New Transformations in the Transition-Metal Catalyzed Hydrofunctionalization of Alkynes

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Abstract

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Chair of the Supervisory Committee:
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Hydrofunctionalization reactions are very useful transformations of unsaturated compounds and their development has been a major focus of research in the field of transition metal catalysis. These reactions allow the rapid build up of molecular complexity of simple substrates in a single transformation and recently significant progress has been made in the development of regio-, stereo- and enantioselective hydrofunctionalizations. Here we describe the development of three reactions involving transition metal-catalyzed hydrofunctionalization. The first is the hydroallylation of alkynes furnishing skipped dienes. Regioselective hydroallylation of nonsymmetrical internal alkynes was achieved through the installation of polar functional group in the propargylic position. This resulted in inductive polarization of the alkyne π bond allowed for the regioselective synthesis of trisubstituted alkenes. The second reaction described is the diastereodivergent hydroarylation of alkynes. Both *Z*- and *E*-styrenes are accessed from one set of starting materials using synergistic Cu/Pd catalysis. The reaction proceeds through tandem

Sonogashira cross-coupling followed by *Z*-selective semireduction and isomerization, where the diastereoselectivity is determined by the stoichiometry of a methanol additive. The last reaction describes the reductive three-component coupling of terminal alkynes, aryl halides and pinacolborane using synergistic Cu/Pd catalysis. Copper-catalyzed hydroboration followed by hydrocupration generates a key heterobimetallic complex, subsequent palladium-catalyzed cross-coupling with aryl halides provides benzylic alkyl boronates. Investigation of other electrophiles and enantioselective variants is currently underway.

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LIST OF ABBREVIATIONS

(*R*)-DTBM-SEGPHOS:	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
6DIPP:	1,3-bis(2,6-diisopropylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene
Ac:	Acetyl
Ar:	Aryl
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn:	Benzyl
Boc:	tert-Butyloxycarbonyl
BrettPhos:	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Bz:	Benzoyl
C:	Celsius
dinnamyl:	3-Phenylprop-2-en-1-yl
COD:	cyclioctadiene
Cy:	Cyclohexyl
dba:	dibenzylideneacetone
DACH Trost:	(1*S*,2*S*)-(–)-1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinobenzoyl)
DavePhos:	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dppf:	diphenyl phosphine ferrocene

dppp: diphenyl phosphine propane

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

Equiv: Equivalent

EtOAc: Ethyl acetate

Et_3N: Triethylamine

Et_2O: Diethyl ether

ESI-MS: Electrospray ionization mass spectrometry

Et: Ethyl

FTIR: Fourier transform infrared spectroscopy

Abbreviations for FTIR peaks

- s: strong
- m: medium
- w: weak
- b: broad

h: Hour

HPLC: High performance liquid chromatography

HRMS: High resolution mass spectrometry

Hz: Hertz

IBox: (2-(4'-dimethylaminophenyl)-6-iodobenzoxazole)

ICy: 1,3-dicyclohexyl imidazolium

IMes: 1,3-Bis-(2,4,6-trimethylphenyl)imidazolium

i-Pr: isopropyl

IPr: 1,3-Bis-(2,6-diisopropylphenyl)imidazolium

IPr*: 1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazolium

I*t*-Bu: 1,3-Bis-(tert-butyl)imidazolium

Me: Methyl

MeOD: deuterated methanol

Mes: Mesityl

MHz: Megahertz

mol: Mole

n-Bu: *n*-butyl

NHC: N-heterocyclic carbene

NMR: Nuclear Magnetic Resonance

Abbreviations for NMR splitting patterns

- s: singlet
- d: doublet
- t: triplet
- q: quartet
- p: pentet
- m: multiplet
- br: broad
- dd: doublet of doublets
- dt: doublet of triplets
- ddt: doublet of doublet of triplets

OTf: Trifluoromethanesulfonate

OTs:	p-Toluenesulfonate
PEPPSI:	(3-chloropyridyl) palladium(II) dichloride
Ph:	Phenyl
Ph_3SiD:	triphenylsilyl deuteride
pin:	pinacolato
PMHS:	polymethylhydrosiloxane
ppm:	parts per million
QPhos:	1,2,3,4,5-Pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
RuPhos**:**	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
rt:	room temperature
SPhos:	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SIMes:	1,3-Bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium
SIPr:	,3-Bis-(2,6-diisopropylphenyl))-4,5-dihydroimidazolinium
t-Bu:	tert-butyl
TBS:	Tert-butyldimethylsilyl
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
THP:	Tetrahydropyran
TIPS:	Triisopropylsilyl
TLC:	Thin layer chromatography
TMB:	1,3,5-Trimethoxybenzene
TMDSO:	Tetramethyldisiloxane
tol:	Tolyl

Xantphos:	4,5-bis(dipheylphosphino)-9,9-dimethylxanthene
XPhos:	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Xyl-MeOBIPHEP:	(*R*)-2,2′-Bis[bis(3,5-dimethyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl

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I would also like to thank my friends I made during my time here. Friends both within the department, within the university but also in Seattle. I feel fortunate to have all of you in my life. I look forward to hearing and seeing what the the future has in store for you.

Finally, I would like to thank my family for their love and support. My sister, Shannon has been in Seattle this entire time and really has been such a rock for me these past 5+ years. This would not have been possible without them.

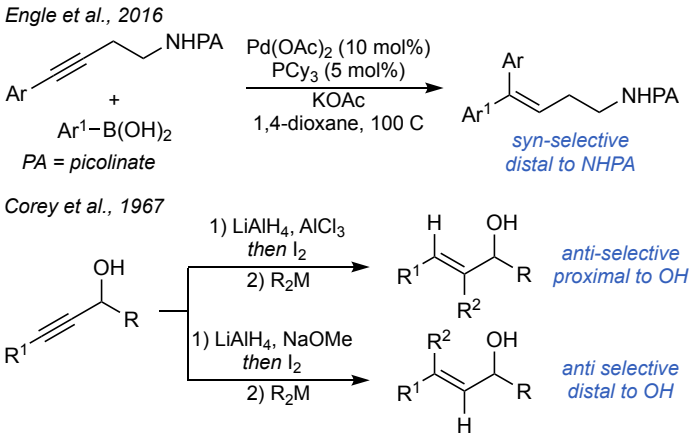
DEDICATION

To my Mom, Dad and Sister (Shannon). It's been a wild ride.

Chapter 1. CATALYTIC ANTI-MARKOVNIKOV HYDROALLYLATION OF TERMINAL AND FUNCTIONALIZED INTERNAL ALKYNES: SYNTHESIS OF SKIPPED DIENES AND TRISUBSTITUTED ALKENES

1.1 INTRODUCTION

Skipped dienes can be found in a variety of natural products.[1] As a result, many efforts have been dedicated to their synthesis. While current methods include cross coupling of alkenyl metal fragments with various electrophiles[2–5] and hydroalkenylation of 1,3-dienes,[6–9] the major limitations include the need to prefunctionalize alkynes, or low diastereoselectivity.[10] Methods for the hydroallylation of terminal alkynes have more recently been developed allowing for the synthesis of skipped dienes, with high selectivity and functional group compatibility.[11–13] However, these approaches are less effective for the hydroallylation of nonsymmetrical internal alkynes for which the scope is limited to aryl-, alkynyl- and silyl-substituted acetylenes.[14–16] In addition to hydroallylation, general methods for the hydrofunctionalization of nonsymmetrical internal alkynes with high regioselectivity are rare. Therefore, the direct transformation of a nonsymmetrical internal alkyne to a trisubstituted alkene remains a synthetic challenge.

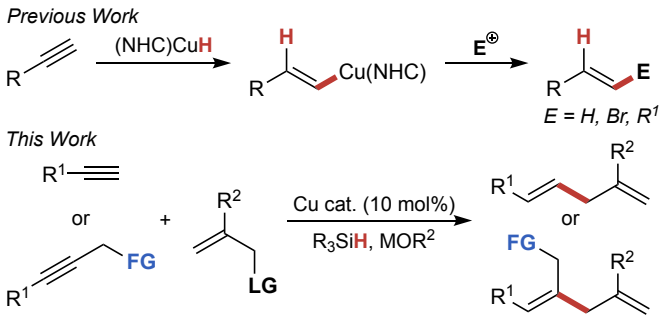


Scheme 1.1. Synthesis of Trisubstituted Alkenes

Recently, Engle et al. (Scheme 1.1) was able to synthesize trisubstituted alkenes

through the hydroarylation of internal alkynes,[17] while hydroalkylation of internal alkynes was shown by Corey et al.[18] The selectivity of both reactions relies on the inherent reactivity of the system with a specific substrate to dictate the regio- and diastereoselectivity of the product.

Our group has recently utilized N-heterocyclic carbene copper(I) hydride ((NHC)CuH) complexes to selectively achieve anti-Markovnikov hydrofunctionalization reactions of terminal alkynes (Scheme 1.2). Using the established reactivity of these complexes, we have successfully achieved the reduction,[19] hydrobromination[20] and hydroalkylation[21,22] of terminal alkynes. We hypothesized that if we could identify an appropriate electrophile, we would be able to utilize the reactivity of (NHC)CuH in the hydroallylation of terminal alkynes (Scheme 1.2). More importantly, if successful, we were interested in expanding our methodology to nonsymmetrical dialkyl substituted internal alkynes providing access to functionalized trisubstituted alkenes. Inspired by Engle's work, we proposed to instead add an electron withdrawing group to the propargylic position to inductively polarize the alkyne and dictate the regioselectivity of the alkyne insertion into the copper hydride bond.



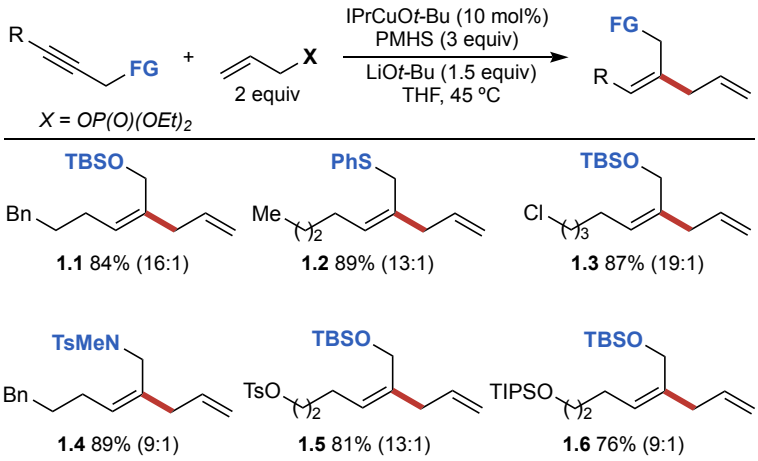
Scheme 1.2. (NHC)CuH Catalyzed Hydrofunctionalization of Alkynes

1.2 Hydroallylation of Internal Alkynes

Optimization of the hydroallylation of terminal alkynes revealed that allyl phosphates were the optimal electrophile for further reaction development and ultimately the best results were obtained using IPrCuO*t*-Bu as the catalyst, polymethylhydrosiloxane (PMHS) as a hydride source and LiO*t*-Bu as a turnover reagent. When the same reaction conditions were applied to the hydroallylation

of nonsymmetrical internal alkynes, simply using THF instead of toluene as the reaction solvent, provided products were in > 76% yield, and ~10:1 regioselectivity (Table 1.1). Protected amines, silyl ethers, and thiols were all tolerated under the reaction conditions. In all cases, hydroallylation occurred at the position closer to the polar functional group, consistent with our proposed inductive polarization of the alkyne.[23]

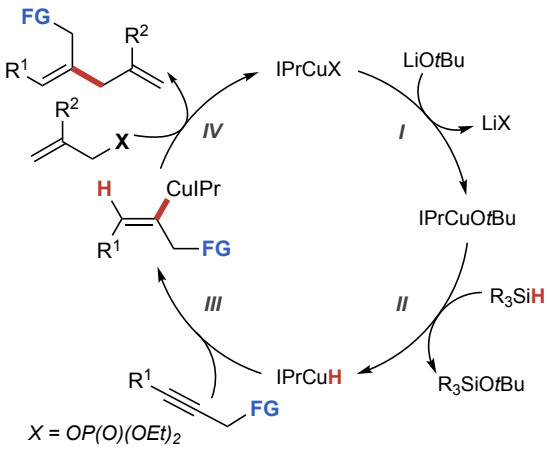
Table 1.1. : Substrate Scope: Hydroallylation of Internal Alkynes



1.3 Mechanism of Hydroallylation

1.3.1 *Proposed Mechanism*

Previous work on copper catalyzed hydrofunctionalization reactions of alkynes provides evidence for the plausibility of the mechanism shown in Scheme 1.3. There is a strong precedent for the elementary steps **I-III**.[19,24–26] with terminal alkynes. The copper precatalyst transmetalates (**I**) with an alkoxide turnover reagent, σ-bond metathesis (**II**) between IPrCuO*t*-

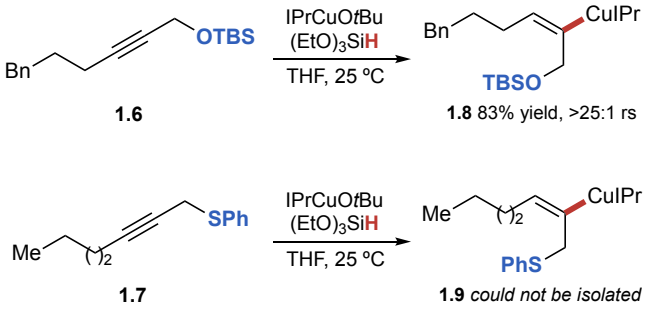


Scheme 1.3. Proposed Catalytic Cycle Hydroallylation of Internal Alkynes

Bu and silane provides IPrCuH. Finally, hydrocupration (**III**) of the alkyne provides the alkenyl copper species. Additionally, stoichiometric reactions demonstrate the feasibility of step **IV** for terminal alkynes. However, the use of nonsymmetrical dialkyl internal alkynes in copper-catalyzed hydrofunctionalization reactions is unprecedented. The regioselectivity observed for these internal alkynes could be a result of either coordination of the copper to the polar functional group or the proposed inductive polarization of the alkyne. Additionally, since ß-elimination was previously reported for the alkylation and arylation of propargylic phosphates,[27,28] we wanted to understand the resistance of the new internal alkenyl copper intermediate to ß-elimination during hydroallylation.

1.3.2 *Stoichiometric Hydrocupration of Internal Alkynes*

Our investigation into the source of regioselectivity for these substrates began with the stoichiometric hydrocupration of the OTBS-substituted alkyne (**1.6**). ^{1}H NMR analysis of the crude reaction mixture indicates that hydrocupration proceeds with >25:1 regioselectivity (Scheme 1.4). X-ray crystallography of the resulting complex confirms the structure of the internal alkenyl copper intermediate (**1.8**) and the crystal was obtained as a single regioisomer (**Error! Not a valid bookmark self-reference.**). Additionally, the X-ray structure shows no coordination between the copper and the oxygen in the OTBS moiety (Cu-O distance 3.22Å). Therefore, we concluded that



Scheme 1.4. Stoichiometric Hydrocupration of Internal Alkynes

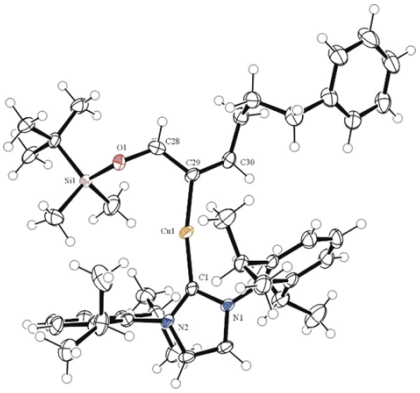


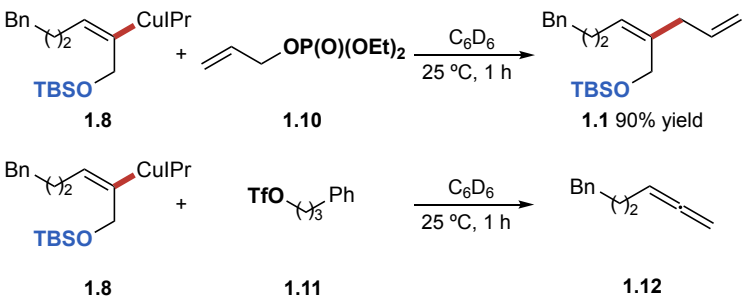
Figure 1.1. ORTEP of OTBS internal alkenyl copper **1.8** with thermal ellipsoids at the 50% probability level. **Error!**

the regioselectivity is not a result of the direct coordination between the copper and polar functional group but more likely results from the inductive polarization of the alkyne. We also found that this particular copper complex is very stable in C_6D_6 at 45 ºC. After 1 h 99% of material remained intact and 79% remained after 24 h.

In contrast, hydrocupration of the thioether substituted alkyne (**1.7**) resulted in ß-elimination, with only a small amount of the alkenyl copper complex visible by ^{1}HNMR. Attempts to isolate this complex yielded only IPrCuSPh (**1.9**) (Scheme 1.4), the product of ß-thiolate elimination. While ß-elimination may prevent isolation of the alkenyl copper intermediate, the product of hydroallylation of the thioether substituted alkyne was successfully isolated, suggesting that hydroallylation outcompetes the ß-thiolate elimination. Together, the reactivity and isolation of these alkenyl copper complexes provide evidence for elementary step **IV** shown in the catalytic cycle (Scheme 1.3) and suggests the source of regioselectivity.

1.3.3 *Allylation and Alkylation of Alkenyl Copper Complex*

We believe that understanding the structure and reactivity of these intermediates could provide insight for further reaction development with alkyl electrophiles. We performed the stoichiometric reactions shown in Scheme 1.5. With allyl phosphate (**1.10**) as the electrophile, we observed 90% formation of the desired product (**1.1**) in 1 h. However, attempted alkylation with an alkyl triflate (**1.8**) resulted in 89% of allene (**1.12**), the expected product of ß-elimination. This difference in product formation reveals a dramatic effect of the electrophile on the reactivity of the copper complex (**1.8**). This



Scheme 1.5. Allylation and Alkylation of OTBS Alkenyl Copper Complex

suggests that hydroallylation with allyl phosphates may be uniquely effective for the synthesis of trisubstituted alkenes and may explain why internal alkynes are not viable substrates for copper-catalyzed hydroalkylation, and other copper-catalyzed hydrofunctionalizations.

1.4 Conclusion

In conclusion, we have developed a new method for the highly selective anti-Markovnikov hydroallylation of alkynes. The reaction is syn-stereospecific and highly regioselective with good functional group tolerance, including esters, nitriles, ketones, silyl ethers and alkyl halides. This method is the first example of using internal alkynes as substrates in copper-catalyzed hydrofunctionalization. Analysis of the reaction mechanism provides evidence for the source of regioselectivity and uncovered an unexpected resistance to ß-elimination of polar functional groups during the course of the catalytic reaction. Furthermore, this method provides direct access to trisubstituted alkenes from simple internal alkynes providing products containing an additional terminal alkene that can be used in further functionalization.

1.5 Experimental

1.5.1 *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. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra

were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C NMR chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm). ^{19}F NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to the internal standard, hexafluorobenzene. 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. 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.

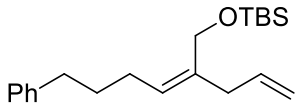
Materials: THF, CH_2Cl_2, Ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous methanol was purchased from Millipore Sigma, and was subsequently degassed and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were stored over 4Å molecular sieves prior to use. Commercial reagents were purchased from Millipore Sigma, TCI America, GFS-Chemicals, Ark-Pharm, Combi-Blocks, Oakwood Chemicals, Strem Chemicals and Alfa Aesar. Dimethylisopropylsilane (Me_2*i*-PrSiH) was purchased from Gelest Inc and was degassed and stored over 4Å molecular sieves.

1.5.2 *General Procedure for the Hydroallylation of Alkynes*

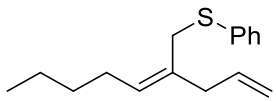
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiO*t*-Bu (60.0 mg, 0.750 mmol, 1.5 equiv), IPrCuO*t*-Bu (26.3 mg, 0.050 mmol, 0.10 equiv) and indicated solvent (5

mL, 0.1 M). To this reaction mixture was added PMHS (1.5 mmol, 3.0 equiv) and alkyne (0.5 mmol, 1.0 equiv). The reaction mixture was stirred at 25 °C until the yellow color disappeared. The allyl diethyl phosphate (1.0 mmol, 2.0 equiv) was added and the reaction mixture was vigorously stirred at indicated temperature. After 24 h, the reaction mixture was filtered through a pad of silica gel and washed with EtOAc. The crude mixture was concentrated under reduced pressure and purified by silica gel chromatography.

1.5.3 *Characterization of Trisubstituted Alkenes (Table 1.1)*

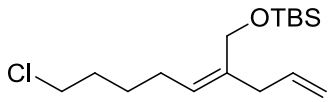


(Z)-((2-allyl-6-phenylhex-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (1.1), compound was isolated as a clear colorless liquid (181.9 mg, 92% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.23 – 7.18 (m, 2H), 7.12 – 7.03 (m, 3H), 5.92 (ddt, J = 16.9, 10.0, 6.8 Hz, 1H), 5.26 (t, J = 7.4 Hz, 1H), 5.18 – 5.03 (m, 2H), 4.15 (s, 2H), 2.99 (d, J = 6.3 Hz, 2H), 2.49 (t, J = 7.6 Hz, 2H), 2.02 (q, J = 7.4 Hz, 2H), 1.59 (p, J = 7.6 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 137.6, 137.2, 128.5, 128.4, 127.3, 125.8, 115.8, 60.3, 38.9, 35.5, 31.7, 27.2, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 330.24, found 330.20. FTIR (neat, cm^{-1}): 3072(m), 2955(s), 2857(s), 1813(m), 1637(m), 1470(m), 1251(s).

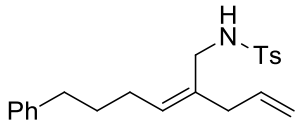


(Z)-nona-1,4-dien-4-yl(phenyl)sulfane (1.2), compound was isolated as a colorless liquid (110.0 mg, 89% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.34 (d, J = 7.2 Hz, 2H), 7.07 – 6.87 (m, 3H), 5.79 (ddt, J = 16.9, 10.0, 6.8 Hz, 1H), 5.27 (t, J = 7.3 Hz, 1H), 5.15 – 4.96 (m, 2H), 3.49 (s, 2H), 2.95 (d, J = 6.8 Hz, 2H), 1.85 (q, J = 7.0 Hz, 2H), 1.50 – 1.00 (m, 4H), 0.82 (t, J = 6.6 Hz, 3H).

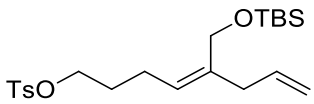
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 136.7, 132.4, 130.9, 130.7, 128.8, 126.5, 116.4, 40.5, 34.6, 32.0, 27.8, 22.5, 14.1. GCMS (EI) calculated for [M]+ 246.14, found 246.20. FTIR (neat, cm^{-1}): 3089.8(s), 3034(s), 2957.2(m),1814.6(m), 1478.4(s), 1392.8(w), 668.9(s).



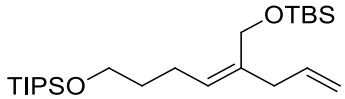
(Z)-((2-allyl-7-chlorohept-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (1.3), compound was isolated as a colorless liquid (133.1 mg, 88% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.89 (ddt, J = 16.9, 10.0, 6.8 Hz, 1H), 5.19 – 5.02 (m, 3H), 4.15 (s, 2H), 3.10 (t, J = 6.6 Hz, 2H), 2.96 (d, J = 6.8 Hz, 2H), 1.89 (q, J = 7.4 Hz, 2H), 1.43 (p, J = 6.6 Hz, 2H), 1.24 (p, J = 7.2, 6.8 Hz, 2H), 0.99 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.1, 126.9, 115.8, 60.3, 45.0, 30.0, 32.3, 27.3, 26.9, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 302.18, found 302.20 FTIR



(Z)-N-(2-allyl-6-phenylhex-2-en-1-yl)-N,4-dimethylbenzenesulfonamide (1.4), compound was isolated as a clear colorless liquid (134.0 mg, 82% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.66 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 7.4 Hz, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.4 Hz, 2H), 6.80 (d, J = 7.8 Hz, 2H), 5.90 (ddt, J = 16.7, 9.3, 7.0 Hz, 1H), 5.27 (t, J = 7.4 Hz, 1H), 5.23 (d, J = 17.3 Hz, 1H), 5.13 (d, J = 10.0 Hz, 1H), 3.53 (s, 2H), 2.89 (d, J = 7.0 Hz, 2H), 2.38 (s, 3H), 2.31 (t, J = 7.7 Hz, 2H), 1.88 (s, 3H), 1.68 (q, J = 7.5 Hz, 2H), 1.40 (p, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 142.0, 136.1, 134.1, 132.4, 131.4, 129.7, 128.4, 128.3, 127.6, 125.8, 116.6, 48.5, 38.9, 35.3, 33.8, 31.3, 27.0, 21.6. GCMS (EI) calculated for [M]+ 383.55, found 383.30. FTIR (neat, cm^{-1}): 3062.4(m), 3027(m), 2925(s), 1809(w), 1637(m), 1455(s), 1340(s), 753(s).



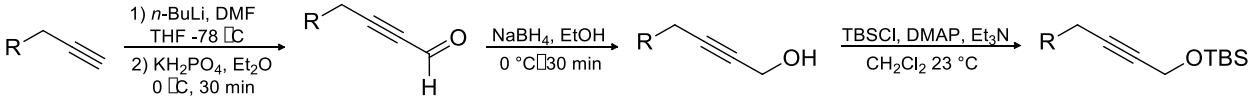
(Z)-5-(((tert-butyldimethylsilyl)oxy)methyl)octa-4,7-dien-1-yl 4-methylbenzenesulfonate (1.5), compound was isolated as a colorless liquid (171.0 mg, 81% yield).[1]H NMR (300 MHz, Benzene-d_6) δ 7.76 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.0 Hz, 2H), 5.81 (ddt, J = 16.8, 10.0, 6.8 Hz, 1H), 5.24 – 4.86 (m, 3H), 4.10 (s, 2H), 3.81 (t, J = 6.3 Hz, 2H), 2.88 (d, J = 6.8 Hz, 2H), 1.91 (q, J = 7.5 Hz, 2H), 1.84 (s, 3H), 1.36 (p, J = 6.7 Hz, 2H), 0.97 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 138.9, 136.8, 133.4, 129.9, 127.9, 125.2, 115.9, 69.9, 60.3, 38.9, 29.2, 26.0, 23.5, 21.7, 18.4, -5.2. GCMS (EI) calculated for [M]+ 424.21, found 424.20. FTIR (neat, cm^{-1}): 3072.8(m), 2954.9(s), 2855.5(s), 1635.8(m), 1471.9(m), 1363.3(s), 1250.9(m), 1075.1(s).

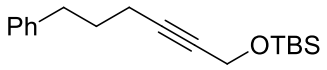


(Z)-6-allyl-12,12-diisopropyl-2,2,3,3,13-pentamethyl-4,11-dioxa-3,12-disilatetradec-6-ene (1.6), compound was isolated as a [1]H NMR (300 MHz, Benzene-d_6) δ 5.93 (ddt, J = 16.9, 9.9, 6.8 Hz, 1H), 5.31 (t, J = 7.4 Hz, 1H), 5.22 – 4.96 (m, 2H), 4.27 (s, 2H), 3.61 (t, J = 6.2 Hz, 2H), 3.00 (d, J = 6.8 Hz, 2H), 2.34 – 2.04 (m, 2H), 1.70 – 1.45 (m, 2H), 1.27 – 1.03 (m, 21H), 1.00 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 137.3, 127.2, 115.7, 63.0, 60.4, 38.9, 33.4, 26.1, 24.2,18.5, 18.2, 12.2, -5.1. GCMS (EI) calculated for [M]+ 426.33, found 426.40. FTIR (neat, cm^{-1}): 2943(s), 2865(s), 1744(w), 1636(w), 1506(w), 1471(s), 1462(s), 1388(w), 1361(w), 1250(s), 1106(s), 1073(s), 1005(m), 913(s), 882(s), 836(s), 774(s).

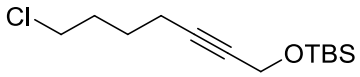
1.5.4 *Alkyne Starting Materials*

The internal alkynes were prepared using known procedure[29–31]

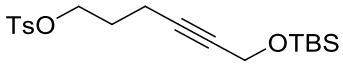




tert-butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane (1.6) compound was isolated as a colorless liquid (2.0 g, 83% overall yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.16 (m, 2H), 7.09 – 6.96 (m, 3H), 4.29 (t, J = 2.2 Hz, 2H), 2.92 – 2.39 (m, 2H), 2.01 (tt, J = 7.0, 2.2 Hz, 2H), 1.64 (p, J = 7.2 Hz, 2H), 0.99 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.57, 128.52, 128.35, 125.89, 84.83, 79.27, 52.00, 34.81, 30.25, 25.91, 18.35, 18.23, -5.02. GCMS (EI) calculated for [M]+ 288.19, found 288.10. FTIR (neat, cm^{-1}): 3063(w), 3027(w), 2950(s), 2930(s), 2899(m), 2857(s), 2231(w), 1604(w), 1496(m), 1461(m), 1370(w), 1253(s), 1136(s), 1080(s), 1002(w), 837(s), 777(s).

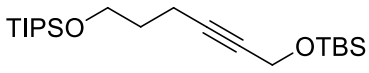


tert-butyl((7-chlorohept-2-yn-1-yl)oxy)dimethylsilane (1.13) compound was isolated as a colorless liquid (4.2 g, 78% overall yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 4.29 (t, J = 2.2 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 2.26 (tt, J = 6.9, 2.2 Hz, 2H), 1.95 – 1.82 (m, 2H), 1.66 (p, J = 7.0 Hz, 2H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.4, 79.5, 52.0, 44.6, 31.7, 26.0, 25.9, 18.4, 18.2, -5.0. GCMS (EI) calculated for [M]+ 260.14, found 260.20. FTIR (neat, cm^{-1}): 2956(s), 2929(s), 2857(s), 1472(m), 1462(m), 1369(m), 1253(s), 1135(s), 1079(s), 1000(m), 938(w), 837(s), 777(s).



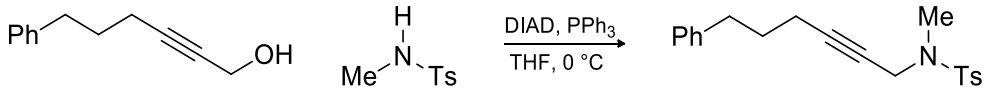
6-((tert-butyldimethylsilyl)oxy)hex-4-yn-1-yl 4-methylbenzenesulfonate (1.14) compound was isolated as a colorless liquid (2.3 g, 63% overall yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.79 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.21 (t, J = 2.2 Hz, 2H), 4.12 (t, J = 6.2 Hz, 2H), 2.45 (s, 3H), 2.27 (tt, J = 6.8, 2.0 Hz, 2H), 1.84 (p, J = 6.6 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 144.8, 133.2, 129.9, 128.0, 82.9, 79.9, 69.0, 51.8, 28.0, 25.9, 21.7, 18.3, 15.1, -5.1. GCMS (EI) calculated for [M]+ 382.16, found 382.20. FTIR (neat, cm^{-1}): 2954(s), 2928(s), 2856(s), 1598(m), 1471(m), 1443(w), 1306(w), 1290(w), 1254(s), 1188(s), 1177(s), 1139(s), 1079(s), 1006(m), 975(m), 933(s), 836(s), 778(s).



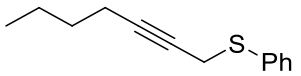
12,12-diisopropyl-2,2,3,3,13-pentamethyl-4,11-dioxa-3,12-disilatetradec-6-yne (1.15), compound was isolated as a colorless liquid (2.6 g, 68% overall yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 4.29 (s, 2H), 3.75 (t, *J* = 6.0 Hz, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.73 (p, *J* = 6.6 Hz, 2H), 1.03 - 1.06 (m, 21H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.11, 78.77, 61.97, 52.08, 31.99, 25.97, 18.43, 18.11, 15.36, 12.08, -5.01. GCMS (EI) calculated for [M]+ 384.29, found 384.30 FTIR (neat, cm^{-1}): 2942(s), 2864(s), 2713(w), 229 (w), 2234(w), 1471(s), 1462(s), 1388(m), 1367(w), 1253(s), 1139(s), 1109(s), 1081(s), 998(s), 972(s), 918(w), 882(s), 837(s), 777(s).

N,4-dimethyl-N-(6-phenylhex-2-yn-1-yl)benzenesulfonamide (1.16):



A reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, 6-phenylhex-2-yn-1-ol (2.0 g, 11.5 mmol, 1.0 equiv), triphenylphosphine (3.3 g, 12.7 mmol, 1.1 equiv), *N*-methyl-*p*-toluenesulfonamide (2.2 g, 11.6 mmol, 1.01 equiv) and THF (115 mL, 0.1 M). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (2.0 mL, 12.1 mmol, 1.05 equiv) drop wise. The reaction mixture was allowed to warm to 23 °C and stirred for 16 h. The THF was removed under reduced pressure and the residue was suspended in hexane and stirred vigorously

for 30 min. The solid triphenylphosphine oxide was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the crude product was purified using silica gel column with EtOAc/Hexane (0 → 10%). The product was isolated as a pale yellow liquid (2.2 g, 55% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.70 (d, J = 8.2 Hz, 2H), 7.14 (m, 2H), 7.11 – 7.03 (m, 1H), 6.97 (d, J = 6.9 Hz, 2H), 6.76 (d, J = 8.0 Hz, 2H), 3.87 (d, J = 2.3 Hz, 2H), 2.60 (s, 3H), 2.34 (t, J = 7.6 Hz, 2H), 1.86 (s, 3H), 1.71 (tt, J = 7.0, 2.2 Hz, 2H), 1.39 (p, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.42, 141.28, 134.20, 129.36, 128.35, 128.32, 127.90, 125.90, 85.99, 72.67, 40.26, 34.65, 34.32, 29.90, 21.39, 17.87. GCMS (EI) calculated for [M]+ 341.14, found 341.20. FTIR (neat, cm^{-1}): FTIR (neat, cm-1): 3062(w), 3026(w), 2937(m), 2861(m), 2361(w), 2222(w), 1598(w), 1496(w), 1453(s), 1347(s), 1305(s), 1195(m), 1163(s), 1119(s), 1089(s), 1019(w), 986(s), 920(s), 815(s).



hept-2-yn-1-yl(phenyl)sulfane (1.6) was prepared according to a known procedure and has been previously characterized.[32]

1.5.5 *Stoichiometric Reaction of Copper Hydride with Internal Alkynes*

Stoichiometric Reaction for the Synthesis of OTBS-substituted Alkenyl Copper (1.8)

In a nitrogen filled glovebox, IPrCuO*t*-Bu (184.2 mg, 0.350 mmol, 1.0 equiv) was weighed in a 20 mL scintillation vial, followed by 500 µL THF. Triethoxysilane (60.4 mg, 0.368 mmol, 1.05 equiv) was weighed into a shell vial and transferred to the reaction with 3 aliquots of 330 µL THF, this mixture was pre-stirred at 25 °C for 15 s resulting in a bright orange solution. Then OTBS-substituted alkyne (**1.6**) (111.1 mg, 0.385 mmol, 1.10 equiv) was weighed into a shell vial and washed into the reaction mixture with 3 aliquots of 330 µL THF. The reaction was vigorously stirred (1500 rpm) at 25 °C for 30 min after which the reaction turned clear. The reaction was

concentrated in vaccuo, and recrystallized from pentane. Due to the high solubility of the alkenyl copper complex, crystals were obtained at -35 °C and had to be washed with cold pentane and stored on dry ice for X-ray Crystallography.

Decomposition of OTBS-substituted Alkenyl Copper

In a nitrogen filled glovebox, OTBS-substituted alkenyl copper (**1.8**) (37.1 mg, 0.05 mmol, 1 equiv) was weighed into a dram vial followed by 150 µL of a 1.0 M stock solution of TMB in C_6D_6. To this was added an additional 350 µL of C_6D_6 and a stir bar. The reaction was capped, wrapped in foil to prevent exposure to light and placed at 45 °C. Aliquots were taken at times 0, 1 h, 4 h and 24 h and monitored by ^{1}H NMR spectroscopy for the decomposition of the alkenyl copper.

Table 1.2. : Decomposition of the OTBS-Substituted Alkenyl Copper (**1.8**)

Time (h)	% Yield
0	100%
1	99%
4	89%
24	79%

Stoichiometric Reaction for Synthesis of Thioether Substituted Alkenyl Copper (**1.9**):

In a nitrogen filled glovebox. IPrCuO*t*-Bu (263.1 mg, 0.5 mmol, 1 equiv) was weighed in a 20 mL scintillation vial, followed by 50 µL THF. Triethoxysilane (86.2 mg, 0.525 mmol, 1.05 equiv) was weighed into a shell vial and transferred to the reaction with 3 aliquots of 330 µL THF, this mixture was pre-stirred at 25 °C for 15 s resulting in a bright orange solution. Then, thioether substituted alkyne (**1.7**) (112.4 mg, 0.550 mmol, 1.10 equiv) was weighed into a shell vial and transferred to the reaction mixture with 3 aliquots of 330 µL THF. The reaction was vigorously stirred (1500 rpm) at 25 °C for 30 min after which the reaction turned clear. The reaction was concentrated in vaccuo, and recrystallized from DCM/pentane.

1.5.6 *Stoichiometric Reaction of OTBS-Substituted Alkenyl Copper (**1.8**) with Allyl Phosphate (**1.10**) and Alkyl Triflate (**1.11**) (Scheme 1.5)*

Reaction with Allyl Phosphate (1.10).

In a nitrogen filled glovebox, a 1-dram vial was charged with a stir bar, OTBS substituted alkenyl Cu 58 (37.1 mg, 0.05 mmol, 1.0 equiv) and 1,3,5-trimethoxybenzene (2.8 mg, 0.17 mmol, 0.33 equiv). The mixture was suspended in 100 µL C_6D_6 and then allyl phosphate 8 (11.7 mg, 0.060 mmol, 1.2 equiv washed in with 4 aliquots of 100 µL C_6D_6) was added to the reaction vial. The reaction mixture was allowed to stir at 25 °C. A 40-µL aliquots were taken at 10 min and 1 hour. The aliquots were diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis.

Table 1.3. : Reaction of OTBS-Substituted Alkenyl Copper (**1.8**) with Allyl Phosphate (**1.10**)

Time (min)	Yield
10	15%
60	90%

Reaction with Alkyl Triflate (1.11).

In a nitrogen filled glovebox, a 1-dram vial was charged with a stir bar, OTBS substituted alkenyl Cu 58 (37.1mg, 0.05 mmol, 1.0 equiv) and 1,3,5-trimethoxybenzene (2.8 mg, 0.17 mmol, 0.33 equiv). The mixture was suspended in 100 µL C_6D_6 and then 3-phenyl-1-propyltriflate 61 (10.0 mg, 0.060 mmol, 1.2 equiv, washed in with 4 aliquots of 100 µL C_6D_6) was added to the reaction vial. The reaction mixture was allowed to stir at 25 ° C. A 40-µL aliquots were taken at 10 min and 1 hour. The aliquot were diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis Table 1.4 shows the yield of the reaction in an hour.

Table 1.4. : Reaction of OTBS-Substituted Alkenyl Copper (**1.8**) with Alkyl Triflate (**1.11**)

Time (min)	Yield (allene **1.12**)
10	54%
60	89%

1.5.7 *X-Ray Crystallography Data Tables*

Internal Alkenyl Copper (1.8)

A clear colorless prism, measuring 0.57 x 0.10 x 0.10 mm^3 was mounted on a loop with oil. Data was collected at -173 °C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 180 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.9% complete to 25° in ϑ. A total of 38772 reflections were collected covering the indices, -16<=h<=16, -24<=k<=24, -17<=l<=17. 7737 reflections were symmetry independent and the Rint = 0.0901 indicated that the data was of less than average quality (0.07). Indexing and unit cell refinement indicated a primitive monoclinic lattice. The space group was found to be P 21/c (No. 14).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker.[33]

Solution by direct methods (SHELXS, SIR97[34,35]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97.[36–38] Scattering factors are from Waasmair and Kirfel.[39] Hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters Ueq were fixed such that they were 1.2Ueq of their parent atom Ueq for CH's and 1.5Ueq of their parent atom Ueq in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares.

The CH2OSiC6H15 moiety (C28,O1,Si1, C40-C45) is disordered.

