Developments in palladium catalyzed reactions: Strategies to synthesize asymmetric 1,5-dienes and 1,4-dicarbonyls

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DEVELOPMENTS IN PALLADIUM CATALYZED REACTIONS: STRATEGIES TO SYNTHESIZE ASYMMETRIC 1,5-DIENES AND 1,4-DICARBONYLS

by

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ABSTRACT

HAI THAI LE : Developments in Palladium Catalyzed Reactions: Strategies to Synthesize Asymmetric 1,5-Dienes and 1,4-Dicarbonyls

(Under the direction of Professor James P. Morken)

This dissertation details recent developments in palladium catalyzed carbon-carbon bond formation reactions with two areas of focus: the palladium catalyzed branched and enantioselective allyl-allyl cross-coupling, and the palladium catalyzed carbonylative conjugate addition. Allyl-allyl cross-coupling presents an opportunity to synthesize 1,5-dienes, a scaffold that resembles subunits of terpenes, a critical building block in nature. Chapter I provides an overview of the developments in the allyl-allyl cross-coupling area. Chapter II, III, and IV detail strategies to construct complex substituted asymmetric 1,5-dienes through branched selective and enantioselective allyl-allyl cross-coupling. In chapter V, the palladium catalyzed carbonylative conjugate addition is discussed. This method enables the synthesis of 1,4-dicarbonyl compounds in an atom economical and environmentally friendly fashion, and provides a direct access to five membered heterocycles, a valuable class of chemicals in medicine.

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Lastly, to my fiancée Nguyen Bao Chau, I thank you for your support, patience, and unconditional love in the last three years. I look forward to the many more great years we shall share in the future.

I dedicate this dissertation to the Le's and the Thai's, the two families my name carries.

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LIST OF ABBREVIATIONS

Å	angstrom
Ac_2O	acetic anhydride
AcOH	acetic acid
aq	aqueous
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Boc_2O	di-*t*-butyl dicarbonate
Bn	benzyl
$B_2(pin)_2$	bis(pinacolato)diboron
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
Bz	benzoyl
Btz	benzothiazole
Bz_2O	benzoic anhydride
cee	conserved enantiomeric excess
cod	1,5-cyclooctadiene
*m*CPBA	*meta*-chloroperoxybenzoic acid
Cy	Cyclohexyl
dba	dibenzylideneacetone
DCM	dichloromethane
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
dpp-benzene	1,2-bis(diphenylphosphino)benzene
dppf	bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
eq.	equation
equiv	equivalents
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
GLC	gas-liquid chromatography
h	hour
hex	hexanes
HG-II	Hoveyda-Grubbs catalyst 2nd generation
HPLC	high performance liquid chromatography
kcal	kilocalorie
L	ligand
LAH	lithium aluminum hydride
L.G.	leaving group

MeOH	methanol
MFB	2,2′-bis(diphenylphosphino)- 6,6′-dimethoxy-1,1′-biphenyl
MS	molecular sieves
nbd	norbonadiene
NHC	N-heterocyclic carbene
$Ni(acac)_2$	nickel(II) acetylacetonate
$Ni(cod)_2$	bis(1,5-cyclooctadiene)nickel
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance spectroscopy
PCy_3	tricyclohexylphosphine
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
pin	pinacol
PPh_3	triphenylphosphine
Py	pyridine
$Pt(dba)_3$	tris(dibenzylideneacetone)platinum
QuinoxP*	2,3-bis(*tert*-butylmethylphosphino)quinoxaline
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
rt	room temperature
SFC	supercritical fluid chromatography
TADDOL	2,2-dimethyl-α, α, α ', α '-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine

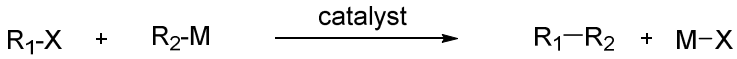
TES	triethylsilyl
Tf	Trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TPAP	tetrapropylammonium perruthenate
TsOH	*p*-toluenesulfonic acid

Chapter I: Metal Catalyzed Allyl-Allyl Cross-Coupling

I. Introduction

The metal catalyzed cross-coupling reaction is one of the most powerful reactions in organic synthesis.[1] This class of reaction offers chemists a versatile strategy to construct a chemical linkage between an organometal nucleophile and an electrophile (Scheme 1.1). As the result, many efforts have been devoted to further developing this reaction and expanding its scope and utility. To recognize its prominence, in 2010, the Nobel Prize in chemistry was awarded to Richard Heck, Akira Suzuki and Ei-ichi Neghishi for their pioneering research in palladium catalyzed cross-coupling.[2]

Scheme 1.1: Metal Catalyzed Cross-Coupling Reaction

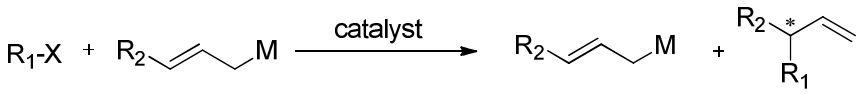


While the metal-catalyzed cross-coupling has undergone rapid development, and many challenging problems in chemical synthesis have been solved, an area that has received less attention is the cross-coupling involving allyl metal reagents. The reasons for this underinvestigation perhaps can be attributed to (a) the stability of allylmetal reagents, and (b) the difficulty to control the regio- and enantioselectivity of the cross-coupling product. Despite these drawbacks, the use of an allylic metal nucleophile are desirable because such transformation facilitates the potential for formation of a C_{sp}^3-C_{sp}^3

[1] de Meijere, A., Diederich, F., Eds.; Metal-Catalyzed Cross-Coupling Reactions, Second Edition; Wiley-VCH: New York, 2008.
[2] "The Nobel Prize in Chemistry 2010". *Nobelprize.org.* Nobel Media AB 2013. Web. 26 Mar 2014. <http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/>

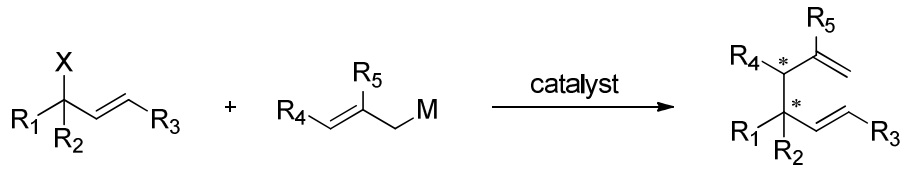
linkage, a carbon stereogenic center, and the product contains malleable olefinic substitution (Scheme 1.2).

Scheme 1.2: Application of Allyl Nucleophiles in Cross-Coupling



Prior to 2010, reports detailing the use of allyl metal reagents in asymmetric cross-coupling reactions were limited to aryl electrophiles;[3] however no method was developed to enable enantioselective cross-coupling of allylmetal reagents with allyl electrophiles. Successful development of allyl-allyl cross-coupling would facilitate the construction of the 1,5-diene motif, a building block scaffold that is highly desired due to its abundant expression in terpene natural products and its utility in chemical reactions (i.e. the Cope rearrangement). Realizing this significance, we have initiated a program aiming to develop a general methodology for 1,5-diene synthesis *via* Pd-catalyzed branch- and enantioselective allyl-allyl cross-coupling (Scheme 1.3).

Scheme 1.3: Pd-Catalyzed Allyl-Allyl Cross-Coupling



[3] a) Y. Hatanaka, Y. Ebina, T. Hiyama *J. Am. Chem. Soc.* **1991**, *113*, 7075. (b) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279. (c) Y. Hatanaka, K. Goda, T. Hiyama, *Tetrahedron Lett.* **1994**, *35*, 6511. (d) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368.

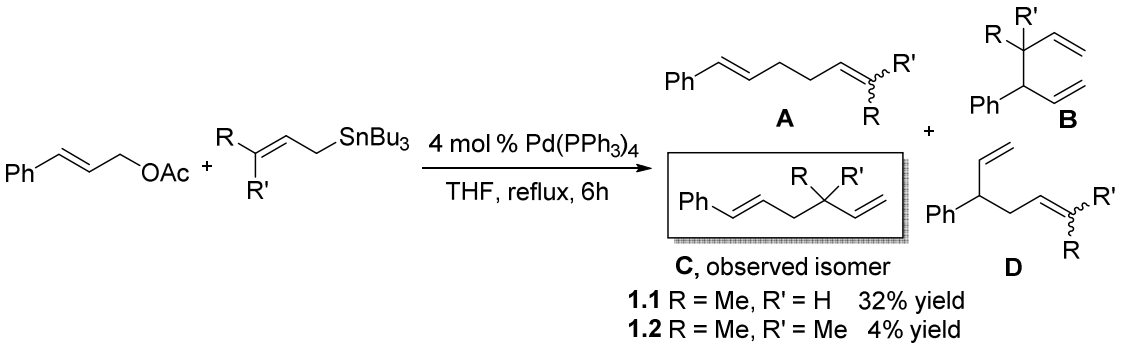
II. Synthesis of 1,5-Dienes *via* Palladium Catalyzed Allyl-Allyl Cross-Coupling

A. Allyl-Allyl Cross-Coupling *via* Outersphere Mechanism

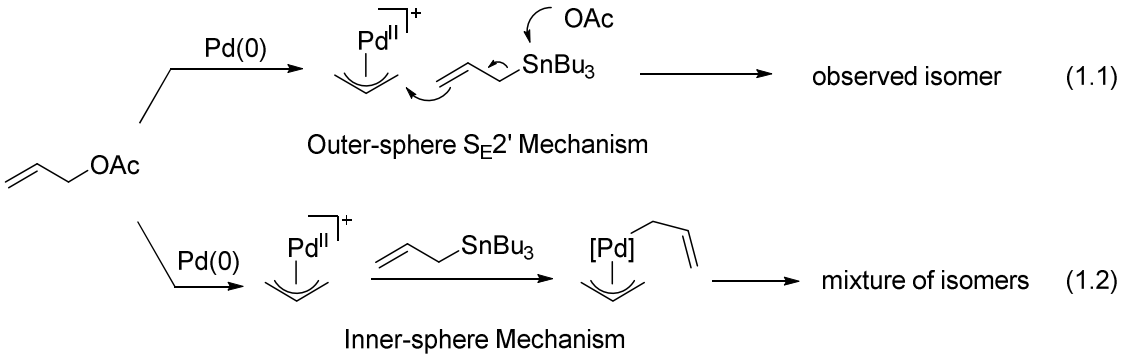
The history of Pd-catalyzed allyl-allyl cross-coupling dates back to 1980 when the research groups of Professor Barry M. Trost [4] and Professor John K. Stille [5] independently reported their discoveries. In their research, Trost *et al.* utilized $Pd(PPh_3)_4$ catalyst to effectively cross-couple allylacetate and allyltributylstannane. While the scope of the reaction was limited with regard to the acetate electrophile, the reaction outcome provided considerable mechanistic insight: 1,5-diene isomer **C** was the only observed product in all reported examples (Scheme 1.4). To rationalize this observation, Trost postulated that the mechanism of the reaction involved an outer-sphere attack of the allylnucleophile to a Pd-π-allyl intermediate (Scheme 1.5, eq. 1.1). Activation of allylstannane by the acetate anion could lead to direct attack at the Pd-π-allyl through an S_E2' pathway, leading to the formation of isomer **C**. Had the reaction proceeded through an inner-sphere mechanism that involved a transmetallation and reductive elimination sequence (Scheme 1.5, eq. 1.2), a distribution of regioisomers would be expected. Additionally, when $SnBu_4$ was subjected to the reaction in place of allylstannane, no coupling product was observed, indicating that perhaps transmetallation is difficult under the reaction conditions.

[4] Trost B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.
[5] Godschalx, J; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599.

Scheme 1.4: Trost Pd-Catalyzed Allyl-Allyl Cross-Coupling

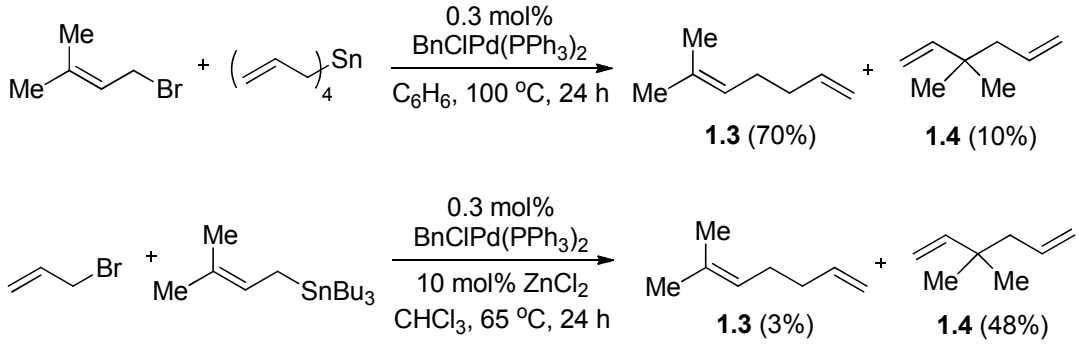


Scheme 1.5: Trost Proposed Reaction Mechanism



In Stille's report, the authors described the use of catalytic palladium (II) for effective cross-coupling of allylbromide and allylstannanes. The reaction conditions could tolerate catalyst loading as low as 0.3 mol % and various solvents could be employed. While minor transpositions of the stannane coupling partners were observed, the predominant products are the linear isomers **1.3**. Interestingly, in an experiment where the substitution patterns of the electrophile and the nucleophile were swapped, the outcome of product regioselectivity was also reversed accordingly, with the bond forming site being the more hindered carbon terminus, and the branch isomer **1.4** was the major product (Scheme 1.6). Though the formation of the minor isomers could not be explained, the product distribution is suggestive of the outer-sphere mechanism.

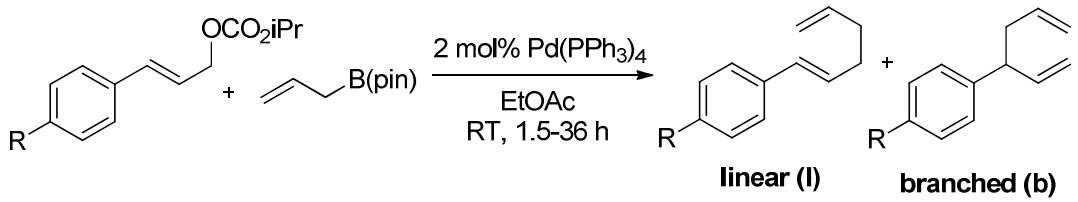
Scheme 1.6: Stille's Mechanistic Investigation



In 2009, in concurrence with our developments on the asymmetric allyl-allyl cross-coupling reaction, the research group of Professor Shū Kobayashi reported a palladium catalyzed method to synthesize linear 1,5-dienes selectively (Scheme 1.7).[6] Using an allylic carbonate and allylboronic acid pinacol ester [allylB(pin)], the researchers were able to effectively synthesize 1,5-dienes at room temperature, in the presence of only 2 mol % catalyst. The significance of this report is that it is among one of the first examples of the successful application of allylB(pin) in the allyl-allyl cross-coupling reaction. However, Kobayashi's method exhibited several limitations. Firstly, aromatic substrates with electron neutral and electron rich substituents yielded products with very high regioselectivity; but this selectivity suffered when substrates bearing electron withdrawing group were employed. Secondly, use of aliphatic substrates resulted in decomposition of the starting materials. In a subsequent report, Kobayashi *et al.* detailed a Ni-catalyzed allyl-allyl cross-coupling. Based on the product distributions, the authors suggested the outer-sphere mechanism for allyl-allyl cross-coupling.[7]

[6] Flegeau, E. F.; Schneider, U.; Kobayashi, U. *Chem. Eur. J.* **2009**, *15*, 12247.
[7] Jiménez-Aquino, A.; Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Commun.* **2011**, *47*, 9456.

Scheme 1.7: Cross-Coupling of Allyl Carbonate and AllylB(pin)

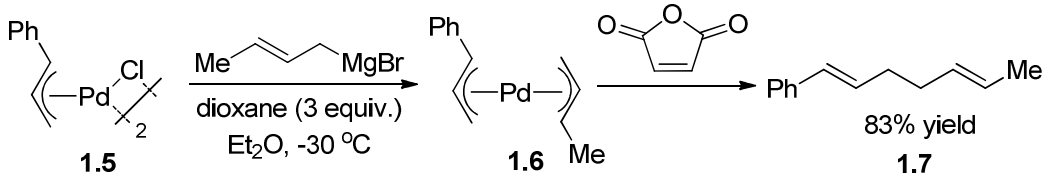


R	H	OMe	CN	CF_3
yield (%)	quant.	93	79	86
l / b	>32:1	>32:1	1:2	4:1

B. Allyl-Allyl Cross-Coupling *via* Inner-sphere Mechanism

In 1984, Schwartz and Goliaszewski reported the formation of linear 1,5-dienes via inner-sphere reductive elimination sequence from bis-η^3-allyl-palladium complexes (Scheme 1.8).[8] By treating allylpalladiumchloride dimer **1.5** with allyl Grignard reagents in diethylether at -30 ^oC, bis-η^3-allyl-palladium intermediate **1.6** could be generated. This complex was stable in solution at low temperature, and no 1,5-dienes were generated unless a π-acidic ligand such as maleic anhydride was added. The authors noted the selectivity of the reaction predominantly favor the "head to head" or linear compound. The addition of dioxane was necessary to precipitate magnesium salt in the reaction mixture to avoid allylic metathesis, leading to homo coupling products.

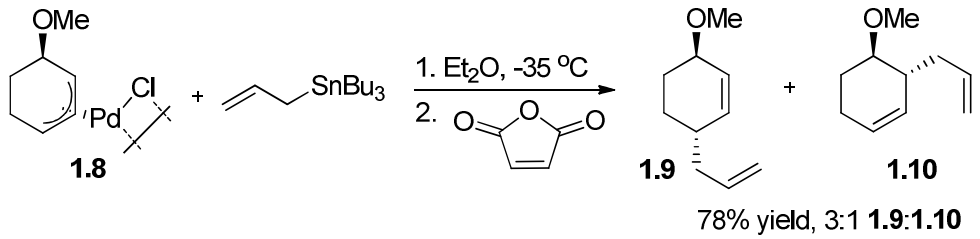
Scheme 1.8: 1,5-Diene Formations Promoted by π-Acidic Ligand



[8] Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028.

In subsequent work, Schwartz and coworkers extended the scope of the reaction to include allylstannanes.[9] Notably, the reaction can be run catalytically, with palladium loading as low as 1 mol %.[9b] When *trans*-Pd-π-allyl **1.8** reacts with allylstannane, a mixture of 1,5 diene products is observed; interestingly, both of these regioisomers retained the *trans*-configuration of the starting materials (Scheme 1.9). This result is consistent with the transmetallation – reductive elimination sequence of the inner-sphere mechanism.

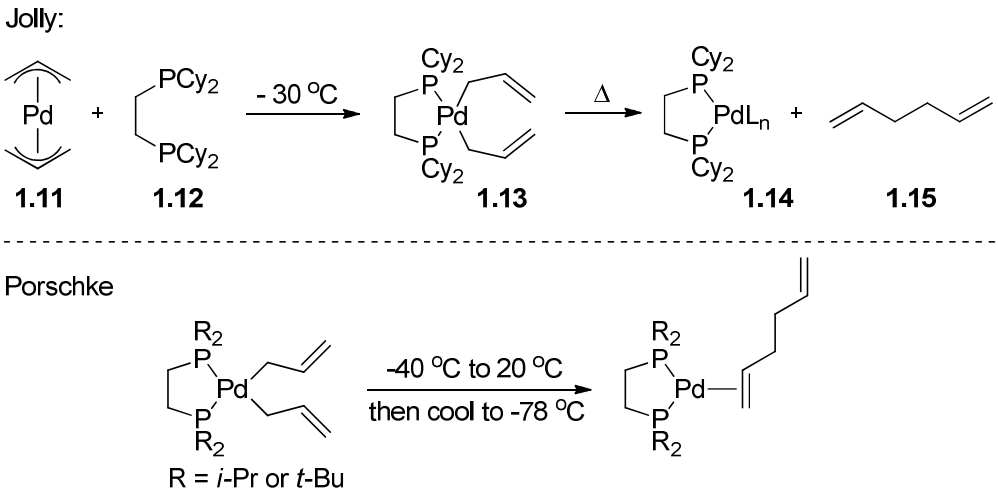
Scheme 1.9: Cross-Coupling with Retention of Configuration



The inner-sphere allyl-allyl cross-coupling was also documented by Professor Peter W. Jolly[10] and Professor Klaus R. Pörschke[11] in their studies on the structure and reactivity of bis-allyl palladium complexes. Jolly described the formation of a bis-η^1-allyl-palladium (Scheme 1.10, **1.13**) upon addition of bidentate phosphine ligand **1.12** to a solution of palladium complex **1.11**. Warming the solution of intermediate **1.13** to room temperature yielded Pd(0) complex **1.14** and 1,5-diene **1.15**. In addition to Jolly's findings, Pörschke reported that under careful temperature controlled conditions, the π-bound 1,5-diene Pd(0) complex could be isolated and characterized. Nevertheless, neither group detailed the mechanism of carbon-carbon bond formation.

[9] (a) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779. For a catalytic method starting from allylic bromides, see (b) Goliaszewski, A.; Schwartz, J. *Organometallics* **1985**, *4*, 417.
[10] Jolly, P. W. *Angew. Chem., Int. Ed.* **1985**, *24*, 283.
[11] Krause, J.; Bonrath, W.; Pörschke, K. R. *Organometallics* **1992**, *11*, 1158.

Scheme 1.10: 1,5-Diene Formations Promoted by Bidentate Phosphine Ligands

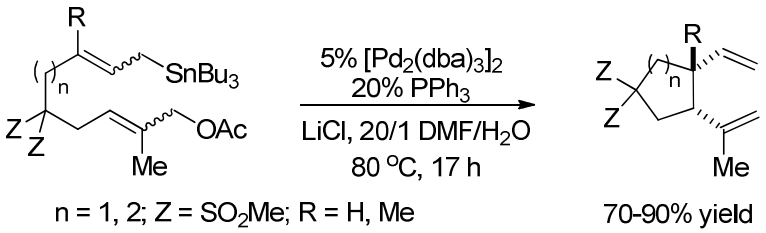


C. Allyl-Allyl Cross-Coupling via Inner-Sphere 3,3' Reductive Elimination

The research group of Professor Antonio M. Echavarran reported the successful formation of cyclic 1,5-dienes via intramolecular allyl-allyl cross-coupling catalyzed by palladium.[12] Notably, depending on the chain length, five or six membered rings can be synthesized with excellent diastereoselectivity, regardless of the olefin configuration of the starting allyl coupling partners. The presence of geminal sulfone groups suggests a Thorpe-Ingold angle constriction is necessary for effective cyclization.

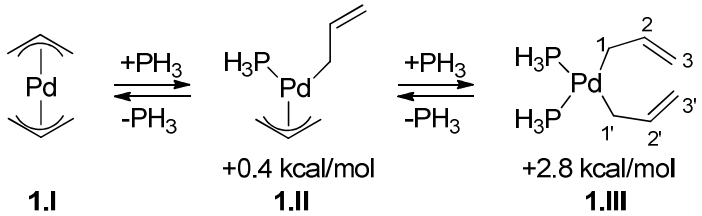
[12] Cuerva, J. M.; Gómez-Bengoa, E.; Méndez, M.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 7540.

Scheme 1.11: Intramolecular Allyl-Allyl Cross-coupling



While no specific mechanism was proposed in the original work, in a subsequent report, Echavarren *et al.* detailed a thorough investigation of the innersphere mechanism utilizing density functional theory (DFT) calculation.[13] This work has shed light on several key mechanistic features of the Pd-catalyzed allyl-allyl cross-coupling reaction. Built upon the findings of previous investigations, the authors calculated the ground state energies of the possible bis-(allyl) Pd intermediates (Scheme 1.12), which may form immediately after transmetallation. The calculations showed that the bis-(η^3-allyl) **1.I** was the most stable intermediate; association of a phosphine ligand led to a slightly higher energy (η^1-allyl)(η^3-allyl) Pd complex (**1.II**), and when an additional phosphine ligand was added, the Pd intermediate might adopt a bis-η^1 conformation (**1.III),** though at 2.8 kcal/mol higher in energy compared to **1.I**.

Scheme 1.12: Ground State Energies of Bis-Allyl-Pd Intermediates

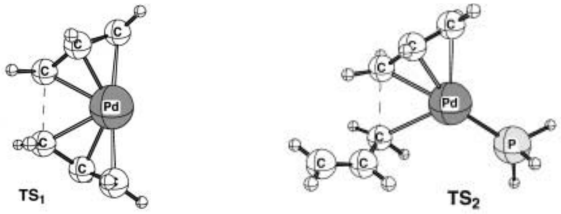


The details of the reductive elimination from complexes in Scheme 12 leading to 1,5-dienes was further studied (Scheme 1.13 and 1.14). Direct reductive elimination from

[13] Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620.

1.I had the highest activation energy, with the barrier as high as 36.6 kcal/mol. This high activation energy is in agreement with experimental observations of the stable bis-(allyl)-Pd complex studied by others.[8, 9] The reductive elimination process from **1.II** also faced a high activation energy barrier, estimated at 23.4 kcal/mol.

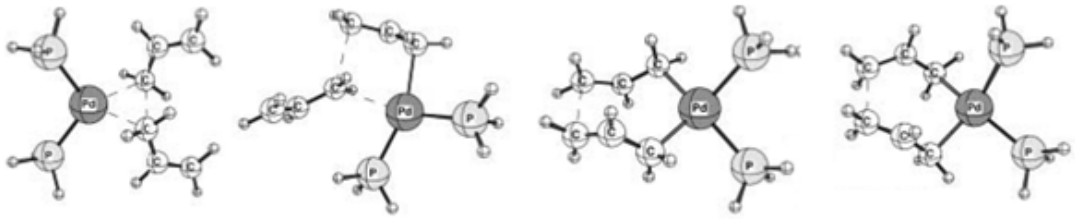
Scheme 1.13: Trasition State Structure for Reductive Elimination from 1.I and 1.II[14]



The calculated reductive elimination barrier from intermediate **1.III** is significantly lower than that of **1.I** or **1.II**. From **1.III**, there exist four potential paths for reductive elimination (Scheme 1.14). The bond formation event may occur at the C1-C1' carbon termini of the two allyl fragments; alternatively, the new linkage may be formed between C1-C3'. Activation energies for these processes were estimated to be 20.9 and 22.8 kcal/mol, respectively. The reductive elimination may also occur at the C3-C3' termini of the allyl fragments. The activation barrier for bond formation at these two termini is calculated to be only 8.5 kcal/mol when the two allyl groups adopt the anti orientation, and 11.1 kcal/mol when they adopt the syn orientation. These lower activation barriers suggest that C3-C3' reductive elimination may be the plausible path for formation of 1,5-dienes.

[14] Source: adapted from reference 13.

Scheme 1.14: Reductive Elimination from I.III[14]

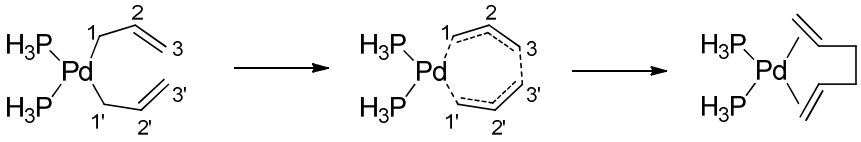


1,1'	1,3'	3,3' (anti)	3,3' (syn)
E_a = 20.8 kcal/mol	E_a = 22.8 kcal/mol	E_a = 8.5 kcal/mol	E_a = 11.1 kcal/mol

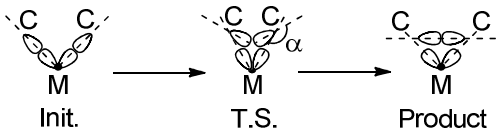
Detailed analysis of the transition state structures provided key explanations for the energy differences. First, employing natural bonding orbital method, Echavarren determined that the C1-C2 and C1'-C2' expressed developing π bond character in the transition state, and both C2 and C2' participate in bonding to the metal (Scheme 1.15). These developing π bonds can stabilize the Pd complex, thus lowering the activation energy barrier for bond formation at the C3-C3' terminals. Second, the C1-C1' reductive elimination proceeds through a three centered transition state which requires a change in orbital alignment. In an analogous example, Morokuma and coworkers studied the activation barrier in reductive elimination of two sp^3 hybridized carbons using $Me_2Pd(PH_3)_2$ as the model system (Scheme 1.16).[15] The researchers estimated that the energy would increase by 25.6 kcal/mol when the α angle is reduced from 180 degree to 130 degree. This high activation energy for $C_{sp}{}^3$-$C_{sp}{}^3$ reductive elimination is in agreement with findings by others.[16]

[15] Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *Organometallics* **2005**, *24*, 715.
[16] Low, J. J.; Goddard, W. A., III *J. Am. Chem. Soc.* **1986**, *108*, 6115.

Scheme 1.15: 3,3'-Reductive Elimination



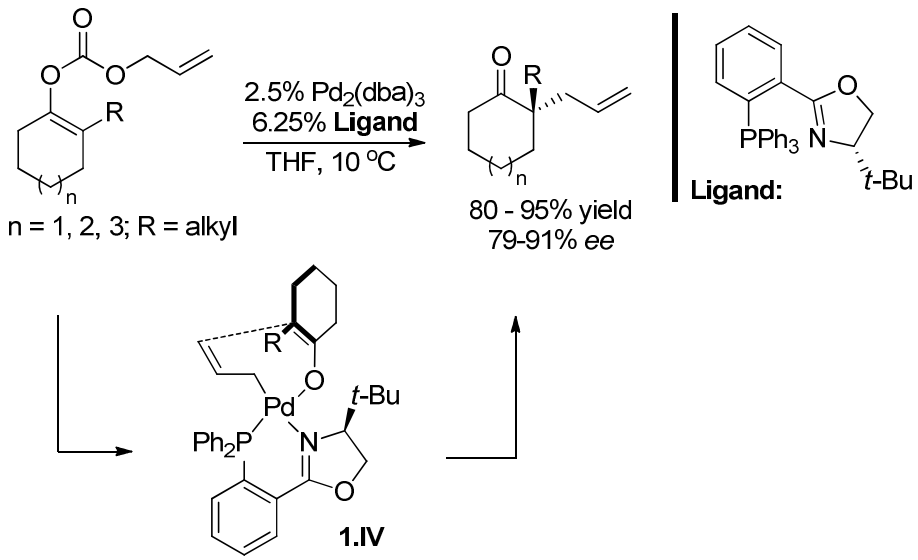
Scheme 1.16: Orbital Analysis of Me-Me Reductive Elimination



Although the 3,3' reductive elimination is a less studied mechanism, researchers have been taking advantage of this unique process to develop new reaction.[17,18] A notable example is the decarboxylative Tsuji allylation reaction developed by Professor Brian M. Stoltz (Scheme 1.17). In a series of reports,[19] Stoltz and coworkers developed an efficient method to synthesize cyclic ketones with an α-allylic all-carbon quaternary center. While enolate nucleophiles are characterized as soft nucleophiles and generally undergo direct attack at the carbon of the metal-allyl complex, in this reaction, Stoltz identified **1.IV** as the resting state of the catalyst. In this structure, the enolate ligand is associated with palladium via the oxygen terminus. The 3,3' reductive elimination from **1.IV** resulted in the observed product.

[17] (a) Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **2001**, *123*, 759; (b) Ariafard, A.; Liu, Z. *J. Am. Chem. Soc*. **2006**, *128*, 13010.
[18] (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978. (c) Brozek, L. A.; Sieber, J. D.; Morken, J. P. *Org. Lett.* **2011**, *13*, 995; (d) Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550.
[19] (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc*. **2004**, *126*, 15044. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc*. **2007**, *129*, 11876; (c) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2009**, *48*, 6840.

Scheme 1.17: Pd-catalyzed Formation of cyclic ketone with α-All Carbon Quaternary Stereo Center



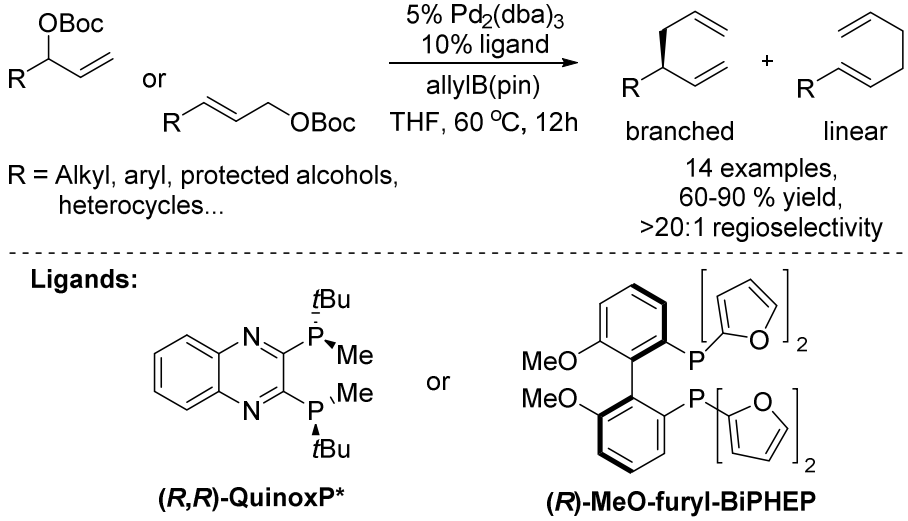
D. Branch- and Enantioselective 1,5-Dienes via Pd-Catalyzed Allyl-Allyl Cross-Coupling

In 2010, efforts in our laboratory unveiled a useful strategy to synthesize branch 1,5-dienes enantioselectively (Scheme 1.18).[20] Starting from carboxylate protected allylic alcohols and allylB(pin), a range of substrates with broad substitution patterns can be tolerated. Two ligands that provided excellent levels of regio- and stereo-induction were (*R*,*R*)-QuinoxP* and (*R*)-MeO-fur-BiPHEP; while the former provided excellent selectivity for aliphatic substrates, the later ligand facilitates the reaction with aromatic substrates more effectively. It is important to discuss the mechanistic principles that

[20] Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

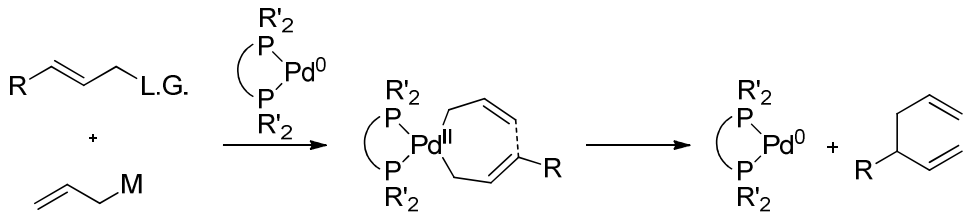
govern products' regioselectivity in this reaction as this sets the cornerstone for our later developments in the allyl-allyl cross-coupling.

Scheme 1.18: Synthesis of Branch and Enantioenriched 1,5-Dienes

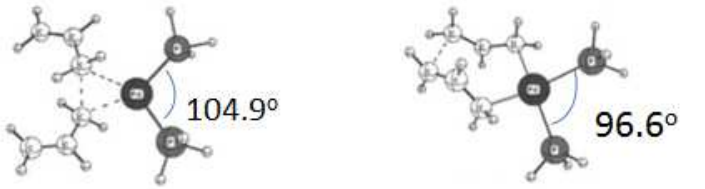


Based on calculation work published by Echavarren,[13] we learned that a plausible reactive intermediate prior to reductive elimination is **I.III**. We surmised that if a substituent is placed on one of the allyl fragments, it is likely that the substitution may be directed away from the metal center to minimize steric interaction (Scheme 1.19). Thus, if the 3,3' reductive elimination occurs from this complex, it would yield branched 1,5-dienes selectively. In addition, our research group has extrapolated the phosphine-palladium-phosphine bite angle of the transition state structure for the bis-η^1-allyl-Pd complexes presented by Echavarren (Scheme 1.20). Intriguingly, it was found that the P-Pd-P angle in the case of the 3,3' reductive elimination transition state is only 96.6°, while that of the 1,1' transition state is 104.9°. This finding suggested that the bidentate ligands' bite angles might provide a lever to influence the reductive elimination pathway for the Pd-bis-allyl complex, with the smaller angle ligands inducing 3,3' reductive elimination, while those with larger bite angle prefering the 1,1' path.

Scheme 1.19: Allyl-Allyl Cross-Coupling with Substituted Allyl Electrophiles



Scheme 1.20: Palladium-Ligand Angles of Transition States[14]



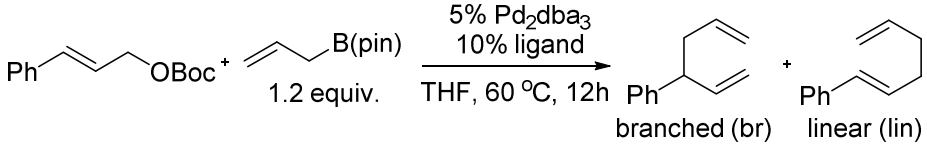
1,1′ reductive elimination 3,3′ reductive elimination

The hypothesis above was verified when multiple bidentate ligands with varying bite angles were tested (Scheme 1.21). In agreement with the calculations, it was found that among the tested bidentate ligands, those with smaller bite angle such as dpp-benzene yielded 1,5-diene with up to 97:3 branch:linear selectivity. Conversely, large bite angle DPEphos provided 1,5-dienes in only 72:28 ratio. When monodentate ligand PPh_3 was employed, only the linear 1,5-diene was observed. These findings provided important guidance in indentifying an effective chiral ligand for the reaction.

Additional experiments have been conducted to study the inner-sphere 3,3' reductive elimination mechanism of the reaction (Scheme 1.22). In a labeling study using α-deuterated allylB(pin), the product 1,5-dienes were observed with deuterium scrambling in 1:1 ratio, while the recovered allylB(pin) was not scrambled. It is believed

that nucleophilic addition of allyl metals usually occurred in an S_E2' fashion,[21] if this reaction proceeded through the outer-sphere mechanism, the expected product would be deuterated exclusively at the terminal carbon, and would not be scrambled as observed. Alternatively, if the allyl fragment from the deuterated allylB(pin) were first transmetallated to the palladium center, followed by reductive elimination (the inner-sphere mechanism), the scrambling might occur through a π-σ-π isomerization at the Pd center *via* an η^1- η^3-bis-allyl-palladium intermediate.[22]

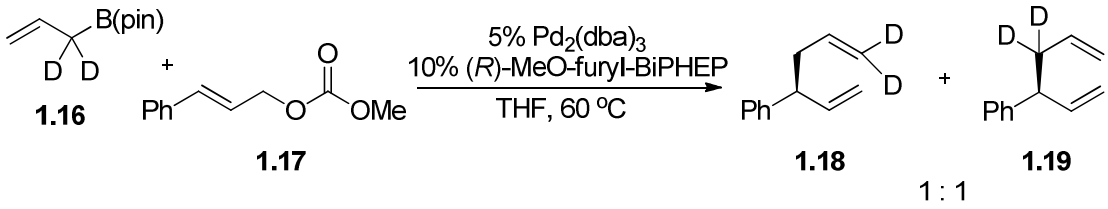
Scheme 1.21: Correlation of Phosphine Ligand Bite Angle and Regioselectivity



entry	ligand	bite angle[a]	% yield[b]	br:lin[c]
1	PPh_3	-	96	1:>20
2	dpp-benzene	83	70	97:3
3	dppf	96	43	94:6
4	DPEphos	102	58	72:28

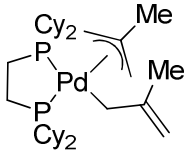
[a] Ligand-preferred bite angle. [b] Yield of purified material. [c] Ratios determined by GC

Scheme 1.22: Deuterium Labeling Experiment

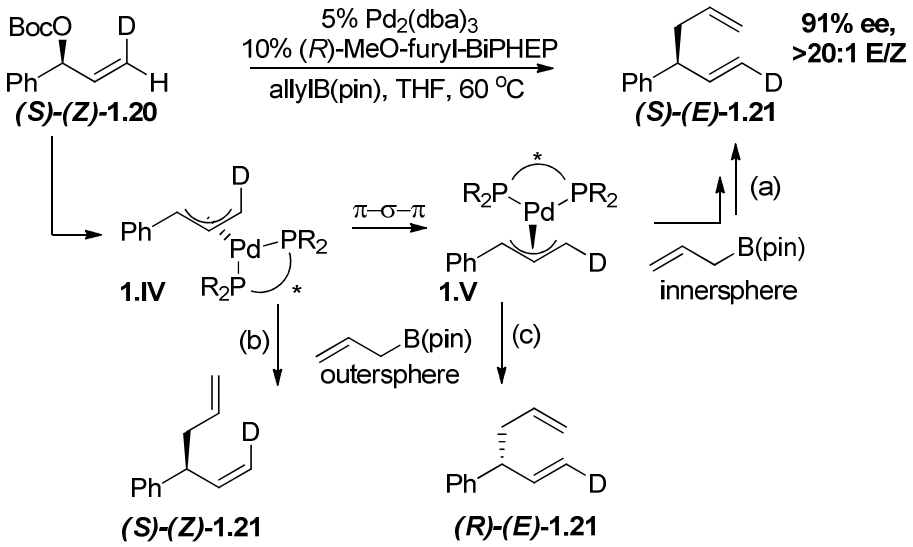


[21] (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963. (c) Hayashi, T.; Kabeta, K.; Yamamoto, T.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 5661. (d) Wickham, G.; Kitching, W. *J. Org. Chem.* **1983**, *48*, 614. (e) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749.

[22] Jolly and Coworkers reported the isolation of η^1- η^3-bis-allyl-palladium complexes. See reference 10



Scheme 1.23: Innersphere Reductive Elimination



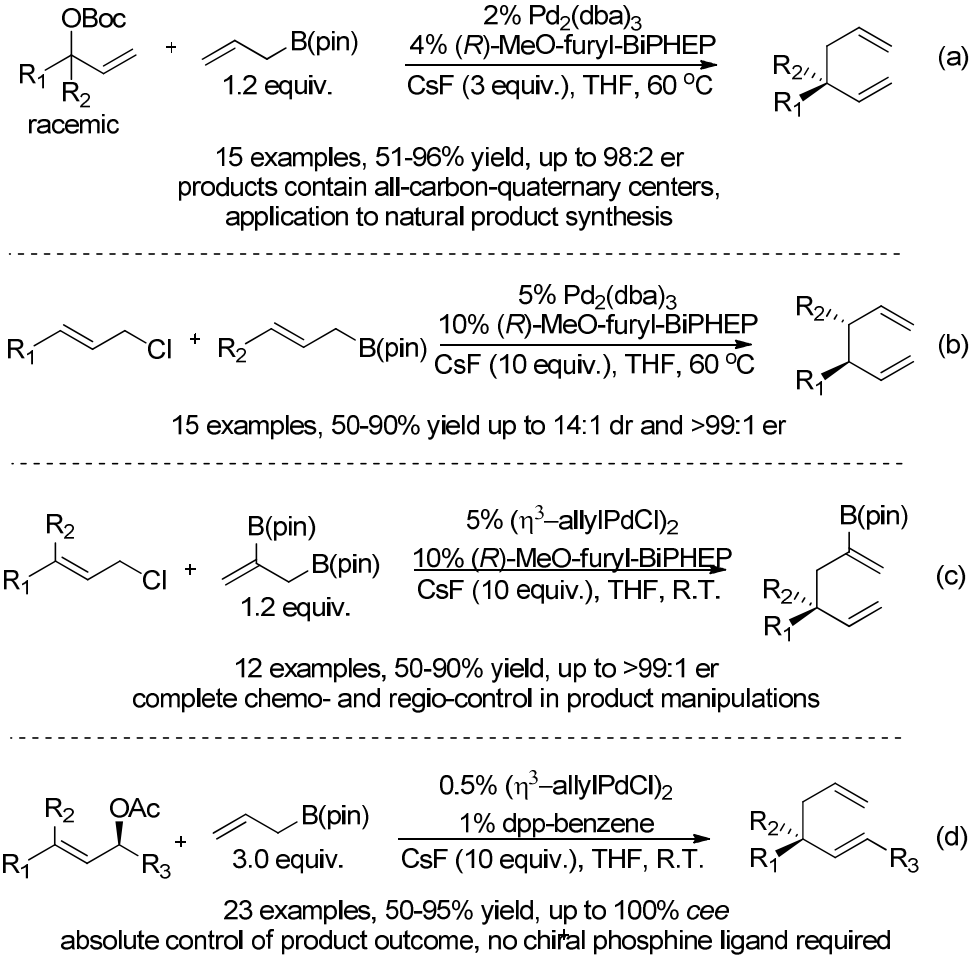
In a subsequent experiment, **(*S*)-(*Z*)-1.20** was synthesized and subjected to the allyl-allyl cross-coupling conditions using (*R*)-MeO-fur-BIPHEP ligand (Scheme 1.23). The reaction yielded predominantly 1,5-diene ***(S)-(E)*-1.21** in 91% *ee*, and >20:1 E/Z. Given that the oxidative addition proceeds through an anti displacement of the leaving group,[23] starting from **(*S*)-(*Z*)-1.20**, Pd-π-allyl complex **1.IV** would be obtained as a single isomer. If the allyl-allyl cross-coupling reaction occured through the outersphere mechanism, the allylB(pin) nucleophile must displace the palladium on **1.IV** from the opposite face; therefore, the expected product would be the ***(S)-(Z)*-1.21**(path b, Scheme 1.23). Alternatively, **1.IV** can undergo π-σ-π isomerization to allow the Pd-allyl to achieve the preferred conformation **1.V**. This process would also isomerize the olefin from *Z* to *E* configuration. From **1.V**, if the C-C bond formed via the outer-sphere pathway, the expected product would be ***(R)-(E)*-1.21** (path c, Scheme 1.23). Since the product observed in this experiment is predominantly the ***(S)-(E)*-1.21**, this suggests that

[23] (a) Hayashi,T.; Hagihara, T.;Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (b) Trost, B.M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

the product of this reaction was formed via the inner-sphere mechanism (path a, Scheme 1.23).

Scheme 1.24: Developments in Pd-Catalyzed

Branched- and Enantioselective Synthesis of 1,5-Dienes



The initial success has paved the way to subsequent advances in the branched and enantioselective allyl-allyl cross-coupling reaction (Scheme 1.24). Starting with racemic trisubstituted allylic Boc protected alcohol, 1,5-dienes bearing all-carbon quaternary centers were synthesized in excellent enantioselectivity (Scheme 1.24, equation a). Using terminally substituted allylB(pin) and allylic chlorides, branch 1,5-dienes with adjacent tertiary stereocenters can be obtained in excellent diastereo- and enantioselectivity.

Further developments led to the successful cross-coupling between partners as described in equation (c) and (d) in Scheme 1.24, rendering 1,5-dienes with well differentiated olefins while omitting the need for elevated reaction temperature and expensive chiral phosphine ligand in the case of (d). These studies will be described in details in subsequent chapters.

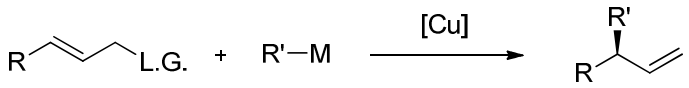
III. Synthesis of 1,5-Dienes *via* Copper Catalyzed Allyl-Allyl Cross-Coupling

Copper is one of the most studied metals in the field of catalysis. This popularity may be attributed to the high tunability, low toxicity and abundance of the copper element. The copper catalyzed conjugated addition reaction is a fundamental reaction that has significantly impacted organic synthesis.[24] Another well-developed field is the copper catalyzed allylic substitution reaction (Scheme 1.25).[25] In this area, progress has been devoted to controlling the stereoselectivity of the reaction product; and recent developments have enabled efficient constructions of asymmetric carbon centers. The

[24] (a) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824; (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pámies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796.
[25] See reference 22 and Geurts, K.; Fletcher, S. P.; van Zijl, A.W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025.

scope of the organometal nucleophiles have been extended to those containing alkyl,[26] aryl,[27] vinyl,[28] allenyl,[29] or alkynyl.[30]

Scheme 1.25: Copper-Catalyzed Asymmetric Allylic Substitution



R' = alkyl, vinyl, phenyl, alkynyl...

While copper catalyzed asymmetric allylic substitution (Cu-AAS) reaction has undergone rapid development, the use of allylic metal nucleophiles has received less attention. Similar to the Pd-catalyzed cross-coupling reaction, the underlying reason for this underdevelopment is the difficulty in controlling regio- and stereoselectivity of the products. Successful application of allylic metal nucleophiles in Cu-AAS is desirable as this offers an alternative method to furnish the valuable 1,5-diene building blocks. In this section, I would like to discuss advances in the copper catalyzed allyl-allyl cross-coupling.

A. Copper-Catalyzed Allyl-Allyl Cross-Coupling Using Allyl-Grignard

The first example of copper catalyzed allyl-allyl cross-coupling dates back to 1977 when Linstrumelle *et al.* reported the synthesis of geraniol via coupling of prenylmagnesium bromide **1.22** and allylic chloride **1.23** in presence of 25 mol % of

---

[26] For selected recent development, see: (a) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nature Chem.* **2011**, *3*, 377; (b) Langlois, J.-B.; Alexakis, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1877; (c) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J.Am. Chem. Soc.* **2012**, *134*, 18573.

[27] For selected recent development, see: (a) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656; (b) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370.

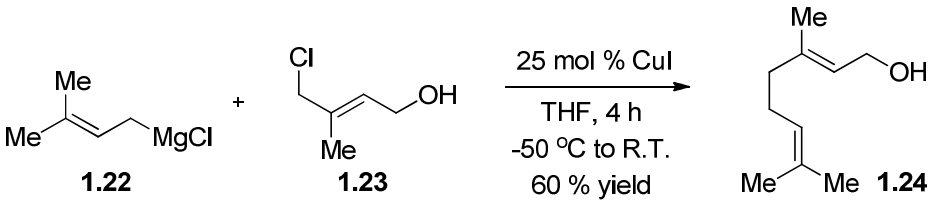
[28] (a) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6613; (b) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315.

[29] Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

[30] Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778.

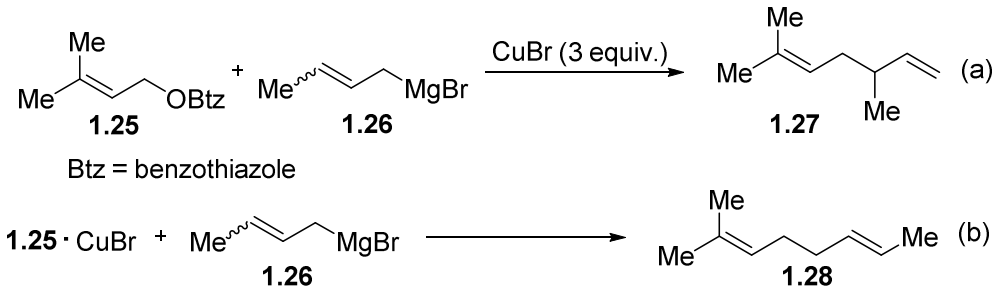
CuI.[31] While this procedure was effective, no mechanistic detail was offered to rationalize the observed product selectivity.

Scheme 1.26: Synthesis of Geraniol via Cu-Catalyzed Allyl-Allyl Cross-Coupling



Several years later, the research group of Professor Vicenzo Calò reported the cross-coupling of crotyl Grignard with benzothiazole protected allylic alcohol **1.25** (Scheme 1.27).[32] Of note, the authors observed the shift in product regioselectivity simply by altering the order of reagent addition. Specifically, upon addition of the electrophile and copper bromide, if allylic Grignard were introduced simultaneously, the reaction yielded 1,5-diene **1.27** as the only reaction product. In contrast, if the electrophile and the copper were pre-complexed prior to allylic Grignard addition, regioisomer **1.28** was observed.

Scheme 1.27: 1,5-Diene Synthesis Using Allylic Benzothiazole

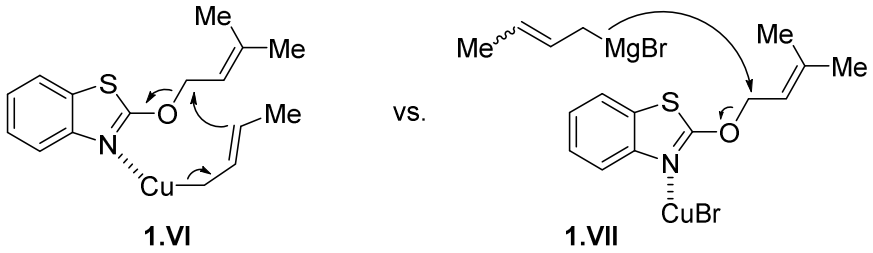


To rationalize the observation above, Calò and coworkers proposed two transition state structures (Scheme 1.28). The preference for **1.27** perhaps stems from intermediate

[31] Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, G. *Tetrahedron Lett* 1977, *13*, 1181.
[32] (a) Caló, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1357; (b) Caló, V.; Lopez, L.; Pesce, G. *J. Chem. Soc. Perkin Trans. I* **1988**, 1301.

1.VI, in which the benzothiazole coordinates with the *in situ* formed allyl copper formed *in situ* through the nitrogen atom. Intramolecular S_N2'attack of the allyl copper to the less substituted site of the allyl electrophile provided the observed product. On the other hand, pre-complexation of the electrophile and CuBr may prevent formation of the allyl copper species (**1.VII**); and the allyl Grignard may attack the electrophile directly at the less substituted terminus to furnish **1.28**. These proposals are in analogy to the inner-sphere and the outer-sphere mechanism in the case of Pd-catalyzed allyl-allyl cross-coupling.

Scheme 1.28: Proposal for Reversed Selectivity Observed by Calò *et al.*



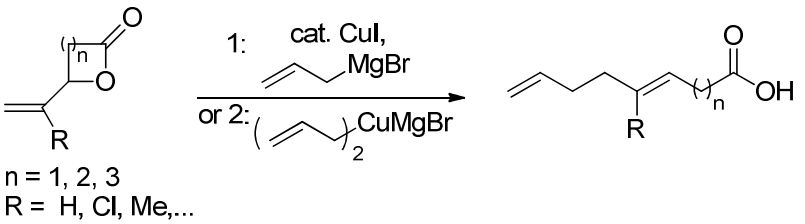
1.VI **1.VII**

From vinylic lactones, Fujiwara and co-workers reported the synthesis of several alkenoic acid derivatives (Scheme 1.29).[33] While the catalytic copper conditions were effective for alkyl, vinyl and aryl addition (condition 1, Scheme 1.29), it was less effective to introduce allyl group to the vinylic lactones (entries 1, 3 and 5). However, when allyl cuprates were prepared in advance, the desired products can be obtained with respectable yields. Of note, this reaction is highly regioselective, with the incoming allyl group added only to terminal olefin of the lactone. In addition, the olefins were formed in up to 92:8 E/Z selectivity. Although this method required the use of stoichiometric amounts of copper reagent, it is still valuable because these alkenoic acids are precursors

[33] (a) Fujisawa, T.; Sato, T.; Kawashima, M.; Nakagawa, M. *Chem. Lett.* **1981**, 1307; (b) Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Tetrahedron Lett.* **1982**, *23*, 3583; (c) Kawashima, M.; Fujisawa, T. *Chem. Lett.* **1984**, 1851.

to many medicinally relevant molecules, including macrolide pyrenophorin and **A26771B** (Scheme 1.30).

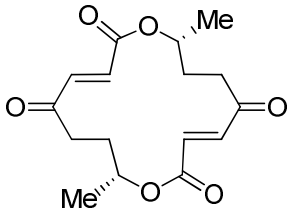
Scheme 1.29: Synthesis of Alkenoic Acid *via* Copper Mediated Allyl-Allyl Cross-Coupling



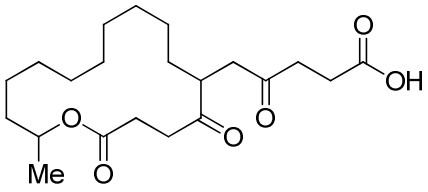
n = 1, 2, 3
R = H, Cl, Me,...

Entry	n	Conditions	Yield (%)	E/Z
1	1	1	25	92:8
2	1	2	77	91:9
3	2	1	9	92:8
4	2	2	41	86:14
5	3	1	trace	-
6	3	2	51	92:8

Scheme 1.30: Examples of Medicinally Relevant Compounds Containing Alkenoic Acid Derivatives



Pyrenophorin



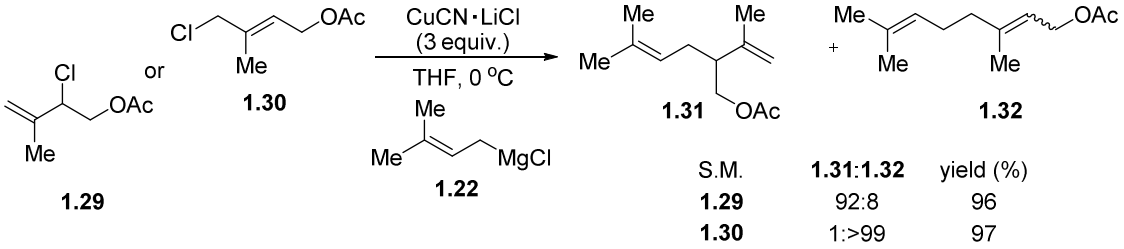
A26771B

In a series of reports, Yamamoto *et al.* described the copper mediated allyl-allyl cross-coupling reaction using CuCN·LiCl (Scheme 1.31).[34] Branched allylic chloride **1.29** gives 1,5-diene **1.31** in 92:8 ratio. However, when the substrate was replaced with the linear chloride **1.30**, 1,5-diene **1.32** is preferred in 99:1 selectivity. These results suggest that 1,5-dienes were generated through an S_N2' attack of the incoming nucleophiles.

[34] (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251; (b) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130.

Another important feature of the reaction is that the acetate group remains intact in all cases.

Scheme 1.31: S_N2' Selective Copper-Catalyzed Allyl-Allyl Cross-Coupling

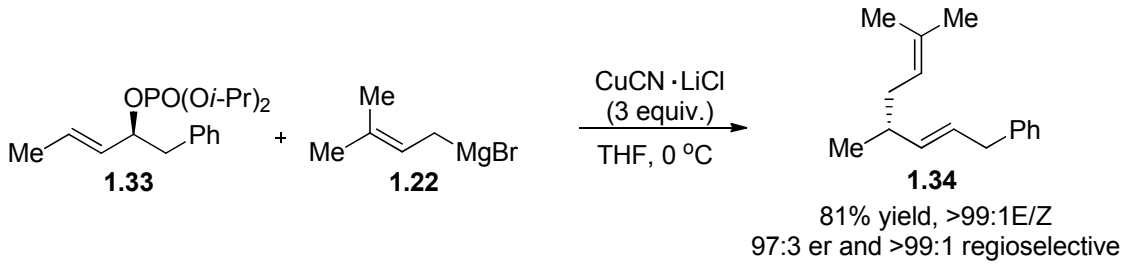


S.M.	**1.31**:**1.32**	yield (%)
1.29	92:8	96
1.30	1:>99	97

While the reaction using allylic chloride yielded product with excellent regioselectivity, the E/Z ratio of the olefins in product **1.32** was only modest, at 84:16. Interestingly, further optimization revealed a dependence of E/Z selectivity of the product olefins on the leaving group, with the phosphate leaving group delivering the highest regioselectivity and *E* selectivity in the reaction. Using allylic phosphate **1.33** (Scheme 1.32), the authors were able to synthesize optically active 1,5-diene **1.34** in 81% yield, with perfect 1,3 chirality transfer and superb levels of E/Z selectivity (Scheme 1.32). Later progress has facilitated the use of catalytic amount of CuCN·LiCl; however, in all cases, mixtures of regioisomers are obtained.[35] The utility of this cross-coupling was further highlighted through the synthesis of Coenzyme Q10, a key component in cellular respiration.[34b]

[35] Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, 6017.

Scheme 1.32: Copper-Mediated Stereospecific Allyl-Allyl Cross-Coupling



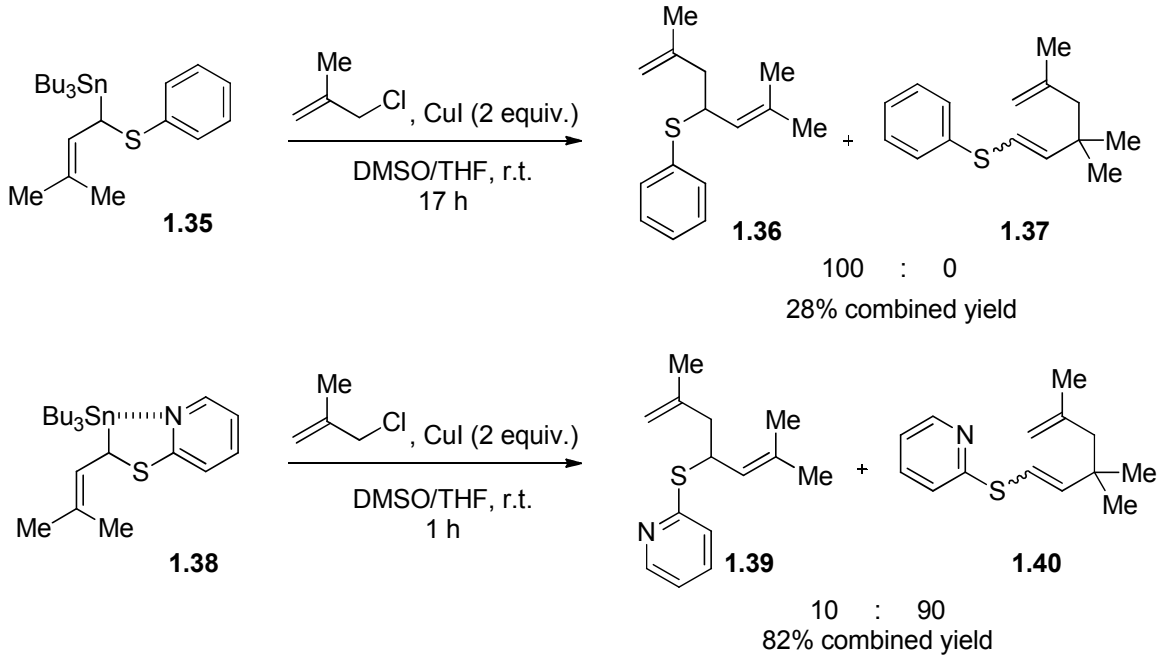
B. Copper-Catalyzed Allyl-Allyl Cross-Coupling Using Other Allyl Organometals

A number of other allylmetal nucleophiles have been investigated for their applications in the copper catalyzed allyl-allyl cross-coupling reaction. Fujiwara and co-workers reported the successful application of allyltin reagents (Scheme 1.33).[36] In this work, the authors described the necessity for having an intramolecular coordination for effective regioselectivity control. Using phenylthioether **1.35** and methallyl chloride as the two cross-coupling partners, 1,5-diene **1.36** was obtained in 28% yield after 17 h, along with a trace amount of the corresponding regioisomer **1.37**. However, when 2-pyridylthioether **1.38** was employed as the allyl organometal, the reaction proceeded smoothly, affording a 9:1 mixture of 1,5-dienes favoring S_N2' product **1.40** in 82% yield within 1 hour. Examination of the leaving group revealed a correlation with the product's regioselectivity, with Cl providing the highest level of S_N2' products, followed by Br and I. While the regioselectivity of 1,5-diene products in the allyl-allyl cross-coupling using

[36] Takeda, T.; Matsunaga, K.; Uruga, T.; Takakura, M.; Fujiwara, T. *Tetrahedron Lett.* **1997**, *38*, 2879.

intramolecular activated allyl tin reagent might be excellent, the E/Z selectivity of the 1,5-dienes was highly substrate dependent.

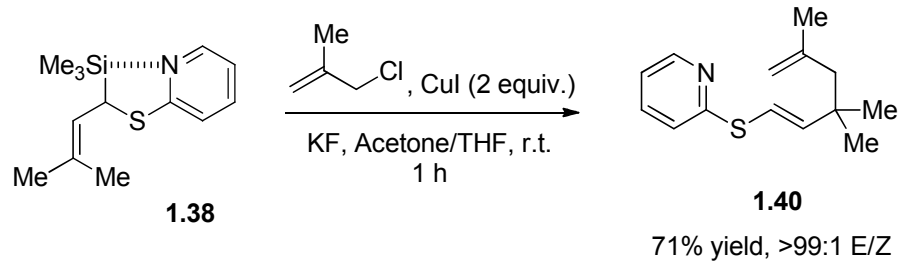
Scheme 1.33: Allyl Tin as an Effective Cross-Coupling Partners



In subsequent work, Fujiwara reported the extension of the allyl organometal nucleophile scope to include allylsilicon compounds (Scheme 1.34).[37] Similar to allyltin, the silicon reagent also required the presence of the intramolecular activating functional group 2-pyridylthioether for effective cross-coupling. Furthermore, addition of KF to the reaction was necessary to achieve high efficiency. Lastly, unlike the allyltin reagents, the resulting olefins in the 1,5-dienes generated from allylsilanes were highly *E* selective.

[37] Takeda, T.; Uruga, T.; Gohroku, K.; Fujiwara, T. *Chem Lett.* **1999**, 821.

Scheme 1.34: Copper-Catalyzed Allyl-Allyl Cross-Coupling with Allyl Silane



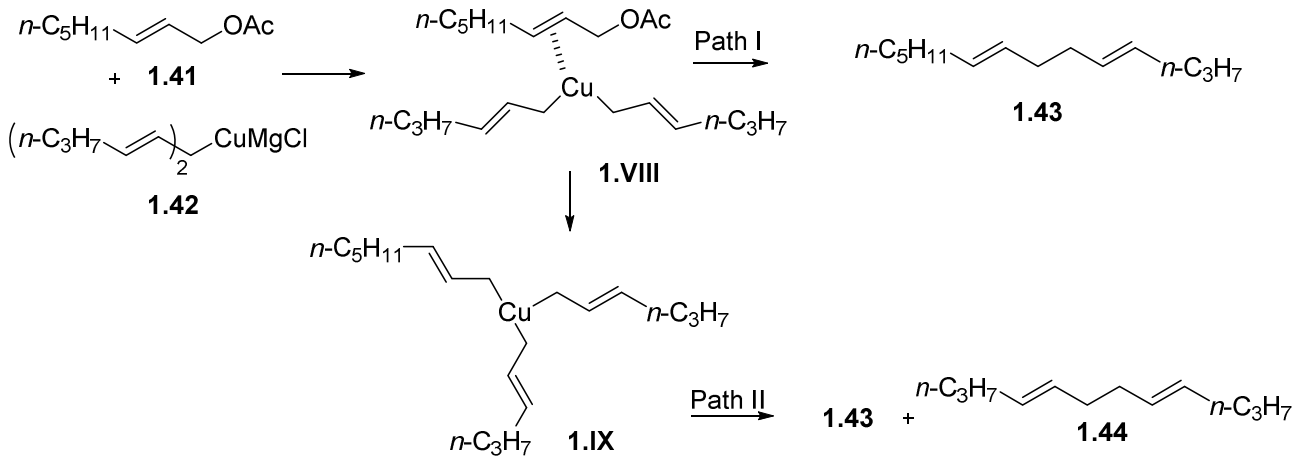
C. Mechanistic Investigation of the Copper-Catalyzed Allyl-Allyl Cross-Coupling

The mechanism of the copper catalyzed allylic substitution has been a topic of considerable interest. As a subclass of this important reaction, insights into the mechanism of the copper-catalyzed allyl-allyl cross-coupling were highly desired. Two pathways are proposed: the first is the direct displacement of Cu(I)allyl (path I, Scheme 1.34), and the second is the reductive elimination from a Cu(III) intermediate (path II, Scheme 1.35). In effort to elucidate the reaction mechanism, Bäckvall and coworkers proposed that the reaction may be indirectly understood through analyzing the product distribution pattern.[38] Specifically, if the 1,5-dienes are formed via direct displacement (**1.VIII**, path I), the cross-coupling product **1.43** should be the only formed product; however, if the reaction proceed *via* reductive elimination from triallyl-Cu intermediate **1.IX**, a 2:1 mixture of **1.43** and **1.44** is expected.

[38] Karlström, A. S. E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981.

Scheme 1.35: Plausible Mechanism of the Copper-Catalyzed

Allyl-Allyl Cross-Coupling



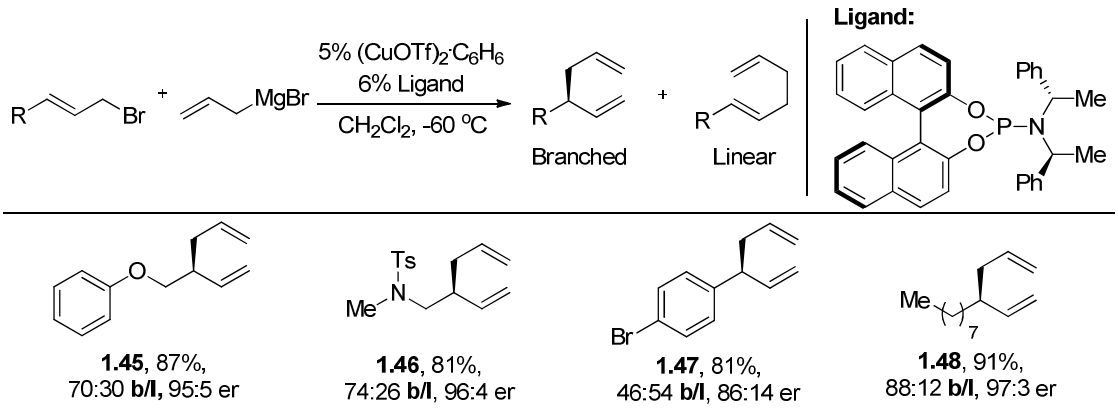
In the reaction employing a stoichiometric amount of copper, the authors consistently observed a 1:1 ratio of **1.43** and **1.44** using a variety of copper sources. Diluting the reaction two fold brought the ratio to 1.6:1 favoring cross-coupling product **1.43**. While the results did not match with the theoretical prediction, the fact that **1.44** was observed suggested the formation of copper (III) in the reaction intermediate. However, when copper was added in catalytic amount to a reaction mixture containing electrophile **1.41** and the corresponding allyl Grignard of **1.42**, the ratio of **1.43**:**1.44** was very close to 2:1. These results implied a concentration phenomenon might complicate the experiment. The authors noted that these observations may not be enough to discount the direct displacement pathway, but it is suggestive of the mechanism in which 1,5-diene formation occurred via the Cu(III) intermediate in the reaction.

D. Enantioselective Allyl-Allyl Cross-Coupling via Copper-Catalyzed Allylic Substitution

In 2013, the first asymmetric copper-catalyzed 1,5-diene synthesis was disclosed by the research group of Professor Feringa (Scheme 1.36).[39] In presence of catalytic amount of $Cu(OTf)_2$, and chiral phosphine ligand, branched and enantioenriched 1,5-dienes can be effectively furnished from readily available allylic bromides and allylmagnesium reagents. Several sources of copper(I) catalysts were effective, but those with less coordinating ligands provided higher enantioselectivity. In addition to allylic Grignard, allyllithium reagents can also be employed to provide 1,5-dienes with high er, albeit lower regioselectivity. The authors also noted the importance of slow addition of the allylmetal reagents for higher branched to linear ratio. Feringa's conditions can be applied to a range of substrates, including those with aliphatic, aromatic, benzyloxy, and N-tosyl functional groups. While the er for most products are good to excellent, the branched to linear selectivity seems to be substrate dependent, with aliphatic substrates providing higher branched to linear ratio.

[39] Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. *J. Am. Chem. Soc.* **2013,** 135, 2140.

Scheme 1.36: Copper-Catalyzed Asymmetric Synthesis of 1,5-Dienes



1.45, 87%, 70:30 **b/l,** 95:5 er

1.46, 81%, 74:26 **b/l**, 96:4 er

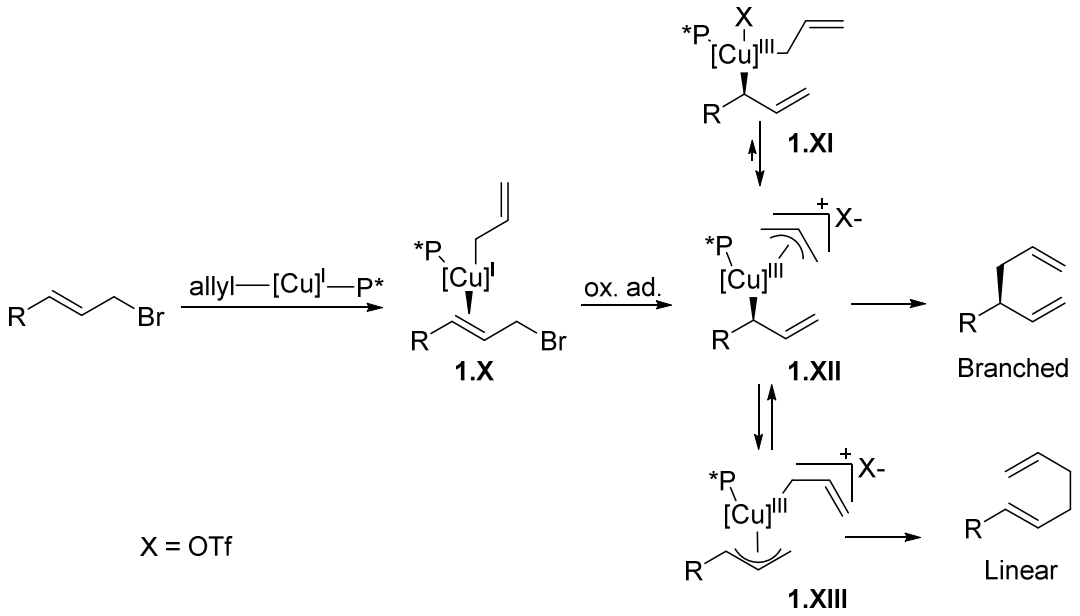
1.47, 81%, 46:54 **b/l**, 86:14 er

1.48, 91%, 88:12 **b/l**, 97:3 er

Based on previous research on the mechanism of copper-catalyzed asymmetric allylic substitution reaction,[38, 40] Feringa proposed the following mechanism to rationalize the reaction outcome (Scheme 1.37). First, the allyl-$[Cu]^{I}$ oxidatively adds to the allyl electrophile. The resulting $[Cu]^{III}$ σ-σ complex **1.X** rearranged to the $[Cu]^{III}$ σ-π **1.XII** where the allyl fragment from the nucleophile adopts the η^3-binding mode. Lastly, reductive elimination from this complex affords the desired branched 1,5-diene. In the event that the reductive elimination is decelerated due to stabilization from a functional group, **1.XII** might also rearrange to achieve the $[Cu]^{III}$ π-σ **1.XIII** where the allyl fragment from the electrophile adopts the η^3 binding mode. Reductive elimination from this intermediate would yield the linear 1,5-diene regioisomer.

[40] (a) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2011**, *112*, 2339; (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884; (c) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615.

Scheme 1.37: Mechanism of the Enantioselective Copper-Catalyzed Allyl-Allyl Cross-Coupling



Overall, Feringa and coworkers have developed the first Cu-catalyzed method in asymmetric allyl-allyl cross-coupling. This reaction offers an alternative strategy to synthesize enantioenriched and branched selective 1,5-dienes compared to the Pd-based reaction. While the enantioselectivity of the 1,5-diene products were excellent in several examples, the substrate dependent regioselectivities leaves room for further developments in this area.

IV. Allyl-Allyl Cross-Coupling Catalyzed by Other Metals

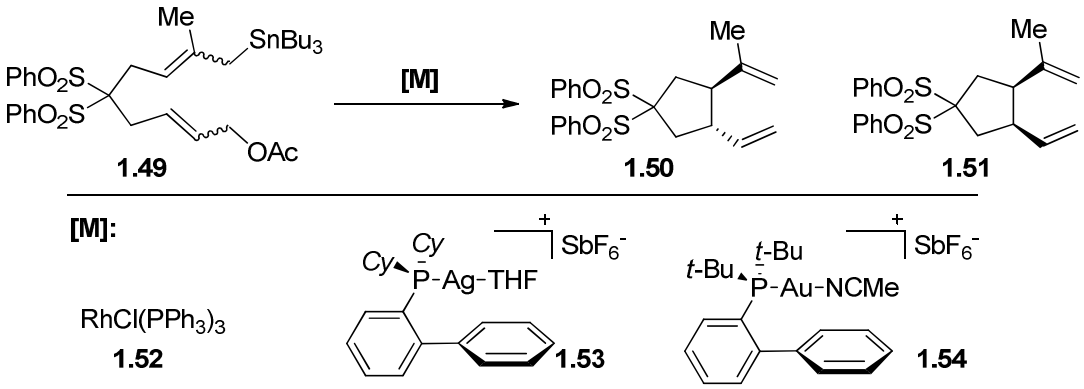
To a lesser extent compared to Pd and Cu catalysts based reactions, allyl-allyl cross-coupling catalyzed by Ag, Au, Ni and Rh have also been investigated. Although these methods have a limited substrate scope, these strategies compliment the Pd and Cu based allyl-allyl cross-coupling.

A. Allyl-Allyl Cross-Coupling Catalyzed by Ag, Au and Rh

In their effort to extend the scope of intramolecular allyl-allyl cross-coupling, the research group of Professor Echavarren disclosed the applicability of $[Rh]^I$, $[Ag]^I$ and $[Au]^I$ complexes for cyclic 1,5-diene synthesis (Scheme 1.38).[41] Using $[RhCl(PPh_3)_3]$ and 5 equivalents of LiCl in DMF, **1.50** and its corresponding diastereoisomer **1.51** were obtained in up to 73% combined yield and 9:1 selectivity favoring the anti 1,5-diene **1.50**. The $[Ag]^I$ complex **1.53** provided 44% yield of **1.50** exclusively. However, the intramolecular cross-coupling was most effective with $[Au]^I$ **1.54** as the catalyst, delivering up to 95% yield of **1.50** selectively within 15 minutes.

