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Steven Chen March 18th, 2020

Allylic C-H Functionalization Studies on Allylbenzene Derivatives.

by

Steven Chen

Simon B. Blakey, Ph.D
Adviser

Emory University Department of Chemistry

Simon B. Blakey, Ph.D

Adviser

Douglas Mulford, Ph.D

Committee Member

Benjamin Reiss, Ph.D

Committee Member

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An abstract of
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Abstract

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Selective C-H functionalization has been an emerging field within organic chemistry in the past few decades due to its potential for more efficient syntheses of essential compounds relevant to the fields of medicine and pharmaceuticals. Allylic C-H functionalization has become an increasingly important area of chemistry research as it presents novel possibilities for efficient and bio sustainable reactions in the laboratory. This study investigates the utilization of Iridium(III)-catalyzed C-H sulfonamidation on allylbenzene derivatives using tosyl azide as the nitrogen source. Subsequently, the study investigates and discusses preliminary results from Iridium(III)-catalyzed C-H amination with a benzyl carbamate as the nitrogen source. The impact of the results is the development of a more efficient and bio sustainable pathway for sulfonamidation, a process which can be applied for more efficient drug synthesis and mechanistic design in the future.

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Acknowledgements

I would first like to thank Dr. Simon Blakey for accepting me as an undergrad to work in his lab, and for providing me the space and guidance to think critically and learn independently within a scientific setting. I have incredible respect for Dr. Blakey as a scientist and visionary leader within the chemistry department and in his work in C-H functionalization.

I would also like to thank Dr. Douglas Mulford for his help as my major advisor and for being an engaging freshman chemistry professor during my first undergraduate course in chemistry, thus sparking my interest in science and technology. Though I might have been a lost freshman who only knew how to play minecraft in class at the time, his course inspired me to pursue my studies in chemistry further.

I would also like to thank Dr. Benjamin Reiss for his continous support for me over the years in research, in writing, and in the arts. Since taking his freshman seminar course on sleep and human health research, I have felt more comfortable, confident, and prepared in taking on challenginge coursework and laboratory work during my years at Emory.

Finally, I would like to thank everyone in the Blakey group for all their support, guidance, and fun times. Each day brought new opportunities and fresh challenges. I would also like to thank everyone else in the chemistry department who have helped me along the way in one way or another. Lastly, I would especially like to thank Amaan Kazerouni for his extremely dedicated guidance and attention towards my learning in the lab. He has gone above and beyond as a graduate student mentor. I wish everyone the best as they continue on the journey of life and hope to keep in touch.

Contents

Introduction:

Historically, organic synthesis has been considered the primary process for synthesizing key molecules. Over the past few years however, C-H functionalization has developed rapidly through the discoveries of new chemical transformations. In 1965, Tsuji et. al. discovered the use of palladium (Pd) catalysts in forming electrophilic π-allyl complexes that react with carbon nucleophiles to produce new carbon-carbon bonds[1]. However, initial experiments by Tsuji et. al. required activated leaving groups at the allylic position in order for the reactions to proceed. As more research was done in this field, allylic C–H functionalization emerged as a powerful alternative for allylic substitution because it does not require pre-functionalized olefin substrates. Over the years, enantioselective allylic C-H functionalization with the use of Pd catalysts have been developed utilizing an oxidative framework. In 2004, White et. al. showed that palladium catalysts can be used for oxidative C-H functionalization to make C–C, C–O, and C–N bonds[2]. Transition metal catalysts are used to form π-allyl intermediates, allowing successful transformations on terminal olefins.

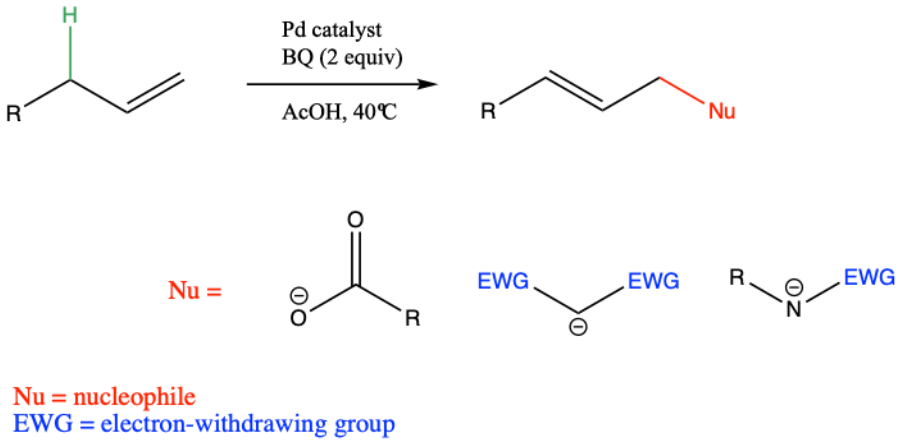


Figure 1: White et. al. - Oxidative C-H functionalization.

Up to this point, two drawbacks were present in allylic C-H functionalization. Firstly, the palladium catalysts have only shown evidence of oxidative C-H functionalization on terminal olefins, with no evidence of activation on *internal* olefins. Secondly, the chemistry published by White et. al. at the time only worked with activated nucleophiles with strong electron-withdrawing groups attached. Two key insights from Cossy et. al. and Tanaka et. al. however suggested that allylic C-H functionalization could be possible on internal olefins. Cossy et. al. was able to synthesize cyclic amines using a RhCp* catalyst and a nitrogen nucleophile with only one electron-withdrawing group[30], sparking the further developments of rhodium-based catalysts. Tanaka et. al. showed that a Cp^ERh(III) catalyst allowed intramolecular allylic C-H amination through a Cp^ERh(III) π-allyl intermediate through selective functionalization of internal olefins[3].

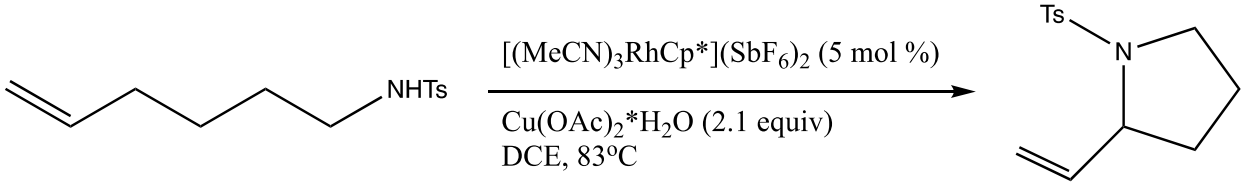


Figure 2: Cossy et. al. 2012 – Cyclic amine synthesis using RhCp*

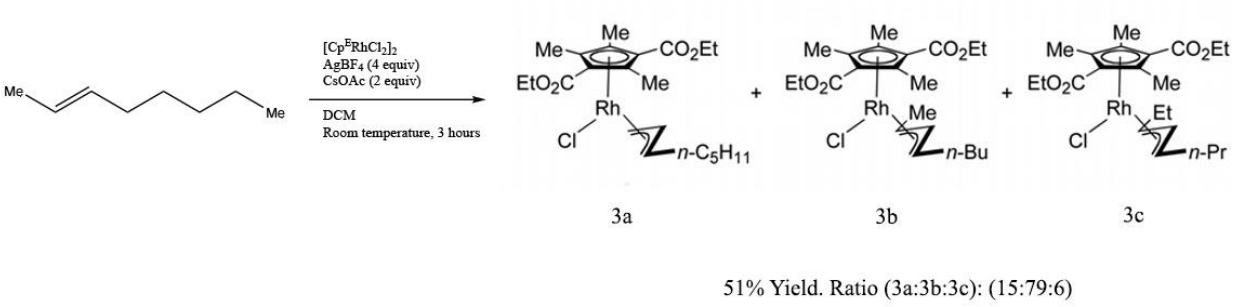


Figure 3: Tanaka et. al. 2016. – Selective coordination of the π -allyl intermediate onto internal olefins[3].

In 2017, after the Blakey group began to build upon these findings, Jacob Burman of the Blakey group reported a method for catalytic intermolecular allylic C–H amination of *trans*-disubstituted olefins, using a Cp*Rh(III) π-allyl intermediate[4]. This methodology was also extended to alcohols and indoles as nucleophiles for allylic C–H etherification and arylation[5]. Glorius et. al. also published results detailing the use of electron-rich aromatics and arylboroxines as nucleophiles for allylic C-H arylation on disubstituted olefins[6, 7].

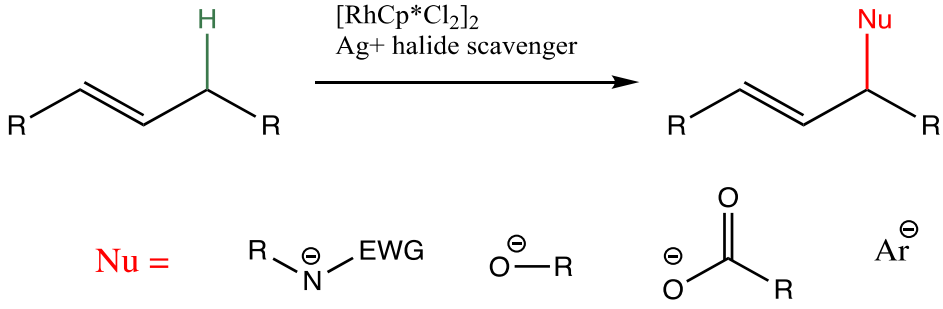


Figure 4: Blakey et. al., Glorius et. al. - Allylic C-H functionalization studies.

