Transition Metal Catalyzed Hydrofunctionalization of Alkynes via 1,2-Boronate Rearrangements

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Abstract

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Hydrofunctionalization of alkynes has emerged as a useful synthetic strategy to build molecular diversity from simple and commercially available starting materials. Utilizing transition metal catalysis different regio and stereochemical products can be synthesized, providing access to *E*-, *Z*-, and 1-1 disubstituted alkenes with high selectivity and broad functional group tolerance. Herein we describe two new selective transition metal catalyzed hydroalkylations of terminal alkynes, to form alkenes with valuable allylic functionality.

The first reaction, described in chapter 1, is the hydroalkylation of terminal alkynes to furnish *E*-allylic alcohols. This transformation proceeds through a highly regio- and

diastereoselective hydrocupration followed by the addition of the reactive alkenyl copper species to an α-halo boronic ester. The proposed mechanism proceeds through the formation of a boronate species that undergoes a stereospecific 1,2-metalite shift to give the allylic boronic ester, which is oxidized with stereochemical inversion to the corresponding alcohol. This method also allows for the selective synthesis of chiral allylic alcohols, from enantioenriched α-halo boronic esters**.**

Following this development, chapter 2 describes the synthesis of *Z*-Michael acceptors via hydroalkylation of conjugated alkynes. The reaction proceeds through the formation of silver acetylide followed by the addition to an alkyl borane species to form the corresponding boronate. This undergoes a stereospecific 1,2-metalite shift, which provides the excellent *Z*-selectivity for the reaction. This method is the first reported *Z*-selective hydroalkylation of conjugated terminal alkynes. The reaction provides access to (*Z*)-α,β-unsaturated esters, amides and ketones, with broad functional group compatibility and tolerance for α-branched boranes, yielding products that are challenging to synthesize via other methods. Key to the development of this reaction was the use of weak inorganic bases. The low solubility of these bases in hydrocarbon solvents limits their effective concentration, suppressing undesired side reactions.

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Ar	aryl
B	base
Bn	benzyl
Boc	tert-butyloxycarbonyl
C	Celsius
Cat	catalyst
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMEDA	1,2-dimethylethylenediamine
DME	dimethoxyethane
DMF	dimethylformamide
DMMS	dimethoxydimethylsilane
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
HPLC		high pressure liquid chromatography
Hz		hertz
IMes		1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr		1,3-bis-(2,6-diisopropylphenyl)imidazolium
i-Pr		isopropyl
IR		infrared
KIE		kinetic isotope effect
L		ligand
M		metal
Me		methyl
min		minutes
mol		mole
MS		mass spectrometry
MTPA		α-methoxy-α-trifluoromethylphenylacetic acid
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
OTf		trifluoromethanesulfonate
PC		photo catalyst
Ph		phenyl
pin		pinacol
Pnth		phthalimide
PMHS		polymethylhydrosiloxane
ppb		parts per billion
ppm		parts per million
PyBox		pyridine bisoxazoline
rac		racemic
Rf		retention factor
SET		single electron transfer
SIPr		1,3-bis-(2,6-diisopropylphenyl)imidazolinium
SN2		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
TM		transition metal

TMB	1,3,5-trimethoxybenzne
TMCTS	2,4,6,8-tetramethylcyclotetrasiloxane
TMDSO	tetramethyldisiloxane
TMPDA	N,N,N',N'-Tetramethyl-p-phenylenediamine
TMS	trimethylsilyl
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

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DEDICATION

In honor of Bev, my first teacher.

CHAPTER 1

STEREOSPECIFIC AND REGIOSELECTIVE SYNTHESIS OF *E*-ALLYLIC ALCOHOLS THROUGH REDUCTIVE CROSS COUPLING OF TERMINAL ALKYNES

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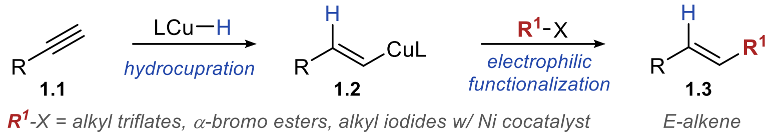
1.1. INTRODUCTION

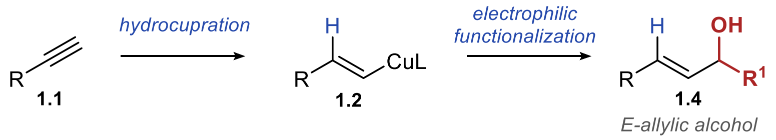
Hydroalkylation of terminal alkynes is a powerful method for making disubstituted alkenes with different substitution patterns and high selectivity.[1-9] Our group has developed several catalytic hydroalkylation reactions that produce *E*-alkenes using an approach with two key steps (Scheme 1.1a): first, hydrocupration of an alkyne[10,11] (**1.1**) forms an alkenyl copper intermediate (**2.1**) with precise control over the regio- and diastereoselectivity;[12-18] second, the alkenyl copper intermediate stereospecifically reacts with various alkyl electrophiles, such as alkyl triflates,[6] α-halo carbonyls,[8] or alkyl halides in the presence of a metal cocatalyst to yield *E*-alkene products (**3.1**).[7] The successful implementation of this strategy requires identifying alkyl electrophiles that are sufficiently reactive to overcome the relatively low reactivity of alkenyl copper complexes, but do not react with copper hydride complexes.

Scheme 0.1 Hydrocupration in Transformations of Terminal Alkynes

a) Hydrocupration of Terminal Alkynes in Synthesis of *E*-Alkenes



b) Hydrocupration of Terminal Alkynes in Synthesis of *E*-Allylic Alcohols

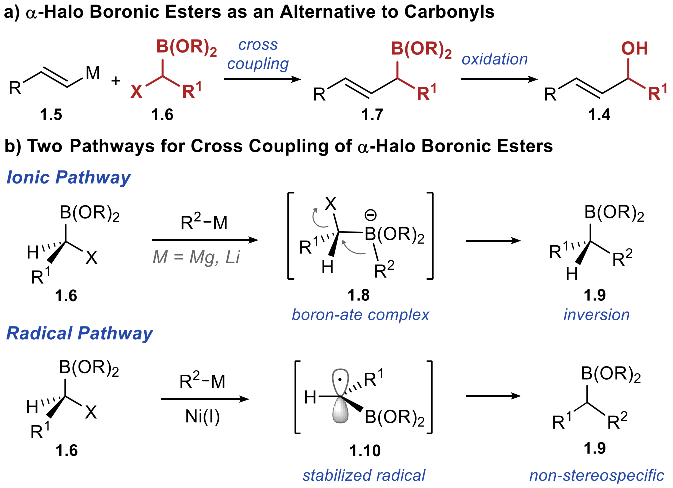


We have been interested in expanding the hydroalkylation approach to enable synthesis of *E*-alkenes with simultaneous introduction of a functional group in the allylic position. Allylic alcohols are particularly attractive targets for such a transformation as they are often featured in bioactive molecules and synthetic intermediates.[19] We reasoned that terminal alkynes can be transformed into allylic alcohols with anti-Markovnikov selectivity through hydrocupration and reaction of the alkenyl copper intermediate (**2.1**) with an appropriate electrophile (Scheme 1.1b).

The most intuitive way to access allylic alcohols from the alkenyl copper intermediate is reaction with aldehydes or ketones. Unfortunately, integrating carbonyls into the hydroalkylation approach outlined in Scheme 1.1a presents several challenges. NHC supported copper hydride complexes involved in formation of the alkenyl copper intermediate efficiently add to carbonyls and promote their reduction.[20-23] Another challenge stems from relatively low reactivity of alkenyl copper intermediates. Despite numerous examples of reactions of allylic[24-31] and propargylic[32,33] copper complexes with carbonyls, we found that under a variety of reaction conditions, stoichiometric reactions between NHC-supported alkenyl copper complexes and aldehydes do not occur (see section 1.4.11).

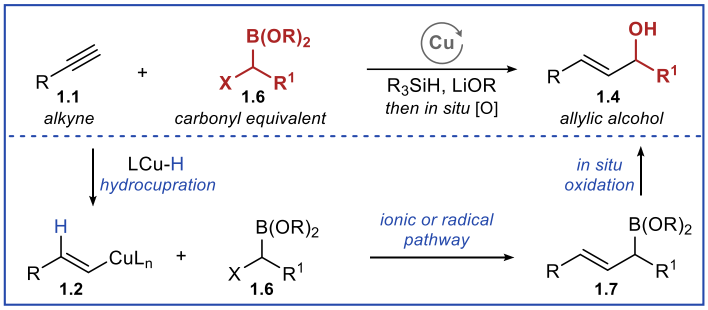
α-Halo boronic esters (**1.6**) can act as a functional equivalent of carbonyl electrophiles. They can be made directly from aldehydes and ketones[34] and provide allylic alcohols (**1.4**) after cross-coupling with alkenyl organometallic reagents (**1.5**) and in situ oxidation (Scheme 1.2a).[35] Furthermore, the key cross-coupling with organometallic compounds can proceed via two distinct mechanisms (Scheme 1.2b). As Matteson's pioneering work has shown, with nucleophilic organolithium and Grignard reagents, the cross-coupling involves the formation of boron-ate complexes (**1.8**) and a subsequent 1,2-metallate shift.[36-39] Alternatively, transition metal catalyzed cross-coupling reactions involve stabilized α-boryl radical intermediates[40-43] (**1.10**) formed through single electron transfer (SET) reduction of α-halo boronic esters.[44-48] Even though the same cross coupling product (**1.9**) is formed in both pathways, mechanistic differences produce two different stereochemical outcomes: the ionic pathway is stereospecific (inversion at the α stereocenter), while the radical pathway leads to the loss of stereochemical information.

Scheme 0.2 α-Halo Boronic Esters as Electrophiles



Alkenyl copper complexes are both nucleophilic and capable of SET reduction of activated organohalides.[8] As a result, both ionic and radical mechanisms offer plausible pathways for coupling with α-halo boronic esters. This creates an opportunity to combine the unique reactivity of α-halo boronic esters with established hydrocupration of alkynes and develop a new method for the synthesis of allylic alcohols. As shown in Scheme 1.3, allylic alcohols (**1.4**) would be generated through a convergent reductive cross coupling of terminal alkynes (**1.1**) and α-halo boronic esters (**1.6**), followed by in situ oxidation.

Scheme 0.3 Proposed Synthesis of Allylic Alcohols



The importance of allylic alcohols in organic synthesis has prompted the development of numerous approaches for their synthesis.[19] For example, asymmetric synthesis of allylic alcohols can be accomplished through kinetic resolution,[49] dynamic kinetic resolution,[50,51] reduction of enones,[52,53] allylic substitution,[54,55] or through organocatalytic tandem reactions.[56] Among methods that result in the formation of a new C-C bond, the most general is the addition of organozinc reagents derived from alkynes through hydrometallation and subsequent transmetalation, pioneered by Opolzer[57] and further developed by Walsh,[58-60] Seto,[61,62] Wipf,[63] and others.[64-66] Other organometallic reagents have also been used, but with less success.[67-70]

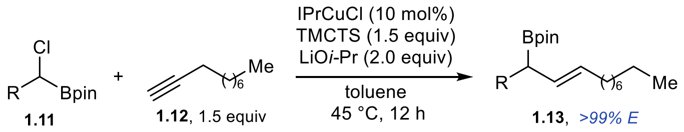
The key feature of the transformation shown in Scheme 1.3 is that it avoids stoichiometric formation of alkenyl metal reagents from alkynes. The benefits of using alkynes directly have been amply demonstrated[71,72] through the pioneering work of Jamison,[73,74] Montgomery,[75-81] Krische,[82,83] and others[84-86] on reductive cross coupling of alkynes with carbonyls. Their approach has provided excellent results in asymmetric synthesis of allylic alcohols starting with internal alkynes.[73,81,83,86] Although terminal alkynes have also been used in these reactions,[77-80] unlike internal alkynes, they have not been amenable to applications in asymmetric synthesis of allylic alcohols.[76,81] We set out to address this challenge by pursuing the development of the asymmetric anti-Markovnikov reductive cross coupling of terminal alkynes and α-halo boronic esters.[87] In the process, we aimed to resolve the underlying mechanistic ambiguity (ionic vs radical) of the reaction and exploit the stereochemical consequences of the actual mechanism.

1.2. RESULTS AND DISCUSSION

1.2.1. *Reaction Development*

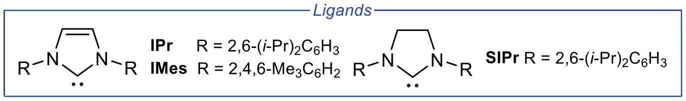
Following the approach outlined in Scheme 1.3, we developed a copper-catalyzed reductive coupling of alkynes and α-halo boronic esters (Table 1.1). The best results were obtained using IPrCuCl as the precatalyst, tetramethylcyclotetrasiloxane (TMCTS) as the hydride source, and LiO*i*-Pr as the turnover reagent (entry 1). A modest excess of alkyne (1.5 equiv) relative to the α-chloro Bpin (pin = pinacolato) was used in the reaction. The results in Table 1.1 show how different reaction parameters affect the yield of the desired product. The highest yields were obtained with copper catalysts supported by IPr and SIPr ligands. IMes, which is closely related to IPr and SIPr, only afforded 19% of **1.13** (entries 2 and 3). The identity of the silane was critical to the success of the reaction. While cyclic tetramer TMCTS and closely related PMHS (PMHS = polymethylhydrosiloxane) showed good reactivity, structurally similar monomeric silanes like DMMS (DMMS = dimethoxy(methyl)silane) gave diminished yields (entries 4 and 5). Other silanes gave little or no desired product (see Table 1.6). Lithium isopropoxide and lithium *tert*-butoxide both worked well as turnover reagents (entries 1 and 7) but changing the counter ion to sodium produced inferior results (entry 6). Lithium methoxide also performed poorly, possibly

Table 0.1 Reaction Development



entry	change from standard conditions	yield
1	none	88%
2	SIPrCuCl *instead of* IPrCuCl	78%
3	IMesCuCl *instead of* IPrCuCl	19%
4	PMHS *instead of* TMCTS	79%
5	DMMS *instead of* TMCTS	24%
6	NaO*i*-Pr *instead of* LiO*i*-Pr	43%
7	LiO*t*-Bu *instead of* LiO*i*-Pr	76%
8	LiOMe *instead of* LiO*i*-Pr	0%
9	THF *instead of* toluene	31%
10	benzene *instead of* toluene	87%
11	isooctane *instead of* toluene	77%
12	25 °C *instead of* 45 °C	47%
14[b]	$Cl(CH_2)Bpin$ *instead of* **1.11**	94%
15[b]	$Br(CH_2)Bpin$ *instead of* **1.11**	58%
16[b]	$I(CH_2)Bpin$ *instead of* **1.11**	0%

[a] Yield determined by GC using internal standard. R = n-Butyl, [b] Product was **1.13-H** with R=H.



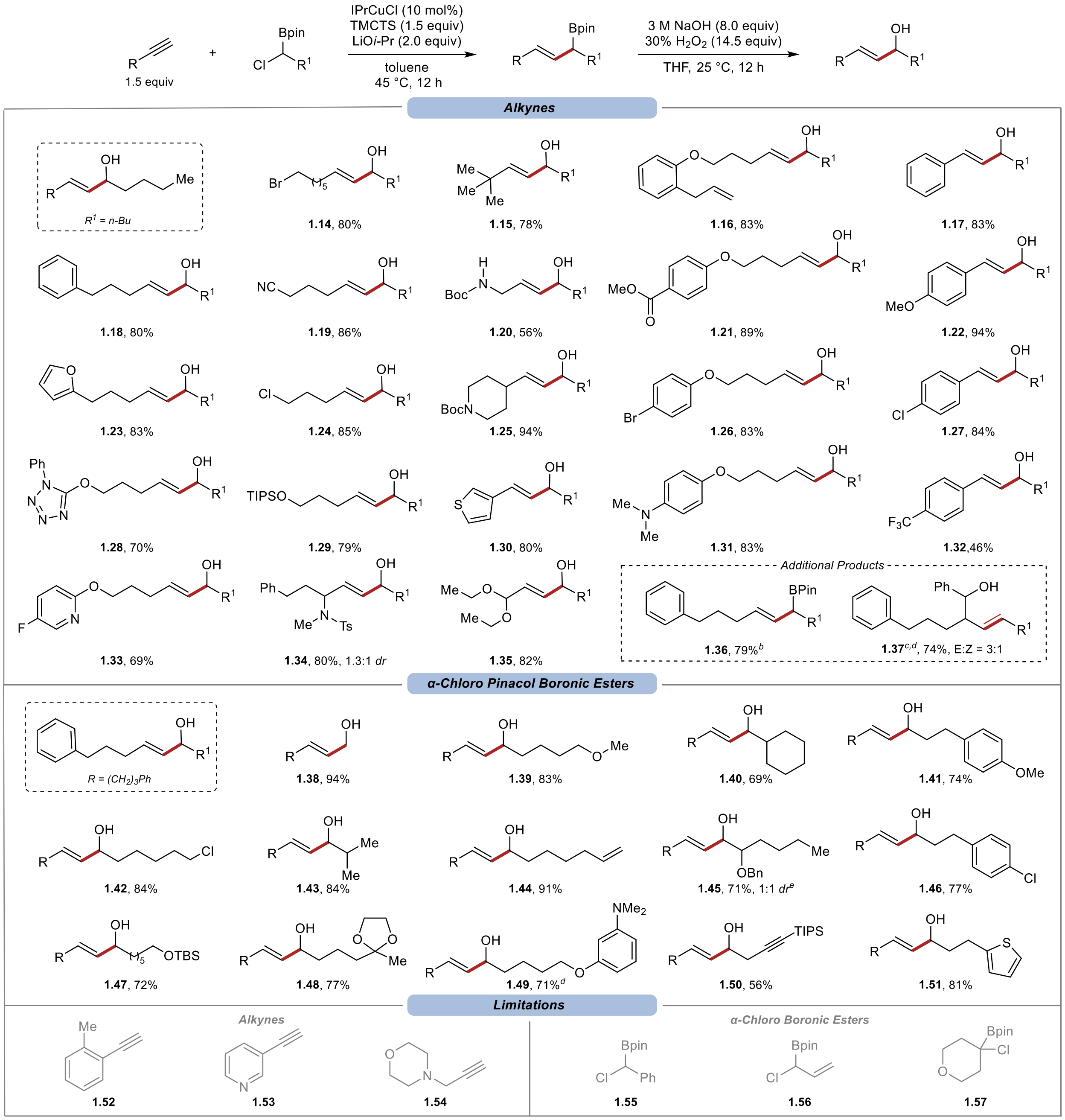
due to low solubility (entry 8). At lower temperature (25 °C), only 47% yield of the product was formed after 12 h (entry 12), and the reaction required 3 days to complete (see Table 1.8). Less sterically demanding $Cl(CH_2)Bpin$ performed better than **1.11** (entry 14). Interestingly, more reactive α-bromo and α-iodo boronic esters performed worse as substrates in the reaction (entries 15 and 16).

1.2.2. *Substrate Scope*

Using our optimized conditions, we explored the scope of the reaction. After in situ oxidation of the allylic boronic esters, various allylic alcohols were obtained in good yields (Table 1.2). In general, we observed only the *E* isomer of the allylic alcohols in ^{1}H NMR of the crude reaction mixtures. Careful GC analysis of the crude reaction mixture containing product **1.18** using authentic samples of *E* and *Z* isomers confirmed an E/Z ratio greater than 200:1 (see section 1.4.9). Alkynes containing alkyl bromides (**1.14**), alkyl chlorides (**1.24**), nitriles (**1.19**), esters (**1.21**), protected amines (**1.25**), protected alcohols (**1.29**), aryl chlorides (**1.27**), aryl bromides (**1.26**), sulfonamides (**1.34**), and acetals (**1.35**) were well tolerated. The presence of mildly acidic Boc-protected primary amine (**1.20**) was not detrimental for the reaction, although the yield of the desired product was diminished. Aryl acetylenes with electron-donating (**1.22**) and mildly electron-withdrawing (**1.27**) functional groups performed well, while the presence of a strongly electron-withdrawing group (**1.32**) resulted in a diminished yield. The reaction also tolerated alkynes with sterically demanding alkyl substituents (**1.15**). Several heterocycles could successfully be incorporated into the alkyne substrates, including furans (**1.23**), tetrazoles (**1.28**), thiophenes (**1.30**), and fluoro pyridines (**1.33**).

Allylic boronic ester **1.36** can be isolated after careful column chromatography in 79% yield. This allows a range of other products can be accessed using established transformations of allylic boronic esters.[88-90] In some instances, crude allylic boronic ester can be used directly in subsequent transformations. For example, when benzaldehyde is added to the crude reaction mixture containing **1.36**, transposed homoallylic alcohol **1.37** is obtained in 74% overall yield.

We also investigated the reactivity of various α-chloro Bpins and found that their functional group compatibility is similar to the selectivity observed in reactions of functionalized alkynes. The unsubstituted α-chloro boronic ester (**1.38**) gave an excellent yield, while additional substitution at the β position of boronic esters (**1.43** and **1.45**) resulted in lower yields.



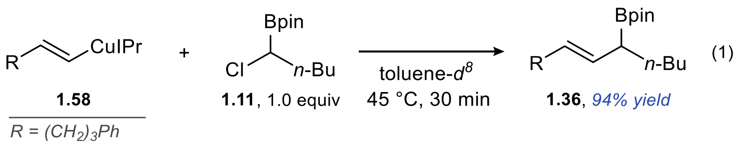
^{a}Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. ^{b}Allylic boronic ester isolated without oxidation (see SI). ^{c}Reaction of **36** with benzaldehyde. ^{d}Reactions performed on 0.25 mmol scale. ^{e}Starting α-chloro boronic ester was a 1:1 mixture of diastereoisomers.

We noted several limitations of the new reaction. Ortho-substituted aryl alkynes (**1.52**) and alkynes containing strongly coordinating groups (**1.53**, **1.54**) gave low yields of allylic alcohol products. α-Chloro boronic esters containing aryl (**1.55**) or alkenyl (**1.56**) substituents at the α-carbon provided no allylic alcohol product. Similarly, α, α-dialkyl-α-halo boronic esters (**1.57**) did not afford the expected tertiary allylic alcohols, indicating the negative effect of steric hindrance on the reaction.

1.2.3. *Comparison with Stoichiometric Alkenylation of α-Chloro Boronic Esters*

The catalytic alkenylation reaction of α-chloro boronic esters is a complement and not a replacement for the stoichiometric reactions performed using alkenyl lithium or Grignard reagents. An excellent recent study by Kazmaier et al.[91] has shown that consistently high yields in stoichiometric alkenylation reactions are observed when at least one of the reactants is sterically hindered. Trisubstituted, *Z*-disubstituted, and 2-alkenyl organometallic reagents generally perform well. With less hindered organometallic reagents, only sterically hindered α-chloro boronic esters perform well. The trends we observed in the catalytic reaction are complementary: less hindered α-chloro boronic esters perform the best and *E*-alkenyl fragments are delivered.

Equation 0.1 Stoichiometric Addition of Alkenyl Copper to α-Chloro Bpin



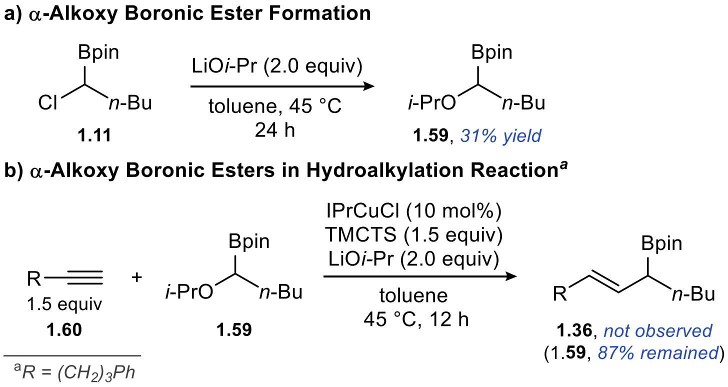
1.2.4. *Reaction Mechanism*

We had two main goals in mind when exploring the reaction mechanism. First, we wanted to establish if the alkenyl copper complex is a catalytic intermediate in the reaction. Second, we wanted to determine if the cross coupling of the alkenyl copper and α-chloro boronic esters proceeds through a radical or ionic mechanism. Establishing the exact mechanism was important because of the differences in the stereochemical outcomes of the two pathways and implications that would have on asymmetric synthesis of allylic alcohols.

Initial mechanistic experiments focused on presumed intermediates in the catalytic reaction. In a stoichiometric experiment, we found that reacting alkenyl copper complex **1.58** with α-chloro boronic ester **1.11** quickly produces allylic boronic ester **1.36** (eq 1.1). This result supports the proposed involvement of an alkenyl copper intermediate and its reaction with α-chloro boronic esters.

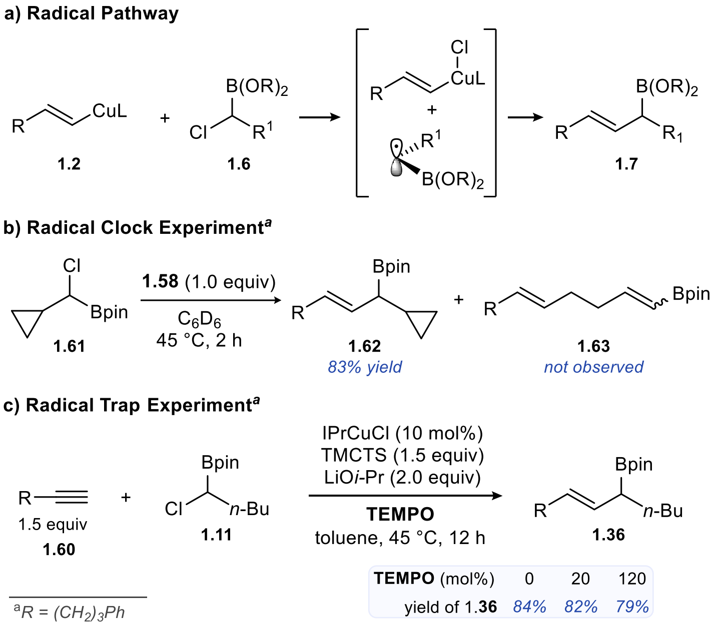
We also examined α-alkoxy boronic esters as possible intermediates in the reaction. As expected, LiOi-Pr reacts with α-chloro boronic ester **1.11** at 45 °C to produce α-alkoxy boronic ester **1.59** (Scheme 1.4a).[92] However, the reaction is slower than the catalytic hydroalkylation reaction performed at the same temperature and affords only 17% of **1.59** after 12 h, and 31% after 24 h. Furthermore, when used as a substrate in a catalytic reaction, α-isopropoxy boronic ester **1.59** did not afford the desired product (Scheme 1.4b) with 87% of **1.59** remaining after 12 h. Together, these results make α-isopropoxy boronic esters unlikely intermediates in the reaction.

Scheme 0.4 α-Alkoxy Boronic Esters as Intermediates



Next, we focused on exploring the mechanism of the key reaction between the alkenyl copper intermediate and the electrophile. A plausible radical mechanism involving SET reduction of α-chloro boronic esters by the alkenyl copper intermediate is presented in Scheme 1.5a. α-Chloro boronic esters have been shown to undergo SET reduction[44-48] to form the stabilized alkyl radical. At the same time, alkenyl copper complex (**1.2**) is known to reduce α-bromo carboxylic esters through SET.[8]

Scheme 0.5 Radical Mechanism



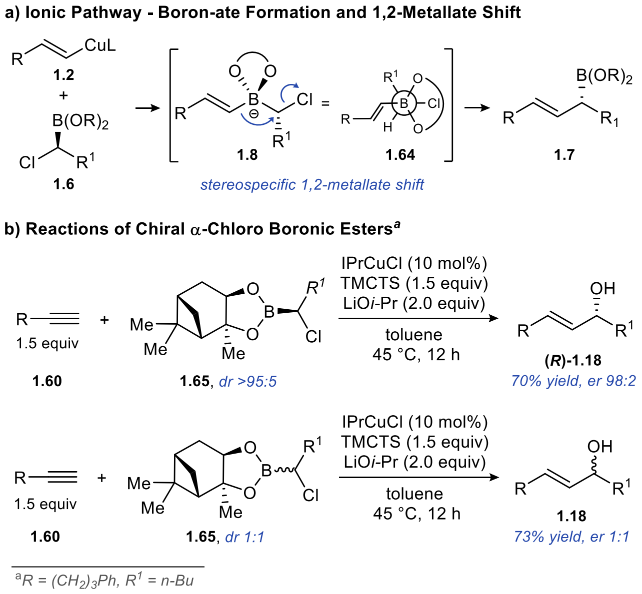
TEMPO (mol%)	0	20	120
yield of **1.36**	*84%*	*82%*	*79%*

To evaluate the relevance of the proposed radical mechanism, we performed radical clock and radical trap experiments. Alkenyl copper **1.58** reacts with cyclopropyl α-chloro Bpin (**1.61**) to produce only the unrearranged product **1.62** in 83% yield (Scheme 1.5b). We also found that up to 120 mol% of TEMPO can be added to the catalytic reaction without a significant decrease in the yield of the allylic boronic ester (Scheme 1.5c). The results of the two experiments are inconsistent with the SET mechanism and the formation of free radical intermediates.[93,94]

An alternative mechanistic hypothesis for the cross coupling is presented in Scheme 6a. The addition of alkenyl copper (**1.2**) to the α-chloro boronic ester (**1.6**) forms a boron-ate complex (**1.8**). This complex undergoes a 1,2-metallate shift exclusively through a conformation with antiperiplanar arrangement of the migrating alkenyl group and the leaving group at the α carbon (see **1.64**).[38] As a result, the cross coupling is stereospecific and proceeds with the inversion of configuration at the α-carbon.

To probe this alternative mechanistic hypothesis, we investigated the reaction with a single enantiomer of α-chloro boronic ester **1.65** (>99% ee, >95:5 dr), prepared using α-pinane diol as a chiral auxiliary (Scheme 1.6). The *R* configuration of the obtained allylic alcohol **(*R*)-1.18** indicates inversion of configuration at the α-carbon of the boronic ester (see section 1.4.10). There is also strong support for the stereospecificity of the reaction. The enantiomeric ratio of the allylic alcohol **(*R*)-1.18** (98:2) reflected the diastereomeric ratio of the starting α-chloro boronic ester (>95:5). Furthermore, the chiral auxiliary alone had no effect on reaction selectivity: a 1:1 mixture

Scheme 0.6 Ionic Mechanism


a) Ionic Pathway - Boron-ate Formation and 1,2-Metallate Shift

b) Reactions of Chiral α-Chloro Boronic Esters[a]

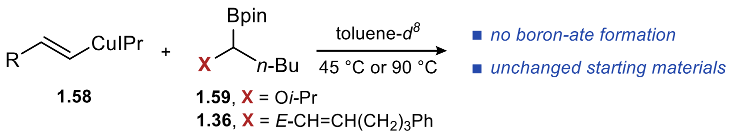
[a] $R = (CH_2)_3Ph$, R^1 = n-Bu

of diastereoisomeric α-chloro boronic esters produced racemic allylic alcohol **1.18** (Scheme 1.6b). Overall, the stereochemical outcomes of these experiments are fully consistent with an ionic mechanism involving boron-ate formation and stereospecific 1,2-metallate shift.[95]

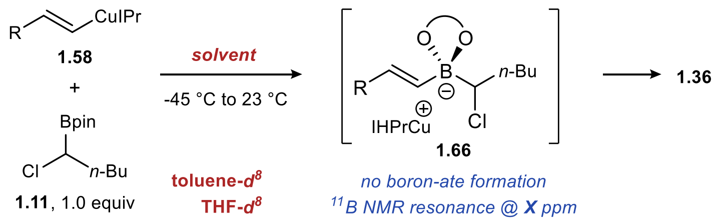
With evidence pointing to the ionic mechanism, we searched for evidence supporting the formation of the boron-ate complex in stoichiometric reactions of alkenyl copper intermediate with various boronic esters. Monitoring stoichiometric reactions of alkenyl copper intermediate (**1.58**) with α-isopropoxy boronic ester **1.59** or allylic boronic ester **1.36** by in situ ^{1}H and ^{11}B NMR showed no change of the starting materials even at 90 °C (Scheme 1.7a). Similarly, monitoring a stoichiometric reaction of **1.58** and α-chloro boronic ester **1.11** in toluene-d^8 at temperatures between -50 °C and 25 °C (Scheme 1.7b) did not provide definitive evidence for the formation of the boron-ate intermediate.

Scheme 0.7 Boron-ate Complex Formation

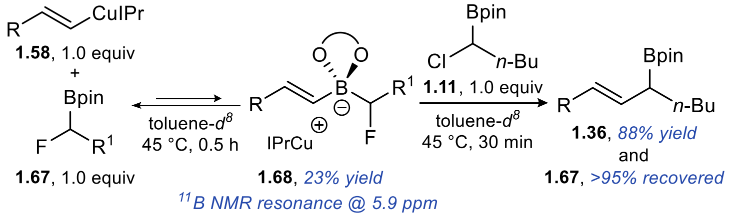
a) Alkenyl Copper Reactions with α-Alkoxy and Allylic Boronic Esters[a]



b) Low Temperature Reactions with α-Chloro Boronic Esters[a]



c) Reaction with α-Fluoro Boronic Esters[a]



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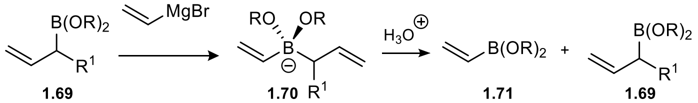
[a] R = $(CH_2)_3Ph$, R^1 = $(CH_2)_2C_6H_4$(4-OMe)

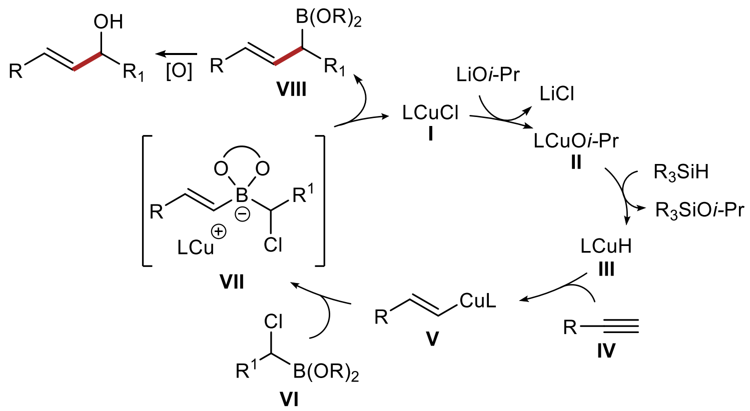
However, the same experiment performed in THF-*d*^{8} provided evidence consistent with the presence of a low concentration of the boron-ate intermediate **1.66** within the temperature range (resonance in ^{11}B NMR at 4.8 ppm). Presumably, the higher dielectric constant of the solvent (ε=7.6 for THF vs ε=2.4 for toluene) helps stabilize **1.66**. This result supports reversible, though unfavorable, boron-ate formation in a reaction of α-chloro boronic esters. Furthermore, in a reaction with α-fluoro boronic ester **1.67**, we saw evidence of the boron-ate formation in 23% yield within 30 min (Scheme 1.7c). The balance of the starting materials remained unchanged after an additional 2 h. Upon addition of α-chloro boronic ester **1.11** to the reaction mixture containing boron-ate complex **1.68**, we observed full recovery of the α-fluoro boronic ester (**1.67**) and the formation of cross-coupling product **1.36**. These results argue for a reversible and thermodynamically unfavorable formation of the boron-ate complex **1.68**.

Equation 0.2 Addition of Alkenyl Grignard to Allylic Boronic Ester



The reactions of the alkenyl copper intermediate with various boronic esters provide a mechanistic basis for understanding the differences in the scopes of this catalytic reaction and the stoichiometric alkenylation with organolithium and Grignard reagents (see above). Kazmaier has recently shown that the main side reaction in stoichiometric alkenylation is the addition of the organometallic reagent to the allylic boronic ester product (eq 1.2).[91] Protonolysis of the resulting boron-ate complex (**1.70**) at the end of the reaction provides a mixture of the desired allylic boronic ester (**1.69**) and the undesired vinyl boronic ester (**1.71**). As a result, good yields in stoichiometric reactions are realized only with substrates that can sterically impede the formation of boron-ate complex **1.70**. We found that the alkenyl copper intermediate does not react with allylic boronic esters, or if it does, the reaction is reversible and thermodynamically unfavorable (see section 1.4.16.6). As a result, the main side reaction described by Kazmaier does not occur in the copper-catalyzed transformation,[96] extending the scope to less sterically demanding substrates.

Scheme 0.8 Proposed Mechanism

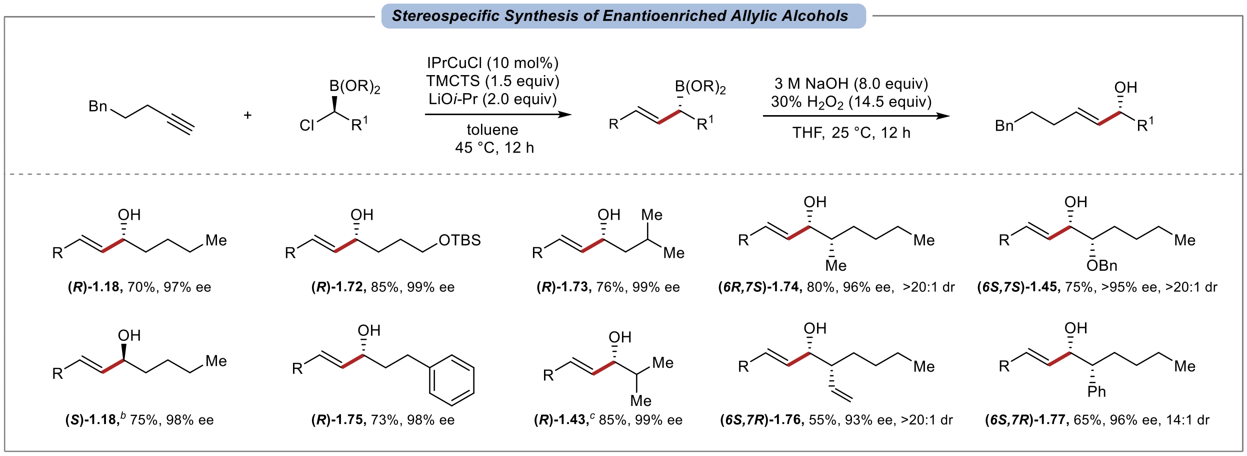


Based on our mechanistic investigation and the established chemistry of copper hydride complexes, we suggest the formation of allylic alcohols proceeds through the mechanism shown in Scheme 1.8. The process starts with the formation of copper hydride (**III**) through transmetalation of copper alkoxide with a silane,[10] followed by the formation of alkenyl copper complex (**V**) through hydrocupration of the terminal alkyne.[10] Addition to α-chloro boronic ester forms boron-ate complex (**VII**). Finally, 1,2-metallate shift, and subsequent oxidation, produce the desired allylic alcohol.

1.2.5. *Application to Asymmetric Synthesis of Allylic Alcohols*

Our mechanistic studies suggest that the new reaction can be applied in the robust and highly selective asymmetric synthesis of allylic alcohols from terminal alkynes. We demonstrated that the stereochemistry of the starting materials fully controls the absolute configuration and enantiomeric excess of the allylic alcohols. The required enantioenriched α-chloro boronic ester can be accessed in several ways using different starting materials.[97] A highly selective asymmetric synthesis from alkyl boronic esters was originally discovered by Matteson[98] and developed by others[99] and relies on chiral auxiliaries. Jacobsen[100] recently reported an approach based on enantioselective catalytic 1,2-metallate shift, while the method reported by XU[34] uses carbonyls as starting materials. Finally, enantioselective hydrogenation also provides access to highly enantioenriched α-chloro boronic esters.[101]

Table 0.2 Synthesis of Enantioenriched Allylic Alcohols



[a]Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. Enantiomeric excess of allylic alcohols determined by chiral HPLC. Boronic ester of (+)-pinanediol was used. R = $(CH_2)_3Ph$. [b]Boronic ester of (-)-pinanediol was used with the opposite absolute configuration at the α carbon. [c]Bpin ester was used.

In practice, we found Matteson's synthesis of chiral α-chloro boronic esters using readily available and affordable α-pinanediol to be highly selective and easy to execute. A range of chiral α-chloro Bpinane esters (pinane = pinane diol) were prepared by this method and used in the hydroalkylation reaction to provide chiral allylic alcohols (Table 1.3). Boronic esters with branching in the β and γ positions gave excellent selectivity (**1.43** and **1.73**). Even boronic esters with linear alkyl substituents reacted with excellent selectivity. This is particularly attractive given that enantioenriched di-alkyl allylic alcohols are difficult to access by direct alkenylation of linear unbranched aldehydes.[102] Products **1.18**, **1.72**, and **1.75** were all obtained in high stereoselectivity and yield, showcasing the utility of our method. Furthermore, access to both (+)-and (-) isomers of pinane diol auxiliary allowed us to prepare *R* and *S* enantiomers of alcohol **1.18**. Enantioenriched α-chloro Bpin esters performed as well as Bpinane esters, providing **1.43** in excellent enantiopurity. Finally, Matteson's homologation method allowed the synthesis of highly enantioenriched allylic alcohols containing two stereocenters with high diastereoselectivity (**1.45**, **1.74**, **1.76**, and **1.77**).

1.3. CONCLUSIONS

In conclusion, we have developed a method for the convergent synthesis of allylic alcohols directly from terminal alkynes. This transformation involves reductive cross coupling of an alkyne with an α-chloro boronic ester followed by in situ oxidation of the boronic ester to an alcohol. The process is highly selective for the *E*-alkene and tolerates a broad range of functional groups. Experimental studies support a mechanism that involves hydrocupration of the alkyne and formation of the alkenyl copper intermediate. Cross coupling of the intermediate with an α-chloro boronic ester involves boronic formation and 1,2-metallate shift. The overall process is stereospecific and proceeds with inversion at the stereocenter of the α-chloro boronic ester, allowing for the convenient synthesis of enantioenriched allylic boronic ester products. This reaction integrates hydrometallation and boron-ate chemistry eschewing the need for stoichiometric organometallic reagents to form the boron-ate complex.

1.4. EXPERIMENTAL

1.4.1. *General Information*

All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk technique, 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 Agilent Technologies Inc. (60Å, 40-60 μm, 230-400 mesh) or activated alumina from Sigma-Aldrich (neutral, 60Å, 40-160 μm). High Pressure Liquid Chromatography was performed using an Agilent LC column (Zorbax CN PrepHT, 21.2 x 250mm, 7μm). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane (TMS) and are referenced relative to residual solvent peak ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm, CD_2Cl_2: δ 5.32 ppm, or toluene-d^8: δ 2.09 ppm). ^{13}C NMR chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.0 ppm or CD_2Cl_2: δ 54.0 ppm). ^{19}F NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to the internal standard, hexafluorobenzene (C_6F_6: δ -164.9 ppm). ^{11}B NMR chemical shifts (δ) are reported in part per million (ppm) downfield of external standard boron trifluoride etherate ($BF_3 \cdot OEt_2$: δ 0.0 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 an Agilent 5973 GC-MS or a Bruker Esquire LC ion trap mass spectrometer. Specific rotations ($[\alpha]_D^t$) were measured using a Jasco P-2000 Polarimeter at the indicated temperature with a sodium lamp (λ = 589 nm) with a 100 mm cell and concentrations (g/(100mL)) reported in the corresponding solvent. 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 and 5.5 min @ 250 °C.

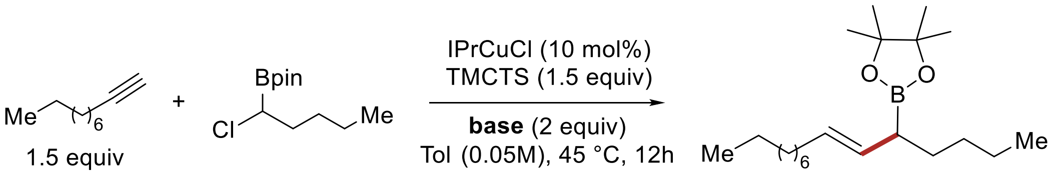
1.4.2. *Materials*

THF, CH_2Cl_2, ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Lithium isopropoxide was purchased from Millipore Sigma and was used without further purification. 2,4,6,8-Tetramethylcyclotetrasiloxane (TMCTS) was purchased from AK Scientific and was used without further purification. 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.

1.4.3. *Reaction Development Details*

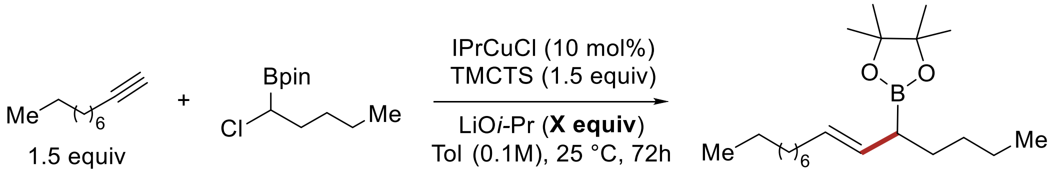
All the reactions shown in table 1.4 to table 1.9 were performed on a 0.05 mmol scale. In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, base, copper catalyst, solvent, silane, and alkyne, sequentially. The reaction mixture was stirred at room temp for 5 minutes, until the yellow color disappeared. Then, α-chloro boronic ester was added with the internal standard 1,3,5-trimethoxybenzene (TMB). The reaction mixture was vigorously stirred at the indicated temperature for the specified time.

Table 0.3 Base Screen



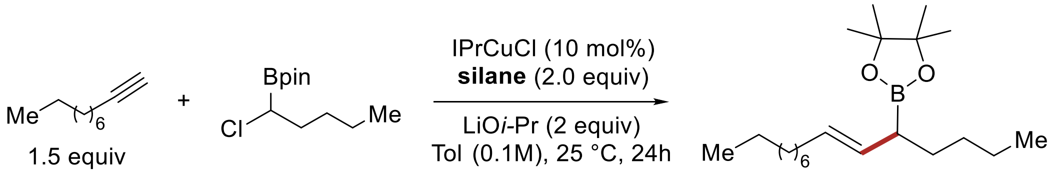
Entry	**Base**	**Yield (%)**
1	LiO*i*-Pr	93
2	NaO*i*-Pr	65
3	KOEt	74
4	LiO*t*-Bu	68
5	NaOMe	22
6	LiOMe	0

Table 0.4 Base Equivalents



Entry	**Base Equivalents**	**Yield (%)**
1	1	45
2	1.5	59
3	2	76
4	3	32

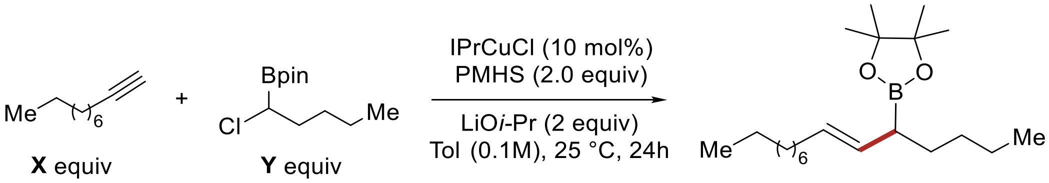
Table 0.5 Silane Screen



Entry	**Silane**	**Yield (%)**

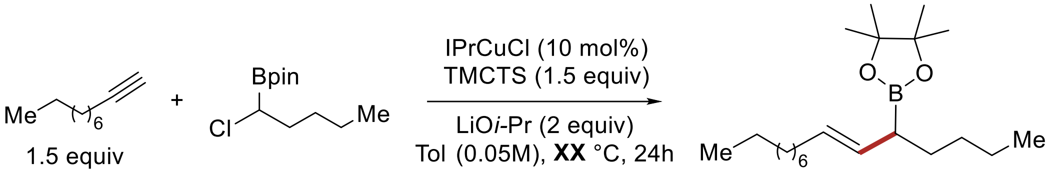
1	TMCTS	70
2	PMHS	60
3	Me(MeO)$_2$SiH	54
4	PhSiH$_3$	12
5	Ph$_3$SiH	5
6	Et$_3$SiH	0
7	TMDSO	7
8	(EtO)$_3$SiH	16
9	Me(EtO)$_2$SiH	6

Table 0.6 Reactant Stoichiometry



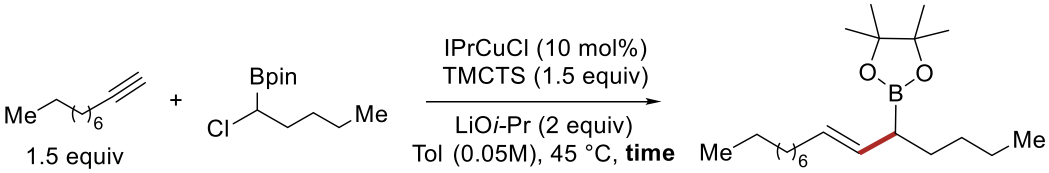
Entry	**X equiv : Y equiv**	**Yield (%)**
1	2 : 1	64
2	1.5 : 1	75
3	1 : 1	44
4	1 : 1.5	47
5	1 : 2	43

Table 0.7 Reaction Temperature



Entry	**Temperature °C**	**Yield (%)**
1	25	61
2	45	84
3	60	82
4	90	75

Table 0.8 Reaction Time



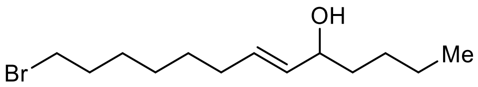
Entry	**Time (hours)**	**Yield (%)**
1	3.5	82
2	8	93
3	30	94
4	96	91

1.4.4. *General Procedure A: Hydroalkylation of Terminal Alkynes with α-Chloro Boronic Esters*

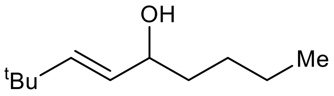
In a nitrogen-filled glovebox, a 20 ml scintillation vial was charged with IPrCuCl (24 mg, 0.05 mmol, 0.1 equiv), LiO*i*-Pr (66 mg, 1 mmol, 2.0 equiv) and a stir bar. To the vial was added

TMCTS (180 mg, 0.75 mmol, 1.5 equiv), alkyne (0.75 mmol, 1.5 equiv), and toluene (0.05 M). The resulting mixture was stirred at 25 °C. A bright yellow color was immediately observed, and the reaction mixture was stirred for 5 minutes with the bright yellow color dissipating to a pale yellow. α-Chloro boronic ester (0.5 mmol, 1.0 equiv) was then added to the reaction vial and the reaction mixture was stirred at 45 °C overnight. The vial was opened to air and THF was added (4 mL), at which point the reaction mixture was cooled to 0 °C. A solution of NaOH (1.0 mL, 3 mmol, 6 equiv, 3.0 M) and H_2O_2 (850 µL, 7.5 mmol, 15 equiv, 30% (w/w) in H_2O) was added dropwise to the cooled reaction mixture and resulting mixture was stirred for 5 minutes before removal from the ice bath. After 12 h at room temperature, the reaction mixture was passed through a plug of Silica with EtOAc, concentrated, and loaded onto an alumina flash chromatography column (neutral, Brockman II, doped with 5% diethylmethylamine). The column was flushed with ten column volumes of hexanes before the product was eluted with a mixture of hexanes/EtOAc.

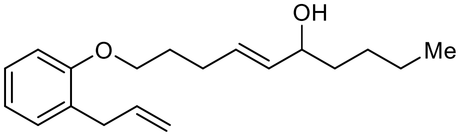
1.4.5. *Characterization of Racemic Allylic Alcohol Products*



(6*E*)-13-bromotridec-6-en-5-ol (1.14) was prepared according to the general procedure A, and was obtained as a colorless liquid (110 mg, 80% yield) after purification by alumina chromatography (0-30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 – 5.58 (m, 1H), 5.46 (dd, *J* = 15.3, 7.1 Hz, 1H), 4.13 – 4.06 (m, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.16 – 2.04 (m, 2H), 1.85 (p, *J* = 7.5 Hz 2H), 1.61 – 1.52 (m, 3H), 1.45 – 1.29 (m, 10H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.4, 131.6, 73.1, 37.1, 33.9, 32.8, 32.0, 29.0, 28.2, 28.0, 27.7, 22.7, 14.1. MS-ESI (m/z): $[M]^+$ calculated for $C_{13}H_{25}BrO$, 276.1; found 276.0. FTIR (neat, cm^{-1}): 3349 (br), 2931 (s), 1669 (w), 1465 (s), 1378 (m), 1259 (m), 1127 (m), 969 (s), 897 (w) 667 (m).

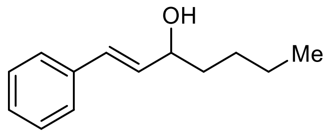


(3*E*)-2,2-dimethylnon-3-en-5-ol (1.15) was prepared according to general procedure A, and was obtained as a light yellow liquid (66 mg, 78% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^1H NMR (300 MHz, Chloroform-*d*) δ 5.65 (d, *J* = 15.7 Hz, 1H), 5.36 (dd, *J* = 15.6, 7.1 Hz, 1H), 4.07-3.99 (m, 1H), 1.57-1.47 (m, 2H), 1.39 – 1.21 (m, 5H), 1.01 (s, 9H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 128.0, 73.5, 37.2, 32.8, 29.6, 27.8, 22.7, 14.1. GCMS (EI) calculated for $C_{11}H_{22}O$ $[M]^+$ 170.2, found 170.2. FTIR (neat, cm^{-1}): 3341 (br), 2956 (s), 2861 (s), 1662 (w), 1463 (m), 1364 (m), 1131 (w), 1023 (m), 972 (m).

