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Transition Metal Catalyzed Regioselective Carbon-Carbon Bond Formation Mediated by Transfer Hydrogenation

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Transition Metal Catalyzed Regioselective Carbon-Carbon Bond Formation Mediated by Transfer Hydrogenation

by

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Dedication

To my family

Acknowledgements

Like most of my colleagues, I have encountered many challenges throughout my graduate education. Fortunately, none of these challenges proved insurmountable, largely due to the tremendous support I have received during my time at the University of Texas in Austin. I would like to thank my advisor, Professor Michael J. Krische, who has created a thriving research environment that has allowed me to flourish as a chemist and develop skills that I will refine throughout the rest of my career. I would like to thank my fellow lab members and collaborators, especially T. Patrick Montgomery and Tom Luong, for facilitating my growth as both a chemist and an individual. Lastly, I would like to express my deepest gratitude to my family, particularly Peggy Goodwin and Shrell Sam, to whom I owe much of my success.

Transition Metal Catalyzed Regioselective Carbon-Carbon Bond Formation Mediated by Transfer Hydrogenation

Brannon Sam, PhD

The University of Texas at Austin, 2015

Supervisor: Michael J. Krische

One of the more formidable challenges in the synthesis of complex organic molecules remains the efficient formation of carbon-carbon bonds. The development of a broad class of reactions to achieve this goal involves the addition of carbon based nucleophiles to carbonyl and imine compounds. Until recently, classical approaches to carbon-carbon bond formation generally required the use of stoichiometric pre-formed organometallic reagents to serve as nucleophiles, which translate into stoichiometric organometallic byproducts. In an effort to minimize nucleophile pre-activation and byproduct formation, our lab has developed efficient methods for carbonyl and imine additions *via in situ* formation of alkyl metal nucleophiles from π-unsaturates. The research reported herein describes our advances in an assortment of transition metal-catalyzed carbon-carbon bond forming reactions mediated by transfer hydrogenation, including regioselective hydrohydroxymethylation, hydrohydroxyfluoroalkylation, and hydroaminomethylation. Additionally, the investigation of regioselective carbonyl vinylation is reported.

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CHAPTER 1: CATALYTIC CARBONYL ALLYLATION EMPLOYING ALLENES AS ALLYL DONORS

1.1 Introduction

Carbonyl allylation, the addition of an allyl group to carbonyl compound, represents an invaluable tool for the generation of carbon-carbon bonds.[1] The utility of carbonyl allylation, particularly asymmetric variants, has been widely illustrated in natural products synthesis.[2] Since the seminal reports of stoichiometric triallylborane addition to aldehydes by Mikhailov and Bubnov in 1964,[3] numerous methods of carbonyl allylation have been developed based on allyl metal reagents.[4,5] Overall, these methods have proven highly effective but are limited by the need to pre-form the allyl metal reagents which reduces reaction economy. Thus, alternative approaches to carbonyl allylation have been developed, including the reduction of metallo-π-allyls from allylic alcohols, carboxylates, or halides[6,7,8,9], carbonyl-ene processes[10,11], and transition metal catalyzed hydrogenative C-C couplings employing π-unsaturates such as dienes, allenes, and allylic carboxylates or halides as allyl donors[12].

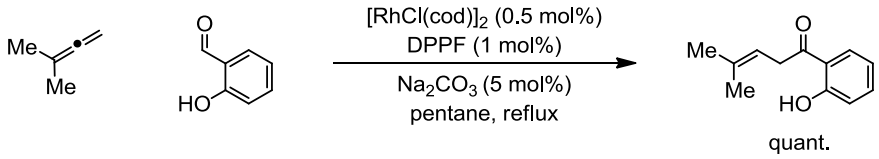
This review aims to survey metal catalyzed approaches to carbonyl allylation employing allenes as allyl donors. This report encompasses both direct and indirect methods of allenes serving as allyl donors. Additionally, applications in natural product synthesis and multi-component couplings are highlighted. Hydroformylation and hydrocarboxylation of allenes are not discussed. To discuss the field in context, the material has been partitioned into acylation reactions and divisions for alkylative, silylative, stannylative, and hydrogenative carbonyl allylations. Divisions are further partitioned if more than one transition metal facilitates the transformation.

1.2 Acylation

1.2.1 Rhodium Catalyzed Hydroacylation

One of the earliest reports on transition metal catalyzed carbonyl allylation involves the rhodium catalyzed regioselective C-C coupling of allenes and aldehydes (Scheme 1.1).[13] This process represents a formal hydroacylation, where the terminal olefin of the allene is reduced by the addition of both a hydride and acyl group, resulting in a β–γ unsaturated ketone. Whereas typical carbonyl allylation results in the formation of a homoallylic alcohol, the product of hydroacylation affords a homoallylic ketone *via* direct addition of allene to an aldehyde, which embodies a formal carbonyl allylation process.

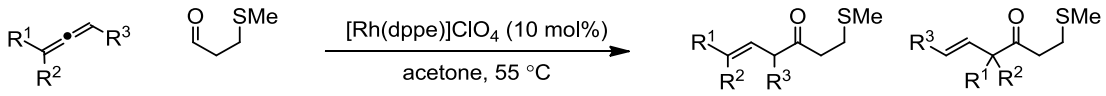
Scheme 1.1. Seminal report of allene hydroacylation.



In this seminal report by Miura and co-workers, the rhodium catalyzed regioselective C-C coupling of terminal allenes and salicylaldehydes affords β–γ unsaturated ketones in high yield (Scheme 1.1).[13] Notably, the hydroxyl group at the 2-position of salicylaldehyde was essential in the reaction as it could not be replaced with benzaldehyde, 4-hydroxybenzaldehyde, or 2-methoxybenzaldehyde. The hydroxyl was postulated to substitute the halide ligand on rhodium and act as a chelating group. Further investigation by Willis and coworkers revealed that other chelating groups, such as thioethers, were suitable in facilitating this transformation in high yield and excellent

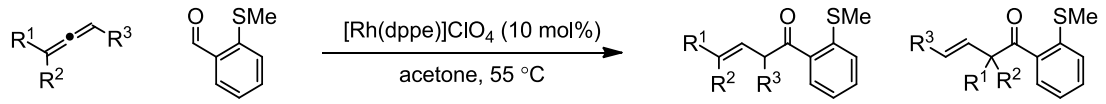
regioselectivity when the termini of the allene were markedly different in size (Tables 1.1 and 1.2).[14a,15]

Table 1.1. Selected examples of Rh catalyzed hydroacylation.



Entry	R^1	R^2	R^3	Yield	rr
1	Pent	H	H	87%	>20:1
2	Pent	H	Me	97%	1.25:1
3	Me	Me	Pent	92%	15:1
4	C_6H_5	H	Pent	89%	>20:1
5	Me	Me	C_6H_5	70%	>20:1
6	CO_2Et	H	Me	96%	>20:1

Table 1.2. Selected examples of Rh catalyzed hydroacylation.

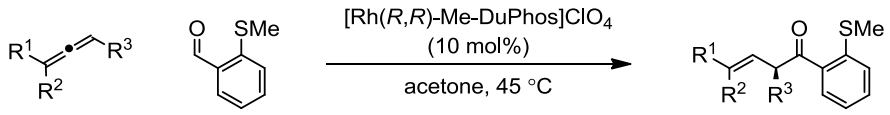


Entry	R^1	R^2	R^3	Yield	rr
1	*i*-Pr	H	Pent	98%	>20:1
2	C_6H_5	H	Me	82%	>20:1
3	C_6H_5	H	*i*-Pr	99%	12:1
4	2-furyl	H	Hex	99%	>20:1
5	C_6H_5	C_6H_5	Et	96%	>20:1
6	4-OMeC_6H_4	H	C_6H_5	32%	1.6:1

Willis et al. also reported an enantioselective protocol employing a rhodium complex, modified by the chiral diphosphine ligand, (*R*,*R*)-Me-DuPhos.[14b,15] Hydroacylation products were generated as single regioisomers, mostly in good yield and

high enantioselectivity (Table 1.3). However, the scope of the reaction was largely limited to the coupling of racemic 1,3-disubstituted allenes to 2-(methylthio)benzaldehyde (Table 1.3, entries 1-5). Attempts to couple racemic tri-substituted allenes resulted in high enantioselectivity but low yields (Table 1.3, entry 6). An enantiomerically enriched allene was also employed under the standard reaction conditions but enantioselectivity of the product remained the same as that from the racemic allene.

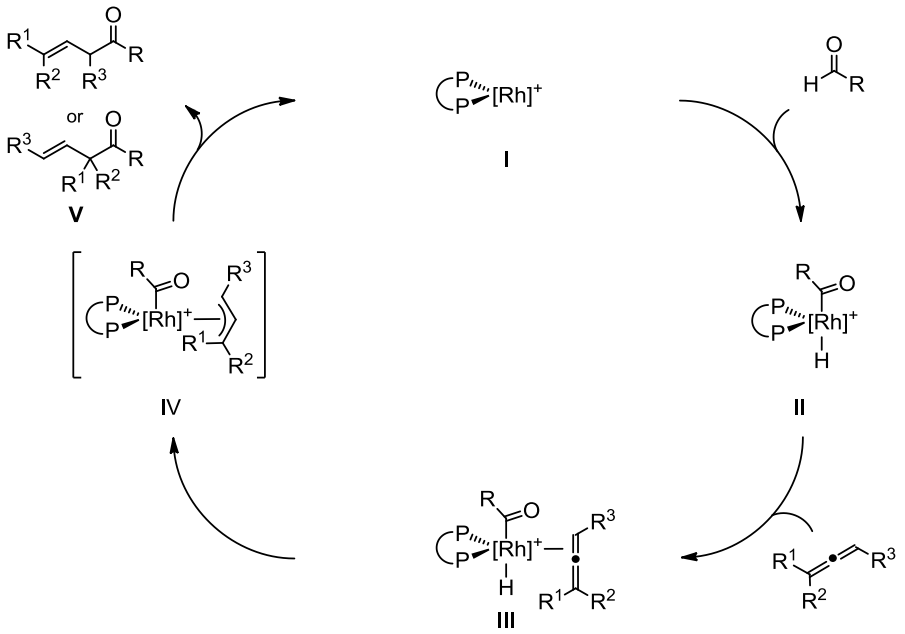
Table 1.3. Selected examples of enantioselective Rh catalyzed hydroacylation.



Entry	R^1	R^2	R^3	Yield	ee
1	C_6H_5	H	Pent	81%	92%
2	C_6H_5	H	Hex	88%	94%
3	C_6H_5	H	Et	76%	91%
4	C_6H_5	H	Me	93%	60%
5	4-$CF_3C_6H_4$	H	Hex	95%	94%
6	C_6H_5	C_6H_5	Hex	25%	94%

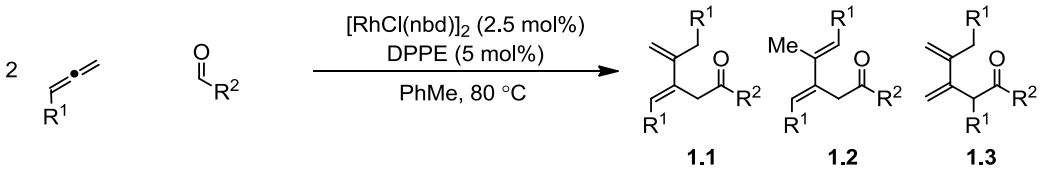
Mechanistic studies on the related rhodium catalyzed intermolecular hydroacylation of alkenes and alkynes may provide insight into allene hydroacylation.[16] The proposed catalytic cycle starts with oxidative addition of the aldehyde C-H bond to the rhodium complex, **II**. Ensuing hydrometallation of the allene affords π-allyl intermediate **IV** that undergoes reductive elimination with the acyl group to deliver the β–γ enone **V** and complete the catalytic cycle. The authors speculate that the chelating group limits decarbonylation of the aldehyde.

Scheme 1.2. Proposed mechanism for Rh catalyzed hydroacylation.



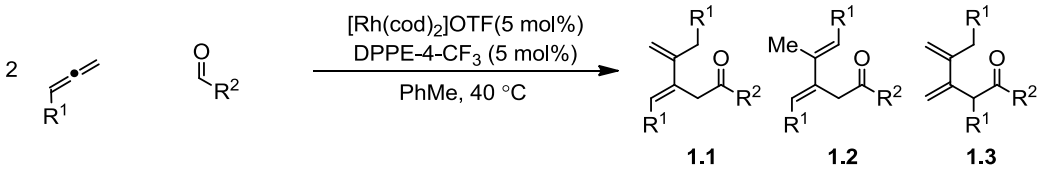
Building on the hydroacylation of allenes, Murakami et al. reported stereoselective 1:2 couplings of aldehydes and mono-substituted allenes (Tables 1.4 and 1.5).[17] Remarkably, divergent regioselectivity between the two constitutional isomers, **1.1** and **1.3**, is controlled by the counterion of the rhodium complex. Employing a neutral rhodium complex furnishes isomer **1.1**, whereas utilizing a cationic rhodium catalyst delivers isomer **1.3**. In contrast to the aforementioned 1:1 couplings of allenes and aldehydes, chelating groups are absent from the aldehyde. Mechanistic studies are inconclusive, but DFT studies by Himo and co-workers postulate that rhodium catalyzes the dimerization of two allenes followed by migratory insertion of the aldehyde and subsequent reductive elimination to deliver β–γ dialkylidene ketones.[17,18]

Table 1.4. Selected examples of enantioselective neutral Rh catalyzed hydroacylation.



Entry	R^1	R^2	Yield (1.1+1.2)	1.1/1.2/1.3
1	$(CH_2)_2C_6H_5$	C_6H_5	82%	87:7:6
2	$(CH_2)_2C_6H_5$	4-$CF_3C_6H_4$	82%	90:7:3
3	$(CH_2)_2C_6H_5$	Cy	63%	90:7:3
4	2-napthyl	Hex	75%	89:6:5
5	2-napthyl	CH_2Cy	79%	90:6:4
6	2-napthyl	$(CH_2)_4OBn$	82%	88:7:5

Table 1.5. Selected examples of enantioselective cationic Rh catalyzed hydroacylation.

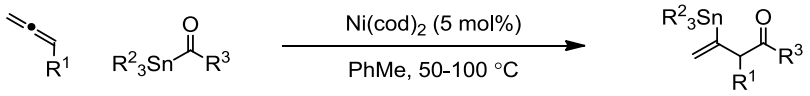


Entry	R^1	R^2	Yield (1.3)	1.1/1.2/1.3
1	$(CH_2)_2C_6H_5$	C_6H_5	67%	1:0:99
2	$(CH_2)_2C_6H_5$	4-$CF_3C_6H_4$	78%	6:0:94
3	$(CH_2)_2C_6H_5$	Cy	61%	5:0:95
4	2-napthyl	Hex	82%	3:0:97
5	2-napthyl	CH_2Cy	79%	7:0:93
6	2-napthyl	$(CH_2)_4OBn$	82%	3:0:97

1.2.2 NICKEL CATALYZED ACYLSTANNYLATION

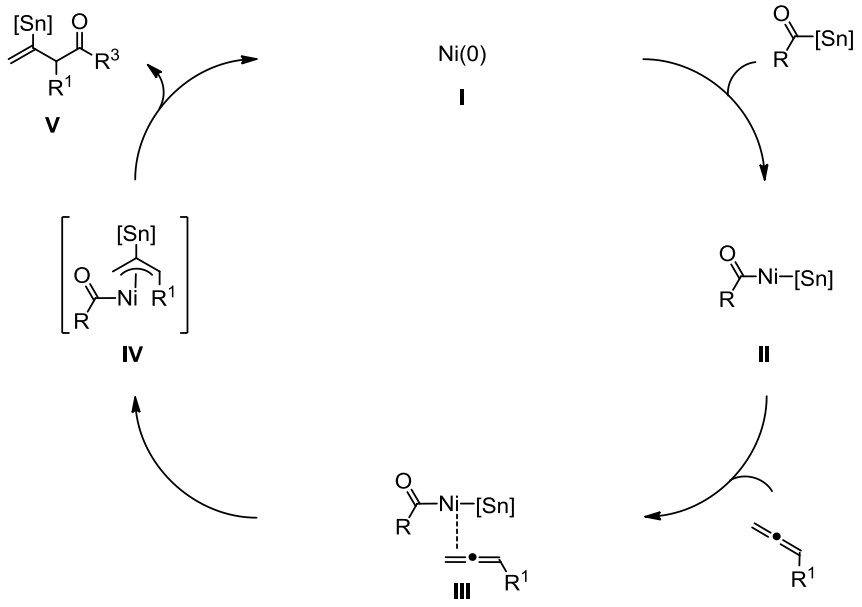
Hiyama and co-workers reported acylstannylation of allenes in the presence of a nickel catalyst.[19] Allylation products were obtained in fair yield with modest regiocontrol favoring branched selectivity (Table 1.6). Allenes with smaller substituents, such as H (Table 1.6, entry 1) and OMe (Table 1.6, entry 6), exhibited excellent levels of regioselectivity, whereas those with larger substituents displayed lower regiocontrol. Hiyama postulates that acylstannation commences with oxidative addition of nickel (0) to the acylstannane to afford intermediate **II** (Scheme 1.3). Complexation of the allene, **III**, and subsequent regioselective insertion yields π-allylnickel intermediate **IV**. Reductive elimination furnishes the desired product **V** and regenerates the nickel (0) catalyst.

Table 1.6. Selected examples of Ni catalyzed acylstannylation.



Entry	R^1	R^2	R^3	Yield	rr
1	H	Me	C_6H_5	64%	97:3
2	H	Bu	C_6H_5	48%	79:21
3	*t*-Bu	Me	C_6H_5	59%	86:14
4	4-OMeC_6H_4	Me	C_6H_5	50%	78:22
5	C_6H_5	Bu	Et	43%	79:21
6	OMe	Bu	Et	48%	95:5

Scheme 1.3. Plausible mechanism for Ni catalyzed hydrostannylation.



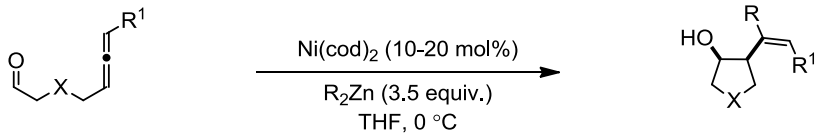
1.3 Alkylative Carbonyl Allylation

1.3.1 NICKEL CATALYZED ALKYLATIVE C-C COUPLING

In the course of developing related nickel catalyzed three component couplings of alkynes, aldehydes, and organozinc reagents,[20,21] Montgomery et al. discovered that a similar catalytic system could be employed to stereoselectively couple allenes and aldehydes.[22a,b] Initial studies involved intramolecular couplings of allenyl-aldehydes in which an organozinc is introduced during the cyclization, affording homoallylic alcohols in good yields and mostly excellent diastereoselectivity as single regioisomers (Table 1.7).[22b] Similar findings were also reported by Kang and co-workers.[22c] As observed with the related alkyne-aldehyde couplings,[20,21] alkyl zinc reagents, both commercial and *in situ* generated from alkyl lithium reagents and zinc chloride, serve as reductants.

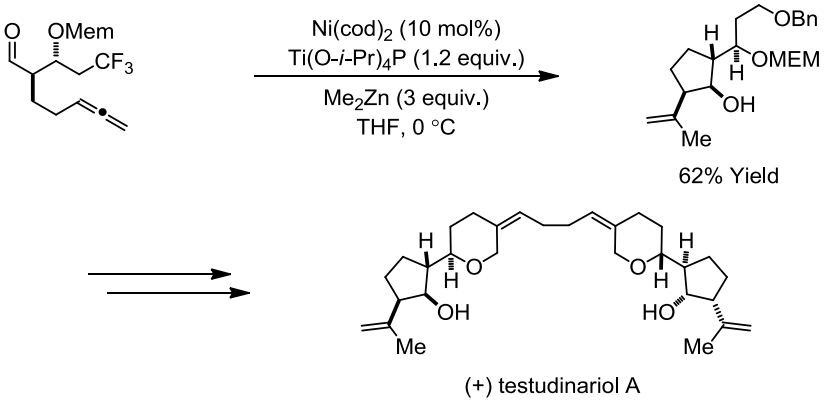
Montgomery illustrated the utility of this cyclization method as the key step in the total synthesis of testudinariol A (Scheme 1.4).[22c]

Table 1.7. Selected examples of stereoselective Ni catalyzed allene-aldehyde cyclizations.



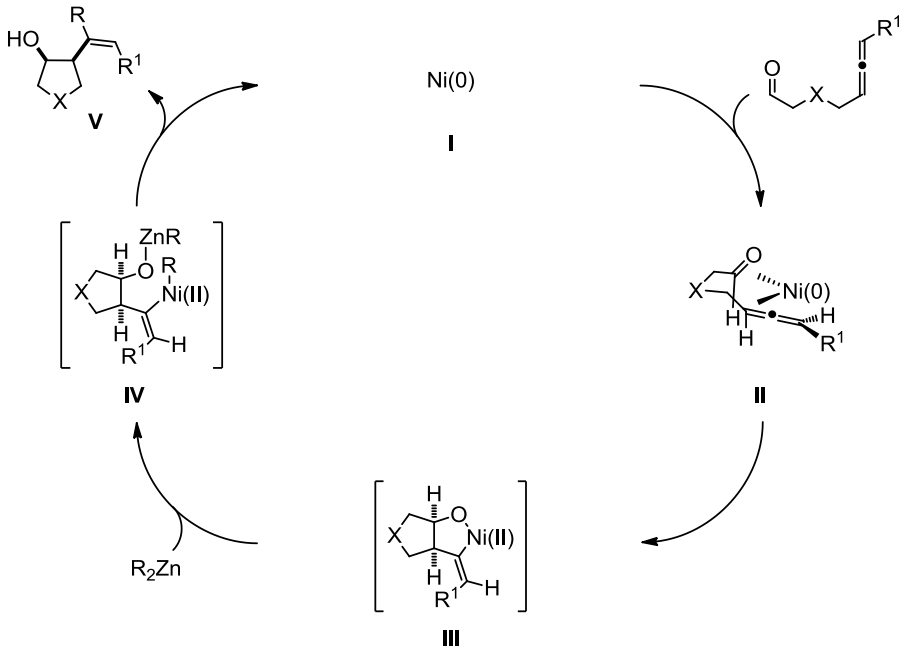
Entry	X	R^1	ZnR_2	Yield	Stereoselectivity
1	NTs	H	$ZnMe_2$	70%	>97:3 dr
2	NTs	H	$ZnEt_2$	64%	>97:3 dr
3	NTs	H	BuLi / $ZnCl_2$	52%	75:25 dr
4	CH_2	H	MeLi / $ZnCl_2$	69%	>97:3 dr
5	CH_2	C_6H_5	MeLi / $ZnCl_2$	71%	>97:3 (*cis*:*trans*) >97:3 (*Z*:*E*)
6	CH_2	Me	MeLi / $ZnCl_2$	77%	>97:3 (*cis*:*trans*) 80:20 (*Z*:*E*)

Scheme 1.4. Key step employing Ni catalyzed allene-aldehyde coupling in the enantioselective total synthesis of (+)-testudinariol.

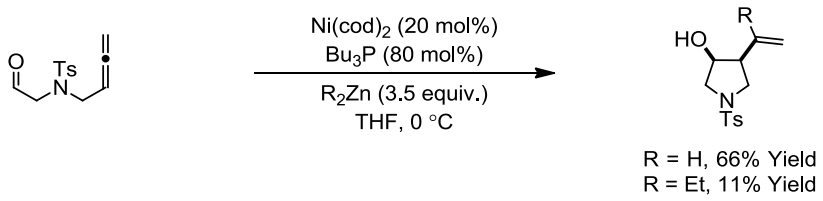


Although several potential mechanisms may explain the alkylative cyclization, the authors favor a three-component coupling involving nickel metallacycles (Scheme 1.5). The postulated mechanism begins with complexation of the allenyl-aldehyde by the nickel catalyst, **II**. Then oxidative cyclization of the internal allenyl olefin, aldehyde, and nickel (0) complex, **III**. Transmetallation of the resulting metallacycle with an organozinc reagent cleaves the Ni-O bond, **IV**. Subsequent reductive elimination furnishes the product of carbonyl allylation **V** and completes the catalytic cycle. Interestingly, a cyclization conducted with diethyl zinc as reductant in the presence of basic phosphine ligand, Bu_3P, was found to proceed largely in the absence of alkylation (Scheme 1.6). Thus, phosphine ligand may promote β-hydride elimination for alky groups of the organozinc reagents possessing β-hydrogens during the transmetallation to the nickel center.

Scheme 1.5. Proposed mechanism for stereoselective Ni catalyzed alkylative allenyl-aldehyde cyclization.

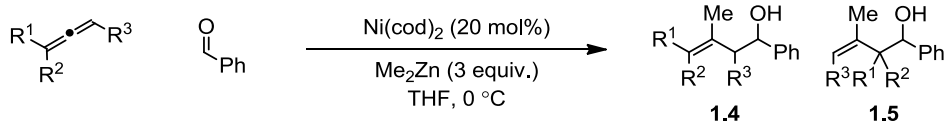


Scheme 1.6. Stereoselective Ni catalyzed allene-aldehyde cyclization in the presence of Bu_3P as ligand.



A subsequent study by Montgomery revealed that an intermolecular variant was attainable but with decreased yields and regioselectivity (Table 1.8).[22d] In contrast to the intermolecular nickel catalyzed allene-aldehyde couplings reported by Jamison,[23] where C-C coupling occurs at the center, sp-hybridized carbon of the allene to produce an allylic alcohol, these intermolecular couplings by Montgomery favor C-C coupling at sp^2-hybridized carbons of the termini of the allene to generate a homoallylic alcohol.

Table 1.8. Selected examples of intermolecular Ni catalyzed alkylative allene-aldehyde couplings.

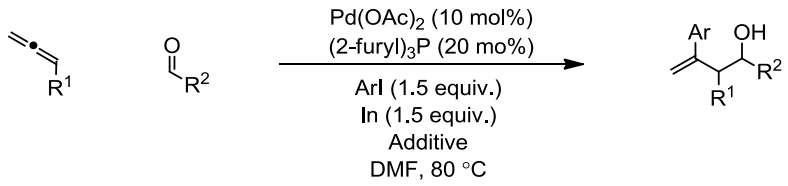


Entry	R^1	R^2	R^3	Yield (1.4)	Yield (1.5)
1	C_6H_5	H	H	21%	60% (7:3 dr)
2	Me	Me	H	67%	-
3	C_6H_5	Me	H	35%	36% (4:1 dr)
4	Me	Me	CO_2Et	66% (19:1 dr)	-

1.3.2 PALLADIUM CATALYZED ARYLATIVE ALLYLATION

In 2000, a palladium-indium mediated Barbier-type allylation of aldehydes with allenes was reported by Grigg et al.[24] In these seminal reports of palladium catalyzed alkylative carbonyl allylation employing an allene, homoallylic alcohols were generated in modest yield and complete regiocontrol from aryl iodides, allenes, and carbonyl compounds.[24a,b] Subsequent studies into additive effects by Grigg and co-workers revealed that piperdine (1 equiv.) or CuI (20 mol%) may improve yields while shortening reaction times (Table 1.9).[25] Further studies expanded the scope of carbonyl compounds to include cyclic ketones, α-β unsaturated aldehydes, and allenyl-carbonyls.[26]

Table 1.9. Selected examples of intermolecular Pd-In mediated arylative allene-aldehyde couplings.

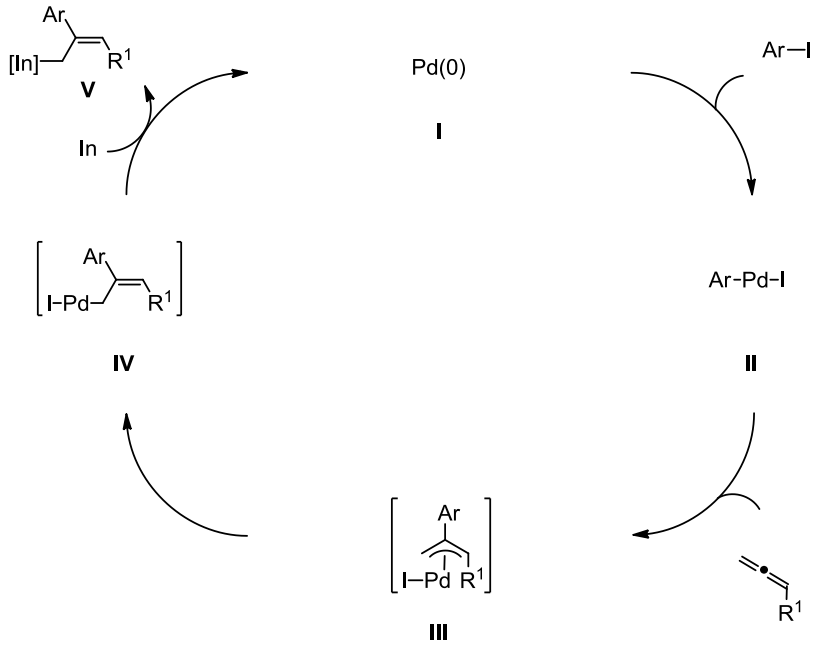


Entry	R^1	R^2	Ar	Additive	Yield
1	H	C_6H_5	C_6H_5	-	43%
2	H	C_6H_5	C_6H_5	Piperdine	83%
3	H	4-$OMeC_6H_4$	2-$OMeC_6H_4$	-	60%
4	H	4-$OMeC_6H_4$	2-$OMeC_6H_4$	Piperdine	89%
5	CH_2NPhth	4-$OMeC_6H_4$	2-thienyl	Piperdine	53% (38:62 dr)
6	CH_2NPhth	4-$CO_2MeC_6H_4$	4-MeC_6H_4	CuI	77% (43:57 dr)

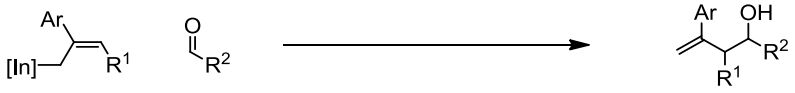
Grigg postulates that the initial π-allylpalladium intermediate **III** is formed *via* oxidative addition of Pd(0) to the aryl halide, **II**, followed by regioselective insertion of the allene (Scheme 1.7). Subsequent isomerization to the σ-allylhaptomer **IV** and

reductive transmetallation involving indium produces the allylindium species **V** and regenerates the palladium (0) catalyst. Lastly, the nucleophilic allylindium species adds to the carbonyl group affording the homoallylic alcohol (Scheme 1.8).

Scheme 1.7. Proposed mechanism for Pd catalyzed generation of allylindium species from allenes.



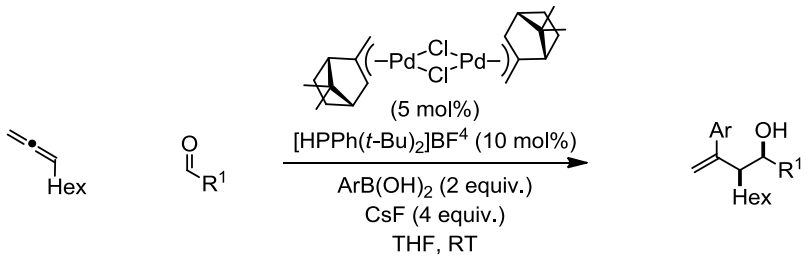
Scheme 1.8. Proposed carbonyl allylation via allylindium species.



Ensuing investigations by Malinakova and Hopkins led to the development of a stereoselective variant of palladium catalyzed arylative coupling of allenes and aldehydes.[27] In contrast to prior reports of Pd-In mediated Barbier-type allylations,[24-26] arylboronic acids were utilized in lieu of aryl iodides and indium. Homoallylic alcohols

were generated in good yield and moderate diastereoselectivity towards the *syn*-isomer (Table 1.10). Additional investigations by Yu and Lu expanded the scope of this transformation to include aldehyde tethered arylboronic acids as coupling partners to furnish cyclic homoallylic alcohols.[28]

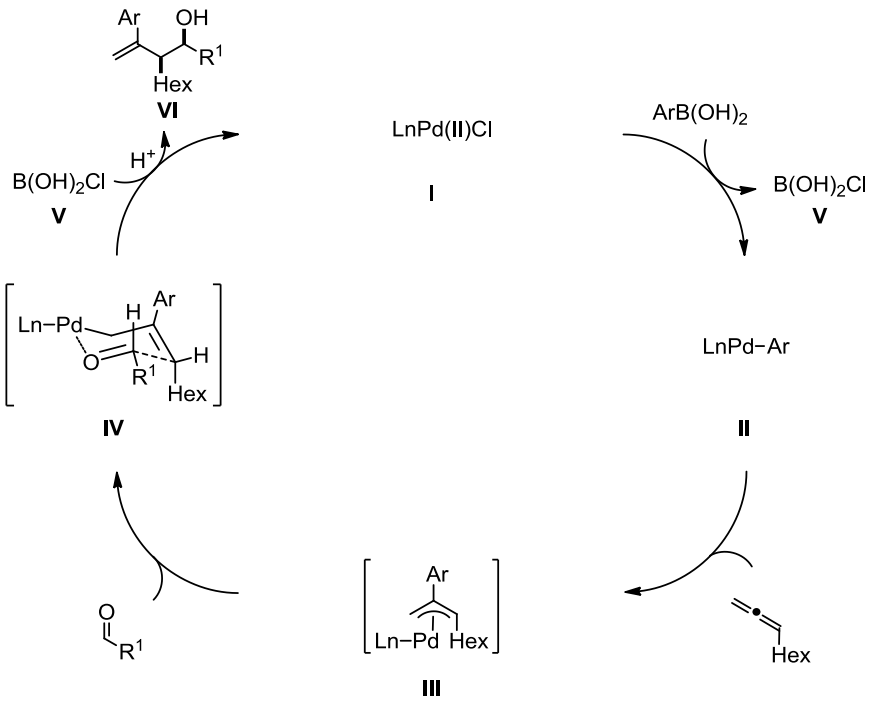
Table 1.10. Selected examples of Pd catalyzed arylative couplings of allenes and aldehydes.



Entry	R^1	Ar	Yield	dr
1	C_6H_5	4-$OMeC_6H_4$	76%	5.3:1
2	4-$NO_2C_6H_4$	4-$OMeC_6H_4$	85%	1.9:1
3	3-pyridil	4-$OMeC_6H_4$	71%	8.1:1
4	2-furanyl	4-$OMeC_6H_4$	76%	4.4:1
5	4-$OMeC_6H_4$	4-$OMeC_6H_4$	54%	32:1
6	*c*-Hex	4-$OMeC_6H_4$	46%	3:1

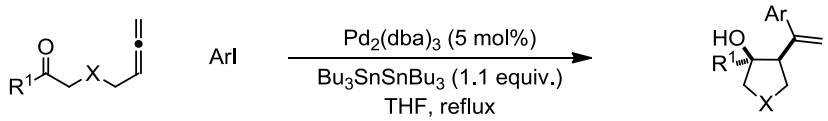
A plausible mechanism begins with the transmetallation of palladium complex **I** with boronic acid to give intermediate **II** (Scheme 1.9). Regioselective insertion of the allene into intermediate **II** generates π-allylpalladium intermediate **III**. Subsequent carbonyl addition *via* a six-membered chairlike transition state, **IV**, and alkoxide exchange with **V** delivers the *syn*-selective homoallylic alcohol **VI** upon isolation and regenerates the palladium catalyst.

Scheme 1.9. Plausible mechanism for Pd catalyzed arylative couplings of allenes and aldehydes.



Kang and Ha reported a palladium catalyzed arylative cyclization of allenyl-aldehydes and ketones with aryl iodides and hexa-*n*-butyldistannane.[29] Prior reports of palladium (0) catalyzed carbostannylation of allenes generating aryl-substituted allylstannanes[30] inspired investigation into arylative cyclization of allenyl-aldehydes. As a result of tandem allene carbostannylation and carbonyl allylation, cyclopentanols were obtained in good yield but with low diastereoselectivity, slightly favoring the *cis*-isomer (Table 1.11).

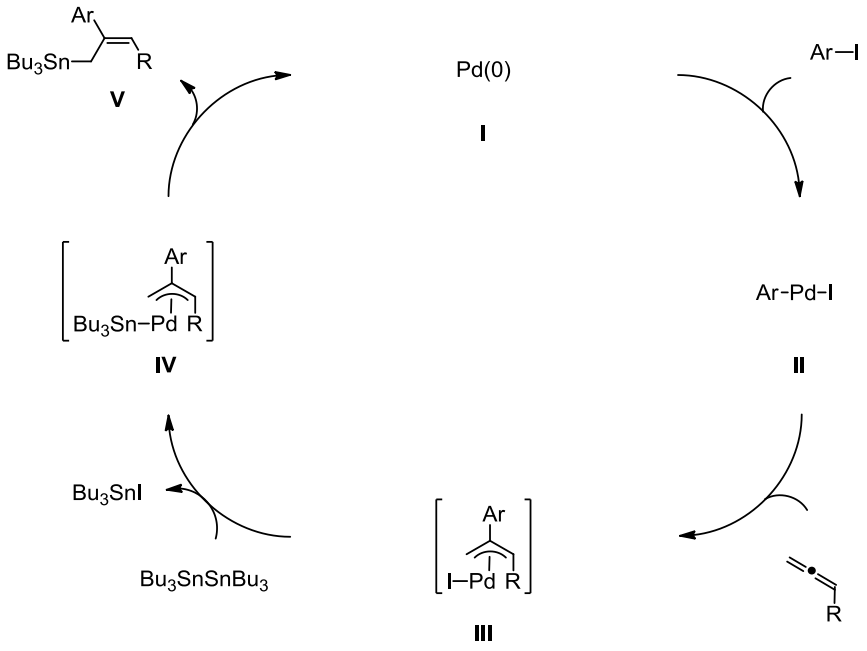
Table 1.11. Selected examples of Pd catalyzed arylative cyclizations of allenyl-aldehydes.



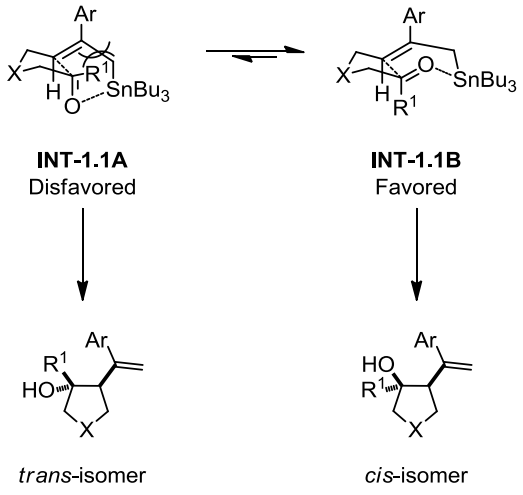
Entry	R^1	X	Ar	Yield	dr
1	H	NTs	C_6H_5	75%	53:22
2	H	NTs	4-$OMeC_6H_4$	86%	59:27
3	H	NTs	2-thienyl	87%	63:24
4	H	$C(CO_2Et)_2$	C_6H_5	91%	62:29
5	Me	NTs	4-$OMeC_6H_4$	83%	78:5
6	Me	$C(CO_2Et)_2$	2-thienyl	94%	>99:1

The catalytic reaction may proceed *via* two separated parts: carbostannylation and carbonyl allylation (Schemes 1.10 and 1.11, respectively). First, the aryl iodide undergoes oxidation addition with palladium (0) complex **I** to give a palladium (II) intermediate **II** (Scheme 1.10). Subsequent insertion of the allene into this palladium (II) intermediate delivers a π-allylpalladium intermediate **III**. Transmetallation of intermediate **III** with hexa-*n*-butyldistannane generates intermediate π-allylpalladium intermediate **IV**. Regioselective reductive elimination affords allylstannane **V** and regenerates the palladium (0) catalyst. Lastly, the *in situ* generated allylstannane proceeds with carbonyl additional via a six-membered chairlike transition state, **INT-1.1B**, to deliver the *cis*-selective cyclopentanol (Scheme 1.11).

Scheme 1.10. Proposed mechanism for Pd catalyzed arylstannation of allenes.



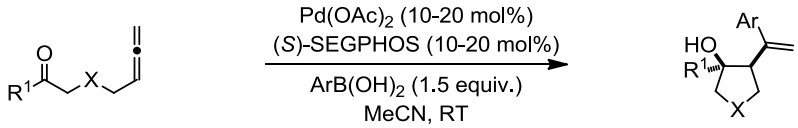
Scheme 1.11. Rationale for stereochemistry in the Pd catalyzed carbocyclization of allenyl-carbonyls.



Tsukamoto et al. subsequently reported an asymmetric variant for the Pd catalyzed arylative cyclizations of allenyl-aldehydes.[31] By employing chiral diphosphine

ligand (*S*)-SEGPHOS and arylboronic acids in lieu of aryl iodides and toxic distannanes, diastereomerically pure *cis*-fused five and six-membered cyclic homoallylic alcohols were afforded in good yield and mostly excellent enantioselectivity (Table 1.12). Notably, allenyl-ketones exhibited lower enantioselectivity than allenyl-aldehydes, suggesting that more sterically encumbered systems hinder asymmetric induction.

Table 1.12. Selected examples of enantioselective Pd catalyzed arylative cyclizations of allenyl-aldehydes.

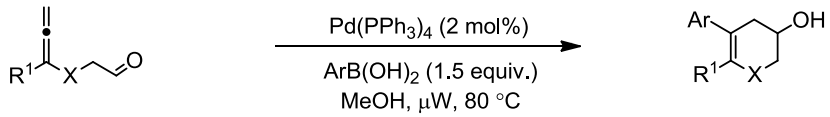


Entry	R^1	X	Ar	*n*	Yield	ee
1	H	NTs	C_6H_5	1	90%	95%
2	H	NTs	2-thienyl	1	85%	89%
3	Me	NTs	4-AcC_6H_4	1	79%	51%
4	H	NTs	4-AcC_6H_4	2	99%	99%
5	H	O	4-AcC_6H_4	1	76%	96%
6	H	$C(CO_2Et)_2$	4-AcC_6H_4	1	74%	96%

In a separate report, Tuskamoto et al. describes the synthesis of 3-substituted-3-cycloalken1-ols from microwave-assisted palladium (0) catalyzed alrylative cyclization of allenyl-aldehydes (Table 1.13).[32] Interestingly, this protocol generates *endo*-olefin containing cyclic compounds in contrast to the aforementioned reports which afford *exo*-olefins. In contrast to the carbopalladation mechanism proposed for the exo-olefin containing products, Tuskamoto proposes an "anti-Wacker"-type cyclization[33]. Microwave irradiation served a critical role in the suppression of an acyclic γ-δ

unsaturated ketone side-product formed via hydroarylation of the starting allenyl-aldehyde.

Table 1.13. Selected examples of Pd catalyzed arylative cyclizations of allenyl-aldehydes affording *endo*-olefin adducts.

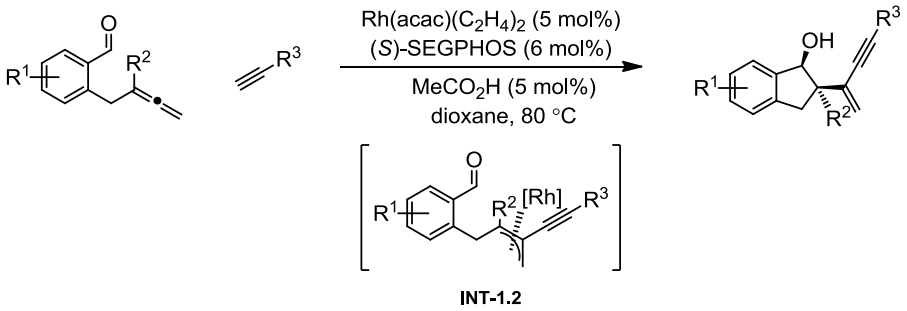


Entry	R^1	X	Ar	Yield
1	H	Me_2C	C_6H_5	84%
2	H	Me_2C	2-furyl	94%
3	H	Me_2C	4-$OMeC_6H_4$	quant.
4	Me	Me_2C	4-$OMeC_6H_4$	89%
5	H	CH_2	4-$OMeC_6H_4$	78%
6	Me	Me_2C	4-$OMeC_6H_4$	72%

1.3.3 Rhodium Catalyzed Alkynylative Carbocyclization

More recently, Hayashi et al. developed an enantioselective rhodium catalyzed alkynylative cyclization of allenyl-aldehydes.[34] In the presence of a chirally-modified rhodium (I) complex, coupling of terminal alkynes to allenyl-aldehydes delivered *cis*-indanol derivatives in good yield and excellent enantiomeric excess (Table 1.14). The reaction is postulated to proceed with tandem allene-alkyne coupling[35] and carbonyl allylation through intermediate **INT-1.2**.

Table 1.14. Selected examples of Rh catalyzed alkynylative cyclizations of allenyl-aldehydes.



INT-1.2

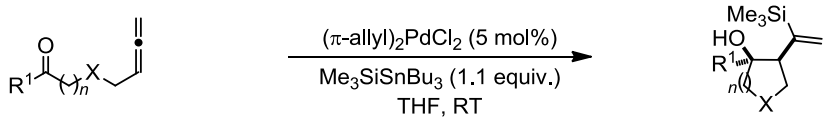
Entry	R^1	R^2	R^3	Yield	ee
1	H	H	$SiPh_3$	80%	99%
2	5-OMe	H	$SiPh_3$	80%	97%
3	4-OMe	H	$SiPh_3$	62%	99%
4	H	Me	$SiPh_3$	76% (3:1 dr)	81% (43%)
5	H	H	C_6H_5	50%	98%
6	H	H	1-napthyl	64%	98%

1.4 Silylative Carbonyl Allylation

1.4.1 Palladium Catalyzed Silylative Allylation

In 2002, a palladium catalyzed silylative carbocyclization of allenyl-aldehydes and ketones was reported by Kang and co-workers.[36] Previous reports of both, the palladium catalyzed silastannylation of allenes[37] and the palladium or platinum catalyzed addition of allylstannanes to aldehydes[38], inspired the tandem sequence. Diastereomerically pure *cis*-cyclopentanols and cyclohexanols were obtained in good yield as a result of tandem silastannylation employing trimethylsilyl-tributylstannane ($Me_3SiSnBu_3$) and allyl addition of allenyl-carbonyls (Table 1.15).

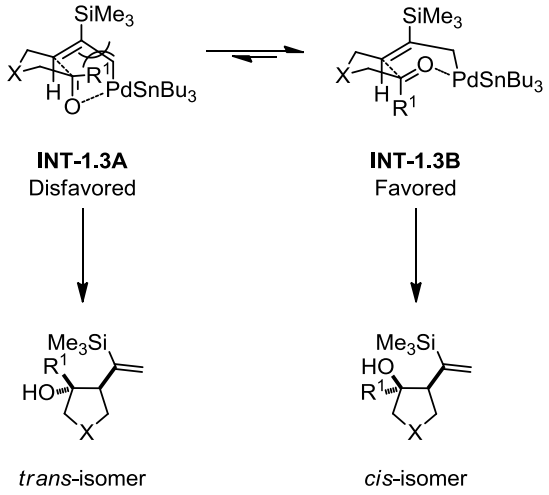
Table 1.15. Selected examples of Rh catalyzed silylative cyclizations of allenyl-aldehydes.



Entry	R^1	X	*n*	Yield
1	H	NTs	1	71%
2	H	$C(CO_2Et)_2$	1	66%
3	Me	NTs	1	68%
4	H	NTs	2	62%
5	H	O	2	68%
6	Me	$C(CO_2Et)_2$	2	65%

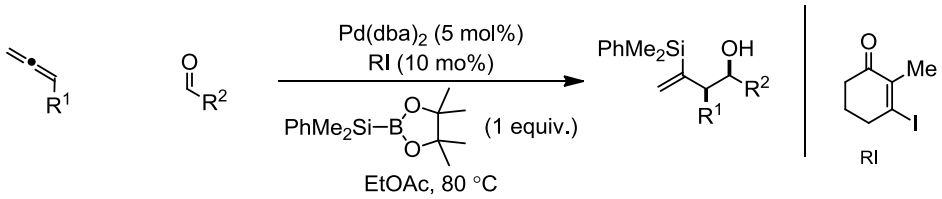
Although the mechanism has yet to be elucidated, it is presumed that $Me_3SiPdSnBu_3$ is formed *via* oxidation addition to the palladium catalyst. Subsequent insertion of the allene into $Me_3SiPdSnBu_3$ yields a π-allylpalladium complex that undergoes intramolecular carbonyl addition to furnish the *cis*-cycloalkanol. The *cis*-selectivity may arise from the energetic differences in the transition states, where **INT-1.3B** is energetically more stable than **INT-1.3A**, based on steric hindrance between the TMS and R^1 groups (Scheme 1.12).

Scheme 1.12. Rationale for stereochemistry in the Pd catalyzed silylative carbocyclization of allenyl-carbonyls.



Following Kang's report, Cheng published a one-pot protocol for the stereoselective synthesis of homoallylic alcohols via carbonyl addition of 2-silylboronates generated *in situ* from the palladium catalyzed silaboration of allenes.[39] Treatment of monosubstituted alky and aryl allenes with stoichiometric 2-(dimethylphenylsilanyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane in the presence of catalytic $Pd(dba)_2$ and an alkenyl iodide delivered the *syn*-selective branched allylation products in good yield and excellent diastereoselectivity (Table 1.16). One advantage to this methodology is that it does not require an external Lewis acid, such as $AlCl_3$, BF_3•OEt_2, or $Sc(OTf)_3$, in contrast to most allylation of aldehydes employing allylboronates.[40,41]

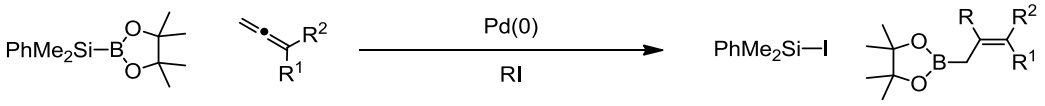
Table 1.16. Selected examples of intermolecular Pd catalyzed silylative allene-aldehyde couplings.



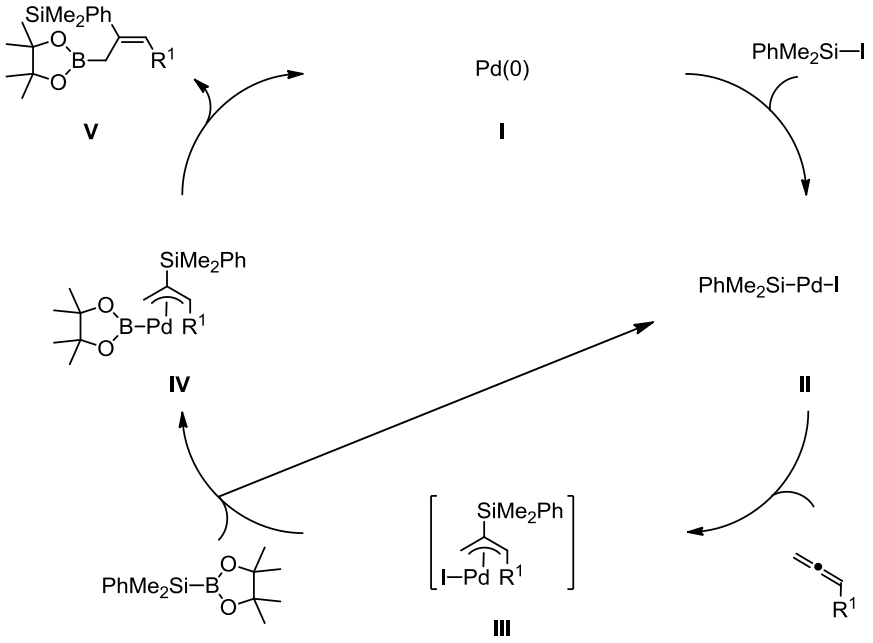
Entry	R^1	R^2	Yield	dr
1	C_6H_5	C_6H_5	96%	>99:1
2	C_6H_5	2-thienyl	74%	>99:1
3	C_6H_5	Pent	67%	>99:1
4	*n*-Bu	C_6H_5	92%	95:5
5	*c*-Hex	C_6H_5	75%	93:7
6	*c*-Pent	C_6H_5	85%	93:7

The catalytic reaction is postulated to proceed *via* three separated parts. First, the alkenyl iodide may serve as an initiator, reacting with allene and borysilane to afford a silyl iodide (Scheme 1.13). The resulting silyl iodide undergoes oxidation addition with the palladium (0) complex **I** to give a palladium (II) intermediate **II** (Scheme 1.14). Subsequent insertion of the allene into this palladium (II) intermediate delivers a π-allylpalladium intermediate **III**. Transmetallation of intermediate **III** with borylsilane regenerates intermediate **II** and furnishes π-allylpalladium intermediate **IV**. Regioselective reductive elimination affords allylborate **V** and regenerates the palladium (0) catalyst. Lastly, the *in situ* generated allylborate may proceed with carbonyl additional via a six-membered chairlike transition state to deliver the *syn*-selective homoallylic alcohol (Scheme 1.15).

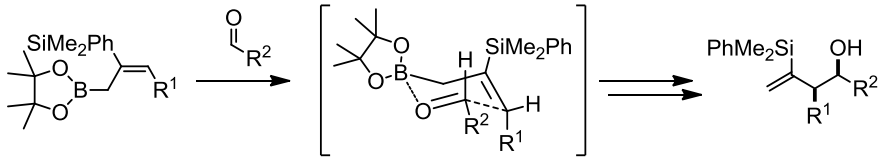
Scheme 1.13. Generation of silyl-iodide from silylborolane.



Scheme 1.14. Proposed mechanism for the Pd catalyzed silaboration of allenes.



Scheme 1.15. Proposed stereoselective carbonyl allylation via allyborate addition.

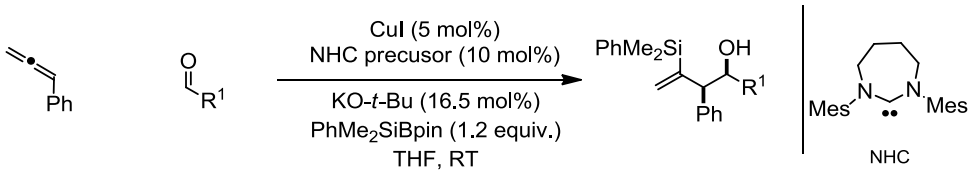


1.4.2 COPPER CATALYZED SILYLATIVE C-C COUPLING

Following Cheng's seminal work on palladium catalyzed silylative stereoselective carbonyl allylations employing allenes,[39] Procter reported a copper (I)-*N*-heterocyclic carbene catalyzed variant, citing cost efficiency and reduced toxicity of the transition

metal catalyst as inspiration.[42] Under Cu catalysis, phenylallene was converted into *syn*-selective homoallylic alcohols in good yields in modest to excellent diastereoselectivity (Table 1.17). Notably, the stereoselectivity of these Cu-NHC catalyzed transformations are generally not as high as those reported under Pd catalysis[39]. In addition, the authors postulated that carbonyl addition proceeds through an allyl copper intermediate rather than an allyborate as proposed by Cheng[39].

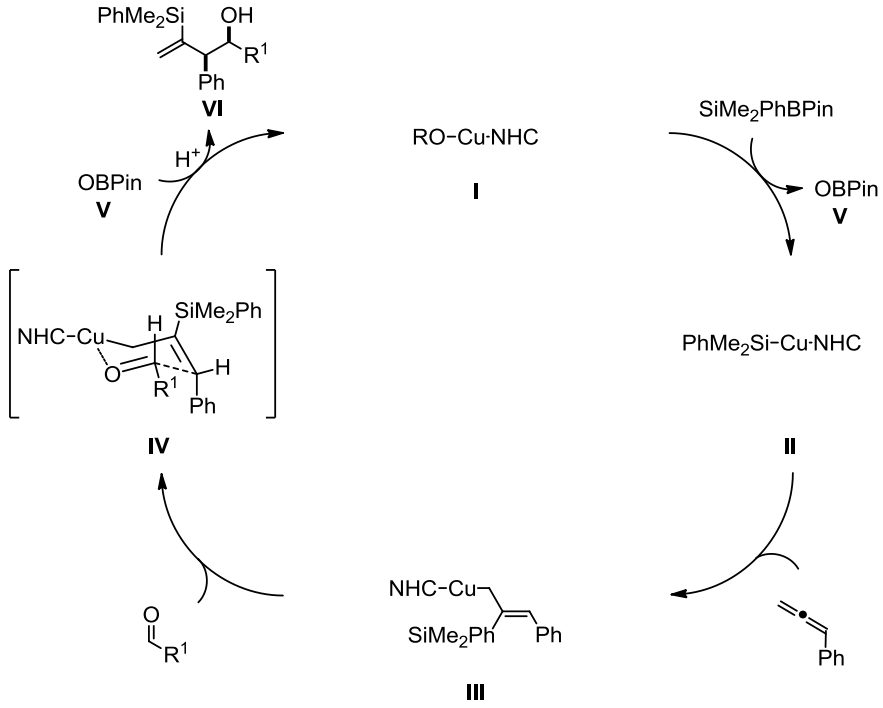
Table 1.17. Selected examples of intermolecular Cu-NHC catalyzed silylative allene-aldehyde couplings.



Entry	R^1	Yield	dr
1	C_6H_5	78%	88:12
2	2,4,6-$Me_3C_6H_2$	68%	>98:2
3	$(CH_2)_2C_6H_5$	67%	89:11
4	Et	86%	95:5
5	*c*-Hex	60%	>98:2
6	*c*-Pr	56%	91:9

The postulated mechanism begins with the formation of the ligated copper alkoxide **I** (Scheme 1.16). Subsequent transmetallation of intermediate **I** with the silylborane yields copper-silyl intermediate **II**. Regioselective insertion of the allene affords allylcopper intermediate **III** which undergoes carbonyl addition *via* a six-membered chairlike transition state and alkoxide exchange with **V** to complete the catalytic cycle and deliver the *syn*-selective homoallylic alcohol **VI** upon isolation.

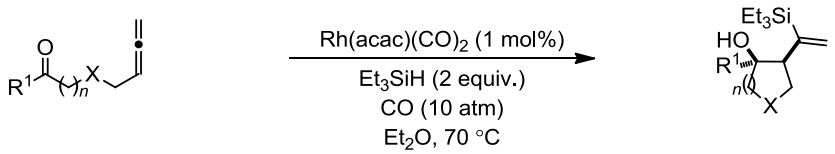
Scheme 1.16. Proposed mechanism for the Cu catalyzed silylative carbonyl allylation.



1.4.3 RHODIUM CATALYZED HYDROSILYLATION

Yu and co-workers reported a rhodium catalyzed silylative cyclization of allenyl aldehydes and ketones.[43] Homoallylic alcohols within five and six-membered rings are obtained in modest yields as single diastereomers (*syn*-isomers) upon treatment of variety of allenyl carbonyl compounds in the presence of triethylsilane, carbon monoxide, and a rhodium catalyst (Table 1.18). Interestingly, these reactions required an atmosphere of CO, presumably due to the facile regeneration of catalyst. Even at low pressures (1 atm) of CO, the reaction did not proceed. Although mechanistic studies were not performed, the authors postulated that a hydrometallative pathway, where the insertion of rhodium into triethylsilane generates the initial metal hydride, may be in operation.

Table 1.18. Selected examples of Rh catalyzed silylative carbocyclization of allenyl-aldehydes or ketones.

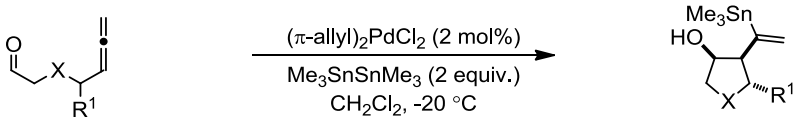


Entry	R^1	X	*n*	Yield
1	H	NTs	1	74%
2	H	$C(CO_2Et)_2$	1	68%
3	H	O	2	68%
4	H	NTs	2	61%
5	Et	NTs	2	56%
6	Me	$C(CO_2Et)_2$	2	56%

1.5 Stannylative Carbonyl Allylation

Palladium catalyzed stannylcarbocyclizations of allenyl-aldehydes was reported by Yu and co-workers.[44] Stereoselective protocols for the synthesis of exclusively *cis*- or *trans*-stereoisomers in high yield were developed (Table 1.19 and Table 1.20). Adaptation of the aforementioned silylative carbocyclization of allenyl-carbonyls by Kang,[36] where substitution of the trimethylsilylstannane with hexamethylditin ($Me_3SnSnMe_3$), led to *cis*-selective stannylcarbocyclizations of allenyl-aldehydes (Table 1.19).

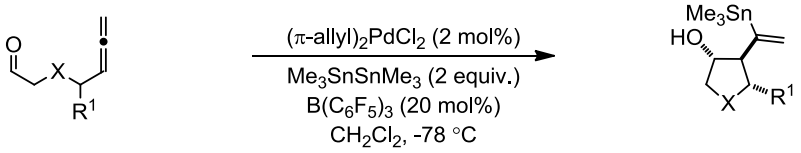
Table 1.19. Pd catalyzed stannylcarbocyclizations of allenyl-aldehydes affording *cis*-isomers.



Entry	R^1	X	Yield
1	H	NTs	91%
2	H	$C(CO_2Et)_2$	78%
3	H	O	77%
4	Me	NTs	81%
5	$(CH_2)_2C_6H_5$	NTs	86%

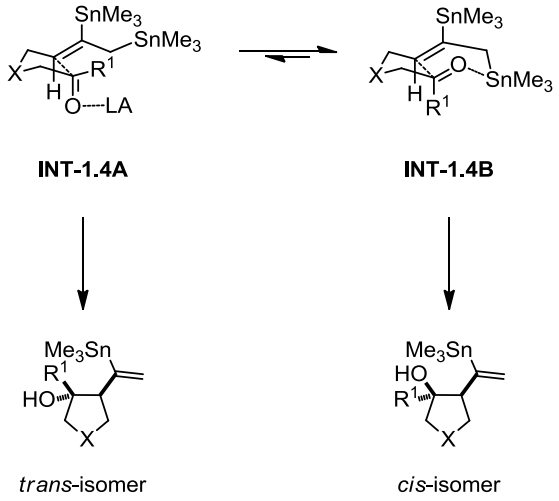
Interestingly, the addition of Lewis acid co-catalyst induced stereoselective formation of the *trans*-isomer (Table 1.20). The Lewis acid was postulated to reverse the π-facial selectivity based on an open-chained arrangement for the allylic transfer, **INT-1.4A**, whereas the closed structure **INT-1.4B** delivered the typical *cis*-adduct (Scheme 1.17).

Table 1.20. Pd catalyzed stannylcarbocyclizations of allenyl-aldehydes affording *trans*-isomers.



Entry	R^1	X	Yield
1	H	NTs	81%
2	H	$C(CO_2Et)_2$	71%
3	H	O	63%
4	Me	NTs	83%
5	$(CH_2)_2C_6H_5$	NTs	81%

Scheme 1.17. Rationale for stereochemistry in the Pd catalyzed stannylcarbocyclizations of allenyl-aldehydes.

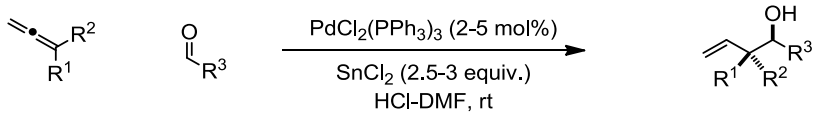


1.6 Hydrogenative Allylation

1.6.1 Palladium Catalyzed Hydrostannylation

In 2000, Cheng and Chang reported a highly regio- and stereoselective protocol for the palladium catalyzed allylation of aldehydes employing allenes.[45] In the presence of tin (II) chloride, hydrochloric acid, and $(PPh_3)_2PdCl_2$ as catalyst, allenes undergoes hydrostannylation to furnish nucleophilic allyltrichlorotins that add to carbonyl compounds affording branched products of carbonyl allylation in modest yields and complete regiocontrol. Larger substituents, such as aryl and cyclohexyl groups, on the allenes (Table 1.21, entries 4 and 5) displayed higher diastereoselectivity (*anti*) compared to linear alkyl-substituted allenes (Table 1.21, entry 6).

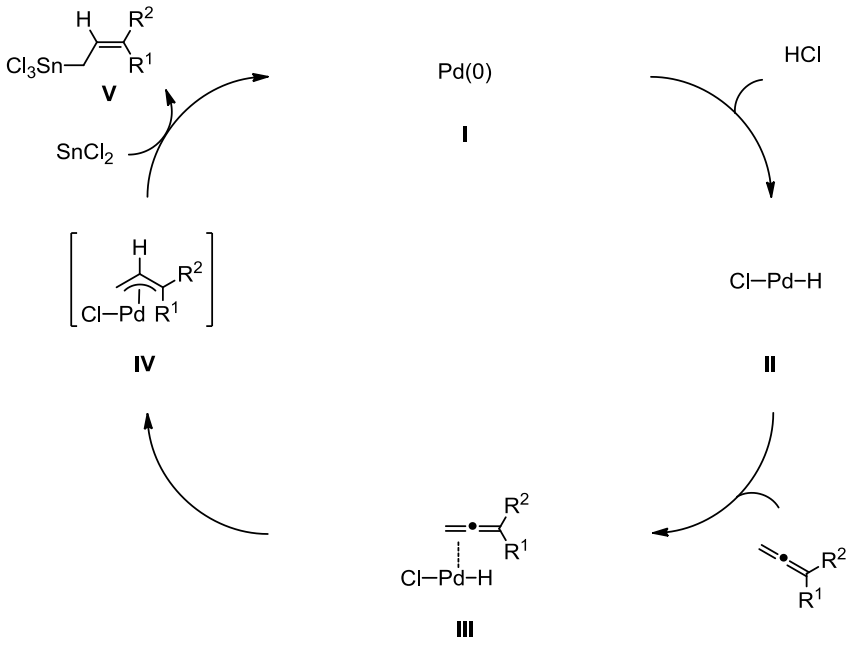
Table 1.21. Selected examples of aldehyde allylation *via* Pd catalyzed *in situ* hydrostannylation of allenes.



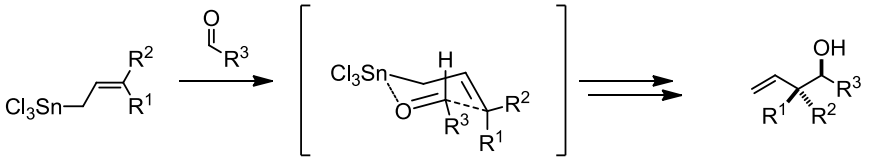
Entry	R^1	R^2	R^3	Yield	dr
1	Me	Me	C_6H_5	95%	-
2	Me	Me	$C_6H_5C{=}CH$	75%	-
3	Me	Me	$H_2C{=}CH(CH_2)_8$	54%	-
4	H	C_6H_5	C_6H_5	72%	>99:1
5	H	*c*-Hex	C_6H_5	79%	95:5
6	H	Pent	C_6H_5	78%	64:36

Cheng proposed that hydrochloric acid undergoes oxidation addition with palladium (0) complex **I** to give palladium (II) hydride **II** (Scheme 1.18). Complexation of the allene with the palladium hydride, **III**, facilitates regioselective hydrometallation to generate π-allylpalladium intermediate **IV**. Reductive transmetallation of intermediate **IV** with tin (II) chloride generates intermediate allylstannane **V**. Lastly, the *in situ* generated allylstannane proceeds with carbonyl additional *via* a six-membered chairlike transition state, where the larger substituent of the allene is equatorial, to deliver the homoallylic alcohol (Scheme 1.19).

Scheme 1.18. Proposed mechanism for Pd catalyzed hydrostannylation of allenes.



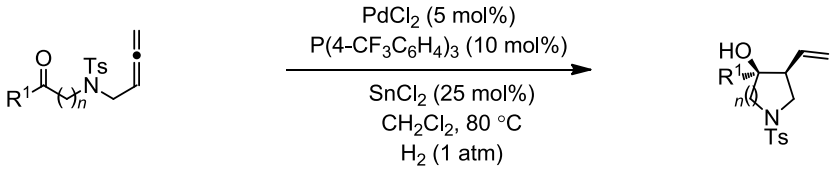
Scheme 1.19. Proposed carbonyl allylation via allylstannane.



1.6.2 PLATINUM CATALYZED REDUCTIVE CYCLIZATION

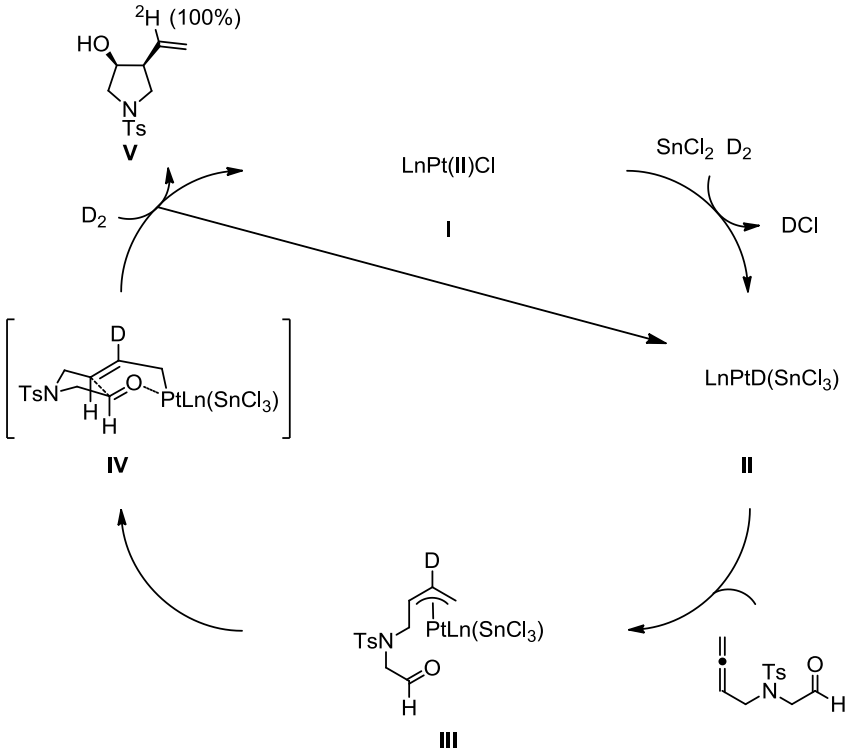
Platinum (II) catalyzed reductive cyclization of allenyl-aldehydes and ketones were reported by Jang and co-workers in 2010.[46] Under an atmosphere of hydrogen gas, allenyl-carbonyls were subjected to a platinum catalyst, $PtCl_2$, and tin (II) chloride co-catalyst. Reductive cyclization proceeded to deliver cyclic homoallylic alcohols in high yield and modest diastereoselectivity for aldehydes (Table 1.22, entries 1 and 2). For the allenyl-ketone, diastereomerically pure *cis*-selective cyclic alcohol was obtained in low yield (Table 1.22, entry 3). Notably, the carbonyl scope was quite limited.

Table 1.22. Examples of Pt catalyzed reductive cyclization of allenyl-carbonyls.



Entry	R^1	*n*	Yield	dr
1	H	1	90%	7:1
2	H	2	83%	3:1
3	C_6H_5	1	17%	>99:1

Scheme 1.20. Proposed mechanism for the Pt catalyzed reductive cyclization of allenyl-carbonyls.

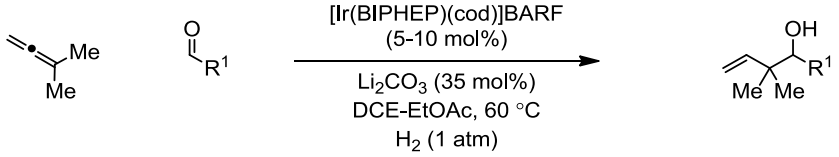


Jang performed an isotopic labeling study to probe the mechanism. The reductive cyclization was run under 1 atm of deuterium and otherwise standard conditions. Deuterium was completely incorporated at the internal vinylic position of the coupling product **V** which leads to the following proposed mechanism (Scheme 1.20). Platinum deuteride **II** is formed from $SnCl_2$, D_2, and phosphine-ligated $PtCl_2$. Regioselective hydrometallation of the allene affords π-allylpalladium intermediate **III**. Subsequent carbonyl allylation proceeds *via* a six-membered chairlike transition state **IV**. The resulting metal alkoxide is cleaved by D_2 to furnish the *cis*-homoallylic alcohol and regenerate palladium intermediate **II**.

1.6.3 Iridium Catalyzed Hydrogenative and Transfer Hydrogenative C-C Coupling

In 2007, Krische and co-workers reported a regioselective direct reductive coupling of allenes and aldehydes to furnish products of reverse prenylation.[47,48] Under 1 atm of hydrogen, an array of aldehydes were treated with lithium carbonate and cationic iridium complex [Ir(BIPHEP)(cod)]BARF in the presence of 1,1-dimethylallene, furnishing homoallylic alcohols bearing all-carbon quaternary centers in good yields and complete regiocontrol (Table 1.23). Interestingly, attempts to employ allene gas were thwarted by hydrogenation of the homoallylic alcohol. Importantly, these intermolecular couplings represent a fundamental shift in carbonyl allylation reactions, where π-unsaturates may serve directly as allyl donors without the need for generating stoichiometric allyl metal reagents.

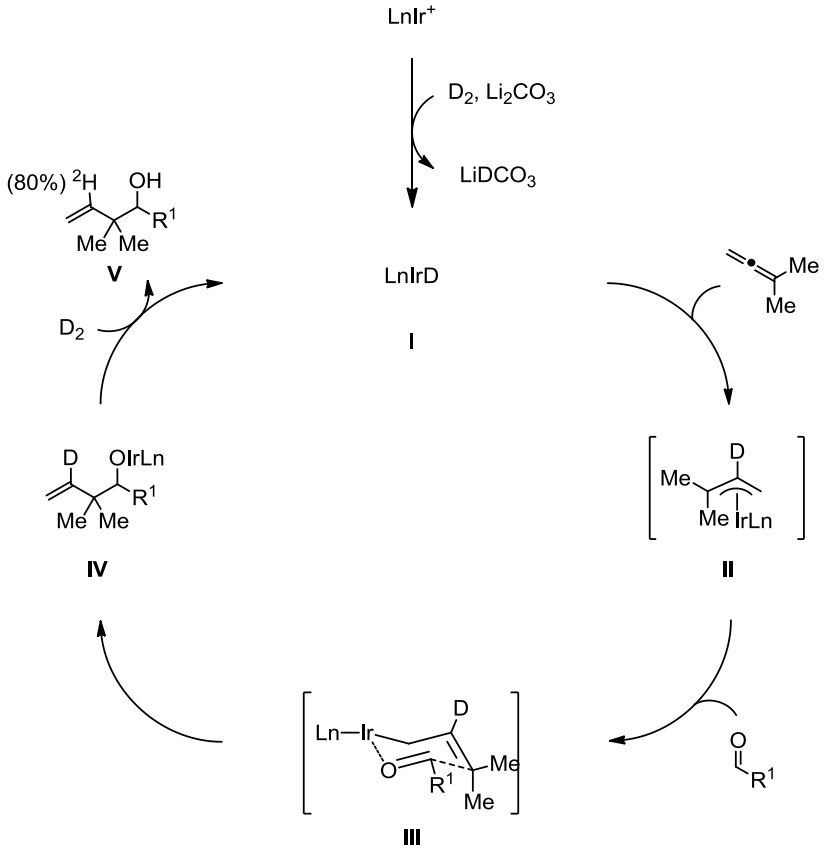
Table 1.23. Selected examples of Ir catalyzed hydrogenative couplings of 1,1-dimethylallene and aldehydes.



Entry	R^1	Yield
1	C_6H_5	68%
2	4-$OMeC_6H_4$	80%
3	3,5-$Cl_2MeC_6H_3$	74%
4	2-thienyl	60%
5	CH_2OBn	80%
6	CH_2NPhth	70%

Krische conducted an isotopic labeling study to gain further insight into the mechanism. The reductive coupling was run under 1 atm of deuterium and otherwise standard conditions. Deuterium was significantly incorporated (80%) at the internal vinylic position of the coupling product **V** which supports the following postulated mechanism (Scheme 1.21). Iridium deuteride **I** was formed in the presence of deuterium and lithium carbonate. Regioselective hydrometallation of the allene affords π-allylpalladium intermediate **II**. By way of the primary σ-allyl haptomer, regioselective carbonyl addition at the more substituted position of the allene may proceed *via* a closed six-membered chair-like transition state, **III**, to generate an iridium alkoxide **IV**. The resulting alkoxide is cleaved by D_2 to furnish homoallylic alcohol **V** and regenerate the iridium catalyst **I**.

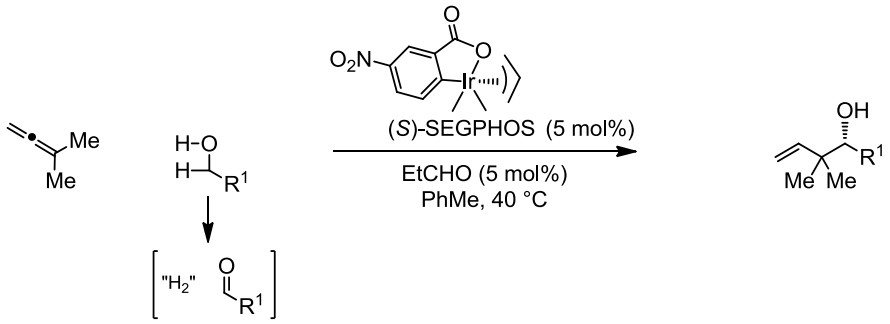
Scheme 1.21. Proposed mechanism of Ir catalyzed hydrogenative coupling of 1,1-dimethylallene and aldehydes.



Despite the success of the hydrogenative allene-aldehyde couplings, Krische envisioned a more efficient process, where a benign alcohol serves as both a hydrogen source and carbonyl coupling partner for allenes *via* transfer hydrogenation. Shortly thereafter, this transformation would be realized in the transfer hydrogenative iridium catalyzed couplings of allenes and alcohols, otherwise under the same conditions as the hydrogenative couplings with aldehydes.[49] Additionally, it was found that isopropanol could serve as a terminal reductant by being a hydrogen donor. Later, Krische et al. developed a cyclometallated iridium complex that rendered this transformation enantioselective (Tables 1.24 and 1.25).[50,51] Krische demonstrated the utility of this

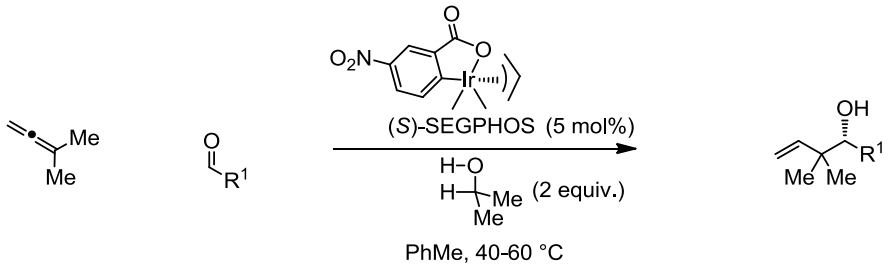
transfer hydrogenative coupling in the synthesis of the bryostatin A-ring fragment (Scheme 1.22).[52]

Table 1.24. Selected examples of enantioselective Ir catalyzed transfer hydrogenative couplings of 1,1-dimethylallene and alcohols.



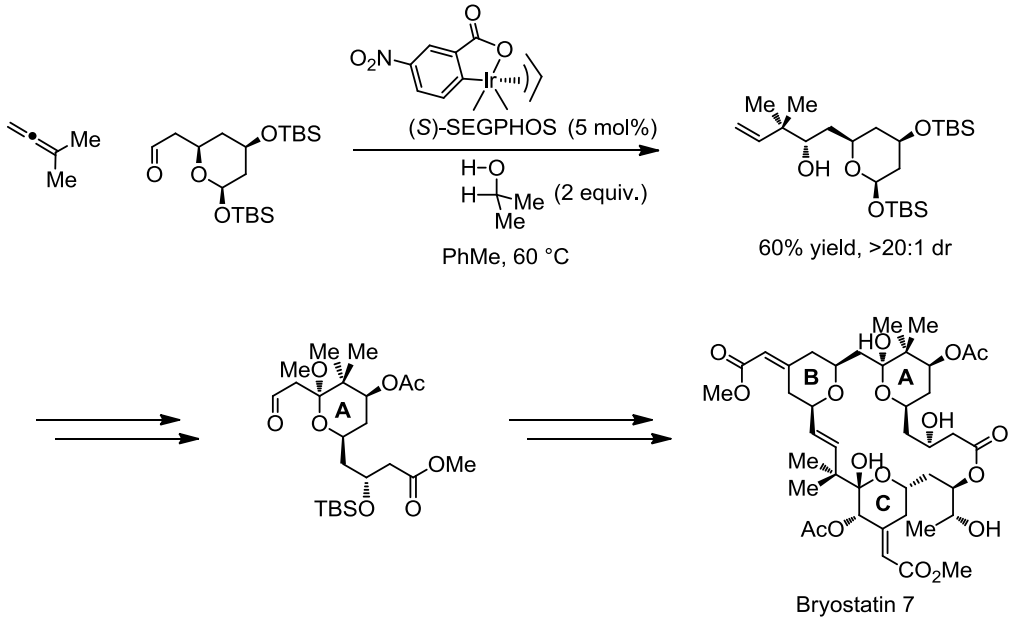
Entry	R^1	Yield	ee
1	C_6H_5	85%	86%
2	4-BrC_6H_4	80%	90%
3	$HC{=}CC_6H_5$	84%	87%
4	$(CH_2)_2OBn$	68%	88%
5	$(CH_2)_2C_6H_5$	90%	91%
6	octyl	94%	90%

Table 1.25. Selected examples of enantioselective Ir catalyzed transfer hydrogenative couplings of 1,1-dimethylallene and aldehydes.



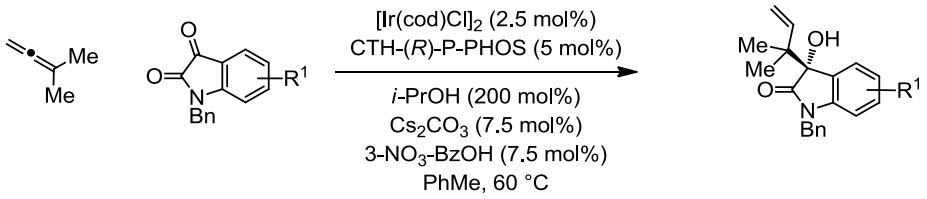
Entry	R^1	Yield	ee
1	C_6H_5	94%	84%
2	4-BrC_6H_4	96%	90%
3	$HC{=}CC_6H_5$	81%	93%
4	$(CH_2)_2OBn$	65%	89%
5	$(CH_2)_2C_6H_5$	84%	87%
6	Octyl	71%	92%

Scheme 1.22. Application of Ir catalyzed transfer hydrogenative allene-aldehyde coupling in the enantioselective total synthesis of Bryostatin 7.



Further investigation by Krische and co-workers revealed that *N*-benzyl substituted isatins were suitable coupling partners under iridium catalyzed transfer hydrogenation (Table 1.26). This transformation generated enantio-enriched products of carbonyl reverse prenylation bearing two contiguous quaternary centers.

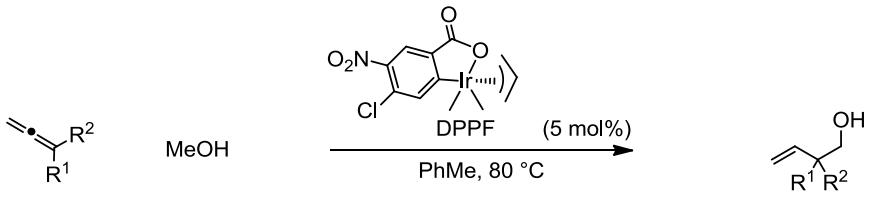
Table 1.26. Enantioselective Ir catalyzed reverse prenylation of isatins.



Entry	R^1	Yield	ee
1	H	90%	96%
2	5-Br	86%	90%
3	5-Me	79%	93%
4	5-OMe	81%	96%
5	6-Cl	80%	93%
6	6-Br	70%	93%
7	7-Br	79%	94%

Iridium catalyzed allene-methanol couplings were also investigated.[53] Ferrocene based diphosphines proved to be critical in promoting an efficient coupling. In the presence of a DPPF ligated iridium complex, an array of 1,1-disubstituted allenes were coupled to methanol furnishing homoallylic, neopentyl alcohols in modest yields and as single regioisomers (Table 1.27). Competition kinetics experiments revealed that methanol dehydrogenation was rate limiting, which contrasts similar couplings to benzyl alcohol. This process represents the first examples of the direct conversion of methanol to higher alcohols under the conditions of homogeneous catalysis.

Table 1.27. Selected examples of Ir catalyzed transfer hydrogenative couplings of 1,1-disubstituted allenes and methanol.



Entry	R^1	R^2	Yield
1	CH_2OPMB	Me	67%
2	CH_2OPMB	*c*-Pr	60%
3	CH_2OPMB	Bn	68%
4	CH_2NPhth	Me	70%
5	CH_2NPhth	*c*-Pr	67%
6	CH_2NPhth	Bn	65%

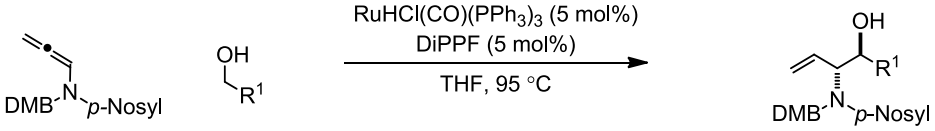
1.6.4 RUTHENIUM CATALYZED TRANSFER HYDROGENATIVE C-C COUPLING

Although iridium catalyzed enantioselective couplings of 1,1-dimethylallene and carbonyls were well-developed, iridium catalyzed diastereoselective allene-carbonyl couplings remained elusive. An investigation into other metal sources revealed that certain ruthenium complexes facilitate diastereoselective transfer hydrogenative couplings of allenes to carbonyl compounds.[48]

Ruthenium catalyzed diastereoseletive *anti*-aminoallylation of aldehydes *via* transfer hydrogenative coupling to allenamides was reported by Krische et al. in 2009.[54a] Building on this initial report, Krische subsequently revealed that alcohols also engaged in diastereoseletive *anti*-aminoallylation *via* coupling to amino-substituted allenes (Table 1.28).[54b] Exposure of primary alcohols and an allenamide to the ruthenium(II) catalyst derived *in situ* from the commercially available components $RuHCl(CO)(PPh_3)_3$ and

DIPPF ligand in THF afforded *anti*-aminoallylation products in high yield with complete *anti*-diastereocontrol. Collectively, these processes represent an alternative to the use of amino-substituted allylboranes in the aminoallylation of carbonyl compounds.[55]

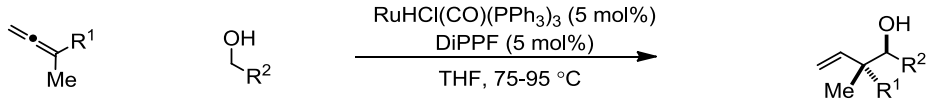
Table 1.28. Selected examples of Ru catalyzed transfer hydrogenative couplings of allenamides and alcohols.



Entry	R^1	Yield
1	4-$NO_2C_6H_4$	86%
2	C_6H_5	71%
3	2-furyl	89%
4	$HC{=}CC_6H_5$	85%
5	$(CH_2)_2OBn$	89%
6	Hex	68%

These conditions were adapted to use 1,1-disubstituted allenes, enabling generation of all-carbon quaternary stereocenters (Table 1.29).[56] Notably, certain fluorinated alcohols react under ruthenium transfer hydrogenation conditions, providing an alternative to the addition of *C*-nucleophiles to the corresponding, less tractable fluorinated aldehydes.[56b]

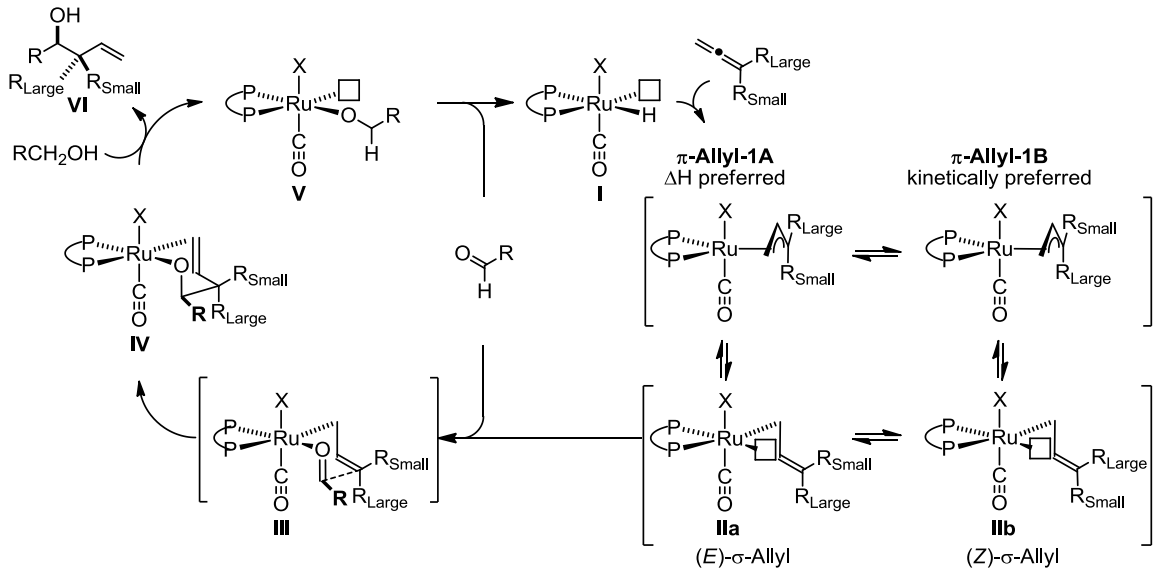
Table 1.29. Selected examples of Ru catalyzed transfer hydrogenative couplings of 1,1-disubstituted allenes and alcohols.



Entry	R^1	R^2	Yield	dr
1	C_6H_5	C_6H_5	99%	6:1
2	CH_2OPMB	Hex	86%	4:1
3	CH_2NPhth	4-$CF_3C_6H_4$	99%	14:1
4	C_6H_5	CH_2CF_3	77%	>20:1
5	C_6H_5	$(CH_2)_2CF_3$	92%	>20:1
6	CH_2NPhth	CH_2F	72%	4:1

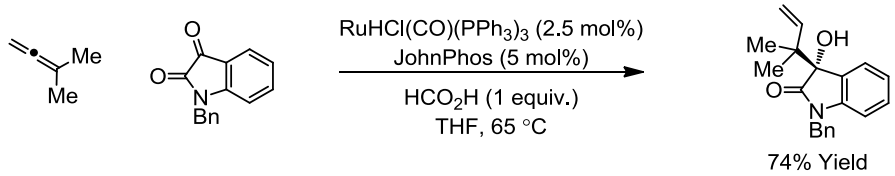
Isotopic labeling and competition kinetics experiments were conducted to gain further insight into the mechanism. The collective data suggest the following catalytic mechanism (Scheme 1.23). The catalytic cycle begins with regioselective hydrometallation of the allene to form a 1,1-disubstituted π-allylruthenium intermediates, **π-Allyl 1A** and **π-Allyl 1B**. Although hydrometallation from the allene π-face proximal to the smaller group is anticipated to be kinetically preferred, rapid isomerization of **π-Allyl 1B** enables conversion to the more stable complex **π-Allyl 1A**. By way of the primary σ-allyl haptomer **IIa**, regioselective carbonyl addition at the more substituted position of the allene may proceed *via* a closed six-membered chair-like transition state, **III**. Protonolysis of the resulting ruthenium alkoxide **IV** by a reactant alcohol releases the homoallylic alcohol **VI** and produces ruthenium alkoxide **V**. Subsequent β-hydride elimination furnishes aldehyde and regenerates ruthenium hydride complex **I** to complete the catalytic cycle.

Scheme 1.23. Proposed mechanism for Ru catalyzed transfer hydrogenative couplings of 1,1-disubstituted allenes and alcohols.



A similar catalytic system was employed in the ruthenium catalyzed reverse prenylation of isatin (Scheme 1.24).[57] Notably, the ruthenium catalyzed conditions tolerated a non-protected isatin, in contrast to the previous reports under iridium catalysis. Also, formic acid was employed as terminal reductant.

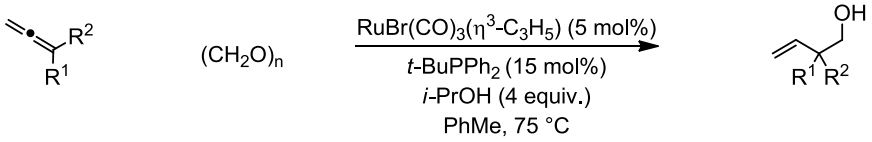
Scheme 1.24. Ru catalyzed reverse prenylation of isatin.



Whereas iridium catalysts successfully coupled methanol and allenes, Krische and co-workers report the complementary coupling of paraformaldehyde and allenes *via* ruthenium catalyzed transfer hydrogenation. Primary neopentyl alcohols were obtained in good with complete levels of branched selectivity (Table 1.30).[58] These conditions

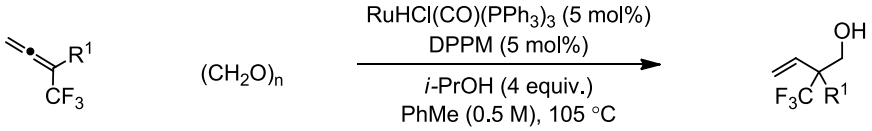
were adapted to employ trifluoromethyl-substituted allenes in the formation of CF_3-bearing all-carbon quaternary centers for which few methods[59] have been reported (Table 1.31).[60] Interestingly, formaldehyde was reported to act as both coupling partner and reductant.[58,60]

Table 1.30. Selected examples of Ru catalyzed transfer hydrogenative couplings of 1,1-disubstituted allenes and paraformaldehyde.



Entry	R^1	R^2	Yield
1	Me	C_6H_5	86%
2	Me	4-$OMeC_6H_4$	74%
3	Me	4-ClC_6H_4	77%
4	Me	CH_2OTBS	76%

Table 1.31. Selected examples of Ru catalyzed transfer hydrogenative couplings of CF_3-substituted allenes and paraformaldehyde.



Entry	R^1	Yield
1	C_6H_5	78%
2	4-$OMeC_6H_4$	75%
3	4-ClC_6H_4	68%
4	2-naphthyl	67%

1.7 Conclusion

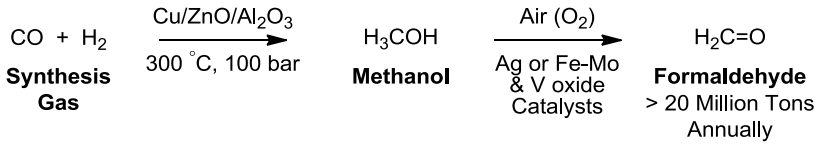
Modern methods for carbon-carbon bond formation have focused on increasing reaction efficiency. As a result, improved methods of carbonyl allylation have received significant attention. Over the last two decades, an alternative strategy of carbonyl allylation has emerged by employing allenes as allyl donors. State-of-the art methods employ metal catalyzed direct coupling of allenes to carbonyl compounds in the absence of toxic and/or mass intensive reagents, such as stannanes and silanes, respectively. However, much remains to be accomplished, particularly with respect to the development of enantioselective protocols, if these metal catalyzed approaches are to succeed traditional allylmetal reagents.

CHAPTER 2: REGIODIVERGENT HYDROHYDROXYMETHYLATION OF 2-SUBSTITUTED DIENES*

2.1 Introduction

Hydroformylation, the byproduct-free synthesis of aldehydes from α-olefins and synthesis gas (CO/H_2), is one of the largest volume applications of homogenous transition metal catalysis.[1] As progress in this area continues, attempts to extend hydroformylation beyond α-olefins to 1,3-dienes,[2] allenes,[3] and alkynes[4] have proven challenging due to incomplete regioselectivity and/or "over-hydroformylation" to form dialdehyde products. Paraformaldehyde is a highly tractable compound derived from synthesis gas and manufactured on enormous scale (Scheme 2.1). As certain late transition metal catalysts were recently shown to promote reductive C-C couplings of π-unsaturated reactants to aldehydes *via* transfer hydrogenation,[5] attempts were made to exploit this powerful methodology in the hydrohydroxymethylation of π-unsaturates, where paraformaldehyde serves as a C1-feedstock.

Scheme 2.1. Production of formaldehyde from synthesis gas.

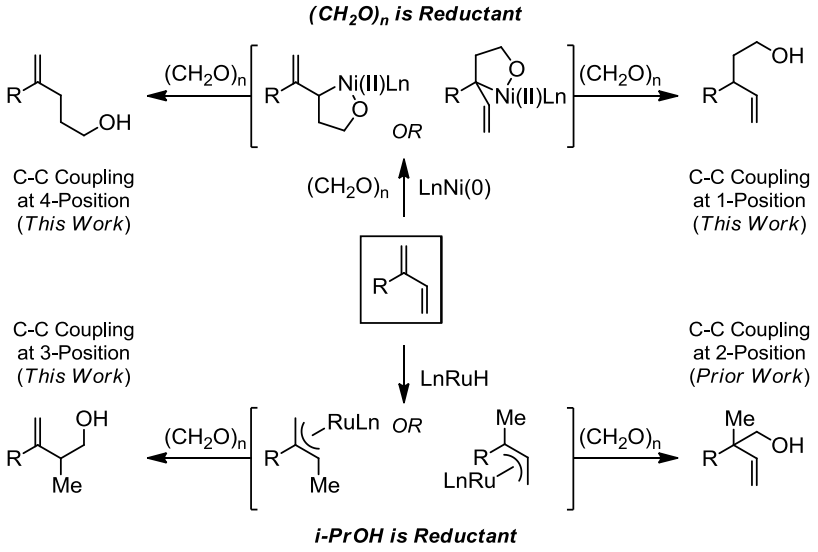


Toward this end, the reductive coupling of 2-substituted 1,3-dienes to paraformaldehyde was explored under these conditions of C-C bond forming transfer hydrogenation in response to the lack of efficient methods for diene hydroformylation.[6]

* Köpfer, A.; Sam, B.; Breit, B.; Krische, M. J. *Chem. Sci.* **2013**, *4*, 1876.
Acknowledgement is made to M. J. K. and B. B. for project oversight and A. K. for reaction discovery and scope evaluation of C1- and C4-selective couplings.

Herein, we report regiodivergent reductive coupling of paraformaldehyde at positions C1, C2, and C3 of the diene was accomplished *via* metal catalysts based on nickel, cationic ruthenium and neutral ruthenium, respectively. For dienes with silyl and stannyl substituents at the C2-position, nickel catalysts were found to promote coupling predominantly at the C4-position. These methods provide an alternative to diene hydroformylation, for which regioselective formation of different constitutional isomers has not been achieved (Scheme 2.2).

Scheme 2.2. Regioselective hydrohydroxymethylation of 2-substituted dienes *via* ruthenium or nickel catalyzed reductive coupling to paraformaldehyde.



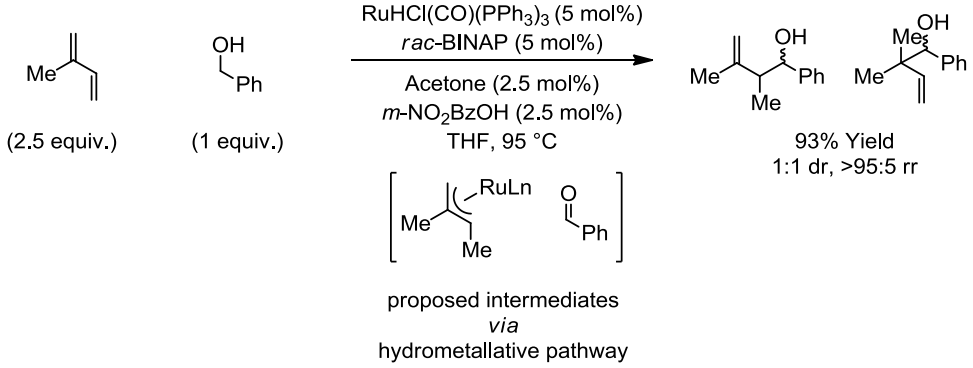
2.2 C3- and C2-Regioselective Hydrohydroxymethylations

2.2.1 BACKGROUND

Initial studies on the reductive coupling of 2-substituted butadienes to higher alcohols and aldehydes found that neutral ruthenium catalysts promoted regioselective

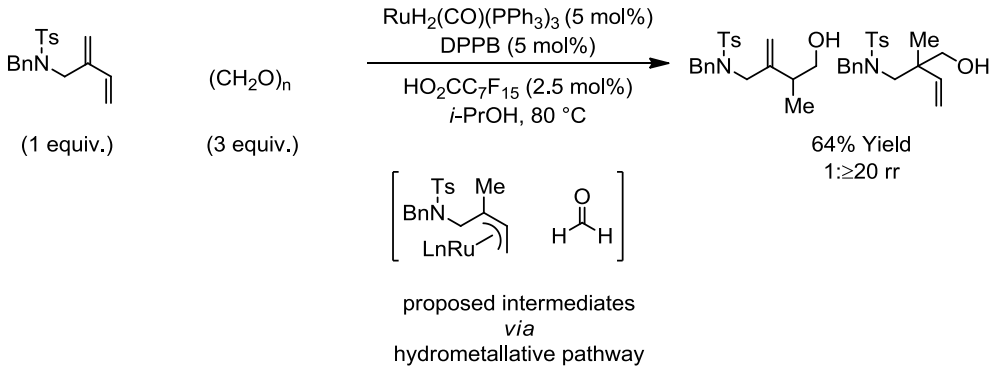
reductive coupling at the C3-position of the diene *via* hydrometallation of the less substituted olefin to form a nucleophilic 1,2-disubstituted π-allylruthenium intermediate (Scheme 2.3).[7,8] Under these conditions, attempts to couple less sterically demanding carbonyl compounds, such as paraformaldehyde, led to a significant erosion of C3-regioselectivity into the C2-coupling product. As a result, investigation into regioselective coupling of paraformaldehyde to the C2-position of 2-substituted butadienes ensued to develop hydrohydroxymethylation products incorporating all-carbon quaternary centers.

Scheme 2.3. Selected example of regioselective reductive coupling of benzyl alcohol to the C3-position of isoprene mediated by transfer hydrogenation.



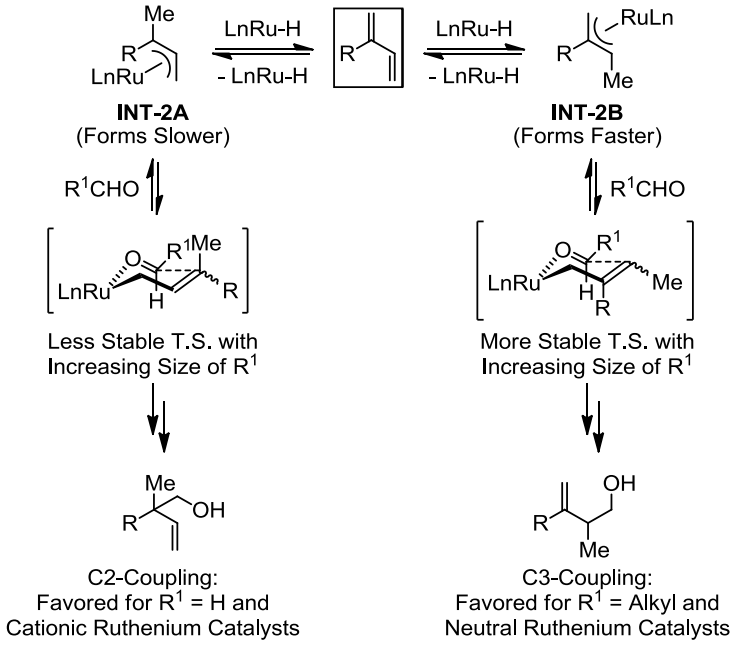
Ruthenium catalysts that embody more cationic character promoted coupling at the C2-position of the diene.[6] It was hypothesized that the cationic character of the ruthenium (II) complex reversibly hydrometallates all positions of the 1,3-diene, enabling access to the isomeric 1,1-disubstituted π-allylruthenium intermediate **INT-2B** (Scheme 2.4). This intermediate undergoes coupling to formaldehyde at the C2-position of the diene, delivering a homoallylic alcohol bearing an all-carbon quaternary center.

Scheme 2.4. Selected example of regioselective reductive coupling of paraformaldehyde to the C2-position of a 2-substituted diene mediated by transfer hydrogenation.

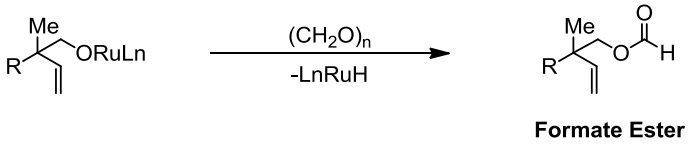


Notably, employing cationic ruthenium (II) catalysts in couplings of 2-substituted butadienes to higher aldehydes resulted in significant erosion of C2-regioselecitivity to the C3-coupling product,[9] suggesting a Curtin-Hammett scenario may be operative (Scheme 2.5). Such cationic ruthenium complexes are readily generated through the acid-base reaction of $RuH_2(CO)(PPh_3)_3$ and $HO_2CC_7F_{15}$ in the presence of DPPB.[10] Both isopropanol and paraformaldehyde may act as terminal reductant, with the latter resulting in conversion of the reaction product to small quantities of the formate ester, which were cleaved upon isolation (Scheme 2.6).

Scheme 2.5. Partitioning C2- and C3-regioselectivity in the ruthenium catalyzed reductive coupling of 2-substituted dienes to formaldehyde.



Scheme 2.6. Mechanistic rationale of formate ester generation.



In any event, 2-substituted butadienes 2.1-2.11 were coupled to paraformaldehyde, affording neopentyl alcohols 2.1b-2.11b in moderate to good isolated yields and with good to excellent ratios of C2-regioselectivity.

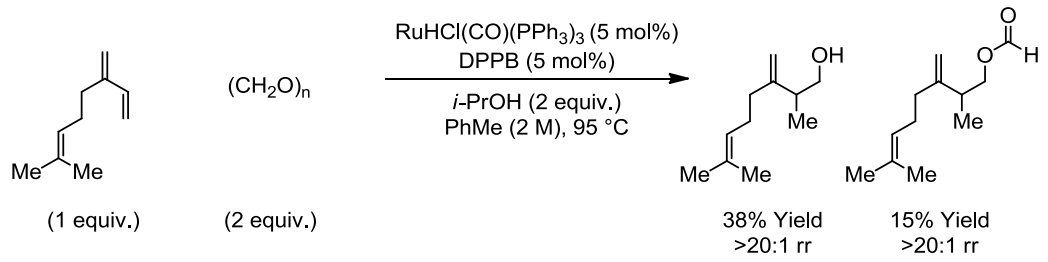
Having achieved regioselective reductive coupling of 2-substituted butadienes to formaldehyde at the C2-position, an analogous set of hydrohydroxymethylation products formed from coupling at the C3-position was sought. Based on the previous findings that regioselective couplings at the C3-position of isoprene were favored for neutral ruthenium catalysts and higher aldehydes,[7] it was postulated that neutral ruthenium

complexes may catalyze the C3-regioselective reductive coupling of similar 2-substituted dienes and paraformaldehyde.

2.2.2 REACTION DEVELOPMENT

To test this hypothesis, mycerene (1 equiv.) was exposed to paraformaldehyde (2 equiv.) in the presence of $RuHCl(CO)(PPh_3)_3$ (5 mol%), 1,4-bis(diphenylphosphino)butane (DPPB) (5 mol%), and isopropanol (2 equiv.) in toluene at 95 °C. The desired homoallylic alcohol was obtained as a single regioisomer in 38% yield, in addition to 15% yield of the corresponding formate ester (Scheme 2.7). As observed with the related C2-regioselective hydroxymethylations, paraformaldehyde may contribute as a terminal reductant to deliver the corresponding formate ester of the C3-regioselective coupling products. Notably, attempts to employ paraformaldehyde as both coupling partner and the sole terminal reductant resulted in low conversion to product.

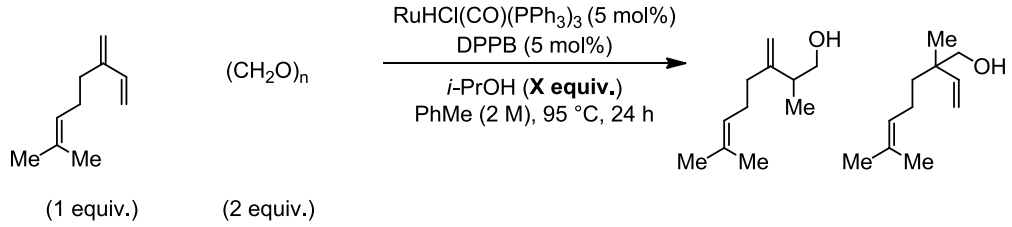
Scheme 2.7. C3-regioselective coupling of myrcene to paraformaldehyde.



A screening of exogenous reductants, including isopropanol, formic acid, and others, revealed that isopropanol provided the highest yields of product, yet formate still persisted. It was hypothesized that employing a larger excess of isopropanol would

suppress formate production by competing with excess formaldehyde for reduction of the ruthenium alkoxide intermediate. Indeed, upon an assay of isopropanol loadings, it was found that five equivalents were optimal (Table 2.1, entry 4). Interestingly, employing more than five equivalents of isopropanol adversely affected the regioselectivity, despite the use of a neutral ruthenium catalyst (Table 2.1, entry 5).

Table 2.1. Effect of isopropanol loading on C3-regioselective couplings.[a]



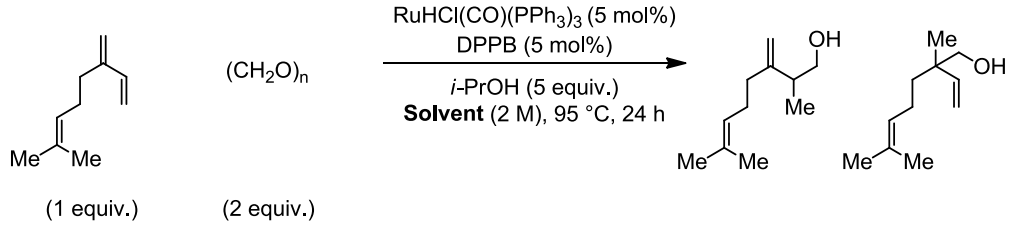
Entry	Reductant	Equiv.	Yield	rr
1	none	-	Trace	n.d.
2	*i*-PrOH	2.0	38%	>20:1
3	*i*-PrOH	4.0	42%	>20:1
4	*i*-PrOH	5.0	50%	>20:1
5	*i*-PrOH	8.0	48%	4:1

[a]Cited yields are of regioisomeric mixtures isolated by silica gel chromatography. Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of crude reaction mixtures.

At high loadings (8 equiv.), the volume of isopropanol exceeds that of the reaction solvent, toluene. Hence, the more polar isopropanol was the predominate solvent, and polar solvents tend to promote coordinative unsaturation of transition metal complexes. With respect to the neutral ruthenium complex, $RuHCl(CO)(PPh_3)_3$, isopropanol may solvate the chloride ligand, thereby increasing the cationic character of the ruthenium complex. As eluded to previously, ruthenium catalysts with greater

cationic character favor reductive coupling of formaldehyde at the C2-position of the diene. Further probing of solvent supported this hypothesis (Table 2.2). Less polar solvents such as toluene and dioxane (Table 2.2, Entries 1-2) favored the desired coupling at the C3-position of myrcene, whereas more polar solvents such as acetonitrile and isopropanol favored C2-regioselectivity (Table 2.2, Entries 4-6). Upon further variation of temperature, it was found that conducting the reaction at 115 °C furnished the desired homoallylic alcohol in 61% isolated yield as a single regioisomer, albeit with incomplete conversion.

Table 2.2. Effect of solvent on C3-regioselective couplings.[a]



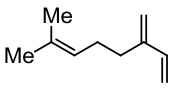
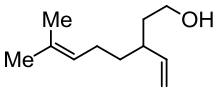
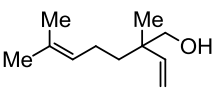
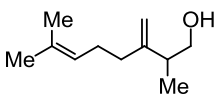
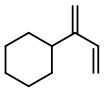
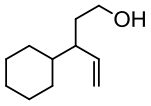
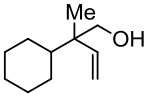
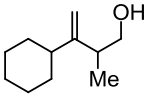
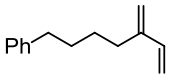
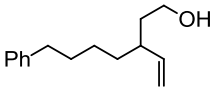
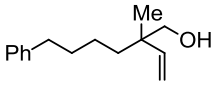
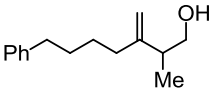
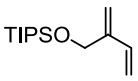
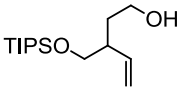
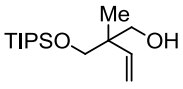
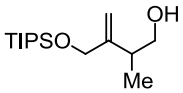
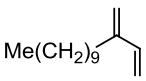
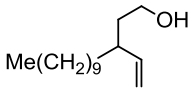
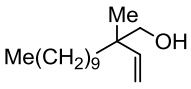
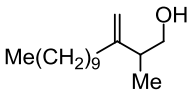
Entry	Solvent	Yield	rr
1	PhMe	50%	>20:1
2	1,4-Dioxane	55%	>20:1
3	THF	36%	6:1
4	DCE	52%	1:1
5	MeCN	65%	1:2
6	*i*-PrOH	63%	1:3

[a]Cited yields are of regioisomeric mixtures isolated by silica gel chromatography. Regioisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.

2.2.3 REACTION SCOPE

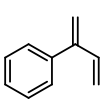
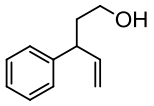
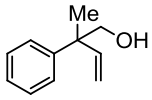
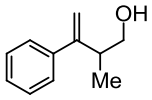
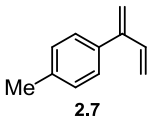
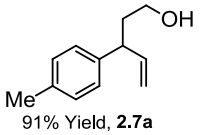
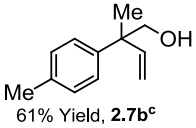
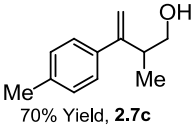
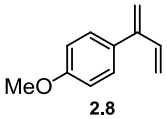
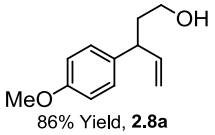
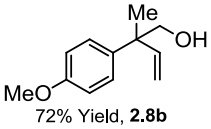
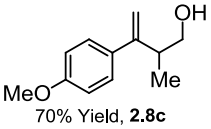
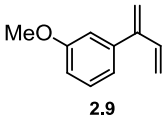
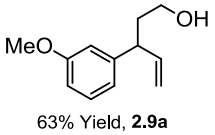
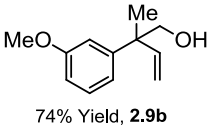
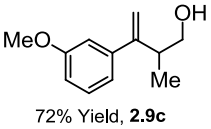
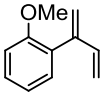
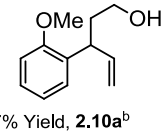
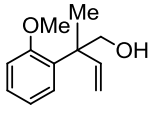
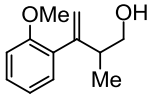
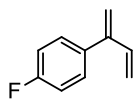
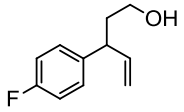
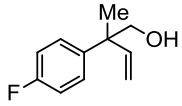
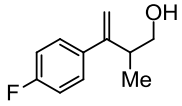
To evaluate the scope of these conditions, an array of 2-alkyl-1,3-butadienes **2.1**-**2.5** (Table 2.3) and 2-aryl-1,3-butadienes **2.6**-**2.11** (Table 2.4) were assayed in the reductive coupling to paraformaldehyde. Withstanding minor adjustments to reaction temperature, these conditions proved general affording the homoallylic alcohols **2.1c**-**2.11c**, respectively, in moderate to good yields and excellent levels of C3-regioselectivity, which nicely complement an analogous set of C2-regioselective hydrohydroxymethylation products **2.1b**-**2.11b**. Having achieved both C3- and C2-regioselective reductive couplings of 2-substituted-butadienes **2.1**-**2.11** to formaldehyde, an analogous set of products **2.1a**-**2.11a** derived from coupling to the C1-position of the diene were sought.

Table 2.3. Regiodivergent ruthenium and nickel catalyzed reductive coupling of 2-alkyl-1,3-butadienes to formaldehyde.

Dienes 1a-11a	**Coupling at C1**	**Coupling at C2**	**Coupling at C3**
Prepared *via* Ru-catalyzed enyne metathesis or Kumada coupling of the Grignard reagent derived from chloroprene	$Ni(cod)_2$ (10 mol%) PCy_3 (10 mol%) Cs_2CO_3 (20 mol%) $(CH_2O)_n$ (4 equiv.) Diene **1-11** (1 equiv.) PhMe (0.25 M) 75 °C, 24 h	$RuH_2(CO)(PPh_3)_3$ (5 mol%) DPPB (5 mol%) $HO_2CC_7F_{15}$ (5 mol%) $(CH_2O)_n$ (3 equiv.) Diene **1-11** (1 equiv.) *i*-PrOH-Me_2CO (1 M, 9:1) 80 °C, 20 h	$RuHCl(CO)(PPh_3)_3$ (5 mol%) DPPB (5 mol%) *i*-PrOH (5 equiv.) $(CH_2O)_n$ (2 equiv.) Diene **1-11** (1 equiv.) 1,4-Dioxane (2 M) 95 °C, 24 h
			
2.1	68% Yield, **2.1a** 10:1, **2.1a**:**2.1d**	76% Yield, **2.1b**[d] 4:1, **2.1b**:**2.1c**	61% Yield, **2.1c**[e] 1:>20, **2.1b**:**2.1c**
			
2.2	39% Yield, **2.2a**[b] 5:1, **2.2a**:**2.2d**	62% Yield, **2.2b**[d] >20:1, **2.2b**:**2.2c**	80% Yield, **2.2c** 1:8, **2.2b**:**2.2c**
			
2.3	75% Yield, **2.3a** 7:1, **2.3a**:**2.3d**	63% Yield, **2.3b**[d] 8:1, **2.3b**:**2.3c**	67% Yield, **2.3c**[e] 1:17, **2.3b**:**2.3c**
			
2.4	50% Yield, **2.4a**[b] 2:1, **2.4a**:**2.4d**	76% Yield, **2.4b** >20:1, **2.4b**:**2.4c**	81% Yield, **2.4c** 1:>20, **2.4b**:**2.4c**
			
2.5	69% Yield, **2.5a** 8:1, **2.5a**:**2.5d**	57% Yield, **2.5b**[d] 8:1, **2.5b**:**2.5c**	62% Yield, **2.5c**[e] 1:>20, **2.5b**:**2.5c**

[a]Cited yields are of regioisomeric mixtures isolated by silica gel chromatography. Regioisomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. [b]$Ni(cod)_2$ (20 mol%), Cy_3P (20 mol%). [c] *i*-PrOH-Me_2CO (1M, 1:1). [d]Reaction conducted at 90 °C. [e]Reaction conducted at 115 °C. [f]Product of over-reduction not present unless noted.

Table 2.4. Regiodivergent ruthenium and nickel catalyzed reductive coupling of 2-aryl-1,3-butadienes to formaldehyde.

Dienes 1a-11a Prepared *via* Ru-catalyzed enyne metathesis or Kumada coupling of the Grignard reagent derived from chloroprene	**Coupling at C1** $Ni(cod)_2$ (10 mol%) PCy_3 (10 mol%) Cs_2CO_3 (20 mol%) $(CH_2O)_n$ (4 equiv.) Diene **1-11** (1 equiv.) PhMe (0.25 M) 75 °C, 24 h	**Coupling at C2** $RuH_2(CO)(PPh_3)_3$ (5 mol%) DPPB (5 mol%) $HO_2CC_7F_{15}$ (5 mol%) $(CH_2O)_n$ (3 equiv.) Diene **1-11** (1 equiv.) *i*-PrOH-Me_2CO (1 M, 9:1) 80 °C, 20 h	**Coupling at C3** $RuHCl(CO)(PPh_3)_3$ (5 mol%) DPPB (5 mol%) *i*-PrOH (5 equiv.) $(CH_2O)_n$ (2 equiv.) Diene **1-11** (1 equiv.) 1,4-Dioxane (2 M) 95 °C, 24 h
 **2.6**	 72% Yield, **2.6a** 3:1, **2.6a**:**2.6d**	 55% Yield, **2.6b**[c] >20:1, **2.6b**:**2.6c** 8:1, **2.6b**:**2.6e**	 65% Yield, **2.6c** 1: >20, **2.6b**:**2.6c**
 **2.7**	 91% Yield, **2.7a** 3:1, **2.7a**:**2.7d**	 61% Yield, **2.7b**[c] >20:1, **2.7b**:**2.7c** 4:1, **2.7b**:**2.7e**	 70% Yield, **2.7c** 1:20, **2.7b**:**2.7c**
 **2.8**	 86% Yield, **2.8a** 7:1, **2.8a**:**2.8d**	 72% Yield, **2.8b** >20:1, **2.8b**:**2.8c**	 70% Yield, **2.8c** 1:20, **2.8b**:**2.8c**
 **2.9**	 63% Yield, **2.9a** 4:1, **2.9a**:**2.9d**	 74% Yield, **2.9b** >20:1, **2.9b**:**2.9c**	 72% Yield, **2.9c** 1: >20, **2.9b**:**2.9c**
 **2.10**	 57% Yield, **2.10a**[b] 7:1, **2.10a**:**2.10d**	 68% Yield, **2.10b** >20:1, **2.10b**:**2.10c**	 70% Yield, **2.10c** 1:>20, **2.10b**:**2.10c**
 **2.11**	 74% Yield, **2.11a** 4:1, **2.11a**:**2.11d**	 65% Yield, **2.11b**[c] >20:1, **2.11b**:**2.11c** 8:1, **2.11b**:**2.11e**	 65% Yield, **2.11c**[e] 1:>20, **2.11b**:**2.11c**

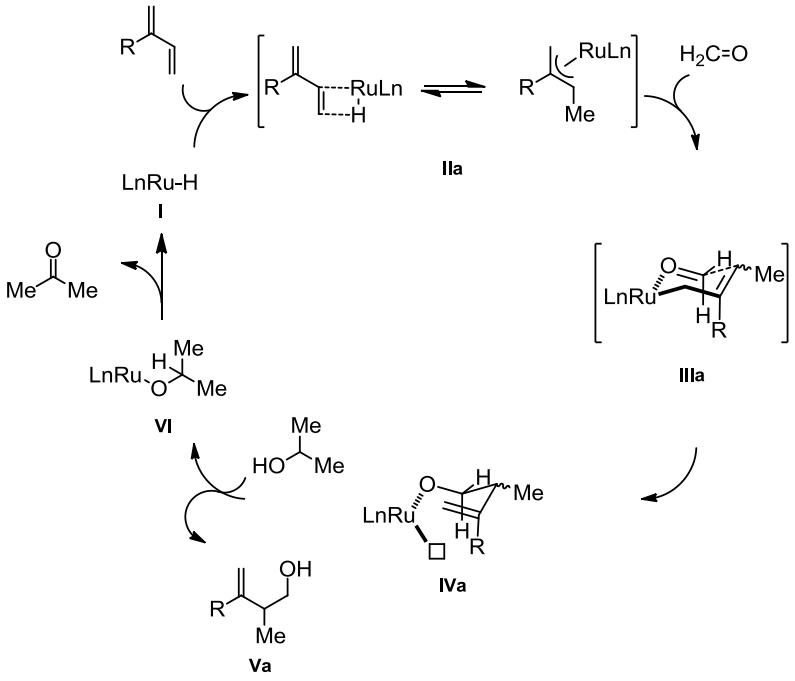
[a]Cited yields are of regioisomeric mixtures isolated by silica gel chromatography. Regioisomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. [b]$Ni(cod)_2$ (20 mol%), Cy_3P (20 mol%). [c] *i*-PrOH-Me_2CO (1M, 1:1). [d]Reaction conducted

at 90 °C. [e]Reaction conducted at 115 °C. [f]Product of over-reduction not present unless noted.

2.2.4 POSTULATED REACTION MECHANISMS

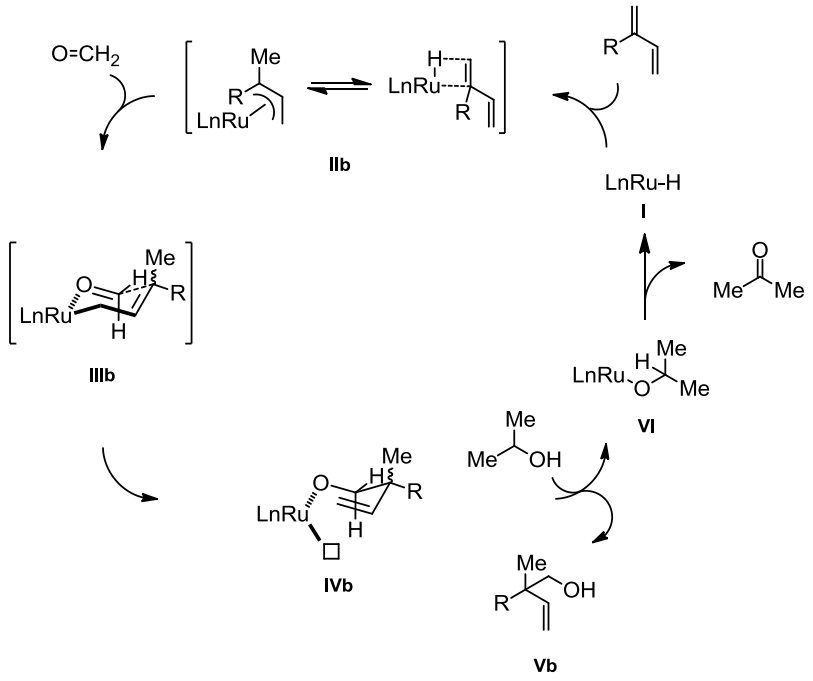
A hydrometallative pathway is proposed, as found in related ruthenium catalyzed diene-aldehyde couplings (Scheme 2.8).[7-8] The catalytic cycle opens with regioselective hydroruthenation of the 1,3-butadiene to form a 1,2-disubstituted π-allylruthenium intermediate, **IIa**.[11] By way of the more stable primary σ-allyl haptomer, regioselective carbonyl addition at the C3-position of the diene may proceed *via* a closed six-membered chair-like transition state, **III**. Protonolysis of the resulting ruthenium alkoxide releases the C3-adduct **Va** and produces ruthenium isopropoxide **VI**. Subsequent β-hydride elimination furnishes the benign by-product, acetone, and regenerates the ruthenium hydride complex, **I**, to complete the catalytic cycle.

Scheme 2.8. Proposed mechanism for regioselective coupling to C3-position of diene.



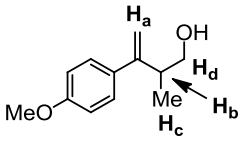
Regioselective reductive coupling at the diene C2-position may occur in a similar fashion, in which regioselective hydrometallation of the 1,3-butadiene generates a 1,1-disubstituted π-allylruthenium intermediate, **IIb**, that leads to the C2-adduct **Vb** (Scheme 2.9).

Scheme 2.9. Proposed mechanism for regioselective coupling to C2-position of diene.



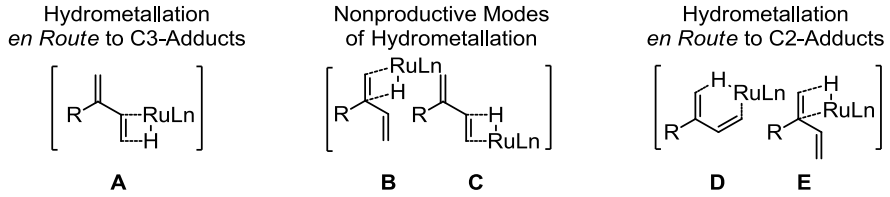
Isotopic labeling studies were conducted under standard conditions for coupling at the diene C3-posiiton using *deuterio*-paraformaldehyde, d_8-isopropanol, and both *deuterio*-paraformaldehyde and d_8-isopropanol (Scheme 2.10). The observed patterns of deuterium incorporation clearly exclude diene hydroformylation-aldehyde reduction pathways.[1d] Also, it appears that both paraformaldehyde and isopropanol contribute significantly as terminal reductant, and therefore, a hydride donor. The pattern of deuterium incorporation observed in the C3-selective coupling suggests hydrometallation modes **A** and **C** predominate and occur reversibly (Scheme 2.11). Notably, scarce deuterium at the former diene C1-position was observed, suggesting hydrometallation modes **D** and **E** do not occur frequently.

Scheme 2.10. Isotopic labeling studies involving ruthenium catalyzed reductive coupling of diene **2.8** to paraformaldehyde at the C3-position.[a]



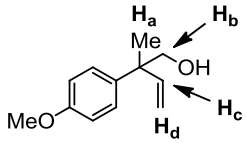
$(CD_2O)_n$ + *i*-PrOH	$(CH_2O)_n$ + *i*-PrOH-d_8	$(CD_2O)_n$ + *i*-PrOH-d_8
H_a (0% ^2H)	H_a (5% ^2H)	H_a (1% ^2H)
H_b (25% ^2H)	H_b (12% ^2H)	H_b (31% ^2H)
H_c (13% ^2H)	H_c (8% ^2H)	H_c (17% ^2H)
H_d (>95% ^2H)	H_d (1% ^2H)	H_d (>95% ^2H)

Scheme 2.11. Modes of diene hydrometallation.



In contrast, under the conditions that promote C2-selective reductive coupling, the pattern of deuterium incorporation suggests rapid, reversible diene hydrometallation at all positions of the diene prior to C-C coupling (Scheme 2.12).[6a] Significant incorporation of deuterium at the diene C1-position suggests hydrometallation modes **D** and **E** are now readily traversed. These data are consistent with the hypothesis that enhanced cationic character and coordinative unsaturation associated with the C2-regioselective catalyst, $RuH(O_2CC_7F_{15})(CO)(DPPB)(PPh_3)$, enables access to additional hydrometallation modes and thus, π-allylruthenium isomers, that are seldom accessed using neutral ruthenium catalysts.

Scheme 2.12. Isotopic labeling studies involving ruthenium catalyzed reductive coupling of diene **2.8** to paraformaldehyde at the C2-position.[a]



$(CD_2O)_n$ + *i*-PrOH	$(CH_2O)_n$ + *i*-PrOH-d_8	$(CD_2O)_n$ + *i*-PrOH-d_8
H_a (5% ^2H)	H_a (52% ^2H)	H_a (17% ^2H)
H_b (>95% ^2H)	H_b (0% ^2H)	H_b (>95% ^2H)
H_c (17% ^2H)	H_c (46% ^2H)	H_c (77% ^2H)
H_d (13% ^2H)	H_d (51% ^2H)	H_d (59% ^2H)

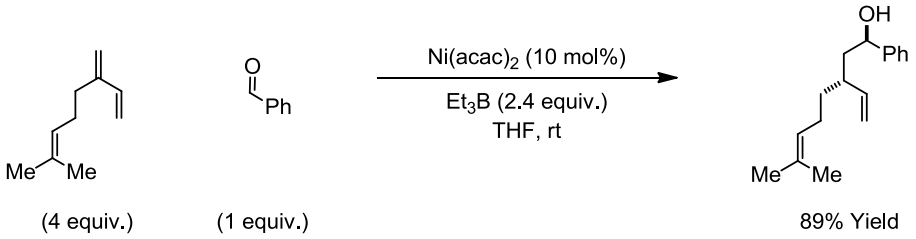
2.3 C1- and C4-Regioslective Hydrohydroxymethylations

2.3.1 BACKGROUND

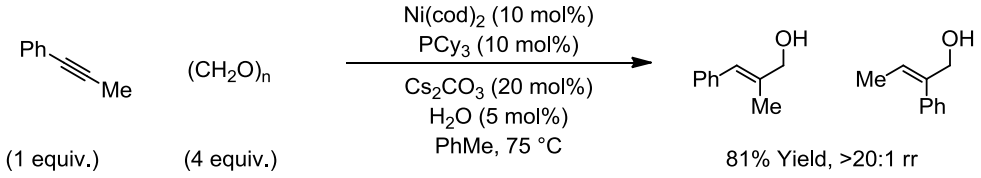
Based on the work of Tamaru, such C1-regioselectivity is evident in the nickel (0) catalyzed diene-aldehyde reductive couplings,[12,13] which are known to operate through a mechanism involving diene-aldehyde oxidative coupling.[14] One of the major drawbacks of these couplings is the need for exogenous terminal reductants that are either pyrophoric (e.g. Et_2Zn, Et_3B) or highly mass intensive (e.g. R_3SiH) (Scheme 2.13). Previously, conditions were identified for the nickel (0) catalyzed reductive coupling of alkynes to formaldehyde, employing paraformaldehyde as both coupling partner and as reductant *via* transfer hydrogenation (Scheme 2.14). Thus, exogenous reductants were not employed.[15] Similar to the nickel (0) catalyzed diene-aldehyde coupling, the alkyne-formaldehyde coupling is also proposed to occur through oxidative coupling. Therefore, it was postulated that applying these conditions to the coupling of 2-substituted dienes with formaldehyde could lead to the desired C1-regioselective products, without the

drawbacks of the reductants employed in prior nickel (0) catalyzed reductive couplings of dienes (Scheme 2.15).