The allylic C-H amination reaction proceeds in a two-step catalytic pathway, first through a π-allyl intermediate utilizing an external oxidant to substitute the allylic C-H bond for a C-OAc bond. Subsequently, the reaction undergoes an S_N1 substitution to form the desired product[29]. In order to optimize the reaction for increased efficiency, further investigations were performed utilizing an internal oxidant.

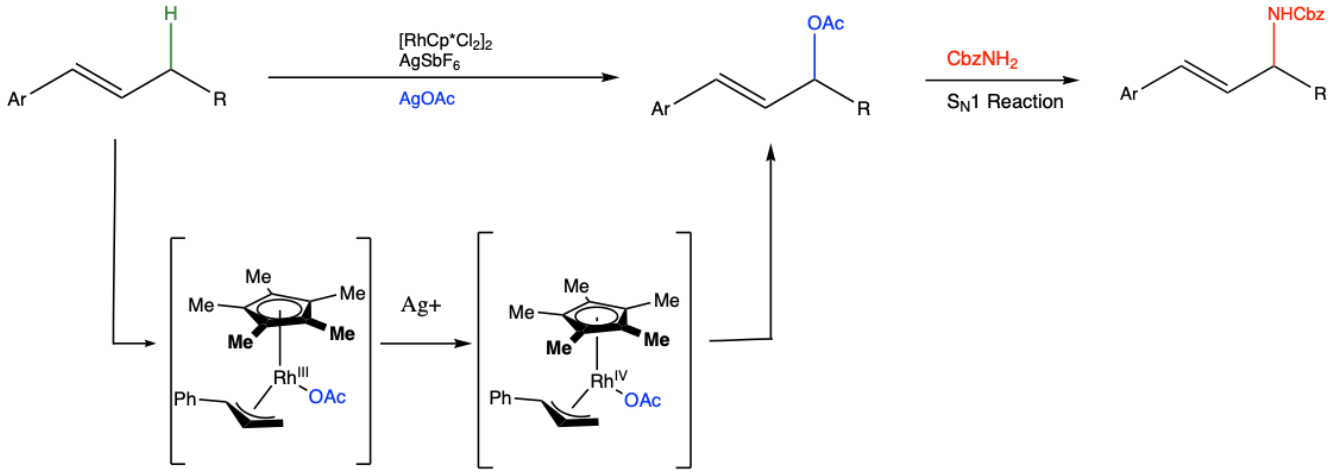


Figure 5: Reaction pathway for allylic C-H functionalization using an external oxidant - AgOAc[29].

Jacob Burman of the Blakey group recently published studies on utilizing dioxazolones for the allylic C-H amidation of unactivated mono-, di-, and trisubstituted olefins[14]. Rovis et. al. also

published work on using dioxazolone chemistry for allylic C-H amidation[8]. Dioxazolones have been proposed to be capable of oxidizing Cp*Rh(III) and Cp*Ir(III) complexes to the corresponding Cp*M(V) nitrenoids, utilizing the N-O bond of the dioxazolone as an internal oxidant. Dioxazolones are also surprisingly selective for the branched regioisomer position.

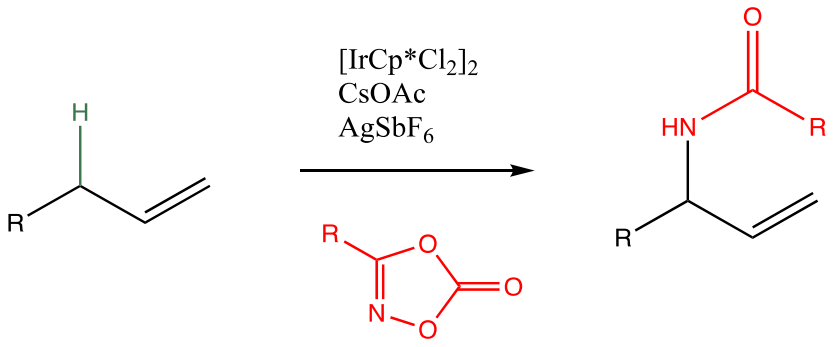


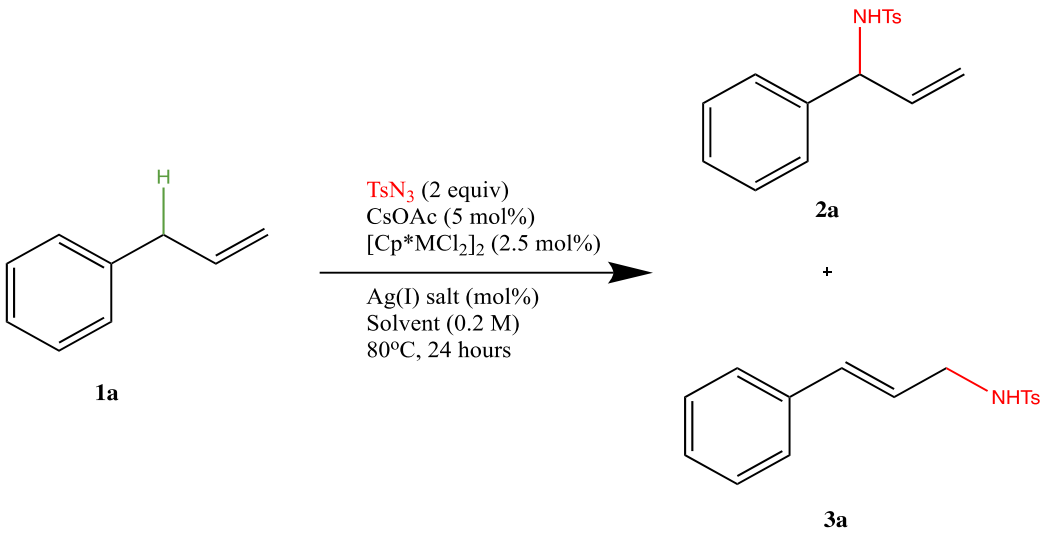
Figure 6: Blakey et. al., Rovis et. al. - Allylic C-H amidation using dioxazolones.

The issue with Dioxazolones is that due to their innate decomposition pathway during the metal catalysis, they can only perform amidations. Amides are not ideal protecting groups since they typically require harsh chemical conditions to remove. In my research, we build upon the previous studies on dioxazolone chemistry by investigating the use of tosyl azide (TsN_3) as a nitrogen source to selectively deliver tosylamides at the branched position of allylbenzenes. Tosyl azide has been utilized previously as a nitrenoid precursor in directed C(sp2)-H amination methods[25]. Tosyl azide was also hypothesized to be a good nitrenoid precursor since sulfonyl protecting groups can be more easily cleaved under reductive conditions, allowing for a more efficient transformation compared to that of a traditional amide protecting group. In studying C-

H sulfonamidation using tosyl azide, the study attempts to find a method of amidation that yields a practically simpler protecting group removal process.

Results:

Initial optimization studies were conducted by other graduate and undergraduate students in the Blakey group. $[RhCp^*Cl_2]_2$ was used as the precatalyst, $AgSbF_6$ as the halide scavenger, and CsOAc as the carboxylate base for the initial deprotonation at the allylic C-H position. Under initial conditions **(Table 1)**, allylbenzene successfully underwent sulfonamidation to produce the branched and linear products. Initially, Iridium(III) and Rhodium(III) catalysts were tested, and the amount of $AgSbF_6$ was increased. These reactions resulted in little to no yields. When $AgNTf_2$ was used as the halide scavenger, the branched regioisomer yield only increased to 23%, however, we observed no trace of the linear regioisomer. The selectivity for the branched regioisomer was striking and initiated greater focus on developing reaction conditions that can selectively increase the yield for the branched product. In doing so, it was noted that highly-flourinated solvents such as TFE and HFIP increased the yield dramatically, while still showing no traces of the linear regioisomer. In cases where HFIP was required to be boiled above the boiling point, reactions were performed in a sealed tube.



Trial	$[MCp^*Cl_2]_2$	Ag(I) (mol %)	Solvent	% Yield **2a**	%Yield **3a**
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10)	DCE	13	4
2	$[IrCp^*Cl_2]_2$	$AgSbF_6$ (10)	DCE	17	8
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (40)	DCE	trace	0
4	$[IrCp^*Cl_2]_2$	$AgSbF_6$ (40)	DCE	trace	0
5	$[IrCp^*Cl_2]_2$	$AgBF_4$ (10)	DCE	<5	trace
6	$[IrCp^*Cl_2]_2$	AgOTs (10)	DCE	<5	trace
7	$[IrCp^*Cl_2]_2$	$AgNTf_2$ (10)	DCE	23	0
8	$[IrCp^*Cl_2]_2$	$AgNTf_2$ (10)	TFE	55	0
9	$[IrCp^*Cl_2]_2$	$AgNTf_2$ (10)	HFIP	60	0

Table 1: Sulfonamidation reaction on allylbenzene – optimization trials. Includes schematic of the reaction along with significant trials. Reactions were run using 0.1 mmol allylbenzene, 0.4 mmol TsN_3, 0.005 mmol CsOAc, 0.0025 mmol $AgNTf_2$, 0.0025 $[IrCp^*Cl_2]_2$. Isolated Yields.

