Development of Palladium and Hypervalent Iodine(III) Catalyzed Alkene Difunctionalization Reactions; Hydroamination, Carboamination, Aminofluorination & Diamination

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Abstract

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

The investigation and development of synthetic methodologies for direct alkene difunctionalization is described. The utility of these processes is demonstrated by the synthesis of a number of functionalized nitrogen-containing heterocycles, including pyrrolidines and morpholines. As these are commonly-encountered motifs in a variety of medicinally active compounds, and useful synthetic molecules such as organocatalysts, ligands, or auxillaries, efficient and stereoselective methods for their preparation are of great interest to the synthetic community. This dissertation describes the use of palladium and hypervalent iodine-catalyzed reactions for the direct conversion of unactivated aminoalkenes into synthetically useful building blocks through the introduction of a C-N bond with simultaneous formation of either a second C-N bond, or a C-F, C-H or C-C bond, depending on the choice of reaction conditions.

In Chapter 1, a palladium-catalyzed hydroamination reaction is used as the key step in the stereoselective synthesis of 2,5-disubstituted and 2,3,5-trisubstituted morpholines. Lewis acid-catalyzed ring opening of carbamate-protected aziridines with allyl alcohol was observed to consistently display selectivity for substitution at the more hindered position. Subsequent hydroamination of the resulting aminoalkenes gives 2,5-disubstituted and 2,3,5-trisubstituted morpholine products in high yields with excellent diastereoselectivities. The reaction was also amended to a one-pot sequence with comparable scope and efficiency to the two-step sequence.

Chapter 2 outlines studies with palladium catalysts and a number of alkyl-, silyl- and aryl-substituted hypervalent iodine(III) reagents, which led to the successful development of an intramolecular aminoalkynylation reaction operating under a Pd(II)/(IV) catalytic cycle. Investigation of a number of reaction parameters revealed strong preferences for both linear alkynyl(aryl)iodine reagents with silyl substitution at the acetylenic carbon, in conjunction with use of diamine ligands bearing relatively wide bite angles, such as 4,5-diazafluoren-1-one.

Finally, the intramolecular aminofluorination and diamination of *para*-toluoyl protected aminoalkenes is achieved using catalytic quantities of chiral and achiral iodine sources. *N*-fluoropyridinium salts were discovered to be effective promoters of the re-oxidation of iodine(I) to iodine(III) *in situ.* Both 3-amino- and 3-fluoro-piperidine products are accessed with moderate to excellent yields. Notably, only the *endo*-cyclized product was observed in reaction mixtures.

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Abbreviations

Ac:	Acetyl
Ar:	Aryl
Bn:	Benzyl
Boc:	*tert*-Butyloxycarbonyl
Cbz:	Carbobenzyloxy
CNC:	2,6-Bis(NHC)-pyridine
COSY:	Correlation spectroscopy
Cy:	Cyclohexyl
DCE:	Dichloroethane
DCM:	Dichloromethane
DEAD:	Diethyl diiospropylazodicarboxylate
DIAD:	Diisopropyl azodicarboxylate
DMSO:	Dimethyl sulfoxide
dr:	Diastereomeric ratio
E^+:	Electrophile
ee:	Enantiomeric excess
ESI MS:	Electrospray ionization mass spectrometry
FTIR:	Fourier transform infrared spectroscopy
GC/MS:	Gas chromatography/mass spectrometry
hr:	Hour
HPLC:	High Performance Liquid Chromatography

Hz:	Hertz
L:	Ligand
LAH:	Lithium Aluminum Hydride
LDA:	Lithium diisopropylamide
MEC-31:	1,1’-Difluoro-2,2’-bipyridinium (bis)tetrfluoroborate
Mes:	Mesityl
MHz:	Megahertz
mp:	Melting point
Ms:	Mesyl
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
PG:	Protecting group
Phth:	Phthalyl
PNP:	2,6-Bis(diphenylphosphinomethyl)-pyridine
ppm:	Parts per million
rbf:	Round bottom flask
rs:	Regioselectivity
rt:	Room temperature
TBAF:	Tetrabutylammonium fluoride
TBAT:	Tetrabutylammonium difluorotriphenylsilicate
TfO:	Trifluoromethanesulfonate
TFA:	Trifluoromethylcarboxylate
THF:	Tetrahydrofuran
TIPS:	Triisopropylsilyl
TLC:	Thin layer chromatography
TMS:	Trimethylsilyl
Tol:	Toluene
Ts:	*p*-Toluenesulfonyl
TsCl:	*p*-Toluenesulfonylchloride

Acknowledgements

There are a lot of people that I'm grateful and thankful to here at the University of Washington. I want to thank my advisor Forrest Michael for expanding the way I think about chemistry and the scientific process by lending me his perspective and creativity, and for his knowledge and patience. Somewhere along the way I ended up with this fantastic education, and I'm not sure when that happened, but I'm very thankful that he never truly settles for the answer "I don't know" from his students because I think that's a big part of it.

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Finally I want to thank my family, who always support me and love me and inspire me by example. And I want to thank Richard Rucker for making my life outside of graduate school an adventure and for his support and love.

Dedication

To my family,

Mom, Dad, Neil

To my found family,

Brittney

&

Richard

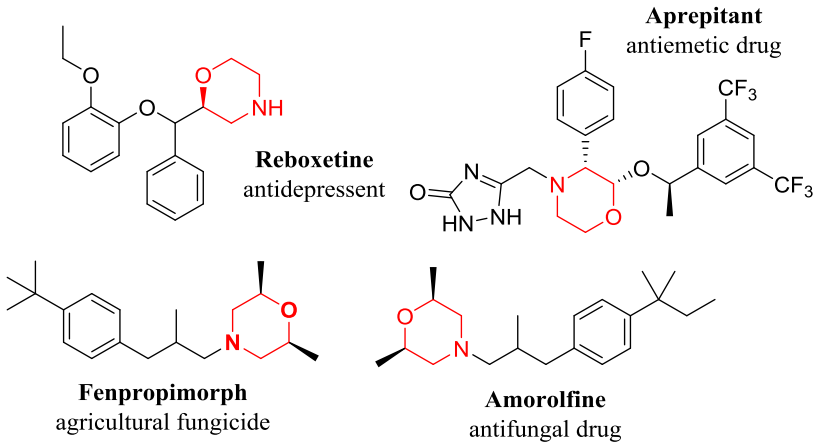
Chapter 1

PALLADIUM-CATALYZED DIASTEREOSELECTIVE SYNTHESIS OF MORPHOLINES[1]

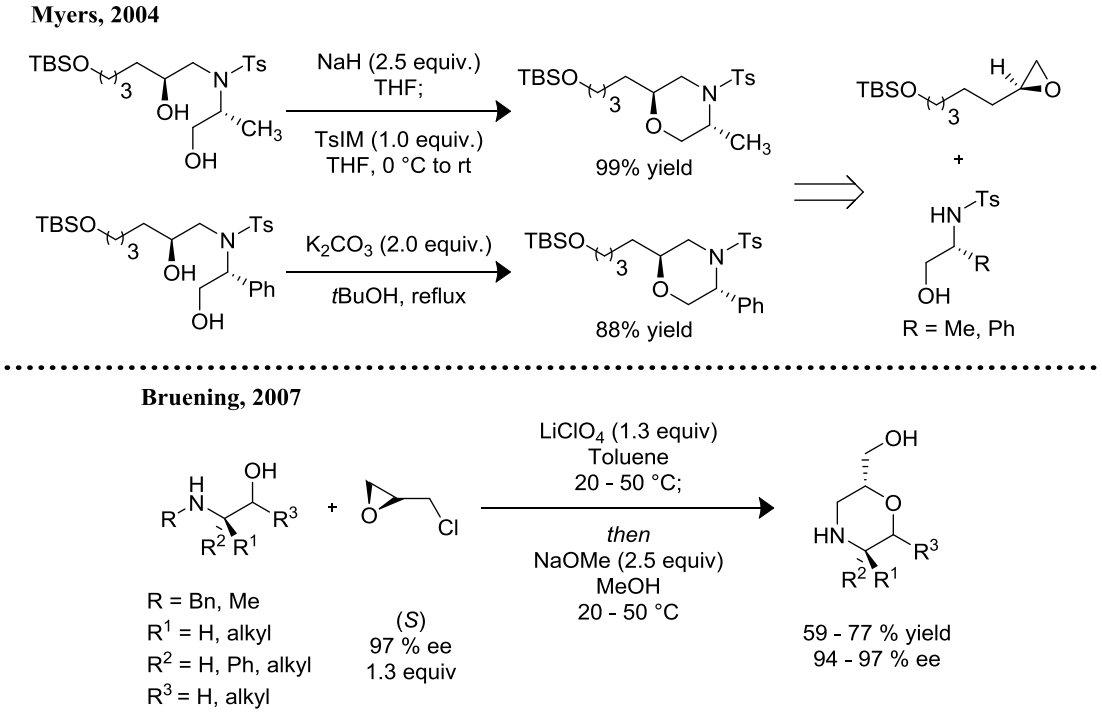
Section 1. Introduction

Morpholines are frequent substructures in biologically and pharmaceutically prescribed organic molecules (Figure 1.1).[2,3,4] For example, reboxetine is a prescribed antidepressant, fenpropimorph and amorolfine are used as fungicides, and aprepitant is an antiemetic used in chemotherapy. As a consequence of their ubiquity in pharmaceutical chemistry, countless methods for the syntheses of morpholines have been reported.[1,3,5] However, many existing routes require multiple steps and are poorly convergent, often relying on condensation of a 1,5-diol.[6]

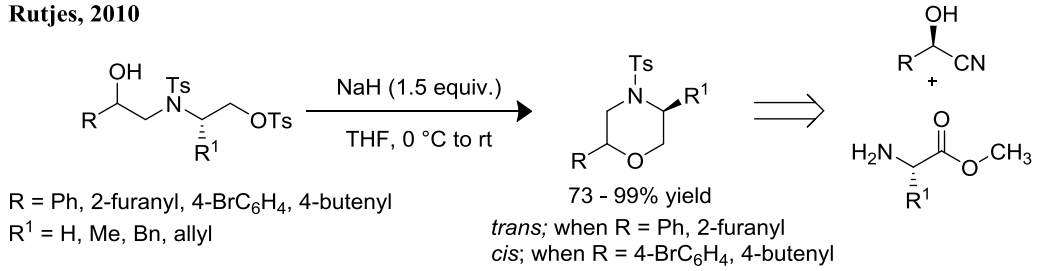
Figure 1.1. Biologically active morpholine containing compounds



Scheme 1.1. Aminolysis of enantiopure expoxides with chiral β-amino alcohols



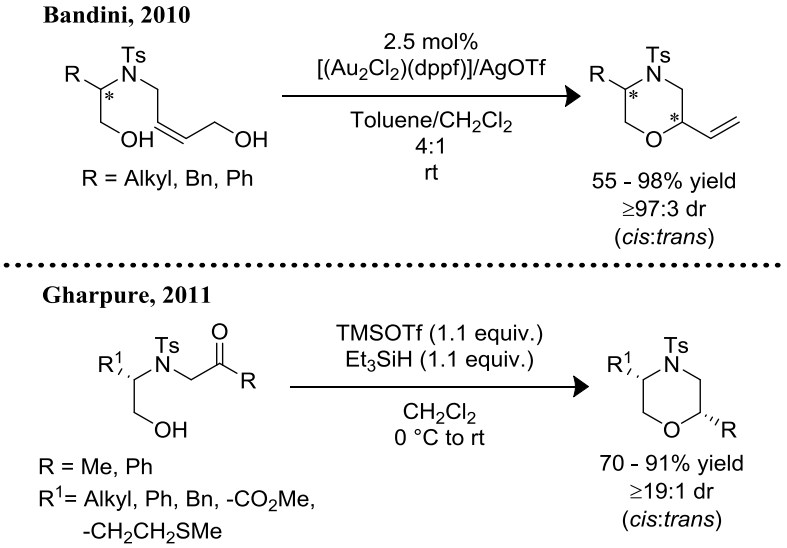
Scheme 1.2. Rutjes: Reductive amination using enantiopure cyanohydrins and aminoesters



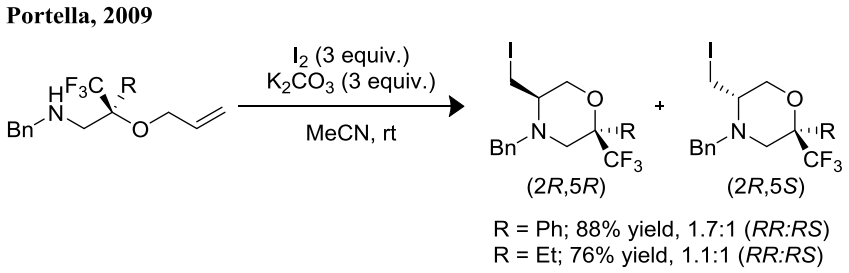
Despite the large number of morpholine syntheses, synthetic routes to stereopure morpholines bearing a 2,5-disubstitution pattern are particularly uncommon. Two main strategies have been employed. In the first, two enantiopure reagents are coupled, thereby guaranteeing the desired diastereomer. In this class, Myers[7] (Scheme 1.1) and Breuning[8]

reported the aminolysis of enantiopure epoxides with enantiopure aminoalcohols to generate 2,5-disubstituted morpholines, and Rutjes (Scheme 1.2) performed a reductive amination on enantiopure cyanohydrins with enantiopure aminoesters.[9] Alternately, the morpholine ring can be closed in a diastereoselective reaction of a single enantiopure

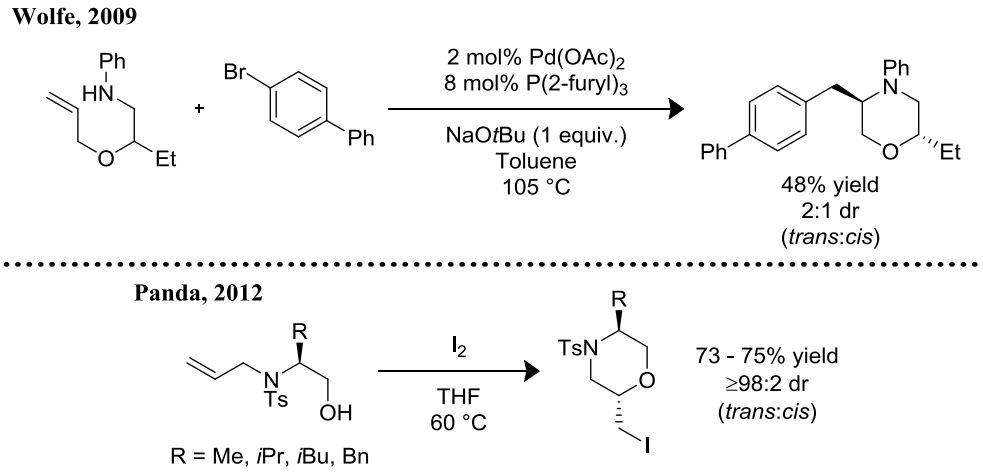
Scheme 1.3. *Cis*-selective morpholine forming ring closures



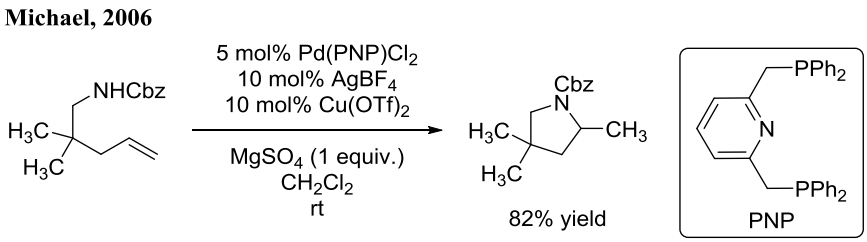
Scheme 1.4. Portella: Synthesis of 2,2,5-trisubstitued morpholines



Scheme 1.5. ***Trans*-selective morpholine forming ring closures**



Scheme 1.6. Palladium-catalyzed intramolecular hydroamination



starting material. Most of these methods are either *cis*-selective or poorly diastereoselective. Bandini[10] and Gharpure[11] have reported diastereoselective ring closures to give *cis*-substituted morpholines (Scheme 1.3). Portella obtained 2,2,5-trisubstituted morpholines by iodoamination of an aminoalkene, but with poor diastereoselectivity (Scheme 1.4).[12] Wolfe has employed a ring-closing carboamination of alkenes to form morpholines, but the 2,5-disubstitution pattern gives low diastereoselectivity (Scheme 1.5).[13] To our knowledge, only Panda has reported a highly

trans-diastereoselective 2,5-disubstituted morpholine synthesis, by using an iodoalkoxylation ring closing reaction (Scheme 1.5).[14]

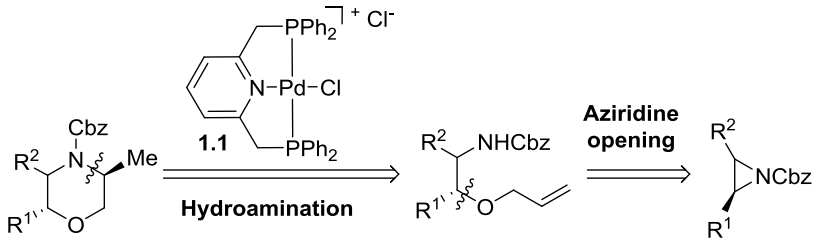
Recently, we reported a facile synthesis of nitrogen heterocycles that utilizes a mild palladium-catalyzed hydroamination reaction as the key cyclization step (Scheme 1.6).[15,16] The success of this hydroamination depends on the use of a tridentate pincer ligand on palladium to prevent β-hydride elimination. In this chapter, the extension of this method to the synthesis of morpholines in a two-step, one-pot procedure is described.

Section 2. Results and Discussion

1.2.a Retrosynthetic Strategy

Retrosynthetically (Scheme 1.7), the morpholine ring can be divided into two fragments: an aziridine and an allylic alcohol. Coupling of the two could be accomplished by Lewis acid-catalyzed ring opening of the appropriately protected aziridine with allyl alcohol. Subsequent hydroamination would close the heterocyclic ring and yield the desired morpholine. Two issues need to be resolved in carrying out this set of transformations: 1) the aziridine opening must proceed regioselectively, and 2) the hydroamination reaction must be highly diastereoselective.

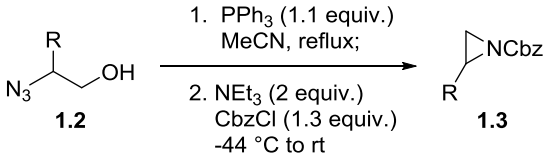
Scheme 1.7. Proposed retrosynthetic pathway to 2,3,5-trisubstituted morpholines



1.2.b Synthesis of the Aziridines

Preparation of the aziridine substrates was accomplished using two major routes. For the monosubstituted aziridines, the azidoalcohols were prepared from the commercially available expoxides via nucleophilic ring opening by sodium azide. Using the Staudinger reaction, the azides **1.2** were then reduced to the aziridine, which was protected *in situ*. The low yields of many of the aziridine substrates **1.3** are a reflection of the difficulty in isolation due to acid-catalyzed decomposition during column chromatography (Table 1.1). This could be attenuated by treating the silica gel with triethylamine (up to 3%), but not completely eliminated. The *trans*- and *cis*-2,3-dimethyl substituted aziridines **1.3i,j** were synthesized in reasonable yields by epoxidation of *cis*- or *trans*-butene respectively, followed by the same sequence used in the preparation of their monosubstituted counterparts (Scheme 1.8). Finally, the 2-methyl-3-phenyl aziridines **1.3k,l** were accessed

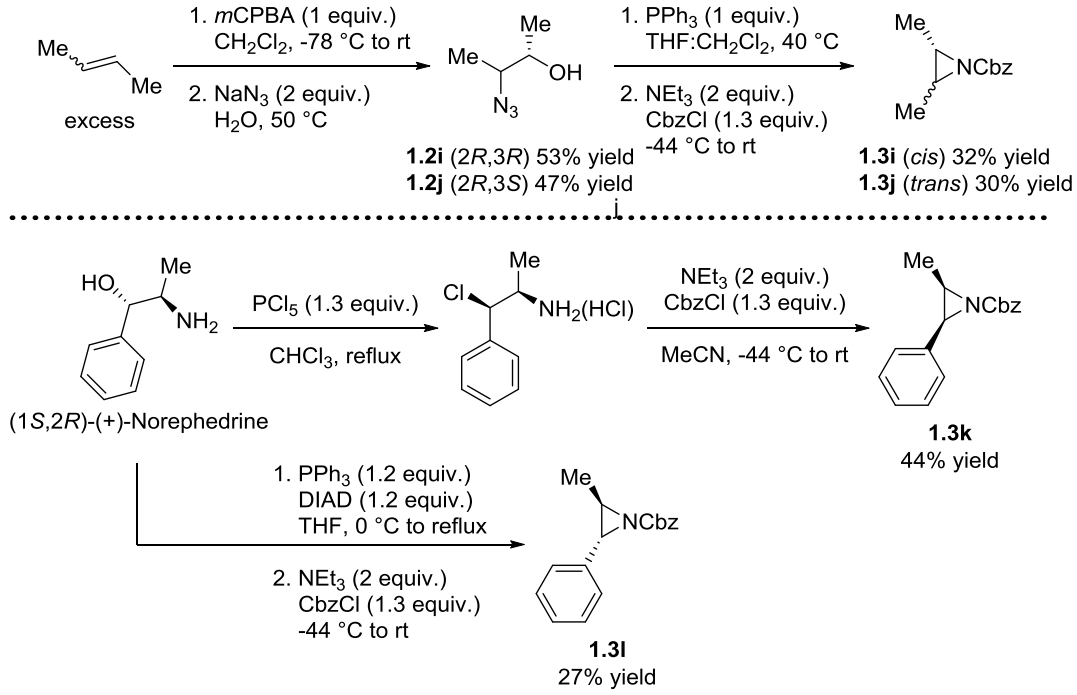
Table 1.1. Synthesis of monosubstituted aziridines using the Staudinger reaction



Entry	Substrate	R	Product	Yield[a] (%)
1	**1.2c**	Et	**1.3c**	53
2	**1.2d**	*n*-Bu	**1.3d**	45
3	**1.2e**	*c*-Hex	**1.3e**	21
4	**1.2f**	*t*-Bu	**1.3f**	53
5	**1.2g**	Ph	**1.3g**	34

[a] Isolated yields.

Scheme 1.8. Synthesis of the disubstituted aziridines



from norephedrine. The *trans*-isomer was made via the Mitsunobu reaction and the *cis*-isomer was obtained by nucleophilic substitution of the chloride previously installed with phosphorous pentachloride; both mechanisms proceed through inversion of the stereocenter *alpha* to nitrogen. (Scheme 1.8).

1.2.c Preparation of Aminoalkenes via Lewis Acid-Catalyzed Aziridine Ring Opening

Regioselective ring opening of aziridines under acidic conditions continues to be a challenging problem.[17] Aziridines with aryl, vinyl, or alkynyl substituents at the 2-position are known to give high selectivity for attack at the substituted position.[18,19] On the other hand, alkyl-substituted aziridines usually are attacked at the less hindered

Scheme 1.9. Lewis acid catalyzed ring opening of aziridines at the less substituted position

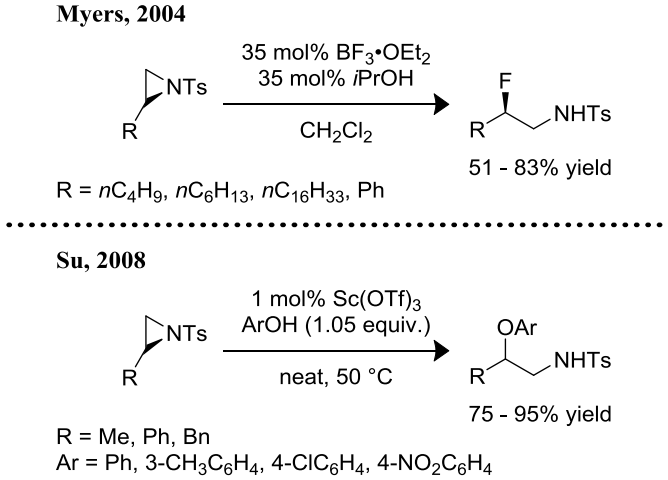
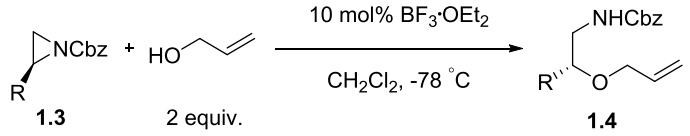


Table 1.2. Opening of aziridines with allyl alcohol



1.3 2 equiv. 1.4

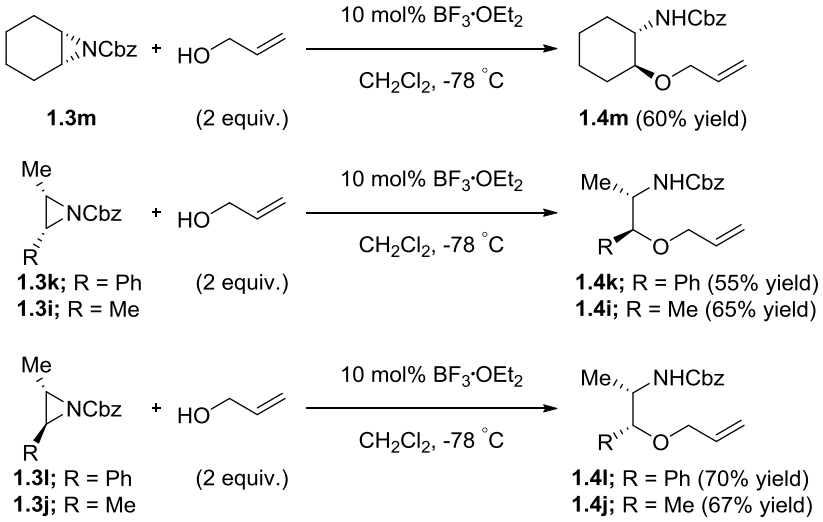
Entry	R	Product	Yield[a] (%)
1	H	**1.4a**	68
2	Me	**1.4b**	77
3	Et	**1.4c**	81
4	*n*-Bu	**1.4d**	75
5	*c*-Hex	**1.4e**	80
6	*t*-Bu	**1.4f**	62
7	Ph	**1.4g**	66
8	Bn[20]	**1.4h**	46

[a] Isolated yields.

unsubstituted position or provide mixtures of regioisomers, even under Lewis acidic conditions.[21] There are very few examples of selective attack on monosubstituted alkyl aziridines at the more substituted position.[22]

Nevertheless, initial studies of the reaction of Cbz-protected aziridines **1.3** with allyl alcohol indicated that many Lewis acids were effective at promoting the ring opening, including $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $Zn(OTf)_2$, and $Yb(OTf)_3$. The highest yields were obtained upon treatment of the aziridine with 2 equivalents of allyl alcohol in the presence of 10 mol% $BF_3{\cdot}OEt_2$ at -78 ^{o}C. Under these conditions, monosubstituted aziridines were opened in good yields to give a single regioisomer, resulting from attack exclusively at the more substituted position (Table 1.2).

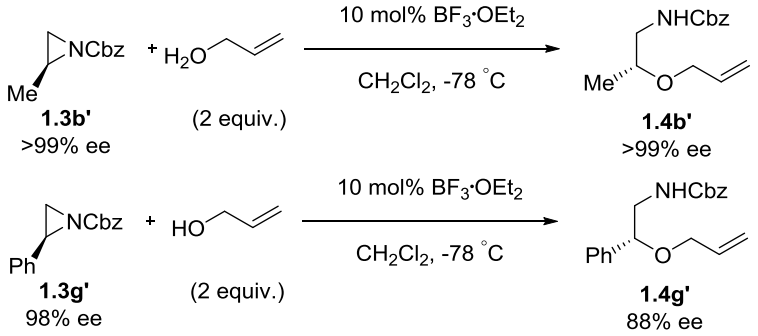
Scheme 1.10. Opening of disubstituted aziridines with allyl alcohol



Ring opening of several disubstituted aziridines also gave the desired aminoalkene products (Scheme 1.7). Aziridines **1.3k** and **1.3l** each gave a single regioisomeric product resulting from attack adjacent to the phenyl group. In all cases, inversion of stereochemistry at the substitution site was observed, giving the product as a single diastereomer. Further confirmation of the stereospecificity of the ring opening was obtained in the reaction of the enantioenriched methyl substituted aziridine **1.3b'** (Scheme 1.8). No loss of enantiopurity was observed in the aminoalkene product **1.4b'** by chiral HPLC. However, when the analogous enantioenriched phenyl substituted aziridine **1.3g'** (Scheme 1.8) was used, partial racemization of the stereocenter was observed, suggesting that some of the reaction proceeds through a carbocation intermediate.

Overall, the inversion of stereochemistry at the displacement site is most consistent

Scheme 1.11. Ring opening of enantioenriched aziridines with allyl alcohol



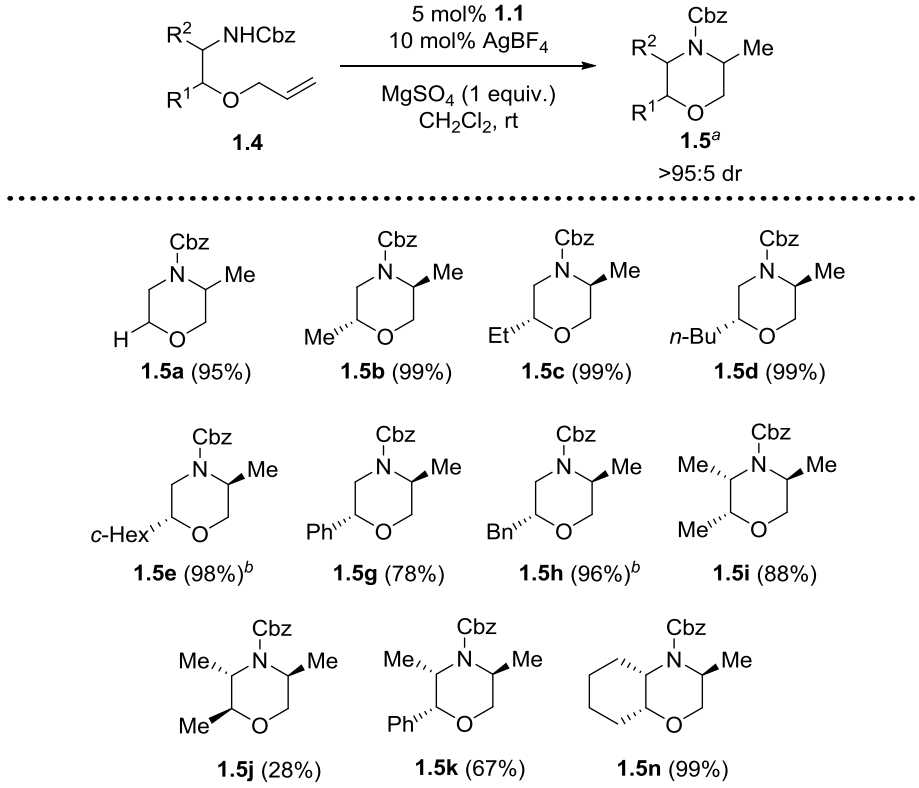
with S_N2 attack on a Lewis acid-coordinated aziridine. The fact that displacement occurs selectively at the more substituted position in 2-alkylaziridines is indicative of substantial carbocationic character at the displacement site in the S_N2 transition state and is quite rare for aziridines, even with Lewis acid activation. As there are examples of aziridine ring openings catalyzed by BF_3OEt_2 that are opened at the less substituted position in the presence of stoichiometric nucleophiles (sulfides, hydroxyl amines), the regioselectivity can be attributed to the carbamate protecting group either by stabilization of the electropositive carbon and fast nucleophilic displacement, or perhaps by participation of the carbamate to form an oxazoline intermediate; both would be consistent with the observed stereochemistry.

1.2.d Synthesis of the morpholines

Treatment of aminoalkene substrates **1.4** under previously reported hydroamination conditions (5 mol% **1.1**, 10 mol% $AgBF_4$, 1 equiv. $MgSO_4$) afforded the corresponding morpholines in excellent yields (Table 1.3).[17] Disubstituted morpholines bearing linear and branched alkyl groups, as well as aryl groups, were

formed as a single diastereomer. For some substrates, the addition of TMSOTf as a co-catalytic acid was required for complete conversion.[16] In the absence of the $PdPNPCl_2$, no reaction occurs with TMSOTf. Trisubstituted morpholines were also formed as a single diastereomer from the cyclization of disubstituted aminoalkene substrates (**1.4i,j,k,n**).

Table 1.3. Morpholine prepared through hydroamination

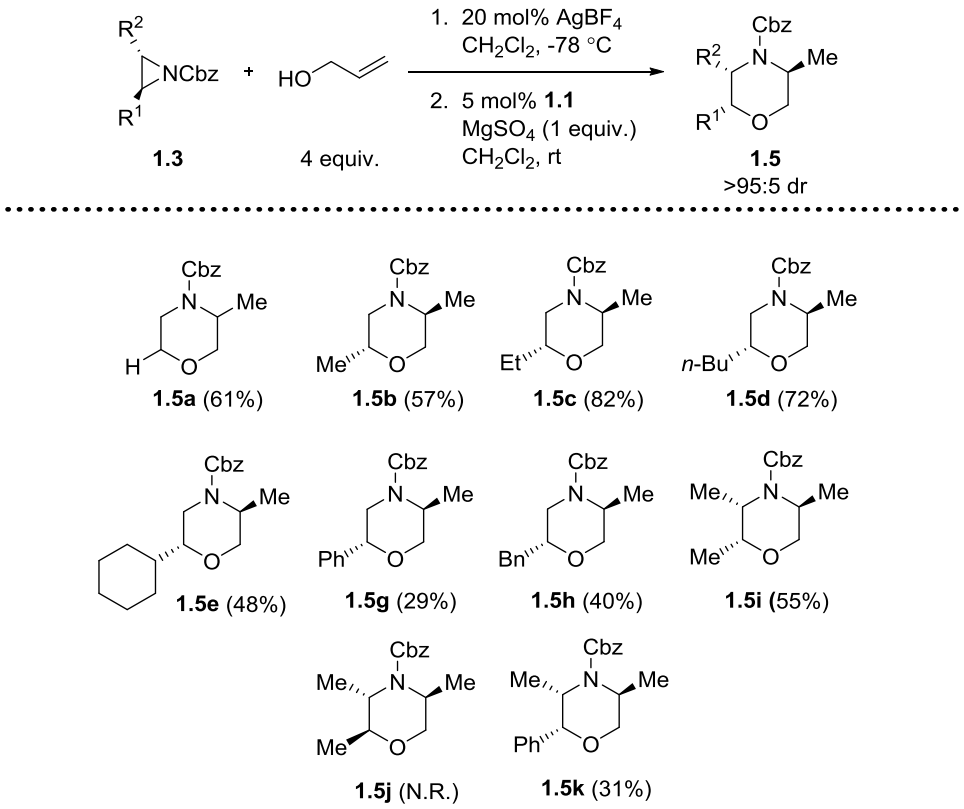


[a] Isolated yields. [b] 0.25 equivalents of TMSOTf added.

1.2.e Development of a one-pot procedure

Since the $AgBF_4$ required for activation of the Pd precatalyst is itself a mild Lewis acid, a one-pot ring-opening/hydroamination procedure was investigated. $AgBF_4$ proved to be an effective catalyst for the aziridine opening, thereby eliminating the need to isolate the aminoalkene intermediate. After further optimization, treatment of the aziridine with 20 mol% $AgBF_4$ and 4 equivalents of allyl alcohol at -78 ^oC to form

Table 1.4. One-pot synthesis of morpholines



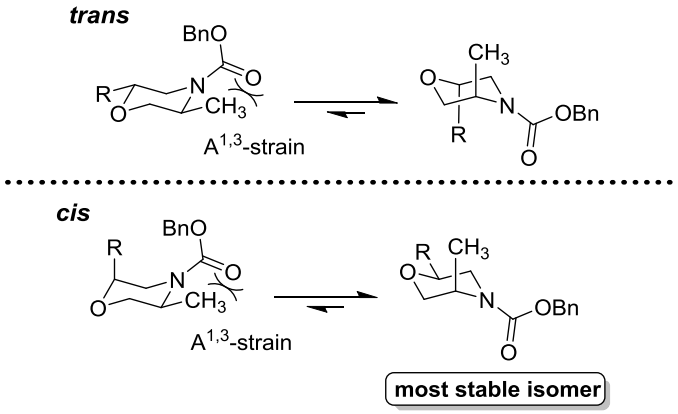
[a] Isolated yields.

the aminoalkene intermediate, followed by addition of 5 mol% of the palladium catalyst and 1 equivalent $MgSO_4$ at room temperature gave the desired morpholine product (Table 1.4) in a convenient one-pot procedure. The overall yields from this procedure are comparable to that obtained from the two-step sequence with the exception of a few substrates.

1.2.f Observed stereochemistry of the morpholines

The stereochemistry of the disubstituted morpholine products was determined to be *trans* based on ^{1}H NMR coupling constants and NOESY data. The morpholine ring

Figure 1.2. Conformations of the 2,5-disubstituted morpholine stereoisomers

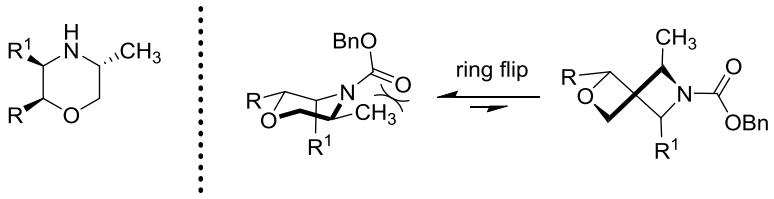


adopts a chair conformation, with the 2- and 5-substituents in a *trans*-diaxial orientation (Figure 1.2). This conformation is preferred as it avoids $A^{1,3}$ strain between the carbamate protecting group on the nitrogen and the 5-methyl substituent (~3.4-4.7 kcal/mol).[23] The combined *A* values of the 2- and 5-alkyl substituents (1.8-3 kcal/mol) are also further diminished by the absence of one axial proton on each side due to the heteroatoms. The failure of the *tert*-butyl substituted aminoalkene **1.4f** to

cyclize is consistent with this conformation, as the *A*-value of an axial *tert*-butyl group is approximately 5 kcal/mol, and so both conformations would be quite unfavorable. Notably, the observed *trans* stereoisomer is not the thermodynamically preferred isomer in these carbamate-protected morpholines; rather the *cis* isomer is more stable as the 2-substituent is equatorial and avoids any 1,3-diaxial interactions.