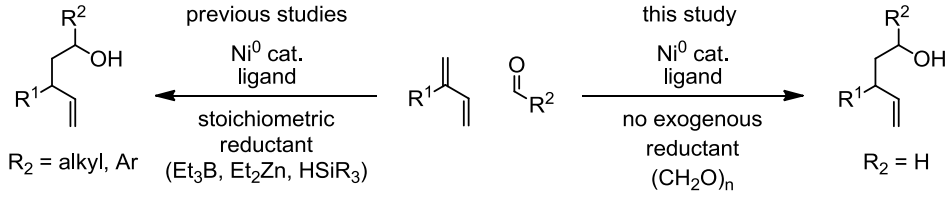
Scheme 2.13. Selected example of regio- and diastereoselective Ni catalyzed coupling of myrcene to benzaldehyde employing pyrophoric reducing agent.



Scheme 2.14. Selected example of regio- and stereoselective Ni catalyzed coupling of alkyne to formaldehyde in the absence of exogenous reductant.



Scheme 2.15. Contrast of previously developed methods requiring stoichiometric amounts of reductant and the reductive coupling reported here.



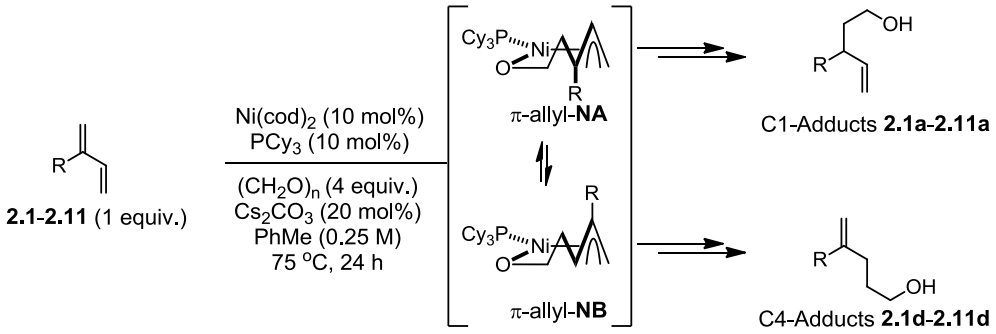
2.3.2 REACTION DEVELOPMENT AND SCOPE

In analogy to the nickel catalyzed couplings of alkynes and paraformaldehyde (Scheme 14),[15] myrcene (1 equiv.) and paraformaldehyde (4 equiv.) were exposed to $Ni(cod)_2$ (10 mol%), PCy_3 (10 mol%), Cs_2CO_3 (20 mol%), and H_2O (5 mol%) in toluene at 75 °C. To our delight, the desired bis-homoallylic alcohol was isolated in 68% yield and good regioselectivity with coupling occurring at the C1- and C4-positions of the diene in a 10:1 ratio, respectively. During screening for optimal conditions, the influence of H_2O (5 mol%) was negligible and subsequently, removed from the reaction to provide the coupling product in the same 68% yield (Table 2.3). Interestingly, it was found that formalin could be employed as a formaldehyde source in lieu of paraformaldehyde when coupling to myrcene under identical reactions conditions, affording the coupling product in 60% yield. Given that paraformaldehyde acts as electrophile and reducing agent, generating formate, the coupling products **2.1a**-**2.11a** appear as the formate esters, which are cleaved in the course of isolation (Tables 2.3 and 2.4).

The partitioning of C1-adducts **2.1a**-**2.11a** and C4-adducts **2.1d**-**2.11d** in these nickel catalyzed processes may be understood as follows. As demonstrated by Ogoshi, oxidative coupling occurs reversibly in stoichiometric reactions of nickel (0), 1,3-dienes, and aldehydes to furnish isolable π-allylalkoxynickel (II) complexes that have been characterized by single crystal x-ray diffraction analysis.[16] In the case of isoprene, coupling at C1 was kinetically preferred (87:13, C1:C4) but over time, the isomeric ratio shifts to favor coupling at C4 (18:82, C1:C4). In analogy, the transient π-allylalkoxynickel (II) complexes π-allyl-**NA** and π-allyl-**NB** are proposed as reactive intermediates *en route* to C1-adducts **2.1a**-**2.11a** and C4-adducts **2.1d**-**2.11d**, respectively (Scheme 2.16). The collective data suggest that under catalytic conditions, a preference for coupling at the C1-position may arise from conversion of the kinetically preferred π-

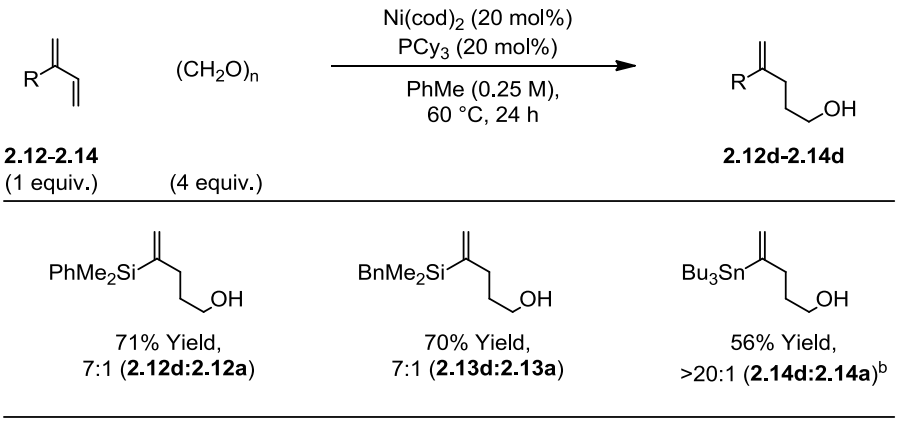
allyl-**NA** to product occurring more rapidly than equilibration between π-allyl-**NA** and π-allyl-**NB**.

Scheme 2.16. Mechanistic basis for partitioning C1- and C4-regioselectivity in the nickel catalyzed reductive coupling of 2-substituted dienes to formaldehyde.[16]



Based on this analysis, diene substituents capable of weakening the newly formed C-C bond may enable reversible oxidative coupling, and therefore equilibration between π-allyl-**NA** and π-allyl-**NB**, potentially leading to an increased proportion of the C4-adduct.[17] Toward this end, silyl- and stannyl-substituted butadienes **2.12**-**2.14** were prepared, as hyperconjugation between the C-Si or C-Sn σ-bond and the σ* orbital of the newly formed C-C bond at C1 should weaken the latter and accelerate isomerization between π-allyl-**NA** and π-allyl-**NB**. Formation of the C4-adducts **2.12d**-**2.14d** should be favored, as π-allyl-**NB** was anticipated to be thermodynamically more stable.[16] To our delight, exposure of 1,3-dienes **2.12**-**2.14** to nickel catalyzed conditions indeed provide a predominance of the C4-regioselective coupling products **2.12d**-**2.14d** (Table 2.5).

Table 2.5. C4-regioselective Ni catalyzed couplings of 2-silyl- and 2-stannyl-1,3-butadienes to formaldehyde.[a]

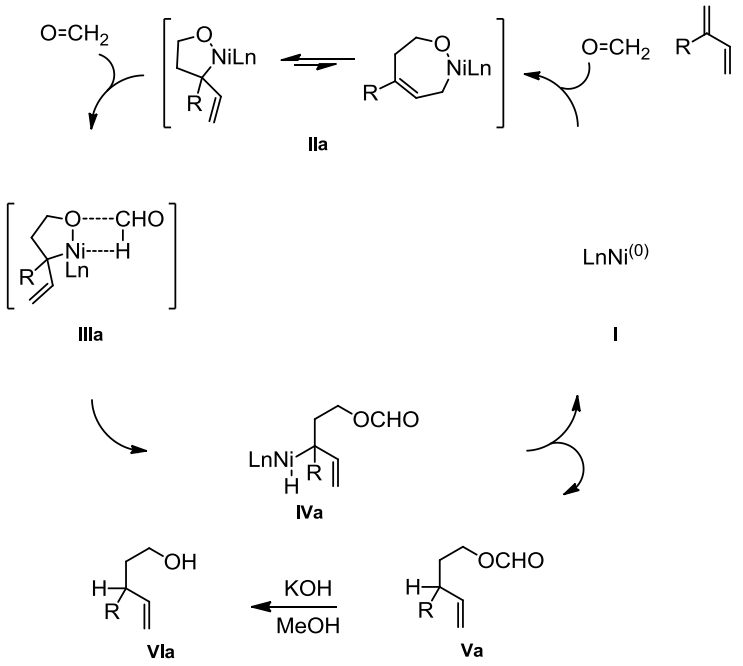


[a]Yield of material isolated by silica-gel chromatography. Regioisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Reaction conducted at 75 °C.

2.3.3 POSTULATED REACTION MECHANISMS

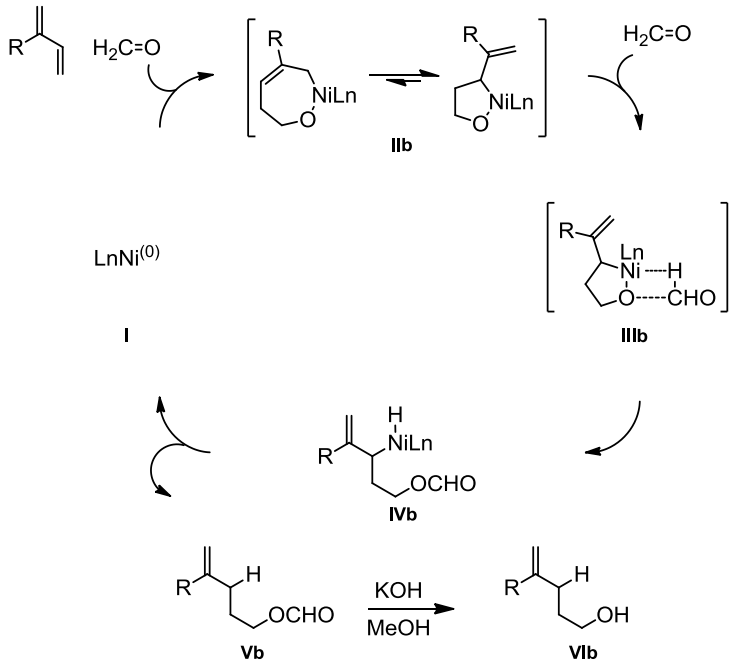
An oxidative coupling pathway is proposed, as found in related nickel catalyzed diene-aldehyde couplings (Scheme 2.17).[12-13] The catalytic cycle begins with oxidative cyclization of the 1,3-butadiene, formaldehyde, and nickel (0) complex to form oxanickel (II) cycle intermediates, **IIa**, where the C-C coupling occurs at the C1-position of the diene. Subsequent cleavage of the Ni-O bond and hydride transfer from formaldehyde, **IIIa**, delivers nickel hydride intermediate **IVa** which may undergo β-hydride elimination to furnish the coupling product as formate ester **Va**, and regenerate the nickel (0) complex, completing the catalytic cycle. Notably, the formate ester is isolable. Upon a basic work-up with methanolic KOH, the desired C1-adduct **VIa** is obtained.

Scheme 2.17. Proposed mechanism for regioselective coupling to C1-position of diene.



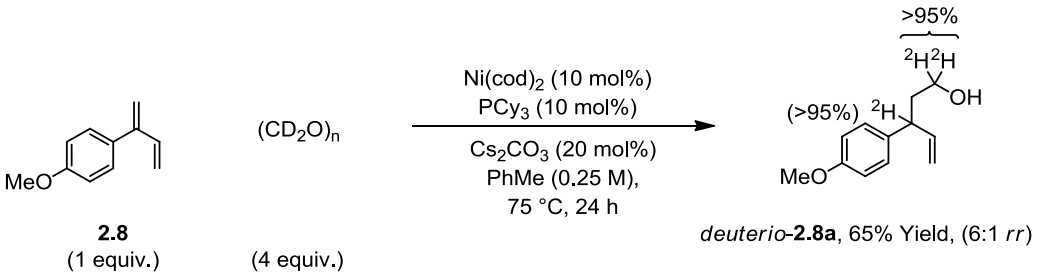
Alternatively, a similar mechanism may be invoked to account for the C4-regioselective couplings, where C-C coupling occurs at the C4-position of the diene during the initial oxidative cyclization event, **IIb** (Scheme 2.18).

Scheme 2.18. Proposed mechanism for regioselective coupling to C4-position of diene.



Isotopic labeling studies were conducted under standard conditions for nickel catalyzed C-C coupling at the diene C1-position using *deuterio*-paraformaldehyde (Scheme 2.19). Deuterium is incorporated exclusively and completely at the former diene C2-position. In addition, complete retention of deuterium is observed at the carbinol methylene. The absence of deuterium at other positions suggests hydrometallative pathways are not operative. Hence, these data are consistent with C-C bond formation *via* an oxidative coupling mechanism, as established in stoichiometric reactions of dienes and aldehydes or ketones with $Ni(cod)_2$.[16]

Scheme 2.19. Isotopic labeling studies involving Ni catalyzed reductive coupling of diene **2.8** to paraformaldehyde at the C1-position.



2.8 (1 equiv.) (4 equiv.) *deuterio*-**2.8a**, 65% Yield, (6:1 *rr*)

2.4 Conclusion

In summary, regiodivergent reductive coupling of dienes **2.1**-**2.11** to paraformaldehyde was achieved at the diene C1, C2, and C3 positions, employing metal catalysts based on nickel, cationic ruthenium, and neutral ruthenium, respectively. Changing the 2-substituent of the butadiene to silicon or tin allowed for the first report of C4-regioselective reductive coupling of 2-substituted butadienes and aldehydes. For the ruthenium catalyzed processes, diene hydrometallation serves to generate a nucleophilic allylruthenium intermediate, which undergoes addition to formaldehyde by way of the primary σ-allylruthenium haptomer. Whereas cationic ruthenium catalysts hydrometallate reversibly, the neutral ruthenium catalysts engage in kinetically controlled diene hydrometallation, thus enabling formaldehyde addition from regioisomeric π-allylruthenium intermediates. For the nickel catalyzed processes, a mechanism involving diene-formaldehyde oxidative coupling is operative and formaldehyde serves dually as reducing agent and electrophile. Overall, the present transformations offer potential alternatives to the hydroformylation of 2-substituted butadienes, and in certain cases represent the only catalytic methods available to achieve these particular one carbon homologations.

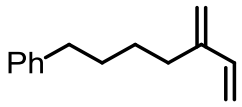
2.5 Experimental Section

General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringe. Reaction tubes were oven-dried and cooled under a stream of argon. Reactions tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Toluene and 1,4-dioxanes were purified from sodium and benzophenone. $RuHCl(CO)(PPh_3)_3$was prepared according to literature procedure.[18] $Ni(cod)_2$ and all ligands were used as received from Strem Chemicals Inc. Isopropanol (99.8%, extra dry) and paraformaldehyde were obtained and used as received from Acros Organics. For nickel catalysis, paraformaldehyde was purchased and immediately taken into the drybox, where it was stored in the refrigerator. $Ni(cod)_2$, PCy_3, and Cs_2CO_3 were purchased from Aldrich and stored in the drybox prior to use. Unless noted otherwise, 2-substituted dienes **2.1-2.14** were prepared in accordance with literature procedure.[19,20] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F_{254}) and products were visualized by UV, $KMnO_4$ and/or anisaldehyde stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[21] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Coupling constants are reported in Hertz (Hz).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini or 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini or 400 (100 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00 s).

Experimental Procedures and Spectroscopic Data for Novel Dienes

(5-methylenehept-6-en-1-yl)benzene (2.3)



(5-methylenehept-6-en-1-yl)benzene (**9**) was prepared by modifying an iron catalyzed coupling method reported by Cossy and coworkers.[22]

To a flame dried one neck round bottom flask equipped with a magnetic stir bar was added $FeCl_3$ (0.49 mg, 3.0 mmol, 20 mol%) and THF (50 ml). It was cooled to 0 °C followed by addition of 1-iodo-4-phenylbutane[23] (3.9 g, 15 mmol, 1.0 equiv.) The

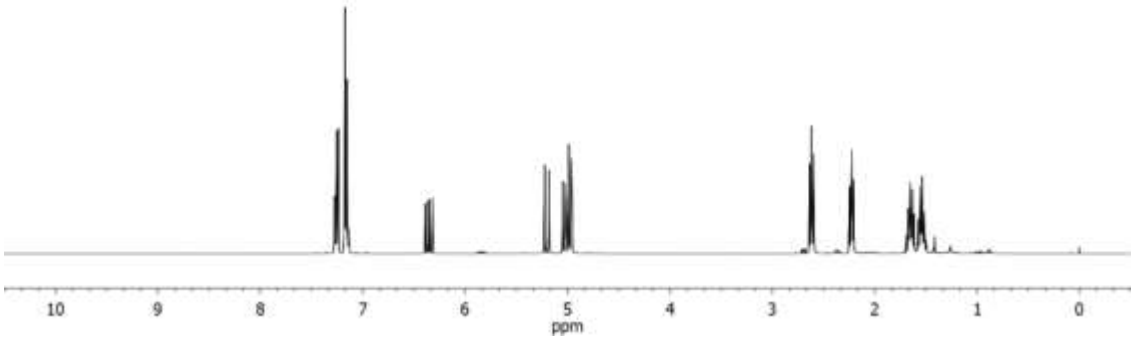
resulting solution was stirred at 0 °C for 10 min and a solution of chloroprene Grignard (43 ml, 30 mmol, 0.7 M in THF, 2.0 equiv.) and TMEDA (4.3 ml, 29 mmol, 1.9 equiv.) was added drop-wise over 1 h. After further 2 h at 0 °C, the reaction mixture was quenched by adding an aqueous saturated NH_4Cl solution. After extractive workup and evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound (1.5 g, 53%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H), 7.19 – 7.13 (m, 3H), 6.35 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.20 (ddd, *J* = 17.6, 1.1, 0.5 Hz, 1H), 5.07 – 4.93 (m, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.23 (t, *J* = 8.0 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.58 – 1.49 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 142.6, 138.9, 128.3, 128.2, 125.6, 115.6, 113.1, 35.8, 31.4, 31.2, 27.7.

HRMS (CI) Calcd. For $C_{14}H_{18}$ [M^+]: 186.1409, Found: 186.1405.

FTIR (in $CDCl_3$): 3086, 3026, 2932, 2858, 1594, 1496, 1453, 1030, 991, 893, 744, 697 cm^{-1}.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6
5
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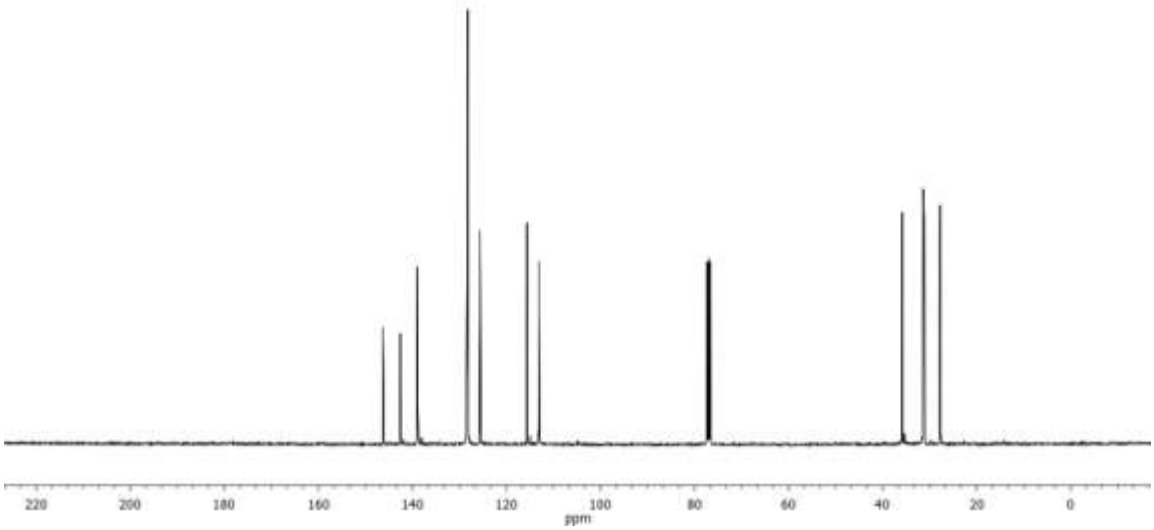
220
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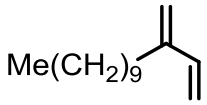
180
160
140
120
100
80
60
40
20
0
ppm

3-methylenetridec-1-ene (2.5)



3-methylenetridec-1-ene (**2.5**) was prepared by applying a iron catalyzed coupling method reported by Cossy to a new substrate.[21]

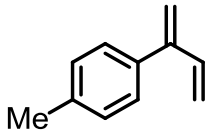
To a flame dried one neck round bottom flask equipped with a magnetic stir bar was added $FeCl_3$ (0.49 mg, 3.0 mmol, 20 mol%) and THF (50 mL). It was cooled to 0 °C followed by addition of 1-bromodecane (3.3 g, 15 mmol, 1.0 equiv.) The resulting solution was stirred at 0 °C for 10 min and a solution of chloroprene Grignard (43 mL, 30 mmol, 0.7 M in THF, 2.0 equiv.) and TMEDA (4.3 mL, 29 mmol, 1.9 equiv.) was added drop wise over 2 h. After further 2 h at 0 °C, the reaction mixture was quenched by adding an aqueous saturated NH_4Cl solution. After extractive workup and evaporation of the solvent, the residue was distilled (5 Torr, 85 °C) to furnish the title compound (0.4 g, 14%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 5.01 – 4.97 (m, 2H), 2.20 (t, *J* = 7.7 Hz, 2H), 1.53 – 1.43 (m, 2H), 1.35 – 1.22 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 139.2, 115.5, 113.1, 32.0, 31.5, 29.7, 29.6, 29.4, 28.3, 22.8, 14.2.

Spectral data correspond to that reported in literature.[24]

1-(buta-1,3-dien-2-yl)-4-methylbenzene (2.7)



1-(buta-1,3-dien-2-yl)-4-methylbenzene (**2.7**) was prepared by modifying an enyne metathesis method reported by Mori and coworkers.[19a]

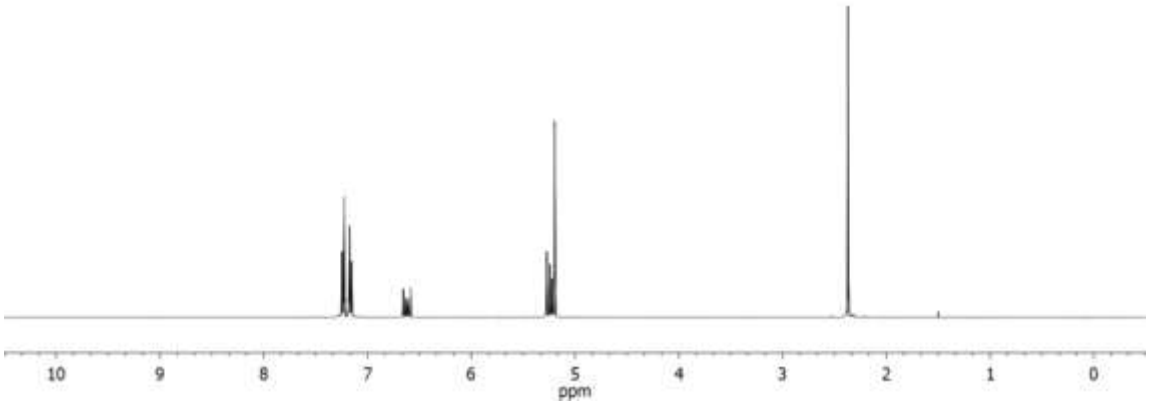
A 100 mL round-bottom flask was charged with Grubb's 2nd generation catalyst (85 mg, 0.10 mmol, 2 mol%), 4-tolylacetylene (0.63 mL, 5.0 mmol, 100 mol%), and toluene (50 mL, 0.1 M). The reaction vessel was purged with ethylene gas followed by heating to 80 °C under 1 atm of ethylene gas. The reaction mixture was allowed to stir for 6 h at 80 °C and cooled to ambient temperature. Ethyl vinyl ether (several drops) was added and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 2% EtOAc/hexane) to afford the title compound (0.50 g, 70%) as a colorless liquid.

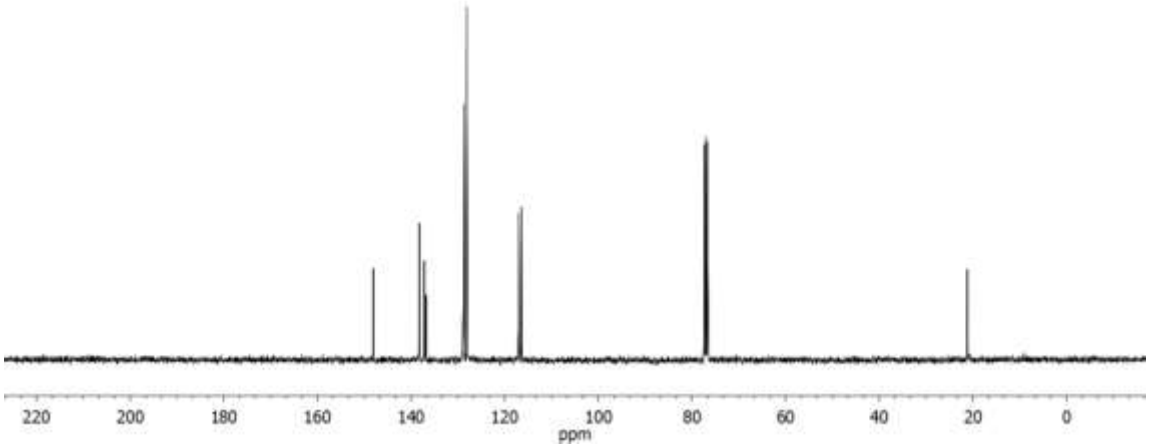
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.27 – 7.21 (m, 2H), 7.20 – 7.12 (m, 2H), 6.68 – 6.56 (m, 1H), 5.30 – 5.26 (m, 1H), 5.26 – 5.21 (m, 1H), 5.21 – 5.17 (m, 2H), 2.37 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ148.1, 138.2, 137.2, 136.8, 128.8, 128.1, 117.0, 116.4, 21.2.

HRMS (CI) Calcd. For $C_{11}H_{12}$ $[M]^+$: 144.0937, Found: 144.0937.

FTIR (in $CDCl_3$): 3087, 3026, 2921, 1512, 1437, 1379, 1020, 991, 893, 823, 729, 695 cm^{-1}.




220
200
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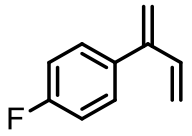
ppm

1-(buta-1,3-dien-2-yl)-4-fluorobenzene (2.11)



1-(buta-1,3-dien-2-yl)-4-fluorobenzene (**2.11**) was prepared by modifying a nickel catalyzed coupling method reported by Kumada and coworkers.[25]

To a 300 mL sealed tube (sealing was used to prevent loss of chloroprene) equipped with a magnetic stir bar was added Ni(dppe)Cl_2 (0.26 g, 0.50 mmol, 1 mol%), Et_2O (10 ml) and then chloroprene (6.6 g, 75 mmol, 1.5 equiv.). The mixture was cooled to 0 °C and stirred for 5 min. Then 4-fluorophenylmagnesiumbromide (100 mL, 50 mmol, 0.5 M in Et_2O) was added drop-wise under inert atmosphere followed by addition of toluene (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for 40 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). After evaporation of the solvents, the mixture was purified by distillation (5 Torr, 50 °C) to furnish the title compound (3.5 g, 47%) as a colorless liquid.

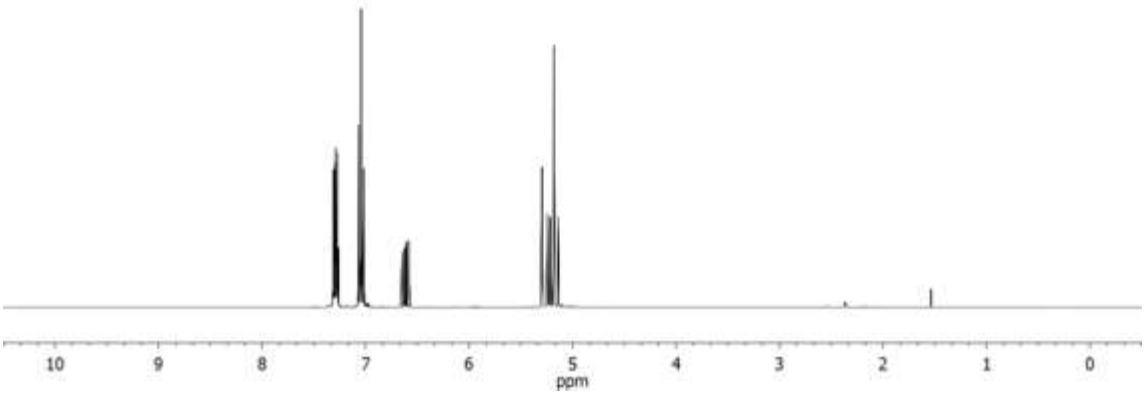
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (m, 2H), 7.09 – 6.99 (m, 2H),
6.61 (ddd, *J* = 17.2, 10.7, 0.6 Hz, 1H), 5.32 – 5.27 (m, 1H), 5.23 (ddd, *J* = 10.7, 1.2, 0.6 Hz, 1H), 5.20 – 5.11 (m, 2H).

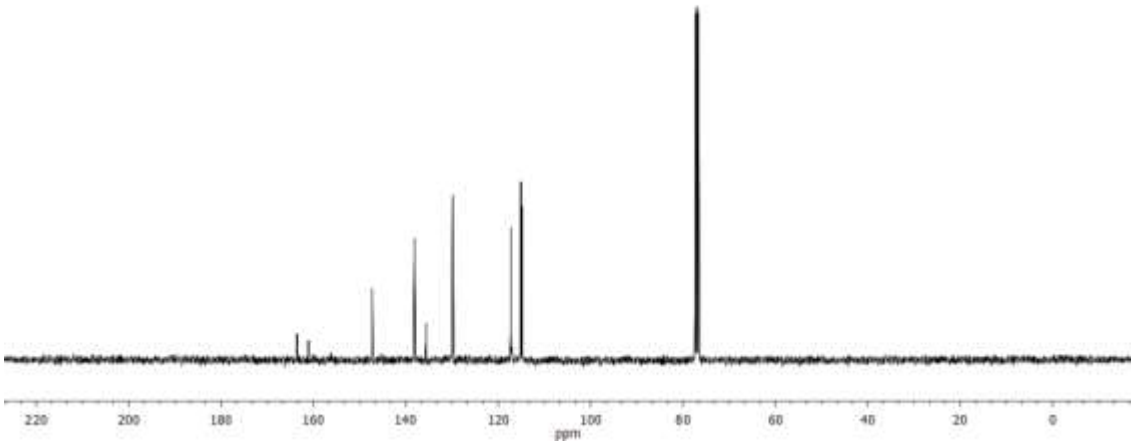
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d, J = 245.9 Hz), 147.2, 138.1, 135.6 (d, J = 3.2 Hz, 2C), 129.9 (d, J = 8.0 Hz), 117.2, 117.1, 115.0 (d, J = 21.5 Hz, 2C).

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.17 (m_c).

HRMS (CI) Calcd. For $C_{10}H_8F$ $[M]^+$: 148.0688, Found: 148.0689.

FTIR (in $CDCl_3$): 3091, 2970, 1738, 1604, 1507, 1366, 1317, 1296, 1220, 1158, 1095, 1037, 1014, 991, 899, 838, 818, 735, 663 cm^{-1}.

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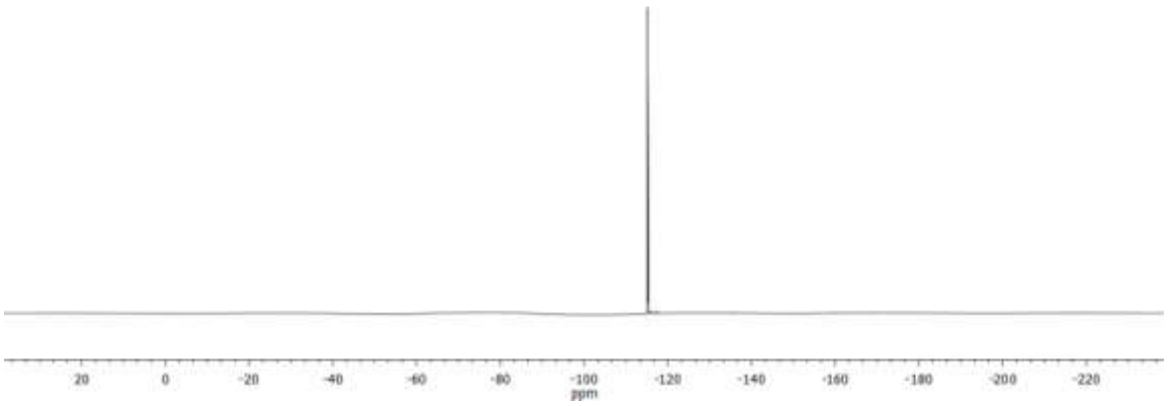
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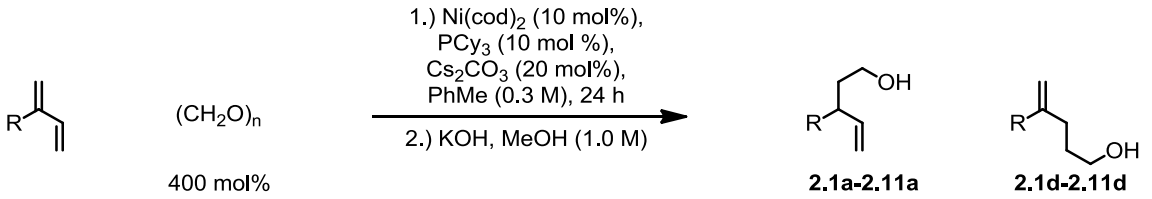
ppm

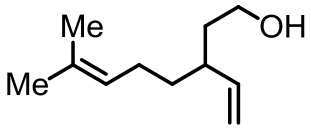
Experimental Procedures and Spectroscopic Data for the Nickel Catalyzed Regioselective Couplings at the C_1 – position



General Procedure A for the coupling of 2-substituted dienes 2.1-2.11 to paraformaldehyde

An oven dried re-sealable pressure flask equipped with stir bar was charged with $Ni(cod)_2$ (14 mg, 0.050 mmol, 10 mol%), PCy_3 (14 mg, 0.050 mmol, 10 mol%), Cs_2CO_3 (33 mg, 0.100 mmol, 10 mol%) and paraformaldehyde (60 mg, 2.0 mmol, 400 mol%) inside of a drybox. The flask was sealed and removed from the drybox. Under a flow of argon, toluene was added to the flask (2 mL, 0.3 M relative to diene). While stirring, the diene (0.5 mmol, 100 mol%) was added. The flask was sealed and placed in an oil bath at 75 °C for 24 h. The reaction mixture was allowed to cool to room temperature, at which point methanolic KOH (1.0 M) was added and stirred for 2 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with HCl (1.0 M). The organics were removed and the aqueous layer was extracted twice with CH_2Cl_2 (15 mL). The combined organics were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2) to furnish the title compounds.

7-methyl-3-vinyloct-6-en-1-ol (2.1a)



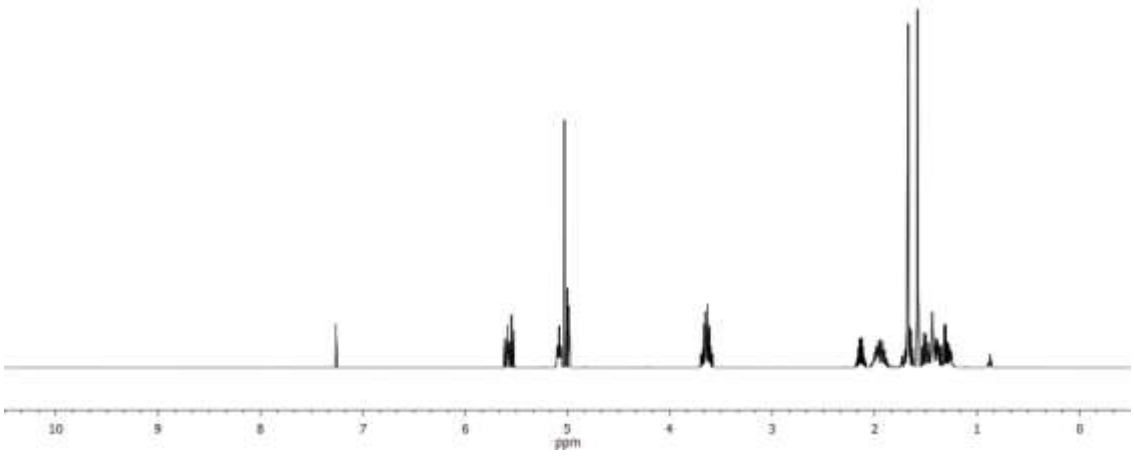
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.1**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (57 mg, 68%, 10:1 r.r.) as a colorless oil.

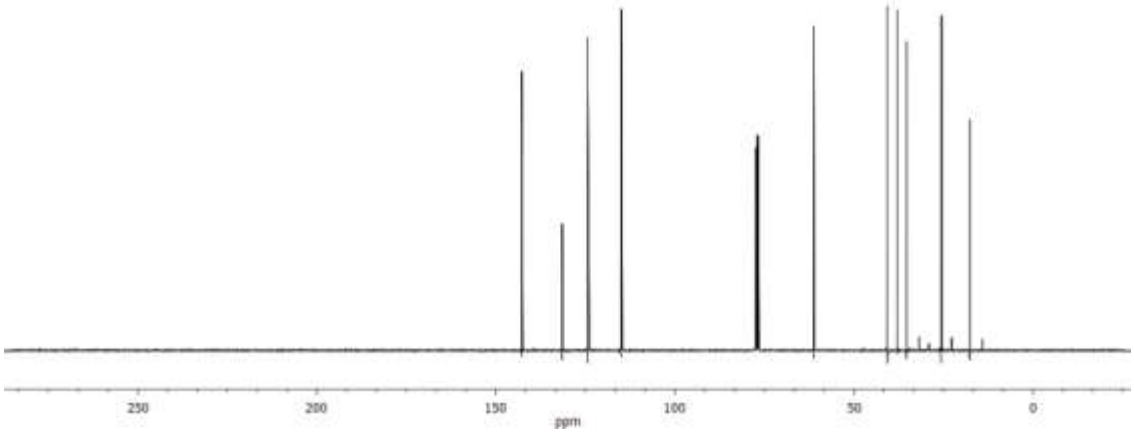
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (m_c, 1H), 5.12 – 5.05 (m, 1H), 5.03 (s, 1H), 5.01 – 4.97 (m, 1H), 3.71 – 3.57 (m, 2H), 2.20 – 2.07 (m, 1H), 2.05 – 1.85 (m, 2H), 1.74 – 1.62 (m, 4H), 1.58 (s, 3H), 1.55 – 1.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 131.5, 124.4, 115.0, 61.3, 40.8, 37.8, 35.3, 25.7, 25.6, 17.7.

HRMS (APCI) Calcd. For $C_{11}H_{20}O$ $[M+H]^+$: 169.1587, Found: 169.1588.

FTIR (in $CDCl_3$): 3321, 3076, 2965, 2916, 2856, 1639, 1449, 1419, 1376, 1053, 995, 911, 832, 735, 682 cm^{-1}.


10
9
8
7
6
5
4
3
2
1
0
ppm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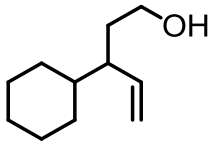
ppm

3-cyclohexylpent-4-en-1-ol (2.2a)



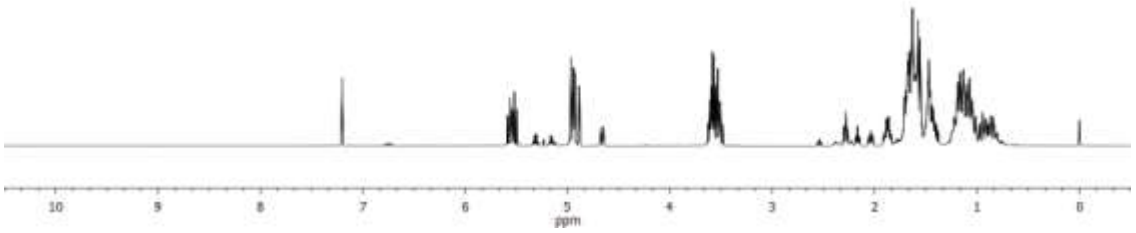
In modification to **General Procedure A** (*via* diene **2.2**), the reaction was conducted at 0.3 mmol scale with 15 mol% of $Ni(cod)_2$ and 15 mol% of PMe_3 as ligand. After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (31 mg, 61%, 5.3:1.5:1:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (ddd, J = 17.0, 9.9, 9.9 Hz, 1H), 5.07 – 4.90 (m, 2H), 3.69 – 3.54 (m, 2H), 2.01 – 1.87 (m, 1H), 1.79 – 1.43 (m, 8H), 1.31 – 0.84 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 115.6, 61.7, 47.1, 42.0, 34.6, 31.0, 29.7, 26.7, 26.6.

HRMS (CI) Calcd. For $C_{11}H_{21}O$ $[M+H]^+$: 169.1592, Found: 169.1590.

FTIR (in $CDCl_3$): 3288, 2922, 2852, 2360, 2340, 1448, 1055, 911, 667 cm^{-1}.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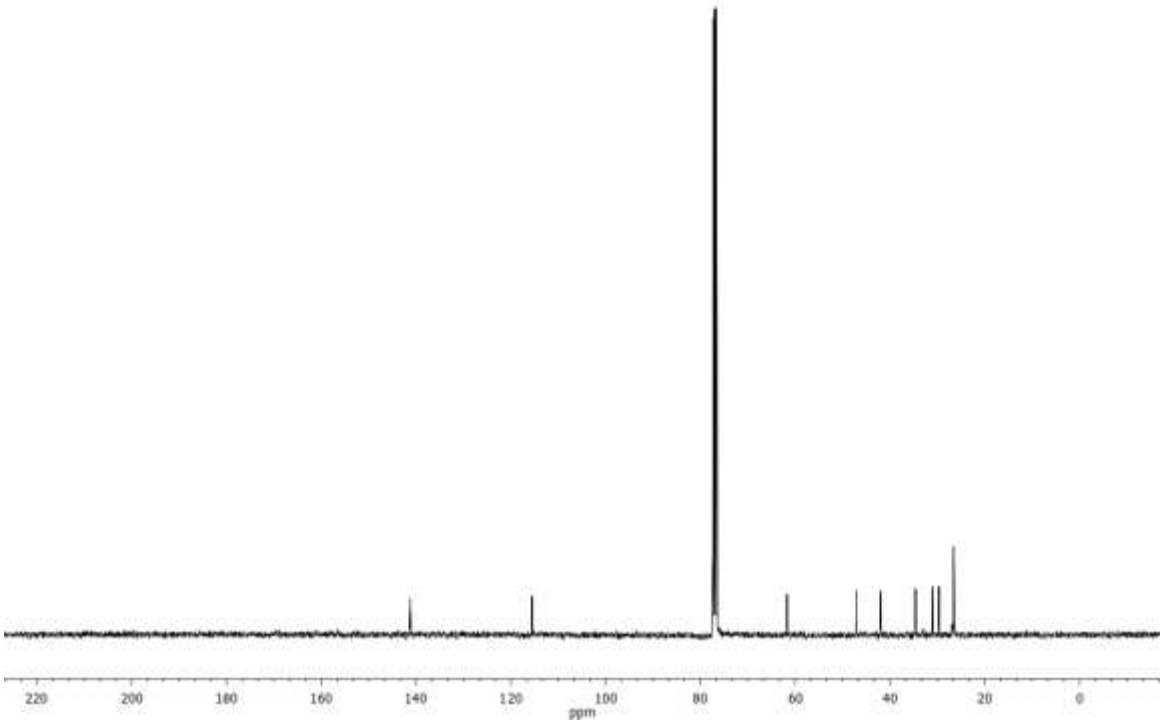
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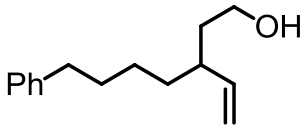
ppm

7-phenyl-3-vinylheptan-1-ol (2.3a)



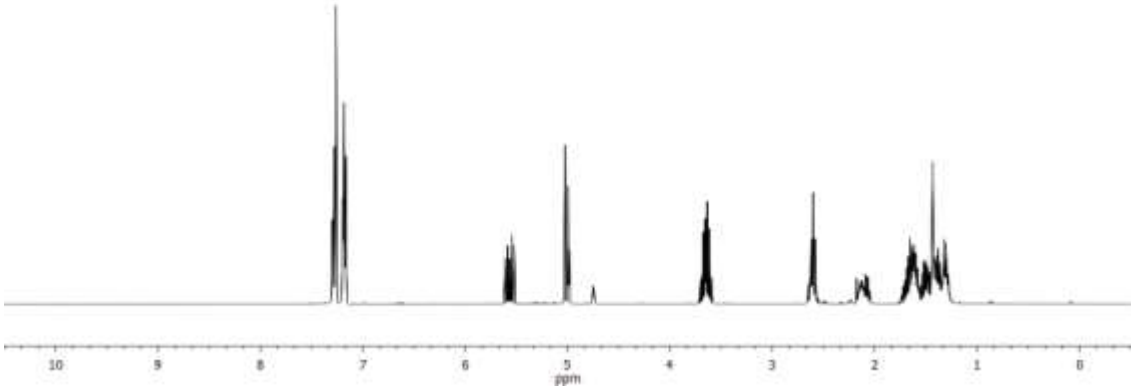
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.3**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (82 mg, 75%, 7:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 5.64 – 5.49 (m, 1H), 5.05 – 5.01 (m, 1H), 5.01 – 4.97 (m, 1H), 3.71 – 3.58 (m, 2H), 2.67 – 2.55 (m, 2H), 2.19 – 2.05 (m, 1H), 1.76 – 1.25 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 142.7, 128.3, 128.2, 125.6, 114.8, 61.3, 41.1, 37.8, 35.9, 35.0, 31.5, 26.8.

HRMS (APCI) Calcd. For $C_{15}H_{23}O$ $[M+H]^+$: 219.1743, Found: 219.1744.

FTIR (in $CDCl_3$): 3319, 3063, 3026, 2928, 2856, 1640, 1604, 1496, 1453, 1418, 1050, 1029, 995, 910, 745, 697 cm^{-1}.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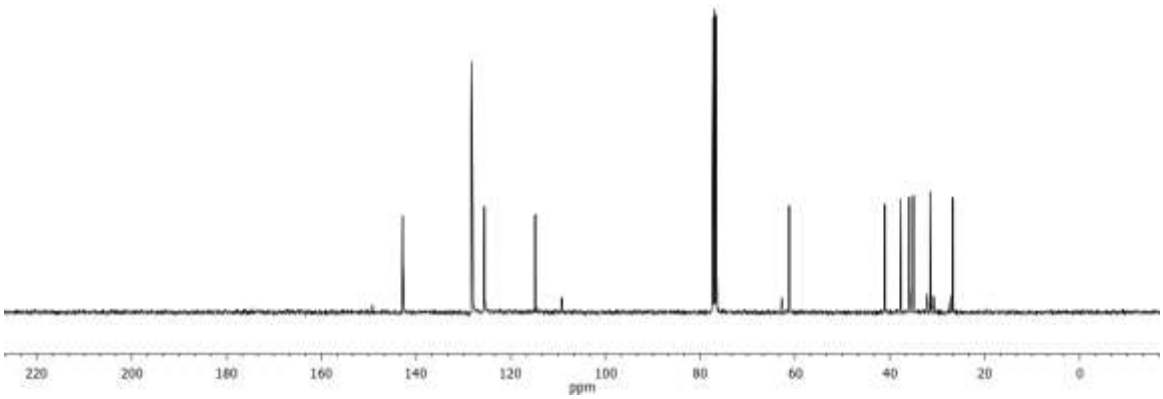
220
200
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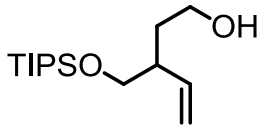
ppm

3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-ol (2.4a)



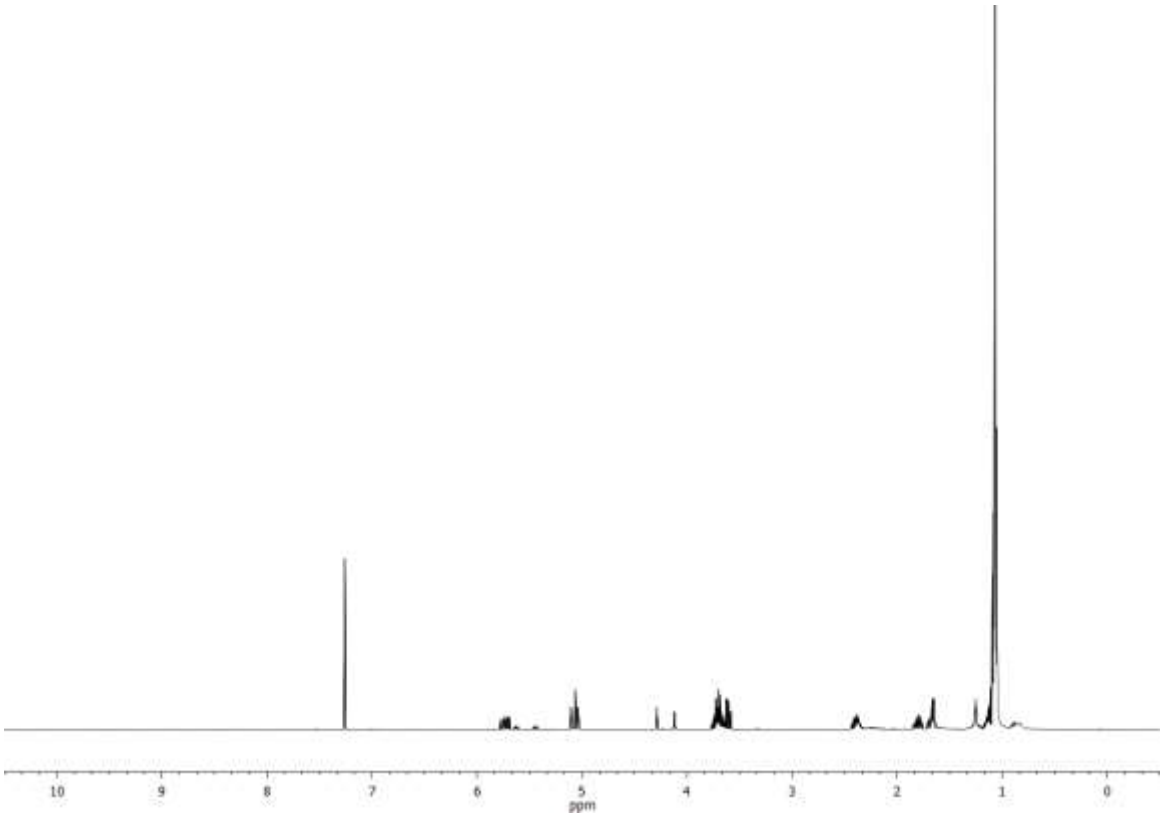
In modification to **General Procedure A** (*via* diene **2.4**), the reaction was conducted with 20 mol% of $Ni(cod)_2$ and 20 mol% of PCy_3. After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (41 mg, 50%, 2:1 r.r (to all other isomers)) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddd, J = 17.3, 10.3, 8.4 Hz, 1H), 5.14 – 5.00 (m, 2H), 3.78 – 3.56 (m, 4H), 2.47 – 2.34 (m, 1H), 1.71 – 1.61 (m, 2H), 1.13 – 1.02 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 115.6, 67.0, 61.3, 44.4, 35.1, 18.0, 18.0, 11.9.

HRMS (CI) Calcd. For $C_{15}H_{33}O_2Si$ $[M+H]^+$: 273.2250, Found: 273.2250.

FTIR (in $CDCl_3$): 3345, 2942, 2892, 2865, 1641, 1463, 1383, 1247, 1106, 1055, 1013, 995, 915, 881, 795, 680, 658 cm^{-1}.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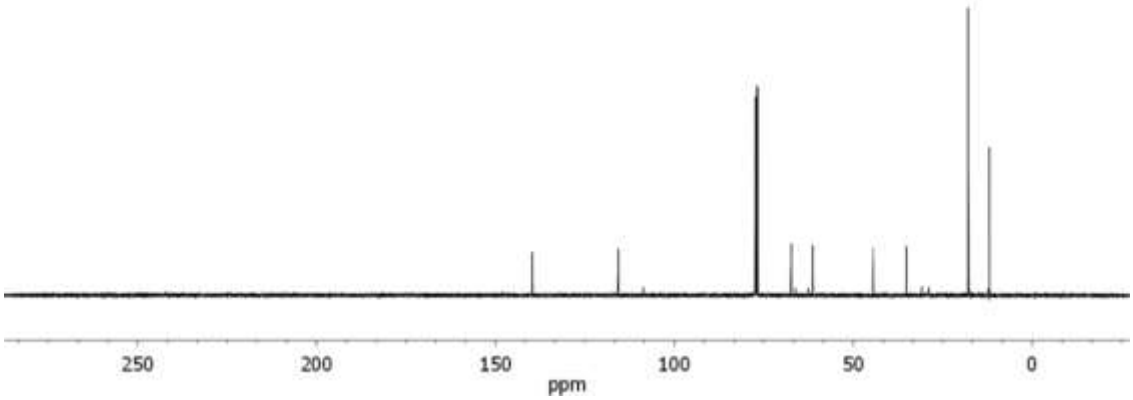
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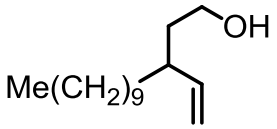
ppm

3-decylpent-4-en-1-ol (2.5a)



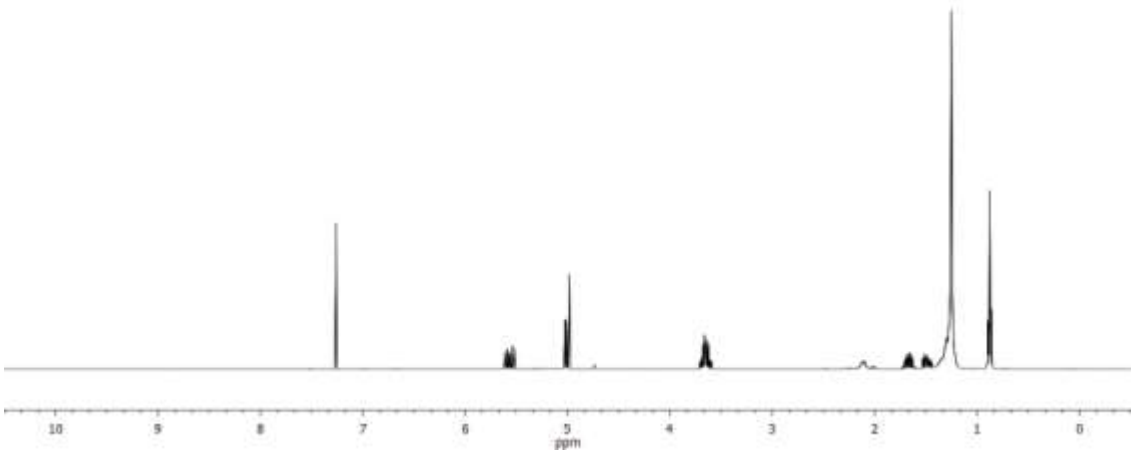
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.5**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (78 mg, 69%, 11:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 – 5.47 (m, 1H), 5.06 – 4.95 (m, 2H), 3.71 – 3.59 (m, 2H), 2.19 – 2.06 (m, 1H), 1.75 – 1.59 (m, 1H), 1.55 – 1.43 (m, 1H), 1.40 – 1.16 (m, 19H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 114.7, 61.4, 41.2, 37.9, 35.2, 31.9, 29.7, 29.7, 29.6, 29.3, 27.1, 22.7, 14.1.

HRMS (APCI) Calcd. For $C_{15}H_{31}O$ $[M+H]^+$: 227.2369, Found: 227.2373.

FTIR (in $CDCl_3$): 3329, 2922, 2853, 1639, 1465, 1418, 1378, 1051, 995, 911, 721, 682 cm^{-1}.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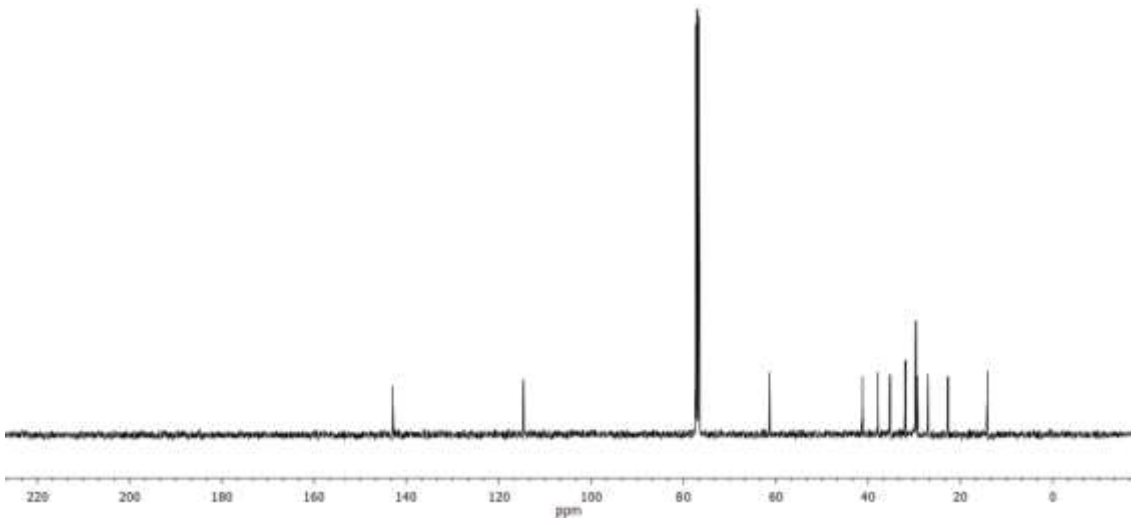
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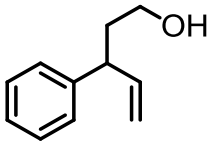
3-phenylpent-4-en-1-ol (2.6a)



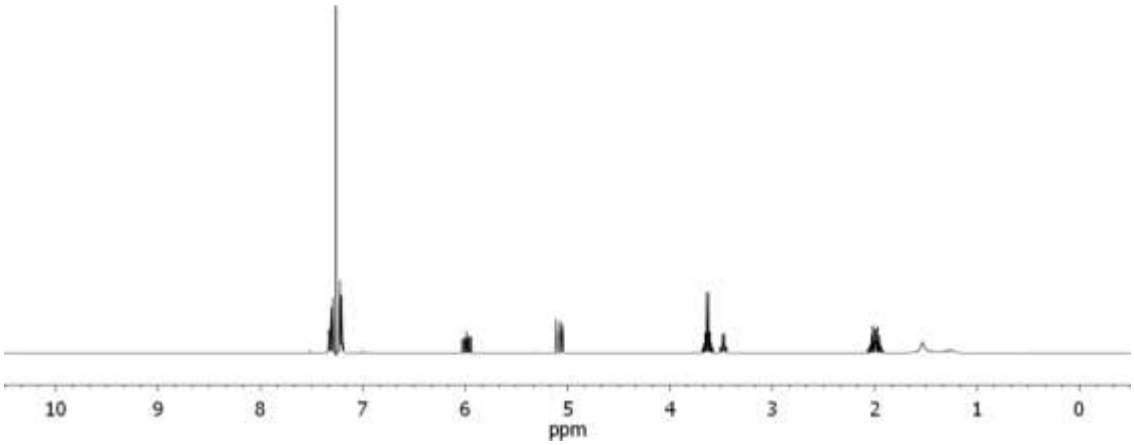
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.6**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (58 mg, 72%, 3:1 r.r.) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 5.98 (ddd, J = 17.4, 10.1, 7.5 Hz, 1H), 5.15 – 5.01 (m, 2H), 3.71 – 3.55 (m, 2H), 3.48 (q, J = 7.6 Hz, 1H), 2.09 – 1.90 (m, 2H), 1.27 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 141.8, 128.6, 127.6, 126.4, 114.4, 61.0, 46.3, 38.0.

HRMS (CI) Calcd. For $C_{11}H_{15}O$ $[M+H]^+$: 163.1123, Found: 163.1126.

Spectral data corresponds to that previously reported.[26]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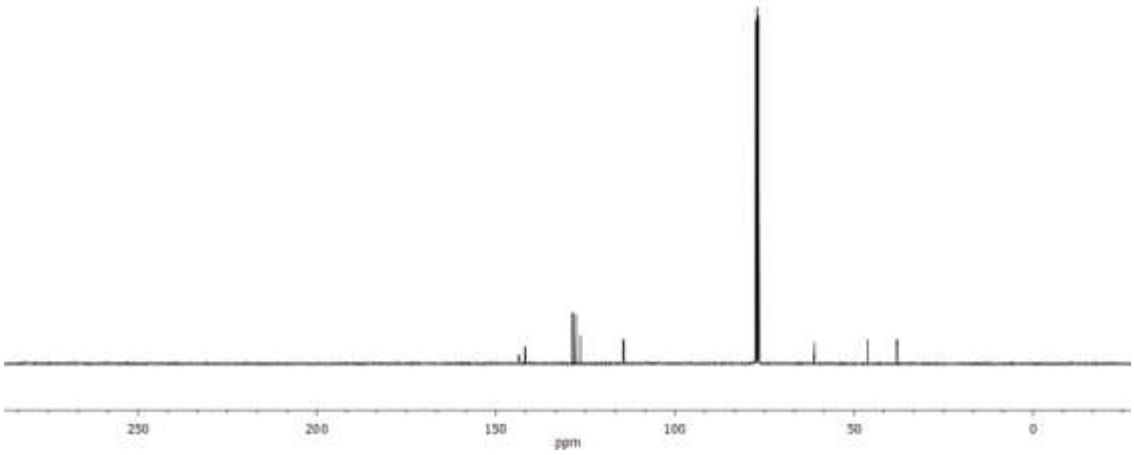
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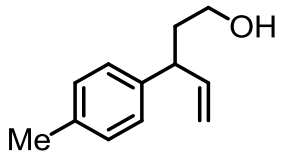
3-(4-methylphenyl)pent-4-en-1-ol (2.7a)



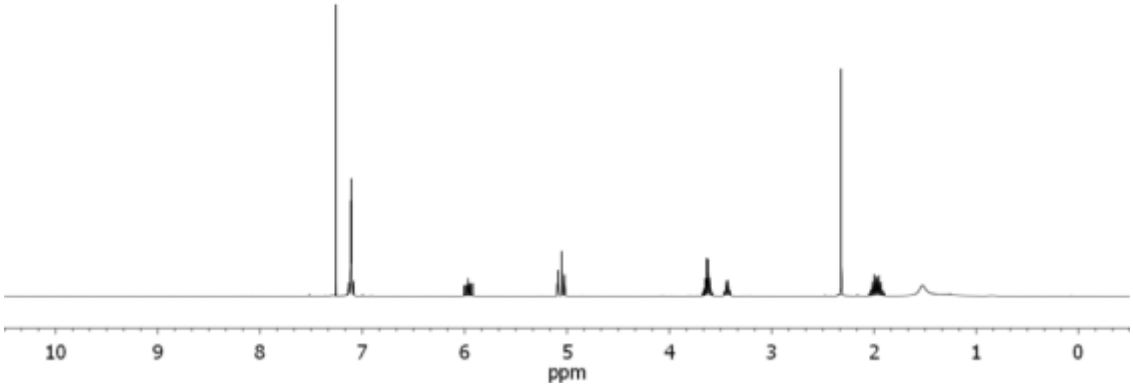
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.7**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (80 mg, 91%, 3:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.07 (m, 4H), 5.96 (ddd, J = 17.5, 10.2, 7.6 Hz, 1H), 5.12 – 5.00 (m, 2H), 3.69 – 3.57 (m, 2H), 3.43 (q, J = 7.6 Hz, 1H), 2.32 (s, 3H), 2.06 – 1.89 (m, 2H), 1.42 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 140.6, 135.9, 129.3, 127.4, 114.2, 61.1, 45.9, 38.0, 21.0.

HRMS (CI [NH_3]) Calcd. For $C_{12}H_{20}NO$ $[M+NH_4]^+$: 194.1545, Found: 194.1541.

FTIR (in $CDCl_3$): 3318, 2924, 2873, 1636, 1513, 1413, 1184, 1109, 1043, 1020, 994, 912, 814, 734 cm^{-1}.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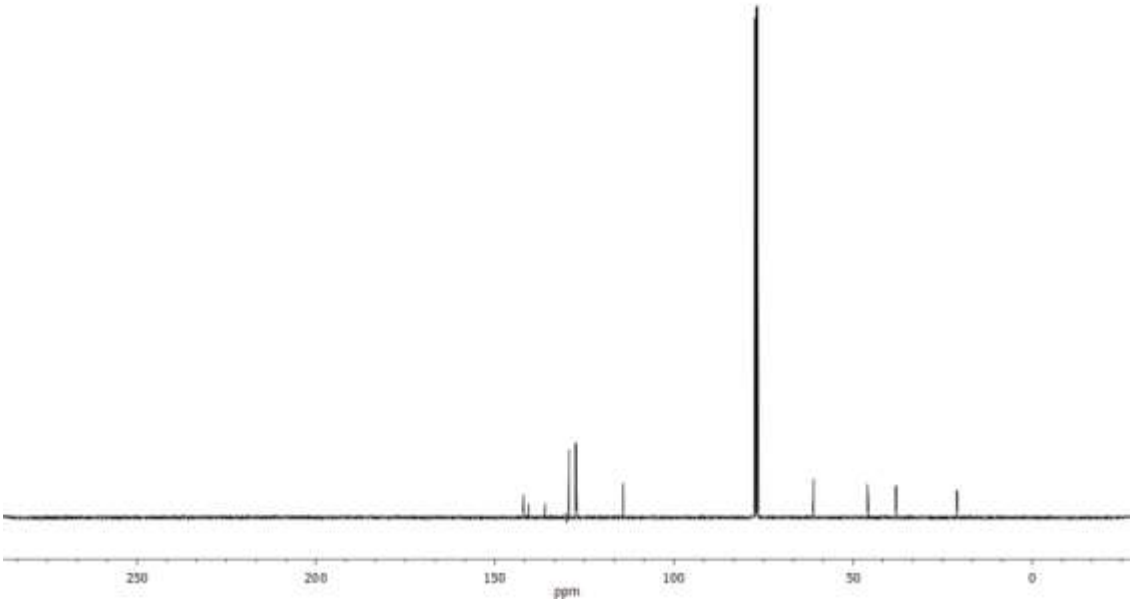
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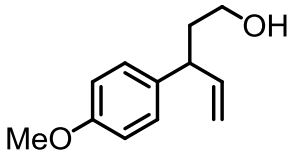
3-(4-methoxyphenyl)pent-4-en-1-ol (2.8a)

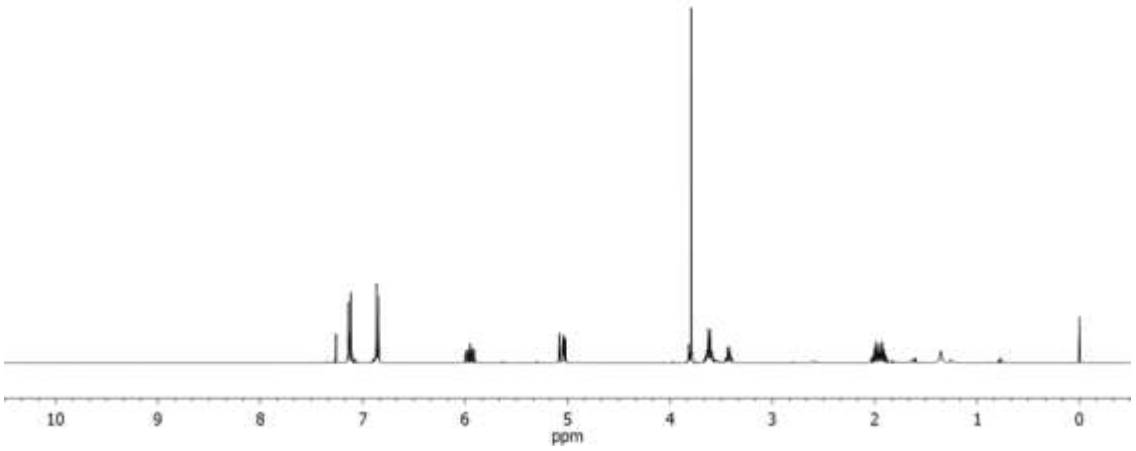


The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.8**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (83 mg, 86%, 7:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.09 (m, 2H), 6.89 – 6.82 (m, 2H), 5.95 (ddd, J = 17.4, 10.2, 7.5 Hz, 1H), 5.11 – 4.99 (m, 2H), 3.79 (s, 3H), 3.67 – 3.57 (m, 2H), 3.43 (q, J = 7.7 Hz, 1H), 2.06 – 1.87 (m, 2H), 1.51 (br s, J = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 128.6, 114.2, 114.1, 61.2, 55.4, 45.5, 38.2.

Spectral data corresponds to that previously reported.[27]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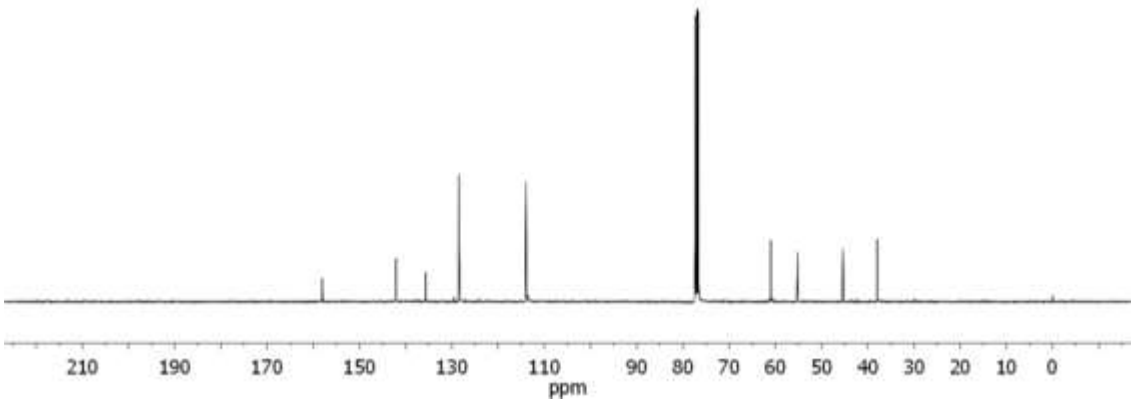
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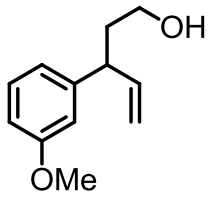
3-(3-methoxyphenyl)pent-4-en-1-ol (2.9a)



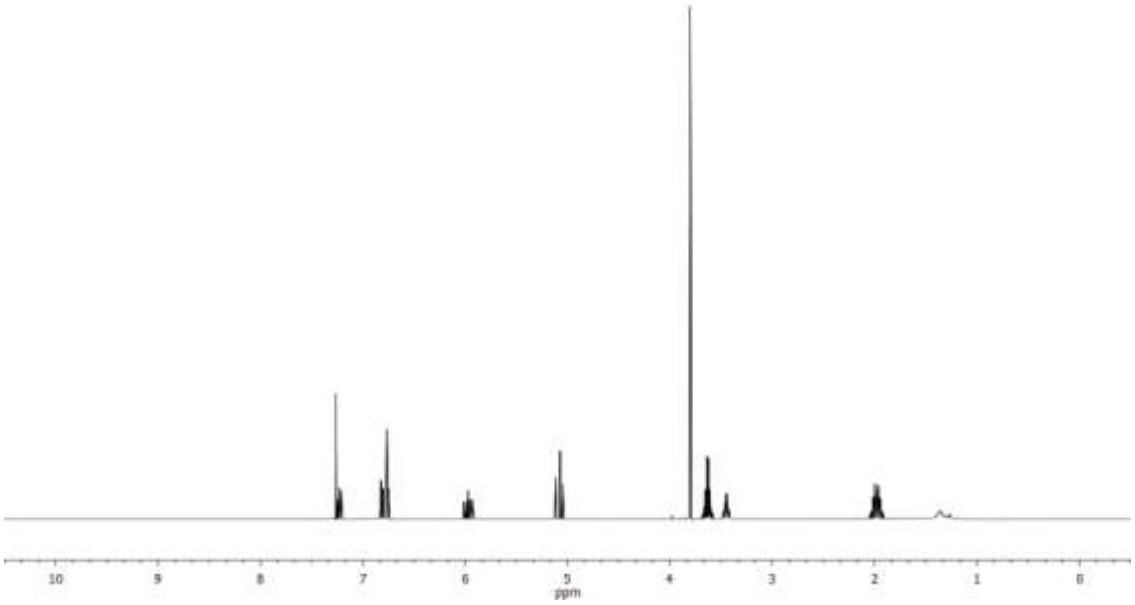
The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.9**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (61 mg, 63%, 4:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.19 (m, 1H), 6.84 – 6.79 (m, 1H), 6.78 – 6.72 (m, 2H), 5.97 (ddd, J = 17.5, 10.2, 7.6 Hz, 1H), 5.15 – 5.01 (m, 2H), 3.80 (s, 3H), 3.70 – 3.56 (m, 2H), 3.45 (q, J = 7.6 Hz, 1H), 2.12 – 1.85 (m, 2H), 1.31 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 145.4, 141.6, 129.6, 119.9, 114.5, 113.5, 111.5, 61.0, 55.2, 46.4, 37.9.

HRMS (EI) Calcd. For $C_{13}H_{19}OSi$ $[M]^+$: 192.1150, Found: 192.1146.

FTIR (in $CDCl_3$): 3338, 2935, 2835, 1599, 1583, 1487, 1453, 1433, 1317, 1259, 1253, 1041, 995, 915, 876, 781, 729, 700 cm^{-1}.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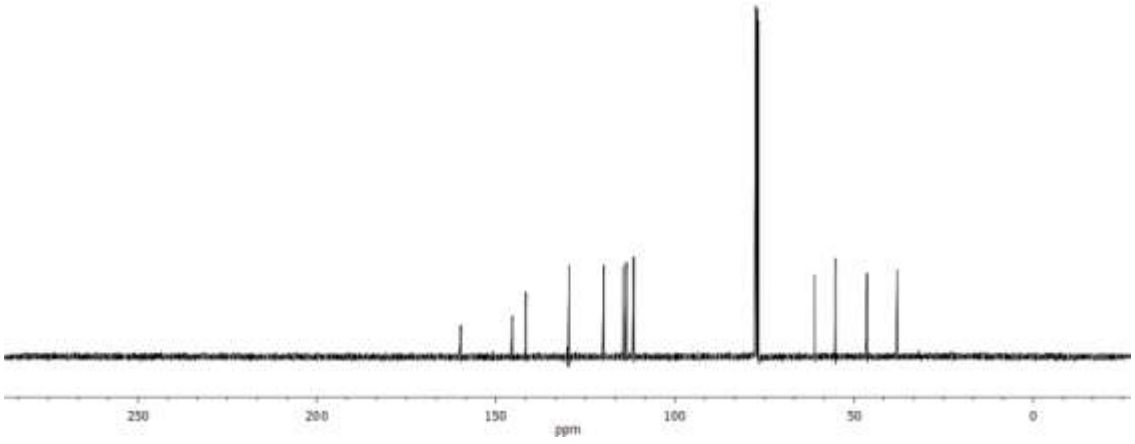
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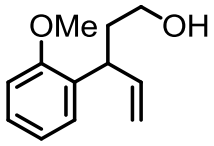
ppm

3-(2-methoxyphenyl)pent-4-en-1-ol (2.10a)



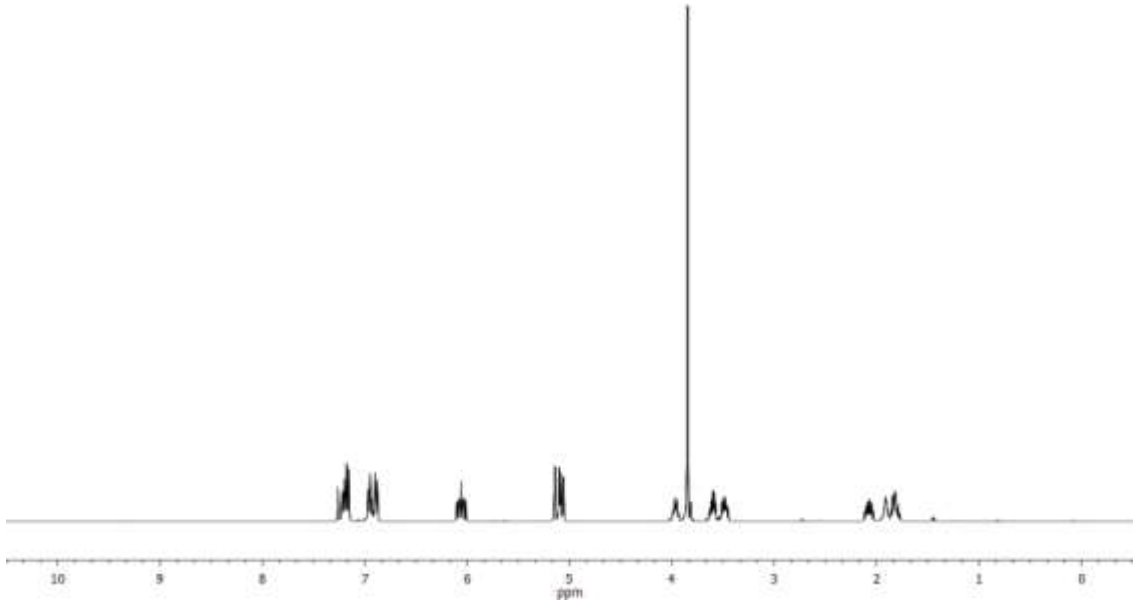
In modification to **General Procedure A** (*via* diene **2.10**), the reaction was conducted with 20 mol% of $Ni(cod)_2$ and 20 mol% of PCy_3. After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (55 mg, 57%, 7:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.10 (m, 2H), 7.00 – 6.84 (m, 2H), 6.06 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H), 5.20 – 5.03 (m, 2H), 4.02 – 3.91 (m, 1H), 3.85 (s, 3H), 3.64 – 3.53 (m, 1H), 3.53 – 3.40 (m, 1H), 2.15 – 2.02 (m, 1H), 1.91 (br s, 1H), 1.88 – 1.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 141.3, 131.7, 128.1, 127.3, 121.0, 114.2, 110.7, 60.9, 55.6, 38.0, 37.6.

HRMS (APCI) Calcd. For $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1151.

FTIR (in $CDCl_3$): 3350, 3075, 2938, 2836, 1636, 1598, 1585, 1491, 1463, 1438, 1288, 1239, 1181, 1099, 1050, 1028, 913, 791, 751, 672 cm^{-1}.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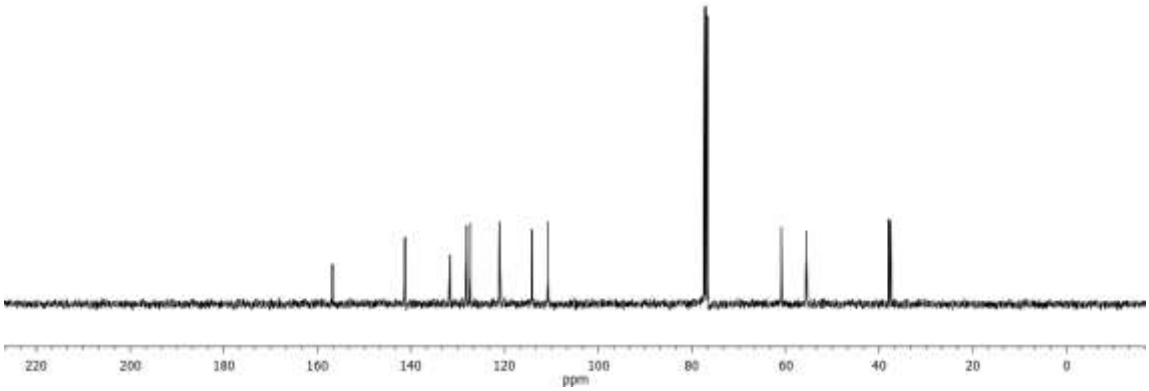
220
200
180
160
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120
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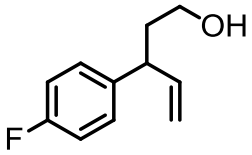
80
60
40
20
0
ppm

3-(4-fluorophenyl)pent-4-en-1-ol (2.11a)



The reaction was conducted in accordance with **General Procedure A** (*via* diene **2.11**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (67 mg, 74%, 4:1 r.r.) as a colorless oil.

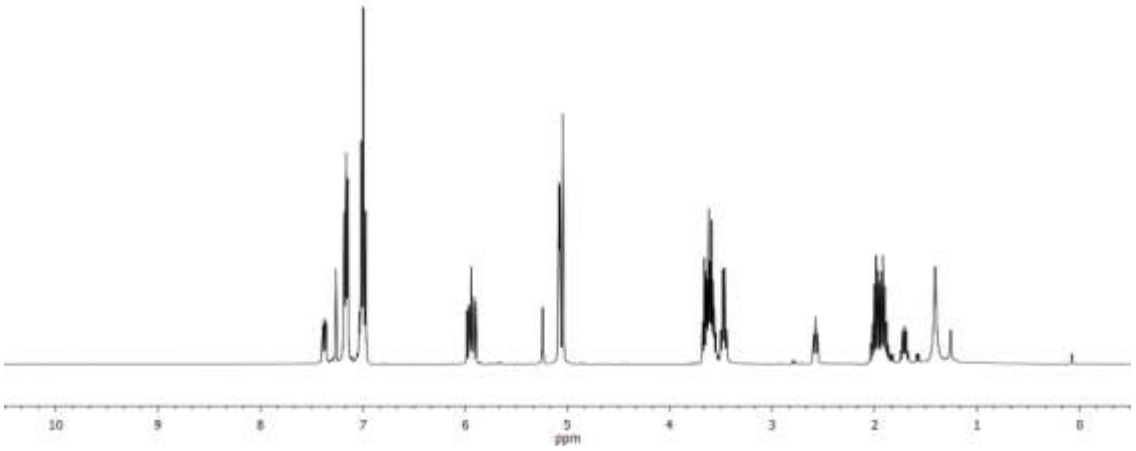
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.13 (m, 2H), 7.05 – 6.95 (m, 2H), 5.94 (ddd, *J* = 17.4, 9.9, 7.5 Hz, 1H), 5.11 – 5.02 (m, 2H), 3.69 – 3.54 (m, 2H), 3.47 (q, *J* = 7.6 Hz, 1H), 2.05 – 1.85 (m, 2H), 1.41 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (d, *J* = 244.3 Hz), 141.6, 139.3, 128.9 (d, *J* = 7.8 Hz, 2C), 115.3 (d, *J* = 21.1 Hz, 2C), 114.6, 60.7, 45.3, 38.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.9 (m_c).

HRMS (CI) Calcd. For $C_{11}H_{12}OF$ $[M]^+$: 180.0950, Found: 180.0949.

FTIR (in $CDCl_3$): 3316, 2937, 1637, 1602, 1508, 1413, 1221, 1159, 1096, 1045, 1015, 916, 832, 741 cm^{-1}.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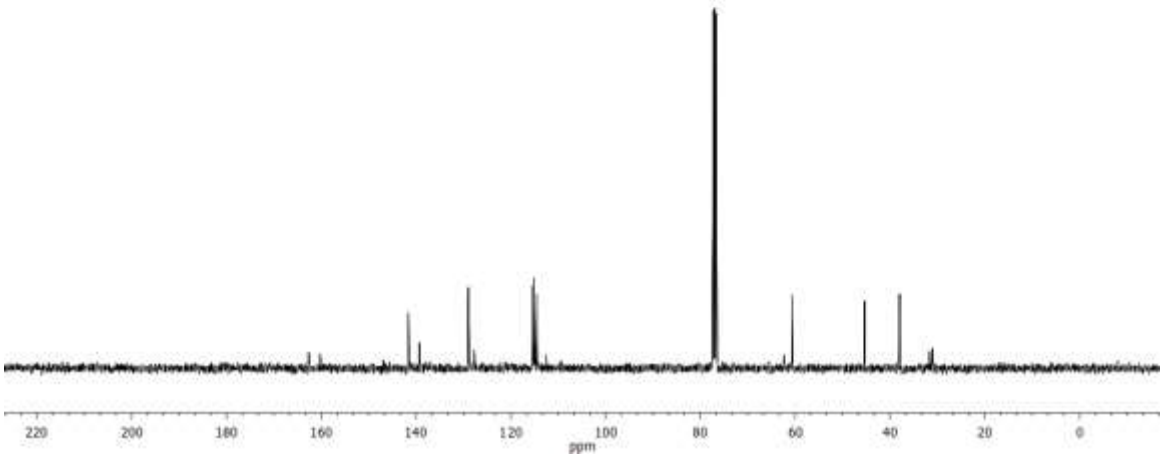
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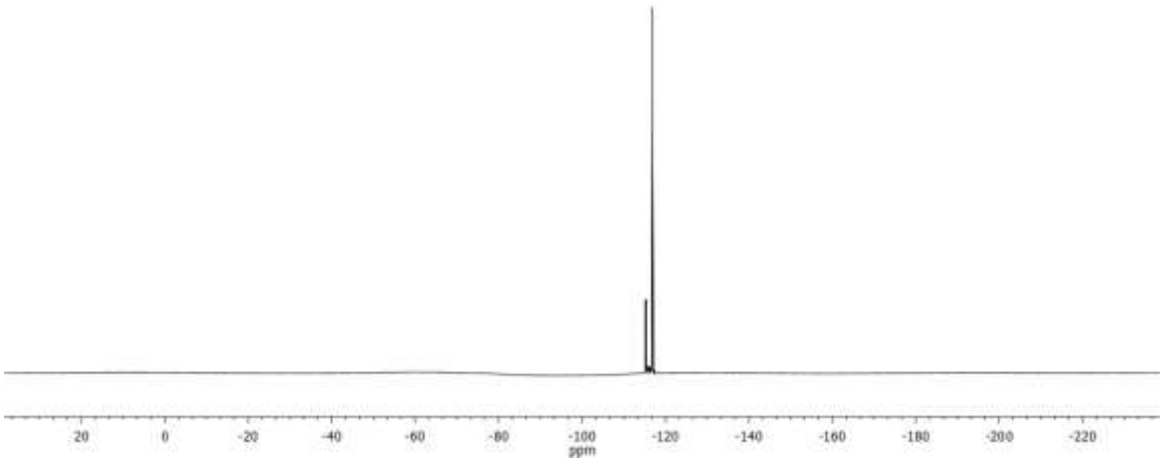
ppm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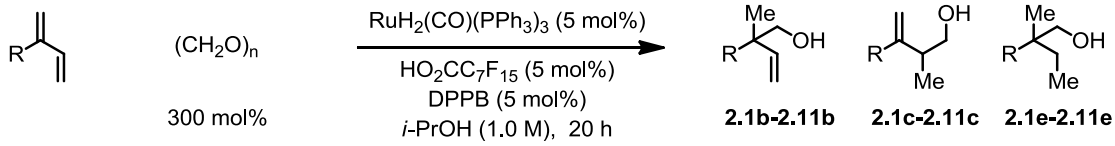
ppm

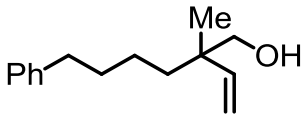
Experimental Procedures and Spectroscopic Data for the Ruthenium Catalyzed Regioselective Couplings at the C_2 – position



General Procedure B for the coupling of 2-substituted dienes 2.1-2.11 to paraformaldehyde[6a]

To a pressure tube equipped with a magnetic stir bar was added $RuH_2(CO)(PPh_3)_3$ (13.8 mg, 0.015 mmol, 5 mol%) and 1,4-bis(diphenylphosphino)butane (DPPB) (6.4 mg, 0.030 mmol, 5 mol%), and pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol%). Paraformaldehyde (27.0 mg, 0.60 mmol, 300 mol%) was added. The tube was sealed with a rubber septum, purged with argon and 2-propanol (0.3 mL, 1.0 M with respect to diene) and diene (0.30 mmol, 100 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2) under the conditions noted to furnish the all-carbon quaternary center containing homoallylic alcohols.

2-methyl-6-phenyl-2-vinylhexan-1-ol (2.3b)



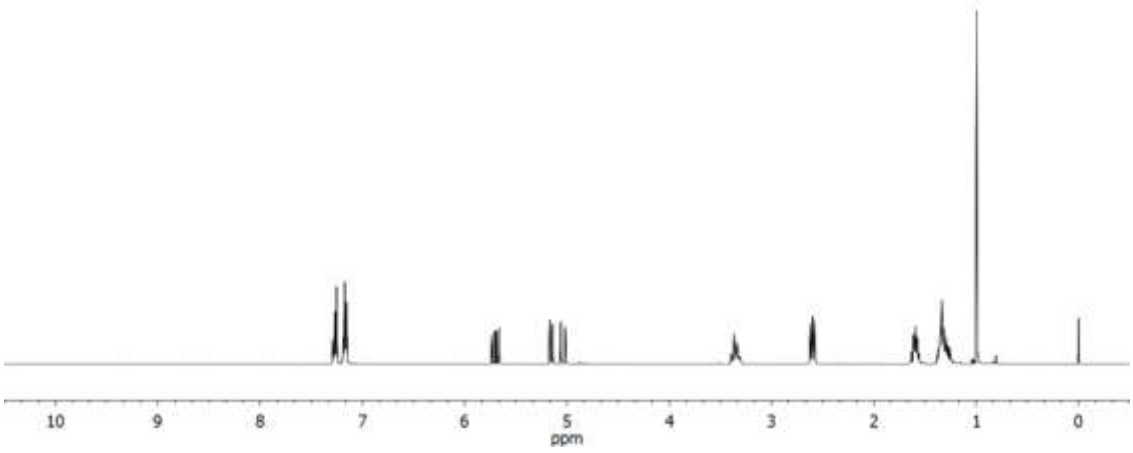
The reaction was conducted in accordance with **General Procedure B** (*via* diene **2.3**). After heating the reaction at 90°C for 20 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (41.4 mg, 63%, >8:1 r.r.) as a colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 2H), 7.20 – 7.12 (m, 3H), 5.70 (dd, J = 17.6, 10.9 Hz, 1H), 5.16 (dd, J = 10.9, 1.3 Hz, 1H), 5.04 (dd, J = 17.6, 1.3 Hz, 1H), 3.43 – 3.27 (m, 2H), 2.66 – 2.53 (m, 2H), 1.65 – 1.53 (m, 2H), 1.40 – 1.21 (m, 5H), 1.00 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 144.1, 142.7, 128.3, 128.2, 125.6, 114.6, 70.2, 42.3, 37.0, 35.9, 32.3, 23.5, 19.6.

HRMS (CI) Calcd. For $C_{15}H_{22}O$ $[M]^+$: 218.1671, Found: 218.1169.

FTIR (in $CDCl_3$): 3394, 2933, 2859, 1639, 1603, 1496, 1453, 1414, 1373, 1217, 1030, 908, 755, 731, 698 cm^{-1}.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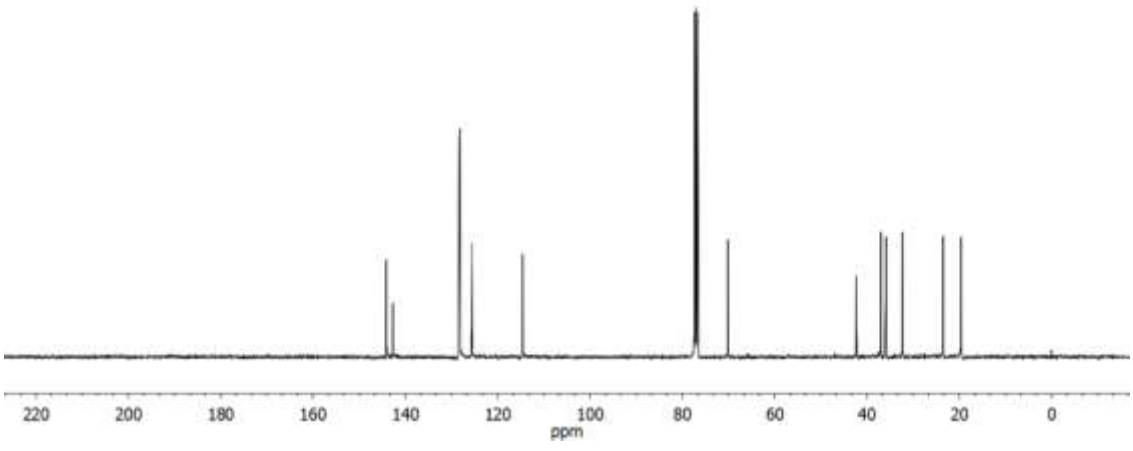
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200
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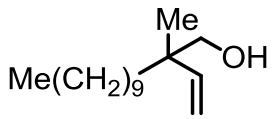
ppm

2-methyl-2-vinyldodecan-1-ol (2.5b)



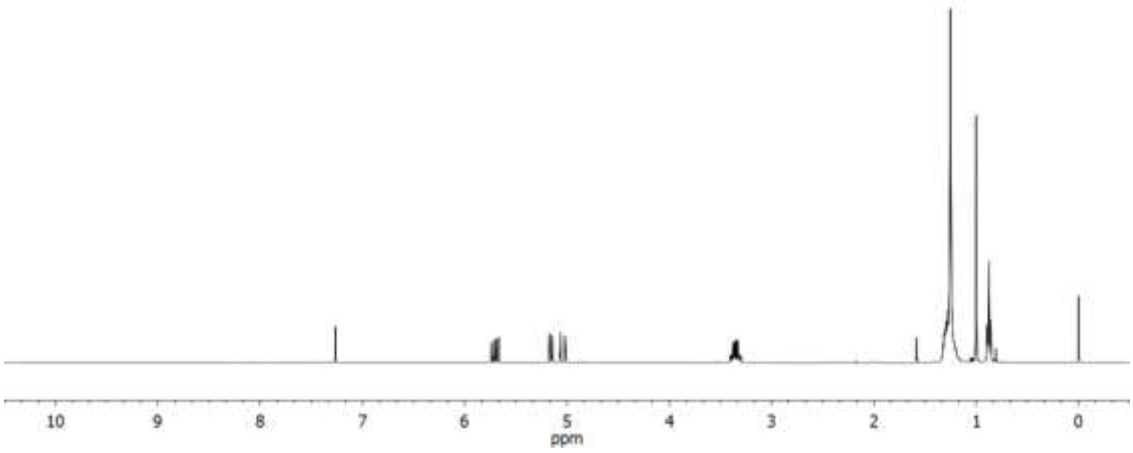
The reaction was conducted in accordance with **General Procedure B** (*via* diene **2.5**). After heating the reaction at 90°C for 20 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (39.0 mg, 57%, 8:1 r.r.) as a colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.70 (dd, J = 17.6, 10.9 Hz, 1H), 5.16 (dd, J = 10.9, 1.4 Hz, 1H), 5.04 (dd, J = 17.6, 1.4 Hz, 1H), 3.35 (qd, J = 10.6, 6.3 Hz, 2H), 1.38 – 1.13 (m, 19H), 1.00 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 144.3, 114.5, 70.2, 42.3, 37.2, 31.9, 30.5, 29.7, 29.6, 29.3, 23.76, 22.7, 19.6, 14.1.

HRMS (CI) Calcd. For $C_{15}H_{31}O$ $[M+H]^+$: 227.2375, Found:227.2378.

FTIR (in $CDCl_3$): 3372, 2924, 2853, 1639, 1466, 1414, 1377, 1215, 1035, 909, 759, 734 cm^{-1}.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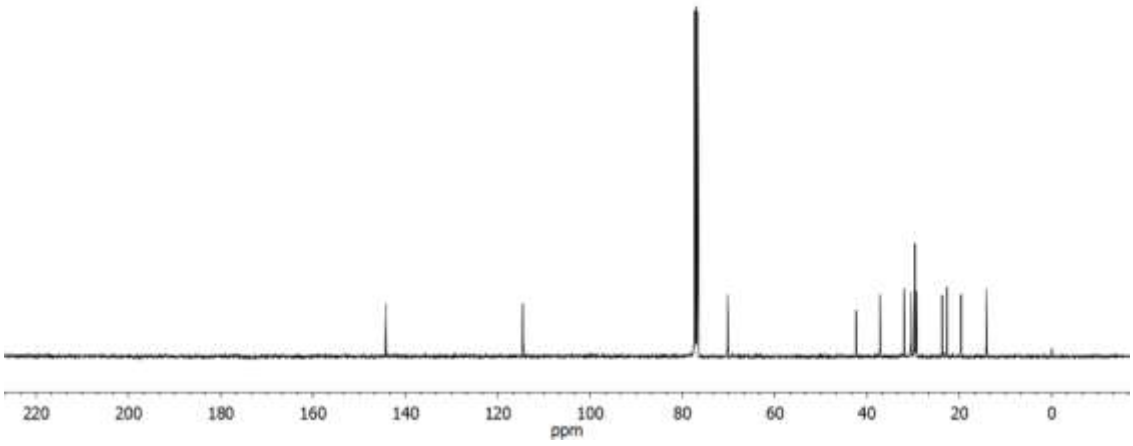
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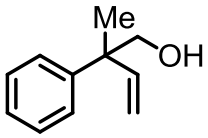
ppm

2-methyl-2-phenylbut-3-en-1-ol (2.6b)

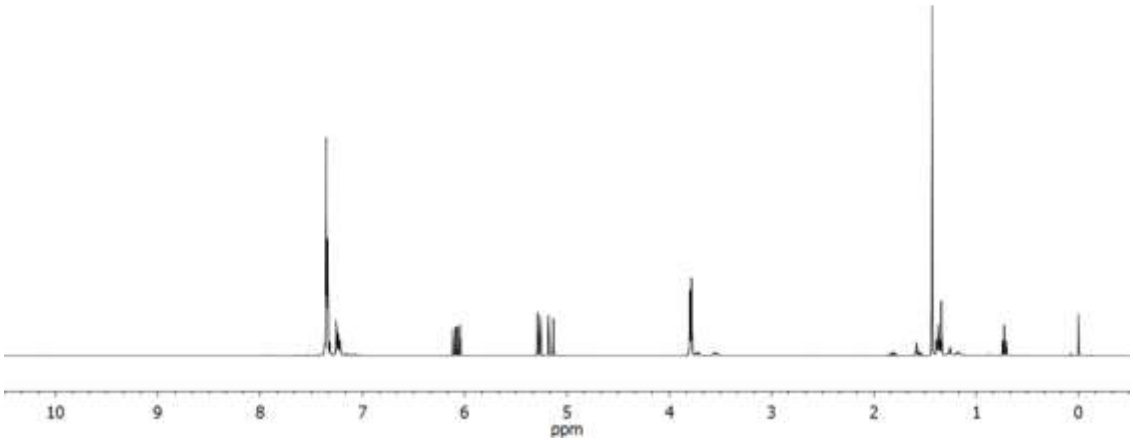


In modification to **General Procedure B**, the reaction was conducted using 1:1 acetone : isopropanol [1M] as solvent (*via* diene **2.6**). After heating the reaction at 80°C for 20 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (26.9 mg, 55%, >20:1 r.r., 7:1 (product: over-reduced product)) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.40 – 7.15 (m, 5H), 6.08 (dd, J = 17.6, 10.8 Hz, 1H), 5.27 (d, J = 10.8 Hz, 1H), 5.16 (d, J = 17.6 Hz, 1H), 3.79 (d, J = 6.4 Hz, 2H), 1.43 (s, 3H),
1.37 (t, J = 6.6 Hz, 1H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 144.4, 143.5, 128.5, 128.4, 126.9, 126.8, 126.5, 114.6, 69.9, 47.0, 22.6.

Spectral data correspond to that reported in literature.[20]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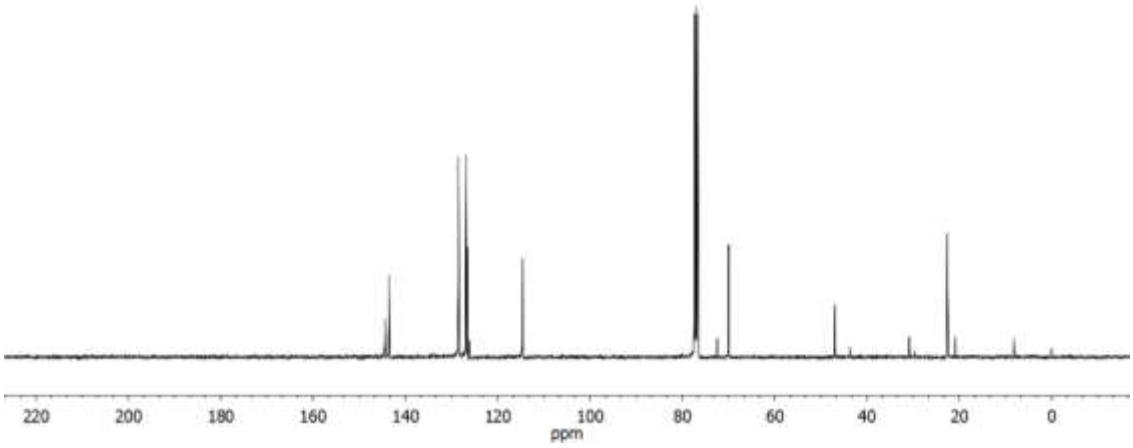
220
200
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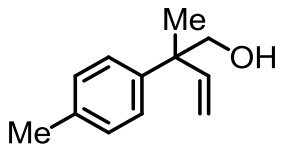
ppm

2-methyl-2-(p-tolyl)but-3-en-1-ol (2.8b)



In modification to **General Procedure B**, the reaction was conducted using 1:1 acetone : isopropanol [1M] as solvent (*via* diene **2.8**). After heating the reaction at 80°C for 20 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (32.1 mg, 61%, >20:1 r.r., 4:1 (product: over-reduced product)) as a yellow oil.

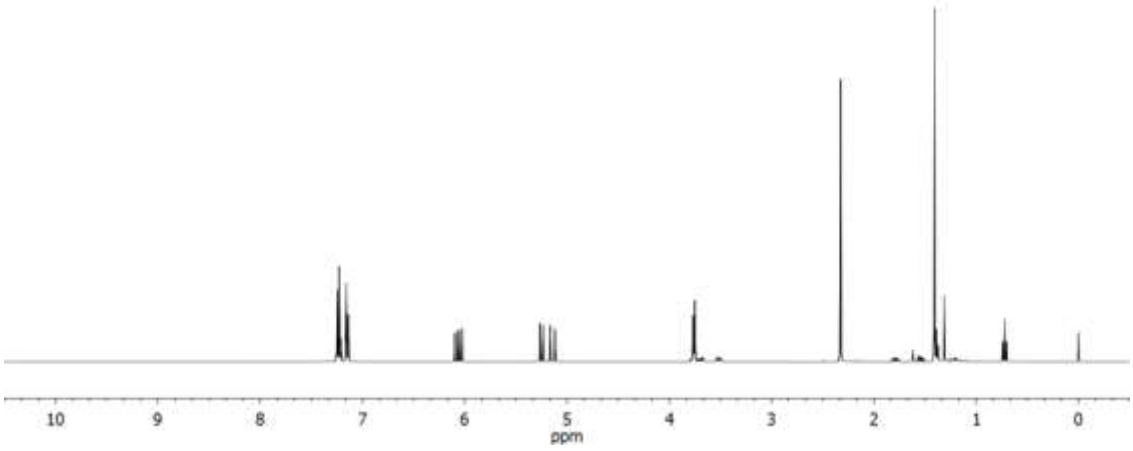
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28 – 7.20 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.06 (dd, J = 17.6, 10.8 Hz, 1H), 5.25 (dd, J = 10.8, 1.2 Hz, 1H), 5.14 (dd, J = 17.6, 1.2 Hz, 1H), 3.80 – 3.72 (m, 2H), 2.33 (s, 3H), 1.44 – 1.35 (m, 4H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 143.7, 141.4, 136.1, 129.2, 126.7, 114.4, 70.0, 46.6, 22.6, 20.9.

HRMS (CI) Calcd. For $C_{12}H_{16}O$ $[M]^+$: 176.1201, Found: 176.1201.

FTIR (in $CDCl_3$): 3385, 2967, 2923, 2876, 1634, 1513, 1454, 1412, 1378, 1192, 1116, 1037, 1017, 914, 814, 756, 725 cm^{-1}.

Spectral data correspond to that reported in literature.[28]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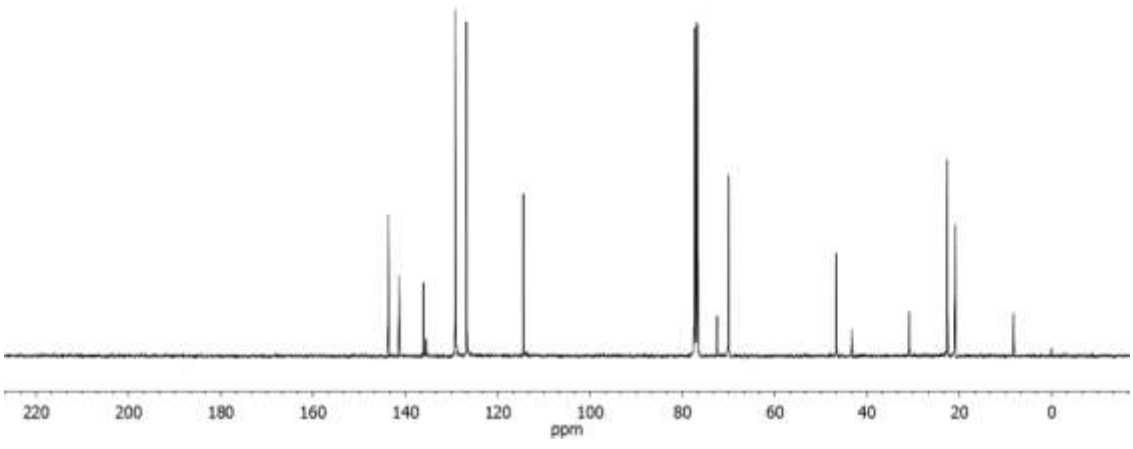
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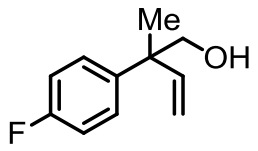
ppm

2-(4-fluorophenyl)-2-methylbut-3-en-1-ol (2.11b)



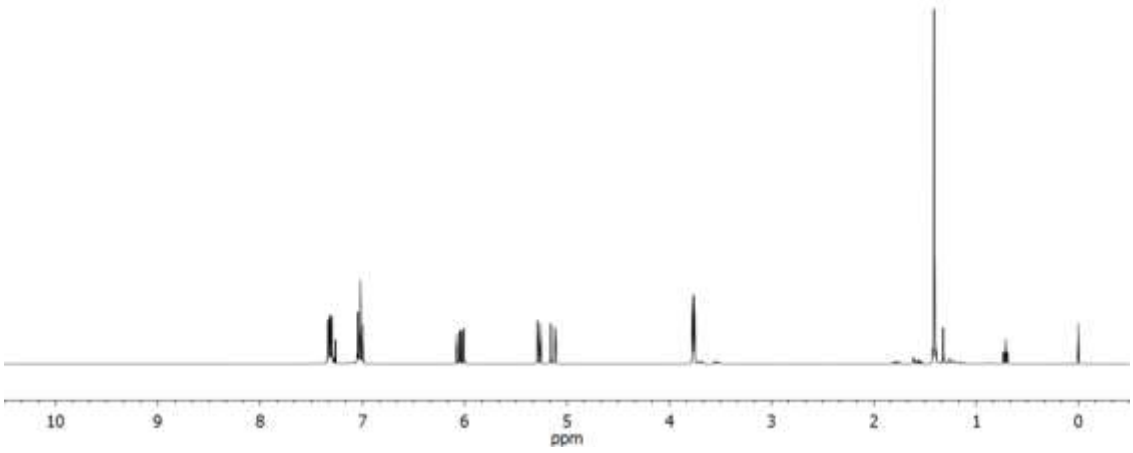
In modification to **General Procedure B**, the reaction was conducted using 1:1 acetone : isopropanol [1M] as solvent (*via* diene **2.11**). After heating the reaction at 80°C for 20 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (35.3 mg, 65%, >20:1 r.r., 8:1 (product: over-reduced product)) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 2H), 7.06 – 6.98 (m, 2H), 6.04 (dd, J = 17.6, 10.8 Hz, 1H), 5.27 (dd, J = 10.8, 1.1 Hz, 1H), 5.14 (dd, J = 17.6, 1.1 Hz, 1H), 3.76 (d, J = 6.4 Hz, 2H), 1.45 – 1.36 (m, 4H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 161.4 (d, J = 245.4 Hz), 143.4, 140.1 (d, J = 3.0 Hz), 128.5 (d, J = 7.8 Hz), 115.1 (d, J = 20.9 Hz), 114.8, 69.9, 46.5, 22.8.

^{19}F NMR(376 MHz, $CDCl_3$): δ -116.67 – -116.90 (m).

Spectral data correspond to that reported in literature.[20]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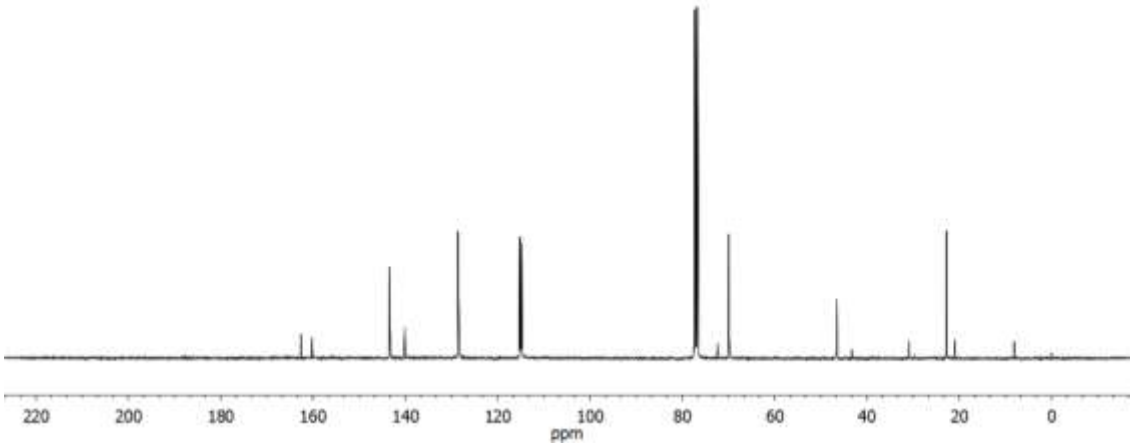
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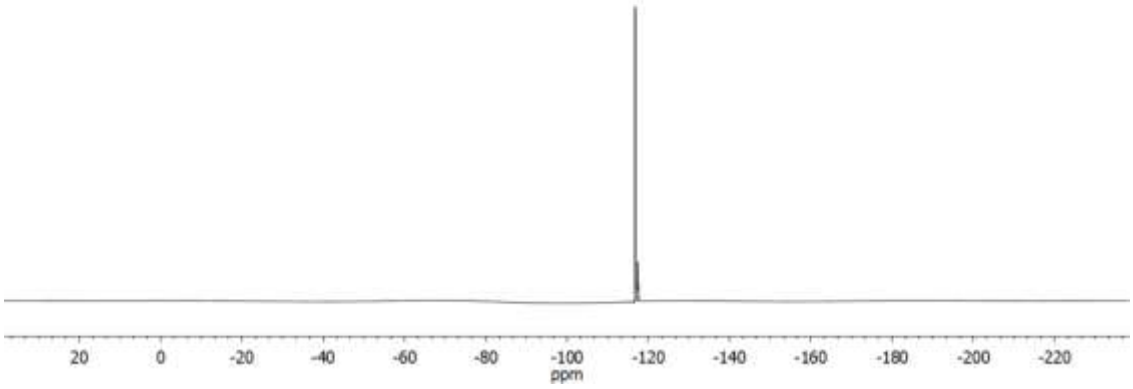
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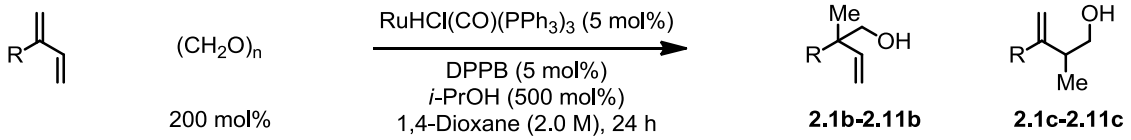
ppm

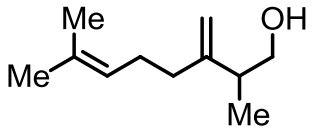
Experimental Procedures and Spectroscopic Data for the Ruthenium Catalyzed Regioselective Couplings at the C_3 – position



General Procedure C for the coupling of 2-substituted dienes 2.1-2.11 to paraformaldehyde

To a pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (14.1 mg, 0.015 mmol, 5 mol%) and 1,4-bis(diphenylphosphino)butane (DPPB) (6.4 mg, 0.030 mmol, 5 mol%). Paraformaldehyde (18.0 mg, 0.60 mmol, 200 mol%) was added. The tube was sealed with a rubber septum, purged with argon and 1,4-dioxane (0.15 mL, 2.0 M with respect to diene), diene (0.30 mmol, 100 mol%) and 2-propanol (0.11 mL, 1.5 mmol, 500 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for 24 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2) under the conditions noted to furnish the homoallylic alcohols.

2,7-dimethyl-3-methyleneoct-6-en-1-ol (2.1c)



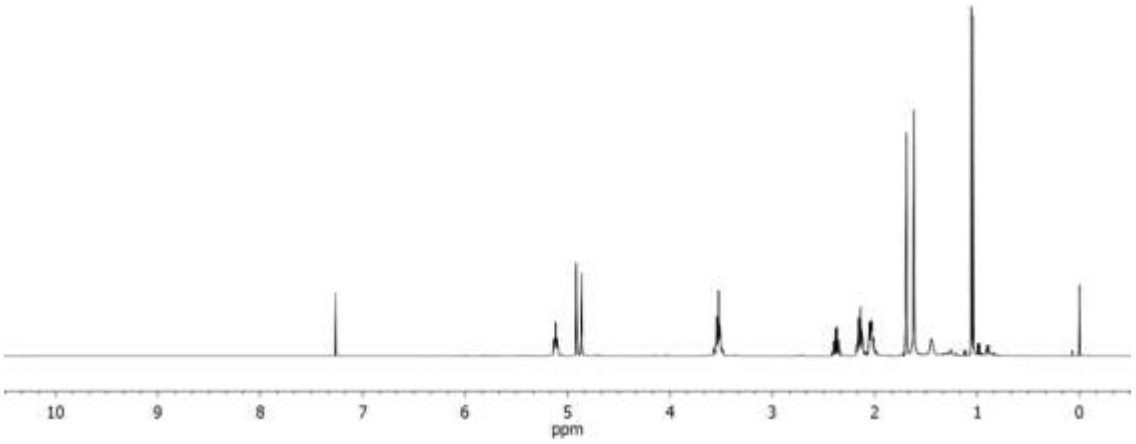
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.1**). After heating the reaction at 115°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (30.8 mg, 61%, >20:1 r.r.) as a colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.14-5.10 (m, 1H), 4.93 – 4.89 (m, 1H), 4.87 – 4.83 (m, 1H), 3.61 – 3.43 (m, 2H), 2.45 – 2.30 (m, 1H), 2.19 – 2.08 (m, 2H), 2.08 – 1.98 (m, 2H), 1.69 (d, J = 1.1 Hz, 3H), 1.66 – 1.58 (m, 3H), 1.45 (s, 1H), 1.05 (d, J = 7.0 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 150.9, 131.9, 123.9, 110.0, 65.8, 42.5, 34.0, 26.5, 16.2.

HRMS (CI) Calcd. For $C_{11}H_{19}O$ $[M-H]^+$: 167.1436, Found: 167.1434.

FTIR (neat): 3329, 3076, 2966, 2924, 2876, 1642, 1452, 1376, 1220, 1107, 1028, 981, 891, 831, 734 cm^{-1}.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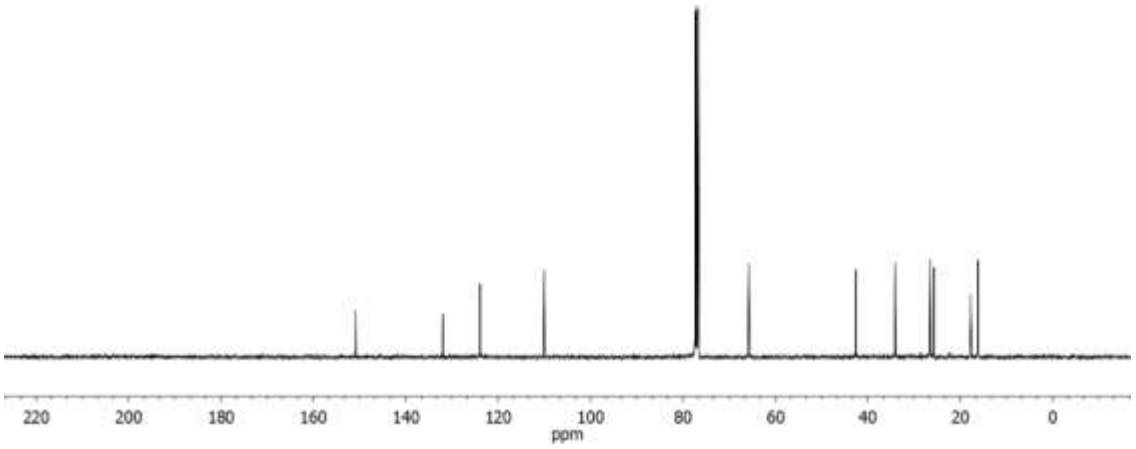
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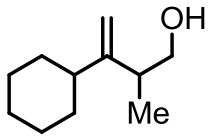
ppm

3-cyclohexyl-2-methylbut-3-en-1-ol (2.2c)



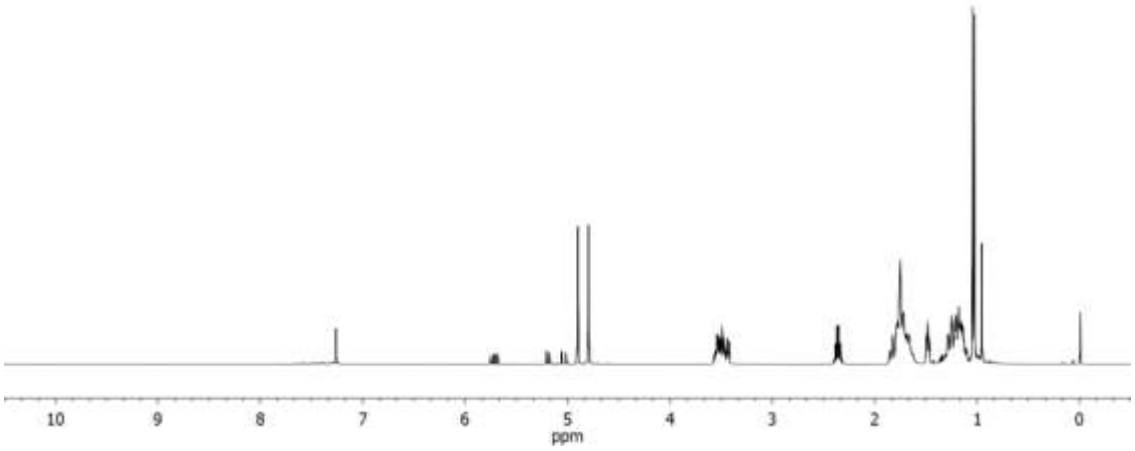
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.2**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (40.9 mg, 81%, 8:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.79 (s, 1H), 3.60 – 3.45 (m, 2H), 2.42 – 2.30 (m, 1H), 1.89 – 1.56 (m, 6H), 1.48 (t, J = 6.1 Hz, 1H), 1.38 – 1.08 (m, 5H), 1.04 (d, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 157.4, 107.7, 66.4, 43.9, 41.4, 33.2, 33.0, 26.9, 26.8, 26.3, 17.3.

HRMS (CI) Calcd. For $C_{11}H_{21}O$ $[M+H]^+$: 169.1592, Found: 169.1594.

FTIR (neat): 3362, 2924, 2852, 1639, 1448, 1025, 980, 886, 844, 734, 697 cm^{-1}.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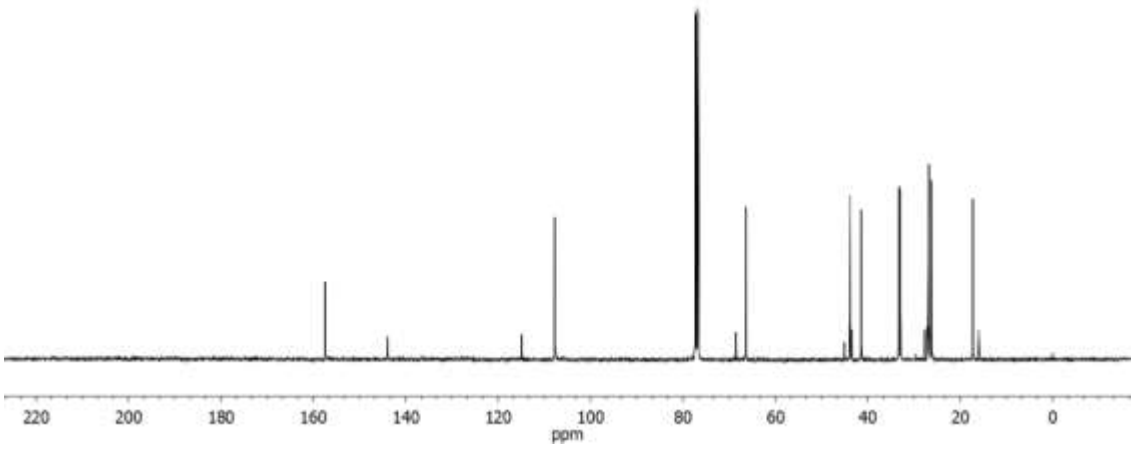
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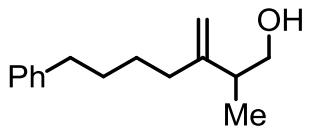
ppm

2-methyl-3-methylene-7-phenylheptan-1-ol (2.3c)



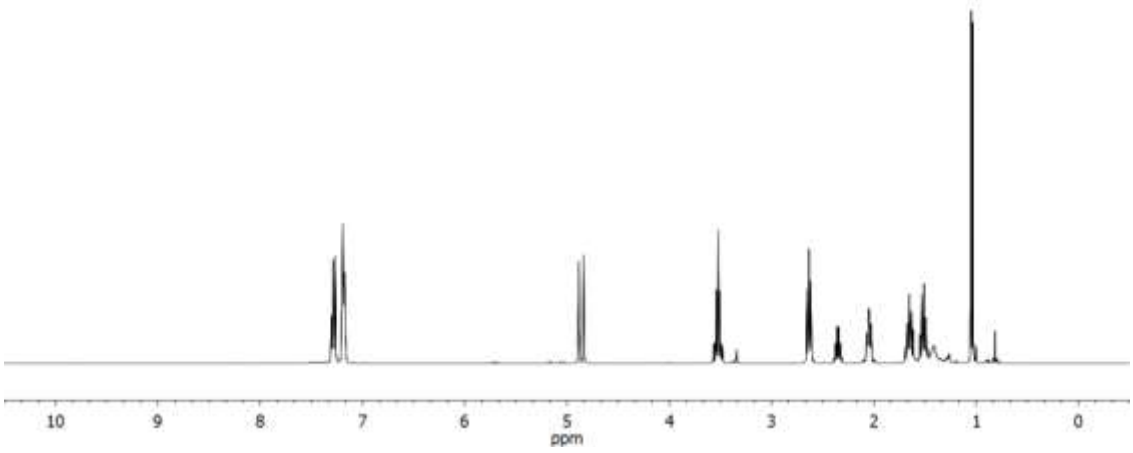
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.3**). After heating the reaction at 115°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (43.9 mg, 67%, 17:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.32 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 4.91 – 4.87 (m, 1H), 4.84 (s, 1H), 3.60 – 3.45 (m, 2H), 2.68 – 2.59 (m, 2H), 2.41 – 2.29 (m, 1H), 2.13 – 1.96 (m, 2H), 1.71 – 1.59 (m, 2H), 1.58 – 1.47 (m, 2H), 1.42 (s, 1H), 1.04 (d, J = 7.0 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 151.1, 142.5, 128.4, 128.3, 125.7, 109.8, 65.9, 42.2, 35.8, 34.2, 31.2, 27.5, 16.3.

HRMS (CI) Calcd. For $C_{15}H_{22}O$ $[M]^+$: 218.1671, Found: 218.1672.

FTIR (neat): 3355, 3026, 2931, 2858, 1641, 1603, 1496, 1453, 1028, 979, 908, 890, 732, 698 cm^{-1}.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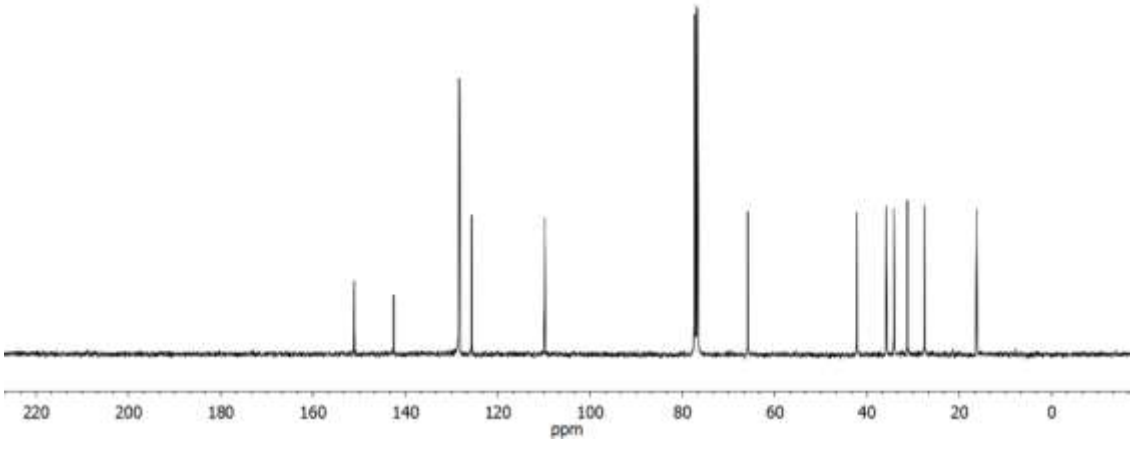
220
200
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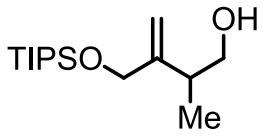
ppm

2-methyl-3-(((triisopropylsilyl)oxy)methyl)but-3-en-1-ol (2.4c)



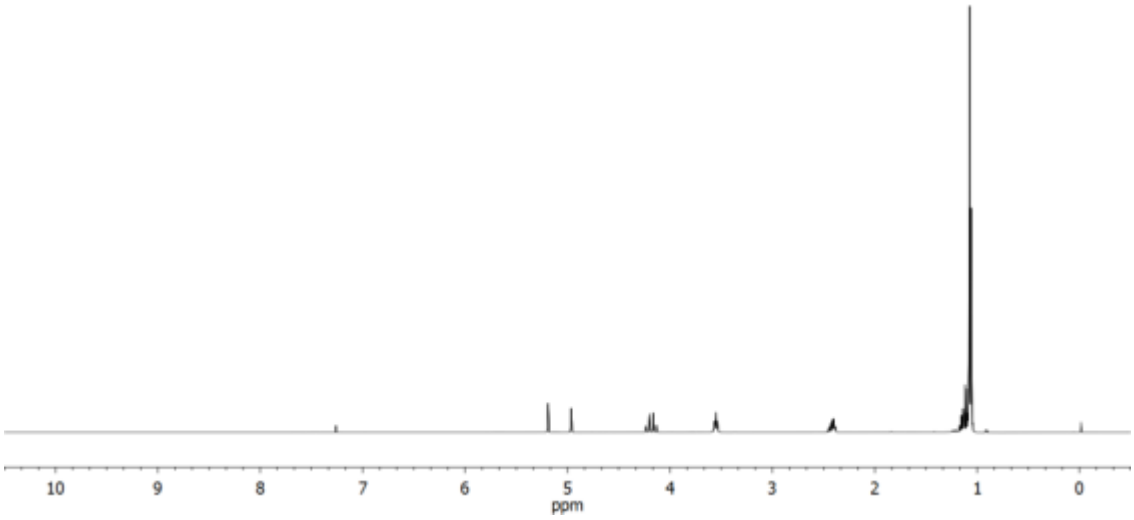
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.4**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (66.0 mg, 81%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.19 (q, *J* = 1.5 Hz, 1H), 4.96 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.63 – 3.47 (m, 2H), 2.49 – 2.35 (m, 2H), 1.18 – 1.02 (m, 24H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 150.3, 111.6, 66.9, 65.6, 40.1, 18.0, 16.3, 11.9.

HRMS (CI) Calcd. For $C_{15}H_{33}O_2Si$ $[M+H]^+$: 273.2250, Found: 273.2253.