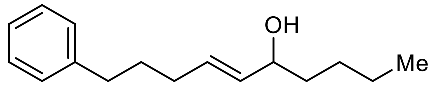


(6*E*)-10-[2-(prop-2-en-1-yl)phenoxy]dec-6-en-5-ol (1.16) was prepared according to general procedure A, and was obtained as a yellow liquid (121 mg, 84% yield) after purification by alumina chromatography (0-40% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.11 (m, 2H), 6.92 – 6.79 (m, 2H), 5.99 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.69 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.52 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.11 – 4.99 (m, 2H), 4.10 – 3.93 (m, 3H), 3.40 (d, *J* = 6.6 Hz, 2H), 2.31 – 2.19 (m, 2H), 1.95 – 1.83 (m, 2H), 1.56 – 1.28 (m, 7H), 0.90 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 137.1, 134.1, 130.6, 129.8, 128.7, 127.3, 120.4, 115.3, 111.2, 73.0, 67.0, 37.1, 34.5, 29.0, 28.8, 27.7, 22.7, 14.1. MS-ESI (m/z): $[M-OH]^+$ calculated for

$C_{19}H_{27}O$, 271.2; found 271.1. FTIR (neat, cm^{-1}): 3357 (br), 3075 (w), 2930 (s), 2859 (s), 1637 (w), 1600 (m), 1493 (s), 1454 (s), 1243 (s), 1047 (s), 970 (s), 911 (m), 750 (s).

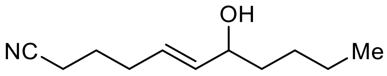


(1*E*)-1-phenylhept-1-en-3-ol (1.17) was prepared according to general procedure A and was obtained as a yellow liquid (79 mg, 83% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 7.29 – 7.23 (m, 2H), 7.15 – 7.02 (m, 3H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.09 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.06 – 3.93 (m, 1H), 1.59 – 1.20 (m, 6H), 0.99 (s, 1H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 137.5, 133.6, 130.0, 128.9, 127.7, 126.9, 73.0, 37.6, 28.1, 23.1, 14.3. GCMS (EI) calculated for [M]$^+$ 190.1, found 190.1. FTIR (neat, cm^{-1}): 3350 (br), 3026 (m), 2929 (s), 2858 (s), 1599 (w), 1494 (m), 1448 (m), 1131 (m), 966 (s), 749 (s), 693 (s).

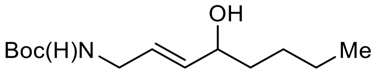


(6*E*)-10-phenyldec-6-en-5-ol (1.18) was prepared according to general procedure A and was obtained as a light-yellow liquid (93 mg, 80% yield) after purification by alumina chromatography (0-25% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.24 – 7.13 (m, 3H), 5.71 – 5.59 (m, 1H), 5.47 (ddt, *J* = 15.3, 6.9, 1.3 Hz, 1H), 3.93 – 3.81 (m, 1H), 2.62 (t, *J* = 7.3 Hz, 2H), 1.97 – 1.83 (m, 2H), 1.72 (p, *J* = 7.7 Hz, 2H), 1.55 – 1.46 (m, 3H), 1.38 – 1.24 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 133.7, 131.4, 128.5, 128.4, 125.8, 73.2, 37.1, 35.4, 31.8, 31.0, 27.8, 22.7, 14.1. GCMS (EI) calculated for [M]$^+$

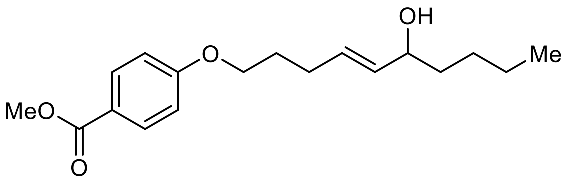
232.2, found 232.0. FTIR (neat, cm^{-1}): 3359 (br), 3025 (m), 2929 (s), 2857 (s), 1603 (w), 1496 (m), 1453 (m), 968 (m), 746 (m), 699 (s).



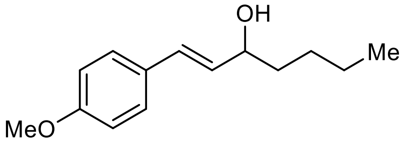
(5*E*)-7-hydroxyundec-5-enenitrile (1.19) was prepared according to general procedure A and was obtained as a clear colorless liquid (78 mg, 86% yield) after purification by alumina chromatography (0-70% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 – 5.50 (m, 2H), 4.00 – 3.89 (m, 1H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.72 – 1.59 (m, 2H)., 1.57 – 1.46 (m, 3H), 1.38 – 1.24 (m, 4H) 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 128.5, 119.6, 72.6, 37.1, 30.9, 27.6, 24.8, 22.6, 16.4, 14.1. GCMS (EI) calculated for $[M]^+$ 181.1, found 181.3. FTIR (neat, cm^{-1}): 3434 (br), 2931 (s), 2859 (s), 2247 (m), 1669 (w), 1456 (m), 1379 (m), 1133 (m), 970 (s), 897 (w), 731 (w).



tert-butyl N-[(2*E*)-4-hydroxyoct-2-en-1-yl]carbamate (1.20) was prepared according to general procedure A and was obtained as a colorless liquid (69 mg, 56% yield) after purification by alumina chromatography (0-60% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 – 5.52 (m, 2H), 4.57 (s, 1H), 4.16 – 4.04 (m, 1H), 3.80 – 3.62 (m, 2H), 1.57 – 1.48 (m, 2H), 1.45 (s, 9H), 1.41 – 1.18 (m, 5H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 135.0, 127.3, 79.5, 77.4, 76.9, 72.3, 42.0, 37.0, 28.5, 27.6, 22.7, 14.1. MS-ESI (m/z): $[M+Na]^+$ $C_{13}H_{25}NNaO_3$, 266.2, found 266.0. FTIR (neat, cm^{-1}): 3355 (br), 2930 (s), 2860 (s), 1708 (s), 1695 (s), 1527 (s), 1251 (m), 1172 (s), 970 (m), 864 (w), 733 (m).

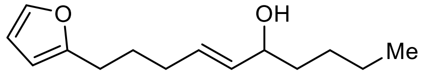


methyl 4-{[(4*E*)-6-hydroxydec-4-en-1-yl]oxy}benzoate (1.21) was prepared according to general procedure A and was obtained as a clear yellow liquid (137 mg, 89% yield) after purification by alumina chromatography (0-45% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 6.93 – 6.85 (m, 2H), 5.74 – 5.61 (m, 1H), 5.52 (dd, *J* = 15.5, 6.8 Hz, 1H), 4.10 – 3.97 (m, 3H), 3.88 (s, 3H), 2.19 – 2.06 (m, 2H), 1.86 – 1.71 (m, 2H), 1.58-1.42 (m, 3H), 1.36 – 1.23 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 162.9, 134.3, 131.6, 130.2, 122.4, 114.1, 72.9, 67.3, 51.9, 37.1, 28.6, 28.5, 27.7, 22.6, 14.1. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{18}H_{26}NaO_4$, 329.2; found, 329.2. FTIR (neat, cm^{-1}): 3421 (br), 2952 (s), 2870 (s), 1719 (s), 1606 (s), 1511 (s), 1435 (s), 1254 (s), 1105 (s), 670 (s), 771 (s), 679 (s).

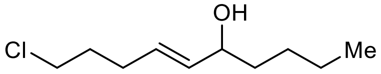


(1*E*)-1-(4-methoxyphenyl)hept-1-en-3-ol (1.22) was prepared according to general procedure A and was obtained as a yellow liquid (103 mg, 94% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 6.89 – 6.82 (m, 2H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.08 (dd, *J* = 15.9, 7.0 Hz, 1H), 4.30 – 4.19 (m, 1H), 3.81 (s, 3H), 1.66 – 1.50 (m, 3H), 1.44 – 1.28 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 130.6, 129.7, 129.6, 127.7, 114.0, 73.2, 55.3, 37.2, 27.7, 22.7, 14.1.

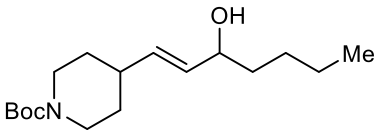
GCMS (EI) calculated for $[M]^+$ 220.1, found 220.1. FTIR (neat, cm^{-1}): 3366 (br), 2930 (s), 2858 (m), 1608 (m), 1511 (s), 1464 (w), 1249 (s), 1174 (m), 1036 (m), 967 (w), 817 (w).



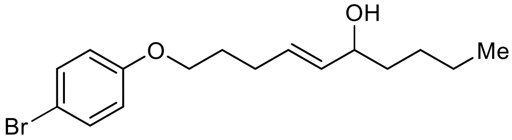
(6*E*)-10-(furan-2-yl)dec-6-en-5-ol (1.23) was prepared according to general procedure A and was obtained as a yellow liquid (92 mg, 83% yield) after purification by alumina chromatography (0-45% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 1H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.99 – 5.96 (m, 1H), 5.63 (dt, *J* = 15.2, 6.7 Hz, 1H), 5.48 (dd, *J* = 15.4, 7.0 Hz, 1H), 4.08 – 4.00 (m, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.13 – 2.05 (m, 2H), 1.79 – 1.68 (m, 2H), 1.58 – 1.47 (m, 3H), 1.39 – 1.29 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 140.8, 134.0, 131.0, 110.1, 104.9, 73.1, 37.1, 31.6, 27.7, 27.6, 27.4, 22.7, 14.1. GCMS (EI) calculated for $[M]^+$ 222.2, found 222.2. FTIR (neat, cm^{-1}): 3355 (br), 2944 (s), 2859 (s), 1669 (w), 1597 (m), 1506 (s), 1147 (s), 1007 (s), 969 (s), 923 (w), 796 (m), 727 (s).



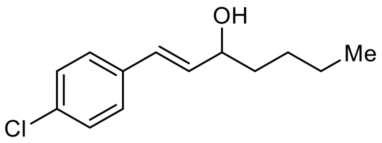
(6*E*)-10-chlorodec-6-en-5-ol (1.24) was prepared according to general procedure A and was obtained as a light yellow liquid (81 mg, 85% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^1H NMR (300 MHz, C_6D_6) δ 5.41 – 5.21 (m, 2H), 3.88-3.76 (m, 1H), 3.10 (t, *J* = 6.6 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.51 – 1.22 (m, 8H), 0.95 – 0.77 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.7, 129.6, 72.9, 44.3, 37.1, 32.0, 29.3, 27.7, 22.7, 14.1. GCMS (EI) calculated for $[M]^+$ 190.1, found 190.1. FTIR (neat, cm^{-1}): 3358 (br), 2929 (s), 2859 (s), 1669 (w), 1467 (m), 1271 (m), 1130 (m), 970 (s), 730 (w), 655 (m).



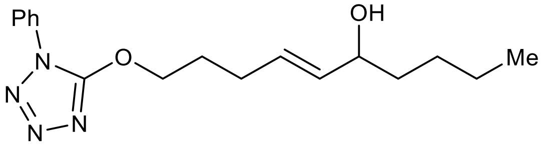
tert-butyl 4-[(1*E*)-3-hydroxyhept-1-en-1-yl]piperidine-1-carboxylate (1.25) was prepared according to general procedure A and was obtained as a yellow liquid (140 mg, 94% yield) after purification by alumina chromatography (0-65% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (dd, *J* = 15.6, 6.2 Hz, 1H), 5.45 (dd, *J* = 15.7, 6.3 Hz, 1H), 4.06 (dd, *J* = 12.7, 6.5 Hz, 3H), 2.72 (t, *J* = 12.7 Hz, 2H), 2.19 – 2.02 (m, 1H), 1.71 – 1.62 (m, 2H), 1.57 – 1.47 (m, 2H), 1.45 (s, 9H), 1.40 – 1.16 (m, 7H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 135.0, 132.0, 79.3, 72.8, 38.4, 37.1, 31.7, 28.4, 27.6, 22.6, 14.0. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{17}H_{31}NNaO_3$, 320.2; found 320.3. FTIR (neat, cm^{-1}): 3437 (br), 2931 (s), 2858 (s), 1700 (s), 1419 (s), 1366 (s), 1171 (s), 970 (s), 867 (m), 769 (m), 679 (m).



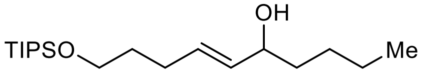
(6*E*)-10-(4-bromophenoxy)dec-6-en-5-ol (1.26) was prepared according to general procedure A and was obtained as a yellow liquid (135 mg, 83% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 6.81 – 6.72 (m, 2H), 5.67 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.51 (dd, *J* = 15.4, 6.8 Hz, 1H), 4.10 – 4.00 (m, 1H), 3.93 (t, *J* = 6.4 Hz, 2H), 2.28 – 2.16 (m, 2H), 1.93 – 1.79 (m, 2H), 1.58 – 1.46 (m, 2H), 1.40 – 1.21 (m, 5H) 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 134.2, 132.2, 130.3, 116.3, 112.7, 72.9, 67.4, 37.1, 28.6, 28.6, 27.7, 22.7, 14.1. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{16}H_{22}BrO$, 309.1; found 309.1. FTIR (neat, cm^{-1}): 3358 (br), 2929 (s), 2858 (s), 1591 (m), 1487 (s), 1285 (s), 1243 (s), 1071 (s), 970 (s), 821 (s), 640 (m).



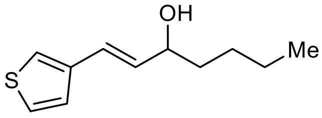
(1*E*)-1-(4-chlorophenyl)hept-1-en-3-ol (1.27) was prepared according to general procedure A and was obtained as a yellow solid (89 mg, 80% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.27 (d, *J* = 15.8 Hz, 1H), 5.94 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.02 – 3.88 (m, 1H), 1.50 – 1.23 (m, 6H), 1.04 (s, 1H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 135.9, 134.2, 133.4, 129.0, 128.6, 128.0, 72.7, 37.6, 28.0, 23.1, 14.3. GCMS (EI) calculated for $[M]^+$ 224.1, found 224.1. FTIR (neat, cm^{-1}): 3348 (br), 2955 (s), 2929 (s), 2858 (s), 1491 (s), 1465 (w), 1090 (m), 1012 (m), 966 (m), 857 (w), 809 (m).



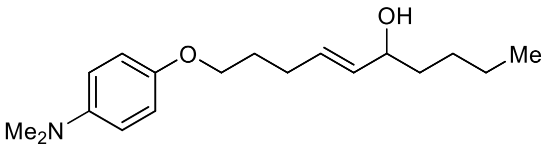
(6*E*)-10-[(1-phenyl-1H-1,2,3,4-tetrazol-5-yl)oxy]dec-6-en-5-ol (1.28) was prepared according to general procedure A and was obtained as a yellow liquid (110 mg, 70% yield) after purification by alumina chromatography (0-60% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.56 - 7.49 (m, 2H), 7.48 – 7.40 (m, 1H), 5.71 – 5.57 (m, 1H), 5.55 - 5.46 (m, 1H), 4.64 (t, *J* = 6.5 Hz, 2H), 4.08 – 3.95 (m, 1H), 2.28 – 2.13 (m, 2H), 2.00 (dt, *J* = 8.1, 6.3 Hz, 2H), 1.74 (br, 1H), 1.61 – 1.39 (m, 2H), 1.38 – 1.19 (m, 4H), 0.94 – 0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 134.9, 133.5, 129.6, 129.2, 129.0, 121.6, 73.5, 72.7, 37.1, 28.2 (2C), 27.7, 22.6, 14.1. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{17}H_{23}N_4O$, 299.2; found, 299.0. FTIR (neat, cm^{-1}): 3412 (br), 2955 (m), 2929 (m), 2858 (m), 1596 (s), 1563 (s), 1505 (s), 1460 (m), 1381 (w), 1021 (w), 759 (m).



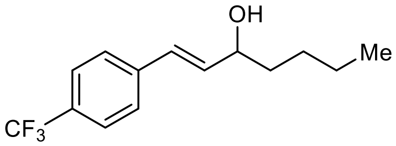
(6*E*)-10-{[tris(propan-2-yl)silyl]oxy}dec-6-en-5-ol (1.29) was prepared according to general procedure A and was obtained as a light yellow liquid (129 mg, 79% yield) after purification by alumina chromatography (0-55% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dt, *J* = 15.2, 6.5 Hz, 1H), 5.48 (dd, *J* = 15.4, 7.0 Hz, 1H), 4.10 – 3.97 (m, 1H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.19 – 2.06 (m, 2H), 1.68 – 1.44 (m, 5H), 1.37-1.26 (m, 4H), 1.12-1.01 (m, 21H), 0.90 (t, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.6, 131.6, 73.2, 62.8, 37.2, 32.6, 28.6, 27.8, 22.7, 18.1, 14.1, 12.3, 12.1. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{19}H_{40}NaO_2Si$, 351.3; found, 351.3. FTIR (neat, cm^{-1}): 3347 (br), 2940 (s), 2865 (s), 1463 (m), 1382 (w), 1107 (s), 968 (m), 882 (m), 789 (w), 680 (m).



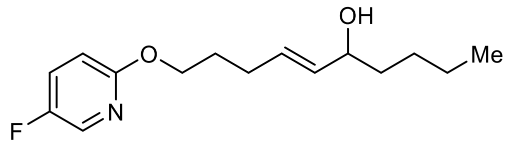
(1*E*)-1-(thiophen-3-yl)hept-1-en-3-ol (1.30) was prepared according to general procedure A and was obtained as a yellow solid (79 mg, 80% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 6.99 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.87 – 6.82 (m, 1H), 6.80 – 6.73 (m, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 5.92 (dd, *J* = 15.9, 6.5 Hz, 1H), 4.03 – 3.90 (m, 1H), 1.53 – 1.21 (m, 6H), 1.04 (s, 1H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 140.1, 133.4, 126.1, 125.4, 124.3, 122.2, 72.9, 37.6, 28.1, 23.1, 14.3. GCMS (EI) calculated for $[M]^+$ 196.1, found 196.1. FTIR (neat, cm^{-1}): 3366 (br), 2955 (s), 2929 (s), 2857 (s), 1465 (w), 1129 (w), 963 (s), 864 (w), 830 (w), 769 (s).



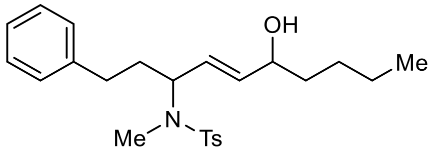
(6*E*)-10-[4-(dimethylamino)phenoxy]dec-6-en-5-ol (1.31) was prepared according to general procedure A and was obtained as a light pink solid (120 mg, 83% yield) after purification by alumina chromatography (0-60% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 – 6.69 (m, 4H), 5.73 – 5.62 (m,1H), 5.51 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.76 (s, 6H), 2.17 – 2.04 (m, 2H), 1.81 – 1.66 (m, 2H), 1.59 – 1.47 (m, 2H), 1.40 – 1.25 (m, 5H) 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 145.8, 134.0, 130.7, 115.6, 115.1, 73.0, 67.9, 41.9, 37.1, 29.0, 28.7, 27.7, 22.7, 14.1. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{18}H_{28}NO$, 274.2, found 274.3. FTIR (neat, cm^{-1}): 3368 (br), 2933 (s), 2869 (s), 1517 (s), 1476 (w), 1253 (m), 1045 (w), 963 (w), 824 (w).



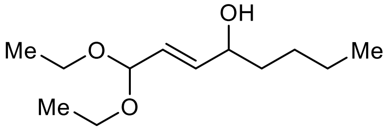
(1*E*)-1-[4-(trifluoromethyl)phenyl]hept-1-en-3-ol (1.32) was prepared according to general procedure A and was obtained as a yellow solid (59 mg, 46% yield) after purification by alumina chromatography (0-50% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.33 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.35 – 4.28 (m, 1H), 1.71 – 1.55 (m, 4H), 1.40 – 1.33 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.44, 135.47, 129.45 (q, *J* = 32.8 Hz), 128.65, 126.67, 125.60 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 272.0 Hz), 77.42, 76.91, 72.81, 37.16, 27.69, 22.74, 14.10. ^{19}F NMR (470 MHz, $CDCl_3$) δ -65.5. GCMS (EI) calculated for $[M]^+$ 258.1, found 258.1. FTIR (neat, cm^{-1}): 3363 (br), 2933 (m), 2859 (w), 1616 (w), 1326 (s), 1166 (m), 1124 (s), 1068 (s), 1016 (w), 969 (w), 820 (w).



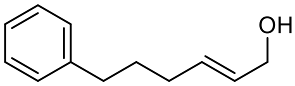
(6*E*)-10-[(5-fluoropyridin-2-yl)oxy]dec-6-en-5-ol (1.33) was prepared according to general procedure A and was obtained as a yellow liquid (92.3 mg, 69% yield) after purification by alumina chromatography (0-60% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.02 – 7.90 (m, 1H), 7.32 (ddd, *J* = 9.1, 7.6, 3.1 Hz, 1H), 6.76 – 6.65 (m, 1H), 5.68 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.56 – 5.39 (m, 1H), 4.25 (t, *J* = 6.5 Hz, 2H), 4.12 – 3.93 (m, 1H), 2.25 – 2.13 (m, 2H), 1.96 – 1.70 (m, 2H), 1.62 – 1.45 (m, 3H),1.34 – 1.20 (m, 4H), 0.99 – 0.77 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.2, 155.4 (d, *J* = 245.6 Hz), 134.1, 133.1 (d, *J* = 25.0 Hz), 130.6, 126.6 (d, *J* = 21.1 Hz), 111.7, 73.0, 65.8, 37.1, 28.7, 28.6, 27.7, 22.7, 14.1. ^{19}F NMR (470 MHz, CDCl$_3$) δ -142.6. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{15}H_{22}FNO_2Na$, 290.2; found, 290.0. FTIR (neat, cm^{-1}): 3390 (br), 2955 (m), 2930 (m), 2858 (m), 1487 (s), 1372 (m), 1227 (m), 1013 (w), 826 (w), 739 (w).



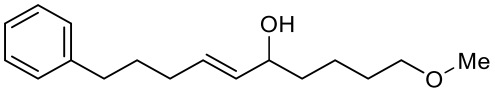
N-[(4*E*)-6-hydroxy-1-phenyldec-4-en-3-yl]-N,4-dimethylbenzene-1-sulfonamide (1.34) was prepared according to general procedure A and was obtained as a yellow liquid (167.0 mg, 80% yield) with a 1.3:1 dr (determined by NMR analysis of the isolated product), after purification by alumina chromatography (0-50% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) *major* *isomer:* δ 7.68 (d, *J* = 8.3, 2H), 7.32 - 7.26 (m, 4H), 7.23 – 7.18 (m, 1H), 7.18 – 7.11 (m, 2H), 5.53 – 5.31 (m, 2H), 4.55 – 4.40 (m, 1H), 3.97 – 3.85 (m, 1H), 2.73 (s, 3H), 2.61 (t, *J* = 8.2 Hz, 2H), 2.41 (s, 3H), 1.85 – 1.71 (m, 2H), 1.40 – 1.18 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 3H). *minor isomer peak:* δ 2.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *major isomer* δ 143.2, 141.5, 137.0, 136.8, 129.6, 128.5, 128.5, 127.5, 127.0, 126.1, 72.3, 58.1, 37.0, 33.9, 32.7, 28.8, 27.7, 22.7, 21.6, 14.1. *minor isomer* δ 143.2, 141.5, 137.0, 136.8, 129.6, 128.5, 128.5, 127.4, 126.9, 126.1, 72.2, 58.1, 36.9, 33.9, 32.7, 28.8, 27.6, 22.7, 21.6, 14.1. (Assignment of ^{13}C NMR signals of each diastereomers based on the assumption that the relaxation time of each corresponding carbons in those two compounds are identical.) MS-ESI (m/z): $[M+NH_4]^+$ calculated for $C_{24}H_{37}N_2O_3S$, 433.2; found, 433.1. FTIR (neat, cm^{-1}): 3525 (br), 3026 (m), 2955 (s), 2929 (s), 2860 (s), 1598 (m), 1495 (s), 1465 (s), 1333 (s), 1266 (s), 1158 (s), 1088 (m), 975 (m), 925 (m), 815 (s), 737 (s), 660 (m).



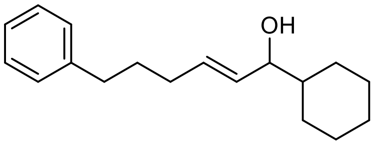
(2*E*)-1,1-diethoxyoct-2-en-4-ol (1.35) was prepared according to general procedure A and was obtained as a light yellow liquid (88 mg, 82% yield) after purification by alumina chromatography (0-50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.76 – 5.62 (m, 1H), 4.90 (d, *J* = 5.1 Hz, 1H), 4.21 – 4.08 (m, 1H), 3.73 – 3.57 (m, 2H), 3.58 – 3.42 (m, 2H), 1.59 – 1.46 (m, 3H), 1.35 (d, *J* = 9.1 Hz, 4H), 1.22 (t, *J* = 7.0 Hz, 6H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 127.4, 101.1, 71.9, 61.0, 36.8, 27.6, 22.6, 15.2, 14.0. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{12}H_{24}NaO_3$, 239.2; found 239.0. FTIR (neat, cm^{-1}): 3408 (br), 2974 (s), 2930 (s), 2872 (s), 1675 (w), 1467 (m), 1337 (m), 1134 (s), 1052 (s), 980 (s).



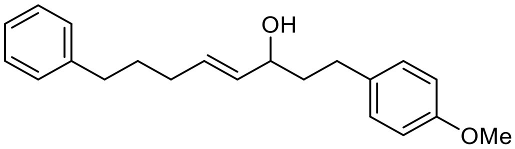
(2*E*)-6-phenylhex-2-en-1-ol (1.38) was prepared according to general procedure A and was obtained as a light yellow liquid (83 mg, 94% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.31 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H) 5.80 – 5.53 (m, 2H), 4.05 (d, *J* = 4.8 Hz, 1H), 2.62 (t, *J* = 7.9 Hz, 2H), 2.09 (q, *J* = 6.2 Hz, 2H), 1.71 (p, *J* = 7.6 Hz, 2H), 1.32 (m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.0, 132.6, 130.1, 128.8, 128.6, 126.1, 63.8, 35.7, 32.2, 31.4. GCMS (EI) calculated for $[M]^+$ 176.1, found 176.1. FTIR (neat, cm^{-1}): 3333 (br), 3025 (s), 2929 (s), 2856 (s), 1669 (w), 1603 (w), 1495 (m), 1458 (m), 1086 (m), 970 (s), 747 (s), 698 (s).



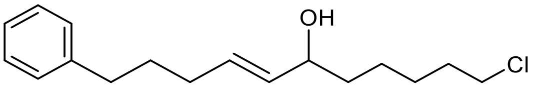
(6*E*)-1-methoxy-10-phenyldec-6-en-5-ol (1.39) was prepared according to general procedure A and was obtained as a colorless liquid (108 mg, 82% yield) after purification by alumina chromatography (0-45% EtOAc in hexanes). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.31 – 7.23 (m, 2H), 7.21 – 7.12 (m, 3H) 5.70 – 5.59 (m, 1H), 5.46 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.28 (s, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.15 – 2.01 (m, 2H), 1.78 – 1.61 (m, 2H), 1.58 – 1.46 (m, 5H), 1.45 – 1.32 (m, 2 H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.6, 133.9, 131.0, 128.4, 128.3, 125.7, 72.7, 72.7, 58.2, 37.2, 35.3, 31.8, 31.1, 29.9, 22.2. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{17}H_{26}O$, 245.2; found 245.0. FTIR (neat, cm^{-1}): 3400 (br), 3025 (m), 2929 (s), 2857 (s), 1670 (w), 1603 (w), 1496 (m), 1453 (s), 1118 (s), 968 (s), 748 (m), 699 (s).



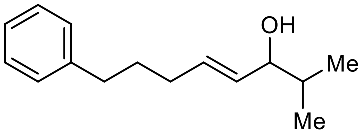
(2*E*)-1-cyclohexyl-6-phenylhex-2-en-1-ol (1.40) was prepared according to general procedure A and was obtained as a colorless liquid (89 mg, 69% yield) after purification by alumina chromatography (0-30% EtOAc in hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.27 (t, *J* = 7.5 Hz, 2H), 7.21 – 7.14 (m, 3H), 5.65 – 5.58 (m, 1H), 5.46 (dd, *J* = 15.4, 7.4 Hz, 1H), 3.77 – 3.72 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.12 – 2.05 (m, 2H), 1.84 (d, *J* = 13.0 Hz, 1H), 1.77 – 1.61 (m, 6H), 1.45 – 1.29 (m, 2H), 1.27 – 1.12 (m, 3H), 1.02 – 0.91 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.0, 132.7, 132.4, 128.8, 128.6, 126.0, 77.9, 44.2, 35.8, 32.3, 31.6, 29.3, 29.1, 27.1, 26.7, 26.6. GCMS (EI) calculated for $[M]^+$ 258.2, found 258.3. FTIR (neat, cm^{-1}): 3367 (br), 3025 (m), 2922 (s), 2851 (s), 1603 (w), 1496 (m), 1450 (s), 1080 (w), 1003 (m), 969 (m), 891 (w), 747 (m), 698 (s).



(*E*)-1-(4-methoxyphenyl)-8-phenyloct-4-en-3-ol (1.41) was prepared according to general procedure A and was obtained as a clear yellow liquid (115 mg, 74% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.22 – 7.07 (m, 5H), 6.86 – 6.78 (m, 2H), 5.67 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.50 (dd, *J* = 15.4, 6.8 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.79 (s, 3H), 2.75 – 2.52 (m, 4H), 2.15 – 2.02 (m, 2H), 1.92 – 1.64 (m, 4H), 1.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 142.4, 134.1, 133.4, 131.9, 129.4, 128.5, 128.4, 125.8, 113.9, 72.4, 55.3, 39.2, 35.5, 31.8, 31.0. MS-ESI (m/z): $[M+NH4]^+$ calculated for $C_{21}H_{30}NO_2$, 328.2, found 328.1. FTIR (neat, cm^{-1}): 3389 (br), 3061 (m), 2931 (s), 2855 (s), 1879 (w), 1668 (m), 1611 (s), 1519 (s), 1245 (s), 970 (m), 821 (m), 699 (m).

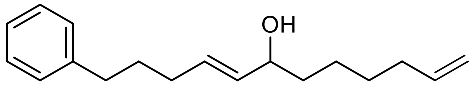


(4*E*)-11-chloro-1-phenylundec-4-en-6-ol (1.42) was prepared according to general procedure A and was obtained as a yellow liquid (118 mg, 84% yield) after purification by alumina chromatography (0-30% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34 – 7.24 (m, 3H), 7.23 – 7.13 (m, 3H), 5.66 (dt, *J* = 15.4, 7.4 Hz, 1H), 5.47 (ddt, *J* = 15.4, 7.0, 1.3 Hz, 1H), 4.12 – 3.96 (m, 1H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.69 – 2.57 (m, 2H), 2.15 – 2.01 (m, 2H), 1.83 – 1.67 (m, 4H), 1.56 – 1.34 (m, 7H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.3, 133.5, 131.6, 128.5, 128.3, 125.8, 72.9, 45.0, 37.1, 35.4, 32.6, 31.8, 30.9, 26.8, 24.8. MS-ESI (m/z): [M-OH]$^+$ calculated for $C_{17}H_{24}Cl$, 263.2; found, 263.0. FTIR (neat, cm^{-1}): 3366 (br), 3025 (m), 2932 (s), 2857 (s), 1602 (w), 1495 (s), 1453 (s), 1309 (m), 969 (s), 768 (m), 699 (s).

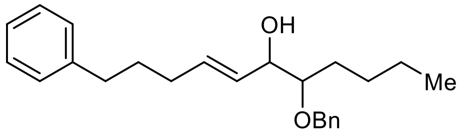


(4*E*)-2-methyl-8-phenyloct-4-en-3-ol (1.43) was prepared according to general procedure A and was obtained as a colorless liquid (91 mg, 84% yield) after purification by alumina chromatography (0-30% EtOAc in hexanes). ^{1}H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.10 (m, 3H) 5.65 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.47 (dd, *J* = 15.4, 6.6 Hz, 1H), 3.76 (t, *J* = 6.6 Hz, 1H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.18 – 2.01 (m, 2H), 1.78 – 1.59 (m, 3H) 1.48 – 1.36 (m, 1H), 0.97 – 0.78 (m, 6H). ^{13}C NMR (126 MHz, CD$_2$Cl$_2$) δ 143.0, 132.5, 132.4, 128.9, 128.7, 126.1, 78.4, 35.8, 34.3, 32.3, 31.6, 18.5, 18.4. GCMS (EI) calculated for [M]$^+$ 218.2, found

218.1. FTIR (neat, cm^{-1}): 3376 (br), 3026 (m), 2930 (s), 2870 (s), 1603 (w), 1496 (m), 1457 (s), 1382 (w), 1014 (s), 969 (s), 746 (m), 699 (s).

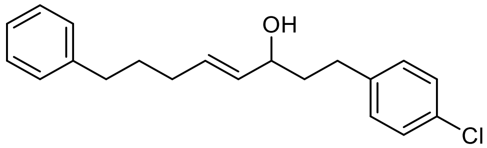


(4*E*)-1-phenyldodeca-4,11-dien-6-ol (1.44) was prepared according to general procedure A and was obtained as a colorless liquid (121 mg, 91% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.27 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.21 – 7.13 (m, 3H), 5.82 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1H), 5.69 – 5.59 (m, 1H), 5.46 (ddt, *J* = 15.3, 7.0, 1.4 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.92 (ddt, *J* = 10.2, 2.4, 1.3 Hz, 1H), 4.05 – 3.97 (m, 1H), 2.65 – 2.58 (m, 2H), 2.11 – 2.00 (m, 4H), 1.75 – 1.65 (m, 2H), 1.53 – 1.30 (m, 7H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.0, 139.5, 134.3, 131.6, 128.9, 128.7, 126.1, 114.5, 73.3, 37.7, 35.7, 34.2, 31.5, 29.9, 25.5. GCMS (EI) calculated for $[M]^+$ 258.2, found 258.3. FTIR (neat, cm^{-1}): 3347 (br), 3062 (m), 3025 (m), 2928 (s), 2856 (s), 1640 (m), 1496 (s), 1453 (s), 968 (s), 909 (m), 747 (m), 699 (s).

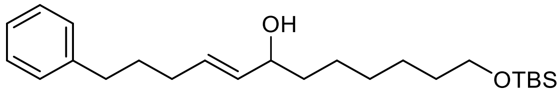


(*E*)-7-(benzyloxy)-1-phenylundec-4-en-6-ol (1.45) was prepared according to general procedure A and was obtained as a clear colorless liquid (125 mg, 71% yield, 1:1 dr) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) *major isomer:* δ 7.42 – 6.88 (m, 10H), 5.78 – 5.56 (m, 1H), 5.42 (td, *J* = 15.9, 7.1 Hz, 1H), 4.61 – 4.42 (m, 2H), 4.20 – 4.11 (m, 1H), 3.35 (dt, *J* = 8.0, 3.7 Hz, 1H), 2.64 – 2.33 (m, 3H), 2.09 – 1.93 (m, 2H), 2.09 – 1.96 (m, 2H), 1.54 – 1.38 (m, 2H), 1.30 – 1.16 (m, 4H), 0.84 –

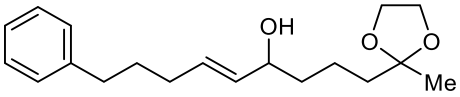
0.77 (m, 3H) *minor isomer peaks*: δ 4.01 – 3.90 (m, 1H), 3.30 – 3.18 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) *major isomer*: δ 142.5, 138.7, 133.9, 129.7, 128.6, 128.6, 128.0, 127.9, 125.9, 82.8, 74.5, 72.6, 35.5, 32.1, 31.0, 30.2, 28.1, 23.1, 14.2. *minor isomer*: δ 142.5, 138.5, 133.5, 128.9, 128.6, 128.4, 127.9, 127.8, 125.8, 82.6, 73.8, 72.4, 35.5, 32.0, 30.9, 29.4, 27.3, 22.9, 14.2. MS-ESI (m/z): $[M+NH4]^+$ calculated for $C_{24}H_{36}NO_2$, 370.3, found 370.2. FTIR (neat, cm^{-1}): 3448 (br), 3084 (w), 2929 (s), 1696 (w), 1603 (w), 1497 (m), 1453 (m), 1376 (m), 1222 (m), 1065 (m), 969 (m), 690 (m).



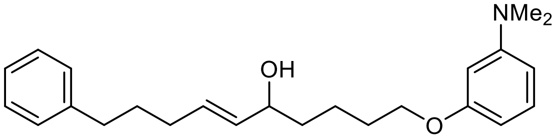
(4*E*)-1-(4-chlorophenyl)-8-phenyloct-4-en-3-ol (1.46) was prepared according to general procedure A and was obtained as a colorless liquid (119 mg, 77% yield) after purification by alumina chromatography (0-40% EtOAc in hexanes). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.38 – 7.07 (m, 9H), 5.67 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.50 (dd, *J* = 15.3, 6.8 Hz, 1H), 4.09 – 3.96 (m, 1H), 2.78 – 2.53 (m, 4H), 2.16 – 2.01 (m, 2H), 1.88 – 1.63 (m, 4H), 1.48 (s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.9, 141.3, 133.8, 132.1, 131.7, 130.3, 128.8, 128.7, 126.1, 72.5, 39.2, 35.7, 32.2, 31.5, 31.4. GCMS (EI) calculated for $[M]^+$ 314.1, found 314.2. FTIR (neat, cm^{-1}): 3348 (br), 3025 (m), 2929 (s), 2856 (s), 1603 (w), 1491 (s), 153 (s), 1092 (s), 1015 (s), 969 (s), 835 (m), 748 (m), 699 (s).



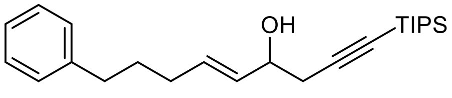
(*E*)-12-((tert-butyldimethylsilyl)oxy)-1-phenyldodec-4-en-6-ol (1.47) was prepared according to general procedure A and was obtained as a clear colorless liquid (141 mg, 72% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 3H), 7.20 (m, 2H), 5.67 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.50 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.19 – 2.04 (m, 2H), 1.75 (m, 2H), 1.53 (m, 3H), 1.35 (s, 5H), 1.33 – 1.24 (m, 2H), 0.93 (s, 9H), 0.09-0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 133.7, 131.5, 128.6, 128.4, 125.8, 73.2, 63.4, 37.4, 35.5, 32.9, 31.8, 31.0, 29.5, 26.1, 25.9, 25.6, 18.5, -5.1. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{24}H_{41}OSi$, 373.3, found 373.3. FTIR (neat, cm^{-1}): 3355 (br), 3062 (m), 2929 (s), 2856 (s), 1496 (m), 1462 (m), 1361 (w), 1255 (m), 1099 (s), 968 (m), 836 (s), 775 (m).



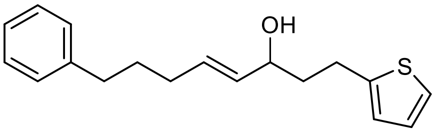
(*E*)-1-(2-methyl-1,3-dioxolan-2-yl)-9-phenylnon-5-en-4-ol (1.48) was prepared according to general procedure A and was obtained as a clear colorless liquid (117 mg, 77% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 2H), 7.17 (m, 3H), 5.65 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.47 (ddt, *J* = 15.3, 6.9, 1.3 Hz, 1H), 4.10 – 3.97 (m, 1H), 3.99 – 3.83 (m, 4H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.16 – 2.02 (m, 2H), 1.79 – 1.58 (m, 5H), 1.56 – 1.39 (m, 4H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 133.6, 131.5, 128.5, 128.4, 125.8, 110.2, 73.0, 64.7, 39.1, 37.6, 35.4, 31.8, 30.9, 23.8, 20.2. MS-ESI (m/z): $[M+NH4]^+$ calculated for $C_{19}H_{32}NO_3$, 322.2; found 322.0. FTIR (neat, cm^{-1}): 3448 (br), 3026 (m), 2929 (s), 1696 (m), 1603 (m), 1497 (m), 1376 (m), 1222 (m), 1065 (m), 969 (m), 690 (m).



(6*E*)-1-[3-(dimethylamino)phenoxy]-10-phenyldec-6-en-5-ol (1.49) was prepared according to general procedure A, but on a 0.25 mmol scale, and was obtained as a yellow liquid (65 mg, 71% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.30 – 7.22 (m, 2H), 7.21 – 7.03 (m, 4H), 6.32 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.72 – 6.19 (m, 2H), 5.73 – 5.60 (m, 1H), 5.48 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.10 – 4.00 (m, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 2.90 (s, 6H), 2.62 (t, *J* = 7.8, 2H), 2.15 – 2.01 (m, 2H), 1.82 – 1.64 (m, 4H), 1.61 – 1.43 (m, 5H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 160.6, 152.6, 143.0, 134.1, 131.7, 130.0, 128.8, 128.6, 126.0, 105.9, 102.5, 99.9, 73.2, 68.0, 40.8, 37.5, 35.7, 32.1, 31.4, 29.8, 22.5. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{24}H_{34}NO_2$, 368.3; found 368.3. FTIR (neat, cm^{-1}): 3388 (br), 3025 (m), 2930 (s), 2857 (s), 1614 (s), 1502 (s), 1452 (s), 1353 (m), 1239 (s), 1151 (s), 969 (m), 827 (w), 749 (m), 686 (m).

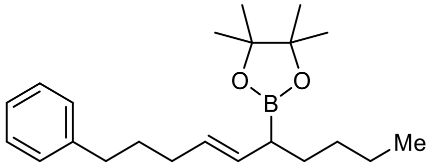


(*E*)-9-phenyl-1-(triisopropylsilyl)non-5-en-1-yn-4-ol (1.50) was prepared according to general procedure A and was obtained as a clear yellow liquid (104 mg, 56% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 2H), 7.19 – 7.09 (m, 3H), 5.80 – 5.65 (m, 1H), 5.52 (ddt, *J* = 15.4, 6.3, 1.4 Hz, 1H), 4.26 – 4.11 (m, 1H), 2.64 – 2.56 (t, *J* = 7.7 Hz, 2H), 2.55 – 2.40 (m, 2H), 2.09 – 2.00 (m, 2H), 1.70 (q, *J* = 7.8 Hz, 2H), 1.05-0.98 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 132.5, 131.4, 128.6, 128.4, 125.8, 104.5, 83.8, 70.9, 35.5, 31.8, 30.8, 29.5, 18.8, 11.4. MS-ESI (m/z): $[M+NH4]^+$ calculated for $C_{24}H_{42}NOSi$, 388.3; found 388.2. FTIR (neat, cm^{-1}): 3338 (br), 3063 (m), 2940 (s), 2864 (s), 2173 (s), 1495 (m), 1464 (m), 1382 (m), 1243 (w), 966 (m), 883 (m), 746 (w).



(*E*)-8-phenyl-1-(thiophen-2-yl)oct-4-en-3-ol (1.51) was prepared according to general procedure A and was obtained as a clear yellow liquid (116 mg, 81% yield) after purification by alumina chromatography (0-35% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 – 7.16 (m, 2H), 7.15 – 7.07 (m, 3H), 7.04 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.84 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.78 – 6.73 (m, 1H), 5.61 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.43 (ddt, *J* = 15.4, 7.0, 1.3 Hz, 1H), 4.08 – 3.99 (m, 2H), 2.93 – 2.81 (m, 2H), 2.59 (t, *J* = 7.1 H, 2H), 2.06 – 1.95 (m, 2H), 1.95 – 1.74 (m, 2H), 1.65 (p, *J* = 7.6 Hz, 2H) 1.43 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.9, 142.4, 133.1, 132.2, 128.5, 128.4, 126.8, 125.8, 124.3, 123.1, 77.6, 76.7, 72.1, 39.1, 35.5, 31.8, 30.9, 26.0. MS-ESI (m/z): [M-OH]$^+$ calculated for $C_{18}H_{22}S$, 269.1, found 268.9. FTIR (neat, cm^{-1}): 3369 (br), 3062 (m), 2922 (s), 2854 (s), 1653 (w), 1603 (m), 1497 (m), 1453 (m), 1030 (m), 969 (m), 850 (w), 698 (s).

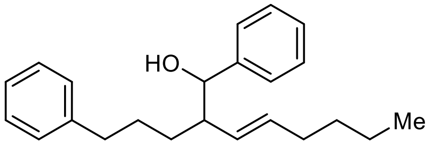
1.4.6. *Allylic Boronic Ester Product*



(*E*)-4,4,5,5-tetramethyl-2-(10-phenyldec-6-en-5-yl)-1,3,2-dioxaborolane (1.36), compound was prepared according to general procedure A, but instead of oxidizing the product *in situ*, the crude reaction mixture was filtered through a silica gel plug with EtOAc (20 mL). The filtrate was washed with brine (3 × 25 mL). The organic phase was dried over Na_2SO_4, and then concentrated under vacuum. The residue was then purified by silica gel chromatography (0-10%

diethyl ether in hexanes) and the product was isolated as a colorless liquid (136 mg, 79% yield). ;This compound decomposes on silica gel and it is best to perform the column chromatography in less than 10 minutes to preserve the yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.20 – 7.16 (m, 3H), 5.46 – 5.31 (m, 2H), 2.64 – 2.57 (m, 2H), 2.11– 1.97 (m, 2H), 1.81 – 1.63 (m, 3H), 1.56 – 1.28 (m, 6H), 1.24 (s, 12H), 0.95 – 0.84 (t, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 131.7, 129.2, 128.6, 128.3, 125.7, 83.1, 35.3, 32.4, 31.6, 31.5, 30.8, 24.9, 24.8, 22.8, 14.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.15. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{22}H_{36}BO_2$, 343.3; found 343.2. FTIR (neat, cm^{-1}): 2927 (s), 2857 (m), 1718 (w), 1617 (w), 1457 (w), 1371 (m), 1319 (m), 1269 (w), 1143 (s).

1.4.7. *Homoallylic Alcohol Product*

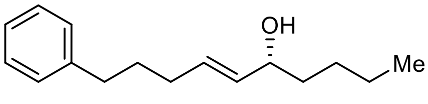


(*E*)-2-butyl-1,7-diphenylhept-3-en-1-ol (1.37), the reaction was performed according to general procedure A (at a 0.25 mmol scale), but instead of oxidizing the product *in situ*, the crude reaction mixture was filtered through a silica gel plug with EtOAc (25 mL). The filtrate was washed with brine (3 × 25 mL). The organic phase was dried over Na_2SO_4, and then concentrated under vacuum to afford the crude allylic boronic ester (**1.36**). The purity of crude allylic boronic ester was determined by ^{1}H NMR. This crude allylic boronic ester (0.2 mmol, 1.0 equiv) was added to a vial, followed by benzyl aldehyde (0.8 mmol, 4.0 equiv) and anhydrous toluene (1 mL, 0.2 M). The reaction mixture was allowed to stir at 60°C overnight under N_2 atmosphere. Upon completion, the solvent was removed under vacuum and the residue was purified by silica gel chromatography (0-15% EtOAc in hexanes) and isolated as a colorless liquid (60 mg, 74% yield overall) as a mixture of isomers (3:1, E:Z) as measured by ^{1}H NMR. The dr could not be established by ^{1}H NMR but is expected to be 1:1.[1] ^{1}H NMR (300 MHz, CDCl$_3$) *major isomer:* δ 7.28 – 7.04 (m, 8H), 7.02 – 6.97 (m, 2H), 5.64 (dt, *J* = 11.0, 7.3 Hz, 1H), 4.30 – 4.21 (m, 1H), 2.67 – 2.11 (m, 4H), 2.06 – 1.92 (m, 2H), 1.57 – 1.12 (m, 8H), 0.87 – 0.78 (m, 3H) *minor isomer peak:* δ 5.54 (dt, *J* = 15.4, 6.7 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) *major isomer:* δ 142.8, 142.6, 135.2, 129.9, 128.4, 128.3, 128.3, 127.6, 127.1, 125.7, 77.6, 77.5, 76.7, 46.0, 35.9, 32.0, 31.1, 29.2, 27.8, 22.5, 14.1. *minor isomer* δ 142.8, 142.6, 135.2, 129.9, 128.4, 128.3, 128.3, 127.6, 127.1, 125.7, 77.0, 46.0, 35.9, 32.5, 31.8, 30.6, 27.8, 22.3, 14.1. MS-ESI (m/z): [M+NH4]$^+$ calculated for $C_{23}H_{34}NO$, 340.3, found 340.1. FTIR (neat, cm^{-1}): 3368 (br), 3026 (m), 2956 (s), 2929 (s), 1603 (w), 1496 (m), 1464 (m), 1457 (m), 1363 (w), 1013 (m), 969 (m), 746 (m), 698(s).

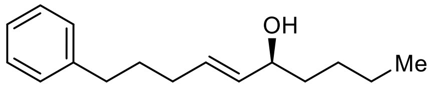
1.4.8. *Enantioenriched Allylic Alcohols*

Enantioenriched allylic alcohols **(*R*)-1.18**, **(*S*)-1.18**, **(*R*)-1.72**, **(*R*)-1.73,** and **(*R*)-1.75** were prepared according to general procedure A using enantioenriched α-chloro pinanediol boronic esters **1.65**, **1.117**, **1.118**, **1.119**, **1.120** and 5-phenylpentyne (**1.60**). Allylic alcohol **(*R*)-1.43** was prepared according to general procedure A using enantioenriched α-chloro pinacol boronic ester (**1.121**) and 5-phenylpentyne (**1.60**). Enantiomeric excess (ee) was determined by chiral HPLC either of the product alcohol or the benzoyl derivative of the product alcohol.

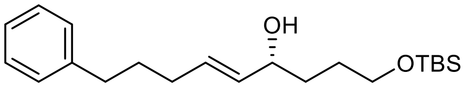
Note: Because mobile phases with low polarity (often < 0.1% iPrOH in hexanes) were used in HPLC analyses of benzoyl derivatives, retention times of some isomers may not be identical in the results of chiral and enantioenriched samples due to minor solvent variations.



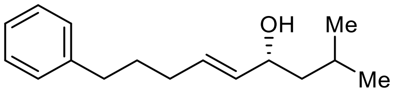
(5*R*,6*E*)-10-phenyldec-6-en-5-ol ((*R*)-1.18), compound was prepared according to general procedure A and was purified by alumina chromatography (0-25% EtOAc in hexanes) and was isolated as a colorless liquid (97 mg, 70% yield, 97% ee). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 5.68 – 5.59 (m, 1H), 5.46 (dd, *J* = 15.4, 7.0 Hz, 1H), 4.04 – 3.97 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.11 – 2.03 (m, 2H), 1.75 – 1.65 (m, 2H), 1.56 – 1.38 (m, 3H), 1.35 – 1.25 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.0, 134.4, 131.5, 128.9, 128.7, 126.1, 73.3, 37.6, 35.7, 32.2, 31.5, 28.2, 23.1, 14.3. GCMS (EI) calculated for $[M]^+$ 232.2, found 232.0. FTIR (neat, cm^{-1}): 3345 (br), 3026 (m), 2929 (s), 2856 (s), 1604 (w), 1496 (m), 1453 (m), 968 (m), 746 (m), 699 (s). Enantiomeric excess was determined by chiral HPLC of the alcohol. CHIRALPAK AD-H column (0.2% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 61.6 min (major), 70.9 min (minor). $[\alpha]_D^{23}$ = +4.9 (c 0.51, $CHCl_3$).



(5*S*,6*E*)-10-phenyldec-6-en-5-ol ((*S*)-1.18), compound was prepared according to general procedure A and was purified by alumina chromatography (0-25% EtOAc in hexanes) and was isolated as a colorless liquid (104 mg, 75% yield, 98% ee). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 5.67 – 5.60 (m, 1H), 5.47 (dd, *J* = 15.4, 7.0 Hz, 1H), 4.04 – 3.97 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.11 – 2.03 (m, 2H), 1.75 – 1.65 (m, 2H), 1.55 – 1.39 (m, 3H), 1.36 – 1.25 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 143.0, 134.4, 131.5, 128.7, 128.4, 126.1, 73.3, 37.6, 35.7, 32.2, 31.5, 28.2, 23.1, 14.3. GCMS (EI) calculated for $[M]^+$ 232.2, found 232.0. FTIR (neat, cm^{-1}): 3342 (br), 3026 (m), 2928 (s), 2857 (s), 1604 (w), 1496 (m), 1453 (m), 968 (m), 746 (m), 699 (s). Enantiomeric excess was determined by chiral HPLC of the alcohol. CHIRALPAK AD-H column (0.2% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 62.7 min (minor), 67.5 min (major). $[\alpha]_D^{23}$ = -5.2 (c 0.81, $CHCl_3$).