In the trisubstituted morpholine series, the *syn*-disubstituted aminoalkenes (**1.4i,k,n**) cyclize quickly to place the new methyl stereocenter *trans* to both existing stereocenters. NOESY data were consistent with the morpholines (**1.5i,k,n**) adopting a mixture of a twist-boat and a chair conformation.[25] The twist-boat conformation has been previously observed for *trans* 2,6-disubstituted piperazines, and is the only way to avoid $A^{1,3}$ strain between the carbamate and both substituents alpha to nitrogen.[16] In contrast, their *anti*-disubstituted aminoalkene (**1.4j,l,m**) counterparts were much poorer substrates and **1.4l** and **1.4m** completely failed to cyclize.

Figure 1.3. Conformations of 1.4i, 1.4k and 1.4n

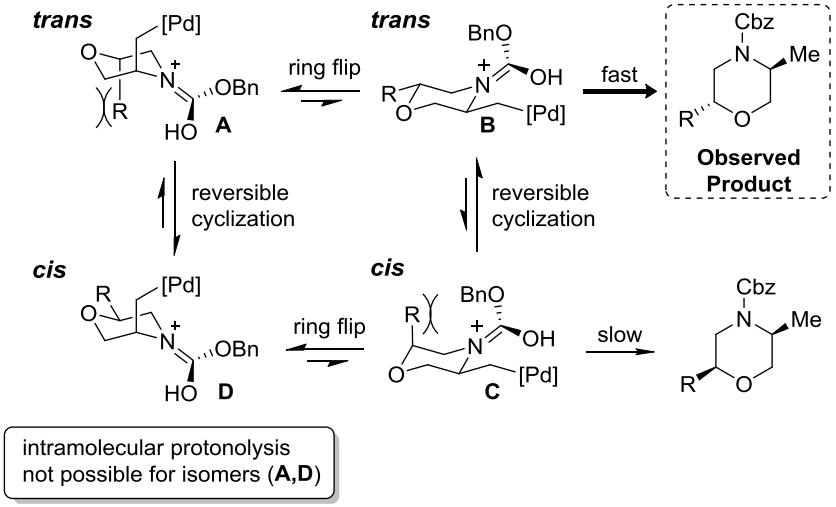


1.2.g Proposed stereochemical rationale for the observed morpholine products

Our proposed model to explain the stereoselectivity is depicted in Figure 1.4. Any such model must account for the preferred formation of the thermodynamically less

stable *trans* isomer and the significant difference in reactivity between *syn*- and *anti*-stereoisomers in the formation of trisubstituted morpholines. Reversible cyclization of the aminoalkene gives the key palladium-alkyl intermediate as one of four possible conformations **A**-**D**.[16] As previously noted, $A^{1,3}$ strain predicts that axial-equatorial conformer **D** should be the most stable, but it does not lead to the observed *trans* product. Therefore, we propose that the protonolysis of the palladium-alkyl complex must occur intramolecularly via transfer from the carbamate group. Only conformations in which the Pd occupies an equatorial position (**B**, **C**) are capable of

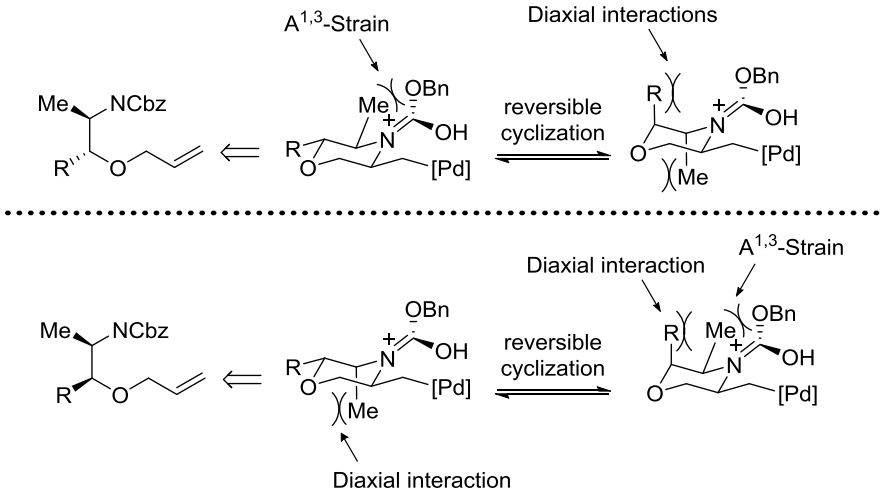
Figure 1.4. Proposed stereochemical rationale depicting the four possible palladium-alkyl intermediate *en route* to the morpholine products



undergoing an intramolecular protonolysis. Of these, conformation **B**, with an equatorial R group, is the more stable and leads to the observed *trans* product. This stereochemical model also provides an explanation for the difficulty in cyclizing *anti*-

disubstituted aminoalkenes (**1.4j,l,m**). In both chair conformations, the palladium-alkyl intermediate must endure an unfavorable interaction.

Figure 1.5. Stereochemical model for the trisubstituted morpholines



Section 3. Conclusions

In conclusion, we have developed a convergent, high-yielding, and diastereoselective synthesis of 2,5-disubstituted and 2,3,5-trisubstituted morpholines, employing a palladium-catalyzed hydroamination as the key ring-forming step. A variety of alkyl and aryl substituted aziridines can be used as starting materials in either a two-step sequence, or a one-pot domino reaction sequence.

Section 4. Experimental

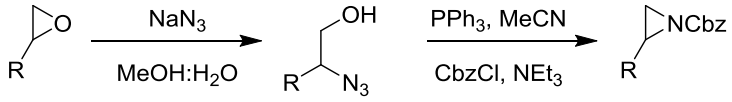
General Procedures. All reactions were performed under a nitrogen atmosphere using flame-dried glassware and standard air-free techniques. Column chromatography was performed using silica gel (Whatman, 60Å, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of trimethylsilane and are referenced relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts are referenced to the carbon resonance of the deuterated solvent $CDCl_3$ (77.0 ppm). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and assignment. Mass spectra were collected on a JEOL HX-110 Mass Spectrometer or a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer. Optical rotations ($[\alpha]_D^{22}$ values) are reported in 10^{-1} deg cm^2 g^{-1}. Chiral HPLC analysis was performed on Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 215 nm; column, DIACEL CHIRALPAK AD-H and CHIRALPAK OD-H; mobile phase, hexanes/2-propanol.

Materials. Dichloromethane, acetonitrile, diethyl ether, and tetrahydrofuran were degassed with nitrogen and dried by passing through a column of neutral alumina. Toluene was degassed with nitrogen and dried by passing through a column of neutral

alumina and a column of Q5 reactant. All other solvents were distilled before use and stored under an atmosphere of nitrogen and on 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4Å molecular sieves and were used without further purification. Commercial reagents were purchased from Sigma-Aldrich or VWR and were used as received. 2,6-Bis(diphenylphosphinomethyl)pyridine dichloropalladium (**1.1**) was prepared according to literature procedure.[24]

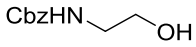
1.4.a Synthesis of aziridines

General scheme for the preparation of aziridines from epoxides



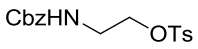
General Procedure A for preparation of the azidoalcohols: Sodium azide (2 equiv) was dissolved in methanol:water (3:1, 1.2 M) in a 3-neck round-bottomed flask fitted with a reflux condenser and stir bar. The epoxide was then added and the mixture was refluxed until TLC (90:10, hexanes:ethyl acetate) indicated disappearance of starting material, then cooled to room temperature, concentrated, and extracted with dichloromethane (3x). The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated to give the product, which was used without further purification.

General Procedure B for the preparation of the aziridines: Triphenylphosphine (1.1 equiv) was dissolved in acetonitrile (0.7 M) in a three-neck round-bottomed flask fitted with reflux condenser and stir bar. The azidoalcohol (from **procedure A**) was added and the mixture refluxed until TLC indicated disappearance of starting material (90:10, hexanes:ethyl acetate). The reaction mixture was then cooled to -44 °C, and triethylamine (2 equiv) was slowly added. Benzyl chloroformate (1.3 equiv) was added dropwise and the mixture was stirred for 4 hours. Water and dichloromethane were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified via column chromatography (hexanes:ethyl acetate; silica loaded with 2% triethylamine) to give the desired aziridine.



Benzyl (2-hydroxyethyl)carbamate: 2-Ethanolamine hydrochloride (1.95 g, 20 mmol) was dissolved in tetrahydrofuran (40 mL) in a round-bottomed flask. A 10% solution of sodium bicarbonate in water was added, and the flask was cooled to 0 °C. Benzyl chloroformate (3.42 mL, 24 mmol) was added dropwise and the mixture was gradually warmed to room temperature and stirred overnight. Pentane was added to crystallize the product. The residue was filtered to remove unreacted starting material and the product was recrystallized from hexanes/ethyl acetate to give the title compound (3.60 g, 18.4 mmol, 92%). Spectra matched literature values.[25] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (5

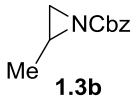
H, m, Ph), 5.39 (1 H, br s, N*H*), 5.10 (2 H, s, C*H*$_2$OCO), 3.65 (2 H, m, CH$_2$C*H*$_2$), 3.30 (2 H, m, C*H*$_2$CH$_2$), 2.92 (1 H, br s, O*H*).



2-(Benzyloxycarbonylamino)ethyl 4-methylbenzenesulfonate: Benzyl (2-hydroxyethyl)carbamate (1.95 g, 10 mmol) and dimethylaminopyridine (0.24 g, 2 mmol) were placed in a round-bottomed flask under nitrogen. Dichloromethane (10 mL) was added and the flask was cooled to 0 °C. Triethylamine (1.53 mL, 11 mmol) was added, followed by a solution of tosyl chloride (2.1 g, 11 mmol) in dichloromethane (10 mL). The solution was allowed to warm to room temperature overnight. The mixture was concentrated, then dissolved in ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude residue was purified by column chromatography (40:60 to 100:0, ethyl acetate:pentane) to give the title compound (3.5 g, 10 mmol, quantitative). Spectra matched literature values.[26] ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.78 (2 H, d, *J* = 8.2 Hz, Ts), 7.37 (7 H, m, Ph and Ts), 5.10 (s, 2 H, s, C*H*$_2$OCO), 5.02 (1 H, br s, N*H*), 4.08 (2 H, t, *J* = 6.0 Hz, CH$_2$C*H*$_2$), 3.45 (2 H, t, *J* = 6.0 Hz, C*H*$_2$CH$_2$), 2.43 (3 H, s, C*H*$_3$).

1.3a

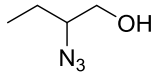
B**enzyl aziridine-1-carboxylate (1.3a)**: Sodium hydride (60% suspension in mineral oil; 0.19 g, 8.3 mmol) was suspended in tetrahydrofuran (15 mL) in a round-bottomed flask and cooled to –78 °C. 2-(Benzyloxycarbonylamino)ethyl 4-methylbenzenesulfonate (1.57 g, 4.5 mmol) was added and the mixture was stirred briefly at that temperature before being warmed to room temperature, then heated to reflux and stirred overnight. The mixture was then allowed to cool to room temperature, filtered, concentrated, and purified by column chromatography (40:60 to 100:0, ether:pentane) to give **1.3a** (0.71 g, 4.0 mmol, 89%). Spectra matched literature values.[2] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.33 (5 H, m, Ph), 5.14 (2 H, s, CH_2OCO), 2.22 (4 H, s, CH_2 x 2).



1.3b

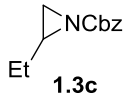
Benzyl 2-methylaziridine-1-carboxylate (1.3b): 2-Methylaziridine (1.4 mL, 18 mmol) and triethylamine (4.8 mL, 35 mmol) were dissolved in diethyl ether (35 mL) in a round-bottomed flask and cooled to –44 °C. Benzyl chloroformate (2.6 mL, 18 mmol) was added dropwise. The mixture was stirred 1.5 hours and was quenched by addition of water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentratred. The crude oil was purified by column chromatography (80:20

hexanes:ethyl acetate) to give **1.3b** as a colorless oil (3.09 g, 16.2 mmol, 90%). FTIR (film, cm^{-1}): 3062, 3003, 2969, 2963, 2360, 2341, 1700, 1540, 1456, 1258, 1151, 668; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.34 (5 H, m, Ph), 5.13 (2 H, s, C*H*$_2$OCO), 2.53 (1 H, dquin, *J* = 3.9, 5.7 Hz, C*H*CH$_3$), 2.34 (1 H, d, *J* = 5.7 Hz, C*H*$_2$), 1.97 (1 H, d, *J* = 3.9 Hz, C*H*$_2$), 1.29 (3 H, d, *J* = 5.7 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 135.8, 128.4, 128.1, 67.9, 33.8, 32.6, 17.3; HRMS calculated for $[M+H]^+$ 299.1027, found 299.1027.



1.2c

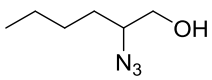
2-Azidobutan-1-ol (1.2c): 1,2-Epoxybutane (1.2 mL, 14 mmol) was used in general procedure A to give the title compound as a crude orange oil (1.17 g, 10.1 mmol, 73%), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (1 H, m, C*H*N$_3$), 3.38 (1 H, dd, 1H, *J* = 3.3, 12.4 Hz, C*H*$_2$OH), 3.25 (1 H, dd, *J* = 7.4, 12.4 Hz, C*H*$_2$OH), 1.97 (1 H, br s, O*H*), 1.52 (2 H, pent, *J* = 7.8 Hz, C*H*$_2$CH$_3$), 0.97 (3 H, t, *J* = 7.5 Hz, C*H*$_3$).



1.3c

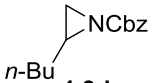
Benzyl 2-ethylaziridine-1-carboxylate (1.3c): 2-Azidobutan-1-ol (1.16 g, 10 mmol) was used in general procedure B to give **1.3c** as a light yellow oil (1.09 g, 5.3 mmol, 53%).

FTIR (film, cm^{-1}): 2966, 2879, 1720, 1456, 1412, 1379, 1297, 1206, 1065, 738, 697; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.35 (5 H, br m, Ph), 5.13 (2 H, s, C*H*$_2$OCO), 2.42 (1 H, m, C*H*Et), 2.33 (1 H, d, *J* = 6.0 Hz, C*H*$_2$N), 2.00 (1 H, d, *J* = 3.9 Hz, C*H*$_2$N), 1.60-1.46 (2 H, m, CH_3CH_2), 1.03 (3 H, t, *J* = 7.5 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 135.7, 128.2, 127.8, 67.7, 39.3, 31.2, 25.0, 10.5; HRMS calculated for $[M+H]^+$ 206.1178, found 206.1179.



1.2d

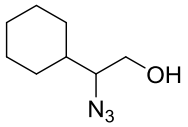
2-Azidohexan-1-ol (1.2d): 1,2-Epoxyhexane (1.2 mL, 10 mmol) was used in general procedure A to give the title compound as a crude orange oil (1.17, 8.2 mmol, 82%), which was used without purification. ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (1 H, br m, C*H*N_3), 3.40 (1 H, dd, *J* = 3.6, 12.6 Hz, C*H*$_2$OH), 3.26 (1 H, dd, *J* = 7.2, 12.3 Hz, C*H*$_2$OH), 1.91 (1 H, br s, O*H*), 1.47 (2 H, m, CHC*H*$_2$CH$_2$), 1.35 (4 H, m, (C*H*$_2$)$_2$CH$_3$), 0.91 (3 H, t, *J* = 6.9 Hz, C*H*$_3$).



1.3d

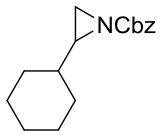
Benzyl 2-butylaziridine-1-carboxylate (1.3d): 2-Azidohexan-1-ol (1.17 g, 8.2 mmol) was used in general procedure B to give **1.3d** as a pale yellow oil (0.843 g, 3.6 mmol, 45%). FTIR (thin film, cm^{-1}): 2931, 2856, 1722, 1455, 1297, 1203, 1065, 734, 697; ^1H

NMR (300 MHz, $CDCl_3$): δ 7.36 (5 H, br m, Ph), 5.13 (2 H, s, C*H*$_2$OCO), 2.42 (1 H, m, C*H*N), 2.33 (1 H, d, *J* = 6.3 Hz, C*H*$_2$N), 1.98 (1 H, d, *J* = 3.9 Hz, C*H*$_2$N), 1.56-1.28 (6 H, m, (C*H*$_2$)$_3$CH$_3$), 0.89 (3 H, t, *J* = 7.1 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 135.7, 128.3, 127.8, 67.7, 38.2 31.6, 28.7, 22.1, 13.8; HRMS calculated for $[M+H]^+$ 292.3913, found 292.1913.



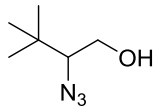
1.2e

2-Azido-2-cyclohexylethanol (1.2e): Vinylcyclohexane (1.24 mL, 9.1 mmol) was dissolved in CH_2Cl_2 (11 mL). *m*-CPBA (2.08 g, 77% pure, 9.3 mmol) was added, and the mixture was stirred 6 h at room temperature, then filtered and washed with CH_2Cl_2. This organic layer containing the crude epoxide was then used in general procedure A to give the title compound as an orange oil (1.54 g, 9.1 mmol, quantitative). This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (1 H, m, C*H*N$_3$), 3.43 (1 H, dd, *J* = 3.0, 12.3 Hz, C*H*$_2$OH), 3.31 (1 H, dd, *J* = 7.8, 12.3 Hz, C*H*$_2$OH), 1.75 (6 H, m, cyclohexyl), 1.23 (2 H, m, cyclohexyl), 1.05 (3 H, m, cyclohexyl).



1.3e

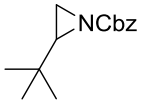
Benzyl 2-cyclohexylaziridine-1-carboxylate (1.3e): 2-Azido-2-cyclohexylethanol (1.54 g, 9.1 mmol) was used in general procedure B to give **1.3e** as a light yellow oil, (0.495 g, 1.91 mmol, 21%). FTIR (film, cm^{-1}): 2925, 2851, 1723, 1450, 1419, 1379, 1295, 1211, 734, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5H, br m, Ph), 5.13 (2 H, s, CH_2OCO), 2.27 (2 H, m, C*H*N and CH_2N), 2.05 (1 H, d, *J* = 3.6 Hz, CH_2N), 1.92 (1 H, m, C*H* cyclohexyl), 1.71 (4 H, m, cyclohexyl), 1.20-1.11 (6 H, m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 136.0, 128.4, 128.1, 127.8, 67.9, 43.3, 40.1, 30.5, 30.3, 29.5, 26.2, 25.6, 25.5; HRMS calculated for $[M+H]^+$ 260.1651, found 260.1628.



1.2f

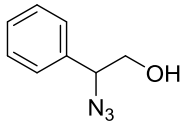
2-Azido-3,3-dimethyl-1-butanol (1.2f): *m*-CPBA (2.144 g, 77%, 9.3 mmol) was dissolved in dichloromethane (11 mL) and 3,3-dimethyl-1-butene (1.17 mL, 9.1 mmol) was added. The mixture was stirred for 3 hours, then filtered, and the residue was washed with dichloromethane. The organic filtrate was transferred to a round-bottomed flask and water (4.5 mL), sodium azide (1.188 g, 18.2 mmol), and ammonium chloride (0.732 g, 13.6 mmol) were added. The mixture was vigorously stirred and heated to 50 °C open to

air until dichloromethane had evaporated, and then heated to 80 °C for 12 h. The layers were separated and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the title compound as an orange oil (1.30 g, 9.1 mmol, quantitative). This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (2 H, m, C*H*N_3 and C*H*$_2$OH), 3.26 (1 H, dd, *J* = 9.9, 12.3 Hz, C*H*$_2$OH), 2.02 (1 H, br s, O*H*), 0.90 (9 H, s, (C*H*$_3$)$_3$C).



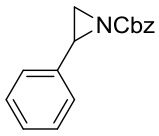
1.3f

Benzyl 2-*tert*-butylaziridine-1-carboxylate (1.3f): 2-Azido-3,3-dimethyl-1-butanol (1.30 g, 9.1 mmol) was used in general procedure B to give **1.3f** as a colorless oil, (1.13 g, 4.8 mmol, 53%). FTIR (film, cm^{-1}): 2957, 1725, 1479, 1410, 1385, 1364, 1306, 1269, 1200, 1149, 1028, 982, 802, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5 H, m, Ph), 5.12 (2 H, s, C*H*$_2$OCO), 2.28 (1 H, dd, *J* = 6.3, 3.9 Hz, C*H*), 2.23 (1 H, d, *J* = 6.3 Hz, C*H*$_2$N), 2.10 (1 H, d, *J* = 3.6 Hz, C*H*$_2$N), 0.93 (9 H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 136.0, 128.4, 128.1, 127.8, 67.8, 47.2, 30.3, 28.5, 26.1; HRMS calculated for $[M+H]^+$ 234.1494, found 234.1488.



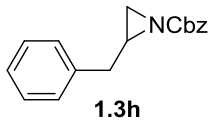
1.2g

2-Azido-2-phenylethanol (1.2g): Styrene oxide (1.41 mL, 12.3 mmol) was used in general procedure A to give the title compound as a yellow oil (1.75 g, 10.7 mmol, 88%), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (5 H, m, Ph), 4.68 (1 H, t, *J* = 6.7 Hz, C*H*N_3), 3.76 (2 H, d, *J* = 6.3 Hz, CH_2OH), 1.99 (1 H, br s, O*H*). Minor product (2-azido-1-phenylethanol): 4.88 (1 H, dd, *J* = 4.2, 7.7 Hz, C*H*(OH)Ph), 3.47 (2 H, m, CH_2N_3), 2.38 (1 H, br s, O*H*).



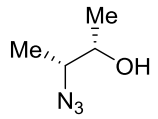
1.3g

Benzyl 2-phenylaziridine-1-carboxylate (1.3g): 2-Azido-2-phenylethanol (1.75 g, 10.7 mmol) was used in general procedure B to give **1.3g** as a colorless oil, (0.921 g, 3.6 mmol, 34%). FTIR (film, cm^{-1}): 3033, 2956, 1723, 1497, 1454, 1400, 1317, 1299, 1280, 1226, 1175, 1082, 753, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (10 H, br m, Ph x 2), 5.15 (1 H, d, *J* = 12.3 Hz, CH_2OCO), 5.10 (1 H, d, *J* = 12.3 Hz, CH_2OCO), 3.47 (1 H, dd, *J* = 3.9, 6.3 Hz, C*H*N), 2.68 (1 H, d, *J* = 6.3 Hz, CH_2N), 2.28 (1 H, d, *J* = 3.6 Hz, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0, 136.8, 135.6, 128.5, 128.4, 128.3, 128.2, 127.8, 126.1, 68.3, 39.3, 35.1; HRMS calculated for $[M+H]^+$ 254.1178, found 254.1180.



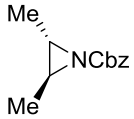
1.3h

Benzyl 2-benzylaziridine-1-carboxylate (1.3h): Triphenylphosphine (4.167 g, 15.9 mmol) was dissolved in toluene (8 mL) and cooled to 0 °C. Diisopropylazodicarboxylate (2.86 mL, 14.5 mmol) was added dropwise, and the mixture was stirred 20 minutes. A solution of phenylalaninol (2.0 g, 13.2 mmol) in toluene (32 mL) was added and the mixture was refluxed for 24 h, then cooled to room temperature. Triethylamine (3.70 mL, 26.5 mmol) was added. The mixture was cooled to –44 °C and benzyl chloroformate (2.08 mL, 14.5 mmol) was added dropwise. The mixture was stirred 2 h, then quenched by adding water. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (85:15, hexanes:ethyl acetate) to give **1.3h** as a colorless oil (1.24 g, 4.6 mmol, 35%). FTIR (film, cm^{-1}): 3012, 2928, 1719, 1497, 1454, 1406, 1294, 1195, 1058, 741, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (10 H, br m, Ph x 2), 5.14 (2 H, s, CH_2OCO), 3.00 (1 H, m, C*H*N), 2.70 (2 H, m, PhCH_2CH), 2.41 (1 H, d, *J* = 5.4 Hz, CH_2N), 2.11 (1 H, d, *J* = 3.0 Hz, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 137.5, 135.7, 128.7, 128.4, 128.1, 127.9, 126.5, 68.0, 38.4, 38.2, 31.5; HRMS calculated for $[M+H]^+$ 206.1178, found 206.1179.



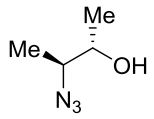
1.2i

(2*R*,3*S*)-3-Azidobutan-2-ol (1.2i): *Trans*-2-butene (about 7 mL, 87 mmol) was condensed into a round-bottomed flask at –78 °C and dichloromethane (1 mL) was added. A solution of *m*-CPBA (3.9 g, 77% pure, 17.4 mmol) in dichloromethane (35 mL) was added dropwise. The mixture was stirred at –78 °C for 2 h, then warmed to room temperature. 1M NaOH was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL) and the combined organic layers were transferred to a round-bottomed flask. A solution of sodium azide (2.3 g, 34.8 mmol) in water (30 mL) was added to the dichloromethane solution, and the mixture was heated at 50 °C. The mixture was cooled and the aqueous residue was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the title compound as a colorless oil (0.984 g, 8.5 mmol, 47%). This compound was used without further purification. ^{1}H NMR: δ 3.81 (1 H, m, C*H*OH), 3.55 (1 H, dq, *J* = 3.9, 6.6 Hz, C*H*N_3) 1.25 (3 H, d, *J* = 6.6 Hz, CH_3), 1.18 (3 H, d, *J* = 6.3 Hz, CH_3).



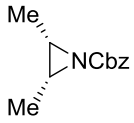
1.3i

(*2R,3R*)-Benzyl 2,3-dimethylaziridine-1-carboxylate (1.3i)[27]: Triphenylphosphine (2.23 g, 8.5 mmol) was added to a solution of (2*R*,3*S*)-3-Azidobutan-2-ol (0.984 g, 8.5 mmol) in THF:DCM (1:1, 10 mL). The mixture was heated at 40 °C overnight, then cooled to –44 °C and triethylamine (2.36 mL, 17 mmol) was slowly added. Benzyl chloroformate (1.58 mL, 11.1 mmol) was added drop wise. The mixture was stirred 4 h, then quenched with water. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed (95:5, hexanes:ethyl acetate; silica loaded with 3% triethylamine) to give **1.3i** as a colorless oil, (0.528 g, 2.57 mmol, 30%). IR (film, cm^{-1}): 3031, 2968, 1716, 1451, 1381, 1338, 1299, 1200, 1066, 1018, 750, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5 H, br m, Ph), 5.16 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 5.12 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 2.26 (2 H, m, C*H* x 2), 1.24 (6 H, d, *J* = 5.1 Hz, C*H*$_3$ x 2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 136.0, 128.4, 128.2, 128.1, 67.8, 40.5, 16.3; GC/MS (CI) m/z 207 (M^+, 5), 148 (5), 116 (8), 91 (100), 70 (28); HRMS calculated for $[M+H]^+$ 206.1178, found 206.1179.



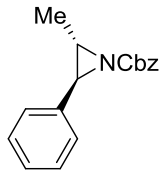
1.2j

(2*R*,3*R*)-3-Azidobutan-2-ol (1.2j): Prepared as for (2*R*,3*S*)-3-azidobutan-2-ol, using *cis*-2-butene (about 3.5 mL, 43.5 mmol). The product is a colorless oil, (0.946 g, 4.61 mmol, 53%). ^{1}H NMR (300 MHz): δ 3.61 (1 H, dq, *J* = 2.1, 6.3 Hz, C*H*N_3), 3.37 (1 H, quin, *J* = 6.6 Hz, C*H*OH), 2.06 (1 H, s, O*H*), 1.28 (3 H, d, *J* = 6.6 Hz, CH_3), 1.05 (3 H, d, *J* = 6.3 Hz, CH_3).



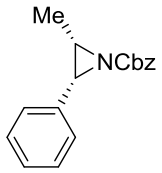
1.3j

(2*R*,3*S*)-Benzyl 2,3-dimethylaziridine-1-carboxylate (1.3j): Prepared as for **1.3j**, using (2*R*,3*R*)-3-azidobutan-2-ol, **1.2j** (500 mg, 4.6 mmol). The product **1.3j** is a colorless oil (300 mg, 1.47 mmol, 32%). IR (thin film, cm^{-1}): 2932, 1721, 1454, 1426, 1380, 1287, 1225, 1104, 1055, 752, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (5 H, br m, Ph), 5.12 (2 H, s, CH_2OCO), 2.24 (2 H, m, C*H* x 2), 1.22 (6 H, d, *J* = 5.1 Hz, CH_3 x 2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 136.0, 128.4, 128.1, 128.0, 67.8, 37.5, 12.5; HRMS calculated for $[M+H]^+$ 206.1180, found 206.1179.



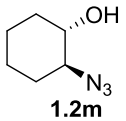
1.3k

(2*R*,3*R*)-Benzyl 2-methyl-3-phenylaziridine-1-carboxylate (1.3k): Triphenylphosphine (2.09 g, 7.95 mmol) was dissolved in tetrahydrofuran (15 mL) in a round-bottomed flask. The mixture was cooled to 0 °C and diisopropylazodicarboxylate (1.56 mL, 7.94 mmol) was added dropwise. The mixture was stirred 20 min, then a solution of (1*S*,2*R*)-(+)-norephedrine (1.0 g, 6.6 mmol) in tetrahydrofuran (7 mL) was added dropwise. The mixture was refluxed for 10 h, then cooled to 0 °C, and triethylamine (2.03 mL, 14.6 mmol) was added. Benzyl chloroformate (1.13 mL, 7.94 mmol) was added dropwise, and the mixture was stirred 3.5 h, then quenched by addition of water. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was chromatographed (95:5, hexanes:ethyl acetate) to give **1.3k** as a colorless oil (0.478 g, 1.79 mmol, 27%). FTIR (film, cm^{-1}): 2958, 2930, 1717, 1457, 1380, 1299, 1278, 1186, 1029, 749, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (10 H, br m, Ph x 2), 5.17 (1 H, d, *J* = 12.0 Hz, C*H*$_2$OCO), 5.12 (1 H, d, *J* = 12.0 Hz, C*H*$_2$OCO), 3.24 (1 H, d, *J* = 3.3 Hz, PhC*H*N), 2.66 (1 H, m, CH_3C*H*N), 1.39 (3 H, d, *J* = 5.7 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 136.7, 135.7, 128.47, 128.43, 128.3, 128.2 127.7, 126.2, 68.0, 46.0, 43.4, 16.0; HRMS calculated for $[M+H]^+$ 268.1337, found 268.1339.



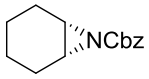
1.3l

(*2R,3S*)-Benzyl 2-methyl-3-phenylaziridine-1-carboxylate (1.3l): The aziridine was prepared according to literature procedure,[28] except the final purification step (column chromatography using 1:1, hexanes:ethyl acetate) was skipped. Instead, upon removal of the $CHCl_3$ solvent, the crude aziridine residue was dissolved in acetonitrile (3.3 mL) and the solution cooled to 0 °C. Triethylamine (0.92 mL, 6.6 mmol) was slowly added. Benzyl chloroformate (0.61 mL, 4.3 mmol) was added dropwise, and the reaction mixture stirred at 0 °C until TLC (90:10, hexanes:ethyl acetate) indicated disappearance of starting material. The reaction was then warmed to room temperature, filtered, and the filtrate concentrated to give an oily residue, which was purified via column chromatography (95:5, hexanes:ethyl acetate) to give **1.3l** as a colorless oil (0.388 g, 1.45 mmol, 44%). FTIR (film, cm^{-1}): 3032, 2960, 2883, 1721, 1453, 1419, 1273, 1229, 1188, 740, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (10 H, m, Ph x 2), 5.17 (2 H, s, C*H*$_2$OCO), 3.67 (1 H, d, *J* = 6.3 Hz, PhC*H*N), 2.85 (1 H, quintet, *J* = 5.7 Hz, CH_3C*H*N), 1.02 (3 H, d, *J* = 5.7 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 135.9, 134.6, 128.5, 128.3, 128.18, 128.17, 127.6, 127.4, 68.1, 44.0, 40.0, 12.7; HRMS calculated for $[M+H]^+$ 268.1334, found 299.1339.



1.2m

(1*S*,2*S*)-2-azidocyclohexanol (1.2m): Prepared according to literature procedure.[29] Spectral data matched literature values: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (1 H, m, C*H*N_3), 3.16 (1 H, m, C*H*OH), 2.25 (1 H, s, O*H*), 2.03 (2 H, m, -CH_2-), 1.74 (2 H, br m, -CH_2-), 1.28 (4 H, m, -CH_2-).



1.3m

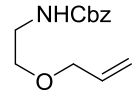
Benzyl 7-aza-bicyclo[4.1.0]heptanecarbamate (1.3m): Prepared according to a modified literature procedure.[1] (1*S*,2*S*)-2-Azidocyclohexanol (5.96 g, 42.2 mmol) was dissolved in acetonitrile (70 mL) in a three-neck round-bottomed flask equipped with a reflux condenser, thermometer, and a stir bar. Triphenylphosphine (12.1 g, 46 mmol) was added, and the mixture was heated to 75 °C for 4 h. The mixture was cooled to 0 °C and triethylamine (11.7 mL, 84 mmol) was added. Benzyl chloroformate (6.6 mL, 46 mmol) was added drop wise and the mixture was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for 4 h. Water was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x). The combined organic layers were washed with brine and dried over magnesium sulfate, then concentrated to give a

crude white residue. This residue was extracted with hexanes (5x) and the extracts concentrated to give a yellowish oil, which was purified by column chromatography (85:15, hexanes:ethyl acetate) to give **1.3m** as a colorless oil (9.17 g, 39.6 mmol, 94%). FTIR (film, cm^{-1}): 2937, 2859, 1718, 1497, 1440, 1418, 1379, 1344, 1278, 1219, 1189, 1087, 1016, 962, 770, 751, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (5 H, br s, Ph), 5.11 (2 H, s, C*H*$_2$OCO), 2.65 (2 H, br m, C*H*N x 2), 1.92 (2 H, m, -C*H*$_2$-), 1.82 (2 H, m, -C*H*$_2$-), 1.40 (2 H, m, -C*H*$_2$-), 1.24 (2 H, m, -C*H*$_2$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 136.0, 128.4, 128.1, 67.7, 37.0, 23.6, 19.7; HRMS calculated for $[M+H]^+$ 232.1338, found 232.1332.

1.4.b Synthesis of hydroamination substrates (aziridine ring-opening reactions)

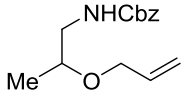
General Procedure C: To a solution of the aziridine in dichloromethane (0.4 M) was added allyl alcohol (2 equiv). The reaction mixture was cooled to –78 °C, and boron trifluoride diethyl etherate (10 mol%) was added. The mixture was stirred at –78 °C until TLC indicated consumption of starting material (80:20, hexanes:ethyl acetate). The reaction mixture was warmed to -40 °C and stirred for 15 min, then saturated sodium bicarbonate was added to quench the reaction. The reaction mixture was then warmed to room temperature. The layers were separated and the aqueous layer extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting crude product

was purified via column chromatography (hexanes:ethyl acetate) to yield the ring-opened product in the indicated amount.



1.4a

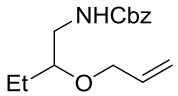
Benzyl 2-(allyloxy)ethylcarbamate (1.4a): Performed General Procedure C on **1.3a** (0.136 g, 0.677 mmol) except using scandium triflate as catalyst (10 mol %). Product **1.4a** formed as a colorless oil, (0.108 g, 0.459 mmol, 68%). IR (film, cm^{-1}): 3338, 2865, 1711, 1531, 1454, 1255, 1146, 1100, 1016, 927, 737, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (5 H, br s, Ph), 5.88 (1 H, ddt, *J* = 10.4, 17.1, 5.7 Hz, C*H*=CH_2), 5.25 (1 H, dd, *J* = 1.5, 17.4 Hz, CH=C*H*$_2$), 5.18 (1 H, dd, *J* = 1.2, 10.3 Hz, CH=C*H*$_2$), 5.10 (2 H, s, C*H*$_2$OCO), 3.97 (2 H, d, *J* = 5.4 Hz, C*H*$_2$CH=CH_2), 3.49 (2 H, m, C*H*$_2$), 3.39 (2 H, m, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 136.4, 134.2, 128.3, 127.9, 117.1, 71.8, 68.8, 66.5, 40.8; HRMS calculated for $[M+H]^+$ 236.1284, found 236.1289.



1.4b

Benzyl 2-(allyloxy)propylcarbamate (1.4b): Performed General Procedure C on **1.3b** (0.166 g, 0.865 mmol). Product **1.4b** formed as a colorless oil, (0.166 g, 0.666 mmol, 77%). IR (film, cm^{-1}): 3339, 2975, 1707, 1527, 1454, 1376, 1336, 1251, 1122, 1000, 923,

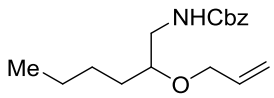
736, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (5 H, br m, Ph), 5.88 (1 H, ddt, *J* = 10.5, 17.1, 5.5 Hz, C*H*=CH_2), 5.24 (1 H, dd, *J* = 1.5, 17.1 Hz, CH=C*H*$_2$), 5.14 (1 H, dd, *J* = 1.5, 10.5 Hz, CH=C*H*$_2$), 5.10 (2 H, s, C*H*$_2$OCO), 4.04 (1 H, dd, *J* = 5.0, 12.5 Hz, C*H*$_2$CH=CH_2), 3.90 (1 H, dd, *J* = 5.5, 12.5 Hz, C*H*$_2$CH=CH_2), 3.58 (1 H, sextet, *J* = 6.0 Hz, C*H*O), 3.41 (1 H, ddd, *J* = 3.5, 6.5, 13.5 Hz, C*H*$_2$N), 3.10 (1 H, ddd, *J* = 5.0, 7.0, 13.5 Hz, C*H*$_2$N), 1.13 (3 H, d, *J* = 6.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 136.5, 134.7, 128.3, 127.9, 116.7, 73.5, 69.4, 66.5, 45.8, 16.9; HRMS calculated for $[M+H]^+$ 250.1442, found 250.1445.



