Hydroalkylation of Alkynes Catalyzed by Transition Metals

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Abstract

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Alkynes are a fundamental class of compounds in chemistry. One such use for alkynes is the formation of alkenes, another class of compounds that have been a subject of interest due to their significance in biologically active molecules and highly variable structures. Most alkenes exist in either a *Z* or *E* conformation and can have up to four unique substituents branching from them. Formation of alkenes via the reduction of alkynes controlled by transition metal catalysts to favor certain stereo- and regioisomers is an important goal in organic synthesis, which has led to the development of novel methods. Here, we describe two such methods for the synthesis of alkenes from alkynes. The first method allows for the formation of isomerically enriched *Z*-alkenes from the reductive cross coupling of terminal alkynes with bulky alkylboranes. This silver-catalyzed hydroalkylation method utilizes a 1,2-metalate shift to accomplish its stereoselectivity. Significantly, this method improves upon prior work by allowing for the formation of increasingly complex products by expanding the scope of this type of reaction to include secondary alkylboranes. The second method, whose development is incomplete, harnesses the steric and electronic biases of silyl-protected alkynes to regioselectively synthesize alkenes via nickel-

catalyzed hydroalkylation with alkyl iodides. Regioselectivity in this method is substrate dependent, as alkylation can occur at either position on the alkyne depending upon the silyl protecting group used.

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LIST OF ABBREVIATIONS

Å:	Angstrom
Ac:	Acetyl
Ar:	Aryl
9-BBN	9-Borabicyclo(3.3.1)nonane
Bn:	Benzyl
Bz:	Benzoyl
DMF:	Dimethylformamide
ESI MS:	Electrospray Ionization Mass Spectrometry
Et:	Ethyl
EWG:	Electron Withdrawing Group
GC/MS:	Gas Chromatography/ Mass Spectrometry
h:	Hour
Hz:	Hertz
IMes:	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidine
i-Pr:	*iso*-Propyl
IPr:	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidine
L_n:	Ligand
Me:	Methyl
Mes:	Mesityl
MHz:	Megahertz
mp:	Melting Point
Ms:	Mesyl

NHC:	*N*-Heterocyclic carbene
NMR:	Nuclear Magnetic Resonance

Abbreviations for NMR Splitting:

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

Ph:	Phenyl
PG:	Protecting Group
ppm:	Parts Per Million
rt:	Room Temperature
TBS:	*tert*-Butyldimethylsilyl
t-Bu:	*tert*-Butyl
Tf:	Trifluoromethanesulfonyl
THF:	Tetrahydrofuran
TLC:	Thin Layer Chromatography
TMS:	Tetramethylsilane
Tri:	2,4-bis[2,6-bis(1-methylethyl)phenyl]-2,4-dihydro-5-phenyl-3H-1,2,4-Triazol-3-ylidene
Ts:	*para*-Toluenesulfonyl

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I should also thank the other professors that have guided me through graduate school. Professor Forrest Michael, who I was fortunate enough to share weekly group meetings with, was a constant force of growth for my education. His encyclopedic knowledge could consistently call upon references and their significance to the field, which was incredibly beneficial when analyzing novel science. My thanks also goes out to my current and former committee members: Matt Golder, Alshakim Nelson, and Jesse Zalatan. Their critique and encouragement have been essential for me to get to this point.

Thank you to the other members of the Lalic Lab. For my mentors, Megan Armstrong, Madison Goodstein, and Avijit Hazra, it's hard to believe how much they taught me about their chemistry while juggling me between their projects. Their different styles each taught me

something unique. Even while I was working on my project independently, Mitchell Lee, James Baumann, and Derek Obenschain were always happy to guide me in the right direction and seed prospective experiments in my head. For the members of my cohort, Austin Shaff, Brianne King, and Anton Taraskin, not was your lighthearted company a warm welcome to graduate school but you also allowed me to share in my sufferings while dealing with classes. For my juniors, Crystal Chung, Bradley Gardner, Langxuan Yang, Bofei Wang, and Yimin Lang, thank you for encouraging me to be a good role model.

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Finally, without the support and love of my family, I never would have been able to achieve what I have done. To my parents, Tim and Sheila, who have always looked after my best interests and encouraged me every step of the way, and my favorite sister, Bethany, whose footsteps I followed for so long, thank you.

For the myriad others who have accompanied me that I failed to mention, thank you, too.

DEDICATION

To my parents, Tim and Sheila,

my sister, Bethany,

and the friends I made along the way,

I am blessed to have you in my life.

Chapter 1. (Z)-Selective Hydroalkylation of Terminal Alkynes with Secondary Alkylboranes

1.1 Introduction

Alkenes are a fundamental building block of organic chemistry. Their abundance in pharmaceuticals and natural products have made them a prime target for synthetic method development. The defining element of an alkene, a singular π bond, prevents rotation about the bond and, consequentially, gives rise to different isomeric forms.[1] For disubstituted alkenes, *E* and *Z* stereoisomers present distinct characteristics and require different methods for their formation.[2] Due to the reactivity of the π bond, many methods have been developed to construct a wide variety of stereoselective alkenes.

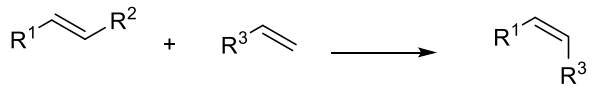
Of these two stereoisomers, *Z*-alkenes offer the unique challenge of being thermodynamically unstable relative to *E*-alkenes, which limits the routes in which they can be synthesized. An efficient synthesis of a Z-alkene should form a new alkene from the convergence of multiple starting molecules that do not have pre-set stereochemistry across the site at which the molecular fragments are being added, or coupled, to one another. Previous methods have managed to exhibit some, but not all, of the factors fundamental to an ideally efficient convergent synthesis.[3] For instance, the classical method of forming *Z*-alkenes is via unstable ylides undergoing the Wittig reaction, though the products of this reaction suffer from poor diastereoselectivity. More modern methods include cross-metathesis, semi-reduction, and cross coupling, though each method is limited in its efficiency.

For cross metathesis (Scheme 1.1a), chiral catalysts developed in the last decade have allowed for thermodynamically unfavorable *Z*-alkenes to be synthesized in good yields and excellent

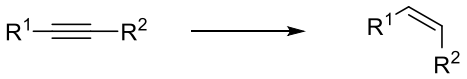
stereoselectivities. However, the considerations that must be made toward the electronic properties and equivalence for each alkene reactant limit this reaction's efficacy. For metathesis, conditions and catalysts require significant modification depending upon the alkene's properties, such as functional groups present upon the fragment and the alkene's electron density, which can pose a challenge when attempting to combine complex fragments. Cross metathesis typically requires significant excess of one alkene being used, which is atomically, and potentially economically, inefficient.[4]

Scheme 1.1. *Methods of* Z*-Alkene Synthesis*

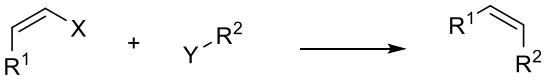
a) Cross Metathesis:



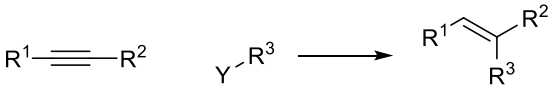
b) Semireduction:



c) Cross Coupling:



d) Reductive Coupling (this work):

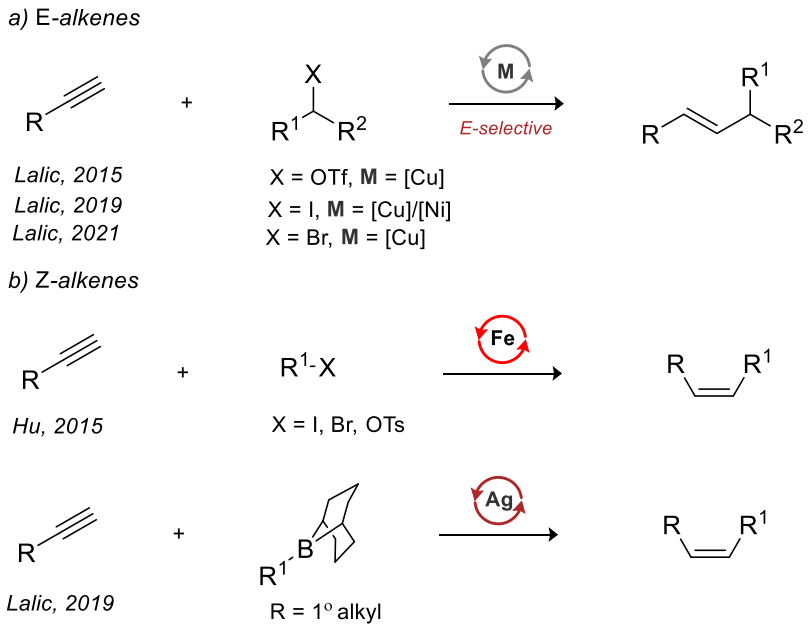


Semireduction (Scheme 1.1b) suffers due to no new C-C bond being formed, which is inefficient in applications where number of steps and cumulative yield are critical. In the construction of large molecular skeleton over many steps, any step that does not add to the structure and only modifies the preexisting structure is not ideal. Furthermore, diastereoselective semireduction is limited to molecules with internal alkynes with no other π-systems that would be

undesirably reduced, which limit their scope.[5] Lastly, cross coupling (Scheme 1.1c) sets the geometry of the alkene prior to the reaction itself, so other steps are necessary to form the alkene and its substitution pattern.[6]

Compared to these methods, reductive coupling accomplishes the formation of an alkene along with establishing its stereochemistry while also forming a new C-C bond (Scheme 1.1d). Hydroalkylation is merely one branch of reductive coupling, though many reactions have been developed that utilize this efficient process for the sake of novel transformations. An example of hydroalkylation of alkynes has been presented by Hu, whose radical initiated Fe-catalyzed reductive coupling yields *Z*-alkenes in in moderate yields and good diastereomeric ratios of > 9:1 (Scheme 1.2b).[7]

Scheme 1.2. *Alkene Synthesis via Hydroalkylation*



In a similar vein to Hu's work, our lab has been dedicated to developing hydroalkylation reactions that offer methods of efficiently synthesizing diastereoselective alkenes from alkynes via transition metal catalysis. Reductive coupling methods developed in our lab address these

fundamental problems with other methods of alkene formation that hinder their use in total synthesis applications. Hydroalkylation has been a successful method for the synthesis of *E*-alkenes through the utilization of terminal alkynes with alkyl iodides, alkyl triflates, and α-bromo carbonyls (Scheme 1.2a).[8–10] Additionally, prior work in our lab has established an efficient silver-catalyzed synthesis of *Z*-alkenes that utilizes terminal alkynes and primary alkylboranes (Scheme 1.2b).[11]

However, this method was limited due its inability to couple alkynes with increasingly substituted alkylboranes. In light of this challenge, we investigated how to iterate upon this reaction to expand its scope to secondary alkylboranes and allow for the synthesis of more complex *Z*-alkenes via silver-catalyzed hydroalkylation.