My research within the Blakey group primarily involved optimization and running reactions on allylbenzene derivatives to test the flexibility of the reaction on similar substrates. With a yield of 60% for the allylbenzene substrate, we turned our attention to the substrate scope – an examination on a reaction's tolerance for substrates that are similar to allylbenzene (its

derivatives). I ran reactions under General Procedure B for substrates **1b, c, d, e f**, yielding products **2b, c, d, e, f.**

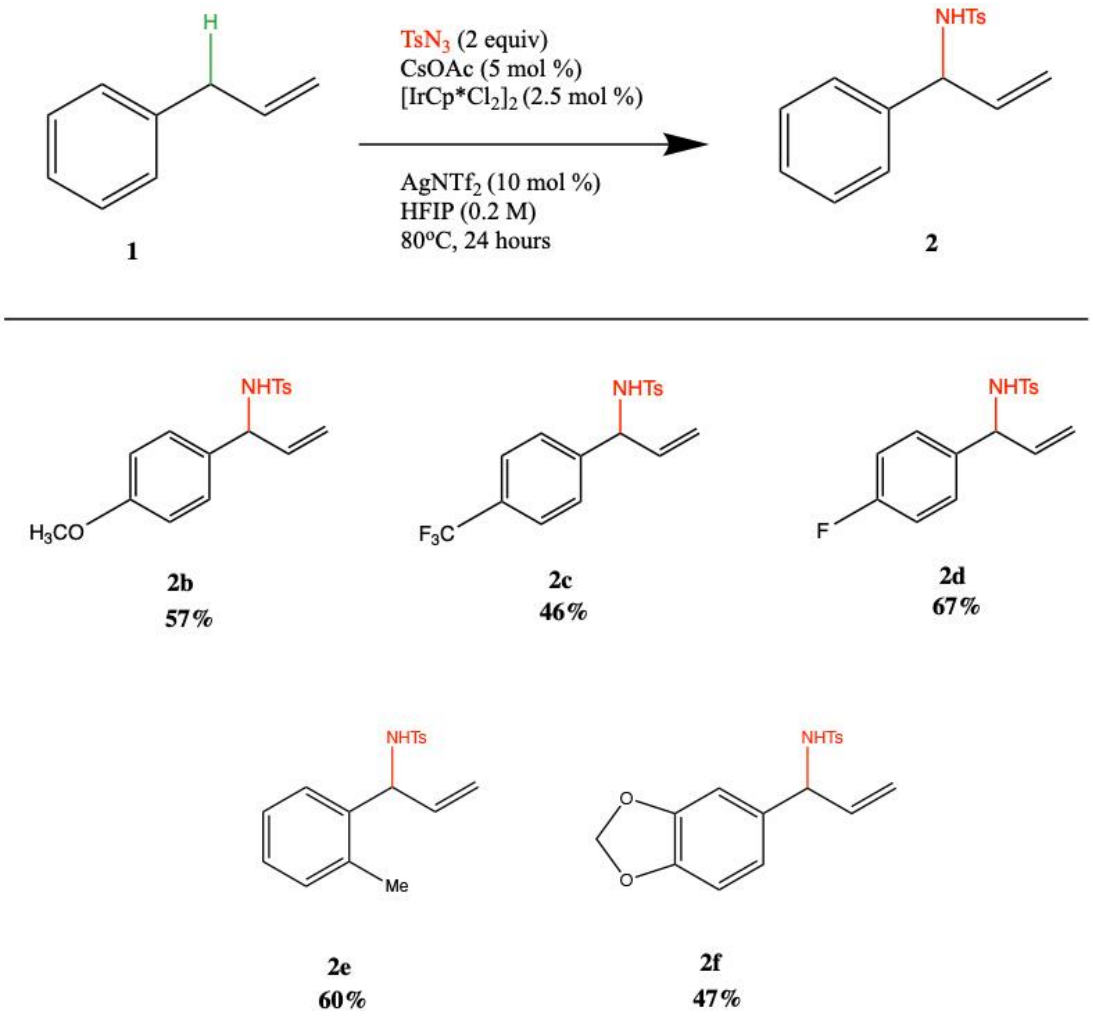


Figure 7: Substrate Scope – Steven Chen.

In addition to the reactions I ran, the remaining substrate scope was performed by other graduate students in the lab. Their results are shown in the following table.

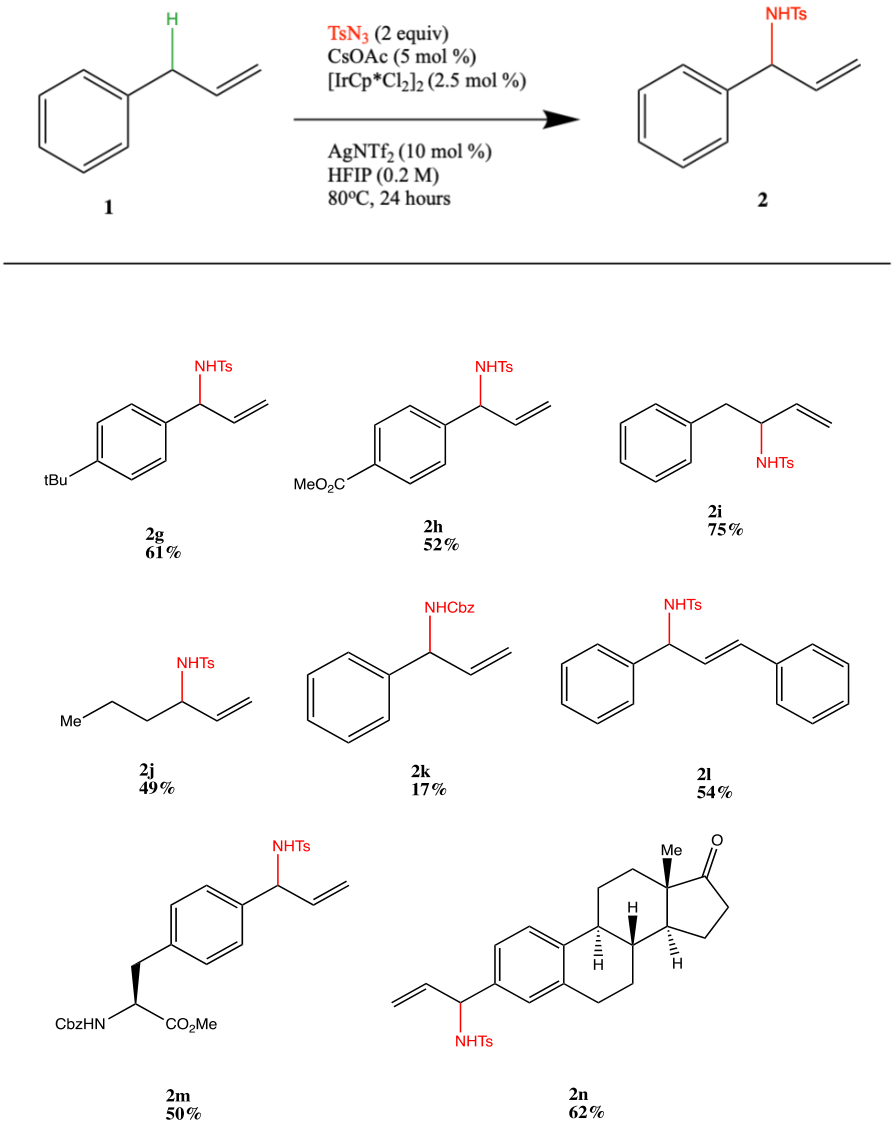
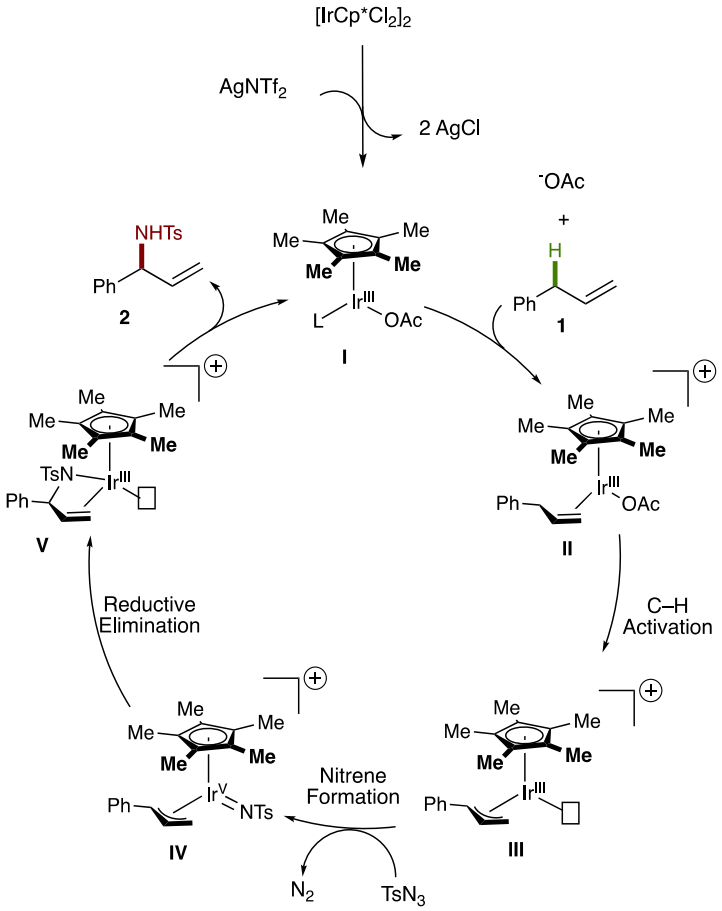


Figure 8. Substrate Scope – Amaan Kazerouni, Taylor Nelson, Kim Sharp.

