Transition Metal Catalyzed Functionalization of Alkynes

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Abstract

Transition Metal Catalyzed Functionalization of Alkynes

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Alkynes are important building blocks of chemistry. Here we have described four new transition metal catalyzed transformations of alkynes. These transformations generate new C–C σ bonds that are fundamental in organic synthesis. The first is a copper-catalyzed anti-Markovnikov hydroallylation of alkynes. This reaction generates 1,4 or skipped dienes and makes use in-situ generated copper hydride intermediate to achieve high *E*-selectivity. Unsymmetrical internal alkynes were also utilized in this method. Selectivity was achieved through inductive polarization of the triple bond by placing an electron withdrawing heteroatoms at the propargyl position of the alkyne.

Following this, the development of a photoinduced copper-catalyzed alkylation of terminal alkynes with alkyl iodides is discussed. The reaction proceeds though copper acetylide intermediate which is activated by blue light that facilitates the desired coupling. It provides access to challenging dialkyl internal alkynes and serves as an alternative to the challenging Sonogashira coupling. Key to the success of the reaction was the use of terpyridine ligand to suppress the undesired light-promoted polymerization of the starting material.

In the third chapter, a new method of hydroalkylation of terminal alkynes is described that generates disubstituted *E*-alkenes. The reaction makes use of a copper catalysts and a nickel co-catalyst to couple terminal alkynes and alkyl iodides. Such use of alkyl iodides expands the scope of hydroalkylation method Mechanistic study reveals that copper catalyst is responsible for the high selectivity of the transformation, whereas nickel catalysts promote the important cross-coupling step with alkyl iodide.

Finally, the fourth chapter describes a new hydroalkylation reaction that generates E-alkenyl carbonyl species. The reaction is achieved via copper hydride addition to alkynes followed by the coupling of α-bromocarbonyls. Mechanistic study reveals a single electron transfer process is responsible for the desired cross coupling of alkenylcopper intermediate.

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LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
B	Base
Bn	benzyl
Boc	tert-butyloxycarbonyl
C	Celsius
cat.	catalyst
CPCM	conductor-like polarizable continuum model
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIAD	Diisopropyl azodicarboxylate
DMEDA	1,2-Dimethylethylenediamine
DMF	dimethylformamide
dtbpy	4,4’-Di-tert-butyl-2,2’-dipyridine
E+	electrophile
EI	electron ionization
equiv	equivalents
ESI	electrospray ionization

Et	ethyl
FID	flame ionization detector
FTIR	Fourier transform infrared

FTIR band abbreviations

s	strong
m	medium
w	weak
br	broad

GC	gas chromatography
GPC	gel permeation chromatography
h	hour
Hex	hexanes
Hz	hertz
ICP	inductively coupled plasma
Ipr	1,3-Bis-(2,6-diisopropylphenyl)imidazolium
i-Pr	isopropyl
IR	infrared
KIE	kinetic isotope effect
L	ligand
LED	light emitting diode
M	metal
Me	methyl
min	minutes

mol	mole
MS	mass spectrometry
n-Bu	butyl
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance

NMR splitting pattern abbreviations

s	singlet
d	doublet
t	triplet
q	quartet
p	pentet
h	heptet
m	multiplet
br	broad

ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethanesulfonate
Ph	phenyl
pin	pinacol
PMHS	polymethylhydrosiloxane
ppb	parts per billion
ppm	parts per million
PyBox	pyridine bisoxazoline
Rf	retention factor

SCE	saturated calomel electrode
S_E2	substitution electrophilic bimolecular
SET	single electron transfer
SIPr	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium
S_N2	substitution nucleophilic bimolecular
TBAF	tetrabutylammoium fluoride
TBS	tert-butyldimethylsilyl
t-Bu	tert-butyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxy
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMB	1,3,5-trimethoxybenzne
TMDSO	tetramethyldisiloxane
TMPDA	N,N,N’,N’-Tetramethyl-p-phenylenediamine
TMS	Tetramethylsilane
TMS	trimethylsilyl
tpy	2,2':6',2"-terpyridine
tpy’	4,4',4"-tri-tert-butyl-2,2':6',2"-terpyridine
Tri	2,4-bis[2,6-bis(1-methylethyl)phenyl]-2,4-dihydro-5-phenyl-3H-1, 2,4-Triazol-3-ylidene
Ts	p-poluenesulfonyl
Xantphos	4,5-bis(dipheylphosphino)-9,9-dimethylxanthe

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DEDICATION

To my Maa, Baba and all the teachers.

Chapter 1.

CATALYTIC ANTI-MARKOVNIKOV HYDROALLYLATION OF TERMINAL AND FUNCTIONALIZED INTERNAL ALKYNES

Portions of this chapter as well as figures, schemes, and tables were adapted or reproduced from the following manuscript, with permission from Mailig, M.[†]; Hazra, A.[†]; Armstrong, M. K.; Lalic, G. "Catalytic Anti-Markovnikov Hydroallylation of Terminal and Functionalized Internal Alkynes: Synthesis of Skipped Dienes and Trisubstituted Alkenes." *J. Am. Chem. Soc.* **2017**, *139*, 6969-6977. Copyright 2017 American Chemical Society.

1.1 INTRODUCTION

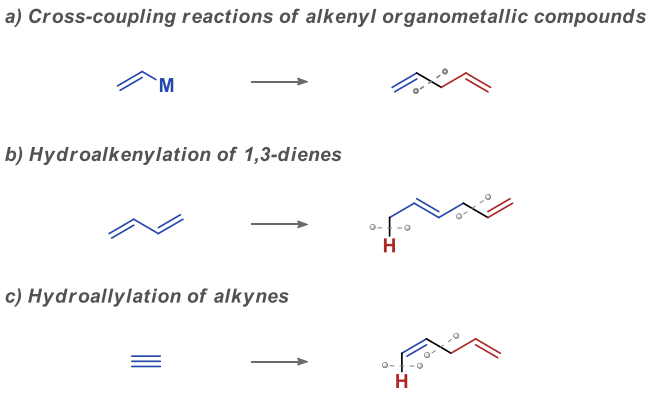
Skipped or 1,4-dienes are an important class of compounds found in many natural products[1]. The importance of this class of compounds and the challenges associated with their preparation[2] have provided a strong incentive for the development of new methods for their synthesis. Traditionally, stoichiometric methods for the synthesis of alkenes, such as Julia[3], Takai[4], or Wittig[5] olefination reactions, have been used to prepare skipped dienes. In 2007, Micalizio et al. reported an excellent stoichiometric reaction specifically designed for the synthesis of skipped dienes[6–8]. This reaction involves titanium-mediated coupling of allylic alcohols with alkynes

Over the last ten years, the focus has mostly been on the development of new catalytic reactions that yield skipped dienes. These catalytic reactions generally belong to one of the three major classes: 1) Cross-coupling reactions of alkenyl organometallic reagents with electrophiles, 2) hydroalkenylation of 1,3-dienes, and 3) hydroallylation of alkynes (**Scheme 1.1**).

Transition metal catalyzed cross-coupling reactions of various organometallic reagents with a variety of electrophiles have been used to access skipped dienes[9–15]. The most notable examples of this approach are catalytic enantioselective reactions of alkenylboron[16,17] and alkenylaluminum[18–20] compounds with allylic electrophiles. Another excellent method, developed by Sigman et al., is based on a variation of the cross-coupling approach, and involves palladium-catalyzed reaction of 1,3-butadiene with enol triflates and alkenylboron compounds[2].

Hydroalkenylation of 1,3-dienes also provides skipped dienes and can be accomplished using Co[21–24], Ni[25], or Fe[26] catalysts. A major advantage of hydroalkenylation methods over cross-coupling reactions is that substrates do not need to be pre-functionalized. Furthermore, this approach allows the preparation of highly substituted skipped dienes, which may be difficult to prepare using other methods. One drawback of the hydroalkenylation approach is that a mixture of diastereoisomers is often obtained[22], although high diastereoselectivity can be achieved[26].

Scheme1.1 General Strategy for the synthesis of skipped dienes

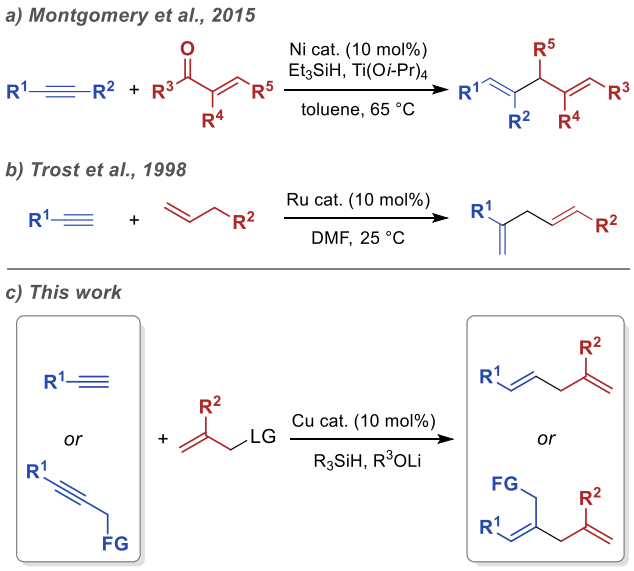


Finally, skipped dienes can also be prepared by hydroallylation of alkynes[27–30]. While less common than cross-coupling and hydroalkenylation reactions, hydroallylation methods have proven to be highly effective. Recently, Montgomery et al. reported an excellent method for the synthesis of skipped dienes shown in **Scheme 1.2a**[30]. In this formal hydroallylation reaction,

alkynes are reductively coupled with enones in the presence of a nickel catalyst, a silane, and a stoichiometric amount of Ti(O*i*-Pr)$_4$. Excellent regio- and diastereoselectivity was observed with a wide range of substrates, together with a good functional group compatibility. The reaction works particularly well with symmetrical internal alkynes and alkyl aryl alkynes.

Several methods for Markovnikov hydroallylation of alkynes are known. The most general is the ruthenium-catalyzed hydroallylation of terminal alkynes reported by Trost et al. in 1998 (**Scheme 1.2b**)[27,28]. The reaction proceeds with excellent Markovnikov selectivity (with respect to the alkyne) and has exceptional substrate scope and functional group compatibility. This method has been successfully used with complex substrates and as a key step in the synthesis of natural products[27,31]. Lee and Trost have later shown that good regioselectivity can also be obtained using boro[32]-, silyl[33]-, and alkynyl[34]-substituted internal alkynes. Overall, this reaction is one of the most well-developed and broadly applicable methods for the synthesis of skipped dienes[35,36].

Scheme 1. 2 Hydroallyalation of alkynes for the synthesis of Skipped dienes

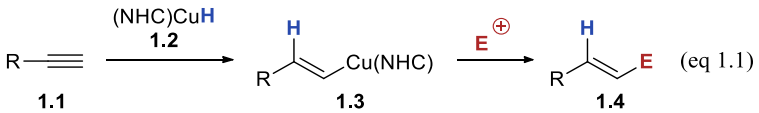


In this article, we describe the development of a direct hydroallylation of terminal alkynes (**Scheme 1.2c**) with regioselectivity opposite from the Markovnikov selectivity of Trost's method. We also demonstrate that nonsymmetrical dialkyl-substituted alkynes can be used as substrates to provide trisubstituted alkene products with excellent regioselectivity. This class of substrates has not been previously used in the synthesis of skipped dienes, or in any other copper-catalyzed hydrofunctionalization reaction. We demonstrate that hydroallylation can be used in synthesis of complex trisubstituted alkenes. Finally, we also describe our investigation of the reaction mechanism, which suggests a new role of the alkoxy turnover reagent and provides a new insight into the structure, stability, and reactivity of the β-functionalized alkenyl copper complexes.

1.2 RESULTS AND DISCUSSION

1.2.1 *Reaction Development*

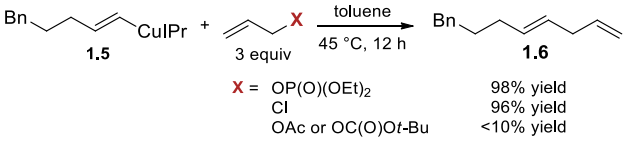
In the last several years, our group has focused on the development of a general approach to the hydrofunctionalization of alkynes. Several groups, including ours, have shown that syn-diastereospecific hydrocupration of alkynes, followed by electrophilic functionalization of the alkenyl copper intermediate can be used to accomplish a range of hydrofunctionalization reactions with excellent anti-Markovnikov regioselectivity and *E* diastereoselectivity (eq 1). Using this approach, Tsuji et al. developed a catalytic hydrocarboxylation of alkynes[37], while our group developed catalytic methods for the hydrobromination[38] and hydroalkylation[39,40] of alkynes. We anticipated that the same approach could be used to accomplish an anti-Markovnikov hydroallylation of alkynes.



(eq 1.1)

Stoichiometric experiments shown in **Scheme 1.3** demonstrate that both allyl chloride and allyl phosphate are competent electrophiles in a reaction with isolated alkenyl copper complex **1.5**.

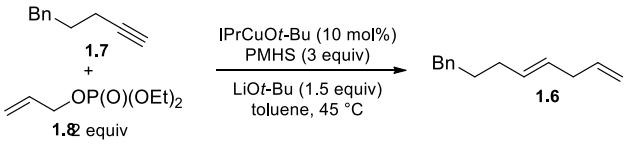
Scheme 1.3 Stoichiometric allylation of an alkenyl copper complex



Using these results as a starting point we were able to develop a method for the catalytic hydroallylation of terminal alkynes, shown in **Table 1.1**. The best results were obtained using IPrCuO*t*-Bu as a catalyst, polymethylhydrosiloxane (PMHS) as a hydride source, and LiO*t*-Bu as a turnover reagent. The reaction is performed in toluene and is completed after 16 h at 45 °C. During our efforts to identify the best conditions for the hydroallylation reaction, we made several observations summarized in **Table 1.1**.

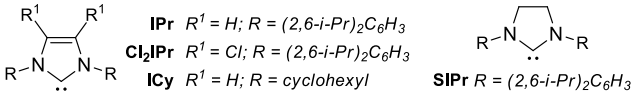
Even though both allyl chloride and allyl phosphate gave high yields in the stoichiometric reaction with the alkenyl copper complex, in the catalytic reaction, allyl phosphate provided a significantly higher yield of the desired product (entries 1 and 2). The less reactive electrophiles, such as allyl acetate and allyl carbonate did not provide the desired product. NHC copper(I) *tert*-butoxide performed better than NHC copper(I) chloride as a catalyst precursor (entries 1 and 3). As in other catalytic transformations that involve hydrocupration of alkynes[38–41], we found that copper complexes supported by IPr or SIPr ligands are the most effective catalysts. Closely related ligands shown in entries 5, 6, and 7 gave significantly lower yields of the desired product. Although the exact reason for the superior performance of these two ligands is not clear, we suspect that it is related to the lower aggregation and higher stability of copper hydride complexes supported by these sterically hindered ligands.

Table 1.1 Reaction Development



entry	*change from standard conditions*	*yield*[a]
1.	none	89%[b]
2.	allyl chloride as an electrophile	44%
3.	IPrCuCl as catalyst	69%
4.	SIPrCuCl as catalyst	59%
5.	Cl_2IPrCuCl as catalyst	31%
6.	ICyCuCl as catalyst	42%
7.	IPr*CuCl as catalyst	36%
8.	chlorobenzene	88%
9.	THF	76%
10.	dioxane	72%
11.	isooctane	88%
12.	$(Me_2HSi)_2O$ instead of PMHS	86%
13.	*t*-Bu_2SiH_2 instead of PMHS	28%
14.	$(EtO)_3SiH$ instead of PMHS	16%
15.	Et_3SiH instead of PMHS	0%

[a] GC yields are reported. All reactions performed on 0.1 mmol scale.
[b] Yield of the pure isolated product is reported.



IPr* R^1 = H; R = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)

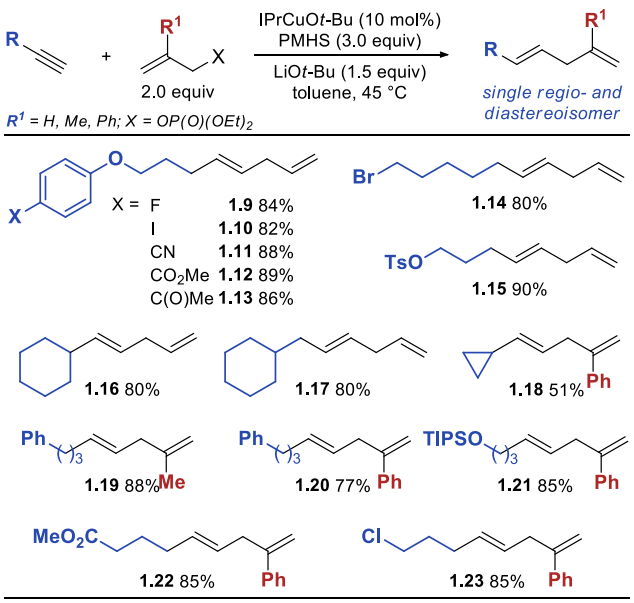
Finally, a wide range of copper complexes supported by phosphine ligands were completely ineffective as catalysts in the hydroallylation reaction (see Supporting Information for details). Surprisingly, the catalytic system commonly used in hydrofunctionalization of styrenes, including hydroallylation, was also completely ineffective[42]. This observation further supports our observations that the NHC-copper complexes are uniquely effective in hydrofunctionalization of alkynes. High yields in the hydroallylation reaction were obtained in both aromatic hydrocarbon solvents, such as toluene and chlorobenzene, and in ethereal solvents such as THF and 1,4-dioxane (entries 8, 9, and 10). Surprisingly, isooctane was also an effective solvent (entry 11). Silane choice proved to be essential for the success of the reaction. PMHS and $(Me_2HSi)_2O$ both performed well (entries 1 and 12). However, highly reactive $(EtO)_3SiH$ (entry 14) gave significantly lower yield of the desired product, while a variety of other di and trialkyl substituted silanes also provided very little of the desired hydroallylation product (entries 13 and 15).

1.2.2 *Substrate Scope*

Hydroallylation of terminal alkyne:

Hydroallylation of a wide range of terminal alkynes can be accomplished using the optimized reaction conditions (**Table 1.2**). In all cases, a single regioisomer and *E*-diastereoisomer of the desired product is obtained. The observed selectivity is in line with the results of the stoichiometric hydrocupration of terminal alkynes, which is syn-diastereospecific and selective for the anti-Markovnikov product[41]. Furthermore, the reaction can be performed in the presence of a wide range of functional groups. Electrophilic carboxylic acid derivatives, such as esters and nitriles, are compatible with the reaction conditions (compounds **1.11** and **1.12**). Surprisingly, ketones are also tolerated, despite reports of rapid reduction of ketones under similar reaction conditions (compound **1.13**)[43,44]. Alkyl electrophiles such as alkyl chlorides, bromides, and tosylates (compounds **1.14**, **1.15**, **1.23**), as well as aryl fluoride and aryl iodide (compounds **1.9** and **1.10**), are also compatible with the reaction conditions and provide functionalized skipped dienes.

Table 1.2 Substrate Scope

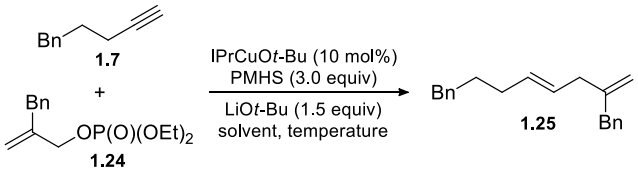


[a] All reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported.

Variation of the electrophilic components of the hydroallylation reaction proved to be significantly more challenging. Substitution at the central carbon of the allylic electrophile led to a dramatic decrease in reactivity. In fact, from a range of 2-substituted allylic electrophiles we explored, only phenyl- and methyl-substituted substrates provided the desired products in significant yields under the standard reaction conditions described in Table 1. These two electrophiles reacted with a variety of alkynes, as shown in Table 2 (entries **1.18**-**1.23**).

The failure to obtain the desired product with substituted phosphates led us to explore conditions that in our preliminary reaction optimization provided promising results. We found that isooctane gave results superior to those obtained in toluene (**Table 1.3, entry 3**). Surprisingly, while increasing the reaction temperature to 60 °C marginally effected the yield of the desired product, a further increase to 90 °C resulted in the formation of the desired product in 90% yield (entries 4 and 5). A similar increase in temperature with toluene as the solvent was not productive (entry 2).

Table 1.3 Solvent and temperature effects in reactions with 2-substituted allylic electrophiles[a]

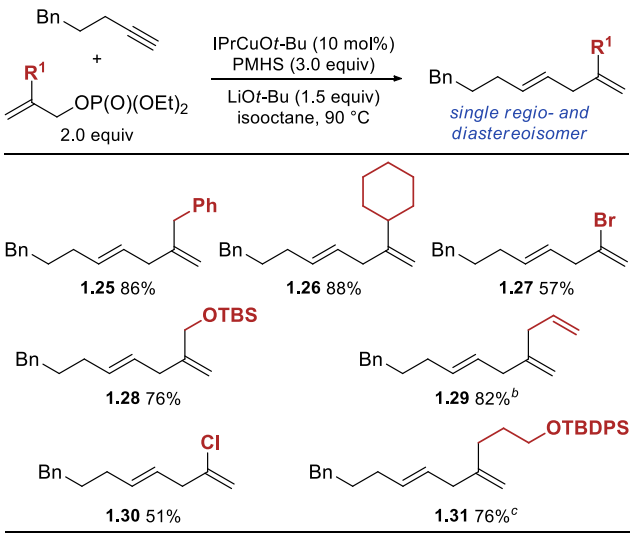


entry	solvent	temperature	yield[a]
1.	toluene	45 °C	15%
2.	toluene	90 °C	22%
3.	isooctane	45 °C	68%
4.	isooctane	60 °C	63%
5.	isooctane	90 °C	90%

[a] GC yields at the full conversion of **7** are reported.

Using the reaction conditions shown in entry 5 of **Table 1.3**, we were able to perform hydroallylation reaction with various substituted allylic phosphates (**Table 1.4**). Sterically hindered substituents and functionalized alkyl substituents are well-tolerated (compounds **1.26**, **1.28**, and **1.31**). Chloro- and bromo-substituted electrophiles provide functionalized products which can be further derivatize (compounds **1.27** and **1.30**).

Table 1.4 Reactions of 2-substituted allylic electrophiles[a]

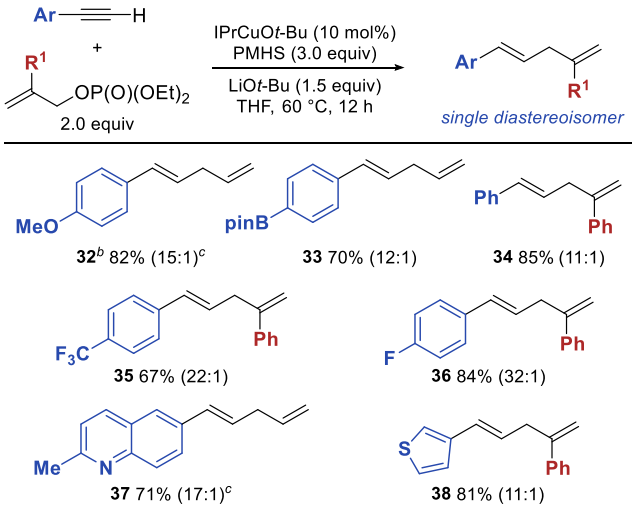


[a] Unless otherwise noted, all reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. [b] Reaction performed on 0.15 mmol scale. [c] Reaction performed on 0.25 mmol scale.

Hydroallylation of aryl alkynes.

Aryl alkynes are often poor substrates for reactions catalyzed by late transition metal complexes. The increased acidity of the alkynes makes the formation of the metal acetylide difficult to avoid, especially in the presence of a strong base such as LiO*t*-Bu. Furthermore, the presence of the aryl substituent can influence the regioselectivity of the hydrometallation step. Our initial attempts to achieve hydroallylation of aryl alkynes using the standard reaction conditions were not successful. However, the change of the solvent to THF and the increase of the reaction temperature to 60 °C allowed hydroallylation of several aryl and heteroaryl alkynes (**Table 1.5**). Both electron-withdrawing and electron-donating substituents on the arene were tolerated (**1.32** and **1.35**). However, somewhat lower yield of **1.35** suggests that the with highly acidic aryl alkynes the formation of the acetylide may be a problem. Finally, in all reactions only one diastereoisomer is formed and good anti-Markovnikov regioselectivity is observed (>10:1).

Table 1.5 Reactions of aryl alkynes[a]

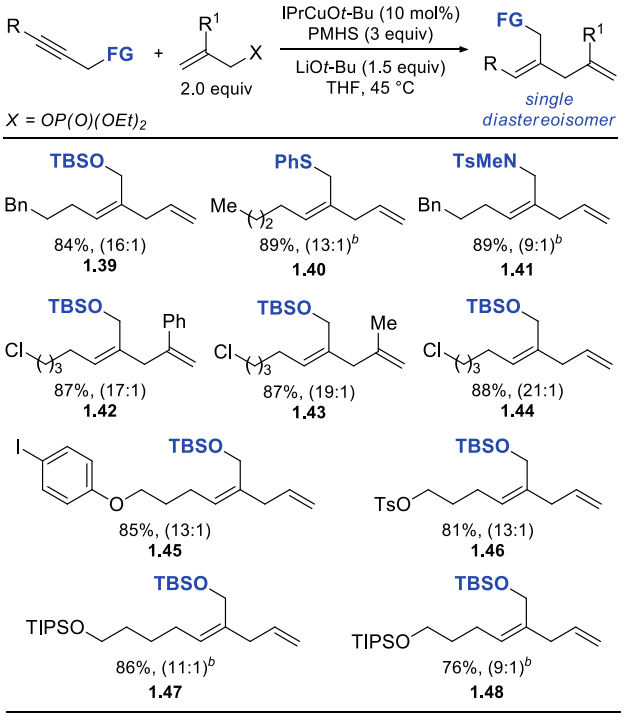


[a] All reactions performed on 0.5 mmol scale. Yields of pure isolated major regioisomer of the products are reported. Regioselectivity reported in parenthesis was determined by GC analysis of the crude reaction mixture. [b] 3.0 Equivalents of phosphate were used. [c] Reaction performed on 0.25 mmol scale.

Hydroallylation of internal alkynes.

One of the major challenges in the hydroallylation of alkynes is the reactivity of nonsymmetrical internal alkynes. To achieve good regioselectivity with this class of substrates, the existing methods require significant electronic or steric differentiation of the alkyne substituents. As a result, the use of internal alkynes in the synthesis of skipped dienes has been generally limited to reactions of aryl[30]-, alkynyl[34]-, and silyl[36]-substituted alkyl acetylenes. In the light of these constraints, we were interested in exploring the reactivity of differentially functionalized dialkyl alkynes. We found that good regioselectivity (~10:1) can be obtained with substrates containing a polar functional group in the propargylic position. With minor changes in the standard reaction conditions, we were able to accomplish the regio- and diastereoselective synthesis of skipped dienes that contain a trisubstituted alkene (**Table 1.6**).

Table 1.6. Hydroallylation of internal alkynes[a]



[a] Yields of the isolated pure major regioisomer are reported. Regioselectivities reported in parenthesis were obtained by GC analysis of the crude reaction mixtures prior to purification. Reactions performed on 0.5 mmol scale. [b] Reaction performed in isooctane at 60 °C.

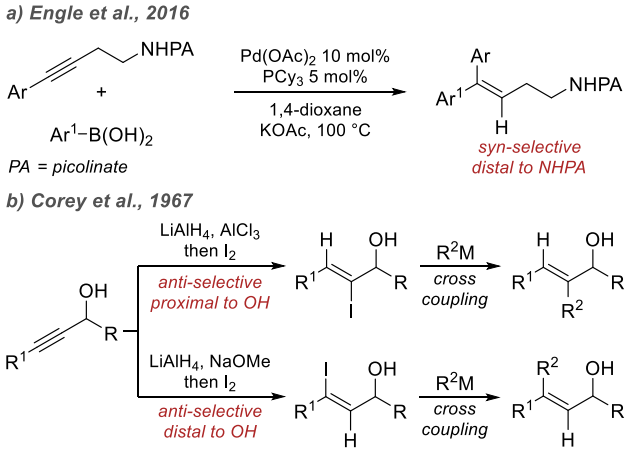
Derivatives of propargylic alcohols, amines, and thiols were all effective in controlling the regioselectivity of the hydroallylation (compounds **1.39**-**1.41**). In all cases, the allylation occurred at the position closer to the functional group (FG, in **Table 1.6**). With substrates in which both sides of the alkyne contain a polar functional group, the one closer to the alkyne had a dominant effect and controlled the selectivity (compounds **1.45**-**1.48**). As the examples of hydroallylation reaction shown in **Table 1.6** demonstrate, the overall scope of the reaction with internal alkynes generally mimics the scope observed with terminal alkynes. *It is worth noting that the trisubstituted alkene products shown in Table 6 are isolated as a single regio- and diastereoisomer after purification by silica gel column chromatography.*

Hydroallylation of internal alkynes in the synthesis of complex trisubstituted alkenes.

The hydroallylation of internal alkynes is also interesting in the context of the synthesis of trisubstituted alkenes. Selective synthesis of this class of alkenes is still a major challenge, as detailed in reviews and recent publications by Negishi et al.[45–47] The transformation of internal alkynes into trisubstituted alkenes is a potentially efficient and appealing synthetic strategy. However, it is difficult to achieve transformations of internal alkynes to trisubstituted alkenes with high regio- and diastereoselectivity. Recently, Engle et al. reported a breakthrough in this area, using homopropargylic picolinamide directing group to achieve selective hydroarylation of internal alkynes (**Scheme 1.4a**).[48] The best method for the hydroalkylation of internal alkynes relies on the cross coupling of alkenyl iodides prepared by Corey's selective hydroalumination of propargylic alcohols (**Scheme 1.4b**).[49] The hydroallylation of internal alkynes described in **Table 1.6** allows the regio- and diastereoselective synthesis of trisubstituted alkenes from internal alkynes. Considering that the reaction is syn-selective and the allylation occurs proximal to the directing group, our method provides an excellent complement to the existing methods shown in

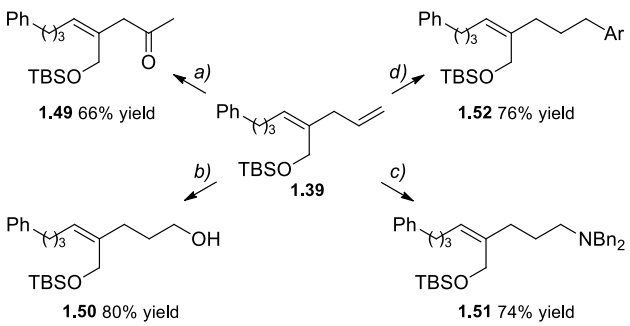
Scheme 1.4. The terminal alkene of the hydroallylation products is a versatile synthetic handle that can be used to access a variety of more complex trisubstituted alkenes. We demonstrated that the terminal alkene of the hydroallylation products can be selectively elaborated through oxidation, hydration, hydroamination, and hydroarylation (**Scheme 1.5**).

Scheme 1.4 Synthesis of trisubstituted alkenes from internal alkynes.



The hydroallylation of internal alkynes described in **Table 1.6** allows the regio- and diastereoselective synthesis of trisubstituted alkenes from internal alkynes. Considering that the reaction is syn-selective and the allylation occurs proximal to the directing group, our method provides an excellent complement to the existing methods shown in **Scheme 1.4**. The terminal alkene of the hydroallylation products is a versatile synthetic handle that can be used to access a variety of more complex trisubstituted alkenes. We demonstrated that the terminal alkene of the hydroallylation products can be selectively elaborated through oxidation, hydration, hydroamination, and hydroarylation (**Scheme 1.5**).

Scheme 1.5. Elaboration of trisubstituted alkenes prepared by hydroallylation**.**



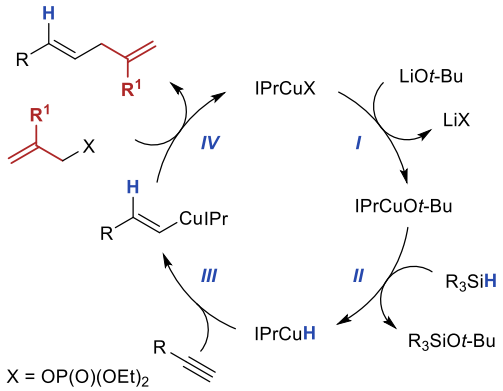
Conditions: ***a)*** $PdCl_2$ (15 mol%), CuCl (1.4 equiv) O_2, DMF:H_2O (7:1), 24 h; ***b)*** 9-BBN (1.1 equiv), 1,4-dioxane, 60 °C, 12 h; then $NaBO_3$ (3.3 equiv), THF, 25 °C, 4 h; ***c)*** 9-BBN (1.0 equiv), 1,4-dioxane, 60 °C, then ICyCuCl (5 mol%, Li*O*t-Bu (1.1 equiv), Bn_2NOBz (1.0 equiv), toluene, 60 °C; ***d)*** 9-BBN (1.0 equiv), 1,4-dioxane, 2. $Pd(OAc)_2$ (1 mol%), PCy_3 (2 mol%), Cs_2CO_3 (3.0 equiv), 1,4-dioxane, 100 °C, 24 h.

1.2.3 *Mechanism*

Previous work on copper-catalyzed hydrofunctionalization reactions makes the general mechanism shown in **Scheme 1.6** plausible. Elementary steps I, II, and III have strong precedent in the literature in the form of stoichiometric experiments that demonstrate their feasibility.[37,50–52] Stoichiometric reactions shown in **Scheme 1.3** also demonstrate the feasibility of the elementary step IV (**Scheme 1.6**).

However, one observation called into question the proposed mechanism. We noticed that the stoichiometric reaction of alkenyl copper complex **1.5** with 1 equiv of allyl phosphate takes more than 24 h to complete (see SI for details), while under the same reaction conditions the catalytic reaction is completed in 16 h. This observation indicates that the proposed allylation of the alkenyl copper complex is kinetically incompatible with the proposed mechanism of the hydroallylation reaction.

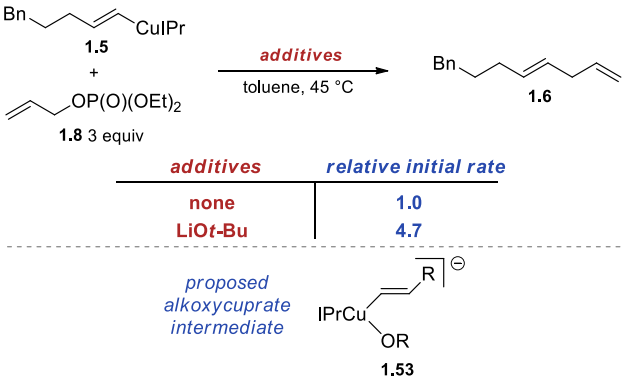
Scheme 1.6. Proposed mechanism of hydroallylation



To resolve this apparent paradox, we explored the effect of individual components of the catalytic reaction on the rate of allylation of the alkenyl copper complex (**Scheme 1.7**). In the presence of LiO*t*-Bu, the initial rate of the stoichiometric allylation of alkenyl copper complex **1.5** was 4.7 times higher than in its absence (see SI for details). To separate the effect of lithium ions and of the alkoxide we measured the rate of the reactions in the presence of both 12-crown-4 and LiO*t*-Bu. The crown ether has only a minor effect on the initial rate (see SI for details), indicating that the alkoxide is likely responsible for the observed rate increase. We also found that the effect is solvent dependent and was much smaller in THF (1.6-fold acceleration with LiO*t*-Bu vs 4.7 in benzene) (see SI for details).

In related catalytic transformations, it has been shown that the identity of the metal alkoxide turnover reagent can have a significant effect on the overall rate of the reaction. In instances in which the NHC ligand used to support the copper catalyst contains a sulfonate group, the identity of the sulfonate counterion derived from the metal alkoxide has been shown to effect the selectivity of the reaction between the organocopper intermediate and the electrophile.[42,53–56] However, the results shown in **Scheme 1.7** provide the first direct evidence for participation of the alkoxide anion in the electrophilic functionalization of the organocopper intermediate.

Scheme 1.7. Effect of base on the allylation of an alkenyl copper complex



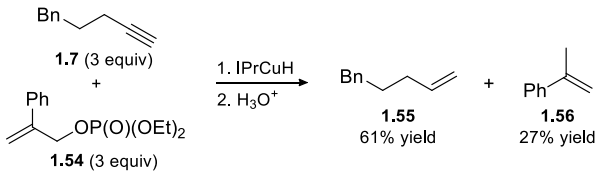
One plausible explanation for the rate increase in the presence of the alkoxide is the formation of alkoxycuprate (**1.53**) (**Scheme 1.7**), which acts as the reactive nucleophile in the reaction with allyl phosphates. Alkoxycuprates have been postulated as reactive intermediates in asymmetric reactions of alkyl lithium reagents performed in the presence of a stoichiometric amount of copper and chiral alkoxide.[57,58] There are also examples of isolated and characterized alkoxycuprates.[59]

We investigated the interaction of the alkenyl copper **1.5** with LiO*t*-Bu using in situ ^{1}H and ^{13}C NMR and found no evidence for the cuprate formation. Never the less, if the reversible formation of the alkoxycuprate is unfavorable under the reaction conditions, we would not observe the cuprate by NMR. In that case, the cuprate could still contribute to the increased rate of the allylation in a typical Curtin-Hammett scenario (low equilibrium concentration and high reactivity).

The third step of the proposed catalytic cycle also required additional verification, as it was not consistent with our previous work on copper-catalyzed hydrofunctionalizations of alkynes. One of the key features of (NHC)CuH complexes is that they quickly reduce a range of organic electrophiles including alkyl iodides,[60] alkyl triflates, [60] propargylic epoxides,[61] and carbonates.[62] As a result, in both hydroalkylation and hydrobromination of alkynes selective hydrocupration in the presence of the electrophile was not possible. Instead, hydroalkylation was shown to proceed

through a different mechanism that involves a series of dinuclear analogues of the intermediates proposed in **Scheme 1.6**. In the hydrobromination reaction, on the other hand, slow addition of the electrophile was necessary in order to avoid its reduction. In contrast to these two hydrofunctionalization reactions, the mechanism of the hydroallylation (**Scheme 1.6**) requires selective hydrocupration of alkynes by IPrCuH in the presence of the allyl phosphate.

Scheme 1.8. Hydrocupration of alkynes in the presence of allyl phosphate

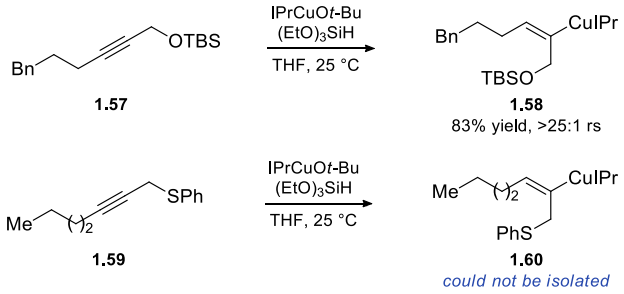


The result of the competition experiment shown in **Scheme 1.8** provides evidence that selective hydrocupration of the alkyne is feasible. The alkene product **1.55**, which is obtained by the protonation of the alkenyl copper complex, is formed about two times faster than **1.56**, which is formed by phosphate reduction. The competitive reduction of the phosphate is consistent with the fact that more than one equivalent of an allylic phosphate is generally required for the complete consumption of an alkyne in the hydroallylation reaction.

Hydrocupration of internal alkynes. Nonsymmetrical internal alkynes have not previously been used as substrates in copper-catalyzed hydrofunctionalization reactions. As a result, we were interested in the inherent regioselectivity of the hydrocupration of these substrates, as well as in the source of the regioselectivity. We were also curious about the apparent resistance of the resulting alkenyl copper complexes to β-elimination of the polar functional groups. Such β-elimination reactions from alkenyl copper intermediates are well-documented in catalytic reductions of propargylic electrophiles[61–63] and in copper-catalyzed alkylation and arylation of propargylic phosphates.[64,65]

To explore the regioselectivity of the hydrocupration and the stability of the alkenyl copper complex, we performed the stoichiometric hydrocupration of OTBS-substituted alkyne **1.57** (**Scheme 1.9**). ^{1}H NMR analysis of the crude reaction mixture indicated that hydrocupration proceeds with excellent regioselectivity (rs >25:1). We were able to obtain an X-ray crystal structure of hydrocupration product **1.58**, and thus unambiguously establish the regioselectivity of the hydrocupration (see **Fig. 1.1**).

Scheme 1.9. Stoichiometric hydrocupration of internal alkynes



Alkenyl copper complex **1.58** proved to be quite stable in C_6D_6 solution at 45 °C: after 1 h, 99% of material remained intact, while after 24 h, 79% of the material was still present in solution (see SI for details). On the other hand, the hydrocupration product obtained from thioether substituted alkyne **1.59** was significantly more prone to elimination. We could identify a small amount of the expected alkenyl copper complex **1.60** by ^{1}H NMR analysis of the reaction mixture. However, attempts to isolate **1.60** yielded only IPrCuSPh, the expected product of the β-thiolate elimination. The formation of the hydroallylation product **1.40** (**Table 1.6**) suggests that the allylation of the alkenyl copper intermediate can outcompete the β-thiolate elimination.

The stoichiometric hydrocupration of OTBS-substituted alkyne **1.57**, also provides important information about the source of the regioselectivity in the hydrocupration. The oxygen atom in ROTBS moiety is significantly less basic than oxygen atom in dialkyl ethers,[66,67] and has been shown not to coordinate even highly electrophilic metal complexes, such as $TiCl_4$.[68] Furthermore,

the X-ray structure of the alkenyl copper complex **1.58** (**Figure 1.1**) reveals no interaction between the OTBS and copper (Cu-O distance is 3.22 Å). Based on these considerations, we conclude that the regioselectivity is not a result of a direct interaction between OTBS and the catalyst. Instead, the likely explanation is that the inductive effect of the OTBS substituent causes polarization of the alkyne and results in the observed regioselectivity. Similar electronic effects were recently invoked by Hartwig et al.[69] to rationalize regioselectivity in the hydroamination of alkenes containing homoallylic directing groups.

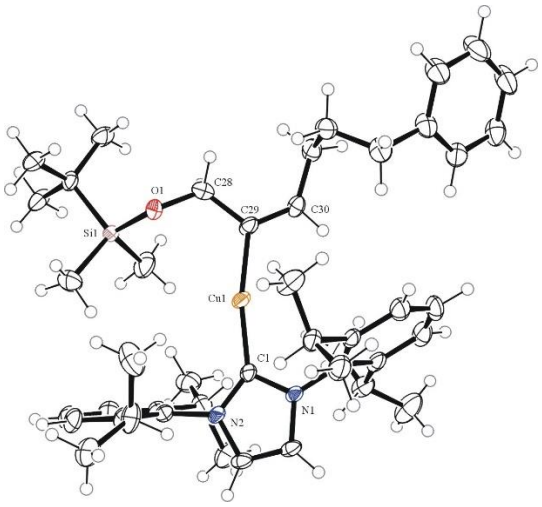
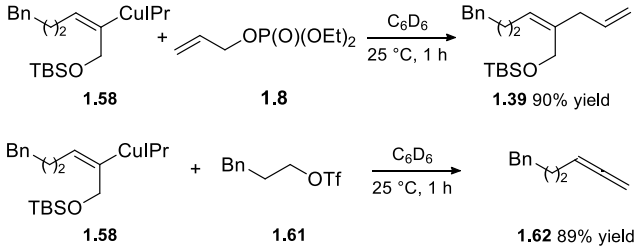


Figure 1.1 ORTEP presentation of the crystal structure of alkenyl copper complex 58. **with thermal ellipsoids at the 50% probability level. Disorder omitted for clarity (see SI for details).**

Allylation vs. alkylation of alkenyl copper complexes 1.58. After exploring the structure and stability of **1.58**, we examined its reactivity. We performed stoichiometric reactions with two carbon based electrophiles that can produce trisubstituted alkenes (**Scheme 1.10**). In the reaction with allyl phosphate (**1.8**), we observed the formation of the desired product in 90% yield within 1 h at 25 °C. It is interesting to note that this allylation reaction is significantly faster than the reaction of terminal alkenyl copper complex (**1.5**) with the same electrophile (**Scheme 1.3**).

The alkylation of alkenyl copper complexes with alkyl triflates is the key step in the catalytic hydroalkylation of alkynes previously developed in our lab. With terminal alkenyl copper complexes, the stoichiometric alkylation reaction proceeds quickly to produce the alkylation product in 50% yield, together with the formation of half an equivalent of the dinuclear alkenyl copper complex. In the reaction of the alkenyl copper complex **1.58** with alkyl triflate **1.61**, we observed elimination product **1.62** in 89% yield. The unexpected elimination reaction shows the dramatic effect the electrophile has on the reactivity of alkenyl copper complexes derived from internal alkynes and may explain why internal alkynes, such as **1.57**, are not viable substrates in the catalytic hydroalkylation reaction. These results also emphasize the unique potential of the hydroallylation reaction as a method for the regio- and diastereoselective synthesis of trisubstituted alkenes from internal alkynes.

Scheme 1.10. Allylation and alkylation of alkenyl copper complex 1.58



1.3 CONCLUSION

We have developed a new method for the anti-Markovnikov hydroallylation of alkynes. The hydroallylation is *syn*-stereospecific and highly regioselective, which in most cases leads to the formation of a single product. The reaction can be performed in the presence of a wide range of functional groups, including esters, nitriles, ketones, sulfonate esters, alkyl halides, aryl halides, sulfonamides, thioethers, and silyl ethers. The new method provides stereoselective access to a

range of skipped dienes from readily available starting materials. The method also allows regio- and stereoselective synthesis of trisubstituted alkenes from functionalized internal alkynes. This is a major advantage of the hydroallylation reaction over the recently reported copper-catalyzed hydroalkylation reaction, which was limited to transformations of terminal alkynes. Our studies of the key steps of the proposed catalytic cycle suggest that divergent reactivity of the key alkenyl copper intermediate with alkyl triflates and allyl phosphates is responsible for this major difference in scope of the two reactions. These studies also suggest an unexpected role of LiO*t*-Bu in allylation step of the catalytic cycle. We have also uncovered unexpected resistance of alkenyl copper complexes to β-elimination of polar functional groups and interesting differences in the reactivity of alkenyl copper complexes derived from internal alkynes toward allylic and alkyl electrophiles.

Experimental

1.3.1 *General Procedures*

All reactions were performed under an atmosphere of nitrogen with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a nitrogen-filled glovebox (NexusII 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). ^{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 the residual solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C 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, C_6D_6: δ 128.1 ppm,

CD_2Cl_2: δ 54.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet m = multiplet, br = broad), integration, and coupling constants in Hertz (Hz). 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. 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.

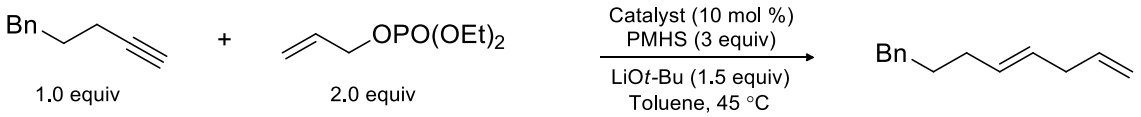
1.3.2 *Materials*

Toluene, benzene, ether, DCM, and THF were dried by passing through columns of neutral alumina. 1,4-dioxane was distilled over calcium hydride, degassed, and stored over activated molecular sieves. All other solvents were used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Common commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., TCI America, or STREM Chemicals, Inc. $(Me_2SiH)_2O$ (TMDSO) was purchased from Oakwood Chemical and vacuum transferred over calcium hydride before use. Cesium fluoride was purchased from Matrix Scientific or Sigma Aldrich. The material was dried rigorously by flame-drying under vacuum followed by grinding with a mortar and pestle in a glove box. This process was repeated three times. 2,6-Lutidine was purchased from TCI America and distilled over calcium hydride, then vacuum transferred from aluminum trichloride. Triflic anhydride was purchased from Oakwood Chemical and vacuum transferred over P_2O_5.

1.3.3 *Reaction Development*

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, LiO*t*-Bu, catalyst (either a copper complex (Table 1.7), or copper (I) triflate benzene complex and ligand (Table 1.8)), solvent, silane, and alkyne respectively. The reaction mixture was allowed to stir at 25 °C until the yellow color disappears. The allyl diethyl phosphate and 1,3,5-trimethoxy benzene, (TMB, internal standard) were added and the reaction mixture was vigorously stirred at 45 °C.

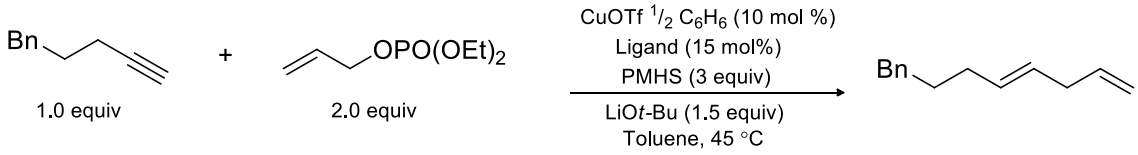
Table 1.7: Catalyst Screen



Entry	Catalyst	% Yield
1	IPrCuO*t*-Bu	89%
2	IPrCuCl	69%
3	SIPCuCl	59%
4	Cl_2IPrCuCl	31%
5	ICyCuCl	42%
6	IPr*CuCl	36%
7	IAdCuCl	36%

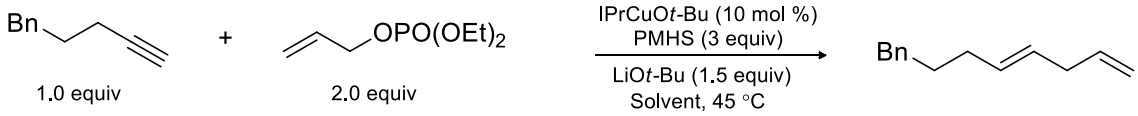
The NHC copper complexes used above was prepared from a known literature procedure and have been characterized.

Table 1.8: Ligand Screen



Entry	Ligand	% Yield
1	BINAP	1%
2	SEGPHOS	0%
3	Xantphos	3%
4	Bis(2-dicyclohexylphosphinophenyl)ether	1%
5	DPPB	1%
6	DPPF	1%
7	PCy_3	3%

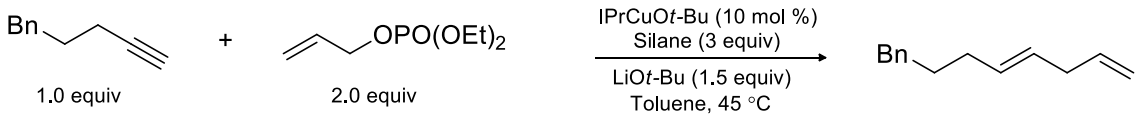
Table 1.9: Solvent Screen



Entry	Solvent	% Yield
1	Toluene	89%
2	Isooctane	88%
3	THF	76%
4	DME	71%
5	DCE	43%
6	Dioxane	72%

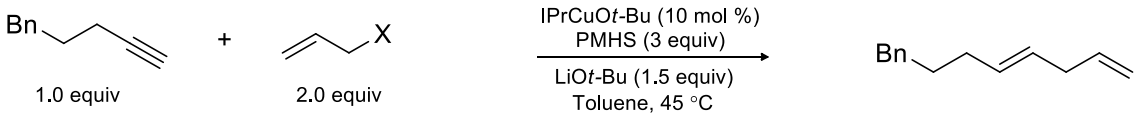
7	Chlorobenzene	88%
8	Acetonitrile	50%

Table 1.10: Silane Screen



Entry	Silane	% Yield
1	PMHS	89%
2	TMDSO	86%
3	Di-tert-butylsilane	28%
4	Triethylsilane	0%
5	Triethoxysilane	16%
6	Dimethylisopropylsilane	5%
7	Ditertmethylsilane	0%

Table 1.11: Allyl Electrophile Screen



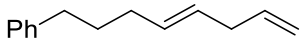
Entry	Allyl Electrophile	% Yield
1	Allyl phosphate	89%
2	Allyl chloride	44%

1.3.4 *General Method for the Catalytic Hydroallylation of Alkynes*

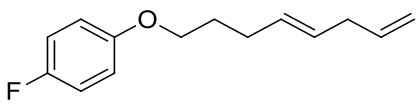
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiO*t*-Bu (60.0 mg, 0.750 mmol, 1.5 equiv), IPrCuO*t*-Bu (26.3 mg, 0.050 mmol, 0.10 equiv) and indicated solvent (5 mL, 0.1 M). To this reaction mixture was added PMHS (1.5 mmol, 3.0 equiv) and alkyne (0.5 mmol, 1.0 equiv). The reaction mixture was stirred at 25 °C until the yellow color disappeared. To this reaction mixture was added allyl diethyl phosphate (1.0 mmol, 2.0 equiv) and the reaction mixture was vigorously stirred at the indicated temperature. After 20 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 column.

The regioselectivity of the hydroallylation of internal alkynes and aryl alkynes was determined by GC analysis of the crude reaction mixture.

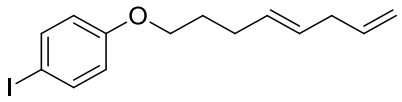
1.3.5 *Characterization of Hydroallylation Products*



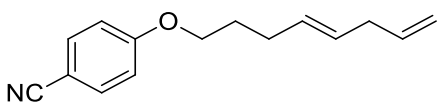
(E)-octa-4,7-dien-1-ylbenzene (1.6), compound was isolated as a clear colorless liquid (129.0 mg, 89% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.20 – 7.17 (m, 2H), 7.12 – 7.00 (m, 3H), 5.81 (ddt, J = 16.6, 10.1, 6.4 Hz, 1H), 5.48 – 5.28 (m, 2H), 5.14 – 4.88 (m, 2H), 2.70 – 2.66 (m, 2H), 2.47 (t, J = 7.7 Hz, 2H), 1.97 – 1.91 (m, 2H), 1.58 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 137.5, 131.4, 128.6, 128.4, 128.3, 125.8, 114.9, 36.9, 35.5, 32.2, 31.3. GCMS (EI) calculated for [M]+ 186.14, found 186.20. FTIR (neat, cm^{-1}): 3064(m), 3028(s), 2931(s), 1958(w), 1638(m), 678(s).



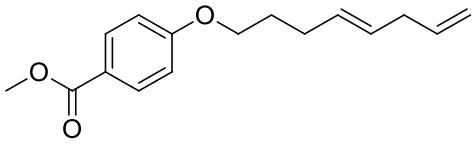
(E)-1-fluoro-4-(octa-4,7-dienyloxy)benzene (1.9), compound was isolated as a clear colorless liquid (130.0 mg, 84% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 6.82 – 6.74 (m, 2H), 6.61 – 6.54 (m, 2H), 5.78 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.46 – 5.28 (m, 2H), 5.07 – 4.95 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.07 – 1.99 (m, 2H), 1.62 (p, *J* = 7.5, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.2 (d, *J* = 237.8 Hz), 155.3 (d, *J* = 1.6 Hz), 137.3, 130.5, 128.8 , 115.8 (d, *J* = 23.0 Hz), 115.6 (d, *J* = 8.0 Hz), 115.1, 68.0, 36.8, 29.1, 29.0. ^{19}F NMR (471 MHz, $CDCl_3$) δ -124.41. GCMS (EI) calculated for [M]+ 220.13 found 220.20. FTIR (neat, cm^{-1}): 1726(m), 1693(m), 1636(m), 1505(s), 1474(s), 1434(m), 1293(s), 1248(s), 1209(s).



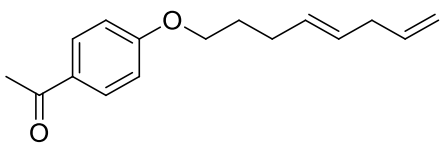
(E)-1-iodo-4-(octa-4,7-dienyloxy)benzene (1.10), compound was isolated as a clear colorless liquid (134.0 mg, 82% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.37 (d, *J* = 8.9 Hz, 2H), 6.38 (d, *J* = 8.9 Hz, 2H), 5.77 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.44 – 5.24 (m, 2H), 5.08 – 4.90 (m, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.72 – 2.58 (m, 2H), 2.02 – 1.96 (m, 2H), 1.58 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 138.3, 137.3, 130.4, 128.9, 117.1, 115.1, 82.6, 67.4, 36.8, 29.0. GCMS (EI) calculated for [M]+ 328.03, found 328.10. FTIR (neat, cm^{-1}): 3084(m), 2940(s), 2871(m), 1636(s), 1586(s), 1484(s), 1282(s), 1244(s), 988(s), 712(s).



(E)-4-(octa-4,7-dien-1-yloxy)benzonitrile (1.11), compound was isolated as a clear colorless liquid (114.2 mg, 88% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.01 (d, J = 8.8 Hz, 2H), 6.34 (d, J = 8.8 Hz, 2H), 5.77 (ddt, J = 16.7, 10.2, 6.4 Hz, 1H), 5.41 – 5.35 (m, 1H), 5.32 – 5.26 (m, 1H), 5.04 – 4.93 (m, 2H), 3.32 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H), 1.96 – 1.92 (m , 2H), 1.50 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 137.2, 134.1, 130.1, 129.2, 119.4, 115.3, 115.1, 103.9, 67.7, 36.8, 28.9, 28.8. GCMS (EI) calculated for [M]+ 227.13, found 227.20. FTIR (neat, cm^{-1}): 3072(m), 3036(m), 2943(m), 2226(s), 1720(w), 1606(s), 1478(m), 680(s).

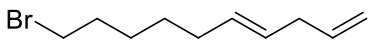


(E)-methyl 4-(octa-4,7-dien-1-yloxy)benzoate (1.12), compound was isolated as a clear colorless liquid (100.8 mg, 89% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 8.15 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 5.78 (ddt, J = 16.7, 10.2, 6.4 Hz, 1H), 5.45 – 5.25 (m, 2H), 5.08 – 4.94 (m, 2H), 3.54 (s, 3H), 3.48 (t, J = 6.4 Hz, 2H), 2.67 – 2.63 (m, 2H), 2.01– 197 (m, 2H), 1.57 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 163.0, 137.2, 131.7, 130.3, 129.0, 122.5, 115.1, 114.2, 67.5, 51.9, 36.8, 28.9, 28.9. GCMS (EI) calculated for [M]+ 260.14, found 260.20. FTIR (neat, cm^{-1}): 3079(m), 3000(m), 2950(s), 1750(w), 1718(s),1637(m), 1450(m), 1315(s), 771(s).

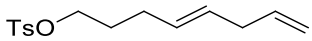


(E)-1-(4-(octa-4,7-dien-1-yloxy)phenyl)ethanone (1.13), compound was isolated as a clear colorless liquid (105.2 mg, 86% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.83 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 5.79 (ddt, J = 16.6, 10.1, 6.4 Hz, 1H), 5.46 – 5.28 (m, 2H), 5.07 –

4.98 (m, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.16 (s, 3H), 2.05 – 1.98 (m, 2H), 1.60 (p, *J* =7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 163.1, 137.2, 130.6, 130.2, 130.1, 128.9, 115.0, 114.1, 67.4, 36.7, 28.9, 28.8, 26.4. GCMS (EI) calculated for [M]+ 244.15, found 244.10. FTIR (neat, cm^{-1}): 3075(w), 3002(w), 2942(w), 2849(w), 1678(s), 1637(w), 1601(s), 1508(s), 1470(w), 1420(w), 1358(s), 1306(s), 1255(s), 1171(s), 1115(w), 1075(w), 970(w), 914(w), 834(s).

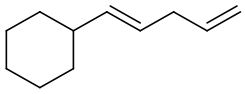


(E)-10-bromodeca-1,4-diene (1.14), compound was isolated as a clear colorless liquid (81.0 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.82 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.47 – 5.25 (m, 2H), 5.14 – 4.96 (m, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 2.79 – 2.57 (m, 2H), 1.90 – 1.77 (m, 2H), 1.46 (p, *J* = 6.6 Hz, 2H), 1.23 – 0.99 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 131.3, 128.1, 114.9, 36.8, 34.0, 32.8, 32.4, 28.7, 27.8. GCMS (EI) calculated for [M]+ 216.05, found 216.10. FTIR (neat, cm-^{1}): 2933(s), 2856(s), 1637(s), 1459(s), 1437(s), 1337(w), 970(s), 757(s).

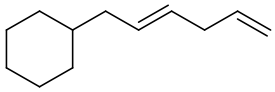


(E)-octa-4,7-dien-1-yl 4-methylbenzenesulfonate (1.15), compound was isolated as a clear colorless liquid (190.1 mg, 90% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.76 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 5.77 – 5.64 (m, 1H), 5.25 – 4.94 (m, 4H), 3.81 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 1.84 (s, 3H), 1.84 – 1.73 (m, 2H), 1.33 (p, *J* = 7.5 Hz , 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 137.0, 133.3, 129.9, 129.4, 129.3, 127.9, 115.0, 69.9, 36.6, 28.6, 28.2,

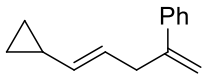
21.7. GCMS (EI) calculated for [M]+ 280.11, found 280.10. FTIR (neat, cm^{-1}): 3072(m), 3035(m), 2924(m), 1750(w), 1638(m), 1479(m),1362(s).



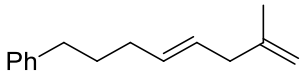
(E)-penta-1,4-dienylcyclohexane (1.16), compound was isolated as a clear colorless liquid (60.0 mg, 80% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 5.89 – 5.77 (m, 1H), 5.61 – 5.31 (m, 2H), 5.23 – 4.76 (m, 2H), 2.70 (d, J = 5.4 Hz, 2H), 1.87 (t, J = 12.8 Hz, 1H), 1.78 – 1.51 (m, 4H), 1.58 (d, J = 14.5 Hz, 1H), 1.29 – 0.95 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.7, 125.1, 114.8, 40.8, 36.9, 33.3, 26.4, 26.3. GCMS (EI) calculated for [M]+ 150.14, found 150.10. FTIR (neat, cm^{-1}): 3085 (w), 2926(s), 2851(s), 1718(s), 1638(s), 1449(m), 1334(m), 736(s).



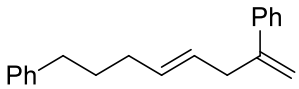
(E)-hexa-2,5-dienylcyclohexane (1.17), compound was isolated as a clear colorless liquid (66.0 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.83 (ddt, J = 16.6, 10.0, 6.3 Hz, 1H), 5.52 – 5.33 (m, 2H), 5.19 – 4.83 (m, 2H), 2.74 – 2.69 (m, 2H), 1.90 (t, J = 5.3 Hz, 2H), 1.79 – 1.51 (m, 5H), 1.31 – 1.00 (m, 4H), 0.93 – 0.76 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 130.4, 128.6, 114.8, 40.8, 38.1, 36.9, 33.2, 26.8, 26.5. GCMS (EI) calculated for [M]+ 164.16, found 164.20. FTIR (neat, cm^{-1}): 3079(m), 2922(s), 2851(s), 1638(s), 1448(s), 969(s).



(E)-(5-cyclopropylpenta-1,4-dien-2-yl)benzene (1.18), compound was isolated as a clear colorless liquid (72.0 mg, 51% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.38 (d, J = 7.6 Hz, 2H), 7.12 – 7.06 (m, 3H), 5.59 (dt, J = 14.2, 6.8 Hz, 1H), 5.37 (s, 1H), 5.11 (s, 1H), 4.98 (dd, J = 14.2, 8.4 Hz, 1H), 3.12 (d, J = 6.8 Hz, 2H), 1.24 – 1.12 (m, 1H), 0.49 – 0.42 (m, 2H), 0.23 – 0.18 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 141.3, 136.1, 128.3, 127.5, 126.1, 125.3, 112.8, 38.3, 13.7, 6.6. GCMS (EI) calculated for [M]+ 184.13, found 184.10. FTIR (neat, cm^{-1}): 2936(m), 3058(w), 1723(s), 1685(s), 1448(s), 1266(s), 1025(s), 736(s), 701(s).