FTIR (neat): 3348, 2942, 2866, 1650, 1463, 1385, 1247, 1087, 1060, 1031, 996, 899, 881, 817, 792, 734, 681, 658 cm^{-1}.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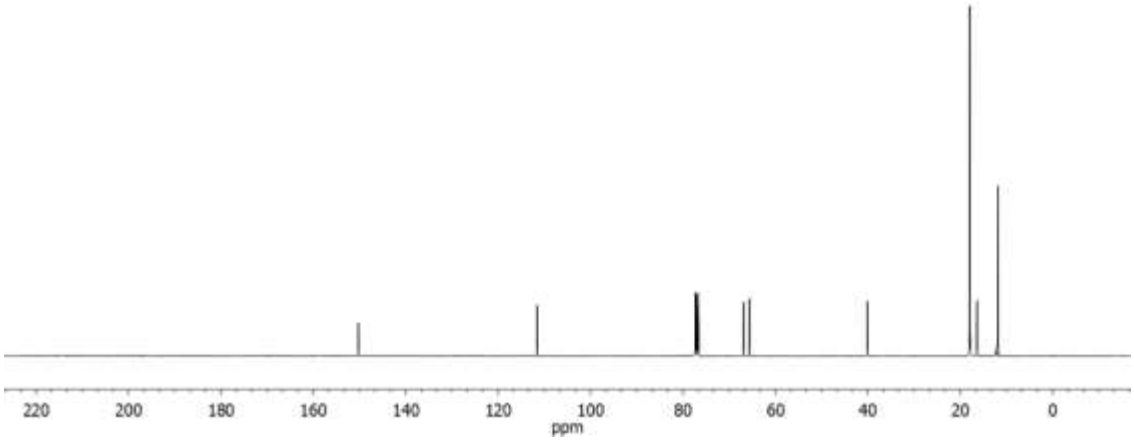
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20
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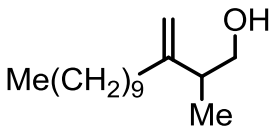
ppm

2-methyl-3-methylenetridecan-1-ol (2.5c)



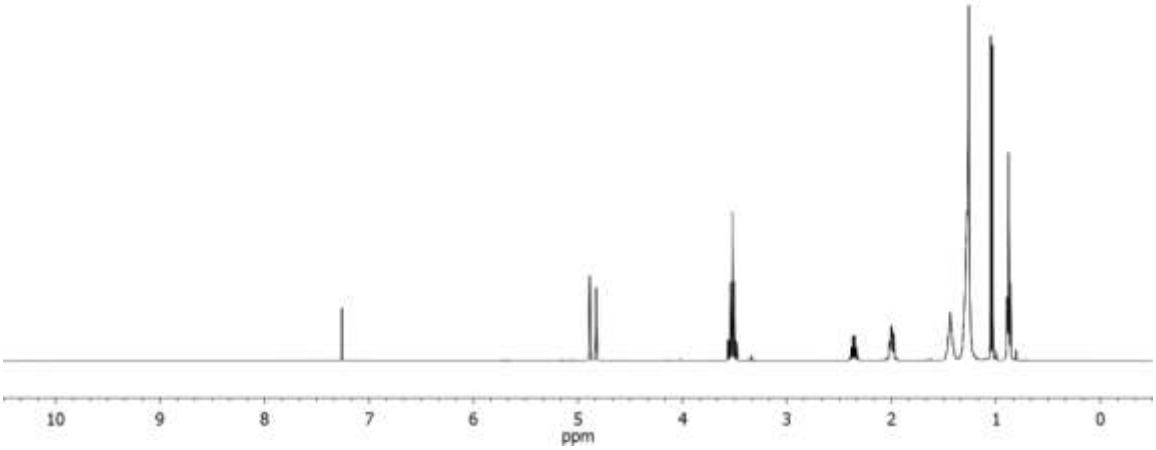
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.5**). After heating the reaction at 115°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (42.1 mg, 62%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 4.89 (q, J = 1.4 Hz, 1H), 4.83 (dd, J = 1.4, 0.8 Hz, 1H), 3.58 – 3.46 (m, 2H), 2.41 – 2.31 (m, 1H), 2.06 – 1.94 (m, 2H), 1.50 – 1.37 (m, 1H), 1.36 – 1.17 (m, 16H), 1.04 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 151.4, 109.7, 65.8, 42.3, 34.3, 31.9, 29.6 (s, 2C), 29.6, 29.5, 29.3, 28.0, 22.7, 16.3, 14.1.

HRMS (CI) Calcd. For $C_{15}H_{31}O$ $[M+H]^+$: 227.2375, Found: 227.2373.

FTIR (neat): 3362, 2957, 2923, 2853, 1642, 1464, 1377, 1028, 980, 907, 890, 734 cm^{-1}.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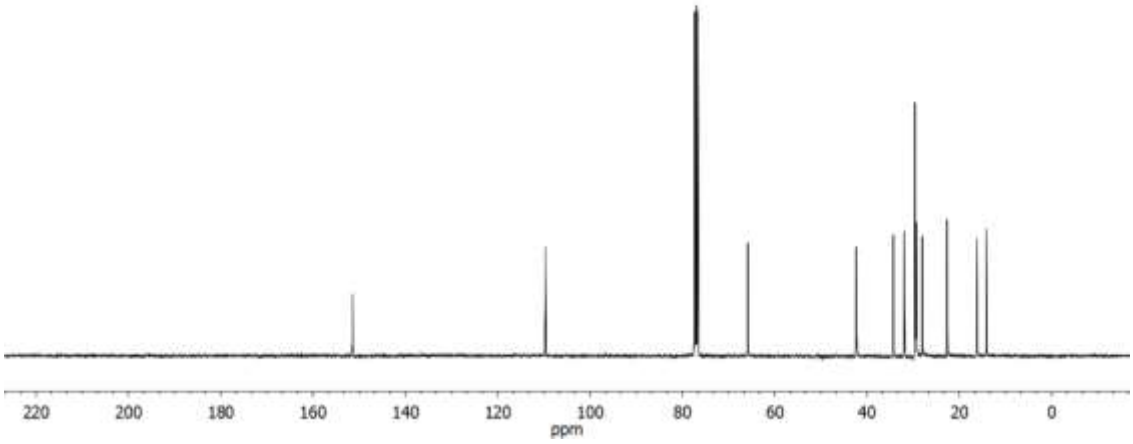
220
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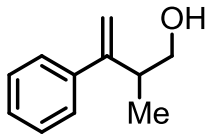
ppm

2-methyl-3-phenylbut-3-en-1-ol (2.6c)



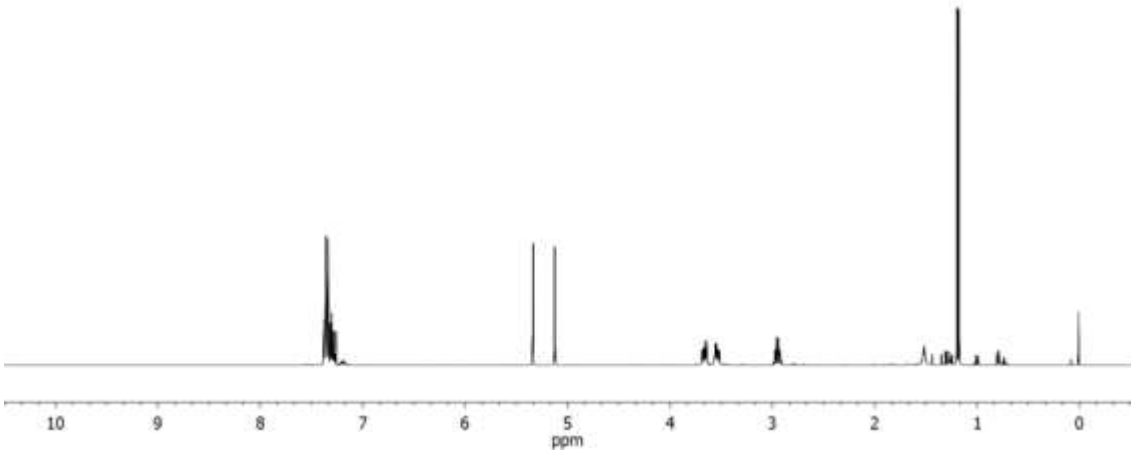
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.6**). After heating the reaction at 115°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (31.6 mg, 65%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.38 – 7.26 (m, 5H), 5.34 (d, J = 1.0 Hz, 1H), 5.13 (t, J = 1.1 Hz, 1H), 3.66 (dd, J = 10.7, 6.0 Hz, 1H), 3.54 (dd, J = 10.7, 5.9 Hz, 1H), 3.01 – 2.89 (m, 1H), 1.52 (s, 1H), 1.19 (d, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ151.2, 142.13, 128.3, 127.5, 126.6, 112.8, 66.5, 40.8, 16.7.

HRMS (CI) Calcd. For $C_{11}H_{14}O$ $[M]^+$: 162.1045, Found: 162.1044.

FTIR (neat): 3349, 3056, 2964, 2928, 2875, 1625, 1600, 1574, 1493, 1453, 1261, 1025, 979, 899, 777, 700 cm^{-1}.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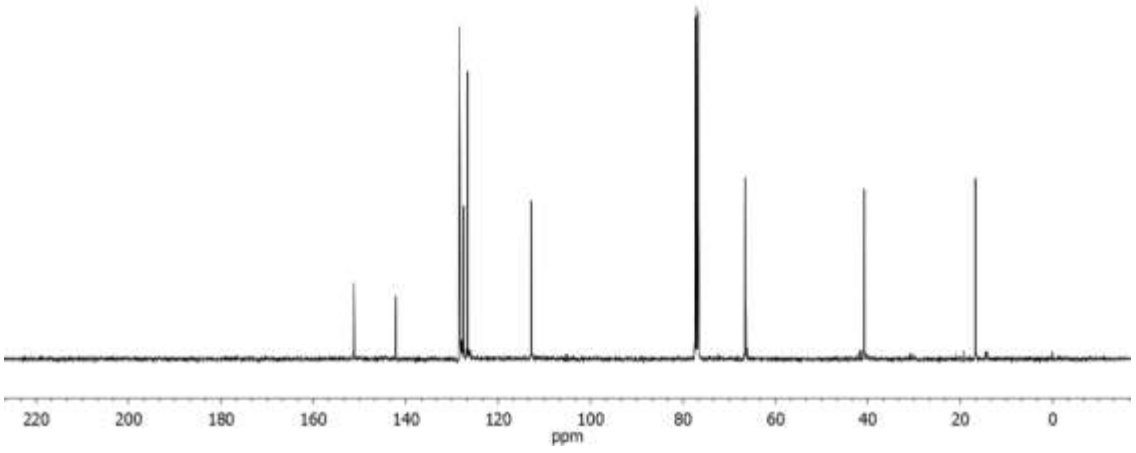
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200
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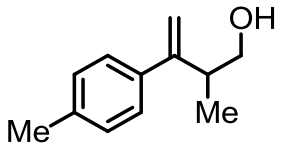
ppm

2-methyl-3-(4-methyl)but-3-en-1-ol (2.7c)



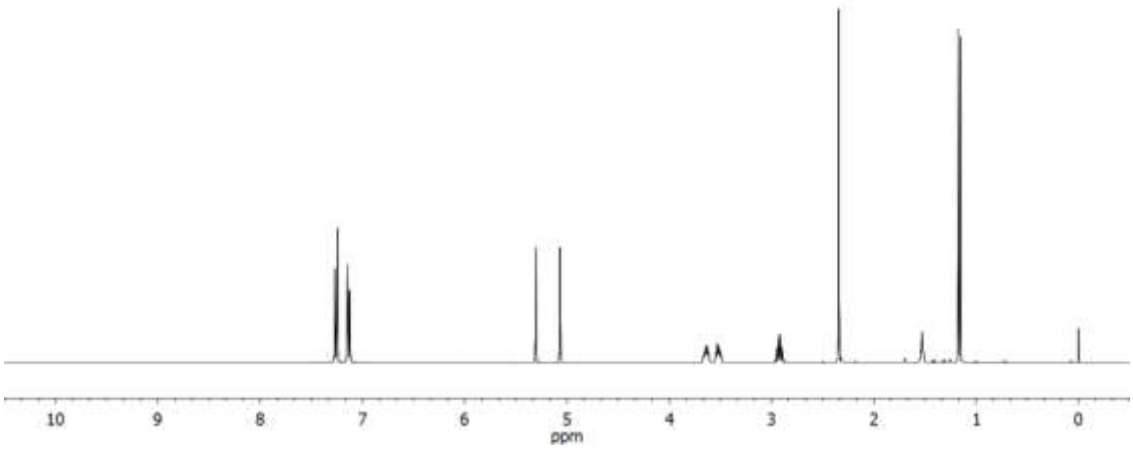
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.7**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (36.8 mg, 70%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28 – 7.23 (m, 2H), 7.13 (dd, *J* = 8.4, 0.5 Hz, 2H), 5.30 (d, *J* = 1.0 Hz, 1H), 5.07 (t, *J* = 1.1 Hz, 1H), 3.71 – 3.58 (m, 1H), 3.57 – 3.46 (m, 1H), 2.98 – 2.87 (m, 1H), 2.34 (s, 3H), 1.53 (t, *J* = 5.0 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ151.0, 139.1, 137.2, 129.0, 126.4, 112.1, 66.5, 40.7, 21.1, 16.7.

HRMS (CI) Calcd. For $C_{12}H_{16}O$ $[M]^+$: 176.1201, Found: 176.1198.

FTIR (neat): 3332, 2963, 2923, 2874, 1623, 1511, 1454, 1403, 1213, 1117, 1027, 979, 896, 823, 734 cm^{-1}.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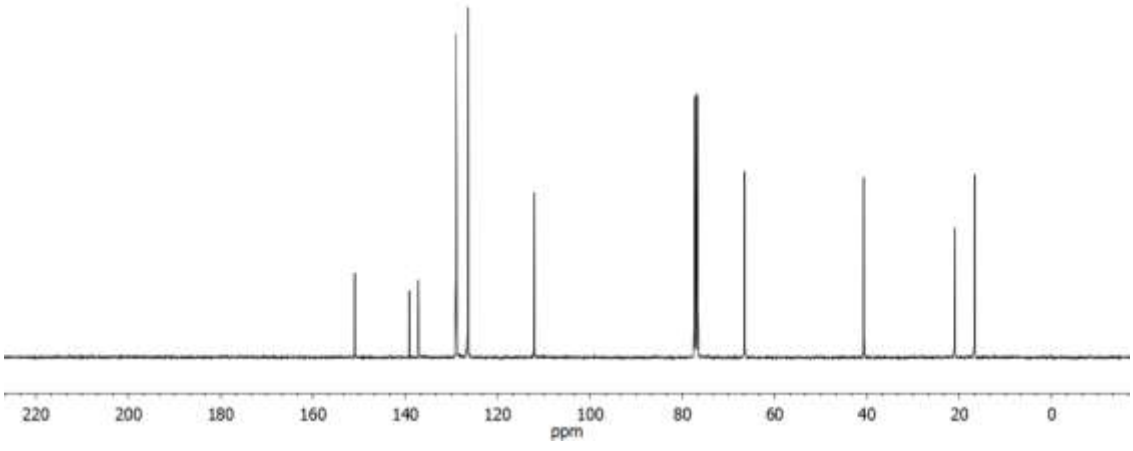
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200
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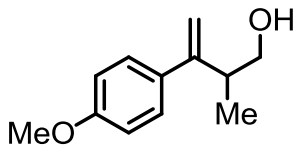
ppm

3-(4-methoxyphenyl)-2-methylbut-3-en-1-ol (2.8c)



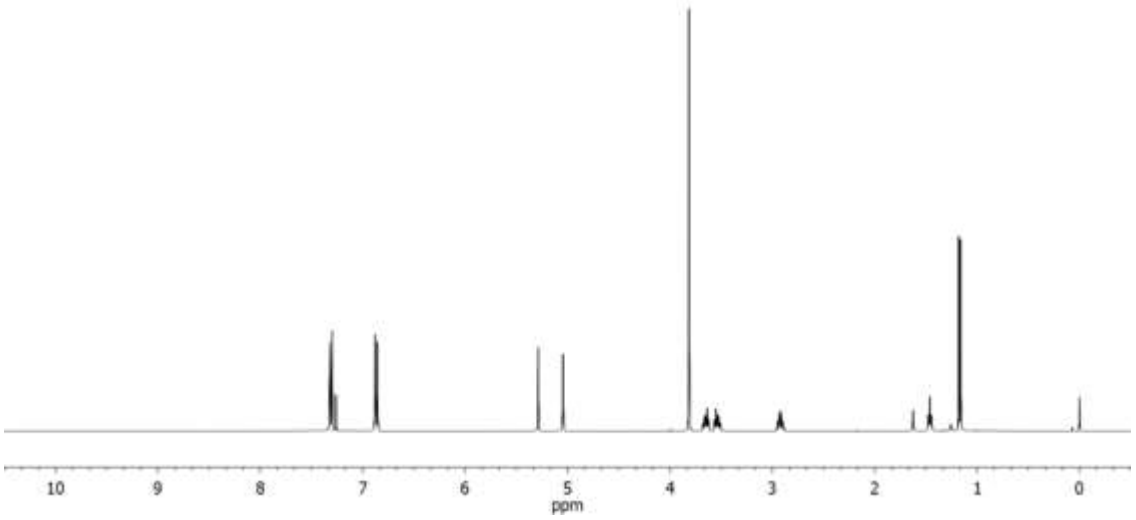
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.8**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (40.6 mg, 70%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 2H), 6.90 – 6.84 (m, 2H), 5.29 (d, J = 0.9 Hz, 1H), 5.04 (s, 1H), 3.81 (s, 3H), 3.70 – 3.60 (m, 1H), 3.59 – 3.48 (m, 1H), 2.98 – 2.87 (m, 1H), 1.46 (t, J = 6.1 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ159.1, 150.5, 134.4, 127.6, 113.7, 111.5, 66.5, 55.3, 40.1, 16.8.

FTIR (neat): 3385, 2961, 2932, 2836, 1607, 1573, 1509, 1462, 1411, 1292, 1179, 1114, 1028, 978, 896, 804, 734, 696 cm^{-1}.

Spectral data correspond to that reported in literature.[29]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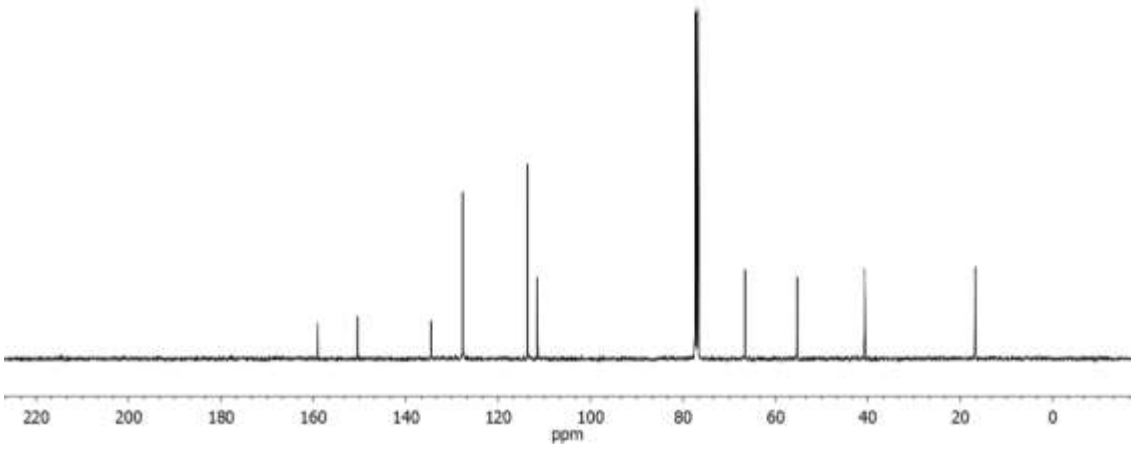
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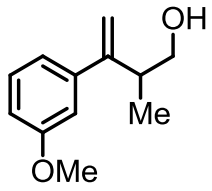
ppm

3-(3-methoxyphenyl)-2-methylbut-3-en-1-ol (2.9c)



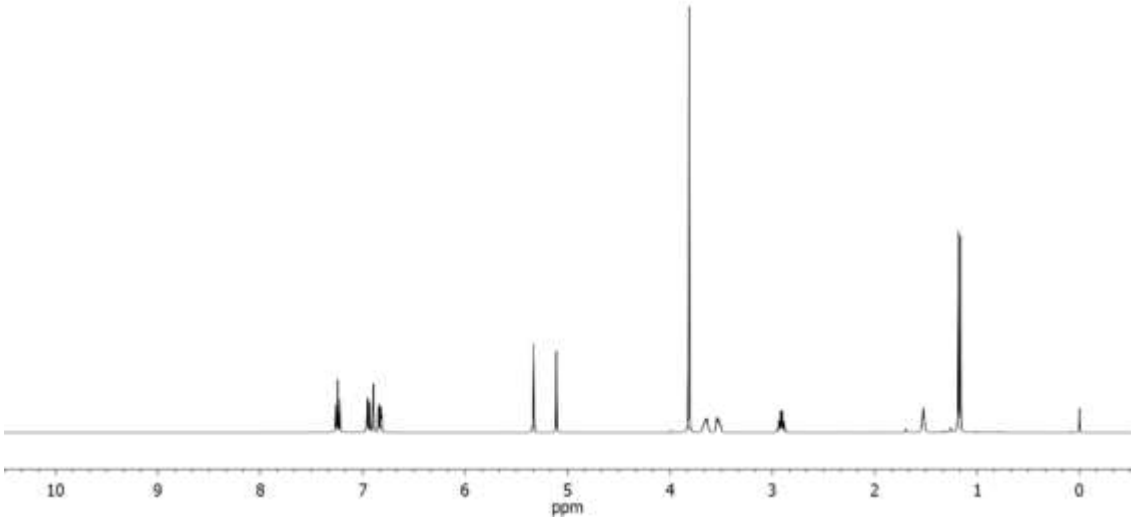
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.9**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 25% EtOAc/hexane) to furnish the title compound (41.4 mg, 72%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 1H), 6.98 – 6.87 (m, 2H), 6.83 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 5.33 (d, J = 0.9 Hz, 1H), 5.11 (s, 1H), 3.81 (s, 3H), 3.70 – 3.61 (m, 1H), 3.58 – 3.46 (m, 1H), 2.97 – 2.85 (m, 1H), 1.52 (s, 1H), 1.17 (d, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 159.5, 151.1, 143.7, 129.3, 119.1, 112.9, 112.6, 112.6, 66.5, 55.2, 40.8, 16.7.

FTIR (neat): 3361, 2962, 2876, 2834, 1597, 1575, 1487, 1463, 1428, 1317, 1286, 1219, 1180, 1114, 1028, 978, 907, 881, 782, 729 cm^{-1}.

Spectral data correspond to that reported in literature.[29]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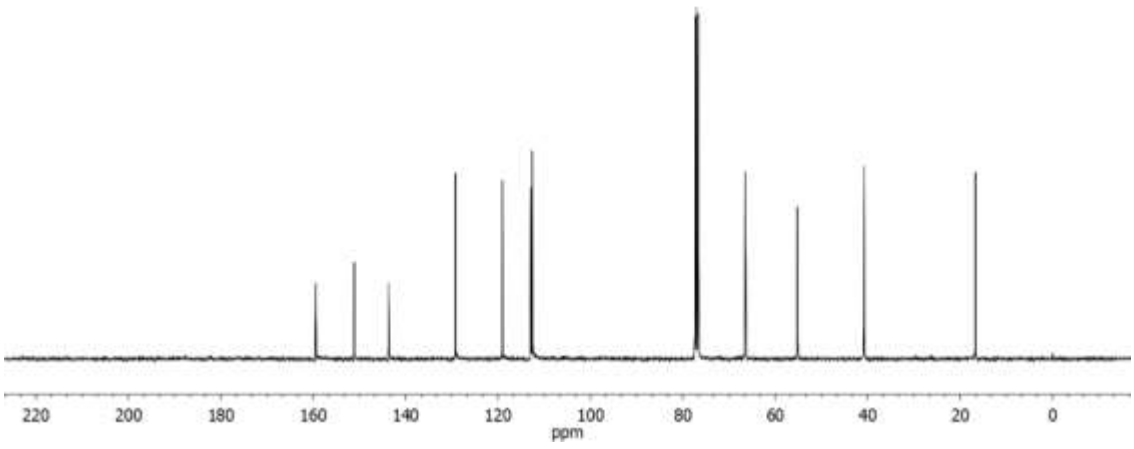
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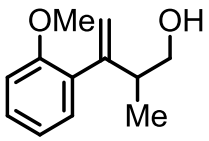
60
40
20
0
ppm

3-(2-methoxyphenyl)-2-methylbut-3-en-1-ol (2.10c)



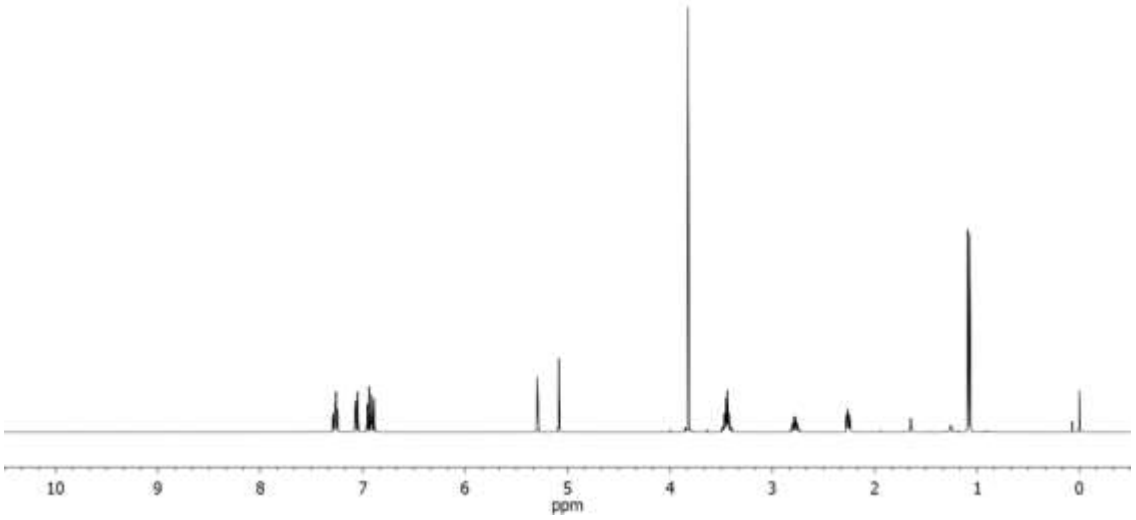
The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.10**). After heating the reaction at 95°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (40.6 mg, 70%, >20:1 r.r.) as a yellow oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 1H), 7.06 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.97 – 6.87 (m, 2H), 5.32 – 5.26 (m, 1H), 5.08 (d, *J* = 1.7 Hz, 1H), 3.82 (s, 3H), 3.51 – 3.37 (m, 2H), 2.83 – 2.71 (m, 1H), 2.30 – 2.22 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 156.2, 149.0, 131.3, 130.5, 128.5, 120.6, 115.9, 110.6, 65.9, 55.5, 43.2, 16.1.

HRMS (CI) Calcd.For $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1152.

FTIR (neat): 3393, 2961, 2835, 1630, 1597, 1578, 1489, 1455, 1435, 1291, 1238, 1180, 1161, 1107, 1078, 1025, 978, 905, 846, 804, 751, 733 cm^{-1}.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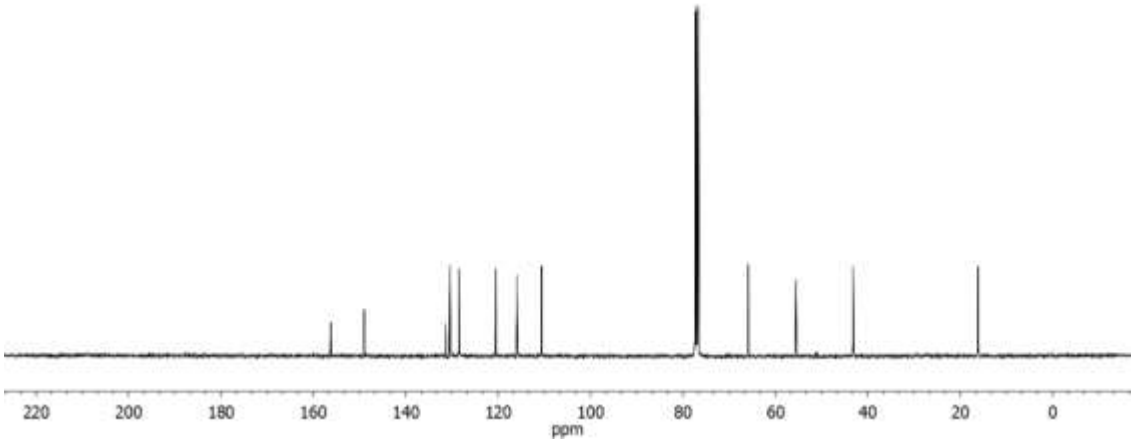
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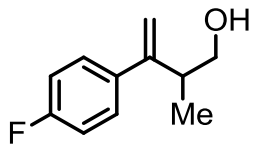
ppm

3-(4-fluorophenyl)-2-methylbut-3-en-1-ol (2.11c)



The reaction was conducted in accordance with **General Procedure C** (*via* diene **2.11**). After heating the reaction at 115°C for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (35.1 mg, 65%, >20:1 r.r.) as a yellow oil.

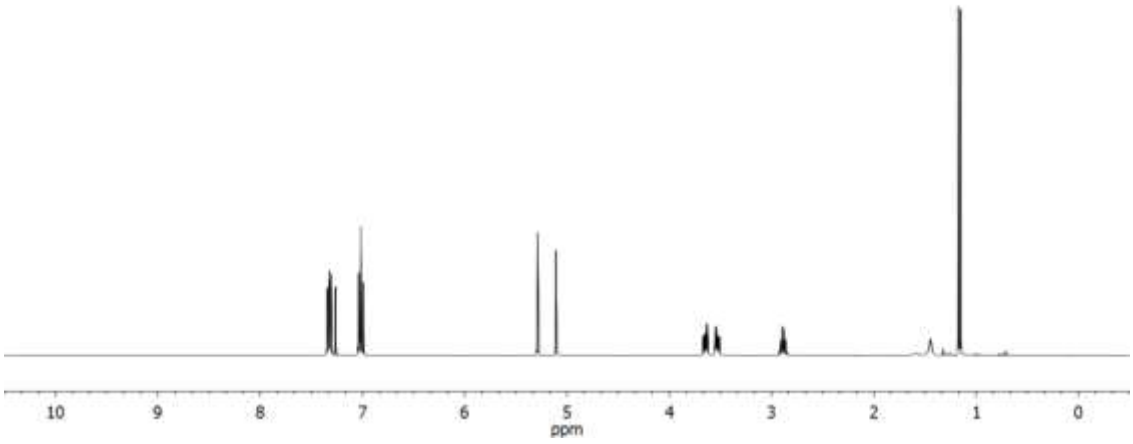
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 2H), 7.06 – 6.97 (m, 2H), 5.29 (d, J = 0.8 Hz, 1H), 5.11 (t, J = 0.9 Hz, 1H), 3.65 (dd, J = 10.7, 6.1 Hz, 1H), 3.53 (dd, J = 10.7, 5.9 Hz, 1H), 2.94 – 2.83 (m, 1H), 1.45 (s, 1H), 1.16 (d, J = 6.9 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 162.3 (d, J = 246.2 Hz), 150.3, 138.1 (d, J = 3.2 Hz), 128.2 (d, J = 7.9 Hz), 115.1 (d, J = 21.3 Hz), 112.9, 66.4, 40.9, 16.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.16 – -115.38 (m).

HRMS (CI) Calcd. For $C_{11}H_{13}OF$ $[M]^+$: 180.0950, Found: 180.0950.

FTIR (in $CDCl_3$): 3346, 2964, 2929, 1625, 1602, 1508, 1456, 1401, 1223, 1160, 1098, 1027, 979, 904, 839, 816, 735, 696 cm^{-1}.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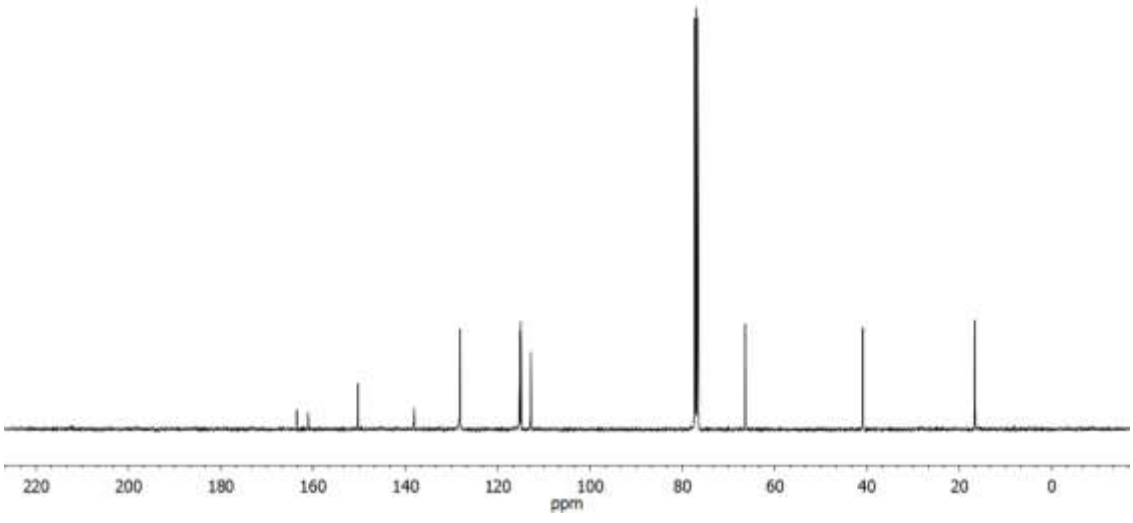
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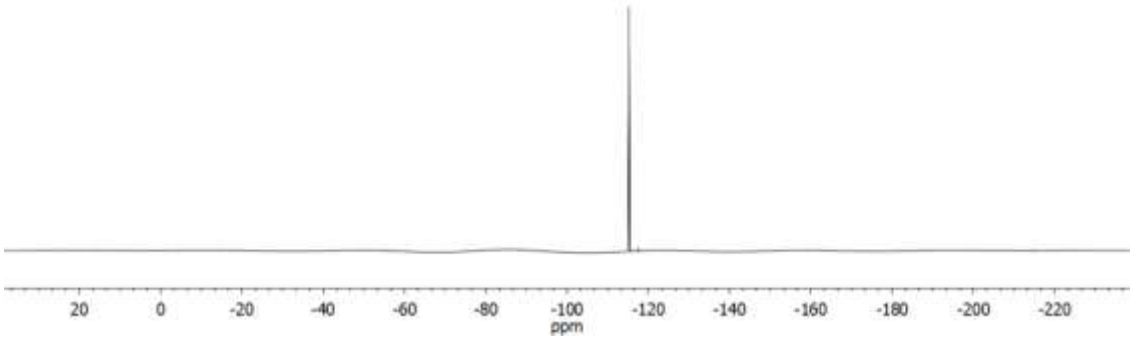
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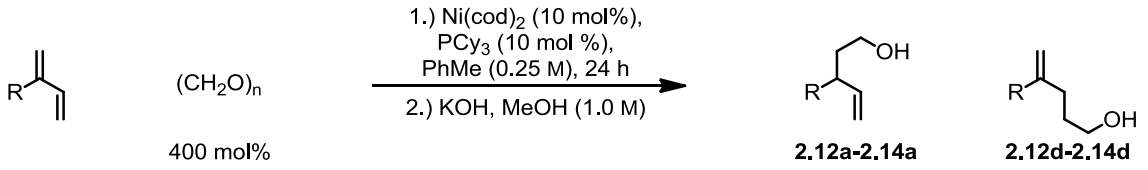
ppm

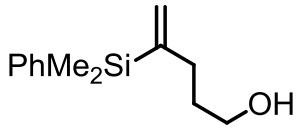
Experimental Procedures and Spectroscopic Data for the Nickel Catalyzed Regioselective Couplings at the C_4 – position



General Procedure D for the coupling of 2-substituted dienes 2.12-2.14 to paraformaldehyde

An oven dried re-sealable pressure flask equipped with stir bar was charged with $Ni(cod)_2$ (28 mg, 0.10 mmol, 20 mol%), PCy_3 (28 mg, 0.10 mmol, 20 mol%) and paraformaldehyde (60 mg, 2.0 mmol, 400 mol%) inside of a drybox. The flask was sealed and removed from the drybox. Under a flow of argon, toluene was added to the flask (2 mL, 0.25 M relative to diene). While stirring, the diene (0.5 mmol, 100 mol%) was added. The flask was sealed and placed in an oil bath at 60 °C for 24 h. The reaction mixture was allowed to cool to room temperature, at which point methanolic KOH (1.0 M) was added and stirred for 2 hours. CH_2Cl_2 (30 mL) was added and the mixture was washed with HCl (1.0 M). The organics were removed and the aqueous layer was extracted twice with CH_2Cl_2 (15 mL). The combined organics were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2) to furnish the title compounds.

4-(dimethyl(phenyl)silyl)pent-4-en-1-ol (2.12d)



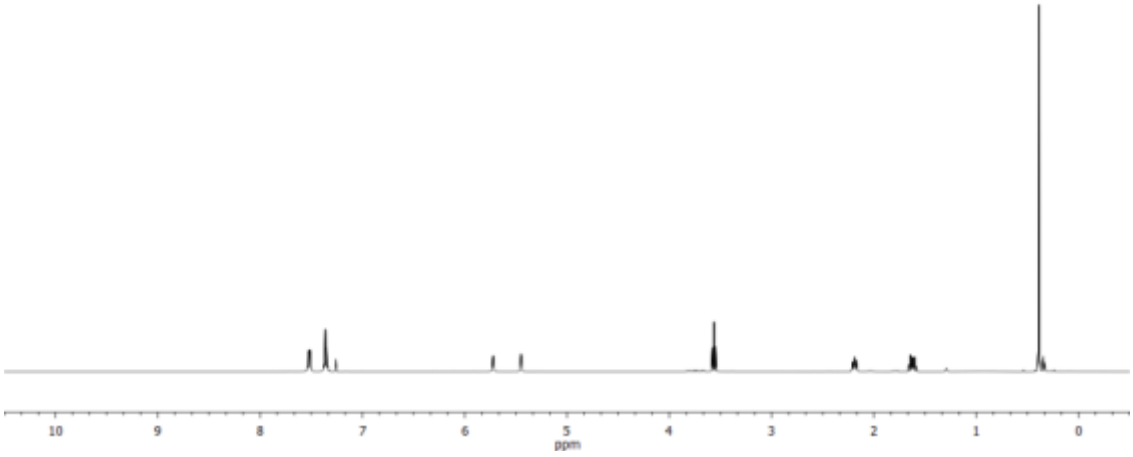
The reaction was conducted in accordance with **General Procedure D** (*via* diene **2.12**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, DCM) to furnish the title compound (78 mg, 71%, 7:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 – 7.48 (m, 2H), 7.40 – 7.32 (m, 3H), 5.78 – 5.67 (m, 1H), 5.51 – 5.37 (m, 1H), 3.56 (t, J = 6.5 Hz, 2H), 2.19 (t, J = 7.7 Hz, 2H), 1.70 – 1.53 (m, 2H), 0.39 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 138.1, 133.9, 129.0, 127.8, 127.8, 126.1, 62.6, 31.9, 31.7, -3.0.

HRMS (CI) Calcd. For $C_{13}H_{19}OSi$ $[M-H]^+$: 219.1205, Found: 219.1208.

FTIR (in $CDCl_3$): 3334, 3050, 2941, 1625, 1427, 1248, 1111, 1055, 924, 832, 816, 774, 730, 699, 668 cm^{-1}.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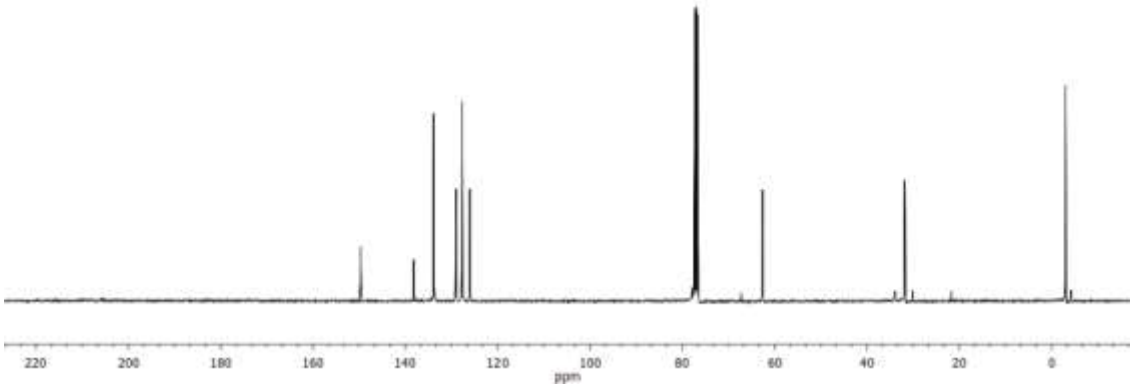
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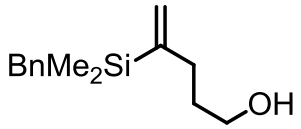
ppm

4-(dimethyl(benzyl)silyl)pent-4-en-1-ol (2.13d)

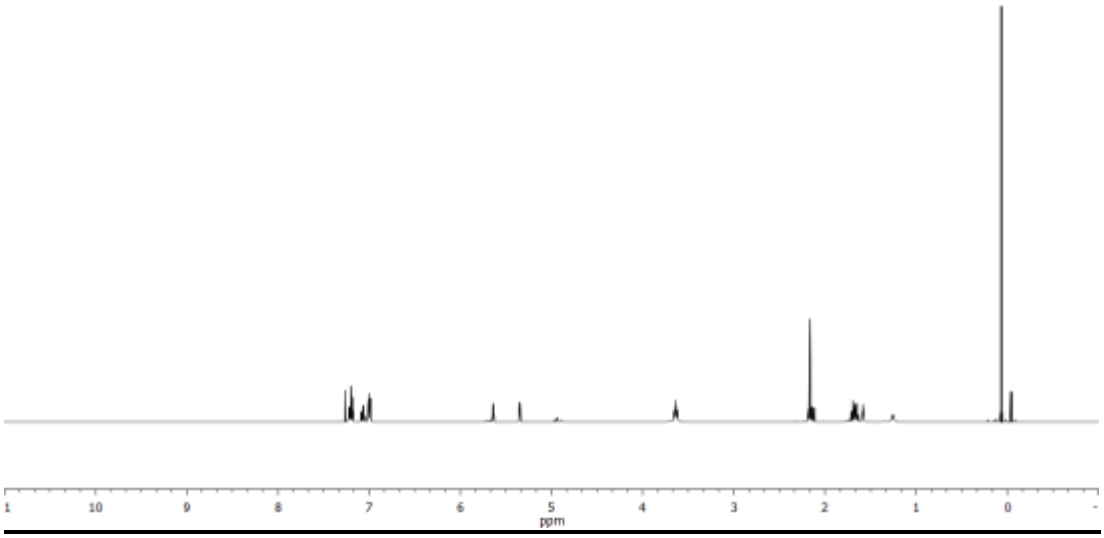


The reaction was conducted in accordance with **General Procedure D** (*via* diene **2.13**). After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, DCM) to furnish the title compound (82 mg, 70%, 7:1 r.r.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 7.07 (app. t, J = 7.4 Hz, 1H), 7.02 – 6.97 (m, 2H), 5.64 (dt, J = 2.9, 1.6 Hz, 1H), 5.36 – 5.33 (m, 1H), 3.64 (t, J = 6.5 Hz, 2H), 2.21 – 2.09 (m, 4H), 1.73 – 1.62 (m, 2H), 1.26 (br s, 1H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 140.0, 128.3, 128.3, 128.2, 125.4, 124.1, 62.8, 32.1, 31.9, 25.6, -3.5.

HRMS (APCI) Calcd. For $C_{14}H_{23}OSi$ $[M-H]^+$: 235.1518, Found: 235.1517.


1
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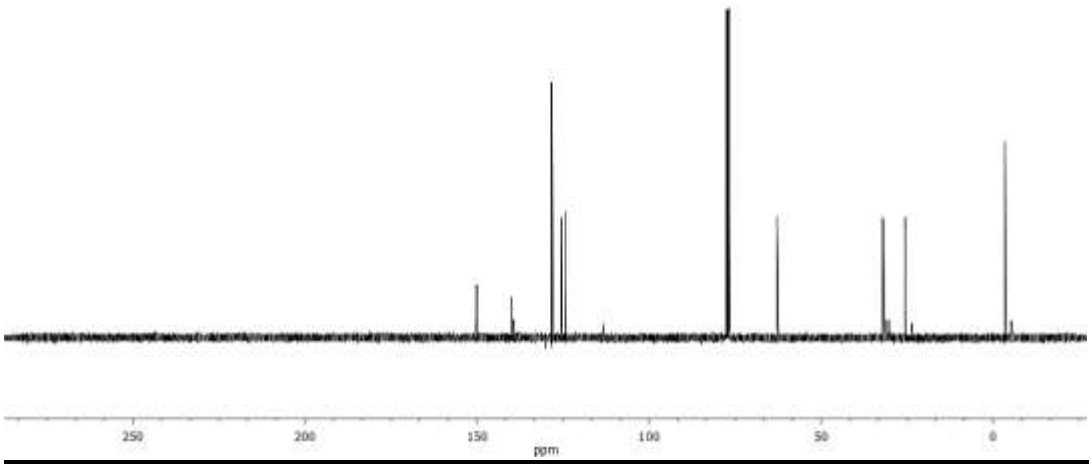
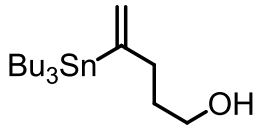
ppm


250
200
150
100
50
0
ppm

4-(tributylstannyl)pent-4-en-1-ol (2.14d)



In modification to **General Procedure D** (*via* diene **2.14**), the reaction was conducted at 75 °C. After heating the reaction for 24 hours and workup, the mixture was purified by flash column chromatography (SiO_2, DCM) to furnish the title compound (105 mg, 56%, >20:1 r.r.) as a colorless oil.

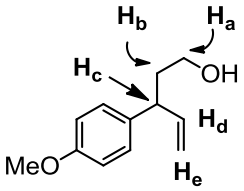
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (dt, J = 2.8, 1.5 Hz, and $J_{Sn\text{-}H}$ = 68.7 Hz, 1H), 5.14 (m_c, 1H), 3.65 (dd, J = 6.3, 4.5 Hz, and $J_{Sn\text{-}H}$ = 31.4 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 1.65 (m_c, 2H), 1.57 – 1.42 (m, 6H), 1.40 – 1.21 (m, 6H), 0.99 – 0.81 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 125.3, 62.8, 37.5, 32.5, 29.2, 27.5, 13.8, 9.7.

HRMS (CI) Calcd. For $C_{17}H_{36}OClSn$ $[M+Cl]^-$: 411.1477, Found: 411.1487.

Spectral data correspond to that reported in literature.[30]

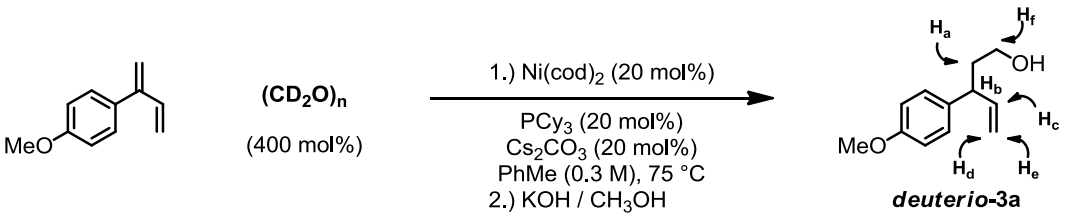
Deuterium Labeling of Nickel Catalyzed Coupling at the C_1-position

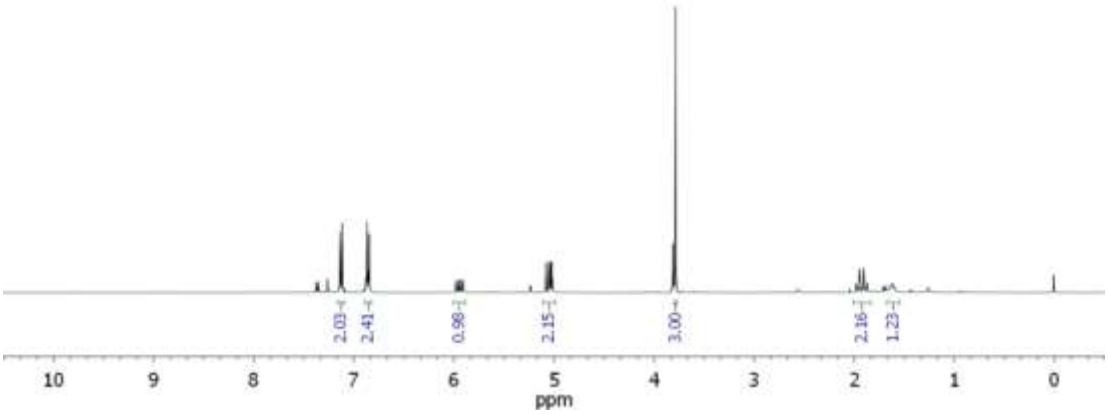


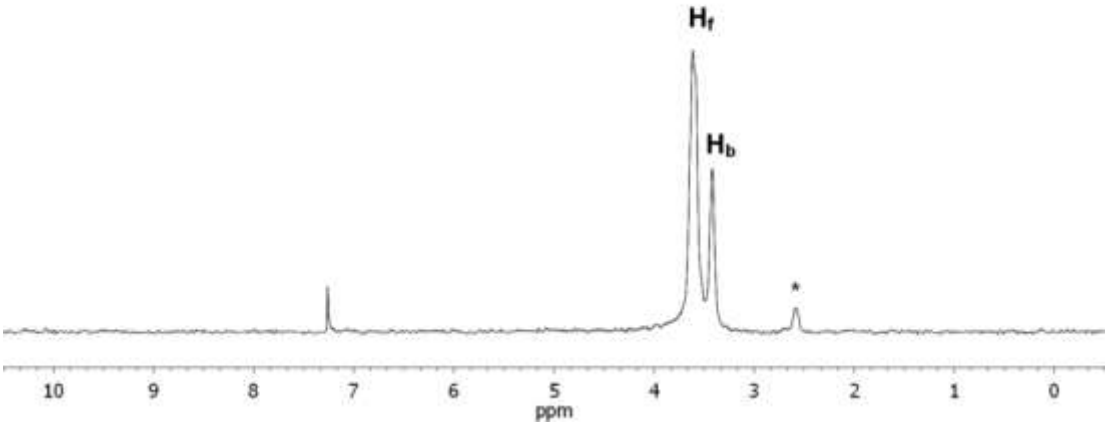
$(CD_2O)_n$
H_a (>95% ^2H)
H_b (0% ^2H)
H_c (>95% ^2H)
H_d (0% ^2H)
H_e (0% ^2H)

The above values represent the average of two trials. The extent of deuterium incorporation was determined for the major regioisomer (alcohol **2.8a**).

Diene **3** was subjected to one experiment employing ***deuterio***-paraformaldehyde under otherwise the same conditions to furnish 3-(4-methoxyphenyl)pent-4-en-1-ol (**3a**). The extent of deuterium incorporation was determined in the isolated product ***deuterio*-3-(4-methoxyphenyl)pent-4-en-1-ol** by integration of the corresponding signals in ^1H NMR (400 MHz, $CDCl_3$) and ^2H NMR (77 MHz, $CHCl_3$).

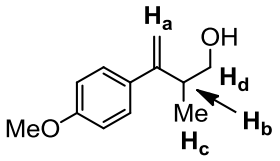






(*Inseparable regioisomer)

Deuterium Labeling of Ruthenium Catalyzed Coupling at the C3-position

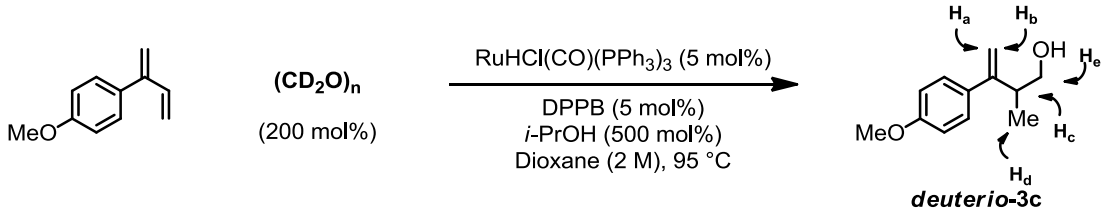


$(CD_2O)_n$ + *i*-PrOH	$(CH_2O)_n$ + *i*-PrOH-d_8	$(CD_2O)_n$ + *i*-PrOH-d_8
H_a (0% ^2H)	H_a (5% ^2H)	H_a (1% ^2H)
H_b (25% ^2H)	H_b (12% ^2H)	H_b (31% ^2H)
H_c (13% ^2H)	H_c (8% ^2H)	H_c (17% ^2H)
H_d (>95% ^2H)	H_d (1% ^2H)	H_d (>95% ^2H)
65% Yield (20:1 rr)	60% Yield (12:1 rr)	64% Yield (17:1 rr)
Experiment 1	**Experiment 2**	**Experiment 3**

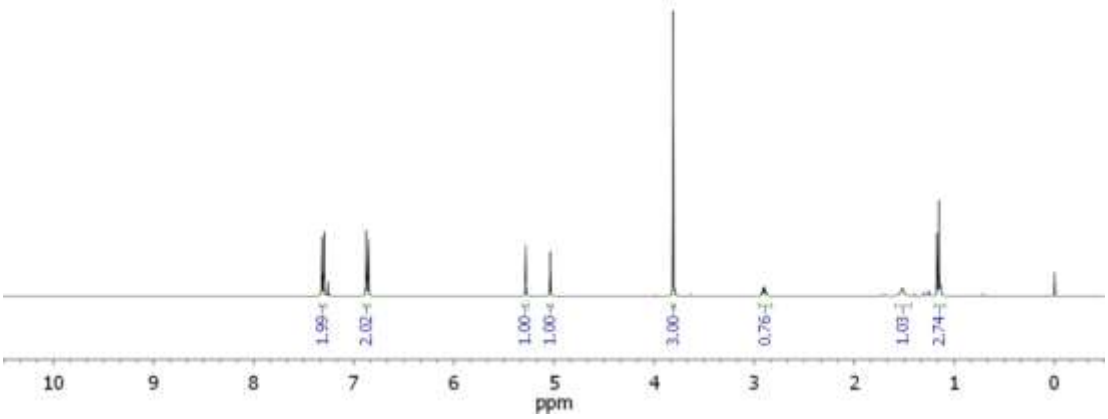
The above values represent the average of two trials. The extent of deuterium incorporation was determined for the major regioisomer (alcohol **2.8c**).

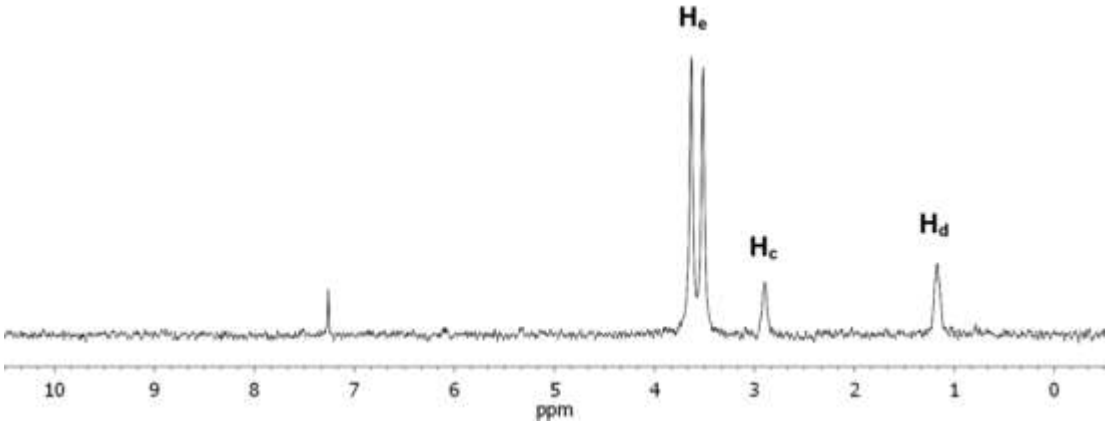
Diene **3** was subjected to three separate experiments employing ***deuterio***-paraformaldehyde, ***d*$_8$**-isopropanol, and both ***deuterio***-paraformaldehyde and ***d*$_8$**-isopropanol under otherwise the same conditions to furnish 3-(4-methoxyphenyl)-2-methylbut-3-en-1-ol (**3c**). The extent of deuterium incorporation was determined in the isolated product ***deuterio*-3-(4-methoxyphenyl)-2-methylbut-3-en-1-ol** by integration of the corresponding signals in ^1H NMR (400 MHz, $CDCl_3$) and ^2H NMR (77 MHz, $CHCl_3$).

Experiment 1.

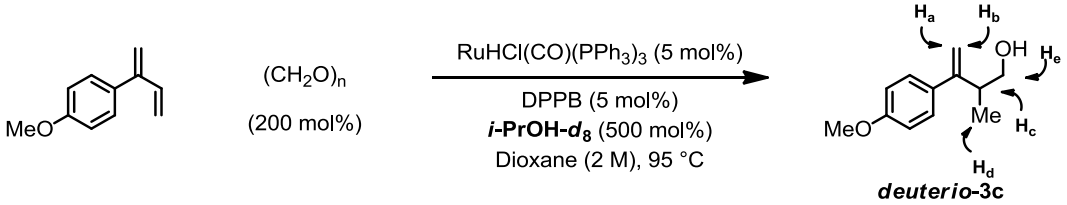


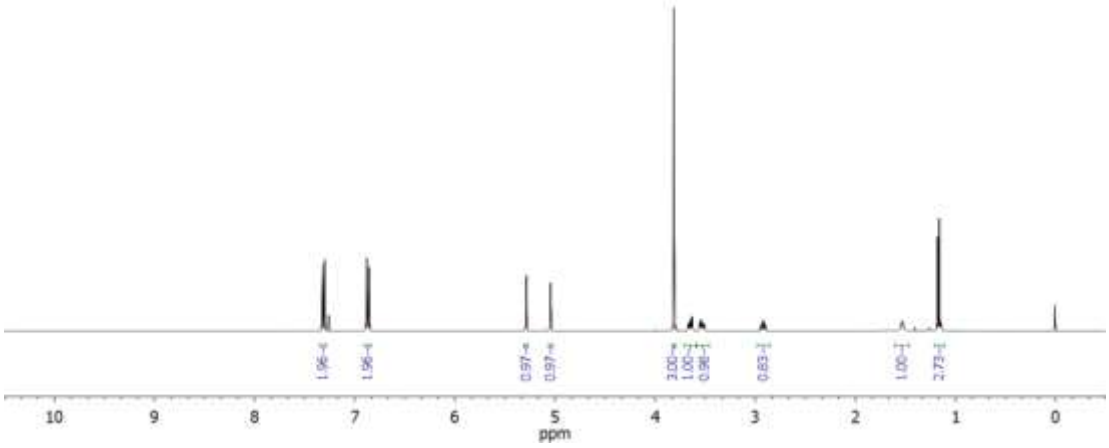
***deuterio*-3c**

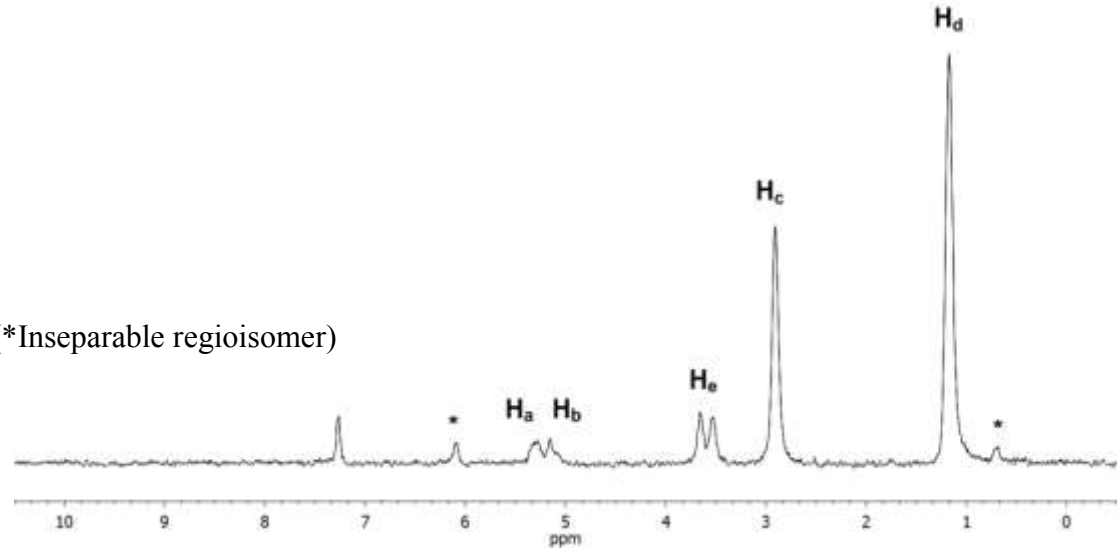




Experiment 2.

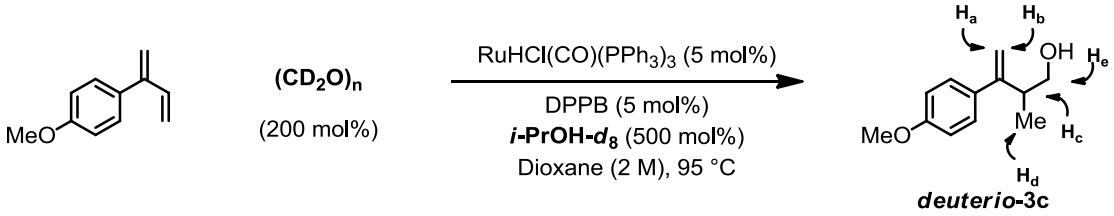




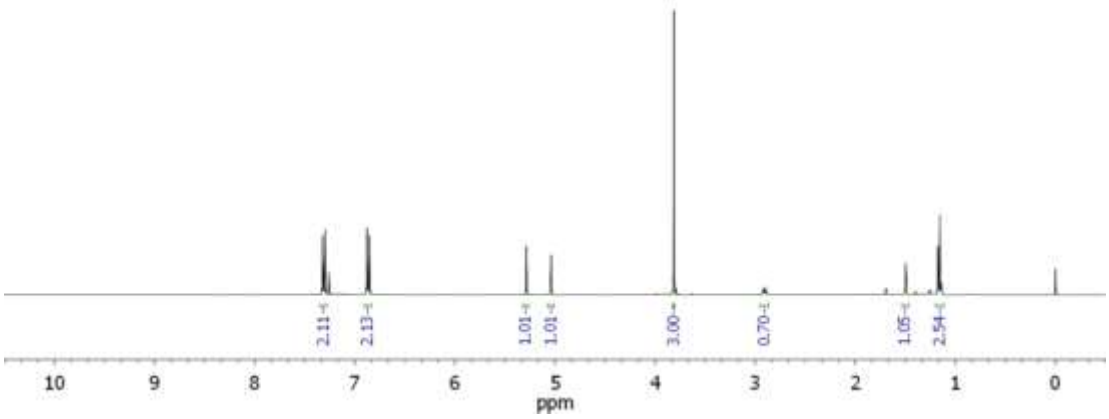


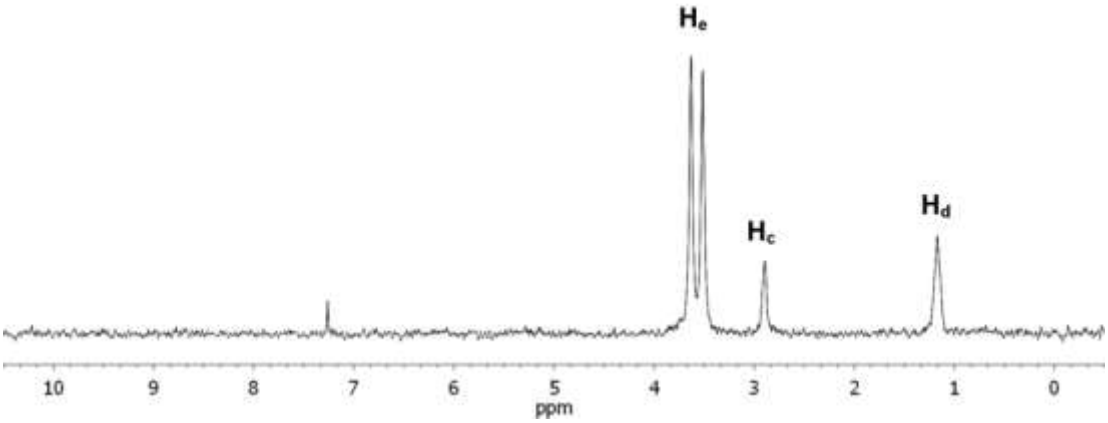
(*Inseparable regioisomer)

Experiment 3.



***deuterio*-3c**





CHAPTER 3: FORMATION OF ALL-CARBON QUATERNARY CENTERS *VIA* HYDROHYDROXYALKYLATIONS OF 1,1-DISUBSTITUTED ALLENES*†

3.1 Introduction

Organofluorine chemistry has emerged as one of the most attractive research areas in organic synthesis. The unique ability of fluorine to affect the properties of organic molecules through strong polar interactions, due to its high electronegativity and relatively close size to hydrogen, has made the atom vital in the development of pharmaceuticals[1,2], agrochemicals[3], materials[4], and tracers for positron emission tomography (PET)[5] (Figure 3.1). For example, incorporating fluorine into pharmaceuticals may modulate acidity, metabolic stability, and protein binding affinity.[1] Indeed, more than 20% of approved pharmaceutical agents and 30-40% of commercially available agrochemicals are organofluorine compounds,[1,6] which is astonishing given that few known organofluorine compounds exist in nature.[7]

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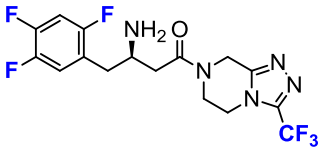
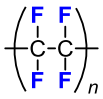
† Sam, B.; Luong, T.; Krische, M. J. *Angew. Chem.* **2015**, doi:10.1002/ange.201500238; *Angew. Chem. Int. Ed.* **2015**, doi:10.1002/anie.201500238. Acknowledgement is made to M. J. K. for project oversight and T. L. for scope evaluation and product derivatization.

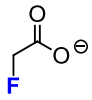
Figure 3.1. Selected examples of organofluorine compounds.



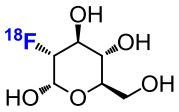
Januvia®
Merck & Co.
(pharmaceutical)



Teflon®
Dupont Co.
(material)



Fluoroacetate
(agrochemical)



Fluorodeoxyglucose
(PET tracer)

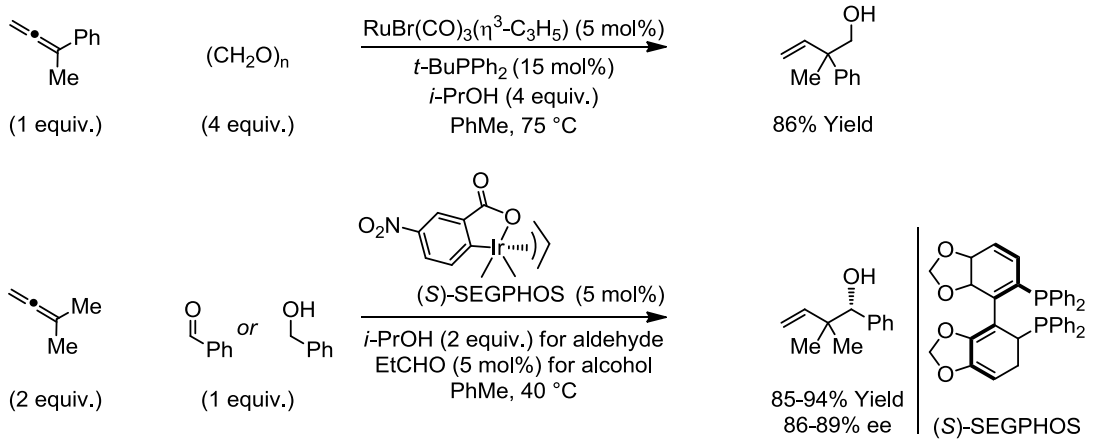
Accordingly, many powerful methods for the introduction of fluorine and fluorine containing functional groups have been developed.[8] Remarkably, despite years of investigation, there is a paucity of methods for the formation of all-carbon quaternary centers incorporating a trifluoromethyl group and the addition of non-stabilized *C*-nucleophiles to fluorinated aldehydes[9]. As certain metal catalysts were recently shown to promote reductive C-C couplings of π-unsaturated reactants to aldehydes *via* transfer hydrogenation,[10] efforts were made to exploit this technology in the hydrohydroxymethylation of 1-aryl-1-trifluoromethylallenes[11] and hydrohydroxyfluoroalkylation of both 1,1-dialkylallenes and 1-alkyl-1-arylallenes[12].

3.2 CF_3-Bearing All Carbon Quaternary Centers *via* Hydrohydroxymethylation of CF_3-Allenes

3.2.1 BACKGROUND

The formation of all-carbon quaternary centers has received significant attention in organic synthesis.[13] Of particular importance is the synthesis of biologically active compounds such as carotenoids and steroids, which contain all carbon quaternary centers.[14] Few protocols exist involving the incorporation of fluorine, specifically the trifluoromethyl group, into quaternary carbon centers.[15] Recently, methods for the formation of all-carbon quaternary centers have been reported *via* metal catalyzed, transfer hydrogenative couplings of 1,1-disubstituted allenes and aldehydes or alcohols, including allene hydrohydroxymethylations (Scheme 3.1).[11,16,17] Thus, methods for alcohol mediated reductive couplings of paraformaldehyde to allenes[14a] provide an alternative to hydroformylation which is often problematic for compounds that contain more than one unit of unsaturation. Toward this end, investigation into the reductive coupling of 1-aryl-1-trifluoromethylallenes to paraformaldehyde ensued to furnish homoallylic alcohols bearing a trifluoromethyl substituted all-carbon quaternary center.[11]

Scheme 3.1. Selected examples of transfer hydrogenative couplings of allenes and carbonyl groups.



3.2.2 SYNTHESIS OF CF_3-ALLENES

Investigation into the hydrohydroxymethylation 1-aryl-1-trifluoromethylallenes required a method for the preparation of these trifluoromethyl containing allenes. Although syntheses involving propargyl substitution using CF_3 nucleophiles are reported,[18] these methods do not permit formation of 1-aryl-1-trifluoromethylallenes. Syntheses involving introduction of the trifluoromethyl group at an early stage have also been reported, but do not employ readily accessible starting materials and are not step-economic (Scheme 3.2).[19] Classical strategies for allene synthesis, such as the Doering-LaFlamme method,[20] were unsuccessful. Hence, an effective protocol for the synthesis of 1-aryl-1-trifluoromethylallenes was developed (Table 3.1).

Scheme 3.2. Known synthesis of 1-aryl-1-CF_3-allenes.

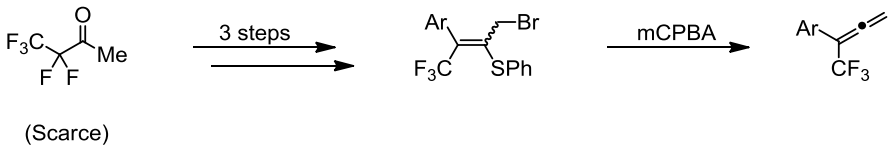
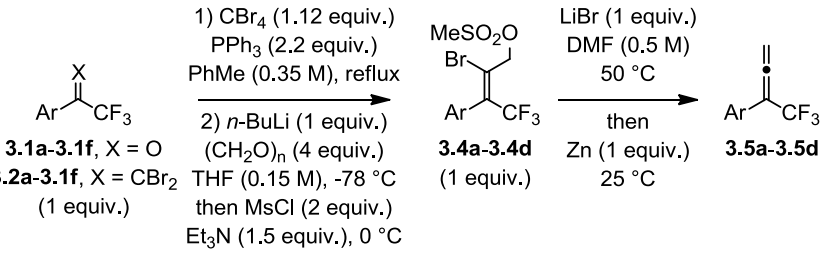
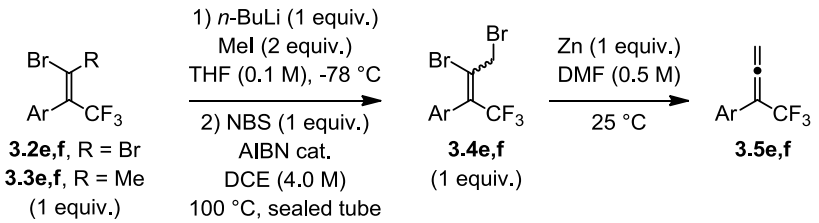


Table 3.1. Novel synthesis of 1-aryl-1-CF_3-allenes.[a]



aryl group	**3.2a-3.2f**, Yield	**3.4a-3.4d**, Yield	**3.5a-3.5d**, Yield
3.1a, Ar = C_6H_5	**3.2a**, 81%	**3.4a**, 49%	**3.5a**, 78%
3.1b, Ar = 3-MeC_6H_4	**3.2b**, 82%	**3.4b**, 37%	**3.5b**, 86%
3.1c, Ar = 4-$MeOC_6H_4$	**3.2c**, 91%	**3.4c**, 48%	**3.5c**, 72%
3.1d, Ar = 2-napthyl	**3.2d**, 84%	**3.4d**, 38%	**3.5d**, 77%
3.1e, Ar = 3,5-$Cl_2C_6H_3$	**3.2e**, 82%		
3.1f, Ar = 4-ClC_6H_4	**3.2f**, 84%		



aryl group	**3.3e,f**, Yield	**3.4e,f**, Yield	**3.5e,f**, Yield
3.1e, Ar = 3,5-$Cl_2C_6H_3$	**3.3e**, 73%	**3.4e**, 56%	**3.5e**, 56%
3.1f, Ar = 4-ClC_6H_4	**3.3f**, 81%	**3.4f**, 43%	**3.5f**, 84%

[a]Yields are of material isolated by silica gel chromatography.

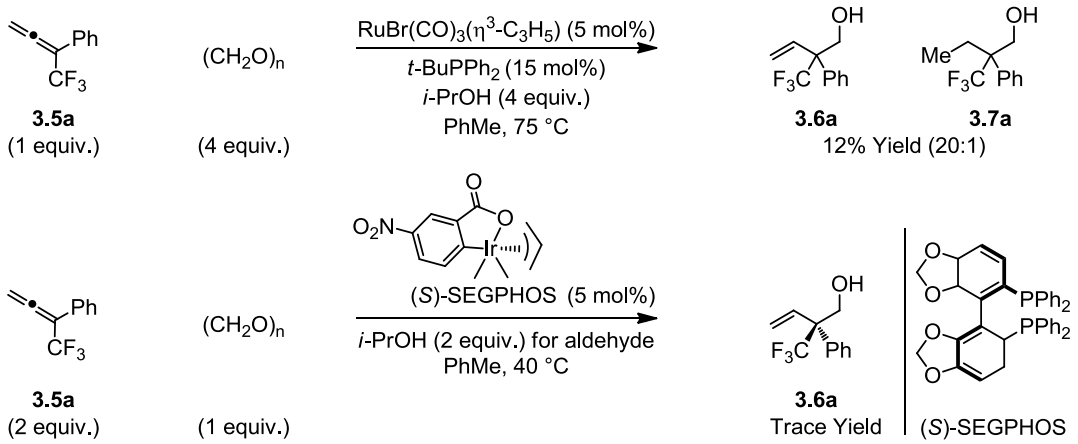
Corey-Fuchs olefination of the aryl trifluoromethyl ketones **3.1a-3.1f**[21] delivered the corresponding methylene dibromides **3.2a-3.2f**. Lithiation[22] of the resulting methylene dibromides **3.2a-3.2d** followed by treatment with paraformaldehyde and quenching with methanesulfonyl chloride afforded the allylic sulfonates **3.4a-3.4d**, which

appeared as single geometrical isomers. The allylic sulfonates **3.4a**-**3.4d** were converted to the corresponding allylic bromides, *in situ*, and then exposed to zinc dust[23] to form allenes **3.5a**-**3.5d** in good isolated yield. The vinyl lithium species derived from methylene dibromides **3.2e**,**f** did not react efficiently with paraformaldehyde, but was methylated in good yield to form adducts **3.3e**,**f** as single geometrical isomers. Allylic bromination, which occurs with scrambling of olefin geometry, followed by treatment with zinc dust provided allenes **3.5e**,**f**.

3.2.3 REACTION DEVELOPMENT

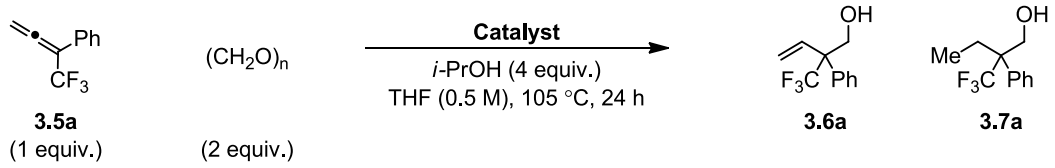
With a serviceable route to 1-aryl-1-CF_3-allenes, the reductive coupling of paraformaldehyde to 1-phenyl-1-trifluoromethylallene commenced. Exposure to conditions previously developed for ruthenium catalyzed reductive coupling of 1,1-disubstituted allenes to paraformaldehyde[16a] provided the desired reductive coupling product in poor yield (12%) as a single regioisomer, but also as an inseparable mixture with hydrogenated coupling product (<1% yield). Under iridium catalysis,[17b] only trace product was detected (Scheme 3.3). Surveying additional previously developed conditions for ruthenium catalyzed reductive couplings of unsaturates to aldehydes afforded more promising results.[16,17] By employing the catalyst system of $RuHCl(CO)(PPh_3)_3$ (5 mol%) and DiPPF (5 mol%) in combination with 1-phenyl-1-trifluoromethylallene (1 equiv.), paraformaldehyde (2 equiv.), and isopropanol as terminal reductant (4 equiv.) at 105 °C for 24 hours in tetrahydrofuran provided the desired product in 46% yield, as a single compound.[16e]

Scheme 3.3. Initial results of CF_3-allene reductively coupling to paraformaldehyde.



Ensuing optimization of the catalyst system followed with assaying metal complexes and ligand combinations. Various ruthenium (II) complexes were evaluated in the absence of exogenous ligand (Table 3.2). Although, $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ furnished the highest yield of coupling product, small quantities of the hydrogenated product were apparent (Table 3.2, entry 5). Screening additional reactions conditions employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$, such as exogenous ligand, time, and stoichiometry, failed to deliver any significant improvement. Hence, $RuHCl(CO)(PPh_3)_3$, which provided coupling product in 37% yield without the hydrogenated side-product, was evaluated as the base catalyst (Table 3.2, entry 4).

Table 3.2. Selected assay of metal complexes in the coupling of CF_3-allene to paraformaldehyde.[a]



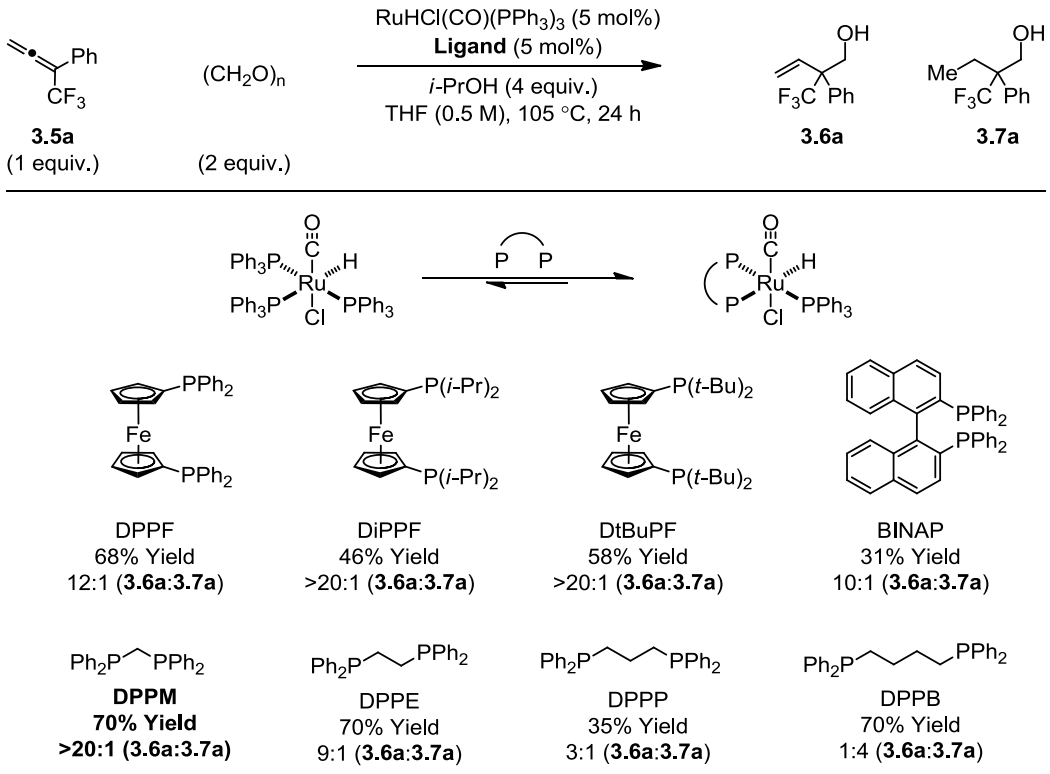
3.5a (1 equiv.) (2 equiv.) **3.6a** **3.7a**

Entry	Catalyst	Loading	Yield	3.6a : 3.7a
1	None	-	-	-
2	$RuBr(CO)_3(\eta^3\text{-}C_3H_5)$	5 mol%	Trace	n.d.
3	$RuH_2(CO)(PPh_3)_3$	5 mol%	18%	>20:1
4	$RuHCl(CO)(PPh_3)_3$	5 mol%	37%	>20:1
5	$Ru(O_2CCF_3)_2(CO)(PPh_3)_2$	5 mol%	51%	13:1
6	$[RuCl_2(p\text{-cymene})]_2$	2.5 mol%	-	-

[a]Yields are of material isolated by silica gel chromatography. Ratios of **3.6a**:**3.7a** were determined by ^{19}F NMR analyses of crude reaction mixtures.

As previously shown, the combination of $RuHCl(CO)(PPh_3)_3$ and exogenous ligand, DiPPF, led to a higher yield (46%) rather than $RuHCl(CO)(PPh_3)_3$ alone (37% yield). Thus, exogenous ligands were assayed in the reaction conditions. Bidentate ferrocene-based ligands, DPPF and DtBuF, improved the overall yield of coupling product, 68% and 58%, respectively with more significant quantities of hydrogenated side-product **3.7a** occurring for DPPF (Table 3.3). Based on this data, it appears that more electron-rich ferrocene-based phosphines such as DiPPF and DtBuF, suppress formation of the hydrogenated side-product, relative to the less electron rich DPPF.

Table 3.3. Selected assay of ligands in the coupling of CF_3-allene to paraformaldehyde.[a]

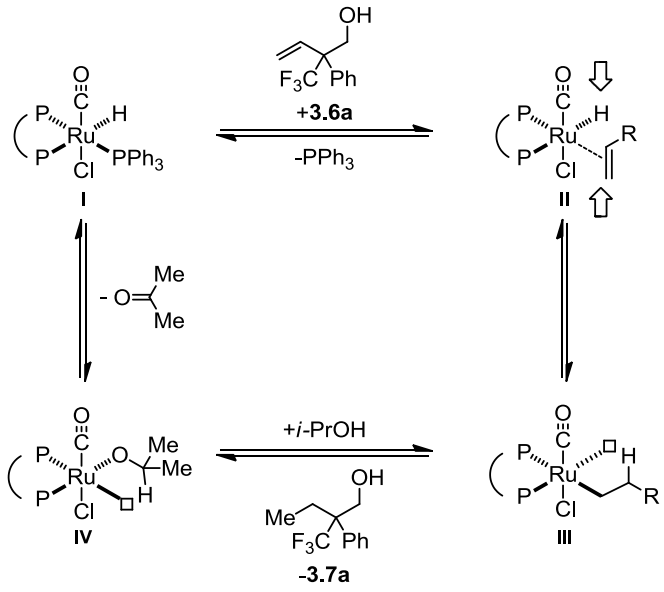


[a]Yields are of material isolated by silica gel chromatography. Ratios of **3.6a**:**3.7a** were determined by ^{19}F NMR analyses of crude reaction mixtures.

Interestingly, the screening of alkyl-linked bis-aryl-phosphines showed that the amount of hydrogenated side-product increases with bite angle, suggesting sterics may be a factor. The alkyl-linked bis-aryl-phosphine with a single methylene link, DPPM, suppressed side-product formation, whereas the phosphine with a butyl link, DPPB, produced the largest quantity of over-reduced product, while both ligands furnished overall coupling yields of 70%. This trend may be rationalized as follows. Once the desired homoallylic alcohol **3.6a** is formed, the olefin may coordinate to the metal *via* ligand exchange with triphenylphosphine (PPh_3), **II**, (Scheme 3.4). As the carbon linker of the phosphine ligand lengthens, the bite angle increases and pushes the hydride and

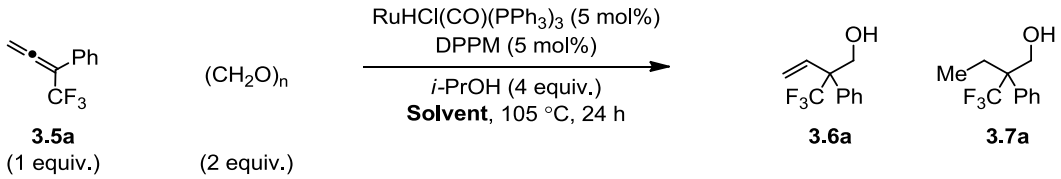
olefin closer together, facilitating hydrometallation, **III**, and subsequent protonolysis, **IV**, to yield the hydrogenated coupling product **3.7a**.

Scheme 3.4. Rationale for ligand influence on hydrogenated coupling product formation.



With a serviceable catalyst system consisting of $RuHCl(CO)(PPh_3)_3$ and DPPM, optimization continued with the screening of solvent. An assay of solvent and solvent concentration revealed that only significantly more polar solvents than tetrahydrofuran, such as acetonitrile, impeded the reaction (Table 3.4, entry 6). The higher boiling point solvent, toluene, provided similar reactivity to tetrahydrofuran (Table 3.4, entry 3), prompting its selection over tetrahydrofuran given the reaction temperature of 105 °C. Notably, subsequent re-assaying of selected ligands with toluene as solvent did not provide any significant changes in reactivity.

Table 3.4. Selected solvent assay in the coupling of CF_3-allene to paraformaldehyde.[a]

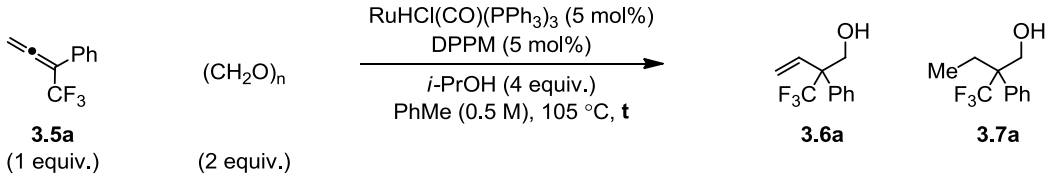


Entry	Solvent	Concentration	Yield	3.6a : 3.7a
1	THF	0.5 M	70%	>20:1
2	THF	1.0 M	67%	>20:1
3	PhMe	0.5 M	70%	>20:1
4	Dioxane	0.5 M	69%	>20:1
5	DCE	0.5 M	64%	>20:1
6	MeCN	0.5 M	28%	>20:1

[a]Yields are of material isolated by silica gel chromatography. Ratios of **3.6a**:**3.7a** were determined by ^{19}F NMR analyses of crude reaction mixtures.

Remarkably, screening of reaction times revealed that the coupling reaction is nearly complete with 98% conversion of the starting material in as little as 10 minutes (Table 3.5, entry 3). Although no starting material was detected at 30 minutes (Table 3.5, entry 5), one hour was selected as an appropriate reaction time to carry across an array of substrates as the extended time did not appear detrimental (Table 3.5, entries 6 and 7). Given the swiftness of the reaction, it was postulated that milder reactions conditions, such as lower catalysts loadings and/or lower temperatures, may prove sufficient. However, screening of these parameters significantly decreased the coupling yields.

Table 3.5. Selected screening of reaction time in the coupling of CF_3-allene to paraformaldehyde.[a]



Entry	Time	Conversion	3.6a : 3.7a
1	3 m	49%	>20:1
2	5 m	74%	>20:1
3	10 m	98%	>20:1
4	20 m	99%	>20:1
5	30 m	100%	>20:1
6	60 m	100%	>20:1
7	120 m	100%	>20:1

[a]Yields are of material isolated by silica gel chromatography. Ratios of **3.6a**:**3.7a** were determined by ^{19}F NMR analyses of crude reaction mixtures.

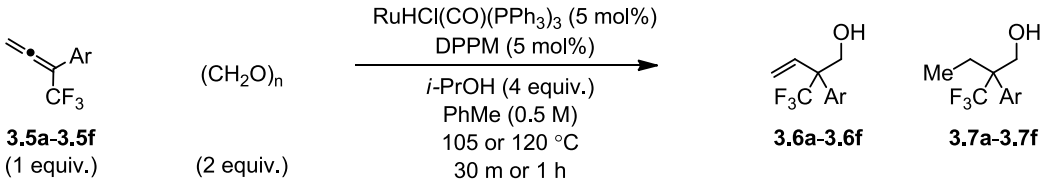
To our delight, these conditions employing the catalyst system of $RuHCl(CO)(PPh_3)_3$ (5 mol%) and DPPM (5 mol%) in combination with 1-phenyl-1-trifluoromethylallene (1 equiv.), paraformaldehyde (2 equiv.), and isopropanol as terminal reductant (4 equiv.) at 105 °C for one hour in toluene delivered the desired neopentyl, homoallylic alcohol bearing a CF_3 group in 78% yield, as a single compound **3.6a**.

3.2.4 REACTION SCOPE

To assess the scope of these conditions, an array of 1-aryl-1-trifluoromethylallenes **3.5b**-**3.5f** was assayed in the reductive coupling to paraformaldehyde (Table 3.6). Withstanding minor adjustments for temperature and time, trifluoromethyl substituted neopentyl alcohols **3.6b**-**3.6f** were furnished in good

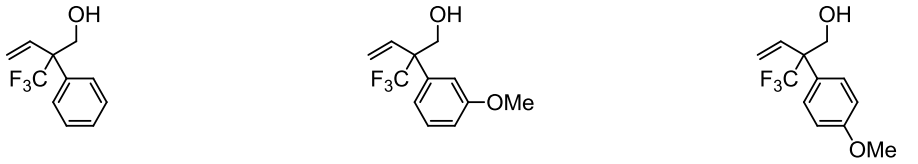
yields, as single regioisomers, mostly with suppression of the hydrogenated side-product. To evaluate scalability, CF_3-allene **3.6a** was subjected to the standard reaction conditions and delivered roughly one gram of the desired product without erosion of yield or product selectivity.

Table 3.6. Ruthenium catalyzed hydrohydroxymethylation of CF_3-allenes.[a]



3.5a-3.5f (1 equiv.) (2 equiv.) **3.6a-3.6f** **3.7a-3.7f**

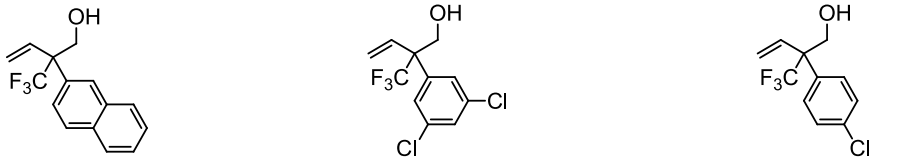
3.5a, Ar = C_6H_5	**3.5b**, Ar = 3-$OMeC_6H_4$	**3.5c**,Ar = 4-$OMeC_6H_4$
3.5d, Ar = 2-Napthyl	**3.5e,** Ar = 3,5-$Cl_2C_6H_3$	**3.5f**, Ar = 4-ClC_6H_4



78% Yield
20:1 (**3.6a:3.7a**)
105 °C, 1 h

65% Yield
>20:1 (**3.6b:3.7b**)
120 °C, 30 m

75% Yield
>20:1 (**3.6c:3.7c**)
105 °C, 1 h



67% Yield
>20:1 (**3.6d:3.7d**)
105 °C, 1 h

73% Yield
16:1 (**3.6e:3.7e**)
120 °C, 30 m

68% Yield
>20:1 (**3.6f:3.7f**)
120 °C, 30 m

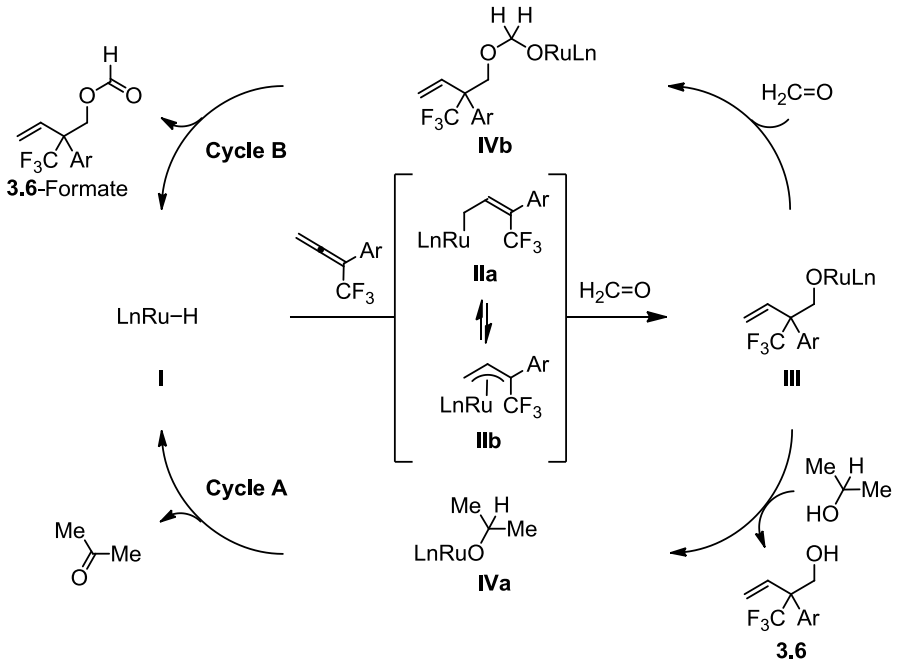
[a]Yields are of material isolated by silica gel chromatography. Ratios of **3.6**:**3.7** were determined by ^{19}F NMR analyses of crude reaction mixtures.

3.2.5 POSTULATED REACTION MECHANISM

A hydrometallative pathway is proposed, as found in related ruthenium catalyzed allene-aldehyde couplings (Scheme 3.5).[16,17] The catalytic cycle opens with

regioselective hydrometallation of the allene to form a 1,1-disubstituted π-allylruthenium intermediate.[24,25] By way of the primary σ-allyl haptomer, regioselective carbonyl addition at the more substituted position of the allene may proceed *via* a closed six-membered chair-like transition state (not depicted). Protonolysis of the ruthenium alkoxide by isopropanol releases the CF_3-adduct **3.6** and produces ruthenium isopropoxide. Subsequent β-hydride elimination furnishes the benign by-product, acetone, and regenerates the ruthenium hydride complex to complete the catalytic cycle. Alternatively, as discussed in chapter two, ruthenium alkoxide **III** may undergo formaldehyde addition to form ruthenium alkoxide **IVb**. β-hydride elimination releases the formate ester of the coupling product **3.6**-Formate and regenerates the ruthenium hydride complex to close the catalytic cycle. Notably, the isolable formate ester **3.6**-Formate was cleaved in the course of isolation.

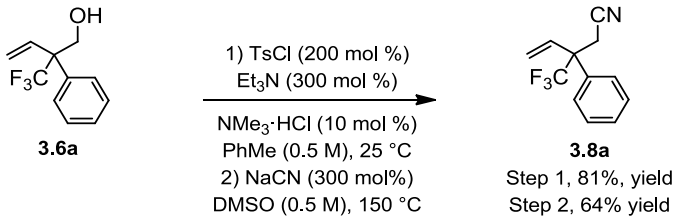
Scheme 3.5. Proposed mechanism for coupling of paraformaldehyde to CF_3-allenes.



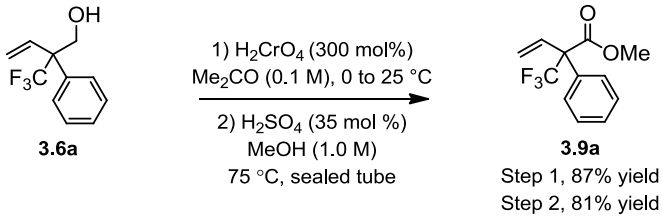
3.2.6 PRODUCT DERIVATIZATION

To demonstrate the utility of the reaction products, neopentyl alcohol **3.6a** was converted to the corresponding *p*-toluenesulfonate and reacted with sodium cyanide in DMSO solvent. Nitrile **3.8a** was formed in moderate yield, despite the notoriously low rates typically observed in S_N2 reactions of neopentyl electrophiles (Scheme 3.6). Jones oxidation of neopentyl alcohol **3.6a** and subsequent Fischer esterification provides the methyl ester **3.9a** (Scheme 3.7).

Scheme 3.6. Conversion of CF_3-bearing neopentyl alcohol **3.6a** to a nitrile.



Scheme 3.7. Conversion of CF_3-bearing neopentyl alcohol **3.6a** to an ester.

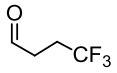
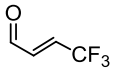
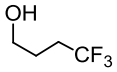
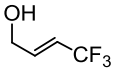


3.3 Ruthenium Catalyzed C-C Coupling of Fluorinated Alcohols with Allenes

3.3.1 BACKGROUND

Very few systematic studies on the addition of non-stabilized *C*-nucleophiles to fluorinated aldehydes exist.[9] Metal catalyzed additions of *C*-nucleophiles to fluorinated aldehydes are largely limited to carbonyl-ene, Mukaiyama aldol, and Friedel-Crafts reactions,[26] likely stemming from their intractability and propensity to engage in self-condensation or suffer reduction upon exposure to main group organometallics such as Grignard reagents.[9a,b] In contrast, the corresponding fluorinated alcohols are stable, abundant, and relatively inexpensive (Table 3.7); thus, they are often used as solvents or additives in chemical synthesis.[27]

Table 3.7. Prices for selected fluorinated aldehydes and alcohol congeners.[a]

			
NOT COMMERCIAL	$2,824 / mol	$7,263 / mol	NOT COMMERCIAL
			
$139 / mol	$1,027 / mol	$1,051 / mol	$1,054 / mol

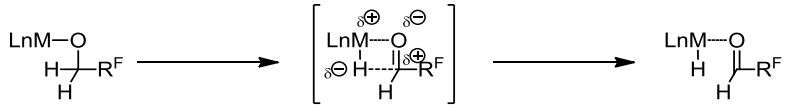
[a]Prices of commercially available material from Oakwood Chemical with the exception of 2-fluoroethanol (Matric Scientific Inc.) as of 3/7/2015.

Under the conditions of metal catalyzed transfer hydrogenative carbonyl addition,[10] alcohols serve as synthetic equivalents to their carbonyl congeners, enabling additions that would otherwise be unattainable due to the intractability of the corresponding aldehydes. For example, highly tractable 1,3-diols can be used in catalytic enantioselective double allylations or crotylations *via* redox-triggered carbonyl addition, whereas the corresponding 1,3-dialdehydes are relatively unstable.[28] In such redox-triggered carbonyl additions, hydrogen is transferred from alcohols to π-unsaturated reactants to generate transient carbonyl-organometal pairs that combine to form products of addition.[10] Pairwise generation of the transient aldehyde and organometallic nucleophile mitigates competing decomposition.

The feasibility of engaging fluorinated alcohols in redox-triggered carbonyl addition was rendered uncertain by three issues: (a) the relatively high strength of carbinol C-H bonds in fluorinated alcohols,[9] (b) the increased endothermicity of dehydrogenation, which being reversible would shorten the lifetime of the transient aldehyde,[29] and (c) the large destabilizing effect of fluoroalkyl groups on the transition state for β-hydride elimination (up to 15 kcal/mol)[29] (Scheme 3.8). Herein, we report that

certain fluorinated alcohols may participate in redox-triggered carbonyl allylation, as illustrated by their regio- and diastereoselective ruthenium catalyzed C-C coupling to 1,1-disubstituted allenes to furnish adducts bearing all-carbon quaternary stereocenters.[16,17,30,31]

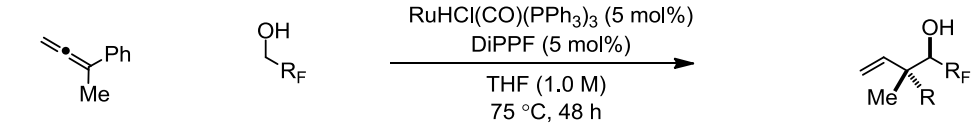
Scheme 3.8. Inductive fluoroalkyl moieties raise the energetic barrier to β-hydride elimination.



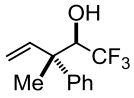
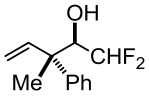
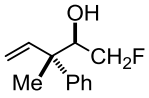
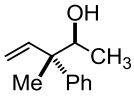
3.3.2 REACTION DEVELOPMENT

In initial experiments, fluoroethanols **3.11a-3.11c** and ethanol **3.11d** were treated with 1-methyl-1-phenylallene **3.10a** under conditions for the coupling of non-fluorinated alcohols to 1,1-disubstituted allenes (Table 3.8).[16e] Exposure of trifluoroethanol **3.11a** (1 equiv.) and allene **3.10a** (3 equiv.) to the ruthenium (II) catalyst derived *in situ* from $RuHCl(CO)(PPh_3)_3$ (5 mol%) and exogenous ligand, DIPPF (5 mol%), in tetrahydrofuran at 75 ^oC for 48 hours did not provide the desired adduct **3.12a**. However, as anticipated based on the relative transition state energies for β-hydride elimination,[29] decreasing degree of fluoro-substitution increases reaction efficiency. The reaction of difluoroethanol **3.11b** and fluoroethanol **3.11c** delivered the desired adducts **3.12b** and **3.12c** in less than 5% and 60% yield, respectively, whereas the reaction of ethanol itself provided adduct **3.12d** in 73% yield as a single diastereomer.

Table 3.8. Initial probe of fluoroethanols and ethanol.



3.10a (3 equiv.) | **3.11a-3.11d** (1 equiv.) | **3.12a-3.12d**

3.11a, $R_F = CF_3$	**3.11b**, $R_F = CHF_2$	**3.11c**, $R_F = H_2CF$	**3.11d**, $R_F = CH_3$
			
Not Detected, **3.12a**	<5% Yield, **3.12b** 2:1 dr	60% Yield, **3.12c** >20:1 dr	73% Yield, **3.12d** >20:1 dr

[a]Cited yields are of material isolated by silica gel chromatography and represent the average of two runs. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.

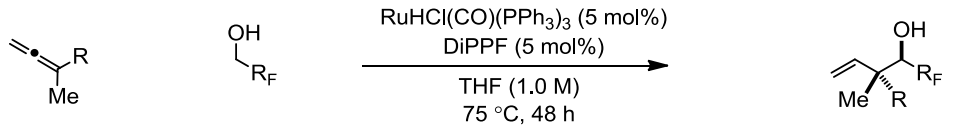
An extensive effort to enhance conversion in the reactions of trifluoroethanol **3.11a** and difluoroethanol **3.11b** through variation of ligand, ruthenium precatalyst and other parameters was attempted to no avail. In contrast, for the reaction of fluoroethanol **3.11c**, simply extending the reaction time allowed the desired adduct **3.12c** to be obtained in 75% isolated yield. In general, the coupling of fluorinated alcohols occurs under essentially the same conditions as non-fluorinated alcohols,[16e] but longer reaction times were required in some cases.

3.3.3 Reaction Scope

To test the generality of these conditions, fluoroethanol **3.11c**, 3,3,3-trifluoropropanol **3.11e**, 4,4,4-trifluorobutanol **3.11f**, and 4,4,4-trifluorobut-2-en-1-ol **3.11g** were assayed in transfer hydrogenation mediated couplings to 1,1-disubstituted allenes **3.10a**-**3.10d**. Withstanding minor adjustments to temperature, time, and/or

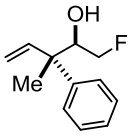
solvent concentration, coupling products **3.12c**, **3.12e**-**3.12s** were obtained in good yields and diastereoselectivities (Table 3.9). Unsubstituted and substituted aryl groups were well tolerated as phenyl, *p*-methoxyphenyl, and 3,5-dichlorophenyl substituted allenes **3.10a**, **3.10c**, and **3.10d**, respectively, coupled to the selected fluorinated alcohols in good yields. Remarkably, complete levels of *anti*-diastereoselectivity were observed in these reactions of the fluorinated alcohols with 1-methyl-1-aryl substituted allenes, as determined by ^{1}H NMR analysis of the crude reaction mixtures. Even for the phthalimidomethyl substituted allene **3.10b**, good levels of *anti*-diastereoselectivity (4:1 - 6:1 dr) were evident in the formation of adducts **3.12h**-**3.12j**. The transient (*E*)- and (*Z*)-σ-allylruthenium intermediates for other dialkyl substituted allenes are quite similar in energy resulting in lower diastereoselectivity. Conversion of the trifluoromethylated allylic alcohol **3.11g** to adducts **3.12g**, **3.12k**, **3.12o** and **3.12s** is noteworthy, as fluorinated allylic alcohols are known to undergo internal redox isomerization upon exposure to closely related ruthenium (II) catalysts.[32]

Table 3.9. Ruthenium catalyzed hydrohydroxyfluoroalkylation of allenes.

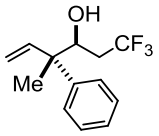


3.10a-3.10d (3 equiv.) **3.11c, 3.11e-3.11g** (1 equiv.) **3.12c**, **3.12e-3.12s**

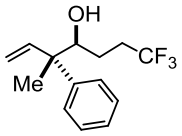
3.10a, R = C_6H_5 **3.10b**, R = CH_2NPhth **3.10c**, R = 4-$MeOC_6H_4$ **3.10d**, R = 3,5-$Cl_2C_6H_3$
3.11c, R_F = CH_2F **3.11e**, R_F = CH_2CF_3 **3.11f**, R_F = $(CH_2)_2CF_3$ **3.11g**, R_F = CH=$CHCF_3$



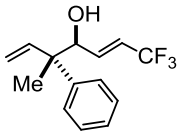
75% Yield, **3.12c**[b]
>20:1 dr



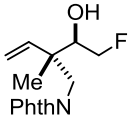
77% Yield, **3.12e**
>20:1 dr



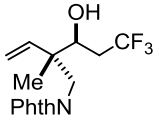
92% Yield, **3.12f**
>20:1 dr



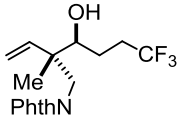
87% Yield, **3.12g**[d]
>20:1 dr



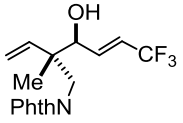
72% Yield, **3.12h**[b,c]
4:1 dr



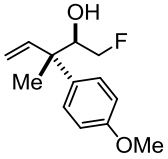
65% Yield, **3.12i**[c]
5:1 dr



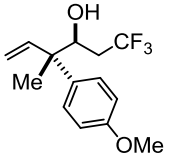
85% Yield, **3.12j**[c]
5:1 dr



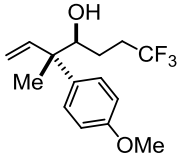
87% Yield, **3.12k**[c,d]
6:1 dr



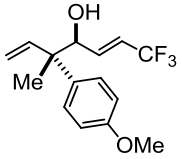
60% Yield, **3.12l**[b]
>20:1 dr



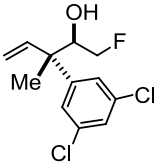
86% Yield, **3.12m**
>20:1 dr



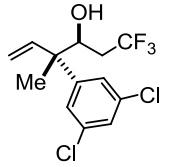
88% Yield, **3.12n**
>20:1 dr



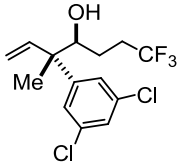
68% Yield, **3.12o**[d]
>20:1 dr



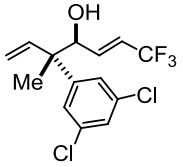
65% Yield, **3.12p**[b]
>20:1 dr



85% Yield, **3.12q**
>20:1 dr



89% Yield, **3.12r**
>20:1 dr



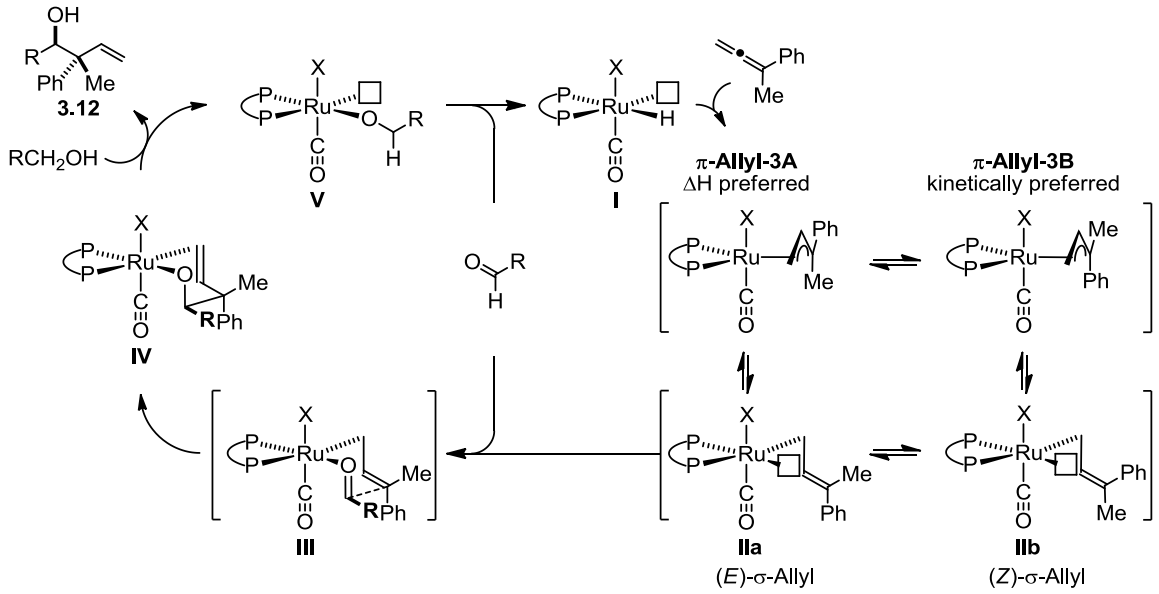
80% Yield, **3.12s**[e]
20:1 dr

[a]Cited yields are of material isolated by silica gel chromatography and represent the average of two runs. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b]72 h. [c]95 °C. [d]0.1 M THF. [e]0.05M THF.

3.3.4 POSTULATED REACTION MECHANISM

A hydrometallative pathway is proposed, as found in related ruthenium catalyzed allene-aldehyde couplings (Scheme 3.9).[16-17] The catalytic cycle opens with regioselective hydroruthenation of the allene to form a nucleophilic 1,1-disubstituted π-allylruthenium intermediate. The stoichiometric reaction of $HXRu(CO)(PR_3)_3$ (X = Cl, Br) with allenes or dienes to furnish π-allylruthenium complexes has been described.[24] Although hydrometallation from the allene π-face proximal to the smaller methyl group is anticipated to be kinetically preferred, rapid isomerization of **π-Allyl 3B** enables conversion to the more stable complex **π-Allyl 3A**.[16e,25] By way of the primary (*E*)-σ-allyl haptomer, regioselective carbonyl addition at the more substituted position of the allene may proceed *via* a closed six-membered chair-like transition state, **III**, to form the *anti*-diastereomer. Protonolysis of the ruthenium alkoxide, **IV**, by another unit of alcohol releases the fluorinated-adduct **3.12** and produces a ruthenium alkoxide. Subsequent β-hydride elimination affords a unit of aldehyde and regenerates the ruthenium hydride complex, **I**, to complete the catalytic cycle.

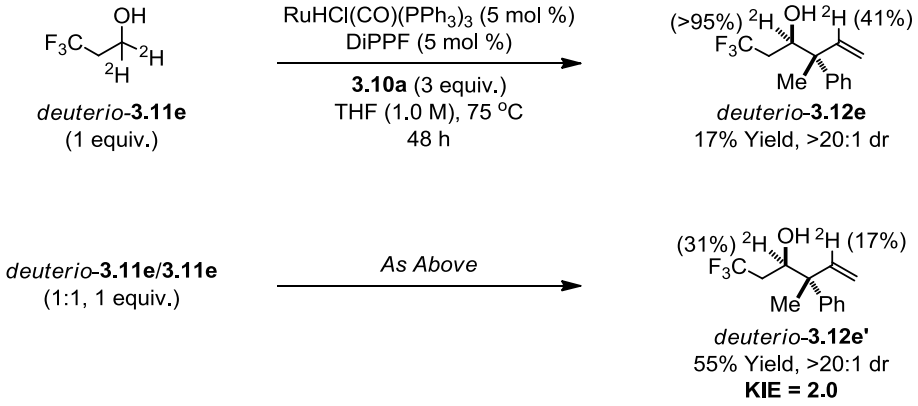
Scheme 3.9. Proposed mechanism for coupling of fluorinated alcohols to allenes.



A series of competition kinetics experiments were conducted to corroborate the anticipated effects of fluorination on the β-hydride elimination event.[27] Coupling of *deuterio*-3,3,3-trifluoropropanol **3.11e**, which is fully deuterated at the carbinol position (i.e. > 95% ^{2}H), with allene **3.10a** under standard reaction conditions furnished *deuterio*-**3.12e** in 17% yield (Scheme 3.10). Deuterium is completely retained at the carbinol position of *deuterio*-**3.12e**, suggesting that the secondary alcohol product is inert with respect to dehydrogenation. Incomplete deuterium incorporation at the interior vinylic position of *deuterio*-**3.12e** (41% ^{2}H) may be due to β-hydride elimination of the allylruthenium intermediate to form diene byproducts, which are detected in the crude reaction mixture and may account for the requirement of excess allene. Adventitious water also may diminish the extent of deuterium incorporation.[33] The relatively low isolated yield of *deuterio*-**3.12e** compared to non-isotopically labeled material **3.12e** suggests that the dehydrogenation events involving alcohols *deuterio*-**3.11e** or **3.11e** are

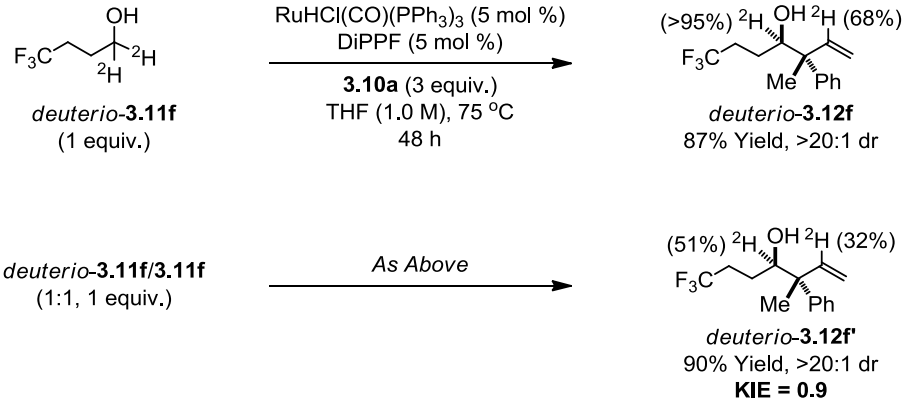
turn-over limiting. Indeed, when this transformation is conducted using equimolar quantities of **3.11e** and *deuterio*-**3.11e**, a primary kinetic isotope effect of 2.0 is observed in the formation of *deuterio*-**3.12e'**.

Scheme 3.10. Competition kinetics studies involving ruthenium catalyzed reductive coupling of allene **3.10a** to *deuterio*-3,3,3-trifluoropropanol **3.11e**.



In contrast, when an analogous set of experiments was performed on *deuterio*-4,4,4-trifluorobutanol **3.11f** (Scheme 3.11), for which the inductive CF_3 moiety is more distant from the carbinol position, a kinetic isotope effect of 0.9 is observed. These data suggest that for 4,4,4-trifluorobutanol **3.11f**, β-hydride elimination is not turn-over limiting and that an inverse secondary isotope effect, associated with turn-over limiting carbonyl addition, may be evident.

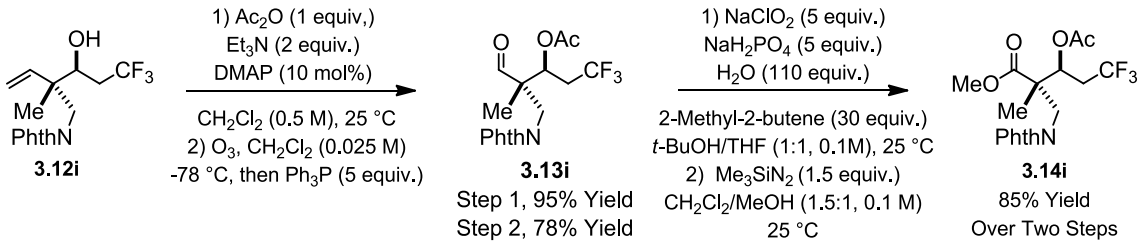
Scheme 3.11. Competition kinetics studies involving ruthenium catalyzed reductive coupling of allene **3.10a** to *deuterio*-4,4,4-trifluorobutanol **3.11f**.



3.3.5 PRODUCT DERIVATIZATION

To demonstrate the utility of these organofluorine products, neopentyl alcohol **3.12i** was converted to the corresponding acetate and subjected to ozonolysis. Aldehyde **3.13i** was formed in good yield and further elaborated to afford the β-amino ester **3.14i** (Scheme 3.12). Thus, novel CF_3-containing non-proteinogenic amino acids are readily accessible.

Scheme 3.12. Conversion of CF_3-bearing neopentyl alcohol **3.12i** to a β-amino ester.



3.4 Conclusion

In summary, regioselective couplings of 1,1-disubstituted allenes to paraformaldehyde and fluorinated alcohols were achieved *via* ruthenium catalyzed transfer hydrogenation. The hydrohydroxymethylation of 1-aryl-1-trifluoromethylallenes afforded CF_3-bearing neopentyl alcohols, which is one of a limited number of methods available for the generation of all-carbon quaternary centers incorporation a trifluoromethyl group. As a result of this investigation, a novel synthetic route to 1-aryl-1-trifluoromethylallenes, which may prove useful in other methodological endeavors, was also developed. The hydrohydroxyfluoroalkylation of 1,1-disubstituted allenes delivered homoallylic alcohols incorporating an all-carbon quaternary center and fluorine containing functional groups with good levels of diastereoselectivity. Hence, redox-triggered carbonyl addition allowed stable, abundant fluorinated alcohols to serve as synthetic equivalents to intractable fluorinated aldehydes. As corroborated by competition kinetics, the partial positive charge accumulating in the transition state for β-hydride elimination of the ruthenium alkoxide poses an increasingly significant energetic barrier for alcohols bearing increasingly inductive fluoroalkyl groups. This insight into the critical role of β-hydride elimination will guide the design of improved second-generation catalyst for the direct C-H functionalization of fluorinated alcohols. Collectively, these studies of ruthenium catalyzed C-C bond forming transfer hydrogenations represent new means of accessing diverse organofluorine compounds.

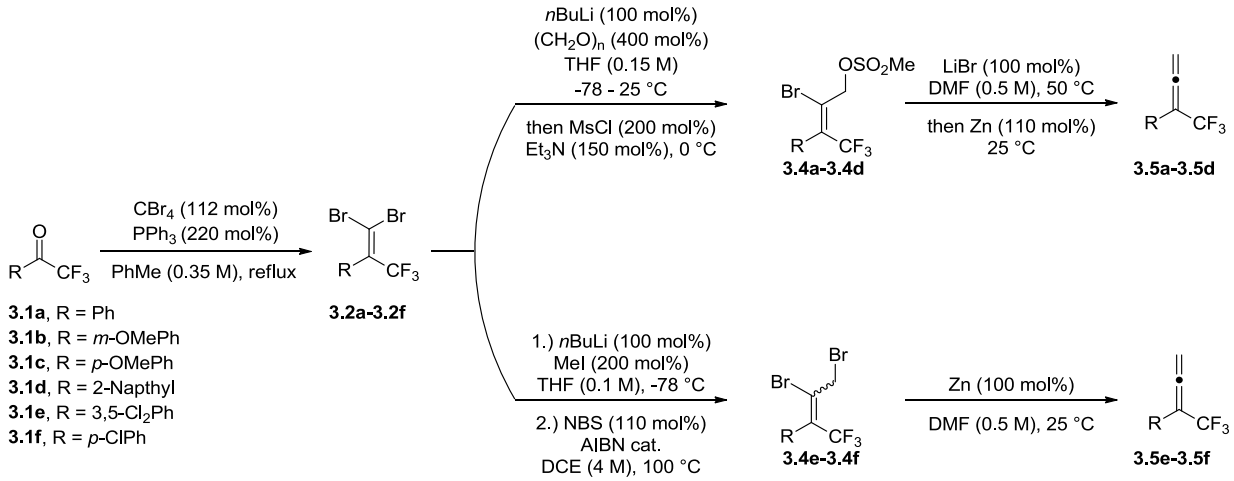
3.5 Experimental Section

3.5.1 Experimental Details for Section 3.2

General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringes. Reaction tubes and flasks were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Toluene (PhMe) and tetrahydrofuran (THF) were distilled from sodium and benzophenone. 1,2-dichloroethane (DCE) was distilled from CaH_2. $RuHCl(CO)(PPh_3)_3$was prepared according to literature procedure.[34] 2-propanol (99.8%, extra dry), methanesulfonyl chloride (MsCl) 99.5% and lithium bromide 99%+, anhydrous were obtained from Acros Organics. Paraformaldehyde was used as received from Aldrich Chemical Company, Inc. MsCl was distilled over phosphorous pentoxide (P_2O_5) prior to use. Triethylamine was purchased from Fischer Scientific and stored over. Carbon tetrabromide and *p*-toluenesulfonyl chloride were purchased and used as received from TCI America. Triphenylphosphine, 1,1-bis(diphenylphosphino)methane (DPPM), 1,1-bis(dicyclohexylphosphino)methane (DCyPM), 1,2-bis(dicyclohexylphosphino)ethane (DCyPE), N-Bromosuccinimide (NBS), and Zn dust, <10 μm, were purchased from Sigma-Aldrich. 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF), 1,1′-bis(di-*tert*-butylphosphino)ferrocene (DtBPF), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) were obtained from Strem Chemicals Inc. All ligands were used as received. NBS was recrystallized according to the method of McCoy.[35] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F_{254}) and products were visualized by UV, $KMnO_4$

and/or anisaldehyde stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[36] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-res olution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer.

Experimental Procedures and Spectral Data for the Preparation of Allenes 3.5a-3.5f



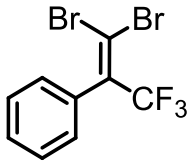
Representative procedure for the preparation of 2-Aryl-1,1-dibromo-3,3,3-trifluoropropenes 3.2a-3.2f

2-Aryl-1,1-dibromo-3,3,3-trifluoropropenes **3.2a-3.2f** were prepared in accordance with the literature procedure reported by Uno.[21c]

To a 500mL three-necked round bottom flask equipped with a magnetic stir bar and reflux condenser was added PPh_3 (14.4 g, 55 mmol, 220 mol%). The flask was sealed with rubber septa, purged with argon, and toluene (71 mL, 0.35 M) was added. The mixture was stirred until PPh_3 dissolved, at which point CBr_4 (9.3g, 28 mmol, 112 mol%) was quickly added under a flow of argon. After stirring for an additional 30 min, at

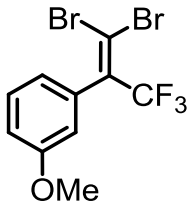
which point the mixture was bright yellow, the trifluoracetyl compound **3.1b** (5.0 g, 25 mmol, 100 mol%) was dropwise added via syringe over 15 min. The mixture was stirred for an additional 30 min and then refluxed overnight. The reaction mixture was allowed to cool to room temperature, at which point hexane (50 mL) was added to precipitate salts. The suspension was filtered through a pad of silica, washing with 5% EtOAc/hexane. Then the filtrate was quenched with water (100 mL). The organics were removed and the aqueous layer was extracted twice with toluene (2 × 100 mL). The combined organics were washed with water (100 mL), sat. $NaHCO_3$ (2 × 100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. Purification under the noted conditions furnished the title compound **3.2b**.

(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2a)



The reaction was conducted on a 150 mmol scale (*via* ketone **3.1a**). After aqueous work-up, the crude residue was purified by distillation (bp 38 °C/0.15 mmHg) (lit,[21c] 94-104 °C/11 mmHg) to furnish the title compound **3.2a** (40.0 g, 81%) as a colorless oil. Spectral data is consistent with the reported literature data.[21b,21c]

1-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)-3-methoxybenzene (3.2b)



The reaction was conducted on a 25 mmol scale (*via* ketone **3.1b**). After aqueous work-up, the crude residue was purified by distillation (bp 82 °C/0.15 mmHg) to furnish the title compound **3.2b** (7.2 g, 82%) as a colorless oil.

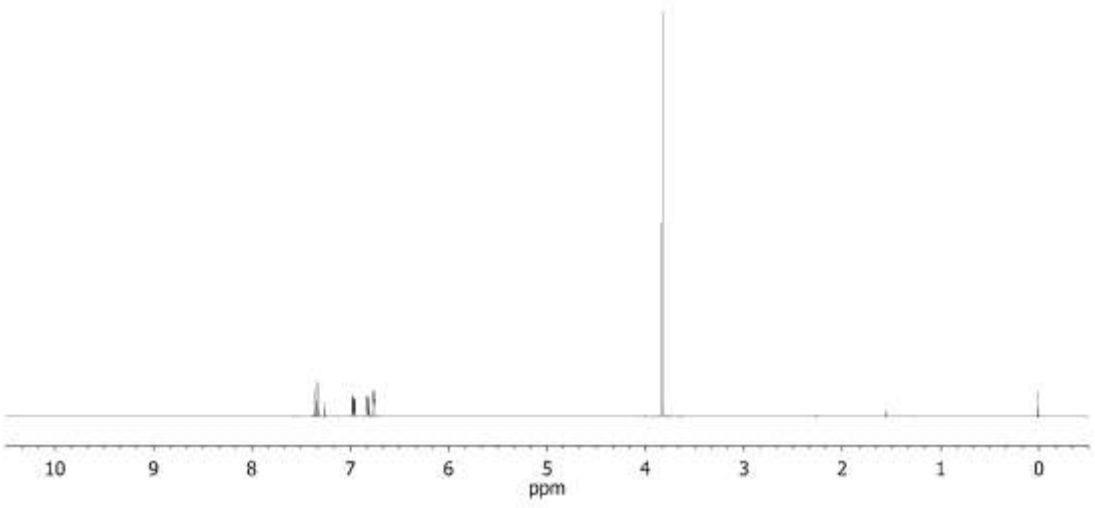
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.31 (m, 1H), 6.97 (ddd, J = 8.4, 2.6, 0.9 Hz, 1H), 6.85 – 6.80 (m, 1H), 6.78 – 6.74 (m, 1H), 3.83 (s, 3H).

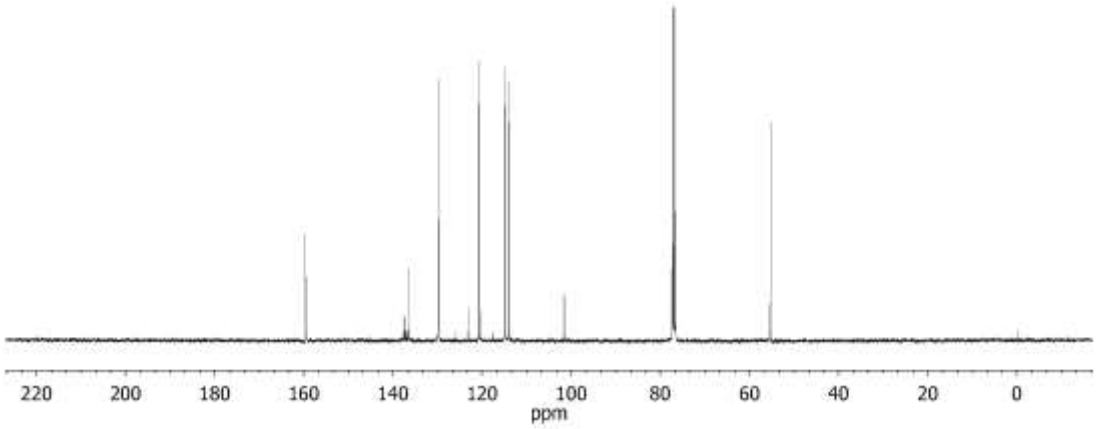
^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 137.4 (q, J = 32.7 Hz), 136.5, 129.9, 120.8, 121.8 (q, J = 276.1 Hz), 114.9, 114.1, 101.6 (q, J = 2.8 Hz), 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -58.6.

LRMS (EI): m/z 361 $[M+H]^+$

FTIR (neat): 2943, 2837, 1598, 1580, 1487, 1465, 1431, 1298, 1284, 1240, 1179, 1128, 1043, 995, 983, 875, 854, 802, 782, 747, 703, 676 cm^{-1}.

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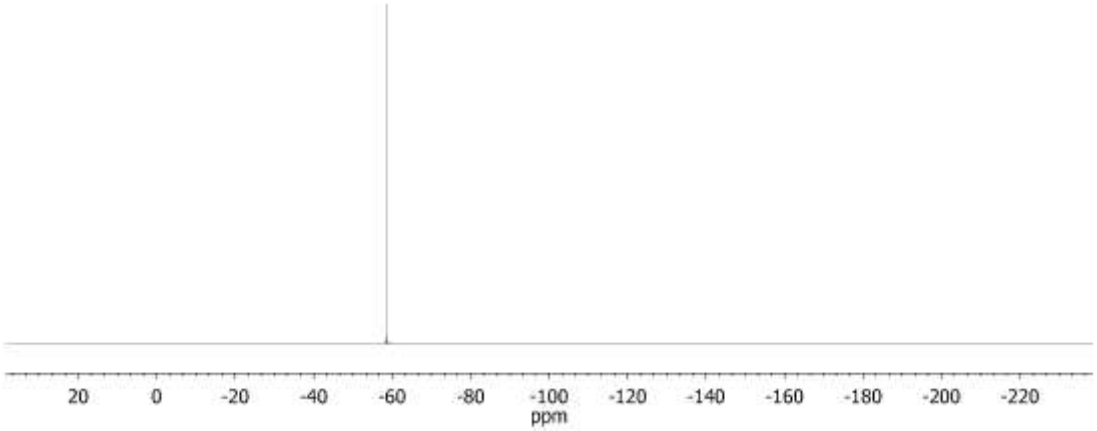
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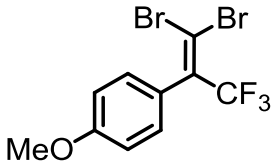
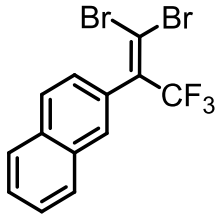
ppm

1-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)-4-methoxybenzene (3.2c)



The reaction was conducted on a 25 mmol scale (*via* ketone **3.1c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.2c** (8.1 g, 91%) as a colorless oil. Spectral data is consistent with the reported literature data.[21c]

2-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)naphthalene (3.2d)



The reaction was conducted on a 22 mmol scale (*via* ketone **3.1d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.2d** (7.0 g, 84%) as a colorless oil.