The structure is of high quality and ready for publication. Table 1.5 summarizes the data collection details. Figure 1.2 shows an ORTEP[40] of the asymmetric unit.

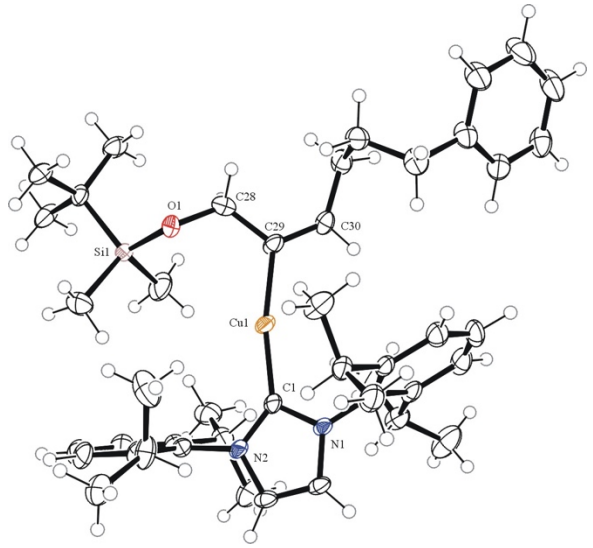


Figure 1.2. ORTEP of the structure with thermal ellipsoids at the 50% probability level. Disorder omitted for clarity.**Error! Reference source not found.**.

Table 1.5. : Crystallographic data for the structures provided

Empirical formula	C45 H65 Cu N2 O Si	
Formula weight	741.62	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 21/c	
Unit cell dimensions	a = 14.0458(9) Å	alpha = 90°
	b = 20.6508(13) Å	beta = 93.587(4)°
	c = 14.4990(9) Å	gamma = 90°
Volume	4197.3(5) Å3	
Z, Calculated density	4, 1.174 Mg/m3	
Absorption coefficient	0.583 mm-1	
F(000)	1600	

Crystal size	0.57 x 0.10 x 0.10 mm
Theta range for data collection	1.453 to 25.497°
Limiting indices	-16<=h<=16, -24<=k<=24, -17<=l<=17
Reflections collected / unique	38772 / 7737 [R(int) = 0.0901]
Completeness to theta = 25.000	99.9 %
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	7737 / 0 / 530
Goodness-of-fit on F2	0.996
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0876
R indices (all data)	R1 = 0.0818, wR2 = 0.1034
Largest diff. peak and hole	0.520 and -0.320 e. $Å^3$

IPrCuSPh (1.9)

A colorless prism, measuring 0.18 x 0.10 x 0.03 mm^3 was mounted on a loop with oil. Data was collected at -173 °C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.8% complete to 25° in ϑ. A total of 279563 reflections were collected covering the indices, -26<=h<=26, -19<=k<=19, -31<=l<=31. 8132 reflections were symmetry independent and the Rint = 0.0521 indicated that the data was of good. Indexing and unit cell refinement indicated a primitive orthorhombic lattice. The space group was found to be P b c a (No. 61).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker.[33]

Solution by direct methods (SHELXS, SIR97[34,35]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97[36–38]. Scattering factors are from Waasmair and Kirfel.[39] Hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters Ueq were fixed such that they were 1.2Ueq of their parent atom Ueq for CH's and 1.5Ueq of their parent atom Ueq in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares.

The structure is of high quality and ready for publication. Table 1.6 summarizes the data collection details. Figure 1.3 shows an ORTEP[40] of the asymmetric unit.

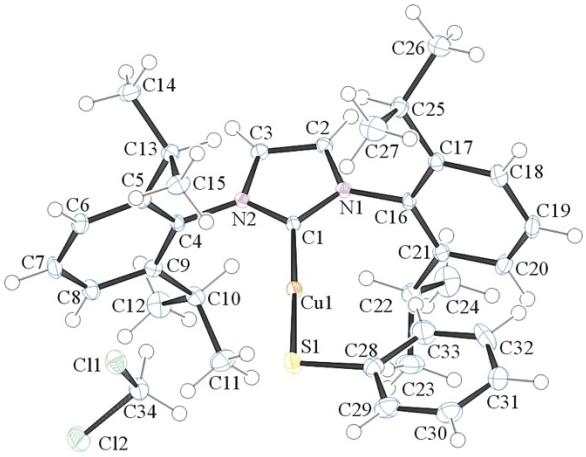


Figure 1.3. ORTEP of the structure with thermal ellipsoids at the 50% probability level. Disorder omitted for clarity. **Error! Reference source not found.**.

Table 1.6. : Crystallographic data for the structures provided

Empirical formula	C34 H43 Cl2 Cu N2 S
Formula weight	646.20
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	P b c a	
Unit cell dimensions	a = 19.5368(7) Å	α= 90°.
	b = 14.2533(5) Å	β= 90°.
	c = 23.4566(9) Å	γ = 90°.
Volume	6531.8(4) $Å^3$	
Z	8	
Density (calculated)	1.314 Mg/m^3	
Absorption coefficient	0.922 mm^{-1}	
F(000)	2720	
Crystal size	0.18 x 0.10 x 0.03 mm^3	
Theta range for data collection	1.74 to 28.34°.	
Index ranges	-26<=h<=26, -19<=k<=19, -31<=l<=31	
Reflections collected	279563	
Independent reflections	8132 [R(int) = 0.0521]	
Completeness to theta = 25.00°	99.8 %	
Max. and min. transmission	0.9729 and 0.8517	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8132 / 0 / 363	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0363, wR2 = 0.0854	
R indices (all data)	R1 = 0.0474, wR2 = 0.0921	
Largest diff. peak and hole	2.562 and -0.522 e. $Å^3$	

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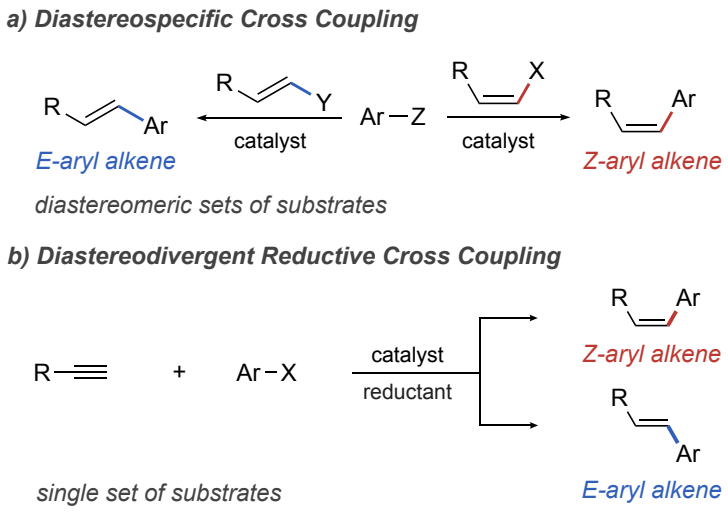
Chapter 2. DIASTEREODIVERGENT REDUCTIVE CROSS COUPLING OF ALKYNES THROUGH TANDEM CATALYSIS: *Z*- AND *E*-SELECTIVE HYDROARYLATION OF TERMINAL ALKYNES

2.1 INTRODUCTION

Alkenes play an important role in organic chemistry, both as common structural elements of organic molecules and as intermediates in organic synthesis. The preparation of the E and Z isomers of an alkene generally requires the synthesis of two different sets of precursors,[1,2] often using different synthetic routes. For example, in extensively used cross-coupling reactions, the stereochemistry of the alkene product is determined by the stereochemistry of the starting material.[2] As a result, the synthesis of *E*- and *Z*-aryl alkenes involves separate cross-coupling reactions of two diastereomeric alkene fragments with a functionalized arene (Scheme 2.1a).

Although rare, stereodivergent methods that allow the synthesis of both alkene isomers from the same starting materials are known. For example, both isomers can be formed by the semireduction of an alkyne.[3–7] Whereas this approach allows control over the double bond geometry and stereodivergence, no new carbon-carbon bond is formed. A more efficient approach is offered by alkene cross metathesis,[8–10] which leads to fragment coupling through the formation of a new

double bond and allows the control of the double bond geometry. The stereochemistry of the product is primarily determined by the catalyst used in the reaction.[11–15] The downside of this approach is that the selective formation of the desired cross metathesis product often necessitates the use of specific combinations of substrates and/or a large excess of one of the substrates.

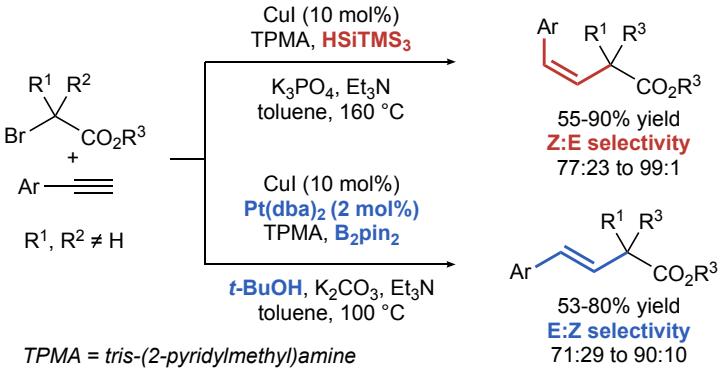


Scheme 2.1. Stereoselectivity in Cross Coupling

Reductive cross-coupling reactions of alkynes also provide an excellent opportunity for stereodivergent alkene synthesis. Like the alkene cross metathesis reaction, these transformations are responsible both for the formation of a new C-C bond and for setting the stereochemistry of the alkene product. Therefore, in principle, a single hydroarylation reaction could provide access to both diastereoisomers of an aryl alkene from a single alkyne substrate (Scheme 2.1b). Despite the development of numerous reactions for the hydroarylation of alkynes, diastereodivergent methods remain rare.[16]

Recently, a diastereodivergent hydroalkylation of aryl alkynes (Scheme 2.2) was reported by Nishikata et al.[17] demonstrating the feasibility of diastereodivergent reductive cross-coupling. Although no detailed mechanistic analysis was reported, the diastereodivergence seems to result from fundamentally different mechanisms for the two reactions. The *Z*-products are proposed to

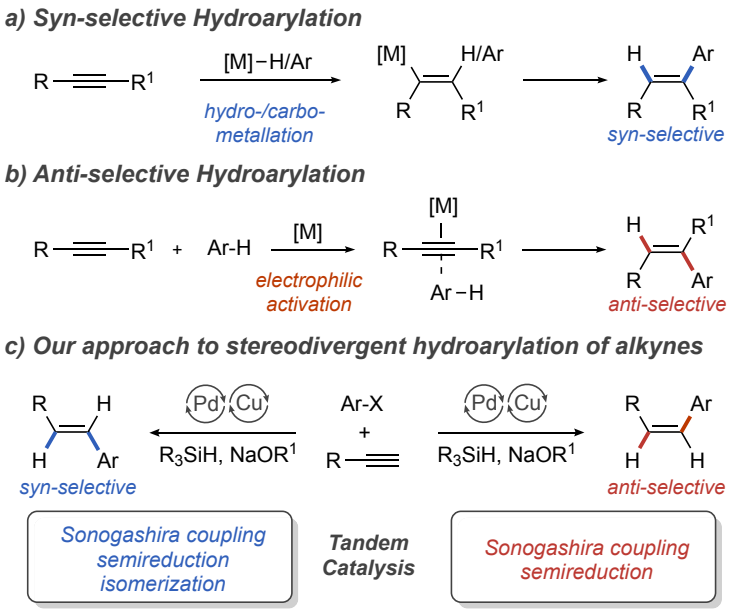
be formed through radical bromoalkylation, followed by the reduction of alkenyl bromide. The formation of *E*-alkenes, on the other hand, likely involves hydroboration followed by Suzuki cross-coupling.



Scheme 2.2. Diastereodivergent Reductive Alkylation

Mechanistic analysis of known hydroarylation reactions suggests why stereodivergence has been difficult to achieve. Most current methods are based on syn-stereospecific carbo-[18–22] or hydrometalation[23–25] of alkynes, which forces the syn-selective hydroarylation and prevents the formation of the other isomer (Scheme 2.3a).

To our knowledge, the only approach to catalytic anti-selective hydroarylation was developed by Fujiwara in 2000 (Scheme 2.3b).[26–28] Using a palladium or platinum catalyst, anti-selective hydroarylation is accomplished through electrophilic activation of alkynes.[28–30] Unfortunately, the Friedel-Crafts mechanism[31] of this reaction limits the scope to highly electron-rich arenes and electrophilic alkynes, such as propiolates. Furthermore, products of dialkenylation and diarylation are often formed. Finally, it is important to note that all three mechanistic approaches to hydroarylation shown in Scheme 2.3 (a and b) have been difficult to apply to reactions of terminal alkynes, making hydroarylation of this important class of substrates particularly challenging.[32,33]



Scheme 2.3. Methods for the Hydroarylation of Alkynes

Seeking to exploit the full potential of hydroarylation chemistry, we were interested in developing a diastereodivergent hydroarylation of terminal alkynes that would provide access to both *Z*- and *E*-aryl alkenes. Considering the diastereospecific nature of current hydroarylation methods we decided to explore a fundamentally different approach based on tandem catalysis.

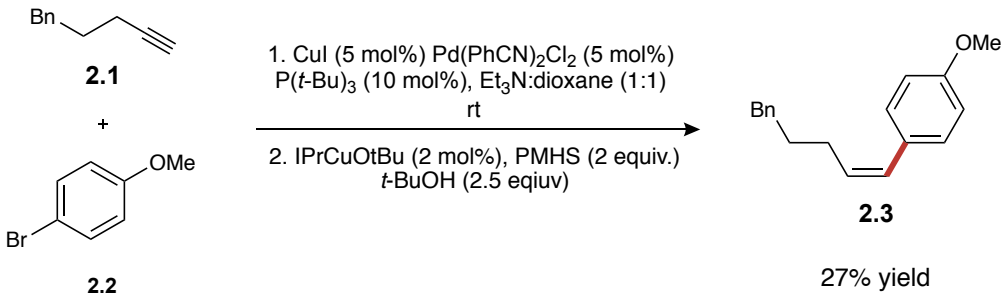
Tandem catalysis has recently received a lot of attention as an efficient strategy for the development of new catalytic transformations.[34,35] Performing two or more catalytic reactions in the same flask enables a more economical use of energy and time, and minimizes the use of reaction workup and product purification.[34] At the same time, tandem catalysis allows the development of transformations that are difficult to accomplish relying on a single catalytic cycle.[36–42]

We reasoned that the *Z*-selective hydroarylation could be achieved using tandem Sonogashira coupling[43,44] and *Z*-selective semireduction.[5] Based on the seminal work by Sadighi et al.[45] and the subsequent work by Tsuji[46] and our group,[47] we planned to use the same NHC copper catalyst to

promote Sonogashira coupling and to achieve semireduction in the presence of a silane and an alcohol (Scheme 2.3c). *E*-aryl alkenes could be accessed using the same catalyst system through Sonogashira coupling and semireduction, followed by isomerization of the Z product. *E*-styrenes are known to be significantly more stable than Z isomers, and several distinct mechanisms for palladium-catalyzed isomerization have been established.[48]

2.2 Reaction Development: *Z*-Selective Hydroarylation of Terminal Alkynes

Based on our general strategy outlined in Scheme 2.3c, we initially explored *Z*-selective hydroarylation and found that Sonogashira coupling under a variety of known conditions followed by in situ copper-catalyzed semireduction was an ineffective method for hydroarylation. The best result (27% yield) was obtained using modified Fu-Buchwald Sonogashira conditions[49] with conditions for the semireduction previously reported by our group[47] (Scheme 2.4, See Experimental for details).



Scheme 2.4. 2 step-1 pot Sonogashira followed by *Z*-selective semireduction

These results demonstrate the major challenge in tandem catalysis of ensuring that the catalytic reactions involved in the process are mutually compatible. Cross-talk between components of different catalytic cycles often leads to side reactions and catalyst deactivation or decomposition.[34,35] In our case, the major concern was the ability of palladium catalysts to react

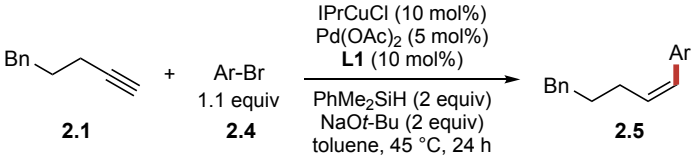
with silanes and unsaturated compounds in a variety of ways. For example, previously, when the product of a Sonogashira reaction was treated with a silane *in situ*, exclusive formation of the alkane product was observed,[50] consistent with the general propensity of palladium complexes to promote over-reduction of aryl alkynes.[5,51] Palladium catalysts have also been shown to promote isomerization of *Z*-alkenes[52] in the presence of hydride donors, such as tin hydrides and silanes.[53] Furthermore, palladium-catalyzed hydrosilylation of alkenes[54,55] and alkynes[56–58] is also known. Overall, even though both Sonogashira and semireduction reactions are well-established, merging them into a single process presents significant challenges, and requires a catalyst system that will selectively promote the desired combination of reactions and suppress other well-established reaction pathways.

Based on this analysis, we focused on finding a combination of a palladium catalyst and a silane that would minimize the possible side reactions. Considering our previous work on the *Z*-selective semireduction of alkynes, we focused on exploring various combinations of IPrCuO*t*-Bu and palladium catalysts in the presence of a silane and an alkoxide (Table 2.1). We observed a wide range of reactions promoted by various Cu/Pd catalyst combinations, including alkyne homocoupling, reduction of the aryl bromide,[50] and hydrosilylation of the terminal and internal alkynes (see Experimental for details).[54]

The performance of various phosphine ligands in the hydroarylation reaction revealed some general trends that guided further reaction development. Homocoupling of the alkyne was a major product with common bidentate ligands, such as BINAP (Table 2.1, entry 1). Monodentate trialkyl phosphine ligands, such as PCy_3, fully suppressed the homocoupling, but greatly decreased conversion (entry 2).

With dialkylbiaryl phosphine ligands,[59,60] such as XPhos and SPhos, full consumption of the starting material was achieved, although hydrosilylation and reduction of the starting materials dominated (entries 3 and 4). Interestingly, ligand **L1**[61] showed significantly higher selectivity for the desired alkene product than the closely related SPhos (entries 4 vs 5). The use of **L1** eliminated the aryl bromide reduction and suppressed hydrosilylation of the alkynes, resulting in increased yield of the hydroarylation product (entry 5). Hydrosilylation was further suppressed by switching to dimethylisopropylsilane (Me_2i-PrSiH), resulting in clean formation of the Sonogashira product and a slow semireduction (entry 6). Full conversion of the Sonogashira product was achieved only after 72 h, and the product was obtained in 87% yield and 28:1 *Z:E* selectivity. The semireduction was dramatically faster when 1.5 equivalents of MeOH was added after the Sonogashira coupling was completed (entry 7). Within two hours of the MeOH addition we observed the formation of the desired Z alkene in 94% yield and 19:1 *Z:E* selectivity. Once the terminal alkyne (**1.1**) has been consumed, the timing of the MeOH addition is not critical. The same results were obtained with MeOH added two or twenty-four hours after the start of the reaction.

Table 2.1. Reaction Development

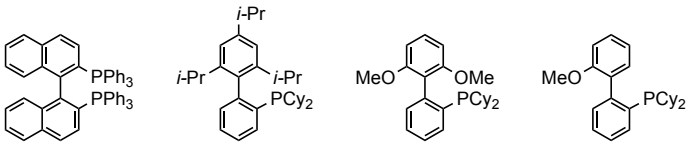


2.1 **2.4** **2.5**

Major Side Products

entry	*deviation from above*	*yield*[a]	*conversion*
1.	BINAP	14%	71%
2.	PCy_3	2%	44%
3.	XPhos	8%	100%
4.	SPhos	26%	100%
5.	none	47%	100%
6.	Me_2i-PrSiH	43%(87%)[b]	100%
7.	Me_2i-PrSiH, MeOH[c]	94%	100%

Ar = 4-butylbenzene [a]GC yields are reported. [b]Yield after 72 h reported in parenthesis. [c]MeOH added after the consumption of **1** (2 h). Total reaction time 4 h.



BINAP **XPhos** **SPhos** **L1**

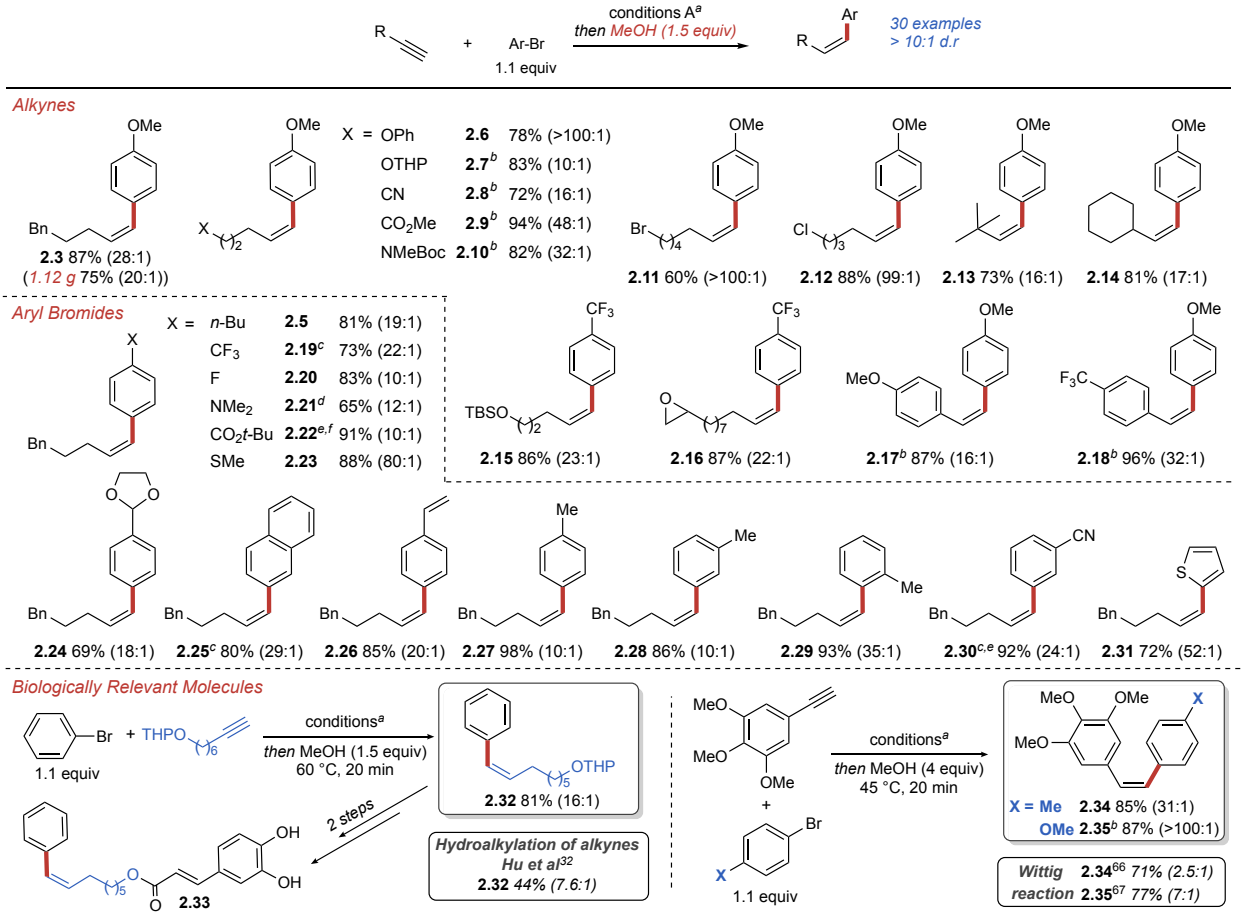
In a control experiment, we discovered that adding the silane at the beginning of the reaction was beneficial. Under standard conditions described in entry 7 (Table 2.1), 99% of the Sonogashira product was formed after 2 h, while in the absence of the silane, only 24% of the coupling product was formed at the same time point.[62] Another interesting aspect of our Sonogashira reaction is the tolerance of a copper co-catalyst. Previously, Buchwald et al. have documented deleterious effect of copper co-catalysts in a Sonogashira reaction promoted by a closely related palladium catalyst stabilized by XPhos ligand.[63]

2.3 Substrate Scope: *Z*-Selective Hydroarylation

Having established the reactions conditions for the *Z*-selective hydroarylation of terminal alkynes (Table 2.1, entry 7), we explored the scope of the reaction (Table 2.2). Alkynes containing reductively labile functional groups such as an alkyl chloride (**2.12**), alkyl bromide (**2.11**), ester (**2.9**), and nitrile (**2.8**) were compatible with this reaction. In addition, the reaction could be successfully performed in the presence of epoxides (**2.16**), silyl ethers (**2.15**), and protected amines (**2.10**). Notably, both electron-rich and electron-deficient aryl alkynes were competent coupling partners in this reaction (**2.17** and **2.18**).

A wide range of aryl bromides could also be used as substrates (Table 2.2). Both electron-rich (**2.3** and **2.21**) and electron-poor (**2.19**, **2.22** and **2.30**) aryl bromides were viable substrates, as were heteroaryl bromides. A variety of functional groups were tolerated on the arene substrate, including thioethers (**2.23**), acetals (**2.24**), and alkenes (**2.26**). Finally, products derived from ortho-, meta-, and para-substituted aryl bromides were isolated in high yields and good to excellent diastereoselectivities (**2.27**-**2.29**).

Table 2.2. : Scope of *Z*-Selective Hydroarylation



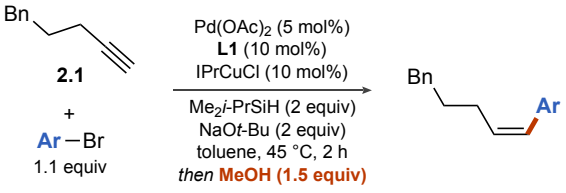
Reactions performed on 0.5-mmol scale. Reported are isolated yields of purified mixtures of product diastereoisomers. *Z*:*E* ratios of products determined by GC analysis of crude reaction mixtures are reported in paranthesis. [a]Conditions: IPrCuCl (10 mol%), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), Me_2*i*-PrSiH (2 equiv), NaO*t*-Bu (2 equiv), toluene, 45 °C, 2 h. [b]Reaction conditions: IPrCuCl (10 mol%), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), Me_2*i*-PrSiH (2 equiv), LiO*t*-Bu (2 equiv), toluene, 45 °C, 3 h, then MeOH (4 equiv) and NaO*t*-Bu (2 equiv), 60 °C. [c]*i*-BuOH was used instead of MeOH. [d]Reaction performed at 0 °C. [e]*t*-BuOH was used instead of MeOH and the semireduction was performed at 60 °C after addition of alcohol. [f]Reaction was monitored by GC.

To demonstrate the utility of the new method, we prepared **2.3** on a gram scale. We also used the hydroarylation reaction in the synthesis of biologically relevant compounds shown in Table 2.2. These applications allow us to make a direct comparison to other methods previously used to accomplish the synthesis of aryl alkenes. Compound **2.32** was used in the synthesis of caffeic acid derivative **2.33**, which showed selective antiproliferative activity in certain highly metastatic carcinoma cell lines.[64] The compound was originally prepared using a Wittig reaction (25% yield and 3.3:1 *Z*:*E* selectivity).[64] More recently, Hu et al. prepared **2.32** by *Z*-selective hydroalkylation of aryl acetylenes using 3 equiv of the alkyl iodide (44% yield and 7.6:1 *Z*:*E* selectivity).[32] The hydroarylation of terminal alkyne shown in Table 2.2 provided **2.32** in 81% yield and 16:1 *Z*:*E*

selectivity. Compounds **2.34** and **2.35** are among the most active analogues of natural product Combretastatin A4, which is a potent inhibitor of tubulin polymerization.[65] Like many other analogues, these have been prepared with relatively low *Z*-selectivity using Wittig reaction.[66,67] Using our hydroarylation reaction both compounds were prepared in high yield (>80%) and with excellent *Z*-selectivity (>30:1).

To ensure high *Z*-selectivity in synthesis of compounds shown in Table 2.2, we monitored the reaction progress by TLC, and stopped the reactions when the products of the Sonogashira coupling were consumed. Careful monitoring of the reaction progress by gas chromatography (GC) established that in several representative cases, high Z-selectivity (10:1) can be achieved in a twenty-minute window within the first hour after the addition of MeOH (Table 2.3). In the absence of MeOH, isomerization is significantly slower and good *Z*-selectivity is observed even 24 h after the complete consumption of the Sonogashira product (Table 2.1, entry 6: after 96 h, we obtained the *Z*-alkene in 87% yield and *Z*:*E* = 11:1).

Table 2.3. : Change in *Z*-Selectivity Over Time



Ar	20 min	25 min	30 min	35 min	40 min	Yield[d]
MeO	20:1	18:1	13:1	10:1	10:1	92 - 95
O, O	>100:1[c]	18:1	18:1	17:1	13:1	70 - 79
[b]	28:1	28:1	27:1	26:1	25:1	84 - 89

[a]Reported selectivities of crude reaction mixture. [b]*i*-BuOH used instead of MeOH [c]Reaction mixture contains <10% internal alkyne. [d]Reported yields are of combined *Z* and *E* isomers except where noted.

We found it convenient that the rate of the semireduction can be adjusted by varying the temperature and the alcohol additive. The semireduction of internal alkynes containing an electron-

deficient arene was slow in the presence of MeOH and significantly faster in the presence of isobutanol (*i*-BuOH). For example, with MeOH as an additive, the syntheses of compounds **2.19** and **2.25** required more than 24 h, while with *i*-BuOH the reductions were completed in less than 2 h. Conversely, under the standard reaction conditions, the reduction of the Sonogashira products with electron-rich aryl bromides (**2.21**) was completed in several minutes, which made monitoring the reaction progress difficult and resulting in low *Z*-selectivity. At a lower temperature, the reduction was completed in 6 h. Finally, in syntheses of several products shown in Table 2.2, we used LiO*t*-Bu instead of NaO*t*-Bu. We noticed that this was required with more acidic alkynes that contain electron-withdrawing groups. In these reactions, NaO*t*-Bu was completely ineffective in promoting Sonogashira coupling and we could recover the starting materials. Monitoring reactions between different alkynes and the two bases by in situ ^{1}H NMR did not reveal any clear differences in these reactions.

2.4 Reaction Development: *E*-Selective Hydroarylation of Terminal Alkynes

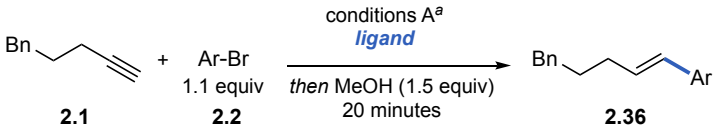
Next, we explored the development of *E*-selective hydroarylation of alkynes. The formation of the *E* isomer would involve the execution of the following three catalytic processes in tandem: Sonogashira coupling, semireduction, and alkene isomerization (Scheme 2.3c). The feasibility of this approach was supported by the strong thermodynamic preference for the *E* isomer of aryl alkenes. For example, the equilibrium constant for isomerization of *Z*-1-phenyl-1-propene to the E isomer is 32.2.[48] Furthermore, several mechanisms for palladium-catalyzed alkene isomerization have been established through detailed mechanistic studies.[48]

Despite numerous documented mechanisms for palladium-catalyzed isomerization of aryl alkenes, previous efforts to develop preparatively useful method for this transformation encountered significant problems. Spencer et al. have shown that $(MeCN)_2PdCl_2$ promotes alkene isomerization through a cationic intermediate.[52] Good yields and selectivities are obtained under mild reaction conditions. However, the reaction is limited to electron-rich aryl alkenes that can support the formation of the carbenium intermediate. A more general method based on reversible hydropalladation of alkenes was later developed by Jung et al.[53] However, they found that if silane is used as a hydride source, a significant amount of alkane product is formed well before the thermodynamic *E:Z* ratio of alkenes can be reached. To avoid the reduction of alkenes, Jung et al. used *n*-Bu_3SnH (2.2 equivalents) as a hydride source.

Based on Jung's report and our observation that isomerization of the *Z*-alkene occurs after the Sonogashira product is completely consumed, we explored the formation of *E*-alkenes using the standard reaction conditions and a range of phosphine ligands (Table 2.4). QPhos and DavePhos provided promising initial results and showed fast isomerization to the *E*-isomer. Unfortunately, after 24 h, the reaction with the QPhos ligand afforded the alkene mixture with *E:Z* ratio of only 5.2:1.

In the reaction with DavePhos, we observed a significant amount of hydrosilylation products before *E*-alkene was the dominant component

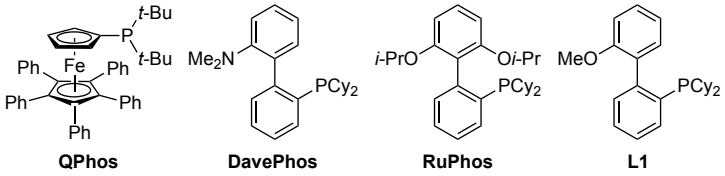
Table 2.4. : Isomerization of the Aryl Alkene Product



Ar = 4-(OMe)C_6H_4

entry	*ligand*	*yield*[b]	*E:Z ratio*
1.	QPhos	100%	1.9:1
2.	DavePhos	81%	1:2.5
3.	SPhos	69%	1:2.8
4.	RuPhos	81%	1:1.2
5.	**L1**	90%	1:29
6.	**L1** (*6 days*)	95%	2:1
7.	**L1** (*5 equiv of MeOH, 24 h*)	94%	>100:1

[a]See Table 2. [b]Combined yields of *E*- and *Z*-alkenes determined by GC.



QPhos **DavePhos** **RuPhos** **L1**

in the mixture. **L1**, which was initially optimized for the formation of Z isomer, led to the slowest isomerization of the *Z*-alkene, but with no side reactions. Even after 6 days, 95% of the alkene was present as a mixture of the two isomers (*E:Z* = 2:1) (entry 6).

Prompted by the excellent combined yield of the alkene obtained with **L1**, we explored the effect of other reaction parameters on isomerization hoping to identify a perturbation of the standard reaction conditions that would allow us to achieve full isomerization of *Z*-alkenes. Surprisingly, we found that *E*-alkenes could be obtained using the standard conditions for *Z*-selective hydroarylation with one simple change in reaction stoichiometry. With a larger excess of MeOH additive (5 equiv), isomerization proceeds within 24 h to provide *E*-alkenes in excellent yield and high selectivity (*E:Z* >100:1)(entry 7). In contrast to the *Z*-selective hydroarylation, strict monitoring of the reaction progress was not necessary, as we generally observed <5% yield of the alkane over-reduction product after 24 h.

2.5 Substrate Scope: *E*-Selective Hydroarylation

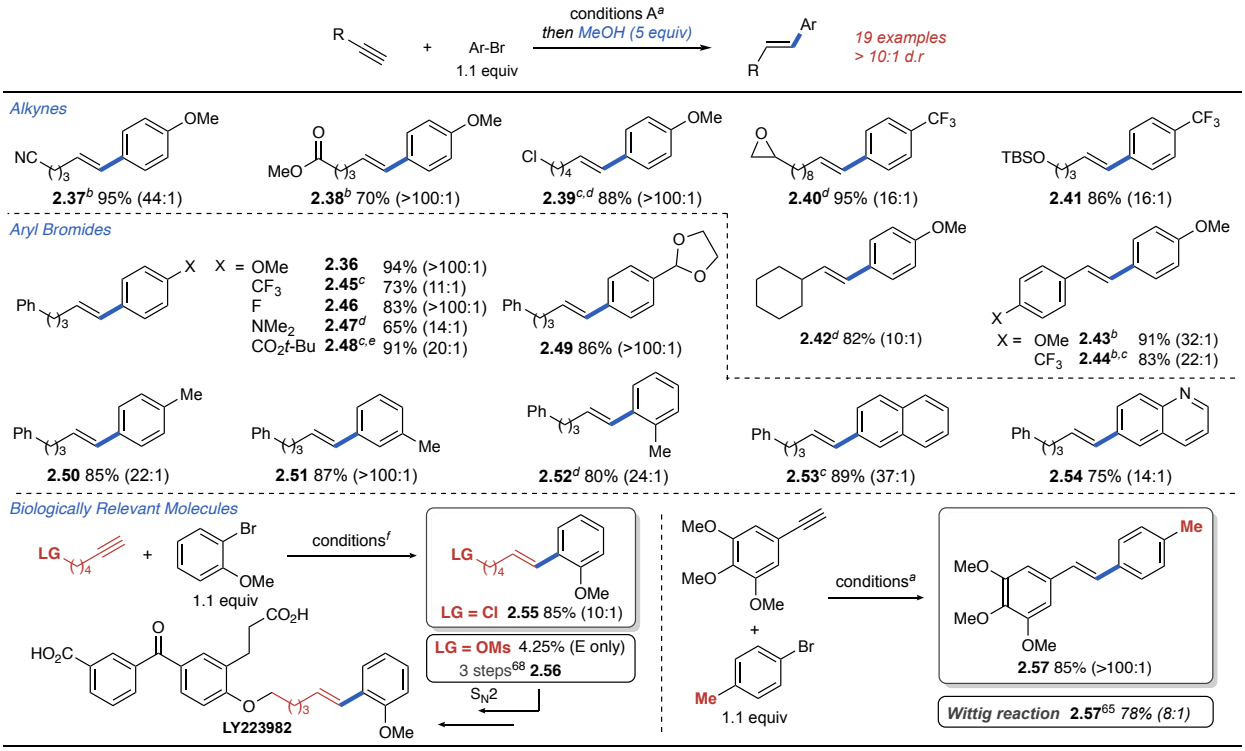
The addition of excess MeOH allowed the synthesis of a wide range of *E*-aryl alkenes in yields and diastereoselectivities that were comparable to those observed in the synthesis of *Z*-alkenes (Table 2.5) We observed a similar functional group compatibility and general scope of the reaction. Nitriles, esters, epoxides, alkyl halides, tertiary amines, acetals, and silyl ethers were all compatible with the reaction conditions. Both aryl and alkyl alkynes were, again, viable substrates.

We have also used the *E*-selective hydroarylation in the synthesis of biologically active compounds or their precursors. Electrophile **2.56** was previously used in the synthesis of **LY223982**, a Leukotriene B_4 antagonist developed by Ely Lilly & Co.[68] **2.56** was originally prepared in 3 steps and 5% yield and was used in alkylation of a phenol en route to the target

molecule.[68] We have prepared an alternative electrophile **2.55** in one step from commercially available materials, in 88% yield and in excellent selectivity (>100:1). We have also prepared **2.57** in 85% yield and >100:1 selectivity. In the context of an SAR study of Combretastatin A4,[65] **2.57** was previously prepared using Wittig reaction in 71% yield as a mixture of E and Z isomers (E:Z = 1:2.5).

Overall, the two hydroarylation reactions shown in Table 2.2 and Table 2.5 allow us to access both *Z*- and *E*-aryl alkenes, using one set of starting materials and reagents, and one catalyst system.

Table 2.5. : Scope and Applications of the *E*-Selective Hydroarylation

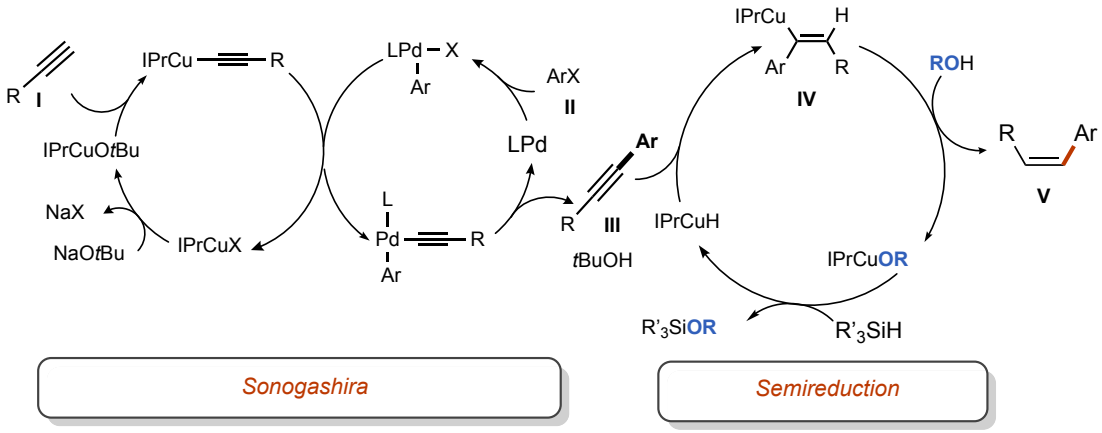


Reactions performed on 0.5-mmol scale. Reported are isolated yields of purified mixtures of product diastereoisomers. *E:Z* ratios of products determined by GC analysis of crude reaction mixtures are reported in paranthesis. [a]Conditions: IPrCuCl (10 mol%), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), Me_2i-PrSiH (2 equiv), NaO*t*-Bu (2 equiv), toluene, 45 °C. [b]Reaction conditions: $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), IPrCuCl (10 mol%), Me_2i-PrSiH (2 equiv), LiO*t*-Bu (2 equiv) toluene, 45 °C, 2 h, then NaO*t*-Bu (2 equiv) and MeOH (4 equiv) 60 °C. [c]*i*-BuOH used instead of MeOH, [d]Reaction placed at 60 °C after addition of alcohol. [d]0.5 equiv Me_2i-PrSiH added after 2 h in addition to 5.0 equiv MeOH, [e]*t*-BuOH used instead of MeOH. [f]$Pd(OAc)_2$ (10 mol%), **L1** (20 mol%) and reaction run at 60 °C.