It is important to establish reaction sufficiency among the derivatives so that there is empirical evidence that the reaction performs well not only on a starting substrate (allylbenzene) but also on species that are similar to it at the molecular level. The sulfonamidation displayed strong

tolerance among various substrate conditions at the electronics and sterics level. Substrates with strong electron-donating groups (electron rich) **(1b and 1g)** yielded excellent yields at >50%. Species with strong electron-withdrawing groups **(1c and 1h)** also yielded satisfactory results. The sulfonamidation reaction is also tolerant in aryl-flouride conditions as indicated by **1d**, with a yield of 67%. Safrole **(1f),** a derivative with even more pronounced electron density, yielded a 47% yield after an increased reaction time to 48 hours (my initial reaction under 24 hours had a lower yield, and the final reaction was performed by other graduate students in lab). The remaining reactions (performed by other graduate students) also yielded excellent results: O-allyltoluene also required 48 hours to produce a 60% yield of its product **(1e),** presumably due to the steric hindrance of the ortho-methyl group. 4-Phenylbutene **(1i)** and 1-hexene **(1j)** proceeded through nonconjugated π-allyl complexes, which also ended up pushing the reaction time to 48 hours, both with excellent yields. The sulfonamidation reaction was successful on a 1,2 disubstituted olefin **(1l)** as well – indication that the reaction proceeds smoothly on internal olefins. The reaction also works well when performed on key biological molecules **(1m and 1n).** The crude reaction mixtures consisted primarily of branched tosylamide products and small amounts of starting material. Occasionally, $TsNH_2$ was observed in the crude ^1H NMR. Otherwise, no additional products were observed. It is important to note that for substrate **1k**, with the sulfonamidation done using $CbzN_3$ as the nitrogen source, produced a yield of 17%. In subsequent experiments on my project, we will continue to examine the effect of Cbz-insertion on the branched regioisomer.

The sulfonamidation reaction is hypothesized to proceed in a similar fashion to that of the dioxazolone allylic C-H amidation. The halide scavenger – $AgNTf_2$ along with CsOAc – activates the Iridium(III) catalyst initially **(I)**. Following coordination of the olefin **(1)**, a concerted-metalation-deprotonation (CMD) of the allylic C-H bond produces a Cp*Ir(III)- π-allyl complex **(II)** – resulting in the C-H bond activation **(III)** as well as formation of acetic acid in solution. Nitrogen gas release from the decomposition of TsN_3 drives the forward reaction, pushing towards the formation of the Cp*Ir(V) nitrenoid **(IV).** The nitrenoid complex undergoes reductive elimination to form the C-N bond at the original allylic position of the π-allyl complex **(V).** Protodemetalation of the tosylamide complex produces the branched sulfonamide regioisomer **(2)** – our intended product. The Cp*Ir(III) catalyst is also regenerated.



Schematic 1: Sulfonamidation reaction pathway.

Further Studies:

We published the results of the successful sulfonamidation reaction in the *Journal of Organic Chemistry* in August 2019[9]. Subsequently, I proceeded to investigate the implications of a benzyl carbamate insertion to the branched regioisomer of allylbenzene and its derivatives.

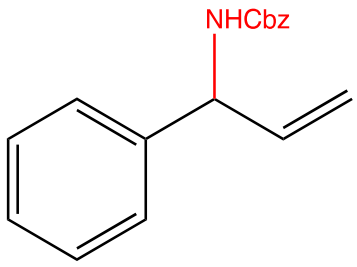
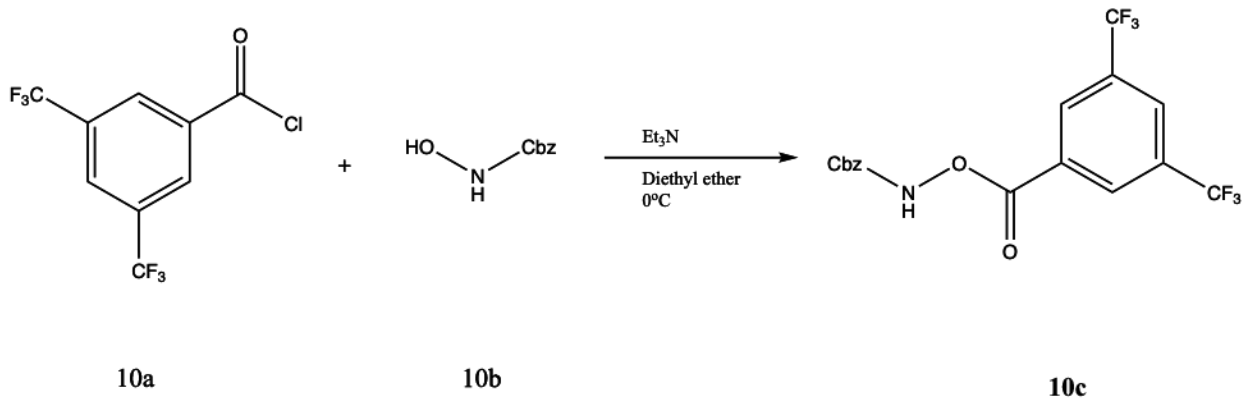


Figure 9: Intended product of benzyl carbamate insertion on allylbenzene **(2k).**

As the -Cbz functional group is a more pharmaceutically practical functional group (rather than -NHTs), it is important to understand how the reaction can be optimized to deliver a much greater yield with the benzyl carbamate functional group. I proceeded with similar conditions as the sulfonamidation reaction under General Procedure B in order to find a starting place for the research. In the previous sulfonamidation reaction, using $CbzN_3$ as a substrate yielded a branched regioisomer yield of 17%. In an attempt to increase the yield of the reaction, I

hypothesized that a higher yield could be achieved by using a substrate with a better leaving group, such as in a bis-trifluoromethyl-substituted compound **(10c),** which was reported in recent literature by Chang et. al.[10]. In synthesizing the proper substrate, 3,5-bis(trifluoromethyl)benzoyl chloride **(10a)** was reacted with benzyl N-hydroxy-carbamate **(10b)** to produce the intended bis-trifluoromethyl-substituted compound **(10c)** for the insertion reaction.

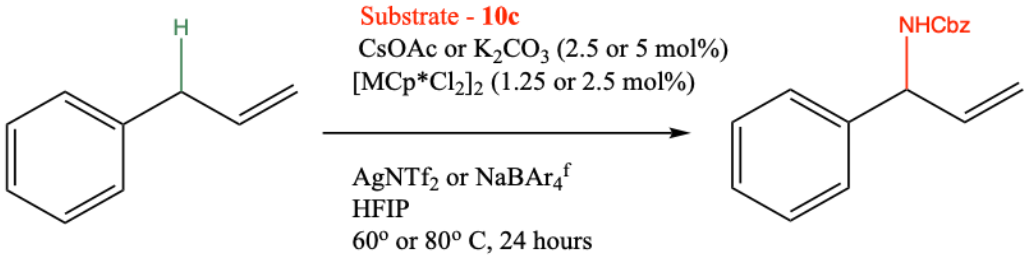


10a 10b 10c

Figure 10: Synthesis of a bis-trifluoromethyl-substitued substrate **(10c)**.

The reaction was run initially under conditions similar to General Procedure B, with the -Cbz substrate **(10c)** being used in place of TsN_3. This reaction yielded no trace of the intended branched regioisomer product **(trial 1)**. In trying to optimize the reaction to at least attain a yield for the branched regioisomer, the halide scavenger was switched to $NaBAr_{f4}$ from $AgNTf_2$, and CsOAc was switched to K_2CO_3. This switch was inspired from Chang et. al. where he utilizes those conditions to perform a reaction of similar scope[10]. Since the -Cbz substrate does not dissolve in TFE (which was used for the highest yield in Chang. Et. al.), HFIP was used as per

the original procedure done before[9]. The allylic benzyl carbamate reaction yielded trace amounts of the linear regioisomer, as detected through ^{1}H NMR spectroscopy, and no trace of the branched regioisomer.



Trial	[MCp*Cl$_2$]$_2$	Halide Scavenger	Base	Solvent and Temperature	Yield
1	[IrCp*Cl$_2$]$_2$	AgNTf$_2$	CsOAc	HFIP 80$_o$C	None
2	[IrCp*Cl$_2$]$_2$ (2.5 mol %)	NaBAr$_{f4}$ (10 mol %)	K$_2$CO$_3$	HFIP 60$_o$C	None, trace amounts of linear regioisomer in crude reaction products.

Table 2: Benzyl carbamate insertion initial trials. Trial 2 yielded trace results of the linear regioisomer, but no traces of the branched regioisomer were detected throughout.

Another substrate was also used to test the feasibility of the sulfonamidation reaction – Cbz-NH-OPiv. The substrated was synthesized based on previous literature[11] and reacted under conditions similar to that of General Procedure B, with the desired substrate **(11c)** in place of TsN$_3$ and TFE

being used instead of HFIP as the solvent. The desired substrate was synthesized using benzyl-hydroxycarbamate **(11a)** and 2,2-dimethylpropanyl-chloride **(11b).**

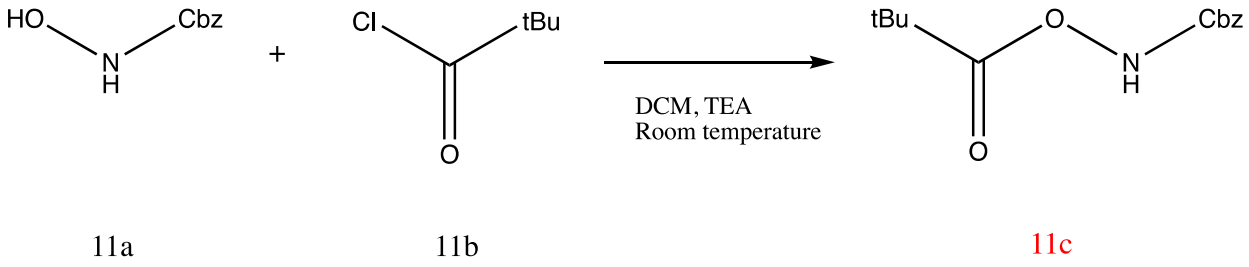
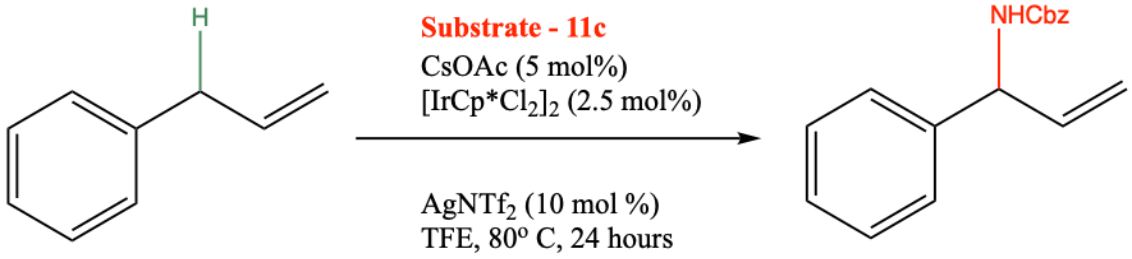


Figure 11: Synthesis of OPiv-NH-Cbz.



