

# Oxidative Difunctionalizations of Alkenes

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## Abstract

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A plethora of natural products and valuable pharmaceuticals contain nitrogen heterocycles. Many of those scaffolds can be achieved by difunctionalizations of tethered aminoalkenes. The main focus of this dissertation is the development of more efficient methods of alkene difunctionalizations that lead to substituted piperidines and pyrrolidines. Palladium-catalyzed method featured incorporation of alcohols to yield *exo*-cyclized products. Diamination and aminofluorination methods were developed under metal-free conditions with hypervalent iodine as oxidant and showed high preference for *endo* cyclization.

A scope of carbamate-protected aminoalkenes were cyclized in presence of palladium catalyst and alcohol solvents acted as external nucleophiles. Primary and secondary alcohols and acetic acid were suitable nucleophiles and afforded cyclic aminoethers and aminoesters in good yields. This method was highly regioselective for formation of 5-*exo* products. Interestingly, use of a palladium catalyst with halide ligands in polar solvents favored *endo* cyclization.

Oxidative difunctionalizations under metal-free conditions were also developed. Hypervalent iodine reagents served as oxidants and were activated by strong Bronsted acids. Diamination products were achieved by employing various sulfonimides as external sources of

nitrogen while tetrafluoroboric acid effectively gave aminofluorination products. The counterions of these Bronsted acids were incorporated into the product to yield substituted amino- and fluoropiperidines with high preference for *endo* cyclization.

We sought to develop an enantioselective version of aminofluorination method by employing chiral iodine reagents. In order to make the use of chiral reagents practical conditions with catalytic amount of iodine were developed. Alternative oxidants such as xenon difluoride and *meta*-chloroperoxybenzoic acid were used to reoxidize the aryl iodide and products were afforded in yields comparable with conditions employing stoichiometric amounts of hypervalent iodine. Chiral iodine reagents were also tested in catalytic amounts and afforded products in very good yields but did not induce enantioselectivity.

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## List of Abbreviations

Ac:	Acetyl
Ar:	Aryl
BHT:	2,6-di- <i>tert</i> -butyl-4-methylphenol
Bn:	Benzyl
Bz:	Benzoyl
Boc:	<i>tert</i> -Butyloxycarbonyl
Bu:	Butyl
C:	Celsius
Cbz:	Carbobenzyloxy
COSY:	Correlation spectroscopy
Cy:	Cyclohexyl
d:	Day
DMF:	Dimethyl formamide
DMSO:	Dimethyl sulfoxide
dr:	Diastereomeric ratio
E <sup>+</sup> :	Electrophile
equiv.:	Equivalent
ESI-MS:	Electrospray ionization mass spectrometry
FTIR:	Fourier transform infrared spectroscopy
h:	Hour
HPLC:	High performance liquid chromatography

HRMS:	High resolution mass spectrometry
Hz:	Hertz
LAH:	Lithium aluminum hydride
LDA:	Lithium diisopropylamide
Me:	Methyl
MHz:	Megahertz
mol:	Mole
ND:	Not determined
NFBS:	<i>N</i> -fluorobenzenesulfonimide
NMR:	Nuclear magnetic resonance
PNZ	( <i>para</i> -Nitro)carbonyloxy

Abbreviations for NMR splitting patterns

s:	singlet
d:	doublet
t:	triplet
q:	quartet
p:	pentet
m:	multiplet
br:	broad
Nu:	Nucleophile
OAc	Acetate
OTf:	Trifluoromethanesulfonate
OTFA:	Trifluoroacetate

OTs:	<i>p</i> -Toluenesulfonate
PG:	Protecting Group
Ph:	Phenyl
Phth:	Phthalyl
ppm:	parts per million
<i>p</i> -tol:	<i>para</i> -toluoyl
rbf:	round bottomed flask
rt:	room temperature
TFA:	Trifluoroacetic acid
TfOH:	Trifluoromethanesulfonic acid
THF:	Tetrahydrofuran
TLC:	Thin layer chromatography
TMS:	Tetramethylsilane
Tol:	Toluene
Troc:	2,2,2-Trichloroethyloxycarbonyl
Ts:	<i>p</i> -Toluenesulfonyl

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Thank you all!

## **Dedication**

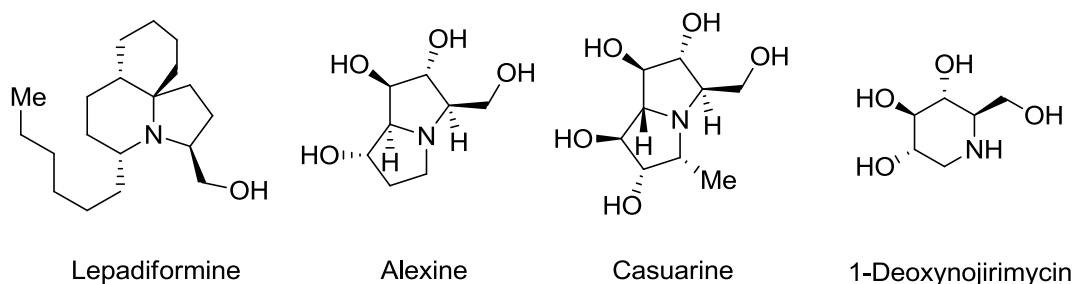
In loving memory of my grandfather Dmitry Ivanovich Latyshev

# Chapter 1: Development of a Palladium-Catalyzed Alkoxyamination of Alkenes Using N-Fluorobenzenesulfonimide as Oxidant

## Section 1: Introduction

Many alkaloids with indolizidine, pyrrolizidine and pyrrolidine scaffolds are medicinally valuable compounds (Figure 1.1). These compounds have shown to be worthwhile candidates for treatment of cancer<sup>1, 2</sup>, HIV<sup>3</sup> and diabetes<sup>2</sup>, and serve as potential antiviral<sup>5</sup> and antiarrhythmic drugs<sup>1</sup>.

**Figure 1.1. Examples of Biologically Active Compounds**

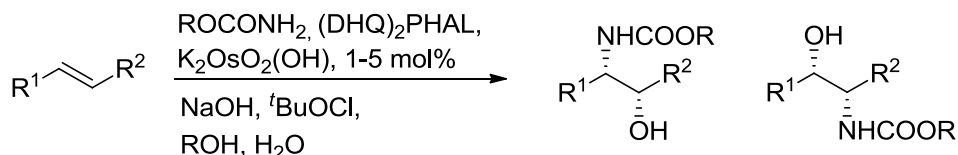


Such compounds can be accessed by oxidative difunctionalization of a carbon-carbon double bond. Oxyamination is the simultaneous addition of nitrogen and oxygen atoms across the alkene which is a powerful synthetic method. Intramolecular oxyamination would provide a facile route to substituted piperidines and pyrrolidines.

Several examples of selective difunctionalizations of alkenes have been previously reported, most commonly aminohydroxylation<sup>4,5</sup> and aminoacetoxylation reactions.<sup>6,7</sup> In his keystone work, the Sharpless group developed an osmium-catalyzed method of preparing vicinal aminoalcohols.<sup>8,9</sup> The method provides excellent yields, enantioselectivities and

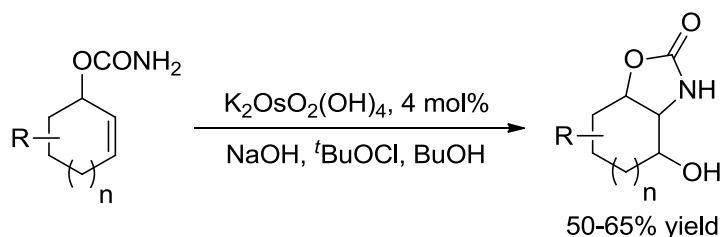
diastereoselectivities but regioselectivity is an issue<sup>8</sup> and an expensive and highly toxic osmium catalyst is required for the desired reactivity (Scheme 1.1).

**Scheme 1.1. Sharpless' Osmium Catalyzed Aminohydroxylation of Alkenes**



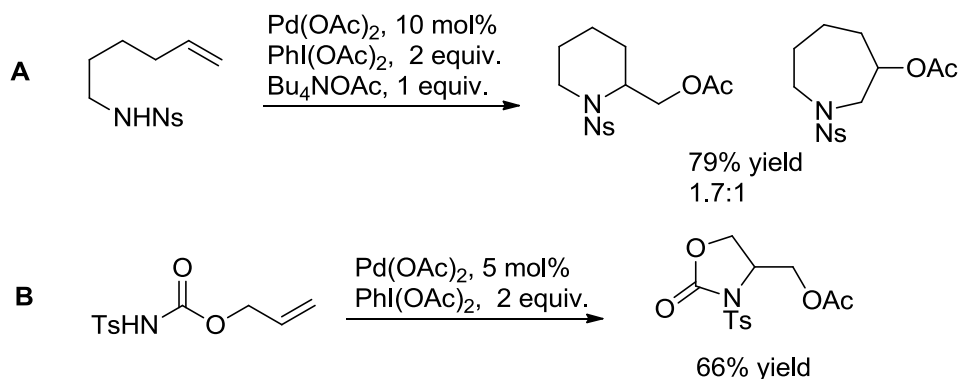
In response to the regioselectivity issue in Sharpless' method Donohue and coworkers tethered the source of nitrogen to an allylic alcohol<sup>10</sup> (Scheme 1.2). Despite solving the regioselectivity problem, products were afforded in modest yields.

**Scheme 1.2. Intramolecular Osmium-Catalyzed Oxyamination by Donohue**



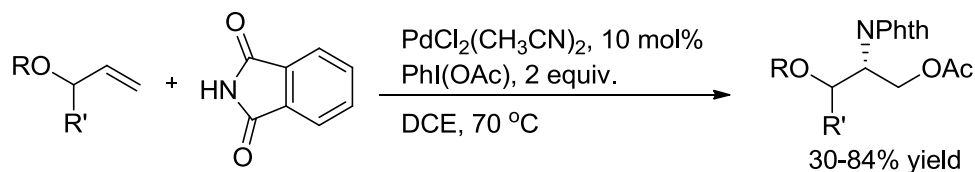
In addition several promising palladium-catalyzed methods emerged. Sorensen *et al.* achieved moderate to good yields of cyclized aminoester products under mild conditions (Scheme 1.3).<sup>11</sup> However, substrates with a sulfonamide group suffered from poor regioselectivity, affording a mixture of *exo* and *endo* products (Scheme 1.3A). Carbamate substrates afforded *N*-tosyloxazolidone products as single regioisomers but in lower yields (Scheme 1.3B).

### Scheme 1.3. Intramolecular Aminoacetoxylation by Sorensen



Stahl and co-workers developed the first intermolecular aminoacetoxylation method of alkenes where palladium catalyzed addition of acetate and phthalamide across the double bond (Scheme 1.4).<sup>12</sup> This method affords vicinal aminoalcohols from simple alkenes with exceptional regioselectivity. Despite a broad scope of reactivity, both yields and regioselectivity depended on the presence of an ether group  $\alpha$  to the alkene.

### Scheme 1.4. Intermolecular Aminoacetoxylation by Stahl

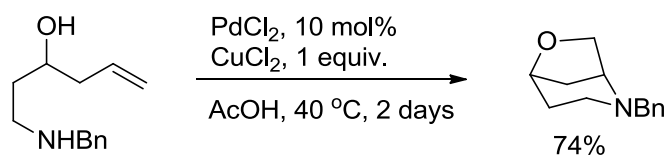


All of these described methods greatly enrich the synthetic toolbox, but none of them offer direct formation of aminoethers from alkenes. Direct introduction of an alkoxy group in such a process is quite rare<sup>13-15</sup>, but would greatly increase the potential utility of this type of transformation by allowing the direct formation of protected alcohols or ethers from alkenes.

One of example of direct incorporation of an alkoxy group was developed by Szolcsányi *et al.* Scheme 1.5 shows a palladium catalyzed route to 6-oxa-2-azabicyclo[3.2.1]octane skeleton<sup>13</sup>. This reaction features intramolecular attack of nitrogen on the alkene and subsequent

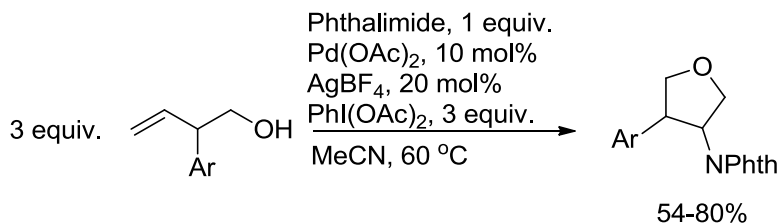
ether formation with the hydroxyl group on the substrate backbone. Bicyclic aminoethers can be furnished in good yield but the reaction requires stoichiometric copper and takes 2 days to reach completion.

### Scheme 1.5. Alkoxyamination by Szolcsányi



Sanford *et al.* have developed a palladium-catalyzed route to 3-aminotetrahydrofurans from unsaturated alcohols<sup>14</sup> (Scheme 1.6). Good yields could only be achieved from substrates bearing an aryl substituent (alkyl groups gave the desired products in greatly diminished yields). Furthermore, electron-rich aryl groups gave poor diastereoselectivity.

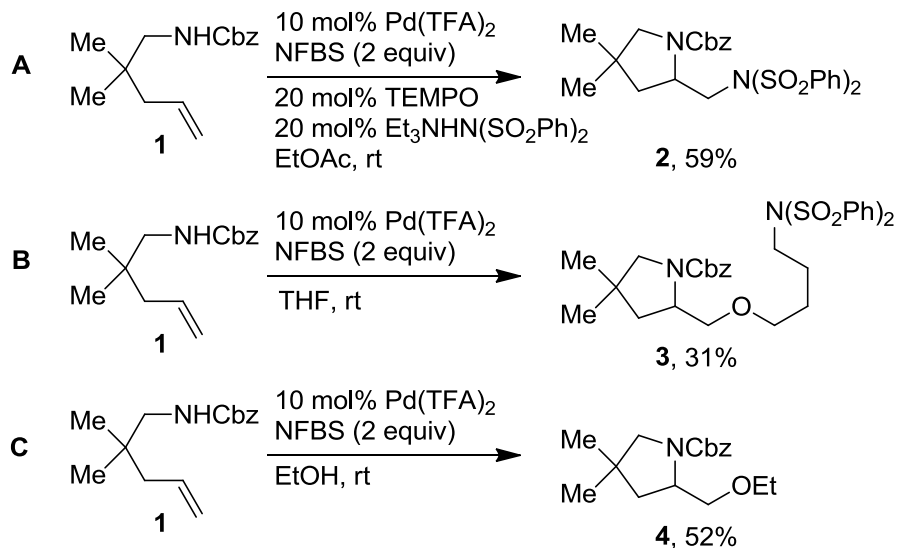
### Scheme 1.6. Alkoxyamination by Sanford



A recently developed diamination method from our group<sup>16</sup> shed some light on the scope of nucleophiles (Scheme 1.7). *N*-Fluorobenzenesulfonimide (NFBS) was used as oxidant and source of electrophilic nitrogen to yield diamination products in ethyl acetate. However, when the diamination reaction was performed in THF, an unusual byproduct **3**, was isolated, resulting from ring opening and nucleophilic incorporation of THF into the product. This result suggested that oxygen could be a suitable nucleophile and led us to explore alcohols for incorporation (Scheme 1.7B). Gratifyingly, substituting ethyl acetate for ethanol afforded 52% of the desired

aminoether **4** and showed that direct formation of cyclic aminoethers is possible in a single step (Scheme 1.7C).

### Scheme 1.7. Palladium-Catalyzed Diamination and Alkoxyamination

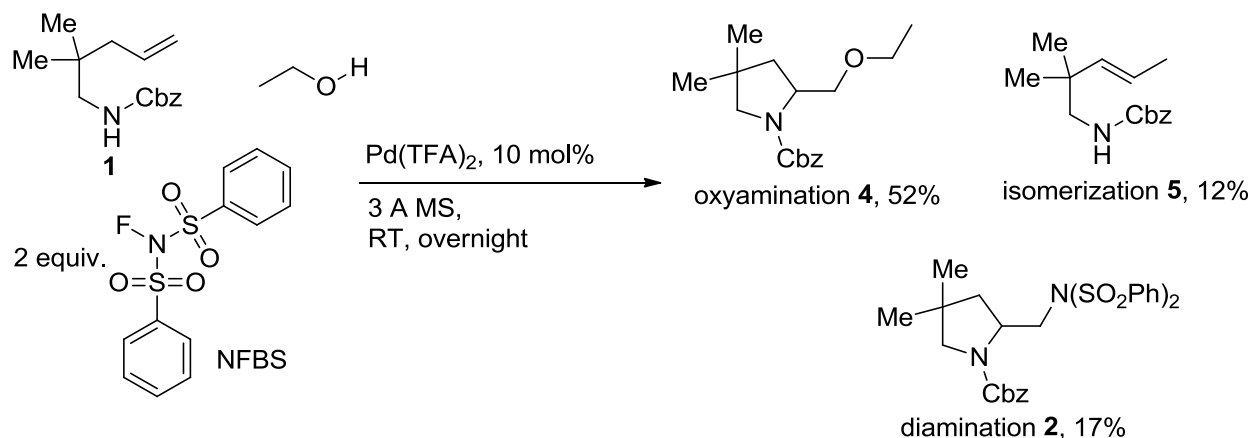


## Section 2: Results and Discussion

### 1.2.a. Nitrogen Protecting Group Screen

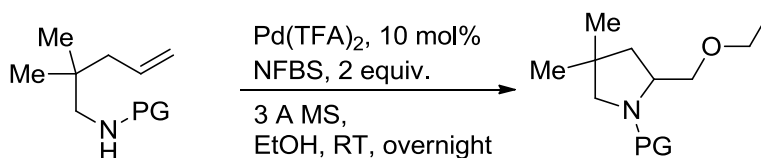
Originally, we replicated the diamination conditions, with the simple exception of substituting ethanol for ethyl acetate (Scheme 1.8). Under these conditions, 52% yield of the desired product was isolated, which was a promising initial result. We also isolated isomerization (**5**) and diamination (**2**) byproducts.

### Scheme 1.8. Initial Attempt at Alkoxyamination



The next step was to probe how various protecting groups on the nitrogen perform under the reaction conditions. Various carbamates, amide, urea and sulfonamide groups were tested. The tosyl, Troc, Boc and *p*-toluamide protecting groups gave no desired product. However, Cbz-protected substrate-rate as well as, *p*-nitrobenzyloxy and *t*-butyl urea afforded cyclized amino-ether products in reasonable yields (Table 1.1). Based on these results and its commercial availability and synthetic utility we determined Cbz to be the most suitable protecting group for alkoxyamination reaction.

**Table 1.1. Nitrogen Protecting Group Screen**

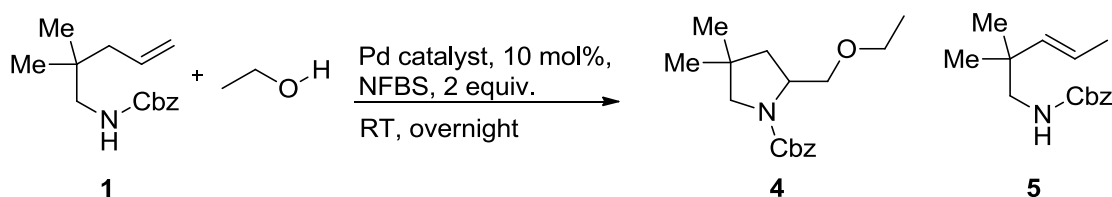


Entry	Protecting group	Yield, %
1	Cbz	52
2	PNZ	55
3	<i>t</i> -butyl urea	50
4	<i>p</i> -tol	NA
5	Boc	NA
6	Troc	NA
7	Ts	NA

### 1.2.b. Catalyst and Oxidant Screen

Several palladium catalysts were tested. Each palladium source gave full conversion of the substrate but the best yield and lowest amount of isomerization was observed with  $\text{PdCl}_2(\text{MeCN})_2$ . The second best catalyst was  $\text{Pd}(\text{TFA})_2$ , which was the catalyst of choice for diamination and carboamination methods, yielding 48% of **4** and 14% of **5**.

**Table 1.2. Scope of Palladium Catalysts**

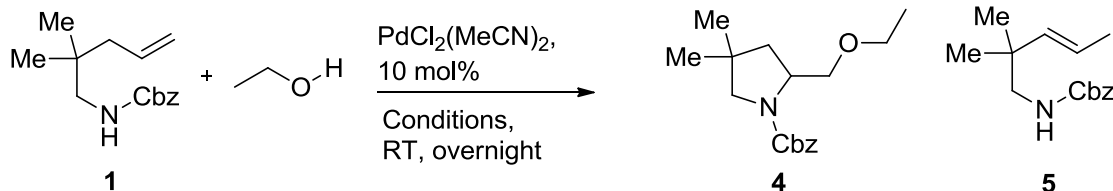


Entry	Catalyst	<b>4</b> , % yield	<b>5</b> , % yield
1	$\text{Pd}(\text{TFA})_2$	48	14
2	$\text{PdSO}_4$	33	30
3	$\text{Pd}(\text{OAc})_2$	36	29
4	$\text{PdCl}_2(\text{MeCN})_2$	63	None

### 1.2.c. Further Optimization

After establishing that  $\text{PdCl}_2(\text{MeCN})_2$  is the best catalyst for this transformation, we sought to further improve the yield by testing other variables such as concentration, catalyst loading and quantity of NFBS. The results are summarized in Table 1.3 below.

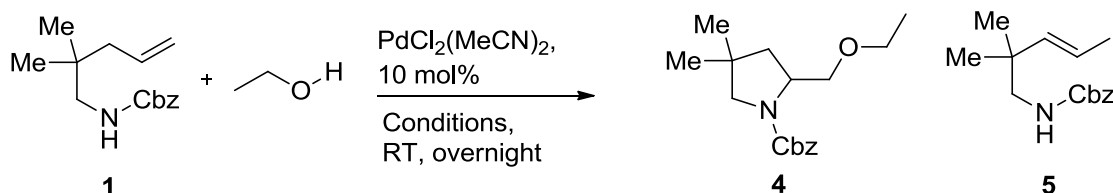
Removing the sieves had no noticeable effect; neither did twofold decrease in concentration or cooling the reaction to 0 °C. Hoping to more efficiently utilize the catalyst and oxidant we lowered these amounts (entries 5, 6). In both instances yields were decreased and an appreciable amount of isomerization byproduct **5** was observed.

**Table 1.3. Alkoxyamination Optimization**

Entry	Conditions	<b>4</b> , % yield	<b>5</b> , % yield
1	No sieves	62	Trace
2	0 °C	61	None
3	[0.025M]	66	None
4	3 equiv. NFBS	63	None
5	1.3 equiv. NFBS	38	13
6	5 mol% catalyst	56	10

Yields determined by GC-MS with dodecane as internal standard

We had previously learned from the diamination and carboamination methods that radical scavenger additives decreased the amount of isomerization byproducts, so we decided to test BHT and TEMPO under alkoxyamination conditions. We also tested the effect Brønsted bases and acids could have on the outcome (Table 1.4).

**Table 1.4. Effects of Additives on Alkoxyamination**

Entry	Additive	<b>4</b> , % yield	<b>5</b> , % yield
1	BHT, 1 equiv.	13	27
2	TEMPO, 30mol%	32	7
3	$\text{CF}_3\text{COOH}$ , 1 equiv.	34	8
4	$\text{K}_2\text{CO}_3$ , 1 equiv.	51	none
5	$\text{NaH}$ , 1.3equiv.	15	24
6	Lutidine, 20mol%	63	none
7	<i>di-tert</i> -butyl-pyridine, 20 mol%	67	none

Yields determined by GC-MS with dodecane as internal standard

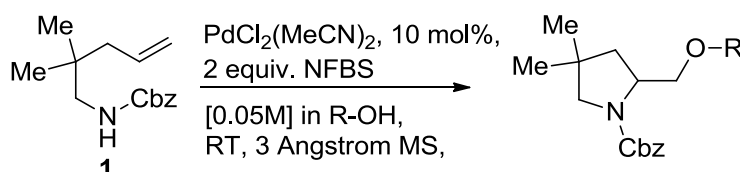
Regrettably, in the case of alkoxyamination the effect of the radical scavengers, BHT and TEMPO, was detrimental (entry entries 1, 2). The crude proton NMR spectra of these reactions

were complicated with unidentified byproducts and only 13% of desired product **4** was observed by GC-MS, in the case of BHT, and 32% with addition of TEMPO. Furthermore, isomerization byproduct **5**, was observed in 27% and 7% yield, respectively. The addition of trifluoroacetic acid decreased the yield and so did NaH (entries 3, 5). A small increase in yield over original conditions was observed with the addition 20 mol% of *di-tert*-butylpyridine, giving a yield of 67% (entry 7).

### 1.2.d. Nucleophile Scope

After establishing that any deviation from conditions with 10 mol% of PdCl<sub>2</sub>(MeCN)<sub>2</sub> as catalyst and 2 equivalents of NFBS gave either no appreciable improvement in yield or had detrimental effects, we sought to examine the alcohol scope under these original conditions. We were pleased to see that various primary and secondary alcohols were successfully incorporated, yielding the desired products in good yields (Table 1.5).

**Table 1.5. Alkoxyamination Nucleophile Scope**



Entry	R-OH	% yield
1	MeOH*	<b>12</b> , 52%
2	EtOH**	<b>4</b> , 63%
3	1-PrOH	<b>13</b> , 57%
4	1-BuOH	<b>14</b> , 63%
5	2-PrOH	<b>15</b> , 66%
6	AcOH*	<b>16</b> , 55%
7	Trifluoroethanol	None
8	t-Butanol	none

\*Pd(TFA)<sub>2</sub> was used instead of PdCl<sub>2</sub>(MeCN)<sub>2</sub>

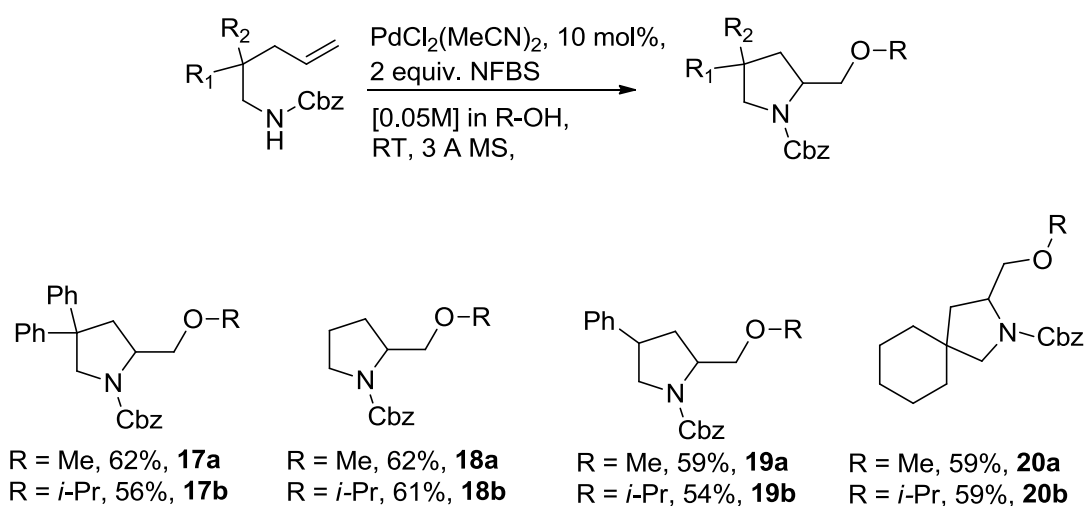
\*\*A trace of 6-*endo* product was observed (see section 1.2g)

Acetic acid also proved to be a suitable nucleophile, giving 55% of the desired product. Interestingly, Pd(TFA)<sub>2</sub> was a better catalyst for incorporation of methanol and acetic acid to yield *exo* cyclization products.

### 1.2.e. Substrate Scope

We were pleased to see that various aminoalkenes were appropriate substrates. Alkenes with different substitution patterns on the backbone gave comparable yields of the desired products (Figure 1.2). We chose methanol as a representative 1° alcohol and *iso*-propanol as a representative 2° alcohol.

**Figure 1.2. Alkoxyamination Substrate Scope**

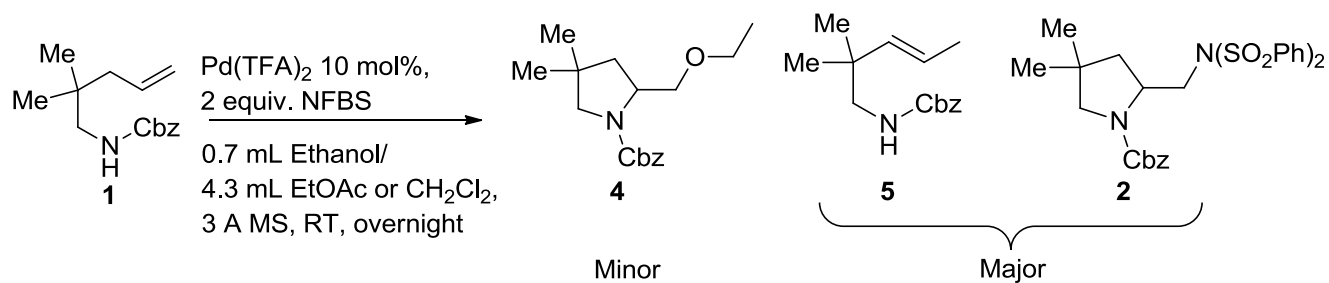


Substrates with disubstituted and monosubstituted backbones gave good yields of the cyclized amino ethers. It is noteworthy that the substrate with an unsubstituted backbone yielded products **18a** and **18b** while the same substrate failed to afford product under diamination conditions.

### 1.2.f. More Efficient Use of Nucleophile

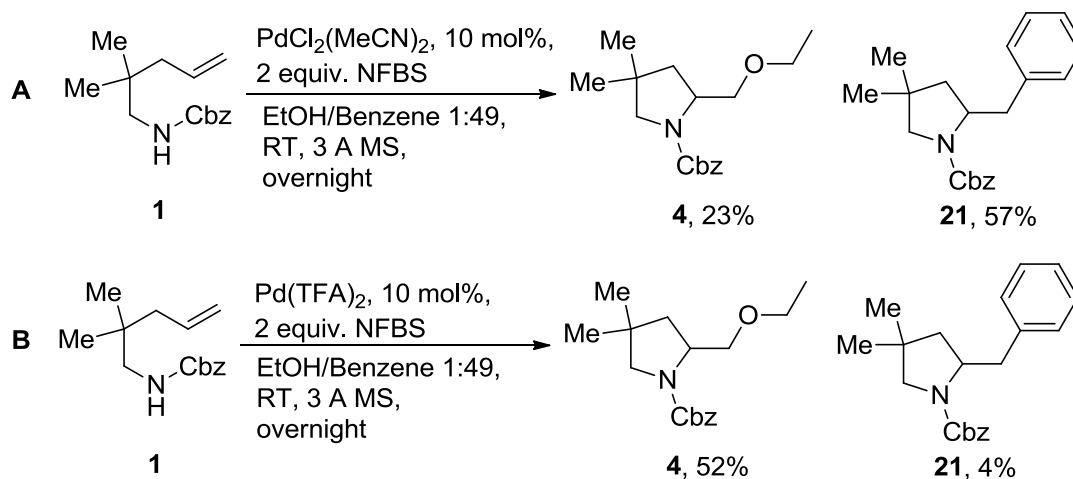
To enhance the utility of this method we sought to lower the amount of nucleophile required. Previously alcohols were used as solvents but such method prohibits efficient use of high molecular weight and/or expensive nucleophiles. We began our studies by testing solvents using a 6:1 mixture of non-nucleophilic co-solvent and ethanol. The screen revealed that using dichloromethane or ethyl acetate as co-solvent yielded a mixture of isomerization and diamination as major components of the reaction mixture (Scheme 1.9).