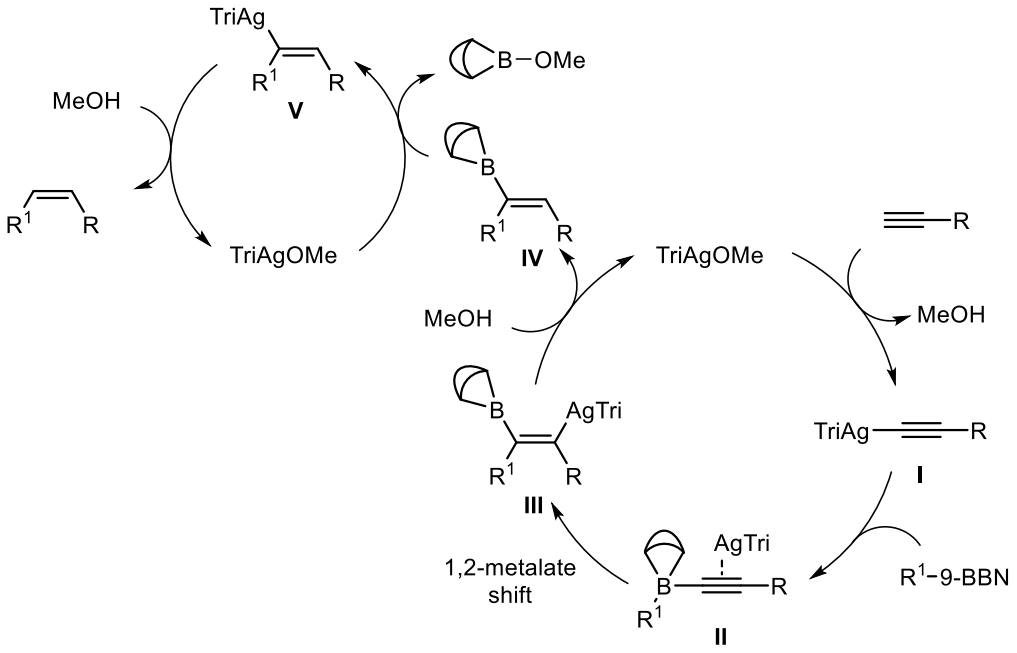
1.2 Results and Discussion

1.2.1 *Preliminary Results*

Recent investigations into the mechanism of the silver-catalyzed hydroalkylation of terminal alkynes with primary alkylboranes offered insight on how to approach the task of modifying the reaction to support bulkier alkylboranes (Scheme 1.3).[12] In this transformation, a base reacts with an alkyne to form a metal acetylide **I**, which can then add to an alkylborane to form an alkynylboronate. The alkynylboronate **II**, whose alkyne is weakened by π-coordination of the Ag catalyst, then undergoes intramolecular attack upon the alkyne by an alkyl substituent of the alkylborane via a rate limiting 1,2-metalate shift. Stereochemistry is set at this step, as the migrating alkyl group must, relative to the bulky metal complex, add to the opposite side of the alkyne to force the formation of the alkenyl silver complex. The resulting tetrasubstituted alkene **III** then undergoes protodemetalation to recycle the Ag catalyst, which is followed by

transmetalation with the silver catalyst, then another demetalation step to yield the product and the recycled catalyst.

Scheme 1.3. *Proposed Mechanism of Hydroalkylation with Alkylboranes*



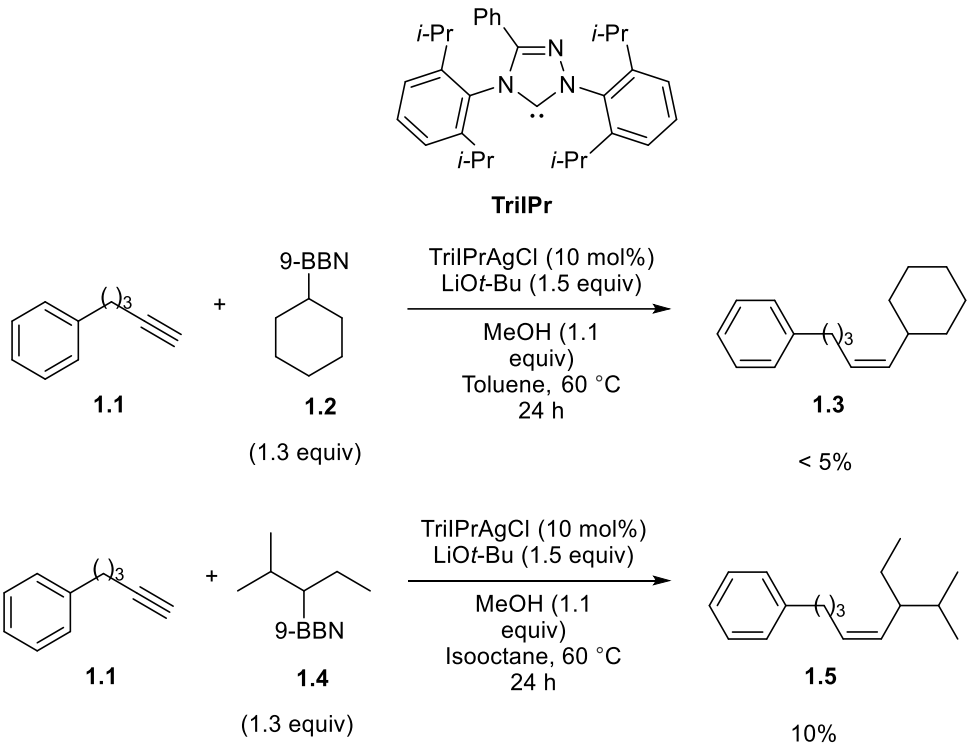
The basis for this mechanism can be found in investigations that began in the 1960s and 70s. Brown's synthesis of alkynylboronates via lithium acetylides supports the formation the silver acetylide **I** in our reaction.[13] Suzuki's work to understand the *cis* stereochemistry caused by the 1,2-metalate shift of the alkynylboronate **II** gives reason as to why *Z*-alkene products are produced in great diastereoselectivity.[14] The *cis* conformation is expected to be increasingly favored as the steric bulk of the trialkylborane increases due to the greater steric clash of the *syn* alkyl and dialkylboryl groups that would be present in the *E*-alkene product. A critical step of this mechanism is the *Z*-selective 1,2-metalate shift, whose existence is well-founded. In Zweifel's work, there is evidence for π-system activation via iodonium, which then allows for a 1,2-metalate shift to be *Z*-selective, as the migrating alkyl group must add to the opposite side of the iodonium to overlap the $\sigma^*_{C\text{-}I}$ orbital and break the corresponding C-I bond.[15] Analogous to this, Wrackmeyer

proposed the π-activation of alkynylboronates via a platinum complex, [16] which, along with the X-ray crystal structure of TriIPrAg-coordinated alkynylborane **II**, supports our catalyst's ability to promote *Z*-alkene formation through its Lewis acidity.[11] To round out the catalytic cycle, NMR experiments that observe the alkenyl ^{1}H chemical shift support the formation of the alkenyl silver complex **V** from the alkenylborane **IV** and subsequent protodemetalation to yield the *Z*-alkene, though there is no direct evidence to support the formation of alkenylborane **IV** from the tetrasubstituted alkene **III**.

Adapting this mechanism to secondary alkyl boranes posed itself as a challenge, as a secondary group would be sterically more similar to the previously used non-migrating group, 9-BBN, which could then lead to undesired products as a result of the improper group migrating.[17] Furthermore, with increased steric hindrance of the migrating group, slower reaction times and consequential side reactions had to also be considered. Ideally, this increased hindrance would also improve the diastereomeric ratio of product, though these ratios were already excellent for primary alkylboranes (>300:1 *Z*:*E*).

Initial inquiries into adapting the reaction conditions that were successful for primary alkylboranes began with 5-phenyl-1-pentyne **1.1** and 9-cyclohexyl-9-borobicyclo[3.3.1]nonane **1.2**, which yielded trace amounts of *Z*-alkene product **1.3** (Scheme 1.4). During this initial screening process, it was discovered that alkylborane **1.4** and changing the solvent to isooctane improved the yield to 10% with 95:5 *Z*:*E* regioselectivity. Thus, this alkylborane was used for further reaction optimization.

Scheme 1.4. *Preliminary Reaction Conditions*



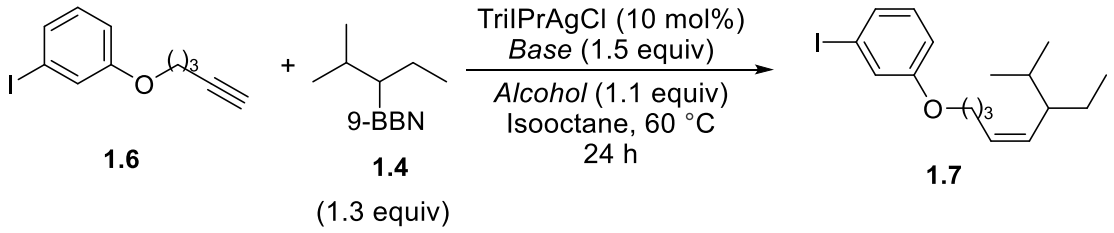
1.2.2 *Reaction Optimization*

With an initial yield used as a starting point, the reaction conditions were gradually modified in order to improve the yield of the *Z*-alkene product while maintaining a high diastereomeric purity. This process began with the modification of reagents and their equivalents, which was followed by observing the effects of temperature and time upon the reaction. Once yields began to plateau, greater alterations, such as variable solvents, catalysts, and alternative alkylboranes were tested.

Taking into account Brown's work on the formation of lithium acetylides and the established need for the reaction to have an alcohol present to facilitate multiple protodemetalation steps, a series of reactions using six lithium bases and six alcohols were prepared (Table 1.1). Alkyne **1.6** was used for this series of experiments to gauge whether the optimization of conditions was improving the yields of multiple substrates. It was found that the reaction failed to proceed

when amine, silyl, or highly nucleophilic bases were used, though both *tert*-butoxide and isopropoxide bases were moderately successful, with the highest yield being 42%. In the case of lithium isopropoxide, the reaction was tolerable of each alcohol, though the yield of each of these reactions failed to surpass the yield of the reaction with lithium *tert*-butoxide and neopentyl alcohol, which was found to be the optimal combination of alcohol and base for these conditions.

Table 1.1 Alcohol and Base Screen

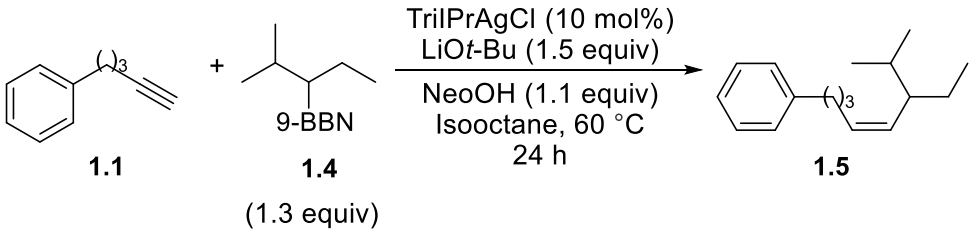


	MeOH	EtOH	*i*-PrOH	*t*-BuOH	NeoOH	*t*-AmOH
LiHMDS	0	0	0	0	19	0
$LiNH_2$	0	0	0	0	0	0
LiO*i*-Pr	25	34	17	15	30	12
LiO*t*-Bu	17	28	1	5	42	6
LiOMe	0	1	2	41	11	6
LiOTMS	0	0	0	0	0	0

To further the improve the yield, the four most promising base and alcohol pairs were subjected to a series of reactions where both solvent and temperature were modified. Aside from the original solvent, toluene, similar nonpolar solvents were used: benzene, chlorobenzene, and isooctane. In each of these four solvents, reactions were performed with each base and alcohol pair at 45 °C, 60 °C, and 75 °C (Table 1.2). Isooctane proved itself to be the most successful solvent

regardless of temperature or reagent used. For both base and alcohol pairs that included lithium isopropoxide, reactions at 75 °C proved to be most successful, whereas reactions including lithium *tert*-butoxide were most successful at 60 °C. Overall, the highest yield was achieved with neopentyl alcohol, lithium *tert*-butoxide, and isooctane at 60 °C, with a yield of 42%. Taking into account the need for only one equivalent of both alcohol and base in the reaction, varying excesses of each reactant aside from the alkyne were tested.

Table 1.2. Solvent and Temperature Screen

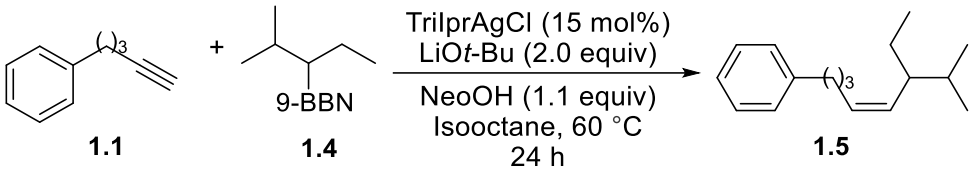


Temperature (°C)	Solvent	Yield (%)
45	Isooctane	27
45	Benzene	14
45	Toluene	13
45	Chlorobenzene	7
60	Isooctane	42
60	Benzene	17
60	Toluene	14
60	Chlorobenzene	6
75	Isooctane	27
75	Benzene	6
75	Toluene	7
75	Chlorobenzene	3

Though excesses of these reagents did not inhibit the reaction, there were only minor improvements to the yield aside from using a slightly increased amount of catalyst and base. Considering the complete consumption of the alkyne when the reaction was stopped and the minor impact of these excess reagents, these results indicated that either the alkyne was undergoing some side reaction to form an alternative product or the catalyst was degrading during the reaction.