2.6 MECHANISTIC STUDIES

2.6.1 *Proposed Mechanism: Z-Selective Hydroarylation*

Considering the established mechanisms of the Sonogashira coupling[44] and the copper-catalyzed semireduction,[46,47] a plausible mechanism for the *Z*-selective hydroarylation is presented in Scheme 2.5. Monitoring the reaction progress confirmed that the starting materials (**I** and **II**) are fully converted to the Sonogashira product **III** before the semireduction.

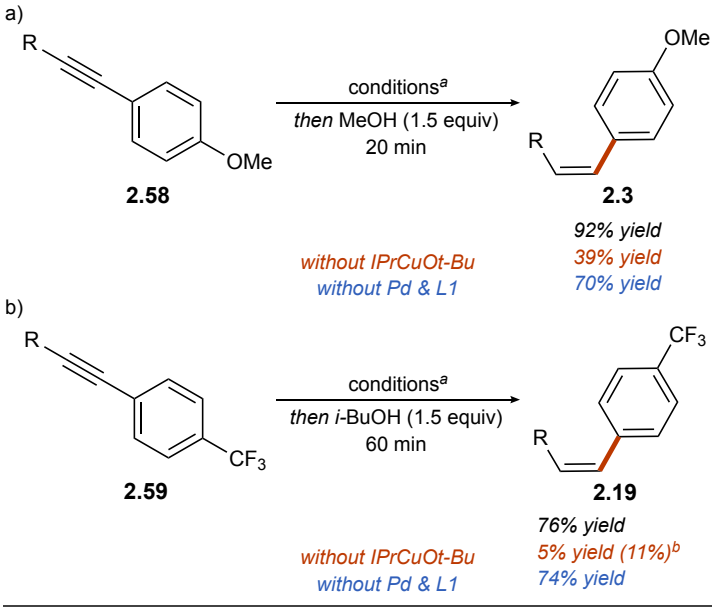


Scheme 2.5. Plausible Mechanism of *Z*-Selective Hydroarylation

2.6.2 *Role of Pd and Cu Catalysts in the Z-Selective Semireduction*

In the context of this general mechanism, we were interested in understanding the relative contributions of the two catalysts to the individual steps of the reaction. First, we explored the role of the palladium catalyst in the semireduction and found evidence that under certain reaction conditions the semireduction of the Sonogashira product is more complicated than Scheme 2.5 suggests. Experiments presented in Scheme 2.6a show that both palladium and copper catalysts independently promote selective semireduction. These results suggest that in the catalytic hydroarylation both catalysts likely contribute to the semireduction of intermediate **III**.[69] However,

in the absence of the copper catalyst, palladium-catalyzed semireduction does not result in complete conversion and the maximum yield of the semireduction product was 41% after 24 h (see Experimental). Furthermore, the relative contributions of the palladium and copper catalysts to the semireduction depend on the alcohol additive used in the reaction.



[a]$Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), IPrCuO*t*-Bu (10 mol%), Me_2*i*-PrSiH (2 equiv), NaO*t*-Bu (1 equiv), *t*-BuOH (1 equiv), toluene, 45 °C. [b]Yield after 24 h. R = $Ph(CH_2)_3$.

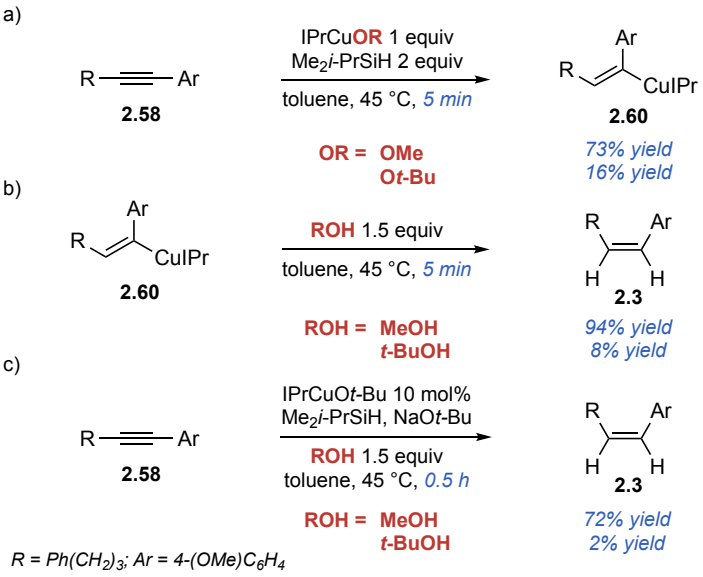
Scheme 2.6. Role of Pd and Cu Catalysts in the *Z*-Selective Semireduction

When *i*-BuOH is used instead of MeOH, the contribution of the palladium catalyst is significantly reduced, and the semireduction is mostly effected by the copper catalyst (Scheme 2.6b). Control experiments presented in the Experimental confirm that palladium contribution depends on the alcohol additive and not the substrate of the reaction.

2.6.3 *Effect of MeOH on Z-Selective Semireduction*

We were also interested in understanding the role of the alcohol additive and the reasons for the changes to the standard conditions that were necessary with certain substrates. Initially, we explored the mechanism behind the significant acceleration of the semireduction in the presence of MeOH additive, which we observed in both *E*- and *Z*-selective hydroarylation reaction. We found that the rate of the stoichiometric hydrocupration is significantly higher using IPrCuOMe vs IPrCuO*t*-Bu (Scheme 2.7a) (See Experimental for complete kinetics data), although IPrCuOMe is only partially soluble in toluene. Considering that the alkoxide group plays no role in the

hydrocupration of the alkyne, this observation implies significant difference in the rate of IPrCuH formation from IPrCuOR and a silane. These results are consistent with a computational study, which attributed a high activation barrier for the reaction between NHCCuOR and trialkylsilanes to significant steric repulsion in the transition state.[70] Surprisingly, this effect has not been experimentally observed in reactions mediated by (NHC)CuH.

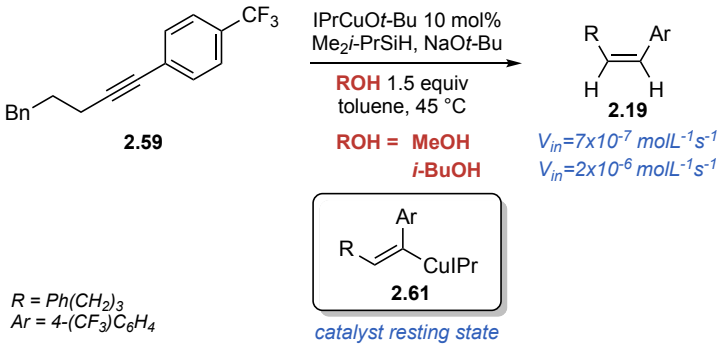


Scheme 2.7. Effect of MeOH on Semireduction

The rate of protonation of the alkenyl copper intermediate **2.60** was also significantly higher with MeOH than with *t*-BuOH, as demonstrated by the stoichiometric experiment shown in Scheme 2.7b. Consistent with stoichiometric experiments, we found that the catalytic semireduction of **2.58** was significantly faster in the presence of MeOH than in the presence of *t*-BuOH (Scheme 2.7c). Significant concentration of the alkenyl copper intermediate **2.60** was observed during copper-catalyzed semireduction in the presence of either alcohol. This result indicates that the protonation of the intermediate is at least partially rate limiting. Overall, it is likely that MeOH accelerates the semireduction by facilitating both the formation of the IPrCuH and the protonation of the alkenyl copper intermediate.

2.6.4 *i-BuOH in Semireduction*

To understand the effect of *i*-BuOH additive in reactions with electron-deficient aryl bromides, we did initial rate measurements for the semireduction performed in the presence of MeOH and *i*-BuOH (Scheme 2.8). The experiment confirmed that the reaction is faster in the presence of *i*-BuOH. In both reactions, we observed a significant amount of the alkenyl copper intermediate (**2.61**) throughout the course of the reaction (18-20% of alkenyl copper in the reaction with 20 mol% loading of IPrCuO*t*-Bu, see Experimental for details). These results suggest that the resting state of the catalyst in the reaction of electron-deficient alkynes is the alkenyl copper intermediate and that the turnover limiting step is the protonation of this intermediate. Somewhat surprisingly, these results indicate that the protonation of the alkenyl copper intermediate is significantly faster with *i*-BuOH than with MeOH.



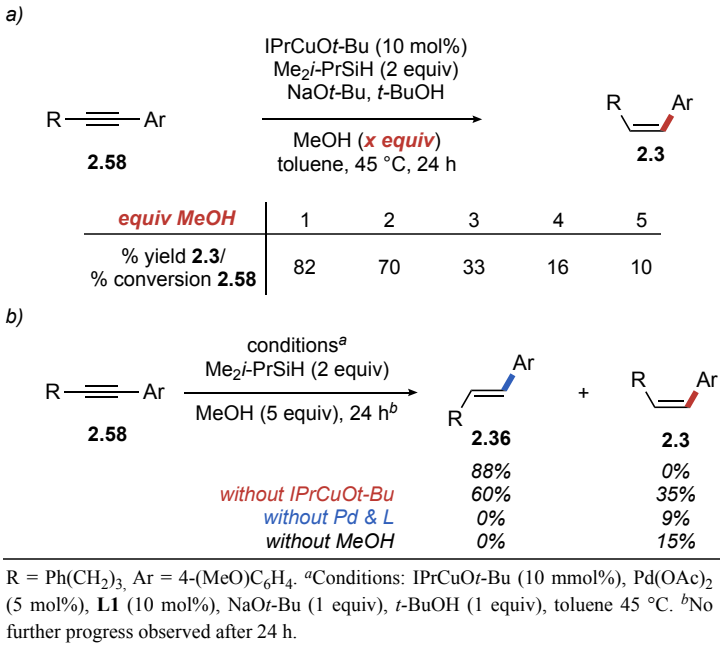
Scheme 2.8. *i*-BuOH in Semireduction

2.6.5 *Role of Pd and Cu Catalysts in the E-Selective Hydroarylation*

Finally, we also explored aspects of the reaction mechanism specific to the conditions employed in the synthesis of *E*-aryl alkenes. In this case, the relative contributions of palladium and copper catalysts to the semireduction was dramatically different from their contributions in the *Z*-selective reaction. With 5 equivalents of MeOH, copper-catalyzed semireduction of the Sonogashira product

provides only 10% of the desired product and 10% conversion. The data in Scheme 2.9a shows the impact the increasing amounts of methanol have on the copper-catalyzed semireduction. These results are consistent with competitive protonation of IPrCuH by methanol we previously observed in the semireduction reaction.[47]

The major implication of these results is that under conditions used in *E*-selective hydroarylation, the semireduction is predominantly mediated by the palladium catalyst and is promoted by excess MeOH. Experiments shown in Scheme 2.9b confirm the more prominent role of the palladium catalyst and the key role of MeOH in *E*-selective hydroarylation.



R = $Ph(CH_2)_3$, Ar = 4-$(MeO)C_6H_4$. [a]Conditions: IPrCuO*t*-Bu (10 mmol%), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), NaO*t*-Bu (1 equiv), *t*-BuOH (1 equiv), toluene 45 °C. [b]No further progress observed after 24 h.

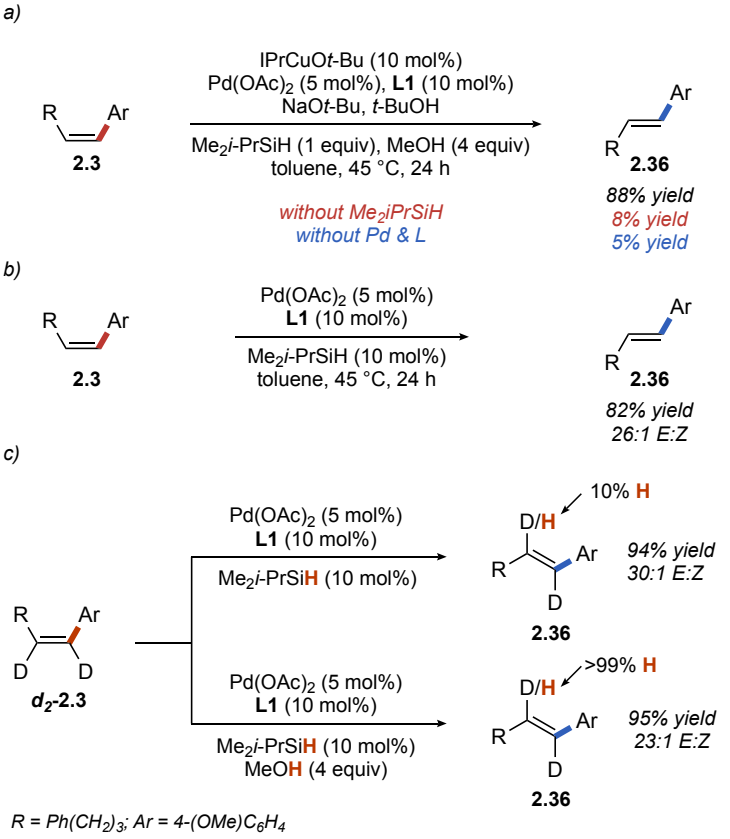
Scheme 2.9. Role of Pd Catalyst ad MeOH in *E*-Selective Hydroarylation

2.6.6 *Palladium-Catalyzed Alkene Isomerization*

We were also interested in understanding the mechanism of alkene isomerization in the *E*-selective hydroarylation. Based on available precedents, isomerization through reversible hydrocupration of aryl alkenes seems unlikely under the conditions employed in our reaction.[4,71] Control experiments shown in Scheme 2.9b and Scheme 2.10a demonstrate that isomerization

requires both the palladium catalyst and the silane. Furthermore, we found that isomerization can be effectively accomplished using only the palladium catalyst and a substoichiometric amount of a silane (Scheme 2.10b). Interestingly, in contrast to the results reported by Jung,[53] we did not observe the formation of the alkane products. Based on observations we made during the development of the reaction, we believe that both the ligand and the silane used in the reaction are responsible for this difference.

Considering the conditions necessary for isomerization, it seems likely that the formation of *E*-aryl alkene proceeds though a reversible hydropalladation of the alkene, one of the established mechanisms for alkene isomerization. Further evidence for this mechanism was provided by isotope incorporation experiments (Scheme 2.10c). With 10 mol% of silane, we observed selective and full incorporation of a proton into ***d*$_2$-2.3**. The position of the proton incorporation is consistent with the established regioselectivity of styrene hydropalladation.[72] In the presence of MeOH, we observed the complete exchange of the same deuterium label, suggesting that the mechanism remains the same in the presence of methanol. The extent of deuterium exchange in the presence of MeOH suggests fast exchange between Pd-H and MeOH.[73]



Scheme 2.10. Palladium Catalyzed Aryl Alkene Isomerization

In summary, our exploration of the reaction mechanism provided insight into the roles of the two catalysts and the effects that alcohol additives and various changes from the standard reaction conditions have on the reaction. The most interesting finding is that the alcohol additive changes the role of each of the two catalysts in the hydroarylation. *i*-BuOH inhibits palladium catalyzed semireduction, while excess MeOH, suppresses copper-catalyzed semireduction and promotes both the palladium-catalyzed semireduction and alkene isomerization. This complementary reactivity of the two metal catalysts is essential for the success of the hydroarylation.

2.7 Conclusion

In conclusion, we have developed a diastereodivergent method for hydroarylation of terminal alkynes. The new method involves a sequence of catalytic reactions promoted by a combination of palladium and copper catalysts operating in tandem. The *Z*-selective hydroarylation is achieved through Sonogashira coupling of alkynes and aryl bromides, followed by semireduction. The *E*-selective hydroarylation involves an additional isomerization of the Z-aryl alkene. The new hydroarylation reactions allow access to both isomers of aryl alkenes using the same set of starting materials, and the same combination of catalysts. The hydroarylation reactions have excellent substrate scopes and functional group compatibility and provide the desired products in high yields and with high diastereoselectivity. Mechanistic experiments indicate different roles of palladium and copper catalysts in *Z*- and *E*-selective hydroarylation reactions. While both are involved in the Sonogashira coupling, the semireduction is predominantly promoted by a copper catalyst in the *Z*-selective reaction, while the palladium catalyst is necessary for both the semireduction and isomerization in the *E*-selective reaction.

2.8 EXPERIMENTAL

2.8.1 *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. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C NMR chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm). ^{19}F NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to the internal standard, hexafluorobenzene. 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. 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.

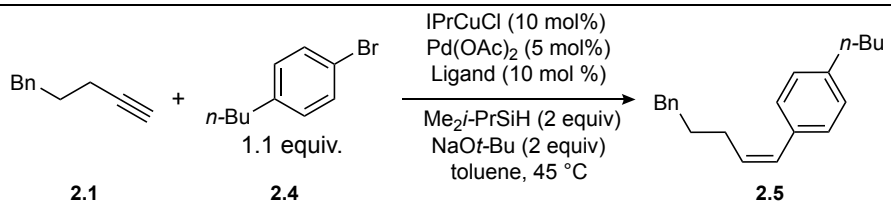
Materials: THF, CH_2Cl_2, Ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous methanol was purchased from Millipore Sigma, and was

subsequently 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, Ark-Pharm, Combi-Blocks, Oakwood Chemicals, Strem Chemicals and Alfa Aesar. Dimethylisopropylsilane (Me_2*i*-PrSiH) was purchased from Gelest Inc and was degassed and stored over 4Å molecular sieves.

2.8.2 *Reaction Development (Table 2.1)*

All reactions were performed on a 0.05 mmol scale with the stoichiometry shown in Tables S1-S3. In a nitrogen-filled glovebox a dram vial was charged with a stir bar, NaO*t*-Bu, 5-phenyl-1-pentyne, 1,3,5-trimethoxy benzene (TMB, used as an internal standard for GC), $Pd(OAc)_2$, IPrCuCl, ligand (Table 2.6), 1-bromo-4-butylbenzene, silane (
Table 2.7) and toluene. The reaction mixture was stirred at 45 ºC and monitored by Gas Chromatography for reaction completion. Aliquots were taken at 4 h, 8 h, and 24 h time points.

Table 2.6. Ligand Screen

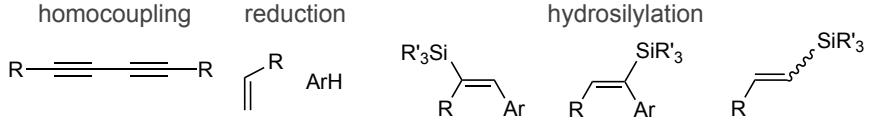


2.1 **2.4** **2.5**

Entry	Ligand	Temperature (ºC)	Time (h)	Yield (%)
1	XPhos	45	24	8
2	**L1**	45	24	47
3	**L1**	25	24	0
4	RuPhos	45	24	1
5	PCy_3	45	24	0
6	dppf	45	24	0
7	dppp	45	24	0
8	DTBM-SEGPhos	45	24	0
9	DavePhos	45	24	21
10	BINAP	45	24	0
11	Xyl-MeOBIPHEP	45	24	0
12	DACH Trost	45	24	0

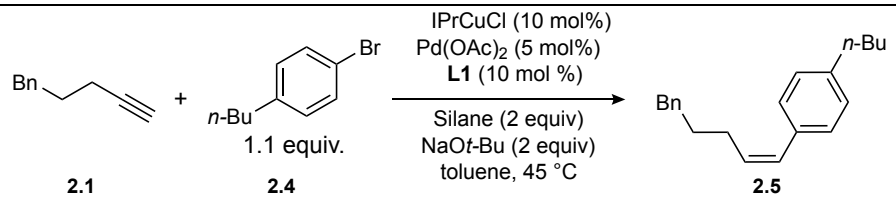
13	SPhos	45	24	26
14	QPhos	45	24	13

Major Side Products[a]



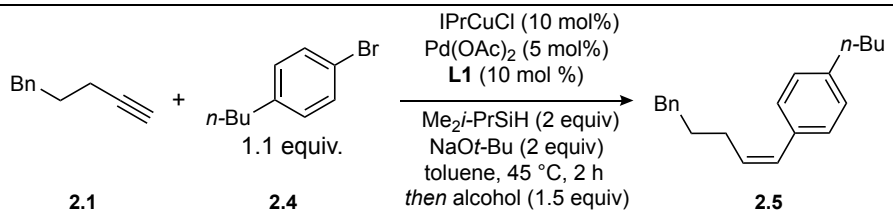
[a]Side products determined by GC-MS analysis of the aliquots and known palladium chemistry.

Table 2.7. Silane Screen



Entry	Silane	Time (h)	Sonogashira Yield (%)	Z-alkene Yield (%)
1	Me_2PhSiH	24	5	27
2	$MePh_2SiH$	24	5	18
3	Ph_3SiH	24	9	10
4	Ph_2SiH_2	24	0	0
5	$PhSiH_3$	24	0	0
6	Et_3SiH	24	3	0
7	*t*-Bu_2SiH_2	24	0	6
8	Me_2*i*-PrSiH	24	91	0
9	*t*-Bu_2MeSiH	24	86	0
10	(O*t*-Bu)$_2$MeSiH	24	0	25
11	$(OEt)_3SiH$	24	2	0
12	$(OMe)_2MeSiH$	24	0	0
13	$(OEt)_2MeSiH$	24	0	0
14	TMDSO	24	10	12
15	PMHS	24	1	6

Table 2.8. Alcohol Additive Screen



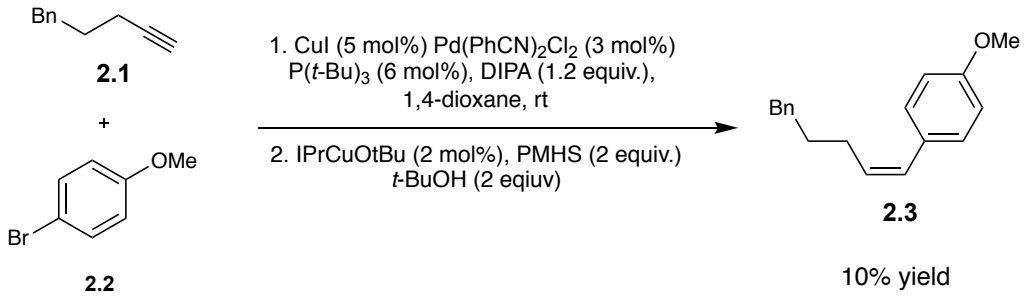
Entry	Alcohol	Time (h)*	Sonogashira Yield (%)	Z-alkene Yield (%)	Z:E Ratio
1	MeOH	4	0	100	33/1
2	*i*-BuOH	4	0	100	25/1

3	Neopentanol	4	0	100	21/1
4	*t*-BuOH	4	73	27	--
5	*i*-PrOH	4	17	58	--

2.8.3 *Standard Sonogashira Coupling Followed by Semireduction*

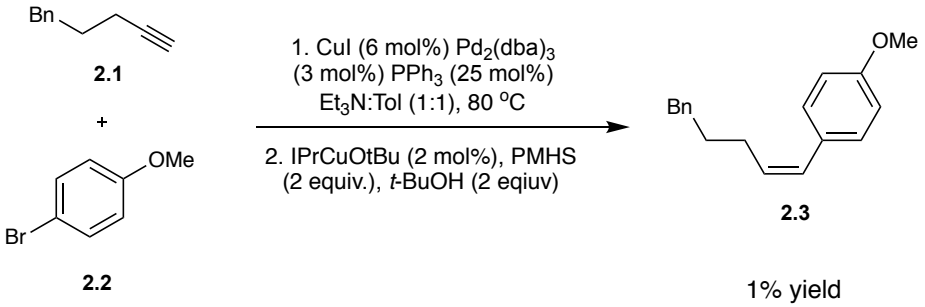
General Procedure (Scheme 2.4)

All manipulations were performed in a nitrogen-filled glovebox. Each Sonogashira coupling was performed according to the procedure reported in the literature. Reactions were performed on a 0.05 mmol scale and monitored by GC. Sonogashira coupling was determined to be complete upon full consumption of the aryl bromide. Standard semireduction conditions[47] were then applied, and reactions were allowed to stir at 25 ^{o}C for 1 h, at which point a 30 μL aliquot was taken, pushed through a plug of silica with EtOAc, and analyzed by GC. Every reaction was heated to 45 ^{o}C, 60 ^{o}C and 90 ^{o}C to encourage semireduction. At each temperature, reactions were monitored by GC, and if no change was seen after 1 h, reactions were moved to the next temperature. Reactions were monitored at 90 ^{o}C until no further change occurred.



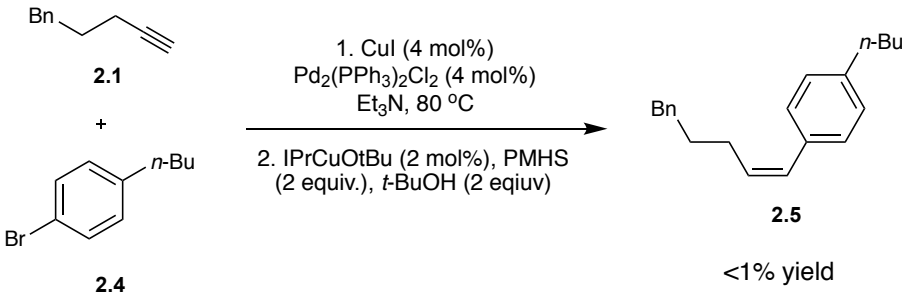
Scheme 2.11. Literature Sonogashira Followed by Semireduction

Sonogashira coupling[49] determined complete at 16 h. Semireduction was stopped at 20 h. Yield determined by GC.



Scheme 2.12. Literature Sonogashira Followed by Semireduction

Sonogashira coupling[74] determine complete at 24 h. Semireduction was stopped at 24 h. Yield determined by GC.



Scheme 2.13. Literature Sonogashira Followed by Semireduction

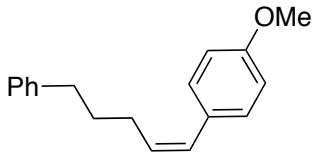
Sonogashira coupling[75] determined complete at 16 h. Semireduction was stopped at 24 h. Yield determined by GC.

2.8.4 *General Procedure for the Hydroarylation of Terminal Alkynes: Synthesis of Z-Styrenes (Table 2.2)*

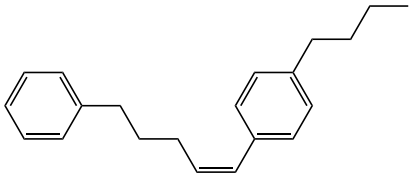
In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and NaO*t*-Bu (96.1 mg, 1.00 mmol, 2.0 equiv). To this was added alkyne (0.50 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.025 mmol, 0.100 equiv) IPrCuCl (24.4 mg, 0.050 mmol, 0.10 equiv), **L1** (19 mg, 0.050 mmol, 0.10 equiv), aryl bromide (0.550 mmol, 1.10 equiv), Me_2*i*-PrSiH (102.3 mg, 1.00 mmol, 2.00 equiv), and toluene (5 mL). The reaction mixture was stirred at 45 °C, and the reaction progress was monitored by TLC. When the starting alkyne was fully consumed, methanol (24.0 mg, 0.750

mmol, 1.5 equiv) was added and stirring was continued at 45 °C. 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 dieastereoselectivity of the reactions. The crude reaction mixture was concentrated under reduced pressure and the product was purified by silica gel chromatography. The ratio of stereoisomers for each product was again determined by GC analysis of the isolated product.

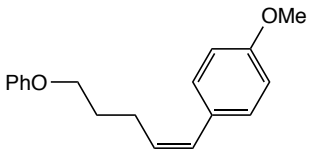
2.8.5 *Characterization of Hydroarylation Products: Z-Styrenes (Table 2.2)*



1-methoxy-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.3), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 20:1). The compound was purified by silica gel chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (110.0 mg, 87% yield, Z:E = 28:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.44 – 7.17 (m, 7H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 11.7 Hz, 1H), 5.69 (dt, *J* = 11.7, 7.2 Hz, 1H), 3.88 (s, 3H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.55 – 2.27 (dt, *J* = 7.6, 7.2 Hz, 2H), 1.87 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 158.6, 142.7, 131.3, 130.7, 130.3, 129.0, 128.8, 128.6, 126.1, 113.9, 55.6, 35.9, 32.1, 28.5. GCMS (EI) calculated for [M]+ 252.15, found 252.3. FTIR (neat, cm^{-1}): 3028(m), 3006(m), 2924(m), 2857(m), 1605(s), 1508(s), 1247(s), 673(s).

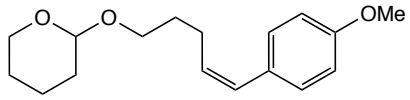


1-butyl-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.5), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (100% Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 19:1).The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 5%) and isolated as a colorless oil (113 mg, 81% yield, Z:E = 19:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 6.99 (m, 11H), 6.41 (d, *J* = 11.6 Hz, 1H), 5.65 (dt, *J* = 11.6, 7.3 Hz, 1H), 2.81 – 2.49 (m, 5H), 2.49 – 2.30 (m, 3H), 1.93-1.69 (m, 2H), 1.69 – 1.52 (m, 2H), 1.47 – 1.28 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 141.3, 135.3, 131.9, 129.4, 128.8, 128.6, 128.4, 128.3, 125.8, 35.7, 35.5, 33.7, 31.8, 28.3, 22.5, 14.1. GCMS (EI) calculated for [M]+ 278.20, found 278.3. FTIR (neat, cm^{-1}): 3062(m), 2955(m), 2929(m), 2857(m), 1604(s), 1454(s), 844(s), 752(s) 699(s).

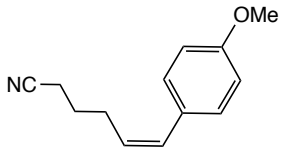


1-methoxy-4-[(1*Z*)-5-phenoxypent-1-en-1-yl]benzene (2.6), compound was prepared according to the general procedure, TLC in 10% EtOAc/Hex showed that the starting alkyne was consumed after 3 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 80:1).The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 10%) and isolated as

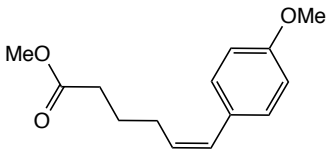
a colorless oil (105 mg, 78% yield, Z:E > 100:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H), 7.27 – 7.20 (m, 2H), 6.98 – 6.90 (m, 1H), 6.92 – 6.82 (m, 4H), 6.41 (d, *J* = 11.5 Hz, 1H), 5.68 – 5.55 (m, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 2.53 (q, *J* = 7.3 Hz, 2H), 1.95 (p, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.4, 130.3, 130.1, 129.5, 129.3, 120.7, 120.1, 114.7, 113.7, 67.3, 55.4, 29.7, 25.3. GCMS (EI) calculated for [M]+ 268.15, found 268.1. FTIR (neat, cm^{-1}): 3005 (m), 2937(m), 2863(m), 2172(m), 1601(s), 1510(s), 837(s), 753(s) 691(s).



2-{[(4*Z*)-5-(4-methoxyphenyl)pent-4-en-1-yl]oxy}oxane (2.7), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 9:1).The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 30%) and isolated as a colorless oil (104 mg, 75% yield, Z:E = 10:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.37 (d, *J* = 11.4 Hz, 1H), 5.58 (dt, *J* = 11.4, 7.3 Hz, 1H), 4.55 (s, 1H), 3.87 – 3.73 (m, 5H), 3.52 – 3.37 (m, 2H), 2.53 – 2.23 (m, 2H), 1.89 – 1.41 (m, 8H).^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 130.8, 130.5, 130.1, 128.8, 113.7, 98.95, 67.0, 62.4, 55.4, 30.9, 30.2, 25.6, 25.4, 19.7. GCMS (EI) calculated for [M]+ 276.17, found 276.3. FTIR (neat, cm^{-1}): 3006(m), 2942(m), 2869(m), 2246(s), 1608(s), 1511(s), 839(s), 734(m).

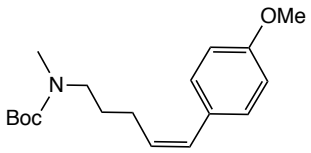


(5*Z*)-6-(4-methoxyphenyl)hex-5-enenitrile (2.8), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 3 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 16:1).The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 40%) and isolated as a colorless oil (72 mg, 72% yield, Z:E = 16:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.45 (d, *J* = 11.6 Hz, 1H), 5.49 (dt, *J* = 11.6, 7.1 Hz, 1H), 3.82 (s, 3H), 2.55 – 2.40 (m, 2H), 2.42 – 2.27 (m, 2H), 1.91 – 1.72 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 130.5, 130.0, 129.8, 128.3, 119.7, 113.9, 55.4, 27.6, 25.9, 16.8. GCMS (EI) calculated for [M]+ 201.12, found 201.2. FTIR (neat, cm^{-1}): 3054(m), 2985(m), 2924(m), 2838(m), 2305(s), 2248(s), 1608(s), 1266(m) 895(s) 839(9).



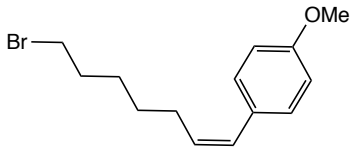
methyl (5*Z*)-6-(4-methoxyphenyl)hex-5-enoate (2.9), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was

consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 45:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 40%) and isolated as a colorless oil (111 mg, 94% yield, Z:E = 48:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.39 (d, *J* = 11.6 Hz, 1H), 5.70 - 5.38 (m, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 2.45 - 2.27 (m, 4H), 1.88 - 1.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 158.4, 130.2, 130.1, 130.0, 129.3, 113.7, 55.3, 51.5, 33.6, 28.0, 25.2. GCMS (EI) calculated for [M]+ 234.13, found 234.2. FTIR (neat, cm^{-1}): 3005(m), 2949(m), 2836(m), 2255(m), 1736(s), 1608(s), 836(s), 734(s).

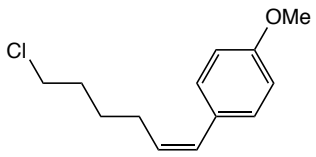


tert-butyl N-[(4*Z*)-5-(4-methoxyphenyl)pent-4-en-1-yl]-N-methylcarbamate (2.10), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 3 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 30:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 40%) and isolated as a pale yellow oil (119 mg, 82% yield, Z:E = 32:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.36 (d, *J* = 11.6 Hz, 1H), 5.56 (dt, *J* = 11.6, 7.1 Hz, 1H), 3.81 (s, 3H), 3.22 (t, *J* = 7.3 Hz, 2H), 2.82 (s, 3H), 2.46 – 2.21 (m, 2H), 1.75 – 1.56 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 155.9, 130.5, 130.0, 128.9, 127.1, 113.7, 79.3, 55.3, 48.7, 34.3, 28.6,

26.0. GCMS (EI) calculated for [M]+ 305.20, found 305.1. FTIR (neat, cm^{-1}): 3005(m), 2974(m), 2932(m), 2836(m), 1694(s), 1608(s), 1511(s), 883(s).

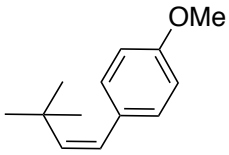


1-[(1*Z*)-7-bromohept-1-en-1-yl]-4-methoxybenzene (2.11), compound was prepared according to the general procedure, TLC in 10% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 1 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 90:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (85 mg, 60% yield, Z:E > 100:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.36 (d, *J* = 11.6 Hz, 1H), 5.55 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.82 (s, 3H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.50 – 2.18 (m, 2H), 2.00 – 1.72 (m, 2H), 1.53 – 1.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 131.1, 130.4, 130.0, 128.6, 113.6, 55.4, 34.1, 32.8, 29.3, 28.5, 28.0. GCMS (EI) calculated for [M]+ 282.06, found 282.1. FTIR (neat, cm^{-1}): 3003(m), 2926(m), 2852(m), 2172(m), 1609(s), 1511(s), 835(s), 734(s) 678(s).

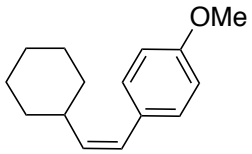


1-[(1*Z*)-6-chlorohex-1-en-1-yl]-4-methoxybenzene (2.12), compound was prepared according to the general procedure, TLC in 10% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 2 h. An aliquot of

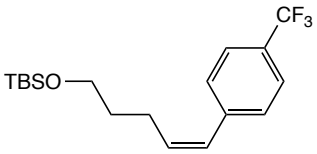
the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 90:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (99.3 mg, 88% yield, Z:E = 99:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 11.5 Hz, 1H), 5.72 – 5.41 (m, 1H), 3.82 (s, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.48 – 2.26 (m, 2H), 1.89 –-1.74 (m, 2H), 1.68 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 130.7, 130.4, 130.0, 129.0, 113.7, 55.4, 45.0, 32.3, 27.9, 27.3. GCMS (EI) calculated for [M]+ 224.10, found 224.2. FTIR (neat, cm^{-1}): 3054(m), 2958(m), 2864(m), 2305(m), 1608(s), 1511(s), 896(s), 741(s).



1-[(1Z)-3,3-dimethylbut-1-en-1-yl]-4-methoxybenzene (2.13) compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 15:1). The compound was purified by silica gel chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (69.0 mg, 73% yield, Z:E = 16:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.10 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.35 (d, *J* = 12.5 Hz, 1H), 5.56 (d, *J* = 12.5 Hz, 1H), 3.80 (s, 3H), 0.99 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-d) δ 158.2, 142.7, 131.8, 130.2, 126.9, 113.1, 55.3, 34.2, 31.4. GCMS (EI) calculated for [M]+ 190.29, found 190.5. FTIR (neat, cm-1): 2927 (s), 2852 (s), 1605(s), 1509(s), 1245(s), 6774(m).

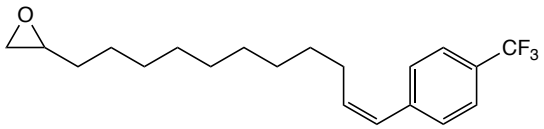


1-[(Z)-2-cyclohexylethenyl]-4-methoxybenzene (2.14) compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 15:1). The compound was purified by silica gel chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (88.0 mg, 81% yield, Z:E = 17:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.26 (d, *J* =8.8 Hz, 2H), 6.92 (d, 8.8 Hz, 2H), 6.30 (d, *J* = 11.7 Hz, 1H), 5.50 – 5.40 (t, *J* = 11.7, 1H), 3.86 (s, 3H), 2.72 – 2.54 (m, 1H), 1.88 – 1.68 (m, 5H), 1.45 – 1.16 (m, 5H). ^{13}C NMR (126 MHz, Chloroform-d) δ 158.3, 137.7, 130.7, 129.9, 126.4, 113.7, 55.4, 37.0. 33.5, 26.2, 25.9. GCMS (EI) calculated for [M]+ 216.32, found 216.5. FTIR (neat, cm-1): 2925 (s), 2850 (s), 1608(s), 1511(s), 1245(s), 677(m).



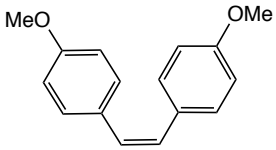
tert-butyldimethyl{[(5*Z*)-6-[4-(trifluoromethyl)phenyl]hex-5-en-1-yl]oxy}silane (2.15), compound was prepared according to the general procedure, TLC in 10% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 23:1).The compound was purified by silica gel chromatography with

EtOAc/Hex (0 → 15%) and isolated as a colorless oil (148 mg, 86% yield, Z:E = 23:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 11.8 Hz, 1H), 5.95 – 5.63 (m, 1H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.58 – 2.21 (m, 2H), 1.83 – 1.58 (m, 2H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.4, 134.9, 129.1, 128.6 (q, *J* = 31.9 Hz), 128.1, 125.2 (q, *J* = 4.1 Hz), 124.4 (q, *J* = 271.7 Hz), 62.5, 33.0, 26.0, 25.2, 18.4, -5.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5. GCMS (EI) calculated for [M]+ 358.19, found 358.3. FTIR (neat, cm^{-1}): 3013(m), 2930(m), 2865(m), 2175(m), 1919(s), 1616(m), 1473(s), 836(s) 775(s).