**Scheme 1.9. Alkoxyamination with Ethanol in Co-Solvents**



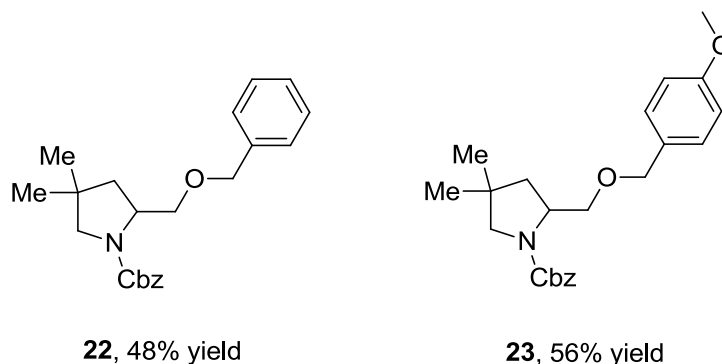
A carboamination method was developed in our lab. When benzene was used as the solvent, arene acted as a nucleophile and incorporated (**21**) in a similar fashion to NFBS or alcohols.<sup>17</sup> When benzene was tested as a co-solvent we were surprised not to observe any carboamination in a 1:1 mixture of benzene and ethanol and Pd(TFA)<sub>2</sub> as catalyst. The same result was obtained with Pd(OAc)<sub>2</sub> as catalyst. Selectivity was reversed in favor of carboamination when using PdCl<sub>2</sub>(MeCN)<sub>2</sub> in the same solvent mixture yielding only 23% of **4** and 57% of **21** (Scheme 1.10A). These results suggested that with a choice of a proper catalyst benzene can be a suitable co-solvent. Indeed, even when a 1:49 mixture of ethanol/benzene is used, only 4% of carboamination product **21** was isolated (Scheme 1.10B).

### Scheme 1.10. Alkoxyamination vs. Carboamination Competition



Using our new findings we subjected aminoalkenes under alkoxyamination conditions in benzene with 10 equivalents of benzyl and *p*-methoxybenzyl alcohols. Gratifyingly, this scheme directly afforded benzyl, (**22**), and PMB, (**23**), protected alcohols in 48% and 56% yield, respectively (Figure 1.3).

**Figure 1.3. Incorporation of Bn and PMB Alcohols with Alkoxyamination Method**

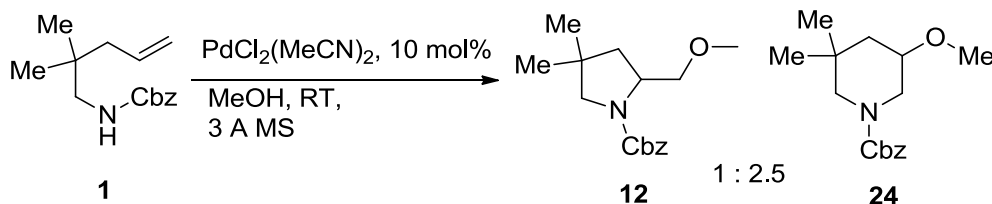


#### 1.2.g. Solvent Effect on Regioselectivity

When methanol or acetic acid was used as solvent (1.2.d) and  $\text{PdCl}_2(\text{MeCN})_2$  as a catalyst the yield of the desired products was low (Scheme 1.11). After isolating the products we

learned that the side product was the 6-*endo* regioisomer. Furthermore, under these conditions, 6-*endo* regioselectivity (**24**) was favored 2.5:1 over 5-*exo* cyclization (**12**).

**Scheme 1.11. Reverse in Regioselectivity: 6-*Endo* Alkoxyamination**



This reversal of regioselectivity was observed when methanol or acetic acid was used as solvents. This seems to correlate with the polarity of the reaction mixture. To test this hypothesis we used mixtures of methanol with a less polar co-solvent to see if this would affect regioselectivity. The results are summarized in Table 1.6.

**Table 1.6. Solvent Effect on Regiochemistry of Alkoxyamination**

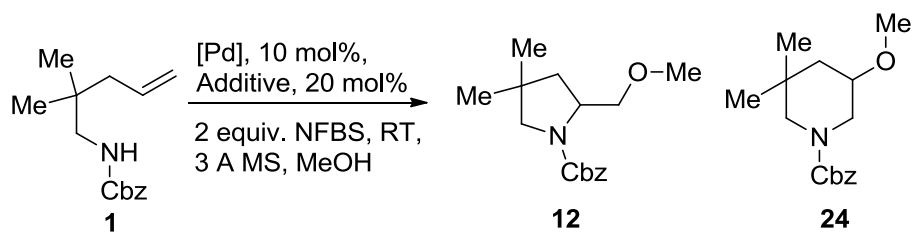
Entry	Co-Solvent	MeOH : Co-Solvent	<b>12:24</b>
1	EtOAc	20:80	70:30
2	EtOAc	60:40	45:55
3	EtOAc	80:20	40:60
4	$\text{CCl}_4$	60:40	53:47
5	Diethyl Ether	60:40	48:52
6	1,4-dioxane	60:40	67:33
7	DMF	60:40	11:89

We began with different ratios of ethyl acetate to methanol (entry 1-3) and observed a switch in regioselectivity favoring 6-*endo* product as the proportion of methanol (and polarity) increased. Addition of a less polar co-solvent such as carbon tetrachloride or 1,4-dioxane favored 5-*exo* selectivity (entries 4, 6). Finally, the reaction in polar solvent such as DMF favored formation of 6-*endo* product over 5-*exo* in 8:1 ratio. These results supported our hypothesis that 6-*endo* cyclization was favored in more polar solvents.

### 1.2.h. Halide Effect on Regioselectivity

Since the 6-*endo* product was observed when PdCl<sub>2</sub>(MeCN)<sub>2</sub> was used as catalyst and not with Pd(TFA)<sub>2</sub>, we suspected that the ligand on palladium might have an impact on the regiochemical outcome of this reaction. We decided to employ Pd(TFA)<sub>2</sub> in conjunction with various halide salts to test this hypothesis (Table 1.7).

**Table 1.7. Halide Effect on Regioselectivity**



Entry	[Pd]	Additive (20 mol%)	<b>12:24</b>
1	Pd(TFA) <sub>2</sub>	None	<b>12</b> only
2	Pd(TFA) <sub>2</sub>	LiCl	1:1.8
3	Pd(TFA) <sub>2</sub>	LiBr	1:1.8
4	Pd(TFA) <sub>2</sub>	Bu <sub>4</sub> NBr	1:2.2
5	PdCl <sub>2</sub> (MeCN) <sub>2</sub>	None	1:2.5
6	PdCl <sub>2</sub>	None	1:1

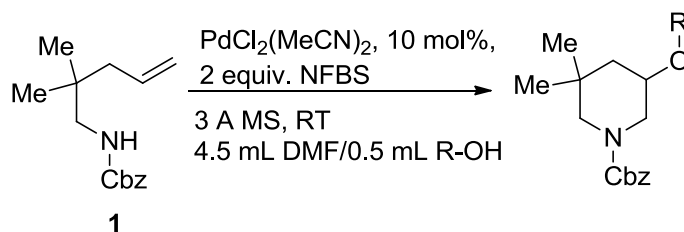
Ratios determined by <sup>1</sup>H NMR spectroscopy

It was evident that the presence of either chloride or bromide in the reaction mixture gave substantial amounts of the 6-*endo* product, whereas, product **24** was not observed in the absence of halide (entry 1). We also tested dependence of regioselectivity on the ligand: presence of acetonitrile ligand versus TFA did not seem to have any effect on regioselectivity as ratios of **12:24** are similar when using PdCl<sub>2</sub>(MeCN)<sub>2</sub> compared with Pd(TFA)<sub>2</sub> with halide salt additives (entry 5 versus entries 1-4).

### 1.2.i. Development of 6-Endo Alkoxyamination.

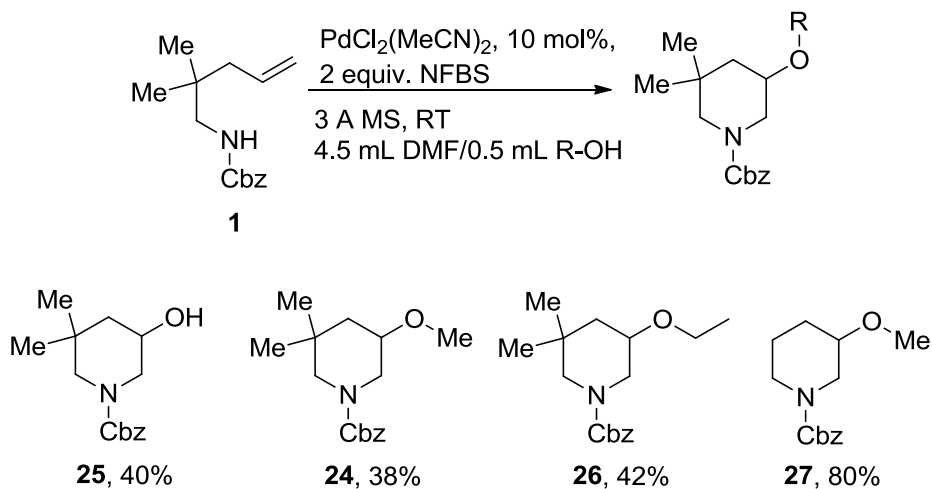
As previously mentioned, since polar solvents favor the formation of 6-*endo* products, the reaction in DMF gave almost exclusively the 6-*endo* product. We saw such a finding as an opportunity to develop a 6-*endo* selective method and probed a number of substrates under conditions favoring 6-*endo* cyclization (Scheme 1.12).

#### Scheme 1.12. 6-Endo Alkoxyamination Optimized Conditions



Under optimized conditions we were able to selectively form 6-*endo* cyclized products in modest yields (Figure 1.4). Only the most polar nucleophiles were considered. Gratifyingly, water, methanol and ethanol afforded exclusively 6-*endo* products, albeit in low yields. Remarkably, the substrate with an unsubstituted backbone yielded 80% of the 6-*endo* product **27**.

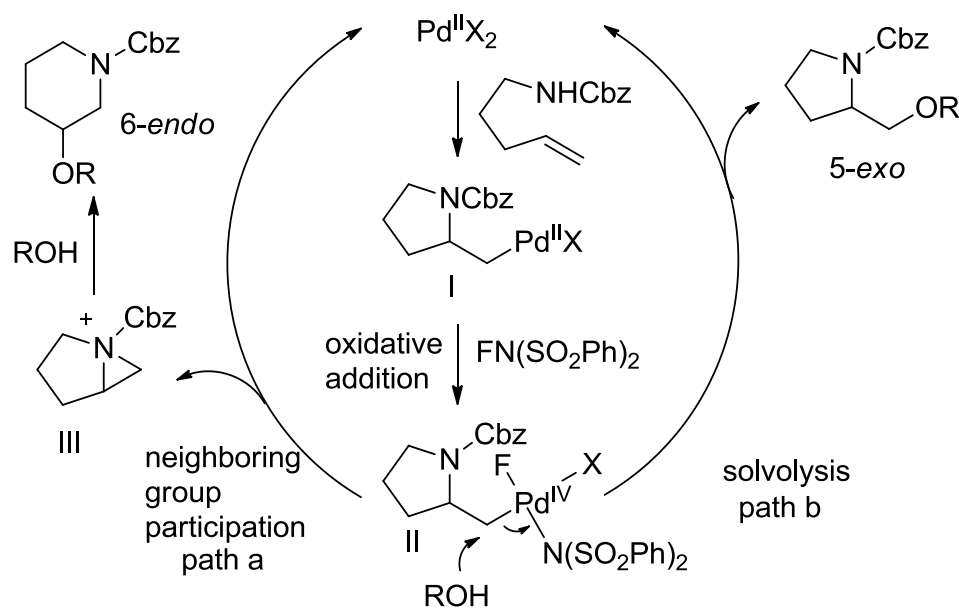
#### Figure 1.4. Scope of 6-Endo Alkoxyamination



### 1.2.j. Proposed Mechanism

Based on mechanistic studies of diamination and carboamination<sup>18</sup> we propose a plausible mechanism for desired product formation in Scheme 1.13 below. Initial *exo*-selective aminopalladation occurs to generate complex **I**. Oxidative addition of NFBS generates a Pd(IV) species **II**, which can undergo nucleophilic substitution by the alcohol to generate the 5-*exo* cyclization product.

**Scheme 1.13. Plausible Mechanism of Alkoxyamination**



The origin of the 6-*endo* product is currently unclear. One possibility is that under highly polar reaction conditions, aziridinium species **III** could be generated upon departure of the Pd, and preferential internal attack would lead to selective formation of the 6-*endo* product.

### Section 3: Conclusion

In summary, we have successfully developed a Pd-catalyzed alkoxyamination of protected aminoalkenes using NFBS as oxidant. This method allows direct formation of cyclic aminoethers which can serve as precursors to biologically active compounds. Primary and

secondary alcohols, water and acetic acid were suitable nucleophiles. The regioselectivity could be controlled by careful choice of catalyst and solvent combination, leading to selective formation of either the 5-*exo* or 6-*endo* cyclization products. We also developed conditions allowing use of lower amount of nucleophile which makes incorporation of high boiling (such as benzyl or PMB) or expensive alcohols more practical. The direct formation of benzyl and PMB protected alcohols could also save several synthetic steps.

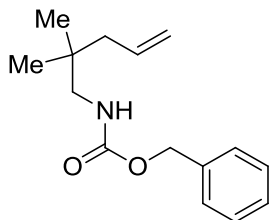
#### Section 4: Experimental

**General Procedures.** All reactions were performed under nitrogen atmosphere using flame-dried glassware. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were collected on a Hewlett Packard 5971A Gas Chromatograph - Mass Spectrometer or Bruker Esquire 1100 Liquid Chromatograph - Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometers. <sup>1</sup>H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to TMS (0.00 ppm) or residual protonated CHCl<sub>3</sub> (7.26 ppm). <sup>13</sup>C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of CDCl<sub>3</sub> (77.0 ppm).

**Materials.** All commercial reagents were used as received. CH<sub>2</sub>Cl<sub>2</sub> was degassed and dried on solvent columns of neutral alumina. EtOAc was used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4Å molecular sieves, and were used without further purification.

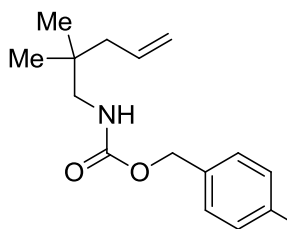
### Synthesis and Characterization of Starting Materials

Benzyl 2,2-dimethylpent-4-enylcarbamate (**1**)<sup>19</sup>, benzyl 2,2-diphenylpent-4-enylcarbamate (**17**)<sup>20</sup>, benzyl (1-allyl-cyclohexylmethyl)-carbamate (**20**)<sup>20</sup>, benzyl 2-phenylpent-4-enylcarbamate (**19**)<sup>19</sup>, benzyl pent-4-enylcarbamate (**18**)<sup>19</sup>, were synthesized according to previously reported methods and spectral data match literature values.



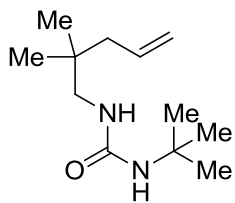
**Benzyl 2,2-dimethylpent-4-enylcarbamate (1).** <sup>1</sup>H NMR (300 MHz,

CDCl<sub>3</sub>): δ 7.37-7.33 (m, 5H), 5.88-5.74 (m, 1H), 5.11 (s, 2H), 5.07-5.00 (m, 2H), 4.78 (br, 1H), 3.04 (d, *J* = 6.6 Hz, 2H), 1.98 (d, *J* = 7.2 Hz, 2H), 0.89 (s, 6H).



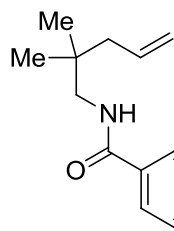
**4-Nitrobenzyl 2,2-dimethylpent-4-enylcarbamate (6).** <sup>1</sup>H NMR

(300 MHz, CDCl<sub>3</sub>): δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 5.79 (m, 1H), 5.20 (s, 2H), 5.08 (m, 2H), 4.92-4.79 (br, 1H), 3.05 (d, *J* = 6.6 Hz, 2H), 1.98 (d, *J* = 7.3 Hz, 2H), 0.89 (s, 6H).

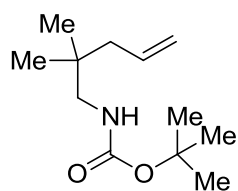


**1-(2,2-Dimethylpent-4-enyl)-3-*t*-butylurea (7).**<sup>19</sup> <sup>1</sup>H NMR (500 MHz,

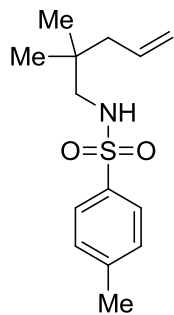
CDCl<sub>3</sub>): δ 5.90-5.75 (m, 1H), 5.08-4.97 (m, 2H), 4.50 (br, 2H), 2.95 (d, *J* = 6.0 Hz, 2H), 1.95 (d, *J* = 7.0 Hz, 2H), 1.32 (s, 6H).



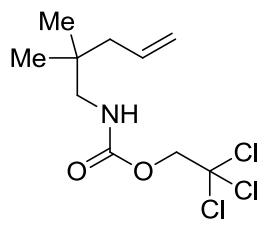
**4-Methyl-N-(2,2-dimethylpent-4-enyl)benzamide (8).**<sup>16</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.16 (br, 1H) 5.89 (ddt, *J* = 11.1, 18.0, 7.2 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 5.07 (d, *J* = 6.0 Hz, 1H), 3.31 (d, *J* = 6.3 Hz, 2H), 2.40 (s, 3H), 2.06 (d, *J* = 7.8 Hz, 2H), 0.96 (s, 6H).



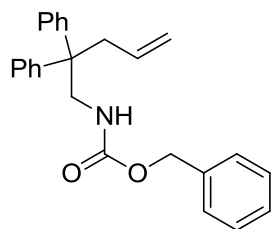
**tert-Butyl 2,2-dimethylpent-4-enylcarbamate (9).**<sup>16</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 5.9-5.7 (m, 1H), 5.1-4.9 (m, 2H), 4.55 (br, 1H), 2.95 (d, *J* = 6.6 Hz, 2H), 1.96 (d, *J* = 7.5 Hz, 2H), 1.43 (s, 9H), 0.87 (s, 6H).



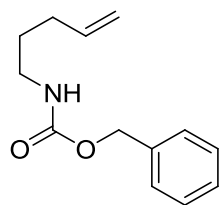
**2,2-Dimethyl-(4-methylbenzenesulfonyl)-pent-4-en-1-amine (10).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.72 (ddt, *J* = 10.2, 17.7, 7.2 Hz, 1H), 5.04-4.97 (m, 2H) 4.41 (br, 1H), 2.68 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.95 (d, *J* = 7.2 Hz, 2H), 0.86 (s, 6H).



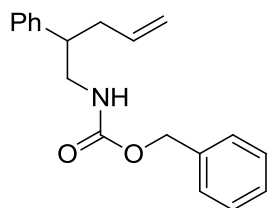
**2,2,2-trichloroethyl 2,2-dimethylpent-4-enylcarbamate (11).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.91 – 5.73 (m, 1H), 5.06 (m, 3H), 4.73 (s, 2H), 3.06 (dd,  $J = 6.5, 3.9$  Hz), 2.01 (d,  $J = 5.7$  Hz, 2H), 0.92 (s, 6H).



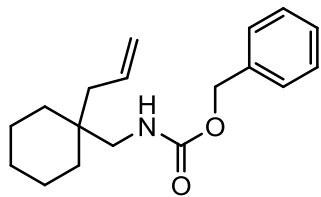
**Benzyl 2,2-diphenylpent-4-enylcarbamate (17).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34-7.17 (m, 15H), 5.65 (ddt,  $J = 9.9, 16.5, 7.5$  Hz, 1H), 5.05 (s, 2H), 5.01-4.97 (m, 2H), 4.36 (br, 1H), 3.96 (d,  $J = 6.0$  Hz, 2H), 2.89 (d,  $J = 7.2$  Hz, 2H).



**Benzyl pent-4-enylcarbamate (18).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36-7.31 (m, 5H), 5.79 (ddt,  $J = 10.2, 17.4, 7.2$  Hz, 1H), 5.10-4.96 (m, 4H), 4.78-4.76 (br s, 1H), 3.21 (q,  $J = 6.6$  Hz, 2H), 2.08 (quin.,  $J = 7.2$  Hz, 2H), 1.65-1.58 (m, 2H).



**Benzyl 2-phenylpent-4-enylcarbamate (19).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.32-7.15 (m, 10H), 5.75-5.61 (m, 1H), 5.06-4.97 (m, 4H), 4.60 (br s, 1H), 3.66-3.61 (m, 1H), 3.25 (ddd,  $J = 13.5, 9, 4.8$  Hz, 1H), 2.89-2.85 (m, 1H), 2.41-2.30 (m, 2H).



**Benzyl (1-allylcyclohexylmethyl)carbamate (20).**  $^1\text{H}$  NMR (300

MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37-7.33 (m, 5H), 5.83 (ddt,  $J = 10.8, 17.6, 8.0$  Hz, 1H), 5.10-5.03 (m, 4H), 4.75 (br s, 1H), 3.13-3.11 (d,  $J = 6.3$  Hz, 2H), 2.04 (d,  $J = 7.2$  Hz, 1H), 1.51-1.26 (m, 10H).

## Procedures for oxyamination

### Procedure A

$\text{Pd}(\text{TFA})_2$  (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158 g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry  $\text{N}_2$  gas. The substrate (0.250 mmol) was dissolved in 5 mL of the corresponding alcohol and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask via syringe with subsequent washing of the sieves with ethyl acetate. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

### Procedure B

$\text{PdCl}_2(\text{MeCN})_2$ <sup>21</sup> and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3-Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry  $\text{N}_2$  gas. The substrate (0.250 mmol) was dissolved in 5 mL of the corresponding alcohol and added to the flask. The reaction was stirred overnight and then was diluted with ethyl acetate and separated from the

sieves and magnetic stirbar by decantation. The mixture was concentrated under reduced pressure and chromatographed on silica gel using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

### Procedure C

Pd(TFA)<sub>2</sub> (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3-Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N<sub>2</sub> gas. The substrate (0.250 mmol) and 10 equivalents of the corresponding alcohol (2.5 mmol) were dissolved in 5 mL of benzene and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

### Procedure D

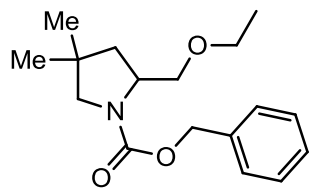
Pd(TFA)<sub>2</sub> (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3 Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N<sub>2</sub> gas. The substrate (0.250 mmol) was dissolved in 5 mL of glacial acetic acid and added into the flask. The reaction was stirred overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by decantation. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

**Procedure E**

Pd(TFA)<sub>2</sub> (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar, capped with a rubber septum and placed under dry N<sub>2</sub> gas. The substrate (0.250 mmol) was dissolved in a mixture of 1 mL of the corresponding alcohol and 4 mL of dimethylformamide and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure (0.1 torr) at 50 °C and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

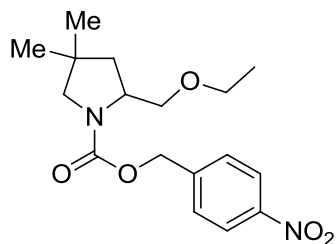
**Procedure F**

Pd(TFA)<sub>2</sub> (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar, capped with a rubber septum and placed under dry N<sub>2</sub> gas. The substrate (0.250 mmol) was dissolved in a mixture of 0.5 mL of deionized water and 4.5 mL of dimethylformamide and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure (0.1 torr) at 50 °C and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.



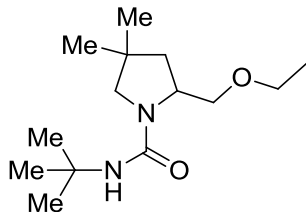
**Benzyl 2-(ethoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate (4).**

Prepared according to procedure B. 63% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.43-7.26 (m, 5H), 5.25-5.07 (m, 2H), 4.06-3.96 (m, 1H), 3.78-3.68 (m, 0.5H), 3.68-3.60 (m, 0.5H), 3.60-3.45 (m, 2H), 3.45-3.32 (m, 2H), 3.01 (d,  $J = 10$  Hz, 1H), 1.90-1.78 (m, 1H), 1.78-1.68 (m, 1H), 1.22-1.05 (m, 2H), 1.09 (s, 3H), 0.99 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.3, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 72.3 (minor), 71.0 (major), 66.8 (minor), 66.5 (major), 66.7, 59.7, 57.1 (major), 56.5 (minor), 43.9 (minor), 42.8 (major), 37.5 (major), 37.1 (minor), 26.6, 26.0, 15.2. FTIR (neat,  $\text{cm}^{-1}$ ): 2959, 2870, 1703, 1415, 1358, 1190, 1109. MS (EI): 291.2 ( $\text{M}^+$ , 0.3%), 232.2 ( $[\text{M} - \text{CH}_2\text{OCH}_2\text{CH}_3]^+$ , 27%), 188.2 ( $[\text{M} - \text{PhCH}_2\text{OCO}]^+$ , 44%), 91.1 ( $\text{Bn}^+$ , 100%). HRMS (FAB): calculated for  $\text{C}_{17}\text{H}_{26}\text{NO}_3 = 292.1913$ , found = 292.1911.



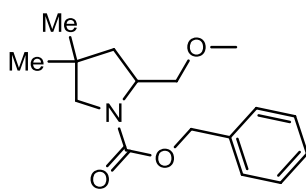
**4-Nitrobenzyl 2-(ethoxymethyl)-4,4-dimethylpyrrolidine-1-**

**carboxylate (6a).** Prepared according to procedure A. 55% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.20 (d,  $J = 8.5$  Hz, 2H), 7.49 (d,  $J = 7.3$  Hz, 2H), 5.33 – 5.15 (m, 2H), 4.08 – 3.95 (br m, 1H), 3.60 (m, 2H), 3.45 (m, 3H), 3.05 (d,  $J = 10.9$  Hz, 1H), 1.80 (m, 2H), 1.16 (d,  $J = 5.8$  Hz, 2H), 1.11 (s, 3H), 0.99 (s, 3H).



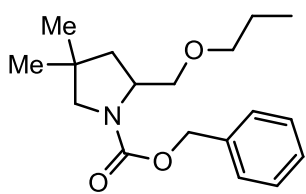
***N*-tert-butyl-2-(ethoxymethyl)-4,4-dimethylpyrrolidine-1-**

**carboxamide (7a).** Prepared according to procedure A. 50% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.10 (s, 1H), 3.89 – 3.71 (m, 2H), 3.55 – 3.46 (m, 2H), 3.46 – 3.28 (m, 2H), 2.76 (d,  $J = 10.8$  Hz, 1H), 1.88 – 1.76 (m, 1H), 1.31 (s, 9H), 1.21 (t,  $J = 7.0$  Hz, 3H), 1.04 (s, 3H), 0.94 (s, 3H).



**Benzyl 2-(methoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate**

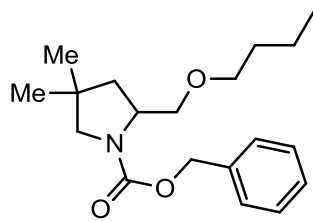
**(12).** Prepared according to procedure A. Clear oil, 52% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.43-7.30 (m, 5H), 5.25-5.09 (m, 2H), 4.08-3.02 (m, 1H), 3.69-3.45 (m, 2H), 3.45-3.12 (m, 6H), 3.01 (d,  $J = 10$  Hz, 1H), 1.87-1.78 (m, 1H), 1.78-1.71 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.3, 136.9, 128.4, 127.8, 127.6, 74.3, 73.1, 66.8 (minor), 66.6 (major), 59.64 (minor), 59.1 (major), 57.0 (major), 56.3 (minor), 43.6 (minor), 42.4 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat,  $\text{cm}^{-1}$ ): 2958, 2872, 1703, 1452, 1415, 1358, 1188, 1101. MS (EI): 277.2, ( $\text{M}^+$ , 0.3%), 232.2 ( $[\text{M} - \text{CH}_2\text{OCH}_3]^+$ , 27%), 188.2 ( $[\text{M} - \text{PhCH}_2\text{OCO}]^+$ , 37%), 91.1 ( $\text{Bn}^+$ , 100%). HRMS (FAB): calculated for  $\text{C}_{16}\text{H}_{24}\text{NO}_3 = 278.1756$ , found = 278.1761.



**Benzyl 4,4-dimethyl-2-(propoxymethyl)pyrrolidine-1-carboxylate**

**(13).** Prepared according to procedure B. 57% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,

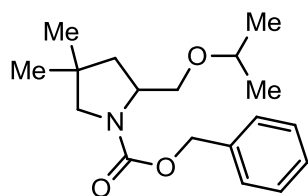
observed as a mixture of rotamers)  $\delta$ : 7.42-7.29 (m, 5H), 5.25-5.09 (m, 2H), 4.07-4.0 (m, 1H), 3.71-3.66 (m, 0.5H), 3.66-3.57 (m, 1H), 3.50-3.45 (m, 0.5H), 3.45-3.38 (m, 1H), 3.38-3.30 (m, 1H), 3.01 (d,  $J = 10$  Hz, 1H), 1.85-1.77 (m, 1H), 1.77-1.72 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.94-0.87 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 73.0, 72.3 (minor), 71.0 (major), 66.8 (minor), 66.5 (major), 59.6, 57.1 (major), 56.5 (minor), 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 26.6, 26.0, 22.9, 10.5. FTIR (neat,  $\text{cm}^{-1}$ ): 2960, 2872, 1703, 1415, 1359, 1190, 1103, 698. MS (EI): 305.2 ( $\text{M}^+$ , 0.4%), 232.2 ( $[\text{M} - \text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3]^+$ , 30%), 188.2 ( $[\text{M} - \text{PhCH}_2\text{OCO}]^+$ , 53%), 91.1 ( $\text{Bn}^+$ , 100%). HRMS (FAB): calculated for  $\text{C}_{18}\text{H}_{28}\text{NO}_3 = 306.2069$ , found = 306.2063.



**Benzyl 4,4-dimethyl-2-(butoxymethyl)pyrrolidine-1-carboxylate**

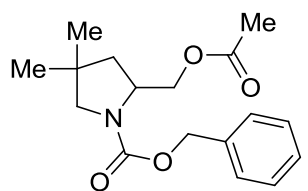
**(14)**. Prepared according to procedure B. 63% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers)  $\delta$ : 7.35-7.29 (m, 5H), 5.25-5.09 (m, 2H), 4.07-4.00 (m, 1H), 3.70-3.68 (m, 0.5H), 3.60-3.57 (m, 1H), 3.49-3.34 (m, 3.5H), 3.01 (d,  $J = 10$  Hz, 1H), 2.27-1.79 (m, 1H), 1.79-1.72 (m, 1H), 1.53-1.48 (m, 2H), 1.36-1.33 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H), 0.90-0.86 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 72.4, 71.1, 66.7 (minor), 66.5 (major), 59.6, 57.1 (major), 56.5 (minor), 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 31.7, 26.6, 26.0, 19.3, 13.9. FTIR (neat,  $\text{cm}^{-1}$ ): 2958, 2870, 1703, 1415, 1359, 1190, 1103. MS

(EI): 319.2 ( $M^+$ , 0.8%), 232.2 ( $[M - CH_2O(CH_2)_3CH_3]^+$ , 45%), 188.2 ( $[M - PhCH_2OCO]^+$ , 79%), 91.1 ( $Bn^+$ , 100%). HRMS (FAB): calculated for  $C_{19}H_{30}NO_3 = 320.2226$ , found = 320.2220.



**Benzyl 2-(isopropoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate**

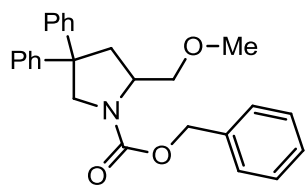
**(15).** Prepared according to procedure B. 66% yield. Clear oil.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.38-7.28 (m, 5H), 5.25-5.08 (m, 2H), 4.01-3.96 (m, 1H), 3.79-3.73 (m, 0.5H), 3.67-3.62 (m, 0.5H), 3.57-3.44 (m, 2H), 3.44-3.29 (m, 1H), 3.01 (d,  $J = 10$  Hz, 1H), 1.87-1.81 (m, 1H), 1.77-1.67 (m, 1H), 1.13-1.09 (m, 6H), 1.10 (s, 3H), 0.98 (s, 1H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 137.1 (major), 136.9 (minor), 128.4, 127.8, 127.8, 72.0 (major), 71.9 (minor), 69.9 (minor), 68.8 (major), 66.8 (minor), 66.5 (major), 59.7, 57.4 (major), 56.7 (minor), 44.0 (minor), 42.9 (major), 37.5 (major), 37.1 (minor), 26.6, 26.0, 22.3, 22.0. FTIR (neat,  $cm^{-1}$ ): 2964, 2871, 1703, 1415, 1359, 1332, 1190 1100. MS (EI): 305.2 ( $M^+$ , 0.4%), 232.2 ( $[M - CH_2OCH_2CH(CH_3)_2]^+$ , 39%), 188.2 ( $[M - PhCH_2OCO]^+$ , 63%), 91.1 ( $Bn^+$ , 100%). HRMS (FAB): calculated for  $C_{18}H_{28}NO_3 = 306.2069$ , found = 306.2064.