Further investigation on the effect of time and temperature relative to the reaction's completion was performed in order to better understand the relationship between residual alkyne, product yield, and catalyst degradation. Three reactions were set up simultaneously: one under normal conditions, another with double catalyst loading, and a third under normal conditions with additional catalyst added after 8 hours. Though the reaction with doubled catalyst loading proceeded more swiftly during the first 8 hours of the reaction, its yield after 24 hours was similar to the yield of the normal reaction conditions. For the reaction that included additional catalyst added later, there was only a 5% increase in yield after 24 hours relative to the normal conditions. In each case, yields plateaued after 24 hours and decreased by 1-2% over the next 48 hours, which indicated that there was little issue with running the reaction too long. Additionally, after 8 hours, 25% of the alkyne had not been consumed while having a product yield of 40% under otherwise normal reaction conditions, whereas the reaction with double catalyst loading had 17% unconsumed alkyne and 43% yield. For each reaction, alkyne was completed consumed after 24 hours.

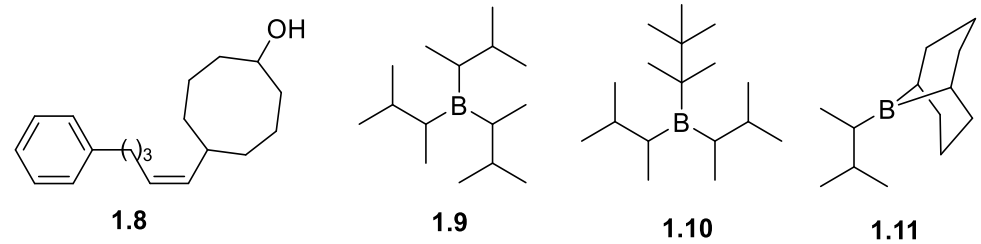
Table 1.3. Significance of Reaction Temperature Upon Alkyne Consumption



1.1 **1.4** **1.5**

Temperature (°C)	Yield (%)	Residual Alkyne (%)
25	4	68
45	27	45
60	46	0
75	27	19
90	20	6

Considering these results, time-dependent catalyst degradation did not appear to be significant, as yields were similar even when additional catalyst was added later. Side reactions limiting yield appeared to be significant, particularly after 8 hours, where the proportion of alkyne consumed relative to the change in yield increased. The effect of temperature upon the reaction's yield was also monitored more closely (Table 1.3). When the reaction's temperature was either increased or decreased, product yields fell and residual alkyne quantities rose. This trend became more extreme as temperatures increasingly diverged from 60 °C, as only 4% and 20% yield were attained at 25 °C and 90 °C, respectively.



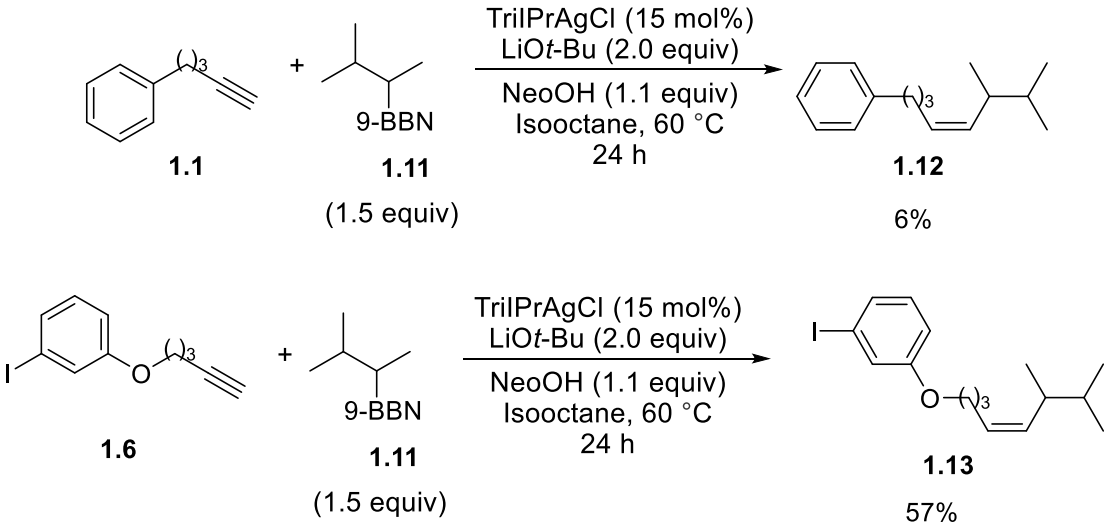
1.8 **1.9** **1.10** **1.11**

potential side product *alternative alkyl boranes*

Figure 1.1. Modification of the Alkylborane to Limit Side Reactions

One postulated side product was alkene **1.8**, which would result from the migration of the cyclooctyl ring rather than the preferred alkyl group on alkylborane **1.4** (Figure 1.1).[18] Due to this possible competitive migration, alternative secondary alkylboranes were considered for their use in this reaction. Thexylborane **1.10** was promising, as a tertiary group would be less likely to migrate due to its steric hindrance. Another approach included trialkylborane **1.9**, where each alkyl group was identical, so there would be no competition. Unfortunately, both methods failed, as the steric hindrance of each alkyl group makes the formation of a trisubstituted alkylborane prohibitively unfavorable. To further probe the impact of alternative alkylboranes, alkylborane **1.11** was also synthesized and tested against a variety of alkynes (Scheme 1.5). Though some yields were moderately improved with the use of this alkylborane, the sharp loss in yield for the 5-phenyl-1-pentyne-derived product **1.12** indicated that this alkylborane would be an effective but not broadly viable alternative.

Scheme 1.5. *Reactions with 2-methyl-2-butene*



Due to plateauing yields after modifying every other aspect of the reaction, alterations to the catalyst were considered. Silver NHC catalysts are believed to be ideal for this hydroalkylation

reaction due to the metal's ability to coordinate to the alkyne due to its Lewis acidity while the steric hindrance of the NHC provides diastereoselectivity, so four other silver NHC catalysts (Figure 1.2) were tested. These catalysts were tested in seven solvent mixtures in a 3:2 ratio of novel solvent to isooctane, with each solvent being chosen for its similar polarity to isooctane: chlorobenzene, toluene, benzene, trifluoromethylbenzene, xylenes, cyclohexane, and pentane. The latter two of these solvents did not inhibit the reaction for at least one of the chosen catalysts, with both pentane and cyclohexane showing promise for TriIPrAgCl and TriMesAgCl. These four catalyst and solvent pairs were then used in reactions with the four alcohol and base pairs previously identified in earlier screens. As a result of these experiments, it was determined that TriIPrAgCl and TriMesAgCl has similar reactivities in both cyclohexane and isooctane. However, reactions using TriMesAgCl yielded the product alkene with lower selectivity, with a *Z*:*E* ratio of up to 75:25, which indicated that the steric bulk of the TriIPr NHC ligand is likely responsible for the reaction's strong diastereoselectivity. No alternative alcohol and base pair notably improved the yield of the reaction in conjunction with these solvents and catalysts.

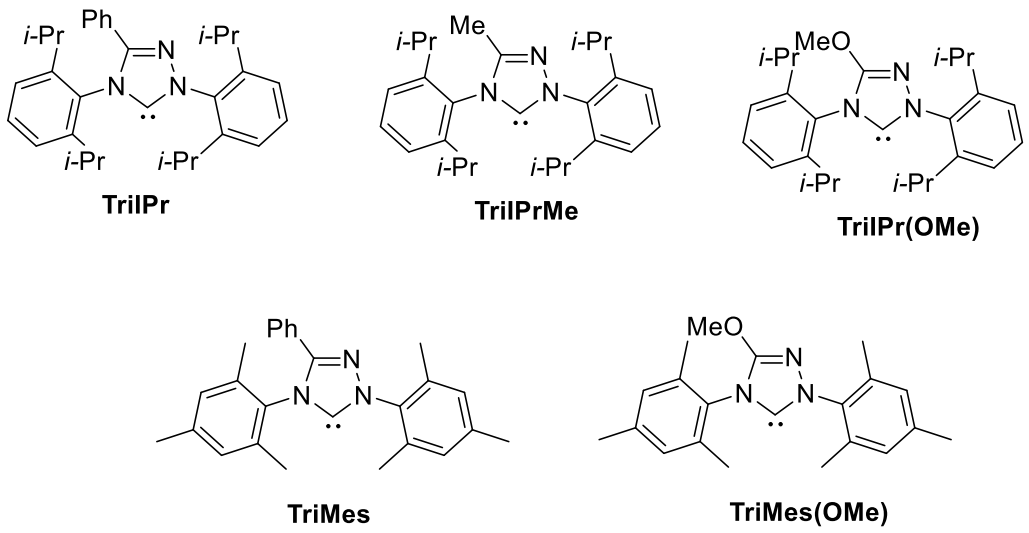
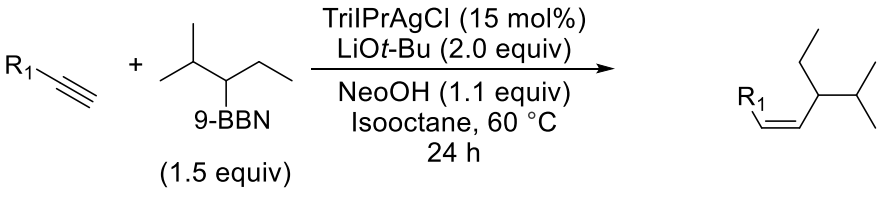


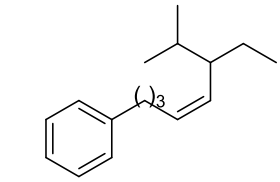
Figure 1.2. Triazole NHC Catalysts

1.2.3 *Substrate Scope*

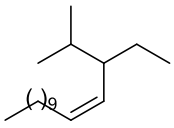
This reaction proceeded in moderate yield for a wide variety of alkynes and tolerated a number of functional groups, including esters, silyl-protected alcohols, halides, nitriles, terminal alkenes, furans, and amides (Table 1.4). These products were obtained highly selectively, favoring the *Z*-alkene (*Z*:*E* > 95:5). A limitation for this reaction is that it is largely incompatible with alcohols and carboxylic acids.

Table 1.4. Substrate Scope

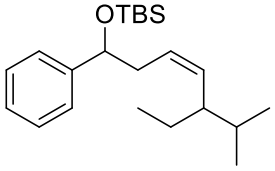




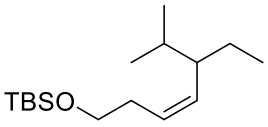
1.5 47% (45%)



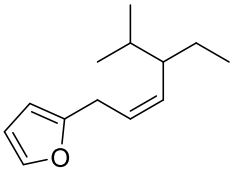
1.14 41%[a]



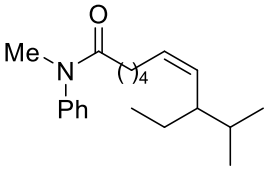
1.15 37%[a]



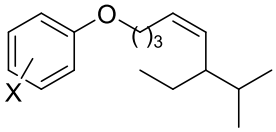
1.16 46%



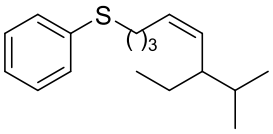
1.17 27%



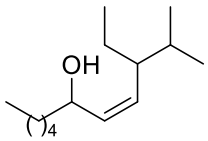
1.18 55%[a]



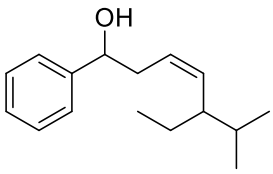
X = 4-CF_3 **1.19** 30% (30%)
4-Br **1.20** 25%[a] (15%)
4-CO_2Me **1.21** 44%
4-CN **1.22** 26% (25%)
3-I **1.7** 58%
2-allyl **1.24** 53%



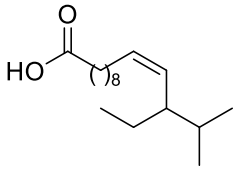
1.25 46%



1.26 0%



1.27 11%



1.28 0%

GC Yield (NMR Yield). All products obtained in > 95:5 *Z*:*E* ratio. Alkylboranes were prepared in situ by stirring corresponding alkene (1 equiv) and 9-borabicyclo[3.3.1]nonane dimer (0.45 equiv) overnight at 60°C. [a]Reaction Conditions: TrIlPrAgCl (15 mol%), alkyl borane (1.5 equiv), LiO*i*-Pr (2.0 equiv), EtOH (1.1 equiv), and isooctane (1.0 M), 60 °C, 24 h.