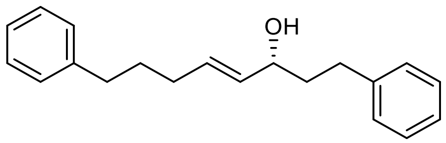


(4*R*,5*E*)-1-[(tert-butyldimethylsilyl)oxy]-9-phenylnon-5-en-4-ol ((*R*)-1.72), compound was prepared according to general procedure A and was purified by alumina chromatography (0-30% EtOAc in hexanes) and was isolated as a yellow liquid (148.0 mg, 85% yield, 99% ee). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 5.76 – 5.58 (m, 1H), 5.49 (ddt, *J* = 15.4, 6.7, 1.3 Hz, 1H), 4.16 – 3.97 (m, 1H), 3.74 – 3.54 (m, 2H), 2.77 – 2.54 (m, 3H), 2.38 (s, 1H), 2.17 – 1.99 (m, 2H), 1.80 – 1.53 (m, 6H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 133.6, 131.1, 128.5, 128.3, 125.8, 72.6, 63.4, 35.4, 34.7, 31.8, 30.9, 29.0, 26.0, 18.4, -5.3. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{21}H_{35}OSi$, 331.2; found, 331.0. FTIR (neat, cm^{-1}): 3364 (br), 3026 (m), 2926 (s), 2855 (s), 1604 (w), 1463 (m), 1255 (m), 1096 (s), 1005 (m), 968 (m), 835 (s), 775 (m), 698 (m). Enantiomeric excess was determined by chiral HPLC results of its benzoyl derivative. CHIRALPAK AD-H column (0.05% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 14.7 min (major), 16.1 min (minor). $[\alpha]_D^{22}$ = +5.8 (c 1.15, $CHCl_3$).

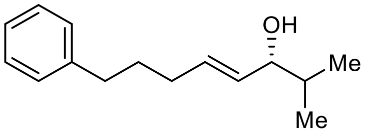


(4*R*,5*E*)-2-methyl-9-phenylnon-5-en-4-ol ((*R*)-1.73), compound was prepared according to general procedure A and was purified by alumina chromatography (0-20% EtOAc in hexanes) and was isolated as a yellow liquid (88.1 mg, 76% yield, 99% ee). ^1H NMR (500 MHz, $CDCl_3$) δ

7.29 - 2.26 (m, 2H), 7.20 - 7.17 (m, 3H), 5.66 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.47 (dd, *J* = 15.4, 7.6 Hz, 1H), 4.17 – 4.05 (m, 1H), 2.62 (t, *J* = 8.2 Hz, 2H), 2.12 – 2.01 (m, 2H), 1.73 - 1.69 (m, 3H), 1.52 – 1.37 (m, 2H), 1.36 – 1.23 (m, 2H), 0.98 – 0.88 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 134.0, 131.3, 128.5, 128.4, 125.8, 71.4, 46.6, 35.5, 31.8, 31.0, 24.7, 23.0, 22.6. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{16}H_{24}ONa$, 255.2; found, 255.0. FTIR (neat, cm^{-1}): 3356 (br), 3025 (w), 2953 (s), 2928 (s), 2866 (m), 1495 (m), 1453 (m), 968 (m), 747 (w), 698 (s). Enantiomeric excess was determined by chiral HPLC of its benzoyl derivative. CHIRALPAK AD-H column (0.1% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 14.5 min (major), 16.0 min (minor). $[\alpha]_D{}^{22}$ = +8.2 (c 1.03, $CHCl_3$).



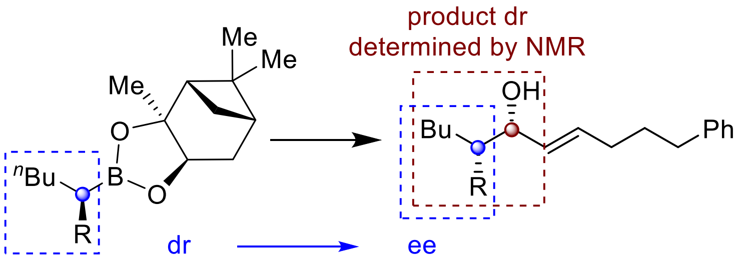
(3*R*,4*E*)-1,8-diphenyloct-4-en-3-ol ((*R*)-1.75), compound was prepared according to general procedure A and was purified by alumina chromatography (0-20% EtOAc in hexanes) and was isolated as a yellow liquid (102.1 mg, 73% yield, 98% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.28 (m, 4H), 7.24 – 7.15 (m, 6H), 5.69 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.59 – 5.46 (m, 1H), 4.16 – 4.04 (m, 1H), 2.79 – 2.55 (m, 3H), 2.23 – 2.01 (m, 2H), 1.96 – 1.65 (m, 4H), 1.54 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 142.1, 133.4, 131.9, 128.5, 128.4, 128.4, 125.9, 125.8, 72.4, 38.9, 35.5, 31.9, 31.8, 30.9. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{20}H_{24}ONa$, 303.2; found, 303.0. FTIR (neat, cm^{-1}): 3354 (br), 3025 (m), 2928 s), 2856 (s), 1602 (m), 1495 (s), 1456 (s), 1030 (m), 969 (m), 769 (s), 698 (s). Enantiomeric excess was determined by chiral HPLC of the alcohol. CHIRALPAK AD-H column (0.4% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 61.5 min (major), 67.3 min (minor). $[\alpha]_D{}^{22}$ = +4.9 (c 0.98, $CHCl_3$).



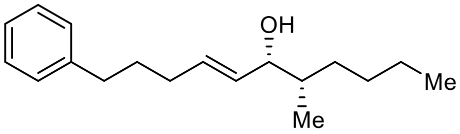
(3*R*,4*E*)-2-methyl-8-phenyloct-4-en-3-ol ((*R*)-1.43), compound was prepared according to general procedure A starting from enantioenriched α-chloro pinacol boronic ester (**1.121**) and was purified by alumina chromatography (0-20% EtOAc in hexanes) and was isolated as a yellow liquid (92.9 mg, 85% yield, 99% ee). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 5.66 (dtd, *J* = 15.4, 6.5, 0.9 Hz, 1H), 5.48 (ddt, *J* = 15.4, 7.2, 1.3 Hz, 1H), 3.96 – 3.47 (m, 1H), 2.76 – 2.42 (m, 2H), 2.28 – 1.97 (m, 2H), 1.90 – 1.66 (m, 3H), 1.44 (s, 1H), 1.01 – 0.86 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.5, 132.6, 131.8, 128.5, 128.4, 125.8, 78.3, 35.5, 33.9, 31.9, 31.1, 18.3, 18.3. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{15}H_{22}ONa$, 241.2; found, 241.0. FTIR (neat, cm^{-1}): 3385 (br), 3026 (m), 2956 (s), 2929 (s), 2870 (m), 1603 (w), 1496 (s), 1453 (s), 1381 (w), 1013 (m), 969 (m), 746 (m), 699 (s). Enantiomeric excess was determined by chiral HPLC results of its benzoyl derivative. CHIRALPAK AD-1 column (0.2% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 19.5 min (major), 23.6 min (minor). $[\alpha]_D^{22}$ = -5.9 (c 1.08, CHCl$_3$).

Enantioenriched Allylic Alcohols with Consecutive Stereocenters

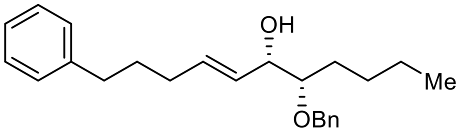
Scheme 0.9 ee and dr for Consecutive Stereocenter Substrates



The diastereomeric ratio (dr) of compounds ***(6R,7S)*-1.74**, ***(6S,7S)*-1.45**, ***(6S,7R)*-1.76**, and ***(6S,7R)*-1.77** was determined by ^{1}H NMR. Enantiomeric excess (ee) of compounds ***(6R,7S)*-1.74**, ***(6S,7S)*-1.45**, ***(6S,7R)*-1.76**, and ***(6S,7R)*-1.77** was determined by analysis of the corresponding alkyl boronic ester precursors **1.122**, **1.125**, **1.123**, and **1.124**.

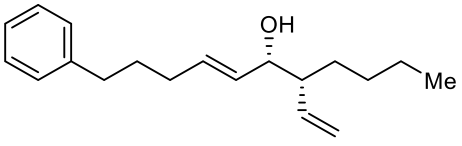


(4*E*,6*R*,7*S*)-7-methyl-1-phenylundec-4-en-6-ol ((*6R,7S*)-1.74), compound was prepared according to general procedure A and was purified by alumina chromatography (0-20% EtOAc in hexanes) and was isolated as a yellow liquid (104.2 mg, 80% yield, 96% ee, >20:1 dr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.28 – 7.11 (m, 3H), 5.76 – 5.57 (m, 1H), 5.49 (m, 1H), 3.92 (dd, *J* = 6.9, 4.9 Hz, 1H), 2.63 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.16 – 2.05 (m, 2H), 1.80 – 1.66 (m, 2H), 1.59 – 1.03 (m, 9H), 0.94 – 0.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 132.1, 128.5, 128.4, 125.8, 77.6, 77.0, 76.7, 39.0, 35.5, 32.4, 31.9, 31.0, 29.6, 23.1, 14.8, 14.2. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{18}H_{28}ONa$, 283.2; found, 283.1. FTIR (neat, cm^{-1}): 3380 (br), 3025 (m), 2955 (s), 2928 (s), 2856 (s), 1496 (m), 1453 (s), 1377 (w), 968 (m), 744 (m), 698 (s). The ee was determined based on its α-chloro Bpinane precursor **1.122**. $[\alpha]_D^{23}$ = -14.3 (c 1.16, $CHCl_3$).

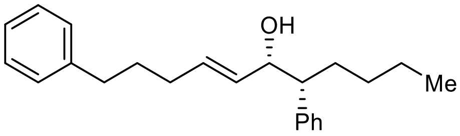


(4*E*,6*S*,7*S*)-7-(benzyloxy)-1-phenylundec-4-en-6-ol ((*6S,7S*)-1.45), compound was prepared according to general procedure A and was purified by alumina chromatography (0-40% EtOAc in hexanes) and was isolated as a yellow liquid (132.1 mg, 75% yield, >20:1 er, >20:1 dr). ^{1}H

NMR (300 MHz, CDCl$_3$) δ 7.29 – 7.17 (m, 7H), 7.13 – 7.05 (m, 3H), 5.79 – 5.60 (m, 1H), 5.39 (ddt, *J* = 15.4, 7.2, 1.5 Hz, 1H), 4.62 – 4.38 (m, 2H), 3.95 (t, *J* = 6.9 Hz, 1H), 3.24 (td, *J* = 6.2, 4.8 Hz, 1H), 2.63 – 2.48 (m, 2H), 2.10 – 1.95 (m, 2H), 1.70 – 1.60 (m, 2H), 1.59 – 1.10 (m, 7H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.3, 138.4, 133.5, 129.8, 128.5, 128.4, 128.3, 127.9, 127.8, 125.7, 82.7, 74.3, 72.5, 35.4, 31.9, 30.8, 30.1, 27.2, 23.0, 14.1. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{24}H_{32}O_2Na$, 375.2; found, 375.1. FTIR (neat, cm^{-1}): 3436 (br), 3026 (m), 2929 (s), 2857 (s), 1603 (w), 1495 (m), 1453 (s), 1207 (w), 1093 (s), 1028 (m), 970 (m), 744 (m), 698 (s). The er was determined based on its α-chloro Bpinane precursor **1.125**. $[\alpha]_D^{23}$ = +19.7 (c 1.28, CHCl$_3$).

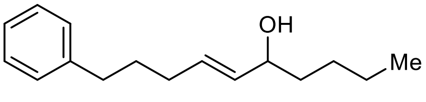


(4*E*,6*S*,7*R*)-7-ethenyl-1-phenylundec-4-en-6-ol ((*6S,7R*)-1.76), compound was prepared according to general procedure A and was purified by alumina chromatography (0-30% EtOAc in hexanes) and was isolated as a yellow liquid (75.0 mg, 55% yield, 93% ee, >20:1 dr). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 5.79 – 5.52 (m, 2H), 5.52 – 5.38 (m, 1H), 5.23 – 5.07 (m, 2H), 3.83 (t, *J* = 7.1 Hz, 1H), 2.69 – 2.56 (m, 2H), 2.18 – 1.95 (m, 3H), 1.81 – 1.66 (m, 3H), 1.47 (m, 1H), 1.36 – 1.15 (m, 5H), 0.93 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.4, 139.4, 133.2, 131.4, 128.5, 128.3, 125.7, 118.0, 75.2, 51.1, 35.4, 31.8, 30.9, 30.1, 29.5, 22.7, 14.0. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{19}H_{28}ONa$, 295.2; found, 295.1. FTIR (neat, cm^{-1}): 3420 (br), 3026 (m), 2929 (s), 2858 (s), 1635 (w), 1496 (m), 1452 (m), 969 (m), 912 (m), 735 (m), 698 (m). The ee was determined based on its α-chloro Bpinane precursor **1.123**. $[\alpha]_D^{23}$ = +7.3 (c 1.13, CHCl$_3$).

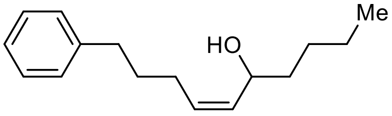


(4*E*,6*S*,7*R*)-1,7-diphenylundec-4-en-6-ol ((*6S,7R*)-1.77), compound was prepared according to general procedure A and was purified by alumina chromatography (0-30% EtOAc in hexanes) and was isolated as a yellow liquid (111.6 mg, 65% yield, 96% ee, 14:1 dr). ^{1}H NMR (300 MHz, $CDCl_3$) *major isomer:* δ 7.55 – 6.78 (m, 10H), 5.70 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.62 – 5.34 (m, 1H), 4.14 (t, *J* = 7.6 Hz, 1H), 2.99 – 2.48 (m, 3H), 2.18 – 2.05 (m, 2H), 1.84 – 1.67 (m, 3H), 1.67 – 1.51 (m, 1H), 1.43 – 1.37 (m, 1H), 1.32 – 1.03 (m, 4H), 0.81 (t, *J* = 7.2 Hz, 3H). *minor isomer peak*: 5.36 (dd, *J* = 15.4, 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 141.7, 133.5, 131.8, 128.9, 128.6, 128.6, 128.4, 126.8, 125.8, 52.8, 35.5, 31.9, 31.8, 30.9, 29.7, 22.8, 14.1, 11.1. MS-ESI (m/z): $[M+NH_4]^+$ calculated for $C_{23}H_{34}ON$, 340.3; found, 340.2. FTIR (neat, cm^{-1}): 3435 (br), 3062 (w), 3026 (m), 2928 (s), 2857 (s), 1602 (m), 1497 (s), 1457 (m), 1378 (w), 1081 (w), 1030 (m), 969 (m), 747 (m), 699 (s). The ee was determined by its α-chloro Bpinane precursor **1.124**. $[\alpha]_D^{23}$ = -12.9 (c 1.14, $CHCl_3$).

1.4.9. *Determination of E/Z Selectivity*



(6*E*)-10-phenyldec-6-en-5-ol (**18**)

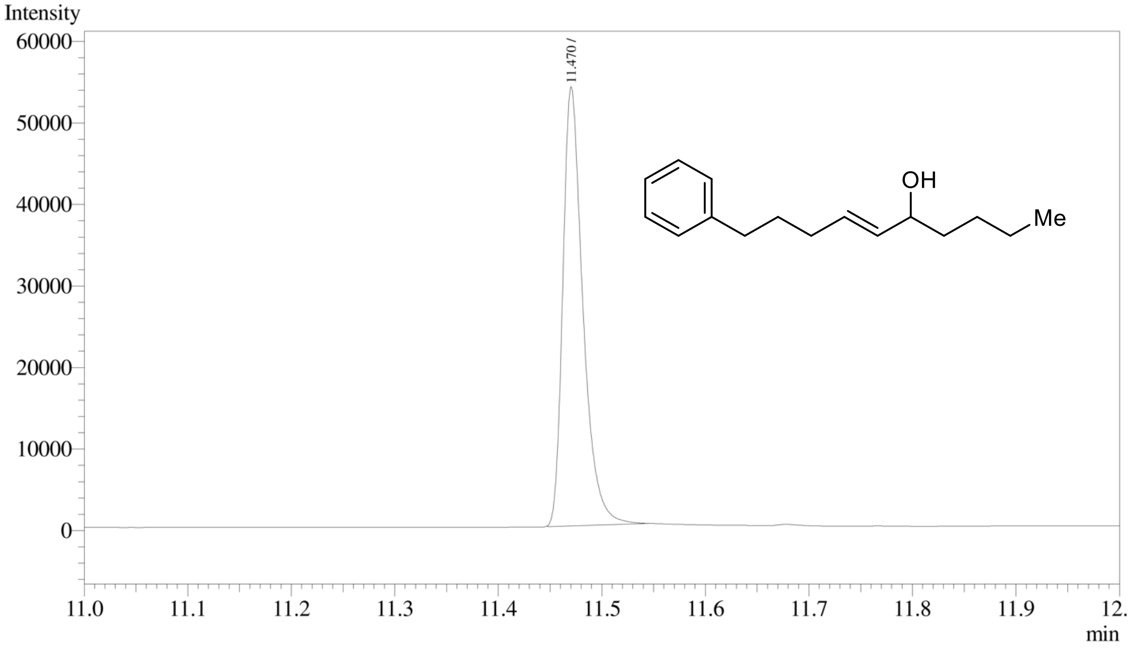


(6*Z*)-10-phenyldec-6-en-5-ol (***Z*-18**)

(6*Z*)-10-phenyldec-6-en-5-ol (*Z*-1.18) was synthesized according to a previously reported procedure[104] and isolated as a colorless liquid (32.0 mg, 39% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.20 – 7.16 (m, 2H), 7.10 – 7.05 (m, 3H), 5.40 (ddt, *J* = 11.1, 8.4, 1.3 Hz, 1H), 5.36 – 5.29 (m, 1H), 4.29 – 4.23 (m, 1H), 2.47 (td, *J* = 7.5, 3.3 Hz, 2H), 2.04 – 1.89 (m, 2H), 1.59 – 1.50 (m, 3H), 1.40 – 1.22 (m, 5H), 0.96 (s, 1H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 142.4, 134.4, 130.8, 128.8, 128.7, 128.4, 126.2, 67.6, 37.9, 35.7, 31.7, 28.0, 27.4, 23.1, 14.3. GCMS (EI) calculated for $[M]^+$ 232.2, found 232.1. FTIR (neat, cm^{-1}): 3366 (br), 3025 (m), 2929 (s), 2858 (s), 1603 (w), 1496 (w), 1465 (m), 1020 (m), 742 (w), 698 (m).

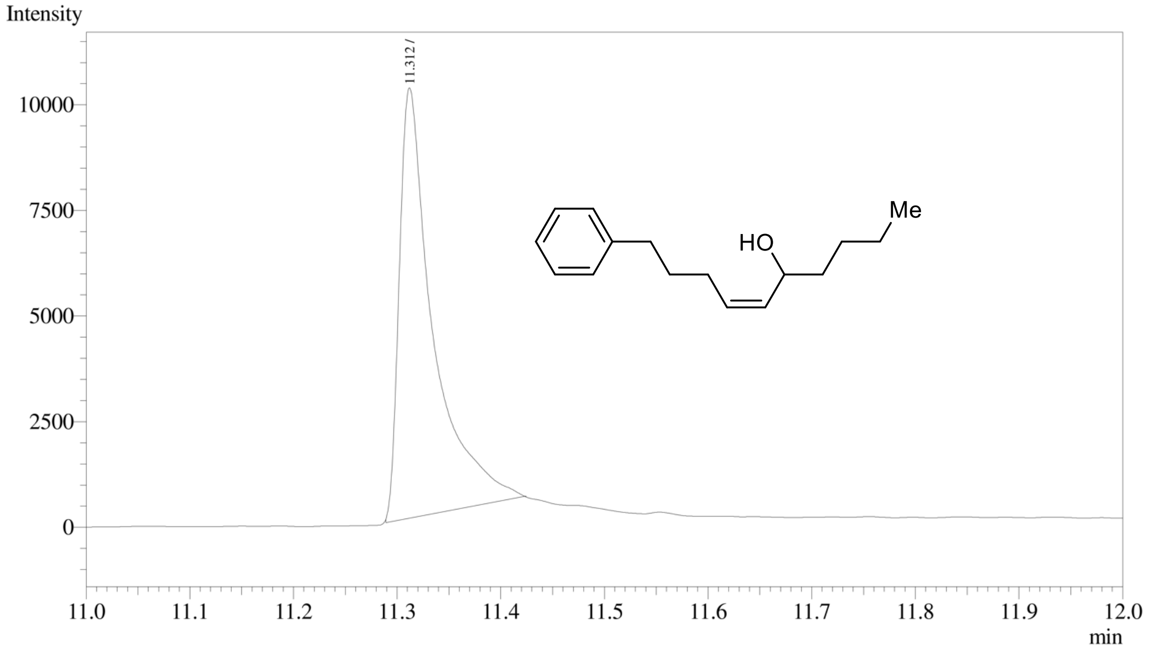
To determine the E:Z ratio of the reaction, the GC traces of (6*E*)-10-phenyldec-6-en-5-ol (**1.18**) and (6*Z*)-10-phenyldec-6-en-5-ol (***Z*-1.18**) were analyzed. Provided are GC traces of pure (6*E*)-10-phenyldec-6-en-5-ol, pure (6*Z*)-10-phenyldec-6-en-5-ol, a mixture of both pure isomers, and a GC trace of the crude reaction mixture of the synthesis of (6*E*)-10-phenyldec-6-en-5-ol at the end of the oxidation as described in general method A.

GC trace of isolated (6*E*)-10-phenyldec-6-en-5-ol (**1.18**).



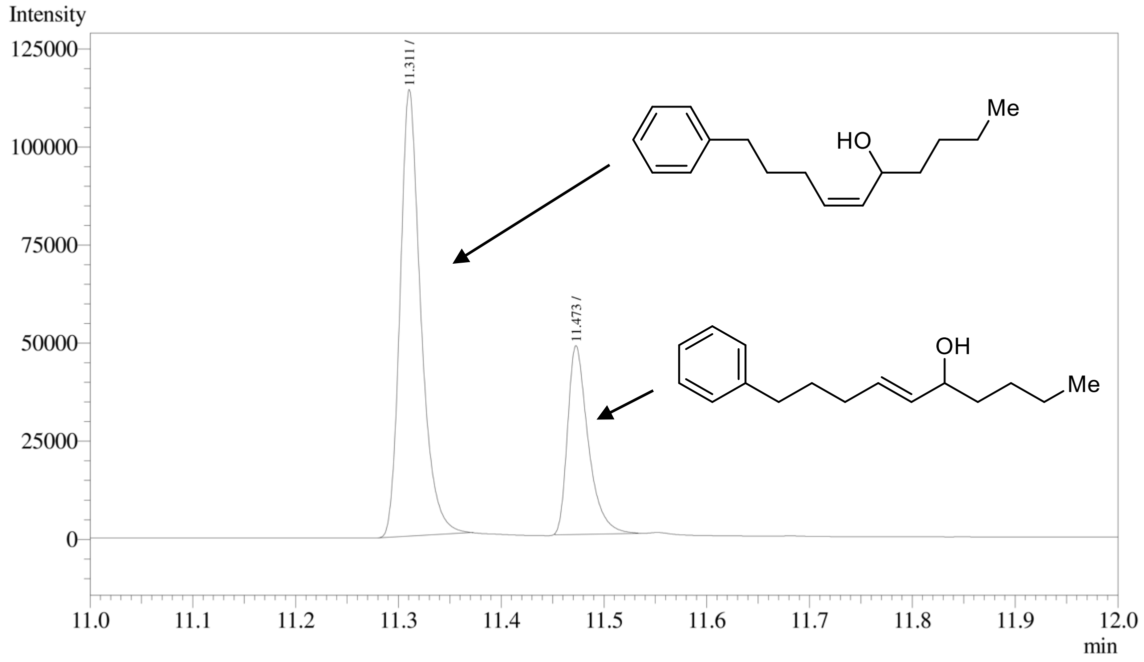
Peak#	Ret.Time	Area	Height	Conc.
1	11.470	72761	52203	100.000
Total		72761	52203	

GC trace of isolated (6*Z*)-10-phenyldec-6-en-5-ol (***Z*-1.18**).



Peak#	Ret.Time	Area	Height	Conc.
1	11.312	23196	10012	100.000
Total		23196	10012	

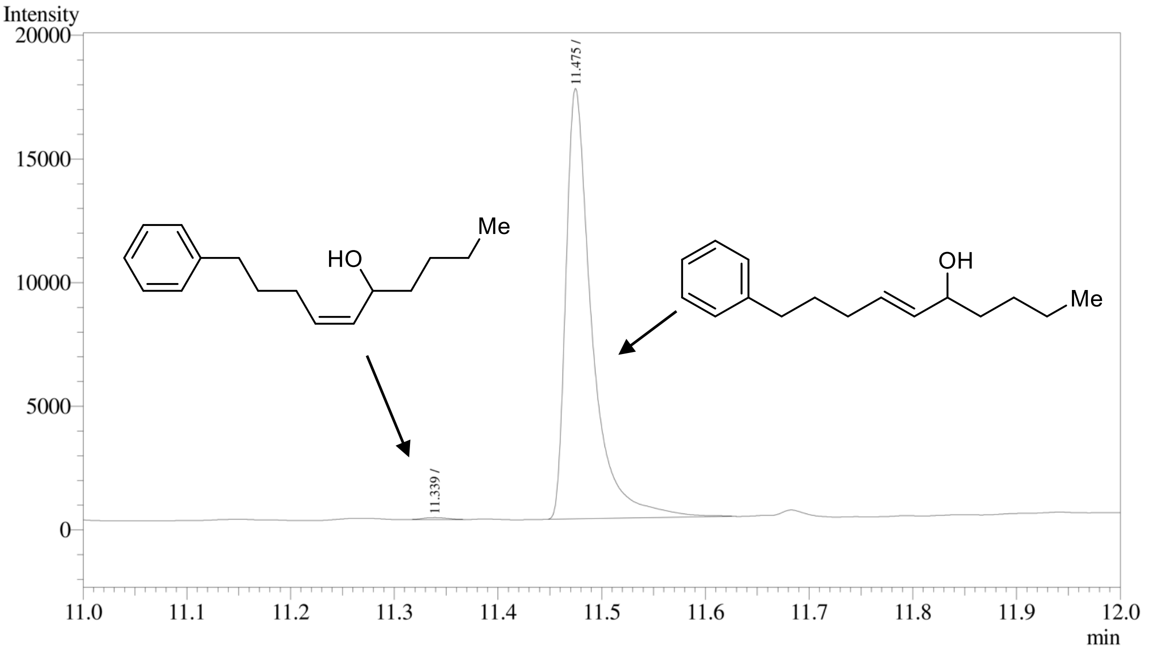
GC trace of a mixture of (6*E*)-10-phenyldec-6-en-5-ol (**1.18**) and (6*Z*)-10-phenyldec-6-en-5-ol (***Z*-1.18**).



Peak#	Ret.Time	Area	Height	Conc.
1	11.311	160028	112310	70.424
2	11.473	67207	47372	29.576
Total		227235	159682	

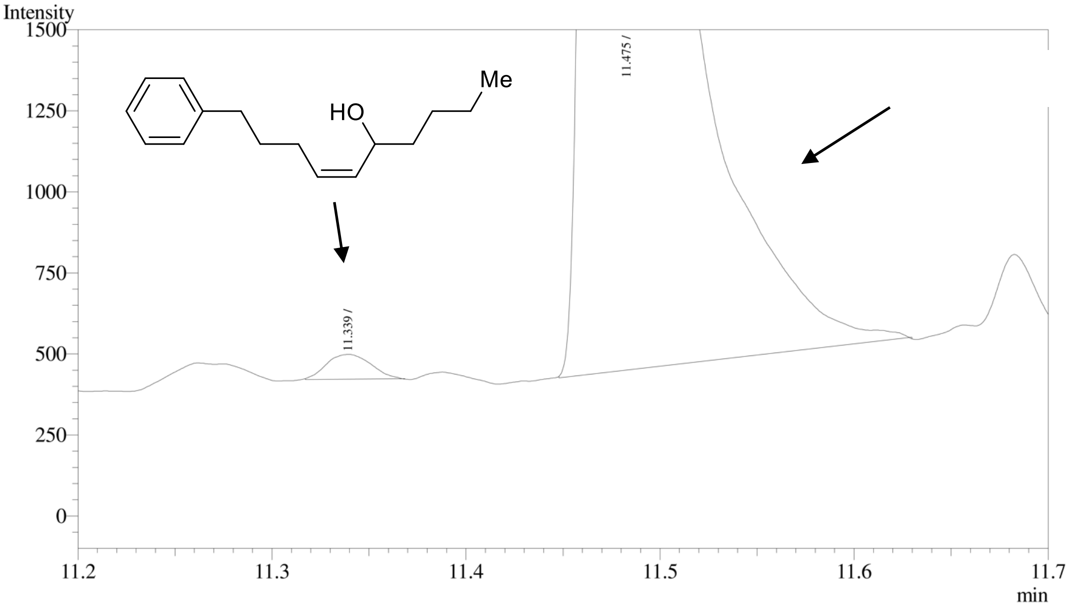
E/Z selectivity was determined by GC/FID analysis of an aliquot taken from a crude reaction mixture at the end of the oxidation as described in general procedure A.

GC trace of crude reaction mixture after oxidation.



Peak#	Ret.Time	Area	Height	Conc.
1	11.339	119	75	0.390
2	11.475	30424	17161	99.610
Total		30543	17236	

Magnified GC trace of crude reaction mixture.



Peak#	Ret.Time	Area	Height	Conc.
1	11.339	119	75	0.390
2	11.475	30424	17161	99.610
Total		30543	17236	

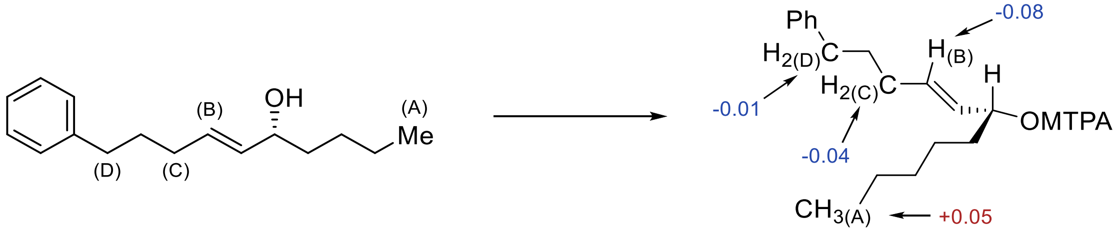
The relative concentration of the two isomers is 255:1 E to Z.

1.4.10. *Absolute Configuration of Allylic Alcohols - Mosher Ester Analysis*

The absolute configuration of compounds **(*R*)-1.18**, **(*S*)-1.18**, and **(*R*)-1.43** was determined by Mosher ester analysis. Preparation of the Mosher esters were performed according to a previously reported procedure.[105] In a nitrogen-filled glovebox, a 4 ml scintillation vial was charged with allylic alcohol (0.03 mmol, 1.0 equiv), dry pyridine (7.8 mg, 0.1 mmol, 3.1 equiv) and a stir bar. To the vial was added $CDCl_3$ (0.5 mL) and *R*-(−)-Mosher's acid chloride (*R*-(−)-MTPA) (15 mg, 0.06 mmol, 1.9 equiv). The reaction was stirred at room temperature and monitored by NMR. After two hours the reaction was complete and analyzed by ^1H NMR. This same procedure was repeated using *S*-(+)-MTPA instead of *R*-(−)-MTPA. The two ^1H NMR spectra were compared to determine the absolute configuration of the allylic alcohol.

Note: The *R*-(−)-MTPA gives the (*S*)-Mosher ester product and *S*-(+)-MTPA gives the (*R*)-Mosher ester product due to the change in group priority.[105] The values reported are for the final (*S*)- and (*R*)- Mosher ester product designations.

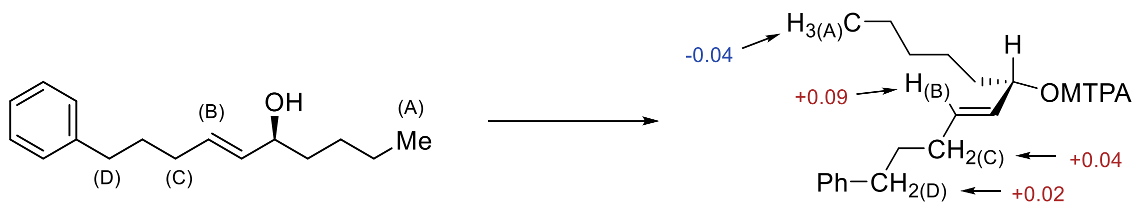
Table 0.9 Mosher ester data for (R)-1.18



	δ *S*-ester	δ *R*-ester	Δδ^{SR} = (δ$_S$ - δ$_R$)	
	(*R*)-1.18-(*S*) (ppm)	**(*R*)-1.18**-(*R*) (ppm)	ppm	Hz (500 MHz)
CH_3-(A)	0.87	0.82	+0.05	+25
CH-(B)	5.76	5.84	-0.08	-40
CH_2-(C)	2.03	2.07	-0.04	-20

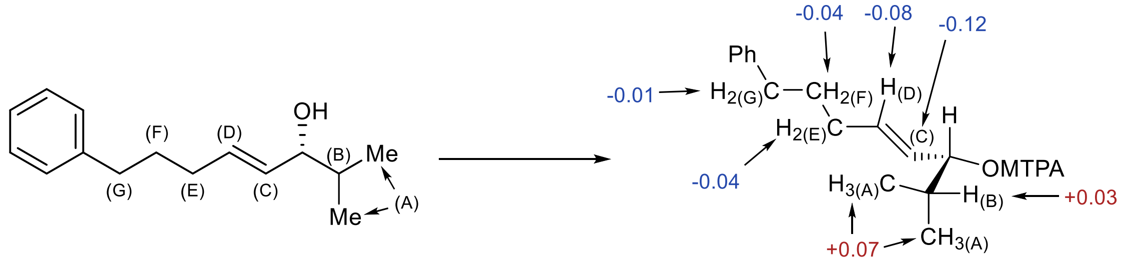
CH_2-(D)	2.57	2.58	-0.01	-5

Table 0.10 Mosher ester data for (S)-1.18



	δ *S*-ester	δ *R*-ester	$\Delta\delta^{SR} = (\delta_S - \delta_R)$	
	(*S*)-1.18-(*S*) (ppm)	**(*S*)-1.18**-(*R*) (ppm)	ppm	Hz (500 MHz)
CH_3-(A)	0.83	0.87	-0.04	-20
CH-(B)	5.85	5.76	+0.09	+45
CH_2-(C)	2.08	2.04	+0.04	+20
CH_2-(D)	2.59	2.57	+0.02	+10

Table 0.11 Mosher ester data for (R)-1.43

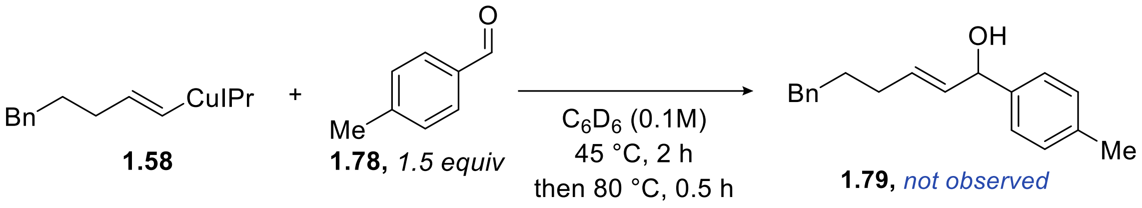


	δ *S*-ester	δ *R*-ester	$\Delta\delta^{SR} = (\delta_S - \delta_R)$	
	(*R*)-1.43-(*S*) (ppm)	**(*R*)-1.43**-(*R*) (ppm)	ppm	Hz (500 MHz)
2x CH_3-(A)	0.90	0.83	+0.07	+35
CH-(B)	1.90	1.87	+0.03	+15
CH-(C)	5.32	5.44	-0.12	-60

CH-(D)	5.76	5.84	-0.08	-40
CH_2-(E)	2.05	2.09	-0.04	-20
CH_2-(F)	1.66	1.70	-0.04	-20
CH_2-(G)	2.57	2.58	-0.01	-5

1.4.11. *Addition of Alkenyl Copper to Aldehydes*

1.4.11.1. Addition to Aryl Aldehydes



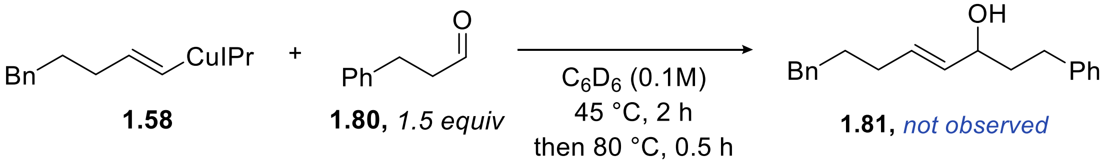
1.58

1.78, *1.5 equiv*

1.79, *not observed*

In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (14.6 mg, 0.025 mmol, 1.0 equiv). To this vial was added *p*-tolualdehyde (**1.78**) (4.5 mg, 0.038 mmol, 1.5 equiv), internal standard TMB (2.1 mg, 0.013 mmol) and C_6D_6 (0.1 M). The reaction was stirred for 4 hours at 45 °C and then an aliquot (100 µL) was analyzed by NMR. No product was observed, and the reaction temperature was increased to 80 °C for 30 minutes at which point the reaction mixture was analyzed by NMR and GC-MS and no product formation was observed.

1.4.11.2. Addition to Alkyl Aldehydes



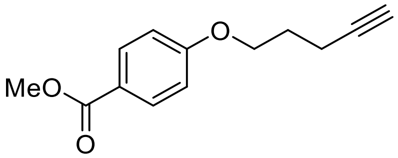
1.58

1.80, *1.5 equiv*

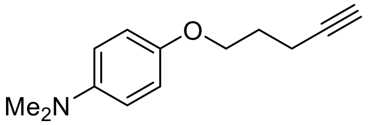
1.81, *not observed*

In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (14.6 mg, 0.025 mmol, 1.0 equiv). To this vial was added 3-phenylpropinal (**1.80**) (4.5 mg, 0.038 mmol, 1.5 equiv), internal standard TMB (2.1 mg, 0.013 mmol) and C_6D_6 (0.1 M). The reaction was stirred for 4 hours at 45 °C and then an aliquot (100 µL) was analyzed by NMR. No product was observed, and the reaction temperature was increased to 80 °C for 30 minutes at which point the reaction mixture was analyzed by NMR and GC-MS and no product formation was observed.

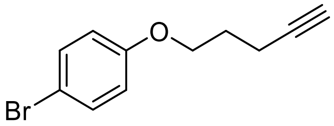
1.4.12. *Alkyne Starting Materials*



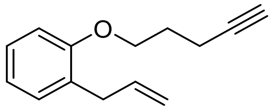
methyl 4-(pent-4-yn-1-yloxy)benzoate (1.81), was synthesized according to a known literature procedure and has been previously characterized.[106]



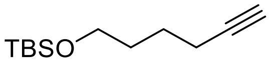
N,N-dimethyl-4-(pent-4-yn-1-yloxy)aniline (1.82), was synthesized according to a known literature procedure and has been previously characterized.[107]



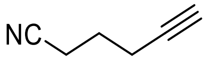
1-bromo-4-(pent-4-yn-1-yloxy)benzene (1.83), was synthesized according to a modified procedure and has been previously characterized.[107]



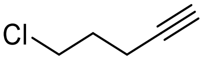
1-(pent-4-yn-1-yloxy)-2-(prop-2-en-1-yl)benzene (1.84), was synthesized according to a known procedure and has been previously characterized.[108]



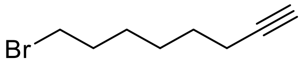
tert-butyldimethyl(hex-5-yn-1-yloxy)silane (1.85), was synthesized according to a modified procedure and has been previously characterized.[109]



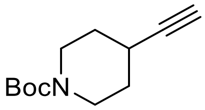
hex-5-ynenitrile (1.86), was purchased from Oakwood Chemical and vacuum distilled over calcium hydride before use.



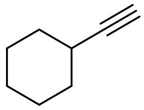
5-chloropent-1-yne (1.87), was purchased from TCI America and vacuum distilled over calcium hydride before use.



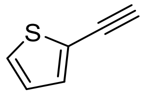
8-bromooct-1-yne (1.88), was synthesized according to a modified procedure and has been previously characterized.[110]



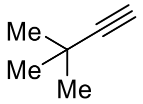
N-Boc-4-ethynylpiperidine (1.89), was purchased from Combi-Blocks and used without further purification.



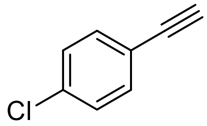
Ethynylcyclohexane (1.90), was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



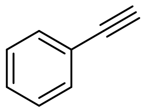
2-ethynylthiophene (1.91), was purchased from Combi-Blocks and vacuum distilled over calcium hydride before use.



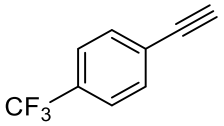
3,3-dimethylbut-1-yne (1.92), was purchased from Milipore Sigma and vacuum distilled over calcium hydride before use.



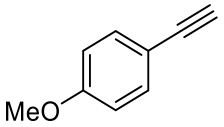
1-chloro-4-ethynylbenzene (1.93), was purchased from TCI America and used without further purification.



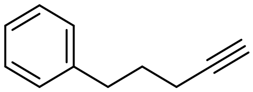
Ethynylbenzene (1.94), was purchased from TCI America and used without further purification.



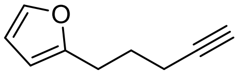
1-ethynyl-4-(trifluoromethyl)benzene (1.95), was purchased from TCI America and vacuum distilled over calcium hydride before use.



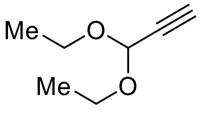
1-ethynyl-4-methoxybenzene (1.96), was purchased from Alfa Aesar and vacuum distilled over calcium hydride before use.



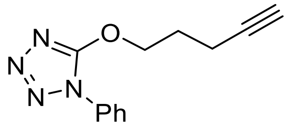
(pent-4-yn-1-yl)benzene (1.97) was purchased from GSF Chemicals and vacuum distilled over calcium hydride before use.



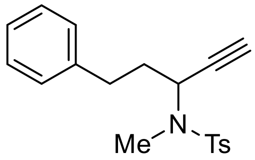
2-(pent-4-yn-1-yl)furan (1.98), was synthesized according to a modified procedure and has been previously characterized.[111]



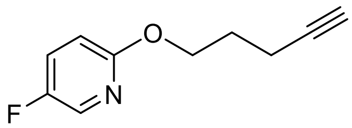
3,3-diethoxyprop-1-yne (1.99), was purchased from Combi-Blocks and used without further purification.



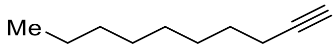
5-(pent-4-yn-1-yloxy)-1-phenyl-1H-1,2,3,4-tetrazole (1.100), was synthesized according to a known literature procedure and has been previously characterized.[107]



N,4-dimethyl-N-(5-phenylpent-1-yn-3-yl)benzene-1-sulfonamide (1.101), To a reaction flask was added α-ethynylbenzenepropanol (740 mg, 4.6 mmol, 1.0 equiv), triphenylphosphine (1.4 g, 5.4 mmol, 1.2 equiv), N-methyl-*p*-toluenesulfonamide (1.02 g, 5.4 mmol, 1.2 equiv) and THF (20 ml). Azodicarboxylic acid bis (2-methoxyethyl) ester (1.3 g, 5.4 mmol, 1.2 equiv) dissolved in THF (10 ml) was then added dropwise at room temperature and the reaction mixture was stirred for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (0-20% EtOAc in hexanes) to afford desired product as yellow solid (840 mg, 56% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.27 (m, 4H), 7.24 – 7.18 (m, 3H), 4.74 (td, *J* = 7.7, 2.3 Hz, 1H), 2.89 – 2.73 (m, 5H), 2.43 (s, 3H), 2.08 (d, *J* = 2.3 Hz, 1H), 2.04 – 1.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 140.7, 135.2, 129.5, 128.5 (2C), 127.8, 126.2, 79.4, 74.3, 49.6, 35.9, 32.1, 29.6, 21.6. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{19}H_{21}NO_2SNa$, 350.1; found, 350.0. FTIR (neat, cm^{-1}): 3277 (br), 3026 (m), 2932 (m), 1597 (m), 1495 (m), 1453 (m), 1336 (s), 1160 (s), 1088 (m), 946 (w), 813 (w), 659 (m).



5-fluoro-2-(pent-4-yn-1-yloxy)pyridine (1.102), was synthesized according to a known literature procedure and has been previously characterized.[112]



dec-1-yne (1.12), was purchased from Oakwood Chemical and vacuum distilled over calcium hydride before use.

1.4.13. *Racemic a-Chloro Boronic Ester Starting Materials*

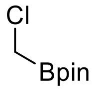
1.4.13.1. General Procedures for the Preparation of α-Chloro Boronic Esters

Procedure B

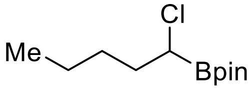
According to the published procedure,[113] a reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DCM (290 μL, 4.5 mmol, 1.5 equiv) and THF (0.5 M). The mixture was cooled to -100 °C with a liquid nitrogen and ethanol bath. *n*-Butyllithium (1.3 mL, 1.1 mmol, 1.05 equiv, 2.5 M in Hexanes) was added dropwise down the sides of the flask to the cooled mixture. The resulting mixture was allowed to stir for 30 minutes at which point the alkyl boronic ester (3.0 mmol, 1.0 equiv) dissolved in diethyl ether (2 M) was added. The reaction mixture was allowed to slowly warm to room temperature and was stirred overnight. A large amount of DCM (50-100 mL) was added to precipitate out any lithium salts which were then filtered off. The organic layer was then washed with brine (3 x 20 mL) and dried over sodium sulfate. After the removal of solvent in vacuo, the residue was purified by distillation to afford α-chloro boronic esters. Alternatively, a crude mixture of α-chloro boronic esters was used without further purification.

Procedure C

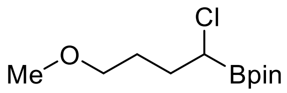
According to the published procedure,[114] to a mixture of magnesium turnings (350 mg, 14.4 mmol, 1.8 equiv) in dry THF (2 M) was added a small portion of a solution of alkyl bromide (8.0 mmol, 1.0 equiv) in THF (0.5 M). An iodine crystal was added, and the reaction mixture was heated by heating gun to activate the Grignard formation. The remainder of the solution of alkyl bromide in THF was then added dropwise. The reaction mixture was stirred at 60 °C until most of magnesium reacted. The freshly prepared solution of Grignard reagent (7.5 mmol, 1.5 equiv) in THF was added dropwise to a separate flask containing a solution of 2-(dichloromethyl)-1,3,2-dioxaborolane (1.1 g, 5.0 mmol, 1.0 equiv) in THF (0.2 M) cooled to –78 °C under argon atmosphere. $ZnCl_2$ (340 mg, 2.5 mmol, 0.5 equiv) was added, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with an aqueous solution of NH_4Cl and extracted with EtOAc (3 ×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by distillation to afford the α-chloro boronic esters or the α-chloro boronic esters were used as a crude mixture without further purification.



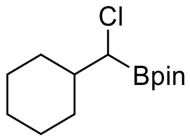
2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.103), was purchase from Combi-Blocks and used without further purification.



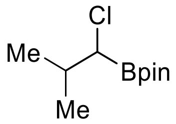
2-(1-chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.11), was synthesized according to procedure B and has been previously characterized.[115]



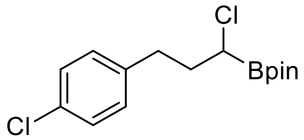
2-(1-chloro-4-methoxybutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.104), was synthesized according to procedure C and has been previously characterized.[116]



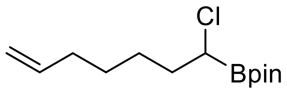
2-(chloro(cyclohexyl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.105), was synthesized according to procedure B and has been previously characterized.[117]



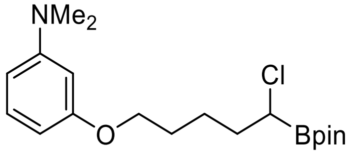
2-(1-chloro-2-methylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.106), was synthesized according to procedure B and has been previously characterized.[118]



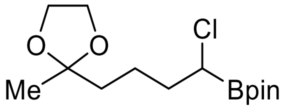
2-[1-chloro-3-(4-chlorophenyl)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.107), was synthesized according to procedure B and has been previously characterized.[119]



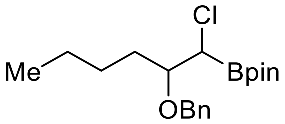
2-(1-chlorohept-6-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.108), was synthesized according to procedure C and has been previously characterized.[117]



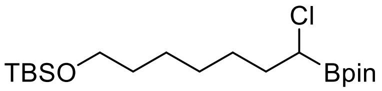
3-{[5-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]oxy}-N,N-dimethylaniline (1.109), was synthesized according to procedure C and has been previously characterized.[118]



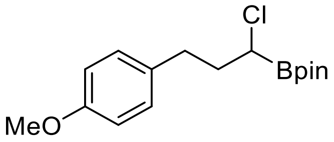
2-[1-chloro-4-(2-methyl-1,3-dioxolan-2-yl)butyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.110), was synthesized according to procedure B from 4,4,5,5-tetramethyl-2-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-1,3,2-dioxaborolane and was utilized in the subsequent reaction as a crude mixture without further purification.



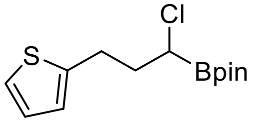
2-[2-(benzyloxy)-1-chlorohexyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.111), was synthesized according to procedure B and has been previously characterized.[119]



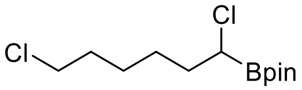
Tert-butyl({[7-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl]oxy})dimethylsilane (1.112), was synthesized according to procedure B and has been previously characterized.[120]



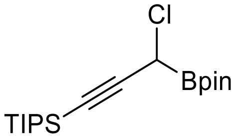
2-[1-chloro-3-(4-methoxyphenyl)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.113), was synthesized according to procedure B and has been previously characterized.[117]



2-[1-chloro-3-(thiophen-2-yl)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.114), was synthesized according to procedure B from 4,4,5,5-tetramethyl-2-[(thiophen-2-yl)methyl]-1,3,2-dioxaborolane[121] and was utilized in the subsequent reaction as a crude mixture without further purification.



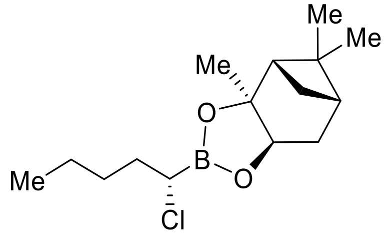
2-(1,6-dichlorohexyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.115), was synthesized according to procedure B and has been previously characterized.[117]



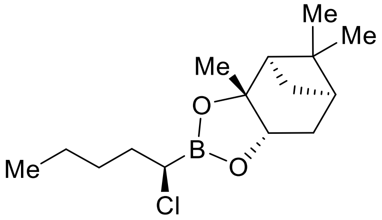
(4-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-yn-1-yl)triisopropylsilane (1.116), A flame dried Schlenk flask was charged with triisopropyl(prop-1-yn-1-yl) silane (590 mg, 3.0 mmol, 1.0 equiv) and anhydrous THF (7 mL). The mixture was cooled to -78 °C and n-BuLi (1.3 mL, 3.3 mmol, 1.1 equiv, 2.5 M) was added dropwise. The reaction mixture was stirred at -78°C under N_2 atmosphere for 10 min. Then a solution of pinacol (dichloromethyl) boronate (630 mg, 3.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was stirred for an additional 3 hours at -78 ˚C under N_2 atmosphere. The reaction mixture was then diluted with pentane (10 mL) and washed with saturated NH_4Cl (3 × 15 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude product was used directly in the next step after determining of the portion of α-chloro-Bpin to starting material by NMR.

1.4.14. *Enantioenriched a-Chloro Boronic Ester Starting Materials*

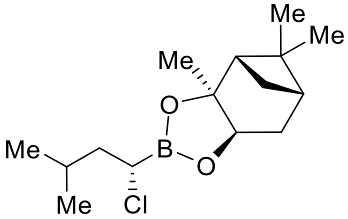
Enantioenriched α-Chloro Bpinane



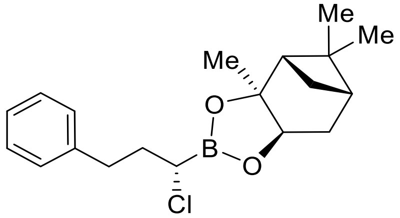
(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*)-1-chloropentyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.$0^{2,6}$] decane (1.65), was prepared according to a known procedure and has been previously characterized.[122]



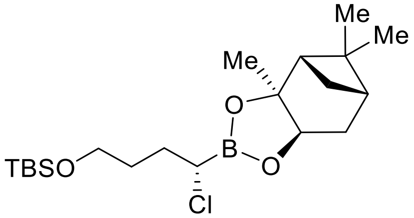
(1*R*,2*R*,6*S*,8*R*)-4-[(1*R*)-1-chloropentyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.0²,⁶] decane (1.117), was prepared according to the modified procedure by using (-)-pinanediol,[123] a reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DCM (380 μL, 6 mmol, 2.0 equiv) and THF (12 mL, 0.5 M). The mixture was cooled to -100 °C with a liquid nitrogen and ethanol bath. *n*-Butyllithium (3.6 mmol, 1.2 equiv, 2.5M in Hexanes) was added dropwise down the sides of the flask to the cooled mixture. The reaction mixture was allowed to stir for 30 minutes and then (1*R*,2*R*,6*S*,8*R*)-4-butyl-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.$0^{2,6}$]decane (708 mg, 3 mmol, 1.0 equiv) in THF (3 mL) and anhydrous $ZnCl_2$ (650 mg, 4.8 mmol, 1.6 equiv) was added. The reaction mixture was allowed to slowly warm to room temperature and monitored by NMR. Once complete, the reaction mixture was diluted with hexanes and then saturated NH_4Cl (25 mL) was added. The aqueous phase was removed, and the organic phase was then washed with water (20 mL) and brine (20 mL), and the organic phase was dried with anhydrous sodium sulfate and concentrated under vacuum. The purity of the resulting product was determined by NMR and used without further purification.



