Myers-Inspired Selenium-Mediated Isomerization: An Efficient Generation of Contra-Thermodynamic Allenes and Alkenes with the Potential for Reductive Deamination of Primary Amines and Metal-Free Hydrogenation of Dienes

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Abstract

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Samuel Dane Landing

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

Novel methods of catalytic metal-free isomerization reactions are scarce. By combining precedents in reductive defunctionalization reactions, coupled with previous advances in selenium-catalyzed C-N bond forming reactions, we have developed a contemporary but efficient manner of reaching contra-thermodynamic isomers of alkenes and alkynes. These isomerizations follow a well envisioned mechanistic path that may lead to further development in reductive deamination reactions, such as the reduction of primary amines such as anilines, and diamines to monoenes.

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LIST OF ABBREVIATIONS

yy:	[yyyyy]
Ac:	Acetyl
Ar:	Aryl
Bn:	Benzyl
Bz:	Benzoyl
DCM	Dichloromethane
Ns:	Nitrobenzenesulfonamide

Abbreviations for NMR Splitting:

s:	singlet
d:	doublet
t:	triplet
q:	quartet
quin:	quintet
m:	multiplet

hr:	Hour
Hz:	Hertz
Me:	methyl
ppm:	Parts Per Million
TMS:	Trimethylsilyl
rt:	room temperature

ACKNOWLEDGEMENTS

I owe my accomplishments to those at the University of Washington Chemistry Department. Most of all my advisor Forrest Michael, whom without his vigilant efforts to sway my ever-distracted brain, I would not be where I am today. I also owe my success to the members of the Michael group. Without them I would never have continued to push myself harder. The same can be said for the friends I have made along the way in the form of those such as faculty members in the NMR facility, Student undergraduate services such as Eric Camp and Brandon Bol. I owe my initial guidance in finding a group to Xiaosong Li and Alshakim Nelson, both of which pointed me in the right direction in my first few quarters. I also appreciate the help from the friends and colleagues I have come to know in the Nelson lab, as well as many other labs that I will undoubtedly forget to mention. Thank you all for every single moment. Special thanks to Michaela Priszner my program advisor for keeping me apprised of everything I would ever need to know about to succeed.

I would also like to thank my thesis committee for all the help they were by attending and reviewing my candidacy. I chose you two specifically because I enjoyed my time learning from you in my graduate coursework. During those times I gained a lot of respect for each of you. Matthew Golder, you showed me a welcome heart in your group when I was still deciding which research group, I wanted to be in. I ultimately chose the Michael group, but had always wished I had done more with your group! Ashleigh Theberge, you showed me a level of kindness and sympathy when I was sick and kept the class engaging even if I wasn't present for those days. Your mentorship skills are amazing and I definitely have added you to my "sit still and listen" list with the others I've mentioned here, you are a very considerate educator, and it makes someone with ADHD like myself much more welcome in the learning process due to the effortless way you

breakdown jargon midsentence. That’s an impressive skill which I hope to flatteringly appropriate.

Thank you all.

DEDICATION

This thesis is dedicated to the ones who have taken care of me – those who continue to look out for me and cheer me on. This is dedicated to my mom, LaDonna Landing and my brother Lukas Landing, who is infinitely smarter than I am. You both have done so much and tolerated so much and we have struggled so much. I only hope that I will continue to make you proud.

This is also dedicated to my family and non-familial "family" thank you Aunt Julie and grandma for the amazing care packages. Thank you Drew for being a thorn in my a■■, rooting on for me, keeping me grounded, and calling me on my bull■■■■. Let's change the world bud.

~ In Memoriam ~

Lawrence Fryer - Loving Uncle - 2016

David Landing - Father - 2018

Henry Fryer - Grandpa - 2020

******

Dad, your heart couldn't take it— much sooner than ours. You were spared the sight of COVID. Your empathy would have angered you so much to see me struggle but your pride would have yelled at me to never stop. Luke has taken good care of your chrysanthemums.

******

Grandpa, I know you knew COVID was coming, and you couldn't see anymore —
I forgive you.

PREFACE

[**]

Chapter 1. BACKGROUND

Section 1: INTRODUCTION

This thesis is a summary of my work in Dr Forrest E. Michael's group. The intended foci for this project were the contra-thermodynamic isomerization of allylic and propargylic amines to terminal alkenes and allenes respectively. This work formally spanned September 2022 to May 2023. I had the pleasure of throwing out all of my research that transpired from March through June 2022, which covered the exact same research published in fantastic coverage by the Maulide group[1]. My research started by evaluating electrophilic n-amination reactions to facilitate reaching a diazene intermediate previously published by Andrew Myers and coworkers in the 1990s[2] but grew to evaluate much more. The entire project, while incomplete, invites inquiry into how we should review and investigate contra-thermodynamic isomerization, and if it can be done without the need for expensive or toxic source metals, such as iridium or cobalt.

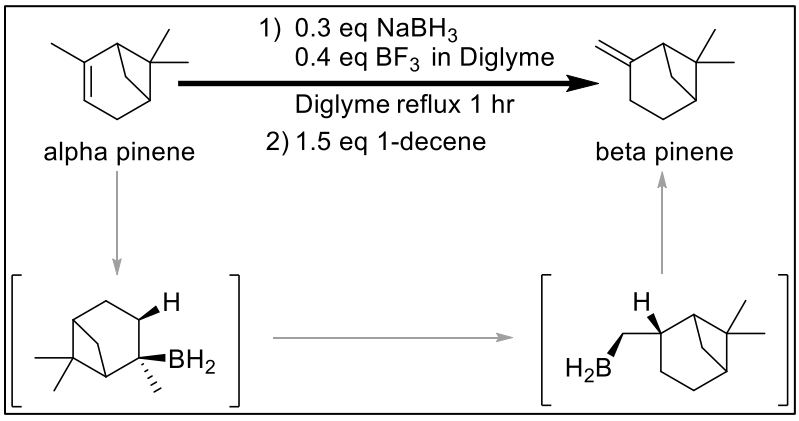
This chapter will serve as an introduction into the literature that defines contra-thermodynamic isomerization, how our work in selenium catalyzed reactions can contribute to this regime of reactions, and as a jumping off point for those who wish to continue or contribute to the research of contra-thermodynamics.

Section 2: CONTRA-THERMODYNAMIC ISOMERIZATION

Contra-thermodynamic isomerization (CTI) encompasses a variety of reactions, all involve the transformation of a lower energy starting material to a less stable product via an excited intermediate. While CTI can be applied across a multitude of reaction types and chemical species,

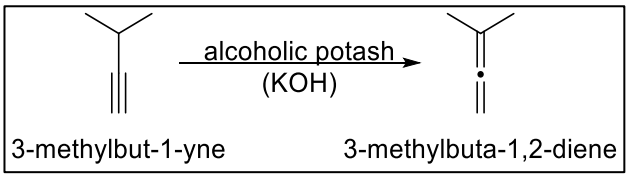
including olefins, sugars, and alkynes. However, our focus will lie predominantly on the isomerization of alkenes and alkynes into terminal alkenes and allenes respectively.

Some of the early reports of contra-thermodynamic isomerizations involved alkenes undergoing hydroboration reactions. Bhatt and Brown showed that conversion of an organoborane from the internal alkene to the terminal alkene was possible through displacement and without rearrangement. The authors showed that by converting a stable alkene into an organoborane, the organoborane would undergo isomerization in a manner than could be converted to the contra-thermodynamic isomer[3] (contra-therm)(**Scheme 1**).



