Palladium-Catalyzed Cross-Couplings of 2-Alkylaziridines and Alkenylboronic Acids

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Abstract

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A new method to synthesize substituted homoallylic amines is reported. Homoallylic amines are important structural moieties in natural products and pharmaceutical agents. The reaction couples *N*-nosyl-2-alkylaziridines with alkenylboronic acids under palladium catalysis. This work examines the role of base and proton donor additive in facilitating formation of the desired product. The reaction has promising yields and appears to have a wide substrate scope. This work expands upon the Michael lab's previous work with cross-couplings of alkyl aziridines and arylboronic acids.

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List of Abbreviations

Acetyl-CoA:	Acetyl Coenzyme A
Ar:	Aryl
Boc:	*tert*-Butyloxycarbonyl
bpy:	2,2'-Bipyridine
Cbz:	Carbobenzyloxy
cod:	Cyclooctadiene
dba:	Dibenzylideneacetone
DMA:	*N*,*N*-Dimethylacetamide
DME:	Dimethoxyethane
ESI-MS:	Electrospray ionization mass spectrometry
equiv:	Equivalent
Et:	Ethyl
IR:	Infrared spectroscopy
h:	Hour
Hz:	Hertz
J:	NMR coupling constant
L:	Ligand
Me:	Methyl
MHz:	Megahertz
NMR:	Nuclear Magnetic Resonance

Abbreviations for NMR splitting:

s:	singlet
d:	doublet

t:	triplet
q:	quartet
m:	multiplet

Np:	1-Naphthyl
Ns:	4-Nitrobenzenesulfonyl
Ph:	Phenyl
phen:	1,10-Phenanthroline
ppm:	Parts per million
Pr:	Propyl
R:	Alkyl (unspecified)
THF:	Tetrahydrofuran
TIPS:	Triisopropylsilyl
Ts:	*p*-Toluenesulfonyl

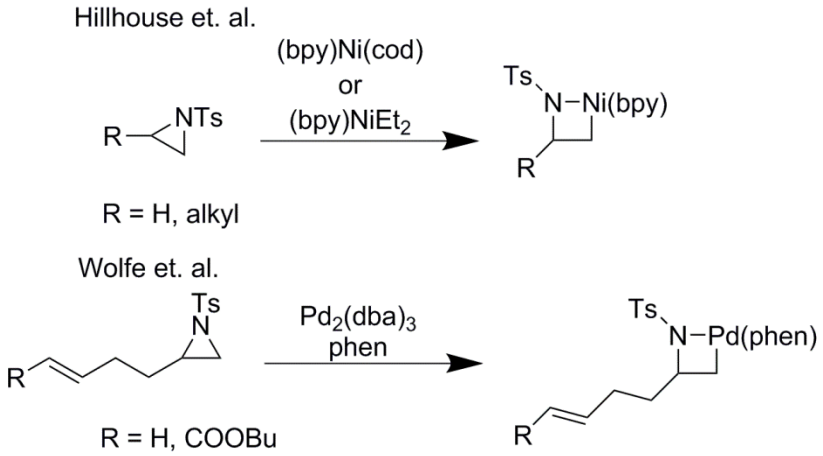
Acknowledgements

I would like to thank Dr. Forrest Michael for all his help. I would like to thank Michael lab members: George Andrew Holtzen, Derek Obenschain, John Tabor, and Wei Pin Teh, who made coming to lab fun and enjoyable. I would also like to thank Dr. Megan Duda for her initial guidance on my project. I would also like to thank my undergraduate advisors, Dr. Adam Glass and Dr. Justin Lytle, for all their help and teaching me about research. I would like to thank my parents and brothers for all their love and support. Thank you all so much!

Palladium-Catalyzed Cross-Couplings of 2-Alkylaziridines and Alkenylboronic Acids

Section 1: Introduction

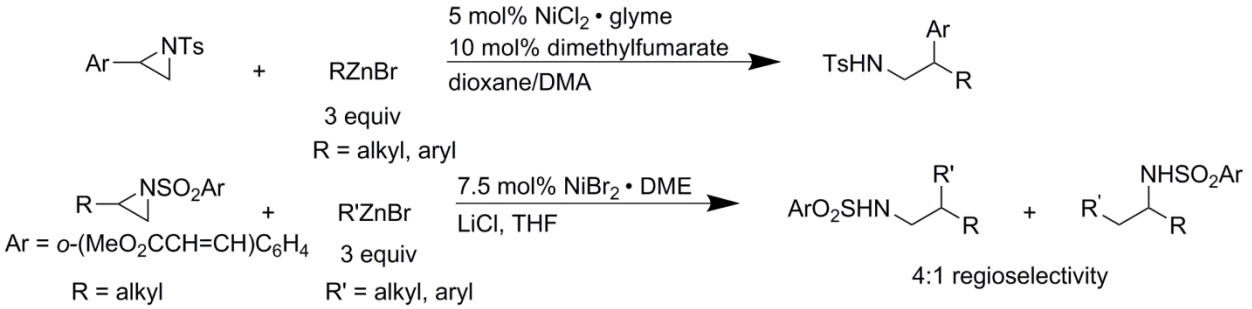
Aziridines are invaluable in organic synthesis due to their versatility, providing access to a plethora of nitrogen-containing compounds.[1] Hillhouse[2] and Wolfe[3] independently demonstrated that transition metal catalysts, such as nickel and palladium, can oxidatively add the carbon-nitrogen bond of azirdines to afford four-membered azametallacycles (Scheme 1). These azametallacycles, stabilized by diamine ligands, were isolated and characterized. Although the synthetic applications remain underexplored, these works demonstrated that nickel and palladium can be used to activate aziridines, so they can act as electrophiles and participate in further reactions.



