensed. Purification by a short silica gel column (20:1–pentane:ether) to remove residual triphenylphosphine oxide afforded pure dienylazide as a colorless oil (200 mg, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (d, *J* = 11.7 Hz, 1H), 5.36 (dt, *J* = 11.7, 7.5 Hz, 1H), 4.97 (s, 1H), 4.84 (s, 1H), 3.29 (t, *J* = 6.9 Hz, 2H), 2.36 (q, *J* = 6.6 Hz, 2H), 1.90 (s, 3H),1.69 (quint., *J* = 7.5 Hz, 2H).

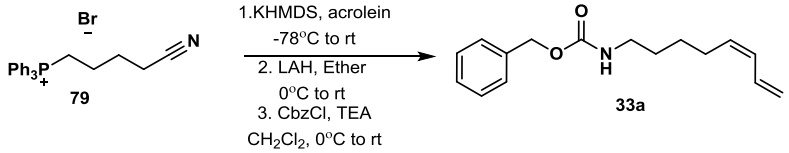


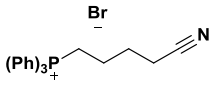
***(Z)*-6-Methylhepta-4,6-dien-1-amine (78).** To a flame dried reaction flask under N_2 was added a solution of azide or nitrile (0.200 mg, 1.32 mmol) in ether (5 mL) to a suspension of lithium aluminum hydride (100 mg, 2.6 mmol) in ether (25 mL) at 0 °C. The reaction was allowed to slowly warm to room temperature and stir until starting material was consumed (TLC). The reaction was cooled to 0 °C and was quenched by the slow addition of 1M NaOH (~5mL) and was allowed to stir an additional 30 min. The white solid was removed by filtration over celite and was washed with ether. The filtrate was dried with $MgSO_4$, filtered and concentrated to yield the corresponding amine as a colorless oil (142 mg, 86% yield), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 – 5.95 (m, 1H), 5.70 (d, *J* = 11.7 Hz, 1H), 5.52

– 5.47 (m, 1H), 5.92 – 5.16 (m, 2H), 4.80 – 4.69 (m, 4H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.17 – 2.15 (m, 2H), 1.7 (s, 3H), 1.42 (m, 2H).

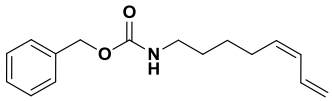


(*Z*)-Benzyl 6-methylhepta-4,6-dienylcarbamate (25a). To a reaction flask was added *(E)*-6-methylhepta-4,6-dien-1-amine (**78**) (0.142 g, 1.1 mmol), CH_2Cl_2 (10 mL), triethylamine (0.17 mL, 1.2 mmol) and placed under a nitrogen atmosphere. The mixture was cooled to 0 °C and to the mixture was added benzyl chloroformate (0.18 mL, 1.3 mmol) dropwise over a period of 5 minutes. The reaction was allowed to slowly warm to room temperature and stir overnight. The reaction quenched with water (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and combined organic layers were washed with 0.5M citric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered and condensed. Purification by flash chromatography (8:1, hexanes:EtOAc) afforded the product as a colorless oil (0.052 g, 18% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 5H), 5.86 (d, *J* = 12 Hz, 1H), 5.37 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.09 (s, 2H), 4.95 (s, 1H), 4.82 (s, 1H), 4.75 (br s, 1H), 3.21 (q, *J* = 6.5 Hz, 2H), 2.30 (q, *J* = 6.5 Hz, 2H), 1.86 (s, 3H), 1.63 – 1.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 141.5, 136.6, 131.6, 130.2, 128.5, 128.5, 128.1, 115.4, 66.6, 40.7, 30.3, 25.7, 23.3. GC/MS (EI, m/z): 259(2) $[M]^+$, 107(56), 91(100). FTIR ($CDCl_3$, cm^{-1}): 3334, 3066, 3033, 2936, 1698, 1538, 1520, 1498, 1456, 1373, 1255, 1136, 1027, 892, 696.



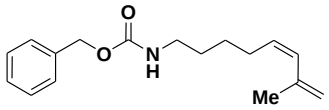


(4-Cyanobutyl)triphenylphosphonium bromide (79). Synthesized according to a literature procedure.[26] ^{1}H NMR (300 MHz, $CDCl_3$): 7.93 – 7.70 (m, 15 H), 4.11 – 4.01 (m, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.20 – 2.13 (m, 2H), 1.90 – 1.85 (m, 2H).



(*Z*)-Benzyl octa-5,7-dienylcarbamate (33a). Under an atmosphere of N_2, (**79**, 1.27 g, 3 mmol) was dissolved in 10 mL THF. Then KHMDS (20% w/v, 3.0 mmol) was added dropwise and allowed to stir for 30 minutes and the mixture was cooled to -78 °C. Then acrolein was added dropwise to the mixture, which was allowed to stir for 1 hour. The mixture was then warmed to room temperature and allowed to stir an additional hour. The reaction was then quenched with water (20 mL). The mixture was extracted with ether (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to 5 mL under reduced pressure. Purification by flushing through a silica plug (20:80, ether:pentane) gave the crude product. The crude product was used without further purification. To a vacuum dried flask

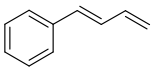
under N_2, lithium aluminum hydride (0.114 g, 3 mmol) was added to the flask followed by 5 mL of ether. The mixture was cooled to 0 °C, and the crude dienyl nitrile was dissolved in 5mL of ether and added dropwise over 10 min. The mixture was monitored by TLC (20:80, EtOAc:hexanes) until the dienyl amine was consumed, about 1 h. It was then quenched with 2 mL of 1 M NaOH, diluted with ether and filtered through a pad of celite. The filtrate was dried with Na_2SO_4, filtered and concentrated to afford a clear oil as the crude product. To a flame dried flask, the crude dienyl amine was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Triethylamine (0.76 mL, 7.25 mmol) was then added to the mixture which was allowed to stir at 0 °C for 10 min. Benzyl chloroformate (0.89 mL, 5.25 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature and stir over-night. The mixture was diluted with CH_2Cl_2 and washed with 1 M HCl (2 x 25 mL) and sat. $NaHCO_3$ (1 x 25 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (10:90, EtOAc:hexanes) and a clear oil was obtained (0.205 g, 26% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.40 – 7.32 (m, 5H), 7.16 (dt, *J* = 16.5, 10.5 Hz, 1H), 6.02 (t, *J* = 11 Hz, 1H), 5.42 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.20 (d, *J* = 17.0 Hz, 1H), 5.15 – 5.10 (m, 4H), 4.78 (br s, 1H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.54–1.50 (m, 2H), 1.45 – 1.41 (m, 2H). ^{13}C NMR (125 MHz, CD_3Cl): 156.3, 136.6, 132.1, 129.6, 128.5, 128.1, 128.0, 117.1, 66.5, 40.9, 29.5, 27.2, 26.6. FTIR ($CDCl_3$, cm^{-1}): 3333, 3083, 3067, 3029, 3005, 2935, 2859, 1699, 1533, 1555, 1437, 1249, 1132, 1025, 999, 905, 698. GC/MS (EI, m/z): 259(1) $[M]^+$, 107(36), 91(100).



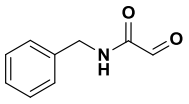
(Z)-benzyl 7-methylocta-5,7-dienylcarbamate (35a). Under an atmosphere of N_2, (**79**, 1.27 g, 3 mmol) was dissolved in 10 mL THF. Then KO^{t}Bu (336 mg, 3.0 mmol) was added and allowed to stir for 30 minutes and the mixture was cooled to -78 °C. Then methacrolein (0.37 mL, 4.5 mmol) was added dropwise the mixture, which was allowed to stir for 1 hour. The mixture was then warmed to room temperature and allowed to stir an additional hour. The reaction was then quenched with water (20 mL). The mixture was extracted with ether (3 x 25 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to 5 mL under reduced pressure. Purification by a silica plug with (20:80, ether:pentane) gave the crude product. The crude product was used without further purification. To a vacuum dried flask under N_2, lithium aluminum hydride (0.114 g, 3 mmol) was added to the flask followed by 5 mL of ether. The mixture was cooled to 0 °C, and the crude dienyl nitrile was dissolved in 5mL of ether and added dropwise over 10 min. The mixture was monitored by TLC (20:80, EtOAc:hexanes) until the dienyl amine was consumed. It was then quenched with 2 mL of 1 M NaOH, diluted with ether and filtered through a pad of celite. The filtrate was dried with Na_2SO_4, filtered and concentrated to afford a clear oil as the crude product. To a flame dried flask, the crude dienyl amine was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. Triethylamine (0.5 mL, 5.0 mmol) was then added to the mixture which was allowed to stir at 0°C for 10 min. Benzyl chloroformate (0.59 mL, 3.5 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature and stir over night. The mixture was

diluted with CH_2Cl_2 and washed with 1 M HCl (2 x 25 mL) and sat. NaOH (1 x 25 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (10:90, EtOAc:hexanes) and a clear oil was obtained (0.075 g, 9% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 5H), 5.84 (d, *J* = 11.5 Hz, 1H), 5.36 (dt, *J* = 11.5, 7.0 Hz, 1H), 5.09 (s, 2H), 4.94 (s, 1H), 4.82 (s, 1H), 4.73 (br s, 1H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.28 (q, *J* = 7.0 Hz, 2H), 1.86 (s, 3H), 1.53 – 1.51 (m, 2H, 1.43 – 1.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 141.7, 136.8, 136.6, 131.2, 131.1, 128.5, 128.1, 115.2, 66.6, 41.0, 29.6, 28.1, 27.2, 23.4. GC/MS (EI, m/z): 273(1) $[M]^+$, 182(14), 121(49), 91(100). FTIR ($CDCl_3$, cm^{-1}): 3335, 3087, 3066, 3000, 2967, 2930, 2857, 1699, 1538, 1455, 1252, 1135, 1025, 890, 755, 736, 696.

1.3.3 Synthesis of 1,3-dienes



(E)-4-phenyl-1,3-butadiene (60). Synthesized according to literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.79 (dd, *J* = 15.3, 10.2, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.52 (dt, *J* = 16.8, 10.2 Hz, 1H), 5.34 (d, *J* = 16.5 Hz, 1H), 5.18 (d, *J* = 9.9 Hz, 1H).



Benzyl glyoxamide (59). Synthesized according to literature.[28] ^{1}H NMR (300 MHz, $CDCl_3$, 3Å MS): 9.29 (s, 1H), 7.30-7.19 (m, 5H), 6.87 (br s, 1H), 4.65 (d, *J* = 6.0 Hz, 2H).

1.4 General Procedures and Characterization for Hydroamination

General Hydroamination Conditions:

(A)

In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium[10a] (0.05 equiv.), $AgBF_4$ (0.1 equiv.) and $MgSO_4$ (1.0 equiv.) were added to a round-bottomed flask. The flask was capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.1 M) was added. To the stirring mixture was added a solution of the substrate (1 equiv.) in CH_2Cl_2 (0.1 M) by syringe. The reaction was stirred for 2 – 16 h while monitoring for the disappearance of the starting material by TLC. After the substrate has been consumed, the mixture was filtered through a plug of celite. Purification by column chromatography (100% CH_2Cl_2, unless otherwise noted) afforded pure products.

(B)

In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (0.05 equiv.), $AgBF_4$ (0.1 equiv.), $MgSO_4$ (1 equiv.), and the substrate (1 equiv.) were added to a round-bottomed flask. The flask was capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.1 M) was added. The reaction was stirred for 2 – 16 h while monitoring for the disappearance of the protected aminodiene by TLC. After the substrate has been consumed, the mixture was filtered through a plug of celite. Purification by column chromatography (100% CH_2Cl_2) afforded pure product.

(C) prepatory scale

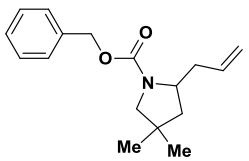
In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (0.05 equiv.), $AgBF_4$ (0.1 equiv.) and $MgSO_4$ (0.5 equiv.) were added to a round-bottomed flask. The flask was

capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.2 M) was added. To the stirring mixture was added a solution of the substrate (1 equiv.) and $MgSO_4$ (0.5 equiv) in CH_2Cl_2 (0.2 M) by syringe. The reaction was stirred for 18 h. and then filtered through a pad of celite. Purification by column chromatography (100% CH_2Cl_2) afforded pure product.

(D)

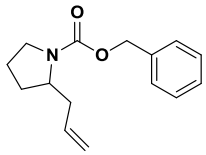
In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (0.05 equiv.), $AgPF_6$ (0.1 equiv.) and $MgSO_4$ (1.0 equiv.) were added to a round-bottomed flask. The flask was capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.1 M) was added. To the stirring mixture was added the substrate (1 equiv.). The reaction was stirred overnight. The mixture was filtered through a plug of celite and concentrated under reduced pressure. Purification by column chromatography (100% CH_2Cl_2, unless otherwise noted) afforded pure products.

1.4.1 Characterization of Hydroamination Products

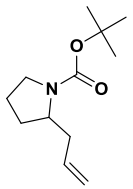


Benzyl 2-allyl-4,4-dimethylpyrrolidine-1-carboxylate (18a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.026 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$, observed as a 1:1 mixture of rotamers): δ 7.36 – 7.30 (m, 10H, both), 5.76 – 5.62 (m, 2H, both),

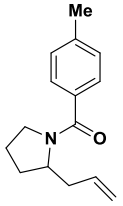
5.21 – 4.98 (m, 8H, both), 3.94 (m, 2 H, both), 3.48 (d, *J* = 10.5 Hz, 1H, minor), 3.37 (d, *J* = 10.0 Hz, 1H, major), 2.98 (d, *J* =10.0, 2H, both), 2.73 (br s, 1H, major), 2.54 (br s, 1H, minor), 2.32 – 2.27 (m, 2H, both), 1.78 (dd, *J* = 12.5, 7.5 Hz, 2H, both), 1.07 (s, 6H, both), 0.97 (s, 6H, both). ^{13}C NMR (125 MHz, $CDCl_3$): 155.3, 155.0, 137.1, 136.9, 134.3, 134.1, 128.4, 127.8, 127.7, 127.6, 117.6, 117.4, 66.8, 66.4, 59.6, 59.5, 56.9, 56.3, 45.4, 44.7, 39.3, 38.1, 37.0, 26.4, 26.37, 26.0, 25.9. GC/MS(CI, m/z): 273(1) $[M]^+$, 188(19), 91(100). FTIR ($CDCl_3$, cm^{-1}): 3067, 3034, 2957, 2870, 1703, 1466, 1446, 1412, 1357, 1329, 1186, 1099, 1029, 991, 915, 770, 737, 698.



Benzyl 2-allylpyrrolidine-1-carboxylate (20a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.026 g, 99% yield), spectral data matches literature data.[29] ^{1}H NMR (300 MHz, $CDCl_3$, observed as a 1:1 mixture of rotamers): δ 7.37 – 7.27 (m, 5H), 5.78 – 5.70 (m, 1H), 5.20 – 4.99 (m, 4H), 3.92 (s, 1H), 3.42 (s, 2H), 2.59 (s, 1H, major), 2.42 (s, 1H, minor), 2.20 – 2.13 (m, 1H), 1.92 – 1.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 137.2, 137.0, 135.0, 134.9, 128.5, 127.9, 127.8, 117.3, 117.2, 66.7, 66.5, 57.3, 56.8, 53.5, 46.9, 46.5, 39.0, 38.0, 30.0, 29.2, 23.7, 22.9.

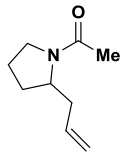


***Tert*-butyl 2-allylpyrrolidine-1-carboxylate (20b).** General hydroamination conditions A, 0.1 mmol, colorless oil (0.026g, 76% yield), spectral data matches literature data.[30] ^{1}H NMR (300 MHz, $CDCl_3$): Observed as a 1:1 mixture of rotamers δ 5.78 – 5.67 (m, 1H), 5.07 – 5.01 (m, 2H), 3.84 – 3.76 (m, 2H, major + minor), 3.30 (s, 2H), 2.52 – 2.40 (m, 2H, major + minor), 2.51 – 2.05(m, 1H), 1.83 – 1.73 (m, 4H), 1.45 (s, 9H).

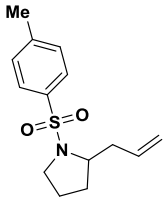


1-(4-Methylbenzoyl)-2-allylpyrrolidine (20c). General hydroamination conditions A, 0.1 mmol, colorless oil (0.026g, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$, observed as a 6:1 mixture of rotamers): δ 7.41 (d, *J* = 7.5 Hz, 2H, major), 7.35 (br s, 2 H, minor), 7.18 (d, *J* = 8.0 Hz, 4H, both), 5.89 – 5.81 (m, 1H, major), 5.42 (br s, 1H, minor), 5.13 (d, *J* = 19.5 Hz, 1 H, major), 5.09 (d, *J* = 11.0 Hz, 1H, major), 4.95 (br s, 1H, minor), 4.87 (br s, 1 H, minor), 4.34 (m, 1H, major), 3.96 (br s, 1 H, minor), 3.76 (br s, 1H, minor), 3.51 (br s, 1H, minor), 3.43 (m, 2H, major), 2.67 (m, 2H, both), 2.41 (m, 2H, both), 2.37 (s, 6H, both), 2.08 – 2.01 (m, 1 H, major). 1.95 (br s, 2H,

minor), 1.87 – 1.85 (m, 1H, major), 1.78 – 1.66 (m, 4H, both). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 140.0, 134.7, 134.5, 128.8, 127.4, 117.5, 56.6, 50.5, 37.6, 29.5, 25.0, 21.4. GC/MS (EI, m/z): 229(1) $[M]^+$, 188(19), 119(100), 91(21), 65(10), 41(5). FTIR ($CDCl_3$, cm^{-1}): 3074, 2970, 2921, 2871, 1623, 1566, 1410, 1353, 1182, 1042, 995, 912, 891, 828, 745.

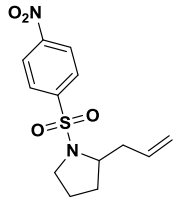


1-Acetyl-2-allylpyrrolidine (20d). General hydroamination conditions A, 0.1 mmol, colorless oil (0.015 g, 99% yield), spectral data matches literature data.[31] ^{1}H NMR (300 MHz, $CDCl_3$, observed as a 3:2 mixture of rotamers): δ 5.84 – 5.62 (m, 1H), 5.09 (d, *J* = 15.7 Hz, 1H), 5.02, (d, *J* = 8.9 Hz, 1H), 4.18 – 4.04 (m, 1H, major), 3.94 – 3.74 (m, 1H, minor), 3.59 – 3.30 (m, 2H), 2.64 – 2.47 (m, 1H, major), 2.41 – 2.26 (m, 1H, minor), 2.17 – 2.01 (m, 4H, major +minor), 1.98 – 1.66 (m, 4H).

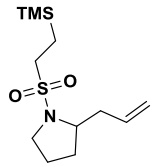


2-Allyl-1-tosylpyrrolidine (20e). General hydroamination conditions A, 0.1 mmol, colorless oil (0.019g, 72% yield), spectral data matches literature data.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.78 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.12 – 5.03

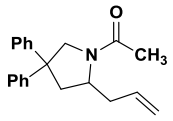
(m, 2H), 3.65 (dq, *J* = 13.1, 3.8 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.16 (dt, *J* = 10.3, 7.2 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.42 (s, 3H), 2.29 (dt, *J* = 14.8, 7.6 Hz, 1H), 1.86–1.70 (m, 1H), 1.70 – 1.42 (m, 3H).