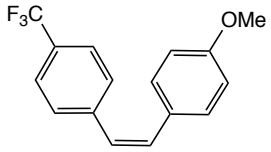


2-[(9*Z*)-10-[4-(trifluoromethyl)phenyl]dec-9-en-1-yl]oxirane (2.16), compound was prepared according to the general procedure, TLC in 10% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv of MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 22:1).The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (143 mg, 87% yield, Z:E = 22:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 11.7 Hz, 1H), 5.77 (dt, *J* = 11.7, 7.3 Hz, 1H), 3.03 – 2.82 (m, 1H), 2.74 (t, *J* = 4.5 Hz, 1H), 2.56 – 2.39 (m, 1H), 2.39 – 2.20 (m, 2H), 1.72 – 1.03 (m, 21H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.5, 135.5, 131.9, 129.0, 128.5 (q, *J* = 32.3 Hz), 125.1 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.0 Hz), 52.5, 47.2, 32.6, 29.9, 29.5, 29.4, 29.2, 29.0, 28.7, 26.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.4. GCMS (EI) calculated

for [M]+ 326.19, found 326.3. FTIR (neat, cm^{-1}): 3055(m), 2929(m), 2855(m), 2305(m), 1613(s), 1422(s), 896(s), 740(s).

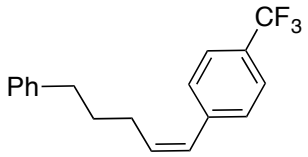


1-methoxy-4-[(*Z*)-2-(4-methoxyphenyl)ethenyl]benzene (2.17), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 16:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 45%) and isolated as a white solid (105 mg, 87% yield, Z:E = 16:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.7 Hz, 4H), 6.77 (d, *J* = 8.7 Hz, 4H), 6.44 (s, 2H), 3.79 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 130.2, 130.1, 128.5, 113.7, 55.3. GCMS (EI) calculated for [M]+ 240.12, found 240.2. FTIR (neat, cm^{-1}): 3054(m), 2958(m), 2937(m), 2838(m), 1607(s), 1511(s), 836(s), 740(s).



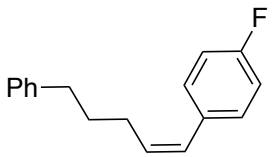
1-[(*Z*)-2-(4-methoxyphenyl)ethenyl]-4-(trifluoromethyl)benzene (2.18), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60

°C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 31:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a pale yellow oil (133 mg, 96% yield, Z:E = 32:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 12.2 Hz, 1H), 6.50 (d, *J* = 12.2 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 159.2, 141.5, 132.0, 130.3, 129.2, 128.9 (q, *J* = 32.1 Hz), 128.5, 127.3, 125.3 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.6 Hz), 113.9, 55.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5. GCMS (EI) calculated for [M]+ 278.09, found 278.1. FTIR (neat, cm^{-1}): 3010(m), 2956(m), 2837(m), 1607(s), 1508(s), 882(s), 830(s) 730(s).

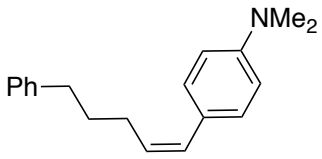


1-[(1*Z*)-5-phenylpent-1-en-1-yl]-4-(trifluoromethyl)benzene (2.19), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2h. After the addition of 1.5 equiv *i*-BuOH, monitoring the reaction progress by TLC (100% Hex) revealed that the internal alkyne intermediate was consumed after 2 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 20:1). The compound was purified by silica gel column chromatography (100% Hex) and a filtration through a short plug of alumina (100% Hex). The compound was isolated as a clear colorless oil (107 mg, 73% yield, Z:E = 22:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.05 (m, 8H), 6.46 (d, *J* = 11.6 Hz, 1H), 5.81 (dt, *J* = 11.7, 7.4 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.35 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.81 (p, *J* = 7.6Hz, 2H). GCMS (EI) calculated for [M]+ 290.13, found 290.5. ^{19}F NMR (471 MHz, Chloroform-d) δ -65.2. ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.1,

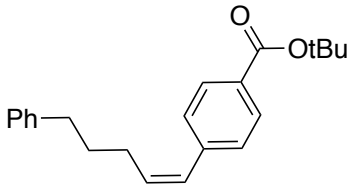
141.1, 134.8, 129.0, 128.6 (q, J = 35.2 Hz), 128.5, 128.2, 127.7, 126.0, 125.5 (q, J = 3.0 Hz), 124.4 (q, J = 276.5 Hz), 35.6, 31.6, 28.1. FTIR (neat, cm^{-1}): 3088(w), 3065(w), 3028(m), 2931(m). 2849(w), 1612(w), 1478(w), 1322(s), 1165(s), 1120(s), 1068(s), 673(s).



1-fluoro-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.20), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (100% Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 9:1). The compound was purified by silica gel column chromatography (100% Hex) and a filtration through a short plug of alumina. The compound was isolated as a clear colorless oil (105 mg, 83% yield, Z:E = 10:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.23 (m, 3H), 7.23 – 7.13 (m, 4H), 7.04 – 6.95 (m, 2H), 6.39 (d, J = 11.7 Hz, 1H), 5.68 (dt, J = 11.6, 7.3 Hz, 1H), 2.64 (t, J = 7.7 Hz, 2H), 2.33 (dt, J = 7.6, 7.3 Hz, 2H), 1.79 (p, J = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 161.5 (d, J = 246.1 Hz), 142.3, 133.8 (d, J = 3.1 Hz), 132.5, 130.4 (d, J = 7.9 Hz), 128.6, 128.4, 128.3, 125.9, 115.1 (d, J = 21.3 Hz), 35.6, 31.7, 28.1. ^{19}F NMR (471 MHz, Chloroform-d) δ -123.5. GCMS (EI) calculated for [M]+ 240.13, found 240.2. FTIR (neat, cm^{-1}): 3058(w), 3028(w), 2931(m), 1597(m), 1500(m), 1456(m), 1225(s), 1158(s), 857(m).

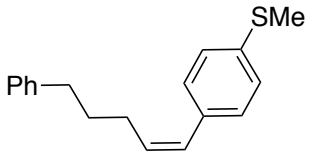


N,N-dimethyl-4-[(1*Z*)-5-phenylpent-1-en-1-yl]aniline (2.21), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, the reaction mixture was then moved to 0 ºC to slow the rate of isomerization, and the reaction progress was monitored progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 6 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 12:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (10% Et_2O/Hex). Compound was isolated as a clear colorless liquid (85 mg, 65% yield, Z:E = 12:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.16 (t, *J* = 7.5 Hz, 2H), 7.11 – 7.05 (m, 5H), 6.59 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 11.6 Hz, 1H), 5.42 (dt, *J* = 11.5, 7.2 Hz, 1H), 2.84 (s, 6H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.31 (dt, *J* = 7.6, 7.2Hz, 2H), 1.69 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 149.3, 142.6, 129.8, 129.1, 128.6, 128.4, 126.5, 125.8, 112.3, 40.6, 35.7, 32.0, 28.5. GCMS (EI) calculated for [M]+ 265.18, found 265.3. FTIR (neat, cm^{-1}): 3088(w), 3036(m), 2924(m), 2849(m), 2797(w), 1605(s), 1515(s), 1351(m), 1158(m), 679(s).



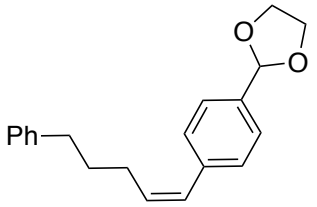
tert-butyl 4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzoate (2.22), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv *t*-BuOH to prevent transesterification, monitoring the reaction progress by GC revealed that the internal alkyne intermediate was consumed after 75 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 9:1). The

compound was purified by silica gel column chromatography (EtOAc/Hex 0→15%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil. (128 mg, 79% yield, Z:E = 10:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.21 – 7.10 (m, 5H), 7.12 – 7.00 (m, 2H), 6.36 (d, *J* = 11.7 Hz, 1H), 5.68 (dt, *J* = 11.7, 7.3 Hz, 1H), 2.53 (t, *J* = 7.5, 2H), 2.27 (dt, *J* = 7.5, 7.3 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-d) δ 165.7, 142.2, 141.9, 134.5, 130.1, 129.4, 128.7, 128.6, 128.5, 128.4, 125.9, 80.9, 35.5, 31.6, 28.3, 28.3. GCMS (EI) calculated for [M]+ 322.19, found 322.4. FTIR (neat, cm^{-1}): 3058(w), 3028(m), 2976(s), 2931(s), 2849(m), 1709(s), 1597(s), 1456(s), 1292(s), 1165(s), 1105(s), 852(m), 740(m), 695(s), 681(m).

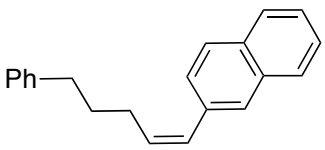


1-(methylsulfanyl)-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.23), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (5% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 1 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 80:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (118 mg, 88% yield, Z:E = 80:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.19 – 7.12 (m, 3H), 7.12 – 7.02 (m, 6H), 6.27 (d, *J* = 11.7 Hz, 1H), 5.56 (dt, *J* = 11.6, 7.3 Hz, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.38 (s, 3H), 2.26 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.68 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.3, 136.6, 134.7, 132.5, 129.3, 128.7, 128.6, 128.4, 126.5, 125.8, 35.6,

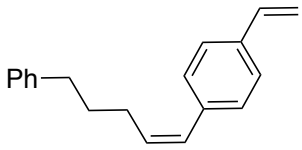
31.8, 28.3 16.0. GCMS (EI) calculated for [M]+ 268.13, found 268.3. FTIR (neat, cm^{-1}): 3088(w), 3065(w), 3021(m), 2924(s), 2849(m), 1597(m), 1493(s), 1090(m), 830(m), 673(s)



2-{4-[(1*Z*)-5-phenylpent-1-en-1-yl]phenyl}-1,3-dioxolane (2.24), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 45 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 18:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→15%). The compound was isolated as a clear colorless oil (102 mg, 69% yield, Z:E = 18:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 4H), 7.17 (dd, *J* = 14.7, 7.4 Hz, 3H), 6.45 (d, *J* = 11.7 Hz, 1H), 5.81 (s, 1H), 5.71 (dt, *J* = 11.6, 7.3 Hz, 1H), 4.18 – 4.06 (m, 2H), 4.06 – 3.97 (m, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.37 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.78 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.3, 138.7, 136.2, 133.1, 129.0, 128.8, 128.5, 128.4, 126.3, 125.8, 103.8, 65.4, 35.6, 31.7, 28.2. GCMS (EI) calculated for [M]+ 294.16, found 294.4. FTIR (neat, cm^{-1}): 3058(w), 3028(m), 2924(s), 2887(s), 2857(w), 1605(m), 1381(m), 1217(m), 1083(s), 941(m), 703(s), 681(s).

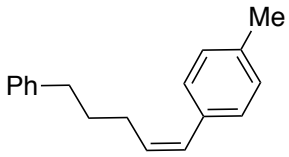


2-[(1*Z*)-5-phenylpent-1-en-1-yl]naphthalene (2.25), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv *i*-BuOH, monitoring the reaction progress by TLC (5% Et_2O in Hex) revealed that the internal alkyne intermediate was consumed after 20 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 29:1). The compound was purified by silica gel column chromatography (Et_2O/Hex 0→5%) and a filtration through a short plug of alumina (5% Et_2O/Hex). The compound was isolated as a clear colorless oil (109 mg, 80% yield, Z:E = 29:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.73 – 7.64 (m, 3H), 7.59 (s, 1H), 7.40 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.17 – 7.11 (m, 2H), 7.09 – 7.03 (m, 3H), 6.49 (d, *J* = 11.6 Hz, 1H), 5.67 (dt, *J* = 11.6, 7.3 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.37 (dt *J* = 7.5, 7.3 Hz, 2H), 1.72 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.4. 135.4, 133.5, 133.1, 132.4, 129.5, 128.6, 128.6, 128.4, 127.7, 127.7, 127.5, 127.4, 126.1, 125.9, 125.8, 35.6, 31.8, 28.4. GCMS (EI) calculated for [M]+ 272.16, found 272.3. FTIR (neat, cm^{-1}): 3051(m), 3021(m), 2924(s), 2849(m), 1597(m), 1493(m), 1448(m), 822(s), 748(s), 695(s).

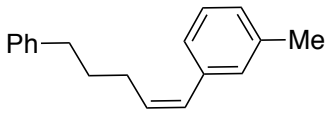


1-ethenyl-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.26), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (5% Et_2O//Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 19:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→5%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (105

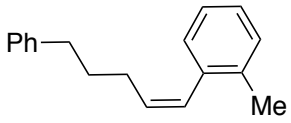
mg, 85% yield, Z:E = 20:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.26 – 7.13 (m, 7H), 6.70 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.40 (d, *J* = 11.7 Hz, 1H), 5.82 – 5.58 (m, 2H), 5.22 (d, *J* = 10.9 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.37 (dt, *J* = 7.7, 7.2 Hz, 2H), 1.78 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.4, 137.5, 136.8, 136.0, 132.8, 129.1, 129.1, 128.6, 128.4, 126.2, 125.9, 113.6, 35.6, 31.8, 28.4. GCMS (EI) calculated for [M]+ 248.16, found 248.2. FTIR (neat, cm^{-1}): 3080(w), 3058(w), 3021(m), 3006(m), 2924(s), 2857(m), 1620(m), 1605(m), 1500(s), 1456(s), 986(m), 904(m), 845(s), 678(s).



1-methyl-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.27), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (5% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 9:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (116 mg, 98% yield, Z:E = 10:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.35 – 7.05 (m,9H), 6.41 (d, *J* = 11.6 Hz, 1H), 5.65 (dt, *J* = 11.6, 7.3 Hz, 1H), 2.69 – 2.60 (m, 2H), 2.45 – 2.30 (m,5H), 1.79 (p, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.4, 136.2, 134.9, 131.9, 129.2, 128.8, 128.6, 128.4, 128.4, 125.8, 35.6, 31.9, 28.3, 21.3. GCMS (EI) calculated for [M]+ 236.16, found 236.2. FTIR (neat, cm^{-1}): 3058(w), 3021(m), 2924(s), 2857(m), 1597(w), 1508(w), 1448(m), 830(m), 695(s), 681(s).

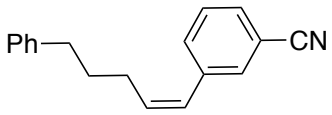


1-methyl-3-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.28), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (5% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 9:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (102 mg, 86% yield, Z:E = 10:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.19 – 7.02 (m, 6H), 6.99 – 6.90 (m, 3H), 6.31 (d, *J* = 11.7 Hz, 1H), 5.57 (dt, *J* = 11.9, 7.3 Hz, 1H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.32 – 2.21 (m, 5H), 1.68 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.5, 137.8, 132.5, 129.6, 129.5, 128.6, 128.4, 128.2, 127.4, 125.9, 125.8, 123.3, 35.6, 31.8, 28.3, 21.6. GCMS (EI) calculated for [M]+ 236.16, found 236.2. FTIR (neat, cm^{-1}): 3065(w), 3028(m), 2924(s), 2849(m), 1605(m), 1582(w), 1493(m), 1456(m), 792(m), 748(m), 675(s).

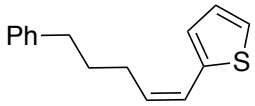


1-methyl-2-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.29), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (5% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 35:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→10%) and a filtration through

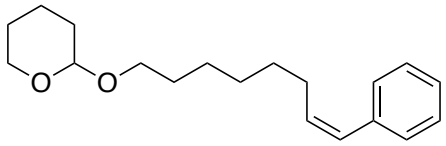
a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (110 mg, 93% yield, Z:E = 35:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.20 – 6.96 (m, 9H), 6.36 (d, *J* = 11.4 Hz, 1H), 5.63 (dt, *J* = 11.5, 7.4 Hz, 1H), 2.48 (t, *J* = 7.6 Hz, 2H), 2.22 – 2.04 (m, 5H), 1.62 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.5, 136.9, 136.3, 132.4, 129.9, 129.1, 128.5, 128.4, 126.9, 125.8, 125.5, 120.1, 35.6, 31.8, 28.1, 20.0. GCMS (EI) calculated for [M]+ 236.16, found 236.2. FTIR (neat, cm^{-1}): 3058(w), 3021(m), 2924(s), 2857(m), 1597(m), 1485(m), 1448(s), 1031(m), 740(s), 695(s).



3-[(1*Z*)-5-phenylpent-1-en-1-yl]benzonitrile (2.30), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv *i*-BuOH, monitoring the reaction progress by GC revealed that the internal alkyne intermediate was consumed after 2 h. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 20:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→5%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (114 mg, 92% yield, Z:E = 24:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.35 (m, 4H), 7.21 – 6.99 (m, 5H), 6.30 (d, *J* = 11.7 Hz, 1H), 5.71 (dt, *J* = 11.7, 7.4 Hz, 1H), 2.58 – 2.49 (t, *J* = 7.6Hz, 2H), 2.27 – 2.15 (m, 2H), 1.69 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 141.9, 139.8, 135.1, 133.1, 132.1, 130.0, 129.0, 128.8, 128.4, 127.2, 125.9, 119.0, 112.4, 35.4, 31.4, 28.0. GCMS (EI) calculated for [M]+ 247.14 found 247.3. FTIR (neat, cm^{-1}): 3058(m), 3021(m), 2924(s), 2857(m), 2223(s), 1597(m), 1448(m), 904(m), 800(s), 740(m), 695(s).

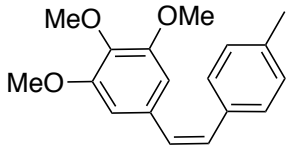


2-[(1*Z*)-5-phenylpent-1-en-1-yl]thiophene (2.31), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (10% Et_2O//Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 50:1). The compound was purified by silica gel column chromatography (EtOAc/Hex 0→5%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (82 mg, 72% yield, Z:E = 52:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.42 (s, 1H), 7.39 – 7.27 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 3H), 7.09 – 6.96 (m, 2H), 6.62 (d, *J* = 11.1 Hz, 1H), 5.67 (dt, *J* = 11.5, 7.2 Hz, 1H), 2.76 (t, *J* = 7.8 Hz, 2H), 2.53 (dt, *J* = 7.5, 7.2 Hz, 2H), 1.90 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.4, 140.9, 130.7, 128.6, 128.5, 127.2, 126.8, 125.9, 125.1, 122.3, 35.8, 31.4, 29.0. GCMS (EI) calculated for [M]+ 228.10, found 228.3. FTIR (neat, cm^{-1}): 3058(m), 3021(s), 2924(s), 2849(s), 1597(m), 1493(s), 1446(s), 1031(m), 845(m), 730(m), 740(s), 695(s).

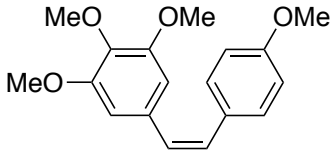


2-{[(7Z)-8-phenyloct-7-en-1-yl]oxy}oxane (2.32) compound was prepared according to the general procedure, TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, the reaction was moved to 60 ^{o}C and monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 30 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 16:1). The compound was purified by silica gel column chromatography

(EtOAc/Hex 0→40%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (117 mg, 81% yield, Z:E = 16:1). This compound has been previously synthesized and spectra matches literature values.[32]



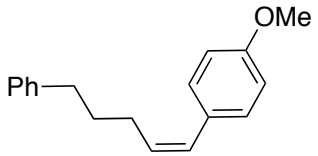
1,2,3-trimethoxy-5-[(Z)-2-(4-methylphenyl)ethenyl]benzene (2.34) compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2.5 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 20 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 31:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 25%) and isolated as a pale yellow oil (120 mg, 85% yield, Z:E = 31:1). This compound has been previously synthesized and spectra matches literature values.[66]



1,2,3-trimethoxy-5-[(Z)-2-(4-methoxyphenyl)ethenyl]benzene (2.35) compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH the reaction was moved to 60 °C and, monitoring the reaction progress by TLC (20% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 10 min. An aliquot of the crude reaction mixture was analyzed

by GC to obtain the isomeric ratio (Z:E = >100:1). The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 25%) and isolated as a pale yellow oil (131 mg, 87% yield, Z:E = >100:1). This compound has been previously synthesized and spectra matches literature values.[66]

2.8.6 *Gram Scale Reaction*



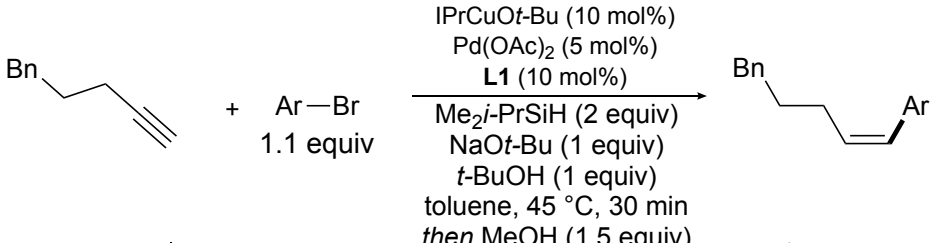
1-methoxy-4-[(1*Z*)-5-phenylpent-1-en-1-yl]benzene (2.3), compound was prepared according to the general procedure, TLC in 100% Hex showed that the starting alkyne was consumed after 2 h. After the addition of 1.5 equiv MeOH, monitoring the reaction progress by TLC (10% EtOAc/Hex) revealed that the internal alkyne intermediate was consumed after 15 min. An aliquot of the crude reaction mixture was analyzed by GC to obtain the isomeric ratio (Z:E = 18:1). The compound was purified by silica gel chromatography (EtOAc/Hex 0→10%) and a filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (1.1247 g, 75% yield, Z:E = 20:1).

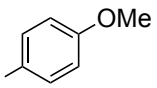
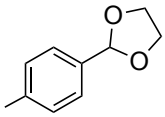
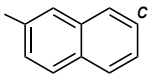
2.8.7 *Selectivity Studies (Table 2.3)*

In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and NaO*t*-Bu (9.6 mg, 0.10 mmol, 2.0 equiv). To this was added 5-phenyl-1-pentyne (7.2 mg, 0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol, 0.05 equiv) IPrCuCl (2.4 mg, 0.005 mmol, 0.10 equiv), **L1** (1.9 mg, 0.0050 mmol, 0.10 equiv), aryl bromide (0.055 mmol, 1.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.00 equiv), and toluene (0.5 mL). The reaction mixture was stirred at 45 °C, and the

reaction progress was monitored by TLC. When the starting alkyne was fully consumed, methanol (2.4 mg, 0.0750 mmol, 1.5 equiv) was added and stirring was continued at 45 °C. 30 μL aliquots were taken at 20 min, 25 min, 30 min, 35 min and 40 min passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.9. Selectivity for Z-Styrene Over Time



Ar =	20 min[b]	25 min	30 min	35 min	40 min	Yield Range
	20:1	18:1	13:1	10:1	10:1	92 - 95
	>100:1[d]	18:1	18:1	17:1	13:1	70 - 79
	28:1	28:1	27:1	26:1	25:1	84 - 89

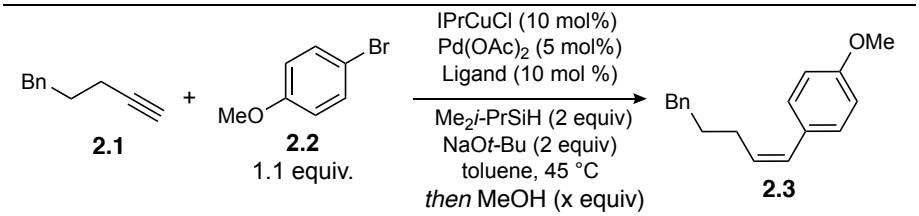
[a]Selectivity determined by GC analysis of crude reaction mixture. [b]Time after the addition of alcohol. [c]*i*-BuOH used instead of MeOH. [d]Reaction mixture contains <10% internal alkyne.

2.8.8 *Optimization of E-Selective Hydroarylation (Table 2.4)*

In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and NaO*t*-Bu (9.6 mg, 0.100 mmol, 2 equiv). To this was added **1** (7.20 mg 0.050 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol, 0.05 equiv) IPrCuCl (2.4 mg, 0.0050 mmol, 0.10 equiv), ligand (0.10 equiv), **2.2** (0.0550 mmol, 1.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.00 equiv), and toluene (0.5 mL). The reaction mixture was stirred at 45 °C, and the reaction progress was monitored by TLC. When the starting alkyne was fully consumed, methanol was added and stirring was continued at 45 °C.

The reaction progress was monitored by GC for complete isomerization to the *E*-alkene. The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography. The ratio of stereoisomers for each product was determined by GC analysis of a crude reaction mixture.

Table 2.10. Reaction Development: *E*-Selective Hydroarylation



Entry	Ligand	Yield 20 min (E:Z)
1	QPhos	100% (1.9:1)
2	DavePhos	81% (1:2.5)
3	RuPhos	69% (1:2.8)
4	Sphos	81% (1:1.2)
5	L1	90% (1:29)
6	L1 (6 days)	95% (2:1)
7	L1 (5 equiv MeOH)	94% (>100:1)

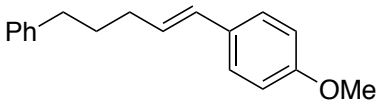
[a]Combined yields and E:Z selectivity determined by GC

2.8.9 *General Procedure for the Hydroarylation of Terminal Alkynes: Synthesis of E-Styrenes (Table 2.5)*

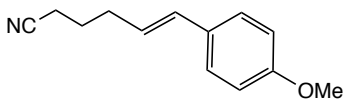
In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and NaO*t*-Bu (96.1 mg, 1.00 mmol, 2 equiv). To this was added alkyne (0.50 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.025 mmol, 0.100 equiv) IPrCuCl (24.4 mg, 0.050 mmol, 0.10 equiv), **L1** (19 mg, 0.050 mmol, 0.10 equiv), aryl bromide (0.550 mmol, 1.10 equiv), Me_2*i*-PrSiH (102.3 mg, 1.00 mmol, 2.00 equiv), and toluene (5 mL). The reaction mixture was stirred at 45 °C, and the reaction progress was monitored by TLC. When the starting alkyne was fully consumed, methanol (80.1 mg, 2.50 mmol, 5.00 equiv) was added and stirring was continued at 45 °C. The reaction progress was

monitored by GC for complete isomerization to the E-alkene (usually less than 24 h). The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography. The ratio of stereoisomers for each product was determined by GC analysis of a purified reaction mixture.

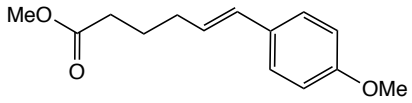
2.8.10 *Characterization of Hydroarylation Products: E-Styrenes (Table 2.5)*



1-methoxy-4-[(1*E*)-5-phenylpent-1-en-1-yl]benzene (2.36), compound was prepared according to the general procedure. After 2 h TLC in 100% hexane showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 12 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the E-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →10%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (118 mg, 94% yield, 1 isomer). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.37 – 7.12 (m, 8H), 6.84 (d, *J* = 8.7 Hz,2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.80 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.30 – 2.18 (m, 2H), 1.80 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 158.8, 142.6, 130.8, 129.7, 128.6, 128.5, 128.4, 127.1, 125.8, 114.0, 55.4, 35.5, 32.7, 31.3. GCMs (EI) calculated for [M]+ 252.15, found 252.3. FTIR (neat, cm^{-1}): 3088(w), 3021(m), 2924(m), 1605(s), 1500(s), 1478(w), 1247(s), 1165(s), 1038(s), 964(m), 733(m), 673(s).

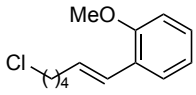


(5*E*)-6-(4-methoxyphenyl)hex-5-enenitrile (2.37), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH, the reaction mixture was stirred at 60 °C. After 12 hours a 30 µL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 45%) and isolated as a pale yellow oil (96 mg, 95% yield, E:Z = 44:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (s, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 5.98 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.81 (s, 3H), 2.45 – 2.34 (m, 4H), 1.84 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 131.4, 130.0, 127.2, 125.4, 119.7, 114.0, 55.3, 31.7, 25.2, 16.4. GCMS (EI) calculated for [M]+ 201.12, found 201.2. FTIR (neat, cm^{-1}): 3004(m), 2935(m), 2836(m), 2245(m), 1607(s), 1512(s), 836(s), 736(s).

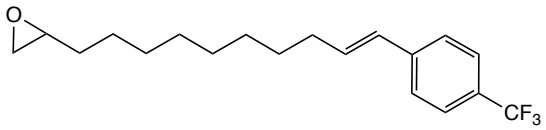


methyl (5*E*)-6-(4-methoxyphenyl)hex-5-enoate (2.38), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH, the reaction mixture was stirred at 60 °C. After 12 hours a 30 µL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 40%) and isolated as a clear oil (81 mg, 70% yield, E:Z = >100:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.27 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.34 (d, J = 15.8 Hz, 1H), 6.11 – 5.95 (m, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.45 – 2.30 (m, 2H), 2.34 – 2.14 (m, 2H), 1.81 (p, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 158.9, 130.5, 130.2, 127.4, 127.1, 114.0, 55.3, 51.5, 33.5, 32.4, 24.7. GCMS

(EI) calculated for [M]+ 234.13, found 234.2. FTIR (neat, cm^{-1}): 3000(m), 2951(m), 2057(m), 1736(s), 1607(s), 1512(s), 839(s).

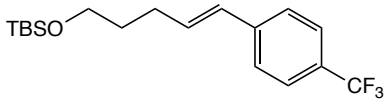


1-[(1*E*)-6-chlorohex-1-en-1-yl]-2-methoxybenzene (2.39), compound was prepared according to the general procedure. TLC in 10% EtOAc/Hex showed that the starting alkyne was fully consumed after 2 h. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (91 mg, 85% yield, E:Z = 10:1) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.05 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.92 – 1.76 (m, 2H), 1.70 – 1.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 130.6, 129.9, 127.2, 127.2, 114.1, 55.4, 45.1, 32.3, 32.2, 26.8. GCMS (EI) calculated for [M]+ 224.10, found 224.2. FTIR (neat, cm^{-1}): 3055(m), 2986(m), 2937(m), 2305(m), 1608(s), 1511(s), 896(s), 740(s).

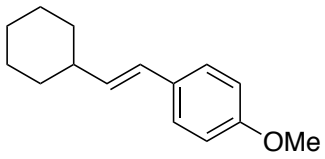


2-[(9*E*)-10-[4-(trifluoromethyl)phenyl]dec-9-en-1-yl]oxirane (2.40), compound was prepared according to the general procedure. TLC in 10% EtOAc/Hex showed that the starting alkyne was fully consumed after 2 h. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 12 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (154 mg, 95% yield, E:Z = 16:1). ^{1}H NMR (500 MHz,

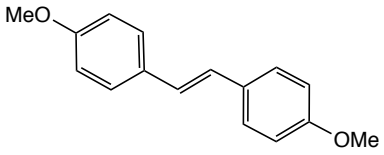
Chloroform-*d*) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 6.48 – 6.26 (m, 2H), 2.96 – 2.84 (m, 1H), 2.79 – 2.70 (m, 1H), 2.50 – 2.42 (m, 1H), 2.23 (q, *J* = 7.2 Hz, 2H), 1.67 – 1.10 (m, 20H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.4. ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.5, 134.2, 128.7, 128.7 (q, *J* = 32.1 Hz)), 125.6, 125.5 (q, *J* = 3.8 Hz) 124.4 (q, *J* = 271.6 Hz), 52.5, 47.2, 33.2, 32.6, 29.6, 29.5, 29.3, 29.2, 26.1. GCMS (EI) calculated for [M]+ 326.19, found 326.3. FTIR (neat, cm^{-1}): 3044(m), 2928(m), 2855(m), 1740(m), 1615(m), 1465(s), 834(s), 757(s),



tert-butyldimethyl{[(4*E*)-5-[4-(trifluoromethyl)phenyl]pent-4-en-1-yl]oxy}silane (2.41), compound was prepared according to the general procedure. TLC in 10% EtOAc/Hex showed that the starting alkyne was fully consumed after 2 h. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 12 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (148 mg, 86% yield, E:Z = 16:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.59 – 6.16 (m, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.31 (q, *J* = 6.9 Hz, 2H), 1.79 – 1.58 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.5, 133.6, 129.2, 128.7 (q, *J* = 32.2 Hz), 126.2, 125.6 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 271.7 Hz), 62.5, 32.4, 29.6, 26.1, 18.2, -5.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.4. GCMS (EI) calculated for [M]+ 358.19, found 358.3. FTIR (neat, cm^{-1}): 2930(m), 2895(m), 2858(m), 1915(m), 1615(s), 1473(s), 835(s), 735(s).

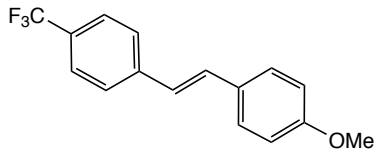


1-[(Z)-2-cyclohexylethenyl]-4-methoxybenzene (2.42) compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →10%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (118 mg, 94% yield, E:Z = 10:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.03 (dd, *J* = 16.0, 6.9 Hz, 1H), 3.80 (s, 3H), 2.17 – 2.01 (m, 1H), 1.89 – 1.61 (m, 5H), 1.42 – 1.06 (m, 5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.7, 134.8, 131.0, 127.1, 126.7, 114.0, 55.4, 41.2, 33.2, 26.3, 26.2. GCMS (EI) calculated for [M]+ 216.32, found 216.5. FTIR (neat, cm-1): 2923 (s), 2845 (s), 1605(s), 1511(s), 1246(s), 678(m).

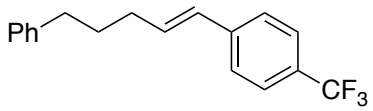


1-methoxy-4-[(*E*)-2-(4-methoxyphenyl)ethenyl]benzene (2.43), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 4 equiv of MeOH, the reaction mixture was stirred at 60 °C. After 12 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by trituration with Hex and isolated as a white solid (109 mg, 91% yield, E:Z = 32:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.4 Hz, 4H), 7.06 – 6.71 (m, 6H), 3.83 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 130.2, 130.1, 128.5, 113.7,

55.3. GCMS (EI) calculated for [M]+ 240.12, found 240.2. FTIR (neat, cm^{-1}): 3055(m), 2987(m), 2305(m), 1609(s), 1514(s), 896(s), 740(s).

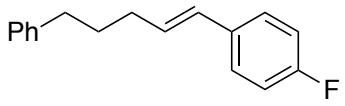


1-methoxy-4-[(*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl]benzene (2.44), compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 2 h. After the addition of 2 equiv of NaO*t*-Bu and 6 equiv of *i*-BuOH, the reaction mixture was stirred at 60 °C. After 12 hours a 30 µL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 40%) and isolated as a pale yellow solid (115 mg, 83% yield, E:Z = 22:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.58 (s, 4H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 16.4 Hz, 1H), 6.98 (d, *J* = 16.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.0, 141.3, 130.9, 129.6, 129.0 (q, *J* = 32.1 Hz), 126.4, 125.7 (q, *J* = 4.3 Hz), 125.1, 124.4 (q, *J* = 271.4 Hz), 114.4, 55.5. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.4. GCMS (EI) calculated for [M]+ 278.09, found 278.1. FTIR (neat, cm^{-1}): 3053(s), 2986(m), 2839(m), 2305(m), 1603(s), 1510(s), 835(s), 740(s).



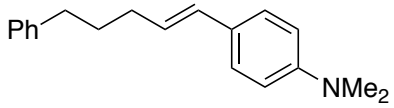
1-[(1*E*)-5-phenylpent-1-en-1-yl]-4-(trifluoromethyl)benzene (2.45), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 2.0 equiv of *i*-BuOH were added and the reaction mixture was stirred at 45 °C. After 1 h a 30 µL aliquot was taken and analysis by GC for confirmed complete isomerization

to the *E*-alkene. The compound was purified by silica gel chromatography (Hex 100%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (120 mg, 83% yield, E:alkane = 11:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.14 (s, 3H), 7.10 (d, *J* = 7.1 Hz, 3H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.3, 6.6 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.25 – 2.13 (m, 2H), 1.73 (p, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.3, 141.4, 133.6, 129.3, 128.7 (q, *J* =19.5 Hz), 128.6, 128.5, 125.7, 125.6, 125.4 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 271.2 Hz), 35.5, 32.7, 30.9. GCMS (EI) calculated for [M]+ 290.12, found 290.5. FTIR (neat, cm^{-1}): 3028(m), 2934(m), 2858(w), 1615(m), 1454(w), 1326(s), 1164(s), 1122(s), 1068.2(s), 1016(w), 747(w), 699(m).

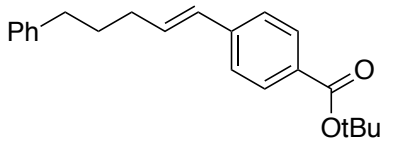


1-fluoro-4-[(1*E*)-5-phenylpent-1-en-1-yl]benzene (2.46), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Hex 100%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (103 mg, 86% yield, 1 isomer). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.29 – 7.17 (m, 5H), 7.14 (d, *J* = 6.7 Hz, 3H), 6.99 – 6.86 (m, 2H), 6.30 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.19 (dt, *J* = 8.2, 7.6, 6.2 Hz, 2H), 1.85 – 1.66 (m, 2H). ^{19}F NMR (471 MHz, Chloroform-d) δ -123.85. ^{13}C NMR (126 MHz, Chloroform-d) δ 162.0 (d, *J* = 245.6 Hz), 142.4, 134.1 (d, *J* = 2.7 Hz), 130.4, 129.2, 128.6 (d, *J* = 17.5 Hz), 127.4 (d, *J* = 7.8 Hz), 125.9,

115.5, 115.4, 35.5, 32.6, 31.1. GCMS (EI) calculated for [M]+ 240.13, found 240.2. FTIR (neat, cm^{-1}): 3058(w), 3021(m), 2924(s), 2849(m), 1597(m), 1508(s), 1448(w), 1225(s), 1158(m), 956(m), 837(m), 748(m), 688(s).

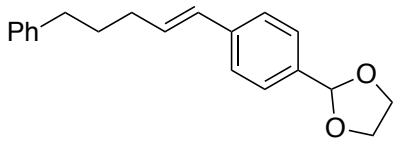


N,N-dimethyl-4-[(1*E*)-5-phenylpent-1-en-1-yl]aniline (2.47), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH and 0.50 equiv Me_2*i*-PrSiH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →15%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (124 mg, 93% yield, E:Z = 14:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.24 – 7.01 (m, 8H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.21 (d, *J* = 15.8 Hz, 1H), 5.92 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.84 (s, 6H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.21 – 2.04 (m, 2H), 1.68 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 149.8, 142.7, 130.1, 128.6, 128.4, 126.9, 126.7, 126.4, 125.7, 112.7, 40.7, 35.5, 32.7, 31.5. GCMS (EI) calculated for [M]+ 265.18, found 265.3. FTIR (neat, cm^{-1}): 3085(w), 3028(m), 2934(m), 2854(m), 1615(s), 1512(s), 1351(m), 1146(m), 672(s).



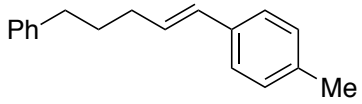
tert-butyl 4-[(1*E*)-5-phenylpent-1-en-1-yl]benzoate (2.48), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 2.0 equiv of *t*-BuOH (used to prevent transesterification) were added and the reaction

mixture was stirred at 60 °C. After 30 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →10%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (125 mg, 78% yield, E:alkane = 10:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.24 (m, 2H), 7.21 (d, *J* = 7.3 Hz, 4H), 6.44 (d, *J* = 16.1 Hz, 1H), 6.36 (dt, *J* = 14.6, 6.5 Hz, 1H), 2.69 (t, *J* = 7.9 Hz, 2H), 2.33 – 2.25 (m, 2H), 1.84 (p, *J* = 7.1 Hz, 2H), 1.60 (s, 13H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.3, 142.0, 133.3, 129.8, 129.7, 128.6, 128.5, 125.9, 125.7, 120.1, 80.9, 35.7, 32.7, 30.9, 28.4. GCMS (EI) calculated for [M]+ 322.19, found 322.4. FTIR (neat, cm^{-1}): 3027(w), 2977(m), 2932(m), 2857(m), 1710(s), 1606(s), 1455(m), 1367(m), 1293(s), 1165(s), 1118(s), 747(m), 699(m).