(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*)-1-chloro-3-methylbutyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0²,⁶]decane (1.118), was prepared according to a known procedure and has been previously characterized.[122]

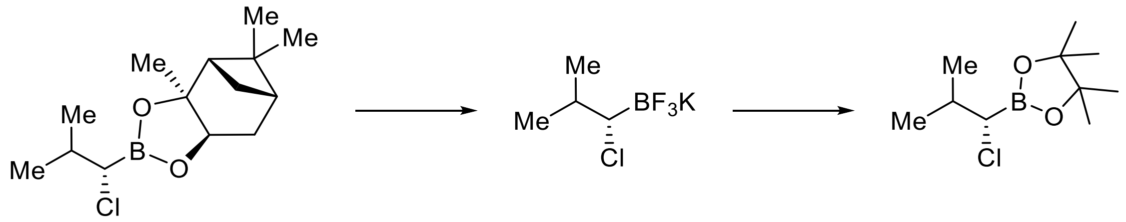


(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*)-1-chloro-3-phenylpropyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0²,⁶]decane (1.119), was prepared according to a known procedure and has been previously characterized.[124]



tert-butyl[(4*S*)-4-chloro-4-[(1*S*,2*S*,6*R*,8*S*)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.0²,⁶] decan-4-yl]butoxy]dimethylsilane (1.120), was prepared according to the modified procedure,[123] a reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DCM (380 μL, 6 mmol, 2.0 equiv) and THF (12 mL, 0.5 M). The mixture was cooled to -100 °C with a liquid nitrogen and ethanol bath. *n*-Butyllithium (3.6 mmol, 1.2 equiv, 2.5M in Hexanes) was added dropwise down the sides of the flask to the cooled mixture. The reaction mixture was allowed to stir for 30 minutes and then tert-butyldimethyl{3-[(1*S*,2*S*,6*R*,8*S*)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.0^{2,6}]decan-4-yl]propoxy}silane[125] (1.1 g, 3 mmol, 1.0 equiv) in THF (3 mL) and anhydrous $ZnCl_2$ (650 mg, 4.8 mmol, 1.6 equiv) was added. The reaction mixture was allowed to slowly warm to room temperature and monitored by NMR. Once complete, the reaction mixture was diluted with hexanes and then saturated NH_4Cl (25 mL) was added. The aqueous phase was removed, and the organic phase was then washed with water (20 mL) and brine (20 mL), and the organic phase was dried with anhydrous sodium sulfate and concentrated under vacuum. The purity of the resulting product was determined by NMR and used without further purification.

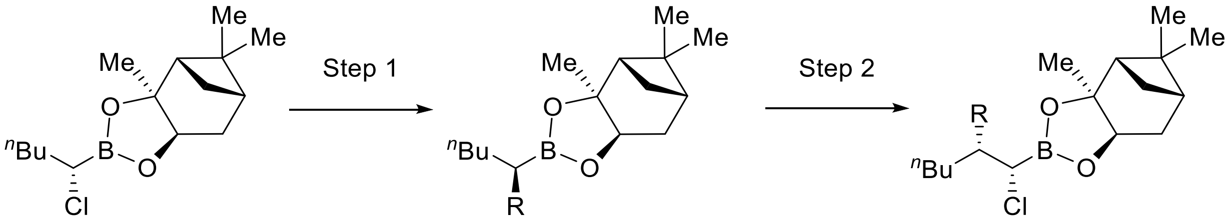
1.4.14.1. Enantioenriched α-Chloro Bpin



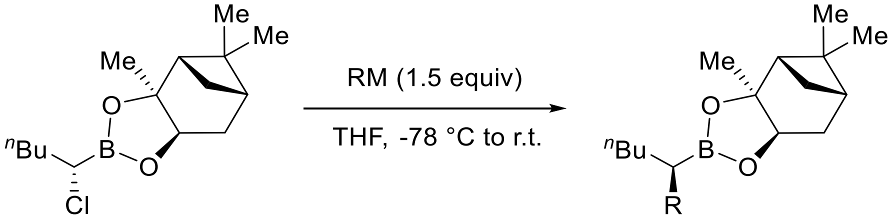
2-[(1*S*)-1-chloro-2-methylpropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.121), was synthesized according to a modified procedure.[116] (1*S*,2*S*,6*R*,8*S*)-4-[(1S)-1-chloro-2-methylpropyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.$0^{2,6}$]decane[126] (920 mg, 3.4 mmol, 1.0 equiv) was dissolved in acetonitrile (7 mL). To this solution aqueous potassium bifluoride (3.4 mL, 17 mmol, 5.0 equiv, 5.0 M) was added and the reaction was allowed to stir for 4 hours at room temperature. The aqueous phase was extracted with acetonitrile (2 x 10 mL) and dried using Na_2SO_4, then concentrated under reduced pressure. The resulting solid was washed with chloroform to yield the potassium trifluoroborate salt which was used in the next step without further purification. Potassium (*S*)-(1-chloro-2-methylpropyl)trifluoroborate (516 mg, 2.6 mmol, 1.0 equiv) was suspended in THF (5 mL), and then $SiCl_4$ (0.60 mL, 5.2 mmol, 2.0 equiv) was added. The reaction was stirred for 1 h at room temperature and then was cooled to 0 °C. MeOH (1.3 mL) and pinacol (0.61 g, 5.2 mmol, 2.0 equiv) were added sequentially and the reaction was stirred for 1 h at 0 °C. The reaction was then filtered through a plug of silica gel, concentrated under vacuum and then purified by flash chromatography by silica gel chromatography (10% ethyl acetate in hexanes) to afford the product as a colorless liquid (385 mg, 42% yield total over the two steps). The characterization data matched previously reported data.[127]

1.4.14.2. Enantioenriched β-Substituted α-Chloro Bpinanes

Enantioenriched β-substituted α-chloro boronic esters were prepared via the following two steps:

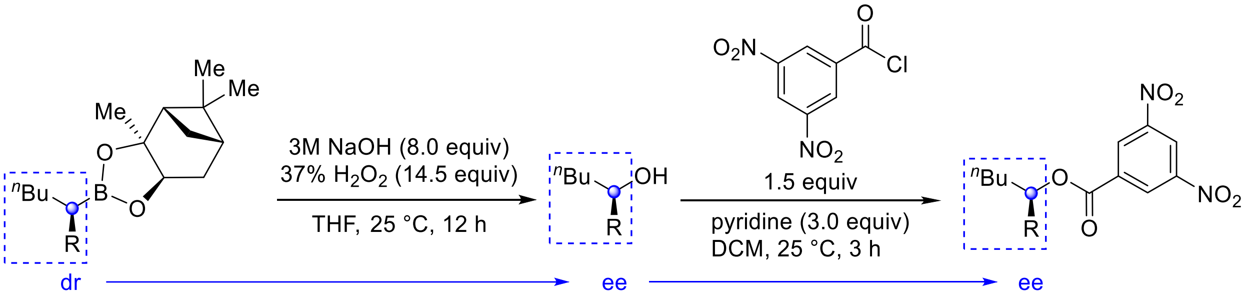


General Procedure D for the Preparation of Enantioenriched α-Substituted Pinanediol Boronic Esters:

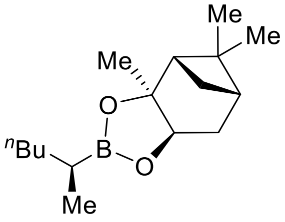


According to the published procedure,[128] a reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar and a solution of compound **1.65** (1140 mg, 4 mmol, 1.0 equiv) in THF (20 mL, 0.2 M). The mixture was cooled to -78 °C with a dry ice and acetone bath. The organometallic reagent (6 mmol, 1.5 equiv) was then added dropwise. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was diluted with hexanes and then saturated NH_4Cl (25 ml) was added. The aqueous phase was removed, and then the organic phase was washed with water (20 mL) and brine (20 mL), and the organic phase was dried over anhydrous sodium sulfate. The solution was concentrated and purified by silica gel column chromatography to afford the crude product. The purity of the resulting product was determined by NMR and used without further purification in Step 2.

Determination of Diastereomeric Ratio of Enantioenriched α-Substituted Pinanediol Boronic Esters:

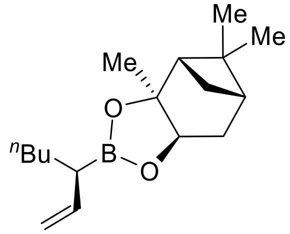


The dr of enantioenriched α-substituted pinanediol boronic esters were determined via HPLC of the corresponding alcohols or the 3,5-dinitrobenzoyl derivative of the corresponding alcohols.

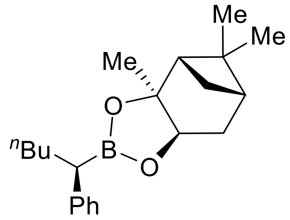


(1*S*,2*S*,6*R*,8*S*)-4-[(2*S*)-hexan-2-yl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.0²,⁶]decane (1.122), prepared according to general procedure D using a solution of MeMgBr in Et_2O (3.0 M) as nucleophile, affording the crude product as a colorless liquid with 98:2 dr. The dr was determined via HPLC after oxidation to the corresponding alcohol and esterification with 3,5-

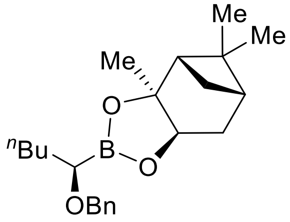
dinitrobenzyol chloride, on a CHIRALPAK AD-H column (1% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 17.4 min (major), 20.2 min (minor).



(1*S*,2*S*,6*R*,8*S*)-4-[(3*R*)-hept-1-en-3-yl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.0^{2,6}] decane (1.123), prepared according to general procedure D using a solution of vinylmagnesium chloride in THF (1.6 M) as nucleophile, and $ZnCl_2$ (540 mg, 4.0 mmol, 1.0 equiv) was added, affording the crude product as a yellow liquid with a 97:3 dr. The dr was determined via HPLC after oxidation to the corresponding alcohol and esterification with 3,5-dinitrobenzyol chloride, on a CHIRALPAK OD-H column (1% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 37.3 min (major), 63.6 min (minor)

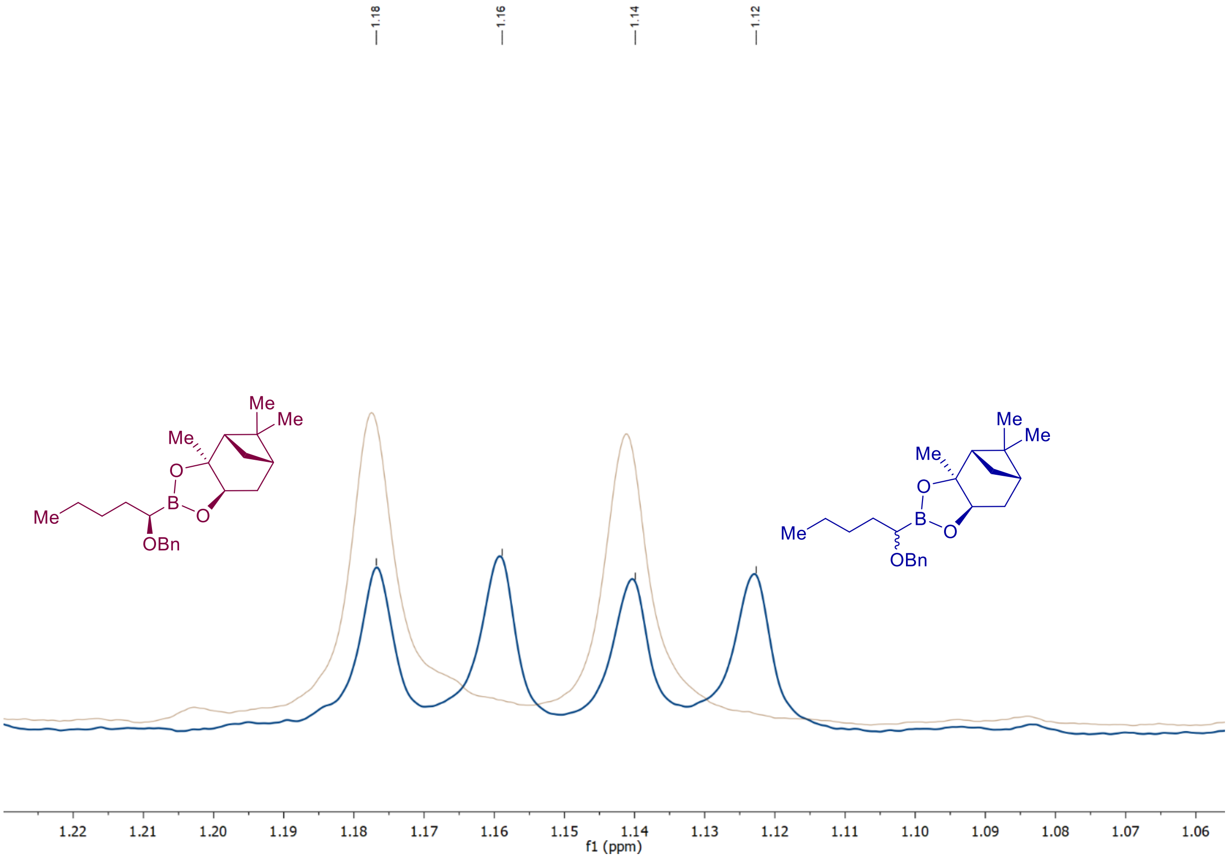


(1*S*,2*S*,6*R*,8*S*)-2,9,9-trimethyl-4-[(1*R*)-1-phenylpentyl]-3,5-dioxa-4-boratricyclo[6.1.1.0^{2,6}] decane (1.124), prepared according to general procedure D using a solution of phenylmagnesium chloride in THF (2.0 M) as nucleophile, affording the crude product as a yellow liquid with a 98:2 dr. The dr was determined via HPLC after oxidation to the corresponding alcohol, on a CHIRALPAK AD-H column (0.4% 2-PrOH in hexanes, 1.0 mL/min, detected at 220 nm wavelength) with t_r = 27.3 min (minor), 29.6 min (major).

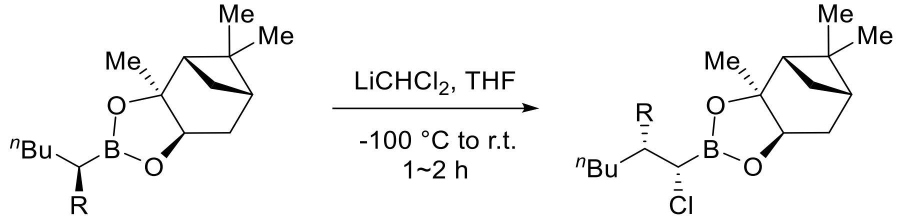


(1*S*,2*S*,6*R*,8*S*)-4-[(1R)-1-(benzyloxy)pentyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0^{2,6}]decane (1.125), was prepared according to a known procedure and has been previously characterized.[123] The dr was estimated to be 20:1 via ^{1}H NMR. The peak position of 1S epimer was verified by preparing an epimer mixture via transesterification of the racemic pinacol α-benzyloxy boronic ester with (+)-pinanediol (Figure 1.1).[123]

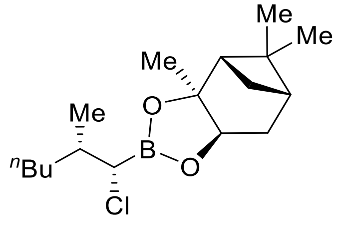
Figure 0.1 dr of Compound 1.125



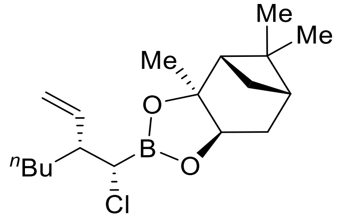
General procedure E for the Preparation of Enantioenriched β-Substituted α-Chloro Pinanediol Boronic Esters



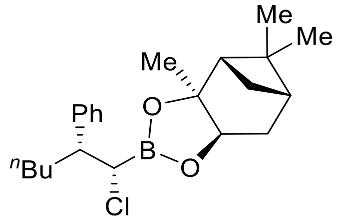
According to the modified procedure,[123] a reaction flask was flame-dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DCM (380 µL, 6 mmol, 2.0 equiv) and THF (12 mL, 0.5 M). The mixture was cooled to -100 °C with a liquid nitrogen and ethanol bath. *n*-Butyllithium (3.6 mmol, 1.2 equiv, 2.5M in Hexanes) was added dropwise down the sides of the flask to the cooled mixture. The reaction mixture was allowed to stir for 30 minutes and then the alkyl pinanediol boronic ester prepared in Step 1 (3 mmol, 1.0 equiv) in THF (3 mL) and anhydrous $ZnCl_2$ (650 mg, 4.8 mmol, 1.6 equiv) was added. The reaction mixture was allowed to slowly warm to room temperature and monitored by NMR. Once complete, the reaction mixture was diluted with hexanes and then saturated NH_4Cl (25 mL) was added. The aqueous phase was removed, and the organic phase was then washed with water (20 mL) and brine (20 mL), and the organic phase was dried with anhydrous sodium sulfate. The solution was concentrated, and the residue was purified by silica gel column chromatography to afford the crude product. The purity of the resulting crude product was determined by NMR and used without further purification in the subsequent reaction.



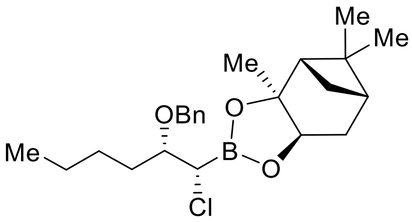
(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*,2*S*)-1-chloro-2-methylhexyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0^{2,6}]decane (1.126), prepared according to general procedure E, affording the crude product as a colorless liquid.



(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*,2*R*)-1-chloro-2-ethenylhexyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0^{2,6}]decane (1.127), prepared according to general procedure E, but no $ZnCl_2$ was added, affording the crude product as a colorless liquid.

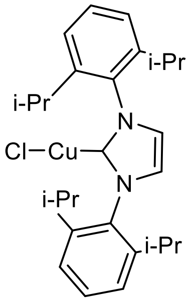


(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*,2*R*)-1-chloro-2-phenylhexyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.0^{2,6}]decane (1.128), prepared according to general procedure E, affording the crude product as a colorless liquid.

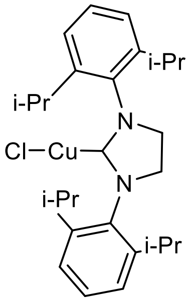


(1*S*,2*S*,6*R*,8*S*)-4-[(1*S*,2*S*)-2-(benzyloxy)-1-chlorohexyl]-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.$0^{2,6}$]decane (1.129), was prepared according to a general procedure E and has been previously characterized.[123]

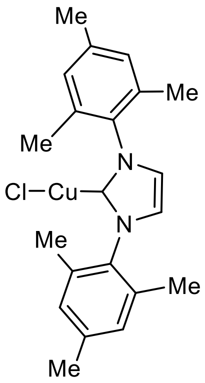
1.4.15. *Catalyst Synthesis*



IPrCuCl (1.130), was prepared according to a known procedure and has been previously characterized.[129]



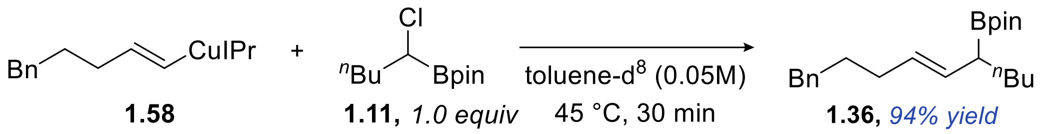
SIPrCuCl (1.131), was prepared according to a known procedure and has been previously characterized.[129]



IMesCuCl (1.132), was prepared according to a known procedure and has been previously characterized.[129]

1.4.16. *Mechanistic Studies*

Scheme 0.10 Stoichiometric Reaction with Alkenyl Copper and α-Chloro Boronic Ester



Alkenyl copper complex (**1.58**) was prepared from a known literature procedure and has been previously characterized.[130]

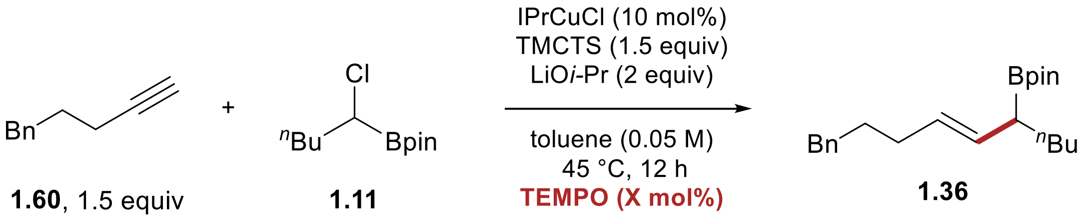
In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (17.9 mg, 0.03 mmol, 1.0 equiv). To this vial was added α-chloro boronic ester (**1.11**) (7.0 mg, 0.03 mmol, 1.0 equiv), internal standard TMB (2.5 mg, 0.02 mmol) and toluene-d^8 (0.05 M). The reaction yield was monitored by NMR.

Table 0.12 Stoichiometric Reaction of Alkenyl Copper and α-Chloro Boronic Ester

Time	Yield of 1.36 (%)
10 minutes	87
30 minutes	94
1.5 hours	95

1.4.16.1. Investigation of the Radical Mechanism

Radical Trap Probe

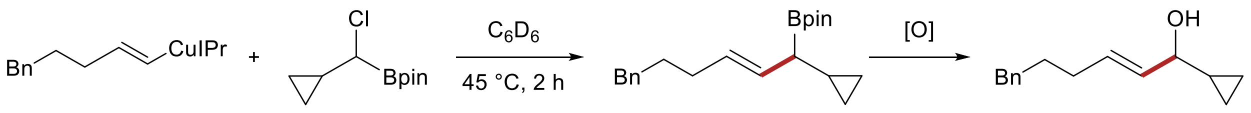


In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiO*i*-Pr (20.2mg, 0.40 mmol, 2.0 equiv) and IPrCuCl (9.8 mg, 0.02 mmol, 0.1 equiv). To this vial was added 5-phenylpentyne (**1.60**) (48.0 mg, 0.30 mmol, 1.5 equiv), TMCTS (72.2 mg, 0.3 mmol, 1.5 equiv) and toluene (0.05 M). The resulting mixture was then stirred at 25 °C until the yellow color faded. α-Chloro boronic ester (**1.11**) (46.6 mg, 0.20 mmol), internal standard TMB (36.1 mg, 0.20 mmol) and required amount of TEMPO was transferred to the reaction flask. The reaction mixture was stirred at 45 °C overnight. Then, an aliquot (100 μL) from the reaction mixture was passed through a plug of silica with ethyl acetate, concentrated and analyzed by NMR. Table 1.14 shows the product yield with different amounts of TEMPO.

Table 0.13 Radical Trap Probe

Entry	mol % of TEMPO	Yield of 1.36 (%)
1	0	83
2	20	82
3	150	73

Radical Clock Experiment

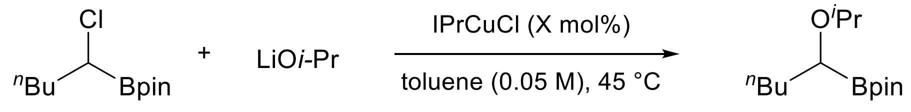


1.58 **1.61**, 1.0 equiv **1.62**, 83% (by NMR) **1.133**, 60% yield

In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar and alkenyl copper (**1.58)** (119.5 mg, 0.20 mmol). To this vial was added α-chloro boronic ester (**1.61**) (53.2 mg, 0.20 mmol, 1 equiv) internal standard TMB (33.4 mg, 0.20 mmol) and C_6D_6 (0.05 M). The reaction mixture was stirred at 45 °C for 2 h and analyzed by NMR (NMR yield of the allylic boronic ester = 84%). Then the reaction mixture was then oxidized with H_2O_2/NaOH following general procedure A. The resulting mixture was passed through a plug of silica, concentrated, and then purified by silica chromatography (0-20% EtOAc and hexanes) to afford **1.133** as a yellow liquid (26.0 mg, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.22 – 7.14 (m, 3H), 5.79 – 5.64 (m, 1H), 5.61 - 5.53 (m, 1H), 3.45 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.63 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.21 – 2.02 (m, 2H), 1.83 – 1.67 (m, 2H), 1.61 (s, 1H), 1.05 - 0.94 (m, 1H), 0.63 – 0.45 (m, 2H), 0.39 – 0.30 (m, 1H), 0.29 – 0.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 132.0, 131.5, 128.6, 128.4, 125.8, 35.5, 31.9, 31.0, 17.7, 3.2, 2.1. MS-ESI (m/z): $[M-OH]^+$ calculated for $C_{15}H_{19}$, 199.1; found, 198.8. FTIR (neat, cm^{-1}): 3358 (br), 3025 (s), 2958 (s), 2923 (s), 1668 (m), 1467 (m), 1032 (m), 978 (s), 730 (w).

1.4.16.2. Evaluating α-Isopropoxy Boronic Ester as a Potential Intermediate

α-Isopropoxy Boronic Ester Formation



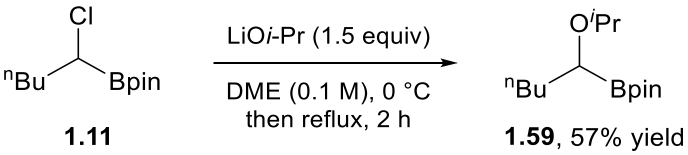
1.11 2.0 equiv **1.59**

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar and LiO*i*-Pr (13.2 mg, 0.20 mmol, 2.0 equiv) and required amount of IPrCuCl catalyst (no catalyst or 4.9 mg, 0.01 mol, 0.1 equiv). To this vial was added α-chloro boronic ester (**1.11**) (23.3 mg, 0.10 mmol), internal standard TMB (8.4 mg, 0.05 mmol) and toluene (0.05 M). The reaction mixture was stirred at 45 °C. An aliquot (100 µL) of the crude reaction mixture, at the reported times, was passed through a plug of silica with ethyl acetate, concentrated, and analyzed by NMR.

Table 0.14 Yield of 1.59

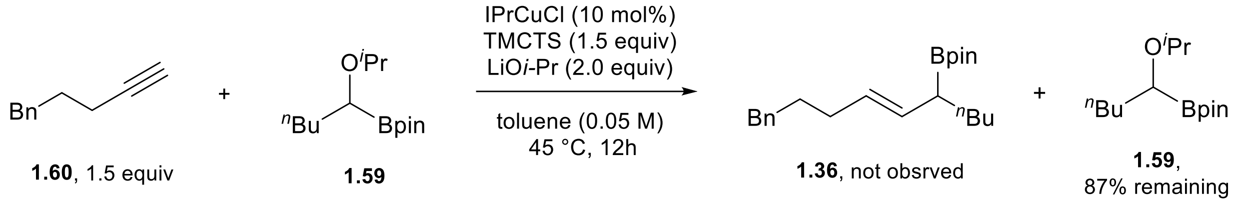
Time (hours)	No IPrCuCl	10 mol% IPrCuCl
2	6	8
4	9	10
8	12	14
12	17	20
27	31	43

1.4.16.3. Synthesis of 4,4,5,5-tetramethyl-2-[1-(propan-2-yloxy)pentyl]-1,3,2-dioxaborolane



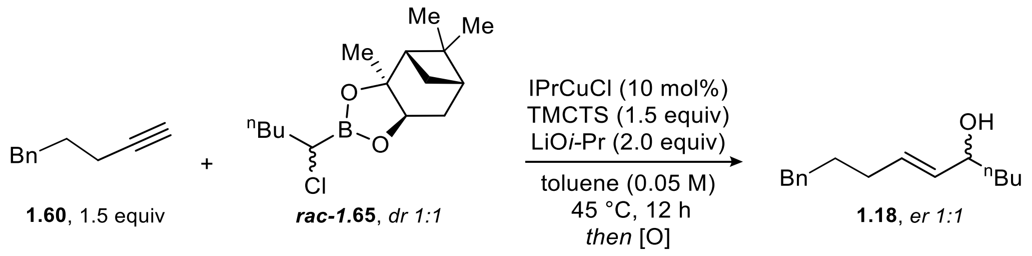
4,4,5,5-tetramethyl-2-[1-(propan-2-yloxy)pentyl]-1,3,2-dioxaborolane (**1**.**59**), A flask was charged with LiO*i*-Pr (200 mg, 3.0 mmol, 1.5 equiv) and anhydrous DME (20 mL). The solution was cooled to 0 °C and **1.11** (465 mg, 2.0 mmol, 1.0 equiv) was added. The reaction was warmed to room temperature and then refluxed for 2 hours. The reaction mixture was filtered through a plug of silica and concentrated under vacuum. The crude product was then purified by silica gel chromatography (15% Et_2O in hexanes) to give **1.59** as a colorless liquid (293 mg, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (hept, *J* = 6.0 Hz, 1H), 3.19 (t, *J* = 6.9 Hz, 1H), 1.61 – 1.55 (m, 2H), 1.40-1.28 (m, 4H), 1.26 (s, 6H), 1.25 (s, 6H), 1.13 (d, *J* = 6.1 Hz, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.5, 71.2, 31.7, 28.8, 24.9, 24.5, 22.8, 22.2, 14.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.59. GCMS (EI) calculated for $[M]^+$ 256.2, found 256.2. FTIR (neat, cm^{-1}): 2974 (s), 2927 (s), 2861 (s), 1457 (m), 1388 (s), 1146 (s), 1049 (m), 967 (w), 847 (w).

1.4.16.4. α-Isopropoxy Boronic Ester in Hydroalkylation Reaction

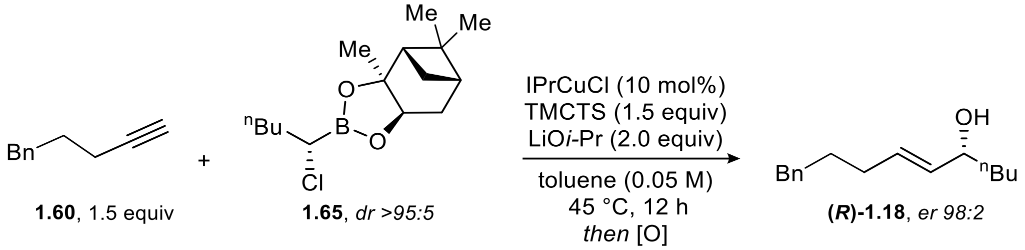


According to general procedure A, in a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiO*i*-Pr (13.2mg, 0.20 mmol, 2.0 equiv) and IPrCuCl (4.9 mg, 0.01 mmol, 0.1 equiv). To this vial was added 5-phenylpentyne (**1.60**) (21.6 mg, 0.15 mmol, 1.5 equiv), TMCTS (36.0 mg, 0.15 mmol, 1.5 equiv) and toluene (0.05 M). The resulting mixture was then stirred at 25 °C until the yellow color disappeared. α-Isopropoxy pentyl boronic ester (**1.59**) (25.6 mg, 0.10 mmol) and internal standard TMB (9.4 mg, 0.56 mmol) were transferred to the reaction mixture. The reaction mixture was stirred at 45 °C overnight. The reaction was then concentrated and analyzed by NMR. The allylic boronic ester product (**1.36**) was not observed and 87% of the starting α-isopropoxy boronic ester (**1.59**) was present in the final reaction mixture.

1.4.16.5. Investigating the Ionic Mechanism and Origin of Enantioselectivity

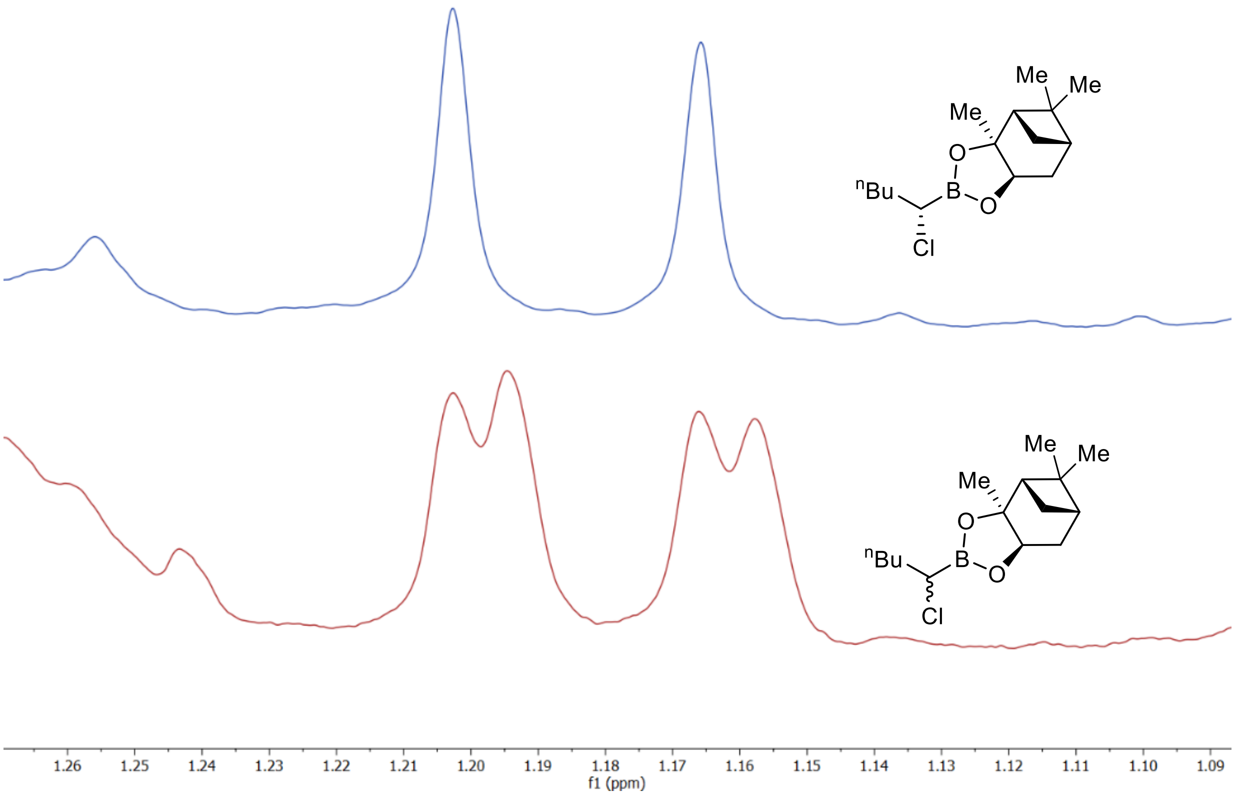


The α-chloro pinanediol boronic ester with a diastereomeric mixture of (**1.65**) was prepared according to according to a reported procedure from compound **1.11**.[131] The diastereomeric ratio was assessed using the characteristic pinanyl proton that appears as a doublet between δ 1.1-1.2 in $CDCl_3$ (J = 11.1 Hz) and was found to be 1:1 (Figure 1.2).[123] The reaction was performed according to general procedure A (16 mg, 73% yield) with characterization matching compound **1.18**. The resulting alcohol (**1.18**) was a 1:1 mixture of the R and S enantiomer. Enantiomeric ratio of the alcohol product was determined by chiral HPLC. CHIRALPAK AD-H column (0.02% 2-PrOH in hexanes, 0.6 mL/min, detected at 220 nm wavelength) with t_r = 68.9 min (major), 79.7 min (minor).



The enantioenriched α-chloro pinanediol boronic ester was prepared as referenced above (**1.65**). The diastereomeric ratio was assessed using the characteristic pinanyl proton that appears as a doublet between δ 1.1-1.2 in $CDCl_3$ (J = 11.1 Hz) compared to the racemic sample and was found to be >20:1 (Figure 1.2).[123] The resulting alcohol is listed as product (**(*R*)-1.18**) and was found to have an enantiomeric ratio of 98:2 (see characterization of product (**(*R*)-1.18**) for details).

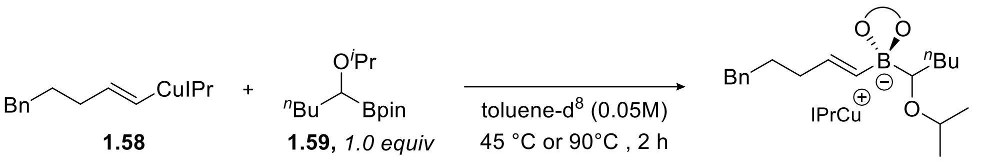
Figure 0.2 Diastereomeric ratio determination of 1.65



Diastereomeric ratio determination of the enantioenriched α-chloro pinanediol boronic ester (**1.65**) utilizing the characteristic pinanyl proton in comparison to the alpha-center-racemic sample (***rac*-1.65**).[123]

1.4.16.6. Investigation of Boron-ate Complex Formation

Alkenyl Copper and α-Isopropoxy Boronic Ester

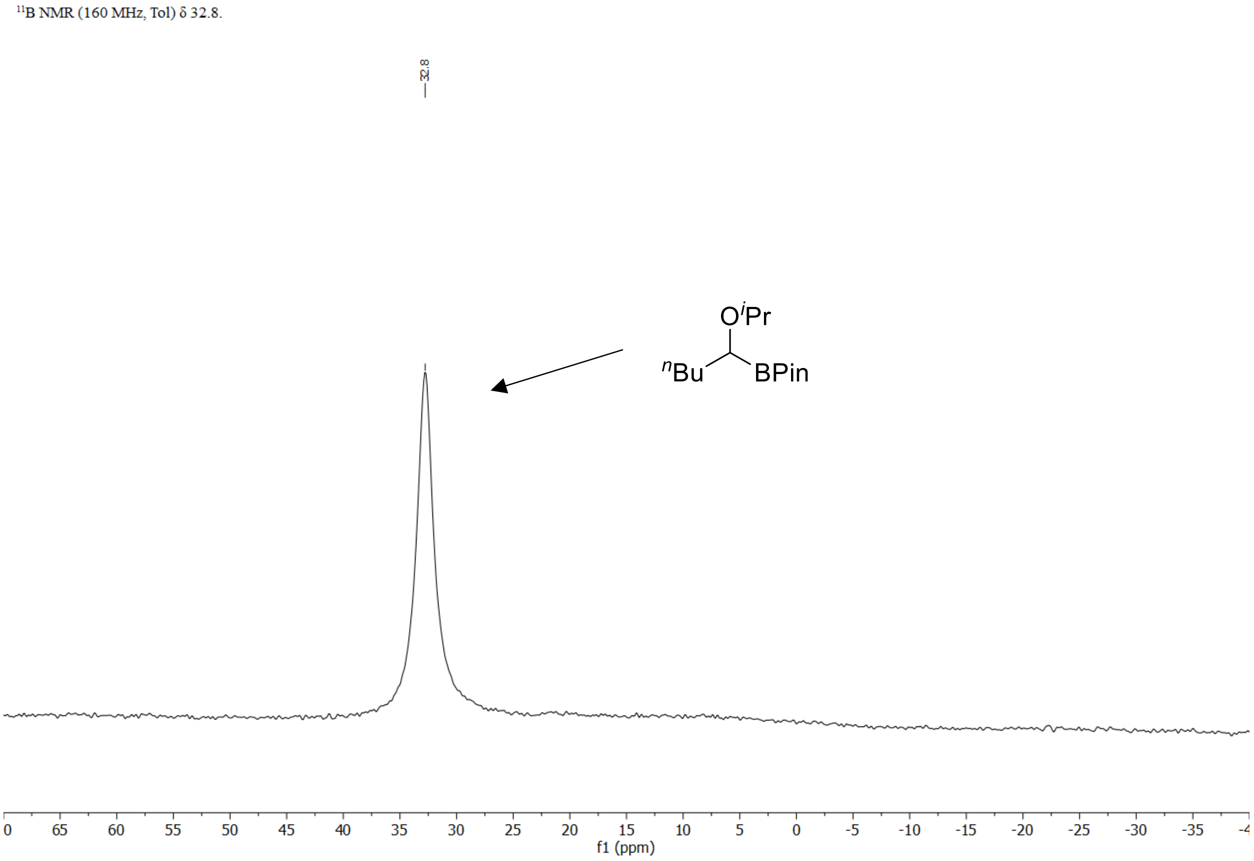


1.134, *Not Observed*

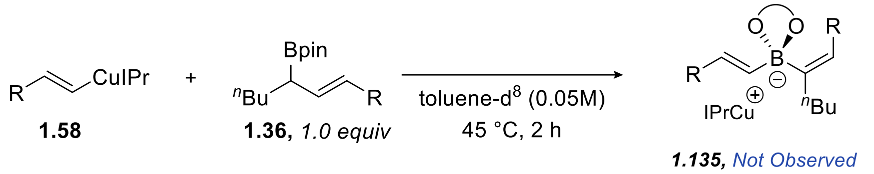
Unchanged Starting Materials

In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (14.6 mg, 0.025 mmol, 1.0 equiv). To this vial was added α-isopropoxy boronic ester (**1.59**) (6.4 mg, 0.025 mmol, 1.0 equiv), internal standard TMB (2.1 mg, 0.013 mmol) and toluene-d^{8} (0.05 M). The reaction was stirred at 45 °C and monitored by ^{1}H and ^{11}B NMR. This procedure was repeated with the reaction stirred at 90 °C instead of 45 °C. In both cases there was no change observed in the starting materials or evidence for boron-ate formation (**1.134**) by ^{1}H and ^{11}B NMR.

Figure 0.3 ^{11}B NMR of the reaction of 1.58 with 1.59 at 45 °C.



Alkenyl Copper and Allylic Boronic Ester



1.135, Not Observed

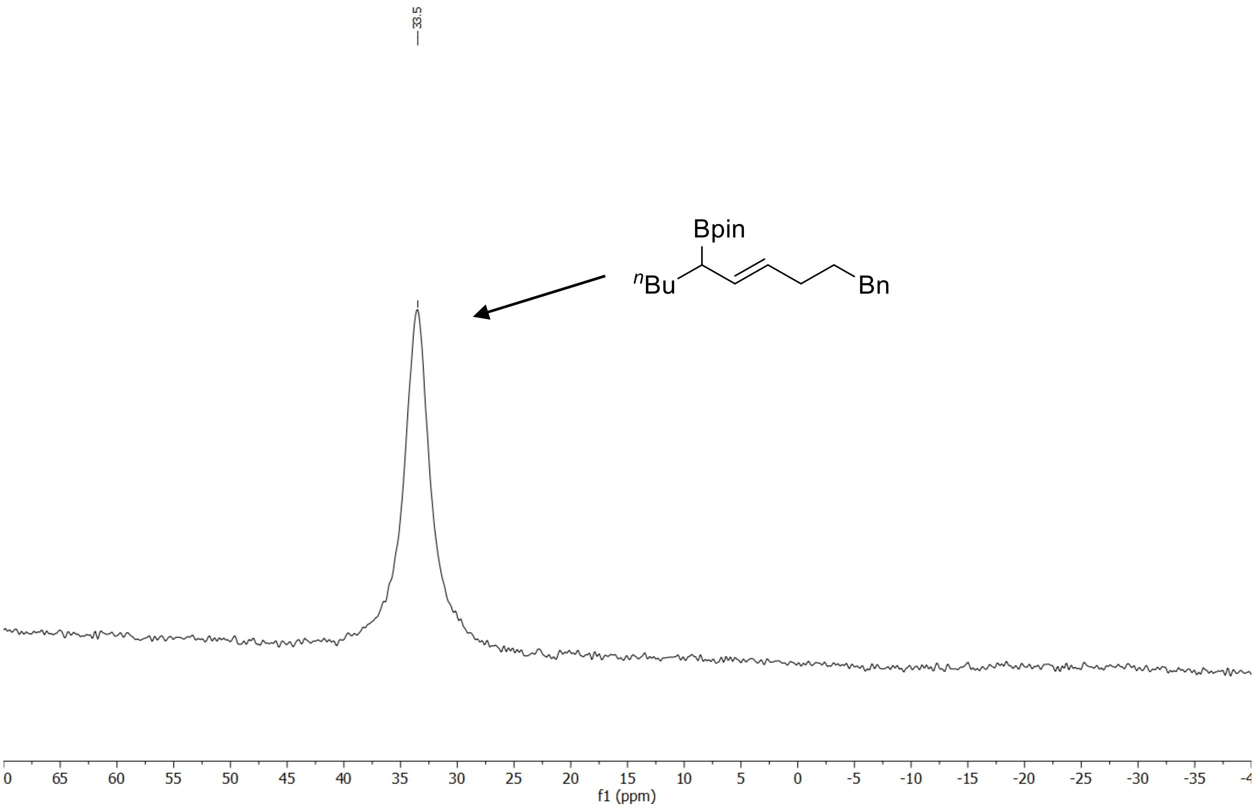
Unchanged Starting Materials

${}^{a}R = (CH_2)_3Ph$

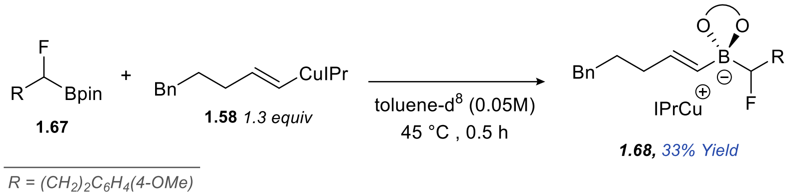
In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (14.6 mg, 0.025 mmol, 1.0 equiv). To this vial was added the allylic boronic ester (**1.36**) (8.6 mg, 0.025 mmol, 1.0 equiv), internal standard TMB (2.1 mg, 0.013 mmol) and toluene-d^8 (0.05 M). The reaction was stirred at 45 °C monitored by ^1H and ^{11}B NMR. There was no change observed in the starting materials or evidence for boron-ate formation (**1.135**) by ^1H and ^{11}B NMR.

Figure 0.4 ^{11}B NMR of the reaction of 1.58 with 1.36 at 45 °C.

^{11}B NMR (160 MHz, Tol) δ 33.5.



Alkenyl Copper and α-Fluoro Boronic Ester



α-Fluoro boronic ester (**1.67**) was prepared according to a previously reported procedure.[132]

In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (29.9 mg, 0.05 mmol, 1.3 equiv). To this vial was added the α-fluoro boronic ester (**1.67**) (11.3 mg, 0.04 mmol, 1.0 equiv), internal standard TMB (4.2 mg, 0.03 mmol) and toluene-d^8 (0.05 M). The reaction was stirred at 45 °C and monitored by ^{1}H and ^{11}B NMR.

Figure 0.5 ^{11}B NMR of the reaction of 1.3 equiv. of 1.58 with 1.67 after 30 minutes at 45 °C.

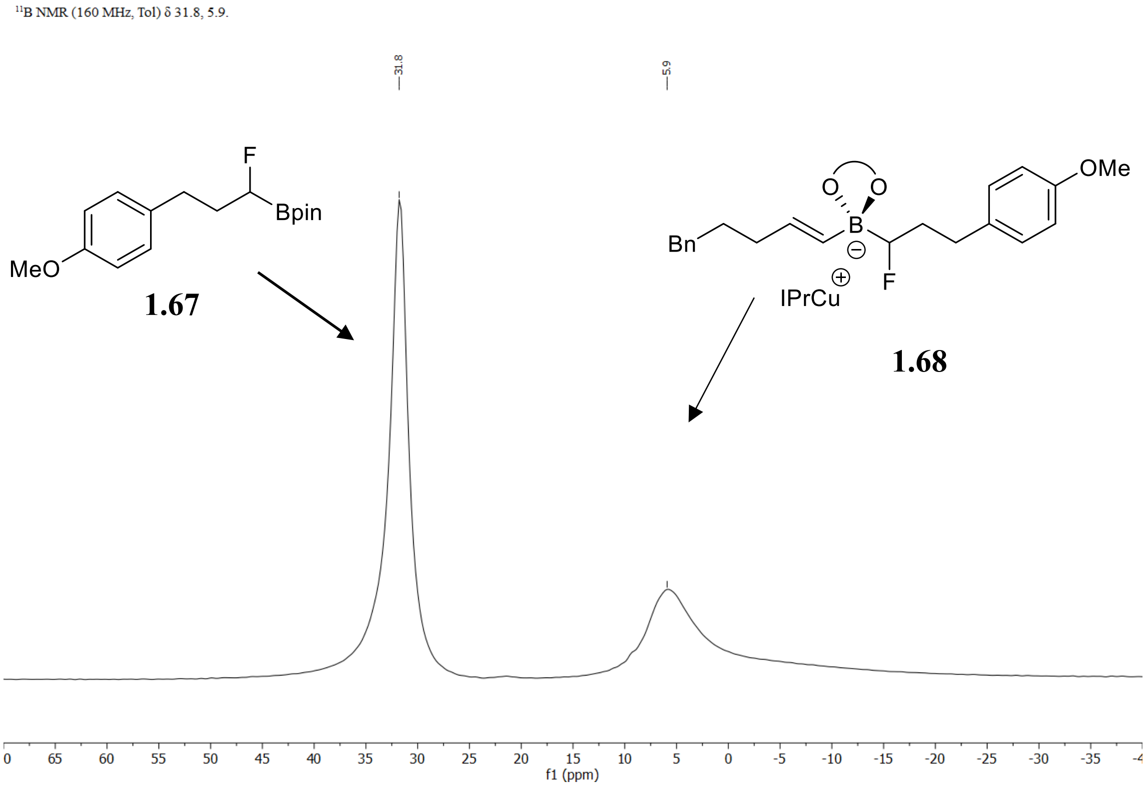


Figure 0.6 ^{1}H NMR of the reaction of 1.3 equiv of 1.58 with 1.67 after 30 minutes at 45 °C.