2-Allyl-1-(4-nitrophenylsulfonyl)pyrrolidine (20f). General hydroamination conditions A, 0.1 mmol, white solid (0.0288g, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.4, 7.0 Hz, 1H), 5.11 (dd, *J* = 17.0, 0.9 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 3.72 (dq, 12.0, 4.0 Hz, 1H), 3.46 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1H), 3.20 (dt, *J* = 10.0, 7.5 Hz, 1H), 2.62–2.57 (m, 1H), 2.34 – 2.29 (m, 1H), 1.91 – 1.82 (m, 1H), 1.75 – 1.69 (m, 1H), 1.65 – 1.57 (m, 2H). ^{13}C NMR (125 MHz, CD_3Cl): δ 150.0, 143.8, 133.9, 128.5, 124.3, 188.2, 60.1, 49.2, 40.6, 30.1, 24.0. GC/MS (EI, m/z): 296(1) $[M]^+$, 257(6), 256(13), 255(100), 209(3), 186(25), 122(54), 92(10), 76(22), 50(9), 41(23). FTIR ($CDCl_3$, cm^{-1}): 315, 2977, 1640, 1605, 1532, 1478, 1448, 1400, 1350, 1306, 1259, 1198, 1163, 1091, 1058, 1012, 992, 855, 807, 772, 135, 687, 622. mp: 75 °C.

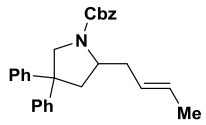


2-Allyl-1-(2-(trimethylsilyl)ethylsulfonyl)pyrrolidine (20g). General hydroamination conditions A, 0.1 mmol, colorless oil (0.020g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.08 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.06 (d, *J* = 9.0 Hz, 1H), 3.91 (dq, *J* = 11.5, 4.0 Hz, 1H), 3.43 (dt, *J* = 10.0, 7.0 Hz, 1H), 3.29 (ddd, *J* = 10.0, 6.5, 5.5 Hz, 1H), 2.87 (dd, *J* = 10.0, 8.5 Hz, 2H), 2.53 – 2.48 (m, 1H), 2.24 – 2.18 (m, 1H), 2.00 – 1.81 (m, 3H), 1.78 – 1.74 (m, 1H), 1.10 – 0.98 (m, 2H), 0.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.5, 117.7, 59.3, 48.8, 46.9, 30.5, 24.7, 10.1, -2.0. ESI MS: 276 $[M+H]^+$, 551 $[2M+H]^+$, 568 $[2M+NH_4]^+$. FTIR ($CDCl_3$, cm^{-1}): 3078, 2954, 2898, 1443, 1416, 1333, 1251, 1198, 1167, 1141, 1061, 990, 916, 895, 862, 843, 784, 759, 734, 700, 628.



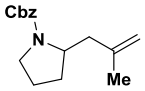
1-(2-Allyl-4,4-diphenylpyrrolidin-1-yl)ethanone (22d). General hydroamination conditions A, 0.1 mmol, colorless oil (0.030 g, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Observed as a 3:2 mixture of rotamers): δ 7.31 – 7.13 (m, 10H, both), 5.78 – 5.68 (m, 2H, both), 5.14 – 4.99 (m, 3H, both), 4.29 (d, *J* = 11.0 Hz, 1H, major), 4.10 – 4.05 (m, 1H, minor), 3.89 (d, *J* = 10.5 Hz, 1H, major), 3.80 – 3.76 (m, 1H, minor), 3.52 (d, *J* = 12.0 Hz, 1H, minor), 2.92 (ddd, *J* = 12.5, 7.0, 2.0 Hz, 1H, minor), 2.84 (ddd, *J* = 13.0, 7.0, 2.0 Hz, 1H, major), 2.76 – 2.73 (m, 2H, both),

2.52 – 2.49 (m, 2H, both), 2.34 (dd, *J* = 13.0, 9.0 Hz, 2H, both), 2.29 – 2.27 (m, 2H, both), 2.10 (s, 3H, major), 2.03 (s, 3H, minor). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 169.1, 145.5, 145.43, 144.9, 144.8, 134.0, 132.6, 128.8, 128.7, 126.7, 126.6, 126.4, 126.3, 126.2, 118.9, 117.8, 58.4, 56.4, 55.9, 54.8, 53.0, 52.2, 44.1, 42.1, 39.7, 37.2, 23.3, 21.4. GC/MS (CI, m/z): 305(2) $[M]^+$, 264(60), 222(100). FTIR (CH_2Cl_2, cm^{-1}): 3059, 3026, 2975, 2925, 2868, 1637, 1490, 1472, 1443, 1415, 1349, 1269, 1222, 1193, 1156, 1113, 1061, 1033, 995, 915, 774, 750, 722.

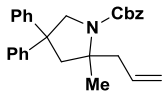


(*E*)-Benzyl 2-(but-2-enyl)-4,4-diphenylpyrrolidine-1-carboxylate (24a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.026g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Observed as a 1:1 mixture of rotamers): δ 8.02 – 7.77 (m, 30H, both), 6.12 – 5.96 (m, 2H, both), 5.92 (d, *J* = 12.5 Hz, 1H, A), 5.80 (q, *J* = 12.5 Hz, 2H, both), 5.72 (d, *J* = 12.5 Hz, 1H, B), 5.39 (dd, *J* = 11.5, 2.0 Hz, 1H, A), 5.22 (dd, *J* = 11.5, 1.5 Hz, 1H, B), 4.40 – 4.30 (m, 2H, both), 4.26 (d, *J* = 11.5 Hz, 1H, A), 4.22 (d, *J* = 11.5 Hz, 1H, B), 3.44 – 3.35 (m, 2H, both), 3.34 – 3.31 (m, 1H, A), 3.17 – 3.14 (m, 1H, B), 3.03 (dd, *J* = 12.5, 9.5 Hz, 1H, A), 2.97 (dd, *J* = 12.5, 9.5 Hz, 1H, B), 2.85 (dd, *J* = 15.0, 8.0 Hz, 1H, A), 2.84 (dd, *J* = 15.0, 8.0 Hz, 1H, B), 2.27 (d, *J* = 7.0 Hz, 3H A), 2.26 (d, *J* = 6.5 Hz, 3H, B). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 154.5, 145.7, 145.66, 145.1, 144.9, 137.1, 136.9, 128.53, 128.51, 128.5, 128.44, 128.4, 128.34, 127.9, 127.8, 127.7, 127.5, 126.8, 126.5, 126.45, 126.42, 126.35, 126.3, 126.24, 126.22, 126.1, 66.8,

66.6, 56.7, 56.2, 56.15, 56.1, 52.8, 52.6, 43.7, 42.8, 37.5, 36.5, 18.1. ESI MS: 412 $[M+H]^+$, 429 $[M+NH_4]^+$. FTIR ($CDCl_3$, cm^{-1}): 3085, 3060, 3028, 2960, 2901, 2880, 2854, 1949, 1879, 1807, 1701, 1597, 1496, 1448, 1412, 1358, 1337, 1268, 1212, 1180, 1156, 1132, 1104, 1075, 1028, 1005, 967, 910, 769, 750, 693.

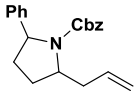


Benzyl 2-(2-methylallyl)pyrrolidine-1-carboxylate (26a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.018 g, 70%). ^1H NMR (500 MHz, $CDCl_3$, Observed as a 1:1 mixture of rotamers): δ 7.38 – 7.30 (m, 10H, both), 5.18 – 5.10 (m, 4H, both), 4.77 (s, 1H, A), 4.74 (s, 1H, B), 4.68 (s, 1H, A), 4.65 (s, 1H, B), 4.06 (br s, 1H, A), 3.99 (br s, 1H, B), 3.44, (s, 2H), 2.62 (d, *J* = 12.5 Hz, 1H, A), 2.43 (d, *J* = 13.0 Hz, 1H, B), 1.96 (dd, *J* = 13.0, 10.0 Hz, 4H, both), 1.86 – 1.78 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 154.7, 143.3, 142.9, 137.1, 136.9, 136.5, 128.4, 127.9, 127.8, 127.7, 112.7, 112.4, 66.7, 66.4, 56.1, 55.5, 46.5, 46.2, 42.7, 41.7, 29.7, 28.9, 23.4, 22.6, 22.4, 22.3. GC/MS (EI, m/z): 204(14) $[M\text{-allyl}]^+$, 160(16), 91(100), 55(3). FTIR ($CDCl_3$, cm^{-1}): 3032, 2966, 2878, 1702, 1694, 1455, 1417, 1357, 1337, 1117, 1097, 891, 804, 769, 742, 698.



Benzyl 2-allyl-2-methyl-4,4-diphenylpyrrolidine-1-carboxylate (28a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.026g, 95% yield), ^1H NMR (500 MHz,

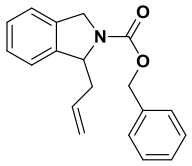
$CDCl_3$): (Observed as a 2:1 mixture of rotamers): δ 7.37 – 7.10 (m, 30H, both), 5.66 – 5.56 (m, 2H, both), 5.22 (d, *J* = 2.5 Hz, 2H, both), 5.15 (s, 4H, both), 4.97 (d, *J* = 8.5 Hz, 2H, both), 4.91 (d, *J* = 17.5 Hz, 1H, major), 4.84 (d, *J* = 17.0 Hz, 1H, minor), 4.62 (d, *J* = 12.0 Hz, 1H, minor), 4.49 (d, *J* = 12.0 Hz, 1H, major), 3.80 – 3.76 (m, 4H, both), 2.92 – 2.86 (m, 4H, both), 2.52 – 2.28 (m, 3H) 1.04 (d, *J* = 2.5 Hz, 3H, major), 0.94 (d, *J* = 2.0 Hz, 3H, minor). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 153.4, 146.2, 146.1, 145.9, 145.8, 137.3, 136.6, 134.1, 133.8, 128.5, 128.47, 128.46, 128.4, 128.0, 127.9, 127.8, 127.7, 126.7, 126.67, 126.6, 126.56, 126.3, 126.29, 126.2, 126.17, 118.8, 118.7, 67.1, 66.3, 63.3, 62.6, 56.8, 56.2, 50.9, 48.9, 44.5, 43.2, 26.2, 24.9. ESI MS: 412 $[M+H]^+$. FTIR (CH_2Cl_2, cm^{-1}): 3060, 3030, 2976, 2934, 1949, 1875, 1804, 1702, 1639, 1599, 1497, 1483, 1447, 1407, 1354, 1305, 1265, 1218, 1185, 1109, 1069, 129, 1002, 918, 767, 751, 736. 698.



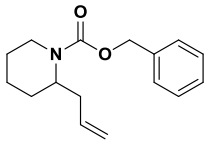
Benzyl 2-allyl-5-phenylpyrrolidine-1-carboxylate (30a). General Hydroamination Conditions A, 0.1 mmol, colorless oil (0.029 g, 90% yield). ^{1}H NMR (500 MHz, C_6D_6): (observed as a 3:1 mixture of diastereomers and a 1:1 mixture of rotamers of major diastereomer) δ 7.31 – 6.89 (m, 10H, all), 6.80 (br, 2H, major diastereomer, single rotamer), 5.74 (ddt, *J* = 17.0, 10.0, 7.7 Hz, 1H, major diastereomer, both rotamers), 5.59 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, minor diastereomer, both rotamers), 5.19 – 4.96 (m, 2H, all), 4.92 (d, *J* = 12.7 Hz, 1H, major diastereomer, both rotamers), 4.82 (d, *J* = 8.2 Hz, 1H, major diastereomer, both rotamers), 4.26

(td, *J* = 8.9, 2.6 Hz, 1H, major diastereomer, both rotamers), 4.11 (br, 1H, minor diastereomer, single rotamer), 3.98 (td, *J* = 9.7, 2.2 Hz, 1H, minor diastereomer, single rotamer), 3.05 (br, 1H, minor diastereomer, single rotamer), 2.92 (br d, *J* = 9.8 Hz, 1H, major diastereomer, both rotamers), 2.53 (d, *J* = 10.7 Hz, 1H, minor diastereomer, single rotamer), 2.19 (dt, *J* = 13.4, 8.6 Hz, 1H, all), 2.02 – 1.91 (m, 1H, all), 1.76 – 1.66 (m, 1H, all), 1.61 – 1.51 (m, 1H, both diastereomers, singe rotamer), 1.50 – 1.41 (m, 1H, both diastereomers, single rotamer), 1.39 – 1.24 (m, 2H, all). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.5 (minor diastereomer, single rotamer), 154.5 (major diastereomer, both rotamers), 154.3 (minor diastereomer, single rotamer), 144.7 (major diastereomer, both rotamers), 143.6 (minor diastereomer, both rotamers), 136.8 (minor diastereomer, both rotamers), 136.6 (major diastereomer, both rotamers), 135.2 (minor diastereomer, single rotamer), 135.2 (major diastereomer, both rotamers), 135.0 (minor diastereomer, both rotamers), 128.4 (minor diastereomer, both rotamers), 128.3 (major diastereomer, both rotamers), 128.1 (major diastereomer, both rotamers), 128.0 (minor diastereomer, single rotamer), 127.9 (minor diastereomer, single rotamer), 127.4 (minor diastereomer, both rotamers), 127.2 (major diastereomer, both rotamers), 126.7 (minor diastereomer, both rotamers), 126.6 (major diastereomer, both rotamers), 125.6 (minor diastereomer, both rotamers), 125.1 (major diastereomer, both rotamers), 117.5 (minor diastereomer, single rotamer), 117.4 (major diastereomer, both rotamers), 117.2 (minor diastereomer, single rotamer), 66.8 (minor diastereomer, both rotamers), 66.4 (major diastereomer, both rotamers), 61.7 (minor diastereomer, both rotamers), 61.6 (major diastereomer, both rotamers), 58.4 (major diastereomer, both rotamers), 57.8 (minor diastereomer, both rotamers), 38.6 (minor diastereomer, both rotamers), 37.4 (major

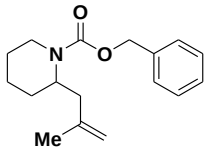
diastereomer, both rotamers), 32.7 (major diastereomer, both rotamers), 31.8 (minor diastereomer, both rotamers), 26.5 (minor diastereomer, both rotamers), 25.4 (major diastereomer, both rotamers). FTIR ($CDCl_3$, cm^{-1}): 3321, 3073, 3031, 2934, 2855, 1950, 1877, 1805, 1696, 1602, 1530, 1454, 1339, 1248, 1129, 1045, 1005, 951, 900, 752, 697. ESI MS: 321.9 $[M+H]^+$.



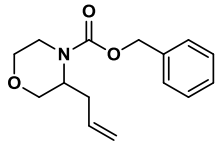
Benzyl 1-allylisoindoline-2-carboxylate (32a). General hydroamination conditions B, 0.1 mmol, colorless oil (0.028g, 96% yield), ^1H NMR (500 MHz, $CDCl_3$, Observed as a 1:1 mixture of rotamers): δ 7.43 – 7.32 (m, 8H, both), 7.27 – 7.19 (m, 10H, both), 5.59 – 5.45 (m, 2H, both), 5.29 – 5.18 (m, 4H, both), 5.00 (d, *J* = 18.0 Hz, 1H, rotamer A), 4.96 (d, *J* = 17.5 Hz, 1H, rotamer B), 4.94 (d, *J* = 16.5 Hz, 1H, rotamer A), 4.89 (d, *J* = 17.0 Hz, 1H, rotamer B), 4.82 (d, *J* = 15.0 Hz, 1H, rotamer A), 4.77 (d, *J* = 14.5 Hz, 1H, rotamer B), 4.60 (d, *J* = 14.5 Hz, 2H, both), 2.91 (ddd, *J* = 14.0, 7.5, 6.5 Hz, 1H, rotamer A), 2.76 (ddd, *J* = 14.0, 7.5, 6.5 Hz, 1H, rotamer B), 2.70 – 2.66 (m, 1H, rotamer A), 2.60 – 2.56 (m, 1H, rotamer B). ^{13}C NMR (125 MHz, $CDCl_3$): 154.8, 154.5, 140.3, 140.0, 136.9, 136.7, 136.6, 136.4, 132.9, 132.6, 128.5, 128.46, 128.04, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 127.28, 122.7, 122.6, 122.5, 122.3, 118.6, 118.5, 67.1, 66.8, 63.2, 62.6, 52.7, 52.3, 39.6, 38.3. ESI MS: 294 $[M+H]^+$. FTIR ($CDCl_3$, cm^{-1}):3073, 3031, 3005, 2976, 2951, 2918, 2866, 1958, 1811, 1703, 1642, 1613, 1590, 1533, 1495, 1443, 1410, 1363, 1390, 1283, 1212, 1184, 1099, 1024, 1000, 967, 915, 802, 769, 750, 731, 698.



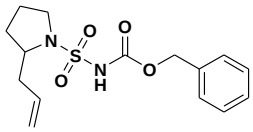
Benzyl 2-allylpiperidine-1-carboxylate (34a). General hydroamination conditions A, 0.2 mmol, colorless oil (0.051 g, 98%), spectral data matches literature data.[32] ^{1}H NMR (300 MHz, $CDCl_3$): Observed as a mixture of rotamers δ 7.43 – 7.27 (m, 5H), 5.83 – 5.61 (m, 1H), 5.16 – 4.95 (m, 4H), 4.45 – 4.26 (m, 1H), 4.13 – 3.99 (m, 1H, major + minor), 2.85 (t, *J* = 13.4 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.32 – 2.19 (m, 1H), 1.70 – 1.53 (m, 6H).



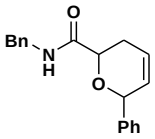
benzyl 2-(2-methylallyl)piperidine-1-carboxylate (36a). General hydroamination conditions A, 0.1 mmol, colorless oil (0.021 g, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 5H), 5.11 (d, *J* = 1.5 Hz, 2H), 4.73 (s, 1H), 4.69 (s, 1H), 4.47 (m, 1H), 4.05 (d, *J* = 12.6 Hz, 1H), 2.88 (td, *J* = 13.2, 2.4 Hz, 1H), 2.36 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.20 (dd, *J* = 13.2, 7.8 Hz, 1H, both), 1.71 – 1.65(m, 4H), 1.59 (d, *J* = 1.2, Hz, 3H), 1.43 – 1.37(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 142.7, 137.0, 132.1, 128.4, 127.9, 127.8, 112.7, 66.8, 48.7, 39.2, 38.2, 27.4, 25.5, 22.0, 18.7. GC/MS (EI, m/z): 273(1) $[M]^+$, 218(18) $[M\text{-allyl}]^+$, 174(33), 91(100). FTIR ($CDCl_3$, cm^{-1}): 3071, 3028, 2934, 2859, 1695, 1422, 1343, 1259, 1166, 1136, 1088, 1072, 1050, 1028.