Scheme 1 Early report of contra-thermodynamic isomerization by Bhatt and Brown

Less commonly is the application of contra-thermodynamic isomerization of alkynes, however two methods have been presented as such. These include positional isomerizations such as zipper reactions with KAPA to produce terminal alkynes from internal alkynes, or constitutional isomerizations such as the transformation of an alkyne to an allene. The latter was shown as early as 1888 by Faworski by isomerizing 3-methylbutyne to 3-methylbuta-1,2-diene **(Scheme 2)**[4]. The former described by Brown and Yamashita in 1974 detailed the use of Potassium 3-aminopropylamide (KAPA) and is built on previous investigations supported by base-catalyzed alkyne-allene mechanism (**Figure 2**)[5]



Scheme 2 Isomerization of alkynes to allenes observed by favorksi

Modern CTIs mainly aim to overcome the stabilizing hyperconjugative effects of internal alkenes to produce terminal alkenes or to convert trans/E isomer to the more strained cis/Z isomer with less orbital overlap. These transformations are typically achieved using light catalyzed reactions, falling broadly into two categories: E-Z isomerizations and regioisomerizations or translocations.

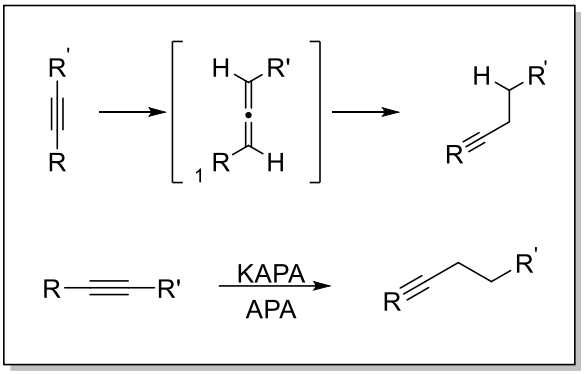


Figure 2 Zipper isomerization of alkynes

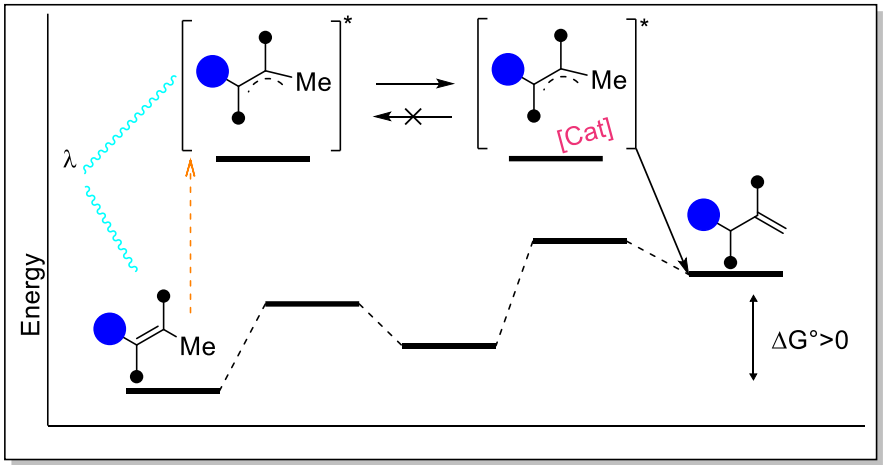


Figure 1 Excited state-mediated isomerization irreversibly converts stable molecules into their contratherms.

Most techniques for CTI rely on transition metal catalysts and photo-initiated mechanisms, creating a kinetic or thermodynamic entry point to the desired, less stable isomer through a high-energy intermediate (**Figure 1**). This intermediate is typically easier to achieve from the thermodynamically stable compound, is formed irreversibly, and is less stable than the resulting CTI isomer.[6]

Of the more recent photocatalytic methods Independently, the Knowles Group and the Wendlandt Group reported similar achievements in this regime. Both groups published transition metal, photo-catalyzed transformations through similar means but slightly different and novel mechanisms. The Knowles group showed a narrower application, focusing mainly on isopropylidene species. Wendlandt, however, showed increased scope, including terpenoid-like and natural products, but at the cost of using a rather specific decatungstate cocatalyst(**Figure 3**).[7,8]

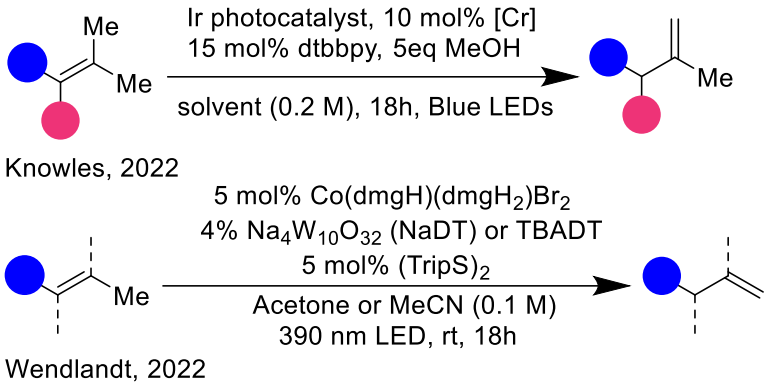


Figure 3 Recent photocatalyzed contra-thermodynamic isomerization of olefins.

These methods could represent a recent crowning achievement in contra-thermodynamic isomerization by actualizing photocatalytic utilities beyond chain-walking isomerizations or simple base-promoted reactions. However, the need for more accessible means of isomerization techniques or the inclusion of new entry points for the synthetic "tool-belt" remains a motivator to gravitate away from Expensive rare earth metals or complex ligands.

Section 3: Selenium-Catalyzed C-N Bond Forming Reactions

Our group has developed many diverse amination reactions , including diamination, allylic, and propargylic aminations. By utilizing selenium or sulfur-based catalysts, we've shown that you can efficiently aminate alpha to non-sp3-carbon centers to generate various protected amines in the

form of sulfonamides and sulfamates. By doing so, several opportunities exist to further exploit the reactivity of the adjacent pi-systems as well as the amine itself. This challenge is devising amenable conditions for sulfonamide sp/sp^2 reactivity. This challenge is partly due to the reduced solubility of reacted side products upon deprotection of the amine, where the presence of sulfinate or sulfite anions could coordinate and or precipitate with counter ions present, functionally increasing any solvation-based challenges. It is worth noting that this is only a challenge when a reaction is diffusion limited. For work in allylic amination, and propargylic amination, this is not an issue directly, but becomes a hurdle in my work[9–11].

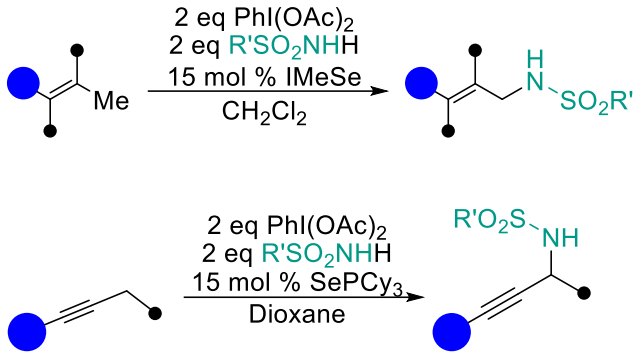


Figure 4 Summaries of Selenium catalyzed Allylic and Propargylic aminations of the Michael Group.