1.4c

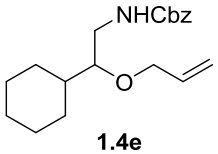
Benzyl 2-(allyloxy)butylcarbamate (1.4c): Performed General Procedure C on **1.3c** (0.095 g, 0.490 mmol). Product **1.4c** formed as a colorless oil, (0.104 g, 0.396 mmol, 81%). IR (film, cm^{-1}): 3330, 2929, 1707, 1528, 1459, 1341, 1253, 1142, 1071, 1025, 925; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (5 H, br s, Ph), 5.88 (1 H, ddt, J = 5.7, 10.2, 17.0 Hz, C*H*=CH_2), 5.25 (1 H, d, *J* = 17.1 Hz, CH=C*H*$_2$), 5.15 (1 H, dd, *J* = 1.2, 10.2 Hz, CH=C*H*$_2$), 5.10 (3 H, s, C*H*$_2$OCO and N*H*), 3.98 (2 H, m, C*H*$_2$CH=CH_2), 3.40 (2 H, m, C*H*$_2$N and C*H*O), 3.15 (1 H, ddd, *J* = 5.4, 6.0, 12.9 Hz, C*H*$_2$N), 1.54 (2 H, m, C*H*$_2$$CH_3$), 0.92 (3 H, t, *J* = 7.4 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 136.5, 134.8, 128.4, 128.0, 127.8, 116.9, 78.9, 70.2, 66.6, 43.44, 24.4, 9.5; GC/MS (CI) m/z 263 $[M^+]$

(1), 192 (16), 148 (20), 91 (100); HRMS calculated for $[M+H]^+$ 264.1588, found 264.1599.



1.4d

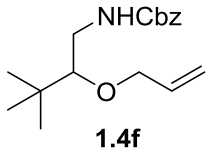
Benzyl 2-(allyloxy)hexylcarbamate (1.4d): Performed General Procedure C on **1.3d** (0.140 g, 0.600 mmol). Product **1.4d** formed as a colorless oil, (0.131 g, 0.449 mmol, 75%). IR (film, cm^{-1}): 3340, 3066, 3033, 2956, 2932, 2861, 1722, 1518, 1455, 1340, 1250, 1142, 1092, 997, 923, 736, 697; ^{1}H NMR (300 MHz): δ 7.33 (5 H, br s, Ph), 5.63 (1 H, ddt, *J* = 10.8, 17.1, 5.7 Hz, C*H*=CH_2), 5.25 (1 H, dd, *J* = 0.9, 17.1 Hz, CH=CH_2), 5.15 (1 H, dd, *J* = 0.9, 10.5 Hz, CH=CH_2), 5.10 (3 H, s, CH_2OCO and N*H*), 3.99 (2 H, m, CH_2CH=CH_2), 3.41 (2 H, m, CH_2N and C*H*O), 3.13 (1 H, ddd, *J* = 6.0, 7.2, 11.7 Hz, CH_2N, 1.42 (6 H, m, *(*CH_2*)*$_3$$CH_3$), 0.90 (3 H, t, *J* = 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 136.5, 134.8, 128.4, 128.0, 127.9, 116.9, 77.8, 70.2, 66.6, 43.8, 31.4, 27.3, 22.7, 13.9; HRMS calculated for $[M+H]^+$ 292.1908, found 292.1914.



1.4e

Benzyl 2-(allyloxy)-2-cyclohexylethylcarbamate (1.4e): Performed General Procedure C on **1.3e** (0.100 g, 0.386 mmol). Product **1.4e** formed as a colorless oil, (0.098 g, 0.308

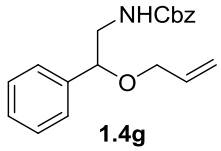
mmol, 80%). IR (film, cm^{-1}): 3336, 2925, 2848, 1720, 1509, 1452, 1243, 1066; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5 H, br s, Ph), 5.86 (1 H, ddt, *J*= 10.5, 17.8, 5.7 Hz, C*H*=CH_2), 5.24 (1 H, dd, *J* = 1.2, 17.4 Hz, CH=CH_2), 5.16 (1 H, dd, *J* = 1.3, 10.4 Hz, CH=CH_2), 5.10 (2 H, br s, CH_2OCO), 4.97 (1 H, br s, N*H*), 3.97 (2 H, m, CH_2CH=CH_2), 3.48 (2 H, m, CH_2N and C*H*O), 3.17 (1 H, m, CH_2N, 1.71 (5 H, m, cyclohexyl), 1.51 (1 H, m, cyclohexyl), 1.19 (3 H, m, cyclohexyl), 1.01 (2 H, m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 136.6, 134.9, 134.6, 128.4, 128.0, 116.9, 82.3, 72.1, 71.2, 69.8, 66.6, 55.5, 41.3, 39.7, 39.1, 29.8, 29.1, 29.0, 28.5, 26.4,26.3, 26.2, 26.1, 26.0; HRMS calculated for $[M+H]^+$ 318.2067, found 318.2067.



1.4f

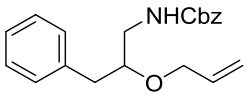
Benzyl 2-(allyloxy)-3,3-dimethylbutylcarbamate (1.4f): Performed General Procedure C on **1.3f** (0.200 g, 0.427 mmol). Product **1.4f** formed as a colorless oil, (0.077 g, 0.264 mmol, 61%). IR (film, cm^{-1}): 3339, 2962, 1709, 1537, 1473, 1341, 1238, 1061; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (5 H, br s, Ph), 5.84 (1 H, ddt, *J*= 10.4, 17.1, 5.6 Hz, C*H*=CH_2), 5.23 (1 H, dd, *J* = 1.5, 17.1, CH=CH_2), 5.13 (1 H, dd, *J* = 1.5, 10.4, CH=CH_2), 5.12 (2 H, s, CH_2OCO), 5.00 (1 H, br s, N*H*), 3.96 (1 H, dd, *J* = 5.1, 12.9 Hz, CH_2CH=CH_2), 3.91 (1 H, dd, *J* = 5.4, 12.9 Hz, CH_2CH=CH_2), 3.61 (1 H, m, C*H*O), 3.52 (2 H, m, CH_2N), 0.95 (9 H, s, (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 136.7,

134.6, 128.4, 127.9, 116.6, 71.8, 69.6, 66.6, 58.4, 34.2, 27.0; HRMS calculated for $[M+H]^+$ 292.1914, found 292.1913.



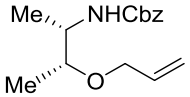
1.4g

Benzyl 2-(allyloxy)-2-phenylethylcarbamate (1.4g): Performed General Procedure C on **1.3g** (0.124 g, 0.490 mmol). Product **1.4g** formed as a colorless oil, **(**0.101 g, 0.324 mmol, 66%). IR (film, cm^{-1}): 3342, 3032, 2934, 2863, 1721, 1516, 1454, 1253, 1143, 1099, 1067, 999, 926, 754, 700; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (10 H, br s, Ph x 2), 5.88 (1 H, ddt, *J* = 10.5, 16.5, 5.7 Hz, C*H*=CH_2), 5.23 (1 H, dd, *J* = 1.5, 17.1 Hz, CH=C*H*$_2$), 5.16 (1 H, dd, *J* = 1.5, 10.5 Hz, CH=C*H*$_2$), 5.14 (1 H, s, N*H*), 5.11 (2 H, br s, C*H*$_2$OCO), 4.45 (1 H, dd, *J* = 3.5, 8.3 Hz, PhC*H*O), 3.95 (1 H, dd, *J* = 5.1, 12.6 Hz, C*H*$_2$CH=CH_2), 3.79 (1 H, dd, *J* = 6.0, 12.6 Hz, C*H*$_2$CH=CH_2), 3.56 (1 H, m, C*H*$_2$N), 3.28 (1 H, ddd, *J* = 4.2, 8.7, 13.2 Hz, C*H*$_2$N); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 139.1, 136.5, 134.3, 128.5, 128.4, 128.0, 126.6, 117.0, 80.0, 69.6, 66.6, 47.3; HRMS calculated for $[M+H]^+$ 312.1593, found 312.1602.



1.4h

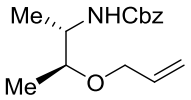
Benzyl 2-(allyloxy)-3-phenylpropylcarbamate (1.4h): Performed General Procedure C on **1.3h** (0.107 g, 0.400 mmol). Product **1.4h** formed as a colorless oil, (0.060 g, 0.184 mmol, 46%). IR (film, cm^{-1}): 3338, 2918, 2863, 1718, 1522, 1454, 1336, 1255, 1086, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (10 H, br s, Ph x 2), 5.78 (1 H, ddt, *J*= 10.6, 17.4, 5.7 Hz, C*H*=CH_2), 5.21 (1 H, d, *J* = 17.4 Hz, CH=CH_2), 5.14 (1 H, d, *J* = 10.8 Hz, CH=CH_2), 5.11 (3 H, s, CH_2OCO and N*H*), 3.90 (1 H, dd, *J* = 5.1, 12.6 Hz, CH_2CH=CH_2), 3.84 (1 H, dd, *J* = 6.6, 12.6 Hz, CH_2CH=CH_2), 3.65 (1 H, m, C*H*O), 3.40 (1 H, m, CH_2N), 3.14 (1 H, ddd *J* = 5.7, 6.0, 12.9 Hz, CH_2N), 2.87 (1 H, dd, *J* = 6.3, 13.8 Hz, PhCH_2CH), 2.74 (1 H, dd, *J* = 6.3, 13.5 Hz, PhCH_2CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 137.6, 136.5, 134.5, 129.3, 128.4, 128.3, 128.0, 126.3, 117.1, 78.7, 70.6, 66.6, 43.7, 38.4; HRMS calculated for $[M+H]^+$ 326.1711, found 326.1750.



1.4i

Benzyl (2*R*,3*S*)-3-(allyloxy)butan-2-yl carbamate (1.4i): Performed General Procedure C on **1.3i** (0.035 g, 0.169 mmol). Product **1.4i** formed as a colorless oil, (0.030 g, 0.113 mmol, 67%). IR (film, cm^{-1}): 3333, 3066, 3039, 2978, 2937, 2875, 1705, 1505, 1454, 1375, 1343, 1308, 1239, 1064, 1002, 924, 775, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ

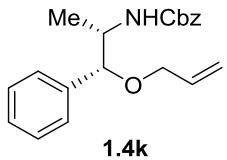
7.35 (5 H, br s, Ph), 5.87 (1 H, ddt, *J* = 11.1, 17.1, 5.4 Hz, C*H*=CH_2), 5.23 (1 H, dd, *J* = 0.9, 17.1 Hz, CH=CH_2), 5.13 (1 H, d, *J* = 11.1 Hz, CH=CH_2), 5.10 (2 H, s, CH_2OCO), 5.09 (1 H, br s, N*H*), 4.06 (1 H, dd, *J* = 3.9, 12.6 Hz, CH_2CH=CH_2), 3.87 (1 H, dd, *J* = 5.7, 12.6 Hz, CH_2CH=CH_2), 3.75 (1 H, m, CH_3C*H*O), 3.54 (1 H, m, CH_3C*H*N), 1.12 (6 H, *J* = 6.3 Hz, CH_3 x 2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 136.5, 134.9, 128.4, 128.0, 127.9, 116.5, 76.3, 69.7, 66.4, 50.5, 15.9, 14.4; HRMS calculated for $[M+H]^+$ 264.1603, found 264.1600.



1.4j

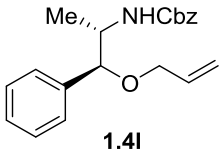
Benzyl (2*R*,3*R*)-3-(allyloxy)butan-2-yl carbamate (1.4j): Performed General Procedure C on **1.3j** (0.100 g, 0.487 mmol). Product **1.4j** formed as a colorless oil, (0.083 g, 0.315 mmol, 65%). IR (film, cm^{-1}): 3332, 2976, 2341, 1718, 1508, 1455, 1375, 1339, 1240, 1068, 925, 738, 697, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5 H, br s, Ph), 5.87 (1 H, ddt, *J* = 10.5, 17.1, 5.4 Hz, C*H*=CH_2), 5.24 (1 H, dd, *J* = 0.9, 17.1 Hz, CH=CH_2), 5.14 (1 H, d, *J* = 10.5 Hz, CH=CH_2), 5.10 (2 H, s, CH_2OCO), 4.97 (1 H, br s, N*H*), 4.07 (1 H, dd, *J* = 5.1, 12.6 Hz, CH_2CH=CH_2), 3.88 (1 H, dd, *J* = 5.4, 12.6 Hz, CH_2CH=CH_2), 3.75 (1 H, br m, C*H*O), 3.44 (1 H, m, C*H*N), 1.18 (3 H, *J* = 6.6 Hz, CH_3), 1.13 (3 H, d, *J* = 6.3 Hz, CH_3). ^{13}C NMR (100 MHz $CDCl_3$): δ 156.1, 136.6, 134.9, 128.4, 128.0, 127.9, 116.6,

76.5, 70.0, 66.5, 50.9, 18.1, 16.2; HRMS calculated for $[M+H]^+$ 264.1593, found 264.1599.



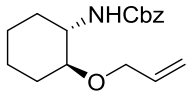
1.4k

Benzyl (1*S*,2*R*)-1-(allyloxy)-1-phenylpropan-2-ylcarbamate (1.4k): Performed General Procedure C on **1.3k** (0.131 g, 0.490 mmol). Product **1.4k** formed as a colorless oil, (0.112 g, 0.344 mmol, 70%). IR (film, cm^{-1}): 3386, 2975, 1702, 1497, 1450, 1405, 1348, 1268, 1209, 1154, 1104, 1076, 1028, 745, 699; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (10 H, br s, Ph x 2), 5.90 (1 H, dddd, *J* = 4.8, 5.7, 10.5, 17.1, C*H*=CH_2), 5.25 (1 H, dd, *J* = 1.5, 17.1 Hz, CH=CH_2), 5.16 (1 H, dd, *J* = 1.5, 10.5 Hz, CH=CH_2), 5.12 (3 H, s, CH_2OCO and N*H*), 4.53 (1 H, d, *J* = 2.7 Hz, PhC*H*O), 4.04 (1 H, dd, *J* = 4.8, 12.9 Hz, CH_2CH=CH_2), 3.95 (1 H, m, CH_3C*H*N), 3.81 (1 H, dd, *J* = 5.7, 12.9 Hz, CH_2CH=CH_2), 1.01 (3 H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ δ 155.6, 138.7, 136.6, 134.5, 128.4, 128.3, 128.0, 127.5, 126.7, 116.7, 82.7, 70.1, 66.5, 51 .9, 30.8, 14.1; HRMS calculated for $[M+H]^+$ 326.1742, found 326.1758.



1.4l

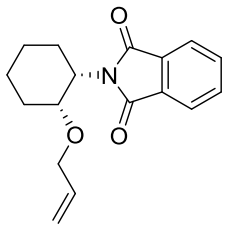
Benzyl (1*R*,2*R*)-1-(allyloxy)-1-phenylpropan-2-ylcarbamate (1.4l): Performed General Procedure C on **1.3l** (0.083 g, 0.310 mmol). Product **1.4l** formed as a colorless oil, (0.055 g, 0.169 mmol, 55%). IR (film, cm^{-1}): 3332, 3031, 2976, 1718, 1508, 1453, 1339, 1231, 1058, 1028, 924, 738, 699; ^{1}H NMR (300 MHz): δ 7.26 (10 H, br s, Ph x 2), 5.85 (1 H, ddt, *J* = 10.5, 17.1, 5.4 Hz, C*H*=CH_2), 5.25 (1 H, dd, *J* = 1.5, 17.1 Hz, CH=CH_2), 5.15 (1 H, dd, *J* = 1.8, 10.5 Hz, CH=CH_2), 4.99 (2 H, s, CH_2OCO), 4.86 (1 H, br s, N*H*), 4.30 (1 H, d, *J* = 3.0 Hz, C*H*O), 3.95 (2 H, m, CH_2CH=CH_2 and CH_3C*H*N), 3.75 (1 H, dd, *J* = 6.0, 12.6 Hz, CH_2CH=CH_2), 1.15 (3 H, d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz $CDCl_3$): δ 155.8, 138.7, 134.4, 128.4, 128.2, 127.9, 127.8, 127.1, 116.8, 82.6, 69.9, 66.4, 17.7, 17.6; HRMS calculated for $[M+H]^+$ 326.1744, found 326.1758.



1.4m

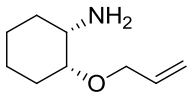
Benzyl (1*S*,2*S*)-2-(allyloxy)cyclohexylcarbamate (1.4m): Performed General Procedure C on **1.3m** (0.200 g, 0.865 mmol). Product **1.4m** formed as a light yellow oil, (0.150 g, 0.518 mmol, 60%). IR (film, cm^{-1}): 3327, 2934, 2859, 1697, 1535, 1452, 1316, 1258, 1232, 1130, 1084, 1048, 922, 737, 696; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (5 H, br s, Ph), 5.86 (1 H, ddt, *J*= 10.8, 17.4, 5.1 Hz, C*H*=CH_2), 5.28 (1 H, dd, *J* = 0.9, 17.4 Hz,

CH=C*H*$_2$), 5.12 (1 H, d, *J* = 10.8 Hz, CH=C*H*$_2$), 5.09 (2 H, s, C*H*$_2$OCO), 4.79 (1 H, br s, N*H*), 4.09 (1 H, dd, *J* = 5.4, 12.6 Hz, C*H*$_2$CH=CH$_2$), 3.90 (1 H, dd, *J* = 5.9, 12.6 Hz, C*H*$_2$CH=CH$_2$), 3.49 (1 H, m, C*H*O), 3.12 (1 H, m, C*H*N), 2.16 (1 H, m, -C*H*$_2$-), 2.00 (1 H, m, -C*H*$_2$-), 1.75-1.71 (1 H, m, -C*H*$_2$-), 1.59 (1 H, br m, -C*H*$_2$-), 1.27 (4 H, m, -C*H*$_2$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 136.6, 135.1, 128.4, 128.0, 127.9, 116.6, 79.5 69.3, 66.4, 54.2, 31.2, 29.8, 23.8, 23.5; HRMS calculated for $[M+H]^+$ 290.1711, found 290.1758.



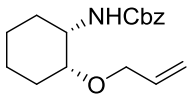
2-((1*R*,2*S*)-2-(allyloxy)cyclohexyl)isoindoline-1,3-dione: Triphenylphosphine (0.847 g, 3.2 mmol) was dissolved in tetrahydrofuran (1 mL) in a round-bottomed flask. The flask was cooled to 0 °C and diisopropylazodicarboxylate (0.65 mL, 3.2 mmol) was added drop wise. The mixture was stirred for 30 minutes and 3 mL tetrahydrofuran was added to dissolve the precipitated white solid. A solution of *trans*-2-allyloxycyclohexanol (prepared according to literature procedures[30]) (0.5 g, 3.2 mmol) in tetrahydrofuran (1 mL) was added and the mixture was stirred for 2.5 h and allowed to warm to room temperature. Phthalimide (0.476 g, 3.2 mmol) was added in one portion and the reaction was stirred overnight. The solvent was removed from the mixture and the residue was

chromatographed (85:15 hexanes:ethyl acetate) to give the title compound (0.585 g, 2.05 mmol, 64%). IR (film, cm^{-1}): 2985, 2959, 1771, 1709, 1643, 1374, 1331, 1093; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (2 H, m, phthalimide), 7.68 (2 H, m, phthalimide), 5.66 (1 H, ddt, *J* = 10.5, 17, 5 Hz, C*H*=CH_2), 5.15 (1 H, d, *J* = 17 Hz, CH=C*H*$_2$), 4.93 (1 H, d, *J* = 10.5 Hz, CH=C*H*$_2$), 4.16 (1 H, dt, *J* = 2.5, 10.5 Hz, C*H*O), 4.03 (1 H, dd, *J* = 5.0, 13.2 Hz, C*H*$_2$CH=CH_2), 3.71-3.69 (2 H, m, C*H*$_2$CH=CH_2 and C*H*N), 3.08 (1 H, dq, *J* = 3.5, 13.2 Hz, -C*H*$_2$-), 2.01 (1 H, d, *J* = 14.0 Hz, -C*H*$_2$-), 1.91 (1 H, d, *J* = 13.0 Hz, -C*H*$_2$-), 1.71-1.60 (2 H, m, -C*H*$_2$-), 1.48-1.42 (2 H, m, -C*H*$_2$-), 1.36-1.28 (1 H, m, -C*H*$_2$-); ^{13}C NMR (100 MHz $CDCl_3$): δ 168.7, 134.9, 133.6, 131.9, 122.9, 116.2, 75.6, 69.8, 55.5, 28.3, 25.9, 23.8, 19.3; GC/MS (CI) m/z 244 $[M\text{-}Allyl]^+$ (8), 228 (11), 207 (100), 191 (11), 207 (73), 148 (50), 138 (24), 130 (32), 97 (29), 76 (32), 41 (70).



***cis*-2-Allyloxycyclohexanamine**: To a solution of 2-((1*R*,2*S*)-2-(allyloxy)cyclohexyl)isoindoline-1,3-dione (1.70 g, 5.96 mmol) in diethyl ether (15 mL) was added hydrazine hydrate (0.45 g, 8.94 mmol), and the solution warmed to 80 °C, and stirred until TLC (80:20, hexanes:ethyl acetate) indicated consumption of the starting material. The heat was then removed and the reaction mixture left to stir overnight. The solid precipitate, which formed during the reaction, was removed by filtration, and the filtrate concentrated. The resulting oil was triturated with diethyl ether. The resulting

solid was removed by filtration, and the filtrate concentrated to yield the title compound as a crude oil (0.780 g, 5.02 mmol, 84%), which was used without further purification ^{1}H NMR (300 MHz): δ 5.93 (1 H, ddt, *J* = 10.2, 17.7, 5.4 Hz, C*H*=CH_2), 5.27 (1 H, d, *J* = 17.7 Hz, CH=C*H*$_2$), 5.15 (1 H, d, *J* = 10.2 Hz, CH=C*H*$_2$), 4.06 (1 H, dd, *J* = 4.8, 12.3 Hz, C*H*$_2$CH=CH_2), 3.94 (1 H, dd, *J* = 5.1, 12.6 Hz, C*H*$_2$CH=CH_2), 3.49-3.23 (2 H, m), 2.87-2.85 (1 H, m), 1.59-1.21 (9 H, m).



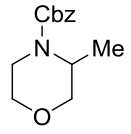
1.4n

Benzyl *cis*-2-allyloxycyclohexylcarbamate (1.4n): To a mixture of *cis*-2-allyloxycyclohexanamine (0.780g, 5.02 mmol) and triethylamine (0.810 mL, 5.80 mmol) in dichloromethane (15 mL) was slowly added benzyl chloroformate (0.82 mL, 5.80 mmol). The reaction mixture stirred overnight. The reaction was quenched with 1M HCl, stirred, and the layers separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude oil was then purified via column chromatography (90:10, hexanes:ethyl acetate; SiO_2 and $AgNO_3$ stationary phase) to give the desired product **1.4n** (0.670 g, 2.31 mmol, 46%) as a colorless oil. IR (film, cm^{-1}): 3338, 2934, 2860, 1720, 1500, 1453, 1334, 1305, 1216, 1125, 1044, 920, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5 H, br s, Ph), 5.89 (1 H, ddt, *J* = 10.6, 15.9, 5.4 Hz, C*H*=CH_2), 5.25 (1 H, dd, *J* = 1.7, 17.4 Hz, CH=C*H*$_2$), 5.12 (1 H, d, *J* = 10.6 Hz, CH=C*H*$_2$), 5.09 (3

H, s, C*H*$_2$OCO and N*H*), 4.05 (1 H, dd, *J* = 5.1, 12.6 Hz, C*H*$_2$CH=CH$_2$), 3.85 (1 H, dd, *J* = 5.7, 12.6 Hz, C*H*$_2$CH=CH$_2$), 3.66 (1 H, m, C*H*O), 3.58 (1 H, br m, C*H*N), 1.94 (1 H, m, -C*H*$_2$-), 1.50 (8 H, m, -C*H*$_2$-) ^{13}C NMR (100 MHz $CDCl_3$): δ 155.7, 136.6, 135.0, 128.4, 128.0, 127.9, 116.3, 75.5, 69.2, 66.4, 51.8, 27.9, 27.7, 24.0, 19.5; HRMS calculated for $[M+H]^+$ 290.1711, found 290.1756.

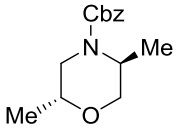
1.4.c Synthesis of morpholines and stereochemical rationale

Hydroamination condition[31]: In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (**1.1**) (5 mol%), silver tetrafluoroborate (10 mol%), and magnesium sulfate (1 equivalent) were placed in a round-bottomed flask with a stir bar. The flask was capped, removed from the glove box, and placed under nitrogen. Dichloromethane (0.5-1.0 mL) was added and the mixture was stirred for 10 minutes. The substrate was dissolved in dichloromethane (0.5-1.0 mL) and added to the flask. The mixture was stirred overnight or until TLC (80:20, hexanes:ethyl acetate) indicated completion. The mixture was filtered through a plug of celite, concentrated and chromatographed (generally 80:20, hexanes:ethyl acetate) to give the product in the indicated yield.



1.5a

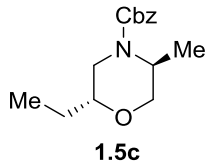
Benzyl 3-methylmorpholine-4-carboxylate (1.5a): Performed Hydroamination Procedure on **1.4a** (24 mg, 0.1 mmol). Product **1.5a** formed as a colorless oil, (23 mg, 0.095 mmol, 95%). IR (film, cm^{-1}): 2924, 1701, 1418, 1346, 1300, 1276, 1227, 1132, 1101, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5 H, br m, Ph), 5.14 (2 H, br s, CH_2OCO), 4.14 (1 H, m, C-3 C*H*), 3.85 (1 H, dd, *J* = 3.4, 11.2 Hz, C-6 C*H*), 3.77 (1 H, dd, *J* = 2.2, 13.3 Hz, C-5 C*H*), 3.65 (1 H, br d, *J* = 11.1 Hz, C-2 C*H*), 3.59 (1 H, dd, *J* = 3.0, 11.7 Hz, C-2 C*H*), 3.44 (1 H, dt, *J* = 3.0, 11.8 Hz, C-6 C*H*), 3.22 (1 H, dt, *J* = 3.8, 12.9 Hz, C-5 C*H*), 1.27 (3 H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (125 MHz $CDCl_3$): δ 155.1, 136.5, 128.4, 128.0, 127.8, 70.7, 67.1, 66.7, 47.1, 39.1, 14.8; HRMS calculated for $[M+H]^+$ 236.1285, found 236.1289.



1.5b

Benzyl 2,5-dimethylmorpholine-4-carboxylate (1.5b): Performed Hydroamination Procedure on **1.4b** (25 mg, 0.1 mmol). Product **1.5b** formed as a colorless oil, (25 mg, 0.099 mmol, 99%). IR (film, cm^{-1}): 2973, 2873, 1698, 1421, 1303, 1247, 1213, 1147, 1112, 1028, 752, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (5 H, br m, Ph), 5.18 (1 H, d,

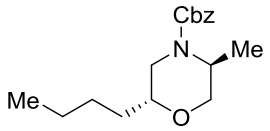
J = 12.6 Hz, C*H*$_2$OCO), 5.12 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 4.04 (2 H, m, C-2 C*H* and C-5 C*H*), 3.93 (1 H, dd, *J* = 3.9, 11.7 Hz, C-6 C*H*), 3.53 (1 H, dd, *J* = 3.0, 13.5 Hz, C-3 C*H*), 3.45 (1 H, dd, *J* = 3.9, 13.5 Hz, C-3 C*H*), 3.33 (1 H, dd, *J* = 2.7, 11.7 Hz, C-6 C*H*), 1.28 (3 H, d, *J* = 6.9 Hz, C*H*$_3$), 1.24 (3 H, d, *J* = 6.6 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 155.9, 136.7, 128.5, 128.0, 127.8, 68.2, 67.1, 64.0, 47.6, 43.3, 16.4, 15.5; GC/MS (CI) m/z 249 $[M]^+$ (9), 234 (9), 190 (13), 158 (13), 91 (100); HRMS calculated for $[M+H]^+$ 250.1442, found 250.1446.



1.5c

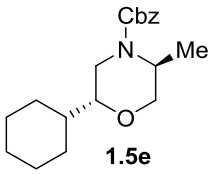
Benzyl 2-ethyl-5-methylmorpholine-4-carboxylate (1.5c): Performed Hydroamination Procedure on **1.4c**, (26 mg, 0.1 mmol). Product **1.5c** formed as a colorless oil, (26 mg, 0.099 mmol, 99%). FTIR (film, cm^{-1}): 2964, 2866, 1701, 1456, 1421, 1296, 1246, 1141, 1115, 1088; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5 H, br m, Ph), 5.17 (1 H, d, *J* = 12.6 Hz, C*H*$_2$OCO), 5.13 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 4.09 (1 H, m, C-5 C*H*), 3.85 (1 H, dd, *J* = 3.9, 11.7 Hz, C-6 C*H*$_2$), 3.63 (2 H, m, C-2 C*H* and C-3 C*H*$_2$), 3.42 (1 H, dd, *J* = 4.5, 13.8 Hz, C-3 C*H*$_2$), 3.32 (1 H, dd, *J* = 2.7, 11.7 Hz, C-6 C*H*$_2$), 1.74 (1 H, m, CH_3C*H*$_2$), 1.50 (1 H, m, CH_3C*H*$_2$), 1.28 (3 H, d, *J* = 6.9 Hz, C-5 C*H*$_3$), 0.90 (3 H, t, *J* = 7.5 Hz, C*H*$_3$$CH_2$); ^{13}C NMR (125 MHz $CDCl_3$): δ 155.7, 136.7, 128.4, 127.9, 127.7, 76.5,

73.7, 67.0, 63.9, 47.4, 41.4, 22.6, 15.5, 9.8; HRMS calculated for $[M+H]^+$ 264.1586, found 264.1579.



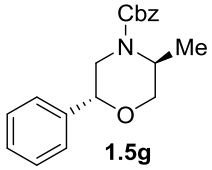
1.5d

Benzyl 2-butyl-5-methylmorpholine-4-carboxylate (1.5d): Performed Hydroamination Procedure on **1.4d**, (29 mg, 0.1 mmol). Product **1.5d** formed as a colorless oil, (29 mg, 0.099 mmol, 99%). FTIR (film, cm^{-1}): 2934, 2868, 1701, 1454, 1423, 1349, 1304, 1251, 1141, 1102, 963, 747, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (5 H, br m, Ph), 5.18 (1 H, d, *J* = 12.5, C*H*$_2$OCO), 5.11 (1 H, d, *J* = 12.5, C*H*$_2$OCO), 4.09 (1 H, m, C-5 C*H*), 3.86 (1 H, dd, *J* = 4.0, 12.0 Hz, C-6 C*H*$_2$), 3.73 (1 H, m, C-2 C*H*), 3.67 (1 H, dd, *J* = 2.2, 13.5 Hz, C-3 C*H*$_2$), 3.42 (1 H, dd, *J* = 4.2, 13.5 Hz, C-3 C*H*$_2$), 3.33 (1 H, dd, *J* = 2.5, 12.0 Hz, C-6 C*H*$_2$), 1.73 (1 H, m, $CH_3CH_2CH_2CH_2$), 1.45 (1 H, m, $CH_3CH_2CH_2CH_2$), 1.29 (7 H, m, $CH_3CH_2CH_2$ and C-5 C*H*$_3$), 0.88 (3 H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (125 MHz $CDCl_3$): δ 155.7, 136.7, 128.4, 128.0, 127.7, 72.2, 67.0, 63.9, 47.4, 41.79, 29.2, 27.6, 22.5, 15.5, 14.0; HRMS calculated for $[M+H]^+$ 292.1908, found 292.1914.



1.5e

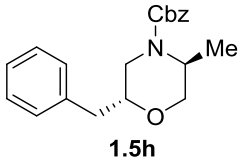
Benzyl 2-cyclohexyl-5-methylmorpholine-4-carboxylate (1.5e): Performed Hydroamination Procedure on **1.4e**, (32 mg, 0.1 mmol). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (5 μL) was added. Product **1.5e** formed as a colorless oil, (31 mg, 0.098 mmol, 98%). FTIR (film, cm^{-1}): 2922, 2850, 1703, 1424, 1307, 1247, 1110; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (5 H, br m, Ph), 5.20 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 5.08 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 4.09 (1 H, m, C-5 C*H*), 3.82 (2 H, m), 3.35 (3 H, m), 1.89-1.67 (6 H, m, cyclohexyl), 1.28 (3 H, d, *J* = 6.9 Hz, C*H*$_3$) 1.16 (3 H, m, cyclohexyl), 0.89 (2 H, m, cyclohexyl); ^{13}C NMR (125 MHz $CDCl_3$): δ 155.6, 136.7, 128.5, 128.0, 127.8, 67.1, 64.5, 47.5, 39.3, 35.5, 29.8, 29.4, 28.6, 26.3, 25.9, 25.8, 15.6; HRMS calculated for $[M+H]^+$ 318.2056, found 318.2067.



1.5g

Benzyl 2-phenyl-5-methylmorpholine-4-carboxylate (1.5g): Performed Hydroamination Procedure on **1.4g**, (31 mg, 0.1 mmol). Product **1.5g** formed as a colorless oil, (24 mg, 0.078 mmol, 78%). IR (film, cm^{-1}): 2911, 1698, 1423, 1246, 1107; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (10 H, br m, Ph x 2), 5.22 (1 H, d, *J* = 12.3 Hz,

C*H*$_2$OCO), 5.10 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 4.89 (1 H, t, *J* = 3.2 Hz, C-2 C*H*), 4.26 (1 H, dd, *J* = 2.7, 13.8 Hz, C-6 C*H*$_2$), 4.07 (1 H, ddq, *J* = 2.7, 4.2, 6.9 Hz, C-5 C*H*), 3.75 (1 H, dd, *J* = 4.2, 11.4 Hz, C-3 C*H*$_2$), 3.73 (1 H, dd, *J* = 4.2, 14.1 Hz, C-6 C*H*$_2$), 3.36 (1 H, dd, *J* = 2.4, 11.7 Hz, C-3 C*H*$_2$), 1.36 (3 H, d, *J* = 6.6 Hz, C*H*$_3$); ^{13}C NMR (125 MHz $CDCl_3$): δ 155.3, 138.5, 136.6, 128.5, 128.4, 128.0, 127.9, 127.6, 127.1, 73.2, 67.1, 64.7, 47.7, 40.7, 15.6; GC/MS (CI) m/z 281 $[M-30]^+$ (20), 253 (11), 207 (54), 135 (100), 107 (50), 91 (37); HRMS calculated for $[M+H]^+$ 312.1596, found 312.1601.



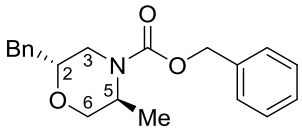
1.5h

Benzyl 2-benzyl-5-methylmorpholine-4-carboxylate (1.5h): Performed Hydroamination Procedure on **1.4h**, (33 mg, 0.1 mmol). TMSOTf (5 µL) was added. Product **1.5h** formed as a colorless oil, (32 mg, 0.096 mmol, 96%). IR (film, cm^{-1}): 2933, 1698, 1497, 1453, 1423, 1350, 1305, 1275, 1245, 1213, 1104, 1048, 740, 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (5 H, br m, Ph of Cbz), 7.21 (5 H, br m, Ph), 5.25 (1 H, d, *J* = 12.0 Hz, C*H*$_2$OCO), 5.14 (1 H, d, *J* = 12.0 Hz, C*H*$_2$OCO), 4.18 (1 H, m, C-5 C*H*), 4.01 (1 H, dd, *J* = 3.8, 11.5 Hz, C-6 C*H*$_2$), 3.98-3.97 (1 H, m, C-2 C*H*), 3.71 (1 H, dd, *J* = 1.8, 13.8 Hz, C-3 C*H*$_2$), 3.41 (1 H, dd, *J* = 2.7, 12.0 Hz, C-6 C*H*$_2$), 3.32 (1 H, dd, *J* = 4.0, 14.0 Hz, C-3 C*H*$_2$), 2.93 (m, 2H, C*H*$_2$Ph), 1.29 (3 H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (125 MHz

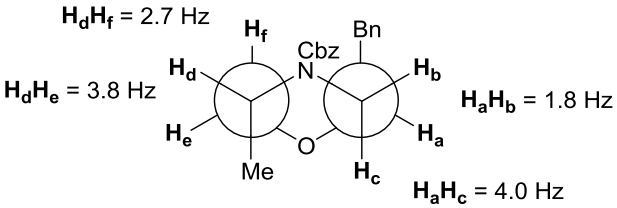
$CDCl_3$): δ 155.7, 137.7, 136.5, 129.3, 128.5, 128.4, 128.1, 128.0, 126.3, 73.7, 67.2, 64.4, 47.3, 39.9, 36.5, 15.2; HRMS calculated for $[M+H]_+$ 326.1748, found 326.1758.

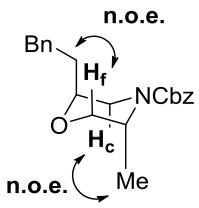
Stereochemistry Assignment of 1.5a-h (2,5-disubstituted morpholine products):

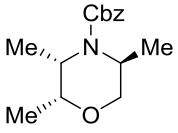
Stereochemistry of the disubstituted morpholine products was assigned by ^{1}H NMR, COSY and NOESY analysis of **1.5h**; the remaining substrates were assigned by analogy to **1.5h**. Stereochemistry was assigned as *trans* based upon ^{1}H NMR vicinal coupling constants of the proton at C-2 (labeled **Ha**) to the two adjacent diastereotopic protons at C-3 (labeled **Hb** (equatorial) and **Hc** (axial)), as well as the proton at C-5 (labeled **Hd**) to the protons at C-6 (labeled **He** (equatorial) and **Hf** (axial)). Four small couplings were observed (J = 1.8, 2.7, 3.8 and 4.0 Hz); the lack of any large coupling constant between **Ha** or **Hd** and their adjacent protons indicates that the compound exists as the *trans* isomer. NOESY data indicated the orientation of the substituents at positions C-2 and C-5 is *trans*-diaxial. NOESY signals were observed between **Hf** and the benzyl group, and **Hc** and the methyl substituent strongly suggesting the benzyl group and the methyl group are both axial. The analogous axial NOESY interactions for the diequatorial product were completely absent (**Hd** and **Hb**; **He** and **Ha**).