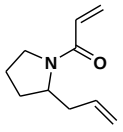
Benzyl 3-allylmorpholine-4-carboxylate (38a). General hydroamination conditions A, 0.2 mmol, yellow oil (0.051g, 99%). ^{1}H NMR (500 MHz, CDCl3): δ 7.42 – 7.28 (m, 5H), 5.73 br, 1H), 5.19 – 5.08 (m, 3H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.05 (br, 1H), 3.94 – 3.72 (m, 3H), 3.53 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.46 (t, *J* = 12.1 Hz, 1H), 3.20 (t, *J* = 11.1 Hz, 1H), 2.49 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.3, 136.5, 134.4, 128.4, 128.0, 127.9, 117.8, 68.2, 66.9, 50.9, 39.5, 33.4. ESI MS: 278.9 $[M+NH_4]^+$, 261.9 $[M+H]^+$. FTIR ($CDCl_3$, cm^{-1}): 3352, 3066, 2963, 2856, 1699, 1641, 1497, 1455, 1639, 1599, 1497, 1483, 1447, 1407, 1354, 1305, 1265, 1218, 1185, 1109, 1069, 129, 1002, 918, 767, 751, 736, 698.



benzyl 2-allylpyrrolidin-1-ylsulfonylcarbamate (56). General hydroamination conditions D, 0.1 mmol, colorless oil (0.032g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (br s, 1H), 7.36 (br s, 5H), 5.79 – 5.20 (m, 1H), 5.17 (s, 2H), 5.07 (d, *J* = 15.9 Hz, 1 H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.14 – 4.06 (m, 1 H), 3.54 – 3.37 (m, 2H), 2.55 – 2.47 (m, 1H), 2.28 – 2.21 (m, 1H), 1.92 – 1.67 (m, 4H).



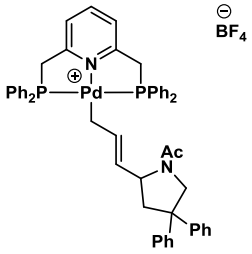
N-benzyl-6-phenyl-3,6-dihydro-2H-pyran-2-carboxamide (61). In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (0.05 equiv.), $AgBF_4$ (0.1 equiv.), $MgSO_4$ (1 equiv.), and **59** were added to a round-bottomed flask. The flask was capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.1 M) was added followed by **60**. The reaction was stirred overnight. The mixture was filtered through celite and concentrated under reduced pressure. Observed as a 1:1 mixture of two separable diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 10H), 6.94 (br s, 1H), 6.17 – 6.11 (m, 1H), 6.03 – 5.97 (m, 1H), 5.35 (s, 1H), 4.56 (dd, *J* = 15.0, 6.3 Hz, 1H), 4.34 (dd, *J* = 15.0, 5.1 Hz, 1H), 4.11 (dd, *J* = 10.8, 3.9 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.38 – 2.27 (m, 1H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.18 (m, 10H), 6.91 (br s, 1H), 5.96 – 5.90 (m, 1H), 5.66 (dt, *J* = 10.2, 1.2 Hz, 1H), 5.18 (s, 1H), 4.45 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.31 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.27 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.35 – 2.25 (m, 1H).



1-(2-allylpyrrolidin-1-yl)prop-2-en-1-one (63). General hydroamination conditions A, 0.1 mmol, colorless oil (0.016g, 97% yield). Spectra matches literature data.[33] ^{1}H NMR (300 MHz,

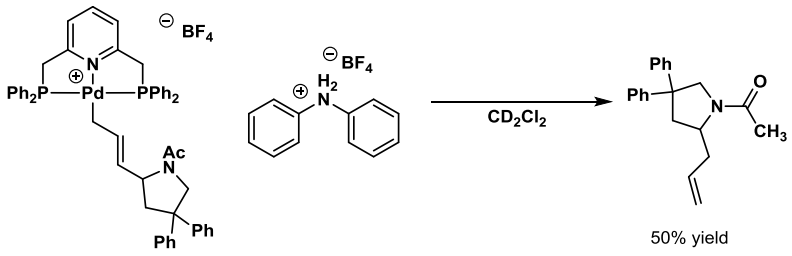
$CDCl_3$, Observed as a 3:2 mixture of rotamers): δ 6.54 – 6.33 (m, 4H, both), 5.86 – 5.72 (m, 2H, both), 5.71 – 5.64 (m, 2H, both), 5.14 – 5.04 (m, 4H, both), 4.28 – 4.21 (m, 1H, major), 4.21 – 3.98 (m, 1H, minor), 3.65 – 3.49 (m, 4H, both), 2.69 – 2.61 (m, 1H, major), 2.39 – 2.31 (m, 1H, minor), 2.25 – 2.11 (m, 2H, both), 2.04 – 1.74 (m, 8H, both).

1.4.2 Synthesis and Reactivity of Pd(PNP)allyl complex



(PNP)palladium allyl complex (40). In a glovebox, (PNP)Pd-pentafluorobenzonitrile complex[10c] (94.9 mg, 0.10 mmol) was added to a reaction flask and capped with a septum. The mixture was removed from the box, placed under a nitrogen atmosphere, and dissolved in CH_2Cl_2 (2.0 mL). A solution of (*E*)-*N*-(2,2-diphenylhepta-4,6-dienyl)acetamide **(21d)** (30.5 mg, 0.10 mmol) and *N*,*N*-dimethylaniline (0.038 mL, 0.30 mmol) in CH_2Cl_2 (3.0 mL) was then added. The mixture was allowed to stir for 20 min and was quenched with 0.1 M citric acid (5.0 mL) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give crude product as reddish oil. The oil was dissolved in CH_2Cl_2 (1.0 mL) and was precipitated with ether. The mixture was filtered and the resulting air-stable yellow solid was washed with ether (3 x 2.0 mL) and pentane (3 x 2.0

mL) to yield pure product (64.0 mg, 66 % yield). ^{1}H NMR (500 MHz, $CDCl_3$, Observed as a 4:1 mixture of rotomers): δ 7.96 – 7.77 (m, 1H, both), 7.72 – 7.56 (m, 10H, both), 7.54 – 7.40 (m, 12H, both), 7.36 – 7.00 (m, 10H, both), 5.43 (dt, *J* = 15.1, 7.6 Hz, 1H, minor), 5.19 (dt, *J* = 16.2, 9.0 Hz, 1H, major), 4.89 (d, *J* = 12.8 Hz, 1H, major), 4.76 (dd, *J* = 14.6, 7.9 Hz, 1H, minor), 4.64 – 4.29 (m, 5H, both), 4.22 (d, *J* = 11.7 Hz, 1H, minor), 3.84 (br, 1H, minor), 3.62 (d, *J* = 10.9 Hz, 1H, minor), 3.35 (dd, *J* = 15.6, 8.4 Hz, 1H, major), 3.17 (d, *J* = 12.0 Hz, 1H, major), 2.71 (br, 2H, minor), 2.68 – 2.56 (m, 2H, major), 2.55 – 2.48 (m, 1H, major), 2.43 – 2.35 (m, 1H, minor), 2.05 (s, 3H, minor), 1.97 (dd, *J* = 12.2, 9.9 Hz, 1H, major), 1.89 (dd, *J* = 12.5, 9.7 Hz, 1H, minor), 1.62 (s, 3H, major). ^{31}P NMR (202 MHz, $CDCl_3$): δ 23.6 (major), 23.2 (minor). FTIR ($CDCl_3$, cm^{-1}): 3047, 3018, 2953, 2915, 1628, 1462, 1437, 1059, 913, 847, 728, 694. ESI MS: 885.6 $[M\text{-}BF_4]^+$.



1-(2-Allyl-4,4-diphenylpyrrolidin-1-yl)ethanone (22d). (PNP)palladium allyl complex **(40)**, (14.6 mg, 0.015 mmol) was added to a vial under N_2, followed by 0.6 mL of CD_2Cl_2. Then diphenylammonium tetrafluoroborate[34] (5.8 mg, 0.023 mmol) was added to the solution, and the mixture was analyzed by ^{1}H and ^{31}P NMR spectroscopy, which indicated that the Pd allyl complex was completely consumed. The mixture was then filtered through a silica plug (5%

Et_3N/CH_2Cl_2) and 1,3-dinitrobenzene (3.8 mg, 0.015 mmol) was added as an internal standard. By ^1H NMR spectroscopy, the product was obtained in 50% yield.

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Chapter 3

Synthesis and Applications of NHC Palladium Complexes

Section 1. Introduction

Recently *N*-heterocyclic carbenes (NHCs) have emerged as useful ligands in transition metal catalysis.[1] In many instances, catalysts have been transformed by replacing phosphines with NHCs (*Figure 3.1*).[2] Not only have these NHC variants shown increased reactivity, but they have exhibited increased stability towards oxidation.[2] The sterics and electronics of NHCs have been shown to be very tunable,[3] although these properties are not as widely understood or readily assessed as those of the phosphines. Studies have shown that NHCs are good σ donors, and their capability as electron donating ligands exceeds that of many of the most electron donating phosphine ligands.[4]

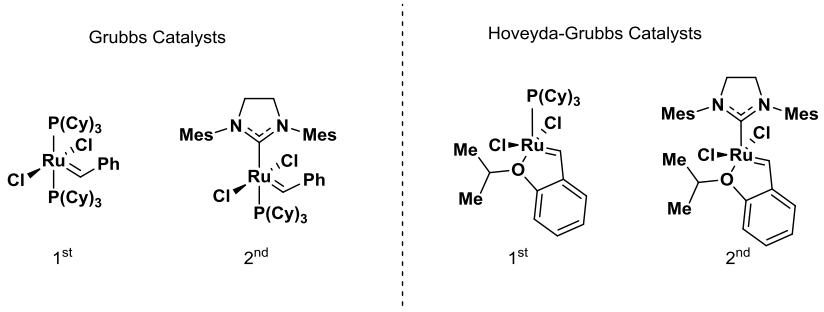


Figure 3.1. Notable Examples of NHC's Replacing Phosphine Ligands

As previously discussed in chapter 2 of this thesis, our lab has developed a mild room temperature palladium-catalyzed hydroamination of protected aminoalkenes to create pyrrolidines and piperidines (*Figure 3.2*).[5] This reaction is highly atom economical, utilizing low catalyst loading and affording high yields. While this reaction is remarkable, new catalysts

that are more air and moisture stable are still needed. Additionally, improved routes to chiral ligands for enantioselective catalysis were also desired. We sought to expand the scope of the hydroamination reaction through the development of new achiral and chiral NHC catalysts.

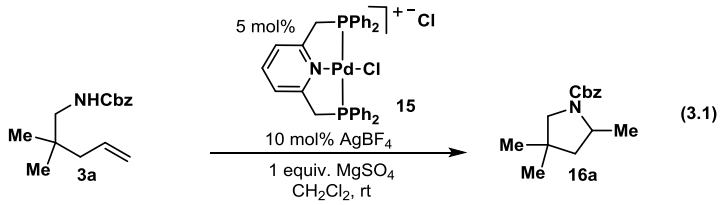


Figure 3.2. Pd-catalyzed hydroaminations of tethered aminoalkenes

Initial studies of this hydroamination reaction revealed that a tridentate ligand was key, due to its ability to occupy coordination sites on the metal center, and thus prevent non-productive β-hydride elimination pathways (*Figure 3.3*). During initial studies of this reaction many tridentate ligands were examined, such as PCP, PPP, and NNN motifs. While all of these ligands satisfy the necessary coordination number, only the PNP pincer ligands promoted hydroamination.

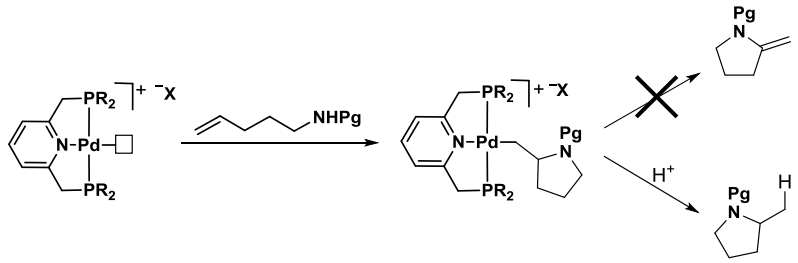


Figure 3.3. Role of Tridentate Ligands in Hydroamination

Noting the role that NHCs have played as ligands in transition metal catalysis, conversion of the aryl phosphines of catalyst **15** to NHCs could change the efficiency of the catalyst. Thus, the exchange of the two ligands would create a CNC-Pd complex that would most likely be a

very capable hydroamination catalyst. The electronics of a CNC ligand would remain quite similar to the previous PNP ligand, and the improved electron donating ability of NHCs may even accelerate electrophilic reactions with key palladium alkyl intermediates. Additionally, these complexes have the potential to be more air and moisture stable.

Literature searches revealed that a few CNC pincer Pd complexes had previously been prepared (*Figure 3.4*).[6,8] Many of these complexes have been successfully used as catalysts for cross-coupling reactions, such as the Heck, Suzuki, and Sonogashira reactions.[7,8] A major advantage of these catalysts has been their robustness, which allows for reactions to be run at high temperatures without catalyst decomposition.[6]

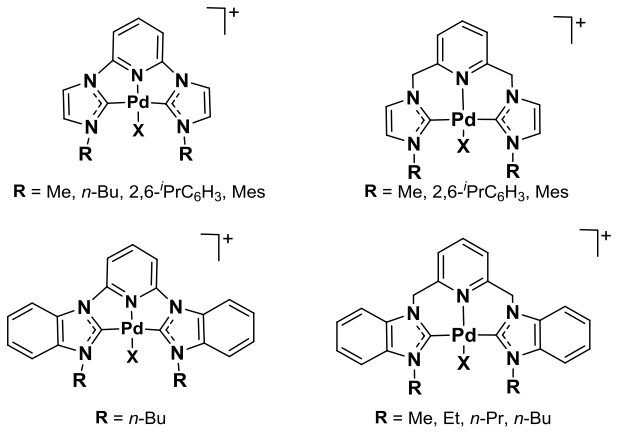


Figure 3.4. Previously Synthesized CNC Pd-Complexes

During initial work towards the development of the hydroamination of alkenes, catalyst **81** was examined. This complex resulted in complete isomerization of the alkene (*Figure 3.5*).[9] The known low solubility of this catalyst was blamed for its inactivity, which led to the synthesis of **82**. Complex **82** includes methylene linkers between the NHC and pyridine to disrupt the planar structure and thereby increase its solubility. When using **82** as the catalyst in the reaction,

the major product was still alkene isomerization, though now some hydroamination product was formed. This result led to the synthesis of a catalyst that could increase the solubility but not sterically disturb the open coordination site, **83**.[10] When **83** was examined, full consumption of the starting material was seen along with a slightly higher conversion to product. While these specific catalysts did not prove to be highly effective in the hydroamination reaction, these initial results demonstrate that other CNC catalysts still have the potenial to be very efficient.

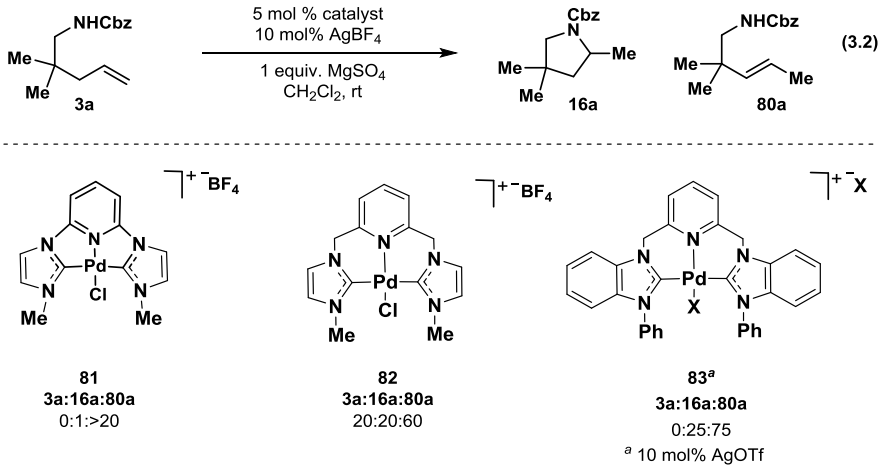


Figure 3.5. Previous Hydroamination Results with NHC catalysts

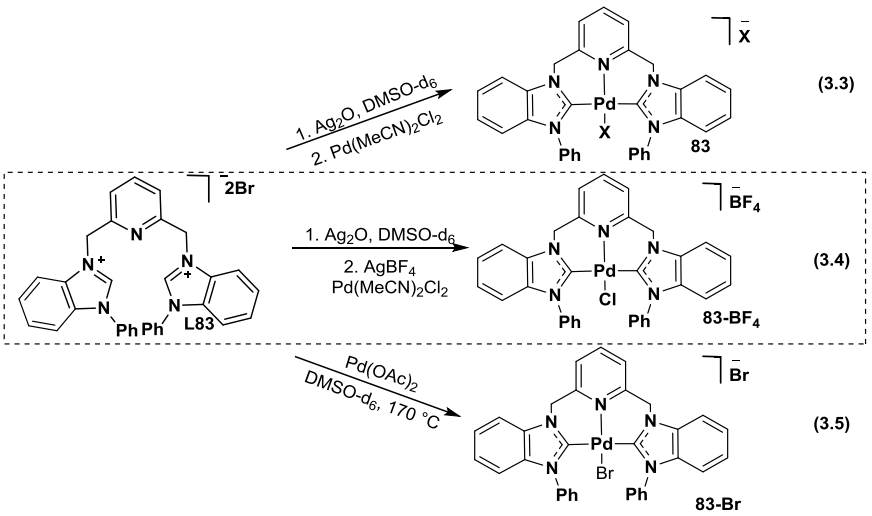
Section 2. Results and Discussion

3.2.1 Development of CNC catalysts for Hydroamination

Previous work in our lab on these CNC Pd(II) complexes had identified reproducibility issues for these synthesis, so our initial goal was to develop a reliable synthesis and purification. Several syntheses have been reported for palladium complexes of CNC pincer ligands, and these routes differ only in the final couterions in the complex (Scheme 3.1). Catalyst **83** was initially synthesized using Ag_2O as a mild base, creating an intermediate Ag(I)-NHC complex. This

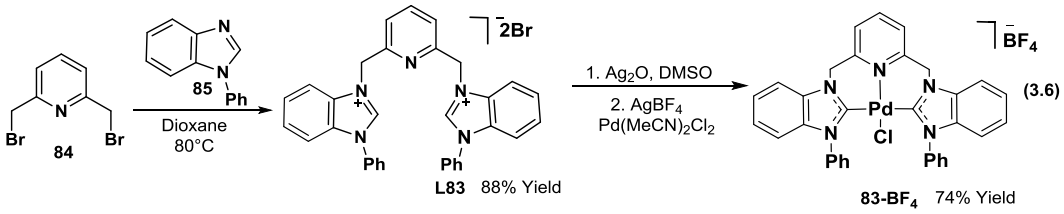
Ag(I) complex underwent transmetallation to palladium creating the pincer complex as seen in eq 3.3. This synthesis was known to suffer from reproducibility and purification issues. A very similar one pot reaction was developed by Cavell[7b], which involves a Ag(I) counterion exchange before transmetallation to Pd (eq 3.4). This method was used to synthesize **81** and **82**. A third route, eq 3.5, has been identified by Crabtree[6] and Hahn[7c] which uses $Pd(OAc)_2$ and high temperatures to deprotonate the imidazolium rings and coordinate Pd to the NHC while retaining the ligand's original counterions. Using CNC ligand **L83**, we evaluated the efficiency of these three syntheses (Scheme 3.1). Direct comparison using ^{1}H NMR spectroscopy revealed that the one pot reaction (eq 3.4) was the only route to that led to appreciable formation of a complex with this ligand.

Scheme 3.1. *Syntheses of Pincer (CNC)Pd Complexes*



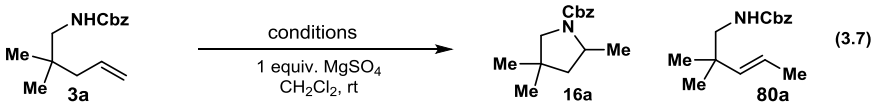
Using this one pot method, we were able to synthesize this new complex as a white bench stable solid in 3 steps with an overall yield of 65% (Scheme 3.2).