Section 4: Reductive Deoxygenations

Most of the chemistry presented in this thesis is based on two fundamental chemistries seen in the literature, the isomerization of a diazene, and the reductive deamination of sulfonamides. This chemistry is based on two understandings for experimentation. Firstly, are the reductive deoxygenations provided by Andrew Myers and coworkers in the 1990s . Secondly is the N-alkylation performed by Fukuyama, which provides an understanding for the conditions that allow

us to sulfonate our amines. All of the following chemistry is based off of the Myers' chemistry[2,12,13](**Figure 5**)

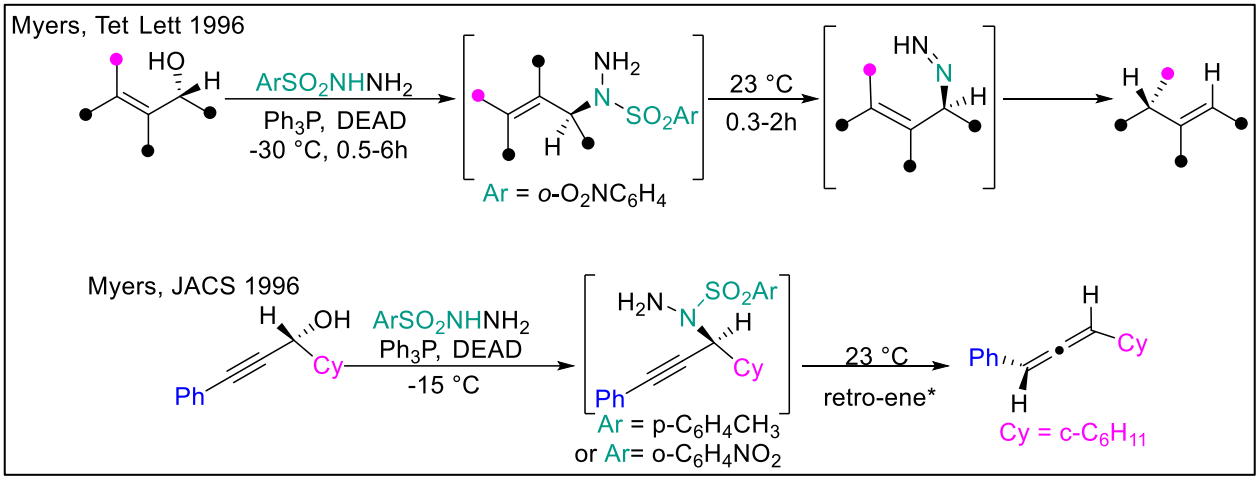


Figure 5: Summary of primary reactions reported by Myers and coworkers.

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Chapter 2. REACTION DEVELOPMENT OF CONTRA-THERMODYNAMIC ISOMERIZATION

Section 1: INTRO

Development of stereochemical manipulations takes many forms, from enantio- or diastereoselective to stereo-retentive. However, not every reaction can be driven to the ideal product yield due to the energetic cost or efficiency. Many desired products are contra-thermodynamic and require multiple manipulations to reach. In addition to this hurdle, the overlap in where selenium catalyzed reactions can ameliorate this problem is underdeveloped. To that end we looked for new methods of contra-thermodynamic manipulations utilizing selenium catalysts.

Our products formed from allylic amination and propargylic amination bear a striking resemblance to the intermediates described in chemistry by Myers in the 1990s. Specifically our sulfonamides are electrophilic amination precursors to Myers' hydrazine intermediate and the reactive diazene intermediates described by Myers. The diazene intermediate performs a [3,3]-sigmatropic reaction in the case of the alkenes or retro-ene reaction when converting from propargyl system to allenes. These also happen to be contra-thermodynamic. Noticing the similarity of our work to Myers we took to developing a strategy to further our synthetic tool chest by studying whether there was the capability to observe an overall contra-thermodynamic isomerization. [1,2,3]

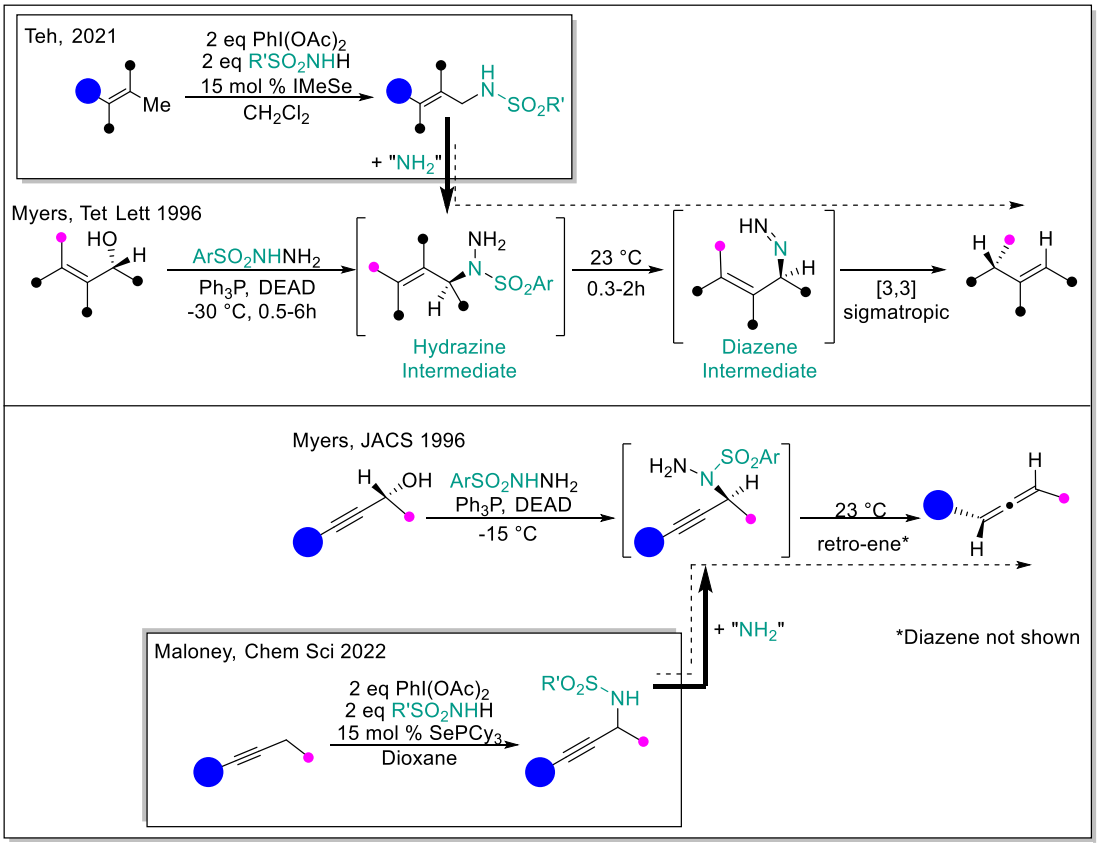


Figure 6: Introduction of our allylic amination as a method toward products reported by Myers and coworkers.

Section 2: RESULTS

To utilize Myers' allene synthesis or their translocation of alkenes, we need an efficient method to irreversibly generate the diazene through amination of the protected sulfonamide. Shi and coworkers demonstrated that hydroxylamines like O-(4-nitrobenzoyl)hydroxylamine (**Figure 7** Primary hydroxylamine used for electrophilic amination.) can serve as electrophilic nitrogen sources when the parent amine is deprotonated to act as a nucleophile[14,15]. O-(4-nitrobenzoyl)hydroxylamine offers relative stability under ambient conditions and a controllable degradation temperature. Our investigation began by evaluating the amination of propargyl amines under these conditions, using butynl-1-benzene-derived propargylamine (**Table 1**). However, the observed conditions were not ideal. We tested different bases and hydroxylamine equivalents but

found inconsistent isomerization promotion compared to expectations. Although Table 1 narrowed down favorable conditions for isomerization, concerns were raised about product loss and recovery challenges.