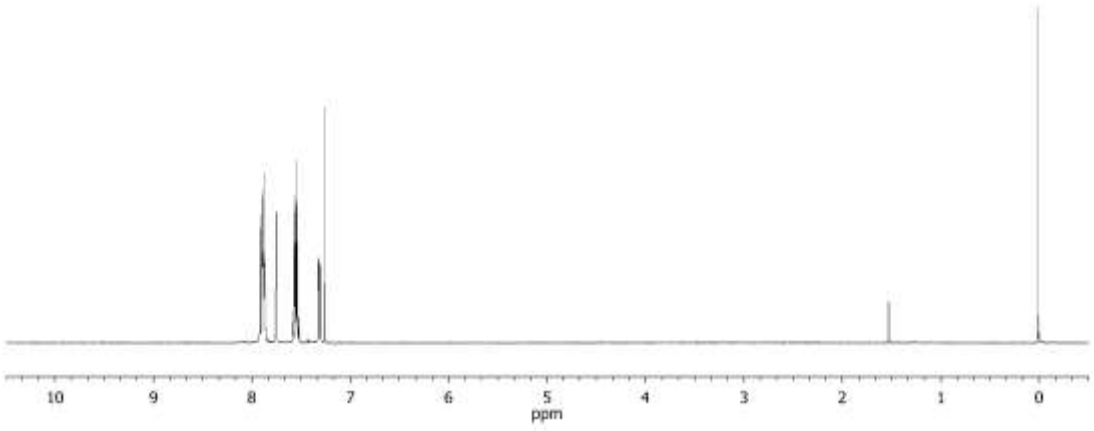
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.85 (m, 3H), 7.75 (d, J = 1.4 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.31 (dd, J = 8.5, 1.7 Hz, 1H).

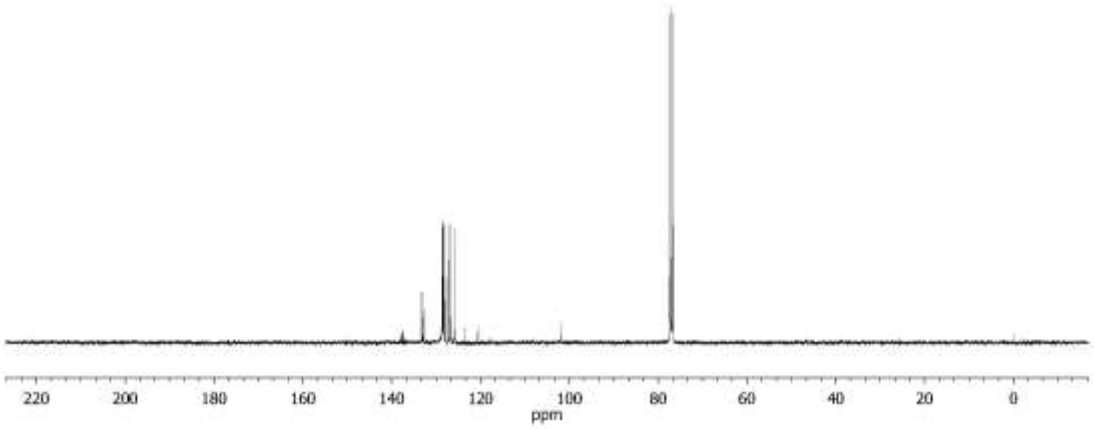
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6 (q, J = 32.6 Hz), 133.2, 132.9, 132.8, 128.6, 128.5, 128.3, 127.8, 127.2, 126.7, 125.6, 121.96 (q, J = 276.2 Hz), 101.9 (q, J = 3.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3.

LRMS (EI): m/z 381 $[M+H]^+$

FTIR (neat): 3059, 1599, 1581, 1505, 1289, 1269, 1243, 1204, 1180, 1166, 1124, 1017, 991, 962, 898, 866, 853, 816, 801, 769, 751, 736, 688 cm^{-1}.

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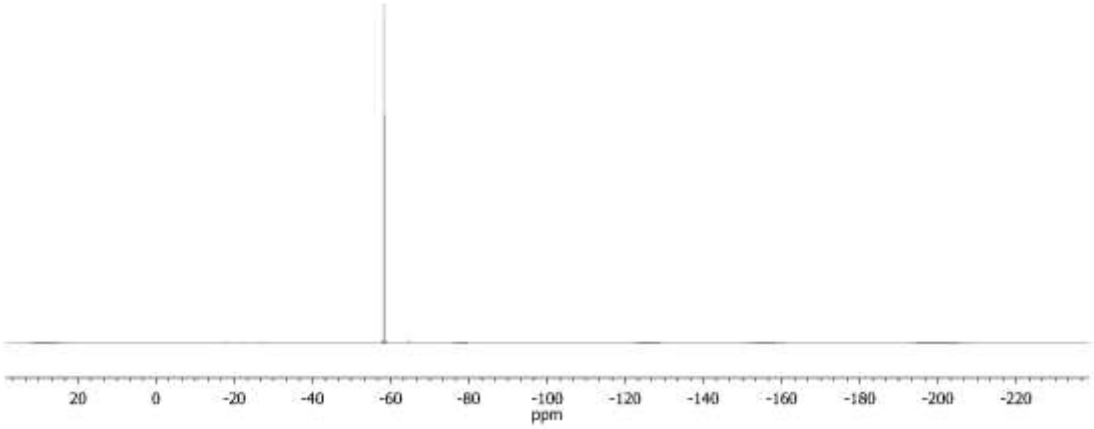
ppm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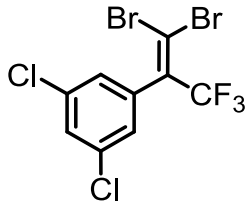
ppm

1,3-dichloro-5-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2e)



The reaction was conducted on a 25 mmol scale (*via* ketone **3.1e**). After aqueous work-up, the crude residue was purified by distillation (bp 84 °C/0.1 mmHg) to furnish the title compound **3.2e** (8.2 g, 82%) as a colorless oil.

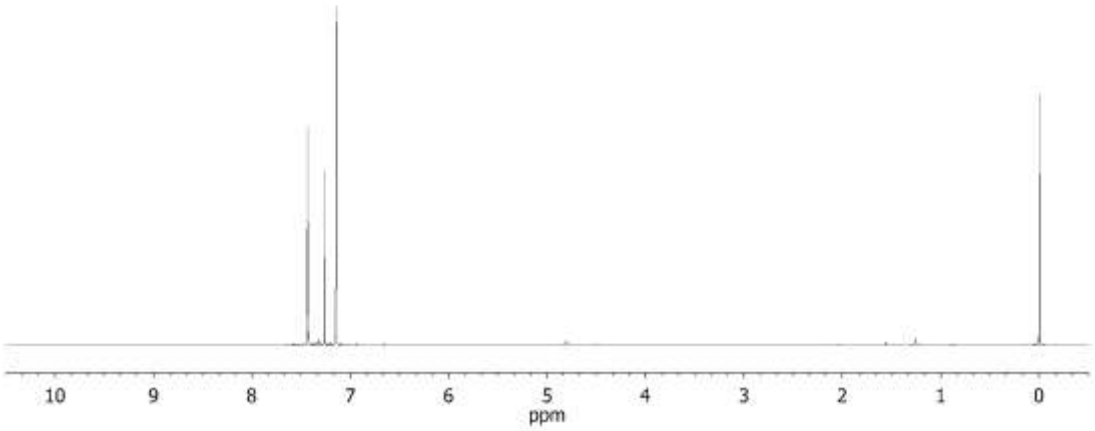
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, J = 1.9 Hz, 1H), 7.14 (d, J = 1.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 135.5, 135.2 (q, J = 33.4 Hz), 129.7, 127.2, 121.4 (q, J = 276.2 Hz), 103.6 (q, J = 2.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -58.4.

LRMS (CI): m/z 399 $[M]^+$

FTIR (neat): 1589, 1561, 1413, 1295, 1203, 1177, 1135, 1103, 1008, 867, 838, 803, 705, 690, 661 cm^{-1}.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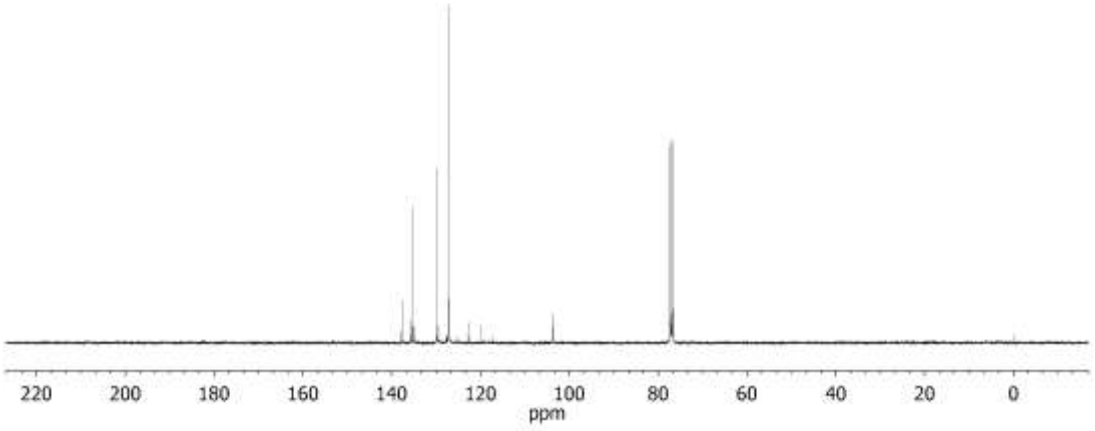
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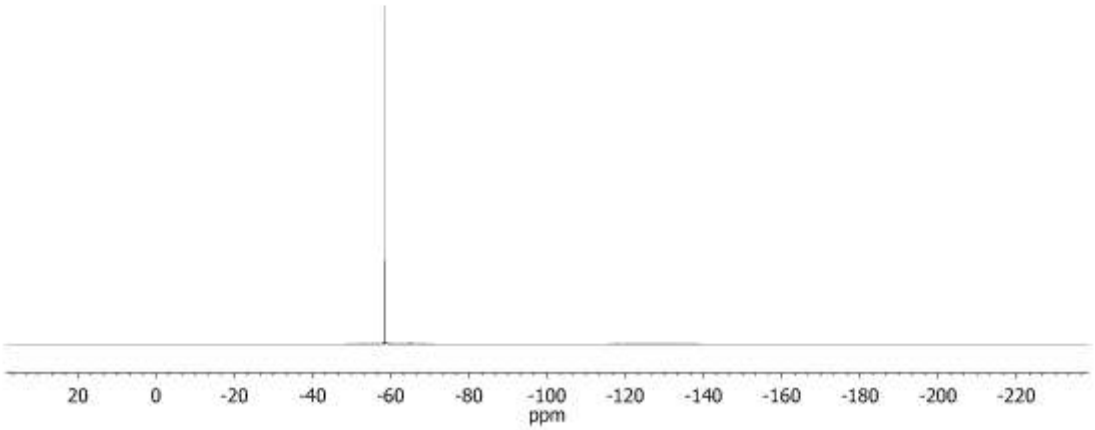
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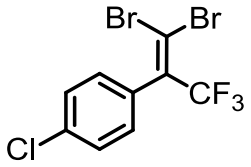
ppm

1-chloro-4-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2f)



The reaction was conducted on a 25 mmol scale (*via* ketone **3.1f**). After aqueous work-up, the crude residue was purified by distillation (bp 79 °C/ 0.15 mmHg) (lit,[21c] 123 °C/12 mmHg) to furnish the title compound **3.2f** (7.6 g, 84%) as a colorless oil. Spectral data is consistent with the reported literature data.[21c]

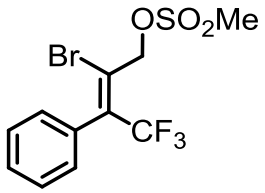
Representative procedure for the preparation of methanesulfonates 3.4a-3.4d:

Methanesulfonates **3.4a-3.4d** were prepared by modifying a literature procedure reported by Li and co-workers.[22]

To a 1 L three neck round bottom flask equipped with a magnetic stir bar was added **3.2a** (14.2 g, 43 mmol, 100 mol%). The flask was sealed with rubber septa, purged with argon, and THF (430 mL, 0.1 M) was added. Upon cooling to -78 ºC, Butyl lithium (2.5 M in hexanes, 17.0 mL, 43 mmol) was slowly added to the mixture and stirred for 30 min at this temperature. Paraformaldehyde (5.2 g, 172 mmol, 400 mol%) was added and let warm to room temperature while stirring overnight. Then the reaction mixture was cooled to 0 ºC. Triethylamine (9.0 mL, 65 mmol, 150 mol%) was added and stirred for 30 min, followed by dropwise addition of MsCl (6.7 mL, 86 mmol, 200 mol%) and stirring for 2 h at this temperature. The reaction mixture was quenched with 1 M HCl (200 mL) and

extracted with Et_2O (3 × 150 mL). The organic phase was washed with water (150 mL), brine (150 mL), and dried (Na_2SO_4).The crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compounds **3.4a**.

(*E*)-2-bromo-4,4,4-trifluoro-3-phenylbut-2-en-1-yl methanesulfonate (3.4a)



The reaction was conducted on a 43 mmol scale (*via* **3.2a**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **3.4a** (7.7 g, 49%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.42 (m, 3H), 7.25 – 7.19 (m, 2H), 5.27 (q, J = 1.0 Hz, 2H), 3.16 (s, 3H).

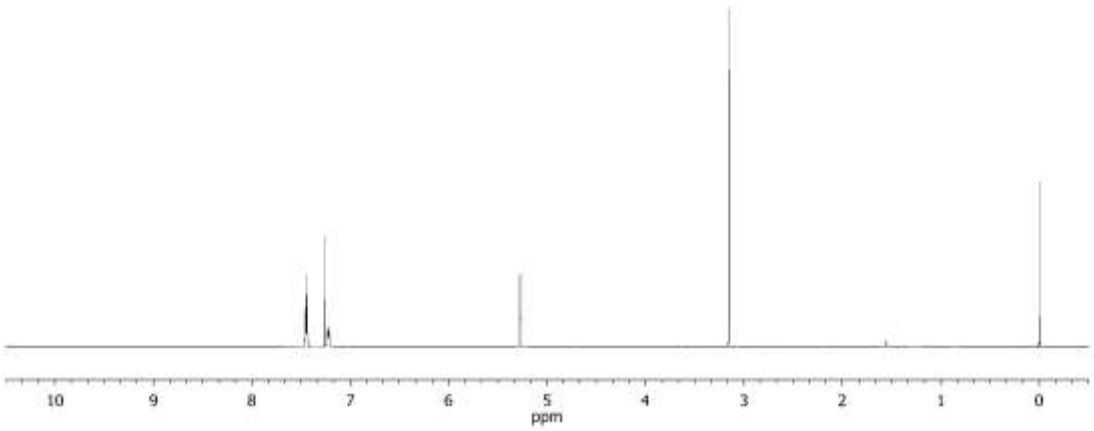
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (q, J = 31.8 Hz), 134.6, 130.1 (q, J = 2.8 Hz), 129.4, 128.6 (d, J = 22.2 Hz), 121.8 (q, J = 277.1 Hz), 69.0 (q, J = 3.5 Hz), 38.2.

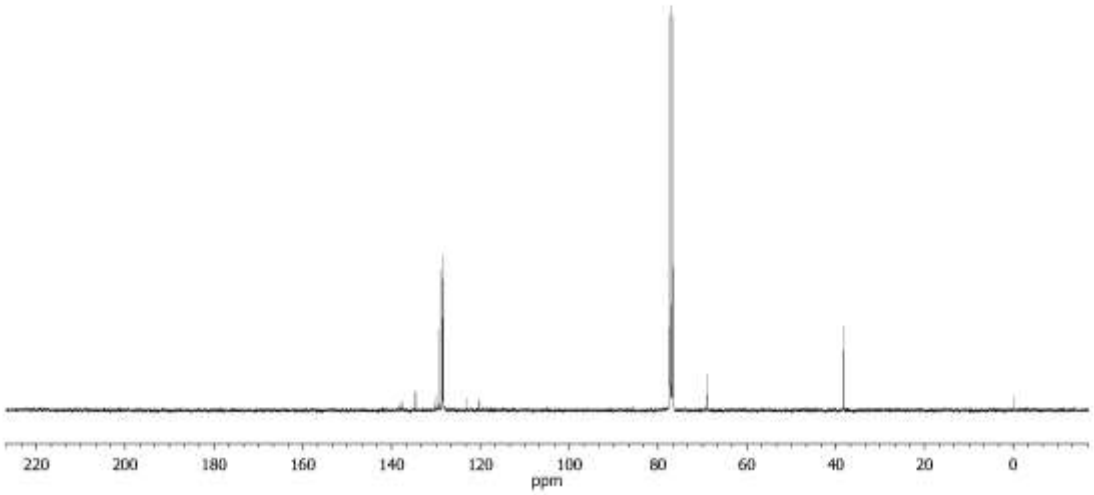
^{19}F NMR (376 MHz, $CDCl_3$): δ -55.7.

LRMS (CI): m/z 360 $[M]^+$

FTIR (neat): 3028, 1643, 1381, 1349, 1332, 1297, 1261, 1202, 1171, 1117, 1032, 1016, 999, 988, 978, 957, 928, 912, 834, 783, 761, 748, 697, 658 cm^{-1}.

mp (air): 81-83 °C

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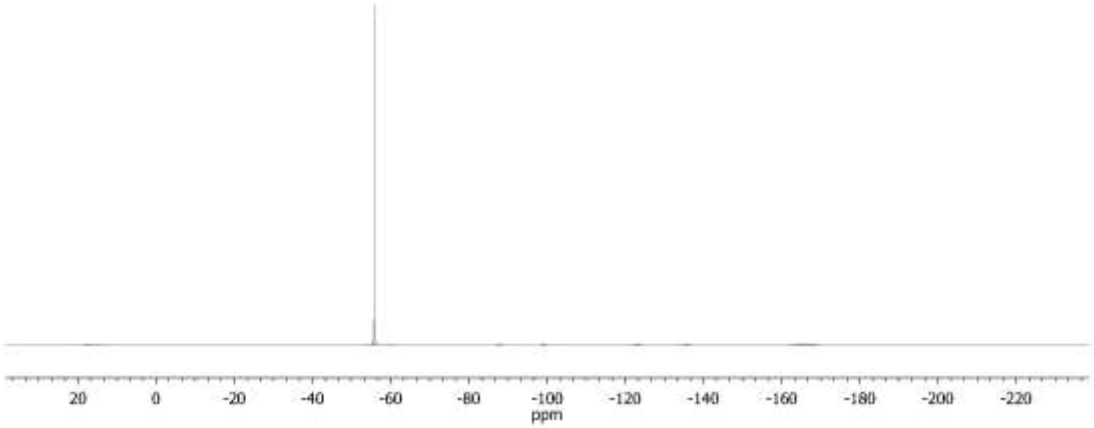
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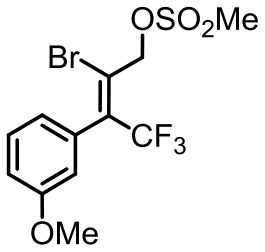
(*E*)-2-bromo-4,4,4-trifluoro-3-(3-methoxyphenyl)but-2-en-1-yl methanesulfonate (3.4b)



The reaction was conducted on a 5.5 mmol scale (*via* **3.2b**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **3.4b** (787 mg, 37%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 1H), 6.97 (dddd, J = 8.4, 3.6, 2.8, 0.8 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.75-6.74 (m, 1H), 5.27-5.26 (m, 2H), 3.83 (s, 3H), 3.15 (s, 3H).

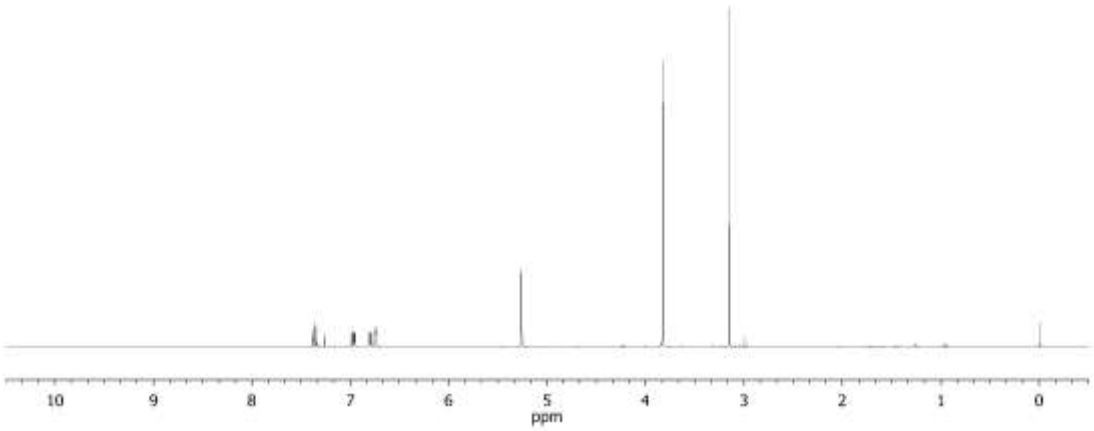
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 137.7 (q, J = 32.0 Hz), 135.7, 130.0, 129.8, 121.7 (q, J = 275.3 Hz), 120.6, 114.9, 114.1, 69.0 (q, J = 3.0 Hz), 55.4, 38.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -55.7.

LRMS (EI): m/z 295 $[M\text{-}CH_3O_3S]^+$

FTIR (neat): 1599, 1580, 1489, 1466, 1431, 1360, 1302, 1243, 1172, 1125, 1046, 951, 818, 737, 705 cm^{-1}.

mp (air): 73-75 °C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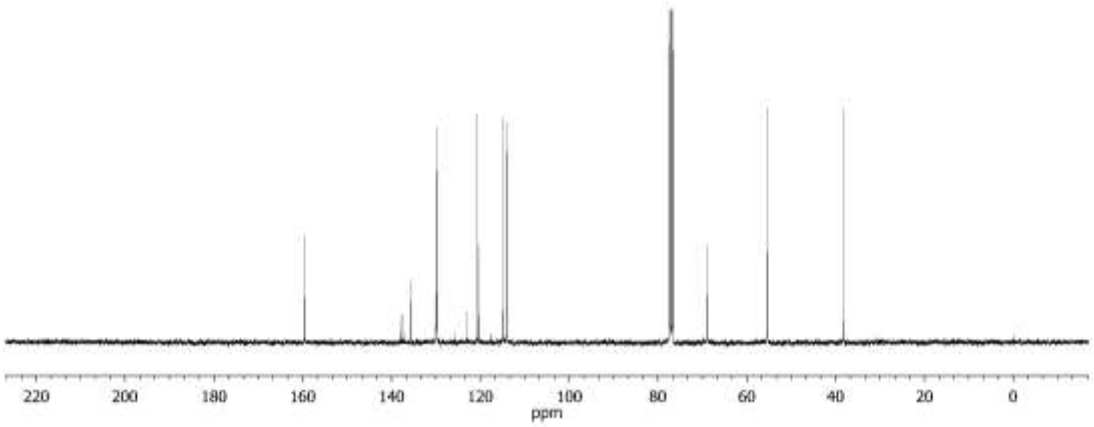
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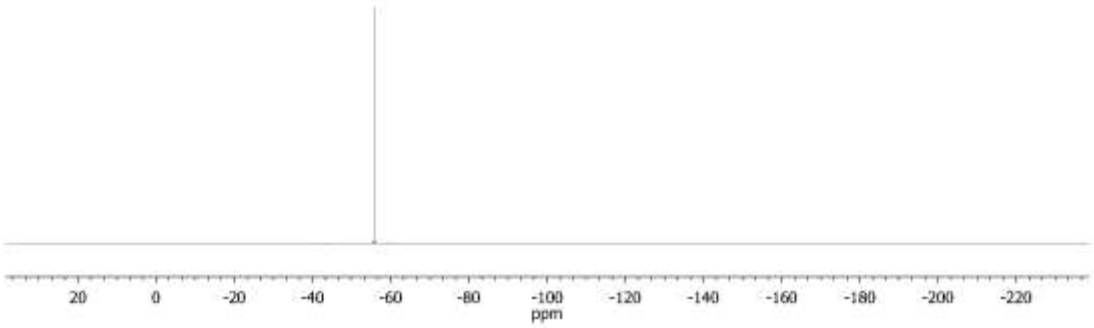
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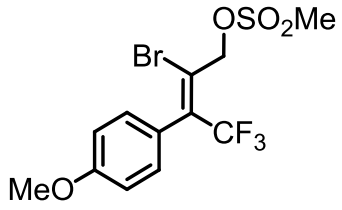
(*E*)-2-bromo-4,4,4-trifluoro-3-(4-methoxyphenyl)but-2-en-1-yl methanesulfonate (3.4c)



The reaction was conducted on a 16 mmol scale (*via* **3.2c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **3.4c** (3.1 g, 48%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.14 (m, 2H), 6.97-6.94 (m, 2H), 5.26 (q, J = 0.8 Hz, 2H), 3.84 (s, 3H), 3.15 (s, 3H).

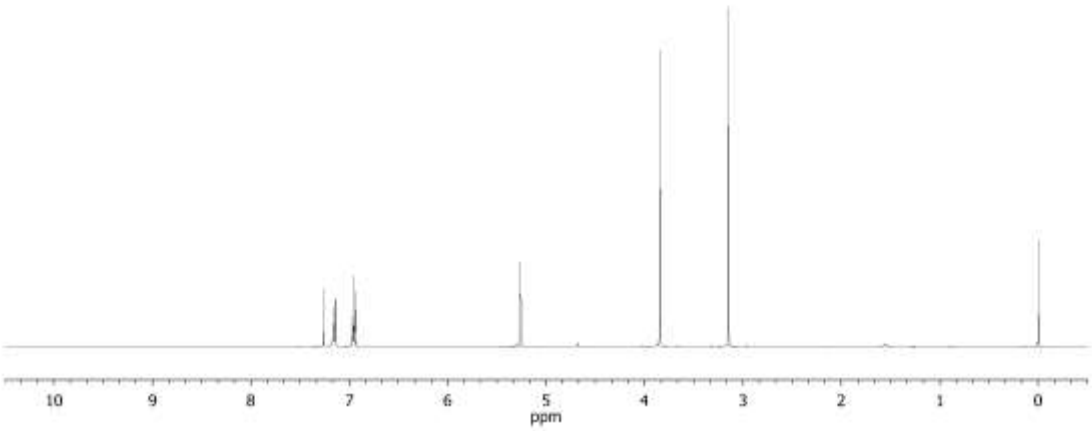
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 137.7 (q, J = 31.1 Hz), 130.2, 130.0, 126.8, 121.9 (q, J = 275.5 Hz), 114.0, 69.1, 55.3, 38.2.

^{19}F NMR (400 MHz, CDCl3): δ -55.8

LRMS (EI) m/z 295 $[M\text{-}CH_3O_3S]^+$

FTIR (neat): 1637, 1608, 1512, 1458, 1353, 1302, 1250, 1208, 1166, 1107, 1026, 984, 961, 921, 850, 834, 769, 664 cm^{-1}.

mp (air): 119-120 °C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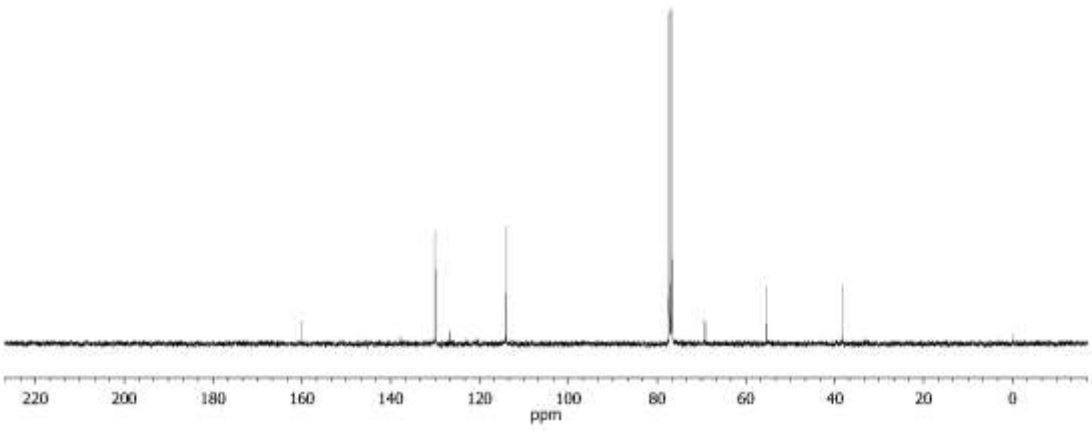
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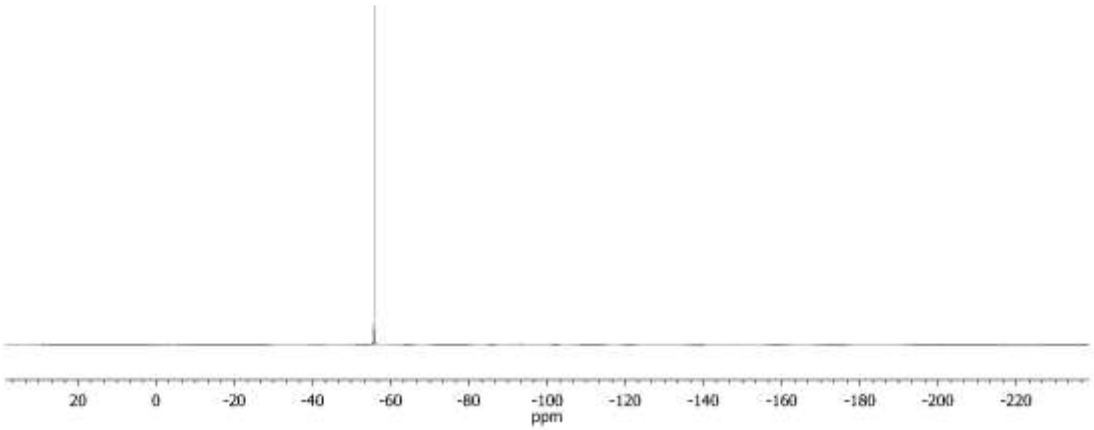
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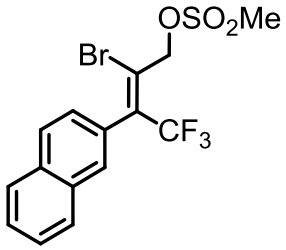
(*E*)-2-bromo-4,4,4-trifluoro-3-(naphthalen-2-yl)but-2-en-1-yl methanesulfonate (3.4d)



The reaction was conducted on a 2.6 mmol scale (*via* **3.2d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound **3.4d** (404 mg, 38%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.90-7.86 (m, 2H), 7.74 (s, 1H), 7.56 (dddd, *J* = 12.0, 9.2, 6.8, 2.0 Hz, 2H), 7.30 (dd, *J* = 2.0, 8.6 Hz, 1H) 5.33 (s, 2H), 3.17 (s, 3H).

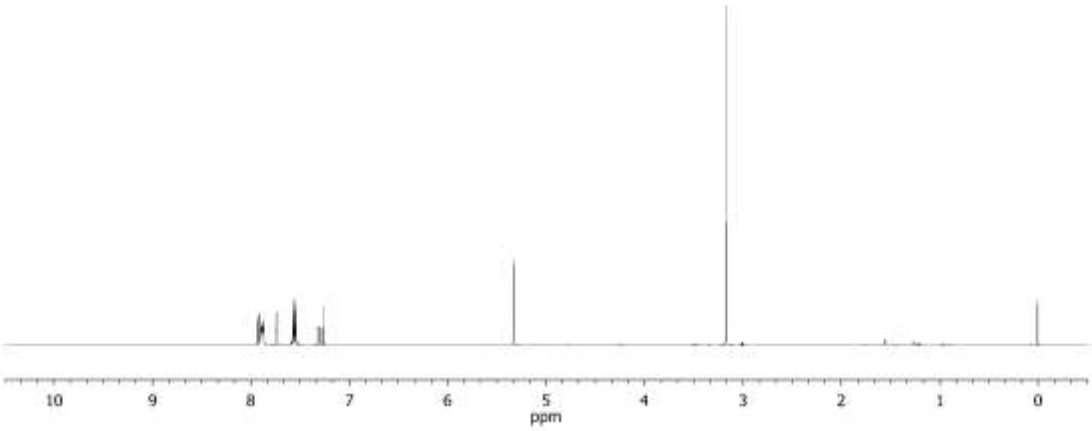
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (q, *J* = 32.0 Hz), 133.3, 132.9, 131.9, 130.4, 128.6, 128.3, 127.8, 127.2, 126.8, 125.5, 121.9 (q, *J* = 276.1 Hz), 69.0 (q, *J* = 3.7 Hz), 38.3.

^{19}F NMR(400 MHz, CDCl3): δ -55.5

LRMS (CI): m/z 315 $[M\text{-}CH_3O_3S]^+$

FTIR (neat): 2360, 1635, 1361, 1295, 1246, 1169, 1129, 954, 818, 750, 685 cm^{-1}.

mp (air): 106-109 °C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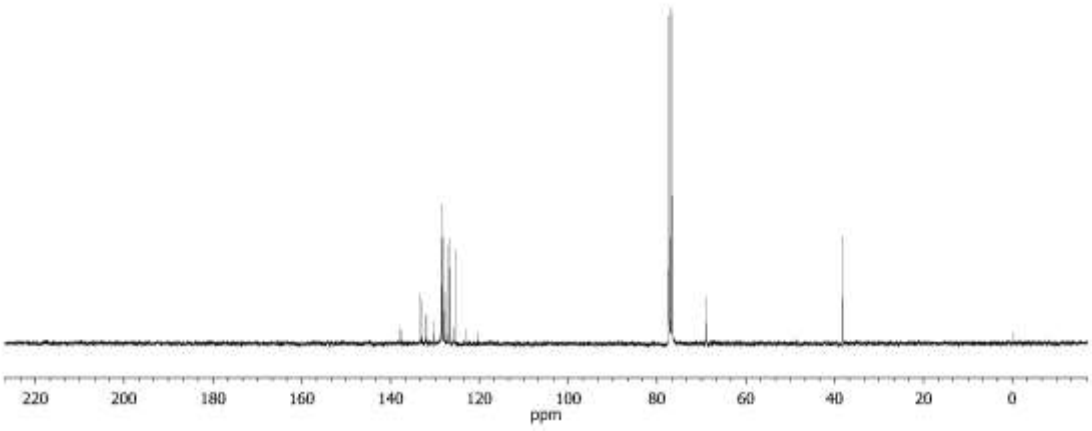
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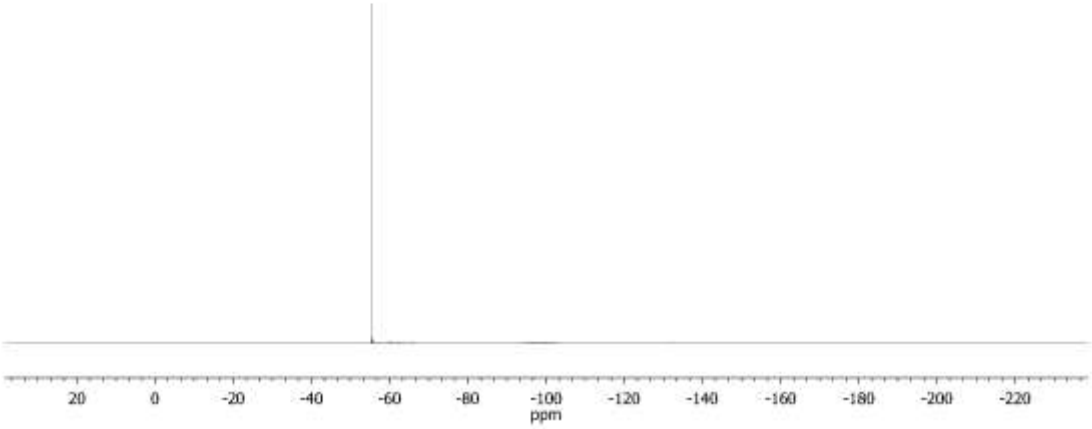


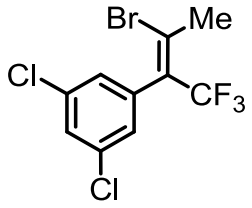
Representative procedure for the preparation of 1,1,1-trifluorobut-2-enes 3.3e,f:

1,1,1-trifluorobut-2-enes **3.3e**,**f** were prepared by modifying a literature procedure reported by Li and co-workers.[22]

To a 250 mL round bottom flask equipped with a magnetic stir bar was added **3.2e** (3.0 g, 7.5 mmol, 100 mol%). The flask was sealed with a rubber septum, purged with argon, and THF (75 mL, 0.1 M) was added. Upon cooling to -78 ºC, Butyl lithium (2.5 M in hexanes, 3.0 mL, 7.5 mmol) was slowly added to the mixture and stirred for 30 min at this temperature. Methyl iodide (0.9 mL, 15 mmol, 200 mol%) was added and stirring continued at -78 ºC for 2 hours. The reaction mixture was quenched with distilled water

(50 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed brine (100 mL), and dried (Na_2SO_4).The crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.3e**.

(*E*)-1-(3-bromo-1,1,1-trifluorobut-2-en-2-yl)-3,5-dichlorobenzene (3.3e)



The reaction was conducted on a 7.5 mmol scale (*via* **3.2e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.3e** (1.8 g, 73%) as a colorless oil.

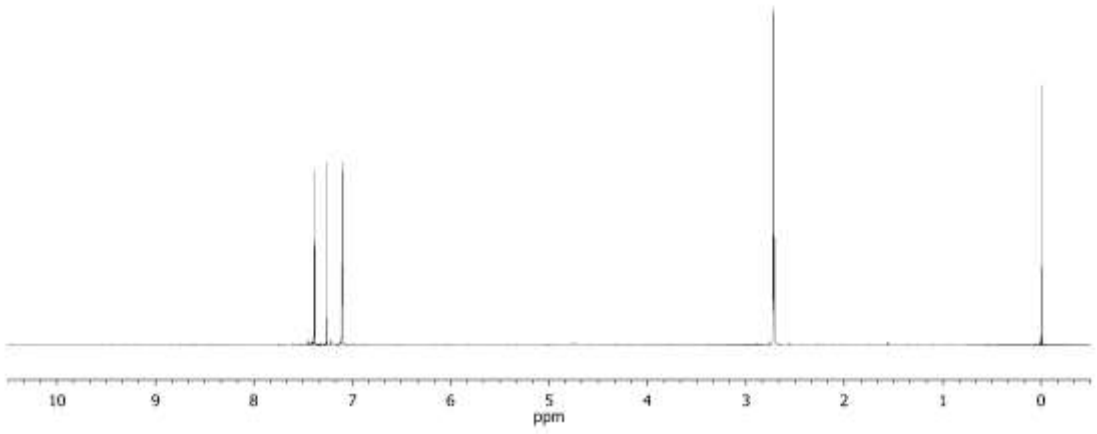
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 1.8 Hz, 2H), 2.72 (q, *J* = 2.2 Hz, 3H).

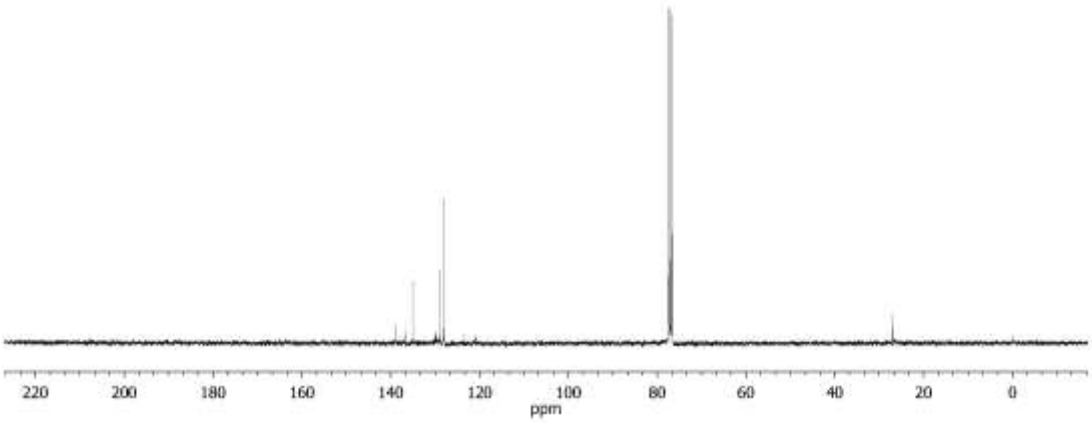
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 136.8, 135.0, 128.9, 127.9, 122.1 (q, *J* = 276.1 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ-56.1.

LRMS (CI): m/z 335 $[M+H]^+$

FTIR (neat): 1644, 1588, 1562, 1434, 1413, 1385, 1298, 1256, 1219, 1176, 1124, 1103, 1025, 999, 980, 862, 805, 762, 711, 697, 656 cm^{-1}.

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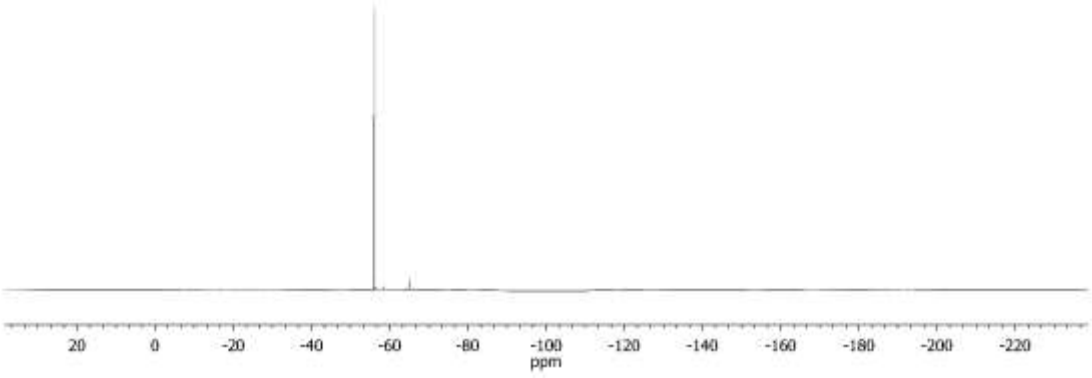
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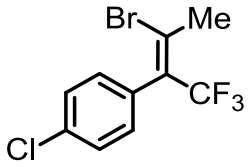
(*E*)-1-(3-bromo-1,1,1-trifluorobut-2-en-2-yl)-4-chlorobenzene (3.3f)



The reaction was conducted on a 7.5 mmol scale (*via* **3.2f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.3f** (1.8 g, 81%) as a colorless oil.

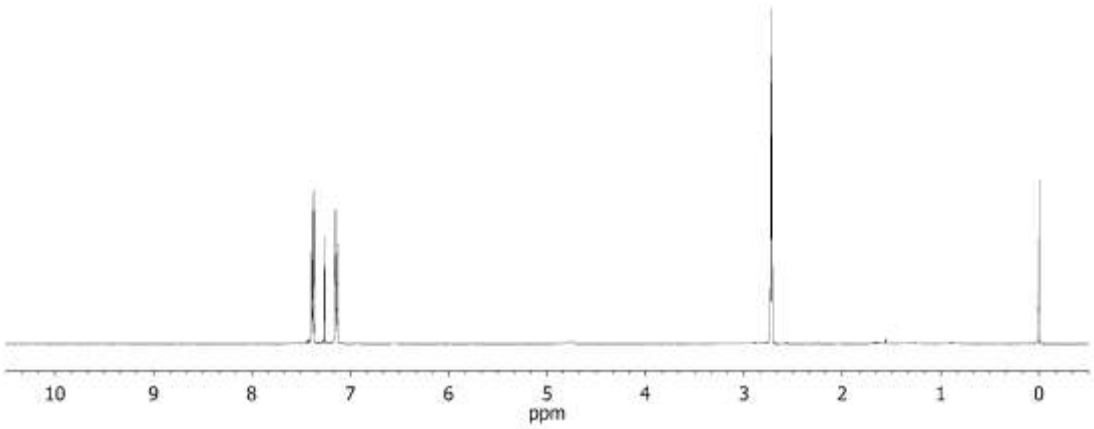
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 2H), 7.17 – 7.10 (m, 2H), 2.82 – 2.55 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.7, 130.7, 128.7, 122.4 (q, J = 276.1 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -56.2.

LRMS (CI): m/z 301 $[M+H]^+$

FTIR (neat): 3091, 2970, 1738, 1604, 1507, 1366, 1317, 1296, 1220, 1158, 1095, 1037, 1014, 991, 899, 838, 818, 735, 663 cm^{-1}.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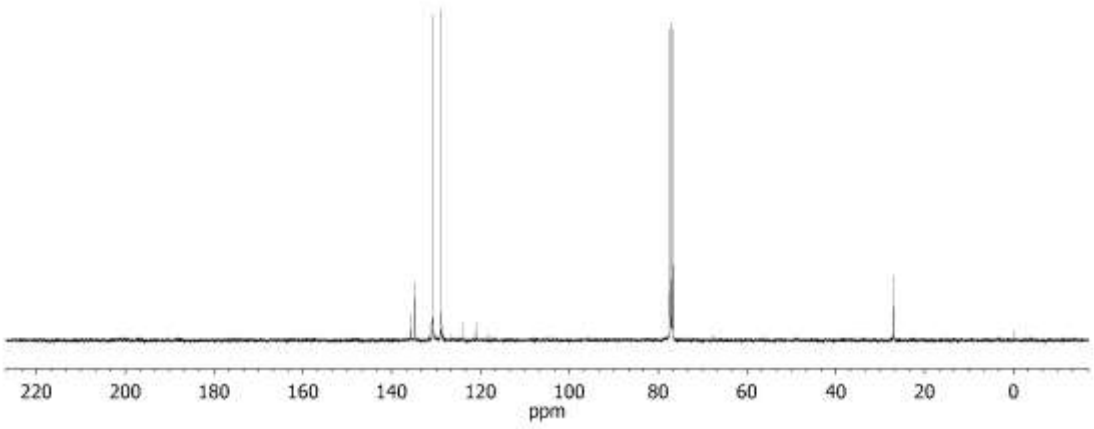
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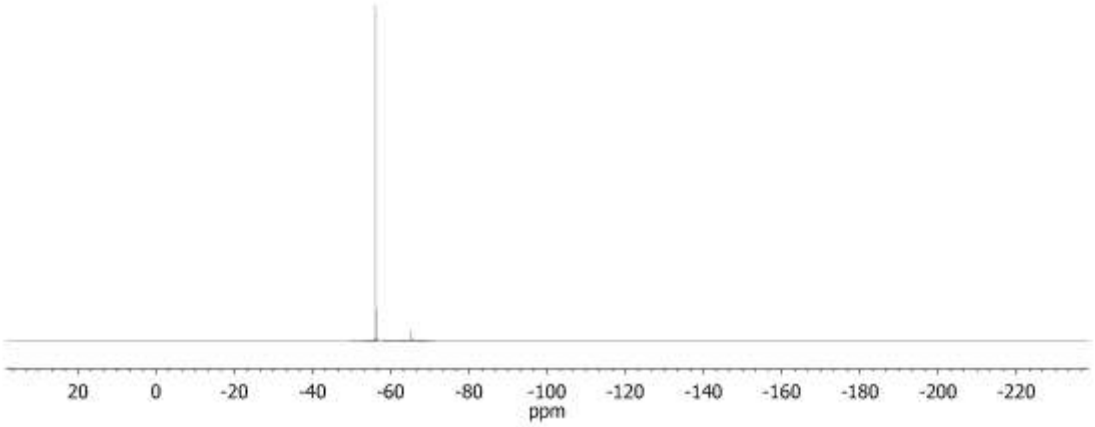
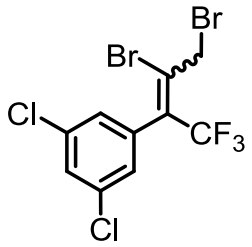


Representative procedure for the preparation of 3,4-dibromo-1,1,1-trifluorobut-2-enes 3.4e,f:

To an oven-dried pressure tube equipped with magnetic stir bar was added **3.3e** (1.0 g, 3 mmol, 100 mol%), NBS (590 mg, 3.3 mmol, 110 mol%), and AIBN cat. The flask was sealed with a rubber septum, purged with argon, and DCE (0.75 mL, 4.0 M) was added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to 100 ºC for 24 hours. The reaction mixture was allowed to cool to room temperature, at which point 10% $Na_2S_2O_3$ (3 mL) was added and stirred for 30 min. The mixture was diluted with distilled water (15 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was washed with distilled water (15 mL), brine (15 mL), and dried (Na_2SO_4). The

crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4e**.

1,3-dichloro-5-(3,4-dibromo-1,1,1-trifluorobut-2-en-2-yl)benzene (3.4e)



The reaction was conducted on a 3 mmol scale (*via* **3.3e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4e** (690mg, 56%, *E*/*Z* : 54/46) as a colorless oil.

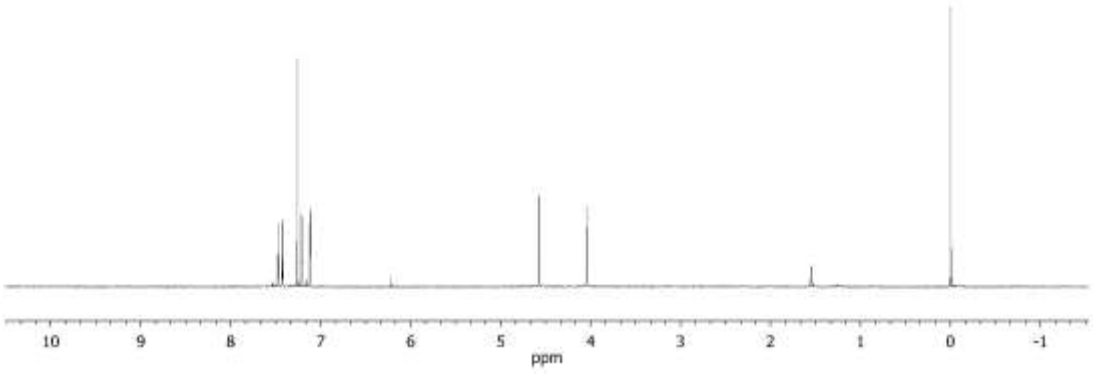
^{1}H NMR (400 MHz, $CDCl_3$): (*E*-isomer) δ 7.43 (t, *J* = 1.9 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 2H), 4.58 (q, *J* = 1.0 Hz, 2H). (*Z*-isomer) δ 7.48 (t, *J* = 1.9 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 2H), 4.05 (q, *J* = 0.9 Hz, 2H)

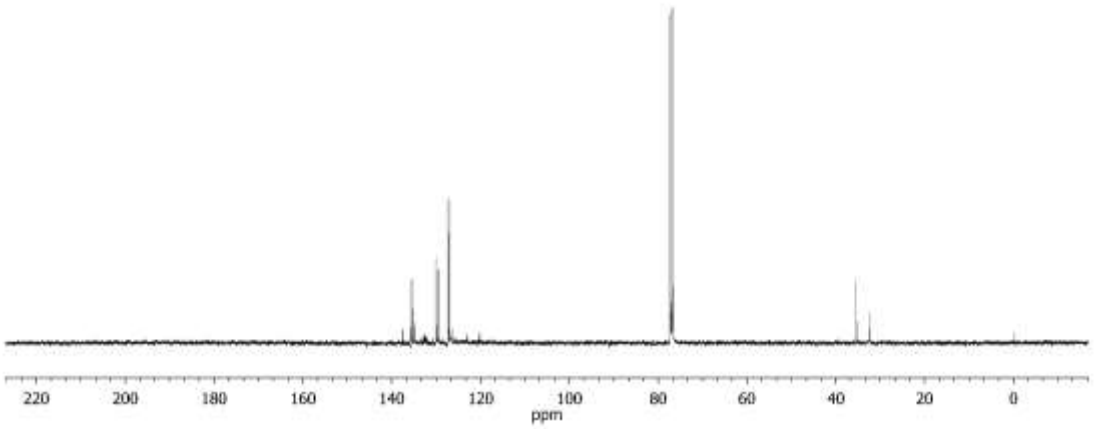
^{13}C NMR (100 MHz, $CDCl_3$): (*E*/*Z*-isomers) δ 137.5, 135.8, 135.6, 135.3, 134.9, 130.0, 129.6, 127.3, 126.9, 121.6 (q, *J* = 277.0 Hz), 121.6 (q, *J* = 276.4 Hz), 35.3, 32.3 (q, *J* = 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): (*E*-isomer) δ -56.6. (*Z*-isomer) δ -59.5.

LRMS (CI): m/z 413 $[M+H]^+$

FTIR (neat): 1621, 1586, 1561, 1429, 1412, 1389, 1300, 1219, 1183, 1219, 1129, 999, 979, 916, 899, 863, 836, 807, 721, 708, 696, 684, 656 cm^{-1}.

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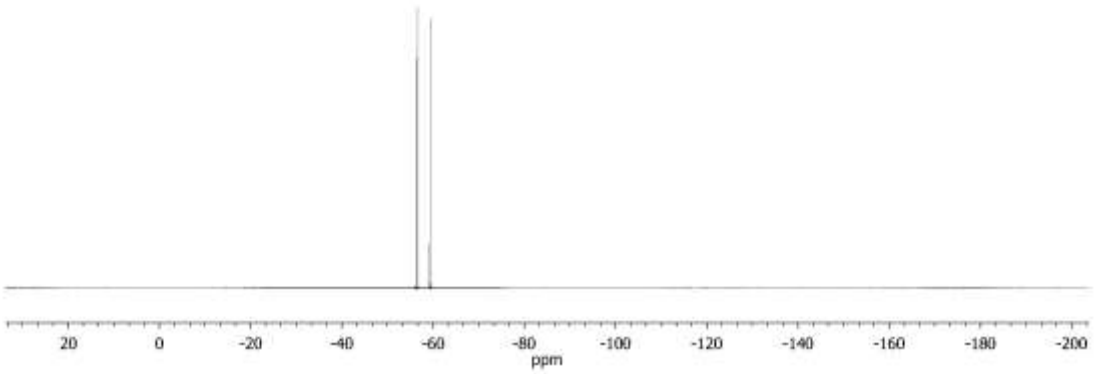
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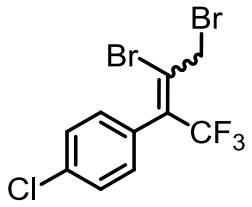
1-chloro-4-(3,4-dibromo-1,1,1-trifluorobut-2-en-2-yl)benzene (3.4f)



The reaction was conducted on a 3 mmol scale (*via* **3.3f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4f** (469 mg, 43%, *E*/*Z* : 39/61) as a colorless oil.

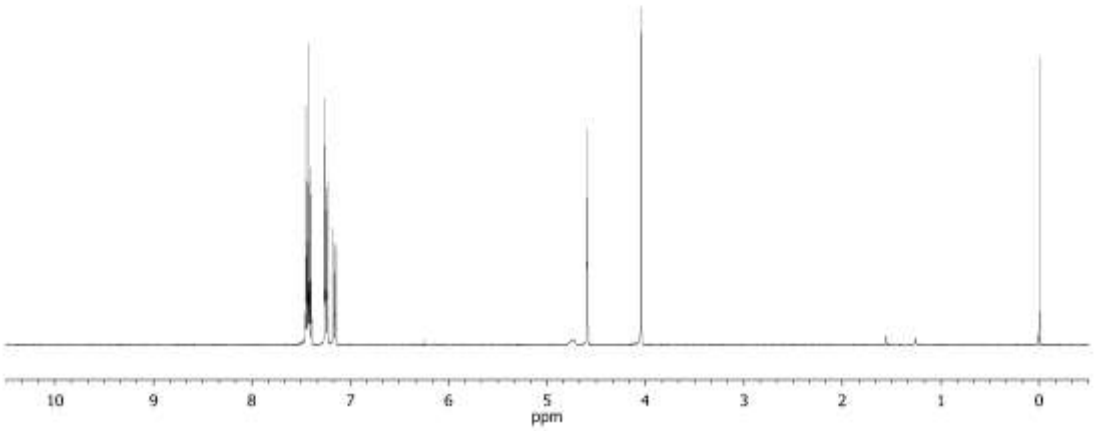
^{1}H NMR (400 MHz, $CDCl_3$): (*E*-isomer) δ 7.42 – 7.38 (m, 2H), 7.18 – 7.13 (m, 2H), 4.59 (q, *J* = 1.9 Hz, 2H). (*Z*-isomer) δ 7.47 – 7.42 (m, 2H), 7.26 – 7.21 (m, 2H), 4.04 (q, *J* = 1.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): (*E*/*Z*-isomers) δ 135.9, 135.4, 134.7, 134.5, 134.2, 133.5, 130.8, 130.2, 129.9, 129.3, 128.9, 128.8, 121.9 (q, *J* = 277.1 Hz), 121.8 (d, *J* = 276.4 Hz), 35.8, 32.7 (q, *J* = 3.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): (*E*-isomer) δ -56.7. (*Z*-isomer) δ -59.7.

LRMS (CI): m/z 381 $[M+H]^+$

FTIR (neat): 1623, 1593, 1490, 1427, 1398, 1309, 1263, 1217, 1178, 1126, 1091, 1017, 954, 931, 892, 827, 771, 733, 725, 655 cm^{-1}.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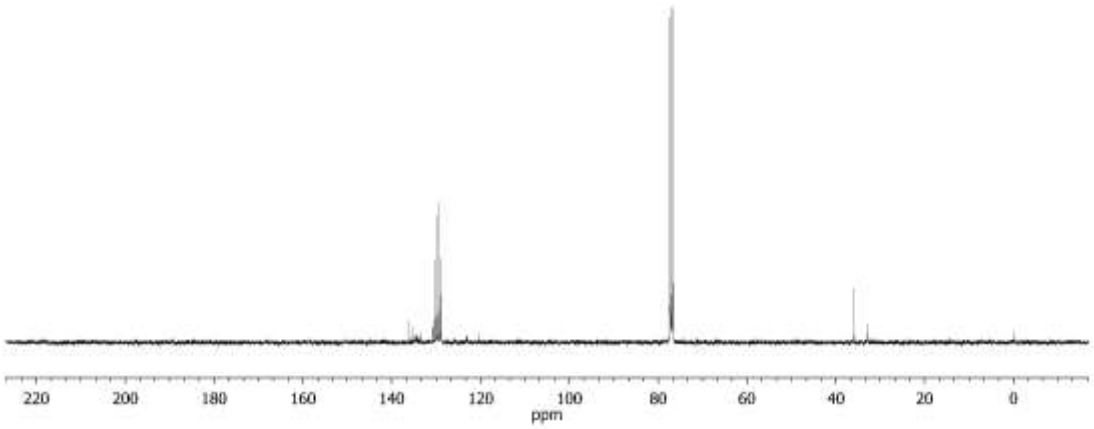
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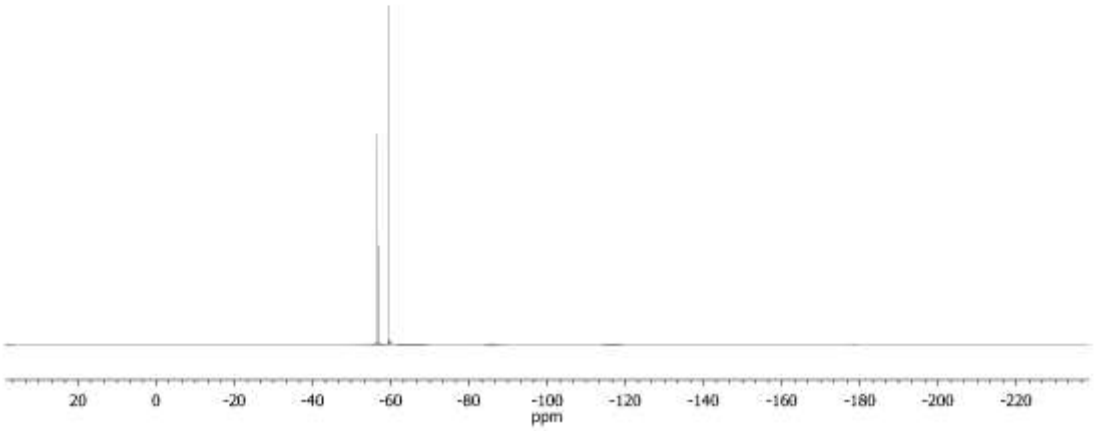


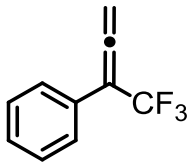
Representative procedure for the preparation of CF_3-allenes 3.5a-3.5d:

Trifluoromethyl-containing allenes **3.5a-3.5d** were prepared by modifying an existing literature procedure reported by Knochel.[37]

To a 250 mL three-necked round bottom flask equipped with a magnetic stir bar and reflux condenser was added methansulfonate **3.4a** (7.7 g, 21 mmol, 100 mol%) and lithium bromide (1.9 g, 21 mmol, 100 mol%). The flask was sealed with rubber septa, purged with argon, and DMF (43 mL, 0.5 M) was added, and the mixture was heated to 50 ºC for 5 hours. Upon cooling to room temperature, Zn dust (1.5 g, 23.5 mmol, 110 mol%) was added and stirred for 24 hours. The reaction mixture was quenched with 1 M

HCl (50 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to furnish the title compound **3.5a** as a colorless oil.

(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5a)



The reaction was conducted on a 21 mmol scale (*via* **3.4a**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to furnish the title compound **3.5a** (3.1 g, 78%) as a colorless oil.

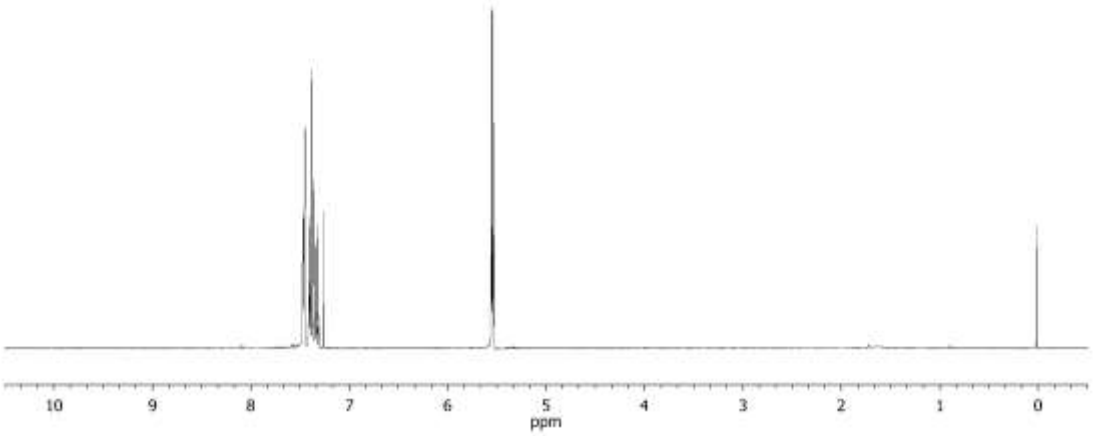
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.29 (m, 5H), 5.54 (q, J = 3.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5 (q, J = 4.1 Hz), 128.7, 128.2, 123.3 (q, J = 273.8 Hz), 101.8 (q, J = 34.4 Hz), 83.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.47.

LRMS (CI): m/z 185 $[M+H]^+$

FTIR (neat): 3066.5, 1974, 1720, 1600, 1498, 1454, 1304, 1270, 1170, 1034, 1001, 937, 914, 866, 764, 739, 693, 693, 660 cm^{-1}.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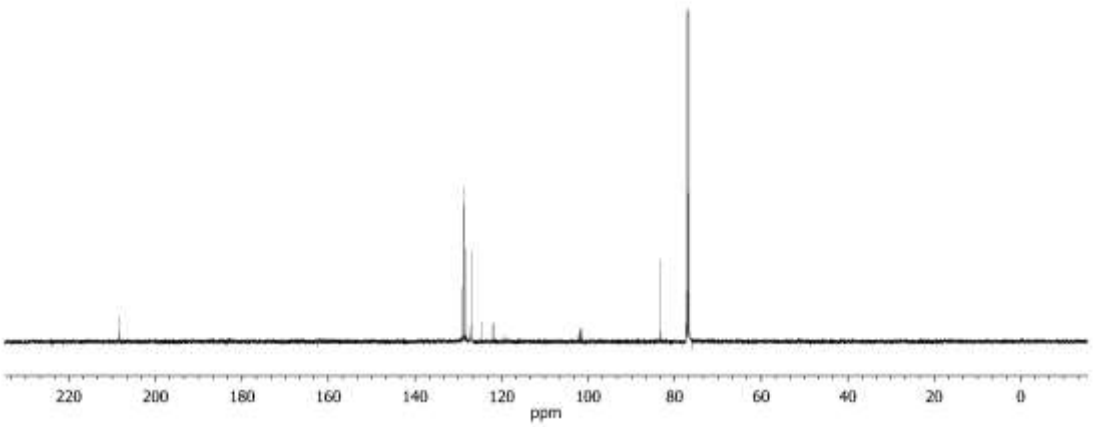
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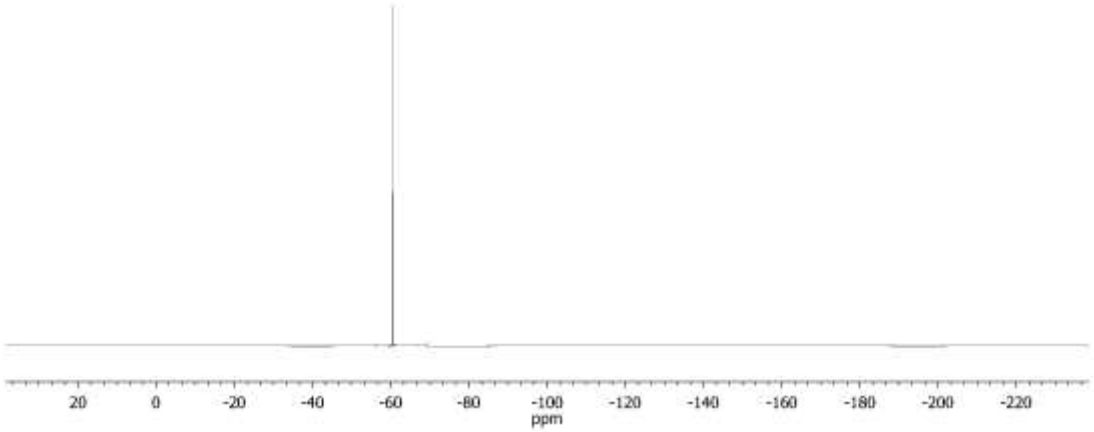
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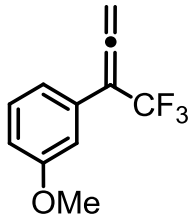
1-methoxy-3-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5b)



The reaction was conducted on a 1.8 mmol scale (*via* **3.4b**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5b** (334 mg, 86%) as a pale yellow oil.

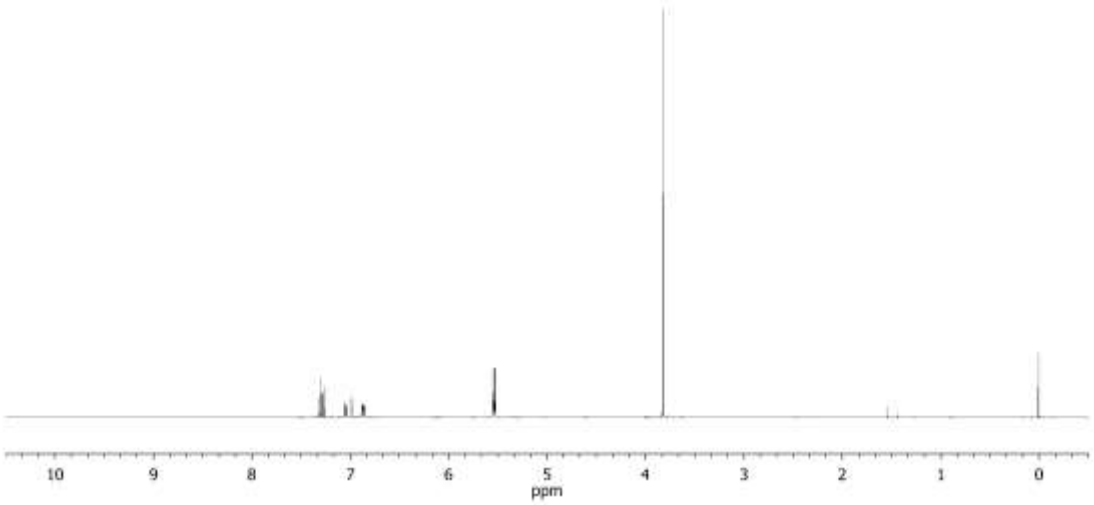
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.0, 16.0 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.86 (dd, *J* = 2.4, 8.0 Hz, 1H), 5.53 (q, *J* = 3.6 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ δ 208.6 (q, *J* = 3.7 Hz), 159.8, 130.5, 129.7, 123.3 (q, *J* = 272.3 Hz), 119.5, 113.6, 113.0, 101.7 (q, *J* =34.2 Hz), 83.5, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.3.

LRMS (EI): m/z 215 [M+H]

FTIR (neat): 1601, 1582, 1491, 1312, 1283, 1235, 1184, 1116, 1051, 974, 961, 868, 780, 729, 696 cm^{-1}.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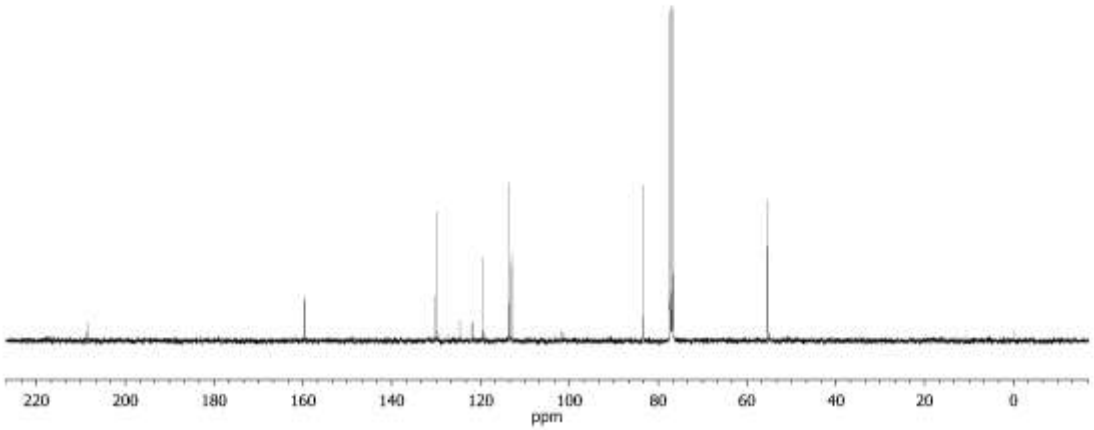
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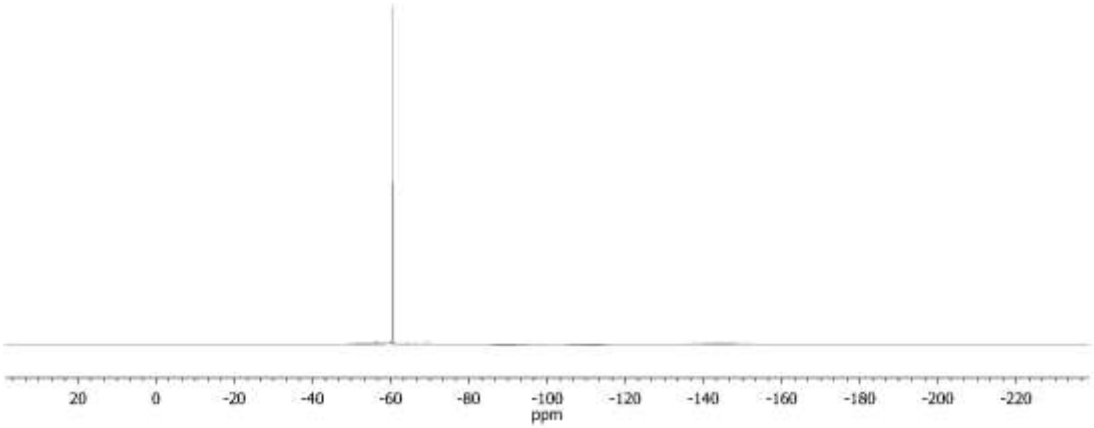
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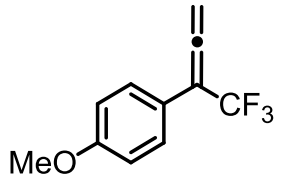
1-methoxy-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5c)



The reaction was conducted on a 5.1 mmol scale (*via* **3.4c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5c** (792 mg, 72%) as a yellow oil.

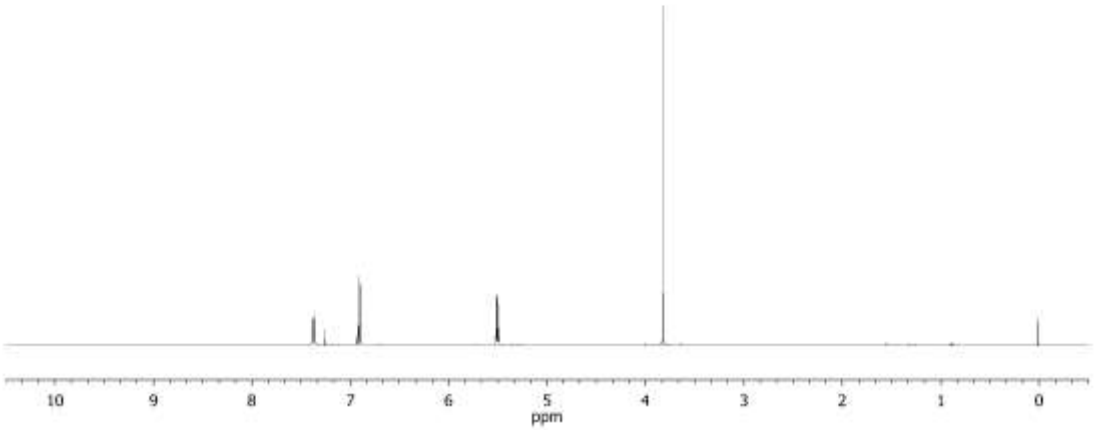
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 9.2 Hz, 2H), 6.90 (ddd, J = 3.2, 5.2, 9.2 Hz, 2H), 5.50 (q, J = 3.2 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): 208.1 (q, J = 3.7 Hz), 159.5, 128.4, 123.4 (q, J = 272.3 Hz), 121.2, 114.2, 101.4 (q, J = 34.0 Hz), 83.3, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.7.

LRMS (EI): m/z 215 [M+H]

FTIR (neat): 1712, 1609, 1306, 1250, 1165, 1117, 1102, 1032, 938, 831, 731 cm^{-1}.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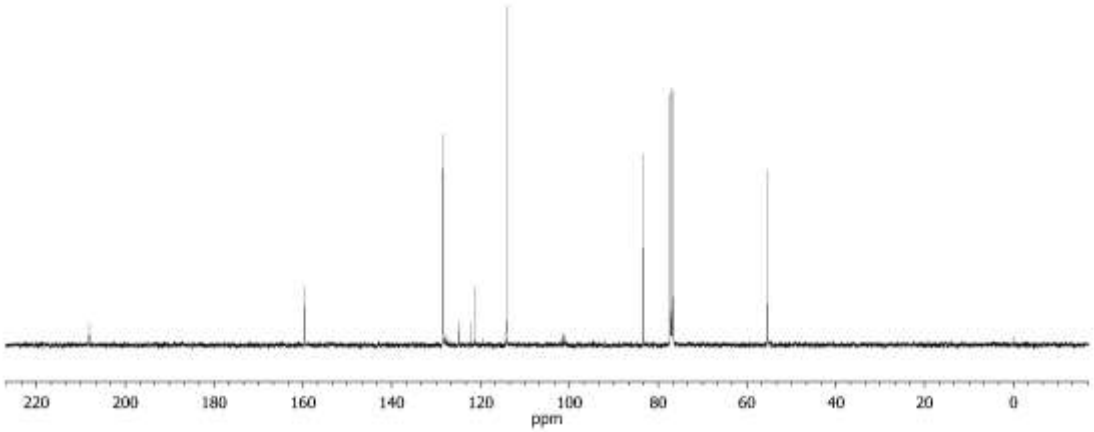
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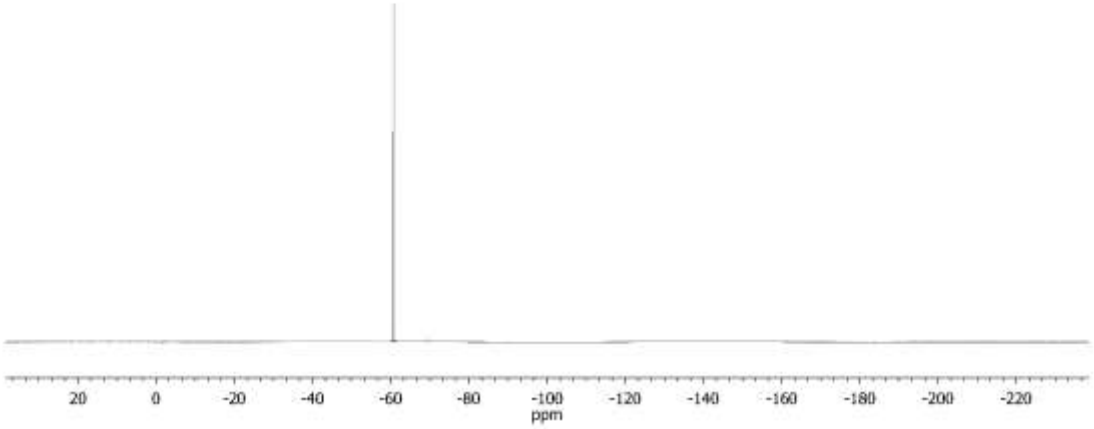
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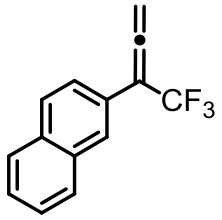
2-(1,1,1-trifluorobuta-2,3-dien-2-yl)naphthalene (3.5d)



The reaction was conducted on a 1.3 mmol scale (*via* **3.4d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5d** (241 mg, 77%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.85-7.80 (m, 3H), 7.54-7.47 (m, 3H), 5.62 (q, J = 3.6 Hz, 2H).

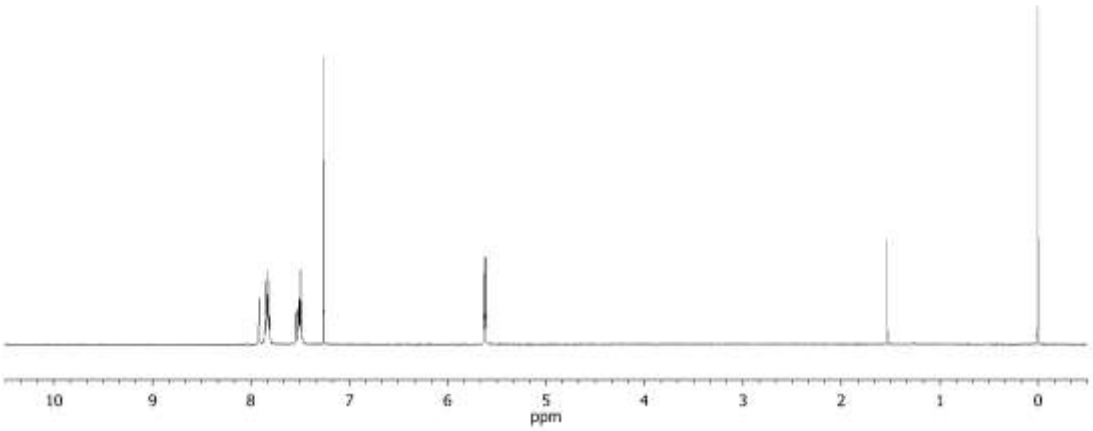
^{13}C NMR (100 MHz, $CDCl_3$ δ 208.9 (q, J = 4.5 Hz, 1C), 133.3, 132.8, 128.4, 128.3, 127.6, 126.6, 126.6, 126.3, 126.0 (q, J = 1.5 Hz, 1C), 124.8, 123.5 (q, J = 272.5 Hz), 102.1 (q, J = 34.2 Hz), 83.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.22.

LRMS (CI): m/z 235 $[M+H]^+$

FTIR (neat): 3046, 1969, 1935, 1598, 1507, 1307, 1265, 1245, 1209, 1163, 1133, 1108, 1022, 968, 925, 874, 861, 854, 834, 818, 747, 727 cm^{-1}.

mp (air): 54-56 °C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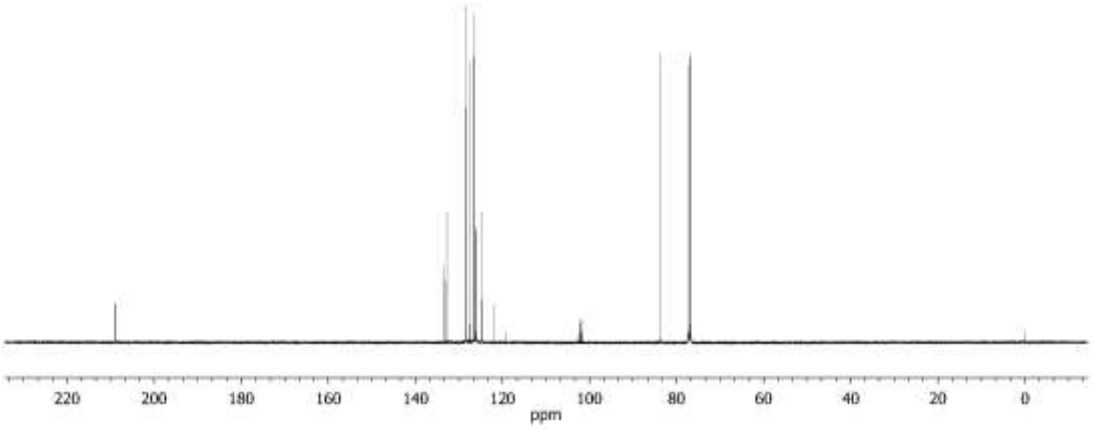
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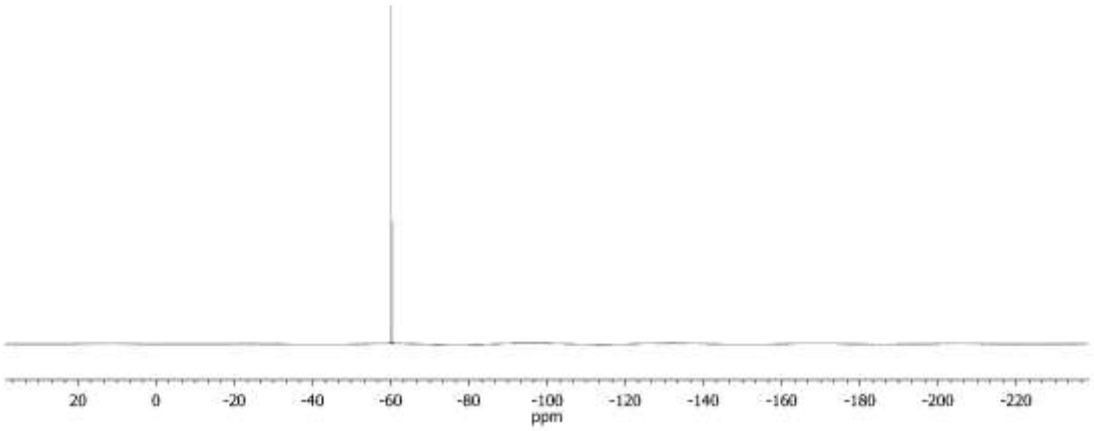


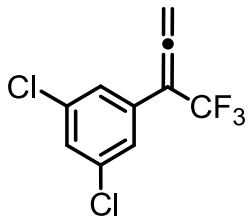
Representative procedure for the preparation of CF_3-allenes 3.5e,f:

Trifluoromethyl-substituted allenes **3.5e**,**f** were prepared by modifying an existing literature procedure reported by Lin.[23]

To a 25 mL three neck round bottom flask equipped with a magnetic stir bar was added 3,4-dibromo-1,1,1-trifluorobut-2-enes **3.4e** (549 mg, 1.3 mmol, 100 mol%). The flask was sealed with rubber septa, purged with argon, and DMF (2.6 mL, 0.5 M) was added, followed by Zn dust (87 mg, 1.33 mmol, 100 mol%) and stirred for 48 h at 25 °C. The reaction mixture was quenched with 1 M HCl (15 mL) and extracted with Et_2O (3 × 10

mL). The organic phase was washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compounds **3.5e**.

1,3-dichloro-5-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5e)



The reaction was conducted on a 1.3 mmol scale (*via* **3.4e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5e** (194 mg, 56%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 3H), 5.64 (q, J = 3.2 Hz, 2H).

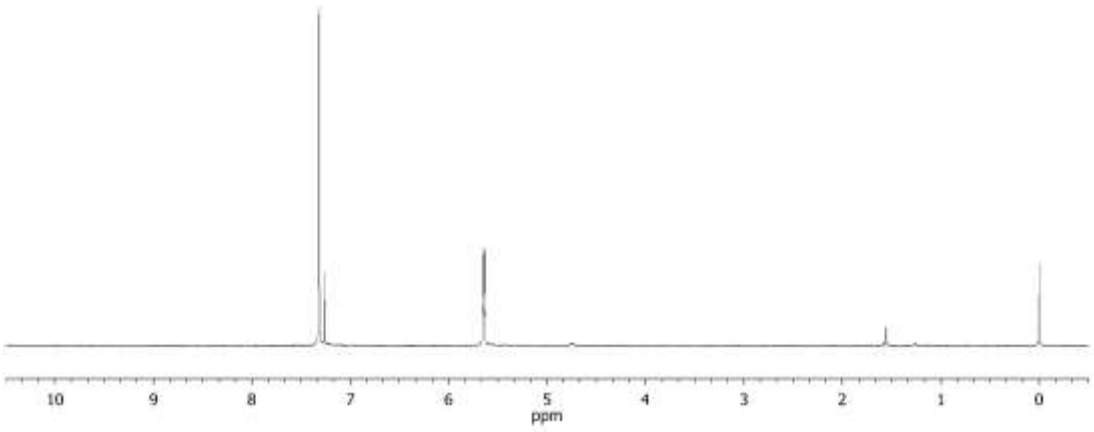
^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6 (q, J = 3.8 Hz), 135.4, 132.3, 128.3, 125.4, 122.8 (q, J = 273.9 Hz), 100.4 (q, J = 35.5 Hz), 84.7.

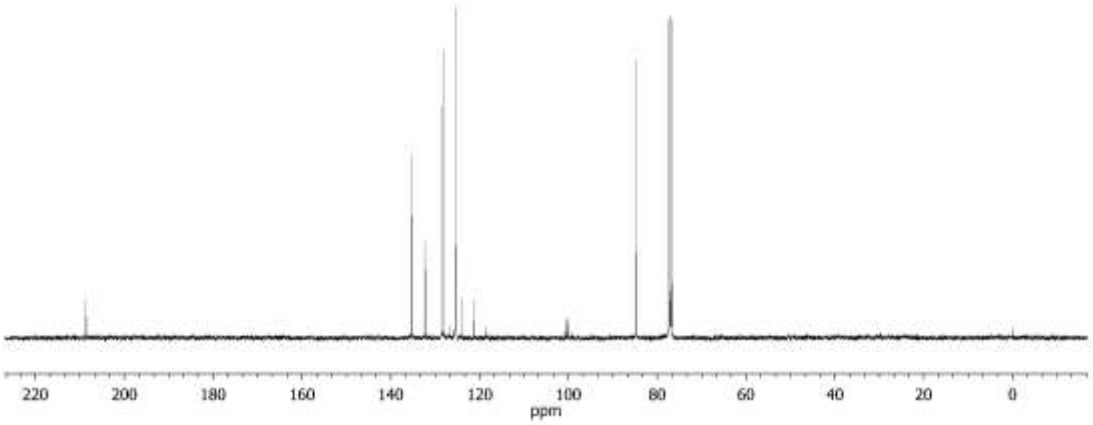
^{19}F NMR (376 MHz, $CDCl_3$): δ -60.5.

LRMS (CI): m/z 253 $[M+H]^+$

FTIR (neat): 3077, 2994, 1962, 1928, 1750, 1589, 1562, 1445, 1438, 1408, 1316, 1289, 1242, 1173, 1109, 986, 873, 857, 800, 775, 699, 685, 659 cm^{-1}.

mp (air): 51-55 °C

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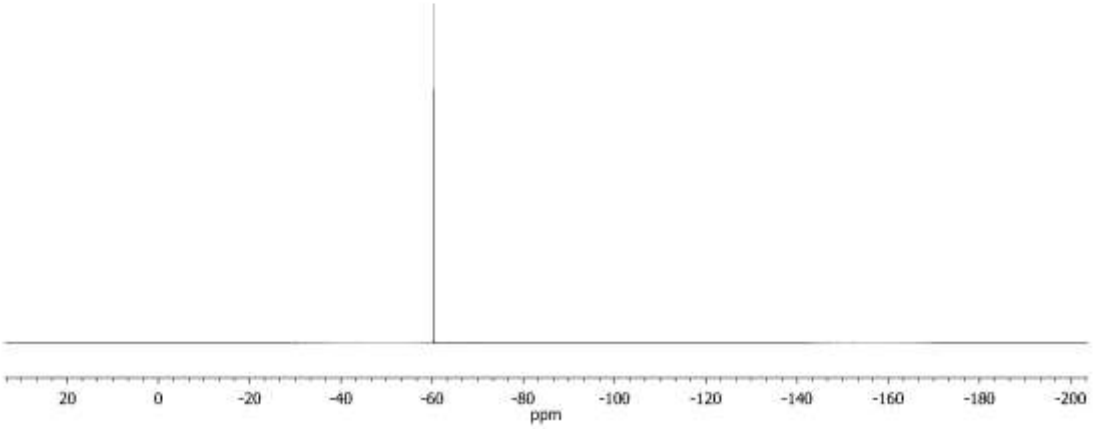
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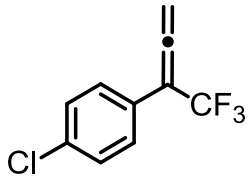
1-chloro-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5f)



The reaction was conducted on a 5.3 mmol scale (*via* **3.4f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5f** (1.0 g, 84%) as a colorless oil.

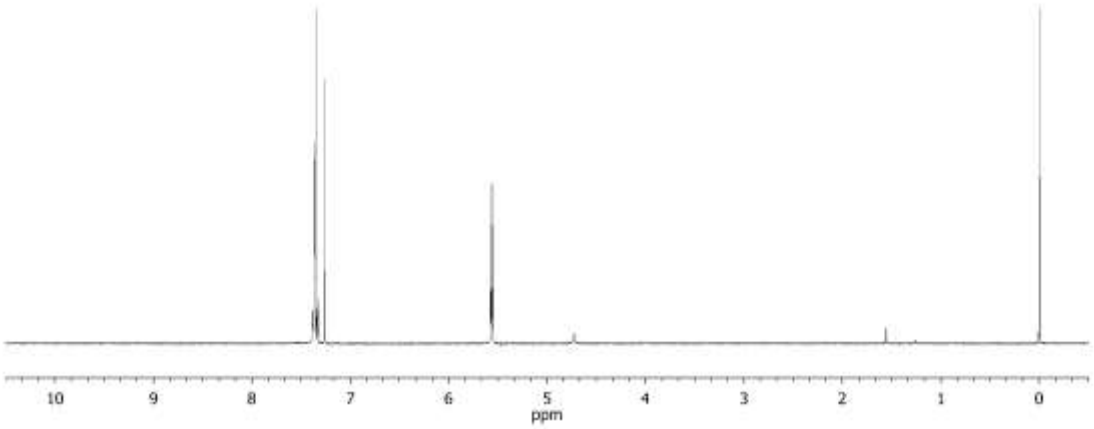
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 5.56 (q, J = 3.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4 (q, J = 4.2 Hz), 134.2, 128.9, 128.3, 127.6, 123.1 (q, J = 273.8 Hz), 101.1 (q, J = 34.9 Hz), 83.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.6.

LRMS (CI): m/z 219 $[M+H]^+$

FTIR (neat): 1972, 1936, 1595, 1494, 1317, 1305, 1289, 1255, 1172, 1117, 1101, 1092, 1016, 935, 867, 828, 751, 735, 718, 707 cm^{-1}.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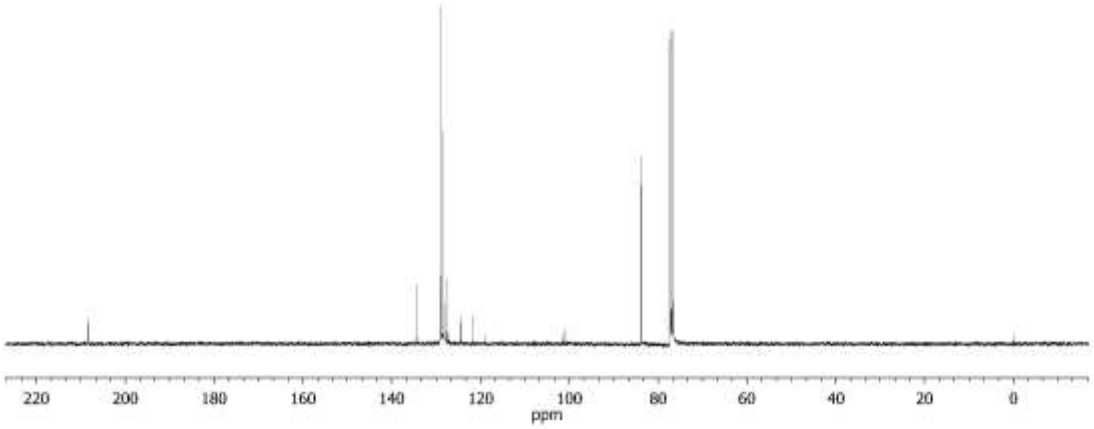
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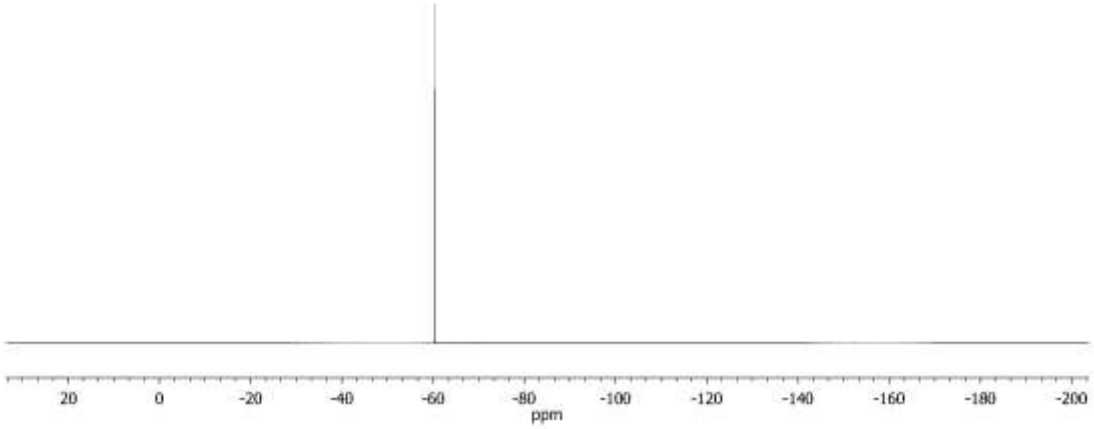
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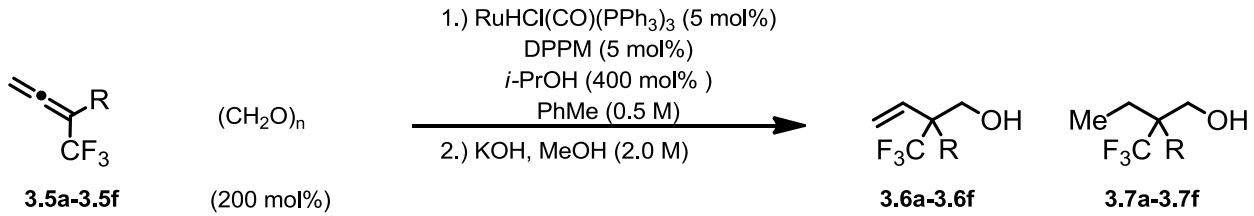
Experimental Procedures and Spectral Data for CF_3-allene Hydrohydroxymethylation

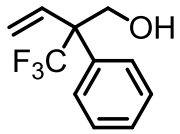


3.5a-3.5f (200 mol%) **3.6a-3.6f** **3.7a-3.7f**

General Procedure for the coupling of CF_3-allenes (3.5a-3.5f) to paraformaldehyde

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.6 mg, 0.010 mmol, 5 mol%), 1,1-bis(diphenylphosphino)methane (DPPM) (3.8 mg, 0.010 mmol, 5 mol%), and paraformaldehyde (12.0 mg, 0.40 mmol, 200 mol%). The tube was sealed with a rubber septum, purged with argon and toluene (0.4 mL, 0.5 M with respect to allene), allene (0.200 mmol, 100 mol%) and 2-propanol (61 μL, 0.8 mmol, 400 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. The reaction mixture was concentrated *in vacuo,* then diluted with Et_2O (20 mL), and washed with 1 M HCl. The organics were removed and the aqueous layer was extracted Et_2O (2 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2) to furnish the title compounds.

2-phenyl-2-(trifluoromethyl)but-3-en-1-ol (3.6a)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5a**) at 105°C for 1 h. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (33.6 mg, 78%, 20:1 (**3.6a**:**3.7a**)) as a yellow oil.

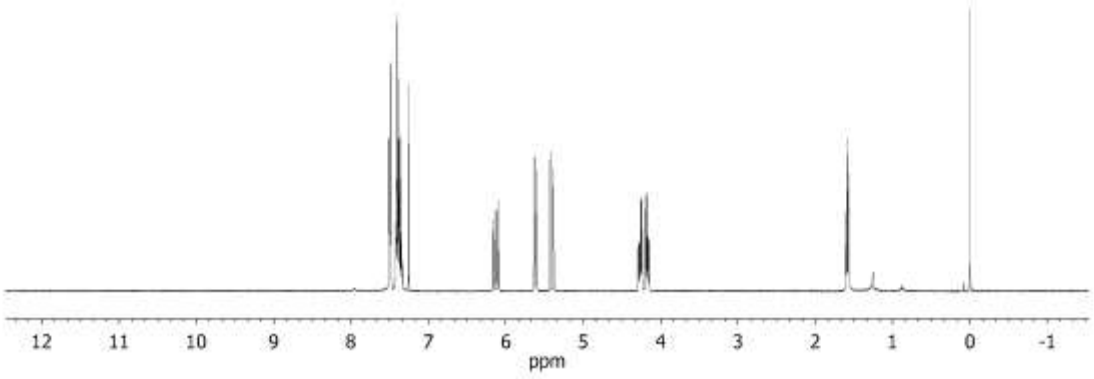
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.46 (m, 2H), 7.44 – 7.32 (m, 3H), 6.13 (dd, *J* = 17.9, 11.3 Hz, 1H), 5.62 (d, *J* = 11.3 Hz, 1H), 5.40 (d, *J* = 17.8 Hz, 1H), 4.26 (dd, *J* = 11.8, 6.7 Hz, 1H), 4.17 (dd, *J* = 11.8, 7.2 Hz, 1H), 1.59 (t, *J* = 7.1 Hz, 1H).

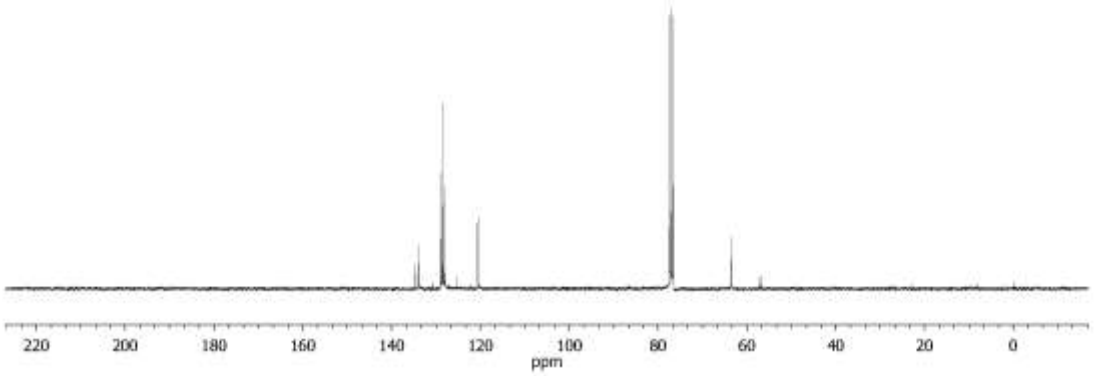
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 133.8, 129.0, 128.5, 128.2, 126.6 (q, *J* = 284.7 Hz), 120.6, 63.4, 56.9 (q, *J* = 22.6 Hz).

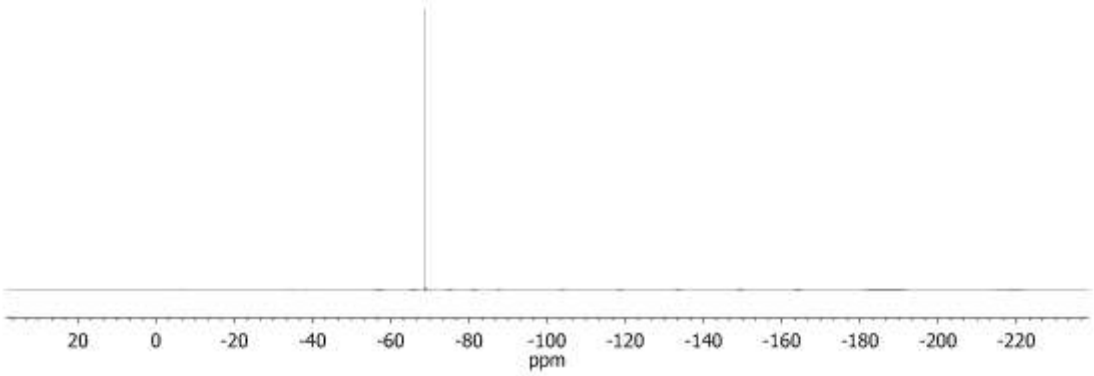
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.9.

LRMS (CI): m/z 199 $[M\text{-}OH]^+$

FTIR (neat): 3411, 1640, 1498, 1449, 1250, 1145, 1047, 1012, 935, 877, 761, 733, 699 cm^{-1}.




220
200
180
160
140
120
100
80
60
40
20
0
ppm


20
0
-20
-40
-60
-80
-100
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-140
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-180
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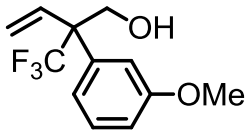
-220
ppm

2-(3-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6b)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5b**) at 120°C for 30 min. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (32.1 mg, 65%, >20:1 (**3.6b**:**3.7b**)) as a yellow oil.

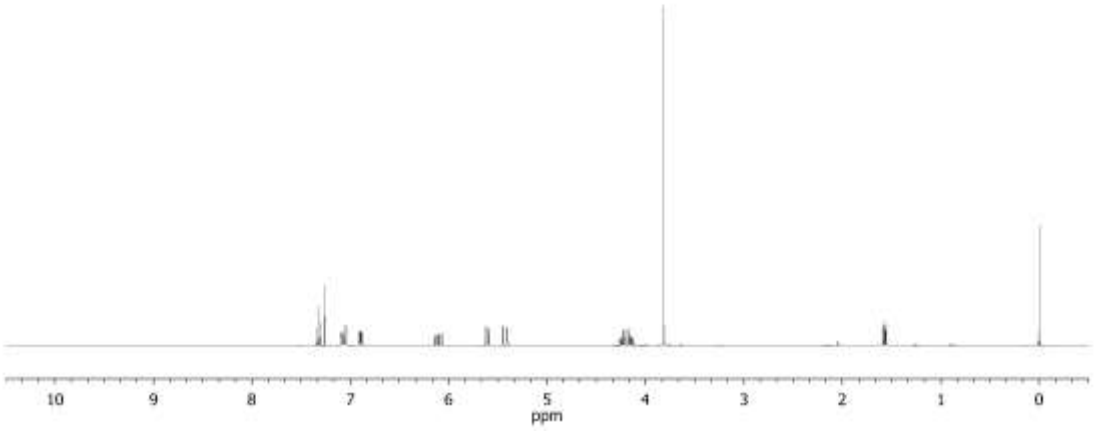
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.09-7.07 (m, 1H), 7.05-7.04 (m, 1H), 7.89 (dddd, *J* = 8.2, 3.4, 2.8, 0.8 Hz, 1H), 6.11 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 5.42 (d, *J* = 17.8 Hz, 1H), 4.24 (dd, *J* = 11.8, 7.2 Hz, 1H), 4.15 (dd, *J* = 11.8, 7.2 Hz, 1H), 3.81 (s, 3H), 1.59-1.55 (m, 1H).

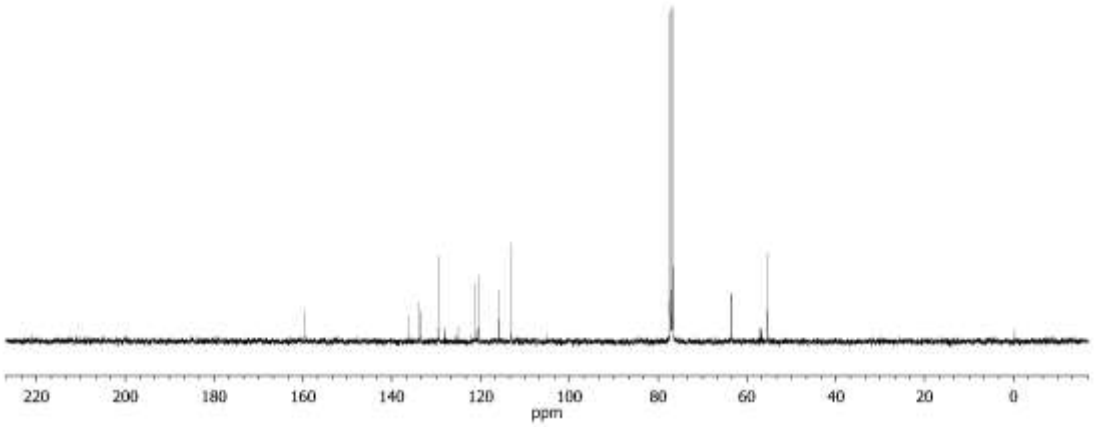
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 136.2, 133.7, 129.5, 126.5 (d, *J* = 282.7 Hz), 121.1, 120.5, 115.7, 113.0, 63.6, 56.9 (q, *J* = 22.3 Hz), 55.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.6.

LRMS (CI): m/z 229 $[M\text{-}OH]^+$

FTIR (neat): 3458, 29.45, 2360, 1603, 1584, 1492, 1253, 1168, 1140, 1041, 940, 881, 816, 780, 732, 700 cm^{-1}.

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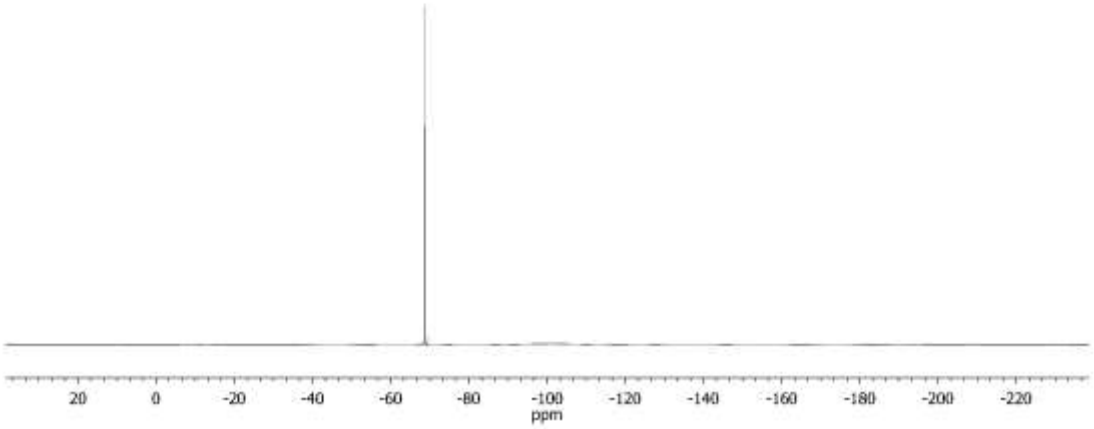
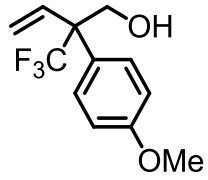
160
140
120
100
80
60
40
20
0
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

2-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6c)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5c**) at 105°C for 1 h. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (36.8 mg, 75%, >20:1 (**3.6c**:**3.7c**)) as a yellow oil.

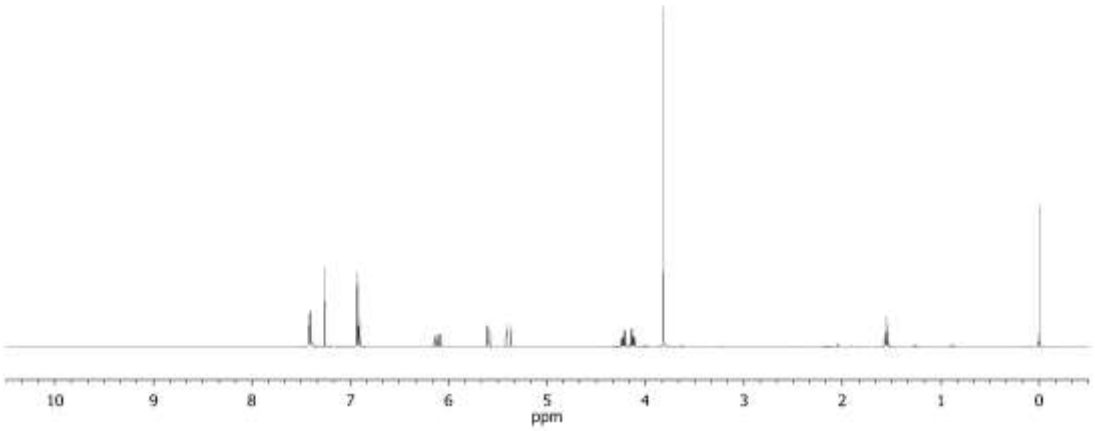
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.91 (ddd, *J* = 10.8, 6.4, 4.0 Hz, 2H), 6.11 (dd, *J* = 17.8, 11.4 Hz, 1H), 5.60 (d, *J* = 11.4 Hz, 1H), 5.39 (d, *J* = 17.8 Hz, 1H), 4.23 (dd, *J* = 11.6, 7.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.82 (s, 3H), 1.55 (t, *J* = 7.0 Hz).

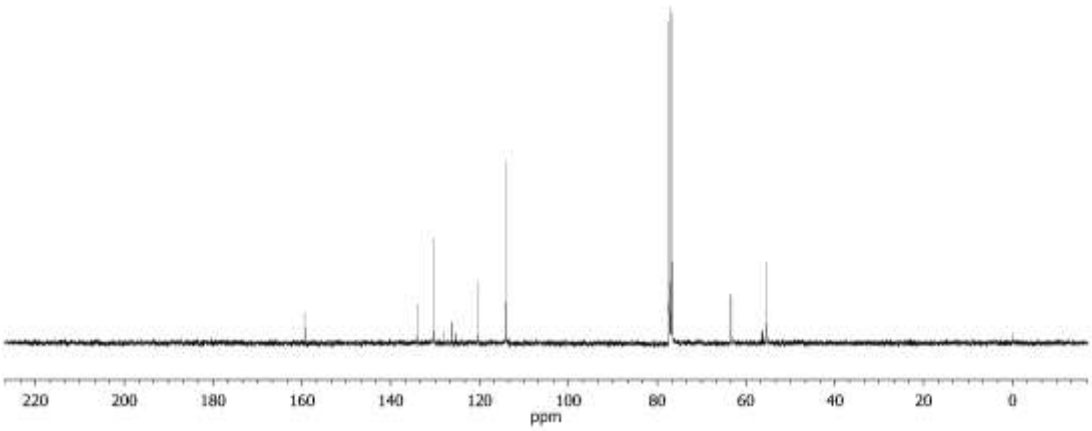
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 134.0, 130.3, 126.6 (q, *J* = 283.5 Hz), 126.3, 120.4, 113.9, 63.3, 56.4 (q, *J* = 23.1 Hz), 55.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -69.3.

LRMS (CI): m/z 229 $[M\text{-}OH]^+$

FTIR (neat): 3454, 1612, 1582, 1466, 1253, 1144, 1034, 932, 827, 738, 667 cm^{-1}.

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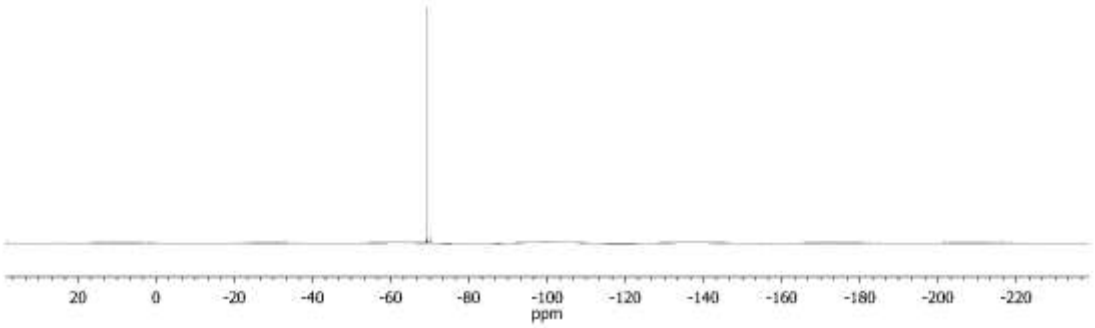
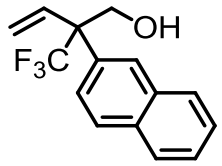
80
60
40
20
0
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

2-(naphthalen-2-yl)-2-(trifluoromethyl)but-3-en-1-ol (3.6d)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5d**) at 105 °C for 1 h. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (35.7 mg, 67%, >20:1 (**3.6d**:**3.7d**)) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.92 – 7.81 (m, 3H), 7.59 (d, J = 8.8 Hz, 1H), 7.56 – 7.47 (m, 2H), 6.22 (dd, J = 17.8, 11.2 Hz, 1H), 5.67 (d, J = 11.2 Hz, 1H), 5.43 (d, J = 17.8 Hz, 1H), 4.38 (dd, J = 11.9, 6.7 Hz, 1H), 4.26 (dd, J = 11.9, 7.0 Hz, 1H), 1.64 (t, J = 7.0 Hz, 1H).

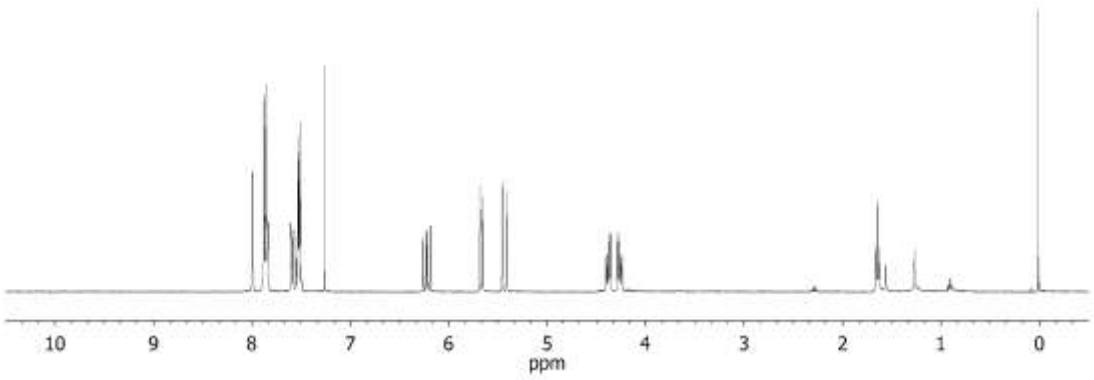
^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 133.0, 132.7, 131.9, 128.9, 128.4, 128.1, 127.4, 126.8, 126.7 (q, J = 285.1 Hz), 126.4, 126.1, 120.9, 63.5, 57.1 (q, J = 22.8 Hz).

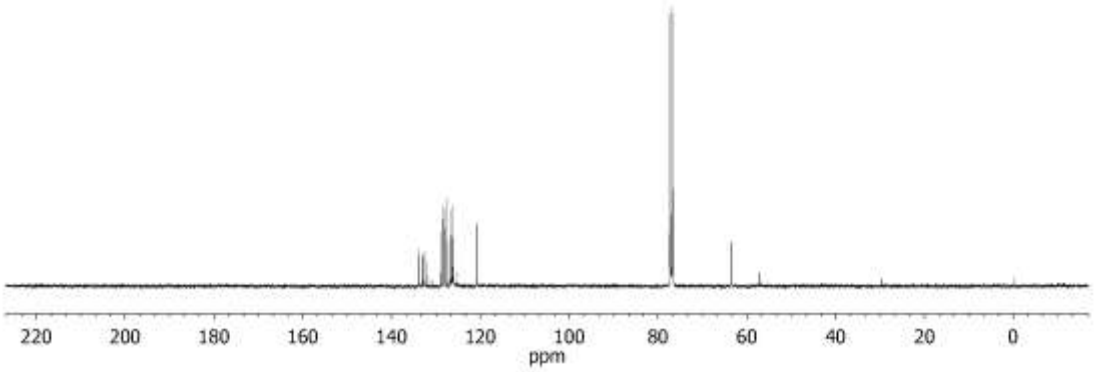
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.6.

LRMS (EI): m/z 266 $[M]^+$

FTIR (neat): 3332, 2918, 1596, 1510, 1413, 1363, 1325, 1255, 1209, 1168, 1145, 1125, 1081, 10501, 994, 964, 935, 909, 864, 810, 751, 728, 685, 660 cm^{-1}.

mp (air): 64-67 °C

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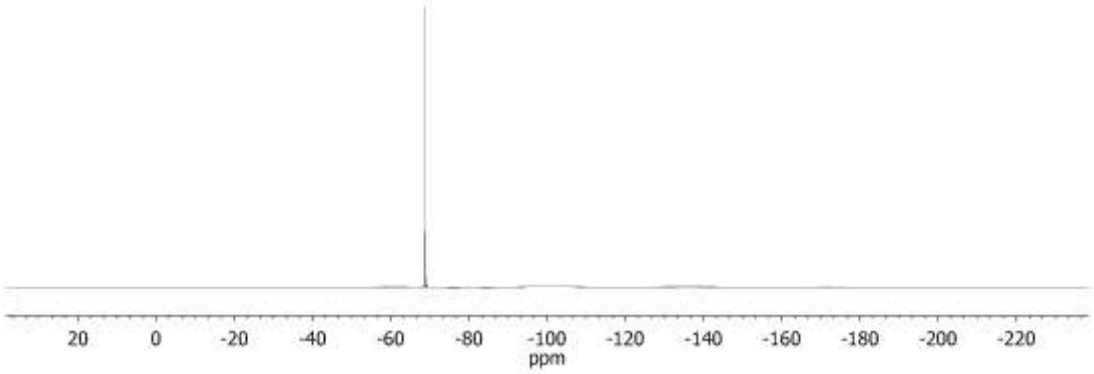
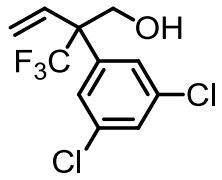
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

2-(3,5-dichlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6e)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5e**) at 120 °C for 30 min. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (38.7 mg, 68%, 16:1 (**3.6e**:**3.7e**)) as a yellow oil.

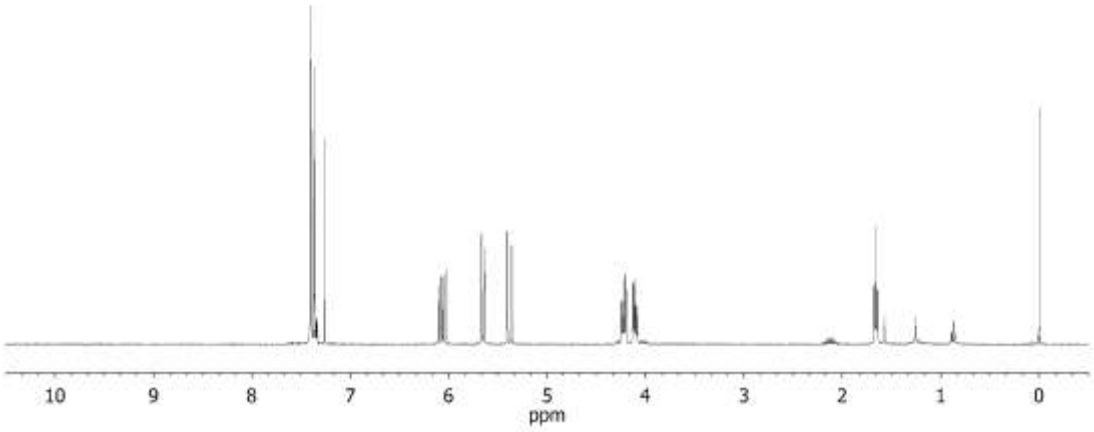
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.39 (m, 2H), 7.37 (t, *J* = 1.8 Hz, 1H), 6.07 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.65 (d, *J* = 11.3 Hz, 1H), 5.38 (d, *J* = 17.8 Hz, 1H), 4.22 (dd, *J* = 11.9, 6.9 Hz, 1H), 4.11 (dd, *J* = 11.9, 6.5 Hz, 1H), 1.66 (t, *J* = 6.8 Hz, 1H).

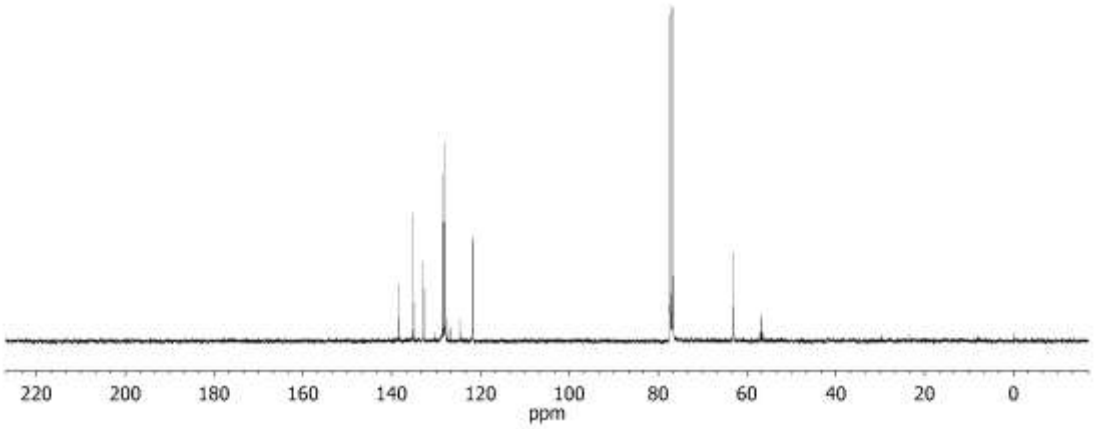
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 135.1, 132.8, 128.6, 127.9, 126.0 (q, *J* = 284.8 Hz), 121.7, 63.1, 56.8 (q, *J* = 23.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.9.

LRMS (EI): m/z 285 $[M+H]^+$

FTIR (neat): 3398, 1589, 1564, 1420, 1258, 1156, 1051, 997, 941, 859, 801, 771, 731, 688 cm^{-1}.

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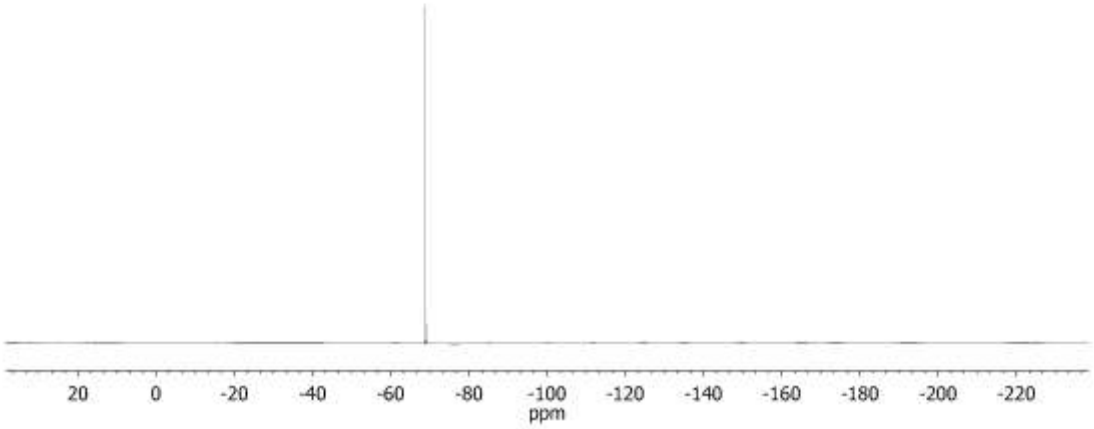
ppm


20
0
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-40
-60
-80
-100
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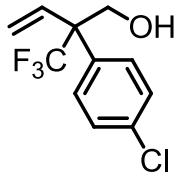
-140
-160
-180
-200
-220
ppm

2-(4-chlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6f)



The reaction was conducted in accordance with **General Procedure** (*via* allene **3.5f**) at 120°C for 30 min. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 h. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (36.3 mg, 73%, >20:1(**3.6f**:**3.7f**)) as a yellow oil.

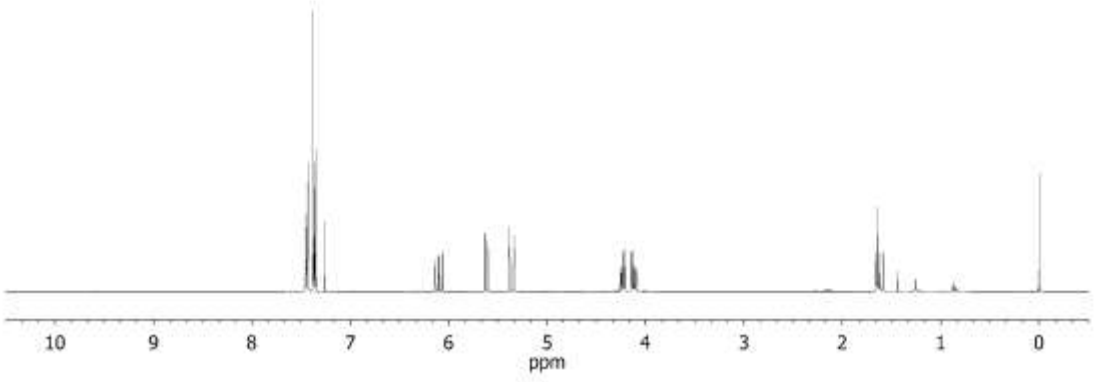
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.40 (m, 2H), 7.39 – 7.33 (m, 2H), 6.10 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.62 (d, *J* = 11.2 Hz, 1H), 5.36 (d, *J* = 17.8 Hz, 1H), 4.23 (dd, *J* = 11.9, 7.0 Hz, 1H), 4.12 (dd, *J* = 11.9, 6.7 Hz, 1H), 1.64 (t, *J* = 7.0 Hz, 1H).

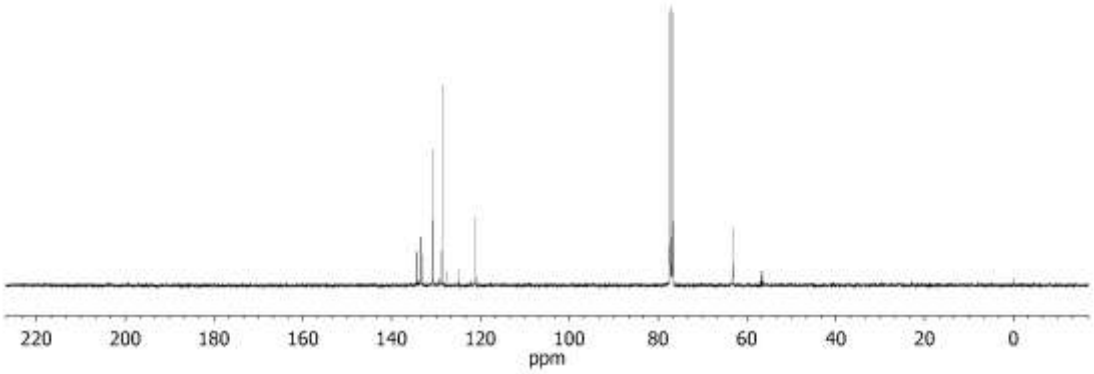
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 133.5, 133.2, 130.6, 128.7, 126.4 (q, *J* = 284.8 Hz), 121.1, 63.2, 56.7 (q, *J* = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -69.2.

LRMS (CI): m/z 233 $[M\text{-}H_2O+H]^+$

FTIR (neat): 3429, 2908, 1642, 1597, 1496, 1258, 1150, 1098, 1047, 1013, 935, 878, 821, 747, 732, 662 cm^{-1}.

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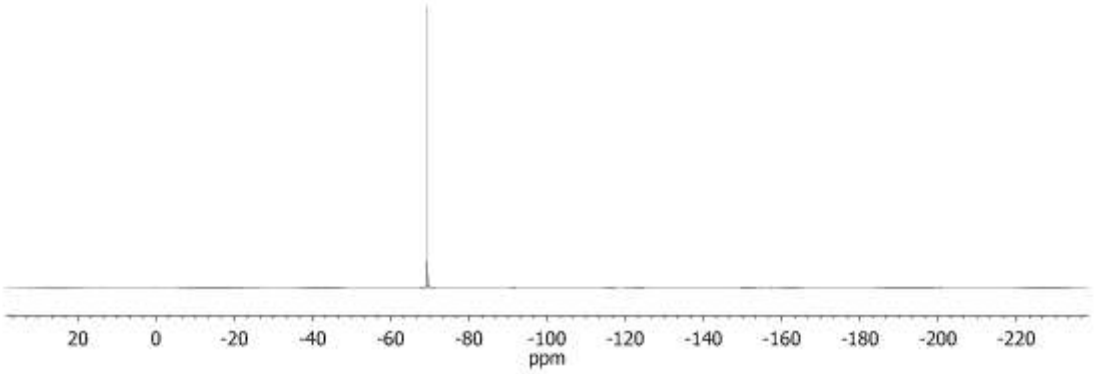
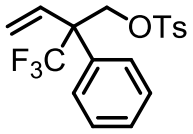
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

Experimental Procedures and Spectral Data for the Derivatization of Product 3.6a

2-phenyl-2-(trifluoromethyl)but-3-en-1-yl 4-methylbenzenesulfonate



To an oven-dried pressure tube equipped with magnetic stir bar was added **3.6a** (153 mg, 0.708 mmol, 100 mol%) and trimethylamine hydrogen chloride (6.8 mg, 0.071 mmol, 10 mol%). The flask was sealed with a rubber septum, purged with argon, and toluene (0.7 mL, 1.0 M with respect to **3.6a**) and Et_3N (0.3 mL, 2.124 mmol, 300 mol%) were added. Then, TsCl (270 mg, 1.416 mmol) in toluene (0.7 mL, 2.0 M with respect to TsCl) was dropwise added over 5 min. The rubber septum was quickly replaced with a screw cap and the reaction was stirred at 25 °C for 20 h, at which point distilled water (10 mL) was added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to afford the title compound (211 mg, 81%) as a colorless oil.