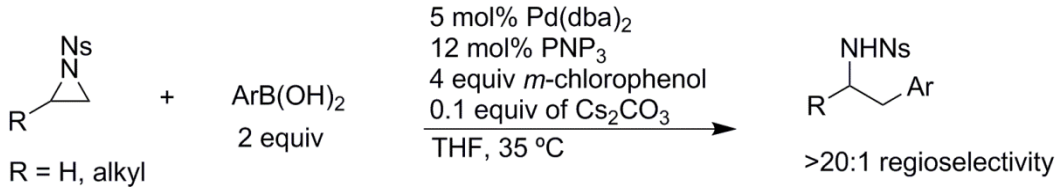
Scheme 1: Azametallacyclobutanes synthesized from aziridines by Hillhouse[2] and Wolfe[3].

Following Hillhouse and Wolfe, Doyle demonstrated two methods to couple aziridines with organozinc reagents using nickel catalysis (Scheme 2).[4] There are separate reaction conditions for coupling aryl and alkyl aziridines. Each employ different sulfonyl protecting

groups on the aziridine and utilize different nickel catalysts. The method for coupling aryl aziridines generated branched products in complete regioselectivity and in moderate yields. [4a] The method for coupling alkyl aziridines generated a mixture of linear and branched products in about 4:1 regioslectivity.[4b] In addition to poor regioselectivity, another drawback is the requirement for stoichiometric amounts of air-sensitive alkylzinc bromides. Despite the limitations, Doyle was the first to show that alkyl and aryl aziridines could be coupled with organometallic nucleophiles under mild conditions.



Scheme 2: Doyle's method for coupling aziridines with alkylzinc bromides, facilitated by nickel catalysts.[4]



Scheme 3: Previous work from the Michael lab that demonstrates a palladium-catalyzed cross-coupling of alkyl aziridines and arylboronic method to synthesize β-phenethylamines.[5]

The Michael lab expanded on this by developing a palladium-catalyzed cross-coupling of alkyl aziridines with arylboronic acids (Scheme 3).[5] This method addressed certain limitations of Doyle's work. This method improves the regioselectivity of the addition, favoring the linear product in ratios >20:1 and employs a boronic acid as the organometallic nucleophile, which broadens the scope of potential coupling substrates. Furthermore, the method utilized the commercially-available 4-nitrobenzenesulfonyl protecting group and air-stable boronic acids. An attribute of this method is the excess of the *m*-chlorophenol additive. The addition of excess

phenol has shown to substantially increase yields and prevents the formation of side products. Duda et. al. proposed that the phenol undergoes reversible protonolysis of the intermediate azapalladacycle, generating a palladium phenoxide intermediate (Figure 1). This helps reduce the lifetime of the ring-opened intermediates that are prone to β-hydride elimination and allows the boronic acid to undergo transmetalation, giving the desired product. Based on the success in coupling arylboronic acids, I decided to explore the possibility of using alkenylboronic acids to generate substituted homoallylic amines.

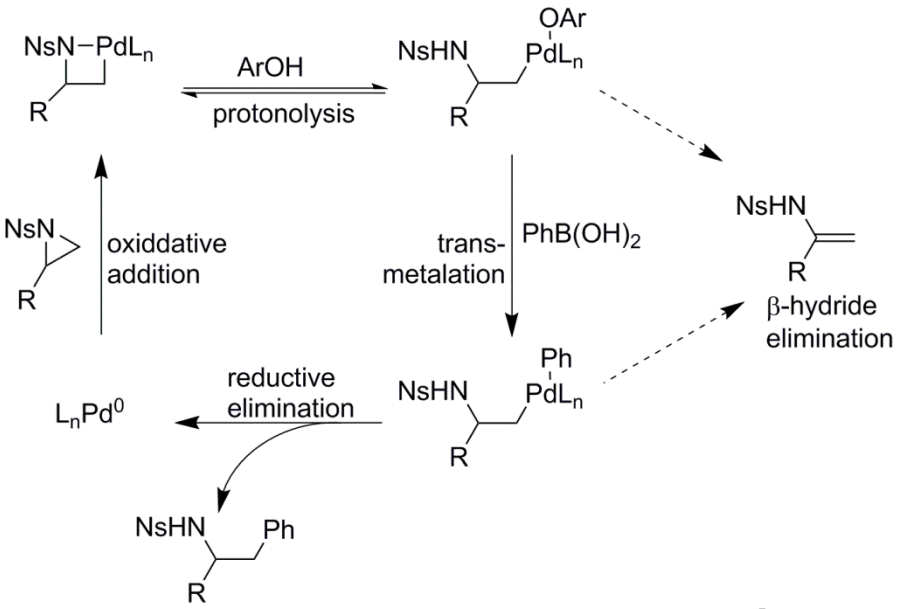


Figure 1: Proposed catalytic cycles from Duda et. al.[5]