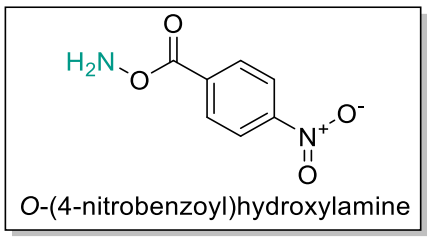
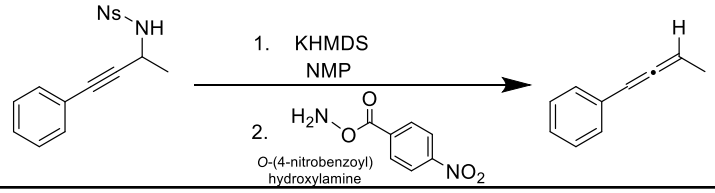


Figure 7 Primary hydroxylamine used for electrophilic amination.

To address the issues, we transitioned to a higher molecular weight substrate, namely 4-nitro-N-(1-phenyl-4-(TMS)but-3-yn-2-yl)benzenesulfonamide (**Table 2:** New Screen of hydroxylamine and base). In the second screening, we once again evaluated different equivalents of base and hydroxylamine, but the results showed little to no increase in yield for a given reaction. Notably, the deprotection of the TMS group on the alkyne's terminal end was observed, which was not ideal.

Since no significant change in yield occurred, we conducted nucleophilic trapping reactions to investigate whether the base hindered its own deprotonation or if the deprotonated sulfonamide reacted too quickly to be available for electrophilic hydroxylamine.

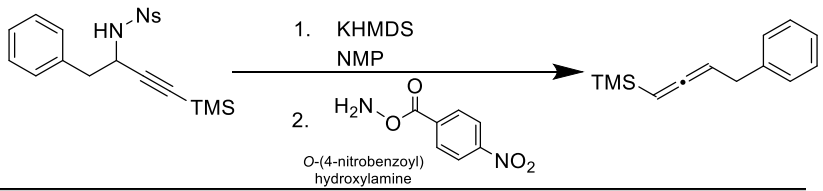
Table 1



Entry	Equivalents Base	-ONH2	T (hrs)	Hivac used?	Yield
1	1.2	1	48	yes	3%
2	1.5	1.5	48	yes	5%
3	1.5	1.5	24	no	46%
4	1.2	1	24	no	21%
5	1.5	1.5	24	no	38%
6	2	2	24	no	31%

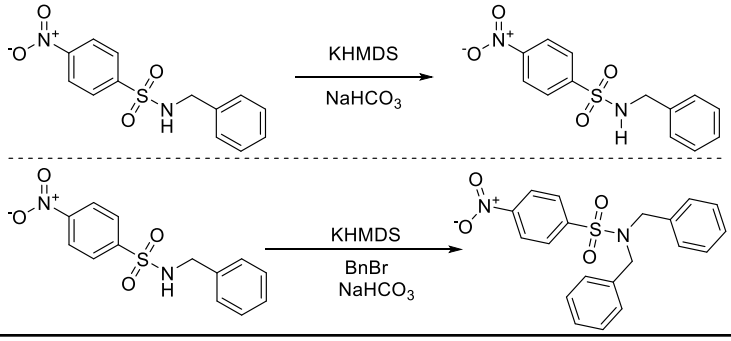
Nucleophilic trapping experiments were performed at different temperatures to determine the optimal reactivity for the base. These experiments confirmed favorable deprotonation for electrophilic amination. However, altering the temperature of the standard reaction led to freezing of the solvent, becoming the limiting factor.

Table 2: New Screen of hydroxylamine and base



	Equivalents		Yield	Yield
Entry	Base	-ONH2	(Protected)	(Unprotected)
1	1.1	1.1	20%	13%
2	1.5	1.1	2%	15%
3	2.0	1.1	0%	8%
4	1.1	1.5	16%	20%
5	1.5	1.5	3%	25%
6	2.0	1.5	1%	12%
7	1.1	2.0	26%	11%
8	1.5	2.0	3%	29%

Table 3 Summary of Surrogate Base evaluation



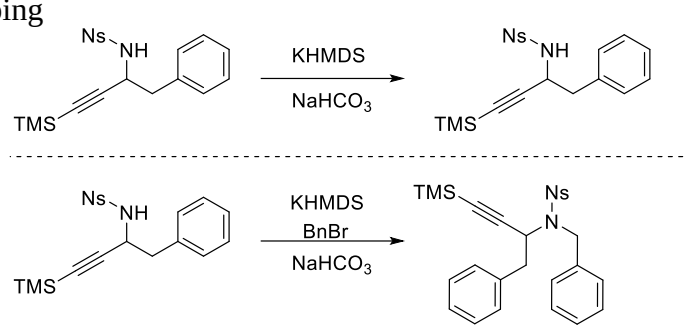
Entry	[SM]M	[Base]M	BnBr eq	recovery
1	0.164	0.00	0.0	100%
2	0.164	0.00	0.0	93%
3	0.164	0.18	0.0	87%
4	0.164	0.18	0.0	85%
5	0.164	0.18	2.0	75%
6	0.164	0.18	1.1	74%

Due to a supply chain issue, we switched to an even higher molecular weight substrate with a less base-labile protecting group in the form of TBDPS in the form of the tert-butyl(pent-4-yn-1-

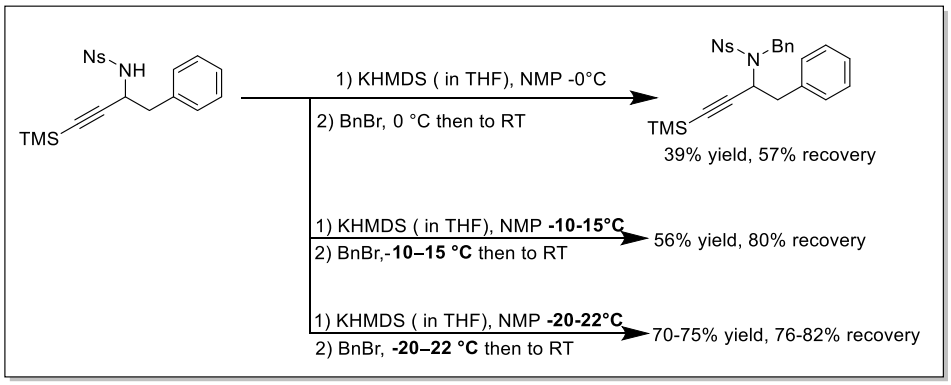
yloxy)diphenylsilane.

Concurrently, we explored the literature for alternative methods of electrophilic amination using our hydroxylamine, other hydroxylamines, or changes in the base or deprotonation temperature. Unfortunately, the literature-based screening did not yield substantial increases in yield but instead resulted in various ratios of a new side product not observed in previous substrates. The most likely cause of this side product is an internal nucleophilic displacement of the silyl protecting group

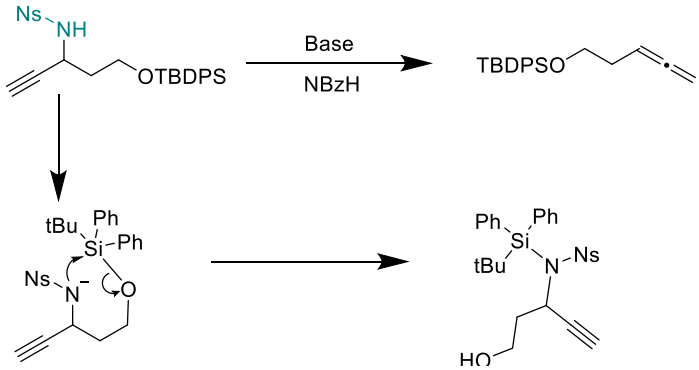
Table 4 Summary of Deprotonation controls and Nucleophilic Trapping



Entry	[SM]	[Base]	BnBr eq	recovery
1	0.164	0.00	0	100%
2	0.164	0.18	0	81%
3	0.164	0.18	0	75%
4	0.510	0.56	0	73%
5	0.510	0.56	1.1	62%
6	0.164	0.18	2	57%
7	0.164	0.18	0	54%
8	0.324	0.36	0	52%
9	0.244	0.27	0	52%



Scheme 3 Summary of Nucleophilic trapping experiment on propargyl sulfonamide.