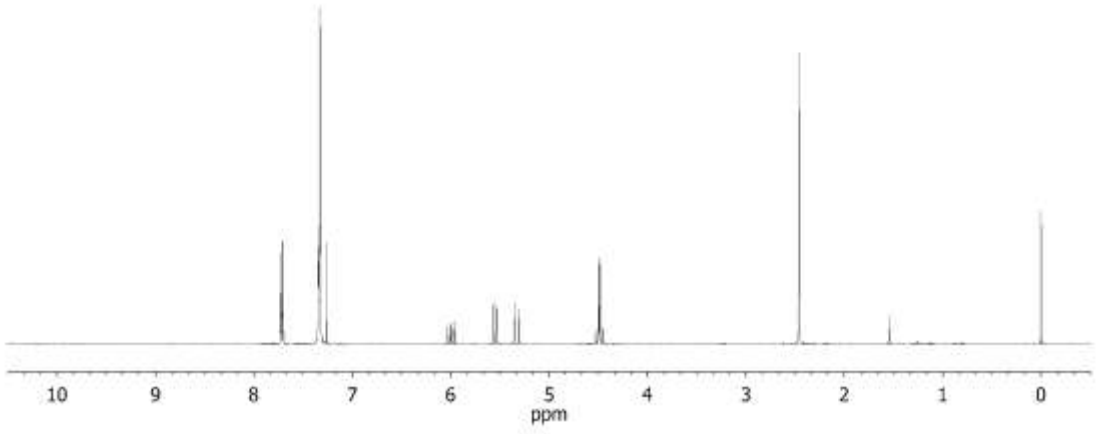
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 2H), 7.36 – 7.29 (m, 7H), 6.00 (dd, J = 17.8, 11.3 Hz, 1H), 5.55 (d, J = 11.3 Hz, 1H), 5.33 (d, J = 17.8 Hz, 1H), 4.55 – 4.41 (m, 2H), 2.46 (s, 3H).

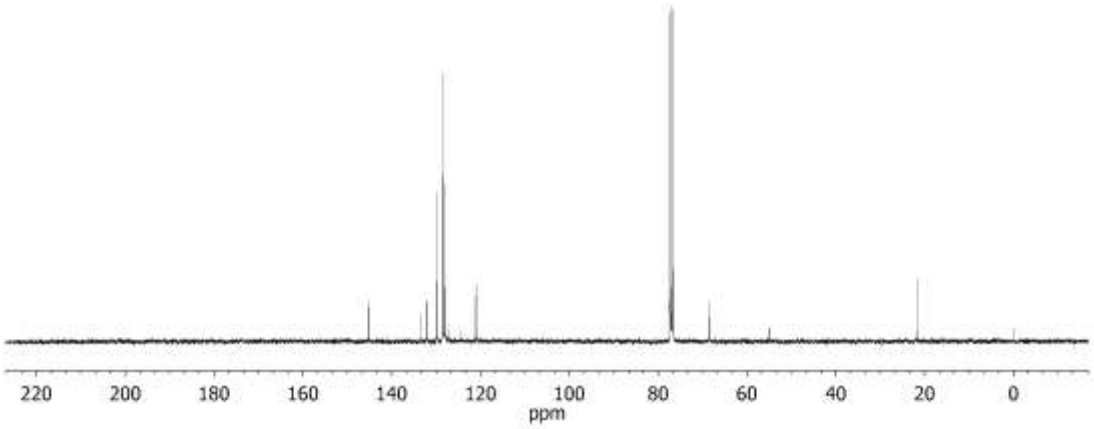
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 133.5, 132.2, 132.1, 129.9, 128.5, 128.0, 125.7 (q, J = 285.0 Hz), 121.0, 68.5, 55.0 (q, J = 24.6 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.7.

LRMS (CI): m/z 371 $[M+H]^+$

FTIR (neat): 3064, 1598, 1496, 1450, 1367, 1294, 1250, 1189, 1175, 1153, 1096, 1070, 990, 939, 885, 825, 812, 791, 763, 739, 699, 665 cm^{-1}.

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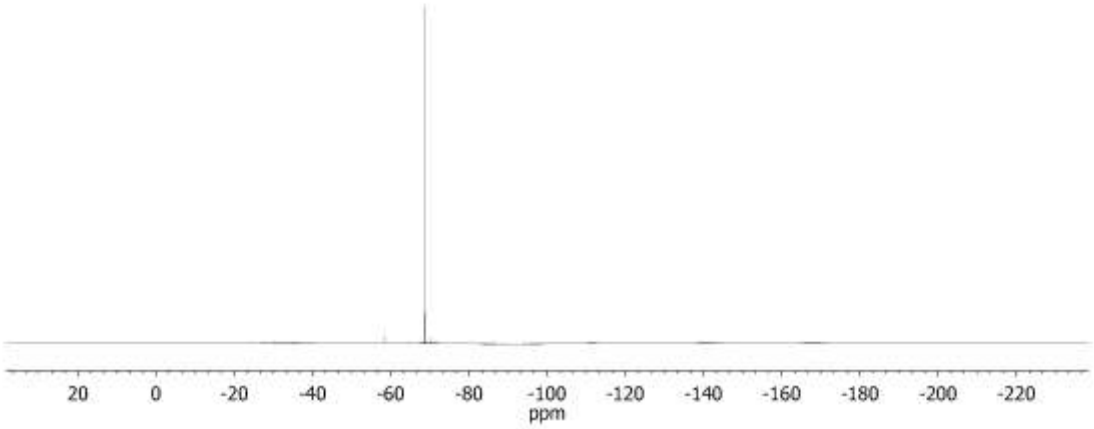
160
140
120
100
80
60
40
20
0
ppm


20
0
-20
-40
-60
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-100
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-140
-160
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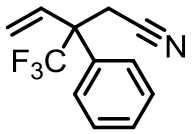
-220
ppm

3-phenyl-3-(trifluoromethyl)pent-4-enenitrile (3.8a)



3-phenyl-3-(trifluoromethyl)pent-4-enenitrile was prepared by modifying a literature procedure reported by Kuwahara.[38]

To an oven-dried pressure tube equipped with magnetic stir bar was added 2-phenyl-2-(trifluoromethyl)but-3-en-1-yl-4-methylbenzenesulfonate (180 mg, 0.486 mmol, 100 mol%) and sodium cyanide (NaCN) (71.5 mg, 1.458 mmol, 300 mol%). The tube was sealed with a rubber septum, purged with argon and DMSO (1.0 mL, 0.5 M with respect to tosylate) was added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to 150 °C for 45 h. The reaction mixture was allowed to cool to room temperature, at which point Et_2O (20 mL) and water (20 mL) were added. The organics were removed and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 15% Et_2O/pentane) to afford the title compound **3.8a** (70.0 mg, 64%) as a colorless oil.

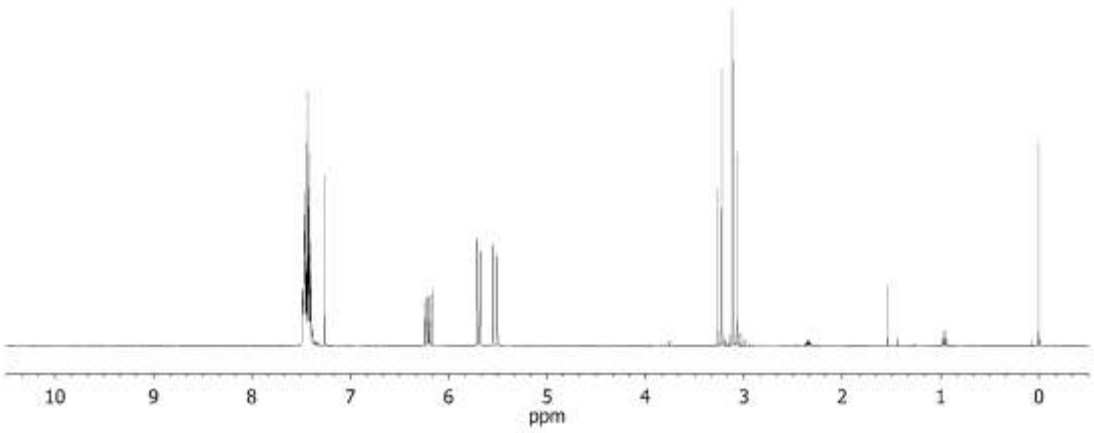
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.36 (m, 5H), 6.21 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.69 (d, *J* = 11.2 Hz, 1H), 5.53 (d, *J* = 17.7 Hz, 1H), 3.43 – 3.00 (m, 2H).

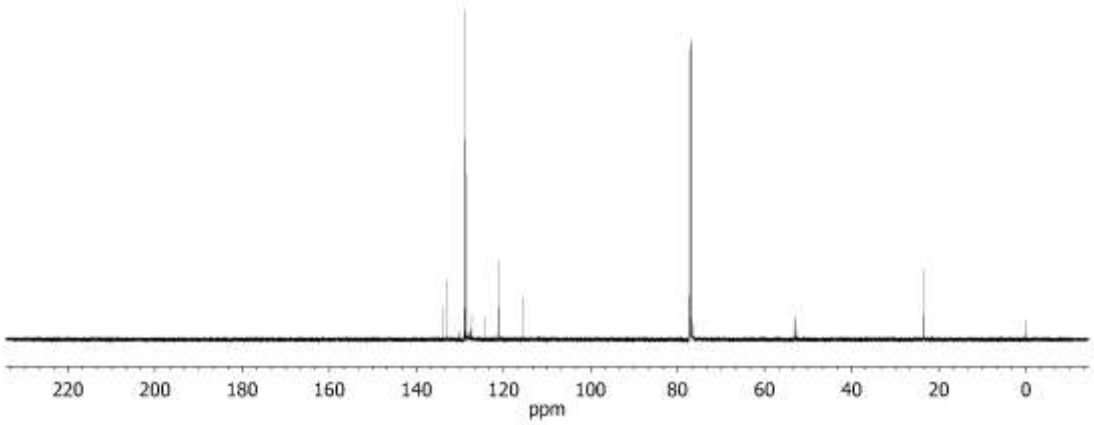
^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 133.1 (q, J = 1.5 Hz), 129.0, 128.8, 128.3 (q, J = 1.2 Hz), 125.8 (q, J = 284.5 Hz), 121.0, 115.6, 53.0 (q, J = 25.1 Hz), 23.6 (q, J = 2.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.6.

LRMS (CI): m/z 266 $[M+H]^+$

FTIR (neat): 2255, 1497, 1150, 1251, 1153, 1004, 975, 941, 904, 763, 733, 698 cm^{-1}.

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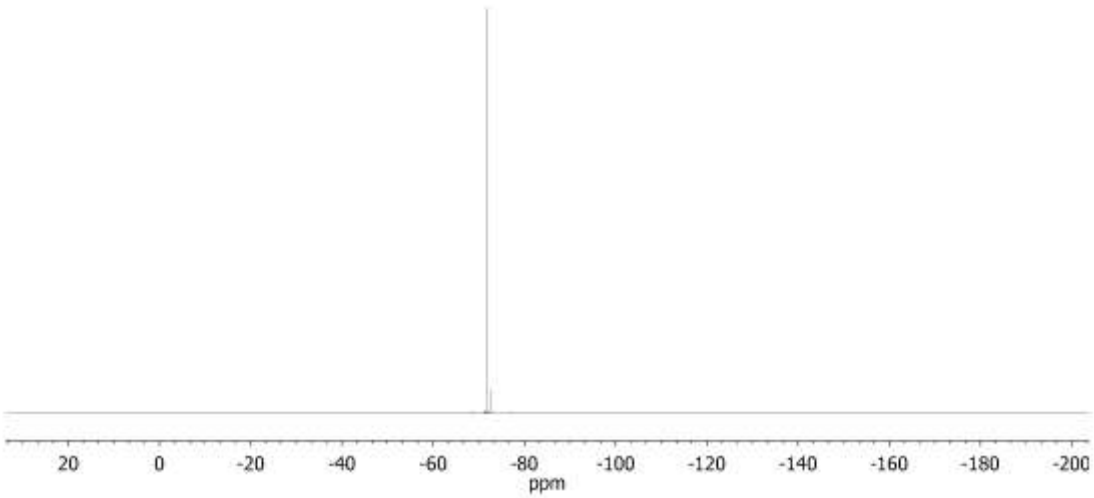
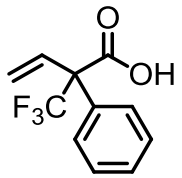
180
160
140
120
100
80
60
40
20
0
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

2-phenyl-2-(trifluoromethyl)but-3-enoic acid



2-phenyl-2-(trifluoromethyl)but-3-enoic acid was prepared by modifying an oxidation procedure reported by Berkowitz.[39]

To a flame-dried round bottom flask equipped with magnetic stir bar was added **3.6a** (153 mg, 0.708 mmol, 100 mol%). The flask was sealed with a rubber septum, purged with argon, and acetone (7.0 mL, 0.1 M with respect to **3.6a**) was added. The mixture was cooled to 0 °C, at which point freshly prepared H_2CrO_4 (0.58 mL, 3.66 M, 300 mol%) was dropwise added. The reaction mixture was allowed to warm to room temperature and stir for 2 h, at which point 2-propanol (10 mL) was slowly added. The precipitated salts were filtered through a pad of cotton, washing with CH_2Cl_2 (30 mL). The filtrate was washed with 1 M HCl (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 40% EtOAc/hexane) to afford the title compound (141 mg, 87%) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (br s, 1H), 7.52 – 7.33 (m, 5H), 6.29 (dd, J = 17.7, 11.2 Hz, 1H), 5.68 (d, J = 11.0 Hz, 1H), 5.48 (d, J = 18.0 Hz, 1H).

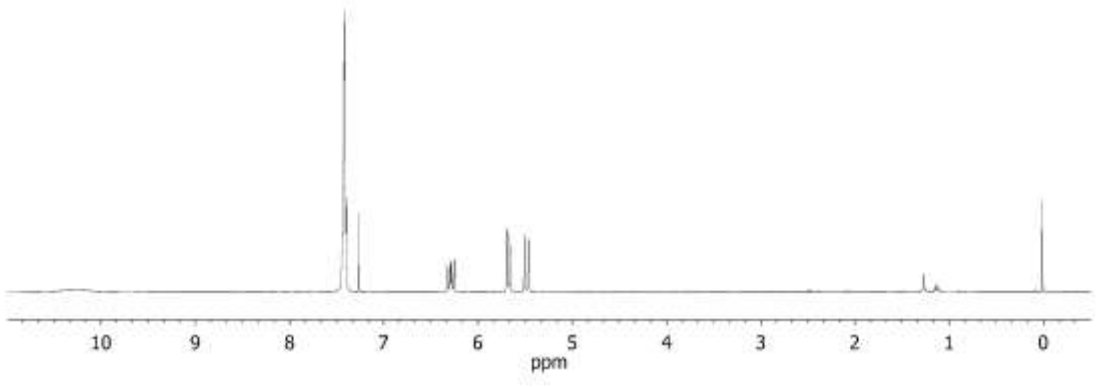
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 133.3, 131.1, 128.9, 128.7, 128.6, 124.3 (q, J = 283.9 Hz), 121.9, 63.8 (q, J = 25.7 Hz).

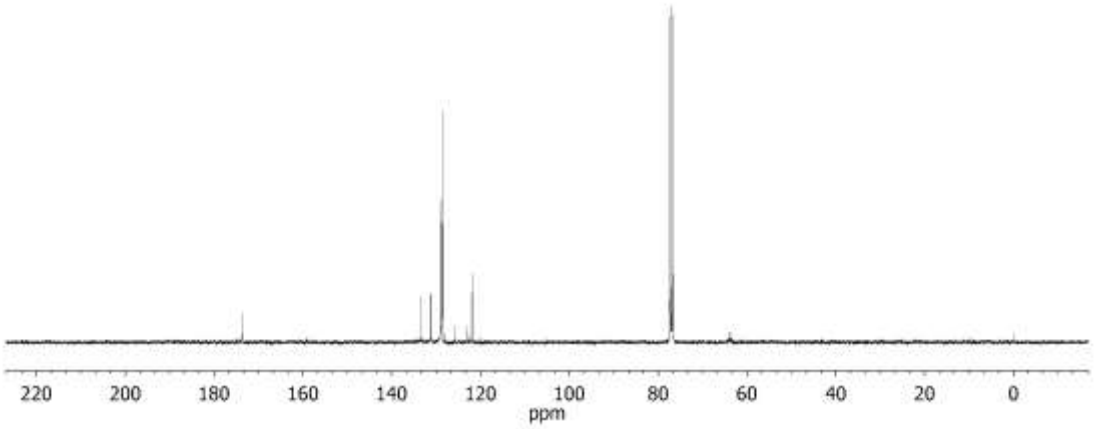
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.5.

LRMS (CI): m/z 231 $[M+H]^+$

FTIR (neat): 2918, 1716, 1638, 1494, 1452, 1394, 1328, 1266, 1219, 1177, 1155, 1124, 1082, 1015, 1004, 992, 937, 917, 876, 762, 709, 697, 671, 655 cm^{-1}.

mp (air): 98-100 °C

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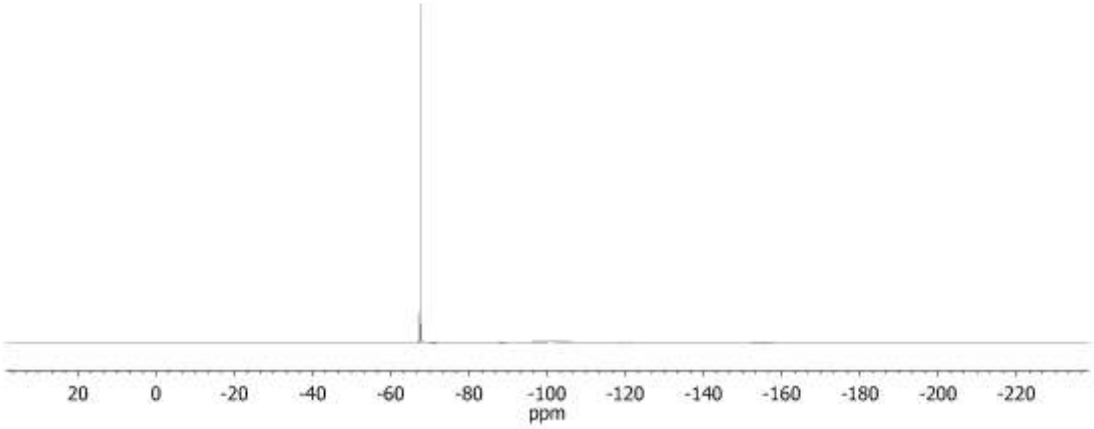
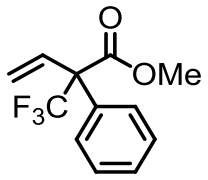
0
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

methyl 2-phenyl-2-(trifluoromethyl)but-3-enoate (3.9a)



To an oven-dried pressure tube equipped with magnetic stir bar was added 2-phenyl-2-(trifluoromethyl)but-3-enoic acid (46.0 mg, 0.2 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and methanol (0.2 mL, 1 M with respect to acid) and conc. Sulfuric acid (4 μL) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated at 75°C for 18.5 h. The reaction mixture was allowed to cool to room temperature, at which point CH_2Cl_2 (10 mL) was added and quenched with distilled water. The organics were removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound **3.9a** (39.4 mg, 81%) as a yellow oil.

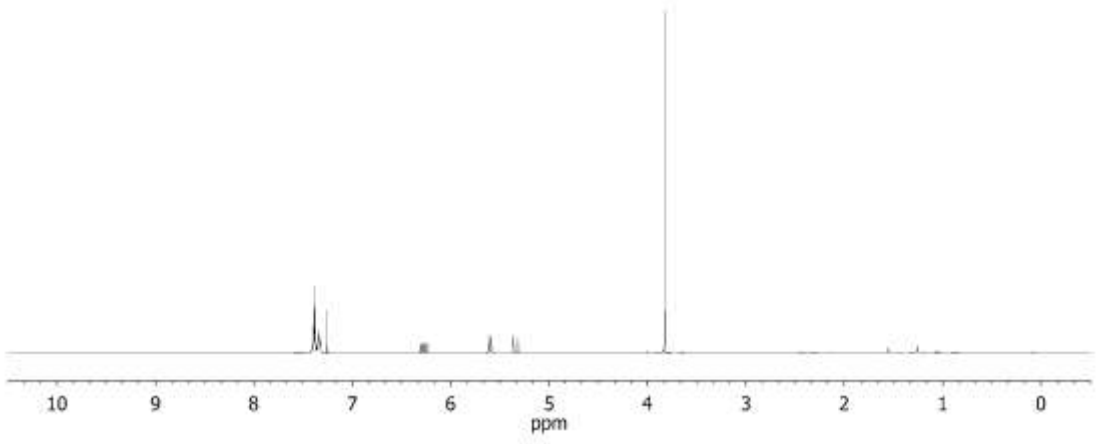
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.29 (m, 5H), 6.27 (dd, J = 17.7, 11.1 Hz, 1H), 5.60 (d, J = 11.1 Hz, 1H), 5.34 (d, J = 17.7 Hz, 1H), 3.82 (s, 3H).

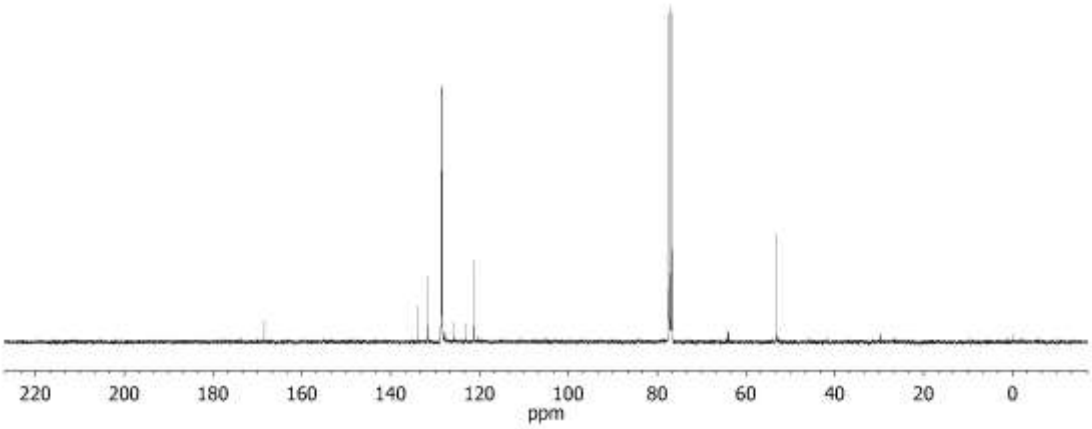
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 133.9, 131.7, 128.6, 128.6, 128.5, 124.5 (q, J = 283.7 Hz), 121.2 , 64.0 (q, J = 25.3 Hz), 53.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.4.

LRMS (CI): m/z 245 $[M+H]^+$

FTIR (neat): 2957, 1745, 1640, 1498, 1451, 1436, 1331, 1267, 1238, 1163, 1125, 1084, 1031, 1006, 940, 903, 800, 766, 719, 697, 655 cm^{-1}.

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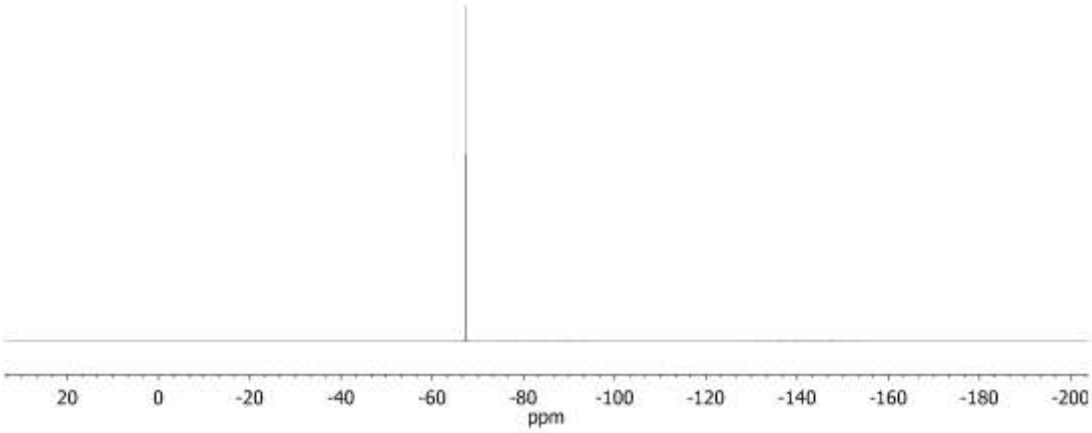
ppm

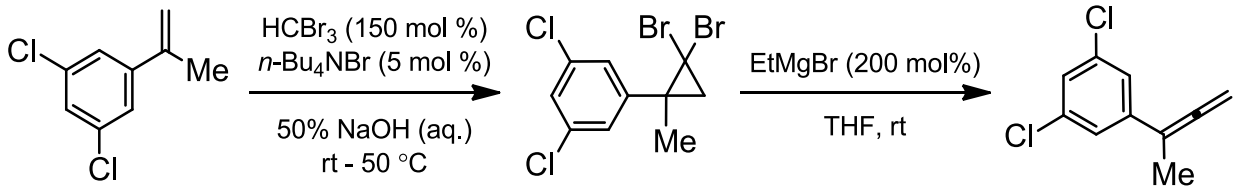

20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

3.5.2 EXPERIMENTAL DETAILS FOR SECTION 3.3

General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringes. Reaction tubes and flasks were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Tetrahydrofuran (THF) was distilled from sodium and benzophenone. $RuHCl(CO)(PPh_3)_3$was prepared according to literature procedure.[34] Fluorinated alcohols were used as received from Matrix Scientific and Oakwood Chemical. Allenes 2a[16a], 2b[16e], and 2c[40] were prepared according to literature procedure. 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF) was obtained from Strem Chemicals Inc and used as received. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F_{254}) and products were visualized by UV, $KMnO_4$, and/or Magic Seebach stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[36] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuterochloroform. ^{13}C

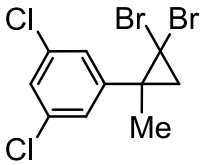
NMR spectra were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00 s).

Experimental Procedure and Spectral Data for the Preparation of Allene 3.10d



3.10d

1,3-dichloro-5-(2,2-dibromo-1-methylcyclopropyl)benzene



In modification to literature procedure,[41] a flame-dried 50 mL round-bottom flask was charged with 1,3-dichloro-5-(prop-1-en-2-yl)benzene[42] (4.7 g, 25 mmol, 100 mol%), $CHBr_3$ (3.3 mL, 38 mmol, 150 mol%,) and *n*-Bu_4NBr (0.3 g, 1.3 mmol, 5 mol%). To this stirring mixture was dropwise added 50% aqueous NaOH (4.4 mL, 55 mmol, 200

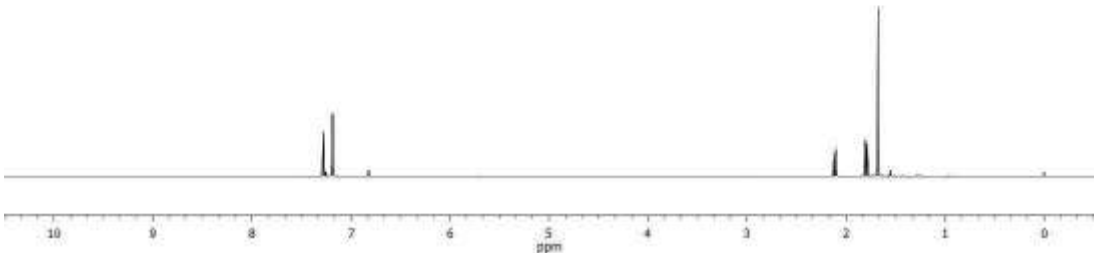
mol%) at ambient temperature. After the addition was complete, the reaction mixture was heated to 50 °C and stirred for 24 hours, then quenched with water (20 mL). The layers were separated, and the aqueous phase was extracted with chloroform (3 × 25 mL). The combined organic phases were successively washed with 1.0 M HCl (2 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to afford the title compound (4.5 g, 50%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J = 1.9 Hz, 1H), 7.18 (d, J = 1.9 Hz, 2H), 1.95 (dd, J = 126.8, 7.8 Hz, 2H), 1.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 134.9, 127.6, 127.2, 35.2, 34.7, 33.8, 27.3.

HRMS (CI) Calcd. For $C_{10}H_8Br_2Cl_2$ $[M]^+$: 355.8366, Found: 355.8366.

FTIR (neat): 2927, 1588, 1561, 1427, 1414, 1384, 1316, 1255, 1134, 1103, 1080, 1062, 1022, 940, 906, 858, 798, 763, 730, 704, 683 cm^{-1}.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3
2
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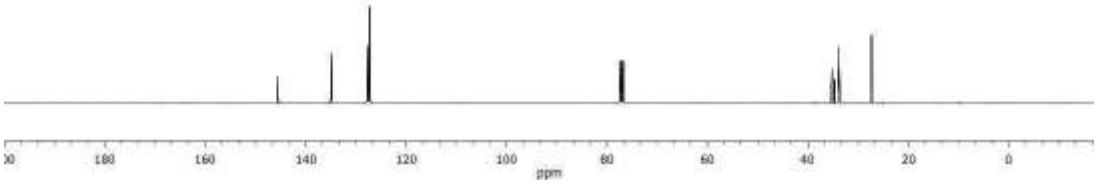
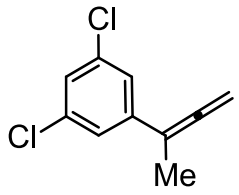
0
ppm


180
160
140
120
100
80
60
40
20
0
ppm

1-(buta-2,3-dien-2-yl)-3,5-dichlorobenzene (3.10d)



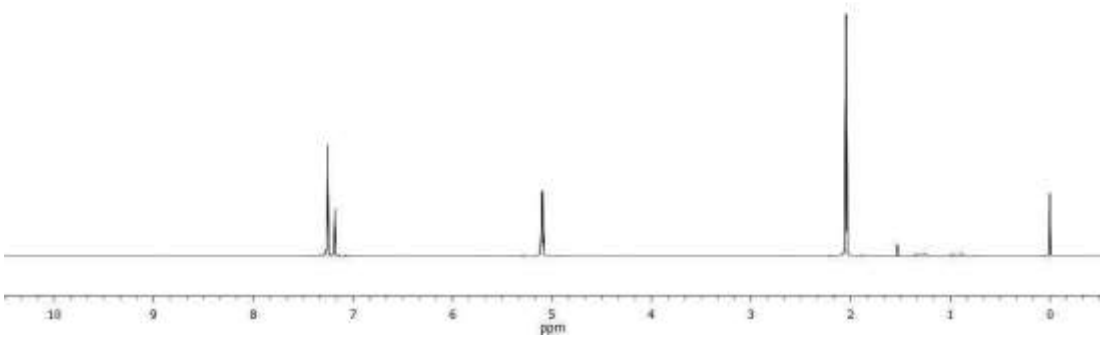
In modification to literature procedure,[43] a flame-dried 50 mL round-bottom flask was charged with 1,3-dichloro-5-(2,2-dibromo-1-methylcyclopropyl)benzene (1.4 g, 4 mmol, 100 mol%) and THF (8 mL, 0.5 M). To this stirring mixture was dropwise added 3.0 M ethylmagnesium bromide in THF (2.7 mL, 8 mmol, 200 mol%) at ambient temperature under argon. After stirring for 1 hour, the reaction was quenched with 1.0 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with petroleum ether (2 × 20 mL). The combined organic phases were washed with water (2 × 15 mL), then brine (2 × 15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound (318 mg, 40%) as a yellow oil.

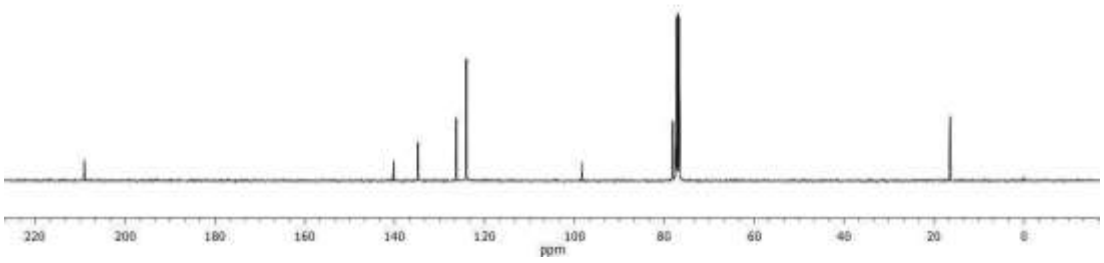
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.23 (m, 2H), 7.18 (t, J = 1.9 Hz, 1H), 5.10 (q, J = 3.0 Hz, 2H), 2.05 (t, J = 3.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.07, 140.24, 134.84, 126.32, 124.05, 98.39, 78.07, 16.37.

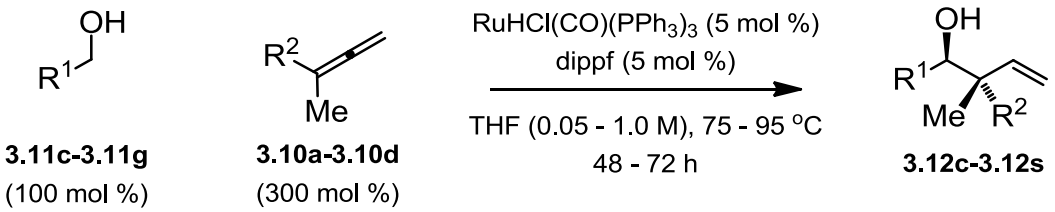
HRMS (CI) Calcd. For $C_{10}H_8Cl_2$ $[M]^+$: 198.0080, Found: 198.0080.

FTIR (neat): 1941, 1696, 1583, 1559, 1424, 1407, 1371, 1278, 1255, 1172, 1139, 1099, 952, 905, 852, 796, 729, 686 cm^{-1}.




220
200
180
160
140
120
100
80
60
40
20
0
ppm

Experimental Procedures and Spectral Data for Adducts 3.12c-3.12s



3.11c-3.11g (100 mol %)

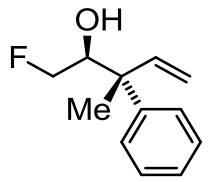
3.10a-3.10d (300 mol %)

3.12c-3.12s

General Procedure A for the coupling of alcohols (1c-1g) to allenes (2a-2d)

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF) (4.2 mg, 0.010 mmol, 5 mol%), and alcohol (0.200 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and THF (0.05 – 1.0 M with respect to alcohol) and allene (0.600 mmol, 300 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds with yields averaged over two trials.

1-fluoro-3-methyl-3-phenylpent-4-en-2-ol (3.12c)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (29.1 mg, 75%, >20:1 *dr*) as a yellow oil.

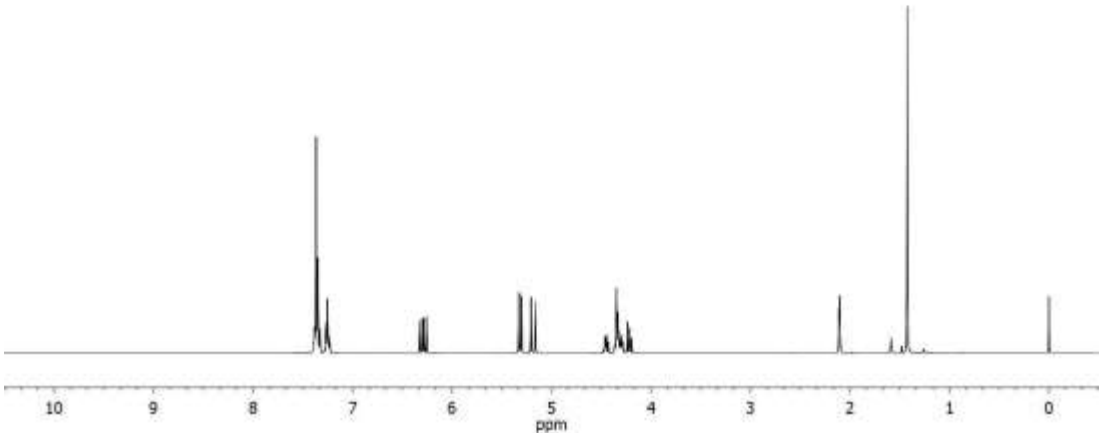
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 4H), 7.31 – 7.19 (m, 1H), 6.29 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.51 – 4.15 (m, 3H), 2.11 (d, *J* = 2.9 Hz, 1H), 1.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 142.1, 128.6, 126.8, 126.7, 115.0, 85.0 (d, *J* = 166.4 Hz), 75.7 (d, *J* = 17.7 Hz), 47.5 (d, *J* = 6.9 Hz), 20.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -228.6 – -229.1 (m).

HRMS (CI) Calcd. For $C_{12}H_{15}OF$ $[M]^+$: 194.1107, Found: 194.1107.

FTIR (neat): 3450, 2978, 1637, 1599, 1494, 1446, 1415, 1376, 1289, 1097, 1065, 998, 923, 764, 746, 700 cm^{-1}.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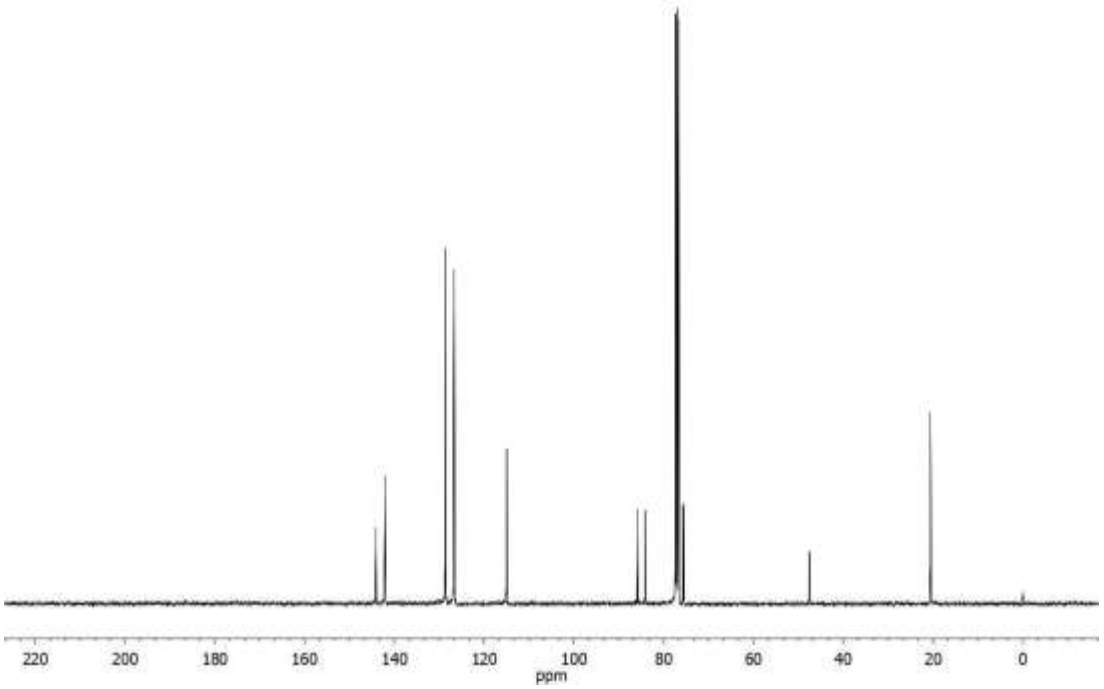
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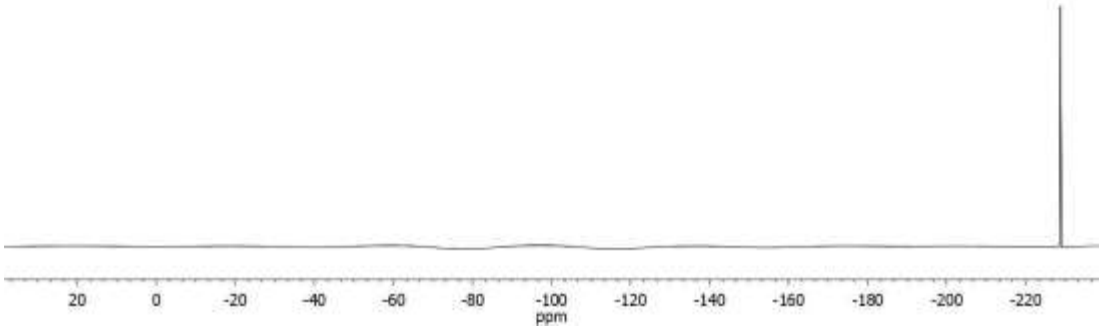
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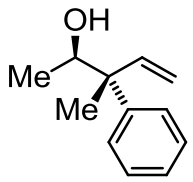
-220

3-methyl-3-phenylpent-4-en-2-ol (3.12d)



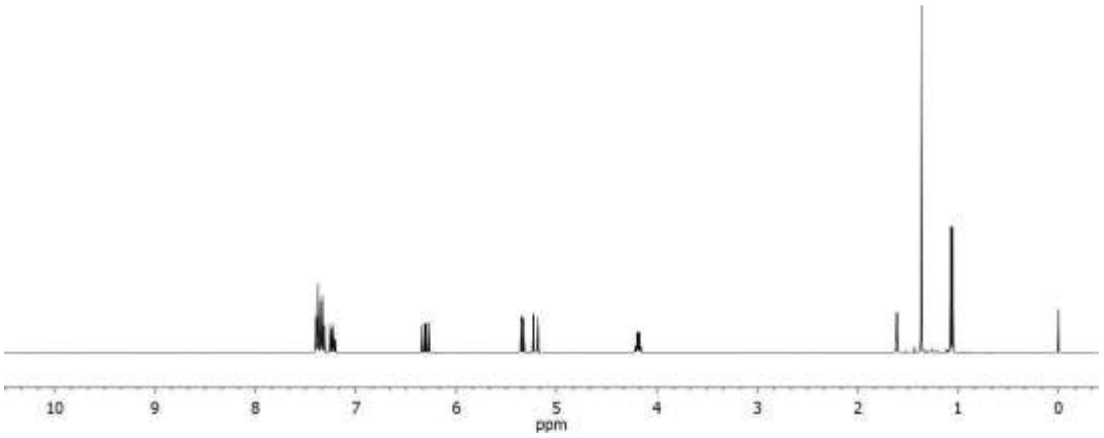
The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (25.7 mg, 73%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.30 (m, 4H), 7.25 – 7.19 (m, 1H), 6.30 (dd, J = 17.7, 10.9 Hz, 1H), 5.34 (dd, J = 10.9, 1.3 Hz, 1H), 5.21 (dd, J = 17.7, 1.3 Hz, 1H), 4.19 (qd, J = 6.3, 3.2 Hz, 1H), 1.61 (d, J = 3.1 Hz, 1H), 1.36 (s, 3H), 1.06 (d, J = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 142.7, 128.5, 126.8, 126.4, 115.1, 73.1, 49.7, 20.0, 17.2.

HRMS (CI) Calcd. For $C_{12}H_{15}O$ $[M-H]^+$: 175.1123, Found: 175.1122.

FTIR (neat): 3443, 2976, 2934, 1637, 1599, 1492, 1445, 1414, 1373, 1265, 1157, 1101, 1060, 1015, 918, 842, 760, 699 cm^{-1}.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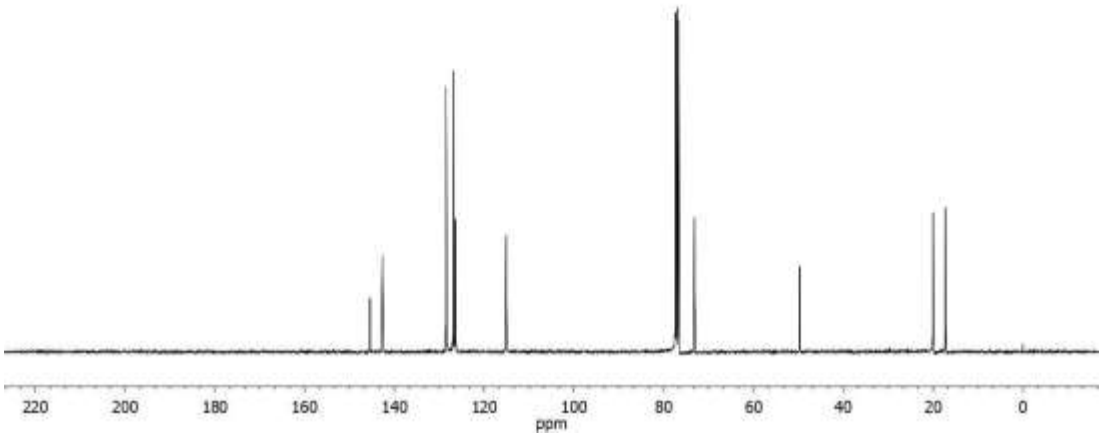
220
200
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60
40
20
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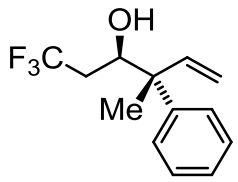
ppm

1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (3.12e)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (37.6 mg, 77%, 20:1 *dr*) as a yellow oil.

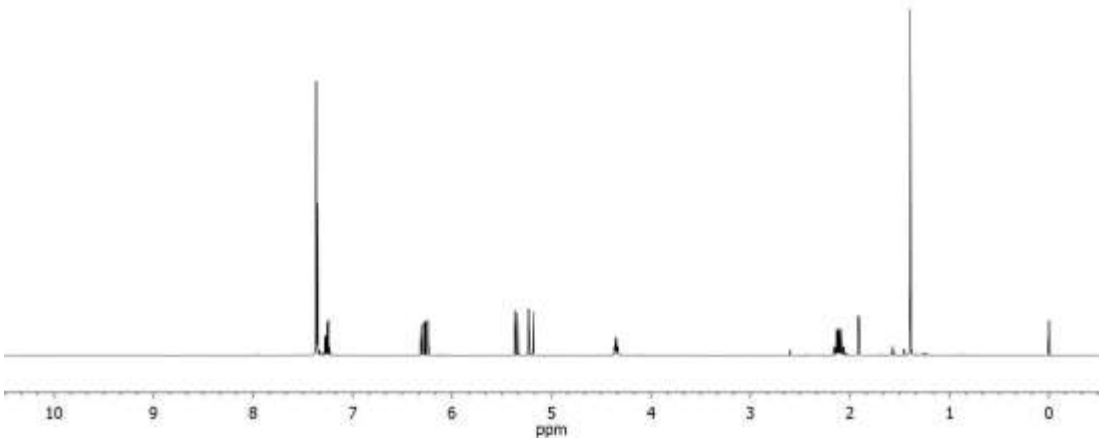
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.35 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.40 – 4.30 (m, 1H), 2.20 – 2.04 (m, 2H), 1.91 (dt, *J* = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 141.8, 128.8, 126.9 (q, *J* = 277.0 Hz), 126.9, 126.7, 115.8, 71.5 (d, *J* = 2.5 Hz), 49.3, 36.4 (q, *J* = 27.4 Hz), 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.9 Hz).

HRMS (CI) Calcd. For $C_{13}H_{15}OF_3$ $[M]^+$: 244.1075, Found: 244.1074.

FTIR (neat): 3472, 2982, 1638, 1600, 1495, 1446, 1430, 1413, 1378, 1328, 1254, 1119, 1009, 927, 876, 837, 768, 746, 700 cm^{-1}.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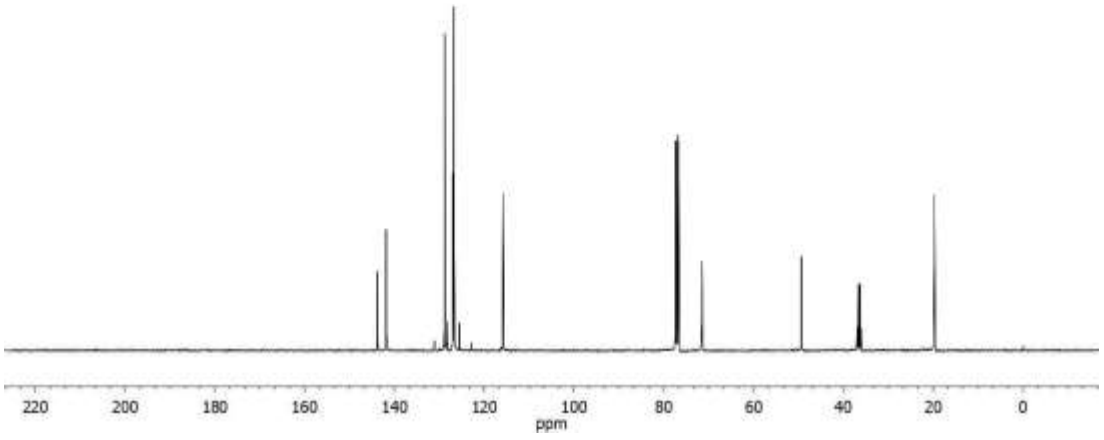
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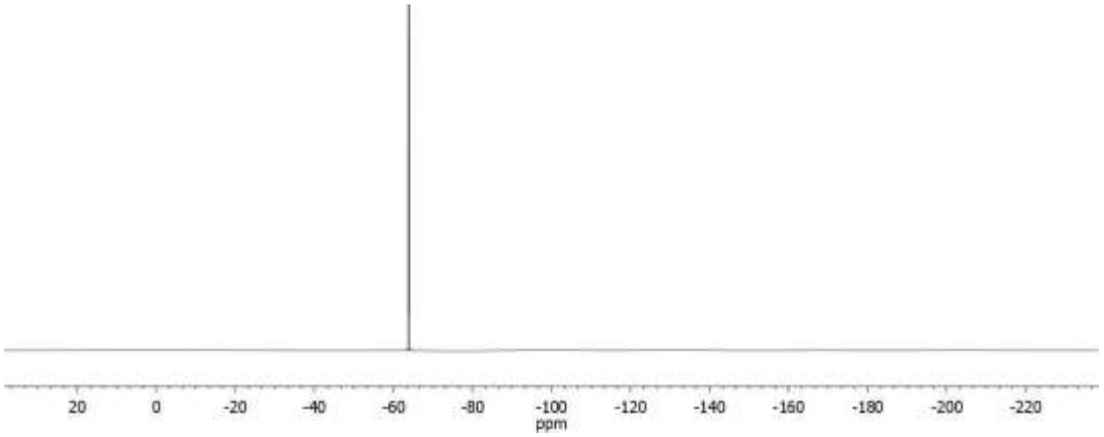
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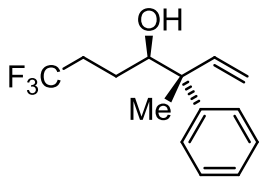
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (3.12f)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (47.5 mg, 92%, >20:1 *dr*) as a yellow oil.

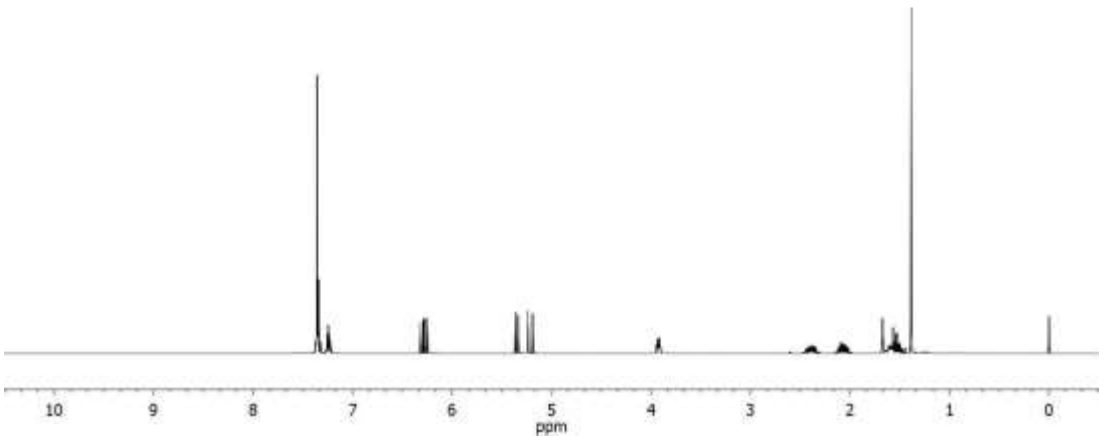
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, J = 17.7, 10.9 Hz, 1H), 5.35 (dd, J = 10.9, 1.1 Hz, 1H), 5.21 (dd, J = 17.7, 1.1 Hz, 1H), 3.93 (dt, J = 10.5, 2.8 Hz, 1H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

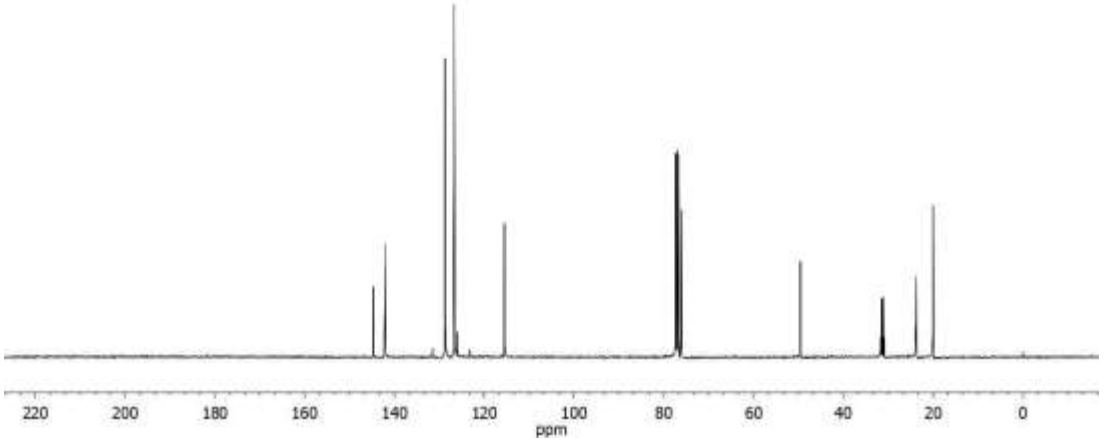
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 142.1, 128.7, 127.4 (q, J = 276.3 Hz), 126.7, 126.7, 115.5, 76.1, 49.5, 31.3 (q, J = 28.6 Hz), 23.8 (d, J = 2.7 Hz), 20.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, J = 11.1 Hz).

HRMS (CI) Calcd. For $C_{14}H_{16}OF_3$ $[M-H]^+$: 257.1153, Found: 257.1157.

FTIR (neat): 3458, 2983, 1638, 1600, 1494, 1446, 1416, 1376, 1280, 1252, 1224, 1132, 1078, 1047, 1017, 922, 838, 764, 742, 700 cm^{-1}.

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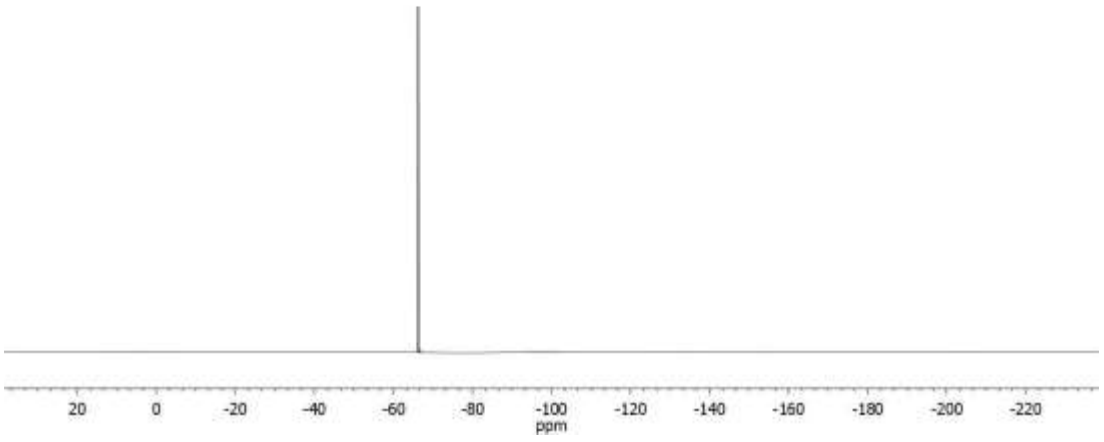
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-140
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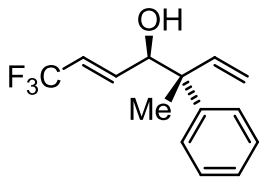
ppm

(*E*)-7,7,7-trifluoro-3-methyl-3-phenylhepta-1,5-dien-4-ol (3.12g)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10a** and THF (2.0 mL, 0.1 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (44.6 mg, 87%, >20:1 *dr*) as a yellow oil.

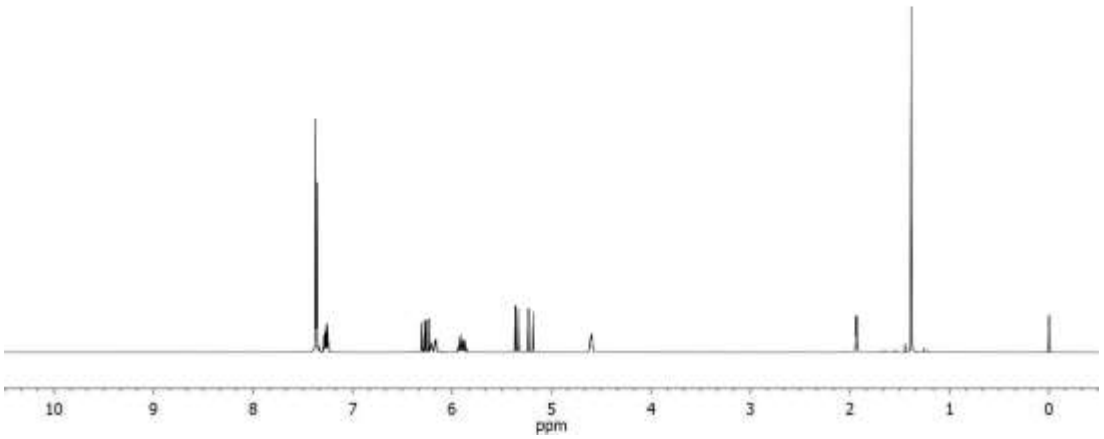
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 4H), 7.30 – 7.23 (m, 1H), 6.27 (dd, J = 17.6, 10.9 Hz, 1H), 6.23 – 6.14 (m, 1H), 5.95 – 5.84 (m, 1H), 5.35 (dd, J = 10.9, 0.9 Hz, 1H), 5.21 (dd, J = 17.6, 0.9 Hz, 1H), 4.64 – 4.57 (m, 1H), 1.95 – 1.91 (m, 1H), 1.38 (s, 3H).

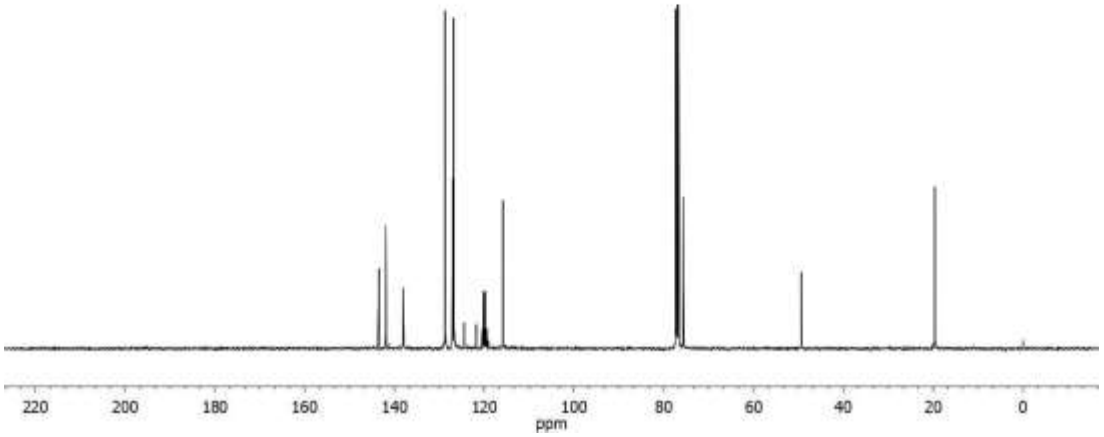
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.9, 138.1 (q, J = 6.3 Hz), 128.7, 127.0, 126.8, 123.1 (q, J = 269.3 Hz), 119.9 (q, J = 33.8 Hz), 115.9, 75.6, 49.4, 19.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.0 – -64.1 (m).

HRMS (CI) Calcd. For $C_{14}H_{16}OF_3$ $[M+H]^+$: 257.1153, Found: 257.1155.

FTIR (neat): 3461, 2980, 1682, 1638, 1600, 1495, 1446, 1415, 1376, 1308, 1265, 1117, 1095, 1030, 976, 924, 868, 763, 735, 700 cm^{-1}.

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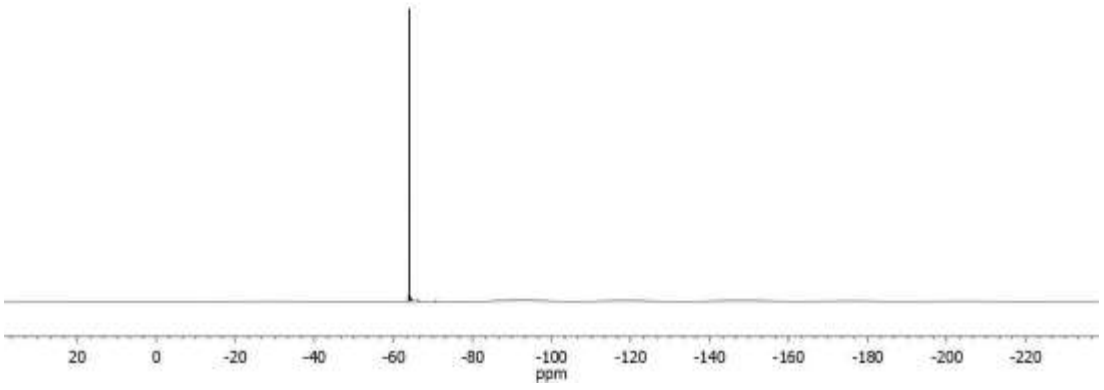
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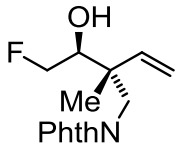
ppm

2-(2-(2-fluoro-1-hydroxyethyl)-2-methylbut-3-en-1-yl)isoindoline-1,3-dione (3.12h)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (32.7 mg, 72%, 4:1 *dr*) as a yellow oil.

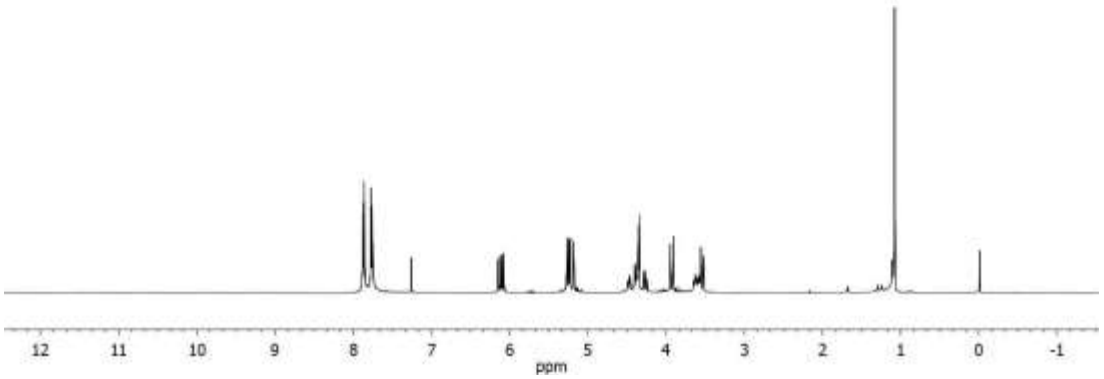
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.3, 3.1 Hz, 2H), 6.11 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 5.20 (d, *J* = 17.8 Hz, 1H), 4.51 – 4.22 (m, 3H), 3.96 – 3.49 (m, 2H), 3.66 – 3.57 (m, 1H), 1.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 138.2, 134.4, 131.6, 123.6, 116.2, 84.4 (d, *J* = 168.6 Hz), 73.1 (d, *J* = 18.4 Hz), 45.3 (d, *J* = 6.4 Hz), 44.6, 18.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -227.0 (td, *J* = 47.3, 18.0 Hz).

HRMS (CI) Calcd. For $C_{15}H_{17}NO_3F$ $[M+H]^+$: 278.1192, Found: 278.1193.

FTIR (neat): 3477, 2979, 1772, 1701, 1612, 1468, 1435, 1393, 1333, 1190, 1172, 1069, 1000, 916, 796, 754, 716, 667 cm^{-1}.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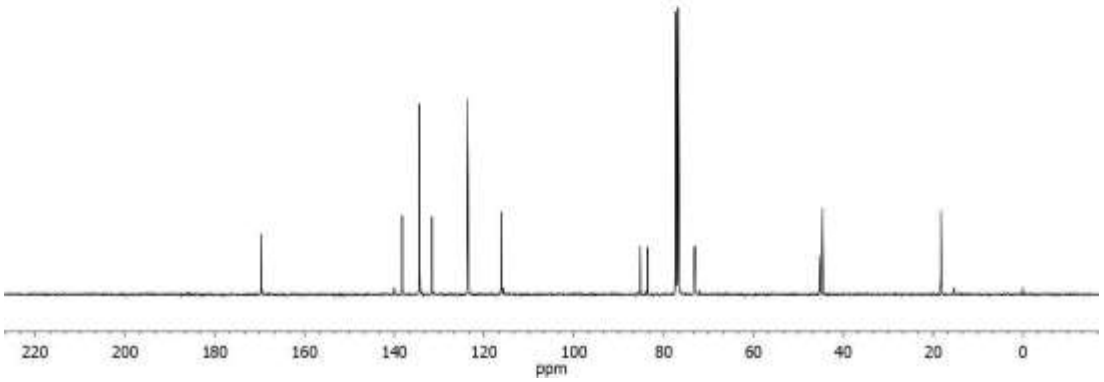
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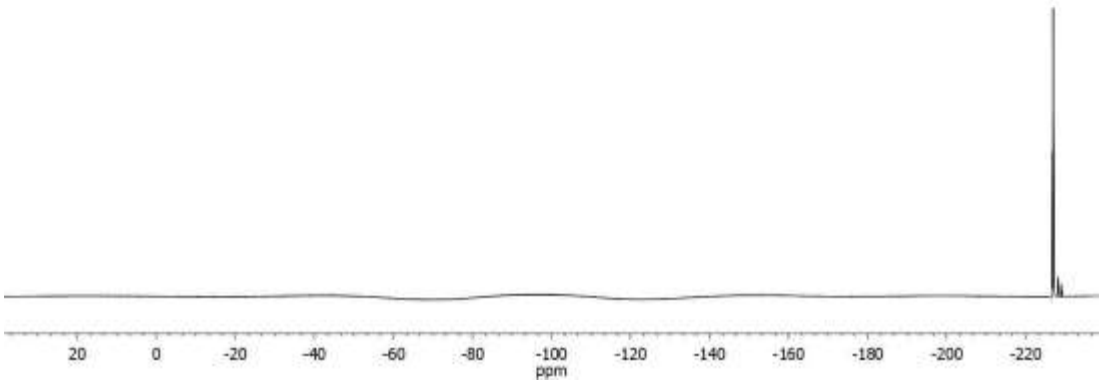
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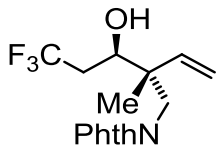
2-(5,5,5-trifluoro-3-hydroxy-2-methyl-2-vinylpentyl)isoindoline-1,3-dione (3.12i)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (42.5 mg, 65%, 5:1 *dr*) as a yellow oil.

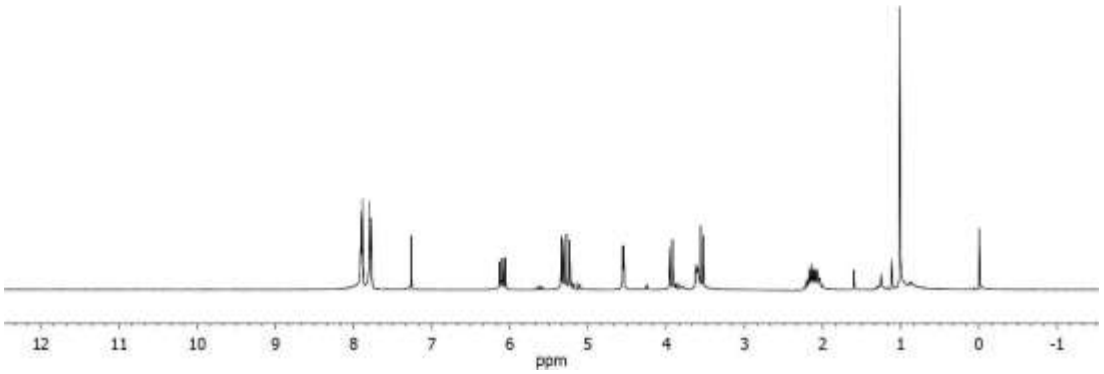
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.10 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.33 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.26 (dd, *J* = 17.7, 1.1 Hz, 1H), 4.54 (dd, *J* = 4.9, 1.3 Hz, 1H), 3.74 (dd, *J* = 156.5, 14.2 Hz, 2H), 3.65 – 3.59 (m, 1H), 2.26 – 1.99 (m, 2H), 1.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 137.8, 134.5, 131.6, 126.8 (q, *J* = 277.0 Hz), 123.8, 117.0, 68.6 (d, *J* = 2.7 Hz), 46.7, 44.1, 36.2 (q, *J* = 27.5 Hz), 18.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.8 Hz).

HRMS (CI) Calcd. For $C_{16}H_{17}NO_3F_3$ $[M+H]^+$: 328.1161, Found: 328.1163.

FTIR (neat): 3470, 2978, 1772, 1702, 1613, 1469, 1434, 1394, 1380, 1350, 1272, 1253, 1213, 1110, 1084, 1010, 947, 922, 903, 877, 842, 796, 759, 722 cm^{-1}.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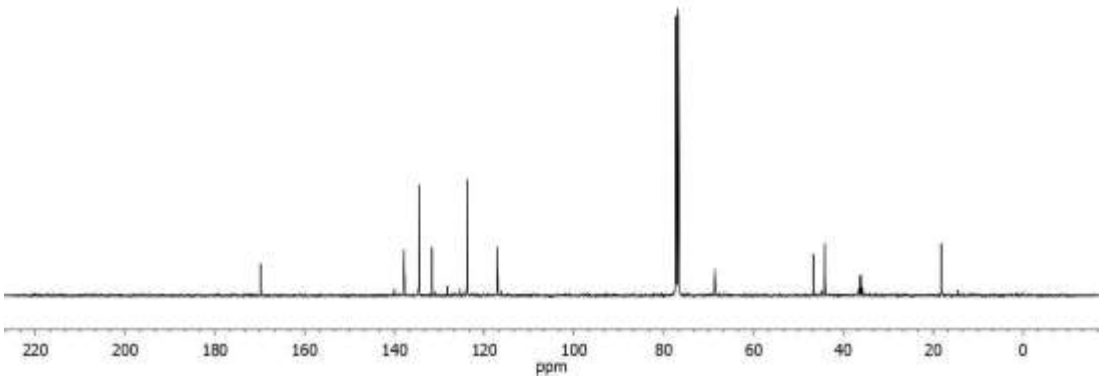
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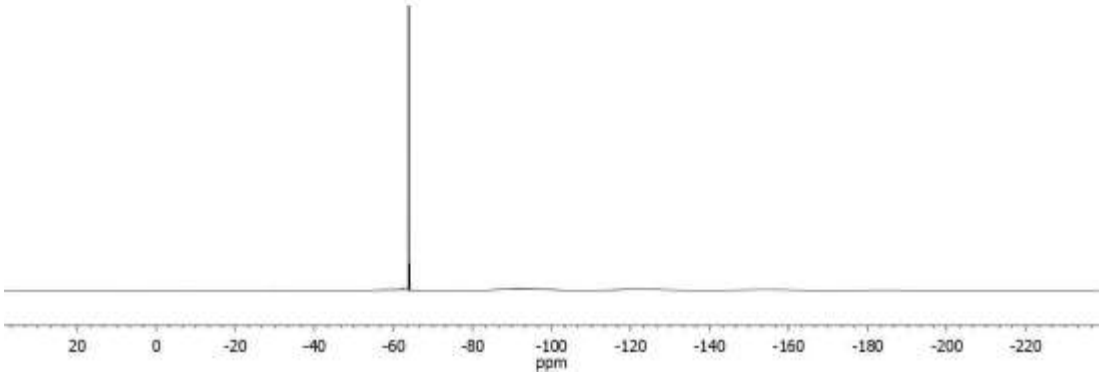
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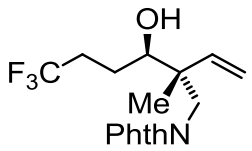
2-(6,6,6-trifluoro-3-hydroxy-2-methyl-2-vinylhexyl)isoindoline-1,3-dione (3.12j)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (58.0 mg, 85%, 5:1 *dr*) as a yellow oil.

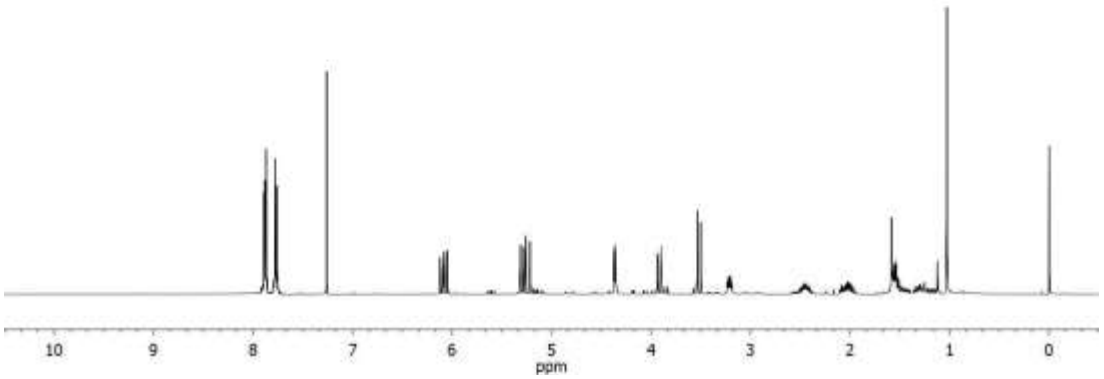
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.08 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.30 (dd, *J* = 11.0, 0.8 Hz, 1H), 5.24 (dd, *J* = 17.7, 1.2 Hz, 1H), 4.36 (dd, *J* = 4.8, 1.6 Hz, 1H), 3.72 (dd, *J* = 160.5, 14.1 Hz, 2H), 3.25 – 3.16 (m, 1H), 2.52 – 2.35 (m, 1H), 2.13 – 1.94 (m, 1H), 1.58 – 1.50 (m, 2H), 1.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 138.6, 134.5, 131.6, 127.5 (q, *J* = 272.1 Hz), 123.7, 116.4, 72.6, 46.8, 44.8, 31.3 (q, *J* = 28.6 Hz), 23.8 (d, *J* = 2.7 Hz), 18.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, *J* = 11.1 Hz).

HRMS (CI) Calcd. For $C_{17}H_{19}NO_3F_3$ $[M+H]^+$: 342.1317, Found: 342.1319.

FTIR (neat): 3470, 2918, 1910, 1772, 1702, 1613, 1469, 1452, 1436, 1393, 1333, 1289, 1252, 1228, 1190, 1128, 1084, 1018, 927, 850, 795, 756, 721, 684 cm^{-1}.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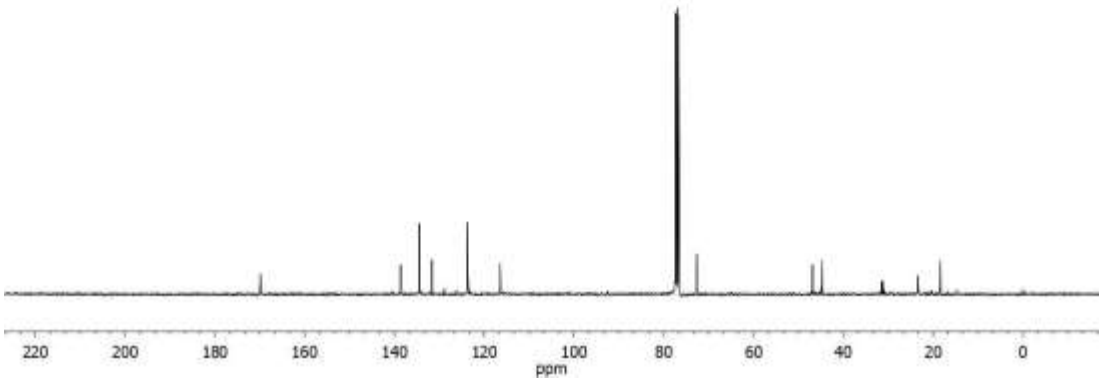
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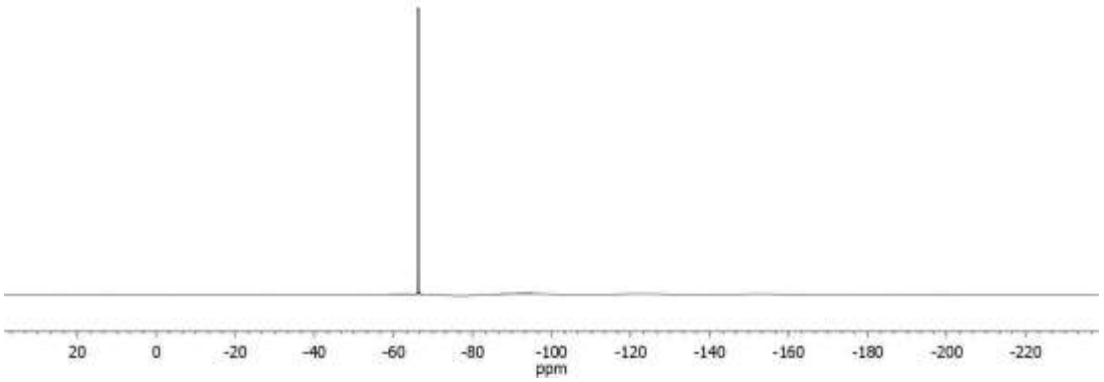
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-80
-100
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-140
-160
-180
-200
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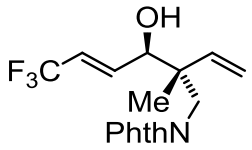
ppm

(*E*)-2-(6,6,6-trifluoro-3-hydroxy-2-methyl-2-vinylhex-4-en-1-yl)isoindoline-1,3-dione (3.12k)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10b** and THF (2.0 mL, 0.1 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (59.0 mg, 87%, 6:1 *dr*) as a yellow oil.

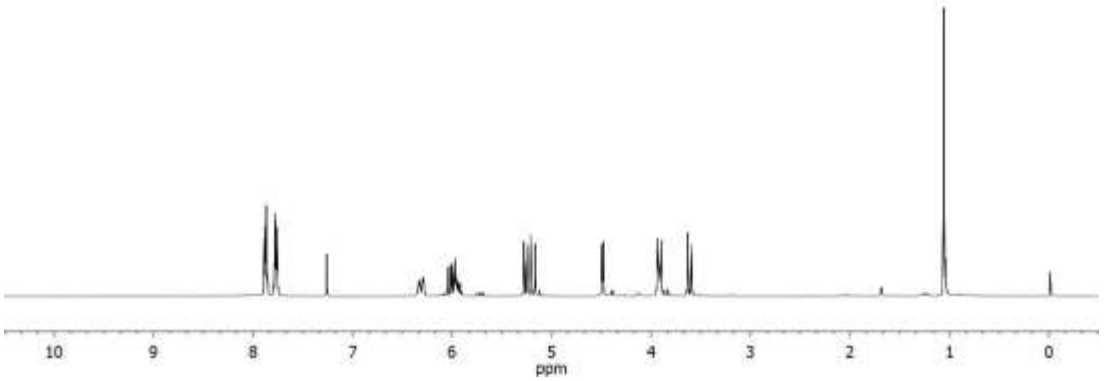
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.36 – 6.26 (m, 1H), 6.01 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.98 – 5.88 (m, 1H), 5.26 (d, *J* = 11.0 Hz, 1H), 5.19 (d, *J* = 17.7 Hz, 1H), 4.49 (d, *J* = 5.0 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.76 (dd, *J* = 122.3, 14.2 Hz, 2H), 1.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 138.1, 137.6 (q, *J* = 6.3 Hz), 134.5, 131.6, 123.7, 123.1 (q, *J* = 269.3 Hz), 120.1 (q, *J* = 33.7 Hz), 116.6, 72.7, 46.6, 44.3, 18.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.0 – -64.1 (m).

HRMS (CI) Calcd. For $C_{17}H_{17}NO_3F_3$ $[M+H]^+$: 340.1161, Found: 340.1159.

FTIR (neat): 3465, 2981, 1772, 1701, 1613, 1469, 1435, 1417, 1393, 1325, 1268, 1190, 1115, 1093, 1018, 963, 946, 920, 895, 868, 795, 721 cm^{-1}.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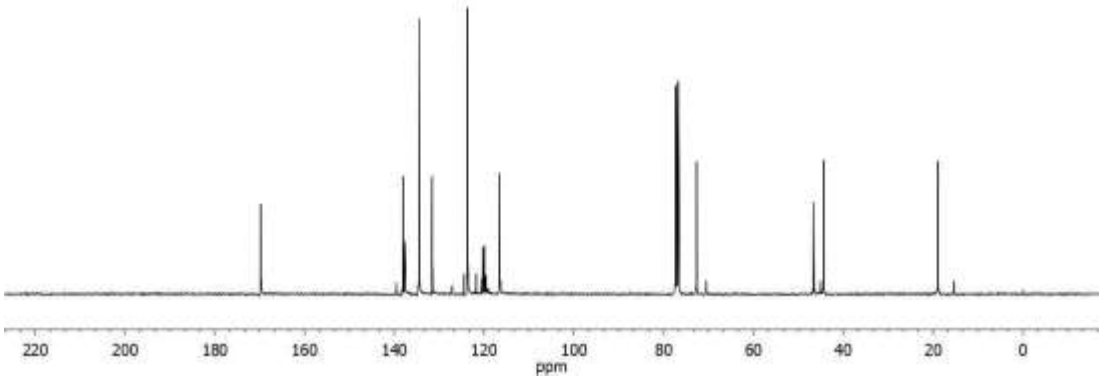
ppm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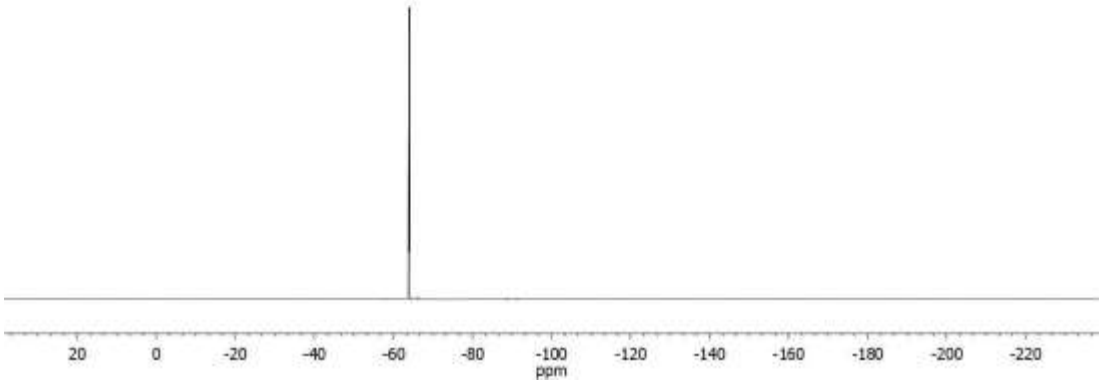
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-80
-100
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-120
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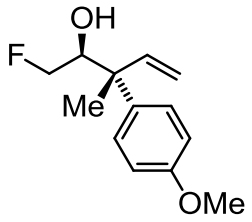
-220

1-fluoro-3-(4-methoxyphenyl)-3-methylpent-4-en-2-ol (3.12l)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (26.9 mg, 60%, >20:1 *dr*) as a yellow oil.

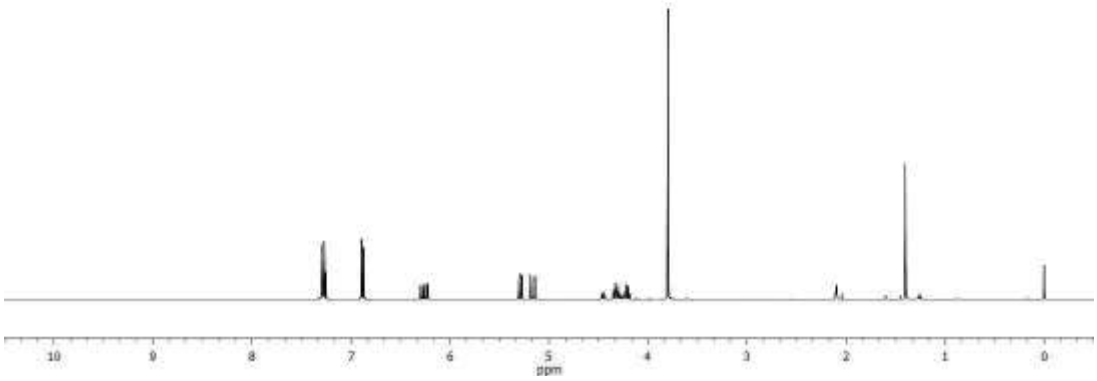
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 6.91 – 6.85 (m, 2H), 6.26 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.29 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.16 (dd, *J* = 17.7, 1.1 Hz, 1H), 4.48 – 4.17 (m, 3H), 3.80 (s, 3H), 2.10 (s, 1H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 142.3, 135.0, 127.8, 114.7, 113.9, 85.1 (d, *J* = 166.3 Hz), 75.7 (d, *J* = 17.6 Hz), 55.2, 46.9 (d, *J* = 6.9 Hz), 20.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -228.5 – -229.1 (m).

HRMS (ESI) Calcd. For $C_{13}H_{17}FO_2$ $[M+Na]^+$: 247.1150, Found: 247.1110.

FTIR (neat): 3478, 2966, 2835, 2360, 1635, 1609, 1579, 1511, 1463, 1414, 1374, 1294, 1248, 1183, 1095, 1057, 1031, 1008, 910, 829, 794, 731 cm^{-1}.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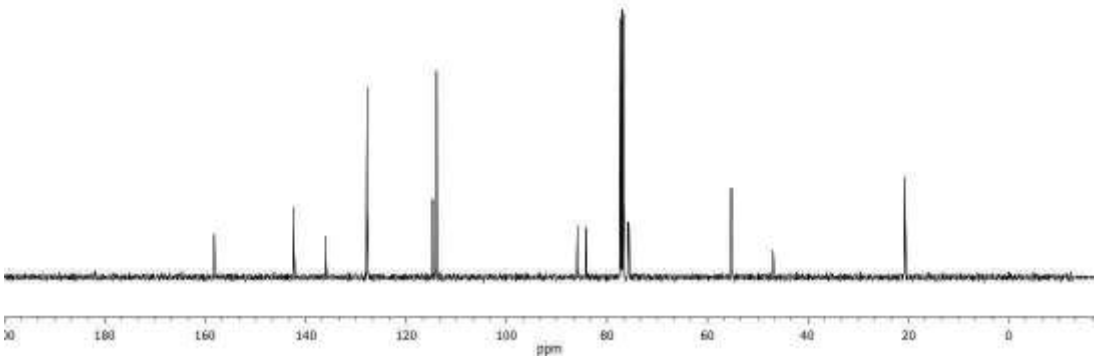
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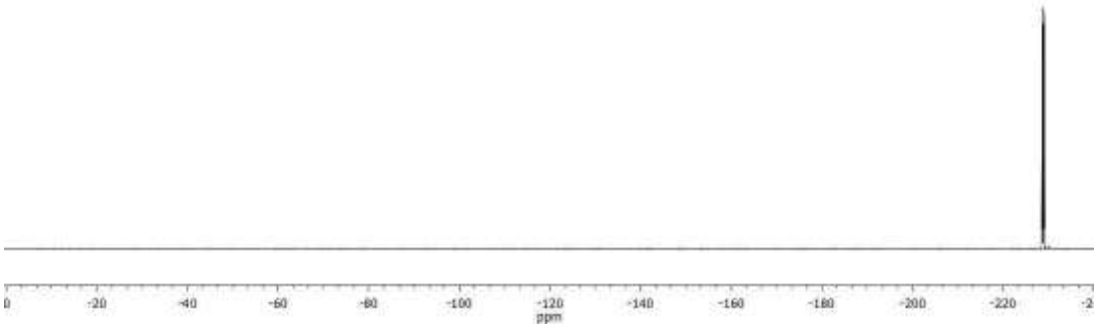
ppm


0
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-100
-120
ppm
-140
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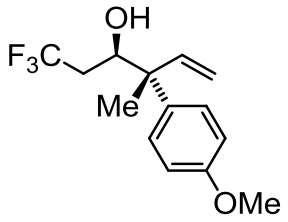
-180
-200
-220
-2

1,1,1-trifluoro-4-(4-methoxyphenyl)-4-methylhex-5-en-3-ol (3.12m)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (47.7 mg, 86%, >20:1 *dr*) as a yellow oil.

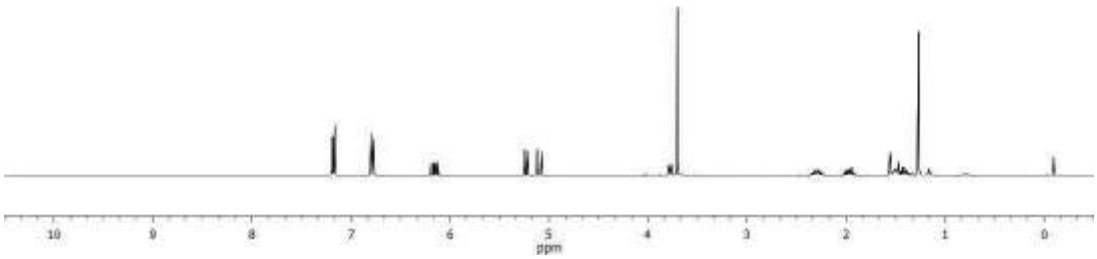
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.25 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.33 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.19 (dd, *J* = 17.7, 1.1 Hz, 1H), 4.35 – 4.27 (m, 1H), 3.80 (s, 3H), 2.17 – 2.02 (m, 2H), 1.90 – 1.86 (m, 1H), 1.27 (s, 3H).

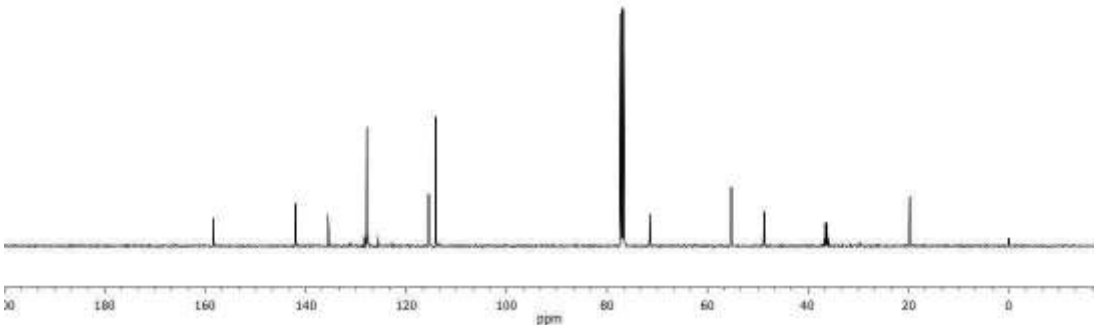
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 142.0, 136.0, 126.9 (q, *J* = 277.2 Hz), 115.5, 114.1, 71.5 (d, *J* = 2.4 Hz), 55.2, 48.7, 36.4 (q, *J* = 27.4 Hz), 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.6 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{14}H_{17}F_3O_2$ $[M+Na]^+$: 297.1073, Found: 297.1071.

FTIR (neat): 3538, 2977, 1609, 1512, 1464, 1412, 1376, 1328, 1292, 1250, 1182, 1122, 1032, 907, 876, 829, 794, 729 cm^{-1}.

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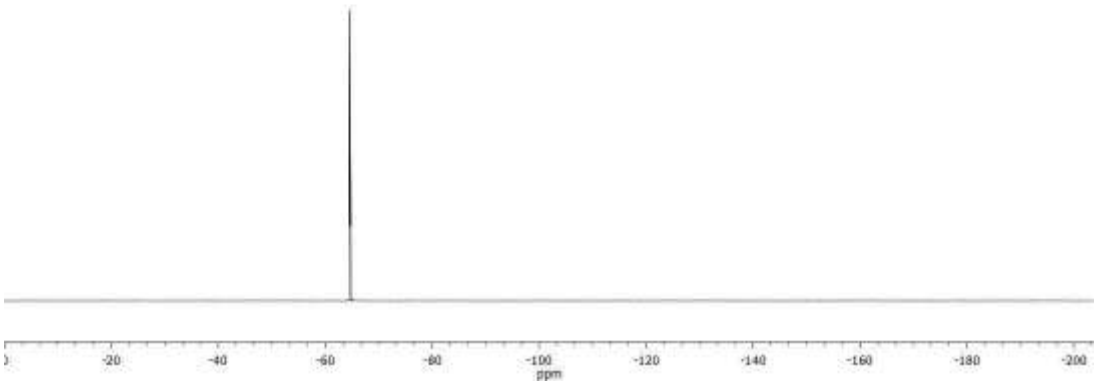
20
0
ppm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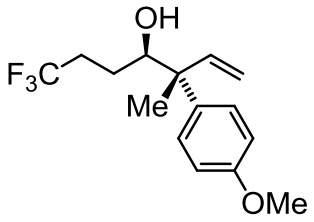
-200
ppm

7,7,7-trifluoro-3-(4-methoxyphenyl)-3-methylhept-1-en-4-ol (3.12n)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (50.7 mg, 88%, >20:1 *dr*) as a yellow oil.

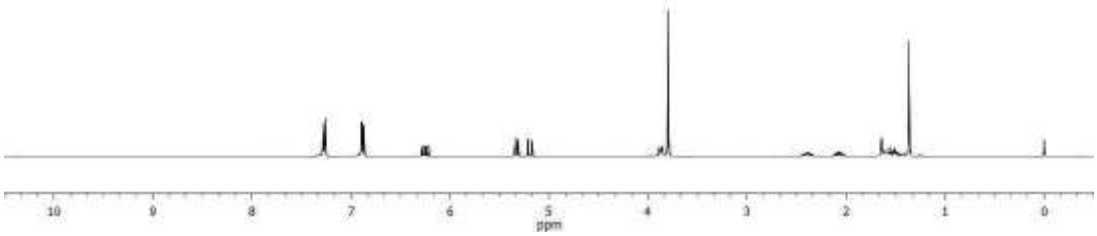
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.25 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.33 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.19 (dd, *J* = 17.7, 1.1 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.80 (s, 3H), 2.53 – 2.31 (m, 1H), 2.18 – 1.92 (m, 1H), 1.69 – 1.41 (m, 3H), 1.37 (s, 3H).

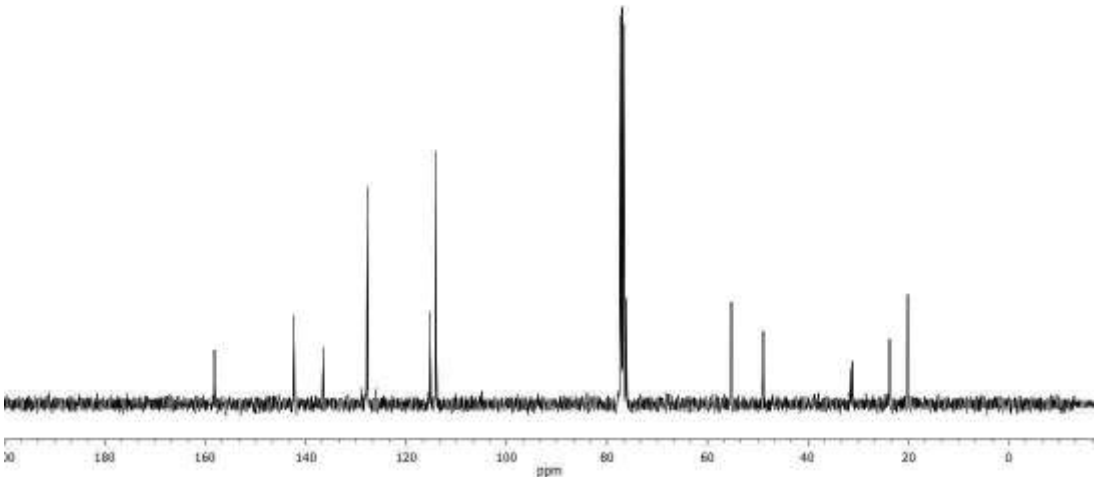
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 142.3, 136.5, 127.7, 127.4 (q, *J* = 276.1 Hz), 115.2, 114.0, 76.2, 55.2, 48.9, 31.3 (q, *J* = 28.6 Hz), 23.8 (d, *J* = 2.7 Hz), 20.1 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{15}H_{19}F_3O_2$ $[M+Na]^+$: 311.1229, Found: 311.1229.

FTIR (neat): 3546, 2985, 1585, 1561, 1416, 1380, 1287, 1253, 1220, 1136, 1093, 1048, 1017, 907, 858, 799, 730, 693 cm^{-1}.

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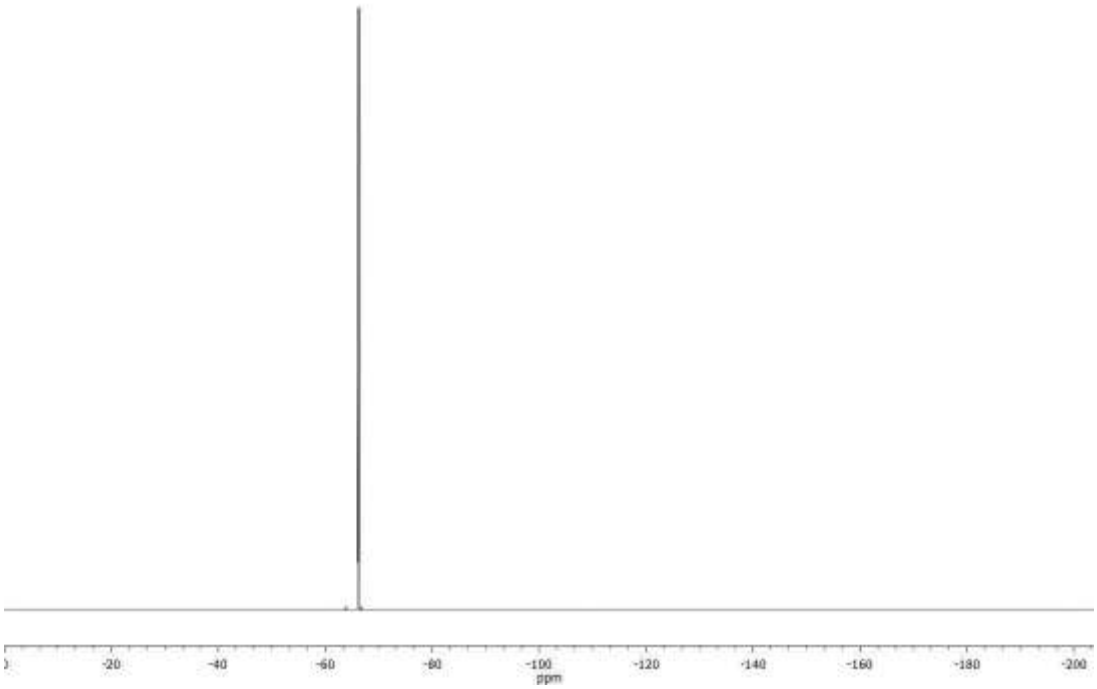
ppm


-20
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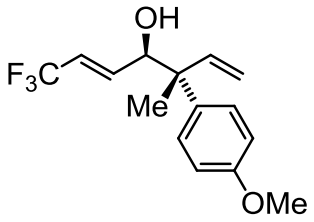
-140
-160
-180
-200
ppm

(*E*)-7,7,7-trifluoro-3-(4-methoxyphenyl)-3-methylhepta-1,5-dien-4-ol (3.12o)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10c** and THF (2.0 mL, 0.1 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (38.9 mg, 68%, >20:1 *dr*) as a yellow oil.

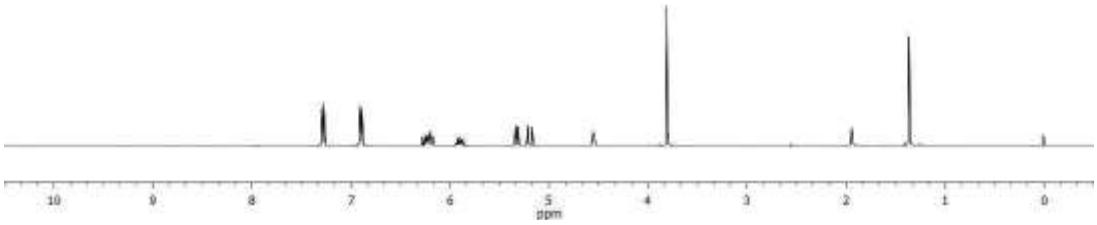
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 9.3 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.32 – 6.12 (m, 2H), 5.96 – 5.83 (m, 1H), 5.33 (d, J = 10.9 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 4.55 (s, 1H), 3.81 (s, 3H), 1.94 (s, 1H), 1.37 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 142.2, 138.2 (q, *J* = 6.2 Hz), 135.3, 127.9, 123.0 (q, *J* = 269.4 Hz), 119.8 (q, *J* = 33.9 Hz), 115.5, 75.7, 55.3, 48.8, 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0 – -65.0 (m).

HRMS (ESI) Calcd. For $C_{15}H_{17}F_3O_2$ $[M+Na]^+$: 309.1073, Found: 309.1071.

FTIR (neat): 3565, 2837, 1609, 1511, 1465, 1290, 1251, 1184, 1114, 1092, 1069, 1031, 979, 908, 829, 790, 732, 674 cm^{-1}.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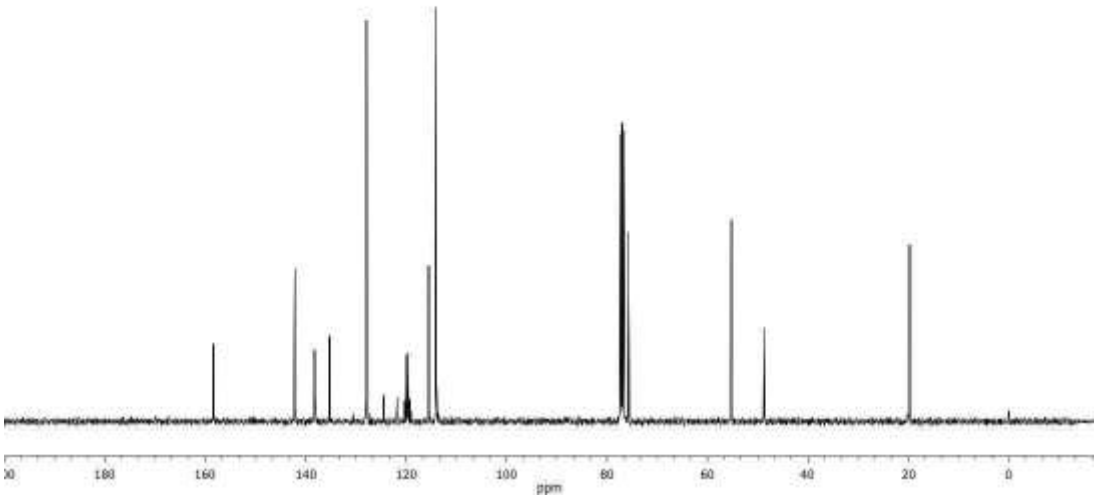
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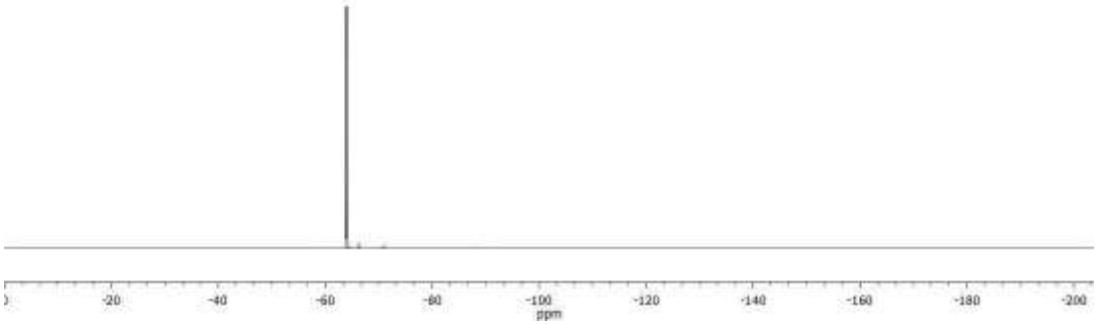
ppm


-20
-40
-60
-80
-100
ppm
-120
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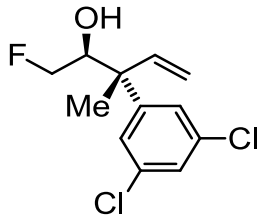
3-(3,5-dichlorophenyl)-1-fluoro-3-methylpent-4-en-2-ol (3.12p)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (34.2 mg, 65%, >20:1 *dr*) as a yellow oil.

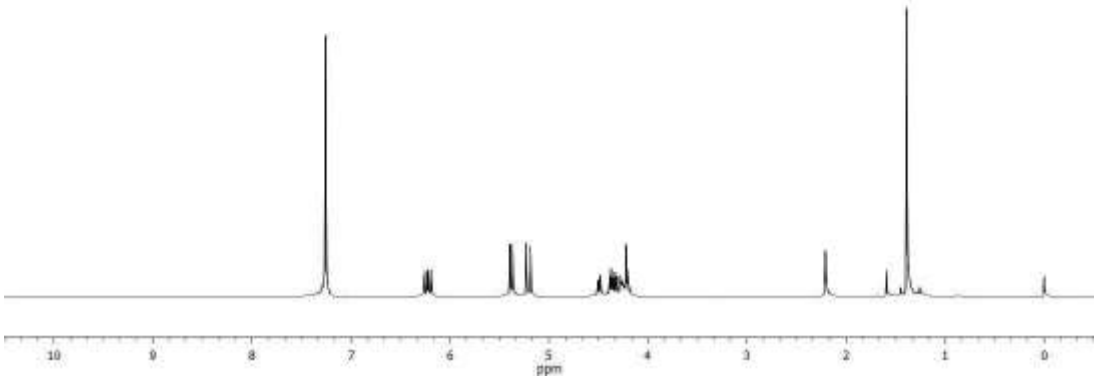
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 3H), 6.22 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.38 (d, *J* = 10.9 Hz, 1H), 5.21 (d, *J* = 17.7 Hz, 1H), 4.54 – 4.11 (m, 3H), 2.21 (d, J = 2.1 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.29, 140.4, 135.1, 127.0, 125.6, 116.3, 84.7 (d, *J* = 166.8 Hz), 75.2 (d, *J* = 18.2 Hz), 47.6 (d, *J* = 6.6 Hz), 21.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -229.0 (td, *J* = 49.6, 15.6 Hz).

HRMS (CI) Calcd. For $C_{12}H_{14}Cl_2FO$ $[M+H]^+$: 263.0406, Found: 263.0407.

FTIR (neat): 3600, 2981, 1585, 1416, 1414, 1374, 1294, 1248, 1183, 1070, 1066, 1057, 1031, 1008, 916, 833, 794, 731 cm^{-1}.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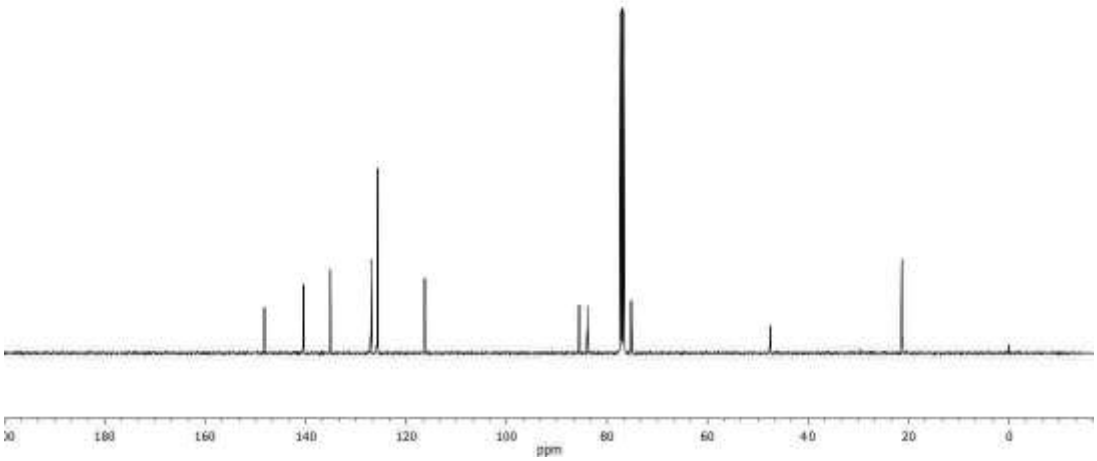
0
ppm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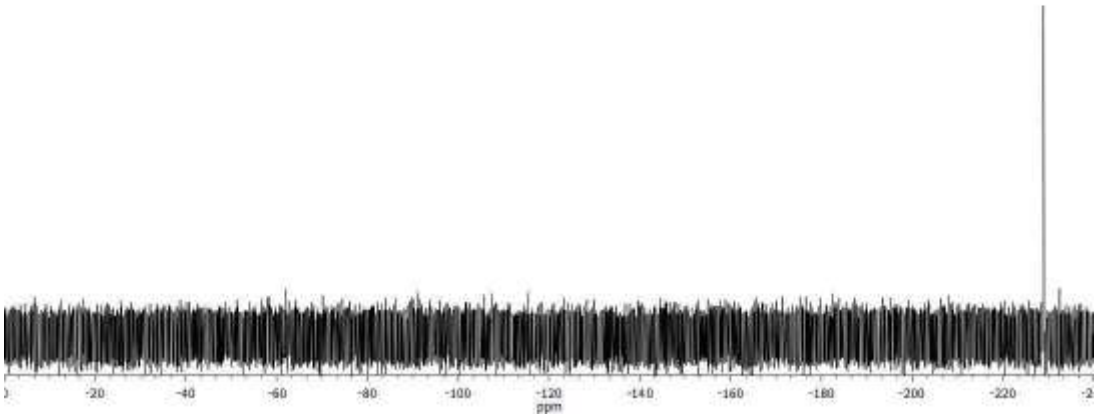
0
ppm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-40
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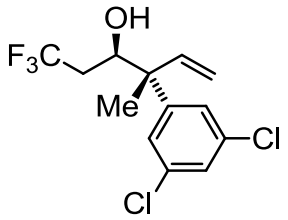
ppm
-140
-160
-180
-200
-220

4-(3,5-dichlorophenyl)-1,1,1-trifluoro-4-methylhex-5-en-3-ol (3.12q)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (53.2 mg, 85%, >20:1 *dr*) as a yellow oil.

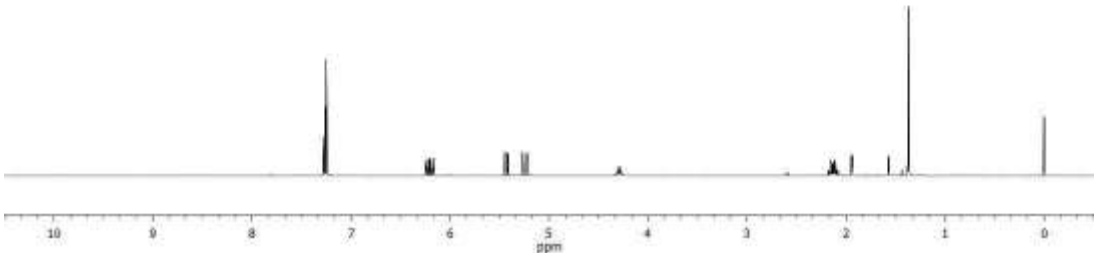
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 3H), 6.20 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.43 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.24 (dd, *J* = 17.7, 0.7 Hz, 1H), 4.34 – 4.20 (m, 1H), 2.21 – 2.06 (m, 2H), 1.95 (d, *J* = 3.5 Hz, 1H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 140.4, 135.3, 127.2, 126.9 (q, *J* = 277.2 Hz), 125.7, 117.1, 71.3 (d, *J* = 2.5 Hz), 49.5, 36.7 (q, *J* = 27.3 Hz), 20.6

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.8 (t, *J* = 10.8 Hz).

HRMS (CI) Calcd. For $C_{13}H_{13}Cl_2F_3O$ $[M]^+$: 312.0296, Found: 312.0300.

FTIR (neat): 3515, 2923, 2360, 2342, 1585, 1561, 1415, 1382, 1325, 1255, 1120, 1008, 929, 907, 875, 857, 842, 799, 732, 691 cm^{-1}.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4
3
2
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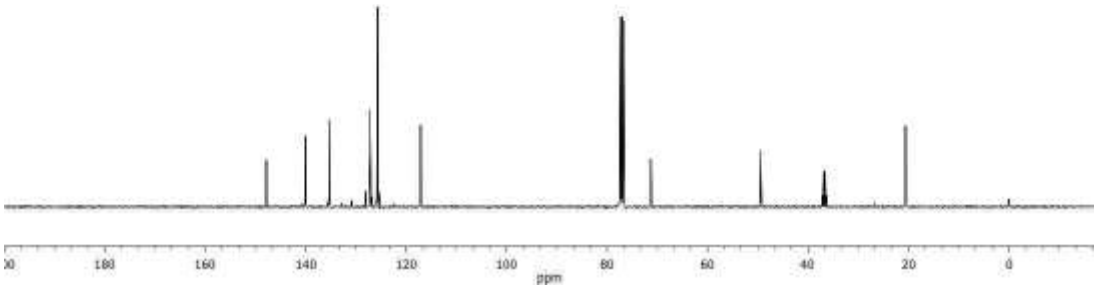
0
ppm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80
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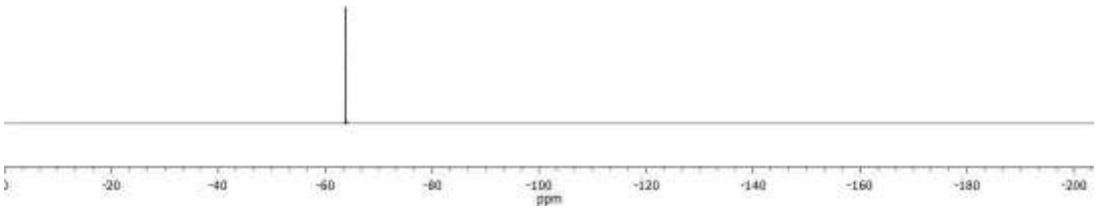
ppm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-40
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-100
ppm
-120
-140
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-180
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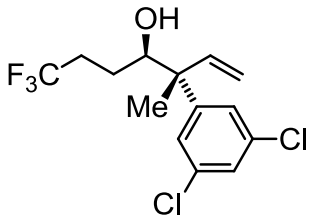
3-(3,5-dichlorophenyl)-7,7,7-trifluoro-3-methylhept-1-en-4-ol (3.12r)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (58.2 mg, 89%, >20:1 *dr*) as a yellow oil.

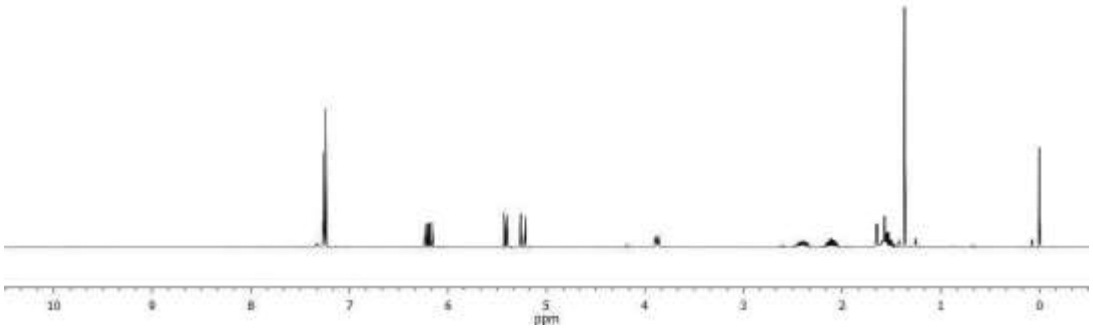
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 3H), 6.19 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.40 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.24 (dd, *J* = 17.6, 0.7 Hz, 1H), 3.88 (dt, *J* = 10.4, 3.2 Hz, 1H), 2.50 – 2.30 (m, 1H), 2.21 – 2.02 (m, 1H), 1.67 – 1.46 (m, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 140.7, 135.3, 127.3 (q, *J* = 276.1), 127.0, 125.6, 116.8, 75.9, 49.8, 31.1 (q, *J* = 28.6 Hz), 23.9, 20.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -65.9 (t, *J* = 11.0 Hz).

HRMS (CI) Calcd. For $C_{14}H_{15}Cl_2F_3O$ $[M]^+$: 326.0452, Found: 326.0426.

FTIR (neat): 3541, 2985, 1585, 1561, 1416, 1380, 1287, 1253, 1220, 1136, 1093, 1048, 1017, 907, 858, 799, 730, 693 cm^{-1}.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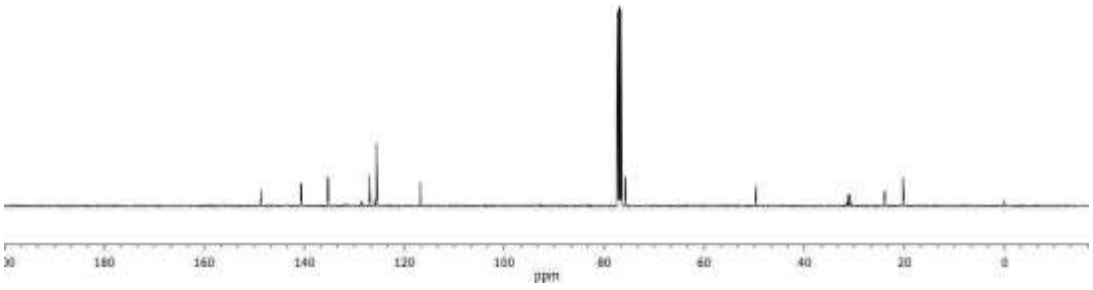
0
ppm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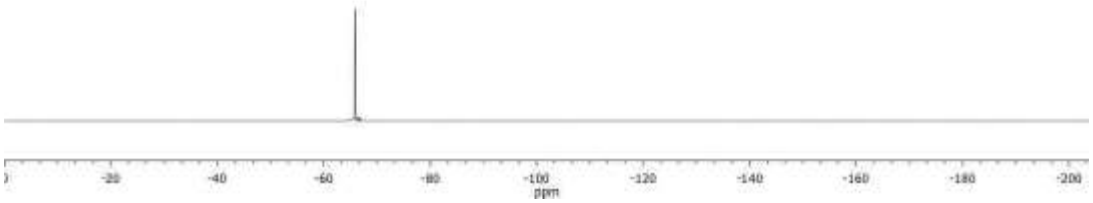
ppm


-20
-40
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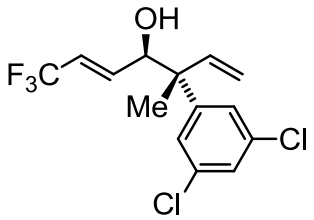
-80
-100
ppm
-120
-140
-160
-180
-200

(*E*)-3-(3,5-dichlorophenyl)-7,7,7-trifluoro-3-methylhepta-1,5-dien-4-ol (3.12s)



The reaction was conducted in accordance with **General Procedure A** *via* allene **3.10d** and THF (4 mL, 0.05 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (52.0 mg, 80%, >20:1 *dr*) as a yellow oil.

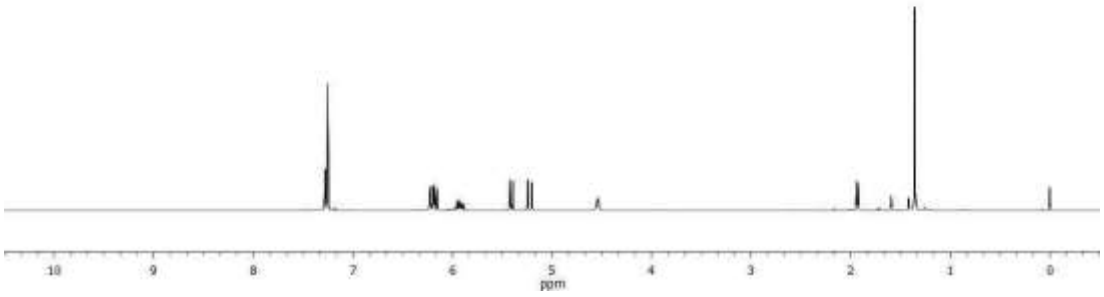
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 3H), 6.27 – 6.11 (m, 2H), 5.98 – 5.86 (m, 1H), 5.40 (dd, J = 10.8, 0.6 Hz, 1H), 5.23 (dd, J = 17.6, 0.6 Hz, 1H), 4.58 – 4.48 (m, 1H), 1.93 (d, J = 4.2 Hz, 1H), 1.36 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.9, 138.1 (q, J = 6.3 Hz), 128.7, 127.0, 126.8, 123.1 (q, J = 269.3 Hz), 120.8 (q, J = 34.0 Hz), 115.9, 75.6, 49.4, 19.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.1 – -64.2 (m).

HRMS (CI) Calcd. For $C_{14}H_{14}Cl_2F_3O$ $[M+H]^+$: 325.0374, Found: 325.0374.

FTIR (neat): 3469, 2982, 1682, 1585, 1561, 1416, 1383, 1312, 1265, 1123, 975, 931, 906, 858, 799, 730, 691 cm^{-1}.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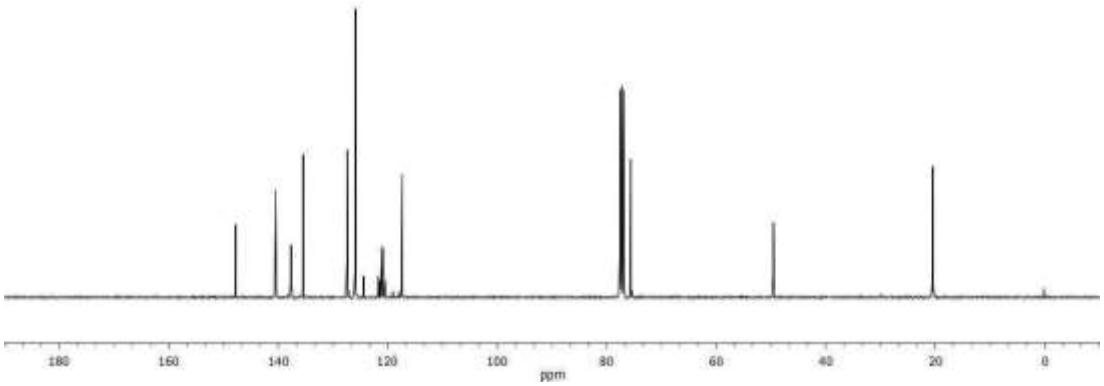
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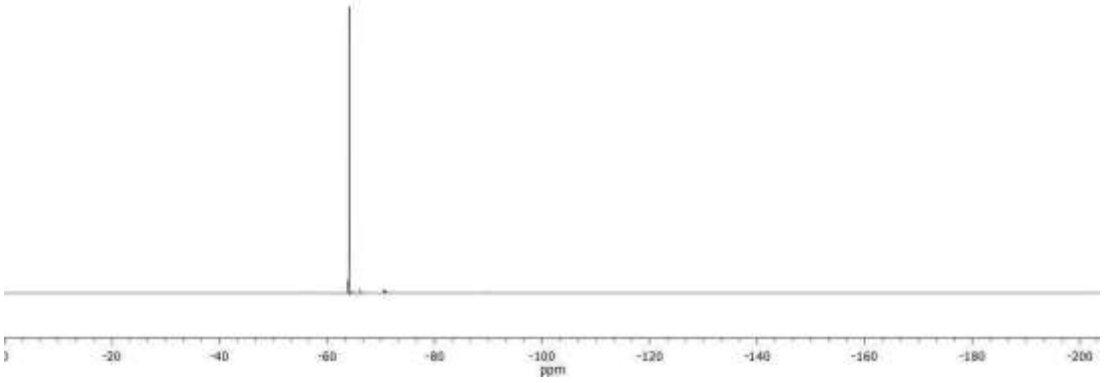
ppm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ppm
-120
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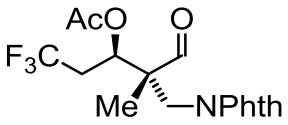
-160
-180
-200

Experimental Procedure and Spectral Data for Preparation of β-amino ester 3.14i

5-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluoro-4-formyl-4-methylpentan-3-yl acetate (3.13i)



In modification to literature procedure,[44] to a flame-dried 50 mL round-bottom flask charged with alcohol **3.12i** (130 mg, 0.400 mmol, 100 mol%) and CH_2Cl_2 (0.8 mL, 0.5 M) was added triethylamine (80 mg, 0.800 mmol, 200 mol%), *N,N*-dimethylaminopyridine (4.9 mg, 0.040 mmol, 10 mol%) and acetic anhydride (60 mg, 0.600 mmol, 150 mol%) at ambient temperature. After stirring for 2 hours, the reaction was quenched with pH 7 phosphate buffer (15 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; 10% EtOAc/hexane) to provide the corresponding acetate (140 mg, 0.380 mmol, 95%) as a colorless oil, which was immediately subjected to ozonolysis.

In modification to literature procedure,[45] the acetate was dissolved in CH_2Cl_2 (15 mL, 0.03 M) and cooled to -78 °C. O_3 was directed into the solution until it turned deep blue. The resulting solution was purged with argon to remove the excess of O_3. Triphenylphosphine (189 mg, 1.90 mmol, 500 mol%) was added and the solution was allowed to warm up to room temperature with stirring over 4 hours. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2; 20% EtOAc/hexane) to afford the title compound (109 mg, 78%) as a colorless oil.

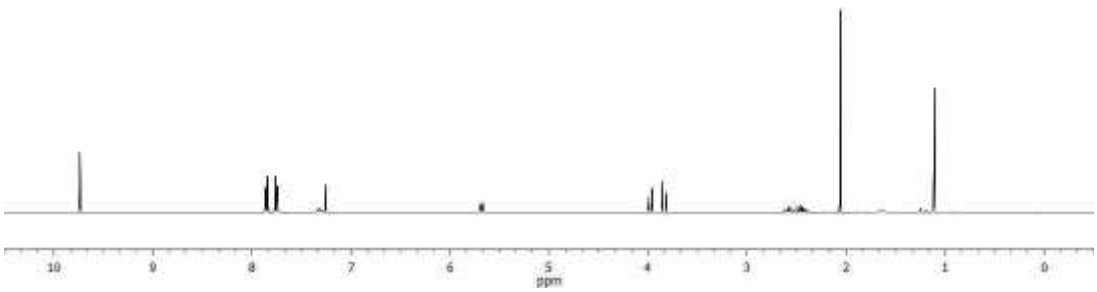
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.89 – 7.80 (m, 2H), 7.76 – 7.72 (m, 2H), 5.68 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.91 (dd, *J* = 55.3, 14.4 Hz, 2H), 2.63 – 2.37 (m, 2H), 2.06 (s, 3H), 1.11 (s, 3H).

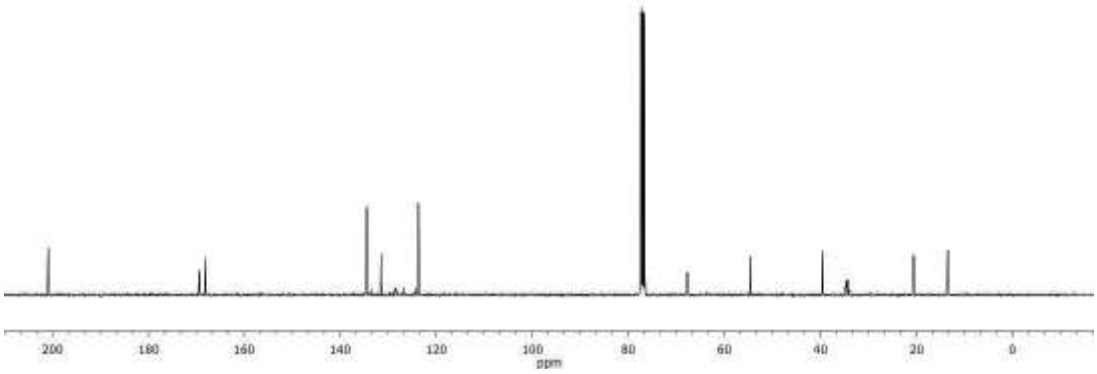
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 169.4, 168.2, 134.5, 131.5, 125.6 (q, *J* = 271.1 Hz), 123.7, 67.7 (d, *J* = 2.7 Hz), 54.7, 39.7, 34.4 (q, *J* = 29.0 Hz), 20.6, 13.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{17}H_{16}F_3NO_5$ $[M+Na]^+$: 394.0873, Found: 394.0877.

FTIR (neat): 3472, 2977, 1772, 1702, 1468, 1434, 1393, 1379, 1349, 1333, 1272, 1252, 1212, 1128, 1110, 946, 904, 904, 877, 841, 795, 721, 685 cm^{-1}.

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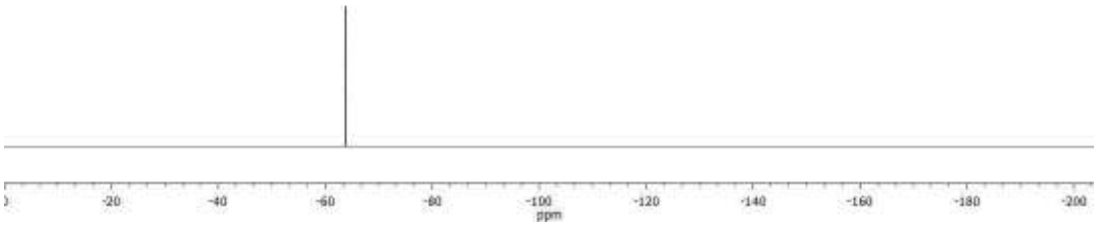
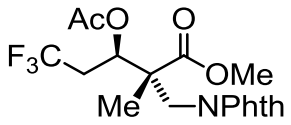

-20
-40
-60
-80
-100
ppm
-120
-140
-160
-180
-200

Methyl 3-acetoxy-2-((1,3-dioxoisoindolin-2-yl)methyl)-5,5,5-trifluoro-2-methylpentanoate (3.14i)



In modification to literature procedure,[10] a flamed-dried 50 mL round-bottom flask was charged with aldehyde **4i** (109 mg, 0.300 mmol, 100 mol%), THF (3 mL), and *t*-BuOH (3 mL). To this stirring solution was added 2.0 M 2-methyl-2-butene in THF (4.5 mL, 9.00 mmol, 3000 mol%), then an aqueous solution comprised of $NaClO_2$ (136 mg, 1.50 mmol, 500 mol%) and NaH_2PO_4 (207 mg, 0.057 mmol, 500 mol%) in H_2O (0.5 mL). The reaction was stirred at room temperature at ambient temperature for 4 hours, and then diluted with ethyl acetate (5 mL) and poured into brine (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was carried onto the next step without further purification.

To a solution of crude residue in CH_2Cl_2 (1.5 mL) and MeOH (1 mL) was added 2.0 M Me_3SiCHN_2 in hexanes (0.23 mL, 0.450 mmol, 150 mol%) at ambient temperature. After stirring for 10 minutes, the mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 30% EtOAc/hexane) to afford the title compound (88.6 mg, 85% over two steps) as a white oil.