[41] Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, 47, 1883.

Scheme 1.38: Allyl-Allyl Cross-Coupling Catalyzed by Rh, Au and Ag Catalysts

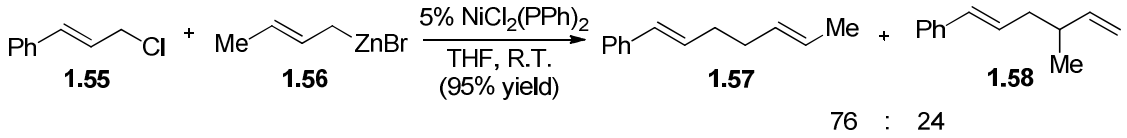


Using **1.54** as the catalyst of choice, Echavarren examined the scope of the intramolecular allyl-allyl cross-coupling reaction. Five and six membered cyclic 1,5-dienes can all be effectively generated, and all *E* or *Z* olefin isomers of the starting materials can be used in the reaction. Through an example employing diastereoenriched starting materials, the authors found that both diastereomers delivered the same 1,5-diene configuration. Based on this observation and other NMR studies, the authors proposed a mechanism involving formation of allyl cation from the allylic acetate, facilitated by [Au] catalyst. The allyl cation was then trapped with the allyl stannane, forming the observed 1,5-diene product.

B. Allyl-Allyl Cross-Coupling Catalyzed by Nickel

The first example of Ni-catalyzed allyl-allyl cross-coupling was illustrated by the Nakamura research group in 1988. Using allyl chloride starting materials, Nakamura was able to cross-couple allylzinc compounds in the presence of nickel catalysts (Scheme 1.39). In this early example, the regioselectivity of the product 1,5-diene was poor, favoring the linear isomer.

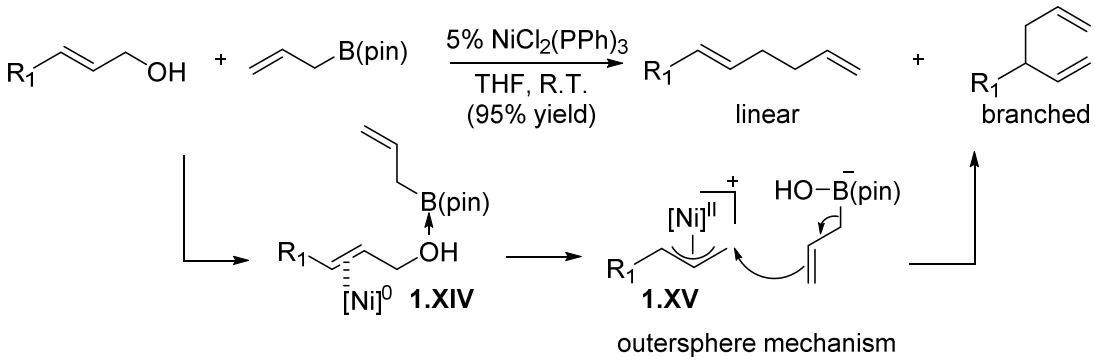
Scheme 1.39: The first example of Ni catalyzed allyl-allyl cross-coupling



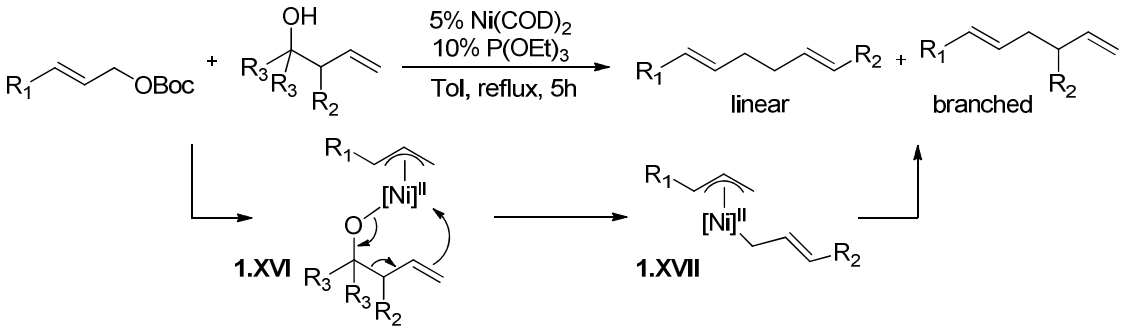
In the same report describing the Pd-catalyzed allyl-allyl cross-coupling of Boc protected allylic alcohol and allylB(pin),[6] Kobayashi and coworkers demonstrated the superior advantages of Ni catalysts over Pd ones. Specifically, the use of Ni suppressed β-H elimination side reaction and provided the 1,5-diene in up to 95% yield. In their subsequent report, the same group extended the scope of their electrophile class to include allylic alcohols (Scheme 1.40).[7] This reaction demonstrated excellent efficiency, providing products with up to quantitative yield and >99:1 regioselectivity favoring the linear isomer. In this report, Kobayashi reasoned that coordination of the lone pair electron on oxygen to the empty p orbital on boron provided sufficient activation for the $[Ni]^0$ catalyst to oxidatively add to the allyl alcohol (**1.XIV**), forming $[Ni]^{II}$-(π-allyl) intermediate **1.XV**. From here, outer-sphere S_E2' attack of the allyl boron anion to the least hindered allyl terminus facilitated formation of the linear 1,5-diene. While they did not rule out the 1,1' inner-sphere reductive elimination of the bis-(allyl)$[Ni]^{II}$ complex,[42] the proposed mechanism explained the reaction regioselectivity.

[42] See part II.B of this chapter.

Scheme 1.40: Nickel Catalyzed Allyl-Allyl Cross-Coupling of Allylic Alcohols and AllylB(pin)



Scheme 1.41: Allyl-Allyl Cross-Coupling with Homoallylic Alcohol Nucleophiles



The Ni-catlayzed allyl-allyl cross-coupling was also studied by Orito *et al*.[43] Particularly of note, in this reaction, no allylic metal coupling partner was necessary, and the nucleophile can be replaced by tertiary homoallylic alcohols (Scheme 1.41). The authors rationalized this unusual mode of reactivity by invoking association of the alcohol to the $[Ni]^{II}$-π-allyl complex (**1.XVI**). This facilitated the transfer of the allyl fragment to $[Ni]^{II}$, leading to formation of intermediate **1.XVII**. Inner-sphere reductive elimination from this complex afforded the 1,5-diene product, but it is unclear which allyl binding mode is preferred for this reductive elimination. Orito's work demonstrated a new class of nucleophile that can be applied in the allyl-allyl cross-coupling reaction.

[43] Sumida, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett*. **2008**, *10*, 1629.

V. Conclusion

Metal catalyzed allyl-allyl cross-coupling offers a powerful strategy to synthesize compounds containing the 1,5-diene motif. Efforts have extended the scope of the reaction to many metal catalysts and allylmetal reagents. At the present, two of the most studied metal catalysts include copper and palladium. The challenges in controlling reaction regio- and enantioselectivity have been addressed, and the reaction has proven its power through applications in synthesis of natural products and medicinally relevant chemicals.

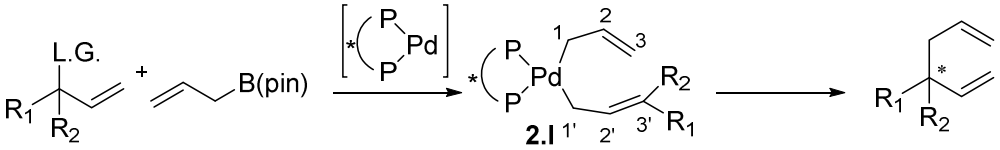
Chapter II: Synthesis of 1,5-Dienes Containing All-Carbon Quaternary Centers

Natural products and biologically active compounds containing all-carbon quaternary centers are important structures in medicine. Due to the steric congestion, syntheses of these all-carbon quaternary centers have been an ongoing challenge in organic synthesis. It is even more arduous to construct enantioenriched structures of this type; this difficulty is attributed to the reduced bias between the enantiotopic faces of the starting materials. Methods to introduce asymmetric all-carbon-quaternary centers have been developed, but their scopes and scales are restricted. Thus, additional enantioselective strategies to synthesize all-carbon quaternary center are highly desired.

Building on the success of the first allyl-allyl cross-coupling method,[1] we envisioned that such a strategy may provide a powerful approach to synthesize compounds containing the all-C quaternary motif. As explained in scheme 2.1, we hypothesized that if the 3,3' reductive elimination mechanism is operative on a Pd-bis-(η^1-allyl) intermediate (**2.I**), generated from a tertiary allylic electrophile and allylB(pin), 1,5-dienes bearing an all-C quaternary center may be synthesized. In this chapter, the formation of 1,5-diene compounds containing all carbon quaternary stereogenic centers is described.

[1] Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

Scheme 2.1: Hypothesis on the formation of All-Carbon Quaternary 1,5-Dienes



I. Methods to Construct All-Carbon Quaternary Center

Among the developed methods to produce all-carbon quaternary centers, Diel-Alder reactions of 1,1–disubstituted olefins catalyzed by chiral Lewis acids is a powerful tool.[2] Additionally, the Heck reaction[3], enolate arylation[4] and enolate allylation[5] have been illustrated to efficiently furnish quaternary centers. Within the area of conjugate addition[6] and allylic substitution[7], copper-catalyzed reactions are unambiguously the most powerful and rapidly evolving method to construct molecular building blocks with quaternary centers. Herein, I would like to discuss the copper-catalyzed allylic substitution and the enolate allylation reactions in more detail because these two reactions display analogous features to the Pd-catalyzed allyl-allyl cross-coupling reaction.

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[2] (a) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 798. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.***1999**, *121*, 7582. For a review on enantioselective Diels-Alder reaction, see: (c) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

[3] (a) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. (b) Shibasaki, M.; Borden, C.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (c) Shibasaki, M.; Erasmus, M. V.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533. (d) For comprehensive review, see Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

[4] Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

[5] (a) Mohr, J. T.; Stoltz, B. M. *Chem.–Asian J.* **2007**, *2*, 1476. (b) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952.

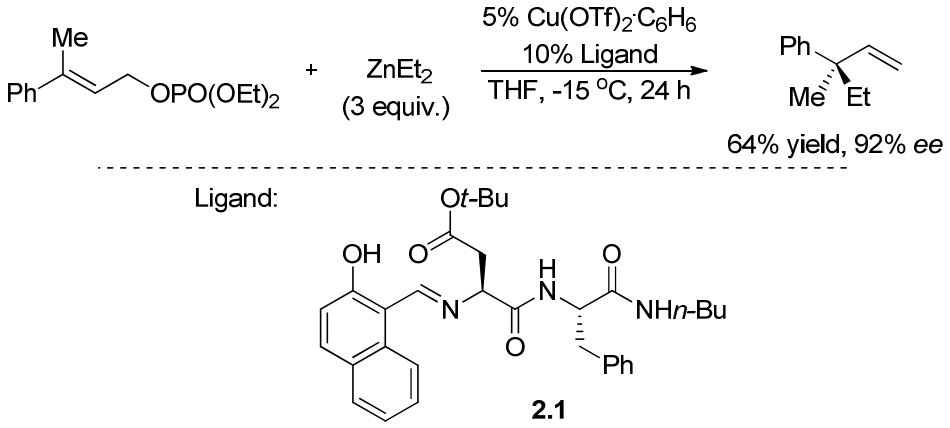
[6] (a) Alexakis, A.; Bäckvall, J.-E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (b) Harutyunyan, S. R.; Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (c) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295.

[7] (a) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A.; *Chem. Commun.* **2004**, 1779. (b) Helmchen, G.; Ernst, M.; Paradies, G. *Pure Appl. Chem.* **2004**, *76*, 495. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (d) Bruneau, C.; Renaud, J. L.; Demerseman, B. *Pure Appl. Chem.* **2008**, *80*, 861. (e) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

A. Copper-Catalyzed Asymmetric Allylic Substitution

In 2001, the research group of Professor Amir H. Hoveyda reported the use of chiral peptide ligands in the construction of all carbon quaternary centers *via* the Cu-catalyzed asymmetric allylic substitution (Cu-AAS).[8] In this report, a number of peptide-based ligands were surveyed and all-carbon quaternary centers were generated from tri-substituted allylic phosphates and excess dialkyl zinc. Later optimization efforts revealed that **2.1** was the best ligand for this transformation (Scheme 2.2).[9]

Scheme 2.2: Cu-Catalyzed Asymmetric Allylic Alkylation

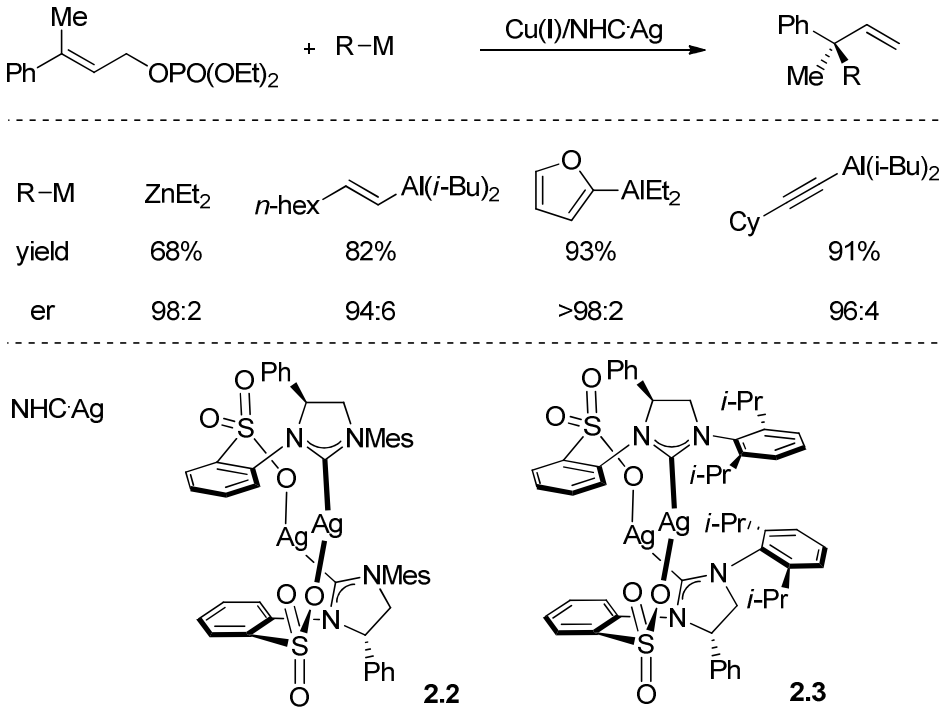


Subsequent developments led to the identification of Ag·NHC complexes as a more effective class of ligands for Cu-AAS (Scheme 2.3). Use of Ag·NHCs facilitated the enantioselective addition of a wide range of metal based nucleophiles, including alkyl,[10] vinyl,[11] aryl[12] and alkynyl.[13] Additionally, this class of ligands allowed the reaction to proceed effectively at lower catalyst loadings comparing to the Cu-peptide ligand system (as low as 0.5%

[8] Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2001**, *40*, 1456.
[9] Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676.
[10] Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.
[11] Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 14315.
[12] Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8370.
[13] Dabrowski, J. A.; Gao, F; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778.

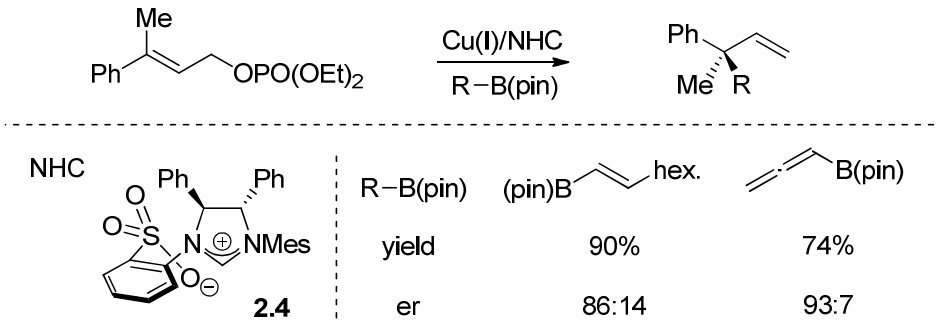
in selected examples). The scope of the nucleophile in the Cu-AAS reaction was further extended to include boronic acid pinacolester based reagents with the use of metal free sulfone NHC **2.4** (Scheme 2.4).[14] These improvements were significant not only in the type of functionality that can be introduced at the stereogenic center, but it also enabled the use of the stable boron reagents, thus rendering it operationally simple.

Scheme 2.3: Cu-Catalyzed Asymmetric Allylic Substitution Using Ag-NHC Ligands



[14] (a) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490; (b) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2012**, 51, 6613.

Scheme 2.4: Use of Boron Based Metal Reagents in Cu-AAS

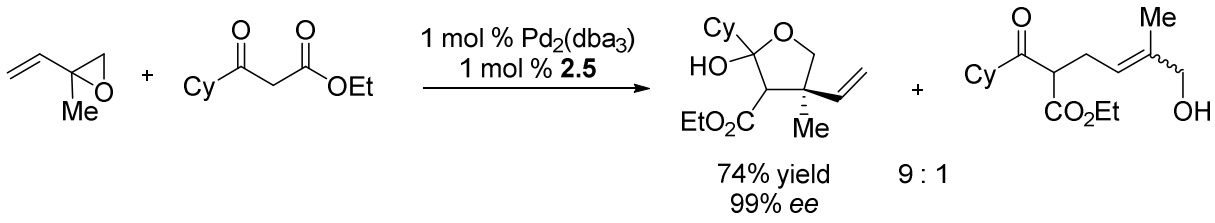


B. Palladium-Catalyzed Enolate α-Allylation

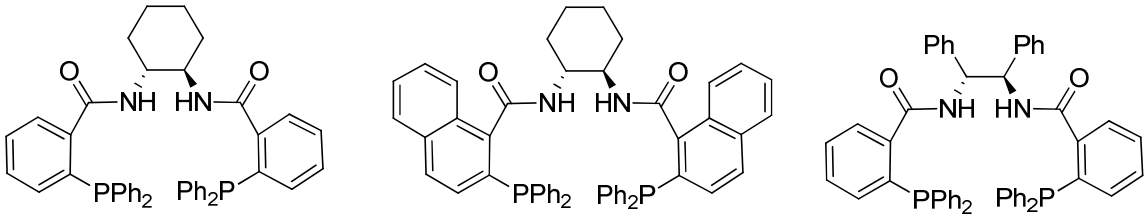
Formation of all-carbon quaternary centers has also been achieved with palladium catalysis. In 2001, Trost and co-workers reported the synthesis of tetrahydrofuran containing all carbon quaternary centers with high levels of enantiocontrol via the addition of β-ketoesters to isoprene monoepoxide (Scheme 2.5).[15] The spectacular feature of this reaction is the preference for the formal S_N2 attack of the nucleophile to the tertiary epoxide center, leading to the formation of compounds with an all carbon quaternary center. To explain this mode of reactivity, Trost reasoned that with the appropriate ligand, upon oxidative addition of Pd(0) to the vinyl epoxide, the π-allyl fragment would oriented in such a way to induce favorable interactions between the alcohol group with the nucleophile. This orientation directs the attack of the nucleophile to the α-carbon of the alcohol, resulting to the overall formal S_N2 addition of the β-ketoester to the isoprene monoepoxide and generating the quaternary center.

[15] Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001,** *123,* 12907.

Scheme 2.5: Pd-Catalyzed Formation of Compounds Containing All-Carbon Quaternary Center



Scheme 2.6: Ligands Developed by Trost and Co-Workers for the Pd-catalyzed Asymmetric Alkylation Reaction

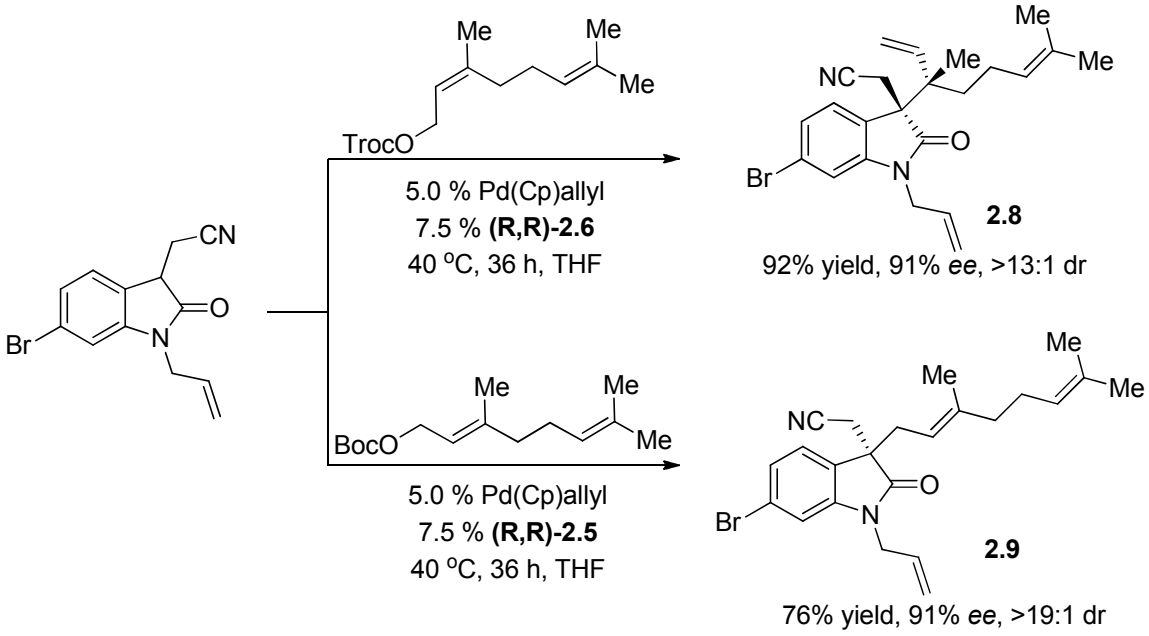


2.5 **2.6** **2.7**

More recently, Trost and coworkers have extended the scope of the Pd-π-allyl field to achieve prenylation of oxindoles (Scheme 2.7).[16] This example represented the first example of a Pd-catalyzed method to synthesize compounds containing two adjacent quaternary carbon centers in an enantioselective and diastereoselective fashion. The interesting feature of this reaction is that the regioselectivity of products is tunable by varying the configuration of the starting materials. Starting materials with *cis* configuration provide products with vicinal quaternary carbon centers (**2.8**), while *trans*-substrates provide the corresponding regioisomer **2.9**.

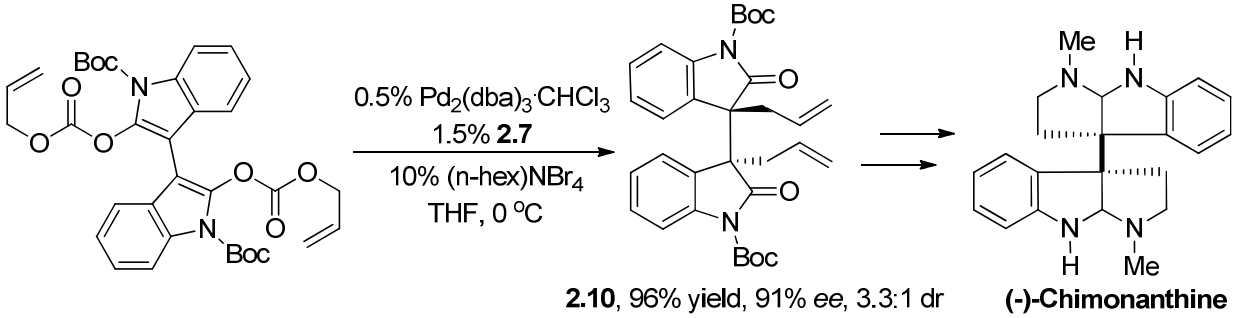
[16] Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328.

Scheme 2.7: Asymmetric Construction of Vicinal All-Carbon Quaternary Stereocenters



Carrying on the development of Pd-catalyzed alkylation of oxindoles, Trost *et. al.* later disclosed the decarboxylative alkylation of dienol dicarbonate.[17] The reaction can be conducted in gram scale with as low as 1 mol % catalyst loading, achieving excellent yields and enantioselectivity. More importantly, this method enabled the rapid assembly of **2.10**, which can be converted to a range of cyclotryptamine alkaloid natural products in a few steps.

Scheme 2.8: Pd-Catalyzed Decarboxylative Alkylation of Dienol Dicarbonate



[17] Trost, B. M.; Osipov, M. *Angew Chem, Int. Ed.* **2013**, *52*, 9176.

Stemming from these developments pioneered by the Trost group, Pd-catalyzed enolate α-allylation has undergone rapid development, and associated strategies have subsequently been documented.[18] The broad substrate scope and the application toward natural product syntheses has proven the reaction's capability. Thus, it will be an important reaction in the organic chemists' tool kits.

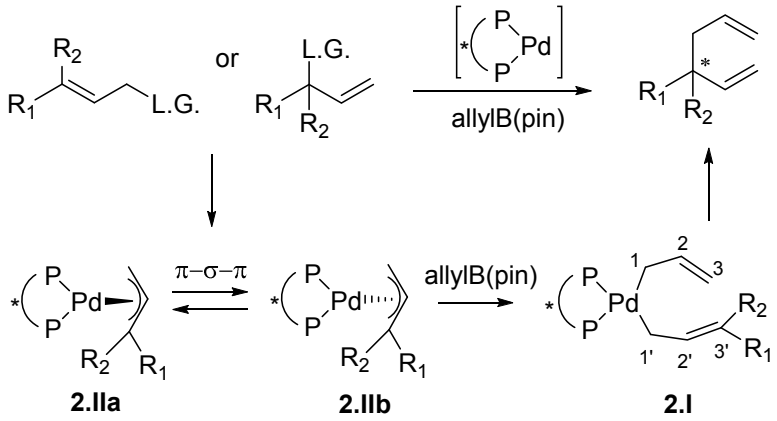
[18] Selected examples: (a) Franckevicius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264. (b) Kaiser, T.; Yang, J. *Eur. J. Org. Chem.* **2013**, 3983. (c) Ghosh, S.; Bhunia, S.; Kakde, B. N.; De, S.; Bisai, A. *Chemical Communications* **2014**, *50*, 2434.

II. Asymmetric Synthesis of 1,5-Dienes with All-Carbon Quaternary Center

A. Hypothesis and Challenges

Stemming from the success of the first enantioselective allyl-allyl cross-coupling developed by Dr. Ping Zhang and Dr. Laura Brozek in our laboratory[1], we sought to further address other challenges utilizing this new reaction. We envisioned that if the palladium catalyst can oxidatively add to tri-substituted allyl electrophiles to generate a Pd-π-allyl intermediate (**2.IIa** or **2.IIb,** Scheme 2.9), transmetallation from allylB(pin) to these intermediates would then effectively generate the Pd-bis-(allyl) complex. Under appropriate control of a bidentate ligand, this complex may achieve the bis (η^1-allyl) configuration (**2.I**). From here, a 3,3' reductive elimination event may furnish the 1,5-diene containing an all-carbon quaternary center.

Scheme 2.9: Formation of 1,5-Dienes Containing All-Carbon Quaternary Center



Several difficulties may be envisioned in this approach. First, it is well known that Pd-π-allyl complexes may undergo rapid π-σ-π isomerization, this property allows the Pd metal to

isomerize to the preferred face of the π-allyl.[19] This isomerization is the central feature providing high level of enantioselectivity for 1,5-diene products in previous work. In the first asymmetric allyl-allyl cross-coupling, the substituents on the allyl group were well differentiated (i.e. R_1 = carbon substitution versus R_2 = hydrogen). In this new approach, both substitutents R_1 and R_2 are carbon based. As a result, the preference for one face of the π-allyl versus the other is lessened. The reduced facial bias may lead to decreased enantioselectivity in the reaction.

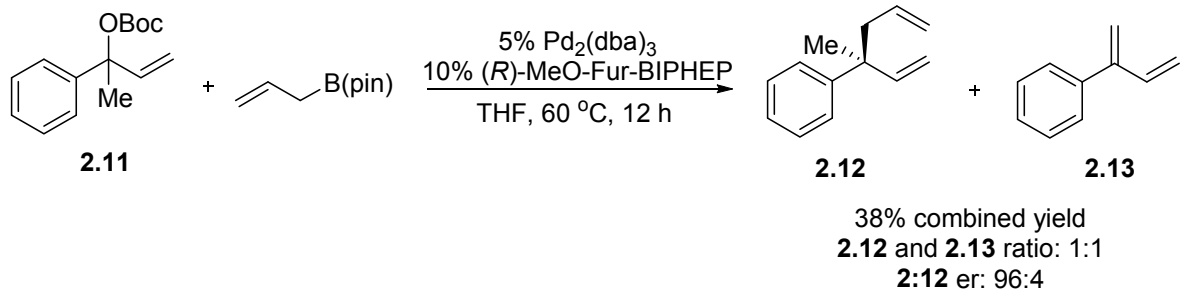
In addition to asymmetric selectivity, the presence of an additional carbon substituent would render a more sterically encumbered metal-π-allyl complex. This increase in steric congestion may cause the Pd-π-allyl intermediate to undergo β-hydride elimination reaction, giving rise to elimination side products.[20]

B. Optimization Results

To initiate the study, Boc protected tertiary allylic alcohol **2.11** was applied as the model substrate. The allyl-allyl cross-coupling reaction was carried out using the conditions optimized in previous allyl-allyl cross-coupling work (Scheme 2.10). To our delight, the desired 1,5-diene **2.12** was observed. More astoundingly, the enantioselectivity of **2.12** was excellent, at 96:4 er. However, the reaction products were obtained as a 1:1 mixture with 1,3-diene **2.13**.

[19] (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *155*, 35.
[20] Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc*. **1994**, *116*, 11151.

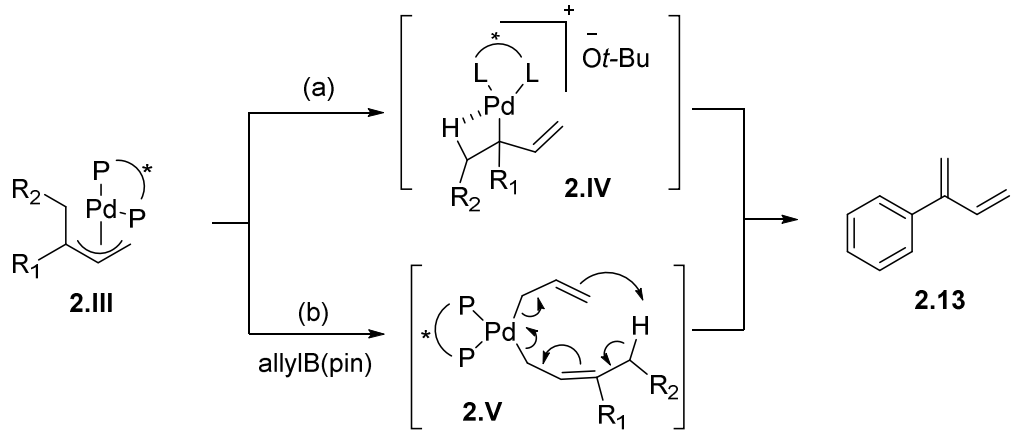
Scheme 2.10: Initial All-Carbon Quaternary Center Formation



While a significant amount of **2.13** side product was observed, the initial result was encouraging as the desired 1,5-diene was furnished in high level of enantioselectivity. To further optimize the reaction, a method to suppress 1,3-diene formation is necessary. It is well known that the Pd-π-allyl intermediate formed upon oxidative addition to the allyl electrophile may give rise to elimination product via β-H elimination process (path a, scheme 2.11).[21] Additionally, with regard to the Pd-bis-(allyl) system, which may form upon transmetallation from allylB(pin), Keinan and co-workers had proposed a metallo-ene hyride abstraction mechanism (path b), which may also give rise to the same elimination side product.[20]

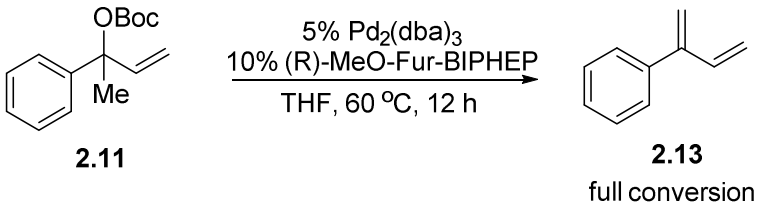
[21] Selected examples: (a) Tsuji, J.;Yamakawa,T.; Kaito, M.; Mandai, T. *Tetrahedron Lett*. **1978**, *19*, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301. (c) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **2007**, *119*, 5956.

Scheme 2.11: Plausible Mechanism to Yield 1,3-Diene Side Products



To gain insight into the major cause of 1,3-diene formation, a control experiment was designed (Scheme 2.12). Starting material **2.11** was subjected to the similar conditions as the cross-coupling reaction described in Scheme 2.10, while omitting allylB(pin). After 12 hours, complete conversion of the starting material to 1,3-diene **2.13** was observed. While this result did not discount the formation of 1,3-diene via the metallocene hydride abstraction (path b, Scheme 2.11), it suggested that β-hydride elimination in path a is an operative mechanism leading to the undesired side product in this allyl-allyl cross-coupling.

Scheme 2.12: β-Hydride Elimination As a Mechanism to Formation of 1,3-Dienes

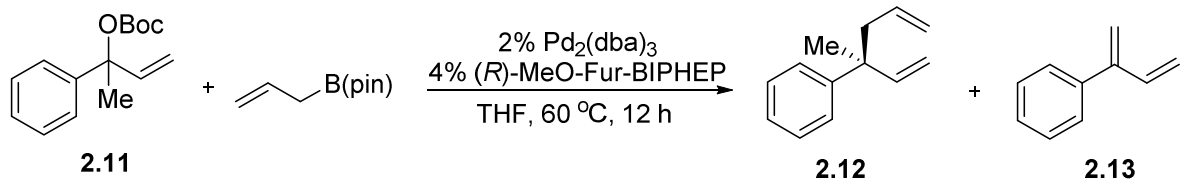


Based on the information gained from the control experiment, we hypothesized that by improving the rate of the transmetallation process, the Pd-π-allyl intermediate **2.III** may be rapidly converted to **2.V**, thereby minimizing the chance for β-H elimination to occur. To

achieve rate acceleration, a number of base additives that were previously shown to accelerate transmetallation in the Suzuki-Miyaura cross-coupling reaction were examined (Table 2.1).[22] Addition of Cs_2CO_3 and CsF facilitated formation of **2.12** and **2.13** mixture in 2:1 and 5:1 ratio, respectively, favoring the desired 1,5-diene (entry 1 and 2). Increasing the concentration of CsF to 3 equivalents enabled formation of the mixture with up to 9:1 ratio favoring **2.12** (entry 3). In addition to base additive, H_2O was also shown to improve the outcome in the Suzuki cross-coupling reaction.[23] Use of water as a co-solvent in a 10:1 THF/H_2O mixture in the reaction rendered the formation of a 14:1 mixture of **2.12**/**2.13** (entry 4). Finally, combining both CsF and the THF/H_2O solvent system provided an astounding result: 1,5 diene **2.12** was obtained in >20:1 selectivity over the side product **2.13** (entry 5). Notably, in all examples, the regio- and enantioselectivity of the 1,5-diene product remained unchanged. This observation suggested that the selectivity determining step in the reaction may be the reductive elimination process.

[22] Use of Cs_2CO_3 in Pd-catalyzed cross-couplings: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109. (c) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (d) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. Use of CsF in Pd-catalyzed cross-couplings: Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
[23] (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.-Eur. J.* **2011**, *17*, 2492. (b) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (c) Suzaki, Y.; Osakada, K. *Organometallics* **2006**, *25*, 3251.

Table 2.1: Optimization of Allyl-Allyl Cross-Coupling of 2.11 and AllylB(pin)



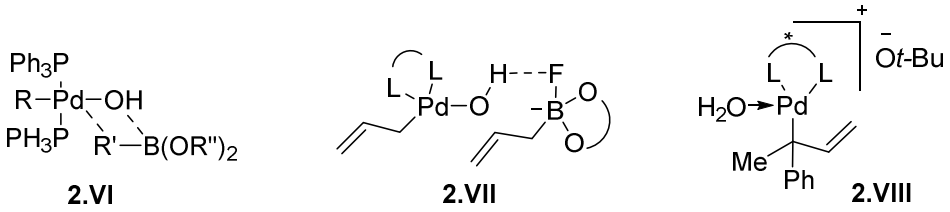
2.11 **2.12** **2.13**

entry	Conditions	**2.12:2.13**[a]	% yield[b]	er of **2.12**[c]
1	10% catalyst, Cs_2CO_3 (1.2 equiv)	2:1	90	96:4
2	10% catalyst, CsF (1.2 equiv)	5:1	79	96:4
3	CsF (3 equiv)	9:1	82	95:5
4	THF/H_2O (10:1)	14:1	88	96:4
5	CsF (3 equiv), THF/H_2O (10:1)	>20:1	90	96:4

[a] Determined by ^{1}H NMR. [b] Combined yield of **2.12** and **2.13**. [c] Ratios determined by Chiral GC

The specific role of H_2O in improving reaction selectivity is not well understood. Several research groups suggested the transmetallation was accelerated by the formation of [Pd^{II}-OH] complex, which might facilitate transmetallation in an intramolecular fashion (**2.VI** in Scheme 2.14).[23] However, it is clear in entry 5 of Scheme 2.13 that CsF and H_2O exhibited a cooperative effect in facilitating 1,5-diene formation. A plausible explanation is that H_2O and CsF may assist transmetallation in a way similar to **2.VII**, in which hydrogen bonding between fluorine and the hydrogen of the palladium hydroxo intermediate accelerates the transmetallation process. Alternatively, H_2O may serve as a labile ligand which outcompetes the C-H agostic interaction with the Pd metal center and prevents β-H elimination to occur (**2.VIII**).

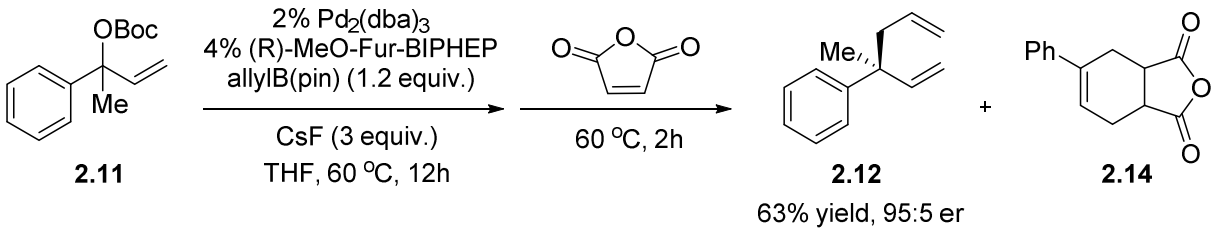
Scheme 2.13: Plausible Roles of H_2O



With regard to accelerating the transmetallation process, Dr. Ping Zhang independently evaluated the use of other allylmetal reagents, including allyl Grignard and allyl zinc reagents;[24] however, the use of allylB(pin) in conjuction with 3 equivalents of CsF and 10:1 THF/H_2O solvent system proved to be optimal for the formation of 1,5-dienes containing an all-carbon quaternary center.

Under the optimized reaction conditions, the amount of 1,3-diene was minimized. However, the 1,3- and the 1,5-dienes are difficult to separate using silica gel column chromatography. To solve this problem, upon completion of the initial cross-coupling sequence, the crude mixture was treated with maleic anhydride at 60 ^oC for 2 hours. During this process, the1,3-diene undergoes Diels-Alder reaction, forming product **2.14**, which is significantly more polar. Thus, the two product can be easily separated, and pure 1,5-diene can be obtained.

Scheme 2.14: Removal of the 1,3-Diene Side Product

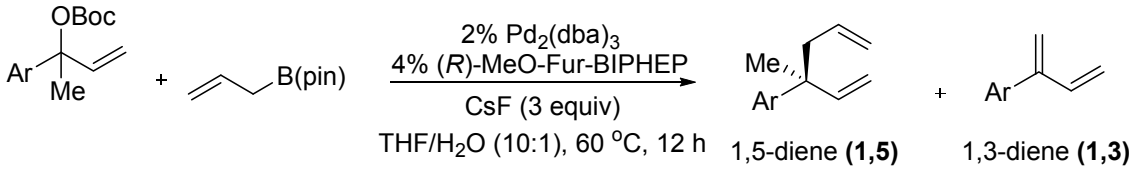


[24] Zhang, P., Ph.D. Dissertation, Boston College, 2011, pg. 180.

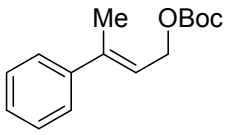
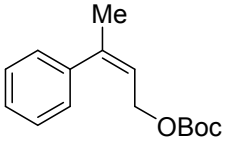
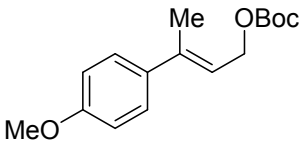
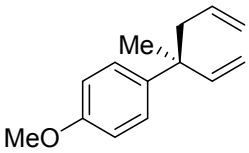
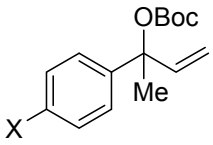
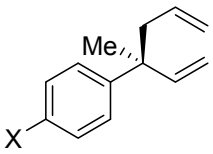
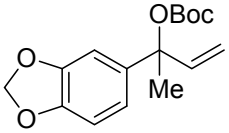
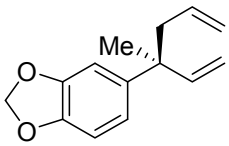
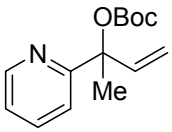
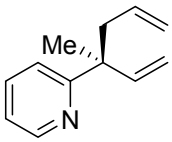
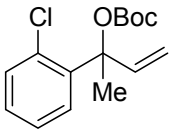
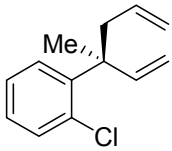
C. Substrate Scope Survey of the Pd-Catalyzed Allyl-Allyl Cross-Coupling in Synthesis of 1,5-Dienes Containing All-Carbon Quaternary Center

Using the optimized conditions, a range of starting materials was evaluated to gain insight on the scope and limitations of the cross-coupling reaction (Table 2.2). As shown in entry 1 and 2, regioisomers of **2.11** were employed as starting materials. Interestingly, both strating materials provided the same 1,5-diene product **2.12** in identical level of enantioselectivity. This observation highlights the power of our cross-coupling method as it suggests that either olefin configuration of the starting material will deliver the same expected product. This Pd-catalyzed allyl-allyl cross-coupling reaction can tolerate various alkyl, halide, and oxygen containing functional groups at the meta and para position on the aryl ring (entry 3-7). In entry 8, substrate with 2-pyridyl substitution provided the corresponding 1,5-diene in excellent yield and selectivity. Notably, H_2O addition was not necessary for this substrate. While it is not entirely clear, the nitrogen atom on the pyridyl ring might coordinate to the palladium metal center in the intermediate stage, thus blocking the open coordination site required for β-hydride elimination. Lastly, an aromatic substrate containing ortho substitution can also be employed efficiently in the cross-coupling reaction despite the steric congestion imposed by the forming adjacent quaternary stereogenic center (entry 9).

Table 2.2: Aryl Substituted Starting Materials



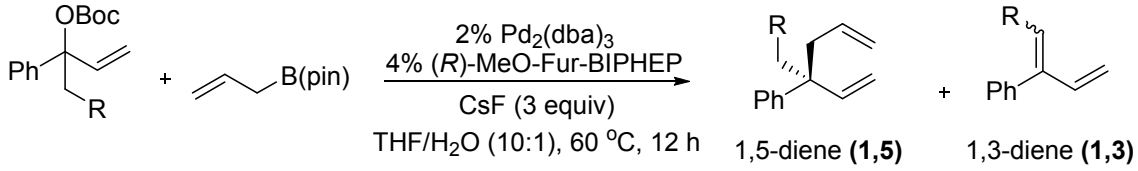
1,5-diene **(1,5)** 1,3-diene **(1,3)**

entry	S.M.	Product	Yield[a]	**1,5**:**1,3**[b]	er[c]
1		**2.12**	86	>20:1	96:4
2		**2.12**	80	11:1	96:4
3			83	12:1	95:5
4	 Cl		70	>20:1	95:5
5	Br		90	20:1	94:6
6	Me		76	17:1	96:4
7			94	6:1	96:4
8[d]			81	>20:1	95:5
9			97	4:1	92:8

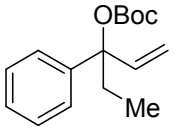
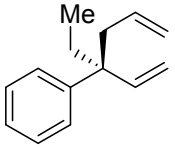
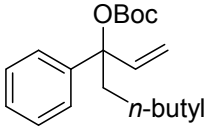
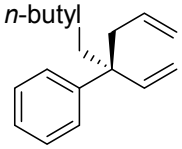
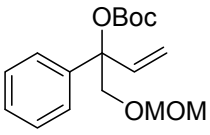
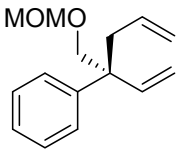
[a] Combined yield of **1,5** and **1,3**. [b] Determined by ^{1}H NMR. [c] Ratios determined by Chiral GC.
[d] Reaction was carried out in anhydrous THF

In all substrates surveyed in Table 2.2, one of the substituents at the forming quaternary center is always methyl; however, this is not a requirement. Table 2.3 displays several substrates containing longer aliphatic chains (entry 1 and 2). While the enantiomeric purity of the corresponding 1,5-diene products is comparable to previous examples, the **1,5**:**1,3** ratio decreased. In entry 3, a MOM protected alcohol was employed effectively and provided exceptional **1,5**:**1,3** selectivity. Similar to the 2-pyridyl substrate (entry 7, Table 2.2), the reaction can be carried out in anhydrous THF, suggesting a beneficial coordinative effect provided by the oxygen atom on the molecule.

Table 2.3: Starting Materials Containing Longer Aliphatic Substitutions



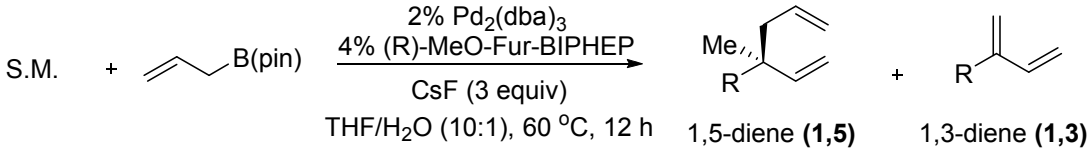
1,5-diene **(1,5)** 1,3-diene **(1,3)**

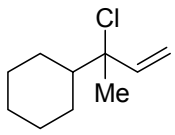
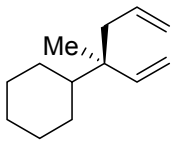
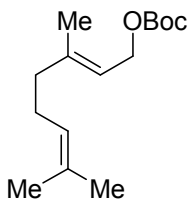
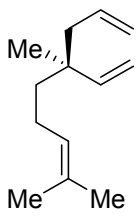
entry	S.M.	Product	Yield[a]	**1,5**:**1,3**[b]	er[c]
1			97	6:1	94:6
2			78	6:1	94:6
3[d]			58	>20:1	90:10

[a] Combined yield of **1,5** and **1,3**. [b] Determined by ^{1}H NMR. [c] Ratios determined by Chiral GC.
[d] Reaction was carried out in anhydrous THF.

To see if aromatic substitution is a requirement in the cross-coupling reaction, all-alkyl substituted substrates were examined (Table 2.4). In the case of a cyclohexyl-methyl-substituted electrophile (entry 1), it was determined that the more reactive allylic chloride is necessary to afford the corresponding 1,5-diene in reasonable yield. Notably, the enantioselectivity of this reaction was comparable to that with the aromatic substituted substrates. Geraniol derived substrate furnished good yield and regioselectivity (entry 2), but the er of the corresponding 1,5-diene was only moderate, at 76:24. This observation suggests that the asymmetric induction stems from the steric differentiation between the two substitutions at the forming stereo center. The minimal size difference between a methyl versus a methylene is not enough for the catalyst system to induce high enantioselectivity.

Table 2.4: Substrate Containing All Aliphatic Substitutions



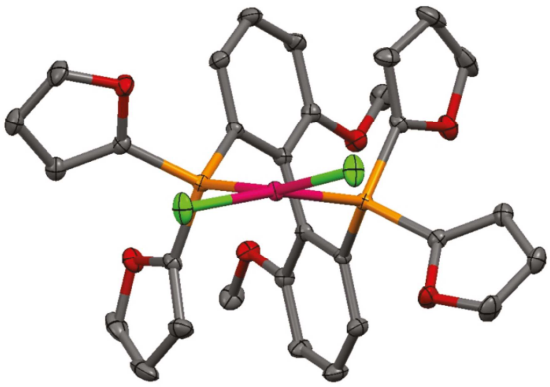
entry	S.M.	Product	Yield[a]	**1,5**:**1,3**[b]	er[c]
1[d, e]			45	8:1	93:7
2			96	4:1	76:24

[a] Combined yield of **1,5** and **1,3**. [b] Determined by ^{1}H NMR. [c] Ratios determined by Chiral GC.
[d] Mixture of regioisomers. [e] Reaction was carried out in anhydrous THF.

D. Origin of Enantioselectivity

Experiments designed to help understand the stereoinduction in the Pd-catalyzed allyl-allyl cross-coupling have been carried out in our laboratory. Michael Ardolino was able to obtain the crystal structure of (*R*)-Meo-Fur-BIPHEP·$PdCl_2$ complex.[25] X-ray analysis of this complex revealed that the (*R*)-MeO-Fur-BIPHEP ligand is chelated to the palladium metal center, forming a seven membered ring. In this conformation, the furyl substitution on phosphorous adopted pseudo-equatorial and pseudo-axial positions on the ring. Additionally, the pseudo-equatorial furyl group pointed toward the palladium, causing the two chloride groups to sit above and below the square plane of the Pd metal. This is an important feature to explain the stereo induction in allyl-allyl cross-coupling reaction.

Scheme 2.15: Crystal Structure of (*R*)-MeO-Fur-BIPHEP·$PdCl_2$

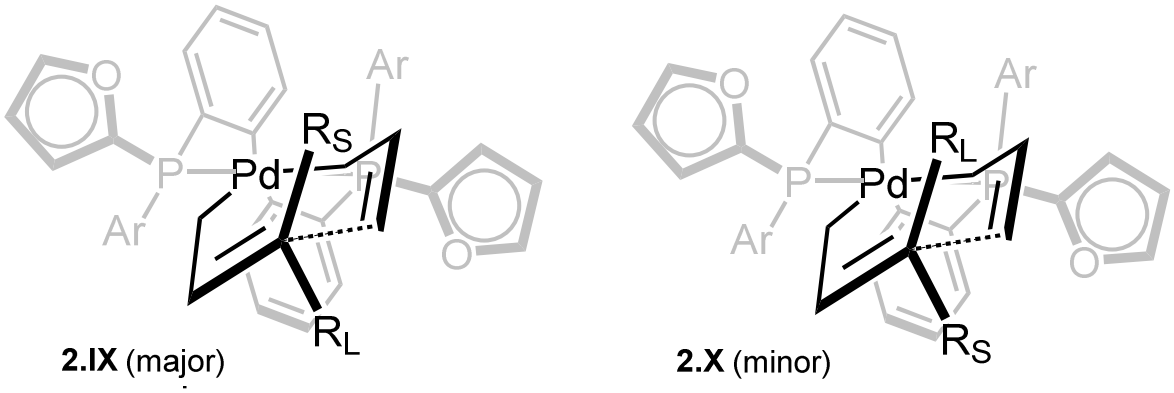


A model for the observed enantioselectivity is postulated in Scheme 2.16. The computational studies published by Echavarren and coworkers suggested that the 3,3' reductive elimination occurred via a chair like transition state.[26] Collectively with the information gained

[25] Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.
[26] Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**,*8*, 3620.

from the crystal structure, we proposed that the reductive elimination is the stereo determining step in our Pd-catalyzed allyl-allyl cross-coupling reaction (Scheme 2.16). Upon formation of the Pd-bis-(η^1-allyl) intermediate, the two allyl groups tilt to minimize steric interactions with the pseudo-equatorial furyl ring. Additionally, the olefins on the substituted allyl fragment adopted the *E* configuration, with R_L being the *trans* group. This conformation allowed minimization of $A^{(1,3)}$ strain imposed by the R substituents. This model is consistent with the observation in entry 2 of Table 2.4 in which substrate with two similar sized substituents yielded 1,5-diene with lower enantioselectivity.

Scheme 2.16: Proposed Model for the Observed Selectivity

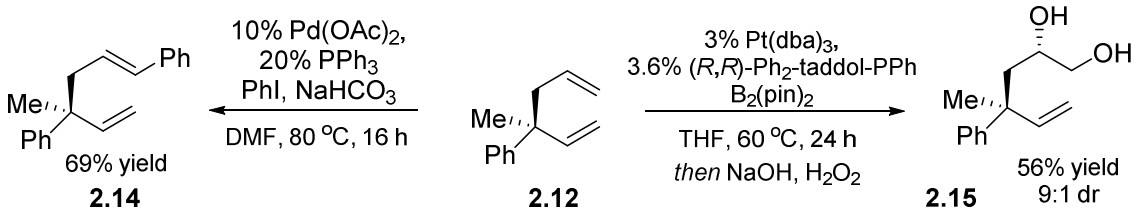


E. Utilities of the Product 1,5-Diene

With access to 1,5-diene building blocks, we sought to explore the utility of this product. In particular, we aimed to demonstrate the ability to selectively manipulate each of the olefin functional handles on the 1,5-diene compounds, because this feature is critical in complex

multistep synthesis. As shown in Scheme 2.17, the less hindered olefin in **2.12** selectively undergoes the Heck reaction to yield di-phenyl **2.14**.[27] Alternatively, **2.12** may also be converted to diol **2.15** by Pt-catalyzed diboration then oxidation.[28] In both examples, the more hindered olefin was left untouched and could be used for subsequent transformations. This observed site selectivity perhaps stems from the unfavorable development of tortional strain that occurs between the quaternary center and the metal catalyst center at the more hindered olefin. All in all, the ability to differentiate the π-system further illustrates the versatility of our 1,5-diene building blocks.

Scheme 2.17: Utility of 1,5-Diene Compounds



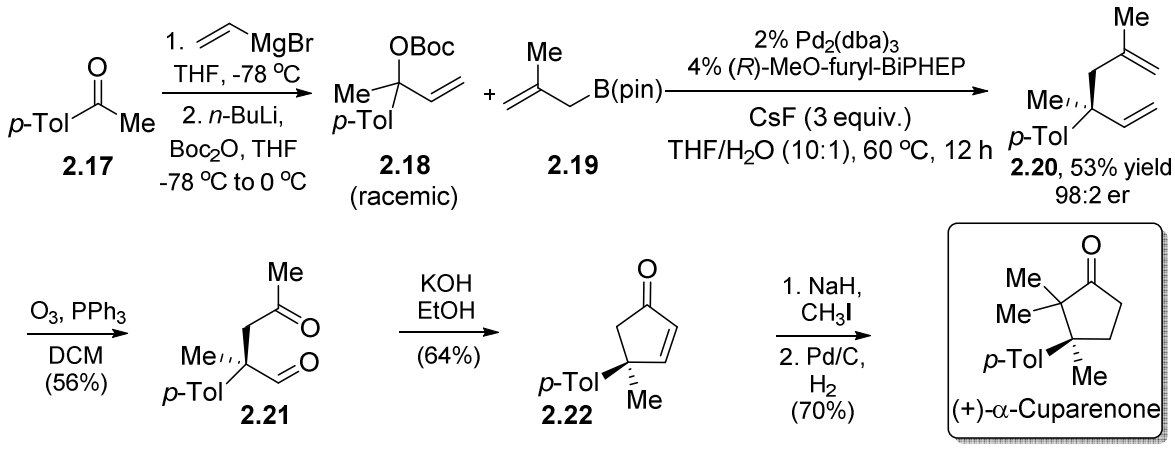
The applicability of our Pd-catalyzed allyl-allyl cross-coupling was further highlighted through the formal synthesis of (+)-α-cuparenone (Scheme 2.18). α-Cuparenone is a small naturally occurring compound belonging to the sequisterpene family of natural products. The (+)- enantiomer is an essential oil found in *Mayur Pankhi* tree,[29] while the (-)-enantiomer has been isolated from the liverwort *Mannia Fragrans*.[30] The structure of α-cuparenone comprises a cyclopentenone core containing two adjacent all-carbon quaternary centers at the α- and the β-

[27] Jeffery, T. *Tetrahedron Lett*. **1985**, *26*, 2667. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
[28] Kliman, L. T.;Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 13210.
[29] Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, *5*, 3.
[30] Benesova, V. *Collect. Czech. Chem. Commun.* **1976,** 3812.

sites. Due to its structural complexity, α-cuparenone has drawn considerable attention from the synthetic community.[31]

Allyl-allyl cross-coupling of Boc protected allylic alcohol **2.18**, which can be obtained easily in two steps from 4-methyl-acetophenone (**2.17**), and methalylB(pin) **2.19** produced 1,5-diene **2.20** in 53% yield and excellent level of enantioselectivity (Scheme 2.18). Ozonolysis of the 1,5-diene followed by PPh_3 reduction afforded aldehyde **2.21**, which underwent aldol cyclization/elimination reaction readily upon treatment with base. From here, α-dimethylation followed by hydrogenation nicely yielded (+)-α-cuparenone. The overall sequence is only five steps starting from the allyl-allyl cross-coupling reaction, which was the shortest asymmetric synthesis of (+)-α-cuparenone at the time.

Scheme 2.18: Synthesis of (+)-α-Cuparenone



[31] Comprehensive summary of syntheses of α-cuparenone: (a) Natarajan, A.; Ng, D.; Yang, Z.; Garcia-Garibay, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6485. Catalytic enantioselective synthesis of a similar natural product, enokipodin B:(b) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441.

III. Conclusion

The scope of the Pd-catalyzed allyl-allyl cross-coupling has been extended to include the construction of 1,5-dienes containing all-carbon quaternary centers. The excellent selectivity observed in this reaction is the consequence of the rapid π-σ-π isomerization of Pd-π-allyl intermediate, combined with effective ligand control of the the 3,3' reductive elimination process. In this work, we identified the combined use of both CsF and THF/H_2O solvent system to effectively diminish the formation of 1,3-diene side products, which arose from β-hydride elimination. The scope of this allyl-allyl cross-coupling includes both aromatic and aliphatic subtrates, and product utility has been demonstrated through the subsequent manipulation of the product 1,5-diene and through the synthesis of the natural product (+)-α-cuparenone.

IV. Experimental Procedure:

A. General Procedure

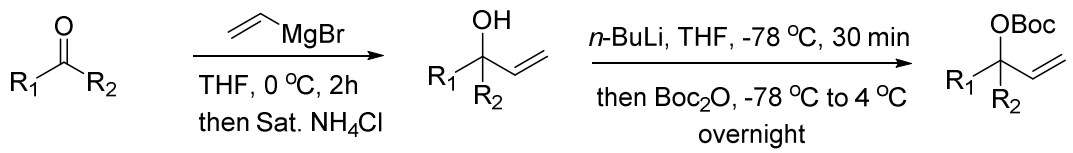
^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz) or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the reference ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Gemini-500 (125 MHz) or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the reference ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). Highresolution mass spectra (ESI) were obtained at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230"450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm) or potassium permanganate ($KMnO_4$) in water. Analytical chiral gas-liquid chromatography (GC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco β-Dex 120 column or an Agilent Technologies 6850 equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco Chiraldex GTA with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was

performed on a Thar SFC equipped with a Waters 2998 photodiode array detector and an analytical-2-prep column oven with methanol as the modifier. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1120 compact chromatograph equipped with gradient pump and variable wavelength detector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. X-Ray crystallography was performed on a Bruker Kappa Apex Duo fully automated single crystal diffractometer, duo wavelength system with high brightness copper source, and anomalous dispersion was used.

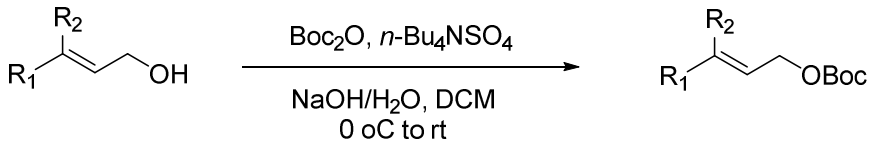
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) was purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Tris(dibenzylideneacetone) dipalladium(0) [$Pd_2(dba)_3$] was purchased from Strem Chemicals, Inc. (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl [(*R*)-MeO-Fur-BIPHEP] was purchased from Strem Chemicals, Inc. or Aldrich, or generously donated from Solvas. Allylboronic acid pinacol ester [allylB(pin)] was generously donated by Frontier Scientific, Inc. MethallylB(pin) was synthesized as described in the literature.1 All other reagents were purchased from either Fisher or Aldrich and used without further purification.

B. Preparation and Charaterization of Starting Materials



Representative Procedure A:1 To a flame-dried round-bottom flask equipped with a stir bar was added 1.0 M vinylmagnesium bromide in THF (15.0 mL, 15.0 mmol) and THF (10 mL).

The solution was cooled to 0 °C and acetophenone (1.20 g, 10.0 mmol) in THF (10 mL) was added dropwise *via* cannula. The reaction was allowed to stir at 0 °C for 2 hours. The reaction was then quenched with sat. NH_4Cl (aq.), and extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (15:1 hexanes/EtOAc) to afford 1.20 g (81% yield) of 2-phenylbut-3-en-2-ol as a light yellow oil. R_f = 0.26 (3:1 hexanes/EtOAc, stain in $KMnO_4$). To a seperate flame-dried round-bottom flask equipped with stir bar was added 2-phenylbut-3-en-2-ol (1.20 g, 8.10 mmol) and THF (16.0 mL). The solution was cooled to -78 °C (dry ice/acetone) followed by dropwise addition of *n*-butyllithium (3.55 mL, 8.51 mmol) in hexane (2.40 M). The reaction was allowed to stir for 30 minutes at -78 °C, after which Boc_2O (2.29 g, 10.5 mmol) in THF (5.0 mL) was added dropwise *via* cannula. The reaction was allowed to warm to 4 ^oC in a cold room and stir overnight. The reaction was diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 1.65 g (82% yield) of *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate as a light yellow oil. R_f = 0.39 (8:1 hexanes/EtOAc, stain in $KMnO_4$). [1]

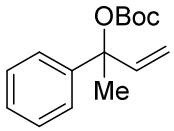


Representative Procedure B: To a round-bottom flask equipped with a stir bar was added geraniol (1.54 g, 10.0 mmol) and methylene chloride (5 mL). The resulting solution was charged

with Boc_2O (2.60 g, 12.0 mmol) and Bu_4NHSO_4 (68.0 mg, 0.2 mmol). The solution was cooled to 0 °C and aqueous NaOH (5.4 mL, 30% solution in H_2O) was added dropwise. The solution was allowed to stir overnight at room temperature. The reaction mixture was diluted with diethyl ether and water, and then extracted into diethyl ether three times. The combined organics were washed with 1M HCl, water, brine, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford 1.85 g (73% yield) of (*E*)-*tert*-butyl (3,7-dimethylocta-2,6-dien-1- yl) carbonate as a light yellow oil. R*f* = 0.55 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of (E)-tert-butyl (3,7-dimethylocta-2,6-dien-1-yl) carbonate **(Table 2.4, entry 2, starting material).** From commercially available geraniol, procedure **B** was followed. Spectral data is in accordance with literature.[32]

Preparation of tert-butyl (2-phenylbut-3-en-2-yl) carbonate **(2.11)**. From commercially available acetophenone, procedure **A** was followed.

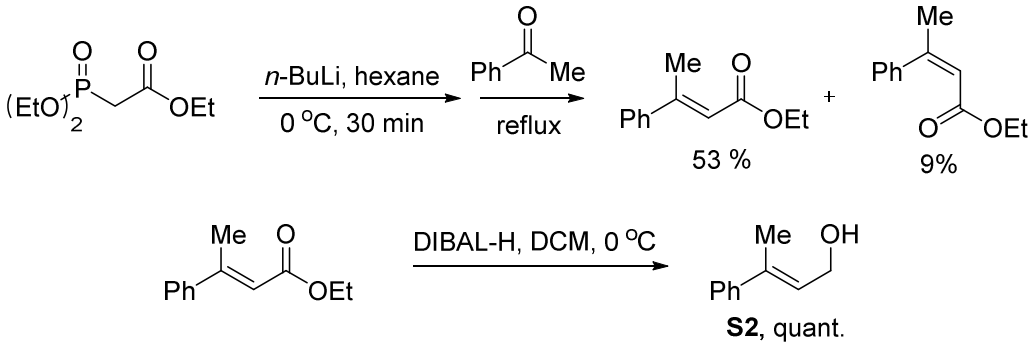


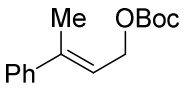
***tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (2.11)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (9H, s, C(C**H$_3$**)$_3$), 1.87 (3H, s, OCC**H$_3$**), 5.27 (1H, dd, *J* = 10.5, 0.5 Hz, CH=C**H**$_{cis}$H$_{trans}$), 5.28 (1H, dd, *J* = 17.5, 0.5 Hz, CH=CH$_{cis}$**H**$_{trans}$), 6.34 (1H, dd, *J* = 17.5, 10.5 Hz, C**H**=CH$_2$), 7.24-7.27 (1H, m, Ar-**H**), 7.32-7.35 (2H, m, Ar-**H**), 7.37-7.40 (2H, m, Ar-**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 27.8, 81.8, 83.8, 115.1, 125.1, 127.2, 128.2, 141.0, 143.7, 151.5; IR (neat): 2980.4 (w), 2943.7 (w), 1743.1 (s), 1448.4 (w), 1368.7 (m), 1276.6 (s), 1254.2 (s), 1150.0 (s), 1070.5 (m), 792.9 (m), 699.1 (m) cm^{-1}; HRMS (ESI+) for $C_{10}H_{11}$ [M-

[32] Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 7899.

OBoc]: calculated: 131.0681, found: 131.0859; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, flashed with 100:1 hexanes/EtOAc) to afford 1.65 g (82% yield) of a light yellow oil. R*f* = 0.39 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

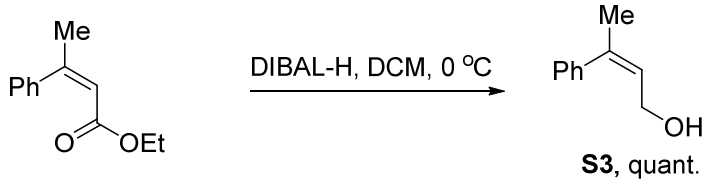
Preparation of (E)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate **(Table 2.2, entry 1, starting material)**. From allylic alcohol **S2**, synthesized as shown below, procedure **B** was followed.



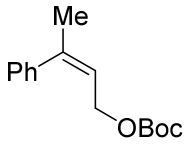


(*E*)-*tert*-butyl (3-phenylbut-2-en-1-yl) carbonate: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (9H, s, C(C**H**$_3$)$_3$), 2.31 (3H, d, *J* = 1.0 Hz, C**H**$_3$C=CH), 4.80 (2H, d, *J* = 7.0 Hz, C=CHC**H**$_2$OBoc), 5.93 (1H, tq, *J* = 7.0, 1.0 Hz, C=C**H**CH$_2$), 7.26-7.29 (1H, m, Ar-**H**), 7.32-7.35 (2H, m, Ar-**H**), 7.40-7.42 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): $ 16.2, 27.7, 68.9, 82.0, 121.0, 125.8, 127.5, 128.2, 140.4, 142.5, 153.5; IR (neat): 2979.7 (w), 2939.9 (w), 1735.6 (s), 1445.2 (w), 1390.0 (m), 1333.2 (s), 1270.8 (s), 1156.6 (s), 1086.1 (m), 927.4 (w), 860.3 (m), 751.3 (m), 695.0 (m) cm^{-1}; HRMS (ESI+) for $C_{10}H_{11}$ [M-OBoc]: calculated: 131.0861, found: 131.0866; The unpurified reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford 2.20 g (79% yield) of a light yellow oil. R*f* = 0.71 (3:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of (Z)-tert-butyl (3-phenylbut-2-en-1-yl) carbonate **(Table 2.2, entry 2, starting material)**. From allylic alcohol **S3**, synthesized as shown below, procedure **B** was followed.

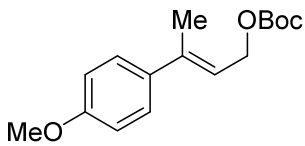


S3, quant.



(*Z*)-*tert*-butyl (3-phenylbut-2-en-1-yl) carbonate. ^{1}H NMR (500 MHz, DCl_3): δ 1.47 (9H, s, C(C**H**$_3$)$_3$), 2.09-2.10 (3H, m, C**H**$_3$C=CH), 4.50 (2H, dd, *J* = 7.0, 1.0 Hz, C=CHC**H**$_2$OBoc), 5.67-5.70 (1H, m, C=C**H**CH$_2$), 7.17-7.19 (1H, m, Ar-**H**), 7.26-7.29 (2H, m, Ar-**H**), 7.32-7.36 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 27.8, 64.7, 81.9, 120.9, 127.4, 127.7, 128.2, 140.3, 142.8, 153.5; IR (neat): 2978.5 (w), 2932.6 (w), 1736.8 (s), 1493.7 (w), 1444.1 (w), 1368.6 (m), 1273.4 (s), 1251.6 (s), 1159.1 (s), 1092.4 (m), 860.3 (m), 793.3 (m), 701.6 (m) cm-1; HRMS (ESI+) for $C_{10}H_{11}$ [M-OBoc]: calculated: 131.0861, found: 131.0864; The reaction mixture was purified on silica gel (50:1 hexanes/EtOAc) to afford 398 mg (89% yield) of a light yellow oil. R*f* = 0.51 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

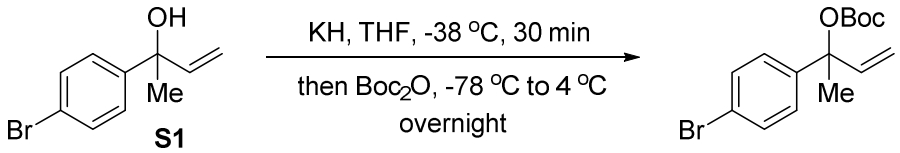
Preparation of (E)-tert-butyl (3-(4-methoxyphenyl)but-2-en-1-yl) carbonate **(Table 2.2, entry 3, strating material)**. From commercially available 4'-methoxyacetophenone, procedure **A** was followed. *tert*-Butyl (2-(4-methoxyphenyl)but-3-en-2-yl) carbonate was originally formed, which was isomerized to the corresponding linear isomer upon silica gel chromatography.



(*E*)-*tert*-butyl (3-(4-methoxyphenyl)but-2-en-1-yl) carbonate (Table 2, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (9H, s, C(C**H**$_3$)$_3$), 2.10 (3H, s, C**H**$_3$C=CH), 3.81 (3H, s, OC**H**$_3$), 4.77 (2H, d, *J* = 7.0 Hz, C**H**$_2$OBoc), 5.85-5.88 (1H, m, ArMeC=C**H**), 6.84-6.87 (2H, m, Ar-**H**), 7.33-7.36 (2H,

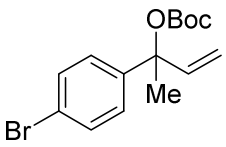
m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2, 27.8, 55.2, 64.0, 82.0, 113.6, 119.4, 126.9, 34.9, 139.9, 153.6, 159.1; IR (neat): 2979.5 (w), 2934.4 (w), 2836.9 (w), 1734.7 (s), 1645.2 (m), 1711.7 (s), 1458.7 (w), 1368.4 (m), 1271.6 (s), 1243.5 (s), 1155.3 (s), 1083.4 (m), 825.1 (m), 792.6 (m) cm^{-1}; HRMS (ESI+) for $C_{11}H_{13}O$ [M-OBoc]: calculated: 161.0966, found: 161.0969; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 873 mg (75% yield) of a light yellow oil. R*f* = 0.42 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of 2-(4-bromophenyl)but-3-en-2-yl tert-butyl carbonate **(Table 2.2, entry 5, starting material)**. From commercially available 4'-bromoacetophenone, procedure A was followed for the synthesis of allylic alcohol (**S-1**), which was converted to the carbonate as shown below.



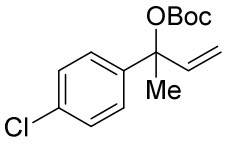
Procedure: A flame-dried round-bottom flask was charged with KH (562.0 mg, 30 wt % in mineral oil, 4.2 mmol) and purged with N_2 three times. Dry hexane (5 mL) was added and the flask was gently swirled. Once the KH settled on the bottom of the flask, hexane was removed *via* cannula. This process was repeated twice, then THF (4.0 mL) was added to create a suspension. The suspension was transferred *via* cannula to another flame-dried round-bottom flask containing a solution of allylic alcohol (**S1**) (852.0 mg, 4.0 mmol) in THF (3.0 mL) at -78 °C. The reaction was allowed to stir for 30 minutes at this temperature, followed by addition of Boc_2O (1.13 g, 5.2 mmol) in THF (1.0 mL) *via* cannula. The reaction was allowed to warm to 4

°C in a cold room and stir overnight. The reaction was diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 1.10 g (84% yield) of a light yellow oil. R*f* = 0.50 (8:1 hexanes/EtOAc, stain in $KMnO_4$).



2-(4-bromophenyl)but-3-en-2-yl *tert*-butyl carbonate: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (9H, s, C(C**H$_3$**)$_3$), 1.84 (3H, s, OCC**H$_3$**), 5.26-5.29 (2H, m, CH=C**H$_2$**), 6.30 (1H, dd, *J* = 17.0, 11.0 Hz, C**H**=CH$_2$), 7.26 (2H, ddd, *J* = 8.5, 2.5, 2.0 Hz, Ar-**H**), 7.46 (2H, ddd, *J* = 8.5, 2.5, 2.0 Hz, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 27.7, 82.0, 83.2, 115.5, 121.3, 126.9, 131.3, 140.5, 142.9, 151.4; IR (neat): 2980.5 (w), 2935.2 (w), 1742.2 (s), 1488.1 (w), 1368.4 (m), 1280.2 (s), 1253.7 (s), 1153.1 (s), 1113.6 (m), 1090.9 (s), 1077.2 (s), 1008.2 (s), 926.3 (m), 820.9 (s), 720.2 (m) cm-1; HRMS (ESI+) for $C_{10}H_{10}Br$ [M-OBoc]: calculated: 208.9966, found: 208.9975.

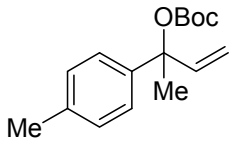
Preparation of tert-butyl-(2-(4-chlorophenyl)but-3-en-2-yl)carbonate **(Table 2.2 , entry 4, starting material):** From commercially available 4-chloroacetophenone, procedure **A** was followed.



***tert*-butyl-(2-(4-chlorophenyl)but-3-en-2-yl)carbonate:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (9H, s, C(C**H$_3$**)$_3$), 1.85 (3H, s, CC**H$_3$**), 5.25-5.29 (2H, m, CH=C**H$_2$**), 6.30 (1H, dd, *J* = 17.4, 10.8 Hz, CC**H**=CH$_2$), 7.29-7.31 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 27.8, 82.0, 83.2, 115.5, 126.6, 128.4, 133.1,

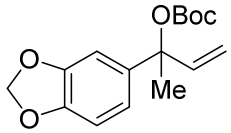
140.6, 142.3, 151.4; IR (neat): 2981.0 (w), 2004.2 (w), 1745.7 (s), 1492.0 (w), 1369.5 (m) 1284.6 (s), 1158.2 (s), 1013.2 (s), 827.7 (w), 421.7 (w) cm^{-1}; HRMS (ESI+) for $C_{10}H_{10}Cl$ [M-OBoc]: calculated: 165.0471, found: 165.0464. The unpurified material was used for the subsequent coupling reaction without further purification.

Preparation of tert-butyl (2-(p-tolyl)but-3-en-2-yl) carbonate **(Table 2.2, entry 6)**. From commercially available 4'-methylacetophenone, procedure **A** was followed.



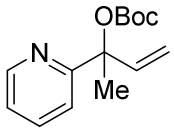
***tert*-butyl (2-(*p*-tolyl)but-3-en-2-yl) carbonate (Table 2.2, entry 5)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (9H, s, C(C**H**$_3$)$_3$), 1.87 (3H, s, OCC**H**$_3$), 2.34 (3H, s, Ar-C**H**$_3$), 5.26 (1H, d, *J* = 11.0 Hz, CH=C**H**$_{cis}$H$_{trans}$), 5.28 (1H, d, *J* = 17.5 Hz, CH=CH$_{cis}$**H**$_{trans}$), 6.35 (1H, ddd, *J* = 17.5, 11.0, 0.5 Hz, C**H**=CH$_2$), 7.16 (2H, d, *J* = 8.0 Hz, Ar-**H**), 7.28 (2H, d, *J* = 8.0 Hz, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 25.7, 27.7, 81.6, 83.7, 114.8, 124.9, 128.9, 136.8, 140.7, 141.1, 151.5; IR (neat): 2979.9 (w), 2933.0 (w), 1743.0 (s), 1513.2 (w), 1455.9 (w), 1368.0 (m), 1274.9 (s), 1252.7 (s), 1122.0 (s), 1093.4 (s), 1073.1 (m), 850.6 (m), 791.2 (m), 533.4 (w) cm^{-1}; HRMS (ESI+) for $C_{11}H_{13}$ [M-OBoc]: calculated: 145.1017, found: 145.1023; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes:EtOAc) to afford 1.91 g (89% yield) of a light yellow oil. R*f* = 0.49 (8:1 hexanes:EtOAc, stain in $KMnO_4$).