1.5h

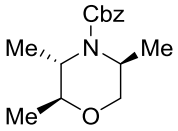






1.5i

Benzyl 2,3,5-trimethylmorpholine-4-carboxylate (1.5i): Performed Hydroamination Procedure on **1.4i**, (26 mg, 0.100 mmol). Product **1.5i** formed as a colorless oil, (23 mg, 88%). IR (film, cm^{-1}): 3360, 2920, 1702, 1452, 1405, 1270, 1122, 1062; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (5 H, br m, Ph), 5.16 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 5.10 (1 H, d, *J* = 12.3 Hz, C*H*$_2$OCO), 3.91 (3 H, m), 3.70 (1 H, m, C-5 C*H*), 3.41 (1 H, m), 1.34 (3 H, d, *J* = 6.3 Hz, C-5 C*H*$_3$), 1.13 (3 H, d, *J* = 6.9 Hz, C*H*$_3$), 1.10 (3 H, d, *J* = 6.3 Hz, C*H*$_3$); ^{13}C NMR (125 MHz $CDCl_3$): δ 156.0, 136.7, 128.4, 128.0, 126.2, 72.0, 70.5 66.9, 52.6, 46.7, 19.2, 18.2, 12.9; GC/MS (CI) m/z 248 $[M\text{-}Me]^+$ (7), 204 (5), 172 (9), 128 (5), 91 (100); HRMS calculated for $[M+H]^+$ 264.1593, found 264.1599.



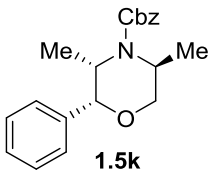
1.5j

2, 3, 5-Trimethylmorpholine-4-carboxylic acid benzyl ester (1.5j): Performed hydroamination procedure on **1.4j**, (53 mg, 0.2 mmol). **1.5j** formed as a colorless oil, (15 mg, 0.056 mmol, 28%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.04 (ddq, *J* = 2.4, 3.0, 6.0 Hz, 1H), 3.69 (dd, *J* = 3.2, 11.4 Hz, 1H), 3.64 (dd, *J* = 2.4, 11.4 Hz, 1H), 3.33 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz $CDCl_3$): δ 156.9, 136.6, 128.4, 128.0, 77.4, 69.5, 66.9, 52.5., 48.8, 19.3, 18.5, 16.5; IR (film, cm^{-1}): 2978, 1708, 1451, 1404, 1287, 1145, 1057; HRMS calculated for $[M+H]^+$ 264.1592, found 264.1600.

Stereochemistry Assignment of 1.5j (2,3,5-trisubstituted morpholine product arising from the *anti*-disubstituted aminoalkene):

Stereochemistry of the trisubstituted morpholine product **1.5j** was verified by literature comparison to ^{1}H NMR data for the unprotected morpholine product.[32] This analysis confirmed that the deprotected substrate **1.5j** adopts a chair conformation, where the methyl substituents at C-2 and C-5 are *cis* to each other. The C-5 proton has no large coupling constant, meaning the C-5 methyl is axial. Deprotection (palladium on carbon, hydrogen, MeOH, room temperature, 12 hours) gave the free amine substrate in nearly

quantitative yield (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (1 H, dd, *J* = 2.6, 11.0 Hz, C-6 CH_2), 3.64 (1 H, dd, *J* = 0.5, 11.0 Hz, C-6 CH_2), 3.23 (2 H, m, C-2 C*H* and C-3 C*H*), 2.84 (1 H, dddq, *J* = 0.6, 1.8, 2.6, 6.6 Hz, C-5 C*H*), 1.21 (3 H, d, *J* = 6.3 Hz, CH_3), 1.10 (3H, d, *J* = 6.6 Hz, C-5 CH_3), 0.99 (3H, d, *J* = 6.3 Hz, CH_3).

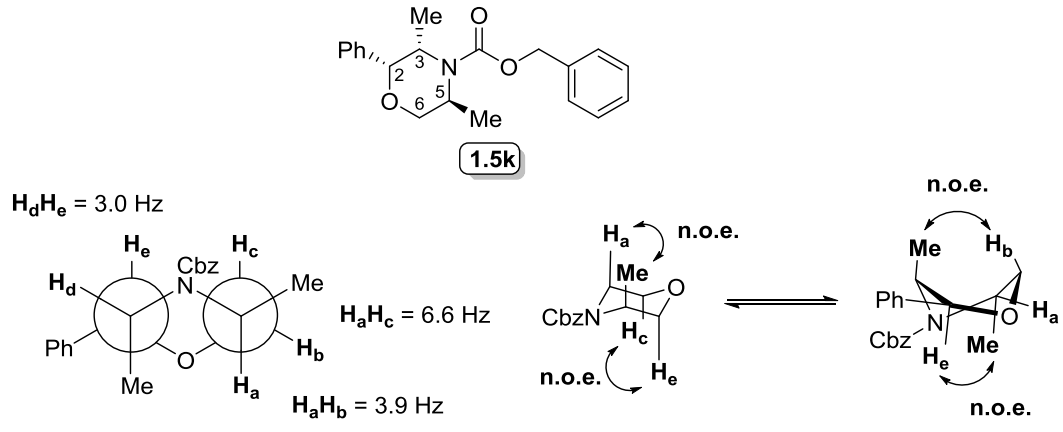


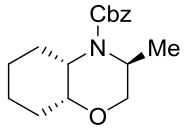
1.5k

(*2R,3R,5R*)-Benzyl 2-phenyl-3,5-dimethylmorpholine-4-carboxylate (1.5k): Performed Hydroamination Procedure on **1.4k**, (33 mg, 0.100 mmol). Product **1.5k** formed as a colorless oil, (22 mg, 0.067 mmol, 67%). IR (film, cm^{-1}): 3032, 2970, 2877, 1704, 1451, 1406, 1270, 1209, 1153, 1107, 1073, 745, 699; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (10 H, br m, Ph x 2), 5.22 (1 H, d, *J* = 12.3 Hz, CH_2OCO), 5.13 (1 H, d, *J* = 12.3 Hz, CH_2OCO), 5.00 (1 H, d, *J* = 3.0 Hz, C-2 C*H*), 4.29 (1 H, dq, *J* = 3.0, 6.9 Hz, C-3 C*H*), 4.17 (1 H, dd, *J* = 3.9, 11.4 Hz, C-6 CH_2), 3.87 (1 H, dquin, *J* = 3.9, 6.6 Hz, C-5 C*H*), 3.63 (1 H, dd, *J* = 6.6, 11.4 Hz, C-6 CH_2), 1.45 (1 H, d, *J* = 6.6 Hz, C-5 CH_3), 0.92 (3 H, d, *J* = 6.9 Hz, C-3 CH_3); ^{13}C NMR (125 MHz $CDCl_3$): δ 156.0, 139.3, 136.6, 128.5, 128.2, 128.0, 127.3, 125.7, 77.8, 67.0, 53.5, 46.9, 29.7, 13.3; HRMS calculated for $[M+H]^+$ 326.1746, found 326.1758.

Stereochemistry Assignment of 1.5i, 1.5k and 1.5n (2,3,5-trisubstituted morpholine products arising from the *syn*-disubstituted aminoalkene):

Stereochemistry of the trisubstituted morpholine product **1.5k** was assigned by ^{1}H NMR, COSY and NOESY analysis; **1.5i, 1.5n** were assigned by analogy to **1.5k**. Stereochemistry of the methyl group at position 5 was assigned as *anti* to the two existing substituents at C-2 and C-3. A small and a medium (J = 3.9, 6.6 Hz) ^{1}H NMR vicinal coupling constant were observed for the proton at C-5 (labeled **Ha**) between the two adjacent diastereotopic protons at C-6 (labeled **Hb** and **Hc**). Due to the uncertainty of the **HcHa** coupling as either large or small (J = 6.6 Hz), the data was inconclusive in assigning one diastereomer over the other. NOESY data confirmed that **1.5k** exists as a combination of two conformations, a twist-boat and a chair. Strong interactions were observed between **Ha** and the methyl group at C-3, and between **Hc** and **H**, which are consistent with a chair structure where the C-5 methyl is *anti* to the C-2 phenyl and the C-3 methyl. NOEs were also observed between the C-5 methyl and **He,** and also the C-3 methyl and **Hb**, which are consistent with a twist-boat.





1.5n

Benzyl 3-methyloctahydrobenzo[1,4]oxazine-4-carboxylate (1.5n): Performed Hydroamination Procedure on **1.4n,** (58 mg, 0.2 mmol). Product **1.5n** formed as a colorless oil, (58 mg, 0.198, 99%). IR (film, cm^{-1}): 3032, 2935, 2863, 1705, 1497, 1448, 1408, 1341, 130, 1278, 1256, 1244, 1130, 1116, 1100, 1070, 957, 769, 751, 697; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.31 (5 H, br m, Ph), 5.17 (1 H, d, *J* = 12.5 Hz, C*H*$_2$OCO), 5.11 (1 H, d, *J* = 12.0 Hz, C*H*$_2$OCO), 4.02 (1 H, dd, *J* = 4.0, 11.5 Hz, C-6 C*H*$_2$), 3.95 (1 H, br m, C-3 C*H*), 3.80 (1 H, m, C-2 C*H*), 3.73 (1 H, m, C-5 C*H*), 3.46 (1 H, dd, *J* = 6.5, 11.5 Hz, C-6 C*H*$_2$), 1.91 (1 H, m, -C*H*$_2$-), 1.74 (2 H, m, -C*H*$_2$-), 1.63 (1 H, m, -C*H*$_2$-), 1.44 (3 H, m, -C*H*$_2$-), 1.34 (3 H, d, *J* = 6.0 Hz, C-5 C*H*$_3$), 1.26 (1 H, m, -C*H*$_2$-); ^{13}C NMR (125 MHz $CDCl_3$): δ 156.0, 136.7, 128.4, 127.9, 127.8, 71.5, 70.2, 66.8, 54.6, 46.7, 31.2, 27.0, 24.5, 19.5; HRMS calculated for $[M+H]^+$ 290.1752, found 290.1748.

1.4.d One-pot synthesis of morpholines

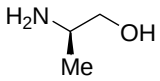
One-pot conditions: In a glove box, silver tetrafluoroborate (20 mol%) was placed in round-bottomed flask with a stir bar. The flask was capped, removed from the glove box, and placed under nitrogen. Dichloromethane was added (0.5-1.0 mL) and the solution cooled to -78 ^{o}C. Allyl alcohol (4 equiv) was slowly added. A solution of aziridine (1

equiv) in dichloromethane was added and the reaction mixture stirred at -78 °C until TLC (80:20, hexanes:ethyl acetate) indicated disappearance of starting material. The reaction was warmed to room temperature.

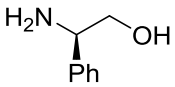
In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (**1.1**) (5 mol %) and magnesium sulfate (1 equiv) were placed in a round-bottomed flask with a stir bar. The flask was capped, removed from the glove box, and placed under nitrogen. Dichloromethane (0.5-1.0 mL) was added and the mixture was stirred for 10 min. The solution of catalyst and drying agent was then transferred to the first reaction flask via cannula. The reaction mixture was then stirred until TLC indicated disappearance of starting material. The reaction was filtered through a plug of celite, concentrated, and the crude residue was purified via column chromatography (90:10 or 80:20, hexanes:ethyl acetate) to give the product.

1.4.e Synthesis of chiral reagents

Procedure for the reduction of the amino acids: Amino acid (1 equiv.) was added to a solution of lithium aluminum hydride (2 equiv.) in THF (0.6 M) at 0 ˚C. The reaction was mixture was then heated to reflux and stirred overnight. The reaction mixture was cooled to room temperature and slowly quenched by drop wise addition of a minimal amount of 6M NaOH, then filtered, through celite while washing with THF, and the filtrate concentrated to give the crude product, which was recrystallized with toluene to afford the amino-alcohol.



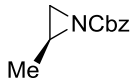
(*L*)-alaninol: Performed the reduction procedure with (*L*)-alanine (3.56 g, 40 mmol, 1 equiv) to afford the aminoalcohol (2.45 g, 82%), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (1 H, m, C*H*$_2$), 3.24 (1 H, m, C*H*$_2$), 3.02 (1 H, m, C*H*), 2.04 (3 H, br s, N*H*$_2$ and O*H*), 1.06 (3 H, d, *J* = 6.3 Hz, C*H*$_3$).



(*L*)-phenyl glycine: Performed the reduction procedure with (*L*)-alanine (6.05 g, 40 mmol, 1 equiv) to afford the aminoalcohol (4.38 g, 80%), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (5 H, m, Ar), 3.97 (1 H, dd, *J* = 4.2, 8.1 Hz, NC*H*), 3.66 (I H, dd, *J* = 4.5, 10.8 Hz, C*H*$_2$O), 3.47 (1 H, dd, *J* = 8.4, 10.8 Hz, C*H*$_2$O), 2.01 (3 H, br s, N*H*$_2$ and O*H*).

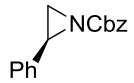
Procedure for the formation of the aziridines: The unprotected aziridines were prepared according to literature procedure,[33] and the crude aziridine product was then protected. Triethylamine (2 equiv.) was added to a solution of the aziridine in toluene (0.3 M) at 0 ˚C. Benzyl chloroformate (1.1 equiv.) was added drop wise, and the mixture warmed to room temperature over 4 hours. The reaction mixture was quenched with

water, the resulting layers separated, and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (95:5, Hex:EA; silica loaded with 2:93:5, NEt_3:Hex:EA solution) to give the purified Cbz-protected aziridine.



1.3b'

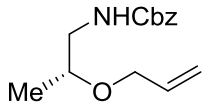
(*S*)-Benzyl-2-methylaziridine-1-carboxylate (1.3b'): The aziridine **1.3b'** was prepared according to the aziridine formation procedure to give the Cbz-protected aziridine (0.158 g, 83%). Spectra matched values provided for the racemic-compound **1.3b.** $[\alpha]_D^{22}$ +28.1 (*c* 0.5 in CH_2Cl_2). HPLC: analysis DIACEL CHIRALPAK OD-H column (hexanes/isopropanol 90/10, flow rate 1 mL/min, 215 nm) eluted as two peaks, t_R = 6.3 min (major; area = 99.55) and 7.1 min (minor; area = 0.45), >99% ee.



1.3g'

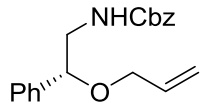
(*S*)-Benzyl-2-phenylaziridine-1-carboxylate (1.3g'): The aziridine **1.3g'** was prepared according to the aziridine formation procedure to give the Cbz-protected aziridine (0.131 g, 52%). Spectra matched values provided for the racemic-compound **1.3g.** $[\alpha]_D^{22}$ -123.5 (*c* 0.5 in CH_2Cl_2). HPLC: analysis DIACEL CHIRALPAK OD-H column

(hexanes/isopropanol 90/10, flow rate 1 mL/min, 215 nm) eluted as two peaks, t_R = 6.3 min (major; area = 99.35) and 7.1 min (minor; area = 0.65), 98% ee.



1.4b'

Benzyl 2-(allyloxy)propylcarbamate (1.4b'): Performed **General Procedure C** provided (in **Section 1.4.b**) on (*S*)-benzyl-2-methylaziridine-1-carboxylate **1.3b'** (0.044 g, 0.2 mmol). Product formed as pale yellow oil, (0.038 g, 71%). Spectra matched values provided for the racemic-compound **1.4b.** $[\alpha]_D^{22}$ +29.0 (*c* 0.5 in CH_2Cl_2). HPLC: analysis DIACEL CHIRALPAK AD-H column (hexanes/isopropanol 98/2, flow rate 1 mL/min, 215 nm) eluted as two peaks, t_R = 17.0 min (minor) and 18.2 min (major), >99% ee.



1.4g'

Benzyl 2-(allyloxy)2-phenylethylcarbamate (1.4g'): Performed **General Procedure C** provided (in **Section 1.4.b**) on (*S*)-benzyl-2-methylaziridine-1-carboxylate **1.3g'** (0.038 g, 0.2 mmol). Product formed as pale yellow oil, (0.042 g, 67%). Spectra matched values provided for the racemic-compound **1.4g.** $[\alpha]_D^{22}$ +4.5 (*c* 0.5 in CH_2Cl_2). HPLC: analysis

DIACEL CHIRALPAK AD-H column (hexanes/isopropanol 98/2, flow rate 1 mL/min, 215 nm) eluted as two peaks, t_R = 17.3 min (minor; area = 18.53) and 18.2 min (major; area = 81.47), 88% ee.

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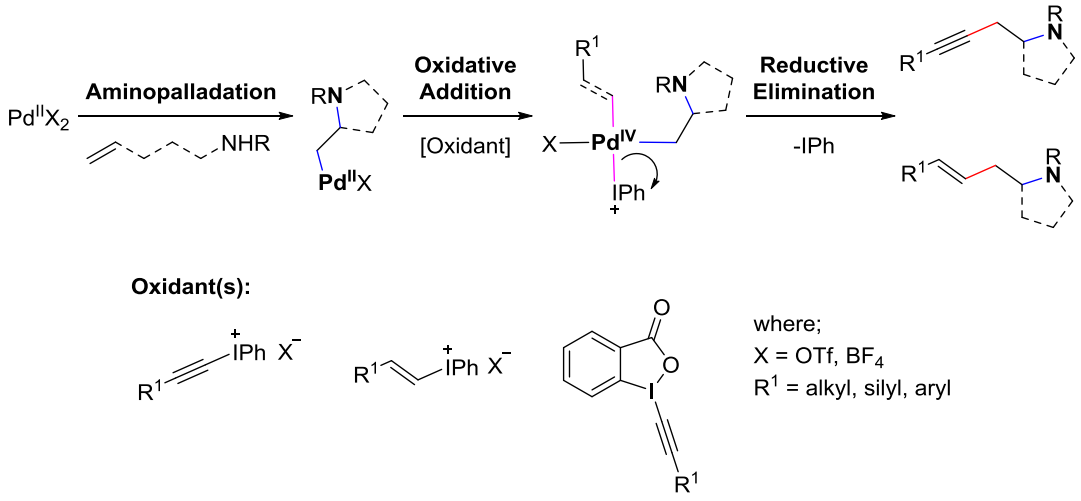
Chapter 2

PALLADIUM-CATALYZED CARBOAMINATION USING HYPERVALENT IODINE(III) REAGENTS

Section 1. Introduction

Efficient methods for the formation of heterocycles, such as pyrrolidines, which are frequently-encountered substructures in biologically-active molecules, continue to be valued by synthetic chemists. Such compounds are known to have medicinal and therapeutic properties and find use in anti-fungal, anti-viral, and anti-bacterial applications, as well as in enzyme inhibition.[1] Not surprisingly, many of these valuable small molecules are natural products; consequently, the total synthesis of natural products containing pyrrolidine functionality continues to be vigorously pursued.[2] Additionally, pyrrolidines have found applications in organic chemistry as chiral ligands,[3] chiral auxiliaries,[4] and organocatalysts.[5] As a result of their medicinal value, utility, and frequency in complex natural products, a number of synthetic routes to the pyrrolidine scaffold have been devised,[6] including substitution reactions, cycloadditions,[7] rearrangements,[8] as well as transition metal-mediated cyclizations,[9] and halocyclizations.[10] In particular, the transition metal-catalyzed aminoalkene cyclization reaction [11] is a noteworthy approach as it allows simultaneous formation of two new bonds whilst imparting all the advantages that a metal catalyst may offer, such as excellent stereocontrol and mild reaction conditions.

Scheme 2.1. Proposed palladium(IV) carboamination pathway

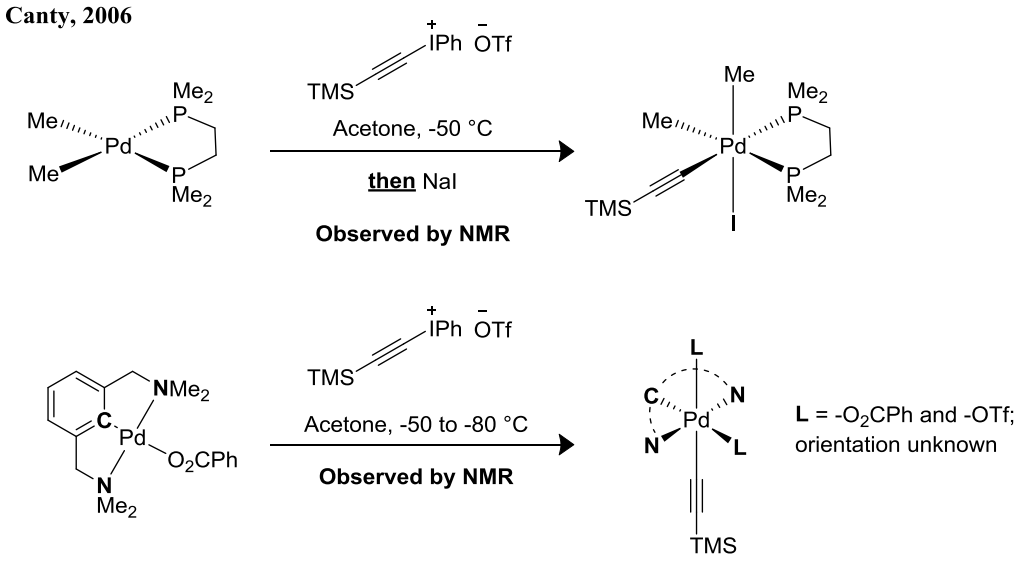


While various transition metal-catalyzed aminoalkene cyclization reactions are known, such as hydroamination, diamination, and alkoxyamination, the products of such transformations generally do not contain a nonaromatic alkene or an alkyne, which are useful functional groups. Traditionally, the synthesis of a C(sp^3)—C(sp) bond would utilize a nucleophilic source of alkyne obtained by deprotonation of a terminal acetylenic proton. This approach is highly effective as evidenced by the popularity of the Sonogashira reaction.[12] However, a transition metal-catalyzed aminoalkenylation or aminoalkynylation of an alkene, in contrast, would require an umpolung of reactivity with respect to the alkene or alkyne reaction partner. Such reactions of electrophilic alkyne sources with nucleophilic partners are underdeveloped in comparison, but a few useful reagents have emerged in the sphere of organometallic chemistry, such as sulfone-substituted acetylenes, halogenoacetylenes, and alkynyliodonium salts. [13]

To this end, we hypothesized that alkenyl or alkynyl iodine(III) reagents may be used with a transition metal, such as palladium, to achieve the aminoalkynylation or aminoalkenylation of alkenes (Scheme 2.1). It was anticipated that the use of an appropriate palladium(II) catalyst could enable the system to operate through a palladium(IV) intermediate, achieved by oxidative addition of the Pd(II) catalyst to the alkynyl- or alkenyl-iodine bond. This octahedral complex would then reductively eliminate to form the desired product and regenerate the active catalyst. Crucial to this proposal is the requirement that oxidation of the metal center to palladium(IV) must occur.

While the number of reactions operating under a Pd(II)/(IV) catalytic regime is considerably lower than those using the Pd(0)/(II) redox cycle, many of these transformations are enabled by the use of hypervalent iodine(III) reagents. In particular, alkynyl(aryl)iodonium salts are extremely reactive and electrophilic reagents. First reported by Koser in 1981, these iodine(III) compounds adopt a bent or T-shaped geometry, where there exists a weak, highly polarized 3-center-4-electron bond between the iodine and its apical ligands.[14] As a consequence of the outstanding leaving group ability of the aryliodonium group, these salts have been used as efficient alkynylating reagents in a number of reactions, such as the *alpha*-alkynylation of enolates.[15]

Scheme 2.2. Oxidative Addition of Phenyl(Alkynyl)Iodonium Reagents by Palladium



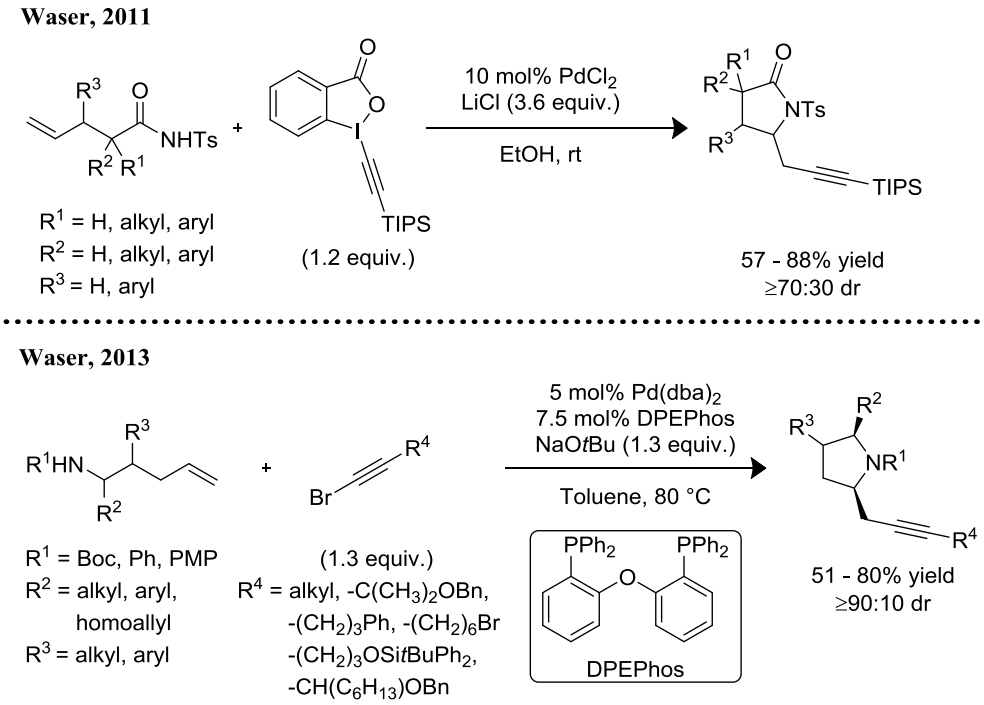
With respect to their applications in Pd(II)/(IV) catalysis, several reports have shown that alkynyl(aryl)iodonium salts are effective in promoting oxidation of Pd(II) to Pd(IV). Canty has reported octahedral palladium(IV) intermediates resulting from oxidative addition into an alkynyliodonium bond by NMR at low temperatures, as well as crystal structures of the analogous platinum systems (Scheme 2.2).[16] Furthermore, several groups have reported palladium(IV) species which have been achieved by oxidation of Pd(II) with hypervalent iodine(III) reagents. van Koten reported the oxidation of platinum and palladium pincer complexes with $PhICl_2$.[17] Sanford and coworkers achieved reductive elimination from a palladium(IV) complex generated by the delivery of "$^{+}CF_3$" to the metal by Togni's reagent,[18] as well as a number of other iodine(III) reagents such as $PhICl_2$, $[Ar_2I]BF_4$, and iodine(III) benzoates.[19] Szabo and coworkers reported the

arylation of allylic acetates with di(aryl)iodonium reagents, which was inferred to go through a Pd(IV) intermediate.[20]

Despite their interesting reactivity and utility in oxidation of Pd(II) complexes, historically the application of alkynyl(aryl)iodonium salts has been limited by thermal instability and a propensity to generate carbenes, which then undergo non-specific side reactions. However, their decomposition can be attenuated by judicious selection of the iodonium counterion or increasing the steric bulk of the acetylene substituent.[26] Zhdankin has shown that complexation of iodonium salts to crown ethers can also stabilize these reagents, allowing their handling in air at room temperature. Another successful technique has been the synthesis of ethynylbenziodoxolone reagents (EBX-reagents) that incorporate the iodine moiety into a neutral 5-membered heterocyclic ring, thereby significantly enhancing the stability of these reagents.[21]

Prior to beginning any of our own investigations, Waser and coworkers were the first to report the oxyalkynylation[22] of unactivated alkene substrates using the TIPS-EBX reagent. During the course of our initial investigations, they reported the first aminoalkynylation[23] of unactivated alkene substrates using the TIPS-EBX oxidant with palladium(II) chloride (Scheme 2.3). Lactones and lactams were formed in good yields, and the reaction was tolerant of β-hydrogens in the final product, as well as functional groups such as bromo, suggesting it may be orthogonal to Pd(0) processes, highlighting what is often an advantage of palladium(II)/(IV) chemistry. Unfortunately, the range of nucleophiles was limited, and neither system could be amended to the direct synthesis of

Scheme 2.3. Aminoalkynylation of unactivated alkenes



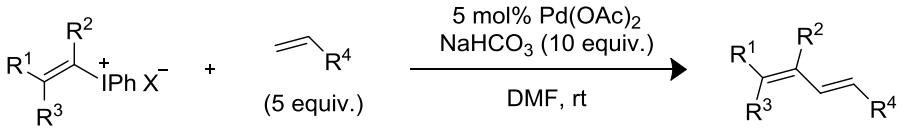
either tetrahydrofurans or pyrrolidines, necessitating a further reduction step. Furthermore, the TIPS-substituted acetylene was a critical element, as substitution to even a phenyl or the less sterically-hindered TMS group resulted in a reduced yield, making further modification of the pendant alkyne functionality less convenient.

In 2013, the Waser group extended their chemistry to include differentially-substituted acetylenes through the use of a Pd(0) precatalyst, a phosphine ligand, and by switching to bromoalkynes as the electrophilic alkyne source (Scheme 2.3).[24]

Critical to the success of their system was the use of the DPEPhos ligand. *In situ* hydrogenation using Pd/C in one pot gave the alkyl-substituted pyrrolidine and

Scheme 2.4. Synthesis of dienes using Pd (0) and alkenyl(aryl)iodonium salts

Moriarty, 1991



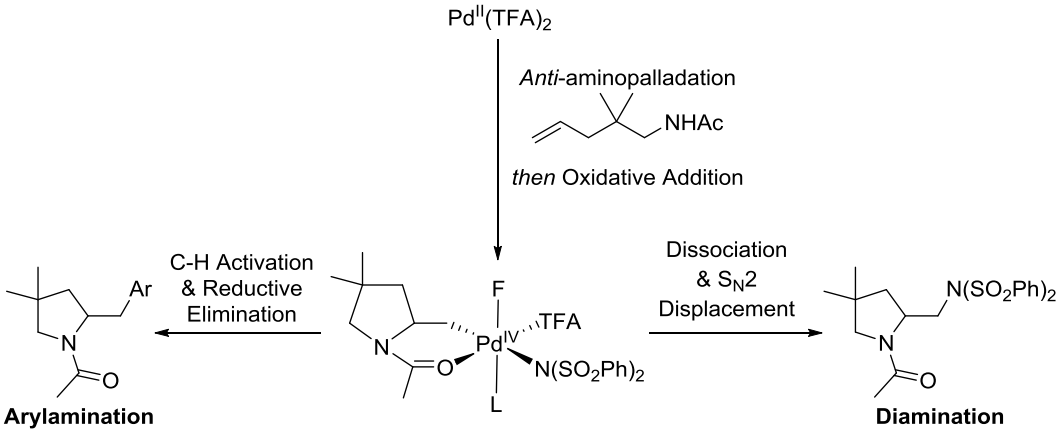
R^1 = Ph, 1-cyclohexenyl, OTs, *n*Bu
R^2 = H
R^3 = H, *n*Bu, OTs
X = BF_4, OTs

60 - 85% yield
R^4 = $COCH_3$, Ph, CHO, CO_2CH_3

tetrahydrofuran products, although introduction of substitution to the heterocyclic backbones generally resulted in decreased yields and examples of functional groups were limited to alkyl, aryl, or ether substituents.

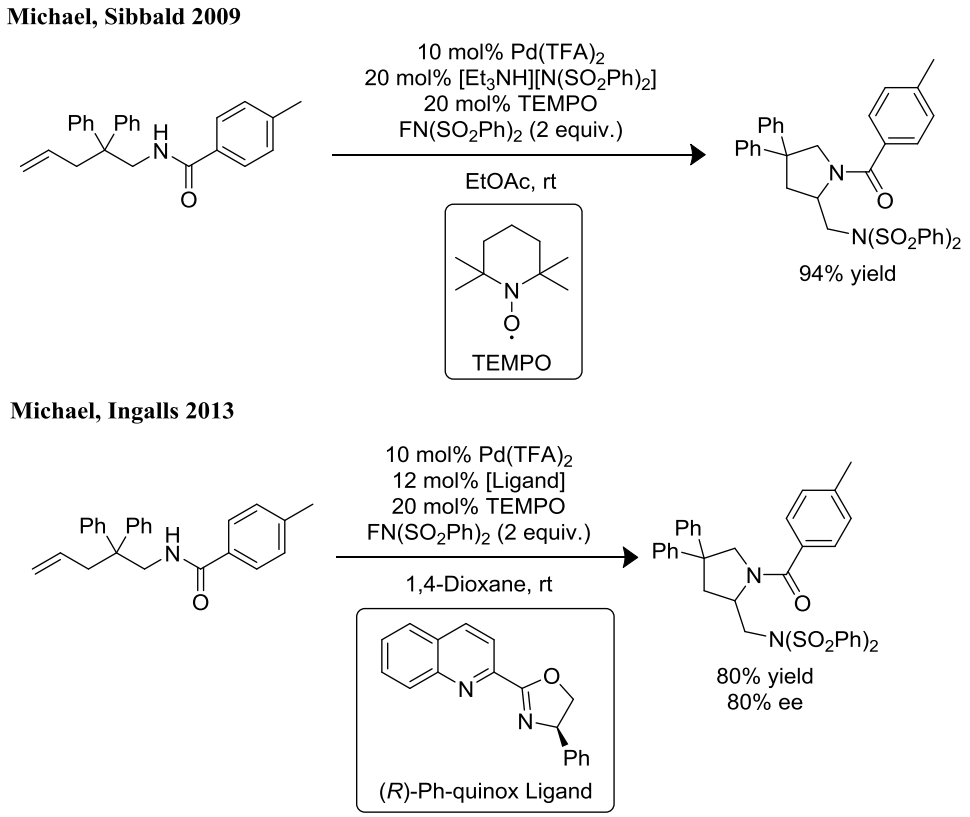
To date, the analogous transformations of oxyalkenylation or aminoalkenylation with alkenyl(aryl)iodonium reagents remain undeveloped. Use of these reagents in Heck-type coupling processes with palladium was first reported in 1991 by Moriarty and coworkers (Scheme 2.4).[25] Further reactivity with organometallic species has been reported in the synthesis of fluoroalkenes,[26] or substituted alkenes.[27] These reagents have been used successfully under Stille, Heck and Sonogashira type conditions demonstrating that they can oxidize palladium(0).[28] Similar to the alkynyl(aryl)iodonium reagents, these reagents are prone to decomposition via deprotonation of the α-hydrogen of the iodonium leaving group and generation of carbene intermediates.[29]

Scheme 2.5. Proposed palladium(IV) species in the aryl- and diamination reactions



Our own lab has been interested in exploring the application of Pd(II)/(IV) catalysis to effect aminofunctionalization of double bonds. Through mechanistic studies of the palladium-catalyzed alkene diamination and arylamination reactions developed by us, we have proposed that a common Pd(IV) intermediate is formed in both reactions (Scheme 2.5). Through the choice of appropriate reagents, this intermediate can undergo divergent reactivity to afford either the arylamination or diamination product. Specifically, an *intramolecular* arylamination reaction could be achieved by conducting the reaction in an aromatic solvent, such as toluene. When a nonaromatic solvent was used, the benzenesulfonimide anion of the oxidant (*N*-fluorobenzenesulfonimide) incorporated, resulting in alkene diamination[30] (Scheme 2.6).[31] An enantioselective variant of the diamination reaction was subsequently developed featuring the phenyl-substituted quinolineoxazoline ligand (Scheme 2.6). Inclusion of 12 mol% of the chiral diamine nitrogen ligand gave excellent

Scheme 2.6. Palladium-Catalyzed Diamination Utilizing NFBS



enantioselectivities for a number of geminally substituted aminoalkene substrates with a variety of nitrogen protecting groups.[32]

In view of the studies highlighting the capability of iodine(III) reagents to effectively oxidize Pd(II) to Pd(IV), we thought that we could develop an aminoalkynylation reaction utilizing the conditions developed in our laboratory for operating under a Pd (II)/(IV) catalytic cycle. Considering the mechanism of the diamination/arylamination reaction, inclusion of a sufficiently reactive oxidant in place of the NFBS should promote the same oxidative addition step and subsequent C-C bond

formation. As previously noted, a key advantage of the (alkynyl)phenyliodonium salts is the excellent leaving group ability of iodobenzene. In theory, this would not only aid in the reductive elimination step by forming a short-lived Pd—iodobenzene bond—thus creating a 5-coordinate species prone to reductive elimination—but also assist in the initial oxidative addition of the alkynyl—iodine bond itself. Importantly, we were also interested in the potential application of such conditions in the comparably-underdeveloped alkene aminoalkenylation, which would provide the sought-after pyrrolidine scaffold with pendant alkenyl instead of alkynyl functionality.[33]

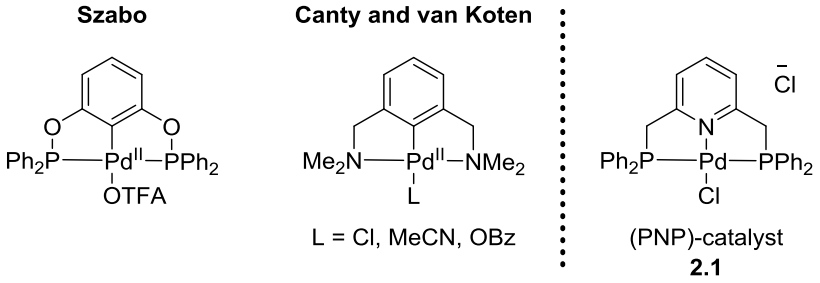
Initial studies will focus on the amino alkynylation transformation. We anticipate it will be more well-behaved and though the strategy of using a hypervalent iodine(III) alkyne source with Pd(II)/(IV) has been reported in the synthesis of beta-lactams, it has not been reported in the the direct synthesis of pyrrolidines. As a closely related analogue, this will be a good place to start studying the reactivity of these types of systems. Furthermore, as an enantioselective variant of the diamination has been developed, we propose that the same ligand class could promote an asymmetric variant of the mechanistically-similar carboamination. In this chapter, progress toward these goals is discussed.