Trial	[MCp*Cl2]2	Halide Scavenger	Base	Solvent and Temperature	Yield
1	[IrCp*Cl2]2 (2.5 mol %)	AgNTf2 (10 mol %)	CsOAc (5 mol %)	TFE 80oC	None.

Table 3: Benzyl carbamate insertion with OPiv-NH-Cbz.

The reaction yielded no traces of the intended branched regioisomer. Continued studies will be performed after my time at Emory to further investigate the sulfonamidation reaction and how it

can be optimized to increase the yield for the branched regioisomer with a benzyl carbamate insertion.

In addition to my work optimizing for the benzyl carbamate insertion, I also helped the Blakey group prepare a key substrate for ongoing research in the lab. Recent work from Rovis et. al. has illuminated a mechanism for Rh(III)-catalyzed pyrrolidine formation through unactivated terminal alkenes as 4-carbon partners[12]. Our goal in moving forward is to test enantioselective versions of the Rhodium catalyst used by Rovis et. al. to see if they can enantioselectively aziridinate an unactivated olefin. I helped to synthesize a key substrate for later experimentations – Ts- NH-OPiv **(12c)**[13].

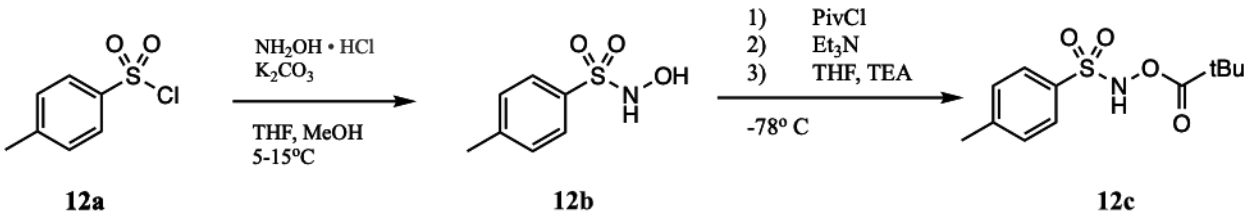


Figure 12: Synthesis of Ts- NH-OPiv **(12c).**

The reaction proceeded smoothly and I was successfully able to synthesize the desired product at a 67.3% yield.

Conclusion:

During my time in the Blakey group, I was able to successfully learn and perform key sulfonamidation reactions on allylbenzene derivatives to aid with the development of a substrate scope. My results indicated strong functional group tolerance for the sulfonamidation at the allylic position for allylbenzene, using TsN_3 as the nitrenoid precursor. It is propsed that the reaction proceeds via a mechanism similar to that of an allylic C-H amidation using dioxazolone chemistry, through an inner-sphere C-N reductive elimination of a Cp*Ir(III)- π-allyl nitrenoid complex. In addition, I was able to further optimize and test out the allylic C-H benzyl carbamate insertion on allylbenzene. Although I did not achieve a significant yield, there are new leads to which further research can be generated to examine the feasibility of an allylic benzyl carbamate insertion at greater yields. I was also able to aid the Blakey group in synthesizing a key substrate for further research on enantioselective aziridination on unactivated olefins using metal catalysts.

Experimental Information / Supplemental Info (SI):

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with anhydrous solvents in either the oven or in flame-dried glassware under the standard Schlenk technique. Anhydrous dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were obtained by passage through activated alumnia using a *Glass Contours* solvent purification system. 1,2-Dichloroethane (DCE), 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were distilled over CaH_2 and stored over activated molecular

sieves. Solvents for workup, extraction, and column chromatography were used as received from commercial suppliers without purification.

$Pd(PPh_3)_4$, LiCl, K_2CO_3, $NaBAr_{f4}$, $AgSbF_6$, $AgBF_4$, AgOTs, $AgNTf_2$, CsOAc, $[Cp^*IrCl_2]_2$, and $[Cp^*RhCl_2]_2$ were stored and weighed in a nitrogen-filled glovebox. Tosyl azide (TsN_3)[14], $[IrCp^*Cl_2]_2$,and$[RhCp^*Cl_2]_2$ [15] were synthesized according to previously reported methods. All other chemicals were purchased from Sigma-Aldrich, Strem Chemicals, Oakwood Chemicals, Alfa Aesar, or Combi-Blocks, and were all used without further purification.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were taken on the following: Varian Inova 600 spectrometer (600 MHz ^1H, 151 MHz ^{13}C), Bruker 600 spectrometer (600 MHz ^1H, 151 MHz ^{13}C), Varian Inova 500 spectrometer (500 MHz ^1H, 126 MHz ^{13}C), Varian Inova 400 spectrometer (400 MHz ^1H, 100 MHz ^{13}C). All were taken at room temperature in $CDCl_3$ (chlorofrom, neutralized and dried over anhydrous K_2CO_3) with an internal $CHCl_3$ as the reference (7.26ppm for ^1H, 77.16 ppm for ^{13}C), unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (J values) were reported in Hertz (Hz). Multiplicity is indicated through standard abbrievations (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = mulitplet, br = broad). Infrared (IR) spectra were taken on a Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded using a Thermo Electron Corporation Finigan LTQFTMS (Mass Spectrometry Facility, Emory University). Analytical thin layer chromatography (TLC) were performed on precoated glass backed Silicycle SiliaPure 0.25 mm silica gel 60 plates and

visualized with UV light, ethanolic p-anisaldehyde, or aqueous potassium permanganate ($KMnO_4$). Flash column chromatography was performed using Silicycle SiliaFlash F60 silica gel (40-63 um) on a Biotage Isolera One system. Preparatory TLC was performed on precoated glass backed Silicycle SiliaPure 1.0 mm silica gel 60 plates.

The olefinic substrates for the reaction came from commercial sources or were synthesized through previously known procedures. Substrates **1a, 1b, 1e,** and **1f** were used without further purification upon purchase from commercial sources. **1g**[17]**, 1h**[18]**, 1l**[19]**,** and **1m**[20] were prepared according to previously reported procedures.

General Procedure A: Optimization of Allylic C−H Sulfamidation Reaction. (this procedure details the steps taken towards optimization of reaction conditions for the sulfonamidation of -NHTs onto allylbenzene. The features of this reaction were optimized primarily by Amaan M. Kazerouni and Taylor F. Nelson from the Blakey group. The reaction served as a precedent and guide to my later work with the substrate scope) In a nitrogen-filled glovebox, CsOAc (0.0009 g, 0.005 mmol, 0.05 equiv), the Ag halide scavenger (0.010− 0.040 mmol, 0.10−0.40 equiv, as indicated), and $[MCp^*Cl_2]_2$ (0.0025 mmol, 0.025 equiv) were added to an oven-dried 4 mL vial along with a magnetic stir bar and a Teflon-septum screw cap. The vial was capped and brought out of the glovebox. The indicated solvent (0.50 mL), allylbenzene **(1a)** (0.013 mL, 0.10 mmol, 1 equiv, with a microsyringe), and TsN_3 (0.030 mL, 0.20 mmol, 2 equiv, with a microsyringe) were added. The vial was then sealed with Teflon tape and parafilm and placed in an aluminum heating block preheated to 80 °C, and stirred for 24 h. Afterwards, the vial was removed from

heat and allowed to cool to room temperature. The reaction was filtered through a pipet containing Celite with EtOAc (10 mL), and the filtrate was concentrated under reduced pressure. The product was purified through flash chromatography on silica gel (10−30% EtOAc in Hexanes), providing the branched tosylamide (**2a)** and the linear tosylamide (**3a)**. Spectral data match those previously reported in the literature[7, 26].

4-Methyl-N-(1-phenylallyl)benzenesulfonamide (2a). $_1$H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, J = 8.3 Hz, 2H), 7.24−7.18 (m, 5H), 7.12−7.07 (m, 2H), 5.86 (ddd, J = 16.9, 10.5, 5.7 Hz, 1H), 5.16−5.08 (m, 2H), 4.97−4.86 (m, 2H), 2.39 (s, 1H) ppm.

N-Cinnamyl-4-methylbenzenesulfonamide (3a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, J = 8.3 Hz, 2H), 7.42−7.10 (m, 7H), 6.44 (d, J = 15.9 Hz, 1H), 6.02 (dt, J = 15.8, 6.4 Hz, 1H), 4.46 (t, J = 6.2 Hz, 1H), 3.76 (td, J = 6.3, 1.5 Hz, 2H), 2.42 (s, 3H) ppm.