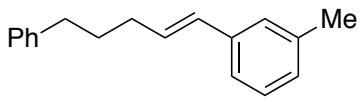


2-{4-[(1*E*)-5-phenylpent-1-en-1-yl]phenyl}-1,3-dioxolane (2.49), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →15%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (126 mg, 86% yield, 1 isomer). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.43 – 7.20 (m, 7H), 7.17 (d, *J* = 7.1 Hz, 3H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.77 (s, 1H), 4.21 – 3.89 (m, 4H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.31 – 2.13 (m, 2H), 1.79 (p, *J* = 7.6 Hz, 2H. ^{13}C NMR (126 MHz, Chloroform-d) δ 142.4, 138.8, 136.5, 131.3, 129.9, 128.5, 128.4,

126.7, 126.0, 125.8, 103.7, 65.3, 35.5, 32.6, 31.0. GCMS (EI) calculated for [M]+ 294.16, found 294.4. FTIR (neat, cm^{-1}): 3088(w), 3027(m), 2931(s), 2887(m), 2857(m), 1479(m), 1426(w), 1390(m), 1081(s), 969(s), 678(s).

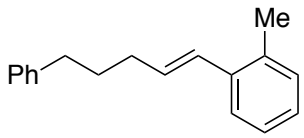


1-methyl-4-[(1*E*)-5-phenylpent-1-en-1-yl]benzene (2.50), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →5%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (101 mg, 85% yield, E:alkane = 22:1). ^1H NMR (300 MHz, Chloroform-d) δ 7.40 – 7.20 (m, 7H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.81 – 2.67 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 2.36 – 2.23 (m, 2H), 1.86 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 1542.5 136.6, 135.2, 130.2, 129.6, 129.3, 128.6, 128.4, 126.0, 125.8, 35.5, 32.7, 31.2, 21.5. GCMS (EI) calculated for [M]+ 236.16, found 236.2. FTIR (neat, cm^{-1}): 3080(w), 3021(m), 2924(s), 2849(m), 1605(w), 1508(m), 1453(m), 1032(w), 966(s), 735(m), 678(s).



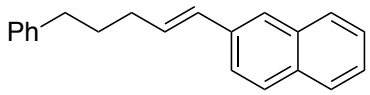
1-methyl-3-[(1*E*)-5-phenylpent-1-en-1-yl]benzene (2.51), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 24

h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →5%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (103 mg, 87% yield, 1 isomer). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.24 (m, 2H), 7.24 – 7.12 (m, 6H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.2, 6.8 Hz, 1H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.35 (s, 3H), 2.31 – 2.18 (m, 2H), 1.82 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.3, 136.4, 134.9, 129.9, 129.3, 129.0, 128.3, 128.2, 125.7, 125.6, 35.3, 32.4, 31.0, 21.0. GCMS (EI) calculated for [M]+ 236.16, found 236.2. FTIR (neat, cm^{-1}): 3059(w), 3022(m), 2931(s), 2849(m), 1603(w), 1502(m), 1454(m), 1031(w), 965(s), 738(m), 691(s).

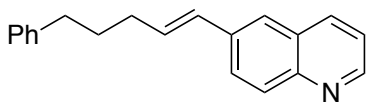


1-methyl-2-[(1*E*)-5-phenylpent-1-en-1-yl]benzene (2.52), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 5.0 equiv of MeOH and 0.50 equiv Me_2*i*-PrSiH were added and the reaction mixture was stirred at 45 °C. After 24 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →5%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (95 mg, 80% yield, E:Z = 24:1). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.31 (d, J = 5.9 Hz, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.15 – 6.99 (m, 6H), 6.50 (dd, J = 15.6, 1.6 Hz, 1H), 6.00 (dt, J = 15.4, 6.9 Hz, 1H), 2.59 (t, J = 7.7 Hz, 2H), 2.29 – 2.11 (m, 5H), 1.73 (p, J = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.5, 137.1, 135.0, 132.0, 130.3, 128.6, 127.0, 126.1, 125.9, 125.6, 35.5, 33.0, 31.5, 20.0. GCMS (EI) calculated for [M]+ 236.16,

found 236.2. FTIR (neat, cm^{-1}): 3062(w), 3026(m), 2931(s), 2856(m), 1602(w), 1495(m), 1454(m), 1031(w), 964(s), 743(s), 698(s).

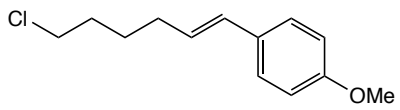


2-[(1*E*)-5-phenylpent-1-en-1-yl]naphthalene (2.53), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 2.0 equiv of *i*-BuOH were added and the reaction mixture was stirred at 45 °C. After 30 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →10%) and filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (121 mg, 89% yield, E:alkane = 37:1). ^1H NMR (300 MHz, Chloroform-d) δ 7.73 – 7.61 (m, 3H), 7.62 – 7.43 (m, 2H), 7.39 – 7.26 (m, 2H), 7.24 – 7.04 (m, 6H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.7, 6.8 Hz, 1H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.21 (m, 2H), 1.77 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.5, 135.4, 133.9, 132.8, 131.2, 130.5, 128.6, 128.5, 128.2, 127.9, 127.8, 126.3, 125.9, 125.6, 125.5, 123.7, 35.6, 32.8, 31.2. GCMS (EI) calculated for [M]+ 272.16, found 272.3. FTIR (neat, cm^{-1}): 3058(m), 3028(m), 2931(m), 2855(m), 1598(m), 1496(m), 1478(m), 1453(m), 962(m), 745(s), 678(s).

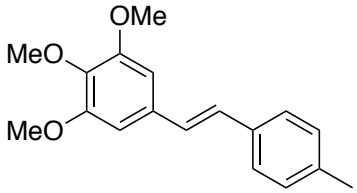


6-[(1*E*)-5-phenylpent-1-en-1-yl]quinolone (2.54), compound was prepared according to the general procedure. After 2 h TLC in 100% Hex showed that the starting alkyne was fully consumed. 2.0 equiv of MeOH were added and the reaction mixture was stirred at 45 °C. After 1 h a 30 μL aliquot was taken and analysis by GC for confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography (Et_2O/Hex 0 →25%) and

filtration through a short plug of alumina (10% Et_2O/Hex). The compound was isolated as a clear colorless oil (103 mg, 75% yield, E:alkane = 14:1). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.87 (s, 1H), 8.09 (dd, *J* = 16.2, 8.5 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.65 (s, 1H), 7.44 – 7.30 (m, 4H), 7.25 (q, *J* = 10.7 Hz, 4H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.43 (dt, *J* = 15.3, 6.8 Hz, 1H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.41 – 2.31 (m, 2H), 1.89 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 149.8, 147.9, 142.3, 136.1, 135.8, 132.4, 129.7, 129.6, 128.6, 128.5, 128.4, 127.3, 125.9, 124.8, 121.4, 35.5, 32.7, 31.0. GCMS (EI) calculated for [M]+ 273.15, found 273.3. FTIR (neat, cm^{-1}): 3062(w), 3025(m), 2930(s), 1590(w), 1497(s), 1454(m), 1118(w), 962(m), 839(m), 747(m), 699(s).

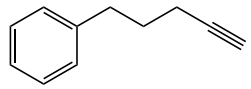


1-[(1*E*)-6-chlorohex-1-en-1-yl]-4-methoxybenzene (2.55), compound was prepared according to the general procedure. TLC in 10% EtOAc/Hex showed that the starting alkyne was fully consumed after 2 h. 5.0 equiv of *i*-BuOH were added and the reaction mixture was stirred at 45 °C. After 12 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by silica gel chromatography with EtOAc/Hex (0 → 15%) and isolated as a colorless oil (99 mg, 88% yield, E:Z = >100:1) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.05 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.92 – 1.76 (m, 2H), 1.70 – 1.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 130.6, 129.9, 128.0, 127.2, 114.1, 55.4, 45.1 32.3, 32.2, 26.8. GCMS (EI) calculated for [M]+ 224.10, found 224.2. FTIR (neat, cm^{-1}): 3055(m), 2986(m), 2937(m), 2305(m), 1608(s), 1511(s), 896(s), 740(s).

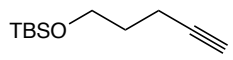


1,2,3-trimethoxy-5-[(E)-2-(4-methylphenyl)ethenyl]benzene (2.57) compound was prepared according to an altered general procedure. LiO*t*-Bu was used in place of NaO*t*-Bu as a turnover reagent. TLC in 20% EtOAc/Hex showed that the starting alkyne was consumed after 4 h. After the addition of 2 equiv of NaO*t*-Bu and 5 equiv of MeOH. The reaction mixture was stirred at 60 °C. After 24 hours a 30 μL was taken and analysis by GC confirmed complete isomerization to the *E*-alkene. The compound was purified by trituration with Hex and isolated as a white solid (115 mg, 85% yield, 1 isomer). This compound has been previously synthesized and spectra matches literature values.[66]

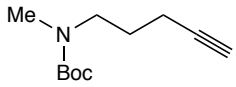
2.8.11 *Alkyne Starting Materials*



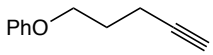
5-phenyl-1-pentyne (2.1) was purchased from GFS Chemical and distilled over calcium hydride under reduced pressure before use.



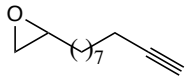
tert-butyldimethyl(pent-4-yn-1-yloxy)silane (2.62) was prepared according to a known procedure and has been previously characterized.[76]



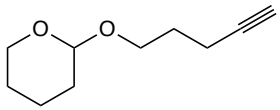
tert-butyl N-methyl-N-(pent-4-yn-1-yl)carbamate (2.63) was prepared according to a known procedure and has been previously characterized.[77]



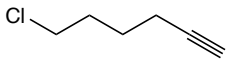
(pent-4-yn-1-yloxy)benzene (2.64) was prepared according to a known procedure and has been previously characterized.[78]



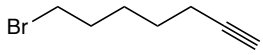
2-(dec-9-yn-1-yl)oxirane (2.65) was prepared according to a known procedure and has been previously characterized.[79]



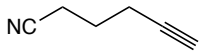
2-(pent-4-yn-1-yloxy)tetrahydra-2*H*-pyran (2.66) has been previously characterized and spectral data match literature values. [80]



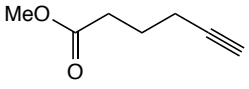
6-chlorohex-1-yne (2.67) was purchased from TCI America and distilled over calcium hydride under reduced pressure before use.



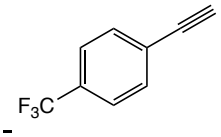
7-bromohept-1-yne (2.68) was prepared according to a known procedure and has been previously characterized.[81]



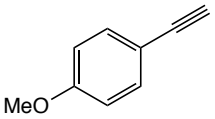
hex-5-ynenitrile (2.69) was purchased from Oakwood Chemical and distilled over calcium hydride under reduced pressure before use.



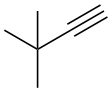
methyl hex-5-ynoate (2.70) was purchased from Fischer Scientific and distilled over calcium hydride under reduced pressure before use.



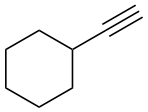
1-ethynyl-4-(trifluoromethyl)benzene (2.71) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



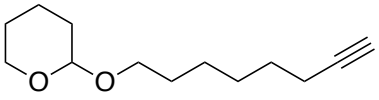
1-ethynyl-4-methoxybenzene (2.72) was purchase from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



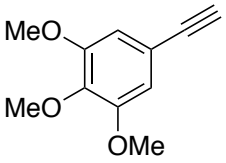
3,3-dimethylbut-1-yne (2.73) was purchased from Milipore Sigma and distilled over calcium hydride under reduced pressure before use.



ethynylcyclohexane (2.74) was purchased from Milipore Sigma and distilled over calcium hydride under reduced pressure before use.

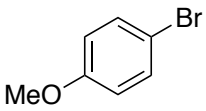


2-(oct-7-yn-1-yloxy)oxane (2.75) was prepared according to a known literature procedure and has been previously characterized.[82]

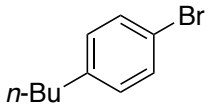


5-ethynyl-1,2,3-trimethoxybenzene (2.76) was prepared according to a known literature procedure and has been previously characterized.[83]

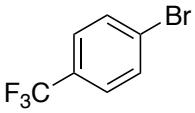
2.8.12 *Aryl Bromide Starting Materials*



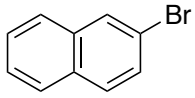
4-bromoanisole (2.2) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



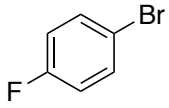
1-bromo-4-butylbenzene (2.4) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



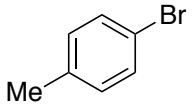
4-bromobenzotrifluoride (2.77) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



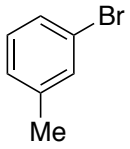
2-bromonaphthalene (2.78) was purchased from Ark-Pharm and used without purification.



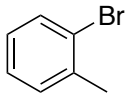
1-bromo-4-fluorobenzene (2.79) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



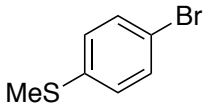
4-bromotoluene (2.80) was purchased form Alfa Aesar and using without purification.



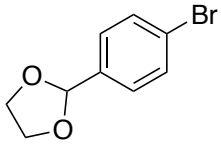
3-bromotoluene (2.81) was purchased form TCI America and distilled over calcium hydride under reduced pressure before use.



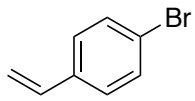
2-bromotoluene (2.82) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



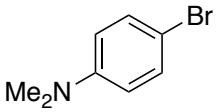
1-bromo-4-(methylsulfanyl)benzene (2.83) was purchased from Oakwood Chemicals and used without purification.



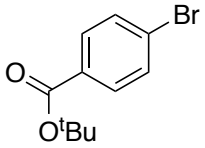
1-bromo-4-phenyl-1,3-dioxolane (2.84) was purchased from Ark-Pharm and distilled over calcium hydride under reduced pressure before use.



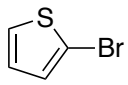
4-bromostyrene (2.85) was purchased from TCI America and degassed before use.



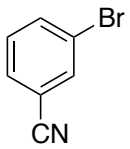
4-bromo-N,N-dimethylaniline (2.86) was purchased from Oakwood Chemicals and used without purification.



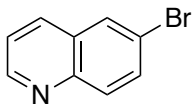
tert-butyl-4-bromobenzoate (2.87) was purchased from Ark-Pharm and distilled over calcium hydride under reduced pressure before use.



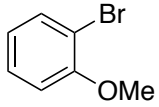
2-bromothiophene (2.88) was purchased from Combi-Blocks and distilled over calcium hydride under reduced pressure before use.



3-bromobenzonitrile (2.89) was purchased from Ark-Pharm and used without purification.

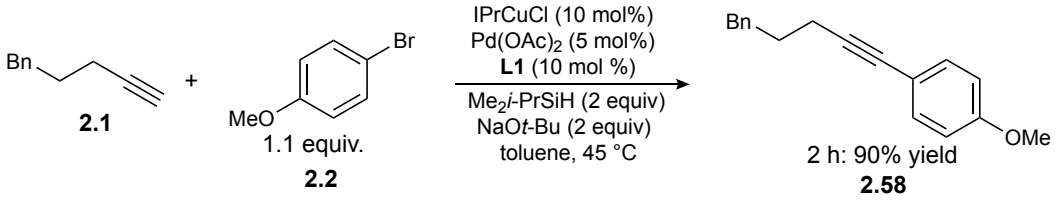


6-bromoquinoline (2.90) was purchased from Ark-Pharm and distilled over calcium hydride under reduced pressure before use.



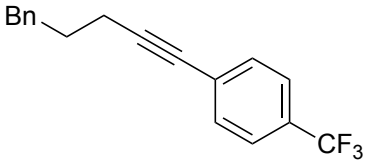
2-bromoanisole (2.91) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.

2.8.13 *Synthesis of Internal Alkyne Intermediate*



Scheme 2.14. Synthesis of Internal Alkyne

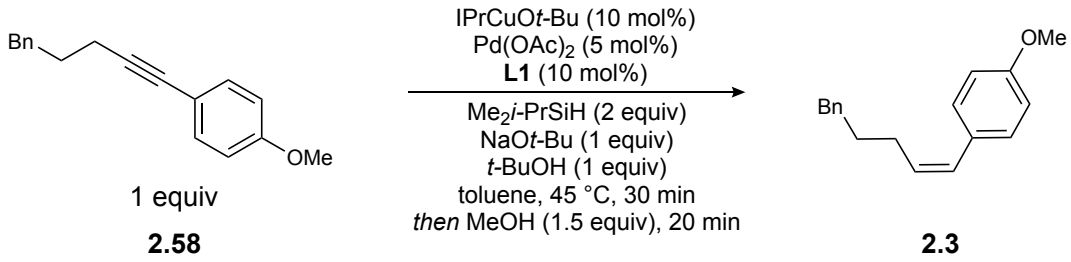
In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and NaO*t*-Bu (96.1 mg, 1.00 mmol, 2 equiv). To this was added alkyne (**1**) (0.50 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.025 mmol, 0.100 equiv) IPrCuCl (24.4 mg, 0.050 mmol, 0.10 equiv), **L1** (19 mg, 0.050 mmol, 0.10 equiv), aryl bromide (2.**2**) (102.9 mg, 0.550 mmol, 1.10 equiv), Me_2*i*-PrSiH (102.3 mg, 1.00 mmol, 2.00 equiv), and toluene (5 mL). The reaction mixture was stirred at 45 °C, and monitored by TLC until starting alkyne was fully consumed, 2 h. TLC 100% Hex. Compound was purified by silica gel column chromatography (Et_2O/Hex 0→10%) and passed through a short plug of alumina (10% Et_2O/Hex) **2.58** was isolated as a clear colorless liquid (113 mg, 90% yield). This compound has been previously synthesized and spectra matches literature values.[84]



1-(5-phenylpent-1-yn-1-yl)-4- (trifluoromethyl)benzene (2.59), was synthesized according to the above procedure, but has previously been synthesized and spectra matches literature values.[84]

2.8.14 *Mechanistic Studies: Semireduction*

Catalytic Semireduction: Contribution of Pd and Cu catalysts (Scheme 2.6)



Scheme 2.15. Conditions for Probing Mechanism of Catalytic Semireduction with MeOH

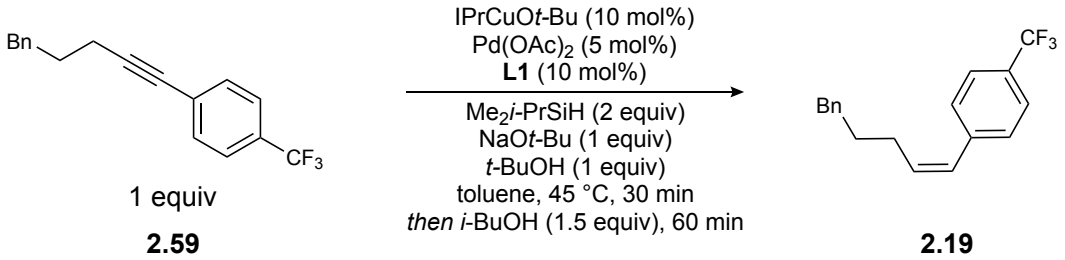
In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then MeOH (2.4 mg, 0.075 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 45 °C and 30 μL aliquots were taken at 10 min, 20 min, 30 min and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.11. Relative Role of Pd/Cu Catalysts in Semireduction

Reaction Conditions	yield (10 min)	yield (20 min)	yield (30 min)	yield (24 h)
Above Conditions	78%	86% (18:1) *	86% (18:1) *	80% (3:1) *
No Cu	38%	39%	40%	41%
No Pd/L	64%	70%	71%	99% (48:1) *

*Z:E diastereoselectivity determine by GC analysis. Yield of major isomer is reported

Catalytic Semireduction: EWG with *i*-BuOH (Scheme 2.6)



Scheme 2.16. Conditions Probing Mechanism of Catalytic Semireduction with *i*-BuOH with EWG

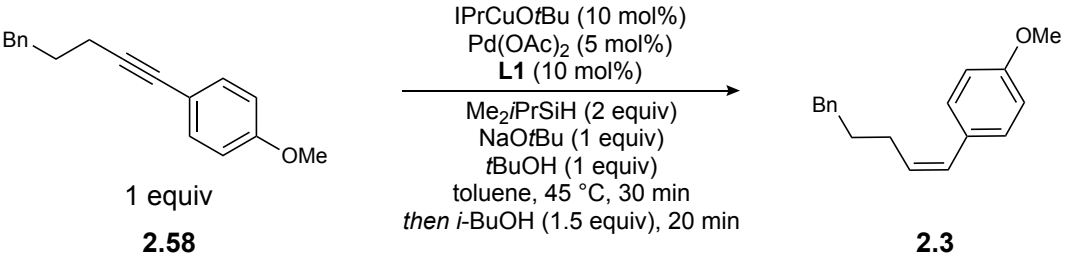
In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.59** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then *i*-BuOH (4.1 mg, 0.075 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 45 °C and 30 µL aliquots were taken at 30 min, 60 min and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.12. Catalytic Semireduction with EWG with *i*-BuOH

Reaction Conditions	yield (30 min)	yield (60 min)	yield (24 h)
Above Conditions	58%	76% (38:1) *	36% (2:1) *
No Cu	1%	5%	11%
No Pd/L	40%	52%	74%

*Z:E diastereoselectivity determined by GC analysis. Yield of major isomer is reported

Catalytic Semireduction: *i*-BuOH with other Substrates (Scheme 2.6)



Scheme 2.17. Conditions Probing Mechanism of Catalytic Semireduction with *i*-BuOH for EDG

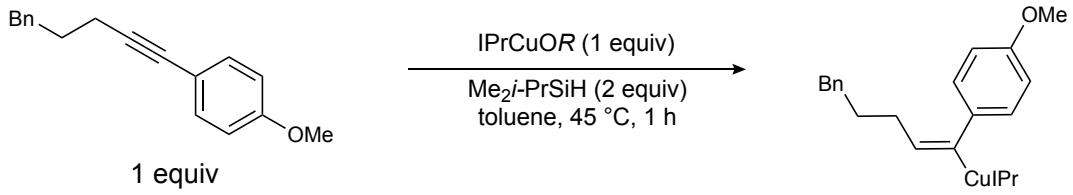
In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then *i*-BuOH (4.1 mg, 0.075 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 45 °C and 30 μL aliquots were taken at 10 min, 20 min, 30 min and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.13. Relative Contribution of Pd/Cu Catalysts with *i*-BuOH

Reaction Conditions	yield (10 min)	yield (20 min)	yield (30 min)	yield (24 h)
Above Conditions	39%	57%	66%	74%
No Cu	1%	2%	6%	9%
No Pd/L	26%	39%	49%	56%

*Z:E diastereoselectivity determine by GC analysis. Yield of major isomer is reported

Stoichiometric Hydrocupration of Internal Alkyne: Effect of IPrCuOR (Scheme 2.7)



Scheme 2.18. Stoichiometric Hydrocupration of Internal Alkyne with IPrCuOR

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, IPrCuOR (0.050 mmol, 1.0 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C and 15 μL aliquots were taken every min for 10 min, and then every 5 min for 1 hour and passed through a short plug of silica in the glovebox with 1.5 mL of Ether and analyzed

by Gas Chromatography. The reported yield of **2.60** is based on the yield of alkene obtained after quenching of the reaction mixture.

Table 2.14. Hydrocupration of Internal Alkyne with IPrCuO*t*-Bu

Time (min)	% **2.58**	% yield (**2.60**)
0	96	0
1	93	3
2	91	8
3	86	9
4	83	13
5	78	16
6	82	17
7	72	21
8	71	22
9	70	23
10	70	24
15	60	27
20	54	36
25	0	48
30	37	45
45	29	68
60	20	74

Table 2.15. Hydrocupration of Internal Alkyne with IPrCuOMe

Time (min)	% **2.58**	% yield (**2.60**)
0	100	0
1	47	51
2	28	65
3	26	73
4	23	74
5	20	73
6	18	78
7	19	78
8	17	80
9	15	85
10	15	86
15	13	88

20	13	88
25	13	87
30	10	90
45	10	93
60	8	93

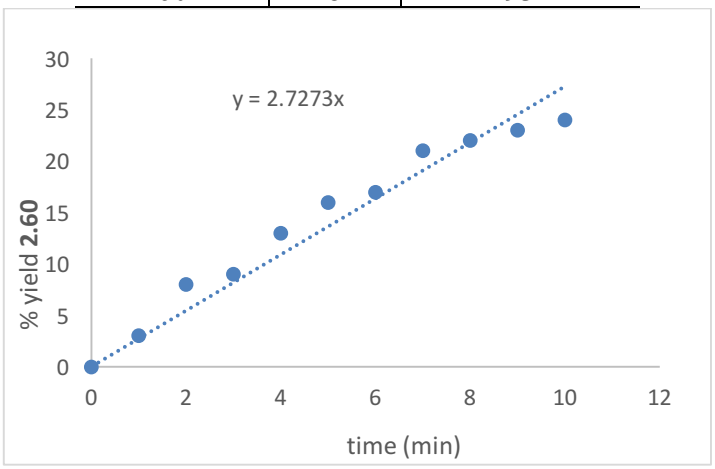


Figure 2.1. Hydrocupration of Internal Alkyne with IPrCuO*t*-Bu **Error! Reference source not found.**.

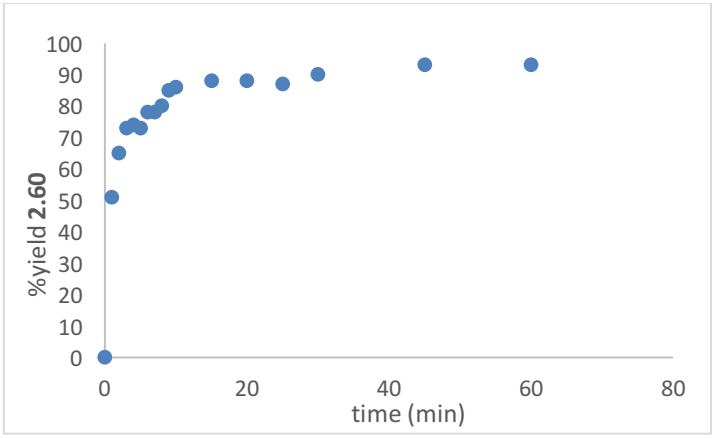


Figure 2.2. Hydrocupration of Internal Alkyne with IPrCuOMe **Error! Reference source not found.**.

Control Experiments for Quenching Alkenyl Copper with Dibromotetrachloroethane

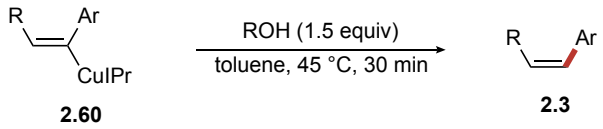
Quenching of IPrCuOt-Bu

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, IPrCuO*t*-Bu (2.6 mg, 0.0050 mmol, 0.1 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv), MeOH (2.4 mg, 0.075 mmol, 1.5 equiv), $Br_2Cl_4C_2$ (65.1 mg, 0.2 mmol, 4 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C and 15 µL aliquots were taken at 20 min 1 hour and 2 hours, passed through a short plug of silica with 1.5 mL of EtOAc and analyzed by Gas Chromatography. Over the course of the reaction there was no formation of alkenyl copper or vinyl bromide product and quantitative recovery of the internal alkyne. This indicated that in the presence of 4 equivalents of dibromotetrachloroehtane the catalyst could not turnover, thus confirming it as an effective quenching method.

Quenching of Alkenyl Copper

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv). To this was added **2.60** (3.5 mg, 0.0050 mmol, 0.1 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), NaO*t*-Bu (4.8 mg, 0.050 mmol, 1 equiv), MeOH (2.4 mg, 0.075 mmol, 1.50 equiv), $Br_2Cl_4C_2$ (65.1 mg, 0.2 mmol, 4 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C and 15 µL aliquots were taken at 20 min 1 hour and 2 hours, passed through a short plug of silica with 1.5 mL of EtOAc and analyzed by Gas Chromatography. Over the course of the reaction we observe only the formation of 1 equivalent of alkenyl bromide (relative to the amount of **2.60** used in the reaction) and the quantitative recovery of the internal alkyne. This indicated that in the presence of 4 equivalents of dibromotetrachloroehtane the alkenyl copper could not turnover and regenerate the active catalyst, thus confirming it as an effective quenching method.

Stoichiometric Protonation of Alkenyl Copper (2.60) (Scheme 2.7)



Scheme 2.19. Stoichiometric Protodemetalation with ROH

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, alkenyl copper **2.60** (17.6 mg, 0.050 mmol, 1.00 equiv). To this was added TMB (2.8 mg. 0.017 mmol, 0.33 equiv), alcohol (0.075 mmol, 1.5 equiv) and toluene (0.50 mL). The reaction was placed at 45 °C and 15 μL aliquots were taken every min for the first 5 min and then every 5 min for 20 min. Aliquots were quenched into $Br_2Cl_4C_2$ (1.6 mg, 0.005 mmol, 0.04 equiv) and passed through a short plug of silica with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.16. Stoichiometric Protonation of Alkenyl Copper with *t*-BuOH

Time (min)	alkenyl copper (**2.60**)	% yield **2.3**	% yield **2.3** (corrected)
0	86	5	0
1	85	7	2
2	86	9	4
3	85	10	5
4	82	12	7
5	84	13	8
10	70	21	16
15	67	25	20
20	61	27	22

Table 2.17. Stoichiometric Protonation of Alkenyl Copper with MeOH

Time (min)	alkenyl copper (**2.60**)	% yield **2.3**
0	100	0
1	34	68
2	22	79
3	0	90
4	0	94
5	0	94

10	0	104
15	0	105
20	0	106

Yields for *t*-BuOH are corrected to to 0 based on initial formation of alkene before alcohol was added

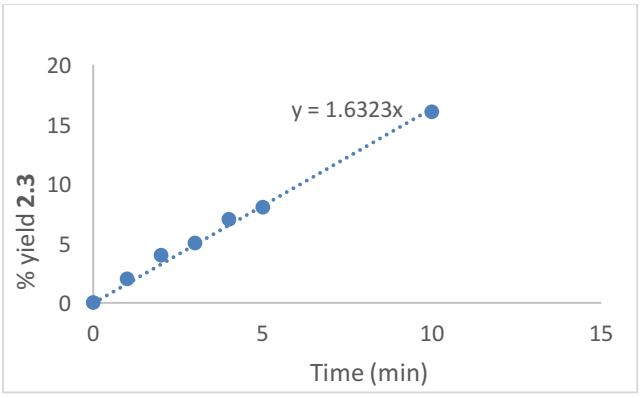


Figure 2.3. Stoichiometric Protonation of Alkenyl Copper with *t*-BuOH **Error! Reference source not found.**.

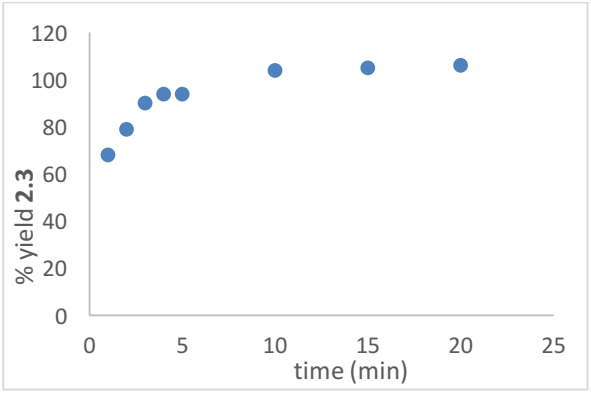
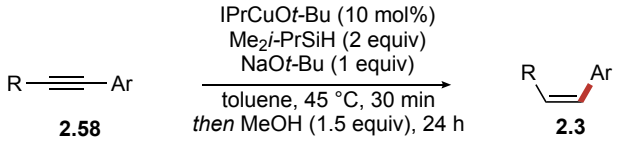


Figure 2.4. Stoichiometric Protonation of Alkenyl Copper with MeOH **Error! Reference source not found.**.

Copper-Catalyzed Semireduction of Sonogashira: Effect of ROH (Scheme 2.7)



Scheme 2.20. Catalytic Semireduction using ROH

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), alcohol (0.075 mmol, 1.5 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C 15 μL aliquots were taken, and quenched into $Br_2Cl_4C_2$ (3.4 mg, 0.004 mmol, 0.04 equiv) and diluted with 0.50 mL of Ether, passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.18. Copper-Catalyzed Semireduction of Sonogashira with MeOH

Time (min)	% yield **2.3**
0	0
10	37
20	61
30	72
2 h	79
7 h	80
24 h	82

Table 2.19. Copper-Catalyzed Semireduction of Sonogashira with *t*-BuOH

Time (min)	% **2.58**	% yield **2.3**
1	98	0
5	100	0
10	100	0
20	95	0
30	95	2
60	90	1
90	96	4
5 h	83	8
8 h	69	16
24 h	73	23

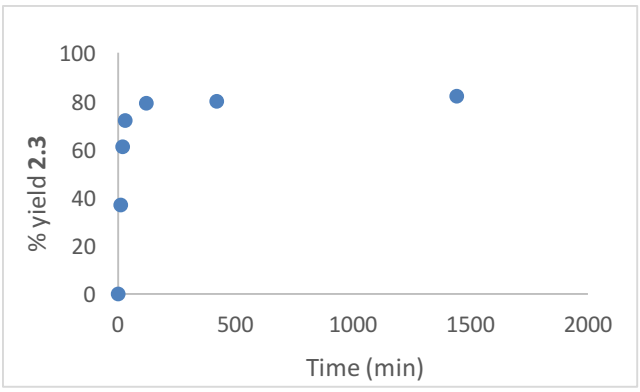


Figure 2.5. Copper-Catalyzed Semireduction of Sonogashira with MeOH **Error! Reference source not found.**.

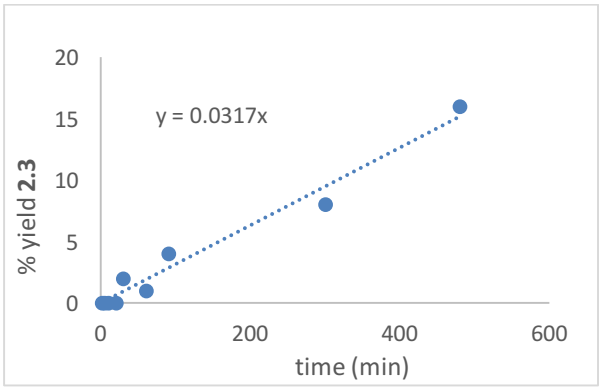
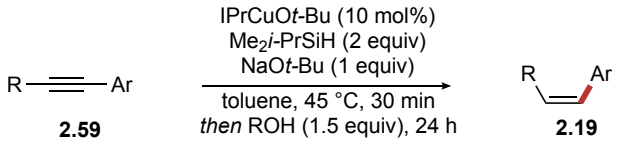


Figure 2.6. Copper-Catalyzed Semireduction of Sonogashira with *t*-BuOH **Error! Reference source not found.**.

Copper Catalyzed Semireduction: Electron poor substrates and *i*-BuOH (Scheme 2.8)

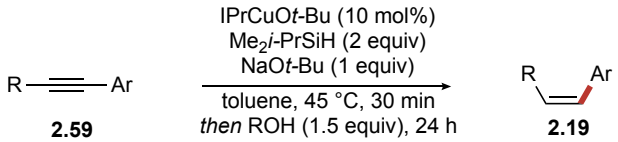


Scheme 2.21. Catalytic Semireduction using *i*-BuOH

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.59** (14.4 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), alcohol (0.075 mmol, 1.5 equiv) and toluene (0.50 mL). The reaction mixture

was stirred at 45 °C 15 μL aliquots were taken, and quenched into $Br_2Cl_4C_2$ (3.4 mg, 0.004 mmol, 0.04 equiv) and diluted with 0.50 mL of Ether, passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Copper Catalyzed Semireduction: Electron poor substrates and *i*-BuOH (Scheme 2.8)



Scheme 2.22. Catalytic Semireduction using *i*-BuOH and EWG

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.59** (14.4 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me$_2$*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), alcohol (0.075 mmol, 1.5 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C 15 μL aliquots were taken, and quenched into $Br_2Cl_4C_2$ (3.4 mg, 0.004 mmol, 0.04 equiv) and diluted with 0.50 mL of Ether, passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.20. Copper-Catalyzed Semireduction of EWG Sonogashira with MeOH

Time (min)	% **2.59**	% yield **2.19**	alkenyl copper
0	97	0	0
2	92	0	4
4	91	2	6
6	90	3	6
8	91	4	6
10	86	4	7
12	93	5	8
14	89	6	8
16	88	7	9
18	87	7	10
20	88	8	10

Table 2.21. Copper-Catalyzed Semireduction of EWG Sonogashira with *i*-BuOH

Time (min)	% **2.59**	% yield **2.19**	alkenyl copper (**2.61**)
0	100	0	0
2	95	2	5
4	88	5	10
6	83	11	10
8	80	15	9
10	75	17	8
12	74	18	10
14	69	19	10
16	69	21	10
18	69	22	10
20	70	23	10

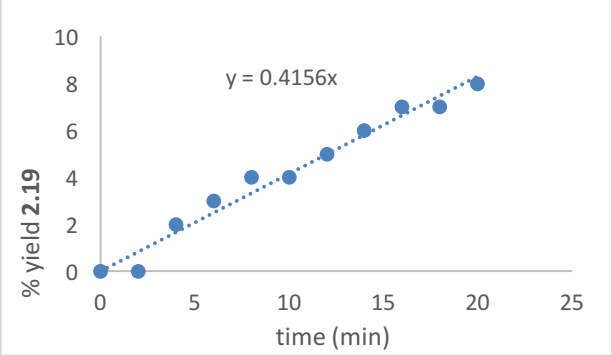


Figure 2.7. Copper-Catalyzed Semireduction of EWG Sonogashira with MeOH **Error! Reference source not found.**

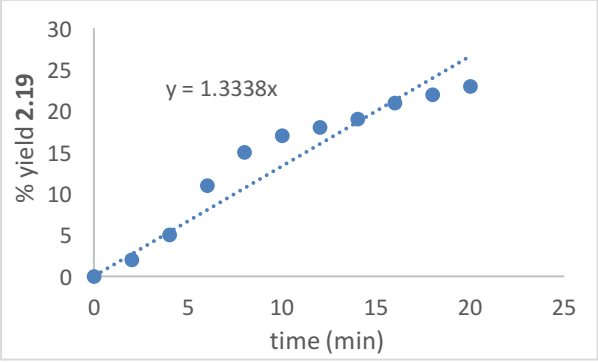
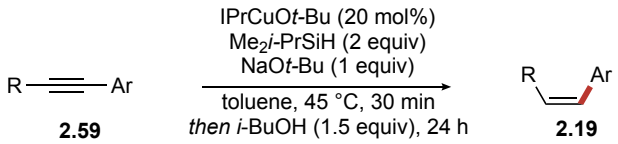


Figure 2.8. Copper-Catalyzed Semireduction of EWG Sonogashira with *i*-BuOH **Error! Reference source not found.**

Copper-Catalyzed Semireduction: 20 mol% IPrCuO*t*-Bu with 2.59



Scheme 2.23. Catalytic Semireduction with 20 mol% IPrCuO*t*-Bu

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.59** (14.4 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), IPrCuO*t*-Bu (5.2 mg, 0.01 mmol, 0.20 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *i*-BuOH (0.075 mmol, 1.5 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C 15 µL aliquots were taken, and quenched into $Br_2Cl_4C_2$ (3.4 mg, 0.004 mmol, 0.04 equiv) and diluted with 0.50 mL of Ether, passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.22. Copper-Catalyzed Semireduction: 20% IPrCuO*t*-Bu with **2.59**

Time (min)	% **2.59**	% yield **2.19**	alkenyl copper (**2.61**)
0	100	0	0
2	84	1	20
4	85	1	18
6	82	2	19
8	78	2	20
10	79	2	21
12	89	3	18
14	82	4	18
16	82	4	19
18	78	4	20
20	78	4	20
25	75	5	20
30	71	5	21

45	72	7	18
60	75	8	18
90	68	10	19
120	64	11	20

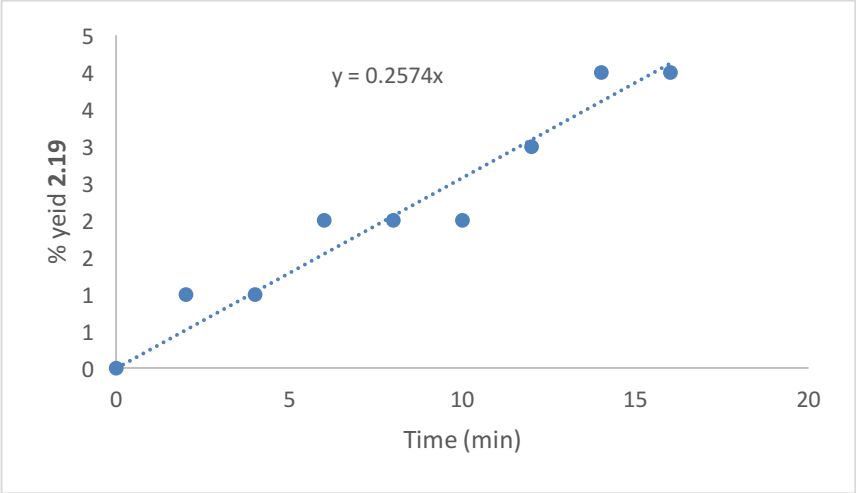
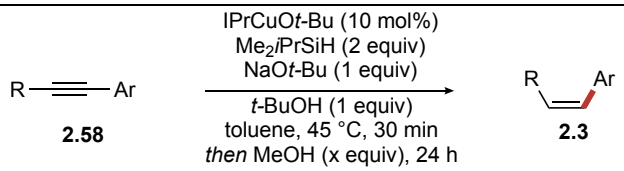


Figure 2.9. Copper-Catalyzed Semireduction of EWG Sonogashira with MeOH **Error! Reference source not found.**

2.8.15 *Effect of MeOH Stoichiometry on Copper Catalyzed Semireduction*

Copper-catalyzed Semireduction of Sonogashira intermediate: Effect of MeOH

Table 2.23. Copper-Catalyzed Semireduction of Sonogashira intermediate: Effect of MeOH

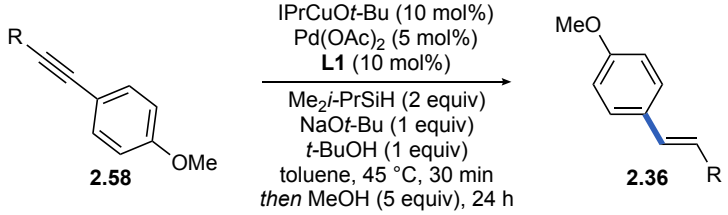


equiv of MeOH	Yield (30 min)	yield (4 h)	yield (7 h)	yield (24 h)
1	65%	70%	86%	89%
2	50%	66%	73%	75%
3	32%	33%	33%	35%
4	16%	16%	17%	17%
5	10%	10%	10%	10%

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then MeOH (x equiv) was added. The reaction mixture was stirred at 45 °C and 30 µL aliquots were taken at 30 min, 4 h, 7 h and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

2.8.16 *Mechanistic Studies: Isomerization (Scheme 2.9)*

Catalytic Semireduction and Isomerization of the Sonogashira intermediate to the *E*-alkene



Scheme 2.24. Catalytic Semireduction and Isomerization of Internal Alkene

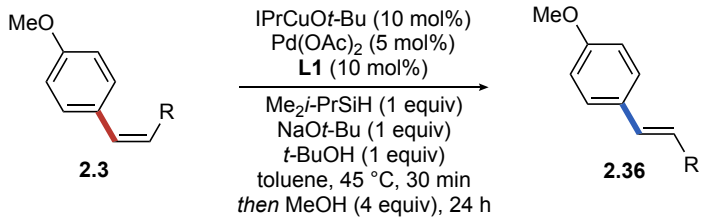
In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.58** (12.5 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (10.2 mg, 0.10 mmol, 2.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then MeOH (8.0 mg, 0.25 mmol, 5 equiv) was added. The reaction mixture was stirred at 45 °C and 30 µL aliquots were taken at 20 min, 4 h, 7 h, and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.24. Relative Contribution of Pd/Cu Catalysts to Semireduction Isomerization

Reaction Conditions	yield (20 min)	yield (4 h)	yield (7 h)	yield (24 h)
Above Conditions	20%	50%	60%	88%
No Cu	0% (83%)[a]	0% (33%)[a]	40%	60%
No Pd/L	0% (97%)[a]	0% (95%)[a]	0% (95%)[a]	0% (90%)[a]
No MeOH	0% (100%)[a]	0% (97%)[a]	0% (92%)[a]	0% (87%)[a]

[a]Yield of Sonogashira starting material, mass balance is Z alkene.