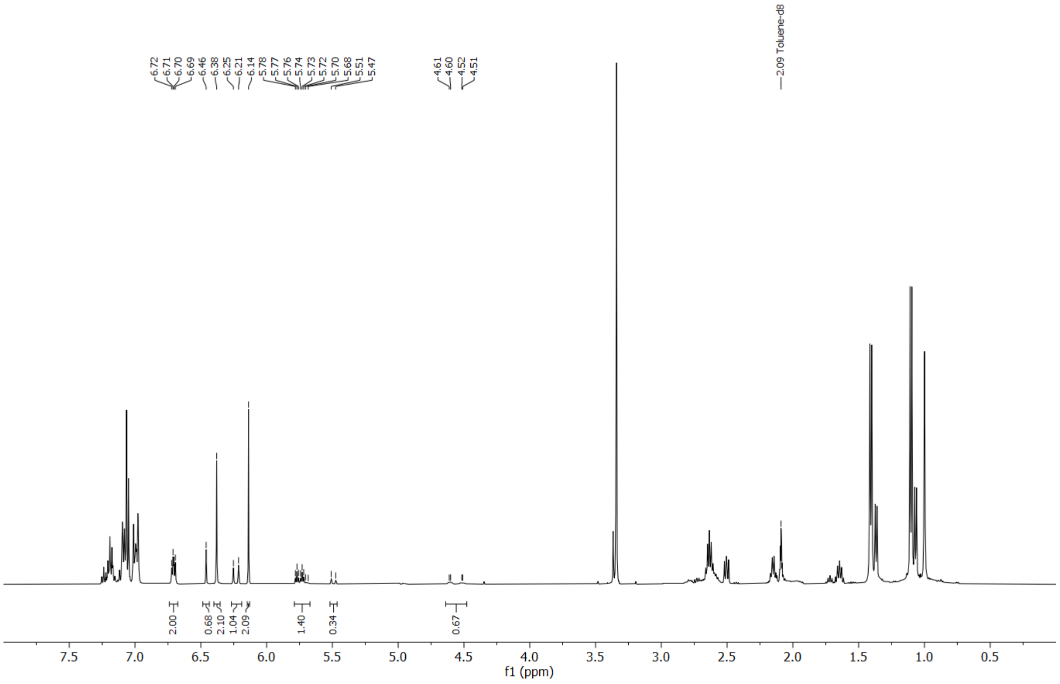
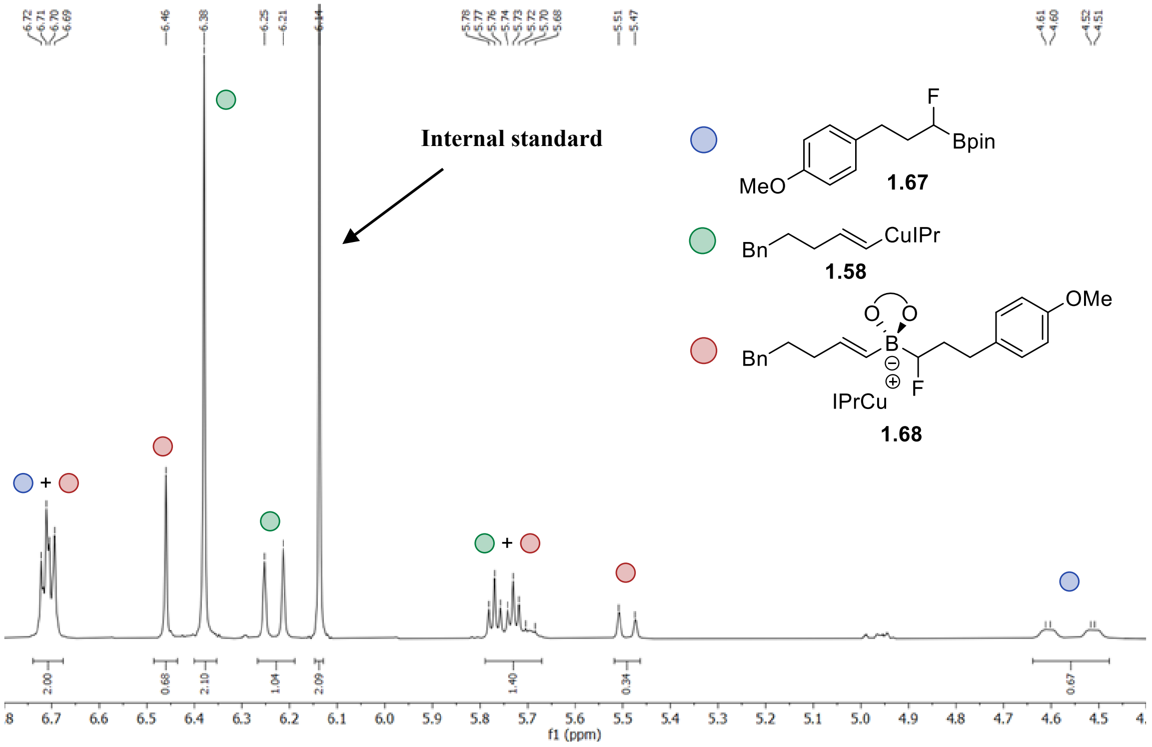
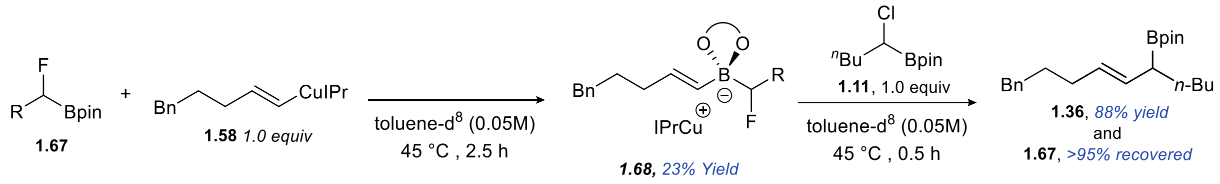


Figure 0.7 Figure 1.7 Magnified ^{1}H NMR of the reaction of 1.3 equiv of 1.58 with 1.67 after 30 minutes at 45 °C.





R = $(CH_2)_2C_6H_4$(4-OMe)

In a nitrogen-filled glovebox, a 4 mL scintillation vial was charged with a stir bar and alkenyl copper (**1.58**) (14.6 mg, 0.025 mmol, 1.0 equiv). To this vial was added the α-fluoro boronic ester[132] (**1.67**) (8.6 mg, 0.025 mmol, 1.0 equiv), internal standard TMB (2.1 mg, 0.013 mmol) and toluene-d^8 (0.05 M). The reaction was stirred at 45 °C and was monitored by ^{1}H and ^{11}B NMR for 2.5 hours. Between 30 minutes and 2.5 hours there was no observed change by ^{1}H or ^{11}B NMR. After 2.5 hours α-chloro boronic ester (**1.11**) (5.8 mg, 0.025 mmol, 1.0 equiv) was added and the reaction was stirred for 30 minutes at 45 °C and monitored by ^{1}H.

Figure 0.8 Magnified ^{1}H NMR of 1.0 equiv of 1.58 with 1.67 after 2.5 h at 45 °C.

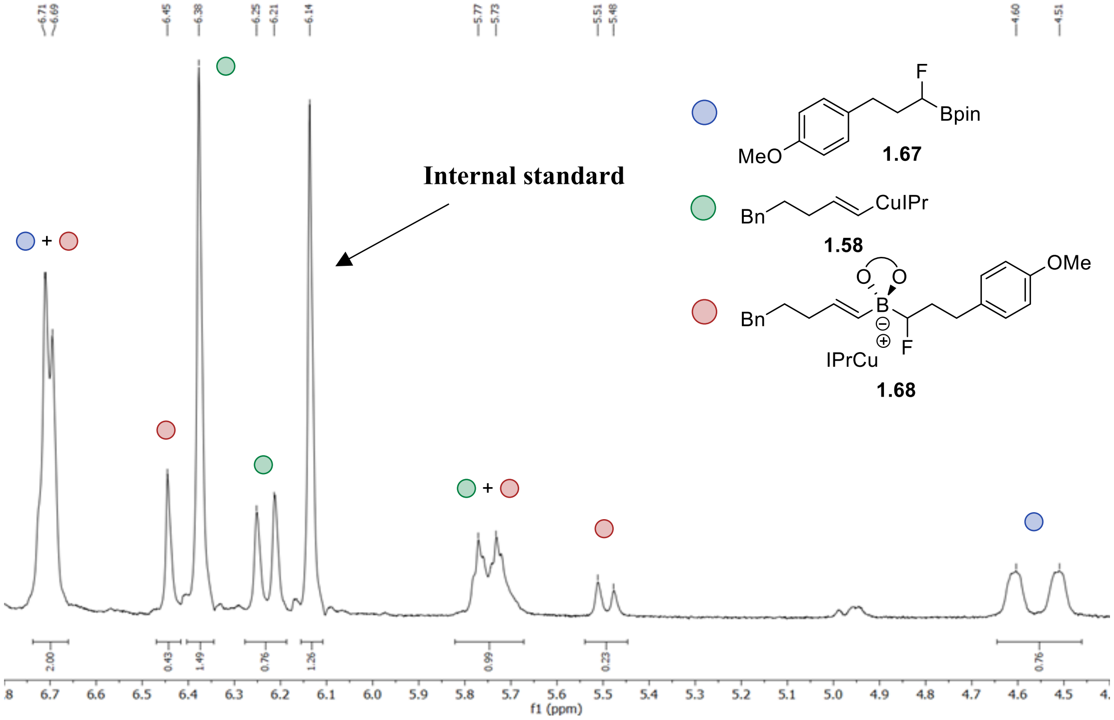
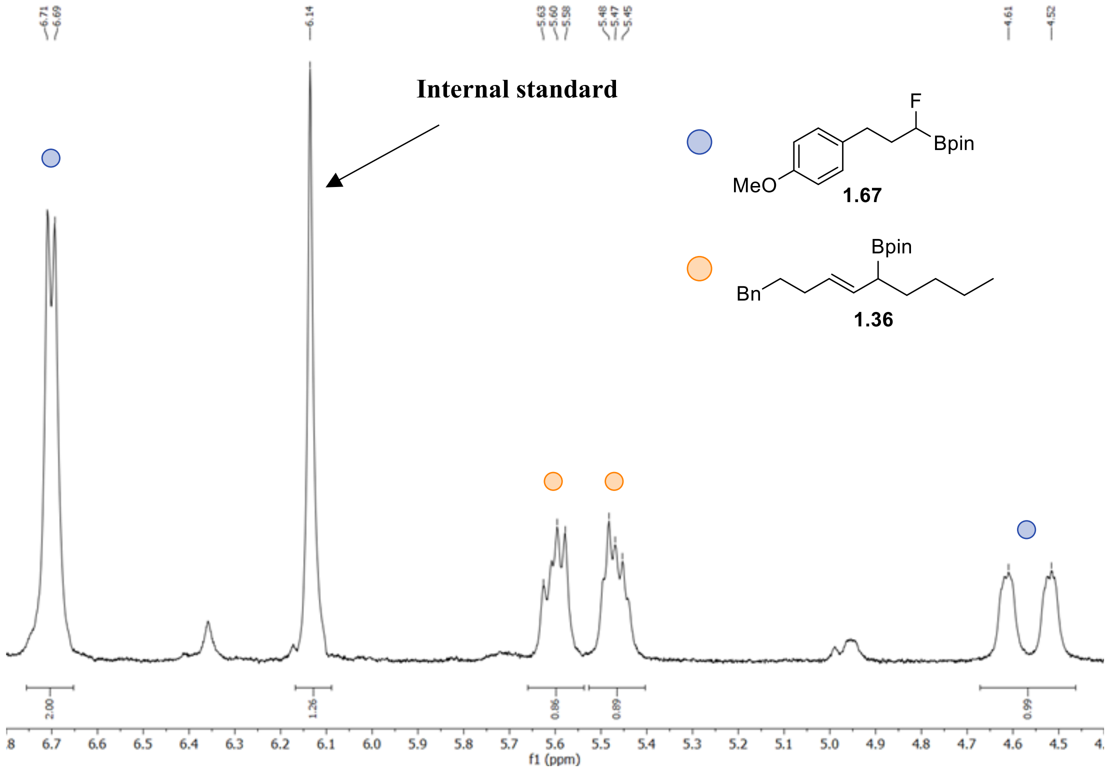
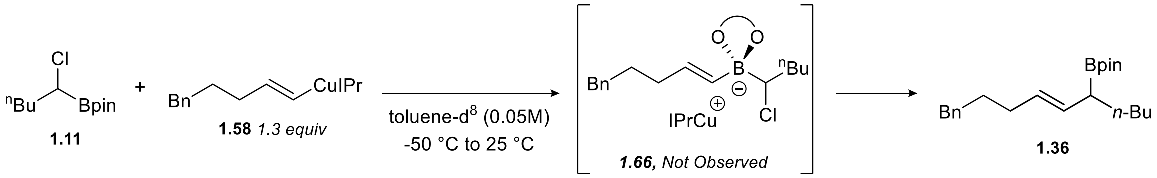


Figure 0.9 Magnified ^{1}H NMR of the reaction of 1.0 equiv of 1.58 with 1.67



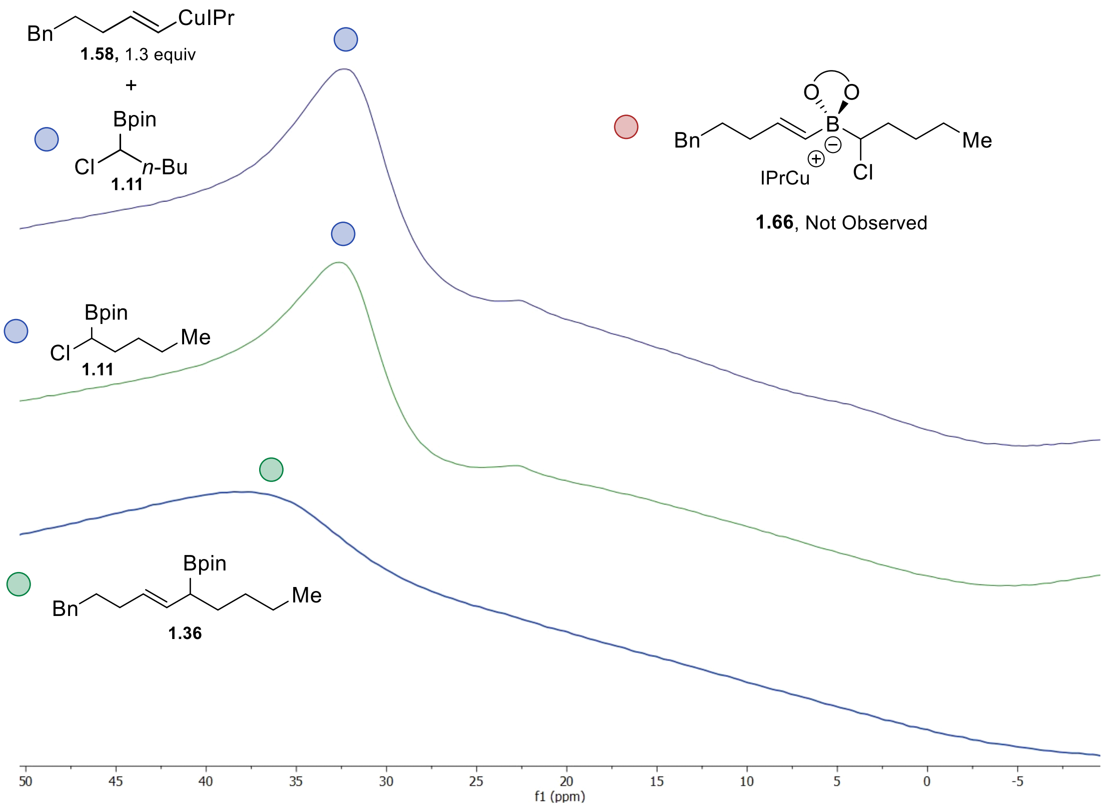
Magnified ^{1}H NMR of the reaction of 1.0 equiv of 1.58 with 1.67, 30 minutes after the addition of 1.0 equiv of α-chloro Bpin (1.11) at 45 °C.

Alkenyl Copper and α-Chloro Boronic Ester at Low Temperature



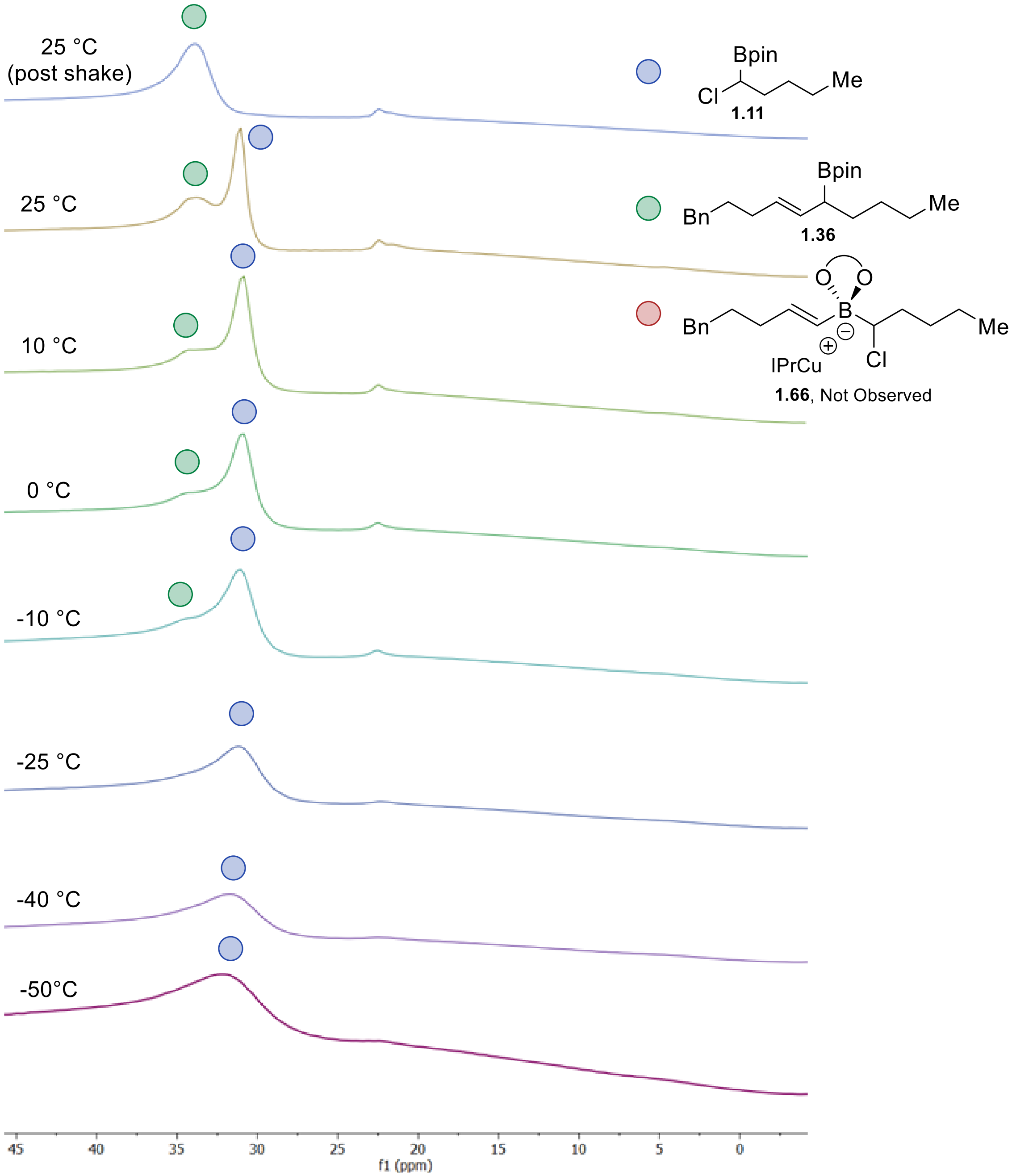
In a nitrogen-filled glovebox, a quartz J-Young NMR tube was charged with alkenyl copper (**1.58**) (23.3 mg, 0.04 mmol, 1.3 equiv) and internal standard TMB (2.5 mg, 0.02 mmol) along with 300 µL of toluene-d^8. The NMR tube was sealed removed from the glovebox. It was then frozen in liquid nitrogen and the α-chloro boronic ester (**1.11**) (7.0 mg, 0.03 mmol, 1.0 equiv) was added under nitrogen in solution of toluene-d^8 (0.1 M). The NMR tube was kept in a liquid nitrogen bath until just before it was to be analyzed, at which time it was warmed to -78 °C and inserted into the pre-cooled NMR. The reaction was monitored by ^{1}H and ^{11}B NMR beginning at -50 °C and warming up to 25 °C in regular temperature increments, taking ^{1}H and ^{11}B at each increment. After reaching 25 °C the reaction was removed from the NMR, briefly shaken in order to mix the insoluble IPrCuCl crashing out of solution and then returned to the NMR.

Figure 0.10 ^{11}B NMR at -50 °C in toluene-*d*^{8} of 1.11



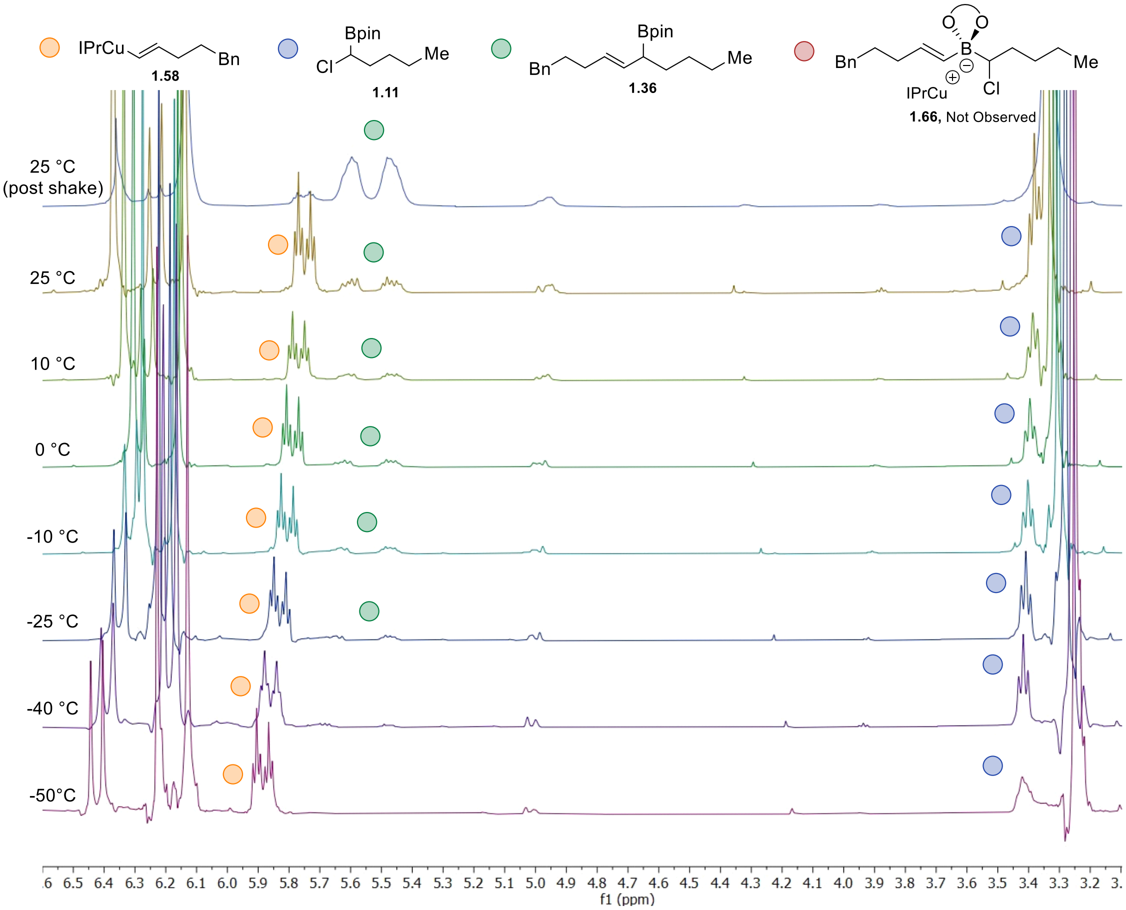
^{11}B NMR at -50 °C in toluene-*d*^{8} of 1.11 (middle spectrum), 1.36 (lower spectrum) and the reaction of 1.3 equiv of 1.58 with 1.11 (top spectrum).

Figure 0.11 Variable Temperature ^{11}B NMR

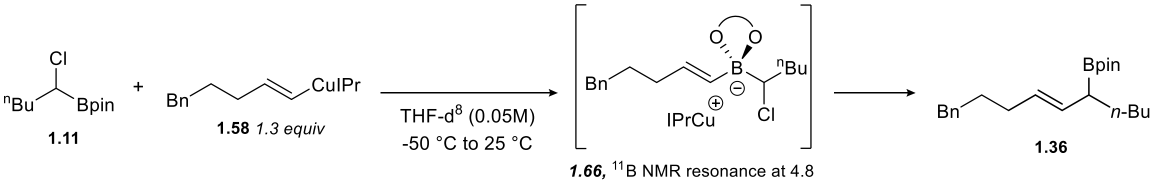


^{11}B NMR of the reaction in toluene-d^8 of 1.3 equiv of 1.58 with 1.11 at increasing temperatures from -50 °C (bottom spectrum) to 25 °C (top two spectra).

Figure 0.12 Magnified Cross Section of Variable Temperature ^{1}H NMR

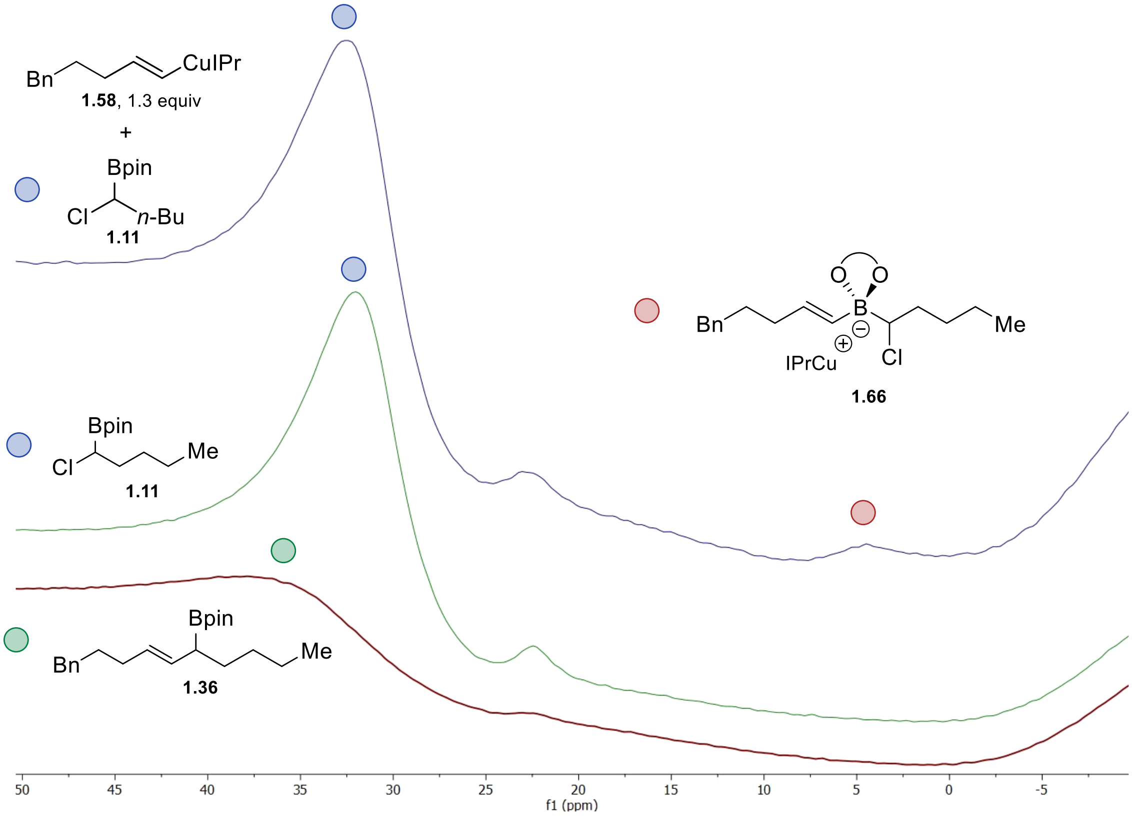


Magnified cross section of the ^{1}H NMR of the reaction in toluene-d^8 of 1.3 equiv of 1.58 with 1.11 at increasing temperatures from -50 °C (bottom spectrum) to 25 °C (top two spectra).



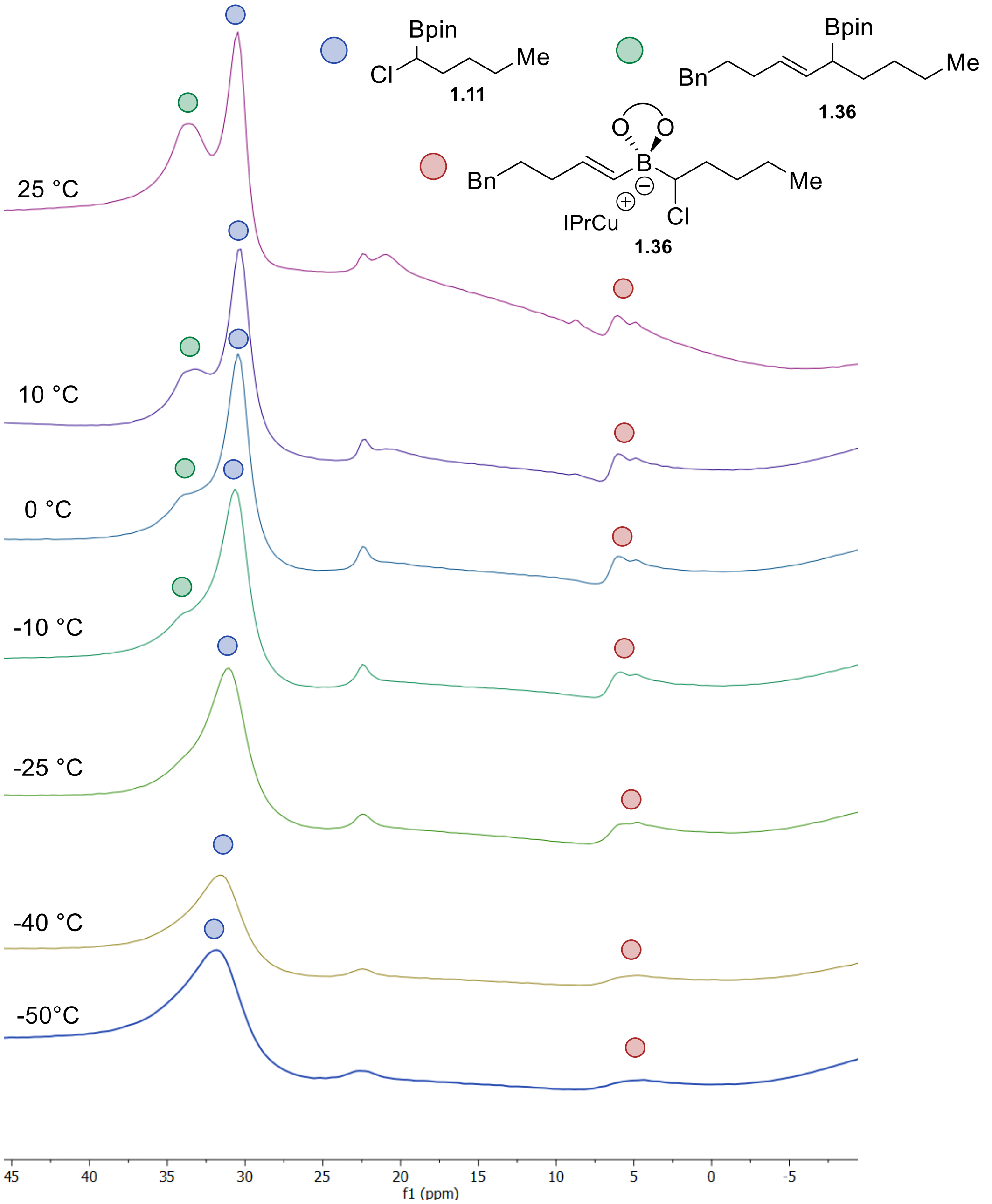
In a nitrogen-filled glovebox, a quartz J-Young NMR tube was charged with alkenyl copper (**1.58**) (23.3 mg, 0.04 mmol, 1.3 equiv) and internal standard TMB (2.5 mg, 0.02 mmol) along with 300 μL of THF-d^8. The NMR tube was sealed removed from the glovebox. It was then frozen in liquid nitrogen and the α-chloro boronic ester (**1.11**) (7.0 mg, 0.03 mmol, 1.0 equiv) was added under nitrogen in solution of THF-d^8 (0.1 M). The NMR tube was kept in a liquid nitrogen bath until just before it was to be analyzed, at which time it was warmed to -78 °C and inserted into the pre-cooled NMR. The reaction was monitored by ^{11}B NMR beginning at -50 °C and warming up to 25 °C in regular temperature increments, taking ^{11}B at each increment.

Figure 0.13 ^{11}B NMR at -50 °C in THF



^{11}B NMR at -50 °C in THF of 1.11 (middle spectrum), 1.36 (lower spectrum) and the reaction of 1.3 equiv of 1.58 with 1.11 (top spectrum).

Figure 0.14 Variable Temperature ^{11}B NMR in THF-d^8



^{11}B NMR of the reaction in THF-d^8 of 1.3 equiv of 1.58 with 1.11 at increasing temperatures from -50 °C (bottom spectrum) to 25 °C (top spectrum).

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CHAPTER 2

SELECTIVE SYNTHESIS OF Z-MICHAEL ACCEPTORS VIA HYDROALKYLATION OF CONJUGATED ALKYNES

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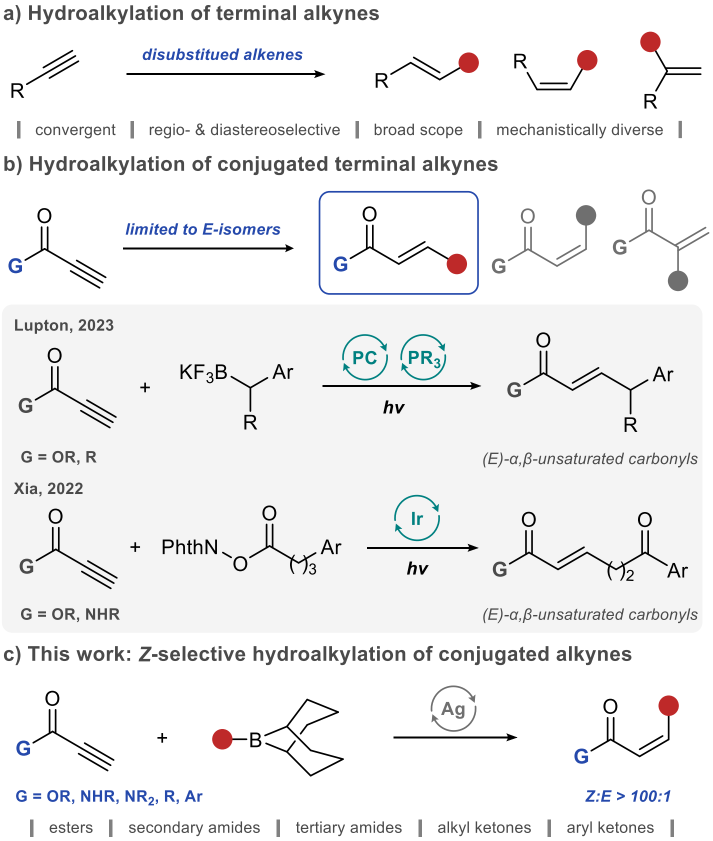
2.1. INTRODUCTION

α,β-Unsaturated carbonyls exhibit unique reactivity and are valuable intermediates in the synthesis of complex organic molecules.[1] Furthermore, their reactivity enables important biological applications. α,β-Unsaturated carbonyls are Michael acceptors and readily react with nucleophilic amino acid side chains (primarily Cystine) to make covalent adducts.[2] As a result, Michael acceptors have become indispensable in the development of biological probes and therapeutics.[3] Whether for synthetic or biological purposes, precise control over the substitution pattern and the geometry of the π-bond is often required. For example, *E*- and *Z*-Michael acceptor will yield different products in a wide range of transformations.[4]

Hydroalkylation of conjugated alkynes is potentially a general yet underexplored approach to synthesizing Michael acceptors. Catalytic methods for hydroalkylation of simple terminal alkynes offer precise control over regio- and stereoselectivity, providing access to *E*-, *Z*-, and 1,1-disubstituted alkenes with high selectivity (Scheme 2.1a).[5]. In principle, applying these methods to conjugated alkynes would enable the selective and convergent synthesis of all three isomers of conjugated alkenes.

Unfortunately, virtually none of the methods developed for hydroalkylation of simple terminal alkynes can be applied to the synthesis of Michael acceptors, in part due to the high reactivity of these compounds. As good electrophiles and radical acceptors, conjugated alkenes interfere with the two most common mechanistic paradigms for hydroalkylation reactions: metal hydride and free radical additions to alkynes. For instance, conjugated alkenes formed as intermediates in copper hydride-mediated transformations of alkynes are reduced to saturated carbonyls.[6]

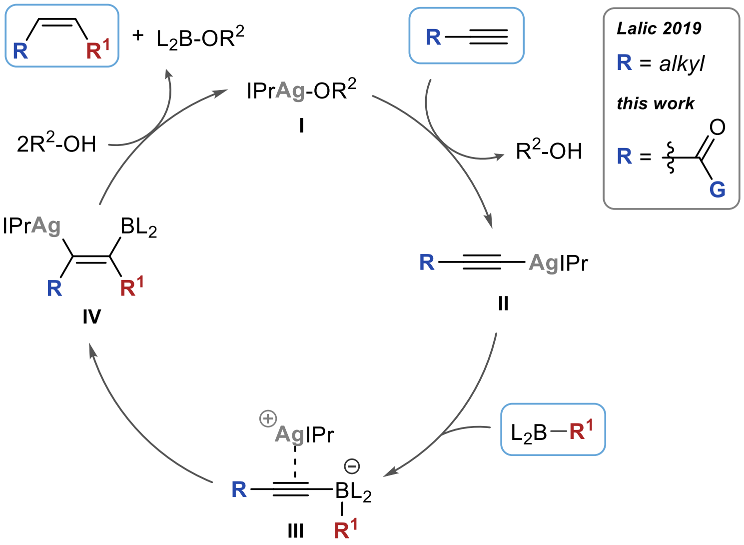
Figure 2.1 Hydroalkylation in the Synthesis of Disubstituted Alkenes



Recently, Xia[7] and Lupton[8] reported two methods specifically developed for conjugated alkynes (Scheme 2.1b). However, both transformations yielded only moderate amounts of *E*-Michael acceptors with limited substrate scopes. The synthesis of (*Z*)-α,β-unsaturated carbonyls is more challenging due to their tendency to isomerize into the more stable *E*-isomer,[9] and no methods for *Z*-selective hydroalkylation of conjugated alkynes have been reported so far.

Herein, we report the synthesis of *Z*-Michael acceptors through hydroalkylation of conjugated alkynes (Scheme 2.1c). α,β-Unsaturated esters, secondary and tertiary amides, aryl amides, and aryl and alkyl ketones can all be accessed with excellent *Z*-selectivity. The new method complements olefin cross-metathesis,[9-10] which is currently the only convergent catalytic method that allows synthesis of certain types of *Z*-Michael acceptors.[11,12]

Figure 2.2 Postulated Mechanism of Hydroalkylation



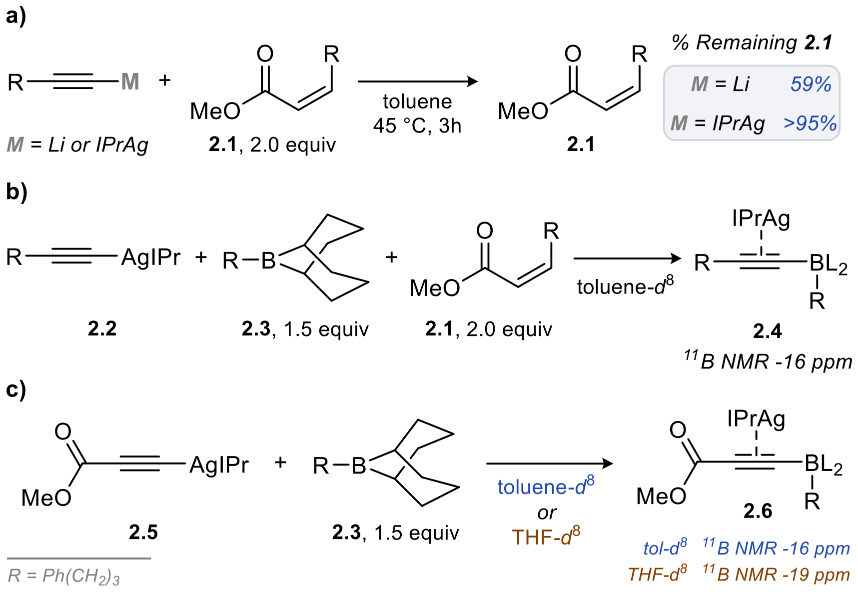
In 2019, we reported a new approach to *Z*-selective hydroalkylation of terminal alkynes with alkyl boranes as alkylating reagents.[5b] We recognized that the mechanism of this hydroalkylation (Scheme 2.2, R = alkyl),[13] which does not involve strongly nucleophilic or radical intermediates, may be well-suited for hydroalkylation of conjugated alkynes. In the established mechanism alkylation is driven by the electrophilicity of the alkyl borane and the silver catalyst, which promote boron-ate complex formation and the 1,2-metallate shift. With the idea that the same mechanism could be operational in hydroalkylation of conjugated alkynes, we set out to explore the feasibility of such a reaction.

2.2. PRELIMINARY RESULTS

First, we explored the compatibility of the key nucleophilic intermediate, silver acetylide, with α,β-unsaturated carbonyls. Silver acetylide **2.2**, which was previously reported by our group,[13] was exposed to α,β-unsaturated ester **2.1** in toluene, and over 95% of the starting alkene remained intact after 3 h (Scheme 3a). Under the same reaction conditions, the analogous lithium acetylide led to the consumption of 41% of the alkene, pointing to the lower reactivity of the silver acetylide. Moreover, when the silver acetylide was exposed to a mixture of α,β-unsaturated ester **2.1** and alkyl borane **2.3**, the equilibrium with the boron-ate complex was established,[13] as indicated by the appearance of a resonance at -16 ppm in ^{11}B NMR spectrum of the reactions mixture (Scheme 3b) (see section 2.6.3.2 for details).[14] At the same time, the conjugated alkene remained intact. The unexpected difference in the reactivity of alkyl boranes and α,β-unsaturated carbonyls in this competition experiment supported the feasibility of the proposed hydroalkylation of conjugated alkynes.

We anticipated that using conjugated instead of nonconjugated alkynes would affect several aspects of the hydroalkylation. For instance, the alkyne polarization induced by the carbonyl group is expected to facilitate the formation of the metal acetylide (II) and promote the turnover-limiting 1,2-metallate shift[13] (III and IV).[15] Our major concern was that the lower nucleophilicity of the acetylide derived from a conjugated alkyne may hinder the formation of the boronate complex. To investigate, we prepared silver acetylide **2.5** and examined its reaction with the alkyl borane (Scheme 2.3c). The boron-ate complex was formed, although it was present in the reaction mixture at a lower concentration than in the reaction with acetylide **2.2** (see section 2.6.3.4).

Figure 2.3 Preliminary Stoichiometric Experiments

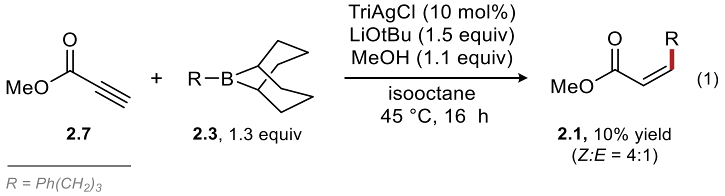


2.3. REACTION DEVELOPMENT

Encouraged by the results of the preliminary stoichiometric experiments, we explored catalytic hydroalkylation of methyl propiolate (**2.7**) using previously reported reaction conditions (eq 2.1).[5b] A complete consumption of the starting material yielded the desired hydroalkylation product in 10% yield and (4:1) *Z*-selectivity, together with a mixture of *E* and *Z* isomers of β,γ-unsaturated ester (8% yield) and a low molecular weight polymers. In a control experiment, we confirmed that LiO*t*-Bu alone leads to the fast and complete consumption of the propiolate ester (see section 2.6.4.1) that yields low molecular weight oligomers, as indicated by the analysis of the reaction mixture by gel permeation chromatography. We concluded that this base-promoted oligomerization of the alkyne prevents the hydroalkylation reaction in the presence of the LiO*t*-Bu.

Considering the acidity of the propiolate ester, we reasoned that a base weaker than LiO*t*-Bu would still promote the formation of silver acetylide while suppressing the undesired reaction pathways. Weak inorganic bases, such as carbonates, seemed particularly well suited for this purpose. The low solubility of these bases in hydrocarbon solvents would ensure their low effective concentration, further limiting potential side reactions.

Equation 2.1 Hydroalkylation of Methyl Propiolate

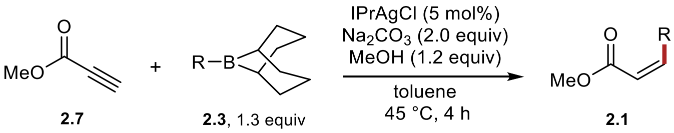


An exploration of various inorganic bases in the reaction of **2.7** with alkyl borane in the presence of an alcohol and the silver catalyst led to the development of the reaction shown in Table 2.1. Sodium carbonate with methanol provided the best results, furnishing the desired (*Z*)-α,β-unsaturated ester in 92% yield with >100:1 *Z*-selectivity. Silver catalysts supported by related NHC ligands gave similar results to IPrAgCl.

Surprisingly, the alcohol used in the reaction had a large effect on the reaction rate. With EtOH, the rate was significantly lower (33% after 1h vs 79% with MeOH, entries 1 and 4). The reaction was even slower with secondary and tertiary alcohols (entries 5 and 6). Other inorganic bases, such as potassium carbonate or potassium phosphate performed generally well (entries 7 and 8), while more soluble alkoxide bases performed poorly (entries 9 and 10). LiOMe performed modestly under the reaction conditions, possibly owing to its low solubility in toluene (entry 10). Nonpolar solvents, such as benzene and isooctane, generally performed well (entries 12 and 13), while THF gave a diminished yield (entry 14). The reaction was complete after 4 hours at 45 °C and was significantly slower at room temperature (entry 15), giving a diminished yield even after 24 hours (see section 2.6.4.1). A modest excess of alkyl borane (1.3 equiv) was optimal, with the alkyl borane prepared in situ via hydroboration of the corresponding alkene prior to the reaction.[16]

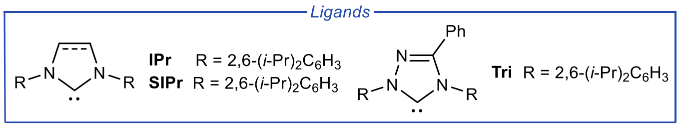
Finally, alkyl boronic esters were not viable substrates, presumably due to their lower Lewis acidity and inability to support the formation of the boron-ate complex.

Table 2.1 Reaction Development[a]



Entry	*Change from standard conditions*	*Yield*
1	none	92% (79%)[b]
2	SIPrAgCl *instead of* IPrAgCl	88%
3	TriAgCl *instead of* IPrAgCl	85%
4	EtOH *instead of* MeOH	87% (33%)[b]
5	*i*-PrOH *instead of* MeOH	66%[c]
6	*t*-AmylOH *instead of* MeOH	11%[d]
7	K_2CO_3 *instead of* Na_2CO_3	79%
8	K_3PO_4 *instead of* Na_2CO_3	84%
9	NaO*t*-Bu *instead of* Na_2CO_3	9%
10	LiO*t*-Bu *instead of* Na_2CO_3	15%
11	LiOMe *instead of* Na_2CO_3	48%
12	benzene *instead of* toluene	87%
13	isooctane *instead of* toluene	85%
14	THF *instead of* toluene	31%
15	25 °C *instead of* 45 °C	51%
16	Bpin *instead of* 9-BBN	0%[e]

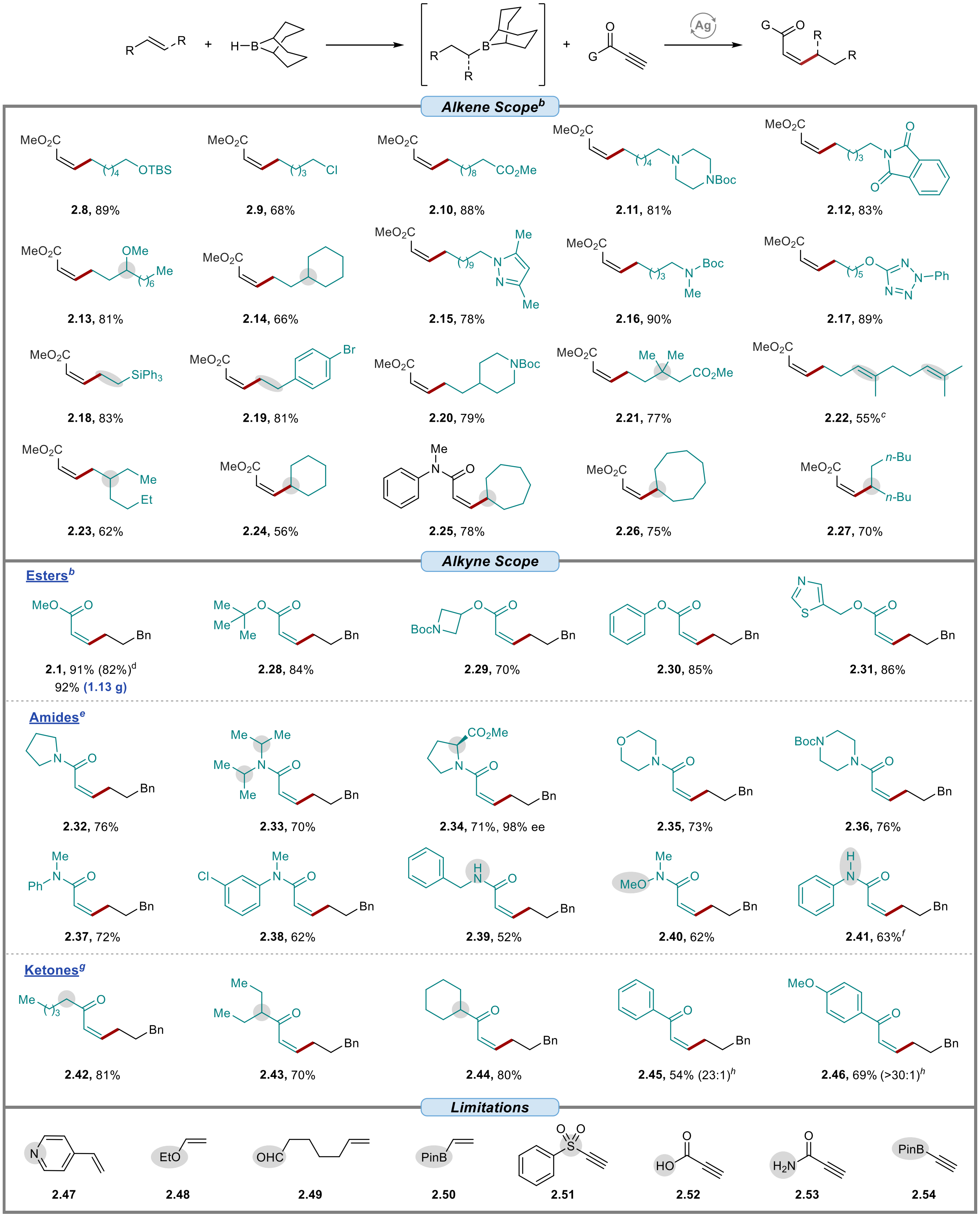
[a] Yield determined by GC using internal standard. R = $Ph(CH_2)_3$. [b] Yield after 1 hour. [c] 73% yield after 24 hours. [d] 32% yield after 48 hours. [e] >95% alkyl Bpin remaining after 4 hours.



2.4. SUBSTRATE SCOPE

We explored the scope of the hydroalkylation using standard reaction conditions shown in Table 2.1. Various alkyl boranes were prepared by in situ hydroboration of alkenes and used in the subsequent hydroalkylation without purification or solvent exchange. The hydroalkylation reaction proved to be remarkably general, providing the (*Z*)-α,β-unsaturated esters with >100:1 *Z*-selectivity. Primary alkyl boranes prepared from activated alkenes such as vinyl silanes (**2.18**), styrenes (**2.19**), and conjugated dienes (**2.22**), performed well in the reaction. At the same time, a

Scheme 2.1 Substrate Scope[a]



[a] Yields of isolated products. Z:E > 100:1. Reactions performed on a 0.5 mmol scale. [b] Reaction conditions for esters: IPrAgCl (5 mol%), alkyne (1.0 equiv), alkyl borane (1.3 equiv), Na_2CO_3 (2 equiv), MeOH (1.2 equiv), toluene (5 mL), 45 °C, 4 h. [c] 1.7:1 dr for the ε,ζ-alkene (1.4:1 in the starting material (see section 2.6.13)). [d] Reaction performed using AgBr and IPrHCl instead of IPrAgCl (see the section2.6.9). [e] Reaction conditions for amides: IPrAgCl (5 mol%), alkyne (1.5 equiv), alkyl borane (1.0 equiv),

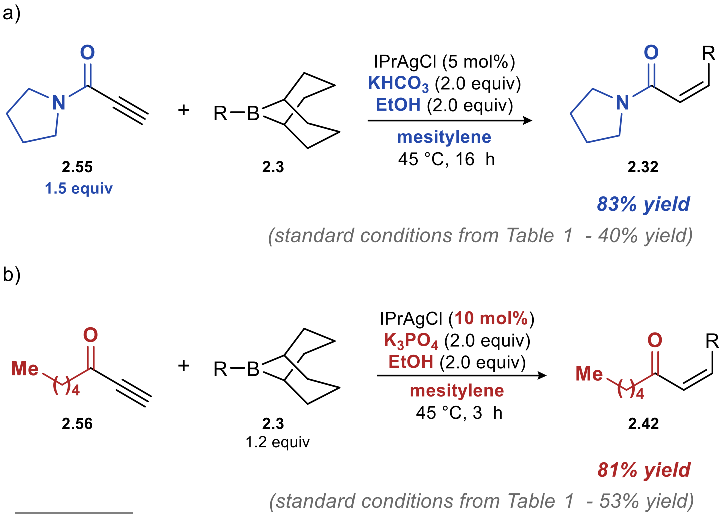
$KHCO_3$ (2 equiv), EtOH (2 equiv), mesitylene, 45°C, 16 h. [f] Na_2CO_3 was used instead of $KHCO_3$. [g] Reaction conditions for ketones: IPrAgCl (10 mol%), alkyne (1.0 equiv), alkyl borane (1.2 equiv), K_3PO_4 (2 equiv), EtOH (2 equiv), mesitylene, 45°C, 3 h. [h] Isolated as a mixture of α,β- and β,γ-unsaturated ketones (see the 2.6.11.2).

range of functional groups was tolerated in the reaction, which was successfully performed in the presence of protected alcohols (**2.8**), alkyl chlorides (**2.9**), esters (**2.10**, **2.21**), Boc-protected secondary amides (**2.11**, **2.16**, and **2.20**), aryl bromides (**2.19**), and a variety of nitrogen-containing heterocycles, such as pyrazole (**2.15**), tetrazole (**2.17**), piperidine (**2.20**), and piperazine (**2.11**). More sterically hindered alkyl boranes, prepared from 1,1-disubstituted alkenes (**2.23**), also worked well under our reaction conditions. Surprisingly, even secondary alkyl boranes participate in the reaction, providing access to α-branched *Z*-Michael acceptors. These compounds are challenging to synthesize via current methods, with only a handful of reported examples obtained in low yields.[10b] It is also worth noting that secondary alkyl boranes are not viable substrates in hydroalkylation of nonconjugated terminal alkynes,[5b] which points to unique reactivity of conjugated alkynes.