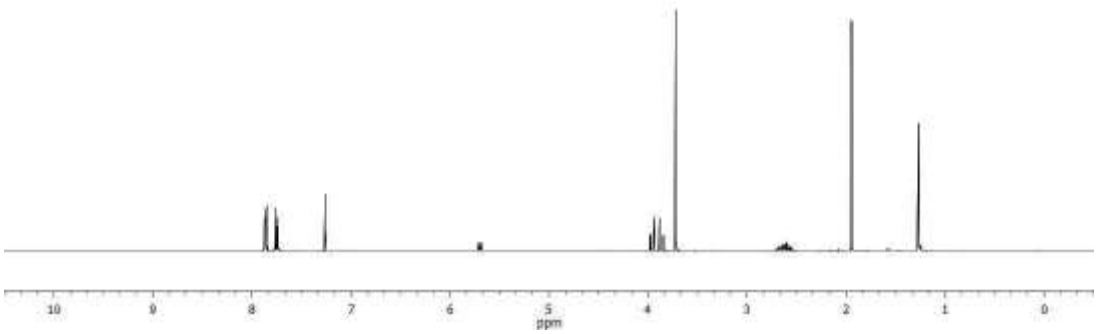
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 2H), 7.76 – 7.73 (m, 2H), 5.70 (dd, *J* = 10.0, 1.4 Hz, 1H), 3.91 (dd, *J* = 37.3, 14.4 Hz, 2H), 3.72 (s, 3H), 2.75 – 2.49 (m, 2H), 1.94 (s, 3H), 1.27 (s, 3H).

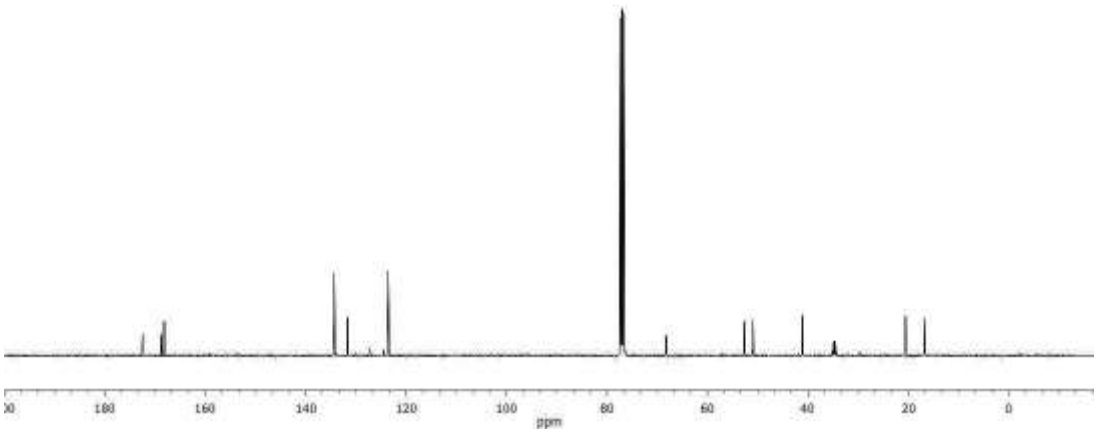
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.78, 168.1, 134.3, 131.7, 125.6 (q, *J* = 269.8 Hz), 123.6, 68.2 (d, *J* = 2.6 Hz), 52.7, 50.9, 41.1, 34.7 (q, *J* = 29.0 Hz), 20.6, 16.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.3 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{18}H_{18}F_3NO_6$ $[M+Na]^+$: 424.0978, Found: 424.0980.

FTIR (neat): 3467, 2954, 2253, 1772, 1704, 1469, 1436, 1394, 1379, 1349, 1273, 1253, 1131, 1084, 1010, 905, 841, 722 cm^{-1}.

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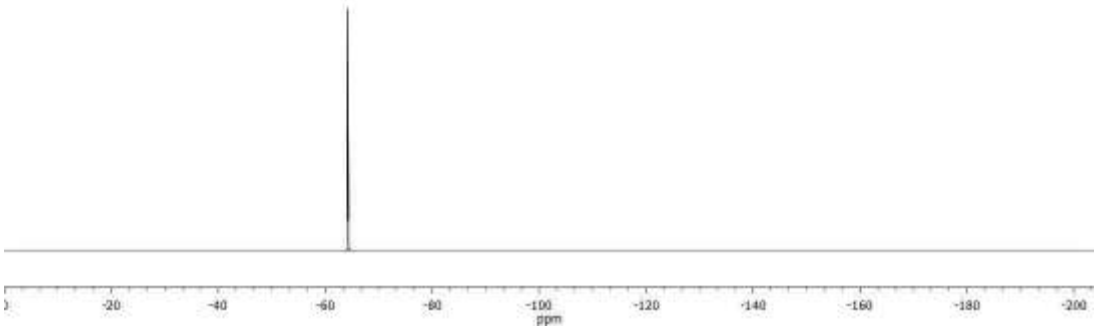
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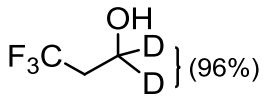
Experimental Procedures and Spectral Data for the Preparation of *deuterio*-Alcohols

1,1,-dideuterio-3,3,3-trifluoropropan-1-ol (*deuterio*-**3.11e**)



In modification to literature procedure,[46] a 50 mL round-bottom flask was charged with 5% ruthenium on carbon (2.6 g, 100 wt%), 3,3,3-trifluoropropan-1-ol (2 mL, 22 mmol, 100 mol%), and deuterium oxide (22 mL, 1.0 M). Under 1 atm of hydrogen gas, the reaction mixture was allowed to stir for 24 hours at 80 °C and then cooled to ambient temperature. The reaction mixture was filtered over a pad of Celite topped with sand. The filtrate was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O (15 mL), brine (15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was then re-subjected to the above conditions, furnishing the title compound (1.1 g, 43%) as a yellow oil. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in ^{1}H NMR (400 MHz, $CDCl_3$) and ^{2}H NMR (77 MHz, $CHCl_3$) and HRMS of the corresponding tosylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (t, J = 6.2 Hz, 0.08H), 2.38 (q, J = 10.8 Hz, 2H), 1.90 (s, 1H).

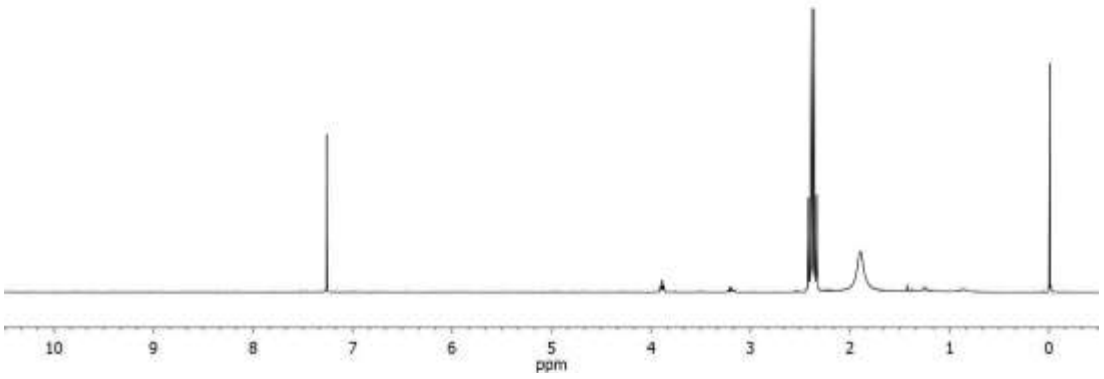
^{2}H NMR (77 MHz, $CDCl_3$): δ 3.88 (s, 1.92H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 126.4 (q, J = 276.3 Hz), 55.5 (t, J = 22.3 Hz), 36.5 (q, J = 27.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.6 (t, J = 10.9 Hz).

LRMS (EI): m/z 33 $[M\text{-}CH_2CF_3+H]^+$

FTIR (neat): 3356, 2120, 1733, 1433, 1369, 1262, 1128, 1092, 1066, 978, 923, 886, 847, 660 cm^{-1}.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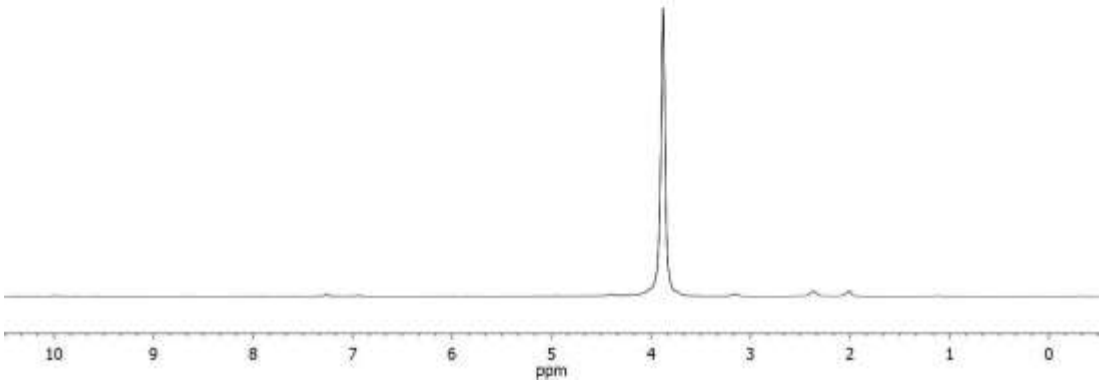
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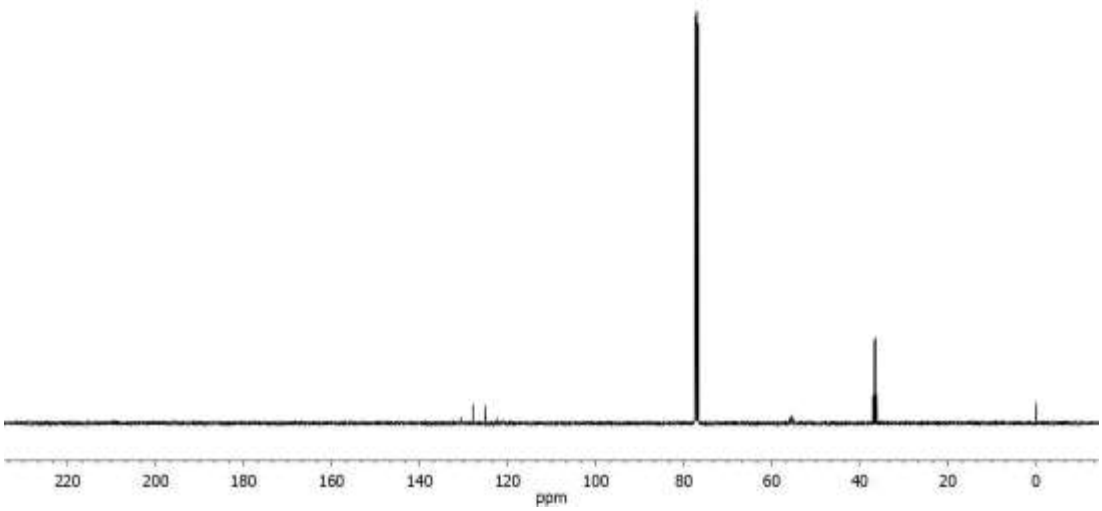
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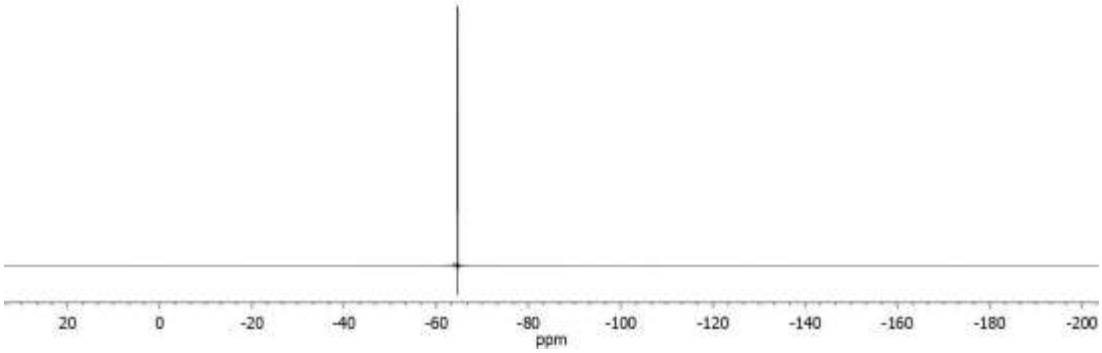
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-80
-100
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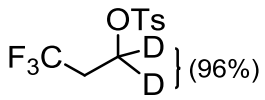
-200
ppm

1,1,-dideuterio-3,3,3-trifluoropropyl 4-methylbenzenesulfonate (*deuterio*-**3.15e**)



In modification to literature procedure,[47] an oven-dried pressure tube equipped with magnetic stir bar was charged with *p*-toluenesulfonyl chloride (0.1 g, 0.592 mmol, 130 mol%), *N,N*-dimethylaminopyridine (5.6 mg, 0.010 mmol, 10 mol%), and *deuterio*-alcohol **1e** (53 mg, 0.456 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and CH_2Cl_2 (0.5 mL) and pyridine (0.5 mL) were added. The rubber septum was quickly replaced with a screw cap and the reaction was stirred at ambient temperature for 72 hours. Then the reaction mixture was quenched with 1.0 M HCl (2 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with H_2O (5 mL), brine (5 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to afford the title compound (31.4 mg, 25%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.20 (t, *J* = 6.1 Hz, 0.07H), 2.52 (q, *J* = 10.2 Hz, 2H), 2.46 (s, 3H).

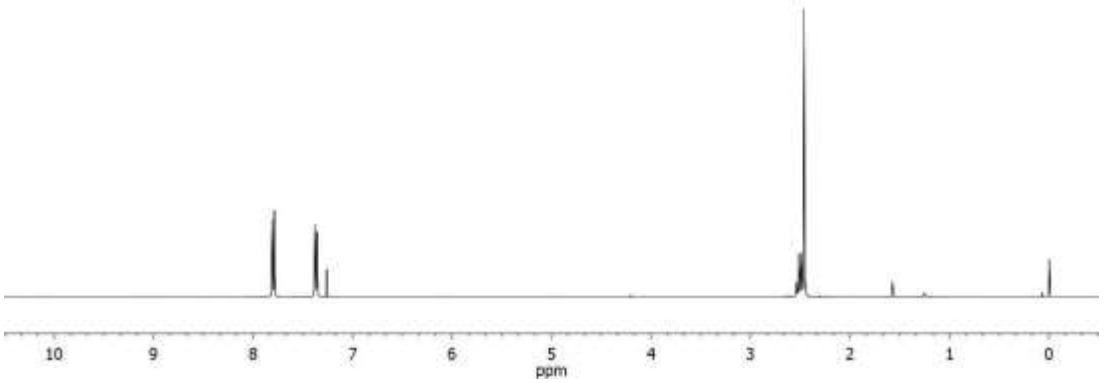
^{2}H NMR (77 MHz, $CDCl_3$): δ 4.21 (s, 1.93H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 132.3, 130.0, 127.9, 125.0 (q, *J* = 276.7 Hz), 62.7 – 61.1 (m), 33.6 (q, *J* = 29.7 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -61.7 (t, *J* = 10.1 Hz).

HRMS (ESI) Calcd. For $C_{10}H_9D_2F_3O_3S$ $[M+Na]^+$: 293.0403, Found: 293.0403.

FTIR (neat): 2924, 1598, 1495, 1427, 1364, 1290, 1264, 1193, 1180, 1139, 1095, 1060, 1020, 970, 876, 815, 769, 734, 704, 661 cm^{-1}.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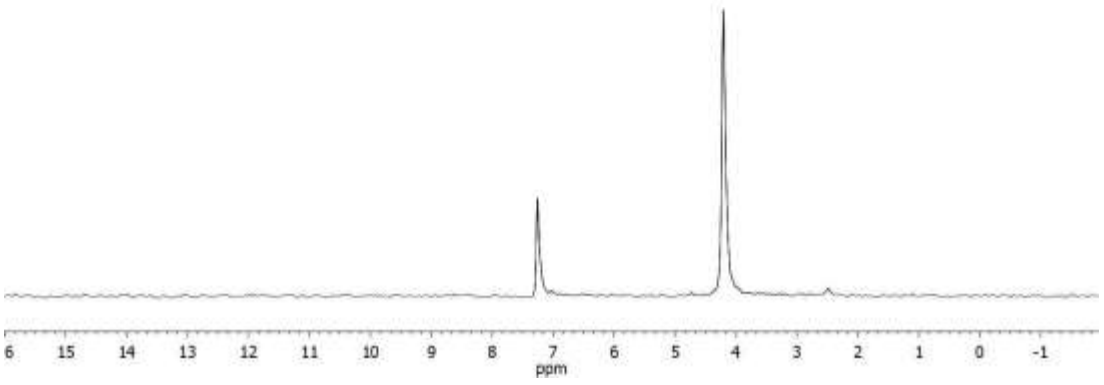
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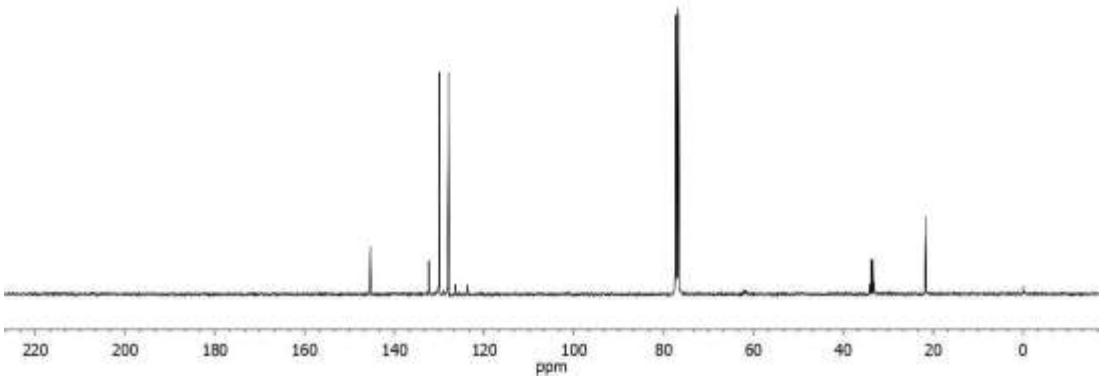
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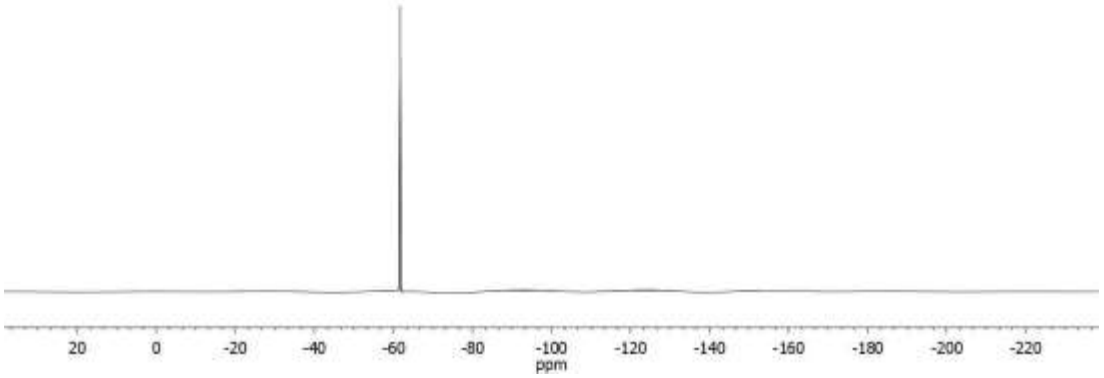
ppm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-120
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-160
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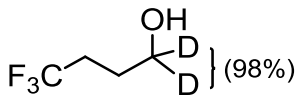
ppm

1,1,-dideuterio-4,4,4-trifluorobutan-1-ol (*deuterio*-3.11f)



In modification to literature procedure,[11] a 50 mL round-bottom flask was charged with 5% ruthenium on carbon (0.3 g, 50 wt%), 4,4,4-trifluorobutan-1-ol (0.6 g, 5 mmol, 100 mol%), and deuterium oxide (10 mL, 0.5 M). Under 1 atm of hydrogen gas, the reaction mixture was allowed to stir for 24 hours at 80 °C and then cooled to ambient temperature. The reaction mixture was filtered over a pad of Celite topped with sand. The filtrate was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O (15 mL), brine (15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was then re-subjected to the above conditions, furnishing the title compound (0.27 g, 44%) as a colorless oil. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in ^1H NMR (400 MHz, $CDCl_3$) and ^2H NMR (77 MHz, $CHCl_3$) and HRMS of the corresponding tosylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 – 3.66 (m, 0.05H), 2.29 – 2.14 (m, 2H), 1.84 – 1.76 (m, 1.94H), 1.33 (s, 1H).

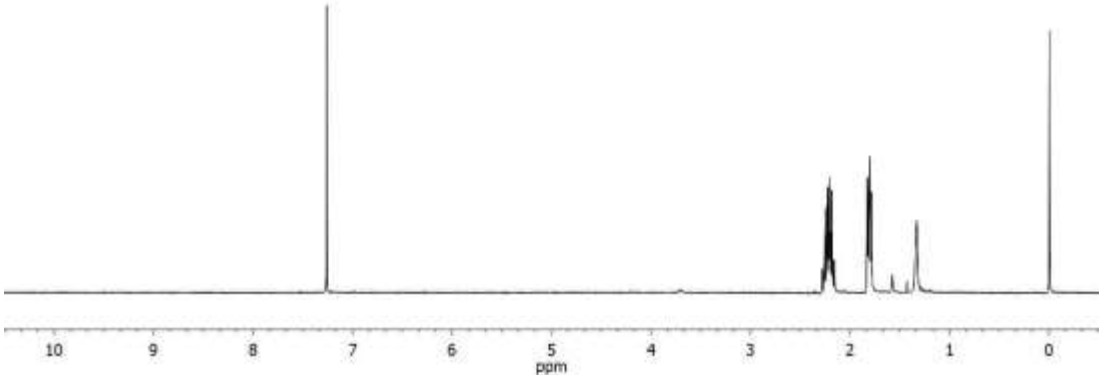
^{2}H NMR (77 MHz, $CDCl_3$): δ 3.69 (s, 1.95H), 1.79 (s, 0.06H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3 (q, J = 275.8 Hz), 61.1, 30.3 (q, J = 28.6 Hz), 24.8 (q, J = 2.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.4 (t, J = 11.0 Hz).

LRMS (EI): m/z 33 $[M\text{-}CH_2CF_3+H]^+$

FTIR (neat): 3336, 2956, 1454, 1389, 1336, 1312, 1252, 1139, 1076, 1063, 1019, 1002, 968, 899, 849, 834 cm^{-1}.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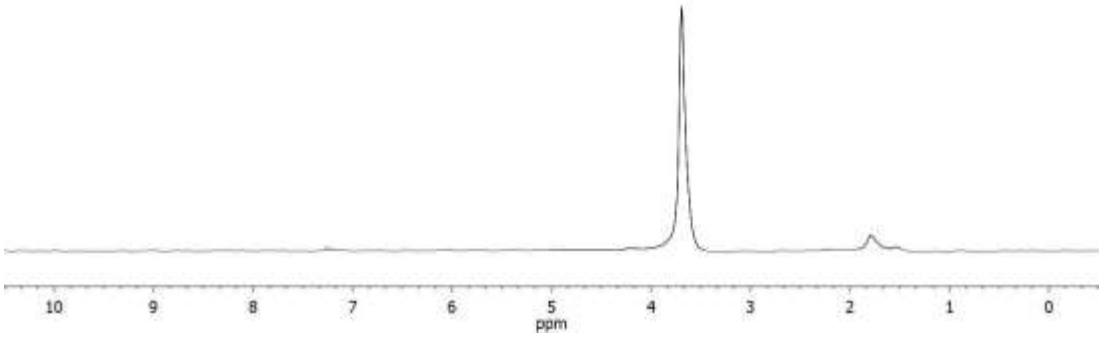
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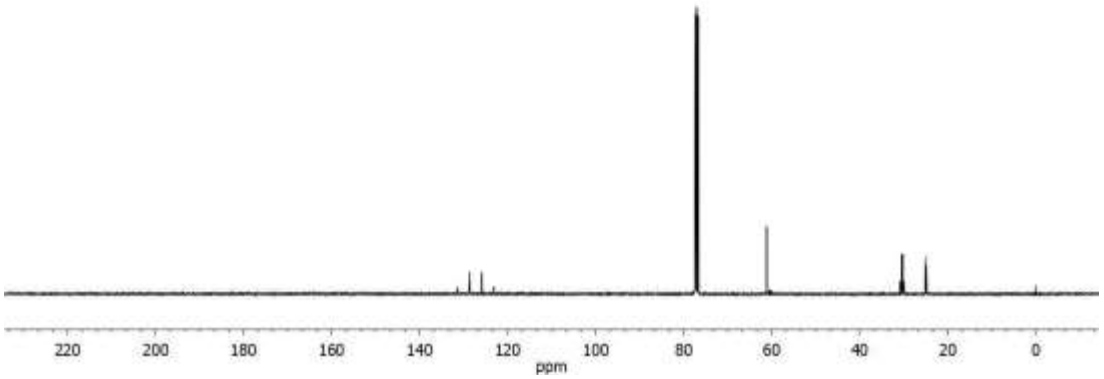
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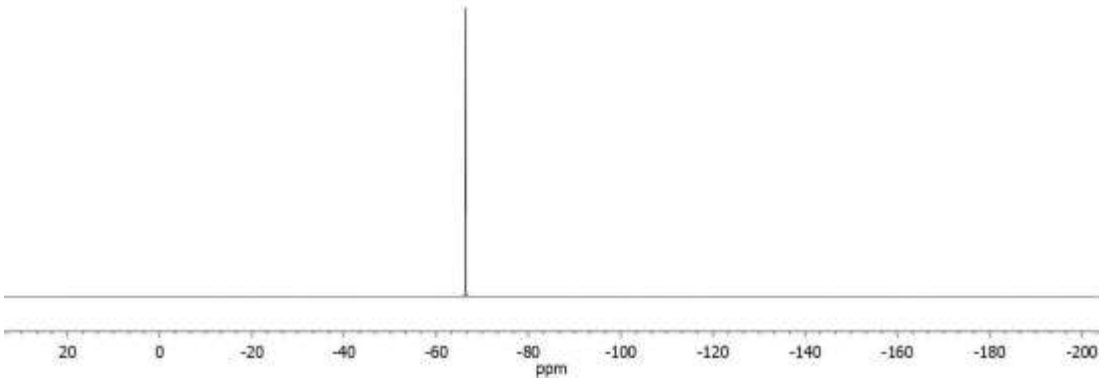
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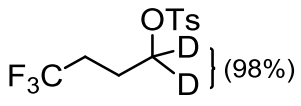
ppm

1,1,-dideuterio-4,4,4-trifluorobutyl 4-methylbenzenesulfonate (*deuterio*-**3.15f**)



In modification to literature procedure,[12] an oven-dried pressure tube equipped with magnetic stir bar was charged with *p*-toluenesulfonyl chloride (31.5 mg, 0.180 mmol, 130 mol%), *N,N*-dimethylaminopyridine (1.7 mg, 0.010 mmol, 10 mol%), and *deuterio*-alcohol **1f** (18 mg, 0.140 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and CH_2Cl_2 (0.3 mL) and pyridine (0.3 mL) were added. The rubber septum was quickly replaced with a screw cap and the reaction was stirred at ambient temperature for 72 hours. Then the reaction mixture was quenched with 1.0 M HCl (1 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with H_2O (5 mL), brine (5 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 15% EtOAc/hexane) to afford the title compound (10.6 mg, 27%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.07 (t, *J* = 6.4 Hz, 0.04H), 2.46 (s, 3H), 2.26 – 2.09 (m, 2H), 1.96 – 1.84 (m, 1.96H).

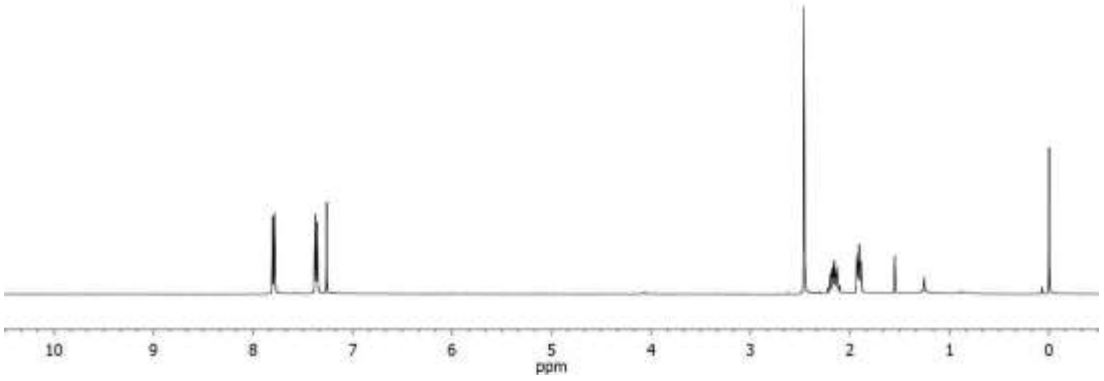
^{2}H NMR (77 MHz, $CDCl_3$): δ 4.08 (s, 1.96H), 1.90 (s, 0.04H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 132.8, 130.0, 127.9, 126.60 (d, *J* = 276.3 Hz), 77.6, 30.1 (q, *J* = 30.7 Hz), 21.8 (d, *J* = 3.2 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.5 (t, *J* = 10.6 Hz).

HRMS (ESI) Calcd. For $C_{11}H_{11}D_2F_3O_3S$ $[M+Na]^+$: 307.0555, Found: 307.0559.

FTIR (neat): 2957, 1598, 1495, 1451, 1396, 1361, 1324, 1292, 1257, 1246, 1191, 1179, 1139, 1097, 1065, 1004, 961, 891, 814, 720, 688, 661 cm^{-1}.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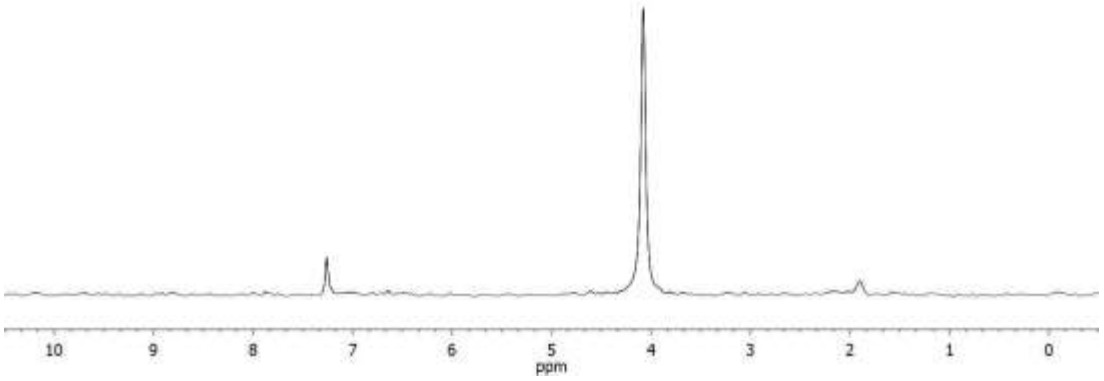
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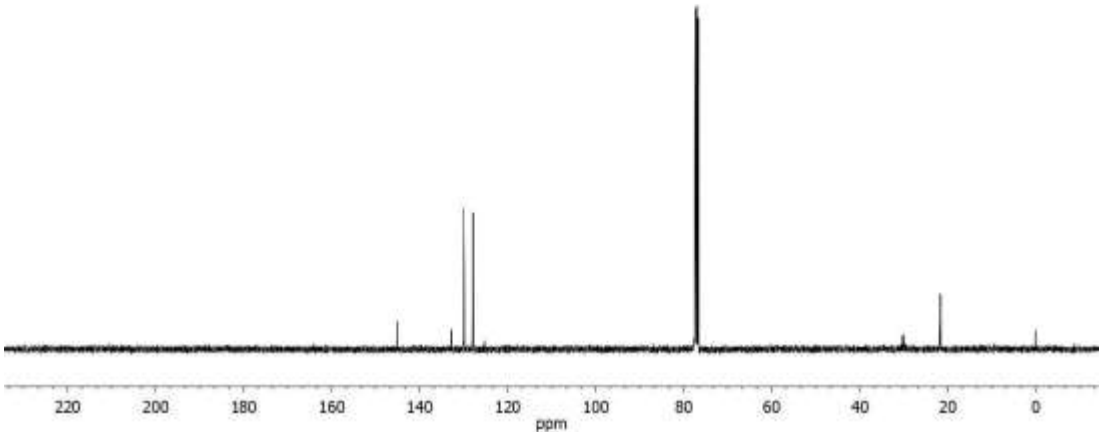
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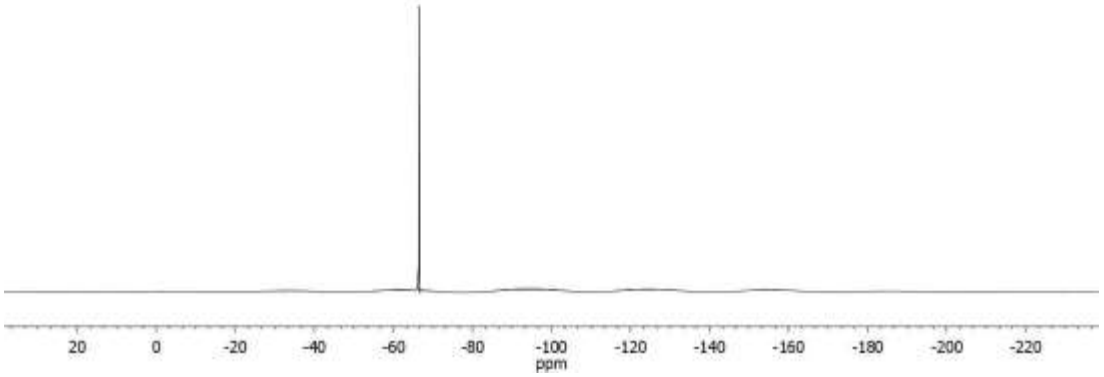
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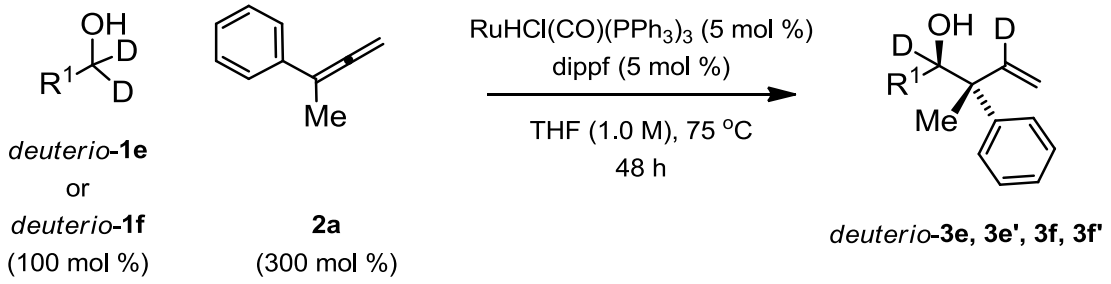
ppm

VI. Experimental Procedures and Spectral Data for Deuterium Labeling



deuterio-**1e** or *deuterio*-**1f** (100 mol %)

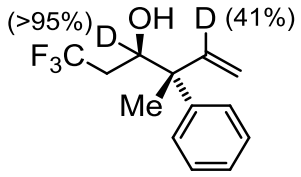
2a (300 mol %)

deuterio-**3e, 3e', 3f, 3f'**

General Procedure B for the coupling of *deuterio*-alcohols (3.11e-3.11f) to allene (3.10a)

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF) (4.2 mg, 0.010 mmol, 5 mol%), and alcohol (0.200 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and THF (0.2 mL, 1.0 M with respect to alcohol) and allene **3.10a** (78 mg, 0.600 mmol, 300 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to 75 °C for 48 hours. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds with yields averaged over two trials. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in 1H NMR (400 MHz, $CDCl_3$) and 2H NMR (77 MHz, $CHCl_3$), averaged over two trials.

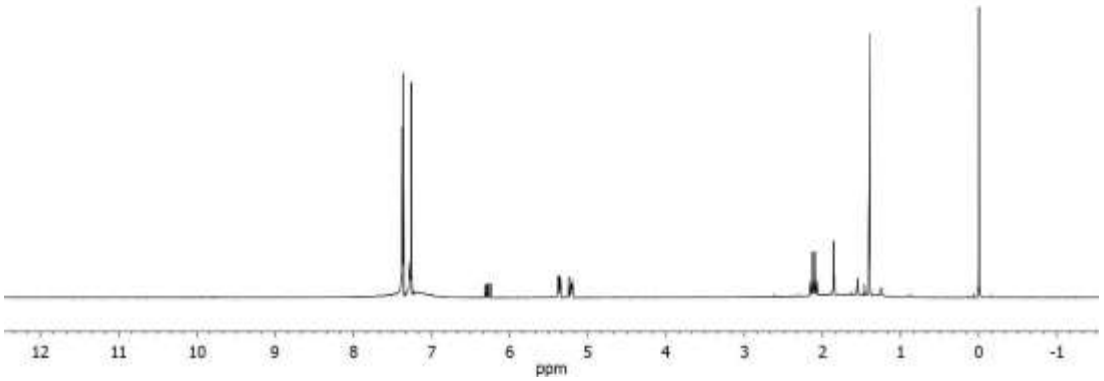
1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (*deuterio*-3.12e)



The reaction was conducted in accordance with **General Procedure B** *via deuterio*-**3.11e** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (8.3 mg, 17%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, J = 17.7, 10.9 Hz, 0.59H), 5.35 (dd, J = 10.9, 1.0 Hz, 1H), 5.21 (dd, J = 17.7, 1.0 Hz, 1H), 2.20 – 2.04 (m, 2H), 1.91 (dt, J = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.41 ^{2}H), 4.35 (s, 1 ^{2}H).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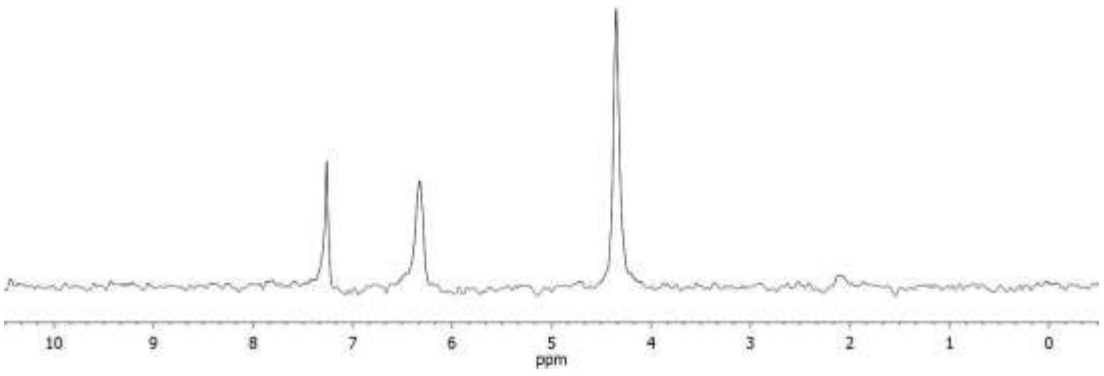
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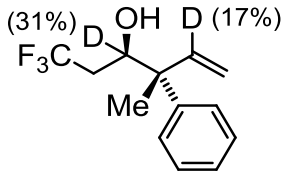
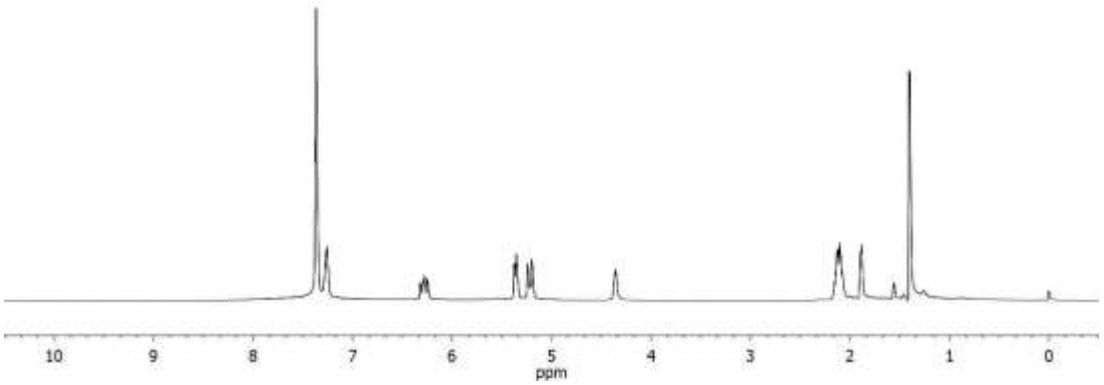
1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (*deuterio*-3.12e')



The reaction was conducted in accordance with **General Procedure B** *via* a 1:1 mixture of *deuterio*-**3.11e** : **3.11e** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (26.9 mg, 55%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 0.83H), 5.35 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.40 – 4.30 (m, 0.69H), 2.20 – 2.04 (m, 2H), 1.91 (dt, *J* = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.17 ^{2}H), 4.35 (s, 0.31 ^{2}H).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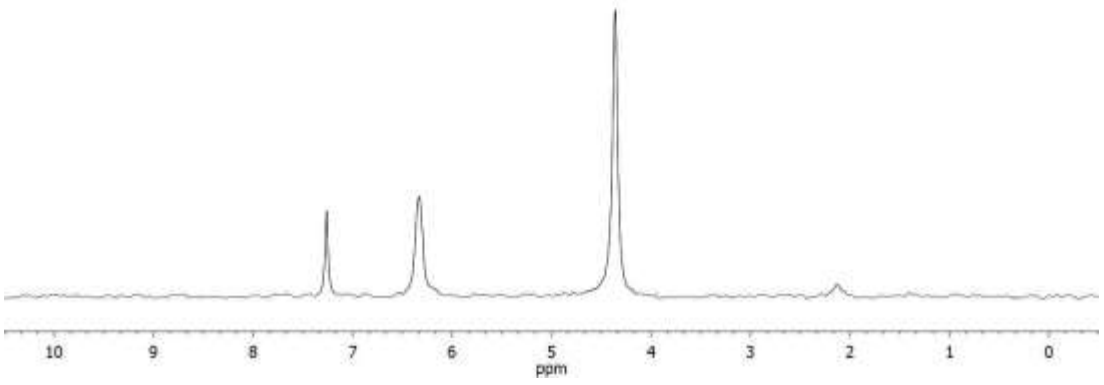
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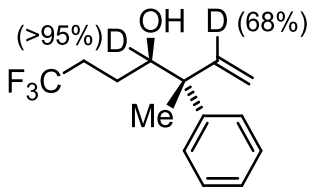
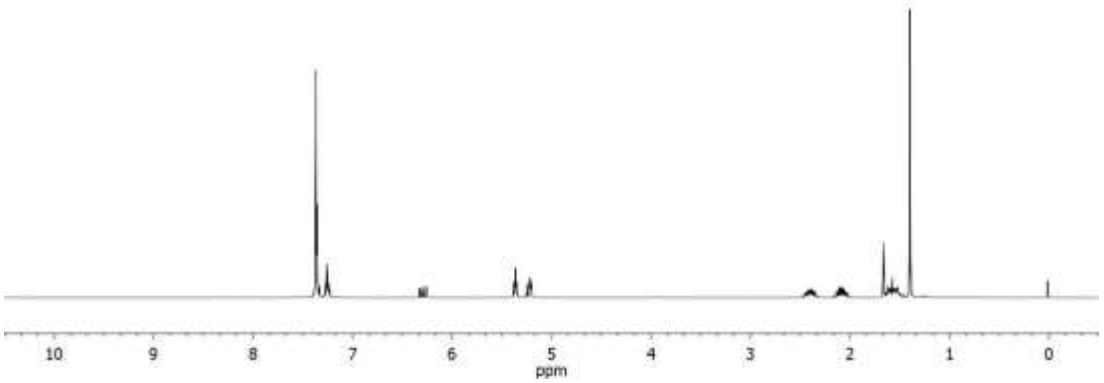
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (*deuterio*-3.12f)



The reaction was conducted in accordance with **General Procedure B** *via deuterio*-**3.11f** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (44.9 mg, 87%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, J = 17.7, 10.9 Hz, 0.32H), 5.35 (dd, J = 10.9, 1.1 Hz, 1H), 5.21 (dd, J = 17.7, 1.1 Hz, 1H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.68H), 3.93 (s, 1H).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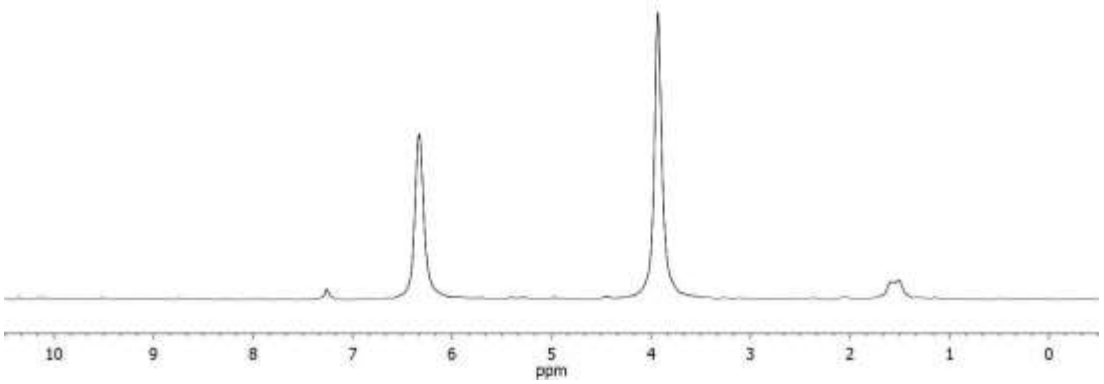
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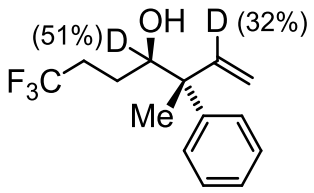
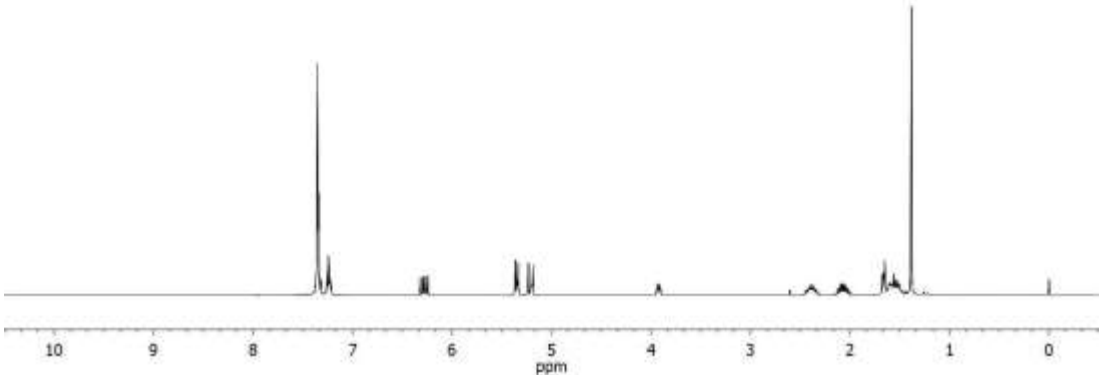
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (*deuterio*-3.12f')



The reaction was conducted in accordance with **General Procedure B** *via* a 1:1 mixture of *deuterio*-**3.11f** : **3.11f** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (46.5 mg, 90%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 0.68H), 5.35 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.1 Hz, 1H), 3.93 (dt, *J* = 10.5, 2.8 Hz, 0.49H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.32H), 3.93 (s, 0.51H).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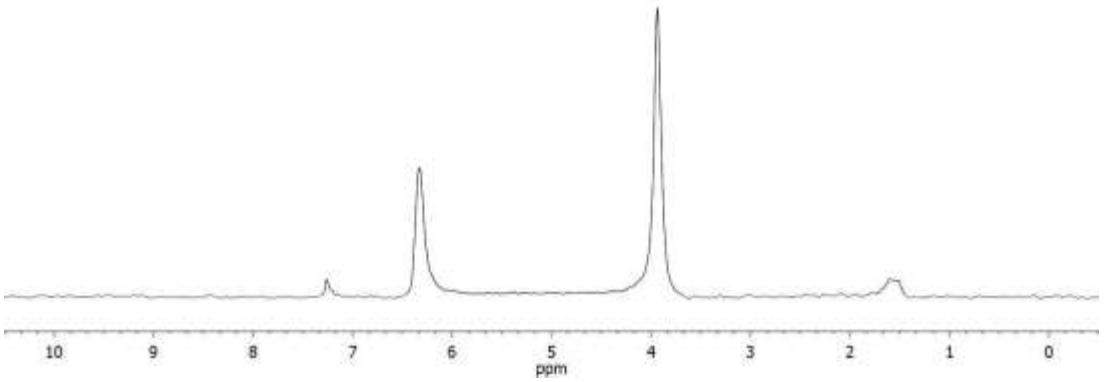
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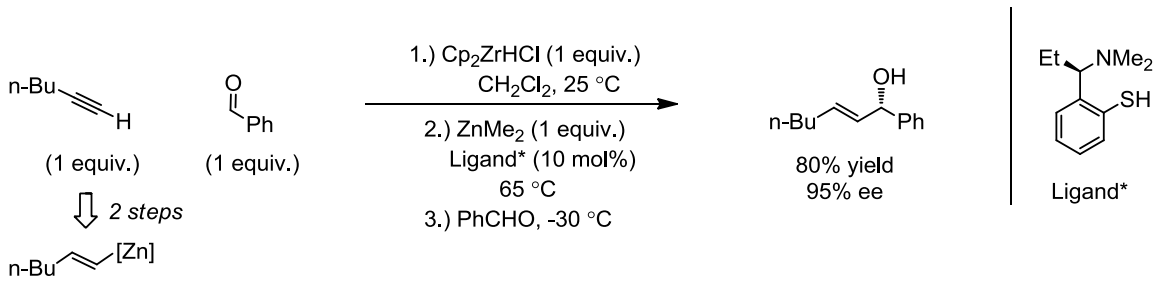
CHAPTER 4: DIRECT REGIOSELECTIVE CARBONYL VINYLATION*

4.1 Introduction

Allylic alcohols are versatile building blocks in organic synthesis. Their synthetic utility arises from the presence of a double bond in the allylic moiety and the hydroxyl group that may be modified synthetically.[1] Among existing methods, carbonyl vinylation represents a convergent protocol for preparing allylic alcohols. Classical protocols, such as those as reported by Oppolzer and Wipf, utilize stoichiometrically generated vinyl metal reagents to perform these carbonyl additions.[2] Although these methods produce allylic alcohols in high yield and high enantioselectivity, their generation of stoichiometric organometallic waste during the pre-activation of the alkyne as a nucelophile, i.e. hydrozirconation and subsequent transmetallation to zinc, renders them less attractive for large-scale applications (Scheme 4.1).

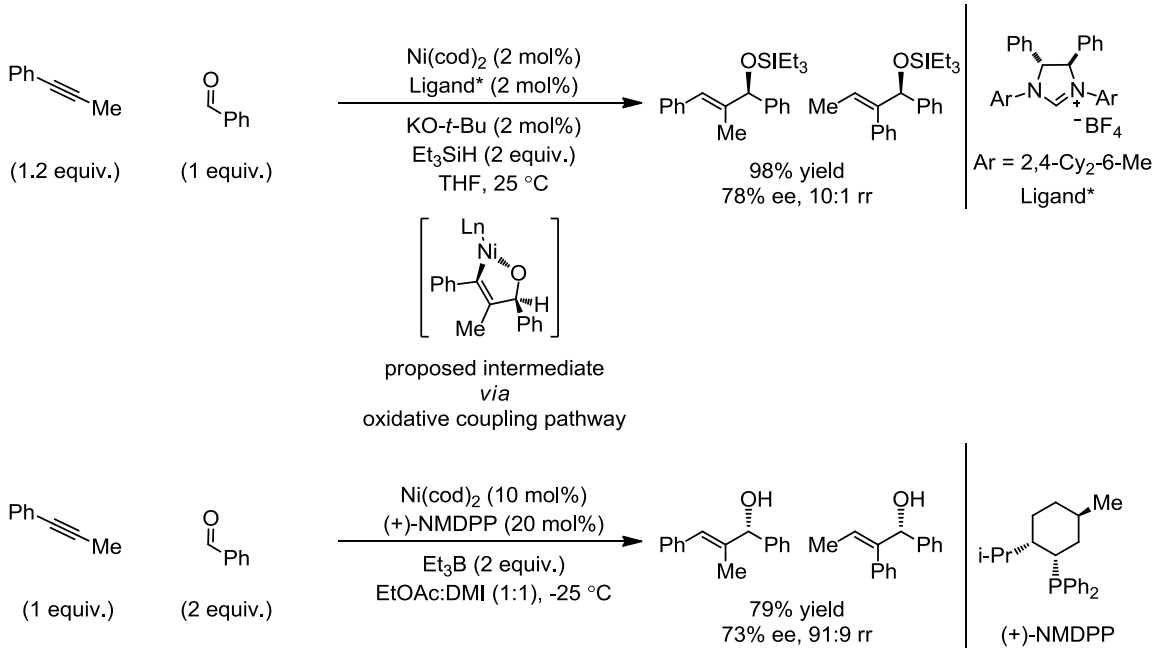
Scheme 4.1. Selected example of regio- and enantioselective alkyne vinylation requiring pre-activation.



* Leung, J. C.; Patman, R. L.; Sam, B.; Krische, M. J. *Chem. Eur. J.* **2011**, *17*, 12437. Acknowledgment is made to M. J. K. for project oversight and J. C. L. and R. L. P. for reaction discovery, optimization, and scope evaluation.

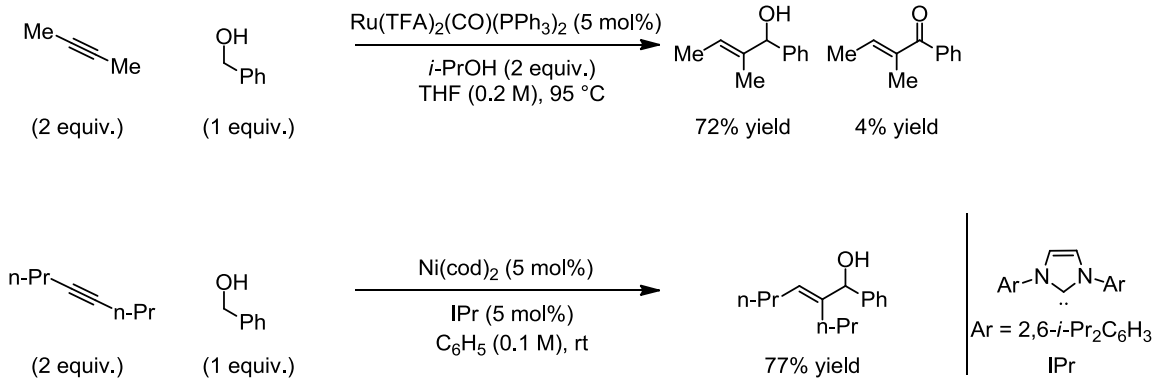
Modern efforts have focused on circumventing alkyne activation by directly using alkynes as nucleophilic coupling partners in transition metal catalyzed reductive couplings to carbonyl compounds. Early reports employed rhodium[3], titanium[4], and nickel[5] as catalysts in reductive cyclizations of acetylenic aldehydes. Later, intermolecular variants of the nickel-catalyzed couplings were developed.[6,8] In solving the issue of alkyne activation, collectively, these approaches introduce a new issue: the generation of stoichiometric metallic byproducts as each method employs a metallic terminal reductant, such as silanes, boranes, and organozinc reagents. For example, Montgomery and coworkers reported the regio- and enantioselective vinylation of non-symmetric alkynes, such as 1-phenylpropyne, *via* nickel catalysis employing two equivalents of the mass intensive, triethylsilane (Et_3SiH), as terminal reductant (Scheme 4.2).[6e] Similarly, Jamison *et al.* reported the same transformation under similar nickel catalyzed conditions but employing two equivalents of the pyrophoric, triethylborane (Et_3B), as terminal reductant.[6b]

Scheme 4.2. Selected examples of nickel catalyzed regioselective alkyne vinylation.



In recent studies from our laboratory, it was found that direct reductive coupling of an alkyne to a carbonyl compound is possible by way of ruthenium catalyzed transfer hydrogenation (Scheme 4.3).[7] Under conditions of transfer hydrogenation, products of carbonyl vinylation were obtained in good yields by employing formic acid or alcohols as the terminal reductants in the couplings of alkynes to aldehydes or alcohols, respectively. Notably, this work primarily focused on the reductive coupling of a symmetrical alkyne, 2-butyne. Similarly, conditions for nickel catalyzed transfer hydrogenative coupling of symmetrical alkynes to alcohols have been reported more recently.[8]

Scheme 4.3. Selected examples of metal catalyzed alkyne vinylation mediated by transfer hydrogenation.



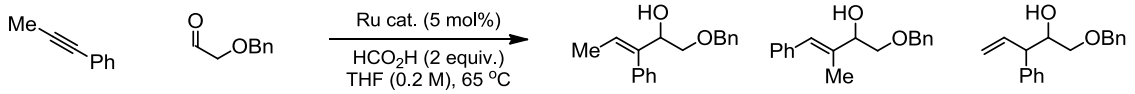
A subsequent study of the ruthenium catalyzed process revealed that regioselective reductive couplings of nonsymmetrical alkynes and paraformaldehyde were possible under similar conditions.[9] In an effort to expand the scope of this methodology, a survey of higher aldehydes was undertaken. Herein, we report ruthenium catalyzed regioselective reductive couplings of nonsymmetric 1,2-disubstituted alkynes to aldehydes, furnishing trisubstituted allylic alcohols in good to excellent regioselectivity.[10]

4.2 Reaction Development

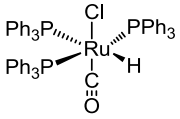
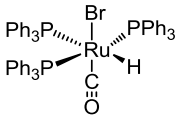
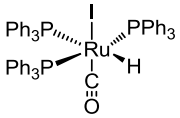
To probe the feasibility of a general regioselective process, an initial experiment was conducted using 1-phenylpropyne **4.1a** (2 equiv.), α-benzyloxyacetaldehyde **4.2a** (1 equiv.), $RuHCl(CO)(PPh_3)_3$ (5 mol%), and formic acid (2 equiv.) as terminal reductant. Unfortunately, the product of carbonyl vinylation was obtained in low yield, 23%, as a 2:1 mixture of regioisomers, along with an additional isomeric product (Table 4.1, entry 1). In parallel studies on the reductive coupling of nonsymmetric alkynes and paraformaldehyde, it was that found that regioselectivities were improved by employing

tetrabutylammonium iodide as an additive.[9] Based on this observation, the discrete $RuHX(CO)(PPh_3)_3$ complexes, where X was Br or I, were prepared in the same fashion as the aforementioned chloride complex.[11] With these complexes in hand, an assay was conducted in the reductive coupling of 1-phenylpropyne to α-benzyloxyacetaldehyde under identical conditions of the $RuHCl(CO)(PPh_3)_3$. Whereas the bromide complex only showed a slight improvement in yield (Table 4.1, entry 2), the iodide complex improved both yield, and more importantly, regioselectivity between **4.3a** and *iso*-**4.3a** (Table 4.1, entry 3). Unfortunately, an increased proportion of isomeric *allyl*-**4.3a** was also observed when employing the iodide complex, prompting additional optimization.

Table 4.1. Effects of halide ligand on regio- and stereoselectivity.[a]



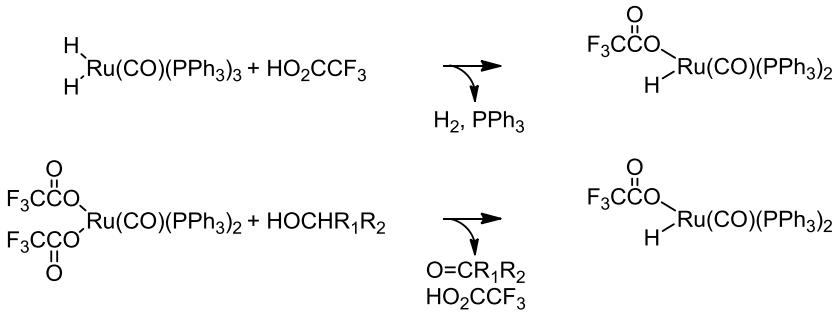
4.1a (2 equiv.) | **4.2a** (1 equiv.) | **4.3a** | *iso*-**4.3a** | *allyl*-**4.3a**

Entry	Ru Complex	Additive	Yield	4.3a:*iso*-4.3a	4.3a: *allyl*-4.3a
1		—	23%	2:1	5:1
2		—	31%	2:1	6:1
3		—	40%	17:1	2:1

[a]Yields are of combined isomeric materials. Regio- and stereoselectivity was determined *via* ^1H NMR analysis of crude reaction mixtures.

Acid-base reactions between ruthenium hydride complexes and carboxylic acids have been widely reported in the literature.[11] For example, $RuH_2(CO)(PPh_3)_3$ is known to react with trifluoroacetic acid (HO_2CCF_3) to form $RuH(O_2CCF_3)(CO)(PPh_3)_2$, triphenylphosphine ($PPh_3$), and elemental hydrogen (H_2) (Scheme 4.4).[12] Additionally, both stoichiometric and catalytic reactions of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ with alcohols to produce $RuH(O_2CCF_3)(CO)(PPh_3)_2$ and aldehydes or ketones are known.[11-12]

Scheme 4.4. Acid-base reaction of ruthenium hydride complex with carboxylic acid.

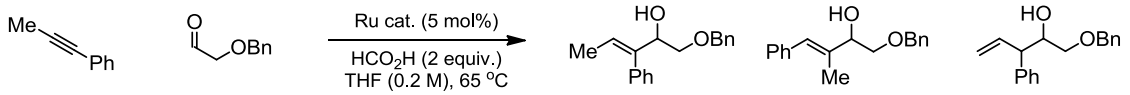


Furthermore, previous studies in our lab employed $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as a catalyst in transfer hydrogenative carbonyl vinylation,[7] prompting the examination of trifluoroacetic acid as additive to potentially form $RuX(O_2CCF_3)(CO)(PPh_3)_3$, where X was Cl, Br, or I. However, measuring such minute quantities of trifluoroacetic acid proved cumbersome. Hence, a tractable alternative, perfluorooctanoic acid ($HO_2CC_7F_{15}$), was employed. It was hypothesized that ligand exchange may be rapid and that the different ligands may facilitate different steps in the catalytic cycle.

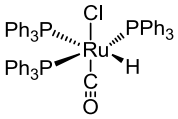
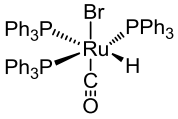
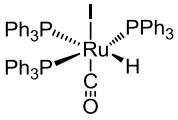
The addition of perfluorooctanoic acid in combination with the ruthenium chloride complex improved the yield and ratio to *allyl*-**4.3a** but did not enhance regioselectivity between **4.3a** and *iso*-**4.3a** (Table 4.2, entry 1). No significant improvement was observed with the bromide complex (Table 4.2, entry 2). In contrast,

the combination of perfluorooctanoic acid with the iodide complex furnished **4.3a** as a single regioisomer in 71% yield with an improved ratio of **4.3a** to *allyl*-**4.3a** of 8:1 (Table 4.2, entry 3). Hence, the specific combination of iodide and fluorocarboxylate ligands appeared essential in obtaining high yields and regioselectivity.

Table 4.2. Effects of halide ligand and acid cocatalyst on regio- and stereoselectivity.[a]



4.1a (2 equiv.) | **4.2a** (1 equiv.) | **4.3a** | *iso*-**4.3a** | *allyl*-**4.3a**

Entry	Ru Complex	Additive	Yield	4.3a:*iso*-4.3a	4.3a: *allyl*-4.3a
1		$C_7F_{15}CO_2H$	36%	1:1	7:1
2		$C_7F_{15}CO_2H$	35%	2:1	8:1
3		$C_7F_{15}CO_2H$	71%	>20:1	8:1

[a]Yields are of combined isomeric materials. Regio- and stereoselectivity was determined *via* ^{1}H NMR analysis of crude reaction mixtures.

Attempts to prepare the discrete $RuI(O_2CR_F)(CO)(PPh_3)_3$, where R_F was CF_3 or C_7F_{15}, were unsuccessful. However, it was hypothesized that iodide would rapidly exchange with a carboxyl ligand of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ to generate $RuI(O_2CCF_3)(CO)(PPh_3)_2$ *in situ*. Subsequent evaluation of iodide sources revealed ammonium tetrabutylammonium iodide, Bu_4NI, to be effective in promoting high levels of regioselectivity when combined with $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$. Thus, evaluation of

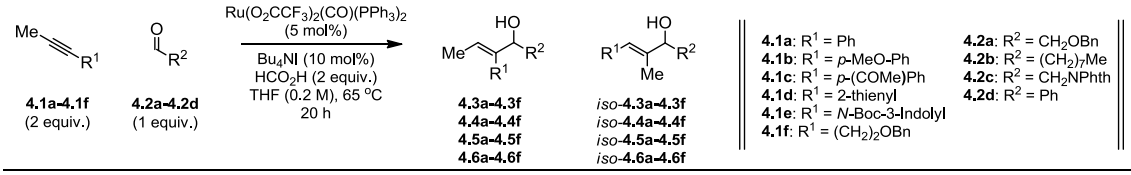
the 1-phenylpropyne **4.1a** coupling to α-benzyloxyacetaldehyde **4.2a** resumed under the aforementioned conditions. At lower concentration, the formation of *allyl*-**4.3a** was suppressed and good regiocontrol was retained. Two equivalents of formic acid proved optimal. Lower loadings of formic acid reduced both the yield of **4.3a** and the ratio of **4.3a** to *allyl*-**4.3a**. Finally, the optimal loading of iodide was found to be vital in suppression of both *iso*-**4.3a** and *allyl*-**4.3a**. Thus, the desired trisubstituted allylic alcohol was furnished as a single regioisomer with complete stereocontrol and without *allyl*-**4.3a** in 75% yield by employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ (5 mol%), Bu_4NI (10 mol%), and formic acid (2 equiv.) in THF at 65 °C.

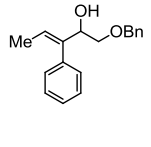
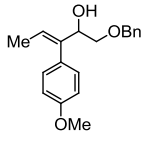
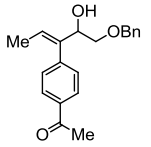
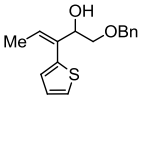
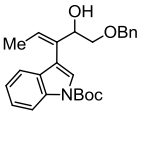
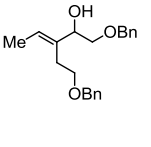
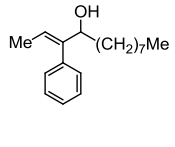
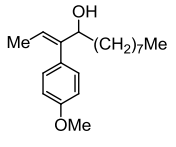
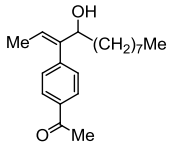
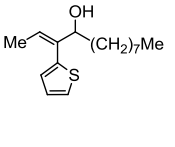
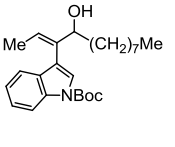
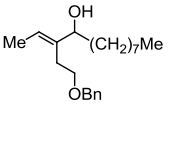
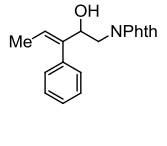
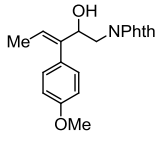
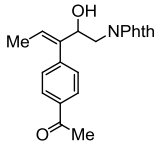
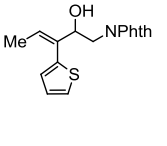
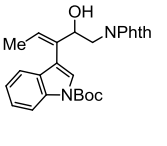
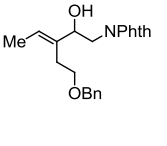
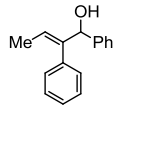
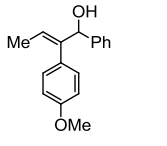
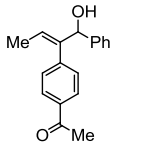
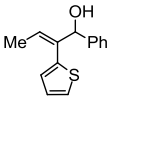
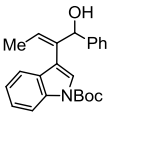
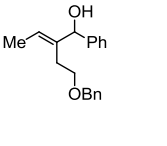
4.3 Reaction Scope

To evaluate the scope of these conditions, the direct, catalytic vinylation of α-benzyloxyaldehyde **4.2a**, nonal **4.2b**, α-*N*-phthalimidoacetaldehyde **4.2c**, and benzaldehyde **4.2d** was conducted employing 1-phenylpropyne **4.1a**. The desired trisubstituted alcohols **4.3a**-**4.6a** were delivered in good yields as mostly a single isomeric products with complete stereocontrol. With these results in hand, a larger assay of nonsymmetric propynes **4.1b**-**4.1f** with aryl, heteroaryl, and alkyl substituents was screened in the coupling to aldehydes **4.2a**-**4.2d**. The corresponding allylic alcohols **4.4a**-**4.6f** were obtained in moderate to good yields with good to excellent regioselectivity and complete stereocontrol (Table 4.3). Additionally, in contrast to the previously reported couplings of 2-butyne to alcohols,[7] over-oxidation of the allylic alcohols to α,β-unsaturated ketones was not observed. It is postulated that this side reaction is suppressed by lower reaction temperatures, shorter reaction times, and the

presence of iodide which may occupy open sites on the ruthenium complex needed for oxidation of the alcohol.

Table 4.3. Regio- and stereoselective ruthenium catalyzed reductive coupling of nonsymmetric alkynes **4.1a**-**4.1f** to aldehydes **4.2a**-**4.2d**. [a]



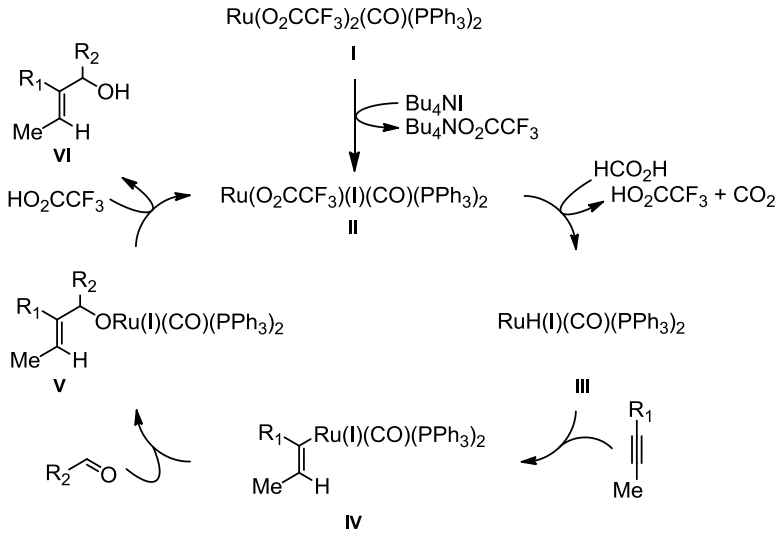
					
75% Yield **4.3a** >20:1, **4.3a**:*iso*-**4.3a** >20:1, *E*:*Z*	63% Yield **4.3b**[e] 11:1, **4.3b**:*iso*-**4.3b** >20:1, *E*:*Z*	80% Yield **4.3c**[d] 8:1, **4.3c**:*iso*-**4.3c** >20:1, *E*:*Z*	67% Yield **4.3d** 11:1, **4.3d**:*iso*-**4.3d** >20:1, *Z*:*E*	77% Yield **4.3e** >20:1, **4.3e**:*iso*-**4.3e** >20:1, *E*:*Z*	62% Yield **4.3f**[d] 14:1, **4.3f**:*iso*-**4.3f** >20:1, *E*:*Z*
					
74% Yield **4.4a**[b,c] >20:1, **4.4a**:*iso*-**4.4a** >20:1, *E*:*Z*	77% Yield **4.4b**[b,c] 17:1, **4.4b**:*iso*-**4.4b** >20:1, *E*:*Z*	80% Yield **4.4c**[b,c] 17:1, **4.4c**:*iso*-**4.4c** >20:1, *E*:*Z*	55% Yield **4.4d**[b,c] 5:1, **4.4d**:*iso*-**4.4d** >20:1, *Z*:*E*	76% Yield **4.4e**[b] >20:1, **4.4e**:*iso*-**4.4e** >20:1, *E*:*Z*	61% Yield **4.4f**[b] >20:1, **4.4f**:*iso*-**4.4f** >20:1, *E*:*Z*
					
90% Yield **4.5a**[g] 18:1, **4.5a**:*iso*-**4.5a** >20:1, *E*:*Z*	88% Yield **4.5b**[g] 13:1, **4.5b**:*iso*-**4.5b** >20:1, *E*:*Z*	86% Yield **4.5c**[g] 8:1, **4.5c**:*iso*-**4.5c** >20:1, *E*:*Z*	78% Yield **4.5d**[g] 11:1, **4.5d**:*iso*-**4.5d** >20:1, *Z*:*E*	95% Yield **4.5e**[g] >20:1, **4.5e**:*iso*-**4.5e** >20:1, *E*:*Z*	52% Yield **4.5f**[f] >20:1, **4.5f**:*iso*-**4.5f** >20:1, *E*:*Z*
					
85% Yield **4.6a**[h] >20:1, **4.6a**:*iso*-**4.6a** >20:1, *E*:*Z*	84% Yield **4.6b** 9:1, **4.6b**:*iso*-**4.6b** >20:1, *E*:*Z*	79% Yield **4.6c**[i] >20:1, **4.6c**:*iso*-**4.6c** >20:1, *E*:*Z*	40% Yield **4.6d** 8:1, **4.6d**:*iso*-**4.6d** >20:1, *Z*:*E*	63% Yield **4.6e** >20:1, **4.6e**:*iso*-**4.6e** >20:1, *E*:*Z*	62% Yield **4.6f** >20:1, **4.6f**:*iso*-**4.6f** >20:1, *E*:*Z*

[a]Yields are of material isolated by silica gel chromatography. Regio- and stereoselectivity was determined *via* ^{1}H NMR analysis of crude reaction mixtures. [b]The reaction was conducted for 16 h. [c]5 mol% Bu_4NI was employed. [d]The reaction was conducted at 0.5 M concentration. [e]The reaction was conducted at 1.0 M concentration. [f]The reaction was conducted at 2.0 M concentration for 24 h. [g]The reaction was conducted for 15 h. [h]The reaction was conducted at 45 °C for 48 h. [i]1.5 equiv. HCO_2H was employed.

4.4 Postulated Reaction Mechanism

A hydrometallative pathway is proposed, beginning with the *in situ* generation of $RuI(O_2CCF_3)(CO)(PPh_3)_2$, **II**, *via* exchange of a carboxylate ligand of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ and iodide of Bu_4NI (Scheme 4.5). Ensuing carboxylate exchange with formic acid releases trifluoroacetic acid to generate $RuI(O_2CH)(CO)(PPh_3)_2$ (not depicted) which eliminates carbon dioxide to deliver $RuHI(CO)(PPh_3)_2$, **III**. Subsequent regioselective hydrometallation of the alkyne furnishes a vinylruthenium intermediate, **IV**, that may undergo carbonyl addition to produce ruthenium alkoxide **V**. Protonolysis of the ruthenium alkoxide by trifluoroacetic acid releases the product of carbonyl vinylation, **VI**, and regenerates $RuI(O_2CCF_3)(CO)(PPh_3)_2$ which may re-enter the catalytic cycle.

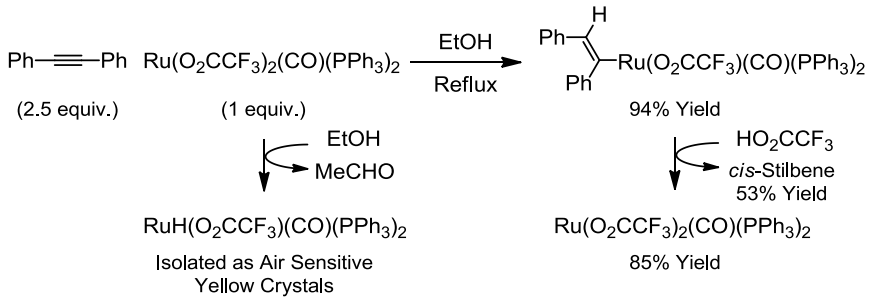
Scheme 4.5. A plausible mechanism for aldehyde vinylation under ruthenium catalysis.



The proposed hydrometallative mechanism is supported by the stoichiometric conversion of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ to $RuH(O_2CCF_3)(CO)(PPh_3)_2$ *via* transfer

hydrogenation conditions using ethanol as terminal reductant,[12b] and the subsequent reaction of $RuH(O_2CCF_3)(CO)(PPh_3)_2$ with 1,2-diphenylethyne to provide the corresponding vinylruthenium complex (Scheme 4.6).[13] The regioselectivity of hydrometallation, favoring the placement of ruthenium adjacent to the aryl substituent of alkynes **4.1a**-**4.1e**, may be driven by additional stabilization associated with π-benzyl character of this vinyl intermediate. In the case of the dialkyl substituted alkyne **4.1f**, the Lewis basic benzyl ether moiety may direct the regioselectivity of hydrometallation *via* chelation to the ruthenium complex.[14] When a weaker chelating group was present on a dialkyl substituted alkyne, such as a silyl group instead of a benzyl group, the regioselectivity eroded to 1:1. Notably, oxidative coupling pathways may not be excluded on the basis of the available data and may account for contra-steric regiocontrol in the C-C coupling event.

Scheme 4.6. Reported stoichiometric transformations corroborating hydrometallation.



4.5 Conclusion

In summary, a highly regio- and stereoselective vinylation protocol has been developed for the synthesis of trisubstituted alcohols *via* ruthenium catalysis. Nonsymmetric disubstituted alkynes were reductively coupled to aldehydes, enabled by

transfer hydrogenation, employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ and Bu_4NI as catalysts. It was discovered that the iodide additive played a critical role in directing regioselectivity. Additionally, the regioselectivity observed in these reactions complement the previously reported vinylation methods. Based on these findings, enantioselective variants may be possible and are currently under investigation.

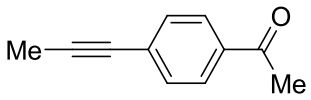
4.6 Experimental Section

General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringe. Reaction tubes were oven-dried and cooled under a stream of argon. Reactions tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Tetrahydrofuran was obtained from solvent delivery system (Innovative Technology Inc. Ps-MD-5). $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ was prepared according to literature procedure.[12a] 1-Phenyl-1-propyne was used as received from Sigma Aldrich. Alkynes **4.1b** and **4.1d** were prepared *via* Sonogashira coupling in accordance with literature procedure employing commercially available aryl iodides.[15] Alkyne **4.1f** was also prepared in accordance with literature procedure.[16,17] Commercially available aldehydes were purified by distillation prior to use. Aldehydes **4.2a** and **4.2c** were prepared according to literature procedures.[18,19] Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}) and products were visualized by UV, $KMnO_4$ and/or anisaldehyde stain. Preparative column chromatography employing silica gel was performed according to the method of Still.[20] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative

intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini or 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Experimental Procedures and Spectroscopic Data for Preparation for Alkynes 4.1c & 4.1e

1-(4-(Prop-1-ynyl)-phenyl)-ethanone (4.1c)



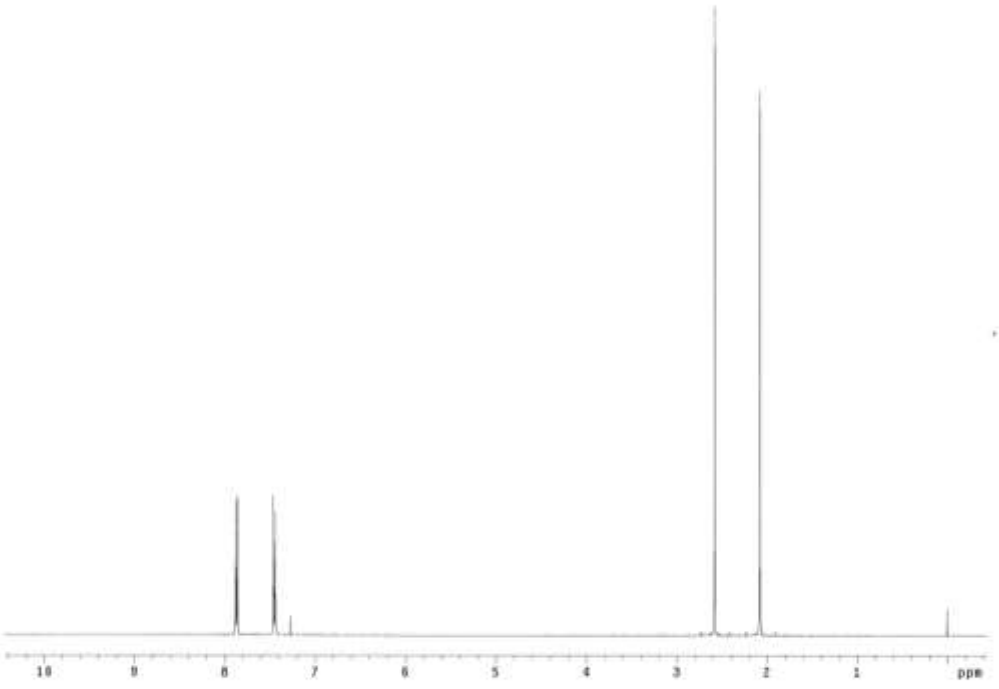
General Procedure for Sonogashira Coupling: A one neck 250 mL round bottom flask was equipped with a magnetic stir bar, 24/40 rubber septa, and then purged with argon. After purging, $Pd(PPh_3)_4$ (289 mg, 0.25 mmol, 1 mol%), CuI (190 mg, 1.00 mmol, 4 mol%), and 1-(4-Iodophenyl)-ethanone (6.08g, 24.7 mmol, 100 mol%) were added. The flask was purged again with argon and THF (50 mL, 0.5M) and TEA (6.89 mL, 49.4 mmol, 200 mol%) were added. The reaction mixture was cooled to -78 ^{o}C and placed under vacuum. A balloon of propyne gas, roughly the size of the flask, was attached to the reaction vessel using a 12" 18 gauge needle. The flask was equipped with a small argon balloon and the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. The reaction mixture was filtered through Celite with the aid of ether. The solution was concentrated, transferred to a 250 mL separatory funnel containing of ether (50 mL), and saturated NH_4Cl (aq.) (100 mL) was added. The organic phase was collected and the aqueous phase was extracted with three portions of ether (50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash column

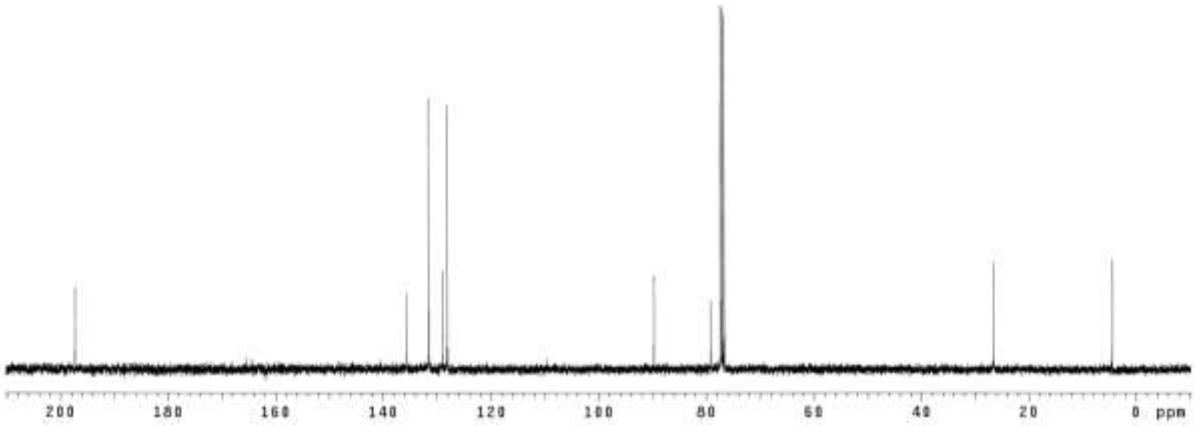
chromatography (SiO_2, 2% EtOAc/Hexane) to afford the title compound (3.83 g, 98%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz), 2.58 (s, 3H), 2.08 (s, 3H).

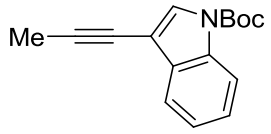
^{13}C NMR (100 MHz, $CDCl_3$): 197.3, 135.6, 131.5, 129.0, 128.1, 89.7, 79.2, 26.5, 4.4.

FTIR (Solid): 3067, 2910, 2252, 2212, 1677, 1598, 1552, 1399, 1355, 1257, 1181, 956, 834cm^{-1}.


10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0 ppm

***t*-Butyl-3-(prop-1-ynyl)-1H-indole-1-carboxylate (4.1e)**



To a one neck 250 mL round bottom flask equipped with a magnetic stir bar was added indole (2.00 g, 17.1 mmol, 100 mol%) as a solution in DMF (35 mL, 0.5 M). Potassium hydroxide (2.39 g, 42.6 mmol, 250 mol%) was added and the mixture was allowed to stir for 20 minutes. Iodine (4.38 g, 17.3, 101 mol%) was added and the mixture was allowed to stir for one hour. The reaction mixture was poured into a 1L Erlenmeyer flask containing ice water (400 mL). A precipitate was collected by vacuum filtration and used immediately the subsequent transformation (the crude product decomposes over time).

To a one neck 250 mL round bottom flask equipped with a magnetic stir bar was added 3-iodo-1H-indole (4.15 g, 17.1 mmol, 100 mol%), DMAP (104 mg, 0.86 mmol, 5 mol%), and DCM (55 mL, 0.3M). To the stirred mixture was added $(Boc)_2O$ (3.73 g, 17.1 mmol, 100 mol%) in portions and the mixture was allowed to stir 16 hours. The reaction mixture was diluted with DCM (150 mL) and transferred to a 250 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with three portions of DCM (50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentration under vacuum. The crude residue was used in the subsequent transformation.

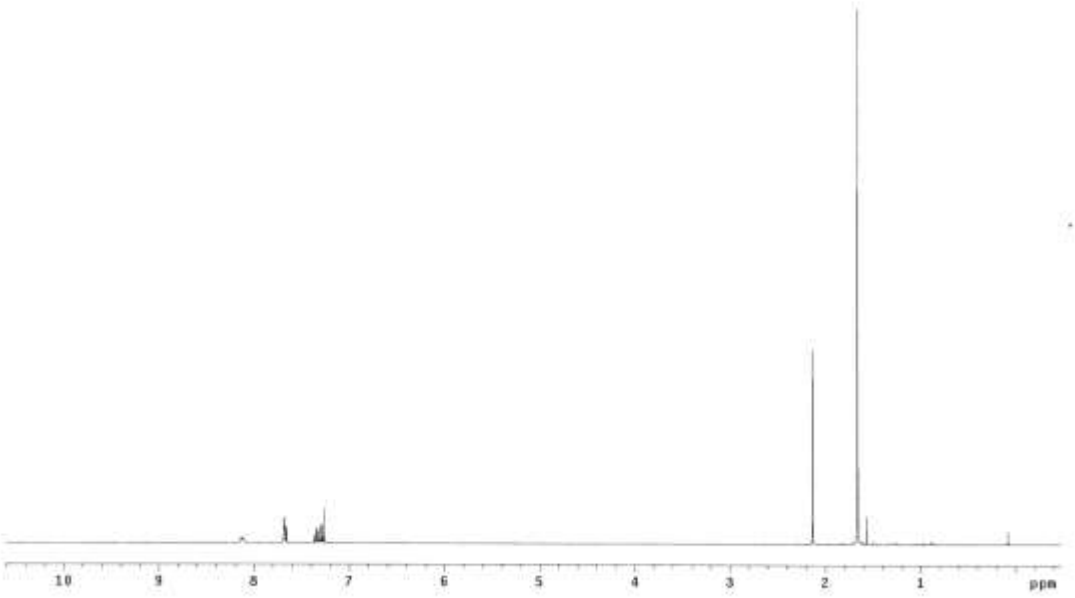
The general procedure for Sonogashira coupling (*vida supra*) was employed using *t*-butyl-3-iodo-1H-indole-1-carboxylate (5.87 g, 17.1 mmol, 100 mol%) as the limiting reagent. The residue was purified by flash column chromatography (SiO_2, 2% EtOAc/Hexane) to afford the title compound (4.09 g, 94% over three steps) as a clear syrup which was stored cold.

^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, J = 7.5 Hz, 1H), 7.72-7.62 (m, 2H), 7.38-7.27 (m, 2H), 2.13 (s, 3H), 1.66 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): 149.1, 134.5, 130.8, 128.1, 124.9, 123.0, 120.0, 115.1, 104.0, 89.1, 84.0, 71.2, 28.1, 4.6.

HRMS (CI) Calcd. for $C_{16}H_{17}NO_2$ $[M]^{+\cdot}$: 255.1259, Found: 255.1261.

FTIR (in $CDCl_3$): 2979, 1733, 1450, 1367, 1232, 1153, 1098, 908, 730 cm^{-1}.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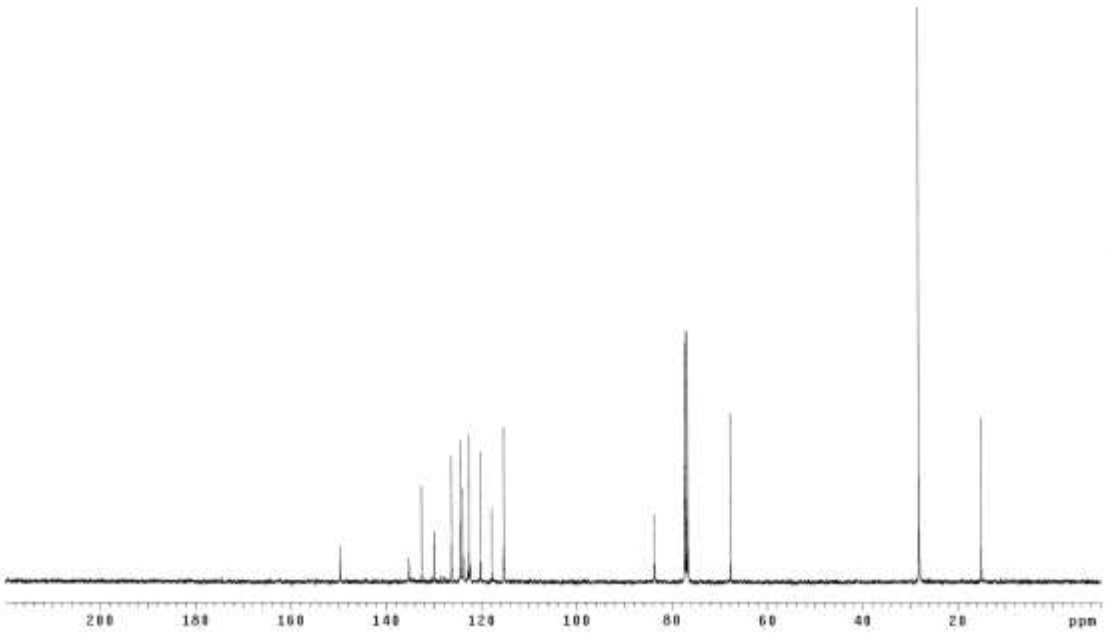
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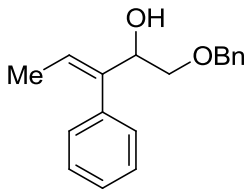
Experimental Procedures and Spectroscopic Data for Preparation for the Coupling of Non-symmetric Alkynes to Aldehydes

General Procedure for the coupling of nonsymmetric alkynes 4.1a-4.1f to aldehyde 4.2a-4.2d

To a pressure tube equipped with magnetic stir bar was added $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ (13.2 mg, 0.015 mmol, 5 mol%) and Bu_4NI (11.1 mg, 0.030 mmol, 10 mol%). The aldehyde (**4.2a-4.2d)** (0.30 mmol, 100 mol%) was added. The tube was sealed with a rubber septum, purged with argon and THF (1.5 mL, 0.2 M with respect to aldehyde), alkyne (0.60 mmol, 200 mol%) and HCO_2H (22.6 μL, 0.6 mmol, 200 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the 65 °C for the indicated time. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2) under the conditions noted to furnish allylic alcohols.

(*E*)-1-(benzyloxy)-3-phenylpent-3-en-2-ol (4.3a)



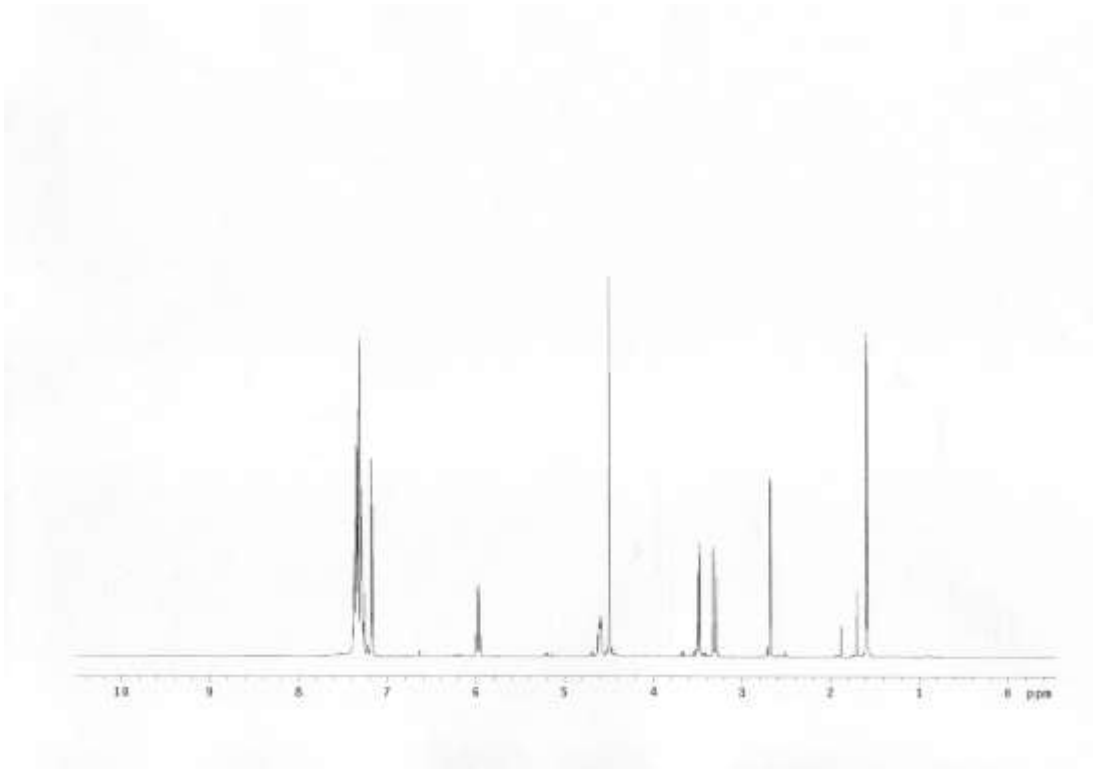
General Procedure (*via* alkyne 4.1a): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (60.4 mg, 75%, >20:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 8H), 7.17 (m, 2H), 5.98 (dq, J = 6.8, 1.2 Hz, 1H), 4.62-4.58 (m, 1H), 4.49 (s, 2H), 3.88 (dd, J = 9.6, 3.2 Hz, 1H), 3.31 (dd, J = 9.6, 8.0 Hz, 1H), 2.68 (d, J = 3.2 Hz, 1H), 1.59 (dd, J = 6.8, 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 138.1, 137.8, 129.1, 128.4, 128.1, 127.7, 126.9, 124.0, 74.5, 73.5, 73.2, 14.3.

HRMS (CI) Calcd. For $C_{18}H_{20}O_2$ (M^+): 268.1463, Found: 268.1462.

FTIR (in $CDCl_3$): 3446, 3053, 3028, 2920, 2857, 1502, 1454, 1435, 1201, 1103, 1071, 736, 698 cm^{-1}.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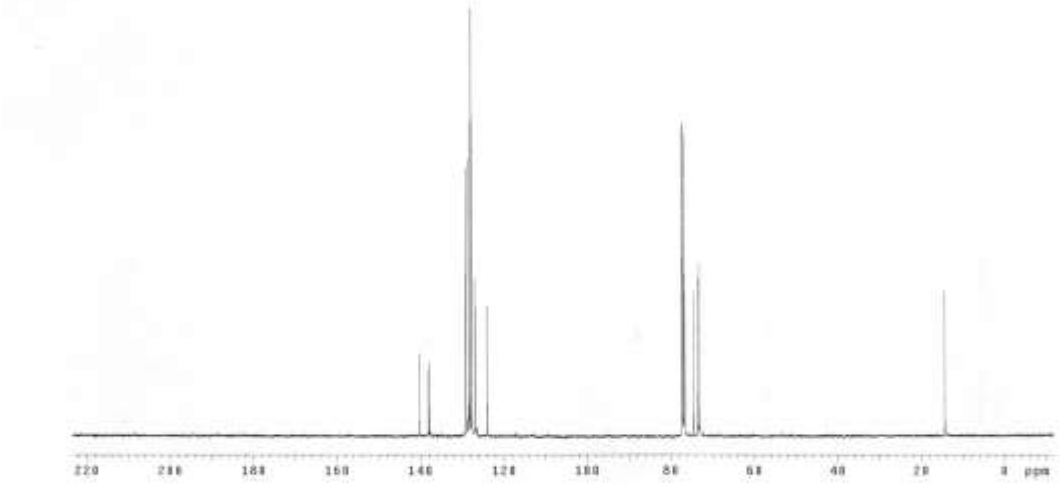
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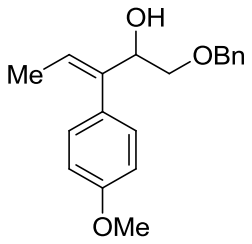
(*E*)-1-(benzyloxy)-3-(4-methoxyphenyl)pent-3-en-2-ol (4.3b)



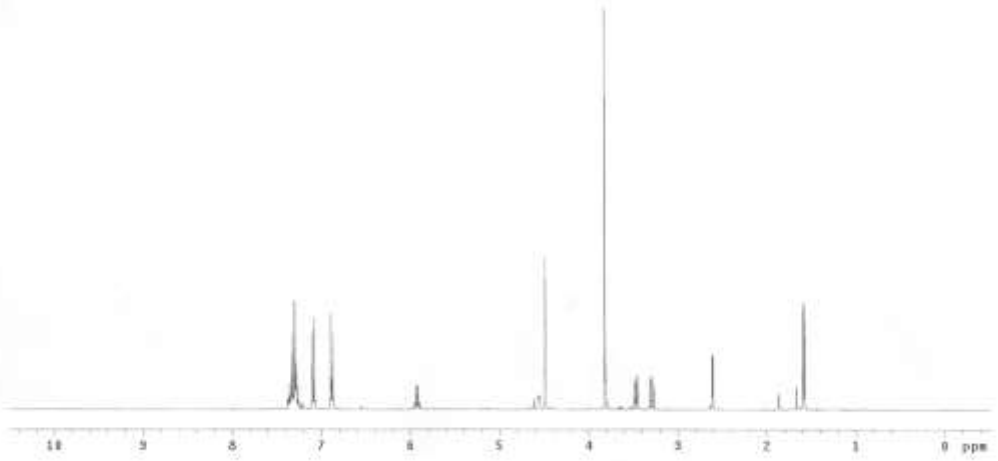
General Procedure (*via* alkyne 4.1b): In modification to the general procedure, the reaction was conducted at 1.0 M concentration. The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (60.0 mg, 67%, 11:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 7.09 (d, *J* = 6.8, 2.0 Hz, 2H), 6.88 (d, *J* = 6.8, 2.0 Hz, 2H), 5.93 (dq, *J* = 6.8, 1.2 Hz, 1H), 4.57-4.55 (m, 1H), 4.48 (s, 2H), 3.82 (s, 3H), 3.47 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.28 (dd, *J* = 9.6, 8.0 Hz, 1H), 2.61 (d, *J* = 3.2 Hz, 1H), 1.59 (dd, *J* = 6.8, 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 139.6, 137.9, 130.1, 128.4, 127.7, 123.8, 113.5, 74.6, 73.7, 73.2, 55.2, 14.3.

HRMS (CI) Calcd. For $C_{19}H_{22}O_3$ (M^+): 298.1569, Found: 298.1569.

FTIR (in $CDCl_3$): 3448, 3021, 2914, 2853, 1606, 1499, 1450, 1246, 1103, 1027, 827, 734, 694 cm^{-1}.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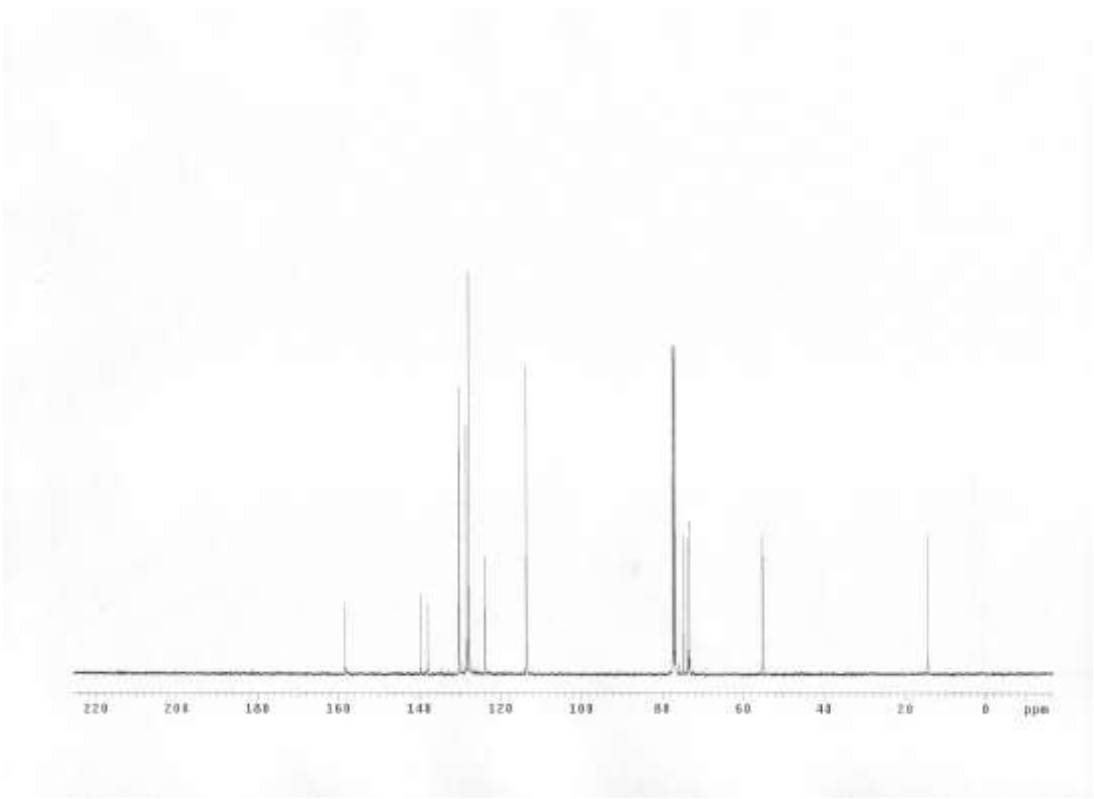
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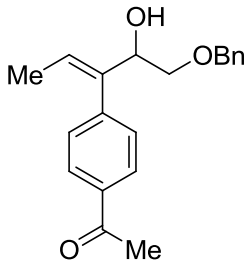
(*E*)-1-(4-(5-(benzyloxy)-4-hydroxypent-2-en-3-yl)phenyl)ethanone (4.3c)



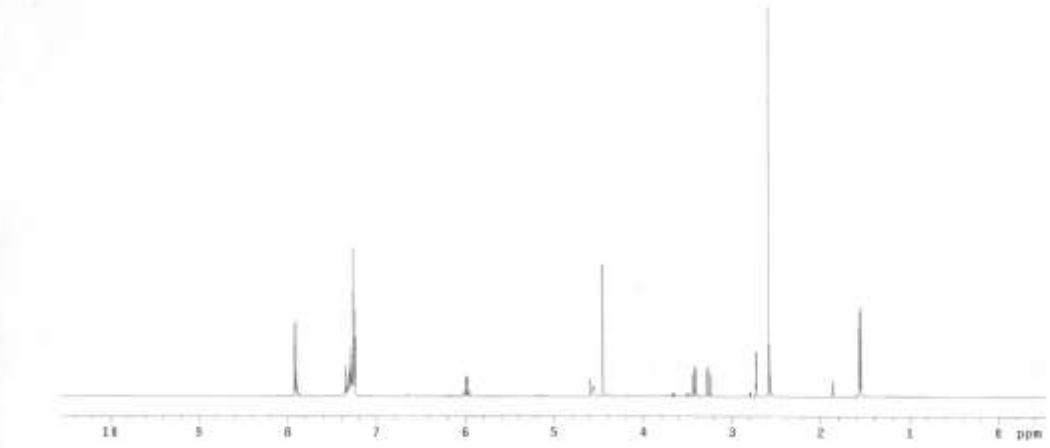
General Procedure (*via* alkyne 4.1c): In modification of the general procedure, the reaction was conducted at 0.5 M concentration. The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (74.5 mg, 80%, 8:1 r.r.) as a yellow oil. (Note: A mixture of 17:1 **4.3c**:*allyl*-**4.3c** was observed)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.35-7.24 (m, 7H), 5.99 (dq, *J* = 6.8, 1.2 Hz, 1H), 4.58-4.54 (m, 1H), 4.45 (s, 2H), 3.43 (dd, *J* = 9.6, 3.2Hz, 1H), 3.26 (d, *J* = 9.6, 8.0 Hz, 1H), 2.73 (d, *J* = 3.2 Hz, 1H), 2.59 (s, 3H), 1.56 (dd, *J* = 6.8, 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 143.4, 139.4, 137.6, 135.7, 129.4, 128.4, 128.2, 127.7, 125.2, 74.3, 73.3, 73.2, 26.5, 14.3.

HRMS (CI) Calcd. For $C_{20}H_{23}O_3$ $[M-H]^+$: 311.1647, Found: 311.1646.

FTIR (in $CDCl_3$): 3439, 3034, 2905, 2852, 1677, 1601, 1545, 1401, 1357, 1268, 1099, 965, 827, 729, 634 cm^{-1}.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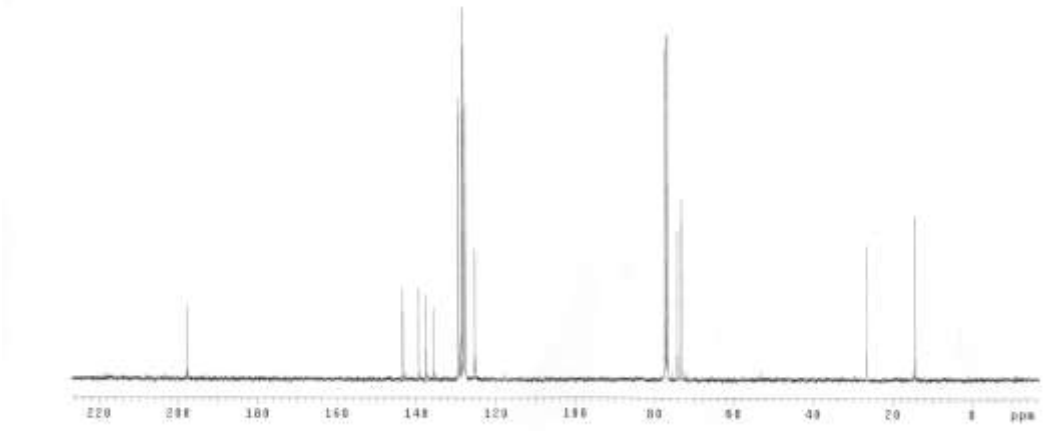
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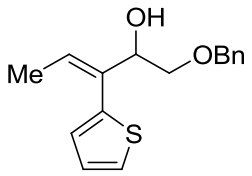
(*Z*)-1-(benzyloxy)-3-(thiophen-2-yl)pent-3-en-2-ol (4.3d)



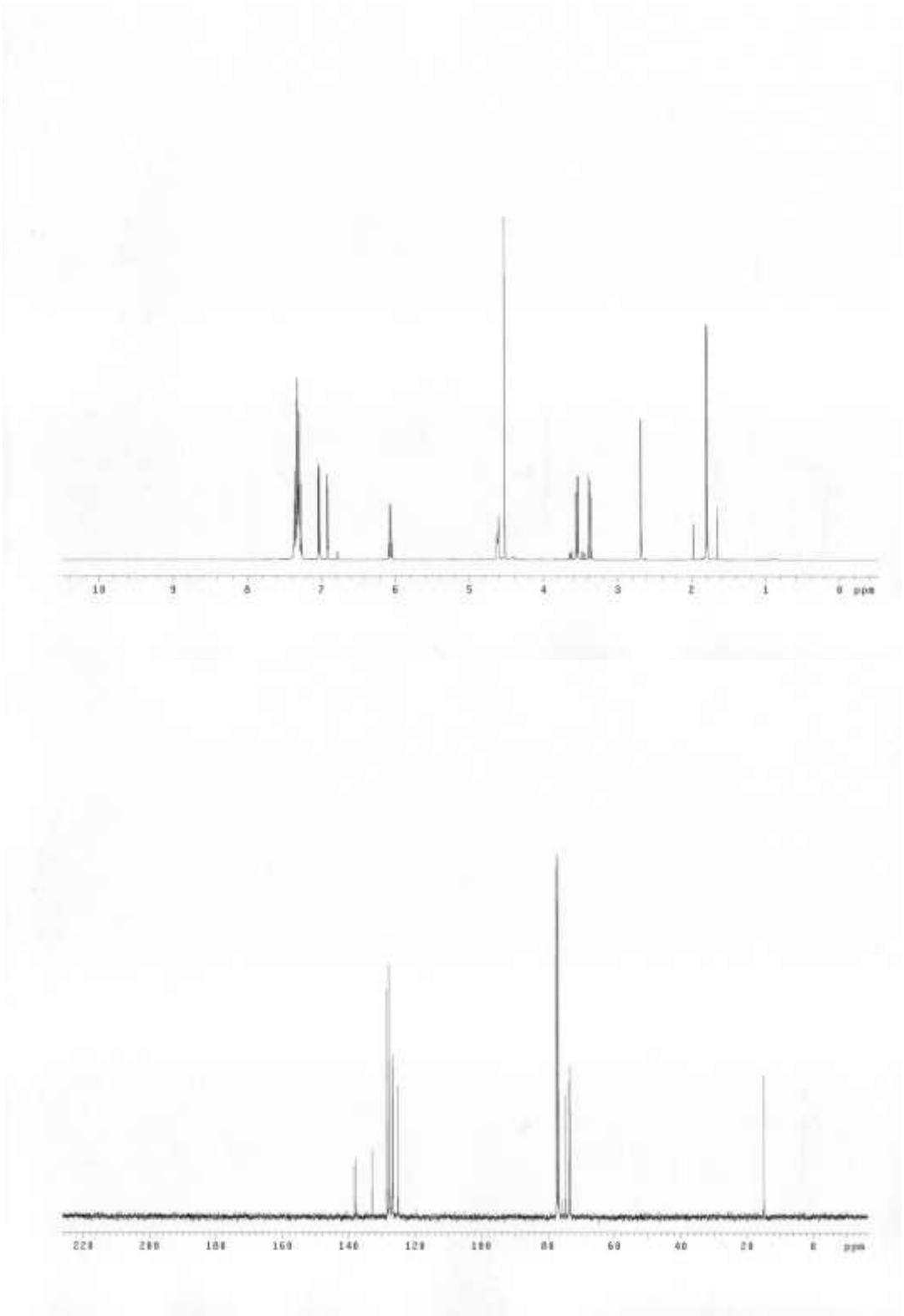
General Procedure (*via* alkyne 4.1d): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (55.1 mg, 67%, 11:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 6H), 7.03 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.92 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.07 (dq, *J* = 6.8, 1.2 Hz, 1H), 4.63-4.60 (m, 1H), 4.52 (s, 2H), 3.55 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.37 (dd, *J* = 9.6, 8.4 Hz, 1H), 2.68 (d, *J* = 2.8 Hz, 1H), 1.79 (dd, *J* = 6.8, 1.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 137.8, 132.9, 128.4, 127.7, 126.8, 126.7, 126.6, 125.1, 74.7, 73.7, 73.2.

HRMS (CI) Calcd. For $C_{16}H_{18}O_2S$ (M^+): 275.1106, Found: 275.1105.

FTIR (in $CDCl_3$): 3420, 3026, 2915, 2853, 1453, 1362, 1312, 1226, 1209, 1097, 1068, 845, 733, 691 cm^{-1}.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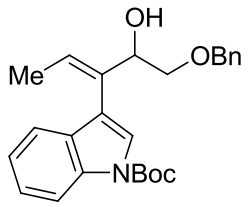
(*E*)-tert-butyl 3-(5-(benzyloxy)-4-hydroxypent-2-en-3-yl)-1*H*-indole-1-carboxylate (4.3e)



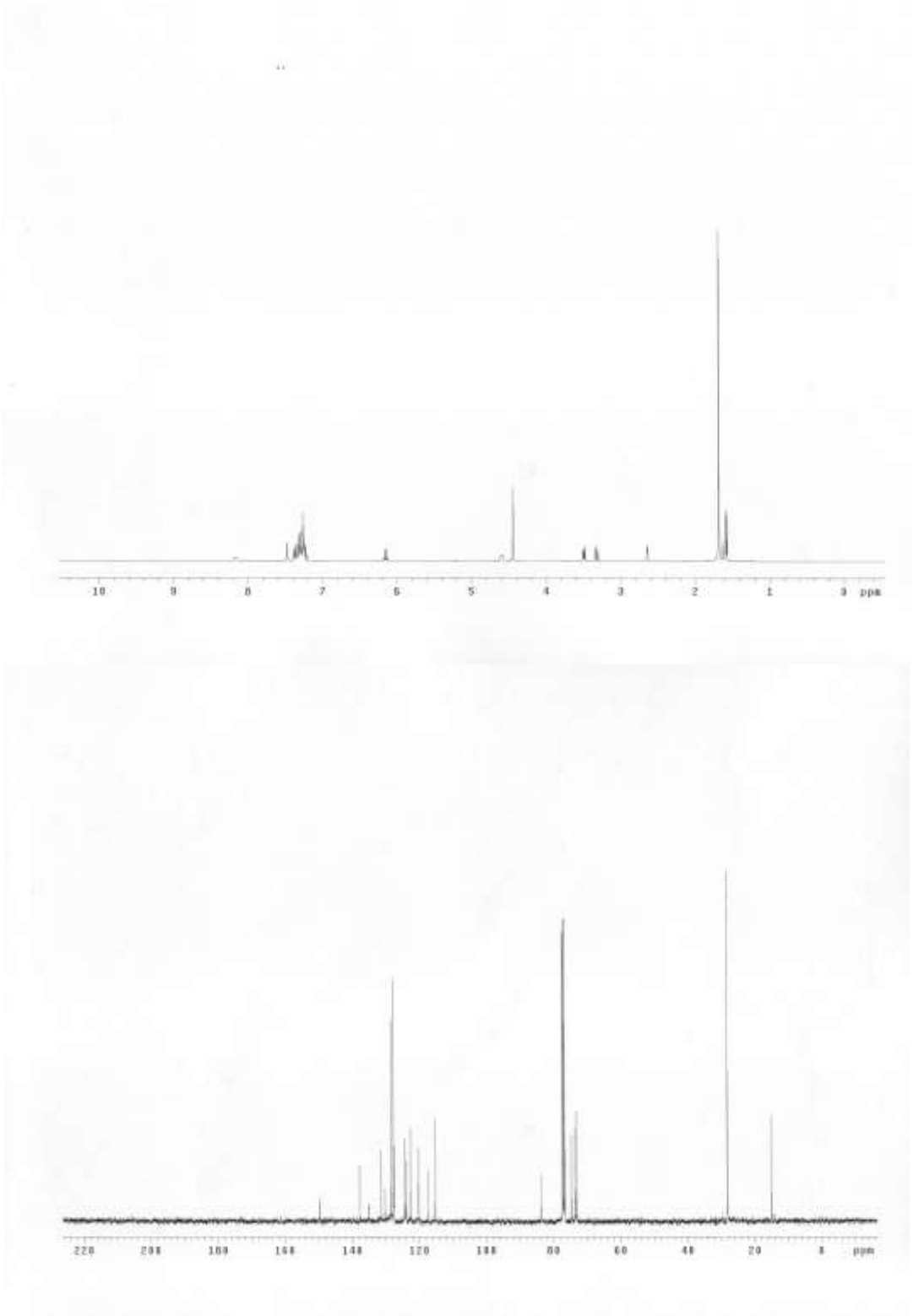
General Procedure (*via* alkyne 4.1e): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (94.1 mg, 77%, >20:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 1H), 7.47 (s, 1H), 7.38-7.21 (m, 8H), 6.16 (dq, J = 6.8, 1.2 Hz, 1H), 4.60-4.58 (m, 1H), 4.44 (s, 2H), 3.49 (dd, J = 9.6, 3.6 Hz, 1H), 3.32 (dd, J = 9.6, 8.4 Hz, 1H), 2.64, (d, J = 3.2 Hz, 1H), 1.69 (s, 9H), 1.59 (J = 6.8, 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 137.8, 135.0, 131.4, 130.2, 128.3, 127.7, 127.5, 124.3, 123.9, 122.6, 120.2, 117.3, 115.2, 83.7, 74.7, 73.6, 73.2, 28.2, 15.0.

HRMS (CI) Calcd. For $C_{25}H_{29}NO_4$ (M^+): 407.2097, Found: 407.2097.

FTIR (in $CDCl_3$): 3461, 2977, 2914, 2849, 1727, 1457, 1375, 1259, 1159, 1068, 849, 770, 745, 700 cm^{-1}.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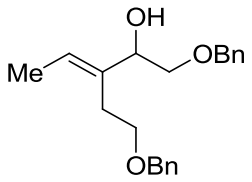
(*E*)-1-(benzyloxy)-3-(2-(benzyloxy)ethyl)pent-3-en-2-ol (4.3f)



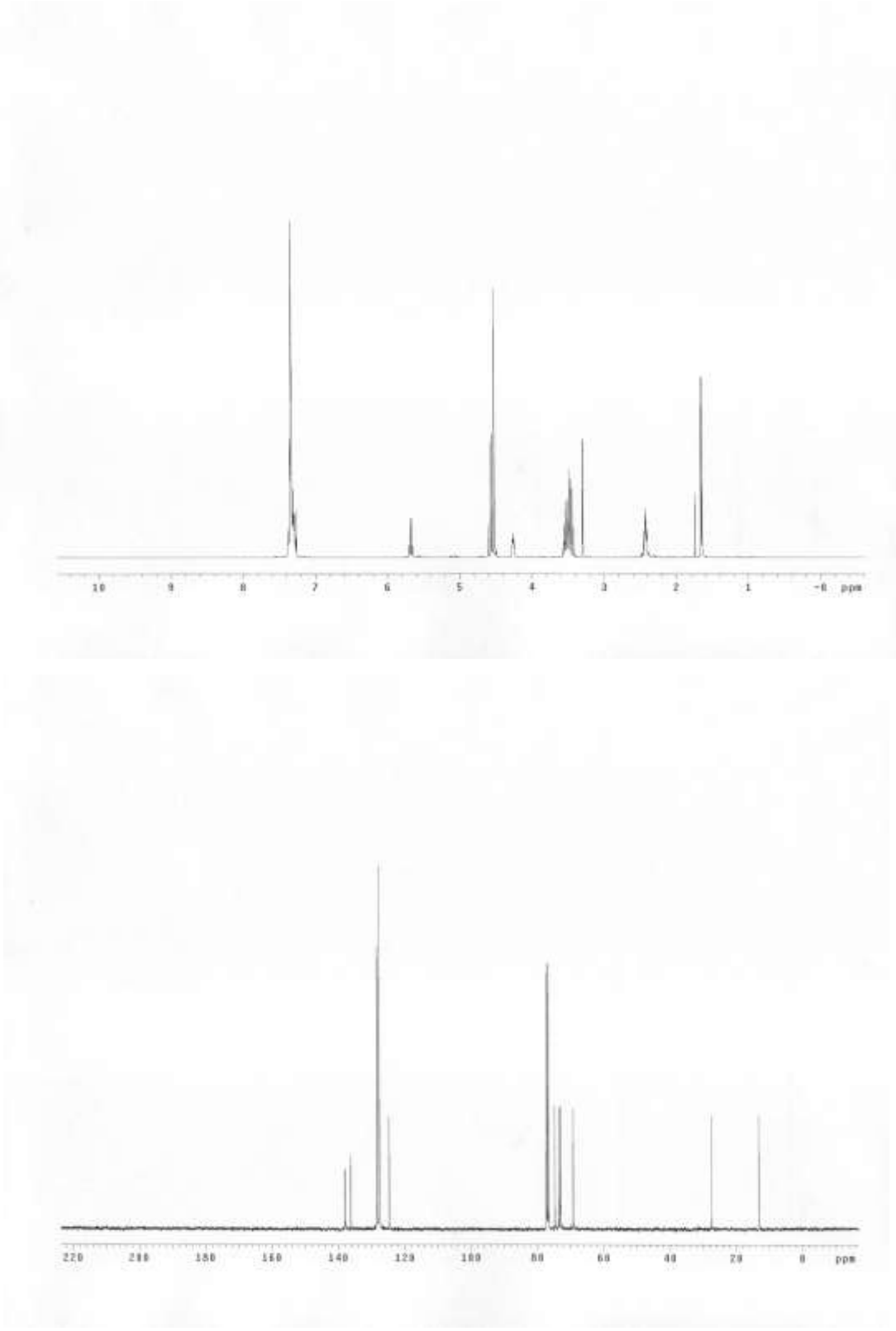
General Procedure (*via* alkyne 4.1f): In modification to the general procedure, the reaction was conducted at 0.5 M concentration. The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/Hexane) to furnish the title compound (60.7 mg, 62%, 14:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 10H), 5.70-5.65 (q, J = 6.8 Hz, 1H), 4.60-4.52 (m, 4H), 4.28-4.24 (m, 1H), 3.57-3.42 (m, 4H), 3.30 (d, J = 3.2 Hz, 1H), 2.47-2.39 (m, 2H), 1.65 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 137.8, 136.2, 128.4, 128.3, 127.7, 127.6, 124.6, 74.8, 73.6, 73.2, 73.0, 69.3, 27.4, 13.2.

HRMS (CI) Calcd. For $C_{21}H_{27}O_3$ $[M+H]^+$: 327.1960, Found: 327.1959.

FTIR (in $CDCl_3$): 3424, 3056, 3023, 1495, 1453, 1354, 1201, 1097, 1068, 1014, 745, 695 cm^{-1}.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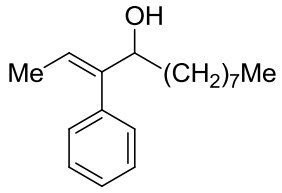
(*E*)-3-phenyldodec-2-en-4-ol (4.4a)



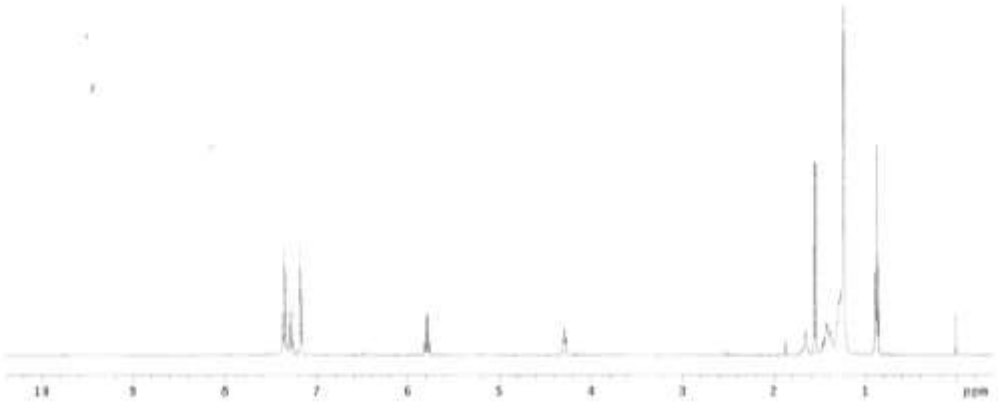
General Procedure (*via* alkyne 4.1a): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (69.7 mg, 89%, >20:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 2H), 7.30-7.26 (m, 1H), 7.18-7.15 (m, 2H), 5.79 (dq, *J* = 6.8, 0.8 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 1H), 1.65 (s, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.48-1.35 (m, 2H), 1.31-1.24 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 138.1, 129.3, 128.0, 126.8, 122.8, 76.9, 35.6, 31.8, 29.5, 29.4, 29.2, 25.7, 22.6, 14.2, 14.1.

HRMS (CI) Calcd. For $C_{18}H_{27}O$ $[M-H]^+$: 259.2062, Found: 259.2060.

FTIR (in $CDCl_3$): 3342, 2924, 2854, 1600, 1493, 1440, 908, 840, 765, 733, 701 cm^{-1}.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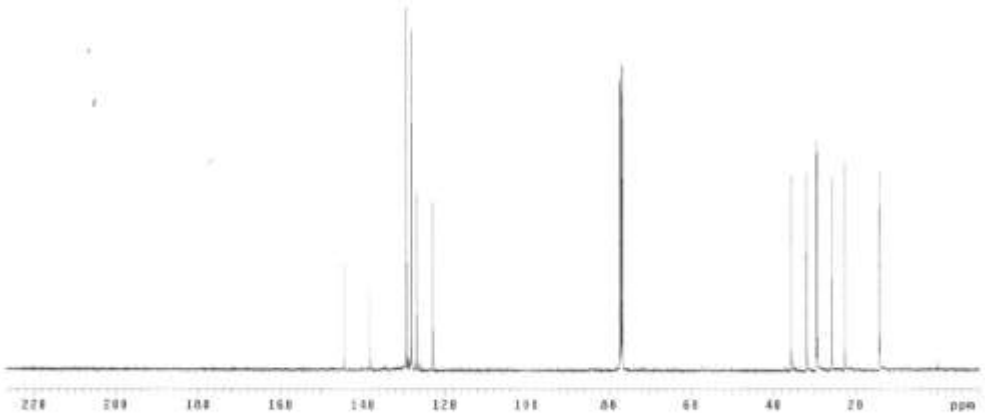
220
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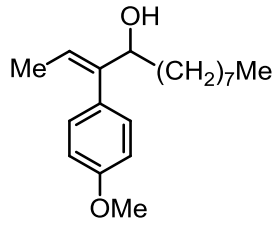
ppm

(*E*)-3-(4-methoxyphenyl)dodec-2-en-4-ol (4.4b)



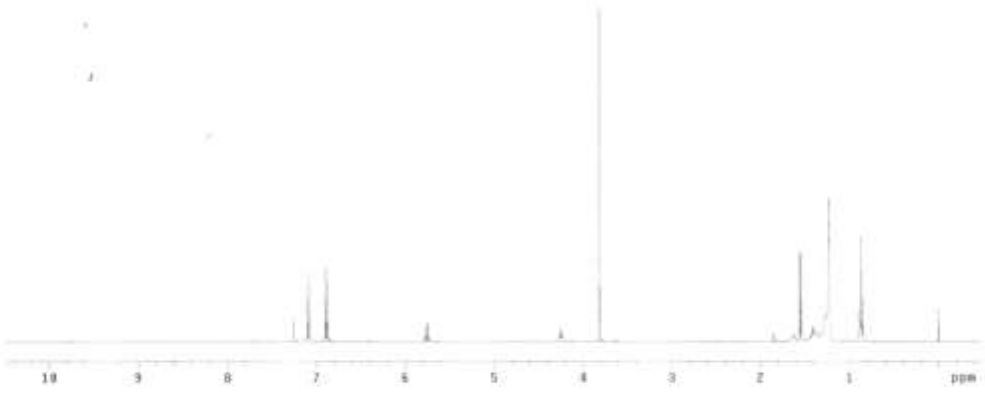
General Procedure (*via* alkyne 4.1b): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 8% EtOAc/Hexane) to furnish the title compound (67.1 mg, 77%, 17:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dt, *J* = 9.2, 2.8 Hz, 2H), 6.89 (dt, *J* = 9.2, 2.8 Hz, 2H), 5.75 (dq, *J* = 6.8, 0.8 Hz, 1H), 4.25 (t, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 1.63 (s, 1H), 1.55 (dd, *J* = 6.8, 0.4 Hz, 3H), 1.45-1.34 (m, 2H), 1.32-1.23 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 143.9, 130.3, 130.2, 122.8, 113.5, 77.0, 55.1, 35.6, 31.8, 29.5, 29.5, 29.2, 25.7, 22.6, 14.3, 14.1.

HRMS (CI) Calcd. For $C_{19}H_{30}O_2$ (M^+): 290.2246, Found: 290.2245.

FTIR (in $CDCl_3$): 3385, 2924, 2854, 1608, 1510, 1464, 1286, 1244, 1176, 1036, 908, 832, 732 cm^{-1}.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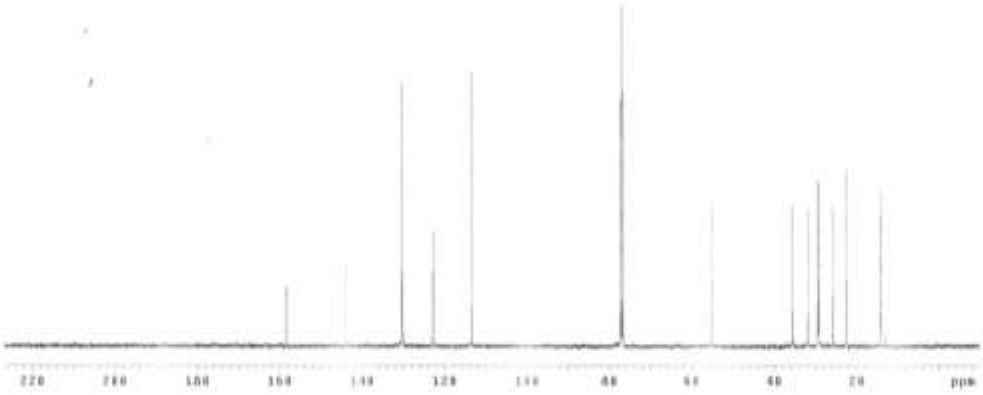
220
200
180
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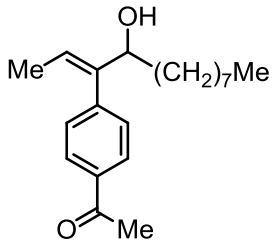
ppm

(*E*)-1-(4-(4-hydroxydodec-2-en-3-yl)phenyl)ethanone (4.4c)



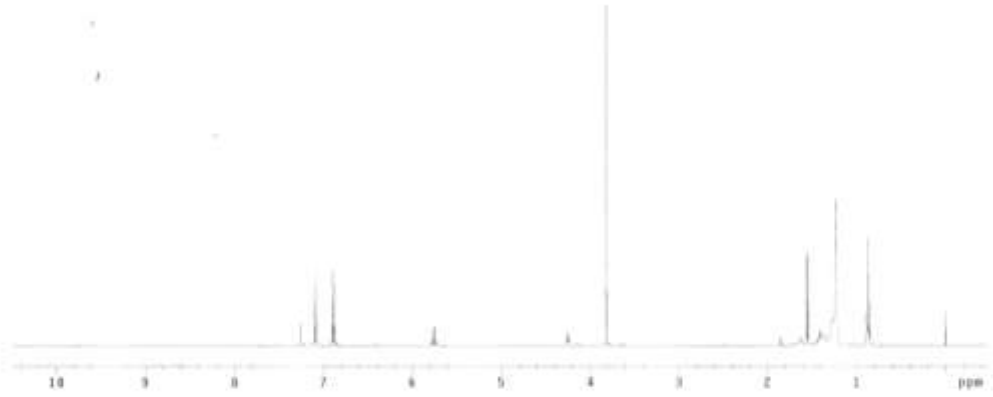
General Procedure (*via* alkyne 4.1c): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/Hexane) to furnish the title compound (74.4 mg, 82%, 17:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.28 (m, 2H), 5.84 (q, *J* = 6.8 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 1H), 2.60 (s, 3H), 1.87 (s, 1H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.41-1.34 (m, 2H), 1.29-1.21 (m, 12H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 143.6, 135.6, 129.6, 128.1, 124.0, 76.7, 35.6, 31.8, 29.4, 29.4, 29.1, 26.5, 25.6, 22.6, 14.3, 14.0.