Scheme 3.2. *Formation of CNC-Pd complex* ***83-BF$_4$***



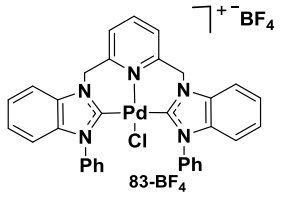
After this synthesis was developed, complex **83** was tested as a catalyst in the hydroamination reaction with substrate **3a** using standard hydroamination conditions (entry 1, Table 3.1). Gratifyingly, this catalyst gave hydroamination as the major product (**16a**) with only minor amounts of alkene isomerization (**80a**). A short optimization of the counterion and stoichiometry of the silver salt was conducted. Overall, this catalyst gave the hydroamination product as the major product in all reactions, but the use of a OTf counterion was crucial to achieving extremely high conversion to the hydroamination product. We also found that the catalyst loading could be reduced to 5 mol% with no loss of conversion (entry 6, Table 3.1).

Table 3.1. Optimization of Hydroamination with **83-BF_4**



entry	mol% Pd (**83-BF_4**)	Ag^I (mol%)	**3a:16a:80a**[a]
1	10	$AgBF_4$ (20)	0:90:10
2	10	$AgBF_4$(10)	0:95:5
3	5	$AgBF_4$(5)	0:75:25
4	10	AgOTf(20)	0:99: trace
5	10	AgOTf (10)	0:99:trace
6	5	AgOTf (5)	0:100:0

[a] ratios determined by ^{1}H NMR

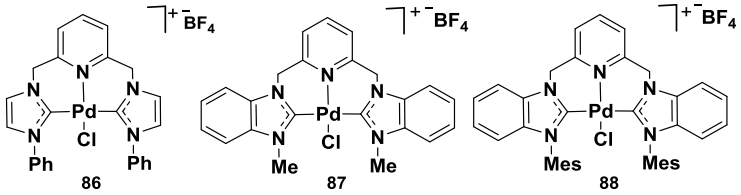


With a very active CNC hydroamination catalyst now developed, we decided to examine the NHC component of the ligand. *N*-phenyl imidazole (**86**), *N*-methyl benzimidazole (**87**), and *N*-mesityl benzimidazole (**88**) complexes were synthesized in an analogous fashion and examined in the test reaction (Table 3.2). Each of these catalysts produced hydroamination products, but in all cases greater quantities of the alkene isomerization byproducts were seen than in reactions with complex **83-BF_4**. Similarly to **83-BF_4**, test reactions with AgOTf increased the amount of the hydroamination product. When a substrate with greater Thorpe-Ingold effect was used with **87** (entry 6), only hydroamination was observed. Altogether, these experiments suggest that these catalysts are less efficient hydroamination catalysts than **83-BF_4**.

Table 3.2. Hydroamination Reactions with other CNC-Pd Complexes

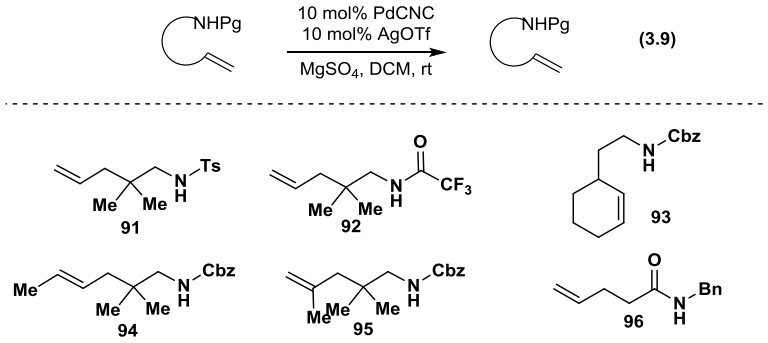
entry	R	Pd (5 mol%)	Ag^{I} (5 mol%)	**3a:16a:80a**
1	Me	**10**	$AgBF_4$	0:65:35
2	Me	**10**	AgOTf	0:75:25
3	Me	**11**	$AgBF_4$	50:20:30
4	Me	**11**	AgOTf	20:55:25
5	Me	**12**	AgOTf	30:60:10
6	Ph	**11**	AgOTf	0:100:0[b]

[a] ratios determined by ^{1}H NMR. [b] **1a:89a:90a**



Previous work has shown that the scope of the intramolecular hydroamination with **15** was quite comprehensive, especially with carbamate and amide substrates. While carbamates are synthetically useful protecting groups, we wanted to examine the scope of other possible substrates. Using this CNC catalyst, we sought to increase the protecting group scope to include sulfonamides and trifluoroacetamides. Similarly, di-substituted *cis* and *trans* alkenes and internal amides also did not undergo hydroamination with the PNP hydroamination catatlyst, so these substrates were also examined with **83-BF_4**. Unfortunately, this catalyst was inactive towards all of these types of substrates (Scheme 3.3)

Scheme 3.3. *Aminoalkenes that are Unreactive in Hydroamination with* ***83-BF$_4$***



3.2.2 Towards the Development of Enantioselective Hydroaminations

Many chiral PNP catalysts were previously synthesized for this hydroamination reaction, but they all failed to give enantioenriched products. We hoped that this new CNC ligand scaffold could lead to the development of an enantioselective reaction. Early studies by Danopoulos discovered that these types of CNC catalysts exist as enantiomers due to the twisted backbone that results from the puckering of the two six-membered chelate rings.[7a] These helical structures have a C2 conformation with an axis of symmetry following the Cl-Pd-N bonds as shown in *Figure 3.6*. Crabtree[6] studied these CNC complexes with several inner and outer sphere counterions, it was found that different outersphere counterions vastly changed the rates at which these enantiomers can interconvert. ^{1}H NMR coalescence temperatures of the enantiomers with an outersphere counterion of either BF_4 or OTs were found to be much higher than those of more nucleophilic halides. Generally the temperatures for complexes with a BF_4 or OTs counterions were around 343 K or higher.[6c] Complexes with coalescence temperatures higher than room temperature have a distinct AB pattern in the ^{1}H NMR spectrum for the

methylene linkers between the NHC and the pyridine. Complexes **83-BF_4**, **86, 87** and **88** all have this distinct AB pattern in their ^{1}H NMR spectra at room temperature, although exact coalescence temperatures have not been measured.

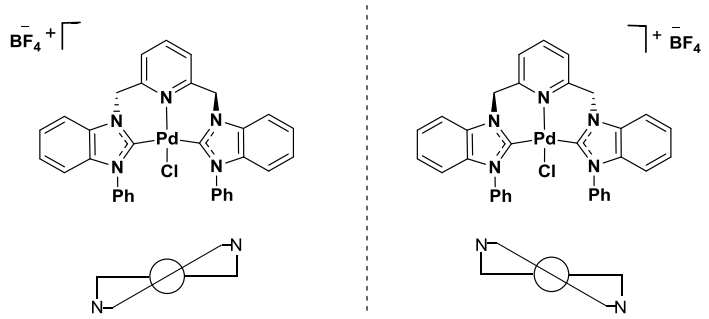
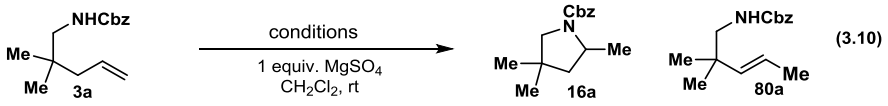


Figure 3.6. Atropisomers of **83-BF_4**, Newman-projections along the Pd-N bonds

During our optimization studies, we found that when a more coordinating counterion such as tosylate was used with catalyst **83-BF_4**, the reactivity was diminished, but hydroamination was still the major product (Table 3.3, entry 1). By utilizing the inherent axial chirality of this CNC catalyst, we hypothesized that chiral counterions could give enantioenriched products. Coordination or association of chiral counterions to the enantiomers in **83-BF_4** would create diastereomers, which, in turn, could lead to differing reactivities in catalytic reactions that would allow for the chiral information to be passed to the substrate. Alternatively, the chiral counterion could change the relative stability of the two diastereomers and make one predominate producing an enantioenriched product. Chiral sulfonates and phosphonates were both examined in the hydroamination reaction, but both inhibited the reaction even at elevated temperatures (Table 3.3, entries 2 – 4). While neither of these chiral counterions allowed hydroamination to occur, potential still exists for the possibility of asymmetric reactions to occur with these CNC catalysts in other reactions.

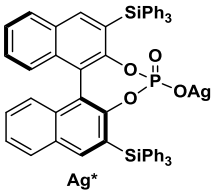
Table 3.3. Hydroamination with Chiral Counterions and **83-BF_4**

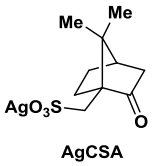


(3.10)

entry	mol% Pd (**83-BF_4**)	Ag^I (mol%)	**3a:16a:80a**[a]
1	5	AgOTs (5)	60:40:0
2	5	AgCSA(5)	100:0:0
3	10	Ag*(10)	100:0:0
4[b]	10	Ag*(10)	100:0:0

[a] ratios determined by ^{1}H NMR [b] Toluene, 100°C





3.2.3 Chiral Pincer CNC Ligands

Due to the lack of reactivity with chiral counterions, our goal of creating an enantioselective hydroamination shifted to the synthesis of chiral CNC ligands. We envisioned creating chiral ligands by functionalizing one of two different positions of these catalysts (*Figure 3.7*). The first of these would be to add a substituent to the methylene linker of the pyridine, thereby making it a chiral center (type a). By adding a methyl substituent on the benzylic carbon we sought to exploit the inherent C2 symmetry of these types of catalysts. Hopefully, this chiral ligand would create a significantly more stable diastereomer and that would be able to impart the backbone stereochemistry to the active site of the catalyst. These CNC complexes would be similar to the phosphine versions that have been previously synthesized.[11] The second type

would be to synthesize chiral benzimidazoles or imidazoles, where the incorporation of chiral substituents would create chiral ligands (type b).

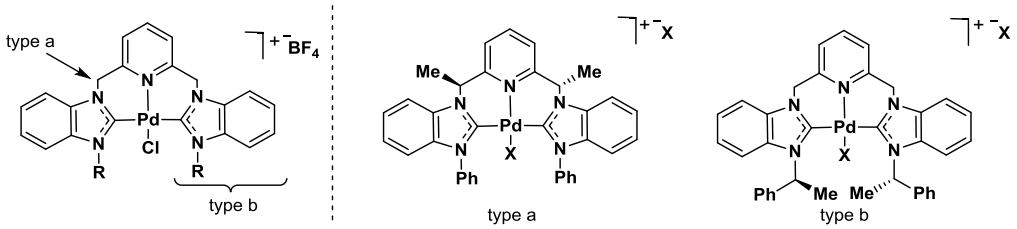
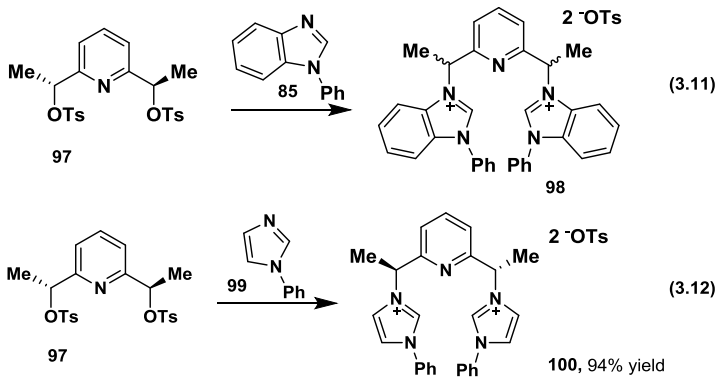


Figure 3.7. Two Types of Chiral CNC Complexes

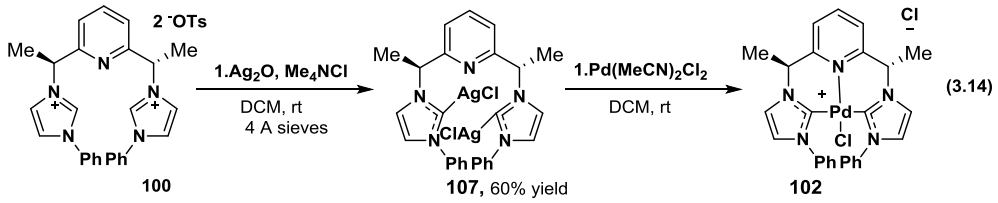
The synthesis of a type a chiral ligand began with the substitution reaction of the *N*-phenyl benzimidazole (**85**) and a secondary tosyl protected chiral pyridine (Scheme 3.4, eq 3.11). While this specific step has not been shown to cleanly furnish the expected S_N2 inversion product, previous examples have been accomplished with phosphine[11] and imidazole[12] nucleophiles. We found that when **85** was reacted in either 1,4-dioxane or toluene a mixture of diastereomers was produced. The mixture of isomers is likely due to competetive S_N1 and S_N2 reactivity. Reasoning that a switch to a slightly better nucleophile could increase the amount of S_N2 product, *N*-phenyl imidazole was used instead. Using neat *N*-phenyl imidazole only one diastereomeric product was observed by ^{1}H NMR spectroscopy, which was isolated in a 94% yield.

Scheme 3.4. *Benzimidazole and imidazole substitution reactions*



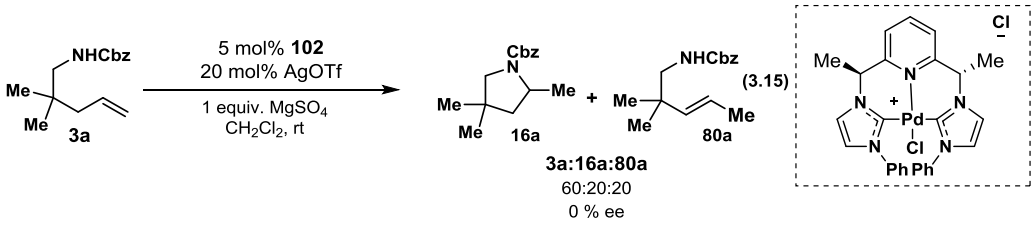
This ligand synthesis method resulted in the formation of **100** with tosylate counterions, which are known to be very coordinating counterions which would probably inhibit hydroamination. We reasoned that forming the Ag(I) NHC complex in the presence of a tetraalkylammonium chloride salt could replace the tosylate counterion with a chloride. This reaction removed a majority of the tosylate counterions and produced **101** that cleanly proceeded[13] to a Pd(II) complex **102** when reacted with $Pd(MeCN)_2Cl_2$.

Scheme 3.5. *Formation of Pd catalyst **102***



102 was tested under standard hydroamination conditions. We found that this catalyst does promote minor amounts of hydroamination, although no enantioenrichment of the product was observed (Scheme 3.6).

Scheme 3.6. *Hydroamination with catalyst* **102**



Development of a chiral CNC catalyst was then focused on catalyst type b, which relied on the synthesis of chiral benzimidazoles and imidazoles. Three target molecules were identified for their various properties (*Figure 3.8*). **103** was chosen because it is a well-known chiral benzimidazole that can be easily synthesized, although free rotation around the C-N bond may limit the ability of **103** to transfer chiral information to a substrate. Amidine **104** has a chiral backbone that includes an *N*-phenyl substituent similar to the achiral CNC complexes we synthesized. Compound **105** is a unique example of a fused bicycle with a highly rigid structure and has a similar steric environment to oxazolines.

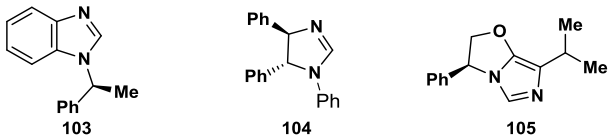
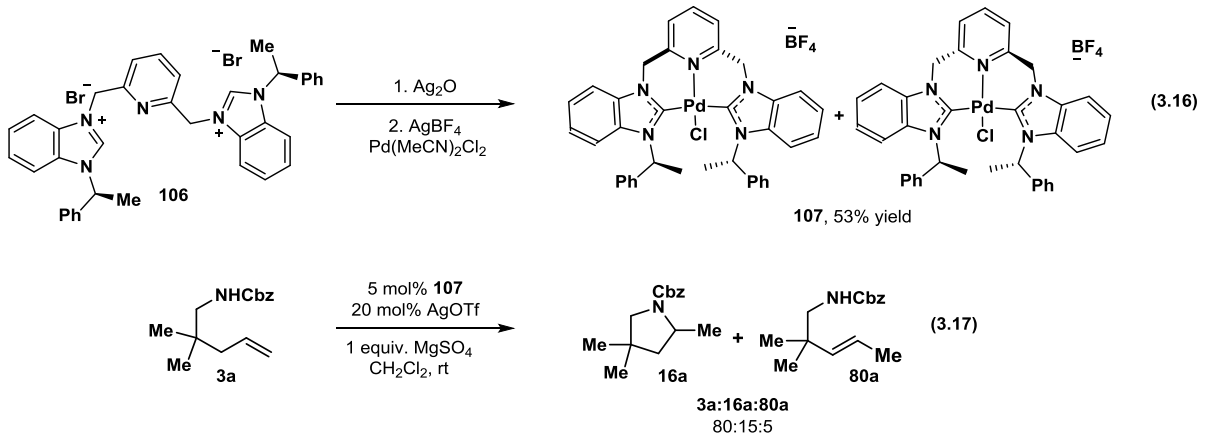


Figure 3.8. Chiral Benzimidazoles Amidines, and Imidazoles.

Using the chiral benzimidazole **103**, a pincer ligand **106** was synthesized in the same manner as the previous ligands. **106** was subjected to the one pot procedure to give a 1:1 mixture of new palladium complexes **107**. A literature search revealed that a similar chiral imidazole[14] has been used to make a CNC Pd complex, but the inherent axial chirality of these complexes

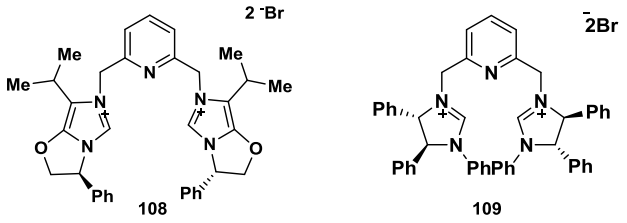
created a mixture of diastereomers. When this mixture of complexes was tested under standard hydroamination conditions, it produced only minor amounts of hydroamination product with starting aminoalkene as the major product (Scheme 3.7). The lack of reactivity with **107** may be due to the large *N*-substituents on the benzimidazoles inhibiting the coordination of the substrate.

Scheme 3.7. *Formation of **107** and Application to Hydroamination*



Next, we focused on chiral amidine **104**. A procedure for the formation of **104** was not readily available, but a Hartwig-Buchwald cross coupling was developed (see Section 4 for details). And recently, a short synthesis of the chiral imidazole **105** was recently published.[15] Using the standard reaction procedure, **104** and **105** were cleanly converted into ligands **108** and **109**, respectively. For both of these ligands, a Pd complex was never successfully isolated even after attempting with several different routes.