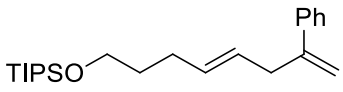


(E)-(7-methylocta-4,7-dien-1-yl)benzene (1.19), compound was isolated as a clear colorless liquid (114.2 mg, 88% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.18 (t, J = 7.9 Hz, 2H), 7.10 – 7.06 (m, 3H), 5.46 – 5.36 (m, 2H), 4.85 (s, 1H), 4.82 (s, 1H), 2.66 (d, J = 5.8 Hz, 2H), 2.50 – 2.46 (t, 2H), 1.97 – 193 (m, 2H), 1.66 (s, 3H), 1.60 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 142.7, 131.9, 128.6, 128.4, 128.3, 125.8, 110.4, 41.4, 35.5, 32.2, 31.4, 22.5. GCMS (EI) calculated for [M]+ 200.16, found 200.20. FTIR (neat, cm^{-1}): 3072(m), 3028(m), 2933(s), 1813(w), 1650(m), 1470(m), 677(s).

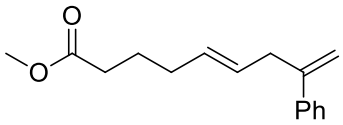


(E)-octa-4,7-diene-1,7-diyldibenzene (1.20), compound was isolated as a clear colorless liquid (101.0 mg, 77% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.49 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 7.19 – 6.75 (m, 5H), 5.56 – 5.39 (m, 2H), 5.38 (s, 1H), 5.10 (d, J = 1.5 Hz, 1H), 3.14 (d, J = 5.7 Hz, 2H), 2.41 (t, 2H), 2.05 – 1.76 (m, 2H), 1.54 (p, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 147.3, 142.6, 141.3, 132.3, 128.6, 128.6, 128.3, 128.2, 127.5, 126.2, 125.7, 112.8, 38.5, 35.4, 32.2, 31.3. GCMS (EI) calculated for [M]+ 262.17, found 262.20. FTIR (neat, cm^{-1}): 3061(m), 3025(m), 2926(s), 2854(s), 1643(s), 1602(s), 1494(s), 1452(s), 1074(s), 894(s), 698(s).

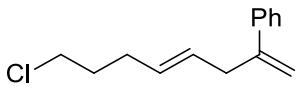


(E)-triisopropyl((7-phenylocta-4,7-dien-1-yl)oxy)silane (1.21), compound was isolated as a clear colorless liquid (228.0 mg, 85% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.40 – 7.37 (m, 2H), 7.16 – 7.06 (m, 3H), 5.64 – 5.41 (m, 2H), 5.39 (s, 1H), 5.11 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.14 (d, *J* = 5.8 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.58 (p, *J* = 7.5 Hz, 2H), 1.11 – 1.03 (m, 21H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 141.2, 132.3, 128.3, 127.8, 127.5, 126.1, 112.8, 62.9, 38.4, 32.8, 29.0, 18.2, 12.1. GCMS (EI) calculated for [M]+ 282.24, found 358.30. FTIR (neat, cm^{-1}): 3090(m), 3035.7(m), 2942(s), 1811.7(m),1627.1(m), 1366.1(m), 1106.4(s).

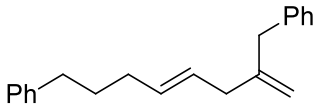


(E)-methyl 8-phenylnona-5,8-dienoate (1.22), compound was isolated as a clear colorless liquid (155.0 mg, 85% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.36 (d, *J* = 7.7 Hz, 2H), 7.14 – 7.06 (m, 3H), 5.44 (dt, *J* = 14.0, 6.7 Hz, 1H), 5.37 (s, 1H), 5.29 (dt, *J* = 14.0, 6.8 Hz, 1H), 5.07 (s, 1H), 3.32 (s, 3H), 3.08 (d, *J* = 6.6 Hz, 2H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.84 – 1.80 (q, *J* = 7.2 Hz, 2H), 1.55 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 147.0, 141.1, 131.4, 128.8, 128.3, 127.5, 126.1, 112.9, 51.6, 38.4, 33.4, 31.9, 24.6. GCMS (EI) calculated for [M]+ 244.15, found

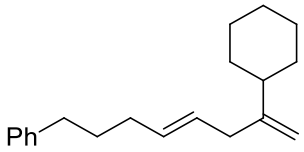
244.20. FTIR (neat, cm^{-1}): 3090(m), 30359(m), 2950(s), 1740(s), 1627(m), 1480(m), 1173(m), 680(s).



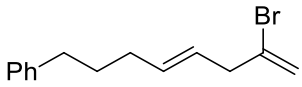
(E)-(8-chloroocta-1,4-dien-2-yl)benzene (1.23), compound was isolated as a clear colorless liquid (94.0 mg, 85% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 1H), 5.56 (dt, *J* = 14.5, 6.3 Hz, 1H), 5.45 (dt, *J* = 14.5, 6.4 Hz, 1H), 5.36 (s, 1H), 5.08 (s, 1H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.20 (d, *J* = 6.3 Hz, 2H), 2.20 – 2.12 (m 2H), 1.80 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0, 141.1, 130.6, 129.2, 128.3, 127.5, 126.1, 113.0, 44.4, 38.4, 32.2, 29.9. GCMS (EI) calculated for [M]+ 220.10, found 220.20. FTIR (neat, cm^{-1}): 3058(m), 3027(w), 2930(s), 1724(m), 1685(s), 1597(s), 1494(s), 1447(s), 1027(s), 700(s).



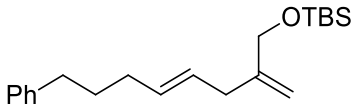
(E)-(2-methyleneoct-4-ene-1,8-diyl)dibenzene (1.25), compound was isolated as a clear colorless liquid (119.0 mg, 86% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.22 – 7.16(m, 6H), 7.13 – 7.04 (m, 4H), 5.50 – 5.25 (m, 2H), 4.94 (s, 1H), 4.83 (s, 1H), 3.28 (s, 2H), 2.65 (d, *J* = 5.7 Hz, 2H), 2.48 (t, *J* = 7.4, 2H), 2.02 – 1.87 (m, 2H), 1.59 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 142.7, 139.8, 132.3, 129.2, 128.6, 128.4, 128.1, 126.2, 125.8, 111.9, 42.9, 39.0, 35.5, 32.2, 31.4. GCMS (EI) calculated for [M]+ 276.19, found 276.30. FTIR (neat, cm^{-1}): 3083(m), 3025(s), 2928(s), 2854(s), 1643(s), 1602(s), 1494(s), 1452(s), 1029(m), 895(m), 739(s), 698(s).



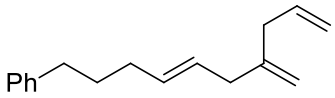
(E)-(7-cyclohexylocta-4,7-dienyl)benzene (1.26), compound was isolated as a clear colorless liquid (118.0 mg, 88% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (m 2H), 7.18 (m, 3H), 5.63 – 5.16 (m, 2H), 4.74 (s, 1H), 4.70 (s, 1H), 2.80 – 2.69 (m, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.07 (m, 2H), 1.96 – 1.58 (m, 8H), 1.36 – 1.04 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 142.7, 131.7, 128.9, 128.6, 128.4, 125.7, 107.7, 44.1, 38.5, 35.9, 32.5, 32.2, 31.4, 26.9, 26.6. GCMS (EI) calculated for [M]+ 268.22, found 268.20. FTIR (neat, cm^{-1}): 3084(s), 3026(s), 2925(s), 2851(s), 1956(w), 1811(w), 1640(s), 1603(s), 1495(s), 1451(s), 909(s), 887(s), 743(s), 698(s).



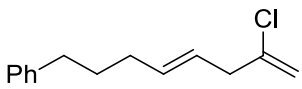
(E)-(7-bromoocta-4,7-dienyl)benzene (1.27), compound was isolated as a clear colorless liquid (75.0 mg, 57% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.24 – 7.17 (m 2H), 7.14 – 7.02 (m 3H), 5.50 – 5.07 (m, 4H), 2.91 (d, *J* = 5.3 Hz, 2H), 2.45 (t, *J* = 7.4 2H), 2.00 – 1.75 (m, 2H), 1.54 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 134.1, 133.3, 128.6, 128.4, 125.9, 125.8, 116.7, 44.8, 35.4, 32.1, 31.0. GCMS (EI) calculated for [M]+ 264.05, found 264.10. FTIR (neat, cm^{-1}): 3084(m), 3025(m), 2930(s), 1720(s), 1628(s), 1602(m), 1452(s), 750(s), 609(s)**.**



(E)-tert-butyldimethyl(2-methylene-8-phenyloct-4-enyloxy)silane (1.28), compound was isolated as a clear colorless liquid (125.0 mg, 76% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.32 – 7.15 (m, 2H), 7.13 – 6.98 (m, 3H), 5.66 – 5.32 (m, 2H), 5.24 (s, 1H), 4.97 (s, 1H), 4.08 (s, 2H), 2.74 (d, *J* = 4.3 Hz, 2H), 2.48 (t, *J* = 7.7 Hz, 2H), 2.09 – 1.84 (m, 2H), 1.60 (p, *J* = 7.5 Hz, 2H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 142.6, 132.1, 128.6, 128.4, 127.8, 125.8, 109.2, 65.8, 36.3, 35.5, 32.2, 31.3, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 330.24, found 330.30. FTIR (neat, cm^{-1}): 3083(w), 3026(m), 2954(s), 2928(s), 2856(s), 1653(s), 1604(w), 1453(m), 1251(s), 1111(s), 1080(s), 836(s), 775(s).

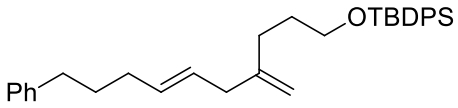


(E)-(7-methylenedeca-4,9-dien-1-yl)benzene (1.29), compound was isolated as a clear colorless liquid (28.0 mg, 82% yield). The reaction was performed on 0.1 mmol scale. ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.26 – 7.17(m, 2H), 7.13 – 7.02 (m, 3H), 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.51 – 5.28 (m, 2H), 5.10 – 4.97 (m, 2H), 4.91 (s, 1H), 4.88 (s, 1H), 2.77 – 2.65 (m, 2H), 2.48 (t, *J* = 7.7 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.60 (p, *J* = 7.5, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5, 142.7, 136.4, 132.2, 128.8, 128.4, 128.1, 125.8, 116.3, 110.7, 40.6, 39.5, 35.5, 32.2, 31.4. GCMS (EI) calculated for [M]+ 226.17, found 226.20. FTIR (neat, cm^{-1}): 3078 (m), 3026(m), 1700(w), 1641(s), 1603(m), 1217(s), 754(s).

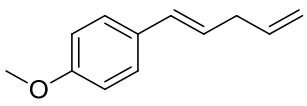


(E)-(7-chloroocta-4,7-dienyl)benzene (1.30), compound was isolated as a clear colorless liquid (50.0 mg, 51% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.19 (d, *J* = 7.7 Hz, 2H), 7.12 – 7.01

(m, 3H), 5.43 – 5.21 (m, 2H), 5.07 (s, 1H), 4.88 (s, 1H), 2.81 (d, *J* = 5.2 Hz, 2H), 2.45 (t, *J* = 7.7 Hz, 2H), 1.94 – 1.80 (m, 2H), 1.54 (p, *J* = 7.5, 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 141.9, 134.1, 128.6, 128.4, 125.8, 125.3, 112.3, 42.5, 35.4, 32.1, 31.1. GCMS (EI) calculated for [M]+ 220.10, found 220.20. FTIR (neat, cm^{-1}): 3089(m), 3033(m), 2932(s), 1633(s), 1478(s), 1128(m), 968(m), 699(s), 677(s).

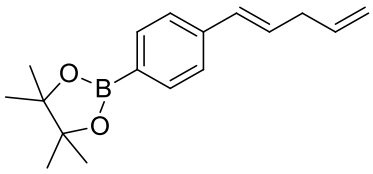


(E)-tert-butyl(4-methylene-10-phenyldec-6-enyloxy)diphenylsilane (1.31), compound was isolated as a clear colorless liquid (101.0 mg, 76% yield). The reaction was performed on 0.25 mmol scale. ^{1}H NMR (300 MHz, Benzene-d_6) δ 8.02 – 7.48 (m, 4H), 7.28 – 7.19 (m, 6H), 7.20 – 7.15 (m, 2H), 7.13 – 7.02 (m, 3H), 5.58 – 5.20 (m, 2H), 4.87 (s, 1H), 4.83 (s, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.68 (d, *J* = 4.9 Hz, 2H), 2.49 (t, *J* = 7.7 Hz, 2H), 2.13 (t, *J* = 7.8 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.78 – 1.67 (m, 2H), 1.61 (p, *J* = 7.6 Hz, 2H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 142.7, 135.7, 134.2, 131.9, 129.6, 128.6, 128.4, 128.3, 127.7, 125.8, 109.6, 63.7, 39.8, 35.5, 32.2, 32.2, 31.4, 30.8, 27.0, 19.4. GCMS (EI) calculated for [M]+ 482.30, found 482.30. FTIR (neat, cm^{-1}): 3069(s), 3025(m), 2930(s), 2856(s), 1644(s), 1495(s), 1427(s), 1187(s), 1111(s), 890(m), 700(s).

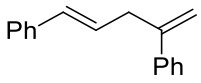


(E)-1-methoxy-4-(penta-1,4-dien-1-yl)benzene (1.32), compound was isolated as a colorless liquid (71.2 mg, 82% yield, rs = 15:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.00 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.84 (ddt,

J = 16.6, 10.1, 6.7 Hz, 1H), 5.21 – 4.89 (m, 2H), 3.30 (s, 3H), 2.93 – 2.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 136.9, 130.6, 130.4, 127.3, 126.1, 115.6, 114.1, 55.4, 37.1. GCMS (EI) calculated for [M]+ 174.10, found 174.10. FTIR (neat, cm^{-1}): 3070(m), 3034(m), 2835(m), 1637(m), 1464(s), 1126(s), 679(s)

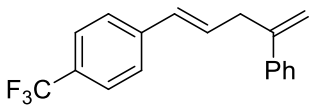


(E)-4,4,5,5-tetramethyl-2-(4-(4-phenylpenta-1,4-dien-1-yl)phenyl)-1,3,2-dioxaborolane (1.33), compound was isolated as a colorless liquid (94.6 mg, 70% yield, rs = 12:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 8.16 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.27 (d, *J* = 15.9 Hz, 1H), 6.06 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.75 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.13 – 4.86 (m, 2H), 2.78 – 2.53 (m, 2H), 1.14 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 136.4, 135.2, 131.0, 129.5, 125.6, 125.5, 115.9, 83.8, 25.0.GCMS (EI) calculated for [M]+ 270.10, found 270.10. FTIR (neat, cm^{-1}): 3077(m), 3026(m), 2977(s), 1741(s), 1637(m), 1464(m), 963(m).

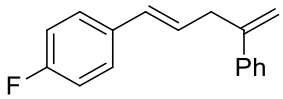


(E)-penta-1,4-diene-1,4-diyldibenzene (1.34), compound was isolated as a white solid (94.0 mg, 85% yield, rs = 11:1). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.15 – 7.13 (m, 2H), 7.13 – 7.06 (m, 3H), 7.06 – 6.98 (m, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.40 (s, 1H), 5.09 (s, 1H), 3.22 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 141.1, 137.7, 131.8, 128.6, 128.5, 128.2, 127.6, 127.2, 126.2, 126.1, 113.5, 38.8.

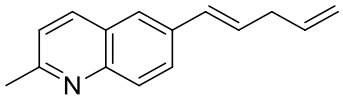
GCMS (EI) calculated for [M]+ 220.13, found 220.20. FTIR (neat, cm^{-1}): 3082(m), 3053(s), 2985(m), 1951(w), 1626(m), 1447(m), 746(s).



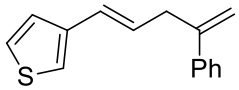
(E)-1-(4-phenylpenta-1,4-dien-1-yl)-4-(trifluoromethyl)benzene (1.35), compound was isolated as a white solid (97 mg, 67% yield, rs = 22:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H),7.20 – 7.18 (m, 2H), 7.13 – 7.07 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.21 – 6.01 (m, 2H), 5.40 (s, 1H), 5.04 (s, 1H), 3.16 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.2 , 141.1 , 140.8 , 131.1 , 130.6 , 129.1 (q, *J* = 32.2 Hz), 128.5 , 127.8 , 126.4 , 126.1 , 125.6 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 271.8 Hz), 113.8 , 38.8 . ^{19}F NMR (471 MHz, $CDCl_3$) δ -65.60. GCMS (EI) calculated for [M]+ 288.11, found 288.20. FTIR (neat, cm^{-1}):3054(m), 2987(m), 1921(w), 1650(m), 741(s), 706(s).



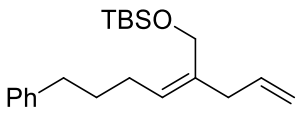
(E)-1-fluoro-4-(4-phenylpenta-1,4-dien-1-yl)benzene (1.36), compound was isolated as a white solid (100.2 mg, 84% yield, rs = 32:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.37 (m, 2H), 7.22 – 7.18 (m, 2H), 7.15 – 7.13 (m, 1H), 7.12 – 7.06 (m, 3H), 7.06 – 6.98 (m, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.40 (s, 1H), 5.09 (s, 1H),3j.22 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.2 (d, *J* = 245.8 Hz), 146.6, 141.0, 133.8 (d, *J* = 2.9 Hz), 130.6 , 128.5 , 127.9 , 127.9 , 127.7 (d, *J* = 7.5 Hz), 126.1, 115.5 (d, *J* = 21.9 Hz), 113.5, 38.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.29. GCMS (EI) calculated for [M]+ 238.12, found 238.10. FTIR (neat, cm^{-1}): 3057(m), 3025(m), 1920(w), 1625(m), 970(s), 895(s).



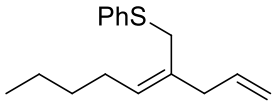
(E)-2-methyl-6-(penta-1,4-dien-1-yl)quinolone (1.37), compound was isolated as a pale yellow liquid (37.1mg, 71% yield, rs = 17:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 8.21 (d, J = 8.8 Hz, 1H), 7.63 – 7.41 (m, 2H), 7.36 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 15.9 Hz, 1H), 6.12 (dt, J = 15.9, 6.7 Hz, 1H), 5.84 (ddt, J = 16.7, 10.1, 6.7 Hz, 1H), 5.21 – 4.94 (m, 2H), 2.85 – 2.76 (m, 2H) 2.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 147.4, 136.3, 136.2, 135.2, 130.4, 129.5, 128.8, 127.4, 126.8, 124.9, 122.4, 116.0, 37.2, 25.3. GCMS (EI) calculated for [M]+ 209.12, found 209.10. FTIR (neat, cm^{-1}): 3060(m), 3055(m), 1637(s). 1750(m), 968(s), 755(s)



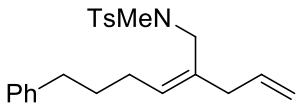
(E)-3-(4-phenylpenta-1,4-dien-1-yl)thiophene (1.38), compound was isolated as a white solid (91.6 mg, 81% yield, rs = 11:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.47 – 7.32 (m, 2H), 7.32 – 7.19 (m, 2H), 7.13 – 7.06 (m, 1H), 6.91 (dd, J = 5.1, 1.3 Hz, 1H), 6.79 (dd, J = 5.1, 2.9 Hz, 1H), 6.67 (dd, J = 3.1, 1.2 Hz, 1H), 6.30 (d, J = 15.9 Hz, 1H), 6.02 (dt, J = 15.9, 6.7 Hz, 1H), 5.40 (s, 1H), 5.08 (s, 1H), 3.18 (d, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 141.1, 14038, 128.5, 128.1, 127.6, 126.1, 126.1, 125.9, 125.2, 121.1, 113.5, 38.7. GCMS (EI) calculated for [M]+ 226.08, found 226.10. FTIR (neat, cm^{-1}): 3060(m), 3052(s), 1755(w), 1624(m), 968(s), 896(s).



(Z)-((2-allyl-6-phenylhex-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (1.39), compound was isolated as a clear colorless liquid (181.9 mg, 84% yield, rs = 16.1). ^{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).

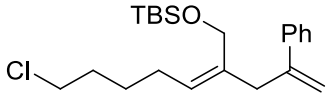


(Z)-nona-1,4-dien-4-yl(phenyl)sulfane (1.40), compound was isolated as a colorless liquid (110.0 mg, 89% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.07 – 6.87 (m, 3H), 5.79 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.15 – 4.96 (m, 2H), 3.49 (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).

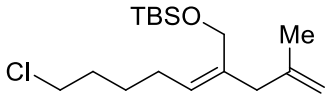


(Z)-N-(2-allyl-6-phenylhex-2-en-1-yl)-N,4-dimethylbenzenesulfonamide (1.41), compound was isolated as a clear colorless liquid (134.0 mg, 89% yield, rs = 9:1). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (d,

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).

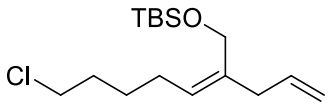


(Z)-tert-butyl((7-chloro-2-(2-phenylallyl)hept-2-en-1-yl)oxy)dimethylsilane (1.42), compound was isolated as a colorless liquid (164.5 mg, 87% yield, rs = 17:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.46 (d, *J* = 7.1 Hz, 1H), 7.14 – 7.19 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.48 (d, *J* = 1.7 Hz, 1H), 5.28 – 4.92 (m, 2H), 4.13 (s, 2H), 3.41 (s, 2H), 3.03 (t, *J* = 6.5 Hz, 2H), 1.83 (q, *J* = 7.2 Hz, 2H), 1.39 – 1.21 (m, 2H), 1.23 – 1.09 (m, 2H), 0.99 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 141.2, 136.9, 128.6, 128.2, 127.3, 126.4, 114.3, 60.2, 45.0, 40.2, 31.9, 27.0, 26.7, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 378.21, found 378.30. FTIR (neat, cm^{-1}): 2954.0 (s), 2855.7(s), 1625.5(w), 1444.2(m), 1250.7(m), 1073.3(s).

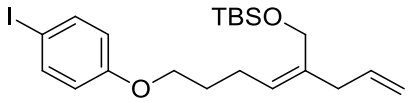


(Z)-tert-butyl((7-chloro-2-(2-methylallyl)hept-2-en-1-yl)oxy)dimethylsilane (1.43), compound was isolated as a colorless liquid (131.6 mg, 87% yield, rs = 19:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.17 (t, *J* = 7.4 Hz, 1H), 4.91 (s, 2H), 4.12 (s, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 2.91 (s,

2H), 1.92 (q, *J* = 7.4 Hz, 2H), 1.70 (s, 3H), 1.45 (p, *J* = 6.6 Hz, 2H), 1.26 (p, *J* = 7.5 Hz, 2H), 0.99 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 137.1, 128.3, 112.0, 59.8, 45.0, 43.5, 32.3, 27.3, 26.9, 26.1, 22.2, 18.5, -5.2. GCMS (EI) calculated for [M]+ 316.20, found 316.20. FTIR (neat, cm^{-1}): 2954.9(s), 286.7(s), 1647.59m), 1472.0(m), 1250.7(m), 1075.69(m).

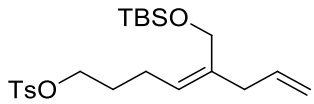


(Z)-((2-allyl-7-chlorohept-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (1.44), compound was isolated as a colorless liquid (133.1 mg, 88% yield, rs = 21:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.89 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.19 – 5.02 (m, 3H), 4.15 (s, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 2.96 (d, *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, 32.3, 30.0, 27.3, 26.9, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 302.18, found 302.20 FTIR (neat, cm^{-1}): 3076.5(m), 2954.3(s), 2856.4(s), 1636.1(m), 1471.89(m), 1250.9(m), 1706.0(m).

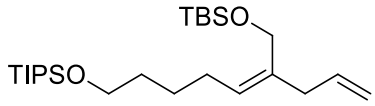


(Z)-((2-allyl-6-(4-iodophenoxy)hex-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (1.45), compound was isolated as a colorless liquid (200.0 mg, 85% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.14 (s, 1H), 6.83 – 6.88 (m, 3H), 5.89 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.22 (t, *J* = 7.4 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.19 (s, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 2.97 (d, *J* = 6.8 Hz, 2H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.64 (p, *J* = 6.6 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 138.4, 137.01, 129.5, 126.4, 120.6, 115.8, 114.6, 67, 60.3, 38.9, 29.6, 26.1, 24.2,

18.5, -5.2. GCMS (EI) calculated for [M]+ 472.13, found 472.00. FTIR (neat, cm^{-1}): 3073.0(m), 2953.7(s), 2855.6(s), 1636.3(m), 1471.3(m), 1246.0(s),1079.0(m).

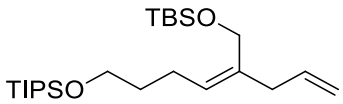


(Z)-5-(((tert-butyldimethylsilyl)oxy)methyl)octa-4,7-dien-1-yl 4-methylbenzenesulfonate (1.46), compound was isolated as a colorless liquid (171.0 mg, 81% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.76 (d, *J* = 7.9 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 5.81 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 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).



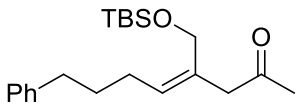
(Z)-6-allyl-13,13-diisopropyl-2,2,3,3,14-pentamethyl-4,12-dioxa-3,13-disilapentadec-6-ene (1.47), compound was isolated as a colorless liquid (189.4 mg, 86% yield, rs = 11:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.25 (t, *J* = 7.3 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.15 (s, 2H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.84 (d, *J* = 6.8 Hz, 2H), 2.06 – 2.10 (m, 2H), 1.52 – 1.58(m, 2H), 1.42 (p, *J* = 7.5 Hz, 2H), 1.05 – 1.07 (m, 21H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 137.3, 127.7, 115.7, 63.4, 60.4, 38.9, 32.8, 27.5, 26.4, 26.1, 18.5, 18.2, 12.2, -5.1. GCMS (EI) calculated for [M]+440.35, found 440.40. FTIR (neat, cm^{-1}):

2945 (s), 2867(s), 1636(w), 1471(s), 1462(s), 1388(m), 1360(w), 1250(s), 1105(s), 1071(s), 1013(s), 912(s), 882(s), 836(s).



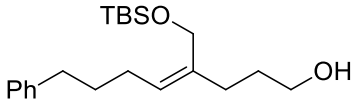
(Z)-6-allyl-12,12-diisopropyl-2,2,3,3,13-pentamethyl-4,11-dioxa-3,12-disilatetradec-6-ene (1.48), compound was isolated as a colorless liquid (162.0 mg, 76% yield, rs = 9:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.93 (ddt, *J* = 16.9, 9.9, 6.8 Hz, 1H), 5.31 (t, *J* = 7.4 Hz, 1H), 5.22 – 4.96 (m, 2H), 4.27 (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).

1.3.6 *Elaboration of Trisubstituted alkenes prepared by Hydroallylation (Scheme 1.5) :*



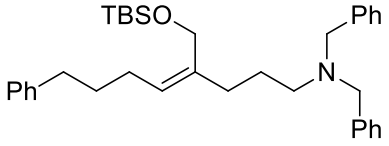
(Z)-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-2-one (1.49) Compound **1.39** was subjected to standard wacker oxidation procedure.[70] A scintillation vial was charged with stir bar, $PdCl_2$ (6.7 mg, 0.037 mmol, 0.15 equiv), CuCl (32.3 mg, 0.33 mmol, 1.4 equiv), and DMF:H_2O (3 mL, 7:1, 0.1 M). The reaction mixture was stirred at room temperature for 1 hour

under oxygen atmosphere. To this reaction mixture was added compound **1.39** (82.56 mg, 0.25 mmol, 1.0 equiv) and the reaction mixture was stirred at room temperature under oxygen atmosphere for 24 hours. The reaction mixture was dilute with water and was extracted with diethyl ether. The combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column. The compound was isolated as a colorless liquid (57.2 mg, 66% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 5.34 (t, *J* = 7.3 Hz, 1H), 4.17 (s, 2H), 3.16 (s, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.15 (s, 3H), 2.14 – 2.07 (m, 2H), 1.72 (p, *J* = 7.5 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 142.2, 133.7, 130.4, 128.5, 128.4, 125.9, 60.8, 49.8, 35.4, 31.4, 29.4, 27.2, 26.0, 18.4, -5.4. GCMS (EI) calculated for [M]+ 346.23, found 346.30. FTIR (neat, cm^{-1}): 3063(m), 3026(m), 2953(s), 1716(s), 938(m).



(Z)-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-ol (1.50) Compound **1.39** was subjected to hydroboration using a known procedure[71] and then the alkylborane product was subjected to oxidation using a known procedure.[72] In a nitrogen-filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (61.0 mg, 0.25 mmol, 0.55 equiv), 1, 4-dioxane (1 mL, 0.5 M) and compound **1.39** (165.3 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred overnight at 60 °C. The solvent was removed under reduced pressure. To the resulting reaction mixture was added a solution $NaBO_3{*}H_2O$ (159.7 mg, 1.6 mmol, 3.3 equiv) in THF:H_2O (910 µL, 1:1, 0.5 M). The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was dilute with water and was extracted with diethyl ether. The combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on

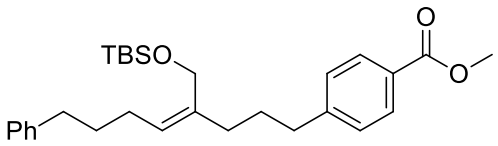
a silica gel column. The compound was isolated as a colorless liquid (140.2 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.25 – 7.14 (m, 2H), 7.14 – 7.03 (m, 3H), 5.36 – 5.17 (t, *J* = 6.3 Hz, 1H), 4.12 (s, 2H), 3.47 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.00 (q, *J* = 7.4 Hz, 2H), 1.76 – 1.50 (m, 4H), 0.97 (s, 10H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.4, 128.5, 128.40, 127.1, 125.8, 62.6, 60.8, 35.5, 31.7, 31.4, 31.0, 27.2, 26.1, 18.4, -5.2. GCMS (EI) calculated for [M]+ 348.25, found 348.20. FTIR (neat, cm^{-1}): 3340(br,s), 3026(m), 2927(s), 2855(s), 1471(s), 1070(s), 836(s).



(Z)-N,N-dibenzyl-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-amine (1.51)

Compound **39** was subjected to hydroamination using a known procedure.[71] In a nitrogen-filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (61.0 mg, 0.25 mmol, 0.5 equiv), 1, 4-dioxane (1 mL, 0.5 M) and compound **1.39** (165.3 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred overnight at 60 °C. The solvent was removed under reduced pressure. The reaction mixture was transferred to a 25 mL reaction flask. To the reaction mixture was added LiO*t*Bu (44 mg, 0.55 mmol, 1.1 equiv), ICyCuCl (8.3 mg, 0.025 mmol, 0.05 equiv), and Toluene (10 mL, 0.05M). The reaction flask was taken out of the glove box and put on the manifold using standard air-free techniques. A solution of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (158.7 mg in 400 µL Toluene, 0.500 mmol, 1.0 equiv) was added over 4 hours to the stirred reaction mixture at 60 °C. After addition of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine, the reaction mixture was allowed to stirred at 60 °C and the consumption of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine was monitored by TLC. The reaction mixture was filtered through a plug of silica gel with DCM. The solvent was

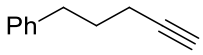
removed under reduced pressure and the crude product was purify by a silica gel column. The compound was isolated as a pale yellow liquid (195 mg, 74% yield). ^{1}H NMR (300 MHz, Benzene-d6) δ 7.41 (d, J = 7.2 Hz, 4H), 7.27 – 7.18 (m, 6H), 7.12 – 7.04 (m, 5H), 5.12 (t, J = 7.3 Hz, 1H), 4.12 (s, 2H), 3.51 (s, 4H), 2.70 – 2.31 (m, 4H), 2.22 (t, J = 7.7 Hz, 2H), 1.98 (q, J = 7.4 Hz, 2H), 1.73 (p, J = 7.5 Hz, 2H), 1.56 (p, J = 7.5 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 142.5, 140.2, 139.0, 128.9, 128.5, 128.4, 128.2, 126.8, 126.2, 125.8, 60.6, 58.5, 53.5, 35.6, 32.4, 31.7, 27.2, 26.1, 25.8, 18.5, -5.1. FTIR (neat, cm^{-1}): 3026(m), 2928(s), 2855(s), 1602(m), 1360(m), 1070(s), 836(s).



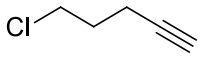
(Z)-methyl 4-(4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-yl)benzoate (1.52) Compound **1.39** was subjected to hydroboration using a known procedure[71] and then the alkylborane product was subjected to Suzuki coupling using a known procedure.[73] In a nitrogen filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (36.6 mg, 0.15 mmol, 0.5 equiv), 1,4-dioxane (550 µL, 0.5 M) and compound **1.39** (99.2 mg, 0.3 mmol, 1 equiv). The reaction mixture was stirred at 100 °C for 24 hours. To the reaction mixture was added Pd(OAc)2 (0.7 mg, 0.003 mmol, 0.01 equiv), tricyclohexylphosphine (1.7 mg, 0.006 mmol, 0.02 equiv), cesium carbonate (293.2 mg, 0.9 mmol, 3 equiv), and 4-bromo-methylbenzoate (71 mg, 0.33 mmol, 1.1 equiv) respectively. The reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with EtOAc and filtered through a plug of silica. The solvent was removed under reduced pressure and the crude product was purify by a silica gel. The compound was isolated as a colorless liquid. The yield was determined by ^{1}H NMR analysis of the crude

product using TMB as internal standard (76 % yield). ^{1}H NMR (300 MHz, Benzene-d6) δ 8.15 (d, J = 8.2 Hz, 2H), 7.25 – 7.15 (m, 2H), 7.13 – 6.99 (m, 5H), 5.20 (t, J = 7.4 Hz, 1H), 4.14 (s, 2H), 3.52 (s, 3H), 2.63 – 2.36 (m, 4H), 2.19 (t, J = 7.7 Hz, 2H), 2.02 (q, J = 7.4 Hz, 2H), 1.83 – 1.36 (m, 4H), 0.96 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 148.4, 142.5, 138.7, 129.8, 128.6, 128.5, 128.4, 127.9, 126.7 125.8, 60.6, 52.0, 35.9, 35.6, 34.5, 31.8, 29.9, 27.2, 26.1, 18.4, -5.2. GCMS (EI) calculated for [M]+ 466.29, found 466.40. FTIR (neat, cm^{-1}): 3026 (m), 2950(s), 2856(s), 1724(s), 1610(m), 1360(m), 836(m).

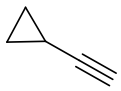
1.3.7 *Alkynes Starting Materials*



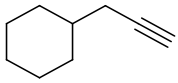
pent-4-yn-1-ylbenzene (1.7) was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



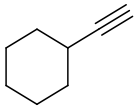
5-chloropent-1-yne (1.S1) was purchased from TCI America and distilled over calcium hydride under vacuum before use.



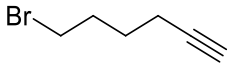
Ethynylcyclopropane (1.S2) was purchased from AK Scientific and distilled over calcium hydride under vacuum before use.



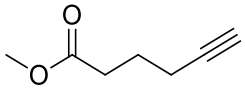
prop-2-yn-1-ylcyclohexane (1.S3) was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



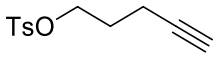
Ethynylcyclohexane (1.S4) was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.



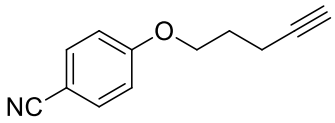
6-bromohex-1-yne (1.S5) was prepared according to a known procedure and has been previously characterized.[74]



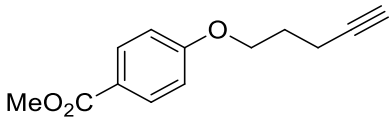
methyl hex-5-ynoate (1.S6) was prepared according to a known procedure and has been previously characterized.[75]



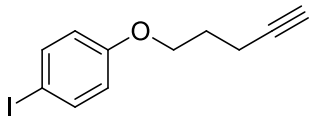
pent-4-yn-1-yl 4-methylbenzenesulfonate (1.S7) was prepared according to a known procedure and has been previously characterized.[76]



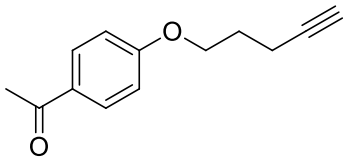
4-(pent-4-yn-1-yloxy)benzonitrile (1.S8) was prepared according to a known procedure and has been previously characterized.



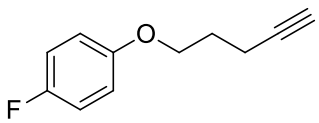
methyl 4-(pent-4-yn-1-yloxy)benzoate (1.S9) was prepared according to a known procedure and has been previously characterized.[39]



1-iodo-4-(pent-4-yn-1-yloxy)benzene (1.S10) A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with 4-iodophenol 2.4 mg, 10.8 mmol, 1.1 equiv), cesium carbonate (4.8 g, 14.7 mmol, 1.5 equiv), and DMSO (20 mL, 0.5 M). To this reaction mixture was added a solution of pent-4-yn-1-yl 4-methylbenzenesulfonate (2.3 g, 9.8 mmol, 1.0 equiv) in DMSO. The reaction mixture was stirred at 60 °C until the tosylate was not observed by TLC. The reaction mixture was diluted with 100 mL ether and quenched with 20 mL of 1 M sodium hydroxide. The aqueous phase was extracted three times and the combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column with EtOAc/Hexane (0 → 10%) to yield a 2.3 g of a white powder, 81% yield.

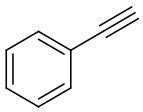


1-(4-(pent-4-yn-1-yloxy)phenyl)ethanone (1.S11) A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), 4-hydroxyacetophenone (1.0 g, 7.7 mmol, 1.1 equiv), THF (14.0 mL, 0.5 M) and 4-pentyn-1-ol (654 µL, 7.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (1.6 mL, 8.4 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to 23 °C and stirred overnight. The THF was removed under reduced pressure and the mixture 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 → 30%) to yield 1.2 g of a white powder, 88% yield. ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.80 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 3.53 (t, J = 6.2 Hz, 2H), 2.15 (s, 3H), 2.04 (td, J = 7.0, 2.7 Hz, 2H), 1.84 – 1.69 (m, 1H), 1.59 (p, J = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, C_6D6) δ 196.7, 162.8, 130.6, 130.3, 114.1, 83.1, 69.2, 66.3, 27.9, 26.3, 15.1. GCMS (EI) calculated for [M]+ 202.10, found 202.20.

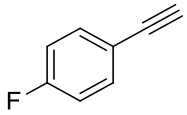


1-fluoro-4-(pent-4-yn-1-yloxy)benzene (1.S12) A reaction flask charged with a stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), 4-fluorophenol (0.86 g, 7.7 mmol, 1.1 equiv),

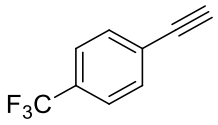
THF (14.0 mL, 0.5 M) and 4-pentyn-1-ol (654 µL, 7.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (1.6 mL, 8.4 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to 23 °C and stirred overnight. The THF was removed under reduced pressure and the reaction mixture 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 → 20%) to yield 1.0 g of a color liquid, 80% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.27 – 7.14 (m, 2H), 7.13 – 6.98 (m, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 2.62 (td, *J* = 7.0, 2.7 Hz, 2H), 2.31 (t, *J* = 2.7 Hz, 1H), 2.19 (p, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.2 (d, *J* = 237.7 Hz), 155.1, 115.7 (d, *J* = 23.0 Hz), 115.5, 83.4, 69.1, 66.7, 28.1, 15.1. GCMS (EI) calculated for [M]+ 178.08, found 178.20. FTIR (neat, cm^{-1}): 3015 (w), 3002(w), 2942 (m), 1678(s), 1637(w), 1601(s), 1508(s), 1470(w), 1420(m), 1358(s), 1306(s), 1255(s), 1171(s), 1115(w), 970(w).



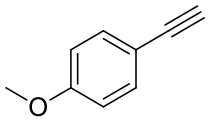
Ethynylbenzene (1.S13) was purchased from Sigma-Aldrich and distilled over sodium borohydride under vacuum before use.



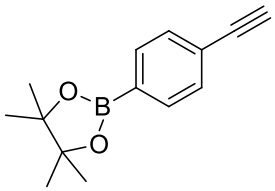
1-ethynyl-4-fluorobenzene (1.S14) was purchased from Sigma-Aldrich and distilled over sodium borohydride under vacuum before use.



1-ethynyl-4-(trifluoromethyl)benzene (1.S15) was purchased from Sigma-Aldrich and distilled over sodium borohydride under vacuum before use.

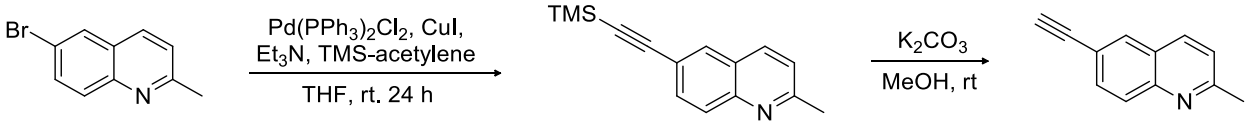


1-ethynyl-4-methoxybenzene (1.S16) was purchased from Sigma-Aldrich and distilled over sodium borohydride under vacuum before use.



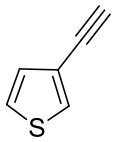
2-(4-ethynylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.S17) was purchased from Sigma-Aldrich and distilled over sodium borohydride under vacuum before use.

6-ethynyl-2-methylquinoline (1.S18)



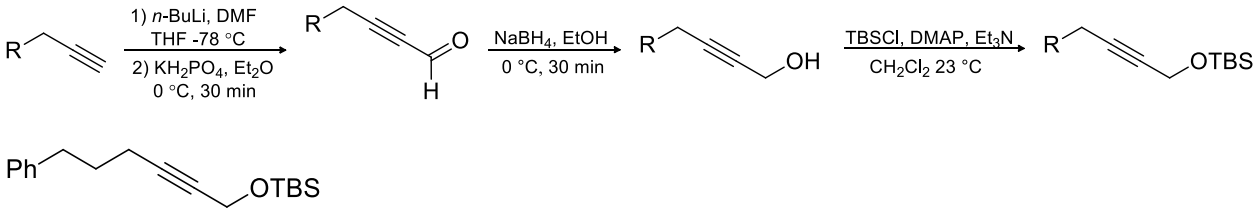
A reaction flask charged with a stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 0.05 equiv) and CuI (19 mg, 0.1 mmol, 0.1 equiv), bromo quinoline (221 mg, 1.0 mmol, 1 equiv) and THF (1 mL, 1 M). To the reaction mixture was added triethylamine (220 µL, 1.55 mmol, 1.55 equiv) and Trimethylsilylacetylene (180 µL, 1.25 mmol, 1.25 equiv) dropwise. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was filtered through a plug of celite

and the solvent was removed under reduced pressure. To the resulting reaction mixture was added a solution of K_2CO_3 (276.4 mg, 2 mmol, 2 equiv) in methanol (3 mL, 0.33 M). The reaction mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the crude product was purify by column chromatography. The compound was isolated as white solid (92 mg, 55% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.02 – 7.89 (m, 3H), 7.71 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 3.16 (s, 1H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 147.5, 136.0, 132.5, 131.9, 128.9, 126.2, 122.9, 119.6, 83.5, 78.1, 25.5.



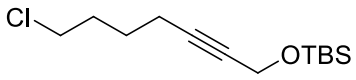
3-ethynylthiophene (1.S19) was purchased from combi-blocks and distilled over sodium borohydride under vacuum before use.

General Procedure for the Synthesis of Internal Alkynes

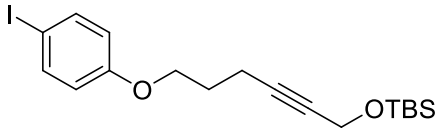


tert-butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane (1.57) compound was isolated as a colorless liquid (2.0 g, 83% overall yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.16 (m, 2H), 7.09 – 6.96 (m, 3H), 4.29 (t, *J* = 2.2 Hz, 2H), 2.92 – 2.39 (m, 2H), 2.01 (tt, *J* = 7.0, 2.2 Hz, 2H), 1.64 (p, *J* = 7.2 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),

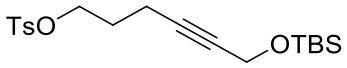
2899(m), 2857(s), 2231(w), 1604(w), 1496(m), 1461(m), 1370(w), 1253(s), 1136(s), 1080(s), 1002(w), 837(s), 777(s).



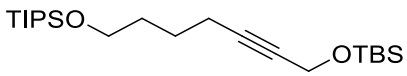
tert-butyl((7-chlorohept-2-yn-1-yl)oxy)dimethylsilane (1.S20) compound was isolated as a colorless liquid (4.2 g, 78% overall yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.29 (t, *J* = 2.2 Hz, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.26 (tt, *J* = 6.9, 2.2 Hz, 2H), 1.95 – 1.82 (m, 2H), 1.66 (p, *J* = 7.0 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).



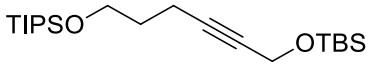
tert-butyl((6-(4-iodophenoxy)hex-2-yn-1-yl)oxy)dimethylsilane (1.S21) compound was isolated as a colorless liquid (2.2 g, 71% overall yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 – 7.11 (m, 2H), 7.10 – 6.65 (m, 2H), 4.30 (t, *J* = 2.2 Hz, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 2.43 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.98 (p, *J* = 6.6 Hz, 2H), 0.90 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 129.5, 120.8, 114.7, 84.3, 79.5, 66.4, 52.1, 28.5, 26.0, 18.4, 15.7, -5.0. GCMS (EI) calculated for [M]+ 430.08, found 430.10. FTIR (neat, cm^{-1}): 2954(s), 2928(s), 28556(s), 1600(s), 1587(s), 1496(s), 1472(s), 1436(w), 1387(w), 1245(s), 1171(w), 1139(m), 1075(s), 1000(w), 938(w), 836(s), 777(s).



6-((tert-butyldimethylsilyl)oxy)hex-4-yn-1-yl 4-methylbenzenesulfonate (1.S22) 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).



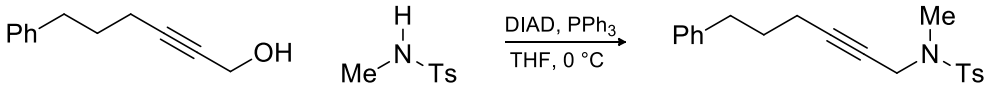
13,13-diisopropyl-2,2,3,3,14-pentamethyl-4,12-dioxa-3,13-disilapentadec-6-yne (1.S23) compound was isolated as a colorless liquid (2.7 g, 68% overall yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.39 – 4.17 (m, 1H), 3.70 (d, *J* = 5.3 Hz, 1H), 2.45 – 2.09 (m, 1H), 1.71 – 1.57 (m, 2H), 1.05 (d, *J* = 3.5 Hz, 9H), 0.97 – 0.87 (m, 5H), 0.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.4, 79.0, 63.0, 52.1, 32.3, 26.0, 25.3, 18.8, 18.5, 18.2, 12.2, -4.9. GCMS (EI) calculated for [M]+ 398.30, found 398.30. FTIR (neat, cm^{-1}): 2943(s), 2893(s), 2865(s), 2713(w), 2234(w), 1462(s), 1388(m), 1387(m), 1253(s), 1139(s), 1109(s), 1081(s), 1011(m), 882(s), 837(s).



12,12-diisopropyl-2,2,3,3,13-pentamethyl-4,11-dioxa-3,12-disilatetradec-6-yne (1.S24) compound was isolated as a colorless liquid (2.6 g, 68% overall yield). ^{1}H NMR (300 MHz,

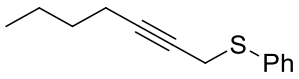
Chloroform-*d*) δ 4.29 (s, 2H), 3.75 (t, *J* = 6.0 Hz, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.73 (p, *J* = 6.6 Hz, 2H), 1.03 - 1.06 (m, 21H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.1, 78.7, 61.9, 52.0, 32.0, 26.0, 18.4, 18.1, 15.4, 12.1, -5.0. GCMS (EI) calculated for [M]+ 384.29, 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.S25)



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) dropwise. 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 143.4, 141.3, 134.2, 129.4, 128.3, 128.3, 127.9, 125.9, 86.0, 72.7, 40.3, 34.6, 34.3, 29.9, 21.4, 17.9. 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).

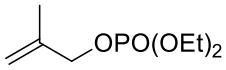


hept-2-yn-1-yl(phenyl)sulfane (1.59) was prepared according to a known procedure and has been previously characterized.[77]

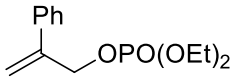
1.3.8 *General Procedure for the synthesis of Allyl Phosphate:*

A reaction flask charged with a stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with DMAP (0.10 equiv), DCM (0.5 M), alcohol (1.0 equiv) and diethyl chlorophosphate (1.01 equiv) respectively. The reaction mixture was cooled to 0 °C and triethylamine (1.5 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with 75 mL DCM and quenched with saturated sodium bicarbonate. The aqueous phase was extracted three times and the combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column.

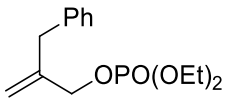
allyl diethyl phosphate (1.8) The compound was isolated as a colorless liquid (2.8 g, 73% yield). This compound has been previously characterized.[78]



diethyl (2-methylallyl) phosphate (1.S26) The compound was isolated as a colorless liquid (1.5 g, 51% yield). This compound has been previously characterized.[78]

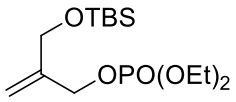


diethyl 2-phenylallyl phosphate (1.54) The corresponding alcohol was prepared from a known literature procedure.[79] The compound was isolated as a colorless liquid (1.9 g, 70% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.51 (m, 2H), 7.37 – 7.27 (m, 3H), 5.57 (s, 1H), 5.44 (s, 1H), 4.93 (d, $J_{P\text{-}H}$ = 7.3 Hz, 2H), 4.02 – 4.12 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.7, 137.4, 128.1, 128.0, 125.9, 115.1, 68.4, 63.6 (d, $J_{C\text{-}P}$ = 5.5 Hz), 15.9 (d, $J_{C\text{-}P}$ = 6.5 Hz). GCMS (EI) calculated for [M]+ 270.10, found 270.20. FTIR (neat, cm^{-1}): 3486(m), 3056(s), 2982(s), 2933(s), 2907(s), 1736(w), 1622 (m), 1525(m), 1444(s), 1393(s), 1264(s), 1166(s), 1099(s), 1025(s), 982(s), 879(w).

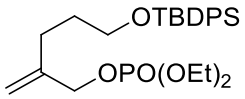


2-benzylallyl diethyl phosphate (1.24) The corresponding alcohol was prepared from a known literature procedure.[78] The compound was isolated as a colorless liquid (1.6 g, 61% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.27 – 7.36 (m, 2H), 7.19-7.24 (m, 3H), 5.19 (s, 1H), 4.97 (s, 1H), 4.41 (d, $J_{P\text{-}H}$ = 7.0 Hz, 2H), 4.04 – 4.14 (m, 4H), 3.43 (s, 2H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.5, 138.3, 128.9, 128.4, 126.4, 114.4, 69.0, 63.7, 39.4, 16.1 (d, $J_{C\text{-}P}$ = 6.4 Hz). GCMS (EI) calculated for [M]+284.12, found 284.20. FTIR (neat, cm^{-1}):

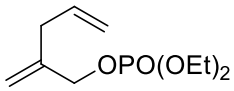
3062(w), 3028(w), 2984(s), 2933(s), 2909(s), 1653(m), 1602(m), 1496(m), 1454(m), 1394((m), 1369(m), 1275(s), 1166(s), 1033(s), 979(s), 875(m), 818(m), 743(m).



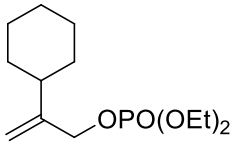
2-((tert-butyldimethylsilyloxy)methyl)allyl diethyl phosphate (1.S27) The starting alcohol was commercially available. The compound was isolated as a colorless liquid (1.4 g, 85% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.24 (s, 1H), 5.19 (s, 1H), 4.54 (d, J_{P-H} = 7.1 Hz, 2H), 4.19 (s, 2H), 4.06 – 4.16 (m, 4H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.5, 112.9, 67.5 (d, J_{C-P} = 5.8 Hz), 63.7, 63.4, 25.80, 18.3, 16.1, -5.5. GCMS (EI) calculated for [M]+ 338.17, found 338.20. FTIR (neat, cm^{-1}): 3412(s), 2982(s), 2950(s), 2904(s), 2856(s), 1660(m), 1472(s), 1463(s), 1444(m), 1392(s), 1369(s), 1258(s), 1166(s), 1032(s), 916(s), 838(s).



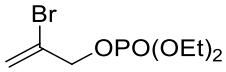
5-(tert-butyldiphenylsilyloxy)-2-methylenepentyl diethyl phosphate (1.S28) The corresponding alcohol was prepared from a known literature procedure. The compound was isolated as a colorless liquid (1.0 g, 41% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 – 7.61 (m, 4H), 7.46 – 7.31 (m, 6H), 5.09 (s, 1H), 4.94 (s, 1H), 4.44 (d, J_{P-H} = 7.0 Hz, 2H), 4.06 – 4.16 (m, 4H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.18 (t, *J* = 7.8 Hz, 2H), 1.74 (p, *J* = 7.3 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.04 (s, 9H).



diethyl 2-methylenepent-4-enyl phosphate (1.S29) The corresponding alcohol was prepared from a known literature procedure.[80] The compound was isolated as a colorless liquid (700 mg, 37% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 16.7, 10.7, 7.0 Hz, 1H), 5.17 – 5.09 (m, 2H), 5.07 (s, 1H), 5.00 (s, 1H), 4.46 (d, J_{P-H} = 7.0 Hz, 2H), 4.08 – 4.18 (m, 4H), 2.84 (d, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 6H).

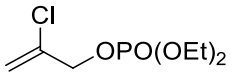


2-cyclohexylallyl diethyl phosphate (1.S30) The corresponding alcohol was prepared from a known literature procedure.[81] The compound was isolated as a colorless liquid (1.3 g, 48% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.07 (s, 1H), 4.94 (s, 1H), 4.49 (d, J_{P-H} = 6.7 Hz, 2H), 4.07 – 4.17 (m, 4H), 1.97 (t, *J* = 11.8 Hz, 1H), 1.78 (t, *J* = 13.4 Hz, 4H), 1.68 (d, *J* = 13.5 Hz, 2H), 1.34 (t, J_{P-H} = 7.1 Hz, 6H), 1.31 – 1.21 (m, 2H), 1.22 – 1.09 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.3 (d, J_{C-P} = 8.4 Hz), 110.6, 69.0, 63.7, 40.7, 32.1, 26.6, 26.2, 16.1 (d, J_{C-P} = 6.5 Hz). GCMS (EI) calculated for [M]+376.15, found 376.20. FTIR (neat, cm^{-1}): 3549(m), 3487(m), 3086(s), 2982(s), 2926(s), 2852(s), 2669(w), 1646(s), 1479(s), 1479(s), 1449(s), 1393(s), 1369(s), 1277(s), 1166(s), 1099(s), 1027(s), 981(s), 890(s).



2-bromoallyl diethyl phosphate (1.S31) The starting alcohol was commercially available. The compound was isolated as a colorless liquid (1.0 g, 73% yield). ^{1}H NMR (300 MHz, Chloroform-

d) δ 6.01 (s, 1H), 5.72 – 5.63 (s, 1H), 4.60 (d, *J* = 7.9, 2H), 4.24 – 4.06 (m, 4H), 1.35 (t, *J* = 7.1, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 128.2, 126.2 (d, J_{C-P} = 8.4 Hz), 118.6, 69.9, 64.0, 16.0. GCMS (EI) calculated for [M]+271.98, found 271.00. FTIR (neat, cm^{-1}): 3546(w), 3101(w), 2983(s), 2933(m), 2909(w), 1644(s), 1639(s), 1479(w), 1444(m), 1394(s), 1369(s), 1277(s), 1167((s), 1099(s), 1033(s), 981(s), 875(m).



2-chloroallyl diethyl phosphate (1.S32) The starting alcohol was commercially available. The compound was isolated as a colorless liquid (850 mg, 73% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.48 (s, 1H), 5.33 (s, 1H), 4.46 (d, *J* = 7.9, 2H), 4.00 – 4.10 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 135.5 (d, J_{C-P} = 8.2 Hz), 127.7, 114.2, 63.5, 15.5 (d, J_{C-P} = 6.3 Hz). GCMS (EI) calculated for [M]+228.03, found 228.10.

A reaction flask charged with a stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with DMAP (0.10 equiv), DCM (0.5 M), alcohol (1.0 equiv) and diethyl chlorophosphate (1.01 equiv) respectively. The reaction mixture was cooled to 0 °C and triethylamine (1.5 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with 75 mL DCM and quenched with saturated sodium bicarbonate. The aqueous phase was extracted three times and the combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column.

1.3.9 *Synthesis and Characterization of Alkyne Starting Materials*

The alkenyl copper **1.5** was prepared from a known literature procedure and has been previously characterized.[50]

In a nitrogen-filled glovebox, a stock solution of alkenyl copper complex **1.5** (191.2 mg, 0.32 mmol, 1.0 equiv) and internal standard TMB (26.8 mg, 0.16 mmol, 0.5 equiv) in 2000 µL toluene was prepared before the experiment. A 500 µL aliquot of the alkenyl copper/TMB stock solution was added to dram vial charged with stir bar and 300 µL of toluene. To this solution was added either allyl electrophile (0.240 mmol, 3.0 equiv). The reaction mixture was stirred at 45 °C. A 50 µL aliquot was taken. The aliquot was diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis. Table 1.12 shows the product yield of the reaction.

Table 1.12: Yield of 1.6 using different electrophile.

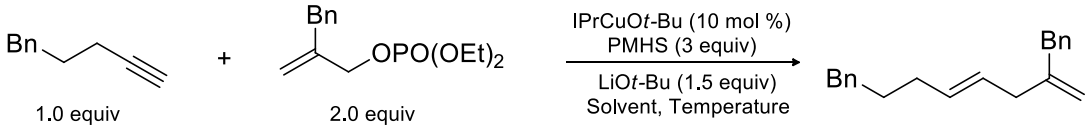
Electrophile	**% Yield 12h**
Allyl phosphate (1.1 equiv)	90% (After 32 h)
Allyl phosphate	98%
Allyl chloride	96%
Allyl acetate	0% (After 24 h)
Allyl carbonate	9% (After24 h)

Optimization for reactions with 2-substituted allylic electrophile (Table 1.12)

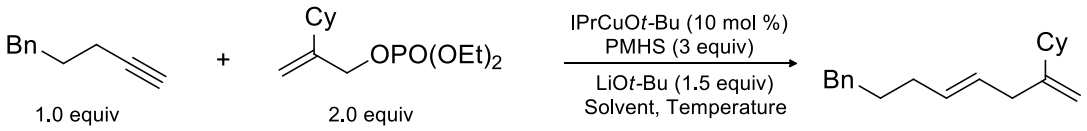
In a nitrogen-filled glovebox, three stock solutions of phenyl pentyne **1.7** with TMB in toluene, isooctane or heptane were prepared directly before the experiment: phenyl pentyne **1.7** (57.6 mg,

0.4 mmol, 4.0 equiv) and TMB (33.6 mg, 0.2 mmol, 0.2 equiv) were combined in 2000 µL toluene, isooctane or heptane. A dram vial was charged with a stir bar, LiO*t*-Bu (12.0 mg, 0.15 mmol, 1.5 equiv), IPrCuO*t*-Bu (5.3 mg, 0.01 mmol, 0.10 equiv), desired solvent (500 µL), PMHS, (18.0 mg, 0.3 mmol, 3.0 equiv), and 500 µL of stock solution of phenyl pentyne **7** with TMB respectively. The reaction mixture was stirred at 25 °C until the yellow color disappeared. To this reaction mixture was added 2-benzylallyl diethyl phosphate (56.69 mg, 0.2 mmol, 2.0 equiv, Table 1.13 entries 1-5) or 2-cyclohexylallyl diethyl phosphate (55.2 mg, 0.2 mmol, 2.0 equiv, Table 1.13 entries 6-7) and the reaction mixture was vigorously stirred at the desired temperature for 16 hours. A 50 µL aliquot was taken. The aliquot was diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis.

Table 1.13: Solvent and temperature effects in reaction with 2-substituted allylic electrophile



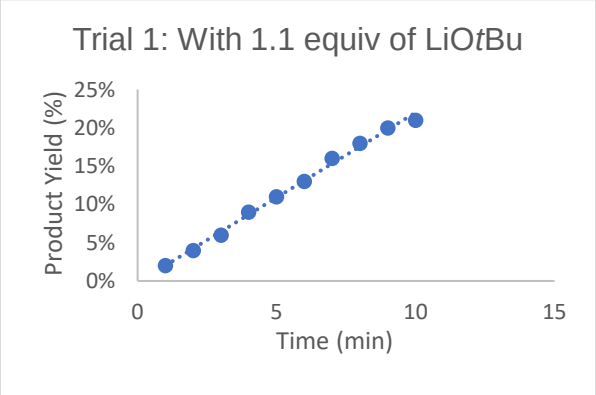
Entry	Solvent	Temperature	Yield
1	toluene	45 °C	15%
2	toluene	90 °C	22%
3	isooctane	45 °C	68%
4	isooctane	60 °C	63%
5	isooctane	90 °C	90%

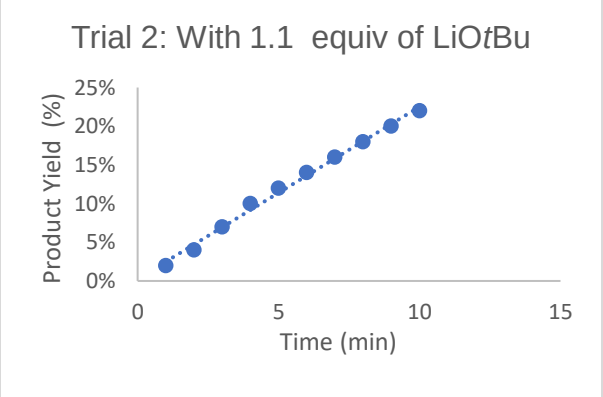


6	isooctane	90 °C	91%
7	heptane	90 °C	95%

1.3.10 *Kinetics Experiments:*

Reaction with Lithium tert-butoxide in Toluene. In a nitrogen-filled glovebox, a dram vial was charged with stir bar, alkenylcopper **1.5** (47.8 mg, 0.08 mmol, 1.0 equiv), and LiO*t*-Bu (7.0 mg, 0.088 mmol, 1.10 equiv). The mixture was suspended with toluene (600 µL) and then allyl diethyl phosphate **1.8** (46.6 mg, 0.240 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 1 min for the first 10 min of the reaction. The 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1400 µL of diethyl ether to quench the reaction before GC analysis. This reaction was done three times. Figure 1.2 shows the graphs of product yield over time. Table 1.14 shows the product yield for the first 10 minutes of the reaction. Table 1.17 shows the initial rates and the relative rate





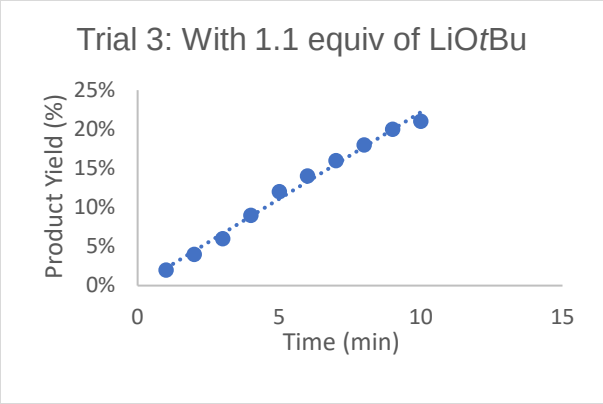
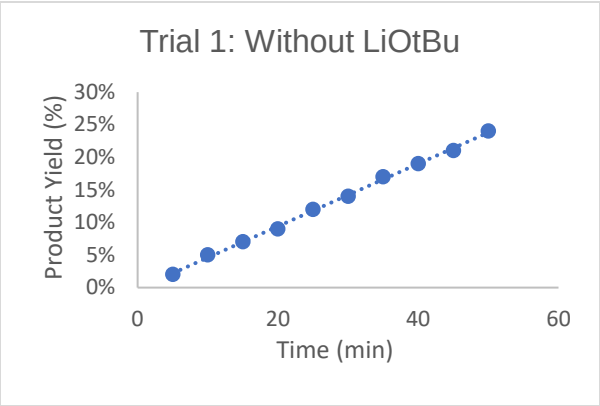


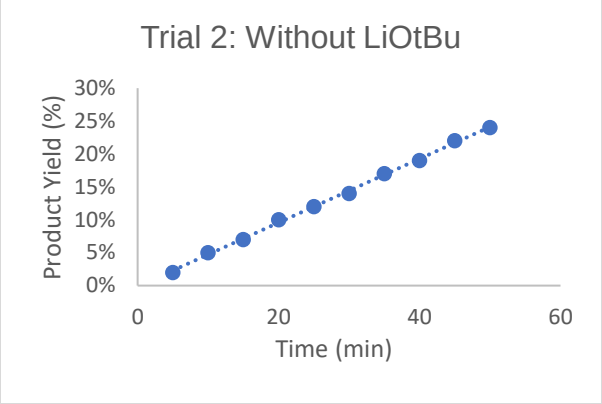
Figure 1.2 Product yield over time with 1.1 equiv of LiO*t*-Bu in toluene.