HRMS (CI) Calcd. For $C_{20}H_{31}O_2$ $[M+H]^+$: 302.2324, Found: 303.2328.

FTIR (in $CDCl_3$): 3422, 2924, 2854, 1677, 1603, 1401, 1357, 1266, 909, 833, 731 cm^{-1}.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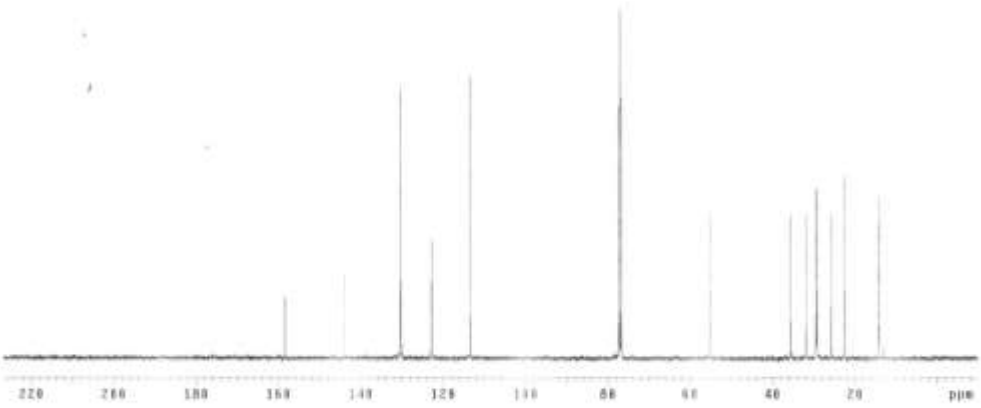
ppm


220
200
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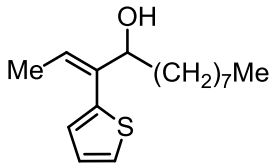
ppm

(*Z*)-3-(thiophen-2-yl)dodec-2-en-4-ol (4.4d)



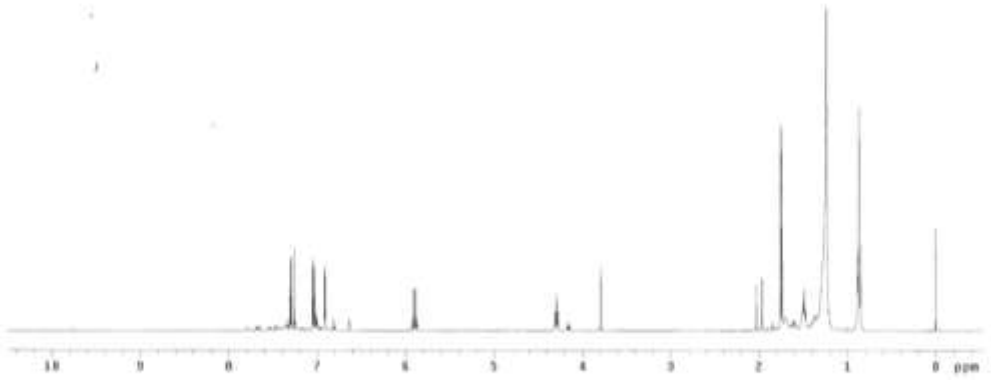
General Procedure (*via* alkyne 4.1d): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (43.9 mg, 55%, 5:1 r.r.) as a yellow oil.

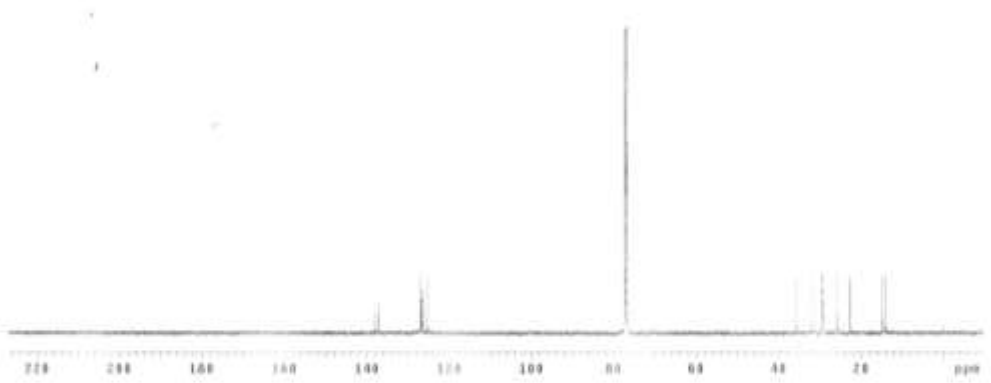
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.05-7.02 (m, 1H), 6.91 (dd, *J* = 3.6, 1.2 Hz, 1H), 5.90 (dq, *J* = 6.8, 0.8 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 1H), 1.75 (dd, *J* = 6.8, 0.4 Hz, 3H), 1.70 (s, 1H), 1.53-1.47 (m, 2H), 1.35-1.24 (m, 12H), 0.87 (t, *J* = 6.8, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 137.2, 126.9, 126.6, 126.1, 125.1, 77.2, 35.7, 31.8, 29.5, 29.4, 29.2, 25.8, 22.6, 14.8, 14.1.

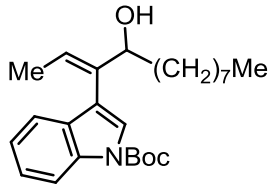
HRMS (CI) Calcd. For $C_{16}H_{26}OS$ (M^+): 266.1704, Found: 266.1700.

FTIR (in $CDCl_3$): 3370, 2923, 2853, 1509, 1436, 1245, 1035, 908, 849, 831, 733, 693 cm^{-1}.





(*E*)-*tert*-butyl 3-(4-hydroxydodec-2-en-3-yl)-1H-indole-1-carboxylate (4.4e)



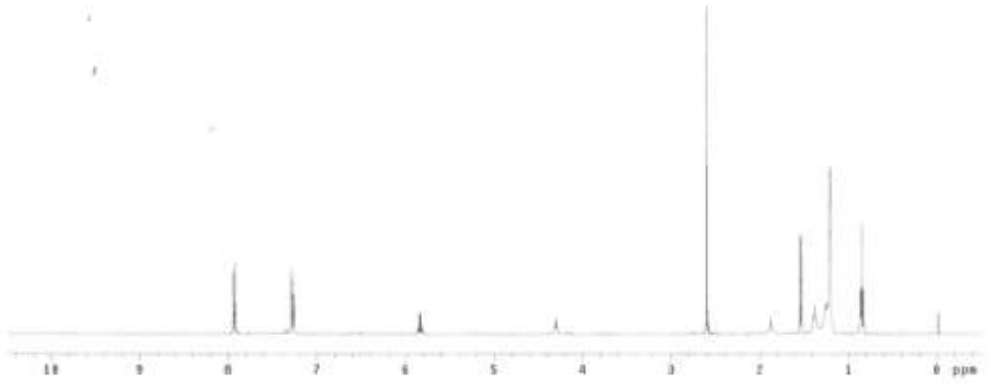
General Procedure (*via* alkyne 4.1e): In modification to the general procedure, 10 mol% of TBAI was employed. After the reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (91.1 mg, 76%, >20:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.33 (dt, J = 7.2, 1.2 Hz, 1H), 7.23 (m, 1H), 5.98 (q, J = 6.8 Hz, 1H), 4.31 (t, J = 6.4 Hz, 1H), 1.69 (s, 10H), 1.56 (d, J = 6.4 Hz, 3H), 1.47-1.41 (m, 2H), 1.30-1.21 (m, 12H), 0.86 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 135.6, 135.0, 130.6, 126.4, 124.2, 123.6, 122.5, 120.3, 117.1, 115.16, 83.6, 77.1, 35.8, 31.8, 29.5, 29.4, 29.2, 28.2, 26.0, 22.6, 15.0, 14.1.

HRMS (CI) Calcd. For $C_{25}H_{37}NO_3$ (M^+): 399.2773, Found: 399.2776.

FTIR (in $CDCl_3$): 3438, 2926, 2854, 1733, 1450, 1371, 1339, 1252, 1155, 1067, 908, 854, 766, 732 cm^{-1}.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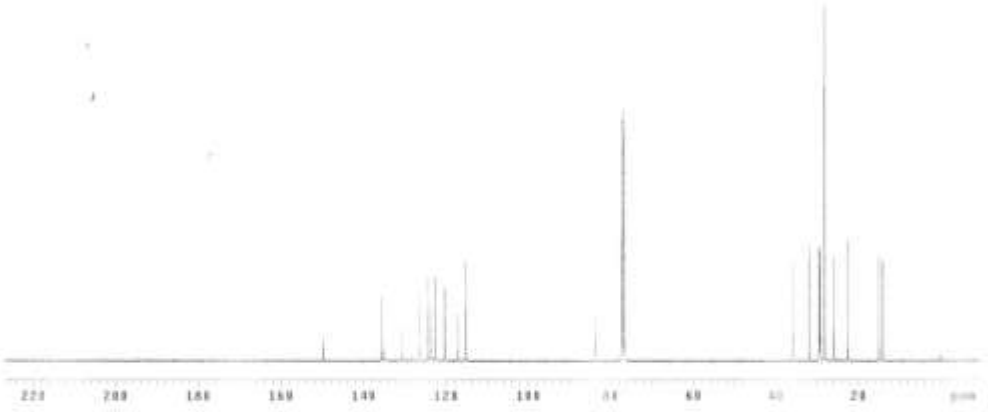
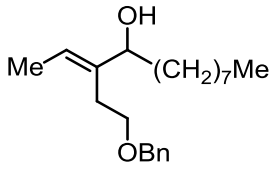


(*E*)-3-(2-(benzyloxy)ethyl)dodec-2-en-4-ol (4.4f)



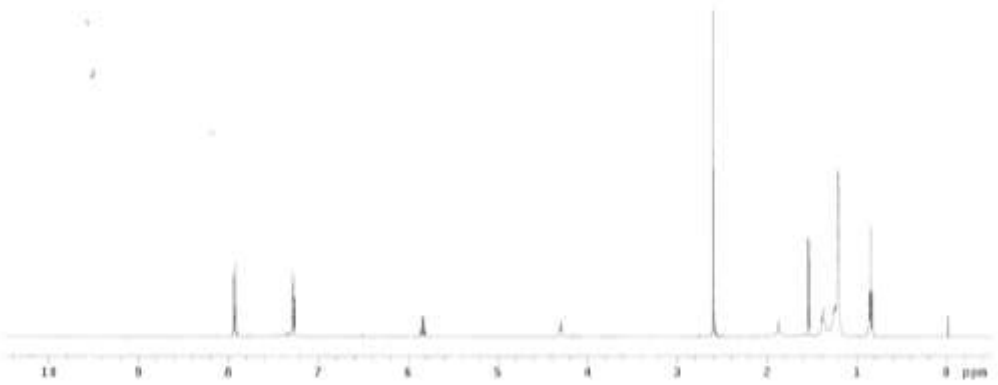
General Procedure (*via* alkyne 4.1f): In modification to the general procedure, 10 mol% of TBAI was employed. The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (58.3 mg, 61%, >20:1 r.r.) as a yellow oil.

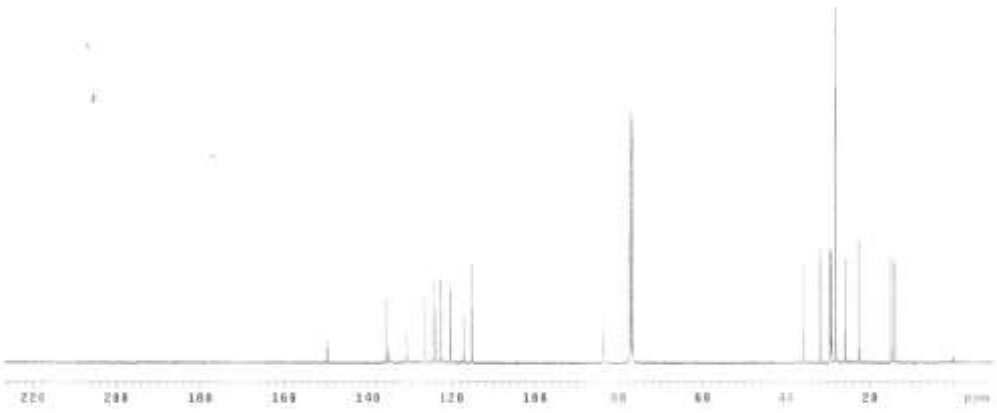
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.54 (q, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 3.95-3.93 (m, 1H), 3.61-3.56 (m, 1H), 3.52-3.46 (m, 1H), 3.20 (d, *J* = 3.2 Hz, 1H), 2.41 (t, *J* = 6.4 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.58-1.52 (m, 1H), 1.46-1.39 (m, 1H), 1.34-1.20 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 137.7, 128.4, 127.7, 127.6, 123.4, 77.2, 73.1 69.4, 36.0, 31.9, 29.6, 29.3, 26.5, 26.0, 22.6, 14.1, 13.2.

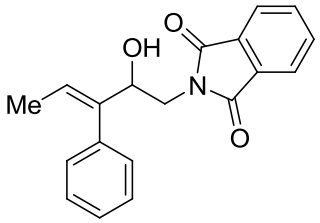
HRMS (CI) Calcd. For $C_{21}H_{33}O_2$ ($M\text{-}H^+$): 317.2481, Found: 317.2479.

FTIR (in $CDCl_3$): 34243419, 2924, 2854, 1454, 1094, 1028, 909, 732, 697 cm^{-1}.





***E*)-2-(2-Hydroxy-3-phenylpent-3-enyl)-isoindoline-1,3-dione (4.5a)**



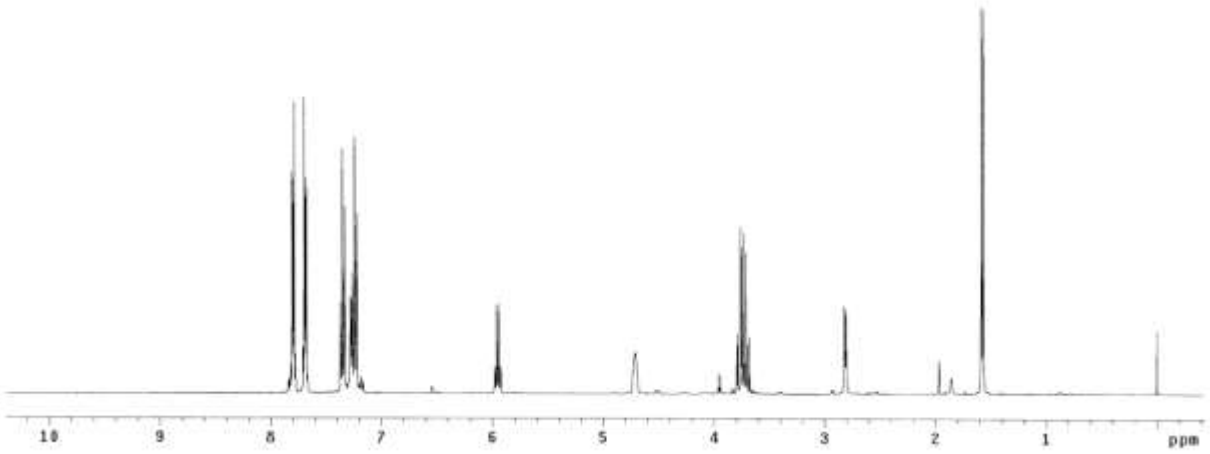
General Procedure (*via* alkyne 4.1a): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/Hexane) to afford the title compound (83.1 mg, 90%, 18:1 r.r.) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (dd, J = 5.4, 3.0 Hz, 2H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H), 7.38-7.32 (m, 2H), 7.30-7.20 (m, 3H), 5.95 (q, J = 6.8 Hz, 1H), 4.78-4.65 (m, 1H), 3.77 (dd, J = 14.3, 3.9 Hz, 1H), 3.70 (dd, J = 14.3, 8.0 Hz, 1H), 2.81 (d, J = 6.1 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 141.0, 137.2, 133.9, 131.8, 129.1, 128.2, 127.1, 124.2, 123.2, 74.2, 43.7, 14.3.

HRMS (CI) Calcd. for $C_{19}H_{18}NO_3$ $[M+H]^+$: 308.1287, Found: 308.1288.

FTIR (in $CDCl_3$): 3470, 1771, 1702, 1493, 1467, 1391, 1073, 1003, 912, 716, 703 cm^{-1}.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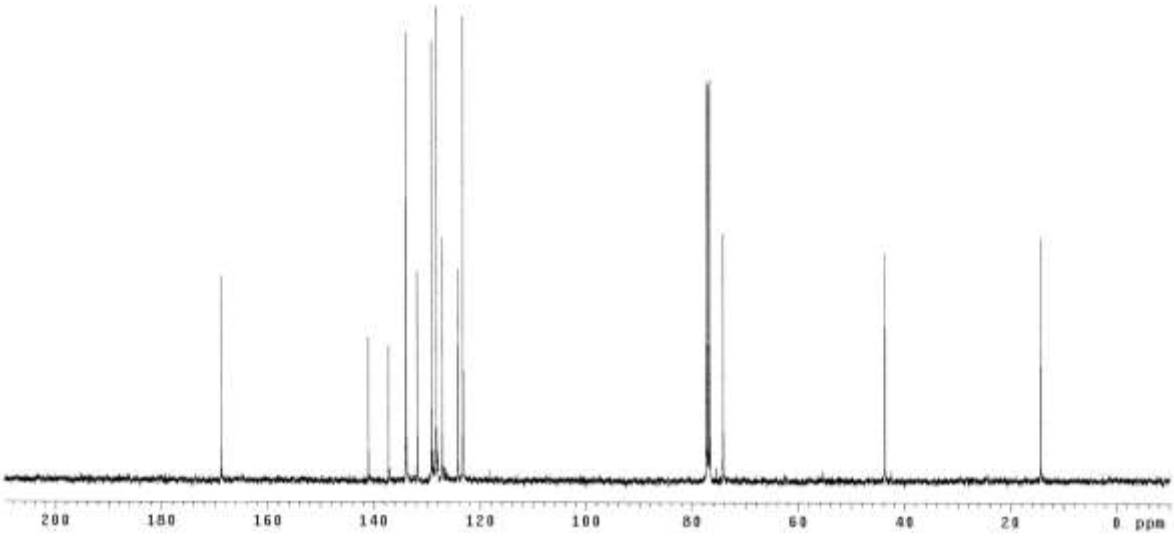
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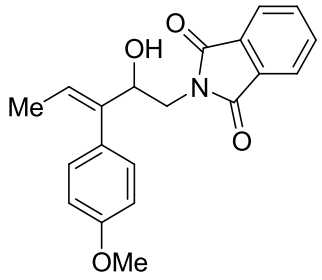
0 ppm

(*E*)-2-(2-Hydroxy-3-(4-methoxyphenyl)-pent-3-enyl)-isoindoline-1,3-dione (4.5b)



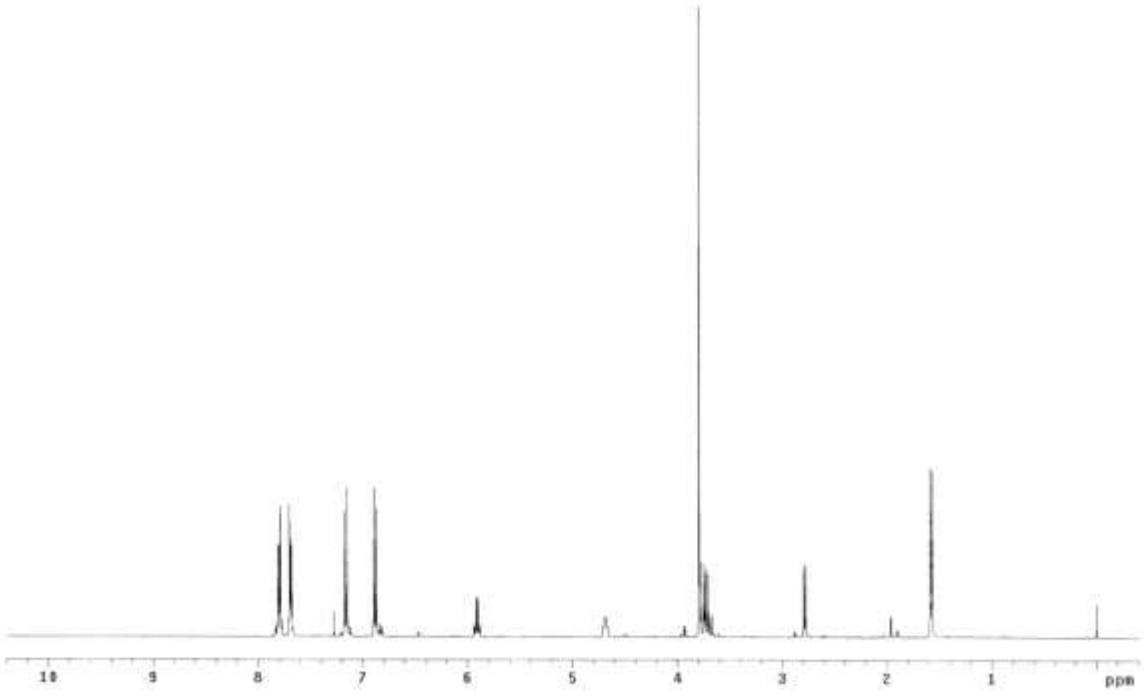
General Procedure (*via* alkyne 4.1b): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/Hexane) to afford the title compound (89.1 mg, 88%, 18:1 r.r.) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (dd, J = 5.5, 2.9 Hz, 2H), 7.69 (dd, J = 5.5, 2.9 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.91 (q, J = 6.8 Hz, 1H), 4.74-4.63 (m, 1H), 3.79 (s, 3H), 3.76 (dd, J = 14.1, 3.9 Hz, 1H), 3.70 (dd, J = 14.1, 8.0 Hz, 1H), 2.78 (d, J = 6.1 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 158.6, 140.5, 133.9, 131.8, 130.2, 129.3, 123.9, 123.2, 113.6, 74.2, 55.1, 43.7, 14.3.

HRMS (CI) Calcd. for $C_{20}H_{19}NO_4$ $[M]^{+\cdot}$: 337.1314, Found: 337.1310.

FTIR (in $CDCl_3$): 3469, 2936, 1771, 1704, 1607, 1510, 1467, 1429, 1392, 1244, 1033, 909, 714 cm^1.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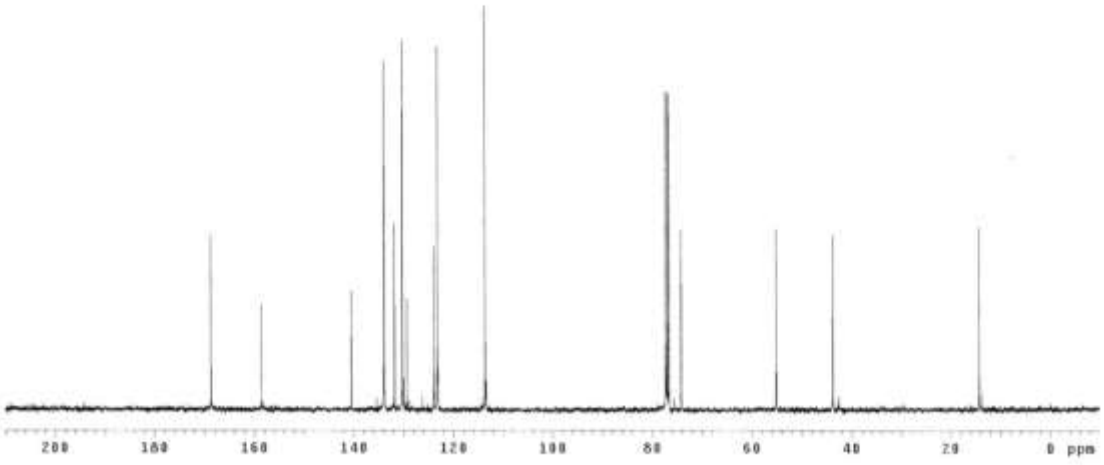
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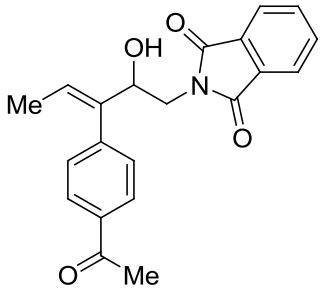
(*E*)-2-(3-(4-Acetylphenyl)-2-hydroxypent-3-enyl)-isoindoline-1,3-dione (4.5c)



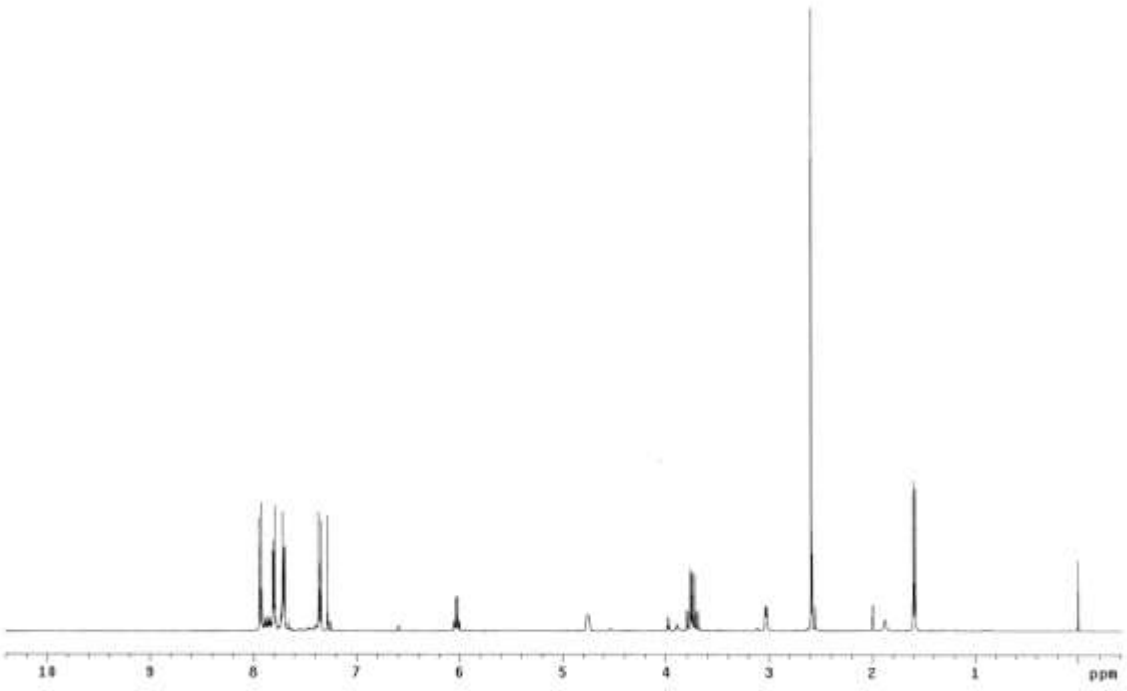
General Procedure (*via* alkyne 4.1c): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30% EtOAc/Hexane) to afford the title compound (90.0 mg, 86%, 8:1 r.r.) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (d, J = 8.5 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 7.70 (dd, J = 5.6, 3.2 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 6.03 (q, J = 6.9 Hz, 1H), 4.79-4.71 (m, 1H), 3.78 (dd, J = 14.3, 3.9 Hz, 1H), 3.71 (dd, 14.3, 7.8 Hz, 1H), 3.03 (d, J = 5.7 Hz, 1H), 2.59 (s, 3H), 1.59 (d, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 197.8, 168.8, 142.7, 140.2, 135.8, 134.1, 131.8, 129.5, 128.3, 125.5, 123.4, 74.0, 43.7, 26.6, 14.4.

HRMS (CI) Calcd. for $C_{21}H_{19}NO_4$ $[M]^{+\cdot}$: 349.1314, Found: 349.1314.

FTIR (in $CDCl_3$): 3469, 1771, 1707, 1679, 1603, 1393, 1268, 908, 724 cm^{-1}.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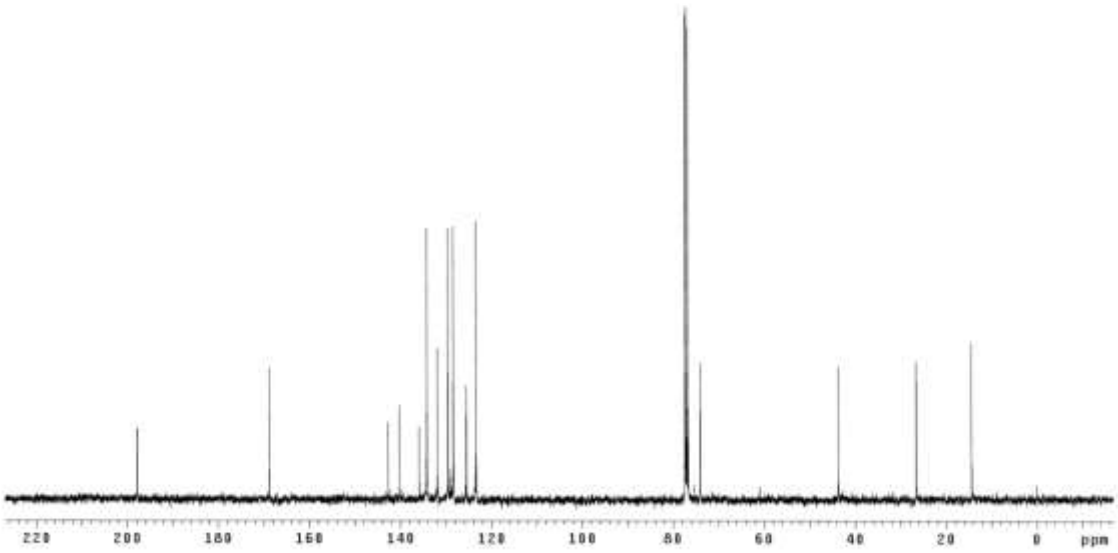
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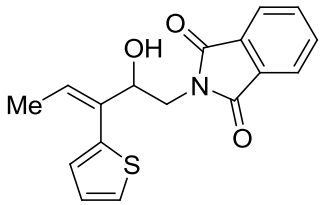
ppm

(*Z*)-2-(2-Hydroxy-3-(thiophen-2-yl)-pent-3-enyl)-isoindoline-1,3-dione (4.5d)



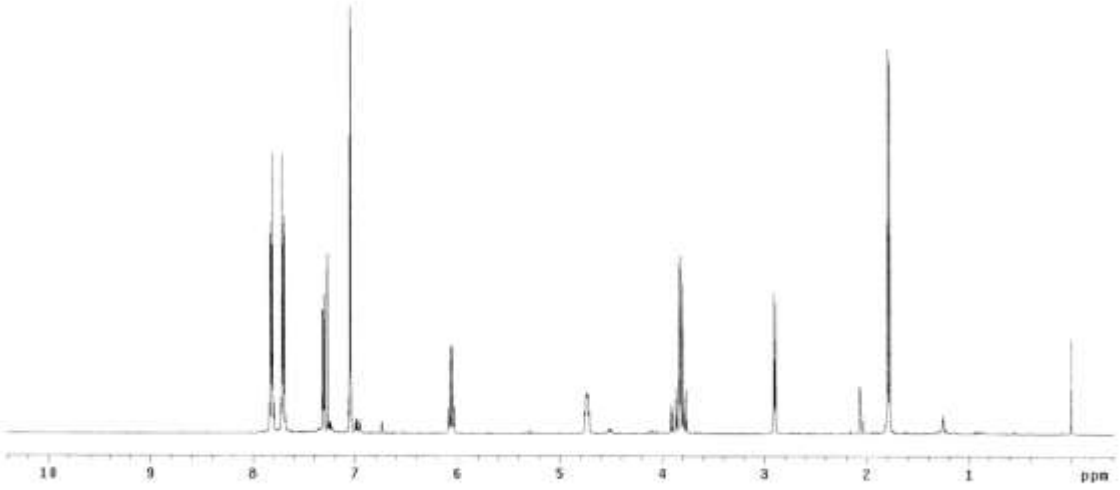
General Procedure (*via* alkyne 4.1d): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/Hexane) to afford the title compound (73.1 mg, 78%, 11:1 r.r.) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (dd, J = 5.6, 3.1 Hz, 2H), 7.70 (dd, J = 5.6, 3.1 Hz, 2H), 7.33-7.28 (m, 1H), 7.07-7.02 (m, 2H), 6.06 (q, J = 6.8 Hz, 1H), 4.78-4.68 (m, 1H), 3.85 (dd, J = 14.3, 4.1 Hz, 1H), 3.79 (dd, J = 14.3, 7.8 Hz, 1H), 2.90 (d, J = 5.7 Hz, 1H), 1.79 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 137.5, 134.0, 133.9, 131.8, 127.0, 126.8, 126.7, 125.5, 123.3, 74.5, 43.8, 14.8.

HRMS (CI) Calcd. for $C_{17}H_{15}NO_3S$ $[M]^{+\cdot}$: 313.0773, Found: 313.0771.

FTIR (in $CDCl_3$): 3465, 2918, 1770, 1701, 1467, 1428, 1392, 848, 713, 695 cm^{-1}.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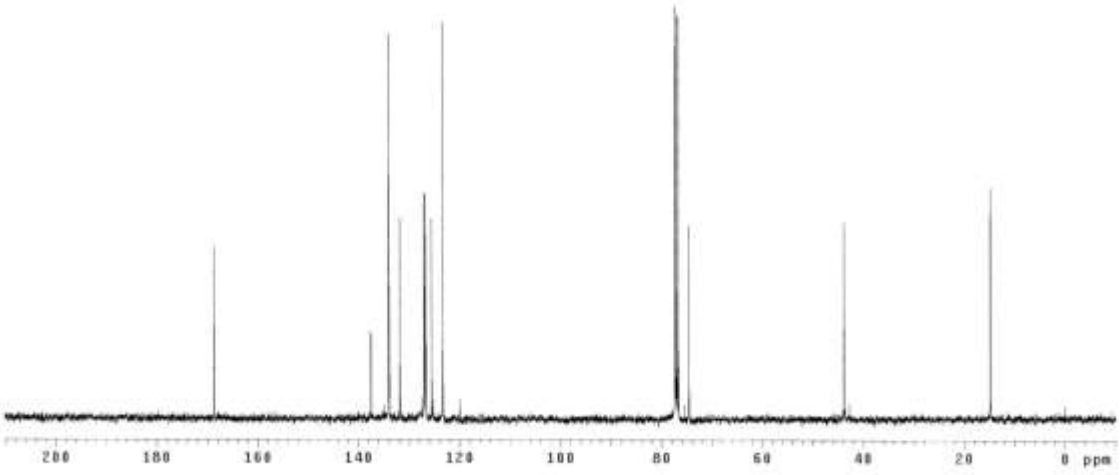
ppm


200
180
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140
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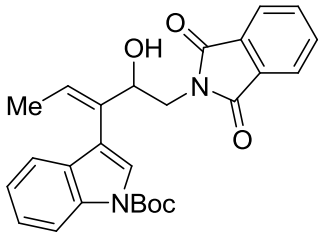
100
80
60
40
20
0 ppm

(*E*)-*t*-Butyl-3-(5-(1,3-dioxoisoindolin-2-yl)-4-hydroxypent-2-en-3-yl)-1H-indole-1-carboxylate (4.5e)



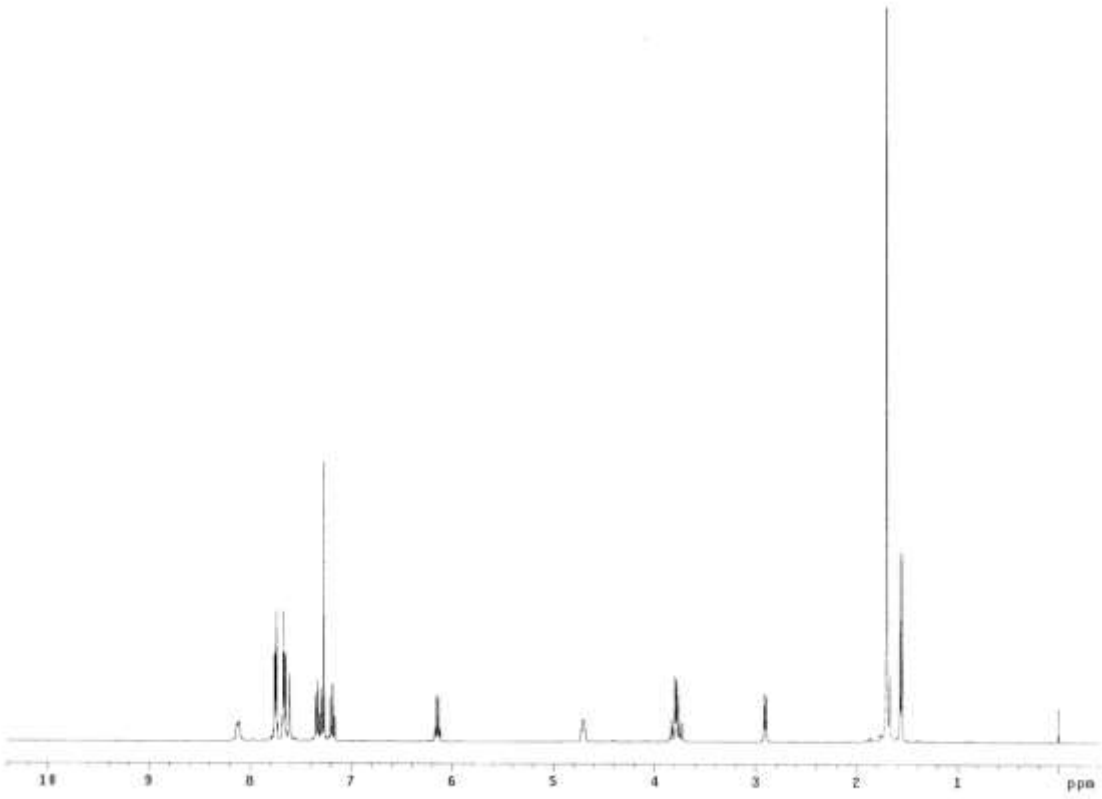
General Procedure (*via* alkyne 4.1e): The reaction was heated for 16 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/Hexane) to afford the title compound (127 mg, 95%, >20:1 r.r.) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (d, J = 7.6 Hz, 1H), 7.75 (dd, J = 5.5, 3.1Hz, 2H), 7.66 (dd, J = 5.5, 3.1 Hz, 2H), 7.61 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.18 (dd, J = 7.8, 7.0 Hz, 1H), 6.14 (q, J = 6.8 Hz, 1H), 4.76-4.64 (m, 1H), 3.82 (dd, J = 14.3 Hz, 1H), 3.75 (dd, J = 14.3, 8.0 Hz, 1H), 2.90 (d, J = 6.7 Hz, 1H), 1.7 (s, 9H), 1.56 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 149.5, 135.0, 133.9, 132.3, 131.7, 130.0, 128.0, 124.3, 124.1, 123.1, 122.6, 120.1, 116.1, 115.1, 83.7, 74.6, 43.7, 28.1, 15.0.

HRMS (CI) Calcd. for $C_{26}H_{26}N_2O_5$ $[M]^{+\cdot}$: 446.1842, Found: 446.1845.

FTIR (in $CDCl_3$): 3460, 2980, 1772, 1705, 1450, 1392, 1371, 1250, 1154, 1071, 909, 767, 714 cm^{-1}.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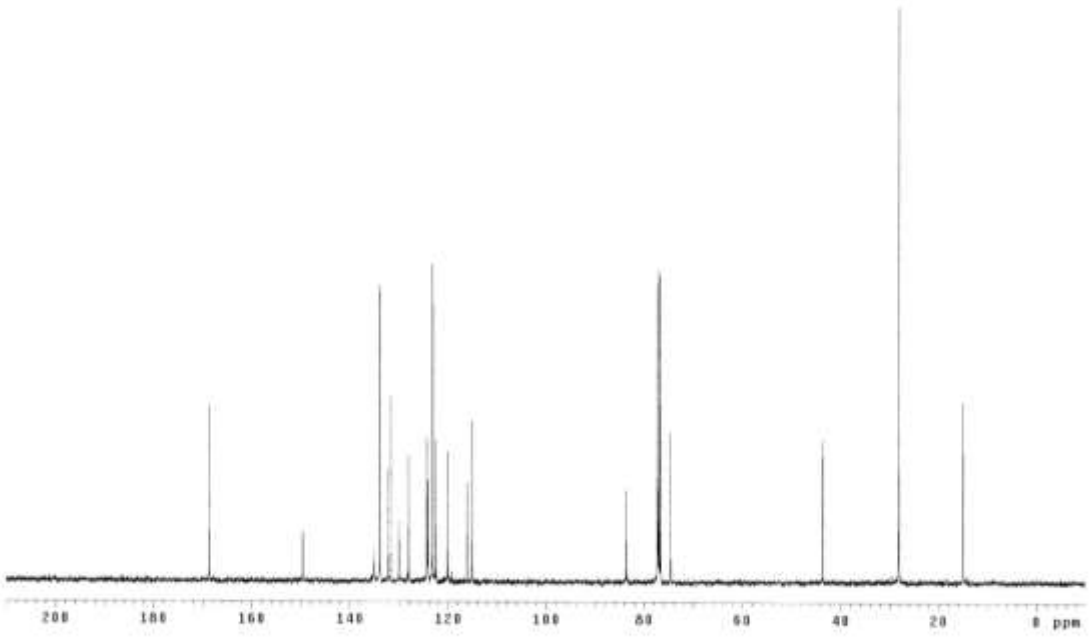
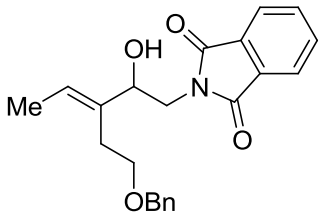
ppm


200
180
160
140
120
100
80
60
40
20
0 ppm

(*E*)-2-(3-(2-(benzyloxy)-ethyl)-2-hydroxypent-3-enyl)-isoindoline-1,3-dione (4.5f)



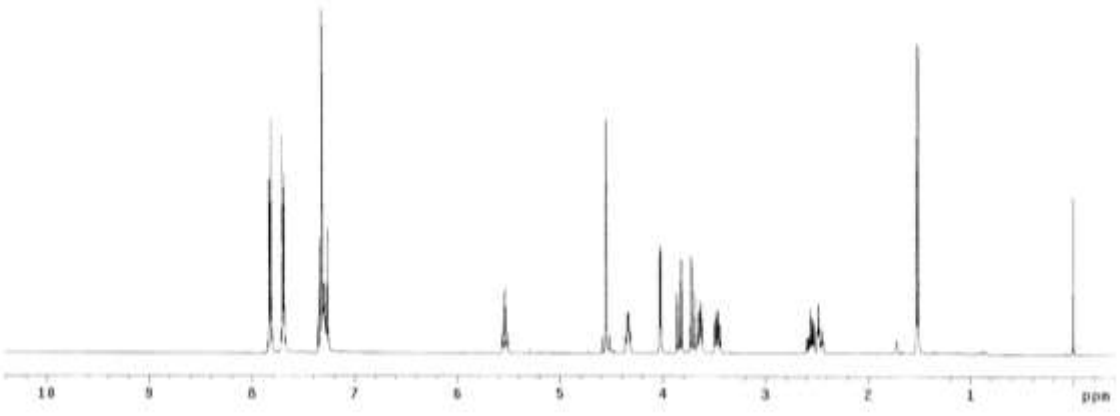
General Procedure (*via* alkyne 4.1f): In modification to the general procedure, the reaction was conducted at 2.0 M concentration. The reaction was heated for 24 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/Hexane) to afford the title compound (57.7 mg, 52%, >20:1 r.r.) as a viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.37-7.24 (m, 5H), 5.54 (q, *J* = 6.9 Hz, 1H), 4.55 (s, 2H), 4.38-4.30 (m, 1H), 4.02 (d, *J* = 4.3 Hz, 1H), 3.84 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.71 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.64 (ddd, *J* = 8.8, 5.2, 4.4 Hz, 1H), 3.47 (ddd, *J* = 9.8, 8.8, 4.4 Hz, 1H), 2.56 (ddd, *J* = 14.6, 9.8, 5.2 Hz, 1H), 2.47 (ddd, *J* = 14.6, 4.4, 4.4 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.4, 137.4, 137.2, 133.8, 132.0, 128.4, 127.8, 127.7, 125.3, 123.2, 73.8, 73.2, 69.2, 42.6, 26.4, 13.2.

HRMS (CI) Calcd. for $C_{22}H_{24}NO_4$ $[M+H]^+$: 366.1705, Found: 366.1703.

FTIR (in $CDCl_3$): 3436, 2860, 1770, 1706, 1467, 1429, 1392, 1088, 714, 698 cm^{-1}.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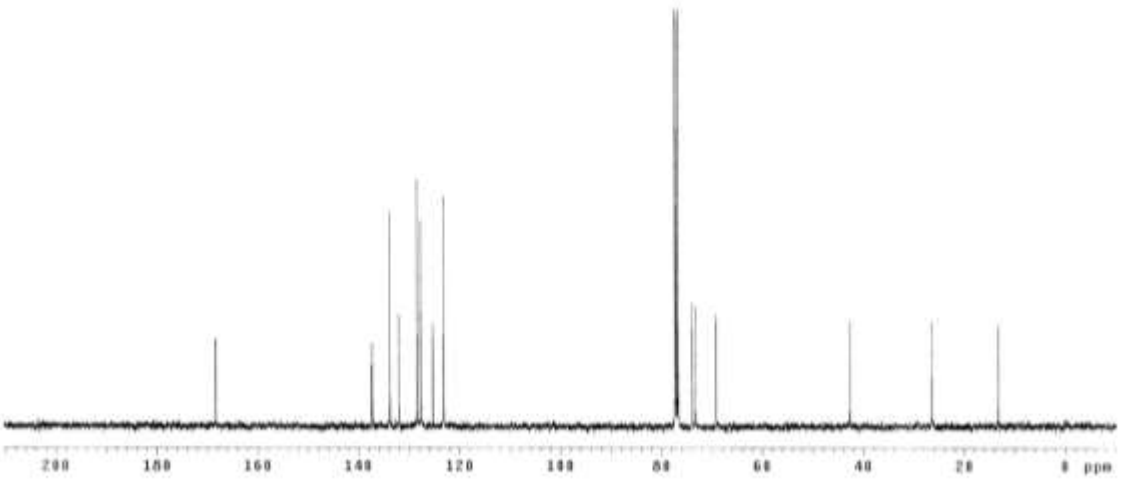
ppm


200
180
160
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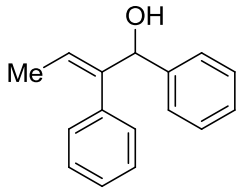
0 ppm

(*E*)-1,2-diphenylbut-2-en-1-ol (4.6a)



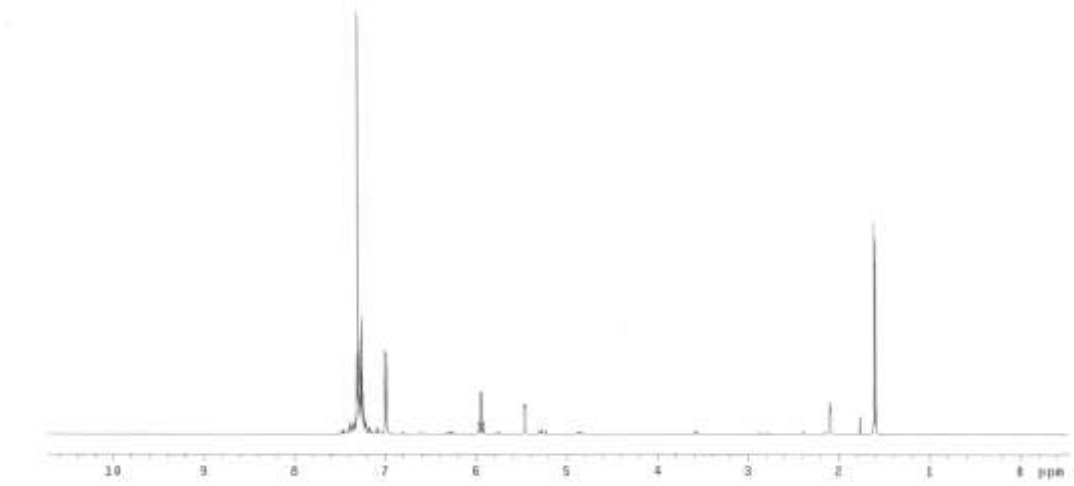
General Procedure (*via* alkyne 4.1a): In modification to the general procedure, The reaction was heated at 45 °C for 48 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (57.2 mg, 85%, >20:1 r.r.) as a yellow oil. (Note: A mixture of 14:1 **4.6a**:*allyl*-**4.6a** was observed.)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 8H), 7.00-6.98 (m, 1H), 5.95 (dq, J = 6.8, 1.2 Hz, 1H), 5.46 (d, J = 3.6 Hz, 1H), 2.09 (m, 1H), 1.61 (dd, J = 6.8, 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 142.2, 137.7, 129.4, 128.1, 127.9, 127.3, 126.9, 126.6, 123.6, 78.4, 14.3.

HRMS (CI) Calcd. For $C_{16}H_{16}O$ (M^+): 224.1201, Found: 224.1202.

FTIR (in $CDCl_3$): 3569.3366, 3056, 3027, 2915, 2853, 1499, 1437, 1056, 1006, 919, 758, 700 cm^{-1}.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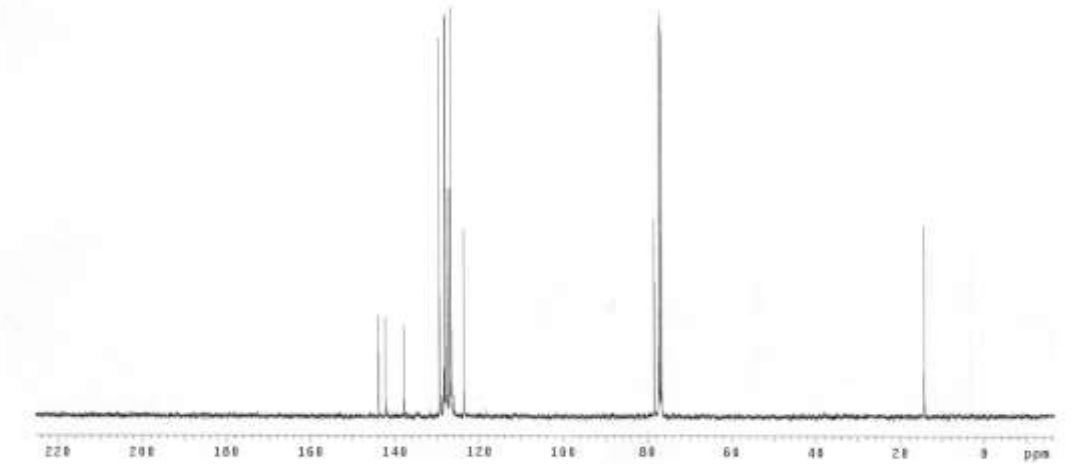
220
200
180
160
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120
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60
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20
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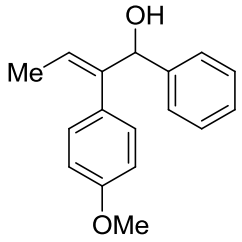
ppm

(*E*)-2-(4-methoxyphenyl)-1-phenylbut-2-en-1-ol (4.6b)



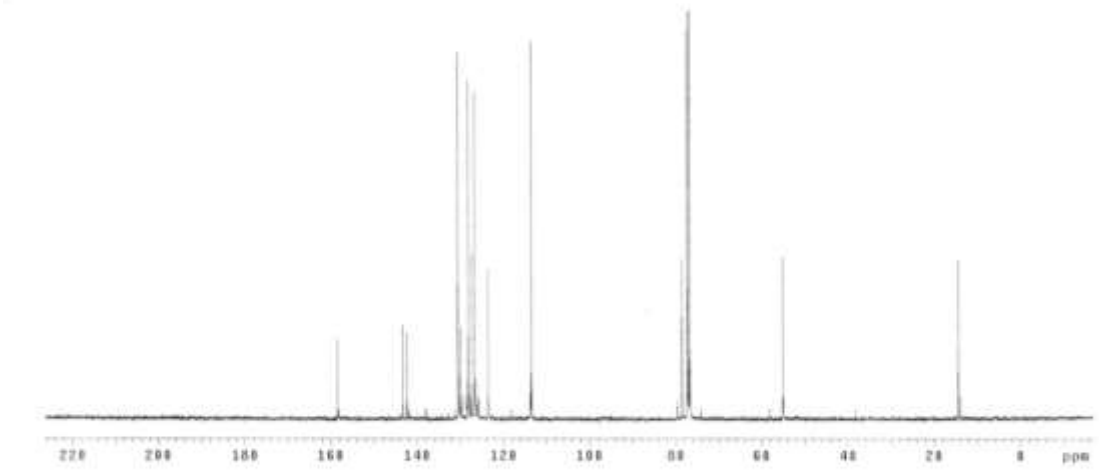
General Procedure (*via* alkyne 4.1b): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (64.1 mg, 84%, 9:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H), 6.91-6.87 (m, 2H), 6.81-6.78 (m, 2H), 5.90 (dq, *J* = 6.8, 1.2 Hz, 1H), 5.42 (s, 1H), 3.77 (s, 3H), 2.07 (s, 1H), 1.58 (dd, *J* = 6.8, 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 143.3, 142.3, 130.5, 129.8, 128.1, 127.2, 126.6, 123.5, 113.4, 78.5, 55.1, 14.4.

HRMS (CI) Calcd. For $C_{16}H_{18}O$ (M^+): 254.1307, Found: 254.1309.

FTIR (in $CDCl_3$): 3408, 3028, 2936, 2908, 2832, 1882, 1606, 1508, 1454, 1287, 1245, 1173, 1030, 834, 736, 701 cm^{-1}.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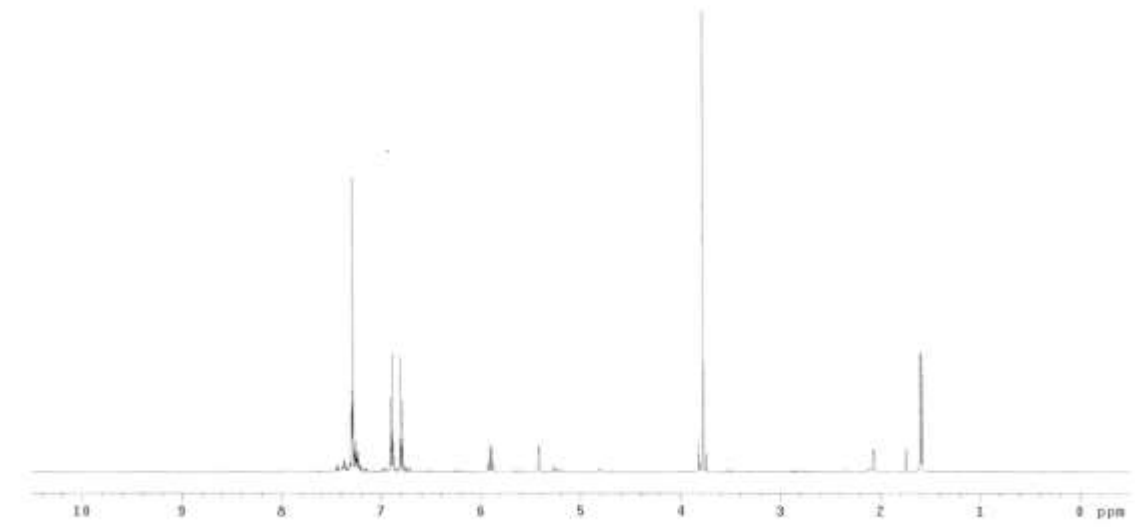
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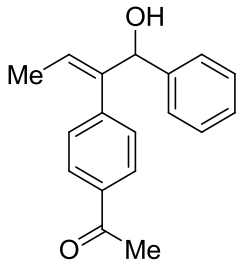
1
0
ppm

(*E*)-1-(4-(1-hydroxy-1-phenylbut-2-en-2-yl)phenyl)ethanone (4.6c)



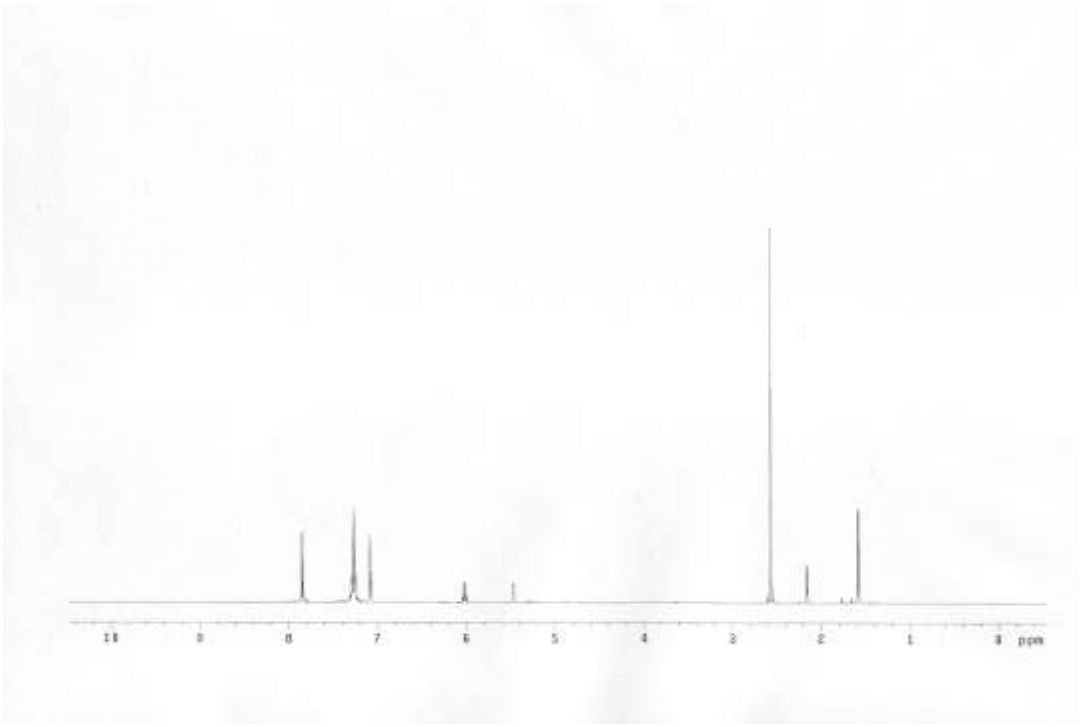
General Procedure (*via* alkyne 4.1c): In modification to the general procedure, 150 mol% of HCO_2H was employed. The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/Hexane) to furnish the title compound (63.1 mg, 79%, >20:1 r.r.) as a yellow oil. (Note: A mixture of 17:1 **6c**:branched allylation product was observed)

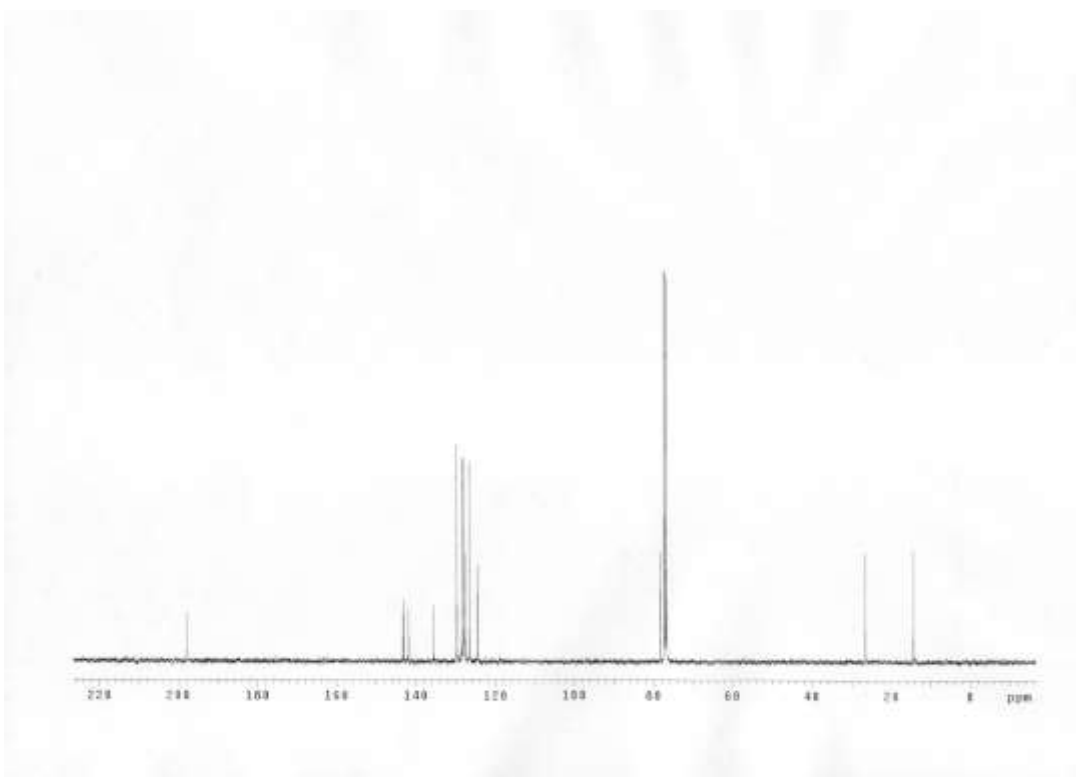
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.4, 2H), 7.31-7.22 (m, 5H), 7.7.08 (d, *J* = 8.4 Hz, 2H), 6.02 (dq, *J* = 6.8, 1.2 Hz, 1H), 5.47 (d, *J* = 3.6 Hz, 1H), 2.57 (s, 3H), 2.16 (d, *J* = 4.0 Hz, 1H), 1.559 (dd, *J* = 6.8, 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 143.3, 143.1, 141.8, 135.6, 129.7, 128.2, 128.0, 127.5, 126.5, 124.5, 78.3, 26.5, 14.4.

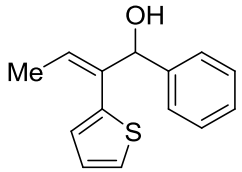
HRMS (CI) Calcd. For $C_{18}H_{19}O_2$ ($M+H^+$): 267.1385, Found: 267.1385.

FTIR (in $CDCl_3$): 3435, 3030, 2914, 2847, 1677, 1606, 1397, 1357, 1263, 1179, 1059, 1014, 956, 854, 698 cm^{-1}.





(*Z*)-1-phenyl-2-(thiophen-2-yl)but-2-en-1-ol (4.6d)



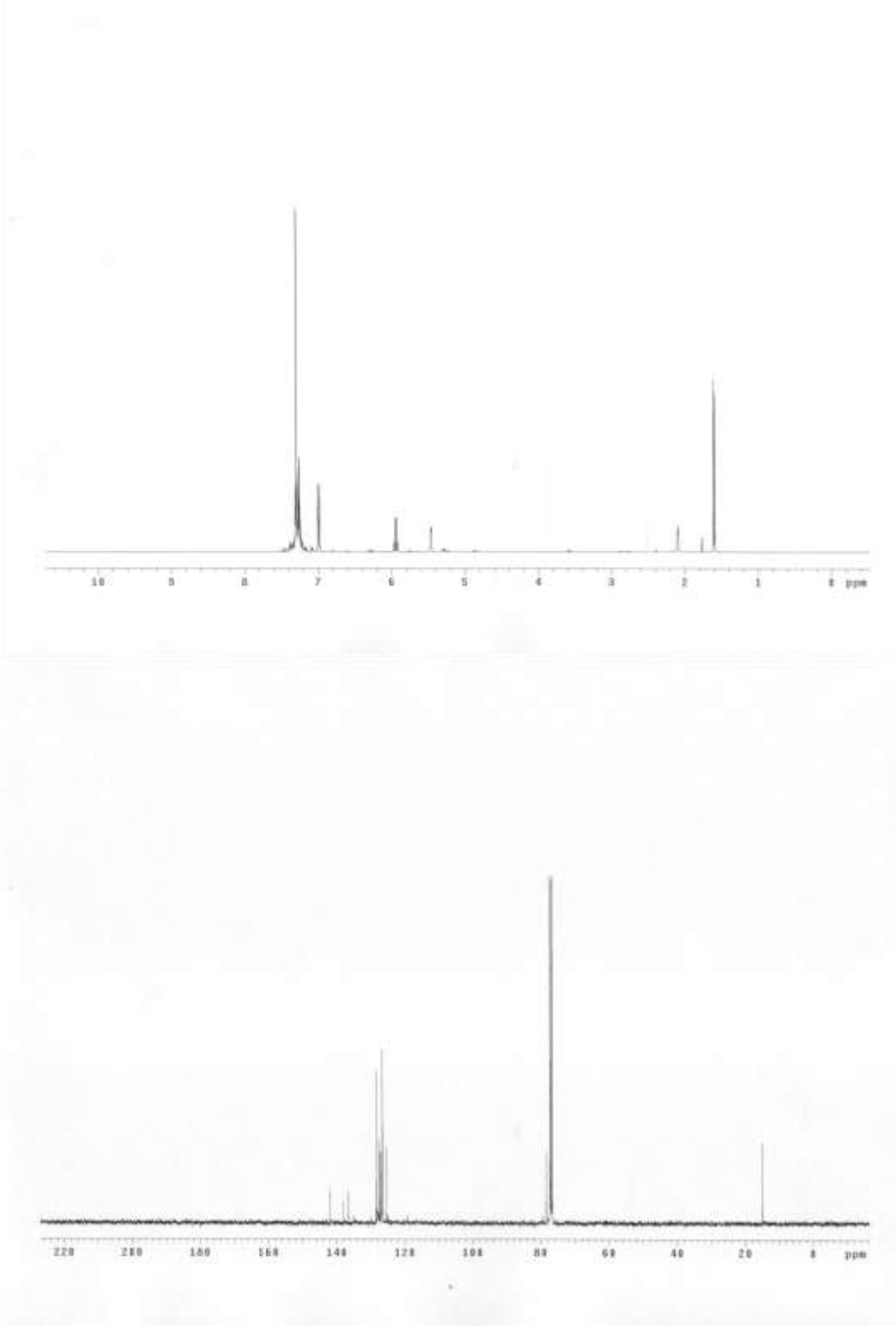
General Procedure (*via* alkyne 4.1d): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (27.6 mg, 40%, 8:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 7.22 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.95 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.76 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.07 (dq, *J* = 6.8, 1.2 Hz, 1H), 5.48 (d, *J* = 4.4 Hz, 1H), 2.12 (d, *J* = 4.8 Hz, 1H), 1.83 (dd, *J* = 7.2, 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 138.0, 136.5, 128.2, 127.5, 127.2, 126.8, 126.6, 126.5, 125.3, 78.4, 15.0.

HRMS (CI) Calcd. For $C_{14}H_{14}OS$ (M^+): 230.0765, Found: 230.0764.

FTIR (in $CDCl_3$): 3379, 3068, 3023, 2857, 1950, 1495, 1445, 1226, 1201, 1043, 1006, 845, 704 cm^{-1}.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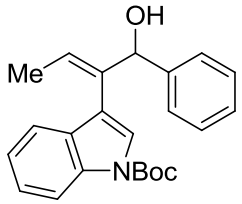
0 ppm

(*E*)-tert-butyl 3-(1-hydroxy-1-phenylbut-2-en-2-yl)-1H-indole-1-carboxylate (4.6e)



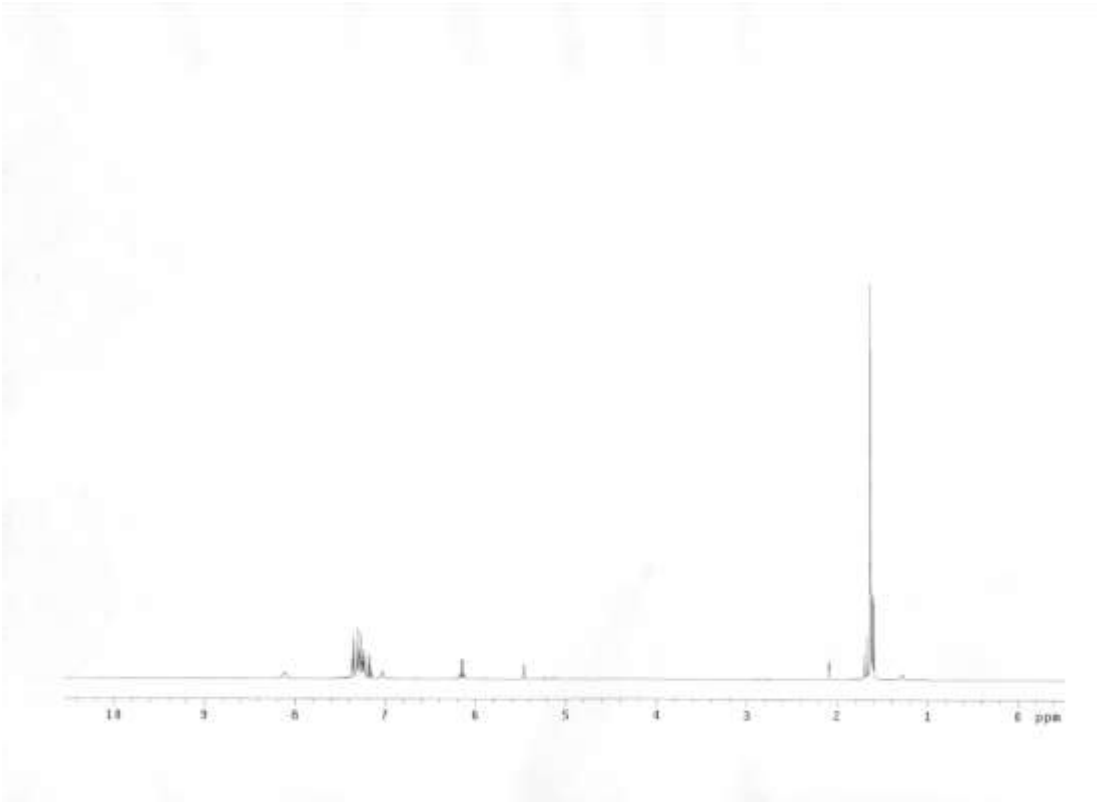
General Procedure (*via* alkyne 4.1e): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% EtOAc/Hexane) to furnish the title compound (68.7 mg, 63%, >20:1 r.r.) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 7.2 Hz, 1H), 7.37-7.34 (m, 2H), 7.31-7.21 (m, 5H), 7.19-7.15 (m, 1H), 7.03 (s, 1H), 6.15 (dq, J = 6.8, 1.2 Hz, 1H), 5.46 (d, J = 3.2 Hz, 1H), 2.09 (d, J = 4.4 Hz, 1H), 1.63 (s, 9H), 1.60 (dd, J = 6.8, 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 142.2, 135.1, 130.4, 128.1, 127.4, 126.9, 126.6, 124.2, 124.0, 122.5, 120.1, 116.8, 115.0, 83.5, 78.3, 28.1, 15.1.

HRMS (CI) Calcd. For $C_{23}H_{25}NO_3$ (M^+): 363.1834, Found: 363.1836.

FTIR (in $CDCl_3$): 3457, 2981, 2928, 2247, 1726, 1450, 1370, 1250, 1148, 1054, 907, 849, 729, 698 cm^{-1}.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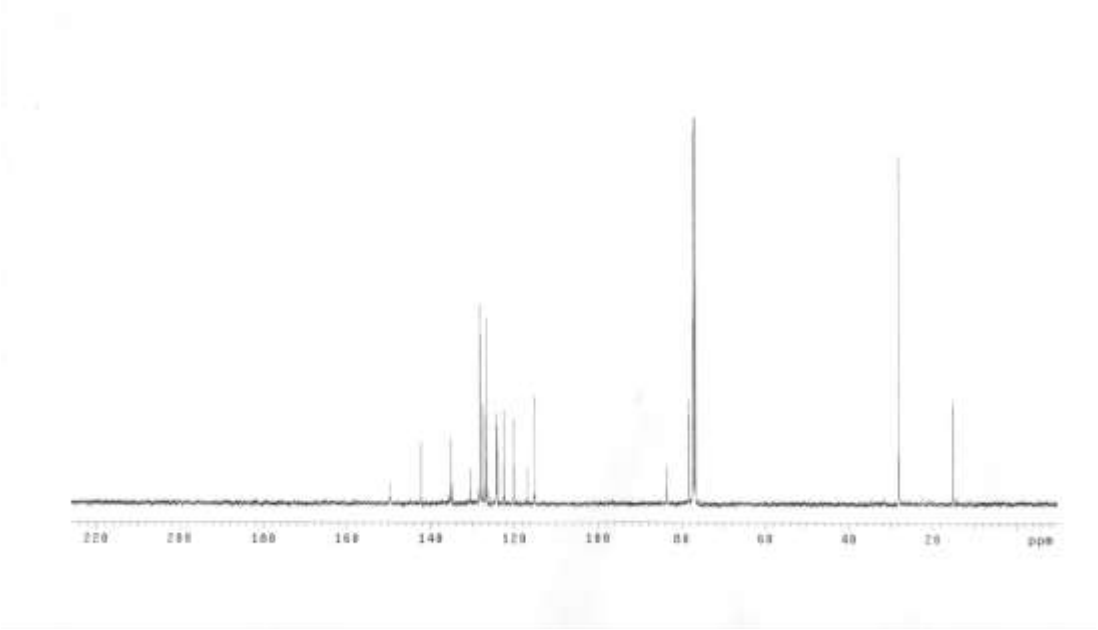
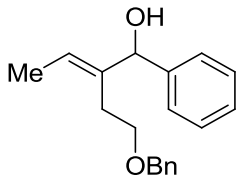

220
200
180
160
140
120
100
80
60
40
20
ppm

(*E*)-2-(2-(benzyloxy)ethyl)-1-phenylbut-2-en-1-ol (4.6f)



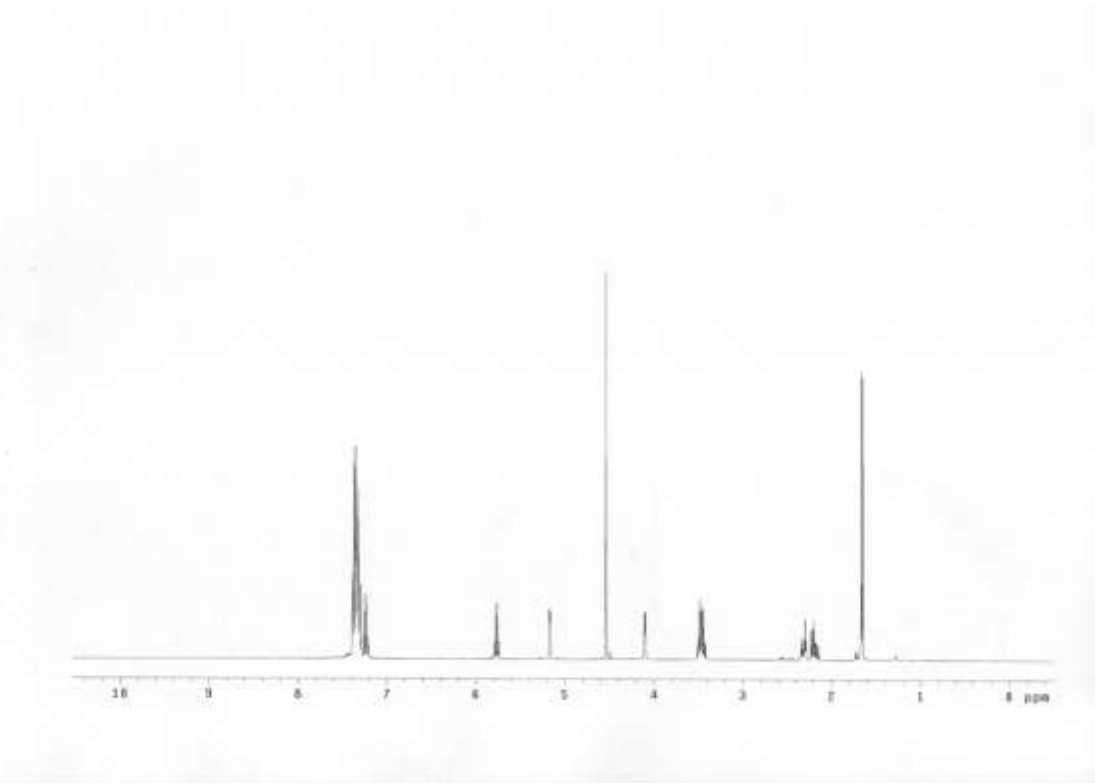
General Procedure (*via* alkyne 4.1f): The reaction was heated for 20 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% EtOAc/Hexane) to furnish the title compound (52.5 mg, 62%, >20:1 r.r.) as a yellow oil.

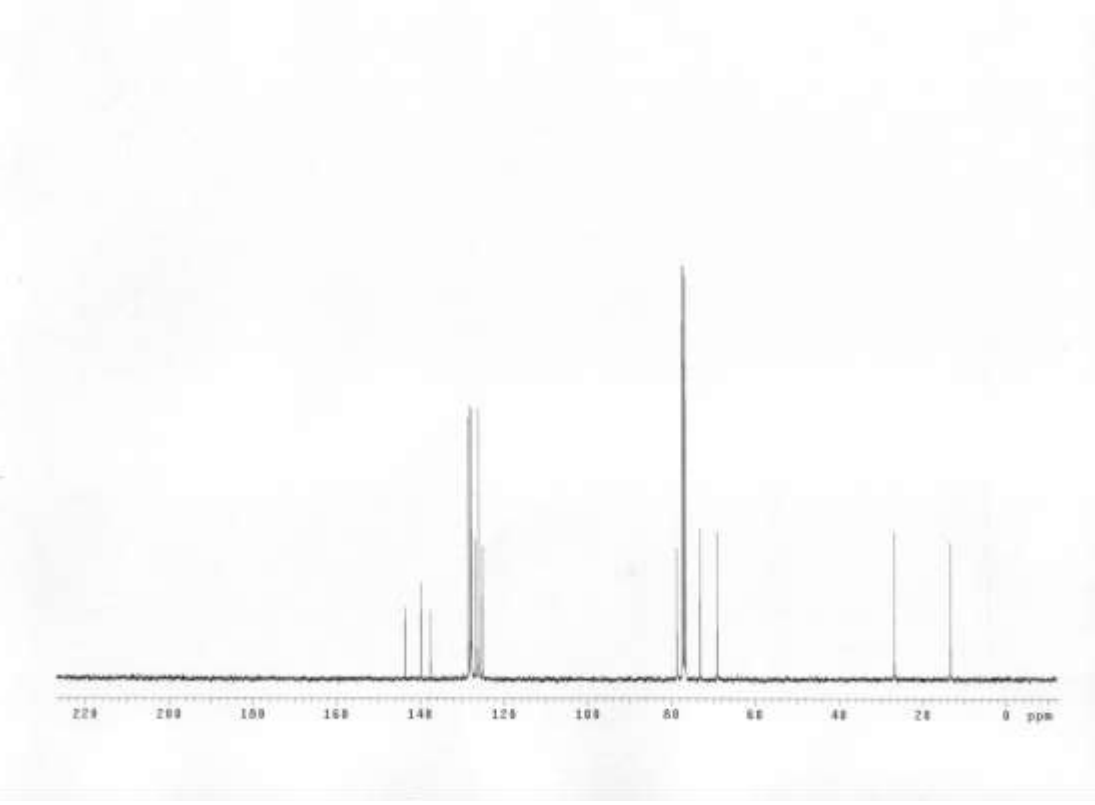
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.30 (m, 9H), 7.25-7.21 (m, 1H), 5.78 (q, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 4.54 (s, 2H), 4.10 (d, *J* = 4.4 Hz, 1H), 3.51-3.42 (m, 2H), 2.35-2.29 (dt, *J* = 14.4, 4.4 Hz, 1H), 2.33-2.14 (m, 1H), 1.66 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 139.7, 137.5, 128.4, 128.0, 127.8, 127.7, 126.7, 126.0, 125.1, 78.6, 73.2, 69.0, 26.8, 13.3.

HRMS (CI) Calcd. For $C_{19}H_{21}O_2$ $[M-H]^+$: 281.1542, Found: 281.1544.

FTIR (in $CDCl_3$): 3399, 3025, 2923, 2861, 1597, 1495, 1450, 1361, 1192, 1094, 1023, 814, 734, 698 cm^{-1}.


10
9
8
7
6
5
4
3
2
1
0 ppm

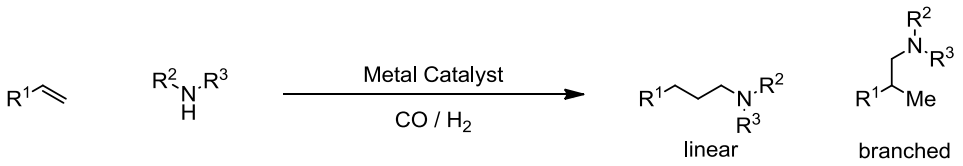

220
200
180
160
140
120
100
80
60
40
20
0 ppm

CHAPTER 5: FORMATION OF ALL-CARBON QUATERNARY CENTERS *VIA* HYDROAMINOMETHYLATION OF ALLENES*

5.1 Introduction

Hydroaminomethylation, the successive one-pot hydroformylation-reductive amination, has emerged as an important atom-efficient method for amine synthesis (Scheme 5.1).[1] Since the pioneering studies of Reppe into hydroaminomethylation at BASF in 1949,[2] relatively few studies have been disclosed until recently.[3] Due in large part to the work of Eilbracht,[4] hydroaminomethylation has been intensively investigated in the last 15 years,[1] and is utilized for the preparation of diverse pharmaceutical ingredients,[5] including cinacalcet (Sensipar, Mimpara),[5,6a] ibutilide (Corvert),[5,6b] and fexofenadine (Allegra, Fexidine, Telfast, Fastofen, Tilfur, Vifas, Telfexo, Allerfexo).[5,6c]

Scheme 5.1. Generic classical hydroaminomethylation of α-olefins.

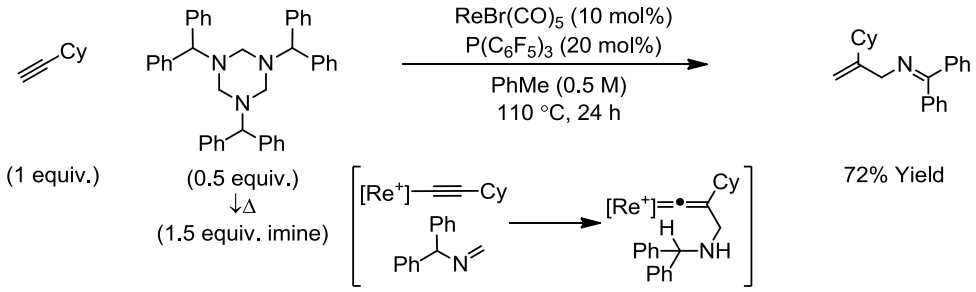


Recent advances in hydroaminomethylation include the use of ammonia as a reactant,[4c,7] regioselective reactions of terminal[8a] and internal[8b] alkenes through ligand control[8] or the use of directing groups[9]. The evolution from rhodium-based to ruthenium-based catalysts,[10] and the emergence of non-carbonylative strategies, including hydroaminoalkylation[11] and photoredox catalysis.[12] The vast majority of methods apply to the hydroaminomethylation of α-olefins. To our knowledge, the hydroaminomethylation of other π-unsaturated reactants, such as dienes or allenes, has

*Acknowledgement is made to Susumu Oda for reaction optimization and scope evaluation.

not been reported.[13] Inspired by these facts and a recent report of terminal alkyne hydroiminomethylation employing triazines as imine surrogates (Scheme 5.2)[14], investigation ensued into a new strategy for hydroaminomethylation *via* isopropanol mediated reductive coupling of 1,1-disubstituted allenes and formimines derived *in situ* from 1,3,5-*tris*(aryl)-hexahydro-1,3,5-triazines. These processes represent the first examples of allene-imine reductive coupling *via* transfer hydrogenation.[15,16,17,18]

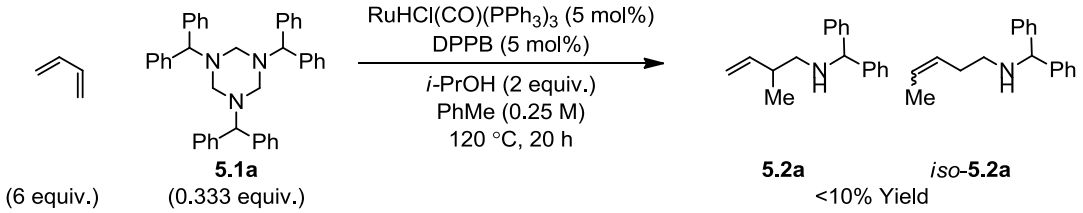
Scheme 5.2. Selected example of alkyne hydroiminomethylation.



5.2 Reaction Development

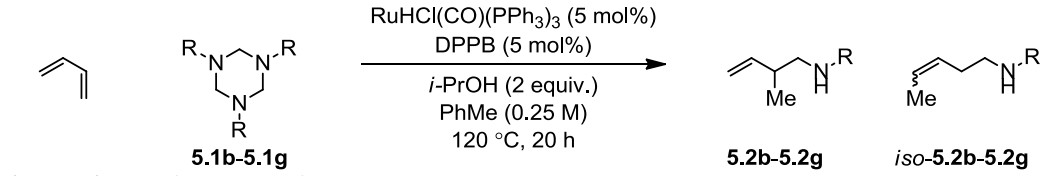
Early studies were inspired by the ruthenium catalyzed reductive coupling of paraformaldehyde to dienes.[13,19] Butadiene (6 equiv.) was exposed to the benzhydryl substituted amine trimer (0.333 equiv.) in the presence of $RuHCl(CO)(PPh_3)_3$ (5 mol%), DPPB (5 mol%), and isopropanol (2 equiv.) in toluene at 120 °C. To our delight, the desired homoallylic amine was obtained but only in trace isolated yield (Scheme 5.3).

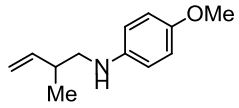
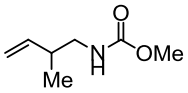
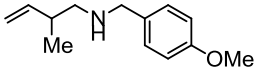
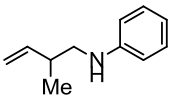
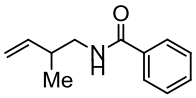
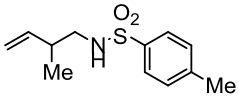
Scheme 5.3. Initial ruthenium catalyzed reductive coupling of butadiene to triazine.



Prior work in hydrogenative metal catalyzed couplings to imines suggested that the *N*-substituent of the imine was critical.[20] Thus, tuning of the hexahydro-1,3,5-triazine ensued toward a similar end. Screening of *N*-substituents revealed only aryl groups, such as 4-methoxyphenyl (PMP) **5.1b** and phenyl **5.1e**, delivered hydroaminomethylation products in any appreciable yield (Table 5.1). Since PMP-substituted amines are readily cleavable, 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazine was selected for further investigation in other ruthenium catalyzed transformations mediated by transfer hydrogenation.[21]

Table 5.1. Selected assay of *N*-substituents in the reductive coupling of butadiene to triazines.[a]

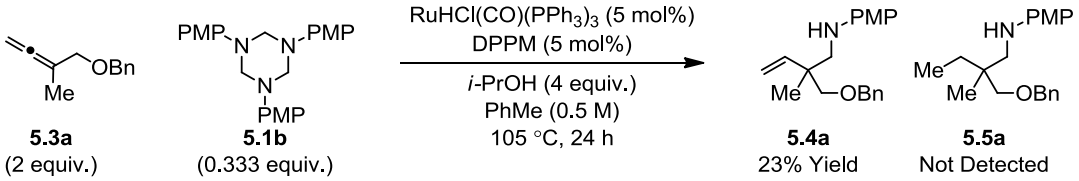


5.1b, R = 4-OMeC$_6$H$_4$ **5.1e**, R = 2-Pyridyl	**5.1c**, R = C(O)OMe **5.1f,** R = C(O)C$_6$H$_5$	**5.1d**,R = PMB **5.1g**, R = Tosyl
 53% Yield 3:1 (**5.2b**:*iso*-**5.2b**)	 Not Detected **5.2c**	 Not Detected **5.2d**
 55% Yield 10:1 (**5.2e**:iso-**5.2e**)	 Not Detected **5.2f**	 Not Detected **5.2g**

[a]Yields are of material isolated by silica gel chromatography.

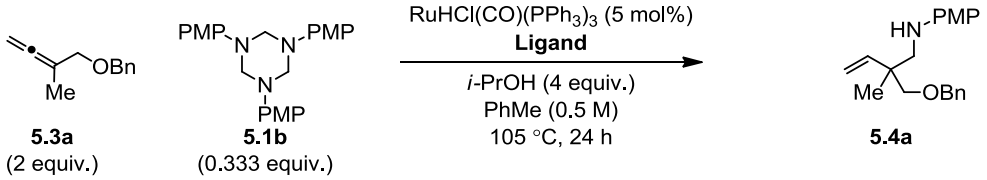
In adaptation of previously developed conditions for ruthenium catalyzed allene hydrohydroxymethylation,[13,22] 1-methyl-1-*O*-benzylmethyl-allene **5.3a** was successfully coupled to hexahydro-1,3,5-triazine **5.1a**, albeit in low yield (24%), by employing the catalyst system of RuHCl(CO)(PPh$_3$)$_3$ (5 mol%) and DPPM (5 mol%) and isopropanol (4 equiv.) as terminal reductant (Scheme 5.4). In contrast to the isopropanol mediated reductive coupling of CF$_3$-allenes to paraformaldehyde, hydrogenated hydroaminomethylation product **5.5a** was not detected. With this promising result, optimization ensued.

Scheme 5.4. Initial reductive coupling of allene to PMP-substituted triazine.



In the absence of exogenous ligand, only a trace quantity of the desired neopentyl amine **5.4a** was delivered as a single regioisomer (Table 5.2, entry 1). Similarly, the use of monodentate ligands such as tricyclohexylphosphine, provided small quantities of the hydroaminomethylation product (Table 5.2, entry 2). In contrast, bidentate phosphine ligands were more effective at enforcing higher conversion to neopentyl amine **5.4a** (Table 5.2, entries 3-8). Remarkably, the saturated congener of DPPM, 1,1-bis(dicyclohexylphosphino)methane (DCyPM), significantly improved the yield (Table 5.2, entry 6). Further surveying of ligands revealed that 1,1-bis(dicyclohexylphosphino)ethane (DCyPE) could afford the desired homoallylic neopentyl amine **5.4a** in 83% yield (Table 5.2, entry 8).

Table 5.2. Select assay of exogenous ligands in the coupling of allene **5.3a** to triazine **5.1b**.[a]



5.3a (2 equiv.) **5.1b** (0.333 equiv.) **5.4a**

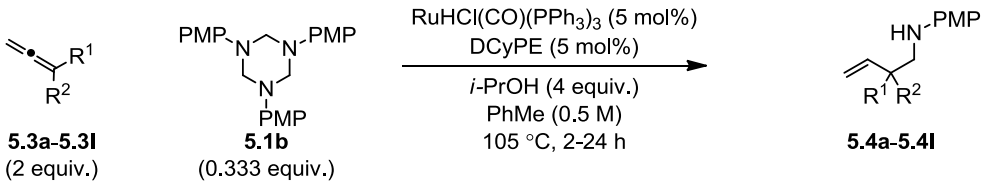
Entry	Ligand	Loading	Yield
1	None	-	7%
2	Cy_3P	10 mol%	8%
3	DPPF	5 mol%	27%
4	DIPPF	5 mol%	26%
5	DPPM	5 mol%	24%
6	DCyPM	5 mol%	43%
7	DPPE	5 mol%	51%
8	DCyPE	5 mol%	83%

[a]Yields are of material isolated by silica gel chromatography.

5.3 Reaction Scope

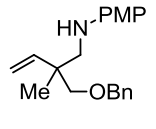
To evaluate the scope of these conditions, an array of 1,1-dialkylallenes **5.3a**-**5.3f** and 1-alkyl-1-arylallenes **5.3g**-**5.3l** were assayed in the reductive coupling to PMP-substituted triazine **5.1b** (Table 5.3). Withstanding minor adjustments for temperature and time, homoallylic neopentyl amines **5.4a**-**5.4l** were furnished in good yields with complete levels of regiocontrol. As illustrated in the formation of adducts **5.4c** and **5.4e**, this methodology permits the generation of congested all-carbon quaternary centers that are vicinal to tertiary stereocenters.

Table 5.3. Ruthenium catalyzed hydroaminomethylation of allenes: Allene scope.[a]

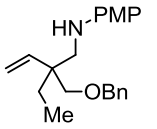


5.3a-5.3l (2 equiv.) | **5.1b** (0.333 equiv.) | **5.4a-5.4l**

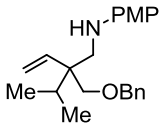
5.3a, R^1 = Me, R^2 = CH_2OBn
5.3b, R^1 = Et, R^2 = CH_2OBn
5.3c, R^1 = *i*-Pr, R^2 = CH_2OBn
5.3d, R^1 = Me, R^2 = CH_2OTBS
5.3e, R^1 = Me, R^2 = Cy
5.3f, R^1 = R^2 = Me
5.3g, R^1 = Me, R^2 = C_6H_5
5.3h, R^1 = Me, R^2 = 4-$MeOC_6H_4$
5.3i, R^1 = Me, R^2 = 4-FC_6H_4
5.3j, R^1 = Me, R^2 = 3,5-$Cl_2C_6H_3$
5.3k, R^1 = Me, R^2 = benzodioxole
5.3l, R^1 = Me, R^2 = 4-$CF_3C_6H_4$



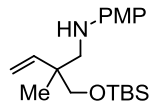
83% Yield, **5.4a**



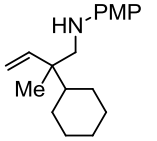
85% Yield, **5.4b**



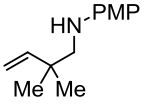
50% Yield, **5.4c**



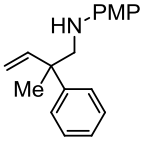
77% Yield, **5.4d**



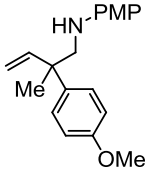
74% Yield, **5.4e**[b]



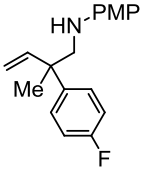
86% Yield, **5.4f**



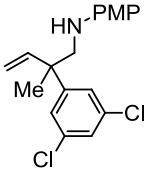
74% Yield, **5.4g**



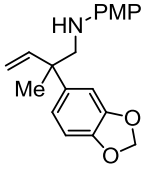
72% Yield, **5.4h**



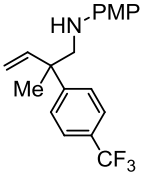
69% Yield, **5.4i**



70% Yield, **5.4j**



67% Yield, **5.4k**



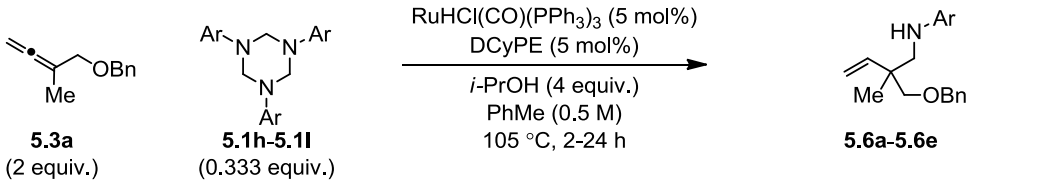
81% Yield, **5.4l**

[a]Yields are of material isolated by silica gel chromatography. [b]**5.3e** (4 equiv.).

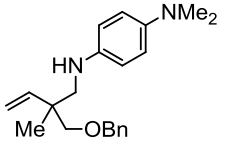
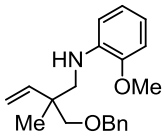
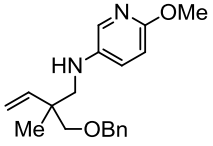
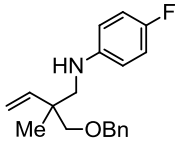
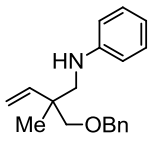
To further assess reaction scope, *N*-substituted hexahydro-1,3,5-triazines **5.1h-5.1l** were exposed to allene **5.3a** under standard conditions (Table 5.4). The reaction is most efficient for electron rich *para*-substituted *N*-phenyl reactants, as demonstrated in the formation of adducts **5.4a** (Table 5.3) and **5.6a** (Table 5.4). However, 1,3,5-tris(2-

methoxyphenyl)-1,3,5-triazine **5.1i** also furnishes hydroaminomethylation product **5.6b** in moderate yield. In addition, heteroaromatic *N*-substituents are tolerated as illustrated in the formation of *N*-pyridyl substituted adduct **5.6c**. Finally, *N*-*para*-fluorophenyl triazine **5.1k** and the parent *N*-phenyl triazine **5.1l** provide adducts **5.6d** and **5.6e**, respectively, in good yield. In parallel to the reductive couplings with butadiene (Table 5.1), *N*-alkyl, *N*-acyl and *N*-sulfonyl triazines did not engage in ruthenium catalyzed C-C coupling under these conditions.

Table 5.4. Ruthenium catalyzed hydroaminomethylation of allenes: Triazine scope.[a]



5.3a (2 equiv.) | **5.1h-5.1l** (0.333 equiv.) | **5.6a-5.6e**

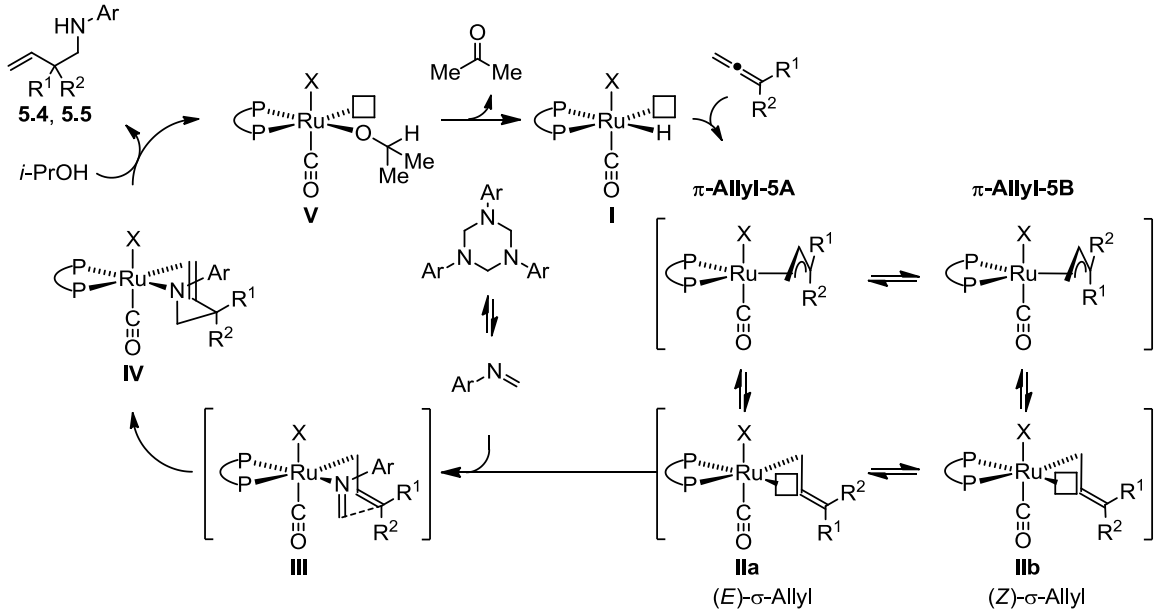
5.1h, Ar = 4-$NMe_2C_6H_4$ **5.1k**, Ar = 4-FC_6H_4	**5.1i**, Ar = 2-$OMeC_6H_4$	**5.1j**, Ar =5-(2-MeO-Pyr) **5.1l**, Ar = C_6H_5
		
82% Yield, **5.6a**	53% Yield, **5.6b**	62% Yield, **5.6c**
		
70% Yield, **5.6d**	61% Yield, **5.6e**	

[a]Yields are of material isolated by silica gel chromatography.

5.4 Postulated Reaction Mechanism

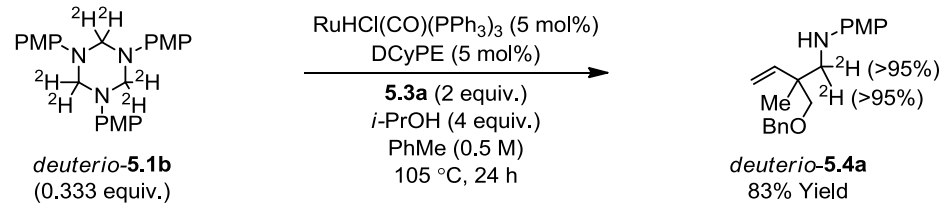
A hydrometallative pathway is proposed, as found in related ruthenium catalyzed allene-aldehyde couplings.[23-24] The catalytic cycle opens with regioselective hydrometallation of the allene to form a 1,1-disubstituted π-allylruthenium intermediate (Scheme 5.5).[25-26] The stoichiometric reaction of $HXRu(CO)(PR_3)_3$ (X = Cl, Br) with allenes or dienes to furnish π-allylruthenium complexes has been described.[25] Such π-allylruthenium species are highly fluxional in nature, undergoing rapid geometrical isomerization by way of the σ-bound haptomers.[23e,26] Through the primary σ-allyl haptomer **IIa** or **IIb**, regioselective formimine addition at the more substituted position of the allene may proceed *via* a closed six-membered chairlike transition state, **III**. Protonolysis of the ruthenium alkoxide **IV** by isopropanol releases the hydroaminomethylation product **5.4** or **5.6** and produces ruthenium isopropoxide **V**. Subsequent β-hydride elimination furnishes the benign by-product, acetone, and regenerates the ruthenium hydride complex to complete the catalytic cycle.

Scheme 5.5. Proposed mechanism for coupling of formimines to allenes.



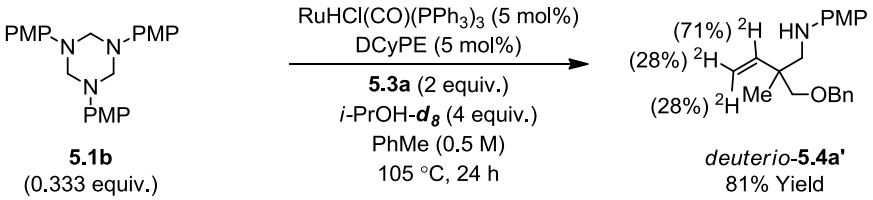
Isotopic labeling studies were conducted under otherwise standard conditions employing deuterated triazine, *deuterio*-**5.1b**, and d_8-isopropanol (Schemes 5.6 and 5.7). The reductive coupling of allene **5.3a** to the deuterated triazine *deuterio*-**5.1b** under standard conditions furnished *deuterio*-**5.4a**, for which deuterium is retained completely at the position adjacent to nitrogen (>95% ^{2}H) (Scheme 5.6). This indicates that the C-N bond of the amine product is not subject to reversible dehydrogenation. Deuterium was not detected at any other positions.

Scheme 5.6. Isotopic labeling *via* reductive coupling of deuterated triazine to allene.



Reductive coupling of allene **5.3a** to triazine **5.1b** using d_8-isopropanol under otherwise standard conditions delivers *deuterio*-**5.4a'**, which incorporates significant quantities of deuterium at the interior vinylic position and, to a lesser extent, the terminal vinylic positions (Scheme 5.7). This pattern of deuterium incorporation suggests allene hydrometallation is fast and reversible and occurs with incomplete regioselectivity. Incomplete deuterium incorporation at the interior vinylic position of *deuterio*-**5.4a'** (71% ^{2}H) is likely a result of β-hydride elimination of the allylruthenium species to form dienes, which are detected in crude reaction mixtures and may explain the requirement of excess allene. Adventitious water may also diminish the extent of deuterium incorporation.[27] As expected based on the coupling of allene **5.3a** to the deuterated triazine *deuterio*-**5.1b** (Scheme 5.6), deuterium was not detected at the position adjacent to nitrogen (Scheme 5.7).

Scheme 5.7. Isotopic labeling via reductive coupling of triazine to allene employing deuterated terminal reductant.



5.5 Conclusion

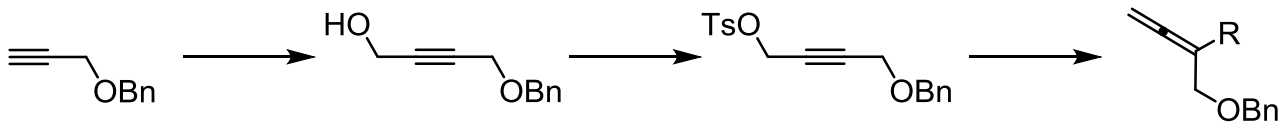
In summary, regioselective couplings of 1,1-dialkylallenes and 1-alkyl-1-arylallenes to *N*-aryl formimines were achieved via ruthenium catalyzed transfer hydrogenation. These reactions occur with complete levels of regiocontrol to deliver the branched products of hydroaminomethylation possessing all-carbon quaternary centers. In addition, these transformations exploit easily prepared and highly tractable saturated *s*-hexahydro-1,3,5-triazines, derived from anilines and formaldehyde, as latent sources of *N*-aryl formimines. Overall, this protocol represents a broad, new strategy for the hydroaminomethylation of π-unsaturated reactants beyond classical carbonylative hydroformylation-reductive amination and may find application in the hydroaminomethylation of alkynes, 1,3-dienes and 1,3-enynes.

5.6 Experimental Section

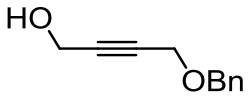
General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringes. Reaction tubes and flasks were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Toluene (PhMe) was distilled from sodium and benzophenone. $RuHCl(CO)(PPh_3)_3$ was prepared according to literature procedure.[28] 2-Propanol (99.8%, extra dry) was obtained from Acros Organics. Allenes **5.3d**[24c], **5.3g**-**5.3l**[22a] were prepared according to literature procedure. Allene **5.3f** was purchased from Alfa Aesar. Triazines **5.1a**-**5.1l** were prepared according to literature procedure.[29] 1,1-Bis(dicyclohexylphosphino)ethane (DCyPE) was obtained from Sigma-Aldrich and used as received. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents

F_{254}) and products were visualized by UV, $KMnO_4$, and/or Magic Seebach stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[30] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00 s).

Experimental Procedure and Spectral Data for the Preparation of Allenes 5.3a-5.3c

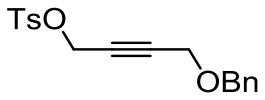


4-Benzyloxybut-2-yn-1-ol



4-Benzyloxybut-2-yn-1-ol was prepared in accordance with the literature procedure reported by Koch.[31] To a stirred solution of benzylpropargylether (15.1 g, 103 mmol, 100 mol%) in anhydrous THF (120 mL) at -78 ºC was added *n*-butyllithium (45 mL of 2.5 M in hexanes, 113 mmol, 110 mol%). After stirring for 2 hours, paraformaldehyde (3.71 g, 124 mmol, 120 mol%) was added portionwise and allowed to warm to room temperature while stirring for 16 hours. The reaction was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc/hexane) to yield a yellow oil (12.1 g, 69 mmol, 67%). The spectroscopic properties matched those reported in the literature.

4-Benzyloxybut-2-ynyltosylate

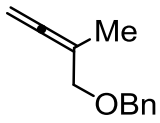


4-Benzyloxybut-2-ynyltosylate was prepared in accordance with the literature procedure reported by Posner and coworkers.[32] To a solution of 4-benzyloxybut-2-yn-1-ol (4.9 g, 28 mmol, 100 mol%) in Et_2O (100 mL) was added freshly ground KOH (7.8 g, 140 mmol, 500 mol%). The mixture was cooled to -30 °C, and tosyl chloride (5.9 g, 31 mmol, 110 mol%) was added in one portion. After stirring at -30 °C for 3 hours, the mixture was added to water (30 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 25% EtOAc/hexane) to furnish the product as a yellow oil (8.3g, 25 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.3 Hz, 2H), 7.40 – 7.27 (m, 7H), 4.77 (t, J = 1.8 Hz, 2H), 4.48 (s, 2H), 4.07 (t, J = 1.8 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (77 MHz, $CHCl_3$): δ 145.2, 137.2, 133.2, 129.9, 128.6, 128.2, 128.1, 128.1, 85.6, 78.4, 71.8, 58.0, 57.1, 21.8.

1-((2-Methylbuta-2,3-dienyloxy)methyl)-benzene (5.3a)



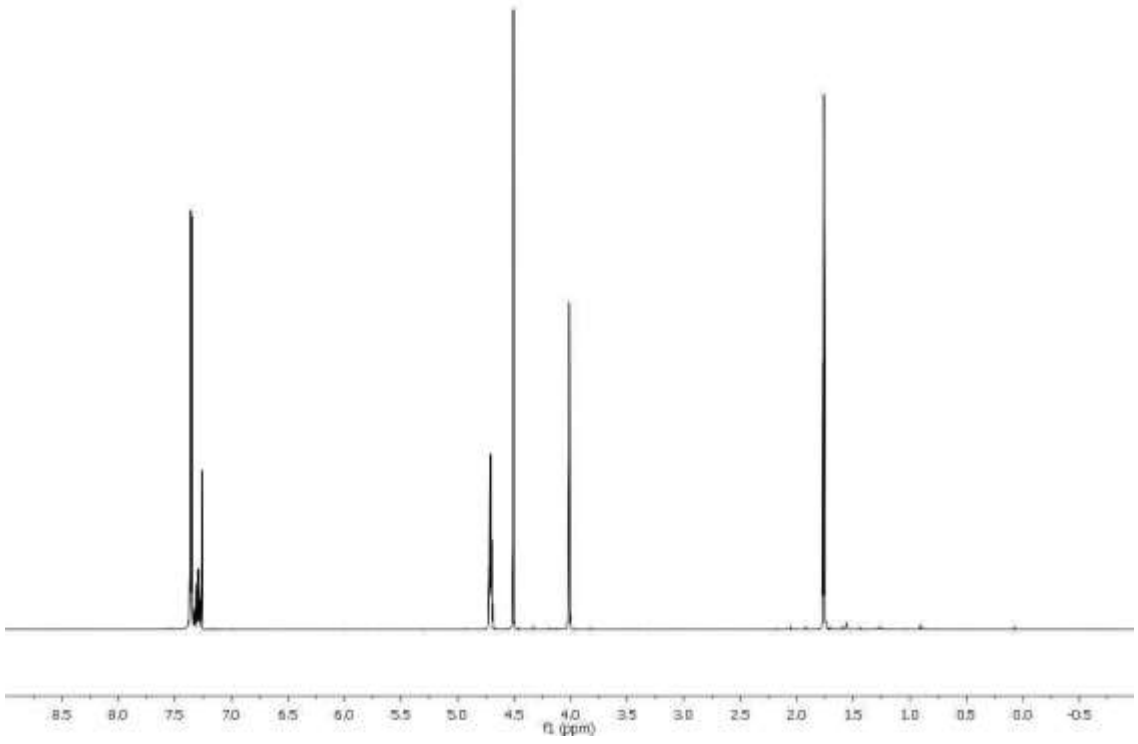
To a cooled (0 ºC) suspension of CuCN (2.69 g, 30.0 mmol, 300 mol%) and LiCl (2.54 g, 60.0 mmol, 600 mol%) in dry THF (50 mL) was added MeMgBr (10.0 mL of a 3.0 M in Et_2O, 30.0 mmol, 300 mol%). After stirring for 30 minutes, the solution was further chilled to -78 ºC and 4-benzyloxybut-2-ynyltosylate (3.30 g, 10.0 mmol, 100 mol%) was added dropwise over 60 minutes. After an hour of stirring at −78 ºC, the reaction was quenched with saturated NH_4Cl. After extraction with Et_2O (3 × 70 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to give allene **1a** (1.57 g, 9.0 mmol, 90%) as a colorless oil.

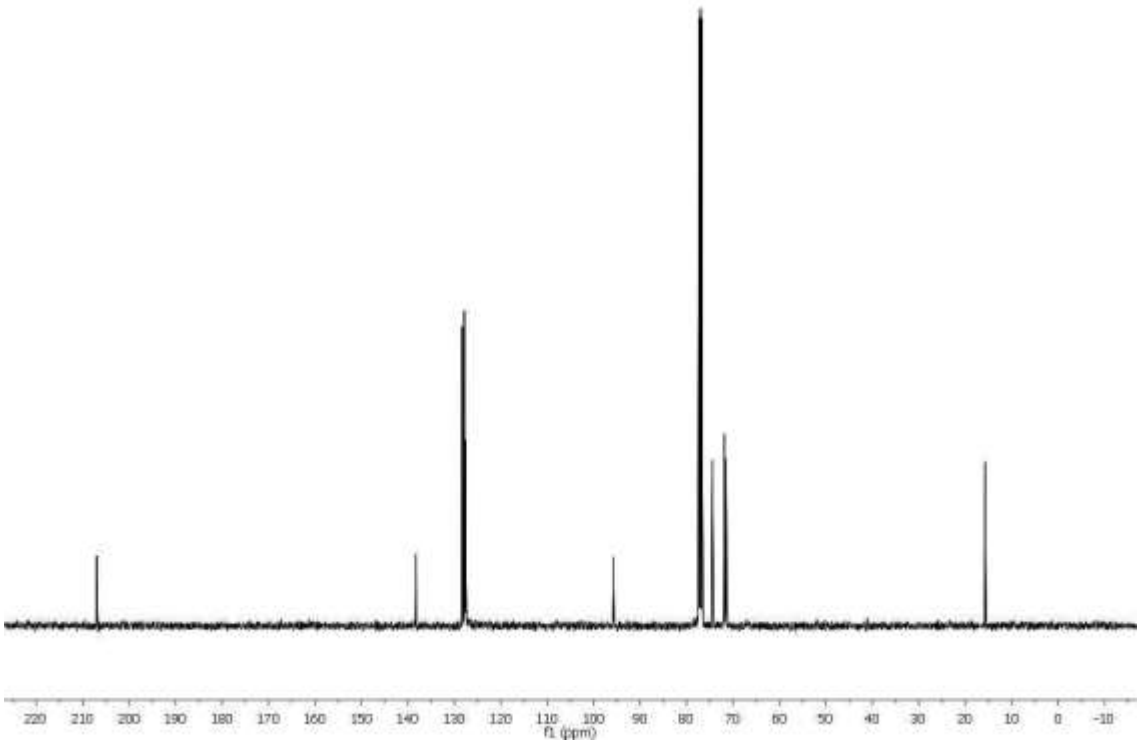
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.28 (m, 5H), 4.71 (dt, *J* = 3.1, 2.2 Hz, 2H), 4.51 (s, 2H), 4.01 (t, *J* = 2.2 Hz, 2H), 1.76 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (77 MHz, $CHCl_3$): δ 207.2, 138.4, 128.5, 128.0, 127.8, 95.9, 74.6, 72.0, 71.6, 15.8.

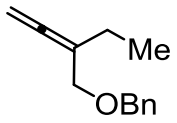
LRMS (ESI): m/z 175 $[M+H]^+$

FTIR (neat): 3030, 2983, 2856, 1959, 1495, 1453, 1370, 1351, 1294, 1203, 1070, 1028, 979, 938, 846, 734, 696 cm^{-1}.


8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-((2-Ethylbuta-2,3-dienyloxy)methyl)-benzene (5.3b)



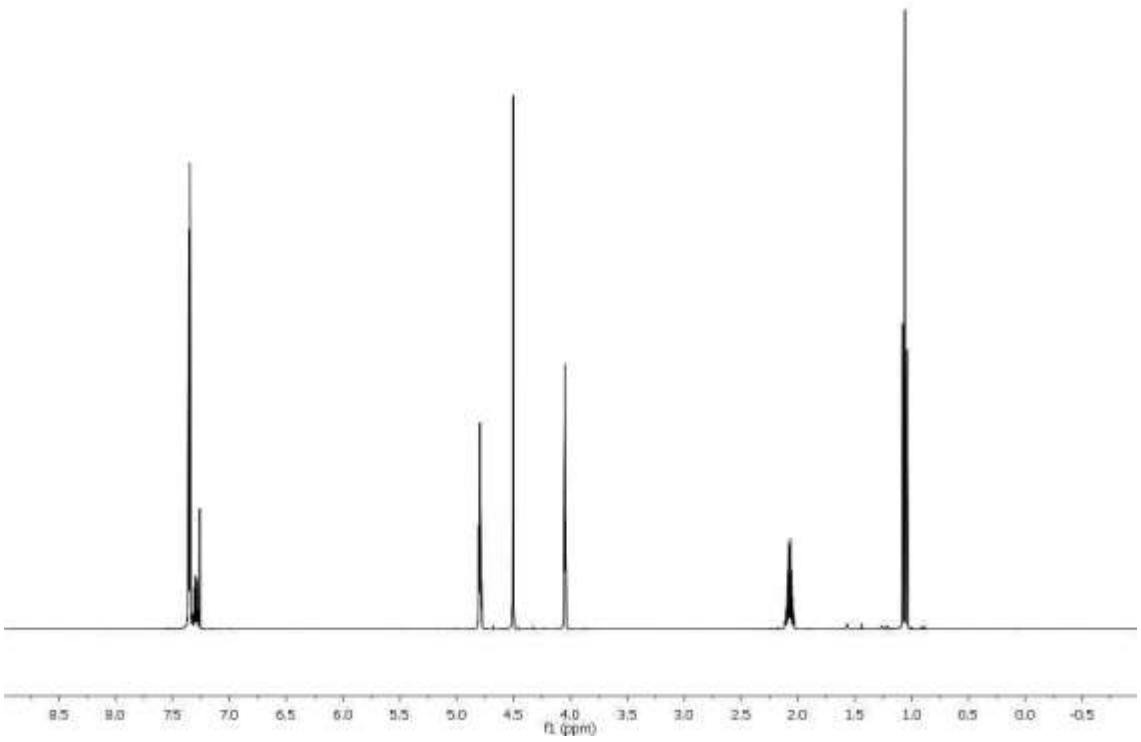
To a cooled (0 ºC) suspension of CuCN (1.34 g, 15.0 mmol, 300 mol%) and LiCl (1.27 g, 30.0 mmol, 600 mol%) in dry THF (25 mL) was added EtMgBr (5.0 mL of a 3.0 M in THF, 15.0 mmol, 300 mol%). After stirring for 30 minutes, the solution was further chilled to -78 ºC and 4-benzyloxybut-2-ynyltosylate (1.65 g, 5.0 mmol, 100 mol%) was added dropwise over 30 minutes. After an hour of stirring at −78 ºC, the reaction was quenched with saturated NH_4Cl. After extraction with Et_2O (3 × 50 mL), the combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to give allene **2a** (0.75 g, 4.0 mmol, 79%) as a colorless oil.

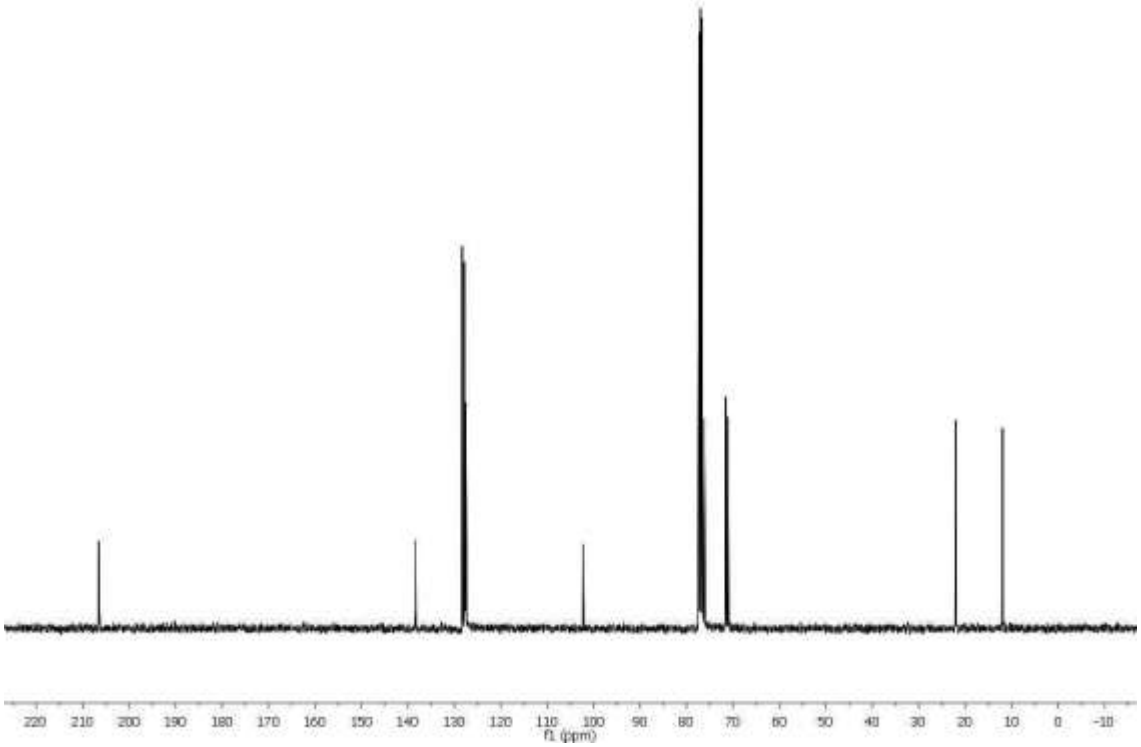
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 4.84 – 4.76 (m, 2H), 4.51 (s, 2H), 4.05 (t, J = 2.1 Hz, 2H), 2.07 (dq, J = 11.1, 3.8 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H).

^{13}C NMR (77 MHz, $CHCl_3$): δ 206.5, 138.4, 128.5, 128.0, 127.7, 102.4, 76.3, 71.7, 71.2, 22.2, 12.1.

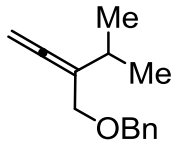
LRMS (ESI): m/z 189 $[M+H]^+$

FTIR (neat): 3030, 2986, 2653, 1956, 1496, 1453, 1354, 1205, 1153, 1205, 1069, 1028, 944, 845, 791, 733, 696 cm^{-1}.


8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-((2-isopropylbuta-2,3-dienyloxy)methyl)-benzene (5.3c)



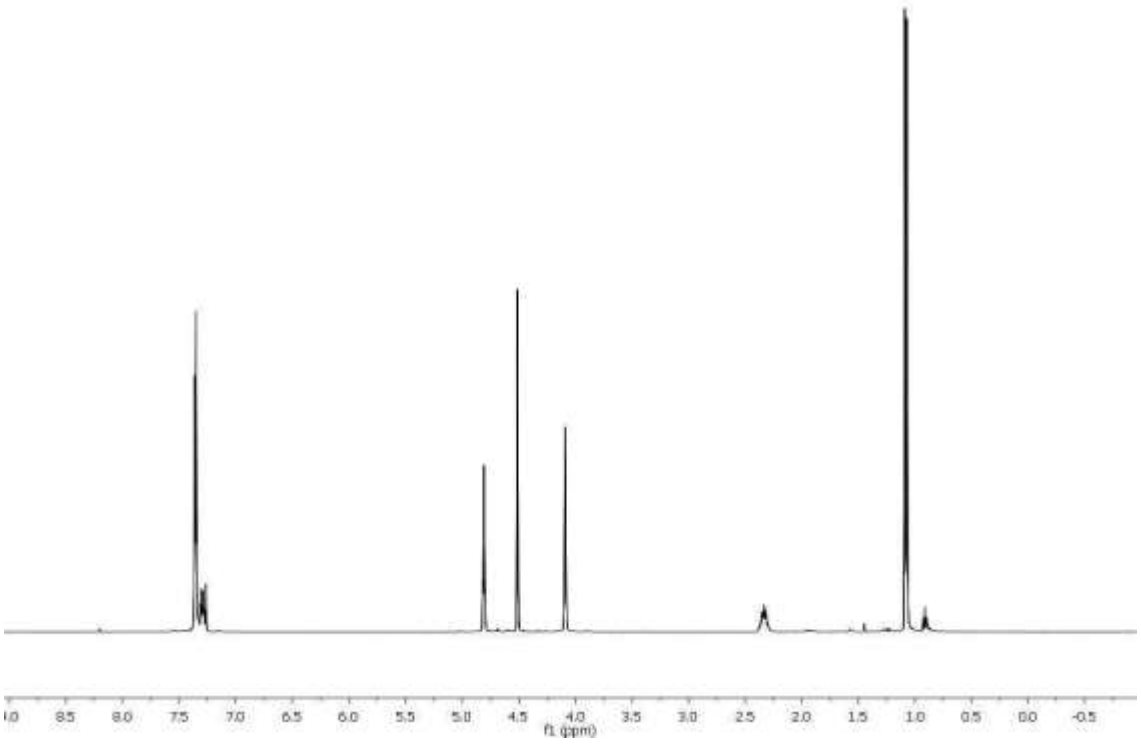
To a cooled (0 ºC) suspension of CuCN (1.34 g, 15.0 mmol, 300 mol%) and LiCl (1.27 g, 30.0 mmol, 600 mol%) in dry THF (25 mL) was added *i*-PrMgBr (7.5 mL of a 2.0 M in THF, 15.0 mmol, 300 mol%). After stirring for 30 minutes, the solution was further chilled to −78 ºC and 4-benzyloxybut-2-ynyltosylate (1.65 g, 5.0 mmol, 100 mol%) was added dropwise over 30 minutes. After an hour of stirring at −78 ºC, the reaction was quenched with saturated NH_4Cl. After extraction with Et_2O (3 × 50 mL), the combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to give allene **3a** (0.63 g, 3.1 mmol, 62%) as a colorless oil.

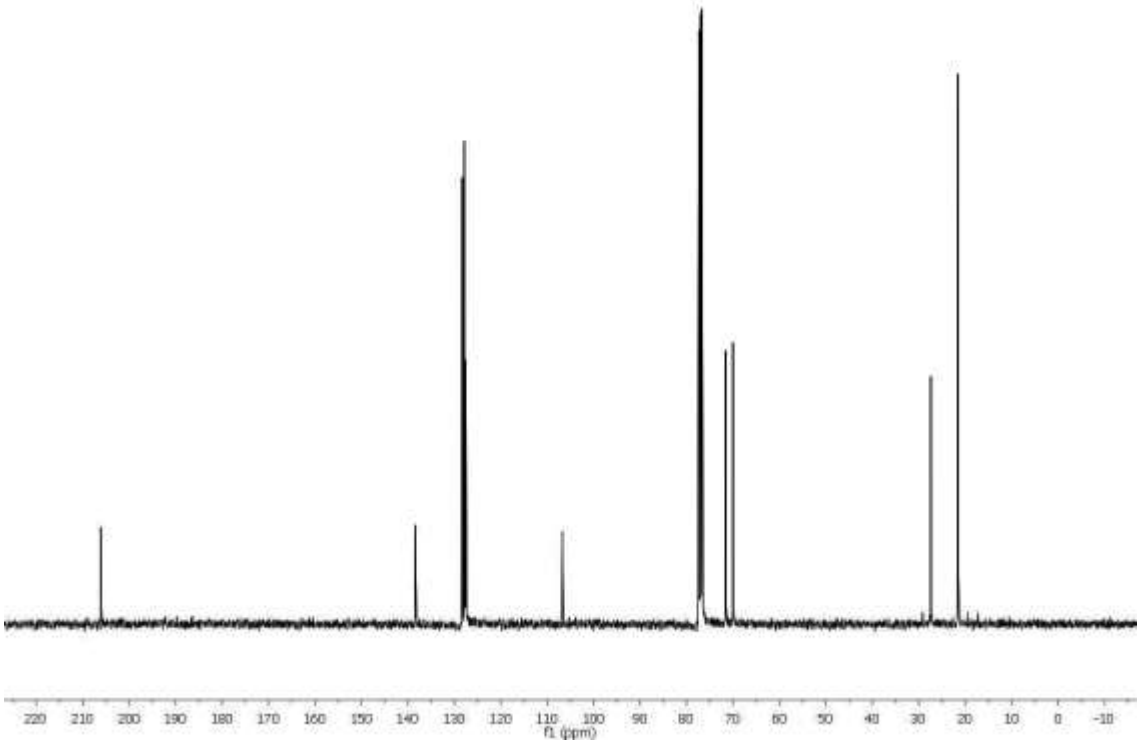
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (m, 5H), 4.81 (dd, *J* = 4.7, 2.1 Hz, 2H), 4.51 (s, 2H), 4.09 (t, *J* = 2.0 Hz, 2H), 2.33 (ddd, *J* = 9.6, 6.7, 3.4 Hz, 1H), 1.08 (dd, *J* = 6.8, 1.5 Hz, 6H).

^{13}C NMR (77 MHz, $CHCl_3$): δ 206.2, 138.5, 128.5, 128.0, 127.7, 106.9, 76.8, 71.7, 70.2, 27.6, 21.7.

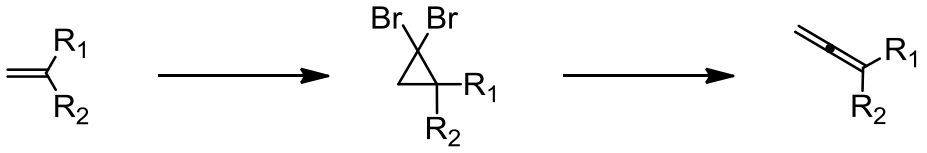
LRMS (ESI): m/z 203 $[M+H]^+$

FTIR (neat): 3030, 2868, 1953, 1723, 1496, 1453, 1382, 1354, 1184, 1066, 1028, 1000, 940, 843, 733, 696 cm^{-1}.