Scheme 4 possible isomerization pathway decreasing the potential yield via 5-member intermediate

through a 5-member intermediate (**Scheme 4**). Full screening details can be found in the appendix.

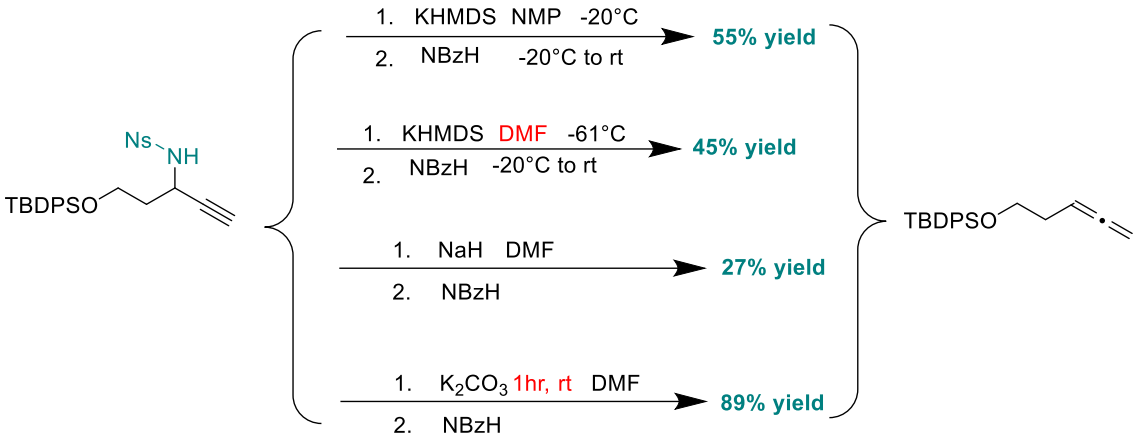


Figure 8 Summary of literature screen.

Eventually, we achieved a yield of 89-90% allene by using potassium carbonate in Dimethylformamide (DMF), paving the way for further exploration. To increase usability and

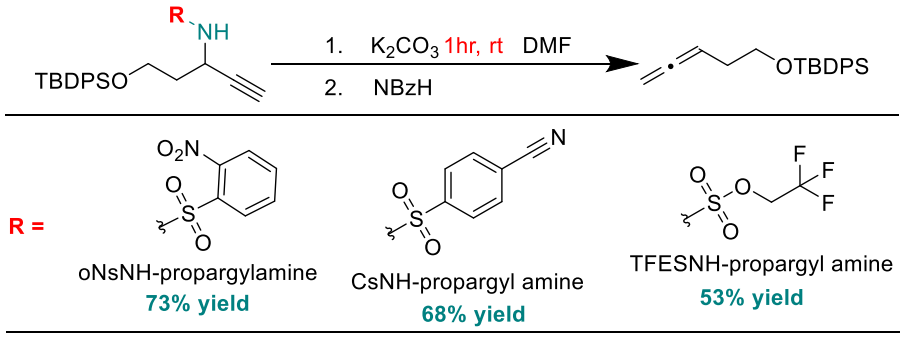


Figure 9 Alternative Sulfonamides

potentially improve yield or reduce side products, we decided to evaluate different sulfonamides/sulfamates. We examined two functionally different amine protecting groups, trifluorethylsulfamate (TFES) and 4-Cyanobenzenesulfonamide (CsNH), as well as 2-nitrobenzenesulfonamide (oNsNH) due to its precedent in Myers' chemistry. While TFES and CsNH resulted in lower yields and new side products, 2-nitrobenzenesulfonamide showed no side products but consistently yielded lower than 4-nitrobenzenesulfonamide propargyl amine (**Figure 9** Alternative Sulfonamides). This discrepancy is likely due to steric hindrance introduced by the ortho nitro moiety, as well as differences in electron withdrawing group possible decreasing the

electron density around the deprotonated nitrogen and decreasing its nucleophilicity towards the hydroxylamine. However, its nucleophilicity being lower could explain, in-part, why less internal isomerization is observed. More ortho positioned sulfonamides and sulfamates would need to be experimented with as well as different electron withdrawing groups at the para position to fully understand the effect on reactivity of the sulfonamide.

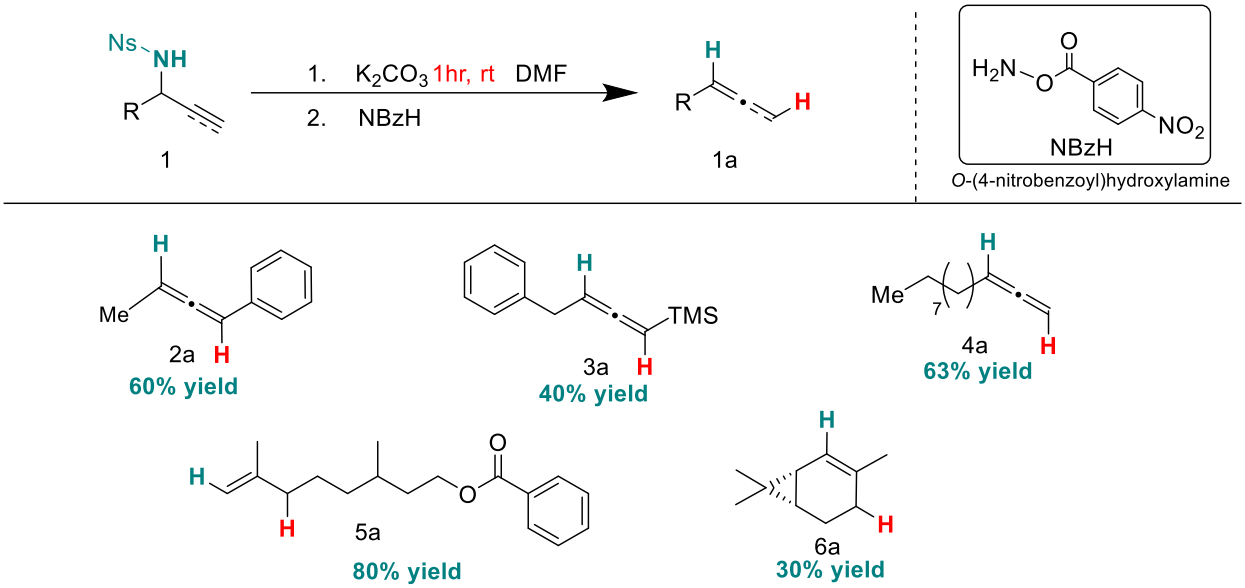
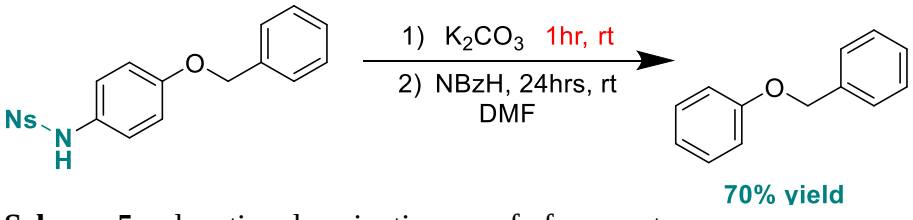


Figure 10 Reaction scope for contra-thermodynamic isomerization of alkynes and alkenes.