**Benzyl 2-(acetoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate**

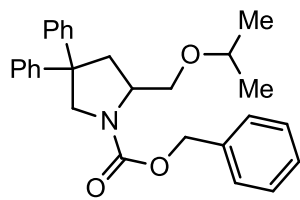
**(16).** Prepared according to procedure D. Colorless oil (55% yield).  $^1H$  NMR (500 MHz,  $CDCl_3$ , observed as a mixture of rotamers):  $\delta$  7.36-7.29 (m, 5H), 5.14 (s, 2H), 5.13 (s, 2H), 4.29 (br s, 1H), 4.17 – 4.15 (m, 2H), 3.52 (d,  $J = 10.5$  Hz, 0.5H), 3.41 (d,  $J = 10$  Hz, 0.5H), 3.02 (d,  $J =$

10.5 Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.83 (dd,  $J = 8.0, 12.3$  Hz, 1H), 1.66-1.57 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor):  $\delta$  20.8 (minor), 20.9 (major), 25.8 (major), 25.9 (minor), 26.4 (major), 26.5 (minor), 29.7 (major + minor), 37.1 (minor), 37.6 (major), 42.3 (major), 43.1 (minor), 55.3 (minor), 56.0 (major), 59.6 (major), 59.7 (minor), 64.8 (major), 65.5 (minor), 66.7 (major), 67.1 (minor), 127.7 (major + minor), 127.9 (major), 128.0 (minor), 128.4 (major + minor), 136.6 (minor), 136.8 (major), 155.2 (major + minor), 170.8 (major + minor). FTIR (neat,  $\text{cm}^{-1}$ ): 3067, 3033, 2958, 2872, 1743, 1703, 1453, 1414, 1360, 1236, 1190, 1102, 1040, 966, 769, 740, 698. HRMS (FAB) calculated for  $\text{C}_{17}\text{H}_{24}\text{NO}_4^+$  306.1706, found 306.1709 (M + H).



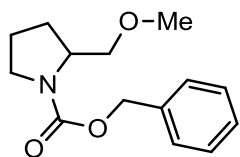
**Benzyl 2-(methoxymethyl)-4,4-diphenylpyrrolidine-1-carboxylate**

**(17a)**. Prepared according to procedure A. 62% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers)  $\delta$ : 7.48-7.19 (m, 15H), 5.32 (d,  $J = 12.5$  Hz, 0.5H), 5.22-5.16 (m, 1H), 5.09 (d,  $J = 12.5$  Hz, 0.5H), 4.75 (d,  $J = 11.1$  Hz, 0.5H), 4.61 (d,  $J = 11.4$  Hz, 0.5H), 3.94-3.84 (m, 1H), 3.7-3.5 (m, 2H), 3.35 (s, 2H), 3.28 (s, 1H), 2.87-2.79 (m, 1H), 2.75-2.69 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.1 (minor), 154.7 (major), 145.5 (major), 144.8 (minor), 136.9, 136.7, 128.5, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 126.8, 126.4, 126.4, 126.3, 126.3, 126.5, 73.6 (minor), 72.5 (major), 66.8, 66.8, 59.2, 56.5, 56.4, 56.3, 55.9, 52.9 (major), 52.7 (minor), 41.8 (minor), 40.5 (major). FTIR (neat,  $\text{cm}^{-1}$ ): 3030, 2927, 2889, 1701, 1447, 1416, 1360, 1197, 1117, 699. MS (ES): 424.4 ( $\text{M}^+ + \text{Na}$ ), 380.2 ( $[\text{M}^+ + \text{Na}] - \text{CH}_2\text{OCH}_3$ ), 288.1. HRMS (FAB): calculated for  $\text{C}_{26}\text{H}_{28}\text{NO}_3 = 402.2069$ , found = 402.2059.



**Benzyl 2-(isopropoxymethyl)-4,4-diphenylpyrrolidine-1-carboxylate**

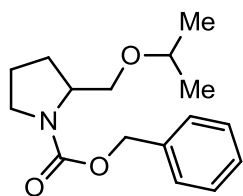
**(17b).** Prepared according to procedure B. 56% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.47-7.14 (m, 15H), 5.27 (d,  $J = 12.5\text{Hz}$ , 0.5H), 5.16 (s, 1H), 5.09 (d,  $J = 12.5\text{Hz}$ , 0.5H), 4.73 (d,  $J = 11.1\text{ Hz}$ , 0.5H), 4.58 (d,  $J = 11.1\text{ Hz}$ , 0.5H), 3.90-3.76 (m, 1H), 3.80-3.70 (m, 0.5H), 3.70-3.66 (m, 1.5H), 3.56-3.53 (m, 0.5H), 3.47-3.35 (m, 1H), 2.89-2.79 (m, 1H), 2.69-2.65 (m, 1H), 1.16-1.05 (m, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.1 (minor), 154.7 (major), 145.7 (major), 145.6 (minor), 145.1 (major), 145.0 (minor), 137.0, 136.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.6, 126.8, 126.5, 126.4, 126.2, 72.1 (major), 72.0 (minor), 69.2 (minor), 68.1 (major), 66.8 (minor), 66.7 (major), 56.9, 56.4, 56.3 (major), 56.2 (minor), 52.9, (major), 52.7 (minor), 42.1 (minor), 40.9 (major), 22.2 (minor), 22.1 (major). FTIR (neat,  $\text{cm}^{-1}$ ): 2971, 1702, 1415, 1109, 699. MS (ES): 430.4 ( $\text{M}^+$ ), 386.2 ( $\text{M}^+ - \text{CO}_2$ ), 280.2. HRMS (FAB): calculated for  $\text{C}_{28}\text{H}_{32}\text{NO}_3 = 430.2382$ , found = 430.2380.



**Benzyl 2-(methoxymethyl)pyrrolidine-1-carboxylate (18a).** Prepared

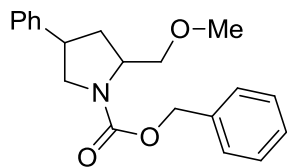
according to procedure A. 62% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.41-7.30 (m, 5H), 5.22-5.12 (m, 2H), 4.02-3.89 (m, 1H), 3.59-3.12 (m, 7H), 2.00-1.82 (m, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 154.9, 136.9 (major), 136.9 (minor), 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 73.5 (minor), 72.8 (major), 66.7 (minor), 66.6 (major), 59.0, 56.9 (major), 56.3 (minor), 46.9 (minor), 46.6 (major), 28.7 (minor), 27.9 (major), 27.8 (minor), 27.0 (major). FTIR (neat,  $\text{cm}^{-1}$ ): 2926, 1699, 1540, 1168. MS (EI): 249.2

( $M^+$ , 0.02%), 204.1 ( $[M - CH_2OCH_3]^+$ , 6%), 160.1 (6%), 91.2 ( $Bn^+$ , 100). HRMS (FAB): calculated for  $C_{14}H_{20}NO_3 = 250.1444$ , found = 250.1445.



**Benzyl 2-(isopropoxymethyl)pyrrolidine-1-carboxylate (18b).** Prepared

according to procedure B. 61% yield. Clear oil.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.44-7.30 (m, 5H), 5.23-5.07 (m, 2H), 4.03-3.94 (m, 1H), 3.63-3.35 (m, 5H), 2.03-1.76 (m, 4H), 1.22 (s, 3H), 0.99 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 154.9, 137.1 (minor), 136.9 (major), 128.4, 127.8, 127.8, 127.8, 77.9 (major), 77.9 (minor), 68.8 (minor), 68.1 (major), 66.7 (minor), 66.5 (major), 57.5 (major), 56.9 (minor), 46.9 (minor), 46.7 (major), 28.8 (minor), 28.0 (major), 23.7 (major), 22.8 (minor), 22.3, 22.0. FTIR (neat,  $cm^{-1}$ ): 2968, 2876, 1703, 1412, 1358, 1105, 697. MS (EI): 277.2 ( $M^+$ , 2%), 204.2 ( $[M - CH_2OCH(CH_3)_2]^+$ , 92%), 160.2 (100%), 91.1 ( $Bn^+$ , 43%). HRMS (FAB): calculated for  $C_{16}H_{24}NO_3 = 278.1757$ , found = 278.1759.



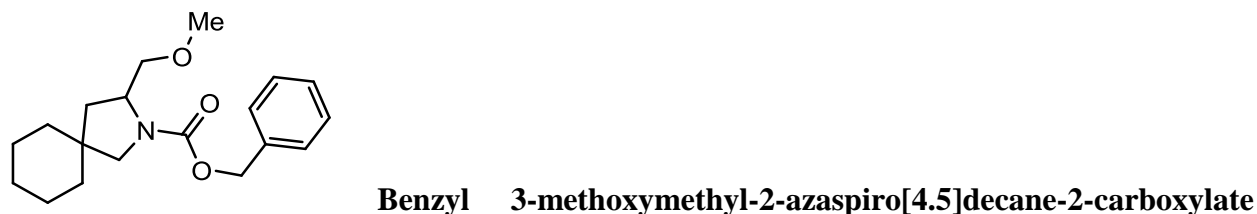
**Benzyl 2-(methoxymethyl)-4-phenylpyrrolidine-1-carboxylate (19a).**

Prepared according to procedure A. 59% yield. Clear oil. An approximately 1:1 mixture of diastereomers was isolated.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.46-7.25 (m, 10H), 5.30-5.12 (m, 2H), 4.29-4.01 (m, 1.5H), 3.95 (t,  $J = 8.5$ , 0.5H), 3.72-3.21 (m, 7H), 2.57-2.30 (m, 1H), 2.22-2.07 (m, 1H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , observed as a mixture of rotamers, major and minor for each diastereomer)  $\delta$ : 154.8 (major), 154.7 (minor), 141.1 (minor), 140.5 (major), 136.8, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 127.2, 127.1, 126.8, 126.7, 74.3 (major), 73.6

(minor), 72.9, 67.3, 66.9, 66.8, 66.7, 59.2 (major), 59.1 (minor), 57.6, (major), 57.4 (minor), 56.9, 53.5 (major), 53.2 (minor), 50.3, 43.2 (major), 42.8 (minor), 42.0 (major), 41.0 (minor), 36.9 (major), 36.4 (minor), 36.0 (major), 35.4 (minor). FTIR (neat,  $\text{cm}^{-1}$ ): 2890, 1700, 1416, 1118, 757. MS (EI): 325.2 ( $\text{M}^+$ , 0.3%), 280.2 ( $[\text{M} - \text{CH}_2\text{OCH}_3]^+$ , 31%), 236.2 (31%), 91.2 ( $\text{Bn}^+$ , 100%). HRMS (FAB):  $\text{C}_{20}\text{H}_{24}\text{NO}_3 = 326.1756$ , found = 326.1742.

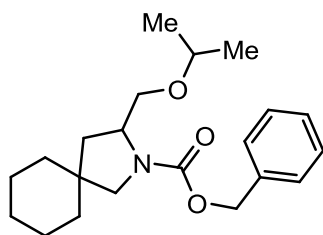


**(19b)**. Prepared according to procedure B. 54% yield. Clear oil. An approximately 1:1 mixture of diastereomers was isolated.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.45-7.22 (m, 10H), 5.27-5.11 (m, 2H), 4.23-4.01 (m, 0.5H), 3.88-3.22 (m, 4.5H), 2.49-2.42 (m, 0.5H), 2.39-2.34 (m, 0.5H), 2.17-2.06 (m, 1H), 1.08 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor for each diastereomer)  $\delta$ : 154.8 (major), 154.6 (minor), 141.2 (minor), 140.7 (major), 136.8, 136.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.2, 127.1, 126.7, 72.1, 69.8, 68.9, 68.6, 68.2, 66.9, 66.8, 66.6, 57.9, 57.4, 57.2, 53.6, 53.2, 43.3, 42.9, 41.9, 40.9, 37.3, 36.4, 35.3, 23.3. FTIR (neat,  $\text{cm}^{-1}$ ): 2970.8, 1701.8, 1414.9, 1111.0, 698.0. MS (EI): 353.2 ( $\text{M}^+$ , 0.3%), 280.2 ( $[\text{M} - \text{CH}_2\text{OCH}(\text{CH}_3)_2]^+$ , 30%), 236.2 (42%), 91.1 ( $\text{Bn}^+$ , 100%). HRMS (FAB):  $\text{C}_{22}\text{H}_{28}\text{NO}_3 = 354.2069$ , found = 354.2055.



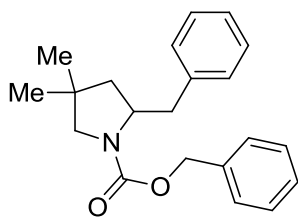
**(20a)**. Prepared according to procedure A. 59% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ :

7.36-7.30 (m, 5H), 5.25-5.08 (m, 2H), 3.98 (br, 1H), 3.65-3.49 (m, 2H), 3.35-3.27 (m, 4H), 2.95 (d,  $J = 10.8$  Hz, 1H), 1.96 (br, 1H), 1.63 (dd,  $J = 8.5, 12.5$  Hz, 1H), 1.43-1.26 (m, 10H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 137.0 (major), 136.8 (minor), 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 74.5 (minor), 73.3 (major), 66.8 (minor), 66.5 (major), 59.1, 57.2, 56.2 (major), 55.5 (minor), 41.4 (major), 41.0 (minor), 39.9, 36.3 (minor), 36.2 (major), 34.7 (minor), 34.6 (major), 26.2, 23.7, 22.8. FTIR (neat,  $\text{cm}^{-1}$ ): 2926, 2854, 1702, 1414, 1116. MS (ED): 317.2 ( $\text{M}^+$ , 0.1%), 272.2 ( $[\text{M} - \text{CH}_2\text{OCH}_2]^+$ , 28%), 228.2 (55%), 91.2 ( $\text{Bn}^+$ , 100%). HRMS (FAB):  $\text{C}_{19}\text{H}_{28}\text{NO}_3 = 318.2069$ , found = 318.2054.



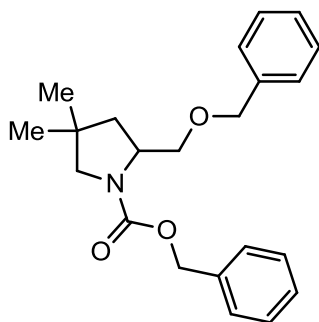
**Benzyl 3-isopropoxymethyl-2-azaspiro[4.5]decane-2-carboxylate**

**(20b)**. Prepared according to procedure B. 59% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35-7.26 (m, 5H), 5.26-5.04 (m, 2H), 3.95 (br, 1H), 3.76-3.27 (m, 4H), 2.96 (d,  $J = 10.8$  Hz, 1H), 1.97 (br, 1H), 1.63 (dd,  $J = 8, 12$  Hz, 1H), 1.53-1.21 (m, 10H), 1.12 (br s, 3H), 1.07 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 137.1 (major), 136.8 (minor), 128.4, 128.0, 127.8, 127.6, 72.0, 70.0 (minor), 69.0 (major), 66.8 (minor), 66.4 (major), 57.3, 56.6 (major), 56.0 (minor), 41.4 (major), 41.0 (minor), 40.3, 36.4 (minor), 36.3 (major), 34.9 (minor), 34.9 (major), 26.1, 23.8, 22.9, 22.1. FTIR (neat,  $\text{cm}^{-1}$ ): 2926, 2856, 1703, 1414, 1359, 1117. MS (ED): 345.2 ( $\text{M}^+$ , 0.2%), 272.2 (32%), 228.2 (72%), 91.2 ( $\text{Bn}^+$ , 100%).  $\text{C}_{21}\text{H}_{32}\text{NO}_3 = 346.2383$ , found = 346.2383.



**Benzyl (2-Benzyl-4,4-dimethyl-pyrrolidine)-1-carboxylate (21).**  $^1\text{H}$

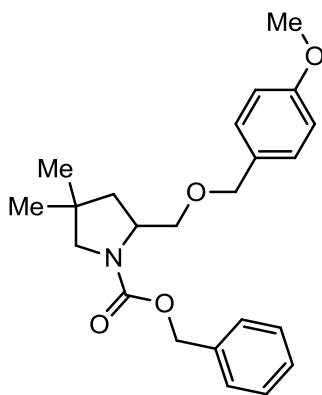
NMR (500 MHz,  $\text{CDCl}_3$  observed as a mixture of rotamers, A and B)<sup>17</sup>: 7.42-7.18 (m, 8H, A + B), 7.06 (d,  $J = 7$  Hz, 1H, A + B), 5.26-5.19 (m, 2H, A + B), 4.13-4.07 (m, 1H, A + B), 3.48 (d,  $J = 11$  Hz, A), 3.44 (d,  $J = 15$  Hz, B), 3.38 (d,  $J = 10.5$  Hz, A), 3.25 (d,  $J = 11$  Hz, B), 2.92-2.89 (m, 1H, A + B), 2.66-2.65 (m, 1H, A + B), 1.65 (m, 1H, A + B), 1.49-1.47 (m, H, A + B), 1.04-1.01 (m, 3H, A + B), 0.94 (br s, 3H, A + B).



**Benzyl 2-benzyloxymethyl-4,4-dimethyl-pyrrolidine-1-carboxylate**

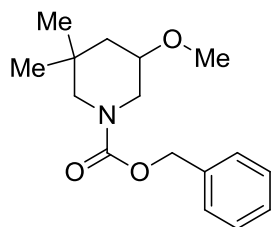
**(22).** Prepared according to procedure C. 48% yield. Clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.43-7.24 (m, 10H), 5.22-5.08 (m, 2H), 4.59-4.46 (m, 2H), 4.15-4.03 (m, 1H), 3.78-3.68 (m, 0.5H), 3.74-3.61 (m, 1H), 3.52-3.50 (m, 1H), 3.04 (d,  $J = 10.5$  Hz), 3.03 (d,  $J = 10.5$  Hz, 1H), 1.90-1.78 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 155.2, 138.6 (major), 138.4 (minor), 137.0, (major), 136.8 (minor), 128.7, 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.4, 73.2, 71.7 (minor), 70.7 (major), 66.8 (minor), 66.5 (major), 59.7, 57.1 (major), 56.4 (minor), 43.6 (minor), 42.5 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat,  $\text{cm}^{-1}$ ): 2957, 2869, 1701, 1416, 1359, 1103. MS

(EI): 353.2 ( $M^+$ , 0.04%), 232.2 (25%), 188.2 (40%), 91.2 ( $Bn^+$ , 100%). HRMS (FAB):  $C_{22}H_{28}NO_3 = 354.2069$ , found = 354.2057.



**Benzyl 2-(4-methoxybenzyloxymethyl)-4,4-dimethyl-pyrrolidine-1-**

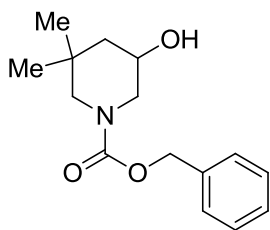
**carboxylate (23).** Prepared according to procedure C. 56% yield. Clear oil.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.43-7.18 (m, 7H), 6.85 (d,  $J = 7.5$  Hz, 2H), 5.18-5.11 (m, 2H), 4.46-4.38 (m, 2H), 4.06-4.01 (m, 1H), 3.80 (s, 3H), 3.66-3.64 (m, 1H), 3.53-3.45 (m, 1H), 3.39 (d,  $J = 10$ Hz, 0.5H), 3.01 (d,  $J = 10.5$  Hz, 1H), 1.88-1.74 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , observed as a mixture of rotamers, major and minor)  $\delta$ : 159.0, 155.2, 137.0 (major), 136.8 (minor), 130.7 (major), 130.4 (minor), 129.0, 128.4, 127.8, 127.6, 113.7, 72.8, 71.5 (minor), 70.5 (major), 66.7 (minor), 66.5 (major), 59.7, 57.1 (major), 56.5 (minor), 55.2, 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat,  $cm^{-1}$ ): 2957, 2869, 1700, 1513, 1416, 1359, 1248, 1173, 1102, 820, 769. MS (ES): 406.3 ( $M^+ + Na$ ), 362.2, 284.0, 270.0. HRMS (FAB): calculated for  $C_{23}H_{30}NO_4 = 384.2175$ , found = 384.2157.



**Benzyl 5-methoxy-3,3-dimethylpiperidine-1-carboxylate (24).**

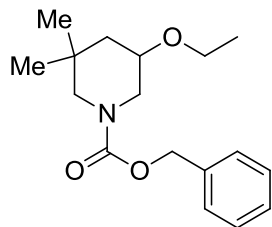
Prepared according to procedure E. Colorless oil (38% yield).  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$

7.41-7.29 (m, 5H), 5.20-5.10 (m, 2H), 4.36-4.34 (m, 0.5H), 4.23-4.16 (m, 0.5H), 3.68-3.58 (m, 1H), 3.36 (d,  $J = 18$  Hz, 3H), 2.74-2.63 (m, 0.5H), 2.65 (d,  $J = 13.5$ Hz), 1.80 (m, 1H), 1.21-1.16 (m, 1H), 0.98 – 0.89 (m, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor):  $\delta$  155.6, 155.5, 136.8, 128.4, 128.0, 127.9, 127.8, 73.2 (minor), 72.8 (major), 67.1, 56.4 (major), 56.3 (minor), 55.0 (major), 54.9 (minor), 47.7, 43.8 (major), 43.8 (minor), 32.2 (major), 32.1, 28.2, 24.9, 24.7. FTIR (neat,  $\text{cm}^{-1}$ ): 2929, 1700, 1430, 1200, 1090. MS (ES): 300  $[\text{M} + \text{Na}]^+$ . HRMS (FAB): calculated for  $\text{C}_{16}\text{H}_{24}\text{NO}_3 = 278.1756$ , found = 278.1747.



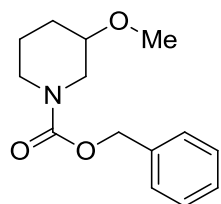
**Benzyl 5-hydroxy-3,3-dimethylpiperidine-1-carboxylate (25).** Prepared

according to procedure F. Colorless oil (40% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41-7.32 (m, 5H), 5.17-5.06 (m, 2H), 4.32-4.20 (m, 1H), 3.90-3.84 (br, 1H), 3.71 (d,  $J = 12.5$  Hz, 0.5H), 3.60 (d,  $J = 12.5$  Hz, 0.5H), 2.68-2.51 (m, 2H), 2.01 (br, 0.5H), 1.77 (d,  $J = 12$  Hz, 1H), 1.70 (br, 0.5H), 1.21 (t,  $J = 11.5$ , 1H), 1.02-0.89 (m, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor):  $\delta$  155.7 (major), 155.4 (minor), 136.7, 128.4, 127.8, 67.2, 64.4 (minor), 64.1 (major), 54.8 (major), 54.6 (minor), 50.7, 46.9 (minor), 46.5 (major), 32.4 (major), 32.4 (minor), 28.3, 24.6. FTIR (neat,  $\text{cm}^{-1}$ ) 3425, 2958, 1679, 1434, 1220, 1061. MS (ES): 286  $[\text{M} + \text{Na}]^+$ , 264  $(\text{M}^+)$ . HRMS (FAB): calculated for  $\text{C}_{15}\text{H}_{22}\text{NO}_3 = 264.1600$ , found = 264.1588.



**Benzyl 5-ethoxy-3,3-dimethylpiperidine-1-carboxylate (26).** Prepared

according to procedure E. Colorless oil (42% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42-7.31 (m, 5H), 5.19-5.05 (m, 2H), 4.42-4.35 (m, 0.5H), 4.28-4.19 (m, 0.5H), 3.78-3.33 (m, 4H), 2.69-2.54 (m, 0.5H), 2.54-2.57 (m, 0.5H), 2.59 (d,  $J = 13\text{Hz}$ , 1H), 1.85-1.67 (m, 1H), 1.25-1.00 (m, 4H), 0.98-0.89 (m, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor):  $\delta$  155.6, 155.3, 136.8, 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 71.4 (minor), 71.0 (major), 67.1 (major), 66.7 (minor), 64.1 (major), 63.9 (minor), 55.0 (major), 54.9 (minor), 48.2, 44.5 (major), 44.1 (minor), 32.3 (major), 32.2 (minor), 28.3, 26.5 (minor), 26.0 (major), 24.7 (minor), 24.5 (major), 15.6. FTIR (neat,  $\text{cm}^{-1}$ ): 2958, 2870, 1702, 1431, 1192, 1107, 698. MS (ES): 314  $[\text{M} + \text{Na}]^+$ , 292  $\text{M}^+$ . HRMS (FAB): calculated for  $\text{C}_{17}\text{H}_{26}\text{NO}_3 = 292.1213$ , found = 292.1918.



**Benzyl 3-methoxypiperidine-1-carboxylate (27).** Prepared according to

procedure E. Colorless oil (80% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41-7.29 (m, 5H), 5.21-5.06 (m, 2H), 3.85 (br, 0.5H), 3.75 (br, 0.5H), 3.62-3.59 (m, 1H), 3.38-3.33 (m, 3H), 3.33-3.22 (br s, 3H), 1.93-1.90 (m, 1H), 1.90 (br s, 1H), 1.54-1.50 (m, 1H), 1.49 (br s, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , observed as a mixture of rotamers, major and minor):  $\delta$  155.4, 136.8, 128.4, 128.0, 127.9, 127.8, 74.6, 67.0, 56.3 (major), 56.1 (minor), 47.3, 47.2, 44.2, 30.0, 29.7, 22.6, 22.1. FTIR

(neat,  $\text{cm}^{-1}$ ): 2942, 2862, 1700, 1430, 1235, 1100. MS (ES): 272  $[\text{M} + \text{Na}]^+$ , 250 ( $\text{M}^+$ ). HRMS (FAB): calculated for  $\text{C}_{14}\text{H}_{20}\text{NO}_3 = 250.1443$ , found = 250.1444.

### Section 5: References

1. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3017.
2. Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615-3618.
3. Zhou, Y.; Murphy, P. V.; *Org. Lett.* **2008**, *10*, 3777-3780.
4. For selected reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (b) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169-1173. (c) Muniz, K. *Chem. Soc. Rev.* **2004**, *33*, 166-174.
5. Donohoe, T. J.; Lindsay-Scott, P. J.; Parker, J. S.; Callens, C. K. *Org. Lett.* **2010**, *12*, 1060-1063. Donohoe, T. J.; Callens, C. K.; Thompson, A. L. *Org. Lett.* **2009**, *11*, 2305-2307.
6. Stoichiometric: Backvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335-342. Catalytic: Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690-7691. Liu, G.; Stahl, S. *J. Am. Chem. Soc.* **2006**, *128*, 7179-7181.
7. Aminotrifluoroacetoxylation of alkenes, see: Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249-1251.
8. For review of Sharpless aminohydroxylation see: Bodkin, J. A., McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2733-2746.
9. Sharpless, K. B.; Patrick, D. W.; Truedale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305-2307. Herranz, E.; Sharpless, K. B.; Biller, S. A. *J. Am. Chem. Soc.* **1978**, *100*

- (11), 3596-3598. Baekvall, J. E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953-1957. Tao, B.; Schligloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507-2510. Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401-404. Han, H.; Cho, C-W.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565-1569. Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949-1952.
10. Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934-12935.
11. Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690-7691.
12. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179-7181.
13. Intramolecular alkoxide (from alkenols): Szolcsanyi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948.
14. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737.
15. Using TEMPO as alkoxy group: Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638-17639
16. Sibbald, P. A.; Michael, F. E.; *Org. Lett.* **2009**, *11*, 1147-1149.
17. Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488-9489.
18. Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.*, **2009**, *131*, 15945-15951
19. Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246-4247
20. Han, X.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747-1749.
21. Michenlin, R. A.; Facchin, G.; Uguagliozzi, P. *Inorg. Chem.* **1984**, *23*, 961-969.

## Chapter 2: Metal-Free Oxyamination, Diamination and Aminofluorination of Alkenes

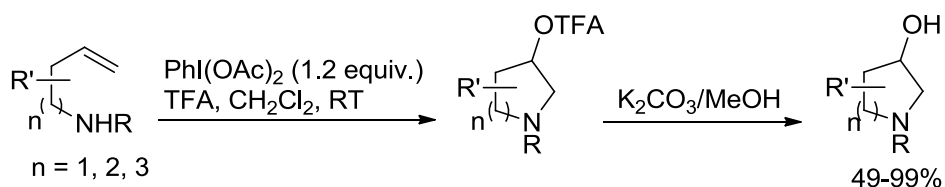
### Part I: Enantioselective Oxyamination of Alkenes

#### Section 1: Introduction

Much progress has been made towards development of selective oxidative difunctionalizations of alkenes, namely aminohydroxylations<sup>1</sup> and dihydroxylations<sup>2</sup>. It is a powerful method of introducing two functional groups across the double bond and can be utilized in synthesis of many biologically active molecules<sup>3</sup>.

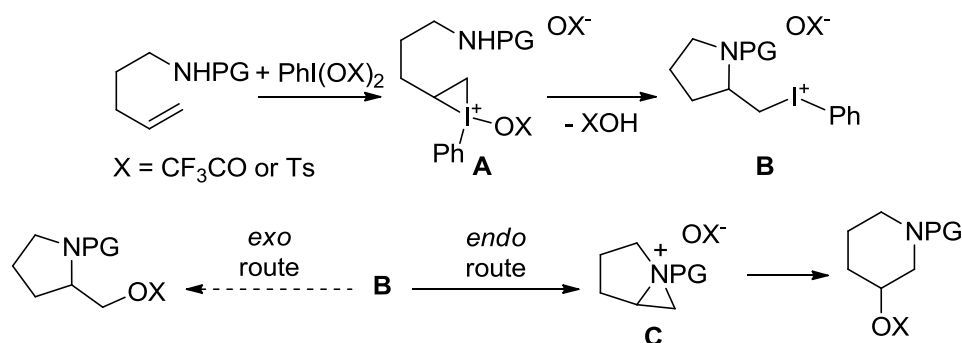
Recently, our group has developed a metal free highly regioselective aminotrifluoroacetoxylation of alkenes<sup>4</sup>. The method involved oxidative cyclization of tosyl protected aminoalkenes with hypervalent iodine as oxidant and a strong Bronsted acid as promoter and external source of oxygen (Scheme 2.I.1).

**Scheme 2.I.1. Metal Free Aminotrifluoroacetoxylation of Alkenes**



This method yields 3-hydroxy cyclized products in good to excellent yield with exceptional regioselectivity. A remarkable feature of this method is that it highly favors *endo*-cyclization, which, to the best of our knowledge is unprecedented<sup>4</sup>. The proposed mechanism is illustrated below in Scheme 2.I.2.

### Scheme 2.I.2. Proposed Mechanism of Metal Free Aminotrifluoroacetylation



We propose that aziridinium ion formation is responsible for the observed overall *endo* selectivity of this transformation. First the alkene is oxidized to generate an iodonium ion, **A**. This intermediate may then be intramolecularly attacked by the sulfonamide to form the kinetically preferred *exo*-cyclization intermediate **B**. It was observed that for more reactive styrenyl substrates, **B** is then rapidly trapped by the trifluoroacetate counterion to form the 5-*exo* products. For less strained and reactive substrates, the nitrogen may eventually displace the iodine to generate an aziridinium ion, **C**<sup>5</sup>. Subsequent nucleophilic attack onto the more substituted carbon of **C** would then generate the *endo* cyclized products.

We sought to enhance this method by developing an enantioselective version. Based on the proposed mechanism enantioselectivity can be induced by providing chiral environment at iodonium ion in **A** before enantiodetermining ring closure. This can be achieved by using chiral hypervalent iodine reagent or employing a chiral activator such as a Lewis acid.

It has been known that chiral hypervalent iodine can induce enantioselectivity in a variety of oxidative additions to alkenes. However, not until very recently have effective iodine reagents been developed<sup>6</sup>. Despite several examples of successful application of chiral hypervalent iodine reagents, this is a new undeveloped field. Additionally, most methods rely on superstoichiometric amounts of a valuable chiral reagent which diminishes practical applications<sup>7</sup>.