Preparation of 2-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-yl-tert-butyl-carbonate **(Table 2.2 , entry 7, starting material)**. From commercially available 3',4'-(methylenedioxy)acetophenone, procedure **A** was followed.



2-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-yl-*tert*-butyl-carbonate : ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (9H, s, C(C**H$_3$**)$_3$), 1.84 (3H, s, CC**H$_3$**), 5.25 (1H, dd, *J* = 10.8, 0.7 Hz, CCH=C**H***cis*H*trans*), 5.27 (1H dd, *J* = 17.4, 0.7 Hz, CCH=CH*cis***H*trans***), 5.95 (2H, s, OC**H$_2$**O), 6.30 (1H, dd, *J* = 17.4, 10.8 Hz, CC**H**=CH$_2$), 6.76 (1H, d, *J* = 8.1 Hz, Ar-**H**), 6.85-6.89 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, CDCl3): δ 25.7, 27.7, 81.7, 83.5, 101.0, 106.1, 107.8, 114.9, 118.4, 137.7, 141.0, 146.6, 147.6, 151.4; IR (neat): 2980.7 (w), 2932.1 (w), 1742.3 (s), 1486.7 (s), 1435.7 (m), 1393.9 (m), 1277.2 (s), 1241.5 (s), 1156.5 (s), 1094.5 (s), 1037.6 (s), 909.5 (m), 810.7 (m), 729.7 (s) cm^{-1}; HRMS (ESI+) for $C_{16}H_{21}O_5$ [M+H]: calculated: 293.1389, found: 293.1375. The unpurified reaction mixture was purified on silica gel (9:1 hexanes/EtOAc) to afford a clear, pale-yellow oil (244 mg, 23% yield). R*f* = 0.12 (19:1 hexanes/EtOAc, stain in $KMnO_4$).

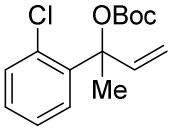
Preparation of tert-butyl-(2-pyridin-2-yl)but-3-en-2-yl)carbonate **(Table 2.2 , entry 8, starting material)**. From commercially available 2-acetylpyridine, procedure **A** was followed.



tert*-butyl-(2-pyridin-2-yl)but-3-en-2-yl)carbonate:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (9H, s, C(C**H$_3$**)$_3$), 1.87 (3H, s, CC**H$_3$**), 5.25 (1H, dd, *J* = 10.9, 0.7 Hz, CCH=C**H$_{cis}$*H*$_{trans}$*), 5.31 (1H, dd, *J* = 17.6, 0.7 Hz, CCH=CH*$_{cis}$***H*$_{trans}$***), 6.44 (1H, dd, *J* = 17.6, 10.9 Hz, CC**H**=CH$_2$), 7.12-7.15 (1H, m, Ar-**H**), 7.37-7.39 (1H, m, Ar-**H**), 7.62-7.65 (1H, m, Ar-**H**), 8.54-8.55 (1H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 27.6, 81.9, 84.0, 15.0, 119.5, 122.0, 136.4, 140.1, 148.6, 151.5, 162.1; IR (neat): 2980.9 (w), 2936.2 (w), 1742.8 (s), 1588.8 (w), 1368.3 (m), 1278.0 (s), 1255.0 (s), 1156.7 (s), 1106.6 (s), 853.6 (m), 748.7 (m), 84.1 (m),

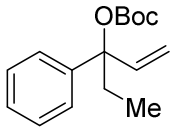
403.3 (w) cm^{-1}; HRMS (ESI+) for $C_{14}H_{20}NO_3$ [M+H]: calculated: 250.1443, found: 250.1440. The unpurified reaction mixture was purified on silica gel (9:1 hexanes/EtOAc) to afford a clear, pale-yellow oil (126 mg, 52% yield). R*f* = 0.22 (9:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of tert-butyl-(2-(chlorophenyl)but-3-en-2-yl)carbonate **(Table 2.2 , entry 9, starting material)**. From commercially available 2'-chloroacetophenone, procedure A was followed.



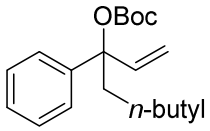
tert*-butyl-(2-(chlorophenyl)but-3-en-2-yl)carbonate:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (9H, s, C(C**H$_3$**)$_3$), 1.95 (3H, s, CC**H$_3$**), 5.23 (1H, d, *J* = 17.6 Hz, CCH=CH*cisH*trans***), 5.28 (1H, d, *J* = 10.9 Hz, CCH=C**H*cis***H*trans*), 6.49 (1H, dd, *J* = 17.6, 10.9 Hz, CC**H**=CH2), 7.20-7.28 (m, 2H, Ar-**H**), 7.35-7.37 (m, 1H, Ar-**H**), 7.47-7.49 (m, 1H, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 27.7, 81.9, 83.2, 115.4, 126.6, 127.8, 128.6, 131.6, 131.7, 139.9, 140.2, 151.4; IR (neat): 2981.4 (w), 2934.2 (w), 1741.4 (s), 1473.1 (w), 1369.2 (m), 1285.8 (s), 1256.3 (m), 1157.2 (s), 1134.2 (m), 1102.3 (m), 1038.8 (m), 926.9 (w), 791.6 (w), 755.5 (w) cm^{-1}; HRMS (ESI+) for $C_{15}H_{23}ClNO_3$ [M+NH_4+]: calculated: 300.1367, found: 300.1371. The unpurified reaction mixture was purified on silica gel (hexanes to 32:1 hexanes/EtOAc) to afford a clear, colorless oil (1.40 g, 67% yield). R*f* = 0.18 (32:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of tert-butyl (3-phenylpent-1-en-3-yl) carbonate **(Table 2.3, entry 1, starting material)**. From commercially available propiophenone, procedure **A** was followed.



***tert*-butyl (3-phenylpent-1-en-3-yl) carbonate**. ^{1}HNMR (500 MHz, $CDCl_3$): δ 0.82 (3H, t, *J* = 7.5 Hz, $CH_2C\mathbf{H_3}$), 1.42 (9H, s, $C(C\mathbf{H_3})_3$), 2.27 (1H, dq, *J* = 14.0, 7.5 Hz, $C\mathbf{H_a}H_bCH_3$), 2.33 (1H, dq, *J* = 14.0, 7.5 Hz, $CH_a\mathbf{H_b}CH_3$), 5.29 (1H, dd, *J* = 11.0, 1.0 Hz, $CH=C\mathbf{H}_{\boldsymbol{cis}}H_{trans}$), 5.32 (1H, dd, *J* = 17.5, 1.0 Hz, $CH=CH_{cis}\mathbf{H}_{\boldsymbol{trans}}$), 6.22 (1H, dd, *J* = 17.5, 11.0 Hz, $C\mathbf{H}=CH_2$), 7.23-7.26 (1H, m, Ar-**H**), 7.31-7.38 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.7, 27.7, 30.9, 81.5, 85.9, 115.1, 125.5, 127.0, 128.0, 140.0, 142.6, 151.4; IR (neat): 3060.8 (w), 2978.5 (m), 2973.4 (w), 2881.6 (w), 1742.5 (s), 1640.1 (w), 1493.9 (w), 1448.3 (m), 1368.2 (m), 1269.4 (s), 1271.1 (s), 1152.7 (s), 1117.0 (m), 866.4 (s), 697.7 (s) cm^{-1}; HRMS (ESI+) for $C_{11}H_{13}$ [M-OBoc]: calculated: 145.1017, found: 145.1021; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 2.97 g (87% yield) of a light yellow oil. R*f* = 0.46 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

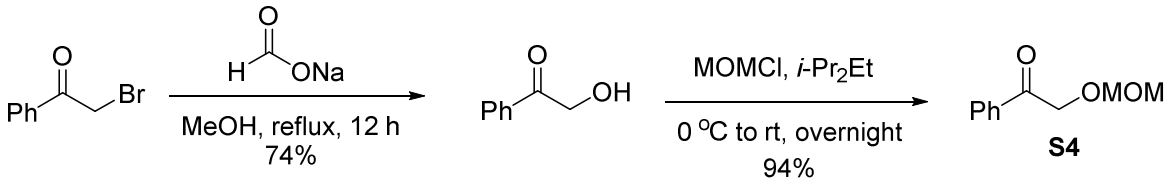
***Preparation of tert-butyl (3-phenyloct-1-en-3-yl) carbonate*(Table 2.3, entry 2, starting material)**. From commercially available hexanophenone, procedure **A** was followed.

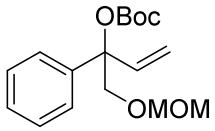


***tert*-butyl (3-phenyloct-1-en-3-yl) carbonate**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H_3}$), 1.14-1.30 (6H, m, $(C\mathbf{H_2})_3CH_3$), 1.42 (9H, s, $C(C\mathbf{H_3})_3$), 2.19-2.30 (2H, m, $C\mathbf{H_2}(CH_2)_3CH_3$), 5.27 (1H, dd, *J* = 11.0, 1.0 Hz, $CH=C\mathbf{H}_{\boldsymbol{cis}}H_{trans}$), 5.30 (1H, dd, *J* = 17.5, 1.0 Hz, $CH=CH_{cis}\mathbf{H}_{\boldsymbol{trans}}$), 6.23 (1H, ddd, *J* = 17.5, 11.0, 0.5 Hz, $C\mathbf{H}=CH_2$), 7.23- 7.26 (1H, m, Ar-**H**), 7.31-7.38 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.4, 22.9, 27.8, 31.9, 37.9, 81.6, 85.7, 114.9, 125.4, 127.0, 128.1, 140.4, 142.9, 151.4; IR (neat):2957.2 (w), 2931.4 (w), 2870.6 (w), 1743.9 (s), 1448.4 (w), 1368.1 (m), 1271.1 (s),

1153.0(s), 1123.9 (s), 910.9 (m), 790.2 (m), 697.8 (s) cm-1; HRMS (ESI+) for $C_{14}H_{19}$ [M-OBoc]: calculated: 187.1487, found: 187.1484; The unpurified reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 100:1 hexanes/EtOAc) to afford 4.11 g (89% yield) of a light yellow oil. R*f* = 0.56 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of tert-butyl (1-(methoxymethoxy)-2-phenylbut-3-en-2-yl) carbonate **(Table 2.3, entry 3, starting material)**. From ketone **S-5**, synthesized as shown below, procedure A was followed.

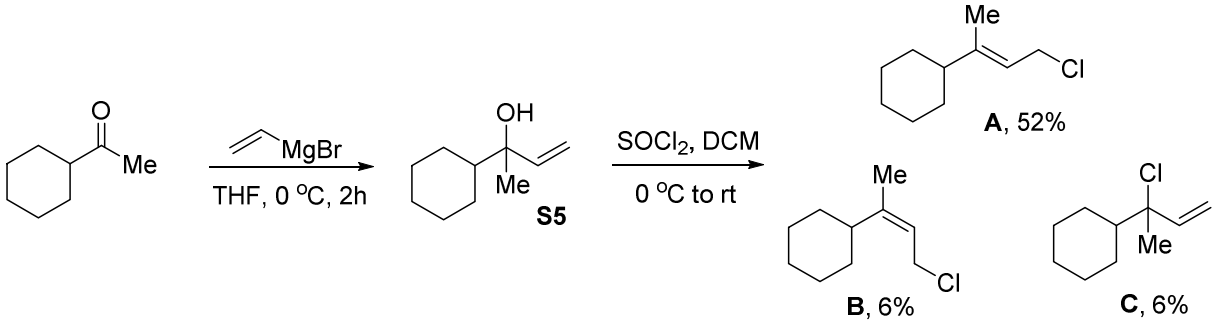




***tert*-butyl (1-(methoxymethoxy)-2-phenylbut-3-en-2-yl) carbonate (Table 2, entry 13)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (9H, s, C(C**H**$_3$)$_3$), 3.21 (3H, s, OC**H**$_3$), 4.13 (1H, d, *J* = 10.0 Hz, CC**H**$_a$H$_b$O), 4.17 (1H, d, *J* = 10.0 Hz, CCH$_a$**H**$_b$O), 4.56 (1H, d, *J* = 6.5 Hz, OC**H**$_a$H$_b$O), 4.59 (1H, d, *J* = 6.5 Hz, OCH$_a$**H**$_b$O), 5.36 (1H, dd, *J* = 17.5, 0.5 Hz, CH=CH$_{cis}$**H**$_{trans}$), 5.40 (1H, dd, *J* = 11.0, 0.5 Hz, CH=C**H**$_{cis}$H$_{trans}$), 6.38 (1H, dd, *J* = 17.5, 1.0, Hz, C**H**=CH$_2$), 7.26-7.29 (1H, m, Ar-**H**), 7.33-7.36 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.7, 55.3, 71.4, 82.0, 84.2, 96.5, 116.9, 125.7, 127.5, 128.1, 137.7, 140.4, 151.3; IR (neat): 2979.7 (w), 2933.7 (w), 2886.8 (w), 2823.9 (w), 1743.8 (s), 1495.0 (w), 1449.2 (w), 1393.9 (m), 1270.9 (s), 1252.2 (s), 1147.8 (s), 1038.5 (s), 918.8 (m), 857.5 (m), 719.7 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{15}O_2$ [M-OBoc]: calculated: 191.1072, found: 191.1073; the unpurified

reaction mixture was purified on silica gel (neutralized with 5% TEA, eluted with 15:1 hexanes/EtOAc) to afford 2.35 g (80% yield) of a light yellow oil. R*f* = 0.30 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Preparation of (4-chlorobut-2-en-2-yl)cyclohexane and (2-chlorobut-3-en-2-yl)cyclohexane . From commercially available 1-cyclohexylethanone, procedure **A** was followed to synthesize allylic alcohol **S5**, which was converted the chlorides as shown below.



Procedure:[33] To a flame-dried round-bottom flask under a N_2 atomosphere was added $SOCl_2$ (1.45 mL, 20.0 mmol) and CH_2Cl_2 (8 mL) at room temperature. The resulting solution was cooled to 0 °C, and 2-cyclohexylbut-3-en-2-ol (**S5**, 308 mg, 2.0 mmol) was added dropwise. The solution was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature and stir for an additional 1.5 h. The solution was then cooled to 0 °C and ice-cold D.I. water was added to quench excess $SOCl_2$. The mixture was extracted with diethyl ether three times. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 220 mg (64% yield) of a light brown oil. The unpurified reaction mixture were used without further purification. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.20-1.35 (m), 1.61 (s), 1.68-1.71 (m), 1.74-1.78 (m), 1.79-1.81(m), 4.11 (**A** & **B**, 2H, d, *J* = 8.0 Hz, CHC**H$_2$**), 5.13 (**C**, 1H, d, *J* =

[33] Penjšević, J.; Šukalović, V.; Andrić, D.; Kostić-Rajačić, S.; Šoškić, V.; and Roglić, G. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 456.

10.8 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.26 (**C**, 1H, d, J = 17.3 Hz, CCH=CH$_{cis}$**H**$_{trans}$), 5.34-5.41 (**B**, m, 1H, C=C**H**), 5.40-5.45 (**A**, m, C=C**H**), 6.01 (**C**, dd, J = 17.2, 10.7 Hz, CC**H**=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 19.8, 26.0, 26.2, 26.5, 30.9, 31.5, 41.3, 47.1, 118.4, 147.9; HRMS (ESI+) for $C_{10}H_{17}$ [M-Cl]: calculated: 137.1330, found: 137.1331.

C. Representative Procedures for Allyl-Allyl Cross-Coupling

Representative Procedure for Pd2(dba)3 Catalyzed Coupling (without water)

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone)dipalladium(0) (3.6 mg, 0.004 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and THF (1.0 mL) in a dry-box under an argon atmosphere. The vial was capped and stirred for 5 minutes, then *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (49.6 mg, 0.20 mmol) was added, followed by allylboronic acid pinacol ester (40.4 mg, 0.24 mmol) and cesium fluoride (91.1 mg, 0.60 mmol). The vial was sealed, removed from the dry-box, and allowed to stir at 60 °C for 12 hours. The vial was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of silica gel and concentrated *in vacuo*. Analysis of the unpurified reaction mixture using ^{1}H NMR was used to determine the ratio of product to elimination product. Silica gel chromatography (pentane) afforded 27.4 mg (82% yield) of a colorless oil, with 7.3:1 allyl-allyl coupling product to elimination product.

Representative Procedure for $Pd_2(dba)_3$ Catalyzed Coupling (with water)

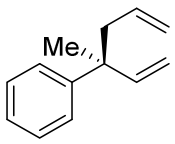
An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with tris(dibenzylideneacetone) dipalladium(0) (3.6 mg, 0.004 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and 1.0 mL of THF in a dry-box under an argon atmosphere. The vial was capped and stirred for 5 minutes, then *tert*-butyl (2-phenylbut-3-en-2-yl) carbonate (49.6 mg, 0.20 mmol) was added, followed by allylboronic acid pinacol ester (40.4 mg, 0.24 mmol) and cesium fluoride (91.1 mg, 0.60 mol). The vial was sealed with a septum, removed from the dry-box, and then deoxygenated water (0.1 mL) was added by syringe under N_2 atomosphere. The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of $MgSO_4$ (top) and silica gel (bottom) and concentrated *in vacuo*. Analysis of the unpurified reaction mixture using ^1H NMR was used to determine the ratio of product to elimination ratio. Silica gel chromatography (pentane) afforded 31.0 mg (90% yield) of a colorless oil of the allyl-allyl coupling product, with less than 5% elimination product.

Representative Procedure for $PdCl_2$ Catalyzed Coupling (with water, without glovebox technologies)

A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with palladium(II) chloride (1.4 mg, 0.008 mmol), (*R*)-(+)-2,2'-bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (4.2 mg, 0.008 mmol), and cesium fluoride (91.1 mg, 0.60 mol). The vial was sealed with a septum and purged three times with N_2. THF (1.0 mL) and deoxygenated water (0.1 mL)

were then added by syringe, followed by the addition of *tert*-butyl (2-phenylbut-3- en-2-yl) carbonate (49.6 mg, 0.20 mmol) and allylboronic acid pinacol ester (40.4 mg, 0.24 mmol), both by syringe. The septum was quickly replaced with a cap, and the vial was sealed again and allowed to stir at 60 °C for 12 hours. The reaction was then cooled to ambient temperature, diluted with diethyl ether, filtered through a plug of $MgSO_4$ (top) and silica gel (bottom) and concentrated *in vacuo*. Analysis of the unpurified reaction mixture using ^{1}H NMR was used to determine the ratio of product to elimination. Silica gel chromatography (pentane) afforded 30.2 mg (89% yield) of a colorless oil, with 17:1 allyl-allyl coupling product to elimination product.

D. Product Characterizations and Proof of Stereochemistry



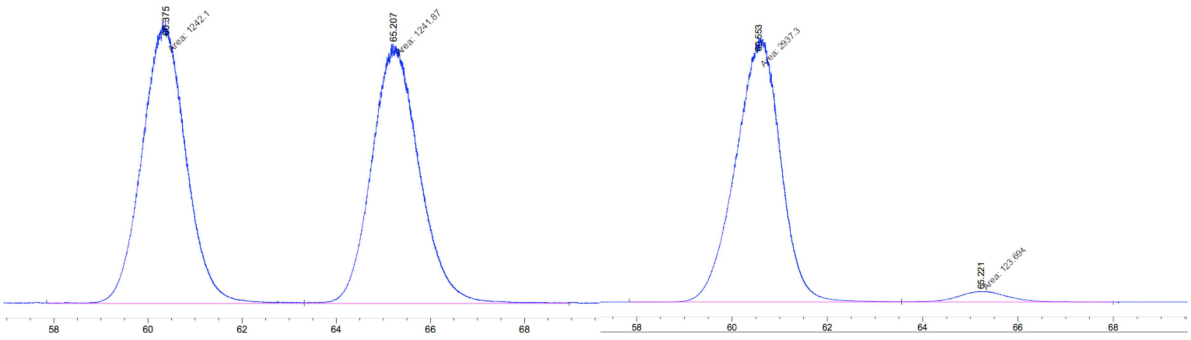
(*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (2.12). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, s, C**H$_3$**), 2.52 (1H, dd, *J* = 14.0, 7.0 Hz, C**H$_a$**H$_b$CH=CH2), 2.57 (1H, dd, *J* = 14.0, 7.0 Hz, CH$_a$**H$_b$**CH=CH2), 4.98-5.14 (4H, m, CCH=C**H$_2$** & CH$_2$CH=C**H$_2$**), 5.62 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.06 (1H, dd, *J* = 17.0, 11.0 Hz, CC**H**=CH$_2$), 7.18-7.22 (1H, m, Ar-**H**), 7.30-7.35 (4H, m, Ar**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 44.0, 45.5, 112.0, 117.2, 125.9, 126.6, 128.1, 135.1, 146.5, 147.0; IR (neat): 3080.8 (w), 3023.5 (w), 3004.7 (w), 2974.9 (w), 2921.5 (w), 1637.6 (w), 1599.9 (w), 1493.1 (w), 1444.5 (w), 1411.6 (w), 1371.5 (w), 1074.6 (w), 1028.9 (w), 995.7 (w), 911.0 (s), 764.2 (s), 697.3 (s) cm^{-1}; HRMS (ESI+) for $C_{13}H_{17}$ [M+H]: calculated: 173.1330, found: 173.1337; $[\alpha]^{20}_D$ = -4.46 (*c* = 1.54, $CHCl_3$).[34] The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (31.0 mg, 90% yield), with less than 5% elimination product. R*f* = 0.75 (8:1 hexane/EtOAc, stain in $KMnO_4$).

[34] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760.

Proof of Stereochemistry:

Enantioselectivity was determined by comparison of the title compound with racemic material prepared using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allylallyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2. Spectra data and optical rotation are in accordance with literature.[4]

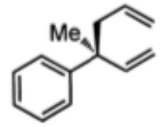
Chiral GC (CD-GTA, Supelco, 60 °C, 25 psi) - analysis of title compound



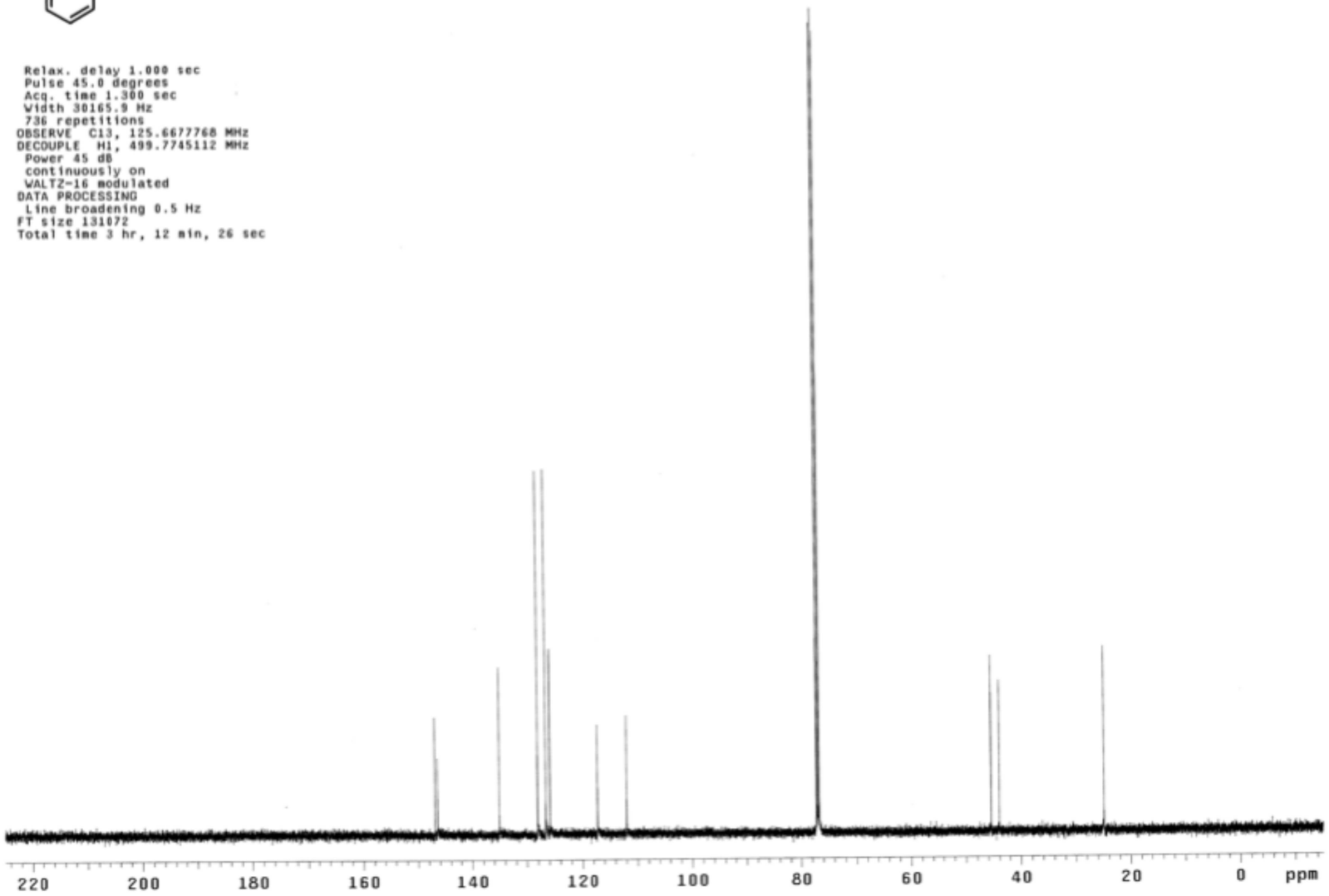
racemic reaction product

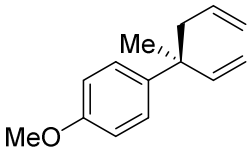
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	60.553	MF	1.0818	2937.30469	45.25162	95.95903
2	65.221	FM	1.1593	123.69395	1.77827	4.04097

Me
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7996.0 Hz
16 repetitions
OBSERVE H1, 499.7720254 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 12 sec
ppm
1
2
3
4
5
6
7
8
9



Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
736 repetitions
OBSERVE C13, 125.6677768 MHz
DECOUPLE H1, 499.7745112 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min, 26 sec

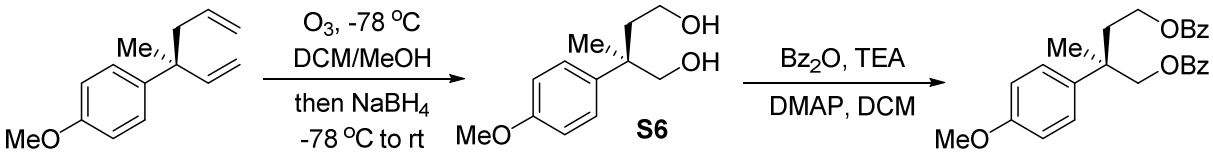




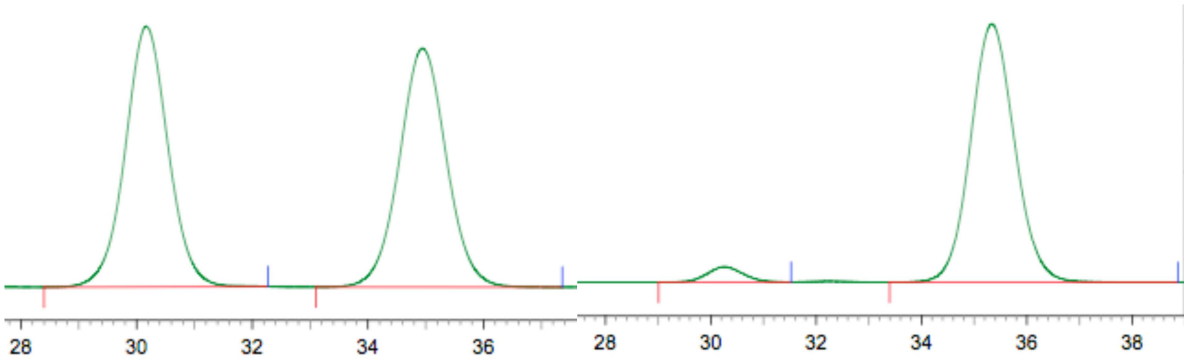
(*S*)-1-methoxy-4-(3-methylhexa-1,5-dien-3-yl)benzene (Table 2.2, entry 3, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (3H, s, C**H$_3$**), 2.48 (1H, dd, *J* = 14.0, 7.0 Hz, C**H$_a$**H$_b$CH=CH$_2$), 2.53 (1H, dd, *J* = 14.0, 7.0 Hz, CH$_a$**H$_b$**CH=CH$_2$), 3.79 (3H, s, OC**H$_3$**), 4.97-5.10 (4H, m, CCH=C**H$_2$** & CH$_2$CH=C**H$_2$**), 5.60 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.02 (1H, dd, *J* = 17.5, 11.0 Hz, CC**H**=CH$_2$), 6.83-6.86 (2H, m, Ar-**H**), 7.22-7.25 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 43.4, 45.6, 55.2, 111.7, 113.4, 117.1, 127.6, 135.2, 139.0, 146.8, 157.6; IR (neat): 3072.7 (w), 3000.7 (w), 2973.7 (w), 2933.0 (w), 2834.5 (w), 1637.1 (w), 1510.3 (s), 1296.3 (m), 1246.3 (s), 1181.1 (s), 1035.5 (s), 996.3 (m), 910.4 (s), 826.6 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}O$ [M+H]: calculated: 203.1436, found: 203.1443; $[\alpha]^{20}_D$ = -6.027 (*c* = 1.14, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (50:1 pentane/Et_2O) to afford a clear, colorless oil (42.0 mg, 83% yield), with 12:1 allyl-allyl coupling product to elimination product. R*f* = 0.56 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Proof of Stereochemistry:

The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester for HPLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by X-ray crystallographic analysis (anomalous dispersion) of the diol (**S6**).



Chiral HPLC (AD-H, Chirapak, 1 mL/min, 2% isopropanol, 220 nm) – analysis of 2-(4-methoxyphenyl)-2-methylbutane-1,4-diyl dibenzoate



racemic reaction product

Retention Time	Area	Area %	Height	Height %
30.257	55422548	4.61	1151133	5.53
35.337	1146702137	95.39	19674468	94.47
Totals	1202124685	100.00	20825601	100.00

X-ray Crystallographic Data for **S6**:

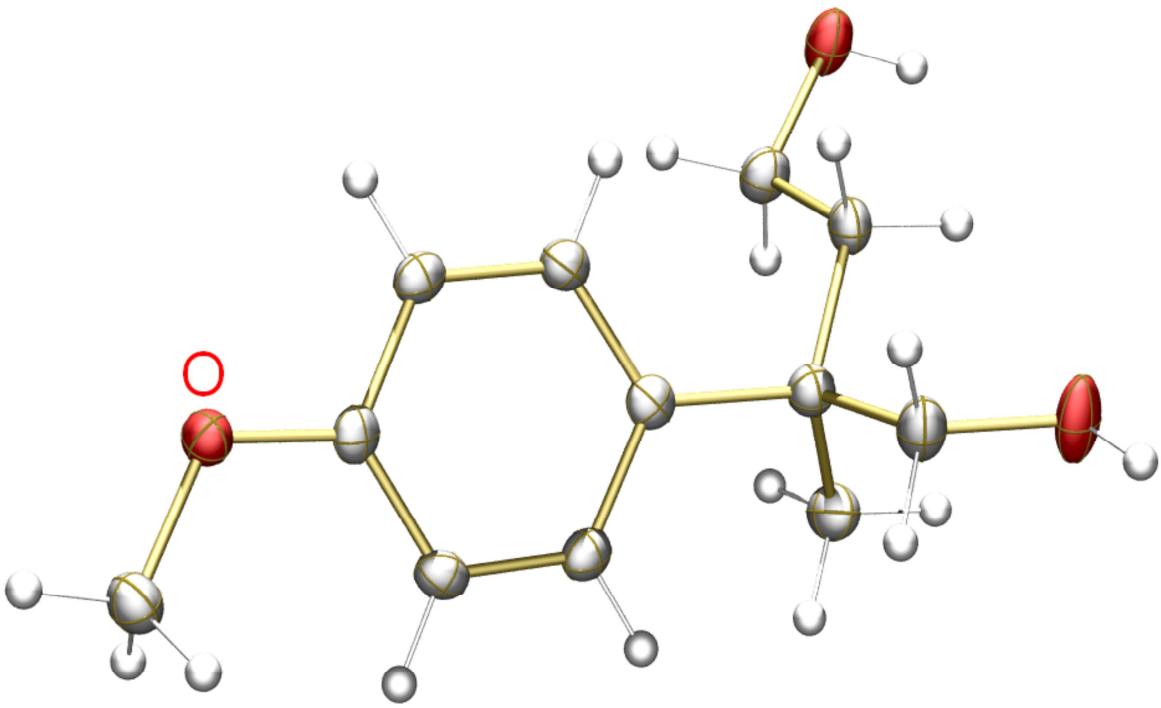


Table 1. Crystal data and structure refinement for $C_{12}H_{18}O_3$.

Identification code	$C_{12}H_{18}O_3$	
Empirical formula	$C_{12}\ H_{18}\ O_3$	
Formula weight	210.26	
Temperature	100(2) K	
Wavelength	1.54178 ≈	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.8880(2) ≈	α= 90∞.
	b = 7.5873(3) ≈	β= 101.821(2)∞.
	c = 12.5089(5) ≈	γ = 90∞.
	Volume 546.97(4) ≈3	
Z	2	
Density (calculated)	1.277 Mg/m3	
Absorption coefficient	0.732 mm-1	
F(000)	228	
Crystal size	0.10 x 0.06 x 0.02 mm3	
Theta range for data collection	3.61 to 68.16∞.	
Index ranges	-7<=h<=6, -9<=k<=8, -15<=l<=15	
Reflections collected	7510	
Independent reflections	1859 [R(int) = 0.0281]	
Completeness to theta = 68.16∞	98.1 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9855 and 0.9304
Refinement method	Full-matrix least-squares on F_2
Data / restraints / parameters	1859 / 3 / 142
Goodness-of-fit on F2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR_2 = 0.0828
R indices (all data)	R1 = 0.0325, wR_2 = 0.0838
Absolute structure parameter	0.05(19)
Extinction coefficient	na
Largest diff. peak and hole	0.216 and -0.158 e.≈-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3) for $C_{12}H_{18}O_3$. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	5875(2)	4852(1)	-1273(1)	22(1)
O(2)	14611(2)	1066(2)	3945(1)	28(1)
O(3)	13718(3)	7591(2)	4063(1)	35(1)
C(1)	7003(3)	4947(2)	-206(1)	18(1)
C(2)	9102(3)	4038(2)	63(1)	19(1)
C(3)	10404(3)	4103(2)	1116(1)	19(1)
C(4)	9658(3)	5045(2)	1945(1)	19(1)
C(5)	7537(3)	5908(2)	1655(1)	20(1)

C(6)	6206(3)	5870(2)	601(1)	19(1)
C(7)	3712(3)	5764(2)	-1573(1)	25(1)
C(8)	11174(3)	5300(2)	3089(1)	21(1)
C(9)	9724(3)	5231(3)	3982(1)	27(1)
C(10)	13205(3)	3989(2)	3359(1)	21(1)
C(11)	12571(3)	2069(2)	3496(1)	23(1)
C(12)	12204(3)	7156(2)	3056(1)	25(1)

Table 3. Bond lengths [≈] and angles [∞] for $C_{12}H_{18}O_3$.

O(1)-C(1)	1.3659(18)
O(1)-C(7)	1.430(2)
O(2)-C(11)	1.436(2)
O(2)-H(2O)	0.851(16)
O(3)-C(12)	1.425(2)
O(3)-H(3O)	0.839(17)
C(1)-C(6)	1.387(2)
C(1)-C(2)	1.395(2)
C(2)-C(3)	1.383(2)
C(2)-H(2B)	0.9500
C(3)-C(4)	1.401(2)
C(3)-H(3B)	0.9500
C(4)-C(5)	1.391(2)

C(4)-C(8)	1.536(2)
C(5)-C(6)	1.389(2)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(8)-C(12)	1.538(2)
C(8)-C(10)	1.539(2)
C(8)-C(9)	1.540(2)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.522(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(1)-O(1)-C(7)	117.36(12)
C(11)-O(2)-H(2O)	107.1(16)
C(12)-O(3)-H(3O)	110.6(17)

O(1)-C(1)-C(6)	124.63(14)
O(1)-C(1)-C(2)	116.05(13)
C(6)-C(1)-C(2)	119.32(14)
C(3)-C(2)-C(1)	120.19(14)
C(3)-C(2)-H(2B)	119.9
C(1)-C(2)-H(2B)	119.9
C(2)-C(3)-C(4)	121.77(14)
C(2)-C(3)-H(3B)	119.1
C(4)-C(3)-H(3B)	119.1
C(5)-C(4)-C(3)	116.60(14)
C(5)-C(4)-C(8)	120.21(14)
C(3)-C(4)-C(8)	122.88(14)
C(6)-C(5)-C(4)	122.65(14)
C(6)-C(5)-H(5A)	118.7
C(4)-C(5)-H(5A)	118.7
C(1)-C(6)-C(5)	119.45(14)
C(1)-C(6)-H(6A)	120.3
C(5)-C(6)-H(6A)	120.3O(1)-C(7)-H(7A)! 109.5
O(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
O(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5

C(4)-C(8)-C(12)	104.31(13)
C(4)-C(8)-C(10)	113.60(13)
C(12)-C(8)-C(10)	107.78(13)
C(4)-C(8)-C(9)	111.65(13)
C(12)-C(8)-C(9)	109.33(14)
C(10)-C(8)-C(9)	109.90(13)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(11)-C(10)-C(8)	116.45(14)
C(11)-C(10)-H(10A)	108.2
C(8)-C(10)-H(10A)	108.2
C(11)-C(10)-H(10B)	108.2
C(8)-C(10)-H(10B)	108.2
H(10A)-C(10)-H(10B)	107.3
O(2)-C(11)-C(10)	110.24(14)
O(2)-C(11)-H(11A)	109.6
C(10)-C(11)-H(11A)	109.6
O(2)-C(11)-H(11B)	109.6
C(10)-C(11)-H(11B)	109.6

H(11A)-C(11)-H(11B)	108.1
O(3)-C(12)-C(8)	111.52(13)
O(3)-C(12)-H(12A)	109.3
C(8)-C(12)-H(12A)	109.3
O(3)-C(12)-H(12B)	109.3
C(8)-C(12)-H(12B)	109.3
H(12A)-C(12)-H(12B)	108.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for $C_{12}H_{18}O_3$. The anisotropicdisplacement factor exponent takes the form: $-2\pi 2[\ h2\ a^*2U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U11	U22	U33	U23	U13	U12
O(1)	23(1)	21(1)	20(1)	0(1)	1(1)	2(1)
O(2)	40(1)	17(1)	24(1)	-1(1)	-6(1)	4(1)
O(3)	49(1)	13(1)	32(1)	1(1)	-15(1)	-4(1)
C(1)	22(1)	12(1)	20(1)	1(1)	2(1)	-3(1)
C(2)	22(1)	14(1)	22(1)	-1(1)	6(1)	-1(1)
C(3)	19(1)	15(1)	24(1)	1(1)	4(1)	0(1)
C(4)	20(1)	14(1)	22(1)	2(1)	4(1)	-2(1)

C(5)	22(1)	16(1)	23(1)	-2(1)	6(1)	-2(1)
C(6)	19(1)	14(1)	25(1)	3(1)	4(1)	2(1)
C(7)	23(1)	24(1)	26(1)	2(1)	1(1)	2(1)
C(8)	21(1)	18(1)	21(1)	-1(1)	2(1)	1(1)
C(9)	27(1)	31(1)	21(1)	-1(1)	3(1)	3(1)
C(10)	22(1)	20(1)	19(1)	0(1)	-1(1)	-1(1)
C(11)	29(1)	16(1)	24(1)	0(1)	3(1)	2(1)
C(12)	28(1)	17(1)	25(1)	1(1)	-4(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\approx^2$x 10^3)for $C_{12}H_{18}O_3$.

	x	y	z	U(eq)
H(2O)	15150(40)	1480(30)	4579(14)	43
H(3O)	14020(40)	8670(20)	4090(20)	52
H(2B)	9638	3373	-479	23
H(3B)	11842	3494	1282	23
H(5A)	6976	6549	2200	24
H(6A)	4762	6472	434	23
H(7A)	3081	5595	-2354	37
H(7B)	3956	7025	-1420	37
H(7C)	2616	5298	-1150	37

H(9A)	8439	6072	3808	40
H(9B)	10707	5536	4689	40
H(9C)	9103	4039	4019	40
H(10A)	14099	4054	2770	25
H(10B)	14246	4379	4043	25
H(11A)	11452	1993	3986	28
H(11B)	11822	1574	2777	28
H(12A)	13071	7218	2458	30
H(12B)	10928	8029	2901	30

Table 6. Torsion angles [∞] for $C_{12}H_{18}O_3$.

C(7)-O(1)-C(1)-C(6)	-0.4(2)
C(7)-O(1)-C(1)-C(2)	179.72(14)
O(1)-C(1)-C(2)-C(3)	177.96(13)
C(6)-C(1)-C(2)-C(3)	-1.9(2)
C(1)-C(2)-C(3)-C(4)	1.1(2)
C(2)-C(3)-C(4)-C(5)	0.1(2)
C(2)-C(3)-C(4)-C(8)	-173.51(15)
C(3)-C(4)-C(5)-C(6)	-0.6(2)
C(8)-C(4)-C(5)-C(6)	173.28(15)
O(1)-C(1)-C(6)-C(5)	-178.35(15)
C(2)-C(1)-C(6)-C(5)	1.5(2)

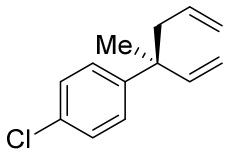
C(4)-C(5)-C(6)-C(1)	-0.3(2)
C(5)-C(4)-C(8)-C(12)	-74.41(18)
C(3)-C(4)-C(8)-C(12)	99.03(17)
C(5)-C(4)-C(8)-C(10)	168.51(14)
C(3)-C(4)-C(8)-C(10)	-18.1(2)
C(5)-C(4)-C(8)-C(9)	43.6(2)
C(3)-C(4)-C(8)-C(9)	-143.01(16)
C(4)-C(8)-C(10)-C(11)	-68.29(18)
C(12)-C(8)-C(10)-C(11)	176.66(14)
C(9)-C(8)-C(10)-C(11)	57.60(19)
C(8)-C(10)-C(11)-O(2)	-168.99(12)
C(4)-C(8)-C(12)-O(3)	-178.69(14)
C(10)-C(8)-C(12)-O(3)	-57.66(17)
C(9)-C(8)-C(12)-O(3)	61.77(18)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for $C_{12}H_{18}O_3$ [≈ and ∞].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(3)#1	0.851(16)	1.891(17)	2.7404(17)	175(2)
O(3)-H(3O)...O(2)#2	0.839(17)	1.865(18)	2.6989(18)	172(2)

Symmetry transformations used to generate equivalent atoms: #1 -x+3,y-1/2,-z+1 #2 x,y+1,z

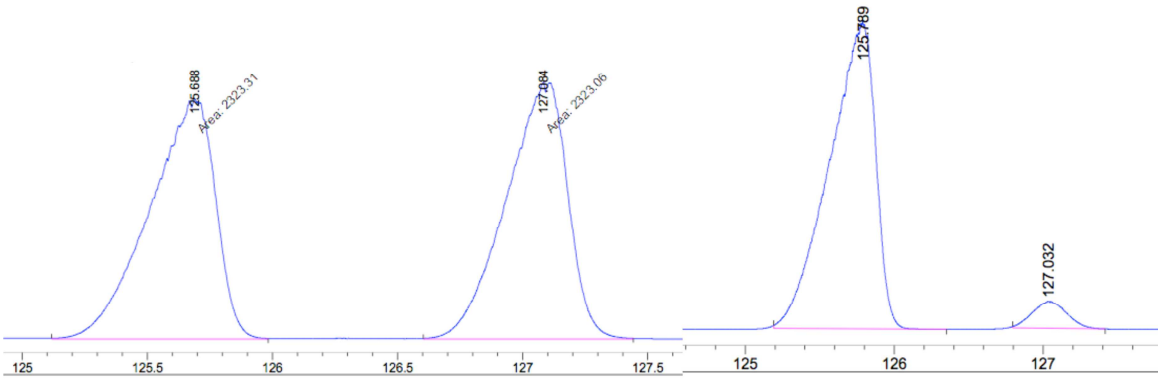


(*S*)-1-chloro-4-(3-methylhexa-1,5-dien-3-yl)benzene (Table 2.2, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (3H, s, CC**H$_3$**), 2.48 (1H, dd, *J* = 13.9, 7.2 Hz, C**H$_a$**H$_b$C=CH$_2$), 2.53 (1H, dd, *J* = 13.9, 7.2 Hz, CH$_a$**H$_b$**C=CH$_2$), 4.99-5.06 (3H, m, CCH=CH$_{cis}$**H$_{trans}$** & CH$_2$CH=C**H$_2$**), 5.13 (1H, d, *J* = 10.8 Hz, CCH=C**H$_{cis}$**), 5.57 (1H, dddd, *J* = 16.8, 9.8, 7.2, 7.2 Hz, CH$_2$C**H**=CH$_2$), 6.00 (1H, dd, *J* = 17.6, 10.8 Hz, CC**H**=CH$_2$), 7.24-7.28 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 43.8, 45.5, 112.4, 117.6, 128.1, 128.2, 131.7, 134.6, 145.5, 146.0; IR (neat): 3081.2 (w), 2924.1 (s), 2867.5 (m), 1638.9 (w), 1493.3 (s), 1461.0 (w), 1399.5 (w), 1372.0 (w), 1097.1 (m), 1012.8 (s), 995.8 (m), 915.6 (s), 825.2 (s), 748.7 (w), 536.6 (w) cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}Cl$ [M+H]: calculated: 207.0941, found: 207.0940; $[\alpha]^{20}_D$ = -2.087 (*c* = 0.40, $CHCl_3$). The unpurified material was purified on silica gel (pentane) to afford a clear, colorless oil (50.8 mg, 70% yield), with less than 5% elimination product. R*f* = 0.70 (pentane, stain in $KMnO_4$).

Proof of Stereochemistry:

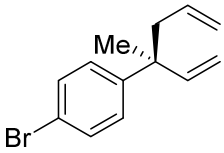
Enantioselectivity was determined by comparison of the title compound with racemic material prepared using 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

Chiral GC (CD-GTA, Supelco, 60 °C, 80 min, 1.0 deg/min to 120 °C, 25 psi)-analysis of title Compound



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	125.789	BB	0.2567	3800.16162	177.55411	93.86945
2	127.032	BB	0.1903	248.18599	15.54616	6.13055



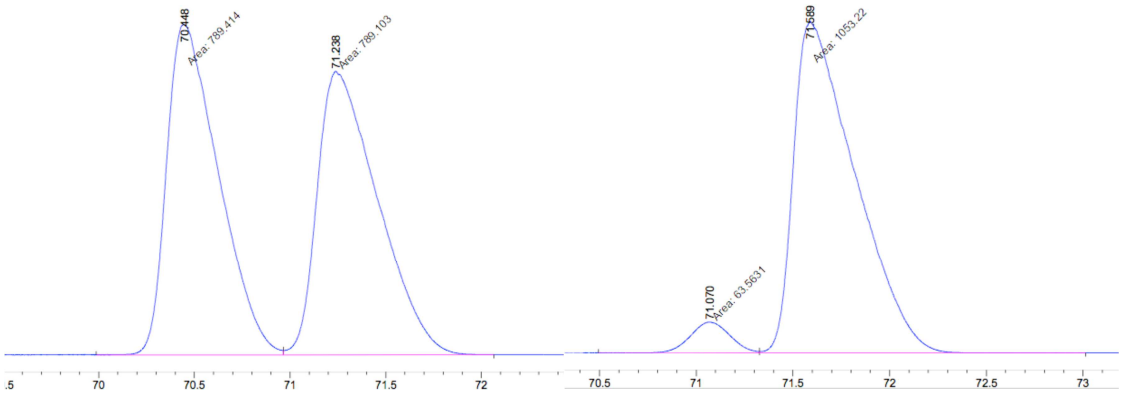
(*S*)-1-bromo-4-(3-methylhexa-1,5-dien-3-yl)benzene (Table 2.2, entry 5, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (3H, s, C**H$_3$**), 2.48 (1H, dd, *J* = 13.5, 7.5 Hz, C**H$_a$**H$_b$CH=CH$_2$), 2.52 (1H, dd, *J* = 13.5, 7.5 Hz, CH$_a$**H$_b$**CH=CH2), 4.99-5.06 (3H, m, CCH=CH$_{cis}$**H$_{trans}$** & CH$_2$CH=C**H$_2$**), 5.14 (1H, dd, *J* = 10.5, 1.0 Hz, CCH=C**H$_{cis}$**H$_{trans}$), 5.57 (1H, dddd, *J* = 17.0, 10.0, 7.5, 7.5 Hz, CH$_2$C**H**=CH$_2$), 6.00 (1H, dd, *J* = 17.5, 10.5 Hz, CC**H**=CH$_2$), 7.18-7.21 (2H, m, Ar-**H**), 7.40-7.43 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 43.9, 45.4, 112.5, 117.6, 119.8, 128.6, 131.1, 134.6, 145.9, 146.0; IR (neat): 3097.2 (w), 3004.2 (w), 2974.9 (w), 2919.3 (w), 2849.9 (w), 1637.9 (w), 1489.7 (m), 1412.9 (w), 1106.4 (m), 1007.5 (s), 912.5 (s), 818.9 (s), 729.3 (m), 533.8 (m) cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}Br$ [M+H]: calculated: 251.0435, found: 251.0430; $[\alpha]^{20}_D$ = -5.363 (*c* = 2.51,

$CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (44.7 mg, 90% yield), with 20:1 allyl allyl coupling product to elimination product. R*f* = 0.72 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Proof of Stereochemistry:

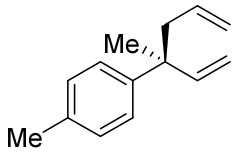
Enantioselectivity was determined by comparison of the title compound with racemic material prepared using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allylallyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

Chiral GC (β-dex, Supelco, 100 °C 10 min, ramp 0.5 deg/min to 180 °C, 25 psi) - analysis of title compound.



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	71.070	MF	0.2384	63.56308	4.44339	5.69163
2	71.589	FM	0.3674	1053.21863	47.77425	94.30837

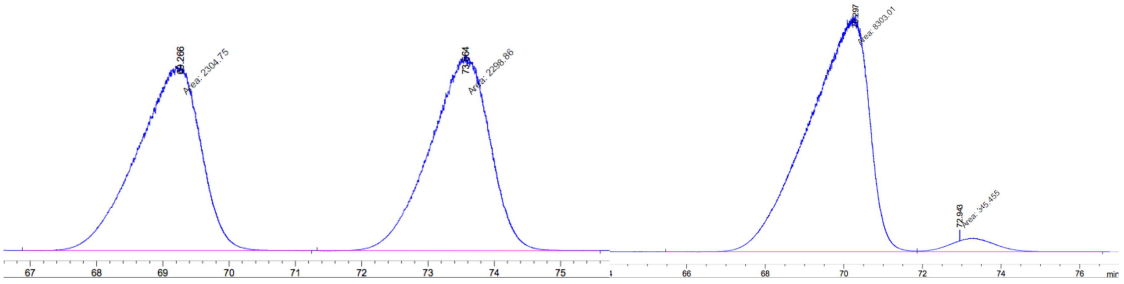


(*S*)-1-methyl-4-(3-methylhexa-1,5-dien-3-yl)benzene (Table 2.2, entry 6, product). ^{1}HNMR (500 MHz, $CDCl_3$): δ 1.35 (3H, s, C**H**$_3$CCH=CH_2), 2.33 (3H, s, ArC**H**$_3$), 2.50 (1H, dddd, *J* = 14.0, 7.0, 1.5, 1.5 Hz, C**H**$_a$H$_b$CH=CH_2), 2.55 (1H, dddd, *J* = 14.0, 7.0, 1.5, 1.5 Hz, CH$_a$**H**$_b$CH=CH_2), 4.97-5.06 (3H, m, CCH=CH$_{cis}$**H**$_{trans}$ & CH_2CH=C**H**$_2$), 5.11 (1H, dd, *J* = 10.5, 1.0 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.61 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, CH_2C**H**=CH_2), 6.03 (1H, dd, *J* = 17.0, 10.5 Hz, CC**H**=CH_2), 7.11-7.13 (2H, m, Ar-**H**), 7.21-7.23 (2H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 24.9, 43.7, 45.5, 111.8, 117.1, 126.5, 128.8, 135.2, 135.3, 144.0, 146.7; IR (neat): 3078.6 (w), 3003.5 (w), 2974.6 (w), 2921.4 (w), 1638.1 (s), 1512.9 (m), 1454.7 (w), 1412.8 (w), 1370.5 (w), 996.0 (m), 910.9 (s), 814.1 (s), 728.6 (m) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}$ [M+H]: calculated: 187.1487, found: 187.1477; $[\alpha]^{20}_D$ = -2.88 (*c* = 1.83, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (27.9 mg, 76% yield), with 17:1 allyl-allyl coupling product to elimination product. R_f = 0.63 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Proof of Stereochemistry:

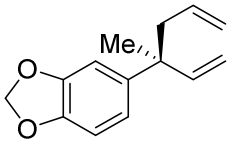
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

Chiral GC (CD-GTA, Supelco, 70 °C, 25 psi) - analysis of title compound.



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	70.297	MF	1.7618	8303.00879	78.54633	96.00559
2	72.943	FM	0.7885	345.45468	7.30192	3.99441

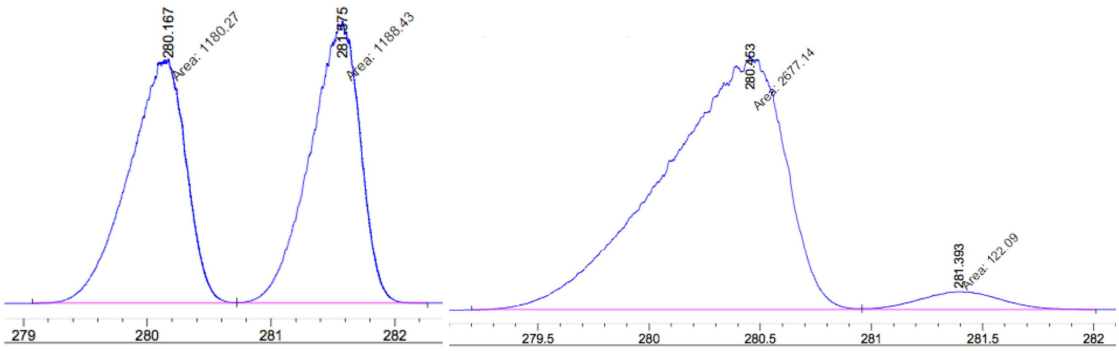


(*S*)-5-(3-methylhexa-1,5-dien-3-yl)benzo[*d*][1,3]dioxole (Table 2.2, entry 7, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, s, CC**H**$_3$), 2.46 (1H, dd, *J* = 13.8, 7.1 Hz, C**H**$_a$H$_b$CH=CH$_2$), 2.51 (1H, dd, *J* = 13.8, 7.1 Hz, CH$_a$**H**$_b$CH=CH$_2$), 4.98-5.03 (2H, m, CH$_2$CH=C**H**$_2$), 5.04 (1H, dd, *J* = 17.4, 1.1 Hz, CCH=CH$_{cis}$**H**$_{trans}$), 5.10 (1H, dd, *J* = 10.8, 1.1 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.60 (1H, dddd, 17.4, 10.3, 7.1, 7.1 Hz, CH$_2$C**H**=CH$_2$), 5.93 (2H, s, OC**H**$_2$O), 6.00 (1H, dd, *J* = 17.4, 10.8 Hz, CC**H**=CH$_2$), 6.73- 6.78 (2H, m, Ar-**H**), 6.82-6.84 (1H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 43.9, 45.6, 100.8, 107.6, 107.7, 111.9, 117.3, 119.5, 135.0, 141.1, 145.5, 146.6, 147.5; IR (neat): 3077.7 (w), 2971.8 (w), 2922.9 (w), 2775.6 (w), 1637.9 (w), 1503.8 (m), 1485.1 (s), 1431.9 (m), 1232.4 (s), 1039.7 (s), 938.4 (m), 912.5 (s), 808.5 (m), 554.3 (w) cm^{-1}; HRMS (ESI+) for $C_{14}H_{17}O_2$ [M+H]: calculated: 217.1229, found: 217.1224; $[\alpha]^{20}_D$ = -1.6 (*c* = 0.69, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (39.4 mg, 94% yield), with 6:1 allyl-allyl coupling product to elimination product. R_f = 0.39 (pentane, stain in $KMnO_4$).

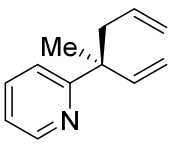
Proof of Stereochemistry:

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

Chiral GLC (CD-GTA, Supelco, 55 °C, 25 psi) analysis of title compound.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	280.453	MM	0.6316	2677.13745	70.64734	95.63845
2	281.393	MM	0.4152	122.08971	4.90134	4.36155



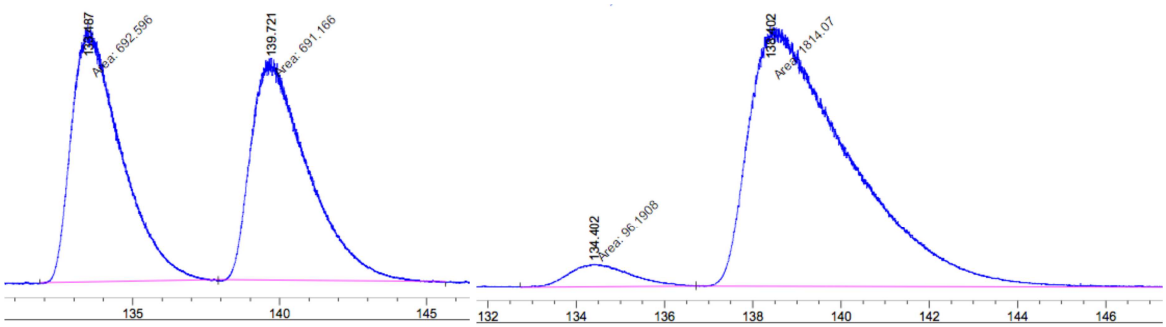
(*S*)-2-(3-methylhexa-1,5-dien-3-yl)pyridine (Table 2.2, entry 8, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (3H, s, CC**H**$_3$), 2.61 (1H, dddd, *J* = 13.9, 7.0, 1.3, 1.3 Hz, C**H**$_a$H$_b$CH=CH$_2$), 2.70 (1H, dddd, *J* = 13.9, 7.5, 1.3, 1.3 Hz, CH$_a$**H**$_b$CH=CH$_2$), 4.97 (1H, dddd, *J* = 9.6, 2.2, 1.3, 1.3 Hz, CH$_2$CH=C**H**$_{cis}$H$_{trans}$), 5.01 (1H, dddd, *J* = 17.0, 2.2, 1.3,

1.3 Hz, $CH_2CH{=}CH_{cis}\mathbf{H}_{trans}$), 5.09 (1H, dd, *J* = 17.5, 1.2 Hz, $CCH{=}CH_{cis}\mathbf{H}_{trans}$), 5.16 (1H, dd, *J* = 10.8, 1.2 Hz, $CCH{=}C\mathbf{H}_{cis}H_{trans}$), 5.62 (1H, dddd, *J* = 17.0, 9.6, 7.5, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 6.19 (1H, dd, *J* = 17.5, 10.8 Hz, $CC\mathbf{H}{=}CH_2$), 7.10 (1H, ddd, *J* = 5.9, 4.9, 1.2 Hz, Ar-**H**), 7.28 (1H, ddd, *J* = 8.1, 1.0, 1.0 Hz, Ar-**H**), 7.60 (1H, ddd, *J* = 8.0, 7.3, 1.9 Hz, Ar-**H**), 8.59 (1H, dq, *J* = 4.7, 1.0 Hz, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5, 45.0, 46.7, 112.6, 117.3, 121.0, 121.1, 135.1, 136.1, 145.5, 148.8, 165.9; IR (neat): 3079.3 (w), 3004.4 (m), 2975.2 (m), 2926.7 (w), 1638.1 (m), 1587.5 (s), 1569.7 (m), 1468.5 (m), 1430.0 (m), 1047.1 (m), 913.4 (s), 788.4 (m), 747.1 (s), 402.7 (w) cm^{-1}; HRMS (ESI+) for $C_{12}H_{16}N$ [M+H]: calculated: 174.1283, found: 174.1291; $[\alpha]^{20}_D$ = +28.4 (*c* = 0.36, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (19:1 pentane/Et_2O) to afford a clear, colorless oil (40.0 mg, 81% yield), with less than 5% elimination product. R_f = 0.26 (9:1 pentane/Et_2O, stain in $KMnO_4$).

Proof of Stereochemistry:

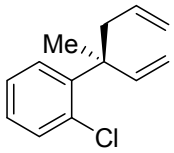
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, table 2.2.

Chiral GC (CD-GTA, Supelco, 55 °C, 25 psi)-analysis of title compound.



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	134.402	MM	1.6146	96.19075	9.92949e-1	5.03547
2	138.402	MM	2.6311	1814.07385	11.49119	94.96453



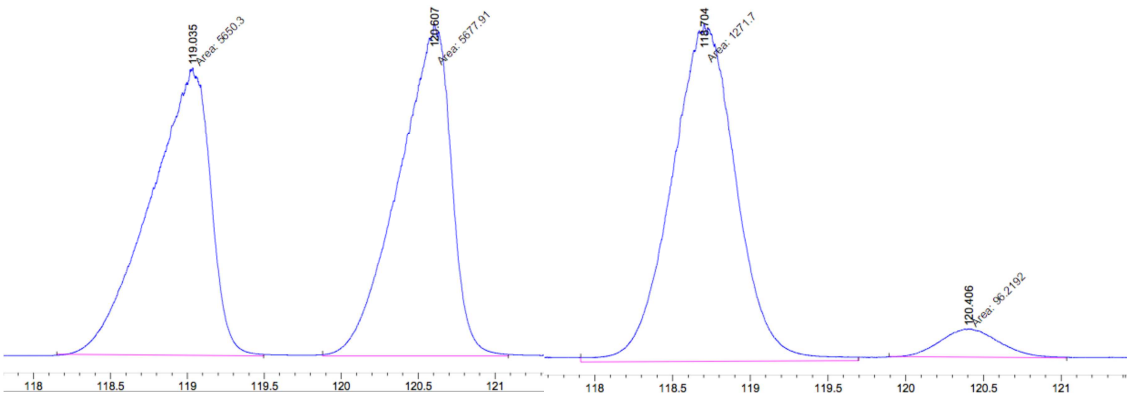
***(S)*-1-chloro-2-(3-methylhexa-1,5-dien-3-yl)benzene (Table 2.2, entry 9).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (3H, s, CC**H**$_3$), 2.63 (1H, dd, *J* = 13.9, 7.2 Hz, C**H**$_a$H$_b$CH=CH$_2$), 3.02 (1H, dd, *J* = 13.9, 7.2 Hz, CH$_a$**H**$_b$CH=CH$_2$), 4.93-4.96 (m, 2H, CCH=CH$_{cis}$**H**$_{trans}$ & CH$_2$CH=C**H**$_{cis}$H$_{trans}$), 5.03 (1H, m, CH$_2$CH=CH$_{cis}$**H**$_{trans}$), 5.10 (1H, dd, *J* = 10.7, 1.0 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.52 (1H, dddd, *J* = 17.0, 10.3, 7.2, 7.2 Hz, CH$_2$C**H**=CH$_2$), 6.20 (1H, dd, *J* = 17.6, 10.7 Hz, CC**H**=CH$_2$), 7.14-7.17 (1H, m, Ar-**H**), 7.19-7.22 (1H, m, Ar-**H**), 7.33-7.35 (1H, m, Ar-**H**), 7.36-7.38 (1H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 42.9, 45.0, 112.3, 117.3, 126.4, 127.6, 129.2, 131.7, 133.8, 134.8, 143.2, 145.7; IR (neat): 3077.2 (w), 3003.9 (w), 2975.9 (w), 2921.8 (w), 1638.5 (w), 1468.2 (m), 1430.2 (m), 1411.7 (m), 1037.9 (m), 993.6 (m), 913.6 (s), 860.0 (m), 757.0 (m) cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}Cl$ [M+H]: calculated: 207.0941, found: 207.0940. $[\alpha]^{20}_D$ = -26.0 (*c* = 0.97, $CHCl_3$). The unpurified reaction

mixture was purified on silica gel (pentane) to afford a clear, colorless oil (38.3 mg, 97% yield), with 4:1 allyl-allyl coupling product to elimination product. R_f = 0.58 (pentane, stain in $KMnO_4$).

Proof of Stereochemistry:

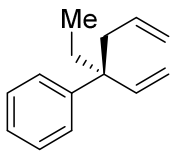
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

Chiral GC (CD-GTA, Supelco, 60 °C, 80 min, 1.0 deg/min to 120 °C, 25 psi)-analysis of the title compound.



racemic reaction product

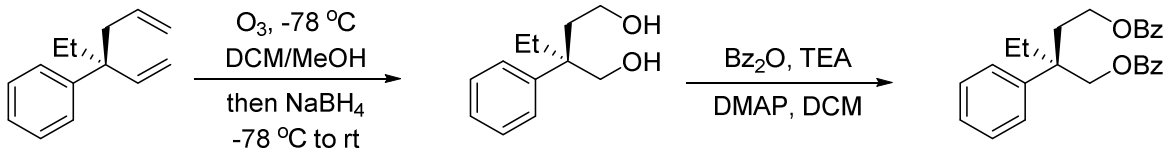
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	118.704	MM	0.4831	1271.70264	43.87696	92.96603
2	120.406	MM	0.4385	96.21922	3.65722	7.03397



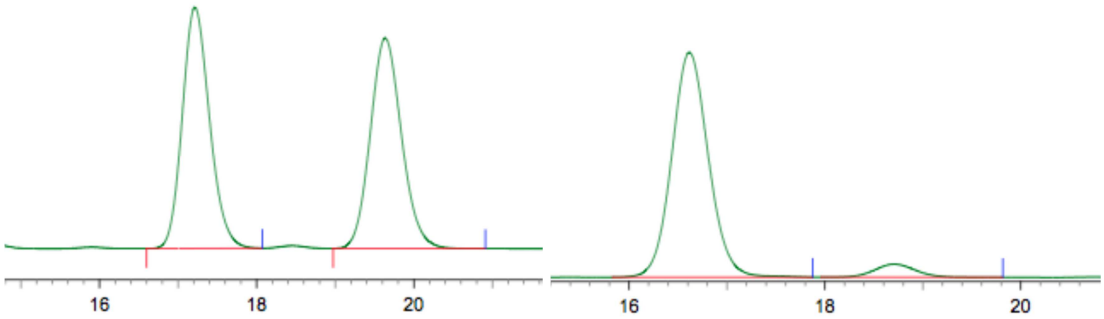
(*S*)-(3-ethylhexa-1,5-dien-3-yl)benzene (Table 2.3, entry 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.78 (1H, dq, *J* = 13.5, 7.5 Hz, C**H**$_a$H$_b$CH$_3$), 1.84 (1H, dq, *J* = 13.5, 7.5 Hz, CH$_a$**H**$_b$CH$_3$), 2.55 (2H, d, *J* = 7.0 Hz, C**H**$_2$CH=CH$_2$), 4.98 (1H, dddd, *J* = 10.5, 2.5, 1.5, 1.0 Hz, CH$_2$CH=C**H**$_{cis}$H$_{trans}$), 5.02 (1H, dddd, *J* = 17.0, 2.0, 1.5, 1.0 Hz, CH$_2$CH=CH$_{cis}$**H**$_{trans}$), 5.10 (1H, dd, *J* = 17.5, 1.0 Hz, CCH=CH$_{cis}$**H**$_{trans}$), 5.22 (1H, dd, *J* = 11.0, 1.5 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.59 (1H, ddt, *J* = 17.5, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 5.94 (1H, dd, *J* = 17.5, 11.0 Hz, CC**H**=CH$_2$), 7.18-7.21 (1H, m, Ar-**H**), 7.29-7.33 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.3, 29.4, 41.2, 47.6, 113.0, 116.9, 125.8, 127.4, 127.9, 135.0, 145.2, 145.5; IR (neat): 3081.4 (w), 3023.4 (w), 3003.9 (w), 2969.5 (w), 2928.9 (w), 2878.8 (w), 1637.3 (w), 1599.2 (w), 1493.5 (w), 1445.0 (m), 1032.3 (m), 910.7 (s), 782.1 (m), 720.2 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}$ [M+H]: calculated: 187.1487, found: 187.1486; $[\alpha]^{20}_D$ = -18.3 (*c* = 0.87, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (34.9 mg, 97% yield), with 6:1 allyl-allyl coupling product to elimination product. R_f = 0.80 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

Proof of Stereochemistry:

The title compound was subjected to ozonolysis and reduction. The resulting diol was protected with benzoic anhydride to afford the dibenzoate ester for HPLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route through the use of 1,2-dis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, table 2.2.

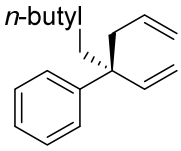


Chiral HPLC (AD-H, Chiralpak, 1mL/min, 2% isopropanol, 220 nm) – analysis of 2- ethyl-2-phenylbutane-1,4-diyl dibenzoate.



racemic reaction product

Retention Time	Area	Area %	Height	Height %
16.617	52915233	93.90	2028796	94.50
18.707	3435601	6.10	118052	5.50
Totals	56350834	100.00	2146848	100.00

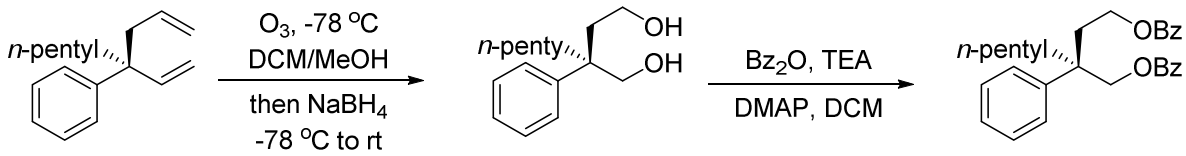


(*S*)-(4-vinylnon-1-en-4-yl)benzene (Table 2.3, entry 2, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.05-1.29 (6H, m, (C**H**$_2$)$_3$CH$_3$), 1.67-1.79 (2H, m, C**H**$_2$(CH$_2$)$_3$CH$_3$), 2.55 (2H, d, *J* = 7.5 Hz, C**H**$_2$CH=CH$_2$), 4.96-5.02 (2H, m, CH$_2$CH=C**H**$_2$), 5.08 (1H, dd, *J* = 17.0, 1.0 Hz, CCH=CH$_{cis}$**H**$_{trans}$), 5.19 (1H, dd, *J* = 10.5, 1.0 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.58 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 5.94 (1H, dd, *J* = 17.0, 10.5 Hz, CC**H**=CH$_2$), 7.16-7.20 (1H, m, Ar-**H**), 7.28-7.32 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.5, 23.4, 32.5, 37.1, 41.9, 47.3, 112.7, 116.9, 125.8, 127.3, 127.9, 135.1, 145.5, 145.8; IR (neat): 3081.1 (w), 3004.0 (w), 2930.7 (m), 2860.5 (w), 1637.5 (w), 1493.8 (w), 1445.3 (m), 1378.1 (w), 1073.2 (m), 910.6 (s), 697.8 (s) cm^{-1}; HRMS (ESI+) for $C_{17}H_{25}$ [M+H]: calculated: 229.1956, found: 229.1954; $[\alpha]^{20}_D$ = -5.29 (*c* = 1.69, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to

afford a clear, colorless oil (34.6 mg, 78% yield), with 6:1 allyl-allyl coupling product to elimination product. R_f = 0.86 (8:1 hexanes/EtOAc, stain in $KMnO_4$).

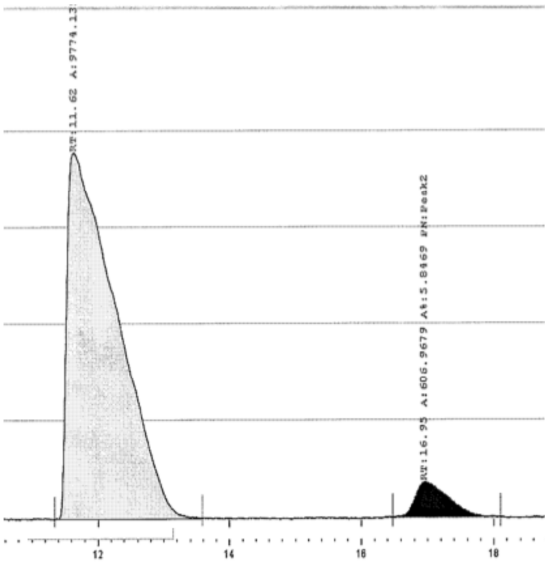
Proof of Stereochemistry:

The title compound was subjected to ozonolysis and reduction, as depicted below. The resulting diol was analyzed by chiral SFC. The analogous racemic material was prepared *via* the same route through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.



Chiral SFC (AS-H, Chiralpak, 3 mL/min, 3% methanol, 220 nm) – analysis of 2-pentyl-2-phenylbutane-1,4-diol.

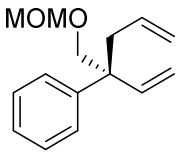
racemic



reaction product

Peak Name	Number	Concentration	Area %	Area	Area Sum
Peak1	1	0	94.1531	9774.1352	
Peak2	2	0	5.8469	606.9679	10381.1031

RT (min)	St. (min)	End (min)	Height
11.62	11.3404	13.5842	189.5781
16.95	16.4748	18.0968	17.9589

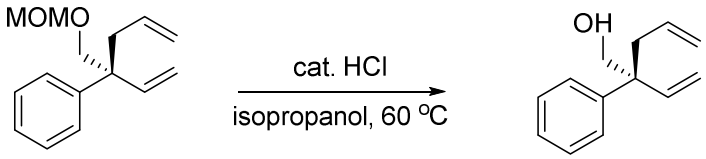


(*R*)-(3-((methoxymethoxy)methyl)hexa-1,5-dien-3-yl)benzene (Table 2.3, entry 3, product). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.67 (2H, d, *J* = 7.0 Hz, C**H**$_2$CH=CH$_2$), 3.25 (3H, s, OC**H**$_3$), 3.78 (1H, d, *J* = 9.0 Hz, CC**H**$_a$H$_b$O), 3.84 (1H, d, *J* = 9.0 Hz, CCH$_a$**H**$_b$O), 4.56 (1H, d, *J* = 6.5 Hz, OC**H**$_a$H$_b$O), 4.59 (1H, d, *J* = 6.5 Hz,

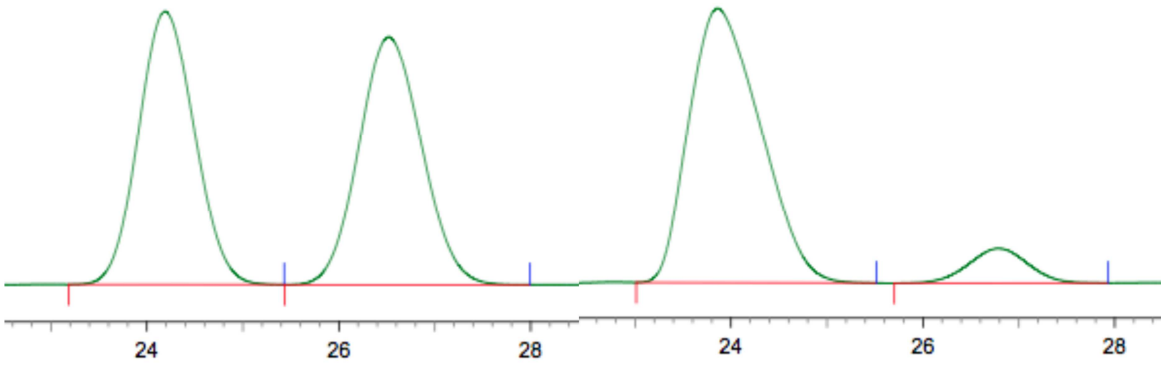
OCH$_a$**H**$_b$O), 5.01 (1H, dddd, *J* = 10.0, 2.0, 1.5, 1.0 Hz, CH$_2$CH=C**H**$_{cis}$H$_{trans}$), 5.06 (1H, dddd, *J* = 17.0, 2.0, 1.5, 1.0 Hz, CH$_2$CH=CH$_{cis}$**H**$_{trans}$), 5.12 (1H, dd, *J* = 17.0, 1.0 Hz, CCH=CH$_{cis}$**H**$_{trans}$), 5.26 (1H, dd, *J* = 11.0, 1.0 Hz, CCH=C**H**$_{cis}$H$_{trans}$), 5.64 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.04 (1H, dd, *J* = 17.0, 11.0 Hz, CC**H**=CH$_2$), 7.19-7.23 (1H, m, Ar-**H**), 7.30-7.36 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, CDCl$_3$): ' 40.3, 48.2, 55.3, 72.5, 96.7, 114.2, 117.7, 126.3, 127.4, 128.0, 134.4, 142.8, 143.4; IR (neat): 3170.5 (w), 3081.9 (w), 2978.5 (m), 2925.9 (w), 2822.2 (w), 1638.2 (w), 1600.1 (w), 1495.3 (w), 1466.8 (w), 1290.2 (w), 1215.8 (m), 1150.9 (m), 1110.5 (s), 998.5 (s), 748.5 (m) cm^{-1}; HRMS (ESI+) for C$_{15}$H$_{21}$O$_2$ [M+H]: calculated: 233.1542, found: 233.1551; $[\alpha]^{20}_D$ = +0.850 (*c* = 1.94, CHCl$_3$). The unpurified reaction mixture was purified on silica gel (100:1 pentane/Et$_2$O) to afford a clear, colorless oil (26.9 mg, 58% yield), with less than 5% elimination product. R$_f$ = 0.51 (8:1 hexanes/EtOAc, stain in KMnO$_4$).