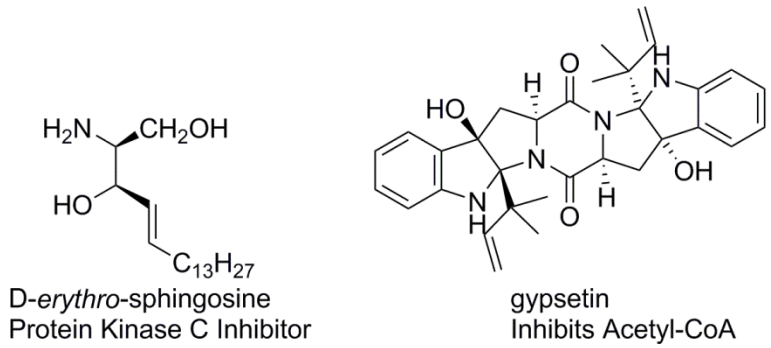


Figure 2: Examples of homoallylic amines in natural products.[6,7]

Homoallylic amines have many uses in organic synthesis and pharmacology. The homoallylic amine moiety is present in a variety of natural products and pharmaceutical agents

(Figure 2). D-*erythro*-Sphingosine can inhibit Protein Kinase C; an implication that can be useful in treating a variety of medical conditions, such as cancer.[6] Gypsetin inhibits Acetyl-CoA, which is helpful in treating hypercholesterolemia.[7] In addition, homoallylic amines are useful building blocks and can be used to synthesize a plethora of natural products. (-)-Antofine[8], an anti-cancer agent, and (+)-α-conhydrine[9], a plant toxin, can both be synthesized from homoallylic amines (Figure 3). My method would give access a larger variety of substituted homoallylic amines, which could be utilized in total synthesis.

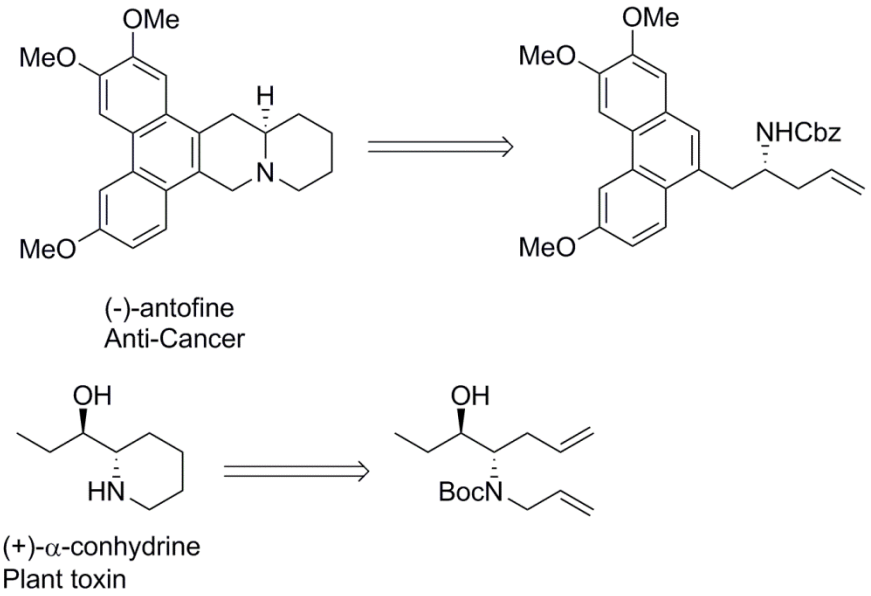
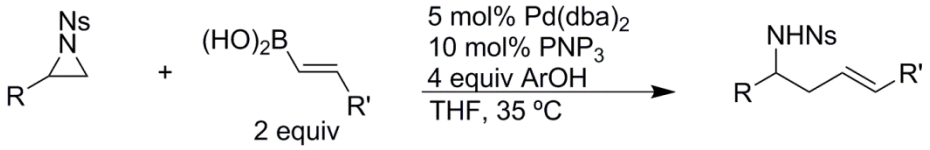


Figure 3: Examples of natural products synthesized from homoallylic amines.[8,9]



Scheme 4: My method for palladium-catalyzed cross-coupling of 2-alkylaziridines and alkenylboronic acids.