1.3 CONCLUSION

A method for the synthesis of *Z*-alkenes from the hydroalkylation of terminal alkynes and secondary alkylboranes has been developed. This procedure is effective for a broad scope of alkynes and produces alkenes in moderate yields. This transformation occurs in high diastereoselectivity, favoring the energetically unfavorable *Z*-alkene. In an improvement upon the previously developed method that utilized primary alkylboranes, alkyl groups with greater steric hindrance are able to migrate during the reaction's 1,2-metalate shift, which broadens the scope of *Z*-alkenes that can be produced via hydroalkylation.

1.4 EXPERIMENTAL

1.4.1 *General Information*

All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a glovebox (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). 1H- and 13C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. 1H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak (CDCl3 (7.26 ppm)). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), coupling constants in Hertz (Hz), integration. Mass spectra were collected on a JEOL HX-110 mass spectrometer. Gas Chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C. Materials: THF, CH2Cl2,

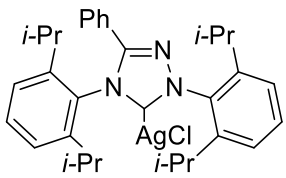
ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous methanol was purchased from Millipore Sigma and was degassed and stored over 4Å molecular sieves. Isooctane was purchased from Fisher Scientific and was degassed and stored over 4Åmolecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were stored over 4Å molecular sieves prior to use. Commercial reagents were purchased from Millipore Sigma, TCI America, GFS-Chemicals, Ark-Pharm, Combi-Blocks, Oakwood Chemicals, Strem Chemicals and Alfa Aesar. 9-BBN Dimer was purchased from Millipore Sigma and recrystallized from THF.

1.4.2 *Reaction Development*

All reactions were performed on a 0.05 mmol scale. In a nitrogen-filled glovebox a dram vial was charged with a stir bar, LiOt-Bu (2.0 equiv), catalyst (15 mol%), 5-phenyl-1-pentyne (1.0 equiv), 1,3,5-trimethoxy benzene (TMB, internal standard), 9-(2-methylpentan-3-yl)-9-borabicyclo[3.3.1]nonane (1.5 equiv), neopentyl alcohol (1.1 equiv) and solvent. The reaction mixture was stirred at 60 °C and monitored by gas chromatography for reaction completion. An aliquot was taken every 24 hours.

1.4.3 *Synthesis of Catalysts*

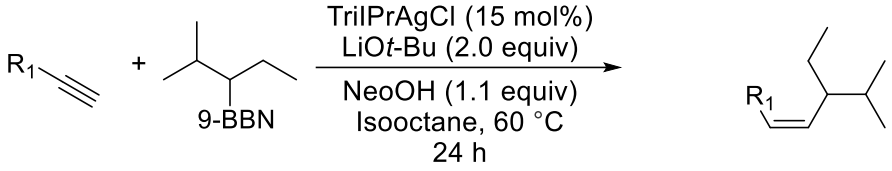
The silver catalysts were synthesized using an adapted procedure from Sadighi et. al. that was used for the synthesis of SIPrAgCl.[19]



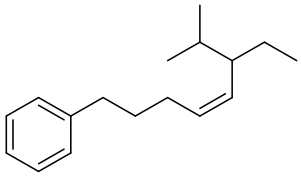
TriIPrAgCl, complex was synthesized from TriHCl,[20] and isolated as a white solid (700.0 mg 67% yield). ^{1}H NMR (300 MHz, CDCl*3*) δ 7.64 – 7.50 (m, 2H), 7.48 – 7.39 (m, 3H), 7.39 – 7.28

(m, 6H), 2.71 – 2.55 (m, 2H), 2.55 – 2.40 (m, 2H), 1.41 – 1.17 (m, 18H), 1.00 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.0 (dd, *J*(^{109}Ag^{13}C) = 265.2 Hz, *J*(^{107}Ag^{13}C) = 229.2 Hz), 153.6, 153.6, 145.7, 145.3, 134.9, 131.8, 131.7, 131.5, 131.5, 129.1, 128.0, 125.3, 124.4, 29.1, 25.1, 24.5, 23.9, 22.9.

1.4.4 *General Procedure for the (*Z*)-Selective Hydroalkylation of Terminal Alkynes*



In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and LiOt -Bu (80.1 mg, 1.0 mmol, 2.0 equiv). To this was added TriIPrAgCl (45.7 mg, 0.075 mmol, 0.15 equiv), alkyne (0.50 mmol, 1.0 equiv), alkylborane (1.5 equiv), neopentyl alcohol (48.5 mg, 0.55 mmol, 1.10 equiv), and isooctane (5 mL). The reaction mixture was heated at 60 °C and stirred for 24 hours. After 24 hours, an aliquot of the crude reaction mixture was analyzed by GC, and the reaction was quenched with the addition of sodium perborate (150 mg, 0.75 mmol, 1.5 equiv) in 5 mL THF and 5 mL deionized water. The mixture was stirred at room temperature for 1 hour, and then extracted with ether (3 x 10 mL) and dried over MgSO4. The crude mixture was concentrated under reduced pressure and purified by silica gel chromatography.

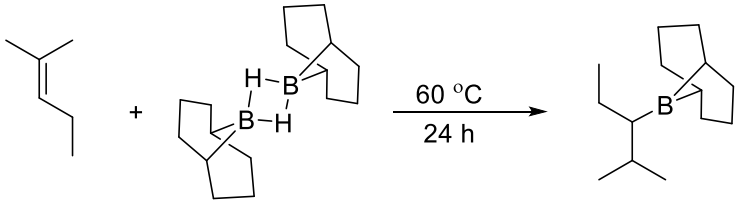


(Z)-(6-ethyl-7-methyloct-4-en-1-yl)benzene (1.5), was synthesized according to the general procedure. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 10%) and isolated as a colorless oil (53.8 mg, 47% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.36 – 7.24

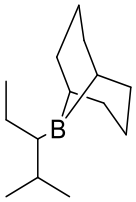
(m, 2H), 7.24 – 7.14 (m, 3H), 5.73 – 5.27 (m, 1H), 5.25 – 4.89 (m, 1H), 2.75 – 2.56 (m, 2H), 2.19 – 1.90 (m, 3H), 1.77 – 1.63 (m, 2H), 1.61 – 1.43 (m, 2H), 1.22 – 1.08 (m, 1H), 0.93 – 0.74 (m, 9H).

1.4.5 *Alkylborane Starting Materials*

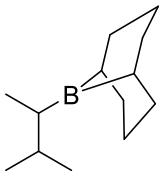
General Procedure for the Hydroboration of Alkenes with 9-BBN:



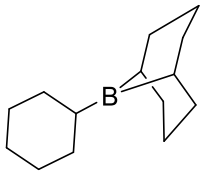
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, 9-BBN dimer (0.55 g, 2.3 mmol, 0.45 equiv), and alkene (5.0 mmol, 1.0 equiv). The reaction is then stirred at 60 °C for 24 hours and used without further purification.



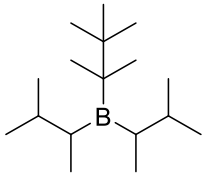
9-(2-methylpentan-3-yl)-9-borabicyclo[3.3.1]nonane (1.4) was used neat and prepared according to the general procedure.



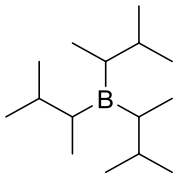
9-(3-methylbutan-2-yl)-9-borabicyclo[3.3.1]nonane (1.11) was used neat and prepared according to the general procedure.



9-cyclohexyl-9-borabicyclo[3.3.1]nonane (1.2) was used neat and prepared according to the general procedure.



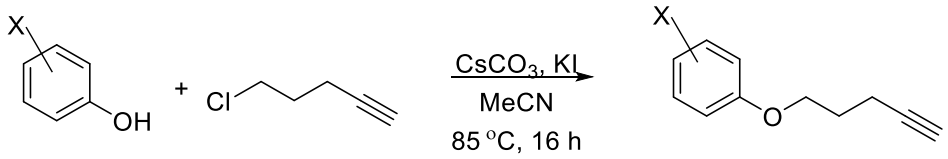
***bis*(3-methylbutan-2-yl)(2,3,3-trimethylbutan-2-yl)borane (1.10).** A reaction flask was charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen to 0 °C. The flask was charged with BH_3·THF (1.0 mL, 1.0 M). Then, 2,3-dimethyl-2-butene (0.12 mL, 1.0 mmol, 1.0 equiv) was added dropwise and the reaction mixture was allowed to stir for one hour. 2-methyl-2-butene (0.32 mL, 3.0 mmol, 3.0 equiv) was then added. The reaction was stirred for 16 hours and then concentrated under reduced pressure in an inert atmosphere.



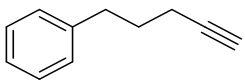
***tris*(3-methylbutan-2-yl)borane (1.9).** A reaction flask was charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen to 0 °C. The flask was charged with BH_3·THF (1.0 mL, 1.0 M). Then, 2-methyl-2-butene (0.42 mL, 4.0 mmol, 4.0 equiv) was added dropwise and the reaction mixture was allowed to stir for 16 hours. The resulting mixture was then concentrated under reduced pressure in an inert atmosphere.

1.4.6 *Alkyne Starting Materials*

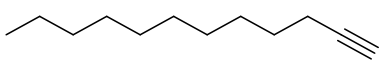
General Procedure for the Preparation of Terminal Alkynes:



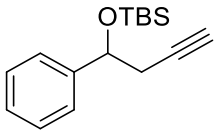
A reaction flask was charged with a stir bar, Cs_2CO_3 (5.0 g, 30.0 mmol, 1.5 equiv), KI (0.65 g, 2.0 mmol, 0.10 equiv), flame-dried under vacuum, and allowed to cool under nitrogen. The flask was then charged with MeCN (67 mL, 0.3 M), 5-chloropent-1-yne (2.1 mL, 20.0 mmol, 1.0 equiv), and desired phenol (22.0 mmol, 1.1 equiv). The reaction flask was then fitted with a reflux condenser and allowed to stir for 16 hours at 85 °C. 1 M HCl (70 mL) was then added to the reaction mixture, then extracted with ether (50 mL x 3). The combined organic layers were then combined and washed with 1 M HCl (50 mL x 2), water (50 mL x 3),brine (100 mL), then dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography. Alkynes **S1.6-S1.11** were prepared using this procedure.



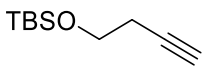
5-phenyl-1-pentyne (1.1) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



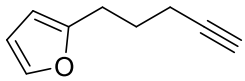
Dodec-1-yne (S1.1) was purchased from TCI America and used without further purification.



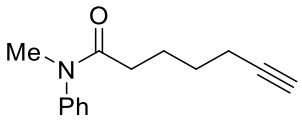
***tert*-butyldimethyl((1-phenylbut-3-yn-1-yl)oxy)silane (S1.2)** was prepared according to a known procedure.[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 4.89 (t, *J* = 6.6 Hz, 1H), 2.75 – 2.49 (m, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 0.97 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H).