Catalytic Semireduction and Isomerization of the *Z*-alkene to *E*-alkene (Scheme 2.10)



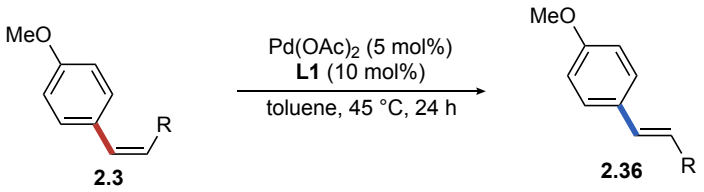
Scheme 2.25. Catalytic Isomerization of *Z*-Styrene to *E*-Styrene

In a nitrogen filled glovebox, a dram vial was charged with a stir bar, NaO*t*-Bu (4.8 mg, 0.050 mmol, 1.0 equiv). To this was added **2.3** (12.6 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), IPrCuO*t*-Bu (2.6 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH (5.1 mg, 0.05 mmol, 1.0 equiv), *t*-BuOH (3.7 mg, 0.050, 1.0 equiv) and toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then MeOH (8.0 mg, 0.25 mmol, 4.0 equiv) was added. The reaction mixture was stirred at 45 °C and 30 µL aliquots were taken at 20 min, 4 h, 7 h, and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.25. Minimum System for Isomerization

Reaction Conditions	Yield (20 min)	Yield (4 h)	Yield (7 h)	Yield (12 h)	yield (24 h)
Above Conditions	80% (74:1)	85% (76:1)	88% (81:1)	88% (100:1)	88% (100:1)
No Me_2*i*-PrSiH	0%	0%	2%	3%	8%
No Pd/L	0%	0%	1%	1%	5%

Conditions for the Isomerization of *Z*-alkenes to *E*-alkenes (Scheme 2.10)



Scheme 2.26. Minimum System for Isomerization

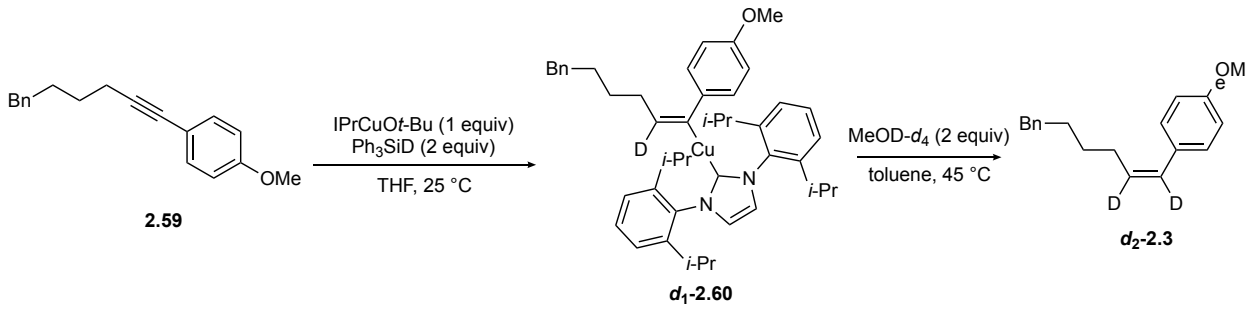
In a nitrogen filled glovebox, a dram vial was charged with a stir bar, **2.3** (12.6 mg, 0.050 mmol, 1.0 equiv), TMB (2.8 mg. 0.017 mmol, 0.33 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), Me_2i-PrSiH (0.50 mg, 0.005 mmol, 0.10 equiv) and toluene (0.50 mL) and the appropriate additive. The reaction mixture was stirred at 45 °C for 30 min, then MeOH (8.0 mg, 0.25 mmol, 4.0 equiv) was added. The reaction mixture was stirred at 45 °C and 30 μL aliquots were taken at 20 min, 4 h, 7 h, and 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography.

Table 2.26. Probing the System for Isomerization

Reaction Conditions	Yield (20 min)	yield (4 h)	yield (7 h)	yield (24 h)
10 mol% Me_2i-PrSiH	18%	47%	69%	88%[a]
10 mol% Me_2i-PrSiH w/ 4 equiv MeOH	9%	15%	46%	82%[a]
Pd_2dba_3 instead of $Pd(OAc)_2$	0%	0%	0%	2%
1 equiv Me_2i-PrSiH	34%	73%	80%	82%[a]
1 equiv Me_2i-PrSiH w/ 4 equiv MeOH	15%	23%	63%	85%[a]
2 equiv Me_2i-PrSiH	28%	95%[b]	82%	78%
2 equiv Me_2i-PrSiH w/ 4 equiv MeOH	11%	85%	93b[b]	81%
Pd_2dba_3 w/ 1 equiv Me_2i-PrSiH	8%	14%	18%	44%[c]
Pd_2dba_3 w/ 2 equiv Me_2i-PrSiH	8%	9%	20%	45%[c]

[a]Remaining material is overreduction to alkane. [b]Full isomerization complete, extended reaction times result in increased reduction to alkane. [c]Remaining material is *Z*-alkene.

2.8.17 *Mechanistic Studies: Deuterium Labeling (Scheme 2.10)*



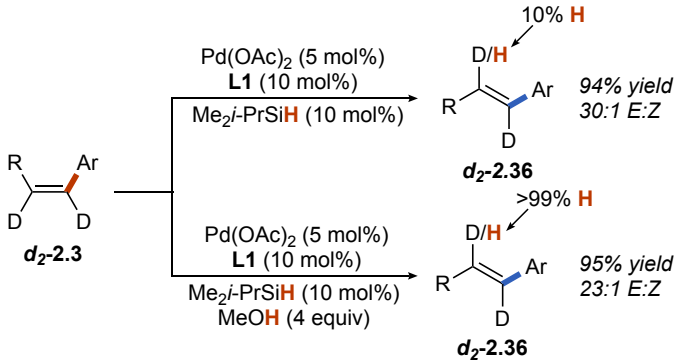
Scheme 2.27. Synthesis of d_2-*Z*-styrene (**d_2-2.3**)

In a nitrogen filled glovebox, IPrCuO*t*-Bu (394.7 mg, 0.750 mmol, 1.0 equiv) was weighed in a 20 mL scintillation vial, followed by 1000 µL THF. **2.58** (225.3 mg, 0.90 mmol, 1.2 equiv) was weighed out and transferred to the reaction with 3 aliquots of 500 µL of THF and reaction mixture was allowed to stir at 25 °C for 1 min resulting in an orange solution. Triphenylsilane-d_1[16] (391.7 mg, 1.5 mmol, 2.00 equiv) was weighed into a shell vial and transferred to the reaction with 3 aliquots of 500 µL THF at which point the reaction turned red. The reaction was vigorously stirred (1500 rpm) at 25 °C for 30 min after which the reaction turned back to a light orange. The reaction was concentrated in vaccuo, dissolved in minimal dichloromethane, layered with pentane and recrystallized at -35 °C. ***d*$_1$-2.60** was then filtered and washed with cold pentane. ***d*$_1$-2.60** was then dissolved in 2 ml of toluene and MeOD-d_4 (54.1 mg, 1.5 mmol, 2.0 equiv) was added. The reaction mixture was stirred until all the solids had dissolved, ~10 min. The reaction was then pushed through a plug of silica with excess EtOAc and purified by silica gel column chromatography. (0→5% EtOAc in hexanes).

Deuterirum Labeling

All glassware was washed with D_2O and then placed in an oven overnight. In a nitrogen filled glovebox, a dram vial was charged with a stir bar ***d*$_2$-2.3** (12.5 mg, 0.050 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.60 mg, 0.0025 mmol, 0.05 equiv), **L1** (1.9 mg, 0.005 mmol, 0.10 equiv), Me_2*i*-PrSiH

(0.50 mg, 0.010 mmol, 0.1 equiv), and d_8-toluene (0.50 mL). The reaction mixture was stirred at 45 °C for 30 min, then MeOH (x equiv) was added. The reaction mixture was stirred at 45 °C and 30 µL aliquots were taken at 24 h passed through a short plug of silica, washed with 1.5 mL of EtOAc and analyzed by Gas Chromatography to ensure completion. Then dimethyl isopterephthalate (2.6 mg, 0.017 mmol, 0.33 equiv) was added as internal standard and proton incorporation was determined by ^{1}H NMR in $CDCl_3$.



Scheme 2.28. Hydride Incorporation During Isomerization of d_2-*Z*-Styrene using Me_2i-PrSiH and MeOH

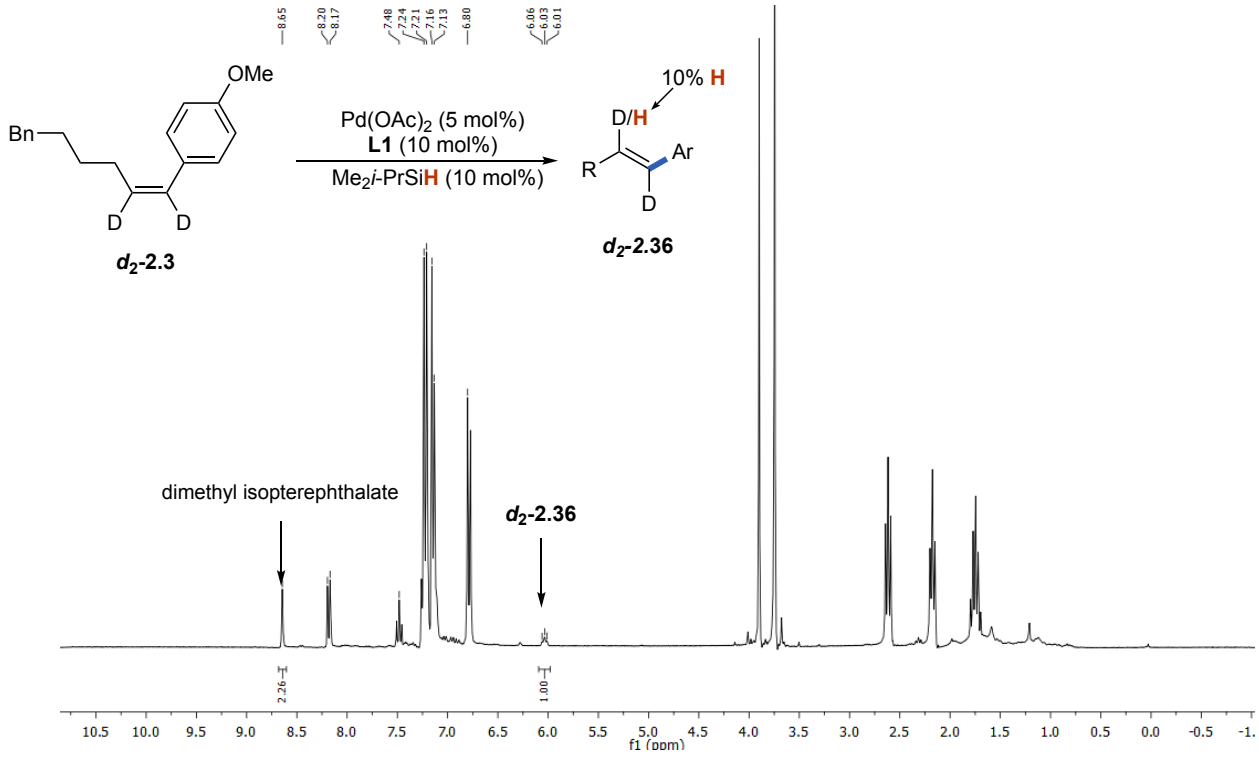


Figure 2.10. Hydride Incorporation during isomerization with 10 mol% silane **Error! Reference source not found.**

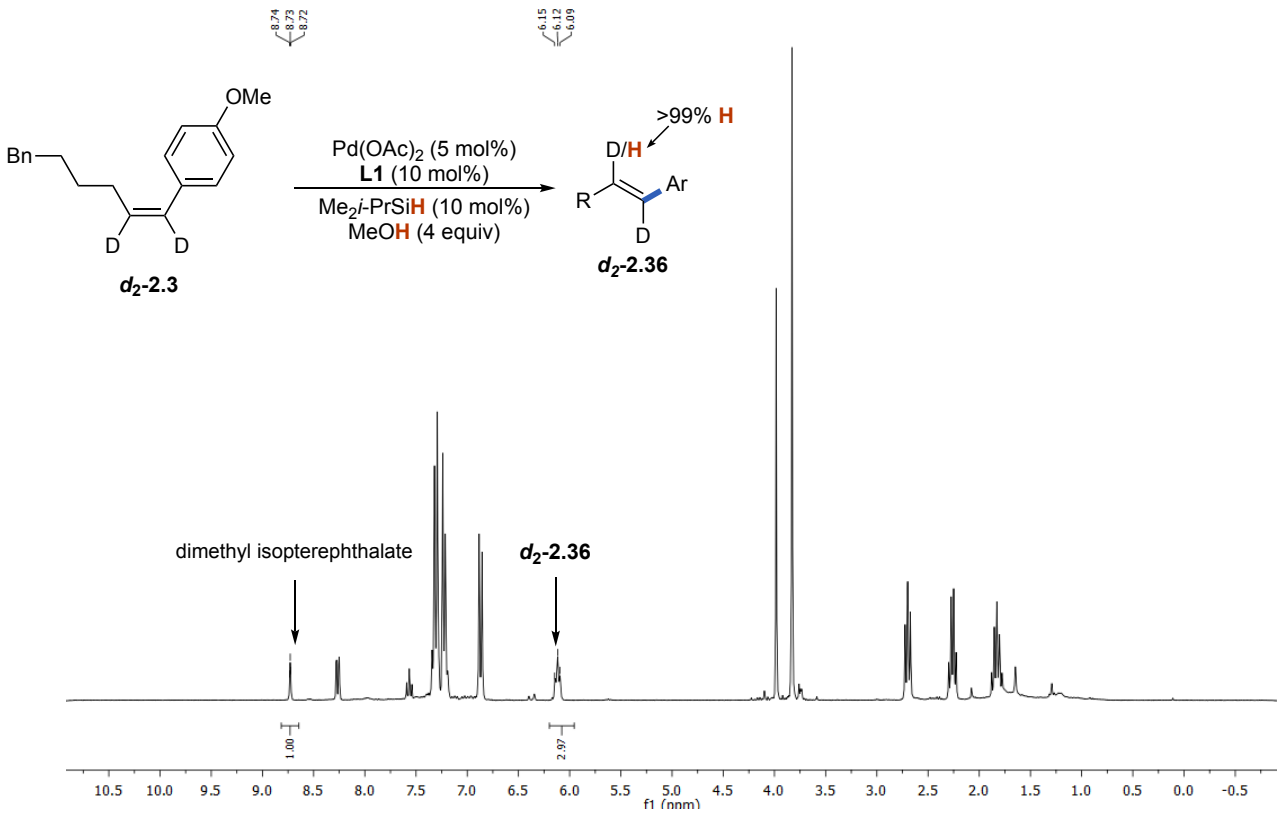


Figure 2.11. Hydride Incorporation during isomerization with 10 mol% silane and 4 equiv MeOH **Error! Reference source not found.**

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Chapter 3. DIFFERENTIAL DIHYDROFUNCTIONALIZATION OF TERMINAL ALKYNES: SYNTHESIS OF BENZYLIC ALKYL BORONATES THROUGH REDUCTIVE THREE-COMPONENT COUPLING

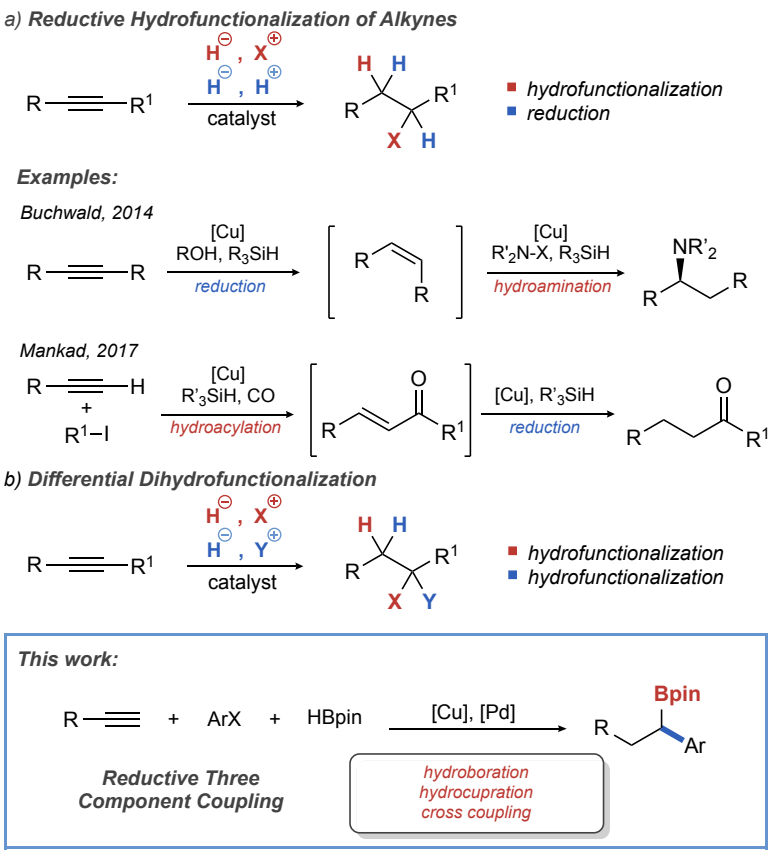
3.1 INTRODUCTION

Alkynes are extensively used in organic synthesis as readily available and versatile intermediates. They participate in a wide range of transformations, the most common of which are C-H functionalization of terminal alkynes, addition to one of the π bonds, and a double addition to both π bonds. Also known, but significantly less common, are reactions that lead to the differential transformation of the two π bonds. One of the simplest and oldest[1] reactions that mechanistically fits this description is the hydration of alkynes, which involves initial hydration followed by a tautomerization.[2–8] This transformation has been known for a long time, and has inspired development of differential transformations of alkyne π bonds using other

hydrofunctionalization reactions. However, these transformations are still rare,[9] and generally rely on intramolecular reactions[10–20] or reactions of alkynes activated by electron-withdrawing groups.[21,22]

Our interest in copper-catalyzed hydrofunctionalization reactions[23–25] led us to explore the application of copper hydride chemistry[26] in differential functionalization of the two alkyne π bonds. Successful applications developed so far have combined copper-catalyzed hydrofunctionalization of one π bond with catalytic reduction of the other (Scheme 3.1a).[27–34] In 2014, Buchwald et al. reported the first example of such a reductive hydrofunctionalization reaction, which combines reduction and hydroamination.[35] More recently, Mankad et al. reported an interesting example of a hydroacylation reaction followed by a reduction.[36]

The methods developed by the Buchwald and Mankad groups demonstrate the utility of copper hydride chemistry in differential transformations of alkyne π bonds. They also suggest a great potential for the development of reactions that would combine copper-catalyzed hydrofunctionalization of one π bond with a different hydrofunctionalization of the other π bond (Scheme 3.1b). Such reactions would significantly

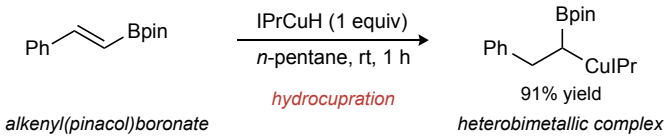


Scheme 3.1. Copper Hydride Chemistry in Differential Functionalization of Alkynes π-Bonds

increase the complexity of the products that can be accessed directly from alkynes and would enhance their utility as synthetic intermediates.

In this paper, we describe a method for the differential dihydrofunctionalization of terminal alkynes that formally combines hydroboration with hydroarylation (Scheme 3.1b). The overall reaction, promoted by synergistic Cu/Pd catalysis, results in reductive coupling of terminal alkynes, aryl bromides, and pinacolborane and the formation of benzylic alkyl boronates.[37–41]

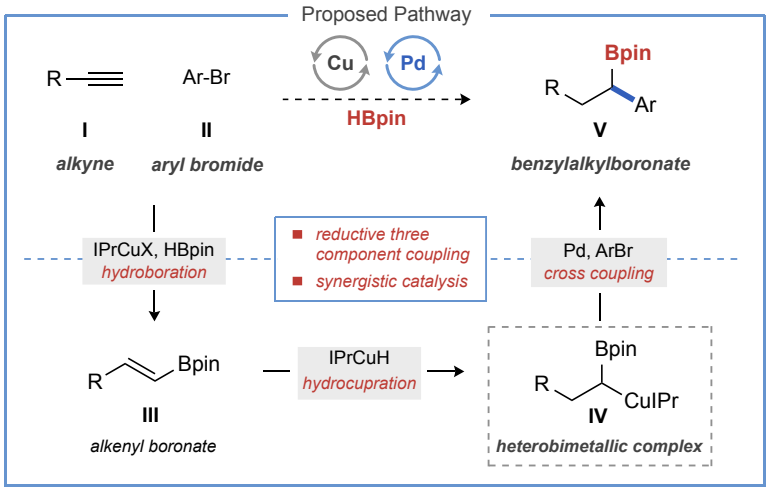
Inspiration for our approach to differential dihydrofunctionalization came from a report by Sadighi et al. in 2006.[42] The authors describe the hydrocupration of alkenyl Bpin by IPrCuH and formation of a heterobimetallic complex (Scheme 3.2.



Scheme 3.2. Hydrocupration of alkenyl Bpin by IPrCuH proving heterobimetallic complex

While we[23,24,43,44] and others[45,46] have previously established that (NHC)copper hydride complexes are excellent catalysts for hydrofunctionalization of alkynes,[26] this report demonstrated that these same complexes also participate in the selective hydrocupration of functionalized alkenes.[47] Our plan was to combine these two facets of the (NHC)CuH chemistry and develop a differential dihydrofunctionalization of alkynes (Scheme 3.3).

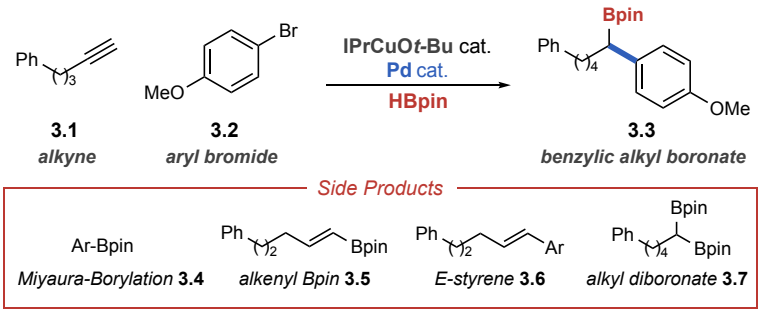
We reasoned that the heterobimetallic intermediate (**IV**) could be accessed directly from alkynes through copper-catalyzed hydroboration and the subsequent hydrocupration of the alkenyl boronate ester (**III**). This simple access to the heterobimetallic intermediate provides an opportunity to systematically explore a wide range of differential dihydrofunctionalization reactions of alkynes through further functionalization of this key intermediate. We chose to pursue palladium-catalyzed cross coupling of the heterobimetallic intermediate (**IV**) with aryl bromides (**II**), inspired by known catalytic arylations of related copper(I) alkyl intermediates.[48–52]



Scheme 3.3. Design of Differential Dihydrofunctionalization

3.2 Reaction Development

Preliminary investigation of the proposed differential dihydrofunctionalization reaction began with 5-phenyl-1-pentyne (**3.1**), 4-bromoanisole (**3.2**) and pinacolborane as coupling partners, with IPrCuO*t*-Bu and a variety of palladium catalysts. Initially, we observed numerous reactions promoted by the Cu/Pd catalyst system. In addition to the desired product (**3.3**), products of Miyaura borylation[53,54] (**3.4**), hydroboration[46,55–58] (**3.5**), hydroarylation[5960] (**3.6**) and geminal diboration (**3.7**) of the alkyne were also observed (Scheme 3.4).



Scheme 3.4. Preliminary Investigation of Differential Dihydrofunctionalization

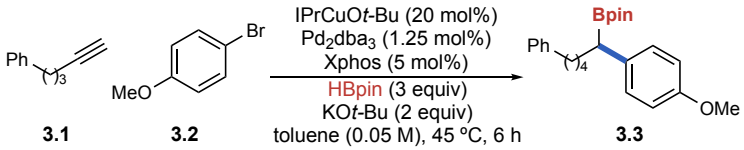
In addition to alkenyl boronate **3.5**, compounds **3.6**[61] and **3.7**[38] could, in principle, also serve as intermediates in the synthesis of the desired product **3.3**. However, careful monitoring of the reaction mixture revealed that the formation of either the *E*-styrene (**3.6**) or alkyl diboronate (**3.7**)

generally corresponded with a decreased yield of the desired product (**3.3**). On the other hand, any alkenyl boronate (**3.5**) formed was consumed over the course of the reaction, resulting in the corresponding increase in yield of the desired product. As a result, we focused on identifying reaction conditions that would minimize both hydroarylation and diboration of the terminal alkyne.

Initially, we found that the identity of the palladium catalyst and the alkoxide additive had the greatest effect on the product distribution. Extensive reaction development focused on these two parameters led to an efficient differential dihydrofunctionalization of terminal alkynes shown in Table 3.1 (entry 1).

During the reaction development, we made several observations summarized in Table 3.1. Considering that Pd_2dba_3[62,63] is rarely used in combination with dialkylbiaryl phosphine ligands, we were surprised that it was a significantly better precatalyst than other common palladium sources. For example, $Pd(OAc)_2$ provided the product in only 54% yield at the full conversion (Table 3.1 entry 2) (see Experimental for further details). IPrCuO*t*-Bu performed better than IPrCuCl as a catalyst

Table 3.1. Reaction Development

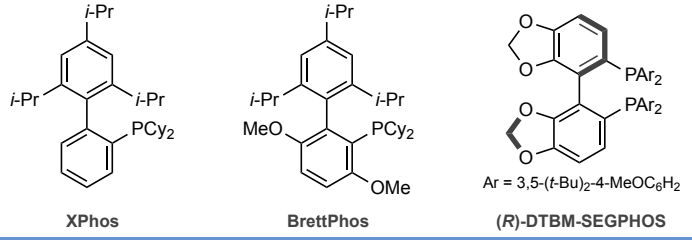


3.1 *alkyne* | **3.2** 2 equiv *aryl bromide* | **3.3** *benzylic alkyl boronate*

Entry	*deviation from above*	*yield*[a]
1	none	86
2	$Pd(OAc)_2$ instead of Pd_2dba_3	54
3	IPrCuCl instead of IPrCuO*t*-Bu	67
4	10 mol% IPrCuO*t*-Bu instead of 20 mol%	31
5	2.5 mol% Pd_2dba_3 instead of 1.25 mol%	59
6	BrettPhos instead of XPhos	20
7	(*R*)-DTBM-SEGPHOS instead of IPr	8
8	NaO*t*-Bu instead of KO*t*-Bu	46
9	LiO*t*-Bu instead of KO*t*-Bu	34
10	benzene instead of toluene	65
11	isooctane instead of toluene	24
12	dioxane instead of toluene	5
13	THF instead of toluene	0
14	0.1 M instead of 0.05 M[b]	74

[a]All reactions performed on 0.05 mmol scale and monitored by GC with 1,3,5-trimethoxy benzene as an internal standard. [b]concentration of alkyne in reaction mixture. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, dba = dibenzylideneacetone, pin = pinacolato.

Ligands



precursor (entry 3). Catalyst loading of both palladium and copper proved crucial. Lower loading of IPrCuO*t*-Bu resulted in decreased yield with full consumption of aryl halide (entry 4). Higher loading of the palladium catalyst increased formation of *E*-styrene (**3.6**) and lowered product yield (entry 5).

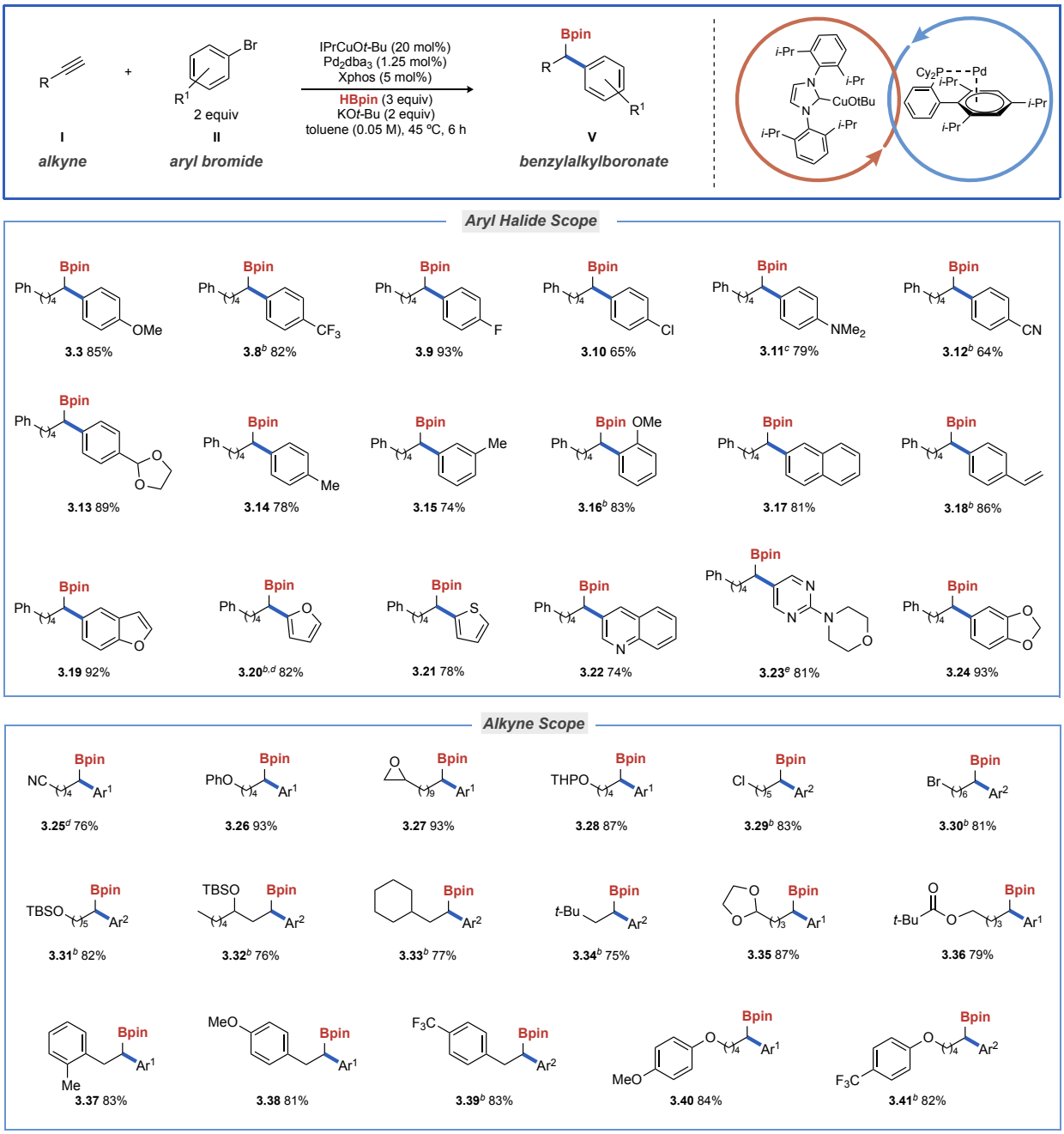
The reaction outcome was also greatly influenced by the choice of phosphine ligand. XPhos[64] provided significantly higher selectivity for the desired product than closely related BrettPhos[65] (entry 6) and other dialkylbiaryl ligands (see Experimental for details). Bisphosphine ligands like (*R*)-DTBM-SEGPHOS, formed the product of diboration (**3.7**) almost exclusively (entry 7). The choice of the alkoxide additive also proved important. KO*t*-Bu was superior to both NaO*t*-Bu and LiO*t*-Bu (entry 8 and 9), increasing conversion of alkenyl Bpin (**3.5**) to product, while suppressing formation of *E*-styrene (**3.6**).

High yields of the differentially dihydrofunctionalized product were obtained in aromatic hydrocarbon solvents such as toluene and benzene (entries 1 and 10), with lower yields in isooctane (entry 11) and minimal reactivity in ethereal solvents (entries 12 and 13) (see Experimental for details). Lastly, we observed that the concentration of the reaction mixture had a significant effect on yield. Doubling the concentration of the reaction mixture (entry 14) decreased the yield.[66]

3.1 SUBSTRATE SCOPE

Having established the conditions for the differential dihydrofunctionalization of terminal alkynes (Table 3.1, entry 1), we explored the scope of the reaction (Table 3.2). A broad range of aryl bromides serve as coupling partners. Both electron-rich (**3.3** and **3.11**) and electron-poor (**3.8** and **3.12**) aryl bromides were viable coupling partners. A variety of functional groups were tolerated, and reaction could be performed in the presence of aryl fluorides (**3.9**), aryl chlorides

Table 3.2. Substrate Scope



[a]Reactions run on 0.5 mmol scale. [b]IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu. [c]toluene:isooctane (1:1) used. [d]GC yield, with 1,3,5-trimethoxybenzene as internal standard. [e]KOTMS used instead of KO*t*-Bu and toluene:THF (1:1) was used. Ar^1 = 4-OMe(C_6H_4), Ar^2 = 4-CF_3(C_6H_4)

(**3.10**) and acetals (**3.13** and **3.24**). Styrenes (**3.18**) were also compatible with the reaction. Products derived from para- (**3.14**), meta- (**3.15**) and ortho- (**3.16**) substituted aryl bromides were isolated in good yields. Notably, a variety of O, N and S containing heterocycles were compatible with this reaction (**3.19** – **3.23**).

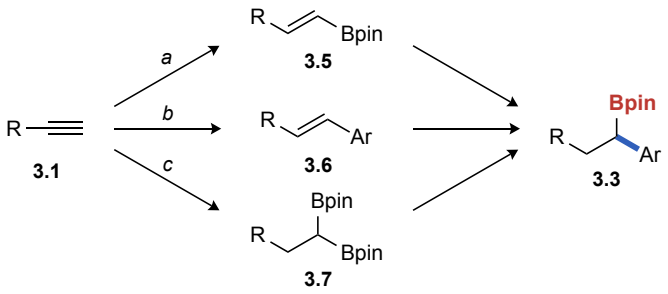
We also explored the scope of the alkyne coupling partner. Alkynes containing nitriles (**3.25**), epoxides (**3.27**), chlorides (**3.29**), bromides (**3.30**), acetals (**3.35**) and esters (**3.36**) were compatible with the reaction conditions. Protected alcohols (**3.28, 3.31** and **3.32**) and functionalized phenyl ethers (**3.26**, **3.40** and **3.41**) were competent coupling partners in the reaction. Propargylic substitution of the alkyne also provided products in good yields (**3.32** – **3.34**). Finally, electron rich (**3.38**) and electron deficient (**3.39**) aryl acetylenes can be utilized in this reaction.

We also noted several limitations of the reaction. The reaction is not compatible with aldehydes, ketones, activated alkenes (such as enones), free alcohols, or tertiary alkyl amines. Furthermore, reactions with several aryl chlorides provided no desired products, suggesting that aryl chlorides are not viable substrates. Finally, internal alkynes, including differentially substituted aryl alkyl alkynes provided no desired product in the reaction.