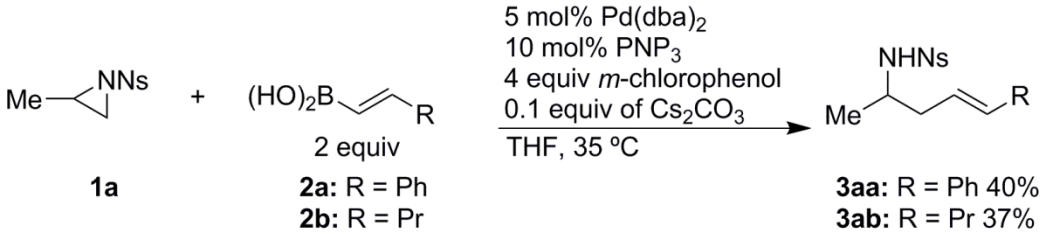
In this thesis, I report the development of a method to couple alkyl aziridines and alkenylboronic acids under mild conditions, using a palladium catalyst (Scheme 4). This method

deviates from the Michael lab's previous aziridine coupling work in that it employs a different proton donor additive and does not require catalytic base.

Section 2: Results and Discussion

2.1 Initial Results

I initially tested the reaction conditions from Duda et. al.[5] for alkyl aziridines and arylboronic acids to see if I could replicate their results with alkenylboronic acids. *N*-Nosyl-2-methylaziridine **1a** was coupled with alkenylboronic acids **2a** or **2b** to yield **3aa** or **3ab** (Scheme 5). The isolated yields of these reactions were poor due to unfavorable reaction conditions.

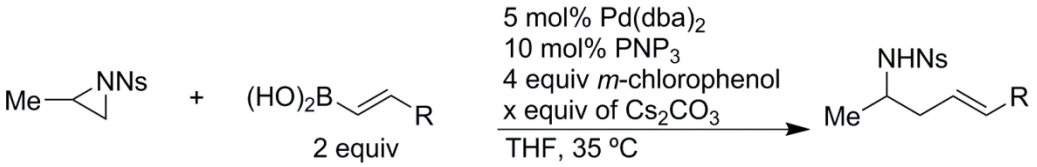


Scheme 5: Initial conditions for cross-coupling reactions *N*-nosyl-2-methylaziridine with alkenylboronic acids.

2.2 Reaction Optimization

Based on my initial results, I first investigated the effects of the added base. **1a** was coupled with either **2a** or **2b** under the initial reaction conditions, but with varying equivalents of cesium carbonate to form **3aa** or **3ab**, respectively (Table 1). I found that the reaction yield was highest when no base was added (entry 1). Increasing the quantity of base from 0 equiv to 0.05 equiv and to 0.1 equiv resulted in a significant drop in yield (entries 2-3). I also found that adding 0.5 equiv or more of base resulted in no desired product (entries 4-7). Under these conditions I propose that the aziridines polymerize, shutting down the desired reaction. This trend differs from the Michael Lab's previous work with arylboronic acids in that catalytic amounts of base are needed to facilitate product formation.

Table 1: Base optimization.



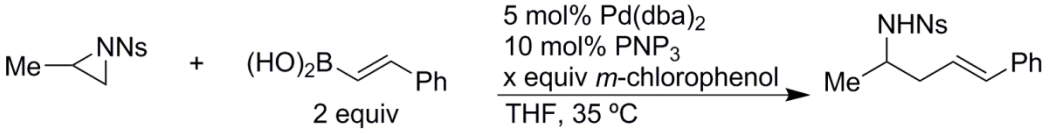
1a **2a:** R = Ph, **2b:** R = Pr **3aa:** R = Ph, **3ab:** R = Pr

Entry	x	%Yield of 3aa[a]	%Yield of 3ab[a]
1	0	80	72
2	0.05	64	53
3	0.1	57	50
4	0.5	0	0
5	1.0	0	0
6	1.1	0	0
7	2.0	0	0

[a]NMR yields using 1,3-dinitrobenzene as an internal standard.

Based on my findings with base optimization, I probed the necessity of the *m*-chlorophenol additive in the reaction. **1a** was coupled with **2a** under reaction conditions with varying equivalents of *m*-chlorophenol and without base (Table 2). Reducing the quantity of *m*-chlorophenol from 4 equiv to 0 equiv significantly decreased the yield from 83% to 59% (entries 1, 5). Adding 0.5 equiv, 1.0 equiv, or 2.0 equiv had similar effects as excluding the *m*-chlorophenol altogether (entries 2-4). This led me to conclude that a large excess of *m*-chlorophenol is needed for the reaction, possibly to facilitate transmetalation of the boronic acid.

Table 2: *m*-Chlorophenol optimization.



1a **2a** **3aa**

Entry	x	%Yield of 3aa[a]
1	0	59
2	0.5	57
3	1.0	60
4	2.0	68
5	4.0	83

[a]NMR yields using 1,3-dinitrobenzene as an internal standard.

2.3 Reaction Scope

Based on previous optimization, I investigated the substrate scope of the reaction. Under the conditions in Figure 4, I had success with varying types of alkyl substituents at the 2 position of the aziridine. Although I was able to facilitate reactions with most substrates and with two different alkenylboronic acids, the isolated yields were poor for some products and other products were not isolable. Also, my conditions did not work as well for bulky substituents on the aziridine, such as an isopropyl group, or with alkylboronic acids.