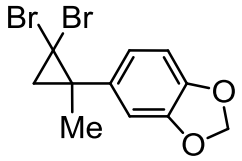

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Experimental Procedure and Spectral Data for the Preparation of Allenes 5.3k, 5.3l



5.3k,l

5-(2,2-dibromo-1-methylcyclopropyl)benzo[d][1,3]dioxole



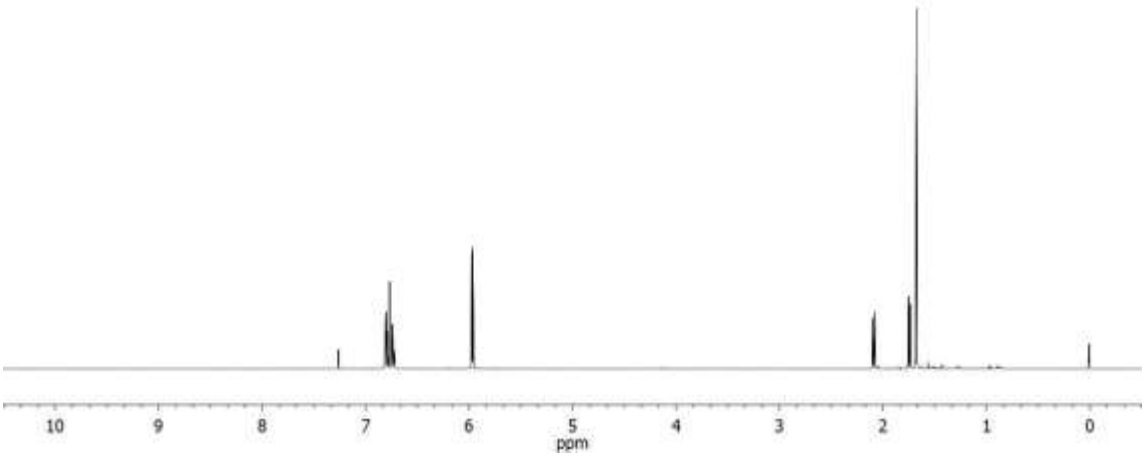
In modification to literature procedure,[33] a flame-dried 50 mL round-bottom flask was charged with 5-(prop-1-en-2-yl)benzo[d][1,3]dioxole[34] (5.0 g, 31 mmol, 100 mol%), $CHBr_3$ (5.4 mL, 62 mmol, 200 mol%,), *n*-Bu_4NBr (1.0 g, 3.1 mmol, 10 mol%), and CH_2Cl_2 (10 mL, 3.0 M). To this stirring mixture was dropwise added 50% aqueous NaOH (6.2 g NaOH, 155 mmol, 500 mol% in 6 mL of H_2O) at ambient temperature. After the addition was complete, the reaction mixture was heated to 50 °C and stirred for 24 hours, then quenched with water (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were successively washed with 1.0 M HCl (2 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound (7.9 g, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 – 6.70 (m, 3H), 5.97 (dd, *J* = 4.6, 1.4 Hz, 2H), 1.92 (dd, *J* = 137.6, 7.6 Hz, 2H), 1.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.6, 136.3, 121.6, 109.1, 108.0, 101.1, 37.0, 35.5, 34.1, 27.8.

LRMS (CI): m/z 334 $[M+]^+$

FTIR (neat): 2982, 2890, 1734, 1608, 1504, 1486, 1435, 1375, 1350, 1240, 1223, 1158, 1109, 1037, 1020, 935, 859, 835, 810, 728, 694 cm^{-1}.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9
8
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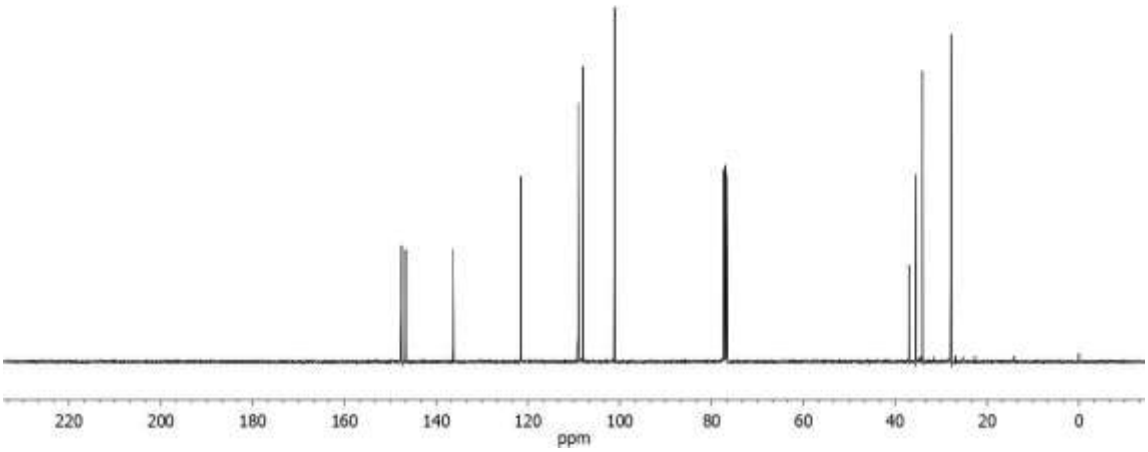
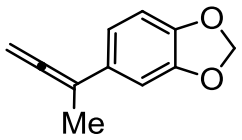
6
5
4
3
2
1
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

5-(buta-2,3-dien-2-yl)benzo[d][1,3]dioxole (5.3k)



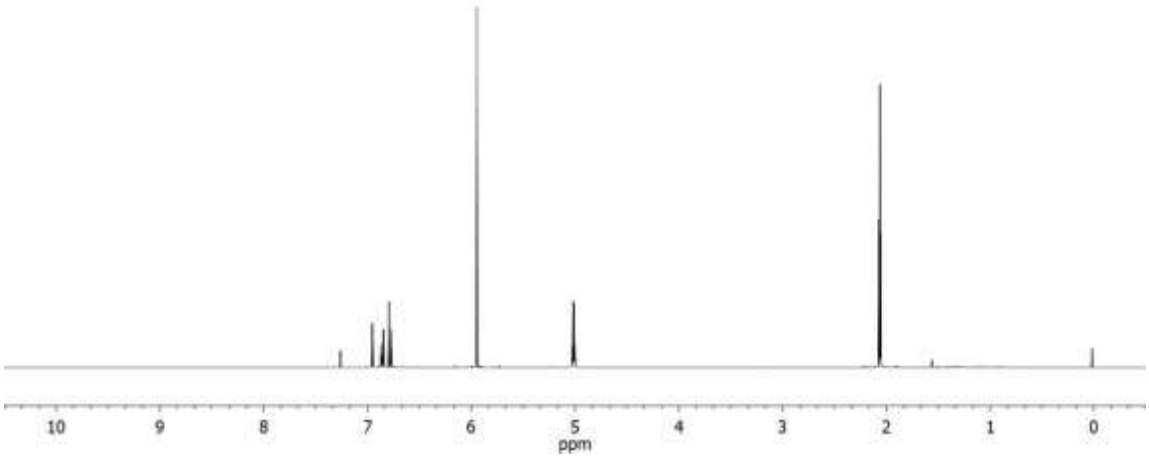
In modification to literature procedure,[35] a flame-dried 50 mL round-bottom flask was charged with 5-(2,2-dibromo-1-methylcyclopropyl)benzo[d][1,3]dioxole (4.0 g, 12 mmol, 100 mol%) and THF (24 mL, 0.5 M). To this stirring mixture was dropwise added 3.0 M ethylmagnesium bromide in THF (7.0 mL, 21 mmol, 180 mol%) at ambient temperature under argon. After stirring for 1 hour, the reaction was quenched with 1.0 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with water (2 × 15 mL), then brine (2 × 15 mL), and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound (1.9 g, 90%) as a yellow oil.

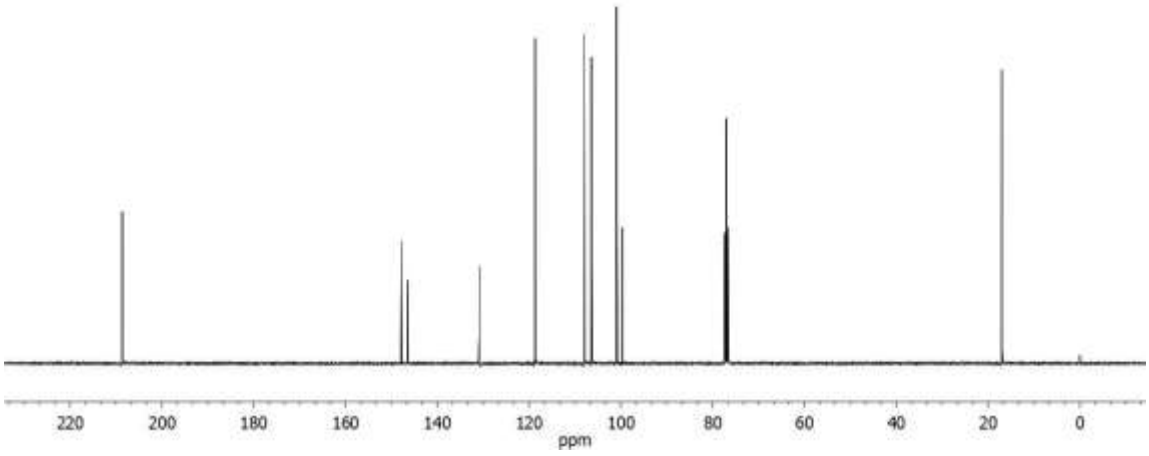
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 – 6.75 (m, 3H), 5.95 (s, 2H), 5.01 (q, J = 3.2 Hz, 2H), 2.06 (t, J = 3.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6, 147.8, 146.4, 130.8, 118.7, 108.0, 106.4, 100.9, 99.6, 77.0, 17.0.

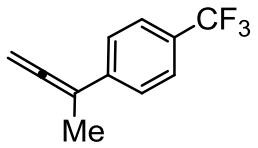
LRMS (CI): m/z 174 $[M+]^+$

FTIR (neat): 2891, 1942, 1736, 1606, 1502, 1485, 1460, 1439, 1371, 1352, 1338, 1288, 1269, 1248, 1230, 1105, 1037, 935, 852, 807, 723, 696 cm^{-1}.




220
200
180
160
140
120
100
80
60
40
20
0
ppm

1-(buta-2,3-dien-2-yl)-4-(trifluoromethyl)benzene (5.3l)



In modification to literature procedure,[8] a flame-dried 50 mL round-bottom flask was charged with 1-(2,2-dibromo-1-methylcyclopropyl)-4-(trifluoromethyl)benzene[36] (9.1 g, 25 mmol, 100 mol%) and THF (50 mL, 0.5 M). To this stirring mixture was dropwise added 3.0 M ethylmagnesium bromide in THF (17 mL, 50 mmol, 200 mol%) at ambient temperature under argon. After stirring for 1 hour, the reaction was quenched with 1.0 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with hexane (2 × 20 mL). The combined organic phases were washed with water (2 × 15 mL), then brine (2 × 15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 100% hexane) to afford the title compound (3.0 g, 60%) as a colorless oil.

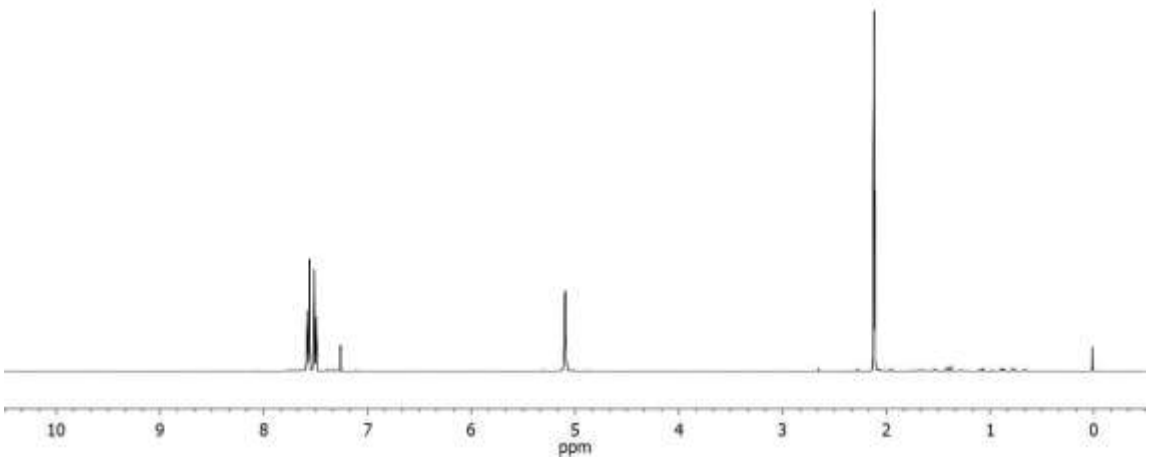
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 5.10 (q, J = 3.0 Hz, 2H), 2.12 (t, J = 3.2 Hz, 3H).

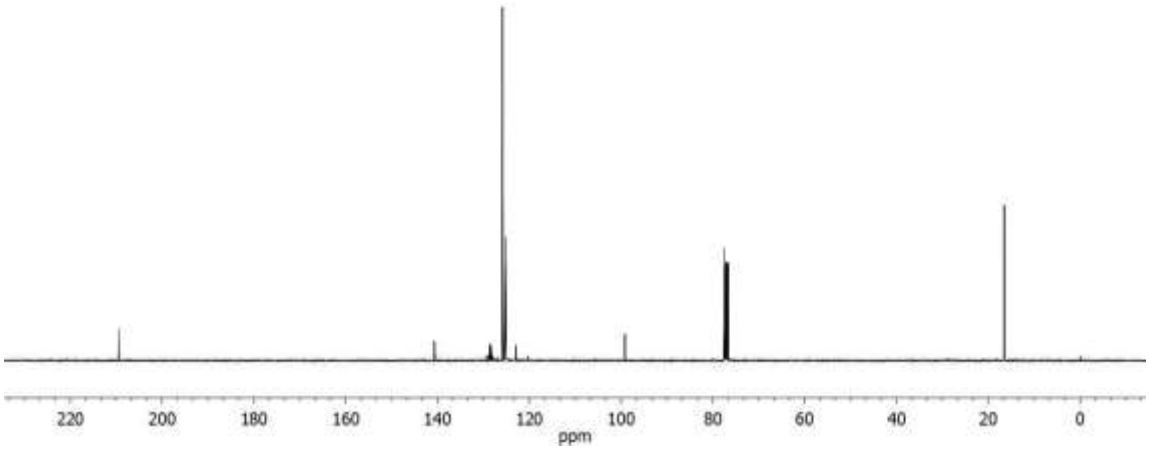
^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 140.7 (q, J = 1.4 Hz), 128.5 (q, J = 32.4 Hz), 125.8, 125.2 (q, J = 3.8 Hz), 124.3 (q, J = 271.7 Hz), 99.2, 77.5, 16.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4.

LRMS (CI): m/z 199 $[M+H]^+$

FTIR (neat): 2929, 1943, 1617, 1459, 1426, 1410, 1324, 1164, 1121, 1110, 1074, 1059, 1016, 927, 840, 706 cm^{-1}.

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60
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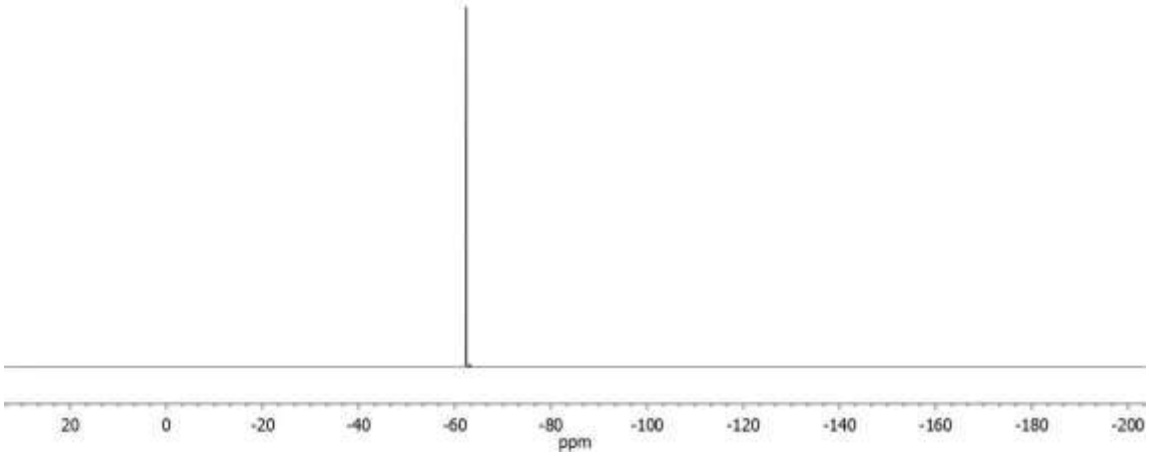
ppm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0
-20
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-60
-80
-100
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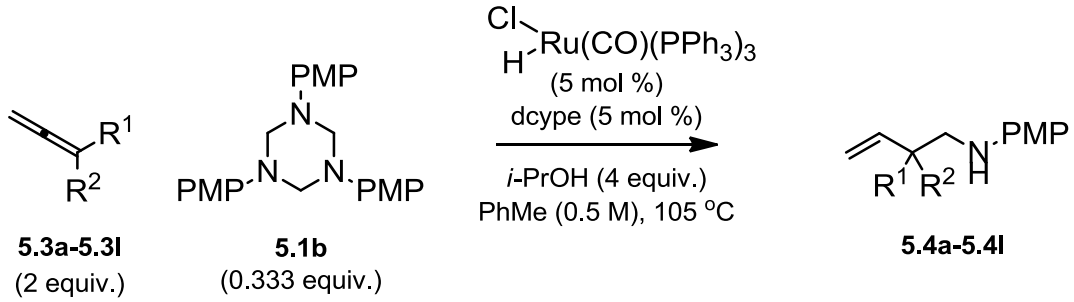
-140
-160
-180
-200
ppm

Experimental Procedures and Spectral Data Adducts 5.4a-5.4l



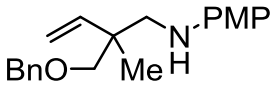
5.3a-5.3l (2 equiv.) **5.1b** (0.333 equiv.) **5.4a-5.4l**

General Procedure for the coupling of triazine 5.1b to allenes (5.3a-5.3l)

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1-bis(dicyclohexylphosphino)ethane (DCyPE) (4.2 mg,

0.010 mmol, 5 mol%), and triazine **5.1b** (27.0 mg, 0.067 mmol (0.200 mmol of formimine), 100 mol%). The tube was sealed with a rubber septum, purged with argon, and toluene (0.5 M with respect to formimine), allene (0.400 mmol, 200 mol%), and isopropanol (61 μL, 0.800 mmol, 400 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds.

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4a)



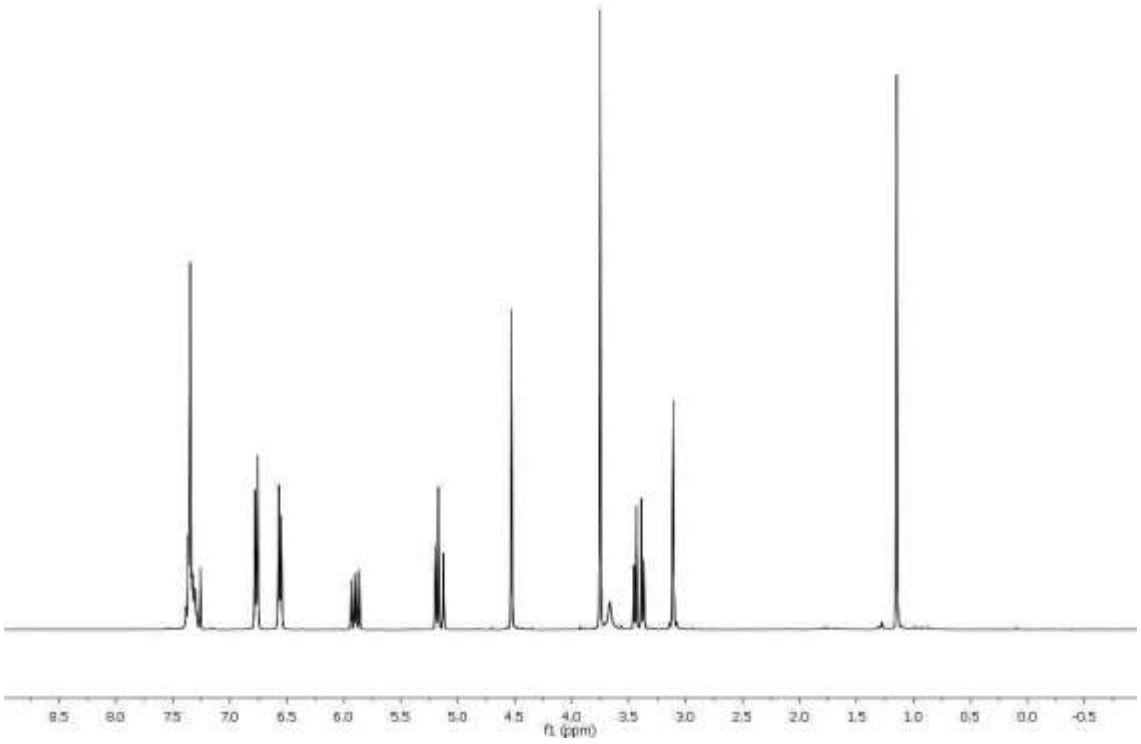
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3a**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (51.7 mg, 83%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 5.90 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.24-5.09 (m, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 3.67 (br, 1H), 3.41 (dd, *J* = 26.4, 8.9 Hz, 2H), 1.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 143.4, 142.7, 138.6, 128.5, 127.7, 127.6, 115.0, 114.5, 114.1, 76.5, 73.5, 56.0, 51.9, 42.2, 20.4.

LRMS (ESI): m/z 312 $[M+H]^+$

FTIR (neat): 3395, 2853, 1618, 1511, 1453, 1415, 1361, 1232, 1179, 1092, 1038, 911, 817,733, 697 cm^{-1}.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5.0
4.5
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2.0
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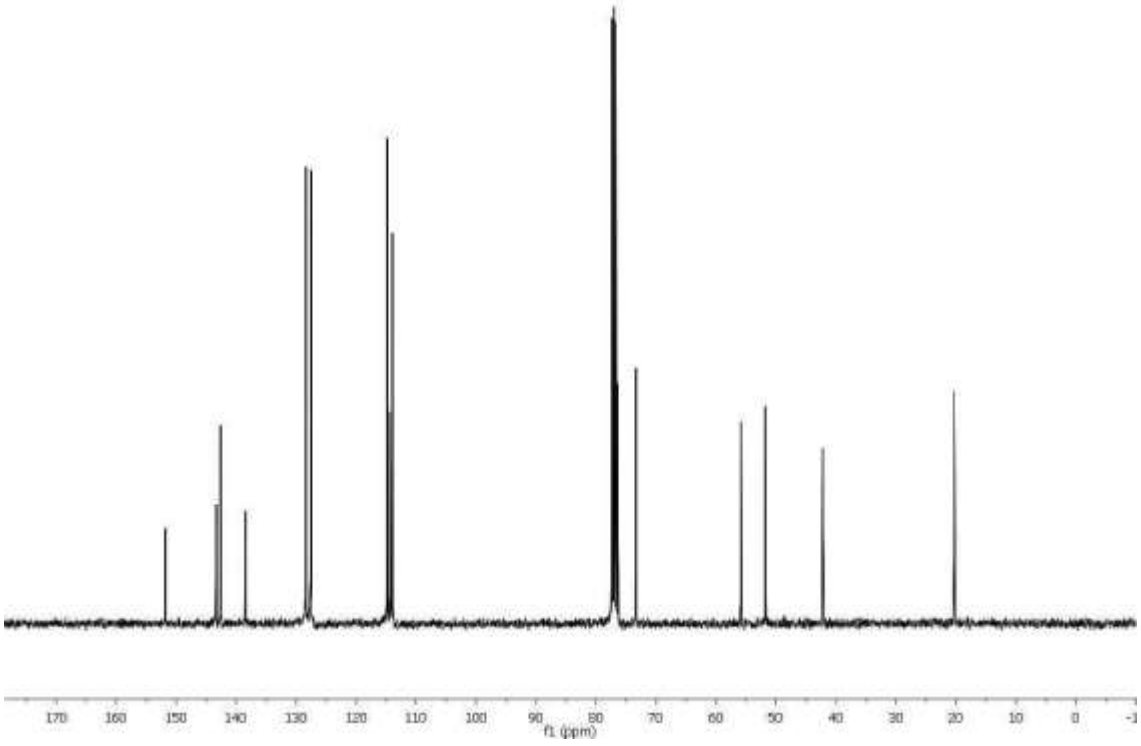
0.5
0.0
-0.5
f1 (ppm)


170
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150
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130
120
110
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90
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70
60
50
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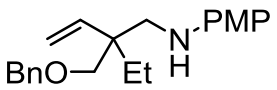
f1 (ppm)

N-(2-benzyloxymethyl-2-ethylbut-3-en-1-yl)-4-methoxyaniline (5.4b)



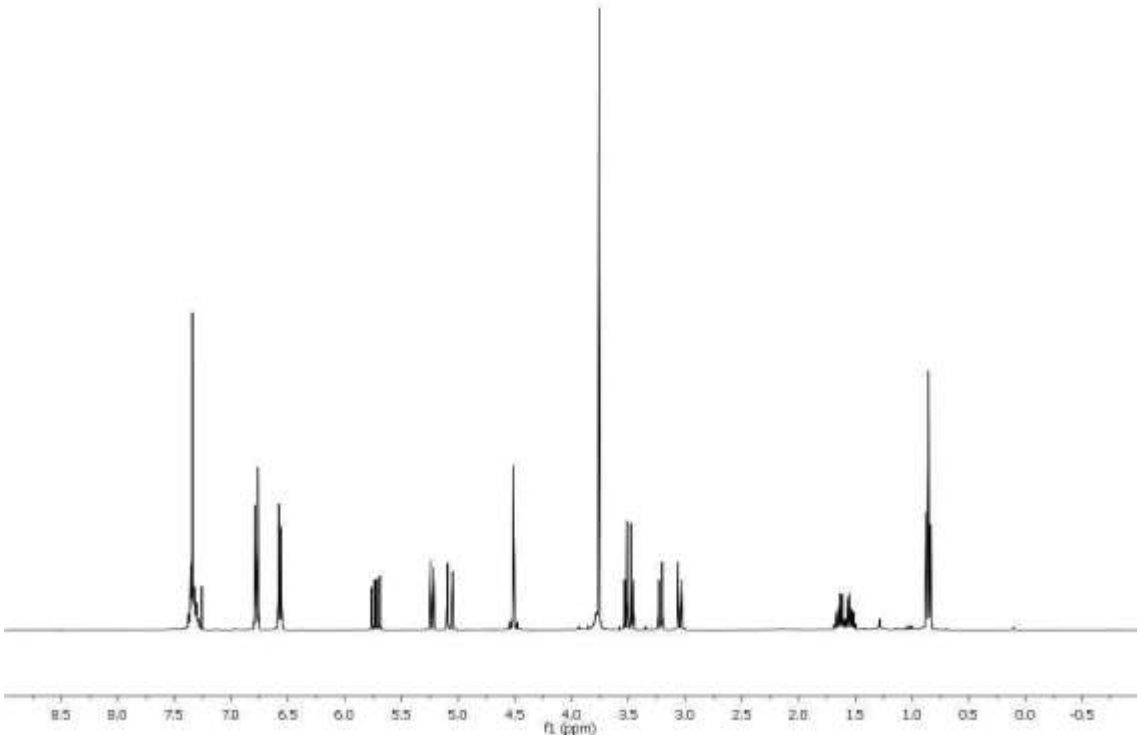
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3b**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (55.3 mg, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 6.78 (d, J = 9.0 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 5.73 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.15 (dd, *J* = 19.1, 14.5 Hz, 2H), 4.51 (s, 2H), 3.78 (br, 1H), 3.76 (s, 3H), 3.50 (dd, *J* = 22.2, 9.0 Hz, 2H), 3.13 (dd, *J* = 67.9, 11.7 Hz, 2H), 1.70-1.48 (m, 2H), 0.86 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 143.5, 141.6, 138.6, 128.5, 127.7, 127.6, 115.1, 115.0, 114.0, 73.5,73.4, 56.0, 50.0, 45.0, 26.7, 8.1.

LRMS (CI): m/z 326 $[M+H]^+$

FTIR (neat): 3384, 2857, 1617, 1511, 1453, 1365, 1232, 1178, 1094, 1038, 908, 817, 730, 697 cm^{-1}.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5.5
5.0
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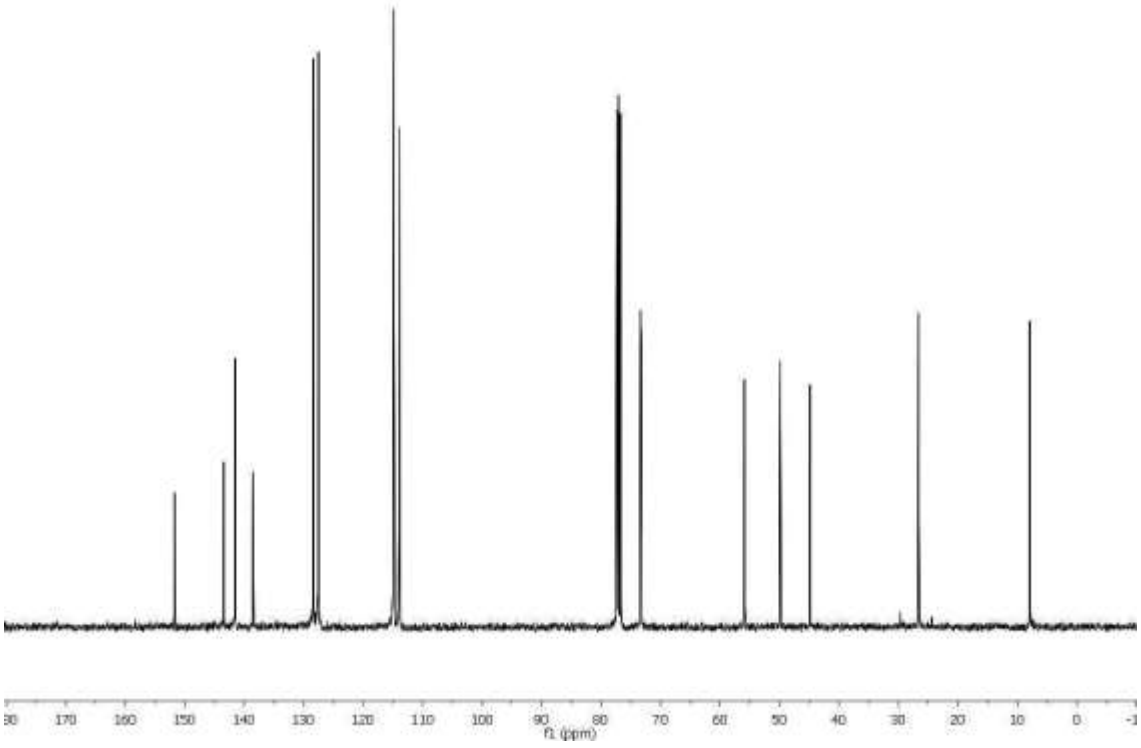
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


180
170
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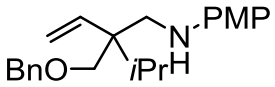
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

N-(2-benzyloxymethyl-2-isopropylbut-3-en-1-yl)-4-methoxyaniline (5.4c)



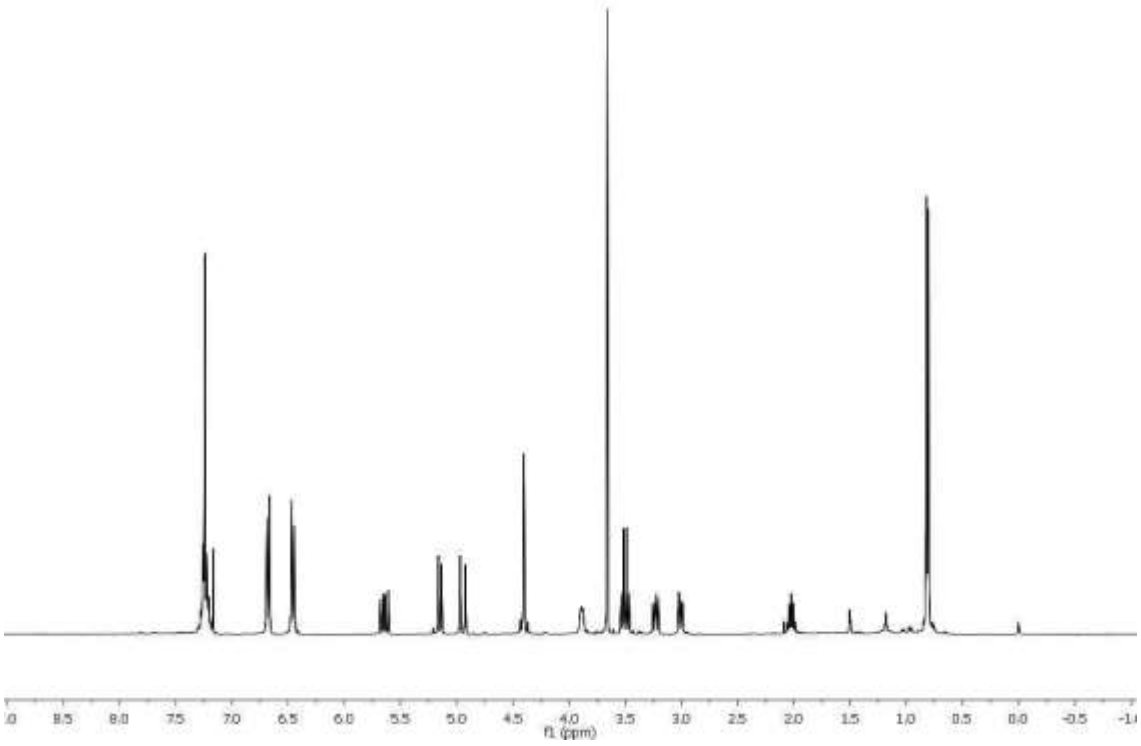
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3c**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 60% EtOAc/hexane) to furnish the title compound (33.8 mg, 50%) as a yellow oil.

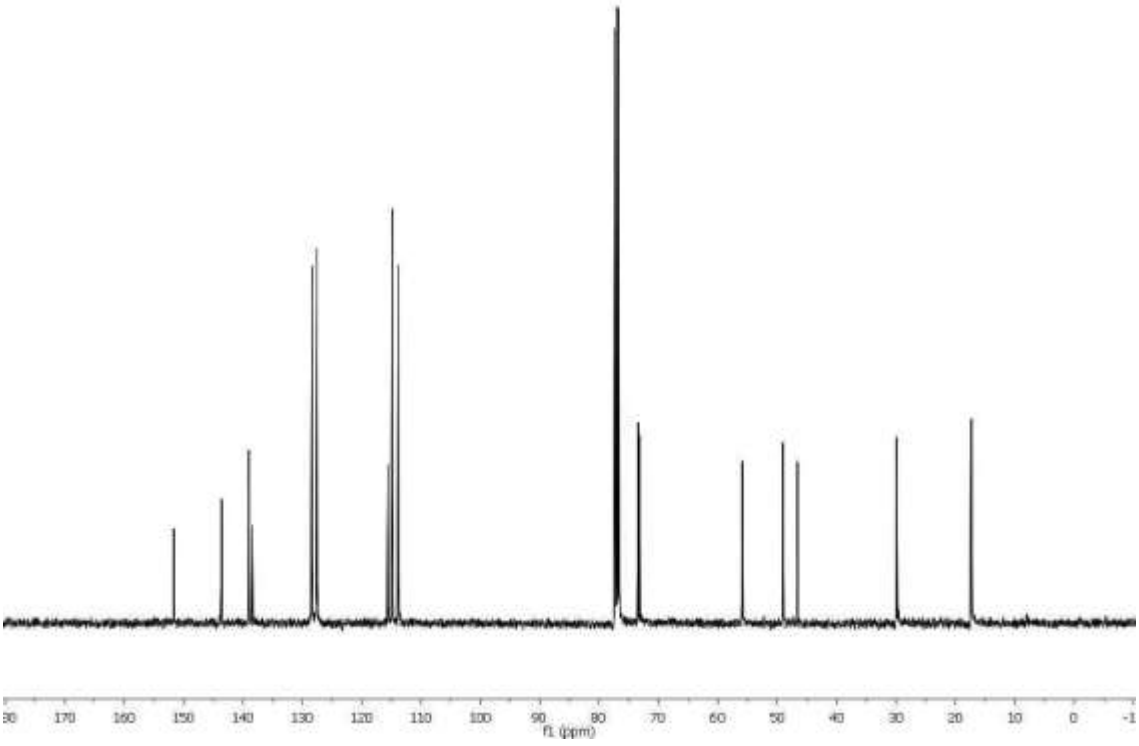
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 8.5 Hz, 2H), 5.74 (dd, *J* = 17.7, 11.6 Hz, 1H), 5.14 (dd, *J* = 81.2, 14.6 Hz, 2H), 4.50 (s, 2H), 3.98 (br, 1H), 3.75 (s, 3H), 3.59 (q, *J* = 9.1 Hz, 2H), 3.32 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.10 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.12 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 143.7, 139.0, 138.5, 128.5, 127.7, 127.6, 115.7, 115.0, 114.0, 73.6, 73.3, 56.0, 49.1, 46.7, 30.0, 17.5, 17.4.

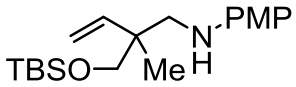
LRMS (ESI): m/z 340 $[M+H]^+$

FTIR (neat): 3377, 2959, 1618, 1511, 1453, 1384, 1365, 1233, 1178, 1090, 1072, 1038, 915, 817, 734, 697 cm^{-1}.


f1 (ppm)


f1 (ppm)

N-(2-*tert*-butyldimethylsiloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4d)



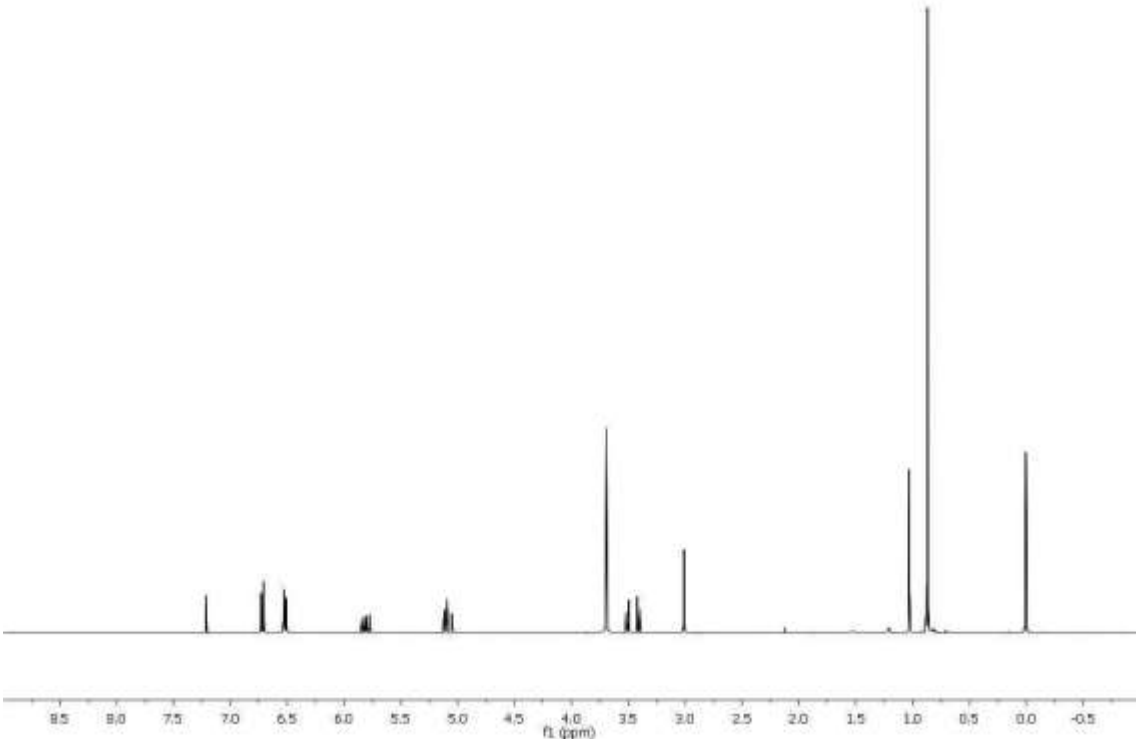
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3d**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (51.7 mg, 77%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 5.86 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.30–5.04 (m, 2H), 3.74 (s, 3H), 3.51 (dd, *J* = 38.4, 9.6 Hz, 2H), 3.06 (s, 2H), 1.08 (s, 3H), 0.92 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 143.6, 142.7, 115.0, 114.5, 114.0, 69.8, 56.0, 51.9, 42.9, 26.1, 19.8, 18.4, -5.4.

LRMS (ESI): m/z 336 $[M+H]^+$

FTIR (neat): 3398, 2953, 2929, 2856, 1512, 1463, 1415, 1388, 1361, 1247, 1233, 1179, 1088, 1040, 1005, 909, 835, 816, 774, 732, 667 cm^{-1}.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5.0
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2.0
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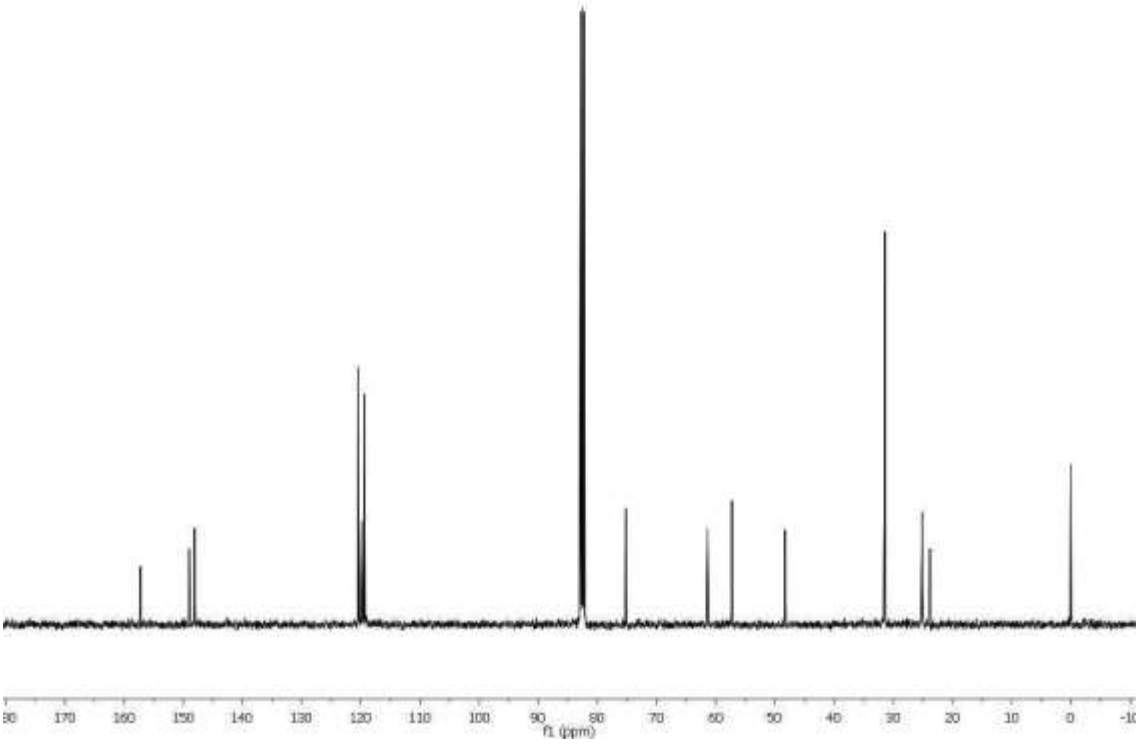
-0.5
f1 (ppm)


180
170
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110
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90
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70
60
50
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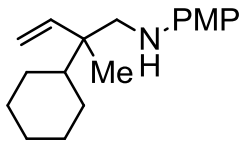
30
20
10
0
f1 (ppm)

N-(2-cyclohexyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4e)



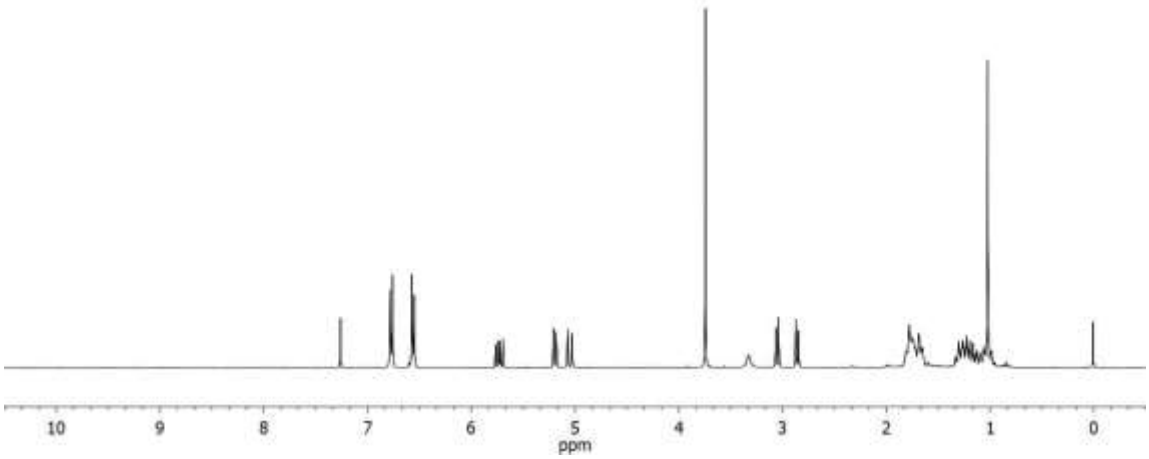
The reaction was conducted in modification to **General Procedure** (*via* 400 mol% of allene **5.3e**). After heating the reaction for 10 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 60% CH_2Cl_2/hexane) to furnish the title compound (40.5 mg, 74%) as a yellow oil.

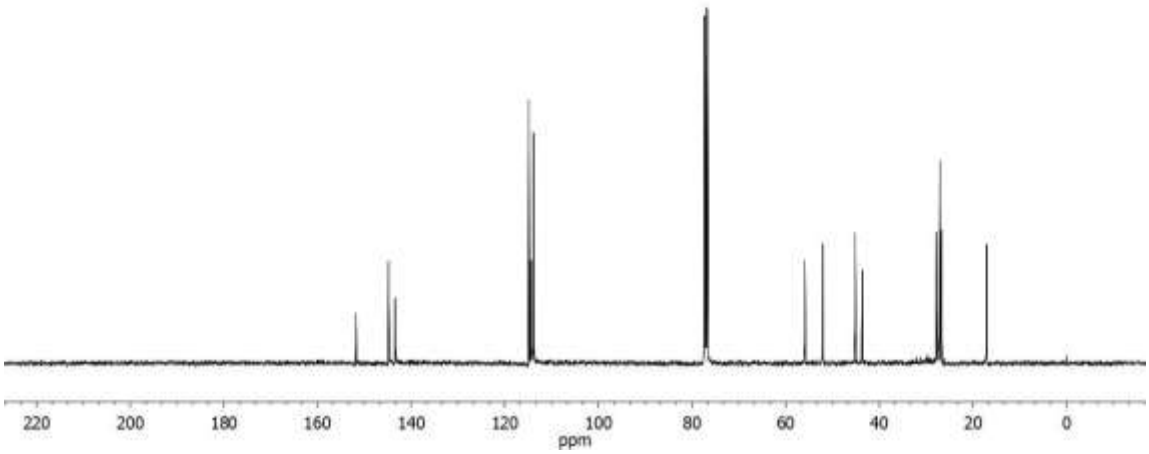
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 5.73 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 17.6 Hz, 1H), 3.74 (s, 3H), 3.33 (s, 1H), 2.95 (dd, *J* = 76.6, 10.9 Hz, 2H), 1.83 – 1.63 (m, 5H), 1.35 – 0.94 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 144.8, 143.4, 114.9, 114.4, 113.9, 55.9, 52.1, 45.1, 43.6, 27.8, 27.2, 27.0, 26.7, 17.1.

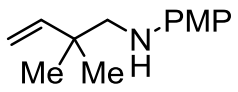
LRMS (CI): m/z 274 $[M+H]^+$

FTIR (neat): 3384, 2924, 2851, 1903, 1618, 1510, 1478, 1449, 1412, 1376, 1306, 1232, 1178, 1124, 1078, 1039, 1005, 913, 815, 766, 741 cm^{-1}.


10
9
8
7
6
5
4
3
2
1
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4f)



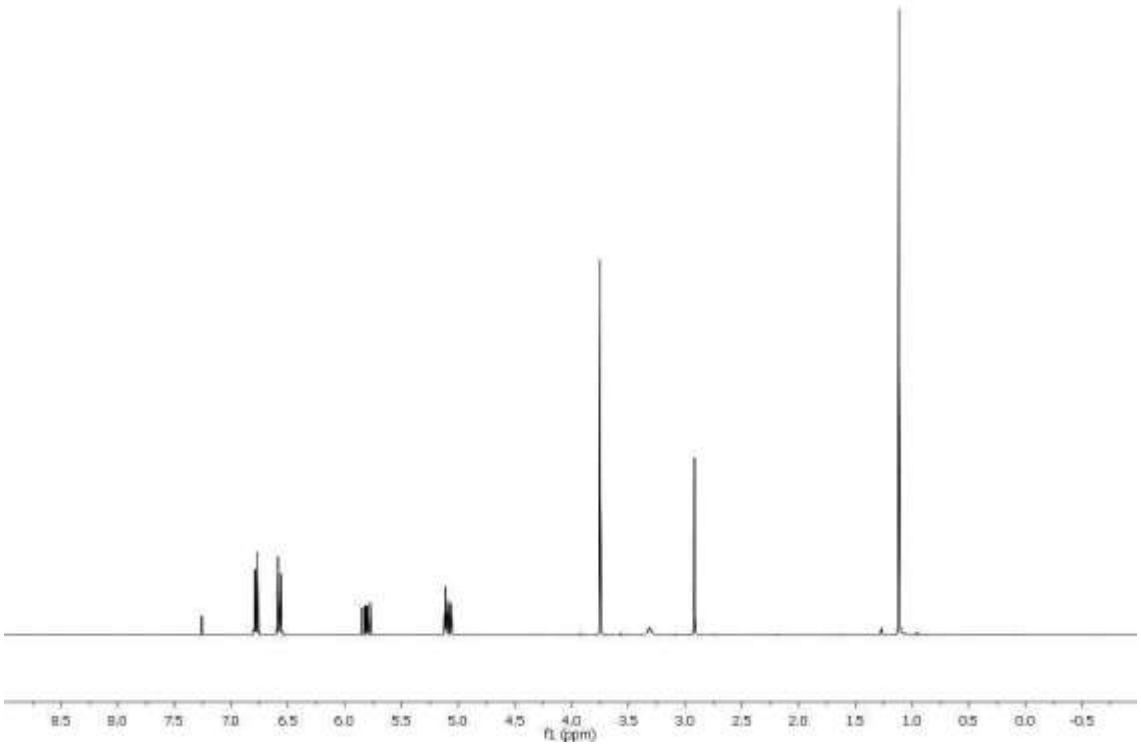
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3f**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (35.4 mg, 86%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 5.81 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.75 (s, 3H), 3.31 (br, 1H), 2.92 (s, 2H), 1.12 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 146.2, 143.4, 114.9, 114.1, 113.1, 55.9, 55.3, 38.0, 25.3.

LRMS (ESI): m/z 206 $[M+H]^+$

FTIR (neat): 3398, 2959, 2830, 1738, 1639, 1510, 1475, 1414, 1380, 1363, 1232, 1178, 1116, 1094, 1037, 1001, 914, 816, 766, 728, 690 cm^{-1}.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7.0
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6.0
5.5
5.0
4.5
4.0
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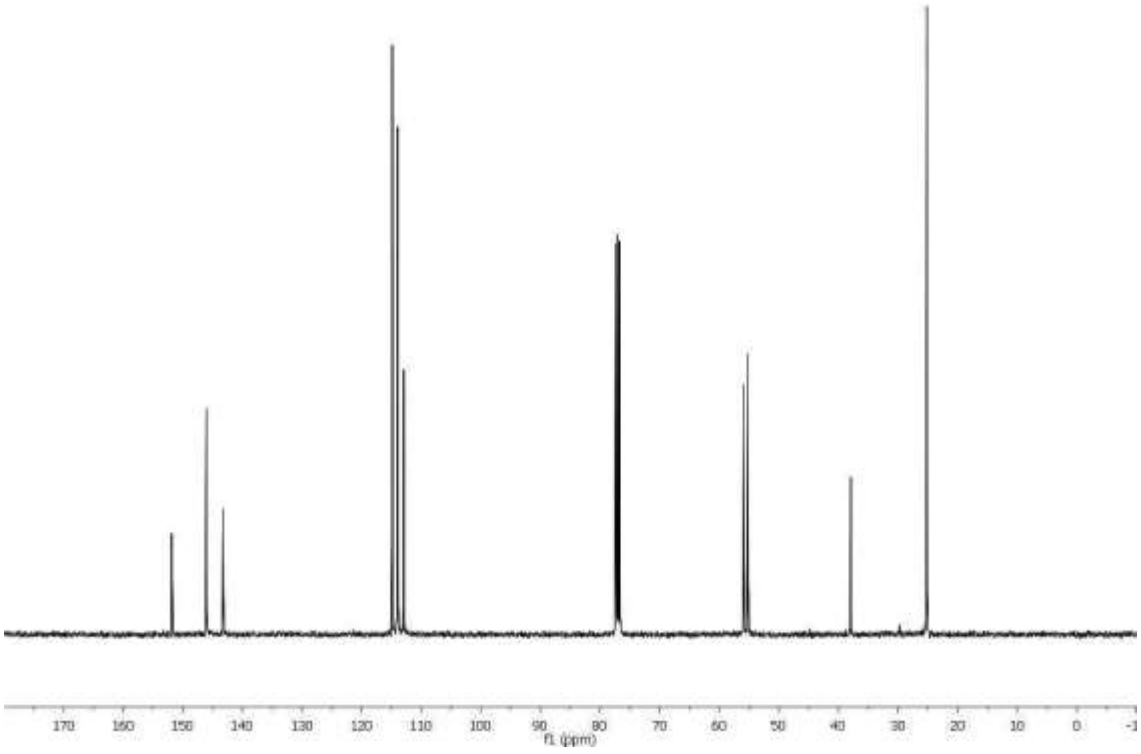
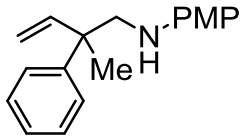
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4-methoxy-N-(2-(4-methoxyphenyl)-2-methylbut-3-en-1-yl)aniline (5.4g)



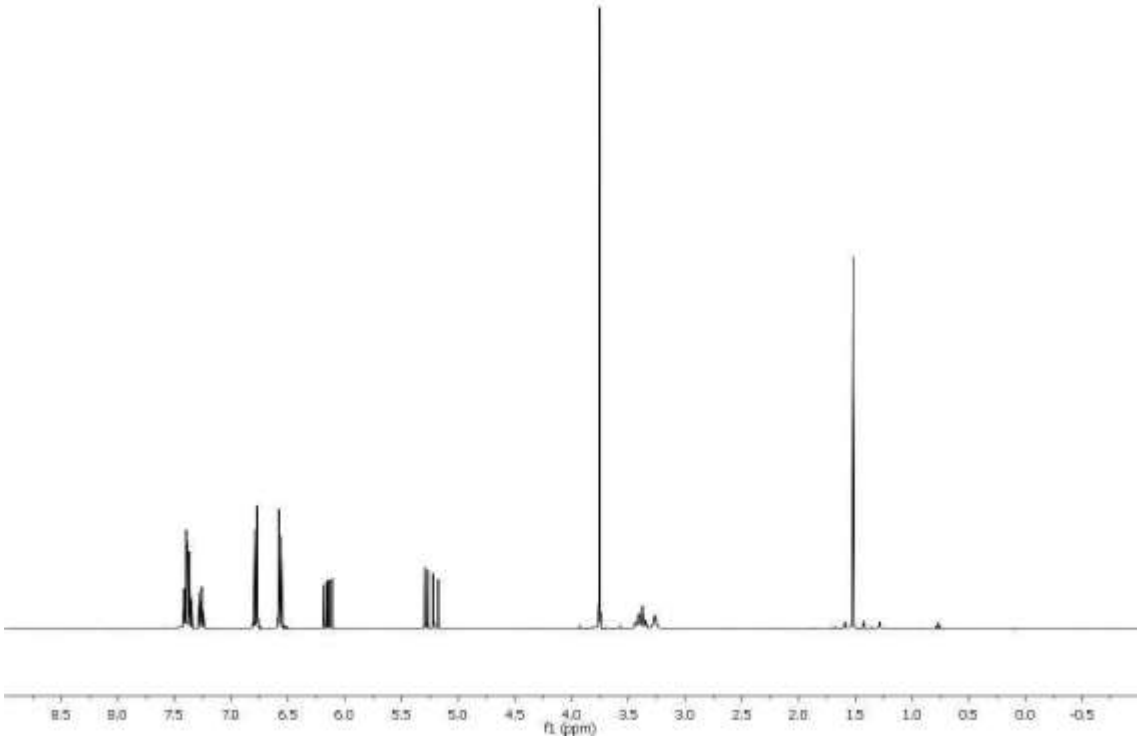
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3g**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (39.7 mg, 74%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 4H), 7.28-7.23 (m, 1H), 6.77 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 9.1 Hz, 2H), 6.13 (dd, J = 17.6, 10.8 Hz, 1H), 5.23 (ddd, J = 18.7, 14.2, 1.1 Hz, 1H), 3.75 (s, 3H), 3.38 (dd, J = 24.5, 11.2 Hz, 1H), 3.25 (br, 1H), 1.52 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 145.3, 144.7, 143.0, 128.6, 126.9, 126.6, 115.0, 114.2, 114.1, 56.0, 54.0, 45.6, 24.5.

LRMS (ESI): m/z 268 $[M+H]^+$

FTIR (neat): 2966, 2829, 1599, 1510, 1479, 1443, 1409, 1372, 1266, 1232, 1178, 1119, 1068, 1035, 918, 816, 761, 736, 699 cm^{-1}.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7.5
7.0
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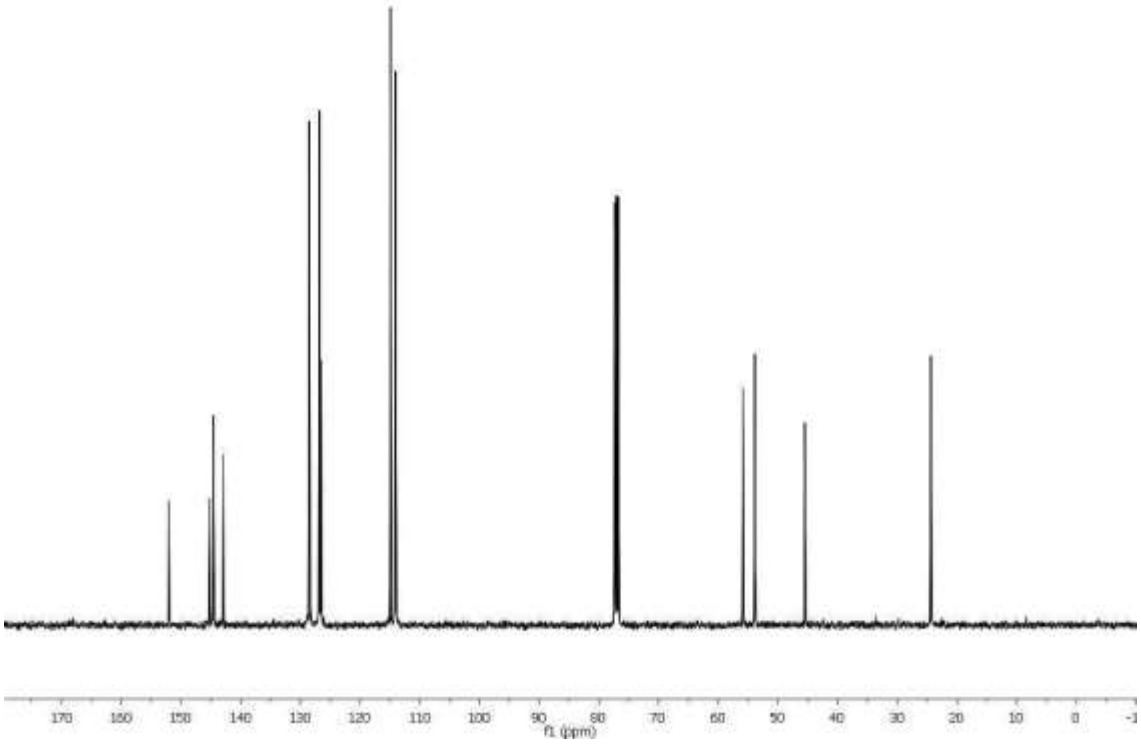
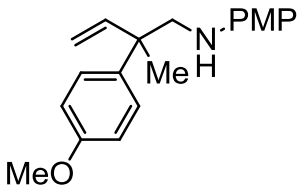
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4-methoxy-N-(2-(4-methoxyphenyl)-2-methylbut-3-en-1-yl)aniline (5.4h)



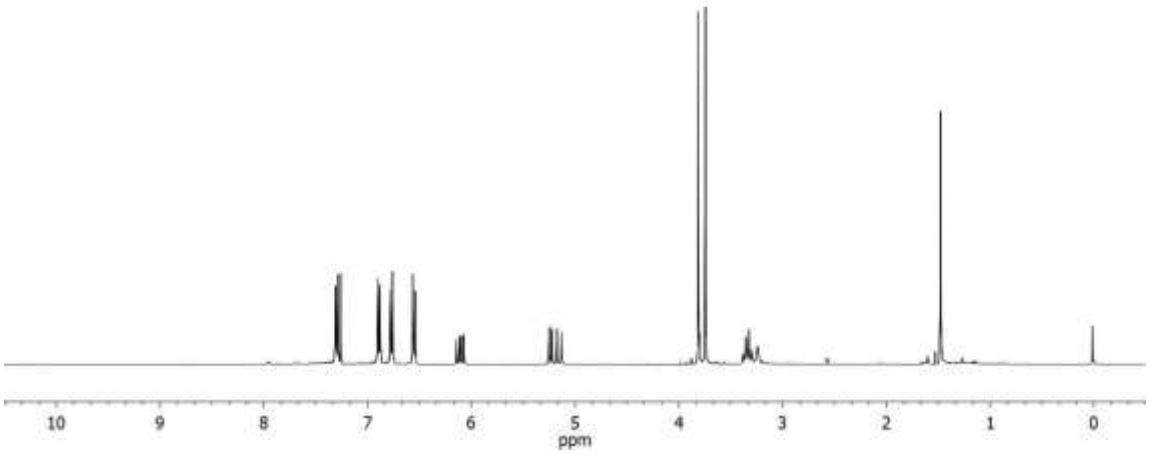
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3h**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 70% CH_2Cl_2/hexane) to furnish the title compound (42.8 mg, 72%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 6.11 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.24 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.15 (dd, *J* = 17.6, 0.9 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.41 – 3.27 (m, 2H), 3.24 (s, 1H), 1.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 151.9, 144.8, 142.9, 137.0, 127.8, 114.8, 114.0, 113.8, 113.7, 55.8, 55.2, 54.0, 44.8, 24.5.

LRMS (CI): m/z 298 $[M+H]^+$

FTIR (neat): 2933, 2833, 1608, 1509, 1463, 1441, 1411, 1297, 1245, 1233, 1180, 1116, 1032, 918, 819, 763 cm^{-1}.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4
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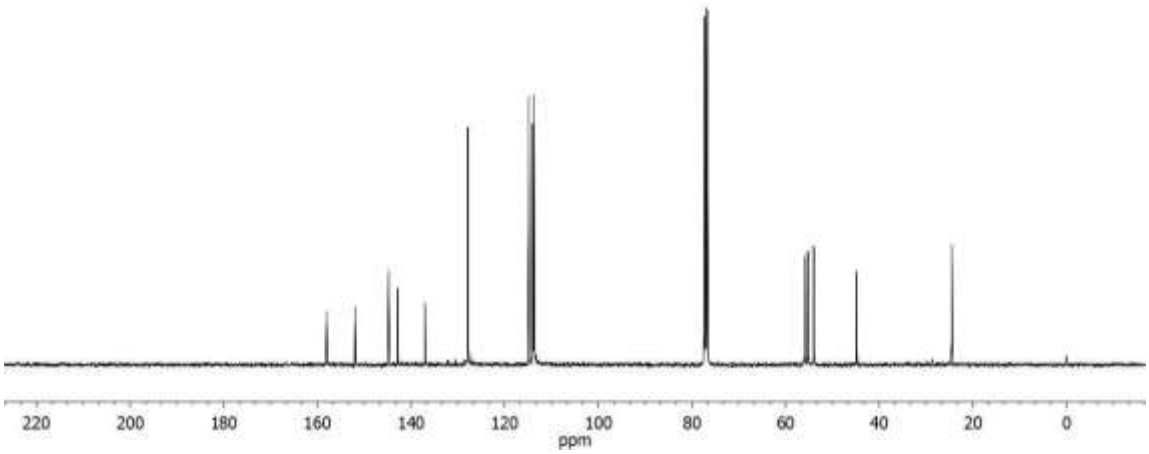
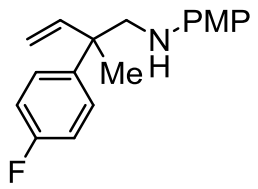
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

4-methoxy-N-(2-methyl-2-(4-fluorophenyl)but-3-en-1-yl)aniline (5.4i)



The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3i**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (39.4 mg, 69%) as a yellow oil.

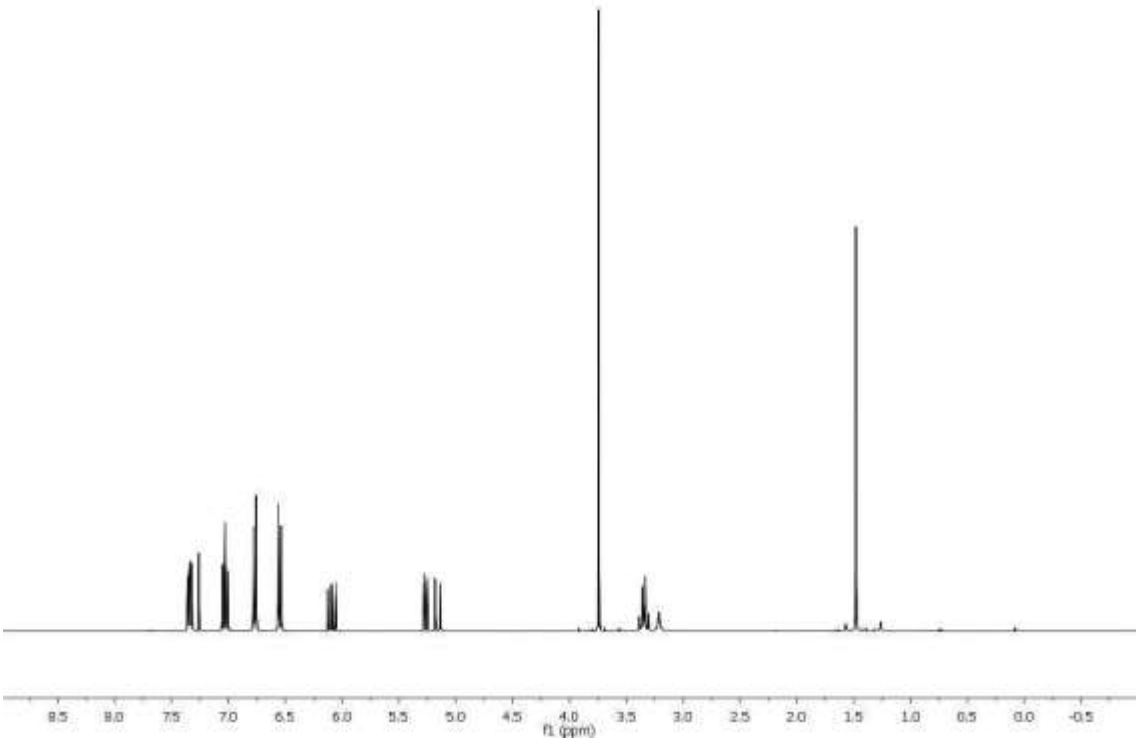
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 9.0, 5.3 Hz, 2H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 6.09 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.21 (ddd, *J* = 18.6, 14.2, 1.1 Hz, 2H), 3.74 (s, 3H), 3.35 (q, *J* = 11.3 Hz, 2H), 3.21 (br, 1H), 1.48 (s, 3H).

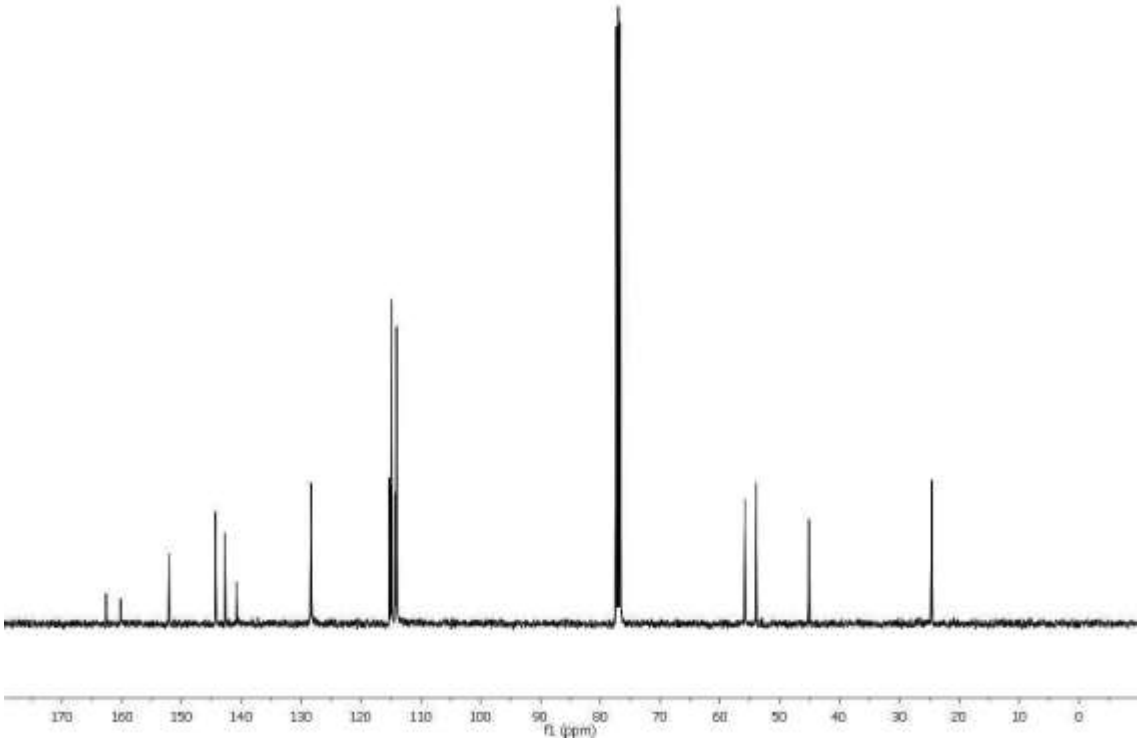
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.57 (d, J = 245.1 Hz), 152.2, 144.5, 142.9, 140.94 (d, J = 3.1 Hz), 128.55 (d, J = 7.8 Hz), 115.31 (d, J = 21.0 Hz), 115.0, 114.4, 114.2, 56.0, 54.1, 45.2, 24.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.8 (tt).

LRMS (ESI): m/z 286 $[M+H]^+$

FTIR (neat): 2931, 2831, 1600, 1508, 1480, 1411, 1373, 1231, 1179, 1163, 1119, 1100, 1064, 1036, 1014, 920, 832, 816, 762, 730 cm^{-1}.

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50
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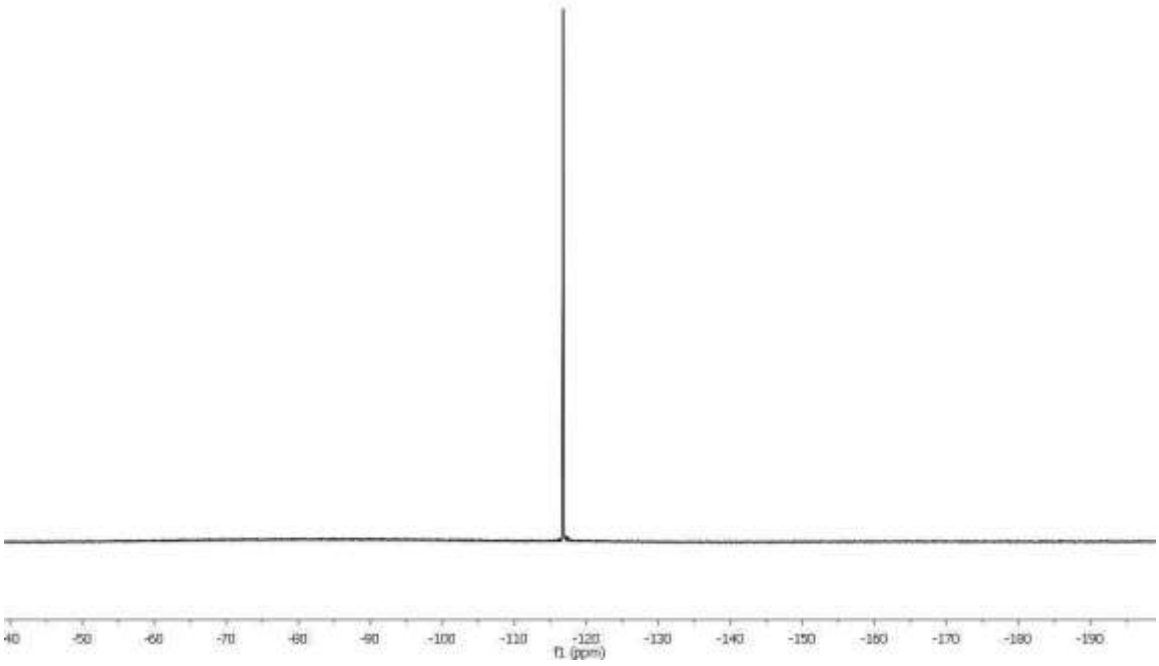
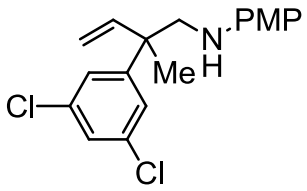
30
20
10
0
f1 (ppm)


-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

N-(2-(3,5-dichlorophenyl)-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4j)



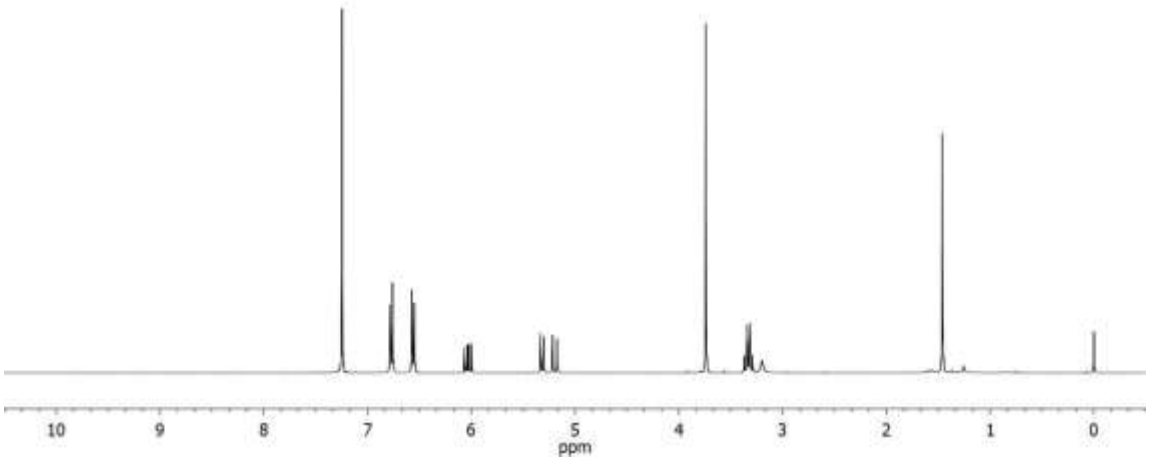
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3j**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 40% CH_2Cl_2/hexane) to furnish the title compound (47.1 mg, 70%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 3H), 6.77 (d, J = 8.9 Hz, 2H), 6.56 (d, J = 8.9 Hz, 2H), 6.03 (dd, J = 17.5, 10.8 Hz, 1H), 5.32 (dd, J = 10.8, 0.8 Hz, 1H), 5.19 (dd, J = 17.6, 0.7 Hz, 1H), 3.74 (s, 3H), 3.33 (dd, J = 11.6 Hz, 2H), 3.20 (s, 1H), 1.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 149.0, 143.0, 142.4, 135.0, 126.8, 125.6, 115.3, 114.9, 114.2, 55.8, 53.7, 45.7, 24.2.

LRMS (EI): m/z 336 $[M]^+$

FTIR (neat): 3400, 2934, 2830, 1584, 1561, 1510, 1464, 1439, 1414, 1273, 1233, 1179, 1129, 1098, 1037, 924, 856, 817, 797, 755, 688 cm^{-1}.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4
3
2
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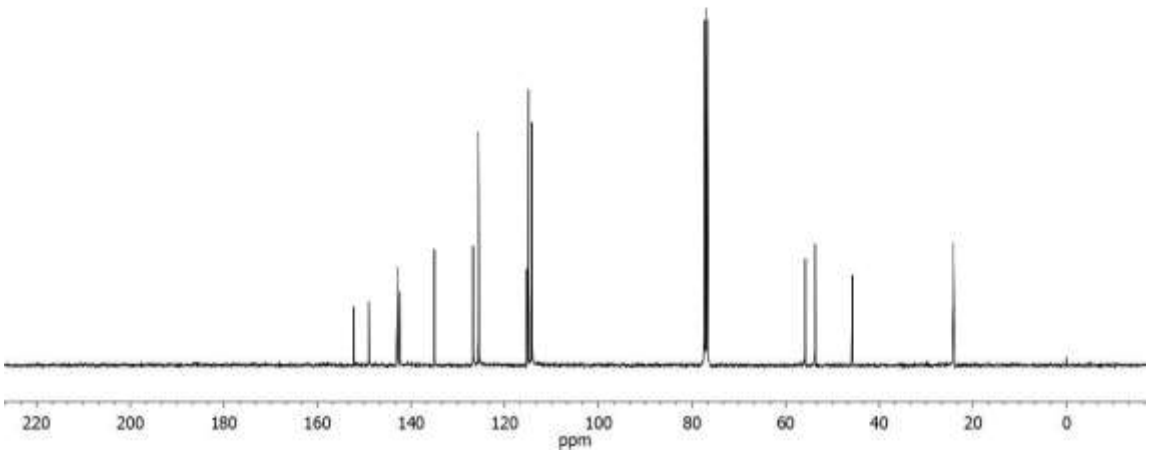
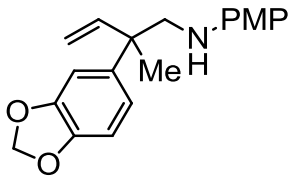
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

N-(2-(benzo[d][1,3]dioxol-5-yl)-2-methylbut-3-en-1-yl)-4-methoxyaniline (5.4k)



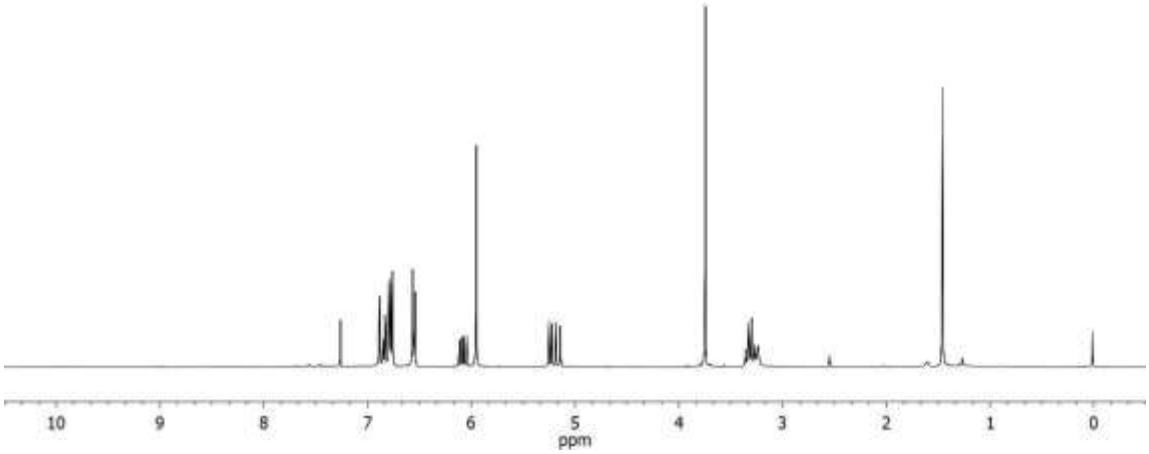
The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3k**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 80% CH_2Cl_2/hexane) to furnish the title compound (41.7 mg, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 – 6.73 (m, 5H), 6.58 – 6.53 (m, 2H), 6.08 (dd, J = 17.6, 10.8 Hz, 1H), 5.95 (s, 2H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 3.74 (s, 3H), 3.31 (dd, *J* = 22.3, 11.2 Hz, 2H), 3.24 (s, 1H), 1.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 147.8, 146.0, 144.6, 142.8, 139.1, 119.7, 114.8, 114.0, 113.8, 108.0, 107.6, 101.0, 55.8, 54.0, 45.3, 24.6.

LRMS (CI): m/z 312 $[M+H]^+$

FTIR (neat): 2896, 1673, 1608, 1510, 1485, 1433, 1232, 1180, 1106, 1036, 933, 860, 815, 754, 667 cm^{-1}.


10
9
8
7
6
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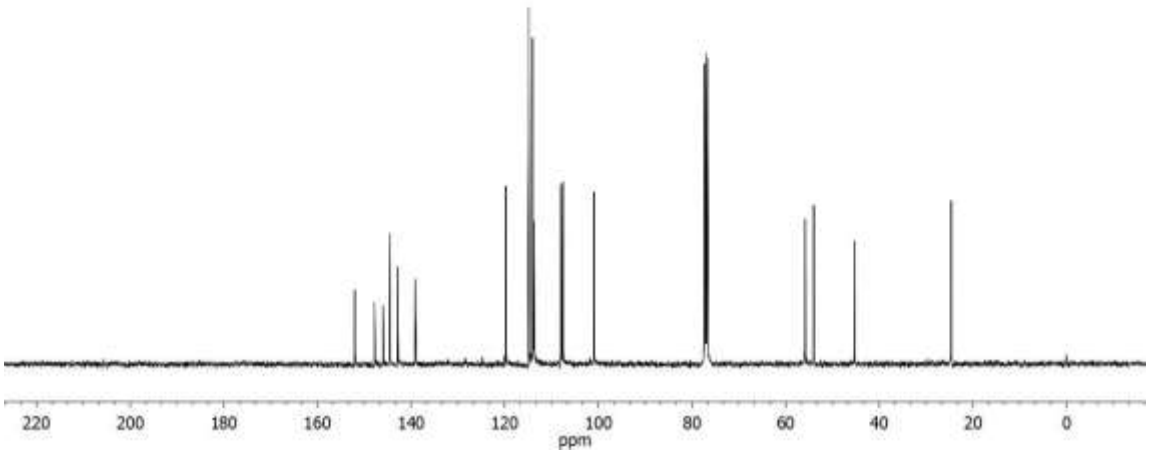
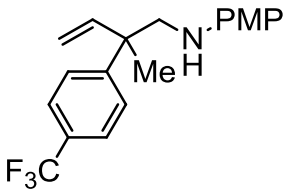
4
3
2
1
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

4-methoxy-N-(2-methyl-2-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)aniline (5.4l)



The reaction was conducted in accordance with **General Procedure** (*via* allene **5.3l**). After heating the reaction for 2 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 40% CH_2Cl_2/hexane) to furnish the title compound (54.3 mg, 81%) as a yellow oil.

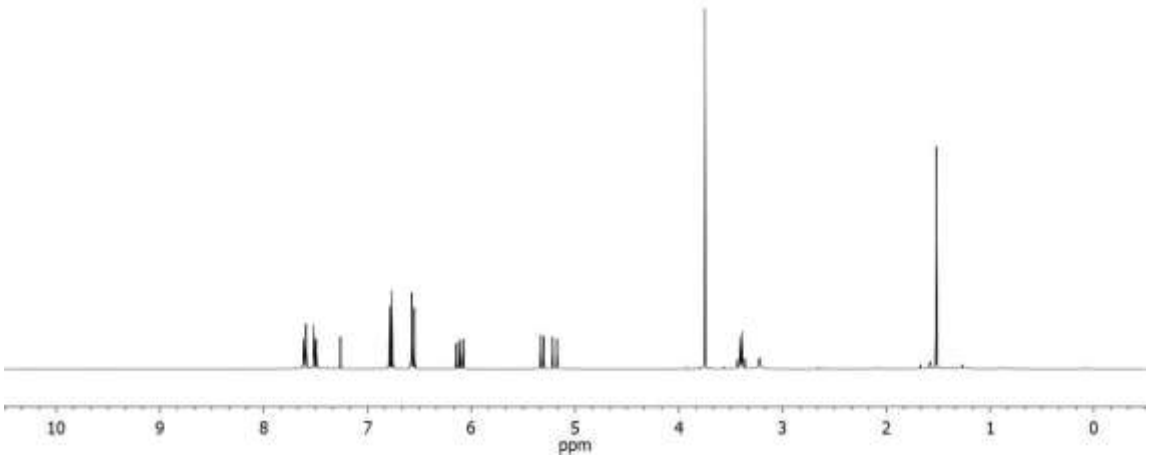
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.58 (m, 2H), 7.54 – 7.48 (m, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 9.0 Hz, 2H), 6.11 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.32 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.19 (dd, *J* = 17.6, 1.0 Hz, 1H), 3.75 (s, 3H), 3.40 (dd, *J* = 11.5 Hz, 2H), 3.22 (s, 1H), 1.52 (s, 3H).

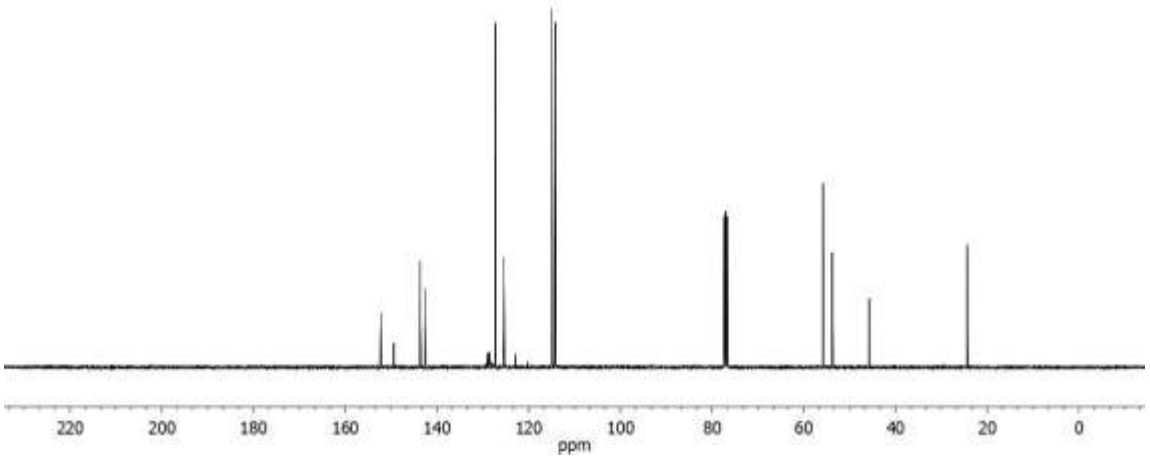
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 149.4, 149.4, 143.7, 142.6, 128.8 (q, J = 32.5 Hz), 127.3, 125.3 (q, J = 3.8 Hz), 124.2 (q, J = 272.0 Hz), 114.9, 114.9, 114.2, 55.8, 53.8, 45.8, 24.4.

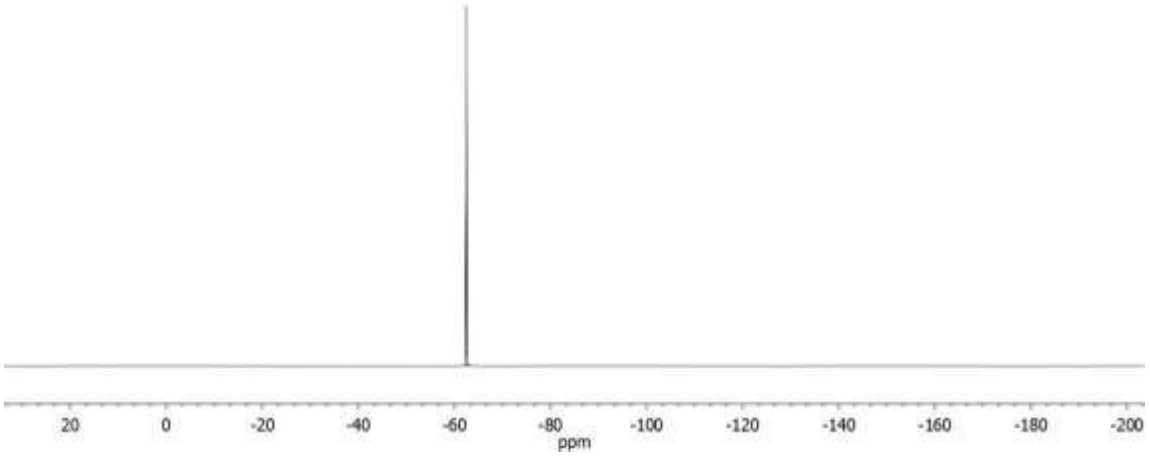
^{19}F NMR (376 MHz, $CDCl_3$): δ -62.48 (s).

LRMS (CI): m/z 336 $[M+H]^+$

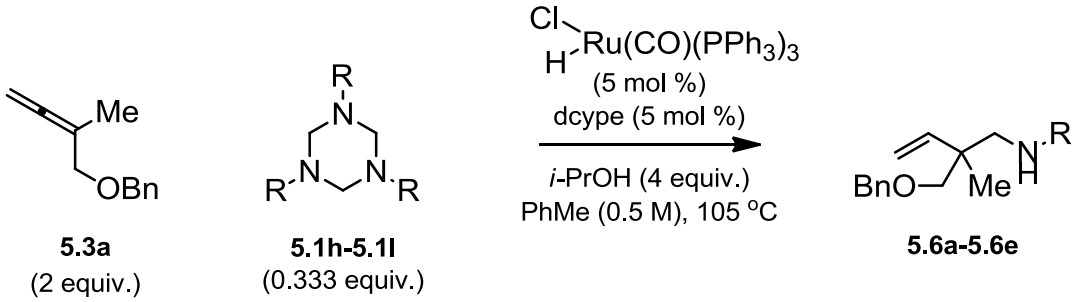
FTIR (neat): 2832, 1617, 1511, 1465, 1410, 1325, 1272, 1234, 1164, 1113, 1075, 1037, 1015, 923, 838, 817, 762, 708 cm^{-1}.




220
200
180
160
140
120
100
80
60
40
20
0
ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

Experimental Procedures and Spectral Data Adducts 5.6a-5.6e



5.3a (2 equiv.)

5.1h-5.1l (0.333 equiv.)

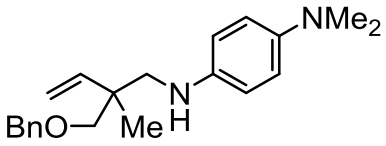
5.6a-5.6e

General Procedure for the coupling of allenes 5.3a with triazines 5.1h-5.1l

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1-bis(dicyclohexylphosphino)ethane (DCyPE) (4.2 mg,

0.010 mmol, 5 mol%), and triazine (0.067 mmol (0.200 mmol of formimine), 100 mol%). The tube was sealed with a rubber septum, purged with argon, and THF (0.5 M with respect to formimine), allene **5.3a** (0.400 mmol, 200 mol%), and isopropanol (61 μL, 0.800 mmol, 400 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds.

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-2-methoxyaniline (5.6a)



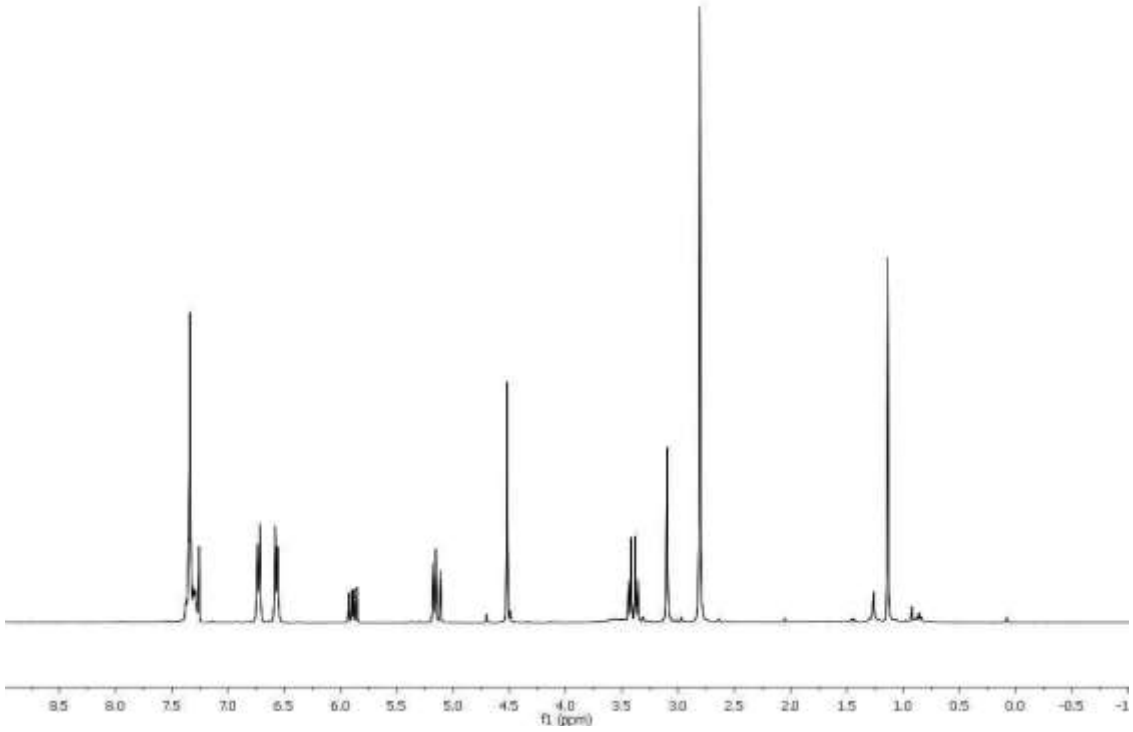
The reaction was conducted in accordance with **General Procedure** (*via* triazine **5.1h**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 17% EtOAc/hexane) to furnish the title compound (53.3 mg, 82%) as a yellow oil.

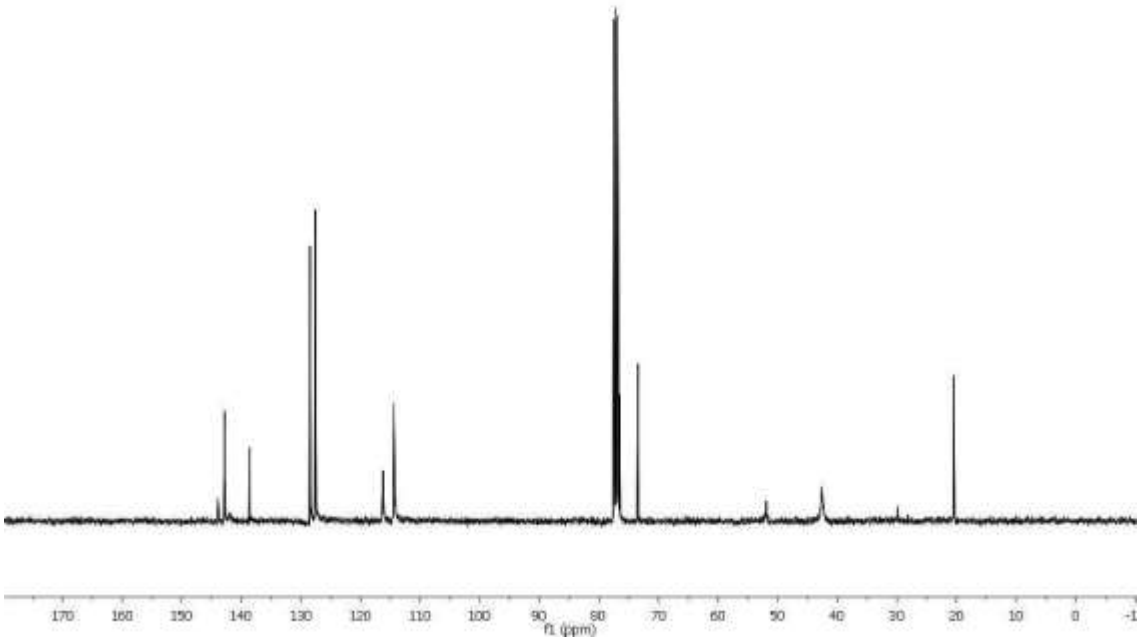
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.29 (m, 5H), 6.73 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 8.7 Hz, 2H), 5.89 (dd, J = 17.6, 11.0 Hz, 1H), 5.29 – 5.03 (m, 2H), 4.52 (s, 2H), 3.40 (dd, J = 24.2, 8.9 Hz, 2H), 3.10 (s, 2H), 2.81 (s, 6H), 1.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 142.8, 138.6, 128.5, 127.7, 127.6, 116.2, 114.4, 114.3, 76.5, 73.5, 51.9, 42.6, 29.9, 20.4.

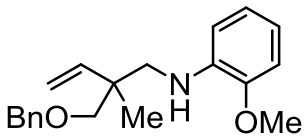
LRMS (ESI): m/z 325 $[M+H]^+$

FTIR (neat): 3382, 2855, 1516, 1475, 1453, 1416, 1302, 1254, 1207, 1161, 1092, 1027, 1002, 945, 915, 811, 734, 697 cm^{-1}.


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-2-methoxyaniline (5.6b)



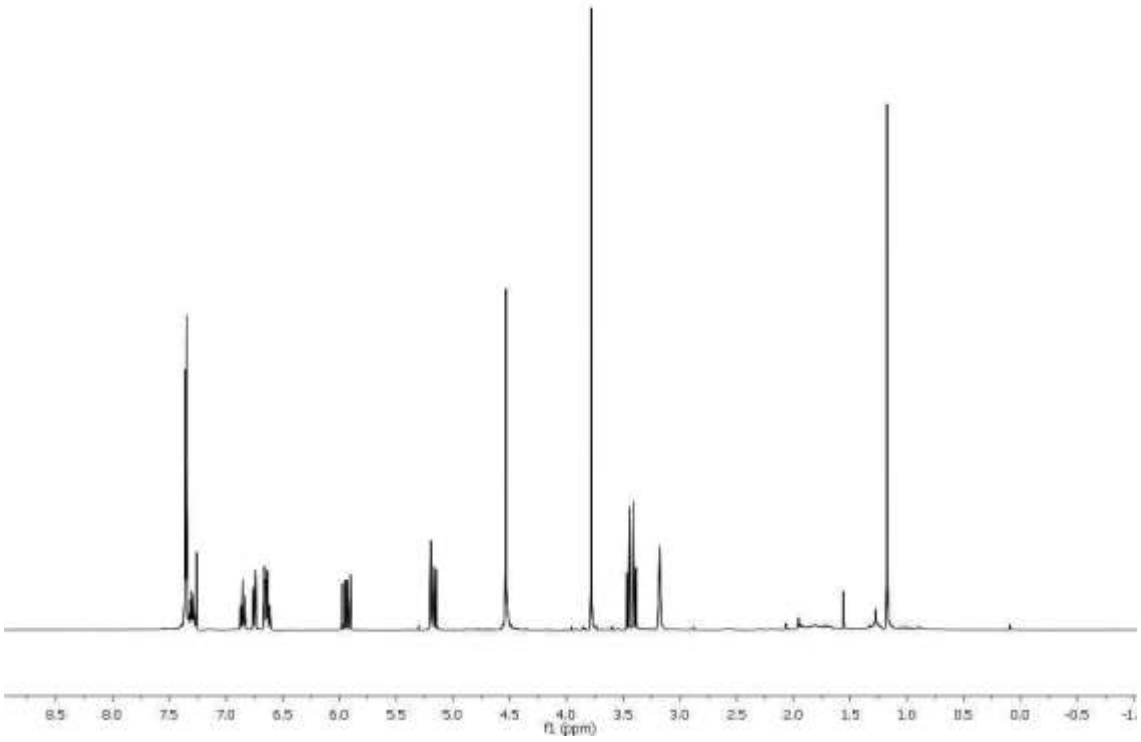
The reaction was conducted in accordance with **General Procedure** (*via* triazine **5.1i**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (33.3 mg, 53%) as a yellow oil.

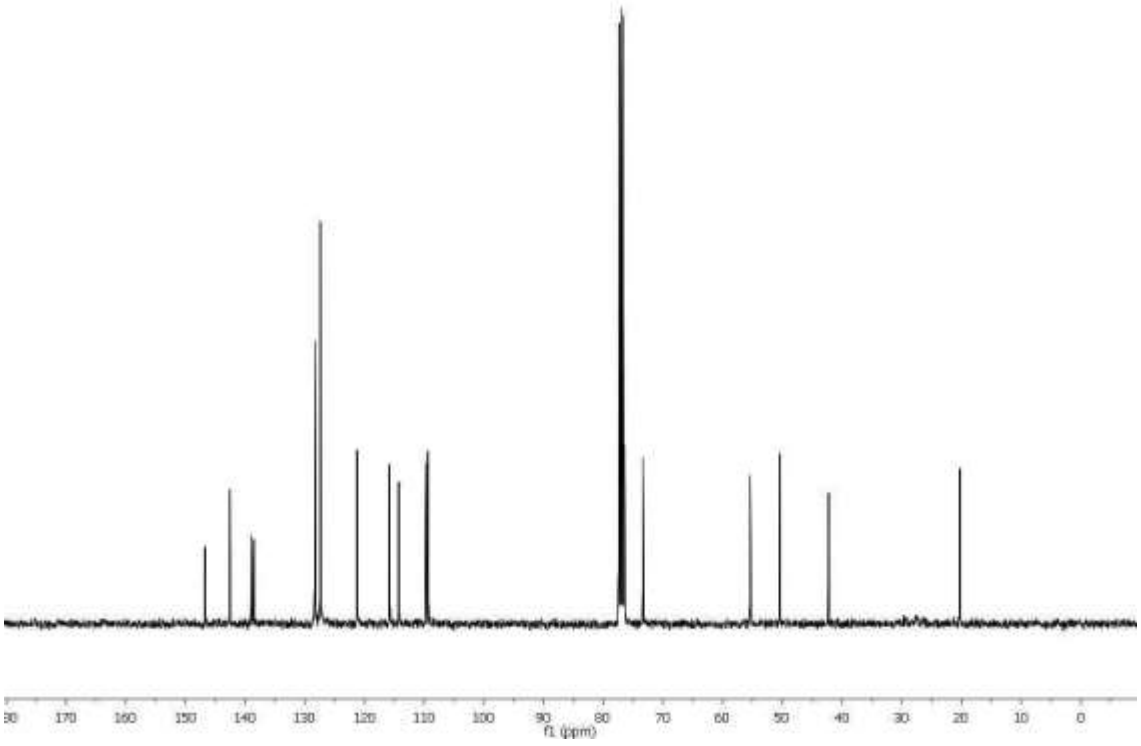
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.27 (m, 5H), 6.85 (td, *J* = 7.6, 1.4 Hz, 1H), 6.75 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.68 – 6.60 (m, 2H), 5.94 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.18 (ddd, *J* = 10.8, 6.3, 1.0 Hz, 2H), 4.53 (s, 2H), 3.78 (s, 3H), 3.43 (dd, *J* = 23.1, 8.9 Hz, 2H), 3.18 (br, 1H), 1.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 142.7, 139.1, 138.7, 128.4, 127.5, 121.3, 115.9, 114.4, 109.8, 109.5, 76.6, 73.5, 55.5, 50.6, 42.4, 20.4.

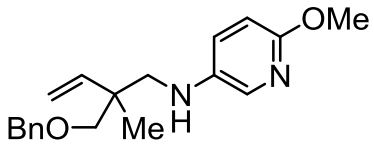
LRMS (ESI): m/z 312 $[M+H]^+$

FTIR (neat): 3418, 2853, 1907, 1601, 1513, 1454, 1430, 1345, 1248, 1221, 1176, 1096, 1049, 1028, 909, 730, 696 cm^{-1}.


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyl-3-pyridylamine (5.6c)



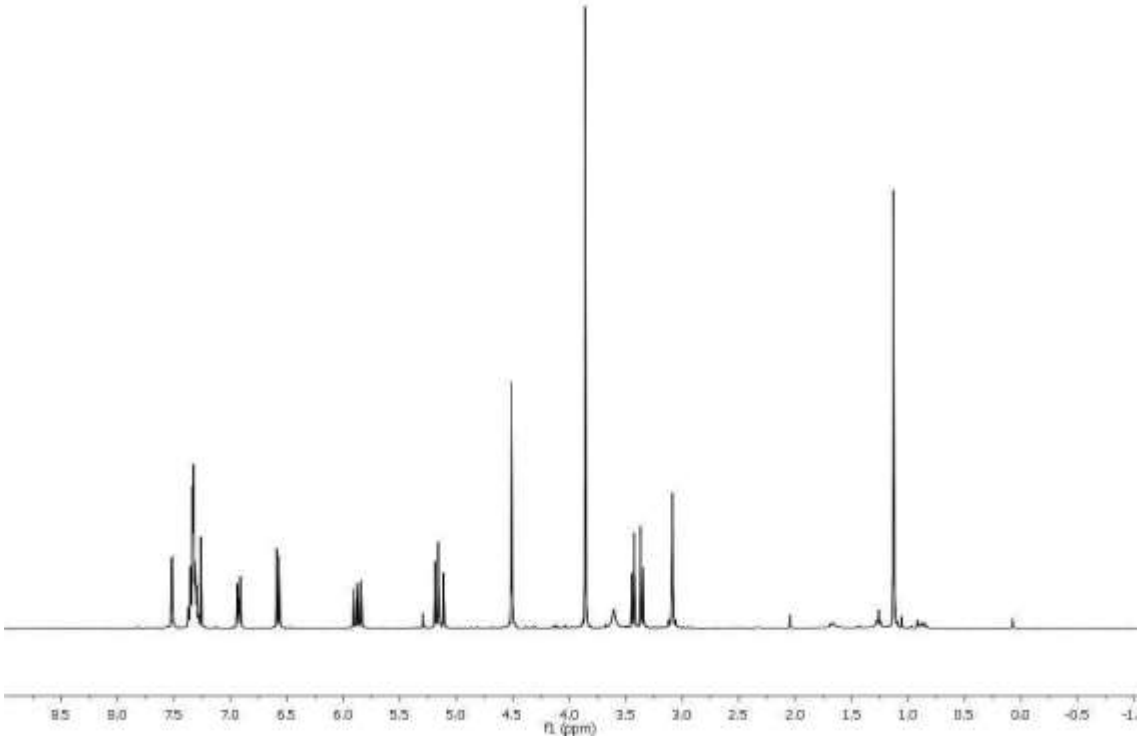
The reaction was conducted in accordance with **General Procedure** (*via* triazine **5.1j**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 17% EtOAc/hexane) to furnish the title compound (38.7 mg, 62%) as a yellow oil.

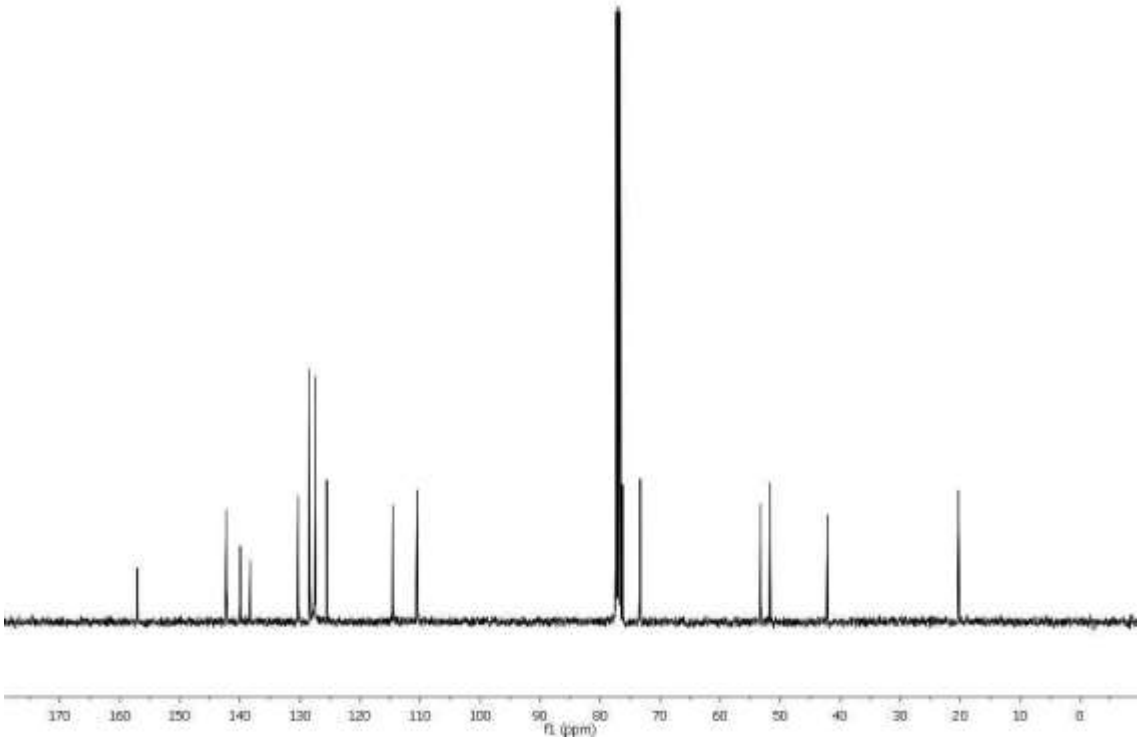
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 3.0 Hz, 1H), 7.40 – 7.27 (m, 5H), 6.92 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.58 (dd, *J* = 8.8, 0.6 Hz, 1H), 5.87 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.15 (ddd, *J* = 18.8, 14.3, 1.1 Hz, 2H), 4.51 (s, 2H), 3.86 (s, 3H), 3.60 (br, 1H), 3.40 (dd, *J* = 31.0, 8.9 Hz, 2H), 3.09 (s, 2H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 142.4, 140.1, 138.4, 130.5, 128.6, 127.8, 127.7, 125.7, 114.7, 110.7, 76.4, 73.5, 53.4, 51.9, 42.3, 20.5.

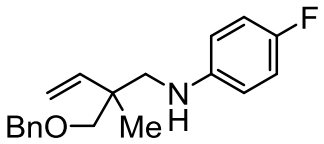
LRMS (ESI): m/z 313 $[M+H]^+$

FTIR (neat): 3383, 2854, 1577, 1493, 1461, 1432, 1379, 1259, 1239, 1205, 1091, 1029, 1008. 911, 821, 732, 697 cm^{-1}.


9.5
9.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-fluoroaniline (5.6d)



The reaction was conducted in accordance with **General Procedure** (*via* triazine **5.1k**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (42.0 mg, 70%) as a yellow oil.

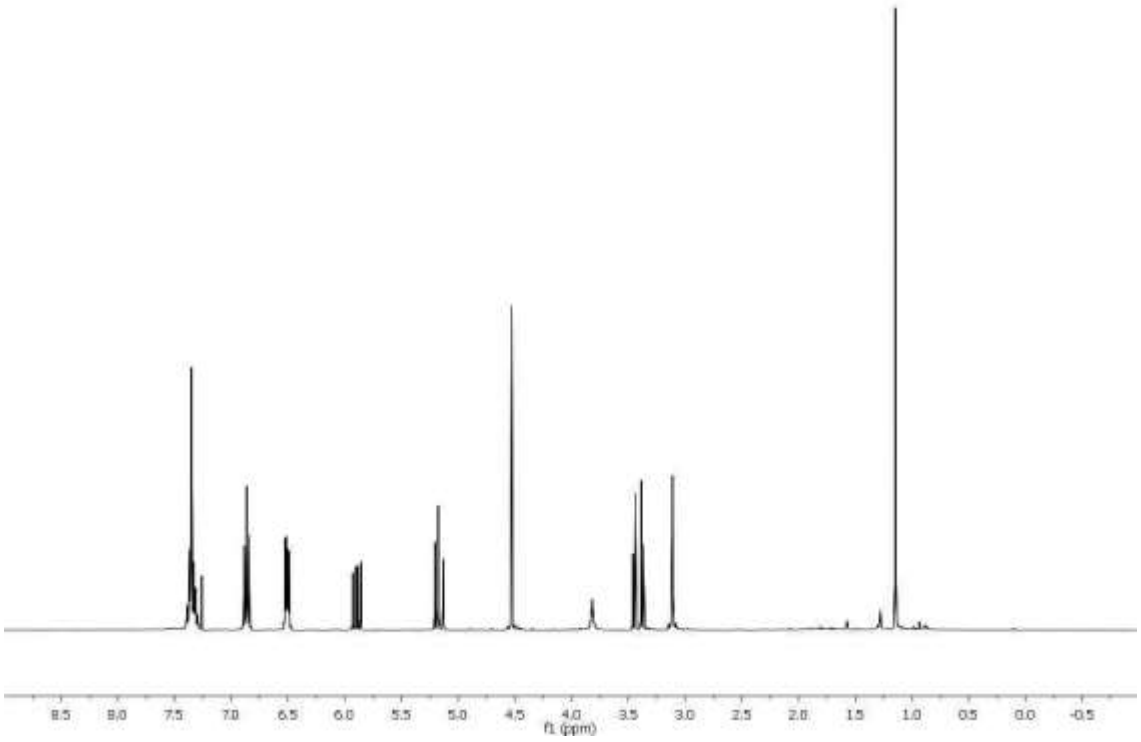
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 2H), 6.86 (t, *J* = 8.8 Hz, 2H), 6.56 – 6.45 (m, 2H), 5.89 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.24 – 5.10 (m, 2H), 4.53 (s, 2H), 3.82 (br, 1H), 3.41 (dd, *J* = 29.3, 8.9 Hz, 2H), 3.11 (s, 2H), 1.15 (s, 3H).

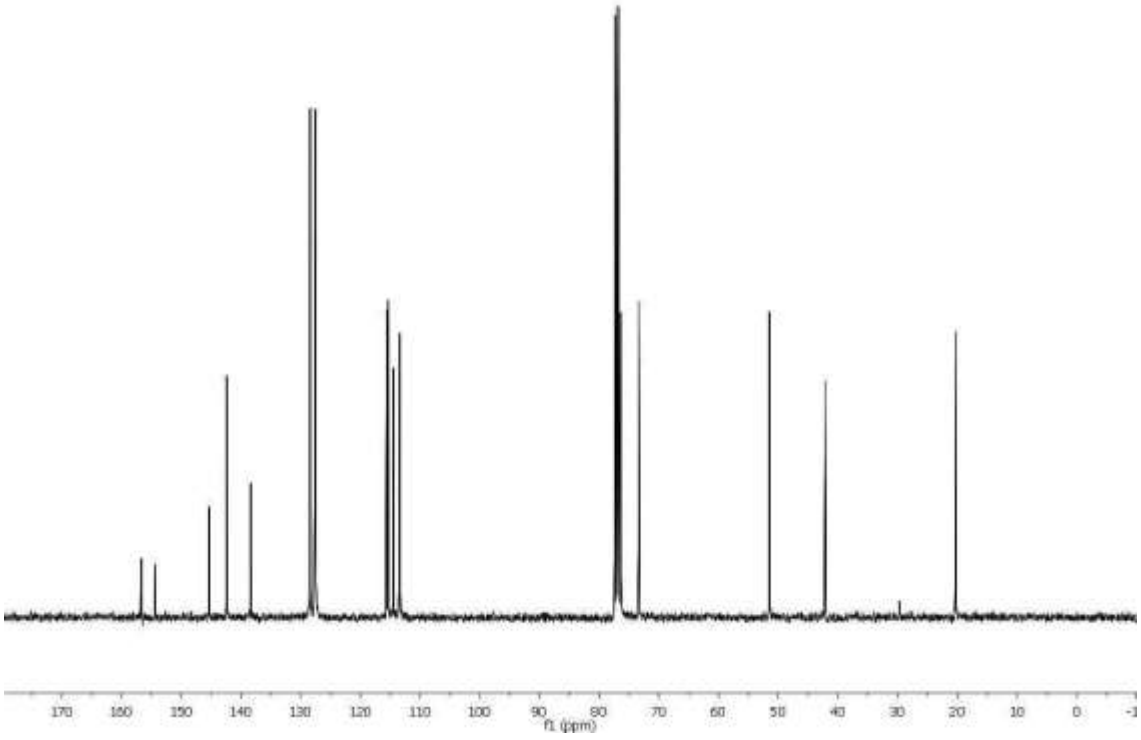
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (d, *J* = 234.3 Hz), 145.4, 142.5, 128.5, 127.7, 127.6, 115.6 (d, *J* = 22.2 Hz), 114.6, 113.6 (d, *J* = 7.3 Hz), 76.5, 73.5, 51.6, 42.3, 20.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -128.8 (s).

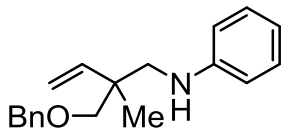
LRMS (ESI): m/z 300 $[M+H]^+$

FTIR (neat): 3396, 2855, 1612, 1509, 1476, 1453, 1416, 1361, 1312, 1252, 1095, 1027, 1003, 909, 817, 782, 732, 697 cm^{-1}.


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-aniline (5.6e)



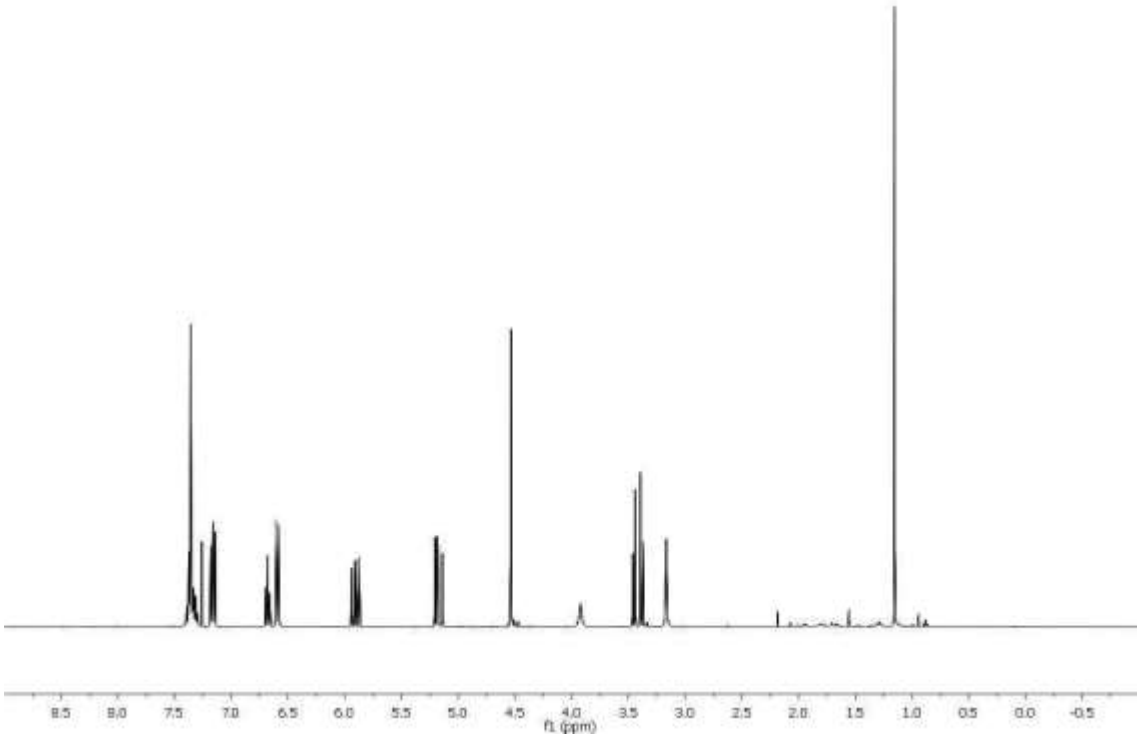
The reaction was conducted in accordance with **General Procedure** (*via* triazine **5.1l**). After heating the reaction for 24 hours, the mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish the title compound (34.2 mg, 61%) as a yellow oil.

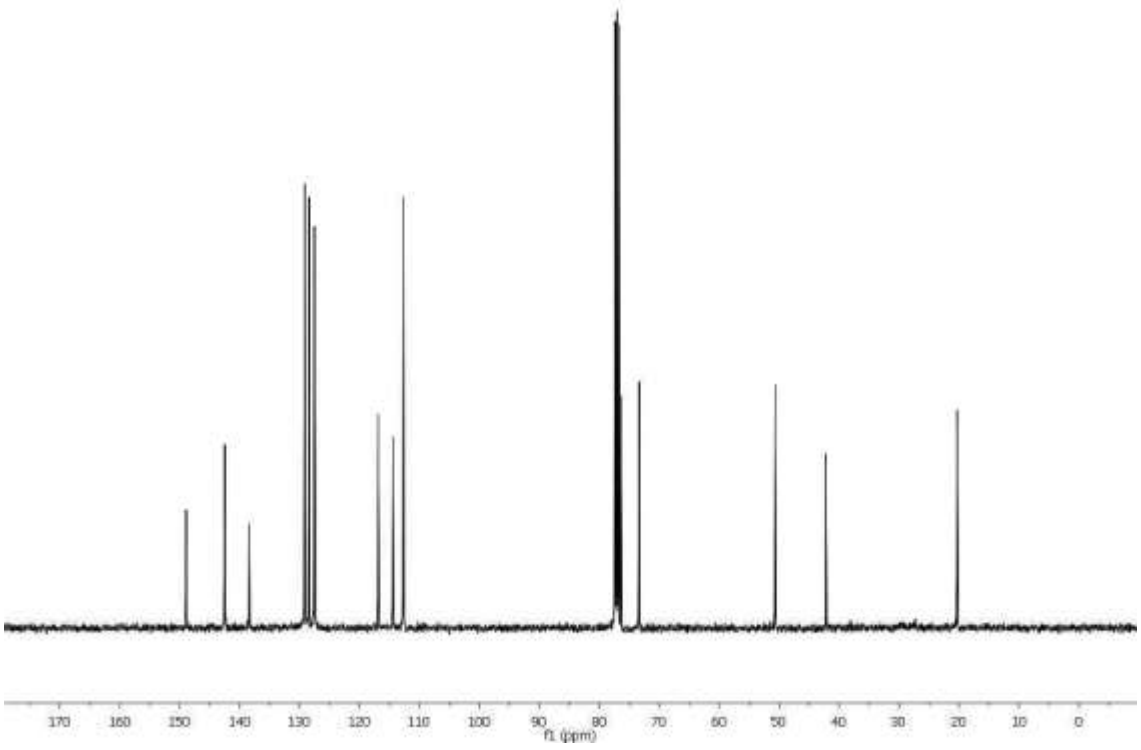
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.28 (m, 5H), 7.21 – 7.12 (m, 2H), 6.73 – 6.64 (m, 1H), 6.59 (dd, *J* = 8.6, 1.0 Hz, 2H), 5.90 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.18 (ddd, *J* = 16.8, 12.3, 1.2 Hz, 2H), 4.53 (s, 2H), 3.92 (br, 1H), 3.42 (dd, *J* = 27.1, 8.9 Hz, 2H), 3.17 (s, 2H), 1.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 142.6, 138.5, 129.3, 128.5, 127.7, 127.6, 117.0, 114.6, 112.8, 76.5, 73.5, 50.8, 42.3, 20.4.

LRMS (ESI): m/z 282 $[M+H]^+$

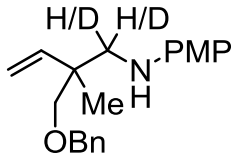
FTIR (neat): 3397, 2854, 1919, 1602, 1506, 1453, 1432, 1361, 1313, 1255, 1204, 1179, 1154, 1093, 1027, 992, 909, 867, 732. 691 cm^{-1}.


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Experimental Procedures and Spectral Data Adducts *deuterio*-5.4a and *deuterio*-5.4a'

N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (*deuterio*-5.4a)

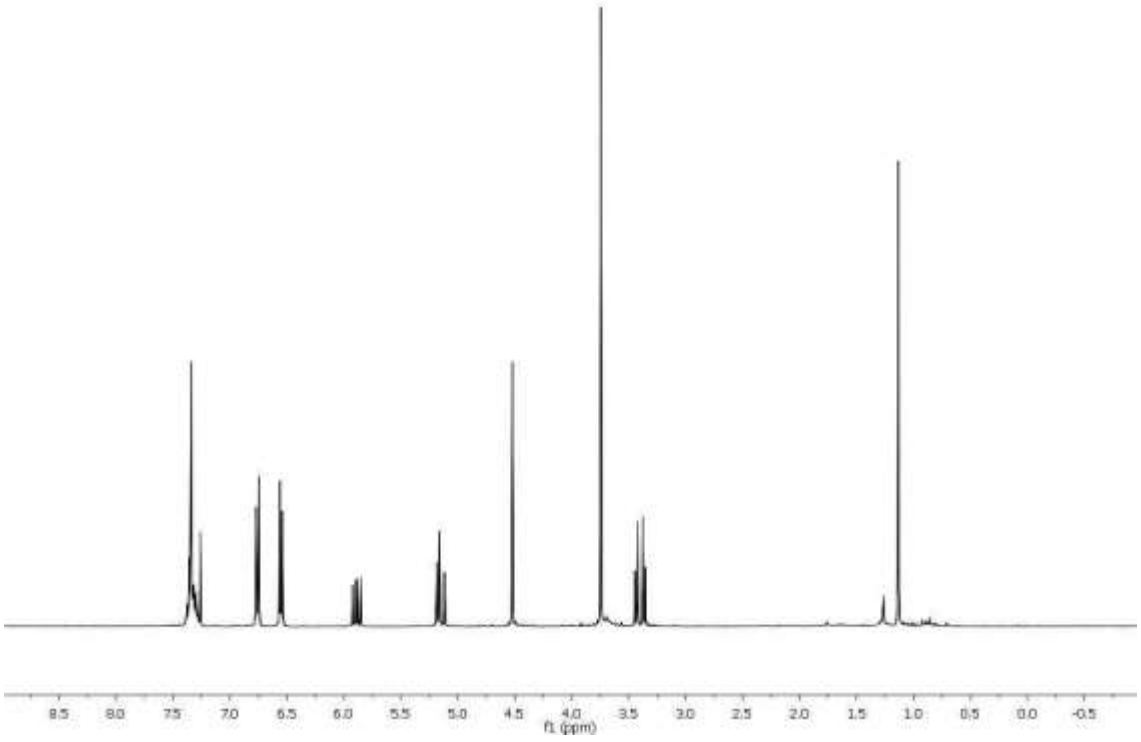


To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1-bis(dicyclohexylphosphino)ethane (DCyPE) (4.2 mg,
0.010 mmol, 5 mol%), and *deuterio*-triazine **5.1b** (0.067 mmol (0.200 mmol of formimine), 100 mol%). The tube was sealed with a rubber septum, purged with argon, and toluene (0.5 M with respect to formimine), allene **5.3a** (0.400 mmol, 200 mol%), and isopropanol (61 μL, 0.800 mmol, 400 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish *deuterio*-**5.4a** in 83% yield.

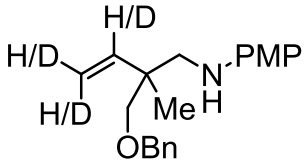
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.28 (m, 5H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 5.89 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.23 – 5.07 (m, 2H), 4.52 (s, 2H), 3.74 (s, 3H), 3.69 (br, 1H), 3.40 (dd, *J* = 26.7, 8.9 Hz, 2H), 1.13 (s, 3H).

^{2}H NMR (77 MHz, $CHCl_3$): δ 3.08.

HRMS (ESI): Calcd. For $C_{20}H_{23}D_2NO_2$ $[M+H]^+$ 314.20840, Found: 314.20850



N-(2-benzyloxymethyl-2-methylbut-3-en-1-yl)-4-methoxyaniline (*deuterio*-5.4a')

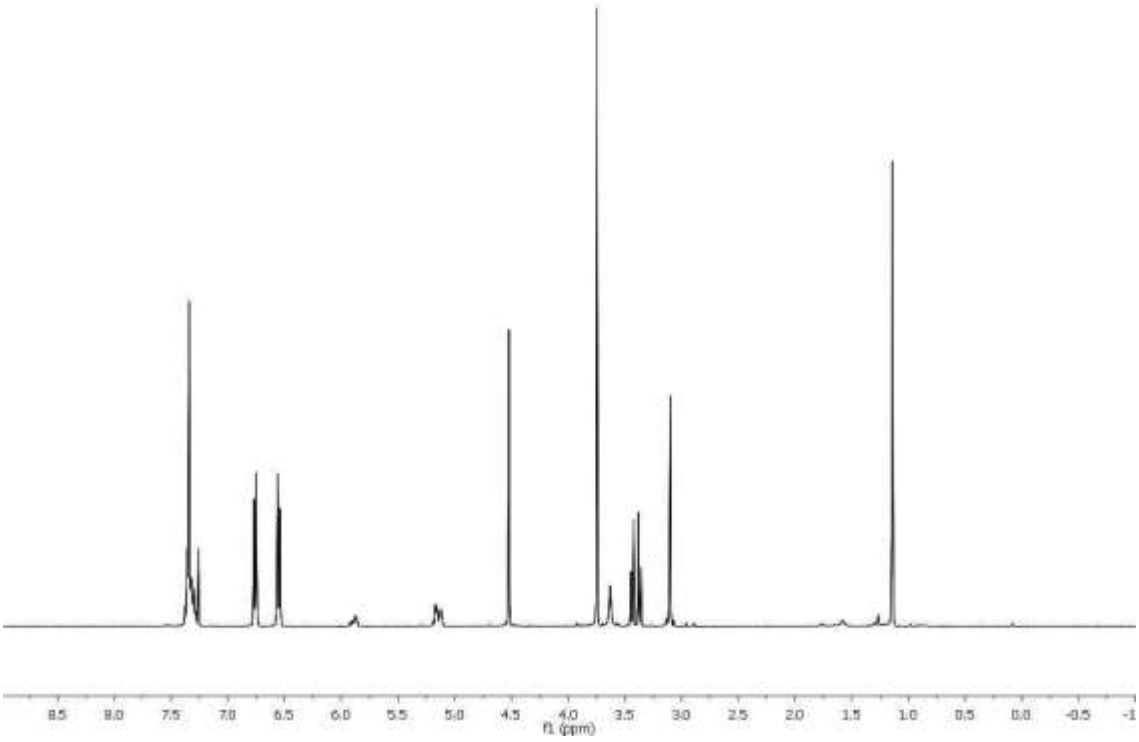


To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1-bis(dicyclohexylphosphino)ethane (DCyPE) (4.2 mg,
0.010 mmol, 5 mol%), and triazine **5.1b** (0.067 mmol (0.200 mmol of formimine), 100 mol%). The tube was sealed with a rubber septum, purged with argon, and toluene (0.5 M with respect to formimine), allene **5.3a** (0.400 mmol, 200 mol%), and d_8-isopropanol (61 μL, 0.800 mmol, 400 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 6% EtOAc/hexane) to furnish *deuterio*-**5.4a'** in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.27 (m, 5H), 6.76 (d, J = 8.9 Hz, 2H), 6.55 (d, J = 8.9 Hz, 2H), 6.00 – 5.80 (m, 0.34H), 5.26 – 5.03 (m, 0.91H), 4.52 (s, 2H), 3.75 (s, 3H), 3.63 (br, 1H), 3.40 (dd, J = 26.0, 8.9 Hz, 2H), 3.10 (s, 2H), 1.14 (s, 3H).

^{2}H NMR (77 MHz, $CHCl_3$): δ 5.92, 5.17.

HRMS (ESI): Calcd. For C20H24DNO2 [M+H]+ 313.20210, Found: 313.20200


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

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