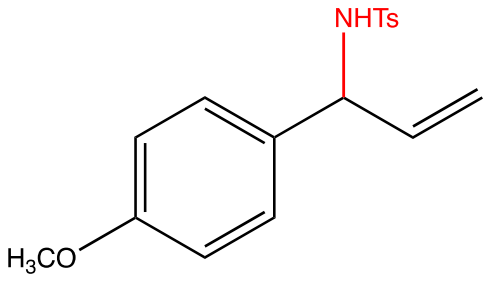
General Procedure B: Allylic C−H Sulfamidation of Allylbenzene Derivatives.

In a nitrogen-filled glovebox, CsOAc (0.0019 g, 0.010 mmol, 0.05 equiv), $AgNTf_2$ (0.0078 g, 0.020 mmol, 0.10 equiv), and $[IrCp^*Cl_2]_2$ (0.0040 g, 0.005 mmol, 0.025 equiv) were added to an oven-dried 7 mL sealed pressure tube (with screw cap) and a magnetic stir bar. The tube was sealed in the glovebox before being brought out. HFIP (0.5 mL) and TsN_3 (0.40 mmol, 2 equiv) were added through the side arm of the tube. Allylbenzene derivatives with known densities were added via microsyringe through the side arm of the pressure tube (0.20 mmol, 1 equiv),

followed by HFIP (0.5 mL) to wash the sides of the tube. All other allylbenzene derivatives (0.20 mmol, 1 equiv) were added as stock solutions in HFIP (0.5 mL). The tube was sealed and placed in an aluminum heating block preheated to 80 °C, and stirred for 24−48 h as indicated. The tube was then removed from heat and allowed to cool to room temperature. The reaction mixture was filtered through a pipet containing Celite with EtOAc (15 mL), and the filtrate was concentrated under reduced pressure. The product was purified through flash chromatography on silica gel (10−30% EtOAc in Hexanes), providing the tosylamide products.

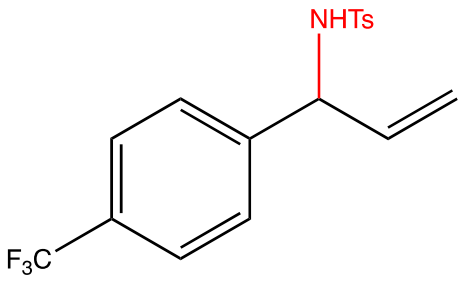
Characterization of Allylic C−H Sulfamidation Products:

*HRMS spectra as well as the majority of ^{13}C spectra were mostly taken and analyzed by graduate students in the Blakey group. ^{1}H NMR spectra for compounds outside of the ones I did for the sulfonamidation substrate scope were taken and analyzed by graduate students in the Blakey group as well.



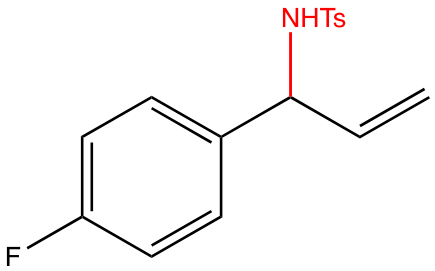
N- (1-(4-Methoxyphenyl)allyl)-4-methylbenzenesulfonamide (2b). Synthesized according to General Procedure B, using 4-allylanisole **(1b)** (0.031 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061

mL, 0.40 mmol, 1 equiv), $[IrCp^*Cl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2b** (0.0365 g, 57% yield). Spectral data match those previously reported in the literature[28]. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 7.63 (d, J = 8.5 Hz, 2H), 7.2 (d, J = 8.6Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 5.85 (ddd, J = 17.2, 10.1, 5.7 Hz, 1H), 5.14-5.08 (m, 2H), 4.95 (d, J = 7.5Hz, 1H), 4.90-4.85 (m, 1H), 3.75 (s, 3H), 2.39 (s, 3H) ppm.

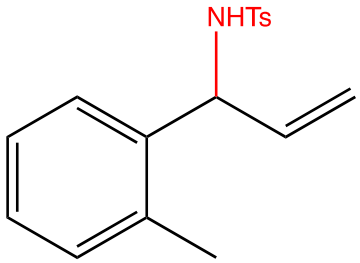


4-Methyl-N-(1-(4-(trifluoromethyl)phenyl)allyl)benzene- sulfonamide (2c). Synthesized according to General Procedure B using 4-allyltrifluorotoluene **(1f)** (0.033 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[IrCp^*Cl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2f** (0.033 g, 46% yield). Spectral data match those previously reported in the literature[8]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.21 (d, J=8.5Hz, 2H), 7.13 (d,J = 8.0Hz, 2H), 5.84 (ddd, J =16.3, 10.3, 5.9 Hz, 1H), 5.37 (d, J = 7.4 Hz, 1H), 5.16 (d, J = 10.3 Hz, 1H), 5.11−4.97 (m, 2H), 2.36 (s, 3H)

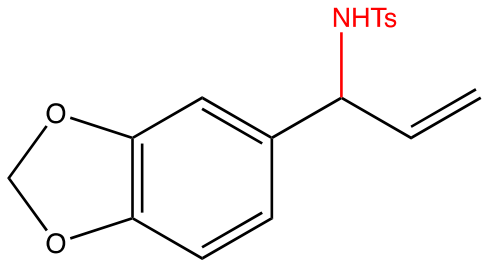
ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz) δ 143.7, 143.27, 143.25, 137.4, 136.4, 130.1 (q, $J_{C–F}$ = 32.5 Hz), 129.6, 129.5, 127.7, 127.3, 125.5 (q, $J_{C–F}$ = 3.8 Hz), 117.9, 59.6, 21.5 ppm; HRMS (+ APCI) calculated for $C_{17}H_{20}F_3N_2O_2S$ $[M + NH_4]^+$ 373.1198, found 373.1192.



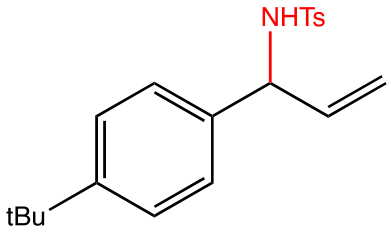
N-(1-(4-Fluorophenyl)allyl)-4-methylbenzenesulfonamide (2d). Synthesized according to General Procedure B using 1-allyl-4- fluorobenzene **(1e)** (0.027 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol. 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2e** (0.0422 g, 67% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61 (d, J = 8.3 Hz, 2H), 7.19 (dd, J = 8.6, 0.8 Hz, 2H), 7.11−7.05 (m, 2H), 6.89 (t, J = 8.7 Hz, 2H), 5.83 (ddd, J = 17.0, 10.3, 5.8 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 5.10−5.06 (m, 2H), 4.96− 4.90 (m, 1H), 2.39 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 151 MHz) δ 162.2 (d, $J_{C=F}$ = 246.3 Hz), 143.5, 137.6, 136.9, 135.3 (d, $J_{C=F}$ = 3.2 Hz), 129.5, 129.0 (d, $J_{C=F}$ = 8.2 Hz), 127.3, 117.1, 115.5 (d, $J_{C=F}$ = 21.5 Hz), 59.3, 21.6; HRMS (+ APCI) calculated for $C_{16}H_{17}FNO_2S$ [M + H] 306.0964, found 306.0954.



4-Methyl-N-(1-(o-tolyl)allyl)benzenesulfonamide (2e). Prepared according to General Procedure B using 1-allyl-2-methylbenzene **(1h)** (0.029 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol. 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 48 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2h** (0.0359 g, 60% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.60 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.07−7.01 (m, 3H), 5.85 (ddd, J = 17.1, 10.3, 5.5 Hz, 1H), 5.21−5.15 (m, 1H), 5.10 (dd, J = 10.3, 1.3 Hz, 1H), 5.06−4.96 (m, 1H), 4.85 (d, J = 7.2 Hz, 1H), 2.37 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 143.3, 137.8, 137.4, 137.1, 135.6, 130.8, 129.5, 127.8, 127.2, 126.9, 126.4, 116.9, 56.5, 21.6, 19.3 ppm; HRMS (+ APCI) calculated for $C_{17}H_{20}NO_2S$ $[M + H]^+$ 302.1215, found 302.1204.

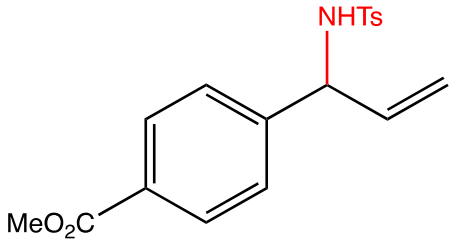


N-(1-(Benzo[d][1,3]dioxol-5-yl)allyl)-4-methylbenzene- sulfonamide (2f). Prepared according to General Procedure B, using safrole **(1g)** (0.029 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 3 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 48 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2g** (0.0311 g, 47% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, J = 8.3 Hz, 2H), 7.21(d, J = 8.5 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.57 (dd, J = 8.0, 1.8 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 5.90 (d, J = 1.5 Hz, 1H), 5.89 (d, J = 1.4 Hz, 1H), 5.82 (ddd, J = 17.2, 10.1, 5.4 Hz, 1H), 5.16−5.08 (m, 2H), 4.88−4.81 (m, 2H), 2.40 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz) δ 147.9, 147.3, 143.4, 137.8, 137.2, 133.4, 129.5, 127.4, 120.8, 116.9, 108.3, 107.7, 101.26, 77.2, 59.8, 21.6 ppm; HRMS (+ APCI) calculated for $C_{17}H_{18}NO_4S$ $[M + H]^+$ 332.0957, found 332.0943.