Section 3: Further Reactivity Investigations

To evaluate whether the reactivity seen so far translates to additional reactivity investigated by myers, we investigated isomerization of a primary amine.[14] The hopes were to open a new line of inquiry into reductive deamination of primary amines. For this purpose, a stable primary amine in



Scheme 5 reduuctive deamination proof of concept.

the form of benzyloxy aniline was utilized and deamination was observed at 70% with no further optimization (**Scheme 5**).

Section 4: CONCLUSIONS

A novel method for contra thermodynamic isomerization of alkenes and alkynes has been presented. This method suffers from underdeveloped scope and begged for earlier and preliminary review of bases rather than the ineffectual use of multiple screens for equivalencies and electrophile/base ratios along with the migration to heavier substrates to correct for any loss to vacuum. Regardless of these faults, the challenges can be overcome and with new evaluations and possible ligands to aid in the solvation of anions generated from the reactions present, this could provide to be a power new avenue for transforming allylic amines and propargylic amines into the consequent terminal alkenes or allenes respectively. The most fortuitous conclusions are the ones regarding future directions, including the reductive deamination of the benzyloxy aniline. Which suggests a similar reaction to that seen by Myers[14]. With this reactivity of primary amines, this leads the door open to applying this chemistry to our other works, which includes the deamination of dienes. These dienes have been shown to be more difficult to make in the lab as are most dienes, and when deaminated they leave two places for reactivity to occur. One allylic amine, and one primary amine. This would allow the first to leave via a typical Myers reductive defunctionalization through a diazene transition state and a [3,3]-sigmatropic rearrangement followed by the propose radical initiated deamination possible through the reductive deamination of primary amines. It is even easy to posit that iterative instances could be undertaken toward metal

free hydrogenation of dienes to monoene or hydrogenation of polymers (**Figure 11** Iterative reductive deamination could lead to metal-free hydrogenation of dienes to monoenes.).

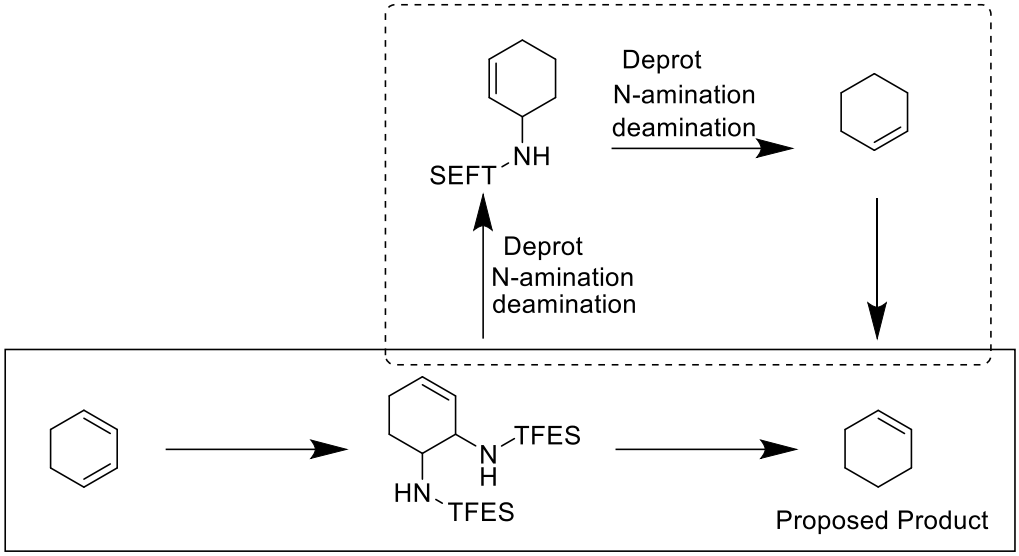


Figure 11 Iterative reductive deamination could lead to metal-free hydrogenation of dienes to monoenes.

Section 5: EXPERIMENTAL

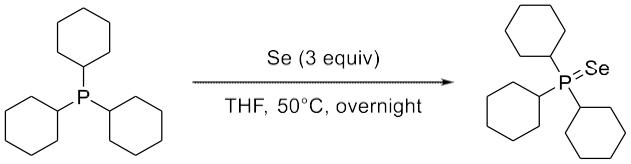
2.5.1 *General Procedure and Materials*

All reactions were performed under a nitrogen atmosphere using oven-dried or flame-dried glassware unless otherwise indicated. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were degassed and dried by passing through a column of activated neutral alumina. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. and stored over activated 3A molecular sieves. N-Methyl-2-pyrrolidone (NMP), Dimethylformamide (DMF), Ethyl acetate (EtOAc), hexanes, and ether (Et_2O) were obtained from Fisher Scientific or Sigma Aldrich and used without further purification. Reagents were purchased from Sigma Aldrich, Tokyo Chemical Industry, Fisher Scientific, Alfa Aesar, Oakwood chemicals and used without further purification unless otherwise indicated. NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499, AV-

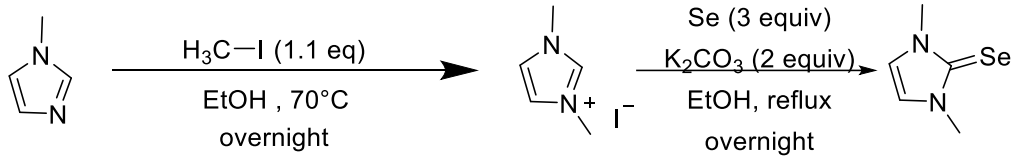
500, GG-500, NEO-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to $CHCl_3$ (7.26 ppm)

2.5.2 *Synthesis and Characterization of Starting Materials*

2.5.2.1 **General Procedure for Synthesis of Selenium Catalysts**



Tricyclohexylphosphine selenide (SePCy3). Synthesis was performed according to literature procedures and was graciously donated by laboratory members: A flame-dried round bottom flask equipped with a magnetic stir bar was charged with tricyclohexylphosphine (10 mmol, 1 equiv.) and selenium powder (30 mmol, 3 equiv) in a glove box. The flask was capped with a rubber septum and transferred outside of the glove box. Dry tetrahydrofuran (20 mL, 0.5 M) was added using a syringe and the septum was replaced with a reflux condenser under nitrogen gas. The reaction was heated to 45 °C and allowed to stir overnight. After cooling to room temperature, the mixture was then flushed through Celite with dichloromethane to remove the residual selenium powder. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product. The crude white solid was recrystallized from acetone and cooled in the freezer overnight to afford the product as white needles[11]



N,N'-dimethylimidazole-2-selenide (SeIMe). A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 1-methylimidazole (2 mL, 25.1 mmol, 1 equiv.) and ethanol

(50 mL, 0.5 M). Methyl iodide (1.72 mL, 27.6 mmol, 1.1 equiv.) was added to the flask, which was equipped with a water condenser. The reaction was heated to 70 °C and allowed to stir overnight. The reaction mixture was then concentrated on a rotary evaporator to afford the crude imidazolium salt. Potassium carbonate (6.9 g, 50.1 mmol, 2 equiv.), selenium powder (5.9 g, 74.3 mmol, 3 equiv.), and ethanol were added to the flask containing the crude reaction product and refluxed overnight. The reaction mixture was filtered through a pad of Celite and washed with dichloromethane (2 x 100 mL). The filtrate was then transferred to a separatory funnel for aqueous workup to remove residual iodide impurities 3x with DCM then dried over magnesium sulfate filtered once more through glass fritted funnel. The filtrate was concentrated under rotary evaporator. The concentrate was recrystallized in methanol to afford the product as pale grey needles.[11]

2.5.2.2 **General Information for Starting Materials**

All propargylic and allylic amines were prepared following literature procedures using selenium catalyst[10,11].

2.5.2.2.1 **Preparation of propargyl amines**.