We next investigated the scope of conjugated alkynes. Alkynyl esters of primary (**2.1**, **2.31**), secondary (**2.29**), and tertiary (**2.28**) alcohols performed well in the reaction. Interestingly, no transesterification was observed for these products despite the presence of methanol and inorganic base. Even a phenoxy ester (**2.30**) was tolerated under the rection conditions with no discernable transesterification. The reaction can be successfully executed outside of the glovebox to prepare more than 1 g of (*Z*)-α,β-unsaturated ester **2.1** in 92% yield. Finally, product **2.1** was prepared in 82% yield using catalyst formed in situ from silver bromide and IPr ligand precursor (see section 2.6.9 for details).

Alkynyl amides proved to be more challenging substrates. Our initial attempts to achieve hydroalkylation of **2.55** were met with limited success, as product **2.32** was formed in 40% yield under the standard reaction conditions shown in Table 2.1 (Scheme 2.4a). Fortunately, by making small adjustments to the reaction conditions (highlighted in blue in Scheme 2.4a), we obtained the desired (*Z*)-α,β-unsaturated amide (**2.32**) in an improved yield of 83%, with *Z*-selectivity exceeding 100:1. The most significant enhancement in yield occurred when we replaced MeOH with EtOH, although this change was accompanied by a reduction in the reaction rate. Additionally, performing the reaction at a lower overall concentration and switching from Na_2CO_3 to $KHCO_3$ further improved the yield (see section 2.6.4.2).

Scheme 2.2 Hydroalkylation of Alkynyl Amides and Ketones[a]



[a] R = $Ph(CH_2)_3$

Under the optimized reaction conditions, other secondary and tertiary amides also performed well, providing (*Z*)-α,β-unsaturated amides with excellent *Z*-selectivity. Amides of cyclic secondary amines were well tolerated, including those derived from pyrrolidine (**2.32**), morpholine (**2.35**), and piperazine (**2.36**). Enantioenriched proline-derived amide (**2.34**) could also be used in a reaction with complete retention of stereochemistry. Sterically demanding α-branched amides (**2.33**), Weinreb amides (**2.40**), and aniline-derived amides (**2.37**, **2.38**) all performed well under the reaction conditions. Secondary alkyl and aryl amides containing acidic N-H bonds (**2.39**, **2.41**) also performed well.

(*Z*)-α,β-Unsaturated ketones are a class of Michael acceptors that are particularly challenging to access. Even the *Z*-selective metathesis reaction, which is generally applicable to the synthesis of (*Z*)-α,β-unsaturated esters[10] and some amides,[9] does not allow access to this class of compounds. Under the standard reaction conditions, the hydroalkylation of alkynyl ketone **2.56** afforded 53% yield of the desired product (Scheme 2.4b).

Similar to our experience with reactions of the alkynyl esters and amides, we found that small changes in reaction conditions (highlighted in red in Scheme 2.4b) significantly improved the reaction yield. With EtOH, a phosphate base, and a slightly higher catalyst loading, the desired product **2.42** was obtained in 81% yield.

Both linear (**2.42**) and α-branched ketones (**2.43**, **2.44**) performed well under these reaction conditions (Table 2.2). Aryl ketones (**2.45**, **2.46**) afforded slightly diminished yields. With these substrates, nonconjugated β,γ-unsaturated ketone byproducts were also formed. These byproducts are likely formed through deprotonation of the initially formed α,β-unsaturated ketones, followed by a kinetic α-selective protonation of the dienolate.[17] Surprisingly, despite the positional isomerization of the alkene, the *Z*-selectivity for the α,β-unsaturated products was high (>100:1) (see section 2.6.11.2).

While the reaction proved to be remarkably general, we also noted several limitations. Alkenes containing reducible groups, such as alkyl bromides and aldehydes, were incompatible with the hydroboration reaction while strongly coordinating groups, such as pyridine, prevented the hydroboration. Trisubstituted and functionalized alkenes, such as acrylate or vinyl ethers, also failed to produce desired products. Some limitations were also noted for the alkyne coupling partners, including alkynyl carboxylic acids and primary amides, possibly due to the presence of acidic protons. Additionally, alkynes conjugated to other electron-withdrawing groups, such as sulfones or boronic esters, also failed to afford the desired products.

2.5. CONCLUSION

In conclusion, we have developed a new method for the synthesis of *Z*-Michael acceptors through hydroalkylation of conjugated alkynes. The new method has an excellent scope and allows the synthesis of (*Z*)-α,β-unsaturated esters, amides, and ketones in the presence of a wide range of functional groups. The unique mechanism of the hydroalkylation based on boron-ate formation and silver-promoted 1,2-metallate shift ensures exceptional *Z*-selectivity across all substrates.

2.6. EXPERIMENTAL

2.6.1. *General Procedures*

All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk technique, or in a glovebox (Nexus II or Genisis, both from Vacuum Atmospheres). Column chromatography was performed using a Biotage Isolara-1SV flash purification system, with silica gel from Agilent Technologies Inc. (60Å, 40-60 µm, 230-400 mesh). High Pressure Liquid Chromatography was performed using an Agilent LC column (Zorbax CN PrepHT, 21.2 x 250 mm, 7 µm). Analytical High Pressure Liquid Chromatography was performed using an Agilent LC column (Zorbax Original CN, 4.6 x 250 mm x 7 µm). Infrared (IR) spectra were recorded on a Perkin Elmer Frontier FTIR. 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 tetramethylsilane (TMS) and are referenced relative to residual solvent peak ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm, CD_2Cl_2: δ 5.32 ppm). ^{13}C NMR chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.0 ppm or CD_2Cl_2: δ 54.0 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 an Agilent 5973 GC-MS or a Bruker Esquire LC ion trap mass spectrometer. Gel permeation chromatography (GPC) data were collected on Agilent 1260 HPLC equipped with a Wyatt 8-angle DAWN NEON light-scattering detector, ViscoStar NEON viscometer, and Optilab NEON refractive index detector. GPC samples (ca. 3 mg/mL) were analyzed at a flow rate of 1 mL/min in chloroform (stabilized with 0.5 – 1.0% ethanol) through two Agilent PLgel MIXED-C columns at 35 °C. Specific rotations ([α]Dt) were measured using a Jasco P-2000 Polarimeter at the indicated temperature with a sodium lamp (λ = 589 nm) with a 100 mm cell and concentrations (g/(100mL)) reported in the corresponding solvent. 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 and 5.5 min @ 250 °C.

2.6.2. *Materials*

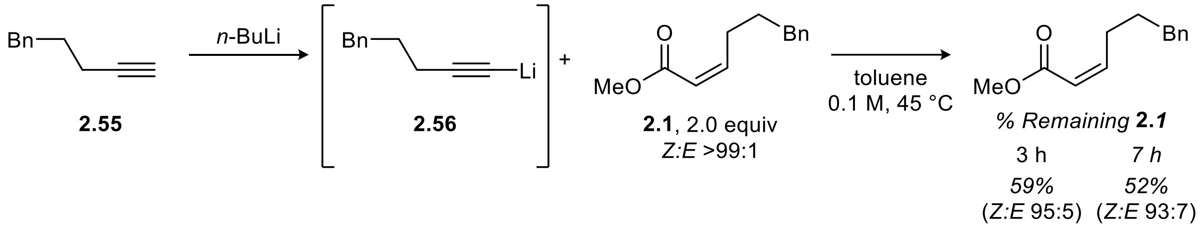
THF, CH_2Cl_2, ether, benzene, and toluene were degassed and dried by passing through columns of neutral alumina. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were stored over 4Å molecular sieves prior to use. Commercial reagents were purchased from Millipore Sigma,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

2.6.3. *Stoichiometric Studies*

2.6.3.1. Addition of Non-Conjugated Acetylides to (*Z*)-α,β-Unsaturated Carbonyls

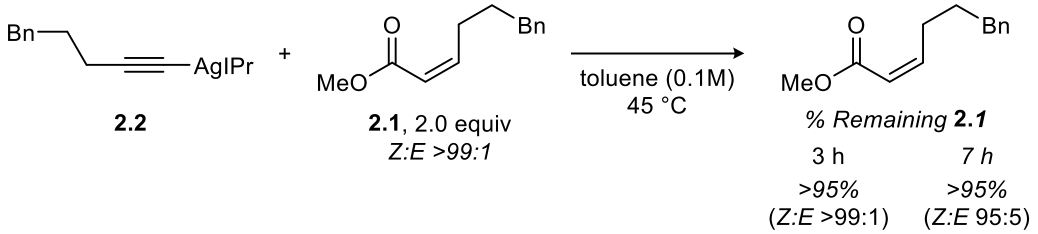
To test the feasibility of making α,β-unsaturated carbonyls utilizing our previous hydroalkylation approach[18] we explored the addition of alkynyl nucleophiles to (*Z*)-α,β-unsaturated esters.

Scheme 2.3 Addition of Non-Conjugated Lithium Acetylide to (Z)-α,β-Unsaturated Carbonyl



A flame dried flask was allowed to cool under nitrogen. It was then charged with 5-phenyl-1-pentyne (46 µL, 0.3 mmol, 1.0 equiv), toluene (0.1 M) and a stir bar. This was then cooled to -78 °C and *n*-BuLi (120 µL, 2.5 M, 0.3 mmol, 1.0 equiv) was added. This mixture was allowed to stir for 30 minutes and then a solution of **2.1** (123 mg, 0.6 mmol, 2.0 equiv) and internal standard 1,3,5-trimethoxybenzene (TMB) (50.5 mg, 0.3 mmol), in toluene (500 µL) was added at -78 °C. The mixture was allowed to warm up to room temperature and then heated to 45 °C. Aliquots of the reaction were taken at the specified time points and analyzed by GC to determine the remaining (Z)-α,β-unsaturated ester (**2.1**).

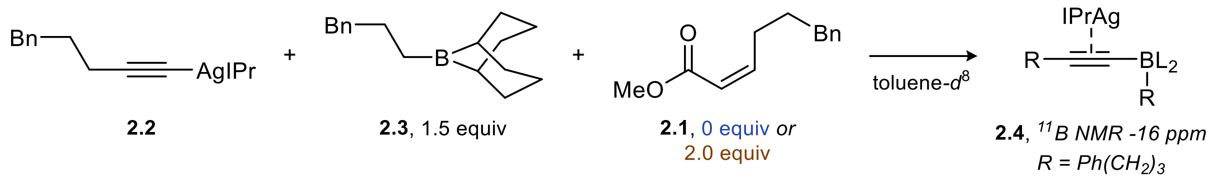
Scheme 2.4 Addition of Non-Conjugated Silver Acetylide to (Z)-α,β-Unsaturated Carbonyl



In a nitrogen-filled glovebox, a dram vial was charged with silver acetylide (**2.2**) (19.2 mg, 0.03 mmol, 1.0 equiv), (Z)-α,β-unsaturated ester (**2.1**) (12.3 mg, 0.06 mmol, 2.0 equiv), toluene (0.1 M), internal standard TMB (5.0 mg, 0.03 mmol), and a stir bar. The resulting mixture was stirred at 45 °C in the glovebox. Aliquots of the reaction were taken at the specified time points and analyzed by GC to determine the remaining (Z)-α,β-unsaturated ester (**2.1**). Silver acetylide (**2.2**) was prepared according to our previously published work and has been characterized.[19]

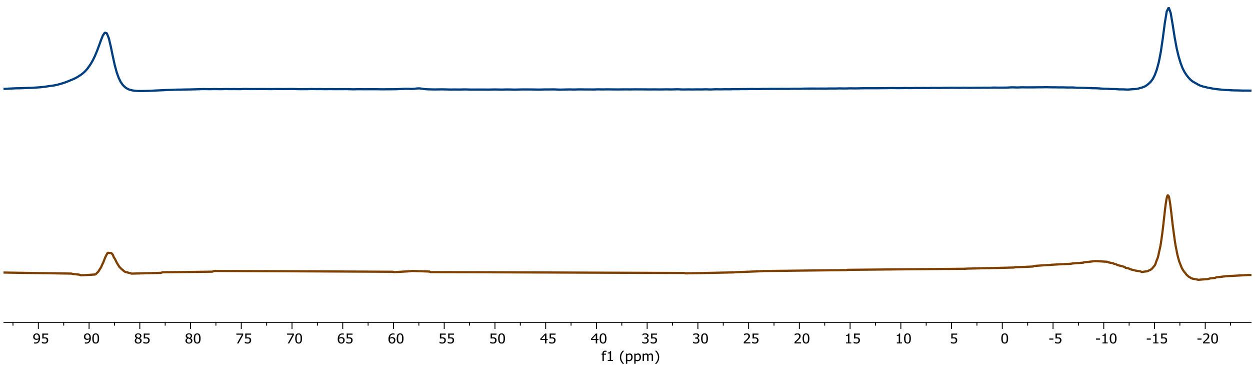
2.6.3.2. Reaction of Non-Conjugated Silver Acetylide with Alkyl Borane in the Presence of (*Z*)-α,β-Unsaturated Carbonyls

Scheme 2.5 Reaction of Non-Conjugated Silver Acetylide with Alkyl Borane in the Presence of (Z)-α,β-Unsaturated Carbonyl



In a nitrogen-filled glovebox, a dram vial was charged with **2.2** (19.2 mg, 0.03 mmol, 1.0 equiv), alkyl borane (**2.3**) (0.05 mmol, 1.5 equiv), toluene-d^8 (0.1 M), TMB, a stir bar and either 0 or 2.0 equiv of (Z)-α,β-unsaturated ester (**2.1**). These two reactions were stirred at 45 °C in the glovebox. An aliquot of each reaction was taken after 10 minutes and placed in a sealed NMR tube. It was then analyzed by ^{1}H and ^{11}B NMR. In both reactions a boron-ate peak was observed at -16.4 ppm which is consistent with the formation of complex **2.4**. Additionally, when 2.0 equiv of **2.1** was included >95% of **2.1** remained at the end of the reaction with no measurable isomerization.

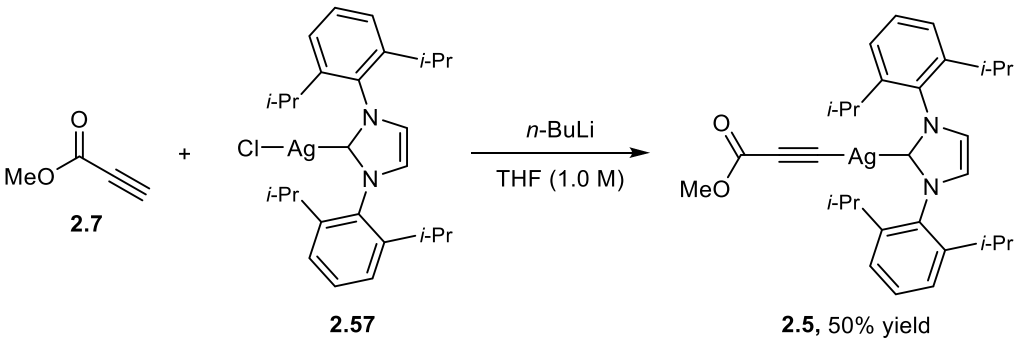
Figure 2.4 ^{11}B NMR of the reaction of 2.2 and 3.2



^{11}B NMR of the reaction of **2.2** and **2.3** with the addition of either 0 (blue) or 2.0 (orange) equiv of **2.1** in toluene-*d*^{8}. Unreacted alkyl borane appears at 88.4 ppm while the boron-ate is at -16.4 ppm.

2.6.3.3. Synthesis of Silver Acetylide 2.5

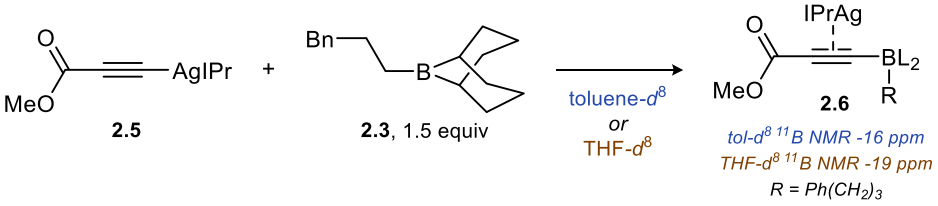
Scheme 2.6 Synthesis of Silver Acetylide 2.5



A flame dried flask was allowed to cool under nitrogen. It was then charged with methyl propiolate (**2.7**) (42.0 mg, 0.5 mmol, 1.0 equiv) and THF (2.0 M). This was then cooled to -78 °C and *n*-BuLi (200 µL, 2.5 M, 0.5 mmol, 1.0 equiv) was added. This solution was allowed to stir for 30 minutes. A separate flask was charged with IPrAgCl (**2.57**) (293.1 mg, 0.55 mmol, 1.1 equiv) and THF (2.0 M) and was cooled to -78 °C. The first flask (methyl propiolate) was cannula transferred to the second flask (IPrAgCl) at -78 °C. This was stirred for 15 minutes at -78 °C at which time it was allowed to warm to room temperature and immediately taken inside a nitrogen filled glovebox and filtered through a plug of celite with THF (5 mL). The resulting solution was concentrated under vacuum in the glovebox to yield a brown powder. This was subsequently dissolved in toluene (20 mL) filtered through a plug of celite to remove lithium chloride. The filtrate was again concentrated under vacuum to yield **2.5** as a light brown powder (144.0 mg, 50% yield). ^{1}H NMR (500 MHz, THF) δ 7.60 (s, 2H), 7.50 (t, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 4H), 3.38 (s, 3H), 2.66 – 2.55 (m, 4H), 1.32 – 1.19 (m, 24H). ^{13}C NMR (126 MHz, THF) δ 154.4, 146.8, 136.2, 131.4, 129.8, 129.1, 125.3, 125.2, 125.1, 67.6, 50.9, 29.7, 25.2, 24.2.

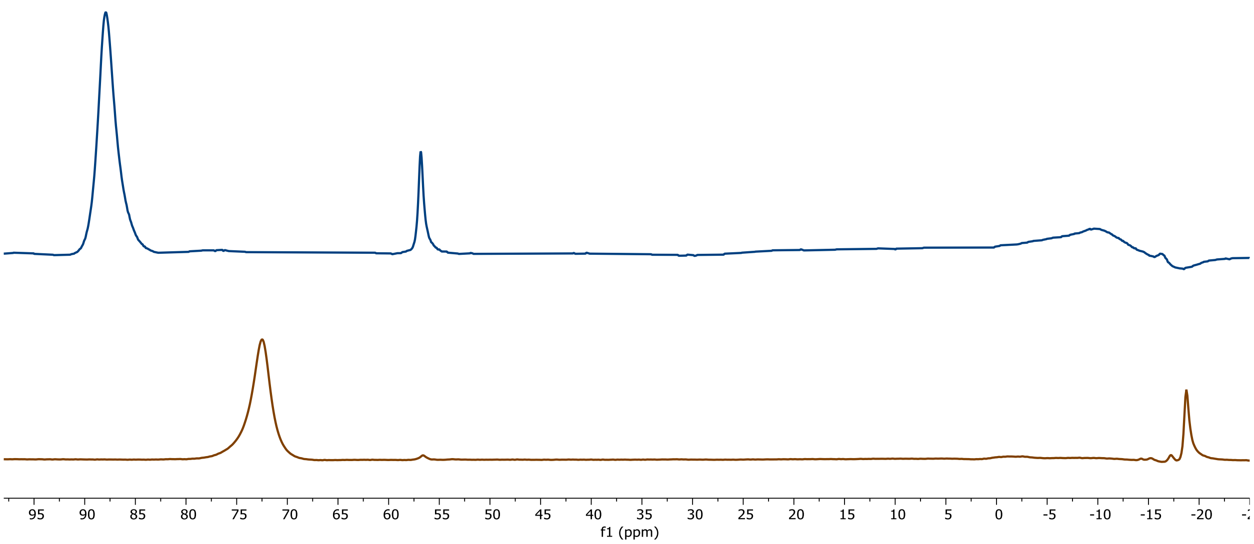
2.6.3.4. Boron-ate formation with Acetylide 2.5

Scheme 2.7 Boron-ate formation with Silver Acetylide 2.5



To probe the formation of the boron-ate complex derived from the addition of a conjugated alkyne acetylide we examined the reaction of conjugated silver acetylide (**2.5**) with **2.3** in both toluene-d^8 and THF-d^8. In a nitrogen-filled glovebox, an NMR tube was charged with **2.5** (17.4 mg, 0.03 mmol, 1.0 equiv), TMB and either toluene-d^8 or THF-d^8 (300 μL). The NMR tube was sealed with a rubber septa and removed from the glovebox. It was then frozen in liquid nitrogen and alkyl borane (**2.3**) (0.05 mmol, 1.5 equiv) in 100 μL of toluene-d^8 or THF-d^8 was added under nitrogen. The NMR tube was removed from liquid nitrogen and thawed until the solvent became a liquid. The solution was gently shaken and was immediately analyzed by ^{11}B NMR at room temperature.

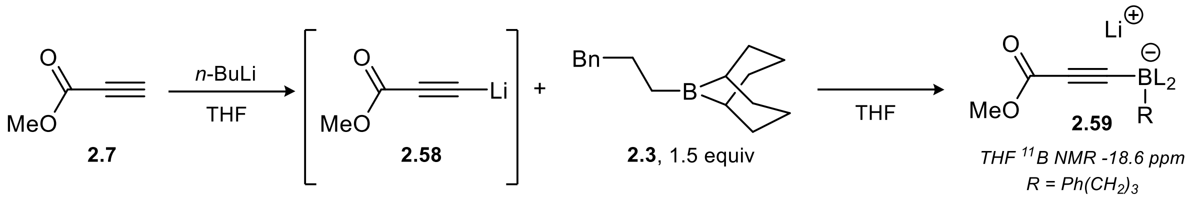
Figure 2.5 ^{11}B NMR Boron-ate formation with Acetylide 2.5



^{11}B NMR of the reaction of **2.5** and **2.3** in either toluene-*d*^{8} (blue) or THF-*d*^{8} (orange). In the toluene-*d*^{8} spectra unreacted alkyl borane (**2.3**) appears at 88.1 ppm while the boron-ate (**2.6**) is at -16.3 ppm. In the THF-*d*^{8} spectra unreacted alkyl borane (**2.3**) appears at 72.4 ppm while the boron-ate (**2.6**) is at -18.7 ppm. Note: we were not able to isolate or confirm the identity of the peak marked * at 56.8 ppm. We believe it is the result of the decomposition of **2.6** or the subsequent 1,2-shift product.

2.6.3.5. Boron-ate formation with Lithium Acetylide 2.58

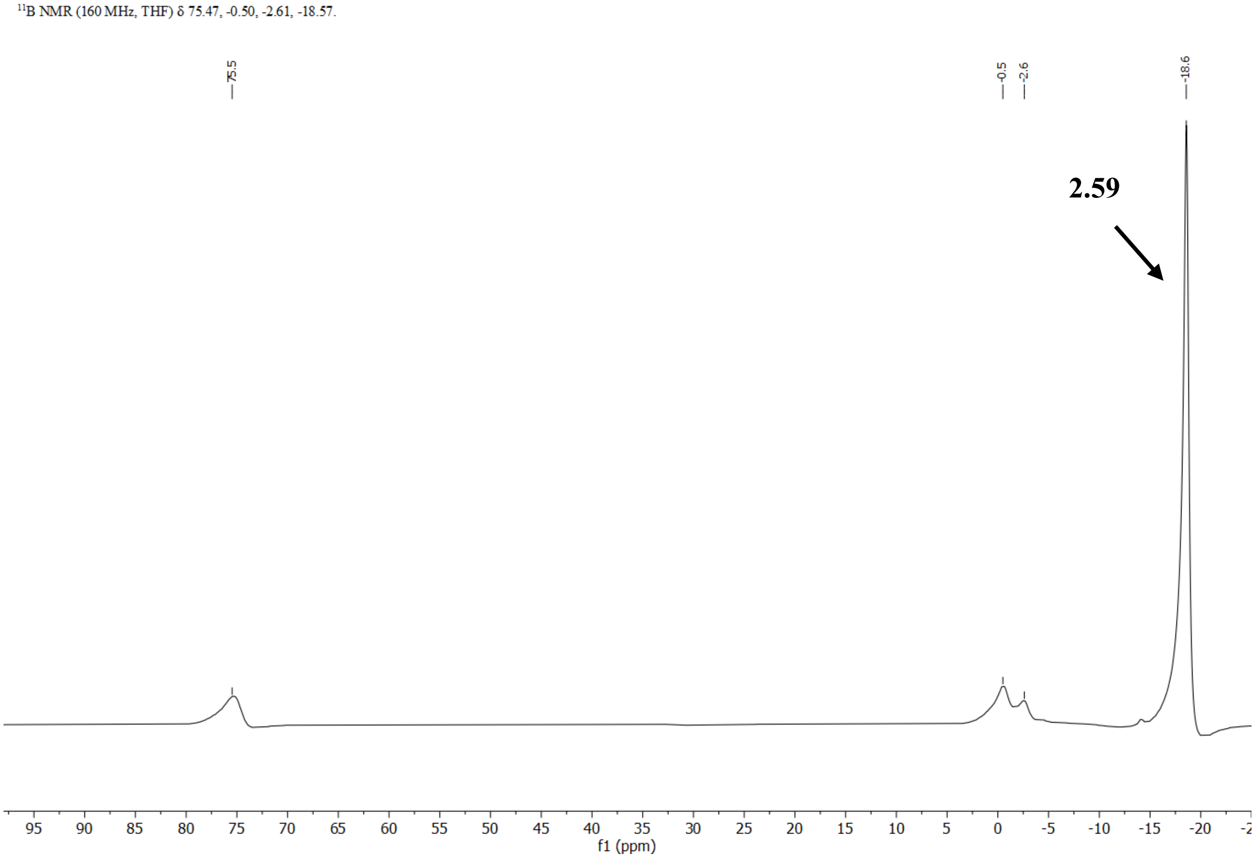
Scheme 2.8 Boron-ate formation with Lithium Acetylide 2.58



To further probe the formation of a boron-ate complex with a conjugated acetylide we decided to employ lithium acetylide (**2.58**) as a more nucleophilic analog of our catalytic species. A flame dried flask was allowed to cool under nitrogen. It was then charged with methyl propiolate (**2.7**)

(25.2 mg, 0.3 mmol, 1.0 equiv) and THF (0.1 M). This was then cooled to -78 °C and *n*-BuLi (120 µL, 2.5 M, 0.3 mmol, 1.0 equiv) was added. This solution was allowed to stir for 30 minutes. A solution of alkyl borane (**2.3**) (0.45 mmol, 1.5 equiv) in THF (200 µL) was added dropwise and the solution was stirred at -78 °C for 15 minutes. The mixture was then allowed to warm to room temperature and an aliquot was taken into a sealed NMR tube under nitrogen and analyzed by ^{11}B NMR.

Figure 2.6 ^{11}B NMR Boron-ate formation with Lithium Acetylide 2.58



^{11}B NMR of the reaction of **2.58** and **2.3** in THF. The unreacted alkyl borane (**2.3**) appears at 75.5 ppm while the boron-ate (**2.59**) is at -18.6 ppm. Note: We were unable to identify the overlapping peaks at -0.5 and -2.6 ppm, but they could be a result of the decomposition **2.58** which by itself is unstable above -78 °C.

The lithium acetylide (**2.58**) appears to form a higher concentration of the boron-ate complex (**2.59**) compared to the analogous conjugated silver acetylide (**2.5**) and boron-ate complex (**2.6**).

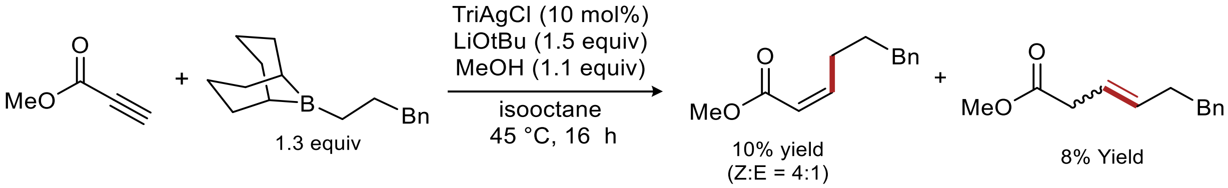
2.6.4. *Reaction Development Details*

All the reactions shown in table 2.2 to table 2.17 were performed on a 0.05 mmol scale. In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, base, silver catalyst, solvent, internal standard 1,3,5-trimethoxybenzene (TMB), alkyne, alkyl borane, and alcohol sequentially. The reaction mixture was vigorously stirred at the indicated temperature for the specified time.

2.6.4.1. Alkynyl Esters:

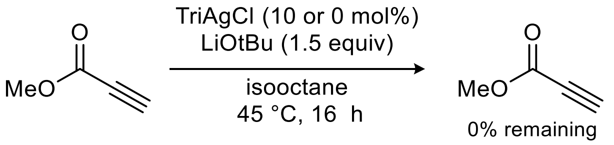
Initial Investigations

Scheme 2.9 Hydroalkylation of Methyl Propiolate[18]



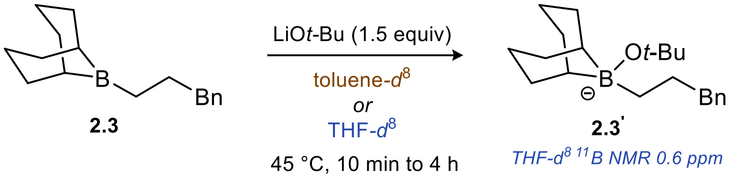
Using our previously reported hydroalkylation conditions led to an *E/Z* mixture of the desired α,β-unsaturated ester and a mixture of *E* and *Z*-isomers of the deconjugated β,γ-unsaturated ester. The starting alkyne was completely consumed during the reaction. GPC analysis of the resulting reaction mixture was consistent with the formation of oligomers.

Scheme 2.10 Consumption of Methyl Propiolate



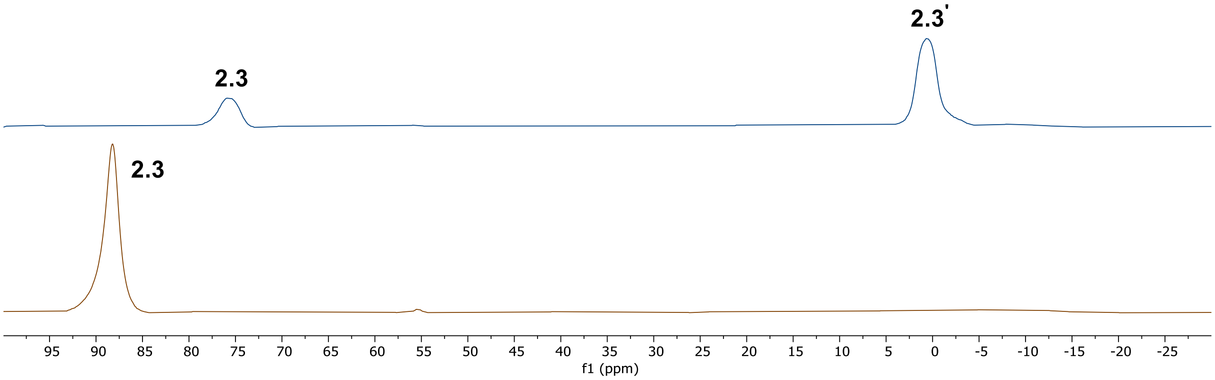
We subjected methyl propiolate to LiO*t*-Bu (2.0 equiv) with and without the TriAgCl catalyst and again saw complete consumption of starting material via ^{1}H NMR for both reactions. GPC analysis of the resulting mixtures was consistent with the formation of oligomers, similar to what was observed under our previously reported conditions. This further demonstrates the incompatibility of LiO*t*-Bu as the base for this hydroalkylation reaction.

Scheme 2.11 Boron-ate Complex Formation in the Presence of Alkoxide



To probe whether the coordination of the LiO*t*-Bu to alkyl borane (**2.3**) might inhibit the addition of silver acetylide, we examined the reaction of alkyl borane (**2.3**) with LiO*t*-Bu in THF and toluene over the course of 4 hours. We observed via ^{11}B NMR that in THF LiO*t*-Bu substantially coordinated to **2.3** forming the corresponding boron-ate complex (**2.3'**) after 10 minutes of stirring and was unchanged after 4 hours of stirring at 45 °C. However, in toluene, no boron-ate peak was observed via ^{11}B NMR at any timepoint indicating that in less polar solvents the coordination of the base is not likely to impede the addition of the silver acetylide.

Figure 2.7 ^{11}B NMR Boron-ate Complex Formation in the Presence of Alkoxide

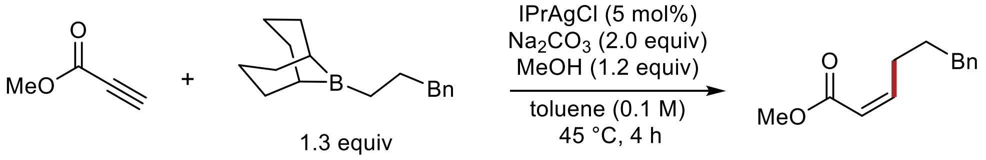


^{11}B NMR of the reaction of **2.3** and LiO*t*-Bu in THF-d^8 (blue) and toluene-d^8 (orange) after 4h at 45°C. In the THF-d^8 spectra unreacted alkyl borane (**2.3**) appears at 75.6 ppm while the boron-ate (**2.3'**) is at 0.6 ppm. In the toluene-d^8 spectra unreacted alkyl borane (**2.3**) appears at 88.2 ppm and no boron-ate peak was observed.

Reaction Development

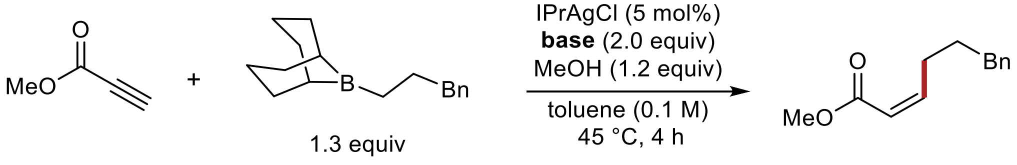
The following is the summary of reaction parameters explored during the development of the hydroalkylation of alkynyl esters.

Table 2.2 Highlighted Alkynyl Ester Reaction Parameters



entry	*change from standard conditions*	*yield*
1	none	92%
2	EtOH *instead of* MeOH	87%
3	*i*PrOH *instead of* MeOH	66%
4	Li_2CO_3 *instead of* Na_2CO_3	47%
5	K_2CO_3 *instead of* Na_2CO_3	84%
6	Cs_2CO_3 *instead of* Na_2CO_3	91%
7	LiO*t*-Bu *instead of* Na_2CO_3	15%
8	LiO*i*-Pr *instead of* Na_2CO_3	21%
9	LiOMe *instead of* Na_2CO_3	79%
10	25 °C *instead of* 45 °C	51%

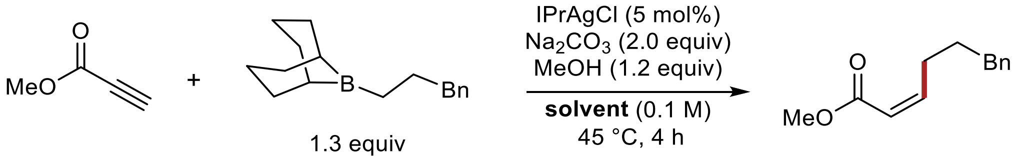
Table 2.3 Alkynyl Ester Base Identity



Entry	**Base**	**Yield (%)**

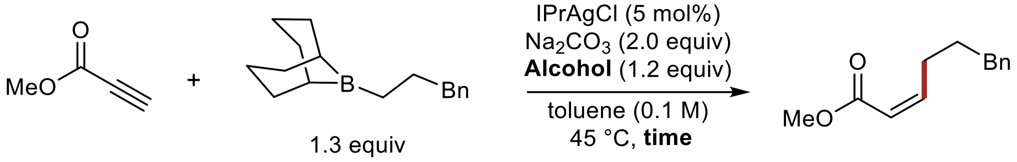
1	Na_2CO_3	92
2	Li_2CO_3	47
3	K_2CO_3	84
4	Cs_2CO_3	91
5	$NaHCO_3$	70
6	$KHCO_3$	90
7	K_3PO_4	84
8	NaO*t*-Bu	9
9	KO*t*-Bu	15
10	LiO*t*-Bu	15
11	LiO*i*-Pr	21
12	LiOEt	22
13	LiOMe	79
14	NaOMe	71
15	KOMe	51
16	Na_2CO_3 (at 25 ˚C)	51 (74 at 24 h)

Table 2.4 Alkynyl Ester Solvent Identity



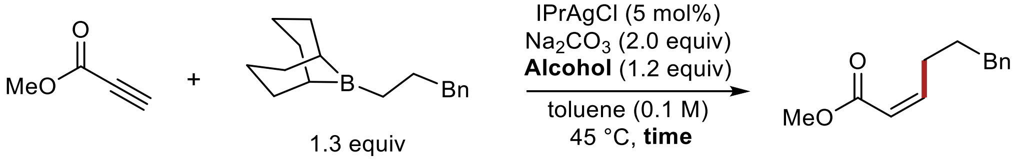
Entry	Solvent	Yield (%)
1	Toluene	92
2	THF	31
3	Benzene	97
4	Isooctane	85

Table 2.5 Alkynyl Ester Alcohol Identity



Entry	Alcohol	Yield 4 h (%)	Yield 24 h (%)
1	MeOH	92	91
2	EtOH	87	88
3	*i*-PrOH	66	73
4	*t*-AmylOH	11	24

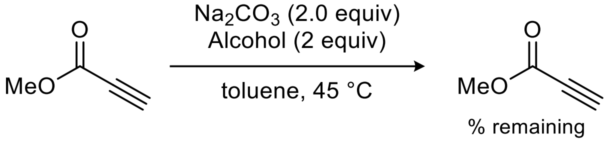
Table 2.6 Alkynyl Ester Reaction Time



Entry	Alcohol	Yield 15 min (%)	Yield 30 min (%)	Yield 1 h (%)	Yield 2 h (%)	Yield 4 h (%)
1	MeOH	14	60	79	83	92

2	EtOH	3	11	33	61	87

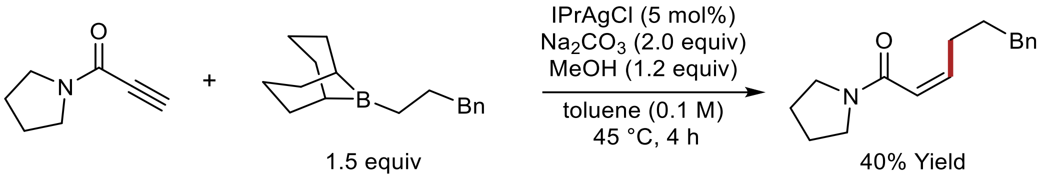
Table 2.7 Alkynyl Ester Stability



Entry	Alcohol	Alkyne Remaining 30 min (%)	Alkyne Remaining 2 h (%)	Alkyne Remaining 4 h (%)
1	MeOH	97	88	83
2	EtOH	99	88	88

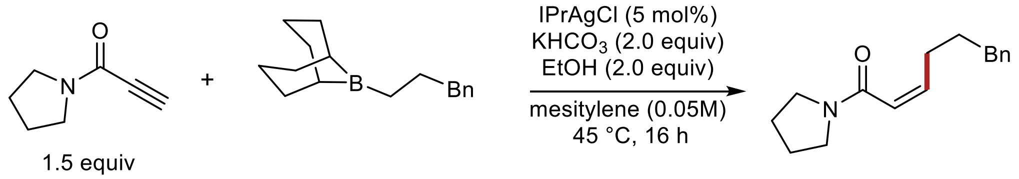
2.6.4.2. Alkynyl Amides:

Alkynyl Amide Reaction Using Alkynyl Ester Conditions



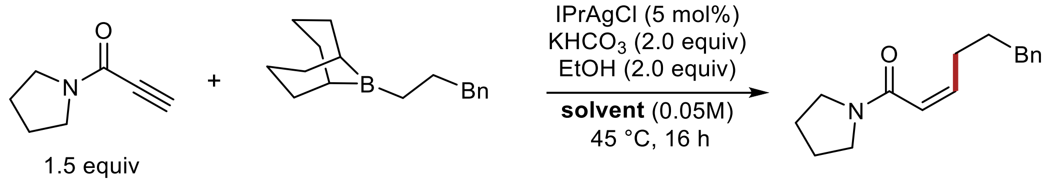
We began our exploration of the alkynyl amide scope by running the reaction with similar conditions to our optimized alkynyl ester conditions.

Table 2.8 Highlighted Alkynyl Amide Reaction Parameters



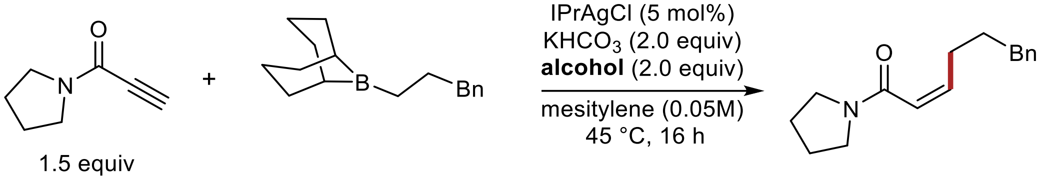
entry	*change from standard conditions*	*yield*
1	none	83%
2	MeOH *instead of* EtOH	60%
3	*i*PrOH *instead of* EtOH	55%
4	1.2 equiv EtOH *instead of* 2.0 equiv EtOH	75%
5	Na_2CO_3 *instead of* $KHCO_3$	78%
6	$NaHCO_3$ *instead of* K_2CO_3	79%
7	K_3PO_4 *instead of* $KHCO_3$	69%
8	toluene *instead of* mesitylene	76%
9	0.1 M *instead of* 0.05 M	61%

Table 2.9 Alkynyl Amide Solvent Identity



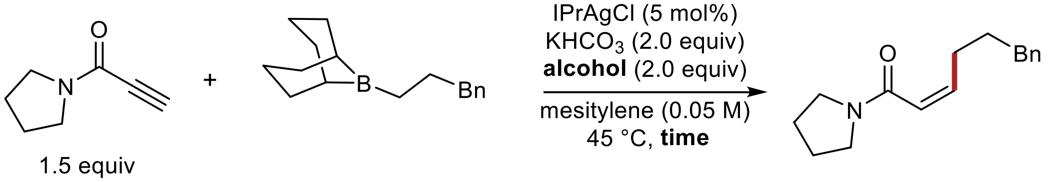
Entry	**Solvent**	**Yield (%)**
1	Mesitylene	83
2	Toluene	77
3	Chlorobenzene	76
4	Benzene	71
5	Isooctane	62
6	THF	33
7	DME	22

Table 2.10 Alkynyl Amide Alcohol Identity



Entry	Alcohol	Yield (%)
1	EtOH	83
2	MeOH	60
3	*i*-PrOH	55
4	*t*-AmOH	30
5	EtOH (1.2 equiv)	75
6	EtOH (3 equiv)	75
7	BnOH	56
8	CF_3CH_2OH	36

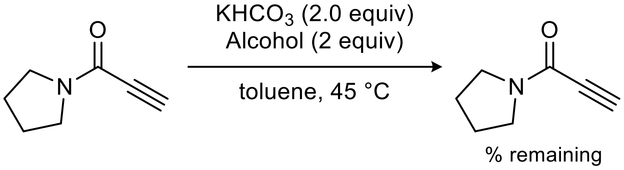
Table 2.11 Alkynyl Amide Reaction Time with Different Alcohols



Entry	Alcohol	Yield 1 h (%)	Yield 3 h (%)	Yield 16 h (%)
1	MeOH	14	54	60
2	EtOH	26	83	83

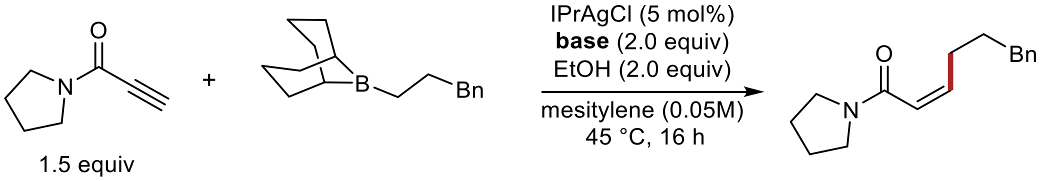
3	*i*-PrOH	2	26	55

Table 2.12 Alkynyl Amide Stability



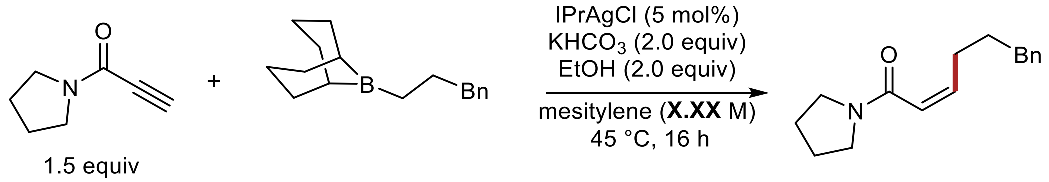
Entry	Alcohol	Alkyne Remaining 1 h (%)	Alkyne Remaining 4 h (%)	Alkyne Remaining 24 h (%)
1	MeOH	97	98	99
2	EtOH	97	99	99

Table 2.13 Alkynyl Amide Base Identity



Entry	Base	Yield (%)
1	$KHCO_3$	83
2	$NaHCO_3$	79
3	Na_2CO_3	78
4	Cs_2CO_3	63
5	K_3PO_4	69
6	LiO*t*-Bu	0

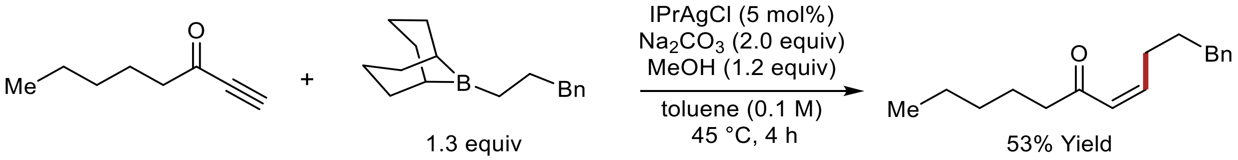
Table 2.14 Alkynyl Concentration



Entry	Concentration	Yield (%)
1	0.05 M	83
2	0.1 M	61
3	0.2 M	62

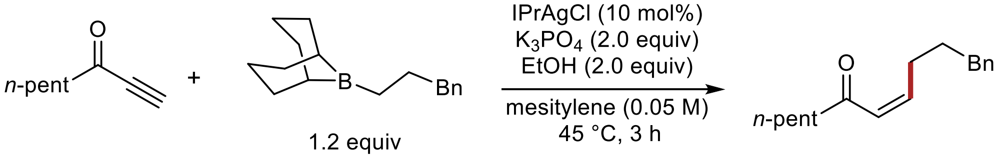
2.6.4.3. Alkynyl Ketones:

Alkynyl Ketones Reaction Using Alkynyl Ester Conditions



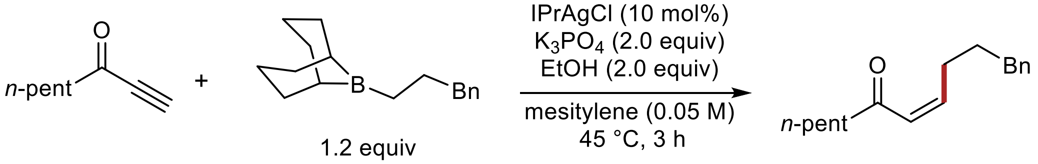
We began our exploration of the alkynyl ketone scope by running the reaction with our optimized conditions for alkynyl esters.

Table 2.15 Alkynyl Ketone Optimization



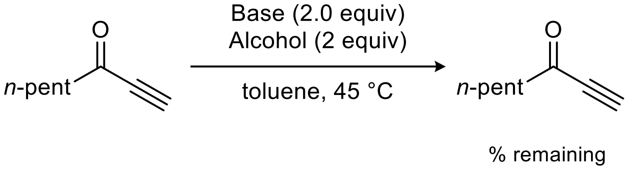
entry	*change from standard conditions*	*yield*
1	none	81%
2	MeOH *instead of* EtOH	63%
3	*i*PrOH *instead of* EtOH	24%
4	1.2 equiv EtOH *instead of* 2.0 equiv EtOH	70%
5	Na_2CO_3 *instead of* K_3PO_4	72%
6	$KHCO_3$ *instead of* K_3PO_4	74%
7	K_2HPO_4 *instead of* K_3PO_4	28%
8	KH_2PO_4 *instead of* K_3PO_4	0%
9	5% IPrAgCl *instead of* 10% IPrAgCl	67%
10	0.1 M *instead of* 0.05 M	77%

Table 2.16 Alkynyl Ketone Reaction Time with Different Alcohols



Entry	Alcohol	Yield 15 min (%)	Yield 30 min (%)	Yield 1 h (%)	Yield 3 h (%)
1	MeOH	60	62	61	62
2	EtOH	35	72	77	80
3	*i*-PrOH	6	19	22	24

Table 2.17 Alkynyl Ketone Stability



Entry	Alcohol	Base	Alkyne Remaining 15 min (%)	Alkyne Remaining 30 min (%)	Alkyne Remaining 1 h (%)	Alkyne Remaining 2 h (%)
1	MeOH	K_3PO_4	51	22	4	0
2	EtOH	K_3PO_4	74	34	10	2
3	MeOH	Na_2CO_3	99	97	95	85
4	EtOH	Na_2CO_3	98	97	97	85

2.6.5. *General Procedure A for α,β-Unsaturated Esters*

In a nitrogen-filled glovebox, a 20 ml scintillation vial was charged with IPrAgCl (13.3 mg, 0.05 mmol, 0.05 equiv), Na_2CO_3 (106 mg, 1.0 mmol, 2.0 equiv) and a stir bar. To the vial was added alkynyl ester (0.5 mmol, 1.0 equiv), alkylborane (0.65 mmol, 1.3 equiv), methanol (19.2 mg, 0.6 mmol, 1.2 equiv) and toluene (0.1 M). The resulting mixture was stirred at 45 °C for 4 hours in the glovebox. After 4 hours, the reaction mixture was passed through a plug of silica and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography.

2.6.6. *General Procedure B for α,β-Unsaturated Amides*

In a nitrogen-filled glovebox, a 20 ml scintillation vial was charged with IPrAgCl (13.3 mg, 0.05 mmol, 0.05 equiv), $KHCO_3$ (100 mg, 1.0 mmol, 2.0 equiv) and a stir bar. To the vial was added alkynyl amide (0.75 mmol, 1.5 equiv), alkylborane (0.5 mmol, 1.0 equiv), ethanol (46.1 mg, 1.0 mmol, 2.0 equiv) and mesitylene (0.05 M). The resulting mixture was stirred at 45 °C overnight in the glovebox. The reaction mixture was then passed through a plug of silica and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography.

2.6.7. *General Procedure C for α,β-Unsaturated Ketones*

In a nitrogen-filled glovebox, a 20 ml scintillation vial was charged with IPrAgCl (26.6 mg, 0.1 mmol, 0.1 equiv), K_3PO_4 (212 mg, 1.0 mmol, 2.0 equiv) and a stir bar. To the vial was added alkynyl ketone (0.5 mmol, 1.0 equiv), alkylborane (0.6 mmol, 1.2 equiv), ethanol (46.1 mg, 1.0 mmol, 2.0 equiv) and mesitylene (0.05 M). The resulting mixture was stirred at 45 °C for 3 hours in the glovebox. After 3 hours, the reaction mixture was passed through a plug of silica and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography.

2.6.8. *Procedure for the Large-Scale Synthesis of 2.1*

A reaction flask was flame dried and allowed to cool under nitrogen. This flask was then charged with a stir bar, IPrAgCl (160 mg, 0.3 mmol, 0.1 equiv), Na_2CO_3 (1.27 g, 12.0 mmol, 2.0 equiv) and toluene (0.1 M). To this flask was added methyl propiolate (**2.7**) (534 µL, 6 mmol, 1.0 equiv), a solution alkyl borane (**2.3**) in toluene (3.9 mL, 2.0 M, 7.8 mmol, 1.3 equiv), and MeOH (291 µL, 7.2 mmol, 1.2 equiv). The mixture was stirred at 45 °C for 12 hours. The reaction mixture was then passed through a plug of silica and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography to yield **2.1** (1.13 g, 92% yield).