Section 2. Results and Discussion

2.2.a Initial Screening

Originally it was envisioned that use of a tridentate ligand could be used to achieve this transformation. Canty and van Koten have demonstrated the feasibility of this step using a tridentate NCN system, while Szabo utilized a POCOP ligand with diaryliodonium salts

Figure 2.1. Pincer complexes



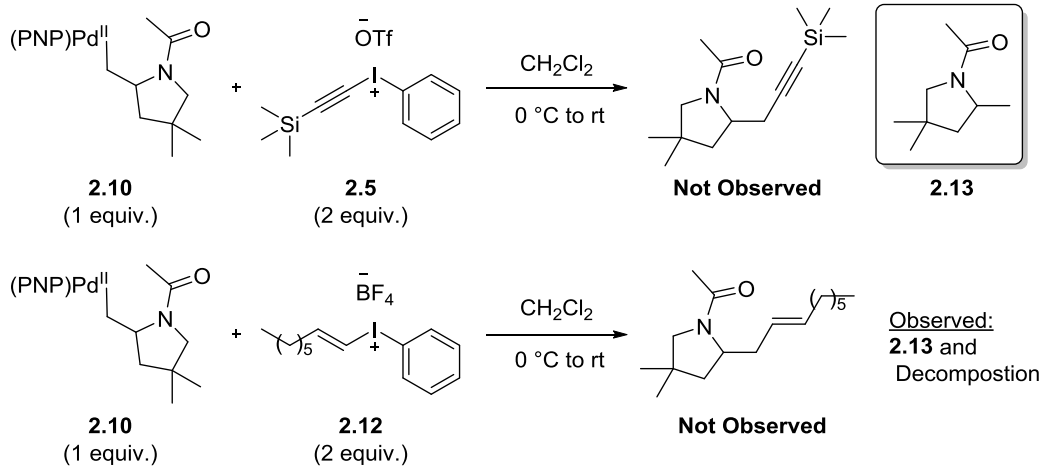
(Figure 2.1). Notably, by ^{31}P NMR, Szabo and coworkers observed no oxidation of the phosphine ligands under the reaction conditions.

We began our studies using the PNP-ligated tridentate palladium catalyst, originally developed in our laboratory for the intramolecular aminoalkene hydroamination reaction. In initial catalytic reactions of the aminoalkene substrate (benzyl 2,2-dimethylpent-4-enylcarbamate, **2.2**) with dodecynyl- (**2.3**), or hexynyl- (**2.4**), or trimethylsilyl-derived alkynyl(phenyl)iodonium reagents (**2.5**) (**2.2-2.5**; see Section 2.4 Experimental), no product was detected. Analysis of the reaction mixtures indicated the starting aminoalkene underwent hydroamination (**2.6**) or isomerization (**2.7**) in most cases. Furthermore, reaction with *tert*-butyl- (**2.8**), hexynyl- (**2.9**), or trimethylsilyl-

(**2.10**) substituted EBX reagents (**2.6-2.10**; see Section 2.4 Experimental), which are more stable, showed no desired reactivity. No product was detected when other palladium (II) salts such as $Pd(OAc)_2$, or $Pd(TFA)_2$ were used in the absence of ligand either.

We next examined stoichiometric reactions (Scheme 2.7) of the isolated PNP palladium alkyl complex (**2.11**), which is the intermediate formed after alkene insertion and cyclization, with both an alkynyl- (**2.5**) and alkenyl- (**2.12)** (phenyl)iodonium reagent. In either case, we could not observe the desired products by ^{1}H-NMR suggesting the oxidation step may be problematic in the PNP-system.

Scheme 2.7. Stoichiometric reactions with the acetamide-Pd-PNP-alkyl complex



When using the tetrafluoroborate derived alkynyl(phenyl)iodonium reagents, such as dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (**2.3**), alkyne hydration (e.g. 2-dodecanone) was observed by NMR as a major side product, suggesting it either undergoes decomposition or participates in other undesirable side reactions. As previously mentioned, the thermal instability of these reagents at ambient temperature has

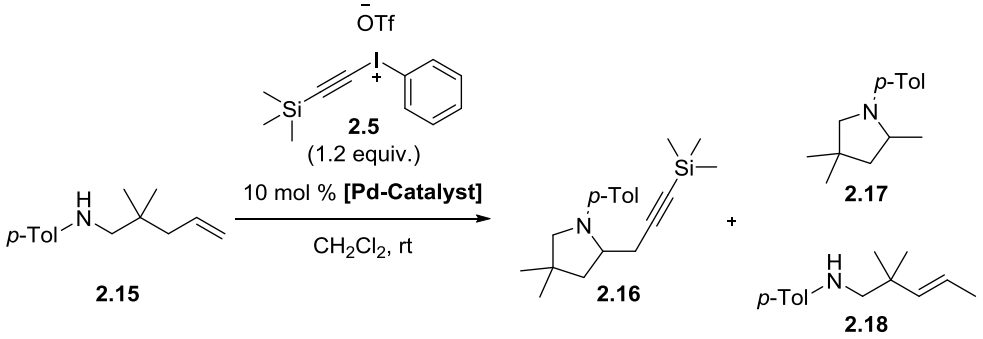
been documented. Stabilization of these reagents has been achieved by complexation of the iodine to 18-crown-6 ether.[34] We employed this technique by complexing dodec-1-ynyl(phenyl)iodonium tetrafluoroborate to 18-C-6 to afford a crystalline complex (**2.14**; see Section 2.4 Experimental) that could be handled at room temperature. Unfortunately, reaction of this temperature-stable variant **2.14** was again unsuccessful, and no aminoalkynylation was observed.

2.2.b Screening using [(trimethylsilyl)ethynyl]phenyliodonium triflate

Encouraged by the results of Canty and coworkers, who observed oxidative addition of [(trimethylsilyl)ethynyl]phenyliodonium triflate (**2.5**) by their NCN-palladium and platinum complexes, we decided to screen this reagent **2.5** with a few catalysts featuring tridentate ligands as well as different Pd(II) sources. Although most catalysts did not produce any detectable product (Table 2.1, Entries 2-5), the use of a tridentate *N*-heterocyclic carbene complex **2.19** (Table 2.1, Entry 1) did provide some product **2.16**, which was encouraging, though the yield was equivalent to the catalyst loading suggesting catalyst turnover may be an issue.

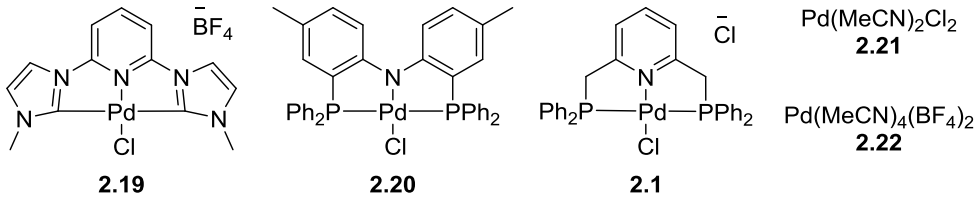
We next examined nitrogen-based ligand systems in an effort to identify conditions capable of promoting alkene aminoalkynylation. In particular, rigid bipyridine ligands such 2,2'-bipyridyl have been reported by Sanford and others to be effective at stabilizing palladium(IV) intermediates. Diamine ligands have also been used with palladium(II)/(IV) processes in our laboratory, such as the use of (*R*)-Ph-quinox ligand in the enantioselective alkene diamination reaction. We investigated a panel of bi- and

Table 2.1. Aminoalkynylation catalyst Screen



Entry	**Catalyst**	Product	Yield[a] (%)
1	**2.19**	**2.16**	10 [b]
2	**2.20** [c]	---	No reaction
3	**2.1** [d]	**2.17**	---
4	**2.21**	**2.18**	---
5	**2.22**	**2.18**	---

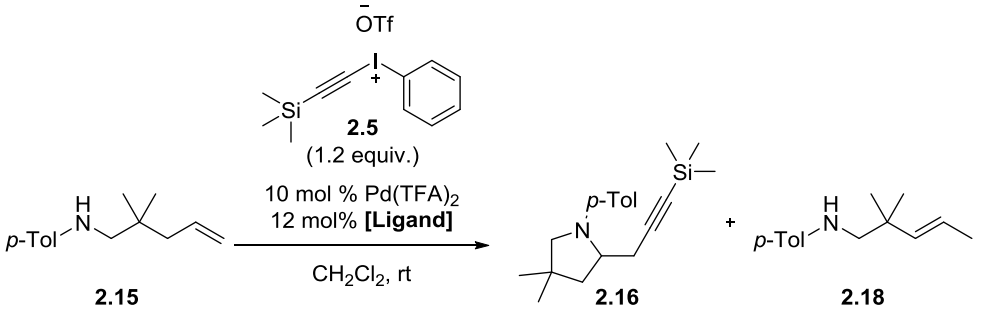
Catalysts =



[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [b] Silyl group was deprotected under the reaction conditions. [c] 10 mol % $AgBF_4$ added to the reaction. [d] 20 mol % $AgBF_4$ was added to the reaction.

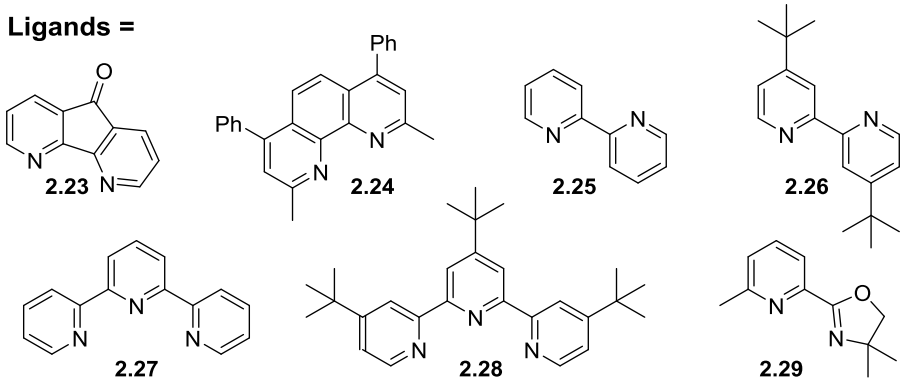
tridentate nitrogen ligands, and were pleased to discover that the 4,5-diazafluoren-9-one **2.23** (Table 2.2, Entry 2) ligand gave 56% yield of the desired product **2.16**. The oxazoline ligand **2.29** (Table 2.2, Entry 8) also gave 10% of product **2.16**. Similar to the catalysts screened in Table 2.1, major side products observed in all other cases (Table 2.2, Entries 1, 3-6) were combinations of isomerization and starting material, with the

Table 2.2. Aminoalkynylation ligand screen using TMS-alkynyl hypervalent Iodine reagent



Entry	**Ligand**	Product	Yield[a] (%)
1	**none**	**2.18**	---
2	**2.23**	**2.16**	56[b]
3	**2.24**	**2.18**	---
4	**2.25**	**2.18**	---
5	**2.26**	**2.18**	---
6	**2.27**	**2.18**	---
7	**2.28**	**---**	Decomposition
8	**2.29**	**2.16**	10

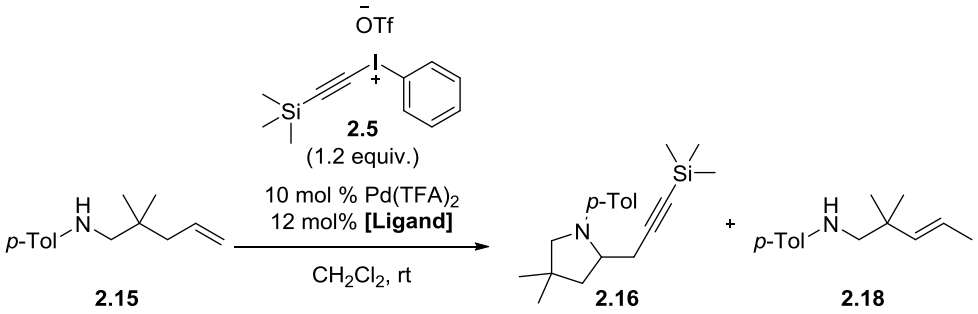
Ligands =



[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [b] Isolated yield.

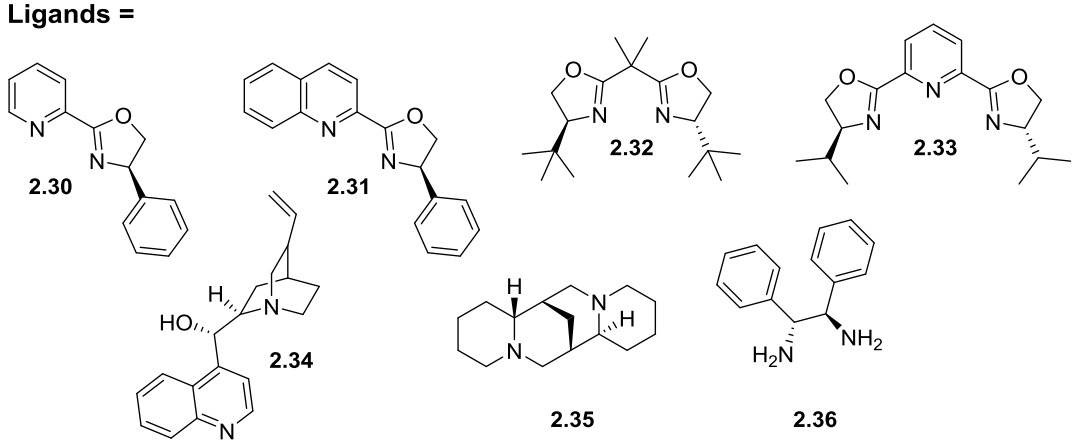
exception of 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (Table 2.2, Entry 8) which gave a complex mixture.

Table 2.3. Screen of chiral ligands



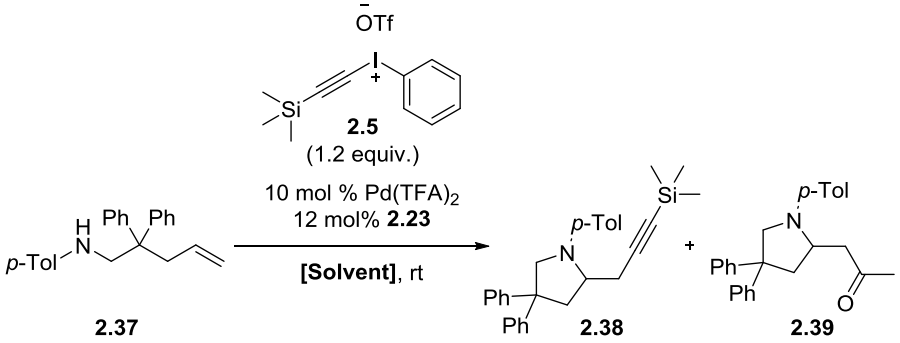
Entry	**Ligand**	Product	Yield[a] (%)
1	**2.30**	**2.16**	10
2	**2.31**	**2.16**	52[b] (23% ee[c])
3	**2.32**	**2.18**	---
4	**2.33**	**2.16**	15[d]
5	**2.34**	**2.18**	---
6	**2.35**	**2.18**	---
7	**2.36**	**2.18**	---

Ligands =



[a] Yield determined by ^{1}H-NMR using 1,3-dinitrobenzene as internal standard. [b] Isolated yield. [c] Enantioselectivity determined by chiral HPLC using an AD-H column, 10% IPA/Hexane, 1 mL/min. [d] Silyl group was deprotected *in situ*.

Table 2.4. Results of the Solvent Screen



Entry	**Solvent (0.1 M)**	Yield[a,b] **2.38 : 2.39** (%)
1	Dichloromethane	56 : N.D.
2	Ethanol	35 : N.D.
3	Ethyl Acetate	58 : 17
4	Dimethylsulfoxide	24 : N.D.
5	Tetrahydrofuran	36 : N.D.
6	Dioxane	32 : N.D.

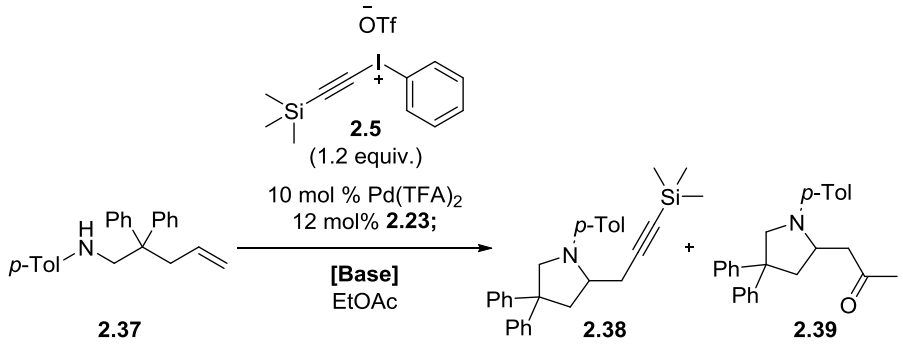
[a] Yields determined by ^{1}H-NMR using 1,3-dinitrobenzene as an internal standard. [b] N.D. = Not Detected.

In light of the modest observed yield when using the oxazoline ligand **2.29**, we investigated a number of chiral diamine ligands in an effort to determine whether an asymmetric aminoalkynylation reaction might be developed. As noted in Table 2.3, use of the oxazoline-based ligands gave some product (Table 2.3, Entries 1,2,4), but the (*R*)-phenyl-quinox ligand **2.31** gave the highest yield when used. Unfortunately, the enantioselectivity was quite low, and so further investigation was not undertaken.

2.2.c Reaction Optimization with [(trimethylsilyl)ethynyl]phenyliodonium triflate

With these initial results, reaction optimization using iodonium reagent **2.5** was undertaken using ligand **2.23**, 4,5-diazafluoren-9-one (Table 2.4). A short solvent screen

Table 2.5. Buffering the Reaction Mixture with Base



Entry	**Base**	**Equiv. of Base**	Yield[a,b] **2.16 : 2.37** (%)
1	$KHCO_3$	1.2	30 : N.D.
2	$KHCO_3$	1.2	25[b]: N.D.
3	$(i\text{-Pr})_2NEt$	1.3	No reaction
4	DBU	1.3	No reaction
5	TMP	1.3	19 : N.D.
6	2,6-Lutidine	1.3	No reaction

[a] Yields determined by ^{1}H-NMR using 1,3-dinitrobenzene as an internal standard. [b] Reaction run at 40 °C. [b] N.D. = Not Detected.

revealed ethyl acetate to be the best choice (Table 2.4, Entry 3), however alkyne hydration (**2.39**) was observed (17%). Since formation of compound **2.39** is presumably acid-catalyzed, we decided to investigate basic additives in an attempt to suppress alkyne hydration.

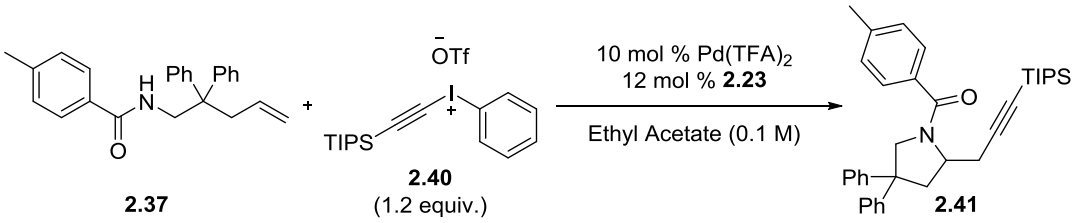
Attempts to attenuate the acidity of the reaction medium through buffering with base were made (Table 2.5). Although compound **2.39** was not observed, the presence of either organic or inorganic bases greatly inhibited the reaction. Inclusion of DBU, Hünig's base, or 2,6-lutidine (Table 2.5, Entries 3,4,6) resulted in no conversion of the

starting material, while the use of potassium bicarbonate or 2,2,6,6-tetramethylpiperidine led to greatly diminished yields of **2.38** (Table 2.5, Entries 1,2,6).

2.2.d Reaction Optimization using [(triisopropylsilyl)ethynyl]phenyliodonium triflate

Since we observed the decomposition of our silylated alkyne under the reaction conditions described in Table 2.4, and inclusion of base inhibited the reaction, we explored the use of the more robust and less acid-labile TIPS group (**2.40**; Table 2.6). We immediately observed an increase in yield of our desired product under the previously optimized conditions to 73% (Table 2.6, Entry 4). The reaction was quite sensitive to time; allowing it to run longer than 40-45 min resulted in both deprotection of the silyl group or hydration of the alkyne, under the reaction conditions (Table 2.6, Entries 1,3,4).

Table 2.6. Optimization with the alkynyl TIPS-reagent

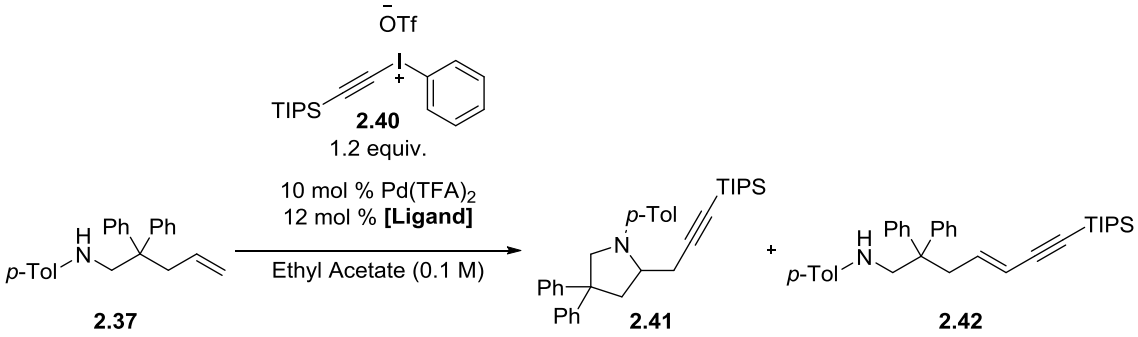


2.37 **2.40** (1.2 equiv.) **2.41**

Entry	**Conditions**	Yield[a] (%)
1	rt; 24 hours	33
2	0 °C (6 hours) then rt; 24 hours	44
3	rt; 1 hour	71
4	rt; 45 minutes	73
5	0.05 M Ethyl Acetate, rt; 45 minutes	51

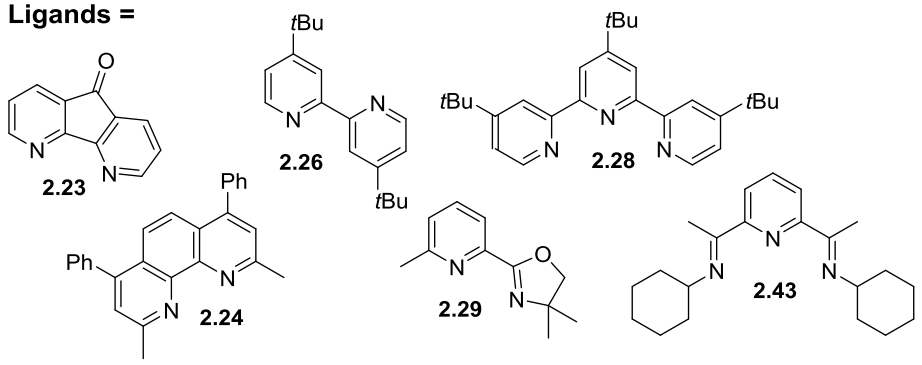
[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard.

Table 2.7. Screen of di- and tridentate nitrogen ligands using the TIPS alkynyl reagent



Entry	**Ligand**	Yield[a,b] **2.41 : 2.42** (%)
1	**2.23**	73 : N.D.
2	**2.24**	29:25
3	**2.26**	16:27
4	**2.28**	No reaction
5	**2.29**	30:12
6	**2.43**	N.D. : 30

Ligands =

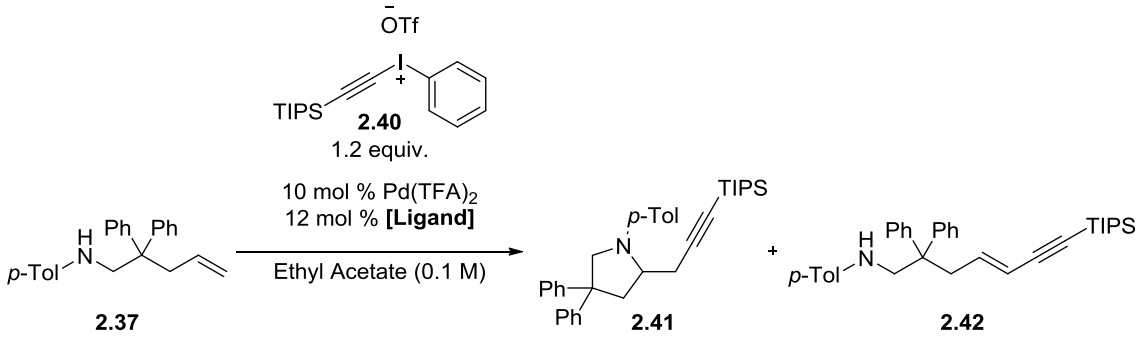


[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard.

[b] N.D. = Not detected.

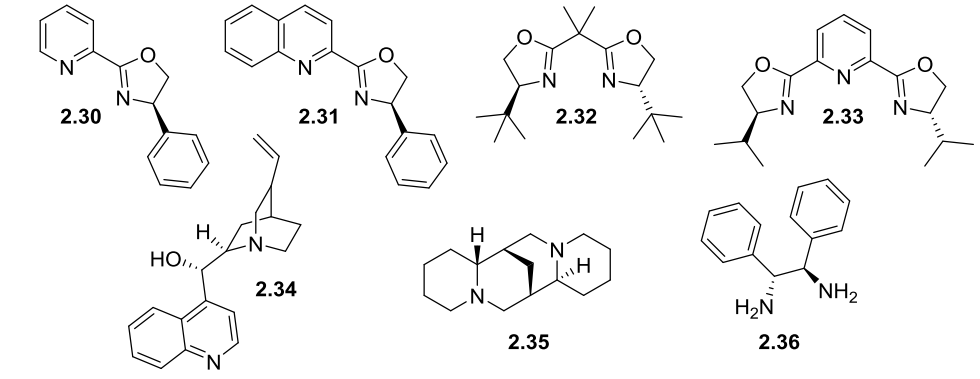
With this new alkynyliodonium reagent **2.40**, the ligand screens described in Tables 2.2 and 2.3 were repeated. Interestingly, while investigating achiral bi- and tridentate nitrogen ligands (Schemes 2.7, 2.8), a new product emerged. Spectroscopic

Table 2.8. Screen of chiral nitrogen ligands using the TIPS alkynyl reagent



Entry	**Ligand**	Yield[a] **2.41 : 2.42** (%)
1	**2.30**	36:trace
2	**2.31**	55[b] (7 % ee[c]):10
3	**2.32**	0 : 38
4	**2.33**	0 : 36
5	**2.34**	0 : 62
6	**2.35**	Not Detected
7	**2.36**	0 : 23

Ligands =



[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard. [b] Isolated yield. [C] Enantioselectivity determined by chiral HPLC using an AD-H chiral column pack, 10% IPA/Hexane, 1 mL/min.

analysis confirmed the formation of the enyne product **2.42**. Use of 4,5-diazafluoren-9-one (**2.23)** gave the best conversion to the aminoalkynylation product **2.41** (Table 2.7,

Entry 1), while many of the ligands gave a mixture of **2.41** and enyne product **2.42** (Table 2.7, Entries 2-4). The terpyridine ligand **2.28** gave no conversion of the starting material suggesting perhaps that the metal center is too sterically hindered to react (Table 2.7, Entry 5).

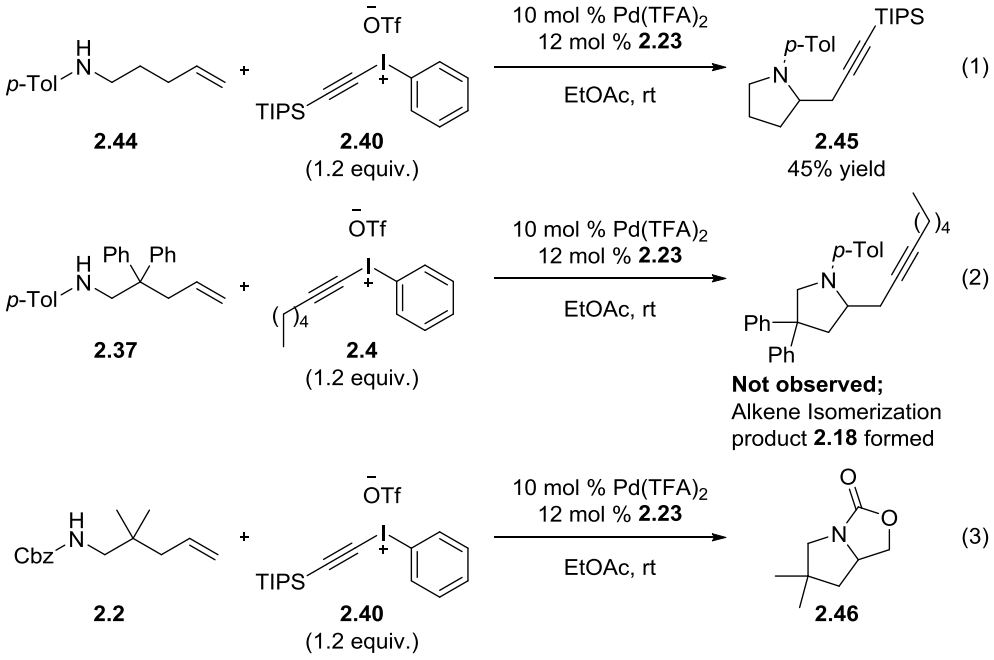
The screen of the chiral ligands (Table 2.8) revealed a reversal of reactivity for many of the ligands which previously gave alkene isomerization. Now, when using the [(trimethylsilyl)ethynyl]phenyliodonium triflate reagent, exclusive formation of **2.42** was observed (Table 2.8, Entries 3,4,5,7). Although the (*R*)-phenyl-quinox ligand **2.31** (Table 2.8, Entry 2) still gave the best conversion to the *exo*-aminoalkynylation product **2.41**, the enantioselectivity was diminished from 23 to 7% ee using the TIPS reagent versus the TMS reagent.

2.2.e Substrate Scope

Using the conditions in entry 1 of Table 2.7, we undertook a brief survey of nitrogen protecting-group and aminoalkene substitution in an effort to explore the scope of compatible aminoalkenes. Use of aminoalkene **2.44**, which lacks any substitution at the 4-position, resulted in a modest yield of the aminoalkynylation product **2.45** (Scheme 2.7, eq 1), and similarly to the Waser system, no reactivity was observed when an alkyl(phenyl)iodonium reagent **2.4** was used (Scheme 2.7, eq 2). Furthermore, swapping the *para*-tolyl protecting group for the benzyl-carbamate protecting group resulted in no desired *exo*-aminoalkynylation and instead participation of the carbamate protecting

group was observed; subsequent decomposition of the incorporated protecting group yields the 2-oxazolidinone product **2.46**. (Scheme 2.7, eq 3).

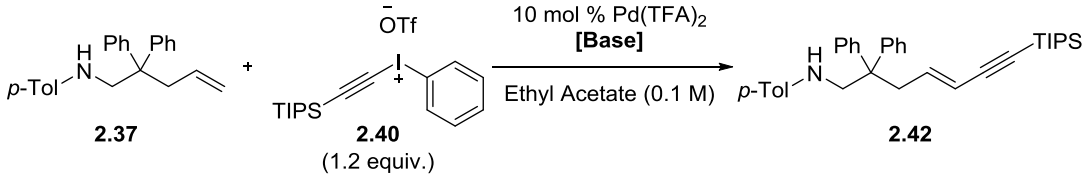
Scheme 2.8. Substrate variations



2.2.f Enyne Coupling Screen

Heck-type couplings using both alkynyl and alkenyl phenyliodonium salts are established. The results leading to the exclusive formation of enyne product when cinchonine (**2.34**) and DPEN (**2.36**) were employed as ligands were interesting, and we hypothesized that the ligands may simply be acting as bases. To test this theory, some organic and inorganic bases were tested under the reaction conditions (Table 2.9). The screen showed that stoichiometric amounts (Table 2.9, Entries 1-4) of even insoluble bases (Table 2.9, Entries 1,2) inhibited or completely stopped the reaction. By switching

Table 2.9. Base Screen to optimize for the enyne product



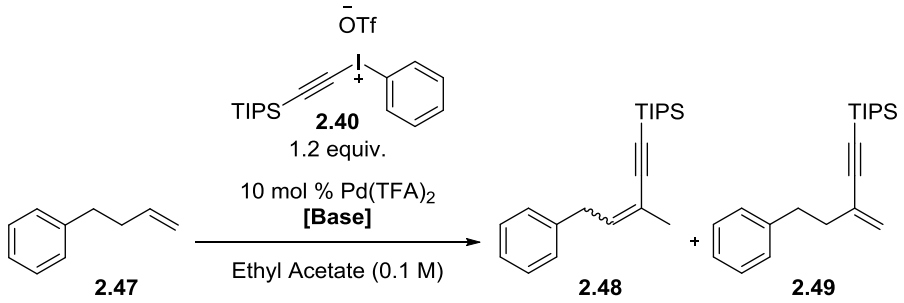
Entry	**Base**	**Equiv. of Base**	Yield[a] (%)
1	NaOAc	2	No reaction
2	K_2CO_3	2	25
3	NEt_3	2	No reaction
4	Cinchonine	1	No reaction
5	Cinchonine	0.12	66

[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard.

to a catalytic amount of base (Table 2.9, Entry 5), the reaction was no longer inhibited, and 66% of the enyne was observed. In both cases where the product was observed, only the terminal regioisomer was present (Table 2.9, Entries 1,5).

To test the generality of the selectivity, a number of bases were investigated using 4-phenyl-1-butene as a simple alkene substrate (Table 2.10). Characteristics such as the steric hindrance of the base (Table 2.10, Entries 1,2,6,7), its solubility (Entry 11), and strength seemed to have no appreciable effect on the selectivity of the coupling, and a mixture of regioisomers was observed. There was also no appreciable change in selectivity whether stoichiometric (Table 2.10, Entries 6-11) or catalytic (Table 2.10, Entries 1-5) amounts of base were employed; though, in the case of the former, the reaction could be inhibited by the presence of base.

Table 2.10. Base Screen with 4-Phenyl-1-butene



Entry	**Base**	**Equiv. of Base**	Ratio[a] (**2.49 : 2.50**)
1	2,6-Lutidine	0.12	3:1
2	2,6-Di-*tert*-butylpyridine	0.12	3:1
3	Triethylamine	0.12	3:1
4	Pyridine	0.12	3:1
5	Cinchonine	0.12	3:2
6	2,6-Lutidine	1.2	N.R.
7	2,6-Di-*tert*-butylpyridine	1.2	3:2
8	Triethylamine	1.2	3:1
9	Pyridine	1.2	N.R.
10	Cinchonine	1.2	N.R.
11	K_2CO_3	2	3:2

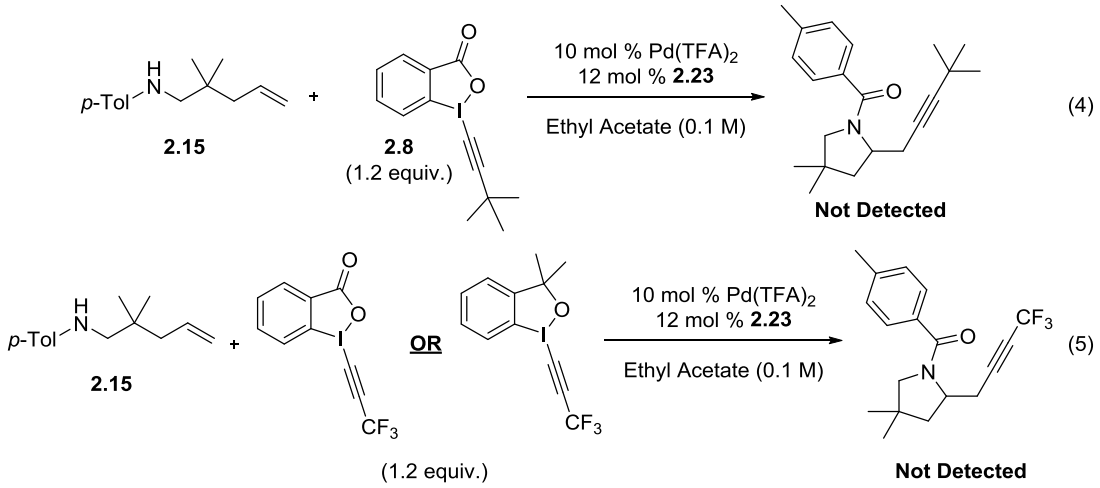
[a] Ratios determined by ^{1}H-NMR spectroscopy.

2.2.g Reactivity of the EBX-reagents

To further optimize the aminoalkynylation reaction, we investigated the (triisopropyl)ethynylbenziodoxolone (**2.50**) reagent using the reaction conditions described in Entry 1 of Table 2.7. Unfortunately, use of this reagent did not promote a more efficient reaction, but rather led to significantly decreased yield and overall reactivity. In fact, only two of the previously screened bidentate and tridentate ligands gave any of the desired *exo*-aminoalkynyation product **2.41** (**2.23**, 4,5-diazafluoren-9-one, 10% yield; **2.34,** cinchonine 23% yield). Screening of the [(*tert*-butyl)ethynyl]

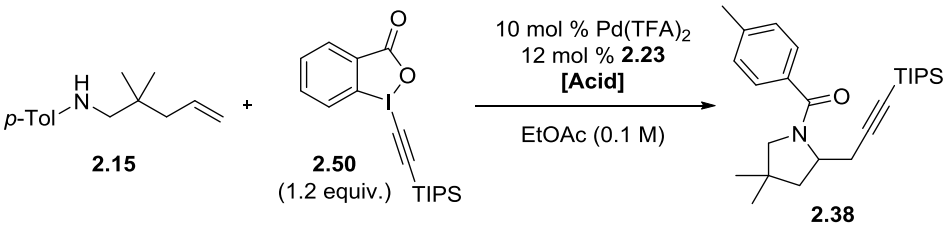
substituted EBX reagent (**2.8**) gave no conversion to the alkylated product (Scheme 2.9, eq 4). Finally, reaction with either of the Togni reagents led to decomposition and no alkynylation was observed (Scheme 2.9, eq 5).