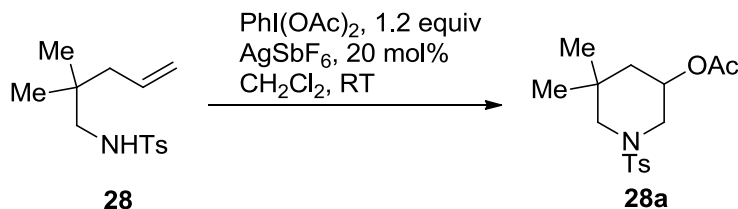
To induce enantioselectivity in oxyamination reaction one could consider using chiral hypervalent iodine reagent or chiral Bronsted acids with nucleophilic counterions to be incorporated. These approaches, however, are highly impractical due to stoichiometric use of chiral reagents. On the other hand, hypervalent iodine reagents can be activated by catalytic amounts of Lewis acids<sup>8</sup>. The counterion to be incorporated would come from the hypervalent iodine reagent. One requirement would be that the Lewis acid has a non-nucleophilic counterion in order to avoid its incorporation. We postulated that if we could find a suitable Lewis acid to catalyze this reaction, using a chiral version of such Lewis acid could open a route to enantioselective *endo* aminotrifluoroacetoxylation.

## Section 2: Results and Discussion

### 2.1.2.a. Lewis Acid-Catalyzed Oxyamination

We began our study by testing if a Lewis acid catalyzed reaction will give comparable results to the Bronsted acid method. Since  $\text{PhI}(\text{TFA})_2$  is capable of reacting without activation, we chose  $\text{PhI}(\text{OAc})_2$  (which will not react without activation) to test Lewis acids. Remarkably, using 20 mol% of  $\text{AgSbF}_6$  afforded 100% yield of the desired product (Scheme 2.I.3).

#### Scheme 2.I.3. Silver-Catalyzed Oxyamination



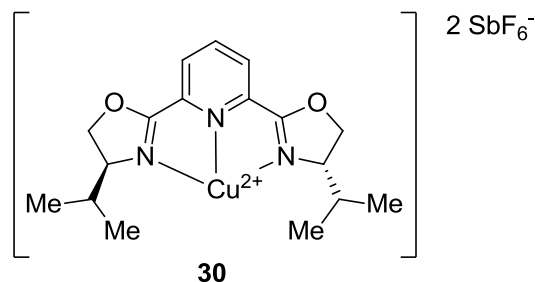
It is noteworthy that the regioselectivity did not change from the Bronsted acid catalyzed reaction and still favored 6-*endo* product in greater than 20:1 ratio. Furthermore, the desired product had a stable acetoxy group and could be isolated as opposed to trifluoroacetate products

which spontaneously hydrolyzed on standing to free alcohols. Also, these new reaction conditions are much milder due to absence of strong trifluoroacetic acid.

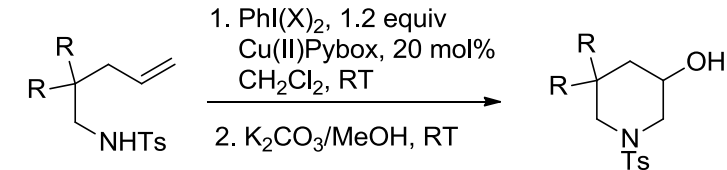
### 2.1.2.b. *Enantioselective Oxyamination*

We chose copper (II) for its commercial availability, low toxicity and a range of ligands that could be used with the metal. A copper-pybox complex with a non-nucleophilic hexafluoroantimonate counterion **30** was employed (Figure 2.I.1).

**Figure 2.I.1. Copper (II) Pybox Hexafluoroantimonate Complex**



Introducing 20 mol% of the complex to catalyze the reaction afforded desired products in excellent yields in less than 15 minutes of reaction time at room temperature (Table 2.I.1). Products with unsubstituted backbone had slightly improved regioselectivity (6:1) over the Bronsted acid method<sup>4,5</sup> (4:1). Oxyamination products were saponified and resulting alcohols were analyzed by chiral HPLC. Unfortunately, all products were found to be racemic.

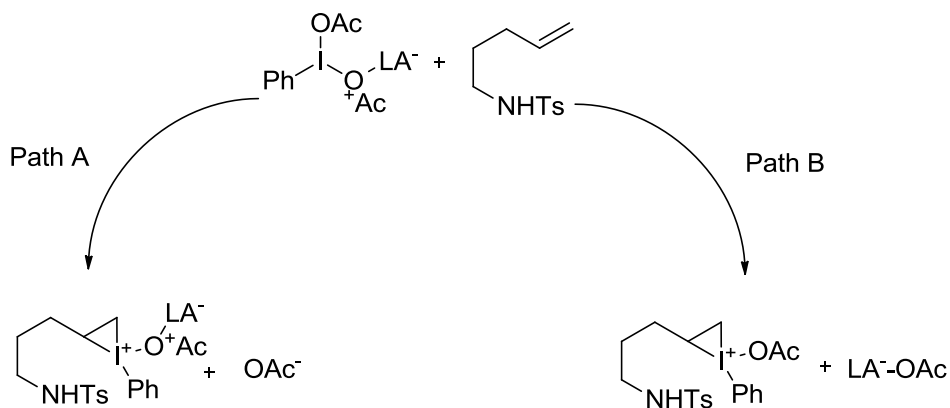
**Table 2.I.1. Oxyamination Catalyzed by a Chiral Lewis Acid**

Entry	Lewis Acid	X	R	Yield	6-endo:5-exo
1	CuPybox	OAc	Me	<b>28c</b> , 92%	>20:1
2	CuPybox	TFA	Me	<b>28c</b> , 93%	>20:1
3	CuPybox	OAc	H	<b>29c</b> , 100%	6:1
4	CuPybox	TFA	H	<b>29c</b> , 86%	4:1

Isolated yields

*2.I.2.c. Proposed Mechanism*

When using  $\text{PhI}(\text{OAc})_2$ , presence of  $\text{Cu}(\text{II})$  pybox complex is essential as no reactivity is observed without it. Racemic products could be explained by copper exchanging the pybox ligand for acetate counterions (Scheme 2.I.4).

**Scheme 2.I.4. Proposed Mechanism**

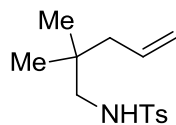
In the first step Lewis acid activates hypervalent iodine towards forming iodonium ion with alkene. Two possible outcomes are envisioned: Path A, where the chiral Lewis acid stays coordinated to the substrate complex and can affect the following attack by nitrogen, and Path B,

where the Lewis acid-OAc adduct leaves the substrate complex and no enantioselectivity could be induced. Path B is consistent with the fact that the products are not enantioenriched.

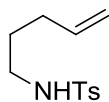
### Section 3: Conclusion

In conclusion, we have shown that the acetoxyamination of alkenes can be catalyzed by Lewis acids in excellent yields. Replacement of a strong Bronsted acid by a catalytic amount of Lewis acid provided milder conditions and allowed formation of stable acetoxyperidene products. In case of tosyl substrate in combination with  $\text{PhI}(\text{OAc})_2$  regioselectivity was slightly improved over the Bronsted acid promoted method. Regrettably, the use of a chiral Lewis acid did not yield enantioenriched products.

### Section 4: Experimental



***N*-(2,2-Dimethylpent-4-enyl)-4-methylbenzenesulfonamide (28).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d, 2 H,  $J = 8.4$  Hz), 7.22 (d, 2 H,  $J = 8.1$  Hz), 5.64 (m, 1 H), 4.92 (m, 3 H), 2.58 (d, 2 H,  $J = 6.9$  Hz), 2.34 (s, 3 H), 1.87 (d, 2 H,  $J = 7.2$  Hz), 0.77 (s, 6 H).

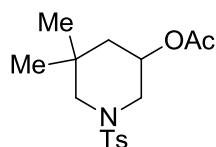


**4-Methyl-*N*-pent-4-enylbenzenesulfonamide (29).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.76 (d, 2 H,  $J = 8.4$  Hz), 7.33 (d, 2 H,  $J = 8.1$  Hz), 5.73 (m, 1 H), 4.99 (m, 2 H), 4.42 (m, 1 H), 2.98 (q, 2 H,  $J = 6.6$  Hz), 2.45 (s, 3 H), 2.07 (q, 2 H,  $J = 6.9$  Hz), 1.59 (m, 2 H).

### General Oxyamination Procedure

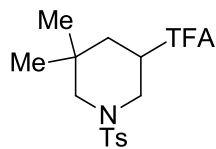
Substrate (0.1mmol) and oxidant (0.12mmol) were dissolved in dichloromethane at room temperature in a 4-dram vial. A solution of  $\text{AgSbF}_6$  or **30** in dichloromethane was added to the vial to make total volume 1mL. Reaction was monitored by TLC. After completion reaction

mixture was quenched with aqueous  $\text{NaHCO}_3$  solution. Organic layer was separated and concentrated under reduced pressure. The residue was dissolved in saturated  $\text{MeOH}/\text{K}_2\text{CO}_3$  solution and let stand 5 minutes at room temperature after which the solution was concentrated under reduced pressure. Residue was suspended in dichloromethane and acidified with 1M HCl. Organic layer was separated, concentrated and run through a silica plug with EtOAc. Products were purified by column chromatography with 20/80 mixture of EtOAc/Hex.



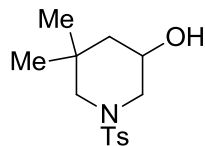
**5,5-Dimethyl-1-(toluene-4-sulfonyl)-piperidin-3-yl acetate (28a).**  $^1\text{H}$  NMR

(300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.63 (d,  $J = 8.2$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 5.07 – 4.93 (m, 1H), 3.59 (dd,  $J = 11.1, 4.3$  Hz, 1H), 3.03 (d,  $J = 11.4$  Hz, 1 H), 2.55 – 2.36 (m, 4H), 2.32 (d,  $J = 11.4$  Hz), 2.01 (s, 3H), 1.68 (dd,  $J = 13.1, 4.3$  Hz, 1H), 1.18 (dd,  $J = 13.1, 9.4$  Hz, 1H), 1.05 (s, 3H), 0.99 (s, 3H).



**5,5-dimethyl-1-(toluene-4-sulfonyl)-piperidin-3-yl trifluoroacetate (28b).**

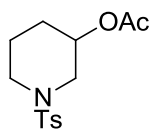
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.66 (d, 2 H,  $J = 8.4$  Hz), 7.36 (d, 2 H,  $J = 8.1$  Hz), 5.197 (p, 1 H,  $J = 4.5$  Hz), 3.72 (dd, 1 H,  $J = 6.9, 4.5$  Hz), 3.11 (d, 1 H,  $J = 11.7$  Hz), 2.61 (dd, 1 H,  $J = 11.1, 8.7$  Hz), 2.46 (s, 3 H), 2.38 (d, 1 H,  $J = 11.7$  Hz), 1.79 (dd, 1 H,  $J = 13.2, 4.5$  Hz), 1.34 (dd, 1 H,  $J = 12.9, 9.6$  Hz), 1.12 (s, 3 H), 1.04 (s, 3 H).



**5,5-Dimethyl-1-(toluene-4-sulfonyl)-piperidin-3-ol (28c):** Condition C, film,

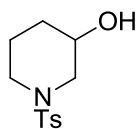
92%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.66 (d, 2 H,  $J = 8.0$  Hz), 7.35 (d, 2 H,  $J = 8.0$  Hz), 4.02 (p,

1 H,  $J = 5.0$  Hz), 3.84 (m, 1 H), 3.23 (d, 1 H,  $J = 11.5$  Hz), 2.46 (s, 3 H), 2.04 (m, 2 H), 1.8-1.6 (m, 2 H), 1.09 (s, 3 H), 1.1-0.9 (m, 1 H), 0.98 (s, 3H).



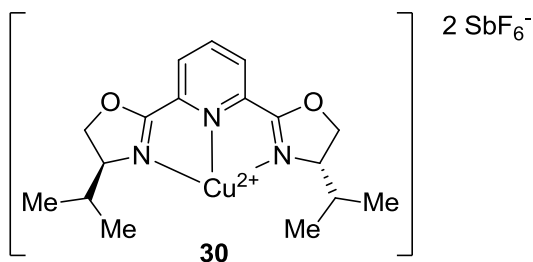
**1-(Toluene-4-sulfonyl)-piperidin-3-yl acetate (29a).**  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 7.63 (d,  $J = 8.3$  Hz, 2H), 7.31 (d,  $J = 8.1$  Hz, 2H), 4.85 (m, 1H), 3.25 (dd,  $J = 11.9, 3.5$  Hz, 1H), 3.13 – 3.03 (m, 1H), 2.93 (dd,  $J = 11.7, 7.1$  Hz, 2H), 2.42 (s, 3H), 2.03 (s, 3H), 1.87 (m, 1 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.45 (m, 1 H).



**1-(Toluene-4-sulfonyl)-piperidin-3-ol (29c):**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.66 (d,

2 H,  $J = 8.0$  Hz), 7.35 (d, 2 H,  $J = 8.0$  Hz), 3.88 (m, 1 H), 3.33 (dd, 1 H,  $J = 11.0, 3.0$  Hz), 3.13 (m, 1 H), 2.80 (m, 1 H), 2.72 (dd, 1 H,  $J = 11.0, 7.5$  Hz), 2.46 (s, 3 H), 1.87 (m, 1 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.40 (m, 1 H).



Copper pybox complex **30** was prepared as standard

solution in dichloromethane according to known procedure<sup>9</sup>.

## Section 5: References

1. For review of Sharpless aminohydroxylation see: Bodkin, J. A., McLeod, M. D. J. *Chem. Soc., Perkin Trans. 1*, **2002**, 2733-2746.
2. Dihydroxylations: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

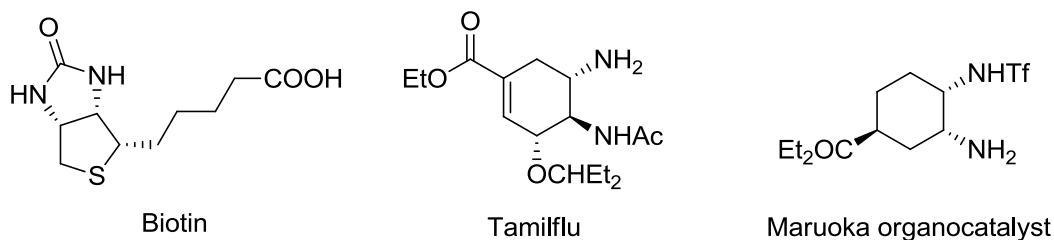
3. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3017. Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615-3618. Zhou, Y.; Murphy, P. V.; *Org. Lett.* **2008**, *10*, 3777-3780.
4. Aminotrifluoroacetoxylation of alkenes, see: Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249-1251.
5. Lovick, H. M. Dissertation: "Applications of Chiral Guanidine Organocatalysts in Asymmetric Transformations Probing Structure Activity Relationships of Artificial Enzyme Active Sites and Development of Metal-Free Oxidative Cyclization Reactions". 2009, University of Washington, Seattle, WA.
6. For synthesis and first use of chiral iodine reagents in asymmetric transformations see: Hirt, U. H.; Wirth, T. *Tetrahedron: Asymmetry*. **1997**, *8*, 23-26. For an overview of chiral hypervalent iodine reagents in asymmetric reactions see: Liang, H.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11849-11851.
7. For first use of catalytic iodine see: Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404.
8. Moriarty, R.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Perkin Trans. 1*, 1987, 559-561. Weinstein, A. B. ACS Org. Div. 2011.
9. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.*, **1996**, *118*, 5814-5815

## Part II: Metal Free Diamination

### Section 1: Introduction

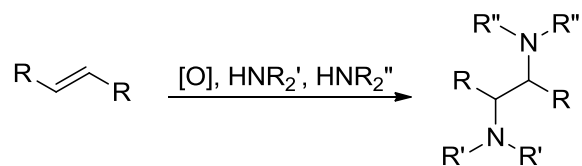
The vicinal diamine moiety is very common in a vast array of valuable organic molecules, including biologically active molecules and additives in organic syntheses (Figure 2.II.1)<sup>1,2</sup>. Biotin is one of essential compound found in nature that contains a 1,2-diamine moiety. Tamiflu is a valuable pharmaceutical which also contains a 1,2-diamine scaffold. Finally, various 1,2-diamines, such as the Maruoka catalyst, have successfully been used as organocatalysts in many enantioselective transformations including oxidations, reductions, oxirane ring openings and many different carbon-carbon bond forming reactions<sup>1</sup>.

**Figure 2.II.1. Valuable Molecules with Ethylenediamine Moiety**



Many methods have been developed to synthesize the 1,2-diamine moiety using a variety of different starting materials, such as substitution of vicinal diols, reduction and addition of organometallic reagents to vicinal diimines, and reductive coupling of imines and *N*-tosylsulfonylimines<sup>1</sup>. However, the most straightforward and atom economical route to vicinal diamines is direct diamination of the double bond, in which two nitrogen atoms are simultaneously introduced across the alkene (Scheme 2.II.1).

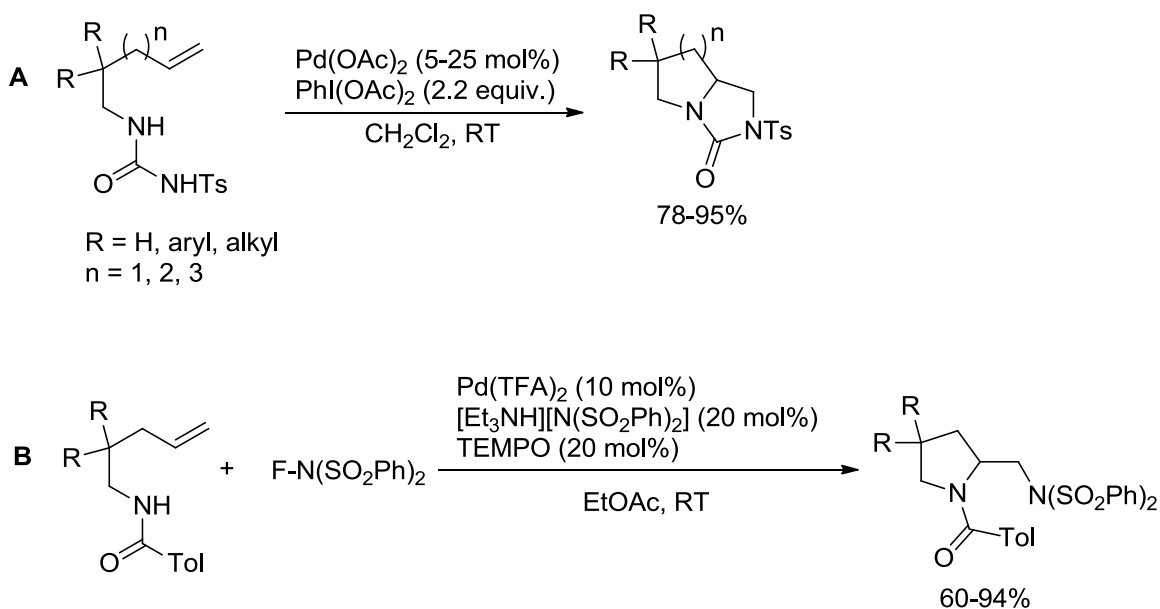
### Scheme 2.II.1. Diamination of Alkenes



While catalytic aminohydroxylation and dihydroxylation methods, including enantioselective variants, have been extensively studied, the closely related diamination reactions are few<sup>1</sup>. It is evident that direct diamination of alkenes requires further development.

One of the first diamination methods came from the Muñiz<sup>3</sup> group. Their design features intramolecular attack on the alkene by a tosyl protected urea and requires palladium for desired reactivity (Scheme 2.II.2 A). Both nitrogen nucleophiles come from the substrate's backbone and products with 5, 6, and 7-membered rings are afforded in good yields. The drawback of this method lies in limitation of substrate scope to ureas.

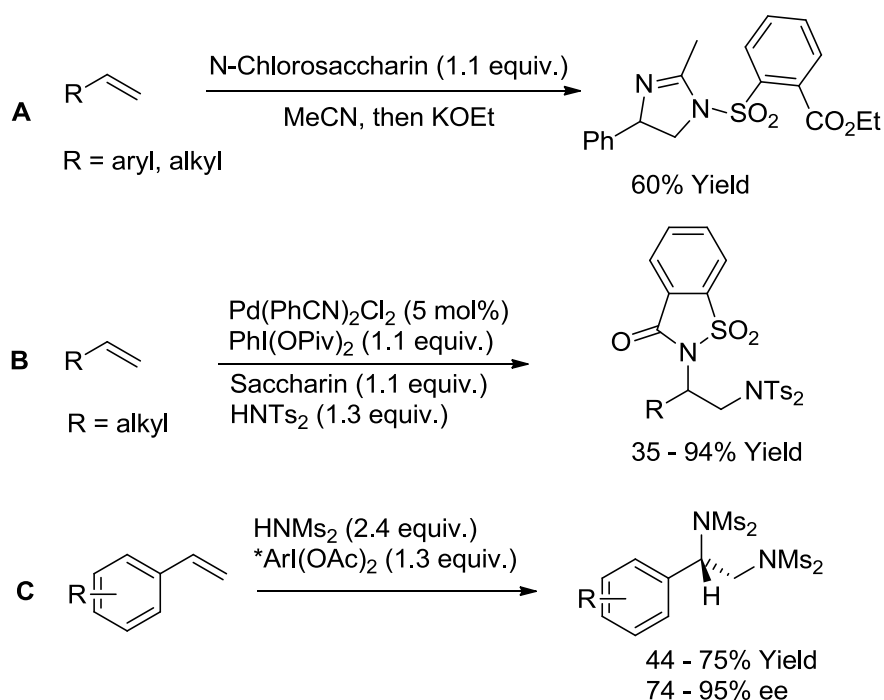
### Scheme 2.II.2. Palladium Catalyzed Intramolecular Diamination Examples



The Michael<sup>4</sup> group has developed an inter/intramolecular diamination of amide and carbamate-protected pentenamine substrates where NFBS would act as an external source of nitrogen (Scheme 2.II.2 **B**). This method is a facile route to aminomethylpyrrolidines under mild conditions and features highly regioselective 5-*exo* cyclizations.

Scheme 2.II.3 depicts some intermolecular diamination methods. One of the first examples is from Booker-Milburn<sup>5</sup> wherein aryl and alkyl alkenes undergo Ritter-type diamination with acetonitrile and *N*-chlorosaccharin in moderate yields (Scheme 2.II.3 **A**). In 2010 Muñiz and co-workers reported a palladium catalyzed diamination of simple alkyl olefins with saccharin and toluenesulfonimide as nitrogen nucleophiles<sup>6</sup> (Scheme 2.II.3 **B**). The reaction proceeded under mild conditions and afforded products in modest to excellent yields.

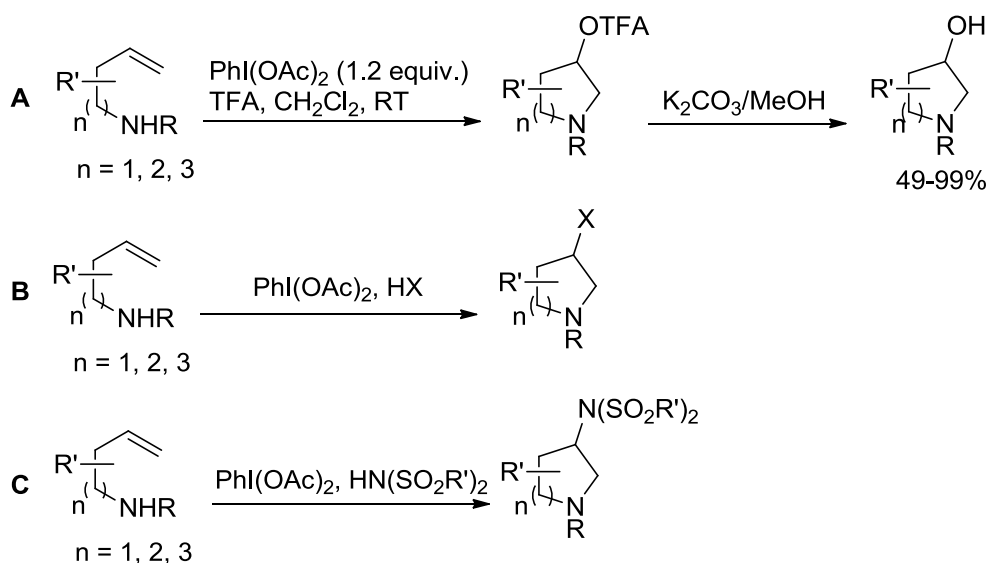
### Scheme 2.II.3. Intermolecular Diamination Methods



The same group reported the first enantioselective metal-free diamination of styrenes in modest to good yields and excellent enantioselectivities<sup>7</sup> (Scheme 2.II.2 C). Enantioenriched products were furnished with the use of a chiral hypervalent iodine reagent. Despite remarkable results, superstoichiometric use of a chiral reagent is a definite drawback.

In light of recent successful development of oxyamination<sup>8</sup> method in our lab we envisioned expanding scope of nucleophiles. Finding a suitable nitrogen nucleophile would open route to metal-free diamination of tethered aminoalkenes.

#### Scheme 2.II.4. Adaptation of Metal Free Oxyamination to Diamination

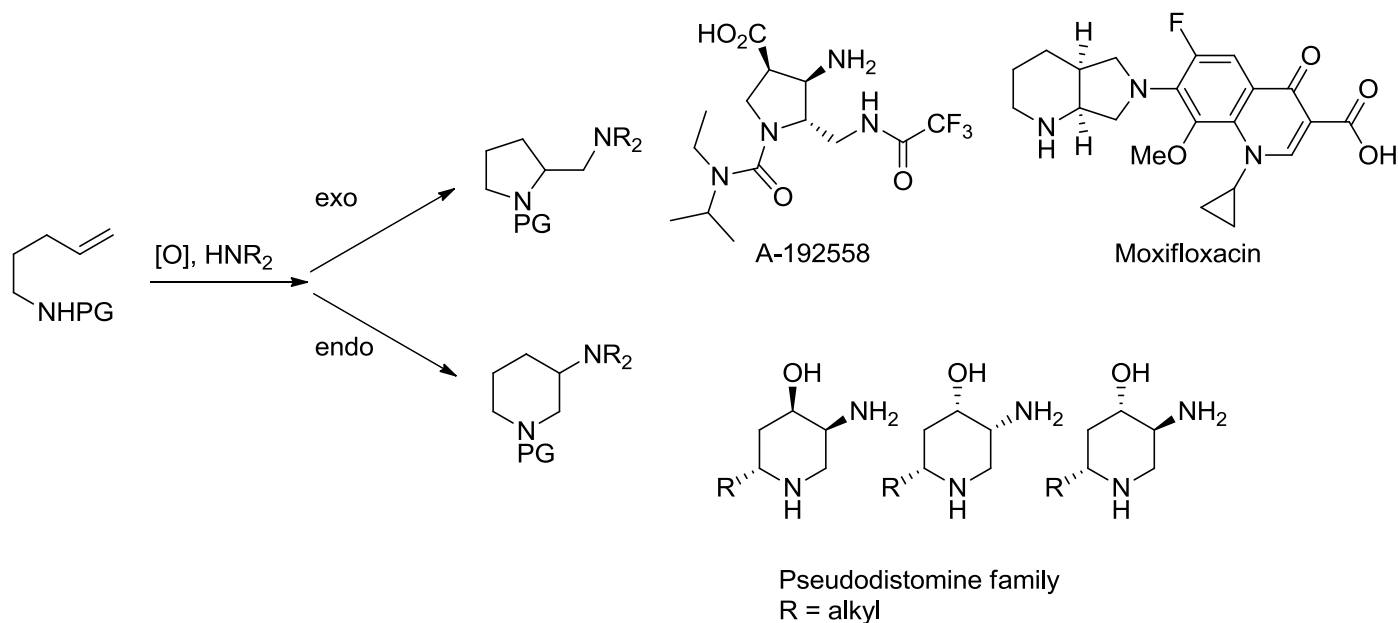


Lovick found that protected aminoalkenes undergo oxidative cyclization promoted by strong Bronsted acids, where the acid counterion ends up incorporated into the cyclized product, ultimately furnishing 3-hydroxy 5,6, and 7-membered nitrogen heterocycles (Scheme 2.II.4 A)<sup>8</sup>. We postulated that any acid strong enough to activate the iodine reagent should also be able to incorporate its counterion to yield the desired product (Scheme 2.II.4 B). Sulfonimides are known to be very acidic with  $pK_a$  comparable to trifluoroacetic acid ( $pK_a$  of TfOH in MeCN is

0.7, while  $\text{Tf}_2\text{NH}$  is 0.3)<sup>9</sup> and should be strong enough Brønsted acids to promote the reaction (Scheme 2.II.4 C).

While Lovick's method exhibited unprecedented 6-*endo* regioselectivity we considered that it might be possible to selectively achieve both the 5-*exo* and 6-*endo* regioselectivities. If a method for controlling the regioselectivity could be developed, various pharmaceutically valuable compounds could be achieved by either method (Scheme 2.II.5).

### Scheme 2.II.5. Two Possible Diamination Outcomes and Target Examples



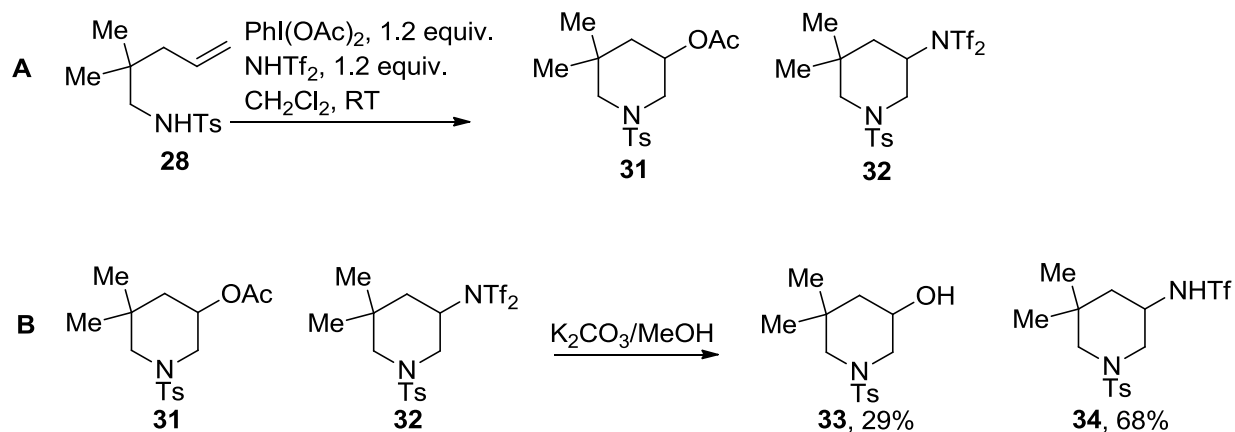
The *exo* route would afford heterocycles present in valuable pharmaceuticals such as moxifloxacin used to treat certain infections such as pneumonia, bronchitis, and sinus, skin, and abdominal infections caused by bacteria<sup>1</sup>. The *endo* cyclization would provide access to 3-aminopiperidines as found in the pseudodistomine alkaloid family, which exhibited strong selective inhibition of a series of glycosidases and which resulted in anticancer and antiviral, particularly anti-AIDS, activity<sup>10</sup>.

## Section 2: Results and Discussion

### 2.II.2.a. Diamination: Initial Screen and Optimization

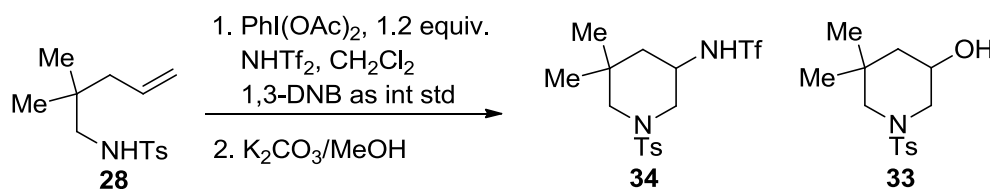
Initially, we treated tosyl protected aminoalkene **28** and diacetoxyiodobenzene with triflimide as the intermolecular nitrogen source and acid promoter (Scheme 2.II.6). We were pleased to see full conversion of the substrate to a mixture of cyclized products. The major component of the mixture was the diamination product **32**. Triflimide **32** was not stable to column conditions which resulted in yield loss.

#### Scheme 2.II.6. Metal-Free Endo Diamination



To avoid this problem, crude mixture was saponified and diamination product **34** was isolated in 68% yield. Subsequent optimization included varying amounts of triflimide and temperature (Table 2.II.1).