Scheme 3.8. *Chiral Ligands **108** and **109***



3.2.4 Development of Bidentate NC Ligands

The inability to synthesize many of the chiral CNC-Pd complexes we had envisioned led us to reconsider our design of chiral NHC ligands. Recalling the success of the quinox ligand in chapter 1, we decided to work towards the synthesis of new bidentate ligands. These bidentate ligands would be composed of an aromatic nitrogen ligand linked to an achiral or chiral NHC, thus producing a NC type ligand. We hoped this design would facilitate new reactivity and selectivity due to the combination of the more electron donating NHC ligand and the large *trans* influence difference between these ligands. Again, the electron donating ability of the NHC may increase the nucleophilicity of any palladium alkyl intermediates which could cause them to react more easily with electrophiles. The *trans* influence would result from the electronic difference between the more electron poor nitrogen ligand compared to the NHC. This difference should increase the likelihood that any alkyl complex formed would be *cis* to the NHC, providing close proximity to a chiral substituent. Similar chiral NC ligands have been successful in obtaining up to 92% ee in allylation reactions.[16]

First, we decided to synthesize a small set of achiral ligands, **110** – **114** (*Figure 3.9*). While these ligands were easily synthesized, unfortunately most did not smoothly undergo transmetallation to form a Pd complex.[17] However, one exception was ligand **114** which was

successfully transmetallated using $Pd(COD)_2Cl_2$ (Scheme 3.9). We reasoned that the failure to form many of these complexes could be due to the problems reported by an early study of pyridine-imidazole Pd complexes, in which the major product is the formation of a bis(NHC)Pd complex.[18] Perhaps the slightly more coordinating pyridine ligand, along with a larger substituent on the NHC in **114** facilitated the formation of this complex.

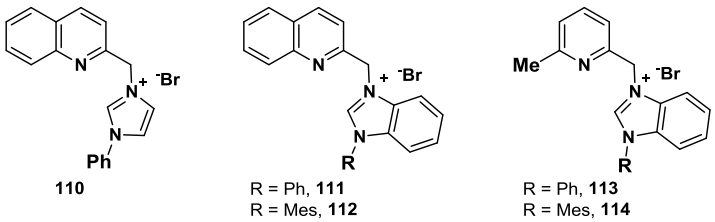
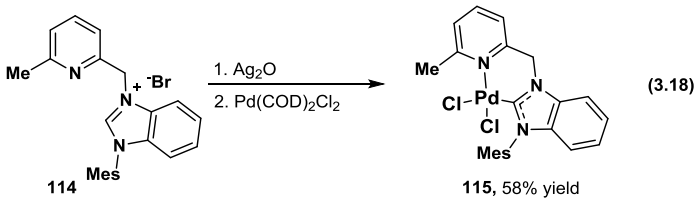


Figure 3.9. NC Ligands **110 – 114.**

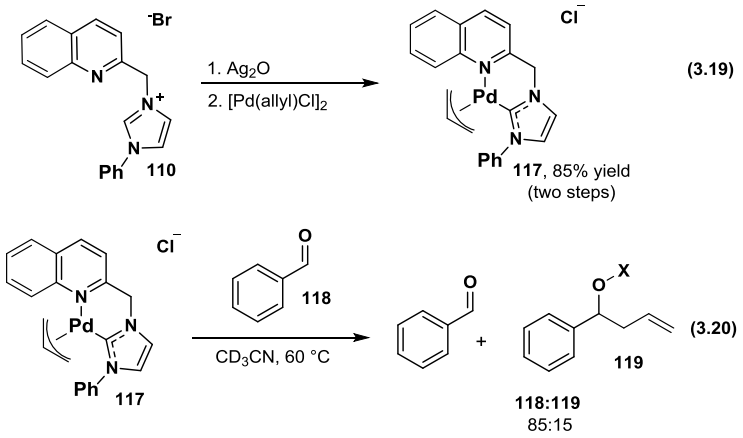
Scheme 3.9. *Formation of achiral NC-Pd complex,* ***115***



Due to the unsuccessful transmetallation of many of these NC ligands to $Pd(MeCN)_2Cl_2$ or $Pd(COD)Cl_2$, we focused on the synthesis of an η^3-allyl Pd complex. Similar NC complexes have been synthesized by Jarvo[19], and using a similar procedure **110** was successfully used to create η^3-allyl Pd complexes in 85% yield (Scheme 3.10). Complex **117** was examined using conditions that Jarvo[19] has reported for the allylation of aldehydes (Scheme 3.10, eq 3.20).

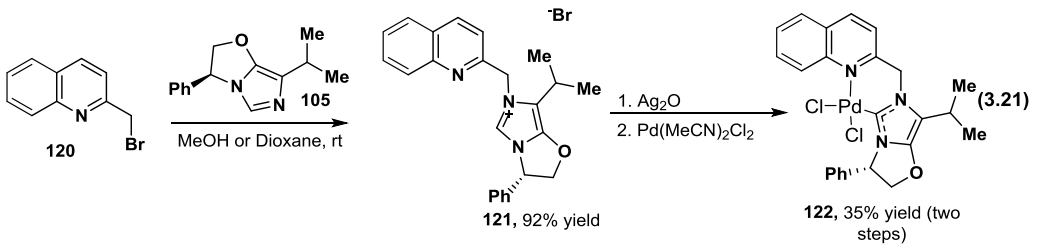
Unfortunately, only a small amount of **117** was converted to the allyl addition product after several days.

Scheme 3.10. *Formation and Reactivity of η^3-allyl NC-Pd Complex, **117**.*



Although achiral ligands **110 – 113** have yet to be successfully turned into Pd complexes, we worked toward a chiral version of these bidentate ligands. Using **105,** we reasoned that this ligand would transfer chirality due to the highly rigid structure that is similar to oxazolines. Additionally, the larger less strained 6-membered chelate ring formed between the N-Pd-NHC would create a wider bite angle that would position the chiral substituent closer to the metal center **(**Scheme 3.11). And, unlike the chiral CNC ligands, it was successfully made into a Pd complex (**122**) in only 3 steps with an overall 32% yield.

Scheme 3.11. *Formation of* ***122***



Section 3. Conclusion

In conclusion, tridentate and bidentate NHC-pyridine Pd catalysts have been developed. Using a tridentate CNC-Pd compound, a room temperature palladium-catalyzed intramolecular hydroamination of aminoalkenes has been accomplished. This reaction produced extremely high conversions of the hydroamination of carbamate protected aminoalkenes. Unfortuately, this catalsyst was unable to expand the substrate scope beyond the initially developed PNP Pd catalyzed reaction. Chiral CNC-Pd complexes were synthesized, but no enantioenriched products were obtained. Finally, a small set of new achiral and chiral bidentate NC ligands were developed along with several Pd complexes.

Section 4. Experimental

3.4.1 General Procedures

All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise indicated. Infrared spectra were measured on a Perkin Elmer Spectrum RX I

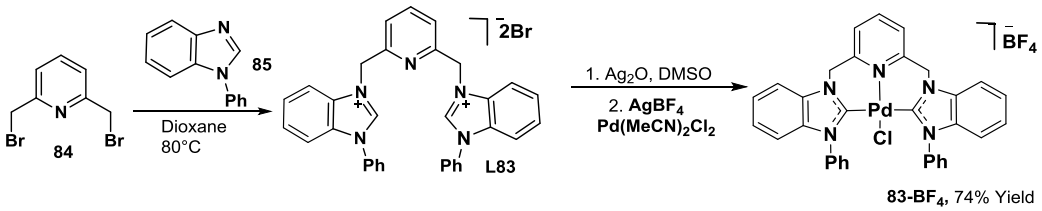
spectrometer. Mass Spectroscopy on a Bruker Esquire 1100 Liquid Chromatograph - Ion Trap Mass Spectrometer or a JEOL HX-110. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker DPX-200, AV-300, AV-301, DRX-499, or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm) or CH_2Cl_2 (5.30 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.0 ppm). Melting points were taken on MEL-TEMP melting point apparatus and are uncorrected. Chiral HPLC analysis was performed on a Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 254 nm; column, DIACEL CHIRALPAK AD-H or CHIRALPAK OD-H; mobile phase, 2-propanol/hexanes. Optical rotations were taken with a Na lamp Jasco DIP-370 digital polarimeter using a Jasco 1 mL polarimeter cell.

3.4.2 Materials

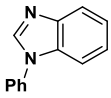
Tetrahydrofuran, diethyl ether, dichloromethane, and acetonitrile were degassed and dried by passing through a column of neutral alumina. 3Å molecular sieves were activated under vacuum at 200 °C for 14 h and stored in an oven at 120°C. Deuterated solvents, $CDCl_3$ and CD_2Cl_2 were obtained from Cambridge Isotope Laboratories, Inc. unless otherwise stated and stored over activated 3Å molecular sieves. Ethyl acetate and 1,4-dioxane was obtained from EMD or Sigma Aldrich and degassed with nitrogen and stored over activated 3Å molecular sieves. Commercially available tetramethylammonium chloride was purified by recrystallization with

ethanol and ether and stored under N_2. Bis(bromomethyl) pyridine (**8**) was obtainef from Sigma-Aldrich and used without further purification.

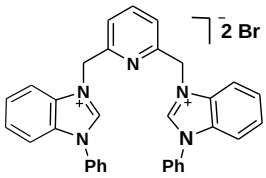
3.4.3 Synthesis of Achiral CNC Ligands and Catalysts



83-BF_4, 74% Yield

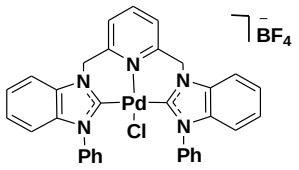


***N*-phenyl-benzimidazole** (**85**). Synthesized according to literature procedures and spectral data matches literature values.[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.87 – 7.90 (m, 1H), 7.60 – 7.40 (m, 6H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.36 – 7.30 (m, 2H).

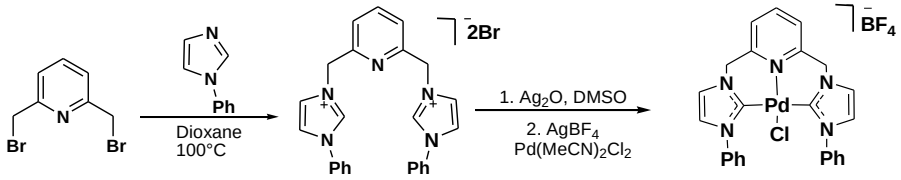


1,1'-(pyridine-2,6-diylbis(methylene))bis(3-phenyl-3H-benzo[d]imidazol-1-ium) bromide (**L83**). Bis(bromomethyl) pyridine (370 mg, 1.4 mmol) and *N*-phenyl benzimidazole (562 mg, 2.9 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry dioxane was added and reaction was heated to 80°C for 16 h. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and

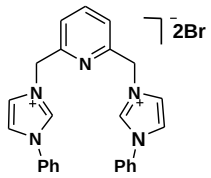
precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (803 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 10.14 (s, 2H), 8.05 (t, *J* = 7.5 Hz, 1H), 7.85 – 7.60 (m, 16H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 5.71 (s, 4H).



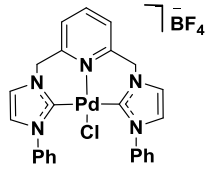
***(N*-phenylbenzimidazole-CNC)PdClBF$_4$ (83-BF$_4$).** **L83** (327 mg, 0.5 mmol) and Ag_2O (116 mg, 0.5 mmol) were added to a Schlenk flask in the glove box. The flask was removed from the glovebox and 6 mL of dry DMSO was added and the mixture was allowed to stir in the dark for two days and it became a gray and opaque. Under N_2, $AgBF_4$ (103 mg, 0.53 mmol) was added and the reaction stirred for 20 minutes. Then $Pd(MeCN)_2Cl_2$ (137 mg, 0.53 mmol) was added and the mixture was allowed to stir in the dark for 1 hour. The mixture was then it was filtered through a pad of celite and the DMSO was removed by distillation under reduced pressure. The residue was washed with dry Et_2O and hot $CHCl_3$ until it was a white solid (270 mg, 74% yield). ^{1}H NMR (500 MHz, DMSO-*d*^{6}): δ 8.31 (t, *J* = 7.5 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.0 Hz, 4H), 7.60 (t, *J* = 8.0 Hz, 3H), 7.51 – 7.45 (m, 9H), 6.44 (d, *J* = 15.5 Hz, 2H), 6.05 (d, *J* = 15.5 Hz, 2H).



***N*-phenylimidazole** (**99**). Synthesized according to literature procedures and spectral data matches literature values.[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.37 (m, 3H), 7.29 (t, *J* = 1.2 Hz, 1H), 7.22 (s, 1H).

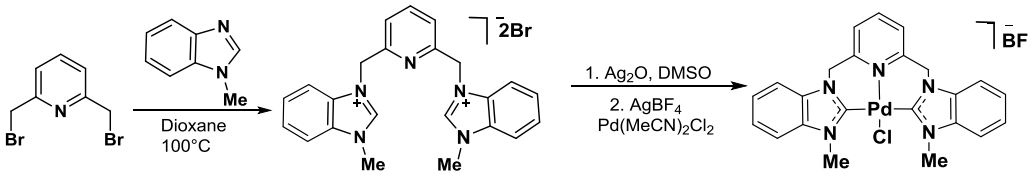


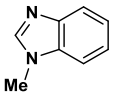
1,1'-(pyridine-2,6-diylbis(methylene))bis(3-phenyl-3H-imidazol-1-ium) dibromide (**L86**). Bis(bromomethyl) pyridine (264 mg, 1.0 mmol) and *N*-phenylimidazole (298 mg, 2.07 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 3 mL of dry dioxane was added and reaction was heated to 80 °C for 16 hours. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (471 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.88 (s, 2H), 8.16 (s, 2H), 8.16 (s, 2H), 7.90 – 7.85 (m, 3H), 7.78 – 7.53 (m, 4H), 7.55 (br s, 8H), 5.90 (s, 4H).



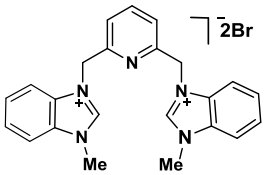
***(N*-phenylimidazole-CNC)PdClBF$_4$** (**86**). **L86** (276 mg, 0.5 mmol) and Ag_2O (116 mg, 0.5 mmol) were added to a Schlenk flask in the glove box. The flask was removed from the

glovebox and 6 mL of dry DMSO was added and the mixture was allowed to stir in the dark for two days or until it became a gray and opaque. Under N_2, $AgBF_4$ (103 mg, 0.53 mmol) was added and the reaction stirred for 20 minutes. Then $Pd(MeCN)_2Cl_2$ (137 mg, 0.53 mmol) was added and the mixture was allowed to stir in the dark for 1 h. The mixture was then was filtered through a pad of celite and the DMSO was removed by distillation under reduced pressure. The residue was dissolved in CH_2Cl_2 and precipitated with Et_2O. A mixture of white and brown precipitate resulted (250 mg). A second purification through dissolving in CH_2Cl_2 and precipitation with Et_2O resulted in a slightly off white solid (140 mg, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (t, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 1.8 Hz, 2H), 7.40 – 7.38 (m, 4H), 7.30 – 7.28 (m, 6H), 7.05 (d, *J* = 1.8 Hz, 2H), 7.75 – 7.63 (m, 4H).

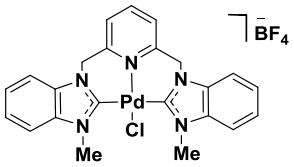




***N*-methyl benzimidazole** (**123**). Synthesized according to literature procedures and spectral data matches literature values.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 – 7.84 (m, 2H), 7.30 – 7.38 (m, 3H), 3.81 (s, 3H).

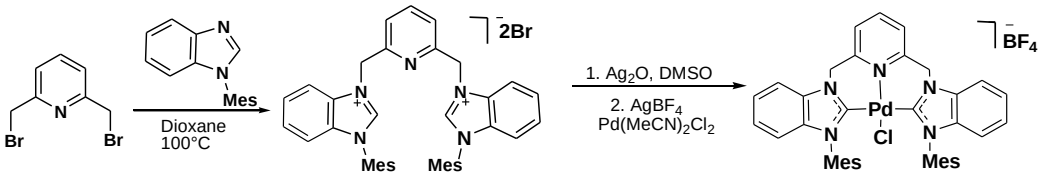


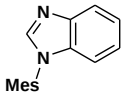
1,1'-(pyridine-2,6-diylbis(methylene))bis(3-methyl-3H-benzo[d]imidazol-1-ium) bromide (**L87**). Bis(bromomethyl) pyridine (132 mg, 0.5 mmol) and *N*-methylbenzimidazole (137 mg, 1.04 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 3 mL of dry dioxane was added and reaction was heated to 80 °C for 16 hours. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O. Spectral data matches literature values.[23] ^{1}H NMR (500 MHz, DMSO-d^6): 9.68 (s, 2H), 8.01 (t, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.66 – 7.64 (m, 4H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 5.81 (s, 4H), 4.03 (s, 6H).



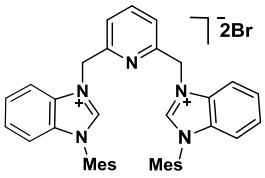
***(N*-methyl benzimidazole-CNC)PdClBF$_4$** (**87**). 1,1'-(pyridine-2,6-diylbis(methylene))bis(3-methyl-3H-benzo[d]imidazol-1-ium) bromide (79 mg, 0.15 mmol) and Ag_2O (35 mg, 0.15 mmol) were added to a Schlenk flask in the glove box. The flask was removed from the glovebox and 3 mL of dry DMSO was added and the mixture was allowed to stir in the dark for

two days or until it became a gray and opaque. Under N_2, $AgBF_4$ (31 mg, 0.16 mmol) was added and the reaction stirred for 20 minutes. Then $Pd(MeCN)_2Cl_2$ (41 mg, 0.16 mmol) was added and the mixture was allowed to stir in the dark for 1 hour. The mixture was then it was filtered through a pad of celite and the DMSO was removed by distillation. The residue was washed with Et_2O and $CHCl_3$ until it was a white solid. ^{1}H NMR (500 MHz, DMSO-d^6): 8.26 (t, J = 7.5 Hz, 1H), 8.10 (d, J = 7.8 Hz, 2H), 8.06 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 7.56 – 7.47 (m, 4H), 6.26 (d, J = 15.3 Hz, 2H), 5.94 (d, J = 15.3 Hz, 2H), 4.23 (s, 6H).

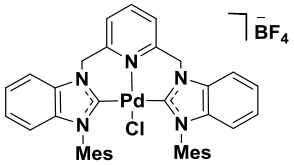




***N*-mesityl benzimidazole** (**124**). Synthesized according to literature procedures and spectral data matches literature values.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 7.9 Hz, 1H); 7.86 (s, 1H); 7.34 – 7.25 (m, 2H); 7.05 – 7.02 (m, 3H); 2.39 (s, 3H); 1.92 (s, 6H).