Scheme 2.9. Reaction with EBX Reagents



As benzoate is generated upon the delivery of the alkyne to the metal centre by the TIPS-EBX reagent, it was hypothesized that one of the reasons low yields of alkynylation product were observed may be its participation in unwanted side reactions. To circumvent this issue, acidic additives were tested (Table 2.11). Though addition of catalytic amounts of acid gave slightly improved yields (Table 2.11, Entries 2-6), the [(triisopropylsilyl)ethynyl]phenyliodonium triflate reagent (**2.40**) remained the better electrophilic alkyne source.

Table 2.11. Screen of acid additives with TIPS-ethynyl EBX reagent



Entry	**Acid**	**Equiv. of Acid**	Yield[a] (%)
1	none	---	10
2	CSA	15 mol%	25
3	CSA	50 mol%	20
4	TsOH	15 mol%	20
5	TsOH	50 mol%	25
6	TfOH	50 mol%	30

[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard.

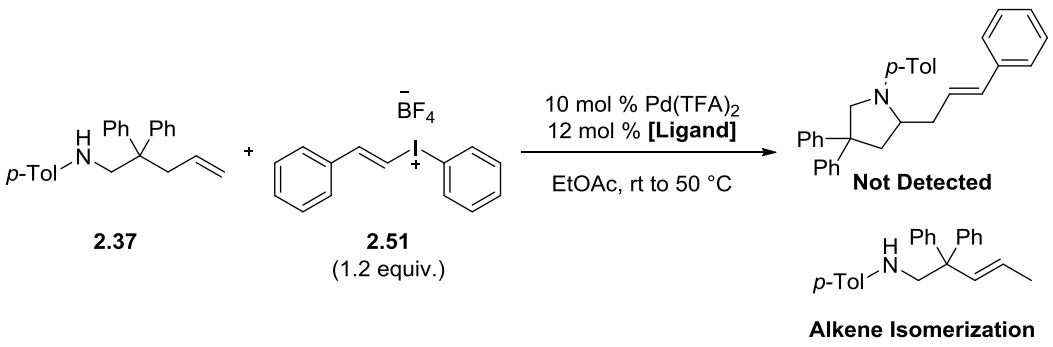
2.2.h Reactivity of 2-Phenylvinyl(phenyl)iodonium tetrafluoroborate

As we had successfully developed an alkene aminoalkynylation reaction utilizing [(triisopropylsilyl)ethynyl]iodonium triflate as the electrophilic alkyne source, we next investigated whether similar reaction conditions were amendable to an analogous alkene aminoalkenylation reaction.

The screen (Table 2.12) revealed no conversion to the desired product when 2-phenylvinyl(phenyl)iodonium tetrafluoroborate (**2.51**) was used, even at elevated temperatures (See Table 2.12 reaction conditions). Conversion of the aminoalkene starting material **2.37** was observed for all cases; however, only alkene isomerization was observed (Table 2.12, Entries 1-6). Additionally, use of the CNC catalyst **2.19** gave no conversion to the desired product (Scheme 2.10), and isomerization, hydroamination

byproducts and aminoalkene starting material were observed. Perhaps a more electron-rich catalyst may be required for this transformation compared to the analogous aminoalkynylation, as a result of the steric hindrance introduced by the alkenyl substituent making it less reactive. Although Malinakova reported these reagents being used in the stoichiometric reaction of a palladium (II) system, we did not observe this same reactivity in our own system, however Malinakova's was a palladacycle that featured two carbon-palladium bonds (Pd-C(sp^2) and Pd-C(sp^3)).[35]

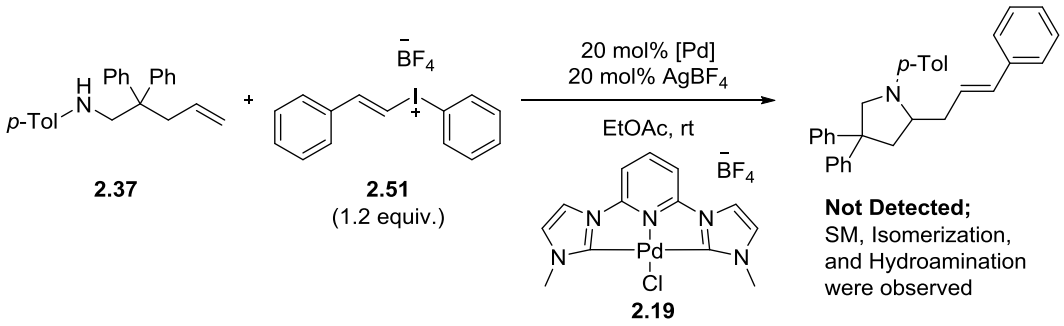
Table 2.12. Ligand screen using 2-phenylvinyl(phenyl)iodonium tetrafluoroborate



Entry	**Ligand**		Product	SM conversion (%)
1	**2.23**	4,5-Diazafluoren-9-one	Isomerization	76
2	**2.24**	Bathocuproine	Isomerization	100
3	**2.26**	Di-*tert*-butylpyridine	Isomerization	87
4	**2.31**	(*R*)-Ph-Quinox	Isomerization	50
5	**2.33**	(*i*Pr)-PyBox	Isomerization	100
6	**2.34**	Cinchonine	Isomerization	100

[a] Yields determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as an internal standard.

Scheme 2.10. Reaction of 2-Phenylvinyl(phenyl)iodonium tetrafluoroborate with a CNC-Pd catalyst 2.19



Section 3. Conclusions

In conclusion, the synthesis and investigation of the reactivity of a variety of silyl, alkyl and aryl substituted hypervalent iodine reagents with palladium catalysts led to the development of an intramolecular aminoalkynyation of alkenes proposed to operate under a palladium(II)/(IV) catalytic cycle. After extensive optimization of reaction parameters, the developed system efficiently promoted the aminoalkynylation of *para*-toluoyl protected aminoalkenes using [(triisopropylsilyl)ethynyl]phenyliodonium triflate **2.40** as hypervalent iodine source and the ligand 4,5-diazafluoren-9-one **2.23**. The reaction proved to be quite sensitive to the nature of the acetylene substituent, and efforts to extend the scope of alkyne reaction partners to include alkyl-substituted alkynyl(iodonium) reagents were not successful. We identified chiral and achiral diamine ligands capable of promoting the reaction, although only modest enantioselectivity was observed in the case of the former. The use of the linear alkynyl reagents gave superior product yield over the use of the corresponding EBX-reagents. The reaction tolerated a

lack of germinal substitution on the aminoalkene (45%), and is an example of the potential utility of palladium(II)/(IV) catalysis in the preparation of heterocyclic scaffolds.

Investigation of reactivity of the corresponding alkenyl(aryl)iodonium reagents did not lead to any incorporation of the alkene moiety. It is clear that the present system did not accommodate the aryl and alkyl substituted vinyl reagents that were explored during this study, but whether or not that is a function of the catalyst reactivity, or the combination of the chosen reagents is as yet undetermined. To date the successful incorporation of any of these vinyl reagents in catalytic Pd(II)/(IV) processes remains unreported and investigations remain ongoing.

Section 4. Experimental

General Procedures. All reactions were performed under a nitrogen atmosphere using flame-dried glassware and standard air-free techniques. Column chromatography was performed using silica gel (Whatman, 60Å, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of trimethylsilane and are referenced relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts are referenced to the carbon resonance of the deuterated solvent $CDCl_3$ (77.0 ppm). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t =

triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and assignment. Mass spectra were collected on a JEOL HX-110 Mass Spectrometer or a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer. Chiral HPLC analysis was performed on Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 215 nm; column, DIACEL CHIRALPAK AD-H and CHIRALPAK OD-H; mobile phase, hexanes/2-propanol.

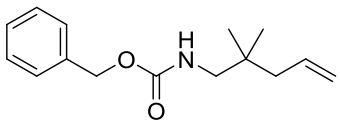
Materials. Dichloromethane, acetonitrile, diethyl ether, and tetrahydrofuran were degassed with nitrogen and dried by passing through a column of neutral alumina. Toluene was degassed with nitrogen and dried by passing through a column of neutral alumina and a column of Q5 reactant. All other solvents were distilled before use and stored under an atmosphere of nitrogen and on 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4Å molecular sieves and were used without further purification. Commercial reagents Palladium(II) trifluoroacetate, Palladium(II) acetate, Silver(I) tetrafluoroborate, 5-Diazafluoren-9-one (**2.23)**, Bathocuproine (**2.24)**, 2,2'-Bipyridyl (**2.25)**, 4,4'-Di-*tert*-butyl-2,2'-bipyridyl (**2.26**), 2,2':6',2"-Terpyridine (**2.27**), 4,4',4"-Tri-*tert*-Butyl-2,2':6',2"-terpyridine (**2.28**), 2,6-Bis[(4*S*)-(-)-isopropyl-2-oxazolin-2-yl]pyridine (**2.33**), cinchonine (**2.34**), (+)-Sparteine (**2.35**), (1*S*,2*S*)-1,2-Bis(2-hydroxyphenyl)ethylenediamine (**2.36**), Togni Reagent II, 4-Phenyl-1-butene (**2.48**) were purchased from Sigma-Aldrich, TCI, Strem, Pressure Chemicals, or VWR and were used as received. The following chemicals were

prepared according to literature procedure; 2,6-Bis(diphenylphosphinomethyl)pyridine dichloropalladium (**2.1**),[36] 2,6-bis-(3-methylimidazolin-2-yliden-1-yl)pyridine chlorotetrafluoroborate palladium (**2.19**),[37] $Pd(MeCN)_2Cl_2$ (**2.21**),[38] $Pd(MeCN)_4(BF_4)_2$ (**2.22**),[39] 2-(4-dimethyl-4,5-dihydrooxazoli-2-yl)-pyridine (**2.29**),[40,41] 2-(4*R*-phenyl-4,5-dihydrooxazoli-2-yl)-pyridine (**2.30**),[40] (4'*R*)-2-(4',5'-Dihydro-4'-phenyl-2'-oxazolyl)quinolone (**2.31**), 2,6-Bis{1-(cyclohexylimino)ethyl}-pyridine (**2.43**),[41] 1-Trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one.[42]

General Procedure for Test Reactions: The palladium source and the ligand were weighed into either a round bottom flask or a vial. The reaction flask was capped with a septum, and degassed with a nitrogen inlet. Solvent (0.1 M with respect to substrate) was added and the reaction stirred for 5 min. The substrate (0.1-0.2 mmol; 1 equiv.) was then added by syringe if it was a liquid, or quickly added as a solid. The oxidant (1.2 equiv.) was added as a solid very quickly thereafter. The septum was replaced after the addition of the oxidant. The reaction was flushed with nitrogen, then monitored by TLC for disappearance of the starting material (8/2, Hexanes/Ethyl Acetate; $KMnO_4$). Once the starting material had been consumed, the reaction had produced palladium black/palladium mirror, or after several days and no products appeared by TLC even after heating, the reaction was cooled to room temperature (if it had been heating), then quenched with sat aq. sodium bicarbonate, and diluted with ethyl acetate. The resulting layers were separated and the aqueous layer was then extracted with ethyl acetate (2 x).

The organic layers were combined, internal standard was added (1,3-Dinitrobenzene; 1 equiv.) and the solution was dried over anhydrous Na_2SO_4. The resulting solution was then decanted, the drying agent was washed with ethyl acetate, and the wash decanted, and then the combined organics were concentrated. Products were purified via column chromatography (Hexanes/Ethyl Acetate).

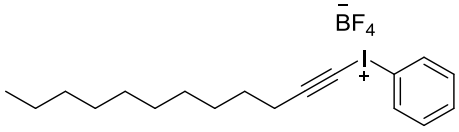
For reactions involving catalysts [PNP]$PdCl_2$ **2.1,** the CNC-PdCl **2.19**, $Pd(MeCN)_4(BF_4)_2$ (**2.22**), or silver tetrafluoroborate, these reagents were weighed out in the glovebox into a round bottom flask, which was capped with a septum, equipped with a stir bar, and the flask was pumped out of the glovebox and placed under nitrogen. All reagents, such as oxidant or substrate were added to the round bottom flask containing the catalysts as a solution. The reaction was then monitored as previously described, and upon completion (either indicated by consumption of starting material or decomposition of the catalyst or lack of reactivity), the reaction was worked up as described above.



2.2

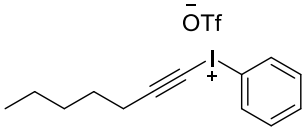
Benzyl 2,2-dimethylpent-4-enylcarbamate (2.2): Compound prepared according to literature procedure. Spectra matched literature values.[43] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.33 (5 H, m, Ar), 5.88-5.74 (1 H, m, C*H*), 5.11 (2 H, s, CH_2O), 5.07-5.00 (2 H, m,

C(H)=CH_2), 4.78 (1 H, br, N*H*), 3.04 (2 H, d, *J* = 6.6 Hz, NHCH_2), 1.98 (2 H, d, *J* = 7.2 Hz, CH_2C(H)), 0.89 (6 H, s, CH_3 x 2).



2.3

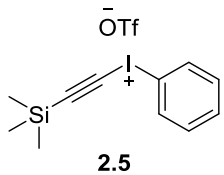
Dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (2.3): Compound prepared according to modified literature procedure.[44] Resulting product readily decomposes at room temperature; it must be stored cold, and kept cold during isolation. Modification to literature procedure; after extracting the resulting product into the dichloromethane, keep the solution cold, and when concentrating the final solution, place the flask in a salt/ice bath, and do not handle the resulting solid above 0 ˚C. Spectra matched literature values. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2 H, d, *J* = 8.1 Hz, Ar), 7.61 (3 H, m, Ar), 1.60 (2 H, m, CH_2(CH_2) $_8CH_3$), 1.31 (16 H, br m, CH_2(CH_2) $_8CH_3$), 0.89 (3 H, t, *J* = 6.7 Hz, CH_3).



2.4

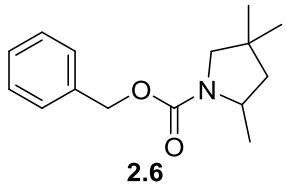
Hept-1-ynyl(phenyl)iodonium triflate (2.4): Compound prepared according to literature procedure.[45] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (2 H, d, *J* = 8.1 Hz, *ortho*-Ar), 7.67 (1

H, t, *J* = 7.5 Hz, *para*-Ar), 7.54 (2 H, m, *meta*-Ar), 2.59 (2 H, t, *J* = 7.2 Hz, C*H*$_2$ (CH$_2$)$_3$CH$_3$), 1.58 (2 H, m, CH$_2$C*H*$_2$ (CH$_2$)$_2$CH$_3$), 1.33 (4 H, m, CH$_2$CH$_2$ (C*H*$_2$)$_2$CH$_3$), 0.89 (3 H, br m, C*H*$_3$); ^{1}H NMR (300 MHz, DMSO): δ 8.29 (2 H, d, *J* = 8.1 Hz, *ortho*-Ar), 7.74 (1 H, t, *J* = 7.5 Hz, *para*-Ar), 7.60 (2 H, m, *meta*-Ar), 2.57 (2 H, t, *J* = 7.2 Hz, C*H*$_2$ (CH$_2$)$_3$CH$_3$), 1.44 (2 H, m, CH$_2$C*H*$_2$ (CH$_2$)$_2$CH$_3$), 1.23 (4 H, m, CH$_2$CH$_2$ (C*H*$_2$)$_2$CH$_3$), 0.81 (3 H, t, *J* = 6.9 Hz, C*H*$_3$).



2.5

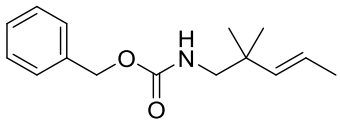
[(Trimethylsilyl)ethynyl](phenyl)iodonium triflate (2.5): Compound prepared according to literature procedure. Spectra matched literature values.[46] ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.08 (2 H, d, *J* = 8.4 Hz, *ortho*-Ar), 7.69 (1 H, t, *J* = 7.2 Hz, *para*-Ar), 7.56 (2 H, m, *meta*-Ar), 0.22 (9 H, s, Si(C*H*$_3$)$_3$).



2.6

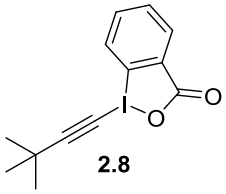
Benzyl 2,4,4-trimethylpyrrolidine-1-carboxylate (2.6): Compound prepared according to literature procedure. Spectra matched literature values.[37] ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.37-7.30 (5 H, m, Ar), 5.21-5.07 (2 H, m, C*H*$_2$O), 3.94 (1 H, br, C*H*(CH$_3$)), 3.39 (1 H,

m, C*H*$_2$N), 3.05 (1 H, d, J = 10.8 Hz, CH(C*H*$_3$)), 1.87 (1 H, dd, J = 7.2, 12.6 Hz, CH(CH$_3$)C*H*$_2$), 1.32-1.24 (4 H, m), 1.11 (3 H, s, C*H*$_3$), 0.98 (3 H, s, C*H*$_3$).



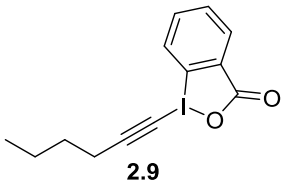
2.7

Benzyl 2,2-dimethylpent-3-enylcarbamate (2.7): Spectra matched literature values.[47] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.35 (5 H, m, Ar), 5.49-5.30 (2 H, m, C(*H*)=C(*H*)), 5.11 (2 H, s, C*H*$_2$O), 4.72 (1 H, br s, N*H*), 3.06 (2 H, d, *J* = 6.3 Hz, NHC*H*$_2$), 1.68 (3 H, d, *J* = 5.1 Hz, C(H)C*H*$_3$), 1.00 (6 H, s, C*H*$_3$ x 2).



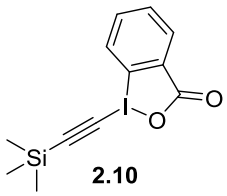
2.8

1-(3,3-Dimethylbutynyl)-1,2-beniodoxol-3(1*H*)-one (2.8): Compound prepared according to literature procedure.[48] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (1 H, m, C-1 Ar), 8.14 (1 H, m, C-3 Ar), 7.76 (2 H, m, C-2,4 Ar), 1.38 (9 H, s, C(C*H*$_3$)$_3$).



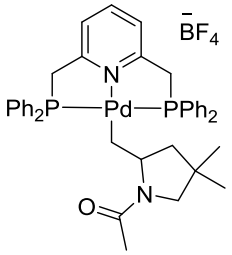
2.9

1-(hexnyl)-1,2-beniodoxol-3(1*H*)-one (2.9): Compound prepared according to literature procedure.[42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (1 H, m, C-1 Ar), 8.16 (1 H, m, C-3 Ar), 7.75 (2 H, m, C-2,4 Ar), 2.60 (2 H, t, *J* = 6.6 Hz, C*H*$_2$(CH_2)$_2$$CH_3$), 1.64-1.41 (4 H, m, CH_2(C*H*$_2$)$_2$$CH_3$), 0.94 (3 H, t, *J* = 7.2 Hz, C*H*$_3$).



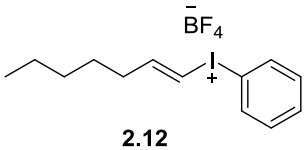
2.10

1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (2.10): Compound prepared according to literature procedure.[42] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (1 H, m, C-1 Ar), 8.20 (1 H, m, C-3 Ar), 7.78 (2 H, m, C-2,4 Ar), 0.32 (9 H, s, Si(C*H*$_3$)$_3$).



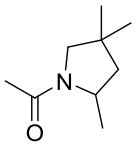
2.11

PNP-Pd Alkyl Complex (2.11): Compound prepared according to literature procedure. Spectra matched literature values.[49] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94-7.44 (23 H, m, Ar), 4.60 (2 H, td, *J* = 4.4, 17.5 Hz, PNP-C*H*$_2$), 4.44 (2 H, td, *J* = 4.7, 17.8 Hz, PNP-C*H*$_2$), 3.77-3.69 (1 H, m), 2.84-2.80 (1 H, m), 2.77 (1 H, d, *J* = 10.7 Hz), 2.60 (1 H, d, *J* = 10.4 Hz), 1.76 (3 H, s, C(O)C*H*$_3$), 1.54 (1 H, d, *J* = 9.3 Hz), 1.03 (1 H, dd, *J* = 6.7, 12.4 Hz), 0.58 (3 H, s, C*H*$_3$), 0.51 (1 H, d, *J* = 12.0 Hz) 0.31 (3 H, s, C*H*$_3$).



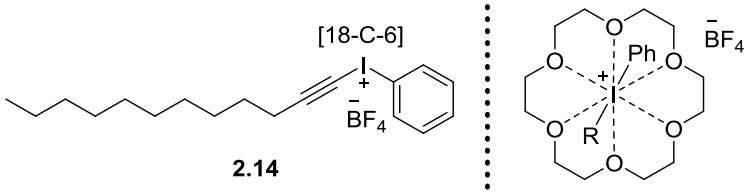
2.12

***E*-Phenyl(1-heptynyl)iodonium tetrafluoroborate (2.12):** Compound prepared according to literature procedure.[50] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (2 H, d, *J* = 9.0 Hz, Ar), 7.53 (3 H, m, Ar), 6.98 (1 H, m, C(*H*)=C(H)I), 6.77 (1 H, d, *J* = 13.8 Hz, C(H)=C(*H*)I), 2.36 (2 H, m, C*H*$_2$C(H)=), 1.47 (2 H, m, CH_2CH_2 (CH_2)$_2CH_3$), 1.27 (4 H, m, CH_2CH_2 (C*H*$_2$)$_2CH_3$), 0.86 (3 H, t, *J* = 7.2 Hz, C*H*$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ -147.



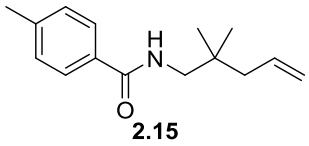
2.13

N-Acetyl-2,4,4-trimethylpyrrolidine (2.13): Spectra matched literature values.[37] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (1 H, br, C*H*(CH_3)), 3.19 (2 H, s, CH_2N), 2.02 (3 H, s, C(O)CH_3), 1.92 (1 H, dd, *J* = 7.5, 12.6 Hz, CH(CH_3)CH_2), 1.36 (1 H, dd, *J* = 9.0, 13.2 Hz, CH(CH_3)CH_2), 1.30 (3 H, d, *J* = 6.0 Hz, C(H)CH_3), 1.13 (3 H, s, CH_3), 1.01 (3 H, s, CH_3).



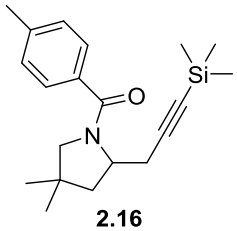
2.14

1-Decynyl(phenyl)(tetrafluoroborato)-λ^3-iodane[18-crown-6] (2.14): Compound prepared according to literature procedure.[51] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (2 H, d, *J* = 8.1 Hz, *ortho*-Ar), 7.68 (1 H, t, *J* = 7.5 Hz, *para*-Ar), 7.58 (2 H, m, *meta*-Ar), 3.64 (24 H, s, 18-C-6), 2.60 (2 H, t, *J* = 7.0 Hz, CH_2(CH_2)$_6$$CH_3$), 1.54 (2 H, m, CH_2CH_2(CH_2)$_5$$CH_3$), 1.25 (10 H, m, CH_2CH_2(CH_2)$_5$$CH_3$), 0.86 (3 H, t, *J* = 6.3 Hz, CH_3).



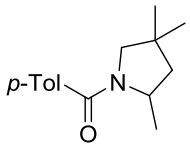
2.15

4-Methyl-N-(2,2-dimethylpent-4-enyl)benzamide (2.15): Compound prepared according to literature procedure.[37] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (2 H, d, *J* = 8.1 Hz, *para*-Tol), 7.23 (2 H, d, *J* = 8.1 Hz, *para*-Tol), 6.15 (1 H, br s, NH), 5.89 (1 H, m, C*H*), 5.08 (2 H, m, CHCH_2), 3.31 (2 H, d, *J* = 6.3 Hz, NCH_2), 2.40 (3 H, s, *para*-Tol CH_3), 2.06 (2 H, d, *J* = 7.5 Hz, CH_2CH), 0.96 (6 H, s, C(CH_3)$_2$).



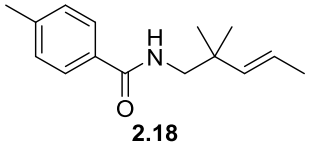
2.16

(4,4-dimethyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-1-yl)(*p*-tolyl)methanone (2.16): Isolated from test reaction (for conditions see Table 1.2, Entry 2). Purified by column chromatography (Hex:EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 7.19 (2 H, d, *J* = 8.1 Hz, *para*-Tol), 4.40 (1 H, m, *J* = 1.8 Hz, NC*H*), 3.08 (2 H, m, NCH_2 and CHCH_2), 2.50 (1 H, dd, *J* = 2.1, 16.8 Hz, CHCH_2), 2.37 (3 H, s, *para*-Tol CH_3), 1.90 (2 H, m, C$(CH_3)_2$CH_2), 1.07 (3 H, s, CH_3), 0.91 (3 H, s, CH_3), 0.19 (9 H, s, Si(CH_3)$_3$); GC/MS: 15.82 min, m/z = 327 (3, M), 216 (45, M-111), 119 (100, TolylCO), 91 (21, Tolyl).



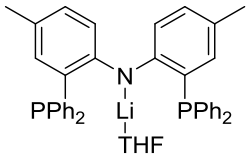
2.17

N-*para*-Toluoyl-2,4,4-trimethylpyrrolidine (2.17): Spectra matched literature values.[37] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (2 H, d, *J* = 7.8 Hz, Ar), 7.18 (2 H, d, *J* = 8.1 Hz, 1H), 4.34 (1 H, br, NC*H*(CH_3)), 3.29 (1 H, d, *J* = 10.2 Hz, NCH_2), 3.12 (1 H, d, *J* = 10.2 Hz, NCH_2), 2.37 (3 H, s, Tol-CH_3), 1.92 (1 H, ddd, *J* = 1.5, 7.2, 12.6 Hz, CH_2), 1.44-1.25 (4 H, m), 1.04 (3 H, s, CH_3), 0.89 (3 H, s, CH_3).

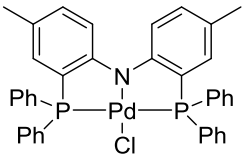


2.18

(*E*)-*N*-(2,2-dimethylpent-3-enyl)-4-methylbenzamide (2.18): Isolated from test reaction (for conditions see Table 1.2, Entry 4). Purified by column chromatography (Hex:EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 7.22 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 6.02 (1 H, br s, NH), 5.46 (2 H, m, C*H*=C*H*), 3.29 (2 H, d, *J* = 6.0 Hz, NCH_2), 2.39 (3 H, s, *para*-Tol CH_3), 1.71 (2 H, d, *J* = 5.4 Hz, CH_2CH), 1.05 (6 H, s, C(CH_3)$_2$); GC/MS: 13.72 min, m/z = 231 (3, M), 119 (100, Tolyl-CO), 91 (23, Tolyl).

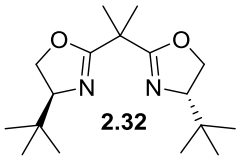


Bis(2-diphenylphosphinotolyl)amine lithium-THF adduct: Compound prepared according to literature procedure with ditoluoyl- instead of diphenyl-substituted aniline.[52] The title compound was isolated as a bright yellow powder following trituration with pentane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (8 H, m, Ph), 7.14 (12 H, m, Ar), 7.04 (2 H, m, Ar), 6.97 (2 H, m, Ar), 3.39 (4 H, m, THF), 2.03 (6 H, s, C*H*$_3$ x 2), 1.03 (4 H, m, THF). ^{31}P NMR (202 MHz, C_6D_6): δ -19.2.



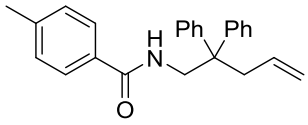
2.20

[PNP]PdCl (2.20): Compound prepared according to literature procedure with lithium-THF adduct of the ligand.[53] Complex was purified by column chromatography (100% Dichloromethane). Complex is a dark green crystalline solid, and in solution changes color based on concentration (observed colors; pink, orange, green, maroon, brown). Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (7 H, m, PPh_2), 7.44 (13 H, m, Ar), 6.88 (2 H, m, Ar), 6.8 (2 H, m, Ar), 2.13 (6 H, s, C*H*$_3$ x 2); ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.7.



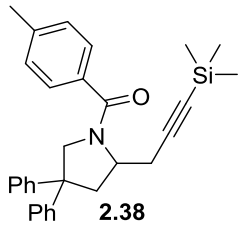
2.32

2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S*,*S*)-*tert*-Butyl bis(oxazoline)] (2.32): Compound prepared according to literature procedure.[54] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (4 H, m, CH_2O x 2), 3.84 (2 H, dd, *J* = 6.9, 9.9 Hz, C*H* x 2), 1.51 (6 H, s, CH_3 x 2), 0.87 (18 H, s, *tert*-Butyl x2).



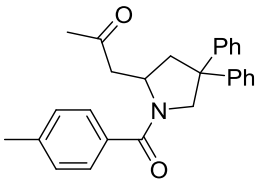
2.37

N-(2,2-Diphenylpent-4-enyl)-4-methylbenzamide (2.37): Compound prepared according to literature procedure.[55] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 7.34 (4 H, m, Ph), 7.25 (6 H, m, Ph) 7.15 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 5.64 (1 H, br s, NH), 5.47 (1 H, m, C*H*), 5.00 (2 H, m, CHCH_2), 4.13 (2 H, d, *J* = 5.7 Hz, NCH_2), 2.91 (2 H, d, *J* = 6.0 Hz, CH_2CH), 2.35 (3 H, s, CH_3).



2.38

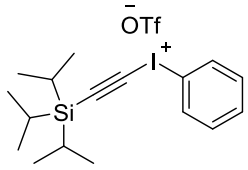
(4,4-diphenyl-2-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-1-yl)(*p*-tolyl)methanone (2.38): Isolated from test reaction (for conditions see Table 1.4, Entry 3). Purified by column chromatography (Hex:EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (2 H, d, *J* = 7.8 Hz, *para*-Tol), 7.20 (11 H, m, 2 x Ph, *para*-Tol), 7.05 (2 H, d, *J* = 7.2 Hz, *para*-Tol), 4.30 (1 H, dd, *J* = 1.8, 11.1 Hz, NCH_2), 4.17 (1 H, m, NC*H*), 3.91 (1 H, d, *J* = 11.1, NCH_2), 3.15 (1 H, dd, *J* = 5.7, 17.1 Hz, CH_2CH), 2.93 (1 H, dd, *J* = 10.2, 12.6 Hz, CHCH_2), 2.87 (1 H, ddd, *J* = 1.2, 6.6, 12.6 Hz, CHCH_2), 2.60 (1 H, dd, *J* = 2.7, 17.1 Hz, CH_2CH), 2.41 (3 H, s, CH_3), 0.41 (9 H, s, Si(CH_3)$_3$).



2.39

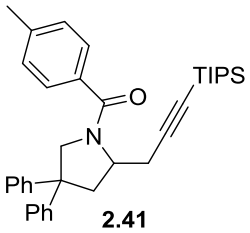
1-(1-(4-methylbenzoyl)-4,4-diphenylpyrrolidin-2-yl)propan-2-one (2.39): Isolated from test reaction (for conditions see Table 1.3, Entry 3). Purified by column chromatography (Hex:EtOAc, 70:30). IR (film, cm^{-1}): 3026, 2923, 1712, 1626, 1615, 1568, 1494, 1410, 1372, 1200, 1228, 1180, 1033, 910, 699 ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (2 H, d, *J* = 8.1 Hz, *para*-Tol), 7.15 (12 H, m, Ph and *para*-Tol), 4.30 (2

H, m, NC*H* and NC*H*$_2$), 3.93 (1 H, d, *J* = 11.1, NC*H*$_2$), 3.33 (1 H, dd, *J* = 3.0, 16.8 Hz, CHC*H*$_2$), 3.09 (1 H, m, C(Ph)$_2$C*H*$_2$), 2.83 (1 H, dd, *J* = 8.1, 17.1 Hz, CHC*H*$_2$), 2.49 (1 H, dd, *J* = 10.5, 12.6 Hz, C(Ph)$_2$C*H*$_2$), 2.41 (3 H, s, *para*-Tol CH_3), 2.17 (3 H, s, $COCH_3$); GC/MS: 21.90 min, m/z = 397 (10, M), 354 (9, M-43), 278 (33, M-119), 119 (100, TolylCO), 91 (40, Tolyl).



2.40

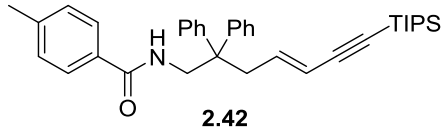
[(Tri*iso*-propyl)ethynyl](phenyl)iodonium triflate (2.40): Compound prepared according to literature procedure.[43] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (2 H, d, *J* = 8.1 Hz, *ortho*-Ar), 7.67 (1 H, t, *J* = 7.2 Hz, *para*-Ar), 7.55 (2 H, m, *meta*-Ar), 1.06 (21 H, m, C*H*$_3$ x 6 and C*H* x 3).



2.41

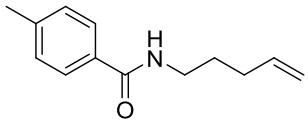
(4,4-Diphenyl-2-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-1-yl)(*p*-tolyl)methanone (2.41): Isolated from test reaction (for conditions see Table 1.6, Entry 4). Purified by column chromatography (Hex:EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (2 H,

d, *J* = 7.8 Hz, *para*-Tol), 7.20 (13 H, m, 2 x Ph, *para*-Tol), 4.33 (1 H, dd, *J* = 1.8, 10.8 Hz, NCH_2), 4.17 (1 H, m, NC*H*), 3.93 (1 H, d, *J* = 11.1, NCH_2), 3.20 (1 H, dd, *J* = 5.4, 17.1 Hz, CH_2CH), 3.00 (1 H, dd, *J* = 10.5, 12.6 Hz, CHCH_2), 2.86 (1 H, ddd, *J* = 1.8, 6.6, 14.4 Hz, CHCH_2), 2.64 (1 H, dd, *J* = 2.7, 17.1 Hz, CH_2CH), 2.41 (3 H, s, CH_3), 1.03 (21 H, s, Si*[CH(*CH_3*)*$_2$*]*$_3$).



2.42

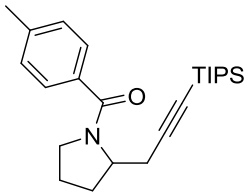
(*E*)-*N*-(2,2-diphenyl-7-(tri*iso*propylsilyl)hept-4-en-6-ynyl)-4-methylbenzamide (2.42): Isolated from test reaction (for conditions see Table 1.8, Entry 5). Purified by column chromatography (1st: Hex:EtOAc, 70:30 then 2nd: 100% DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (12 H, m, Ar), 7.13 (2 H, d, *J* = 7.8 Hz, Ar), 5.75 (1 H, dt, *J* = Hz, C(H)=C(*H*)-alkyne), 5.51 (1 H, d, *J* = 10.8 Hz, C(*H*)=C(H)-alkyne), 4.16 (2 H, m, NHCH_2), 3.28 (2 H, d, *J* = 7.2 Hz, CH_2C(H)=), 1.04 (21 H, m, *i*-Pr x 3).



2.44

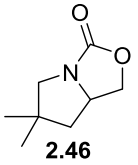
4-Methyl-N-(pent-4-enyl)benzamide (2.44): Compound prepared according to literature procedure.[52] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (2 H, d, *J* = 8.0 Hz, C-2,6 Ar), 7.16 (2 H, d, *J* = 8.0 Hz, C-3,5 Ar), 6.63 (I H, br s, N*H*), 5.79 (1

H, ddt, *J* =7.0, 10.5, 17.0 Hz, C(*H*)=CH_2), 5.02 (1 H, d, *J* = 17.0 Hz, C(H)=CH_2 *trans*), 4.96 (1 H, d, *J* = 10.0 Hz, C(H)=CH_2 *cis*), 3.40 (2 H, q, *J* = 7.0 Hz, N(H)CH_2), 2.35 (3 H, s, CH_3), 2.01 (2 H, q, *J* = 7.0 Hz, CH_2), 1.68 (2 H, quin, *J* = 7.5 Hz, CH_2).



2.45

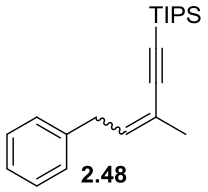
***p*-Tolyl(2-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-1-yl)methanone (2.45):** For reaction conditions see Scheme 1.8, Eq 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (2 H, d, *J* = 7.2 Hz, C-2,6 Ar), 7.18 (2 H, d, *J* = 7.8 Hz, C-3,5 Ar), 4.32 (1 H, br m, C*H*), 3.50 (2 H, m, CH_2N), 2.98 (1 H, dd, *J* = 6.3, 16.5 Hz, C(H)CH_2alkyne), 2.69 (1 H, dd, *J* = 2.1, 16.5 Hz, C(H)CH_2alkyne), 2.37 (3 H, s, CH_3), 1.90 (2 H, m), 1.75 (2 H, m), 1.08 (21 H, m, *i*-Pr x 3).



2.46

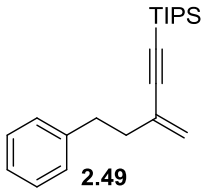
Tetrahydro-6,6-dimethylpyrrolo[1,2-c]oxazol-3(1H)-one (2.46): Spectra matched literature values.[46] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49 (1 H, t, *J* = 7.5 Hz, C*H*), 4.14-4.10 (2 H, m, CH_2O), 3.36 (1 H, d, *J* = 11.5 Hz, CH_2N), 2.91 (1 H, d, *J* = 11.5 Hz,

C*H*$_2$N), 1.82 (1 H, dd, *J* = 5.5, 12.0 Hz, C*H*$_2$CH), 1.43 (1 H, dd, *J* = 9.0, 12.0 Hz, , C*H*$_2$CH), 1.14 (3 H, s, C*H*$_3$), 1.13 (3 H, s, C*H*$_3$).