Table 1.14: Product yield for the first 10 minutes of the reaction of alkenyl copper complex with allyl phosphate and LiO*t*-Bu in toluene.

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Trial 1	2%	4%	6%	9%	11%	13%	16%	18%	20%	21%
Trial 2	2%	4%	7%	10%	12%	14%	16%	18%	20%	22%
Trial 3	2%	4%	6%	9%	12%	14%	16%	18%	20%	21%

Reaction without Lithium tert-butoxide in Toluene. In a nitrogen-filled glovebox, a dram vial was charged with stir bar and alkenylcopper **1.5** (47.8 mg, 0.08 mmol, 1.0 equiv). The mixture was suspended with toluene (600 µL) and then allyl diethyl phosphate **1.8** (46.6 mg, 0.240 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 5 min for the first 50 min of the reaction. The 50- µL aliquot was pipetted onto silica gel plug and rinse through with 1400 µL of diethylether to quench the reaction before GC analysis. This reaction was done three times. Figure 1.3 shows the graphs of product yield over time. Table 1.15 shows the product yield for the first 50 minutes of the reaction. Table 1.17 shows the initial rates and the relative rate.





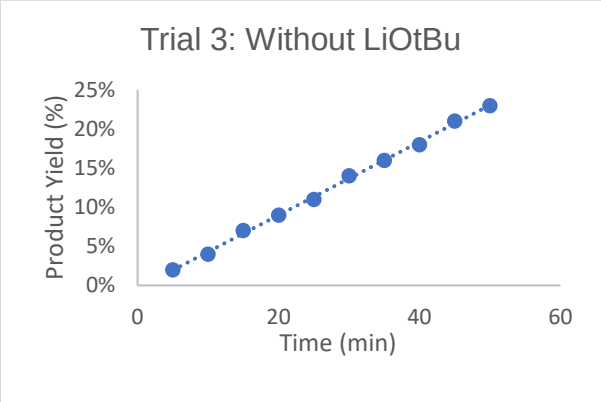


Figure 1.3 Product yield over time without Li*O*t-Bu in toluene**.**

Table 1.15: Product yield for the first 50 minutes of the reaction of alkenyl copper complex with allyl phosphate in toluene.

Time (min)	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**
Trial 1	2%	5%	7%	9%	12%	14%	17%	19%	21%	24%
Trial 2	2%	5%	7%	10%	12%	14%	17%	19%	22%	24%
Trial 3	2%	4%	7%	9%	11%	14%	16%	18%	21%	23%

Reaction with Lithium tert-butoxide and 12-crown-4 in Toluene. In a nitrogen-filled glovebox, a dram vial was charged with stir bar, alkenylcopper **1.5** (47.8 mg, 0.08 mmol, 1.0 equiv), and Li*O*t-Bu (7.0 mg, 0.088 mmol, 1.10 equiv). The mixture was suspended with toluene (600 µL) and then 12-crown-4 (15.5 mg, 0.088 mmol, 1.10 equiv), allyl diethyl phosphate **1.8** (46.6 mg, 0.240

mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added respectively. The reaction mixture was stirred at 45 °C. Aliquots were taken every 1 min for the first 10 min of the reaction. The 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1400 µL of diethyl ether to quench the reaction before GC analysis. Figure 1.4 shows the graph of product yield over time. Table 1.16 shows the product yield for the first 10 minutes of the reaction. Table 1.17 shows the initial rate and the relative rate.

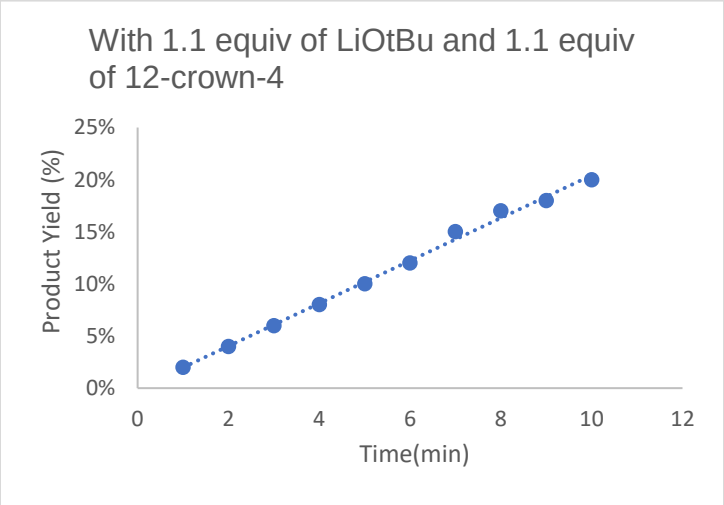


Figure 1.4 Product yield over time without LiO*t*-Bu and 12-crown-4 in toluene.

Table 1.16: Product yield for the first 10 minutes of the reaction of alkenyl copper complex 1.5 with allyl phosphate, LiO*t*-Bu, and 12-crown-4 in toluene.

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Trial 1	2%	4%	6%	8%	10%	12%	15%	17%	18%	20%

Table 1.17: The rate, average rate and the relative rate of the allylation of alkenylcomplex 1.5 with or without the additive in toluene.

Additive	**Trial 1**	**Trial 2**	**Trial 3**	**Average**	**Relative initial rate**
None	0.0048	0.0048	0.0047	0.0048	1.0
LiOtBu	0.0222	0.0222	0.0222	0.0222	4.7

Reaction with Lithium tert-butoxide in THF. In a nitrogen-filled glovebox, a dram vial was charged with stir bar, alkenylcopper **1.5** (47.8 mg, 0.08 mmol, 1.0 equiv), and LiO*t*-Bu (7.0 mg, 0.088 mmol, 1.10 equiv). The mixture was suspended with THF (700 µL) and then allyl diethyl phosphate **1.8** (46.6 mg, 0.24 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in THF (100 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 3 min for the first 30 min of the reaction. The 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1400 µL of diethyl ether to quench the reaction before GC analysis. This reaction was done two times. Figure 1.5 shows the graphs of product yield over time. Table 1.18 shows the product yield for the first 30 minutes of the reaction. Table 1.20 shows the initial rates and the relative rate.

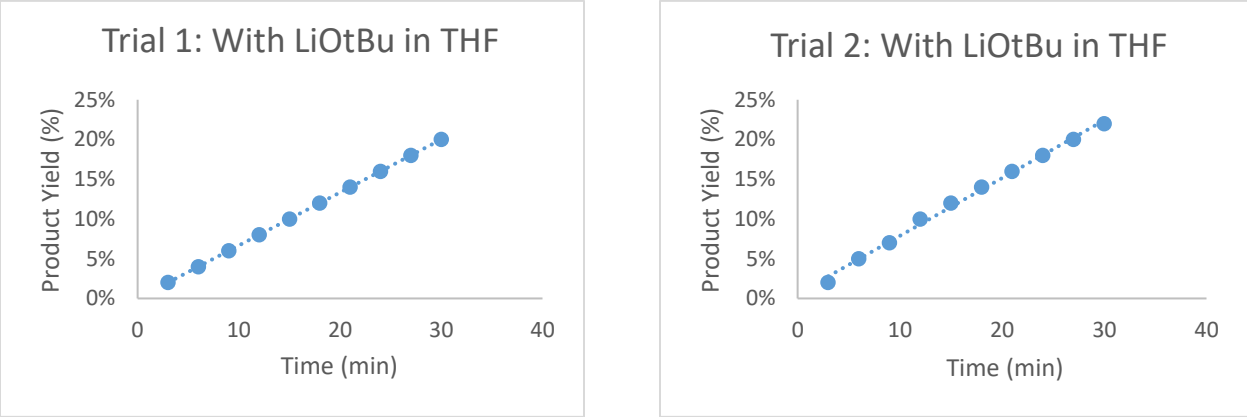
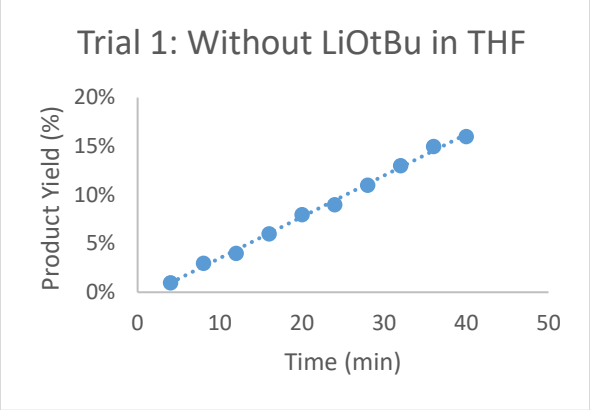


Figure 1.5 Product yield over time with 1.1 equiv of LiO*t*-Bu in THF.

Table 1.18: Product yield for the first 30 minutes of the reaction of alkenyl copper complex 1.5 with allyl phosphate and LiO*t*-Bu in THF.

Time (min)	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**
Trial 1	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%
Trial 2	2%	5%	7%	10%	12%	14%	16%	18%	20%	22%

Reaction without Lithium tert-butoxide in THF. In a nitrogen-filled glovebox, a dram vial was charged with stir bar and alkenylcopper **1.5** (47.8 mg, 0.08 mmol, 1.0 equiv). The mixture was suspended with THF (700 µL) and then allyl diethyl phosphate **1.8** (46.6 mg, 0.24 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in THF (100 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 4 min for the first 40 min of the reaction. The 50- µL aliquot was pipetted onto silica gel plug and rinse through with 1400 µL of diethylether to quench the reaction before GC analysis. This reaction was done two times. Figure 1.6 shows the graphs of product yield over time. Table 1.19 shows the product yield for the first 40 minutes of the reaction. Table 1.20 shows the initial rates and the relative rate.



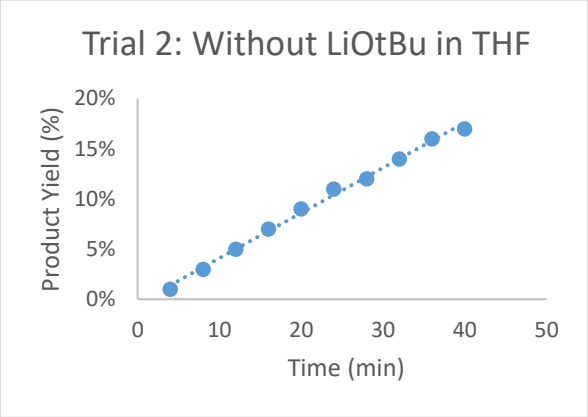


Figure 1.6 Product yield over time without LiO*t*-Bu in THF.

Table 1.19: Product yield for the first 40 minutes of the reaction of alkenyl copper complex **1.5** with allyl phosphate in THF.

Time (min)	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Trial 1	1%	3%	4%	6%	8%	9%	11%	13%	15%	16%
Trial 2	1%	3%	5%	7%	9%	11%	12%	14%	16%	17%

Table 1.20: The rate, average rate and the relative rate of the allylation of alkenylcomplex 1.5 with or without the additive in THF.

Additive	Trial 1	Trial 2	Average	Relative initial rate
None	0.0042	0.0045	0.00435	1.0
LiOtBu	0.0067	0.0073	0.007	1.6

1.3.11 *Competition Experiments*

In a nitrogen-filled glovebox, a dram vial was charged with IPrCuO*t*-Bu (42.0 mg, 0.08 mmol, 1 equiv) and C_6D_6 (550 µL). To the reaction mixture was added triethoxysilane (14.5 µL, 0.084 mmol, 1.05 equiv) which resulted to a bright orange color. The reaction mixture was stirred at 25 °C for 90 s. The reaction mixture was transferred to a dram vial containing phenylpentyne (**7**) (34.6 mg, 0.24 mmol, 3.0 equiv), phosphate **1.54** (64.9 mg, 0.24 mmol, 3.0 equiv), internal standard TMB (6.7 mg, 0.04 mmol, 0.5 equiv) and C_6D_6 (2.0 mL). The reaction mixture was vigorously stirred at 45 °C. After 5 minutes, 50 µL aliquots were taken and was diluted with 500 µL of 1:1 mixture of 0.1 M HCl and ether. The ether layer was extracted and pipetted onto silica plug and rinsed through with 1500 µL of EtOAc. Table 1.21 shows the product yield and the relative rate.

Table 1.21: Yield of competition experiment and the relative rate.

Product	Yield	Relative Rate
55	61%	2.3
56	27%	1

Stoichiometric Reaction of Alkenylcopper Complex 1.5 with LiOtBu

In a nitrogen-filled glovebox, alkenylcopper complex **1.5** (89.6 mg, 0.15 mmol, 1.0 equiv), LiOtBu (14.4 mg, 0.18 mmol, 1.20 equiv), and TMB (12.6 mg, 0.075 mmol, 0.5 equiv) were combined with 400 µL of C_6D_6 and then transferred to a J. Young tube with Teflon plug valve, washing in 2x with 100 µL of C_6D_6. ^{1}H NMR and ^{13}C NMR was taken right away and then the J Young tube was heated to 45 °C. After 1 hour at 45 °C, ^{1}H NMR and ^{13}C NMR was taken again. There were no differences in the chemical shifts and integration between the two NMR time points.

Stoichiometric Reaction of Copper Hydride with Internal Alkynes (Scheme 1.9)

Stoichiometric Reaction for the Synthesis of OTBS-substituted Alkenyl Copper 1.**58.** 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 **1.57** (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.

Stability studies of OTBS-substituted Alkenyl Copper 1.58. In a nitrogen filled glovebox, OTBS-substituted alkenyl copper **1.58** (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, 1h, 4h and 24h and monitored by ^{1}HNMR spectroscopy for the decomposition of the alkenyl copper. Table 1.22 shows the decomposition of complex 58 over time.

Table 1.22: Decomposition of the OTBS-Substituted Alkenyl Copper **1.58**

Time (h)	**Percent of Decomposition**
0.5	100%
1	99%
4	89%
24	79%

Stoichiometric Reaction for synthesis of Thioether substituted alkenyl Copper 1.60. 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 **1.59** (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. X-ray Crystallography revealed that alkenyl copper **1.60** could not be isolated.

Stoichiometric Reaction of OTBS-substituted Alkenyl Copper 1.58 with Allyl Phosphate 1.8 and Alkyl Triflate 1.61 (Scheme 1.10)

Reaction with Allyl Phosphate 1.8. In a nitrogen filled glovebox, a 1-dram vial was charged with a stir bar, OTBS substituted alkenyl copper **1.58** (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 **1.8** (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 1.23 shows the yield of the reaction in an hour.

Table 1.23: Yield of 1.39 formed in an hour.

Time (min)	**Yield**
10	15%
60	90%

Reaction with Alkyl Trilfate 1.61. In a nitrogen filled glovebox, a 1-dram vial was charged with a stir bar, OTBS substituted alkenyl copper **1.58** (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-propyltrilfate **1.61** (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 1.24 shows the yield of the reaction in an hour.

Table 1.24: Yield of 1.62 formed in an hour.

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

1.3.12 *X-Ray Crystallography*

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.

Solution by direct methods (SHELXS, SIR97[82,83]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97.[84,85] Scattering factors are from Waasmair and Kirfel.[86] 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 1.25 summarizes the data collection details. Figure 1.7 shows an ORTEP [84] of the asymmetric unit.

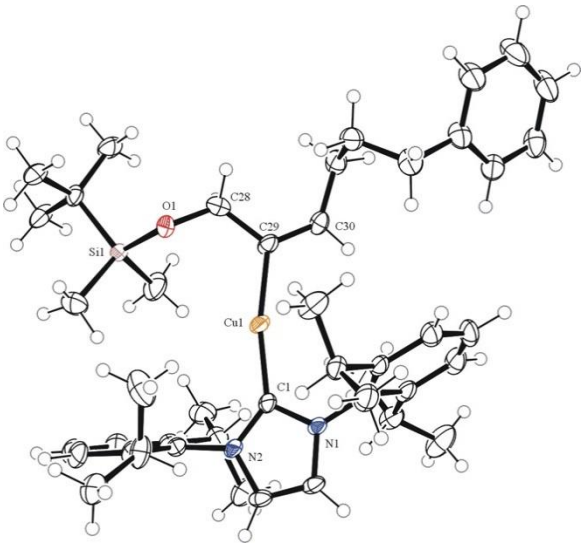


Figure 1.7 ORTEP of the structure with thermal ellipsoids at the 50% probability level. Disorder omitted for clarity.

Table 1.25: 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. Å3

IPrCuSPh

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.

Solution by direct methods (SHELXS, SIR97[82,83]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97.[84,85] Scattering factors are from Waasmair and Kirfel.[86] 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 1.26 summarizes the data collection details. Figure 1.26 shows an ORTEP[84] of the asymmetric unit.

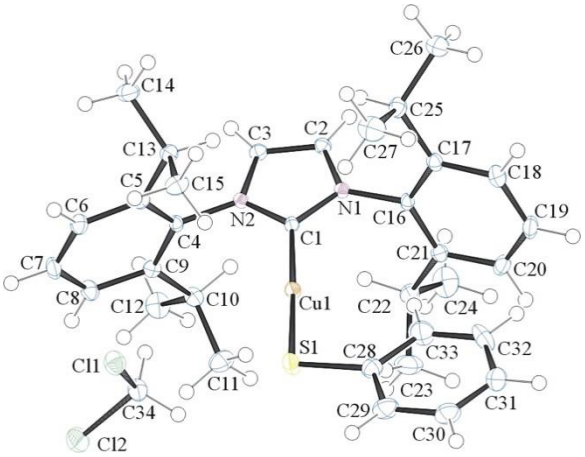


Figure 1.8 ORTEP of the structure with thermal ellipsoids at the 50% probability level.

Table 1.26: 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.

PHOTOINDUCED COPPER-CATALYZED COUPLIN OF TERMINAL ALKYNES AND ALKYL IODIDES

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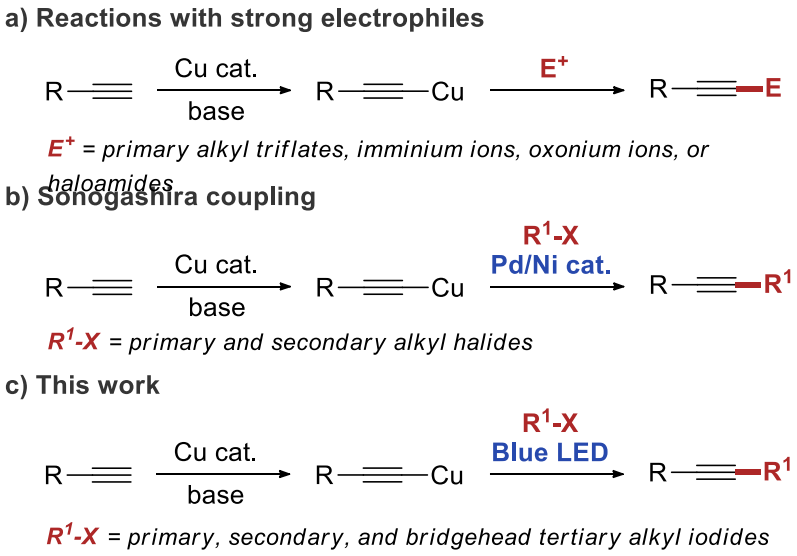
2.1 INTRODUCTION

The alkylation of terminal alkynes and their derivatives is an important approach to the synthesis of internal alkynes. Numerous methods are available for the alkylation of prefunctionalized alkyne substrates, such as haloalkynes,[1–5] metal acetylides,[6–11] alkynyl benziodoxolones,[12–15] and alkynyl sulfones.[16] In comparison, there are significantly fewer methods for the alkylation of terminal alkynes.

Most catalytic methods[17] for the alkylation of terminal alkynes rely on the in situ formation of copper acetylides, which serve as key catalytic intermediates (Scheme 1). They are easily formed from terminal alkynes in the presence of a weak base and a copper salt.[18] However, the low nucleophilicity of copper acetylides makes their alkylation challenging.[18] Direct alkylation

can only be achieved by using strong electrophiles, such as primary alkyl triflates,[19] activated α- and β-haloamides,[20,21] oxocarbenium ions,[22–24] and iminium ions (**Schemea**).[25–27] Alternatively, the alkylation of copper acetylides can be accomplished under Sonogashira conditions,[28,29] which require an additional transition-metal catalyst (**Schemeb**). Although examples of Sonogashira alkylation reactions are relatively rare, the reaction can be accomplished by using primary alkyl halides and a palladium[30] or nickel catalyst.[31,32] More recently, two reports described the extension to reactions of secondary alkyl halides.[33,34] Overall, the Sonogashira reaction still provides the most general method for the alkylation of terminal alkynes.

Scheme 2.1 Copper-Catalyzed Alkylation of Terminal Alkynes

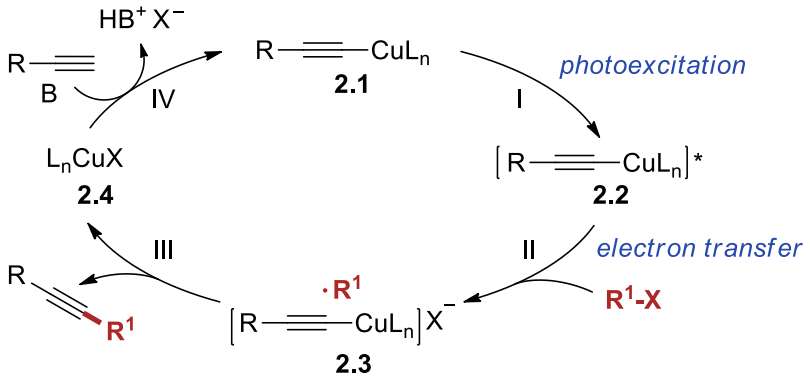


We were interested in developing a light-promoted copper-catalyzed coupling of terminal alkynes and alkyl halides that would obviate the need for palladium or nickel catalysts (**Schemec**). Both metals are significantly more toxic than copper and are often difficult to remove from the alkylation product.

Our approach to the alkylation of terminal alkynes was inspired by photoinduced copper-catalyzed reactions developed independently by the groups of Fu and Peters[35–37] and by Hwang and co-workers.[38–40] The key sequence in the transformations reported by Fu and Peters is the

photoexcitation of the copper–nucleophile complex followed by electron transfer to an alkyl halide. This approach has been applied to alkylations of a range of nitrogen-based nucleophiles.[41–45] Applications to carbon-based nucleophiles have thus far been limited to the alkylation of cyanide[46] and specific types of heteroarenes.[47,48] Numerous investigations of the photophysical properties of copper acetylides suggest that the same approach can be used to accomplish the photoinduced copper-catalyzed alkylation of terminal alkynes according to the mechanism outlined in **Scheme** .

Scheme 2.2 Plausible Mechanism of Photoinduced Alkylation



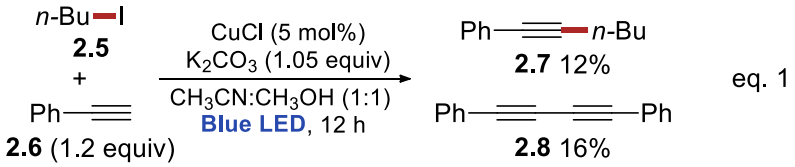
In 2012, simultaneously with the initial report by Fu and Peters,[35] Hwang et al. reported a method for the photoinduced copper-catalyzed arylation of terminal alkynes that involves photoexcitation of the copper acetylide intermediate.[38,49] Prior to Hwang's seminal work, it was known that the photoexcitation of copper acetylide complexes (acetylide→Cu transition) can be achieved with photons of relatively low energy (λ >350 nm).[50–52] The resulting excited states are long-lived (on the order of microseconds), and highly reducing (E1/2=−1.77 V vs. SCE).23c The redox potentials of alkyl iodides (EtI: E1/2=−0.92 V vs. SCE) suggest that they can be reduced by electron transfer from excited complex **2.2**.[53] Finally, organocopper complexes with similar photophysical properties to copper acetylides have been shown to undergo fast quenching of their excited states by electron transfer to a range of organohalides.[51]

2.2 RESULTS AND DISCUSSION

2.2.1 *Reaction Development*

Using the conditions established by Fu[35–37,41,42] and Hwang[38] as a starting point for our experiments, we explored the photochemical reaction of phenylacetylene with *n*-BuI using CuCl as the catalyst and an acetonitrile/methanol mixture as the solvent. The reaction resulted in the formation of only 12 % of the desired product and 16 % of the alkyne dimer. Together, these products accounted for only 28 % of the consumed alkyne. The rest of the starting alkyne was incorporated into low-molecular-weight polymers, identified by gel permeation chromatography (GPC) of the crude reaction mixture (**Scheme**). Similar results were obtained with alkyl- and aryl-substituted alkynes (**Scheme**).

Scheme 2.3 Initial Conditions and Mass Balance Analysis



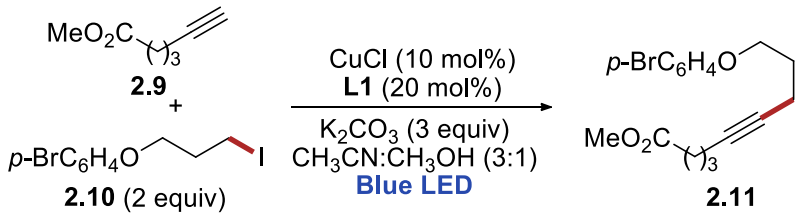
eq. 1

100% Conversion, low molecular weight polymers detected

Control experiments confirmed that polymerization occurs only in the presence of both light and the copper catalyst and suggested that the polymerization involves the photoactivated copper acetylide as a key intermediate. We surmised that with the proper choice of ligand for the copper catalyst, we could modulate the reactivity of the excited copper acetylide complex, suppress the polymer formation, and enable the desired alkylation. This approach was particularly attractive considering that ligand effects on reactivity in related photoexcited copper complexes have been rarely documented.

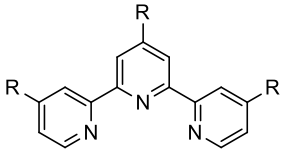
Exploration of a wide range of ligands and other reaction parameters led to the development of the alkylation reaction conditions shown in **Table** . The best results were obtained using 4,4’,4’’-tri-tert-butyl-2,2’:6’,2’’-terpyridine (**L1**) as the ligand, K_2CO_3 as the base, and acetonitrile/methanol (3:1) as the solvent system (entry 1). Throughout the optimization of this reaction, several observations were made, which have been summarized in **Table** .

Table 2.1 Reaction Development

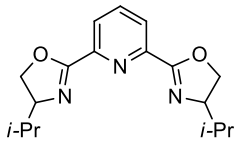


entry	*change from standard conditions*	*yield*[a]
1.	none	90%
2.	No Blue LED	0%
3.	No CuCl	0%
4.	No ligand	20%
5.	**L2** instead of **L1**	51%
6.	**L3** instead of **L1**	14%
7.	**L4** instead of **L1**	14%
8.	CH_3CN	26%
9.	CH_3OH	36%
10.	CH_3CN:CH_3OH (1:1)	74%
11.	Cs_2CO_3 as base	0%
12.	12 mol% **L1**	84%

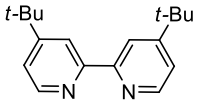
[a] GC yields are reported. All reactions performed on 0.25 mmol scale at 25 °C over 24 h.



R = *t*-Bu **L1**
R = H **L2**



L3



L4

Blue light and the copper catalyst were both necessary for the alkylation (entries 2 and 3). **L1** was determined to be essential for the success of the reaction (entry 4). In the absence of the ligand, we obtained only 20 % of the desired product, with the major product being polymerized

starting material. Replacing **L1** with unsubstituted terpyridine (**L2**) or closely related PyBox (**L3**) compromised the yield (entries 5 and 6). Additionally, structurally similar bidentate ligands, such as dtbpy (**L4**), were found to be ineffective (entry 7). The solvent was also important, with pure acetonitrile or pure methanol both giving significantly lower yields of the alkylation product (entries 8–10). Potassium carbonate was uniquely effective as the base, and even closely related cesium carbonate provided no alkylation product (entry 11). Decreasing the amount of ligand to 12 mol % did not lead to a considerable loss in yield (entry 12). Finally, we found that alkyl bromides and chlorides were not viable substrates.

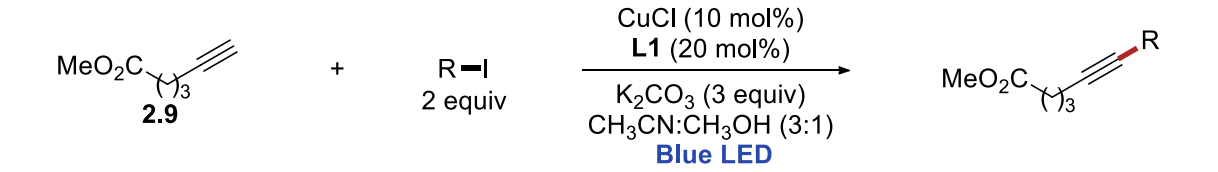
2.2.2 *Substrate Scope*

The standard reaction conditions were effective for a diverse set of electrophiles (**Table**). Primary iodides as well as cyclic and acyclic secondary alkyl iodides were viable substrates and provided the desired alkylation products in high yields. The reaction was compatible with a wide range of functional groups and was successfully accomplished in the presence of aryl bromides (**2.11**), aryl chlorides (**2.12**), alcohols (**2.17**), silyl ethers (**2.18**), nitriles (**2.14**), esters, sulfonamides (**2.26**), and ethers (**2.22**).

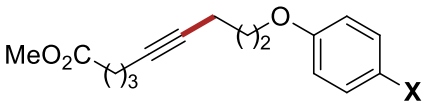
Reactions with tertiary iodides proved to be more difficult. Under the standard reaction conditions, simple *tert*-butyl iodide underwent solvolysis faster than the coupling reaction. Changing to *tert*-butyl bromide slowed down the solvolysis, but no coupling product was obtained. We reasoned that destabilizing the tertiary carbocation intermediate would prevent solvolysis and allow the coupling to proceed. This strategy proved effective, and bridgehead tertiary iodides were found to be viable coupling partners. 1-Adamantyl (**2.29**), bicyclopentyl (**2.28**), and bicyclooctyl (**2.30**) iodide all provided the expected alkylation product in useful yields. These results are worth

noting in light of the difficulties commonly encountered in alkynylations[54] and other cross-coupling reactions of tertiary bridgehead iodides.[55]

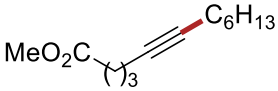
Table 2.2 Scope of Alkyl Iodides[a]



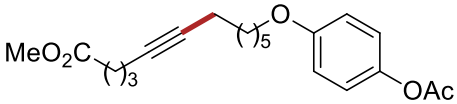
Primary iodides



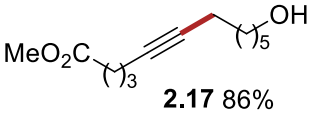
X = Br **2.11** 83%; Cl **2.12** 82%; Ac **2.13** 86%; CN **2.14** 82%



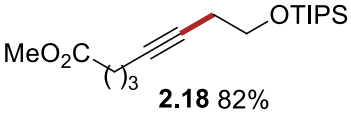
2.15 92%



2.16 85%

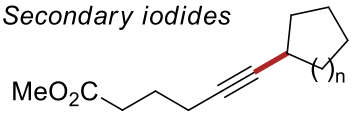


2.17 86%

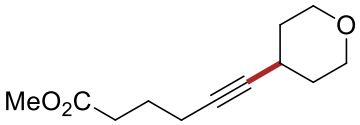


2.18 82%

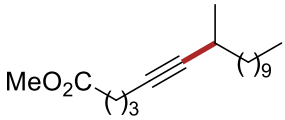
Secondary iodides



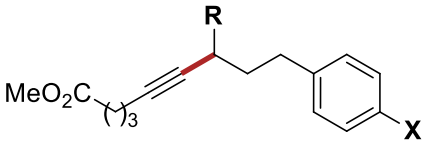
n = 1 **2.19** 92%[b]; 2 **2.20** 96%[b]; 3 **2.21** 91%



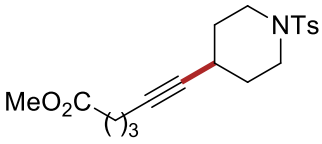
2.22 84%



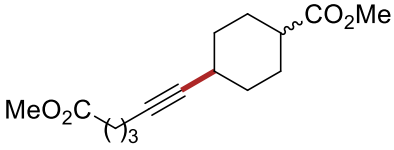
2.23 84%



R = Me, **X** = H **2.24** 85%
R = *i*-Pr, **X** = OMe **2.25** 78%[c]

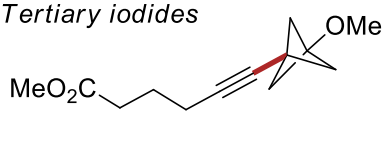


2.26 87%

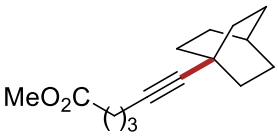


2.27 73% (1:1)

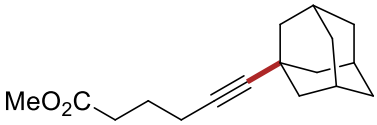
Tertiary iodides



2.28 53%[c,d]



2.30 43%[d]

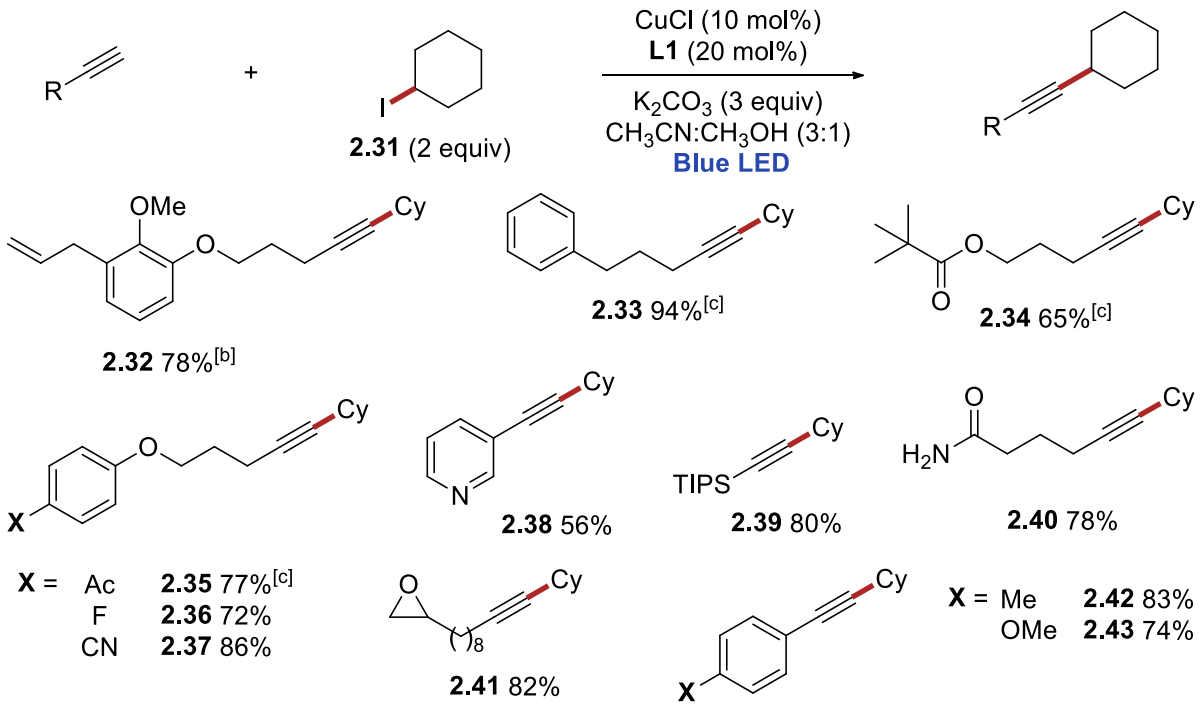


2.29 81%[c,d]

[a] All reactions were performed on a 0.5 mmol scale at 25 °C over 24 h unless otherwise specified. Yields are of the isolated product. The ratio of isomers reported in parenthesis was obtained by GC anlysis of the pure products. [b] 12 mol% ligand was used. [c] Reaction performed on a 0.25 mmol scale. [d] 48 hour reaction time.

We also explored the reaction with a range of terminal alkynes. A broad variety of alkyne coupling partners underwent the photoinduced coupling to furnish the corresponding products in very good yields (**Table**). Esters (**2.34**), nitriles (**2.37**), epoxides (**2.41**), ketones (**2.35**), aryl fluorides (**2.36**), and alkenes (**2.32**) were all compatible with the alkylation reaction. Similarly, the desired product was obtained in excellent yield in the presence of a primary amide (**2.40**), which is known to undergo N alkylation under similar reaction conditions.[42] Finally, aryl (**2.42** and **2.43**) and heteroaryl (**2.38**) alkynes also furnished the desired product in good yields.

Table 2. 3 Scope of Alkynes[a]



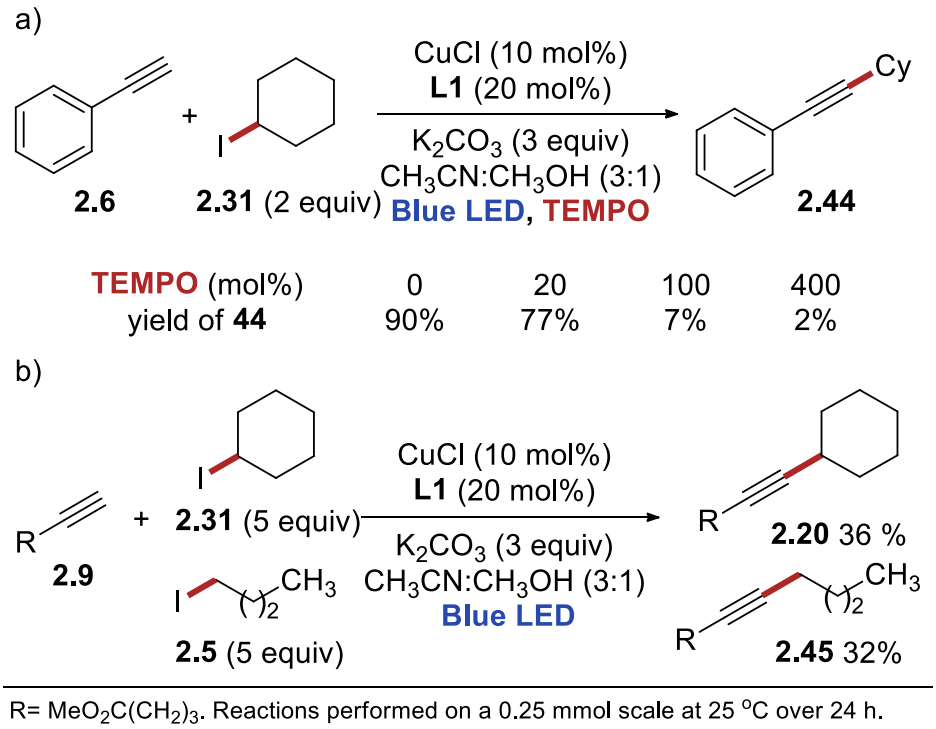
[a] Reactions were performed on a 0.5 mmol scale at 25 °C over 24 h. Yields are of the isolated product. Cy = cyclohexyl. [b] 48 hour reaction time. [c]12 mol% ligand was used.

2.2.3 *Mechanism*

Based on the mechanism of the related photoinduced copper-catalyzed alkylation, we propose that the alkylation of terminal alkynes proceeds according to the mechanism shown in

Scheme 2. In an effort to probe the mechanism of the reaction, we performed the experiments shown in Scheme 3. The presence of one or more equivalents of TEMPO completely shut down the reaction, whereas 20 mol % of TEMPO partially hampered it. Additionally, a cyclohexyl–TEMPO adduct was isolated from the reaction mixture, indicating the presence of alkyl radical intermediates. The results of these experiments suggest the involvement of free-radical intermediates. A competition experiment with a primary and a secondary alkyl iodide resulted in the formation of the two products in similar quantities (**Scheme b**). Considering the relatively small difference in the redox potentials of primary and secondary alkyl halides,[53] this result is consistent with electron transfer as the product- and rate-determining step of the reaction.

Scheme 2.4 Mechanistic Experiments



2.3 CONCLUSION

Overall, we have developed a photoinduced copper-catalyzed coupling of terminal alkynes with unactivated primary, secondary, and tertiary alkyl iodides. The reaction has a broad substrate scope and is compatible with esters, nitriles, alcohols, amides, epoxides, aryl halides, and ethers. The key for the success of the reaction is the tri-tert-butyl-terpyridine ligand, which favors the productive alkylation at the expense of the photoinduced copper-catalyzed polymerization of the starting materials. The alkylation reaction proceeds through a direct coupling between a copper acetylide and an unactivated alkyl iodide, most likely with the involvement of free-radical intermediates.

2.4 EXPERIMENTAL

2.4.1 *General Information*

All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a glovebox (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh. 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), or C_6D_6 (7.16 ppm)). ^{13}C 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, C_6D_6: δ 128.1 ppm). Data are represented as follows: chemical shift, multiplicity (s =

singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), integration, and coupling constants in Hertz (Hz). 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. Gel permeation chromatography was performed using a Waters chromatograph equipped with two 10 μm Malvern columns (300 mm × 7.8 mm) connected in series with increasing pore size (1000, 10 000 Å). ICP-MS experiments were performed using Perkin Elmer Optima 8300 inductively coupled plasma-optical emission spectrometer.

2.4.2 *Materials*

Acetonitrile was degassed and dried by passing through columns of neutral alumina. Methanol was degassed and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. Commercial reagents were purchased from Sigma-Aldrich, TCI America, GFS-Chemicals, and AK-Scientific. K_2CO_3 was purchased from Alfa Aesar. Ligands were purchased from Sigma Aldrich. NHC ligand was synthesizes from known procedure. Blue LED lamps (34W, Kessil A160WE tuna blue) were used to irradiate the reaction. Fig. S1 shows the emission spectra of the light source the reaction chamber. The reaction chamber was composed of a 15.5 cm long dewar with a 7.5 cm internal diameter and 8.5 cm external dimeter and a hose connected to compressed air. The strength of the air flow was adjusted so that the temperature of the chamber never exceeded 25 °C. The reaction mixture was placed 6 cm from the light source.

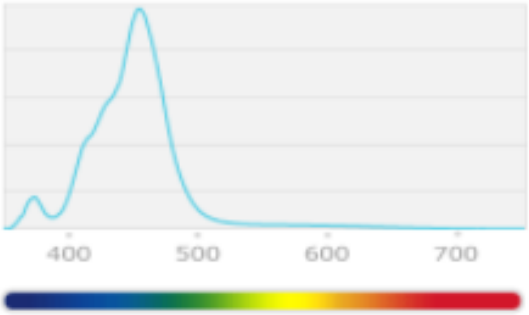


Figure 2.1 Emission spectrum of the Kessil lamp[56]

Figure 2.2 Reaction chamber

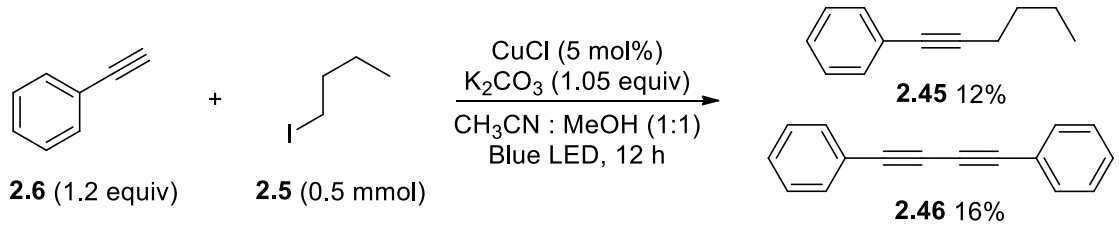
2.4.3 *Alkylation in the Absence of the Ligand*

The results of different combinations of alkynes and alkyl iodides that were tested using conditions similar to those reported by Hwang and Fu are shown in **Scheme** . All reactions were set up in a nitrogen-filled glovebox according to the following procedure. A dram vial was charged

with a Teflon coated stir bar, CuCl, base, solvent and alkyne. The internal standard, 1,3,5-trimethoxy benzene (TMB), and the alkyl iodide were then added. The vial was placed in the reaction chamber (**Figure**) and held in place with a double-sided tape. To maintain a constant temperature over the course of the reaction, a continuous flow of air was passed through the reaction chamber. The reaction was stirred vigorously for the indicated time and yields were determined by GC.

Scheme 2.5 Supplementary Screening of Initial Substrates

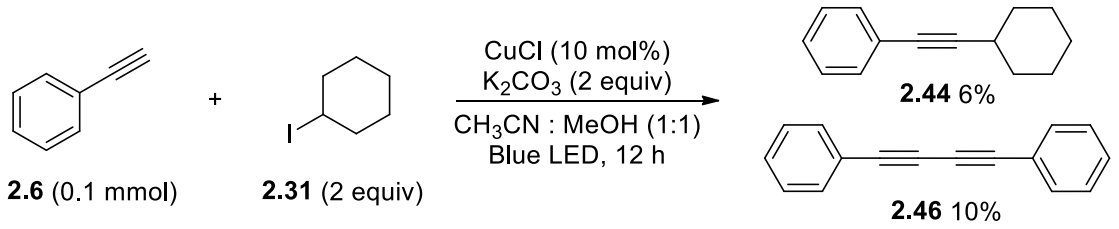
a)



2.6 (1.2 equiv) **2.5** (0.5 mmol)

Starting alkyne was completely consumed within 12h.

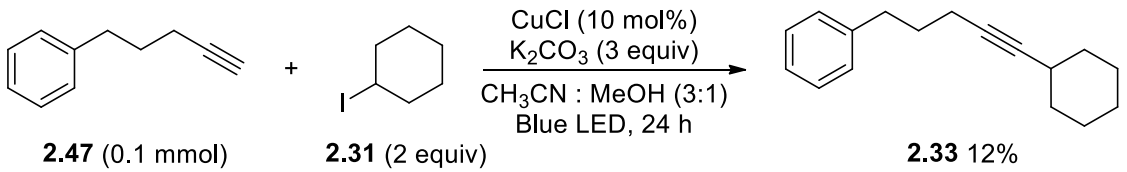
b)



2.6 (0.1 mmol) **2.31** (2 equiv)

Starting alkyne was completely consumed within 12h.

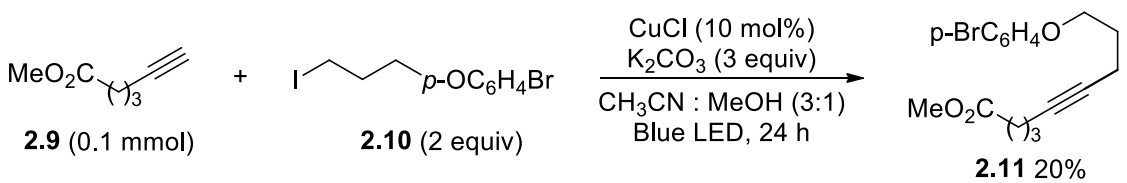
c)



2.47 (0.1 mmol) **2.31** (2 equiv)

33% of the starting alkyne remained after 24h.

d)



2.9 (0.1 mmol) **2.10** (2 equiv)

50% of the starting alkyne remained after 24h.

2.4.4 *Analysis of Literature Results*

Hwang et. al. reported[38] a photoinduced arylation of terminal alkynes, and in the same report described a single example of photoinduced alkylation (Table 2, entry 24 of the paper). In this example, phenylacetylene was reacted with 1-iodobutane to give the alkylated product in an isolated yield of 84%. However, in our hands, using the reported conditions, we obtained only 12% of the desired product and 16% of alkyne homocoupling product at the full conversion of the starting materials (yields determined by GC analysis of the crude reaction mixture using an internal standard) (**Scheme** , and **Scheme a**) The light sources used in our and Hwang's experiments were different. However, it is important to note that we were able to reproduce the arylation of terminal alkynes reported by Hwang in the same paper.

The broad features in the NMR spectrum of isolated product provided by Hwang were consistent with the NMR spectrum of our crude reaction mixture. These features, together with the low mass balance in our reaction, suggested a presence of polymeric species and prompted further analysis of the reaction. Preparative GPC analysis allowed the isolation of the polymeric species with M_w 2.091×10^4 (± 2.688%) and polydispersity of 4.515. Using quantitative GPC analysis, we determined that the polymers accounted for 68% of the starting material. Similar results were obtained with cyclohexyl iodide as the coupling partner. Overall, we believe that our findings are consistent with the experimental evidence provided by Hwang. Similar problems with false isolated yields because of polymeric byproducts have been recently described by Rajanbabu et al.[57]

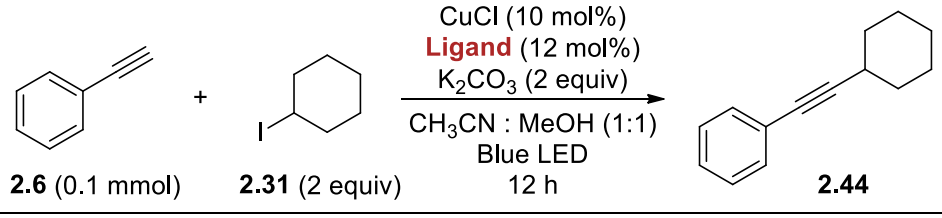
In other experiments described in **Scheme** , we observed similar results including the formation of low molecular weight polymers. However, we did observe some minor differences in products formed and in product distribution. For example, in the experiment using cyclohexyl

iodide and phenylacetylene (**Scheme b**), the homocoupled alkyne further reacted with cyclohexyl iodide to form the ene-yne adduct in trace quantity.

2.4.5 *Reaction Development*

In a nitrogen-filled glovebox, a dram vial was charged with a Teflon coated stir bar, CuCl, ligand, base, solvent, and alkyne. Internal standard, 1,3,5-trimethoxy benzene (TMB), and alkyl iodide were then added. The vial was put in the reaction chamber (**Figure**) and held in place with double-sided tape. A constant flow of air was passed though the chamber to maintain a constant temperature. The reaction was then stirred vigorously for 12 hours and yields were determined by GC.

Table 2.4 Supplementary Ligand Screen

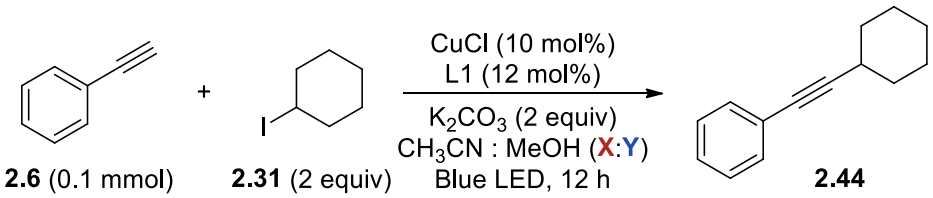


2.6 (0.1 mmol) + **2.31** (2 equiv) → **2.44**

No ligand 6%	**L1** 38%	**L3** 12%	**L4** 0%
L5 7%	**L6** 3%	**L7** 2%	**L8** 7%
L9 5%	**L10** 3%	**L11** 4%	**L12** 9%

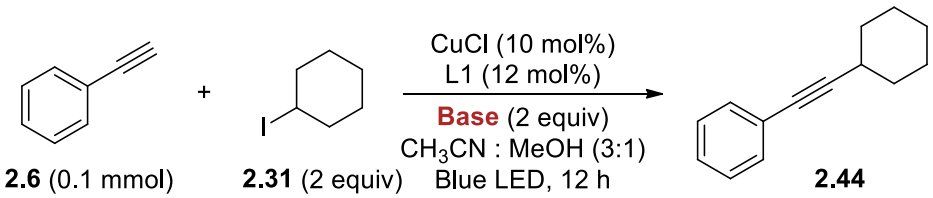
GC yields are reported

Table 2.5 Supplementary Solvent Screen: CH_3CN:CH_3OH



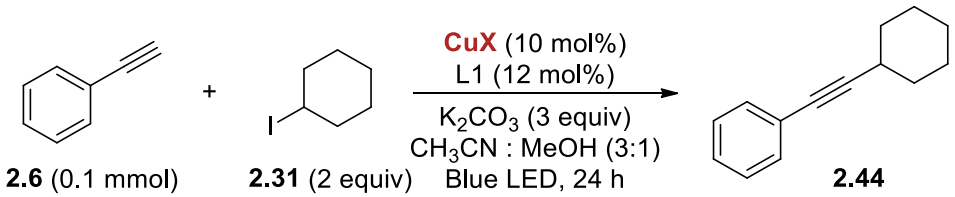
Entry	Acetonitrile: Methanol	Yield (%)
1	1:1	38
2	2:1	51
3	3:1	65
4	4:1	54
5	1:2	35
6	1:3	41
7	1:4	48

Table 2.6 Supplementary Base Screen



Entry	Base	Yield (%)
1	K_2CO_3	65
2	Na_2CO_3	12
3	Cs_2CO_3	0
4	Li_2CO_3	7
5	$KHCO_3$	8
6	K_3PO_4	16
7	K_2HPO_4	13
8	KH_2PO_4	8
9	Et_3N	11
10	K_2CO_3 (3 equiv, 24h)	90

Table 2.7 Supplementary Copper Salt Screen

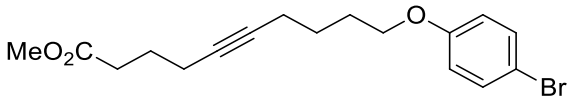


Entry	CuX	Yield (%)
1	CuCl	90
2	CuCl (5 mol%) & L1 (6%)	85
3	$(CuOTf)_2 \cdot C_6H_6$	86
4	$(CuOTf)_2 \cdot C_6H_6$ (no ligand)	12
5	CuI	80

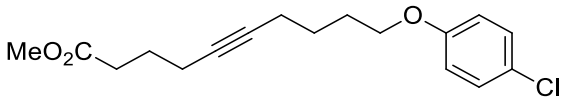
2.4.6 *General Procedure for the Photoinduced Alkylation of Terminal Alkynes*

In a nitrogen-filled glovebox, a 1.5-dram vial was charged with a Teflon coated stir bar, CuCl (5.0 mg, 0.05 mmol, 0.10 equiv.), 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (40.0 mg, 0.10 mmol, 0.20 equiv.) and K_2CO_3 (207.3 mg, 1.50 mmol, 3.0 equiv.). A mixture of 1:3 methanol in acetonitrile (5 mL, 0.1 M) and alkyne (0.50 mmol, 1.0 equiv.) were then added. Alkyl iodide (1.00 mmol, 2 equiv.) was added to the reaction vessel, which was then capped and the reaction mixture was stirred vigorously under the irradiation of blue light in the reaction chamber (Fig. S1). After the indicated time, the reaction was stopped. The reaction mixture was filtered through a pad of silica gel and washed with EtOAc and DCM. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography.

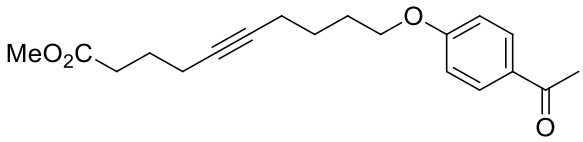
2.4.7 *Characterization of the Internal Alkynes*



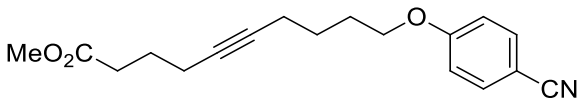
Methyl 9-(4-bromophenoxy)non-5-ynoate (2.11): compound was isolated as a colorless oil (141.3 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.67 (s, 3H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.34 (tt, *J* = 6.8, 2.3 Hz, 2H), 2.21 (tt, *J* = 6.8, 2.3 Hz, 2H), 1.93 (p, *J* = 6.6 Hz, 2H), 1.79 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 158.2, 132.4, 116.5, 112.9, 80.0, 79.8, 66.8, 51.7, 33.0, 28.7, 24.3, 18.4, 15.5. GC/MS (EI) calculated for $[M]^+$ 338.05, found 338.10. FTIR (neat, cm^{-1}): 3094 (w), 3066 (w), 2949 (m), 2847 (w), 1737 (s), 1591 (w), 1576 (w), 1489 (s), 1468 (m), 1436 (m), 1285 (m), 1244 (s), 1171 (m), 1051 (w), 1001 (w), 822 (m).



Methyl 9-(4-clorophenoxy)non-5-ynoate (2.12): compound was isolated as a colorless oil (121.0 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.66 (s, 3H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.34 (tt, *J* = 6.8, 2.3 Hz, 2H), 2.21 (tt, *J* = 6.8, 2.3 Hz, 2H), 1.93 (p, *J* = 6.5 Hz, 2H), 1.79 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 157.7, 129.4, 125.6, 115.9, 80.0, 79.8, 66.8, 51.7, 33.0, 28.7, 24.3, 18.3, 15.5. GC/MS (EI) calculated for $[M]^+$ 294.10, found 294.10. FTIR (neat, cm^{-1}): 3094 (w), 3070 (w), 2950 (m), 2872 (w), 2848 (w), 1736 (s) 1596 (w), 1581 (w), 1492 (s), 1283 (m), 1244 (s), 1169 (m), 1092 (m), 1051 (m), 1005 (m), 947 (w), 825 (m).

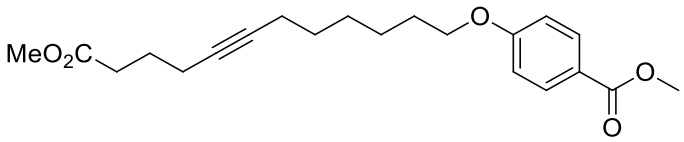


Methyl 9-(4-acetylphenoxy)non-5-ynoate (2.13): compound was isolated as a white solid (130.6 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.11 (t, *J* = 6.2 Hz, 2H), 3.65 (s, 3H), 2.54 (s, 3H), 2.45 – 2.30 (m, 4H), 2.20 (tt, *J* = 6.9, 2.3 Hz, 2H), 1.96 (p, *J* = 6.5 Hz, 2H), 1.78 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 173.8, 163.0, 130.7, 130.4, 114.27, 79.9, 79.8, 66.7, 51.7, 33.0, 28.6, 26.4, 24.3, 18.3, 15.5. GC/MS (EI) calculated for $[M]^+$ 302.15, found 302.20. FTIR (neat, cm^{-1}): 3076 (w), 3042 (w), 2950 (m), 2877 (w), 2846 (w), 1737 (s), 1677 (s), 1601 (s), 1576 (m), 1508 (m), 1434 (m), 1419 (m), 1254 (s) 1170 (m), 1049 (m), 947 (m), 830 (m).

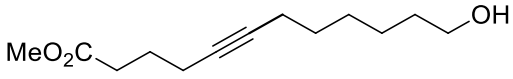


Methyl 9-(4-cyanophenoxy)non-5-ynoate (2.14): compound was isolated as a white solid (117.6 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.64 (s, 3H), 2.44 – 2.27 (m, 4H), 2.24 – 2.12 (m, 2H), 1.94 (p, *J* = 6.5 Hz, 2H), 1.77 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 162.3, 134.0, 119.3, 115.3, 103.9, 80.0, 79.6, 66.9, 51.6, 32.9, 28.4, 24.2, 18.3, 15.4. GC/MS (EI) calculated for $[M]^+$ 285.14, found 385.10. FTIR (neat, cm^{-1}): 3101 (w), 3073 (w), 3047 (w), 2950 (m), 2877 (m), 2845 (m), 2224 (s), 1736 (s), 1606 (s), 1509 (s), 1468 (m), 1436 (m), 1302 (m) 1258 (s), 1172 (s), 1027 (m), 945 (w), 836 (m).

Methyl dodec-5-ynoate (2.15): compound was isolated as a colorless oil (97.0 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.28 – 2.18 (m, 2H), 2.18 – 2.06 (m, 2H), 1.80 (p, *J* = 7.1 Hz, 2H), 1.53 – 1.22 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 81.3, 78.7, 51.5, 32.9, 31.4, 29.1, 28.6, 24.4, 22.6, 18.8, 18.3, 14.1. GC/MS (EI) calculated for $[M]^+$ 210.16, found 210.15. FTIR (neat, cm^{-1}): 2932 (s), 2857 (s), 1737 (s), 1455 (s), 1435 (s), 1368 (m), 1221 (s) 1161 (s), 1058 (w), 999 (w), 862 (w), 727 (w).



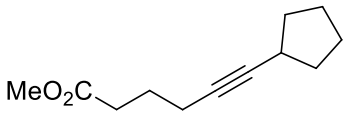
Methyl 4-((12-methoxy-12-oxododec-7-yn-1-yl)oxy)benzoate (2.16): compound was isolated as a colorless oil (152.8 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 3.66 (s, 3H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.27 – 2.07 (m, 4H), 1.87 – 1.72 (m, 4H), 1.61 – 1.35 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 167.9 163.0, 131.7, 122.5, 114.2, 81.1, 79.1, 68.2, 51.9, 51.6, 33.0, 29.1, 29.0, 28.6, 25.7, 24.4, 18.8, 18.4. GC/MS (EI) calculated for $[M]^+$ 360.19, found 360.20. FTIR (neat, cm^{-1}): 3066 (w), 3000 (w), 2940 (s), 2858 (w), 1737 (s), 1716 (s), 1606 (s), 1511 (s), 1436 (s), 1280 (s), 1254 (s), 1168 (s), 1104 (m), 1010 (w), 847 (w), 771 (m), 696 (w).