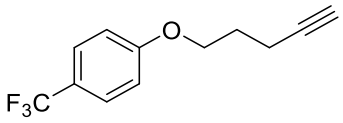
(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (S1.3) was prepared according to a known procedure and has been previously characterized.[22]



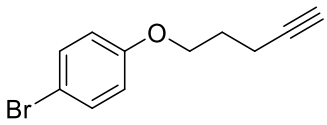
2-(pent-4-yn-1-yl)furan (S1.4) was prepared according to a known procedure and has been previously characterized.[23]



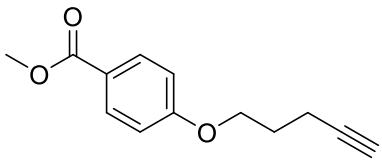
N-methyl-N-phenylhept-6-ynamide (S1.5) was prepared according to a known procedure[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 3.18 (s, 3H), 2.13 – 1.92 (m, 4H), 1.82 (t, *J* = 2.7 Hz, 1H), 1.61 (p, *J* = 7.5 Hz, 2H), 1.36 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.0, 129.6, 127.6, 127.2, 83.9, 68.3, 37.2, 33.3, 27.9, 24.5, 18.0. GCMS (EI) calculated for $[M]^+$ 215.13, found 215.20. FTIR (neat, cm^{-1}): 3306 (s), 2941 (s), 2856 (s), 2249 (s), 1726 (w), 1641 (s), 1595 (s), 1496 (s), 1389 (s), 1292 (m), 1123 (s), 908 (s).



1-(pent-4-yn-1-yloxy)-4-(trifluoromethyl)benzene (S1.6) was prepared according to the general procedure.[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.42 (td, *J* = 6.9, 2.6 Hz, 2H), 2.09 – 1.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 127.0 (q, J = 3.7 Hz), 124.7 (q, J = 270.9 Hz), 123.0 (q, J = 32.7 Hz), 114.6, 83.2, 69.2, 66.5, 28.1, 15.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ -64.45. GCMS (EI) calculated for $[M]^+$ 228.08, found 228.10. FTIR (neat, cm^{-1}): 3308 (s), 3011(w), 2926 (s), 2852 (s), 2361 (w), 2252 (s), 1589 (s), 1519 (s), 1330 (s), 1254 (s0, 1162 (s), 1118 (s), 1068 (s), 1002 (s), 968 (m), 835 (s).

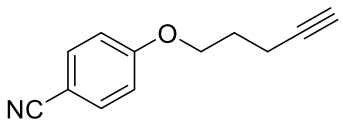


1-bromo-4-(pent-4-yn-1-yloxy)benzene (S1.7) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 2.56 – 2.31 (m, 2H), 2.14 – 1.84 (m, 3H).

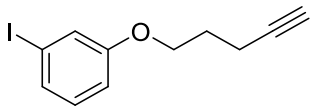


Methyl 4-(pent-4-yn-1-yloxy)benzoate (S1.8) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.44 – 2.33 (m, 2H), 2.16 – 1.72 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 162.7, 131.6, 122.7, 114.1, 83.2, 69.2, 66.3, 51.9, 28.0, 15.1. ESI MS calculated for [M +

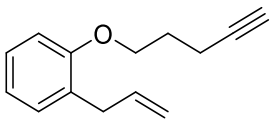
Na]$^+$ 241.2, found 241.2. FTIR (neat, cm^{-1}): 3288 (s), 2936 (m), 2118 (w), 1918 (w), 1715 (s), 1606 (s), 1511 (m), 1254 (s), 1106 (m), 847 (s).



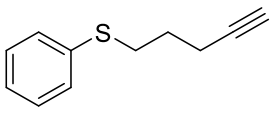
4-(pent-4-yn-1-yloxy)benzonitrile (S1.9) was prepared according to the general procedure and has been previously characterized.[24]



1-iodo-3-(pent-4-yn-1-yloxy)benzene (1.7) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.6 Hz, 2H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 9.7 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 2.53 – 2.38 (m, 2H), 2.15 – 1.95 (m, 3H).

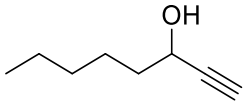


1-allyl-2-(pent-4-yn-1-yloxy)benzene (S1.10) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (q, *J* = 7.2 Hz, 2H), 6.99 – 6.82 (m, 2H), 6.11 – 5.92 (m, 1H), 5.16 – 4.99 (m, 2H), 4.10 (t, *J* = 5.9 Hz, 2H), 3.42 (d, *J* = 6.6 Hz, 2H), 2.55 – 2.38 (m, 2H), 2.14 – 1.92 (m, 3H).

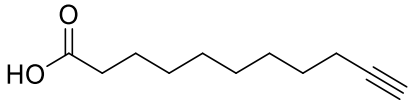


Pent-4-yn-1-yl(phenyl)sulfane (S1.11) was prepared according to the general procedure. ^{1}H

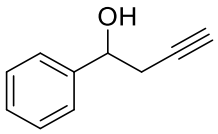
NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 4H), 7.20 (t, *J* = 7.2 Hz, 1H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.37 (td, *J* = 6.9, 2.7 Hz, 2H), 2.00 (t, *J* = 2.3 Hz, 1H), 1.87 (p, *J* = 6.9 Hz, 2H).



Oct-1-yn-3-ol (S1.12) was purchased from TCI America and used without further purification.



Undec-10-ynoic acid (S1.13) was purchased from TCI America and used without further purification.



1-phenylbut-3-yn-1-ol (S1.14) was prepared according to a known procedure and has been previously characterized.[25]

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Chapter 2. REGIODIVERGENT HYDROALKYLATION OF INTERNAL ALKYNES WITH ALKYL IODIDES

2.1 INTRODUCTION

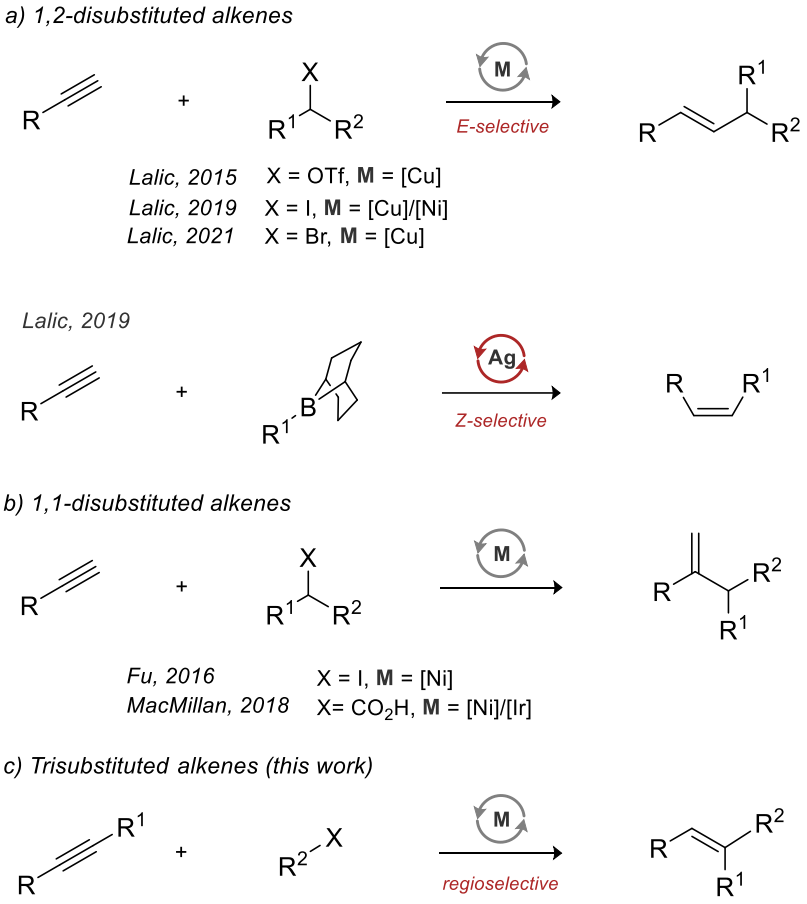
Alkenes are a widely prevalent structural motif in organic chemistry. Natural products and drug molecules both often feature alkenes. The fundamental feature of an alkene is its singular π bond, whose structural rigidity gives rise to a variety of stereo- and regioisomers, all of which can be further modified to provide a wide range of products. Many methods have been developed for the synthesis of alkenes due to their broad relevance. As one of these methods, hydroalkylation is a fundamental transformation that provides stereochemically well-defined alkenes.

Hydroalkylation has shown itself to be an efficient method for the synthesis of a variety of alkenes with differing stereochemical patterns from alkynes. The efficiency of this method is drawn from its capacity to form a new σ C-C bond and an alkene with the desired stereochemistry in the same step, which is in contrast to other methods that rely on at least one of these factors being pre-set within their reactants. Comparatively, the alkynes utilized in hydroalkylation reactions are relatively more simple and readily available. This simplicity also offers the capacity for different transformations to occur on the same starting material, resulting in products with different selectivities.

Disubstituted alkenes with varying stereo- and regioselectivities have been synthesized from alkynes utilizing hydroalkylation methods. *E*-alkenes have been selectively synthesized by our lab via terminal alkynes along with alkyl triflates, alkyl iodides, or α-bromo esters via copper catalyzed methods (Scheme 2.1a).[1-3] We have also demonstrated a silver-catalyzed selective

hydroalkylation for the formation of *Z*-alkenes from terminal alkynes and alkyl boranes (Scheme 2.1b).[4] Both Fu and MacMillan have developed methods for the synthesis of 1,1-disubstituted alkenes from terminal alkynes and nickel or dual nickel/photoredox catalysts, respectively (Scheme 2.1c).[5,6]

Scheme 2.1. *Synthesis of Substituted Alkenes from Hydroalkylation Methods*

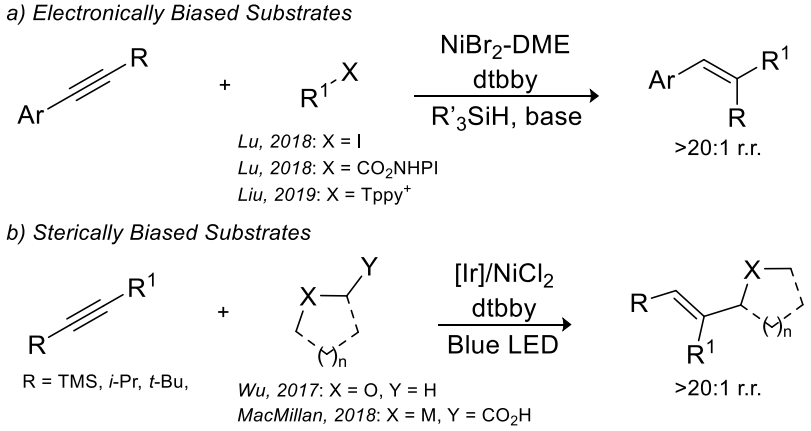


Diastereodivergent methods for the synthesis of alkenes have also been established. These methods of hydroalkylation utilize slight differences within a reaction's conditions to bias the reaction to favor either the *E*- or *Z*-alkene product. Nishikata developed such a method that utilizes terminal alkynes and α-bromo esters in addition to tandem copper and cobalt catalysts.[7] Similarly,

our lab has previously developed a method for the copper and palladium catalyzed hydroarylation of terminal alkynes.[8]

Though a multitude of methods have been developed for the hydroalkylation of terminal alkynes that yield disubstituted alkenes, there are relatively few examples of trisubstituted alkene synthesis via hydroalkylation. In this case, a central challenge to regioselective hydroalkylation is control of the electronic and steric bias of the alkyne's substituents. Depending upon these biases, the syn-selective carbo- or hydrometallation step of the mechanism will favor one regioisomer over the other. Although the mechanism for this nickel-catalyzed reaction is not fully known, evidence put forth by Liu's hydroalkylation of alkynes suggests the existence of a hydrometallation step, rather than a hydroalkylation step, both of which lead to alkylation on a different side of the alkyne.[9] Aryl-substituted internal alkynes have been successfully used in nickel-catalyzed regioselective hydroalkylation methods in the work of Lu and Liu, though these methods are incompatible with alternative alkyl groups (Scheme 2.2a).[9-11] Alternatively, photocatalytic methods have been developed separately by MacMillan and Wu (Scheme 2.2b).[6,12] Both methods rely on sterically biased alkynes, with one substituent being a bulky alkyl or silyl group.