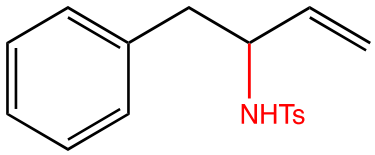
N-(1-(4-(tert-Butyl)phenyl)allyl)-4-methylbenzenesulfonamide (2g). Prepared according to General Procedure B, using 1-allyl-4-(tert-butyl)benzene **(1c)** (0.0350 g, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol. 0.05 equiv) in

HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2c** (0.0422 g, 61% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 5.87 (ddd, J = 17.1, 10.3, 5.9 Hz, 1H), 5.20−5.05 (m, 2H), 5.01 (d, J = 7.3 Hz, 1H), 4.95−4.91 (m, 1H), 2.37 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz) δ 150.8, 143.1, 137.9, 137.4, 136.4, 129.4, 127.4, 126.9, 125.6, 116.7, 59.8, 34.6, 31.4, 21.6 ppm; HRMS (+ APCI) calculated for $C_{20}H_{29}N_2O_2S$ $[M + NH_4]^+$ 361.1950, found 361.1940.

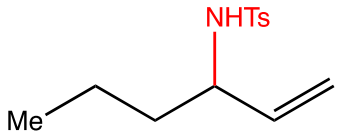


Methyl-4-(1-((4-methylphenyl)sulfonamido)allyl)benzoate (2h). Prepared according to General Procedure B, using 4-methylallylbenzoate **(1d)** (0.0350 g, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol. 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2d** (0.0361 g, 52% yield). ^{1}H NMR ($CDCl_3$, 600 MHz), δ 7.85 (d, J = 8.3 Hz, 2H), 7.61(d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.83 (ddd, J = 16.7, 10.3, 6.0 Hz, 1H), 5.37 (d, J = 7.7 Hz, 1H), 5.16−5.03 (m, 2H), 5.01−4.95 (m, 1H), 3.89

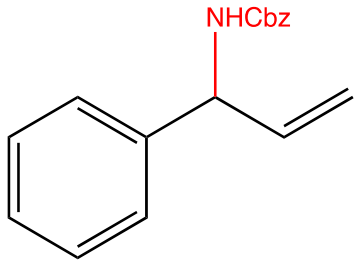
(s, 3H), 2.37 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 151 MHz) δ 166.8, 144.5, 143.6, 137.6, 136.5, 130.0, 129.8, 129.6, 127.3, 126.5, 117.7, 59.7, 52.3, 21.6 ppm; HRMS (+ APCI) calculated for $C_{18}H_{23}N_2O_4S$ $[M + NH_4]^+$ 363.1379, found 363.1376.



4-Methyl-N-(1-phenylbut-3-en-2-yl)benzenesulfonamide (2i). Prepared according to General Procedure B, using 4-phenylbutene **(1i)** (0.030 mL, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[IrCp^*Cl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 48 h. Purified by flash chromatography on silica gel (10−40% EtOAc in Hexanes) to provide **2i** (0.045 g, 75% yield). Spectral data match those previously reported in the literature.[22] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, J = 8.3 Hz, 2H), 7.27−7.16 (m, 5H), 7.05−7.00 (m. 2H), 5.68 (ddd, J = 16.8, 10.4, 6.1 Hz, 1H), 5.10−4.96 (m, 2H), 4.49 (d, J = 7.3 Hz, 1H), 4.07−3.95 (m, 1H), 3.08−2.61 (m, 2H), 2.41 (s, 3H) ppm.

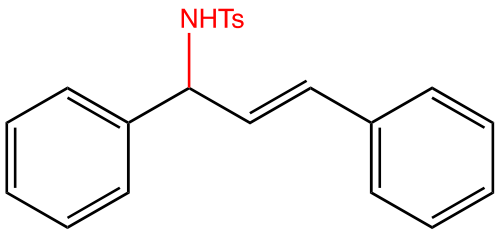


N-(Hex-1-en-3-yl)-4-methylbenzenesulfonamide (2j). Prepared following General Procedure B using 1-hexene (0.025 mL, 0.20 mmol, 1 equiv). Purified by flash chromatography on silica gel (0− 100% Et_2O in Hexanes) to provide a material (0.025 g, 49% yield) as an inseparable mixture of regioisomers (4.5:1.5:1 r.r.). Spectral data match those previously reported in the literature.[23, 24] ^1H NMR ($CDCl_3$, 399 MHz): δ 7.73 (m, 28H), 7.28 (m, 28H), 5.53 (ddd, J = 17.0, 10.3, 6.6 Hz, 9H), 5.45 (dt, J = 15.4, 6.3 Hz, 2H), 5.41−5.28 (m, 3H), 5.14 (dd, J = 15.4, 6.6 Hz, 2H), 5.05 (ddd, J = 15.3, 7.4, 1.7 Hz, 3H), 5.00−4.93 (m, 18 H), 4.58 (d, J = 7.9 Hz, 9H), 4.50 (d, J = 7.6 Hz, 5H), 3.97−3.82 (m, 2H), 3.76 (quint, J = 6.8 Hz, 9H), 3.61 (quint, J = 7.2 Hz, 3H), 2.42 (s, 42H), 1.95−1.80 (m, 5H), 1.56−1.16 (m, 33H), 0.83 (t, J = 7.3 Hz, 42H) ppm.

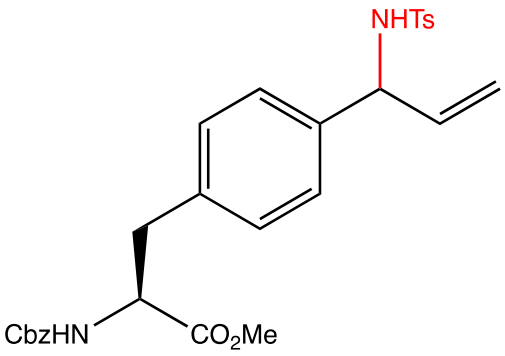


Benzyl (1-Phenylallyl)carbamate (2k). Prepared according to General Procedure B using allylbenzene **(1a)** (0.026 mL, 0.20 mmol, 1 equiv), $CbzN_3$ (0.071 g, 0.40 mmol, 2 equiv), $[IrCp^*Cl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2j** (0.0091 g, 17% yield). Spectral data match those previously reported in the literature[27]. ^1H NMR ($CDCl_3$, 500

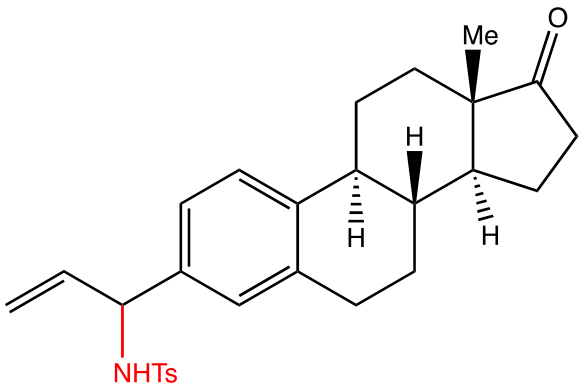
MHz) δ 7.40−7.27 (m, 10H), 6.01 (ddd, J = 16.3, 3 10.6, 5.3 Hz, 1H), 5.37 (br s, 1H), 5.26 (br s, 1H), 5.24−5.20 (m, 2H), 5.16−5.09 (m, 2H) ppm.



(E)-N-(1,3-Diphenylallyl)-4-methylbenzenesulfonamide (2l). Prepared following General Procedure B using 1,3-trans-diphenylpropene (0.038 mL, 0.20 mmol, 1 equiv). Purified by flash chromatography on silica gel (10−30% EtOAc in Hexanes) to provide **2m** (0.0393 g, 54% yield). Spectral data match those previously reported in the literature[4]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, J = 8.3 Hz, 3 2H), 7.28−7.10 (m, 12H), 6.33 (dd, J = 15.8, 1.2 Hz, 1H), 6.07 (dd, J = 15.8, 6.8 Hz, 1H), 5.22 (d, J = 7.3 Hz, 1H), 5.11 (td, J = 7.1, 1.3 Hz, 1H), 2.31 (s, 3H) ppm.

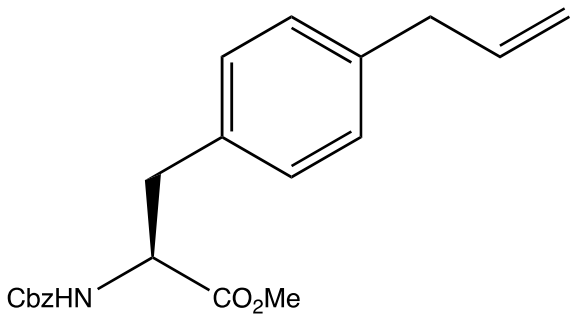


Phenylalanine-Derived Allylbenzene Tosylamide (2m). Prepared according to General Procedure B using Cbz-(p-allyl)-Phe-OMe (1k) (0.071 g, 0.20 mmol, 1 equiv), TsN_3 (0.061 mL, 0.40 mmol, 1 equiv), $[Cp^*IrCl_2]_2$ (0.0040 g, 0.005 mmol, 0.0025 equiv), $AgNTf_2$ (0.0078 g, 0.02 mmol, 0.10 equiv), and CsOAc (0.0019 g, 0.01 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (30−50% EtOAc in Hexanes) to provide the desired product with $TsNH_2$ impurities. Additional purification by preparatory TLC (30% EtOAc in Hexanes, 2 sweeps) provided **2k** (0.0495 g, 50% yield) as an inseparable mixture of diastereomers (1:1 d.r.). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.64 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.40−7.30 (m, 10H), 7.21 (d, J = 8.3 Hz, 2H), 7.21(d, J = 7.9Hz, 2H), 7.03 (d, J = 8.1Hz, 4H), 6.96 (d, J = 8.2Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 5.82 (ddd, J = 16.1, 10.3, 6.0 Hz, 1H), 5.82, (ddd, J = 17.0, 10.3, 6.0 Hz, 1H), 5.19−5.05 (m, 10H), 4.90 (q, J = 5.7 Hz, 2H), 4.73(d, J = 7.3Hz, 1H), 4.73 (d, J = 7.3Hz, 1H), 4.62 (q, J = 6.0 Hz, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.09 (dd, J = 13.9, 5.7 Hz, 1H), 3.08 (dd, J = 14.0, 5.7 Hz, 1H), 3.03 (dd, J = 14.2, 6.2 Hz, 2H), 2.39 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz) δ 171.9, 155.7, 143.5, 138.5, 137.8, 137.07, 137.05, 136.3, 135.1, 129.73, 129.71, 129.6, 129.5, 128.7, 128.4, 128.3, 127.5, 127.4, 117.2, 117.1, 67.2, 59.6, 54.8, 52.5, 37.9, 37.9, 21.6 ppm; HRMS (− APCI) calculated for $C_{28}H_{29}N_2O_6S$ $[M - H]^-$ 521.1746, found 521.1748.