Proof of Stereochemistry:

The title compound was subjected to acid-catalyzed MOM deprotection, as depicted below. The resulting alcohol was subjected to HPLC analysis. The analogous racemic material was prepared *via* the same route through the use of 1,2- bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.2.

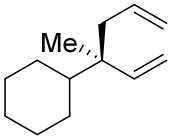


Chiral HPLC (OD-R, Chiracel, 0.5 mL/min, 2% isopropanol, 220 nm) – analysis of 2-phenyl-2-vinylpent-4-en-1-ol.



racemic reaction product

Retention Time	Area	Area %	Height	Height %
23.860	822324844	90.57	15924827	88.91
26.790	85579539	9.43	1987248	11.09
Totals	907904383	100.00	17912075	100.00



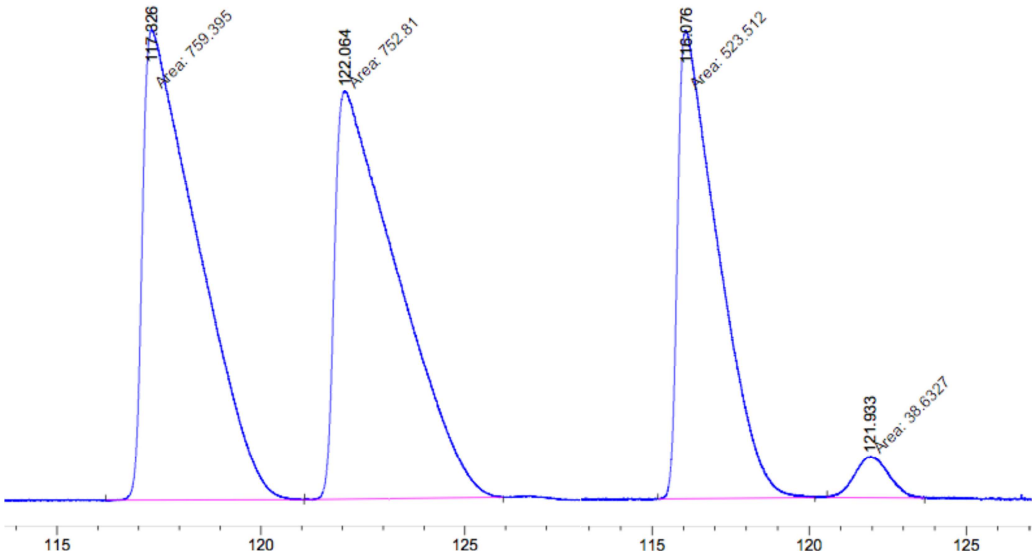
(*S*)-(3-methylhexa-1,5-dien-3-yl)cyclohexane (Table 2.4, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87-0.98 (m), 1.20-1.29 (m), 1.62-1.76 (m), 2.10 (2H, d, *J* = 7.0 Hz, CC**H**$_2$CH), 4.88 (1H, dd, *J* = 17.6, 1.5 Hz, CCH=C**H**$_a$H$_b$), 4.96-5.02 (3H, m, CCH=CH$_a$**H**$_b$ & CH$_2$CHC=C**H**$_2$), 5.70-5.79 (1H, m, CH$_2$C**H**=CH$_2$), 5.75 (1H, dd, *J* = 17.6, 8.7 Hz, CC**H**=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 19.2, 26.8, 27.1, 27.7, 42.2, 43.3, 45.8, 112.1, 116.5, 135.7, 146.1; IR (neat): 2924.6 (s), 2852.8 (m), 1638.3 (w), 1448.9 (m), 1374.2 (w), 1002.7 (w), 909.9 (m); HMRS (ESI+) for $C_{13}H_{22}$ [M+H]: calculated: 179.1805, found: 179.1800; $[\alpha]^{20}_D$ = +6.9 (*c* = 0.96, $CHCl_3$). The unpurified reaction mixture was purified on silica gel

(pentane) to afford a colorless oil (23.3 mg, 45% yield), with 7:1 allyl-allyl coupling product to elimination product. R_f = 0.83 (pentane, stain in $KMnO_4$).

Proof of Stereochemistry:

Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction.

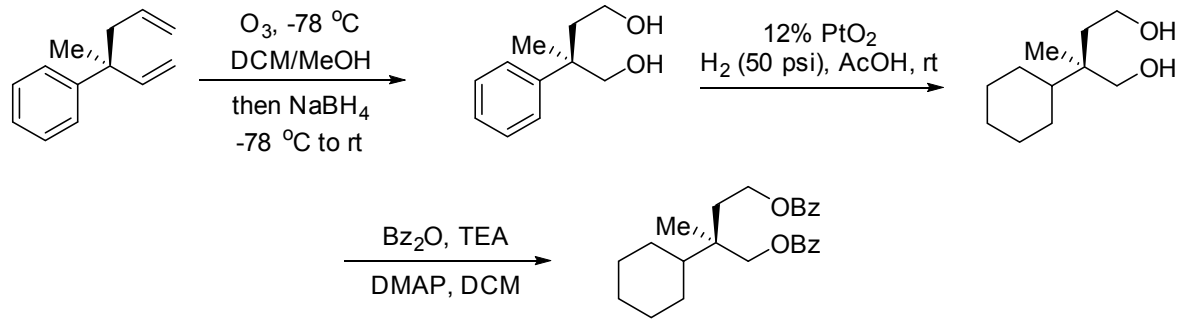
Chiral GC (CD-GTA, Supelco, 70 °C, 20 psi)-analysis of the title compound.

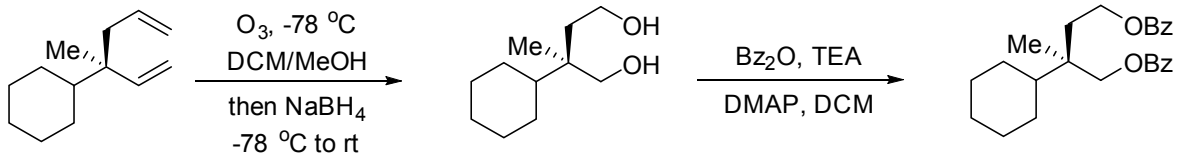


racemic reaction product

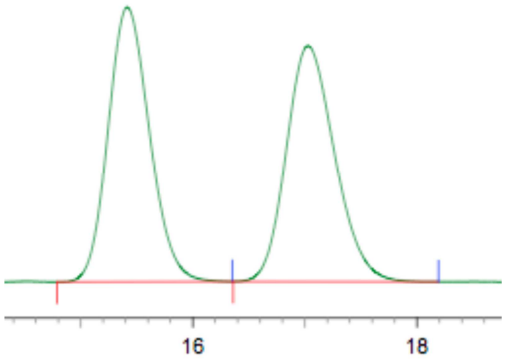
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	116.076	MM	1.4937	523.51239	5.84140	93.12763
2	121.933	MM	1.2522	38.63267	5.14192e-1	6.87237

Absolute stereochemistry was determined by converting the allyl-allyl coupling product to a dibenzoate by ozonolysis/reduction and dibenzoate protection of the corresponding diol, as shown below. *Via* chiral HPLC, the resulting dibenzoate was compared to the one derived from (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene from ozonolysis/reduction, hydrogenation and dibenzoate protection of the resulting diol, as depicted below.[35]



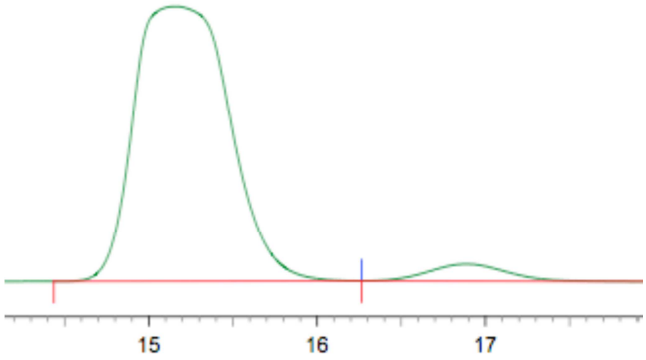


Chiral HPLC (AD-H, Chirapak, 0.5 mL/min, 2% isopropanol, 220 nm) – analysis of 2-cyclohexyl-2-methylbutane-1,4-diyl dibenzoate:

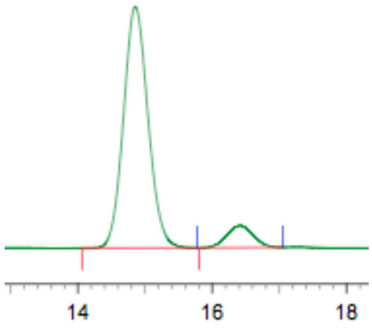


racemic

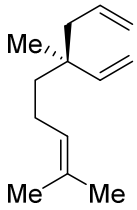
[35] For hydrogenation procedure, see: Hill, R. K.; Cullison, D. A. *J. Am. Chem. Soc.* **1973**, *95*, 1229.



derived from (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene



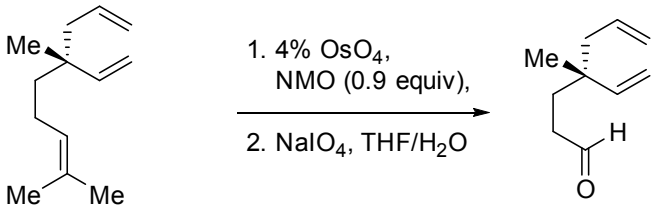
derived from reaction product



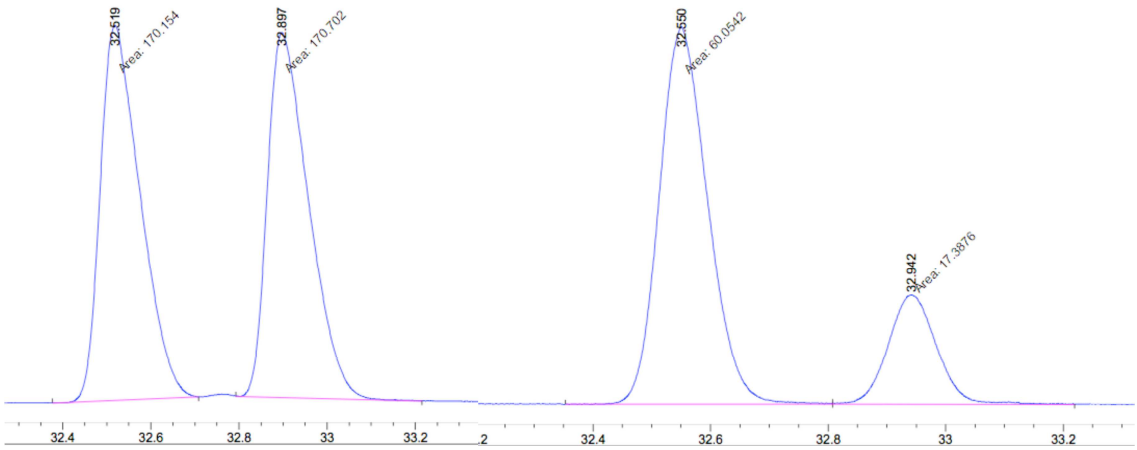
(*S*)-4,8-dimethyl-4-vinylnona-1,7-diene (Table 2.4, entry 2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (3H, s, CH_2=CHCC**H**$_3$), 1.26-1.34 (2H, m, C=CHCH_2C**H**$_2$), 1.58 (3H, s, (C**H**$_3$)$_a$(CH_3)$_b$C=CH), 1.67 (3H, s, (CH_3)$_a$(C**H**$_3$)$_b$C=CH), 1.88 (2H, ddd, *J* = 8.5, 8.0, 8.0 Hz, C=CHC**H**$_2$CH_2), 2.03-2.19 (2H, m, C**H**$_2$CH=CH_2), 4.91 (1H, dd, *J* = 18.0, 1.5 Hz, CCH=CH_{cis}**H**$_{trans}$), 4.98-5.03 (3H, m, CH_2CH=C**H**$_2$ &CCH=C**H**$_{cis}$H$_{trans}$), 5.07-5.10 (1H, m, (CH_3)$_2$C=C**H**), 5.71-5.80 (2H, m, CH_2C**H**=CH_2 & CC**H**=CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 22.7, 22.8, 25.7, 39.5, 40.4, 45.2, 111.7, 116.8, 124.9, 131.1, 135.3, 146.7; IR (neat): 3078.7 (w), 2966.6 (m), 2915.3 (m), 2855.5 (w), 1638.9 (w), 1439.9 (w), 1413.4 (w), 1374.8 (w), 996.4 (m), 910.4 (s), 832.7 (w) cm^{-1}; HRMS (ESI+) for $C_{13}H_{23}$ [M+H]: calculated: 179.1800, found: 179.1795; $[\alpha]^{20}_D$ = +7.45 (*c* = 0.97, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (32.6 mg, 96% yield), with 4:1 allyl-allyl coupling product to elimination product. R_f = 0.81 (8:1 hexane/EtOAc, stain in $KMnO_4$).

Proof of Stereochemistry:

The title compound was subjected to dihydroxylation/cleavage, as depicted below. The resulting aldehyde was subjected to chiral GC analysis. The analogous racemic material was prepared *via* the same route using 1,2- bis(diphenylphosphino)benzene as achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was assigned by analogy to entry 3, Table 2.3.



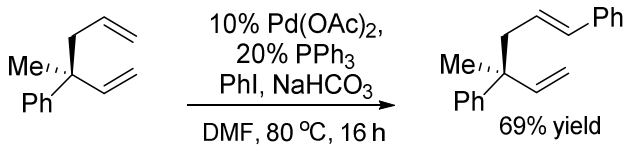
Chiral GC (β-dex, Supelco, 60 ◦C, 10 min, ramp 2 deg/min to 160 ◦C, 25 psi) - analysis of 4-methyl-4-vinylhept-6-enal

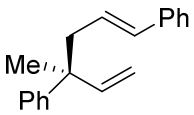


racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.550	MF	0.0952	60.05421	10.51814	77.54754
2	32.942	FM	0.0958	17.38759	3.02506	22.45246

E. **Functionalization of the Allyl-Allyl Coupling Products**

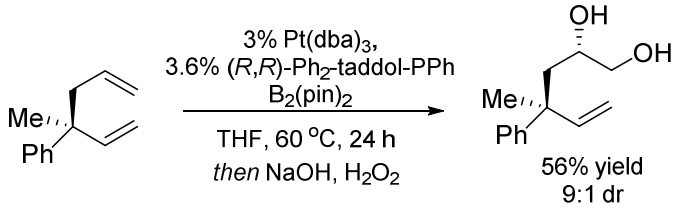


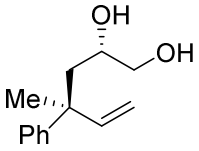


(*S*,*E*)-(4-methylhexa-1,5-diene-1,4-diyl)dibenzene (1.41):[36] To a flame-dried 2-dram vial equipped with a stir bar was added powdered molecular sieves (4 Å, 600 mg) and sodium bicarbonate (63.0 mg, 0.750 mmol). The vial was sealed with a septum and purged three times with N_2. DMF (1.5 mL) was then added by syringe, and the resulting suspension was allowed to stir at room temperature for 15 minutes. The septum was then removed, and triphenylphosphine (15.7 mg, 0.060 mmol) was added all at once to the reaction mixture. The septum was then replaced, and vial was charged with (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (51.6 mg, 0.300 mmol) and iodobenzene (97.9 mg, 0.480 mmol) *via* syringe. The vial was flushed with N_2 for 1 minute. The reaction was allowed to stir for another 15 minutes. The septum was removed again, and $Pd(OAc)_2$ (6.7 mg, 0.030 mmol) was quickly added all at once followed by immediate sealing with a screw cap. The reaction was heated in an oil bath to 80 °C and allowed to stir for 16 h. The red slurry was then cooled to room temperature and water and Et_2O were added. The organic layer was transferred out by a pipet and filtered through a plug of silica gel (bottom) and $MgSO_4$ (top), and the remaining aqueous layer was washed with more ether (3x) and the organics were filtered. The combined organics were concentrated *in vacuo* and purified by silica gel chromatography (100:1 hexanes/ EtOAc) to yield a clear, colorless oil (51.8 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (3H, s, C**H**$_3$), 2.66 (1H, dd, *J* = 14.0, 7.0 Hz, C**H**$_a$H$_b$CH=CHPh), 2.70 (1H, dd, *J* = 14.0, 7.0 Hz, CH$_a$**H**$_b$CH=CHPh), 5.09 (1H, ddd, *J* = 18.0, 1.5, 1.0 Hz, CH=CH$_{cis}$**H**$_{trans}$), 5.15 (1H, dt, *J* = 10.5, 1.0 Hz, CH=C**H**$_{cis}$H$_{trans}$),

[36] Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

6.02 (1H, dddd, J = 15.5, 8.0, 7.5, 1.5 Hz, $CH_2C\mathbf{H}$=CHPh), 6.10 (1H, ddd, J = 17.5, 11.0, 1.0 Hz, $C\mathbf{H}$=CH_2), 6.27 (1H, dd, J = 15.5, 1.5 Hz, CH_2CH=$C\mathbf{H}$Ph), 7.15-7.26 (6H, m, Ar-**H**), 7.30-7.37 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.1, 44.6, 44.7, 112.2, 125.95, 126.03, 126.6, 126.9, 127.0, 128.1, 128.4, 132.4, 137.7, 146.5, 147.0; IR (neat): 3082.3 (w), 3057.7 (w), 3025.6 (w), 2966.1 (w), 2927.0 (w), 1653.4 (s), 1598.6 (w), 1493.1 (m), 1444.7 (m), 1411.3 (w), 1371.7 (w), 965.2 (s), 908.2 (s), 733.9 (s), 696.5 (s) cm^{-1}; HRMS (ESI+) for $C_{19}H_{21}$ [M+H]: calculated: 249.1643, found: 249.1649. $[\alpha]^{20}_D = -45.3$ (c = 2.10, $CHCl_3$).

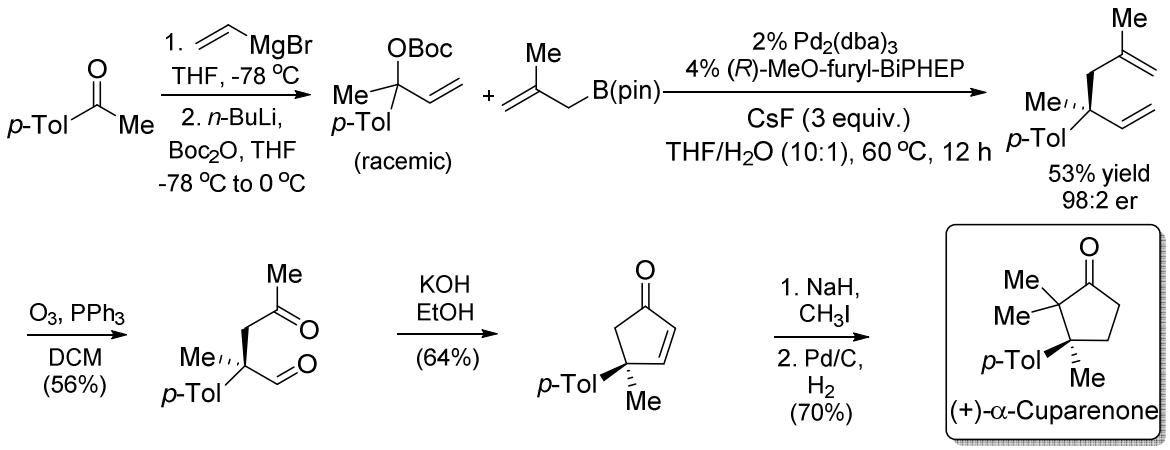


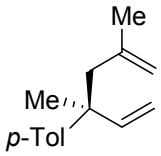


(*S*)-4-methyl-4-phenylhex-5-ene-1,2-diol (1.42):[28] In the dry-box an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar was charged with $Pt(dba)_3$ (8.1 mg, 0.009 mmol), 3,5-(*R*,*R*)-diphenylTADDOLPPh (12.3 mg, 0.010 mmol), $B_2(pin)_2$ (77.0 mg, 0.304 mmol) and THF (2.9 mL, 0.1 M). The vial was sealed with a polypropylene cap and removed from the dry-box. The solution was allowed to stir at 80 °C for 30 minutes, at which time the reaction was cooled to room temperature and brought back into the dry-box. (*S*)-(3-methylhexa-1,5-dien-3-yl)benzene (50.0 mg, 0.290 mmol) was then added to the reaction mixture. The vial was again sealed and removed from the dry-box. The reaction was heated to 60 °C and allowed to stir for 24 h. The reaction was then cooled to 0 °C (icewater bath) and charged with 3 M NaOH (2 mL) and 30% H_2O_2 (w/w) (1 mL). The resulting mixture was allowed to stir for 4 h while slowly warming to room temperature. The mixture was again cooled to 0 °C (ice-water bath) and quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), added drop-wise *via* syringe. The mixture was diluted with water (10 mL) and extracted with

EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash chromatography (silica gel, 1:1 pentane/EtOAc) to afford a clear, pale yellow oil (57.9 mg, 56% yield of title compound), with 1:1.3 desired product to pinacol. R_f = 0.28 (2:3 hexanes/EtOAc, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 3H, C**H**$_3$), 1.91 (2H, d, *J* = 5.4 Hz, C**H**$_2$CHOH), 2.24-2.72 (2H, m, 2(O**H**)), 3.31 (1H, dd, *J* = 11.1, 7.8 Hz, C**H**$_a$H$_b$OH), 3.39 (1H, dd, *J* = 11.1, 3.2 Hz, CH$_a$**H**$_b$OH), 3.66-3.70 (1H, m, CH$_2$C**H**OH), 5.10 (1H, d, *J* = 17.6 Hz, CH=CH$_{cis}$**H**$_{trans}$), 5.14 (1H, d, *J* = 10.9 Hz, CH=C**H**$_{cis}$H$_{trans}$), 6.14 (1H, dd, *J* = 17.6, 10.9 Hz, C**H**=CH$_2$), 7.18-7.21 (1H, m, Ar-**H**), 7.29-7.35 (4H, m, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 43.5, 44.2, 67.3, 69.6, 112.1, 126.2, 126.5, 128.3, 146.7, 147.1; IR (neat): 3364.9 (br, s), 3058.0 (w), 2973.9 (w), 2931.9 (w), 1634.4 (w), 1599.6 (w), 1444.7 (m), 1373.0 (m), 1154.3 (m), 1096.5 (m), 1061.5 (s), 1001.7 (m), 912.8 (s), 764.2 (s), 698.9 (s) cm^{-1}; HRMS (ESI+) for $C_{13}H_{19}O_2$ [M+H]: calculated: 207.1385, found: 207.1395. $[\alpha]_{20D}$ = +35.2 (*c* = 0.52, $CHCl_3$).

F. Synthesis of (+)-α-Cuparenone



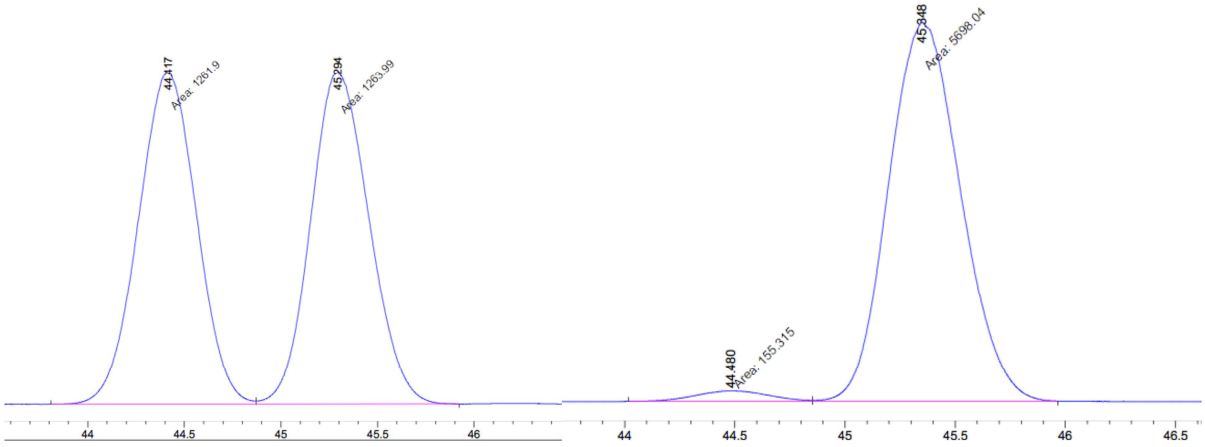


(*R*)-1-(3,5-dimethylhexa-1,5-dien-3-yl)-4-methylbenzene (2.20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (3H, s, ArCC**H**$_3$), 1.43 (3H, s, C**H**$_3$C=CH_2), 2.32 (3H, s, ArC**H**$_3$), 2.51 (1H, d, *J* = 13.3 Hz, CC**H**$_a$H$_b$C), 2.56 (1H, d, *J* = 13.3 Hz, CCH$_a$**H**$_b$C), 4.57 (1H, m, CH_3C=C**H**$_a$H$_b$), 4.77 (1H, m, CH_3C=CH$_a$**H**$_b$), 5.01-5.08 (2H, m, CCH=C**H**$_2$), 6.13 (1H, dd, *J* = 17.4, 10.8 Hz,CC**H**=CH_2), 7.12 (2H, d, *J* = 7.9 Hz, Ar-**H**), 7.25 (2H, d, *J* = 8.2 Hz, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1, 19.82, 19.87, 19.93, 19.98, 38.9, 44.8, 106.5, 109.7, 121.8, 123.9, 130.5, 138.4, 139.6, 142.8; IR (neat): 3080.7 (m), 3023.0 (w), 2968.1 (s), 2922.8 (s), 2874.4 (w), 1639.2 (m), 1512.5 (s), 1455.0 (m), 1412.2 (w), 1372.9 (m), 1074.3 (w), 1019.5 (w), 999.8 (w), 912.1 (s), 891.7 (s), 815.1 (s), 734.1 (w), 516.0 (w); HRMS (ESI+) for $C_{15}H_{21}$ [M+H]: calculated: 201.1643, found: 201.1645; $[\alpha]^{20}_D$ = -14.3 (*c* = 0.83, $CHCl_3$). The unpurified reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil (22.1 mg, 56 % yield), with less than 5% elimination product. R_f = 0.50 (pentane, stain in $KMnO_4$).

Proof of Stereochemistry:

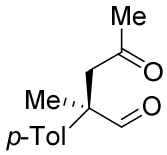
Enantioselectivity was determined by comparison of the title compound with racemic material prepared through the use of 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. Absolute stereochemistry was determined by converting the title compound to α-cuparenone, as depicted below, and comparing the optical rotation with (+)-α-cuparenone reported by the literature.[29]

Chiral GC (!-dex, Supelco, 130 °C, 60 min, 20 psi)-analysis of the title compound.

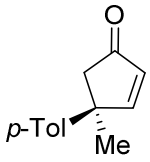


racemic reaction product

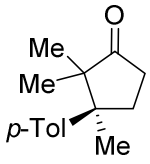
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	44.480	MF	0.3776	155.31520	6.85529	2.65344
2	45.348	FM	0.3797	5698.03809	250.10944	97.34656



(*R*)-2-methyl-4-oxo-2-*p*-tolylpentanal (2.21). To a round-bottom flask equipped with a stir bar was added (*S*)-1-(3,5-dimethylhexa-1,5-dien-3-yl)-4-methylbenzene (60.0 mg, 0.30 mmol) and CH_2Cl_2 (15 mL). The solution was cooled to -78 °C. O_3 gas was bubbled through the solution until a light blue color appeared. N_2 was re-introduced into the flask to remove excess O_3. When the solution went colorless, PPh_3 (393 mg, 1.5 mmol) in CH_2Cl_2 (1.0 mL) was added at once. The solution was warmed to room temperature and stirred under N_2 overnight. Solvent was removed *in vacuo*. The residue was purified by flash chromatography with hexanes/Et_2O (4:1) to afford (*R*)-2-methyl-4-oxo-2-*p*-tolylpentanal as a yellow oil (33.5 mg, 56% yield). Spectral data is in accordance with literature.[31]



(*S*)-4-methyl-4-*p*-tolylcyclopent-2-enone (2.22):[31b] To a round-bottom flask equipped with a stir bar was added (*R*)-2-methyl-4-oxo-2-*p*tolylpentanal (109.4 mg, 0.53 mmol), 1M KOH in EtOH (0.53 ml, 0.53 mmol), and THF (10 mL). The resulting solution was allowed to stir for 1h. Solvent was evaporated *in vacuo*, and the remaining residue was purified flash chromatography with hexanes/Et_2O (20:1 to 2:1) to afford (*S*)-4-methyl-4-*p*tolylcyclopent-2-enone as a colorless oil (62.7 mg, 70% yield). Spectral data is in accordance with literature.[31]



(+)-α-cuparenone: To a round-bottom flask equipped with a stir bar and charged with (*S*)-4,5,5-trimethyl-4-*p*-tolylcyclopent-2-enone (9.5 mg, 0.044 mmol) and Pd/C (4.7 mg, 10 mol %) was added EtOAc (1.0 mL). H_2 atmosphere (1 atm) was introduced. The solution was allowed to stir for 2 h at room temperature, then filtered over celite. The residue upon solvent evaporation *in vacuo* was purified by flash chromatography with hexane/Et_2O (9:1) to yield (+)-α-cuparenone (8.3 mg, 93% yield). Spectral data is in accordance with literature.[31] $[\alpha]^{20}_D = +170$ (*c* = 0.14, $CHCl_3$).

Chapter III: Synthesis of 1,5-dienes with Differentiated π-System

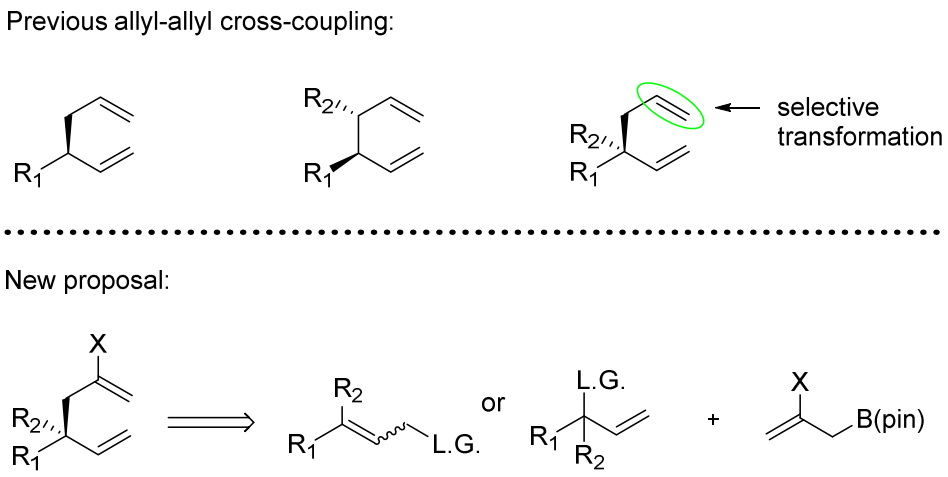
1,5-Diene compounds resemble the substructure of terpenes, an important class of natural products. The enzyme-catalyzed polyene cyclization of terpenes is the believed biosynthetic path to a wide range of diverse and complex natural products relevant in medicine.[1] For this reason, the branched and enantiomerically enriched 1,5-diene compounds have the potential to become powerful building blocks in complex molecular assembly. The synthesis of 1,5-dienes were advanced through the Pd-catalyzed allyl-allyl cross-coupling;[2] however, certain limitations remain. To be useful in long sequence synthesis, the ability to differentiate the olefins in the 1,5-diene system is a critical feature. In chapter II, examples of selective manipulation of a 1,5-diene containing an all-carbon quaternary center was illustrated. While the degree of chemoselectivity was extraordinary, the steric crowding requirement to differentiate the two olefins reduces the general application of these 1,5-dienes (Scheme 3.1) in complex synthesis.

To address the shortcoming, we proposed to preinstall a functional handle on one of the cross-coupling partners so that the product 1,5-diene can be readily differentiated. Three requirements are needed for this functional handle: (a) it must be easily installed on the coupling partner, (b) its presence must not affect the efficiency or selectivity of the cross-coupling process, and (c) it must easily be manipulated after the cross-coupling event. With these

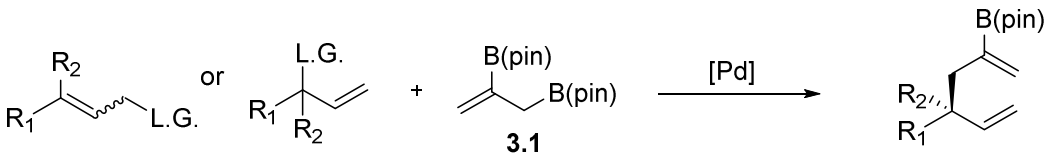
[1] (a) Breitmaier, E. Terpenes, Flavors, Fragrances, Pharmaca, Pheromones; Wiley-VCH: Weinheim, 2006. (b) Medicinal Natural Products: A Biosynthetic Approach; Dewick, P. M., Ed.; Wiley: Chichester, 2002.
[2] (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

requirements in mind, we turned our attention to diboron nucleophile **3.1** (Scheme 3.2). The allyl-allyl cross-coupling of **3.1** with allyl electrophiles will enable the syntheses of borylated 1,5-dienes. In this chapter, I will discuss in detail the synthesis of borylated 1,5-dienes via allyl-allyl cross-coupling and the selective modification of the product olefins.[3]

Scheme 3.1: Proposed Synthesis of Functionally Differentiated 1,5-Diene



Scheme 3.2: Allyl-Allyl Cross-Coupling of Diboron Nucleophile



[3] This work was accomplished in collaboration with Dr. Laura A. Brozek and Dr. Robert E. Kyne. Le, H.; Kyne, R. E.; Brozek, L. A.; Morken, J. P. *Org. Lett.* **2013**, *15*, 1432.

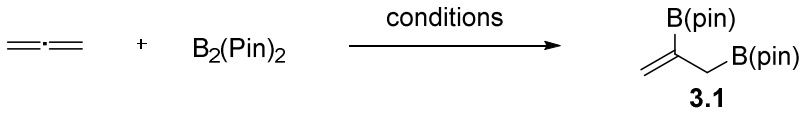
I. Optimization of Diboron Nucleophile 3.1

To implement **3.1** in the coupling reaction, a practical method to synthesize **3.1** is an important requirement. Formation of **3.1** from Pt-catalyzed diboration of allene was reported by Miyaura and coworkers.[4] Following their procedure, we were able to obtain **3.1** in >98% yield using 3% $Pt(PPh_3)_4$ catalyst loading and excess allene gas (entry 1, table 3.1). While this process provided high yield, the high catalyst loading is not desired. Attempts to lower the catalyst loading revealed that the allene diboration is effective at only 0.6% catalyst loading, and a reaction scale of up to 40 mmol (entry 3).

Given the low boiling point of allene (-34 ^oC), the requirement for elevated temperature in the Pt-catalyzed diboration is not preferred. Previously, our group developed the asymmetric diboration of substituted allenes using a Pd catalyst.[5] It was found that the use of palladium with electron rich phosphine ligands accelerated the reaction rate, and the reaction can be conducted at room temperature. Using a combination of 2.5% $Pd_2(dba)_3$ and 6% PCy_3, >98% yield of **3.1** was obtained after 4 hours at room temperature (entry 4, table 3.1). Later experiments identified the optimized conditions to require only 0.25% $Pd_2(dba)_3$, 0.6% PCy_3, and 1.5 equivalents of allene gas. Under these conditions, the reaction was carried out on a 24 mmol scale and >98% yield of **3.1** was obtained.

[4] Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357.
[5] (a) Pelz, N. F.; Woodward,A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328. (b) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

Table 3.1: Synthesis of 3.1 via Metal-Catalyzed Diboration



+ $B_2(Pin)_2$

3.1

entry	catalyst	temp (°C)	scale (mmol)	yield[a] (%)
1[b]	3% $Pt(PPh_3)_4$	80	1	>98
2[b]	0.3% $Pt(PPh_3)_4$	80	20	88
3[b]	0.6% $Pt(PPh_3)_4$	80	40	>98
4[b, c]	2.5% $Pd_2(dba)_3$/6% PCy_3	rt	10	>98
5[d]	0.25% $Pd_2(dba)_3$/0.6% PCy_3	rt	24	>98

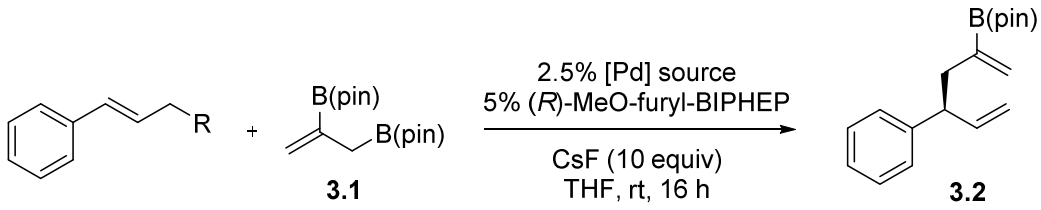
[a] Yields are an average of two or more experiments. [b] Excess allene was used, and reactions were carried out in a high pressure vessel. [c] Reaction was run in a round-bottom flask, under a positive N_2 atmosphere. [d] 1.5 equiv of allene was employed.

II. Optimizations for Allyl-Allyl Cross-Coupling Using Diboron Nucleophile 3.1

Having a practical and reliable method to synthesize the coupling partner **3.1**, we wanted to test its efficiency in the allyl-allyl cross-coupling reaction (Table 3.2). Applying previously studied conditions that use $Pd_2(dba)_3$, (*R*)-MeO-furyl-BIPHEP, and CsF additive, the cross-coupling reaction of acetate and Boc protected cinamyl alcohols with **3.1** resulted in incomplete conversion of the starting material (entry 1 and 2). Changing the starting material to a more reactive cinnamyl chloride substrate resulted in complete conversion under similar reaction conditions (entry 3); however, the desired 1,5-diene **3.2** was isolated in only 38% yield. Gratifyingly, the enantioselectivity of **3.2** was excellent at 99:1 er. To improve the yield of the reaction, other Pd catalysts were surveyed. Using 5% of $[cinnamylPdCl]_2$, **3.2** was formed in

66% yield, while [allylPdCl]$_2$ yielded 77% of the desired 1,5-diene (entry 4 and 5). More importantly, these conditions allow the allyl-allyl cross-coupling reaction to proceed effectively at room temperature and no prolonged heating was required, thus, simplifying the experimental setup. Selecting the conditions in entry 5 of Table 3.2 as the optimized conditions, the general applicability of nucleophile **3.1** was surveyed.

Table 3.2: Optimization results



entry	R	[Pd] source	Conversion[a]	Yield[b]	er[c]
1[d]	OAc	$Pd_2(dba)_3$	25	-	-
2	OBoc	$Pd_2(dba)_3$	80	-	-
3	Cl	$Pd_2(dba)_3$	100	38	99:1
4	Cl	[cinnamylPdCl]$_2$	100	66	99:1
5	Cl	[allylPdCl]$_2$	100	77	99:1

[a] Conversion was determined using ^{1}H NMR. [b] Yield were isolated yield of **3.2.** [c] er was determined by chiral GC. [d] Only 3 equiv of CsF was used.

III. Substrate Scope of the Pd-Catalyzed Allyl-Allyl Cross-Coupling Using Diboron Nucleophile 3.1

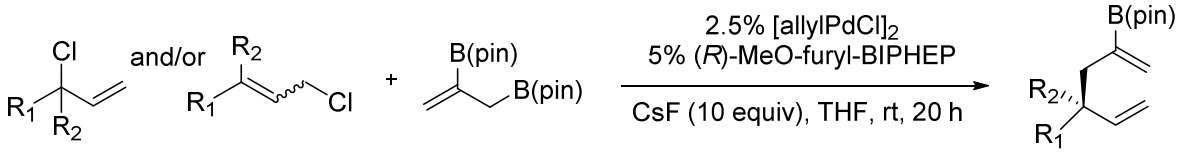
The substrate scope of the allyl-allyl cross-coupling using **3.1** as the nucleophile to synthesize 1,5-dienes with well differentiated π system was examined. Information for substrates

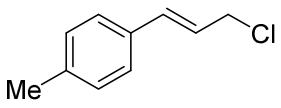
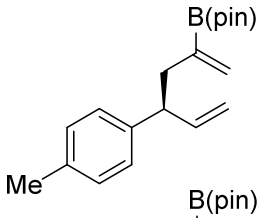
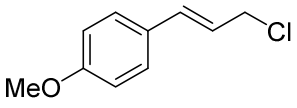
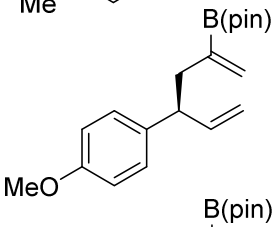
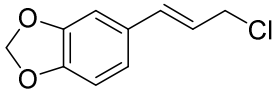
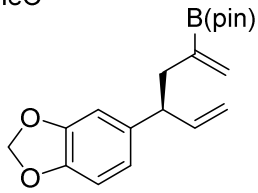
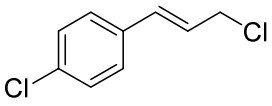
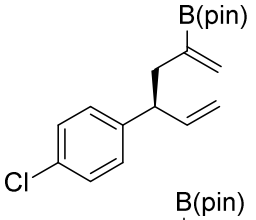
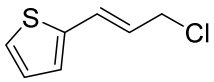
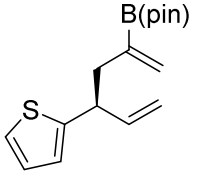
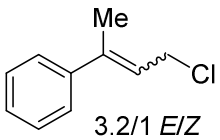
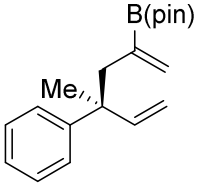
containing aromatic substituents are displayed in Table 3.3. The optimized condition was effective for a wide range of substrates. 1,5-Dienes containing substituents of varying electronic properties at the para position can be generated in good yields and excellent level of enantiopurity (entry 1-4). Substrates with substitution at both the *meta* and *para* position can also be well tolerated (entry 3). The example in entry 5 should be noted because this is the first time a starting material containing thiophene substitution, a common motif in medicinally relevant molecules, was employed in the allyl-allyl cross-coupling.[6] Lastly, under slightly more forcing conditions using 10% catalyst loading and heating to 60 ^{o}C, a 1,5-diene containing an all-carbon quaternary center was furnished in 44% yield and 97:3 er from nucleophile **3.1** and an E/Z mixture of the respective allylic chloride (entry 6).

Similar to aromatic substituted allyl electrophiles, aliphatic allylic chlorides can also be used effectively in the allyl-allyl cross-coupling with **3.1** (Table 3.4). Similar to previous findings in the allyl-allyl cross-coupling, (*R*,*R*)-QuinoxP* ligand provided superior reactivity and enantioselectivity compared to (*R*)-MeO-furyl-BIPHEP for aliphatic substrates (except for the cyclohexyl allyl chloride in entry 4). More interestingly, isomeric mixtures of the starting materials were employed in all examples, but only one isomer of the corresponding 1,5-diene was obtained. This observation further emphasizes the strength of the allyl-allyl cross-coupling method in which the rapid π-σ-π isomerization mechanism of π-allyl palladium complexes diminished the need for prochiral starting materials.[7] Lastly, substrates containing silyl protected alcohols can be utilized in the reaction, though Cs_2CO_3 base was used in place of CsF to avoid silyl deprotection of the alcohol (entry 3).

[6] Gronowitz, S. The Chemistry of Heterocyclic Compounds, Thiophene and Its Derivatives, John Wiley & Sons, 2009.
[7] See chapter I part II D and reference 2 for more detailed discussion.

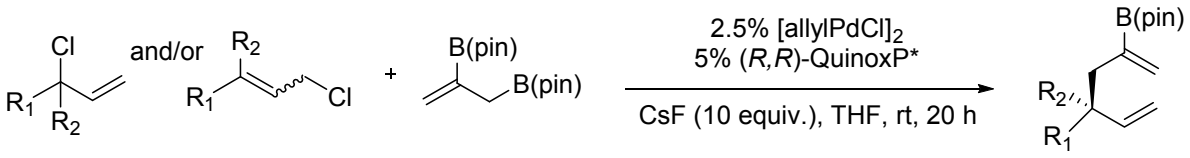
Table 3.3: Allyl-Allyl Cross-Coupling of Aromatic Substituted Starting Materials

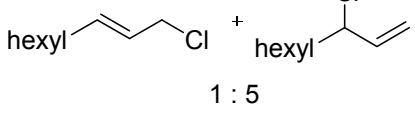
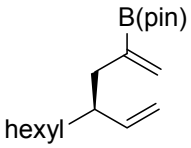
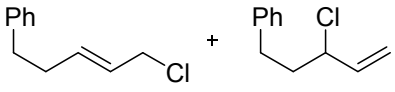
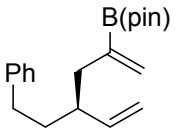
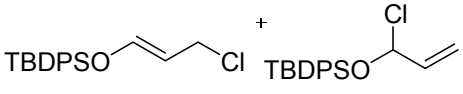
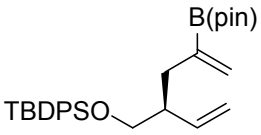
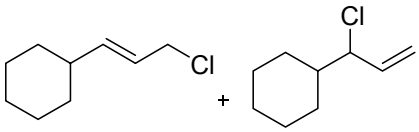
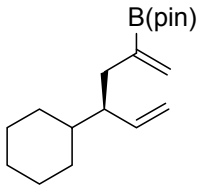


entry	Starting Material	Product	Yield[a]	er[b]
1			67	99:1
2			79	99:1
3			72	96:4
4			78	99:1
5			79	98:2
6[c]	 3.2/1 *E*/*Z*		44	97:3

[a] Yields are average of two or more experiments. [b] Ratios determined by chiral GC or chiral HPLC. [c] Reaction was carried out at 60 °C, 24 h, and in 20:1 THF/H_2O.

Table 3.4: Allyl-Allyl Cross-Coupling of Aliphatic Substituted Starting Materials



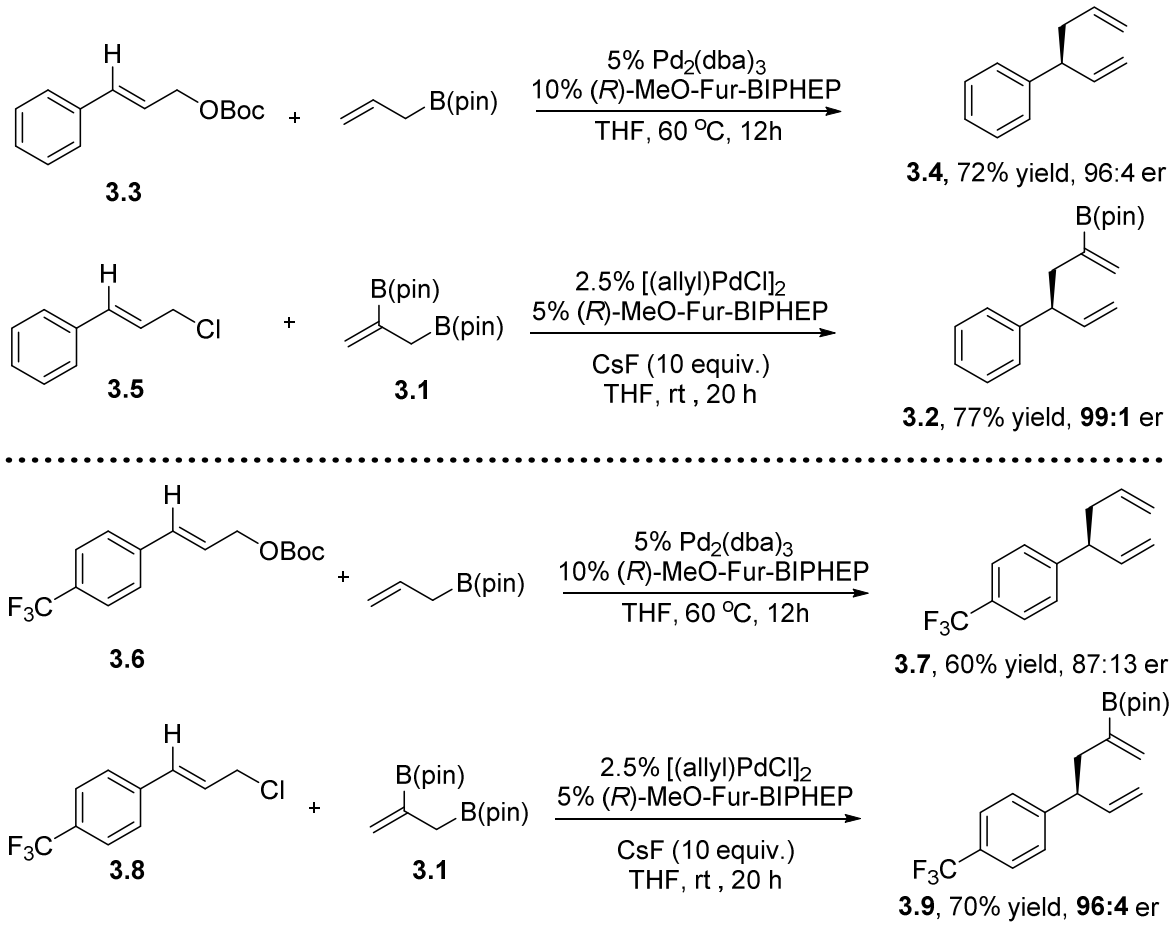
entry	Starting Material	Product	Yield[a]	er[b]
1	 1 : 5		72	95:5
2	 5 : 1		72	92:8
3[c]	 1 : 2		54	94:6
4[d]	 1 : 5		72	96:4

[a] Yields are average of two or more experiments. [b] Ratios determined by chiral GC or chiral HPLC. [c] Cs_2CO_3 was employed in place of CsF. [d] (*R*)-MeO-furyl-BIPHEP was used in place of (*R*,*R*)-QuinoxP*.

In addition to a general substrate scope, a significant advantage in the allyl-allyl cross-coupling with diboron nucleophile **3.1** was the enhanced enantioenrichment of the product 1,5-diene. As shown in the examples in Scheme 3.3, phenyl substituted 1,5-diene **3.4** was synthesized in 96:4 er from allylB(pin) and Boc protected cinnamyl alcohol **3.3**, while the analogous 1,5-diene **3.2** was obtained in 99:1 er using cinnamyl chloride **3.5** and **3.1**.[2a] The

enhancement effect was more profound when a substrate with a more electron withdrawing substituent was applied. Previously, 1,5-diene **3.7** was synthesized in only 87:13 er from allylB(pin) and **3.6**;[2a] when **3.1** was cross-coupled with electrophile **3.8**, 1,5-diene **3.9** was synthesized in 96:4 er.

Scheme 3.3: Improved Enantioenrichment with Diboron Nucleophile 3.1



To explain the enhancement effect, we propose the stereochemical models in Scheme 3.4. In this model, the two allyl fragment reacted through a chair-like transition state, which is dictated by the chiral environment provided by the ligand.[8] In the minor conformation which

[8] See Chapter 2, part II D for more detailed explanations.

leads to the minor enantiomer, the pendant B(pin) would introduced an additional interaction with the pseudoequatorial furyl ring of the phosphine ligand. This unfavorable steric interaction leads to improved enantioselectivity relative to the case of nonborylated nucleophiles.

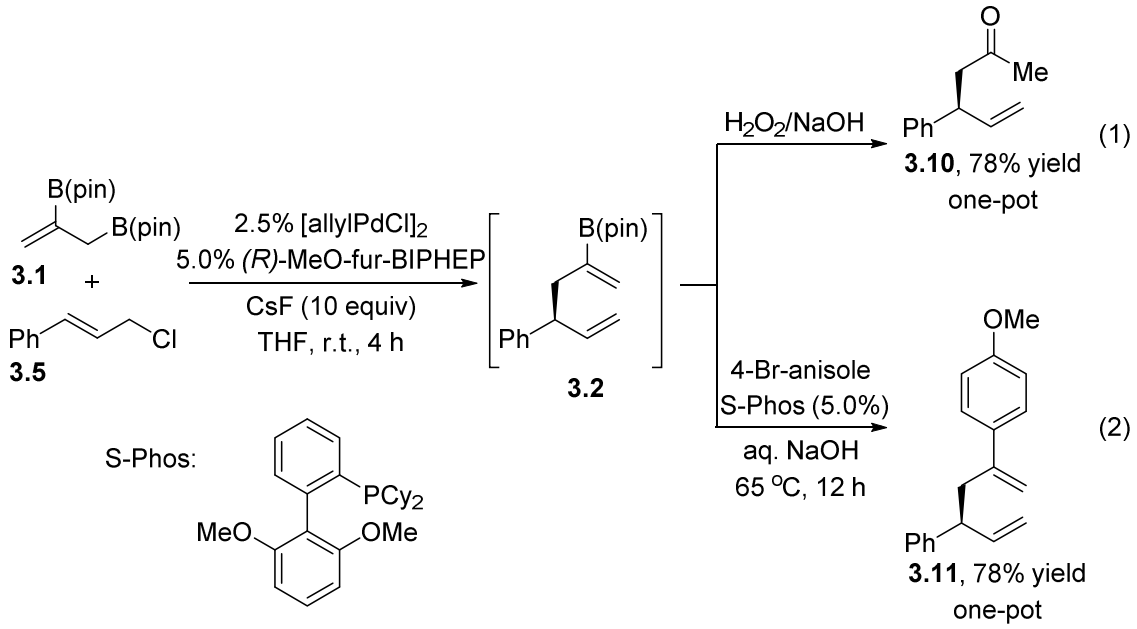
Scheme 3.4: Stereochemical Models for Allyl-Allyl Cross-Coupling Using Nucleophile 3.1

IV. Transformations of the Borylated 1,5-diene

The original objective of this project was to construct 1,5-dienes with well differentiated π-systems. Upon accomplishing the substrate scope studies, we were delighted to observe selective transformation of the borylated 1,5-diene compounds. While the borylated 1,5-dienes can be isolated in pure form using silica gel chromatography, we were interested in their direct conversion in a one pot fashion. As described in Scheme 3.5 (equation 1), upon completion of the initial cross-coupling sequence, the crude reaction was subjected to oxidation using H_2O_2 and NaOH. As expected, the vinylB(pin) was oxidized to form ketone **3.10** in 78% yield. Given the isolated yield of **3.2** was 77% (Table 3.2), the observed yield for **3.10** suggested that the second reaction sequence was essentially quantitative in yield. In a similar fashion, the crude reaction mixture was also treated with arylbromide and S-phos ligand to perform a Suzuki-Miyaura cross-coupling reaction (Scheme 3.5, equation 2). In this example, the corresponding cross-coupling

product **3.11** was formed in 78% yield over two steps. The spectacular feature in this sequence is that no additional palladium was necessary for the Suzuki-Miyaura sequence because the palladium from the initial cross-coupling reaction was still active and efficient. In both of these examples, the non-participating olefin of the 1,5-diene was left intact.

Scheme 3.5: One-pot Conversion of Borylated 1,5-Diene

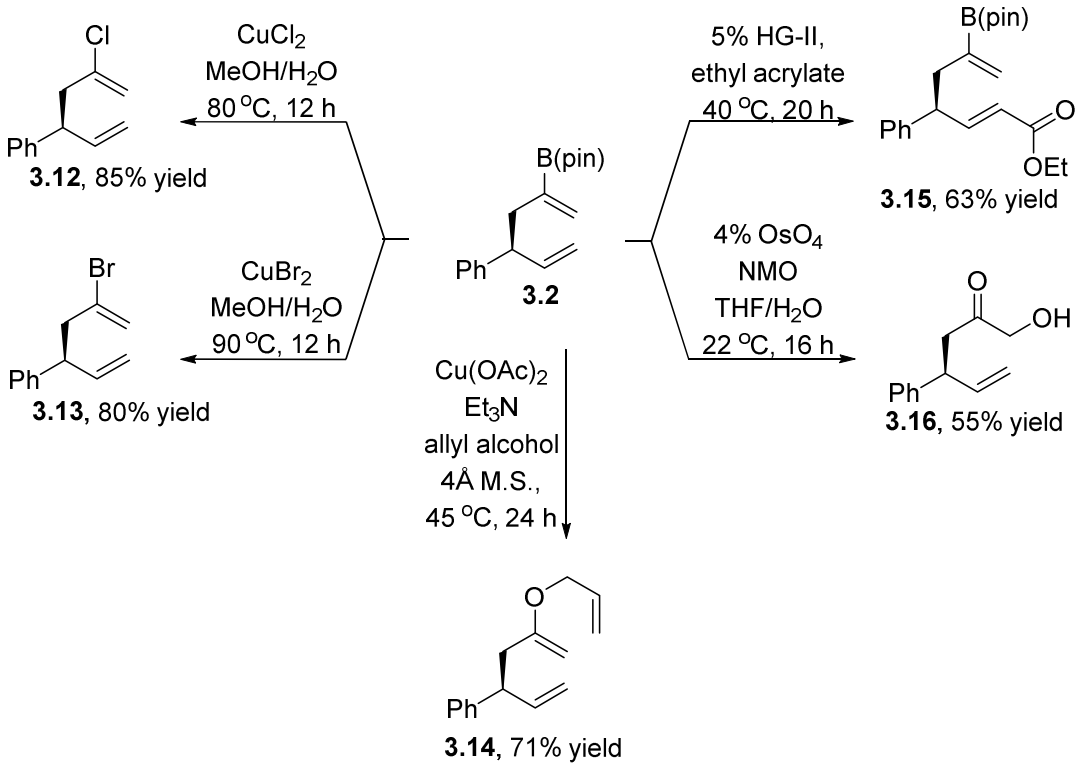


The isolated borylated 1,5-diene **3.2** can be selectively modified by several other transformations (Scheme 3.6). Upon treatment with $CuCl_2$ or $CuBr_2$ salt, the vinylB(pin) group was converted to the corresponding vinyl halide in excellent yield (**3.12** and **3.13**).[9] Following a copper(II) mediated sequence previously developed by Merlic *et al.*,[10] vinylB(pin) **3.2** underwent a Chan-Lam coupling reaction with allyl alcohol to form vinyl allyl ether **3.14** in 71% yield. In addition to transformations at the vinylB(pin) site, the monosubstituted olefin in this system can

[9] Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.
[10] (a) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am.Chem. Soc.* **2010**, *132*, 1202. (b) Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2010**, *12*, 2508.

also be selectively converted. It was found that the steric differentiation between the two olefins was sufficient to perform an olefin metathesis reaction with ethyl acrylate using Hoveyda-Grubbs 2nd generation catalyst to synthesize unsaturated ester **3.15**.[11] Lastly, **3.2** can be converted directly to an α-hydroxy ketone **3.16** under treatment with catalytic OsO_4 and NMO.[12] This observation indicated that the two olefins in the 1,5-diene system also have well differentiated electronic properties.

Scheme 3.5: Selective Transformation of Borylated 1,5-Diene



[11] (a) Garber, S. B.; Kingsbury, J. K.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussman, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (c) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. (d) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

[12] For related osmium-catalyzed dihydroxylation of vinylsilane: (a) Richer, J.-C.; Pokier, M. A.; Maroni, Y.; Manuel, G. *Can. J. Chem.* **1978**, *56*, 2049. (b) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 4260.

V. Conclusion

In this chapter, a method to synthesized enantioenriched 1,5-dienes with well differentiated π-systems from an allyl electrophile and diboron nucleophile **3.1** was described. Using the strategy to pre-functionalize the nucleophile fragment, the product's olefins are readily distinguished by both electronic and steric factors. The degree of differentiation has been studied through multiple transformations subsequent to the cross-coupling event. In addition, the use of diboron nucleophile **3.1** provided enhanced enantioselectivity compared to simple allylB(pin) previously studied.

VI. Experimental Procedure

A. General information

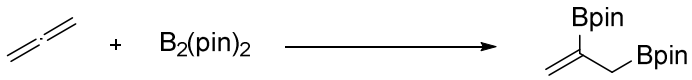
^{1}H NMR spectra were recorded on a Varian Gemini-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, υmax cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, ceric ammonium molybdate (CAM) in water, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral gasliquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco β-Dex 120 column, or a Supelco Asta Chiraldex B-DM with helium as

the carrier gas. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), Toluene (PhMe), and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Triethylamine (TEA) and Ethyl Acetate (EtOAc) were distilled from calcium hydride. Tetrakis(triphenylphosphine)platinum(0) [$Pt(PPh_3)_4$], tris(dibenzylideneacetone) dipalladium(0) [$Pd_2(dba)_3$], tricyclohexylphosphine (PCy_3), 1,2-bis(diphenylphosphino)benzene (dpp-Benzene), (*R*)-(+)-2,2′-bis(di-2-furanylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [(*R*)-MeO(furyl)BIPHEP], (*S*)-(-)-2,2′-bis(di-2-furanylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [(*S*)-MeO(furyl)BIPHEP], (*S*,*S*)-(-)-2,3-Bis(*t*butylmethylphosphino) quinoxaline [(*S*,*S*)-QuinoxP*], and (*R*,*R*)-(-)-2,3-Bis(*t* -butylmethylphosphino)quinoxaline [(*R*,*R*)-QuinoxP*], 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) were purchased from Strem Chemicals, Inc. Pinacolborane (pinBH) was generously donated by BASF. Allylboronic acid pinacol ester (allylBpin) was generously donated by Frontier Scientific. Bis(pinacolato) diboron [$B_2(pin)_2$] was generously donated by Allychem. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

B. Preparation of Diboron Reagent 3.1



3.1

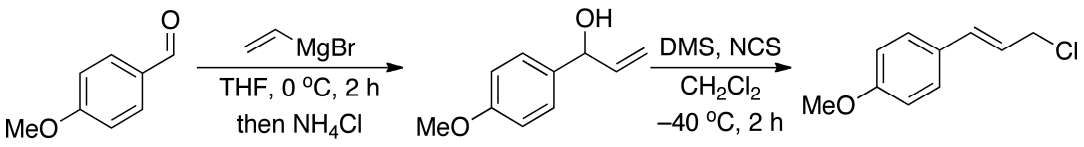
General Procedure A: In the dry-box, a flame-dried 15 mL pressure vessel equipped with a stir bar was charged with $B_2(pin)_2$ (813 mg, 3.2 mmol), $Pt(PPh_3)_4$ (119 mg, 0.096 mmol), and PhMe (6.4 mL). The vessel was then sealed with a septum, removed from the dry-box, placed under an atmosphere of N_2, and vigorously sparged with allene gas for 90 seconds. The septum was then rapidly exchanged for a screw cap, and the reaction was heated to 80 °C for 16 h. At this time, the reaction was cooled to room temperature and concentrated under reduced pressure. The crude reaction mixture was purified by Kügelrohr distillation (0.5 torr, 135 ºC) to afford a clear, colorless oil (1.01 g, >98% yield). R_f = 0.56 (10:1 pentane:diethyl ether, stain in PMA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 (1H, d, br, J = 3.5 Hz), 5.55 (1H, d, br, J = 3.5 Hz), 1.79 (2H, s, br), 1.24 (12H, s), 1.21 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.4, 83.4 (2C), 83.1 (2C), 25.0, 24.8 (4C), 24.7 (4C); IR (neat): 3062 (s), 2979 (w), 1615 (w), 1423 (m), 1344 (s), 1309 (s), 1142 (s), 1006 (w), 969 (w), 864 (w), 848 (w), 709 (w) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{29}O_4B_2$ [M+H]: calculated: 295.2252, found: 295.2258.

General Procedure B: In the dry-box, a flame-dried 100 mL pressure vessel equipped with a stir bar was charged with $Pd_2(dba)_3$ (67 mg, 0.073 mmol), PCy_3 (49.2 mg, 0.175 mmol), and PhMe (2 mL) were added. The solution was stirred for 5 minutes, then $B_2(pin)_2$ (5.66, 24 mmol) was added, The vessel was then sealed with a septum, removed from the dry-box, placed under an atmosphere of N_2. Dried toluene (18 mL) was added; and the flask was cooled to -78 ^{o}C. In a

separate graduated schlenk tube under N_2 atmosphere at -78 ^oC, allene gas was condensed to obtain 2 mL of liquid allene. The liquid allene was then cannulated into the reaction vessel. The septum was then rapidly exchanged for a screw cap, and the reaction was warmed to room temperature and stirred for 16 h. At this time, the reaction concentrated under reduced pressure. The crude reaction mixture was purified by Kügelrohr distillation (0.5 torr, 135 ºC) to afford a clear, colorless oil (7.18 g, >98% yield).

C. Preparation and Characterization of Allylic Chlorides

(*E*)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene (Table 3.3, entry 1, starting material), (*E*)-1-chloro-4-(3-chloroprop-1-en-1-yl)benzene (Table 3.3, entry 4, starting material), (*E*)-(5-chloropent-3-en-1-yl)benzene (Table 3.4, entry 2, starting material), and (*Z*)-*tert*-butyl((4-chlorobut-2-en-1-yl)oxy)diphenylsilane (Table 3.4, entry3, starting material) were prepared as described in the literature and isolated as a mixture of branched and linear isomers. All spectroscopic data was in accordance with the reported values.[13] (*E*)-(4-chlorobut-2-en-2-yl)benzene (Table 3.3, entry 6, starting material) was prepared by the procedure of Kara *et al*, with all spectral data in accordance with the literature.[14]

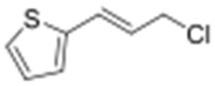


[13] M. J. Ardolino, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 16778.
[14] N. Kishali, M. F. Polat, R. Altundas, Y. Kara, *Helv. Chem. Acta* **2008**, *1*, 67.

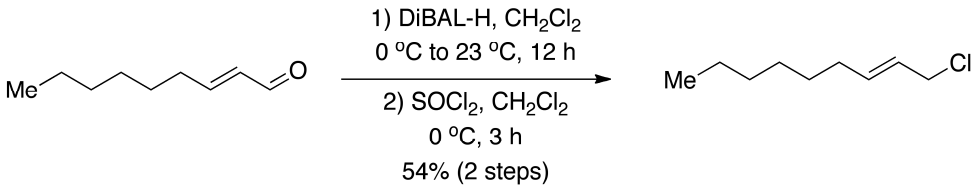
General Procedure C: To a flame-dried round-bottom flask equipped with a stir bar was added 1.0 M vinylmagnesium bromide in THF (17.0 mL, 12.0 mmol) and THF (10 mL). The solution was cooled to 0 °C and 4-methoxybenzaldehyde (1.22 mL, 10.0 mmol) in THF (10 mL) was added dropwise *via* cannula. The reaction was allowed to stir at 0 °C for 2 hours. The reaction was then quenched with sat. NH_4Cl (aq.), and extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The reaction mixture was purified on silica gel (20% EtOAc/hexanes) to afford 1.29 g (78% yield) of 1-(4-methoxyphenyl)prop-2-en-1-ol as a light yellow oil. R_f = 0.20 (20% EtOAc/hexanes, stain in $KMnO_4$). To a separate flame-dried 10 mL round-bottom flask equipped with a stir bar was added *N*-chlorosuccinimide (86.8 mg, 0.65 mmol) and CH_2Cl_2 (2.0 mL) under an atmosphere of nitrogen. The solution was then cooled to –40 ºC and DMS (59.2 µL, 0.8 mmol) was added dropwise *via* syringe. The reaction was allowed to stir for one hour, at which point 1-(4-methoxyphenyl)prop-2-en-1-ol (82.0 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise *via* syringe. The resulting solution was then warmed to 0 ºC and allowed to stir for 1 h. At this time the reaction was diluted with brine (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), and concentrated under reduced pressure. The crude oil was then redissolved in hexanes : H_2O (6 : 1), the layers seperated, and the aqueous layer further extracted with hexanes (3 x 10 mL). The combined organics were concentrated under reduced pressure to afford 88.4 mg (88% yield) of a white solid that was used without further purification.

Preparation of (E)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene (Table 3.3, entry 2, starting material): From commerically available 4-methoxybenzaldehyde, General Procedure C was followed. All spectral data is in accordance with the literature.[13]

Preparation of (E)-5-(3-chloroprop-1-en-1-yl)benzo[d][1,3]dioxole (Table 3.3, entry 3, starting material): From commerically available benzo[*d*][1,3]dioxole-5-carboxaldehyde General Procedure C was followed. All spectral data is in accordance with the literature.[13]



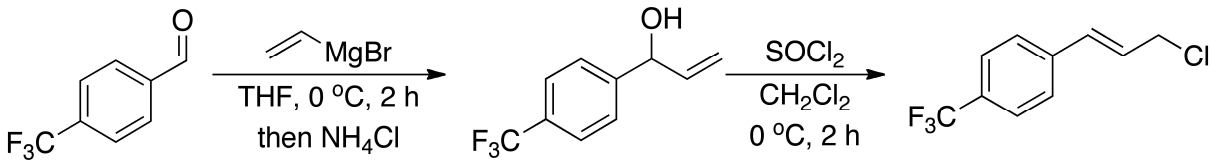
***(E)*-2-(3-chloroprop-1-enyl)thiophene** (Table 3.3, entry 5, starting material)**:** From thiophene-2-carboxaldehyde, General Procedure D was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (1H, d, *J* = 5.0 Hz), 7.01-6.97 (2H, m), 6.81 (1H, d, *J* = 15.0 Hz), 6.18 (1H, dt, *J* = 15.0, 7.5 Hz), 4.20 (2H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7, 127.4, 127.3, 126.8, 125.2, 124.2, 45.2; IR (neat): 2923 (m), 1642 (m), 1437 (m), 1293 (m), 952 (s), 809 (m), 698 (s), 623 (m) cm^{-1}; HRMS (ESI+) for C_7H_8ClS [M+H]: calculated 159.0034, found: 159.0035. The crude material was used without further purification (153.5 mg, 97% yield).



(*E*)-1-chlorononon-2-ene (Table 3.4, entry 1, starting material) was synthesized by the two-step procedure shown above from *trans*-2-nonenal and isolated as a mixture of isomers, with all spectral data in accordance with the literature.[15]

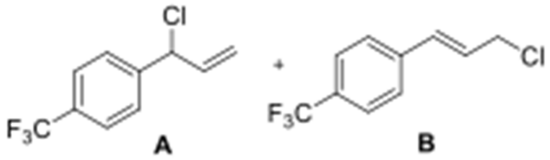
[15] P. Kumar, S. V. Naidu, *J. Org. Chem.* **2005**, *70*, 4207. For branched isomer, see : N. M. Boughdady, K. R. Chynoweth, D. G. Hewitt, *Aust. J. Chem.* **1987**, *40*, 767.

(E)-(3-chloroprop-1-en-1-yl)cyclohexane (Table 3.4, entry 4, starting material)**:** From commerically available cyclohexane carboxaldehyde General Procedure D was followed. All spectral data is in accordance with the literature.[16]



General Procedure D: To a flame-dried round-bottom flask equipped with a stir bar was added 1.0 M vinylmagnesium bromide in THF (12 mL, 12.0 mmol) and THF (10 mL). The solution was cooled to 0 °C and 4-(trifluoromethyl)benzaldehyde (1.37 mL, 10.0 mmol) in THF (10 mL) was added dropwise *via* cannula. The reaction was allowed to stir at 0 °C for 2 hours. The reaction was then quenched with sat. NH_4Cl (aq.), and extracted into diethyl ether three times. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The unpurified reaction mixture was purified on silica gel (15% EtOAc/hexanes) to afford 1.55 g (77% yield) of 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol as a light yellow oil. R_f = 0.28 (15% EtOAc/hexanes, stain in $KMnO_4$). To a separate flame-dried round-bottom flask equipped with a stir bar was added 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (404 mg, 2.0 mmol) and THF (8.0 mL) under an atmosphere of nitrogen. The resulting solution was cooled to 0 ºC and thionyl chloride (1.45 mL, 20.0 mmol) was added dropwise *via* syringe. The resulting solution was allowed to stir for 2 h, at which time the reaction was transferred to a separatory funnel containing ice cold brine (20 mL) and extracted with ice cold CH_2Cl_2 (3 x 20 mL). The combined organics were concentrated under reduced pressure to afford 405 mg (92% yield) of a pale yellow oil which was used without further purification.

[16] M. J. Fuchter, J. N. Levy, *Org. Lett.* **2008**, *10*, 4919.



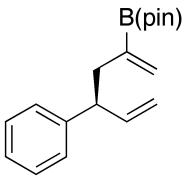
1-(1-chloroallyl)-4-(trifluoromethyl)benzene & **(*E*)-1-(3-chloroprop-1-enyl)-4-(trifluoromethyl)benzene** (**3.8**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63-7.48 (**A** & **B**, 8H, m), 6.69 (**B**, 1H, d, *J* = 15.5 Hz) 6.41 (**B**, 1H, dt, *J* = 15.5, 7.0 Hz), 6.15 (**A**, 1H, ddd, *J* = 17.0, 10.0, 7.0 Hz), 5.48 (**A**, 1H, d, *J* = 7.0 Hz), 5.34 (**A**, 1H, d, *J* = 10.0 Hz), 5.30 (**A**, 1H, d, *J* = 17.0 Hz), 4.25 (**B**, 2H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 139.4, 139.3, 137.0, 132.5, 130.7, 130.4, 130.2, 129.9, 127.8, 127.6, 127.1, 126.9, 125.7, 125.7, 125.6, 125.1, 124.9, 117.8, 62.2, 44.7; IR (neat): 2923 (w), 1616 (m), 1325 (s), 1251 (s), 1166 (s), 1124 (m), 1017 (s), 966 (m) cm^{-1}; HRMS (ESI+) for $C_{12}H_{13}Cl$ [M+H]: calculated 221.0267, found: 221.1116. The crude material was used without further purification (405 mg, 92% yield).

D. Systhesis and chracterizations of allyl-allyl cross-coupling products

General Procedure E: In the dry-box, an oven-dried 1 dram vial equipped with a stir bar was charged with $(\eta^3\text{-allylPdCl})_2$ (1.4 mg, 0.0038 mmol), *(R)*-MFB (3.8 mg, 0.0075 mmol), and THF (0.75 mL). The resulting solution was allowed to stir at room temperature for 5 min. At this time, the vial was sequentially charged with cinnamyl chloride (22.8 mg, 0.15 mmol), **3.1**(53 mg, 0.18 mmol), and CsF (228 mg, 1.5 mmol). The vial was capped and sealed, removed from the dry-box, and allowed to stir at room temperature for 20 h. The slurry was then diluted with

Et_2O, passed through a short plug of silica gel eluting with Et_2O, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (2% Et_2O/pentane) to afford (*S*)-4,4,5,5-tetramethyl-2-(4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane as a clear, colorless oil (33 mg, 77% yield).

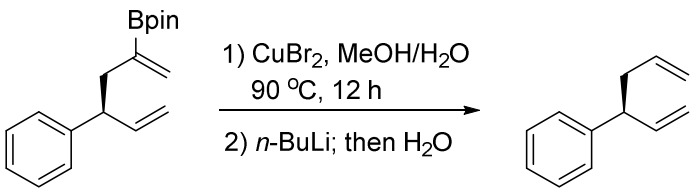
General Procedure F: In the dry-box, an oven-dried 1 dram vial equipped with a stir bar was charged with $(\eta^3\text{-allylPdCl})_2$ (2.5 mg, 0.0069 mmol), *(R,R)*-QuinoxP* (4.7 mg, 0.014 mmol), and THF (1.33 mL, 0.2 M). The vial was capped and allowed to stir for five minutes at room temperature. The vial was opened and sequentially charged with (*E*)-(5-chloropent-3-en-1-yl)benzene (50 mg, 0.277 mmol), **1** (94.7 mg, 0.332 mmol), and CsF (421 mg, 0.014 mmol). The vial was then capped with a rubber septum, sealed with electrical tape, removed from the dry-box, and placed under a positive pressure of nitrogen. Sparged DI water (0.07 mL) was then added *via* syringe, and the rubber septum was rapidly exchanged for a polypropylene cap. The vial was sealed with electrical tape, heated to 60 ºC, and allowed to stir for 16 h. The reaction was then cooled to room temperature, diluted with 6 drops of DI water, and passed through a pipette layered with 4 : 1 Na_2SO_4 : SiO_2. The crude product was concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford (*S*)-4,4,5,5-tetramethyl-2-(4-phenethylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane as a clear, colorless oil (65 mg, 75% yield). R_f = 0.33 (5% EtOAc/hexanes, stain in $KMnO_4$).