Performing the reaction at lower temperature reduced the incorporation of acetate counterion to 18% and 82% of substrate was converted to desired product. Increasing the amount of triflimide to 3 equivalents did not have particular effect on isolated yield (entry 4) affording 78% of the desired product. While  $^1\text{H}$  NMR yields indicated excellent yields, isolation of desired products posed a challenge products were afforded in much lesser quantities than expected.

**Table 2.II.1. Optimization of Diamination with  $\text{PhI}(\text{OAc})_2$** 

Entry	Equiv. $\text{NH}(\text{Tf})_2$	Temperature	<b>33</b> , yield	<b>34</b> , yield
1	1.2	RT	29*	68*
2	1.2	-78 °C→RT	18	82
3	2	-78 °C→RT	9	91
4	3	-78 °C→RT	6	94/78*
5	4	-78 °C→RT	6	94
6	6	RT	33	77
7	6	-78 °C→RT	4	96/73*

Yields determined by  $^1\text{H}$  NMR with 1,3-dinitrobenzene as internal standard

\*Isolated yield

### 2.II.2.b. Further Optimization: Alternative Oxidant

We further sought to optimize the reaction conditions by varying the oxidant. Diacetoxyiodobenzene ( $\text{PhI}(\text{OAc})_2$ ) has a nucleophilic acetate counterion which competes with the triflimide for incorporation. On the other hand, employing iodosyl benzene ( $\text{PhI}=\text{O}$ ) should solve that problem resulting in increased product yield.

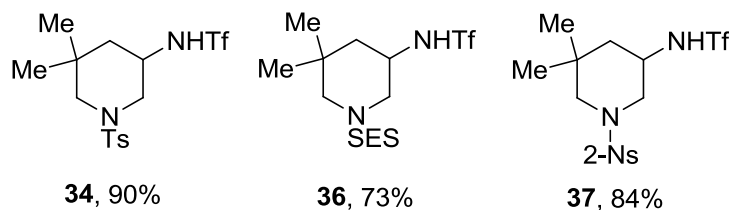
The yield was slightly improved but now a new byproduct was isolated: hydroamination product **35** (Table 2.II.2). Hartwig and coworkers have shown that these substrates undergo hydroamination under strongly acidic conditions<sup>11</sup>. Table 2.II.2 illustrates a set of optimization conditions for product **34**. To minimize formation of the hydroamination byproduct **35** we reduced the amount of triflimide and the desired product was isolated in 90% yield by using 1.2 equivalents of triflimide at room temperature.

**Table 2.II.2. Optimization of Diamination with PhI=O as Oxidant**

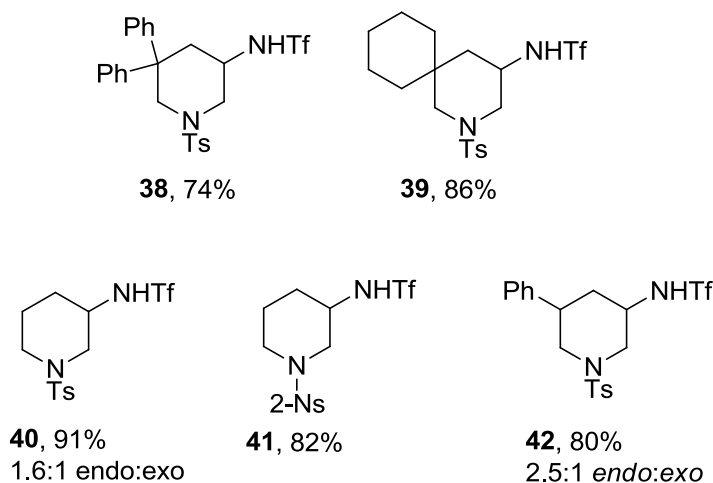
Entry	Equiv. NHTf <sub>2</sub>	Yield, %	Yield, %*
1	5	78	21
2	2	87	Trace
3	1.2	90	Trace

**2.II.2.c. Diamination Substrate Scope**

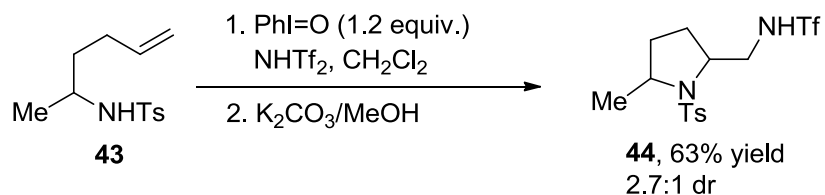
We were pleased to see that various sulfonamides yield diamination products under these conditions (Figure 2.II.2). Both the electron rich SES protecting group and the electron poor nosyl group furnished comparable yields and excellent regioselectivity to the nosyl substrate.

**Figure 2.II.2. Sulfonamide Protecting Group Scope**

Gratifyingly, disubstituted and monosubstituted substrates yielded products in very good yields, albeit moderate diastereoselectivity. Regioselectivity was also moderate for monosubstituted substrates and afforded a mixture of 5-*exo* and 6-*endo* products. The tosyl protected unsubstituted substrate **40** gave very poor regioselectivity but switching the protecting group for nosyl solved this problem and the desired product was furnished as a single 6-*endo* regioisomer in 82% yield.

**Figure 2.II.3. Metal-Free *Endo* Diamination Scope**

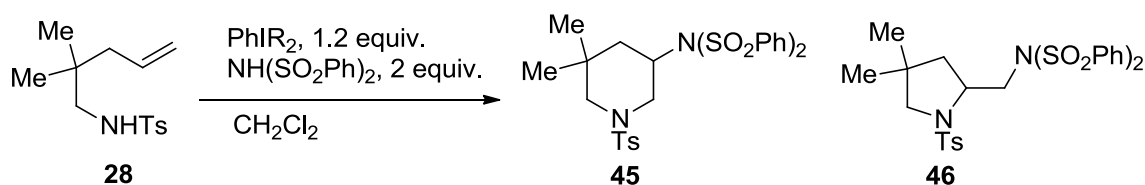
Interestingly, substrate **43** yielded exclusively 5-*exo* cyclization product **44** in moderate yield (Scheme 2.II.7). Evidently, a substituent vicinal to the nitrogen plays a role in regiochemical outcome: similar effect was encountered in the oxyamination method when isopropyl group was used instead of methyl. While the reaction still favored *endo*-cyclization a significant amount of 5-*exo* product was observed (2.3:1 *endo:exo*).

**Scheme 2.II.7. Metal-Free 5-*Exo* Diamination Product****2.II.2.d. Milder Nitrogen Sources**

We sought to expand this method by exploring various milder, less acidic nitrogen sources. Sulfonimides with less electron-withdrawing groups than trifluoromethyl are still fairly acidic ( $pK_a$  7.7 for NHNS<sub>2</sub> in MeCN)<sup>9</sup> and should be strong enough to activate the iodine

reagent. Our first attempt employed benzenesulfonimide as acid and external nitrogen source (Table 2.II.3).

**Table 2.II.3. Diamination with Benzenesulfonimide**

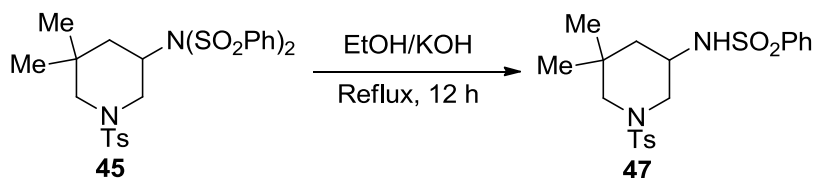


Entry	Oxidant	Temperature	<b>45:46</b>
1	$\text{PhI}=\text{O}$	RT	4:1
2	$\text{PhI}=\text{O}$	60 °C	3:1
3	$\text{PhI}(\text{OAc})_2$	RT	4:1
4	$\text{PhI}(\text{OAc})_2$	RT	12:1

Product ratio was determined by  $^1\text{H NMR}$   
 $^{10}$  mol%  $\text{Cu}(\text{OTf})_2$

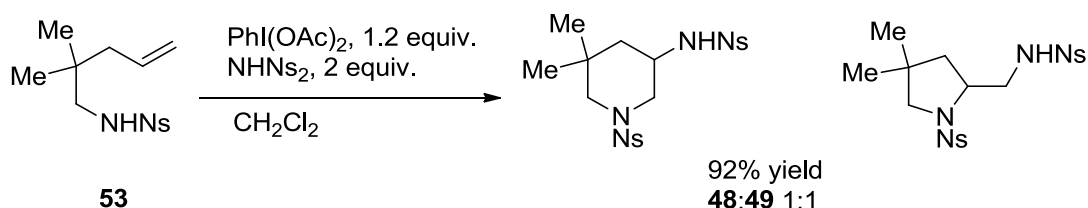
We employed  $\text{PhI}=\text{O}$  and  $\text{PhI}(\text{OAc})_2$  as oxidants. In both cases regioselectivity was moderate. Additionally, the reaction required over a day to complete. Substituting dichloromethane for dichloroethane and heating the mixture to 60 °C afforded full conversion in only a few hours without a significant change in regioselectivity. Surprisingly, addition of 10 mol% of  $\text{Cu}(\text{OTf})_2$  improved the regioselectivity to 12:1 favoring the 6-*endo* product (entry 4). Product **45** was isolated in 96% yield. Further hydrolysis in refluxing ethanol/KOH yielded 91 % of **47** (Scheme 2.II.8).

**Scheme 2.II.8. Deprotection of the Imide**



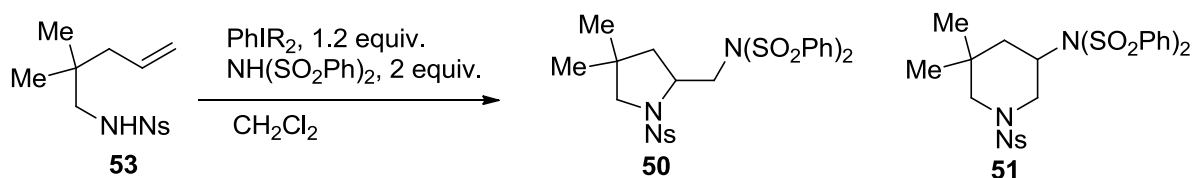
We sought to improve the synthetic utility of the product by substituting the tosyl protecting group for nosyl and employing  $\text{NHNS}_2$  as external nitrogen source (Scheme 2.II.9). Interestingly, the product of imide incorporation was deprotected under reaction conditions to give a mixture of regioisomeric sulfonamide products **48** and **49**. Despite the reaction proceeding in excellent yield (92%), the regioselectivity of the final product was very poor (1:1).

**Scheme 2.II.9. Diamination of Nosyl Protected Substrate with  $\text{HNNS}_2$**



It was becoming evident that while the yields of the diamination products in these reactions were uniformly high, the regioselectivity was becoming an issue. Compromising, we fell back on  $\text{HN(SO}_2\text{Ph)}_2$  and observed a change in regioselectivity from 6-*endo* to 5-*exo* (Table 2.II.4).

**Table 2.II.4. Diamination of Nosyl Protected Substrate with  $\text{NH(SO}_2\text{Ph)}_2$**



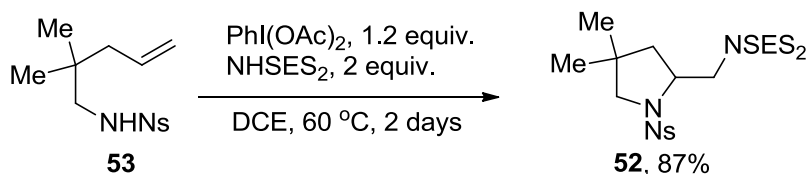
Entry	Oxidant	Temperature	<b>50:51</b>
1	$\text{PhI=O}$	RT	2:1
2	$\text{PhI=O}$	60 °C	2:1
3	$\text{PhI(OAc)}_2$	RT	3:1

Regrettably, regioselectivity was still very modest. However, the observed switch in favor of 5-*exo* product when employing an electron-poor nosyl group gave a promising lead to developing regiochemical control.

### 2.II.2.e. Regioselectivity Switch

Our results suggested that pairing a relatively electron poor protecting group with an electron rich nucleophile can lead to favoring of a 5-*exo*. We decided to couple a nosyl protected substrate with HNSES<sub>2</sub>.

#### Scheme 2.II.10. Diamination of Nosyl Protected Substrate with HNSES<sub>2</sub>.

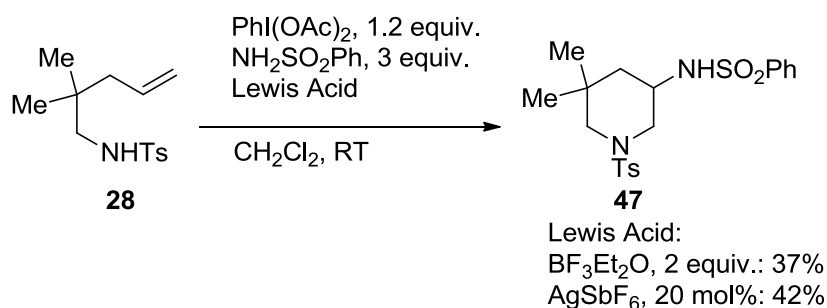


The reaction proved to be very slow and full conversion was not achieved even after several days. Heating the reaction mixture to 60 °C in dichloroethane resulted in conversion to the desired product in 48 hours. Under these conditions we were able to isolate **52** as a single regioisomer in 87% yield (Scheme 2.II.10).

### 2.II.2.f. Diamination with Benzenesulfonamide

The intramolecular diamination method could be further enhanced by employing a simple sulfonamide as the external nucleophile. Such scheme is more atom-economical and allows the use of readily commercially available array of sulfonamides (Scheme 2.II.11). Since sulfonamide itself will not activate hypervalent iodine, a Lewis acid could be employed for this purpose. Advantage of a Lewis acid over a Bronsted acid promoter is the absence of competing counterion nucleophile.

**Scheme 2.II.11. Lewis Acid-Catalyzed 6-*Endo* Diamination with Benzenesulfonamide**



Yields determined by  $^1\text{H}$  NMR with 1,3-dinitrobenzene as internal standard

To our delight we are able to directly incorporate sulfonamide under reaction conditions in 37% yield with  $\text{BF}_3\text{-Et}_2\text{O}$ . Other Lewis acids such as  $\text{AgSbF}_6$  could be used catalytically to afford the desired product in 42% yield. These unoptimized yields showed the possibility of using sulfonamides as nucleophiles under Lewis acidic conditions and opened a promising alternative route to diamination.

### Section 3: Conclusion

Lovick's oxyamination method was successfully adapted to yield diamination products by substituting an oxygen Bronsted acid for a nitrogen-containing Bronsted acid and enhance the *endo*-cyclization scope of tethered aminoalkenes. Diamination with triflimide afforded 3-aminopiperidines in good to excellent yields albeit modest diastereoselectivity. Substituting triflimide for less acidic sulfonimides also afforded desired products but regioselectivity became an issue. A promising method towards direct incorporation of sulfonamides under Lewis acidic conditions was also discovered.

## Section 4: Experimental

### General

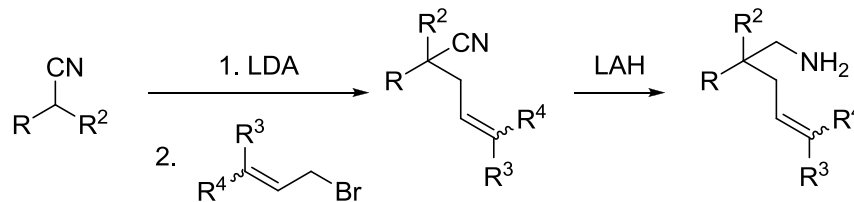
All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. Column chromatography was performed using silica gel (Whatman, 60Å, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AV- 300 or AV-500 spectrometer.  $^1\text{H}$  NMR chemical shifts are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual  $\text{CHCl}_3$  (7.26 ppm). Chemical shifts for carbon are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ( $\text{CDCl}_3$ : 77.2 ppm). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer. Chiral HPLC analysis was performed on a Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 254 nm; column, DAICEL CHIRALPAK AD-H; mobile phase, hexanes/2-propanol.

### Materials

THF,  $\text{CH}_2\text{Cl}_2$  and  $\text{Et}_2\text{O}$  were degassed and dried on columns of neutral alumina. Toluene was degassed and dried on a column of neutral alumina and a Q5 reactant column. 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 4 Å molecular sieves and were used without further purification. Commercial reagents were purchased from Sigma-Aldrich Co. and were used as received.

### Substrates Syntheses

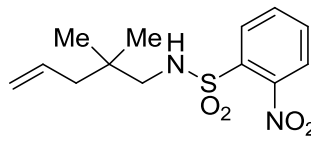
### General Route to Substituted Alkene Substrates:



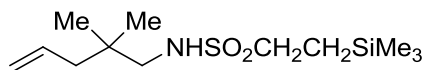
Non-commercially available, substituted amines were synthesized by the known, general route illustrated above. Freshly prepared LDA (1.1 equiv.) was added to the appropriate nitrile (1 equiv.) at  $-78\text{ }^\circ\text{C}$  in THF. The solution was stirred at  $0\text{ }^\circ\text{C}$  for 1 h, and then the required allylic bromide (1 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with addition of water, extracted with  $\text{Et}_2\text{O}$ , organic layers were dried ( $\text{MgSO}_4$ ), and concentrated. The resultant oil was used without purification in the subsequent step. The alkylated nitrile was dissolved in  $\text{Et}_2\text{O}$  and was added to a mixture of LAH (1.5 equiv.) in  $\text{Et}_2\text{O}$  at  $0\text{ }^\circ\text{C}$ . The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by slow addition of 1 M NaOH at  $0\text{ }^\circ\text{C}$ . The slurry was filtered through Celite and concentrated. The resulting amine was then acidified by addition of 2 M HCl in  $\text{Et}_2\text{O}$  (1 equiv.). The mixture was filtered and the solid was rinsed with hexanes and then thoroughly dried *in vacuo* prior to protection.

### Standard Protection Procedure

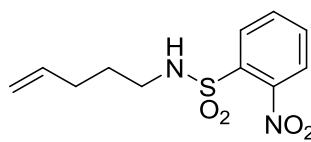
The ammonium salt (1 equiv.) and  $\text{Et}_3\text{N}$  (2 equiv.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (0.5 M) and cooled to  $0\text{ }^\circ\text{C}$ . The sulfonyl chloride (1 equiv.) was then added portionwise. Following addition of the sulfonyl chloride the reaction mixture was stirred at room temperature for four hours. The solution was then washed with 1 M HCl, dried ( $\text{MgSO}_4$ ) and purified by column chromatography,  $\text{EtOAc}/\text{Hexanes}$  (5%→20%  $\text{EtOAc}$ ).



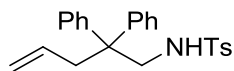
***N*-(2,2-Dimethylpent-4-enyl)-2-nitrobenzenesulfonamide (53).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.13 (d, 1 H,  $J = 5.0$  Hz), 7.88 (m, 1 H), 7.77 (m, 2 H), 5.78 (m, 1 H), 5.36 (m, 1 H), 5.07 (m, 2 H), 2.86 (d, 2 H,  $J = 6.0$  Hz), 2.03 (d, 2 H,  $J = 7.5$  Hz), 0.94 (s, 6 H).



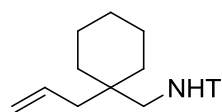
**2-Trimethylsilylethanesulfonic acid (2,2-dimethylpent-4-enyl)-amide (54).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.83 (m, 1 H), 5.11 (m, 2 H), 4.16 (s, 1 H), 2.95 (m, 2 H), 2.90 (d, 2 H,  $J = 7.0$  Hz), 2.05 (d, 2 H,  $J = 7.5$  Hz), 1.05 (m, 2 H), 0.97 (s, 6 H), 0.09 (s, 9 H).

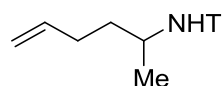


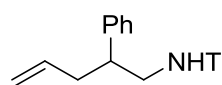
**2-Nitro-*N*-pent-4-enylbenzenesulfonamide (55).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.16 (m, 1 H), 7.89 (m, 1 H), 7.77 (m, 2 H), 5.74 (m, 1 H), 5.31 (br t, 1 H,  $J = 4.8$  Hz), 5.00 (m, 2 H), 3.13 (q, 2 H,  $J = 6.9$  Hz), 2.10 (m, 2 H), 1.64 (p, 2 H,  $J = 6.9$  Hz).

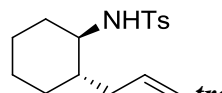


***N*-(2,2-Diphenylpent-4-enyl)-4-methylbenzenesulfonamide (56).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.62 (d, 2 H,  $J = 8.0$  Hz), 7.4-7.2 (m, 8 H), 7.08 (m, 4 H), 5.28 (m, 1 H), 4.98 (m, 2 H), 3.83 (t, 1 H,  $J = 6.5$  Hz), 3.55 (d, 2 H,  $J = 6.5$  Hz), 2.92 (d, 2 H,  $J = 7.0$  Hz), 2.46 (s, 3 H).

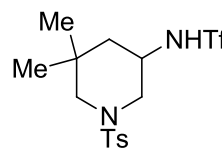

***N*-(1-Allyl-cyclohexylmethyl)-4-methylbenzenesulfonamide (57).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d, 2 H,  $J = 8.4$  Hz), 7.21 (d, 2 H,  $J = 8.1$  Hz), 5.60 (m, 1 H), 4.91 (m, 3 H), 2.63 (d, 2 H,  $J = 6.9$  Hz), 2.33 (s, 3 H), 1.94 (d, 2 H,  $J = 7.5$  Hz), 1.3-1.1 (m, 10 H).


**4-Methyl-*N*-(1-methylpent-4-enyl)-benzenesulfonamide (43).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.78 (d, 2 H,  $J = 8.4$  Hz), 7.32 (d, 2 H,  $J = 8.1$  Hz), 5.70 (m, 1 H), 4.94 (br d, 2 H,  $J = 15.9$  Hz), 4.24 (d, 1 H,  $J = 8.4$  Hz), 3.35 (m, 1 H), 2.45 (s, 3 H), 2.02 (m, 2 H), 1.48 (m, 2 H), 1.04 (d, 3 H,  $J = 6.6$  Hz).


**4-Methyl-*N*-(2-phenylpent-4-enyl)-benzenesulfonamide (58).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d, 2 H,  $J = 8.1$  Hz), 7.25 (m, 5 H), 7.05 (d, 2 H,  $J = 6.6$  Hz), 5.61 (m, 1 H), 4.98 (m, 2 H), 4.12 (m, 1 H), 3.35 (m, 1 H), 3.04 (m, 1 H), 2.80 (p, 1 H,  $J = 6.6$  Hz), 2.45 (s, 3 H), 2.36 (m, 2 H).

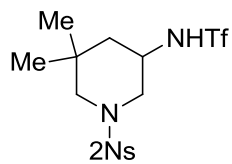

***trans*-*N*-(2-Allyl-cyclohexyl)-4-methylbenzenesulfonamide (59).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.68 (d, 2 H,  $J = 8.4$  Hz), 7.21 (d, 2 H,  $J = 8.1$  Hz), 5.57 (m, 1 H), 4.88 (m, 2 H), 4.08 (d, 1 H,  $J = 8.7$  Hz), 2.81 (dq, 1 H,  $J = 6.6, 3.0$  Hz), 2.36 (s, 3 H), 2.28 (m, 1 H), 1.8-1.4 (m, 4 H), 1.3-0.8 (m, 6 H).

#### New compounds characterization:


***N*-(5,5-dimethyl-1-tosylpiperidin-3-yl)trifluoromethanesulfonamide (34).**

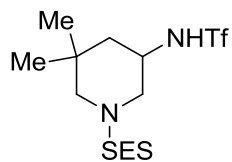
white solid, 90% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.62 (d,  $J = 8.1$  Hz, 2H), 7.33 (d,  $J = 8.1$

Hz, 2H), 5.11 (d,  $J = 8.1$  Hz, 1H), 3.89-3.75 (m, 2H), 3.17 (d,  $J = 11.4$  Hz, 1H), 2.44 (s, 3H), 2.23-2.08 (m, 2H), 1.76-1.70 (m, 1H), 1.15-1.06 (m, 1H), 1.06 (s, 3H), 0.97 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -75. MS (ESI): 415 (M<sup>+</sup>).



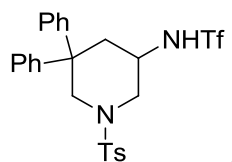
***N*-(5,5-dimethyl-1-(2-nitrophenylsulfonyl)piperidin-3-**

**yl)trifluoromethanesulfonamide (37).** 84%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.04 – 7.96 (m, 1H), 7.79 – 7.62 (m, 3H), 5.30 (br s, 1 H), 3.99 (dd,  $J = 12.2, 4.4$  Hz, 1H), 3.84 (br s, 1H), 3.35 (d,  $J = 12.7$  Hz, 1H), 2.68 – 2.56 (m, 2H), 1.88 – 1.77 (m, 1H), 1.27 (dd,  $J = 16.1, 9.0$  Hz, 1H), 1.01 (s, 6H).



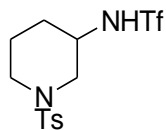
***N*-(5,5-dimethyl-1-(2-(trimethylsilyl)ethylsulfonyl)piperidin-3-**

**yl)trifluoromethanesulfonamide (36).** 73% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.29 – 5.14 (br, 1H), 3.92 (dd,  $J = 11.8, 4.0$  Hz, 1H), 3.78 (ddd,  $J = 7.6, 6.7, 5.5$  Hz, 1H), 3.26 (d,  $J = 12.3$  Hz, 1H), 2.95 – 2.82 (m, 2H), 2.77 – 2.60 (m, 2H), 1.90 – 1.77 (m, 1H), 1.40 – 1.18 (m, 2H), 1.07 (s, 3H), 1.03 (s, 3H), 1.01 – 0.93 (m, 2H), 0.05 (s, 9H).



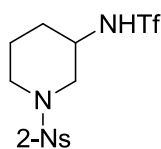
***N*-(5,5-diphenyl-1-tosylpiperidin-3-yl)trifluoromethanesulfonamide (38).**

74%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.64 (d,  $J = 8.2$  Hz, 2H), 7.30 (ddd,  $J = 14.9, 8.6, 2.1$  Hz, 12H), 4.84 (br s, 1H), 3.85 (br s, 1H), 3.51 (m, 2H), 3.25 (d,  $J = 8.8$  Hz, 1H), 2.98 (m, 1H), 2.65 (dd,  $J = 13.3, 3.4$  Hz, 1H), 2.49 – 2.35 (m, 2H), 2.42 (s, 3H).



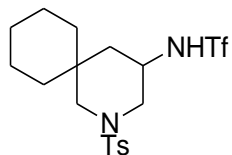
**Trifluoro-*N*-(1-tosylpiperidin-3-yl)methanesulfonamide (40).** 1:1.6 mixture of

regioisomers 5-*exo* (A):6-*endo* (B), 91% combined yield. 7.72(A or B) (d,  $J = 8.1$  Hz, 2H), 7.64(A or B), (d,  $J = 8.1$  Hz, 2H), 7.40-7.30 (A+B) (m), 6.31-6.23 (A) (m, 1H), 5.66(B) (d,  $J = 9$  Hz, 1H), 3.91-3.76(A+B) (m), 3.70-3.17(A+B) (m), 2.86 (A or B) (dd,  $J = 2.7, 12$  Hz, 1H), 2.68-2.57 (A or B) (m, 1H), 2.44 (A+B) (s), 1.97-1.55 (A+B) (m).



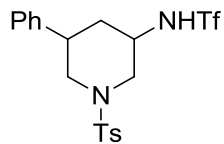
**Trifluoro-*N*-(1-(2-nitrophenylsulfonyl)piperidin-3-yl)methanesulfonamide (41).**

81% yield. NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.04 (d,  $J = 7.3$  Hz, 1H), 7.82 – 7.62 (m, 3H), 5.79 (br s, 1H), 3.82 (br, 1H), 3.65 – 3.52 (m, 1H), 3.39 (m, 2H), 3.19 – 3.06 (m, 1H), 1.99 – 1.65 (m, 5H).



**39 . 86% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.64 (d,  $J = 8.4$  Hz, 2H), 7.34**

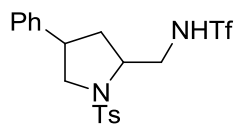
(d,  $J = 8.1$  Hz, 2H), 4.89 (d,  $J = 8.4$  Hz, 1H), 3.90-3.77 (m, 2H), 3.46 (d,  $J = 11.7$  Hz, 1H), 2.44 (s, 3H), 2.28 (m, 1H), 2.11 (d,  $J = 11.7$  Hz, 1H), 1.94-1.83 (m, 1H), 1.67-1.20 (m, 10H), 1.09-0.98 (m, 1H). FTIR ( $\text{cm}^{-1}$ ): 1309, 1251, 1162, 1092, 1033, 996, 974, 916, 815, 733.



**Trifluoro-*N*-(5-phenyl-1-tosylpiperidin-3-yl)methanesulfonamide (42).** 59%

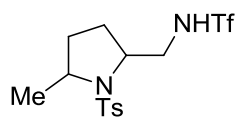
(80% combined). In  $\text{C}_6\text{D}_6$ .  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.46 (d,  $J = 8.1$  Hz, 2H), 7.06 (m, 3H), 6.89 (d,  $J = 8.1$  Hz, 2H), 6.76 (d,  $J = 7.1$  Hz, 2H), 3.93 (d,  $J = 9.2$  Hz, 2H), 3.75 (d,  $J = 7.5$  Hz,

1H), 3.43 (m, 1H), 2.42 (tt,  $J = 12.0, 3.7$  Hz, 1H), 2.0 (s, 3H), 2.0 (m, 1H), 1.89 (t,  $J = 11.6$  Hz, 1H), 1.85 (m, 1H), 1.60 (t,  $J = 11.0$  Hz, 1H).



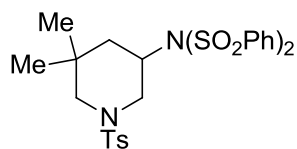
**Trifluoro-*N*-((4-phenyl-1-tosylpyrrolidin-2-yl)methyl)methanesulfonamid**

**(43)**. 21%.  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.58 (t,  $J = 6.5$  Hz, 1H), 7.55 (d,  $J = 8.2$  Hz, 2H), 6.98 (d,  $J = 5.0$ , 2H), 6.81 (d,  $J = 8.1$  Hz, 2H), 6.64 (dd,  $J = 6.6$ , 1H), 5.93 (t,  $J = 5.4$  Hz, 1H), 3.65 – 3.58 (m, 1H), 3.41 (dd,  $J = 13.7, 5.7$  Hz, 1H), 3.09 (t,  $J = 5.6$  Hz, 2H), 2.99 – 2.89 (m, 1H), 2.84 – 2.76 (m, 1H), 1.95 (s, 3H), 1.47 (dd,  $J = 13.0, 6.3$  Hz, 1H), 1.28 – 1.17 (m, 1H).



**Trifluoro-*N*-((5-methyl-1-tosylpyrrolidin-2-**

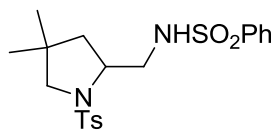
**yl)methyl)methanesulfonamide (44)**. 63 % (2.7:1 dr).  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.64 (major) (d,  $J = 8.2$  Hz, 2H), 7.55 (minor) (d,  $J = 8.2$  Hz, 2H), 6.83 (major+minor) (d,  $J = 8.0$  Hz, 2H), 6.21 (minor) (t,  $J = 5.3$  Hz, 1H), 5.80 (major) (t,  $J = 5.9$  Hz, 1H), 3.93 (major) (m, 1H), 3.45 (minor) (m, 1H), 3.40 – 3.34 (major) (m, 1H), 3.30 – 3.08 (major+minor) (m, 2H), 3.02 (minor) (dd,  $J = 12.6, 6.0$  Hz, 1H), 1.94 (major+minor) (s, 3H), 1.63 – 1.53 (minor) (m, 2H), 1.41 – 1.30 (major) (m, 2H), 1.12 (minor) (d,  $J = 6.5$  Hz, 3H), 0.94 (major) (d,  $J = 6.5$  Hz, 3H), 0.89 – 0.85 (minor) (m, 2H), 0.83 (major) (m, 2H).