Scheme 2.2. *Regiospecific Hydroalkylation of Internal Alkynes*



This work toward the synthesis of trisubstituted alkenes via hydroalkylation of biased alkynes along with our previously developed stereodivergent hydroalkylation of internal alkynes provided the inspiration for a novel method. Herein, we report the current state of our work on the regiodivergent synthesis of trisubstituted alkenes from silyl-protected internal alkynes.

2.2 Results and Discussion

2.2.1 *Reaction Development*

In order to induce regioselective hydroalkylation of an internal alkyne, a variety of directing groups were considered. An electronic bias could be introduced through a variety of functional groups, including aromatic rings, which have been used to induce alkyl addition on the opposite side of the alkyne.[9] An alternative method is the use of chelating groups that direct the metal to the near side of the alkyne.[6] However, as multiple steps are needed to add and remove these directing groups, these methods are inefficient, which limits their use in late stage diversification of multi-step syntheses, where limiting the number of steps is critical.

Silyl groups are commonly used to protect terminal alkynes and are relatively unique due to their electropositive character. Furthermore, the substituents bound to a silyl group provide an attractive handle for the modification of the protecting group's steric and electronic properties. A bulky silane could potentially hinder the adjacent position upon the alkyne, limit the metal's ability to add to this position, and thereby lead to alkyl addition upon the opposite side of the alkyne instead (Figure 2.1). Alternatively, additional electron withdrawing groups upon the silane could result in alkylation at the position adjacent to the silyl group upon the alkyne. As the silane becomes increasingly electronegative, it will attract electrons from the alkyne and make the near side of the alkyne more electron poor, which, in turn, will increasingly favor the addition of the more electronegative atom at this position during the hydrometallation step. Hydrogen is more

electronegative than nickel, so the following alkyl insertion would yield the product with the added alkyl group at the distal position relative to the silyl directing group, replacing Ni.

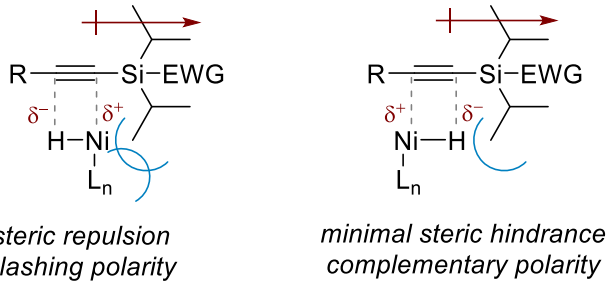
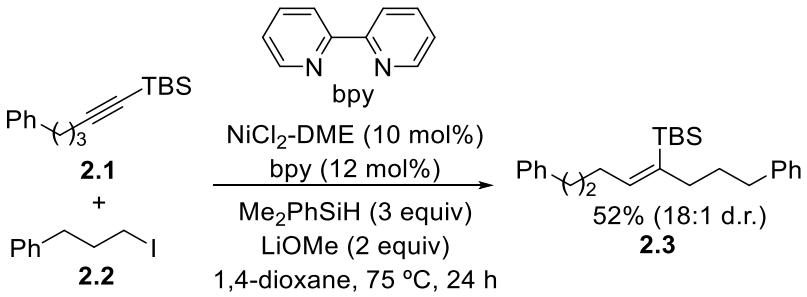


Figure 2.1. Regioselective Hydrometallation's Electronic and Steric Considerations

Taking inspiration from Lu's hydroalkylation of internal aryl alkynes, preliminary reaction conditions were established that utilized TBS as a protecting group, a nickel catalyst, and bipyridine as a ligand (Scheme 2.3). These conditions yielded alkylation adjacent to the silyl protecting group with perfect regioselectivity. However, this method was somewhat unattractive due to its moderate yield of 52%.

Scheme 2.3. *Reaction Conditions for TBS-Protected Alkynes*

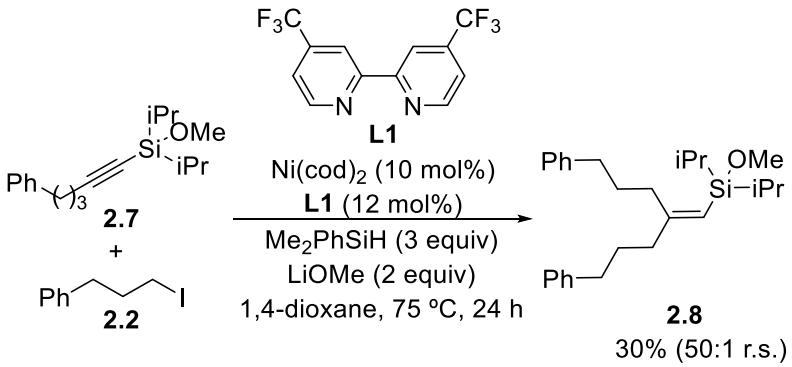


For the other regioisomers, development of an effective directing group was a significant challenge. It was posited that a more sterically hindered and electropositive silyl protecting group would favor the alternative regioisomer due to the metal being less electronegative and bulkier than hydrogen. A variety of silyl protecting groups were envisioned for this reaction, though

procedures for the synthesis of such silanes are not well-developed in literature and many are not commercially available.

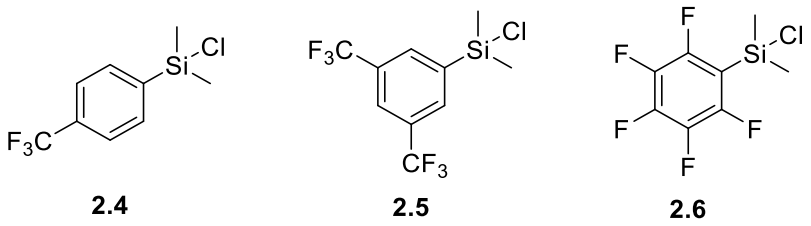
One readily available silane is diisopropyldimethoxysilane, which was an attractive choice for its use as a protecting group due to its bulky alkyl groups and the presence of an electronegative methoxy group. However, utilization of this silane as a protecting group was challenging, as either one or both methoxy groups can be replaced upon attack of the silane by a deprotonated alkyne during the protection reaction. Inhibition of the di-addition product was attempted via modification of the strength of the base, addition speed, reaction time, silane equivalence, and temperature, which provided the mono-addition product in 10% yield. For this silyl-protected alkyne, hydroalkylation conditions were established that favored alkylation on the side of the alkyne opposite of the silyl protecting group. This desired regioisomers was synthesized in 30% yield and a regioisomeric ratio of 50:1 (Scheme 2.4). In consideration of this low yield and the challenging synthesis of the alkyne starting material, alternative silyl protecting groups with similar steric or electronic properties were considered for their viability in this reaction.

Scheme 2.4. *Reaction Conditions for iPr_2OMeSi-Protected Alkynes*



Another potential route to modified phenyl silanes was the Grignard reaction between bromobenzene substituted with electron withdrawing groups and dichlorodimethylsilane, which

was chosen due to its commercial availability. Chlorosilanes **2.4**-**2.6** were chosen for this reaction due to their abundance of fluorine substituents and the possibility that they could electronically bias the alkyne due to fluorine's electronegativity. If sufficiently biased, hydrometallation would favor the addition of hydrogen adjacent to the electron withdrawing silyl group due to hydrogen being more electronegative than nickel. The primary challenges of this Grignard reaction were the possibility of forming the di-addition product, which would yield an inert silane, and the relative polarities of the reactants and products being very similar, which would make isolation challenging via column chromatography. As a result, even after modifying the reaction conditions to favor mono-addition by using dichlorodimethylsilane in excess, the mono-addition product could only be achieved in <10% yield and was highly contaminated with the di-addition product. Utilizing the conditions established for the protection of alkynes with TBSCl, protection reactions were attempted with the novel silyl protecting groups. Unfortunately, these reactions failed and their viability in the hydroalkylation reaction could not be evaluated.



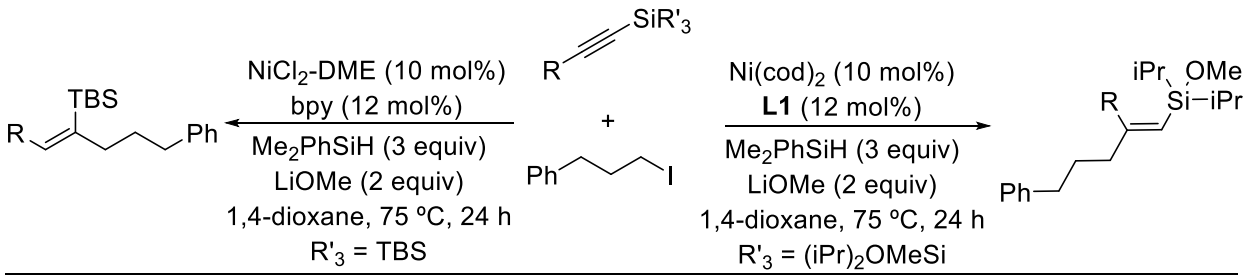
2.4 **2.5** **2.6**

Figure 2.2. Novel Chlorosilanes

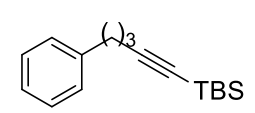
2.2.2 *Substrate Scope*

A number of silyl-protected alkynes were synthesized in preparation for their use in the determination of the breadth of both reactions (Table 2.1). Due to the low yields of these reactions with the test substrate **2.1**, these alkynes were not tested.

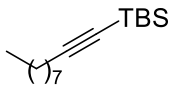
Table 2.1. Substrate Scope Preparation



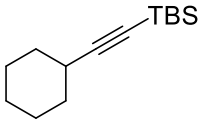
Synthesized TBS-Substituted Alkynes



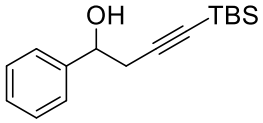
2.1



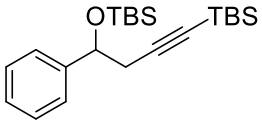
2.9



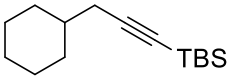
2.10



2.11



2.12



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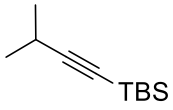

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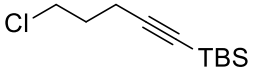

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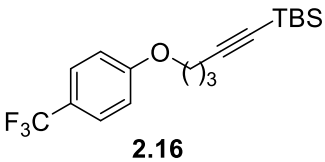

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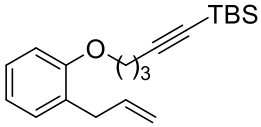

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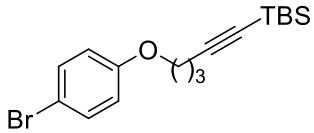

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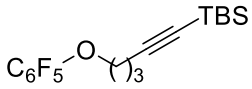

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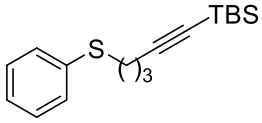

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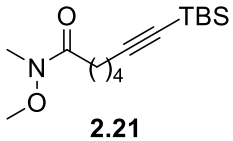
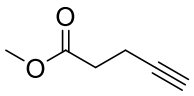


2.21

Synthesized Alkynes



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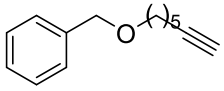

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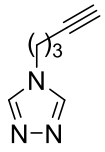

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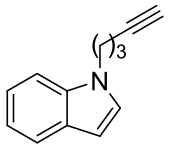

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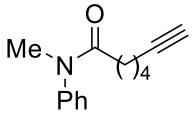

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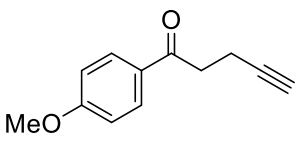

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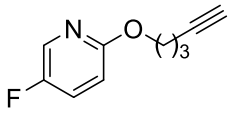

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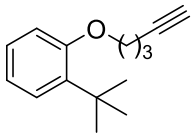

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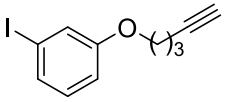

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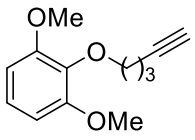


2.31

2.3 CONCLUSION

A method was developed for the regioselective hydroalkylation of silyl-protected alkynes. Though slightly modified reaction conditions and an alternative protecting group were required to synthesize one regioisomer or the other in low-to-moderate yield, both products could be obtained in excellent regioselectivity. Further investigation into this method was not performed due to low yields and the difficultly of substrate synthesis.