(*S*)-4,4,5,5-tetramethyl-2-(4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (3.2): From commercially available cinnamyl chloride (22.9 mg, 0.15 mmol), representative procedure E was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.23 (2H, m), 7.20-7.15 (3H, m), 5.97 (1H, ddd, *J* = 17.0, 10.5, 7.5 Hz), 5.78 (1H, d, br, *J* = 3.5 Hz), 5.53 (1H, d, br, *J* = 3.0 Hz), 5.01 (1H, d, *J* = 10.5 Hz), 4.98 (1H, d, *J* = 17.0 Hz), 3.53 (1H, dd, *J* = 15.0, 7.5 Hz), 2.58 (2H, m), 1.24 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 144.2, 141.9, 131.2, 128.2, 128.1, 127.8, 125.9, 114.2, 83.3 (2H), 49.8, 41.3, 24.8 (4H); IR (neat): 2978 (m), 1616 (w), 1421 (m), 1368 (s), 1309 (s), 1141 (s) cm^{-1}; HRMS (ESI+) for $C_{18}H_{26}BO_2$ [M+H]: calculated 285.1948, found: 285.2020; $[\alpha]^{20}_{D}$ = 5.998 (*c* = 1.53, $CHCl_3$). The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (33 mg, 77% yield). R_f = 0.31 (2% Et_2O/pentane, stain in $KMnO_4$).

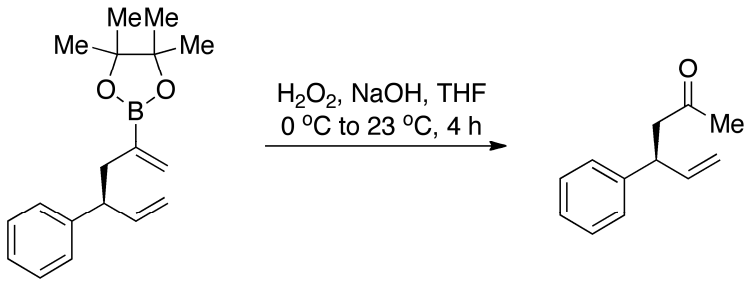
Proof of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by converting the title compound to the corresponding diene as shown below. By optical rotation, the 1,5-diene was compared to the identical compound prepared by allyl-allyl coupling with allylB(pin) as the nucleophile.[5]

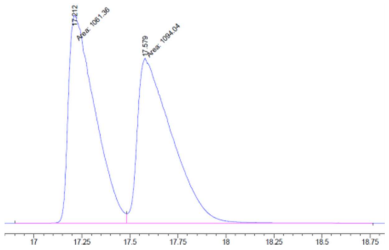


From reference [17]: $[\alpha]^{20}_{D} = +12.24$ (c =0.44, $CHCl_3$)

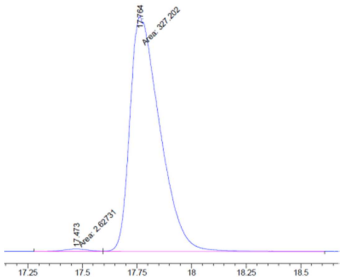
Derived from reaction: $[\alpha]^{20}_{D} = +14.99$ (c =0.40, $CHCl_3$)



Chiral GLC (CD-BDM, Supelco, 110 °C, 25 psi)-analysis of corresponding ketone.



racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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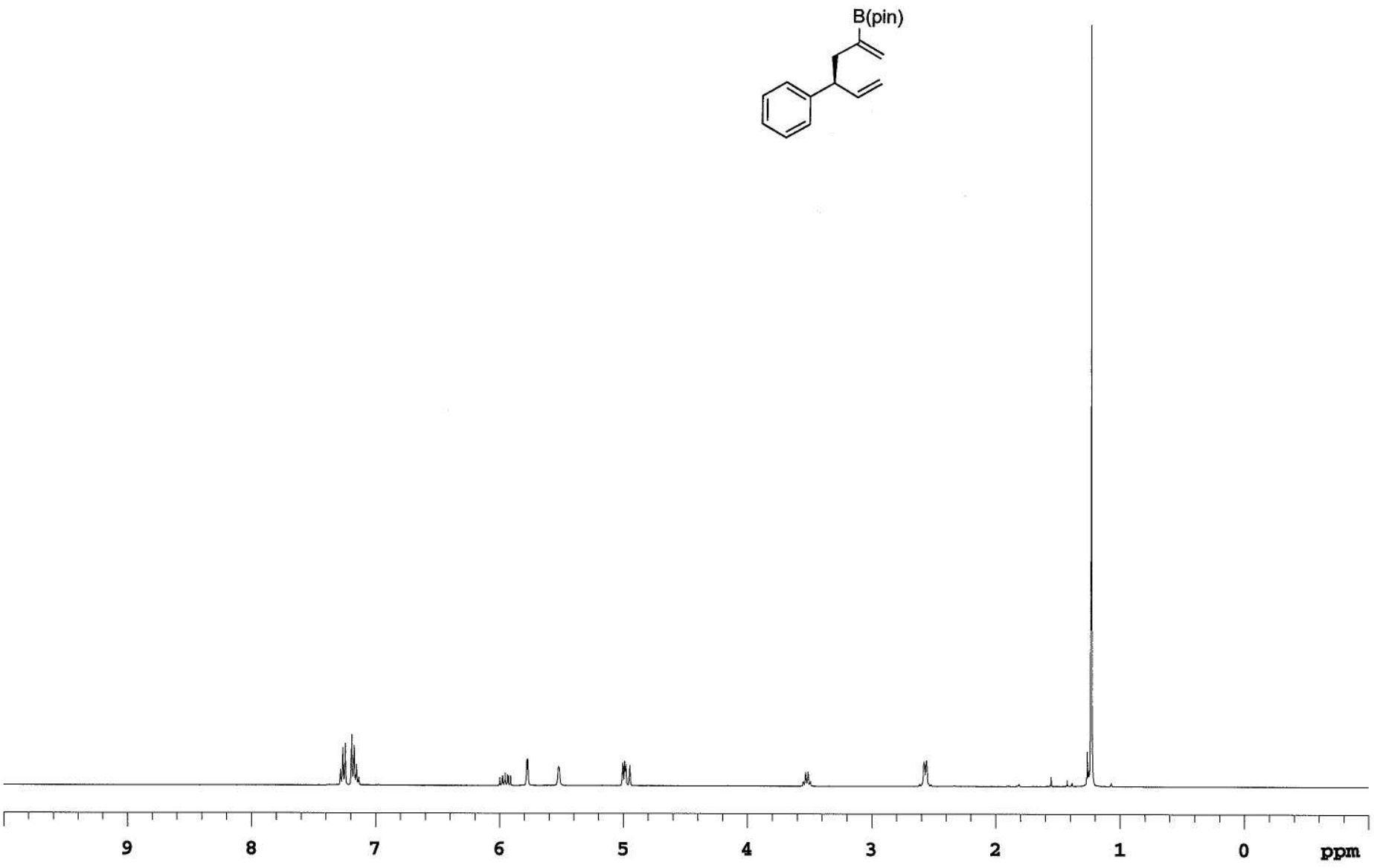
2	17.764	FM	0.1591	327.20193	34.27280	99.20343

[17] P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010** *132*, 10686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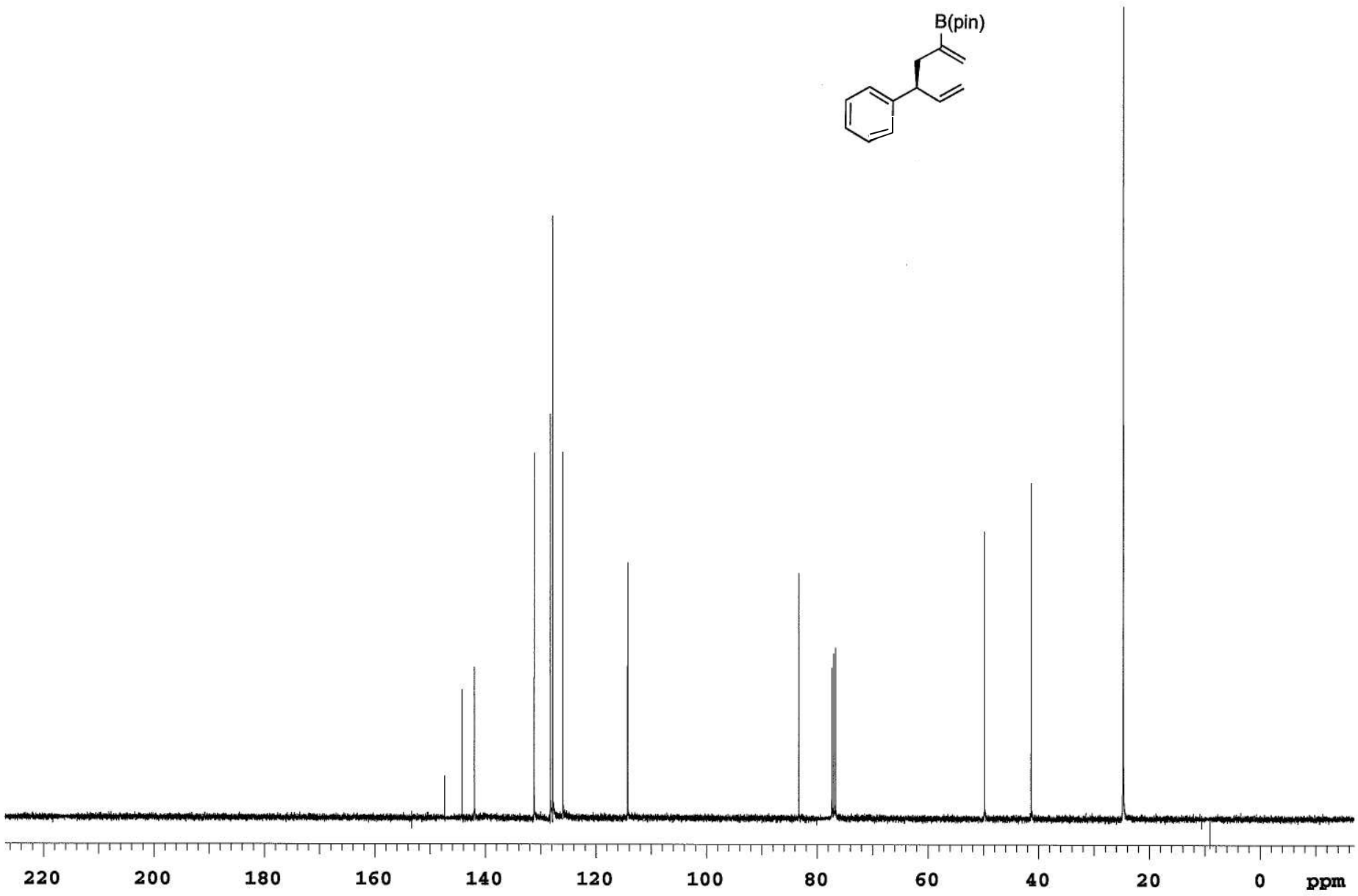
8
7
6
5
4
3
2
1
0
ppm


B(pin)
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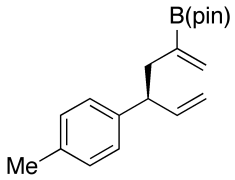
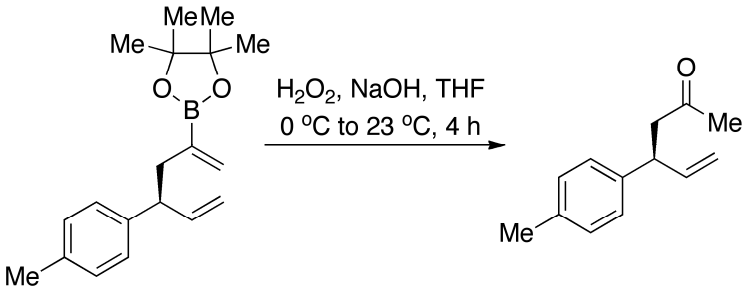
200
180
160
140
120
100
80
60
40
20
0
ppm



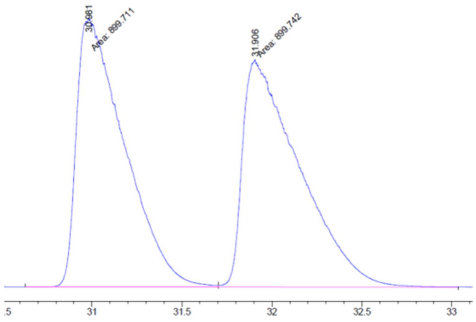
(*S*)-4,4,5,5-tetramethyl-2-(4-p-tolylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (Table 3.3, entry 1, product): From (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene (24.9 mg, 0.15 mmol), general procedure E was used. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (4H, s), 5.94 (1H, ddd, *J* = 17.0, 10.5, 7.5 Hz), 5.77 (1H, d, br, *J* = 3.5 Hz), 5.53 (1H, d, br, *J* = 3.5 Hz), 4.98 (1H, d, *J* = 10.5 Hz), 4.97 (1H, d, *J* = 17.0 Hz), 3.48 (1H, dt, *J* = 15.5, 7.5 Hz), 2.59-2.51 (2H, m), 2.29 (3H, s), 1.24 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 141.2, 135.4, 131.0, 128.9 (2C), 127.7 (2C), 114.0, 83.3 (2C), 49.4, 41.4, 24.8 (4C), 20.9; IR (neat): 2977 (m), 1512 (w), 1368 (s), 1308 (s), 1141 (s), 861 (w), 736 (w) cm^{-1}; HRMS (ESI+) for $C_{19}H_{28}BO_2$ [M+H]: calculated 299.2275, found: 299.2193; $[\alpha]^{20}_D$ = 15.03 (*c* = 1.35, $CHCl_3$). The crude material was purified on silica gel (1% Et_2O/pentane) to afford a clear, colorless oil (32 mg, 67% yield). R_f = 0.28 (1% Et_2O/pentane, stain in $KMnO_4$).

Analysis of Stereochemistry:

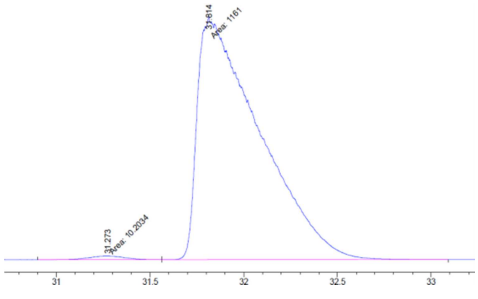
The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



Chiral GLC (CD-BDM, Supelco, 110 °C, 50 min, 25 psi) analysis of corresponding ketone



racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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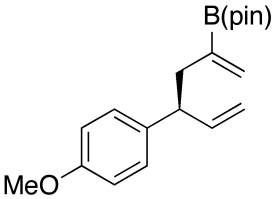
2	31.814	FM	0.3840	1161.00378	50.39377	99.12881

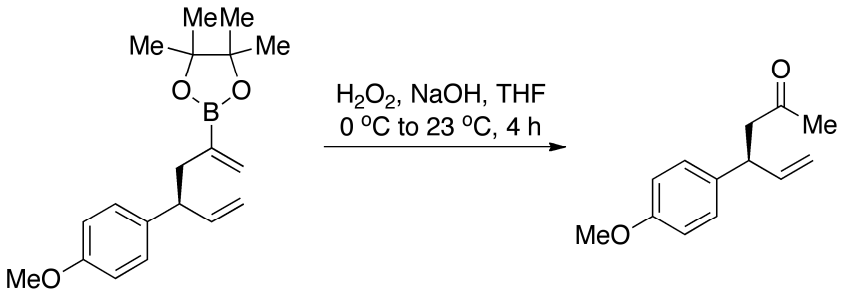


(*S*)-2-(4-(4-methoxyphenyl)hexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3.3, entry 2, product): From (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene (27.4 mg, 0.15 mmol), representative procedure E was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (2H, d, *J* = 8.5 Hz), 6.82 (2H, d, *J* = 8.5 Hz), 5.94 (1H, ddd, *J* = 17.0, 10.5, 7.5 Hz), 5.78 (1H, d, br, *J* = 3.5 Hz), 5.52 (1H, d, br, *J* = 3.0 Hz), 4.99 (1H, d, *J* = 10.5 Hz), 4.95 (1H, d, *J* =

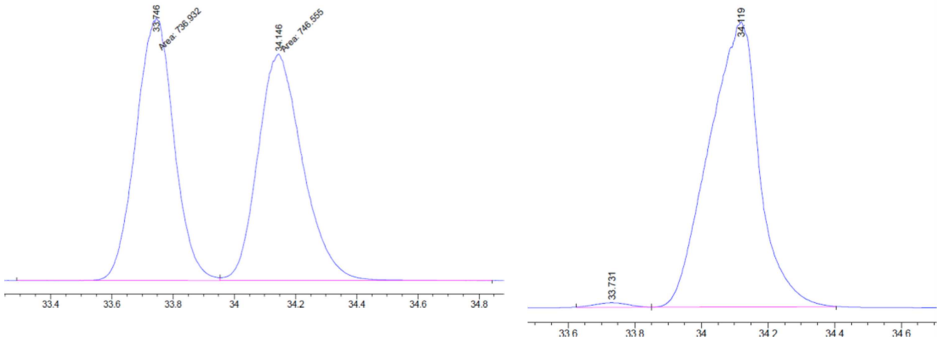
17.0 Hz), 3.78 (3H, s), 3.48 (1H, dt, J = 15.0, 8.0 Hz), 2.57 (1H, dd, J = 14.0, 8.0 Hz), 2.52 (1H, dd, J = 14.0, 8.0 Hz), 1.23 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 142.4, 136.4, 131.1, 128.8 (2C), 113.9, 113.7 (2C), 83.3 (2C), 55.2, 48.9, 41.4, 24.8 (4C); IR (neat): 2977 (m), 2932 (m), 1611 (m), 1510 (s), 1368 (s), 1247 (s), 1141 (s), 1037 (m), 861 (w) cm^{-1}; HRMS (ESI+) for $C_{19}H_{28}BO_3$ [M+H]: calculated 315.2055, found: 315.2072; $[\alpha]^{20}_D$ = 1.470 (c = 0.41, $CHCl_3$). The crude material was purified on silica gel (3% Et_2O/pentane) to afford a clear, colorless oil (36 mg, 79% yield). R_f = 0.20 (3% Et_2O/pentane, stain in $KMnO_4$).

Analysis of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.

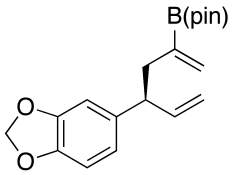


Chiral GLC (CD-BDM, Supelco, 120 °C, 20 min, 25 psi)-analysis of corresponding ketone



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	33.731	MF	0.1313	39.36300	4.99698	1.24246
2	34.120	FM	0.1775	3128.79346	293.76785	98.75754

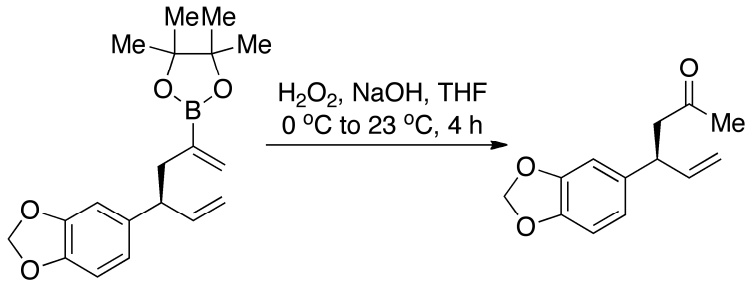


(*S*)-2-(4-(benzo[d][1,3]dioxol-5-yl)hexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3.3, entry 3, product): From (*E*)-5-(3-chloroprop-1-en-1-yl)benzo[*d*][1,3]dioxole (30.1 mg, 0.15 mmol), general procedure E was used. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72-6.69 (2H, m), 6.63 (1H, d, *J* = 8.0 Hz), 5.90 (2H, s), 5.95-5.86 (1H, m), 5.78 (1H, d, br, *J* = 3.5 Hz), 5.53 (1H, d, br, *J* = 3.0 Hz), 4.99 (1H, d, *J* = 10.5 Hz), 4.97 (1H, d, *J* = 14.0 Hz), 3.46 (1H, dt, *J* = 15.0, 7.5 Hz), 2.54 (1H, dd, *J* = 13.5, 7.5 Hz), 2.48 (1H, dd, *J* = 13.5, 7.5 Hz), 1.24 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5, 145.7, 142.1, 138.2, 131.2, 120.8, 114.0, 108.2, 108.0, 100.7, 83.3 (2C), 49.4, 41.4, 24.8 (4C); IR (neat): 2977 (m), 1611 (w), 1486 (s), 1440 (s), 1367 (s), 1308 (s), 1141 (s), 1039 (s), 938 (m), 862 (m), 737 (m) cm^{-1}; HRMS (ESI+) for $C_{19}H_{26}BO_4$ [M+H]: calculated 329.1846, found: 329.1919; $[\alpha]^{20}_D$ = 1.823 (*c* = 2.18, $CHCl_3$). The crude material was purified on

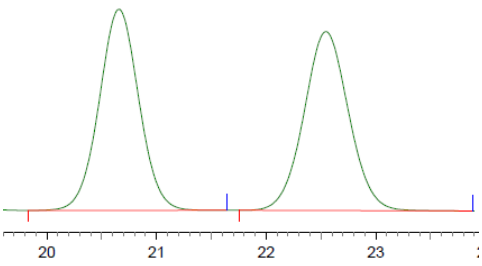
silica gel (3% Et_2O/pentane) to afford a clear, colorless oil (37 mg, 72% yield). R_f = 0.21 (3% Et_2O/pentane, stain in $KMnO_4$).

Analysis of Stereochemistry:

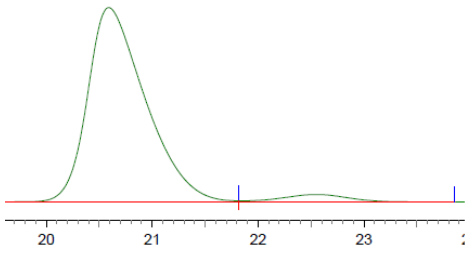
The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



Chiral HPLC (OD-R, Chiracel, 1 mL/min, 0.5% iPA/hexane)-analysis of the corresponding ketone

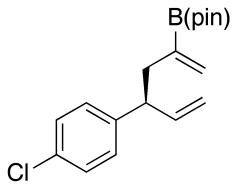


racemic



reaction product

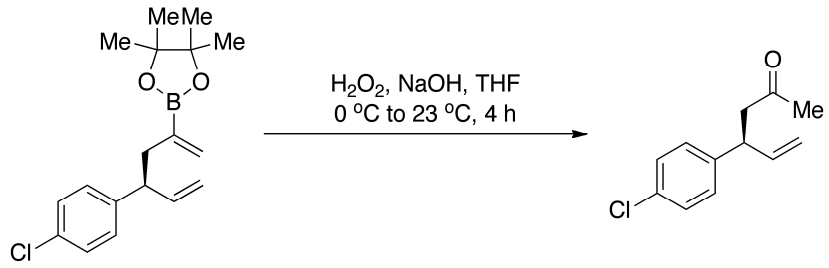
Retention Time	Area	Area %	Height	Height %
20.590	444803996	95.90	11686105	96.35
22.550	19004236	4.10	442123	3.65



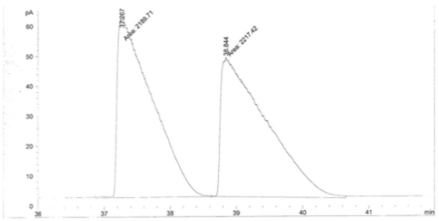
***(S)*-2-(4-(4-chlorophenyl)hexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane** (Table 3.3, entry 4, product). The title compound was prepared *via* General Procedure E for allyl-allyl coupling on a 0.267 mmol scale with (*E*)-1-chloro-4-(3-chloroprop-1-en-1-yl)benzene and a 10% catalyst loading. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.22 (2H, m), 7.12-7.09 (2H, m), 5.93 (1H, ddd, *J* = 17.5, 10.5, 7.5 Hz), 5.78 (1H, d, br, *J* = 3.5 Hz), 5.52 (1H, d, br, *J* = 3.5 Hz), 5.01 (1H, ddd (app dt), *J* = 10.5, 1.5, 1.5 Hz), 4.97 (1H, ddd (app dt), *J* = 17.5, 1.5, 1.5 Hz), 3.51 (1H, ddd (app q), *J* = 7.5, 7.5, 7.5 Hz), 2.57 (1H, dd, *J* = 13.5, 7.5 Hz), 2.51 (1H, dd, *J* = 13.5, 7.5 Hz), 1.23 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 141.6, 131.7, 131.5, 129.3 (2C), 128.4 (2C), 114.6, 83.4 (2C), 49.1, 41.3, 24.8 (4C); IR (neat): 2978 (m), 1637 (w), 1491 (m), 1424 (m), 1389 (s), 1310 (s), 1213 (m), 1141 (s), 1092 (m), 915 (w), 861 (w), 828 (w) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{25}O_2BCl$ [M+H]: calculated: 319.1636, found: 319.1643. $[\alpha]^{20}_{D} = -1.739$ (c = 0.58, $CHCl_3$). The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes) to afford a clear, colorless oil (66 mg, 79% yield). R_f = 0.24 (5% EtOAc/hexanes, stain in $KMnO_4$).

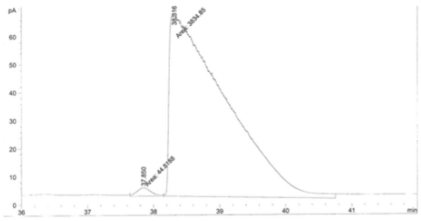
Analysis of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



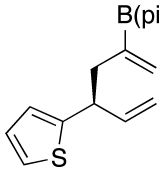
Chrial GLC (CD-BDM, Supelco, 120 °C, 20 psi)-analysis of ketone





racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	37.850	MM	0.2512	44.81876	2.97332	1.15522
2	38.316	MM	0.9887	3834.84570	64.64339	98.84478

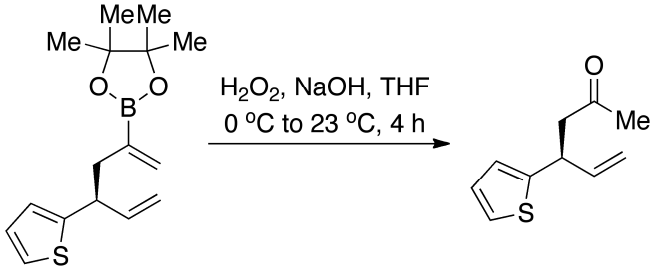


(*S*)4,4,5,5-tetramethyl-2-(4-(thiophen-2-yl)hexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (Table 3.3, entry 5, product): From (*E*)-2-(3-chloroprop-1-en-1-yl)thiophene (21.1 mg, 0.15 mmol), general procedure E was used. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (1H, dd, *J* = 5.0, 1.0 Hz), 6.93 (1H, dd, *J* = 5.0, 3.5 Hz), 6.82-6.81 (1H, m), 5.94 (1H, ddd, *J* = 17.5, 9.5, 8.0 Hz), 5.83 (1H, d, br, *J* = 3.0 Hz), 5.59 (1H, d, br, *J* = 3.0 Hz), 5.06-5.02 (2H, m), 3.86 (1H, dd, *J* = 16.0, 8.0 Hz), 2.69 (1H, dd, *J* = 13.0, 7.5 Hz), 2.60

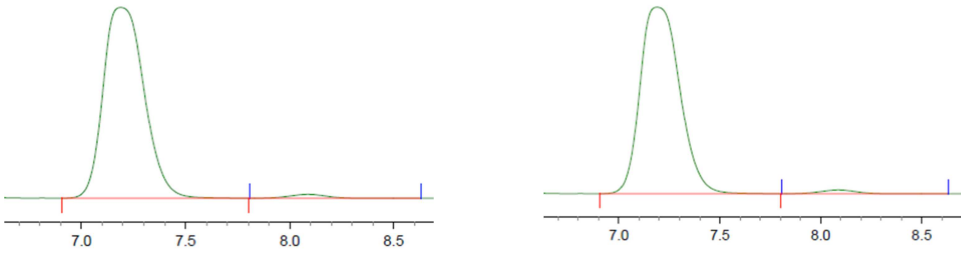
(1H, dd, J = 13.0, 7.5 Hz), 1.26 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 141.4, 131.6, 126.5, 123.4, 123.1, 114.8, 83.4 (2C), 44.9, 42.4, 24.8 (4C); IR (neat): 2927 (s), 1617 (w), 1423 (m), 1388 (s), 1309 (s), 1142 (s), 829 (m), 735 (m) cm^{-1}; HRMS (ESI+) for $C_{16}H_{24}BO_2S$ [M+H]: calculated 291.1512, found: 291.1580; $[\alpha]^{20}_D$ = 29.239 (c = 1.11, $CHCl_3$). The crude material was purified on silica gel (1% Et_2O/pentane) to afford a clear, colorless oil (31 mg, 79% yield). R_f = 0.26 (3% Et_2O/pentane, stain in $KMnO_4$).

Analysis of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.

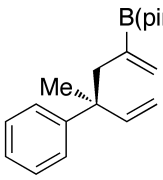


Chiral HPLC (OD-R, Chiracel, 1% i-PA/hexane, 1 mL/min, 220 nm)-analysis of corresponding ketone



racemic reaction product

Retention Time	Area	Area %	Height	Height %
7.190	928560242	98.22	67907201	98.04
8.087	16809644	1.78	1359094	1.96

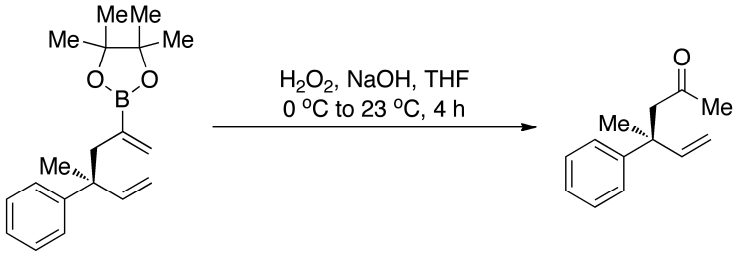


(*S*)-4,4,5,5-tetramethyl-2-(4-methyl-4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (Table 3.3, entry 6, product). The title compound was prepared *via* General Procedure E for allyl-allyl coupling on a 0.300 mmol scale with (*E*)-(4-chlorobut-2-en-2-yl)benzene, at 60 ^{o}C and with a THF/H_2O (20 : 1) mixed solvent system. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.27 (2H, m), 7.27-7.25 (2H, m), 7.15 (1H, app tt, *J* = 6.9, 1.5 Hz), 6.10 (1H, dd, *J* = 17.5, 11.0 Hz), 5.82 (1H, d, br, *J* = 3.5 Hz), 5.40 (1H, d, br, *J* = 3.5 Hz), 5.06 (1H, dd, *J* = 11.0, 1.5 Hz), 5.01 (1H, dd, *J* = 17.5, 1.5 Hz), 2.68 (1H, d, *J* = 12.0 Hz), 2.59 (1H, d, *J* = 12.0 Hz), 1.30 (3H, s), 1.18 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 146.6, 12.8, 127.9 (2C), 126.8 (2C), 125.7, 112.2, 83.3 (2C), 45.5, 44.8, 24.9 (2C), 24.6 (2C), 24.0; IR (neat): 3059 (m), 2977 (w), 1635 (w), 1613 (w), 1444 (m), 1424 (m), 1367 (s), 1307 (s), 1193 (m), 1142 (s), 977 (w), 948 (w), 865 (w), 768 (m), 723 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{28}O_2B$ [M+H]: calculated: 299.2182, found: 299.2170. $[\alpha]^{20}_{D}$ = 4.316 (c = 0.63, $CHCl_3$).

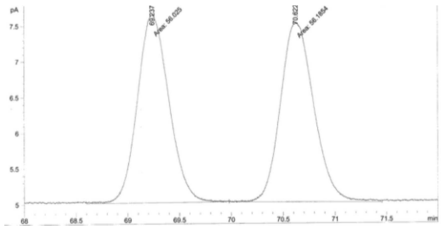
The crude reaction mixture was purified on silica gel (2% EtOAc/hexanes) to afford a clear, colorless oil (40 mg, 44% yield). R_f = 0.11 (2% EtOAc/hexanes, stain in $KMnO_4$).

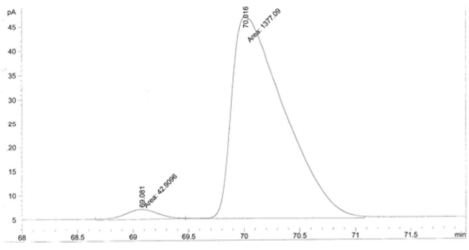
Analysis of Stereochemistry

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



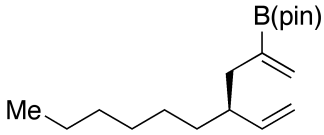
Chrial GLC (CD-BDM, Supelco, 60 °C for 20 min, then 2.5 deg/min to 100 °C 20 psi)-analysis of ketone





racemic reaction product

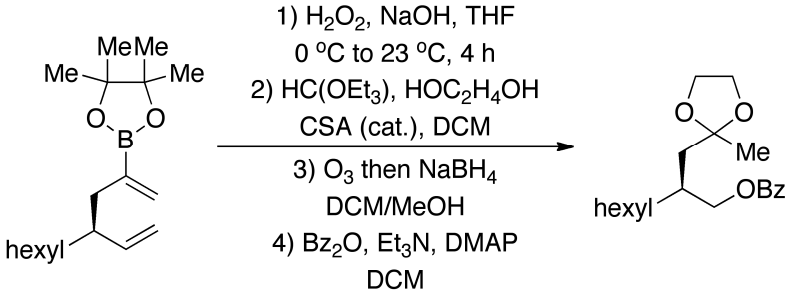
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	69.081	MM	0.3505	42.90964	2.04024	3.02181
2	70.016	MM	0.5481	1377.08679	41.87139	96.97819



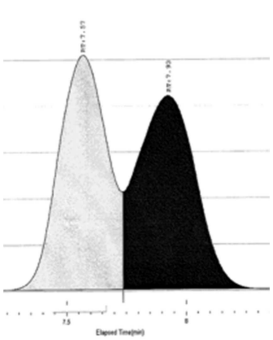
(*S*)-4,4,5,5-tetramethyl-2-(4-vinyldec-1-en-2-yl)-1,3,2-dioxaborolane (Table 3.4, entry 1, product): The title compound was synthesized *via* General Procedure F for the allyl-allyl coupling with 0.311 mmol of (*E*)-1-chloronon-2-ene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (1H, d, br, J = 3.5 Hz), 5.55-5.48 (2H, m), 4.89 (1H, dd, J = 10.5, 2.0 Hz), 4.86 (1H, ddd, J = 17.0, 2.0, 1.0 Hz), 2.22-2.07 (3H, m), 1.41-1.11 (22H, m), 0.85 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 130.3, 114.0, 83.3 (2C), 44.1, 41.2, 34.5, 31.9, 29.4, 27.1, 24.7 (4C), 22.7, 14.1; IR (neat): 3066 (w), 2978 (s), 2926 (s), 2856 (m), 1640 (w), 1616 (w), 1421 (m), 1369 (s), 1308 (s), 1144 (s), 971 (m), 941 (m), 864 (m), 828 (m) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{34}O_2B$ [M+H]: calculated: 293.2652, found: 293.2644. $[\alpha]^{20}_{D} = -4.148$ (c = 2.15, $CHCl_3$). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford a clear, colorless oil (67 mg, 72% yield). R_f = 0.60 (5% EtOAc/hexanes, stain in $KMnO_4$).

Analysis of Stereochemistry

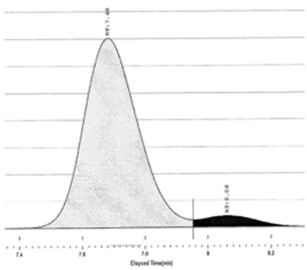
The title compound was converted to a benzoate for SFC analysis as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to compound **3.2**.



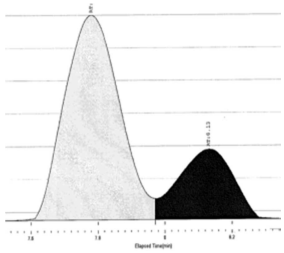
Chrial SFC (OJ-H, Chiralcel, 1.5 mL/min, no modifier, 220 nm)-analysis of benzoate



racemic

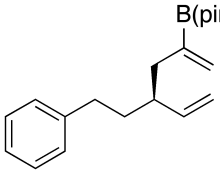


reaction product



product + racemic

Peak Name	Number	Concentration	Area %	Area	Area Sum
Peak1	1	0	94.434	8386.9334	
Peak2	2	0	5.566	494.3331	8881.2666

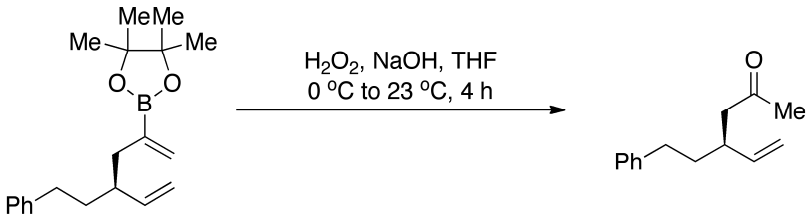


(*S*)-4,4,5,5-tetramethyl-2-(4-phenethylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (Table 3.4, entry 2, product): The title compound was synthesized *via* General Procedure F for the allyl-allyl coupling with 0.277 mmol of (*E*)-(5-chloropent-3-en-1-yl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.22 (2H, m), 7.18-7.12 (3H, m), 5.79 (1H, d, br, *J* = 3.5 Hz), 5.58 (1H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 5.54 (1H, d, br, *J* = 3.5 Hz), 4.99 (1H, dd, *J* = 10.0, 2.0 Hz), 4.94 (1H, ddd, *J* = 17.0, 2.0, 1.0 Hz), 2.66 (1H, ddd, *J* = 14.0, 10.0, 5.0 Hz), 2.50 (1H, ddd, *J* = 14.0, 10.0, 6.5 Hz), 2.27-2.21 (2H, m), 2.20-2.13 (1H, m), 1.77-1.70 (1H, m), 1.53-1.46 (1H, m), 1.21 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 142.7, 130.5, 128.4 (2C), 128.2 (2C), 125.5, 114.7, 83.3 (2C), 43.6, 41.3, 36.2, 33.5, 24.7 (4C); IR (neat): 3063 (m), 2978 (m), 2927 (m), 2858 (w), 1638 (w), 1615 (w), 1496 (m), 1369 (s), 1309 (s), 1189 (s), 970 (w), 942 (w), 911 (m), 863 (m), 828 (m), 699 (m), 671 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{30}O_2B$ [M+H]: calculated: 313.2339, found: 313.2349. $[\alpha]^{20}_D$ =

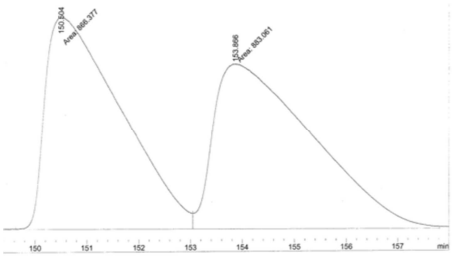
1.760 (c = 1.50, $CHCl_3$). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford a clear, colorless oil (65 mg, 72% yield). R_f = 0.33 (5% EtOAc/hexanes, stain in $KMnO_4$).

Analysis of Stereochemistry

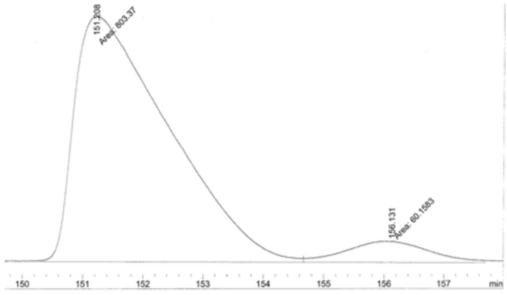
The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



Chrial GLC (CD-BDM, Supelco, 60 °C for 20 min, then 2.5 deg/min to 100 °C, 20 psi)-analysis of ketone



racemic



reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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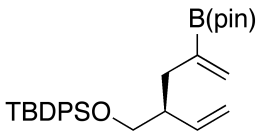
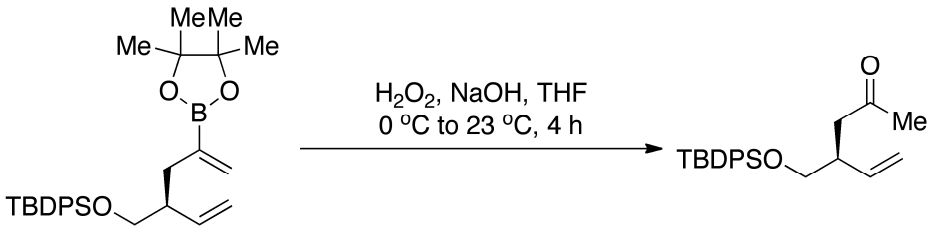
2	156.131	FM	1.5859	60.15827	6.32221e-1	6.96656



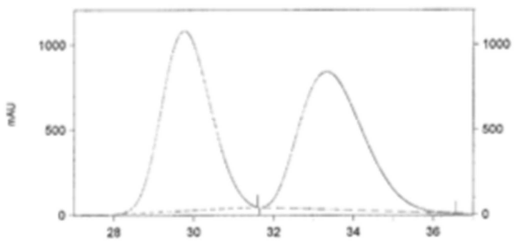
(*S*)-*tert*-butyldiphenyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-vinylpent-4-en-1-yl)oxy)silane (Table 3.4, entry 3, product): The title compound was synthesized *via* General Procedure F for the allyl-allyl coupling with 0.261 mmol of (*Z*)-*tert*-butyl((4-chlorobut-2-en-1-yl)oxy)diphenylsilane and Cs_2CO_3 as the base. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67-7.64 (4H, m), 7.42-7.24 (6H, m), 5.79 (1H, d, br, *J* = 3.5 Hz), 5.66 (1H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 5.55 (1H, d, br, 3.5 Hz), 4.98 (1H, dd, *J* = 11.0, 1.5 Hz), 4.96 (1H, ddd, *J* = 17.0, 2.0, 1.0 Hz), 3.61-3.55 (2H, m), 2.49-2.45 (2H, m), 2.11 (1H, ddd (app q), *J* = 10.5, 10.5, 10.5 Hz), 1.22 (12H, s), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 135.7 (4C), 134.1, 134.0, 130.7, 129.5, 129.4, 127.5 (4C), 115.5, 83.3 (2C), 66.9, 46.5, 36.9, 26.9, 24.7 (4C), 19.4 (3C); IR (neat): 3071 (w), 2977 (m), 2858 (m), 1640 (w), 1472 (s), 1388 (s), 1309 (s), 1213 (w), 1143 (s), 1110 (s), 913 (w), 823 (w), 800 (w), 739 (m), 702 (s), 614 (w), 505 (m) cm^{-1}; HRMS-(ESI+) for $C_{29}H_{41}O_3BSi$ [M+H]: calculated: 477.2996, found: 477.3004. $[\alpha]^{20}_D$ = 3.729 (c = 0.67, $CHCl_3$). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford a clear, colorless oil (68 mg, 54% yield). R_f = 0.25 (5% EtOAc/hexanes, stain in $KMnO_4$).

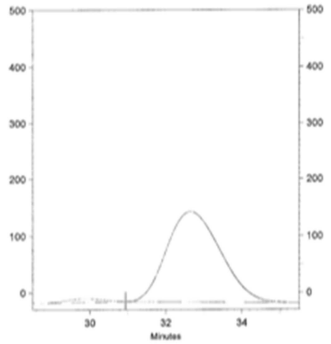
Analysis of Stereochemistry

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



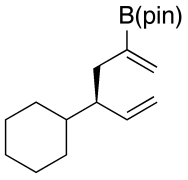
Chrial HPLC (AS-H, Chiralcel, 0.2 mL/min, 0.2% isopropanol, 220 nm)-analysis of ketone





racemic reaction product

Retention Time	Area	Area %	Height	Height %
29.883	7172651	2.65	107482	3.86
32.647	263486670	97.35	2674436	96.14

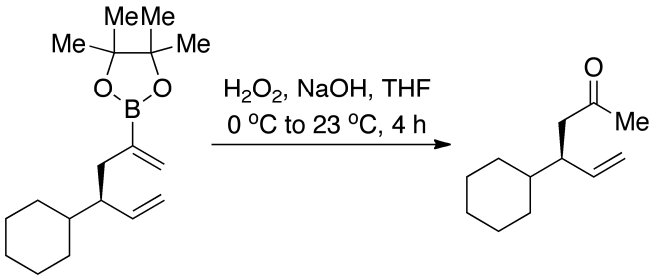


(*S*)-2-(4-cyclohexylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3.4, entry 4, product): From an isomeric mixture of (*E*)-(3-chloroprop-1-en-1-yl)cyclohexane (29 mg, 0.15 mmol), representative procedure E was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58-5.51 (2H, m), 5.77 (1H, d, br, *J* = 3.5 Hz), 4.93 (1H, dd, *J* = 10.5, 2.0 Hz), 4.85-4.81 (1H, m), 2.34 (1H, dd, *J* = 13.0, 5.0 Hz), 2.09 (1H, dd, *J* = 12.5, 9.5 Hz), 2.02 (1H, dddd (app tdd), *J* = 14.0, 9.5, 5.0, 5.0 Hz), 1.71-1.60 (6H, m), 1.25 (12H, s), 1.24-1.01 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 129.9, 114.9, 83.2 (2C), 50.1, 41.4, 37.9, 31.3, 29.1, 26.8, 26.7, 26.6, 24.7 (4C); IR (neat): 2922 (s), 1637 (w), 1447 (m), 1368 (s), 1344 (s), 1142 (s), 939 (m), 890 (m), 864 (m) cm^{-1}; HRMS (ESI+) for

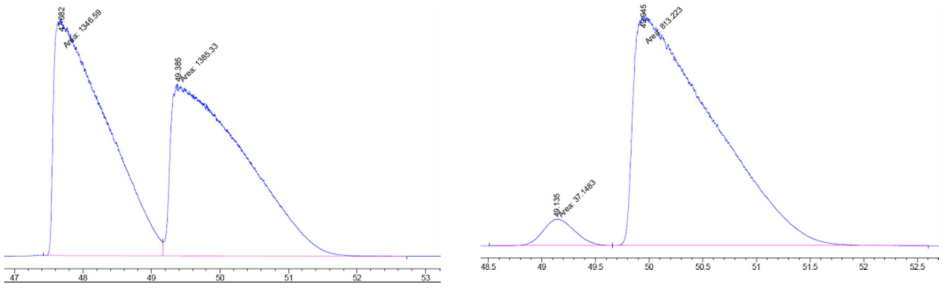
$C_{18}H_{32}BO_2$ [M+H]: calculated 291.2417, found: 291.2509; $[\alpha]^{20}_D = -2.004$ (c = 2.18, $CHCl_3$). The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (35 mg, 66% yield). R_f = 0.23 (2% Et_2O/pentane, stain in $KMnO_4$).

Analysis of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.

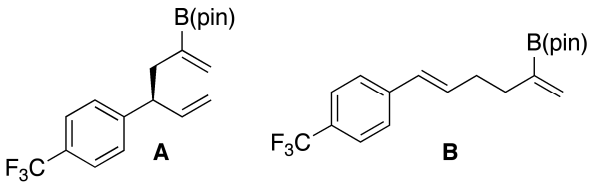


Chiral GLC (CD-BDM, Supelco, 90 °C, 25 psi) analysis of corresponding ketone



racemic reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	49.135	MF	0.3398	37.14832	1.82202	4.36848
2	49.945	FM	0.8543	813.22266	15.86481	95.63152

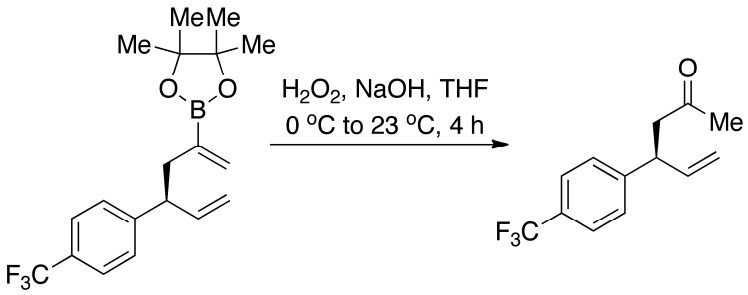


(*S*)-4,4,5,5-tetramethyl-2-(4-(4-(trifluoromethyl)phenyl)hexa-1,5-dien-2-yl)-1,3,2-dioxaborolane & (E)-4,4,5,5-tetramethyl-2-(6-(4-(trifluoromethyl)phenyl)hexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (3.9): General Procedure E was used. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (4H, **A** & **B**, d, *J* = 8.5 Hz), 7.42 (2H, **A** & **B**, d, *J* = 8.5 Hz), 7.29 (2H, **A** & **B**, d, *J* = 13.0 Hz), 6.42-6.31 (**B**, 2H, m), 5.95 (**A**, 1H, ddd, *J* = 17.0, 10.5, 7.5 Hz), 5.83 (**B**, 1H, d, br, *J* = 3.0 Hz), 5.80 (**A**, 1H, d, br, *J* = 3.5 Hz), 5.66 (**B**, d, br, *J* = 3.0 Hz), 5.54 (**A**, 1H, d, br, *J* = 3.0 Hz), 5.05 (**A**, 1H, d, *J* = 10.5 Hz), 4.99 (**A**, 1H, d, *J* = 17.0 Hz), 3.60 (**A**, 1H, dt, *J* = 15.0, 7.5 Hz), 2.60 (**A**, 1H, dd, *J* = 13.0, 7.5 Hz), 2.39-2.33 (**B**, 4H, m), 2.55 (**A**, 1H, dd, *J* = 13.0, 7.5 Hz), 1.26 (**A**, 12H, s), 1.12 (**B**, 12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.22, 148.2, 141.1, 133.7, 131.7, 129.8, 128.7, 128.5, 128.3, 128.2, 126.0, 125.7, 125.4, 125.3, 125.2, 125.14, 125.1, 114.9, 83.4, 49.7, 41.1, 34.9, 32.8, 24.7, 24.6, 10.5; IR (neat): 2979 (m), 1616 (w), 1420 (m), 1369 (m), 1325 (s), 1164 (m), 1124 (s), 1068 (s), 861 (w) cm^{-1}; HRMS (ESI+) for $C_{19}H_{25}BF_3O_2$ [M+H]: calculated 353.1989, found: 353.1903; $[\alpha]^{20}_D = -2.541$ (*c* = 1.28, $CHCl_3$). The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (34 mg, 66% yield). R_f = 0.26 (2% Et_2O/pentane, stain in $KMnO_4$).

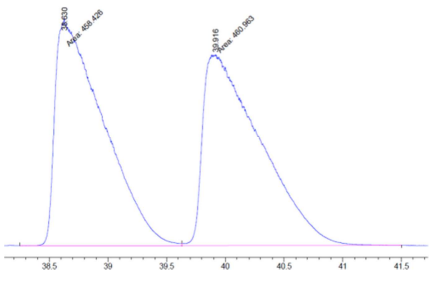
Analysis of Stereochemistry:

The title compound was oxidized with H_2O_2/NaOH to afford the corresponding ketone for GLC analysis, as depicted below. The analogous racemic material was prepared *via* the same

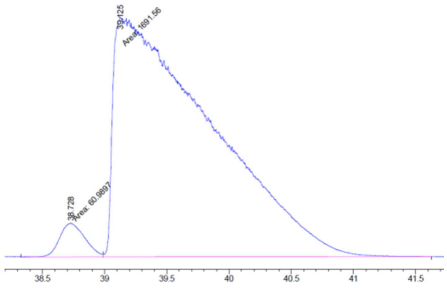
route, using 1,2-bis(diphenylphosphino)benzene as the achiral ligand in the allyl-allyl coupling reaction. The absolute stereochemistry was assigned by analogy to **3.2**.



Chiral GLC (CD-BDM, Supelco, 100 °C, 25 psi)-analysis of corresponding ketone



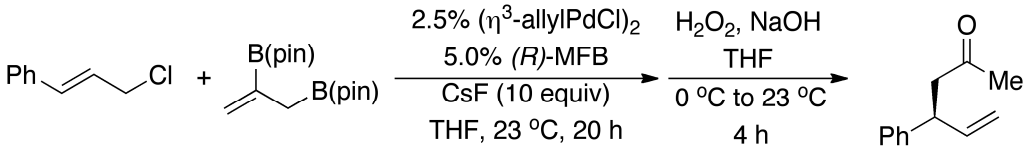
racemic



reaction product

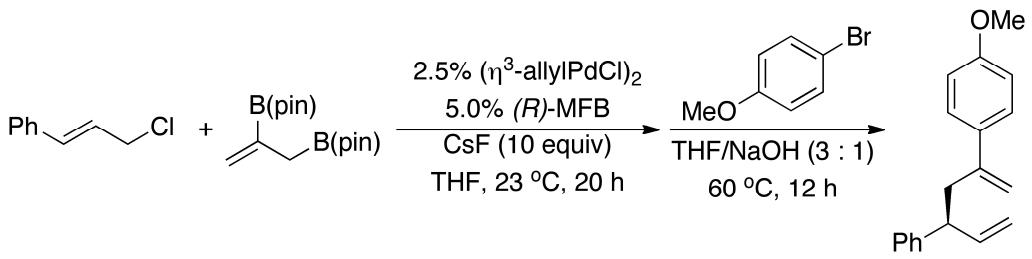
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	38.728	MF	0.2334	60.98970	4.35550	3.48005
2	39.125	FM	0.9116	1691.56177	30.92603	96.51995

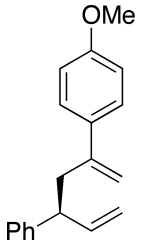
E. Procedures and Characterizations for Derivatives of 3.2



(*S*)-4-phenylhex-5-en-2-one (3.10): From cinnamyl chloride (21.8 mg, 0.15 mmol), General Procedure E was followed for allyl-allyl cross coupling. After allowing to stir for 20 h at room temperature, the vial was cooled to 0 ºC and sequentially charged with THF (2 mL), 3M NaOH (2 mL), and 30%/wt H_2O_2 (1 mL). The resulting biphasic mixture was allowed to stir vigorously while warming to room temperature over 4 h. The reaction was then cooled to 0 ºC and quenched with $Na_2S_2O_3$ (4 mL). The crude mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (10% Et_2O/pentane) to afford a clear, colorless oil (20.6 mg mg, 78% yield). R_f = 0.34 (10% Et_2O/pentane, stain in $KMnO_4$). Spectral data is in accordance with the literature.[18] $[\alpha]^{20}_D$ = –5.625 (*c* = 1.07, $CHCl_3$).

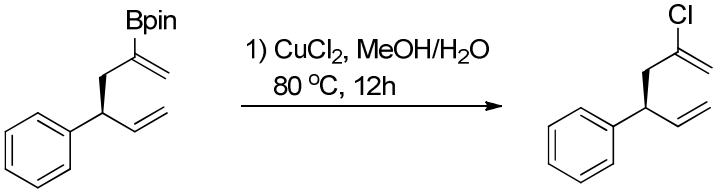
[18] Chen, J.; Peng, Q.; Lei, B.; Hou, X.; Wu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 14180.

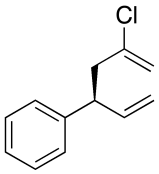




(*S*)-1-methoxy-4-(4-phenylhexa-1,5-dien-2-yl)benzene (3.11): With cinnamyl chloride (21.8 mg, 0.15 mmol), General Procedure E was followed for allyl-allyl cross coupling. After allowing to stir for 20 h at room temperature, the vial was brought back into the dry-box, where it was charged with 4-bromoanisole (33.7 mg, 0.18 mmol) and *S*-Phos (3.1 mg, 0.0075 mmol). The vial was capped with a rubber septum, removed from the dry-box, put under an atmosphere of nitrogen, and charged with 3M NaOH (0.3 mL). The rubber septum was then rapidly exchanged for a polypropylene cap. The vial was subsequently sealed with electrical tape, heated to 60 ºC, and allowed to stir for 12 h. The reaction was allowed to cool to room temperature, diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (33 mg, 78% yield). R_f = 0.25 (2% Et_2O/pentane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.28 (4H, m), 7.25-7.19 (1H, m), 7.18-7.12 (2H, m), 6.88-6.86 (2H, m), 5.98 (1H, ddd, *J* = 17.5, 10.5, 7.5 Hz), 5.14 (1H, d, br, *J* = 1.5 Hz), 5.01 (1H, d, *J* = 10.5 Hz), 4.93 (1H, d, *J* = 17.5 Hz), 4.86 (1H, m), 3.83 (3H, s), 3.40 (1H, dt, *J* = 14.5, 7.5 Hz), 2.93-2.85 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 145.5, 143.9, 141.4, 133.5, 128.3 (2C), 127.7 (2C), 127.5 (2C), 126.2, 114.4, 113.7 (2C), 113.2, 55.3, 47.7, 41.8; IR (neat): 2935

(w), 1624 (m), 1511 (s), 1247 (s), 1179 (s), 1034 (m), 835 (m), 700 (m) cm^{-1}; HRMS (ESI+) for $C_{19}H_{21}O$ [M+H]: calculated 265.1592, found: 265.1601; $[\alpha]^{20}_D = -22.90$ (c = 1.74, $CHCl_3$).

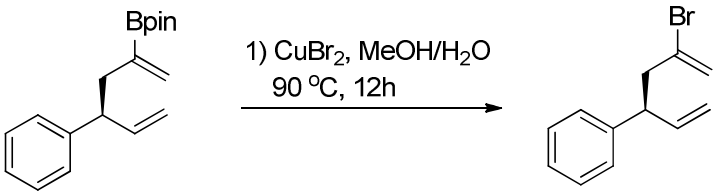


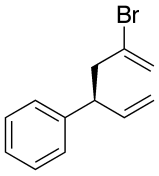


(*S*)-(5-chlorohexa-1,5-dien-3-yl)benzene (3.12): The title compound was synthesized by the procedure of Hartwig *et al*. for the halogenation of vinyl boronic esters.[19] In a 20 mL scintillation vial, (*S*)-4,4,5,5-tetramethyl-2-(4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (**3.2**, 28.4 mg, 0.1 mmol) was dissolved in MeOH/H_2O (1 : 1, 2.5 mL total volume). The biphasic mixture was charged with $CuCl_2 \cdot 2H_2O$ (51.1 mg, 0.3 mmol), the vial was sealed, and the reaction was allowed to stir at 80 ºC for 12 h. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (17.3 mg, 85% yield). R_f = 0.45 (2% Et_2O/pentane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (2H, m), 7.24-7.20 (3H, m), 6.00 (1H, ddd, J = 17.0, 10.0, 7.5 Hz), 5.11-4.99 (4H, m), 3.74 (1H, dt, J = 15.0, 7.5 Hz), 2.74 (1H, dd, J = 14.5, 7.5 Hz), 2.70 (1H, dd, J = 14.5, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.3, 135.1, 134.9, 123.2 (2C), 122.4 (2C), 121.2, 109.1, 108.8, 41.6, 39.9; IR (neat): 2924 (s), 2853 (m), 1635 (s), 1453 (m), 1207 (w), 963 (m), 917 (s), 881 (s), 699 (s), 676 (w) cm^{-1}; HRMS

[19] Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

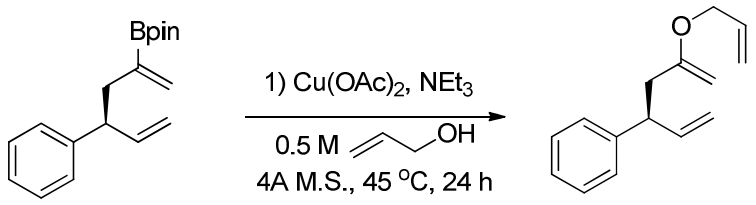
(ESI+) for $C_{12}H_{14}Cl$ [M+H]: calculated 193.0706, found: 193.0791 $[\alpha]^{20}_{D} = 4.109$ (*c* = 0.31 , $CHCl_3$).

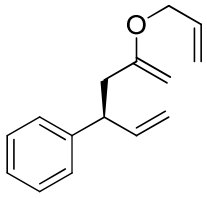




(*S*)-(5-bromohexa-1,5-dien-3-yl)benzene (3.13): The title compound was synthesized by the procedure of Hartwig *et al*. for the halogenation of vinyl boronic esters.[19] In a 20 mL scintillation vial, (*S*)-4,4,5,5-tetramethyl-2-(4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (**3.2**, 28.4 mg, 0.1 mmol) was dissolved in MeOH/H_2O (1 : 1, 2.5 mL total volume). The biphasic mixture was charged with $CuBr_2$ (67 mg, 0.3 mmol), sealed, and the reaction was allowed to stir at 90 ºC for 12 h. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (20.1 mg, 80% yield). R_f = 0.45 (2% Et_2O/pentane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (2H, m), 7.24-7.20 (3H, m), 5.97 (1H, ddd, *J* = 17.5, 10.5, 7.0 Hz), 5.43 (1H, s), 5.36 (1H, s), 5.11-5.06 (2H, m), 3.75 (1H, dt, *J* = 14.5, 7.5 Hz), 2.85 (1H, dd, *J* = 14.5, 7.5 Hz), 2.78 (1H, dd, *J* = 13.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 134.8, 126.7, 123.2 (2C), 122.4 (2C), 121.3, 113.3, 109.9, 42.2, 41.9; IR (neat): 3028 (m), 1630 (m),

1453 (w), 1202 (w), 1030 (w), 917 (s), 887 (s), 754 (s), 698 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{14}Br$ [M+H]: calculated 238.0201, found: 239.0293 $[\alpha]^{20}_D = 9.74$ (c = 0.35 , $CHCl_3$).

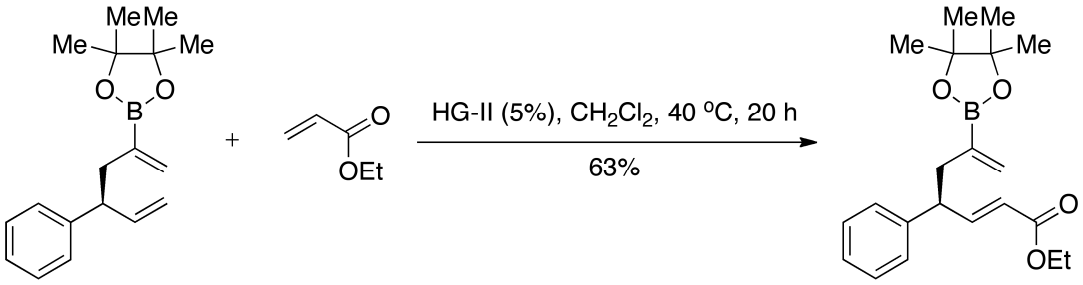


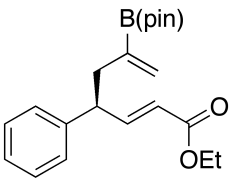


(S)-(5-(allyloxy)hexa-1,5-dien-3-yl)benzene (**3.14**): The title compound was synthesized by the procedure of Merlic *et al*. for the etherification of vinyl boronic esters.[20] In the dry-box, an oven-dried 2 dram vial equipped with a stir bar was charged **4** (27 mg, 0.10 mmol), $Cu(OAc)_2$ (56 mg, 0.2 mmol), NEt_3 (40.5 mg, 0.4 mmol), allylalcohol (0.2 mL, 0.34 mmol), and 100mg activated 4Å M.S. The vial was then capped and sealed with tape, removed from the dry-box, and allowed to stir at 45 ºC for 24 h. The reaction was then cooled to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on neutralized silica gel (2% Et_2O/pentane) to afford a clear, colorless oil (14.4 mg, 71% yield). R_f = 0.6 (2% Et_2O/pentane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.30 (2H, m), 7.18-7.21 (3H, m), 5.92-6.03 (2H, m), 5.32 (1H, d, J = 17.1 Hz), 5.22 (1H, J = 10.5 Hz), 5.04 (1H, J = 10.5 Hz), 5.01 (1H, J = 17.1 Hz), 4.12-4.19 (2H, m), 3.83 (2H, dd, J = 13.5, 2.0 Hz), 3.67 (1H, dd, J = 15.2, 7.6 Hz), 2.56 (1H, dd, J = 14.6, 8.1 Hz), 2.51 (1H, dd, J = 14.0, 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 143.6, 141.3, 133.5, 128.3 (2C), 127.7 (2C), 126.2, 116.8,

[20] R. E. Shade, A. M. Hyde, J.-C. Olsen, C. A. Merlic, *J. Am. Chem. Soc.* **2010**, *132*, 1202

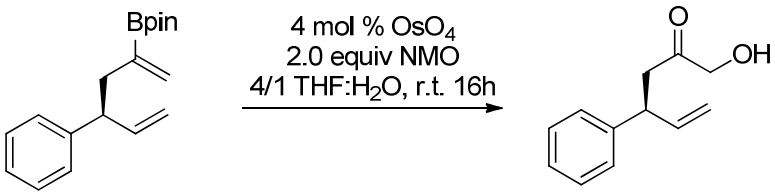
114.3, 83.4, 68.1, 47.1, 41.3; IR (neat): 3027 (w), 1655 (m), 1601 (m), 1230 (s), 914.3 (s), 800 (s), 621 (s). $[\alpha]^{20}_{D} = 0.92$ (c = 1.17, $CHCl_3$).

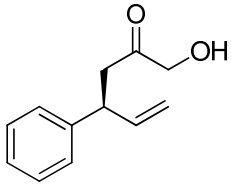




(*S*,*E*)-ethyl 4-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,6-dienoate (3.15): In the dry-box, an oven-dried 1.0 dram vial equipped with a stir bar was charged with (*S*)-4,4,5,5-tetramethyl-2-(4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (50 mg, 0.176 mmol), HG-II (5.6 mg, 0.009 mmol), ethyl acrylate (0.06 mL, 0.528 mmol), and CH_2Cl_2 (0.9 mL, 0.2 M). The vial was then capped and sealed with tape, removed from the dry-box, and allowed to stir at 40 ºC for 20 h. The reaction was then cooled to room temperature and 5 drops of *tert*-butylvinyl ether was added by pipette. The vial was capped and the reaction was allowed to stir at room temperature for 30 minutes. The reaction mixture was then then passed through a 6 cm plug of silica gel (10% ether/pentane) and concentrated under reduced pressure. The crude product was purified on silica gel (3% EtOAc/hexanes) to afford a clear, colorless oil (40 mg, 63% yield). R_f = 0.24 (10% EtOAc/hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.24 (2H, m), 7.24-7.14 (3H, m), 7.07 (1H, dd, J = 15.5, 7.5 Hz), 5.79 (1H, d, br, J = 3.5 Hz), 5.72 (1H, dd, J = 15.5, 1.5 Hz), 5.52 (1H, d, br, J = 3.5 Hz), 4.13 (2H, q, J = 7.0 Hz), 3.68 (1H, dd, J = 15.5, 8.0 Hz), 2.65 (1H, dd, J = 13.5, 8.0 Hz), 2.58 (1H, dd, J = 13.5, 7.5 Hz), 1.26-1.22 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 151.6, 142.1, 132.1, 128.5 (2C), 128.0 (2C), 126.6, 120.9,

83.4 (2C), 60.1, 48.3, 40.8, 24.8, 24.7 (4C), 14.2; IR (neat): 3028 (m), 2979 (w), 1719 (s), 1650 (w), 1425 (m), 1369 (s), 1310 (s), 1271 (m), 1169 (s), 1139 (s), 1096 (w), 1044 (w), 862 (w), 761 (m) cm^{-1}; HRMS-(ESI+) for $C_{21}H_{30}O_4B$ [M+H]: calculated: 357.2237, found: 357.2238. $[\alpha]^{20}_D$ = 2.47 (*c* = 4.000, $CHCl_3$).



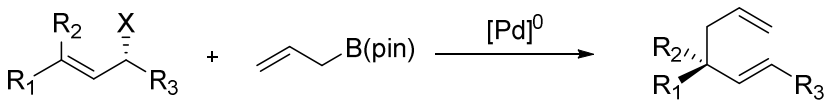


(S)-1-hydroxy-4-phenylhex-5-en-2-one (3.16): To a 2 dram vial equipped with a stir bar was charged with **4** (27 mg, 0.1 mmol), NMO (25 mg, 0.2 mmol), THF (0.4 ml, 0.25 M), H_2O (0.125 mL, 0.8 M); followed by 25 µL of 4%wt OsO_4 in H_2O. The vial was then capped and allowed to stir at room temp. for 16 h. The reaction mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexane) to afford a clear, colorless oil (10.0 mg, 55% yield). R_f = 0.2 (20% EtOAc/hexane, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.33 (2H, m), 7.18-7.24 (3H, m), 5.97 (1H, ddd, *J* = 17.2, 10.3, 7.7 Hz), 5.10 (1H, d, *J* = 10.2 Hz), 5.08 (1H, d, *J* = 17.2 Hz), 4.19 (1H, d, *J* = 19.1 Hz), 4.03 (1H, d, *J* = 19.1 Hz), 3.96 (1H, dd, *J* = 14.4, 7.3 Hz), 2.86 (1H, dd, *J* = 15.9, 7.5 Hz), 2.79 (1H, dd, *J* = 15.6, 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.0, 142.0, 139.9, 128.8 (2C), 127.4 (2C), 126.9, 115.1, 68.8, 44.6, 44.0; IR (neat): 3003 (m), 1719 (s), 1453 (w), 1114 (s), 919 (m), 670 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{14}O_2$ [M+H]: calculated: 191.1207, found: 191.1184. $[\alpha]^{20}_D$ = 31.04 (*c* = 0.34, $CHCl_3$).

Chapter IV: Catalytic Stereo Specific Allyl-Allyl Cross-Coupling of Internal Allyl Electrophiles

Since the discovery of the first branch- and enantioselective allyl-allyl cross-coupling reaction in 2010, the scope of the Pd-catalyzed allyl-allyl cross-coupling has been extended to enable the synthesis of a diverse range of 1,5-diene variants, including 1,5-dienes with all-carbon quaternary center, 1,5-dienes containing adjacent tertiary centers, and 1,5-dienes with well differentiated olefin systems.[1] In efforts to further generalize the scope of the branch- and enantioselective allyl-allyl cross-coupling reaction, we turned our attention to the application of internal allyl electrophile substrates (Scheme 4.1).

Scheme 4.1: Asymmetric Allyl-Allyl Cross-Coupling of Internal Allyl Electrophile



Internal allyl electrophiles were of particular interest because their application in the allyl-allyl cross-coupling reaction would facilitate the rapid construction of complex substituted 1,5-dienes. In addition, the olefins generated in this system are readily distinguished since one is an internal olefin while the other is a terminal olefin. Lastly, we hypothesized that this electrophile motif may present and opportunity for the development of a stereospecific cross-coupling method, in which the absolute configuration of the product is predetermined by that of

[1] (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778. (d) Le, H.; Kyne, R. E.; Brozek, L. A.; Morken, J. P. *Org. Lett.* **2013**, *15*, 1432.

the starting materials; and the use of expensive chiral phosphine ligands is unnecessary. In this chapter, the development of Pd-catalyzed allyl-allyl cross-coupling using internal allyl electrophiles will be discussed.[2, 3]

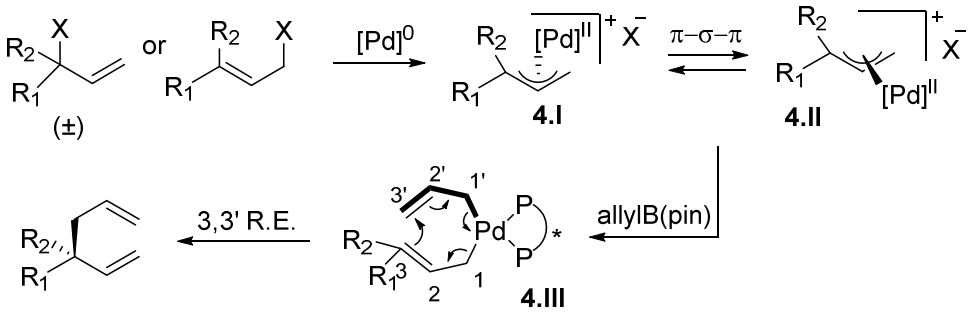
I. Hypothesis and Potential Challenges

A. Hypothesis for the Stereospecific Cross-Coupling

In previous developments in the Pd-catalyzed allyl-allyl cross-coupling, a central feature that allowed the use of racemic starting materials is the rapid π-σ-π isomerization (Scheme 4.2).[4] Upon oxidative addition of $[Pd]^0$ to the allyl electrophile, Pd-π allyl complex **4.I** is generated. The palladium has the ability to quickly interconvert between the two faces of the π-allyl (**4.I** to **4.II** and back) through π-σ-π isomerization. This process is critical as it enables the racemic Pd-π-allyl generated initially to be converted to the preferred configuration dictated by the chiral ligand.

[2] This work was accomplished in collaboration with Amanda Batten. Le, H.; Batten, A.; Morken, J. P. *Org. Lett.* **2014**.
[3] Selected examples of chirality transfer in Pd-catalyzed allylic substitution: (a) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921. (b) Togashi, K.; Terakado, M.; Miyazawa, M.; Yamamoto, K.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3333. (c) Deardorff, D. R.; Taniguchi, C. M.; Nelson, A. C.; Pace, A. P.; Kim, A. J.; Pace, A. K.; Jones, R. A.; Tafti, S. A.; Nguyen, C.; O'Connor, C.; Tang, J.; Chen, J. *Tetrahedron: Asymmetry* **2005**, *16*,1655. (d) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Mosconi, E.; Tolomelli, A. *Org. Lett.* **2008**, *10*, 2425. (e) Jacquet, O.; Legros, J. Y.; Coliboeuf, M.; Fiaud, J.-C. *Tetrahedron* **2008**, *64*, 6530.
[4] (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *155*, 35.

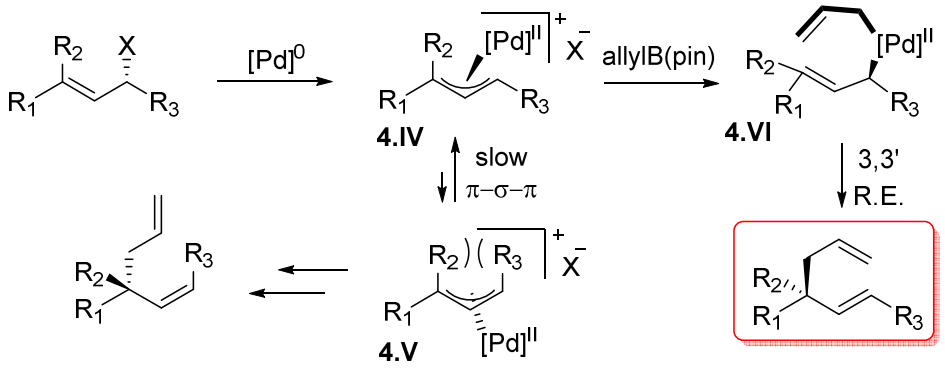
Scheme 4.2: Use of Racemic Substrates Made Possible by π-σ-π Isomerization



While the π-σ-π isomerization is operative in terminal allylic systems, we surmised that a similar process would be sluggish for the internal counterparts. As shown in Scheme 4.3, the palladium catalyst may first oxidatively add to the internal allyl electrophile to generate Pd-π-allyl complex **4.IV**. This process is known to occur via an S_N2' mechanism: the palladium displacs the leaving group from the opposite face.[5] Thus, starting from enantioenriched starting material, formation of enantioenriched **4.IV** is expected, and this may isomerize to **4.V** via a π-σ-π isomerization mechanism. In this process, apart from bringing the metal center to the opposite face, the R_3 group would also be isomerized, resulting in an unfavorable $A^{(1,3)}$ strain between R_2 and R_3.[1a] This unfavorable steric interaction may slow down the π-σ-π process. If transmetallation from allylB(pin) may proceed on the enantioeriched **4.IV** to generate the bis-(η^1-allyl)Pd complex **4.VI**, followed by 3,3' reductive elimination to deliver the desired 1,5-diene, product enantioerichment is dependent only on that of the starting electrophile. If this hypothesis holds true, development of a stereospecific allyl-allyl cross-coupling method is conceivable.

[5] (a) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

Scheme 4.3: Allyl-Allyl Cross-Coupling of Internal Allyl Electrophiles



B. Possible Challenges

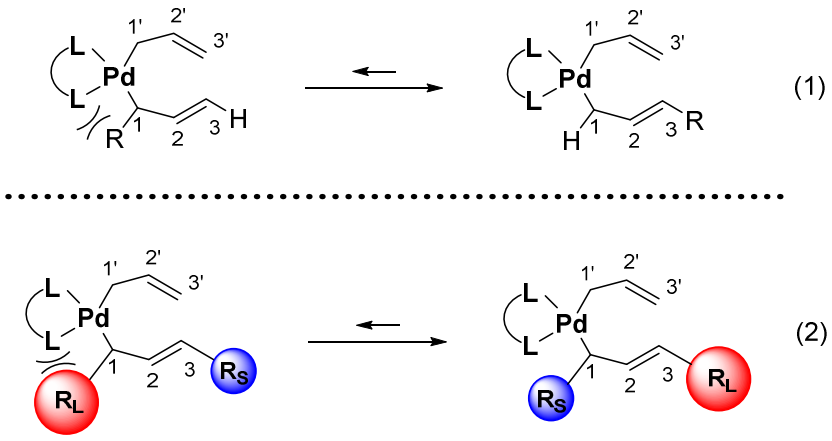
While the use of internal electrophiles offers advantages, we envisioned several difficulties that may arise in the allyl-allyl cross-coupling reaction using this electrophile class. Firstly, increased steric crowding of the substituted palladium-π-allyl species **4.IV** and **4.VI** may result in β-hydride elimination side products.[6] Secondly, it may be more difficult to control the product regioselectivity in the case of internal allyl electrophile.