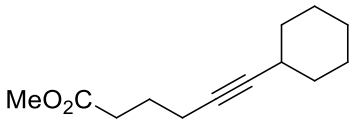
Methyl 12-hydroxydodec-5-ynoate (2.17): compound was isolated as a light yellow oil (96.7 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 – 3.55 (m, 5H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.30 – 2.06 (m, 4H), 1.80 (p, *J* = 7.0 Hz, 2H), 1.62 – 1.30 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9,

81.2, 78.9, 62.9, 51.62, 33.0, 32.7, 29.0, 28.6, 25.3, 24.3, 18.7, 18.3. GC/MS (EI) calculated for $[M]^+$ 226.16, found 226.10. FTIR (neat, cm^{-1}): 3366 (b), 2933 (s), 2858 (m), 1739 (s), 1436 (m), 1368 (w), 1225 (m), 1161 (m), 1055 (m).

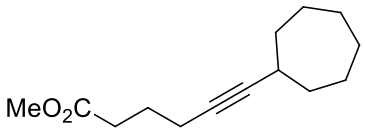
Methyl 8-((triisopropylsilyl)oxy)oct-5-ynoate (2.18): compound was isolated as a colorless oil (133.3 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (t, *J* = 7.3 Hz, 2H), 3.66 (s, 3H), 2.48 – 2.31 (m, 4H), 2.19 (tt, *J* = 6.9, 2.2 Hz, 2H), 1.78 (p, *J* = 7.2 Hz, 2H), 1.26 – 0.84 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 80.1, 78.2, 62.7, 51.6, 33.0, 24.2, 23.4, 18.4, 18.1, 12.1. GC/MS (EI) calculated for $[M]^+$ 326.23, found 326.30. FTIR (neat, cm^{-1}): 2943 (s), 2866 (s), 1740 (s), 1464 (m), 1436 (m), 1381 (w), 1367 (w), 1246 (m), 1109 (s), 882 (m), 681 (m).



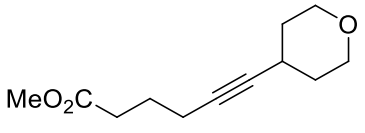
Methyl 6-cyclopentylhex-5-ynoate (2.19): compound was isolated as a clear colorless liquid (89.2 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.60 – 2.51 (m, 1H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.22 (t, *J* = 6.8 Hz, 2H), 1.87 (s, 2H), 1.83 – 1.75 (m, 2H), 1.74 – 1.63 (m, 2H), 1.56 – 1.47 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 85.6, 78.3, 51.5, 34.1, 32.9, 30.3, 24.9, 24.4, 18.4. GC/MS (EI) calculated for $[M]^+$ 194.13, found 194.00. FTIR (neat, cm^{-1}): 2927 (s), 2854 (s), 2358 (w), 2238 (w), 1738 (s), 1451 (s), 1366 (s), 1318 (s), 1235 (s), 1163 (s), 1058 (m), 863 (m), 755 (s).



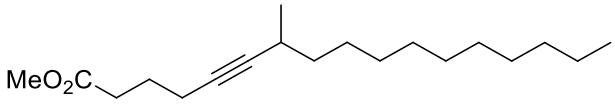
Methyl 6-cyclohexylhex-5-ynoate (2.20): compound was isolated as a clear colorless liquid (99.8 mg, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.36 – 2.26 (m, 1H), 2.22 (t, *J* = 6.8 Hz, 2H), 1.86 – 1.71 (m, 4H), 1.70 – 1.64 (m, 2H), 1.54 – 1.45 (m, 1H), 1.43 – 1.32 (m, 2H), 1.30 – 1.20 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 85.6, 78.6, 51.4, 33.1, 32.9, 29.2, 26.0, 24.9, 24.4, 18.3. GC/MS (EI) calculated for $[M]^+$ 208.15, found 208.10. FTIR (neat, cm^{-1}): 2929 (s), 2852 (s), 2359 (w), 1740 (s), 1449 (s), 1365 (s), 1315 (s), 1222 (s), 1162 (s), 1055 (m).



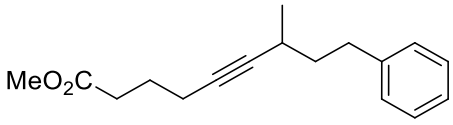
Methyl 6-cycloheptylhex-5-ynoate (2.21): compound was isolated as a clear colorless liquid (101.1 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 3H), 2.51 – 2.43 (m, 1H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.17 (td, *J* = 6.9, 2.1 Hz, 2H), 1.80 – 1.69 (m, 4H), 1.67 – 1.51 (m, 4H), 1.51 – 1.45 (m, 4H), 1.44 – 1.36 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 86.3, 78.8, 51.5, 35.1, 32.9, 31.2, 27.9, 25.6, 24.4, 18.3. GC/MS (EI) calculated for $[M]^+$ 222.16, found 222.10. FTIR (neat, cm^{-1}): 2929 (s), 2856 (s), 2339 (w), 2242 (w), 1737 (s), 1459 (s), 1438 (s), 1366 (s), 1321 (s), 1228 (s), 1159 (s), 1059 (m), 1008 (m), 863 (m).



Methyl 6-(tetrahydro-2H-pyran-4-yl)hex-5-ynoate (2.22): compound was isolated as a clear colorless liquid (88.2 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 – 3.76 (m, 2H), 3.64 (s, 3H), 3.43 (t, *J* = 10.0 Hz, 2H), 2.58 – 2.49 (m, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.20 (t, *J* = 6.7 Hz, 2H), 1.84 – 1.69 (m, 4H), 1.63 – 1.49 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 83.6, 79.8, 66.3, 51.5, 32.8, 32.6, 26.2, 24.2, 18.1. GC/MS (EI) calculated for $[M]^+$ 210.13, found 210.10. FTIR (neat, cm^{-1}): 2956 (s), 2848 (s), 2359 (w), 2247 (w), 1738 (s), 1460 (s), 1438 (s), 1371 (m), 1314 (m), 1238 (s), 1162 (s), 1129 (s), 1085 (s), 1064 (s), 980 (m).

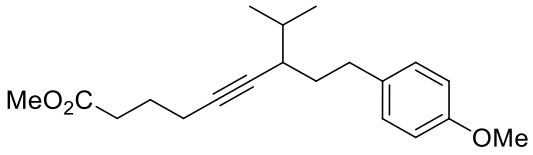


Methyl 7-methylheptadec-5-ynoate (2.23): compound was isolated as a clear colorless liquid (123.6 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.35 – 2.27 (m, 1H), 2.19 (dt, *J* = 7.5, 3.4 Hz, 2H), 1.77 (p, *J* = 7.5 Hz, 2H), 1.43 – 1.18 (m, 18H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 86.1, 78.8, 51.5, 37.4, 32.9, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 27.5, 26.0, 24.4, 22.8, 21.5, 18.3, 14.2. GC/MS (EI) calculated for $[M]^+$ 294.26, found 294.30. FTIR (neat, cm^{-1}): 2925 (s), 2852 (s), 2233 (w), 1743 (s), 1453 (s), 1437 (s), 1374 (s), 1334 (s), 1314 (s), 1222 (s), 1161 (s), 1059 (m), 998 (m) 734 (s).

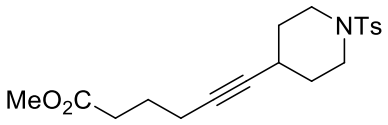


Methyl 7-methyl-9-phenylnon-5-ynoate (2.24): compound was isolated as a clear colorless liquid (109.7 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m,

3H), 3.69 (s, 3H), 2.88 – 2.77 (m, 1H), 2.77 – 2.64 (m,1H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.45 – 2.40 (m, 1H), 2.29 (t, *J* = 6.8 Hz, 2H), 1.86 (p, *J* = 7.1 Hz, 2H), 1.72 (dd, *J* = 15.0, 7.5 Hz, 2H), 1.18 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 142.2, 128.5, 128.3, 125.8, 85.4, 79.6, 51.5, 39.1, 33.8, 32.9, 25.5, 24.4, 21.5, 18.3. GC/MS (EI) calculated for $[M]^+$ 258.16, found 258.20. FTIR (neat, cm^{-1}): 3025 (m), 2920 (s), 2868 (m), 1738 (s), 1603 (m), 1495 (s), 1453 (s), 1437 (s), 1372 (s), 1334 (s), 1247 (m), 1225 (s), 1162 (s), 1059 (m), 1030 (m), 749 (s), 700 (s).

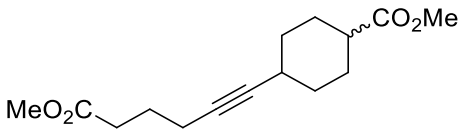


Methyl 7-isopropyl-9-(4-methoxyphenyl)non-5-ynoate (2.25): compound was isolated as a clear colorless liquid (62.4 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 2.89 – 2.68 (m, 1H), 2.66 – 2.52 (m, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 2.28 (dt, *J* = 15.8, 9.7 Hz, 2H), 2.23 – 2.12 (m, 1H), 1.85 (p, 2H), 1.72 – 1.57 (m, 2H), 0.94 (dd, *J* = 6.3, 4.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 157.9, 134.6, 129.5, 113.9, 82.7, 81.5, 55.4, 51.6, 38.5, 35.3, 33.3, 33.1, 31.8, 24.7, 21.2, 18.6, 18.5. GC/MS (EI) calculated for $[M]^+$ 316.20, found 316.20. FTIR (neat, cm^{-1}): 2956 (s), 2869 (s), 1738 (s), 1611 (s), 1583 (w), 1512 (s), 1462 (s), 1438 (s), 1367 (m), 1300 (m), 1246 (s), 1176 (s), 1037 (s).

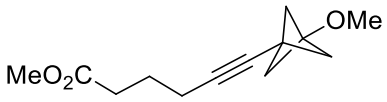


Methyl 6-(1-tosylpiperidin-4-yl)hex-5-ynoate (2.26): compound was isolated as a clear colorless liquid (157.9 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.67 (s, 3H), 3.46 – 3.13 (m, 2H), 2.87 – 2.63 (m, 2H), 2.43 (s, 3H), 2.40 – 2.25 (m,

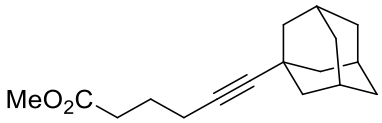
3H), 2.21 – 2.03 (m, 2H), 1.90 – 1.60 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 143.5, 133.4, 129.7, 127.8, 82.34, 81.0, 51.6, 44.6, 32.8, 31.3, 26.3, 24.2, 21.6, 18.1. GC/MS (EI) calculated for $[M]^+$ 363.15, found 363.10. FTIR (neat, cm^{-1}): 2929 (s), 2854 (s), 2304 (w), 1735 (s), 1715 (s), 1438 (s), 1343 (s), 1265 (s), 1165 (s), 1093 (s), 1050 (m), 930 (m).



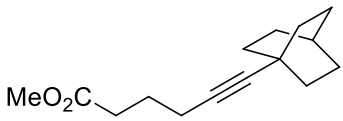
Methyl 4-(6-methoxy-6-oxohex-1-yn-1-yl)cyclohexanecarboxylate (2.27): compound was isolated as a clear colorless liquid (97.1 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 – 3.36 (m, 6H), 2.59 (s, 1H), 2.38 (dt, 2H), 2.30 – 2.12 (m, 3H), 2.01 – 1.62 (m, 7H), 1.52 – 1.18 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 175.9, 173.7, 173.7, 84.9, 83.8, 80.3, 78.9, 51.6, 51.5, 42.4, 42.3, 33.0, 32.9, 32.4, 30.4, 29.0, 28.2, 27.0, 25.1, 24.4, 24.3, 18.3, 18.3 $[M]^+$ 266.15, found 266.20. FTIR (neat, cm^{-1}): 2925 (s), 2862 (s), 2235 (w), 1838 (m), 1738 (s), 1730 (s), 1711 (s), 1477 (s), 1460 (s), 1438 (s), 1376 (m), 1199 (s), 1167 (s), 1039 (m).



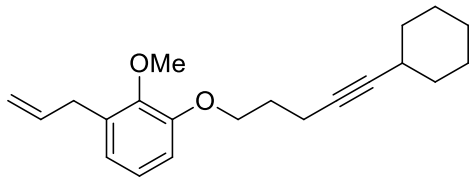
Methyl 6-(3-methoxybicyclo[1.1.1]pentan-1-yl)hex-5-ynoate (2.28): compound was isolated as a clear colorless liquid (29.4 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.22 (s, 3H), 2.37 (t, J = 7.4 Hz, 2H), 2.21 (t, J = 7.0 Hz, 2H), 2.06 (s, 6H), 1.81 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 81.2, 78.2, 67.8, 55.4, 54.1, 51.6, 32.9, 24.0, 21.2, 18.5. GC/MS (EI) calculated for $[M]^+$ 222.13, found 222.20. FTIR (neat, cm-1): 2986 (s), 2914 (s), 2833 (s), 2359 (w), 2220 (w), 1738 (s), 1514 (s), 1460 (s), 1435 (s), 1370 (s), 1317 (s), 1257 (s), 1156 (s), 1121 (s), 1032 (s).



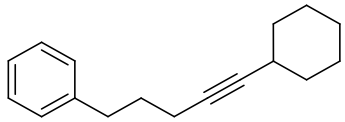
Methyl 6-((3r,5r,7r)-adamantan-1-yl)hex-5-ynoate (2.29): compound was isolated as a clear colorless liquid (52.6 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.22 (t, *J* = 6.9 Hz, 2H), 1.93 (s, 3H), 1.84 – 1.75 (m, 8H), 1.66 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 90.3, 77.6, 51.7, 43.5, 36.6, 33.0, 29.7, 28.3, 24.5, 18.4. GC/MS (EI) calculated for $[M]^+$ 260.18, found 260.20. FTIR (neat, cm^{-1}): 3053 (m), 2910 (s), 2851 (s), 2305 (w), 1731 (s), 1677 (w), 1452 (s), 1265 (s), 1225 (m), 1160 (w), 740 (s), 704 (s).



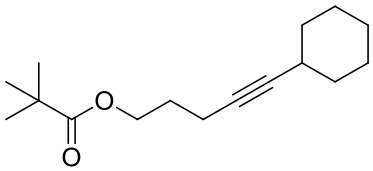
Methyl 6-(bicyclo[2.2.2]octan-1-yl)hex-5-ynoate (2.30): compound was isolated as a colorless oil (50.2 mg, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 6.9 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.71 – 1.47 (m, 12H), 1.30 – 1.16 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 89.3, 78.2, 51.2, 32.9, 32.5, 26.5, 25.9, 24.5, 23.4, 18.4. GC/MS (EI) calculated for $[M]^+$ 234.16, found 234.20. FTIR (neat, cm^{-1}): 2941 (s), 2905 (m), 2863 (m), 1738 (s), 1452 (m), 1434 (m), 1367 (w), 1320 (w), 1221 (m), 1160 (m), 1066 (w).



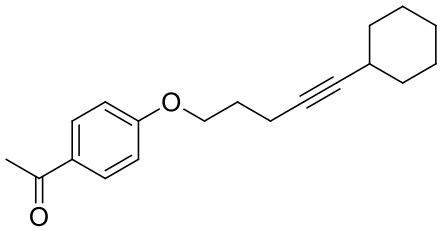
1-Allyl-3-((5-cyclohexylpent-4-yn-1-yl)oxy)-2-methoxybenzene (2.32): compound was isolated as a clear colorless liquid (112.4 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.6 Hz, 1H), 6.80 – 6.61 (m, 2H), 5.96 (ddt, *J* = 16.7, 9.7, 6.7 Hz, 1H), 5.18 – 4.97 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.85 (s, 3H), 3.33 (d, *J* = 6.7 Hz, 2H), 2.47 – 2.20 (m, 3H), 2.08 – 1.92 (m, 2H), 1.83 – 1.60 (m, 4H), 1.48 – 1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 147.0, 137.8, 133.0, 120.6, 115.6, 113.7, 112.6, 85.4, 79.0, 68.0, 56.0, 39.9, 33.2, 29.2, 28.9, 26.0, 25.0, 15.6. GC/MS (EI) calculated for $[M]^+$ 312.21, found 312.20. FTIR (neat, cm^{-1}): 2998 (s), 2929 (s), 2851 (s), 2224 (m), 1638 (s), 1605 (s), 1598 (s), 1513 (s), 1466 (s), 1448 (s), 1420 (s), 1329 (m), 1260 (s), 1233 (s), 1156 (s), 1139 (s), 1037 (s), 993 (m), 913 (m), 849 (m), 802 (s), 747 (s).



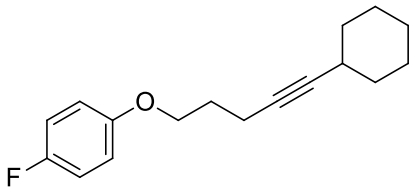
(5-Cyclohexylpent-4-yn-1-yl)benzene (2.33): compound was isolated as a clear colorless liquid (106.3 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.23 – 7.13 (m, 3H), 2.76 – 2.69 (m, 2H), 2.45 – 2.27 (m, 1H), 2.19 (td, *J* = 7.0, 2.1 Hz, 2H), 1.87 – 1.63 (m, 6H), 1.52 – 1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 128.7, 128.4, 125.9, 85.4, 79.7, 34.9, 33.3, 31.0, 29.3, 26.1, 25.1, 18.4. GC/MS (EI) calculated for $[M]^+$ 226.17, found 226.20. FTIR (neat, cm^{-1}): 3025 (m), 2930 (s), 2853 (s), 2236 (w), 1602 (m), 1492 (s), 1449 (s), 1346 (m), 1297 (m), 1216 (m), 1179 (m), 1079 (w).



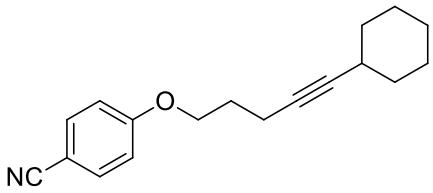
5-Cyclohexylpent-4-yn-1-yl pivalate (2.34): compound was isolated as a clear colorless liquid (81.3 mg, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (t, *J* = 6.3 Hz, 2H), 2.47 – 2.09 (m, 3H), 1.91 – 1.63 (m, 6H), 1.47 – 1.24 (m, 6H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 85.5, 78.5, 63.2, 38.8, 33.2, 29.2, 28.4, 27.3, 26.0, 25.0, 15.6. GC/MS (EI) calculated for $[M]^+$ 250.19, found 250.20. FTIR (neat, cm^{-1}): 2931 (s), 2854 (s), 2358 (w), 2255 (w), 1727 (s), 1480 (s), 1449 (s), 1398 (m), 1364 (m), 1285 (s), 1160 (s), 1037 (m), 914 (m).



1-(4-((5-Cyclohexylpent-4-yn-1-yl)oxy)phenyl)ethanone (2.35): compound was isolated as a clear colorless liquid (109.4 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.14 (t, *J* = 6.3 Hz, 2H), 2.55 (s, 3H), 2.47 – 2.21 (m, 3H), 1.97 (p, *J* = 6.5 Hz, 2H), 1.83 – 1.61 (m, 4H), 1.52 – 1.21 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 163.1, 130.6, 130.3, 114.2, 85.7, 78.5, 66.8, 33.1, 29.2, 28.7, 26.3, 26.0, 25.0, 15.5. GC/MS (EI) calculated for $[M]^+$ 284.18, found 284.10. FTIR (neat, cm^{-1}): 2929 (s), 2853 (s), 2240 (w), 1676 (s), 1601 (s), 1509 (s), 1448 (s), 1420 (s), 1358 (s), 1306 (s), 1256 (s), 1172 (s), 1116 (m).



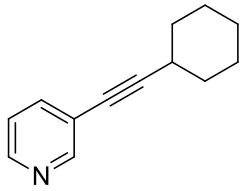
1-((5-Cyclohexylpent-4-yn-1-yl)oxy)-4-fluorobenzene (2.36): compound was isolated as a clear colorless liquid (93.7 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 6.88 (m, 2H), 6.88 – 6.79 (m, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 2.47 – 2.19 (m, 3H), 2.05 – 1.88 (m, 2H), 1.82 – 1.60 (m, 4H), 1.50 (s, 1H), 1.40 – 1.23 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2 (d, *J* = 237.9 Hz), 155.2 (d, *J* = 1.4 Hz), 115.7 (d, *J* = 23.1 Hz), 115.5 (d, *J* = 7.9 Hz), 85.5, 78.7, 67.2, 33.1, 29.1, 28.9, 25.9, 24.9, 15.5. ^{19}F NMR (471 MHz, $CDCl_3$) δ -127.1. GC/MS (EI) calculated for $[M]^+$ 260.16, found 260.20. FTIR (neat, cm^{-1}): 3053 (w), 2932 (s), 2854 (m), 2304 (w), 1507 (s), 1469 (m), 1449 (m), 1256 (s), 1248 (s), 1210 (s), 1097 (m), 1054 (m), 948 (w), 895 (w), 830 (s), 739 (s), 705 (s).



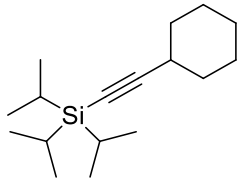
4-((5-Cyclohexylpent-4-yn-1-yl)oxy)benzonitrile (2.37): compound was isolated as a clear colorless liquid (114.9 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 2.35 (td, *J* = 6.2, 1.9 Hz, 2H), 2.32 – 2.24 (m, 1H), 1.94 (p, *J* = 6.2 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.68 – 1.59 (m, 2H), 1.51 – 1.42 (m, 1H), 1.39 – 1.29 (m, 2H), 1.28 – 1.18 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 133.9, 119.2, 115.2, 103.8, 85.7, 78.3, 66.9, 33.1, 29.1, 28.5, 25.9, 24.9, 15.4. GC/MS (EI) calculated for $[M]^+$ 267.16,

found 267.20. FTIR (neat, cm^{-1}): 2929 (s), 2852 (s), 2224 (s), 1598 (s), 1566 (w), 1506 (s), 1467 (m), 1443 (m), 1302 (s), 1258 (s), 1174 (s), 1045 (m), 912 (s), 834 (s), 733 (s).

1045(s).

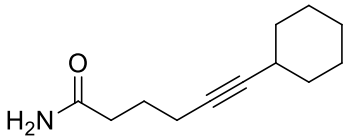


3-(Cyclohexylethynyl)pyridine (2.38): compound was isolated as a colorless oil (52.3 mg, 56% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H), 8.47 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.66 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.20 (dd, *J* = 7.9, 4.9 Hz, 1H), 2.68 – 2.51 (m, 1H), 1.96 – 1.82 (m, 2H), 1.82 – 1.69 (m, 2H), 1.61 – 1.47 (m, 3H), 1.42 – 1.29 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 147.9, 138.5, 122.9, 121.3, 98.1, 77.4, 32.6, 29.8, 25.9, 25.0. GC/MS (EI) calculated for $[M]^+$ 185.12, found 185.10. FTIR (neat, cm^{-1}): 3084 (w), 3027 (w), 2930 (s), 2853 (s), 2230 (w), 1585 (w), 1558 (w), 1476 (m), 1448 (m), 1405 (s), 1184 (w), 1022 (w), 952 (w), 803 (m).

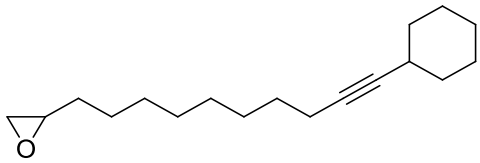


(Cyclohexylethynyl)triisopropylsilane (2.39): compound was isolated as a colorless oil (105.7mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 – 2.27 (m, 1H), 1.87 – 1.65 (m, 4H), 1.60 – 1.42 (m, 3H), 1.37 – 1.30 (m, 3H), 1.22 – 0.95 (m, 21H).1.25 – 0.98 (m, 21H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 113.8, 79.7, 32.9, 30.0, 26.2, 24.6, 18.8, 11.5. GC/MS (EI) calculated for $[M]^+$ 264.23, found 264.20. FTIR (neat, cm^{-1}): 2924 (s), 2858 (s), 2358 (m), 2169 (m), 1462 (m). 1452 (m), 1377 (w), 1353 (w), 1311 (w), 1075 (m).

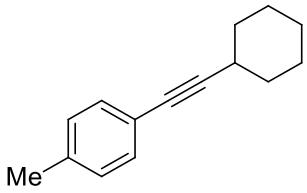


6-Cyclohexylhex-5-ynamide (2.40): compound was isolated as a white solid (75.5 mg, 78% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 – 5.21 (m, 2H), 2.42 – 2.29 (m, 3H), 2.28 – 2.19 (m, 2H), 1.88 – 1.73 (m, 4H), 1.73 – 1.63 (m, 2H), 1.56 – 1.47 (m, 1H), 1.44 – 1.33 (m, 2H), 1.33 – 1.22 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 85.7, 78.7, 34.6, 33.1, 29.1, 25.9, 24.9, 24.8, 18.2. GC/MS (EI) calculated for $[M]^+$ 193.15, found 193.20. FTIR (neat, cm^{-1}): 3358 (s), 3193 (s), 2925 (s), 2851 (s), 2244 (w) 1654 (s), 1428 (m), 1347 (m), 1274 (m), 1130 (w), 911 (m), 735 (m).

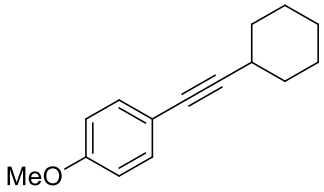


2-(10-Cyclohexyldec-9-yn-1-yl)oxirane (2.41): compound was isolated as a clear colorless liquid (107.5 mg, 82% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 2.90 – 2.80 (m, 1H), 2.70 (t, J = 4.5 Hz, 1H), 2.42 (dd, J = 5.0, 2.7 Hz, 1H), 2.35 – 2.19 (m, 1H), 2.11 (td, J = 7.0, 2.0 Hz, 2H), 1.79 – 1.58 (m, 4H), 1.52 – 1.17 (m, 20H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.7, 80.1, 52.4, 47.1, 33.3, 32.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.8, 26.1, 26.0, 25.0, 18.8. GC/MS (EI) calculated for $[M]^+$ 262.23,

found 262.30. FTIR (neat, cm^{-1}): 2927 (s), 2854 (s), 2660 (w), 2249 (m), 1481 (m), 1448 (s), 1409 (s), 1328 (s), 1257 (s), 1233 (s), 1129 (m), 1012 (m).



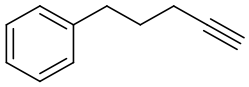
1-(Cyclohexylethynyl)-4-methylbenzene (2.42): compound was isolated as a clear colorless liquid (82.3 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.70 – 2.48 (m, 1H), 2.33 (s, 3H), 1.97 – 1.70 (m, 4H), 1.64 – 1.46 (m, 3H), 1.43 – 1.25 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 131.6, 129.0, 121.2, 93.7, 80.7, 32.9, 29.8, 26.1, 25.1, 21.5. GC/MS (EI) calculated for $[M]^+$ 198.14, found 198.20. FTIR (neat, cm^{-1}): 3027 (w), 2930 (s), 2853 (s), 2228 (w), 1902 (w), 1510 (s), 1448 (m), 1349 (s), 1301 (w), 1258 (w), 1178 (m), 1105 (m), 1020 (m), 815 (m).



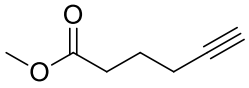
1-(Cyclohexylethynyl)-4-methoxybenzene (2.43): compound was isolated as a clear colorless liquid (79.2 mg, 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.78 – 2.35 (m, 1H), 2.12 – 1.66 (m, 4H), 1.62 – 1.46 (m, 3H), 1.44 – 1.25 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 133.0, 116.5, 113.9, 92.9, 80.4, 55.3, 33.0, 29.8, 26.1, 25.1. GC/MS (EI) calculated for $[M]^+$ 214.14, found 214.20. FTIR (neat, cm^{-1}): 3028

(w), 2929 (s), 2852 (s), 2230 (w), 1606 (s), 1503 (s), 1448 (s), 1287 (s), 1247 (s), 1171 (m), 1105 (s), 1032 (s), 830 (s).

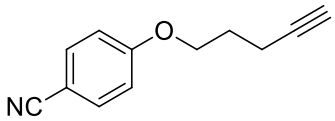
2.4.8 *Alkyne Starting Materials*



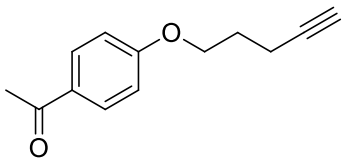
Pent-4-yn-1-ylbenzene (2.47): compound was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



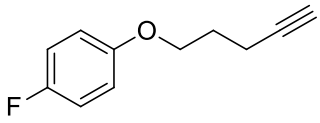
Methyl hex-5-ynoate (2.9): compound was purchased from Alfa Aesar and distilled over calcium hydride under vacuum before use.



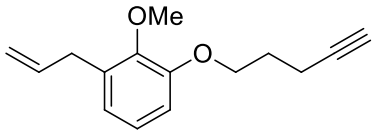
4-(Pent-4-yn-1-yloxy)benzonitrile (2.48): compound was prepared according to a known procedure and has been previously characterized.[58]



1-(4-(Pent-4-yn-1-yloxy)phenyl)ethenone (2.49): compound was prepared according to a known procedure and has been previously characterized.[59]

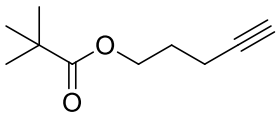


1-Fluoro-4-(pent-4-yn-1-yloxy)benzene (2.50): compound was prepared according to a known procedure and has been previously characterized.[59]

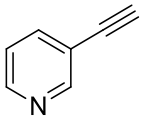


1-Allyl-2-methoxy-3-(pent-4-yn-1-yloxy)benzene (2.51): compound was prepared according to the following procedure. A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), eugenol (1.0 g, 7.7 mmol, 1.1 equiv), THF (14.0 mL, 0.5 M) and 4-pentyn-1-ol (654.0 µL, 7.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (1.6 mL, 8.4 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to 23 °C and stirred overnight. THF was removed under reduced pressure and the mixture was suspended in hexanes and stirred vigorously for 30 min. The solid triphenylphosphine oxide was removed by passing the mixture through a plug of celite. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.88 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 2H), 6.01 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.38 – 4.94 (m, 2H), 4.12 (t, *J* = 6.2 Hz, 2H), 3.88 (s, 3H), 3.48 – 3.14 (m, 2H), 2.46 (td, *J* = 7.0, 2.7 Hz, 2H), 2.19 – 1.81 (m, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 146.7, 137.6, 132.9, 120.4, 115.5, 114.0, 112.4, 83.5, 68.8, 67.5, 55.8, 39.7,

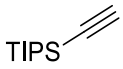
28.1, 15.1. FTIR (neat, cm^{-1}): 3258 (s), 2996 (s), 2927 (s), 2858 (s), 2340 (m), 2122 (m), 1634 (s), 1605 (s), 1512 (s), 1460 (s), 1447 (s), 1421 (s), 1330 (m), 1260 (s), 1234 (s), 1138 (s), 1037 (s), 994 (m), 913 (m), 847 (m), 802 (s), 746 (s).



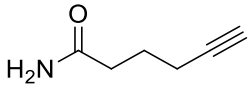
Pent-4-yn-1-yl pivalate (2.52): compound was prepared according to a known procedure and has been previously characterized.[60]



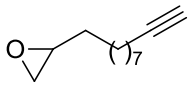
3-Ethynylpyridine (2.53): compound was purchased from Sigma-Aldrich and used directly.



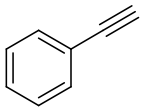
Ethynyltriisopropylsilane (2.54): compound was purchased from Alfa Aesar and used directly.



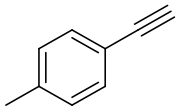
Hex-5-ynamide (2.55): compound was prepared according to a known procedure and has been previously characterized.[61]



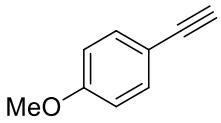
2-(10-Dec-9-yn-1-yl)oxirane (2.56): compound was prepared according to a known procedure and has been previously characterized.[60]



Ethynylbenzene (2.6): compound was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.



1-Ethynyl-4-methylbenzene (2.57): compound was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.

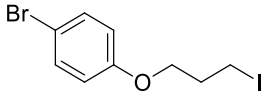


1-Ethynyl-4-methoxybenzene (2.58): compound was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.

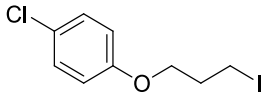
2.4.9 *Iodide Starting Materials*

All the iodides were prepared from the corresponding alcohol using the following procedure. A reaction flask charged with a Teflon coated stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g,

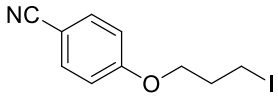
24.0 mmol, 1.2 equiv), imidazole (1.77 g, 26.0 mmol, 1.3 equiv). Anhydrous DCM was added to obtain a concentration of 0.3 M with respect to the alcohol. The flask was placed in an ice-bath and after 5 minutes of stirring, Iodine (6.9 g, 24.0 mmol, 1.2 equiv) was added and stirred for 15 minutes. Alcohol (20.0 mmol, 1.0 equiv) was added dropwise. The reaction was stirred overnight at room temperature.



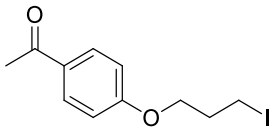
1-Bromo-4-(3-iodopropoxy)benzene (2.10): compound was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.38 (t, *J* = 6.7 Hz, 2H), 2.28 (p, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 132.4, 116.4, 113.2, 67.6, 32.9, 2.4. GC/MS (EI) calculated for $[M]^+$ 339.90, found 339.90. FTIR (neat, cm^{-1}): 3068 (w), 2923 (m), 2875 (m), 1589 (m), 1578 (m), 1488 (s), 1465 (s), 1286 (s), 1245 (s), 1171 (s), 1071 (m), 1001 (w), 820 (s), 639 (m).



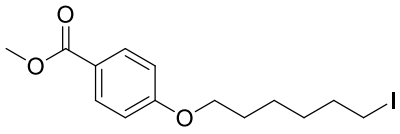
1-Chloro-4-(3-iodopropoxy)benzene (2.59): compound was isolated as a colorless. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.02 (t, *J* = 5.8 Hz, 2H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.39 – 2.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 129.4, 125.9, 115.9, 67.7, 32.9, 2.4. GC/MS (EI) calculated for $[M]^+$ 295.95, found 295.95. FTIR (neat, cm^{-1}): 3052 (w), 2926 (m), 2870 (m), 1595 (m), 1580 (m), 1491 (s), 1466 (m), 1437 (m), 1245 (s), 1090 (m), 1020 (m), 1005 (m), 824 (s).



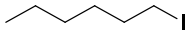
4-(3-Iodopropoxy)benzonitrile (2.60): compound was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 2.28 (p, *J* = 6.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 134.0, 119.2, 115.3, 104.2, 67.7, 32.5, 2.0. GC/MS (EI) calculated for $[M]^+$ 286.98, found 287.00. FTIR (neat, cm^{-1}): 3098 (w), 3074 (w), 2958 (m), 2935 (m), 2882 (w), 2222 (s), 1604 (s), 1574 (s), 1504 (s), 1567 (s), 1504 (s), 1420 (m), 1402 (m), 1299 (s), 1256 (s), 1172 (s), 1016 (s), 839 (s), 719 (m).



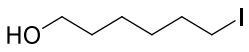
1-(4-(3-Iodopropoxy)phenyl)ethanone (2.61): compound was isolated as a colorless. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.56 (s, 3H), 2.30 (p, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 162.6, 130.7, 130.6, 114.2, 67.6, 32.8, 26.4, 2.2. GC/MS (EI) calculated for $[M]^+$ 304.00, found 304.00. FTIR (neat, cm^{-1}): 3098 (w), 3075 (w), 2948 (m), 2927 (s), 2870 (s), 1939 (w), 1914 (w), 1887 (w), 1663 (s), 1607 (m), 1433 (m), 1420 (m), 1357 (s), 1113 (m), 1050 (m), 836 (s).



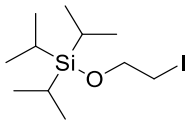
Methyl 4-((6-iodohexyl)oxy)benzoate (2.62): compound has been previously characterized and spectral data match the reported literature values.[62]



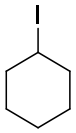
1-Iodohexane (2.63): compound has been previously characterized and spectral data match the reported literature values.[63]



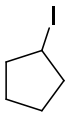
6-Iodohexan-1-ol (2.64): compound has been previously characterized and spectral data match the reported literature values.[64]



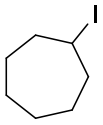
(2-Iodoethoxy)triisopropylsilane (2.65): compound has been previously characterized and spectral data match the reported literature values.[65]



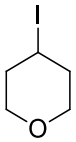
Iodocyclohexane (2.31): compound was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.



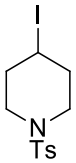
Iodocyclopentane (2.66): compound was purchased from Oakwood Chemicals and distilled over calcium hydride under vacuum before use.



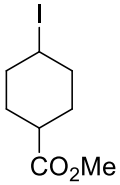
Iodocycloheptane (2.67): compound has been previously characterized and spectral data match the reported literature values. [66]



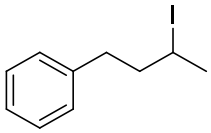
4-Iodotetrahydro-2H-pyran (2.68): compound has been previously characterized and spectral data match the reported literature values. [67]



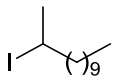
4-Iodo-1-tosylpiperidine (2.69): compound has been previously characterized and spectral data match the reported literature values.[68]



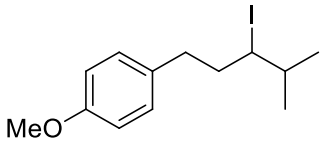
Methyl 4-iodocyclohexanecarboxylate (2.70): compound was prepared using the general method described above. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.67 (s, 1H), 3.72 (s, 3H), 2.52 – 2.39 (m, 1H), 2.23 – 1.92 (m, 4H), 1.91 – 1.67 (m, 4H). GC/MS (EI) calculated for $[M]^{+}$ 268.00, found 268.10.



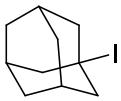
(3-iodobutyl)benzene (2.71): compound has been previously characterized and spectral data match the reported literature values.[69]



2-iodododecane (2.72): compound has been previously characterized and spectral data match the reported literature values.[69]

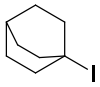


1-(3-Iodo-4-methylpentyl)-4-methoxybenzene (2.73): compound was prepared using the general method described above. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.21 – 3.89 (m, 1H), 3.80 (s, 3H), 2.89 (ddd, *J* = 13.7, 9.4, 4.9 Hz, 1H), 2.77 – 2.50 (m, 1H), 2.29 – 2.15 (m, 1H), 1.88 (dddd, *J* = 14.8, 8.9, 7.4, 3.7 Hz, 1H), 2.00 – 1.79 (m, 1H), 1.35 – 1.19 (m, 1H), 0.97 (dd, *J* = 21.4, 6.5 Hz, 6H).^{3}C NMR (126 MHz, $CDCl_3$) δ 158.1, 133.1, 129.6, 114.0, 55.4, 51.4, 48.0, 40.4, 39.4, 352., 33.5, 23.1, 20.1, 16.5. GC/MS (EI) calculated for $[M]^+$ 318.05, found 318.10. FTIR (neat, cm^{-1}): 2959 (s), 2870 (w), 1611 (s), 1583 (m), 1511 (s), 1462 (s), 1453 (s), 1385 (m), 1367 (m), 1314 (m), 1300 (s), 1246 (s), 1176 (s), 1037(s), 857 (w), 823 (s).



1-iodoadamantane (2.74): compound was purchased from Sigma-Aldrich and used directly.

1-iodo-3-methoxybicyclo[1.1.1]pentane (2.75): compound has been previously characterized and spectral data match the reported literature values.[70]

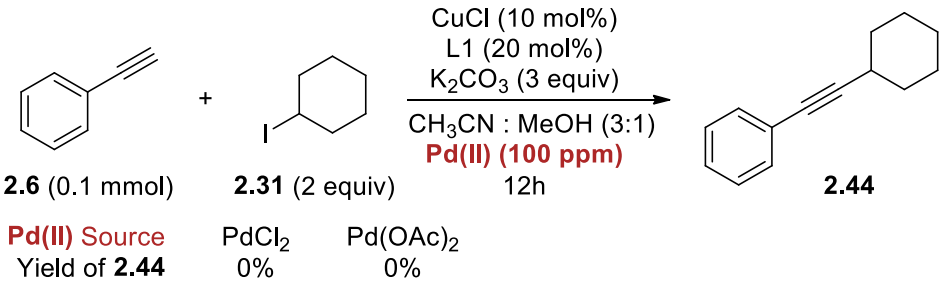


1-iodobicyclo[2.2.2]octane (2.76): compound has been previously characterized and spectral data match the reported literature values[71]

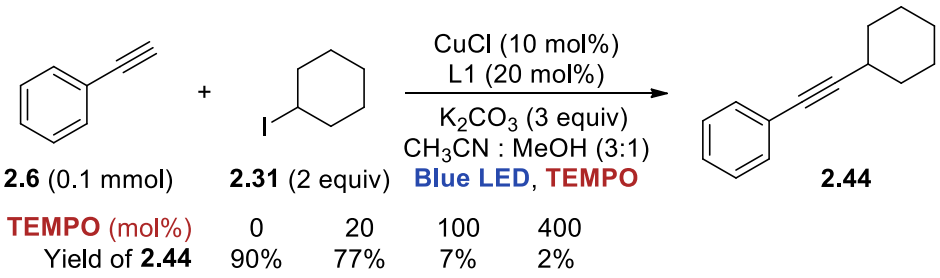
2.4.10 *Analysis of Palladium Impurities and Effects of Palladium(II) on the Reaction*

Trace amounts of palladium are known to perform cross coupling reactions[72] and it has been shown that as low as 100 ppb palladium is adequate for performing Sonogashira coupling[73]. Very often, trace impurities in bases (mostly Na_2CO_3), solvent, ligand or even glassware can be sources of this palladium. In order to assess the concentration of palladium present in our reaction we performed Inductively coupled plasma mass spectrometry (ICP-MS) on our base, ligand and reaction mixture. It was found that both K_2CO_3 and the ligand contain undetectable amounts of palladium (the detection limit for our instrument is 2 ppb). However, the reaction mixture was found to contain 91.2 ppb of palladium. To test the efficacy of palladium in our reaction medium,

we deliberately added 100 ppm palladium(II) from two different sources into separate reactions and performed them without the presence of light. The results have been summarized below. This result is consistent with the fact that photoactivation of copper acetylide is necessary and presence of trace amounts of palladium is *not responsible* for this reaction.



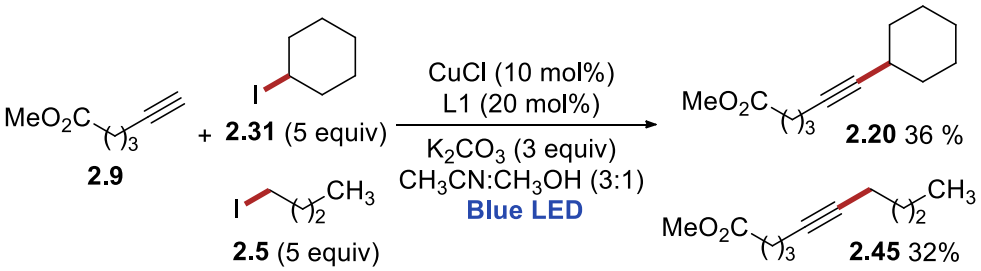
2.4.11 *Radical Trap Experiment*



In a nitrogen-filled glovebox, a dram vial was charged with a Teflon coated stir bar, CuCl (2.5 mg, 0.025 mmol, 0.10 equiv), 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (20.0 mg, 0.050 mmol, 0.20 equiv) and K_2CO_3 (103.8 mg, 0.75 mmol, 3.0 equiv). A mixture of 1:3 methanol in acetonitrile (2.5 mL, 0.1 M) and phenylacetylene (25.5 mg, 0.25 mmol, 1 equiv.) were then added. Internal standard, 1,3,5-trimethoxy benzene (TMB), cyclohexyl iodide (0.5 mmol, 2 equiv) and TEMPO were added to the reaction mixture, which was then capped and stirred vigorously under the irradiation of blue light in the reaction chamber (Fig. S1). After 24h, the reaction was stopped,

and yields were determined by GC. The cyclohexyl-TEMPO adduct was isolated and characterized by NMR and GC/MS. The spectral data match the previously reported values.[74]

2.4.12 *1° vs 2° Alkyl Iodide Competition Experiment*



In a nitrogen-filled glovebox, a dram vial was charged with a Teflon coated stir bar, CuCl (2.5 mg, 0.025 mmol, 0.10 equiv), 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (20.0 mg, 0.050 mmol, 0.20 equiv) and K_2CO_3 (103.8 mg, 0.750 mmol, 3.0 equiv). A mixture of 1:3 methanol in acetonitrile (2.5 mL, 0.1 M) and methyl hex-5-ynoate (31.5 mg, 0.250 mmol, 1 equiv) were then added. Internal standard, 1,3,5-trimethoxy benzene (TMB), and cyclohexyl iodide (0.500 mmol, 2 equiv) were added to the reaction mixture, which was then capped and stirred vigorously under the irradiation of blue light in the reaction chamber (**Figure**). After the indicated time, the reaction was stopped, and yields were determined by GC.

2.5 REFERENCES FOR CHAPTER 2

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Chapter 3.

CATALYTIC STEREOSPECIFIC SYNTHESIS OF *E*-ALKENES THROUGH ANTI-MARKOVNIKOV HYDROALKYLATION OF TERMINAL ALKYNES

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3.1 INTRODUCTION

Alkenes are ubiquitous in organic chemistry. They are used as versatile synthetic intermediates and are common among complex organic molecules with important applications. The importance of alkenes in organic chemistry has fueled persistent efforts aimed at developing new methods for their synthesis. As a result of these efforts, the hydroalkylation of alkynes has recently emerged as a powerful new approach to alkene synthesis. The main benefit of this approach is the use of simple and readily available alkynes as precursors to a variety of alkenes.

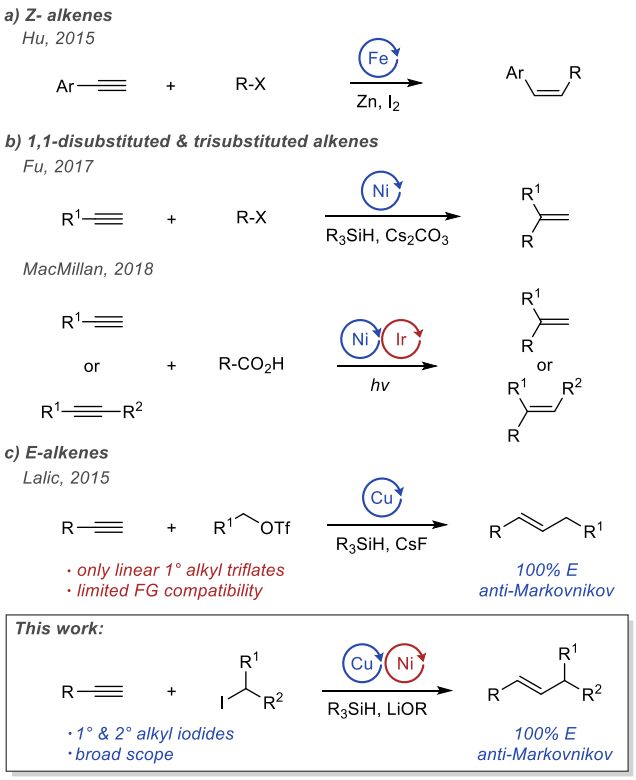
Current methods for the hydroalkylation of alkynes provide access to several classes of alkenes (**Scheme 3.1**). *Z*-substituted aryl alkenes can be prepared using a radical hydroalkylation of aryl alkynes that was reported in 2015 by Hu et al[1] (**Scheme 3.1a**). More recently, Fu et al.[2] developed a selective synthesis of 1,1-disubstituted alkenes through a nickel-catalyzed hydroalkylation of

terminal alkynes (**Scheme 3.1b**). A similar transformation of terminal alkynes into 1,1-disubstituted alkenes was subsequently accomplished by MacMillan et al. using a cooperative photoredox/nickel catalysis (**Scheme 3.1b**).[3,4] This approach has also allowed the transformation of sterically differentiated internal alkynes into trisubstituted alkenes with moderate regioselectivity.[3]

Surprisingly, there are few hydroalkylation methods that effectively target disubstituted *E*-alkenes. In 2015, our group reported the copper-catalyzed hydroalkylation of terminal alkynes using alkyl triflates as electrophiles (**Scheme 3.1c**).[5,6] This transformation demonstrates key benefits of hydroalkylation as an approach to the synthesis of *E*-alkenes. The reaction increases both the structural and the stereochemical complexity of the starting materials. A new C-C bond is formed, and, in the process, the stereochemistry of the new alkene is established. The excellent regioselectivity and diastereospecificity of the reaction allow the exclusive formation of a single *E*-alkene.

Nevertheless, our original hydroalkylation reaction has some significant limitations. The reaction is highly sensitive to steric properties of the electrophile and only linear primary alkyl triflates with no a-branching were viable substrates.

Scheme 3.1. Hydroalkylation of Alkynes



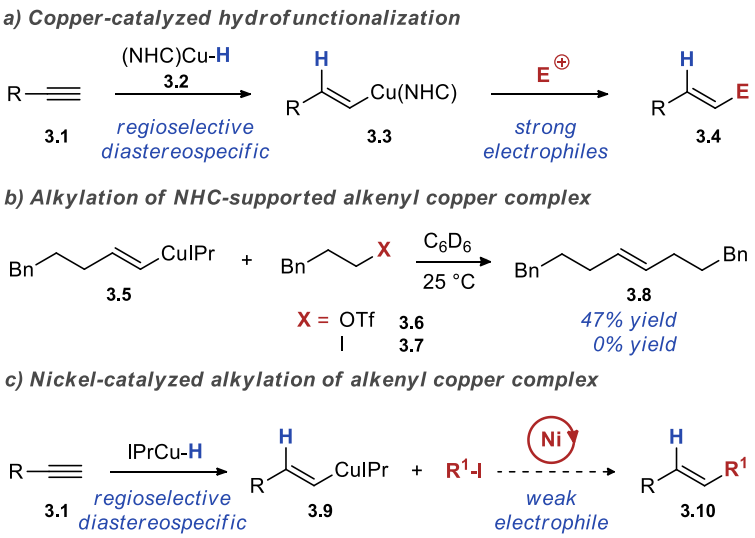
Additionally, both alkyl triflates and reagents used in their preparation are highly reactive, further limiting the reaction scope and introducing practical problems related to the preparation, purification, and stability of the starting electrophiles.

In this communication, we report the development of a new method for the hydroalkylation of terminal alkynes that addresses the key shortcomings of our original hydroalkylation reaction, while retaining its major benefits. We demonstrate that a dual Cu/Ni catalyst system allows the use of both primary and secondary alkyl iodides as coupling partners and enables the stereospecific synthesis of a wide range *E*-alkenes from terminal alkynes.

The hydroalkylation of alkynes that we reported in 2015 involves hydrocupration of an alkyne followed by electrophilic functionalization of alkenyl copper intermediate **3.3** (**Scheme 3.2a**).[7,8] The key hydrocupration step is highly regioselective and syn-stereospecific, ultimately resulting

in excellent regio- and diastereoselectivity of the overall reaction. Unfortunately, the low reactivity of alkenyl copper complexes makes their alkylation difficult. The stoichiometric reaction of alkenyl copper complex **3.5** with alkyl triflate **3.6** provides the desired product, while the less reactive alkyl iodide **3.7** does not react and under more forcing conditions leads to the decomposition of the starting materials (**Scheme 3.2b**).[6] Mankad et al. have made similar observations about the reactivity of alkenyl copper complexes with alkyl halides.[9]

Scheme 3.2 General Strategy



Inspired by the pioneering work of Nakao[10,11] and Brown,[12–14] our plan was to use a nickel co-catalyst to facilitate the cross coupling of the organocopper intermediate with alkyl iodides (**Scheme 3.2c**). The main challenge in implementing this cooperative catalysis[15–17] approach to hydroalkylation of alkynes was a clear overlap in the reactivity of the nickel and the copper catalyst systems. The nickel-catalyzed Markovnikov hydroalkylation[2] (**Scheme 3.1b**) is performed under conditions that are very similar to those required for copper hydride formation. Both reactions

require a combination of a silane and a base additive. In principle, the nickel co-catalyst in the hydroalkylation reaction may promote not only the desired alkylation of the alkenyl copper intermediate, it could also promote a Markovnikov hydroalkylation and compromise the regioselectivity of the overall transformation.

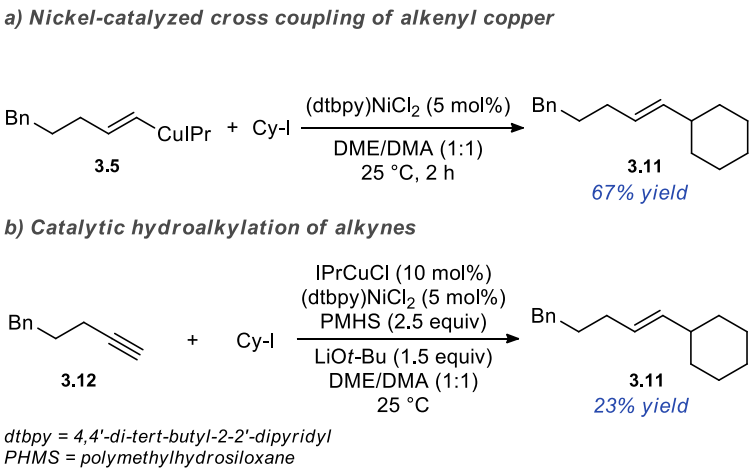
3.2 RESULTS AND DISCUSSION

3.2.1 *Reaction Development*

In our initial experiments we found that the common cross-coupling catalyst (dtbpy)$NiCl_2$ promotes efficient cross coupling of the isolated alkenyl copper intermediate **3.5** and cyclohexyl iodide (**Scheme 3.3a**). However, in a catalytic hydroalkylation reaction, the same nickel catalyst provides desired *E*-alkene in only 23% yield (**Scheme 3.3b**). Equally unsuccessful, were reactions with a variety of mono and bidentate phosphine and nitrogen-based ligands.

Contrary to our expectations, the Markovnikov hydroalkylation product was not a significant byproduct in these reactions. Instead, the major problem was the formation of a mixture of higher molecular weight products. We reasoned that these products are likely formed through Reppe's trimerization[18] and related tetramerization[19] of alkynes promoted by nickel(0) complexes.[20–24] A mechanistically distinct trimerization of alkynes is also promoted by nickel hydride complexes.[25]

Scheme 3.3 Preliminary Results



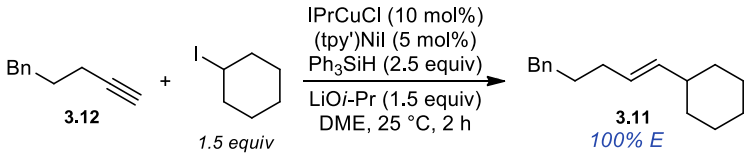
Established mechanisms of these major side reactions suggested that the desired reactivity of the nickel catalyst may be achieved using tridentate ligands. Considering the mechanism of Reppe's trimerization, tridentate ligands should suppress this side reaction by preventing simultaneous coordination of two alkyne molecules.[26] Additionally, the less common trimerization promoted by nickel hydride complexes requires a tricoordinate nickel hydride intermediates.[27] Again, strongly coordinating tridentate ligands should prevent formation of such an intermediate. We also found precedent indicating that the formation of the nickel hydride complexes is suppressed by tricoordinate nitrogen-based ligands.[28] This observation is consistent with Fu's recent finding that tridentate nitrogen-based ligands completely suppress the Markovnikov hydroalkylation of alkynes,[2] although no explanation for this effect was offered. Finally, the documented use of tridentate ligands in nickel-catalyzed cross-coupling reactions[29] of alkyl halides indicates that these ligands should allow the desired cross coupling of alkenyl copper intermediate with alkyl iodides.

Indeed, the use of tridentate ligands was the key modification that allowed us to develop the hydroalkylation reaction shown in **Table 3.1**. The best results in a reaction of terminal alkyne **3.12** and cyclohexyl iodide were obtained using IPrCuCl catalyst and a nickel(I) co-catalyst supported

by tridentate tpy′ ligand (Table 1). Additionally, Ph_3SiH was used as a hydride source and LiO*i*-Pr as a turnover reagent for the copper catalyst (for the role of LiO*i*-Pr, see **Scheme 3.4).**

During the development of the reaction, we made several observations about reaction parameters (**Table 3.1**). Alkyl iodides were superior substrates, while alkyl bromides provided dramatically lower yields (entry 2). As in most other copper-catalyzed hydrofunctionalization reactions of alkynes, catalysts supported by IPr and the closely related SIPr ligands were the only competent catalysts (entry 3). Even IMesCuCl catalyst provided only 5% of the product (entry 4). The identity of the nickel catalyst was also key for the success of the reaction. The catalyst prepared in situ from NiI_2 performed nearly as well as the optimal catalyst, while the catalyst prepared from $NiCl_2$ gave a lower yield (entries 5 and 6). Nickel complexes supported by other closely related ligands were inferior (entries 7-9). With LiO*t*-Bu in place for LiO*i*-Pr we observed a small amount of Sonogashira product and complete recovery of the starting silane (entry 10). These results suggest that IPrCuO*t*-Bu does not readily react with Ph_3SiH to form IPrCuH and instead leads to the formation of copper-acetylide and Sonogashira product. Similarly, changing the alkoxide counter ion from lithium to sodium led to lower yield of the product (entry 11).

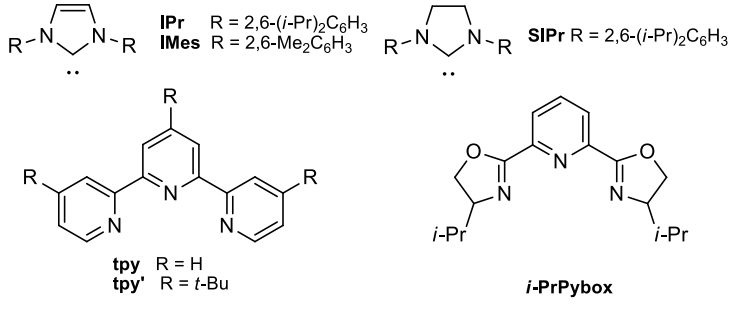
Table 3.1. Reaction Development



entry	*change from standard conditions*	*yield*[a]
1.	none	88%
2.	CyBr *instead of* CyI	2%
3.	SIPrCuCl *instead of* IPrCuCl	87%
4.	IMesCuCl *instead of* IPrCuCl	5%
5.	tpy' + NiI_2 *instead of* (tpy')NiI	82%
6.	(tpy')$NiCl_2$ *instead of* (tpy')NiI	71%
7.	(tpy)NiI *instead of* (tpy')NiI	48%
8.	(dtbpy)$NiCl_2$ *instead of* (tpy')NiI	8%
9.	$NiCl_2$(DME) + *i*-PrPybox *instead of* (tpy')NiI	0%
10.	LiO*t*-Bu *instead of* LiO*i*-Pr	3%
11.	NaO*i*-Pr *instead of* LiO*i*-Pr	34%
12.	THF *instead of* DME	78%
13.	Ph_2MeSiH *instead of* Ph_3SiH	51%
14.	PMHS *instead of* Ph_3SiH	8%
15.	Ph_2SiH_2 *instead of* Ph_3SiH	12%

[a] Determined by GC using internal standard.

Ligands



Among common ethereal solvents, THF was the only solvent other than DME that afforded the desired product in a significant yield (entry 12). Finally, PMHS and silanes closely related to Ph_3SiH, were all significantly inferior to Ph_3SiH (entries 13-15).

3.2.2 *Substrate Scope*

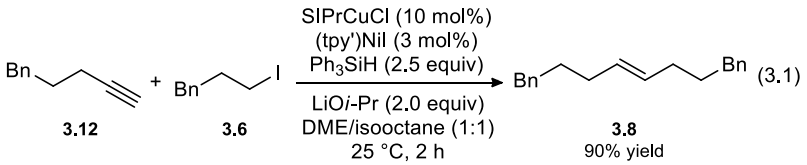
Using the standard conditions shown in **Table 3.1** (entry 1), we explored the scope of the reaction and found that a wide range of *E*-alkenes can be prepared (**Table 3.2**). It is important to note that all products shown in Table 2 are obtained as a single regioisomer and a single diastereoisomer. Even severe steric hindrance in the propargylic position does not impede the formation of the product (**3.17**) and substitution at the propargylic (**3.13**) and homopropargylic position (**3.27**) is tolerated. The reaction is compatible with a wide range of functional groups and can be accomplished in the presence of nitriles (**3.19**), esters (**3.20**), aryl ethers (**3.15**), silyl ethers (**3.13**, **3.17**, **3.21**, and **3.27**), alkenes (**3.15**), alkyl chlorides (**3.26**), sulfonamides (**3.31**), dialkyl anilines (**3.25**), and aryl bromides (**3.18**). The synthesis of compound **3.16** on a 5 mmol scale demonstrates that the reaction can be used as a preparative method. [30]

One of the limitations of our original hydroalkylation method was that nitrogen-based heteroarenes were not compatible with the reaction. The new reaction tolerates a wide range of heteroarenes including furans (**3.23**), 2-chloro-pyridines (**3.24**), pyridazines (**3.30**), thiazoles (**3.28**), pyrimidines (**3.29**), tetrazoles (**3.33**), and benzoxazoles (**3.34**). In general, heteroarenes less basic than pyridine are tolerated, while pyridine and more basic heterocycles are not.

We also explored the reaction with a range of secondary alkyl iodides. Cyclic substrates, such as 5- through 7-membered cyclic alkyl iodides, generally perform well (**3.36**, **3.40**, **3.41**). Acyclic alkyl iodides are also viable substrates, although yields tend to be lower.

Our initial attempts at using primary alkyl iodides as coupling partners were unsuccessful. Under the reaction conditions used for coupling secondary alkyl iodides, product **3.8** was formed in only 32% yield. The major side reactions in this case were the reduction of the alkyl iodide[31] and the

semi-reduction of the alkyne to an alkene. Eventually, we found that with subtle changes to the reaction conditions we can obtain alkene **3.8** in 90% yield (**eq. 3.1**).

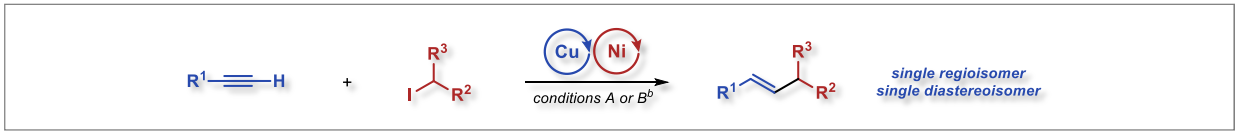


To achieve these results, we changed the catalyst from IPrCuCl to SIPrCuCl, solvent from DME to DME/isooctane (1:1), adjusted the stoichiometry of the turnover reagent (from 1.5 equiv to 2.0 equiv), and lowered the loading of the nickel catalyst (from 5 mol% to 3 mol%).[32]

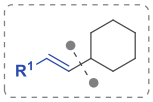
The conditions developed for the synthesis of **3.8**, proved general for a range of primary alkyl halides (**Table 3.2**). In departure from the original hydroalkylation with alkyl triflates, we could achieve hydroalkylation using a-branched (**3.46**, **3.49**, **3.50**, and **3.51**) and even neopentyl-like alkyl iodide (**3.45**) in relatively high yield. Similarly, electrophiles with heteroatoms in the a position (**3.46**), which are incompatible with the previous hydroalkylation, are also tolerated.