2.48

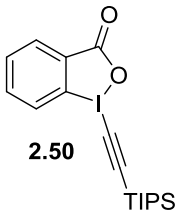
(*E*)-tri*iso*propyl(3-methyl-5-phenylpent-3-en-1-ynyl)silane (2.48): Isolated from test reaction (for conditions see Table 1.10, Entry 5). Purified by column chromatography (Hex:EtOAc, Hex/95:5). Isomers were inseparable. In this reaction they exist in a 2:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (5 H, m, Ph, major and minor), 6.07 (1 H, dt, *J* = 7.5, 1.5 Hz, C(*H*)=C, minor), 5.83 (1 H, dt, *J* = 7.5, 1.5 Hz, C(*H*)=C, major), 3.62 (2 H, d, *J* = 7.5 Hz, C*H*$_2$C(H)=, major), 3.43 (2 H, d, *J* = 7.5 Hz, C*H*$_2$C(H)=, minor), 1.91 (3 H, s, C*H*$_3$, minor), 1.88 (3 H, s, C*H*$_3$, major).



2.49

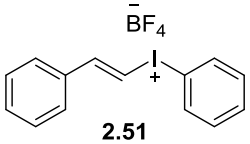
Tri*iso*propyl(3-methylene-5-phenylpent-1-ynyl)silane (2.49): Isolated from test reaction (for conditions see Table 1.10, Entry 5). Purified by column chromatography (Hex:EtOAc, Hex/95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (5 H, m, Ph), 5.35 (1 H, d,

J = 1.8 Hz, C=C*H*$_2$), 5.19 (1 H, d, *J* = 1.8 Hz, C=C*H*$_2$), 2.87 (2 H, t, *J* = 8.0 Hz, PhC*H*$_2$CH$_2$), 2.45 (2 H, t, *J* = 7.8 Hz, PhCH$_2$C*H*$_2$).



2.50

1-[Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (2.50): Compound prepared according to literature procedure.[56] Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (1 H, m, 1 H, C-1 Ar), 8.29 (1 H, m, C-3 Ar), 7.77 (2 H, m, Ar), 1.16 (21 H, m, *i*Pr x 3).



2.51

***E*-Phenyl(2-phenylvinyl)iodonium tetrafluoroborate (2.51):** Compound prepared according to literature procedure.[44] Spectra matched literature values.[57] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (2 H, d, *J* = 7.8 Hz, Ar), 7.78 (1 H, d, *J* = 14.4 Hz), 7.54 (1 H, t, *J* = 7.2 Hz), 7.36 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6, 135.7, 134.1, 132.7, 132.4, 131.3, 129.1, 128.2, 110.6, 96.2.

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Chapter 3

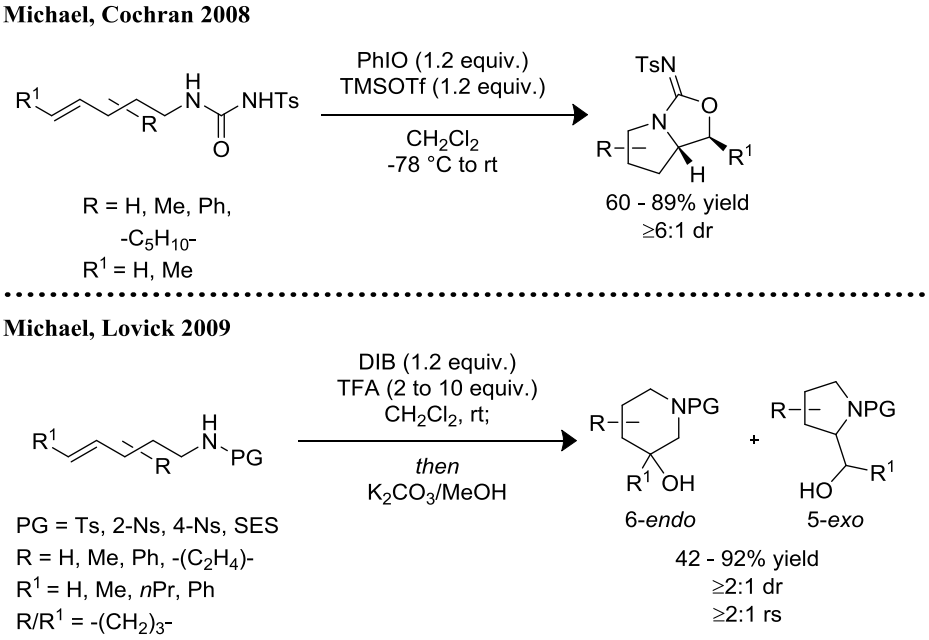
DEVELOPMENT OF CATALYTIC HYPERVALENT IODINE(III) ALKENE DIFUNCTIONALIZATION REACTIONS

Section 1. Introduction

Oxidative difunctionalizations of alkenes, such as the Sharpless dihydroxylation, constitute an efficient and often highly selective method for the construction of complex organic molecules.[1] Previous work in this laboratory has resulted in the development of both metal-free and metal-catalyzed alkene difunctionalization reactions for the preparation of nitrogen-containing heterocycles, including pyrrolidines, piperidines, piperazines, and morpholines. Such scaffolds are of particular interest due to their ubiquity in natural products, potential therapeutic applications, and frequency as substructures in synthetically-useful tools, such as organocatalysts.[2]

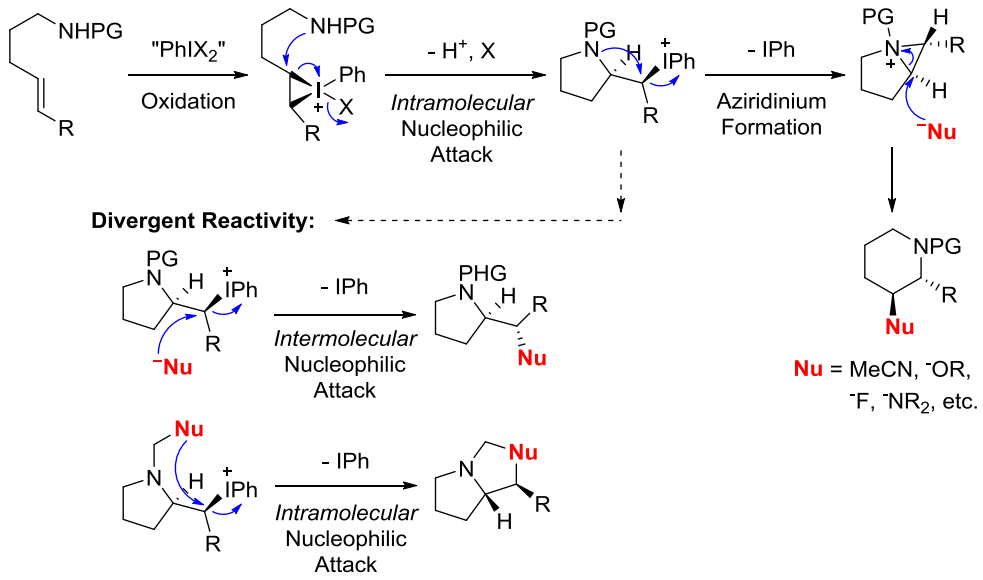
Recently, we reported two oxidative cyclization reactions utilizing iodine(III) reagents.[3,4] In these transformations, vicinal oxyamination products were generated through the iodine(III) mediated *intramolecular* oxidative cyclization of urea, tosyl- and nosyl-protected aminoalkenes. Notably, both reports are metal-free protocols and utilize the bench-stable, commercially available oxidants (diacetoxyiodo)benzene (DIB) and [bis(trifluoroacetoxy)iodo]benezene (PIFA), to yield products with excellent regio- and stereo-selectivities (Scheme 3.1).

Scheme 3.1. Hypervalent iodine promoted oxidative alkene difunctionalizations



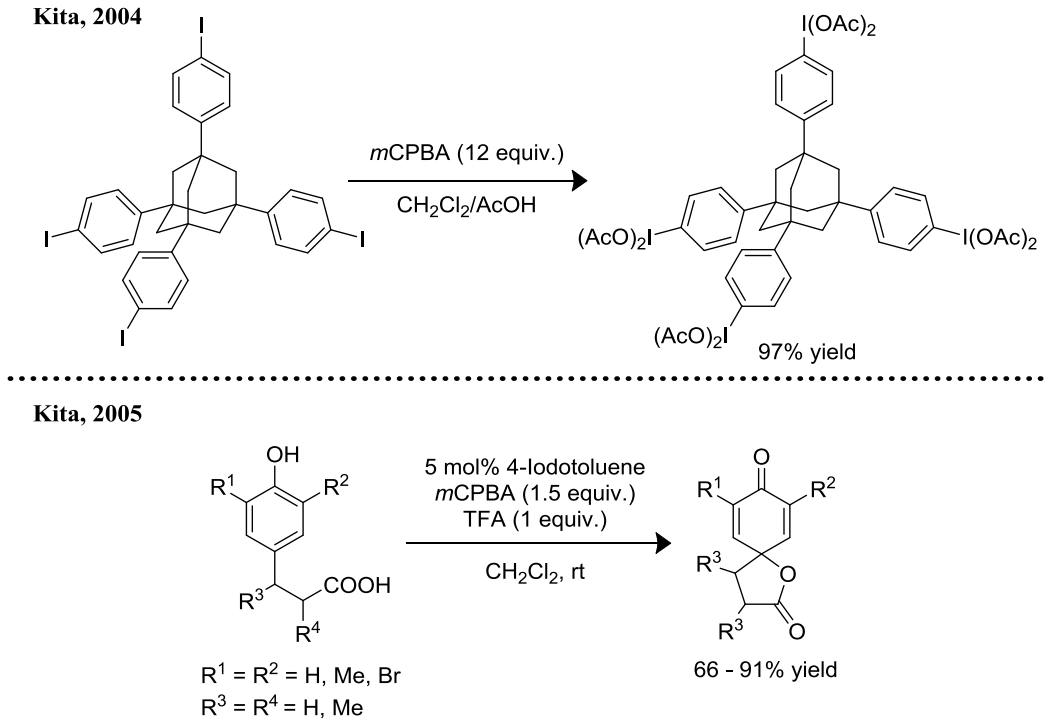
Both of these transformations are proposed to proceed through an iodonium intermediate, which is generated by addition of iodine to the alkene (Scheme 3.2). This highly electrophilic intermediate is then rapidly trapped by the nitrogen of the aminoalkene. In the absence of a sufficiently strong and/or second intramolecular nucleophile, it is postulated that the nitrogen may affect a subsequent cyclization to form the aziridinium, which then undergoes nucleophilic attack to generate the *endo*-cyclization product. Variation of reaction conditions, such as choice of Brønsted acid or solvent, has led to incorporation of different nucleophiles, including acetamide, alcohol, and fluoride.[5]

Scheme 3.2. Proposed mechanism of the *endo*-cyclization



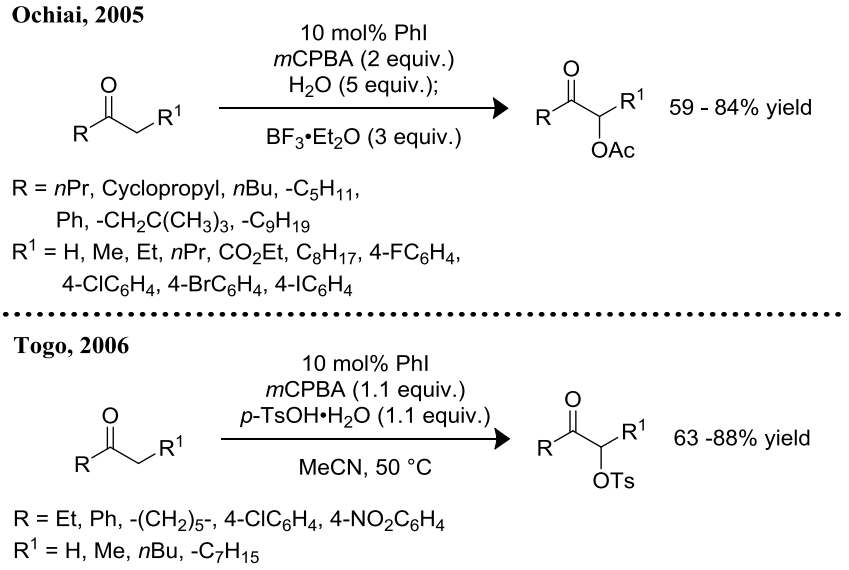
Though these are very useful transformations, they feature stoichiometric amounts of the iodine reagent, which generates stoichiometric amounts of waste; furthermore, when considering possible applications in asymmetric synthesis, the use of stoichiometric or superstoichiometric chiral reagents is often expensive and impractical. In view of these limitations, there continues to be great interest in developing methods to re-oxidize the iodine reagent from iodine(I) to iodine(III) *in situ*. Of the few which do exist, the use of *m*CPBA, first reported by Kita in the stoichiometric oxidation of 1,3,5,7-tetrakis(4-iodophenyl)-adamantane in the presence of acetic acid, continues to be the most utilized (Scheme 3.3).[6] Initial catalytic variants of this approach utilizing stoichiometric quantities of *m*CPBA in conjunction with a catalytic amount of aryl iodide are the first examples of catalytic hypervalent iodine reactions, and were focused on application to oxylactonization reactions[7] (Scheme 3.3) or the *alpha*-functionalization of ketones,[8]

Scheme 3.3. Kita: Development of *m*CPBA as co-oxidant

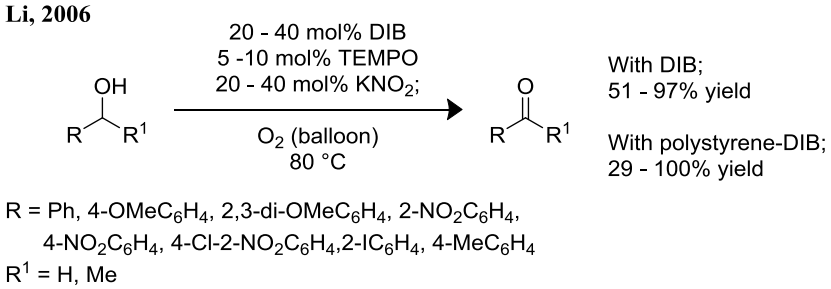


(Scheme 3.4) but have since been extended to include other transformations. The use of catalytic amounts of TEMPO and oxygen has been reported to access both iodine(III) and iodine(V). Li reported the catalytic oxidation of alcohols featuring catalytic iodine, TEMPO, and potassium nitrite with moderate to excellent yields (Scheme 3.5). Interestingly, a recyclable source of the (diacetoxy)iodobenzene was prepared by immobilization in polystyrene. At the end of the reaction, the reduced aryl iodide polymer was collected and regenerated.[9] Vinod reported the use of Oxone to access iodine(V) by the oxidation of iodobenzoic acid to IBX.[10] Recently, Oxone has also been reported to facilitate the generation of the hydroxy(phenyl)iodonium ion, which may be used to synthesize carbamates and benzylic ketones via 1,2-alkyl shift processes mediated

Scheme 3.4. Catalytic hypervalent iodine reactions: α-functionalization of ketones

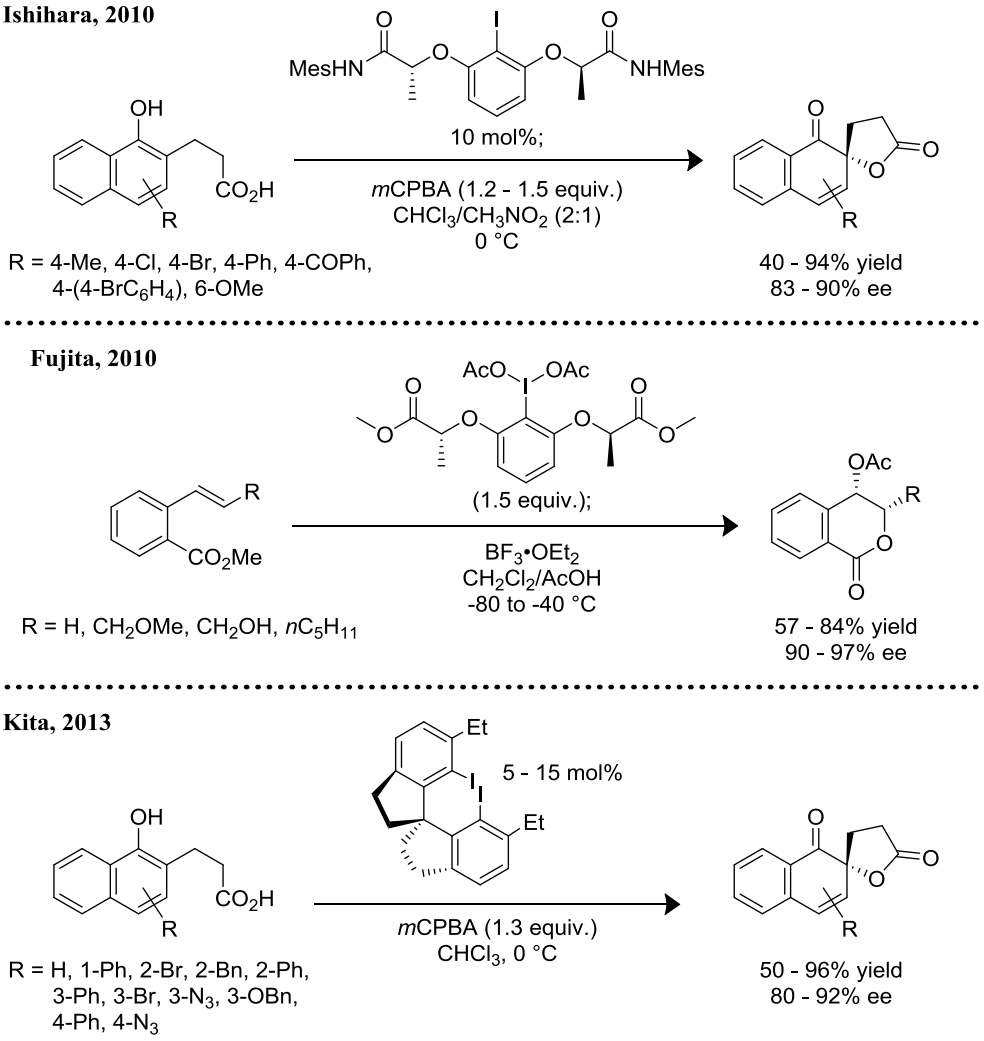


Scheme 3.5. Use of TEMPO/O_2/NO_2 to re-oxidize iodine *in situ*



by iodine(III).[11] Further development of alternative strategies utilizing catalytic iodine would be quite beneficial as it would expand the application of hypervalent iodine reagents. However, with respect to the use of alkenes, development of catalytic approaches remains challenging as oxidation of the substrate e.g. *m*CPBA, can be competitive with oxidation of the iodine(I) reagent to iodine(III).

Scheme 3.6. Chiral hypervalent iodine transformations

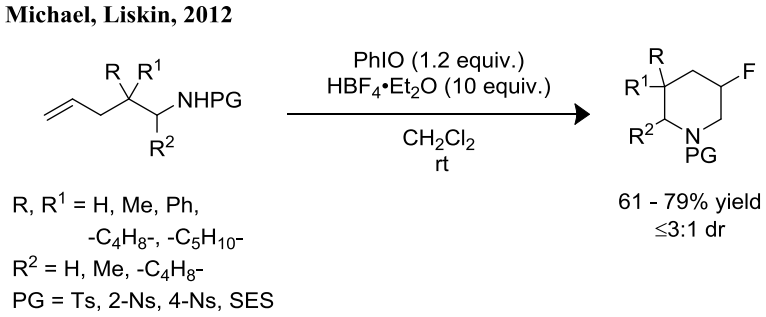


Although hypervalent iodine reagents have become popular due to their low toxicity, wide commercial availability, and convenient handling, variants that promote asymmetric transformations with high enantioselectivity are still quite rare.[12] Even rarer still are chiral transformations which are catalytic in the aryl iodide source. Several strategies have been attempted to adapt hypervalent iodine reagents to chiral

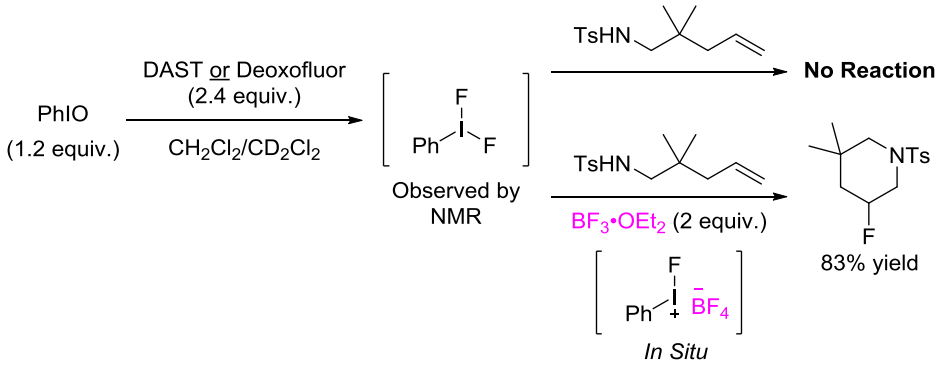
transformations. One of the most successful to date has been the incorporation of *ortho*-chiral moieties on the aryl iodide. In 2010, Ishihara (Scheme 3.6) reported the C_2-symmetric λ^3-iodane, (2*R*,2'*R*)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)bis(*N*-mesitylpropanamide) in the spirolactonization of 4-substituted naphth-1-ols with up to 90% ee.[13] Notably, this chiral λ^3-iodane was used in catalytic amounts with the co-oxidant *m*CPBA. Shortly thereafter, Fujita (Scheme 3.6) reported the (-)-methyl L-lactate-derived (*R*,*R*)-1,3-di(1-(methoxycarbonyl)ethoxy)-2-(diacetoxyiodo)benzene in the oxylactonization of a number of benzoic acid and benzoates with good regioselectivity and high enantioselectivity (up to 97% ee) for the *endo*-cyclization.[14] This reagent has been reported in other chiral transformations, such as styrene dioxygenation and diamination.[12] Kita (Scheme 3.6) has also reported a spirobiindane-based reagent, (+)-(*R*)-6,6'-diethyl-7,7'-diiodo-1,1'-spirobiindane, which could be used catalytically with the co-oxidant *m*CPBA to achieve similar yields, enantioselectivities, and catalyst loadings in the dearomotization of napthols compared to the Ishihara system (See Scheme 3.9), but with more varied substitution of the napthol.[15] Though these systems represent great progress in catalytic, metal-free alkene oxygenation and amination reactions, in general these chiral reagents are still used in stoichiometric quantities to achieve the best possible yields and enantioselectivities.

Our laboratory continues to pursue strategies for alkene difunctionalization promoted by hypervalent iodine(III) reagents. With respect to iodine(III)-mediated alkene aminofluorination (Scheme 3.7), mechanistic studies (Scheme 3.8) indicated that the

Scheme 3.7. *Endo*-cyclization: aminofluorination promoted by HBF_4Et_2O



Scheme 3.8. Mechanistic work implicating the monofluoroiodonium salt



development of a protocol which is catalytic in iodine might be feasible. Specifically, *in situ* generation of the hypervalent iodine(III) difluoride, which was observed to form by ^{1}H-NMR from the reaction of DAST or Deoxofluor with iodosylbenzene, unexpectedly showed no reactivity with the aminoalkene substrate. However, addition of a Lewis acid to activate the complex gave the desired product in 83% yield suggesting the active iodine species is actually the monofluoroiodonium.

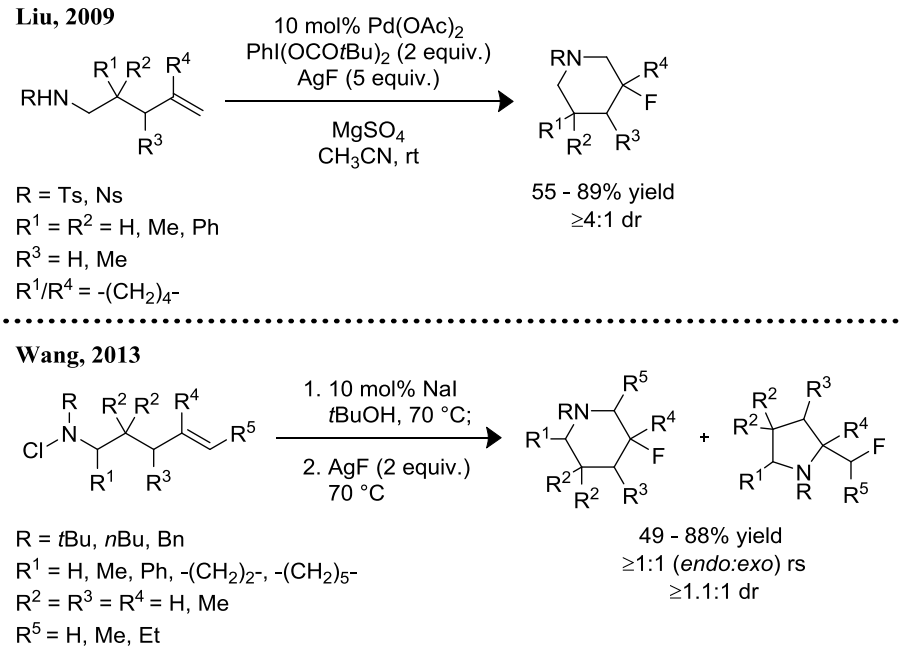
In view of this mechanistic data, it was proposed that the monofluoroiodonium species could alternately be generated by the reaction of an electrophilic fluorine source

such as an *N*-fluoropyridinium salt and an aryl iodide (Scheme 3.11). The main advantage of such a protocol would be the use of catalytic amounts of valuable aryl iodide starting materials, as well as the development of a brand-new, convenient iodine(I) to iodine(III) re-oxidation strategy using commercially available reagents. Other secondary benefits regarding the aminofluorination reaction specifically include eliminating the use of super stoichiometric amounts of acid and obviating the need for pre-synthesis of a chiral or achiral hypervalent iodine complex.

The synthesis of 3-fluoropiperidines products has been reported through the use of hypervalent iodine-mediated alkene aminofluorination. Liu used a Pd-catalyzed aminoalkene cyclization mediated by hypervalent iodine(III) in conjunction with superstoichiometric amounts of silver fluoride as the fluoride source (Scheme 3.9).[16] Silver fluoride was also utilized by Wang in the cyclization of *N*-iodoamines to give 3-fluoropiperidine products in modest to excellent yields and modest diastereo- and regio-selectivities (Scheme 3.9).

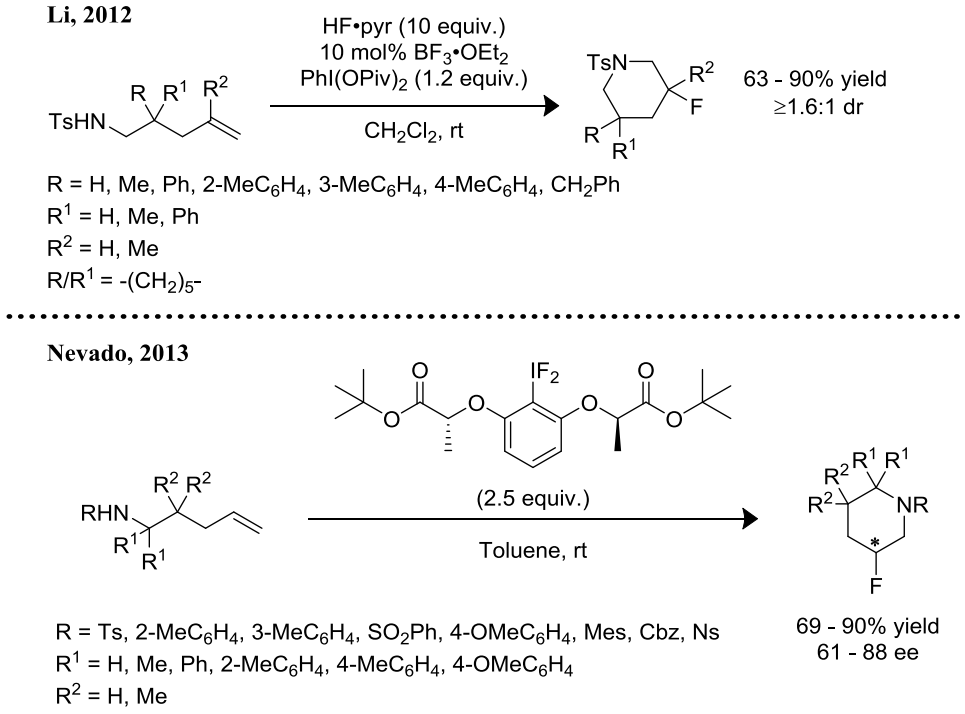
In addition to those promoted by metals, two metal-free alkene aminofluorination protocols are known. The first, reported by Li and coworkers while work on the development of the same transformation was underway in this laboratory, is a hydrogen fluoride-mediated regioselective cyclization to give *endo*-cyclized products (Scheme 3.10).[17] However, this protocol does utilize superstoichiometric amounts of the acid and possesses a limited substrate scope, which are unfortunately features of our own transformation as well (See Scheme 3.7). The second metal-free variant is a notable

Scheme 3.9. Metal-mediated syntheses of 3-fluoropiperidine derivatives



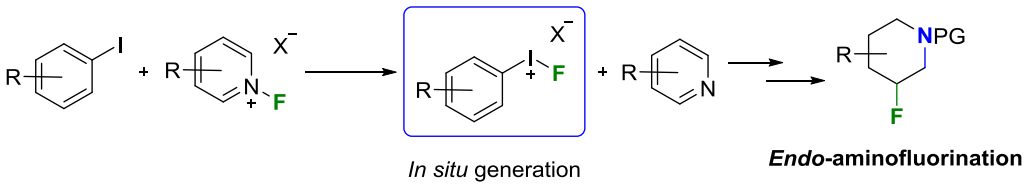
example by Nevado,[18] who utilized a chiral difluoro λ^3-iodane in the enantioselective formation of 3-fluoropiperdines (Scheme 3.10). This reagent features two chiral arms derived from amino acids flanking the iodine atom. The major drawback of the system is that the chiral iodine reagent is used in excess (2.5 equiv.). As it is not commercially available, nor trivial to synthesize and isolate, this diminishes the potential application of the system. Despite this limitation, the transformation is quite interesting considering the prevalence of fluorine in agricultural and medicinal compounds.[19] In view of these methods, complementary strategies which do not rely on large excesses of acid, the use of stoichiometric amounts of expensive metal reagents, or the use of sensitive stoichiometric chiral reagents would be beneficial.

Scheme 3.10. Metal-free syntheses of 3-fluoropiperidines



Development of a catalytic hypervalent procedure would address several of these issues, as well as contribute to the broader criticisms facing hypervalent iodine chemistry, including the aforementioned narrow selection of oxidant choices when developing catalytic hypervalent iodine reactions. Mechanistic studies of our own aminofluorination reaction suggest the key oxidative species is the monofluoroiodonium cation, and we propose to generate it using *N*-fluoropyridinium salts as a source of electrophilic fluorine (Scheme 3.11). This would facilitate the re-oxidation of catalytic aryl iodide *in situ* in a novel manner and may eventually expand the types of substrates or products which could be accessed using our hypervalent iodine chemistry. In this chapter, we explore this approach in the *intramolecular* difunctionalization of alkene substrates.

Scheme 3.11. Proposal: Generation of monofluoroiodonium cations from 1-fluoropyridinium salts



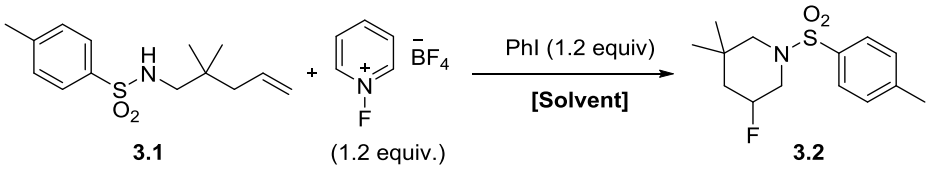
Section 2. Results and Discussion

3.2.a Initial exploration of 1-fluoropyridinium salts

Initial screens began with 1-fluoropyridinium tetrafluoroborate and iodobenzene using the tosyl-protected aminoalkene substrate **3.1** previously utilized by us in alkene aminofluorination, diamination, and oxyamination products. In initial experiments, this fluorinating reagent failed to give the desired product **3.2**, and aminoalkene starting material was recovered at room temperature (Table 3.1, Entry 1) or at 80 ˚C (Table 3.1, Entries 2,3).

We observed that the 1-fluoropyridinium tetrafluoroborate salt displayed relatively poor solubility in the test system; therefore, we explored the more soluble 2,4,6-trimethylfluoropyridinium salt under the same conditions (Table 3.2). We also examined whether the counterion might affect the reactivity of the fluoropyridinium salt (Table 3.2, Entries 3,4). Unfortunately, again no desired product **3.2** was observed, and the aminoalkene starting material **3.1** was recovered.

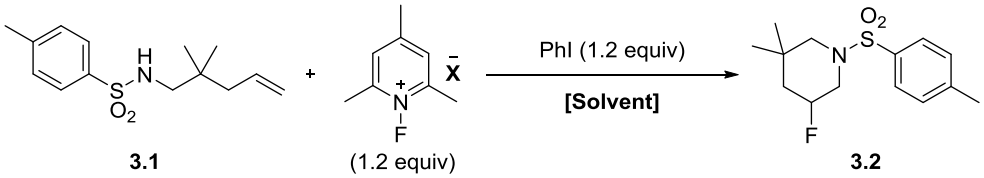
Table 3.1. *endo*-Cyclization screen with 1-fluoropyridinium tetrafluoroborate



Entry	**Solvent**	Temperature	Yield **3.2**[a] (%)
1	CH_2Cl_2	rt	N.R. (SM)
2	$(ClCH_2)_2$	reflux	N.R. (SM)
3	MeCN	reflux	N.R. (SM)

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

Table 3.2. *endo*-Cyclization screen with 1-fluoro-2,4,6-trimethylpyridinium salts



Entry	Counterion (**X**)	Solvent	Temperature	Yield **3.2**[a] (%)
1	BF_4	CH_2Cl_2	rt	N.R. (SM)
2	BF_4	$(ClCH_2)_2$	reflux	N.R. (SM)
3	BF_4	MeCN	reflux	N.R. (SM)
4	OTf	MeCN	reflux	N.R. (SM)

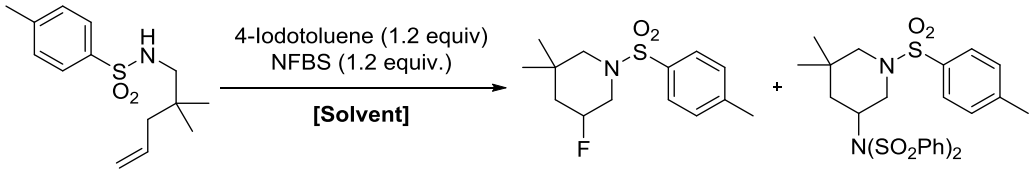
[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

3.2.b Use of more reactive electrophilic fluorine reagents: NFBS, Selectfluor

Given the initial negative results with 1-fluoropyridinium salts, we reasoned that a more reactive electrophilic fluorinating reagent was needed. To this end, we selected *N*-fluorobenzenesulfonimide (NFBS). Use of NFBS gave *endo*-cyclization to form the

diamination product **3.3** (Table 3.3, Entries 2,4) from incorporation of the sulfonimide anion with either poor regioselectivity or low yields at refluxing conditions. When used at room temperature, starting material **3.1** was recovered (Table 3.3, Entries 1, 3).

Table 3.3. *endo*-Cyclization screen with *N*-Fluorobenzenesulfonimide

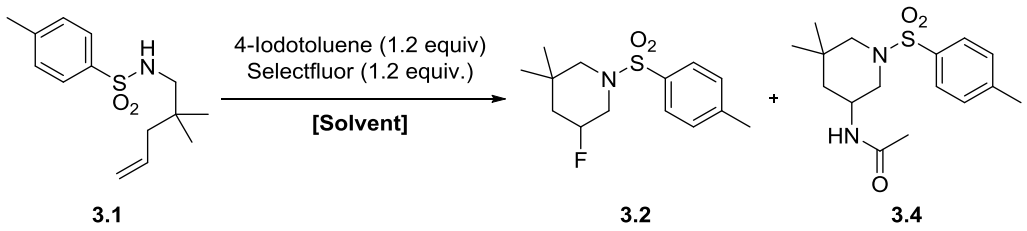


Entry	**Solvent**	Temp	Yield **3.2 : 3.3**[a] (%)
1	CH_2Cl_2	rt	N.R. (SM)
2	$(ClCH_2)_2$	reflux	0 : 65 (*endo*:*exo*, 2:1)
3	MeCN	rt	N.R. (SM)
4	MeCN	reflux	0 : 27 (*exo*)

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

Investigation of Selectfluor as a potential fluorinating reagent in several solvents (Table 3.4) resulted in modest yields of the diamination product **3.4** from the incorporation of the acetonitrile solvent (Table 1.4, Entries 4,5). Formation of the acetamide is a result of the nucleophilic attack on the aziridinium by acetonitrile, followed by hydrolysis of the resulting nitrilium. Finally, subsequent tautomerization gives the 3-aminopiperidine

Table 3.4. *endo*-Cyclization screen with Selectfluor



Entry	**Solvent**	Temp	Yield **3.2 : 3.4**[a] (%)
1	CH_2Cl_2	rt	N.R. (SM)
2	$(ClCH_2)_2$	reflux	N.R. (SM)
3	Chlorobenzene	reflux	N.R. (SM)
4	MeCN	rt	0 : 20
5	MeCN	reflux	0 : 23

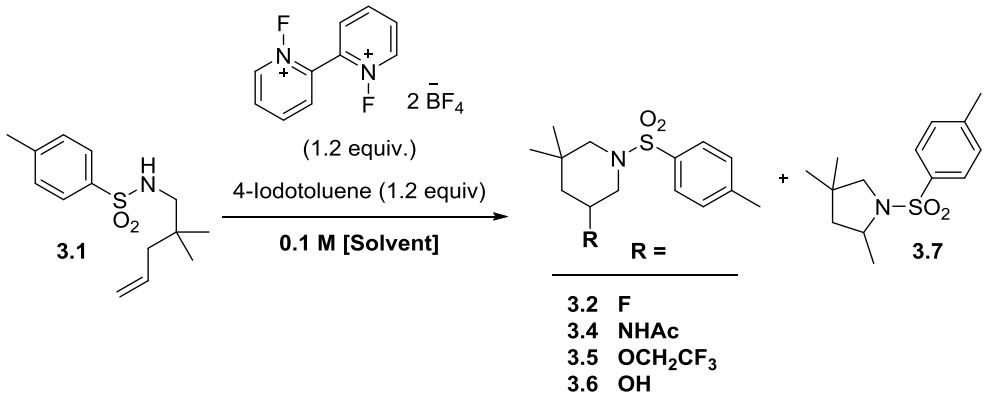
[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

structure.[20] These products have been previously observed in the development of our oxidative chemistry.[5] In the absence of an incorporating solvent, starting material **3.1** was recovered (Table 3.4, Entries 1-3). Higher temperatures were ineffective at promoting any reactivity (Table 3.4, Entries 2,3) and no *endo*-aminofluorination was observed.