Various solutions to address β-hydride elimination byproducts have been developed through the advancement of the Pd-catalyzed allyl-allyl cross-coupling reaction. On the other hand, product regioselectivity in internal allyl electrophiles was not studied. In allyl-allyl cross-coupling reactions where a terminal allyl electrophile is employed, the product regioisomer is determined by the 3,3' reductive elimination from the bis-(η^1-allyl)-Pd (Scheme 4.4, equation 1). There are two regiomeric arrangements for this intermediate, but the isomer in which the R substituent is placed away from the metal center is the dominant form as this conformation

[6] See more on Chapter II part IIB.

minimized steric interaction between the substituent and the Pd metal center.[7] In the case of internal allyl electrophiles, both termini of the allyl fragment are substituted. Thus, the two termini are less differentiated, which may lead to mixture of regioisomers. To address this challenge, we surmised that by controlling the relative size difference between the two substituents of the allyl electrophile, efficient regiocontrol may be realized (Scheme 4.4, equation 2). Experimental optimization is necessary to probe the degree to which sterically differentiated substituents effect product distribution, and will be presented in subsequent sections of this chapter.

Scheme 4.4: Regioselectivity of the Product 1,5-Dienes



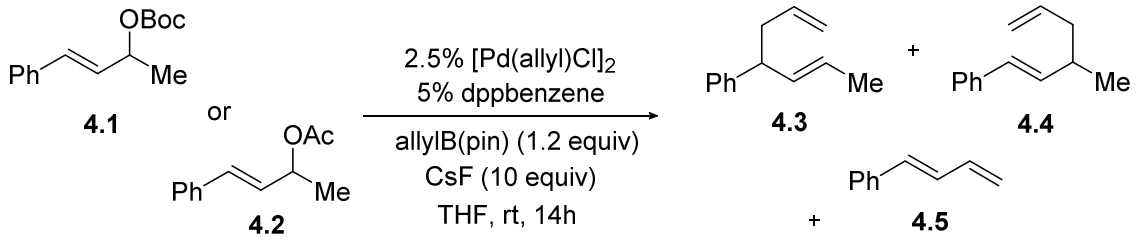
[7] See more details in chapter I, part II D and reference 1a.

II. Optimization

Using Boc protected cinnamyl alcohol **4.1** as the tested starting material, the conditions for standard allyl-allyl cross-coupling reactions were screened and shown in Table 4.1 below. Applying the previously developed conditions, 1,5-diene regioisomers **4.3** and **4.4** were obtained in a mixture with elimination product **4.5** in a 4:1:1 ratio favoring **4.3** (entry 1). To assess the ligand effect on the reaction outcome, PPh_3 and DPEphos were examined (entry 2 and 3). PPh_3 delivered only regioisomer **4.4** in 44% yield with the rest of the mass balance accounted for by side product **4.5**. Use of DPEphos ligand also favored formation of **4.4**, but produced a significant amount of **4.5**. To minimize formation of the undesired elimination product, several other conditions were screened. Neither increasing the reaction temperature to 60 ^{o}C nor replacing the additive from Cs_2CO_3 to CsF showed significant improvement (entry 4 and 5). However, when 15 equivalents of H_2O were added,[8] formation of elimination product **4.5** was diminished (entry 6). Finally, using acetate-protected cinnamyl alcohol **4.2** in place of **4.1** resulted in a 6:2:1 product mixture favoring 1,5-diene **4.3**. Notably, the combined yield of the **4.3** and **4.4** are 88%, with the rest of the mass being accounted for by elimination product **4.5**. This condition was selected as the optimal conditions for our substrate scope survey.

[8] See more on the role of water in Chapter II part II B and reference 1b

Table 4.1: Optimization for Allyl-Allyl Cross-Coupling Using Internal Allyl Electrophile



entry	S.M.	Variations	**4.3**:**4.4**:**4.5**[a]	yield (%)[b]
1	**4.1**	none	4:1:1	66
2[c]	**4.1**	10% PPh_3 ligand	-:1:1	43
3[c]	**4.1**	5% DPEphos ligand	1:10:40	16
4	**4.1**	60 °C	3:1:1	62
5[d]	**4.1**	Cs_2CO_3	3:1:1	78
6	**4.1**	15 equiv H_2O	8:2:1	78
7	**4.2**	3 equiv allylB(pin), 15 equiv H_2O	6:2:1	88

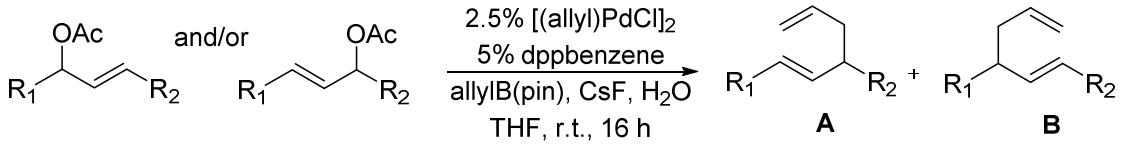
[a] Ratios were determined by crude ^1H NMR. [b] Yields are combined yield of **4.3** and **4.4**. [c] Ligand was used in replacement of dppbenzene. [d] Cs_2CO_3 was used in place of CsF.

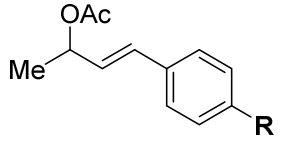
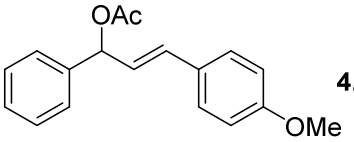
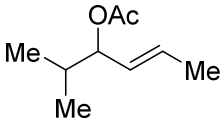
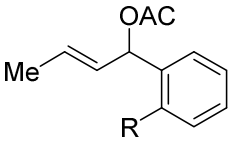
III. Regioselectivity of 1,5-Diene Products

At the onset of the project, we hypothesized that it may be possible to control the product regioselectivity *via* altering the relative size difference of the two substituents on the allyl electrophiles. During the optimization process using **4.1** or **4.2**, we observed a 3:1 or 4:1 regioselectivity favoring product **4.3** depending on the reaction conditions. To further understand the origins of regioselectivity, we examined a range of substrates (Table 4.2). While isosteric to **4.2**, electron donating *p*-OMe **4.8** reduced the regioselectivity of the reaction to 1:1 (entry 2). Substrates with electron withdrawing substituents provided higher regioselectivity favoring isomer **A**, with the *p*-CF_3 substituted **4.11** provided up to 10:1 isomeric ratio (entry 3 and 4). To see whether electronic or steric factors were the major effect governing product regioselectivity,

starting materials **4.12** and **4.13**, which differ only in steric or electronic properties, were tested (entry 5 and 6). Interestingly, both compounds provided low levels of regioselectivity, suggesting a subtle dependence on both electronic and steric factors. It was later determined that substrates with significant steric bias provided the highest levels of regiocontrol. Both *o*-OMe and *o*-Me substituted substrates **4.13** and **4.14** yielded 7:1 mixtures of regioisomers favoring isomer **A**, despite their differences in electronic properties (entry 7 and 8).

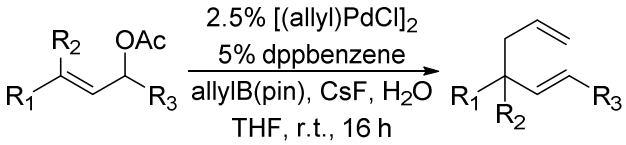
Table 4.2: Regioselectivity in Allyl-Allyl Cross-Coupling using Internal Allyl Electrophile

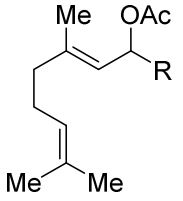
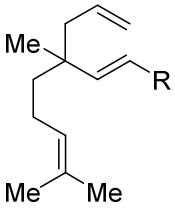
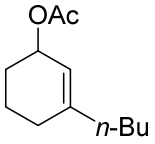
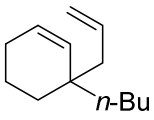
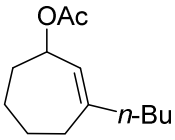
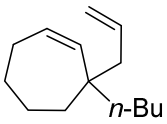
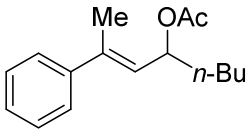
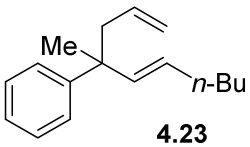
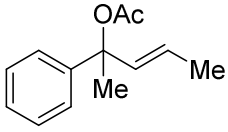
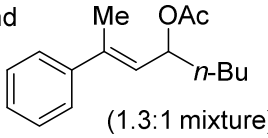
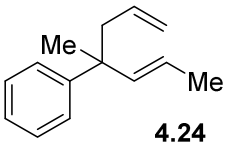


entry	substrate		R	A:B[b]	yield (%)[c]
1		**4.2**	H	3:1	88
2		**4.8**	OMe	1:1	69
3		**4.9**	Cl	4:1	92
4		**4.10**	CF_3	10:1	50
5		**4.11**		1:2	77
6		**4.12**		1:2	80[d]
7		**4.13**	Me	7:1	96
8[e]		**4.14**	OMe	7:1	80

[a] Conditions: 3 equiv. of allylB(pin), 10 equiv. of CsF, 15 equiv. of H_2O, 0.2 M THF. [b] Ratios were determined by ^1H NMR of crudes. [c] Yields are the average of two or more experiments and corrected to account for inseperable elimination product 1,3-diene. [d] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [e] Starting material is a 3:1 mixture of regioisomers favoring the shown configuration.

Table 4.3: Allyl-Allyl Cross-Coupling of Tri-substituted Allyl Acetates



entry	substrate	product	R	yield (%)[a]
1			**4.15** Me	80
2			**4.16** Me[c]	90
3			**4.17** *n*-Bu	75
4			**4.18** *i*-Pr	65
5			**4.19** Cy	74
6			**4.20** Ph	55
7			**4.21**	58
8			**4.22**	78
9			**4.23**	86
10	 and  (1.3:1 mixture)	 **4.24**		78

[a] Yield is the average of two or more experiments.

The observation in Table 4.2 suggested that with significant steric differentiation, a high level of regioselectivity can be achieved. This requirement is of advantage in the synthesis of

1,5-dienes containing all-carbon quaternary centers. As shown in Table 4.3, 1,5-dienes containing all-carbon quaternary centers are synthesized as single product regioisomers with a wide range of allyl electrophiles. Acyclic, aliphatic starting materials were well tolerated and provided good to excellent yields (entry 1 to 5). Cyclic allylic acetates containing 6 or 7 membered ring also were effectively cross-coupled to generate the desired 1,5-dienes (entry 7 and 8). Additionally, aromatic substituted starting materials are also suitable for the reaction, regardless of the position of the aromatic substituents or the relative position of the acetate leaving group (entry 6, 9 and 10).

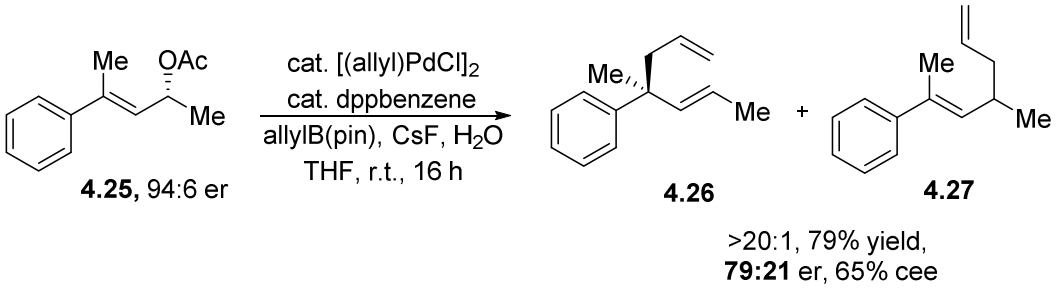
In conclusion, the regioselectivity of 1,5-diene product in Pd-catalyzed allyl-allyl cross-coupling reaction using internal allyl electrophiles depends on both the electronic and steric parameters of the allyl electrophiles. To obtain high level of regioselectivity, substrates with significant steric bias is necessary, and up to >20:1 regioselectivity can be realized. This method is useful in the synthesis of complexly substituted 1,5-dienes containing all-carbon quaternary center.

IV. Stereospecific Allyl-Allyl Cross-Coupling

A. Initial Results

After establishing an understanding of factors controlling the regioselectivity, we studied the efficiency of the stereospecific cross-coupling. Applying the optimized conditions to enantioenriched **4.25**, the anticipated diene **4.26** was observed in >20:1 selectivity and 79% yield (Scheme 4.5); however its er was only 79:21, which correspond to only 65% chirality transfer (cee) from the starting material. This erosion of enantioenrichment was not anticipated in our original hypothesis of the allyl-allyl cross-coupling reaction. Later efforts have revealed a less-studied isomerization mechanism. The solution to overcome this unexpected challenge will be discussed in a subsequent part of this chapter.

Scheme 4.5: Initial Result in Stereospecific Allyl-Allyl Cross-Coupling

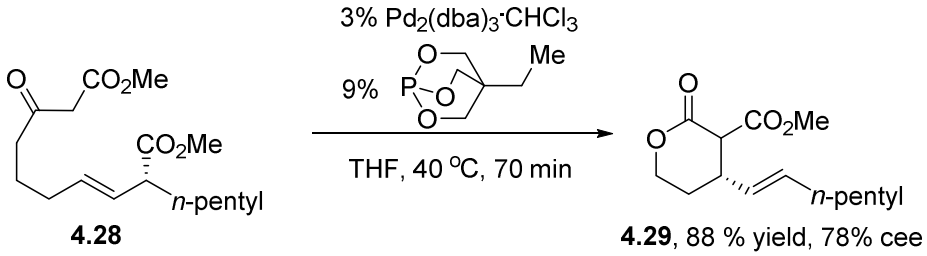


B. Hypothesis for Incomplete Chirality Transfer

To gain insight into the incomplete chirality transfer, we analyzed similar Pd-catalyzed processes reported in literature. In 1984, Tsuji and co-workers reported the Pd-catalyzed intramolecular allylic alkylation to synthesize cyclic lactones (Scheme 4.6).[3a] In this report, the

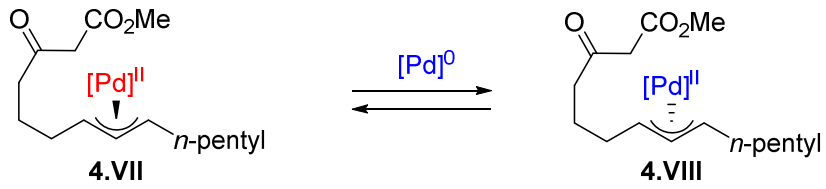
researchers noted incomplete chirality transfer, in which cyclic lactone **4.29** was formed in 88% yield, but with only 78% cee. To rationalize this observation, a redox-transmetallation mechanism was proposed by the researchers (Scheme 4.7). Upon oxidative addition to the substrate, [Pd]-π-allyl intermediate **4.VI** is generated; at this point, available $[Pd]^0$ in the reaction medium might displace the $[Pd]^{II}$ complex on **4.VI** from the opposite face of the π-allyl, thus forming diastereomer **4.VII**, which would lead to the desired product's enantiomer . This mechanism supports the author's observation that increasing the $[Pd]^0$ loading to 20 mol % led to a reduction of chirality transfer to only 41%. Tsuji's proposal was later studied in further mechanistic detail by Bäckvall,[9c, d] Amatore,[9e, f] and others.[9]

Scheme 4.6: Pd-catalyzed Intramolecular Allylic Alkylation



4.28 **4.29**, 88 % yield, 78% cee

Scheme 4.7: Redox-transmetallation proposed by Tsuji *et al*

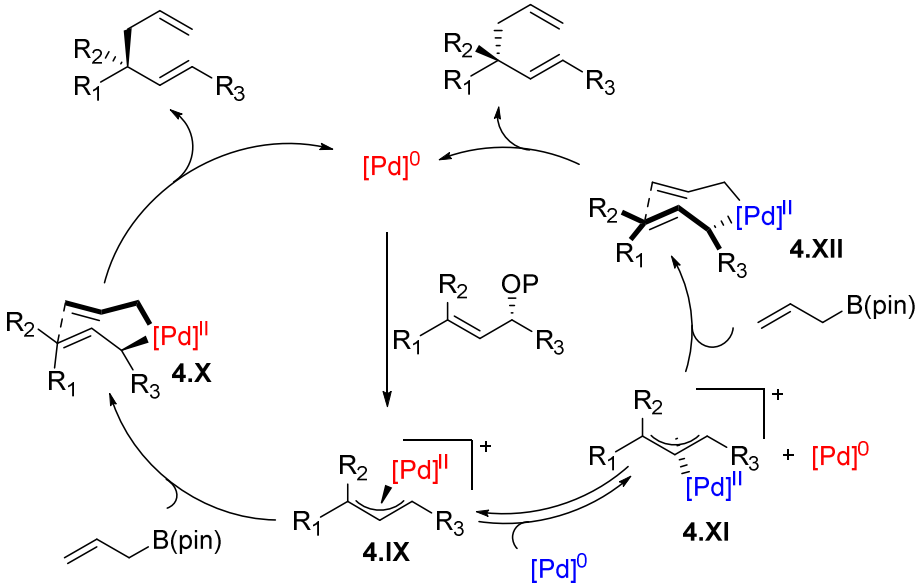


4.VII **4.VIII**

[9] (a) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046. (b) Kurosawa, H.; Ogoshi, S.; Chatani, N.; Kawasaki, Y.; Murai, S.; Ikeda, I. *Chem. Lett.* **1990**, 1745. (c) Bäckvall, J.-E.; Granberg, K. L.; Heumann, A. *Isr. J. Chem.* **1991**, *31*, 17. (d) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (e) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372. (f) Amatore, C.; Jutand, A.; Mensah, L.; Meyer, G.; Fiaud, J.-C.; Legros, J. Y. Eur. *J. Org. Chem.* **2006**, 1185. (g) Blessley, G.; Holden, P.; Walker, M.; Brown, J. M.; Gouverneur, V. *Org. Lett.* **2012**, *14*, 2754. (h) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc.* **2012**, *135*, 443.

In accord with the above proposal, we surmised that a redox-transmetallation mechanism may be operative in our allyl-allyl cross-coupling reaction using internal electrophiles. As depicted in Scheme 4.8, upon oxidative addition to the electrophile, Pd-π-allyl **4.IX** is generated. At this stage, if transmetallation from allylB(pin) is rapid, **4.IX** will be readily converted to the bis-η^1-allyl Pd intermediate **4.X**; a subsequent 3,3'-reductive elimination will then facilitate formation of the desired 1,5-diene in a stereospecific manner. However, if the transmetallation step is slow, the redox-transmetallation process may occur, in which available $[Pd]^0$ in the reaction displaces $[Pd]^{II}$ from the π-allyl **4.IX** and generate enantiomer **4.XI**. If transmetallation from allylB(pin) occurs on **4.XI**, followed by the 3,3' reductive elimination process, the opposite enantiomer of the desired 1,5-diene will be synthesized, resulting in the overall reduction of chirality transfer from the starting material.

Scheme 4.8: Mechanistic Hypothesis in the Allyl-Allyl Cross-Coupling Using Internal Allyl Electrophile



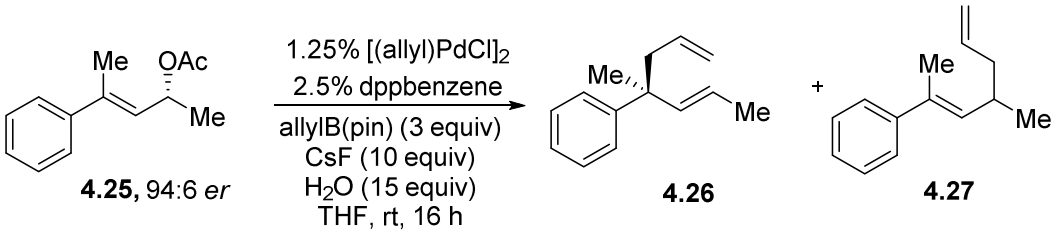
Based on the hypothesis described above, two solutions to minimized the redox-transmetallation mechanism may be possible. First, if the rate of transmetallation can be improved so that its outcompetes redox-transmetallation, all available **4.IX** generated upon oxidative addition may be converted to **4.X**. Secondly, the redox-transmetallation process is second order in [Pd] concentration whereas the transmetallation exibits first order dependence in [Pd]. Thus, lowering the amount of catalyst may retard redox-transmetallation, leading to the overall improvement of stereospecificity for the cross-coupling reaction.

C. Optimization of Stereospecificity of the Allyl-Allyl Cross-Coupling Reaction

To improve the chirality transfer of the cross-coupling reaction, we first attempted to increase the rate of the transmetallation process by increasing the amount of allylB(pin) and CsF additive in the reaction to 10 equivalents and 30 equivalents, respectively (Scheme 4.8, entry 2). In agreement with our hypothesis in section B, increased rate of transmetallation led to improved chirality transfer, and 1,5-diene **4.26** was obtained in 85:15 er, corresponding to 80% cee. To test the second hypothesis, the catalyst loading was reduced (entry 3 - 6). At 1 mol % catalyst loading, **4.26** was obtained in excellent chirality transfer (98% cee), though at the cost of diminished yield and regioselectiviy. Increasing the catalyst loading reduced the chirality transfer. At 2.5 mol % catalyst loading, 90% cee was observed; however, at 10 mol % and 15 mol %, the chiralitry transfer reduced to 47% and 26% cee respectively. The trend in catalyst loading and chirality transfer further supported the hypothesis of a the redox-transmetallation mechanism being operative. Additionally, the observation that elevated CsF and allylB(pin) concentrations lead to improve cee suggested that the redox-transmetallation occurred only on

4.IX and **4.XI**. At this point, it is unclear why the linear regioisomer **4.27** is produced at reduced catalyst loading and elevated CsF and allylB(pin) (entry 2-4)

Table 4.4: Optimization Progress for Stereospecificity in Allyl-Allyl Cross-Coupling



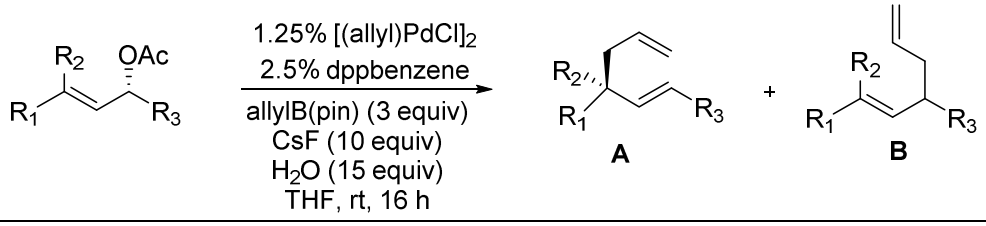
entry	% cat	**4.26**:**4.27**[a]	yield (%)[b]	er[c]	*cee* (%)[d]
1	5	>20:1	79	79:21	65
2[e]	5	3:1	60	85:15	80
3	1	1:1	50	94:6	98
4	2.5	7:1	70	92:8	90
5	10	>20:1	72	71:29	47
6	15	>20:1	73	61:39	26

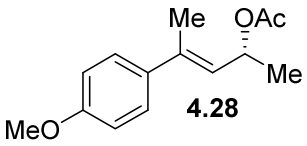
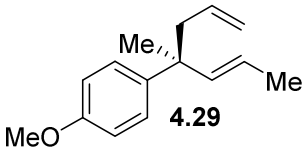
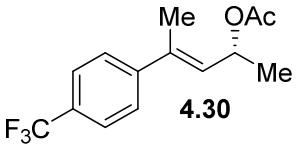
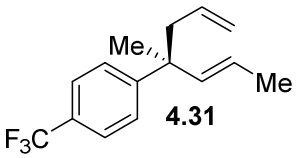
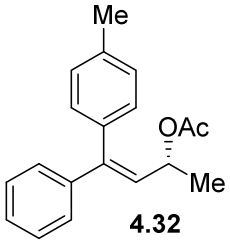
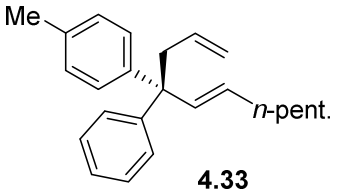
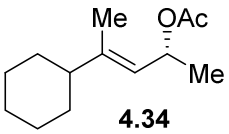
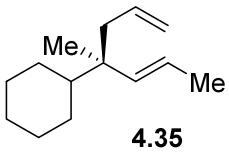
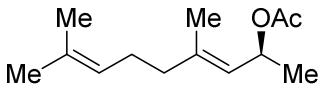
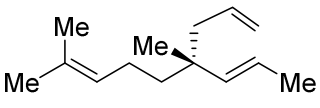
[a] Ratio was determined by ^{1}H NMR. [b] Yields are average of two or more experiments and are combined yields of **4.26** and **4.27**, corrected for inseperable elimination product 1,3-diene. [c] er were determined by chiral GC. [d] cee was calculated as follow: (ee product)/(ee starting material) X 100. [e] 10 equiv allylB(pin) and 30 equiv CsF were employed.

D. Substrate Survey for the Stereospecific Allyl-Allyl Cross-Coupling

Using 2.5% catalyst loading as the optimal conditions, several substrates were surveyed to gain insight to the scope and limitations of the chirality transfer in this cross-coupling reaction (Table 4.5). A smilar catalyst concentration trend was observed for *p*-OMe substituted **4.28**. At 2.5% catalyst loading, the corresponding 1,5-diene product was obtained in 88% cee, while at 10% and 20% catalyst loading, cee dropped to 56% and 48%, respectively. Significant erosion of enantiopurity was observed for electron withdrawing *p*-CF_3 substrate **4.30**, with cee at only 34% (entry 4). When diaryl starting material **4.32** was employed, a moderate level of cee was observed (entry 5). Interestingly, when an all aliphatic substrate was used, an excellent level of chirality transfer was realized. 1,5-Diene containing cyclohexyl-substituted **4.35** was obtained in 100% cee, while gerniol derived 1,5-diene **4.37** was synthesized in 99% cee (entry 6 and 7). The examples in entry 5 and 7 further exemplified the power of the stereospecific cross-coupling reaction because it would be very difficult to synthesize a stereocenter where there is minimal differentiation among the substituents by other means.

Table 4.9: Chirality Transfer Substrate Scope



Entry	Substrate	Product	**A**:**B**[a]	Yield (%)[b]	er[c]	cee
1	 **4.28**	 **4.29**	2:1	70	90:10	88
2[d]			10:1	69	75:25	56
3[e]			>20:1	85	71:29	48
4	 **4.30**	 **4.31**	5:1	69	67:33	34
5	 **4.32**	 **4.33**	>20:1	95	80:20	67
6	 **4.34**	 **4.35**	>20:1	49	94:6	100
7	 **4.36**	 **4.37**	>20:1	54	96:4	99

[a] Ratio was determined by ^{1}H NMR. [b] Yields were average of two or more experiments. [c] er were determined by chiral GC or HPLC. [d] Catalyst loading of 5 mol % was used. [e] Catalyst loading of 10 mol% was used.

V. Conclusion

The scope of the palladium catalyzed allyl-allyl cross-coupling reaction has been extended to include internal allyl electrophiles. Successful application of this electrophile class enables the rapid synthesis of complex substituted 1,5-dienes with readily differentiated π-systems. To effectively control the regioselectivity of the products, it is necessary to use allyl electrophiles containing substituents with significant steric differentiation. This requirement is of great advantage in the synthesis of 1,5-diene containing all-carbon quaternary center. Lastly, internal allyl electrophiles provided additional opportunity to perform stereospecific cross-coupling, thus eliminating the need for expensive chiral phosphine ligands. A redox-transmetallation mechanism was operative in the reaction, which decreased the chirality transfer property of aromatic substituted starting materials. Lowering the catalyst loading helps to overcome this issue.

V. Experimental Procedure

A. General information

^{1}H NMR spectra were recorded on a Varian Gemini-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, υmax cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

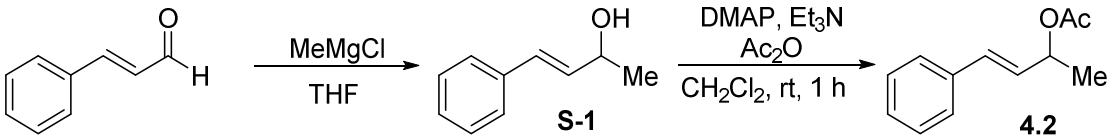
Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate (KMnO4) in water, ceric ammonium molybdate (CAM) in water, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco β-Dex 120 column, or a Supelco Asta Chiraldex B-DM with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar SFC equipped with a

Waters 2998 photodiode array detector and an analytical-2-prep column oven with methanol as the modifier. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1120 compact chromatograph equipped with gradient pump and variable wavelength detector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), Toluene (PhMe), and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Triethylamine (TEA) and Ethyl Acetate (EtOAc) were distilled from calcium hydride. Tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$**],** bis(cyclopentadienyl)zirconium(IV) dichloride ($ZrCp_2Cl_2$), (*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole ((*R*)-(-)-DTBM-Segphos), 1,2-bis(diphenylphosphino)benzene (dpp-Benzene) were purchased from Strem Chemicals Inc. Allylboronic acid pinacol ester [allylB(pin)] was generously donated by Frontier Scientific. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

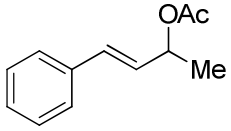
B. Preparation and Characterization of Starting Materials

Synthesis and characterization of (*E*)-4-phenylbut-3-en-2-yl acetate (4.2):



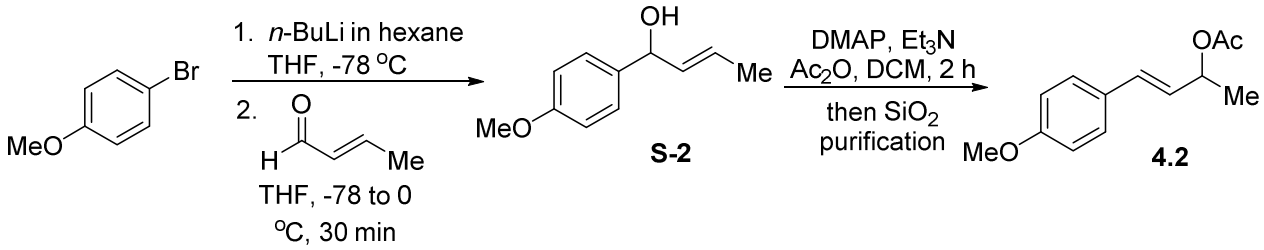
General procedure A: To a flame-dried round-bottomed flask equipped with a stir bar was added 3.0 M methylmagnesium chloride in THF (5.53 mL, 16.5 mmol) and THF (25 mL). The solution was cooled to 0 ºC and cinnamaldehyde (1.88 mL, 14.9 mmol) in THF (5 mL) was added dropwise *via* syringe. The reaction was allowed to stir at 0 ºC for 1 h. The reaction was quenched with water and 0.5 M HCl (aq). The organic layer was separated, and the aq. layer was extracted with ethyl acetate three times. The combined organics were washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo.* **S-1** was then acetylated using procedure **B**.

General Procedure B: A 100 mL round-bottomed flask was charged with **S-1** (2.4 g, 9.5 mmol), 4-dimethylaminopyridine (116 mg, 0.95 mmol) and CH_2Cl_2 (20 mL). Triethylamine (2.7 mL, 19 mmol) was added and the reaction stirred for 20 minutes, followed by the addition of acetic anhydride (1.8 mL, 19 mmol). The reaction was capped with a septum, vented with a needle, and was allowed to stir while warming to room temperature for 1 h. The reaction was then quenched with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 three times. The organic portions were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on silica gel (5% Et_2O/pentane) to afford a colorless oil (88 % yield over 2 steps).



(*E*)-4-phenylbut-3-en-2-yl acetate (4.1): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (3H, d, J = 6.6 Hz), 2.08 (3H, s), 5.53 (1H, quint, J = 6.8 Hz), 6.19 (1H, dd, J = 15.9, 6.8 Hz), 6.60 (1H, d, 15.9 Hz), 7.23-7.26 (1H, m), 7.29-7.34 (2H, m), 7.36-7.39 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3, 21.4, 71.0, 126.5, 127.9, 128.8, 131.5, 136.3, 170.3; IR (neat): 2980 (w), 1732 (s), 1370 (m), 1235 (s), 1040 (m), 966 (m), 951 (m), 748 (m), 693 (m) cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}O_2$ [M+H]: calculated: 190.0994, found: 190.1002. R_f = 0.25 in 5% EtOAc/hexane.

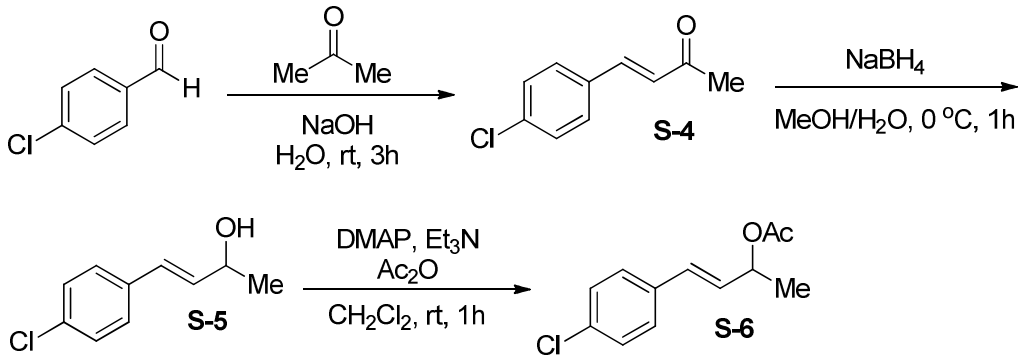
Synthesis and characterization of (*E*)-4-(4-methoxyphenyl)but-3-en-2-yl acetate (4.2):



General Procedure C: A flame-dried round-bottomed flask under N_2 was equipped with a stir bar and charged with 4-bromoanisole (0.12 mL, 1 mmol) and THF (4 mL). The solution was cooled to -78 °C before adding 2.5 M *n*-butyllithium in hexane (0.4 mL, 1.0 mmol) dropwise via syringe. The reaction was stirred for 10 minutes before the dropwise addition of crotonaldehyde (0.85 mL, 1.0 mmol) in THF (1 mL). After 10 minutes at -78 ºC, the reaction was warmed to room temperature and was allowed to stir for 30 min. The reaction was diluted with ether (10 mL) before quenching with water (5 mL) at 0 ºC. The aqueous portion was extracted with ether three times and the organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **S-2**. The alcohol **S-2** was then protected following procedure **B**.

After purification on SiO_2, the product rearranged to the corresponding regioisomer. Spectral data is in accordance with literature values.[10]

Synthesis and characterization of (*E*)-4-(4-chlorophenyl)but-3-en-2-yl acetate (4.9): [10]



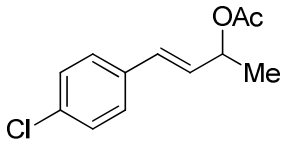
General procedure D:

Step 1: A round-bottom flask equipped with a stir bar was charged with 4-chlorobenzaldehyde (0.56 g, 4.0 mmol) and D.I. water (25.5 mL). A suspension of acetone (1.46 mL, 20.0 mmol) and NaOH (0.58 g, 14.4 mmol) in D.I. water (8.5 mL) was added to the reaction. The mixture was stirred at room temperature for 3 h. The reaction was quenched with water and the aqueous layer was extracted with DCM three times. The organic portion was washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*.

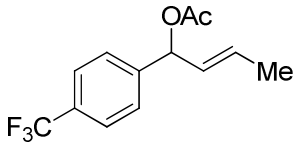
Step 2: A round-bottom flask equipped with a stir bar was charged with **S-4** (0.63 g, 2.6 mmol), H_2O (0.5 mL) and MeOH (2 mL). The solution was cooled to 0 ^oC before $NaBH_4$ (113.5 mg, 3 mmol) was added. The reaction was stirred at room temperature for 1 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The aqueous layer was extracted with CH_2Cl_2 three

[10] Akai, S.; Hanada, R.; Fujiwara, N.; Kita, Y.; Egi, M. *Org. Lett.* **2010**, *12*, 4900

times. The organic portion was dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The allyl alcohol **S-5** was then protected using general procedure **B**. The crude material was purified on silica gel (5% Et_2O/pentane) to afford a clear colorless oil (60% yield over 2 steps).

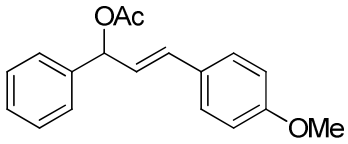


(*E*)-4-(4-chlorophenyl)but-3-en-2-yl acetate (4.9): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (3H, d, *J* = 6.5 Hz), 2.07 (3H, s), 5.50 (1H, app dq, *J* = 13.0, 6.6 Hz), 6.16 (1H, dd, *J*= 15.9, 6.6 Hz), 6.55 (1H, d, *J* = 15.9 Hz), 7.26-7.31 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3. 21.3, 101.7, 127.7, 128.7, 129.5, 133.5, 134.8, 170.2; IR (neat): 2981 (w), 1734 (s), 1492 (m), 1371 (m), 1238 (s), 1094 (m), 1042 (m), 1013 (m), 968 (m), 952 (m), 806 (m) cm^{-1}; HRMS (ESI+) for $C_{12}H_{13}ClO_2$ [M+H]: calculated: 224.0604, found: 224.06115. R_f = 0.24 in 5% EtOAc/hexane.

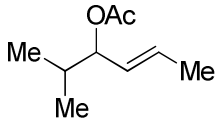


(*E*)-1-(4-(trifluoromethyl)phenyl)but-2-en-1-yl acetate (4.10): From commercially available **1-Bromo-4-(trifluoromethyl)benzene, procedure C and B were followed.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.73 (3H, d, *J* = 6.4 Hz), 2.11 (3H, s), 5.63 (1H, dd, *J* = 15.2, 6.9 Hz), 5.78 (1H, dq, *J* = 15.2, 6.4 Hz), 6.24 (1H, d, *J* = 6.9 Hz), 7.45 (2H, d, *J* = 8.3 Hz), 7.61 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 143.7, 130.6, 130.0 (q, $^2J_{CF}$ = 32.4 Hz), 128.9, 127.0, 125.4 (q, $^3J_{CF}$ = 3.6 Hz), 124.0 (q, $^1J_{CF}$ = 271.7 Hz), 75.6, 21.2, 17.7; IR (neat): 2921(br), 1737 (s), 1371 (m), 1323 (s), 1227(s), 1164 (s), 1122 (s), 1065 (s), 1016 (s), 962 (s), 831 (m) cm^{-1}; HRMS (ESI+) for $C_{11}H_{10}F_3$ [M-OAc+H]: calculated 199.0735, found: 199.0783. The crude material was purified

on silica gel (5% Et_2O/pentane) to afford a colorless yellow oil (86 % yield over 2 steps). R_f = 0.32 in 5% EtOAc/hexane.



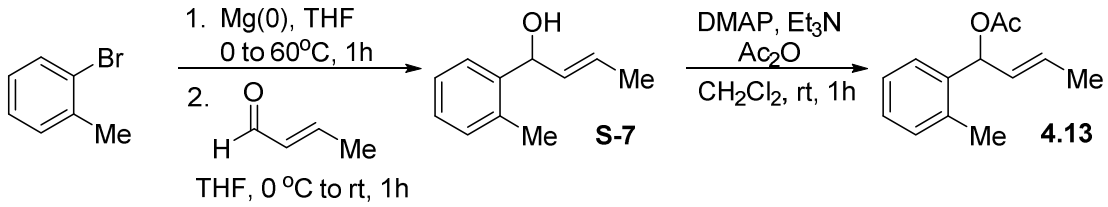
(*E*)-3-(4-methoxyphenyl)-1-phenylallyl acetate (4.11): From commercially available 3-(4-methoxyphenyl)-1-phenyl-propenone, general procedure **D,** step 2 was followed. The allyl alcohol was protected using general procedure **B.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.13 (3H, s), 3.81 (3H, s), 6.22 (1H, dd, *J* = 16.1, 7.3 Hz), 6.42 (d, *J* = 7.3 Hz), 6.58 (1H, d, *J* = 16.1 Hz), 6.84 (2H, d, *J* = 8.8 Hz), 7.28-7.44 (7H, m); ^{13}C NMR (125 MHz $CDCl_3$): δ 21.4, 45.9, 55.3, 76.4, 114.0, 125.3, 127.0, 127.9, 128.0, 128.6, 128.9, 132.3, 139.5, 159.6, 170.1; IR (neat): 2934 (br), 1735(s), 1607 (m), 1512 (s), 1455 (w), 1370 (m), 1300 (w), 1233 (s), 1176 (m) cm^{-1}; HRMS (ESI+) for $C_{18}H_{18}O_3$ [M]: calculated: 282.1256, found: 282.1267. The crude material was used without purification (83% yield over 2 steps). R_f = 0.33 in 10% EtOAc/hexane.



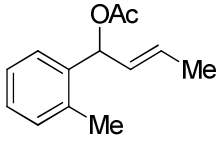
(*E*)-2-methylhex-4-en-3-yl acetate (4.12): From commercially available isopropylmagnesium chloride and crotonaldehyde, general procedure **A** and **B** were followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (6H, app. t, *J* = 6.1 Hz), 1.70 (3H, dd, *J* = 6.6, 1.7 Hz), 1.82 (1H, app octet, *J* = 6.9 Hz), 2.04 (3H, s), 4.98 (1H, t, *J* = 7.1 Hz), 5.39 (1H, ddq, *J* = 15.4, 7.8, 1.7 Hz), 5.70 (1H, dq, *J* = 15.4, 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 18.0, 18.2, 21.3, 32.0, 79.6, 127.8, 129.9, 170.4; IR (neat): 2963 (m), 2934 (w), 2876 (w), 1735 (s), 1469 (w), 1450 (w), 1371 (m), 1236 (s), 1018 (m), 968 (m) cm^{-1}; HRMS (ESI+) for $C_7H_{13}O_2$ [M -OAc]: calculated: 97.1017, found: 97.1020. The crude material was purified on

silica gel (100% pentane) to afford a colorless oil (59% yield over 2 steps). R_f = 0.35 in 5% EtOAc/hexane.

Synthesis and characterization for (*E*)-4-(*o*-tolyl)but-3-en-2-yl acetate (4.13):

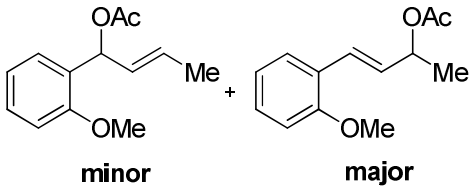


General Procedure E: To a flame-dried round-bottom flask equipped with a stir bar and reflux condenser was added magnesium turnings (280 mg, 11.5 mmol). An additional flame-drying was performed before THF (22 mL) and 2-bromotoluene (1.32 mL, 11 mmol) was added dropwise at 0 ºC. The solution was refluxed at 60 ºC for 1 h, then cooled to 0 ºC before a solution of crotonaldehyde (0.83 mL, 10 mmol) in THF (5 mL) was added dropwise *via* syringe. The reaction was allowed to stir at ambient temperature for 1 h. The reaction was cooled to 0 ºC and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate three times and the combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The allyl alcohol was then protected using general procedure **B**. The crude material was purified on silica gel (5% Et_2O/pentane) to afford **S-8** as a colorless oil (76% yield over 2 steps).



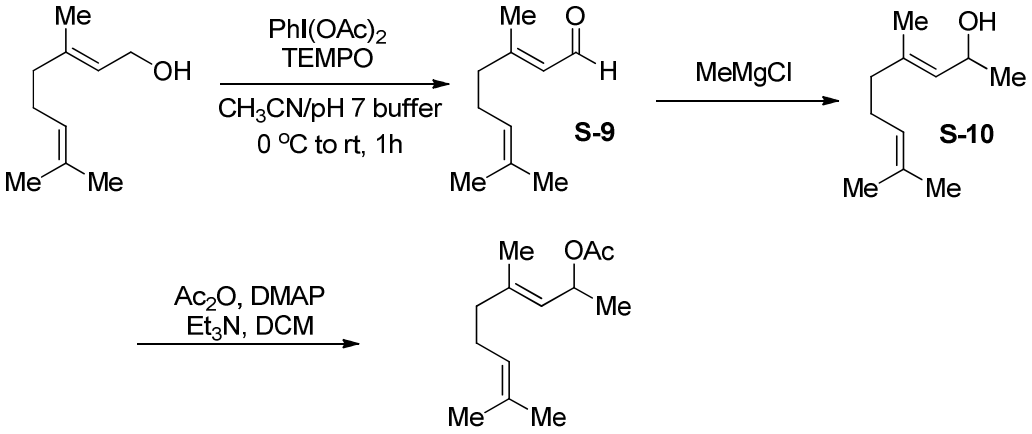
(*E*)-4-(*o*-tolyl)but-3-en-2-yl acetate (4.13): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (3H, d, *J* = 6.6 Hz), 2.08 (3H, s), 2.35(3H, s), 5.55 (1H, app q, *J* = 6.6 Hz), 6.07 (1H, dd, *J* = 15.9, 6.8 Hz), 6.82 (1H, d, *J* = 15.8 Hz), 7.13-7.18 (3H, m), 7.41-7.44(1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.7, 20.5, 21.4, 71.2, 125.6, 126.0, 127.7, 129.5, 130.1,

130.2, 135.4, 135.6, 170.3; IR (neat): 3019 (w), 2979 (w), 2932 (w), 1734 (s), 1486 (w), 1459 (w), 1370 (m), 1234 (s), 1152 (w), 1039 (m), 966 (m), 950 (m), 749 (m) cm^{-1}; HRMS (ESI-) for $C_{13}H_{16}O_2$ [M+H]: calculated: 205.1138, found: 205.0484. R_f = 0.31 in 5% EtOAc/hexane.



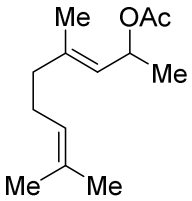
(*E*)-4-(2-methoxyphenyl)but-3-en-2-yl acetate (major – 4.14) and (E)-1-(2-methoxyphenyl)but-2-en-1-yl acetate (minor): From commercially available 1-bromo-2-methoxybenzene, general procedure **E** and **B** were followed. The desired starting material isomerized to its regioisomer during silicagel purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (3H, d, *J* = 6.3 Hz, major), 1.69 (3H, d, *J* = 4.9 Hz, minor), 2.07 (3H, s, major), 2.08 (3H, s, minor), 3.84 (3H, s, minor), 3.85 (3H, s, major), 5.54 (1H, dq, *J* = 6.3, 6.3 Hz, major), 5.62-5.76 (2H, m, minor), 6.22 (1H, dd, *J* = 16.1, 6.8 Hz, major), 6.60 (1H, d, *J* = 5.4 Hz, minor), 6.84-6.99 (3H+1H, m, major+minor), 7.20-7.30 (1H+2H, m, major+minor), 7.36 (1H, d, *J* = 7.4 Hz, minor), 7.42 (1H, d, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 20.4, 21.3, 21.4, 55.4, 55.6, 70.7, 71.5, 110.7, 110.8, 120.6, 125.3, 126.5, 127.0, 127.1, 128.2, 128.6, 128.9, 128.9, 129.3, 156.4, 156.9, 169.9, 170.3; IR (neat): 2978 (br), 2937 (br), 2838 (w), 1731 (s), 1598 (m), 1580 (w), 1490 (m), 1463 (m), 1438 (m), 1370 (m), 1232 (s) cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}O_3$ [M +H]: calculated: 220.1099, found: 220.1109. The crude material was purified on silica gel (10% ether/pentane) to afford a clear oil (42%y after 2 steps). R_f = 0.23 in EtOAc/hexane.

Synthesis and characterization of (*E*)-4,8-dimethylnona-3,7-dien-2-yl acetate (starting material for 4.15)



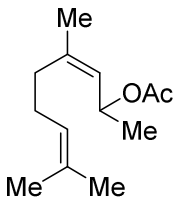
General procedure F: A flame-dried round-bottom flask under N_2 was equipped with a stir bar, and charged with $PhI(OAc)_2$ (44.0 mmol, 14.2 g), TEMPO (4.0 mmol, 270 mg), CH_3CN (34 mL), and aqueous pH 7 buffer (9.6 mL). The solution was cooled to 0 ºC before adding geraniol (40.0 mmol, 6.17 g) *via* syringe. The reaction was allowed to stir while warm to room temperature for 1 h. $Na_2S_2O_3$ was then added. The organic layer was removed and the aqueous layer was extracted with ether three times. The organic portions were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified on silica gel (10% Et_2O/hexane) to afford a colorless oil (4.9 g, 80% yield).

S-9 was subjected to conditions in general procedure **A** and **B** to obtain the desired starting material as a colorless oil (72% yield over 3 steps).

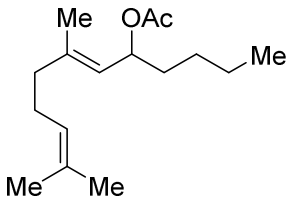


(*E*)-4,8-dimethylnona-3,7-dien-2-yl acetate (starting material for 4.15): ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 6.4 Hz), 1.60 (3H, s), 1.68 (3H, s), 1.70 (3H, d, *J* = 1.3 Hz), 1.97-2.02 (2H, m), 2.01 (3H, s), 2.04-2.12 (2H, m),

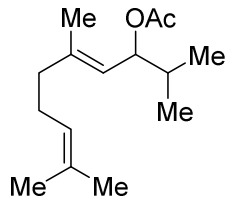
5.07 (1H, br. t, J = 6.8 Hz), 5.16 (1H, d, J = 8.8 Hz), 5.59 (1H, dq, J = 15.1, 6.3 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 16.6, 17.6, 20.9, 21.4, 25.6, 26.3, 39.4, 68.1, 123.8, 124.7, 131.7, 139.4, 170.4; IR (neat): 2974 (w), 2929 (w),1732 (m), 1447 (w), 1369 (m), 1240 (s), 1144 (w), 1040 (m), 951 (w) cm^{-1}; HRMS (ESI+) for $C_{11}H_{19}$ [M-OAc]: calculated: 151.1492, found: 151.1482. R_f = 0.65 in 10% EtOAc.



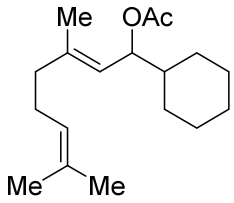
(*Z*)-4,8-dimethylnona-3,7-dien-2-yl acetate (starting material for 4.16): From commercially available *cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol), general procedure **F**, **A**, and **B** were followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, d, J = 6.3 Hz), 1.60 (3H, s), 1.67 (3H, s), 1.72 (3H, d, J = 1.4 Hz), 2.00 (3H, s), 2.01-2.17 (3H, m), 2.21-2.22 (1H, m), 5.09 (1H, br t, J = 6.8 Hz), 5.17 (1H, d, J = 9.3 Hz), 5.59 (1H, dq, J = 15.4, 6.1 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 17.6, 21.2, 21.4, 23.3, 25.7, 26.5, 32.4, 67.8,123.8, 125.4, 132.0, 139.8, 170.3; IR (neat): 2969 (w), 2930 (w),2860 (w), 1734 (m), 1670 (w), 1447 (w), 1369 (m), 1240 (s), 1035 (m), 950 (w) cm^{-1}; HRMS (ESI+) for $C_{11}H_{19}$ [M-OAc]: calculated: 151.1492, found: 151.1534. The crude material was purified on silica gel (2% Et_2O/pentane) to afford a colorless oil (55% yield over 4 steps). R_f = 0.34 in 5% EtOAc/hexane.



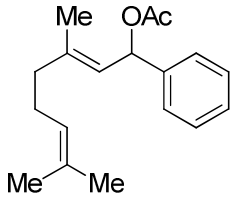
(*E*)-7,11-dimethyldodeca-6,10-dien-5-yl acetate (starting material for 4.17): From commercially available geraniol, and *n*-butyllithium, **procedure F, A,** and **B** was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.0 Hz), 1.17-1.37 (4H, m), 1.44-1.52 (1H, m), 1.60 (3H, s), 1.60-1.66 (1H, m), 1.68 (3H, s), 1.71 (3H, d, *J* = 1.3 Hz), 1.98-2.20 (2H, m), 2.02 (3H, s), 2.06-2.12 (2H, m), 5.04-5.10 (2H, m), 5.47 (1H, dt, *J* = 9.0, 6.8 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 7.0, 9.8, 10.7, 14.4, 15.5, 18.6, 19.2, 20.2, 27.7, 32.5, 64.6, 116.7, 116.9, 124.6, 133.2, 163.4; IR (neat): 2959 (w), 2930 (m), 2860 (w), 1734 (s), 1671 (w), 1443 (w), 1369 (m), 1238 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{25}$ [M-OAc]: calculated: 193.1962, found: 193.1963. The crude material was purified on silica gel (2% Et_2O/pentane) to afford a clear oil (79% yield over 3 steps). R_f = 0.53 in 5% EtOAc/hexane.



(*E*)-2,5,9-trimethyldeca-4,8-dien-3-yl acetate (starting material for 4.18): From commercially available geraniol, and isopropylmagnesium chloride (2M in THF), general procedure **F, A,** and **B** was followed**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, d, *J* = 12.2 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 1.60 (3H, s), 1.67 (3H, s), 1.72 (3H, d, 1.3 Hz), 1.82 (1H, octet, *J* = 6.8 Hz), 2.01-2.04 (2H, m), 2.03 (3H, s), 2.06-2.14 (2H, m), 5.03-5.12 (1H, m), 5.28 (1H, dd, *J* = 9.5, 7.1 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 16.9, 17.7, 17.8, 18.3, 21.3, 25.7, 26.3, 32.5, 39.7, 76.0, 122.0, 124.0, 131.6, 140.8, 170.5; IR (neat): 2964 (w), 2928 (w), 1734 (s), 1671 (w), 1446 (w), 1369 (m), 1239 (s), 1017 (m), 972 (m) cm^{-1}; HRMS (ESI+) for $C_{13}H_{23}$ [M-OAc]: calculated: 179.1805, found: 179.1828. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (68% yield over 3 steps). R_f = 0.4 in 5% EtOAc/hexane.

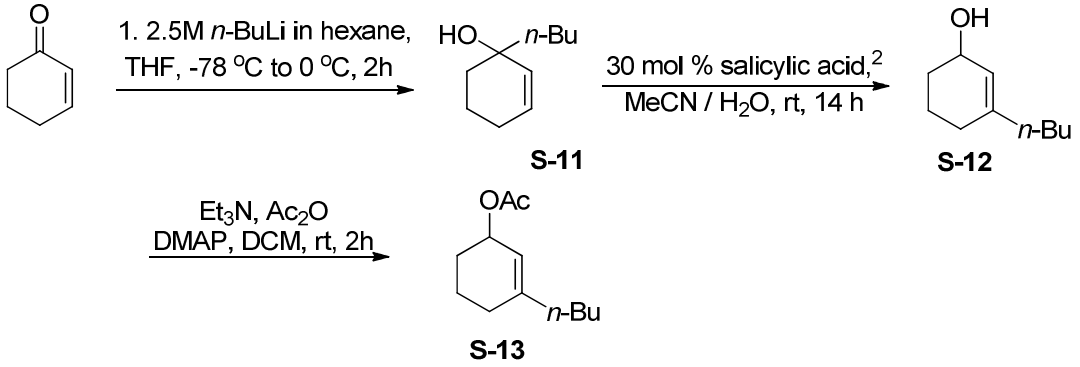


(*E*)-1-cyclohexyl-3,7-dimethylocta-2,6-dien-1-yl acetate (starting material for 4.19): From commercially available geraniol, and cyclohexylmagnesium chloride (2M in Et_2O), general procedure **F, A,** and **B** was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86-1.02 (2H, m), 1.07-1.28 (4H, m), 1.44-1.54 (1H, m), 1.60 (3H, s), 1.62-1.69(2H, m), 1.65 (3H, s), 1.69-1.78 (2H, m), 1.70, (3H, s), 1.98-2.06 (2H, m), 2.00 (3H, s), 2.08-2.14 (2H, m), 5.01-5.10 (2H, m), 5.28 (1H, m); ^{13}C NMR (125 MHz $CDCl_3$): δ 16.9, 17.7, 21.3, 25.7, 25.9, 26.0, 26.2, 26.4, 28.3, 28.9, 39.7, 42.2, 75.3, 122.4, 124.0, 131.6, 140.6, 170.5; IR (neat): 2926 (s), 2854 (m), 1734 (s), 1450 (m), 1369 (m), 1240 (s), 1016 (m), 973 (m) cm^{-1}; HRMS (ESI+) for $C_{16}H_{27}$ [M-OAc]: calculated: 219.2113, found: 219.2123. The crude material was used without purification to give a clear oil (77% yield over 3 steps). R_f = 0.5 in 5% EtOAc/hexane.



(*E*)-3,7-dimethyl-1-phenylocta-2,6-dien-1-yl acetate (starting material for 4.20): From commercially available geraniol, general procedure **F, C,** and then **B** was followed**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (3H, s), 1.65 (3H, s), 1.81 (3H, s), 2.03-2.11 (4H, m), 2.09 (3H, s), 5.02-5.06 (1H, s), 5.40 (1H, d, J = 8.8 Hz), 6.53 (1H, d, J = 8.8 Hz), 7.25-7.30 (1H, m), 7.34 (4H, d, J = 4.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.9, 17.6, 21.3, 25.6, 26.2, 39.5, 72.7, 123.3, 1213.7, 126.5, 127.6, 128.4, 131.8, 140.4, 140.7, 170.2; IR (neat): 2966 (w), 1734 (s), 1369 (m), 1230 (s), 1016, (m), 960 (m), 745 (m), 671 (s); HRMS (ESI+) for $C_{16}H_{22}$ [M-OAc]$^+$: calculated: 214.1722, found: 214.1802. The crude material was purified on silica gel (5% ether/hexane) to afford a colorless oil (55% yield). R_f = 0.29 in 5% ether/hexane.

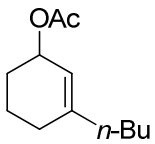
Synthesis and characterization of 3-butylcyclohex-2-en-1-yl acetate (starting material for 4.21):



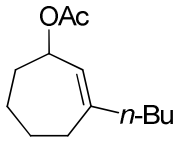
General procedure G:

Step 1: To a flame-dried round-bottomed flask charged with magnetic stir bar, under positive N_2 atmosphere was added by 8 mL THF. The flask was cooled to -78 °C, and 2.4 mL *n*-BuLi (2.54 M in hexane) was added dropwise. Cyclohexenone (0.49 mL, 5.0 mmol in 2 mL THF) was slowly added to the mixture. The flasked was warmed to 0 °C and allowed to stir for 2 hours. The reaction was then quenched with H_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The organics were combined and condensed *in vacuo* to afford **S-11**. The crude oil of **S-11** was used in the next step without further purification.

Step 2: [2] To a round-bottomed flask charged with stir bar and the crude oil of **S-11** was added MeCN (25 mL) and H_2O (D.I., 5 mL), followed by salicylic acid (210 mg, 1.5 mmol). The flask was capped and allowed to stir overnight. Saturated $NaHCO_3$ was added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with Et_2O three times. The combined organics were concentrated *in vacuo* to afford **S-12** as a light, yellow oil. The crude oil of **S-12** was subjected directly to acetylation conditions (general procedure **B**).

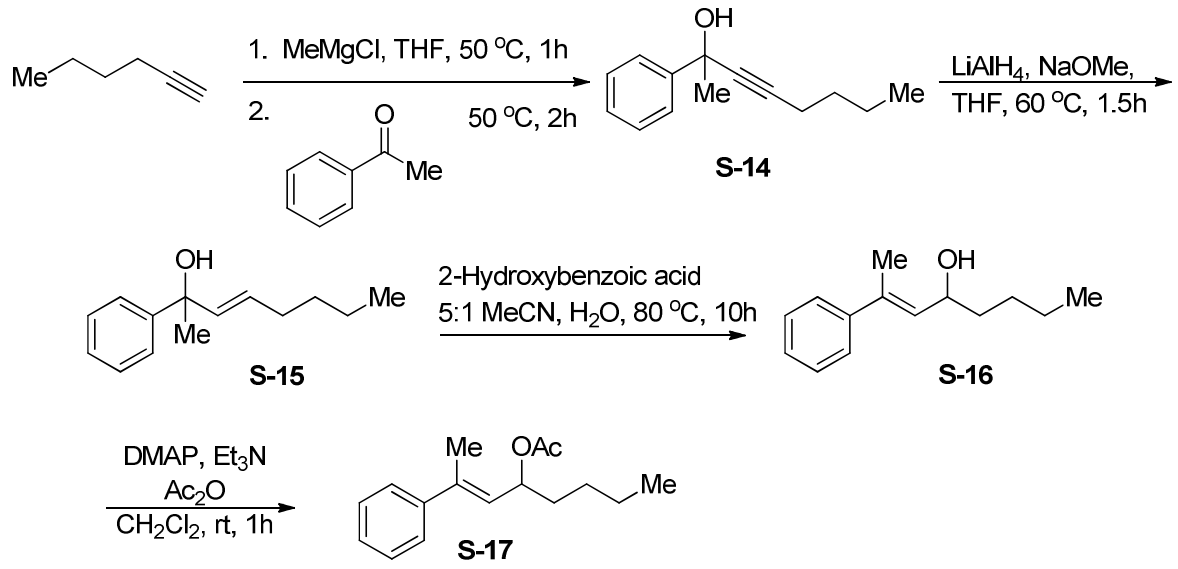


3-butylcyclohex-2-en-1-yl acetate (starting material for 4.21): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 6.8 Hz), 1.29 (2H, tq, J = 14.7, 7.4 Hz), 1.36-1.42 (2H, m), 1.54-1.80 (4H, m), 1.88-195 (1H, m), 1.97-2.00 (3H, m), 2.04 (3H, s), 5.27 (1H, br s), 5.44 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 19.1, 21.5, 22.4, 28.3, 28.4, 29.6, 37.3, 68.9, 119.3, 144.9, 170.9; IR (neat): 2930 (s), 1730 (s), 1369 (m), 1234 (s), 1057 (m), 909 (m); HRMS (ESI+) for $C_{10}H_{17}$ [M-OAc]$^{+}$: calculated: 137.1325, found: 137.1369. The crude material was purified on silica gel (5% ether/hexane) to afford a colorless oil (78% yield over 3 steps). R_f = 0.33 in 5% ether/hexane.



3-butylcyclohept-2-en-1-yl acetate (starting material for 4.22): Starting from cycloheptenone, general procedure **G** was followed; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.1 Hz), 1.25-1.39 (6H, m), 1.59-1.71 (4H, m), 1.78-1.82 (1H, m), 1.88-1.93 (1H, m), 1.94-1.99 (2H, m), 2.05 (3H, s), 2.03-2.18 (2H, m), 5.35-5.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 21.4, 22.3, 26.0, 27.1, 29.8, 32.4, 32.9, 39.8, 74.0, 127.1, 143.9, 170.4; IR (neat): 2926 (m), 1734 (s), 1367 (m), 1237 (s), 1024 (m), 840 (w); HRMS (ESI+) for $C_{11}H_{20}$ [M-OAc]$^{+}$: calculated: 152.1565, found: 152.1593. The crude material was purified on silica gel (5% ether/hexane) to afford a colorless oil. R_f = 0.24 in 5% ether/hexane.

Synthesis and chacracterization of (*E*)-2-phenyloct-2-en-4-yl acetate (starting material for 4.23):

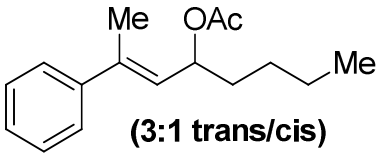


General Procedure H:

Step 1:[3] A flame-dried 2-neck round-bottom flask equipped with a reflux condenser, stir bar, and rubber septum was charged with THF (4 mL), methylmagnesium chloride (2.16 mL, 4.8 mmol, 2.2 M in THF) and 1-hexyne (0.55 mL, 4.8 mmol). The reaction was heated to 50 °C for 1 h, at which point the reaction was cooled to room temperature, and aceteophenone (0.47 mL, 4.0 mmol) was added dropwise *via* syringe. The reaction was warmed to 50 °C, and was allowed to stir for an additional 2 h. The solution was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The organic portions were combined and washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

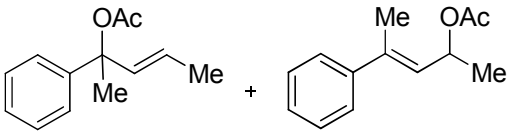
Step 2: Literature procedure was followed to reduce the alkyne and obtain **S-15**.[10]

The allylic alcohol **S-15** was subjected to conditions in procedure **G** (step 2) and procedure **B** to afford the desired allylic acetate **S-17**.



(3:1 trans/cis)

(*E*) & (*Z*)-2-phenyloct-2-en-4-yl acetate (Starting material for 4.23): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (3H, t, *J* = 7.0 Hz, *cis*), 0.86 (3H, t, *J* = 7.0 Hz, *trans*), 1.06-1.19 (m), 1.20-1.34 (m), 1.36-1.48 (m), 1.52-1.60 (m), 1.66-1.74 (m), 1.93 (3H, s, *cis*), 1.99 (3H *trans* + 3H *cis*, s), 2.09 (3H, s, *trans*), 5.14 (1H, dt, *J* = 9.3, 6.6 Hz, *cis*), 5.36 (1H, dd, *J* = 9.3, 1.5 Hz, *cis*), 5.56-5.64 (2H, m, *trans*), 7.11-7.15 (m), 7.18-7.22 (m), 7.24-7.30 (m), 7.32-7.36 (m); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.9, 14.0, 16.5, 21.3, 22.4, 22.6, 26.0, 27.1, 27.2, 34.6, 34.7, 71.7, 72.6, 125.9, 125.9, 126.6, 127.0, 127.3, 127.5, 128.2, 128.2, 138.7, 141.0, 141.1, 142.8, 170.1, 170.5; IR (neat): 2957 (w), 2932 (w), 2861 (w), 1732 (s), 1494 (w), 1445 (w), 1369 (m), 1235 (s), 1016 (m), 950(m) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}$ [M-OAc]: calculated:187.1418, found:187.1491. The crude material was purified on silica gel (10% ether/hexane) to afford a clear oil (24% yield over 4 steps). R_f = 0.33 in 5% EtOAc/hexane.



major **minor**

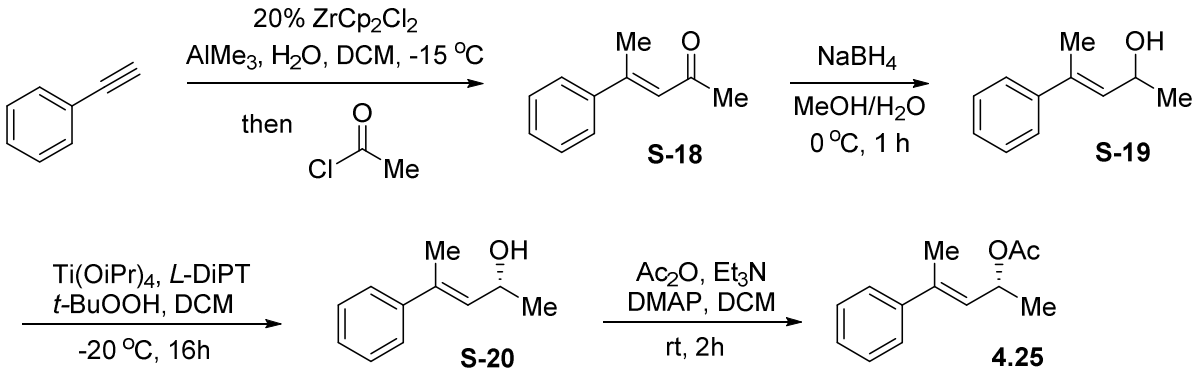
1.4 : 1

(*E*)-2-phenylpent-3-en-2-yl acetate (major) & (*E*)-4-phenylpent-3-en-2-yl acetate (minor) (starting material for 4.24): From commercially available (*E*)-pent-3-en-2-one, procedure **A** and **B** was followed. ^{1}H NMR (500 MHz, $CDCl_3$):1.37 (3H, d, *J* = 6.3 Hz, minor), 1.75 (3H, dd, *J* = 6.4, 1.9 Hz, major), 1.85 (3H, s, major), 2.05 (3H, s, minor), 2.06 (3H, s, major), 2.12 (3H, d, *J* = 1.5 Hz, minor), 5.67 (1H, app dq, *J* = 19.5, 6.4 Hz, major), 5.72-5.79 (2H, m, minor), 5.99 (1H, ddd, J = 15.1, 2.9, 1.4 Hz, major), 7.22-7.28 (1H major + 1 H minor, m), 7.31-7.36 (3H major + 3H

minor), 7.39-7.41 (1H major + 1H minor, m); ^{13}C NMR (125 MHz, $CDCl_3$): 16.3, 17.9, 20.8, 21.4, 22.3, 26.2, 68.3, 83.2, 125.1, 125.9, 126.2, 126.9, 127.0, 127.1, 127.3, 127.4, 127.5, 128.1, 128.2, 128.3, 134.6, 137.9, 142.7, 144.6, 169.4, 170.4; IR (neat): 3026 (w), 2935 (w), 1736 (s), 1494 (m), 1240 (s), 1119 (m), 913 (m), 760 (m), 699 (m); HRMS (ESI+) for $C_{13}H_{16}O_2$ [M-OAc]: calculated 145.1012, found 145.1003. The crude material was purified on silica gel (5% Et_2O/Pentane) to afford a colorless oil (30% yield over 2 steps). R_f = 0.38 in 5% EtOAc/hexane.

Synthesis of enantioenriched starting materials:

Synthesis and characterization of (*E*)-4-phenylpent-3-en-2-yl acetate (4.25)



General Procedure I:

Step 1: Starting from phenylacetylene, literature procedure was followed.[11]

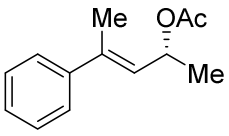
Step 2: General procedure **D**, step 2 was followed.

[11] Dabrowski, J. A.; Haeffner, J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694

Step 3:[12] A flame dried round bottom flask equipped with a stir bar was charged with **S-19** (1.2 g, 7.6 mmol), *L*-(-)-DIPT (1.92 mL, 9.2 mmol), and CH_2Cl_2 (76 mL). The mixture was cooled to -20 ^oC and Ti(O*i*-Pr)$_4$ (2.26 mL, 7.6 mmol) was added. The solution stirred for 30 minutes, then 5.5 M. *t*-BuO_2H in decane (0.84 mL, 4.6 mmol) was added slowly *via* syringe. The reaction was stirred for 16 h. The reaction was then quenched with a cold solution of citric acid (6 g) and $FeSO_4 \cdot 7H_2O$ (16 g) in 50 mL D.I. H_2O and was stirred vigorously at room temperature, until the solution was clear. The organic layer was set aside and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic fractions were concentrated *in vacuo*, and the crude residue was dissolved in diethyl ether (50 mL). To this solution was added a solution of NaOH (20 g) and NaCl (3 g) in H_2O (50 mL) at 0 ^oC. The mixture stirred at 0 ^oC for 1 h before the addition of H_2O (25 mL). The organic layer was removed and the aqueous layer was extracted with ethylacetate three times. The organic portions were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on silica gel to afford the enantioenriched alcohol.

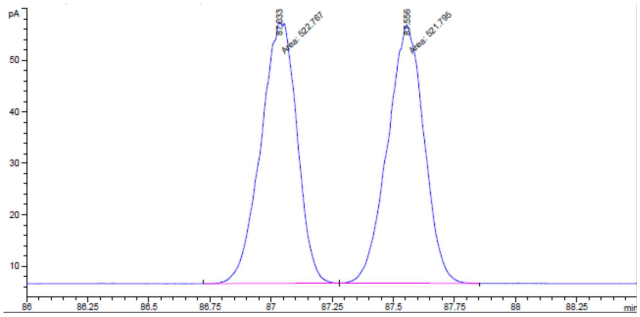
Step 4: General procedure **B** was followed to obtain the desired starting material **4.25**.

[12] (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (c) Li, Z.; Parr, B. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 10942.

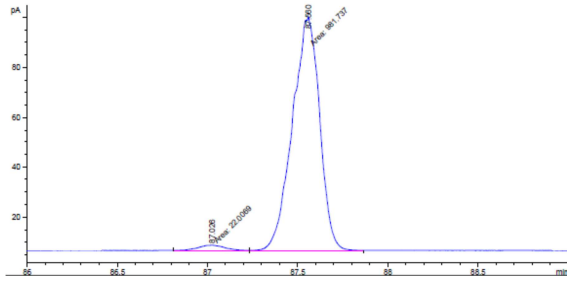


(*E*)-4-phenylpent-3-en-2-yl acetate (4.25): Spectral data is in accordance with literature values.[13]

Analysis of stereo chemistry: The enantiopurity was determined using chiral GLC (Chiral β-dex, Supelco, 60 ^{o}C for 5 minutes, ramp 1 ^{o}C / min to 140 ^{o}C, hold at 140 ^{o}C for 20 minutes, 20 psi, sr = 35:1). The absolute stereochemistry was determined by analogy to reported literature.[5]



Racemic

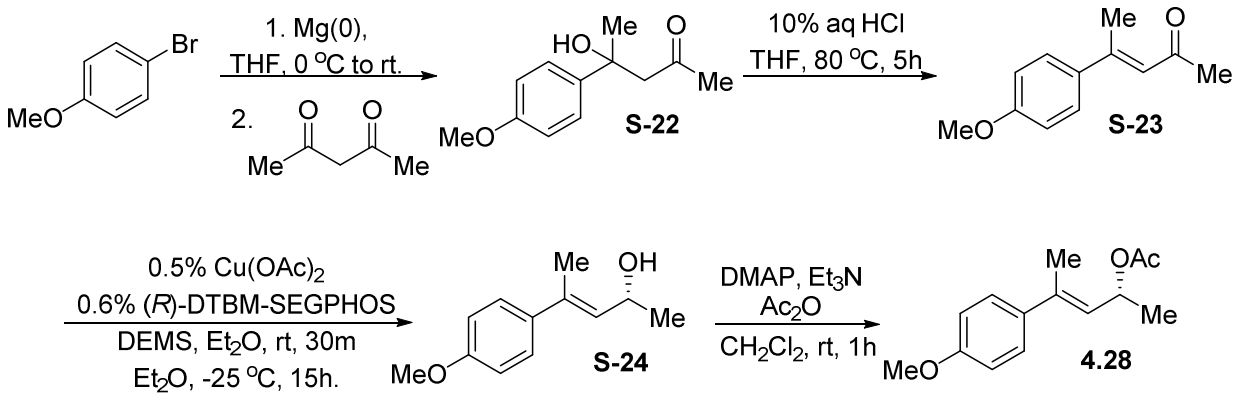


Reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	87.026	MM	0.1676	22.00691	2.18899	2.19248
2	87.560	MM	0.1748	981.73694	93.59392	97.80752
Totals :				1003.74385	95.78291	

[13] Voigtritter, K. R.; Isley, N. A.; Moser, R.; Aue, H. D.; Lipshutz, B. H. *Tetrahedron* **2012**, *68*, 3410

Synthesis and characterization of (*E*)-4-(4-methoxyphenyl)pent-3-en-2-yl acetate (4.28):



General procedure K:

Step 1: Starting with 4-bromoanisole, **S-22** was obtained following literature procedure.[14]

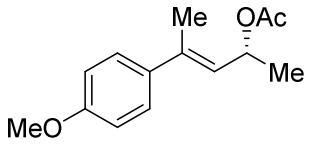
Step 2: Adapted from literature procedure.[14] A round-bottomed flask was equipped with a stir bar and reflux condenser. The flask was charged with **S-22** (3.94 g, 16 mmol), THF (48 mL) and 10% HCl in H_2O (16 mL). The reaction was stirred at 80 °C for 1 h. The reaction was then diluted with H_2O and extracted with ethyl acetate three times. The organic portion was washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on column chromatography (SiO_2, 20% EtOAc/hexanes) to afford ketone **S-23** as a white solid.

Step 3:[7] In the dry-box, an oven-dried 2-dram vial equipped with a stir bar was charged with anhydrous $Cu(OAc)_2$ (4.63 mg, 0.026 mmol) and (*R*)-DTBM-SEGPHOS (30.08 mg, 0.026 mmol). The vial was capped with a rubber septum and brought out of the box. At room temperature, dry ethyl ether (2 mL) and diethoxymethyl silane (2.45 mL, 15.3 mmol) were added under N_2. After stirring for 10 min, the reaction mixture was cooled to -25 °C. A solution of **S-**

[14] Guthrie, J. P.; Wang, X.-P. *Can. J. Chem.* **1992**, *70*, 1055

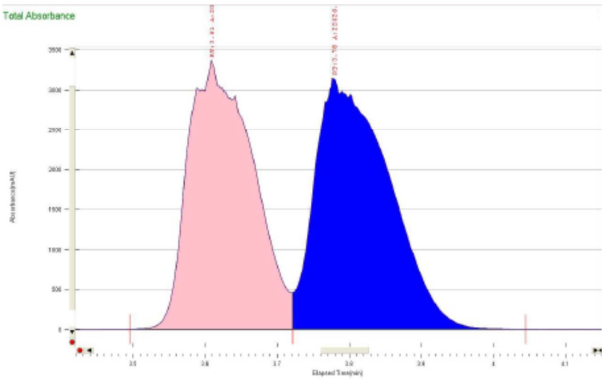
23 (0.82 g, 5.1 mmol) in dry ethyl ether (1 mL) was added slowly *via* syringe. The mixture was stirred for 15 h at -25 ^{o}C. To the mixture was added 1.0 M TBAF in THF (15.3 mL) and the reaction was stirred for an additional 1 h. MeOH (10 mL) was then added, and the reaction was warmed to room temperature, concentrated *in vacuo*, and filtered through a short SiO_2 plug. The crude material was then purified using column chromatography (SiO_2, 20% ethylacetate/hexanes) to afford clean **S-24** as a colorless oil (814.2 mg, 83% yield).