***N*-((5,5-dimethyl-1-tosylpiperidin-3-yl)-*N*-**

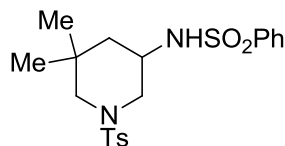
**(phenylsulfonyl)benzenesulfonamide (45)**.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.02 (m, 3H), 7.77 – 7.67 (m, 3H), 7.62 (m, 4H), 7.53 (m, 2H), 7.32 (m, 2H), 4.43 (br m, 1H), 3.56 (d,  $J = 7.0$  Hz,

1H), 3.31 (d,  $J = 11.6$  Hz, 1H), 2.90 (t,  $J = 10.9$  Hz, 1H), 2.45 (s, 3H), 2.06 (m, 2H), 1.39 (d,  $J = 11.7$  Hz, 1H), 1.06 (s, 3H), 0.91 (s, 3H).



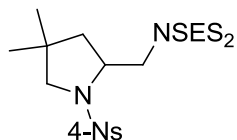
***N*-((4,4-dimethyl-1-tosylpyrrolidin-2-yl)methyl)benzenesulfonamide**

**(46).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.88 (d,  $J = 7.5$  Hz, 2H), 7.66 (d,  $J = 8.1$  Hz, 2H), 7.57 (m, 3H), 7.31 (d,  $J = 7.9$  Hz, 2H), 5.39 (t,  $J = 6.5$  Hz, 1H), 3.57 (br m, 1H), 3.36 – 3.25 (m, 1H), 3.16 (m, 3H), 2.43 (s, 3H), 1.80 – 1.57 (m, 2H), 1.01 (s, 3H), 0.38 (s, 3H).



***N*-(5,5-dimethyl-1-tosylpiperidin-3-yl)benzenesulfonamide (47).**  $^1\text{H}$

NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.28 (d,  $J = 7.4$  Hz, 2H), 8.03 – 7.87 (m, 5H), 7.70 – 7.64 (d,  $J = 6.2$  Hz, 2H), 5.12 (d,  $J = 7.9$  Hz, 1H), 4.11 (dd,  $J = 11.1, 4.2$  Hz, 1H), 3.86 (br m, 1H), 3.57 (d,  $J = 11.5$  Hz, 1H), 2.81 (s, 3H), 2.34 – 2.18 (m, 2H), 1.79 (m, 1H), 1.34 (s, 3H), 1.24 (s, 3H).

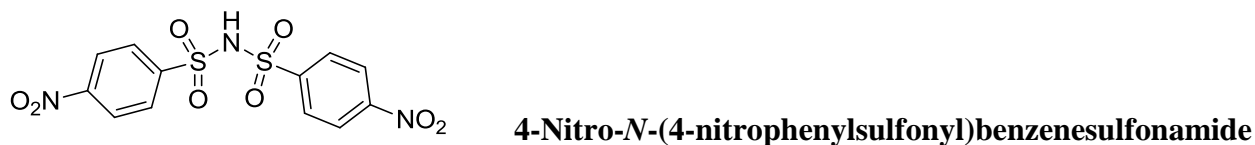


***N*-((4,4-dimethyl-1-(4-nitrophenylsulfonyl)pyrrolidin-2-yl)methyl)-2-**

**(trimethylsilyl)-N-(2-(trimethylsilyl)ethylsulfonyl)ethanesulfonamide (52).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.40 (d,  $J = 8.8$  Hz, 2H), 8.14 (d,  $J = 8.8$  Hz, 2H), 4.56 (dd,  $J = 14.0, 3.5$  Hz, 1H), 3.93 – 3.71 (m, 2H), 3.41 (m, 4H), 3.33 (d,  $J = 10.7$  Hz, 1H), 3.06 (d,  $J = 10.7$  Hz, 1H), 1.90 (dd,  $J = 12.8, 7.5$  Hz, 1H), 1.66 (dd,  $J = 12.7, 7.2$  Hz, 1H), 1.10 (s, 3H), 1.12 – 1.02 (m, 4H), 0.44 (s, 3H), 0.06 (s, 18H).



**ethanesulfonamide (60).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.43 – 3.29 (m, 4H), 1.18 – 1.02 (m, 4H), 0.08 (s, 18H)<sup>12</sup>.



**(61).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.27 (m, 10H), 7.17 (s, 1H).

### Section 5: References

1. Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269 – 275.
2. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580 – 2627.
3. Muñiz, K.; Nieger, M.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2005**, *127*, 14586-14587.
4. Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147-1149.
5. Booker-Milburn, K., Guly, D. J., Cox, B., Procopiou, P. A.; *Org. Lett.*, **2003**, *5*, 3313 – 3315.
6. Iglesias, A., Perez, E. G., Muñiz, K. *Angew. Chem. Int. Ed.*, **2010**, *49*, 8109 – 8111.
7. Roben, C., Souto, J. A., Gonzalez, Y., Lishchinskiy, A., Muñiz, K. *Angew. Chem. Int. Ed.*, **2011**, *50*, 9478 – 9482.
8. Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249-1251.
9. Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. U.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.*, **2011**, *76*, 391–395.

10. Grishina, G. V., Veselov, I. S., Davankov, V. A., Il'in, M. M., Zefirov, N. S.; *Russ. J. Org. Chem.* **2008**, *44*, 282-287.
11. Hartwig, J. F., Schlummer, B.; *Org. Lett.* 2002, *4*, 1471-1474.
12. Weinreb, M. J. *Org. Chem.*, **2003**, *68*, 4112–4115.

## Part III: Metal Free Aminofluorination

### Section 1: Introduction

Fluorination reactions are quickly gaining interest in modern. About 20% of all pharmaceuticals and about 30% of agrochemicals under development or recently introduced on the market contain fluorine. The search for novel molecules having fluorinated groups and the development of efficient access toward them is a challenging task for industrial as well as academic laboratories<sup>1</sup>. Incorporation of fluorine atoms into biologically active molecules influences the pharmaceutical effect of the molecule<sup>2</sup>. Several examples of valuable pharmaceuticals containing fluorine atom are presented in Figure 2.III.1.

**Figure 2.III.1. Valuable Fluorinated Molecules**

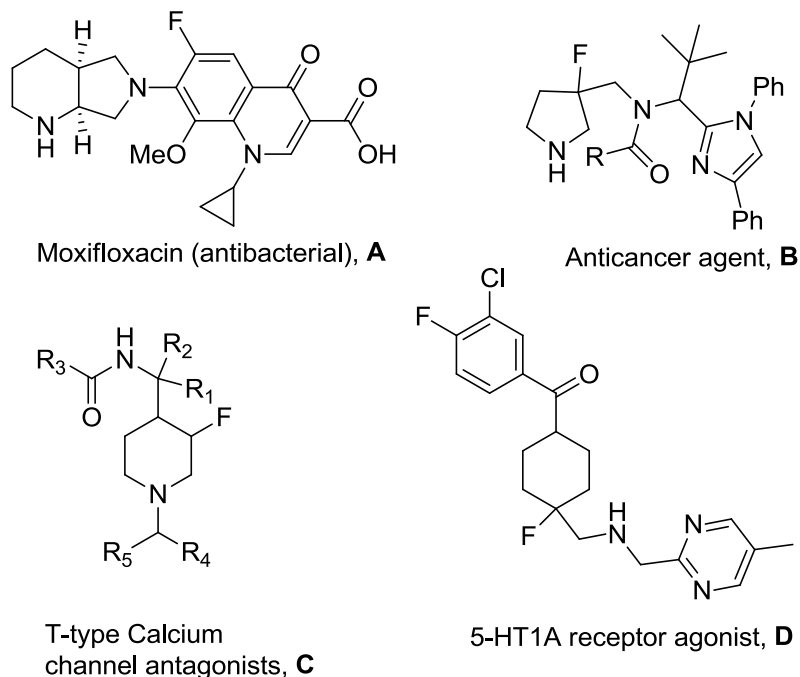
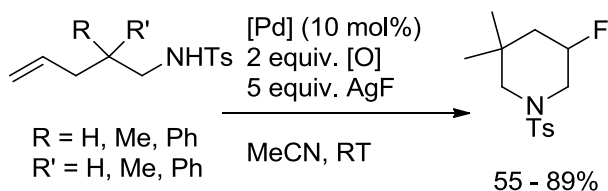


Figure 2.III.1 shows examples of valuable fluorinated pharmaceuticals. Structures **C** and **D** can be accessed by direct aminofluorination of alkenes. There have been only two examples of

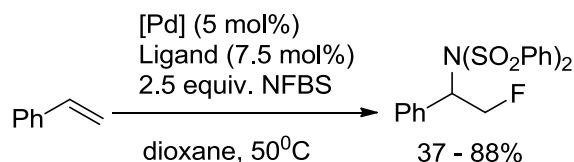
aminofluorination in the recent literature, both from the same group. Liu and co-workers have achieved remarkable results in developing an intramolecular aminofluorination of tethered aminoalkenes<sup>3</sup> (Scheme 2.III.1).

### Scheme 2.III.1. Palladium Catalyzed Intramolecular Aminofluorination



Liu's method is the first one available that allows direct aminofluorination of alkenes but it is not without drawbacks. First, the method relies on 10 mol% of palladium catalyst for reactivity. While the yields achieved were moderate to very good, 5 equivalents of AgF were required for such results. Silver fluoride is an expensive source of fluorine and the use of 5 equivalents is not atom economical. Furthermore, substrate scope was limited to afford only piperidines (on example of an azepane product was achieved in 58% yield as a 5:1 mixture of *endo:exo* regioisomers).

### Scheme 2.III.2. Intermolecular Aminofluorination of Styrenes

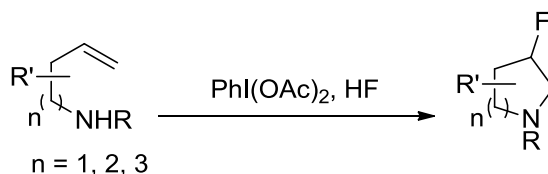


Liu and co-workers also developed an intermolecular aminofluorination of styrenes<sup>4</sup>. In this elegant reaction NFBS serves as oxidant and source of both F and N groups. While the results were very good, the substrate scope is limited to styrenes. Since these are the only two

examples of direct aminofluorination, new more efficient complimentary methods need to be developed.

We sought to continue enhancing the scope of our aminocyclizations using hypervalent iodine and Bronsted acid promoters. Inspired by the success of Lovick's meta-free oxyamination and the subsequent development of a diamination method, we were optimistic that we could apply this principle to aminofluorination (Scheme 2.III.3).

### Scheme 2.III.3. Metal Free Aminofluorination

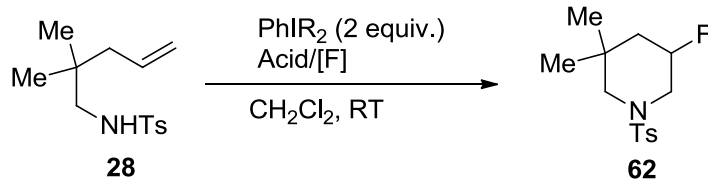


In order to successfully incorporate fluorine in the cyclic framework, a source of fluorine is required under acidic conditions. Aqueous HF is not likely to work, due to competitive incorporation of a hydroxyl group instead of fluorine, so an alternate fluorine source was required.

## Section 2: Results and Discussion

### 2.2.a. Intermolecular Endo Aminofluorination; Initial Attempts

Our initial attempts began with generating HF *in situ*. Two methods were considered: AgF in combination with a strong Bronsted acid or the use of HBF<sub>4</sub>-Et<sub>2</sub>O as both acid promoter and a source of nucleophile. To our satisfaction, we saw formation of desired product using either method (Table 2.III.1).

**Table 2.III.1. Aminofluorination: Initial Attempts**

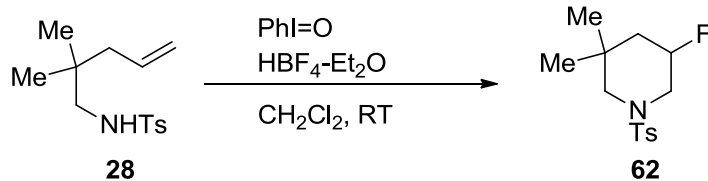
Entry	Oxidant	Acid/[F]	% Yield
1	PhI(OAc) <sub>2</sub>	TfOH/AgF	19 <sup>a,b</sup>
2	PhI(OAc) <sub>2</sub>	HBF <sub>4</sub> -Et <sub>2</sub> O	43 <sup>c</sup>
3	PhI=O	HBF <sub>4</sub> -Et <sub>2</sub> O	59 <sup>c</sup>
4	PhI(OAc) <sub>2</sub>	AgF	18

<sup>a</sup>Isolated yields<sup>b</sup>[0.1M], 5 equiv. AgF, 1.2 equiv. TfOH<sup>c</sup>[0.01M], 2 equiv. HBF<sub>4</sub>-Et<sub>2</sub>O

We were pleased that palladium metal was not required for reactivity. All of these conditions fully converted the substrate to cyclized products. The low yield in entries 1 and 2 is explained by formation of the acetoxyamination byproduct arising from acetate counterion incorporation. To avoid acetate incorporation PhI=O was used instead of Ph(OAc)<sub>2</sub> giving an increased yield of **62**. Interestingly, AgF was a strong enough Lewis acid and 18% of 3-fluoropiperidine was isolated when subjecting the substrate to just 5 equivalents of AgF with PhI=O in dichloromethane (entry 4).

### 2.2.b. Endo Aminofluorination Optimization

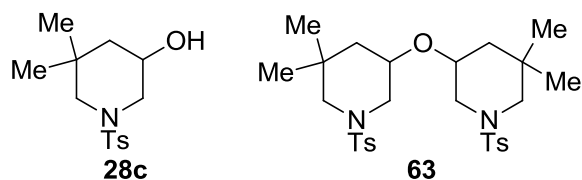
Further optimization of the aminofluorination method included variations in concentration and amount of nucleophile (Table 2.III.2). We learned that increasing the overall concentration afforded lower yields of the desired products and increasing amount of HBF<sub>4</sub>-Et<sub>2</sub>O had favorable effect. The combination of dilution and 10 equivalents of HBF<sub>4</sub>-Et<sub>2</sub>O gave the best isolated yield of 74%. The reaction proceeds very rapidly at room temperature (under 5 min.) and we tried it at 0 °C and -78 °C but the yield remained unaffected (entry 7).

**Table 2.III.2. Aminofluorination Optimization**

Entry	Equiv. HBF <sub>4</sub> -Et <sub>2</sub> O	Concentration, M	Yield, %
1	2	0.1	42
2	2	0.02	54
3	2	0.01	60
4	10	0.1	30
5	10	0.02	67
6	10	0.01	74
7	10	0.01	70*

\*Reaction was performed at -78 °C.

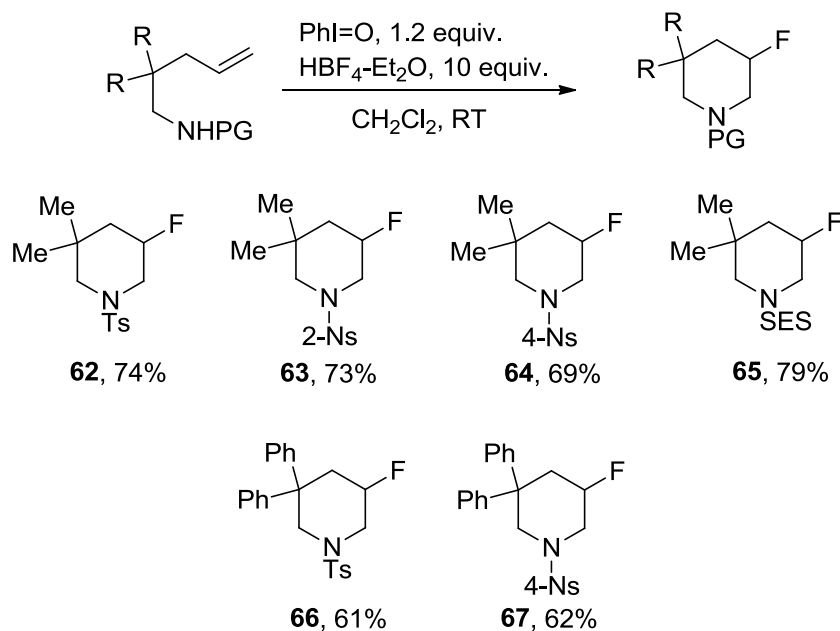
In each case we observed a trace of oxyamination **28c** byproduct and ether dimer formation **63** (Figure 2.III.2). Presumably, these products arise from adventitious water in the reaction mixture.

**Figure 2.III.2. Aminofluorination Byproducts**

### 2.2.c. Endo Aminofluorination Substrate Scope

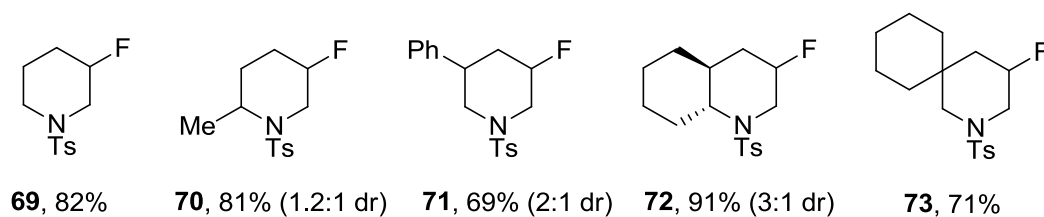
Our initial screen included subjecting substrates with various sulfonamide protecting groups to the optimized reaction conditions (Scheme 2.III.3). Electron rich and electron poor sulfonamide protecting groups performed comparably, affording good yields of desired *endo* products.

### Figure 2.III.3. Sulfonamide Substrate Screen

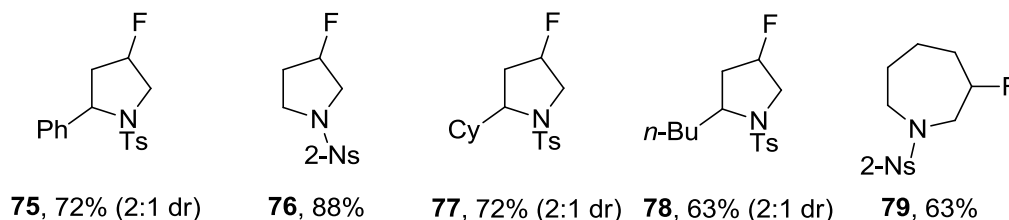


With these results in hand we tested substrates with variously substituted backbones (Figure 2.III.4). We were pleased to see that the optimized conditions afforded diversely substituted 3-fluoropiperidines in good to very good yields. Although diastereoselectivity was modest, exclusively 6-*endo* cyclization products were observed.

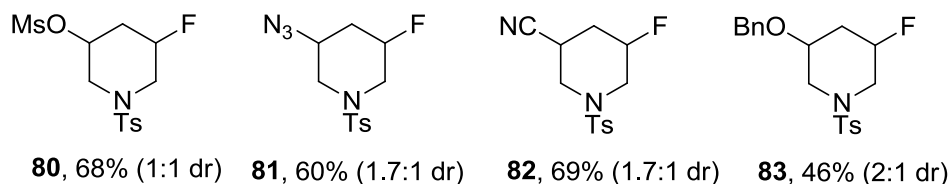
### Figure 2.III.4. 3-Fluoropiperidine Products



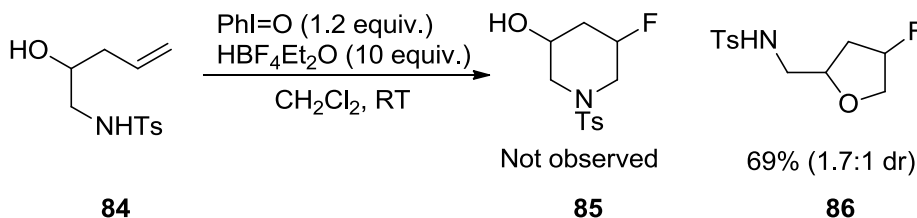
Substrates with 5 and 7 member tethers were also subjected to reaction conditions. 3-fluoropyrrolidines and one 3-fluoroazepane were afforded in good yields and excellent regioselectivity albeit modest diastereoselectivity (Figure 2.III.5).

**Figure 2.III.5. 3-Fluoropyrrolidine and 3-Fluoroazepane Products****2.2.d. Endo Aminofluorination Functional Group Tolerance**

To show the synthetic utility of this method, we probed its functional group tolerance (Figure 2.III.6). Azide, cyano, benzyl and mesyl protected alcohols were tolerant to the reaction conditions and gave the desired products in good yields albeit poor diastereoselectivity.

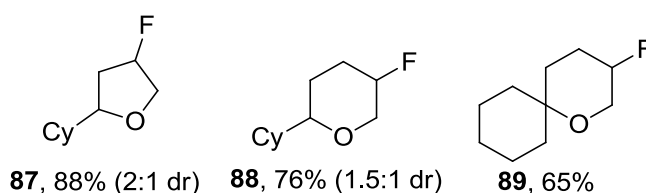
**Figure 2.III.6. Functional Group Tolerance****2.2.e. Endo Oxyfluorination**

When an unprotected tosyl hydroxylamine was subjected to reaction conditions, the expected aminofluorination product was not observed. Instead, an oxyfluorination product **86** was isolated in 69 % yield (Scheme 2.III.4).

**Scheme 2.III.4. Metal-Free Oxyfluorination**

We were very pleased to see that unprotected alcohols are suitable for this method and give a new class of products. This result inspired us to test other alcohols as potential nucleophiles. Gratifyingly, fluorofurans and fluoropyrans were furnished in good yields. Even a tertiary alcohol gave good yield of the desired product, thereby generating a quaternary center (Figure 2.III.7).

**Figure 2.III.7. Metal-Free Oxyfluorination Scope**



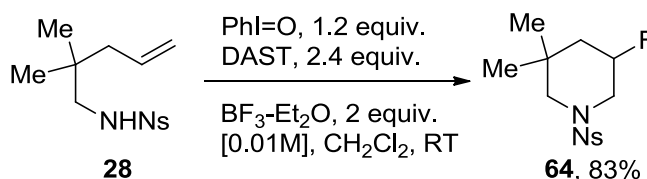
#### 2.2.f. Alternate Approach at Aminofluorination: $\text{PhIF}_2$

An alternate approach to generation of  $\text{PhIF}_2$  oxidant species *in situ* was explored. We reasoned that such transformation could be achieved by combining  $\text{PhI}=\text{O}$  with a deoxyfluorinating agent such as DAST or DeoxoFluor. To test the concept  $\text{PhI}=\text{O}$  in  $\text{CDCl}_3$  was suspended in an NMR tube and added a slight excess of DAST or DeoxoFluor. In a few moments after mixing, the otherwise insoluble  $\text{PhI}=\text{O}$  went into solution. Subsequent  $^{19}\text{F}$  NMR experiment indicated that  $\text{PhIF}_2$  was indeed generated under these reaction conditions<sup>5</sup>.

Inspired by this initial success, we tested subjecting the aminoalkene substrate to this *in situ* generated  $\text{PhIF}_2$ . Combining  $\text{PhI}=\text{O}$ , DeoxoFluor or DAST, and the substrate resulted in no conversion even after a day. This absence of reactivity suggested that  $\text{PhIF}_2$  is not the active fluorinating agent and required further activation. Hypervalent iodine reagents are known to be activated by Lewis acid (see Parts I and II of this chapter) and we chose 2 equivalents of  $\text{BF}_3\cdot\text{Et}_2\text{O}$  for this mission and immediately saw formation of desired product. The result was very

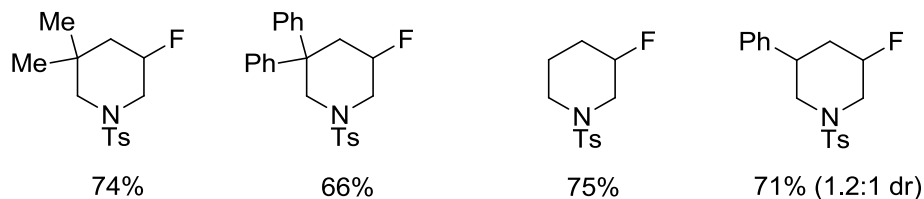
inspiring: 83% of **62** was afforded (Scheme 2.III.5), which was a 14% increase compared to the  $\text{PhI=O}/\text{HBF}_4\text{-Et}_2\text{O}$  combination (DeoxoFluor yielded 55% under same conditions as in Scheme 2.III.5).

**Scheme 2.III.5. Aminofluorination with  $\text{PhIF}_2$**



We subjected other hexenylamine substrates with various backbones to these conditions (Figure 2.III.8). While diastereoselectivities could not be improved, this method gave comparable yields under potentially milder conditions. Unfortunately, yields and diastereoselectivity could be improved.

**Figure 2.III.8. 3-Fluoropiperidines via  $\text{PhIF}_2$**

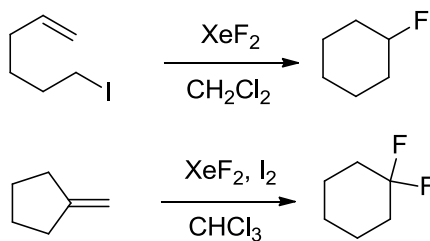


*2.2.g. Alternative Fluoride Sources and Oxidants.*

Previous literature showed that combination of iodine and  $\text{XeF}_2$  can lead to C-F bond formation (Scheme 2.III.6).<sup>6</sup> In this system  $\text{XeF}_2$  will act as primary oxidant and source of fluorine.

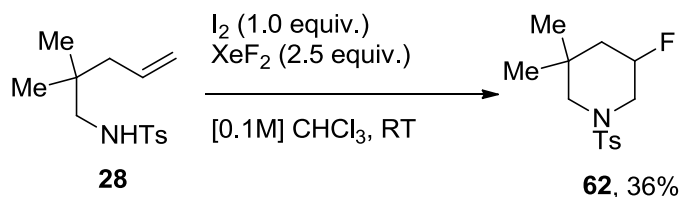
### Scheme 2.III.6. Carbon-Fluorine Bond Formation with XeF<sub>2</sub>

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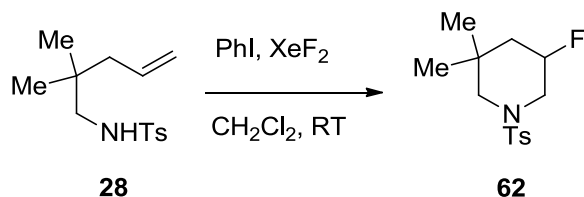


The test of concept was successful: combination of aminoalkene, I<sub>2</sub> and XeF<sub>2</sub> yielded 36% of desired product (Scheme 2.III.7). The low yield was due to the formation of a large amount of unidentified byproducts. Nonetheless, this was a promising lead suggesting that other iodine compounds can be successfully oxidized by XeF<sub>2</sub>.

### Scheme 2.III.7. Aminofluorination with XeF<sub>2</sub> and Elemental Iodine



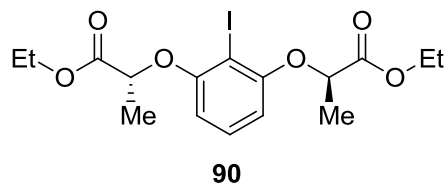
In both cases formation of a RIF<sub>2</sub> species was proposed, hence combination of iodobenzene with XeF<sub>2</sub> could be an alternative route to PhIF<sub>2</sub> formation *in situ*. Subjecting the substrate to 2 equivalents of iodobenzene and 2 equivalents of XeF<sub>2</sub> furnished the desired product in 40% yield. Subjecting substrate just to XeF<sub>2</sub> resulted in formation of decomposition products. Hence we sought to optimize conditions finding optimum oxidant load and concentration (Table 2.III.3).

**Table 2.III.3. Aminofluorination Optimization with XeF<sub>2</sub>**

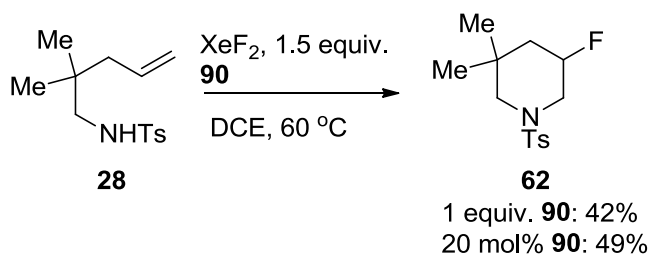
Entry	PhI, mol%	XeF <sub>2</sub> , equiv.	[M]	Yield
1	200	2	0.1	40
2	200	1.5	0.1	38
3	200	2	0.02	78
4	100	2	0.1	38
5	80	2	0.1	46
6	40	2	0.1	32
7	40	2	0.05	50
8	40	2	0.02	70
9	40	2	0.01	81
10	40	1.2	0.1	50% conv.
11	20	1.2	0.02 (80 °C)	80% conv.
12	20	1.5	0.02 (60 °C)	64%

The yield was drastically affected by concentration of the reaction mixture and almost doubled when diluted five-fold (entry 3). Reducing the amount of XeF<sub>2</sub> did not have any effect. With this information in hand, we explored the possibility of using catalytic amount of iodine. Gratifyingly, catalytic load of iodobenzene was just as effective as stoichiometric amounts and 81% of desired product was furnished at 40 mol% of iodobenzene (entry 9).

Ability to employ catalytic iodine made use of chiral reagents more attractive. Recent publications indicated successful induction of enantioselectivity in diamination and spirocyclization reactions under acidic conditions. Hence, a chiral iodine reagent **90** that is known to induce enantioselectivity<sup>7,8,9</sup>, was synthesized and tested under our reaction conditions (Figure 2.III.9).

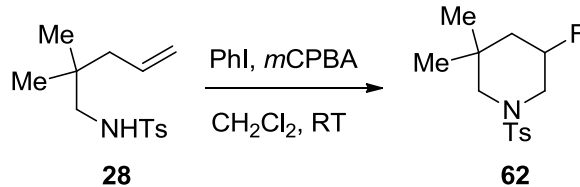
**Figure 2.III.9. Chiral Iodine Reagent**

With the use of **90** elevated temperatures were required to achieve full conversion (Scheme 2.III.8). Unfortunately, the yields were much lower: a stoichiometric amount of **90** gave similar yield to the reaction with 20 mol%. Furthermore, when analyzed on a chiral column on HPLC products from both reactions were racemic.

**Scheme 2.III.8. Aminofluorination with Chiral Iodine Reagent and XeF<sub>2</sub>**

### 2.2.h. Endo Aminofluorination with *m*CPBA as Primary Oxidant

Wirth and co-workers showed that *m*CPBA can oxidize iodobenzene to a hypervalent iodine species<sup>10</sup>. Furthermore, this strategy was successfully employed in enantioselective spirocyclization<sup>9</sup>. Our primary concern was that *m*CPBA would react faster with the alkene part of the substrate than with iodobenzene and form undesired epoxide. Gratifyingly, no epoxide formation was observed and we proceeded to optimize for the fluoropiperidine product (Table 2.III.4).

**Table 2.III.4. Optimization of Endo-Aminofluorination with mCPBA**

Entry	PhI, mol%	mCPBA, equiv.	HBF <sub>4</sub> -Et <sub>2</sub> O, equiv.	Conc.	Yield, %
1	20	2	10	0.02	73
2	10	2	10	0.02	70
3	5	2	10	0.02	56
4	1	2	10	0.02	17
5	20	1.5	10	0.02	57
6	20	1.2	10	0.02	55
7	20	2	5	0.02	67
8	20	2	2	0.02	51
9	20	2	10	0.05	73
10	20	2	10	0.1	53

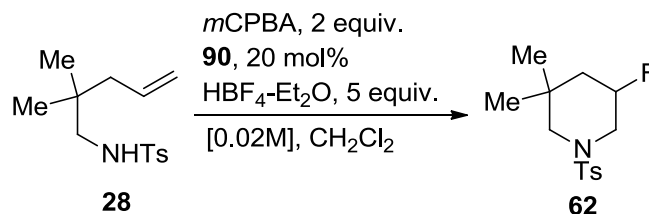
We began by testing lowest practical loading of iodobenzene (entries 1-4). Despite diminished yield, even 1 mol% afforded desired product. Next, we varied amounts of *m*CPBA and HBF<sub>4</sub>-Et<sub>2</sub>O. Any decrease of either reagent led to diminished yields (entries 5-8). Increasing concentration of the reaction mixture also had negative effects (entries 9, 10). While this method did not provide a significant increase in yield, catalytic amount of iodine was used.

### 2.2.i. Enantioselective Endo Aminofluorination with Catalytic Iodine

We were pleased to see good yields with catalytic iodine loading and proceeded to test if chiral iodine reagent **90** would afford enantioenriched products (Table 2.III.5). While the yields were good enantioselectivity induction was very low. The reaction was cooled to 0 °C but enantioselectivity was not improved (entry 2). At -78 °C *m*CPBA was insoluble and no conversion was observed. The mixture was warmed to 0 °C and quenched when all substrate was converted by TLC. The yield remained very good, without change in enantioselectivity (entry 3).