We also noted a few limitations of the hydroalkylation reaction. Protic functional groups, such as hydroxyl and amino are not tolerated. Reducible functional groups, such as aldehydes and activated alkene are also not compatible with reactions conditions. Finally, tertiary alkyl iodides, aryl-substituted alkynes, and disubstituted alkynes did not participate in the hydroalkylation reaction.

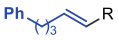
Table 3.2 Substrate Scope



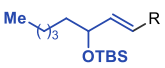
Alkyne Scope



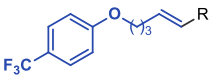
Conditions A



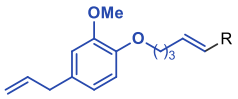
3.11, 85%



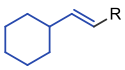
3.13, 73%[c,d]



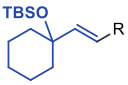
3.14, 88%



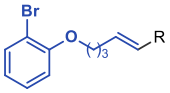
3.15, 86%



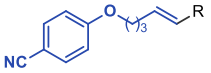
3.16, 92%
84% (5 mmol scale)[e]



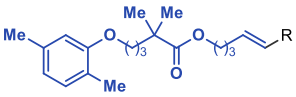
3.17, 87%[d]



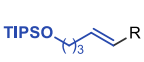
3.18, 60%



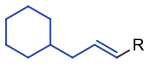
3.19, 86%



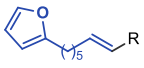
3.20, 84%



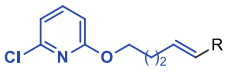
3.21, 87%



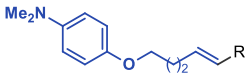
3.22, 90%



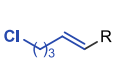
3.23, 84%



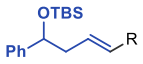
3.24, 77%



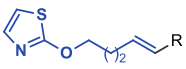
3.25, 72%



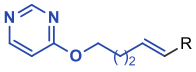
3.26, 86%



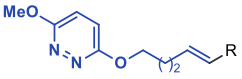
3.27, 75%[d]



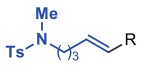
3.28, 83%



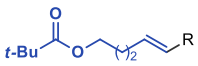
3.29, 74%



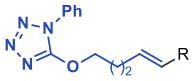
3.30, 68%



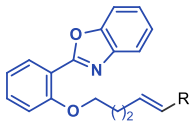
3.31, 82%



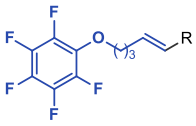
3.32, 65%



3.33, 83%

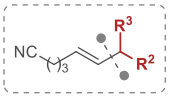


3.34, 80%

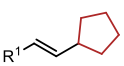


3.35,76%

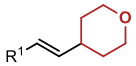
Alkyl Iodide Scope



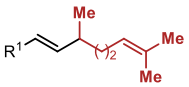
Conditions A



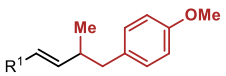
3.36, 85%



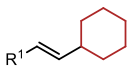
3.37, 90%



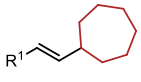
3.38, 68%



3.39, 56%



3.40, 88%



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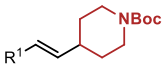
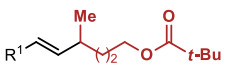
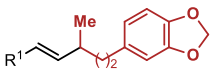


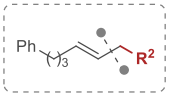
3.42, 81%



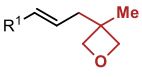
3.43, 77%



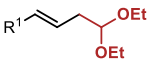
3.44, 65%



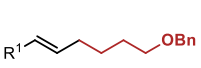
Conditions B



3.45, 72%



3.46, 74%



3.47, 84%

3.48, 55%

3.8, 85%

3.49, 65%

3.50, 81%

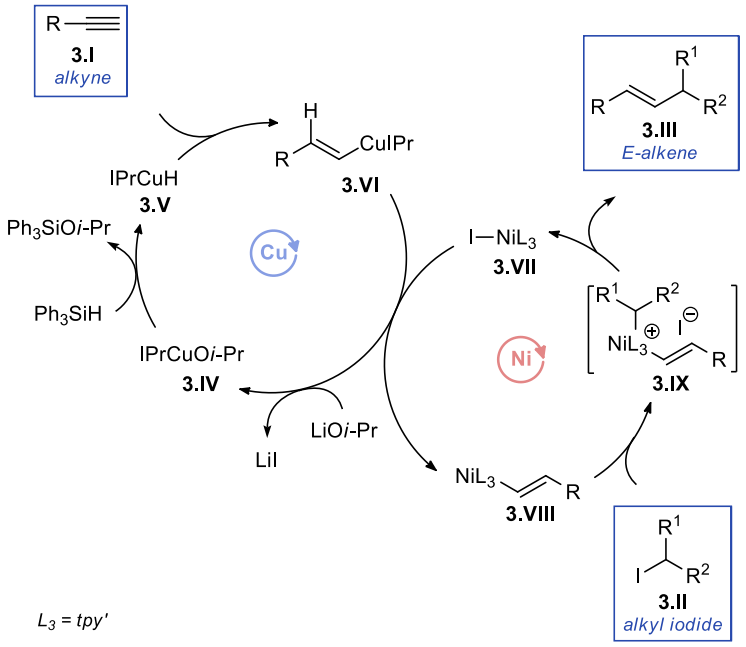
3.51, 90%

3.52, 76%

3.2.3 *Initial Mechanistic Studies*

Considering the generally established mechanisms of copper-catalyzed hydrofunctionalization of alkynes[8] and nickel-catalyzed cross-coupling reactions,[33] we propose that the hydroalkylation reaction proceeds according to the mechanism shown in **Scheme 3.4**. Initial hydrocupration of the alkyne (**3.V→3.VI**) is followed by transmetalation to nickel (**3.VI→3.VIII**). The alkyl iodide is activated by the newly formed alkenyl nickel complex (**3.VIII**). Reductive elimination results in the formation of the desired product and the regeneration of the nickel(I) catalyst (**3.VII**). The copper hydride intermediate (**3.V**) is regenerated in sequential reactions of the copper catalyst with the alkoxide and the silane.

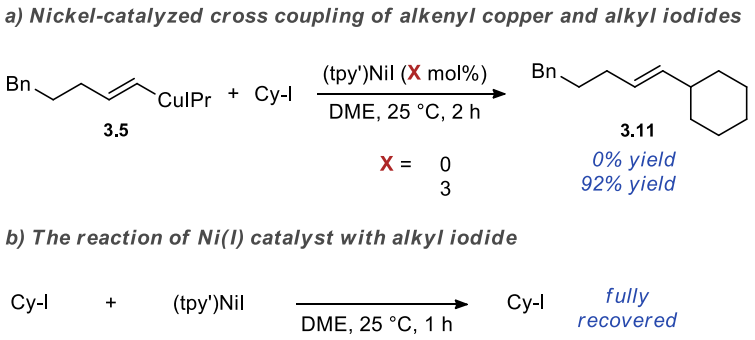
Scheme 3.4. Proposed Mechanism



In preliminary experiments, we probed the proposed interaction of the two established catalytic cycles. In a nickel-catalyzed cross coupling of the presumed alkenyl copper intermediate with a secondary alkyl iodide we obtained the expected *E*-alkene in 92% yield (**Scheme 3.5a**). In the absence of the nickel catalyst we did not detect the formation of the *E*-alkene. These experiments demonstrate the feasibility of the proposed nickel-catalyzed cross-coupling of the alkenyl copper intermediate and an alkyl iodide and establish the need for the nickel catalyst.

Next, we probed the relationship between transmetalation and alkyl halide activation. We propose that the activation of the alkyl iodide happens only after the transmetalation and the formation of the alkenyl nickel intermediate **3.VIII**. In some nickel-catalyzed cross-coupling reactions the activation of the alkyl halide occurs prior to transmetalation.[34,35] To probe this alternative mechanism, we exposed cyclohexyl iodide to our nickel(I) catalyst ((tpy′)NiI). After 1 h at room temperature, the starting alkyl iodide was fully recovered (**Scheme 3.5b**). This result suggests that, in our reaction, transmetalation (**3.VI→3.VIII**) likely precedes the activation of the alkyl iodide (**3.VIII→3.IX**).

Scheme 3.5. Mechanistic Experiments



3.3 CONCLUSION

In conclusion, we have developed a method for anti-Markovnikov hydroalkylation of alkynes using dual Cu/Ni catalyst system. The new method enables stereospecific synthesis of *E*-alkenes through coupling of terminal alkynes and primary or secondary alkyl iodides. The reaction has a broad substrate scope and is compatible with a wide range of functional groups. Preliminary mechanistic studies suggest that nickel catalyst promotes alkylation of a key alkenyl copper intermediate and that transmetalation from copper to nickel occurs prior to the activation of the alkyl iodide. Further studies of the reaction mechanism are underway in our laboratory

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. 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 ($CDCl_3$(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. Gas Chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

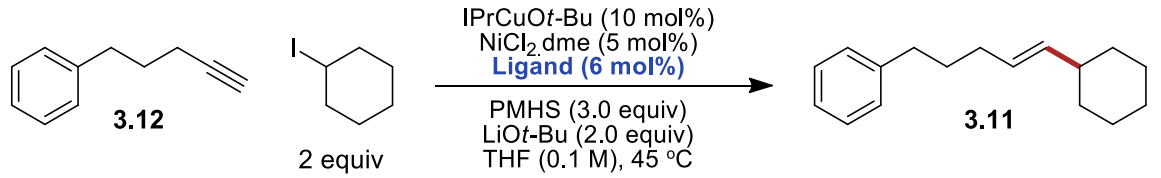
3.4.2 *Materials*

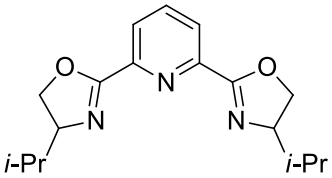
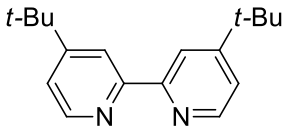
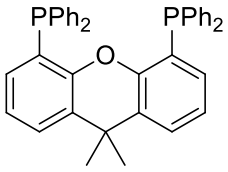
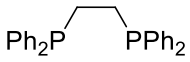
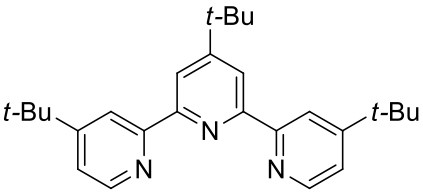
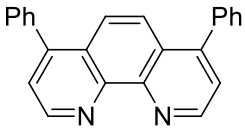
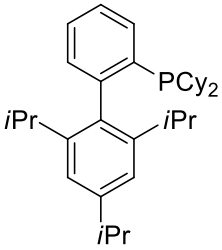
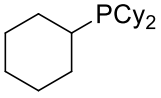
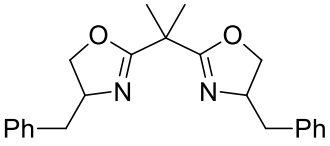
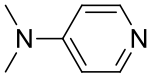
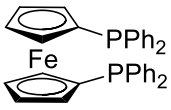
THF, CH_2Cl_2, acetonitrile, DME, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled over calcium hydride, degassed, and stored over 3Å (1-2 mm beads) molecular sieves. Isooctane, chlorobenzene, DCE and heptane were degassed and stored over 3Å (1-2 mm beads) molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. Commercial reagents were purchased from Sigma-Aldrich, TCI America, GFS-Chemicals, and AK-Scientific. Nitrogen and phosphine-based ligands were purchased from Sigma Aldrich. NHC ligand was synthesizes from known procedure. Nickel (I) pre-catalyst was synthesized using known literature procedure.[36,37] Ph_3SiH was purchased from Sigma Aldrich and recrystallized from dry methanol. All commercial alkynes were distilled over $NaBH_4$ and stored over 3Å (1-2 mm beads) molecular sieves. Purchased alkyl iodides (liquid) were distilled over sodium thiosulfate and stored under nitrogen

3.4.3 *Reaction Development for Secondary alkyl iodide*

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, turnover reagent, copper catalyst, solvent, silane, and alkyne respectively. The reaction mixture was stirred at room temp until the yellow color disappeared. Alkyl iodide, dodecane (internal standard), and nickel catalyst were added, and the reaction mixture was vigorously stirred at indicated temperature for 2 hours.

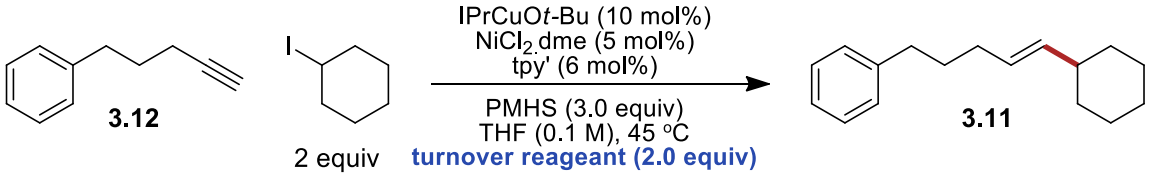
Table 3.3: Ligand screen



No ligand 0%	 **3.SL1** 11%	 **3.SL2** 8%	 **3.SL3** 0%
 **3.SL4** 0%	 **3.SL5** 16%	 **3.SL6** 9%	 **3.SL7** 0%
 **3.SL8** 0%	 **3.SL9** 2%	 **3.SL10** 5%	 **3.SL11** 0%

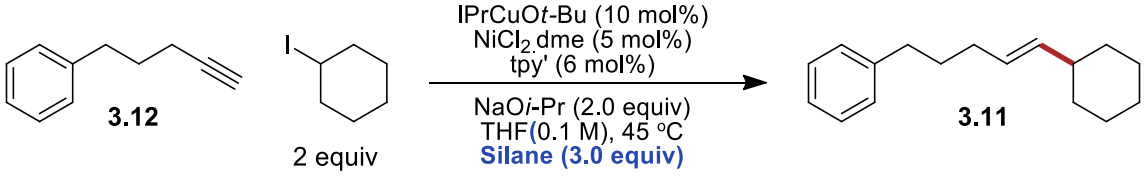
GC yields are reported

Table 3.4: Turnover reagent screen



Entry	Turnover reagent	Yield (%)
1	LiO*t*-Bu	16
2	NaO*t*-Bu	10
3	KO*t*-Bu	0
4	LiO*i*-Pr	16
5	NaO*i*-Pr	32
6	LiOMe	16
7	NaOMe	15
8	$NaOSiMe_3$	5
9	$KOSiMe_3$	5

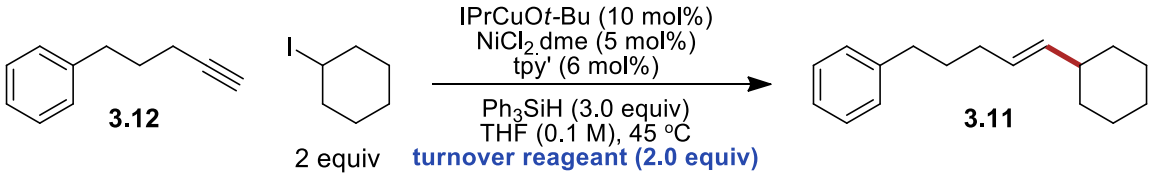
Table 3.5: Silane screen



Entry	Silane	Yield (%)
1	PMHS	32
2	$(EtO)_3SiH$	26
3	Et_3SiH	12

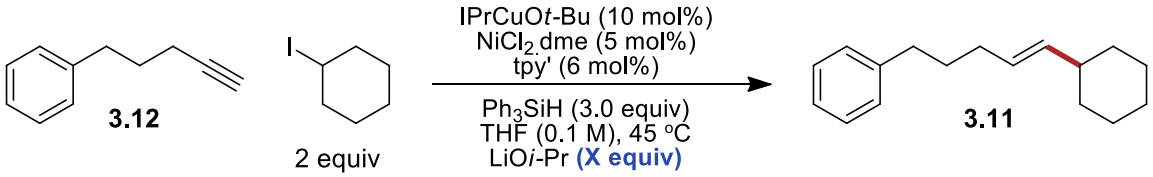
4	(Me)$_2$*i*-PrSiH	36
5	PhMe$_2$SiH	34
6	Ph$_2$SiH$_2$	13
7	Me(OEt)$_2$SiH	3
8	Ph$_3$SiH	38
9	Ph$_2$MeSiH	17
10	(*t*-Bu)$_2$SiH$_2$	28

Table 3.6: Turnover reagent screen



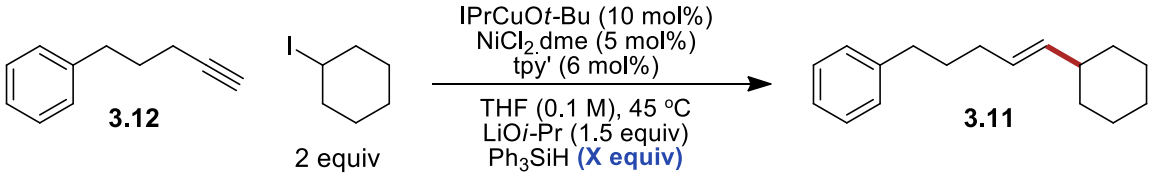
Entry	Turnover reagent	Yield (%)
1	LiO*t*-Bu	11
2	NaO*t*-Bu	3
3	KO*t*-Bu	6
4	LiO*i*-Pr	45
5	NaO*i*-Pr	38
6	LiOMe	5
7	CsF	12

Table 3.7: Stoichiometry of LiO*i*-Pr



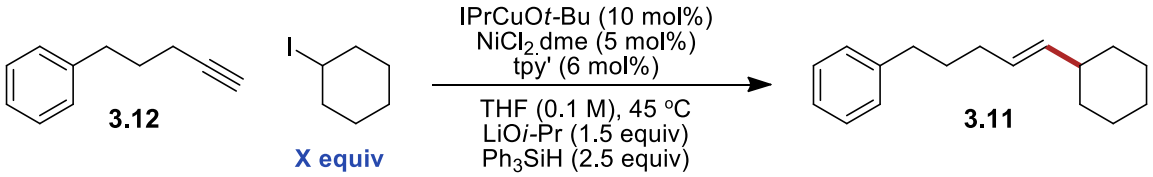
Entry	Equiv	Yield (%)
1	1.5	55
2	2	45
3	2.5	41
4	3	36

Table 3.8: Silane stoichiometry



Entry	Equiv	Yield (%)
1	1.5	46
2	2	38
3	2.5	60
4	3	55

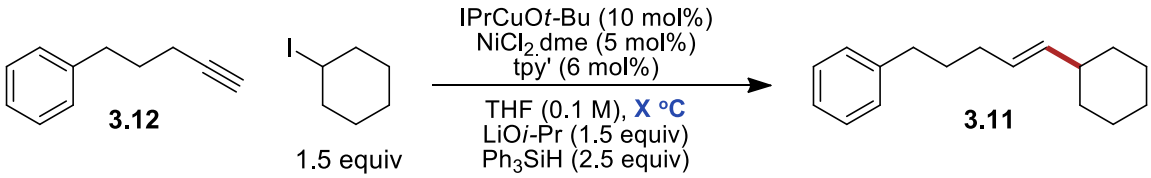
Table 3.9: Alkyl iodide stoichiometry



Entry	Equiv	Yield (%)

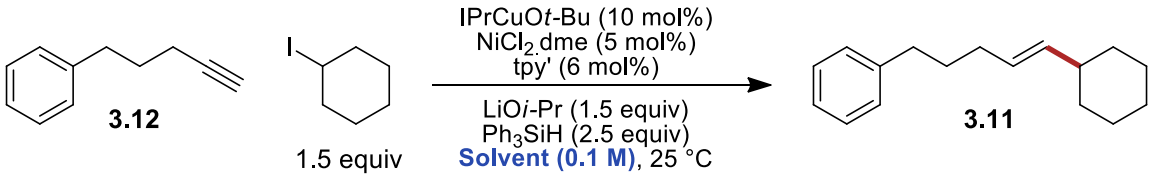
1	1.5	61
2	2	60
3	2.5	55
4	3	52

Table 3.10: Temperature screen



Entry	Temperature (°C)	Yield (%)
1	0	65
2	25	67
3	45	61
4	60	54

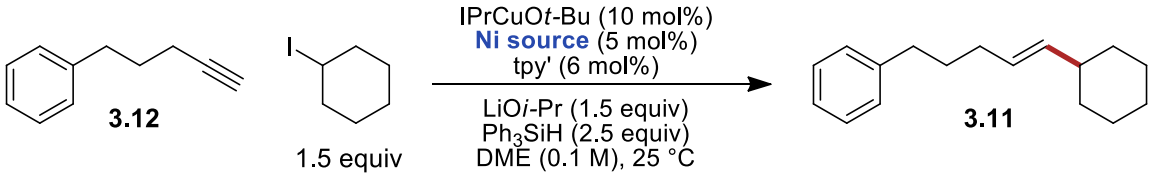
Table 3.11: Solvent screen



Entry	Solvent	Yield (%)
1	THF	67
2	DME	71
3	diethyl ether	60
4	toluene	40

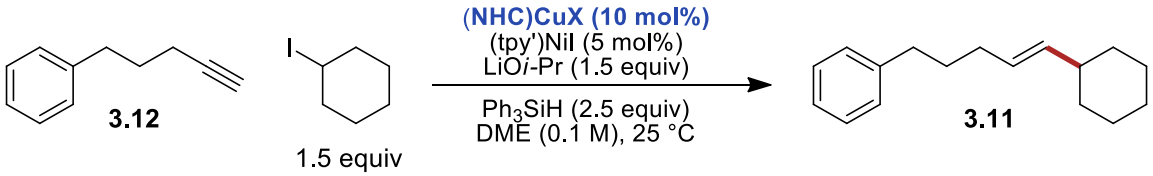
5	isooctane	50
6	DCM	0

Table 3.12: Nickel source screen



Entry	Nickel source	Yield (%)
1	$NiCl_2$.dme	71
2	$NiBr_2$.dme	74
3	(tpy′)NiI (no added ligand)	82
4	$Ni(COD)_2$	57

Table 3.13: NHC ligand screen

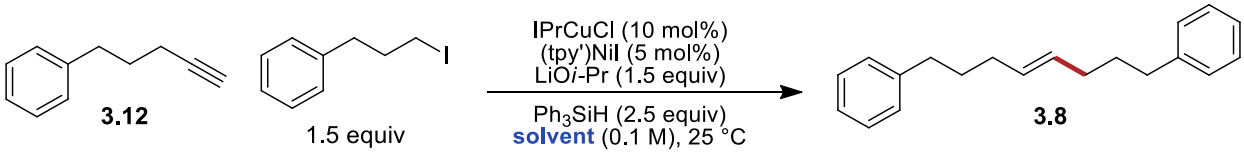


Entry	(NHC)CuX	Yield (%)
1	IPrCuCl	88
2	IPrCuO-*t*Bu	82
3	SIPrCuO-*t*Bu	80
4	SIPrCuCl	87
5	IMesCuCl	5
6	Ipr(Cl_2)CuCl	83

7	IPr(NMe$_2$)CuCl	74
8	IPr*CuCl	70
9	IcyCuCl	3
10	IMeCuCl	2
11	IAdCuCl	2

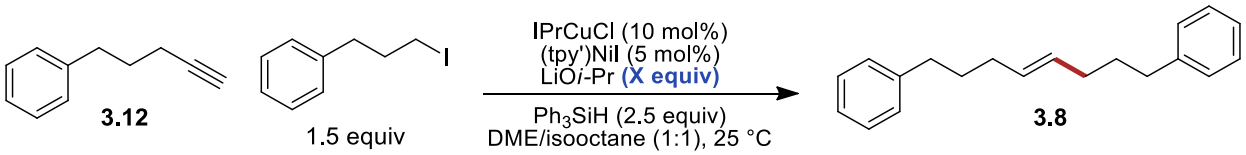
3.4.4 *Reaction Development for primary alkyl iodide*

Table 3.14 Solvent screen



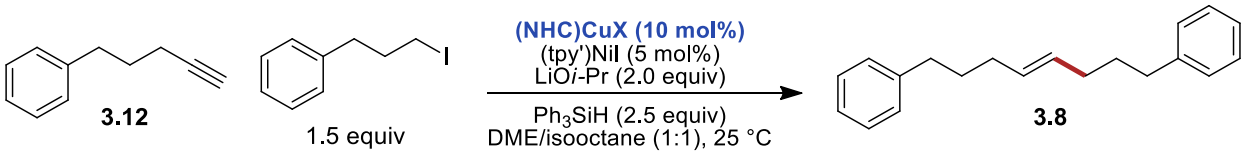
Entry	**Silane**	Yield (%)
1	DME	32
2	THF	26
3	DCM	7
4	toluene	30
5	isooctane	28
6	DME:isooctane (1:1)	42
7	DME:cyclohexane (1:1)	42
8	DME:pentane (1:1)	38

Table 3.15: LiO*i*-Pr stoichiometry



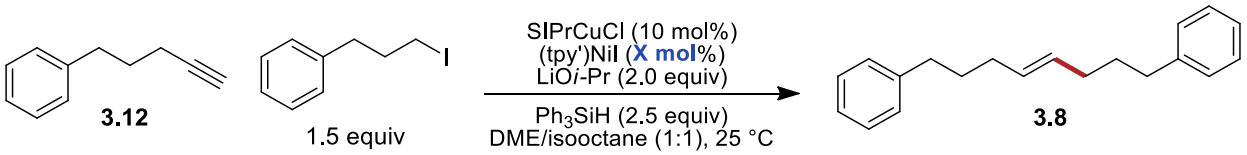
Entry	Equiv	Yield (%)
1	1.5	42
2	2	49
3	2.5	47
4	3	45

Table 3.16: NHC ligand screen



Entry	(NHC)CuX	Yield (%)
1	IPrCuCl	49
2	IPrCuO-*t*Bu	42
3	SIPrCuO-*t*Bu	69
4	SIPrCuCl	76
5	IMesCuCl	3
9	IcyCuCl	1
10	IMeCuCl	3

Table 3.17: Nickel catalyst loading



Entry	mol%	Yield (%)
1	1	79
2	3	90
3	5	76
4	10	62

3.4.5 *Standard condition for the hydroalkylation of alkynes*

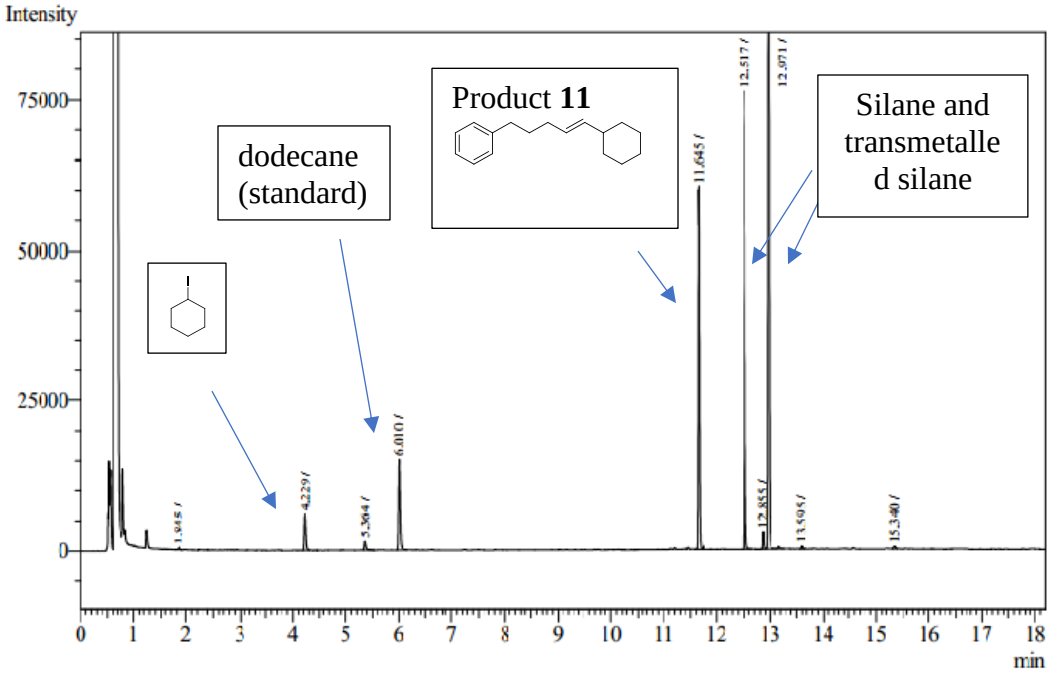
Standard procedure for hydroalkylation of alkyne with secondary alkyl iodides:

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiO*i*-Pr (49.5 mg, 0.75 mmol, 1.5 equiv), IPrCuCl (24.5 mg, 0.050 mmol, 0.10 equiv) and DME (2.0 mL). Ph_3SiH (325.5 mg, 1.25 mmol, 2.5 equiv) and alkyne (0.5 mmol, 1.0 equiv) were added to this solution respectively using 1 mL of DME. The reaction mixture was stirred at 25 °C until the yellow color disappeared. Secondary alkyl iodide (0.75 mmol, 1.5 equiv) and (tpy′)NiI (14.5 mg, 0.025 mmol, 0.05 equiv) were transferred to the reaction mixture by using 2 mL of DME. The reaction mixture was stirred at 25 °C for 2 hours. After 2 hours, 2-aminoethanol, or ammonium fluoride in methanol were added to quench the unreacted silane (caution: gas evolution). The reaction mixture was filtered through a pad of silica gel and washed with EtOAc and DCM. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography.

Standard procedure for hydroalkylation of alkyne with primary alkyl iodides:

In a nitrogen-filled glovebox, scintillation vial was charged with a stir bar, LiO*i*-Pr (66.0 mg, 1.0 mmol, 2.0 equiv), SIPrCuCl (24.5 mg, 0.050 mmol, 0.10 equiv) and DME/isooctane (1:1) (2.0 mL). Ph_3SiH (325.5 mg, 1.25 mmol, 2.5 equiv) and alkyne (0.5 mmol, 1.0 equiv) were added to this solution respectively using 1 mL of DME/isooctane. The reaction mixture was stirred at 25 °C until the yellow color disappeared. Primary alkyl iodide (0.75 mmol, 1.5 equiv) and (tpy′)NiI (14.5 mg, 0.015 mmol, 0.03 equiv) were transferred to the reaction mixture by using 2 mL of DME/isoocane. The reaction mixture was stirred at 25 °C for 2 hours. After 2 hours, 2-aminoethanol, or ammonium fluoride in methanol were added to quench the unreacted silane (caution: gas evolution). The reaction mixture was filtered through a pad of silica gel and washed with EtOAc and DCM. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography

3.4.6 *GC trace of a crude reaction mixture (Table 3.1, Entry 1)*



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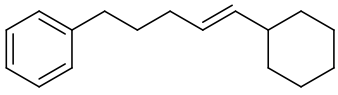
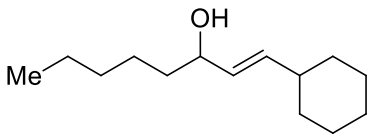
3.4.7 *Characterization of the E-alkene product*

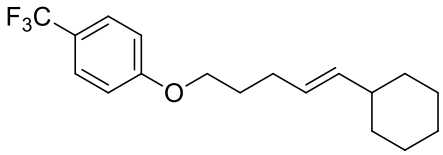


(E)-(5-cyclohexylpent-4-en-1-yl)benzene (11) compound was isolated as a colorless liquid (97.0 mg, 85% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 2H), 7.30 – 7.17 (m, 3H), 5.85 – 4.83 (m, 2H), 2.91 – 2.48 (m, 2H), 2.19 – 1.87 (m, 3H), 1.87 – 1.58 (m, 7H), 1.45 – 0.98 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 137.2, 128.6, 128.4, 127.3, 125.7, 40.9, 35.5, 33.5, 32.3. 31.5, 26.4, 26.3. GCMS (EI) calculated for $[M]^+$ 228.19, found 228.20. FTIR (neat, cm-1): 3024 9 (m), 2922 (s), 2850 (s), 1604 (w), 1495 (m), 1448 9m), 1029 (w), 967 (s), 891 (w), 744 (m), 697 (s).

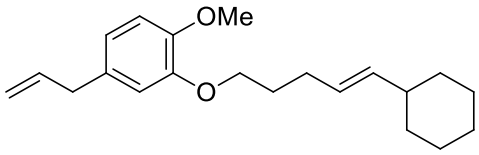


(E)-1-cyclohexyloct-1-en-3-ol (13) compound was isolated as a colorless liquid (76.7 mg, 73% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.40 (ddd, *J* = 15.5, 7.0, 1.1 Hz, 1H), 4.02 (q, *J* = 6.6 Hz, 1H), 2.02 – 1.83 (m, 1H), 1.89 – 1.29 (m, 14H), 1.25 –1.00 (5H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 130.7, 73.5, 40.4, 37.5, 33.1, 33.0, 31.9, 26.3, 26.1, 25.3, 22.7, 14.1. GCMS (EI) calculated for $[M]^+$ 210.20, found 210.20. FTIR (neat, cm-1): 3344 (b), 2923 (s), 2851(s), 1666 (w), 1448 (s), 1377 (w), 1302 (w), 1259 (w), 1129 (w), 1021 (m), 967 (s), 916 (w), 892 (w), 842 (w), 725 (w).

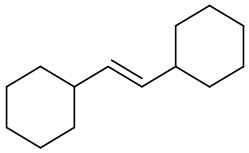


(E)-1-((5-cyclohexylpent-4-en-1-yl)oxy)-4-(trifluoromethyl)benzene (14) compound was isolated as a colorless liquid (137. 4 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 5.53 – 5.28 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.31 – 2.04 (m, 2H), 2.00 – 1.77 (m, 3H), 1.77 – 1.57 (m, 5H), 1.38 – 0.90 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 137.9, 127.0 (q, *J* = 3.6 Hz), 126.3, 124.7 (q, *J* = 270.9 Hz), 122.8 (q, *J* = 32.8 Hz), 114.6, 67.6, 40.8, 33.4, 29.1, 29.0, 26.4, 26.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -64.39. GCMS

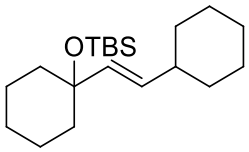
(EI) calculated for $[M]^+$ 312.17, found 312.20. FTIR (neat, cm-1): 3011(w), 2926 (s), 2852 (s), 2361 (w), 1617 (s), 1589 (s), 1519 (s), 1330 (s), 1258 (s0, 1161 (s), 1110 (s), 1068 (s), 1009 (s), 968 (m), 835 (s).



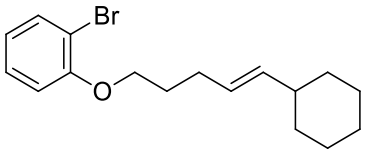
(E)-4-allyl-2-((5-cyclohexylpent-4-en-1-yl)oxy)-1-methoxybenzene (15) compound was isolated as a colorless liquid (135.1mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.7 Hz, 1H), 6.76 – 6.67 (m, 2H), 5.96 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.47 – 5.33 (m, 2H), 5.16 – 4.99 (m, 2H), 3.99 (t, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 3.33 (d, *J* = 6.7 Hz, 2H),2.20 – 2.07 (m, 2H) 1.98 – 1.80 (m, 3H), 1.77 – 1.59 (m, 5H), 1.33 – 0.93 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 147.1, 137.9, 137.5, 132.8, 126.6, 120.6, 115.7, 113.4, 112.5, 68.7, 56.1, 40.8, 39.9, 33.3, 29.2, 29.1, 26.4, 26.2. GCMS (EI) calculated for $[M]^+$ 314.22, found 314.30. FTIR (neat, cm-1): 2999 (w), 2922 (s), 2849 (s), 1638 (m), 1605 (m), 1512 (s), 1465 (s), 1419 (s), 1335 (w), 1260 (s), 1232 (s), 1156 (s), 1139 (s), 1037 (s), 993 (m), 968 (m), 911 (s), 848 (m), 802 (m).



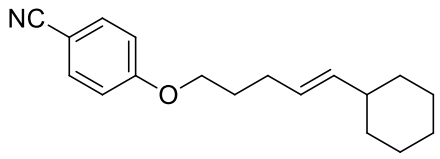
(E)-1,2-dicyclohexylethene (16) compound was isolated as a colorless liquid (88.4 mg, 92% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (d, *J* = 1.9 Hz, 2H), 1.96 – 1.82 (m, 2H), 1.80 – 1.59 (m, 10H), 1.35 – 0.98 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.9, 40.9, 33.6, 26.5, 26.3. GCMS (EI) calculated for $[M]^+$ 192.19, found 192.20. FTIR (neat, cm-1): 3009 (w), 2920 (s), 2850 (s), 1447 (s), 1258 (m), 967 (s), 889 (s), 843 (m).



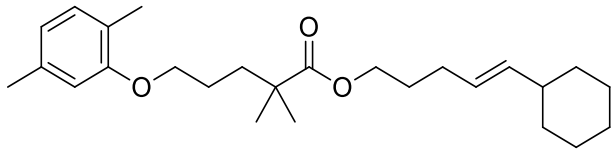
(E)-tert-butyl((1-(2-cyclohexylvinyl)cyclohexyl)oxy)dimethylsilane (17) compound was isolated as a colorless liquid (140.2 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 – 5.40 (m, *J* = 4.2 Hz, 2H), 1.74 – 0.98 (m, 21H), 0.88 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 133.9, 73.3, 40.8, 38.6, 33.0, 26.4, 26.3, 26.2, 26.2, 22.4, 18.5, -1.7 GCMS (EI) calculated for $[M]^+$ 322.27, found 322.30. FTIR (neat, cm-1): 2926 (s), 2853 (s), 1640 (w), 1583 (w), 1462 (s), 1449 (s), 1358 (m), 1250 (s), 1148 (m), 1048 (s), 1022 (s), 977 (w), 898 (w), 834 (s), 772 (s).



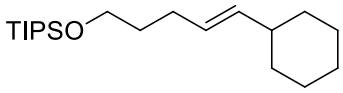
(E)-1-bromo-2-((5-cyclohexylpent-4-en-1-yl)oxy)benzene (18) compound was isolated as a colorless liquid (96.6 mg, 60% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 1H), 7.30 – 7.19 (m, 1H), 6.92 – 6.76 (m, 2H), 5.54 – 5.26 (m, 2H), 4.02 (t, *J* = 6.1 Hz, 2H), 2.32 – 2.09 (m, 2H), 2.03 – 1.82 (m, 3H), 1.80 – 1.58 (m, 5H), 1.38 – 0.90 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 137.7, 133.4, 128.4, 126.4, 121.7, 113.4, 112.4, 68.5, 40.8, 33.3, 29.1, 29.0, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 322.09, found 322.10. FTIR (neat, cm-1): 3065 (m), 3035 (m), 2922 (s), 2850 (s), 2361 (w), 2341 (w), 1688 (w), 1589 (s), 1564 (s), 1481 (s), 1443 (s), 138 (m), 1277 (s), 1249 (s), 1161 (m), 1125 (s), 1052 (s), 1031 (s), 969 (s), 926 (w), 892 (w), 745 (s), 677 (s).



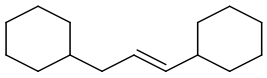
(E)-4-((5-cyclohexylpent-4-en-1-yl)oxy) (19) compound was isolated as a colorless liquid (115.7 mg, 86% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.55 – 4.97 (m, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.32 – 1.97 (m, 2H), 1.94 – 1.78 (m, 3H), 1.72 – 1.57 (m, 5H), 1.31 – 0.93 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 137.9, 134.0, 126.0, 119.3, 115.3, 103.8, 67.7, 40.7, 33.3, 28.9, 26.3, 26.1. GCMS (EI) calculated for $[M]^+$ 269.18, found 269.20. FTIR (neat, cm-1): 3115 (w), 2924 (s), 2850 (s), 2225 (s), 1772 (w), 1653 (s), 1600 (s), 1576 (w), 1507 (s), 1473 (w), 1448 (m), 1301 (m), 1264 (s), 1171 (s), 970 (m), 835 (s), 738 (s), 703 (s).



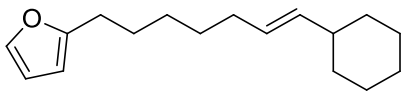
(E)-5-cyclohexylpent-4-en-1-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (20) compound was isolated as a colorless liquid (168.1 mg, 84% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.3 Hz, 1H), 6.61 (s, 1H), 5.45 – 5.26 (m, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.92 (t, *J* = 4.7 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.10 – 2.00 (m, 2H), 1.97 – 1.80 (m, 1H), 1.80 – 1.57 (m, 11H), 1.36 – 0.90 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 157.1, 137.7, 136.5, 130.4, 126.1, 123.7, 120.8, 112.0, 68.0, 63.9, 42.2, 40.8, 37.2, 33.3, 29.0, 28.7, 26.3, 26.2, 25.3, 21.5, 15.9. GCMS (EI) calculated for $[M]^+$ 400.09, found 400.10. FTIR (neat, cm-1): 3091 (m), 3036 (m), 2924 (s), 2851 (s), 1958 (w), 1726 (s), 1615 (s), 1586 (s), 1509 (s), 1474 (s), 1448 (s), 1391 (s), 1265 (s), 1192 (s), 1147 (s), 1049 (s), 969 (s), 893 (m), 802 (s), 677 (s).



(E)-((5-cyclohexylpent-4-en-1-yl)oxy)triisopropylsilane (21) compound was isolated as a colorless liquid (141.1 mg, 87% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 – 5.16 (m, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.13 – 1.98 (m, 2H), 1.97 – 1.82 (m, 1H), 1.77 – 1.54 (m, 7H), 1.32 – 0.98 (m, 26H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 127.3, 63.0, 40.9, 33.4, 33.1, 29.0, 26.4, 26.3, 18.2, 12.2. GCMS (EI) calculated for $[M]^+$ 324.28, found 324.40. FTIR (neat, cm-1): 3017 (w), 2923 (s), 2864 (s), 1463 (s), 1448 (s), 1382 (m), 1349 (w), 1247 (m), 1108 (s), 1069 (s), 1013 (s), 967 (s), 882 (s), 725 (s), 680 (s).

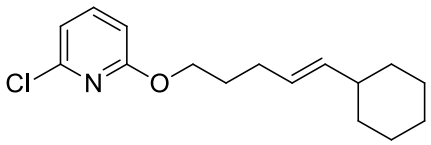


(E)-prop-1-ene-1,3-diyldicyclohexane (22) compound was isolated as a colorless liquid (92.8 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 – 5.02 (m, 2H), 1.97 – 1.75 (m, 3H), 1.77 – 1.58 (m, 10H), 1.38 – 0.79 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 126.3, 41.0, 40.9, 38.4, 33.5, 33.3, 26.9, 26.6, 26.5, 26.3. GCMS (EI) calculated for [M]+ 206.20, found 206.20. FTIR (neat, cm-1): 2921 (s), 2850 (s), 1448 (s), 966 (s), 891 (w). 840 (w).

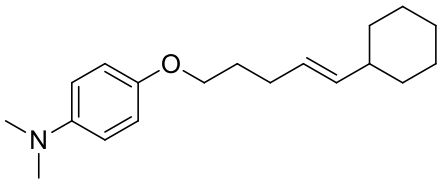


(E)-2-(7-cyclohexylhept-6-en-1-yl)furan (23) compound was isolated as a colorless liquid (103.4 mg, 84% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 0.8 Hz, 1H), 6.30 – 6.23 (m, 1H), 5.97 (d, *J* = 2.4 Hz, 1H) 5.45 – 5.21 (m, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.07 – 1.83 (m, 3H), 1.77 – 1.55

(m, 7H), 1.47 – 0.93 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 140.8, 136.7, 127.7, 110.2, 104.7, 40.8, 33.5, 32.6, 29.5, 28.8, 28.1, 28.1, 26.4, 26.3. GCMS (EI) calculated for $[M]^+$ 246.20, found 246.20. FTIR (neat, cm-1): 3012 (w), 2923 (s), 2851 (s), 1710 (m), 1596 (m), 1508 (m), 1448 (s), 1349 (w), 1147 (s), 1006 (s), 967 (s), 725 (s).

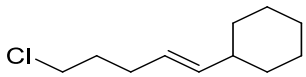


(E)-2-chloro-6-((5-cyclohexylpent-4-en-1-yl)oxy)pyridine (24) compound was isolated as a colorless liquid (107.5 mg, 77% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 5.49 – 5.10 (m, 2H), 4.28 (t, *J* = 6.6 Hz, 2H), 2.13 (dd, *J* = 11.7, 7.2 Hz, 2H), 1.96 – 1.55 (m, 8H), 1.41 – 0.94 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 148.5, 140.6, 137.5, 126.5, 116.1, 109.2, 66.2, 40.8, 33.3, 29.1, 29.0, 26.4, 26.2. GCMS (EI) calculated for $[M]^+$ 279.14, found 279.10. FTIR (neat, cm-1): 2922 (s), 1849 (s), 1590 (s), 1559 (s), 1466 (m), 1442 (s), 1407 9s), 1379 (s), 1300 (s), 1262 (s), 1159 (s), 1072 (m), 1011 (m), 948 (s), 787 (s).

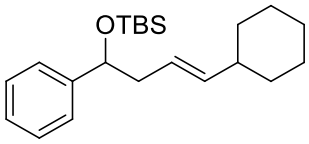


(E)-4-((5-cyclohexylpent-4-en-1-yl)oxy)-N,N-dimethylaniline (25) compound was isolated as a colorless liquid (103.4 mg, 72% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 5.52 – 5.28 (m, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 2.86 (s, 6H), 2.19 – 2.08 (m, 2H), 1.99 – 1.75 (m, 3H), 1.75 – 1.57 (m, 5H), 1.36 – 0.95 (m, 5H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 151.6, 145.8, 137.3, 126.6, 115.6, 115.0, 68.0, 41.9, 40.8, 33.3, 29.4, 29.1, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 287.22, found 280.10. FTIR (neat, cm-1): 3017 (w), 2922 (s), 2850 (s), 1640 (w), 1514 (s), 1478 (m), 1469 (m), 1244 (s), 1056 (w), 967 (m), 815 (s).

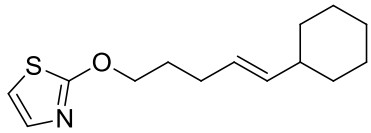


(E)-(5-chloropent-1-en-1-yl)cyclohexane (26) compound was isolated as a colorless liquid (80.0 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 – 5.26 (m, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 2.12 (q, *J* = 6.8 Hz, 2H), 1.95 – 1.86 (m, 1H), 1.81 (p, *J* = 6.8 Hz, 2H), 1.74 – 1.59 (m, 5H), 1.31 – 1.00 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 126.0, 44.5, 40.8, 33.3, 32.6, 29.8, 26.4, 26.2. GCMS (EI) calculated for $[M]^+$ 186.12, found 186.10. FTIR (neat, cm-1): 2989 (m), 2922 (s), 2849 (s), 1447 (s), 1349 (w), 1299 (m), 1288 (m), 969 (s), 892 (m), 842 (m), 726 (m).

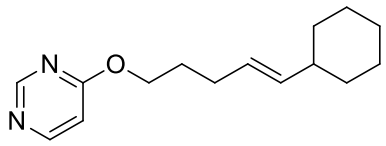


(E)-tert-butyl((4-cyclohexyl-1-phenylbut-3-en-1-yl)oxy)dimethylsilane (27) compound was isolated as a colorless liquid (129.1 mg, 75% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.25 – 7.18 (m, 1H), 5.40 – 5.28 (m, 2H), 4.62 (dd, *J* = 7.4, 5.1 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.31 – 2.24 (m, 1H), 1.92 – 1.83 (m, 1H), 1.73 – 1.59 (m, 5H), 1.31 – 1.19 (m, 2H), 1.19 – 1.10 (m, 1H), 1.07 – 0.96 (m, 2H), 0.88 (s, 9H), 0.02 (s, 3H), -0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 139.1, 128.0, 126.9, 126.1, 124.1, 75.7, 44.6, 40.9, 33.2, 26.4, 26.3, 26.0, 18.4, -4.5, -4.7. GCMS (EI) calculated for $[M]^+$ 344.25, found 344.20. FTIR (neat, cm-1): 3028 (m), 2927 (s),

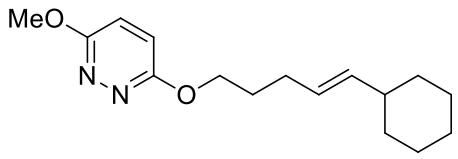
2854 (s), 1602 (w), 1493 (w), 1462 (m), 1450 (s), 1388 (w), 1361 (m), 1256 (s), 1089 (s), 1069 (s), 970 (m), 939 (w), 836 (s), 775 (s), 699 (s).



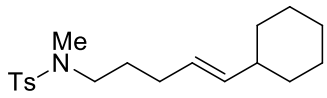
(E)-2-((5-cyclohexylpent-4-en-1-yl)oxy)thiazole (28) compound was isolated as a colorless liquid (104.2 mg, 83% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.4 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 5.58 – 5.11 (m, 2H), 4.37 (t, *J* = 6.4 Hz, 2H), 2.12 (dd, *J* = 12.6, 6.6 Hz, 2H), 1.98 – 1.76 (m, 3H), 1.76 – 1.56 (m, 5H), 1.33 – 0.92 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 137.8, 137.0, 126.0, 110.8, 71.3, 40.7, 33.3, 28.9, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 251.13, found 251.20. FTIR (neat, cm-1): 2922 (s), 2849 (s), 1610 (w), 1522 (s), 1482 (m), 1464 (s), 1381 (m). 1308 9s), 1237 (s), 1213 (s), 1162 (s), 968 (s), 700 (s).



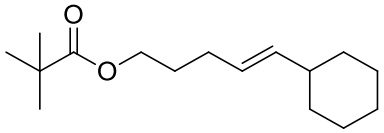
(E)-4-((5-cyclohexylpent-4-en-1-yl)oxy)pyrimidine (29) compound was isolated as a colorless liquid (91.1 mg, 74% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.41 (d, *J* = 5.7 Hz, 1H), 6.71 (d, *J* = 5.7 Hz, 1H), 5.64 – 5.05 (m, 2H), 4.35 (t, *J* = 6.6 Hz, 2H), 2.27 – 1.90 (m, 2H), 2.04 – 1.74 (m, 3H), 1.76 – 1.57 (m, 65), 1.34 – 0.96 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 158.6, 157.1, 137.8, 126.2, 108.8, 66.1, 40.8, 33.3, 29.0, 28.8, 26.4, 26.2. GCMS (EI) calculated for $[M]^+$ 246.17, found 246.20. FTIR (neat, cm-1): 3100 (w), 2956 (s), 2850 (s), 1612 (w), 1582 (s), 1560 (s), 1480 (s), 1464 (s), 1399 (m), 1375 (m), 1264 (s), 986 (s), 835 (s), 742 (s).



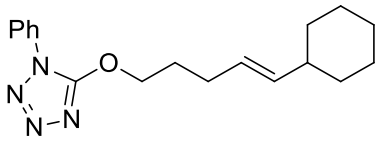
(E)-3-((5-cyclohexylpent-4-en-1-yl)oxy)-6-methoxypyridazine (30) compound was isolated as a colorless liquid (93.9 mg, 68% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 2H), 5.49 – 5.26 (m, 2H), 4.39 (t, *J* = 6.6 Hz, 2H), 4.03 (s, 3H), 2.22 – 2.01 (m, 2H), 2.01 – 1.73 (m, 3H), 1.73 – 1.51 (m, 5H), 1.35 – 0.87 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 161.9, 137.5, 126.5, 121.6, 121.3, 66.8, 54.6, 40.7, 33.3, 29.1, 29.0, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 276.18, found 276.20. FTIR (neat, cm-1): 3064 (m), 2921 (s), 2849 (s), 1613 (w), 1548 (w), 1470 (s), 1449 (s), 1424 (s), 1388 (s), 1339 (w), 1267 (s), 1099 (w), 1015 (s), 969 (s), 846 (s), 790 (m).



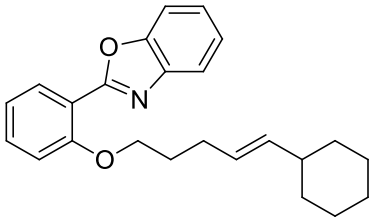
(E)-N-(5-cyclohexylpent-4-en-1-yl)-N,4-dimethylbenzenesulfonamide (31) compound was isolated as a colorless liquid (137.4 mg, 82% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.45 – 5.20 (m, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 2.70 (s, 3H), 2.43 (s, 3H), 2.10 – 1.92 (m, 2H), 1.94 – 1.76 (m, 1H), 1.73 – 1.51 (m, 7H), 1.30 – 0.88 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 137.6, 134.6, 129.6, 127.4, 126.1, 49.7, 40.7, 34.7, 33.2, 29.6, 27.6, 26.2, 26.1, 21.5. GCMS (EI) calculated for $[M]^+$ 335.19, found 335.10. FTIR (neat, cm-1): 3439 (w), 3064, (w), 3012 (w), 2922 (s), 2849 (s), 1622 (w), 1597 (s), 1493 (m), 1448 (s), 1398 (w), 1374 (w), 1341 (s), 1304 (m), 1161 (s), 1118 (m), 1090 (s), 1019 (m), 968 (s), 801 (s), 739 (s), 715 (s), 700 (s), 652 (s).



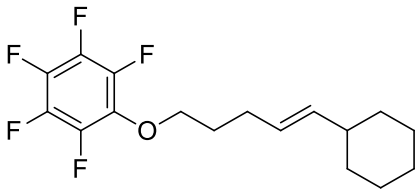
(E)-5-cyclohexylpent-4-en-1-yl pivalate (32) compound was isolated as a colorless liquid (82.0 mg, 65% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 – 5.27 (m, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.14 – 1.97 (m, 2H), 1.98 – 1.80 (m, 1H), 1.79 – 1.59 (m, 7H), 1.34 – 0.95 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 137.7, 126.2, 63.9, 40.8, 38.9, 33.3, 29.0, 28.7, 27.3, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 252.21, found 252.20. FTIR (neat, cm-1): 3441 (w), 3092 (w), 3056 (w), 2925 (s), 2851 (s), 1731 (s), 1481 (s), 1448 (s), 1397 (s), 1365 (s), 1283 (s), 1156 (s), 1036 (s), 969 (s), 892 (m), 771 (s), 677 (s).



(E)-5-((5-cyclohexylpent-4-en-1-yl)oxy)-1-phenyl-1H-tetrazole (33) compound was isolated as a colorless liquid (129.6 mg, 83% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.49 – 7.41 (m, 1H), 5.45 – 5.28 (m, 2H), 4.64 (t, *J* = 6.5 Hz, 2H), 2.21 – 2.08 (m, 2H), 2.02 – 1.78 (m, 3H), 1.75 – 1.55 (m, 5H), 1.33 – 0.94 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 138.2, 133.6, 129.6, 128.8, 125.4, 121.5, 73.6, 40.6, 33.1, 28.6, 26.2, 26.1. GCMS (EI) calculated for $[M]^+$ 312.20, found 312.20. FTIR (neat, cm-1): 3065 (w), 3024 (w), 2922 (s), 2849 (s), 1612 (w), 1595 (s), 1560 (s), 1505 (s), 1447 (s), 1381 (s), 1349 (w), 1331 (w), 1294 (s), 1127 (s), 1094 (s), 1071 (s), 1020 (s), 968 (s), 911 (s), 758 (s), 696 (m), 685 (s).

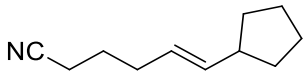


(E)-2-(2-((5-cyclohexylpent-4-en-1-yl)oxy)phenyl)benzo[d]oxazole (34) compound was isolated as a colorless liquid (128.5 mg, 80% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.80 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.58 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.39 – 7.31 (m, 2H), 7.12 – 7.02 (m, 2H), 5.66 – 5.00 (m, 2H), 4.14 (t, *J* = 6.4 Hz, 2H), 2.40 – 2.08 (m, 2H), 2.08 – 1.76 (m, 3H), 1.78 – 1.59 (m, 5H), 1.36 – 0.92 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 158.2, 150.9, 142.1, 137.7, 132.7, 131.6, 126.5, 124.8, 124.3, 120.7, 120.1, 116.9, 113.6, 110.5, 68.5, 40.7, 33.3, 29.2, 29.0, 26.3, 26.2. GCMS (EI) calculated for $[M]^+$ 361.20, found 361.20. FTIR (neat, cm-1): 2923 (s), 2849(m), 1645(w), 1600(w), 1548(w), 1537(w), 1492(w), 1452(s), 1310(w), 1034(w), 968 (s), 909(s), 749(s).

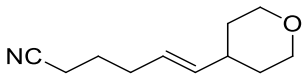


(E)-1-((5-cyclohexylpent-4-en-1-yl)oxy)-2,3,4,5,6-pentafluorobenzene (35) compound was isolated as a colorless liquid (127.0 mg, 76% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 – 5.25 (m, 2H), 4.14 (t, *J* = 6.4 Hz, 2H), 2.22 – 2.10 (m, 2H), 2.00 – 1.76 (m, 3H), 1.76 – 1.59 (m, 5H), 1.37 – 0.93 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (d, *J* = 238.7 Hz), 138.2 (d, *J* = 247.9 Hz), 138.2, 137.4 (d, *J* = 246.7 Hz), 134.1, 125.9, 75.1, 40.9, 33.4, 29.9, 28.6, 26.4, 26.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -159.81 (d, *J* = 20.3 Hz), -166.56 (t, *J* = 20.5 Hz), -166.93 (t, *J* = 21.8 Hz). GCMS (EI) calculated for $[M]^+$ 334.14, found 334.20. FTIR (neat, cm-1): 3079 (w), 3038 (w), 2925 (s),

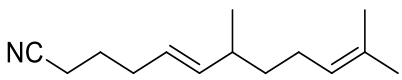
2852 (s), 1814 (w), 1638 (w), 1512 (s), 1482 (s), 1449 (s), 1313 (m), 1160 (s), 1031 (s), 996 (s), 893 (w), 677 (s).



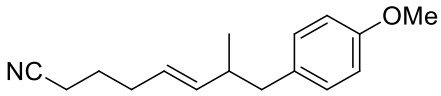
(E)-6-cyclopentylhex-5-enenitrile (36) compound was isolated as a colorless liquid (69.3 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (dd, *J* = 15.3, 7.5 Hz, 1H), 5.38 – 5.19 (m, 1H), 2.47 – 2.23 (m, 3H), 2.14 (q, *J* = 7.0 Hz, 2H), 1.83 – 1.46 (m, 8H), 1.36 – 1.15 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 125.3, 119.8, 43.3, 33.2, 31.2, 25.2, 25.1, 16.3. GCMS (EI) calculated for $[M]^+$ 163.14, found 163.20. FTIR (neat, cm-1): 3020 (w), 2950 (s), 2867 (s), 2245 (m), 1660 (w), 1452 (s), 1425 (m), 1347 (w), 968 (s), 751 (w)



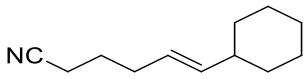
(E)-6-(tetrahydro-2H-pyran-4-yl)hex-5-enenitrile (37) compound was isolated as a colorless liquid (80.6 mg, 90% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 – 5.10 (m, 2H), 3.95 (dd, *J* = 11.4, 2.4 Hz, 2H), 3.40 (td, *J* = 11.6, 2.1 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.26 – 2.09 (m, 3H), 1.73 (p, *J* = 7.2 Hz, 2H), 1.64 – 1.51 (m, 2H).1.52 – 1.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 125.8, 119.5, 67.5, 37.7, 32.6, 31.1, 24.9, 16.1. GCMS (EI) calculated for $[M]^+$ 179.13, found 179.10. FTIR (neat, cm-1): 3008 (w), 2931 (s), 2842 (s), 2755 (w), 2690 (w), 2244 (m), 1620 w), 1441 (s), 1386 (s), 1352 (w), 1236 (s), 1175 (w), 1128 (s), 1093 (s), 1013 (s), 980 (s), 870 (m), 819 (w).



(E)-7,11-dimethyldodeca-5,10-dienenitrile (38) compound was isolated as a colorless liquid (69.8 mg, 68% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 – 5.15 (m, 2H), 5.07 (t, *J* = 7.2 Hz, 1H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.20 – 2.02 (m, 3H), 1.92 (dd, *J* = 15.0, 7.4 Hz, 2H), 1.78 – 1.62 (m, 5H), 1.57 (s, 3H), 1.27 (dd, *J* = 15.0, 7.4 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 131.3, 125.7, 124.6, 119.7, 37.1, 36.4, 31.3, 25.9, 25.7, 25.2, 20.8, 17.7, 16.3. GCMS (EI) calculated for $[M]^+$ 205.18, found 205.20. FTIR (neat, cm-1): 3024 (w), 2960 (s), 2923 (s), 2867 (s), 2246 (m), 1695 (w), 1675 (w), 1453 (s), 1370 (s), 1111 (w), 970 (s), 829 (m), 739 (m).

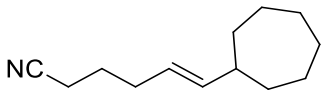


(E)-8-(4-methoxyphenyl)-7-methyloct-5-enenitrile (39) compound was isolated as a colorless liquid (68.1 mg, 56% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.30 (dd, *J* = 15.3, 7.5 Hz, 1H), 5.16 – 4.89 (m, 1H), 3.68 (s, 3H), 2.42 (d, *J* = 7.2 Hz, 2H), 2.37 – 2.20 (m, 1H), 2.08 – 1.92 (m, 4H), 1.61 – 1.45 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 138.2, 132.9, 130.1, 126.1, 119.8, 113.5, 55.2, 42.7, 38.9, 31.1, 25.0, 20.3, 15.9. GCMS (EI) calculated for $[M]^+$ 243.16, found 243.20. FTIR (neat, cm-1): 3028(m), 2954(s), 2867 (s), 2836 (m), 2245 (m), 1611 (s), 1582 (m), 1512 (s), 1454 (s), 1441 (s), 1300(s), 1246 (s), 1177 (s), 1112 (m), 1035 (s), 971 (s), 811 (s), 752 (m).

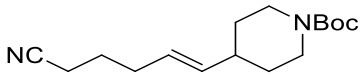


(E)-6-cyclohexylhex-5-enenitrile (40) compound was isolated as a colorless liquid (77.9 mg, 88% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.27 (dt, *J* = 15.5, 6.6 Hz, 1H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.98 – 1.83 (m, 1H), 1.77 – 1.60 (m, 7H),

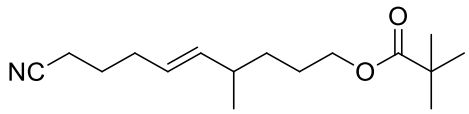
1.30 – 0.98 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 124.7, 119.8, 40.7, 33.1, 31.4, 26.2, 26.1, 25.2, 16.2. GCMS (EI) calculated for $[M]^+$ 177.15, found 177.20. FTIR (neat, cm-1): 3012 (w), 2923 (s), 2849 (s), 2245 (m), 1624 (w), 1448 (s), 1425 (m), 13478 (w), 1258 (w), 970 (s), 892 (w), 842 (w), 679 (w).