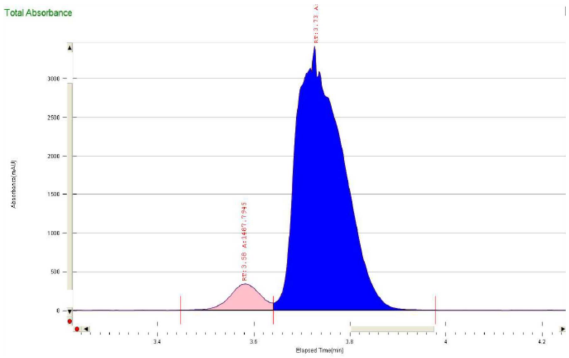
Step 4: General procedure **B** was followed to obtain the desired starting material.



(*E*)-4-(4-methoxyphenyl)pent-3-en-2-yl acetate (4.28): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, d, *J* = 6.3 Hz), 2.05 (3H,s), 2.10 (3H, s), 3.81 (3H, s), 5.67 (1H, d, *J* = 8.8 Hz), 5.76 (1H, dq, *J* = 8.8, 6.3 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 7.34 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3, 20.9, 21.4, 55.3, 68.4, 113.6, 125.9, 126.9, 135.1, 137.3, 159.1, 170.4; IR (neat): 2977(br), 2932 (br), 2837 (w), 1732 (m), 1607 (w), 1513 (m), 1444 (w), 1370 (w), 1289 (w), 1242 (s), 1181 (w), 1036 (m) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}O_3$ [M+H]: calculated: 235.1334, found: 235.1321. The crude material was purified on silica gel (7% ether/pentane) to afford a corlorless oil (15% yield over 4 steps). R_f= 0.12 in 5% EtOAc/hexane.

Analysis of stereo chemistry: The enantiopurity was determined on alohol **S-24** using chiral SFC (OJ-H, Chiralpak, 3mL/min, 4% isopropanol, 100 bar, 35 ^{o}C). The absolute stereochemistry was determined by analogy to reported literature.[13]



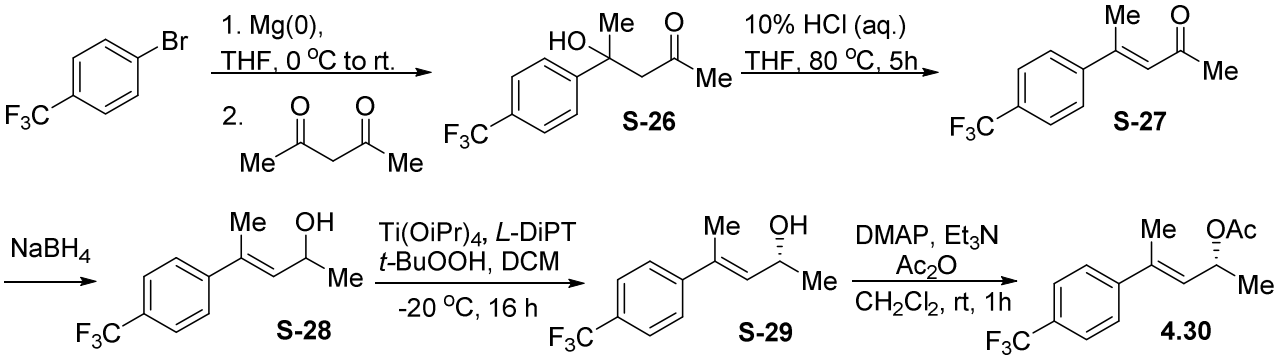


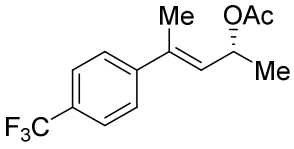
Racemic

Reaction product

Peak No	% Area	Area	RT (min)
1	6.1967	1487.7945	3.58
2	93.8033	22521.5346	3.73
Total:	100	24009.3291	

Synthesis and characterization of (*E*)-4-(4-(trifluoromethyl)phenyl)pent-3-en-2-yl acetate (4.30):

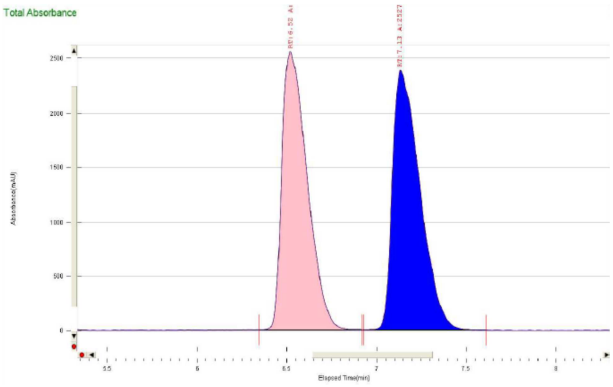




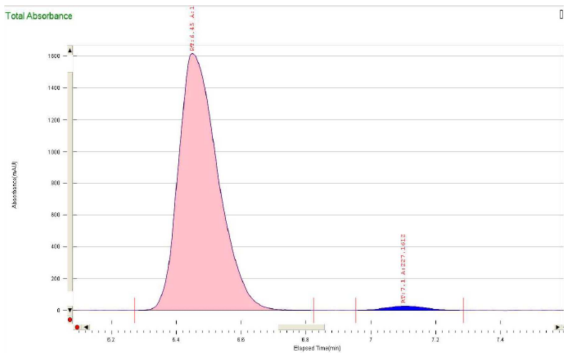
(*E*)-4-(4-(trifluoromethyl)phenyl)pent-3-en-2-yl acetate (4.30): From commercially available 4-bromobenzotrifluoride, procedure **K**, step 1 and 2 was followed, then procedure **I** step 3 and 4 and procedure **B** was followed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (3H, d, J = 5.9 Hz), 2.05 (3H, s), 2.14 (3H, d, J = 1.5 Hz), 5.73-5.80 (2H, m), 7.43 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz); (125 MHz,

$CDCl_3$): δ 16.3, 20.6, 21.3, 68.1, 123.1, 125.1, 125.2, 125.3, 125.4, 126.2, 129.4 (q, $^2J_{CF}$ = 32.4 Hz), 136.7, 146.2, 170.4; IR (neat): 2979 (br), 1738 (m), 1616 (w), 1371 (w), 1326 (s), 1240 (m), 1165 (m), 1124 (m), 1072 (m), 1042 (w), 1014 (w), 946 (w) cm^{-1}; HRMS (ESI+) for $C_{14}H_{15}F_3O_2$ [M+H]: calculated: 273.1102, found: 273.1099. The crude material was purified on silica gel (10% ether/pentane) to afford a colorless oil. R_f= 0.22 in 5% EtOAc/hexanes.

Analysis of stereo chemistry: The enantiopurity was determined on alohol **S-29** using chiral SFC (OD-H, Chiralpak, 3mL/min, 3% Isopropanol, 100 bar, 35 ^oC). The absolute stereochemistry was determined by analogy to reported literature.[12]



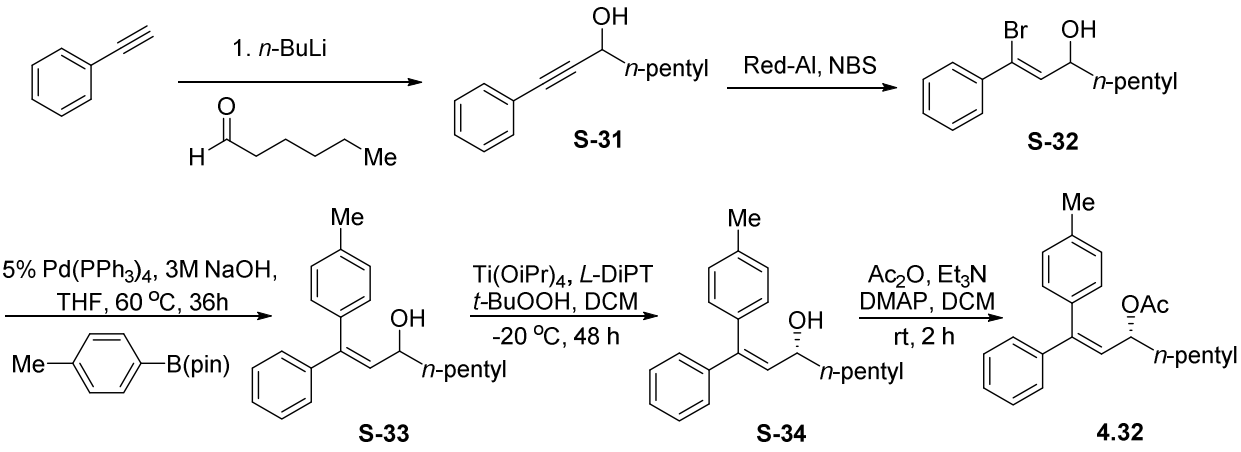
Racemic



Reaction product

Peak No	% Area	Area	RT (min)
1	98.3578	13605.9216	6.45
2	1.6422	227.1612	7.1
Total:	100	13833.0828	

Synthesis and characterization for (*R*, *Z*)-1-phenyl-1-(*p*-tolyl)hept-1-en-3-yl acetate (4.32)



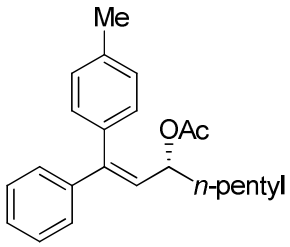
Step 1: To a flame-dried round bottom flask under possitive N_2 pressure was added 2.5M *n*-BuLi (3 mL, 24 mmol), followed by THF (30 mL). The flask was cooled to -78 ^oC and phenyl acetylene (2.2 mL, 20 mmol) in 5 mL THF was added dropwise. After 15 minutes, hexanal (3 mL, 24 mmol) in 5 mL THF was added dropwise via syringe. The reaction was stirred for 1 h at room temperature. The reaction was then worked up by slow addition of H_2O at 0 ^oC. The reaction mixture was then transfered to a separatory funnel; and the organic layer was seperated. The aqueous layer was extracted with ethylacetate 3 times. The organics were combined and condensed *in vacuo*. The crude material was purified on silica gel to afford the desired propargyl alcohol **S-31** as a colorless oil (3.5 g, 80% yield).

Step 2: To a dried round-bottomed flask under positive N_2 pressure was added Red-Al (3.93 mL, 65 wt % in Tol), followed by 30 mL of dried Et_2O. The reaction was cooled to 0 ^oC, then **S-31** in 10 mL Et_2O was added dropwise via syringe. The reaction was stirred for 4 h at room temperature, then freshly D.I. ethylacetate (1 mL, 10 mmol) was added dropwise at 0 ^oC. The reaction was then cooled to -78 ^oC and NBS (2.7 g, 15 mmol) was added at once. The reaction

was then warmed to room temperature and allowed to stir overnight. Saturated aqueous $Na_2S_2O_3$ was added to the mixture at 0 ^oC. The organic layer was seperated and the aqueous layer was extracted with ethyl acetate three times. The combined organics were then condensed *in vacuo* and purified using column chromatography (SiO_2, 10% EtOAc/hex) to afford the desired product (2.3 g, 80 % yield).

Step 3: Inbox, to a 3-neck round-bottomed flask charged with stir bar was added $Pd(PPh_3)_4$ (290 mg, 0.25 mmol), **S-32** (1.4 g, 5.0 mmol), and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane. The flask was capped and brought out of the dry box. A previously oven-dried reflux condenser was added, and the entire system was put under possitive N_2 pressure. 10 mL THF and 3mL of 3M aqueous NaOH was added to the reaction via syringe. The reaction was heated to 60 ^oC for 48 h. The reaction was then cooled to room temperature, and diluted with H_2O and Et_2O. The organic layer was seperated and the aqueous layer was extracted three times with Et_2O. The combined organics was then condensed *in vacuo* and purified using column chromatography (SiO_2, 10% EtOAc/hex) to afford the desired product (1.0 g, 63% yield).

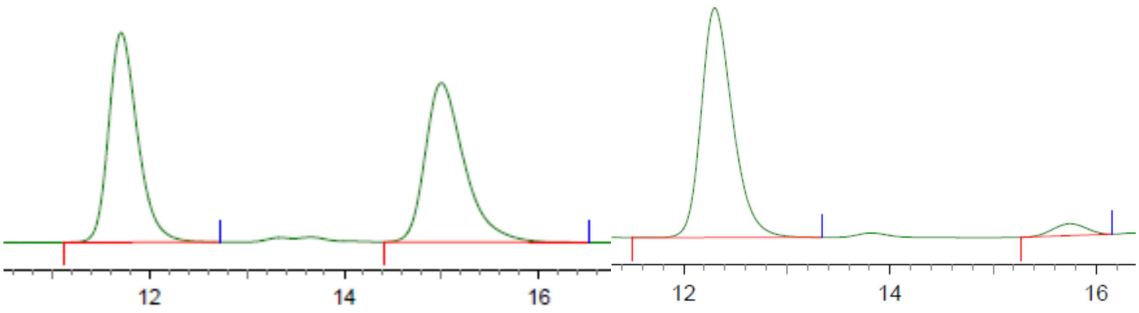
Step 4 and 5 was carried out following general procedure **I**, step 4 and general procedure **B** to afforded the desired starting material.



(*R*, *Z*)-1-phenyl-1-(*p*-tolyl)hept-1-en-3-yl acetate (4.32): ^1H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, *t*, *J* = 9.7, 7.3 Hz), 1.13-1.30 (6H, m), 1.54-1.61 (1H, m), 1.66-1.71 (1H, m), 2.02 (3H, s), 2.38 (3H, s), 5.35 (1H, dt, *J* = 13.2, 6.8 Hz), 5.97 (1H, d, *J* = 9.2 Hz), 7.10 (2H, d, *J* = 8.4 Hz), 7.19 (2H, d, *J* = 7.3 Hz), 7.22-7.29 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 21.2, 21.3, 22.5, 24.7, 31.5, 35.0, 72.9, 127.0, 127.4, 127.6, 128.1, 128.9, 129.4, 136.1, 137.1, 141.9,

144.5, 170.1; IR (neat): 2928 (m), 1733 (s), 1367 (m), 1234 (s), 1016 (m), 821 (m), 763 (s), 696 (s). HRMS (ESI+) for $C_{21}H_{26}$ [M-OAc]$^+$: calculated:278.2035, found: 278.1996. $[\alpha]^{20}_D$ = -3.546 (*c* = 3.654, $CHCl_3$)The crude material was purified on silica gel (5% ether/hexanes) to afford a colorless oil. R_f = 0.24 in 5% ether/hexane.

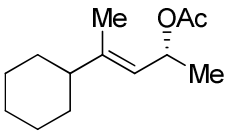
Analysis of stereo chemistry: The enantiopurity was determined on alohol **S-34** using chiral HPLC (AD-H, Chiralpak, 1.0 mL/min, 1% isopropanol/hexane, 254 nm). The absolute stereochemistry was determined by analogy to **4.28**.



Racemic Reaction product

VWD: Signal A, 254 nm Results

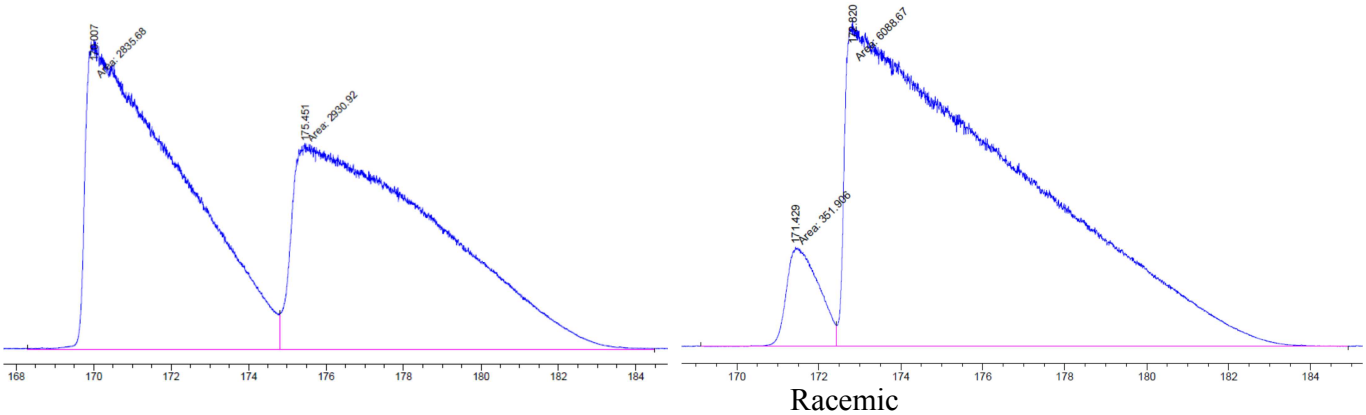
Retention Time	Area	Area %	Height	Height %
12.300	953877701	94.79	44950119	95.11
15.747	52453552	5.21	2312137	4.89
Totals	1006331253	100.00	47262256	100.00



(*R*, *E*)-4-cyclohexylpent-3-en-2-yl acetate (4.34): starting from cyclohexylacetylene, general procedure **I** was followed. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 1.08-1.31 (5H, m), 1.25 (3H, d, J = 6.3 Hz), 1.63-1.72 (3H, m), 1.73-1.86 (3H, m), 1.66 (3H, s), 2.01 (3H, s), 5.14 (1H, d, J = 6.0 Hz), 5.60 (1H, app dq, J = 16.5, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 20.1, 21.5, 26.3, 26.5, 26.6, 31.6, 31.7, 47.0, 68.2, 122.7, 144.6, 170.4; IR (neat): 2852 (m), 1735, (s), 1448 (m), 1368 (m), 1240 (s), 1041 (m), 852 (m); HRMS (ESI+) for $C_{11}H_{19}$ [M-OAc]$^+$: calculated: 151.1481, found: 151.1565; $[\alpha]^{20}_D$ = 19.051 (*c* = 2.150, $CHCl_3$)

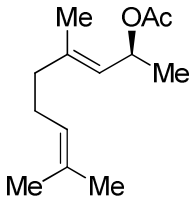
Analysis of stereo chemistry: The enantiopurity was determined using chiral GLC (Chiral β-dex, Supelco, 90 ^oC for 150 minutes, 20 psi, sr = 35:1). The absolute stereochemistry was determined by analogy to reported literature.[12]



Racemic

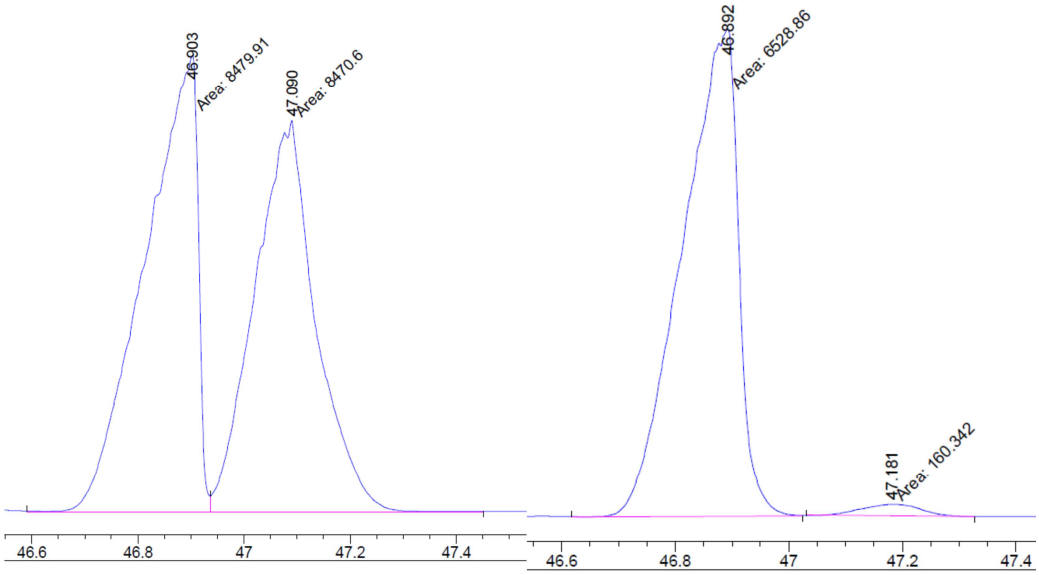
Reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	171.429	MF	0.9040	351.90646	6.48791	5.46390
2	172.820	FM	4.7795	6088.67041	21.23188	94.53610
Totals :				6440.57687	27.71979	



(*S*, *E*)-4,8-dimethylnona-3,7-dien-2-yl acetate (4.36): Starting from geraniol and *D*-DIPT, the desired compound was synthesized using literature procedure.[12]

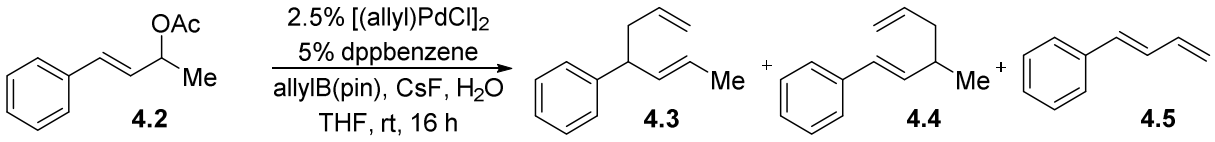
Analysis of stereo chemistry: The enantiopurity was determined using chiral GLC (Chiral β-dex, Supelco, 60 ^{o}C for 10 minutes, ramp 2 ^{o}C/min to 180 ^{o}C, 20 psi, sr = 35:1). The absolute stereochemistry was determined by analogy to reported literature.[5]



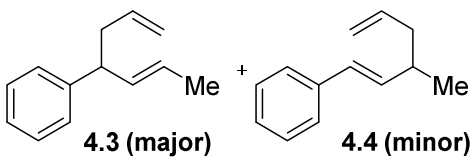
Racemic Reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	46.892	MM	0.1148	6528.85547	947.90997	97.60297
2	47.181	MM	0.1187	160.34241	22.51488	2.39703
Totals :				6689.19788	970.42485	

C. Synthesis and Characterization of the Allyl-Allyl Coupling Products

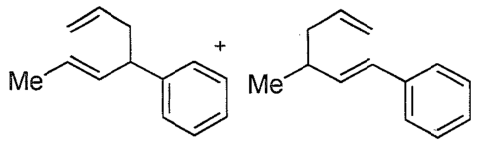


General procedure L: In the dry-box, an oven dried 2-dram vial equipped with a stir bar was charged with (η^3-allylPdCl)$_2$ (1.4 mg, 0.0038 mmol), dppbenzene (4.6 mg, 0.0075 mmol), and THF (0.25 mL). The resulting solution was allowed to stir at room temperature for 5 min. At this time, the vial was sequentially charged with **4.2** (37.2 mg, 0.15 mmol), allylB(pin) (75.6 mg, 0.45 mmol), CsF (228 mg, 1.5 mmol), and THF (0.75 mL). The vial was tightly capped with a rubber septum, removed from the dry-box, and placed under a positive pressure of N_2. Degassed H_2O was then added (40 µL) *via* a glass syringe. The rubber septum was rapidly exchanged with a polypropylene cap, sealed with tape, and the reaction was allowed to stir at room temperature for 16 h. The slurry was diluted with water, the organic layer was separated and the aqueous layer was extracted three times with Et_2O. The organic portion was dried with Na_2SO_4 filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (100% pentane) to yield a 6:2:1 mixture of **4.3**, 4.4, and elimination product 4.5. The combined yield of **4.3** and **4.4** was calculated to be 88%. **4.5** can be removed by treating the mixture with maleic anhydride (30mg, 0.3 mmol) in THF at 60 ^oC for 3 h.

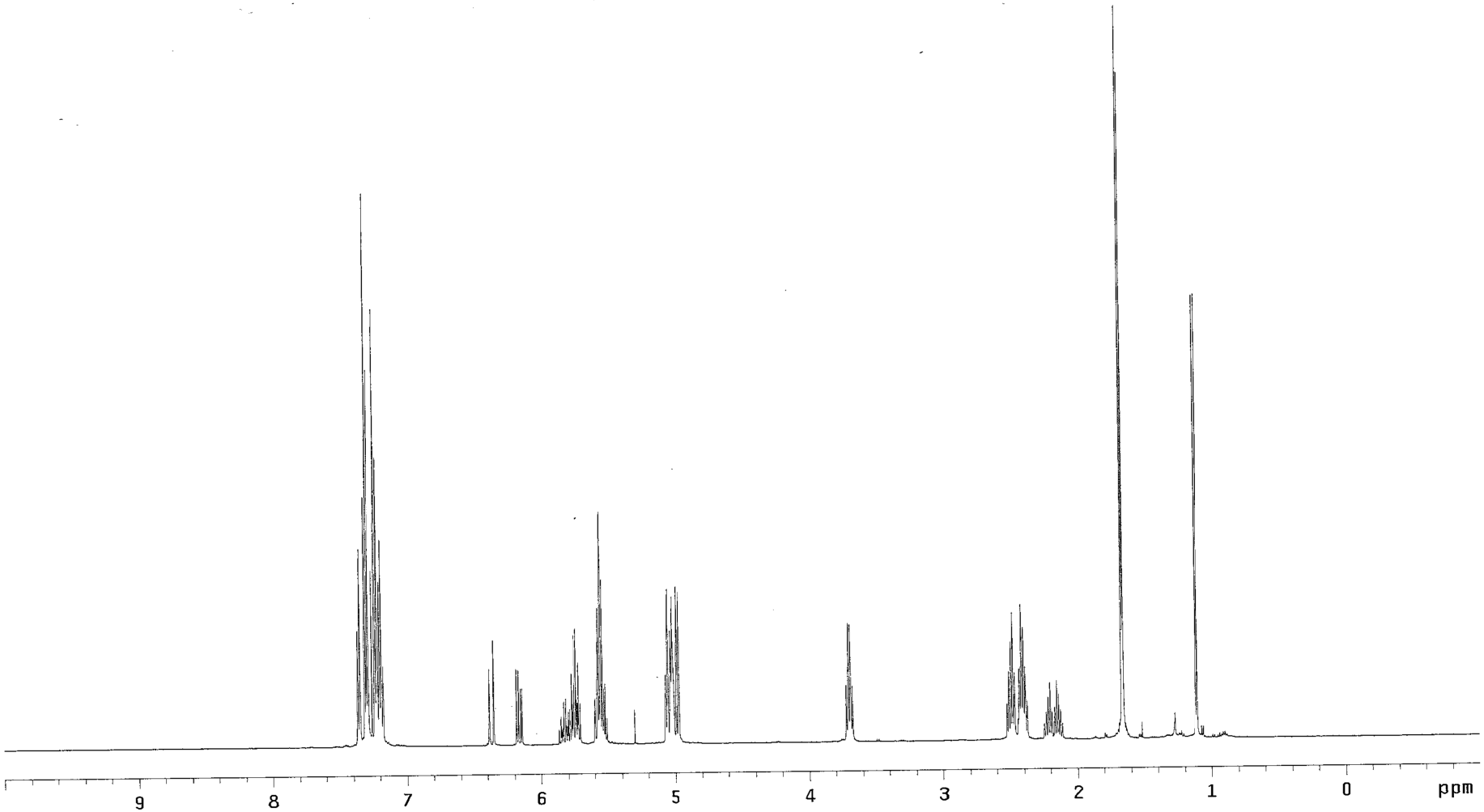


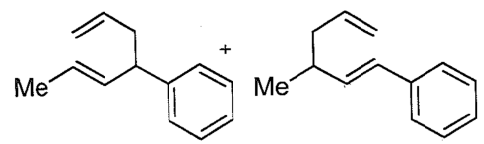
(*E*)-hepta-1,5-dien-4-ylbenzene (4.3, major) & (*E*)-(3-methylhexa-1,5-dien-1-yl)benzene (4.4, minor): ^1H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, J = 6.8 Hz, minor), 1.66 (3H, d, J = 5.6 Hz, major), 2.10-2.26 (2H, m, minor), 2.36-2.54 (2H+1H, m,

major+minor), 3.70 (1H, q, *J* = 8.3 Hz, major), 4.95-5.09 (2H+2H, m, major+minor), 5.50-5.61(2H, m, major), 5.70-5.87(1H+1H, m, major+minor), 6.16 (1H, dd, *J* = 15.9, 7.3 Hz, minor), 6.37 (1H, d, *J* = 15.9 Hz, minor), 7.17-7.38 (5H + 5H, m, major + minor); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.2, 19.9, 36.9, 41.1, 41.4, 43.0, 115.9,116.0, 124.0, 126.0, 126.0, 126.8, 127.3, 128.2, 128.4, 128.5, 133.8, 136.0,136.7, 137.0, 137.8, 144.9); IR (neat): 3077(m), 3026 (m), 2976 (m), 2922 (m), 1640 (m), 1600 (w), 1493(m), 1451 (m), 1072 (w), 1030 (w), 994(s) cm^{-1}; HRMS (ESI+) for $C_{13}H_{17}$ [M +H]: calculated: 173.1330, found: 173.1333. The crude material was purified on silica gel (100% pentane) to afford a colorless oil. R_f = 0.81 in 5% EtOAc/hexane.

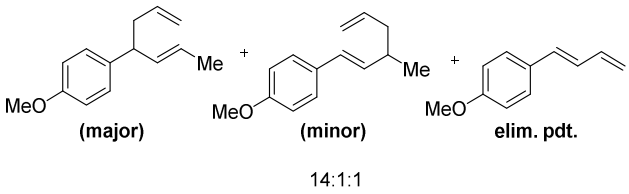


3:1

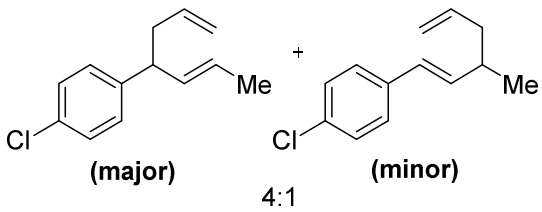




3:1

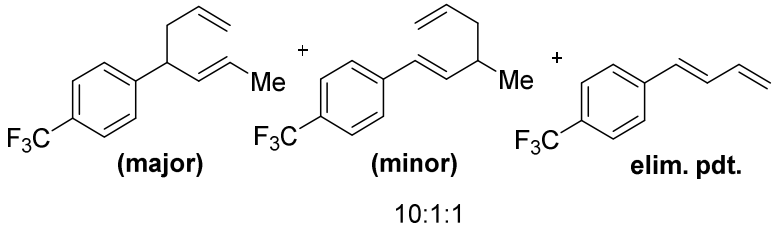


(*E*)-1-(hepta-1,5-dien-4-yl)-4-methoxybenzene (major) & (*E*)-1-methoxy-4-(3-methylhexa-1,5-dien-1-yl)benzene (minor): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H, d, *J* = 6.8 Hz, minor), 1.65 (3H, d, *J* = 4.9 Hz, major), 2.06-2.24 (2H, m, minor), 2.33-2.49 (2H, m, major), 2.82-2.89 (1H, m, minor), 3.65 (1H, td, *J* = 8.3, 6.6 Hz, major), 3.79 (3H, s, major), 3.81 (3H, s, minor), 3.82 (3H, s, elim. pdt.), 4.95-5.06 (2H minor + 2H elim. pdt., m), 4.97 (1H, d, *J* = 10.3 Hz, major), 5.03 (1H, d, *J* = 17.1 Hz, major), 5.47-5.57 (2H, m, major), 5.74 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, major), 5.82 (1H, ddt, *J* = 17.1, 9.8, 7.3 Hz, minor), 6.01 (1H, dd, *J* = 15.6, 7.3 Hz, minor), 6.29-6.32 (1H, m, elim. pdt.), 6.82-6.88 (2H major + 2H minor, m), 7.11-7.16 (2H major + 2H elim. pdt., m), 7.21 (2H elim. pdt., m), 7.29 (2H minor, m); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.1, 41.2, 42.1, 55.2, 113.8, 115.8, 123.7, 128.2, 134.1, 136.8, 137.1, 157.8; IR (neat): 3074 (w), 3007 (w), 2914 (w), 2835 (w), 1609(w), 1510 (s), 1463 (w), 1441 (w), 1302 (w), 1247 (s), 1177 (m), 996 (m) cm^{-1}; HRMS (ESI+) for $C_{14}H_{18}O_1$ [M +H]: calculated: 203.1435, found: 203.1443. The crude material was purified on silica gel (1% ether/pentane) to afford a colorless oil (22 mg, 70% combined yield for both 1,5-diene isomers). R_f= 0.52 in 5% ether/hex



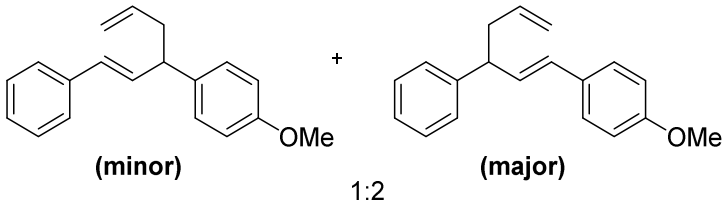
(*E*)-1-chloro-4-(hepta-1,5-dien-4-yl)benzene (major) & (*E*)-1-chloro-4-(3-methylhexa-1,5-dien-1-yl)benzene (minor): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 6.8 Hz, minor), 1.65 (3H, d, *J* = 5.3 Hz, major), 2.09-2.23 (2H, m, minor), 2.34-2.49 (2H + 1H, m, major+minor), 3.67

(1H, q, J = 7.5 Hz, major), 4.99 (1H, d, J = 10.3 Hz, major), 5.03 (1H, d, J = 17.1 Hz, major), 4.96-5.08 (2H, m, minor),5.49-5.47 (2H, m, major), 5.71 (1H, ddt, J = 17.2, 10.3, 6.9 Hz, major), 5.81 (1H, ddt, J = 17.1, 10.1, 7.1 Hz, minor), 6.14 (1H, dd, J = 15.9, 7.5 Hz, minor), 6.32 (1H, d, J = 15.6 Hz, minor), 7.10-7.30 (4H major + 4H minor, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2, 19.8, 36.9,41.1, 41.3, 42.4, 116.1, 116.3, 124.5,127.1, 127.2, 128.5, 128.6, 128.7, 131.6, 133.3, 136.2, 136.8, 143.4; IR (neat): 3077(w), 3013 (w), 2977 (w), 2922 (w), 1640 (w), 1491 (s), 1439 (m), 1371 (w), 1092 (s), 1014 (s), 994 (m), 967 (m), 913(s) cm^{-1}; HRMS (ESI+) for $C_{13}H_{15}Cl$ [M +H]: calculated: 207.0948, found: 207.0941. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (28mg, 92% combined yield both 1,5-diene isomers). R_f = 0.93 in 5% EtOAc/hexane.

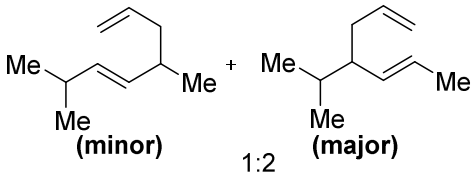


(*E*)-1-(hepta-1,5-dien-4-yl)-4-(trifluoromethyl)benzene (major) & (*E*)-1-(3-methylhexa-1,5-dien-1-yl)-4-(trifluoromethyl)benzene (minor) & (E)-1-(buta-1,3-dien-1-yl)-4-(trifluoromethyl)benzene (elim. pdt.): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, J = 6.9 Hz, elim. pdt.), 1.64 (3H, d, J = 5.4 Hz, major), 1.68 (3H, d, J = 6.4 Hz, minor), 2.11-2.25 (1H, m, minor), 2.37-2.52 (2H+1H, m, major + minor), 3.14 (1H, ap. t, J = 8.0 Hz, minor), 3.67 (1H, q, J = 7.4 Hz, major), 4.94-5.08 (6H, m, major + minor + elim. pdt.), 5.46 (1H, dq, J = 15.6, 6.4 Hz, minor), 5.51-5.62 (2H+1H, m, major + minor), 5.64-5.75 (2H, m, major + minor), 5.75-5.85 (1H, m, elim. pdt.), 6.25 (1H, dd, J = 16.1, 7.8 Hz, elim. pdt.), 6.39(1H, d, J = 15.7 Hz, elim. pdt.); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2, 14.0, 17.9, 19.7, 22.3, 29.7, 34.1, 36.9, 40.1,

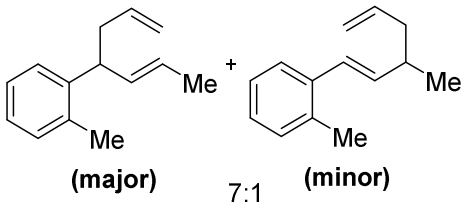
40.9, 41.2, 42.9, 48.6, 116.2, 116.4, 116.5, 119.4, 125.0, 125.2, 125.3 (q, $^3J_{CF}$ = 3.8 Hz), 126.1, 126.5, 127.1, 127.7, 127.8, 127.9, 128.1, 128.2, 128.4, 132.8, 133.5, 135.9, 136.2, 136.6, 138.8, 149.0; IR (neat): 3026 (w), 2917 (w), 1639 (w), 1598 (w), 1493 (m), 1445 (m), 1375 (w), 973 (s), 912 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{15}F_3$ [M +H]: calculated: 241.1204, found: 241.1197. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (17.4mg, 50% combined yield for both 1,5-diene isomers). R_f = 0.8 in 5% ether/hexane



(*E*)-1-methoxy-4-(1-phenylhexa-1,5-dien-3-yl)benzene (minor) & (*E*)-1-methoxy-4-(3-phenylhexa-1,5-dien-1-yl)benzene (major): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54-2.62 (2H major + 2H minor, m), 3.50 (1H major + 1H minor, app dt, J = 14.7, 7.3 Hz), 3.79 (3H major, s), 3.80 (3H minor, s), 4.98 (1H major + 1H minor, d, *J* = 10.4 Hz), 5.05 (1H major + 1 H minor, d = 17.1 Hz), 5.72-5.82 (1H major + 1H minor, m), 6.22 (1H major, dd, *J* = 15.7, 7.3 Hz), 6.31-6.38 (1H major + 2H minor, m), 6.83 (2H major, d, *J* = 8.3 Hz), 6.87 (2H minor, d, *J* = 8.8 Hz), 7.16-7.36 (7H major + 7H minor, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 40.2, 40.3, 48.1, 49.0, 55.2, 55.3, 113.9, 116.3, 126.2, 126.3, 127.1, 127.3, 127.4, 127.8, 128.2, 128.5, 128.6, 128.7, 129.2, 129.5, 129.9, 130.3, 131.4, 133.9, 135.9, 136.7, 137.5, 144.1, 158.1, 158.9; IR (neat): 3001 (w), 1639 (m), 1510 (s), 1463 (m), 1247 (s), 1175 (m), 1035 (m), 993 (m), 699 (m); HRMS (ESI+) for $C_{19}H_{20}O$ $[M+H]^+$: calculated: 265.1592, found: 265.1580. The crude material was purified on silica gel (2% ether/pentane) to afford a clear oil (29 mg, 75% combined yield for both 1,5-diene isomers). R_f = 0.5 in 2% ether/hexane.

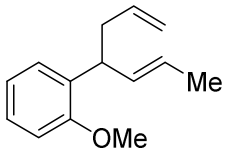


(*E*)-4,7-dimethylocta-1,5-diene (minor) and (*E*)-4-isopropylhepta-1,5-diene (major): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 6.8 Hz, major), 0.89 (3H, d, *J* = 6.8 Hz, major), 0.92-0.98 (3H, m, minor), 0.94 (6H, d, *J* = 6.4 Hz, minor), 1.58 (3H, dd, *J* = 6.8, 2.0 Hz, major), 1.61 (1H, m, major), 1.98 (2H, m, major), 2.04-2.30 (4H, m, major+minor), 2.48-2.62 (2H, m, minor), 4.91-5.05 (4H, m, major+minor), 5.12 (1H, d, *J* = 10.2 Hz, minor), 5.17 (1H, t, *J* = 10.8 Hz, major), 5.53 (1H, dq, *J* = 10.3 Hz, 6.8 Hz, major), 5.70-5.81 (1H major + 1 H minor, m); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.3, 18.7, 20.7, 21.1, 23.3, 23.5, 26.8, 31.7, 32.0, 37.4, 41.9, 42.8, 115.0, 115.4, 124.3, 132.8, 133.0, 136.2, 137.4, 137.9; IR (neat): 2960 (w), 2923 (br), 1465 (w), 1384 (w), 903 (s), 724 (s), 650 (m) cm^{-1}; HRMS (ESI+) for $C_{10}H_{17}$ [M-H]: calculated: 137.1330, found: 137.1328. The crude material was purified on silica gel (100% pentane) to afford a colorless oil. R_f = 0.49 in 5% EtOAc/hexane.

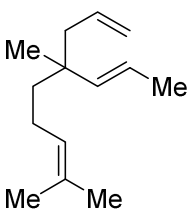


(*E*)-1-(hepta-1,5-dien-4-yl)-2-methylbenzene (major) & (*E*)-1-methyl-2-(3-methylhexa-1,5-dien-1-yl)benzene (minor): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (3H, d, *J* = 6.6 Hz, minor), 1.66 (3H, d, *J* = 4.9 Hz, major), 2.12-2.26 (2H, m, minor), 2.34 (3H, s, minor), 2.36 (3H, s, major), 2.38-2.49 (2H, m, major), 3.84-3.93 (1H, m, major), 4.96-5.08 (2H major + 2H minor, m), 5.48-5.56 (2H, m, major), 5.76 (1H, ddt, 17.1, 10.3, 7.1 Hz, major), 5.83 (1H, ddt, *J* = 17.1, 10.0, 7.1 Hz, minor), 6.10 (1H, dd, *J* = 15.7, 7.6 Hz, minor), 6.55 (1H, d, *J* = 15.9 Hz, minor), 7.06-7.20 (m, major and minor), 7.23 (1H, d, *J* = 7.8 Hz, major), 7.41 (1H, d, *J* = 7.1 Hz minor); ^{13}C NMR (125 MHz, $CDCl_3$): δ major (143.2,

136.9, 135.4, 133.8, 130.3, 126.3, 126.2, 125.7, 123.9, 115.9, 40.7, 38.7, 19.7, 13.3) minor (137.5, 137.0, 135.0, 130.1, 126.7, 126.1, 126.0, 125.5, 115.9, 41.5, 37.2, 20.1, 19.8); IR (neat): 3074 (m), 3017 (m), 2975 (m), 2860 (m), 1640 (m), 1603 (w), 1488 (m), 1461 (m), 1440 (m), 912 (s), 751(s), 726 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{18}$ [M +H]: calculated: 187.1482, found: 187.1487. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (26 mg, 94 % combined yield for both 1,5-diene isomers). R_f = 0.71 in 5% EtOAc/hexane.

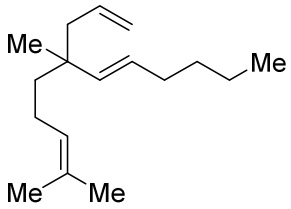


(*E*)-1-(hepta-1,5-dien-4-yl)-2-methoxybenzene: Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65 (3H, d, *J* = 6.8 Hz), 2.38 (1H, app dt, *J* = 14.2, 7.3 Hz), 2.46 (1H, app dt, *J* = 13.7, 5.9 Hz), 3.84 (3H, s), 4.13 (1H, app q, *J* = 6.3 Hz), 4.94 (1H, d, *J* = 10.2 Hz), 5.00 (1H, d, *J* = 17.1 Hz), 5.46-5.53 (1H, m), 5.56-5.61 (1H, m), 5.76 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz), 6.86 (1H, d, *J* = 8.1 Hz), 6.91 (1H, t, *J* = 7.5), 7.14-7.21 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2, 36.1, 40.0, 55.4, 120.6, 124.1, 126.8, 127.7, 133.3, 133.6, 137.2, 156.8; IR (neat): 3073 (w), 3007 (w), 2918 (w), 2835 (w), 1639 (w), 1599 (w), 1490 (s), 1463 (m), 1438 (m), 1238 (s), 1031 (m), 808 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{18}O_1$ [M+H]: calculated: 203.1429, found: 203.1436. The crude material was purified on silica gel (2% ether in pentane) to afford a clear oil (21 mg, 70% yield). R_f = 0.74 in 5% EtOAc/hexane.

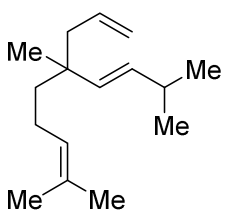


(*E*)-4,8-dimethyl-4-(prop-1-en-1-yl)nona-1,7-diene (4.15): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, s), 1.24-1.29 (2H, m), 1.58 (3H, s), 1.68 (3H, s), 1.69 (3H, s), 1.88 (2H, app dt, *J* = 15.9, 7.3 Hz), 1.99-2.08 (2H, m), 4.90 (1H, d, *J* = 17.6 Hz), 5.00 (1H, s), 5.08 (1H, t, *J* = 7.3 Hz), 5.27-

5.37 (2H, m), 5.76 (1H, ddt, *J* = 18.1, 11.0, 7.6 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 17.5, 18.2, 22.8, 23.5, 25.7, 38.6, 40.9, 45.7, 116.5, 121.8, 125.1, 130.8, 135.7, 139.5; IR (neat): 2964 (m), 2916 (m), 2856 (m), 1639 (w), 1450 (m), 1439 (m), 1377 (m), 995 (m), 972 (s), 911 (s) cm^{-1}; HRMS (ESI+) for $C_{14}H_{25}$ [M+H]: calculated: 193.1956, found: 193.1948. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (23 mg, 80% yield). R_f = 0.89 in 5% EtOac/hexane.

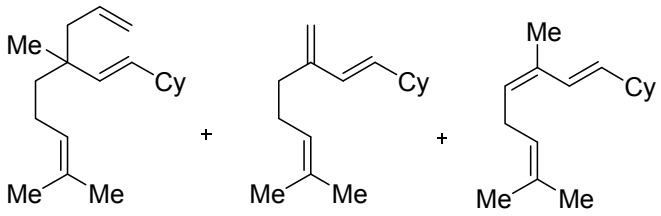


(*E*)-6-allyl-2,6-dimethyldodeca-2,7-diene (4.17): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 6.8 Hz), 0.94 (3H, s), 1.20-1.38 (6H, m), 1.58 (3H, s), 1.67 (3H, s), 1.87 (2H, app dt, *J* = 16.3, 7.8 Hz), 1.98-2.90 (4H, m), 2.22-2.31 (1H, m), 4.98 (1H, d, *J* = 5.4 Hz), 4.99 (1H, s), 5.09 (1H, t, *J* = 7.3 Hz), 5.24-5.34 (2H, m), 5.75 (1H, ddt, *J* = 16.1,10.7, 7.3 Hz); ^{13}C NMR (125 MHz $CDCl_3$): δ 13.9, 17.5, 22.1, 22.9, 23.4, 25.7, 32.0, 32.5, 38.5, 41.0, 45.8, 116.5, 125.2, 127.6, 130.9, 135.7, 138.3; IR (neat): 2959 (s), 2924 (s), 2872 (m), 2856 (m), 1639 (s), 1457 (m), 1377 (m), 995 (m), 974 (s) 911 (s) cm^{-1}; HRMS (ESI+) for $C_{17}H_{31}$ [M+H]: calculated: 235.2426, found: 235.2430. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (28 mg, 79% yield). R_f = 0.87in 5% EtOAc/hexane.



(*E*)-6-allyl-2,6,9-trimethyldeca-2,7-diene (4.18): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, s), 0.97 (6H, d, *J* = 6.6 Hz), 1.20-1.32 (2H, m), 1.59 (3H, s), 1.68 (3H, s), 1.87 (2H, app dt, *J* =

16.4, 7.6 Hz), 2.03 (2H, m), 2.22-2.31 (1H, m), 4.98 (1H, d, *J* = 8.3 Hz), 5.00 (1H, s), 5.08-5.12 (1H, m), 5.24-5.26 (2H, m), 5.69-5.79 (1H, m); ^{13}C NMR (125 MHz $CDCl_3$): δ 17.5, 22.8, 23.0, 23.0, 23.4, 25.7, 31.4, 38.2, 41.0, 45.8, 116.4, 125.2, 130.9, 134.9, 135.2, 135.7; IR (neat): 2960 (s), 2923 (m), 2867 (m), 1638 (w), 1509 (m), 1377 (m), 1102 (w), 995 (m), 974 (s), 911 (s) cm^{-1}; HRMS (ESI+) for $C_{16}H_{29}$ [M+H]: calculated: 221.2269, found: 221.2278. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (21 mg, 63% yield). R_f = 0.9 in 5% EtOAc/hexane.

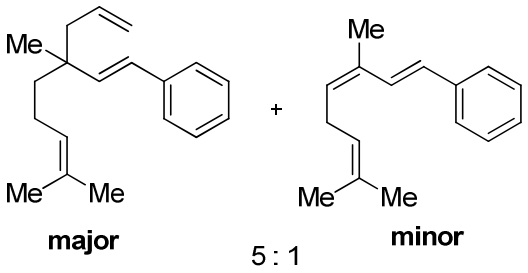


4.19 **S-37** **S-38**

6:2:1

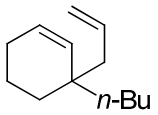
(*E*)-(3-allyl-3,7-dimethylocta-1,6-dien-1-yl)cyclohexane (4.19); (*E*)-(7-methyl-3-methyleneocta-1,6-dien-1-yl)cyclohexane (S-37); ((1*E*, 3*Z*)-3,7-dimethylocta-1,3,6-trien-1-yl)cyclohexane (S-38): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (**4.19**, 3H, s), 1.05-1.21 (**4.19** + **S-37** + **S-38**, m), 1.22-1.34 (**4.19** + **S-37** + **S-38**, m), 1.58 (**4.19**, 3H, s), 1.61 (**S-37**, 3H, s), 1.63-1.78 (**4.19** + **S-37** + **S-38**, m), 1.79 (**S-38**, 3H, s), 1.83-1.96 (**4.19** + **S-37** + **S-38**, m), 1.97-2.09 (**4.19**, 2H, m), 2.12-2.24 (2H **S-37** + 1H **S-38**, m), 2.84 (**S-38**, 2H, br t, *J* = 7.4 Hz), 4.86 (**S-37**, 1H, s), 4.90 (**S-37**, 1H, s), 4.97 (**4.19**, 1H, d, *J* = 6.3 Hz), 4.99 (**4.19**, 1H, s), 5.06-5.14 (**4.19**, 1H, m), 5.14-5.18 (**4.19**, 1H, m), 5.19-5.23 (**4.19**, 1H, m), 5.24 (**S-37**, 1H, d, *J* = 5.9 Hz), 5.25 (**4.19**, 1H, s), 5.62 (**4.19**, 1H, dd, *J* = 15.1, 6.8 Hz), 5.64 (**4.19**, 1H, dd, *J* = 15.7, 6.9 Hz), 5.72-5.79 (**4.19**, 1H, m), 6.02 (**S-37**, 1H, d, *J* = 15.7 Hz), 6.42 (**4.19**, 1H, d, *J* = 15.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 17.7, 20.6, 22.9, 23.4, 25.7, 26.0, 26.1, 26.1, 26.2, 26.2, 26.4, 27.0, 29.7, 32.3, 33.2, 33.5, 33.5, 38.3, 41.0, 41.4, 45.9, 113.1, 116.4, 122.9,

124.4, 125.2, 127.2, 129.3, 130.9, 131.7,131.9, 133.6, 135.7, 136.7; IR (neat): 3073 (w), 2962 (m), 2921 (s), 2851 (s), 1679 (br), 1639 (w), 1448 (s), 1377 (m), 1259 (w), 1103 (br), 995 (m), 971 (s), 910 (s) cm^{-1}; HRMS (ESI+) for $C_{19}H_{33}$ [M +H]: calculated: 261.2582, found: 261.2589. The crude material was purified on silica gel eluted with (100% pentane) to afford a colorless oil (30 mg, 77% yield for **4.19**). R_f = 0.94 in 5% EtOAc/hexane.

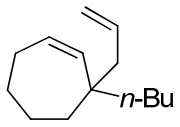


(*E*)-(3-allyl-3,7-dimethylocta-1,6-dien-1-yl)benzene (4.20, major) & ((1*E*,3*Z*)-3,7-dimethylocta-1,3,6-trien-1-yl)benzene (minor): Prepared using general procedure **L** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H major, s), 1.36-1.46 (2H major, m), 1.58 (3H major, s), 1.67 (3H major, s), 1.69 (3H minor, s), 1.72 (3H minor, s), 1.89-1.99 (2H major, m), 1.94 (3H minor, s), 2.15 (1H major, dd, *J* = 13.2, 5.4 Hz), 2.20 (1H major, dd, *J* = 13.2, 5.4 Hz), 2.97 (2H minor, br t, *J* = 6.9 Hz), 5.02 (1H major, s), 5.06 (1H major, d, *J* = 8.3 Hz), 5.07-5.12 (1H major, m), 5.13-5.18 (1H minor, m), 5.43 (1H minor, br t, *J* = 7.3 Hz), 5.75-5.83 (1H major, m), 6.16 (1H major, d, *J* = 16.2 Hz), 6.28 (1H major, d, *J* = 16.6 Hz), 6.56 (1H minor, d, *J* = 16.1 Hz), 7.17-7.23 (1 H major + 1 H minor, m), 7.28-7.33 (2 H major, m), 7.35-7.38 (2 H major + 2 H minor, m), 7.44 (2H minor, d, *J* = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.8, 20.5, 23.0, 23.3, 25.7, 26.7, 30.3, 39.2, 41.0, 45.7, 117.0, 122.5, 124.8, 125.9, 126.0, 126.4, 126.8, 127.0, 127.2, 128.3, 128.5, 128.6, 130.4, 131.2, 135.2, 138.0, 139.1, 145.5; IR (neat): 2966 (m), 1718 (w), 1493 (s), 1377 (s), 1027 (s), 912 (s), 747 (s), 694 (s); HRMS (ESI+) for $C_{19}H_{26}$ $[M+H]^+$ (major): calculated: 253.1944, found: 253.1956. The crude

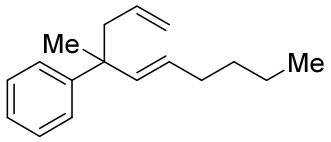
material was purified on silica gel (pentane) to afford a colorless oil (21 mg, 55% yield for **4.20**). R_f = 0.80 in pentane.



3-allyl-3-butylcyclohex-1-ene (4.21): Prepared using general procedure **L**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 6.9 Hz), 1.19-1.37 (6H, m), 1.41-1.46 (2H, m), 1.58-1.62 (2H, m), 1.93 (2H, dddd, *J* = 10.3, 6.4, 4.0, 2.5 Hz), 2.05 (2H, d, *J* = 7.8 Hz), 4.97-5.00 (1H, m), 5.01-5.03 (1H, m); 5.42 (1H, d , *J* = 10.3 Hz), 5.64 (1H, dt, *J* = 9.8, 3.5 Hz), 5.77 (1H, dddd, J = 17.6, 16.6, 10.3, 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 14.1, 19.0, 22.7, 23.6, 25.1, 32.1, 32.3, 39.6, 44.3, 116.6, 126.1, 135.5, 135.6; IR (neat): 2923 (s), 1638 (m), 1455 (s), 1377 (w), 994 (m), 911 (s), 689 (w); HRMS (ESI+) for $C_{13}H_{22}$ $[M+H]^+$: calculated: 179.1755, found: 179.1693. The crude material was purified on silica gel (pentane) to afford a colorless oil (16 mg, 59% yield). R_f = 0.89 in pentane.



3-allyl-3-butylcyclohept-1-ene (4.22): Prepared using general procedure **L**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 6.8 Hz), 1.18-1.39 (6H, m), 1.41-1.60 (4H, m) 1.62-1.77 (2H, m), 2.08-2.18 (4H, m), 4.99-5.02 (2H, m), 5.40 (1H, d, *J* = 11.7 Hz), 5.63 (1H, dt, *J* = 11.8, 5.9 Hz), 5.76-5.84 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 23.6, 24.8, 25.9, 28.2, 29.7, 35.7, 39.0, 42.5, 44.2, 116.7, 129.2, 135.7, 140.1; IR (neat): 2923 (s), 1670 (m), 1457 (m), 1377 (w), 995 (w), 912 (m), 727 (w); HRMS (ESI+) for $C_{14}H_{24}$ $[M+H]^+$: calculated: 193.1956, found: 193.1948. The crude material was purified on silica gel (pentane) to afford a colorless oil (21.9 mg, 78% yield). R_f = 0.88 in pentane.



(*E*)-(4-methyldeca-1,5-dien-4-yl)benzene (4.23): Prepared using general procedure **L**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.0 Hz), 1.29-1.42 (7H, m), 2.07 (2H, d, *J* = 7.0 Hz), 2.46-2.56 (2H, m), 4.94 (H, d, *J* = 9.5 Hz), 5.01 (H, d, *J* = 17.9 Hz), 5.43 (1H, app dt, *J* = 13.4, 6.8 Hz), 5.56-5.66 (2H, m), 7.16-7.20 (1H, m), 7.28-7.35 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 25.6, 31.8, 32.5, 43.2, 46.2, 116.9, 125.7, 126.7, 128.0, 135.5, 148.0; IR (neat): 3075 (w), 2959 (s), 2925 (s), 1639 (w), 1599 (w), 1494 (m), 1458 (m), 1444 (m), 1374 (m), 975 (m), 912 (s), 762 (s), 698 (s) cm^{-1}; HRMS (ESI+) for $C_{17}H_{25}$ [M+H]: calculated: 229.1956, found: 229.1948. The crude material was purified on SiO_2 eluted with (100% pentane) to afford a colorless oil (30 mg, 86% yield). R_f = 0.8 in 5% EtOAc/hexane.

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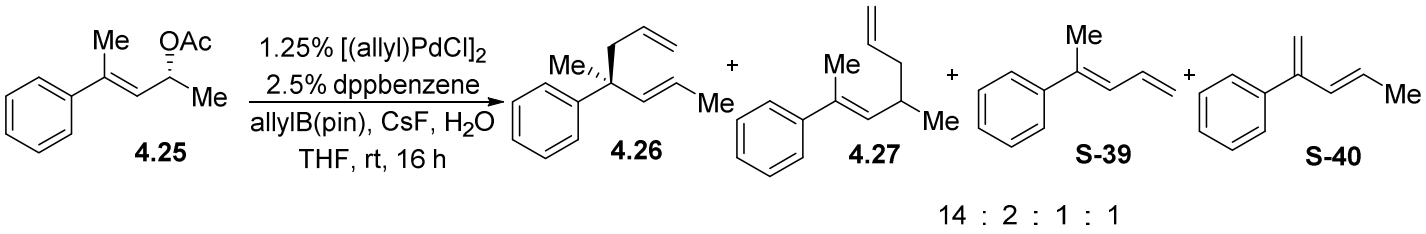
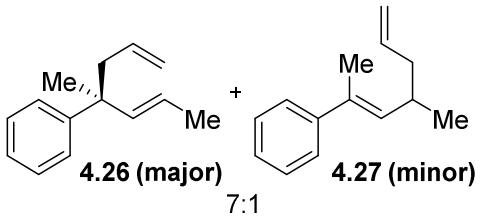


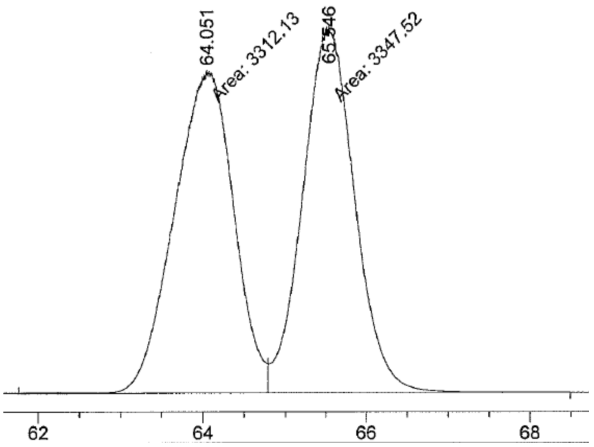
General procedure M: In the dry-box, (η^3-allylPdCl)$_2$ in solution of THF (25.5 µL, 0.00188 mmol) and dppbenzene in solution of THF (43 µL, 0.00375 mmol) was added to an oven dried 2-dram vial equipped with a stir bar. The resulting solution was allowed to stir at room temperature for 5 min. At this time, the vial was sequentially charged with **4.25** (24.3 mg, 0.15 mmol), allylB(pin) (75.6 mg, 0.45 mmol), CsF (228 mg, 1.5 mmol), and THF (0.75 mL). The vial was tightly capped with a rubber septum, removed from the dry-box, and placed under a positive pressure of N_2. Degassed, D.I. water was then added (40 µL) *via* a micro syringe. The rubber septum was rapidly exchanged with a polypropylene cap, sealed with electrical tape, and

the reaction was allowed to stir at room temperature for 16 h. The slurry was then diluted with water, the organic layer was separated and the aqueous layer was extracted three times with Et_2O. The organic portion was combined and dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (100% pentane) to yield a mixture of 14:2:1:1 of **4.26**, **4.27**, **S-39**, **S-38**, respectively. The combined yield of **4.26** and **4.27** was calculated to be 70% yield (19.5 mg). **S-39** and **S-38** can be removed by treating the mixture with maleic anhydride (30 mg, 0.3 mmol) in THF at 60 ^oC for 3 h.

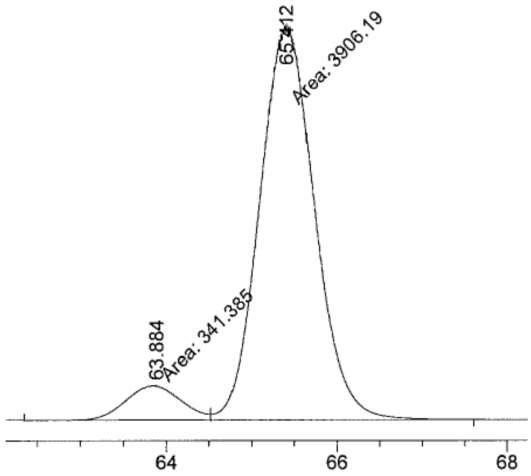


(*E*)-(4-methylhepta-1,5-dien-4-yl)benzene (4.26, major) & (*E*)-(4-methylhepta-2,6-dien-2-yl)benzene (4.27, minor): Prepared using general procedure **M**. ^1H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.8 Hz, minor), 1.34 (3H, s, major), 1.73 (3H, dd, *J* = 6.9, 2.0 Hz, major), 2.04 (3H, d, *J* = 1.5 Hz), 2.11-2.16 (2H, m, minor), 2.44-2.57 (2H major + 1H minor, m), 2.57-2.69 (1H, m, minor), 4.94-5.07 (2H major + 2H minor, m), 5.44 (1H, dq, *J* = 15.7, 6.4 Hz), 5.56-5.64 (2H, m, major+minor), 5.67 (1H, dq, *J* = 15.2, 1.5 Hz, major), 5.82 (1H, ddt, *J* = 17.1, 10.3, 7.3 Hz, minor), 7.16-7.40 (8H, m, major+minor); ^{13}C NMR (125 MHz, $CDCl_3$): δ major: 16.0, 18.1, 20.5, 25.5, 33.2, 41.8, 43.2, 46.1, 115.7, 117.0, 122.3, 125.7, 125.9, 126.5, 126.7, 128.0, 128.1, 133.5, 134.3, 135.4, 137.2, 139.6, 144.0, 147.9; IR (neat): 3075 (w), 3058 (w), 3026 (w), 2966 (m), 2916 (m), 2856 (w), 1639 (w), 1598 (w), 1494 (m), 1445 (m), 1375 (m), 1028 (w), 995 (m), 971 (m) cm^{-1}; HRMS (ESI+) for $C_{14}H_{19}$ [M+H]: calculated: 187.1487, found: 187.1478. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (19.5 mg, 70% combined yield). R_f = 0.78 in 5% EtOAc/hexane.

Analysis of stereo chemistry: The enantiomer ratio of **4.26** was determined using chiral GLC (CD-BDM, Supelco, 80 ^{o}C for 70 minutes, 15 psi, sr = 35:1). The absolute stereo chemistry was determined by analogy to **4.28**.

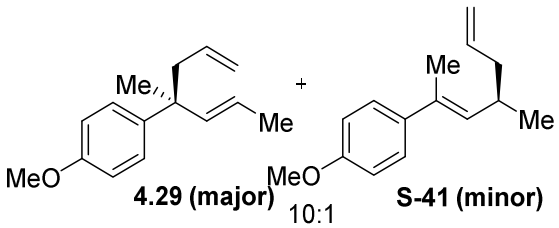


Racemic



Reaction product

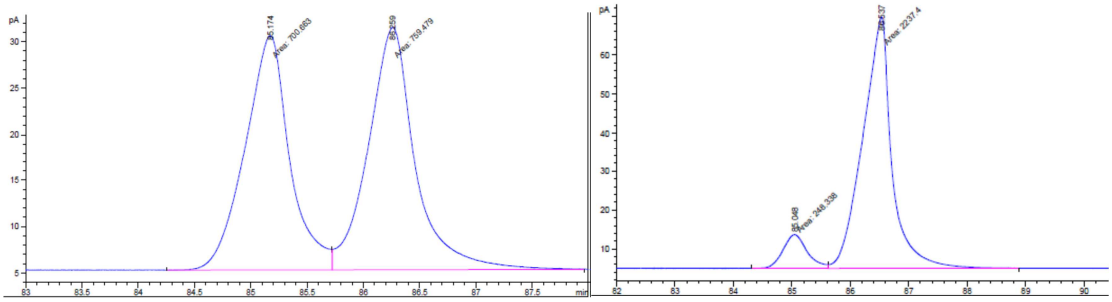
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	63.884	MF	0.7383	341.38510	7.70674	8.03718
2	65.412	FM	0.7424	3906.18921	87.69042	91.96282



(*E*)-1-methoxy-4-(4-methylhepta-1,5-dien-4-yl)benzene (4.29, major) & (*R*,*E*)-1-methoxy-4-(4-methylhepta-2,6-dien-2-yl)benzene (S-41, minor): Prepared using general procedure **M**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J*= 6.8 Hz, minor), 1.33 (3H, s, major), 1.73 (3H, dd, *J* = 6.3, 2.0 Hz, major), 2.03 (3H, d, *J* = 1.5 Hz, minor), 2.42-2.55 (2H major + 2H minor, m),

2.58-2.67 (1H, m, minor), 3.81 (3H, s, major), 3.82 (3H, s, minor), 4.94-5.08 (2H major + 2H minor, m), 5.44 (1H, dq, J = 15.6, 6.3 Hz, major), 5.52 (1H, d, J = 9.3 Hz, minor), 5.56-5.68 (2H, m, major), 5.82 (1H, ddt, J = 17.1, 9.8, 6.8 Hz, minor), 6.83-6.88 (2H, m, minor), 6.86 (2H, d, J = 8.8 Hz, major), 7.25 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz, minor); ^{13}C NMR (125 MHz, $CDCl_3$): δ major: 16.1, 18.1, 20.5, 25.6, 33.1, 41.9, 42.6, 46.2, 55.2, 55.3, 113.3, 113.5, 115.6, 116.9, 122.0, 126.7, 127.6, 127.4, 129.4, 132.8, 135.5, 137.3, 139.9, 140.0, 157.5; IR (neat): 3138 (w), 3001 (m), 2962 (m), 2834 (w), 1638 (w), 1609 (m), 1580 (w), 1511 (s), 1463 (m), 1441 (m), 1374 (w), 1293 (m), 1248 (s), 1182 (m), 1035 (m) cm^{-1}; HRMS (ESI+) for $C_{15}H_{21}O_1$ [M+H]: calculated: 217.1592, found: 217.1591. The crude material was purified on silica gel (100% pentane) to afford a colorless oil (22.7 mg, 86% combined yield). R_f = 0.33 in 5% EtOAc/hexane.

Analysis of stereo chemistry: The enantiomer ratio of **4.29** was determined using chiral GLC (CD-BDM, Supelco, 80 °C, ramp 0.5 °C/min to 115 °C, hold at 115 °C for 30 minutes, 20 psi, sr = 35:1).



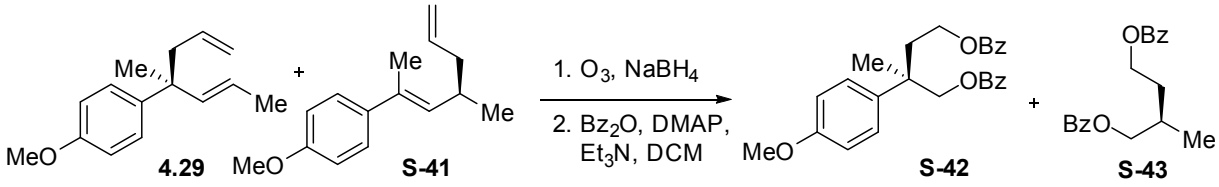
Racemic

Reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	85.048	MF	0.4782	248.33794	8.65465	9.99050
2	86.537	FM	0.5764	2237.40283	64.69248	90.00950
Totals :				2485.74077	73.34713	

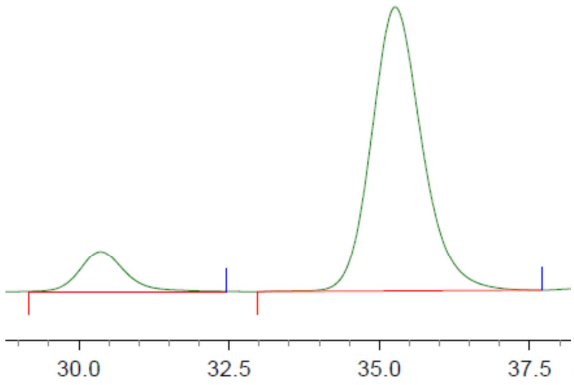
Proof of stereo chemistry:

Mixture of **4.29** and **S-41** was treated with ozonolysis/reduction contitions, followed by alcohol protection with benzyl group to obtain **S-42** and **S-43**, which can be easily separated.



Absolute stereochemistry of **4.29** was determined by comparing the HPLC chromatogram of **S-42** with that of compound reported previously.[1b]

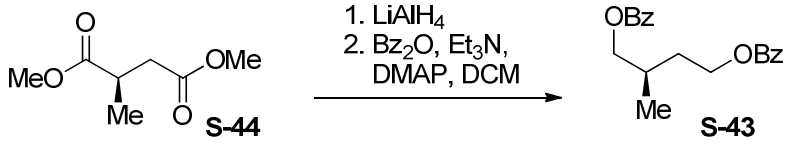
Chiral HPLC: AD-H, Chiralpak, 1.0 mL/min, 2% isopropanol/hex, 254 nm



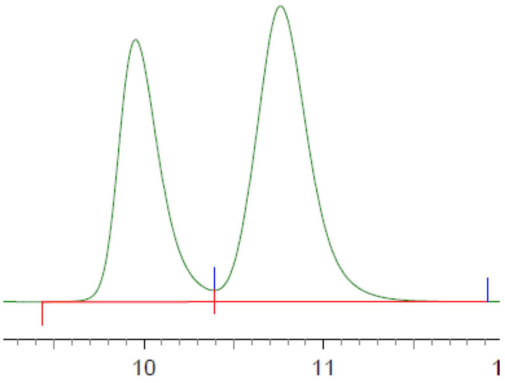
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
30.363	7602484	11.13	145838	12.39
35.263	60721550	88.87	1030928	87.61
Totals	68324034	100.00	1176766	100.00

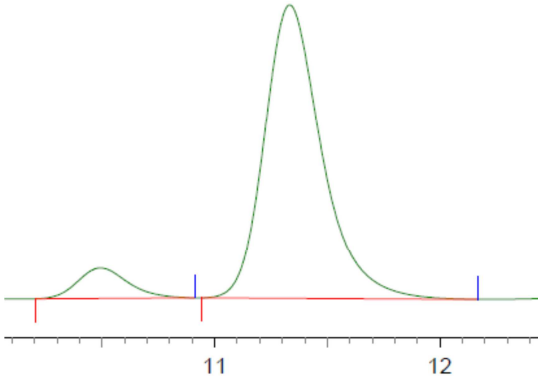
Absolute stereochemistry of the minor isomer **S-41** was determined by comparing with authentic sample of dimethyl (*R*)-(+)-methylsuccinate (**S-44**) via intermediate **S-43**.



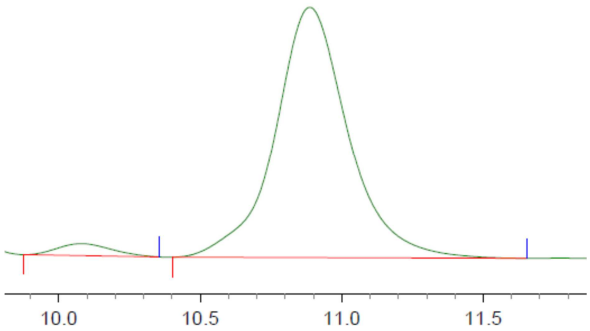
Chiral HPLD: AD-H, Chiralpak, 1.0 ml/min, 1% isopropanol/hex, 254 nm.



Racemic S-43 from racemic S-44



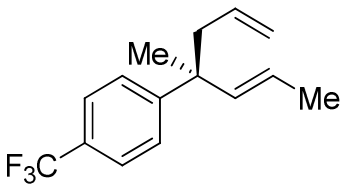
S-43 from authentic S-44



S-43 derived from S-41

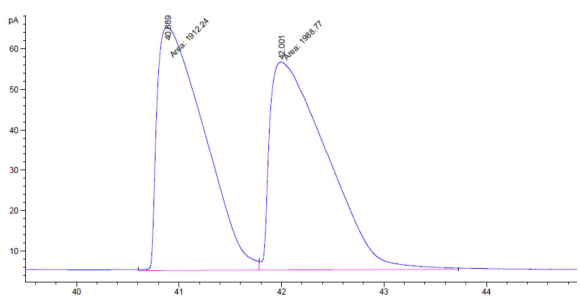
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
10.080	424634	3.37	32151	4.54
10.887	12193245	96.63	675793	95.46
Totals	12617879	100.00	707944	100.00

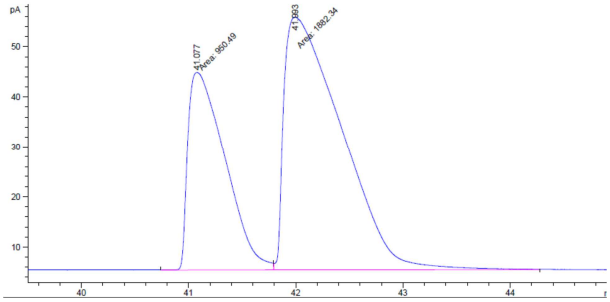


(*E*)-1-(4-methylhepta-1,5-dien-4-yl)-4-(trifluoromethyl)benzene (4.31): Prepared using general procedure **M**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, s), 1.73 (3H, dd, *J* = 6.8, 2.0 Hz), 2.45-2.57 (1H, m), 4.86-5.04 (2H, m), 5.46 (1H, dq, *J* = 15.6, 6.3 Hz), 5.56 (1H, ddt, *J* = 17.1, 9.8, 6.3 Hz), 5.64 (1H, d, *J* = 15.6 Hz), 7.42 (2H, d, *J*= 8.3 Hz), 7.54 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.1, 25.4, 43.4, 46.0, 117.6, 123.2, 124.7, 124.8, 124.9, 127.1, 127.5 (p, $^{1}J_{CF}$ = 32.3 Hz), 134.6, 138.7, 152.0; IR (neat): 2922 (w), 1640 (w), 1617 (w), 1451 (w), 1410 (w), 1326 (s), 1165 (m), 1124 (s), 1071(m), 1016 (m) cm^{-1}; HRMS (ESI+) for $C_{15}H_{18}F_3$ [M+H]: calculated: 255.13606, found: 255.13573. The crude material was purified on silica gel (100% pentane) to afford a clolorless oil (27mg, 69% yield). R_f = 0.8 in 5% EtOAc/hexane.

Analysis of stereo chemistry: The enantiomer ratio of **4.31** was determined using chiral GLC (CD-BDM, Supelco, 80 °C, ramp 0.5 °C/min to 110 °C, hold at 110 °C for 10 minutes, 20 psi, sr = 35:1). Absolute stereochemistry was determined by analogy to **4.29**.

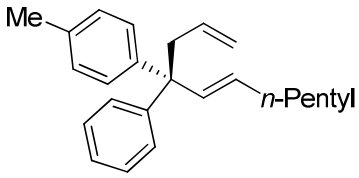


Racemic



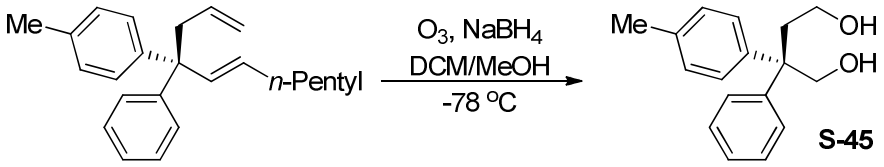
Reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	41.077	MF	0.4012	950.49042	39.48108	33.55262
2	41.993	FM	0.6216	1882.34460	50.47442	66.44738
Totals :				2832.83502	89.95550	

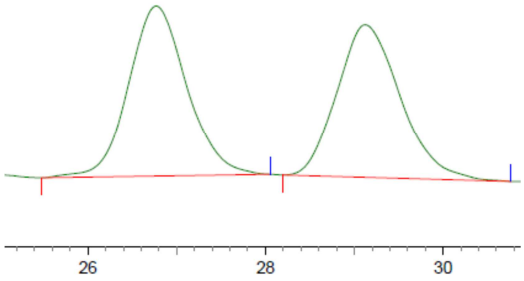


(*R*, *E*)-1-methyl-4-(4-phenylundeca-1,5-dien-4-yl)benzene (4.33): Prepared using general procedure **M.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (3H, t, *J* = 6.9 Hz), 1.41-1.56 (6H, m), 2.25 (2H, app dq, *J* = 7.3 Hz), 2.51 (3H, s), 3.21 (2H, d, *J* = 6.9 Hz), 5.14 (1H, d, *J* = 18.6 Hz), 5.27 (1H, dt, *J* = 15.7, 6.9 Hz), 5.77 (1H, app ddt, *J* = 24.0, 13.7, 10.3, 6.9 Hz), 6.20 (1H, dd, *J* = 15.7, 1.0 Hz), 7.23-7.28 (4H, m), 7.34-7.39 (3H, m), 7.43-7.47 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 20.9, 22.5, 29.1, 30.3, 31.4, 32.8, 44.6, 52.2, 117.2, 125.8, 127.7, 128.5, 128.6, 128.8, 130.9, 135.3, 135.5, 136.6, 144.1, 147.3; IR (neat): 2955 (s), 1510 (m), 1493 (m), 1444 (s), 938 (m), 912 (m), 816 (m), 764 (m), 699 (s); HRMS (ESI+) for $C_{24}H_{30}$ $[M+H]^+$: calculated: 319.2381, found: 319.2440. $[\alpha]^{20}_D$ = 0.543 (*c* = 3.315, $CHCl_3$). The crude material was purified on silica gel (pentane) to afford a colorless oil (45mg, 95% yield). R_f = 0.56 in pentane.