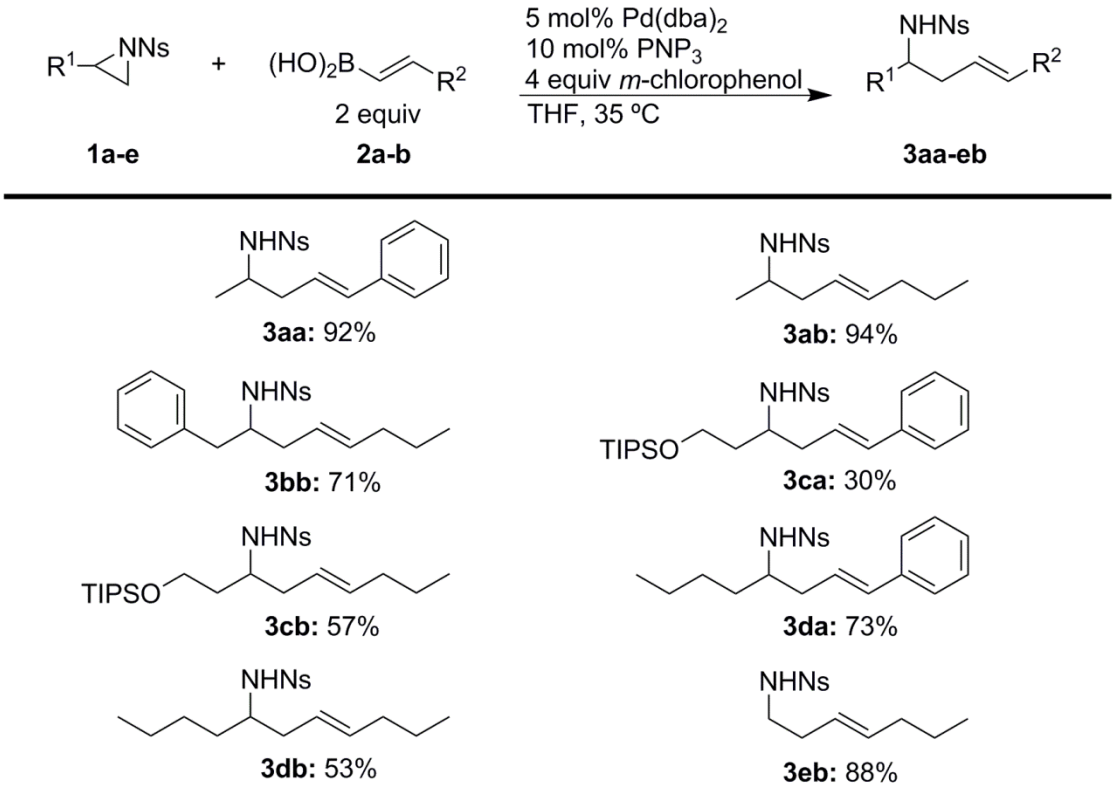


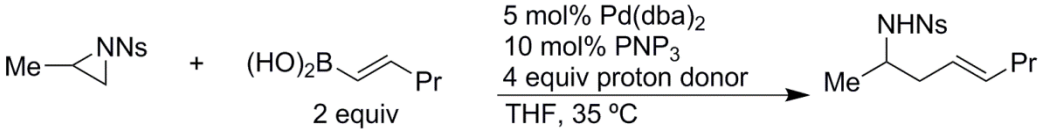
Figure 4: Substrate scope exploration of initial optimized conditions.[a]
[a]Isolated yields

2.4 Additional reaction optimization and scope

Due to the poor isolated yields of several of the products, I decided to optimize the reaction conditions again. This time I focused on the proton donor additive. I tested the reaction with various types of proton donors, such as phenols, water, alcohols, and carboxylic acids

(Table 3). Acetic acid and salicylic acid did not facilitate the reaction very well or at all as the aziridine underwent acid-catalyzed ring-opening (entries 8-9). Water and isopropanol gave similar yields as the initial conditions (entries 6-7). Using a phenol with electron-donating groups, such as 2,5-dimethylphenol, significantly decreased the yield (entry 5). Using phenols with electron-withdrawing groups increased the yield. *o*- and *m*-nitrophenol increased the yield to 82% and 91%, respectively (entries 3-4). The reaction with *o*-nitrophenol had some starting aziridine remaining. Moving the chloro-substituent to the *para* position, increased the yield to 90% (entry 2).

Table 3: Proton donor optimization.



1a **2b** **3ab**

Entry	Proton Donor	%Yield of 3ab[a]
1	*m*-chlorophenol	72
2	*p*-chlorophenol	90
3	*o*-nitrophenol	82
4	*m*-nitrophenol	91
5	2,3-dimethylphenol	40
6	water	72
7	isopropanol	71
8	acetic acid	8
9	salicylic acid	0

[a]NMR yields using 1,3-dinitrobenzene as an internal standard.