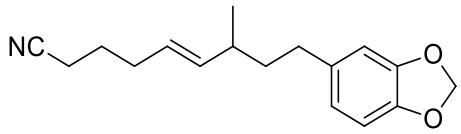
(E)-6-cycloheptylhex-5-enenitrile (41) compound was isolated as a colorless liquid (79.3 mg, 83% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (ddt, *J* = 15.4, 7.3, 1.1 Hz, 1H), 5.32 – 5.16 (m, 1H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.21 – 2.01 (m, 3H), 1.85 – 1.15 (m, 14H).^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 124.1, 119.9, 42.9, 35.0, 31.4, 28.5, 26.4, 25.3, 16.4 GCMS (EI) calculated for $[M]^+$ 191.17, found191.10 . FTIR (neat, cm-1): 2924 (s), 2853 (s), 2361 (m), 2246 (w), 1603 (w), 1460 (s), 1357 (w), 968 (s).



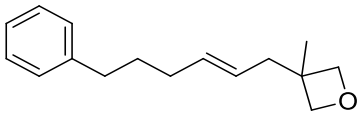
(E)-tert-butyl 4-(5-cyanopent-1-en-1-yl)piperidine-1-carboxylate (42) compound was isolated as a colorless liquid (112.7 mg, 81% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 – 5.12 (m, 2H), 4.03 (d, *J* = 12.2 Hz, 2H), 2.68 (t, *J* = 12.2 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 2.23 – 1.92 (m, 3H), 1.83 – 1.45 (m, 4H), 1.41 (s, 9H), 1.31 – 1.06 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 136.7, 126.1, 119.6, 79.2, 44.0, 38.8, 31.8, 31.2, 28.4, 25.0, 16.2. GCMS (EI) calculated for $[M]^+$ 278.20, found 278.10. FTIR (neat, cm-1): 3020 (m), 2973 (s), 2931 (s), 2849 (s), 2245 (m), 1689 (s), 1490 (s), 1481 (s), 1445 (s), 1423 (s), 1365 (s), 1275 (s), 1232 (s), 1165 (s), 970 (s), 868 (m), 769 (m)



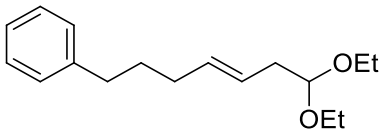
(E)-9-cyano-4-methylnon-5-en-1-yl pivalate (43) compound was isolated as a colorless liquid (102.1 mg, 77% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 – 5.00 (m, 2H), 4.01 (t, *J* = 6.7 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.23 – 1.98 (m, 3H), 1.71 (p, *J* = 7.2 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.40 – 1.15 (m, 11H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 138.5, 126.1, 119.7, 64.5, 38.8, 36.5, 33.1, 31.3, 27.3, 26.6, 25.2, 20.9, 16.4. GCMS (EI) calculated for $[M]^+$ 265.20, found 265.10. FTIR (neat, cm-1): 3012(w), 2958(s), 2246, (m), 1726 (s), 1543 (w), 1480 (s), 1455 (w), 1398 (w), 1366 (w), 1285 (s), 1159 (s), 972 (s), 771 (w), 732 (w).



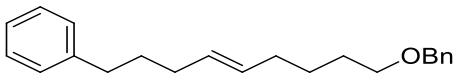
(E)-9-(benzo[d][1,3]dioxol-5-yl)-7-methylnon-5-enenitrile (44) compound was isolated as a colorless liquid (88.1 mg, 65% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 – 6.55 (m, 3H), 5.91 (s, 2H), 5.47 – 5.24 (m, 2H), 2.60 – 2.40 (m, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 2.22 – 2.05 (m, 3H), 1.73 (p, *J* = 7.2 Hz, 2H), 1.54 (q, *J* = 7.8 Hz, 2H), 1.00 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 145.5, 138.6, 136.5, 126.2, 121.0, 119.7, 108.9, 108.1, 100.8, 39.0, 36.3, 33.5, 31.3, 25.2, 20.8, 16.3. GCMS (EI) calculated for $[M]^+$ 271.16, found 271.20. FTIR (neat, cm-1): 3071 (w), 3035 (m), 2927 (s), 1858 (s), 2776 (m), 2246 (s), 1607 (m), 1509 (s), 1489 (s), 1441 (s), 1363 (m), 1244 (s), 1188 (s), 1244 (s), 1188 (s), 1096 (m), 1039 (s), 979 (s), 937 (s), 857 (m), 810 (s), 756 (w).



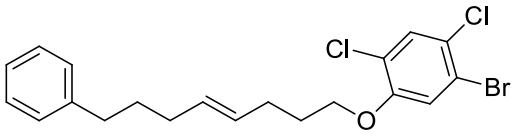
(E)-3-methyl-3-(6-phenylhex-2-en-1-yl)oxetane (45) compound was isolated as a colorless liquid (82.9 mg, 72% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 2H), 7.25 – 7.14 (m, 3H), 5.62 – 5.38 (m, 2H), 4.47 (d, *J* = 5.6 Hz, 2H), 4.37 (d, *J* = 5.6 Hz, 2H), 2.71 – 2.60 (m, 2H), 2.35 (d, *J* = 6.9 Hz, 2H), 2.10 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 133.6, 128.5, 128.3, 125.7, 125.7, 82.2, 42.1, 39.1, 35.4, 32.2, 31.3, 23.6. GCMS (EI) calculated for $[M]^+$ 230.17, found 230.20. FTIR (neat, cm-1): 3061 (m), 3025 (s), 2959 (s), 2925 (s), 2859 (s), 1603 (m), 1496 (s), 1452 (s), 1436 (s), 1378 (w), 1243 (w), 1077 (w), 1030 (w), 979 (s), 906 (s), 831 (s), 746 (s).



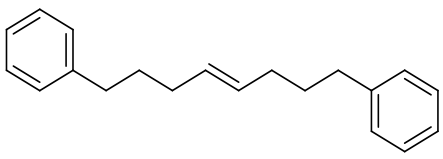
(E)-(7,7-diethoxyhept-4-en-1-yl)benzene (46) compound was isolated as a colorless liquid (97.0 mg, 74% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.11 (m, 2H), 7.12 – 7.00 (m, 3H), 5.64 – 4.99 (m, 2H), 4.39 (t, *J* = 5.8 Hz, 1H), 3.62 – 3.50 (m, 2H), 3.48 – 3.34 (m, 2H), 2.59 – 2.47 (m, 2H), 2.26 (t, *J* = 6.1 Hz, 2H), 1.97 (dd, *J* = 13.9, 6.8 Hz, 2H), 1.68 – 1.53 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 133.0, 128.5, 128.3, 125.7, 125.3, 102.8, 61.1, 37.3, 35.4, 32.2, 31.2, 15.4. GCMS (EI) calculated for $[M]^+$ 262.19, found 262.10. FTIR (neat, cm-1): 3026 (w), 2974 (s), 2927 (s), 1495 (s), 1453 (s), 1371 (s), 1342 (s), 1219 (w), 1126 (s), 1061 (s), 1019 (s), 967 (s), 909 (m), 736 (s), 698 (s).



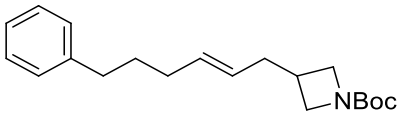
(E)-(9-(benzyloxy)non-4-en-1-yl)benzene (47) compound was isolated as a colorless liquid (129.4 mg, 84% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 6H), 7.22 – 7.06 (m, 4H), 5.73 – 5.19 (m, 2H), 4.50 (s, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 2.81 – 2.41 (m, 2H), 2.19 – 1.87 (m, 4H), 1.74 – 1.57 (m, 4H), 1.51 – 1.36 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 138.8, 130.6, 130.2, 128.6, 128.4, 128.3, 127.7, 127.6, 125.7, 73.0, 70.4, 35.5, 32.5, 32.2, 31.4, 29.4, 26.3 GCMS (EI) calculated for $[M]^+$ 308.21, found 308.20. FTIR (neat, cm-1): 3084 (m), 3061 (m), 3025 (m), 2930 (s), 2853 (s), 1698 (w), 1603 (m), 1495 (s), 1452 (s), 1361 (s), 1307 (w), 1102 (s), 1028 (m), 967 (s), 733 (s), 696 (s).



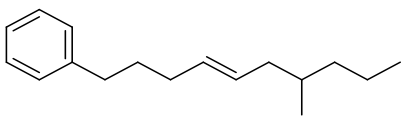
(E)-1-bromo-2,4-dichloro-5-((8-phenyloct-4-en-1-yl)oxy)benzene (48) compound was isolated as a colorless liquid (117.2 mg, 55% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.23 – 6.88 (m, 5H), 6.87 (s, 1H), 5.49 – 5.26 (m, 2H), 3.87 (t, *J* = 6.3 Hz, 2H), 2.63 – 2.33 (m, 2H), 2.11 (dd, *J* = 12.7, 6.8 Hz, 2H), 1.95 (dd, *J* = 13.4, 6.3 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.64 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 142.6, 133.9, 133.3, 131.5, 129.2, 128.5, 128.4, 125.8, 122.4, 114.8, 112.6, 69.0, 35.5, 32.2, 31.3, 28.8, 28.8. GCMS (EI) calculated for $[M]^+$ 426.02, found 426.00. FTIR (neat, cm-1): 3024 (m), 2929 (s), 2853 (s), 1578 (s), 1495 (s), 1472 (s), 1465 (s), 1390 (w), 1346 (s), 1281 (s), 1242 (s), 1124 (s), 1075 (s), 1029 9m), 968 (s), 833 (m), 740 (s).



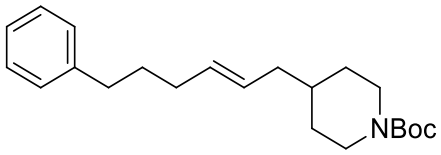
(E)-1,8-diphenyloct-4-ene (8) compound was isolated as a colorless liquid (112.3 mg, 85% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 7.23 – 7.19 (m, 6H), 5.49 – 5.44 (m, 2H), 2.86 – 2.44 (m, 4H), 2.11 – 2.05 (m, 4H), 1.78 – 1.68 (m, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 130.5, 128.6, 128.4, 125.8, 35.5, 32.3, 31.5. GCMS (EI) calculated for [M]+ 264.19, found 264.10. FTIR (neat, cm-1): 3083 (s), 3061 (s), 3024 (s), 2928 (s), 2854 (s), 1603 (m), 1495 (s), 1452 (s), 1075 (w), 1029 (s), 967 (s), 906 (w), 744, (s), 697 (s). This compound was characterized before. The literature value matches with our data. [38]



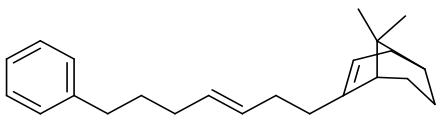
(E)-tert-butyl 3-(6-phenylhex-2-en-1-yl)azetidine-1-carboxylate (49) compound was isolated as a colorless liquid (102.4 mg, 65% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.12 (m, 3H), 5.54 – 5.39 (m, 1H), 5.38 – 5.27 (m, 1H), 3.97 (t, *J* = 8.4 Hz, 2H), 3.55 (dd, *J* = 8.4, 5.4 Hz, 2H), 2.63 – 2.42 (m, 3H), 2.26 (t, *J* = 6.9 Hz, 2H), 2.03 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 142.5, 132.3, 128.5, 128.4, 126.9, 125.8, 79.2, 54.0, 37.2, 35.4, 32.2, 31.2, 28.5, 28.4. GCMS (EI) calculated for $[M]^+$ 315.22, found 315.20. FTIR (neat, cm-1): 3024 (m), 2964 (s), 2931 (s), 2877 (s), 1700 (s), 1603 (w), 1496 (m), 1478 (m), 1453 (s), 1399 (s), 1365 (s), 1294 (m), 1135 (s), 1062 (w), 969 (s), 931 (w), 861 (s), 772 (s), 752 (s), 699 (s).



(E)-(7-methyldec-4-en-1-yl)benzene (50) compound was isolated as a colorless liquid (93.2 mg, 81% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.33 – 7.22 (m, 3H), 5.78 – 5.22 (m, 2H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.28 – 2.03 (m, 3H), 2.01 – 1.89 (m, 1H), 1.84 – 1.74 (m, 2H), 1.62 – 1.49 (m, 1H), 1.50 – 1.35 (m, 3H), 1.26 – 1.13 (m, 1H), 1.07 – 0.87 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 131.2, 129.6, 128.6, 128.4, 125.8, 40.3, 39.1, 35.5, 33.1, 32.4, 31.6, 20.3, 19.6, 14.5. GCMS (EI) calculated for $[M]^+$ 230.20, found 230.20. FTIR (neat, cm-1): 3026 (m), 2955 (s), 2926 (s), 2869 (m), 1619 (w), 1495 (s), 1453 (s), 1377 (s), 1030 (m), 967 (s0, 742 (s), 697 (s), 676 (s).

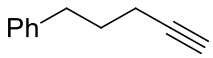


(E)-tert-butyl 4-(6-phenylhex-2-en-1-yl)piperidine-1-carboxylate (51) compound was isolated as a colorless liquid (154.6 mg, 90% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 5.56 – 5.28 (m, 2H), 4.07 (d, *J* = 12.8 Hz, 2H), 2.76 – 2.53 (m, 4H), 2.09 – 1.97 (m, 2H), 1.94 (t, *J* = 6.1 Hz, 2H), 1.77 – 1.58 (m, 4H).1.53 – 1.33 (m, 10H), 1.19 – 0.96 (m, 2H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 142.6, 131.9, 128.5, 128.3, 128.3, 125.7, 79.2, 44.1, 39.7, 36.4, 35.5, 32.2, 32.0, 31.4, 28.6. GCMS (EI) calculated for $[M]^+$ 343.25, found 343.20. FTIR (neat, cm-1): 3050 (w), 3010 (w), 2977 (m), 2972 (s), 2850 (m), 1687 (s), 1425 (s), 1365 (s), 1265 (s), 1242 (m), 1170 (s), 1123 (w), 966 (m), 864 (w). 738 (s), 700 (s)

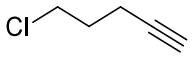


(1S)-8,8-dimethyl-2-((E)-7-phenylhept-3-en-1-yl)bicyclo[3.2.1]oct-2-ene (52) compound was isolated as a colorless liquid (117.1 mg, 76% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 2H), 7.29 – 7.19 (m, 3H), 5.60 – 5.45 (m, 2H), 5.28 (s, 1H), 2.76 – 2.58 (m, 2H), 2.49 – 2.24 (m, 3H), 2.23 – 1.99 (m, 8H), 1.85 – 1.68 (m, 2H), 1.36 (s, 3H), 1.25 (d, *J* = 8.4 Hz, 1H), 0.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 142.7, 130.8, 123.0, 128.6, 128.4, 125.7, 116.1, 46.0, 41.0, 38.1, 37.2, 35.4, 32.2, 31.8, 31.4, 30.6, 26.5, 21.4. GCMS (EI) calculated for $[M]^+$ 308.25, found 308.20. FTIR (neat, cm-1): 3061 (m), 3025 (s), 2983 (s), 2916 (s), 2832 (s), 1604 (w), 1495 (s), 1433 (s), 1380 (s), 1363 (s), 1345 (w), 1264 (w), 1219 (w), 1070 (m), 1030 (m), 966 (s), 886 (w), 791 (m), 744 (s), 697 (s).

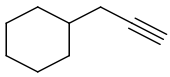
3.4.8 *Alkyne Starting materials*



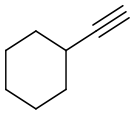
pent-4-yn-1-ylbenzene was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



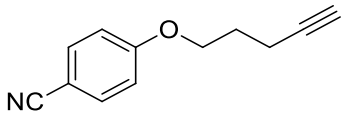
5-chloropent-1-yne was purchased from TCI America and distilled over calcium hydride under vacuum before use.



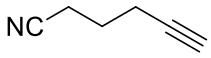
prop-2-yn-1-ylcyclohexane was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



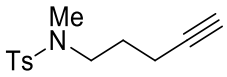
Ethynylcyclohexane was purchased from GSF Chemicals and distilled over calcium hydride under vacuum before use.



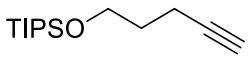
4-(pent-4-yn-1-yloxy)benzonitrile was prepared according to a known procedure and has been previously characterized.[39]



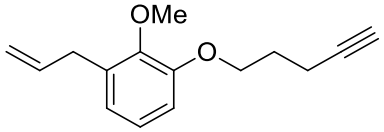
hex-5-ynenitrile was purchased from Oakwood Chemicals and distilled over calcium hydride under vacuum before use.



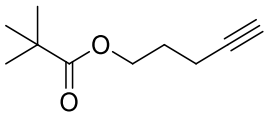
N,4-dimethyl-N-(pent-4-yn-1-yl)benzenesulfonamide was prepared according to a known procedure and has been previously characterized.[6]



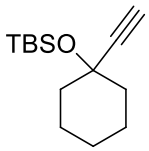
triisopropyl(pent-4-yn-1-yloxy)silane was prepared according to a known procedure and has been previously characterized.[40]



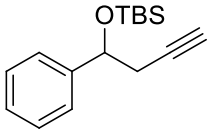
1-Allyl-2-methoxy-3-(pent-4-yn-1-yloxy)benzene was prepared according to a known procedure and has been previously characterized. [41]



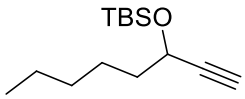
Pent-4-yn-1-yl pivalate compound was prepared according to a known procedure and has been previously characterized. [42]



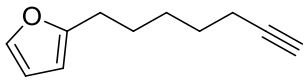
tert-butyl((1-ethynylcyclohexyl)oxy)dimethylsilane was prepared according to a known procedure and has been previously characterized. [43]



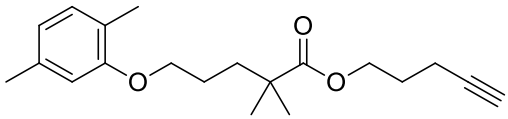
tert-butyldimethyl((1-phenylbut-3-yn-1-yl)oxy)silane was prepared according to a known procedure and has been previously characterized. [44]



tert-butyldimethyl(oct-1-yn-3-yloxy)silane was prepared according to a known procedure and has been previously characterized. [45]

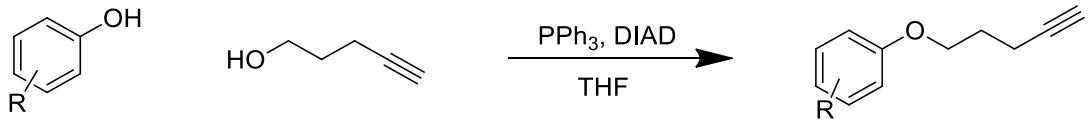


2-(hept-6-yn-1-yl)furan was prepared according to a known procedure and has been previously characterized.[46]

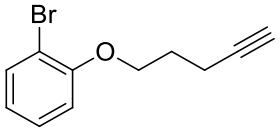


pent-4-yn-1-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.4 Hz, 1H), 6.73 – 6.58 (m, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.94 (s, 2H), 2.36 – 2.27 (m, 5H), 2.21 (s, 3H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.94 – 1.83 (m, 2H), 1.78 – 1.71 (m, 4H), 1.25 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 157.0, 136.5, 130.4, 123.7, 120.8, 112.0, 83.0, 69.1, 68.0, 63.0, 42.2, 37.3, 27.7, 25.3, 25.3, 21.50 15.86, 15.32. GCMS (EI) calculated for $[M]^+$ 316.20, found 316.20. FTIR (neat, cm-1): 3307 (s), 2955 (s), 2925 (s), 2872 (m), 2252 (s), 1721 (s), 1613 (m), 1584 (m), 1508 (s), 1473 (s), 1392 (m), 1268 (s), 1242 (s), 1013 (s), 949 (m), 913 (s), 729 (s).

General procedure for preparation of different terminal alkyne:

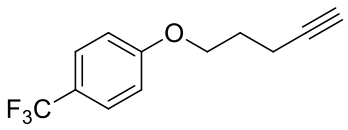


A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), desired phenol (7.7 mmol, 1.1 equiv), THF (14.0 mL, 0.5 M) and 4-pentyn-1-ol (654.0 µL, 7.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (1.6 mL, 8.4 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to 23 °C and stirred overnight. THF was removed under reduced pressure and the mixture was suspended in hexanes and stirred vigorously for 30 min. The solid triphenylphosphine oxide was removed by passing the mixture through a plug of celite. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography. Following alkynes were prepared using this procedure.

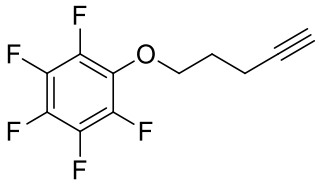


1-bromo-2-(pent-4-yn-1-yloxy)benzene was isolated as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 1H), 7.32 – 7.18 (m, 1H), 6.98 – 6.75 (m, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 2.49 (td, *J* = 7.0, 2.6 Hz, 2H), 2.13 – 2.00 (m, 2H), 1.97 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 133.5, 128.6, 122.1, 113.5, 112.6, 83.6, 69.0, 67.5, 28.3, 15.3. GCMS (EI) calculated for $[M]^+$ 238.00, found 238.10. FTIR (neat, cm-1): 3307 (s), 3065 (m), 3030 (m), 2920

(s), 2850 (s), 2361 (w), 2341 (w), 2252 (s), 1589 (s), 1564 (s), 1480 (s), 1443 (s), 138 (m), 1279 (s), 1249 (s), 1165 (m), 1125 (s), 1052 (s), 1033 (s), 969 (s), 929 (w), 892 (w), 745 (s), 677 (s).

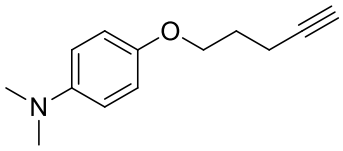


1-(pent-4-yn-1-yloxy)-4-(trifluoromethyl)benzene was isolated as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.42 (td, *J* = 6.9, 2.6 Hz, 2H), 2.09 – 1.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 127.0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

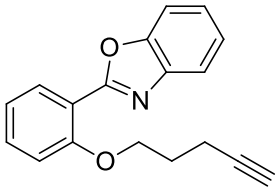


1,2,3,4,5-pentafluoro-6-(pent-4-yn-1-yloxy)benzene was isolated as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (t, *J* = 6.0 Hz, 2H), 2.44 (td, *J* = 6.9, 2.5 Hz, 2H), 2.07 – 1.89 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (d, *J* = 241.6 Hz), 138.2 (d, *J* = 252.6 Hz), 137.5 (d, *J* = 256.8 Hz), 82.9, 74.1, 69.2, 28.9, 14.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ -159.83 (d, *J* = 19.7 Hz), -166.31 (t, *J* = 21.1 Hz), -166.46 (t, *J* = 21.2 Hz). GCMS (EI) calculated for $[M]^+$ 250.04, found

250.10. FTIR (neat, cm-1): 3307 (s), 3080 (w), 3037 (w), 2925 (s), 2852 (s), 2252 (s), 1812 (w), 1512 (s), 1482 (s), 1449 (s), 1373 (m), 1160 (s), 1031 (s), 996 (s), 893 (w), 677 (s).

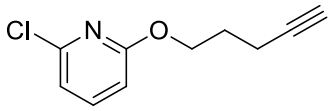


N,N-dimethyl-4-(pent-4-yn-1-yloxy)aniline was isolated as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 – 6.71 (m, 4H), 4.01 (t, *J* = 6.1 Hz, 2H), 2.86 (s, 6H), 2.40 (td, *J* = 7.0, 2.6 Hz, 2H), 2.02 – 1.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 145.8, 115.7, 115.0, 83.8, 68.8, 67.0, 41.9, 28.5, 15.3. GCMS (EI) calculated for $[M]^+$203.13, found 203.10. FTIR (neat, cm-1): 3307 (s), 2978 (s), 2957 (s), 2874 (s), 2252 (s), 1725 (m), 1513 (s), 1471 (m), 1447 (m), 1387 (m), 1293 (m), 1244 (s), 1163 (w), 1105 (m), 1056 (m), 906 (s), 819 (s), 736 (s).

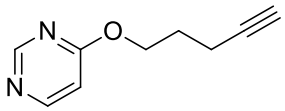


2-(2-(pent-4-yn-1-yloxy)phenyl)benzo[d]oxazole was isolated as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.63 – 7.54 (m, 1H), 7.45 (td, *J* = 7.9, 0.8 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.07 (dd, *J* = 15.0, 7.9 Hz, 2H), 4.22 (t, *J* = 5.8 Hz, 2H), 2.58 (td, *J* = 7.0, 2.6 Hz, 2H), 2.17 – 2.04 (m, 2H), 2.00 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 157.8, 150.7, 142.0, 132.7, 131.4, 124.9, 124.3, 120.9, 120.0, 116.7, 113.4, 110.5, 83.6, 68.9, 67.2, 28.3, 15.1. GCMS (EI) calculated for $[M]^+$ 277.11, found 277.10. FTIR (neat,

cm-1): 3304 (s), 3075 (w), 2940 (s), 2879 (s), 2250 (s), 2117 (m), 1600 (s), 1583 (s), 1548 (s), 1494 (m), 1453 (s), 1310 (m), 1282 (s), 1246 (s), 1121 (s), 1034 (s), 908 (s), 732 (s).

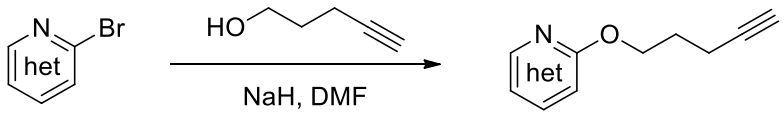


2-chloro-6-(pent-4-yn-1-yloxy)pyridine was isolated as colorless liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 4.39 (t, *J* = 6.2 Hz, 2H), 2.38 (td, *J* = 7.2, 2.6 Hz, 2H), 2.14 – 1.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 148.4, 140.6, 116.3, 109.2, 83.5, 68.9, 65.1, 27.9, 15.3. GCMS (EI) calculated for $[M]^+$ 195.05, found 195.10. FTIR (neat, cm-1): 3305 s), 3152 (m), 2961 (s), 2251 (s), 2118 (w), 1596 (s), 1576 (s), 1550 (s), 1433 (s), 1408 (s), 1378 (s), 1302 (s), 1262 (s), 11600 (s), 1072 (s), 1037 (s), 985 (s), 908 (s), 789 (s).

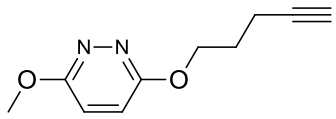


4-(pent-4-yn-1-yloxy)pyrimidine was isolated as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.41 (d, *J* = 5.9 Hz, 1H), 6.72 (dd, *J* = 5.9, 1.0 Hz, 1H), 4.46 (t, *J* = 6.2 Hz, 2H), 2.36 (td, *J* = 7.0, 2.6 Hz, 2H), 2.12 – 1.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 158.4, 156.8, 108.8, 83.1, 69.2, 65.2, 27.8, 15.3. GCMS (EI) calculated for $[M]^+$ 168.03, found 168.10. GCMS (EI) calculated for $[M]^+$ 162.08, found 162.20.

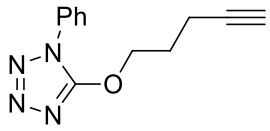
General procedure for preparation of different heterocyclic alkyne:



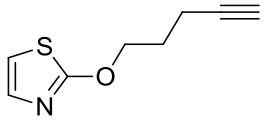
A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with Sodium Hydride (1.5 equiv) and DMF (0.1 M). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added 4-pentyn-1-ol (1.5 equiv) and the reaction mixture was allowed to stir for 30 minutes. After the indicated time, required amount of heterocyclic bromide (1.0 equiv) were added and the mixture was stirred for 2 hours. After 2 hours, the reaction mixture was quenched with water and extracted with diethyl ether. The extract was concentrated under reduced pressure and the crude product was purified by silica gel chromatography . Following alkynes were prepared using this procedure.



3-methoxy-6-(pent-4-yn-1-yloxy)pyridazine was isolated as a colorless liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.92 – 6.90 (m, 2H), 4.52 (t, *J* = 6.2 Hz, 2H), 4.04 (s, 3H), 2.38 (td, *J* = 7.0, 2.6 Hz, 2H), 2.16 – 1.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.7, 121.4, 121.3, 83.3, 68.9, 65.6, 54.5, 27.8, 15.2. GCMS (EI) calculated for $[M]^+$192.09, found 192.10. FTIR (neat, cm-1) 3328 (s), 2852 (s), 2284 (s), 1495 (s), 1444 (s), 1423 (s), 1384 (s), 1337 (m), 1268 (s), 1098 (m), 1038 (s), 1013 (s), 949 (s), 913 (s), 949 (s), 913 (s), 839 (s), 796 (m). 729 (s).

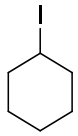


5-(pent-4-yn-1-yloxy)-1-phenyl-1H-tetrazole was isolated as colorless liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.77 – 7.66 (m, 2H), 7.66 – 7.34 (m, 3H), 4.78 (t, *J* = 6.2 Hz, 2H), 2.40 (td, *J* = 6.9, 2.6 Hz, 2H), 2.13 (p, *J* = 6.5 Hz, 1H), 1.99 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 133.5, 129.7, 129.0, 121.7, 82.2, 72.6, 69.8, 27.7, 15.2. GCMS (EI) calculated for $[M]^+$ 228.20, found 228.20. FTIR (neat, cm-1): 3306 (s), 3153 (m), 2252 (s), 1793 (w), 1596 (s), 1563 (s), 1460 (s), 1384 (m), 1295 (m), 1201 (m), 908 (s), 729 (s).

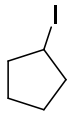


2-(pent-4-yn-1-yloxy)thiazole was isolated as colorless liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.12 (d, *J* = 3.8 Hz, 1H), 6.67 (d, *J* = 3.8 Hz, 1H), 4.51 (t, *J* = 6.1 Hz, 2H), 2.44 – 2.30 (m, 2H), 2.12 – 1.93 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 136.7, 111.0, 82.7, 69.7, 69.2, 27.6, 14.9. GCMS (EI) calculated for $[M]^+$ 167.04, found 167.10.

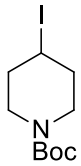
3.4.9 *Alkyl Bromide Starting Material:*



Iodocyclohexane was purchased from Sigma-Aldrich and distilled over calcium hydride under vacuum before use.



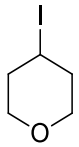
Iodocyclopentane was purchased from Oakwood Chemicals and distilled over calcium hydride under vacuum before use.



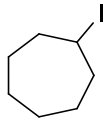
tert-butyl 4-iodopiperidine-1-carboxylate was purchased from Combi Blocks and used directly.

Preparation of alkyl iodides:

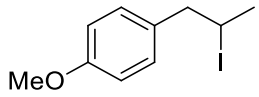
All the iodides were prepared from the corresponding alcohol using the following procedure: A reaction flask charged with a Teflon coated stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), imidazole (1.77 g, 26.0 mmol, 1.3 equiv). Anhydrous THF/MeCN (4:1) was added to obtain a concentration of 0.3 M with respect to the alcohol. The flask was placed in an ice-bath and after 5 minutes of stirring, iodine (6.9 g, 24.0 mmol, 1.2 equiv) was added and the reaction mixture was stirred for additional 15 minutes. Alcohol (20.0 mmol, 1.0 equiv) was added dropwise. The reaction was stirred overnight at room temperature. The reaction mixture was filtered through a plug of celite to separate the solid. Saturated sodium thiosulfate solution was added to the filtrate and the organic phase was extracted. Aqueous layer was extracted one more time with THF. The organic layers were collected and evaporated under reduced pressure. Crude product was purified by silica gel chromatography



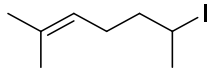
4-Iodotetrahydro-2H-pyran compound has been previously characterized and spectral data match the reported literature values. [41]



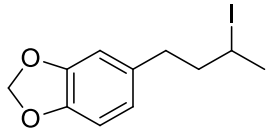
Iodocycloheptane has been previously characterized and spectral data match the reported literature values. [41]



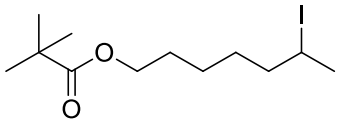
1-(2-iodopropyl)-4-methoxybenzene has been previously characterized and spectral data match the reported literature values. [47]



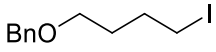
6-iodo-2-methylhept-2-ene has been previously characterized and spectral data match the reported literature values. [48]



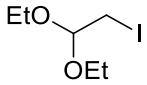
5-(3-iodobutyl)benzo[d][1,3]dioxole has been previously characterized and spectral data match the reported literature values. [49]



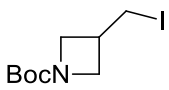
6-iodoheptyl pivalate ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.27 – 4.13 (m, 1H), 4.08 (t, *J* = 6.1 Hz, 2H), 1.94 (d, *J* = 6.9 Hz, 3H), 1.91 – 1.67 (m, 4H), 1.20 (s, 9H).



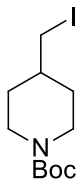
((4-iodobutoxy)methyl)benzene has been previously characterized and spectral data match the reported literature values **.** [50]



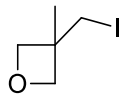
1,1-diethoxy-2-iodoethane has been previously characterized and spectral data match the reported literature values. [51]



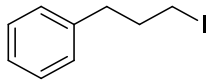
tert-butyl 3-(iodomethyl)azetidine-1-carboxylate has been previously characterized and spectral data match the reported literature value. [52]



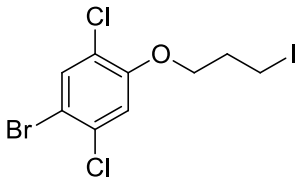
tert-butyl 4-(iodomethyl)piperidine-1-carboxylate has been previously characterized and spectral data match the reported literature value. [53]



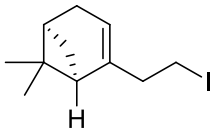
3-(iodomethyl)-3-methyloxetane has been previously characterized and spectral data match the reported literature values. [54]



(3-iodopropyl)benzene has been previously characterized and spectral data match the reported literature values**.** [55]

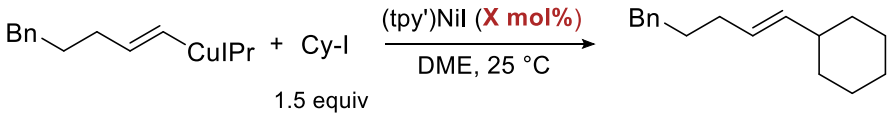


1-bromo-2,5-dichloro-4-(3-iodopropoxy)benzene ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.60 (s, 1H), 7.04 (s, 1H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.44 – 2.23 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 153.99, 133.97, 133.38, 124.50, 115.05, 113.21, 69.05, 32.62, 2.00. GCMS (EI) calculated for $[M]^+$ 407.82, found 407.80. FTIR (neat, cm-1): 3308 (s), 2852 (s), 1472 (s), 1462 (s), 1345 (s), 1282 (s), 1343 (s), 1181 (s), 1125 (s), 1076 (s), 1017 (m), 907 (s), 733 (s).



(1R,5S)-2-(2-iodoethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene has been previously characterized and spectral data match the reported literature values**.** [56]

3.4.10 *Stochiometric reaction of alkenyl copper and iodide with varying amount of (tpy')NiI (Scheme 3.4a):*



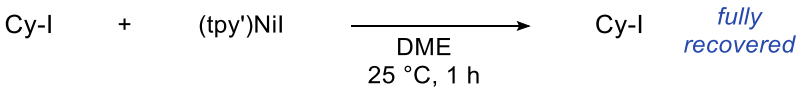
The alkenyl copper was prepared from a known literature procedure and has been previously characterized.

In a nitrogen-filled glovebox, a stock solution of alkenyl copper complex **5** (298.6 mg, 0.5 mmol) and internal standard dodecane in 2000 µL DME was prepared. A 400 µL aliquot of the alkenyl copper/dodecane stock solution was added to dram vial charged with stir bar and 300 µL of DME. Iodocyclohexane (31.5 mg, 0.150 mmol, 1.5 equiv) was added to this solution followed by required amount of (tpy′)NiI and 300 µL of DME. The reaction mixture was stirred at 25 °C for 2 hours. 20 µL aliquot was taken at the end of 2 hours. The aliquot was diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis. Table S13 shows the product yield of the reaction with different amount of Nickel loading.

Table 3.18:

Entry	Amount of (tpy′)NiI (mol%)	Yield of 12 (%)
1	0	0
2	3	92
3	5	90
4	10	81
5	50	41
6	100	42

3.4.11 *Reaction of nickel (I) catalyst with alkyl iodide (Scheme 3.4b):*



In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, (tpy′)NiI (58.6 mg, 0.1 mmol, 1.0 equiv), DME (0.5 mL) and internal standard (dodecane). Iodocyclohexane (21.0 mg, 0.1 mmol, 1.0 equiv) was transferred to the reaction mixture using 0.5 mL DME. The reaction mixture was stirred at room temperature. After 1 h, 20 µL aliquot was taken and passed through a plug of silica using ethyl acetate as eluent. GC analysis of the aliquot indicated full recovery of iodocyclohexane and no formation of iodocyclohexane dimerization product was observed.

3.5 REFERENCES FOR CHAPTER 3

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Chapter 4.

HYDROALKYLATION OF ALKYNES: FUNCTIONALIZATION OF ALKENYL COPPER THROUGH SINGLE ELECTRON TRANSFER CHEMISTRY

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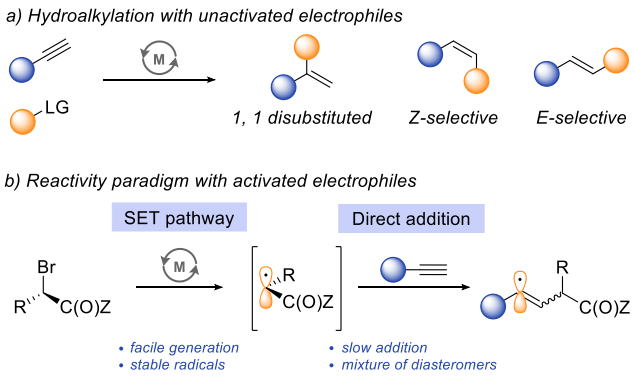
4.1 INTRODUCTION

Selective and efficient synthesis of isomerically pure alkenes is challenging and has continuously inspired the development of new synthetic strategies. One recent approach is hydroalkylation of alkynes,[1–9] which involves the direct coupling of unactivated alkyl electrophiles with alkynes. In the last several years, numerous hydroalkylation methods have been developed and now provide access to all three forms of disubstituted alkenes: 1,1 disubstiuted alkenes, *Z*- and *E*-alkenes (**Scheme 4.1a**). Furthermore, the high selectivity of these processes often enables the formation of a single regio- and stereoisomer of alkene products. Together, these methods have established hydroalkylation of alkynes as one of the most versatile and efficient strategies for selective alkene synthesis.

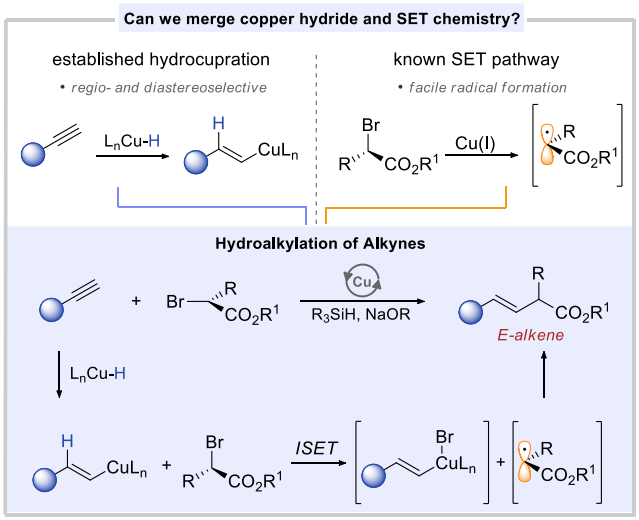
Scheme 4.1 Hydroalkylation of alkynes



Despite these advancements, selective hydroalkylation remains difficult to accomplish with certain functionalized coupling partners. Particularly notable are α-halo carbonyls. These *activated* electrophiles have high redox potentials and readily generate alkyl radicals in the presence of first-row transition-metals through a single electron transfer (SET) process.[10,11] However, leveraging this feature in selective hydroalkylation has proved to be challenging. So far, efforts have focused on the direct addition of these SET-generated alkyl radicals to the alkyne (**Scheme 4.1b**).

Unfortunately, the addition step is slow[12,13] and typically generates a mixture of *E* and *Z* isomers.[12,14–16] As a result, the direct radical addition approach has found success only with activated aryl-substituted alkynes providing the alkene products with varying degrees of *Z*-diastereoselectivity.[17,18]

Scheme 4.2 Overcoming the SET/direct addition pathway

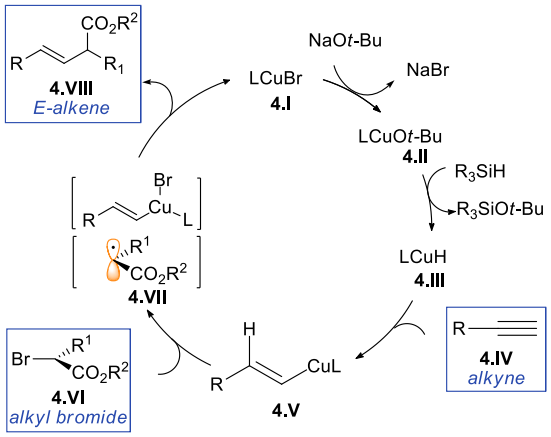


Recent developments in copper hydride chemistry have enabled a new approach to the hydrofunctionalization of alkynes based on the *hydrocupration* of the alkyne and subsequent functionalization of the reactive *E*-alkenyl copper intermediate.[1,3,19–28] We propose to merge the hydrocupration of alkynes with the SET chemistry of α-halo carbonyls in order to achieve a selective hydroalkylation reaction (**Scheme 4.2**). The highly regio- and diastereoselective hydrocupration step would ensure selective formation of the anti-Markovnikov addition product with excellent *E* selectivity. Subsequent halogen atom transfer via inner-sphere SET (ISET)[10] would provide a facile alternative to the high barrier two-electron oxidative addition [29,30] and would lead to the alkylation of the alkenyl copper intermediate. Overall, the proposed combination

of closed-shell copper-hydride addition to alkynes with open-shell SET chemistry provides a new strategy for hydroalkylation of alkynes.[31]

We envision the mechanism of hydroalkylation reaction as shown in Scheme 3. The alkenyl copper intermediate is formed according to the well-established mechanism (**4.I-4.III**).[32] In a key step, the ISET involving alkenyl copper intermediate and an alkyl bromide (**4.VI**) would generate an alkenyl copper(II) species and a carbon-centered radical (**4.VII**).[33] Finally, the reaction of the alkenyl copper(II) intermediate with the free radical delivers the product (**4.VIII**),[34–36] possibly through radical capture followed by reductive elimination.

Scheme 4.3 Proposed catalytic pathway



4.2 RESULTS AND DISCUSSION

4.2.1 *Reaction Development*

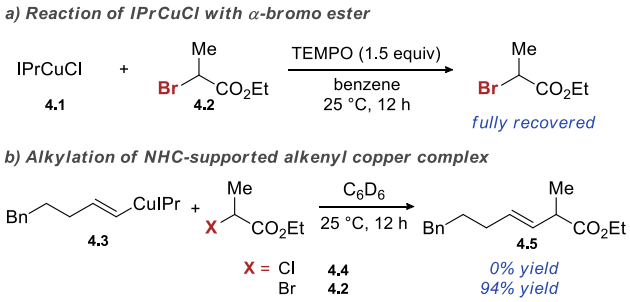
From the outset, we recognized that a generally facile SET oxidation of copper(I) complexes by α-halo carbonyls could prevent the desired two-electron hydrocupration pathway. In effect, we had

to suppress SET oxidation of all copper(I) complexes involved in forming the alkenyl copper intermediate (intermediates **4.I-4.III**).

We reasoned that a catalyst supported by an NHC ligand would allow us to achieve this goal by modulating the oxidation potential of these copper(I) intermediates. NHC ligands, such as IPr, favor the formation of linear two coordinate copper(I) complexes that are unusually resistant to oxidation.[37–41] Hence, we expected that despite the σ-donating ability of NHC ligands, they would yield catalytic copper(I) intermediates with high reduction potentials ($E^0_{1/2}{}^{red}$ [Cu^{II}/Cu^{I}]) and therefore relatively low rates in reaction with α-halo carbonyls. This correlation between the redox potentials of copper(I) complexes and rates of their reactions with α-halo carbonyls through ISET has been established in mechanistic studies of atom transfer radical polymerization (ATRP).[33,42,43] We were also aware that IPr ligand promotes the rapid formation of the alkenyl copper intermediate through hydrocupration. Overall, we hoped that these features of IPr ligand will allow us to merge two-electron hydrocupration pathway with the SET-based alkylation of the alkenyl copper intermediate.

We began our study by measuring the reduction potential of IPrCuCl, a common catalyst in the hydrofunctionalization of alkynes. The anticipated effect of the IPr ligand was evident in the measured anodic peak potential ($E_{p,a}$= 1.68V vs SEC in MeCN; 1.58V vs SCE in DCM),[44] which is high relative to the redox potentials for various copper(I) catalysts ($E^0{}_{½}$ = 0.1V to -0.3V vs SCE in MeCN depending on the ligand) readily oxidized by α-halo carbonyls and used to promote ATRP[33] or related ATR alkylation reactions.[45] As expected, IPrCuCl did not readily react with an α-halo carbonyls. The exposure of secondary α-bromo ester **4.2** ($E^0{}_{½}$ = -0.43V vs. SCE in DMF)[10] to IPrCuCl and TEMPO at 25 °C, resulted in full recovery of the α-bromo ester, indicating that SET did not occur (**Scheme 4.4a**).

Scheme 4.4 Initial stoichiometric experiments

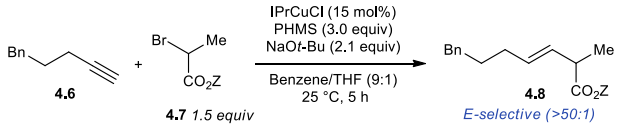


On the other hand, alkenyl copper complex **4.3** was significantly more easily oxidized ($E_{p,a}$ = 0.90V vs. SCE in DCM) and, under similar reaction conditions, readily afforded cross-coupling product **4.5** (**Scheme 4b**). Less reactive electrophiles, such as α-chloro ester **4.4** did not provide the desired coupling product.

Encouraged by the results of our preliminary experiments and using them as a starting point, we developed the catalytic hydroalkylation of terminal alkynes with secondary α-bromo esters shown in Table 1. The best results were obtained using IPrCuCl as the catalyst, polymethylhydrosiloxane (PMHS) as the hydride source, and NaOt-Bu as the turnover reagent. The reaction is performed in a benzene/THF solvent combination and is complete in 5 hours at room temperature. During our efforts to identify the best conditions, we made several observations summarized in **Table 1**. In accordance with the results of the stoichiometric experiments shown in **Scheme 4b**, an α-cholo ester failed to provide any desired product in the catalytic reaction, while the corresponding α-iodo ester gave only 11% yield of the desired product. Copper complexes supported by IPr and SIPr ligand were the best catalysts. Even the closely related IMesCuCl catalyst provided less than 5% yield of the desired product. A catalyst prepared in situ from $Cu(OAc)_2$ and (*R*)-DTBM-Segphos[26] gave similarly low yield of the product. The choice of silane proved crucial to the success of the reaction. PMHS and structurally related tetrameric silicone hydride performed well. More reactive triethoxysilane or less reactive diphenylmethyl silane were ineffective. Sodium alkoxides were

particularly successful in this transformation. Changing the alkoxide counterion from sodium to lithium or potassium led to significantly lower yields. While both sodium tert-butoxide and sodium tert-siloxide were effective turnover reagents, sodium isopropoxide was inferior and sodium methoxide failed to turn over the catalyst, presumably due to lower solubility. The highest yields of the desired product were obtained using a 9:1 benzene/THF solvent mix. Other ratios of these solvents and other aryl/etherial solvent mixtures resulted in depressed yields (see SI, **Table S6**) Benzene or toluene alone provided less of the desired product and a significant amount of the alkyne.

Table 4.1 Reaction Development

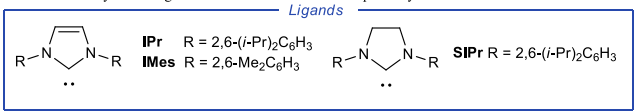


4.6 | **4.7** *1.5 equiv* | **4.8** *E-selective (>50:1)*

entry	*change from standard conditions*	*yield*[a]
1.	none	81%
2.	Chloro ester *instead of* bromo ester	0%
3.	Iodo ester *instead of bromo ester*	11%
4.	SIPrCuCl *instead of* IPrCuCl	72%
5.	IMesCuCl *instead of* IPrCuCl	1%
6.	(*R*)-DTBM-Segphos/Cu(OAc)$_2$ *instead of* IPrCuCl	<5%
7.	Ph_2MeSiH *instead of* PMHS	3%
8.	$Me(OEt)_2SiH$ *instead of* PMHS	0%
9.	$(MeOSiH)_4$ *instead of* PMHS	46%
10.	LiO*t*-Bu *instead of* NaO*t*-Bu	37%
11.	NaO*i*-Pr *instead of* NaO*t*-Bu	22%
12.	NaOSiMe_3 *instead of* NaO*t*-Bu	74%
13.	KO*t*-Bu *instead of* NaO*t*-Bu	0%
14.	Benzene *instead of* Benzene/THF (9:1)	58%
15.	Benzene/THF (1:1) *instead of* Benzene/THF (9:1)	66%
16.	toluene *instead of* Benzene/THF (9:1)	52%
17.	THF *instead of* Benzene/THF (9:1)	27%
18.	Ethyl ester *instead of* pinacolyl ester	61%

[a] Determined by GC using internal standard. Z stands for pinacolyl.

Ligands

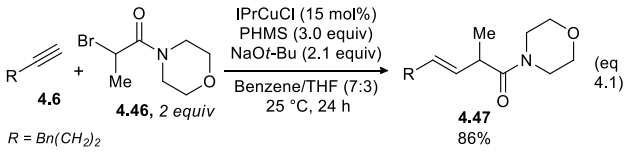


4.2.2 *Substrate Scope*

Using the standard conditions from Table 1, we found that a wide range of *E*-alkenes could be synthesized (**Table 4.2**) with *E*-selectivity greater than 50:1 (see SI). We also found that the reaction is compatible with many functional groups and can be accomplished in the presence of esters (**4.11**), epoxides (**4.10**), nitriles (**4.17**), alkyl chlorides (**4.13**), aryl bromides (**4.24**) and fluorides (**4.9**), acetals (**4.20**), and amides (**4.22**). Sterically demanding alkynes such as **4.15** and **4.25** also performed well under the reaction conditions. The reaction also tolerates several nitrogen-containing heteroarenes, such as halo pyridines (**4.12**, **4.26**), indoles (**4.21**), quinoxalines (**4.16**), phenoxazines (**4.19**), and phenothiazines (**4.14**).

We also explored the reaction with different secondary α-bromo esters. In general, esters of sterically bulky alcohols afforded the desired product in good yield, presumably because of the increased stability of these esters under catalytic conditions. The presence of heteroatomic substituents, such as bromide (**4.37**) or thioether (**4.38**), at the γ position of the ester was well tolerated. Sterically demanding secondary bromides (**4.36**) also gave the product in good yield.

Our initial attempts to couple secondary α-bromo amides were unsuccessful. Under the reaction conditions used for coupling α-bromo esters, product **4.47** was formed in only 47% yield. The primary side reactions were the reductions of both the α-bromo amide and the alkyne. Eventually, we found that by subtly changing the reaction conditions, we could obtain product **4.47** in 86% yield.

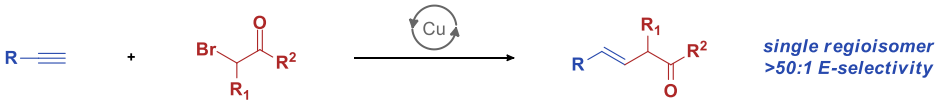


To achieve these results, we lowered the solvent ratio of benzene/THF from 9:1 to 7:3, adjusted the stoichiometry of the reactants, and increased the reaction time to 24 hours.

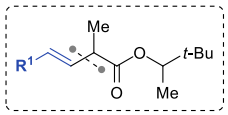
These modified conditions could be applied to the coupling of a variety of secondary α-bromo amides. These included amide derivatives of numerous biologically important amines, such as piperazine (**4.34**), pyrrolidine (**4.32**), indolone (**4.33**), and morpholine (**4.31**). This adaptation could also be used to couple cyclic tertiary α-bromo amides. Tertiary α-bromo-β-lactams (**4.35**), as well as secondary α-bromo-β-lactams (**4.40**) were found to provide the desired products in useful yields. Acyclic tertiary amides or esters failed to provide any product.

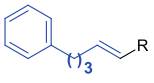
We also noted a few limitations of the present hydroalkylation reaction. Aryl acetylenes (**4.41**) and disubstituted internal alkynes (**4.42**) did not participate in the hydroalkylation reaction. Similarly, α-bromo ketones (**4.43**), α-bromo nitriles (**4.45**), aryl substituted α-bromo esters (**4.44**), and primary α-halo carbonyls were not viable substrates. Finally, protic functional groups, such as hydroxyl groups and unprotected amines, and reducible functional groups, like aldehydes and ketones were not tolerated.

Table 4.2 Substrate Scope [a]

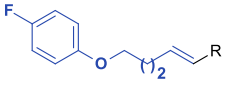


Alkyne Scope

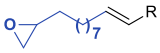




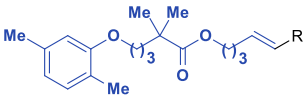
4.8, 80%



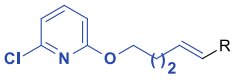
4.9, 80%



4.10, 82%



4.11, 87%



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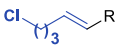

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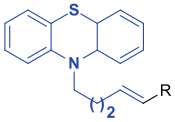

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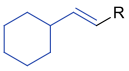

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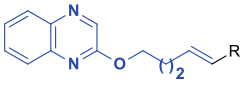

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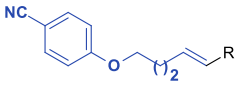

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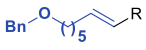

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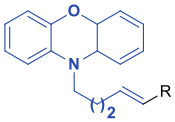

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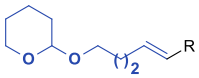

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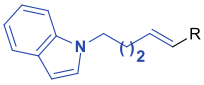

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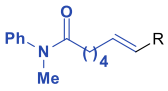

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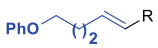

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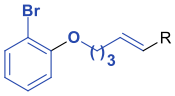

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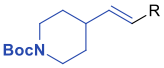

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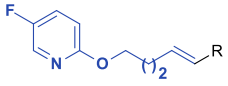
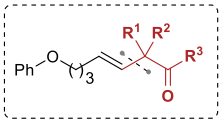
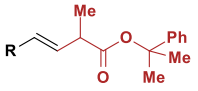


4.26, 74%

Bromocarbonyl Scope





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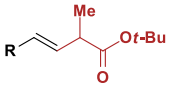

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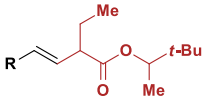

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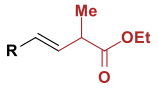

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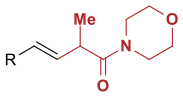

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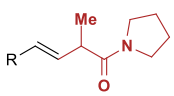

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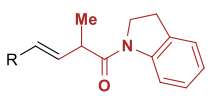

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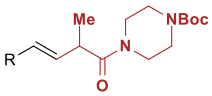

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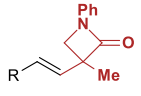

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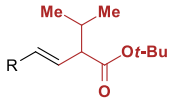

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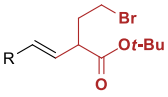

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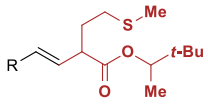

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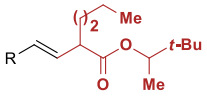

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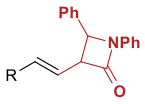
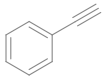


4.40, 72%[d]

Limitations



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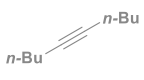

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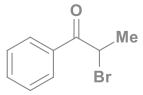

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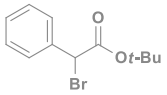


4.44

4.45

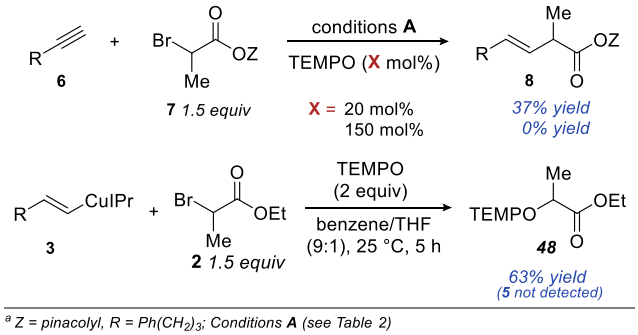
[a] Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. Conditions **A**: IPrCuCl (15 mol%), NaO*t*-Bu (2.1 equiv), bromoester (1.5 equiv), PMHS (3 equiv), benzene/THF (9:1) 5 mL, 5-24 h. [b] NaOTMS was used as base instead of NaO*t*-Bu. [c] 2 equiv of bromoester were used. [d] Conditions **B**: IPrCuCl (15 mol%), NaO*t*-Bu (2.1 equiv), bromoamide (2.0 equiv), PMHS (3 equiv), benzene/THF (7:3) 5 mL, 24h. [e] R = $PhCH_2CH_2CH_2$, 1:1 benzene/THF was used as a solvent.

4.2.3 *Initial Mechanistic Studies*

The key feature of the mechanism proposed in Scheme 3 is the cross coupling of the alkenyl copper intermediate with the α-bromo carbonyl. Although stoichiometric experiments shown in Scheme 4b established the feasibility of this elementary step, the exact mechanism of this process was unclear. While we initially postulated a pathway initiated by SET, a two-electron oxidative addition/reductive elimination sequence is also plausible.

Support for a SET pathway came from radical trap experiments (**Scheme 4.5**). Our previous work has shown that the electrophilic functionalization of the alkenyl copper intermediate, is not affected by the addition of TEMPO.[22] On the other hand, the SET pathway is expected to show sensitivity to TEMPO.[43,46,47] We observed that as little as 20 mol% of TEMPO impacts the catalytic reaction and 1.5 equivalent of TEMPO completely prevents the formation of the alkene product (**Scheme 4.5**). Stochiometric experiment with alkenyl copper revealed that TEMPO inhibits the cross-coupling step of the reaction, producing TEMPO adduct **4.48** as the major product of the reaction (63% yield).

Scheme 4.5 Radical probe trap [a]

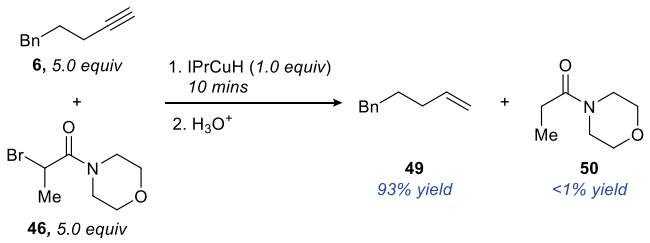


[a] *Z = pinacolyl, R = Ph(CH$_2$)$_3$; Conditions **A** (see Table 2)*

The results of these experiments allow us to exclude the alkylation mechanism involving two electron processes. Distinguishing between different SET mechanisms is much harder. Extensive mechanistic investigations of similar processes involved in ATRP, suggest ISET as the most likely SET mechanism for the reaction of alkenyl copper with an α-bromo carbonyl.[10,33,48] Furthermore, the relatively high redox potential of alkenyl copper intermediate makes the mechanisms involving outer-sphere SET processes unlikely, although we cannot completely exclude them.

We finished our preliminary investigation of the reaction mechanism by measuring redox potentials of other copper complexes involved in the proposed catalytic cycle. We found that IPrCuBr ($E_{p,a}$= 1.51V vs SCE in DCM) and IPrCuO*t*-Bu ($E_{p,a}$= 1.13V vs SCE in DCM) are both less reducing than the alkenyl copper intermediate **4.3**.

Scheme 4.6 Substrate Scope



IPrCuH ($E_{p,a}$= -0.39V vs SCE in THF), on the other hand, is significantly more reducing than alkenyl copper intermediate **4.3**, suggesting a potential for rapid SET with α-bromo carbonyls. Despite the highly reducing nature of IPrCuH, in a competition experiment, IPrCuH reacts significantly faster with a terminal alkyne than with α-bromo amide **4.46** (**Scheme 4.6**). Alkene **4.49**, the nearly exclusive product of the competition experiment, is obtained through hydrocupration and protonation of the alkenyl copper intermediate (**4.3**) upon aqueous workup. Furthermore, a stoichiometric reaction of IPrCuH with α-bromo amide **4.46** is slow and not inhibited by TEMPO, suggesting that the mechanism of the reaction does not involve SET or

radical intermediates (see the SI, **Table 4.S13**). These results indicate surprising resistance of IPrCuH toward SET, despite its highly reducing nature.

4.3 CONCLUSION

In conclusion, we have developed a hydroalkylation of alkynes using α-bromo carbonyls as alkylating reagents. The hydroalkylation reaction affords the *E*-alkene product with high selectivity and is compatible with several classes of alkynes and α-bromo carbonyls. Furthermore, the reaction can be accomplished in the presence of acetals, epoxides, aryl halides, and heteroaromatics. Mechanistic experiments reveal that the direct alkylation of the alkenyl copper intermediate obtained by hydrocupration of an alkyne is accomplished through a SET pathway.

4.4 EXPERIMENTAL

4.4.1 *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. 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 ($CDCl_3$(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. Gas Chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

4.4.2 *Materials*

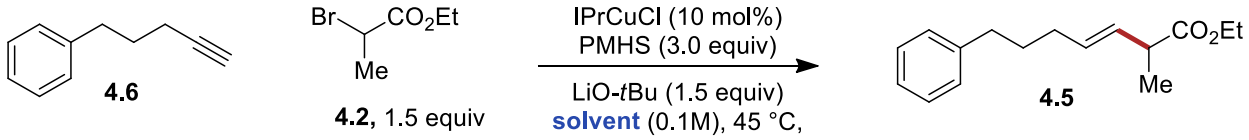
THF, CH_2Cl_2, ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Anhydrous methanol was purchased from Millipore Sigma and was degassed and stored over 4Å molecular sieves. Isooctane was purchased from Fisher Scientific and was degassed and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were stored over 4Å molecular sieves prior to use. Commercial reagents were purchased from Millipore Sigma, TCI America, GFS-Chemicals, Ark-Pharm, Combi-Blocks, Oakwood Chemicals, Strem Chemicals and Alfa Aesar. 9-BBN Dimer was purchased from Millipore Sigma and recrystallized from THF.