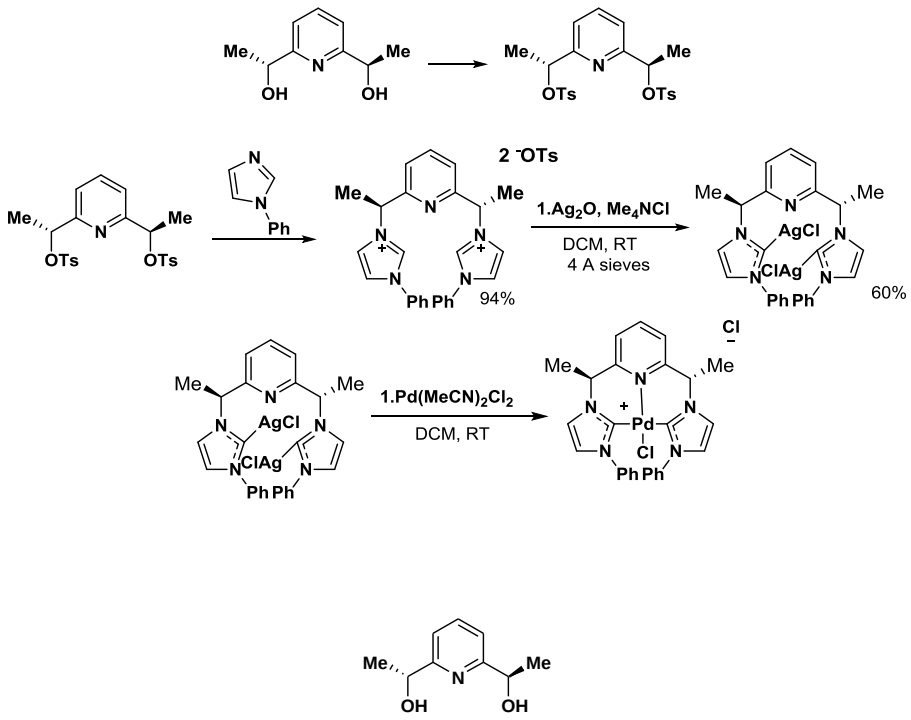
1,1'-(pyridine-2,6-diylbis(methylene))bis(3-methyl-3H-benzo[d]imidazol-1-ium) bromide (**L88**). Bis(bromomethyl) pyridine (106 mg, 0.4 mmol) and *N*-mesityl benzimidazole (189 mg, 0.8 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 3 mL of dry dioxane was added and reaction was heated to 80°C over-night. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The off-white solid was collected via vacuum filtration and washed with Et_2O (236 mg, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): 11.60 (s, 2H), 7.97 (d, J = 9.0 Hz, 2H), 7.80 – 7.75 (m, 5H), 7.59 (t, J = 8.1 Hz, 2H), 7.11 (s, 4H), 6.42 (s, 4H), 2.41 (s, 6H), 2.05 (s, 12H).



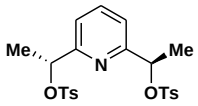
***(N*-methyl benzimidazole-CNC)PdClBF$_4$ (88).** **L88** (206 mg, 0.28 mmol) and Ag_2O (65 mg, 0.28 mmol) were added to a Schlenk flask in the glove box. The flask was removed from the glovebox and 5 mL of dry DMSO was added and the mixture was allowed to stir in the dark for two days or until it became a gray and opaque. Under N_2, $AgBF_4$ (58 mg, 0.30 mmol) was added and the reaction stirred for 20 min. Then $Pd(MeCN)_2Cl_2$ (77 mg, 0.30 mmol) was added and the mixture was allowed to stir in the dark for 1 h. The mixture was then it was filtered through a

pad of celite and the DMSO was removed by distillation. The remaining solid was dissolved in CH_2Cl_2 and precipitated with Ether to obtain a tan solid (200 mg, 89 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): 8.20 (d, *J* = 7.8 Hz, 2H), 8.09 – 8.00 (m, 3H), 7.48 (t, *J* = 8.1 Hz, 2h), 7.30 (d, *J* = 7.8 Hz, 2H), 6.98 – 6.91 (m, 6H), 6.14 (d, *J* = 15.0 Hz, 2H), 5.79 (d, *J* = 15.0 Hz, 2H), 2.32 (s, 6H), 1.99 (s, 6H), 1.83 (s, 6H).

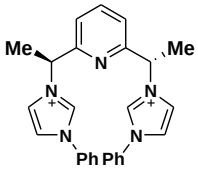
3.4.4 Synthesis of chiral pincer ligands and Pd Catalysts



(*1R,1'R*)-1,1'-(pyridine-2,6-diyl)diethanol (125). Synthesized according to literature procedures and spectral data matches literature values.[25] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 4.90 (q, *J* = 6.6 Hz, 2H), 3.89 (br s, 2H), 1.51 (d, *J* = 6.6 Hz, 6H).

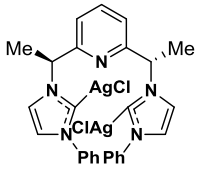


(*1R,1'R*)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl) bis(4-methylbenzenesulfonate) (97). To a solution of *p*-toluenesulfonyl chloride (1.66 g, 8.75 mmol) and triethylamine (1.22 mL, 8.75 mmol) in CH_2Cl_2 (20 mL) at 0°C under N_2 was added (*1R,1'R*)-1,1'-(pyridine-2,6-diyl)diethanol (292 mg, 1.75 mmol). The mixture was allowed to warm to room temperature and stir for 2 days. The mixture was then diluted with CH_2Cl_2 and washed with 1M HCl, and sat. $NaHCO_3$. The organic layer was separated and dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purified by column chromatography (20:80, EtOAc:hexanes) to afford a white solid (180 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 4H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.52 (q, *J* = 6.6 Hz, 2H), 2.40 (s, 6H), 1.52 (d, *J* = 6.6 Hz, 6 H).

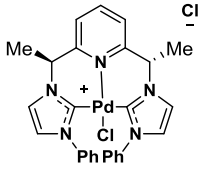


3,3'-(1S,1'S)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl)bis(1-phenyl-1H-imidazol-3-ium) tosylate(100). (*1R,1'R*)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl) bis(4-methylbenzenesulfonate) (157 mg, 0.33 mmol) and *N*-phenyl imidazole (332 mg, 2.31 mmol) were combined in an oven dried dram vial that was cooled under N_2. The vial was capped with a

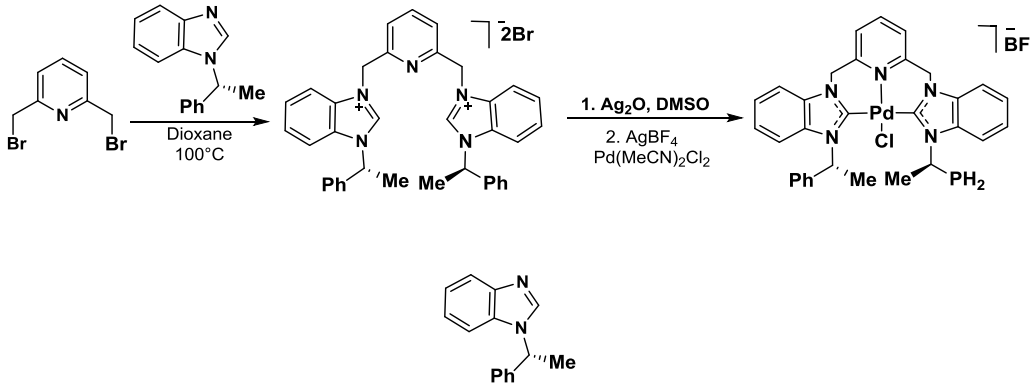
teflon cap and the mixture was heated to 120°C for 72 hours. The mixture was cooled to room temperature and was washed with Et_2O followed by dilution with $CHCl_3$ and precipitation with Et_2O. A hydroscopic off-white solid was collected and stored under N_2 (237 mg, 94 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.59 (s, 2H), 8.24 (s, 2H), 7.78 (d, *J* = 8.1 Hz, 4H), 7.67 – 7.58 (m, 8H), 7.40 – 7.39 (m, 7H), 7.14 (d, *J* = 8.1 Hz, 4H), 6.37 (q, *J* = 6.9 Hz, 2H), 2.34 (s, 6H), 1.91 (d, *J* = 6.9 Hz, 6H).



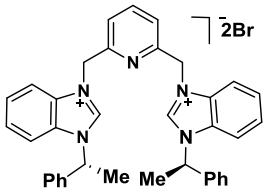
3,3'-(1S,1'S)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl)bis(1-phenyl-imidazolium)Ag_2Cl_2 (**107**) Under a N_2 atmosphere, a flame dried 4 dram vial was equipped with a magnetic stir bar and was charged with 3,3'-(1S,1'S)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl)bis(1-phenyl-1H-imidazol-3-ium) tosylate (198 mg, 0.26 mmol), Ag_2O (240 mg 1.04 mmol) and tetramethylammonium chloride (114 mg, 1.04 mmol). Two to three 4Å sieves were added followed by dry CH_2Cl_2 (1 mL). The mixture was sealed with a teflon cap and allowed heat to 50°C while stirring. After 20 hours, the mixture was passed through a plug of celite, concentrated. The remaining solid was dissolved in a minimal amount of CH_2Cl_2 and precipitated with pentane to give an off-white solid (139 mg, 76 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (m, 2H), 7.59 (s, 2H), 7.43 – 7.26 (m, 13H), 6.03 – 5.92 (m, 2H), 1.99 (d, *J* = 7.2 Hz, 6H).



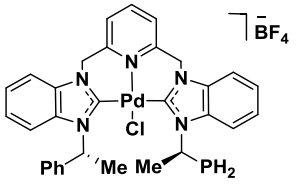
3,3'-(1S,1'S)-1,1'-(pyridine-2,6-diyl)bis(ethane-1,1-diyl)bis(1-phenyl-imidazolium)PdCl$_2$ (102). To an oven dried vial equipped with a stir bar, **101** (20 mg, 0.03 mmol) and Pd(MeCN)$_2$Cl$_2$ were added. Next, 1 mL of dry CH_2Cl_2 was added and the reaction was allowed to stir for 1 h. The mixture was filtered through a pad of celite, and precipitated with dry ether to form a tan solid (14 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.8 Hz, 2H), 8.08 – 8.06 (m, 1H), 7.80 (d, *J* = 1.2 Hz, 2H), 7.38 – 7.34 (m, 10H), 7.05 (d, *J* = 1.2 Hz, 2H), 6.34 (q, *J* = 6.9 Hz, 2H), 2.59 (d, *J* = 6.9 Hz, 6H).



(*R*)-1-(1-phenylethyl)-1H-benzo[*d*]imidazole (**103**). Synthesized according to literature procedures and spectral data matches literature values.[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.35–7.19 (m, 8H), 5.63 (q, *J* = 7.4 Hz, 1H), 2.01 (d, *J* = 7.1 Hz, 3H).

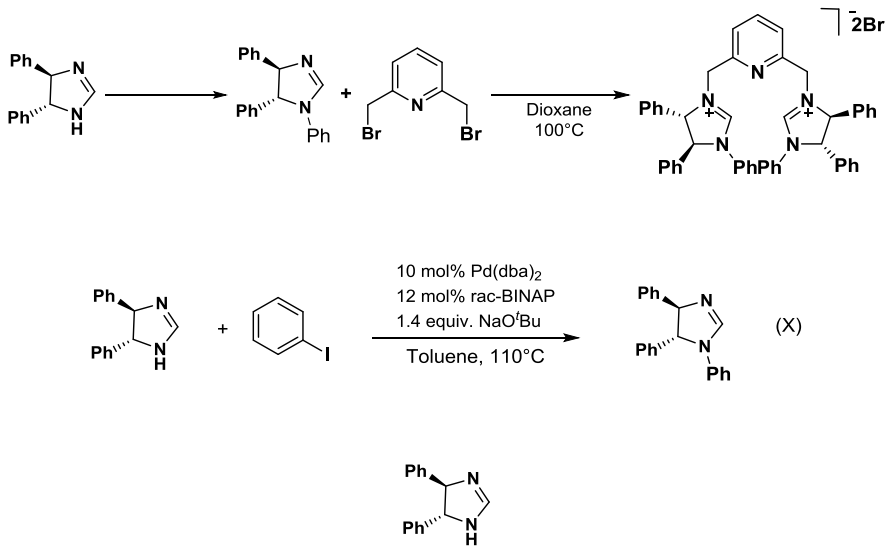


(*R*)-1,1'-(pyridine-2,6-diylbis(methylene))bis(3-((*R*)-1-phenylethyl)-3H-benzo[*d*]imidazol-1-ium) bromide (106). Bis(bromomethyl) pyridine (44 mg, 0.17 mmol) and (*R*)-1-(1-phenylethyl)-1H-benzo[*d*]imidazole (78 mg, 0.34 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 1 mL of dry dioxane was added and reaction was heated to 80°C for 16 hours. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (100 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.97 (s, 2H), 7.78 (s, 3H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.45 – 7.30 (m, 14H), 6.32 (d, *J* = 15.0 Hz, 2H), 6.00 – 5.95 (m, 4H), 2.31 (d, *J* = 6.6 Hz, 2H).

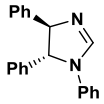


[(*R*)-1-phenylethyl-benzo[*d*]imidazole]Pd(Cl)(BF_4) (107). **106** (89 mg, 0.125 mmol) and Ag_2O (29 mg, 0.125 mmol) were added to a Schlenk flask in the glove box. The flask was removed from the glovebox and 2 mL of dry DMSO was added and the mixture was allowed to stir in the dark for two days or until it became a gray and opaque. Under N_2, $AgBF_4$ (26 mg,

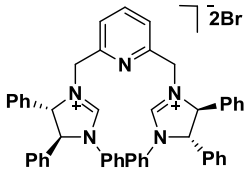
0.132 mmol) was added and the reaction stirred for 20 minutes. Then $Pd(MeCN)_2Cl_2$ (34 mg, 0.132 mmol) was added and the mixture was allowed to stir in the dark for 1 hour. The mixture was then it was filtered through a pad of celite and the DMSO was removed by distillation. The residue was dissolved in CH_2Cl_2 and precipitated with Et_2O. A mixture of white and brown precipitate resulted. A second purification through dissolving in CH_2Cl_2 and precipitation with Et_2O resulted in a slightly off white solid (20 mg, 21% yield). Isolated as a 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (t, *J* = 6.3 Hz, 2H), 7.96 – 7.92 (m, 3H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.32 – 7.20 (m, 13H), 7.16 – 7.03 (m, 4H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 15.0 Hz, 1H), 6.08 (d, *J* = 15.0 Hz, 1H), 5.87 (d, *J* = 15.0 Hz, 1H), 5.87 (d, *J* = 15.0 Hz, 1H), 2.17 (d, *J* = 7.0 Hz, 3H), 1.93 (d, *J* = 7.0 Hz, 3H).



(4*S*, 5*S*)-4,5-Diphenyl-4,5-dihydro-1H-imidazole (**126**). Synthesized according to literature procedures and spectral data matches literature values.[27] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.0 Hz, 4H), 7.30 (d, *J* = 6.6 Hz, 2H), 7.26 (d, *J* = 7.0 Hz, 4H), 5.34 (br s, 1H), 4.69 (s, 2H).

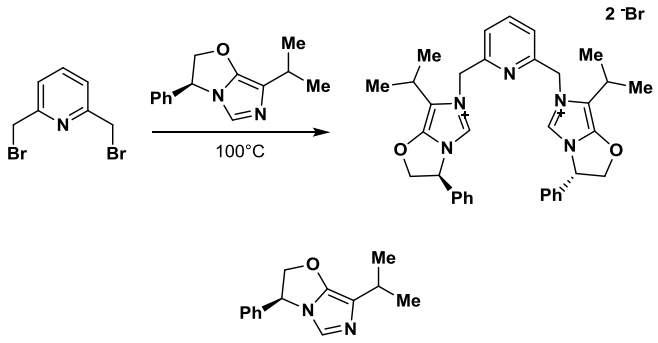


(4*S*, 5*S*)-1,4,5-triphenyl-4,5-dihydro-1H-imidazole (104). To an oven dried vial, Pd(dba)2 (52 mg, 0.09 mmol), rac-BINAP (67 mg, 0.11 mmol), **126** (200 mg, 0.9 mmol), and NaOtBu (141 mg, 1.26 mmol) were added under N_2. Then 1.8 mL of dry Toluene was added. After 5 min, iodobenzene (100 µL, 0.9 mmol) was added and the reaction was heated to 100 ºC and stirred overnight. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and washed with H_2O and sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification using column chromagraphy. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.5 Hz, 1H), 7.39 – 7.17 (m, 12H), 6.91–6.88 (m, 3H), 5.06 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.89 (d, *J* = 7.5 Hz, 1H).

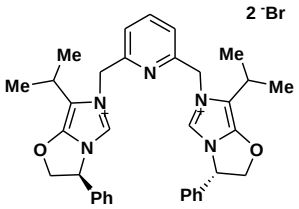


(4*S*,4'*S*,5*S*,5'*S*)-3,3'-(pyridine-2,6-diylbis(methylene))bis(1,4,5-triphenyl-4,5-dihydro-1H-imidazol-3-ium dibromide) (109). Bis(bromomethyl) pyridine (31 mg, 0.12 mmol) and **104** (74 mg, 0.25 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 1 mL of dry dioxane was added and reaction was heated to 80°C for 16 hours. The dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with

Et_2O (50 mg, 50% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 10.86 (s, 2H), 7.52 (d, *J* = 7.2 Hz, 4H), 7.42 – 7.20 (m, 29H), 5.76 (d, *J* = 9.0 Hz, 2H), 5.34 (d, *J* = 15.0 Hz, 2H), 5.01 (d, *J* = 15.0 Hz, 2H), 4.99 (d, *J* = 9.0 Hz, 2H).



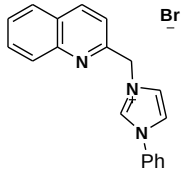
***(S)*-7-Isopropyl-3-phenyl-2,3-dihydro-imidazo[5,1-*b*]oxazole** (**105**). Synthesized according to literature procedures and spectral data matches literature values.[28] ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.43 (m, 3H), 7.17 – 7.19 (m, 2H), 6.94 (s, 1H), 5.42 (t, *J* = 7.2 Hz, 1H), 5.24 (dd, *J* = 8.4 Hz, 7.2 Hz, 1H), 4.72 (dd, *J* = 8.4, 7.2 Hz, 1H), 2.89 (quint., *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 3H).



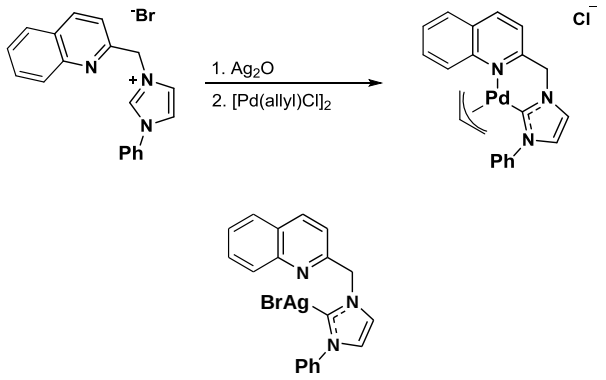
pyridine-2,6-diylbis(methylene))bis((*S*)-7-Isopropyl-3-phenyl-2,3-dihydro-imidazo[5,1-*b*]oxazole) dibromide (108). Synthesized according to a previously reported procedure.[10a] To a Schlenk flask was added 2,6-bis(bromomethyl)pyridine (46 mg, 0.17 mmol) and **27** (84 mg, 0.37mmol) followed by MeOH (5mL). The reaction was allowed to stir for 72 hours and solvents

were removed under reduced pressure. The product was precipitated with dry CH_2Cl_2/Et_2O providing the product as a off white hydroscopic solid (100 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 2H), 7.75 (t, *J* = 4.4 Hz, 1H), 7.42 – 7.26 (m, 12H), 6.76 (dd, *J* = 8.1, 4.8, Hz 2H), 6.45 (d, *J* = 14.7 Hz, 2H), 5.62 (t, *J* = 8.4 Hz, 2H), 5.00 (d, *J* = 14.7 Hz, 2H), 4.77 (dd, *J* = 8.7, 4.8 Hz, 2H), 2.77 (quin, 2H), 1.38 (d, *J* = 6.9 Hz, 6H), 1.07 (d, *J* = 6.6 Hz, 6H).