3.2 Mechanistic Studies

3.2.1 *Evaluation of Catalytic Intermediates*

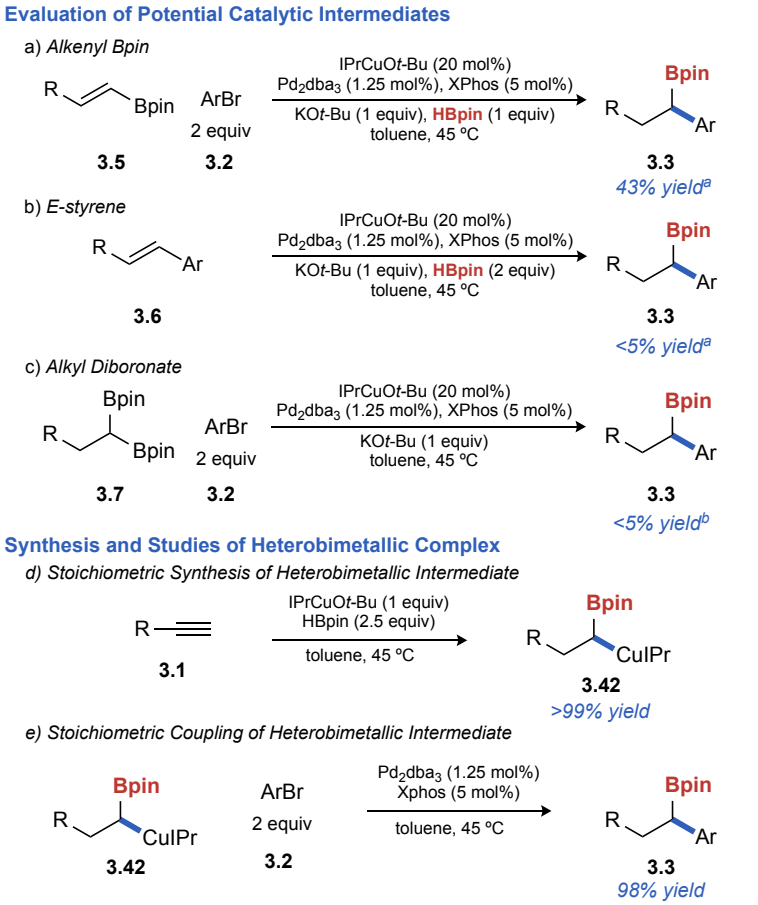
Considering our preliminary observations and the known reactivity of both palladium-catalyzed cross coupling[67,68] and copper-catalyzed hydrofunctionalization reactions,[26] we envisioned three possible pathways for differential dihydrofunctionalization of terminal alkynes (Scheme 3.5): a) copper-catalyzed hydroboration followed by hydrocupration and electrophilic functionalization, b) hydroarylation followed by hydroboration, or c) diboration to generate the alkyl diboronate, followed by mono-selective cross coupling with the aryl halide. Each pathway proceeds through a unique intermediate: a) alkenyl Bpin (**3.5**), b) *E*-styrene (**3.6**) or c) alkyl diboronate (**3.7**).



Scheme 3.5. Possible Pathways for Differential Dihydrofunctionalization of Terminal Alkynes

3.2.2 *Stoichiometric Studies*

We explored the reactivity of each presumed intermediate under the standard conditions for differential dihydrofunctionalization (Scheme 3.6). When alkenyl Bpin (**3.5**) was the substrate, the desired product (**3.3**) was formed in 43% yield after 6 h (Scheme 3.6a), whereas neither *E*-styrene (**3.6**), nor alkyl diboronate (**3.7**) formed the desired product in appreciable yields even after 24 h (Scheme 3.6b and c). In both cases, products of other side reactions were observed and/or starting material was recovered. These results strongly suggest that the operative pathway involves hydroboration of the alkyne (Scheme 3.5a).



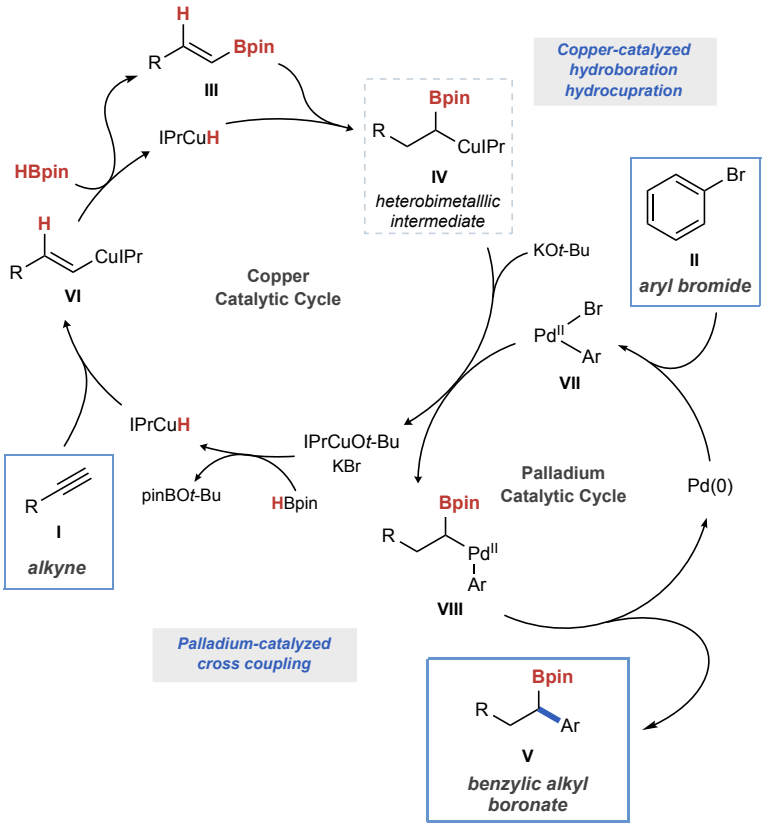
Reactions performed on 0.05 mmol scale and monitored by GC analysis using 1,3,5-trimethoxybenzene as an internal standard. [a]No further change even after 24 h, remaining material is unreacted starting material. [b]No further change even after 24 h, remaining material is 50% unreacted starting material and 45% alkenyl Bpin. R = $Ph(CH_2)_3$, Ar = 4-$OMe(C_6H_4)$.

Scheme 3.6. Mechanistic Experiments

We also wanted to verify that the heterobimetallic complex (**IV**) could be formed directly from terminal alkynes and is the key catalytic intermediate in the reaction. The stoichiometric reaction between terminal alkyne, IPrCuO*t*-Bu, and HBpin resulted in the formation of heterobimetallic complex **3.42**, in excellent yield (Scheme 3.6d). Additionally, the stoichiometric cross coupling between **3.42** and aryl bromide (**3.2**) yielded the desired benzylic alkyl boronate in 98% yield (Scheme 3.6e). Altogether, these results support our proposed pathway.

3.2.3 *Proposed Mechanism*

Considering the results of these experiments, we propose the mechanism outlined in Scheme 3.7. Initial transmetallation between IPrCuO*t*-Bu and HBpin generates IPrCuH, and hydrocupration of the terminal alkyne (**I**) results in alkenyl copper (**VI**). Additional transmetallation between a second equivalent of HBpin and **VI** delivers alkenyl Bpin (**III**) and regenerates IPrCuH. Reinsertion of **III** into IPrCuH furnishes heterobimetallic complex (**IV**).



Scheme 3.7. Proposed Catalytic Cycle

The heterobimetallic complex (**IV**) participates in a standard palladium-catalyzed cross coupling with the aryl bromide to produce the differentially dihydrofunctionalized product **V** and Pd(0). IPrCuO*t*-Bu catalyst is regenerated in the presence of KO*t*-Bu.

3.3 CONCLUSION

In conclusion, we have developed a method for the differential dihydrofunctionalization of alkynes that results in the reductive three-component coupling of terminal alkynes, aryl bromides, and pinacolborane. The benzylic alkyl boronate products are accessed directly from terminal alkynes by accomplishing two different regioselective hydrofunctionalization reactions promoted by a Cu/Pd catalyst system.

The reaction has excellent substrate scope and functional group compatibility, providing the desired products in high yields. The results of mechanistic experiments indicate that the reaction proceeds through copper-catalyzed hydroboration, followed by a second hydrocupration of the alkenyl boronate, and palladium-catalyzed arylation of the resulting heterobimetallic intermediate. The most important finding of our studies is that the heterobimetallic intermediate can be readily accessed directly from the terminal alkyne in the presence of a copper catalyst and HBpin. We believe that the access to this heterobimetallic intermediate provides an exciting opportunity for a systematic development of other differential dihydrofunctionalization reactions.

3.4 EXPERIMENTAL

3.4.1 *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). High Pressure Liquid Chromatography was performed using a Agilent LC column (Zorbax CN PrepHT,

21.2 x 250mm, 7μm). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C 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 ($CDCl_3$: δ 7.26 ppm). ^{13}C NMR chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm). ^{19}F NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to the internal standard, hexafluorobenzene (C_6F_6: δ -164.9 ppm). ^{11}B NMR chemical shifts (δ) are reported in part per million (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), intergration. Mass spectra were collected on a JEOL HX-110 mass spectrometer. 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.

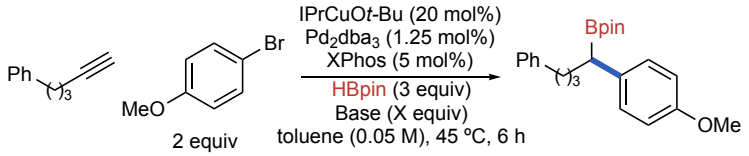
Materials: THF, CH_2Cl_2, ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous isooctane was purchased from Millipore Sigma, and was subsequently degassed and stored over 4Å molecular sieves. Pinacolborane was purchase from TCI America and distilled over calcium hydride under reduced pressure before use. 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.

3.4.2 *Reaction Development (Table 3.1)*

All reactions were performed on a 0.05 mmol scale with the stoichiometry shown in Table 3.3-Table 3.11. In a nitrogen-filled glovebox a dram vial was charged with a stir bar, alkoxide additive (Table 3.3), 5-phenyl-1-pentyne, 1,3,5-trimethoxybenzene (TMB, used as an internal standard for GC), palladium (Table 3.4 and Table 3.9), IPrCuX (Table 3.5 and Table 3.8), ligand (Table 3.6), 4-bromoanisole, HBpin (Table 3.7) and toluene (Table 3.10). The reaction mixture was stirred at 45 ºC. 30 μL aliquots were taken at 6 h, and 24 h time points, pushed through a plug of silica with 1.5 mL of EtOAc and monitored by Gas Chromatography.

During preliminary reaction optimization both aryl chlorides and aryl bromides were explored. Aryl bromides were found to be competent coupling partners, while aryl chlorides did not provide product and were not used in further reaction development.

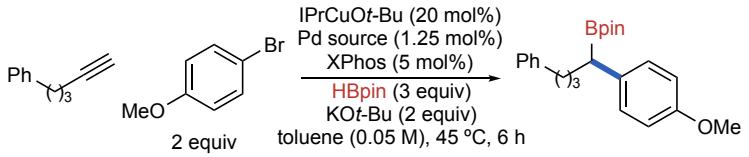
Table 3.3. Alkoxide Additive Screen



3.1 **3.2** **3.3**

Entry	Alkoxide	Stoichiometry	%Yield 6 h	%Yield 24 h
1	NaO*t*-Bu	2 equiv	52	53
2	NaO*t*-Bu	3 equiv	54	56
3	LiO*t*-Bu	2 equiv	18	20
4	LiO*t*-Bu	3 equiv	34	36
5	KO*t*-Bu	1 equiv	5	4
6	KO*t*-Bu	2 equiv	38	40
7	KO*t*-Bu	2.5 equiv	82	85
8	KO*t*-Bu	3 equiv	86	87
9	KO*t*-Bu	4 equiv	73	75
10	KO*t*-Bu	5 equiv	60	62

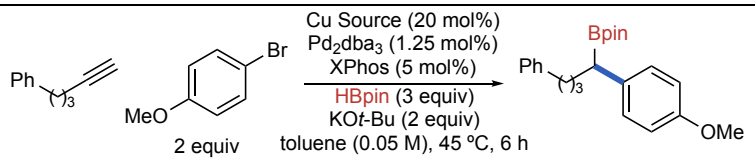
Table 3.4. Palladium Catalyst Screen



3.1 **3.2** **3.3**

Entry	Pd Source	%Yield 6 h	%Yield 24 h
1	$Pd(OAc)_2$	54	56
2	Pd_2dba_3	86	87
3	$Pddba_2$	39	42
4	$Pd(t\text{-}Bu_3)_2$	20	30
5	$Pd(PPh_3)_2Cl_2$	3	4
6	$Pd(TFA)_2$	35	34
7	Peppsi Pd	32	33
8	$Pd(cinnamyl)Cl_2$	15	16
9	$Pd(COD)_2Cl_2$	21	31

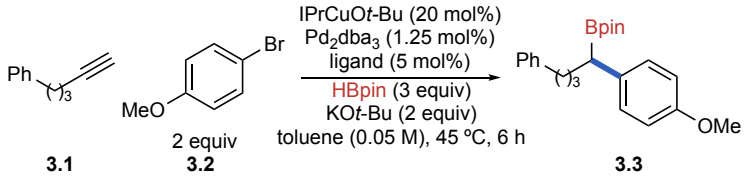
Table 3.5. Copper Catalyst Screen



3.1 **3.2** **3.3**

Entry	Copper Catalyst	%Yield 6 h	%Yield 24 h
1	IPrCuO*t*-Bu	86	87
2	IPrCuCl	67	70
3	SIPrCuCl	58	60
4	SIPrCuO*t*-Bu	54	58
5	IMesCuCl	8	10
6	SIMesCuCl	10	11
7	ICyCuCl	0	0
8	I*t*-BuCuCl	0	1
9	IBoxCuCl	0	0
10	IPr*CuCl	4	7
11	(6DIPP)CuO*t*-Bu	3	3
12	CyIMesCuCl	0	0
13	CyIPrCuCl	3	4
14	CyIBoxCuCl	1	2
15	IPrCuO(2-*t*-Bu-C_6H_4)	43	47

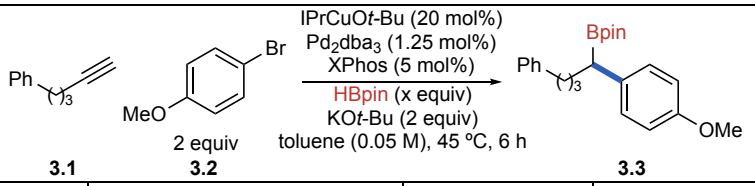
Table 3.6. Ligand Screen



3.1 **3.2** **3.3**

Entry	Ligand	%Yield 6 h	%Yield 24 h
1	XPhos	86	87
2	RuPhos	18	18
3	SPhos	6	8
4	BrettPhos	20	22
5	DavePhos	13	16
6	CPhos	8	15
7	Di-BIME	3	5
8	JosiPhos	4	4
9	Me-DuPhos	2	2
10	PCy_3	5	17
11	(*R*)-DTBM-SEGPhos	8	8
12	QuinoxP	2	5
13	XantPhos	0	0
14	chiraphos	5	6
15	*rac*-BINAP	5	5
16	NMDPP	2	3
17	DPPF	7	7

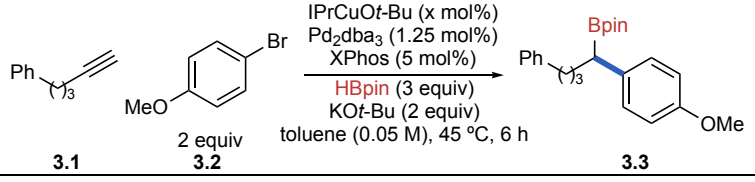
Table 3.7. HBpin Stoichiometry Screen



3.1 **3.2** **3.3**

Entry	Equivalents of HBpin	%Yield 6 h	%Yield 24 h
1	2.0	49	50
2	2.5	61	60
3	2.8	71	74
4	3.0	86	87
5	4.0	55	55
6	5.0	52	53

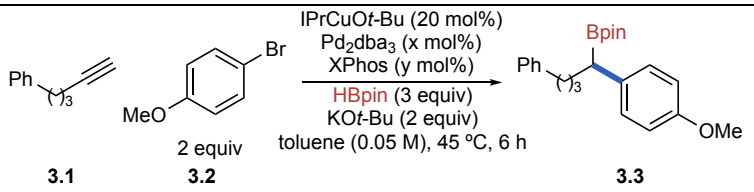
Table 3.8. Copper Catalyst Loading Screen



3.1 **3.2** **3.3**

Entry	Cu catalyst loading	%Yield 6 h	%Yield 24 h
1	10 mol%	31	30
2	15 mol%	62	65
3	20 mol%	86	87

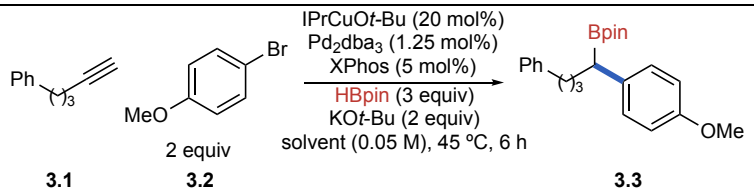
Table 3.9. Palladium Catalyst Loading Screen



3.1 **3.2** **3.3**

Entry	Pd catalyst loading	XPhos Loading	%Yield 6 h	%Yield 24 h
1	1.25 mol%	5 mol%	86	87
2	2.5 mol%	10 mol%	59	60
3	5 mol%	20 mol%	32	32

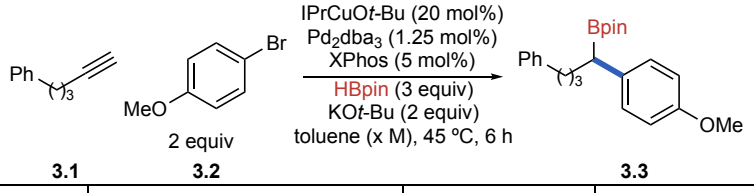
Table 3.10. Solvent Screen



3.1 **3.2** **3.3**

Entry	Solvent	%Yield 6 h	%Yield 24 h
1	toluene	86	87
2	benzene	65	68
3	isooctane	24	24
4	dioxane	5	6
5	THF	0	0
6	ether	0	0
7	DCM	0	0
8	DME	0	0

Table 3.11. Limiting Reagent Concentration Screen



3.1 **3.2** **3.3**

Entry	Concentration (M) (w.r.t alkyne)	%Yield 6 h	%Yield 24 h
1	0.1	74	73
2	0.075	80	81
3	0.05	86	87

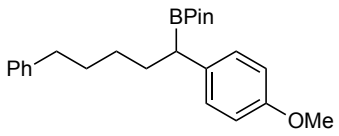
4	0.033	69	68
5	0.025	59	59
6	0.01	55	56

3.4.3 *General Procedure for the Differential Dihydrofunctionalization of Alkynes (Table 3.2)*

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, KO*t*-Bu (122.3 mg, 1.00 mmol, 2.0 equiv), IPrCuO*t*-Bu (52.6 mg, 0.1 mmol, 0.20 equiv), HBpin (192.0 mg, 1.50 mmol, 3.0 equiv), toluene (10 mL, 0.05M) and alkyne (0.5 mmol, 1.0 equiv). The reaction mixture was stirred at 45 °C until the yellow color disappeared. To this reaction mixture was added Pd_2dba_3 (5.7 mg, 0.00625 mmol, 0.0125 equiv), XPhos (11.9 mg, 0.025 equiv) and aryl bromide (1.0 mmol, 2.0 equiv) and the reaction mixture was vigorously stirred at 45 °C. After 6 h a 60 µL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC. Upon consumption of the alkyne, the reaction mixture was diluted with Et_2O, washed with 1 M HCl and brine, dried over Na_2SO_4, filtered through a pad a silica gel and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography.

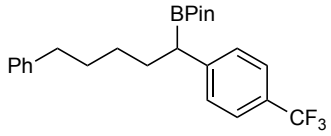
A variety of aryl chlorides were also surveyed under the optimized reaction conditions using 5-phenyl-1-pentyne as a coupling partner, but did not produce the desired product and were not further optimized.

3.4.4 *Characterization of Products of Differential Dihydrofunctionalization (Table 3.2)*

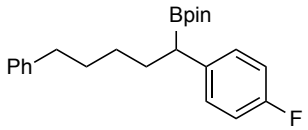


2-[1-(4-methoxyphenyl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3), compound was prepared according to reported procedure and was purified by silica gel column chromatography, 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (162 mg,

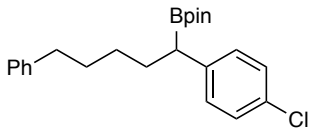
85% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 – 7.23 (m, 3H), 7.21 – 7.06 (m, 5H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 1H), 1.95 – 1.73 (m, 1H), 1.72 – 1.51 (m, 4H), 1.38 – 1.24 (m, 3H), 1.18 (d, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.4, 142.9, 135.5, 129.3, 128.5, 128.3, 125.6, 113.9, 83.3, 55.2, 35.9, 32.9, 31.5, 29.0, 25.0, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.7. GCMS (EI) calculated for [M]+ 380.25, found 380.3. FTIR (neat, cm^{-1}): 3053(m), 2980(s), 2929(s), 2858(m), 1604(m), 1510(s), 1456(m), 1371(m), 1325(m), 1246(m), 1145(s), 1030(m), 851(m), 755(s).



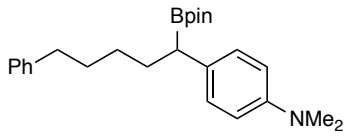
4,4,5,5-tetramethyl-2-{5-phenyl-1-[4-(trifluoromethyl)phenyl]pentyl}-1,3,2-dioxaborolane (3.8), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography, 0-100% DCM in hexanes and was isolated as a clear colorless liquid (171 mg, 82% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.19 (m, 6H), 7.21 – 7.09 (m, 3H), 2.65 – 2.51 (m, 2H), 2.36 (t, *J* = 7.9 Hz, 1H), 1.97 – 1.79 (m, 1H), 1.76 – 1.51 (m, 3H), 1.39 – 1.22 (m, 2H), 1.18 (d, *J* = 5.7 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.9, 142.7, 128.7, 128.5, 128.3, 127.3 (q, *J* = 34.2 Hz), 125.7, 125.3 (q, *J* = 3.7 Hz), 124.8 (q, *J* = 266.7 Hz), 83.6, 35.8, 32.4, 31.4, 28.9, 24.7, 24.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -65.1. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.5. GCMS (EI) calculated for [M]+ 418.23, found 418.4. FTIR (neat, cm^{-1}): 3027(m), 2979(s), 2931(s), 2858(m), 1617(s), 1454(m), 1371(s), 1325(s), 1164(m), 1123(s), 1068(s), 1018(s), 966(m), 851(m), 734(m), 699(m).



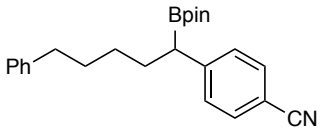
2-[1-(4-fluorophenyl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.9), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes and was isolated as a clear colorless liquid (172 mg, 93% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.32 – 7.10 (m, 8H), 6.93 (t, *J* = 8.8 Hz, 2H), 2.65 – 2.50 (m, 1H), 2.27 (t, *J* = 7.9 Hz, 1H), 1.93 – 1.76 (m, 1H), 1.73 – 1.46 (m, 3H), 1.38 – 1.10 (m, 14H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.1 (d, *J* = 242.3 Hz), 142.8, 139.1, 129.7 (d, *J* = 7.9 Hz), 128.4 (d, *J* = 24.0 Hz), 125.7, 115.0 (d, *J* = 20.9 Hz), 83.4, 35.9, 32.7, 31.4, 28.9, 24.9, 24.7, 24.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -121.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.4. GCMS (EI) calculated for [M]+ 368.23, found 368.3. FTIR (neat, cm^{-1}): 3058(m), 2978(s), 2930(s), 2857(m), 1603(s), 1506(s), 1370(s), 1324(s), 1219(s), 1142(s), 967(m), 852(m), 699(m).



2-[1-(4-chlorophenyl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.10), compound was prepared according to reported procedure and was purified by silica gel chromatography 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (126 mg, 65% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.06 (m,11H), 2.65 – 2.50 (m, 2H), 2.26 (t, *J* = 7.9 Hz, 1H), 1.94 – 1.75 (m, 1H), 1.60 (m, 3H), 1.31 (m, 2H), 1.17 (d, *J* = 6.0 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.8, 142.1, 130.9, 129.8, 128.5, 128.3, 125.7, 120.1, 83.5, 35.9, 32.5, 31.4, 28.9, 24.8, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.3. GCMS (EI) calculated for [M]+ 384.20, found 384.3. FTIR (neat, cm^{-1}): 3059(m), 2979(s), 2931(s), 2858(m), 1604(s), 1490(s), 1366(s), 1322(s), 1143(s), 1091(s), 1015(s), 967(m), 851(m), 699(m).

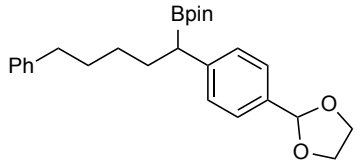


***N,N*-dimethyl-4-[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]aniline (3.11)**, compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu, NaO*t*-Bu instead of KO*t*-Bu and a 1:1 mixture of toluene isooctane, and was purified by prep TLC, 2% TEA, 20% EtOAc in hexanes, and was isolated as a clear colorless liquid (156 mg, 79% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 9.0 Hz, 2H), 7.27 – 7.19 (m, 6H), 6.61 (d, *J* = 9.0 Hz, 2H), 3.01 (s, 6H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.88 - 1.83 (m, 1H), 1.70 - 1.55 (m, 3H), 1.35 - 1.16 (m, 14H) .^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 142.6, 130.4, 130.4, 128.5, 128.4, 125.8, 125.2, 110.8, 83.5, 40.1, 37.8, 36.0, 31.4, 24.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.8. GCMS (EI) calculated for [M]+ 393.28, found 393.3. FTIR (neat, cm^{-1}): 2052(m), 2980(s), 2940(s), 2858(m), 1606(m), 1511(s), 1456(m), 1415(m), 1340(m), 1248(m), 1152(s), 1035(m), 850(m), 755(s), 699(m).

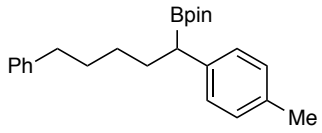


4-[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]benzonitrile (3.12), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel column chromatography, 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (120 mg, 64% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.21 (m, 5H), 7.15 (m, 3H), 2.57 (td, *J* = 7.4, 3.4 Hz, 2H), 2.37 (t, *J* = 7.9 Hz, 1H), 1.98 – 1.81 (m, 1H), 1.75 – 1.55 (m, 3H), 1.39 – 1.24 (m, 4H), 1.17 (d, *J* = 5.0 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.6, 142.6, 132.2, 129.1, 128.5, 128.3, 125.7, 119.5, 109.0, 83.8, 35.8, 32.0, 31.3, 28.8, 25.0, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.3. GCMS (EI) calculated for [M]+ 375.23, found 375.2. FTIR (neat,

cm^{-1}): 3049(m), 2978(s), 2931(s), 2857(m), 2226(s), 1605(s), 1455(m), 1370(s), 1327(s), 1142(s), 967(m), 851(m), 699(m).

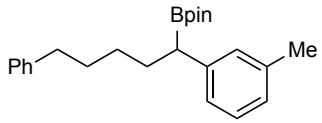


2-{1-[4-(1,3-dioxolan-2-yl)phenyl]-5-phenylpentyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.13), compound was prepared according to reported procedure and was purified by silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (187 mg, 89% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.17 (m, 5H), 7.14 (d, *J* = 8.1 Hz, 2H), 5.77 (s, 1H), 4.29 – 3.88 (m,4H), 2.67 – 2.45 (m, 2H), 2.30 (t, *J* = 7.9 Hz, 1H), 2.00 – 1.74 (m, 1H), 1.74 – 1.46 (m, 3H), 1.46 – 1.20 (m, 2H), 1.16 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.7, 142.8, 134.5, 128.4, 128.4, 128.2, 126.5, 125.6, 104.0, 83.3, 65.4, 35.9, 32.5, 31.5, 28.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.6. GCMS (EI) calculated for [M]+ 422.26, found 422.3. FTIR (neat, cm^{-1}): 3048(m), 2978(s), 2930(s), 2857(s), 1615(s), 1454(m), 1370(m), 1325(s), 1217(m), 1217(m), 1142(m), 1020(m), 966(m), 911(w), 851(m), 699(m).

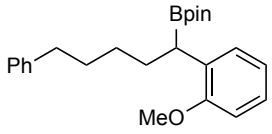


4,4,5,5-tetramethyl-2-[1-(4-methylphenyl)-5-phenylpentyl]-1,3,2-dioxaborolane (3.14), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (142 mg, 78% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.01 (m,10H), 2.57 (t, *J* = 9.0 Hz, 1H), 2.43 – 2.20 (m, 5H), 1.95 – 1.74 (m, 1H), 1.64 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.41 – 1.29 (m, 2H), 1.18

(d, *J* = 7.2 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.8, 140.3, 134.4, 129.3, 129.0, 128.4, 128.3, 125.6, 83.2, 35.9, 32.7, 31.5, 29.0, 24.7, 24.6, 24.6, 21.1. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.3. GCMS (EI) calculated for [M]+ 364.26, found 364.3. FTIR (neat, cm^{-1}): 3059(m), 2977(m), 2857(m), 1604(s), 1512(m), 1453(m), 1370(m), 1325(m), 1142(s), 1030(m), 982(m), 851(m), 734(m).

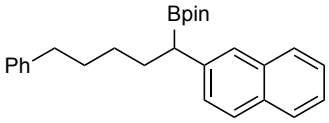


4,4,5,5-tetramethyl-2-[1-(3-methylphenyl)-5-phenylpentyl]-1,3,2-dioxaborolane (3.15), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (134 mg, 74% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.20 (m,3H), 7.21 – 7.08 (m,42H), 7.05 – 6.90 (m, 3H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.29 (d, *J* = 17.0 Hz,4H), 1.97 – 1.76 (m, 1H), 1.64 (m, 7.8 Hz, 3H), 1.35 (t, *J* = 7.8 Hz, 2H), 1.18 (d, *J* = 7.5 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.4, 142.9, 129.3, 128.5, 128.3, 128.2, 126.0, 125.6, 125.4, 83.3, 35.9, 32.7, 31.6, 29.1, 24.9, 24.7, 21.6. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.4. GCMS (EI) calculated for [M]+ 364.26, found 364.3. FTIR (neat, cm^{-1}): 3061(m), 3026(m), 2978(s), 2929(s), 2857(m), 1604(s), 1496(m), 1496(m), 1454(m), 1370(s), 1322(s), 1142(s), 1109(m), 967(m), 864(m), 750(m), 698(m).

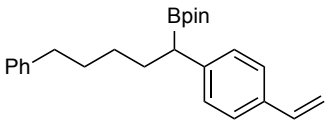


2-[1-(2-methoxyphenyl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.16), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography, 0-100% DCM in

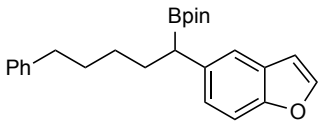
hexanes, and was isolated as a clear colorless liquid (158 mg, 83% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.05 (m, 10H), 6.97 – 6.71 (m, 2H), 3.78 (s, 3H), 2.57 (m, 2H), 2.42 (t, *J* = 7.7 Hz, 1H), 1.95 – 1.75 (m, 1H), 1.75 - 1.55 (m, 3H), 1.42 – 1.14 (m, 14H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.1, 143.1, 132.4, 129.7, 128.5, 128.2, 126.3, 125.5, 120.6, 110.0, 83.1, 55.1, 36.0, 31.6, 30.6, 29.0, 24.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.1. GCMS (EI) calculated for [M]+ 380.25, found 380.3. FTIR (neat, cm^{-1}): 3063(s), 2979(m), 2932(s), 2858(m), 1600(m), 1490(m), 1454(m), 1370(s), 1319(s), 1241(m), 1144(m), 1030(m), 967(m), 851(m), 752(s).



4,4,5,5-tetramethyl-2-[1-(naphthalen-2-yl)-5-phenylpentyl]-1,3,2-dioxaborolane (3.17), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (174 mg, 87% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 – 7.68 (m, 3H), 7.63 (s, 1H), 7.55 – 7.30 (m, 3H), 7.26 (s, 3H), 7.14 (d, *J* = 7.7 Hz, 3H), 2.57 (m, 2H), 2.47 (t, *J* = 7.9 Hz, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.63 (m, 2H), 1.45 – 1.28 (m, 2H), 1.18 (d, *J* = 8.2 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.9, 141.1, 133.9, 131.9, 128.5, 128.3, 127.8, 127.8, 127.6, 127.6, 126.3, 125.7, 125.6, 124.9, 83.4, 35.9, 32.4, 31.6, 29.1, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.8. GCMS (EI) calculated for [M]+ 400.26, found 400.3. FTIR (neat, cm^{-1}): 3059(s), 2978(s), 2930(s), 2857(s), 1632(m), 1601(s), 1506(m), 1454(s), 1370(s), 1329(s), 1269(m), 1210(m), 1135(m), 968(m), 856(s), 748(s), 699(s).

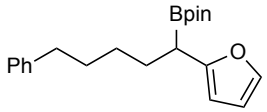


2-[1-(4-ethenylphenyl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.18), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (188 mg, 86% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 – 7.22 (m, 4H), 7.15 (dd, *J* = 15.3, 8.7 Hz, 6H), 6.70 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.70 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.9 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.30 (t, *J* = 7.9 Hz, 1H), 1.87 (dt, *J* = 13.2, 7.9 Hz, 1H), 1.77 – 1.55 (m, 2H), 1.43 – 1.27 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.9, 137.0, 134.7, 128.6, 128.5, 128.3, 126.3, 125.6, 112.6, 111.0, 83.4, 35.9, 32.5, 31.5, 29.0, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.4. GCMS (EI) calculated for [M]+ 376.26, found 376.3. FTIR (neat, cm^{-1}): 3059(m), 2978(s), 2930(s), 2857(m), 1605(m), 1509(s), 1454(s), 1371(s), 1326(s), 1143(s), 851(m), 699(m).

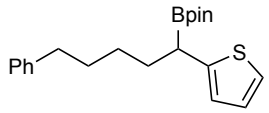


2-[1-(1-benzofuran-5-yl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.19), compound was prepared according to reported procedure and was purified by silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (180 mg, 92% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.26 (s, 2H), 7.21 – 7.07 (m, 4H), 6.77 – 6.68 (m, 1H), 2.68 – 2.50 (m, 2H), 2.43 (t, *J* = 7.9 Hz, 1H), 2.03 – 1.85 (m, 1H), 1.84 – 1.57 (m, 3H), 1.49 – 1.30 (m, 2H), 1.20 (d, *J* = 8.1 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.6, 144.3, 142.9, 140.3, 128.5, 128.3, 125.6, 124.8, 123.8, 120.7, 111.0, 106.5, 83.4, 35.9, 33.0, 31.6, 29.0, 24.8, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.1. GCMS (EI) calculated for [M]+ 390.24, found 390.2. FTIR (neat, cm^{-1}):

3027(m), 2977(m), 2927(s), 1621(m), 1531(m), 1454(s), 1370(m), 1323(m), 1266(m), 1142(s), 1028(m), 860(m), 733(m).

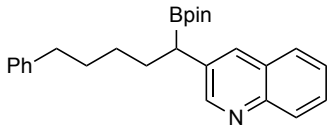


2-[1-(furan-2-yl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.20), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by HPLC, 100% hexanes after, silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid. GC yield (82% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 (s, 1H), 7.33 – 7.22 (m, 8H), 6.26 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.00 (d, *J* = 3.4 Hz, 1H), 2.45 (t, *J* = 7.5 Hz, 1H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.77 (q, *J* = 7.8 Hz, 3H), 1.69 – 1.57 (m, 2H), 1.36 (q, *J* = 8.2 Hz, 1H), 1.22 (d, *J* = 2.7 Hz, 13H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.7, 141.8, 128.5, 128.4, 125.8, 125.7, 109.2, 106.2, 83.0, 35.8, 34.9, 31.3, 29.8, 24.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.4 GCMS (EI) calculated for [M]+ 340.27, found 340.3. FTIR (neat, cm^{-1}): 3024(m), 2976(m), 2927(s), 1616(m), 1530(m), 1454(s), 1372(m), 1319(m), 1265(m), 1140(s), 1036(m), 861(m), 733(m).

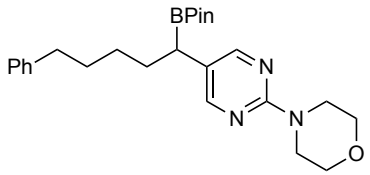


4,4,5,5-tetramethyl-2-[5-phenyl-1-(thiophen-2-yl)pentyl]-1,3,2-dioxaborolane (3.21), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (139 mg, 78% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.1 Hz, 4H), 7.19 – 7.11 (m, 3H), 7.07 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.90 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.79 (d, *J* = 3.5 Hz, 1H), 2.61 (m, 3H), 1.97 – 1.55 (m, 4H), 1.39 (m, 2H), 1.21 (d, *J* = 4.8 Hz, 12H). ^{13}C NMR (126 MHz,

Chloroform-*d*) δ 146.6, 142.8, 128.5, 128.3, 126.8, 125.7, 123.8, 122.5, 83.7, 35.9, 33.8, 31.4, 28.8, 24.9, 24.8, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.1. GCMS (EI) calculated for [M]+ 356.26, found 356.3. FTIR (neat, cm^{-1}): 3064(m), 3064(m), 3026(m), 2978(s), 2931(s), 2857(s), 1604(s), 1496(s), 1454(m), 1370(s), 1327(s), 1143(s), 1030(m), 966(m), 849(m), 750(m), 697(m).

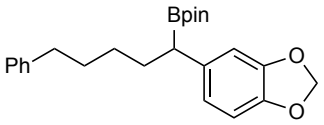


3-[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]quinoline (3.22), compound was prepared according to reported procedure and was purified by prep TLC, 2% Triethylamine, 20% EtOAc in hexanes and was isolated as a clear colorless liquid (148 mg, 74% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.88 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.06 (dd, *J* = 17.9, 7.6 Hz, 2H), 7.67 – 7.59 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.19 – 7.12 (m, 3H), 2.58 (m, 2H), 2.49 (t, *J* = 7.8 Hz, 1H), 1.99 (m, 1H), 1.80 (m, 1H), 1.65 (m, 2H), 1.39 – 1.35 (m, 2H), 1.19 (d, *J* = 7.9 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.1, 146.1, 136.9, 129.5, 129.3, 128.8, 127.3, 126.7, 117.0 , 83.6, 35.9, 32.9, 31.5, 29.0, 25.0, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.1. GCMS (EI) calculated for [M]+ 401.25, found 400.3. FTIR (neat, cm^{-1}): 3095 (m), 3062(s), 2978(s), 2924(s), 2860(s), 1630(m), 1604(s), 1509(m), 1450(s), 1372(s), 1322(s), 1269(m), 1210(m), 1134(m), 968(m), 856(s), 748(s), 699(s).

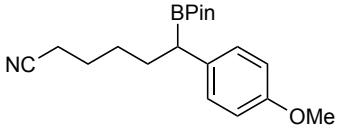


4-{5-[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]pyrimidin-2-yl}morpholine (**3.23**), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu, KOTMS instead of KO*t*-Bu and a 1:1 mixture of toluene and THF.

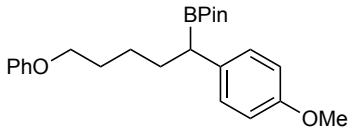
Compound was purified by prep TLC, 2% Triethylamine, 20% EtOAc in hexanes and was isolated as a clear colorless liquid (178 mg, 81% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.37 (s, 2H), 7.43 – 7.13 (m, 7H), 3.84 (qq, *J* = 4.8, 2.3 Hz, 10H), 2.30 (t, *J* = 7.9 Hz, 1H), 2.00 - 1.79 (m, 1H), 1.74 - 1.46 (m, 3H), 1.46 - 1.20 (m, 2H), 1.16 (d, *J* = 6.7Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.2, 129.3, 128.6, 128.4, 125.9, 123.9, 120.8, 83.7, 66.9, 44.6, 35.5, 32.8, 31.1, 29.8, 25.1, 24.8, 24.8. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.7. GCMS (EI) calculated for [M]+ 437.28, found 437.4. FTIR (neat, cm^{-1}): 3104(m), 3095 (m), 3062(s), 2978(s), 2924(s), 2860(s), 1630(m), 1604(s), 1509(m), 1449(s), 1401(s), 1375(s), 1319(s), 1299(m), 1269(m), 1209(m), 1132(m), 1101(m), 966(m), 856(s), 748(s), 699(s).



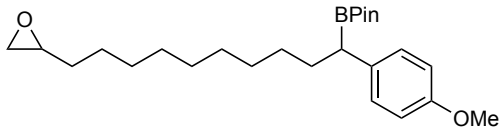
2-[1-(2H-1,3-benzodioxol-5-yl)-5-phenylpentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.24), compound was prepared according to reported procedure and was purified by silica gel column chromatography, 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (184 mg, 93% yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.33 – 7.07 (m,7H), 6.77 – 6.56 (m, 3H), 5.90 (s, 2H), 2.63 – 2.48 (m, 2H), 2.21 (t, *J* = 7.9 Hz, 1H), 1.92 – 1.71 (m, 1H), 1.70 – 1.52 (m, 3H), 1.30 (d, J = 16.1 Hz, 4H), 1.18 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.5, 145.1, 142.8, 137.2, 128.4, 128.2, 125.6, 121.2, 108.9, 108.2, 100.6, 83.4, 35.9, 32.8, 31.5, 28.8, 25.5, 24.7, 24.6. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.0. GCMS (EI) calculated for [M]+ 394.32, found 394.3. FTIR (neat, cm^{-1}): 3062(w), 3021(m), 2984(m), 2934(m), 1672(w), 1604(m), 1489(s), 1444(s), 1246(s), 1142(s), 1040(m), 933(m), 851(m), 755(m).