4.4.3 *Reaction Development*

All the reactions shown in table S1 to table S9 were performed on a 0.1 mmol scale. In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, base, copper catalyst, solvent, internal

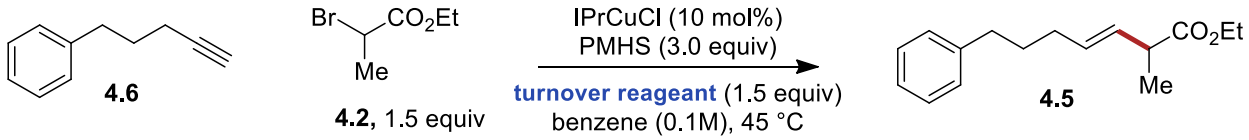
standard, trimethoxybenzene (TMB), silane, and alkyne, respectively. The reaction mixture was stirred at room temp until the yellow color disappeared. Then, secondary alkyl bromide was added, and the reaction mixture was vigorously stirred at the indicated temperature for 5 hours

Table 4.3: solvent screen



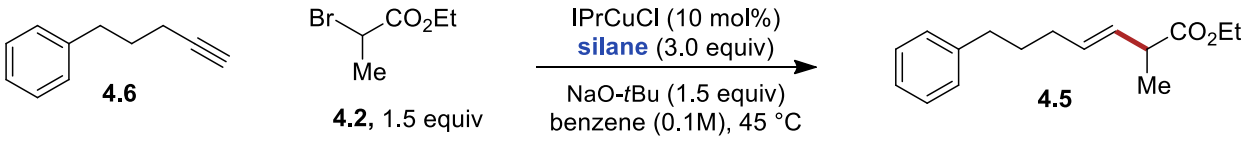
Entry	Solvent	Yield (%)
1	THF	2
2	DME	2
3	benzene	14
4	toluene	6
5	isooctane	8
6	DMF	0
7	DCM	0

Table 4.4: turnover reagent screen



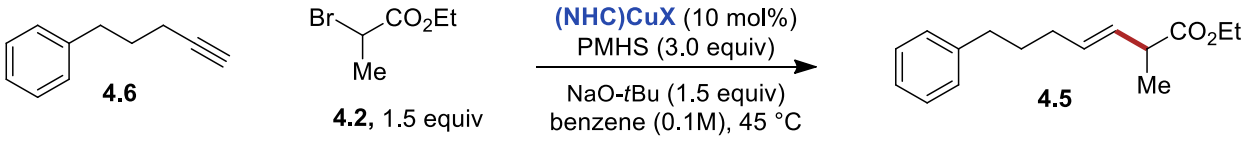
Entry	Turnover reagent	Yield (%)
1	LiO*t*-Bu	14
2	NaO*t*-Bu	32
3	KO*t*-Bu	0
4	LiO*i*-Pr	16
5	NaO*i*-Pr	24
6	LiOMe	2
7	NaOMe	2
8	$NaOSiMe_3$	19
9	$KOSiMe_3$	0

Table 4.5: silane screen:



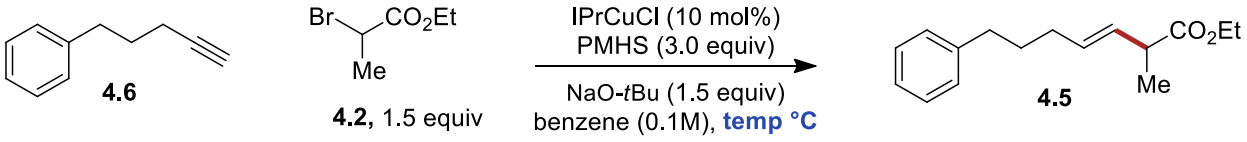
Entry	Silane	Yield (%)
1	PMHS	32
2	$(EtO)_3SiH$	7
3	Et_3SiH	0
4	$(Me)_2i$-PrSiH	8
5	$PhMe_2SiH$	18
6	Ph_2SiH_2	13
7	$Me(OEt)_2SiH$	3
8	Ph_3SiH	0
9	Ph_2MeSiH	21
10	$(t$-Bu$)_2SiH_2$	0

Table 4.6: NHC ligand screen



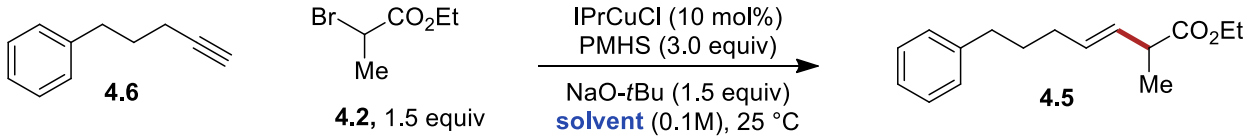
Entry	(NHC)CuX	Yield (%)
1	IPrCuCl	32
2	IPrCuO-*t*Bu	32
3	SIPrCuO-*t*Bu	24
4	SIPrCuCl	26
5	IMesCuCl	3
9	IcyCuCl	0
10	IMeCuCl	0

Table 4.7: temperature screen



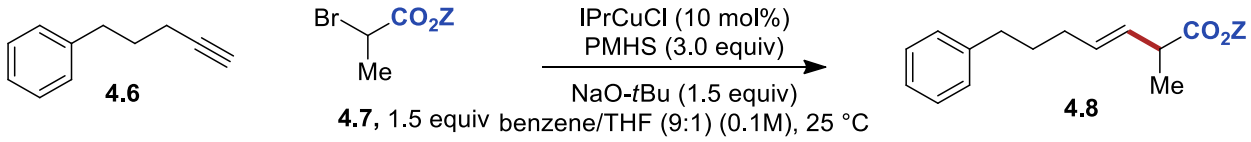
Entry	Temperature (°C)	Yield (%)
1	0	28
2	25	42
3	45	32
4	60	15

Table 4.8: solvent screen



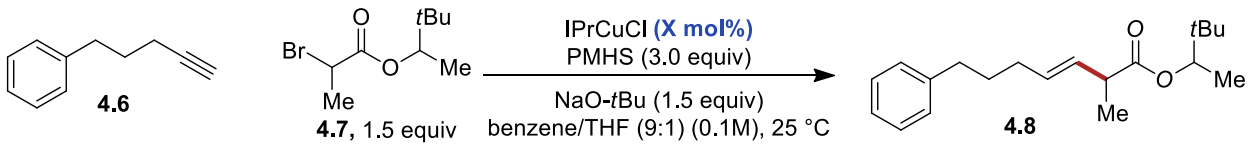
Entry	Solvent	Yield (%)
1	benzene	42
2	THF	26
3	Benzene/THF (9:1)	54
4	Benzene/THF (7:3)	49
5	Benzene/THF (1:1)	49
6	Benzene/DME (9:1)	42
7	Benzene/Ether (9:1)	47
8	Toluene/THF (9:1)	38

Table 4.9: ester variation



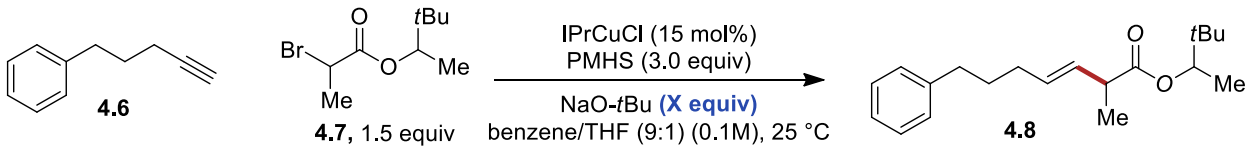
Entry	Ester	Yield (%)
1	Et	54
2	*i*Pr	60
3	Pinacolyl	64

Table *4.10*: catalyst loading



Entry	mol%	Yield (%)
1	5	54
2	10	64
3	15	74
4	20	62

Table 4.11: NaO-tBu stoichiometry



Entry	Equiv	Yield (%)
1	1.5	74
2	2.0	80
3	2.1	81
4	2.2	80
5	2.3	49
6	2.5	42
4	3.0	40

4.4.4 *Standard condition for the hydroalkylation of alkynes*

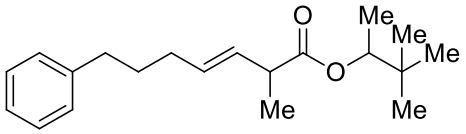
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, NaO*t*-Bu (100.8 mg, 1.05 mmol, 2.1 equiv), IPrCuCl (36.6 mg, 0.075 mmol, 0.15 equiv) and benzene/THF (9:1) (2.0 mL). PMHS (90.0 mg, 1.5 mmol, 3.0 equiv) and alkyne (0.5 mmol, 1.0 equiv) were added to this solution sequentially using 1 mL of benzene/THF (9:1) each. The reaction mixture was stirred at 25 °C until the yellow color disappeared. The α-bromo ester(0.75 mmol, 1.5 equiv) was then transferred to the reaction mixture using 1 mL of benzene/THF (9:1). The reaction mixture was stirred at 25 °C. The reaction progress was monitored by TLC. Upon full consumption of the terminal alkyne (5-24 hours), the reaction mixture was filtered through a pad of silica gel and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by alumina chromatography.

4.4.5 *Determination of the Stereochemistry and Selectivity of the Product*

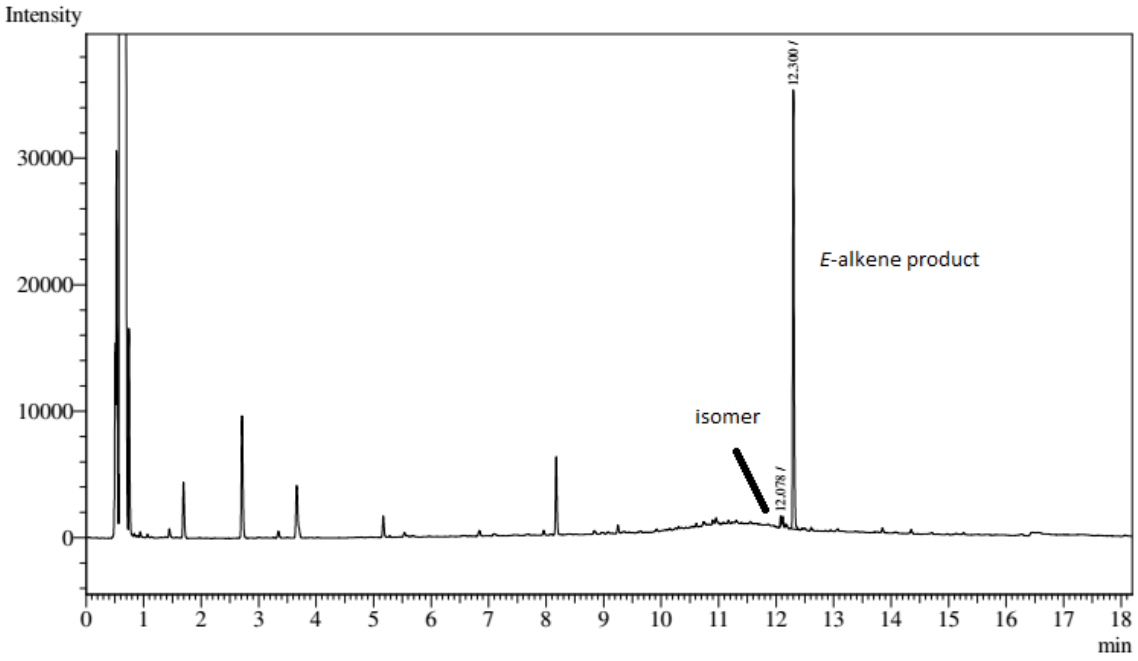
The stereochemistry of the alkene products was determined from the stoichiometric reaction of *E*-alkenylcopper intermediate (**4.5)** with α-bromoester **(4.7)** and the *J*-coupling constant for isolated compounds **4.22, 4.24, 4.27, 4.28, 4.35, 4.36.** In all these compounds, the *J*-coupling constant was found to be >15.4 (compound **4.24** has a coupling constant of 14.6), indicating the formation of the *E*-isomer as the major product.

The selectivity of the hydroalkylation method was determined for several substrates by using GC/FID analysis. The GC-MS analysis of the isolated purified product **4.8** revealed the presence of an additional isomer, which we tentatively assign as a *Z*-alkene product based on our previous work. Other minor impurities did not have the mass of the expected isomeric products. Finally, it is important to note that the diastereoisomers arising from the presence of the two stereocenters (α to the carbonyl and from the pinacolyl alcohol) were not resolved by GC. For compound **4.8**, the same level of selectivity was observed in the crude reaction mixture and the isolated purified product. For compounds **4.15**, **4.30**, **4.31**, and **4.35** a small sample (<1 mg) was taken in a GC vial, diluted with ethyl acetate, and subjected to GC/FID analysis. GC/FID analysis of all these compounds indicates that the *E*-alkene isomer is obtained with selectivity greater than 50:1.

E-selectivity for compound **(4.8)**

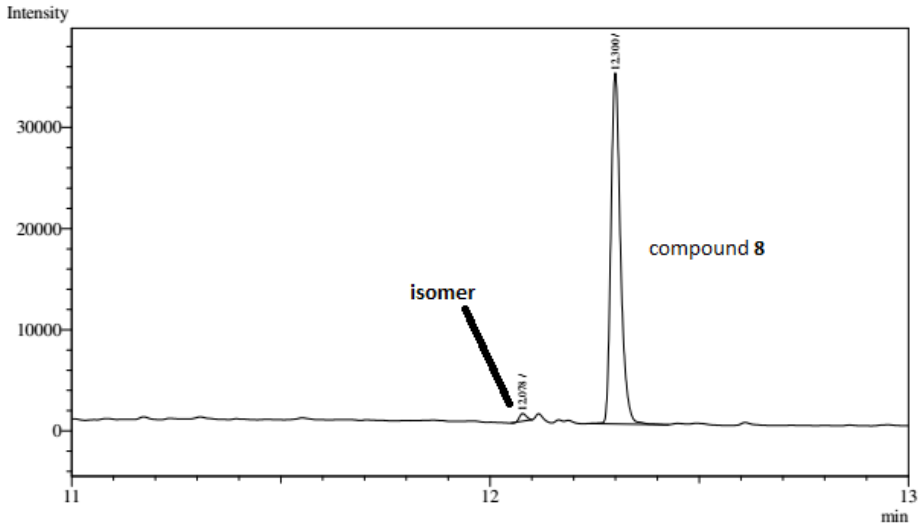


GC trace of the crude reaction of **4.8**



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	12.078	848	711	1.512				
2	12.300	55266	34378	98.488				
Total		56114	35089					

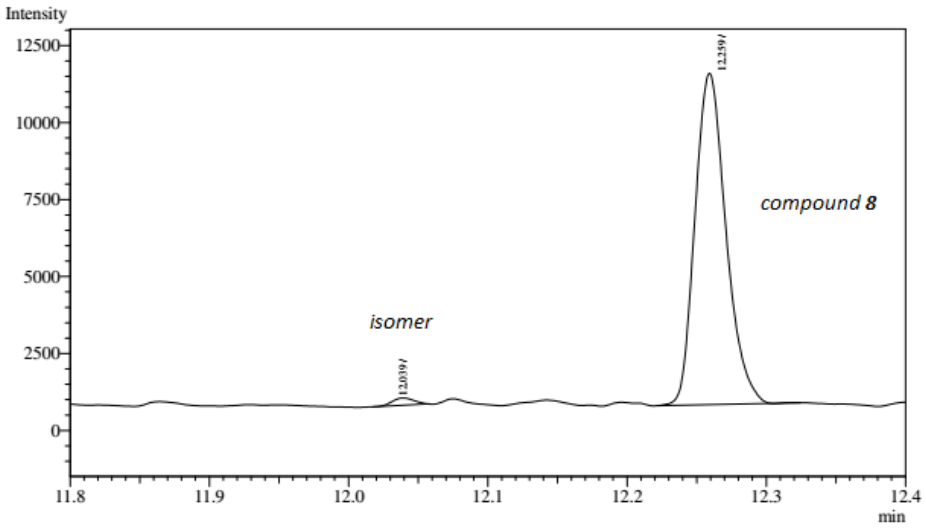
Close-up of the GC trace of crude reaction **4.8**



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	12.078	848	711	1.512				
2	12.300	55266	34378	98.488				
Total		56114	35089					

*E:*others = 65:1

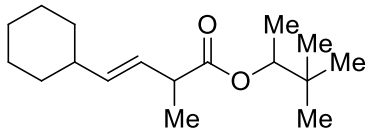
GC trace of isolated compound **4.8**



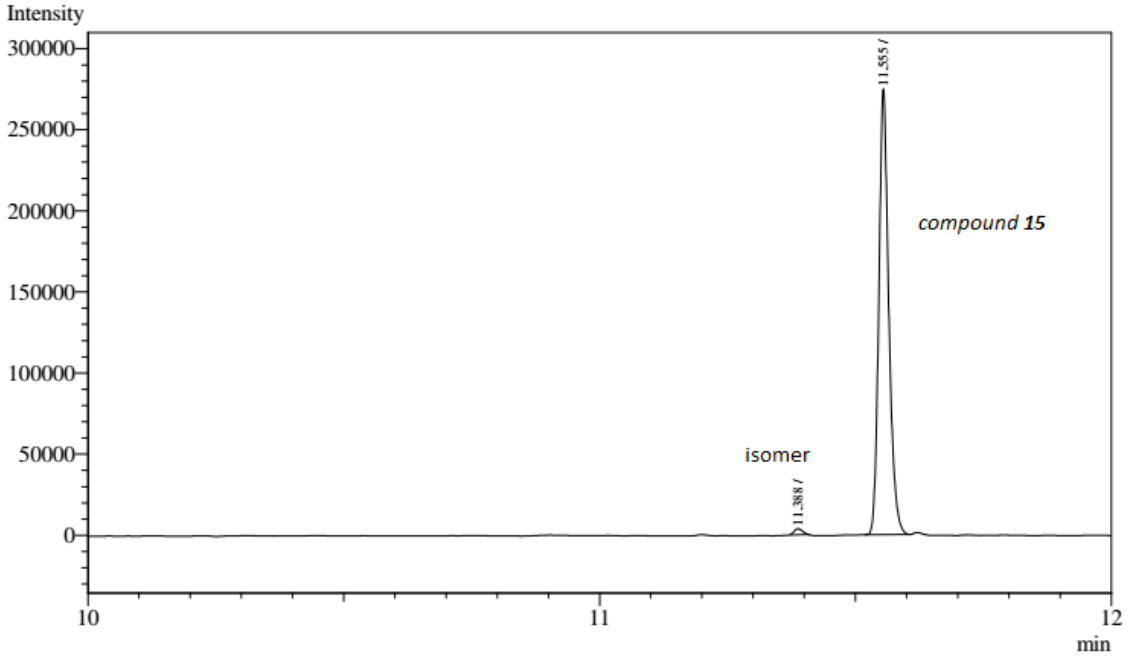
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	12.039	259	230	1.532				
2	12.259	16650	10485	98.468				
Total		16909	10715					

*E:*others = 64:1

_E_-selectivity for compound (4.15)



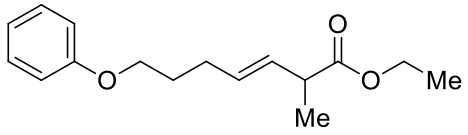
GC trace of isolated compound (**4.15)**



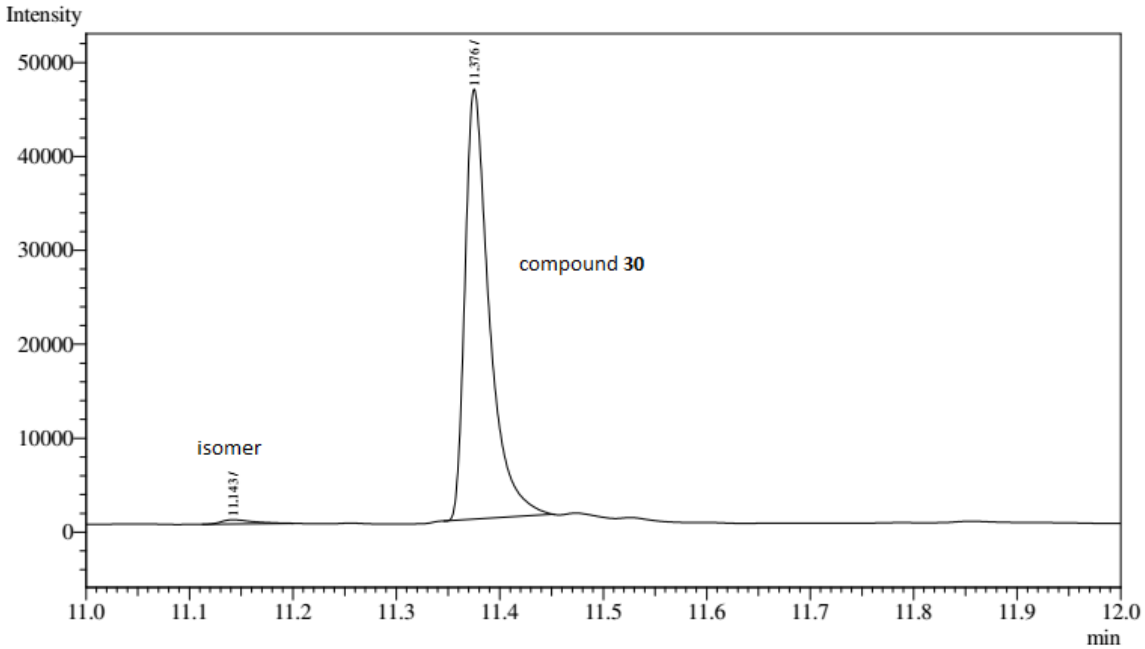
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	11.388	4160	3552	1.111				
2	11.555	370333	265872	98.889				
Total		374493	269424					

*E:*others = 89:1

***E*-selectivity for compound (4.30)**



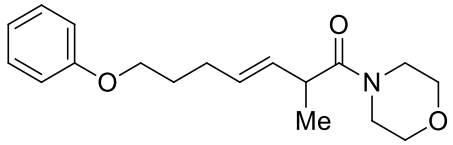
GC trace of isolated compound (**4.30)**



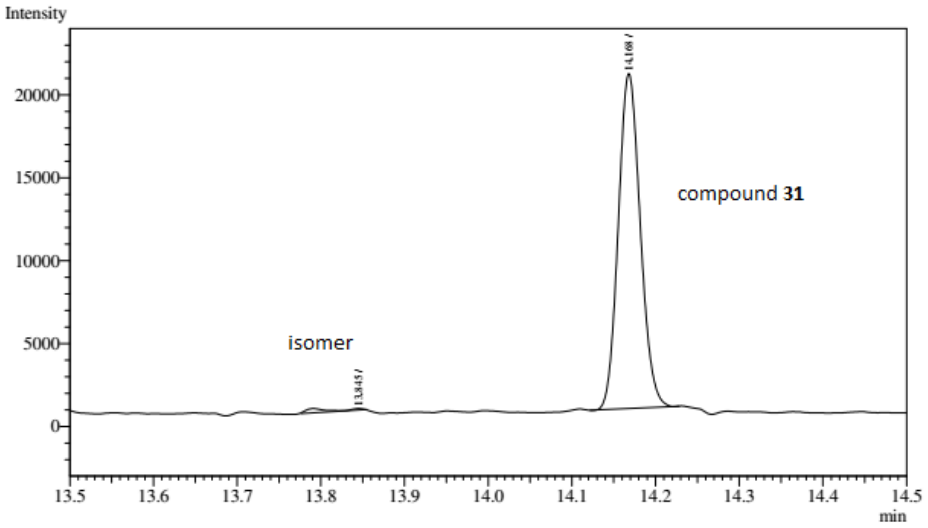
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	11.143	959	447	1.268				
2	11.376	74656	45186	98.732				
Total		75615	45633					

*E:*others = 78:1

***E*-selectivity for compound (4.31)**



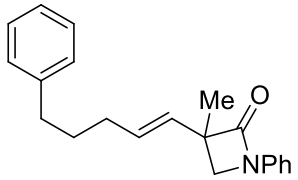
GC trace of isolated compound (**4.31)**



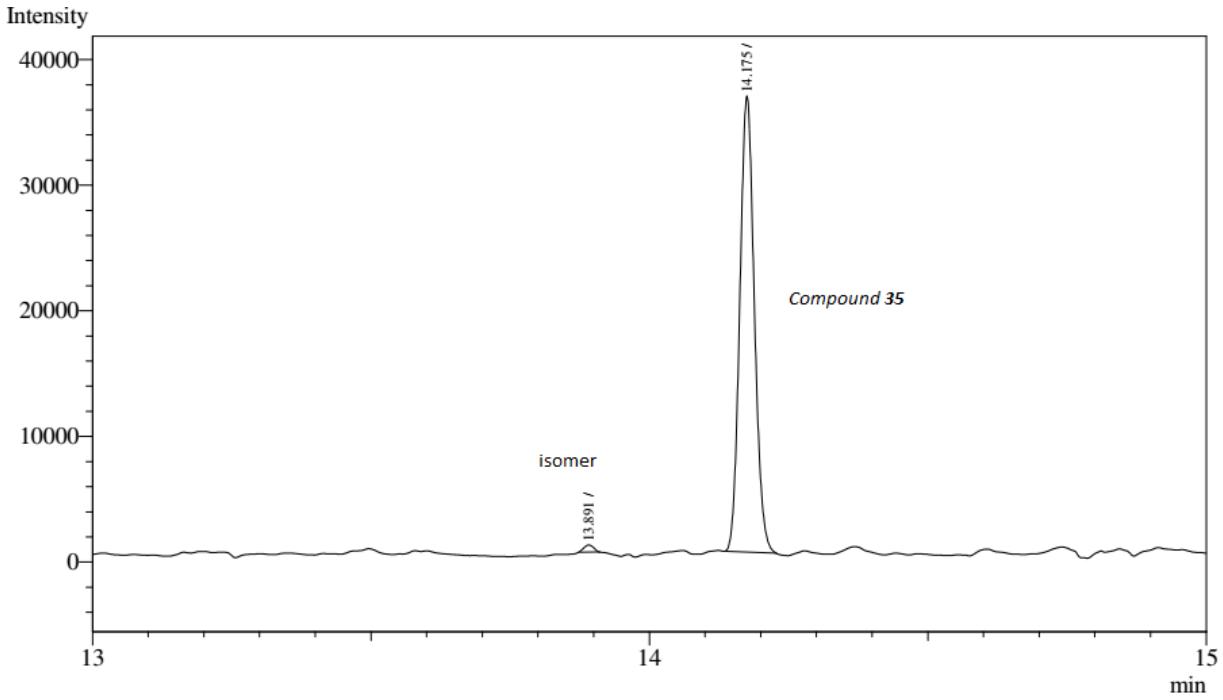
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	13.845	489	89	1.311				
2	14.168	36835	19777	98.689				
Total		37324	19866					

*E:*others = 75:1

***E*-selectivity for compound (4.35)**



GC trace of isolated compound (**4.35)**



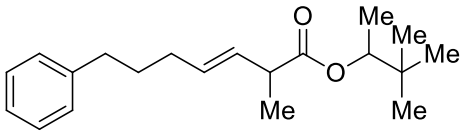
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	13.891	691	564	1.038				
2	14.175	65852	36031	98.962				
Total		66543	36595					

*E:*others = 95:1

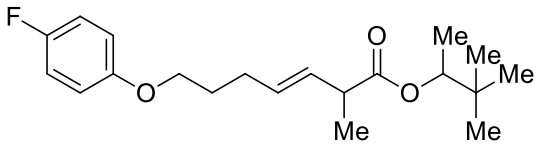
.

4.4.6 *Characterization of the E-alkene product*

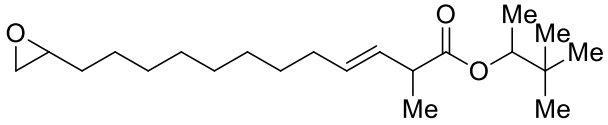
Compounds **4.8-4.26**, **4.29**, **4.38**, and **4.39** contain two stereocenters. In the reaction both diastereoisomers (syn and anti) are formed and are observed in the proton and carbon NMR of these isolated products. This is observed for the protons on the ester fragment. Diastereoisomic protons (when visible) of the ester fragment are annotated as multiples in the proton NMR. In carbon NMR, diastereotopic carbonyl carbons, alkene carbons, and some aliphatic carbons are present as unique signals. For compounds **4.27**, **4.28**, **4.30**, **4.31**, **4.32**, **4.33**, **4.34**, **4.35**, **4.36**, and **4.37**, the product contains only one stereocenter.



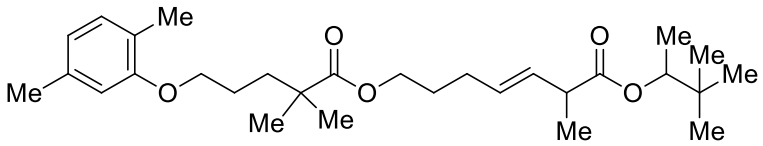
(E)-3,3-dimethylbutan-2-yl 2-methyl-7-phenylhept-3-enoate (4.8) compound was isolated as a colorless liquid (120.9 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.18 – 7.17 (m, 2H), 7.12 – 7.04 (m, 3H), 5.72 – 5.53 (m, 1H), 5.54 – 5.36 (m, 1H), 4.84 (q, J = 6.4 Hz, 1H), 3.15 – 3.00 (m, 1H), 2.51 – 2.41 (m, 2H), 1.91 (q, J = 7.1 Hz, 2H), 1.63 – 1.48 (m, 2H), 1.29 – 1.23 (m, 3H), 1.07 – 1.02 (m, 3H), 0.86 – 0.80 (m, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 174.5, 142.5, 131.7, 131.6, 129.8, 129.7, 128.5, 128.4, 125.8, 77.5, 43.5, 43.4, 35.4, 34.4, 34.3, 32.0, 31.0, 25.8, 17.7, 17.4, 14.9, 14.9. GCMS (EI) calculated for $[M]^+$ 302.22, found 302.30. FTIR (neat, cm-1): 3062 (w), 3026 (s), 2969 (s), 2934 (s), 2872 (s), 1730 (s), 1603 (w), 1496 (s), 1453 (s), 1377 (s), 1252 (s), 1178 (s), 1055 (s), 967 (s).



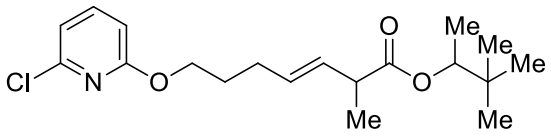
(E)-3,3-dimethylbutan-2-yl 7-(4-fluorophenoxy)-2-methylhept-3-enoate (4.9) compound was isolated as a colorless liquid (134.5 mg, 80% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.93 – 6.81 (m, 2H), 6.73 – 6.62 (m, 2H), 5.82 – 5.66 (m, 1H), 5.59 – 5.43 (m, 1H), 4.93 (q, *J* = 6.4 Hz, 1H), 3.62 – 3.55 (m, 2H), 3.22 – 3.10 (m, 1H), 2.10 (q, *J* = 7.1 Hz, 2H), 1.76 – 1.64 (m, 2H), 1.36 – 1.31 (m, 3H), 1.16 – 1.10 (m, 3H), 0.91 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.4, 157.3 (d, *J* = 237.9 Hz), 155.3 (d, *J* = 1.5 Hz), 130.9, 130.8, 130.2, 130.2, 115.8 (d, *J* = 23.0 Hz), 115.5 (d, *J* = 7.8 Hz), 77.6, 77.6, 67.8, 43.4, 43.4, 34.4, 34.3, 28.9, 25.8, 17.7, 17.6, 17.4, 17.4, 15.4, 14.9, 14.9, 14.9, 14.8. 14.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ -132.26. GCMS (EI) calculated for $[M]^+$ 336.21, found 336.20. FTIR (neat, cm-1): 3154 (m), 2971 (s), 2873 (s), 1717 (s), 1506 (s), 1471 (m), 1456 (m), 1378 (s), 1248 (s), 1209 (s), 1076 (s), 910(s).



(E)-3,3-dimethylbutan-2-yl 2-methyl-12-(oxiran-2-yl)dodec-3-enoate (4.10) compound was isolated as a colorless liquid (138.7 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 – 5.28 (m, 2H), 4.65 (q, *J* = 6.4 Hz, 1H), 3.86 – 3.65 (m, 1H), 3.62 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.47 (dd, *J* = 11.0, 7.1 Hz, 1H), 3.15 – 2.98 (m, 1H), 2.20 (d, *J* = 4.3 Hz, 1H), 2.04 – 1.88 (m, 2H), 1.54 – 1.15 (m, 16H), 1.13 – 1.06 (m, 3H), 0.92 – 0.85 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 174.7, 132.3, 132.1, 131.7, 129.2, 129.2, 77.5, 71.6, 50.6, 43.5, 43.4, 34.4, 34.4, 34.3, 32.5, 29.6, 29.5, 29.5, 29.3, 29.1, 29.1, 25.8, 25.6, 17.7, 17.4, 14.9, 14.9. GCMS (EI) calculated for $[M]^+$ 338.28 found 338.30. FTIR (neat, cm-1): 2926 (s), 2854 (s), 1732 (s), 1604 (w), 1456 (s), 1377 (s), 1254 (m), 1182 (s), 1076 (s), 907 (s).

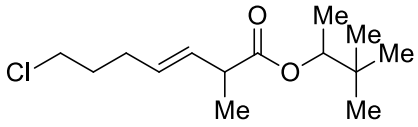


(E)-3,3-dimethylbutan-2-yl 7-((5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoyl)oxy)-2-methylhept-3-enoate (4.11) compound was isolated as a colorless liquid (206.3 mg, 87% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 1H), 6.68 – 6.57 (m, 2H), 5.58 – 5.49 (m, 2H), 4.66 (q, *J* = 6.4 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.92 (t, *J* = 5.5 Hz, 2H), 3.13 – 3.00 (m, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.09 (dd, *J* = 11.3, 6.2 Hz, 2H), 1.78 – 1.63 (m, 6H), 1.26 – 1.18 (m, 9H), 1.13 – 1.08 (m, *J* = 6.4, 2.1 Hz, 3H), 0.90 – 0.84 (m, *J* = 2.1 Hz, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 174.2, 174.1, 157.0, 136.3, 130.5, 130.4, 130.3, 130.3, 123.5, 120.7, 112.0, 67.9, 63.6, 43.3, 43.2, 42.1, 37.2, 34.3, 34.2, 28.8, 28.3, 25.7, 25.2, 25.2, 21.4, 17.5, 17.2, 15.7, 14.8, 14.7. GCMS (EI) calculated for $[M]^+$ 474.33, found 474.40. FTIR (neat, cm-1): 2972 (s), 2922 (s), 2872 (s), 1731 (s), 1614 (w), 1585 (w), 1509 (s), 1462 (m), 1377 (m), 1266 (s), 1193 (s), 1056 (s).

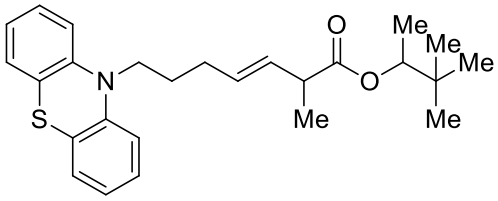


(E)-3,3-dimethylbutan-2-yl 7-((6-chloropyridin-2-yl)oxy)-2-methylhept-3-enoate (4.12) compound was isolated as a colorless liquid (148.3, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 5.64 – 5.46 (m, 2H), 4.62 (q, *J* = 6.4 Hz, 1H), 4.25 (t, *J* = 6.5 Hz, 2H), 3.15 – 2.97 (m, 1H), 2.21 – 2.10 (m, 2H), 1.86 – 1.73 (m, 2H), 1.24 – 1.16 (m, 3H), 1.11 – 1.03 (m, 3H), 0.90 – 0.83 (m, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.4, 163.7, 148.4, 140.6, 130.9, 130.8, 130.1, 130.0, 116.1, 109.2, 77.5, 77.5, 66.0, 43.4, 43.3, 34.3, 34.3, 28.9, 28.5, 25.7, 17.6, 17.3, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 353.18, found 353.20. FTIR (neat, cm-1): 2966 (s), 2872 (m), 1715 (s), 1642 (m), 1591 (s), 1560

(s), 1554 (s), 1456 (s), 1407 (m), 1365 (m), 1300 (s), 1262 (s), 1179 (m), 1160 (s), 1075 (s), 968 (m), 907 (s), 733 (s).

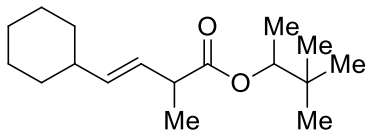


(E)-3,3-dimethylbutan-2-yl 7-chloro-2-methylhept-3-enoate (4.13) compound was isolated as a colorless liquid (96.3 mg, 74% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 5.64 – 5.49 (m, 1H), 5.31 – 5.17 (m, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 3.12 – 2.95 (m, 3H), 1.86 (q, *J* = 7.1 Hz, 2H), 1.50 – 1.39 (m, 2H), 1.25 – 1.18 (m, 3H), 1.07 – 0.99 (m, 3H), 0.82 (s, 9H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 130.9, 130.8, 130.0, 129.9, 77.6, 44.3, 43.4, 43.4, 34.4, 34.3, 32.1, 29.6, 25.8, 17.6, 17.3, 14.9, 14.9. GCMS (EI) calculated for $[M]^+$ 260.15, found 260.20. FTIR (neat, cm-1): 2971 (s), 2914 (s), 1723 (s), 1685 (s), 1645 (m). 1604 (m), 1560 (s), 1538 (s), 1460 (s), 1375 (m), 907 (s).

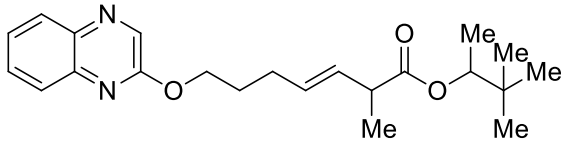


(E)-3,3-dimethylbutan-2-yl 2-methyl-7-(10H-phenothiazin-10-yl)hept-3-enoate (4.14) compound was isolated as a colorless liquid (141.8 mg, 67% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.11 – 7.03 (m, 2H), 7.01 – 6.89 (m, 2H), 6.75 – 6.63 (m, 2H), 6.58 (d, *J* = 8.2 Hz, 2H), 5.66 – 5.50 (m, 1H), 5.39 – 5.22 (m, 1H), 4.90 – 4.75 (m, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.07 – 2.92 (m, 1H), 1.97 – 1.85 (m, 2H), 1.68 – 1.50 (m, 2H), 1.18 – 1.12 (m, 3H), 1.06 – 0.98 (m, 3H), 0.83 – 0.78 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.4, 145.3, 130.7, 130.5, 127.5, 127.3,

125.3, 122.5, 115.6, 77.5, 46.5, 43.4, 43.3, 34.4, 34.3, 29.7, 26.4, 25.8, 17.6, 17.3, 14.9, 14.9. GCMS (EI) calculated for $[M]^+$ 423.22, found 423.20. FTIR (neat, cm-1): 2974 (s), 2914 (s), 1717 (s), 1695 (s), 1646 (s), 166 (w), 1558 (s), 1496 (w), 1456 (s), 1373 (m), 1251 (m), 1177 (w), 1075 (w), 908 (s), 732 (s).

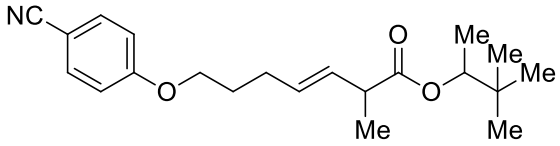


(E)-3,3-dimethylbutan-2-yl 4-cyclohexyl-2-methylbut-3-enoate (4.15) compound was isolated as a colorless liquid (117.1 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 – 5.36 (m, 2H), 4.68 – 4.55 (m, 1H), 3.08 – 2.98 (m, 1H), 1.99 – 1.79 (m, 1H), 1.74 – 1.57 (m, 5H), 1.26 – 1.01 (m, 11H), 0.94 – 0.84 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 174.7, 138.2, 138.0, 126.9, 126.8, 77.4, 43.5, 43.5, 40.65, 34.5, 34.4, 33.1, 33.0, 26.3, 26.2, 25.8, 17.7, 17.4, 15.0, 14.8. GCMS (EI) calculated for $[M]^+$ 266.22 found 266.20. FTIR (neat, cm-1): 2978 (s), 2930 (s), 2854 (s), 1734 (s), 1715 (s), 1448 (s), 1378 (s), 1268 (s), 1075 (s), 1052 (s), 907 (s), 733 (s).

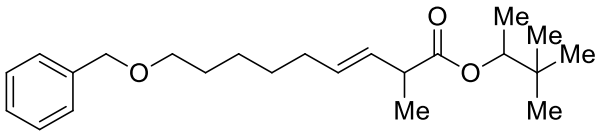


(**E)-3,3-dimethylbutan-2-yl 2-methyl-7-(quinoxalin-2-yloxy)hept-3-enoate (4.16)** compound was isolated as a colorless liquid (135.1 mg, 73% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.42 – 8.35 (m, 1H), 8.15 – 8.09 (m, 1H), 7.94 – 7.86 (m, 1H), 7.34 – 7.25 (m, 1H), 7.22 – 7.17 (m, 1H), 5.71 – 5.58 (m, 1H), 5.50 – 5.35 (m, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.12 – 2.99 (m, 1H), 2.06 – 1.95 (m, 2H), 1.73 – 1.60 (m, 2H), 1.26 – 1.21 (m, 3H), 1.07 – 0.99 (m, 3H), 0.82 – 0.77 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 157.5, 140.5, 139.7, 138.9, 130.8, 130.6, 130.3, 130.2, 130.1, 129.0, 127.3, 126.4, 77.5, 65.8, 43.4, 43.3, 34.3, 34.3, 28.9, 28.4, 25.7,

17.6, 17.3, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 370.23, found 370.30. FTIR (neat, cm-1): 2968 (s), 2932 (s), 2873 (s), 1730 (s), 1700 (m), 1635 (w), 1572 (s), 1472 (m), 1415 (s), 1365 (s), 1338 (w), 1306 (s), 1221 (s), 1076 (s), 912 (s), 762 (s).

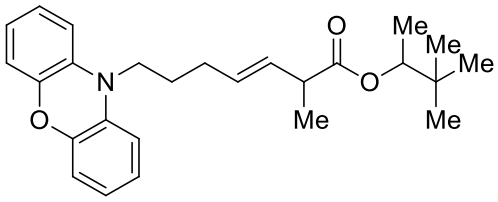


(E)-3,3-dimethylbutan-2-yl 7-(4-fluorophenoxy)-2-methylhept-3-enoate (4.17) compound was isolated as a colorless liquid (135.6 mg, 79% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.02 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 8.1 Hz, 1H), 5.80 – 5.47 (m, 1H), 5.43 – 5.28 (m, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 3.34 – 3.28 (m, 2H), 3.11 – 2.97 (m, 1H), 1.97 – 1.86 (m, 2H), 1.55 – 1.41 (m, 2H), 1.26 – 1.20 (m, 3H), 1.07 – 0.99 (m, 3H), 0.81 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 162.5, 134.0, 130.6, 130.6, 130.5, 130.3, 119.3, 115.3, 77.6, 67.6, 43.4, 43.3, 34.4, 34.3, 28.7, 28.6, 25.8, 17.6, 17.3, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 343.21 found 343.20. FTIR (neat, cm-1): 3154 (w), 2970 (s), 2874 (s), 2226 (s), 1722 (s), 1606 (s), 1539 (m), 1508 (s), 1456 (s), 1366 (s), 1302 (s), 1258 (s), 1171 (s), 1113 (m), 1076 (s), 1052 (m), 907 (s), 834 (s), 737 (s).

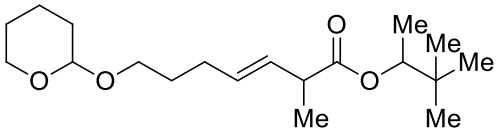


(E)-3,3-dimethylbutan-2-yl 9-(benzyloxy)-2-methylnon-3-enoate (4.18) compound was isolated as a colorless liquid (145.9 mg, 81% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.35 – 7.28 (m, 2H), 7.24 – 7.19 (m, 2H), 7.13 – 7.05 (m, 1H), 5.72 – 5.58 (m, 1H), 5.55 – 5.39 (m, 1H), 4.90 – 4.78 (m, 1H), 4.34 (s, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 3.15 – 3.02 (m, 1H), 1.97 – 1.87 (m, 2H), 1.63 – 1.49 (m, 2H), 1.34 – 1.23 (m, 7H), 1.09 – 1.02 (m, 3H), 0.85 – 0.81 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.4, 138.8, 132.0, 131.8, 129.3, 129.3, 128.4, 127.6, 127.5, 77.4, 72.9, 70.4, 43.4, 43.3, 34.3, 34.2, 32.4, 29.7, 29.1, 25.7, 17.6, 17.3, 14.8, 14.8. GCMS (EI) calculated

for $[M]^+$ 360.27, found 360.30. FTIR (neat, cm-1): 3030 (w), 2970 (s), 2934 (s), 2858 (s), 1718 (s), 1604 (w), 1456 (s), 1394 (w), 1378 (m), 165 (m), 1260 (m), 1184 (s), 1076 (s), 909 (s), 735 (s).

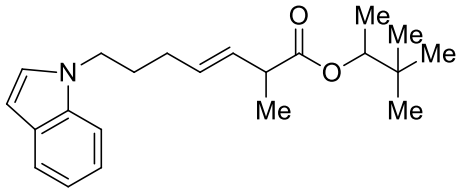


(E)-3,3-dimethylbutan-2-yl 2-methyl-7-(10H-phenoxazin-10-yl)hept-3-enoate (4.19) compound was isolated as a colorless liquid (144.6 mg, 71% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 – 6.73 (m, 2H), 6.68 – 6.60 (m, 4H), 6.46 (d, *J* = 7.9 Hz, 2H), 5.72 – 5.48 (m, 2H), 4.76 – 4.62 (m, 1H), 3.48 (b, 2H), 3.26 – 2.98 (m, 1H), 2.26 – 2.04 (m, 2H), 1.84 – 1.66 (m, 2H), 1.35 – 1.20 (m, 3H), 1.19 – 1.05 (m, 3H), 1.02 – 0.80 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 145.1, 130.7, 130.5, 130.3, 123.7, 120.8, 115.4, 111.4, 77.6, 43.4, 43.3, 34.4, 34.3, 29.7, 25.8, 24.4, 17.7, 17.4, 15.0, 14.9. GCMS (EI) calculated for $[M]^+$ 407.25, found 407.30. FTIR (neat, cm-1): 3067 (w), 2971 (s), 2954 (s), 2873 (m), 1715 (s), 1616 (w), 1592 (w), 1498 (s), 1478 (s), 1379 (s), 1293 (m), 1272 (s), 1187 (m), 1043 (m), 912 (s), 734 (s).

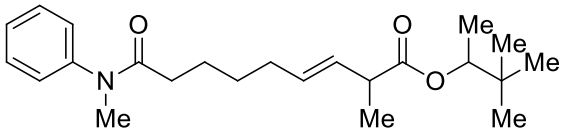


(E)-3,3-dimethylbutan-2-yl 2-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-3-enoate (4.20) compound was isolated as a colorless liquid (89.7 mg, 55% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 5.75 – 5.40 (m, 2H), 4.84 (q, *J* = 6.4 Hz, 1H), 4.58 (t, *J* = 3.2 Hz, 1H), 3.90 – 3.72 (m, 2H), 3.50 – 3.20 (m, 2H), 3.17 – 2.96 (m, *J* = 7.0 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.80 – 1.53 (m, 5H), 1.44 – 1.18 (m, 6H), 1.09 – 0.96 (m, 3H), 0.82 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.5, 131.5, 131.3, 129.7, 129.6, 100.1, 98.9, 77.5, 66.9, 62.3, 43.4, 43.3, 34.4, 34.3, 30.8, 29.4, 29.2,

25.8, 25.6, 19.7, 17.6, 17.4, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 326.25 found 326.30. FTIR (neat, cm-1): 2943 (s), 2872 (s), 1718 (s), 1456 (s), 1378 (s), 1353 (m), 1260 (s), 1183 (s), 1118 (s), 1076 (s), 1032 (s), 908 (s).

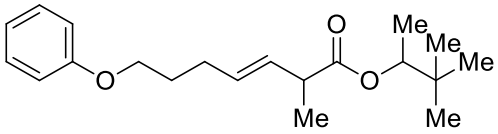


(E)-3,3-dimethylbutan-2-yl 7-(1H-indol-1-yl)-2-methylhept-3-enoate (4.21) compound was isolated as a colorless liquid (119.4 mg, 70% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.21 (m, 1H), 7.19 – 7.09 (m, 2H), 6.54 (d, *J* = 3.0 Hz, 1H), 5.68 – 5.51 (m, 2H), 4.74 (q, *J* = 6.4 Hz, 1H), 4.16 (t, *J* = 6.8 Hz, 2H), 3.23 – 3.07 (m, 1H), 2.15 – 2.05 (m, 2H), 2.03 – 1.89 (m, 2H), 1.34 – 1.26 (m, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.00 – 0.92 (m, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.4, 136.1, 130.7, 130.6, 130.5, 130.4, 128.7, 127.9, 121.5, 121.1, 119.3, 109.5, 101.1, 100.1, 77.7, 45.6, 43.5, 43.3, 34.4, 34.3, 29.7, 29.6, 25.8, 17.6, 17.4, 15.0, 14.9. GCMS (EI) calculated for $[M]^+$ 341.24, found 341.30. FTIR (neat, cm-1): 3030(w), 2970 (s), 2936 (s), 2876 (m), 1717 (s), 1604 (w), 1511 (m), 1463 (s), 1398 (m), 1365 (s), 1335 (m), 1316 (s), 1264 (m), 1182 (s), 1116 (m), 1076 (s), 1052 (m), 970 (w), 910 (s), 739 (s).

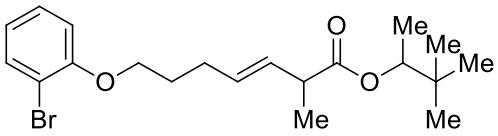


(E)-3,3-dimethylbutan-2-yl 2-methyl-9-(methyl(phenyl)amino)-9-oxonon-3-enoate (4.22) compound was isolated as a colorless liquid (134.4 mg, 72% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.15 – 6.99 (m, 3H), 6.85 (d, *J* = 7.1 Hz, 2H), 5.75 – 5.57 (m, 1H), 5.50 (dt, *J* = 22.0, 6.5 Hz, 1H), 4.93 (q, *J* = 6.4 Hz, 1H), 3.24 – 3.07 (m, 4H), 2.10 (t, *J* = 7.3 Hz, 2H), 2.01 – 1.87 (m, 2H), 1.87 –

1.71 (m, 2H), 1.40 – 1.26 (m, 5H), 1.18 – 1.11 (m, 3H), 0.92 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 174.5, 173.1, 144.3, 131.7, 131.5, 129.8, 129.3, 129.3, 127.7, 127.3, 77.4, 43.3, 43.2, 37.3, 34.3, 34.2, 33.9, 32.1, 28.9, 25.7, 25.1, 17.0, 17.3, 14.8, 14.8.GCMS (EI) calculated for $[M]^+$ 373.26, found 373.30. FTIR (neat, cm-1): 2970 (s), 2936 (s), 2873 (s), 1717 (s), 1700 (m), 1635 (s), 1616 (m), 1596 (s), 1496 (s), 1456 (s), 1365 (s), 1264 (s), 1184 (s), 1118 (m), 1075 (s), 908 (s), 733 (s).

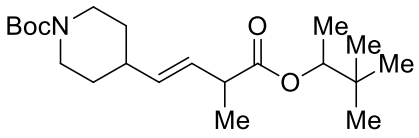


(E)-3,3-dimethylbutan-2-yl 2-methyl-7-phenoxyhept-3-enoate (4.23) compound was isolated as a colorless liquid (120.9 mg, 76% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.16 – 7.09 (m, 2H), 6.98 – 6.76 (m, 3H), 5.70 – 5.56 (m, 1H), 5.49 – 5.35 (m, 1H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.13 – 2.96 (m, 1H), 2.09 – 1.95 (m, 2H), 1.71 – 1.56 (m, 2H), 1.26 – 1.20 (m, 3H), 1.06 – 1.00 (m, 3H), 0.81 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.5, 159.1, 131.0, 130.9, 130.1, 130.1, 129.5, 120.7, 114.6, 77.6, 67.1, 43.5, 43.4, 34.4, 34.3, 28.9, 25.8, 17.6, 17.4, 14.9, 14.9. GCMS (EI) calculated for $[M]^+$ 318.22, found 318.20. FTIR (neat, cm-1): 3084 (s), 3062 (s), 2969 (s), 2872 (s), 1731 (s), 1603 (w), 1453 (s), 1395 (m), 1226 (s), 1076 (s), 967 (s).

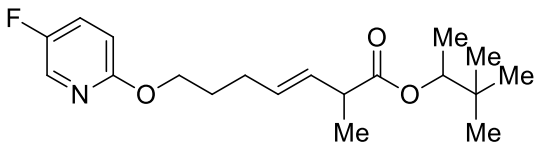


(**E)-3,3-dimethylbutan-2-yl 7-(2-bromophenoxy)-2-methylhept-3-enoate (4.24)** compound was isolated as a colorless liquid (130.7 mg, 66% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.43 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.61 – 6.36 (m, 2H), 5.72 – 5.59 (m, 1H), 5.43 (td, *J* = 14.6, 7.0 Hz, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.12 – 2.99 (m, 1H), 2.13 – 2.02 (m, 2H), 1.68 – 1.55 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.06 – 0.98 (m, 3H), 0.81 (s, 9H) .^{13}C NMR

(126 MHz, $CDCl_3$) δ 174.4, 174.3, 155.4, 133.3, 130.8, 130.6, 130.2, 130.2, 128.4, 121.7, 113.3, 112.3, 77.5, 68.2, 43.3, 43.3, 34.3, 34.2, 28.8, 28.7, 25.7, 17.5, 17.3, 14.8, 14.7. GCMS (EI) calculated for $[M]^+$ 396.13, found 396.20. FTIR (neat, cm-1): 2970 (s), 2874 (m), 1717 (s), 1600 (w), 1575 (w), 1558 (w), 1482 (s), 1465 (s), 1378 (m), 1277 (s), 1248 (s), 1180 (s), 1075 (s), 1052 (s), 909 (s), 734 (s).

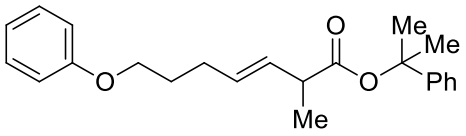


(E)-tert-butyl 4-(4-((3,3-dimethylbutan-2-yl)oxy)-3-methyl-4-oxobut-1-en-1-yl)piperidine-1-carboxylate (4.25) compound was isolated as a colorless liquid (156.1 mg, 85% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 – 5.39 (m, 2H), 4.65 – 4.56 (m, 1H), 4.01 (b , 2H), 3.06 – 2.97 (m, 1H), 2.67 (b, 2H), 2.12 – 2.00 (m, 1H), 1.63 – 1.54 (m, 2H), 1.40 (s, 9H), 1.24 – 1.16 (m, 5H), 1.08 – 1.00 (m, 3H), 0.87 – 0.81 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 174.3, 154.9, 135.9, 135.7, 128.1, 128.0, 79.3, 77.5, 43.3, 43.3, 43.3, 43.3, 38.8, 34.3, 34.3, 31.8, 28.5, 28.5, 25.7, 25.7, 17.6, 17.2, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 367.27 found 367.30. FTIR (neat, cm-1): 2973 (s), 2936 (s), 2872 (s), 1717 (s), 1705 (s), 1684 (s), 1652 (s), 1476 (s), 1456 (s), 1429 (s), 1366 (s), 1274 (m), 1247 (s), 1172 (s), 1115 (m), 1076 (s), 970 (m), 907 (s).

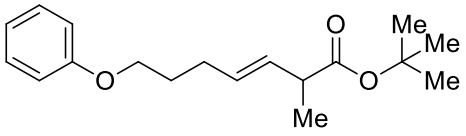


(E)-3,3-dimethylbutan-2-yl 7-((5-fluoropyridin-2-yl)oxy)-2-methylhept-3-enoate (4.26) compound was isolated as a colorless liquid (124.8 mg, 74% yield). ^1H NMR (300 MHz, C_6D_6) δ 7.90 (d, *J* = 3.0 Hz, 1H), 6.68 (td, *J* = 9.0, 3.0 Hz, 1H), 6.34 (dd, *J* = 9.0, 3.5 Hz, 1H), 5.72 – 5.55 (m, 1H), 5.53 – 5.34 (m, 1H), 4.82 (q, *J* = 6.4 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 3.12 – 2.94 (m,

1H), 2.08 – 1.96 (m, 2H), 1.77 – 1.60 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.07 – 0.98 (m, 3H), 0.81 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 160.2, 155.3 (d, *J* = 245.0 Hz), 133.1 (d, *J* = 25.9 Hz), 131.0, 130.9, 130.0, 130.0, 126.5 (d, *J* = 21.3 Hz), 111.6 (d, *J* = 4.0 Hz), 77.5, 65.7, 43.4, 43.4, 34.3, 34.3, 28.9, 28.7, 25.7, 17.6, 17.3, 14.8, 14.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ -139.75.. GCMS (EI) calculated for $[M]^+$ 337.21, found 337.20. FTIR (neat, cm-1): 3028 (w), 2957 (s), 2879 (s), 1730 (s), 1716 (s), 1652 (w), 1609 (w), 1484 (s), 1468 (s), 1375 (s), 1375 (s), 1297 (m), 1262 (s), 1219 (s), 1177 (m), 1078 (m), 1042 (m), 907 (m).

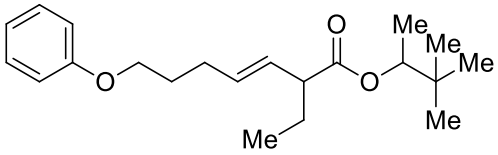


(E)-2-phenylpropan-2-yl 2-methyl-7-phenoxyhept-3-enoate (4.27) compound was isolated as a colorless liquid (144.4 mg, 82% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.33 (d, *J* = 7.4 Hz, 2H), 7.24 – 7.16 (m, 7H), 6.84 – 6.97 (m, 2H), 7.03 – 6.77 (m, 3H), 5.60 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.49 – 5.35 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.12 – 2.95 (m, 1H), 2.11 – 1.96 (m, 2H), 1.72 – 1.57 (m, 7H), 1.19 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 159.2, 146.1, 131.0, 130.2, 129.5, 128.3, 127.1, 124.3, 120.7, 114.7, 81.6, 67.2, 43.8, 29.0, 28.8, 28.6, 17.4. GCMS (EI) calculated for $[M]^+$ 352.20, found 352.20. FTIR (neat, cm-1): 2970 (s), 2916 (s), 2854 (m), 1733 (s), 1717 (m), 1669 (m), 1652 (m), 1666 (m), 1496 (s), 1474 (m), 1436 (m), 1365 (w), 1244 (s), 1172 (w), 1136 (s), 1101 (m), 1077 (m), 1030 (w).

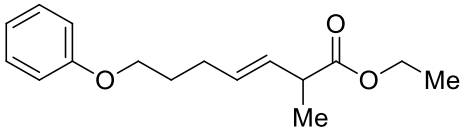


(E)-tert-butyl 2-methyl-7-phenoxyhept-3-enoate (4.28) compound was isolated as a colorless liquid (119.0 mg, 82% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.26 – 7.17 (m, 2H), 6.99 – 6.92 (m,

J = 7.3 Hz, 3H), 5.73 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.60 – 5.43 (m, 1H), 3.71 (t, *J* = 6.4 Hz, 2H), 3.21 – 2.92 (m, 1H), 2.20 – 2.05 (m, 2H), 1.81 – 1.64 (m, 2H), 1.46 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 159.1, 130.5, 130.4, 129.5, 120.6, 114.6, 80.2, 67.0, 43.8, 31.7, 28.9, 28.1, 17.5. GCMS (EI) calculated for $[M]^+$ 290.19 found 290.20. FTIR (neat, cm-1): 2979 (s), 2934 (s), 1717 (s), 1600 (s), 1496 (s), 1472 (m), 1456 (w), 1368 (s), 1245 (s), 1153 (s), 1035 (w), 908 (s).

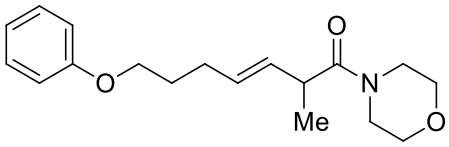


(E)-3,3-dimethylbutan-2-yl 2-ethyl-7-phenoxyhept-3-enoate (4.29) compound was isolated as a colorless liquid (134.6 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.05 – 6.80 (m, 3H), 5.76 – 5.31 (m, 2H), 4.79 – 4.43 (m, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 2.93 – 2.75 (m, 1H), 2.31 – 2.15 (m, 2H), 1.90 – 1.61 (m, 3H), 1.58 – 1.47 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.95 – 0.78 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 173.9, 159.1, 132.2, 132.1, 129.5, 129.0, 128.8, 120.6, 114.6, 77.5, 67.1, 51.5, 51.1, 34.3, 34.2, 29.0, 25.8, 25.8, 25.7, 15.0, 14.9, 11.8, 11.7. GCMS (EI) calculated for $[M]^+$ 332.24 found 332.30. FTIR (neat, cm-1): 3062 (w), 3026 (s), 2963 (s),2934 (s), 2872 (s), 1730 (s), 1603 (s), 1496 (s), 1453 (s), 1395 (m), 1377 **(**s), 1320 (w), 1252 (s), 1178 (s), 1116 (s), 1053 (s), 967 (s).

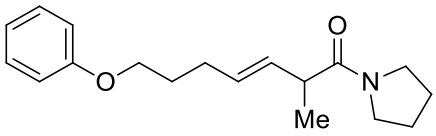


(E)-ethyl 2-methyl-7-phenoxyhept-3-enoate (4.30) compound was isolated as a colorless liquid (93.1 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.07 (m, 2H), 6.86 – 6.73 (m, 3H), 5.57 – 5.31 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.04 – 2.92 (m, 1H), 2.18 –

2.04 (m, 2H), 1.83 – 1.62 (m, 2H), 1.20 – 1.09 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 159.1, 131.0, 130.0, 129.5, 120.6, 114.6, 67.1, 60.6, 43.0, 28.9, 28.9, 17.5, 14.3. GCMS (EI) calculated for $[M]^+$ 262.16 found 262.20. FTIR (neat, cm-1): 2981 (s), 2937 (s), 2850 (m), 1726 (s), 1635 (w), 1600 (m), 1496 (s), 1472 (s), 1245 (s), 1172 (m), 1046 (w), 907 (s).

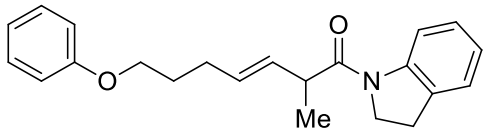


(E)-2-methyl-1-morpholino-7-phenoxyhept-3-en-1-one (4.31) compound was isolated as a colorless liquid (125.8 mg, 83% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.01 (m 2H), 6.94 – 6.61 (m, 3H), 5.60 – 5.23 (m, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 3.59 – 3.22 (m, 8H), 3.23 – 3.05 (m, 1H), 2.12 – 2.02 (m, 2H), 1.77 – 1.66 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 159.1, 130.9, 130.8, 129.5, 120.7, 114.6, 67.1, 66.8, 46.1, 42.3, 39.6, 29.0, 18.3. GCMS (EI) calculated for $[M]^+$ 303.18, found 303.20. FTIR (neat, cm-1): 3154 (w), 2970 (s), 2923 (s), 2858 (s), 1733 (w), 1634 (s), 1558 (s), 1497 (s), 1460 (s), 1433 (s), 1387 (m), 1301 (m), 1228 (s), 1172 (m), 1114 (s), 1028 (s), 910 (s).

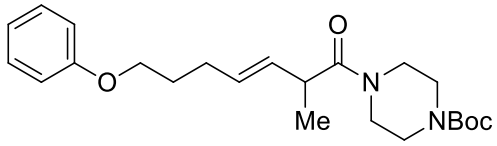


(E)-2-methyl-7-phenoxy-1-(pyrrolidin-1-yl)hept-3-en-1-one (4.32) compound was isolated as a colorless liquid (100.5 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.9 Hz, 2H), 6.88 – 6.69 (m, 3H), 5.47 – 5.37 (m, 2H), 3.83 (t, *J* = 6.4 Hz, 2H), 3.43 – 3.19 (m, 4H), 3.15 – 2.79 (m, 1H), 2.16 – 1.97 (m, 2H), 1.93 – 1.62 (m, 6H), 1.09 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 159.2, 131.1, 130.4, 129.5, 120.7, 114.6, 100.1, 67.2, 46.3, 46.0, 42.2, 29.0, 26.2, 24.3, 18.1GCMS (EI) calculated for $[M]^+$ 287.19, found 287.20. FTIR (neat, cm-1): 3024 (m),

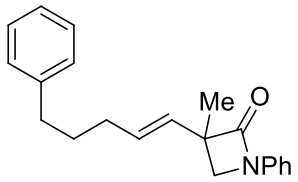
2916 (s), 2872 (m), 1700 (w), 1623 (s), 1600 (m), 1576 (w), 1520 (w), 1496 (m), 1456 (m), 1245 (s), 1172 (w), 1042 (m), 906 (s), 735 (s).