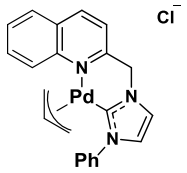
3.4.5 Synthesis of NC Ligands and Catalysts



1-phenyl-3-(quinolin-2-ylmethyl)-1H-imidazol-3-ium bromide (110). 2-bromomethyl quinoline (99 mg, 0.45 mmol) and **99** (65 mg, 0.45 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 1 mL of dry dioxane was added and the mixture was heated to 80°C and stirred overnight. The mixture was cooled to room temperature and then the dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (155 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.32 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.90 (t, *J* = 1.2 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.70 (m, 3H), 7.60 – 7.56 (m, 5H), 7.35 (s, 1H), 6.22 (s, 2H).

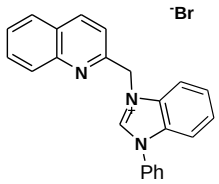


1-phenyl-3-(quinolin-2-ylmethyl)-imidazol-3-ium AgBr (127). Ligand **110** (165 mg, 0.45 mmol) and Ag_2O (57 mg, 0.25 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 4 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting light yellow solid that was used without further purification (210 mg, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.60 – 7.56 (m, 4H), 7.48 – 7.42 (m, 4H), 7.28 (d, *J* = 1.2 Hz, 1H), 5.69 (s, 2H).

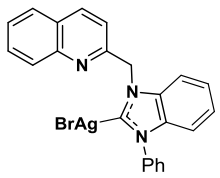


1-phenyl-3-(quinolin-2-ylmethyl)-imidazol-3-ium Pd(allyl)Cl (117). [Pd(allyl)Cl]2 (77.56 mg, 0.21 mmol) was added to an oven dried Schlenk flask in a N_2 glove box. Then **127** (189 mg, 0.40 mmol) was added followed by 4 mL of dry acetonitrile. The mixture was stirred for an

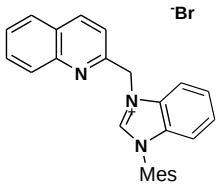
hour and then filtered through a pad of celite. The clear solution was concentrated under reduced pressure, and the resulting solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The solid was collected via vacuum filtration and washed with Et_2O (161 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.82 (t, *J* = 7.2 Hz, 3H), 7.77 – 7.20 (m, 1H), 7.59 – 7.54 (m 1H), 7.48 – 7.37 (m, 5H), 7.24 (d, *J* = 1.2 Hz, 1H), 6.00 – 5.89 (m, 2H), 4.97 (br s, 1H), 4.20 (dd, *J* = 7.5, 1.8 Hz, 1H), 3.12 (d, *J* = 13.2 Hz, 1H), 2.86 (br s, 1h), 1.76 (d, *J* = 12.0 Hz, 1H).



3-phenyl-1-(quinolin-2-ylmethyl)-3H-benzo[d]imidazol-1-ium bromide (111). 2-bromomethyl quinoline (244 mg, 1.1 mmol) and **85** (224 mg, 1.16 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry toluene was added and the mixture was heated to 80°C and stirred overnight. The mixture was cooled to room temperature and then the toluene was removed under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (236 mg, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.76 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 6.9 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.87 – 7.82 (m, 3H), 7.71 – 7.62 (m, 7H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.55 (s, 2H).

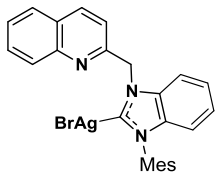


3-phenyl-1-(quinolin-2-ylmethyl)-3-AgBr-benzo[*d*]imidazol-1-ium (128). Ligand **111** (165 mg, 0.45 mmol) and Ag_2O (57 mg, 0.25 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 4 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting light yellow solid that was used without further purification (210 mg, 99 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (t, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.74 – 7.66 (m, 4H), 7.57 – 7.35 (m, 8H), 5.95 (s, 2H).

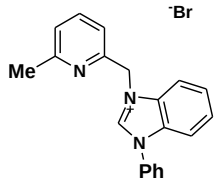


3-mesityl-1-(quinolin-2-ylmethyl)-3H-benzo[*d*]imidazol-1-ium bromide (112). 2-bromomethyl quinoline (244 mg, 1.10 mmol) and **124** (273 mg, 1.16 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry dioxane was added and the mixture was heated to 80°C and stirred overnight. The mixture was cooled to room temperature and then the dioxane was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (390 mg, 72 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ

11.26 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.02 (t, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.66 – 7.54 (m, 4H0, 7.26 – 7.24 (m, 1H), 7.10 (s, 2H), 6.68 (s, 2H), 2.41 (s, 3H), 2.10 (s, 6H).

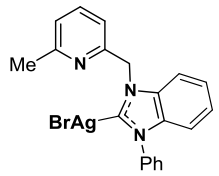


3-mesityl-1-(quinolin-2-ylmethyl)-3-AgBr -benzo[*d*]imidazol-1-ium (129). Ligand **112** (183 mg, 0.40 mmol) and Ag_2O (69 mg, 0.30 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 5 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting light yellow solid that was used without further purification (200 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.67 – 7.55 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.28 (m, 2 H), 7.06 (s, 2H), 7.20 – 7.00 (m, 1H), 6.01 (s, 2H), 2.40 (s, 3h), 1.97 (s, 6H).

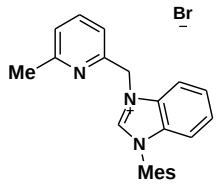


1-((6-methylpyridin-2-yl)methyl)-3-phenyl-3H-benzo[*d*]imidazol-1-ium bromide (113). 2-methyl-6-bromomethyl pyridine (372 mg, 2.00 mmol) and **85** (388 mg, 2.00 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry toluene was the mixture was heated to 100°C and stirred overnight. The mixture was cooled to room

temperature and then the toluene was removed under reduced pressure, and the resulting white solid was stirred with Et_2O for 15 minutes. The white solid was collected via vacuum filtration and washed with Et_2O (500 mg, 66 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.58 (s, 1H), 8.16 (d, *J* = 7.2 Hz, 1H), 7.89 – 7.82 (m, 3H), 7.71 – 7.63 (m, 7H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 2H), 2.48 (s, 3H).

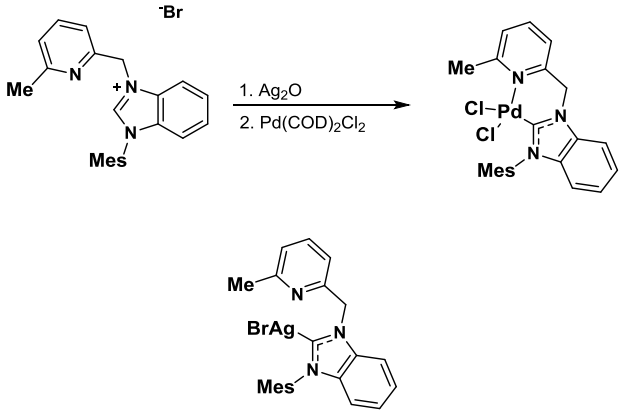


1-((6-methylpyridin-2-yl)methyl)-3-phenyl-3- AgBr -benzo[*d*]imidazol-1-ium (130). Ligand **113** (418 mg, 1.10 mmol) and Ag_2O (191 mg, 0.83 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 10 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting light solid that was used without further purification (200 mg, 37 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 – 7.45 (m, 8H), 7.38 – 7.30 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 5.69 (s, 2H), 2.51 (s, 3H).

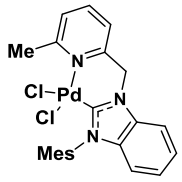


3-mesityl-1-((6-methylpyridin-2-yl)methyl)-3H-benzo[*d*]imidazol-1-ium bromide (114). 2-methyl-6-bromomethyl pyridine (186 mg, 1.00 mmol) and **124** (236mg, 1.00 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry toluene

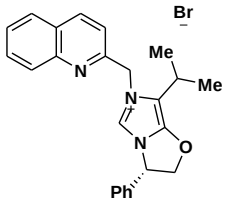
was added and the mixture was heated to 100°C and stirred overnight. The mixture was cooled to room temperature and then the toluene was removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (316 mg, 75 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.06 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.56 (m, 4H), 7.26 – 7.23 (m, 1H), 7.12 – 7.11(m, 1H), 7.10 (s, 2H), 6.35 (s, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.05 (s, 6H).



3-mesityl-1-((6-methylpyridin-2-yl)methyl)-3-AgBr -benzo[d]imidazol-1-ium (131). Ligand **114** (295 mg, 0.70 mmol) and Ag_2O (121 mg, 0.53 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 5 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting light yellow solid that was used without further purification (285 mg, 77 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.39–7.31 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 2H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.78 (s, 2h), 2.55 (s, 3H), 2.39 (s, 3H), 1.94 (s, 6H).

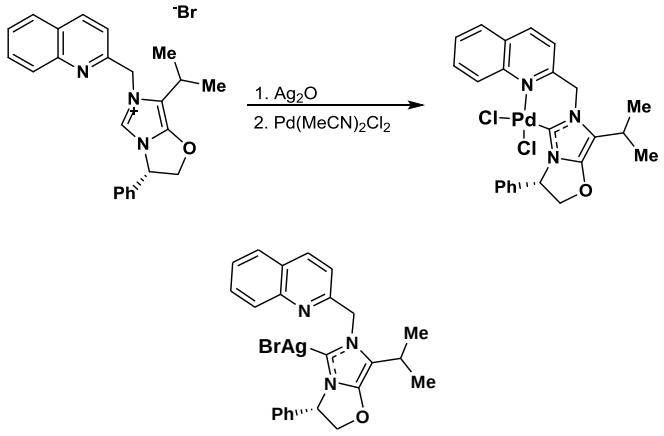


[3-mesityl-1-((6-methylpyridin-2-yl)methyl)-3-benzo[*d*]imidazol-1-ium] $PdCl_2$ (115). $Pd(COD)_2Cl_2$ (80 mg, 0.28 mmol) was added to an oven dried Schlenk flask in a N_2 glove box. Then **114** (148 mg, 0.28 mmol) was added followed by 10 mL of dry methylene chloride. The mixture was stirred for an hour and then filtered through a pad of celite. The clear solution was concentrated under reduced pressure, and the resulting solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The solid was collected via vacuum filtration and washed with Et_2O (90 mg, 58 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.44 (td, *J* = 7.2, 0.9 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.14 (s, 1H), 7.10 (s, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 15.3 Hz, 1H), 5.64 (d, *J* = 15.3 Hz, 1H), 3.21 (s, 3H), 2.44 (s, 3H), 2.08 (s, 3H), 1.90 (s, 3H).



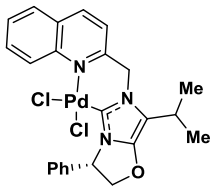
***(S)*-7-isopropyl-3-phenyl-6-(quinolin-2-ylmethyl)-2,3-dihydroimidazo[*5,1-b*]oxazol-6-ium bromide (121)**. 2-bromomethyl quinoline (288 mg, 1.3 mmol) and **105** (296 mg, 1.3 mmol) were combined in a Schlenk flask and evacuated and purged with N_2 (3x). Then 5 mL of dry dioxane was added and reaction was stirred at room temperature overnight. The dioxane was

removed under reduced pressure, and the resulting white solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The white solid was collected via vacuum filtration and washed with Et_2O (540 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.44 – 7.42 (m, 5H), 7.36 (s, 1H), 6.36 (dd, *J* = 8.1, 5.4 Hz, 1H), 6.04 (d, *J* = 15.9 Hz, 1H), 5.70 (d, *J* = 15.9 Hz, 1H), 5.45 (dd, *J* = 9.0, 8.1 Hz, 2H), 4.99 (d, *J* = 7.5, 5.1 Hz, 1H), 3.04 (quint., *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H).

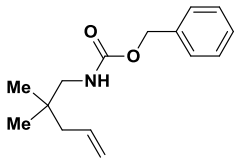


***(S)*-7-isopropyl-3-phenyl-6-(quinolin-2-ylmethyl)-2,3-dihydroimidazo[*5,1-b*]oxazol-6-ium AgBr (132)**. Ligand **121** (306 mg, 0.68 mmol) and Ag_2O (117 mg, 0.51 mmol) were combined in a Schlenk flask in a N_2 glovebox. Then 5 mL of dry methylene chloride was added and the mixture was shielded from light and stirred overnight. The mixture was then filtered through a celite plug and concentrated under reduced pressure, and the resulting in an off-white solid that was used without further purification (250 mg, 66 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.59

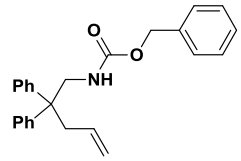
– 7.54 (m, 1H), 7.26 – 7.20 (m, 6H), 5.78 (br s, 1H), 5.31 – 5.24 (m, 3H), 4.79 – 4.74 (m, 1H), 2.87 – 2.78 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H).



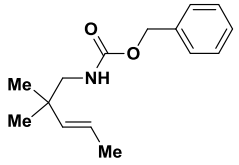
quinoline-2-(methylene)-((*S)*-7-Isopropyl-3-phenyl-2,3-dihydro-imidazo[5,1-*b*]oxazole) $PdCl_2$ (122). **132** (181 mg, 0.33 mmol) and $Pd(MeCN)_2Cl_2$ (84 mg, 0.33 mmol) were combined in a oven dried vial and flushed with N_2. Then 1 mL of dry methylene chloride was added and reaction was stirred for 1 hour. The mixture was filtered through a pad of celite and the solvent was removed under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 and precipitated with Et_2O. The light brown solid was then collected via vacuum filtration and washed with Et_2O (96 mg, 53% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 9.08 (d, *J* = 8.4 Hz, 1H, 7.77 – 7.72 (m, 2H), 7.64 – 7.57 (m, 3H), 7.40 – 7.38 (m 2H), 7.30 – 7.29 (m, 3H), 6.37 – 6.30 (m, 1H), 5.95 (d, *J* = 15.0 Hz, 1H), 5.28 – 5.22 (m, 2H), 4.87 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.03 – 2.92 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H).



Benzyl 2,2-dimethylpent-4-enylcarbamate (3a) Spectral data matches literature values.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 5H), 5.88 – 5.74 (m, 1H), 5.11 (s, 2H), 5.07 – 5.00 (m, 2H), 4.78 (br, 1 H), 3.04 (d, *J* = 6.6 Hz, 2H), 1.98 (d, *J* = 7.2 Hz, 2H), 0.89 (s, 6H).



Benzyl 2,2-diphenylpent-4-enylcarbamate (1a). Spectral data matches literature values.[29] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.20 (m, 15H), 5.70 – 5.40 (m, 1H), 5.20 – 5.00 (m, 4H), 4.50 – 4.20 (m, 1H), 4.01 (d, *J* = 5.8 Hz, 2H), 2.95 (d, *J* = 6.8 Hz, 2H).

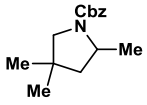


Benzyl 2,2-diphenylpent-3-enylcarbamate (80a). Spectral data matches literature values.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.35 (m, 5H), 5.49 – 5.30 (m, 2H), 5.11 (s, 2H), 4.72 (br, 1H), 3.06 (d, *J* = 6.3 Hz, 2H), 1.68 (d, *J* = 5.1 Hz, 3H), 1.00 (s, 6H).

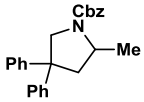
General Hydroamination Conditions:

(A)

In a glove box, Pd catalyst (0.05 equiv.), AgOTf (0.05 equiv.) and $MgSO_4$ (1.0 equiv.) were added to a round-bottomed flask. The flask was capped with a septum, removed from the glove box, placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.1 M) was added. To the stirring mixture was added a solution of the substrate (1 equiv.) in CH_2Cl_2 (0.1 M) by syringe. The reaction was stirred for 16 – 20 h while monitoring for the disappearance of the starting material by TLC. After the substrate has been consumed, the mixture was filtered through a plug of celite.



Benzyl 2,4,4-trimethylpyrrolidine-1-carboxylate (3a): Method A, colorless oil. Spectral data matches literature values.[5a] ^{1}H NMR (300 MHz, $CDCl_3$): 7.37 – 7.30(m, 5H), 5.21 – 5.07(m, 2H), 3.94 (br s, 1H), 3.46 – 3.34 (m, 1H), 3.07 (d, *J* = 10.5 Hz, 1H), 1.91 (dd, *J* = 7.2. 12.6 Hz, 1H), 1.32 – 1.24 (m, 4H), 1.11 (s, 3H), 0.98 (s, 3H).



Benzyl 2-methyl-4,4-diphenylpyrrolidine-1-carboxylate (89a): Method A, colorless oil. Spectral data matches literature values.[29] ^{1}H NMR (300 MHz, $CDCl_3$, observed as a 1:1 ratio of rotamers): δ 7.40 – 7.14 (m, 15 H, both), 5.31 (d, *J* = 12.4 Hz, 1H, rot. A), 5.18 (abq, *J* = 12.4

Hz, 1H, both) 5.09 (d, *J* = 12.4 Hz, 1H, rot. A), 4.74 (dd, *J* = 2.0, 11.6 Hz, 1H, rot. A.), 4.58 (dd, *J* = 1.6, 11.6 Hz, 1H, rot. B), 3.81 – 3.65 (m, 2 H, both), 2.86 – 2.80 (m, 1 H, both), 2.31 (dd, *J* = 9.6, 12.4 Hz, 1H, rot. A), 2.26 (dd, *J* = 9.6, 12.8 Hz, 1H, rot. B), 1.36 (d, *J* = 6.0 Hz, 3H, rot. A), 1.29 (d, *J* = 6.0 Hz, 1H, rot. B.).