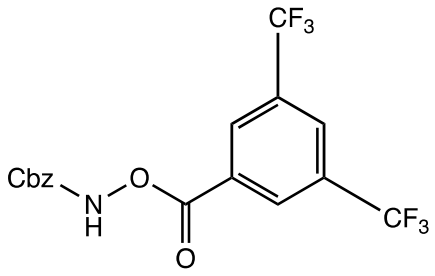
Estrone-Derived Allylbenzene Tosylamide (2n). Prepared following General Procedure B using estrone allylbenzene **(1l)** (0.0503 g, 0.171 mmol, 1 equiv), TsN_3 (0.0524 mL, 0.342 mmol, 2 equiv), $[IrCp^*Cl_2]_2$ (0.0034 g, 0.0043 mmol, 0.0025 equiv), $AgNTf_2$ (0.0063 g, 0.0171 mmol, 0.10 equiv), and CsOAc (0.0016 g, 0.0085 mmol, 0.05 equiv) in HFIP (1.0 mL) at 80 °C for 24 h. Purified by flash chromatography on silica gel (30−50% EtOAc in Hexanes) to provide **2l** (0.0494 g, 62% yield) as an inseparable mixture of diastereomers (2:1 d.r.). ^{1}H NMR ($CDCl_3$, 500 MHz) 7.81 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.4, 4H), 7.30 (d, J = 8.3 Hz, 2H), 7.19 (d, 8.6 Hz, 4H), 7.14 (dd, J = 8.0, 2.9 Hz, 3H), 6.89 (ddd, J = 7.9, 5.6, 2.0 Hz, 3H), 6.78 (dd, J = 3.5, 2.0 Hz, 3H), 5.84 (ddd, J = 15.4, 10.3, 6.0 Hz, 1H), 5.84 (ddd, J = 16.3, 10.3 Hz, 6.0 Hz, 2H), 5.17−5.08 (m, 3H), 4.99 (d, J = 7.0 Hz, 3H), 4.85 (q, J = 5.9 Hz, 3H), 2.85−2.69 (m, 5H), 2.50 (dd, J = 19.1, 8.8 Hz, 3H), 2.42 (s, 3H), 2.40 (s, 6H), 2.40−2.33 (m, 3H), 2.26−2.19 (m, 3H), 2.14 (dt, J = 19.0, 8.9 Hz, 3H), 2.08−2.02 (m, 3H), 2.01−1.91 (m, 6H), 1.69−1.56 (m, 4H), 1.56−1.44 (m, 12H), 1.44−1.32 (m, 3H), 0.90 (s, 3H), 0.90 (s, 6H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 220.8, 143.6, 143.2, 139.53, 139.51, 139.4, 137.95, 137.92, 137.27, 137.26, 137.01, 136.98, 136.90, 129.8, 129.44, 129.42, 127.80, 127.78, 127.4, 126.6, 125.8, 124.6, 124.7, 116.71, 116.68, 59.80, 59.79, 50.6, 48.1, 44.4, 38.23, 38.22, 36.0, 31.7, 29.4, 26.5, 25.83, 25.82, 21.70,

21.66, 21.65, 21.63, 14.0 ppm; HRMS (+ APCI) calculated for $C_{28}H_{34}NO_3S$ [M + H] 464.2259, found 464.2264.

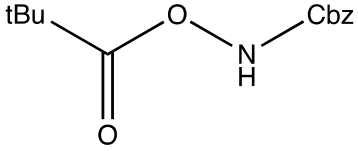


Synthesis of Phenylalanine-Derived Allylbenzene (1k, substrate). In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (0.0553 g, 0.048 mmol, 0.031 equiv) and LiCl (0.3022 g, 7.13 mmol, 4.75 equiv) were added to an oven-dried 15 mL vial equipped with a magnetic stir bar and Teflon-septum screw cap. The vial was capped and brought out of the glovebox. A solution of N-Cbz-(p-OTf)-Phe-OMe (0.7003 g, 1.50 mmol, 1 equiv) in DMF (6.30 mL) was added, followed by neat allyltributylstannane (0.600 mL, 1.67 mmol, 1.1 equiv). The vial was placed in an aluminum heating block preheated to 100 °C and stirred for 12.5 h. The reaction was removed from heat, allowed to cool to room temperature, and quenched with aqueous NH_4OH (1 N, 7.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10.0 mL). The combined organic extracts were washed with brine (2 × 15.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (0−100% EtOAc in Hexanes) providing **1k** (0.297 g, 55% yield). ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43−7.31 (m, 5H), 7.14−7.08 (m, 2H), 7.06−7.00 (m, 2H), 5.95 (ddt, J = 17.5, 9.5, 6.7 Hz 1H), 5.21 (d, J = 8.3 Hz, 1H) 5.15−4.92 (m, 4H), 4.66 (dt, J = 8.3, 5.8

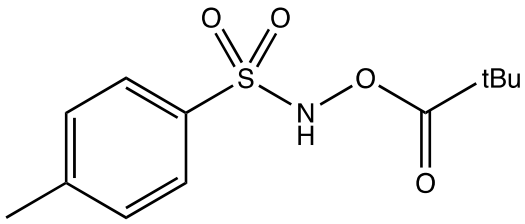
Hz, 1H), 3.73 (s, 3H), 3.36 (dd, J = 6.8, 1.6 Hz, 2H), 3.10 (dd, J = 14.9, 5.8 Hz, 2H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 151 MHz) 172.1, 155.7, 139.0, 137.4, 136.4, 133.4, 129.4, 129.0, 128.6, 128.6, 128.30, 128.2, 116.0, 67.1, 54.9, 52.4, 39.9, 37.9 ppm.



Synthesis of a bis-trifluoromethyl-substitued substrate (10c): Benzyl N-hydroxy-carbamate (302.56 mg, 1.82 mmol, 1 equiv) was added to 14.5 mL of diethyl ether in zero degrees Celsius. 3,5-bis(trifluoromethyl)benzoyl chloride (553.12 mg, 2 mmol, 1.1 equiv) and triethylamine (202.38 mg, 2 mmol, 1.1 equiv) were added. The reaction was stirred for 4-8 hours and monitored by TLC. Afterwards, the insoluble solid was filtered away and the filtrate was collected, washed with saturated $NaHCO_3$ three times, washed with brine, dried over sodium sulfate and concentrated under pressure. The product was purified under column chromatography using 10-50% EtOAc in hexanes. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.51 (s, 2H), 8.3 – 8.35 (s, 1H), 8.15 – 8.2 (s, 1H), 7.4 – 7.45 (m, 5H), 5.25 – 5.28 (s, 2H) ppm.



Synthesis of [(benzyloxy)carbonyl]amino 2,2-dimethylpropanoate (11c): Product was synthesized with benzyl-hydroxycarbamate (1 g, 5.98 mmol, 1 equiv), pivaloylchloride (0.7252 g, 5.98 mmol, 1 equiv), and triethylamine (0.6 g, 5.98 mmol, 1 equiv). The reaction was quenched after 2 hours with 10 mL of water. Organics were extracted into DCM (2x20 mL), dried over sodium sulfate, and concentrated under pressure. $_1$H NMR indicated the product was clean so it proceeded without further purification. $_1$H NMR ($CDCl_3$, 500 MHz) 8.02 (s, 1H), 7.29-7.43 (m, 5H), 5.22 (s, 2H), 1.30 (s, 9H) ppm.



Synthesis of 4-methyl-N-(pivaloyloxy)benzenesulfonamide (12c): Product was synthesized using **12b** (4.14 g, 22.14 mmol, 1 equiv), triethylamine (2.464 g, 24.352 mmol, 1.1 equiv), pivaloylchloride (3.203 g, 26.57 mmol, 1.2 equiv), and THF (83 mL). Reaction was stirred for 4 hours at -78$_o$ C. Afterwards, it was allowed to cool to room temperature and the white solid was filtered away. The filtrate was concentrated under pressure to produce a white solid. The solid was dissolved in 51.75 mL DCM and washed with 2 x 20.7 mL of 1M aqueous HCl, dried over magnesium sulfate, and concentrated under reduced pressure to yield a clean product with a yield of 67.3%. Product was clean without further purification. $_1$H NMR (500 MHz, $CDCl_3$, 25 ºC): δ 9.04 (s, 1H;), 7.81 (d, 2H), 7.35 (d, 2H), 2.44 (s, 3H), 1.10 (s, 9H) ppm.

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