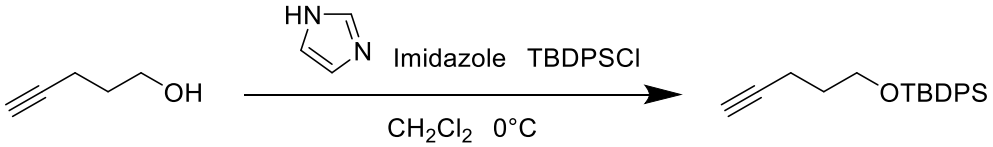
A flame-dried round bottom flask (rbf) charged with N2 and a magnetic stir bar, was then charged with SePCy3 (0.15 equiv.), amine (2 equiv.), and alkyne (1.0 equiv.). Dry dioxane (1 mL, 0.2 M) was added, followed by iodobenzene diacetate (2 equiv.). The solution was stirred at the at room temperature and the reaction was monitored by TLC. Upon completion, an equal volume of ethyl acetate was added to the reaction and the mixture was flushed through a silica gel plug with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude product. The crude product was purified by silica gel chromatography.

2.5.2.2.2 **Preparation of allylic amines.**

A flame-dried rbf equipped with a magnetic stir bar was charged with SeIMe (0.15 equiv.), amine (2 equiv.), and alkene (1.0 equiv.). The rbf was thoroughly flushed with nitrogen and capped with a rubber stopper. Dry dichloromethane (0.2 M) was added followed by iodobenzene diacetate (2 equiv). The solution was stirred at room temperature and the reaction was monitored by TLC. Upon completion, an equal volume of ethyl acetate was added to the reaction and the mixture was flushed through a silica gel plug with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude product, which was then purified by silica gel chromatography.

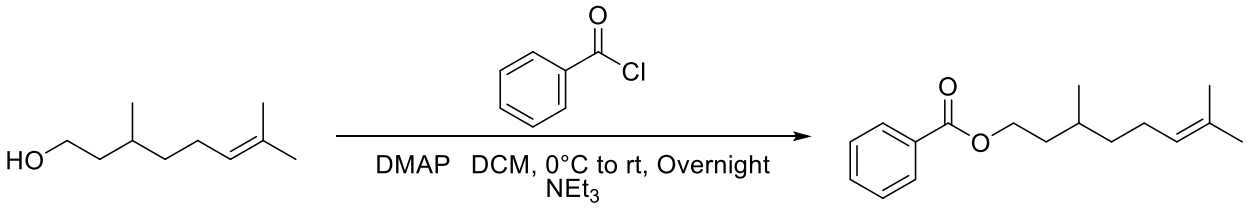
2.5.2.3 **Procedures for Substituent Protection**

2.5.2.3.1 **tert-butyldiphenylsilyl protection of alcohols**



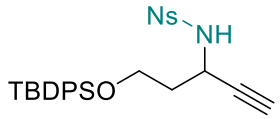
To a solution of the alkyn-ol (1 equiv.) in CH_2Cl_2 (0.5M) at 0 °C was added imidazole (1.3 equiv.) followed by dropwise addition of tert-butylchlorodiphenylsilane (TBDPSCl (1.1 equiv.)). After stirring for 1hr the reaction was quenched with H_2O (equal volume) and was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (2% to 10% ethyl acetate in hexanes) to yield the silyl ether.[15]

2.5.2.3.2 **benzoate protection of alcohols**

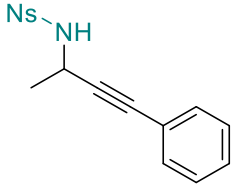


Protection was performed according to previous literature.[11] A flame-dried round bottom flask equipped with a magnetic stir bar was charged with the 1 equivalent of the alcohol and 0.02 equivalents of 4-dimethylaminopyridine. Dry dichloromethane (0.5 M) was added, and the reaction mixture was stirred and cooled to 0°C. Benzoyl chloride (1.1 equiv.) was added to the reaction mixture followed by triethylamine (2 equiv.). The round bottom flask was then allowed to warm to room temperature and stir overnight. The reaction was quenched with water (equal volume) and diluted with ether. The organic layer was then washed with saturated sodium bicarbonate 2x and brine 1x and dried over sodium sulfate. The solvent was then removed under reduced pressure and silica gel chromatography was used to purify the crude products. Purification was performed by flash column chromatography using silica gel 30:70 DCM:Hexane

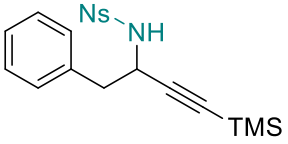
2.5.2.4 **Characterization of Starting Materials**



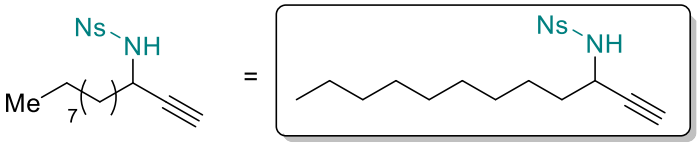
0. **N-(5-((tert-butyldiphenylsilyl)oxy)pent-1-yn-3-yl)-4-nitrobenzenesulfonamide**. Following the general procedure for Selenium catalyzed propargylic amination. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford the product as a white solid 1H NMR (500 MHz, CDCl3) δ 8.30 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.1 Hz, 4H), 7.45 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.2 Hz, 5H), 6.21 (d, J = 8.4 Hz, 1H), 4.61 – 4.53 (m, 1H), 4.05 (td, J = 10.3, 2.9 Hz, 1H), 3.83 – 3.72 (m, 1H), 2.08 (d, J = 2.2 Hz, 1H), 1.90 – 1.74 (m, 1H), 1.09 (s, 9H).



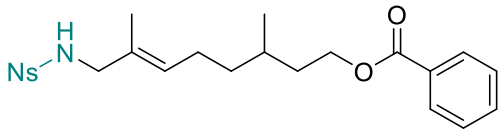
1. **4-nitro-N-(4-phenylbut-3-yn-2-yl)benzenesulfonamide**. Following the general procedure for Selenium catalyzed propargylic amination. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford the product as a white solid.



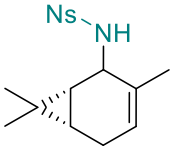
2. **4-nitro-N-(1-phenyl-4-(trimethylsilyl)but-3-yn-2-yl)benzenesulfonamide**. Following the general procedure for Selenium catalyzed propargylic amination Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford the product as a white solid.



3. **N-(dodec-1-yn-3-yl)-4-nitrobenzenesulfonamide**. Following the general procedure for Selenium catalyzed propargylic amination Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a yellow oil.



4. **3,7-dimethyl-8-((4-nitrophenyl)sulfonamido)oct-6-en-1-yl benzoate**. Following the general procedure for Selenium catalyzed *allylic* amination to produce a dark yellow oil. (Purified by silica gel chromatography (85:15 hexanes/ethyl acetate).



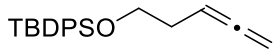
5. **4-nitro-N-((1R,6S)-3,7,7-trimethylbicyclo[4.1.0]hept-3-en-2-yl)benzenesulfonamide**. Following the general procedure for Selenium catalyzed allylic amination, yielded a yellow oil which was purified via column chromatography (85:15, hexanes/ethyl acetate)

2.5.3 *General Procedure for Contra-Thermodynamic Isomerization*

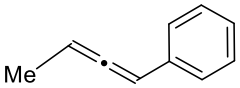
A 1-dram vial equipped with magnetic stir bar was evacuated and backfilled with an N_2 atmosphere. The propargyl or allyl sulfonamide (0.2 mmol) was dissolved in Dimethylformamide (DMF) (0.41M, 0.49 mL), potassium carbonate (5eq, 1 mmol) was added, and the mixture was stirred at room temperature for 50-60 minutes. Hydroxylamine (2 eq, 0.4 mmol) was added, and the mixture was stirred at room temperature for 18-24 hours. To the reaction solution was added chloroform or methylene chloride, the slurry was then run through a glass-frit filter by aspirator-vacuum filtration, and the filtrate was concentrated under reduced pressure by rotary evaporator.