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Appendix A: X-Ray Crystal Structure

Section 1 : X-ray Crystal Stucture of 14 (Chapter 1)

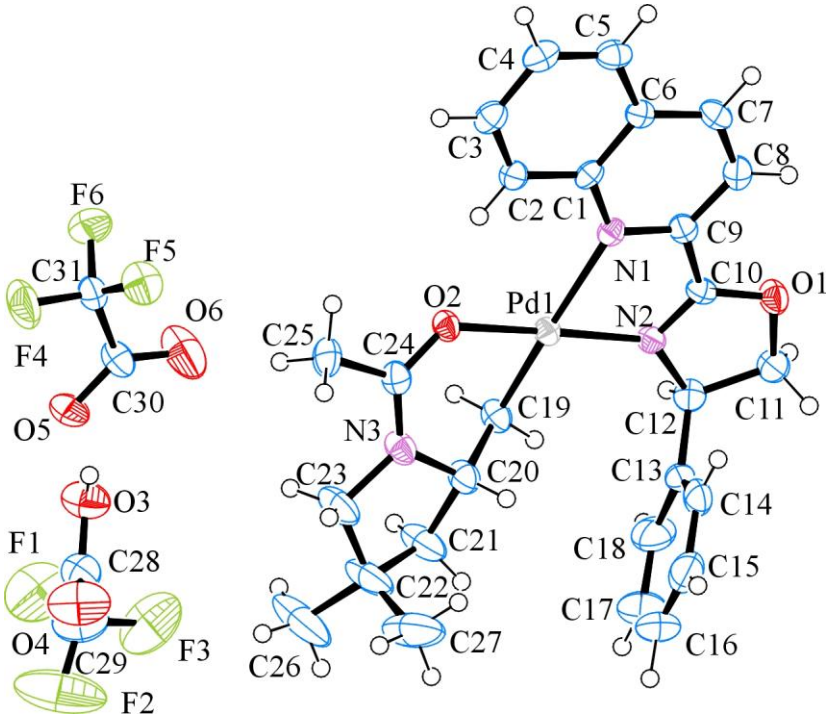

Table A1. Crystal data and structure refinement for **14**

Identification code	**14**	
Empirical formula	C31 H31 F6 N3 O6 Pd	
Formula weight	761.99	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.7794(3) Å	α= 90°.
	b = 12.2839(5) Å	β= 90°.
	c = 38.5200(16) Å	γ = 90°.
Volume	3207.8(2) $Å^3$	
Z	4	
Density (calculated)	1.578 Mg/m^3	

Absorption coefficient	0.661 mm^{-1}
F(000)	1544
Crystal size	0.30 x 0.08 x 0.04 mm^3
Theta range for data collection	2.29 to 28.35°.
Index ranges	-9<=h<=9, -16<=k<=16, -51<=l<=48
Reflections collected	29762
Independent reflections	7939 [R(int) = 0.0489]
Completeness to theta = 25.00°	99.1 %
Max. and min. transmission	0.9741 and 0.8264
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7939 / 0 / 428
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.0855
R indices (all data)	R1 = 0.0587, wR2 = 0.0891
Absolute structure parameter	0.00(3)
Largest diff. peak and hole	0.917 and -1.851 e.$Å^{-3}$

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for **14.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8118(5)	8390(3)	10034(1)	24(1)
C(2)	7986(6)	7270(4)	10120(1)	29(1)
C(3)	7893(7)	6963(3)	10459(1)	32(1)
C(4)	7939(6)	7744(4)	10729(1)	34(1)
C(5)	8097(7)	8813(4)	10653(1)	33(1)
C(6)	8209(5)	9168(3)	10305(1)	24(1)
C(7)	8406(6)	10273(4)	10219(1)	33(1)
C(8)	8462(6)	10569(4)	9877(1)	32(1)
C(9)	8305(5)	9757(3)	9627(1)	26(1)
C(10)	8274(5)	10019(3)	9256(1)	25(1)
C(11)	8512(7)	11029(3)	8772(1)	33(1)
C(12)	8116(7)	9836(3)	8677(1)	30(1)
C(13)	9651(7)	9312(4)	8448(1)	31(1)
C(14)	11550(7)	9151(4)	8572(1)	38(1)
C(15)	12960(10)	8635(4)	8368(2)	57(2)
C(16)	12439(11)	8300(5)	8037(2)	72(2)
C(17)	10625(12)	8468(6)	7917(2)	77(2)
C(18)	9195(9)	8992(5)	8114(1)	54(2)
C(19)	7364(6)	7054(3)	8739(1)	30(1)
C(20)	8859(7)	6206(4)	8654(1)	35(1)
C(21)	8541(10)	5637(4)	8309(1)	56(2)
C(22)	9641(11)	4553(5)	8344(1)	63(2)
C(23)	9168(9)	4221(4)	8715(1)	52(2)
C(24)	8366(6)	5323(3)	9228(1)	32(1)
C(25)	8346(7)	4282(3)	9438(1)	38(1)
C(26)	8788(14)	3698(5)	8090(2)	102(3)
C(27)	11874(12)	4708(6)	8294(2)	90(3)
C(28)	4163(8)	1392(4)	8044(1)	46(1)
C(29)	3402(10)	1534(7)	7675(2)	70(2)
C(30)	3736(7)	2133(4)	9105(1)	38(1)

C(31)	3624(7)	1795(4)	9487(1)	36(1)
N(1)	8160(5)	8695(3)	9692(1)	24(1)
N(2)	8012(5)	9294(2)	9023(1)	25(1)
N(3)	8823(6)	5260(3)	8900(1)	33(1)
O(1)	8544(4)	11052(2)	9153(1)	35(1)
O(2)	7954(5)	6194(2)	9387(1)	28(1)
O(3)	2952(6)	1762(3)	8271(1)	56(1)
O(4)	5749(7)	996(4)	8093(1)	76(1)
O(5)	3728(5)	1374(3)	8893(1)	45(1)
O(6)	3842(9)	3108(3)	9061(1)	83(2)
F(1)	1543(6)	1296(4)	7644(1)	100(2)
F(2)	4420(9)	974(5)	7455(1)	140(2)
F(3)	3554(6)	2567(4)	7582(1)	105(2)
F(4)	3698(6)	723(2)	9536(1)	70(1)
F(5)	5107(4)	2217(3)	9671(1)	49(1)
F(6)	1968(5)	2150(3)	9634(1)	62(1)
Pd(1)	7876(1)	7747(1)	9200(1)	24(1)

Table A3. Bond lengths [Å] and angles [°] for **14**

C(1)-N(1)	1.367(5)	C(9)-N(1)	1.332(5)
C(1)-C(6)	1.419(5)	C(9)-C(10)	1.465(6)
C(1)-C(2)	1.419(5)	C(10)-N(2)	1.276(5)
C(2)-C(3)	1.358(5)	C(10)-O(1)	1.342(5)
C(2)-H(2)	0.9500	C(11)-O(1)	1.470(5)
C(3)-C(4)	1.416(6)	C(11)-C(12)	1.534(6)
C(3)-H(3)	0.9500	C(11)-H(11A)	0.9900
C(4)-C(5)	1.349(6)	C(11)-H(11B)	0.9900
C(4)-H(4)	0.9500	C(12)-N(2)	1.492(5)
C(5)-C(6)	1.411(6)	C(12)-C(13)	1.509(6)
C(5)-H(5)	0.9500	C(12)-H(12)	1.0000
C(6)-C(7)	1.404(6)	C(13)-C(18)	1.379(7)
C(7)-C(8)	1.366(6)	C(13)-C(14)	1.387(6)
C(7)-H(7)	0.9500	C(14)-C(15)	1.390(7)
C(8)-C(9)	1.391(6)	C(14)-H(14)	0.9500
C(8)-H(8)	0.9500		
C(15)-C(16)	1.385(9)	C(25)-H(25B)	0.9800
C(15)-H(15)	0.9500	C(25)-H(25C)	0.9800
C(16)-C(17)	1.330(10)	C(26)-H(26A)	0.9800
C(16)-H(16)	0.9500	C(26)-H(26B)	0.9800
C(17)-C(18)	1.389(8)	C(26)-H(26C)	0.9800
C(17)-H(17)	0.9500	C(27)-H(27A)	0.9800
C(18)-H(18)	0.9500	C(27)-H(27B)	0.9800
C(19)-C(20)	1.491(6)	C(27)-H(27C)	0.9800
C(19)-Pd(1)	1.998(4)	C(28)-O(4)	1.195(6)
C(19)-H(19A)	0.9900	C(28)-O(3)	1.282(6)
C(19)-H(19B)	0.9900	C(28)-C(29)	1.524(8)
C(20)-N(3)	1.499(5)	C(29)-F(2)	1.290(8)
C(20)-C(21)	1.518(6)	C(29)-F(1)	1.299(8)
C(20)-H(20)	1.0000	C(29)-F(3)	1.322(8)
C(21)-C(22)	1.532(7)	C(30)-O(6)	1.212(6)
C(21)-H(21A)	0.9900	C(30)-O(5)	1.240(5)
C(21)-H(21B)	0.9900	C(30)-C(31)	1.532(6)
C(22)-C(23)	1.519(8)	C(31)-F(4)	1.331(5)
C(22)-C(27)	1.538(11)	C(31)-F(6)	1.331(5)
C(22)-C(26)	1.550(9)	C(31)-F(5)	1.336(5)
C(23)-N(3)	1.479(6)	N(1)-Pd(1)	2.233(3)
C(23)-H(23A)	0.9900	N(2)-Pd(1)	2.021(3)
C(23)-H(23B)	0.9900	O(2)-Pd(1)	2.039(2)
C(24)-O(2)	1.264(5)	O(3)-H(3A)	0.8400
C(24)-N(3)	1.303(6)		
C(24)-C(25)	1.515(6)	N(1)-C(1)-C(6)	121.6(4)
C(25)-H(25A)	0.9800	N(1)-C(1)-C(2)	119.6(3)

C(6)-C(1)-C(2)	118.8(3)	C(15)-C(14)-H(14)	119.7
C(3)-C(2)-C(1)	119.9(4)	C(16)-C(15)-C(14)	118.7(6)
C(3)-C(2)-H(2)	120.1	C(16)-C(15)-H(15)	120.7
C(1)-C(2)-H(2)	120.1	C(14)-C(15)-H(15)	120.7
C(2)-C(3)-C(4)	121.1(4)	C(17)-C(16)-C(15)	120.6(6)
C(2)-C(3)-H(3)	119.5	C(17)-C(16)-H(16)	119.7
C(4)-C(3)-H(3)	119.5	C(15)-C(16)-H(16)	119.7
C(5)-C(4)-C(3)	120.2(4)	C(16)-C(17)-C(18)	121.8(6)
C(5)-C(4)-H(4)	119.9	C(16)-C(17)-H(17)	119.1
C(3)-C(4)-H(4)	119.9	C(18)-C(17)-H(17)	119.1
C(4)-C(5)-C(6)	120.7(4)	C(13)-C(18)-C(17)	119.0(6)
C(4)-C(5)-H(5)	119.7	C(13)-C(18)-H(18)	120.5
C(6)-C(5)-H(5)	119.7	C(17)-C(18)-H(18)	120.5
C(7)-C(6)-C(5)	122.0(4)	C(20)-C(19)-Pd(1)	112.1(3)
C(7)-C(6)-C(1)	118.6(4)	C(20)-C(19)-H(19A)	109.2
C(5)-C(6)-C(1)	119.4(4)	Pd(1)-C(19)-H(19A)	109.2
C(8)-C(7)-C(6)	119.3(4)	C(20)-C(19)-H(19B)	109.2
C(8)-C(7)-H(7)	120.3	Pd(1)-C(19)-H(19B)	109.2
C(6)-C(7)-H(7)	120.3	H(19A)-C(19)-H(19B)	107.9
C(7)-C(8)-C(9)	118.3(4)	C(19)-C(20)-N(3)	113.0(4)
C(7)-C(8)-H(8)	120.9	C(19)-C(20)-C(21)	114.8(4)
C(9)-C(8)-H(8)	120.9	N(3)-C(20)-C(21)	101.3(4)
N(1)-C(9)-C(8)	125.2(4)	C(19)-C(20)-H(20)	109.2
N(1)-C(9)-C(10)	113.5(3)	N(3)-C(20)-H(20)	109.2
C(8)-C(9)-C(10)	121.3(4)	C(21)-C(20)-H(20)	109.2
N(2)-C(10)-O(1)	118.2(4)	C(20)-C(21)-C(22)	104.6(4)
N(2)-C(10)-C(9)	122.3(4)	C(20)-C(21)-H(21A)	110.8
O(1)-C(10)-C(9)	119.5(3)	C(22)-C(21)-H(21A)	110.8
O(1)-C(11)-C(12)	105.0(3)	C(20)-C(21)-H(21B)	110.8
O(1)-C(11)-H(11A)	110.7	C(22)-C(21)-H(21B)	110.8
C(12)-C(11)-H(11A)	110.7	H(21A)-C(21)-H(21B)	108.9
O(1)-C(11)-H(11B)	110.7	C(23)-C(22)-C(21)	102.4(4)
C(12)-C(11)-H(11B)	110.7	C(23)-C(22)-C(27)	111.0(6)
H(11A)-C(11)-H(11B)	108.8	C(21)-C(22)-C(27)	111.2(6)
N(2)-C(12)-C(13)	111.4(3)	C(23)-C(22)-C(26)	109.5(6)
N(2)-C(12)-C(11)	102.8(3)	C(21)-C(22)-C(26)	110.5(5)
C(13)-C(12)-C(11)	115.2(4)	C(27)-C(22)-C(26)	111.8(6)
N(2)-C(12)-H(12)	109.0	N(3)-C(23)-C(22)	104.7(4)
C(13)-C(12)-H(12)	109.0	N(3)-C(23)-H(23A)	110.8
C(11)-C(12)-H(12)	109.0	C(22)-C(23)-H(23A)	110.8
C(18)-C(13)-C(14)	119.2(5)	N(3)-C(23)-H(23B)	110.8
C(18)-C(13)-C(12)	120.8(5)	C(22)-C(23)-H(23B)	110.8
C(14)-C(13)-C(12)	119.9(4)	H(23A)-C(23)-H(23B)	108.9
C(13)-C(14)-C(15)	120.6(5)	O(2)-C(24)-N(3)	125.0(4)
C(13)-C(14)-H(14)	119.7	O(2)-C(24)-C(25)	116.9(4)

N(3)-C(24)-C(25)	118.1(4)	O(6)-C(30)-O(5)	130.7(5)
C(24)-C(25)-H(25A)	109.5	O(6)-C(30)-C(31)	113.8(4)
C(24)-C(25)-H(25B)	109.5	O(5)-C(30)-C(31)	115.5(4)
H(25A)-C(25)-H(25B)	109.5	F(4)-C(31)-F(6)	107.2(4)
C(24)-C(25)-H(25C)	109.5	F(4)-C(31)-F(5)	106.3(4)
H(25A)-C(25)-H(25C)	109.5	F(6)-C(31)-F(5)	106.3(4)
H(25B)-C(25)-H(25C)	109.5	F(4)-C(31)-C(30)	113.7(4)
C(22)-C(26)-H(26A)	109.5	F(6)-C(31)-C(30)	111.3(4)
C(22)-C(26)-H(26B)	109.5	F(5)-C(31)-C(30)	111.6(4)
H(26A)-C(26)-H(26B)	109.5	C(9)-N(1)-C(1)	116.9(3)
C(22)-C(26)-H(26C)	109.5	C(9)-N(1)-Pd(1)	110.9(3)
H(26A)-C(26)-H(26C)	109.5	C(1)-N(1)-Pd(1)	132.2(3)
H(26B)-C(26)-H(26C)	109.5	C(10)-N(2)-C(12)	108.0(3)
C(22)-C(27)-H(27A)	109.5	C(10)-N(2)-Pd(1)	115.2(3)
C(22)-C(27)-H(27B)	109.5	C(12)-N(2)-Pd(1)	136.3(2)
H(27A)-C(27)-H(27B)	109.5	C(24)-N(3)-C(23)	123.7(4)
C(22)-C(27)-H(27C)	109.5	C(24)-N(3)-C(20)	124.8(4)
H(27A)-C(27)-H(27C)	109.5	C(23)-N(3)-C(20)	111.3(4)
H(27B)-C(27)-H(27C)	109.5	C(10)-O(1)-C(11)	105.9(3)
O(4)-C(28)-O(3)	127.9(5)	C(24)-O(2)-Pd(1)	128.8(3)
O(4)-C(28)-C(29)	119.9(5)	C(28)-O(3)-H(3A)	109.5
O(3)-C(28)-C(29)	112.3(5)	C(19)-Pd(1)-N(2)	96.24(14)
F(2)-C(29)-F(1)	109.8(7)	C(19)-Pd(1)-O(2)	85.36(13)
F(2)-C(29)-F(3)	107.0(6)	N(2)-Pd(1)-O(2)	175.81(15)
F(1)-C(29)-F(3)	105.5(6)	C(19)-Pd(1)-N(1)	172.23(14)
F(2)-C(29)-C(28)	111.7(5)	N(2)-Pd(1)-N(1)	78.01(12)
F(1)-C(29)-C(28)	112.7(6)	O(2)-Pd(1)-N(1)	100.74(11)
F(3)-C(29)-C(28)	109.7(6)		

Symmetry transformations used to generate equivalent atoms:

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **14**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	12(2)	31(2)	29(2)	3(2)	1(2)	-2(2)
C(2)	26(2)	30(2)	30(2)	-3(2)	2(2)	-4(2)
C(3)	26(2)	35(2)	36(2)	8(2)	3(2)	2(2)
C(4)	28(2)	47(2)	28(2)	5(2)	0(2)	-2(3)
C(5)	30(2)	44(3)	26(2)	-3(2)	-1(2)	0(2)
C(6)	17(2)	31(2)	26(2)	-3(2)	-2(2)	-1(2)
C(7)	38(3)	33(2)	27(2)	-9(2)	-3(2)	-1(2)
C(8)	31(2)	27(2)	38(3)	1(2)	-1(2)	-3(2)
C(9)	21(2)	26(2)	31(2)	-2(2)	-1(2)	1(2)
C(10)	23(2)	30(2)	23(2)	-5(2)	-1(2)	2(1)
C(11)	39(2)	31(2)	29(2)	4(2)	-1(2)	2(2)
C(12)	33(2)	33(2)	24(2)	3(2)	-6(2)	0(2)
C(13)	44(3)	28(2)	22(2)	1(2)	5(2)	-3(2)
C(14)	40(3)	23(2)	51(3)	1(2)	4(2)	1(2)
C(15)	49(3)	38(3)	83(4)	10(3)	24(3)	1(3)
C(16)	79(6)	64(4)	74(4)	-16(3)	49(4)	-2(3)
C(17)	105(6)	84(5)	41(4)	-15(3)	27(4)	-13(4)
C(18)	62(4)	71(4)	29(3)	-1(3)	4(2)	-9(3)
C(19)	36(2)	26(2)	29(2)	-1(2)	-6(2)	3(2)
C(20)	47(3)	27(2)	29(2)	1(2)	-2(2)	3(2)
C(21)	99(5)	39(3)	30(3)	-6(2)	-2(3)	23(3)
C(22)	106(5)	40(3)	42(3)	-10(3)	6(3)	31(3)
C(23)	77(4)	32(3)	48(3)	-9(2)	-3(3)	20(3)
C(24)	30(2)	28(2)	37(3)	-1(2)	-3(2)	-2(2)
C(25)	46(3)	25(2)	42(3)	7(2)	-4(2)	-3(2)
C(26)	199(10)	55(4)	52(4)	-26(3)	-16(5)	41(5)
C(27)	121(7)	84(5)	65(4)	8(4)	41(4)	51(5)
C(28)	51(3)	46(3)	40(3)	1(2)	-2(2)	4(2)
C(29)	66(5)	95(6)	47(4)	9(4)	-2(3)	15(4)
C(30)	45(2)	33(3)	37(3)	-8(2)	-7(2)	1(2)

C(31)	45(3)	25(2)	38(3)	-2(2)	3(2)	-2(2)
N(1)	18(2)	26(2)	27(2)	2(1)	1(1)	0(1)
N(2)	27(2)	24(2)	24(2)	-2(1)	1(2)	2(2)
N(3)	44(2)	26(2)	30(2)	-2(2)	-5(2)	6(2)
O(1)	50(2)	24(1)	30(2)	2(1)	-4(1)	-3(1)
O(2)	31(1)	21(1)	30(1)	0(1)	-1(1)	2(1)
O(3)	62(2)	64(2)	42(2)	-2(2)	0(2)	17(2)
O(4)	65(3)	109(4)	55(3)	7(3)	-4(2)	30(3)
O(5)	56(2)	49(2)	31(2)	-14(2)	1(2)	-2(2)
O(6)	174(5)	42(2)	33(2)	3(2)	-18(2)	2(3)
F(1)	90(3)	148(4)	62(3)	14(3)	-31(2)	-13(3)
F(2)	151(5)	222(6)	46(3)	-29(3)	-7(3)	83(4)
F(3)	116(3)	120(4)	78(3)	66(3)	-5(2)	4(3)
F(4)	128(3)	26(2)	55(2)	2(2)	1(2)	-7(2)
F(5)	56(2)	51(2)	40(2)	2(2)	-15(1)	1(2)
F(6)	50(2)	69(2)	65(2)	-12(2)	23(2)	-9(2)
Pd(1)	24(1)	23(1)	26(1)	-1(1)	-1(1)	1(1)