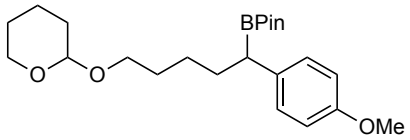
6-(4-methoxyphenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanenitrile (3.25), compound was prepared according to reported procedure and was purified by HPLC, 0-1% IPA in hexanes, after silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid. GC yield (76% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.19 (m, 3H), 6.80 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 2.68 – 2.43 (m, 2H), 2.23 (t, *J* = 7.9 Hz, 1H), 1.94 – 1.71 (m, 1H), 1.71 – 1.58 (m, 3H), 1.38 – 1.24 (m, 2H), 1.18 (d, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 131.6, 127.4, 125.5, 119.8, 114.1, 83.5, 58.9, 31.8, 29.8, 29.5, 25.3, 24.7, 16.5. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.2. GCMS (EI) calculated for [M]+ 375.24, found 375.2. FTIR (neat, cm^{-1}): 3057(m), 2926(s), 2849(s), 2247(s), 2606(s), 1515(s), 1371(s), 1243(s), 1143(s), 1032(s), 967(s), 833(m), 751(m).



2-[1-(4-methoxyphenyl)-5-phenoxypentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.26), compound was prepared according to reported procedure and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (185 mg, 93% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 (s, 3H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.47 (s, 2H), 3.77 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.23 (t, *J* = 7.9 Hz, 1H), 1.91 – 1.73 (m, 1H), 1.71 – 1.51 (m, 2H), 1.43 – 1.23 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 13H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.4, 138.9, 135.4, 129.3, 128.4, 127.6, 127.4, 113.8, 83.3, 72.8, 70.5, 55.2, 32.7, 29.8, 25.8, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 31.9. GCMS (EI) calculated for [M]+ 396.25, found 396.3. FTIR (neat, cm^{-1}):3051(m), 2978(s), 2932(s), 2858(m), 1601(m), 1510(s), 1454(m), 1370(m), 1325(m), 1247(m), 1143(s), 1031(m), 851(m), 755(s).

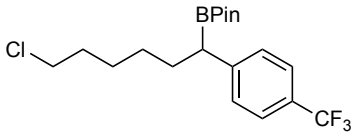


2-[1-(4-methoxyphenyl)-10-(oxiran-2-yl)decyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.27), compound was prepared according to reported procedure and was purified by silica gel column chromatography, 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (193 mg, 93% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 2.94 – 2.84 (m, 1H), 2.79 – 2.69 (m, 1H), 2.46 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.22 (t, *J* = 7.9 Hz, 1H), 1.89 – 1.69 (m, 1H), 1.67 – 1.36 (m, 6H), 1.37 – 1.13 (m, 26H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.3, 135.5, 129.3, 113.8, 83.3, 55.2, 52.5, 47.2, 33.0, 32.6, 29.7, 29.6, 29.6, 29.5, 29.3, 26.1, 24.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.9. GCMS (EI) calculated for [M]+ 416.31, found 416.3. FTIR (neat, cm^{-1}): 3045(m), 2976(s), 2926(s), 2855(m), 1611(m), 1512(s), 1454(m), 1370(s), 1323(s), 1246(m), 1142(s), 1112(m), 1037(m), 967(m), 851(m), 754(m).

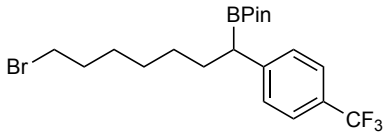


2-[1-(4-methoxyphenyl)-5-(oxan-2-yloxy)pentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.28), compound was prepared according to reported procedure and was purified by prep TLC, 2% Triethylamine in DCM, and was isolated as a clear colorless liquid (176 mg, 78% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95, (d, *J* = 8.8 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 4.59 (t, *J* = 3.5 Hz, 1H), 3.94 – 3.71 (m, 5H), 2.96 (t, *J* = 7.3 Hz, 2H), 1.90 – 1.77 (m, 3H), 1.78 – 1.45 (m, 10H), 1.25 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.2, 136.4, 130.5, 113.8, 99.0, 83.5, 67.4, 62.5, 55.6, 38.1, 30.9, 29.9, 25.7, 24.9, 24.8, 24.7, 22.8, 21.6, 19.8. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.0. GCMS (EI) calculated for [M]+ 404.27, found 404.3. FTIR (neat, cm^{-1}):

3035(m), 2972(s), 2929(s), 2849(m), 1609(s), 1510(s), 1455(m), 1373(s), 1323(s), 1241(m), 1139(s), 1111(m), 1040(m), 966(m), 851(m), 755(m), 699(m).

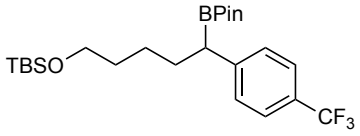


2-{6-chloro-1-[4-(trifluoromethyl)phenyl]hexyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.29), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (163 mg, 83% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.36 (t, *J* = 7.9 Hz, 1H), 1.99 – 1.58 (m, 5H), 1.46 – 1.38 (m, 2H), 1.30 - 1.25 (m, 4H), 1.20 (d, *J* = 4.4 Hz, 11H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.6, 128.4, 127.6 (q, *J* = 34.7 Hz), 125.1 (q, *J* = 5.5 Hz), 124.7 (q, *J* = 265.3 Hz), 83.4, 33.7, 32.6, 32.0, 28.5, 27.9, 24.6, 24.5, 24.5. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -65.0. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.3. GCMS (EI) calculated for [M]+ 390.17, found 390.2. FTIR (neat, cm^{-1}): 3029(m), 2985(s), 2931(s), 2861(s), 1617(s), 1368(m), 1325(s), 1318(m), 1172(m), 1120(s), 1054(m), 1018(s), 967(m), 852(m), 699(m).

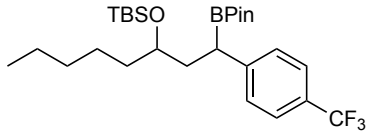


2-{7-bromo-1-[4-(trifluoromethyl)phenyl]heptyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.30), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography, 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (182 mg, 81% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.38 (t, *J* = 6.9 Hz,

2H), 2.36 (t, *J* = 7.9 Hz, 1H), 1.91 – 1.73 (m, 3H), 1.74 – 1.54 (m, 1H), 1.49 – 1.35 (m, 2H), 1.35 – 1.20 (m, 6H), 1.19 (d, *J* = 4.3 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.9, 127.9 (q, *J* = 34.7 Hz), 125.3 (q, *J* = 5.5 Hz), 124.9 (q, *J* = 265.3 Hz), 83.7, 34.0, 32.9, 32.3, 29.1, 28.8, 28.1, 24.9, 24.7, 24.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -65.1. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 31.6. GCMS (EI) calculated for [M]+ 448.14, found 448.2. FTIR (neat, cm^{-1}):2984(m), 2931(s), 2858(s), 1617(s), 1465(m), 1371(s), 1164(m), 1123(s), 1018(s), 967(m), 852(m).

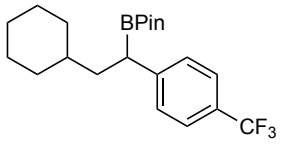


tert-butyldimethyl{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-[4-(trifluoromethyl)phenyl]pentyl]oxy}silane (3.31), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (185 mg, 82% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.36 (t, *J* = 7.9 Hz, 1H), 1.98 – 1.77 (m, 1H), 1.74 – 1.59 (m, 1H), 1.59 – 1.42 (m, 2H), 1.41 – 1.13 (m, 19H), 0.88 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.0, 128.7, 127.3 (q, *J* = 31.1 Hz), 125.3 (q, *J* = 2.5 Hz), 124.7 (q, *J* = 279.3 Hz), 83.6, 63.3, 32.8, 32.4, 26.1, 25.9, 24.9, 24.9, 24.7, 24.7, 18.5, -5.1. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -62.1. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.4. GCMS (EI) calculated for [M]+ 486.29, found 486.3. FTIR (neat, cm^{-1}): 3057(m), 2930(s), 2858(s), 1617(s), 1473(m), 1372(m), 1325(s), 1257(m), 1164(s), 1124(s), 1068(s), 835(m), 699(m).



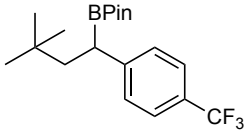
tert-butyl({[1-(4-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-

yl]oxy})dimethylsilane (**3.32**), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by prep TLC, 2% Triethylamine in DCM and was isolated as a clear colorless liquid (199 mg, 76% yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.49 (d, J = 8.0 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 3.57 (dt, *J* = 12.1, 5.9 Hz, 1H), 2.56 (t, *J* = 7.7 Hz, 1H), 1.93 – 1.64 (m, 2H), 1.32 - 1.26 (m, 11H), 1.17 (d, *J* = 3.2 Hz, 12H), 0.88 (s, 9H), -0.01 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 132.2, 129.8 (q, *J* = 32.7 Hz), 127.0 (q, *J* = 3.4 Hz), 126.6, 125.1 (q, *J* = 272.2 Hz), 85.9, 83.4, 38.7, 31.6, 25.9, 25.0, 24.3, 24.0, 23.9, 22.7, 18.4, 14.2, -4.4, -5.0. ^{19}F NMR (470 MHz, Chloroform-*d*) -62.3. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 33.3. GCMS (EI) calculated for [M]+ 514.33, found 499.3. FTIR (neat, cm^{-1}): 3058(m), 2929(s), 2860(s), 1617(s), 1474(m), 1376(m), 1326(s), 1254(m), 1160(s), 1122(s), 1069(s), 835(m), 699(m).

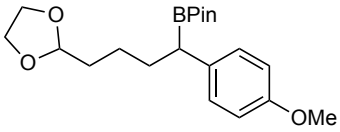


2-{2-cyclohexyl-1-[4-(trifluoromethyl)phenyl]ethyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.33**), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (133 mg, 77% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.52 (t, *J* = 8.1 Hz, 1H), 1.86 – 1.57 (m, 7H), 1.18 (d, *J* = 2.8 Hz, 16H), 0.99 – 0.76 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.2, 128.7, 127.5 (q, *J* = 32.7 Hz), 125.3 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 277.2, Hz), 83.6, 39.9, 36.7, 33.8, 33.0, 26.8, 26.4, 26.4, 24.7, 24.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -64.2. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.5. GCMS (EI) calculated for [M]+ 344.25, found

344.2. FTIR (neat, cm^{-1}): 3051(m), 2980(m), 2924(s), 1617(s), 1448(m), 1381(m), 1324(s), 1163(m), 1123(s), 1068(s), 1018(m), 968(m), 853(m).

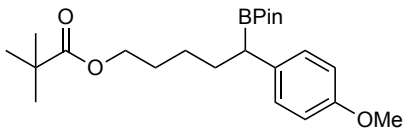


2-[1-(4-methoxyphenyl)-3,3-dimethylbutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.34**), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by prep TLC, 2% Triethylamine in DCM and was isolated as a clear colorless liquid (134 mg, 75% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.46 (dd, *J* = 9.5, 4.1 Hz, 1H), 2.03 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.49 (dd, *J* = 13.3, 4.0 Hz, 1H), 1.14 (s, 12H), 0.90 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 128.5, 127.7 (q, *J* = 266.7 Hz), 127.5 (q, *J* = 34.0 Hz), 125.3 (q, *J* = 3.4 Hz), 120.4, 83.6, 46.5, 31.6, 29.8, 24.7, 24.6, 24.2. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -64.1. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.4. GCMS (EI) calculated for [M]+ 356.21, found 356.2. FTIR (neat, cm^{-1}): 3052(m), 2979(m), 2924(s), 1615(s), 1450(m), 1382(m), 1322(s), 1159(m), 1124(s), 1070(s), 967(m), 853(m).

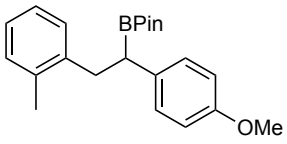


2-[4-(1,3-dioxolan-2-yl)-1-(4-methoxyphenyl)butyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.35), compound was prepared according to reported procedure and was purified by silica gel column chromatography, 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (158 mg, 87% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.79 (t, *J* = 4.9 Hz, 1H), 3.92 – 3.79 (m, 4H), 3.76 (s, 3H), 2.23 (t, *J* = 7.9 Hz, 1H), 1.83 (m, 1H), 1.70 – 1.59 (m, 3H), 1.39 (q, *J* = 7.7 Hz, 2H), 1.19 (d, *J* = 5.9 Hz, 12H). ^{13}C NMR

(126 MHz, Chloroform-*d*) δ 157.4, 135.2, 129.3, 113.8, 104.7, 83.3, 64.9, 55.3, 34.1, 32.9, 24.8, 24.7, 23.9. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.6. GCMS (EI) calculated for [M]+ 362.23, found 361.2. FTIR (neat, cm^{-1}): 3050(m), 2974(s), 2930(s), 2851(s), 1617(s), 1452(m), 1369(m), 1326(s), 1218(m), 1202(m), 1142(m), 1019(m), 911(w), 851(m), 699(m).

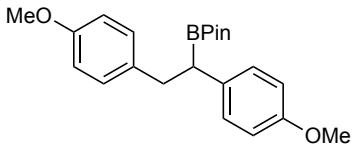


5-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl-2,2-dimethylpropanoate (3.36), compound was prepared according to reported procedure and was purified by silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (159 mg, 79% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.00 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 2.22 (t, *J* = 7.9 Hz, 1H), 1.81 (m, 1H), 1.62 (m, 3H), 1.45 – 1.00 (m, 27H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.5, 157.4, 135.0, 129.2, 113.7, 83.2, 64.3, 55.1, 38.7, 32.4, 28.6, 27.2, 25.5, 24.8, 24.6, 24.6. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.5. GCMS (EI) calculated for [M]+ 404.27, found 404.3. FTIR (neat, cm^{-1}): 3059(m), 2976(s), 2946(s), 2834(m), 1725(s), 1609(s), 1511(m), 1462(m), 1369(s), 1320(s), 1245(s), 1142(s), 1036(m), 967(m), 851(s), 830(m), 756(m).

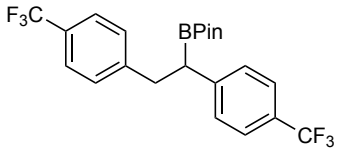


2-[1-(4-methoxyphenyl)-2-(2-methylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.37), compound was prepared according to reported procedure and was isolated as a clear colorless liquid (147 mg, 83% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.09 – 7.03 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 3.85 (s, 3H), 3.12 (dd, *J* = 13.8, 9.9 Hz, 1H), 2.87 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.60 (dd, *J* =

9.9, 6.4 Hz, 1H), 2.28 (s, 3H), 1.13 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.1, 136.4, 135.0, 133.6, 130.1, 129.5, 128.0, 126.0, 125.6, 114.3, 83.5, 70.7, 55.9, 29.8, 24.8, 24.7, 19.5. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.8. GCMS (EI) calculated for [M]+ 352.25, found 352.3. FTIR (neat, cm^{-1}): 2980(s), 2924(s), 2832(m), 1612(s), 1360(m), 1242(s), 1178(m), 1141(m), 1301(s), 970(m), 841(m), 699(m).

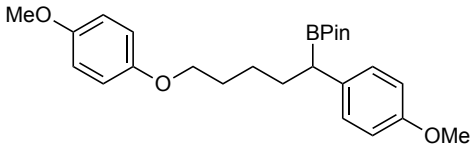


2-[1,2-bis(4-methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.38), compound was prepared according to reported procedure and was purified by silica gel column chromatography 0-10% EtOAc in hexanes and was isolated as a clear colorless liquid (153 mg, 81% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.12 (dd, *J* = 17.3, 8.6 Hz, 4H), 6.79 (dd, *J* = 11.0, 8.5 Hz, 4H), 3.77 (d, *J* = 3.7 Hz, 6H), 3.07 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.87 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.59 (dd, *J* = 9.5, 7.0 Hz, 1H), 1.13 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.8, 157.5, 134.7, 134.1, 129.9, 129.4, 113.8, 113.5, 83.4, 55.3, 55.2, 38.3, 24.9, 24.7, 24.7. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.5. GCMS (EI) calculated for [M]+ 368.22, found 368.2. FTIR (neat, cm^{-1}): 2979(s), 2924(s), 2834(m), 1737(m), 1612(s), 1362(m), 1326(m), 1246(s), 1177(m), 1142(m), 1307(s), 968(m), 841(m), 756(m).

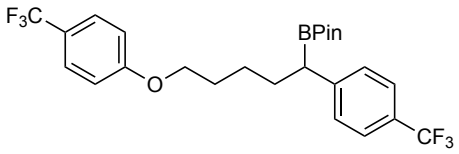


2-{1,2-bis[4-(trifluoromethyl)phenyl]ethyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.39), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography 0-100% DCM in

hexanes, and was isolated as a clear colorless liquid (147 mg, 83% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 – 7.44 (m, 1H), 7.39 (m, 4H), 7.23 – 7.11 (m, 4H), 3.12 (dd, *J* = 13.7, 8.9 Hz, 1H), 2.93 (dd, *J* = 20.6, 13.1 Hz, 1H), 2.63 (t, *J* = 8.2 Hz, 1H), 1.03 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.3, 145.4, 129.2, 128.7, 128.6 (q, *J* = 311.2), 128.3 (q, *J* = 32.3 Hz), 128.1 (q, *J* = 31.0 Hz), 125.5 (q, *J* = 3.8 Hz), 125.2 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 349.3 Hz), 84.0, 38.3, 34.5, 24.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -65.2, -65.3. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.5. GCMS (EI) calculated for [M]+ 444.28, found 444.3. FTIR (neat, cm^{-1}): 2984(m), 2939(m), 1616(s), 2372(w), 1325(s), 1164(m), 1121(s), 1067(s), 1017(m), 848(m).

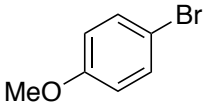


2-[5-(4-methoxyphenoxy)-1-(4-methoxyphenyl)pentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.40), compound was prepared according to reported procedure and was purified by silica gel chromatography 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (179 mg, 84% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.82 (s, 4H), 3.96 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 2.23 (t, *J* = 7.9 Hz, 1H), 1.91 – 1.73 (m, 1H), 1.71 – 1.51 (m, 2H), 1.43 – 1.23 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.5, 153.9, 153.3, 130.4, 120.1, 115.6, 114.8, 113.8, 83.4, 68.4, 55.8, 55.6, 37.9, 29.1, 24.6, 24.2, 24.0, 21.3. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 32.4. GCMS (EI) calculated for [M]+ 426.26, found 426.3. FTIR (neat, cm^{-1}): 3055(m), 2924(s), 2918(s), 2874(m), 1617(s), 1364(m), 1322(m), 1244(s), 1177(m), 1142(m), 1303(s), 966(m), 841(m), 756(m). 699(m).

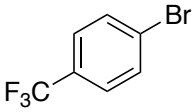


4,4,5,5-tetramethyl-2-{5-[4-(trifluoromethyl)phenoxy]-1-[4-(trifluoromethyl)phenyl]pentyl}-1,3,2-dioxaborolane (3.41), compound was prepared according to reported procedure using IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu, and was purified by silica gel chromatography 0-100% DCM in hexanes, and was isolated as a clear colorless liquid (171 mg, 82% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 8.6, 3.7 Hz, 45H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 3.95 (t, *J* = 6.3 Hz, 3H), 2.40 (t, *J* = 7.9 Hz, 1H), 2.03 – 1.84 (m, 1H), 1.77 (m, 3H), 1.44 (q, *J* = 7.7 Hz, 2H), 1.20 (d, J = 5.2 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.5, 147.5, 128.6, 127.6 (q, J = 32.8), 126.8 (q, J = 3.8 Hz), 125.9 (q, J = 277.1 Hz), 125.2 (q, J = 3.8 Hz), 124.5 (q, J = 272.2 Hz), 122.6 (q, J = 32.8 Hz), 114.4, 83.6, 67.9, 32.0, 29.0, 25.5, 24.6, 24.5. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -64.3, -65.0. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 31.7. GCMS (EI) calculated for [M]+ 502.21, found 502.2. FTIR (neat, cm^{-1}): 3054(m), 2980(s), 2937(s), 2872(m), 1617(s), 1372(m), 1326(s), 1259(m), 1162(m), 1111(s), 1068(m), 836(m).

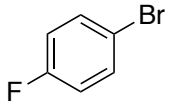
3.4.5 *Aryl Bromide Starting Materials*



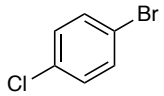
4-bromoanisole (3.2) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



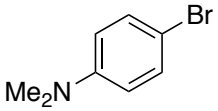
4-bromobenzotrifluoride (3.43) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



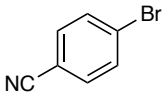
1-bromo-4-fluorobenzene (3.44) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



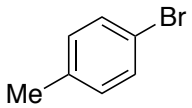
1-bromo-4-chlorobenzene (3.45) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



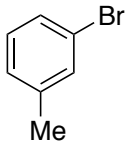
4-bromo-N,N-dimethylaniline (3.46) was purchased from Oakwood Chemicals and used without purification.



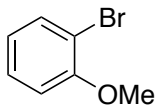
4-bromobenzonitrile (3.47) was purchased from Millipore Sigma and used without purification.



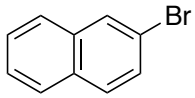
4-bromotoluene (3.48) was purchased form Alfa Aesar and using without purification.



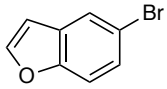
3-bromotoluene (3.49) was purchased form TCI America and distilled over calcium hydride under reduced pressure before use.



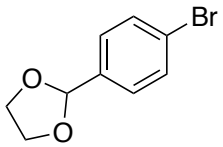
2-bromoanisole (3.50) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



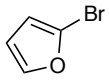
2-bromonaphthalene (3.51) was purchased from Ark-Pharm and used without purification.



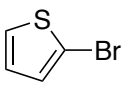
2-bromobenzofuran (3.52) was purchased from Ark-Pharm and used without further purification



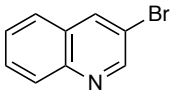
1-bromo-4-phenyl-1,3-dioxolane (3.53) was purchased from Ark-Pharm and distilled over calcium hydride under reduced pressure before use.



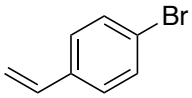
2-bromofuran (3.54) was purchased from TCI chemicals and distilled over calcium hydride under reduced pressure before used.



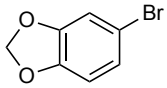
2-bromothiophene (3.55) was purchased from Combi-Blocks and distilled over calcium hydride under reduced pressure before use.



3-bromoquinoline (3.56) was purchased form Millipore Sigma and distilled over calcium hydride under reduced pressure before use.

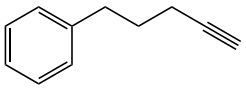


4-bromostyrene (3.57) was purchased from TCI America and degassed before use.

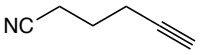


4-Bromo-1,2-(methylenedioxy)benzene (3.58) was purchased from Millipore Sigma and distill over calcium hydride under reduced pressure before use.

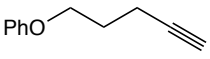
3.4.6 *Alkyne Starting Materials*



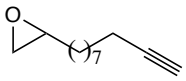
5-phenyl-1-pentyne (3.1) was purchased from GFS Chemical and distilled over calcium hydride under reduced pressure before use.



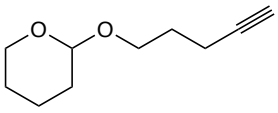
hex-5-ynenitrile (3.59) was purchased from Oakwood Chemical and distilled over calcium hydride under reduced pressure before use.



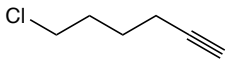
(pent-4-yn-1-yloxy)benzene (3.60) was prepared according to a known procedure and has been previously characterized. [69]



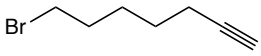
2-(dec-9-yn-1-yl)oxirane (3.61) was prepared according to a known procedure and has been previously characterized.[24]



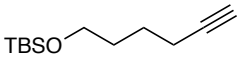
2-(pent-4-yn-1-yloxy)tetrahydra-2*H*-pyran (3.62) has been previously characterized and spectral data match literature values.[70]



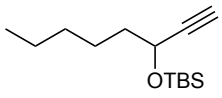
6-chlorohex-1-yne (3.63) was purchased from TCI America and distilled over calcium hydride under reduced pressure before use.



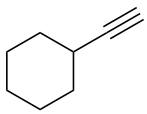
7-bromohept-1-yne (3.64) was prepared according to a known procedure and has been previously characterized.[43]



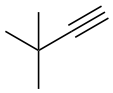
tert-butyldimethyl(pent-4-yn-1-yloxy)silane (3.65) was prepared according to a known procedure and has been previously characterized.[71]



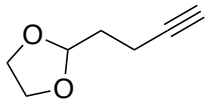
tert-butyldimethyl(oct-1-yn-3-yloxy)silane (3.66) was prepared according to a known literature procedure and has been previously characterized.[72]



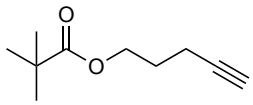
ethynylcyclohexane (3.67) was purchased from Milipore Sigma and distilled over calcium hydride under reduced pressure before use.



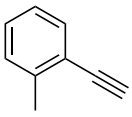
3,3-dimethylbut-1-yne (3.68) was purchased from Milipore Sigma and distilled over calcium hydride under reduced pressure before use.



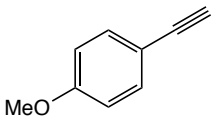
2-(but-3-yn-1-yl)-1,3-dioxolane (3.69) was synthesized according to a known literature procedure and has been previously characterized.[73]



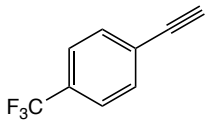
pent-4-yn-1-yl 2,2-dimethylpropanoate (3.70) was synthesized according to a known literature procedure and has been previously characterized.[74]



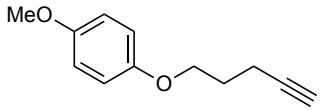
1-ethynyl-2-methylbenzene (3.71) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



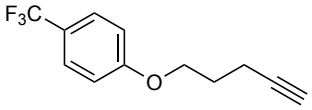
1-ethynyl-4-methoxybenzene (3.72) was purchase from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



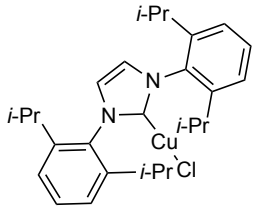
1-ethynyl-4-(trifluoromethyl)benzene (3.73) was purchased from Millipore Sigma and distilled over calcium hydride under reduced pressure before use.



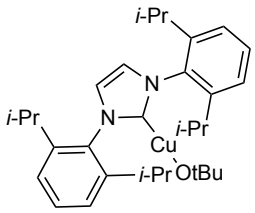
1-methoxy-4-(pent-4-yn-1-yloxy)benzene (3.74) was synthesized according to a known literature procedure and has been previously characterized.[75]



1-(pent-4-yn-1-yloxy)-4-(trifluoromethyl)benzene (**3.75**) was synthesized according to a modified procedure.[75] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.60 – 7.44 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.42 (td, *J* = 6.9, 2.7 Hz, 2H), 2.10 – 1.92 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 127.0 (q, *J* = 3.9 Hz), 124.7 (q, *J* = 270.9 Hz), 123.0 (q, *J* = 32.6 Hz), 114.6, 83.2, 69.2, 66.5, 28.1, 15.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ -64.4.



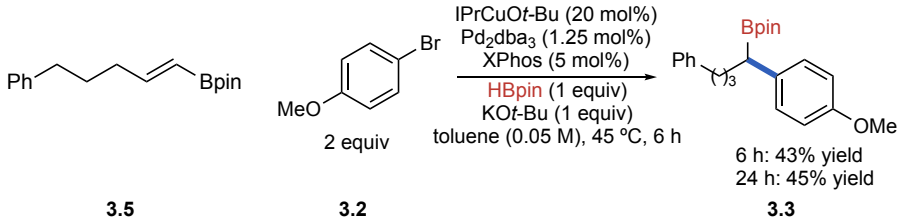
{1-[2,6-bis(propan-2-yl)phenyl]-3-[2-methyl-6-(propan-2-yl)phenyl]-2,3-dihydro-1H-imidazol-2-yl}(chloro)copper (**3.76**), was synthesized according to a known literature procedure and has been previously characterized.[76]



{1-[2,6-bis(propan-2-yl)phenyl]-3-[2-methyl-6-(propan-2-yl)phenyl]-2,3-dihydro-1H-imidazol-2-yl}(tert-butoxy)copper (**3.77**), was synthesized according to a known literature procedure and has been previously characterized.[77]

3.4.7 *Analysis of Potential Catalytic Intermediates (Scheme 3.6)*

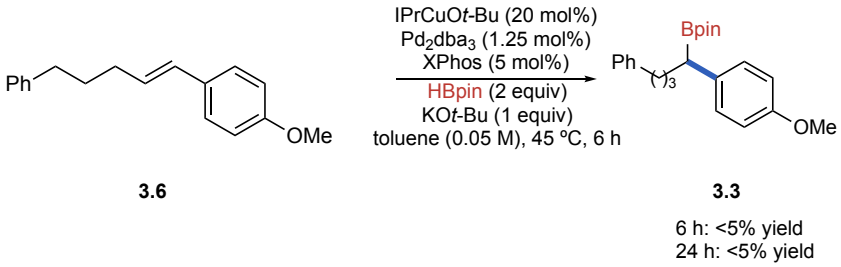
Alkenyl Bpin (**3.5**)



Scheme 3.8. Use of Alkenyl Bpin as Potential Catalytic Intermediate

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, KO*t*-Bu (6.1 mg, 0.050 mmol, 1 equiv), IPrCuO*t*-Bu (5.3 mg, 0.01 mmol, 0.20 equiv), HBpin (6.4 mg, 0.05 mmol, 1.0 equiv), toluene (1 mL) and alkenyl Bpin (**3.5**) (13.6 mg, 0.05 mmol, 1.0 equiv). The reaction mixture was stirred at 45 °C for 1 min. To this reaction mixture was added Pd_2dba_3 (0.6 mg, 0.001 mmol, 0.0125 equiv), XPhos (1.2 mg, 0.0025 equiv) and 4-bromoanisole (**3.2**) (18.7 mg, 0.1 mmol, 2.0 equiv) and the reaction mixture was vigorously stirred at 45 °C. After both 6 h and 24 h a 60 µL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC.

E-styrene (**3.6**)



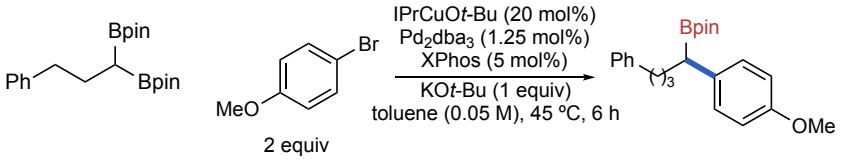
3.6 **3.3**

6 h: <5% yield
24 h: <5% yield

Scheme 3.9. Use of *E*-styrene as Potential Catalytic Intermediate

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, KO*t*-Bu (12.2 mg, 0.10 mmol, 2 equiv), IPrCuO*t*-Bu (5.3 mg, 0.01 mmol, 0.20 equiv), HBpin (12.8 mg, 0.10 mmol, 2.0 equiv), toluene (1 mL) and *E*-styrene (**3.6**) (12.6 mg, 0.05 mmol, 1.0 equiv). The reaction mixture was stirred at 45 °C for 1 min. To this reaction mixture was added Pd_2dba_3 (0.6 mg, 0.001 mmol, 0.0125 equiv) and XPhos (1.2 mg, 0.0025 equiv) and the reaction mixture was vigorously stirred at 45 °C. After both 6 h and 24 h a 60 µL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC.

Alkyl diboronate (**3.7**)



3.7 **3.2** **3.3**

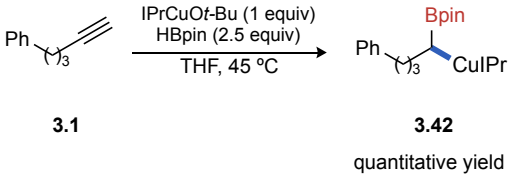
6 h: <5% yield
24 h: <5% yield

Scheme 3.10. Use of Alkyl Diboronate as Potential Catalytic Intermediate

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, KO*t*-Bu (6.1 mg, 0.05 mmol, 1 equiv), IPrCuO*t*-Bu (5.3 mg, 0.01 mmol, 0.20 equiv), toluene (1 mL) and alkyl diboronate (**7**) (18.6 mg, 0.05 mmol, 1.0 equiv). The reaction mixture was stirred at 45 °C for 1 min. To this reaction mixture was added Pd_2dba_3 (0.6 mg, 0.001 mmol, 0.0125 equiv), XPhos (1.2 mg, 0.0025 mmol, 0.05 equiv) and 4-bromoanisole (**3.2**) (18.7 mg, 0.1 mmol, 2.0 equiv) and the reaction

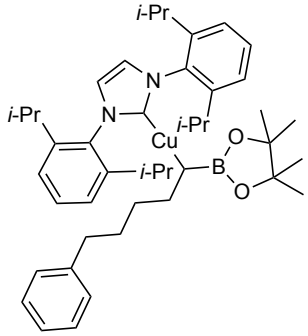
mixture was vigorously stirred at 45 °C. After 6 h and 24 h a 60 μL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC.

3.4.8 *Synthesis of Heterobimetallic Complex (Scheme 3.6)*



Scheme 3.11. Stoichiometric Synthesis of Heterobimetallic Intermediate

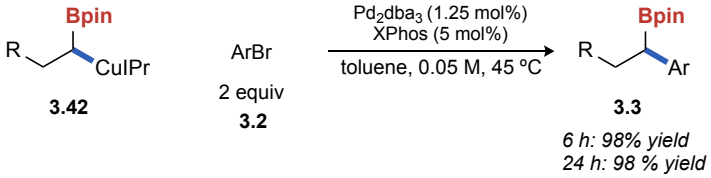
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, IPrCuO*t*-Bu (131.6 mg, 0.250 mmol, 1.0 equiv) and THF (1 mL). To this reaction mixture was added HBpin (80.0 mg, 0.625 mmol, 2.50 equiv) and 5-phenyl-1-pentyne (**3.1**) (37.9 mg, 0.263 mmol, 1.05 equiv) and the reaction mixture was vigorously stirred at 45 °C until the orange color had disappeared. The reaction was removed from hot plate and pentane was carefully layered over the reaction mixture and then placed in a -35 °C freezer overnight. Filtration with cold pentane yielded the desired product as a white solid (180.3 mg, 99% yield).



{1,3-bis[2,6-bis(propan-2-yl)phenyl]-2,3-dihydro-1H-imidazol-2-yl}[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]copper (**3.42**). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 - 7.14 (m, 15H), 6.30 (s, 2H), 2.71 – 2.60 (m, 6H), 2.20 – 2.11 (m, 1H), 1.90 - 1.86 (m, 1H),

1.69 (p, *J* = 7.7 Hz, 2H), 1.52 (t, *J* = 6.0 Hz, 12H), 1.16 (m, 12H), 1.12 (s, 6H), 1.08 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.9, 145.9, 135.5, 130.4, 128.9, 125.4, 124.2, 124.2, 122.2, 120.3, 117.6, 79.7, 37.7, 36.7, 32.7, 29.1, 29.0, 28.8, 25.5, 25.3, 25.1, 23.8. ^{11}B NMR (96 MHz, Chloroform-*d*) δ 28.4. LCMS (ESI) calculated for [M+]: 726.3, found: 726.7.

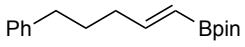
3.4.9 *Palladium-Catalyzed Cross Coupling of Heterobimetallic Complex and ArBr (Scheme 3.6)*



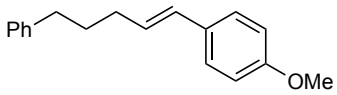
Scheme 3.12. Stoichiometric Coupling of ArBr with Heterobimetallic Complex

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, hetereobimetallic complex (**3.42**) (36.3 mg, 0.05 mmol, 1.0 equiv), XPhos (1.2 mg, 0.0025 mmol, 0.05 equiv) and 4-bromoanisole (**3.2**)(18.7 mg, 0.1 mmol, 2.0 equiv) and the reaction mixture was vigorously stirred at 45 °C. After 6 h and 24 h a 60 µL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC.

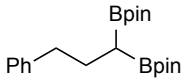
Characterization of Mechanistic Compounds



4,4,5,5-tetramethyl-2-[(1E)-5-phenylpent-1-en-1-yl]-1,3,2-dioxaborolane (**3.5**), compound was synthesized according to known literature procedure and has been previously characterized.[78] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 – 7.22 (m, 3H), 7.21 – 7.12 (m, 3H), 6.65 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.46 (d, *J* = 18.0 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.28 – 2.12 (m, 2H), 1.76 (m, 2H), 1.27 (s, 12H).

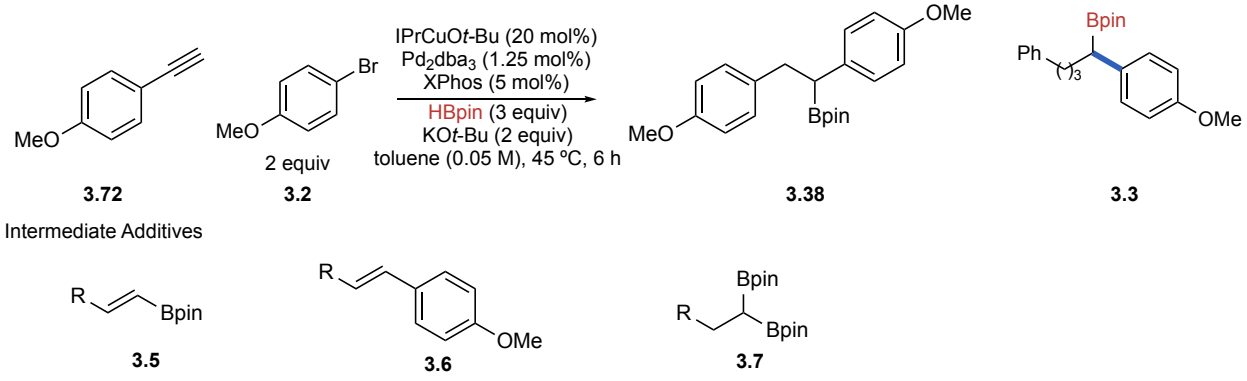


1-methoxy-4-[(1E)-5-phenylpent-1-en-1-yl]benzene (**3.6**), compound was synthesized according to known literature procedure and has been previously characterized.[79] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 – 7.12 (m, 8H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.80 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.30 – 2.18 (m, 2H), 1.80 (p, *J* = 7.5 Hz, 2H).



4,4,5,5-tetramethyl-2-[5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]-1,3,2-dioxaborolane (**3.7**), compound was synthesized according to known literature procedure and has been previously characterized.[39] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.05 (m, 7H), 2.70 – 2.53 (m, 2H), 1.85 (q, *J* = 7.8 Hz, 2H), 1.23 (s, 25H), 0.81 (t, *J* = 7.9 Hz, 1H).

3.4.10 *Evaluation of Catalytic Intermediates in Catalytic Reaction*



Scheme 3.13. Subjection of Potential Catalytic Intermediates to Reaction Conditions

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, KO*t*-Bu (12.2 mg, 0.10 mmol, 2.0 equiv), IPrCuO*t*-Bu (5.3 mg, 0.01 mmol, 0.20 equiv), HBpin (19.2 mg, 0.15 mmol,

3.0 equiv), toluene (1 mL) and 4-ethynylanisole (**3.72**) (6.6 mg, 0.05 mmol, 1.0 equiv). The reaction mixture was stirred at 45 °C for 1 min. To this reaction mixture was added Pd_2dba_3 (0.6 mg, 0.001 mmol, 0.0125 equiv), XPhos (1.2 mg, 0.0025 equiv) and 4-bromoanisole (**3.2**) (18.7 mg, 0.1 mmol, 2.0 equiv) and either alkenyl Bpin (**3.5**), *E*-styrene (**3.6**) or alkyl diboronate (**3.7**) (0.05 mmol, 1.0 equiv). The reaction mixture was vigorously stirred at 45 °C. After 6 h a 60 μL was taken and pushed through a plug of silica with 1.5 mL EtOAc and analyzed by GC.

Table 3.12. Catalytic Intermediate Viability

Entry	Additive	Yield 3.38	Yield 3.3
1	Alkenyl Bpin (**3.5**)	28	33
2	*E*-styrene (**3.6**)	31	0
3	Alkyl diboronate (**3.7**)	42	0

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VITA

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