2.6.9. *Procedure with In Situ Formation of the Catalyst*

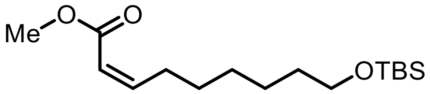
In a nitrogen filled glovebox a dram vial was charged with IPrHCl (6.0 mg, 0.01 mmol, 0.07 equiv), Ag(I)Br (1.9 mg, 0.01 mmol, 0.05 equiv), LiOMe (0.8 mg, 0.02 mmol, 0.1 equiv), Na_2CO_3 (42.4 mg, 0.4 mmol, 2.0 equiv), toluene (500 µL), and a stir bar. This was stirred at 45 °C for 30 minutes. To the vial was added methyl propiolate (**7**) (16.8 mg, 0.2 mmol, 1.0 equiv), alkylborane (**3**) (0.26 mmol, 1.3 equiv), methanol (7.7 mg, 0.24 mmol, 1.2 equiv), internal standard TMB (16.8

mg, 0.1 mmol) and toluene (0.1 M). The resulting mixture was stirred at 45 °C for 4 hours in the glovebox. After 4 hours, an aliquot was taken and analyzed by GC with a crude yield of 82%.

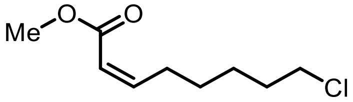
2.6.10. *Characterization of Z-Michael Acceptor Products*

2.6.10.1. Alkyl Borane Scope

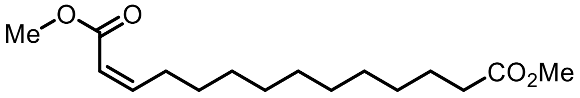
Alkylboranes were used as a 2 M solution in the reaction solvent (toluene or mesitylene) and were synthesized from the corresponding alkene according to a known procedure the day before use.[20]



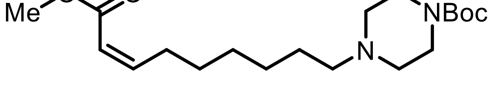
methyl (2*Z*)-9-[(tert-butyldimethylsilyl)oxy]non-2-enoate (2.8), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% Et_2O in hexanes) and was isolated as a colorless liquid (132 mg, 89% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.76 (dt, *J* = 11.5, 1.8 Hz, 1H), 3.70 (s, 3H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.71 – 2.59 (m, 2H), 1.56 – 1.28 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.3, 150.7, 119.7, 63.3, 50.6, 33.2, 29.4, 29.4, 29.2, 26.2, 26.1, 18.6, -5.1. GCMS (EI) calculated for $[M]^+$ 300.2, found 300.2. FTIR (neat, cm^{-1}): 2931 (m), 2857 (m), 1727 (s), 1645 (w), 1438 (w), 1256 (m), 1174 (s), 1099 (s), 836 (s), 774 (s), 670 (w).



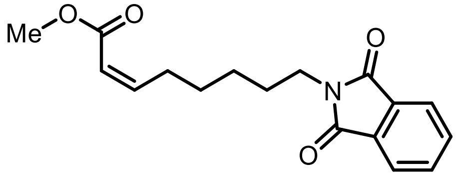
methyl (2*Z*)-8-chlorooct-2-enoate (2.9), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-12% EtOAc in hexanes) and was isolated as a colorless liquid (65 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.79 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.70 (s, 3H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.75 – 2.60 (m, 2H), 1.87 – 1.72 (m, 2H), 1.54 – 1.41 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 150.2, 119.9, 50.6, 44.8, 32.5, 28.8, 28.4, 26.6. GCMS (EI) calculated for $[M]^+$ 190.1, found 190.2. FTIR (neat, cm^{-1}): 2937 (m), 2862 (w), 1721 (s), 1646 (m), 1438 (m), 1181 (m), 1175 (s), 1021 (w), 817 (m), 729 (w), 651 (w).



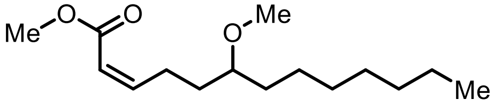
1,14-dimethyl (2*Z*)-tetradec-2-enedioate (2.10), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-20% EtOAc in hexanes) and was isolated as a colorless liquid (125 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.76 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.68 – 2.59 (m, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.47 – 1.37 (m, 2H), 1.34 – 1.23 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 167.0, 151.2, 119.3, 51.6, 51.1, 34.2, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.1, 25.1 (peak overlap resulting in one less signal than expected). MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{16}H_{28}NaO_4$, 307.2; found, 307.1 FTIR (neat, cm^{-1}): 2924 (s), 2853 (m), 1730 (s), 1723 (s), 1646 (w), 1439 (m), 1437 (m), 1168 (s), 1011 (w), 818 (m), 726 (w).



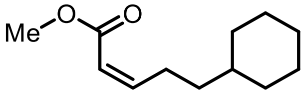
***tert*-butyl 4-[(7*Z*)-9-methoxy-9-oxononon-7-en-1-yl]piperazine-1-carboxylate (2.11)**, compound was prepared according to the general procedure A and was purified by silica gel chromatography (5-40% EtOAc in hexanes) and was isolated as a colorless liquid (140 mg, 81% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.93 – 5.84 (m, 1H), 5.79 (dt, *J* = 11.4, 1.6 Hz, 1H), 3.48 (s, 4H), 3.38 (s, 3H), 2.78 – 2.69 (m, 2H), 2.21 – 1.94 (m, 6H), 1.48 (s, 9H), 1.32 – 1.14 (m, 8H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 154.7, 150.7, 119.7, 79.0, 58.7, 53.3, 50.6, 30.2, 29.5, 29.3, 29.1, 28.5, 27.4, 27.0. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{35}N_2O_4$, 355.3; found, 355.2. FTIR (neat, cm^{-1}): 2924 (m), 2859 (w), 1724 (m), 1696 (s), 1457 (m), 1419 (m), 1366 (m), 1246 (m), 1170 (s), 1126 (m), 1006 (w), 869 (w), 821 (w), 768 (w).



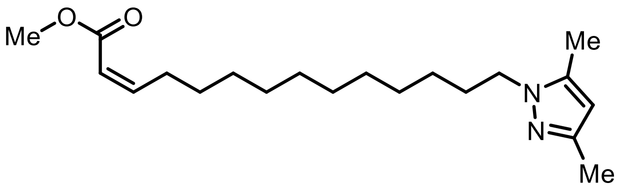
methyl (2*Z*)-8-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)oct-2-enoate (2.12), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-30% EtOAc in hexanes) and was isolated as a white solid (125 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.20 (dt, *J* = 11.5, 7.6 Hz, 1H), 5.75 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.74 – 3.64 (m, 5H), 2.70 – 2.58 (m, 2H), 1.72 – 1.65 (m, 2H), 1.53 – 1.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 166.9, 150.5, 134.0, 132.3, 123.3, 119.6, 51.1, 38.0, 28.9, 28.6, 28.5, 26.6. GCMS (EI) calculated for $[M]^+$ 301.1, found 301.1. FTIR (neat, cm^{-1}): 2936 (m), 2866 (w), 1771 (m), 1707 (s), 1643 (m), 1440 (s), 1394 (s), 1360 (s), 1248 (m), 1187 (s), 1049 (s), 1012 (m), 878 (m), 817 (s), 721 (s), 623 (m), 530 (m).



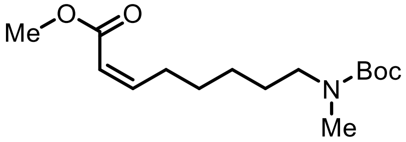
methyl (2*Z*)-6-methoxytridec-2-enoate (2.13), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% EtOAc in hexanes) and was isolated as a colorless liquid (104 mg, 81% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.25 (dt, *J* = 11.5, 7.6 Hz, 1H), 5.78 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.71 (s, 3H), 3.32 (s, 3H), 3.22 – 3.11 (m, 1H), 2.77 – 2.65 (m, 2H), 1.67 – 1.43 (m, 4H), 1.39 – 1.22 (m, 10H), 0.94 – 0.83 (m, 3H). ^{13}C NMR (126 MHz, C$_6$D$_6$) δ 166.4, 150.8, 119.6, 80.6, 56.3, 50.6, 33.8, 33.2, 32.3, 30.3, 29.8, 25.6, 25.5, 23.1, 14.4. GCMS (EI) calculated for [M]$^+$ 256.2, found 256.2. FTIR (neat, cm^{-1}): 2919 (s), 2851 (m), 1724 (s), 1645 (w), 1438 (m), 1407 (w), 1167 (s), 1031 (w), 1000 (w), 819 (m) 729 (w).



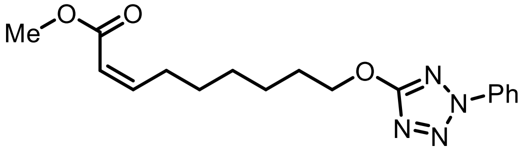
methyl (2*Z*)-5-cyclohexylpent-2-enoate (2.14), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% Et$_2$O in hexanes) and was isolated as a colorless liquid (65 mg, 66% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.23 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.75 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.71 (s, 3H), 2.71 – 2.60 (m, 2H), 1.79 – 1.59 (m, 5H), 1.37 – 1.12 (m, 6H), 0.95 – 0.84 (m, 2H). ^{13}C NMR (126 MHz, C$_6$D$_6$) δ 166.4, 151.1, 119.5, 50.6, 37.7, 37.0, 33.5, 27.0, 26.8, 26.7. GCMS (EI) calculated for [M]$^+$ 196.1, found 196.1. FTIR (neat, cm^{-1}): 2925 (m), 2852 (w), 1724 (s), 1654 (w), 1438 (m), 1173 (s), 1135 (m), 1005 (w), 962 (w), 893 (w), 822 (s).



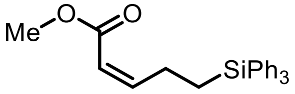
methyl (2*Z*)-14-(3,5-dimethyl-1H-pyrazol-1-yl)tetradec-2-enoate (2.15), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-25% EtOAc in hexanes) and was isolated as a colorless liquid (130 mg, 78% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.90 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.80 (dt, *J* = 11.5, 1.6 Hz, 1H), 5.74 (s, 1H), 3.68 (t, *J* = 7.1 Hz, 2H), 3.38 (s, 3H), 2.80 – 2.72 (m, 2H), 2.34 (s, 3H), 1.84 (s, 3H), 1.74 – 1.66 (m, 2H), 1.37 – 1.13 (m, 16H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 150.8, 146.9, 137.8, 119.7, 104.8, 50.6, 48.5, 30.7, 30.0, 29.9, 29.9, 29.8, 29.7, 29.4, 29.2, 27.0, 13.9, 10.8 (peak overlap resulting in one less signal than expected). GCMS (EI) calculated for $[M]^+$ 334.3, found 334.2. FTIR (neat, cm^{-1}): 2924 (s), 2853 (m), 1722 (s), 1646 (w), 1551 (w), 1457 (s), 1172 (s), 1020 (w), 818 (m), 771 (m), 721 (w).



methyl (2*Z*)-8-{[(*tert*-butoxy)carbonyl](methyl)amino}oct-2-enoate (2.16), compound was prepared according to the general procedure A and was purified by silica gel chromatography (5-40% EtOAc in hexanes) and was isolated as a colorless liquid (128 mg, 90% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.85 (dt, *J* = 11.5, 7.3 Hz, 1H), 5.78 (d, *J* = 11.5 Hz, 1H), 3.37 (s, 3H), 3.26 – 2.82 (m, 2H), 2.76 – 2.50 (m, 5H), 1.48 (s, 9H), 1.34 – 1.21 (m, 4H), 1.17 – 1.08 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 155.5, 150.5, 119.8, 78.7, 70.5, 50.6, 48.7, 34.0, 32.5, 29.1, 28.9, 28.6, 26.8, 26.5, 22.5 (includes *N*-Boc rotamers). GCMS (EI) calculated for $[M]^+$ 285.2, found 285.1. FTIR (neat, cm^{-1}): 2973 (w), 2932 (m), 2861 (w), 1724 (m), 1692 (s), 1644 (w), 1457 (m), 1392 (m), 1364 (m), 1162 (s), 878 (w), 818 (m), 771 (w).

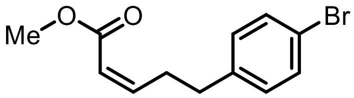


methyl (2Z)-9-[(2-phenyl-2H-1,2,3,4-tetrazol-5-yl)oxy]non-2-enoate (2.17), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-35% EtOAc in hexanes) and was isolated as an opaque liquid (147 mg, 89% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 – 7.47 (m, 2H), 7.05 – 6.97 (m, 2H), 6.95 – 6.86 (m, 1H), 5.87 – 5.74 (m, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.37 (s, 3H), 2.70 – 2.60 (m, 2H), 1.40 – 1.31 (m, 2H), 1.21 – 1.12 (m, 2H), 1.10 – 1.00 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 160.6, 150.5, 134.1, 129.6, 128.6, 121.7, 119.8, 74.1, 50.7, 29.0, 28.9, 28.7, 25.5 (peak overlap resulting in one less signal than expected). GCMS (EI) calculated for $[M]^+$ 330.2, found 330.1. FTIR (neat, cm^{-1}): 2927 (m), 2857 (w), 1718 (s), 1654 (w), 1570 (m), 1562 (s), 1506 (s), 1438 (s), 1296 (m), 1173 (s), 1072 (w), 992 (w), 818 (m), 759 (s), 688 (s), 504 (m).

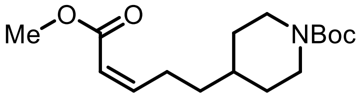


methyl (2*Z*)-5-(triphenylsilyl)pent-2-enoate (2.18), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (155 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 6H), 7.46 – 7.34 (m, 9H), 6.25 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.68 (dt, *J* = 11.4, 1.6 Hz, 1H), 3.65 (s, 3H), 2.93 – 2.70 (m, 2H), 1.56 – 1.48 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

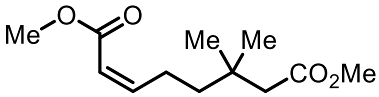
166.9, 152.5, 135.8, 134.8, 129.7, 128.1, 118.5, 51.1, 23.7, 13.2. GCMS (EI) calculated for $[M]^+$ 372.2, found 372.1. FTIR (neat, cm^{-1}): 3069 (w), 2998 (w), 2947 (w), 2883 (w), 1718 (s), 1636 (m), 1427 (s), 1172 (s), 1110 (s), 998 (m), 882 (w), 819 (m), 696 (s), 508 (s).



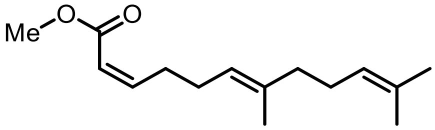
methyl (2*Z*)-5-(4-bromophenyl)pent-2-enoate (2.19), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% EtOAc in hexanes) and was isolated as a colorless liquid (109 mg, 81% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 – 7.19 (m, 2H), 6.66 (d, *J* = 8.3 Hz, 2H), 5.78 – 5.66 (m, 2H), 3.34 (s, 3H), 2.89 – 2.80 (m, 2H), 2.31 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.2, 148.9, 140.3, 131.7, 130.5, 120.4, 120.2, 50.7, 34.5, 30.4. GCMS (EI) calculated for $[M]^+$ 268.0, found 268.0. FTIR (neat, cm^{-1}): 3038 (w), 2947 (w), 2860 (w), 1719 (s), 1646 (m), 1488 (m), 1438 (m), 1405 (m), 1154 (s), 1071 (m), 1011 (s), 802 (s), 731 (w), 623 (w), 511 (m).



***tert*-butyl 4-[(3Z)-5-methoxy-5-oxopent-3-en-1-yl]piperidine-1-carboxylate (2.20)**, compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-30% EtOAc in hexanes) and was isolated as a colorless liquid (111 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 11.5, 7.6 Hz, 1H), 5.78 (dt, *J* = 11.5, 1.7 Hz, 1H), 4.07 (d, *J* = 13.2 Hz, 2H), 3.71 (s, 3H), 2.76 – 2.59 (m, 4H), 1.68 (d, *J* = 14.8 Hz, 2H), 1.46 – 1.35 (m, 12H), 1.19 – 1.02 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 154.7, 150.6, 119.6, 78.8, 70.6, 50.6, 35.9, 35.8, 32.5, 32.2, 28.6, 26.8, 26.4, 22.5 (includes *N*-Boc rotamers). MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{16}H_{27}NNaO_4$, 320.2; found, 320.1. FTIR (neat, cm^{-1}): 2922 (m), 2850 (w), 1691 (s), 1411 (m), 1366 (m), 1247 (m), 1163 (s), 1001 (w), 821 (w), 769 (w).

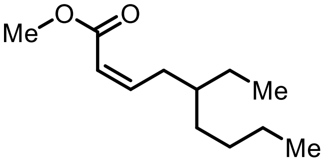


1,7-dimethyl (2*Z*)-6,6-dimethylhept-2-enedioate (2.21), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-20% EtOAc in hexanes) and was isolated as a colorless liquid (88 mg, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dt, *J* = 11.4, 7.6 Hz, 1H), 5.75 (dt, *J* = 11.4, 1.7 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 2.69 – 2.60 (m, 2H), 2.24 (s, 2H), 1.51 – 1.40 (m, 2H), 1.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 166.9, 151.0, 119.2, 51.3, 51.1, 45.9, 41.2, 33.4, 27.2, 24.3. GCMS (EI) calculated for $[M]^+$ 228.1, found 228.1. FTIR (neat, cm^{-1}): 2952 (m), 1722 (s), 1644 (m), 1457 (m), 1438 (m), 1174 (s), 1012 (m), 889 (w), 821 (m), 726 (w).

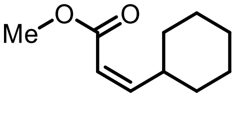


methyl (2*Z*,6)-7,11-dimethyldodeca-2,6,10-trienoate (2.22), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (65 mg, 55% yield, 1.7:1 dr for the ε,ζ-alkene). The dr of the product was determined by GC analysis of the isolated product, the major diastereomer of the ε,ζ-alkene was not assigned. The alkyl borane starting material was prepared from 4,8-dimethylnona-1,3,7-triene (**2.92**) with a 1.4:1 dr (determined by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 11.6, 7.4 Hz, 1H), 5.77 (dt, *J* = 11.6, 1.9 Hz, 1H), 5.18 – 5.03 (m, 2H), 3.71 (s, 3H), 2.74 – 2.64 (m, 2H), 2.18 – 2.10 (m, 2H), 2.10 – 1.95 (m, 4H), 1.72 – 1.65

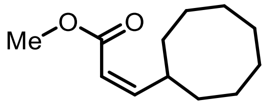
(m, 4H), 1.64 – 1.58 (m, 5H). ^{13}C NMR (126 MHz, C_6D_6) major δ 166.4, 150.2, 136.1, 131.2, 124.9, 123.9, 119.9, 50.6, 40.1, 29.5, 27.7, 27.1, 25.9, 17.8, 16.1. minor δ 166.3, 150.2, 136.2, 131.4, 124.9, 124.8, 119.9, 50.6, 32.3, 29.7, 27.7, 27.0, 23.6, 17.7, 16.1. (Assignment of ^{13}C NMR signals of each diastereomers based on the assumption that the relaxation time of each corresponding carbons in those two compounds are identical.) GCMS (EI) calculated for $[M]^+$ 236.2, found 236.2. FTIR (neat, cm^{-1}): 2965 (w), 2913 (m), 2859 (w), 1725 (s), 1645 (w), 1438 (m), 1174 (s), 1000 (w), 820 (m).



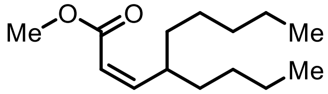
methyl (2Z)-5-ethylnon-2-enoate (2.23), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (61 mg, 62% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (dt, *J* = 11.5, 7.4 Hz, 1H), 5.81 (dt, *J* = 11.5, 1.8 Hz, 1H), 3.71 (s, 3H), 2.69 – 2.57 (m, 2H), 1.47 – 1.37 (m, 1H), 1.36 – 1.21 (m, 8H), 0.92 – 0.84 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 150.3, 119.9, 51.0, 39.6, 33.0, 32.8, 29.1, 26.2, 23.1, 14.2, 11.1. GCMS (EI) calculated for $[M]^+$ 198.2, found 198.2. FTIR (neat, cm^{-1}): 2958 (m), 2929 (m), 2859 (m), 1724 (s), 1646 (m), 1437 (s), 1179 (m), 1168 (s), 1000 (w), 813 (m),727 (w).



methyl (2*Z*)-3-cyclohexylprop-2-enoate (2.24), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% Et_2O in hexanes) and was isolated as a colorless liquid (47 mg, 56% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.80 – 5.66 (m, 2H), 3.66 – 3.55 (m, 1H), 3.37 (s, 3H), 1.77 – 1.69 (m, 2H), 1.62 – 1.49 (m, 3H), 1.33 – 1.22 (m, 2H), 1.08 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.3, 155.7, 117.8, 50.6, 37.4, 32.6, 26.2, 25.8. GCMS (EI) calculated for $[M]^+$ 168.1, found 168.2. FTIR (neat, cm^{-1}): 2925 (m), 2852 (w), 1724 (s), 1654 (w), 1438 (m), 1173 (s), 1135 (m), 1005 (w), 962 (w), 893 (w), 822 (s).

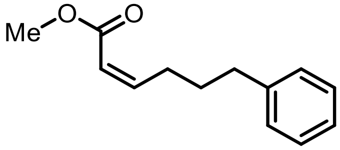


methyl (2*Z*)-3-cyclooctylprop-2-enoate (2.26), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% Et_2O in hexanes) and was isolated as a colorless liquid (73 mg, 75% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.84 (dd, *J* = 11.4, 10.1 Hz, 1H), 5.66 (dd, *J* = 11.4, 1.1 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.37 (s, 3H), 1.67 – 1.42 (m, 12H), 1.35 – 1.26 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 157.0, 116.3, 50.6, 36.3, 32.5, 27.2, 26.8, 25.5. GCMS (EI) calculated for $[M]^+$ 196.2, found 196.2. FTIR (neat, cm^{-1}): 2917 (m), 2850 (w), 1722 (s), 1641 (m), 1457 (w), 1436 (m), 1168 (s), 1007 (w), 828 (m).

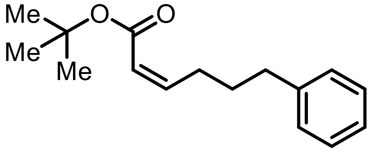


methyl (2*Z*)-4-butylnon-2-enoate (2.27), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (80 mg, 70% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 5.84 (d, *J* = 11.6 Hz, 1H), 5.62 (t, *J* = 11.6, 1H), 3.84 – 3.73 (m, 1H), 3.37 (s, 3H), 1.41 – 1.11 (m, 14H), 0.92 – 0.85 (m, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.6, 155.8, 119.6, 50.6, 38.0, 35.7, 35.5, 32.4, 29.9, 27.3, 23.3, 23.0, 14.3, 14.3. GCMS (EI) calculated for $[M]^+$ 226.2, found 226.2. FTIR (neat, cm^{-1}): 2957 (m), 2925 (m), 2859 (m), 1725 (s), 1654 (w), 1437 (m), 1408 (w), 1173 (s), 998 (w), 822 (m), 727 (w).

2.6.10.2. α,β-Unsaturated Ester Scope

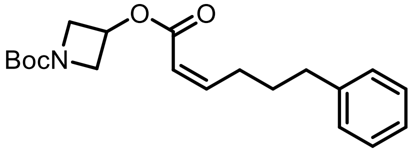


methyl (2*Z*)-6-phenylhex-2-enoate (2.1), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% EtOAc in hexanes) and was isolated as a colorless liquid (93 mg, 91% yield). Compound **2.1** was also isolated on a gram scale using procedure 4.4 Gram Scale Procedure for the Synthesis of **2.1** (1.13 g, 92% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.17 – 7.11 (m, 2H), 7.10 – 7.03 (m, 1H), 7.04 – 6.98 (m, 2H), 5.85 – 5.71 (m, 2H), 3.36 (s, 3H), 2.75 – 2.64 (m, 2H), 2.44 (t, J = 7.5 Hz, 2H), 1.60 – 1.49 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.4, 150.1, 142.4, 128.7, 128.6, 126.1, 120.0, 50.6, 35.8, 31.1, 28.9. GCMS (EI) calculated for $[M]^+$ 204.1, found 204.1. FTIR (neat, cm^{-1}): 3027 (w), 2924 (w), 2860 (w), 1719 (s), 1645 (m), 1497 (m), 1437 (m), 1407 (w), 1172 (s), 1012 (w), 820 (m), 746 (m), 698 (s).

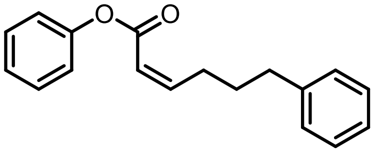


***tert*-butyl (2*Z*)-6-phenylhex-2-enoate (2.28)**, compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% EtOAc in hexanes) and was isolated as a colorless liquid (103 mg, 84% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.17 – 7.12 (m, 2H), 7.09 – 6.99 (m, 3H), 5.84 – 5.73 (m, 2H), 2.76 – 2.67 (m, 2H), 2.50 – 2.43 (m, 2H), 1.62 –

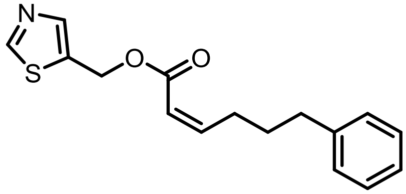
1.52 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 165.6, 148.6, 142.4, 128.8, 128.6, 126.1, 122.1, 79.5, 35.9, 31.3, 28.8, 28.3. GCMS (EI) calculated for $[M]^+$ 246.2, found 246.1. FTIR (neat, cm^{-1}): 2978 (w), 2931 (w), 2861 (w), 1713 (s), 1640 (w), 1457 (w), 1411 (w), 1367 (m), 1214 (m), 1142 (s), 820 (m), 746 (m), 700 (s).



***tert*-butyl 3-{[(2*Z*)-6-phenylhex-2-enoyl]oxy}azetidine-1-carboxylate (2.29)**, compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-25% EtOAc in hexanes) and was isolated as a colorless liquid (120 mg, 70% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 6.33 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.81 (dt, *J* = 11.5, 1.7 Hz, 1H), 5.13 (tt, *J* = 6.7, 4.3 Hz, 1H), 4.20 (ddd, *J* = 10.0, 6.8, 1.2 Hz, 2H), 3.86 (ddd, *J* = 10.0, 4.3, 1.2 Hz, 2H), 2.71 – 2.61 (m, 4H), 1.81 – 1.73 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 165.8, 156.4, 152.0, 142.5, 128.8, 128.7, 126.2, 119.4, 79.8, 63.4, 35.9, 32.6, 31.1, 29.1, 28.5. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{20}H_{27}NNaO_4$, 368.2; found, 368.1. FTIR (neat, cm^{-1}): 2977 (w), 2932 (w), 1704 (s), 1641 (w), 1455 (w), 1391 (s), 1136 (s), 1049 (m), 861 (w), 743 (m), 699 (m).

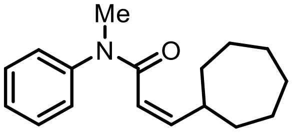


phenyl (2*Z*)-6-phenylhex-2-enoate (2.30), compound was prepared according to the general procedure A and was purified by silica gel chromatography (0-15% EtOAc in hexanes) and was isolated as a colorless liquid (113 mg, 85% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.14 – 7.08 (m, 2H), 7.10 – 6.98 (m, 7H), 6.94 – 6.86 (m, 1H), 5.95 – 5.85 (m, 2H), 2.75 – 2.63 (m, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.61 – 1.49 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.1, 152.5, 151.3, 142.2, 129.5, 128.7, 128.7, 126.2, 125.7, 122.1, 119.5, 35.8, 31.0, 29.1. GCMS (EI) calculated for $[M]^+$ 266.1, found 266.1. FTIR (neat, cm^{-1}): 3028 (w), 2930 (m), 2860 (w), 1736 (s), 1593 (m), 1495 (s), 1411 (m), 1196 (s), 1128 (s), 810 (w), 749 (m), 690 (s).



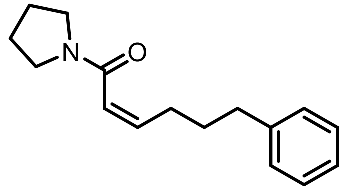
(1,3-thiazol-5-yl)methyl (2*Z*)-6-phenylhex-2-enoate (2.31), compound was prepared according to the general procedure A and was purified by silica gel chromatography (5-35% EtOAc in hexanes) and was isolated as a yellow liquid (123 mg, 86% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 8.18 (s, 1H), 7.64 (s, 1H), 7.17 – 7.13 (m, 2H), 7.10 – 7.04 (m, 1H), 7.01 (d, *J* = 6.9 Hz, 2H), 5.79 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.67 (dt, *J* = 11.4, 1.7 Hz, 1H), 4.92 (s, 2H), 2.68 – 2.60 (m, 2H), 2.42 (t, *J* = 7.7 Hz, 2H), 1.57 – 1.46 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 165.5, 154.4, 151.4, 144.3, 142.2, 133.2, 128.7, 128.7, 126.2, 119.4, 57.2, 35.8, 31.0, 29.0. GCMS (EI) calculated for $[M]^+$ 287.1, found 287.2. FTIR (neat, cm^{-1}): 3027 (w), 2928 (m), 2859 (w), 1718 (s), 1642 (m), 1416 (m), 1144 (s), 1011 (w), 872 (m), 802 (m), 700 (m).

2.6.10.3. α,β-Unsaturated Amide Scope

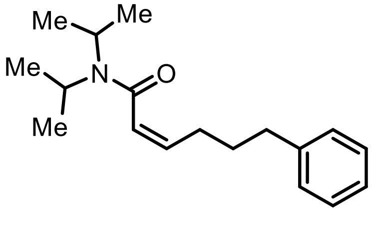


(2*Z*)-3-cycloheptyl-N-methyl-N-phenylprop-2-enamide (2.25), compound was prepared according to the general procedure B and was purified by silica gel chromatography (7-15%

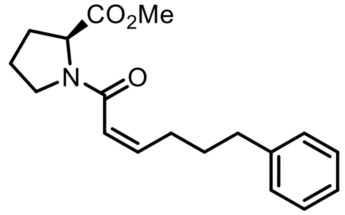
EtOAc in hexanes) and was isolated as a colorless liquid (101 mg, 78% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.01 – 6.77 (m, 5H), 5.69 – 5.48 (m, 2H), 4.04 – 3.82 (m, 2H), 3.13 (s, 3H), 2.03 – 1.88 (m, 2H), 1.64 – 1.22 (m, 10H). ^{13}C NMR (126 MHz, C_6D_6) δ 165.9, 151.0, 144.9, 129.4, 127.4, 126.9, 118.5, 38.7, 36.7, 34.9, 28.8, 26.9. GCMS (EI) calculated for $[M]^+$ 257.2, found 257.2. FTIR (neat, cm^{-1}): 3036 (m) 2921 (s), 2851 (s), 1650 (s), 1595 (s), 1494 (m), 1431 (s) 1339 (s), 1121 (s), 768 (m), 700 (m).



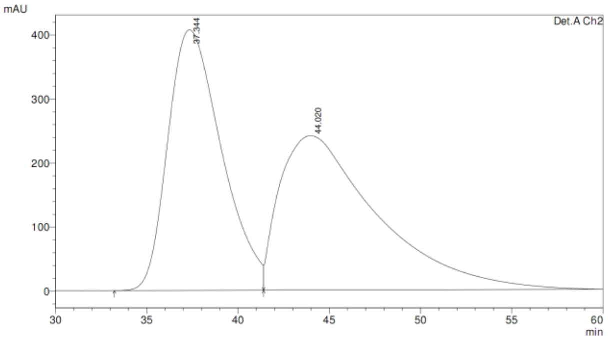
(2*Z*)-6-phenyl-1-(pyrrolidin-1-yl)hex-2-en-1-one (2.32), compound was prepared according to the general procedure B and was purified by silica gel chromatography (15-30% of a 3:1 solution of EtOAc and *i*-PrOH in hexanes) and was isolated as a yellow liquid (92 mg, 76% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.40 – 6.91 (m, 5H), 5.93 – 5.79 (m, 2H), 3.50 – 3.33 (m, 4H), 2.58 – 2.43 (m, 4H), 1.86 – 1.60 (m, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.7, 142.7, 137.7, 128.8, 128.6, 126.0, 125.8, 49.1, 45.4, 35.9, 31.5, 29.4, 20.9. GCMS (EI) calculated for $[M]^+$ 243.2, found 243.1. FTIR (neat, cm^{-1}): 3025 (m), 2929 (s), 2870 (s), 2231 (w), 1645 (s), 1497 (m), 1435 (s), 1367 (s), 1226 (m), 1039 (w), 913 (w), 803 (w), 730 (m), 700 (m).



(2*Z*)-6-phenyl-N,N-bis(propan-2-yl)hex-2-enamide (2.33), compound was prepared according to the general procedure B and was purified by silica gel chromatography (10-20% EtOAc in hexanes) and was isolated as a yellow liquid (95 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 3H), 7.29 – 7.18 (m, 3H), 6.05 (dt, *J* = 11.5, 1.6 Hz, 1H), 5.84 (dt, *J* = 11.5, 7.4 Hz, 1H), 4.29 – 4.06 (m, 1H), 3.70 – 3.47 (m, 1H), 2.72 (t, *J* = 7.9 Hz, 2H), 2.48 – 2.34 (m, 2H), 1.87 – 1.76 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H). GCMS (EI) calculated for $[M]^+$ 273.2, found 273.2. FTIR (neat, cm^{-1}): 3025 (w), 2968 (s), 2933 (s), 2859 (w), 1624 (s), 1443 (m), 1369 (m), 1306 (s), 1214 (w), 1133 (m), 1043 (w), 923 (w), 732 (m).

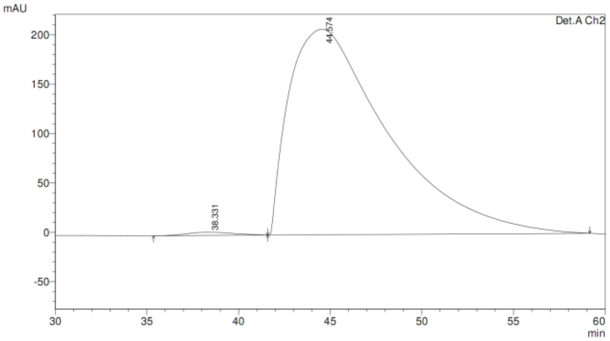


methyl (2*S*)-1-[(2*Z*)-6-phenylhex-2-enoyl]pyrrolidine-2-carboxylate (2.34), compound was prepared according to the general procedure B and was purified by silica gel chromatography (5-45% EtOAc in hexanes) and was isolated as a colorless liquid (107 mg, 71% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 6.07 – 5.92 (m, 2H), 4.45 – 4.36 (m, 1H), 3.70 (s, 3H), 3.65 – 3.46 (m, 2H), 2.67 – 2.61 (m, 2H), 2.61 – 2.48 (m, 2H), 2.30 – 1.84 (m, 4H), 1.79 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 172.8, 165.8, 145.1, 144.5, 142.4, 128.3, 125.7, 121.4, 121.1, 59.7, 58.5, 52.4, 52.2, 47.3, 46.0, 35.6, 31.5, 31.1, 31.1, 29.3, 28.9, 28.9, 24.9, 22.7 (includes amide rotamers). GCMS (EI) calculated for $[M]^+$ 301.2, found 301.1. FTIR (neat, cm^{-1}): 3025 (m), 2951 (s), 2878 (m), 2244 (w), 1738 (s), 1615 (s), 1435 (s), 1361 (s), 1279 (m), 1197 (s), 1095 (w), 1029 (w), 912 (m), 801 (w), 733 (m), 701 (m). Enantiomeric excess was determined by chiral HPLC. CHIRALPAK AD-1 column (2.5% 2-PrOH in hexanes, 1.0 mL/min, detected at 220 nm wavelength) with tr = 44.6 min (major), 38.3 min (minor). $[\alpha]_D^{23}$ = -0.7 (c 1.0, CHCl3).



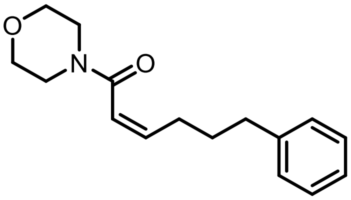
Detector A Ch2 220nm

Peak#	Ret. Time	Area %	Height %
1	37.344	48.037	62.819
2	44.020	51.963	37.181
Total		100.000	100.000

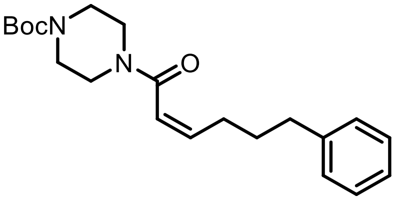


Detector A Ch2 220nm

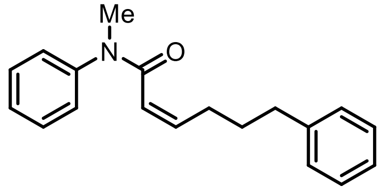
Peak#	Ret. Time	Area %	Height %
1	38.331	0.728	1.554
2	44.574	99.272	98.446
Total		100.000	100.000



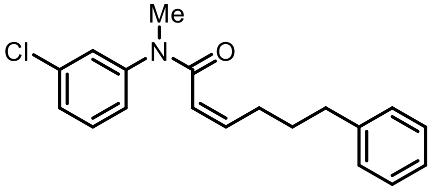
(2*Z*)-1-(morpholin-4-yl)-6-phenylhex-2-en-1-one (2.35), compound was prepared according to the general procedure B and was purified by silica gel chromatography (15-30% of a 3:1 solution of EtOAc and *i*-PrOH in hexanes) and was isolated as a colorless liquid (91 mg, 70% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.31 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 6.01 – 5.86 (m, 2H), 3.65 – 3.52 (m, 6H), 3.51 – 3.38 (m, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.36 – 2.28 (m, 2H), 1.78 – 1.67 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 165.7, 142.5, 141.4, 128.8, 128.6, 126.1, 122.2, 66.8, 66.7, 46.4, 41.7, 35.9, 31.3, 29.3. GCMS (EI) calculated for $[M]^+$ 259.2, found 259.1. FTIR (neat, cm^{-1}): 3025 (w), 2922 (s), 2856 (s), 1627 (s), 1439 (s), 1385 (w), 1272 (m), 1232 (s), 1114 (s), 1039 (m), 913 w), 848 (w), 334 (m), 701 (m).



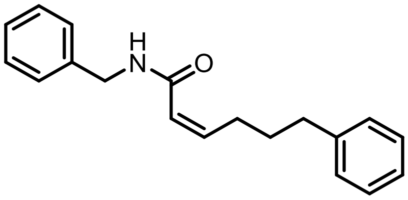
***tert*-butyl 4-[(2*Z*)-6-phenylhex-2-enoyl]piperazine-1-carboxylate (2.36)**, compound was prepared according to the general procedure B and was purified by silica gel chromatography (15-25% of a 1:1 solution of EtOAc and *i*-PrOH in hexanes) and was isolated as a yellow liquid (136 mg, 76% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.29 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 5.98 – 5.86 (m, 2H), 3.54 (m, 2H), 3.46 – 3.30 (m, 6H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.33 – 2.26 (m, 2H), 1.77 – 1.67 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 166.8, 154.8, 142.7, 140.8, 128.8, 128.7, 126.1, 122.7, 80.2, 46.4, 41.4, 35.9, 31.3, 29.4, 28.5. GCMS (EI) calculated for $[M]^+$ 358.2, found 358.1. FTIR (neat, cm^{-1}): 3025 (w), 2977 (m), 2928 (s), 2858 (m), 2245 (w), 1698 (s), 1651 (s), 1634 (s), 1456 (s), 1418 (s), 1366 (m), 1286 (m), 1238 (m), 1169 (s), 1126 (m), 996 (m), 921 (m), 863 (w), 731 (s).



(2*Z*)-N-methyl-N,6-diphenylhex-2-enamide (2.37), compound was prepared according to the general procedure B and was purified by silica gel chromatography (15-30% of a 3:1 solution of EtOAc and *i*-PrOH in hexanes) and was isolated as a yellow oil (100 mg, 72% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.42 – 7.34 (m, 2H), 7.33 – 7.23 (m, 3H), 7.22 – 7.12 (m, 5H), 5.89 – 5.73 (m, 1H), 5.63 (d, *J* = 11.7 Hz, 1H), 3.27 (s, 3H), 2.69 – 2.54 (m, 4H), 1.78 – 1.62 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 144.5, 144.0, 142.4, 129.4, 128.5, 128.3, 127.3, 127.1, 125.7, 121.6, 36.9, 35.7, 31.2, 28.9. GCMS (EI) calculated for $[M]^+$ 279.2, found 279.1. FTIR (neat, cm^{-1}): 3061 (m), 3026 (m), 2926 (s), 2856 (m), 1660 (s), 1595 (m), 1494 (m), 1454 (w), 1429 (w) 1342 (m), 1121 (m), 910 (w), 699 (m).

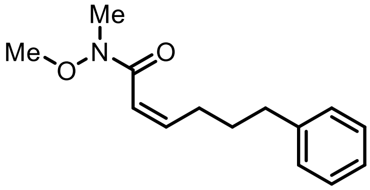


(2*Z*)-N-(3-chlorophenyl)-N-methyl-6-phenylhex-2-enamide (2.38), compound was prepared according to the general procedure B and was purified by silica gel chromatography (10-20% EtOAc in hexanes) and was isolated as a yellow liquid (100 mg, 62 yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 7.28 – 7.12 (m, 4H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.95 (dt, *J* = 11.5, 7.4 Hz, 1H), 5.85 – 5.55 (m, 2H), 3.37 (s, 3H), 2.77 – 2.68 (m, 4H), 1.86 – 1.77 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 166.6, 145.8, 144.8, 142.9, 135.0, 130.8, 128.9, 128.7, 127.7, 127.6, 126.1, 125.9, 122.0, 37.0, 36.1, 31.5, 29.2. GCMS (EI) calculated for $[M]^+$ 313.1, found 313.1. FTIR (neat, cm^{-1}): 3061 (w), 3025 (m), 2926 (m), 2856 (w), 1657 (s), 1590 (s), 1476 (m), 1436 (m), 1336 (m), 1129 (w), 1092 (w), 787 (w), 698 (m).

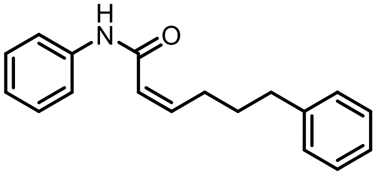


(2*Z*)-N-benzyl-6-phenylhex-2-enamide (2.39), compound was prepared according to the general procedure B and was purified by silica gel chromatography (15-25% EtOAc in hexanes) and was isolated as a colorless solid (72 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 5H), 7.21 (d, *J* = 7.5 Hz, 3H), 6.06 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.83-5.61 (m, 2H), 4.50 (d, *J* = 5.8 Hz, 2H), 2.83 – 2.73 (m, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.86 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 166.6, 145.5, 142.9, 139.4, 129.0, 128.9, 128.7, 128.1, 127.7, 126.1, 123.0, 43.5, 36.0, 31.6, 28.9. GCMS (EI) calculated for $[M]^+$ 279.2, found 279.1.

FTIR (neat, cm^{-1}): 3292 (br) 3062 (w), 3026 (m), 2924 (m), 2856 (w), 1658 (s), 1633 (s), 1540 (s), 1497 (w), 1453 (w), 1237 (w), 698 (s).

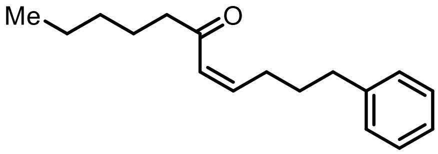


(2*Z*)-N-methoxy-N-methyl-6-phenylhex-2-enamide (2.40), compound was prepared according to the general procedure B and was purified by silica gel chromatography (10-20% EtOAc in hexanes) and was isolated as a colorless liquid (73 mg, 62% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.21 – 7.12 (m, 2H), 7.13 – 7.04 (m, 3H), 6.16 (d, *J* = 11.7 Hz, 1H), 6.03 (dt, *J* = 11.7, 7.3 Hz, 1H), 3.57 (s, 3H), 3.08 (s, 3H), 2.61 – 2.49 (m, 4H), 1.70 – 1.60 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 147.1, 142.4, 128.5, 128.3, 125.8, 118.5, 61.5, 35.7, 32.2, 31.2, 28.9. GCMS (EI) calculated for $[M]^+$ 233.1, found 233.1. FTIR (neat, cm^{-1}): 3062 (w), 3026 (m), 2933 (s), 2857 (m), 1652 (s), 1626 (s), 1498 (w), 1447 (m), 1348 (m), 1178 (w), 1098 (w), 1000 (m), 791 (w), 734 (m), 699 (m).

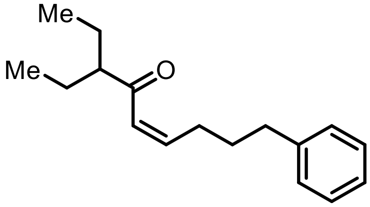


(2*Z*)-N,6-diphenylhex-2-enamide (2.41), compound was prepared according to a modified general procedure B, with the modification of Na_2CO_3 (106 mg, 1.0 mmol, 2.0 equiv) employed as the base instead of the standard $KHCO_3$. It was purified by silica gel chromatography (10-45% EtOAc in hexanes) and was isolated as a white solid (84 mg, 63% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.03 (m, 7H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.56 (s, 1H), 5.76 (dt, *J* = 11.4, 7.6 Hz, 1H), 5.28 (d, *J* = 11.4 Hz, 1H), 2.91 – 2.81 (m, 2H), 2.52 (t, *J* = 7.9 Hz, 2H), 1.72 – 1.60 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.0, 147.0, 142.6, 139.0, 129.1, 128.8, 128.6, 126.1, 124.1, 123.1, 119.8, 36.0, 31.6, 28.8. GCMS (EI) calculated for $[M]^+$ 265.2, found 265.2. FTIR (neat, cm^{-1}): 3314 (br), 3030 (w), 2923 (m), 2857 (w), 1663 (m), 1638 (s), 1595 (s), 1541 (s), 1491 (s), 1444 (s), 1315 (s), 1241 (s), 1151 (m), 906 (w), 808 (m), 751 (s), 692 (s), 570 (m).

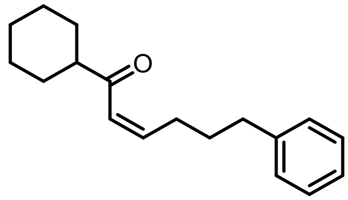
2.6.10.4. α,β-Unsaturated Ketone Scope



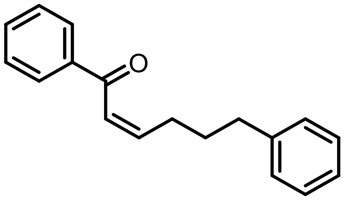
(4*Z*)-1-phenylundec-4-en-6-one (2.42), compound was prepared according to the general procedure C and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (99 mg, 81% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 – 7.21 (m, 2H), 7.22 – 7.14 (m, 3H), 6.15 (dt, *J* = 11.5, 1.7 Hz, 1H), 6.06 (dt, *J* = 11.5, 7.2 Hz, 1H), 2.66 – 2.59 (m, 4H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.77 – 1.70 (m, 2H), 1.59 – 1.53 (m, 2H), 1.34 – 1.25 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 200.1, 147.0, 142.5, 128.8, 128.6, 127.3, 126.1, 44.3, 35.9, 31.8, 31.5, 29.4, 24.0, 22.9, 14.2. GCMS (EI) calculated for $[M]^+$ 244.2, found 244.2. FTIR (neat, cm^{-1}): 3025 (m), 2928 (s), 2858 (s), 1694 (s), 1621 (s), 1497 (m), 1454 (s), 1415 (m), 1128 (w), 1070 (m), 745 (w), 699 (s).



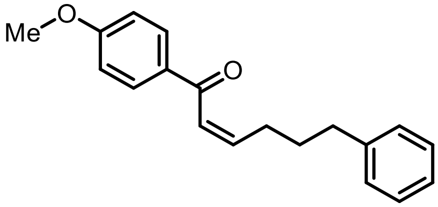
(5*Z*)-3-ethyl-9-phenylnon-5-en-4-one (2.43), compound was prepared according to the general procedure C and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (86 mg, 70% yield). ^1H NMR (300 MHz, C_6D_6) δ 7.15 – 7.00 (m, 5H), 5.92 (dt, *J* = 11.4, 1.6 Hz, 1H), 5.75 (dt, *J* = 11.4, 7.3 Hz, 1H), 2.79 – 2.69 (m, 2H), 2.51 – 2.44 (m, 2H), 2.18 – 2.09 (m, 1H), 1.66 – 1.55 (m, 4H), 1.36 – 1.27 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 203.7, 147.7, 142.5, 128.8, 128.6, 127.1, 126.1, 56.2, 36.0, 31.5, 29.5, 24.5, 12.0. GCMS (EI) calculated for $[M]^+$ 244.2, found 244.2. FTIR (neat, cm^{-1}): 3025 (m), 2961 (s), 2929 (s), 2874 (s), 1687 (s), 1615 (s), 1496 (w), 1458 (m), 1065 (m), 749 (w), 699 (m).



(2*Z*)-1-cyclohexyl-6-phenylhex-2-en-1-one (2.44), compound was prepared according to the general procedure C and was purified by silica gel chromatography (0-10% Et_2O in hexanes) and was isolated as a colorless liquid (103 mg, 80% yield). ^1H NMR (300 MHz, CD_2Cl_2) δ 7.32 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 6.21 (dt, *J* = 11.5, 1.5 Hz, 1H), 6.09 (dt, *J* = 11.5, 7.1 Hz, 1H), 2.68 – 2.55 (m, 4H), 2.41 – 2.26 (m, 1H), 1.87 – 1.63 (m, 7H), 1.34 – 1.17 (m, 5H). ^{13}C NMR (126 MHz, C_6D_6) δ 203.0, 147.6, 142.5, 128.8, 128.6, 126.5, 126.1, 51.4, 36.0, 31.5, 29.5, 28.7, 26.3, 26.0. GCMS (EI) calculated for $[M]^+$ 256.2, found 256.1. FTIR (neat, cm^{-1}): 3025 (m), 2927 (s), 2854 (s), 1687 (s), 1615 (s), 1495 (m), 1450 (s), 1418 (w), 1145 (m), 1067 (m), 1003 (w), 701 (s).



(2*Z*)-1,6-diphenylhex-2-en-1-one (2.45), compound was prepared according to the general procedure C and was purified by silica gel chromatography (0-12% Et_2O in hexanes). Crude ^{1}H NMR of the reaction showed the presence of the β,γ-unsaturated ketone in the reaction mixture with a ratio of 5:1 ((*Z)*-α,β-:β,γ-ketone). However, after column chromatography the product was isolated as a colorless solid and a 23:1 mixture of the (*Z)*-α,β- and β,γ-unsaturated ketones (68 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.00 (m, 2H), 7.69 – 7.62 (m, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.38 – 7.26 (m, 5H), 6.93 (dt, *J* = 11.7, 1.8 Hz, 1H), 6.44 (dt, *J* = 11.6, 7.4 Hz, 1H), 2.81 – 2.75 (m, 4H), 1.95 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 191.0, 148.6, 142.5, 139.2, 132.5, 128.8, 128.7, 128.6, 128.6, 126.1, 124.8, 35.9, 31.4, 29.9. GCMS (EI) calculated for $[M]^+$ 250.1, found 250.1. FTIR (neat, cm^{-1}): 3057 (m), 3021 (m), 3924 (s), 2857 (m), 1665 (s), 1610 (s), 1495 (m), 1446 (s), 1227 (s), 1022 (m) 724 (m), 685 (m).



(2*Z*)-1-(4-methoxyphenyl)-6-phenylhex-2-en-1-one (2.46), compound was prepared according to the general procedure C and was purified by silica gel chromatography (5-15% EtOAc in hexanes) and was isolated as a yellow solid (96 mg, 69% yield). Crude ^{1}H NMR of the reaction showed the presence of the β,γ-unsaturated ketone in the reaction mixture with a ratio of 13:1 ((*Z)*-α,β:β,γ-ketone). However, after column chromatography the (*Z)*-α,β:β,γ-ketone ratio was

>30:1 based in NMR analysis. ^{1}H NMR (300 MHz, C_6D_6) δ 8.00 – 7.90 (m, 2H), 7.15 – 6.99 (m, 5H), 6.68 – 6.56 (m, 3H), 5.93 (dt, *J* = 11.6, 7.5 Hz, 1H), 3.17 (s, 3H), 2.80 – 2.68 (m, 2H), 2.53 – 2.46 (m, 2H), 1.71 – 1.60 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 189.7, 163.5, 147.5, 142.6, 132.3, 130.9, 128.8, 128.6, 126.1, 125.0, 114.0, 54.9, 36.0, 31.5, 29.9. GCMS (EI) calculated for $[M]^+$ 280.2, found 280.1. FTIR (neat, cm^{-1}): 3024 (w), 2929 (m), 2854 (w), 1659 (s), 1600 (s), 1510 (m), 1424 (m), 1235 (s), 1169 (s).