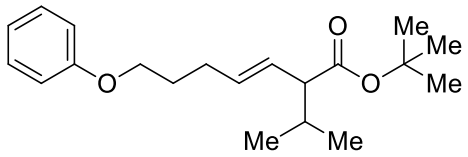
(E)-1-(indolin-1-yl)-2-methyl-7-phenoxyhept-3-en-1-one (4.33) compound was isolated as a colorless liquid (140.8 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.11 (m, 4H), 6.99 (td, *J* = 7.9, 1.0 Hz, 1H), 6.94 – 6.78 (m, 3H), 5.68 – 5.54 (m, 2H), 4.18 – 3.98 (m, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.37 – 3.23 (m, 1H), 3.12 (t, *J* = 8.4 Hz, 2H), 2.27 – 2.16 (m, 2H), 1.92 – 1.76 (m, 2H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 159.1, 143.3, 131.3, 131.2, 130.5, 129.5, 127.6, 124.6, 123.7, 120.6, 117.3, 114.6, 67.1, 47.7, 43.0, 29.0, 28.9, 28.1, 18.1.GCMS (EI) calculated for $[M]^+$ 335.19 found 335.20. FTIR (neat, cm-1): 3024 (m), 2931 (s), 2872 (s), 1654 (s), 1623 (w), 1600 (m), 1558 (m), 1481 (s), 1409 (s), 1338 (w), 1288 (m), 1245 (s), 1172 (w), 1080 (w), 1042 9w), 908 (s), 732 (s).



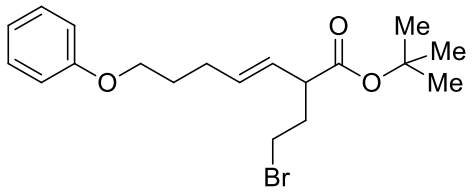
(E)-tert-butyl 4-(2-methyl-7-phenoxyhept-3-enoyl)piperazine-1-carboxylate (4.34) compound was isolated as a colorless liquid (173.0 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.13 (m, 2H), 7.01 – 6.83 (m, 3H), 5.71 – 5.38 (m, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 3.71 – 3.22 (m, 9H), 2.36 – 2.08 (m, 2H), 1.90 – 1.78 (m, 2H), 1.48 (s, 9H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 159.0, 154.6, 130.8, 129.5, 129.4, 120.6, 114.5, 80.2, 67.0, 39.7, 28.9, 28.9, 28.4, 28.4, 18.3, 18.3. GCMS (EI) calculated for $[M]^+$ 402.25 found 402.30 FTIR (neat, cm-1): 2977 (s), 2934 (s), 2867 (s), 1693 (s), 1644 (s), 1600 (s), 1497 (s), 1458 (s), 1418 (s), 1366 (s), 1284 (s), 1245 (s), 1171 (s), 1127 (s), 1021 (s), 911 (s).



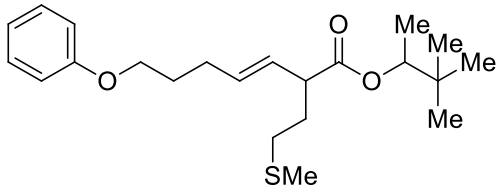
(E)-3-methyl-1-phenyl-3-(5-phenylpent-1-en-1-yl)azetidin-2-one (4.35) compound was isolated as a colorless liquid (129.7 mg, 85% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.41 (d, *J* = 8.1 Hz, 3H), 7.23 – 7.12 (m, 2H), 7.12 – 7.01 (m, 5H), 6.87 (t, *J* = 7.4 Hz, 1H), 5.66 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.36 (d, *J* = 15.6 Hz, 1H), 3.00 (d, *J* = 5.4 Hz, 1H), 2.79 (d, *J* = 5.4 Hz, 1H), 2.44 (t, *J* = 7.6 Hz, 2H), 1.93 – 1.80 (m, 2H), 1.60 – 1.46 (m, 2H), 1.19 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 142.3, 138.6, 131.7, 129.2, 129.1, 128.5, 128.4, 125.8, 123.9, 116.5, 55.4, 52.9, 35.4, 32.2, 30.8, 20.0. GCMS (EI) calculated for $[M]^+$ 305.18 found 305.20. FTIR (neat, cm-1): 3027 (w), 2923 (s), 2848 (s), 1792 (w), 1774 (s), 1739 (s), 1599 (s), 1496 (s), 1387 (s), 1154 (s), 1081 (m), 907 (s), 733 (s).



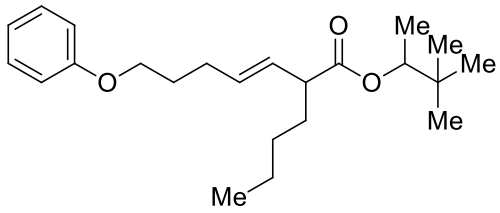
(E)-tert-butyl 2-isopropyl-7-phenoxyhept-3-enoate (4.36) compound was isolated as a colorless liquid (128.9 mg, 81% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.16 – 7.25 (m, 2H), 6.91 – 6.74 (m, 3H), 5.60 (dd, *J* = 15.4, 9.4 Hz, 1H), 5.47 – 5.33 (m, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 8.9 Hz, 1H), 2.22 – 1.91 (m, 4H), 1.69 – 1.54 (m, 2H), 1.38 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 159.2, 132.6, 129.5, 128.3, 120.6, 114.6, 80.2, 67.1, 58.2, 30.9, 29.0, 28.2, 20.8, 19.9. GCMS (EI) calculated for $[M]^+$ 318.22, found 318.20. FTIR (neat, cm-1): 3080 (m), 3026(s), 2970 (s), 2874 (s),1735 (s), 1604 (w), 1453 (s), 1365 (m), 1320 (s), 1226(s), 1177 (s), 1076 (s), 967 (s).



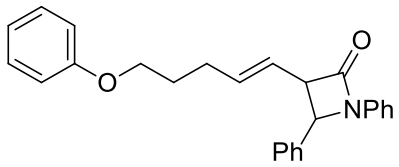
(E)-tert-butyl 2-(2-bromoethyl)-7-phenoxyhept-3-enoate (4.37) compound was isolated as a colorless liquid (149.0 mg, 78% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 6.99 – 6.90 (m, 3H), 5.74 – 5.66 (m, 1H), 5.48 – 5.40 (m, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.46 – 3.32 (m, 2H), 3.20 – 3.11 (m, 1H), 2.31 – 2.21 (m, 3H), 2.06 – 1.98 (m, 1H), 1.94 – 1.85 (m, 2H), 1.47 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 159.1, 133.6, 129.6, 127.4, 120.7, 114.7, 81.0, 67.0, 48.5, 34.9, 31.0, 29.1, 28.9, 28.2. GCMS (EI) calculated for $[M]^+$ 382.11, found 382.20. FTIR (neat, cm-1): 2980 (s), 2934 (s), 1844 (w), 1717 (s), 1700 (m), 1600 (s), 1497 (s), 1456 (w), 1368, (s), 1245 (s), 1153(s) (m), 911 (s).



(E)-3,3-dimethylbutan-2-yl 2-(2-(methylthio)ethyl)-7-phenoxyhept-3-enoate (4.38) compound was isolated as a colorless liquid (145.6 mg, 77% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.15 – 7.04 (m, 2H), 7.00 – 6.85 (m, 3H), 5.60 – 5.33 (m, 2H), 4.83 (q, *J* = 6.4 Hz, 1H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.32 – 3.13 (m, 1H), 2.49 – 2.29 (m, 2H), 2.24 – 2.07 (m, 1H), 2.07 – 1.96 (m, 2H), 1.86 – 1.71 (m, 4H), 1.68 – 1.54 (m, 2H), 1.08 – 1.00 (m, 3H) 0.81 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 173.4, 159.1, 133.1, 133.0, 129.5, 128.1, 128.0, 120.7, 114.6, 77.8, 67.0, 48.5, 49.0, 34.3, 34.2, 31.6, 29.0, 28.9, 25.8, 14.9, 14.8. GCMS (EI) calculated for $[M]^+$ 378.22, found 378.30. FTIR (neat, cm-1): 2968 (m), 2922 (s), 2872 (s), 1717 (s), 1600 (s), 1539 (m), 1496 (s), 1394 (m), 1245 (s), 1712 (m), 1076 (s), 909(s).



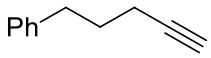
(E)-3,3-dimethylbutan-2-yl 2-butyl-7-phenoxyhept-3-enoate (4.39) compound was isolated as a colorless liquid (158.5 mg, 88% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.15 – 7.12 (m, 2H), 7.00 – 6.65 (m, 3H), 5.66 – 5.39 (m, 2H), 4.86 (q, *J* = 6.4 Hz, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.13 – 2.96 (m, 1H), 2.13 – 1.93 (m, 2H), 1.96 – 1.79 (m, 1H), 1.71 – 1.49 (m, 3H), 1.36 – 1.19 (m, 7H), 1.10 – 1.02 (m, 3H), 0.88 – 0.83 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 174.2, 159.2, 132.0, 131.9, 129.5, 129.3, 129.2, 120.7, 114.7, 77.5, 67.2, 49.9, 34.4, 34.3, 32.4, 32.3, 30.0, 29.5, 29.0, 25.8, 22.6, 15.0, 14.9, 14.0, 14.0. GCMS (EI) calculated for $[M]^+$ 360.27 found 360.30. FTIR (neat, cm-1): 3084(w), 3062 (m), 3026 (s), 2969 (s), 2872 (s), 1732 (s), 1603 (m), 1523 (m), 1453 (s), 1395 (s), 1365 (s), 1320 (w), 1253 (s), 1226 (s), 1177 (s), 1116 (s), 1076 (s), 1053 (s), 967 (s), 747 (s).



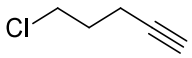
(E)-3-(5-phenoxypent-1-en-1-yl)-1,4-diphenylazetidin-2-one (4.40) compound was isolated as a colorless liquid (137.9 mg, 72% yield). The compound was isolated as a (9:1) mixture of two diastereoisomers, resulted from the two stereogenic centers present in the lactam core. Stereochemistry of the major isomer was not determined. ^{1}H NMR (300 MHz, C_6D_6) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.21 – 7.10 (m, 2H), 7.05 – 6.95 (m, 7H), 6.92 – 6.71 (m, 4H), 5.58 – 5.24 (m, 2H), 4.32 (d, *J* = 2.5 Hz, 1H), 3.67 – 3.40 (m, 3H), 2.11 – 1.97 (m, 2H), 1.68 – 1.49 (m, 2H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 166.1, 159.1, 137.8, 137.6, 135.5, 129.6, 129.3, 129.2, 128.6, 126.0, 124.0, 123.3, 120.7, 117.2, 114.7, 67.0, 63.5, 62.0, 29.2, 28.6. GCMS (EI) calculated for $[M]^+$ 383.19 found 383.20. FTIR (neat, cm-1): 2916 (s), 2848 (m), 1751 (s), 1717 (m), 1662 (m), 1652 (s), 1616 (w), 1599 (s), 1539 (m), 1498 (s), 1464 (m), 1382 (s), 1245 (s), 909 (s), 740 (s).

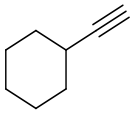
4.4.7 *Alkyne Starting materials*



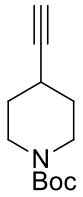
pent-4-yn-1-ylbenzene(4.6) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



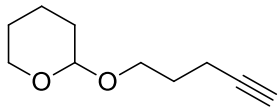
5-chloropent-1-yne(4.S1) was purchased from TCI America and vacuum distilled over calcium hydride before use.



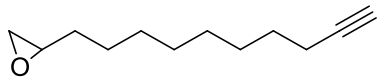
Ethynylcyclohexane(4.S2) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



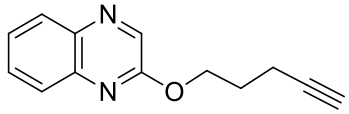
tert-butyl 4-ethynylpiperidine-1-carboxylate(4.S3) was purchased from GSF Chemicals and was used directly.



2-(pent-4-yn-1-yloxy)tetrahydro-2H-pyran(4.S4) has been synthesized by literature procedure and spectral data matches with the literature value. [1]

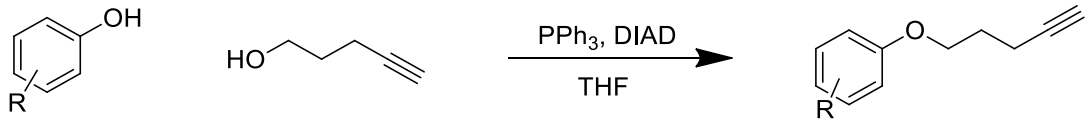


2-(dec-9-yn-1-yl)oxirane(4.S5) has been synthesized by literature procedure and spectral data matches with the literature value.[21]

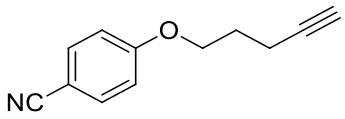


2-(pent-4-yn-1-yloxy)quinoxaline(4.S6) was prepared by literature procedure and has been previously characterized.

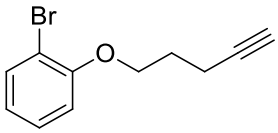
General Method for the Synthesis of alkynes*:*



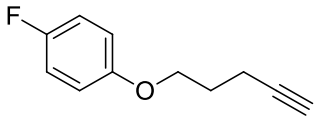
A reaction flask was charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. The flask was then charged with triphenylphosphine (2.2 g, 24.0 mmol, 1.2 equiv), desired phenol (7.7 mmol, 1.1 equiv), THF (14.0 mL, 0.5 M) and 4-pentyn-1-ol (654.0 µL, 7.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C with an ice bath. To the cooled reaction mixture was added DIAD (1.6 mL, 8.4 mmol, 1.2 equiv) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. THF was removed under reduced pressure, and the mixture was suspended in hexanes and stirred vigorously for 30 min. The solid triphenylphosphine oxide was removed by passing the mixture through a plug of celite. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography. Alkynes **4.S7- 4.S13** were prepared using this procedure.



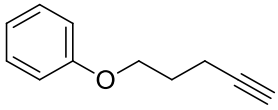
4-(pent-4-yn-1-yloxy)benzonitrile(4.S7) was prepared according to a the general procedure and has been previously characterized.[49]



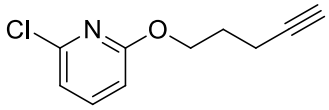
1-bromo-2-(pent-4-yn-1-yloxy)benzene(4.S8) was prepared according to the general procedure and has been previously characterized.[1]



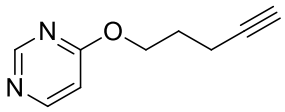
1-fluoro-4-(pent-4-yn-1-yloxy)benzene(4.S9) was prepared according to the general procedure and has been previously characterized.[21]



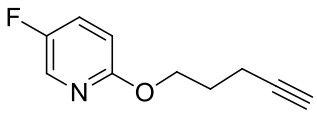
(pent-4-yn-1-yloxy)benzene(4.S10) was prepared according to the general procedure and has been previously characterized.[50]



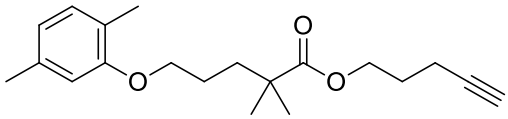
2-chloro-6-(pent-4-yn-1-yloxy)pyridine(4.S11) was prepared according to the general procedure and has been previously characterized.[1]



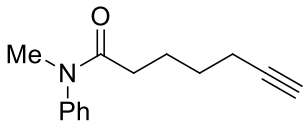
4-(pent-4-yn-1-yloxy)pyrimidine(4.S12) was prepared according to the general procedure and has been previously characterized.[2]



5-fluoro-2-(pent-4-yn-1-yloxy)pyridine(4.S13) was prepared according to the general procedure. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 3.1 Hz, 1H), 7.47 – 7.15 (m, 1H), 6.67 (dd, *J* = 9.0, 3.6 Hz, 1H), 4.33 (t, *J* = 6.2 Hz, 2H), 2.36 (td, *J* = 7.1, 2.7 Hz, 2H), 2.12 – 1.82 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.03, 155.41 (d, *J* = 245.4 Hz), 133.18 (d, *J* = 25.9 Hz), 126.56 (d, *J* = 21.4 Hz), 111.62 (d, *J* = 4.8 Hz), 83.58, 68.90, 64.85, 28.08, 15.34. GCMS (EI) calculated for $[M]^{+}$ 179.09, found 179.10.



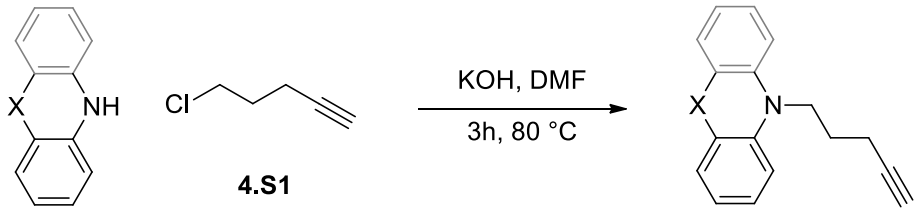
pent-4-yn-1-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate(4.S14) was prepared according to a known procedure and has been previously characterized.[1]



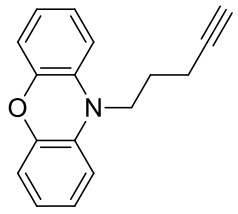
N-methyl-N-phenylhept-6-ynamide(4.S15) was prepared by the general procedure ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 3.18 (s, 3H), 2.13 – 1.92 (m, 4H), 1.82 (t, *J* = 2.7 Hz, 1H), 1.61 (p, *J* = 7.5 Hz, 2H), 1.36 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 172.6, 144.0, 129.6, 127.6, 127.2, 83.9, 68.3, 37.2, 33.3, 27.9, 24.5, 18.0. GCMS (EI) calculated for $[M]^+$ 215.13, found 215.20. FTIR (neat, cm-1): 3306 (s), 2941 (s), 2856 (s), 2249 (s), 1726 (w), 1641 (s), 1595 (s), 1496 (s), 1389 (s), 1292 (m), 1123 (s), 908 (s).

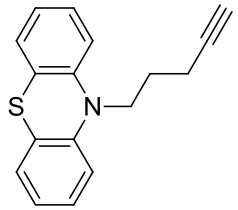
General Method for the Synthesis of alkynes:



A reaction flask was charged with a stir bar, KOH (560.0 mg, 10.0 mmol, 2.0 equiv), and DMF (10 mL). The amine (5.0 mmol, 1.0 equiv) was added to the flask and stirred for 2 minutes at room temperature. Chloro alkyne, XX(600.0 mg, 6.0 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was allowed to stir at 80 °C for 3 hours. After 3 hours, the flask was cooled to room temperature, and water (50 mL) was added to the reaction mixture. The product was extracted with ether (3 times, 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. Alkynes **S16-S18** were prepared using this procedure.

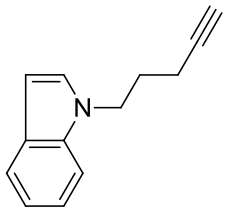


10-(pent-4-yn-1-yl)-10H-phenoxazine(4.S16) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.14 – 6.97 (m, 2H), 6.98 – 6.88 (m, 4H), 6.81 (d, *J* = 7.9 Hz, 2H), 3.90 (t, *J* = 7.9 Hz, 2H), 2.60 (td, *J* = 6.7, 2.6 Hz, 2H), 2.36 (t, *J* = 2.6 Hz, 0H), 2.28 – 1.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 123.7, 121.0, 115.5, 111.3, 83.1, 69.7, 42.7, 23.5, 16.0. GCMS (EI) calculated for $[M]^+$ 249.12, found 249.20. FTIR (neat, cm-1): 3305 (s), 3067 (s), 2960 (s), 2903 (s), 2251 (s), 1628 (s), 1592 (s), 1490 (s), 1380 (s), 1272 (s), 1130 (s), 908 (s).

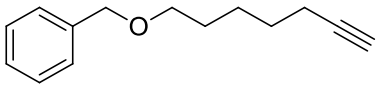


10-(pent-4-yn-1-yl)-10H-phenothiazine(4.S17) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 4H), 6.97 – 6.83 (m, 4H), 4.01 (t, *J* = 6.8 Hz, 2H), 2.34 (td, *J* = 6.9, 2.6 Hz, 2H), 2.09 – 1.98 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 127.5, 127.3, 125.3, 122.6, 115.5, 83.5, 69.2, 45.9, 25.6, 15.9. GCMS (EI) calculated for $[M]^+$ 265.09, found 265.20. FTIR (neat, cm-1): 3306 (s), 3068 (s), 2927 (s), 2250 (s), 1592 (m), 1571 (m), 1459 (s), 1443 (s), 1341 (m), 1285 (s), 1252 (s), 908 (s).

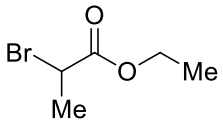


1-(pent-4-yn-1-yl)-1H-indole(4.S18) was prepared according to the general procedure and has been previously characterized.[51]



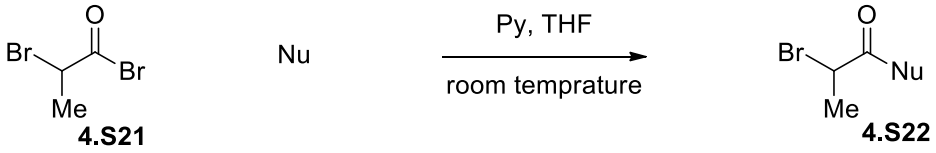
((hept-6-yn-1-yloxy)methyl)benzene(4.S19) was prepared according to a known procedure and has been previously characterized.[52]

4.4.8 *Alkyl Bromide Starting Material:*

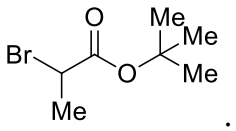


ethyl 2-bromopropanoate(4.S20) was purchased from sigma and vacuum distilled over calcium hydride before use.

Alkyl Bromide Starting Material:



A reaction flask was charged with a stir bar, flame-dried under vacuum, and allowed to cool under nitrogen. The flask was then charged with 2-bromopropanoyl bromide, **4.S21** (2.1 g, 10 mmol, 1 equiv), and THF (50 mL). The flask was cooled to 0 °C in an ice bath nucleophile (15 mmol, 1.5 equiv) and pyridine (1.6 g, 20 mmol, 2.0 equiv) were added, respectively. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then filtered through a plug a celite and concentrated under reduced pressure. The crude product was purified by silica gel chromatography. Compounds **4.S22-4.S30** were prepared using this procedure.



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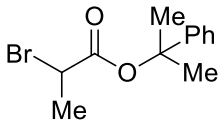
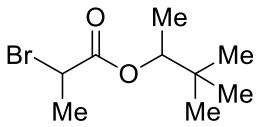
tert-butyl 2-bromopropanoate(4.S22) was prepared according to the general procedure . The spectral data matches with the literature value.[53]



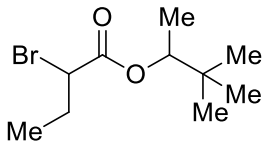
2-phenylpropan-2-yl 2-bromopropanoate(4.S23) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 3H), 7.49 – 7.30 (m, 2H), 4.44 (q, *J* = 6.9 Hz, 1H), 2.04 – 1.79 (m, 9H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 168.2, 145.0, 128.3, 127.2, 124.2, 83.2, 41.5, 28.3, 28.1, 21.5. GCMS (EI) calculated for $[M]^+$ 270.09, found 270.20. FTIR (neat, cm-1):3088 (m), 3061 (s), 3027 (m), 2981 (s), 2930 (s), 2870 (m), 1740 (s), 1496 (s), 1468 (s), 1448 (s), 1366 (s), 1340 (s), 1273 (s), 1226 (s), 1168 (s), 1135 (s), 1101 (s), 1053 (s), 1030 (s), 985 (s).



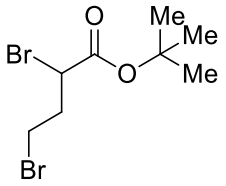
3,3-dimethylbutan-2-yl 2-bromopropanoate(4.S24) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.73 (q, *J* = 6.4 Hz, 1H), 4.37 (q, *J* = 6.9 Hz, 1H), 1.82 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.94 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.54, 169.52, 79.36, 79.31, 40.95, 40.60, 34.47, 34.29, 25.64, 21.83, 21.64, 14.64, 14.36. GCMS (EI) calculated for $[M]^+$ 236.04, found 236.10. FTIR (neat, cm-1): 2960 (s), 2873 (s), 1736 (s), 1466 (m), 1378 (m), 1270 (s), 1231 (m), 1157 (s).

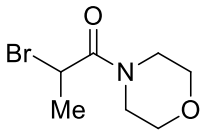


3,3-dimethylbutan-2-yl 2-bromobutanoate(4.S25) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.70 (q, *J* = 6.4 Hz, 1H), 4.17 – 4.06 (m, 1H), 2.18 – 1.88 (m, 2H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.04 – 0.95 (m, 3H), 0.94 – 0.87 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.21, 169.1, 79.4, 48.4, 48.3, 34.4, 34.3, 28.6, 28.4, 25.7, 25.7, 14.7, 14.5, 11.9. GCMS (EI) calculated for $[M]^+$ 250.06, found 250.10.

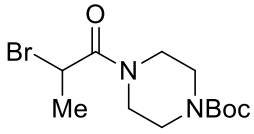
FTIR (neat, cm-1): 2972 (s), 2912 (m), 2876 (m), 1730 (s), 1460 (s), 1367 (s), 1264 (s), 1211 (m), 1163 (s), 1075 (s).



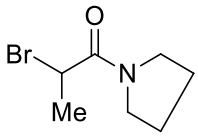
tert-butyl 2,4-dibromobutanoate(4.S26) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.45 – 4.30 (m, 1H), 3.59 – 3.43 (m, 2H), 2.58 – 2.27 (m, 2H), 1.57 – 1.40 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 83.2, 56.5, 45.6, 37.2, 27.9. . GCMS (EI) calculated for $[M]^+$ 299.94, found 300.10. FTIR (neat, cm-1): 2972 (s), 2933 (m), 1730 (s), 1370 (s), 1315 (s), 1246 (s), 1151 (s).



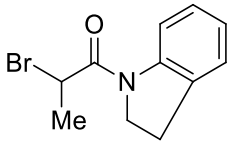
2-bromo-1-morpholinopropan-1-one(4.S27) was prepared according to the general procedure. The spectral data matches with the literature value.[54]



tert-butyl 4-(2-bromopropanoyl)piperazine-1-carboxylate(4.S28) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.53 (q, *J* = 6.5 Hz, 1H), 3.84 – 3.15 (m, 8H), 1.82 (d, *J* = 6.5 Hz, 3H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 154.6, 80.5, 46.0, 42.3, 38.0, 28.5, 21.7. GCMS (EI) calculated for $[M]^+$320.07, found 320.10. FTIR (neat, cm-1): 3053 (a), 2980 (s), 2929 (s), 2864 (s), 1693 (s), 1651 (s), 1447 (s), 1414 (s), 1374 (s), 1345 (s), 1316 (s), 1246 (s), 1154 (s).

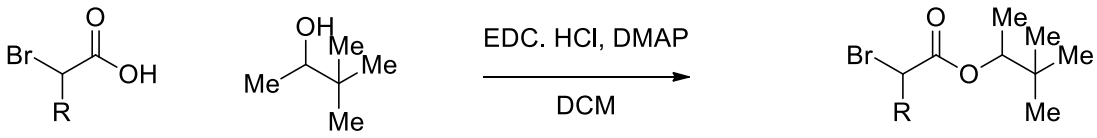


2-bromo-1-(pyrrolidin-1-yl)propan-1-one(4.S29) was prepared according to the general procedure. The spectral data matches with the literature value.[55]



2-bromo-1-(indolin-1-yl)propan-1-one(4.S30) was prepared according to the general procedure. The spectral data matches with the literature value.[54]

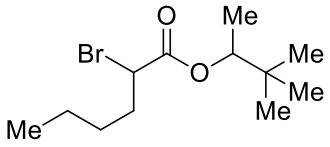
General Procedure for the synthesis of alkyl bromides:



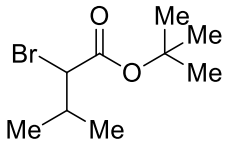
A reaction flask charged with stir bar was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with 2-bromohexanoic acid, (1.94 g, 10 mmol, 1 equiv) and DCM (30 mL). The flask was placed in a 0 ^{o}C bath and allowed to cool down. The nucleophile (12 mmol, 1.5 equiv) and pyridine (1.6 g, 20 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 hours. After 12 hours, the reaction mixture

was filtered through a plug a celite, concentrated under reduced pressure. The crude product was purified by silica gel chromatography

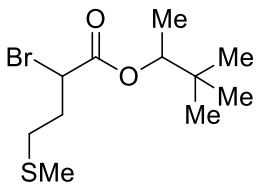
Bromoesters **4.S31-4.S33** were prepared according to the general procedure (method 4).



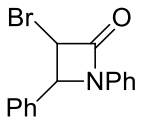
3,3-dimethylbutan-2-yl 2-bromohexanoate(4.S31) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.81 – 4.61 (m, 1H), 4.29 – 4.07 (m, 1H), 2.13 – 1.86 (m, 2H), 1.51 – 1.25 (m, 4H), 1.23 – 1.08 (m, 3H), 1.02 – 0.87 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 79.3, 46.6, 34.7, 34.5, 29.5, 25.7, 22.1, 14.7, 13.8. GCMS (EI) calculated for $[M]^+$ 278.09, found 278.10. FTIR (neat, cm-1): 2960 (s), 2912 (s), 2870 (s), 1735 (s), 1466 (s), 1378 (s), 1270 (s), 1231 (s), 1147 (m).



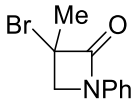
tert-butyl 2-bromo-3-methylbutanoate(4.S32) was prepared according to the general procedure. The spectral data matches with the literature value.[56]



3,3-dimethylbutan-2-yl 2-bromo-4-(methylthio)butanoate(4.S33) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (q, *J* = 6.4 Hz, 1H), 4.53 – 4.35 (m, 1H), 2.72 – 2.52 (m, 2H), 2.40 – 2.11 (m, 2H), 2.12 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.94 – 0.89 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.04, 168.95, 79.77, 45.19, 45.04, 34.55, 34.38, 34.12, 33.97, 31.55, 30.43, 25.75, 15.55, 15.51, 14.79. GCMS (EI) calculated for $[M]^+$ 296.04, found 296.10.



3-bromo-1,4-diphenylazetidin-2-one(4.S34) the compound was prepared according to the known procedure. The spectral data matches with the literature value.[57]



3-bromo-3-methyl-1-phenylazetidin-2-one(4.S35) was prepared according to the literature procedure. The spectral data matches with the literature value.[58]

4.4.9 *Cyclic Voltammetry Experiments:*

Cyclic voltammetry was conducted using an Interface 1010B potentiostat by Gamry. A three-electrode voltametric cell setup was used with a glassy carbon disk working electrode, a platinum wire counter electrode, and a silver-wire pseudo-reference electrode. All potentials were referenced to the $Fc^{0/+}$ redox couple by adding a small amount of ferrocene after each

measurement. All electrochemical measurements were conducted under a dinitrogen atmosphere, at 25 °C. IPrCuCl exhibits a poorly reversible Cu(I/II) redox couple with a half-wave potential of $E_{1/2}$ = 0.858 V vs $Fc^{0/+}$, whereas the alkenyl intermediate **4.3** exhibits an irreversible oxidation ($E_{p,a}$ = 0.44 V vs $Fc^{0/+}$)[59]. This irreversibility is likely due to structural/chemical changes that are incurred upon conversion to Cu(II).

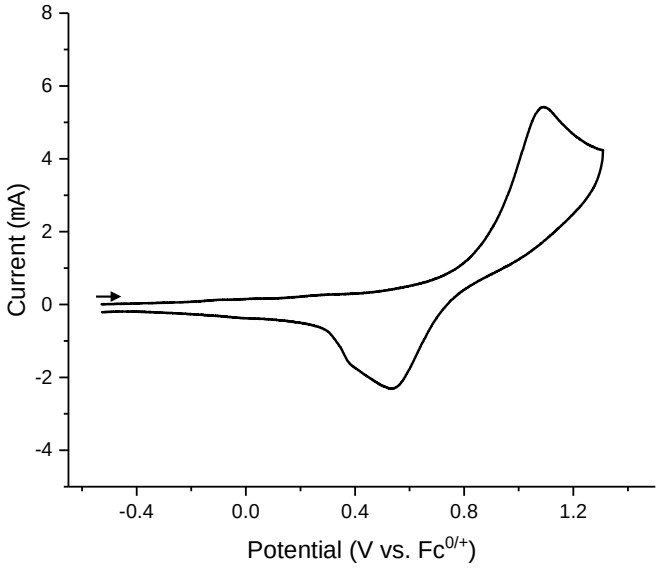


Figure 4.1. Cyclic voltammogram of IPrCuCl recorded with a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ DCM and referenced to ferrocene.

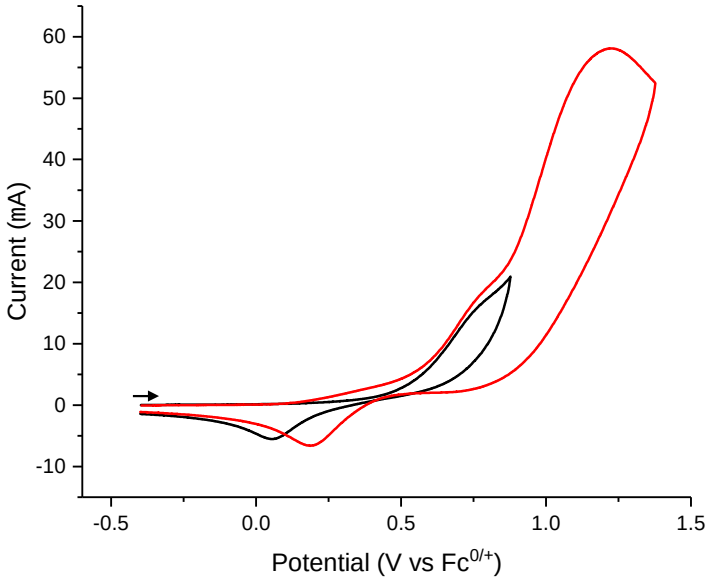


Figure 4.2. Cyclic voltammograms of IPrCuCl recorded within two different potential windows (black and red) with a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ MeCN and referenced to ferrocene. Note that it is difficult to definitively assign the Cu(I/II) oxidation as the first or second feature in the anodic scans, however, we have tentatively assigned it as the second, more intense feature as this is occurs at a similar potential to the oxidation in DCM.

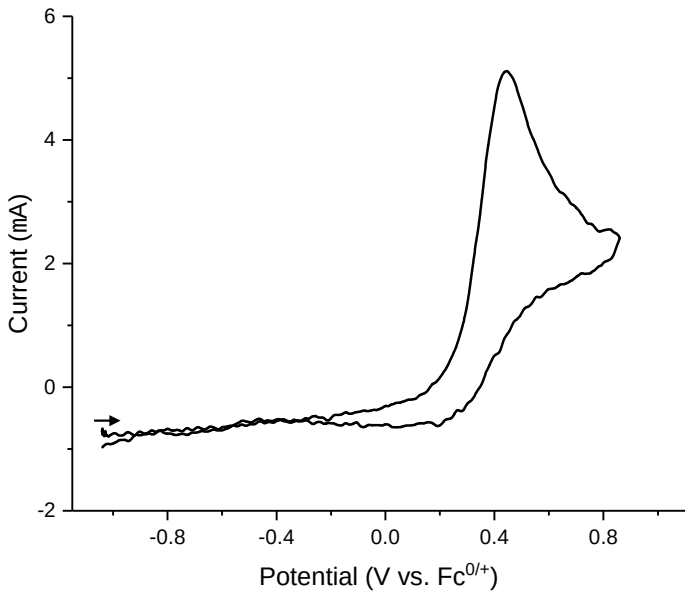


Figure 4.3 Cyclic voltammogram of the alkenyl intermediate **4.3** recorded with a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ DCM and referenced to ferrocene.

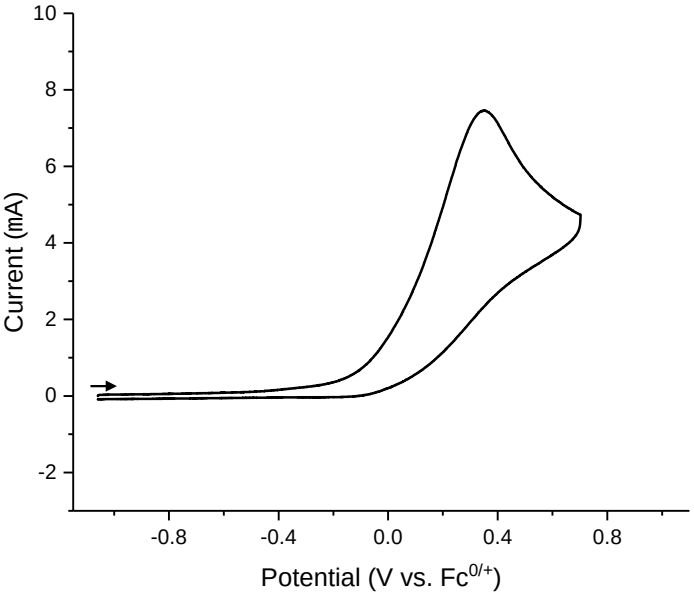


Figure 4.4. Cyclic voltammogram of the alkenyl intermediate **4.3** recorded with a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ THF and referenced to ferrocene.

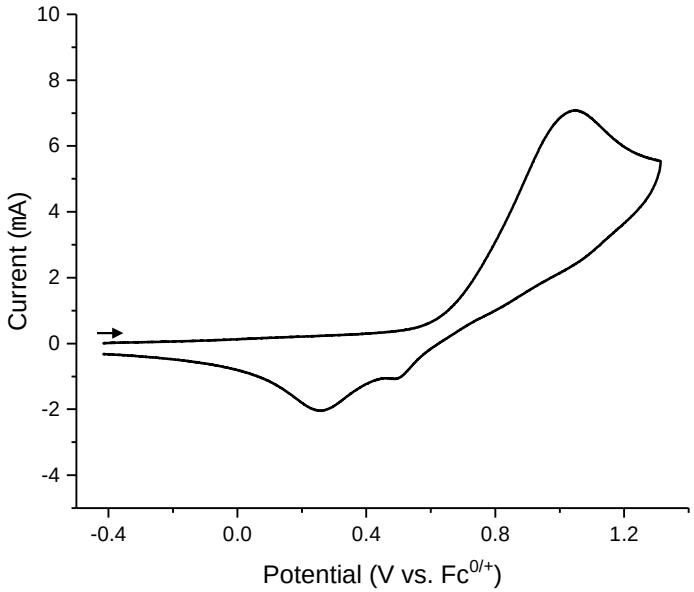


Figure 4.5. Cyclic voltammogram of IPrCuBr recorded at a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ DCM and referenced to ferrocene.

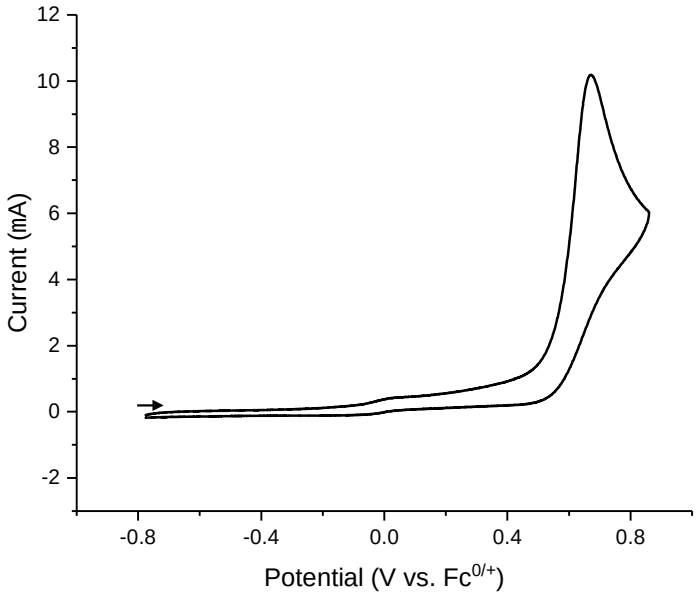


Figure 4.6. Cyclic voltammogram of IPrCuO*t*-Bu) recorded at a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ DCM and referenced to ferrocene.

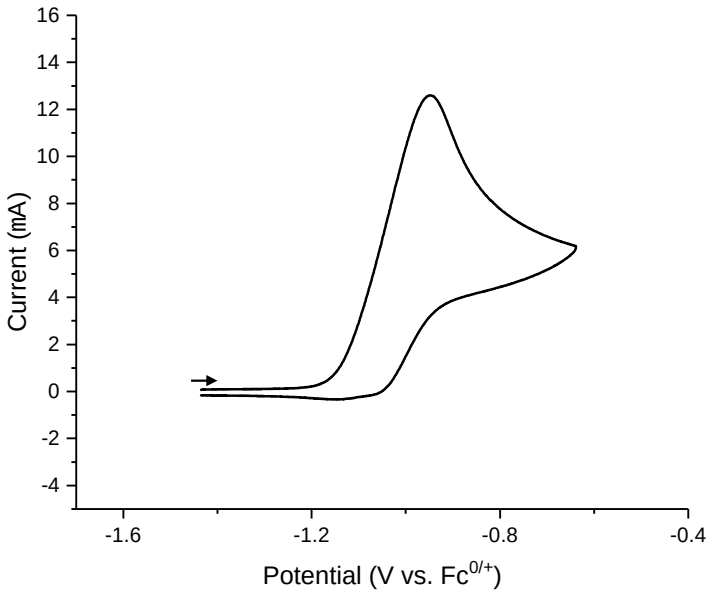


Figure 4.7. Cyclic voltammogram of IPrCuH recorded at a scan rate of 50 mV/s . in 0.1 M $TBAPF_6$ THF and referenced to ferrocene. This compound was generated *in situ* via treatment of IPrCuO*t*-Bu) with $(EtO)_3SiH$, and rapidly decomposed in dichloromethane. Note that $(EtO)_3SiH$ exhibits no redox events on its own when analyzed in 0.1 M $TBAPF_6$ THF.

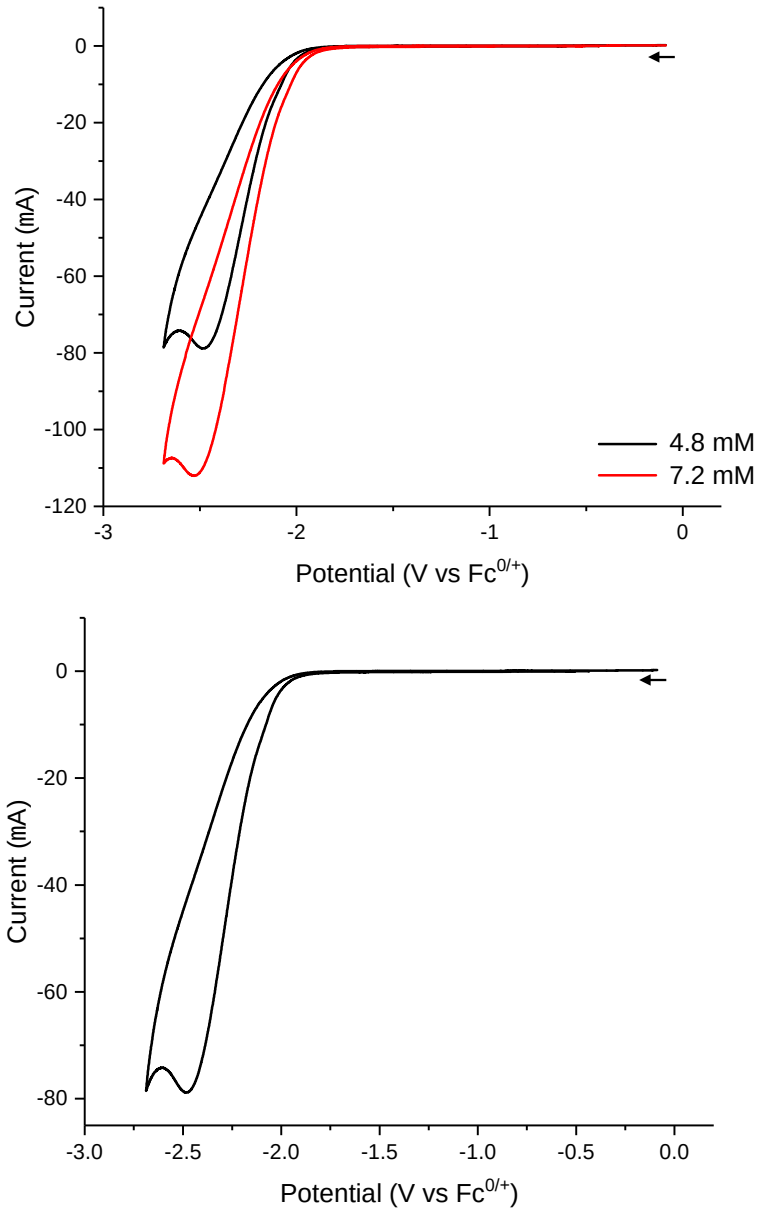


Figure 4.8. Cyclic voltammograms of ethyl 2-bromopropionate recorded at two different concentrations with a scan rate of 50 mV/s in 0.1 M $TBAPF_6$ DCM and referenced to ferrocene.

Table 4.12. Anodic peak potentials ($E_{p,a}$) of IPrCuCl and the alkenyl intermediate **4.3** and the cathodic peak potential ($E_{p,c}$) of ethyl 2-bromopropionate, as well as their open circuit potentials (OCP) recorded in 0.1 M $TBAPF_6$ DCM[a], THF[b], or MeCN[c] with a scan rate of 50 mV/s.

IPrCuCl	**Alkenyl copper (4.3)**	ethyl 2-bromopropionate
$E_{p,a}$ (V vs $Fc^{0/+}$)		$E_{p,c}$ (V vs $Fc^{0/+}$)
1.12[a]; 1.22[c]	0.44[a]; 0.34[b]	–2.44[a]
$E_{p,a}$ (V vs SCE)		$E_{p,c}$ (V vs SCE)
1.58[a]; 1.68[c]	0.90[a]; 0.90[b]	–2.04[a]
OCP (V vs $Fc^{0/+}$)		
–0.53[a]; –0.42[c]	–1.04[a]; –1.06[b]	–0.44[a]

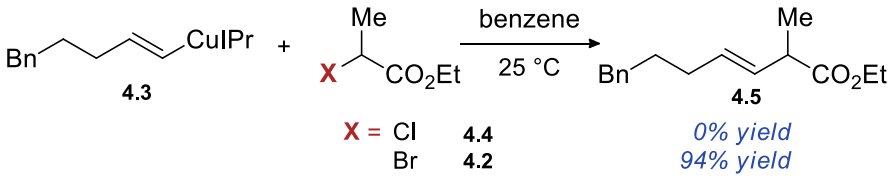
[a] $Fc^{0/+}$ = 0.46 V vs SCE in 0.1 M $TBAPF_6$ DCM. [b] $Fc^{0/+}$ = 0.56 V vs SCE in 0.1 M $TBAPF_6$ THF. [c] $Fc^{0/+}$ = 0.40 V vs SCE in 0.1 M $TBAPF_6$ MeCN.

Table 4.13. Anodic peak potentials ($E_{p,a}$) of IPrCuBr, IPrCu(O^tBu), and IPrCuH, as well as their open circuit potentials (OCP) recorded in 0.1 M $TBAPF_6$ DCM[a] or THF[b] with a scan rate of 50 mV/s.

IPrCuBr	IPrCu(O^tBu)	IPrCuH
	$E_{p,a}$ (V vs $Fc^{0/+}$)	
1.05[a]	0.67[a]	–0.95[b]
	$E_{p,a}$ (V vs SCE)	
1.51[a]	1.13[a]	–0.39[b]
	OCP (V vs $Fc^{0/+}$)	
–0.42[a]	–0.76[a]	–1.44[b]

[a] $Fc^{0/+}$ = 0.46 V vs SCE in 0.1 M $TBAPF_6$ DCM. [b] $Fc^{0/+}$ = 0.56 V vs SCE in 0.1 M $TBAPF_6$ THF.

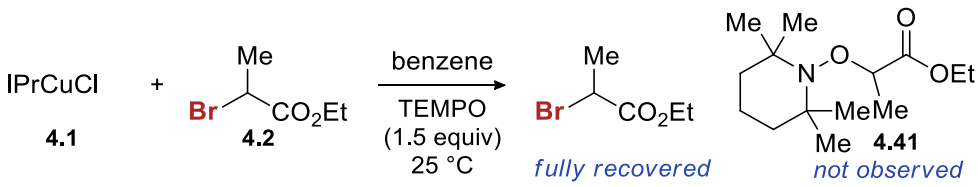
4.4.10 *Reaction of IPrCuCl catalyst with α-bromo esters (Scheme 4a):*



Alkenyl copper complex **4.3** was prepared from a known literature procedure and has been previously characterized.[60]

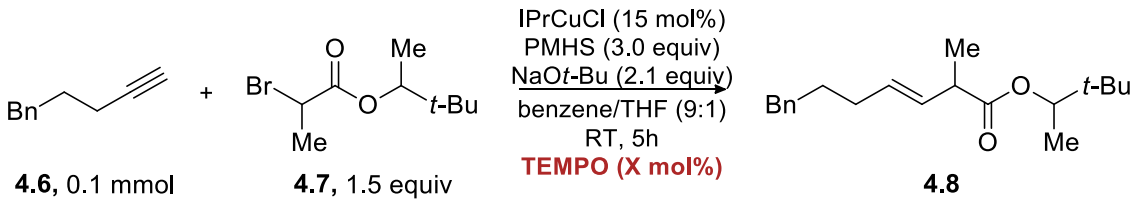
In a nitrogen-filled glovebox, a stock solution of alkenyl copper complex **4.3** (298.6 mg, 0.5 mmol) and internal standard (trimethoxybenzene (TMB)) in 2000 µL benzene was prepared. A 400 µL aliquot of the alkenyl copper/TMB stock solution was added to a dram vial charged with a stir bar. The α-halo ester (0.150 mmol, 1.5 equiv) was added with 600 µL of benzene. The reaction mixture was stirred at 25 °C for 12 hours. A 20 µL aliquot was taken at the end of 12 hours. The aliquot was diluted with 500 µL EtOAc and filtered through a silica gel plug with 1000 µL EtOAc before GC analysis.

4.4.11 *Reaction of IPrCuCl catalyst with α-bromo esters (Scheme 4a):*



In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuCl (**4.1)** (48.7 mg, 0.1 mmol, 1.0 equiv), and internal standard (TMB). Ethyl 2-bromopropionate **4.2** (18.1 mg, 0.1 mmol, 1.0 equiv) and TEMPO (23.4 mg, 0.15 mmol, 1.5 equiv) was transferred to the reaction mixture using 0.5 mL of benzene each. The reaction mixture was stirred at room temperature for 12 hours. After 12 hours, a 20 µL aliquot was taken and passed through a plug of silica with ethyl acetate. GC analysis of the aliquot indicated full recovery of Ethyl 2-bromopropionate **(4.2),** and no formation of the tempo adduct **(4.41)** was observed. The control experiment with ethyl 2-propionate **(2)** and TEMPO also resulted in full recovery of the bromo-ester.

4.4.12 *Radical trap probe (Scheme 5a):*



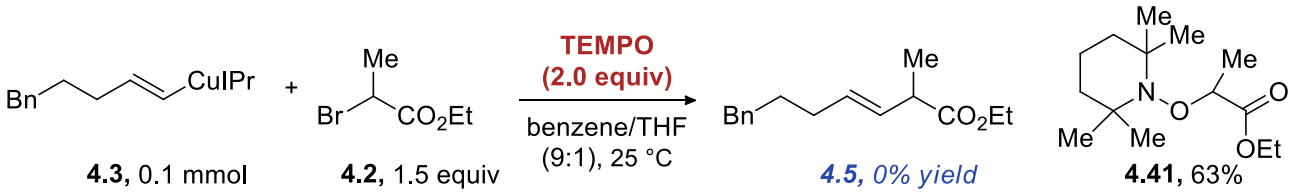
4.6, 0.1 mmol **4.7**, 1.5 equiv **4.8**

In a nitrogen-filled glovebox, a stock solution of phenylpentyne **(4.6)** (144.2 mg, 1.0 mmol) and internal standard (TMB) in 1000 µL benzene/THF (9:1) was prepared. A stock solution of PMHS (180 mg, 3.0 mmol) in 1000 µL benzene/THF (9:1) was also prepared. A dram vial was charged with a stir bar, NaO*t*-Bu (20.2 mg, 0.21 mmol, 2.1 equiv), IPrCuCl (7.4 mg, 0.015 mmol, 0.15 equiv) and benzene/THF (9.1) (0.5 mL). 100 µL of the PMHS stock solution and 100 µL of the phenylpentyne **(4.6)**/TMB stock solution were added to this solution sequentially. The reaction mixture was then stirred at 25 °C until the yellow color disappeared. α-bromo ester **4.7** (31.5 mg, 0.15 mmol, 1.5 equiv) and required amount of TEMPO were transferred to the reaction mixture with 0.3 mL of benzene/THF(9:1) each. After 5 hours, a 20 µL aliquot from the reaction mixture was passed through a plug of silica with ethyl acetate, and analyzed by GC. Table S15 shows the product yield with different amount of TEMPO.

Table 4.14 Radical trap probe:

Entry	mol % of TEMPO	Yield of 4.8 (%)
1	0	81
2	20	15
3	150	0

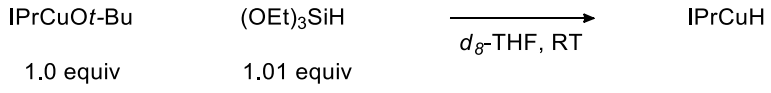
4.4.13 *Stochiometric experiment with TEMPO:*



4.3, 0.1 mmol **4.2**, 1.5 equiv ***4.5**, 0% yield* **4.41**, 63%

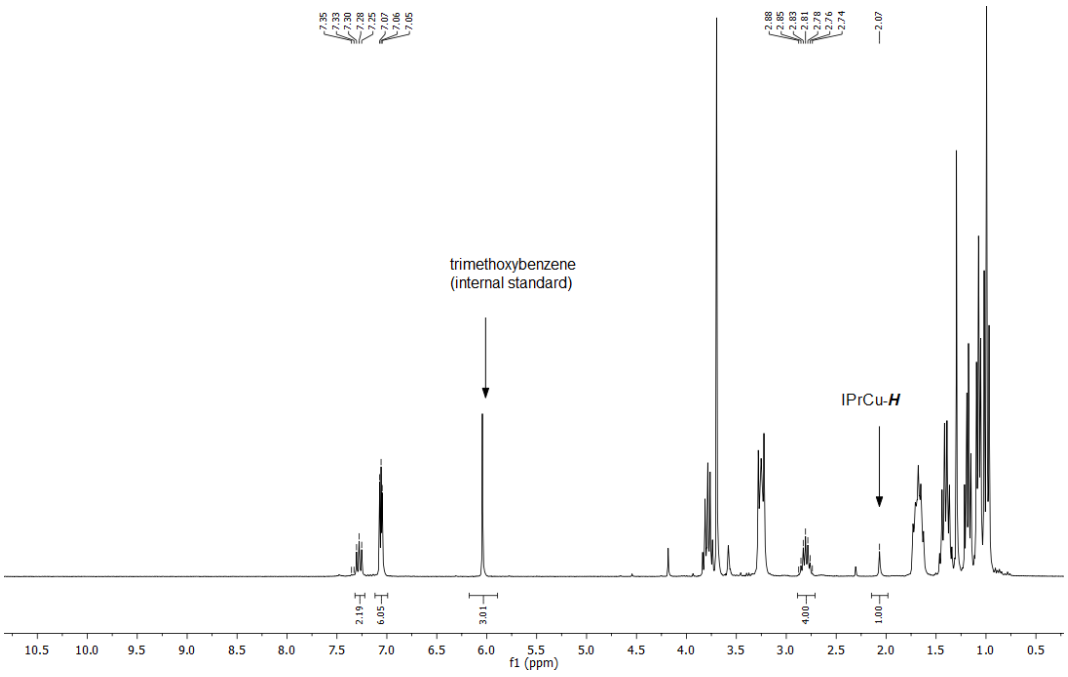
In a nitrogen-filled glovebox, a stock solution of alkenyl copper complex **4.3** (298.6 mg, 0.5 mmol) and internal standard (TMB) in 2000 µL benzene/THF (9:1) was prepared. A 400 µL aliquot of the alkenyl copper/TMB stock solution was added to dram vial charged with a stir bar. α-Bromo ester **4.2** (27.1 mg, 0.150 mmol, 1.5 equiv) and TEMPO (31.2 mg, 0.2 mmol, 2.0 equiv) were transferred to this solution using 300 µL of benzene/THF (9:1) each. The reaction mixture was stirred at 25 °C for 5 hours. After 5 hours, a 20 µL aliquot from the reaction mixture was passed through a plug of silica with ethyl acetate and analyzed by GC-FID/MS. The rest of the reaction mixture was filtered through a pad of silica gel and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography. Compound **4.41** was isolated as an oily liquid. The spectral data matches the literature values.[61]

4.4.14 *The reaction between IPrCuO*t*-Bu and triethoxysilane in the presence of $TBAPF_6$ to generate PrCuH:*



In a glove box, a NMR tube was charged with IPrCuO*t*-Bu (1.0 equiv, 10.5 mg, 0.02 mmols), $TBAPF_6$ (12 mg, this electrolyte was used in the CV experiment and is unreactive with silane and IPrCuO*t*-Bu), internal standard (trimethoxybenzene, TMB) and d_8-THF (0.4 mL). The NMR tube was fitted into a Cajon assembly, pumped out of the glove box, and placed on the manifold using standard Schlenk techniques. Separately, a solution of triethoxysilane (5.8 µL, 0.03 mmol, 1.5 equiv) in d_8-THF (0.2 mL) was prepared and taken up by a gas-tight syringe. The NMR tube was frozen using liquid nitrogen, and the solution of triethoxysilane was added to the NMR tube. The NMR tube was sealed under vacuum and kept frozen using liquid nitrogen. The frozen NMR tube was quickly warmed using a water bath, dried with a tissue, and placed in the NMR probe (probe operating temperature = 298 K). IPrCuO*t*-Bu was fully converted to IPrCuH within 3 minutes of mixing. The NMR experiment shows a newly formed peak at a chemical shift of 2.07 ppm upon mixing the triethoxysilane and IPrCuOt-Bu, which we assign as the Cu-H peak in IPrCuH. This chemical shift is within the range of literature value. (2.62 ppm in C_6D_6[62]).

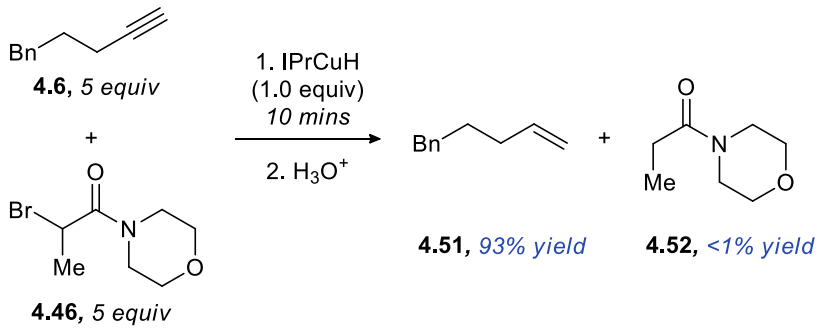
NMR trace of the reaction between IPrCuOt-Bu and triethoxysilane in the presence of $TBAPF_6$ to generate PrCuH:



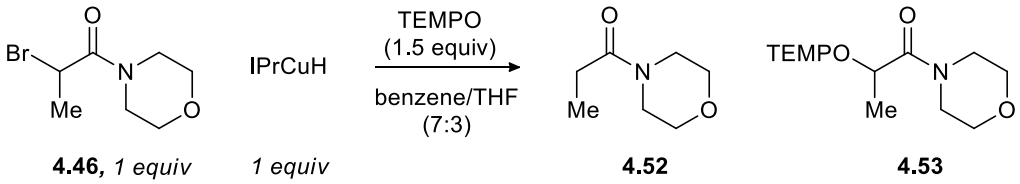
4.4.15 *Competition experiment between alkyne (4.6) and α-bromo amide with IPrCuH:*

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuO*t*-Bu (21.0 mg, 0.04 mmol, 1 equiv), internal standard (trimethoxybenzene, TMB), and 500 µL benzene/THF (7:3). Triethoxysilane (7.4 µL, 0.042 mmol, 1.05 equiv) was added to the dram vial, resulting in bright orange color. The reaction mixture was stirred at 25 °C for 15 seconds. After the indicated time, a mixture of phenylpentyne **(4.6)** (28.8 mg, 0.2 mmol, 5.0 equiv), and α-bromo amide **(4.46)** (44.2 mg, 0.2 mmol, 5.0 equiv) was transferred to the dram vial using 500 µL benzene/THF (7:3).. The reaction mixture was stirred at room temperature for 10 minutes. After 10 minutes, 50 µL aliquot was taken and was diluted with a 500 µL of 1:1 mixture of 0.1 M HCl and ether. The ether layer

was pipetted onto a silica plug and rinsed through with 1500 µL of EtOAc and analyzed by GC. GC analysis indicates 93% formation of the alkene **(4.51)** and less the 1% of the reduced α-bromo amide **(52).**



4.4.16 *Reduction of with α-bromo amide with IPrCuH:*



In a nitrogen-filled glovebox, a stock solution of α-bromo amide **(4.46)** (44.2 mg, 0.2 mmol), and TEMPO (46.8 mg, 0.3 mmol) in 2000 µL benzene/THF (7:3) was prepared. A dram vial was charged with a stir bar, IPrCuO*t*-Bu (21.0 mg, 0.04 mmol, 1 equiv), internal standard (trimethoxybenzene, TMB) and 600 µL benzene/THF (7:3) (500 µL). Triethoxysilane (7.3 µL, 0.042 mmol, 1.05 equiv) was added to the dram vial, resulting in bright orange color. The reaction mixture was stirred at 25 °C for 30 s. 400 µL stock solution of the mixture of α-bromo amide **(4.46)** (1.0 equiv) and TEMPO (1.5 equiv) was transferred to the dram vial.. The reaction mixture was stirred at room temperature for 24 hours. At different time intervals, 50 µL aliquots were taken,

and the aliquots were diluted with a 500 µL of 1:1 mixture of 0.1 (M) HCl and ether. The ether layer was pipetted onto a silica plug and rinsed through with 1500 µL of EtOAc and analyzed by GC. The result of this experiment is shown in table S11.

Table 4.15 reduction of with α-bromo amide with IPrCuH:

Entry	Time (mins)	Yield of 52	Yield of 4.53	Unreacted 4
1	10	<1	Not observed	86
2	1440 (24h)	66	Not observed	6

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VITA

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