Utilizing my newly optimized results, I investigated the substrate scope of the reaction with the two highest yielding additives: *p*-chlorophenol and *m*-nitrophenol (Figure 5). **3ab** was isolated in an 82% yield, using *p*-chlorophenol. **3eb** was isolated in a 92% yield, using *m*-nitrophenol. **3cb** and **3db** displayed excellent NMR yields with both phenols. The newly optimized reaction conditions with *p*-chlorophenol and *m*-nitrophenol afforded increased yields and appeared to have similar substrate scope capabilities.

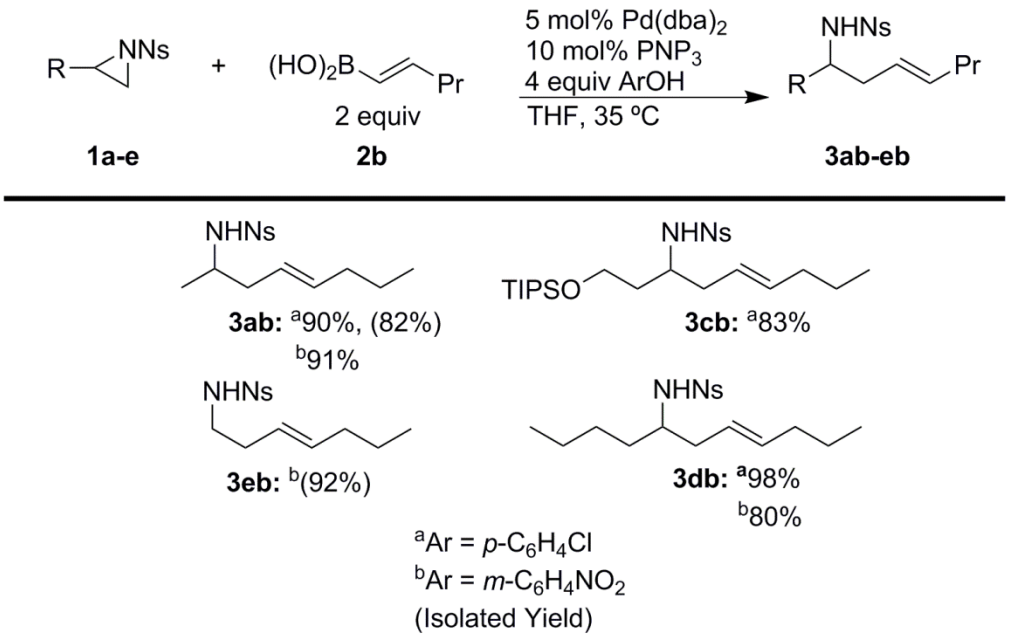


Figure 5: Substrate scope exploration of reoptimized conditions.[c]
[c]NMR yields using 1,3-dinitrobenzene as an internal standard.

Future work will include fully investigating the substrate scope of this reaction with *p*-chlorophenol and *m*-nitrophenol. The goal is to build a synthetic library with compounds **3aa-3eb** and others with varying alkyl aziridines and alkenylboronic acids. Mechanistic insights will also be investigated because the optimized conditions differ from those in Duda et. al.

Section 3: Conclusion

I developed a new method to synthesize substituted homoallylic amines from palladium-catalyzed cross-couplings of *N*-nosyl-2-alkylaziridines and alkenylboronic acids. Attributes of this reaction are an excess of a proton donor additive (*p*-chlorophenol and *m*-nitrophenol) and the omission of base. This reaction has promising yields and is tolerant of a wide variety of functional groups. Future work will explore the substrate scope and attempt to obtain mechanistic insights of this reaction.

Section 4: Experimental

4.1 General Procedures and Materials

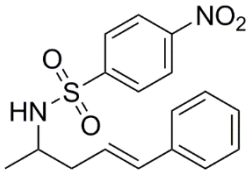
All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise indicated. Infrared spectra were obtained on a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were obtained on Bruker Esquire 1100 Liquid Chromatograph-Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, or DRX-499 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to residual $CHCl_3$ (7.26 ppm) or TMS (0.00 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to the carbon resonance of $CDCl_3$ (77.16 ppm) or TMS (0.00 ppm).

Tetrahydrofuran was degassed and dried by passing through a column of neutral alumina. Deuterated solvent, $CDCl_3$ was obtained from Cambridge Isotope Laboratories, Inc. and was stored over activated 3Å molecular sieves. Ethyl acetate and hexanes were obtained from Fisher Scientific or Sigma Aldrich and used without further purification. Bis(dibenzylideneacetone)palladium(0) was prepared according to a previously published procedure.[10] Cesium carbonate (Aldrich) and tri-1-naphthylphosphine (Strem) were stored in a glove box, under nitrogen. *m*-Chlorophenol was obtained from Aldrich and purified by distillation. *p*-Chlorophenol (Acros Organic) and *m*-nitrophenol (Aldrich) were used without further purification. Alkenylboronic acids were obtained from Frontier Scientific or Acros Organic and used without further purification. All aziridine substrates **(1a-e)** were prepared according to a previously published procedure.[5]