2.4 EXPERIMENTAL

2.4.1 *General Information*

All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a glovebox (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). 1H- and 13C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. 1H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak (CDCl3 (7.26 ppm)). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), coupling constants in Hertz (Hz), integration. Mass spectra were collected on a JEOL HX-110 mass spectrometer. Gas Chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C. Materials: THF, CH2Cl2, ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous methanol was purchased from Millipore Sigma and was degassed and stored

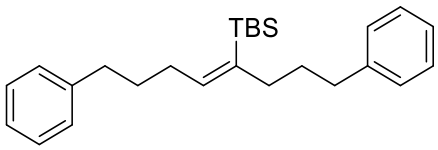
over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were stored over 4Å molecular sieves prior to use. Commercial reagents were purchased from Millipore Sigma, TCI America, GFS-Chemicals, Acros Organics, Ark-Pharm, Combi-Blocks, Oakwood Chemicals, Strem Chemicals, Thermo Fisher Scientific, and Alfa Aesar.

2.4.2 *Reaction Development*

All reactions were performed on a 0.05 mmol scale. In a nitrogen-filled glovebox a dram vial was charged with a stir bar, LiOMe (2.0 equiv), catalyst (10 mol%), ligand (12 mol%), alkyne (1.0 equiv), 1,3,5-trimethoxy benzene (TMB, internal standard), silane (3.0 equiv), alkyl iodide (1.5 equiv) and solvent. The reaction mixture was stirred at 75 °C and monitored by gas chromatography for reaction completion. An aliquot was taken every 24 hours.

2.4.3 *General Procedure for the Hydroalkylation of Silyl-Protected Alkynes: Addition Proximal to Silane*

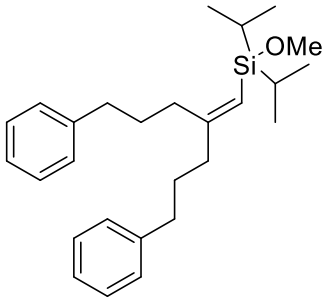
In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and LiOMe (38.0 mg, 1.00 mmol, 2.0 equiv). To this was added alkyne (0.50 mmol, 1.0 equiv), $NiCl_2$·DME (11.0 mg, 0.050 mmol, 5 mol%), **L1** (9.4 mg, 0.060 mmol, 0.12 equiv), alkyl iodide (0.750 mmol, 1.50 equiv), Me_2PhSiH (204.4 mg, 1.50 mmol, 3.00 equiv), and 1,4-dioxane (5 mL). The reaction mixture was stirred at 75 °C, and the reaction progress was monitored by TLC. Upon consumption of the internal alkyne (as monitored by TLC), the reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. An aliquot was analyzed by GC to obtain the diastereoselectivity and regioselectivity of the reactions. The crude reaction mixture was concentrated under reduced pressure and the product was purified by silica gel chromatography. The ratio of isomers for each product was again determined by GC analysis of the isolated product.



(*Z*)-*tert*-butyl(1,8-diphenyloct-4-en-4-yl)dimethylsilane (2.3), was prepared according to the general procedure. The compound was purified by silica gel chromatography with DCM/Hex (0 → 20%) and isolated as a colorless oil (94.7 mg, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 2H), 7.52 – 7.43 (m, 4H), 7.28 (d, *J* = 7.3 Hz, 4H), 4.53 (p, *J* = 3.8 Hz, 1H), 2.73 (dd, *J* = 12.1, 7.8 Hz, 2H), 2.41 (q, *J* = 7.1 Hz, 2H), 1.99 (m, 2H), 1.88 – 1.65 (m, 2H), 1.63 – 1.49 (m, 2H), 1.36 (s, 2H), 1.09 – 1.03 (m, 1H), 0.97 (s, 9H), 0.45 (d, *J* = 3.7 Hz, 6H).

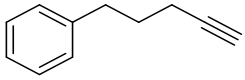
2.4.4 *General Procedure for the Hydroalkylation of Silyl-Protected Alkynes: Addition Distal to Silane*

In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and LiOMe (38.0 mg, 1.00 mmol, 2.0 equiv). To this was added alkyne (0.50 mmol, 1.0 equiv), $Ni(cod)_2$ (13.8 mg, 0.050 mmol, 5 mol%), **L2** (17.5 mg, 0.060 mmol, 0.12 equiv), alkyl iodide (0.750 mmol, 1.50 equiv), Me_2PhSiH (204.4 mg, 1.50 mmol, 3.00 equiv), and 1,4-dioxane (5 mL). The reaction mixture was stirred at 75 °C, and the reaction progress was monitored by TLC. Upon consumption of the internal alkyne (as monitored by TLC), the reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. An aliquot was analyzed by GC to obtain the diastereoselectivity and regioselectivity of the reactions. The crude reaction mixture was concentrated under reduced pressure and the product was purified by silica gel chromatography. The ratio of isomers for each product was again determined by GC analysis of the isolated product.

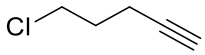


Diisopropyl(methoxy)(5-phenyl-2-(3-phenylpropyl)pent-1-en-1-yl)silane (2.8) was prepared according to the general procedure.

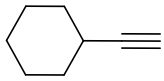
2.4.5 *Alkyne Starting Materials*



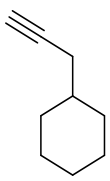
Pent-4-yn-1-ylbenzene (S2.1) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



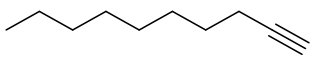
5-chloropent-1-yne (S2.2) was purchased from TCI America and vacuum distilled over calcium hydride before use.



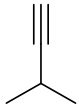
Ethynylcyclohexane (S2.3) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



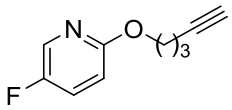
Prop-2-yn-1-ylcyclohexane (S2.4) was purchased from Thermo Fisher Scientific and distilled over calcium hydride before use.



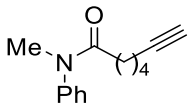
Dec-1-yne (S2.5) was purchased from Oakwood Chemical and distilled over calcium hydride before use.



3-methylbut-1-yne (S2.6) was purchased from Millipore Sigma and distilled over calcium hydride before use.

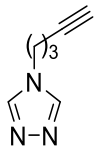


5-fluoro-2-(pent-4-yn-1-yloxy)pyridine (2.28) was prepared according to a known procedure.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 3.1 Hz, 1H), 7.47 – 7.15 (m, 1H), 6.67 (dd, *J* = 9.0, 3.6 Hz, 1H), 4.33 (t, *J* = 6.2 Hz, 2H), 2.36 (td, *J* = 7.1, 2.7 Hz, 2H), 2.12 – 1.82 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 160.03, 155.41 (d, *J* = 245.4 Hz), 133.18 (d, *J* = 25.9 Hz), 126.56 (d, *J* = 21.4 Hz), 111.62 (d, *J* = 4.8 Hz), 83.58, 68.90, 64.85, 28.08, 15.34. GCMS (EI) calculated for $[M]^+$ 179.09, found 179.10.

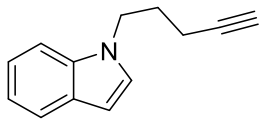


N-methyl-N-phenylhept-6-ynamide (2.26) was prepared according to a known procedure.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 3.18 (s, 3H), 2.13 – 1.92 (m, 4H), 1.82 (t, *J* = 2.7 Hz, 1H), 1.61 (p, *J* = 7.5 Hz, 2H), 1.36 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.0, 129.6, 127.6, 127.2, 83.9, 68.3, 37.2, 33.3, 27.9, 24.5, 18.0. GCMS

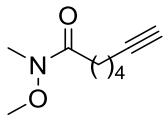
(EI) calculated for $[M]^+$ 215.13, found 215.20. FTIR (neat, cm^{-1}): 3306 (s), 2941 (s), 2856 (s), 2249 (s), 1726 (w), 1641 (s), 1595 (s), 1496 (s), 1389 (s), 1292 (m), 1123 (s), 908 (s).



4-(pent-4-yn-1-yl)-4H-1,2,4-triazole (2.24). Two reaction flasks were charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. The first flask was then charged with DMF (7 mL, 0.7 M) and 5-chloro-1-pentyne (512.8 mg, 5 mmol, 1.0 equiv). 1,2,4-triazole (1036.1 mg, 15 mmol, 3.0 equiv) was added and the mixture was stirred at 70 °C for 20 minutes before being brought to room temperature. In the second flask, NaOH (400.0 mg, 10.0 mmol, 2.0 equiv) was dissolved in DMF (7 mL) before being added to the first flask. The reaction was then stirred for 3.5 hours at 70 °C. The resulting mixture was quenched with 1M HCl (15 mL), extracted with ethyl acetate (15 mL x 3), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.98 (s, 1H), 4.36 (t, J = 6.4 Hz, 2H), 2.28 – 2.05 (m, 5H).

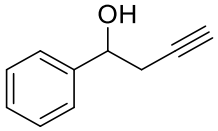


1-(pent-4-yn-1-yl)-1H-indole (2.25) was prepared according to a known procedure and has been previously characterized.[13]

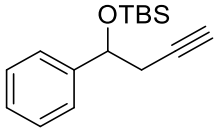


N-methoxy-N-methylhept-6-ynamide (S2.7) was prepared according to a known procedure.[14] ^{1}H

NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.20 (s, 3H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.24 (td, *J* = 7.0, 2.7 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.84 – 1.70 (m, 2H), 1.68 – 1.54 (m, 2H).

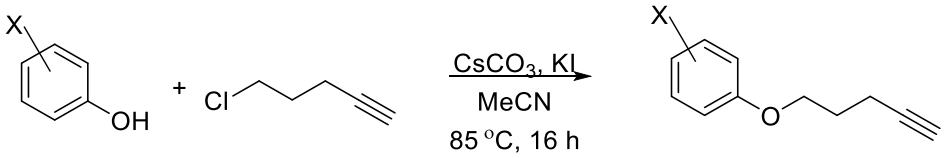


1-phenylbut-3-yn-1-ol (S2.8) was prepared according to a known procedure and has been previously characterized.[15]



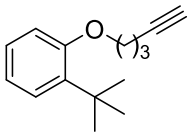
***tert*-butyldimethyl((1-phenylbut-3-yn-1-yl)oxy)silane (S2.9)** was prepared according to a known procedure.[16] ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 4.89 (t, *J* = 6.6 Hz, 1H), 2.75 – 2.49 (m, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 0.97 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H).

General procedure for the preparation of terminal alkynes:

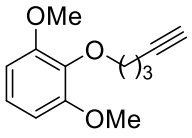


A reaction flask was charged with a stir bar, Cs_2CO_3 (5.0 g, 30.0 mmol, 1.5 equiv), KI (0.65 g, 2.0 mmol, 0.10 equiv), flame-dried under vacuum, and allowed to cool under nitrogen. The flask was then charged with MeCN (67 mL, 0.3 M), 5-chloropent-1-yne (2.1 mL, 20.0 mmol, 1.0 equiv), and desired phenol (22.0 mmol, 1.1 equiv). The reaction flask was then fitted with a reflux condenser and allowed to stir for 16 hours at 85 °C. 1 M HCl (70 mL) was then added to the reaction mixture, then extracted with ether (50 mL x 3). The combined organic layers were then combined and washed with 1 M HCl (50 mL x 2), water (50 mL x 3),brine (100 mL), then dried

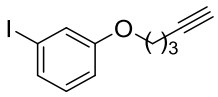
over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography. Alkynes **S2.10**-**2.14** and **2.29**-**2.31** were prepared using this procedure.