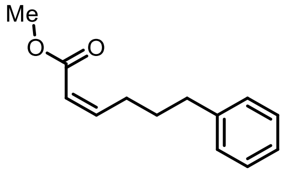
2.6.11. *Determination of Reaction Selectivity*

2.6.11.1. *Z/E* Selectivity for α,β-Unsaturated Esters and Amides

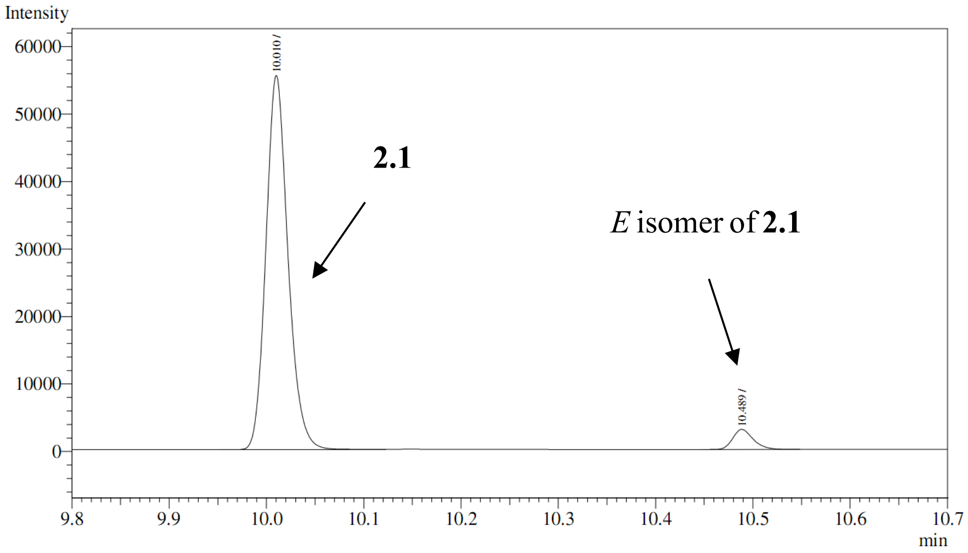
The selectivity of the hydroalkylation reaction of alkynyl esters and amides was determined for select substrates representing (*Z*)-α,β-unsaturated esters and amides. For the selected substrates, the purified *Z*-alkene products were subjected to a modified isomerization procedure[21,22] to obtain a mixture of *Z*- and *E*-isomers: To a dram vial was charged with a stir bar, isolated *Z*-alkene product (0.05 mmol, 1.0 equiv), I_2 (2.5 mg, 0.01 mmol, 0.2 equiv) and cyclohexane (0.05 M). This reaction was left to stir at 80 °C overnight and then was quenched with saturated sodium thiosulfate (1 mL). The product was extracted with diethyl ether (3 ml) and washed with saturated sodium bicarbonate and brine and then dried over $MgSO_4$. The mixture was concentrated under vacuum and the presence of the E isomer was confirmed by ^{1}H NMR analysis.

These *Z/E* mixtures were then used to determine GC retention times of the E isomer to analyze the selectivity in the crude reaction mixtures. Analysis was done using a GC/FID instrument. For the purposes of analysis the *E*- and *Z*-isomers were assumed to give equal GC-FID signal. Preparation of samples for the analysis of the reaction selectivity: After completion of the catalytic reaction, an aliquot of the crude reaction mixture was taken, passed through a plug of silica with ethyl acetate and analyzed by GC. Note: for all reactions the *E*-isomer was never observed in any crude or isolated NMRs or in any GC analysis.

***Z/E* selectivity in the formation of 2.1:**

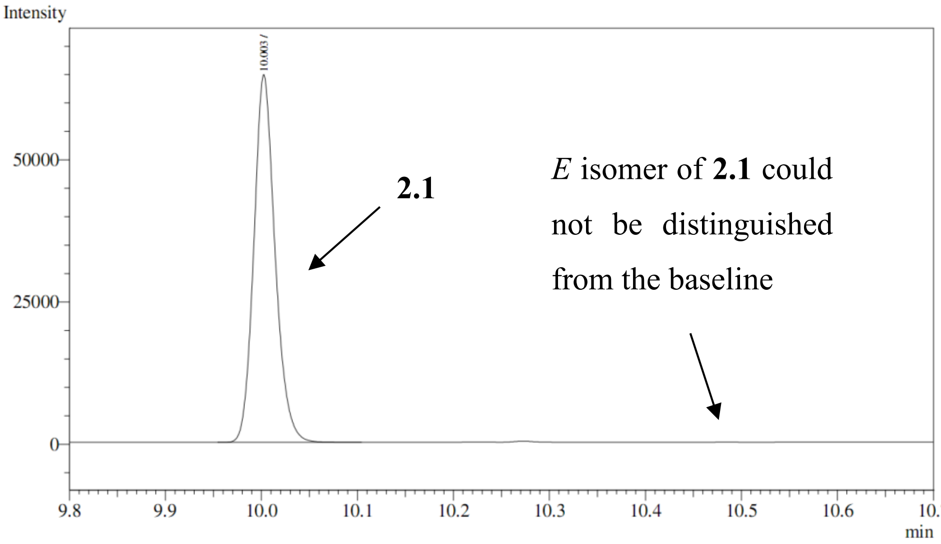


GC trace from the analysis of **2.1** after isomerization (see above):



```
Peak#   Ret.Time      Area      Height    Conc.   Unit  Mark  ID#      Cmpd Name
    1     10.010     87484      54563     0.000
    2     10.489      4369       2926     0.000
Total                91853      57489
```

GC trace from the analysis of a crude reaction mixture containing **2.1**:



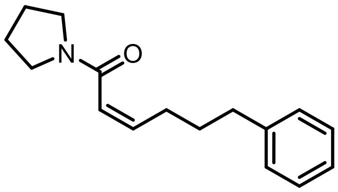
2.1

E isomer of **2.1** could not be distinguished from the baseline

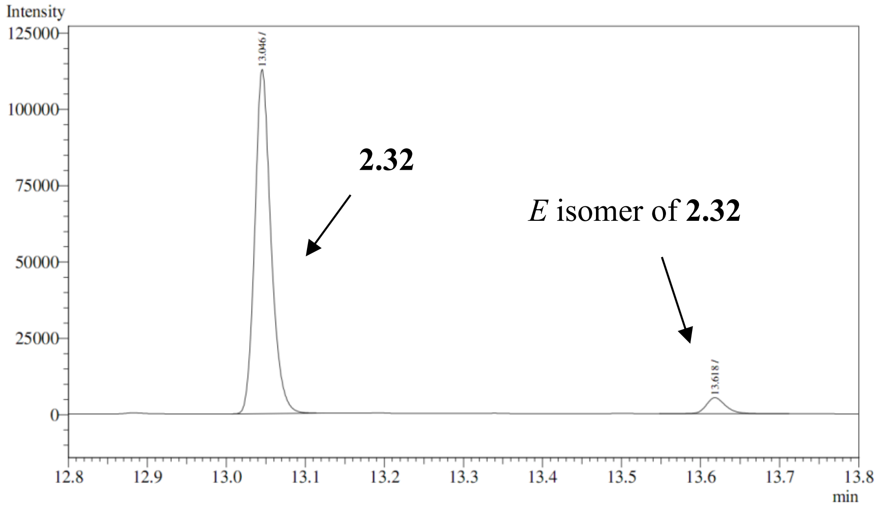
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	10.003	99526	63316	100.000				
Total		99526	63316					

The *Z:E* ratio >100:1.

***Z/E* selectivity in the formation of 2.32:**

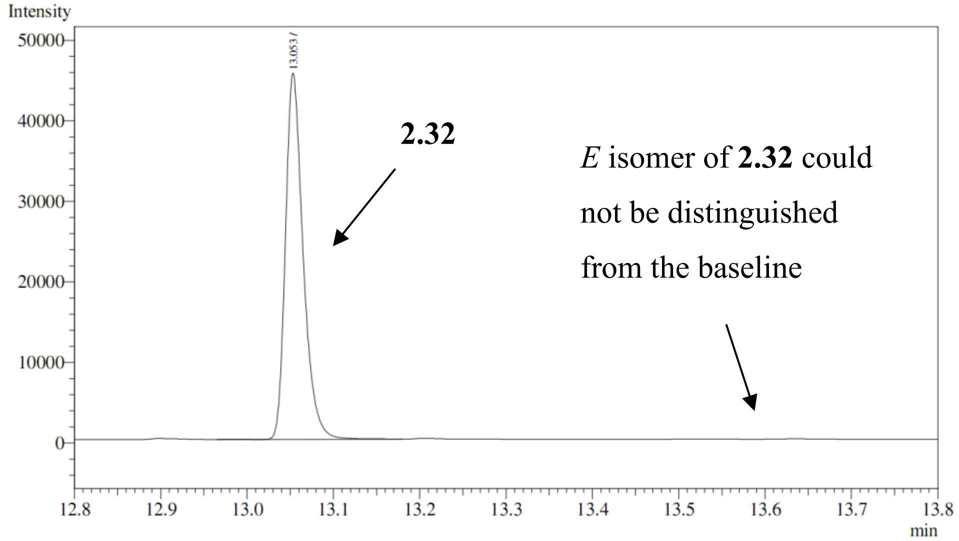


GC trace from the analysis of **2.32** after isomerization (see above):



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	13.046	161077	109763	94.671				
2	13.618	9067	5122	5.329		V		
Total		170144	114885					

GC trace from the analysis of a crude reaction mixture containing **2.32**:



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	13.053	64844	44428	100.000		V		
Total		64844	44428					

The *Z:E* ratio >100:1.

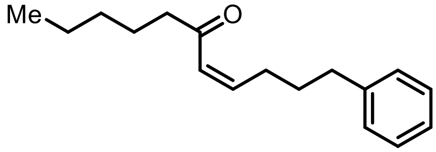
2.6.11.2. Product Selectivity for α,β-Unsaturated Ketones

The selectivity of the hydroalkylation reaction of alkynyl ketones was determined for selected substrates representing alkyl and aryl α,β-unsaturated ketones. For the selected substrates, the purified *Z*-alkene products were isomerized to obtain a mixture of (*Z)*-α,β-, (*E*)-α,β- and β,γ-unsaturated isomers using the following procedure:

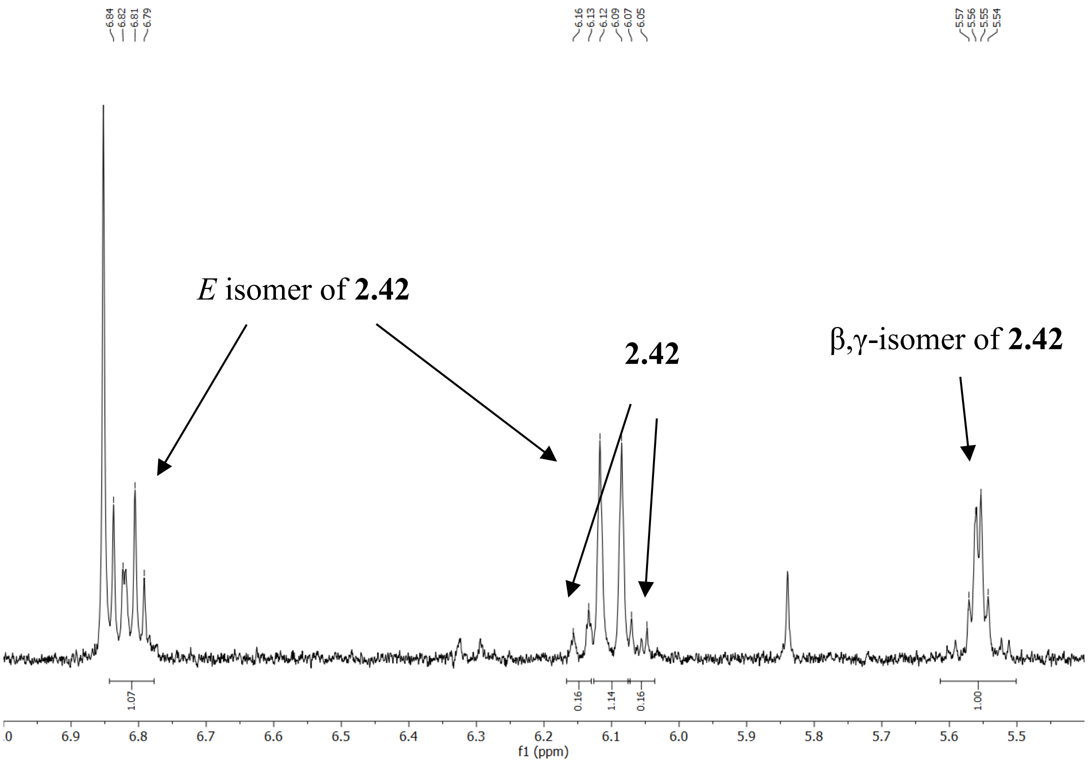
In a nitrogen glovebox a dram vial was charged with a stir bar, isolated (*Z)*-α,β-unsaturated ketone (0.05 mmol, 1.0 equiv), triethylamine (7.6 mg, 0.08 mmol, 1.5 equiv) and acetonitrile (0.1 M). This reaction was left to stir at 45 °C overnight and then was concentrated under vacuum and the presence of the (*Z)*-α,β-, (*E*)-α,β- and β,γ-unsaturated isomers was confirmed by ^{1}H NMR analysis.

It was observed that the (*Z*)-α,β-unsaturated ketone products isomerized during GC analysis. To combat this issue, the (*Z)*-α,β-/(*E*)-α,β-/β,γ-unsaturated mixtures were analyzed via HPLC to determine the selectivity in the crude reaction mixtures. Preparation of samples for the analysis of the reaction selectivity: After completion of the catalytic reaction, an aliquot of the crude reaction mixture was taken, passed through a plug of silica with ethyl acetate, concentrated under vacuum and then dissolved in the appropriate HPLC eluent. Note: for all reactions the *E*-isomer was never observed in any crude or isolated NMRs or in any GC analysis.

Product selectivity in the formation of 2.42:

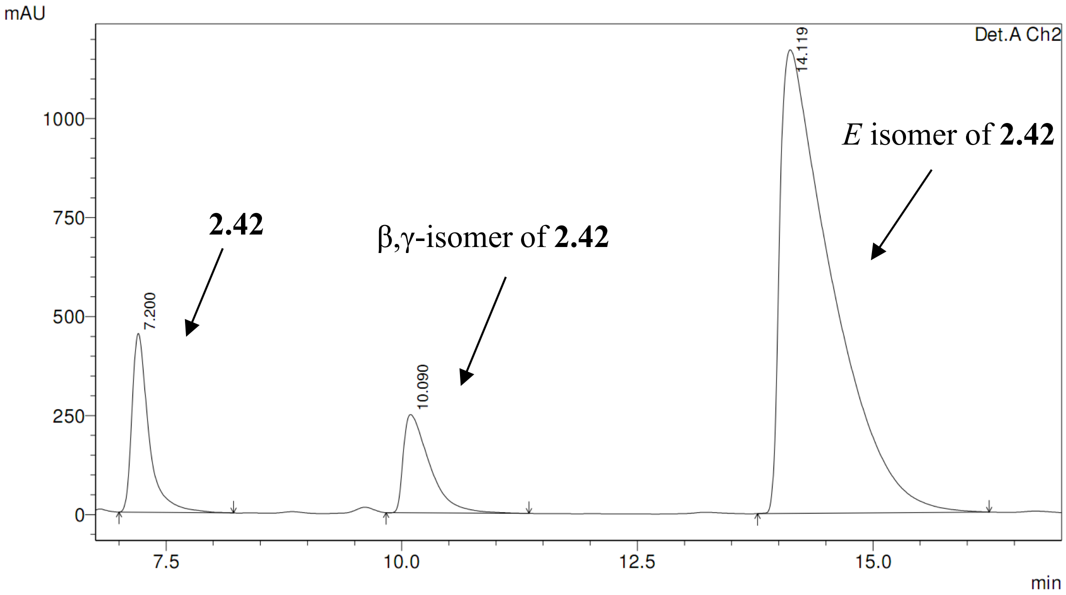


Alkene region of ^{1}H NMR from the analysis of **2.42** after isomerization (see above):



The ratio of isomers for the isomerized sample based on ^{1}H NMR analysis is 1:7.1:3.1 ((*Z*)-α,β-:(*E*)-α,β-:β,γ-ketone).

Analytical HPLC trace from the analysis of **2.42** after isomerization (see above):

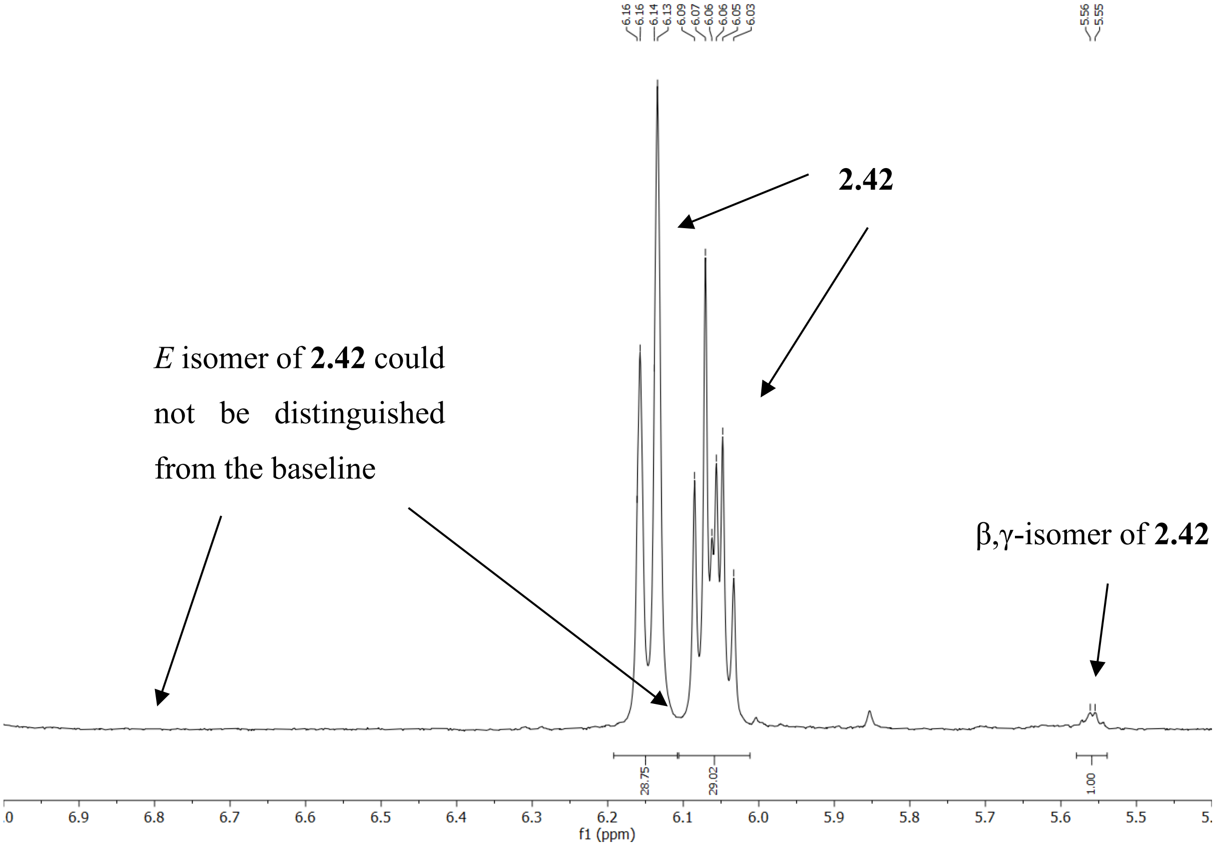


Detector A Ch2 220nm

Peak#	Ret. Time	Area %	Height %
1	7.200	10.191	24.115
2	10.090	8.710	13.280
3	14.119	81.099	62.605
Total		100.000	100.000

We used the ^{1}H NMR to calculate the response factor of each isomer resulting in the same ratio 1:7.1:3.1 ((*Z*)-α,β-:(*E*)-α,β-:β,γ-ketone). Analytical HPLC was performed using Zorbax Original CN column (hexanes, 1.0 mL/min, detected at 220 nm wavelength).

Alkene region of ^{1}H NMR from the crude reaction of **2.42**:



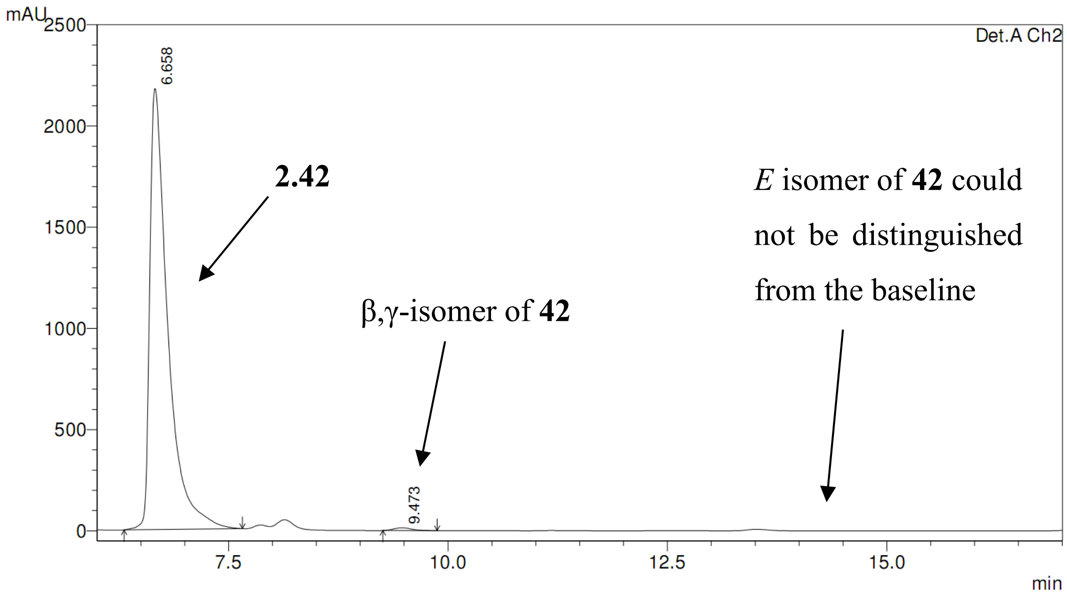
2.42

E isomer of **2.42** could not be distinguished from the baseline

β,γ-isomer of **2.42**

The ratio of isomers for the crude reaction sample based on ^{1}H NMR analysis is >50:1 *Z*:*E* and 29:1 (*Z*)-α,β-:β,γ-ketone.

Analytical HPLC trace from the crude reaction of **2.42**:

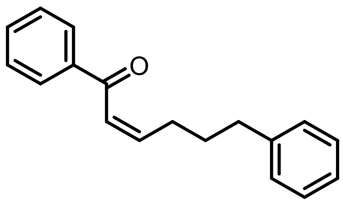


Detector A Ch2 220nm

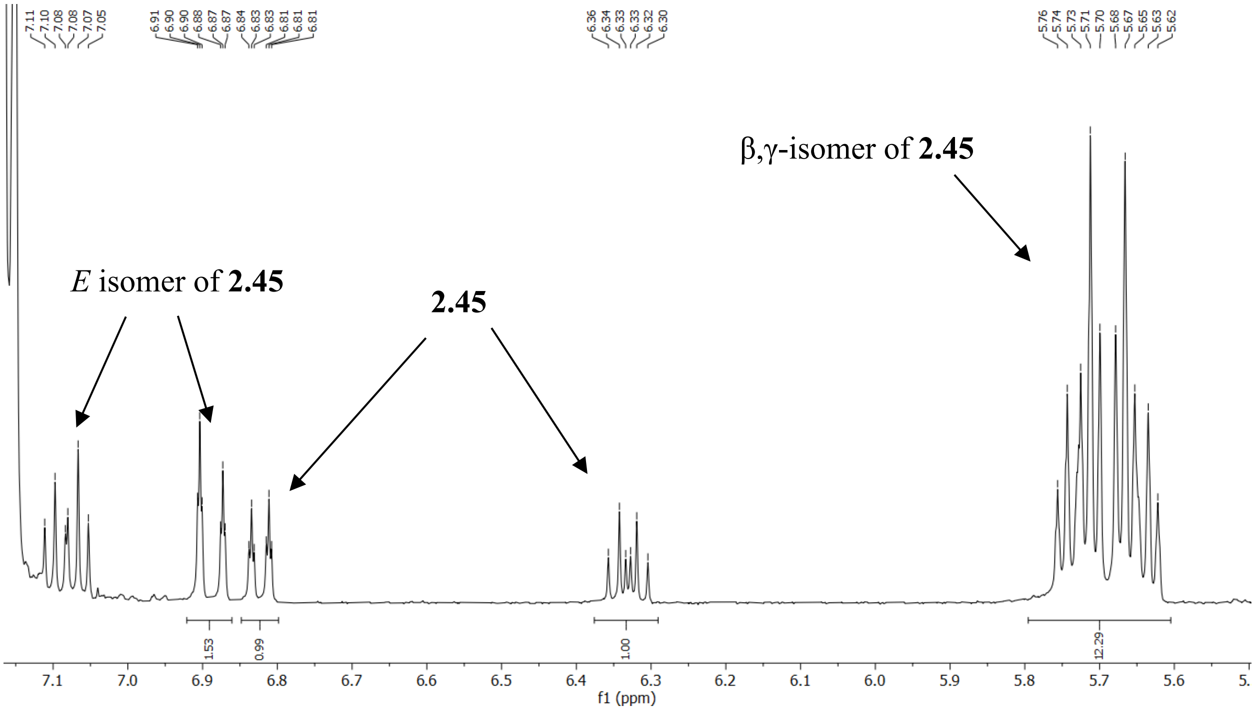
Peak#	Ret. Time	Area %	Height %
1	6.658	99.377	99.376
2	9.473	0.623	0.624
Total		100.000	100.000

Based on the response factor calculated from the isomerized sample the ratio of isomers for the crude reaction sample based on HPLC analysis is >100:1 *Z*:*E* and the (*Z*)-α,β-:β,γ-ketone ratio is 39:1. Analytical HPLC was performed using Zorbax Original CN column (hexanes, 1.0 mL/min, detected at 220 nm wavelength).

Product selectivity in the formation of 2.45:

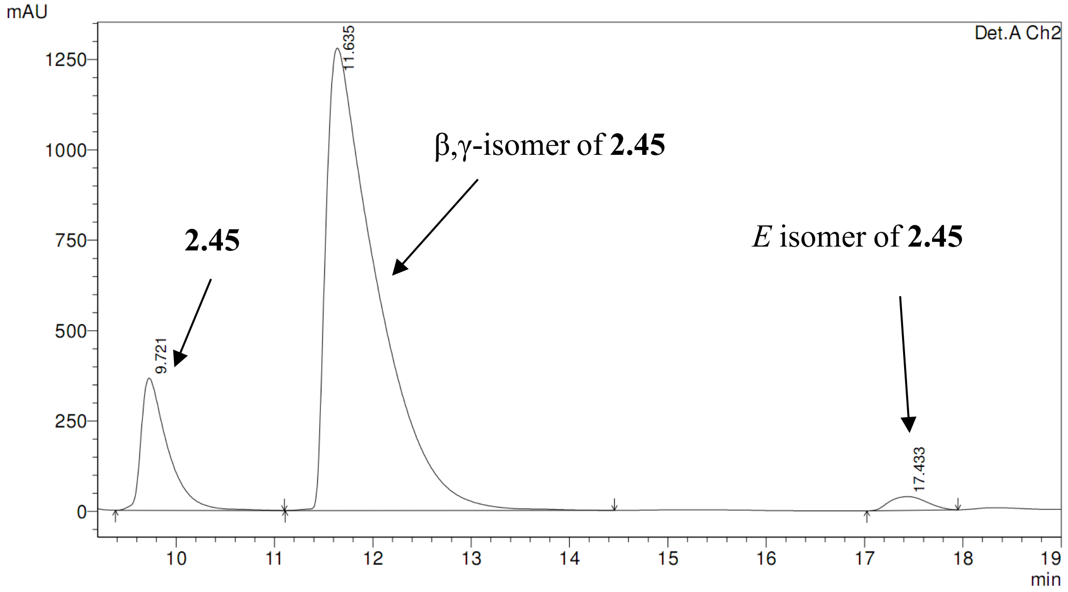


Alkene region of ^{1}H NMR from the analysis of **2.45** after isomerization (see above):



The ratio of isomers for the isomerized sample based on ^{1}H NMR analysis is 1:1.5:6.2 ((*Z*)-α,β-:(*E*)-α,β-:β,γ-ketone). Analytical HPLC was performed using Zorbax Original CN column (hexanes, 1.0 mL/min, detected at 220 nm wavelength).

Analytical HPLC trace from the analysis of **2.45** after isomerization (see above):

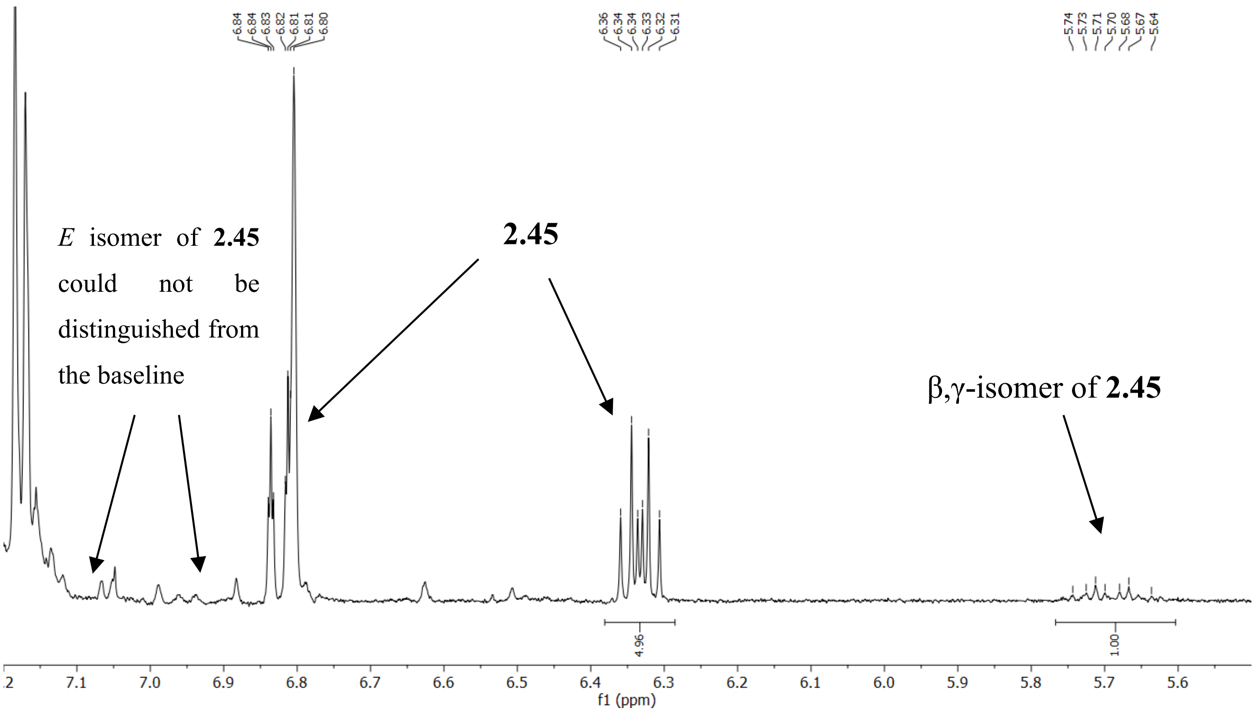


Detector A Ch2 220nm

Peak#	Ret. Time	Area %	Height %
1	9.721	12.750	21.727
2	11.635	85.378	76.002
3	17.433	1.872	2.271
Total		100.000	100.000

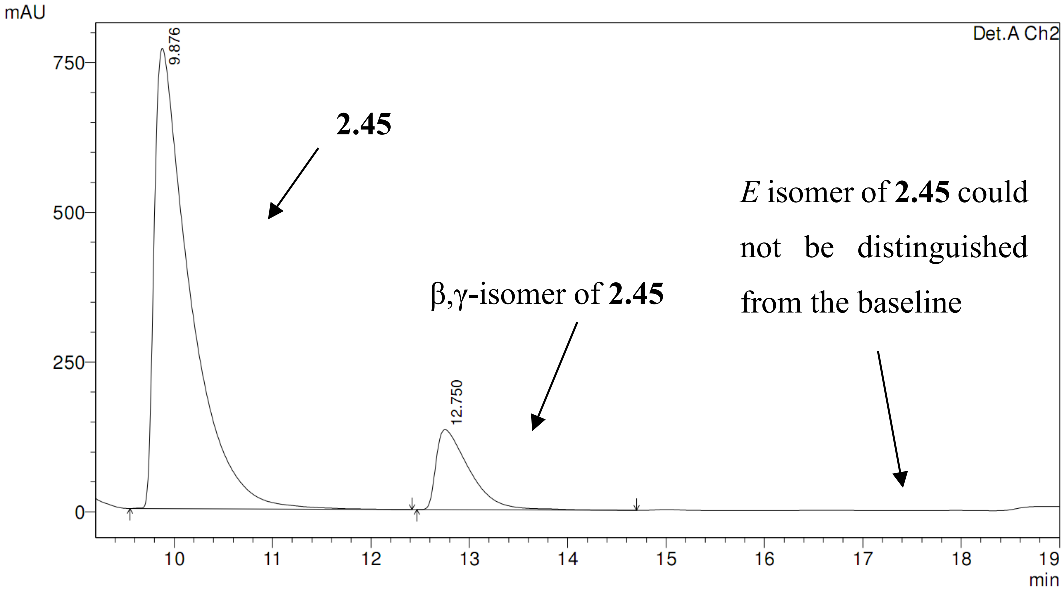
We used the ^{1}H NMR to calculate the response factor of each isomer resulting in the same ratio 1:1.5:6.2 ((*Z*)-α,β-:(*E*)-α,β-:β,γ-ketone).

Alkene region of ^{1}H NMR from the crude reaction of **2.45**:



The ratio of isomers for the crude reaction sample based on ^{1}H NMR analysis is >50:1 *Z*:*E* and 5:1 (*Z*)-α,β-:β,γ-ketone.

Analytical HPLC trace from the reaction of **2.45**:



Detector A Ch2 220nm

Peak#	Ret. Time	Area %	Height %
1	9.876	86.064	85.168
2	12.750	13.936	14.832
Total		100.000	100.000

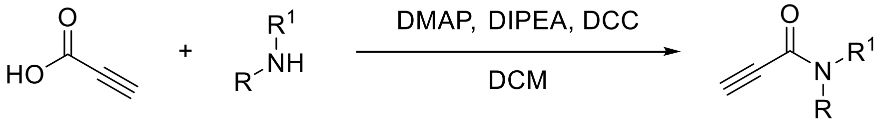
Based on the response factor calculated from the isomerized sample the ratio of isomers for the crude reaction sample based on HPLC analysis is >100:1 *Z*:*E* and 7:1 (*Z*)-α,β-:β,γ-ketone. Analytical HPLC was performed using Zorbax Original CN column (hexanes, 1.0 mL/min, detected at 220 nm wavelength).

2.6.12. *Alkyne Starting Materials*

2.6.12.1. General Procedure D for the Preparation of Conjugated Alkynyl Esters

According to a known procedure,[23] a reaction flask was flame dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DMAP (0.1 equiv), and DCM (0.2 M). The reaction was then cooled to 0 °C and propiolic acid (1.0 equiv) and alcohol or phenol (1.1 equiv) were added. Then a solution a solution of DCC (1.05 equiv) in DCM was added dropwise. The reaction was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was filtered through celite and then concentrated under reduced pressure. The product was further purified by silica gel chromatography to afford the alkynyl ester.

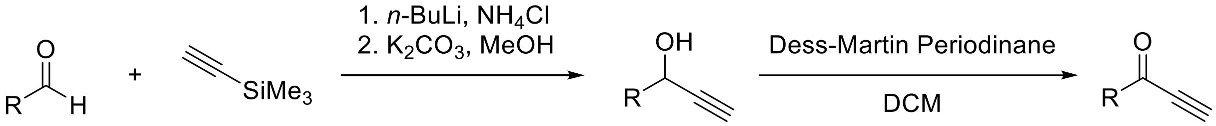
2.6.12.2. General Procedure E for the Preparation of Conjugated Alkynyl Amides



According to a known procedure,[24] a reaction flask was flame dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, DMAP (0.1 equiv), and DCM (0.2 M). The reaction was then cooled to 0 °C and DIPEA (1.05 equiv), DCC (1.1 equiv), and amine (1 equiv) were added, followed by propiolic acid (1.1 equiv) dropwise. The reaction was left stirring overnight at room temperature. The reaction mixture was filtered through celite and then concentrated under reduced pressure. The product was then further purified by silica gel chromatography to afford the alkynyl amide.

2.6.12.3. General Procedures for the Preparation of Conjugated Alkynyl Ketones

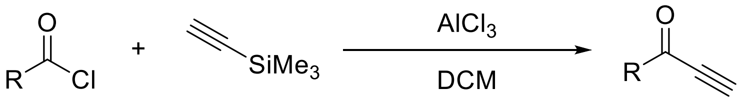
General Procedure F



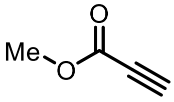
Propargyl Alcohol: According to a known procedure,[23] a reaction flask was flame dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar and trimethylsilyl acetylene (1.1 equiv) and THF (1 M). The reaction was cooled to -78 °C and *n*-BuLi (1.05 equiv) was added. The mixture was stirred for 1 hour at -78 °C then the aldehyde (1 equiv) was added dropwise. The reaction was left stirring for 30 minutes at -78 °C then was allowed to warm to room temperature and stirred for 30 minutes at room temperature. The reaction was quenched with water, and then extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue was dissolved in MeOH (1 M) and then K_2CO_3 (3 equiv) was added. The reaction was left stirring overnight then filtered through celite with DCM. The filtrate was washed with saturated ammonium chloride and brine, dried over $MgSO_4$, then concentrated under reduced pressure. The resulting product was purified by silica gel chromatography to afford the allyl alcohol which was used in the next step without further purification.

Alkynyl Ketone: Adapted from a known procedure,[23] a reaction flask was flame dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar and the propargyl alcohol (1 equiv) in DCM (1 M). Dess-Martin periodinane (1.1 equiv) was then added and the reaction was left to stir at room temperature overnight. The reaction mixture was then filtered through a pad of celite with DCM and washed with saturated sodium bicarbonate and brine and was dried over $MgSO_4$. The mixture was then concentrated under reduced pressure. The resulting product was purified by silica gel chromatography to afford the alkynyl ketone product.

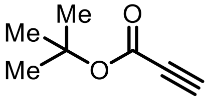
General Procedure G



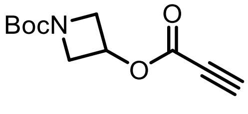
According to a known procedure,[25] a reaction flask was flame dried under vacuum and allowed to cool under nitrogen. The flask was then charged with a stir bar, trimethylsilyl acetylene (1.1 equiv), acyl chloride (1 equiv), and DCM (0.5 M). The reaction was cooled to 0 °C and $AlCl_3$ (3 equiv) was added. After 30 minutes the reaction was allowed to warm to room temperature and was stirred at room temperature for 2 hours. The reaction was quenched with 1 M HCl and extracted with DCM. The organic layers were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The mixture was then concentrated under reduced pressure. The resulting product was purified by silica gel chromatography to afford the alkynyl ketone product.



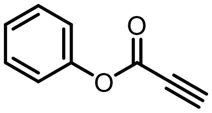
methyl prop-2-ynoate (2.7), was ordered from Oakwood Chemical and distilled over calcium hydride before use.



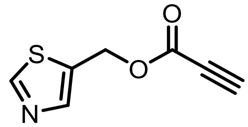
***tert*-butyl prop-2-ynoate (2.60),** was purchased from Combi-Blocks and distilled over calcium hydride before use.



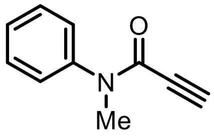
***tert*-butyl 3-(prop-2-ynoyloxy)azetidine-1-carboxylate (2.61)**, compound was prepared according to the general procedure D and was purified by silica gel chromatography (5-35% EtOAc in hexanes) and was isolated as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.26 – 5.17 (m, 1H), 4.25 (ddd, J = 10.2, 6.7, 1.2 Hz, 2H), 3.96 (ddd, J = 10.2, 4.2, 1.2 Hz, 2H), 2.96 (s, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.9, 151.8, 80.1, 76.2, 74.0, 65.1, 55.9, 28.3. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{11}H_{15}NO_4$, 225.1; found, 225.0. FTIR (neat, cm^{-1}): 3199 (m), 2979 (w), 2930 (w), 2110 (m), 1720 (s), 1683 (s), 1417 (s), 1368 (s), 1222 (s), 1141 (s), 1009 (m), 839 (w), 774 (s), 727 (m), 566 (m).



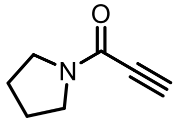
phenyl prop-2-ynoate (2.62), was synthesized according to general procedure D and has been previously characterized.[23]



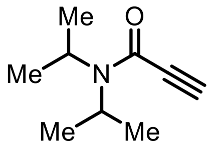
(1,3-thiazol-5-yl)methyl prop-2-ynoate (2.63), compound was prepared according to the general procedure D and was purified by silica gel chromatography (10-40% EtOAc in hexanes) and was isolated as an orange solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.84 (s, 1H), 7.93 (s, 1H), 5.43 (s, 2H), 2.94 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.3, 152.3, 144.7, 131.2, 76.0, 74.1, 59.2. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_7H_5NO_2S$, 167.0; found, 167.0 FTIR (neat, cm^{-1}): 3185 (w), 3079 (m), 2972 (w), 2113 (s), 1701 (s), 1607 (m), 1442 (m), 1366 (m), 1275 (m), 1208 (s), 1113 (s), 950 (s), 874 (s), 748 (s), 643 (m), 603 (s).



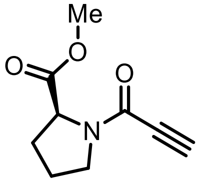
N-methyl-N-phenylprop-2-ynamide (2.64), was synthesized according to a general procedure E and has been previously characterized.[26]



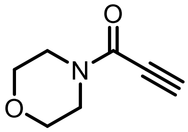
1-(pyrrolidin-1-yl)prop-2-yn-1-one (2.55), was synthesized according to general procedure E and has been previously characterized.[27]



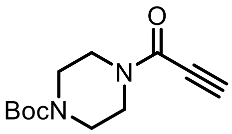
N,N-bis(propan-2-yl)prop-2-ynamide (2.65), compound was prepared according to the general procedure E and was purified by silica gel chromatography (5-35% EtOAc in hexanes) and was isolated as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.70 – 4.49 (m, 1H), 3.73 – 3.50 (m, 1H), 3.01 (s, 1H), 1.38 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, C$_6$D$_6$) δ 152.1, 77.9, 76.6, 50.4, 45.7, 20.5, 20.2 (increased number of peaks due to amide rotamers). GCMS (EI) calculated for [M]$^+$ 153.1, found 153.2. FTIR (neat, cm^{-1}): 3182 (m), 2981 (w), 2936 (w), 2092 (m), 1610 (s), 1436 (m), 1364 (m), 1328 (s), 1208 (m), 1130 (m), 1043 (m), 858 (w), 738 (s), 588 (m).



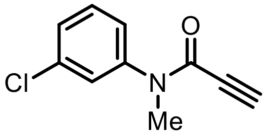
methyl (2*S*)-1-(prop-2-ynoyl)pyrrolidine-2-carboxylate (2.66), is commercially available from Enamine Building Blocks.



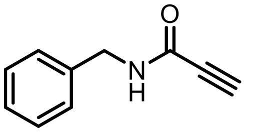
1-(morpholin-4-yl)prop-2-yn-1-one (2.67), was synthesized according to general procedure E and has been previously characterized.[28]



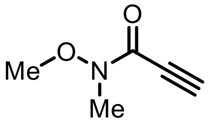
***tert*-butyl 4-(prop-2-ynoyl)piperazine-1-carboxylate (2.68),** was synthesized according to general procedure E and has been previously characterized.[28]



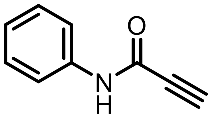
N-(3-chlorophenyl)-N-methylprop-2-ynamide (2.69), compound was prepared according to the general procedure E and was purified by silica gel chromatography (0-40% EtOAc in hexanes) and was isolated as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 3H), 7.24 – 7.16 (m, 1H), 3.32 (s, 3H), 2.86 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.6, 143.6, 142.1, 134.5, 134.4, 130.3, 130.0, 128.3, 127.4, 127.0, 125.5, 123.5, 80.8, 80.1, 75.9, 39.2, 36.3 (increased number of peaks due to amide rotamers). GCMS (EI) calculated for $[M]^+$ 193.0, found 193.1. FTIR (neat, cm^{-1}): 3235 (m), 3062 (w), 2099 (m), 1639 (s), 1591 (m), 1477 (m), 1384 (m), 1291 (m), 1135 (w), 934 (w), 777 (s), 698 (s), 619 (m), 523 (w).



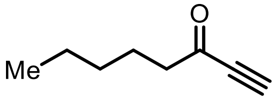
N-benzylprop-2-ynamide (2.70), was synthesized according to general procedure E and has been previously characterized.[29]



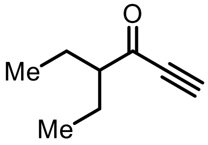
N-methoxy-N-methylprop-2-ynamide (2.71), was synthesized according to general procedure E and has been previously characterized.[28]



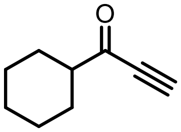
N-phenylprop-2-ynamide (2.72), was synthesized according to general procedure E and has been previously characterized.[26]



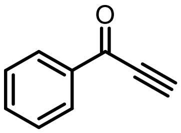
oct-1-yn-3-one (2.56), was synthesized according to general procedure G and has been previously characterized.[30]



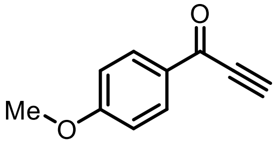
4-ethylhex-1-yn-3-one (2.73), was synthesized according to general procedure F and has been previously characterized.[31]



1-cyclohexylprop-2-yn-1-one (2.74), was synthesized according to general procedure G and has been previously characterized.[30]

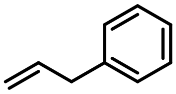


1-phenylprop-2-yn-1-one (2.75), was synthesized according to general procedure G and has been previously characterized.[30]

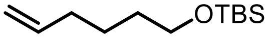


1-(4-methoxyphenyl)prop-2-yn-1-one (2.76), was synthesized according to general procedure F and has been previously characterized.[30]

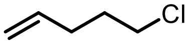
2.6.13. *Alkene Starting Materials*



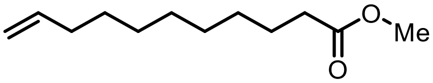
(prop-2-en-1-yl)benzene (2.77), was ordered from TCI America and vacuum distilled over calcium hydride before use.



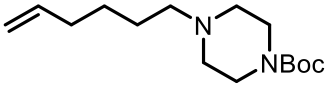
***tert*-butyl(hex-5-en-1-yloxy)dimethylsilane (2.78),** was prepared according to a known procedure and has been previously characterized.[32]



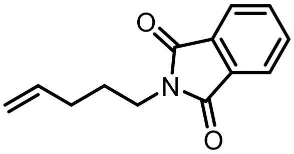
5-chloropent-1-ene (2.79), was purchased from Combi-Blocks and used without further purification.



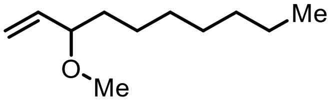
methyl undec-10-enoate (2.80), was prepared according to a known procedure and has been previously characterized.[33]



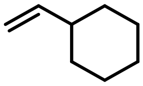
***tert*-butyl 4-(hex-5-en-1-yl)piperazine-1-carboxylate (2.81),** was synthesized according to a known procedure and has been previously characterized.[34]



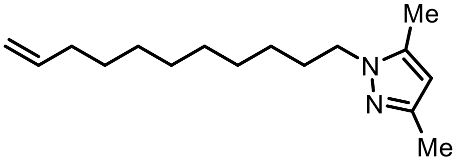
2-(pent-4-en-1-yl)-2,3-dihydro-1H-isoindole-1,3-dione (2.82), is commercially available from Enamine Building Blocks.



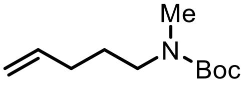
3-methoxyundec-1-ene (2.83), was prepared according to according to a modified procedure.[35] ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.64 (ddd, *J* = 17.0, 10.5, 7.8 Hz, 1H), 5.22 – 5.13 (m, 2H), 3.53 – 3.45 (m, 1H), 3.27 (s, 3H), 1.63 – 1.55 (m, 1H), 1.49 – 1.41 (m, 1H), 1.39 – 1.21 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.1, 117.0, 83.3, 56.2, 35.5, 32.0, 29.7, 29.4, 25.4, 22.8, 14.2. GCMS (EI) calculated for [M]$^+$ 170.2, found 170.2. FTIR (neat, cm^{-1}): 2925 (s), 2857 (m), 2818 (w), 1468 (w), 1096 (s), 994 (m), 921 (s), 686 (w).



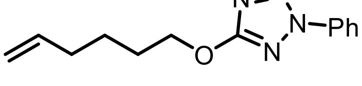
ethenylcyclohexane (2.84), was purchased from TCI America and used without further purification.



1-(dec-9-en-1-yl)-3,5-dimethyl-1H-pyrazole (2.85), compound was synthesized according to a modified procedure[34] and was isolated as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.73 (m, 2H), 5.03 – 4.89 (m, 2H), 3.92 (t, J = 7.3 Hz, 2H), 2.21 (s, 6H), 2.07 – 1.99 (m, 2H), 1.80 – 1.72 (m, 2H), 1.38 – 1.25 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9, 139.1, 138.2, 114.1, 104.6, 48.7, 33.8, 30.5, 29.4, 29.4, 29.2, 29.0, 28.9, 26.7, 13.4, 11.0. GCMS (EI) calculated for $[M]^+$ 248.2, found 248.3. FTIR (neat, cm^{-1}): 2925 (s), 2855 (m), 1555 (m), 1457 (s), 1421 (w) 1387 (w), 993 (w), 907 (m), 772 (m).

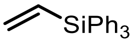


***tert*-butyl N-methyl-N-(pent-4-en-1-yl)carbamate (2.86),** is commercially available from Enamine Building Blocks.

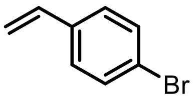


5-(hex-5-en-1-yloxy)-2-phenyl-2H-1,2,3,4-tetrazole (2.87), compound was synthesized according to a modified procedure[36] and was purified by silica gel chromatography (0-25% EtOAc in hexanes) and was isolated as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.57 – 7.50 (m, 2H), 7.48 – 7.42 (m, 1H), 5.86 – 5.72 (m, 1H), 5.11 – 4.94 (m, 2H), 4.73

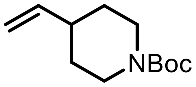
– 4.61 (m, 2H), 2.20 – 2.09 (m, 2H), 1.97 – 1.86 (m, 2H), 1.65 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 160.0, 137.7, 133.3, 129.4, 128.6, 121.2, 115.0, 73.8, 32.9, 27.9, 24.6. MS-ESI (m/z): [M+Na]$^+$ calculated for $C_{13}H_{16}N_4NaO$, 267.1; found, 267.0 FTIR (neat, cm^{-1}): 3071 (w), 2934 (w), 1569 (m), 1558 (s), 1505 (s), 1447 (m), 1383 (m), 1294 (w), 1127 (m), 993 (m), 910 (m), 755 (s), 685 (s).



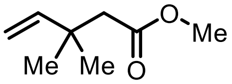
ethenyltriphenylsilane (2.88), was purchased from Combi-Blocks and used without further purification.



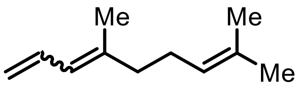
1-bromo-4-ethenylbenzene (2.89), was purchased from TCI America and vacuum distilled over calcium hydride before use.



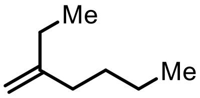
***tert*-butyl 4-ethenylpiperidine-1-carboxylate (2.90),** was purchased from Combi-Blocks and was vacuum distilled over calcium hydride before use.



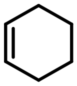
methyl 3,3-dimethylpent-4-enoate (2.91), was purchased from Combi-Blocks and was vacuum distilled over calcium hydride before use.



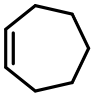
4,8-dimethylnona-1,3,7-triene (2.92), was synthesized according to a known procedure[37] from a diastereomeric mixture of citral and has been previously characterized. The dr of the product was determined to be 1.4:1 by ^{1}H NMR and GC analysis. The identity of the major and minor isomer was not determined.



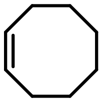
3-methylideneheptane (2.93), was purchased from Combi-Blocks used without further purification.



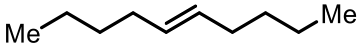
cyclohexene (2.94), was purchased from TCI America and distilled over calcium hydride before use.



cycloheptene (2.95), was purchased from TCI America and vacuum distilled over calcium hydride before use.



cyclooctene (2.96), was purchased from AK Scientific and vacuum distilled over calcium hydride before use.



(5*E*)-dec-5-ene (2.97), was purchased from Combi-Blocks and vacuum distilled over calcium hydride before use.

2.7. REFERENCES

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