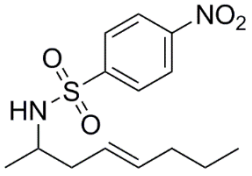
4.2 General Procedure

A flame-dried borosilicate glass vial equipped with a magnetic stirbar was charged with aziridine (0.20 mmol, 1.0 equiv), alkenylboronic acid (0.40 mmol, 2.0 equiv), *m*-chlorophenol (0.80 mmol, 101.3 mg, 4.0 equiv), tri-1-naphthylphosphine (9.9 mg, 0.024 mmol, 0.12 equiv), and bis(dibenzylideneacetone)palladium(0) (5.8 mg, 0.010 mmol, 0.05 equiv). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry tetrahydrofuran (0.5 mL) was added, and the reaction solution was heated to 35 °C and allowed to stir for 48 h. The reaction mixture was then filtered through a plug of silica gel and with ethyl acetate, and concentrated on a rotary evaporator to afford the crude reaction product.

4.3 Characterization of Products

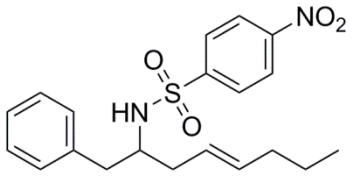


(*E*)-*N*-(4-nitrobenzenesulfonyl)-5-phenylpent-4-en-2-amine (3aa). Prepared according to the general procedure and purified by silica gel chromatography (10% ethyl acetate/ 90% hexanes) to yield the product as an off-white crystalline solid (64.0 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (2H, d, *J* = 8.6 Hz), 7.97 (2H, d, *J* = 8.6 Hz), 7.33-7.13 (5H, m), 6.30 (1H, d, *J* = 15.9 Hz), 5.85-5.71 (1H, m), 4.57 (1H, d, *J* = 7.6 Hz), 3.60-3.46 (1H, m), 2.38-2.18 (2H, m), 1.25 (3H, d, *J* = 6.5 Hz).

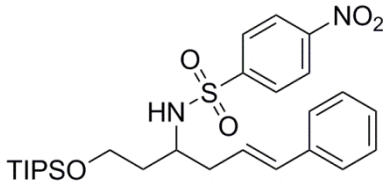


(*E*)-*N*-(4-nitrobenzenesulfonyl)-oct-4-en-2-amine (3ab). Prepared according to the general procedure using *p*-chlorophenol, and purified by silica gel chromatography (5% ethyl acetate/ 95% hexanes) to yield the product as a yellow wax (51.0 mg, 82% yield). IR (thin film): 3377,

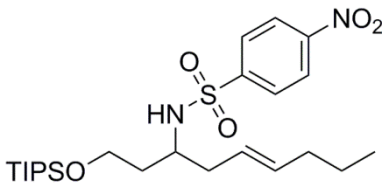
3287, 3104, 2960, 2929, 2872, 2341, 2253, 1607, 1531, 1309, 1166, 1903, 974, 907, 856, 731, 685, 650, 616, 570 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (2H, d, *J* = 8.9 Hz), 8.05 (2H, d, *J* = 8.8 Hz), 5.42 (1H, dt, *J* = 14.5, 7.4 Hz), 5.13 (1H, dt, *J* = 14.8, 7.5 Hz), 4.45 (1H, d, *J* = 7.4 Hz), 3.52-3.37 (1H, m), 2.08 (2H, t, *J* = 7.0 Hz), 1.91 (2H, q, *J* = 6.9 Hz), 1.36-1.18 (2H, m), 1.13 (3H, d, *J* = 6.6 Hz), 0.87 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 146.1, 134.5, 127.3, 123.3, 123.2, 49.1, 39.2, 33.6, 21.4, 20.4, 12.6. MS (ESI, negative mode): $C_{14}H_{19}N_2O_4S$ $[M - H]^-$: 311.



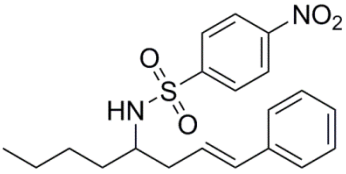
(*E*)-*N*-(4-nitrobenzenesulfonyl)-1-phenyloct-4-en-2-amine (3bb). Prepared according to the general procedure and purified by silica gel chromatography (10% ethyl acetate/ 90% hexanes) to yield the product as a yellow oil (55.5 mg, 71% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (2H, d, *J* = 8.2 Hz), 7.76 (2H, d, *J* = 8.2 Hz), 7.16-7.14 (3H, m), 7.00-6.97 (2H, m), 5.49 (1H, dt, *J* = 16.2, 6.6 Hz), 5.22 (1H, dt, *J* = 15.0, 7.2 Hz), 4.50 (1H, d, *J* = 7.8 Hz), 3.53-3.42 (1H, m), 2.81 (1H, dd, *J* = 13.8, 5.9 Hz), 5.63 (1H, dd, *J* = 13.8, 7.7 Hz), 2.32-2.14 (2H, m), 1.93 (2H, q, *J* = 6.9 Hz), 1.41-1.31 (2H, m), 0.88 (3H, t, *J* = 7.3 Hz).