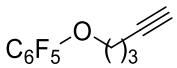
1-(*tert*-butyl)-2-(pent-4-yn-1-yloxy)benzene (2.29) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.24 – 7.14 (m, 1H), 6.98 – 6.87 (m, 2H), 4.13 (t, *J* = 6.1 Hz, 2H), 2.58 – 2.44 (m, 2H), 2.10 (p, *J* = 6.9 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.41 (s, 9H).



1,3-dimethoxy-2-(pent-4-yn-1-yloxy)benzene (2.31) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.86 (s, 6H), 2.50 (td, *J* = 7.2, 2.7 Hz, 2H), 2.04 – 1.91 (m, 3H).

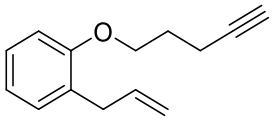


1-iodo-3-(pent-4-yn-1-yloxy)benzene (2.30) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.6 Hz, 2H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 9.7 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 2.53 – 2.38 (m, 2H), 2.15 – 1.95 (m, 3H).

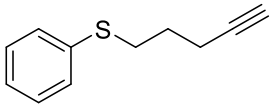


1,2,3,4,5-pentafluoro-6-(pent-4-yn-1-yloxy)benzene (S2.10) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (t, *J* = 6.0 Hz, 2H), 2.44 (td, *J* = 6.9, 2.5

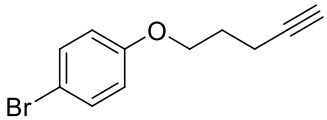
Hz, 2H), 2.07 – 1.89 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (d, *J* = 241.6 Hz), 138.2 (d, *J* = 252.6 Hz), 137.5 (d, *J* = 256.8 Hz), 82.9, 74.1, 69.2, 28.9, 14.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ -159.83 (d, *J* = 19.7 Hz), -166.31 (t, *J* = 21.1 Hz), -166.46 (t, *J* = 21.2 Hz). GCMS (EI) calculated for $[M]^+$ 250.04, found 250.10. FTIR (neat, cm^{-1}): 3307 (s), 3080 (w), 3037 (w), 2925 (s), 2852 (s), 2252 (s), 1812 (w), 1512 (s), 1482 (s), 1449 (s), 1373 (m), 1160 (s), 1031 (s), 996 (s), 893 (w), 677 (s).



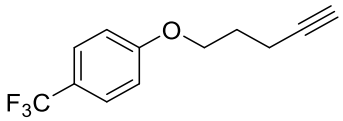
1-allyl-2-(pent-4-yn-1-yloxy)benzene (S2.11) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (q, *J* = 7.2 Hz, 2H), 6.99 – 6.82 (m, 2H), 6.11 – 5.92 (m, 1H), 5.16 – 4.99 (m, 2H), 4.10 (t, *J* = 5.9 Hz, 2H), 3.42 (d, *J* = 6.6 Hz, 2H), 2.55 – 2.38 (m, 2H), 2.14 – 1.92 (m, 3H).



Pent-4-yn-1-yl(phenyl)sulfane (S2.12) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 4H), 7.20 (t, *J* = 7.2 Hz, 1H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.37 (td, *J* = 6.9, 2.7 Hz, 2H), 2.00 (t, *J* = 2.3 Hz, 1H), 1.87 (p, *J* = 6.9 Hz, 2H).



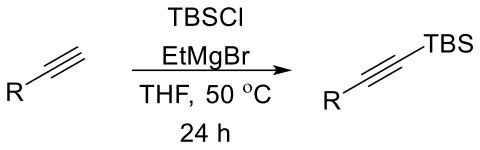
1-bromo-4-(pent-4-yn-1-yloxy)benzene (S2.13) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 2.56 – 2.31 (m, 2H), 2.14 – 1.84 (m, 3H).



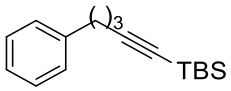
1-(pent-4-yn-1-yloxy)-4-(trifluoromethyl)benzene (S2.14) was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.42 (td, *J* = 6.9, 2.6 Hz, 2H), 2.09 – 1.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 127.0 (q, J = 3.7 Hz), 124.7 (q, J = 270.9 Hz), 123.0 (q, J = 32.7 Hz), 114.6, 83.2, 69.2, 66.5, 28.1, 15.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ -64.45. GCMS (EI) calculated for $[M]^+$ 228.08, found 228.10. FTIR (neat, cm^{-1}): 3308 (s), 3011(w), 2926 (s), 2852 (s), 2361 (w), 2252 (s), 1589 (s), 1519 (s), 1330 (s), 1254 (s0, 1162 (s), 1118 (s), 1068 (s), 1002 (s), 968 (m), 835 (s).

2.4.6 *Silylation of Terminal Alkynes*

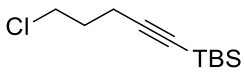
General procedure for the preparation of TBS-protected alkynes:



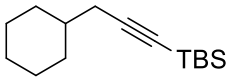
Two reaction flasks were charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. One flask was then charged with THF (5.0 mL, 1.4 M), alkyne (7.0 mmol, 1.0 equiv), and heated to 50 °C. EtMgBr (2.8 mL, 3.0 M) was then added slowly. The reaction was allowed to stir for one hour. To the other flask, TBSCl (1.3 g, 8.4 mmol, 1.2 equiv) was dissolved in THF (2 mL) and then added to the other flask via syringe. The combined mixture was then allowed to stir for 16 hours. The crude product was concentrated under reduced pressure and purified by silica gel chromatography. Protected alkynes **2.1**, **2.9**–**2.21** were prepared using this procedure.



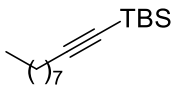
***tert*-Butyldimethyl(5-phenylpent-1-yn-1-yl)silane (2.1)** was prepared according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 2H), 7.09 (d, *J* = 5.5 Hz, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.15 (t, *J* = 7.0 Hz, 2H), 1.73 (p, *J* = 7.0 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H).



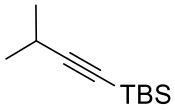
***tert*-Butyl(5-chloropent-1-yn-1-yl)dimethylsilane (2.15)** was prepared according to the general procedure.



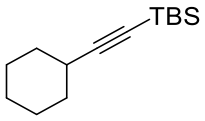
***tert*-Butyl(3-cyclohexylprop-1-yn-1-yl)dimethylsilane (2.13)** was prepared according to the general procedure.



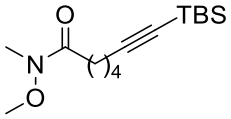
***tert*-Butyl(dec-1-yn-1-yl)dimethylsilane (2.9)** was prepared according to the general procedure.



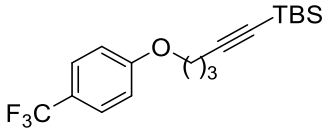
***tert*-Butyldimethyl(3-methylbut-1-yn-1-yl)silane (2.14)** was prepared according to the general procedure.



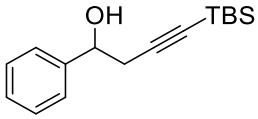
***tert*-Butyl(cyclohexylethynyl)dimethylsilane (2.10)** was prepared according to the general procedure.



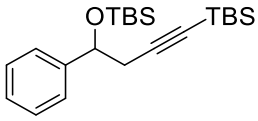
7-(*tert*-butyldimethylsilyl)-N-methoxy-N-methylhept-6-ynamide (2.21) was prepared according to the general procedure.



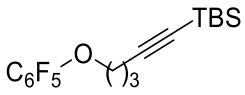
***tert*-Butyldimethyl(5-(4-(trifluoromethyl)phenoxy)pent-1-yn-1-yl)silane (2.16)** was prepared according to the general procedure.



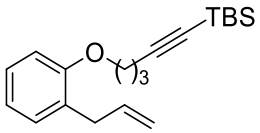
4-(*tert*-butyldimethylsilyl)-1-phenylbut-3-yn-1-ol (2.11) was prepared according to the general procedure.



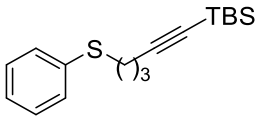
***tert*-Butyl((4-(tert-butyldimethylsilyl)-1-phenylbut-3-yn-1-yl)oxy)dimethylsilane (2.12)** was prepared according to the general procedure.



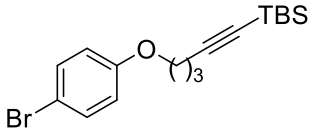
***tert*-Butyldimethyl(5-(perfluorophenoxy)pent-1-yn-1-yl)silane (2.19)** was prepared according to the general procedure.



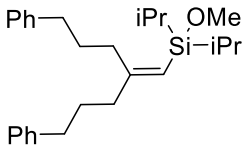
(5-(2-allylphenoxy)pent-1-yn-1-yl)(*tert*-butyl)dimethylsilane (2.17) was prepared according to the general procedure.



***tert*-Butyldimethyl(5-(phenylthio)pent-1-yn-1-yl)silane (2.20)** was prepared according to the general procedure.



(5-(4-bromophenoxy)pent-1-yn-1-yl)(*tert*-butyl)dimethylsilane (2.18) was prepared according to the general procedure.

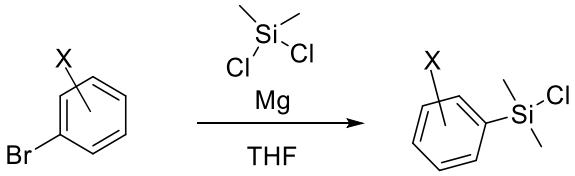


Diisopropyl(methoxy)(5-phenylpent-1-yn-1-yl)silane (2.8). Two reaction flasks were charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. One flask was then

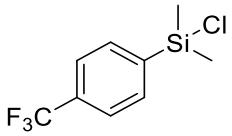
charged with THF (8.0 mL, 0.6 M), alkyne (5.0 mmol, 1.0 equiv), and heated to 50 °C. EtMgBr (2.0 mL, 1.2 M) was then added slowly. The reaction was allowed to stir for two hours. To the other flask, *i*-Pr_2OMeSi (3.0 mL, 15 mmol, 3 equiv) was dissolved in THF (8 mL) and then added dropwise to the other flask via syringe. The combined mixture was then allowed to stir for 2 hours. The crude product was diluted with DCM (15 mL), concentrated under reduced pressure, and purified by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 2H), 7.22 (d, *J* = 7.7 Hz, 3H), 3.80 (s, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 6.9 Hz, 2H), 1.89 (p, *J* = 6.9 Hz, 2H), 1.09 (d, *J* = 4.5 Hz, 12H), 1.05 – 0.97 (m, 2H).

2.4.7 *Novel Silyl Protecting Groups*

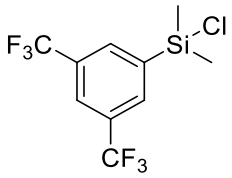
General Procedure for the preparation of novel silyl-protecting groups:



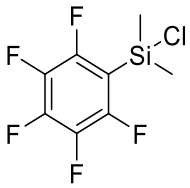
Two reaction flasks were charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. One flask was charged with Mg powder (0.3 g, 13.5 mmol, 1.3 equiv) and fitted with a condenser prior to being dried. This flask was then charged with dichlorodimethylsilane (3.6 mL, 30.0 mmol, 3.0 equiv) and THF (60 mL, 0.2 M). In the other flask, the desired bromobenzene (10.0 mmol, 1.0 equiv) was dissolved in THF (26 mL), then added to the other flask dropwise. After the addition was completed, the flask was heated at 80 °C for 4 hours, then cooled to room temperature and stirred for 16 hours. The crude mixture was filtered through cotton to remove excess magnesium and magnesium salts, concentrated under reduced pressure. This mixture was extracted with n-pentane (100 mL x 3), concentrated under reduced pressure, then distilled under reduced pressure.



Chlorodimethyl(4-(trifluoromethyl)phenyl)silane (2.4) was prepared according to the general procedure.



(3,5-*bis*(trifluoromethyl)phenyl)chlorodimethylsilane (2.5) was prepared according to the general procedure.



Chlorodimethyl(perfluorophenyl)silane (2.6) was prepared according to the general procedure.

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