We also introduced a full equivalent of chiral iodine reagent at room temperature and isolated 80% of desired product in 10% ee (entry 2).

**Table 2.III.5. Enantioselective Aminofluorination with *m*CPBA**



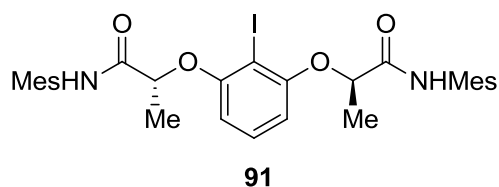
Entry	Temp., °C	% Yield	% ee
1	RT	78	10
2	RT	80	10*
2	0	75	10
3	-78 to 0	75	7

\*1.0 equivalent of **90** was used.

In order to explain such poor enantioselectivity we tested if **90** is stable to reaction conditions. After subjecting **90** to 5 equivalents of HBF<sub>4</sub>-Et<sub>2</sub>O in dichloromethane decomposition of **28** was observed by TLC after a few minutes. Subsequently, we decided to synthesize a reagent with a group less sensitive to reaction conditions, such as an amide

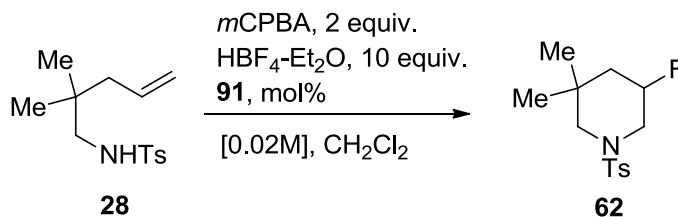
Recent work by Ishihara featured successful use of **91** (Figure 2.III.10) in enantioselective Kita type spirocyclization reaction<sup>9</sup>. Their method employed a catalytic amount of **91** and *m*CPBA as primary oxidant.

**Figure 2.III.10. Chiral Iodine Reagent 91**



We subjected hexenyl substrate **28** to reaction conditions hoping that **91** would be resistant strongly acidic conditions and boost enantioselectivity (Table 2.III.6). Reactions were monitored by TLC and were quenched when starting material disappeared after *ca.* 15 minutes.

**Table 2.III.6. Enantioselective Aminofluorination with 91**

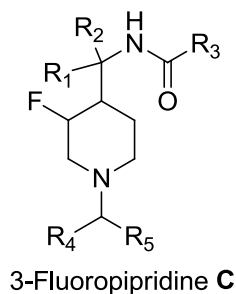


Entry	<b>91</b> , mol%	Temp. °C	% yield
1	100	RT	68
2	20	RT	74
3	20	0 °C	81

### 2.2.j. Synthesis of Biologically Active Fluoropiperidine Scaffold

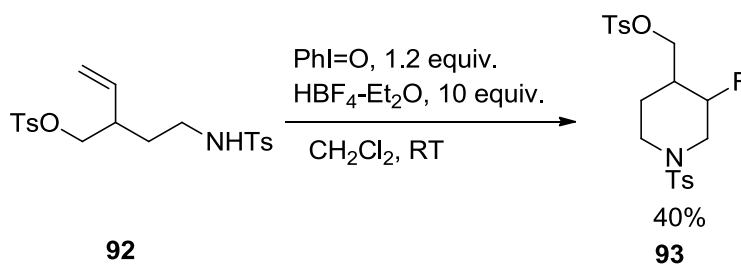
This aminofluorination method was applied in the synthesis of a biologically active scaffold which can serve as a precursor to a patented 3-fluoropiperidine which is a calcium channel blocker<sup>11</sup> (Figure 2.III.11).

**Figure 2.III.11. Patented 3-Fluoropiperidine**



A corresponding aminoalkenyl substrate was synthesized and subjected to aminofluorination conditions. Interestingly, the product was isolated as a single diastereomer in 40% yield (Scheme 2.III.9).

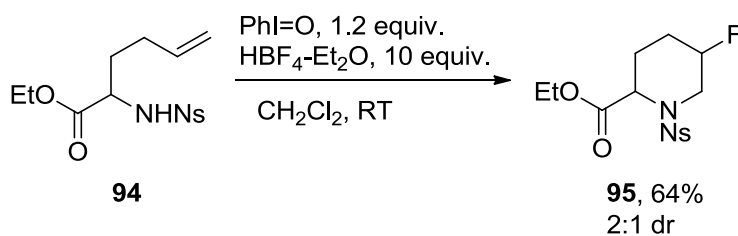
**Scheme 2.III.9. Synthesis of Precursor of C**



*2.2.k. Synthesis of a Fluorinated Unnatural Amino Acid*

A fluorinated ester of pipercolic acid was synthesized by direct aminofluorination of the corresponding aminoalkene. Pipercolic acid and its analogues are widely used as unnatural amino acids in the syntheses of peptidomimetics<sup>12</sup>.

**Scheme 2.III.10. Fluorinated Pipercolic Acid Analogue**



A hexenyl substrate was synthesized according to known procedures and subjected to aminofluorination conditions (Scheme 2.III.10). We were pleased to see tolerance of ester functional group under reaction conditions.

### Section 3: Conclusion

In summary, we have successfully developed a novel metal free aminofluorination method. This method showed high exclusive preference for *endo*-cyclization. We were able to synthesize 5, 6, and 7-membered fluoroamines in good to very good yields. Furthermore, we showed that functional groups such as mesyl and benzyl alcohols, cyano, azido and ethyl esters are well tolerated under reaction conditions. Oxygen was also a suitable nucleophile and we were able to successfully cyclize secondary and tertiary alcohols affording fluorofurans and fluoropyrans. We successfully modified this method to be catalytic in iodine which made use of chiral iodine reagents more attractive. Employment of catalytic amounts of catalytic chiral iodine reagents gave comparable yields to the stoichiometric version but enantioselectivity was not induced. Finally, to show practical application we synthesized a precursor of a pharmaceutically valuable compound and a fluorinated analogue of pipercolic acid.

### Section 4: Experimental

#### General

All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. 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.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer.  $^1\text{H}$  NMR chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual  $\text{CHCl}_3$  (7.26 ppm). Chemical shifts for carbon are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ( $\text{CDCl}_3$ :  $\delta$  77.2 ppm). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling

constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 Mass Spectrometer or a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer. Melting points were determined on a capillary MEL-TEMP melting point apparatus and are uncorrected. Chiral HPLC analysis was performed on a Waters HPLC system consisting of the following: pump, Waters 600E; detector, Waters 474 scanning fluorescence, measured at 254 nm; column, DIACEL CHIRALPAK AD-H; mobile phase, hexanes/2-propanol.

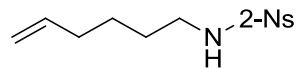
### **Materials**

THF, CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>2</sub>O were degassed and dried on solvent columns of neutral alumina. Toluene was degassed and dried on a solvent column of neutral alumina and a Q5 reactant column, a Cu<sup>II</sup> oxide oxygen scavenger. All other solvents were distilled before use and stored under an atmosphere of nitrogen and on 4 Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4 Å molecular sieves and were used without further purification. Commercial reagents were purchased from Sigma-Aldrich Co. and were used as received.

### **Substrates Syntheses**

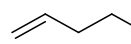
#### **Standard Protection Procedure**

The amine (1 equiv.) and Et<sub>3</sub>N (2 equiv.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) and cooled to 0 °C. The sulfonyl chloride (1 equiv.) was then added portionwise. Following addition of the sulfonyl chloride the reaction mixture was stirred at room temperature for four hours. The solution was then washed with 1 M HCl, dried (MgSO<sub>4</sub>) and purified by column chromatography, EtOAc/Hexanes (5%→20% EtOAc).



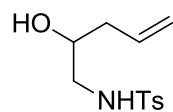
***N*-Hex-5-enyl-4-methylbenzenesulfonamide (96).**  $^1\text{H}$  NMR (500 MHz,

$\text{CDCl}_3$ )  $\delta$ : 8.16 (m, 1 H), 7.88 (m, 1 H), 7.78 (m, 2 H), 5.73 (ddt, 1 H,  $J = 24.0, 10.0, 7.0$  Hz), 5.29 (t, 1 H,  $J = 5.5$  Hz), 4.97 (m, 2 H), 3.13 (q, 2 H,  $J = 6.5$  Hz), 2.03 (q, 2 H,  $J = 7.0$  Hz), 1.55 (p, 2 H,  $J = 7.5$  Hz), 1.43 (p, 2 H,  $J = 7.5$  Hz).



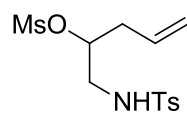
***N*-But-3-enyl-4-methylbenzenesulfonamide (97).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 7.68 (d, 2 H,  $J = 8.1$  Hz), 7.34 (d, 2 H,  $J = 8.1$  Hz), 5.64 (ddt, 1 H,  $J = 17.1, 16.8, 6.9$  Hz), 5.09 (m, 2 H), 4.37 (s, 1 H), 3.05 (q, 2 H,  $J = 6.6$  Hz), 2.46 (s, 3 H), 2.22 (q, 2 H,  $J = 6.6$  Hz).



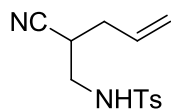
**(±)-*N*-(2-Hydroxypent-4-enyl)-4-methylbenzenesulfonamide (98).** This

compound was synthesized according to previously reported procedure<sup>16</sup>.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.75 (d,  $J = 8.3$ , 2H), 7.31 (d,  $J = 8.3$ , 2H), 5.74 (ddt,  $J = 17.6, 10.6, 7.0$ , 1H), 5.29 (br. s, 1H), 5.12-5.07 (m, 1H), 3.80-3.73 (m, 1H), 3.08 (ddd,  $J = 13.1, 7.3, 3.1$ , 1H), 3.08 (ddd,  $J = 13.1, 7.9, 5.3$ , 1H), 2.49 (br. s, 1H), 2.43 (s, 3H), 2.27-2.14 (m, 2H).

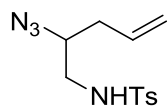


**1-(4-methylphenylsulfonamido)pent-4-en-2-yl methanesulfonate (99).** **99** was

furnished by protecting **98** under standard protection conditions with  $\text{MsCl}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.3$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 5.82 – 5.64 (m, 1H), 5.26 – 5.10 (m, 2H), 4.96 (br, 1H), 4.71 (m, 1H), 3.33 – 3.12 (m, 2H), 3.05 (s, 3H), 2.57 – 2.35 (m, 2H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.8, 136.5, 131.2, 129.8, 127.0, 119.8, 80.0, 45.8, 38.4, 36.7, 21.5. MS (ESI): 356.2 ( $\text{M}^+ + \text{Na}^+$ ), 372.1 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 3292, 3079, 2981, 2939, 1644, 1598, 1432, 1333, 1163, 1094, 917, 816, 664.

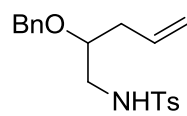


**N-(2-cyanopent-4-enyl)-4-methylbenzenesulfonamide (100).** **99** was dissolved in DMF and 5 equivalents of NaCN were added. The reaction mixture was stirred at 60 °C overnight. After completion the reaction mixture was cooled to room temperature, poured into separatory funnel, diluted with water and extracted with ethyl acetate 3 times. Organic layers were combined, dried over MgSO<sub>4</sub>, and condensed under reduced pressure. The crude mixture was chromatographed on a silica column with EtOAc/Hex to yield pure **100**. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.75 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.42 (td, *J* = 16.7, 7.4 Hz, 1H), 5.17 – 5.10 (m, 2H), 4.63 (br, 1H), 3.48 (m, 1H), 2.61 (m, 2H), 2.45 (s, 3H), 2.39 – 2.25 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 144.0, 136.7, 131.4, 129.8, 127.1, 120.5, 116.6, 49.4, 38.0, 24.1, 21.5. MS (ESI): 287.2 (M<sup>+</sup> + Na<sup>+</sup>). FTIR (cm<sup>-1</sup>): 3272, 3081, 2980, 2926, 2252, 1644, 1599, 1495, 1418, 1329, 1162, 1092, 927, 816, 666.



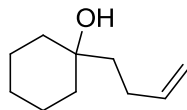
**N-(2-azidopent-4-enyl)-4-methylbenzenesulfonamide (101).** **99** was dissolved in DMF and 5 equivalents of NaCN were added. The reaction mixture was stirred at 60 °C overnight. After completion the reaction mixture was cooled to room temperature, poured into separatory funnel, diluted with water and extracted with ethyl acetate 3 times. Organic layers were combined, dried over MgSO<sub>4</sub>, and condensed under reduced pressure. The crude mixture was chromatographed on a silica column with EtOAc/Hex to yield pure **101**. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.74 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.73 (td, *J* = 17.1, 6.8 Hz, 1H), 5.21 – 5.13 (m, 2H), 4.84 – 4.75 (m, 1H), 3.53 (dd, *J* = 6.9, 4.1 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.87 – 2.78 (m, 1H), 2.44 (s, 3H), 2.30 (t, *J* = 6.5 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ:

143.8, 136.7, 132.3, 129.8, 127.0, 119.4, 61.2, 46.0, 36.3, 21.5. MS (ESI): 303.2 ( $M^+ + Na^+$ ). FTIR ( $cm^{-1}$ ): 3271, 2361, 2109, 1326, 1158, 1092.



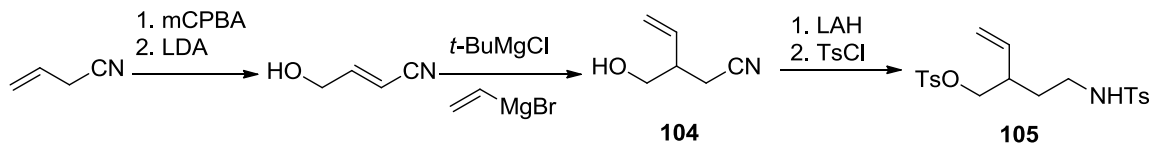
***N*-(2-(benzyloxy)pent-4-enyl)-4-methylbenzenesulfonamide (102).** 1.2

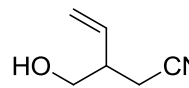
equivalents of NaH (60% dispersion in oil) was dissolved in THF and cooled to 0 °C. 1 equivalent of **98** was dissolved in THF and added dropwise to the flask with NaH. 1.2 equivalents of benzyl chloride was added dropwise to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to room temperature and react overnight. Upon completion, the mixture was quenched with water and extracted with ethyl acetate (x3). Organic layers were combined and dried over  $MgSO_4$  and concentrated under reduced pressure. The crude mixture was chromatographed on a silica column with EtOAc/Hex mixture to yield pure **102**.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.72 (d,  $J = 8.2$  Hz, 2H), 7.37 – 7.22 (m, 8H), 5.63 – 5.50 (m, 1H), 4.98 (m, 2H), 4.45 (d,  $J = 14.6$  Hz, 1H), 4.25 (d,  $J = 14.6$  Hz, 1H), 3.53 (br s, 1H), 3.07 (t,  $J = 5.4$  Hz), 2.46 (d,  $J = 2.8$  Hz, 1H), 2.43 (s, 3H), 2.04 (dd,  $J = 12.3, 6.2$  Hz, 2H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 143.6, 136.1, 136.0, 133.8, 129.7, 128.6, 128.5, 128.4, 127.9, 127.2, 117.8, 69.0, 54.1, 53.8, 39.0, 21.4. MS (ESI): 368.1 ( $M^+ + Na^+$ ). FTIR ( $cm^{-1}$ ): 3520, 3066, 3031, 2978, 2923, 1642, 1598, 1496, 1455, 1337, 1159, 1089, 932, 816, 772, 739, 700, 658.



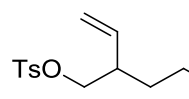
**1-(But-3-enyl)cyclohexanol (103).** Compound was prepared according to

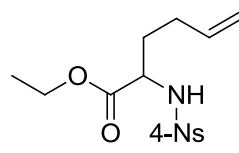
previously reported procedure<sup>17</sup>.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 5.86 (ddt,  $J = 16.9, 10.2, 6.6$  Hz, 1H), 5.04 (dd,  $J = 17.1, 1.6$  Hz, 1H), 4.95 (dd,  $J = 10.2, 1.2$  Hz, 1H), 2.20-2.10 (m, 2 H), 1.68-1.38 (m, 11 H), 1.28 (m, 1 H), 1.22 (s, 1 H).



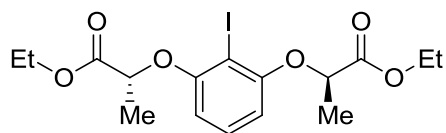
 **3-(Hydroxymethyl)pent-4-enitrile (104)**. This compound was prepared according to previously reported procedure<sup>13</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.81 (t,  $J = 5$  Hz, 1H), 2.50 (dd,  $J = 17.5, 8$  Hz, 1H), 2.54-2.70 (m, 2H), 3.63 (dt,  $J = 11, 6.0$  Hz, 1H), 3.72 (dt,  $J = 11, 5$  Hz, 1H), 5.26 (dt,  $J = 17, 1$  Hz, 1H), 5.28 (dt,  $J = 11, 1$  Hz, 1H), 5.75 (ddd,  $J = 17, 11, 7$  Hz, 1H). Fleming, Fraser F. et al

From Journal of Organic Chemistry, 67(17), 5953-5956; 2002

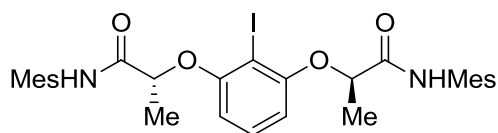
 **2-(2-(4-methylphenylsulfonamido)ethyl)but-3-enyl 4-methylbenzenesulfonate (105)**. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.75 (d,  $J = 8.2$  Hz, 2H), 7.71 (d,  $J = 8.1$  Hz, 2H), 7.34 (d,  $J = 8.2$  Hz, 2H), 7.30 (d,  $J = 8.1$  Hz, 2H), 5.43 (ddd,  $J = 17.5, 10.0, 8.9$  Hz, 1H), 5.08 (d,  $J = 10.0$  Hz, 1H), 5.03 (d,  $J = 17.2$  Hz, 1H), 4.49 (br s, 1H), 3.90 (dd,  $J = 9.6, 5.7$  Hz, 1H), 3.83 (dd,  $J = 9.6, 6.5$  Hz, 1H), 2.98 – 2.81 (m, 2H), 2.45 (s, 3H), 2.43 (s, 4H), 1.68 – 1.59 (m, 1H), 1.45 – 1.38 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 144.9, 143.5, 236.6, 135.8, 132.6, 129.9, 129.7, 127.9, 127.0, 118.8, 72.3, 40.6, 40.5, 30.4, 21.7, 21.5. MS (ESI): 424.2 (M<sup>+</sup>), 446.7 (M<sup>+</sup> + Na<sup>+</sup>), 462.3 (M<sup>+</sup> + K<sup>+</sup>). FTIR (cm<sup>-1</sup>): 3294, 2926, 1598, 1424, 1358, 1331, 1160, 1095, 953, 815, 665.

 **Ethyl 2-(4-nitrophenylsulfonamido)hex-5-enoate (94)**. Compound was synthesized by standard protection the corresponding amine with 4-NsCl. (The amine was

synthesized according to previously reported procedure<sup>14</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 8.34 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 5.73 (td, *J* = 16.8, 6.6 Hz, 1H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.10 – 4.95 (m, 2H), 4.08 – 3.88 (m, 4H), 2.21 – 2.04 (m, 2H), 1.90 – 1.81 (m, 1H), 1.74 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H).



**(2*R*,2'*R*)-Diethyl 2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropionate (90).** Compound was prepared according to previously reported procedure<sup>7</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.24 (t, *J* = 7.2 Hz, 6H), 1.70 (d, *J* = 6.8 Hz, 6H), 4.18–4.24 (m, 4H), 4.75 (q, *J* = 6.8 Hz, 2H), 6.37 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 8.4 Hz, 1H). Reported [ $\alpha$ ]<sub>D</sub> = -21.6 (*c* 1.0 in CH<sub>3</sub>Cl). Observed [ $\alpha$ ]<sub>D</sub> = -18.2 (*c* 1.0 in CH<sub>3</sub>Cl).



**(2*R*,2'*R*)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy)bis(*N*-mesitylpropanamide) (91):** Compound was prepared according to previously reported procedure<sup>9</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.77 (d, *J* = 6.8 Hz, 6H), 2.15 (s, 12H), 2.26 (s, 6H), 5.00 (q, *J* = 6.8 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 4H), 7.34 (t, *J* = 8.4 Hz, 1H), 8.02 (s, 2H). Reported [ $\alpha$ ]<sub>D</sub> = -116.1 (*c* 1.0 in CH<sub>3</sub>Cl). Observed [ $\alpha$ ]<sub>D</sub> = -116.3 (*c* 1.0 in CH<sub>3</sub>Cl).

## Standard Oxidative Cyclization Conditions

### Condition A:

The substrate (0.1 mmol, 1 equiv.) and oxidant (0.12 mmol, 1.2 equiv.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at room temperature. HBF<sub>4</sub>-Et<sub>2</sub>O (100  $\mu$ L, 1 mmol, 10 equiv.) was added in one portion

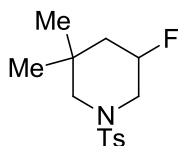
and the solution was then stirred at room temperature for 15 min. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub>. Organic layer was separated and concentrated under reduced pressure. Product was purified on a silica column with ethyl acetate/hexanes solvent mixture.

**Condition B:**

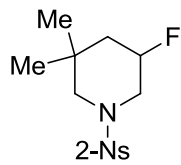
The substrate (0.2 mmol, 1 equiv.) and oxidant (0.24 mmol, 1.2 equiv.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at room temperature and cooled down. HBF<sub>4</sub>·Et<sub>2</sub>O (100 μL, 1 mmol, 5 equiv.) was added in one portion and the solution was then stirred until done by TLC. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub>. Organic layer was separated and concentrated under reduced pressure. Product was purified on a silica column with ethyl acetate/hexanes solvent mixture.

**New compounds characterization:**

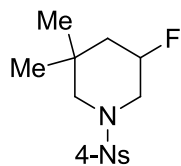
Compounds **62**, **64**, **66**, **69**, **71**, **72**, and **73** match spectroscopic data<sup>3</sup>.



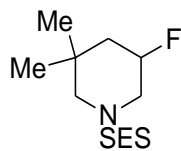
**5-fluoro-3,3-dimethyl-1-tosylpiperidine (62)**. white solid, 74% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.65 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.77 (dtt, *J* = 47.6, 8.4, 4.0 Hz, 1H), 3.61 (ddd, *J* = 12.4, 11.6, 3.6 Hz, 1H), 2.97 (d, *J* = 11.2 Hz, 1H), 2.62 (ddd, *J* = 11.6, 8.0, 7.6 Hz, 1H), 2.44 (s, 3H), 2.38 (d, *J* = 11.2 Hz, 1H), 1.72 (ddd, *J* = 16.8, 13.2, 4.0 Hz, 1H), 1.35 (ddd, *J* = 12.8, 12.8, 8.8 Hz, 1H), 1.03 (s, 3H), 1.02 (s, 3H).



**5-fluoro-3,3-dimethyl-1-(2-nosyl)piperidine (63)**. white solid, 73% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.00 (dd,  $J = 6.6, 2.6$  Hz, 1H), 7.74 – 7.66 (m, 2H), 7.63 (dd,  $J = 7.1, 2.0$  Hz, 1H), 4.80 (dt,  $J = 47.6, 8.3, 4.3$  Hz, 1H), 3.76 (td,  $J = 13.2, 4.1$  Hz, 1H), 3.16 (d,  $J = 12.5$  Hz, 1H), 3.05 (dt,  $J = 12.5, 7.7$  Hz, 1H), 2.85 (d,  $J = 12.6$  Hz, 1H), 1.79 (ddd,  $J = 17.6, 13.4, 4.2$  Hz, 1H), 1.50 (td,  $J = 12.8, 8.7$  Hz, 1H), 1.06 (s, 3H), 1.00 (s, 3H).  $^{13}\text{C}$  NMR (125MHz)  $\delta$ : 133.6, 132.1, 131.6, 131.0, 124.1, 86.1, 84.7, 56.4, 49.3, 49.1, 42.7, 42.6, 32.2, 32.1, 27.5, 25.7. MS (ESI): 317.5 ( $\text{M}^+$ ), 339.3 ( $\text{M}^+ + \text{Na}^+$ ), 355.2 ( $\text{M}^+ + \text{K}^+$ ). FTIR,  $\text{cm}^{-1}$ : 2958, 1545, 1373, 1334, 1165, 1127. HRMS (FAB): calculated 317.0974, measured 317.0964.

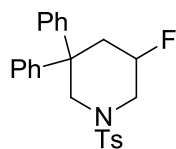


**5-fluoro-3,3-dimethyl-1-(4-nosyl)piperidine (64)**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.39 (d,  $J = 8.8$  Hz, 2H), 7.96 (d,  $J = 8.8$  Hz, 2H), 4.80 (dm,  $J = 47.2$  Hz, 1H), 3.56 (ddd,  $J = 16.0, 11.6, 4.0$  Hz, 1H), 2.97 (d,  $J = 11.6$  Hz, 1H), 2.89 (dt,  $J = 11.6, 7.6$  Hz, 1H), 2.61 (d,  $J = 12.0$  Hz, 1H), 1.71 (ddd,  $J = 20.4, 13.6, 4.0$  Hz, 1H), 1.46 (dt,  $J = 12.8, 8.0$  Hz, 1H), 1.03 (s, 6H).



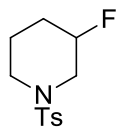
**5-fluoro-3,3-dimethyl-1-(2-(trimethylsilyl)ethylsulfonyl)piperidine (65)**. White solid, 79% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.75 (dm,  $J = 47.5$  Hz, 1H), 3.77-3.64 (m, 1H), 3.17-3.03 (m, 2H), 2.96-2.81 (m, 3H), 1.87-1.69 (m, 1H), 1.62-1.49 (m, 2H), 1.13-0.95 (m, 10H), 0.05 (s, 9H).  $^{13}\text{C}$  NMR (125MHz)  $\delta$ : 86.5, 85.1, 56.6, 49.7, 49.5, 47.0, 42.8, 42.6, 32.1, 32.0, 27.51, 27.49, 25.0, 10.1, -2.0.  $^{19}\text{F}$  (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -183 (m). MS (ESI): 318.4 ( $\text{M}^+ + \text{Na}^+$ ),

334.3 ( $M^+ + K^+$ ). FTIR,  $\text{cm}^{-1}$ : 2952, 1326, 1250, 1151, 1142, 1005, 840, 810. HRMS (FAB): calculated 296.1517, measured 296.1510.



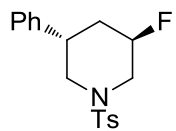
**5-fluoro-3,3-diphenyl-1-tosylpiperidine (66)**. White solid, 62% yield.  $^1\text{H}$  NMR

(400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.65 (d,  $J = 8.4$  Hz, 2H), 7.47 (d,  $J = 8.4$  Hz, 2H), 7.36-7.12 (m, 10H), 4.55 (dm,  $J = 47.2$  Hz, 1H), 4.50 (d,  $J = 12.4$  Hz, 1H), 4.03 (m, 1H), 2.96 (m, 1H), 2.42 (s, 3H), 2.40 (d,  $J = 13.2$  Hz, 1H), 2.29 (dt,  $J = 10.0, 5.6$  Hz, 1H), 2.15 (q,  $J = 11.2$  Hz, 1H).



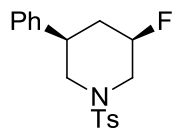
**3-fluoro-1-tosylpiperidine (69)**. White solid, 82% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

$\delta$ : 7.66 (d,  $J = 8.4$  Hz, 2H), 7.33 (d,  $J = 8.4$  Hz, 2H), 4.67 (dm,  $J = 46.8$  Hz, 1H), 3.38 (dd,  $J = 18.4, 11.6$  Hz, 1H), 3.12 (m, 1H), 3.00 (dt,  $J = 11.2, 7.2$  Hz, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.85 (m, 2H), 1.63 (m, 2H).



**trans-3-fluoro-5-phenyl-1-tosylpiperidine (71)**. White solid, 23% yield.  $^1\text{H}$  NMR

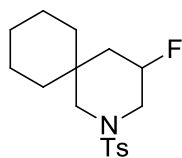
(400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d,  $J = 8.4$  Hz, 2H), 7.35-7.25 (m, 5H), 7.16 (d,  $J = 7.2$  Hz, 2H), 4.90 (br d,  $J = 46.8$  Hz, 1H), 4.13 (m, 1H), 3.92 (m, 1H), 3.25 (m, 1H), 2.62 (dd,  $J = 37.6, 13.2$  Hz, 1H), 2.43 (s, 3H), 2.42 (m, 1H), 2.24 (m, 1H), 1.70 (m, 1H).



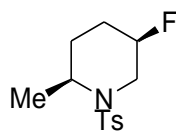
**cis-3-fluoro-5-phenyl-1-tosylpiperidine (71)**. White solid, 46% yield.  $^1\text{H}$  NMR

(400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.64 (d,  $J = 8.0$  Hz, 2H), 7.36-7.25 (m, 5H), 7.17 (d,  $J = 6.4$  Hz, 2H), 4.78

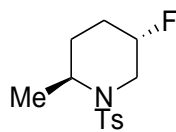
(dm,  $J = 48.4$  Hz, 1H), 4.20 (m, 1H), 3.87 (m, 1H), 2.96 (m, 1H), 2.44 (s, 3H), 2.40 (m, 1H), 2.25 (dt,  $J = 10.4, 4.0$  Hz, 1H), 2.15 (t,  $J = 10.4$  Hz, 1H), 1.64 (m, 1H).



**73.** White solid, 71% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.65 (d,  $J = 8.0$  Hz, 2H), 7.33 (d,  $J = 8.0$  Hz, 2H), 4.77 (dm,  $J = 47.6$  Hz, 1H), 3.61 (ddd,  $J = 13.6, 11.2, 3.6$  Hz, 1H), 3.19 (d,  $J = 12.0$  Hz, 1H), 2.66 (dt,  $J = 11.2, 7.6$  Hz, 1H), 2.44 (s, 3H), 2.42 (d,  $J = 12.0$  Hz, 1H), 1.81 (ddd,  $J = 17.6, 13.2, 4.4$  Hz, 1H), 1.58-1.22 (m, 11H).



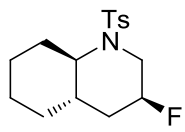
**cis-5-fluoro-2-methyl-1-tosylpiperidine (70).** White solid, 37% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.69 (d,  $J = 8.1$  Hz, 2H), 7.29 (d,  $J = 8.1$  Hz, 2H), 4.56-4.26 (dm,  $J = 48$  Hz, 1H), 4.25-4.14 (m, 1H), 4.08-3.95 (m, 1H), 2.95-2.85 (m, 1H), 2.42 (s, 3H), 1.77-1.48 (m, 4H), 1.03 (d,  $J = 9\text{Hz}$ , 3H).  $^{13}\text{C}$  NMR (125MHz)  $\delta$ : 143.4, 137.6, 126.9, 87.8, 86.4, 47.4, 43.3, 43.1, 28.5, 28.4, 25.6, 25.4, 21.5, 14.8.  $^{19}\text{F}$  (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -180 (m). MS (ESI): 296.2 ( $\text{M}^+ + \text{Na}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2958, 1598, 1457, 1382, 1340, 1152, 1091, 1052, 986, 888, 816. HRMS (FAB): calculated 272.1122, measured 272.1118.



**trans-5-fluoro-2-methyl-1-tosylpiperidine (70).** White solid, 44% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.74 (d,  $J = 8.1$  Hz, 2H), 7.70 (d,  $J = 8.1$  Hz, 2H), 4.66 (br d,  $J = 46.5$  Hz, 1H), 4.22-4.00 (m, 2H), 3.28 (d,  $J = 14.7$  Hz, 0.5H), 3.14 (d,  $J = 15\text{Hz}$ , 0.5H), 2.41 (s, 3H), 1.92-1.77 (m, 2H), 1.35-1.22 (m, 2H), 1.18 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (125MHz)  $\delta$ : 142.9, 137.6, 129.4, 127.3, 85.6, 84.2, 47.7, 43.6, 43.4, 23.8, 23.1, 22.9, 21.5, 15.3.  $^{19}\text{F}$  NMR (282 MHz,

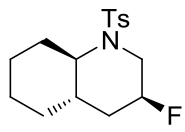
$\text{CDCl}_3$ )  $\delta$ : -183 (m), FTIR ( $\text{cm}^{-1}$ ): 2962, 1438, 1326, 1284, 1260, 1149, 1088, 1010, 976, 808.