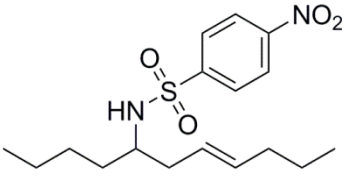
(*E*)-*N*-(4-nitrobenzenesulfonyl)-6-phenyl-1-(triisopropylsilyloxy)hex-5-en-3-amine (3ca). Prepared according to the general procedure and purified by silica gel chromatography (10% ethyl acetate/ 90% hexanes) to yield the product as a yellow oil (31.5 mg, 30% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (2H, d, *J* = 8.9 Hz), 8.00 (2H, d, *J* = 8.9 Hz), 7.30-7.17 (5H, m), 6.31 (1H, d, *J* = 15.9 Hz), 5.97-5.87 (2H, m), 3.96-3.84 (1H, m), 3.79-3-3.70 (1H, m), 3.68-3-3.58 (1H, m), 2.54-2.40 (2H, m), 1.83-1.68 (2H, m), 1.19-1.00 (21H, m).



(*E*)-*N*-(4-nitrobenzenesulfonyl)-1-(triisopropylsilyloxy)non-5-en-3-amine (3cb). Prepared according to the general procedure and purified by silica gel chromatography (5% ethyl acetate/ 95% hexanes) to yield the product as a colorless oil (57.0 mg, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, *J* = 8.4 Hz), 8.05 (2H, d, *J* = 8.4 Hz), 5.84 (1H, d, *J* = 6.7 Hz), 5.42 (1H, dt, *J* = 13.8, 6.6 Hz), 5.19 (1H, dt, *J* = 15.0, 6.9 Hz), 3.86-3.78 (1H, m), 3.69-3.64 (1H, m), 3.51-3.44 (1H, m), 2.34-2.26 (1H, m), 2.25-2.17 (1H, m), 1.90 (2H, dd, *J* = 13.9, 6.9 Hz), 1.70-1.58 (2H, m), 1.36-1.28 (2H, m), 1.14-0.96 (21H, m), 0.87 (3H, t, *J* = 7.3 Hz).

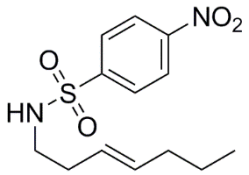


(*E*)-*N*-(4-nitrobenzenesulfonyl)-1-phenyloct-1-en-4-amine (3da). Prepared according to the general procedure and purified by silica gel chromatography (10% ethyl acetate/ 90% hexanes) to yield the product as a tan crystalline solid (56.9 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, *J* = 8.9 Hz), 7.96 (2H, d, *J* = 8.9 Hz), 7.30-7.12 (5H, m), 6.25 (2H, d, *J* = 15.7 Hz), 5.83-3-5.70 (1H, m), 4.42 (1H, d, *J* = 8.5 Hz), 3.51-3.39 (1H, m), 2.43-2.31 (1H, m), 2.27-2.16 (1H, m), 1.32-1.23 (6H, m), 0.86 (3H, t, *J* = 6.9 Hz).



(*E*)-*N*-(4-nitrobenzenesulfonyl)-undec-7-en-5-amine (3db). Prepared according to the general procedure and purified by silica gel chromatography (5% ethyl acetate/ 95% hexanes) to yield the product as a light-yellow oil (53.1 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (2H, d, J = 8.7 Hz), 8.05 (2H, d, J = 8.7 Hz), 5.37 (1H, dt, *J* = 13.8, 6.7 Hz), 5.10 (1H, dt, *J* = 15.0, 7.2

Hz), 4.46 (1H, d, *J* = 8.4 Hz), 3.37-3.26 (1H, m), 2.07 (2H, t, *J* = 6.4 Hz), 1.88 (2H, q, *J* = 7.0 Hz), 1.49-1.12 (8H, m), 0.93-0.75 (6H, m).



(*E*)-*N*-(4-nitrobenzenesulfonyl)-hept-3-en-1-amine (3eb). Prepared according to the general procedure using *m*-nitrophenol and purified by silica gel chromatography (10% ethyl acetate/ 90% hexanes) to yield the product as an off-white crystalline solid (55.0 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (2H, d, *J* = 8.8 Hz), 8.05 (2H, d, *J* = 8.8 Hz), 5.46 (1H, dt, *J* = 13.7, 6.6 Hz), 5.19 (1H, dt, *J* = 14.1, 6.9 Hz), 4.55 (1H, t, *J* = 5.4 Hz), 3.05 (2H, q, *J* = 6.4 Hz), 2.17 (2H, q, *J* = 6.6 Hz), 1.94 (2H, q, *J* = 7.0 Hz), 1.39-1.19 (2H, m), 0.87 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 146.2, 135.1, 128.4, 125.1, 124.5, 42.9, 34.7, 32.7, 22.5, 18.0, 13.7.

Section 5: References

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