3.2.c Utilization of 1,1'-difluoro-2,2'-bipyridinium (bis)tetrafluoroborate

Initial exploration of reactivity using the bipyridinium system (Table 3.5), 1,1'-difluoro-2,2'-bipyridinium (bis) tetrafluoroborate (MEC-31) in a number of solvents did produce some interesting results. A control experiment run in the absence of 4-iodotoluene (Table 3.5, Entry 1) resulted in no formation of any oxidative cyclization products suggesting that the iodine is participating in product formation, and instead the *exo*-hydroamination product **3.7** was observed in 64% yield. This arises from the acid-promoted formation of

Table 3.5. *endo*-Cyclization screen with MEC-31

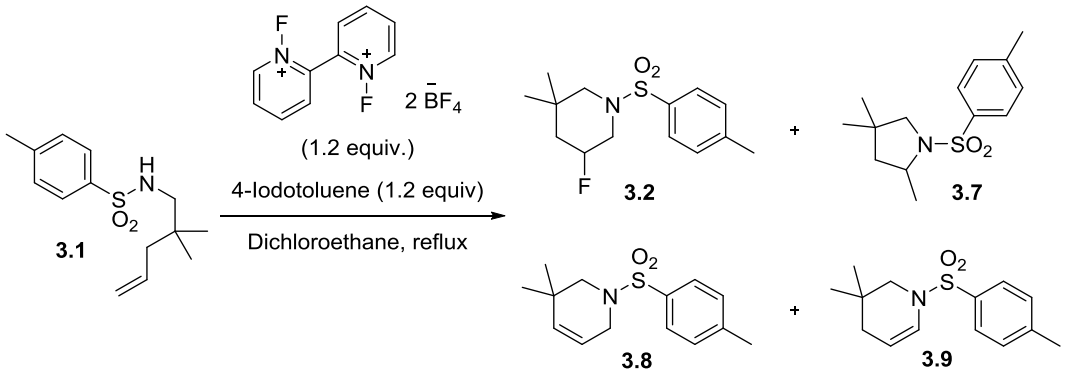


Entry	**Solvent**	Temp	**Product**	Yield[a] (%)
1	MeCN (no Iodine)	reflux	**3.7**	64
2	MeCN	reflux	**3.4**	90
3	DCE	reflux	---	N.R. (SM)
4	Chlorobenzene	reflux	---	N.R. (SM)
5	CF_3CH_2OH	reflux	**3.5**	84
6	$(CF_3)_2CHOH$	reflux	---	Complex Mixture
7	Nitromethane	rt	**3.6**	54

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

a carbenium ion at the internal position of the alkene, and subsequent cyclization suggesting that the fluorinating reagent was decomposing under the reaction conditions to generate HF. The use of fluorinated alcohol solvents (Table 3.5, Entries 5,6) resulted in either incorporation of the alkoxy group or a complex mixture, while use of nitromethane (Table 3.5, Entry 7) led to the formation of the alcohol presumably from water incorporation. Similarly to the formation of the acetamide, the alkoxy- and hydroxy-products arise from attack on the aziridinium intermediate. When acetonitrile was used, the acetamide was incorporated very efficiently in 90% yield by ^{1}H-NMR

Table 3.6. *endo*-Cyclization screen with MEC-31: Investigation of additives



Entry	Additive(s)	Product(s)	Yield[a] (%)
1	none	---	N.R. (SM)
2	10 mol% NaOTf	---	N.R. (SM)
3	10 mol% NaOTf; 1 equiv. MeCN	**3.7 : 3.8/3.9**	15 : 17 : SM

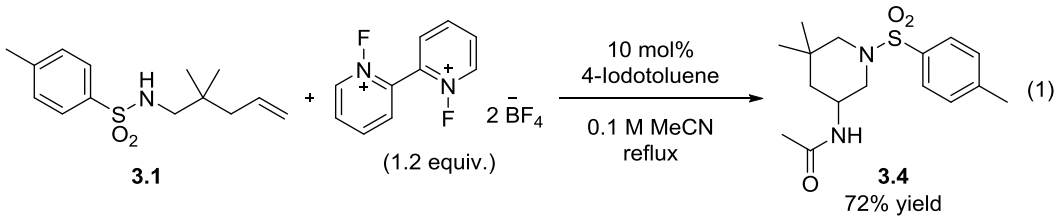
[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

spectroscopy (Table 3.5, Entry 2). Unfortunately, in the comparably less polar solvents such as dichloroethane, or chlorobenzene, (Table 3.5, Entries 3,4) starting material was recovered and no fluorinated products were observed.

We observed that MEC-31 displayed poor solubility the in relatively non-polar solvents such as dichloroethane and chlorobenzene. Sodium triflate has been used by others to increase the solubility of MEC-31[21]; however, in our system, this was not effective in promoting any reaction and starting material **3.1** was recovered (Table 3.6, Entry 2). Although we did not observe any of the desired aminofluorination product when the reaction with sodium triflate in dichloroethane was repeated (Table 3.6, Entry 3) with only one equivalent of acetonitrile, hydroamination **3.7** (15%) and elimination (17%)

products were present. Generation of **3.8** and **3.9** has previously been observed in our chemistry, and arise from base promoted eliminations of in this case most likely the aziridinium. As these are acid and base promoted products respectively, this result is suggestive that inclusion of polar solvents may increase the solubility of these reagents but also accelerate the rate of decomposition of the fluorinating reagent.

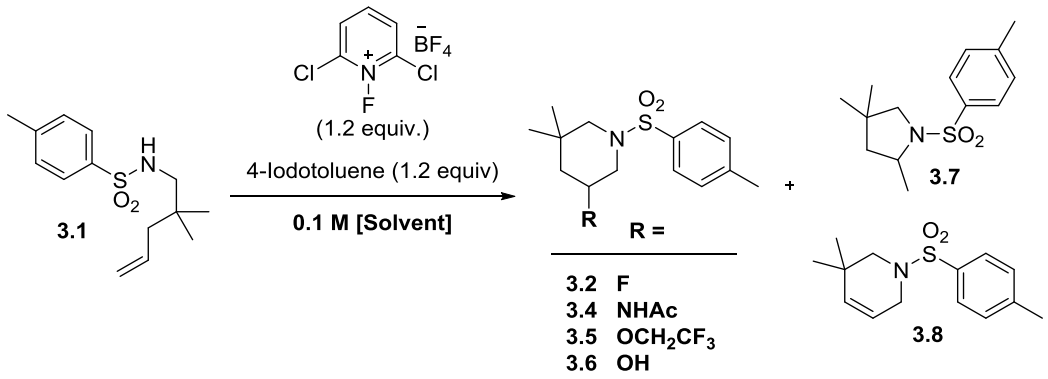
Given the excellent yield of the diamination product **3.4** (90% yield; Table 3.5, Entry 2), we were very interested in adapting these reaction conditions to allow the use of a catalytic amount of iodine. In a reaction (eq 1) using only 10 mol% 4-iodotoluene and stoichiometric 1,1'-difluoro-2,2'-bipyridinium(bis)tetrafluoroborate 72% yield of **3.4** was observed. This result was very encouraging, as it was a successful proof of concept for our iodine re-oxidation strategy.



3.2.d Incorporation of fluoride; 2,6-dichloro-1-fluoropyridinium tetrafluoroborate

As the desired incorporation of fluoride had yet to be observed, we continued our investigations using 2,6-dichloro-1-fluoropyridinium tetrafluoroborate. A control reaction is dichloromethane (Table 3.7, Entry 1) in the absence of aryl iodine resulted in no conversion of the aminoalkene starting material. Inclusion of 4-iodotoluene resulted in

Table 3.7. *endo*-Cyclization screen with 2,6-dichloro-1-fluoropyridinium tetrafluoroborate



Entry	**Solvent**	Temp	**Product**	Yield[a] (%)
1	CH_2Cl_2 (No Iodine)	rt	---	N.R. (SM)
2	CH_2Cl_2	rt	**3.2 : 3.7/3.8**	20 : 23
3	CH_2Cl_2	0 °C	---	N.R. (SM)
4	Et_2O:CH_2Cl_2 (2:1)	rt	---	N.R. (SM)
5	Nitromethane	rt	**3.6**	60
6	MeCN (No Iodine)	rt	---	N.R. (SM)
7	MeCN	reflux	**3.4**	40
8	MeCN	rt	**3.4**	83
9	MeCN (0.01 M)	rt	---	Complex Mixture

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

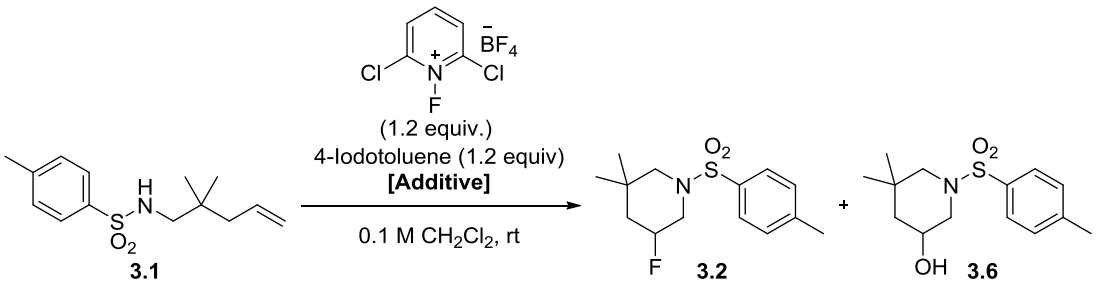
20% yield of the desired *endo*-aminofluorination product in dichloromethane at room temperature (Table 3.7, Entry 2) as well as hydroamination and elimination byproducts. As noted previously, these byproducts are attributed to decomposition of the fluorinating reagent. In an attempt to limit this unproductive pathway, the reaction was repeated at 0 ˚C (Table 3.7, Entry 3); however no reaction was observed at this temperature. Inclusion of diethyl ether as a co-solvent (Table 3.7, Entry 4) resulted in no conversion of the

starting material, and use of nitromethane resulted in oxyamination **3.6** (Table 1.7, Entry 5). When acetonitrile was used in the absence of 4-iodotoluene, no products were observed (Table 3.7, Entry 6), however with iodine 83% of the diamination **3.4** was observed at room temperature (Table 3.7, Entry 7). If the reaction was run at reflux in acetonitrile the yield of **3.4** was diminished to 40% (Table 3.7, Entry 8), and diluting the acetonitrile concentration resulted in a complex mixture (Table 3.7, Entry 9).

3.2.e Reaction optimization using 2,6-dichloro-1-fluoropyridinium tetrafluoroborate

With our exciting, albeit modest result (20% of **3.2**), we examined additives in an effort to increase the yield of alkene aminofluorination using 2,6-dichloro-1-fluoropyridinium tetrafluoroborate. Basic additives were examined as a means to promote the formation of fluoride anion, as well as to limit any acid-promoted side reactions such as hydroamination (Table 3.8). However, the use of sterically-hindered pyridine bases completely inhibited the reaction, and only the aminoalkene starting material was recovered (Table 3.8, Entries 2,3). Inorganic bases, such as cesium carbonate (Table 3.8, Entry 4), afforded a slight increase in aminofluorination, but also resulted in formation of the *endo*-oxyamination cyclization **3.6**.

Table 3.8. Optimization of the *endo*-aminofluorination using 2,6-dichloro-1-fluoropyridinium tetrafluoroborate

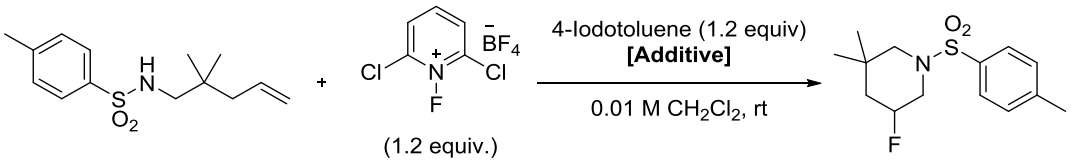


Entry	**Additive(s)**	Yield **3.2 : 3.6**[a] (%)
1	none	20 : 0
2	2,6-Lutidine (1.2 equiv.)	N.R. (SM)
3	2,6-Di-*tert*-butylpyridine (1.2 equiv.)	N.R. (SM)
4	Cs_2CO_3 (1.2 equiv.)	28 : 30

[a] Yield determined by ^{1}H-NMR using 1,3-dinitrobenzene as internal standard.

During the optimization of a tetrafluoroboric acid-promoted alkene aminofluorination reaction previously developed in our lab (Section 1, Scheme 3.7), we observed a marked dependence of product yield on the concentration of the solvent.[5] At higher concentrations, significantly more byproducts derived by reaction with adventitious water, such as *endo*-oxyamination **3.6** or the ether-dimer of 3-fluoropiperidine, were observed than when dilute conditions were used. This strategy proved to be quite effective in this system as well, and dilution of the solvent (Table 3.9, Entry 1) resulted in a 61% yield of the desired product **3.2**.

Table 3.9. Optimization of the *endo*-aminofluorination at dilute concentrations



Entry	Additive(s) (equiv.)	Yield[a] (%)
1	none	61[b]
2	$FSiPh_3$ (1.2 equiv.)	69
3	$FSiPh_3$ (1.2 equiv.); $MgSO_4$ (1 equiv.)	74
4	$FSiPh_3$ (2.4 equiv.)	84
5	$FSiPh_3$ (3.6 equiv.)	88
6	TMSOTf (1.2 equiv.)	8
7	2 % w/v 4 Å molecular sieves	46
8	TBAT (1.2 equiv.)	N.R. (SM)

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [b] At 0.1 M dichloromethane, the yield of the product is 20%.

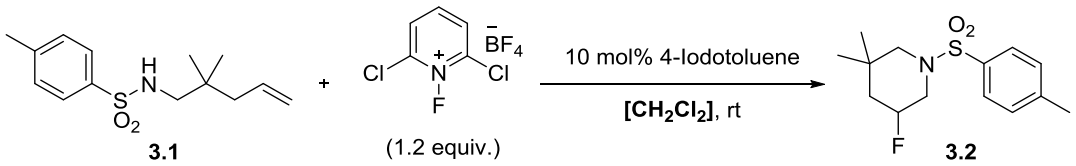
Further screening of additives revealed that inclusion of fluorotriphenylsilane resulted in a modest improvement, while increasing the concentration of fluorotriphenylsilane (Table 3.9, Entries 2-5) also was advantageous, although its role in the reaction was not entirely clear. We hypothesized that fluorotriphenylsilane could be acting as a drying agent, so other additives known to be efficient water scavengers were tested (Table 3.9, Entries 6,7). Addition of TMS triflate (TMSOTf) or molecular sieves resulted in much lower conversions to the desired products suggesting that fluorotriphenylsilane was unlikely to be acting solely as a drying agent. Its role as a potential nucleophilic source of fluoride was also postulated, however inclusion of tetrabutylammonium difluorotriphenylsilicate (TBAT), the commercially available difluorosilicate salt of fluorotriphenylsilane,

completely inhibited the reaction (Table 3.9, Entry 8). Though purely speculative at this point, it could also be acting as a source of small quantities of HF or perhaps a Lewis acid. However, the latter seems unlikely as it is not a highly reactive Lewis acid. Furthermore, addition of TMSOTf triflate (1.2 equiv, 8% yield), which is a well-known and highly reactive Lewis acid, did not improve the yield of the aminofluorination in comparison to when fluorotriphenylsilane (1.2 equiv., 69% yield) was used, suggesting that the fluorotriphenylsilane probably does not act as a Lewis acid in this reaction.

3.2.f Optimization of a catalytic iodine procedure; 2,6-dichloro-1-fluoropyridinium tetrafluoroborate

After optimizing the stoichiometric aminofluorination reaction with 2,6-dichloro-1-fluoropyridinium, we turned to the development of a catalytic procedure as the ultimate goal of this re-oxidation strategy with *N*-fluoropyridinium salts. In an initial reaction using 10 mol% of 4-iodotoluene under the reaction conditions, only 19% yield of the desired product was observed (Table 3.10, Entry 1). Considering the dependence of product yield in the afore-developed stoichiometric reaction on the concentration, a screen was undertaken to see if the catalytic reaction would display the same dependence (Table 3.10). Unfortunately, if the reaction was run relatively concentrated (Table 3.10, Entry 5) or more dilute (Table 3.10, Entry 2), the yield of **3.2** remained around 20% when catalytic amounts of iodine were employed.

Table 3.10. Concentration screen: Catalytic *endo*-aminofluorination using 2,6-Dichloro-1-fluoropyridinium tetrafluoroborate



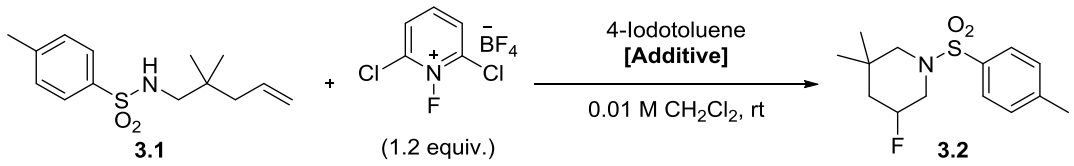
Entry	**Concentration**	Yield **3.2**[a] (%)
1	0.01	19
2	0.015	14
3	0.02	16
4	0.05	16
5	0.1	19

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

As a next course of action, additives were explored. Again, we found inclusion of fluorotriphenylsilane increased the yield of **3.2** (Table 3.11, Entries 2,3). Whether the silane was in excess or merely co-catalytic resulted in similar results. As we had postulated that the silane additive may be a source of hydrogen fluoride, catalytic amounts of fluoride sources were tested. Inclusion of hydrogen fluoride pyridine, HBF_4, or cesium fluoride (Table 3.11, Entries 4-6) either had no effect or led to a decreased yield as compared to the reaction with no additive (Table 3.11, Entries 1) suggesting that is not the role of the silane. Use of tetrabutylammonium salts (TBAF, TBAT; Entries 7,8) completely inhibited the reaction and no product was observed. Increasing the amount of aryl iodide to 20 mol% led to a slight increase of **3.2** (Table 3.11, Entry 9) and inclusion of fluorotriphenylsilane with 20 mol% 4-iodotoluene resulted in about 50% of the desired product **3.2** (Table 3.11, Entry 10). The role of the silane was further investigated via the

use of alternative silane sources. Inclusion of both chlorotriphenylsilane (Table 3.11, Entry 11) or trimethyl(phenyl)silane (Table 3.11, Entry 12) led to about 50% of **3.2**. In particular trimethyl(phenyl)silane is a known non-nucleophilic proton trap that reacts irreversibly with Brønsted acids via cleavage of Si-Ph bond.[22] This data may suggest either an acid-promoted side reaction or decomposition pathway is operative under the reaction conditions, and that the silane's role is actually as a non-nucleophilic acid scavenger.

Table 3.11. Optimization of the catalytic *endo*-aminofluorination using 2,6-dichloro-1-fluoropyridinium tetrafluoroborate



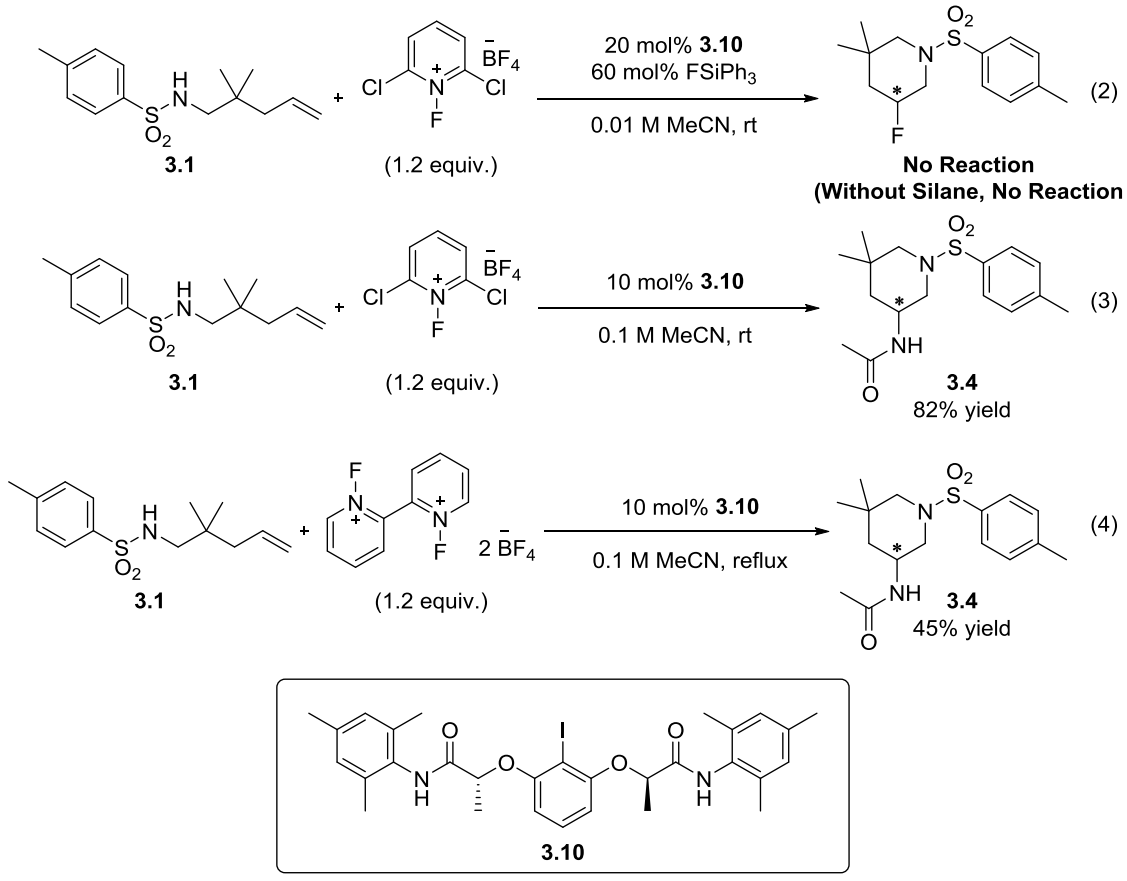
Entry	4-Iodotoluene (mol%)	**Additive(s)**	Yield **3.2**[a] (%)
1	10	none	19
2	10	$FSiPh_3$ (3.6 equiv.)	44
3	10	$FSiPh_3$ (30 mol%)	49
4	10	HF·Pyridine (30 mol%)	8
5	10	$HBF_4 \cdot Et_2O$ (30 mol%)	17
6	10	CsF (30 mol%)	5
7	10	TBAF (30 mol%)	No Reaction
8	10	TBAT (30 mol%)	No Reaction
9	20	none	32
10	20	$FSiPh_3$ (60 mol%)	48
11	20	$ClSiPh_3$ (60 mol%)	42
12	20	$PhSiMe_3$ (60 mol%)	54

[a] Yield determined by ^{1}H-NMR using 1,3-dinitrobenzene as internal standard.

3.2.g Screen of a chiral aryl iodide source

As we had optimized the catalytic aminofluorination procedure to about 50% yield of product (see Table 1.11) in the presence of a catalytic amount of iodide, we investigated the use of a chiral source of the aryl iodine in conjunction with our reoxidation strategy. This transformation is known to proceed through an aziridinium intermediate (see Section 1, Scheme 3.2); therefore, we screened a chiral iodine source **3.10** that has successfully been used in an enantioselective diamination proposed by Muñiz and coworkers to also proceed through an aziridinium intermediate.[23] Unfortunately, under these reaction conditions no aminofluorination product **3.2** was observed (Scheme 3.12, eq 2). With only this preliminary result in hand, it is unclear whether or not there is an issue with the fluorotriphenylsilane additive or perhaps the current reaction conditions; consequently, investigations are ongoing. Using the same chiral iodide source **3.10**, the reaction was run in acetonitrile to generate the diamination product. In contrast to the aminofluorination, the reaction worked with both oxidants. In the presence of 2,6-dichloropyridinium tetrafluoroborate (Scheme 3.12, eq 3), the product **3.4** was observed in 82% yield after several days, and use of 1,1'-difluoro-2,2'-bipyridinium (bis)tetrafluoroborate (Scheme 3.12, eq 4) led to a 45% yield of **3.4**.

Scheme 3.12. Catalytic reactions featuring a chiral aryl iodide



Section 3. Conclusions

In conclusion, a new method of promoting the re-oxidation of iodine *in* situ when carrying out iodine(III) oxidative alkene difunctionalizations was developed. Through the use of either 2,6-dichloro-1-fluoropyridinium tetrafluoroborate or 1,1'-difluoro-2,2'-bipyridinium(bis)tetrafluoroborate and catalytic quantities of an aryl iodide, formation of 3-amino- and 3-fluoro-piperidine derivatives from tosyl protected aminoalkenes was

observed with excellent regioselectivity for *endo*-cyclization with moderate to excellent yields. Importantly, this is a mild oxidative process tolerant of both the aminoalkene starting material and the presence of the resulting product, and generates relatively non-reactive byproducts in the form of 2,6-dichloropyridine and 2,2'-bipyridine that are unlikely to participate in base-promoted side reactions to a significant degree.

Section 4. Experimental

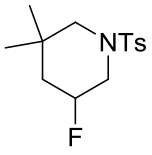
General Procedures. All reactions were performed under a nitrogen atmosphere using flame-dried glassware and standard air-free techniques. Column chromatography was performed using silica gel (Whatman, 60Å, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of trimethylsilane and are referenced relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts are referenced to the carbon resonance of the deuterated solvent $CDCl_3$ (77.0 ppm). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and assignment. Mass spectra were collected on a JEOL HX-110 Mass Spectrometer or a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer. Optical rotations ($[\alpha]_D^{22}$ values) are reported in 10^{-1} deg cm^2 g^{-1}. Chiral HPLC analysis was performed on Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474

scanning fluorescence, measured at 215 nm; column, DIACEL CHIRALPAK AD-H and CHIRALPAK OD-H; mobile phase, hexanes/2-propanol.

Materials. Dichloromethane, acetonitrile, diethyl ether, and tetrahydrofuran were degassed with nitrogen and dried by passing through a column of neutral alumina. Toluene was degassed with nitrogen and dried by passing through a column of neutral alumina and a column of Q5 reactant. All other solvents were distilled before use and stored under an atmosphere of nitrogen and on 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4Å molecular sieves and were used without further purification. Commercial reagents 1-Fluoropyridinium tetrafluoroborate, 2,4,6-Trimethyl-1-fluoropyridinium triflate, 2,4,6-Trimethyl-1-fluoropyridinium tetrafluoroborate, 2,6-Dichloro-1-fluoropyridinium triflate, *N*-Fluorobenzenesulfonimide (NFBS), Selectfluor, Iodobenzene, 4-Iodotoluene, 2,6-Lutidine, 2,6-Di-*tert*-butylpyridine, Cesium carbonate, Fluorotriphenylsilane, Trimethylsilyl trifluoromethanesulfonate (TMSOTf), Tetrabutylammonium difluorotriphenylsilicate (TBAT), 1,1’-Difluoro-2,2’-bipyridinium (bis)tetrafluoroborate from Sigma-Aldrich, TCI, Strem, Pressure Chemicals, or VWR and were used as received.

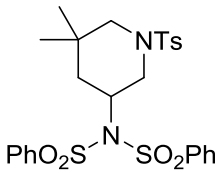
3.1

***N*-(2,2-Dimethylpent-4-enyl)-4-methylbenzenesulfonamide (3.1):** Spectra matched literature values.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (2 H, d, *J* = 8.1 Hz, Ts), 7.29 (2 H, d, *J* = 8.1 Hz, Ts), 5.71 (1 H, m, C*H*), 5.01 (2 H, m, CHC*H*$_2$), 4.33 (1 H, br s, N*H*), 2.69 (2 H, d, *J* = 6.9 Hz, NC*H*$_2$), 2.43 (3 H, s, Ts-C*H*$_3$), 1.96 (2 H, d, *J* = 7.5 Hz, C*H*$_2$CH), 0.86 (6 H, s, C(C*H*$_3$)$_2$).



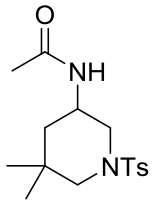
3.2

5-Fluoro-3,3-dimethyl-1-tosylpiperidine (3.2): Spectra matched literature values.[5] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (2 H, d, *J* = 8.0 Hz, Ts), 7.33 (2 H, d, *J* = 7.5 Hz, Ts), 4.77 (1 H, dtt, *J* = 4.5, 8.0, 47.5 Hz, C*H*(F)), 3.62 (1 H, m, CH(F)C*H*$_2$N), 2.97 (1 H, d, *J* = 11.0 Hz, C*H*$_2$N), 2.61 (1 H, m, CH(F)C*H*$_2$N), 2.44 (3 H, s, Ts-C*H*$_3$), 2.37 (1 H, d, *J* = 11.5 Hz, C*H*$_2$N), 1.69 (1 H, m, C*H*$_2$CH(F)), 1.46 (1 H, m, C*H*$_2$CH(F)), 1.03 (3 H, s, C*H*$_3$), 1.02 (3 H, s, C*H*$_3$); GC/MS: 18.29 min, m/z = 285 (21, M), 198 (51, M-87), 155 (42, Ts), 130 (100, M-Ts), 91 (53, Tol).



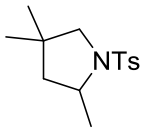
3.3

***N*-(5,5-dimethyl-1-tosylpiperidin-3-yl)benzenesulfonamide (3.3)**: Spectra matched literature values.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (3 H, m, Ph), 7.77 – 7.67 (3 H, m, Ar), 7.62 (4 H, m, Ar), 7.53 (2 H, m, Ar), 7.32 (2 H, m, Ar), 4.39 (1 H, br m, C*H*(N[SO_2Ph]$_2$)), 3.56 (1 H, d, *J* = 7.5 Hz, CH(N[SO_2Ph]$_2$)CH_2N), 3.29 (1 H, d, *J* = 12.0 Hz, CH_2N)), 2.89 (1 H, t, *J* = 10.9 Hz, CH(N[SO_2Ph]$_2$)CH_2N), 2.45 (3 H, s, Ts-CH_3), 2.06 (2 H, m), 1.39 (1 H, d, *J* = 11.7 Hz, CH_2CH), 1.06 (3 H, s, CH_3), 0.91 (3 H, s, CH_3).



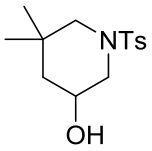
3.4

***N*-[5,5-Dimethyl-1-(toluene-4-sulfonyl)-piperidin-3-yl]-acetamide (3.4):** Spectra matched literature values.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (2 H, d, *J* = 8.1 Hz, Ts), 7.32 (2 H, d, *J* = 7.8 Hz, Ts), 5.35 (1H, br s, NH), 4.15 (1 H, m, C*H*), 3.62 (1 H, dd, *J* = 4.1, 11.0 Hz, NCH_2), 3.03 (1 H, d, *J* = 11.1 Hz, NCH_2), 2.43 (3 H, s, Ts-CH_3), 2.25 (2 H, m, CH_2CH), 1.95 (3 H, s, CH_3), 1.72 (2 H, m, CH_2CH), 1.00 (1 H, m, CH_2CH), 1.06 (3 H, s, CH_3), 0.95 (3 H, s, CH_3); GC/MS: 16.80 min, m/z = 283 (8, M), 128 (100, M-Ts), 91 (45, Tol).



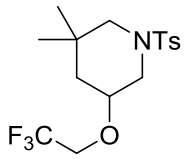
3.7

***N*-(4-Toluenesulfonyl)-2-methylpyrrolidine (3.7):** Spectra matched literature values.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (2 H, d, *J* = 7.8 Hz, Ts), 7.30 (2 H, d, *J* = 7.8 Hz, Ts), 3.64 (1 H, m, C*H*), 3.16 (1 H, d, *J* = 10.5 Hz, NCH_2), 3.06 (1 H, d, *J* = 10.5 Hz, NCH_2), 2.43 (3 H, s, Ts-CH_3), 1.73 (1 H, dd, *J* = 8.0, 12.4 Hz, CH_2CH), 1.40 (3 H, d, *J* = 6.0 Hz, CHCH_3), 1.34 (1 H, m, CH_2CH), 1.03 (3 H, s, CH_3), 0.55 (3 H, s, CH_3); GC/MS: 15.06 min, m/z = 267 (3, M), 252 (98, M-CH3), 155 (74, Tol-SO_2), 91 (100, Tol).



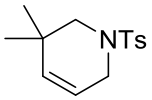
3.6

5,5-Dimethyl-1-(toluene-4-sulfonyl)-piperidin-3-ol (3.6): Spectra matched literature values.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (2 H, d, *J* = 8.0 Hz, Ts), 7.34 (2 H, d, *J* = 8.0 Hz, Ts), 3.99 (1 H, septet, *J* = 4.5 Hz, C*H*), 3.82 (1 H, d, *J* = 10.5 Hz, NCH_2), 3.20 (1 H, d, *J* = 11.0 Hz, NCH_2), 2.43 (3 H, s, Ts-CH_3), 2.02 (2 H, m, CH_2CH), 1.72 (2 H, m, CH_2CH), 1.00 (1 H, m, CH_2CH), 1.06 (3 H, s, CH_3), 0.95 (3 H, s, CH_3); GC/MS: 16.80 min, m/z = 283 (8, M), 128 (100, M-Ts), 91 (45, Tol).



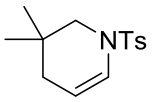
3.5

3,3-Dimethyl-1-tosyl-5-(2,2,2-trifluoroethoxy)piperidine (3.5): Spectra matched literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (2 H, d, *J* = 8.4 Hz, Ts), 7.33 (2 H, d, *J* = 8.1 Hz, Ts), 3.91 (3 H, m, C*H*$_2$CF$_3$, CHC*H*$_2$), 3.75 (1 H, septet, *J* = 4.5 Hz, C*H*), 3.23 (1 H, d, *J* = 11.4 Hz, NC*H*$_2$), 2.43 (3 H, s, Ts-C*H*$_3$), 2.04 (2 H, m, NC*H*$_2$), 2.02 (2 H, m, C*H*$_2$CH), 1.78 (1 H, dd, J = 3.9, 12.9 Hz, C*H*$_2$CH), 1.06-1.00 (1 H, m, C*H*$_2$CH), 1.06 (3 H, s, C*H*$_3$), 0.95 (3 H, s, C*H*$_3$); GC/MS: 18.43 min, m/z = 365 (7, M), 210 (100, M-Ts), 155 (31, Ts), 91 (45, Tol).



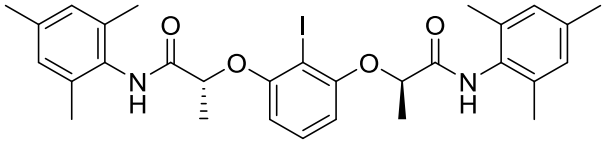
3.8

3,3-Dimethyl-1-tosyl-1,2,3,6-tetrahydropyridine (3.8): Product isolated by column chromatography (90/10, Hexanes/Ethyl Acetate; TLC visualized with $KMnO_4$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (2 H, d, *J* = 8.4 Hz, Ts), 7.31 (2 H, d, *J* = 7.8 Hz, Ts), 5.48 (2 H, m, C*H*=C*H*), 3.48 (2 H, d, *J* = 1.5 Hz, CHC*H*$_2$N), 2.82 (2 H, s, C*H*$_2$N), 2.43 (3 H, s, Ts-C*H*$_3$), 1.05 (6 H, s, C(C*H*$_3$)$_2$); GC/MS: 18.19 min, m/z = 265 (9, M), 155 (9, Ts), 91 (22, Tol), 82 (100, M-183).



3.9

3,3-Dimethyl-1-tosyl-1,2,3,4-tetrahydropyridine (3.9): Product isolated by column chromatography (90/10, Hexanes/Ethyl Acetate; TLC visualized with $KMnO_4$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (2 H, d, *J* = 8.1 Hz, Ts), 7.31 (2 H, d, *J* = 8.1 Hz, Ts), 6.63 (1 H, dt, *J* = 1.8, 8.4 Hz, NC*H*=CH), 4.84 (1 H, dt, *J* = 3.9, 7.9 Hz, NCH=C*H*), 2.92 (2 H, s, CH_2N), 2.42 (3 H, s, Ts-CH_3), 1.69 (2 H, br m, CH_2CH=CH), 0.89 (6 H, s, C(CH_3)$_2$); GC/MS: 18.10 min, m/z = 265 (65, M), 210 (84, M-55), 155 (100, Ts), 91 (81, Tol).



3.10

(2*R*,2'*R*)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)bis(*N*-mesitylpropanamide) (3.10): Compound prepared according to literature procedure.[14] Spectra matched literature values. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (2 H, br s, N*H* x 2), 7.34 (1 H, t, *J* = 8.0 Hz, C-4 ArI), 6.90 (4 H, s, Mes x 2), 6.65 (2 H, d, *J* = 8.0 Hz, C-2 and C-5 ArI), 5.01 (2 H, q, *J* = 6.5 Hz, C*H*(CH_3)O x 2), 2.26 (6 H, s, Mes *para*-CH_3 x 2), 2.14 (12 H, s, Mes *ortho*-CH_3 x 4), 1.78 (6 H, d, *J* = 6.5 Hz, CH(CH_3)O x 2).

Notes to Chapter 3

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Vita

Alicia McGhee was born in Freehold, New Jersey and grew up in Maine. She earned her Bachelor of Science degree in chemistry from the University of Maine, Orono, Maine in 2006. During her undergraduate studies, she worked with Prof. Bruce Jensen on developing new experiments for the undergraduate organic lab curriculum. She then relocated overseas, and completed her Master of Science degree at the University of East Anglia, Norwich, England in 2007. While at UEA, she researched the synthesis and chemistry of chiral sulfinimines and sulfoxides in Prof. Robert Stockman's research group. After some traveling, she moved back to the USA, and relocated to Seattle in the autumn of 2008. She began research in Prof. Forrest Michael's group at the University of Washington that following winter. In 2014, she earned a Doctor of Philosophy degree in organic chemistry from the University of Washington.