HRMS (FAB): calculated 272.1122, measured 272.1120.



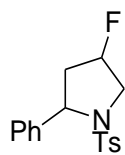
**Trans-3-fluoro-1-tosyl-decahydroquinoline (72)**. 91% yield (1:3 trans:cis).  $^1\text{H}$

NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.73 (d,  $J = 8.4$  Hz, 2H), 7.28 (d,  $J = 8.4$  Hz, 2H), 4.75 (dm,  $J = 49.2$  Hz, 1H), 4.03 (m, 1H), 3.28 (ddd,  $J = 24.4, 14.4, 3.6$  Hz, 1H), 2.75 (dt,  $J = 10.8, 3.6$  Hz, 1H), 2.43 (s, 3H), 2.25 (m, 1H), 1.86 (m, 1H), 1.80-1.62(m, 4H) 1.43 (m, 1H), 1.30-1.10 (m, 3H), 0.96 (m, 1H).



**Cis-3-fluoro-1-tosyl-decahydroquinoline (72)**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ :

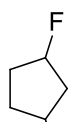
7.67 (d,  $J = 8.0$  Hz, 2H), 7.30 (d,  $J = 8.0$  Hz, 2H), 4.68 (dm,  $J = 44.4$  Hz, 1H), 4.28 (m, 1H), 2.86 (ddd,  $J = 12.4, 8.4, 6.8$  Hz, 1H), 2.45 (m, 1H), 2.43 (s, 3H), 2.20 (m, 1H), 2.10 (m, 1H), 1.84-1.36 (m, 5H), 1.22-1.00 (m, 4H).



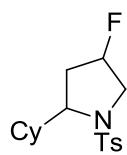
**4-fluoro-2-phenyl-1-tosylpyrrolidine (75)**. White solid, 74% yield (an inseparable

mixture of diastereomers in 1:2 ratio).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.63 (t,  $J = 8.4$  Hz, 1H), 7.39-7.19 (m, 8H), 5.16 (dm,  $J = 44.4$  Hz, 1H), 5.10 (br d,  $J = 52.2$  Hz, 1H), 4.91 (dd,  $J = 3.3, 6.3$  Hz, 0.5H), 4.71 (dd,  $J = 2.7, 6.9$  Hz, 0.5H), 4.08-3.54 (m, 2H), 2.62-2.22 (m, 2H), 2.42 (s, 1.5H), 2.41 (s, 1.5H), 2.15-1.87 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.6 (major), 143.5 (minor), 141.8 (major), 141.5 (minor), 134.7 (major), 134.4 (minor), 129.6 (minor), 129.4 (major), 128.6 (minor), 128.3 (major), 127.8 (minor), 127.6 (major), 127.5 (major), 127.2

(minor), 126.6 (major), 126.3 (minor), 92.7 (major), 91.9 (minor), 91.3 (major), 90.4 (minor), 62.5 (minor), 62.2 (major), 56.2 (minor), 55.5 (major), 56.0 (minor), 55.3 (major), 44.0 (minor), 41.6 (major), 43.9 (minor), 41.4 (major), 21.5.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -173 (m, major), -178 (m, minor). MS (ESI): 320.5 ( $\text{M}^+$ ), 242.4 ( $\text{M}^+ + \text{Na}^+$ ), 358.3 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 3063, 3031, 2928, 2869, 1599, 1495, 1456, 1347, 1162, 1094. HRMS (FAB): calculated 320.1122, measured 320.1110.

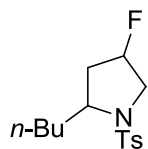


**3-fluoro-1-(2-nosyl)pyrrolidine (76)**. 88% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.00 (d,  $J = 8.4$  Hz, 1H), 7.76 – 7.66 (m, 2H), 7.66 – 7.60 (m, 1H), 5.25 (dm,  $J = 52$  Hz, 1H), 3.78 (dd,  $J = 24.7, 12.5$  Hz, 1H), 3.72 – 3.59 (m, 2H), 3.55 (td,  $J = 10.3, 6.5$  Hz, 1H), 2.32 – 2.22 (m, 1H), 2.15 – 1.98 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 133.7, 131.8, 131.7, 130.5, 124.2, 93.0, 91.6, 54.5, 54.3, 46.1, 32.9, 32.7.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -177 (m). MS (ESI): 297.1 ( $\text{M}^+ + \text{Na}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 3097, 2990, 2902, 1545, 1374, 1355, 1166, 1129, 607. HRMS (FAB): calculated 275.0504, measured 275.0502.

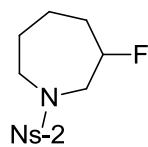


**2-cyclohexyl-4-fluoro-1-tosylpyrrolidine (77)**. 72%, an inseparable mixture of diastereomers A (major) and B (minor) in 2.6:1 ratio.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.70(A+B) (dd,  $J = 11.2, 8.2$  Hz, 2H), 7.30 (A+B) (t,  $J = 8.3$  Hz, 2H), 4.95 (B) (dm,  $J = 53.0$  Hz, 1H), 4.88 (A) (dt,  $J = 55, 5.6$  Hz, 1H), 3.80 (B) (dd,  $J = 22.0, 13.8$  Hz, 1H), 3.71 – 3.56 (A+B) (m, 2H), 3.54 – 3.35 (A+B) (m, 1H), 2.42 (A) (s, 2H), 2.41 (B) (s, 3H), 2.11 – 1.86 (A+B) (m, 2H), 1.32 – 1.06 (A+B) (m, 2H), 1.05 – 0.80 (A+B) (m, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.6 (major),

143.5 (minor), 134.9, 129.8 (major), 129.3 (minor), 127.7 (minor), 127.4 (major), 92.8 (major), 92.4 (minor), 91.4 (major), 91.1 (minor), 65.0 (major), 63.3 (minor), 55.8 (minor), 54.4 (major), 55.6 (minor), 54.2 (major), 41.0, 34.1 (major), 33.7 (minor), 33.9 (major), 33.6 (minor), 30.5 (major), 30.0 (minor),  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -171 (m, major), -177 (m, minor). MS (ESI): 326.3 ( $\text{M}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2928, 2853, 1598, 1450, 1346, 1162, 1093, 1003, 666. HRMS (FAB): calculated 326.1587, measured 326.1584.

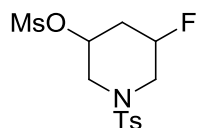


**2-butyl-4-fluoro-1-tosylpyrrolidine (78)**. White solid, 63%, an inseparable mixture of diastereomers A (major) and B (minor) in 2:1 ratio.  $^1\text{H}$  NMR (300 MHz, )  $\delta$ : 7.71 (A+B) (d,  $J = 8.0$  Hz, 2H), 7.37 – 7.25 (A+B) (m, 2H), 5.02 (A) (t,  $J = 53.7$ , 4.5 Hz, 1H), 4.98 (dm,  $J = 52.8$  Hz, 1H), 3.86 – 3.57 (A) (m, 2H), 3.53 – 3.34 (B) (m, 2H), 2.43 (A+B) (s, 3H), 2.30 – 1.70 (A+B) (m, 2H), 1.68 – 1.55 (A+B) (m, 2H), 1.44 – 1.17 (A+B) (m, 4H), 0.91 (A+B) (td,  $J = 6.7$ , 2.1 Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.6 (major), 143.4 (minor), 134.7 (major), 134.6 (minor), 129.7 (major), 129.4 (minor), 127.7 (minor), 127.4 (major), 93.3, 92.0 (minor), 91.9 (major), 90.6, 60.1, 59.1, 55.6 (minor), 54.6 (major), 55.4 (minor), 54.4 (major), 39.9, 36.5, 35.8, 28.5, 27.4, 22.6 (minor) 22.4 (major), 21.5 (minor), 21.6 (major), 14.0.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -172 (m, major), -177 (m, minor). MS (ESI): 300.0 ( $\text{M}^+$ ). 2958, 2932, 2872, 1346, 1162, 1093, 666. HRMS (FAB): calculated 275.0504, measured 275.0502.



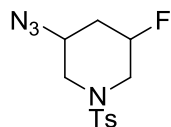
**3-fluoro-1-(2-nosyl)-azepane (79)**. White solid, 63% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.03 – 7.99 (m, 1H), 7.73 – 7.66 (m, 2H), 7.66 – 7.62 (m, 1H), 4.98 – 4.82 (dm,  $J = 47.5$ , 1H), 3.82 (ddd,  $J = 12.0$ , 5.0, 1.5 Hz, 1H), 3.61 (dt,  $J = 13.9$ , 5.1 Hz, 1H), 3.39 (td,  $J =$

14.9, 6.2 Hz, 1H), 3.24 – 3.17 (m, 1H), 2.02 (dd,  $J = 8.0, 4.0$  Hz, 1H), 1.98 (dd,  $J = 9.2, 4.6$  Hz, 1H), 1.85 – 1.75 (m, 3H), 1.65 – 1.56 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 133.5, 132.8, 131.6, 131.0, 124.2, 91.6, 90.2, 52.3, 52.1, 50.1, 32.3, 32.5, 29.4, 20.0, 19.9.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -175 (m). MS (ESI): 303.3 ( $\text{M}^+$ ), 325.3 ( $\text{M}^+ + \text{Na}^+$ ), 341.3 ( $\text{M}^+ + \text{K}^+$ ).



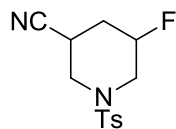
**5-fluoro-1-tosylpiperidin-3-yl methanesulfonate (80)**. 68%, an inseparable

mixture of diastereomers 1:1 ratio  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.46 (d,  $J = 7.7$  Hz, 2H), 6.86 (t,  $J = 7.0$  Hz, 2H), 4.53 (br s, 1H), 4.41 – 4.36 (m, 1H), 4.36 – 4.25 (m, 1H), 4.02 (dm,  $J = 46.5$  Hz, 1H), 2.97 (m, 2H), 2.89 – 2.66 (m, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 1.98 (s, 3H), 1.63 (s, 3H), 1.56 – 1.41 (m, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 133.5, 132.8, 131.6, 131.0, 124.2, 91.6, 90.2, 52.3, 52.1, 50.1, 32.3, 32.5, 29.4, 20.0, 19.9.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$ : -1 (m). MS (ESI): 356.2 ( $\text{M}^+ + \text{Na}^+$ ), 372.1 ( $\text{M}^+ + \text{K}^+$ ).

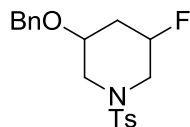


**3-azido-5-fluoro-1-tosylpiperidine (81)**. 60%, an inseparable mixture of

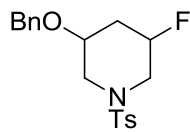
diastereomers in 1:1 ratio.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.71 – 7.64 (m, 2H), 7.35 (t,  $J = 8.1$  Hz, 2H), 4.87 (d,  $J = 47.0$  Hz, 1H), 4.69 (dm,  $J = 47.0$  Hz, 1H), 3.94 (m, 1H), 3.90 – 3.71 (m, 2H), 3.61 (br m, 1H), 2.77 (dd,  $J = 31.4, 12.8$  Hz, 1H), 2.54 – 2.36 (m, 2H), 2.44 (s, 3H), 2.27 (t,  $J = 10.6$  Hz, 2H), 1.64 – 1.60 (m, 2H), 1.50 – 1.46 (m, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 144.3, 144.0, 133.6, 133.1, 130.0, 129.9, 127.5, 85.3, 83.9, 54.1, 53.0, 49.1, 48.9, 48.8, 48.6, 35.8, 35.7, 34.4, 34.2, 21.6. MS (ESI): 323.5 ( $\text{M}^+ + \text{Na}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2926, 2107, 1348, 1167, 1091, 716.



**5-fluoro-1-tosylpiperidine-3-carbonitrile (82)**. 69%, an inseparable mixture of diastereomers A (major) and B (minor) in 1.7:1 ratio.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.72 (A+B) (d,  $J = 7.9$  Hz, 2H), 7.35 (A+B) (dd,  $J = 12.9, 8.0$  Hz, 2H), 5.11 (A) (dm,  $J = 51.5$  Hz, 1H), 5.04 (B) (dm,  $J = 44.0$  Hz, 1H), 4.10 – 4.03 (A) (m, 1H), 3.91 (B) (m, 1H), 3.87 – 3.58 (A+B) (m, 2H), 3.34 – 3.19 (B) (m, 1H), 3.09 (A+B) (m, 2H), 2.93 (B) (m, 1H), 2.78 (B) (dd,  $J = 16.6, 10.8$  Hz, 1H), 2.45 (A) (s, 3H), 2.44 (B) (s, 3H), 2.32 (t,  $J = 16.4$  Hz, 1H), 1.98 – 1.83 (A+B) (m, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 144.6 (major), 144.3 (minor), 133.3 (minor), 133.1 (major), 130.1 (major), 129.8 (minor), 127.8 (minor), 127.4 (major), 117.2 (major), 116.3 (minor), 92.7, 91.3, 55.9 (minor), 55.7 (minor), 55.5, 55.1 (major), 54.9 (major), 38.7 (minor), 38.5 (minor), 36.8 (major), 36.7 (major), 29.7, 25.4, 24.9, 21.6. MS (ESI): 283.1 ( $\text{M}^+$ ), 321.0 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2927, 2250, 1757, 1598, 1346, 1161, 1092, 1041, 667.

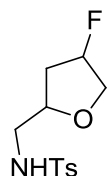


**3-(benzyloxy)-5-fluoro-1-tosylpiperidine (83), minor diastereomer**. 15% yield.  $^1\text{H}$  NMR (500 MHz, )  $\delta$ : 7.73 (d,  $J = 8.0$  Hz, 2H), 7.33 – 7.23 (m, 7H), 5.12 (dd,  $J = 54.7, 3.8$  Hz, 1H), 4.42 (dd,  $J = 35.0, 14.9$  Hz, 2H), 4.14 – 4.06 (m, 1H), 3.90 – 3.80 (m, 1H), 3.72 (dd,  $J = 11.2, 3.4$  Hz, 1H), 3.36 (dd,  $J = 14.7, 4.8$  Hz, 1H), 3.18 (dd,  $J = 14.7, 6.5$  Hz, 1H), 2.44 (s), 2.15 – 2.05 (m, 1H), 1.72 – 1.64 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.4, 137.0, 136.2, 129.7, 128.6, 128.5, 127.8, 127.2, 94.5, 93.1, 73.2, 73.1, 52.8, 50.7, 37.4, 37.2, 21.5. MS (ESI): 364.3 ( $\text{M}^+$ ), 386.2 ( $\text{M}^+ + \text{Na}^+$ ), 402.2 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2929, 2877, 1598, 1496, 1338, 1160, 1090, 1027, 960, 737, 656.

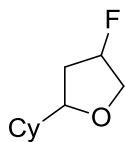


**3-(benzyloxy)-5-fluoro-1-tosylpiperidine, major diastereomer (83).** 31%.  $^1\text{H}$

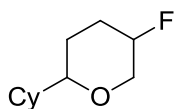
NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.73 (d,  $J = 7.8$  Hz, 2H), 7.34 – 7.21 (m, 10H), 5.12 (d,  $J = 54.8$  Hz, 1H), 4.52 (d,  $J = 14.9$  Hz, 1H), 4.38 (d,  $J = 15.0$  Hz, 1H), 4.00 (dd,  $J = 21.9, 11.3$  Hz, 2H), 3.61 (ddd,  $J = 36.8, 11.2, 3.0$  Hz, 1H), 3.38 (dd,  $J = 14.7, 5.1$  Hz, 1H), 3.19 (dd,  $J = 14.7, 7.4$  Hz, 1H), 2.43 (s, 3H), 2.15 – 1.99 (m, 1H), 1.87 (ddd,  $J = 27.5, 14.8, 4.5$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.3, 137.0, 136.4, 129.7, 129.6, 128.6, 128.5, 127.7, 127.3, 94.3, 92.9, 77.6, 73.8, 73.6, 52.8, 51.7, 36.5, 36.4, 21.5. MS (ESI): 364.3 ( $\text{M}^+$ ), 386.2 ( $\text{M}^+ + \text{Na}^+$ ), 402.2 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 3023, 2919, 2867, 1599, 1495, 1455, 1338, 1158, 1089, 816, 737.



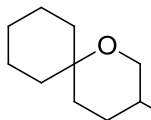
**N-((4-fluoro-tetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide (86).** 74%, an inseparable mixture of diastereomers A (major) and B (minor) in 1.7:1 ratio.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.73 (A+B) (d,  $J = 7.9$  Hz, 2H), 7.31 (A+B) (d,  $J = 7.5$  Hz, 2H), 5.23 (A) (dm,  $J = 54.4$  Hz, 1H), 5.21 (B) (dm,  $J = 54.0$  Hz, 1H), 4.82 (B) (br, 1H), 4.73 (A) (br, 1H), 4.23 – 4.18 (A) (m, 1H), 4.07 – 3.93 (A+B) (m, 2H), 3.67 (B) (dd,  $J = 35.2, 9.6$  Hz, 1H), 3.19 (A+B) (m, 1H), 3.02 (A+B) (m, 1H), 2.43 (A+B) (s, 3H), 2.22 – 2.15 (A+B) (m, 1H), 2.02 – 1.84 (A+B) (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.6 (major), 143.4 (minor), 136.6, 129.8, 127.0, 94.9 (major), 94.3 (minor), 93.5 (major), 92.9 (minor), 76.2, 73.8, 73.6, 46.7, 45.5, 35.9, 35.6, 21.5. MS (ESI): 274.2 ( $\text{M}^+$ ), 296.1 ( $\text{M}^+ + \text{Na}^+$ ), 312.1 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 3279, 2925, 2361, 1598, 1433, 1328, 1161, 1082, 958, 816, 667.



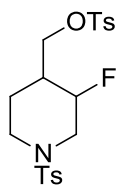
**2-Cyclohexyl-4-fluorotetrahydrofuran (87)**. 88%, 2:1 dr.  $^1\text{H}$  NMR data matches reported values<sup>15</sup>:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.95 – 1.76 (m, 11H), 1.92 – 1.96 (m, 1H), 2.15 – 2.25 (m, 1H), , 5.17 – 5.33 (m, 1H). Another isomer,  $^1\text{H}$  NMR  $\delta$ : 0.88 – 2.00 (m, 12H), 2.18 – 2.33 (m, 1H), 3.48 – 3.68 (m, 2H), 4.08 – 4.17 (m, 1H), 5.14 – 5.30 (m, 1H).



**2-cyclohexyl-5-fluoro-tetrahydro-2H-pyran (88)**. 76%, an inseparable mixture of diastereomers A (major) and B (minor) in 1.5:1 ratio.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.55 (B) (dm,  $J = 46.5$  Hz, 1H), 4.49 (A) (dm,  $J = 49.0$  Hz), 4.18 (A+B) (m, 1H), 3.51 (B) (dd,  $J = 40.3$ , 13.2 Hz, 1H), 3.24 (A) (td,  $J = 10.3$ , 3.4 Hz, 1H), 3.05 – 2.99 (B) (m, 1H), 2.96 (A) (ddd,  $J = 10.9$ , 6.6, 2.0 Hz, 1H), 2.28 – 2.20 (A) (m, 2H), 2.19 – 2.10 (B) (m, 2H), 1.95 – 1.85 (A+B) (m,  $J = 28.4$ , 12.8 Hz, 2H), 1.83 – 1.48 (A+B) (m, 4H), 1.44 – 1.29 (m, 2H), 1.29 – 1.08 (A+B) (m, 4H), 0.99 (A+B) (m, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 87.5 (major), 86.8 (minor), 86.1 (major), 85.5 (minor), 81.8 (minor), 81.6 (major), 70.1 (minor), 69.9 (minor), 69.8 (major), 69.6 (major), 42.9, 42.3, 30.3, 30.1, 29.2, 28.9, 28.6, 28.2, 28.1, 26.7, 26.6, 26.2, 23.0. MS (ESI): 209.3 ( $\text{M}^+ + \text{Na}^+$ ), 226.9 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2927, 2853, 1450, 1096, 1038, 956.

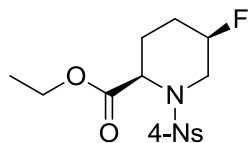


**89**. 55%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.54 (dm,  $J = 48.5$  Hz, 1H), 3.76 (d,  $J = 3.4$  Hz, 1H), 3.72 (dd,  $J = 8.7$ , 3.4 Hz, 1H), 1.98 – 1.79 (m, 4H), 1.79 – 1.70 (m, 2H), 1.68 – 1.47 (m, 2H), 1.47 – 1.22 (m, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 87.3, 86.0, 71.7, 62.8, 62.6, 36.3, 31.8, 30.8, 26.1, 24.6, 24.4, 21.7, 21.5. FTIR ( $\text{cm}^{-1}$ ): 2929, 2857, 1445, 1122, 1080, 1066, 1028, 985, 946, 905.



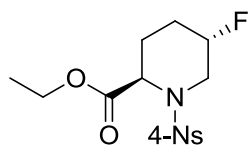
**(3-fluoro-1-tosylpiperidin-4-yl)methyl 4-methylbenzenesulfonate (93).** White solid,

40% yield, single diastereomer.  $^1\text{H}$  NMR (500 MHz, )  $\delta$ : 7.76 (d,  $J = 7.6$  Hz, 2H), 7.62 (d,  $J = 7.5$  Hz, 2H), 7.34 (t,  $J = 7.4$  Hz, 4H), 4.41 (ddt,  $J = 50.0, 10.0, 5.2$  Hz, 1H), 4.31 (td,  $J = 9.9, 5.3$  Hz, 1H), 4.14 (dd,  $J = 10.1, 2.9$  Hz, 1H), 4.05 (dd,  $J = 10.6, 4.7$  Hz, 1H), 3.99 (dd,  $J = 9.6, 6.4$  Hz, 1H), 4.14 (dd,  $J = 10.1, 2.9$  Hz, 1H), 4.05 (dd,  $J = 10.6, 4.7$  Hz, 1H), 3.99 (dd,  $J = 9.6, 6.4$  Hz, 1H), 3.73 (d,  $J = 11.7$  Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.28 – 2.17 (m, 2H), 1.87 – 1.83 (m, 1H), 1.82 – 1.66 (m, 1H), 1.60 – 1.45 (m, 1H), 1.33 – 1.22 (m, 1H), 0.99 – 0.79 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.1, 144.1, 132.8, 132.4, 130.0, 129.9, 129.7, 127.9, 127.6, 87.3, 85.8, 68.8, 49.0, 48.7, 45.1, 41.3, 41.2, 25.8, 25.7, 21.7, 21.5. MS (ESI): 442.2 ( $\text{M}^+$ ), 464.2 ( $\text{M}^+ + \text{Na}^+$ ), 480.1 ( $\text{M}^+ + \text{K}^+$ ). FTIR ( $\text{cm}^{-1}$ ): 2950, 2929, 2862, 1598, 1467, 1346, 1190, 1177, 1094, 938.



**Cis-ethyl 5-fluoro-1-nosylpiperidine-2-carboxylate (95).** 22%.  $^1\text{H}$  NMR

(500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.28 (d,  $J = 8.8$  Hz, 2H), 7.91 (d,  $J = 8.7$  Hz, 2H), 4.66 (br m, 1H), 4.51 (dm,  $J = 47.5$  Hz, 1H), 4.09 – 3.91 (m, 3H), 3.01 (td,  $J = 11.2, 5.1$  Hz, 1H), 2.32 – 2.22 (m, 1H), 2.15 – 2.04 (m, 1H), 1.83 (dd,  $J = 18.3, 9.5$  Hz, 1H), 1.40 – 1.33 (m, 1H), 1.11 (t,  $J = 6.4$  Hz, 3H).



**Trans-ethyl 5-fluoro-1-nosylpiperidine-2-carboxylate (95).** 44%,  $^1\text{H}$  NMR

(300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.33 (d,  $J = 8.6$  Hz, 2H), 7.99 (d,  $J = 8.6$  Hz, 2H), 4.75 (dm,  $J = 48.0$  Hz,

1H), 4.73 (br, 1H), 4.21 – 4.03 (m, 3H), 3.54 (dd,  $J = 41.0, 14.4$  Hz, 1H), 2.03 (m, 2H), 1.59 – 1.56 (m, 1H), 1.24 (t,  $J = 4.5$  Hz, 3H), 1.24 – 1.20 (m, 1H).

### Section 5: References

1. Manteau, B., Pazenok, S., Vors, J-P., Leroux, F. R.; *J. Fluor. Chem.* **2010**, *131*, 140-158.
2. For review of important fluorinated drugs in clinical trials: Ismail, F.; *J. Fluor. Chem.* **2002**, *118*, 27-33.
3. Intramolecular aminofluorination: Liu, G., Yin, G., Wu, T.; *J. Am. Chem. Soc.* **2009**, *131*, 16354-16355.
4. Intermolecular aminofluorination of styrenes: Liu, G., Yinlong, G., Zhou, J., Xu, T., Qui, S.; *J. Am. Chem. Soc.* **2010**, *132*, 2856-2857.
5. Sun, H.; Wang, B.; DiMagno, S. G. *Org. Lett.*, **2008**, *10*, 4413-4416.
6. Zhang, L., Li, Q., Patrick, T. B. *J. Fluor Chem.*, **2000**, *102*, 11-15
7. Intermolecular diamination: Roben, C., Souto, J. A., Gonzalez, Y., Lishchinsliy, A., Muniz, K. *Angew. Chem. Int. Ed.*, **2011**, *50*, 9478 - 9482
8. Intramolecular oxyamination: Farid, U.; Wirth, T. *Angew. Chem. Int. Ed.*, **2012**, *51*, 3462-3465.
9. Kita oxidative spiro lactonization: Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.*, **2010**, *49*, 2175-2177.
10. Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.*, 2006, *45*, 4402 – 4404.
11. Barrow, J. C.; Lindsley, C. W.; Shipe, W. D.; Yang, Z-Q. Patent # 922390, 2006.
12. Jeske, W. P.; Hoppensteadt, D. A.; Lewis, B.; Walenga, J. M.; *Expert Rev. Hematol.*, **2010**, *3*, 527-539.
13. Fleming, F. F. *J. Org. Chem.*, **2001**, *66*, 2171-2174.

14. Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, T. A. *Tet. Lett.*, **1997**, 38, 6301-6304.
15. Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *J. Fluor. Chem.*, **2000**, 104, 277-280.
16. Donohoe, T. J.; Churchill, G. H.; Wheelhouse, K. M. P.; Glossop, P. A. *Angew. Chem. Int. Ed.*, **2006**, 45, 8025-8028.
17. Stefano, N.; Jerome, W. *Org. Lett.*, **2012**, 14, 3563.

## List of References

1. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3017.
2. Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690-7691.
3. Lovick, H. M. Asymmetric Transformations Probing Structure Activity Relationships of Artificial Enzyme Active Sites and Development of Metal-Free Oxidative Cyclization Reactions". 2009, University of Washington, Seattle, WA.
4. Backvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335-342.
5. Bakvall, J. E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953-1957.
6. Barrow, J. C.; Lindsley, C. W.; Shipe, W. D.; Yang, Z-Q. Patent # 922390, 2006.
7. Bodkin, J. A., McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2733-2746.
8. Booker-Milburn, K., Guly, D. J., Cox, B., Procopiou, P. A.; *Org. Lett.*, **2003**, *5*, 3313 – 3315.
9. Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, T. A. *Tet. Lett.*, **1997**, *38*, 6301-6304.
10. Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269 – 275.
11. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737.
12. Donohoe, T. J.; Churchill, G. H.; Wheelhouse, K. M. P.; Glossop, P. A. *Angew. Chem. Int. Ed.*, **2006**, *45*, 8025-8028.

13. Donohoe, T. J.; Callens, C. K.; Thompson, A. L. *Org. Lett.* **2009**, *11*, 2305-2307.
14. Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934-12935.
15. Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615-3618.
16. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.*, **1996**, *118*, 5814-5815
17. Farid, U.; Wirth, T. *Angew. Chem. Int. Ed.*, **2012**, *51*, 3462-3465.
18. Fleming, F. F. *J. Org. Chem.*, **2001**, *66*, 2171-2174.
19. Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638-17639
20. Grishina, G. V., Veselov, I. S., Davankov, V. A., Il'in, M. M., Zefirov, N. S.; *Russ. J. Org. Chem.* **2008**, *44*, 282-287.
21. Han, H.; Cho, C-W.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565-1569.
22. Han, X.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747-1749.
23. Hartwig, J. F., Schlummer, B.; *Org. Lett.* **2002**, *4*, 1471-1474.
24. Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401-404.
25. Herranz, E.; Sharpless, K. B.; Biller, S. A. *J. Am. Chem. Soc.* **1978**, *100*, 3596-3598.
26. Hirt, U. H.; Wirth, T. *Tetrahedron: Asymmetry.* **1997**, *8*, 23-26.
27. Iglesias, A., Perez, E. G., Muñiz, K. *Angew. Chem. Int. Ed.*, **2010**, *49*, 8109-8111.
28. Ismail, F.; *J. Fluor. Chem.* **2002**, *118*, 27-33.
29. Jeske, W. P.; Hoppensteadt, D. A.; Lewis, B.; Walenga, J. M.; *Expert Rev. Hematol.*, **2010**, *3*, 527-539.
30. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

31. Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. U.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.*, **2011**, *76*, 391–395.
32. Liang, H.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11849-11851.
33. Liu, G., Yin, G., Wu, T.; *J. Am. Chem. Soc.* **2009**, *131*, 16354-16355.
34. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179-7181.
35. Liu, G., Yinlong, G., Zhou, J., Xu, T., Qui, S.; *J. Am. Chem. Soc.* **2010**, *132*, 2856-2857.
36. Lovick, H. M. Dissertation: “Applications of Chiral Guanidine Organocatalysts in
37. Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249-1251.
38. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580 – 2627.
39. Manteau, B., Pazenok, S., Vors, J-P., Leroux, F. R.; *J. Fluor. Chem.* **2010**, *131*, 140-158.
40. Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246-4247
41. Michenlin, R. A.; Facchin, G.; Uguagliozzi, P. *Inorg. Chem.* **1984**, *23*, 961-969.
42. Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949-1952.
43. Moriarty, R.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 559-561.
44. Muniz, K. *Chem. Soc. Rev.* **2004**, *33*, 166-174.
45. Muñoz, K.; Nieger, M.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2005**, *127*, 14586-14587.
46. Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169-1173.
47. Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404.
48. Roben, C., Souto, J. A., Gonzalez, Y., Lishchinskiy, A., Muñoz, K. *Angew. Chem. Int. Ed.*, **2011**, *50*, 9478 – 9482.

49. Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488-9489.
50. Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *J. Fluor. Chem.*, **2000**, *104*, 277-280.
51. Sharpless, K. B.; Patrick, D. W.; Truedale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305-2307.
52. Sibbald, P. A.; Michael, F. E.; *Org. Lett.* **2009**, *11*, 1147-1149.
53. Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.*, **2009**, *131*, 15945–15951.
54. Stefano, N.; Jerome, W. *Org. Lett.*, **2012**, *14*, 3563.
55. Sun, H.; Wang, B.; DiMagno, S. G. *Org. Lett.*, **2008**, *10*, 4413-4416.
56. Szolcsanyi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948.
57. Tao, B.; Schligloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507-2510.
58. Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.*, **2010**, *49*, 2175-2177.
59. Weinreb, M. *J. Org. Chem.*, **2003**, *68*, 4112–4115.
60. Weinstein, A. B. *ACS Org. Div.* **2011**.
61. Zhang, L., Li, Q., Patrick, T. B. *J. Fluor Chem.*, **2000**, *102*, 11-15
62. Zhou, Y.; Murphy, P. V.; *Org. Lett.* **2008**, *10*, 3777-3780.

## Vita

Dmitry Liskin was born in the city of Ryazan, Russia. At the age of fifteen he moved to Alpine, CA as an exchange student. Dmitry received his bachelor of science in Biochemistry from Mississippi College, Clinton, MS in 2007. He performed his undergraduate research on synthesis of novel *di*-pseudoacids with Dr. Edward Valente. In the fall of 2007 Dmitry moved to Seattle, WA to begin his graduate career at the University of Washington. Dmitry performed research under the guidance of Professor Forrest E. Michael and earned a Doctor of Philosophy degree in Chemistry from the Organic Division at the University of Washington in 2012.