2.5.3.1 **Characterization of Products**

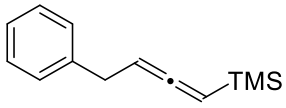
All products were characterized via 500 MHz NMR using an internal standard of 1,3 dinitrobenzene. Due to time constraints and the small yield, crude NMR characterization was performed.



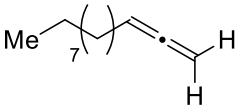
0. **tert-butyl(penta-3,4-dien-1-yloxy)diphenylsilane**. Following the general procedure for contra thermodynamic isomerization. 89% Yield. ^{1}H NMR (500 MHz, CDCl3) δ 5.09 (p, J = 6.9 Hz, 1H), 4.59 (dt, J = 6.3, 2.9 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 2.24 (dtd, J = 9.7, 6.7, 3.3 Hz, 2H), 1.01 (s, 9H).



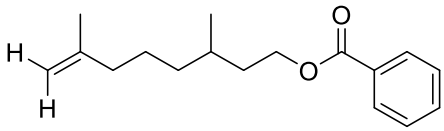
1. buta-1,2-dien-1-ylbenzene. Following the general procedure for contra-thermodynamic isomerization; 60% Yield due to a lack of resolution aromatic region was occluded. Characteristic signals presented 1H NMR (500 MHz, CDCl3) δ 6.07 (s, J = 3.1 Hz, 1H), 5.52 (dd, J = 8.9, 4.8 Hz, 1H), 1.77 (dd, J = 7.3, 3.1 Hz, 3H).[16]



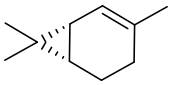
2. trimethyl(4-phenylbuta-1,2-dien-1-yl)silane. Following the general procedure for contra-thermodynamic isomerization. 40% Yield ^{1}H NMR (500 MHz, CDCl3) δ7.15-7.32 (m, 5H), 4.98-4.98(m, 2H), 3.30 (t, 2H), 0.06 (s, 9H).



3. dodeca-1,2-diene. Following the general procedure for contra-thermodynamic isomerization. 63% Yield : ^{1}H NMR (500 MHz, CDCl3) δ 4.99 (m, 2H), 4.63 – 4.46 (m, 2H), 1.98 – 1.81 (m, 2H), 1.32 (s, 2H), 1.18 (s,11H), 0.79 (s, 3H).



4. 3,7-dimethyloct-7-en-1-yl benzoate. Following the general procedure for contra-thermodynamic isomerization. 80% Yield. ^{1}H NMR (500 MHz, CDCl3) δ 7.57 (t, J = 7.4 Hz, 1H), 4.68 (d, J = 12.4 Hz, 2H), 4.37 (q, J = 6.2 Hz, 2H), 2.01 (s, 1H), 1.83 (dd, J = 13.4, 6.5 Hz, 1H), 1.61 (dt, J = 13.9, 6.8 Hz, 1H).



5. (1R,6S)-3,7,7-trimethylbicyclo[4.1.0]hept-2-ene. Following the general procedure for contra-thermodynamic isomerization. 30% Yield. ^{1}H NMR (500 MHz, CDCl3) δ5.29 (s, 1H), 1.93(s 1H), 1.68 (m 1H), 1.57 (m 1H), 1.41(s, 3H), 1.31 (s, 1H), 0.95(s, 1H), 0.82(s3H), 0.69(s, 1H), 0.61(s, 3H)

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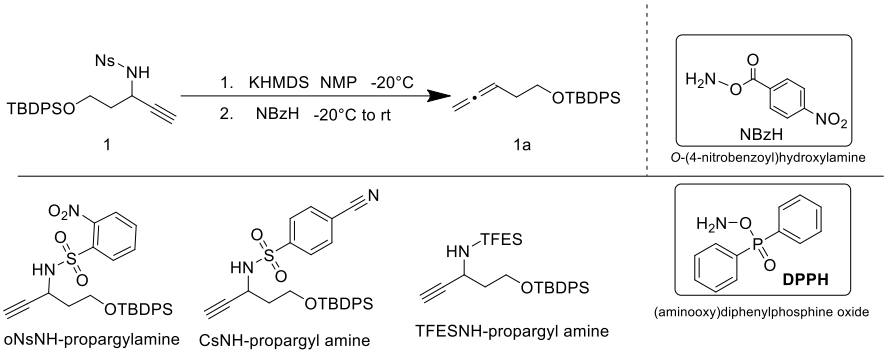
APPENDIX A



Rxn number	Amine	Base	Hydroxylamine	Solvent	temp	SM Yield	SP Yield	Pdt Yield	% recov	Adtn Ordr
1	NsNH2	KHMDS	NBzH	NMP	-20	17%	7%	55%	79%	original
2	" "	" "	" "	" "	" "	26%	3%	47%	76%	original
3	" "	" "	" "	DMF	-60	32%	6%	45%	83%	original
4	" "	" "	DPPH	" "	" "	25%	10%	60%	95%	original
5	NsNH2	NaH	NBzH	DMF	rt	19%	52%	27%	98%	original
6	" "	" "	" "	" "	-20	17%	17%	15%	49%	original
7	" "	" "	" "	Dioxane	60	0%	70%	25%	95%	original
8	" "	" "	" "	" "	15	43%	33%	14%	90%	original
9	" "	" "	DPPH	THF	0	3%	90%	19%	111%	original
10	" "	" "	" "	" "	" "	9%	16%	35%	60%	original
11	" "	" "	" "	Dioxane	60	10%	65%	38%	113%	original
12	NsNH2	K2CO3	NBzH	THF	rt	9%	75%	12%	96%	inverted
13	" "	" "	" "	DMF	" "	7%	3%	89%	99%	original
14	" "	" "	" "	ACN	" "	0%	48%	43%	91%	inverted
15	" "	" "	DPPH	DMF	" "	5%	0%	79%	83%	original
16	**oNsNH2**	K2CO3	NBzH	DMF	rt	16%	0%	73%	89%	original
17	" "	" "	" "	" "	" "	15%	0%	77%	92%	original
18	" "	" "	" "	" "	" "	29%	0%	68%	97%	inverted
19	" "	" "	" "	ACN	" "	36%	0%	57%	93%	original
20	" "	" "	" "	" "	" "	67%	0%	23%	90%	inverted
21	**TFESNH2**	K2CO3	NBzH	DMF	rt	0%	38%	53%	91%	original
22	**CsNH2**	" "	" "	" "	" "	0%	5%	68%	73%	original

rt is nominally 22°C
inverse addition order adds the sulfonamide and hydroxylamine at the same time
followed by subsequent base

VITA

Samuel Dane Landing was born in Colorado Springs, Colorado on March 29, 1992. He attended High School in Widefield at Mesa Ridge High School and graduated in May 2010. The following Fall he attended Fort Lewis College a small 4-year liberal arts college in Durango, Colorado where he double majored in Chemistry and Cellular and Molecular Biology, finishing with a minor in mathematics. In 2015 they graduated and the following summer they attended a post-baccalaureate at Los Alamos National Laboratory studying Catalyst and material development. Between 2015 and 2020 Sam worked in industry jobs as a quality control chemist, followed by attending University of Washington in Fall of 2021 with the intention of acquiring his Masters in Chemistry in order to strengthen his pursuit towards a PhD in organic chemistry.

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