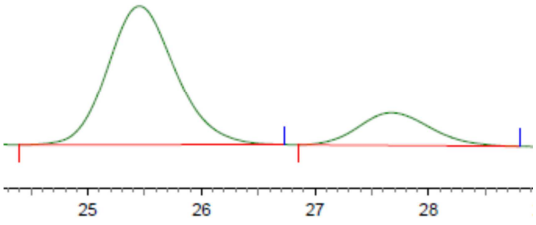
Analysis of stereo chemistry: The titled compound was ozonolyzed to the corresponding 1,4-diol as described in the sequence below. The analogous racemic material was prepared via the same route, using racemic **S-35**.



The enantiopurity was determined on diol **S-45** using chiral HPLC (AD-H, Chiraldex, 1.0 mL/min, 5% isopropanol/hexane, 254 nm). The absolute stereochemistry was determined by analogy to **4.29**.



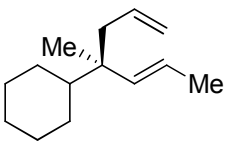
Racemic



Reaction Product

VWD: Signal A,
254 nm Results

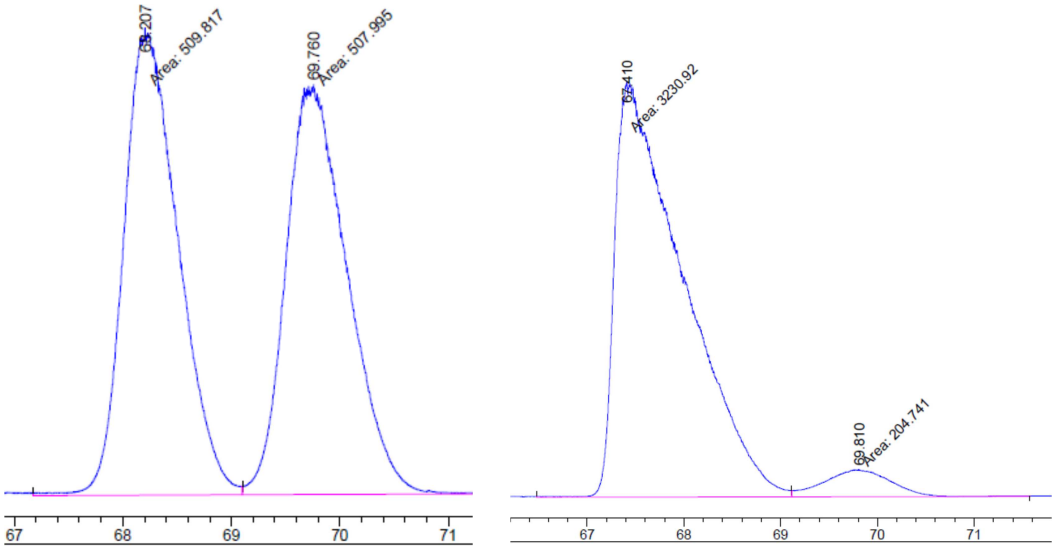
Retention Time	Area	Area %	Height	Height %
25.453	8714425	80.16	208123	81.00
27.670	2157473	19.84	48804	19.00
Totals				
	10871898	100.00	256927	100.00



(*R*, *E*)-(4-methylhepta-1,5-dien-4-yl)cyclohexane (4.35): Prepared using general procedure **M**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, s), 0.87-0.97 (4H, m), 1.06-1.19 (5H, m), 1.62-1.76 (3H, m), 1.68 (3H, dd, *J* = 5.8, 1.5 Hz), 2.06 (2H, d, *J* = 7.3 Hz), 4.96 (1H, d, *J* = 7.8 Hz), 4.99 (1H, s), 5.22-5.30 (1H, m), 5.32 (1H, d, *J* = 17.1 Hz), 5.75 (1H, dddd, *J* = 18.1, 16.6, 10.8, 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.2, 20.1, 26.8, 27.1, 27.2, 27.7, 29.7, 41.2, 43.7, 46.2, 116.2, 122.1, 136.1, 138.7 ; IR (neat): 2921 (s), 1638 (w), 1449 (m), 1377 (m), 995 (w), 974 (s), 908 (s); HRMS (ESI+) for $C_{14}H_{24}$ $[M+H]^+$: calculated: 193.1956, found: 193.1962; $[\alpha]^{20}_D$ = 5.88 (*c* = 0.136, $CHCl_3$).The crude

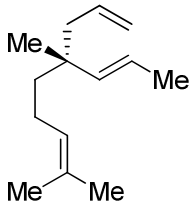
material was purified on silica gel (pentane) to afford a clear oil (49% yield). R_f = 0.85 in pentane.

Analysis of stereo chemistry: The analogous racemic material was prepared via the same route, using the corresponding racemic acetate**.** The enantiopurity was determined using chiral GLC (Chiral β-dex, Supelco, 85 ^{o}C for 100 minutes, 20 psi, sr = 35:1). The absolute stereochemistry was determined by analogy to **4.29**.



Racemic Reaction product

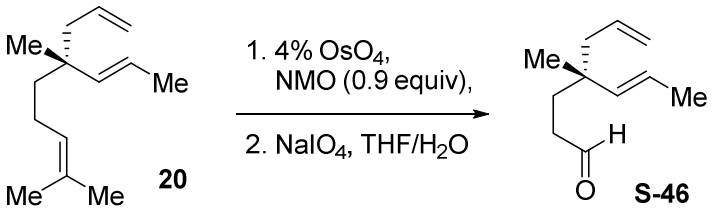
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	67.410	MF	0.8151	3230.91870	66.06355	94.04072
2	69.810	FM	0.7947	204.74057	4.29393	5.95928
Totals :				3435.65927	70.35748	



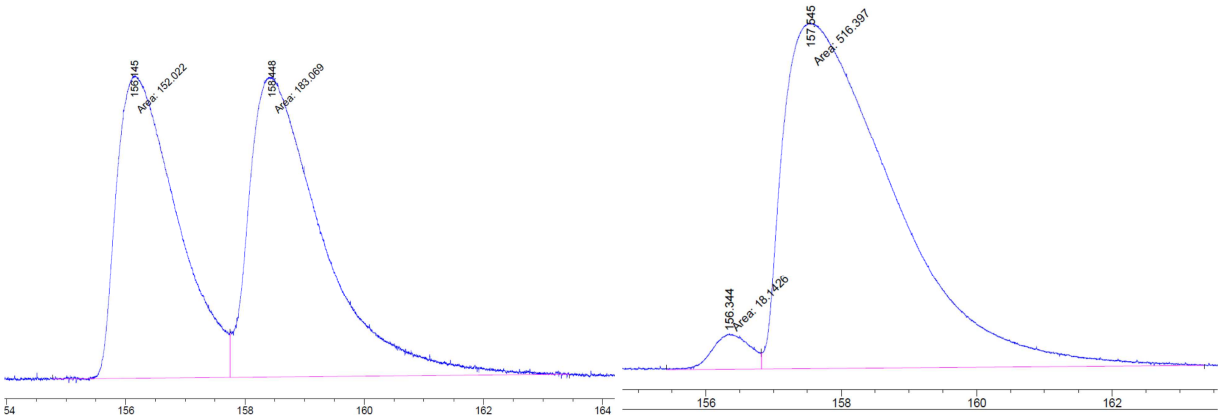
(*R*,*E*)-4,8-dimethyl-4-(prop-1-en-1-yl)nona-1,7-diene (**4.37**): Prepared using general procedure **M**. All spectral information match with the analogous racemic product **4.15**. The crude material was purified on silica gel (pentane) to afford a colorless oil (14 mg, 50% yield). R_f = 0.90 in pentane.

Analysis of stereochemistry:

Product **4.37** was treated with catalytic OsO_4, and NMO followed by $NaIO_4$ diol cleavage to afford **S-46** for GLC analysis. The analogous racemic material was prepared from racemic product **4.15**. The absolute stereochemistry was determined by analogy to **4.29**.



Chiral GLC (CD-BDM, Supelco, 40 ^{o}C, ramp 0.15 ^{o}C to 90 ^{o}C, 90 ^{o}C for 30 minutes, 20 psi, sr: 35:1)



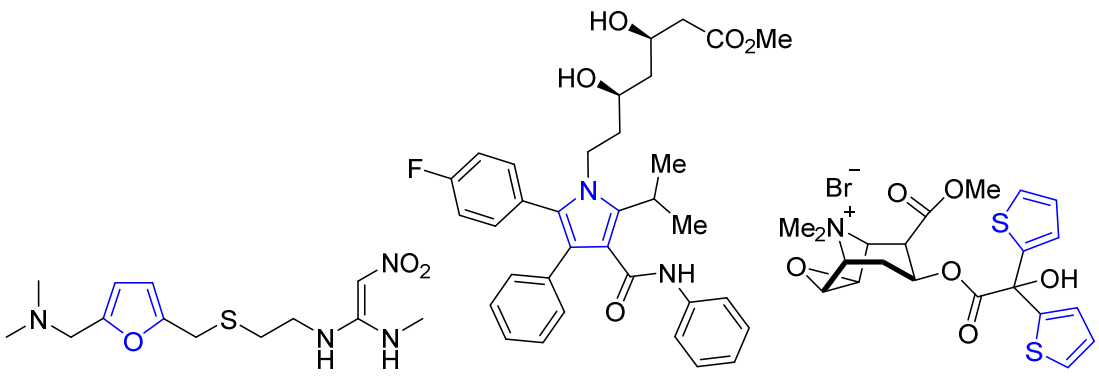
Racemic **S-46** **S-46** from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	156.344	MF	0.6451	18.14260	4.68757e-1	3.39406
2	157.545	FM	1.8869	516.39673	4.56115	96.60594
Totals :				534.53933	5.02991	

Chapter V: Pd-Catalyzed Carbonylative Conjugate Addition

Five membered heterocycles such as furans, thiophenes, and pyrroles are widely abundant in natural products and medicinally relevant molecules (Scheme 5.1).[1] A classical approach to synthesize such molecules is through the Paal-Knorr cyclization of 1,4-dicarbonyls compounds.[2] Strategies to furnish the dicarbonyl intermediates also include the Stetter reaction and the conjugate addition of a masked acylanion to an α,β-unsaturated carbonyl starting materials. While these strategies are useful, complementary methods that expand the reaction scope are desirable. Herein, I would like to document our studies in the area of 1,4-dicarbonyl synthesis. This reaction offers an atom economical and environmentally friendly alternative to access highly substituted 1,4-dicarbonyls from readily available starting materials (Scheme 5.2).[3]

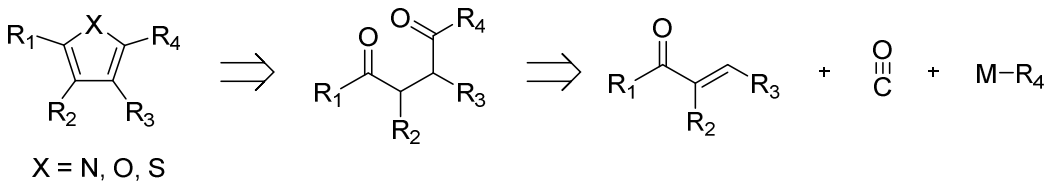
Scheme 5.1: Commercially Available Drugs Contain 5-Membered Heterocycles



Ramitidine (Zantac) Atorvastatin (Lipitor) Tiotropium (Spiriva)

[1] Li, J. L. *Heterocyclic Chemistry in Drug Discovery*, Wiley, **2013**.
[2] (a) Knorr, L. *Ber* **1884**, *17*, 2863. (b) Paal, C. *Ber* **1884**, *17*, 2756.
[3] This work was accomplished in collaboration with Dr. Daniel W. Custar. Custar, D. W.; Le, H.; Morken, J. P. *Org. Lett.* **2010**, *12*, 3760.

Scheme 5.2: Direct Strategy in Synthesis of 1,4-Dicarbonyls



I. Strategies to Synthesize 1,4-Dicarbonyl

A classical method to synthesize 1,4-dicarbonyl compounds is the Stetter reaction, which involves the generation of acylanion from an aldehyde and cyanide anion or heterazolium carbene, followed by addition to an α,β-unsaturated carbonyl.[4] Unfortunately, the scope of the Stetter reaction is limited, and its requirement for the use of reactive aldehydes renders significant benzoin side product formation. Alternatively, 1,4-dicarbonyls can be synthesized via the conjugate addition of stabilized acyl anions. The scope of the acyl metals has been extended to include acyl chromate, cobaltate, cuprate, ferrate, molybdate, and nickelate.[5] While these reaction are efficient in furnishing 1,4-dicarbonyls, the stoichiometric use of toxic metals and their associated cost make these strategies unattractive. More recently, catalytic reactions to synthesize 1,4-dicarbonyls have been developed. Herein, I would like to discuss several notable developments, including their strengths and limitations.

---

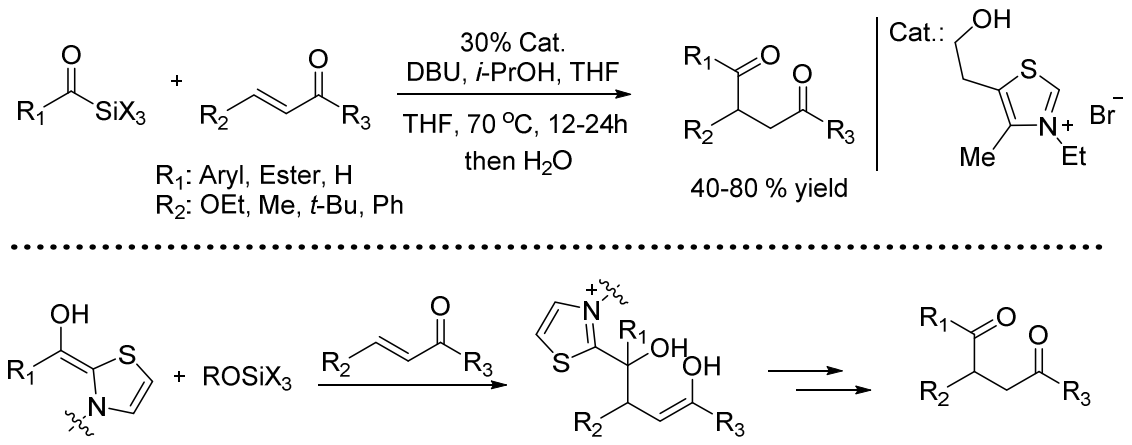
[4] (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639-712. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890-2896.

[5] Chromate: a) Söderberg, B. C.; York, D. C.; Harriston, E. A.; Caprara, H. J.; Flurry, A. H. *Organometallics* **1995**, *14*, 3712; (b) Yamane, M.; Ishibashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **2000**, *2*, 174. Cobaltate: Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955. Cuprate: Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551. Ferrate: Cooke, M. P.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 5222. Molybdate: Barluenga, J.; Rodriguez, F.; Fañanas, F. J. *Chem.—Eur. J.* **2000**, *6*, 1930. Nikelate: Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926.

A. Silyl Stetter Reactions

As previously mentioned, one major drawback of the Stetter reaction is the formation of benzoin byproduct via self-condensation. Upon formation of the acyl anion via addition of the cyanide ion of the heterazolim *in situ*, the acyl anion reacts readily with available aldehyde in the reaction medium. To overcome this problem, Scheidt and co-workers proposed the use of a pre-formed acylsilane in place of an aldehyde (Scheme 5.3).[6] This strategy generates carbene-stabilized acyl anions, which react selectively with the unsaturated carbonyl over the acylsilane, thus avoiding the benzoin side product formation. The scope of this reaction includes both aromatic and aliphatic substituted unsaturated ketones and esters, with yields typically between 40-80%. With regards to the acyl silane, not only aromatic acylsilanes can be used, but also aliphatic acylsilanes are well tolerated.

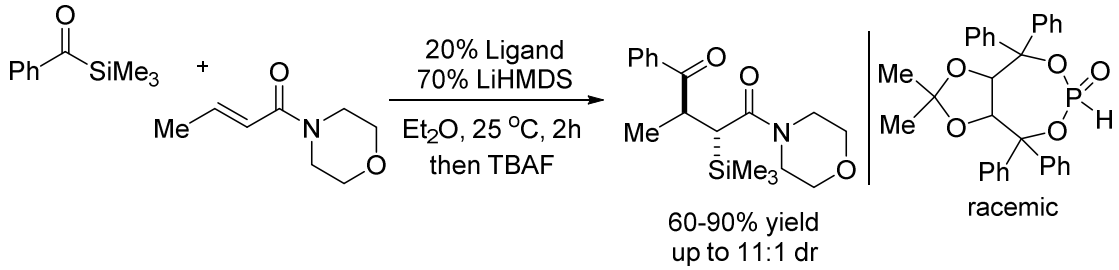
Scheme 5.3: Formation of 1,4-Dicarbonyl Compounds via Silyl Stetter Reaction



[6] Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314.

A contribution from Johnson and co-workers further extended the scope of the silyl Stetter reaction to include α,β-unsaturated amides (Scheme 5.4).[7] In this work, TADDOL phosphites were employed as the catalyst to generate acyl anions *in situ*. An interesting feature of the reaction is that upon Micheal addition of the acyl anions to the α,β-unsaturated carbonyl, a 1,4-retro Brook rearrangement facilitates the formation of an α-silyl-1,4-dicarbonyl in up to 11:1 diastereoselectivity. The α-silyl group may serve as a functional handle for subsequent transformation of the products, thus allowing formation of complexly substituted 1,4-dicarbonyls. One drawback of this reaction is that it is limited to aryl acylsilanes.

Scheme 5.4: Generation of Highly Substituted 1,4-Dicarbonyls



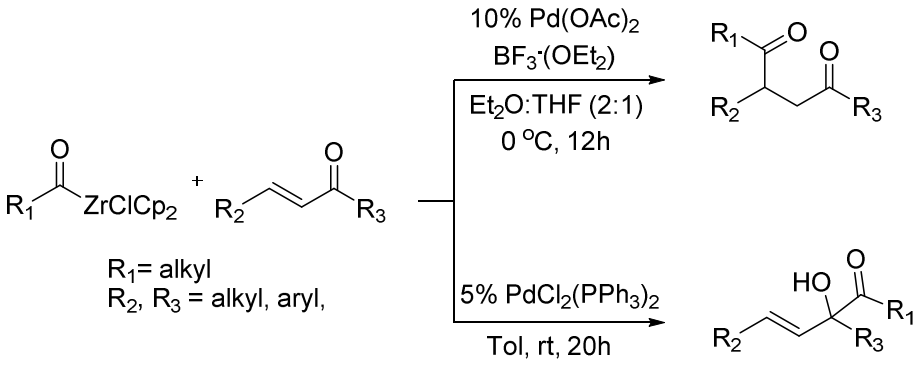
B. Metal Stabilized Acyl Anions

In 1998, Taguchi and co-workers reported the Pd-catalyzed addition of zirconium stabilized acyl anions to α,β-unsaturated carbonyls (Scheme 5.5).[8] Appropriate control of the reaction conditions led to the selective 1,2- or 1,4-addition. Using a combination of catalytic $Pd(OAc)_2$ and $BF_3{\cdot}(OEt_2)$, 1,4-dicarbonyl compounds were obtained. On the other hand, treatment with catalytic $PdCl_2(PPh_3)_2$ lead to exclusive formation of the 1,2-addition product.

[7] Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2377.
[8] Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 8141

While both aliphatic and aromatic unsaturated carbonyl substrates can be employed, only aliphatic acylzirconocenes were studied, perhaps due to limited availability of this reagent class.

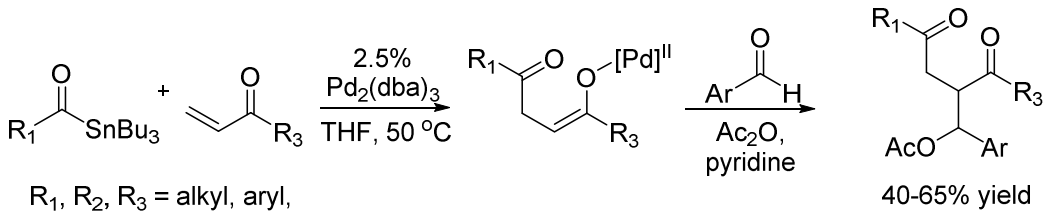
Scheme 5.5: Synthesis of 1,4-Dicarbonyl *via* Conjugate Addition of Acylzirconocene



Synthesis of the 1,4-dicarbonyl functionality *via* Pd-catalyzed conjugate addition of acylstannanes has also been achieved (Scheme 5.6).[9] In the presence of a catalytic amount of $Pd_2(dba)_3$, acylstannanes undergo β-addition to α,β-unsaturated ketone, yielding 1,4-dicarbonyl compounds in reasonable to good yields. Additionally, *in situ* trapping with benzaldehyde afforded α-substituted 1,4-dicarbonyls. Aliphatic and aromatic acylstannanes are tolerated in this reaction, though unsubstituted α,β-unsaturated carbonyls are necessary for efficient Micheal addition.

[9] Shirakawa, E.; Yamamoto, Y.; Nakao, Y.; Tsuchimoto, T.; Hiyama, T. *Chem. Commun.* **2001**, 1926.

Scheme 5.6: Pd-Catalyzed Conjugate Addition of Acylstannanes



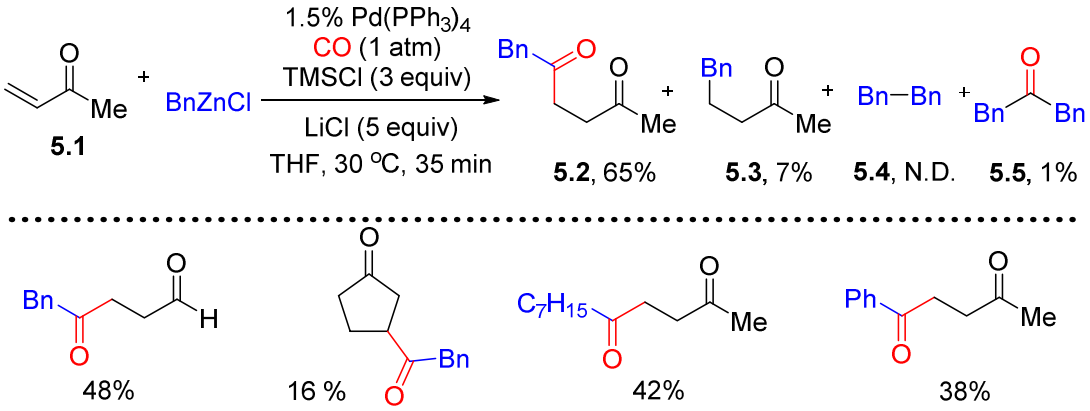
C. Carbonylative Conjugate Addition

Carbonylative C-C bond formation reactions offer powerful and atom economical strategies to quickly assemble complex carbonyls compounds from simple building blocks. Previously, all strategies to synthesize 1,4-dicarbonyls described in section A and B relied on conjugate addition of preformed acyl anions. In view of the carbonylative C-C bond formation strategies, Orito and co-workers have introduced a method to synthesize 1,4-dicarbonyl compounds using the readily available carbon monoxide.[10] In this reaction, presumably the acyl anion equivalent is formed *in situ* in the presence of a palladium catalyst, benzylzinc chloride, α,β-unsaturated carbonyls and atmospheric pressure of carbon monoxide. In addition to the desired 1,4-dicarbonyl compounds **5.2**; several side products were also observed, including the conjugate addition product **5.3**, the homocoupling product **5.4** and the carbonylative homocoupling product **5.5**. To minimize side product formation, it is critical to add an excess amount of LiCl. The scope of Orito's reaction is general and can contain unsaturated aldehydes and cyclic unsaturated ketones, though at diminished yields. Moreover, the reaction is not limited

[10] Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908.

to benzylzinc chloride, other alkyl- and arylzinc reagents are also suitable starting materials for the reaction, thus significantly improving the scope of the reaction. A drawback in Orito's reaction is that it is limited to the use of simple α,β-unsaturated carbonyls, and no example of the use of acyclic β-substituted enones were reported.

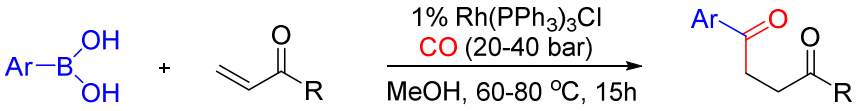
Scheme 5.7: Pd-Catalyzed Carbonylative Conjugate Addition



More recently, a complimentary carbonylative conjugate addition method was reported by Mortreux *et al.* (Scheme 5.8).[11] This work extended the scope of the carbonylative conjugate addition to using Rh based catalysts and arylboronic acids. While the reported compounds were generally obtained in moderate to good yields, the reaction is limited to arylboronic acids and only a few unsaturated carbonyls substrates were surveyed. Additionally, the requirement for prolonged heating under high CO pressure further affect the applicability of the reaction.

[11] (a) Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem Commun.* **2004**, 1520. (b) Chochois, H.; Sauthier, M.; Maerten, E.; Castanet, Y.; Mortreux, A. *Tetrahedron* **2006**, *62*, 11740.

Scheme 5.8: Rh-Catalyzed Carbonylative Conjugate Addition



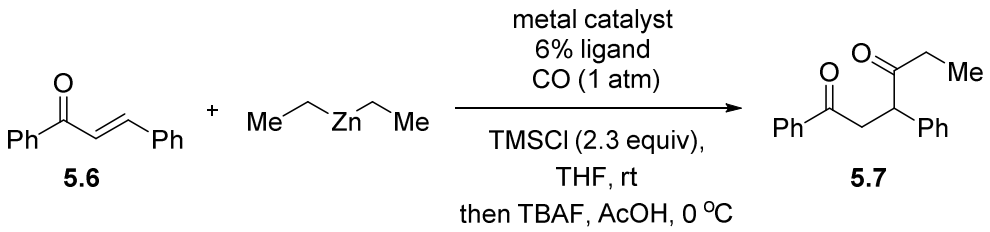
In conclusion, metal catalyzed carbonylative conjugate addition offered an attractive strategy for the synthesis of 1,4-dicarbonyls due to the low cost and readily availability of starting materials. Despite the promising results, many limitations remain, particularly in regards to synthesizing highly substituted 1,4-dicarbonyl compounds.

II. Progresses in the Pd-Catalyzed Carbonylative Conjugate-Addition to Synthesize Complexly Substituted 1,4-Dicarbonyls

A. Optimization

The foremost limitation in carbonylative conjugate addition methods reported previously lay in the use of unsubstituted enone starting materials. To overcome this issue, we set our goal to develop a new method that can tolerate enones containing complex substitution patterns, particularly at the β-carbon position. Using chalcone **5.6** as the test substrate, we investigated the carbonylative conjugate addition starting with conditions previously developed by Orito, except that the more reactive Et_2Zn reagent was employed in place of BnZnCl (Table 5.1, entry 1). To our delight, the desired 1,4-dicarbonyl product **5.7** was obtained in 70% yield. When LiCl was omitted from the reaction, 82% yield of **5.7** was obtained (entry 2). To further understand the importance of the additives, TMSCl was removed; interestingly, the reaction did not proceed and only starting material **5.6** was recovered. Further optimization of the reaction revealed that combinations of $Pd_2(dba)_3$ and either PPh_3 or PCy_3 were suitable catalysts for the reaction (entry 4-8). Notably, only 0.25 mol % catalyst loading is required to maintain reaction efficiency (entry 6 and 7) and the amount of Et_2Zn can be lowered to 0.65 equiv, suggesting that both alkyl groups may participate in the reaction (entry 8). These observations further highlighted the green and atom economical aspects of this reaction. In addition to Pd catalysts, Ni and Pt catalysts were examined, but neither system was effective for the reaction (entry 9 and 10). Starting material **5.6** was recovered using $Ni(cod)_2$ while only the direct conjugate addition product was isolated in the case of using $Pt(dba)_3$.

Table 5.1: Optimization Progress on the Carbonylative Conjugate Addition Reaction



entry[a]	catalyst	ligand	yield (%)[b]
1[c]	5% $Pd(PPh_3)_4$	-	70
2	5% $Pd(PPh_3)_4$	-	82
3[d]	5% $Pd(PPh_3)_4$	-	N.R.
4	2.5% $Pd_2(dba)_3$	PPh_3	85
5	2.5% $Pd_2(dba)_3$	PCy_3	82
6	0.25% $Pd_2(dba)_3$	PPh_3	86
7	0.25% $Pd_2(dba)_3$	PCy_3	86
8[e]	2.5% $Pd_2(dba)_3$	PCy_3	83
9	5% $Ni(cod)_2$	PCy_3	N.R.
10	5% $Pt(dba)_3$	PCy_3	0

[a] Reaction conditions: 1.3 equiv of Et_2Zn, 2.3 equiv of TMSCl, 1 atm of CO, 0.2M THF, rt, 4h. Upon completion, the reaction was quenched at 0 °C with 1.5 equiv AcOH and 1.5 equiv TBAF for 10 min. [b] Yields are average of two or more experiments. [c] 5 equiv of LiCl was added. [d] No TMSCl was added. [e] Reaction with 0.65 equiv Et_2Zn.

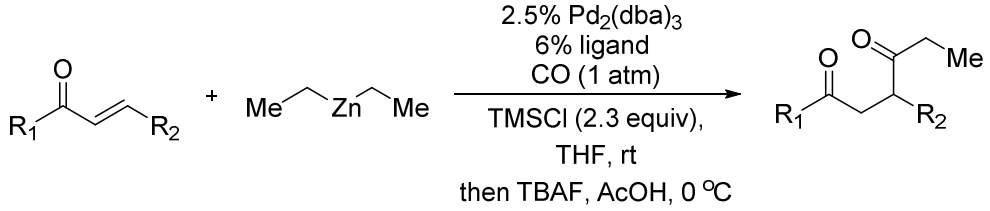
B. Substrate Scope Survey

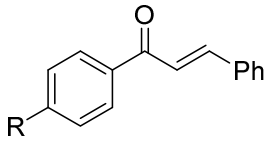
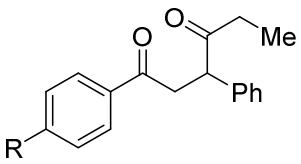
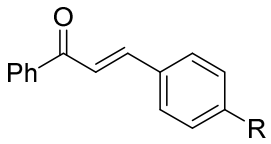
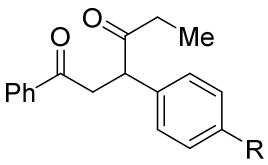
The ability to utilize both PPh_3 and PCy_3 is an important feature of the carbonylative conjugate addition reaction because these ligands are significantly different in both steric and electronic features.[12] Effective use of both ligands will offer additional tuning capability in the case of more complex systems (i.e. late stage installation of the 1,4-dicarbonyl unit in a complex

[12] Tollman, C. A. *Chem Rev.* **1977**, *77*, 313.

molecule). For this reason, both PPh_3 and PCy_3 are surveyed in our substrate scope studies. Table 5.2 provide results for substrates containing all aromatic substituents. Substrates containing either electron donating or electron withdrawing aryl substituents, at the carbonyl carbon or the β-carbon of the enone, were all well tolerated. In these examples, PPh_3 and PCy_3 ligand provided similar yields between 79-87%.

Table 5.2: Substrate Scope Survey of Aryl Substituted Enones

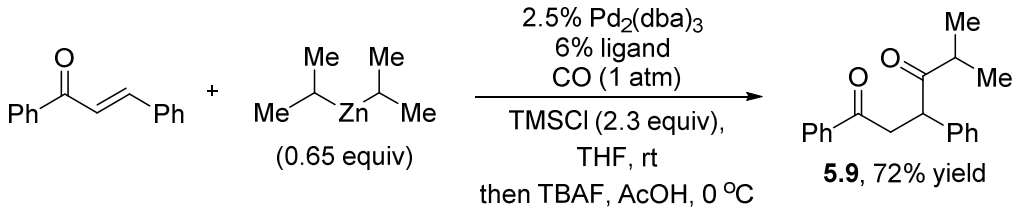


entry[a]	substrate	R	product	yield (%) PPh_3	yield (%) PCy_3
1		Cl		82	80
2		OMe		81	81
3		Cl		84	82
4		OMe		79	80
5		CO_2Me		86	87

[a] Reaction conditions: 1.3 equiv of Et_2Zn, 2.3 equiv of TMSCl, 1 atm of CO, 0.2M THF, rt, 4h. Upon completion, the reaction was quenched at 0 °C with 1.5 equiv AcOH and 1.5 equiv TBAF for 10 min. [b] Yields are average of two or more experiments.

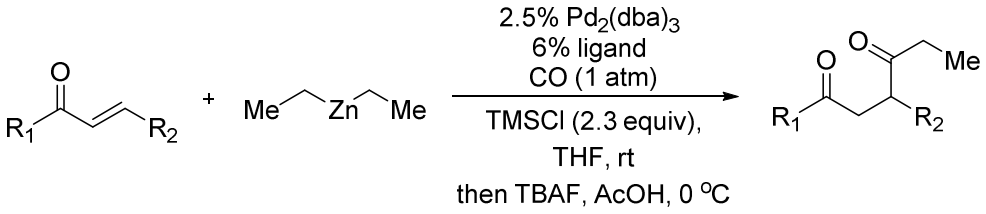
Delighted with the initial substrate scope results, we applied $(i\text{-Pr})_2Zn$ reagent in the reaction (Scheme 5.9) to ensure that the scope of oranozinc is not limited to Et_2Zn. As expected, the desired 1,4-dicarbonyl **5.8** was obtained in 72% yield, requiring only 0.65 equivalents of the organozinc reagent.

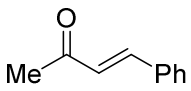
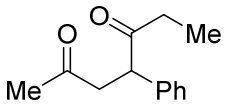
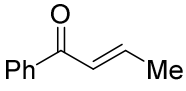
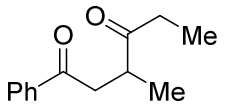
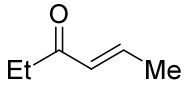
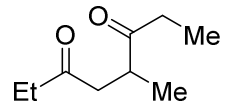
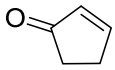
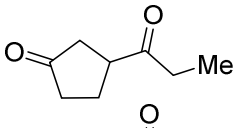
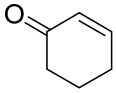
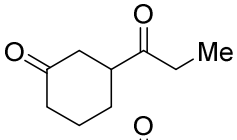
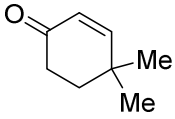
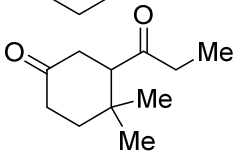
Scheme 5.9: Di-*iso*-Propylzinc Reagent in 1,4-Dicarbonyl Synthesis



Enone starting materials containing aliphatic substituents were also examined (Table 5.3). Substrates containing Me and Ph substituents were both tolerated, regardless of the relative position of these groups (entry 1 and 2). Substrates with all aliphatic substitution can also be employed and provided comparable yields to the aromatic counterparts (entry 3). Previously, Orito and co-workers reported the synthesis of 1,4-dicarbonyls from cyclic enones and BnZnCl; however, they observed severely reduced yields.[10] Under our newly developed conditions, 5- and 6-membered cyclic 1,4-dicarbonyls were synthesized in 48-68% yields (entry 4-5). Using more forcing conditions, including elevated catalyst loading and 1.95 equivalents of Et_2Zn, an α,β-unsaturated cyclohexenone containing an all-carbon quaternary center at the γ-carbon gave rise to the corresponding 1,4-dicarbonyls in up to 72% yield using PPh_3 as the ligand (entry 6).

Table 5.3: Survey of Enone Containing Aliphatic Substituents



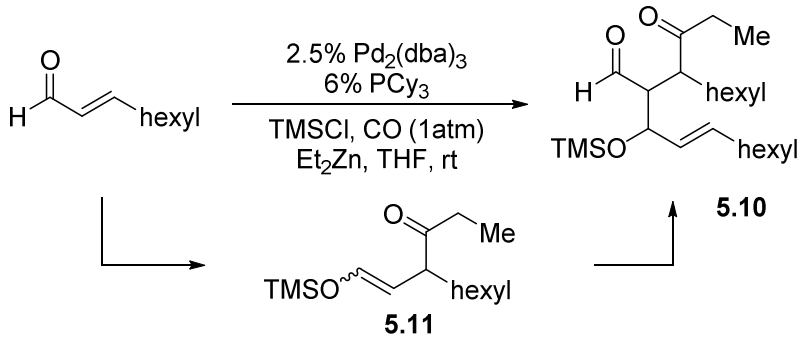
entry[a]	substrate	product	yield (%) PPh_3	yield (%) PCy_3
1			52	82
2			67	66
3			85	86
4			56	48
5			68	67
6[c]			72	55

[a] Reaction conditions: 1.3 equiv of Et_2Zn, 2.3 equiv of TMSCl, 1 atm of CO, 0.2M THF, rt, 4h. Upon completion, the reaction was quenched at 0 °C with 1.5 equiv AcOH and 1.5 equiv TBAF for 10 min. [b] Yields are average of two or more experiments.[c] 10% $Pd_2(dba)_3$, 24% ligand, and 1.95 equiv Et_2Zn was employed.

In an effort to further broaden the scope of the carbonylative conjugate addition reaction, we surveyed the reactivity pattern for α,β-unsaturated aldehydes. Applying the optimized conditions for ketone substrates to cyclohexenal, the desired 1,4-dicarbonyl was not observed. Instead, a product tentatively assigned to be **5.10** was obtained (Scheme 5.10). Formation of **5.10**

was hypothesized to arise from a pathway involving Mukayama aldol reaction between the silyl ether **5.11** (formed *in situ*) and available nonenal in the reaction medium.[13] This problem was overcome by replacing TMSCl with TESCl additive.

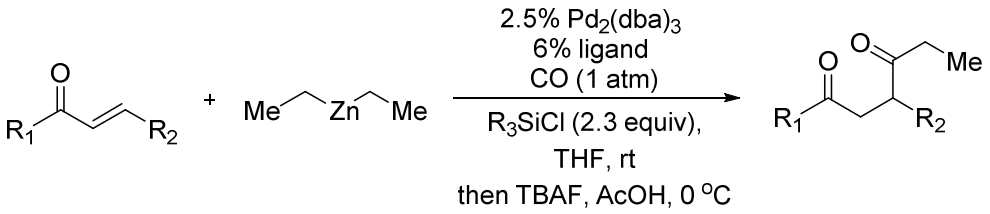
Scheme 5.10: Self-Condensation *via* Mukayama Aldol Mechanism:

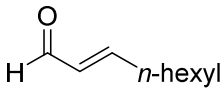
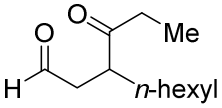
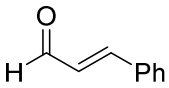
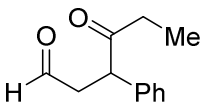
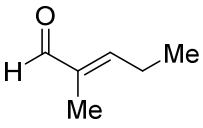
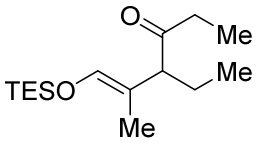
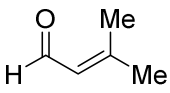
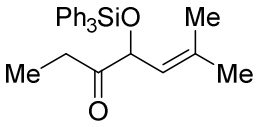


Both aromatic and aliphatic unsaturated aldehydes can be employed in the reaction (Table 5.4, entry 1 and 2), though the aromatic enal reacted with lower yield (39% and 41% yields, entry 2). An unsaturated aldehyde containing substitution at the α-carbon was also well tolerated in this reaction; moreover, the *E*-selective silyl enol ether product may be isolated using silica gel chromatography rather than the desilylative work up procedure (entry 3). Lastly, an aldehyde containing two methyl groups at the β-carbon position yielded 1,2-carbonylative addition product (entry 4 and 5); here, the reaction using Ph_3SiCl provided higher yield compared to the reaction conditions using TESCl.

[13] Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011.

Table 5.4: Aldehyde Starting Materials in Carbonylative Conjugate Addition



entry[a]	substrate	product	R_3SiCl	yield (%)[b]	
				PPh_3	PCy_3
1			Et_3SiCl	78	69
2			Et_3SiCl	41	39
3[c]			Et_3SiCl	90	72
4			Et_3SiCl	41	-
5			Ph_3SiCl	63	60

[a] Reaction conditions: 1.3 equiv of Et_2Zn, 2.3 equiv of R_3SiCl, 1 atm of CO, 0.2M THF, rt, 4h. Upon completion, the reaction was quenched at 0 °C with 1.5 equiv AcOH and 1.5 equiv TBAF for 10 min. [b] Yields are average of two or more experiments. [c] The reaction was worked up with H_2O.

III. Mechanism of the Carbonylative Conjugate Addition Reaction

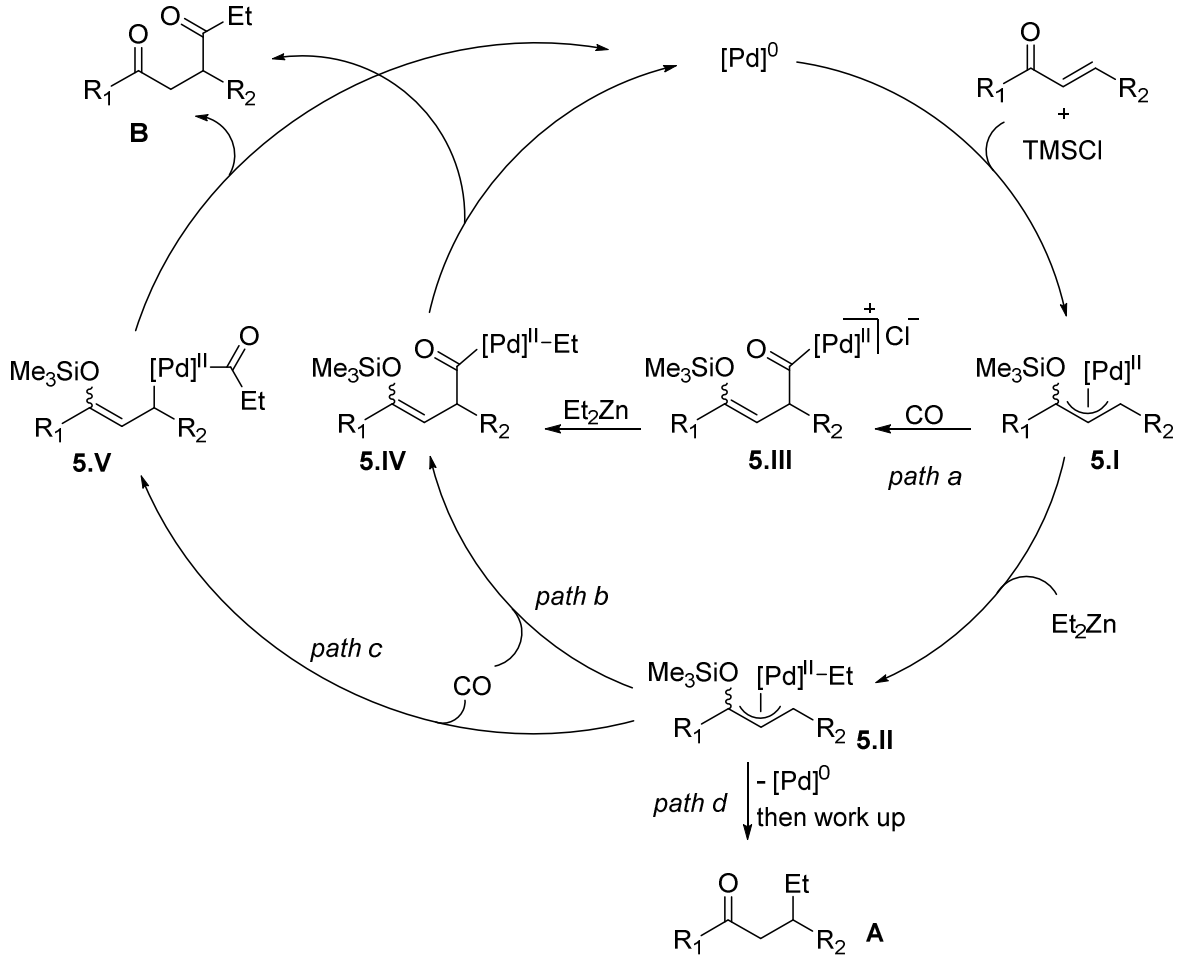
The mechanism of the carbonylative conjugate addition is not well understood, and several reaction paths have been proposed (Scheme 5.11). Oxidative addition of $[Pd]^0$ to the enone in the presence of TMSCl may generate Pd-π-allyl intermediate **5.I**. Formation of similar intermediates from $[Pd]^0$, enone and Lewis acid has been proposed by Orito,[10] and others, including our group.[14] Transmetallation of Et_2Zn to the $[Pd]^{II}$ complex **5.I** may generate intermediate **5.II**. Formation of the alkyl conjugate addition product **A** as a reaction side product, and as the exclusive product in the absence of CO gas, suggests the existence of **5.II** (path d).[14] From **5.II**, CO insertion may occur at either the allylic carbon (path b) or on the alkyl carbon (path c) leading to the formation of intermediate **5.IV** or **5.V**, respectively. The formation of **5.IV** is endorsed by Orito and co-workers.[10] Intermediate **5.V** was suggested by Taguchi *et al.* in the Pd-catalyzed conjugate addition of acylzirconium to enones.[8] An analogous Rh-acyl intermediate which was generated in situ from arylboronic acid and CO gas was also suggested by Mortreux *et al*.[11] From either **5.IV** or **5.V**, reductive elimination, followed by work up would furnish the desired 1,4-dicarbonyl compound **B** and regenerate $[Pd]^0$ for the subsequent catalytic cycle.

In his work to synthesize 1,4-dicarbonyl via Pd-catalyzed carbonylative conjugate addition, Orito and co-workers observed that sterically more hindered *ortho* substituted benzylzinc chlorides provided higher yields than the *para* substituted counterparts.[10] Under the assumption that the more sterically hindered organometals would transmetallate slower, and the transmetallation is the slow step in the reaction, Orito suggested another plausible mechanism

[14] For mechanistically related Pd(0) and Ni (0) catalyzed conjugate addition, see: (a) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *14*, 5160. (b) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944. (c) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505. (d) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1541. (e) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 224. (f) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

(Scheme 5.11, path a). From **5.I**, CO insertion occurrs readily, leading to formation of acyl-$[Pd]^{II}$ intermediate **5.III**. Transmetallation from organozinc to **5.III** generates **5.IV**. Reductive elimination of **5.IV**, followed by oxidative work up would lead to the formation of the desired 1,4-dicarbonyl.

Scheme 5.11: Plausible Mechanism of the Pd-catalyzed Carbonylative Conjugate Addition



IV. Conclusion

In this chapter, the palladium catalyzed carbonylative conjugate addition reaction was described. Using this strategy, compounds containing the 1,4-dicarbonyl motif can be effectively synthesized from simple and readily available starting materials. Both PPh_3 and PCy_3 ligands are equally efficient in the reaction, providing an additional optimization handle. A significant advancement in our new protocol is the capability to tolerate starting materials containing β-substitution, a limitation that many previous reports lacked. This advantage allows the synthesis of complexly substituted 1,4-dicarbonyls.

V. Experimental Procedures

A. General Information

^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm, C_6D_6: 7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, b = broad, m = multiplet), coupling constants (Hz) and integration. $^{13}C\{^{1}H\}$ NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.00 ppm, C_6D_6: 128.0 ppm). Infrared (IR) spectra were recorded on a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) and low-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), ceric ammonium molybdate (CAM), and potassium permanganate ($KMnO_4$).

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran and dichloromethane were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Trimethylsilyl chloride,

trans-2-nonenal, cinnamaldehyde, 3-methyl-2-butenal, 2-methyl-2-pentenal, *trans*-1-phenyl-2-buten-1-one, isovaleraldehyde, and benzaldehyde were distilled from calcium hydride. Triphenylphosphine was recrystallized from ethanol. Methyl 4-(3-oxo-3-phenyl-1-propenyl)benzoate, 4-chlorochalcone, 4-methoxychalcone were purchased from Acros Organics. Triethylsilyl chloride was purchased from Gelest, Inc. and used without further purification. Acetic acid was purchased from Fisher Scientific and used without further purification. Tris(dibenzylideneacetone)dipalladium (0) and tricyclohexylphosphine were purchased from Strem Chemicals, Inc. and used without further purification. Triphenylsilyl chloride, diphenylmethylsilyl chloride, dimethylphenylsilyl chloride, tertrabutylammonium flouride, *trans*-4-phenyl-3-buten-2-one, cyclohexenone, 4,4-dimethyl-2-cyclohexenone, 4-hexen-3-one were purchased from Aldrich and used without further purification.

B. Representative Procedures

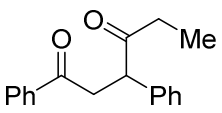
Representative Procedure for Conjugate Addition with Solid α,β-Unsaturated Carbony: In the glove box, $Pd_2(dba)_3$ (6.9 mg, 7.5 μmol) and triphenylphosphine (4.7 mg, 18 μmol) were added to an oven-dried roundbottom flask charged with a magnetic stir bar. The flask was sealed with a rubber septum, removed from the dry box, and placed under atmosphere of argon. To the flask was added tetrahydrofuran (1.0 mL) and was allowed to stir for 30 minutes. Next, CO (balloon) was added to the mixture and the mixture was vented for one minute; the vent was closed and freshly distilled trimethylsilyl chloride (88 μL, 690 μmol) was added followed by a solution of chalcone (62.5 mg, 300 μmol) in tetrahydrofuran (1.0 mL). The mixture was stirred for 10 minutes prior to dropwise addition of diethyl zinc (44 μL, 390 μmol). The mixture was then

allowed to stir for 3 hours under a CO (g) atmosphere. It was then passed through a plug of SiO_2 (60% diethyl ether/hexanes). The material was concentrated *in vacuo* by rotary evaporation and then diluted with tetrahydrofuran (4.2 mL). The mixture was cooled to 0 ^oC and treated with acetic acid (26 μL, 450 μmol) and TBAF (450 μL, 450 μmol, 1.0 M in THF). The reaction mixture stirred for 10 minutes and was quenched with saturated aqueous sodium bicarbonate and the organic layer was separated. The aqueous layer was washed with diethyl ether (5 X 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (15% diethyl ether/hexanes) to afford a clear, colorless oil (67.9 mg, 85.0% yield).

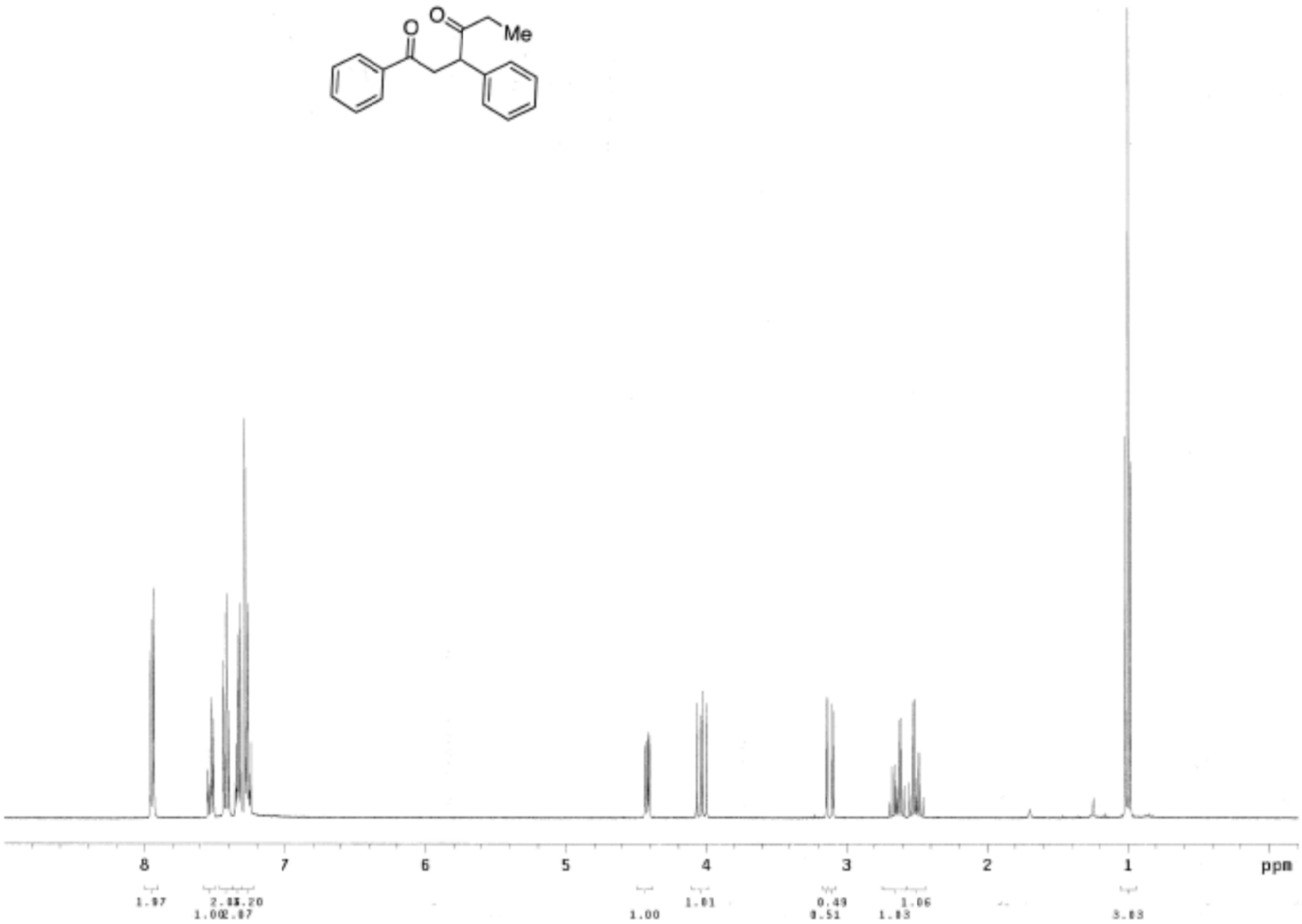
Representative Procedure for Conjugate Addition with Liquid α,β***-Unsaturated Carbonyls:*** In the glove box, $Pd_2(dba)_3$ (6.9 mg, 7.5 μmol) and triphenylphosphine (4.7 mg, 18 μmol) were added to an oven-dried roundbottom flask charged with a magnetic stir bar. The flask was sealed with a rubber septum, removed from the dry box, and placed under atmosphere of argon. To the flask was added tetrahydrofuran (2.0 mL) and was allowed to stir for 30 minutes. Next, CO (balloon) was added to the mixture and the mixture was vented for one minute; the vent was closed and freshly distilled trimethylsilyl chloride (88 μL, 690 μmol) was added and followed by a solution of *trans*-2-nonenal (50.0 μL, 300 μmol). The mixture was stirred for 10 minutes prior to dropwise addition of diethyl zinc (44 μL, 390 μmol). The mixture was then allowed to stir for 4 hours under a CO(g) atmosphere. It was then passed through a plug of SiO_2 (60% diethyl ether/hexanes). The material was concentrated *in vacuo* by rotary evaporation and then diluted with tetrahydrofuran (4.2 mL). The mixture was cooled to 0 ^oC and treated with acetic acid (26 μL, 450 μmol) and TBAF (450 μL, 450 μmol, 1.0 M in THF). The reaction mixture stirred for

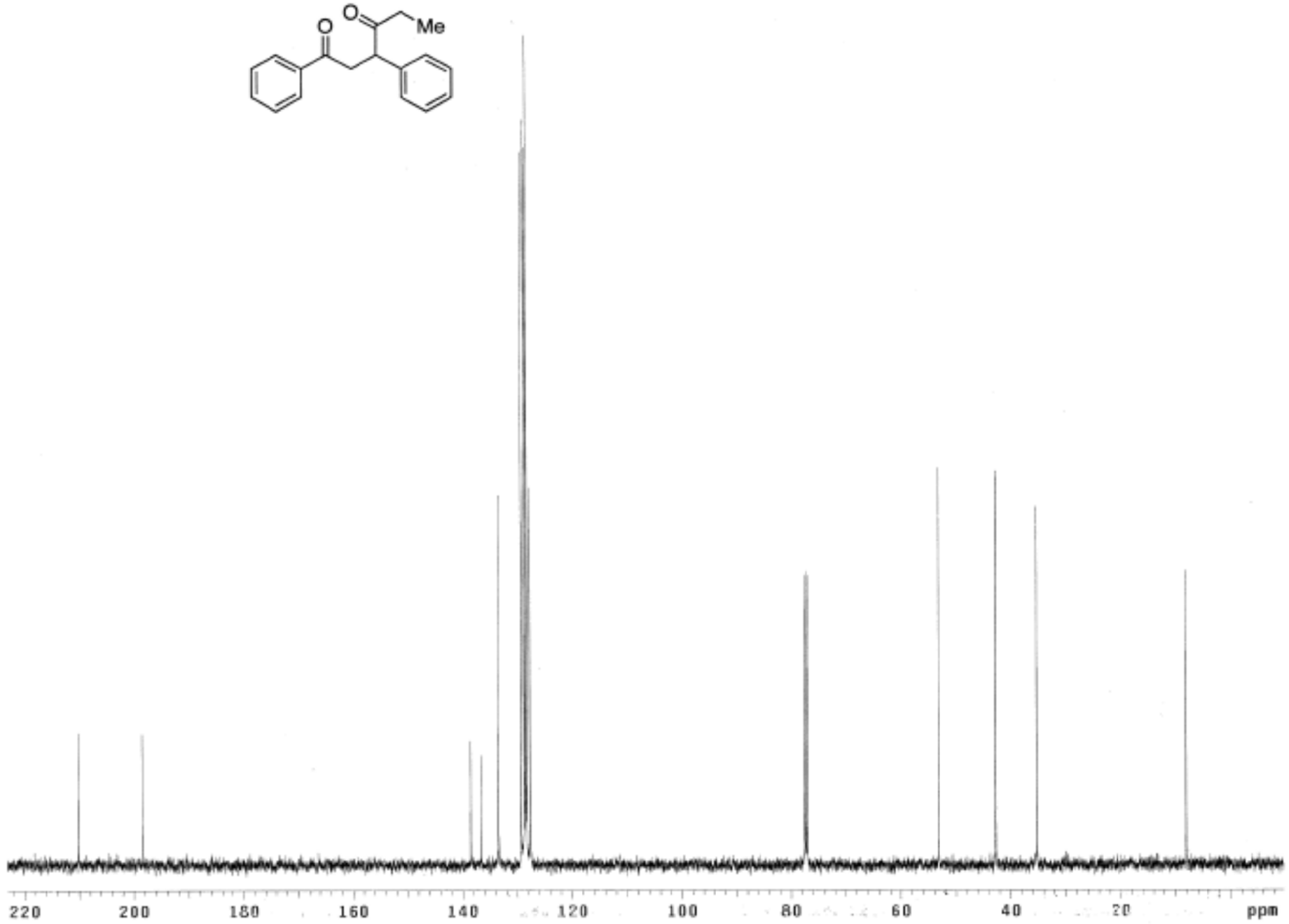
10 minutes and was quenched with saturated aqueous sodium bicarbonate and the organic layer was separated. The aqueous layer was washed with diethyl ether (5 X 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (15% diethyl ether/hexanes) to afford a clear, colorless oil (46.4 mg, 78.0% yield).

C. Characterization of Products



1,3-diphenylhexane-1,4-dione (5.7): Purified on SiO_2 (15% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (bd, J = 8.3 Hz, 2H); 7.52 (tt, J = 6.7, 1.2 Hz, 1H); 7.44-7.39 (m, 2H); 7.35-7.31 (m, 2H); 7.28-7.24 (m, 2H); 4.42 (dd, J = 10.2, 3.5 Hz, 1H); 4.03 (dd, J = 18.0, 10.2 Hz, 1H); 3.11 (dd, J = 18.0, 3.5 Hz, 1H); 2.64 (dq, J = 18.0, 7.4 Hz, 1H); 2.50 (dq, J = 18.0, 7.2 Hz, 1H); 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 198.7, 138.8, 137.0, 133.2, 129.2, 129.1, 129.0, 128.6, 127.6, 53.5, 42.4, 35.2, 8.0; IR (neat) 3028, 1715, 1683, 1398, 753, 700, 690 cm^{-1}; HRMS (ESI+) for $C_{18}H_{18}O_2$ [M+H]: calculated: 267.1385, found: 267.1385.


O
O
Me
8
7
6
5
4
3
2
1
ppm
1.97
2.85.20
1.00 2.87
1.00
1.01
0.49
0.51
1.06
1.83
3.03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180
160
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120
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80
60
40
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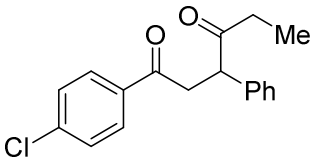
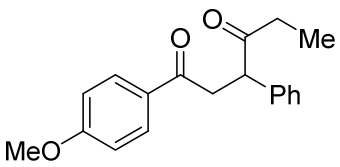
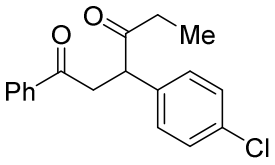
ppm



1-(4-chlorophenyl)-3-phenylhexane-1,4-dione (Table 5.2, entry 1): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to a afford a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (bd, J = 6.9 Hz, 2H); 7.42 (bd, J = 6.8 Hz, 2H); 7.37-7.34 (m, 2H); 7.30-7.27 (m, 3H); 4.42 (dd, J = 10.0, 4.0 Hz, 1H); 4.01 (dd, J = 17.9, 10.1 Hz, 1H); 3.08 (dd, J = 18.1, 3.7 Hz, 1H); 2.63 (dq, J = 17.9, 7.4 Hz, 1H); 2.51 (dq, J = 18.1, 7.3 Hz, 1H); 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 197.0, 139.6, 138.1, 134.8, 129.5, 129.1, 128.8, 128.2, 127.6, 53.0, 42.3, 34.9, 7.8; IR (neat)1714, 1683, 1589, 1400, 1090, 992, 835, 755, 700 cm^{-1} ; HRMS (ESI+) for $C_{18}H_{17}ClO_2$ [M]: calculated: 301.0995, found 301.0999.

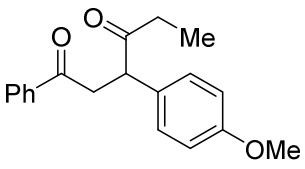


1-(4-methoxyphenyl)-3-phenylhexane-1,4-dione (Table 5.2, entry 2): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to a afford a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (bd, J = 9.1 Hz, 2H); 7.36-7.34 (m, 2H); 7.33-7.26 (m, 3H); 6.91 (bd, J = 9.0 Hz, 2H); 4.42 (dd, J = 10.2, 3.6 Hz, 1H); 4.00 (dd, J = 17.9, 10.3 Hz, 1H); 3.85 (s, 3H); 3.11 (dd, J = 17.8, 3.6 Hz, 1H); 2.66 (dq, J = 17.9, 7.4 Hz, 1H); 2.52 (dq, J = 17.9, 7.4 Hz, 1H); 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 196.7, 163.5, 138.4, 130.3, 129.6, 129.0, 128.3, 127.4, 113.7, 55.4, 53.0, 42.2, 35.0, 7.8; IR (neat) 1714, 1683, 1580, 1533, 1510, 1249, 1180, 1030, 1002, 655, 631 cm^{-1}; HRMS (ESI+) for $C_{19}H_{20}O_3$ [M+1]: calculated: 297.1490, found 297.1498.

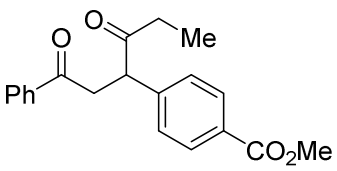


3-(4-chlorophenyl)-1-phenylhexane-1,4-dione (Table 5.2, entry 3): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a white solid. mp= 100-102 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (bd, =

8.2 Hz, 2H); 7.52 (tt, J = 6.7, 1.4 Hz, 1H); 7.41 (bt, J = 8.0 Hz, 2H); 7.30- 7.27 (m, 2H); 7.22-7.19 (m, 2H); 4.38 (dd, J = 10.0, 3.7 Hz, 1H); 3.98 (dd, J = 18.2, 10.2 Hz, 1H); 3.10 (dd, J = 18.0, 3.9 Hz, 1H); 2.63 (dq, J = 18.0, 7.2 Hz, 1H); 2.48 (dq, J = 18.0, 7.3 Hz, 1H); 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 197.8, 136.7, 136.3, 133.4, 133.2, 129.6, 129.2, 128.5, 128.0, 52.2, 42.3, 35.1, 7.8; IR (neat) 2916, 1714, 1681, 1480, 1237, 1110, 1019, 748, 689 cm^{-1}; HRMS (ESI+) for $C_{18}H_{17}ClO_2$ [M]: calculated: 301.0995, found: 301.0994.

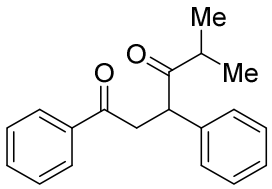


3-(4-methoxyphenyl)-1-phenylhexane-1,4-dione (Table 5.2, entry 4): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a white solid. mp= 89-90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (bd, J = 8.3 Hz, 2H); 7.52 (tt, J = 6.7, 1.4 Hz, 1H); 7.36 (bt, J = 7 Hz, 2H); 7.12 (bd, J = 7.8 Hz, 2H); 6.80 (bd, J = 7.8 Hz, 2H); 4.35 (dd, J = 10.2, 3.8 Hz, 1H); 3.98 (dd, J = 18.0, 10.2 Hz, 1H); 3.77 (s, 3H); 3.08 (dd, J = 18.0, 3.9 Hz, 1H); 2.63 (dq, J = 18.0, 7.4 Hz, 1H); 2.49 (dq, J = 18.0, 7.5 Hz, 1H); 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 198.3, 158.9, 136.5, 133.1, 130.2, 129.3, 128.5, 128.0, 114.4, 55.2, 52.0, 42.4, 34.8, 7.8; IR (neat) 2973, 2936, 1714, 1683, 1609, 1510, 1249, 1116, 993, 690, 681 cm^{-1}; LRMS (ESI+) for $C_{19}H_{20}O_3$ [M+H]: calculated: 297.2, found: 297.2.

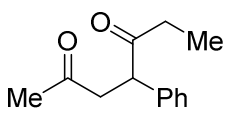


Methyl 4-(1,4-dioxo-1-phenylhexan-3-yl)benzoate (Table 5.2, entry 5): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a pale yellow solid. Mp = 85-87 ^{o}C ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.97 (bd, J = 8.2 Hz, 2H); 7.90 (bd, J = 8.4 Hz, 2H); 7.50 (tt, J = 4.8, 1.2 Hz, 1H); 7.39 (bt, J = 7.8 Hz, 2H); 7.33 (bd, J = 8.3 Hz, 2H); 4.46 (dd, J = 10.0, 3.7 Hz, 1H); 4.01 (dd, J = 18.0, 10.2 Hz, 1H); 3.86 (s, 3H); 3.12 (dd, J = 18.0, 4.0 Hz, 1H); 2.63 (dq, J = 18.0, 7.2 Hz, 1H); 2.45 (dq, J = 18.0, 7.3 Hz, 1H); 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 197.7, 166.6, 143.4, 136.2, 133.3, 130.3, 129.4, 128.5, 128.3, 128.0, 52.9, 52.1, 42.2, 35.2, 7.7; IR (neat) 2918, 1714, 1681, 1608, 1414, 1276, 1110, 762, 748, 706, 689 cm^{-1}; HRMS (ESI+) for $C_{20}H_{20}O_4$ [M+H]: calculated: 325.1440, found: 325.1448.

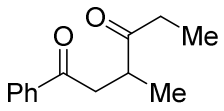


5-methyl-1,3-diphenylhexane-1,4-dione (**5.9**): Purified on SiO_2 (15% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89-7.83 (m, 2H); 7.46 (tt, J = 6.8, 1.5 Hz, 1H); 7.37-7.34 (m, 2H); 7.28-7.25 (m, 2H); 7.21-7.18 (m, 3H); 4.52 (dd, J = 10.2, 3.7 Hz, 1H); 3.95 (dd, J = 18.1, 10.3 Hz, 1H); 3.00 (dd, J = 18.0, 3.6 Hz, 1H); 2.72 (sept, J = 7.1 Hz, 1H); 1.16 (d, J = 7.0 Hz, 3H); 0.84 (dd, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 198.1, 138.3, 136.5, 133.1, 129.0, 128.5, 128.3, 128.0, 127.4, 51.8, 42.5, 39.8, 19.2, 18.3; IR (neat) 2966, 2901, 1711, 1685, 1598, 1493, 1449, 1239, 1017, 753, 699 cm^{-1}; LRMS (ESI+) for $C_{19}H_{20}O_2$ [M+H]: calculated: 281.3, found: 281.2.

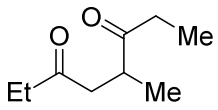


4-phenylheptane-2,5-dione (Table 5.3, entry 1): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.42 (m, 5H); 4.46 (dd, J = 10.4, 4.0 Hz, 1H); 3.71 (dd, J = 18.0, 10.4 Hz, 1H); 2.81 (dd, H = 18.0, 3.7 Hz, 1H); 2.71 (dq, J = 17.8, 3.4 Hz, 2H); 2.39 (s, 3H); 1.20 (t, J =

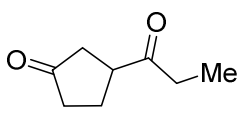
7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 206.7, 138.1, 129.0, 128.1, 127.4, 52.9, 46.6, 34.7, 29.8, 7.7; IR (neat) 2963, 1711, 1515, 1491, 1356, 850, 749, 701, 690 cm^{-1}; LRMS (ESI+) for $C_{13}H_{16}O_2$ [M+H]: calculated: 205.1, found: 205.1.



3-methyl-1-phenylhexane-1,4-dione (Table 5.3, entry 2): Purified on SiO2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (bd, J = 8.2 Hz, 2H); 7.52 (tt, J = 6.7, 1.4 Hz, 1H); 7.41 (bt, J = 7.8 Hz, 2H); 3.52 (dd, J = 18.0, 9.0 Hz, 1H); 3.25-3.17 (m, 1H); 2.91 (dd, J = 18.0, 4.5 Hz, 1H); 2.64 (dq, J = 7.2, 1.8 Hz, 2H); 1.15 (d, J = 7.2 Hz, 3H); 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 199.0, 136.9, 133.8, 129.1, 128.4, 42.5, 41.8, 35.1, 17.7, 8.0; IR (neat) 3061, 1712, 1683, 1458, 1353, 1216, 749, 690 cm^{-1}; HRMS (ESI+) for $C_{13}H_{16}O_2$ [M+H]: calculated: 205.1229, found: 205.1220.

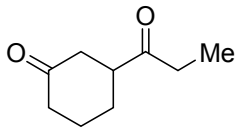


4-methyloctane-3,6-dione (Table 5.3, entry 3): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95-2.86 (m, 1H); 2.81 (dd, J = 17.6, 9.4 Hz, 1H); 2.43 (dq, J = 7.4, 1.0 Hz, 2H); 2.36-2.18 (m, 3H); 0.93 (d, J = 7.1 Hz, 3H); 0.90 (t, J = 7.3 Hz, 3H); 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 210.0, 45.7, 40.9, 36.0, 34.6, 17.1, 7.9, 7.8 cm^{-1}; IR (neat) 2974, 1710, 1459, 1376, 1356, 1116; HRMS (ESI+) for $C_9H_{16}O_2$ [M+H]: calculated: 157.1229, found: 157.1234.

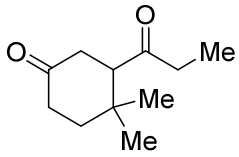


3-propionylcyclopentanone (Table 5.3, entry 4): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (400

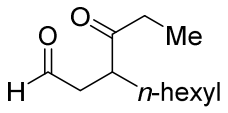
MHz, $CDCl_3$) δ 3.22 (pentet, J = 8.5 Hz, 1H); 2.59 (dq, J = 18.0, 7.2 Hz, 1H); 2.58-2.42 (m, 2H); 2.36-2.10 (m, 4H); 1.96 (ddt, J = 16.8, 9.6, 8.2 Hz, 1H); 1.05 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1, 211.9, 47.9, 40.8, 37.9, 34.9, 26.7, 7.9; IR (neat) 2974, 1739, 1705, 1459, 1406, 1374, 1138, 1113 cm^{-1}; HRMS (ESI+) for $C_9H_{14}O_2$ [M+H]: calculated: 141.0915, found: 141.0912.



3-propionylcyclohexanone (Table 5.3, entry 5):Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (tt, J = 11.0, 4.3 Hz, 1H); 2.55 (dq, J = 18.8, 7.2 Hz, 1H); 2.53-2.24 (m, 5H); 2.09-1.99 (m, 2H); 1.76-1.62 (m, 2H); 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 209.9, 49.8, 42.5, 40.8, 34.1, 27.3, 24.8, 7.5; IR (neat) 2939, 1708, 1450, 1417, 1224, 1123, 964 cm^{-1}; HRMS (ESI+) for $C_9H_{14}O_2$ [M+H]: calculated: 155.1072, found:155.1066.

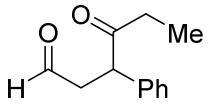


4,4-dimethyl-3-propionylcyclohexanone (Table 5.3, entry 6): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.81 (dd, J = 8.8, 4.9 Hz, 1H); 2.52 (dq, J = 18.4, 7.3 Hz, 1H); 2.50-2.33 (m, 3H); 2.30-2.19 (m, 2H); 1.81 (ddd, J = 12.7, 6.1, 6.1 Hz, 1H); 1.57 (ddd, J = 14.6 ,9.2, 5.6 Hz, 1H); 1.10 (s, 3H); 1.05 (s, 3H); 0.98 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 209.8, 57.1, 39.9, 38.4, 37.5, 33.0, 28.8, 23.3, 7.8; IR (neat) 2958, 1712, 1458, 1415, 1369, 1144 cm^{-1}; HRMS (ESI+) for $C_{11}H_{18}O_2$ [M+H]: calculated: 183.1385, found: 183.1390.

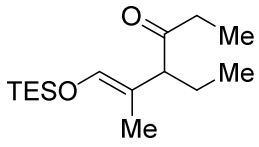


3-propionylnonanal (Table 5.4, entry 1): Purified on SiO_2 (15% diethyl

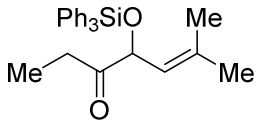
ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H); 3.06-2.94 (m, 2H); 2.66-2.52 (m, 2H); 2.49 (dd, J = 17.9, 3.5 Hz, 1H); 1.63-1.56 (m, 1H); 1.44-1.36 (m, 1H); 1.30-1.27 (m, 8H); 1.07 (t, J = 7.1 Hz, 3H); 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 200.7, 45.1, 44.9, 35.3, 31.6, 31.5, 29.2, 27.0, 22.5, 13.9, 7.6; IR (neat) 2935, 2927, 1709, 1459, 1390, 1109, 741, 735 cm^{-1}; HRMS (ESI+) for $C_{12}H_{22}O_2$ [M+H]: calculated: 199.1698, found: 199.1702.



4-oxo-3-phenylhexanal (Table 5.4, entry 2): Purified on SiO_2 (15% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H); 7.40-7.20 (m, 5H); 4.13 (dd, J = 9.7, 5.2 Hz, 1H); 3.27 (dd, J = 17.6, 10.0 Hz, 1H); 2.56 (dd, J = 17.4, 5.2 Hz, 1H); 2.41 (dq, J = 18.0, 7.7 Hz, 2H); 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 200.0, 137.8, 129.1, 128.1, 127.6, 51.8, 46.8, 34.6, 7.8; IR (neat) 2976, 1712, 1493, 1454, 1120, 755, 701 cm^{-1}; LRMS (ESI+) for $C_{12}H_{14}O_2$ [M+H]: calculated: 191.2, found: 191.2.



***trans*-4-ethyl-5-methyl-6-(triethylsilyloxy)hex-5-en-3-one** (Table 5.4, entry 3): Purified on SiO_2 (5% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1H); 2.86 (dd, J = 7.0, 7.0 Hz, 1H); 2.64 (dq, J = 17.5, 7.3 Hz, 1H); 2.40 (dq, J = 17.5, 7.5 Hz, 1H); 1.82 (dtd, J = 14.6, 7.2, 7.2 Hz, 1H); 1.62-1.51 (m, 1H); 1.54 (s, 3H); 1.12-1.08 (m, 3H); 1.08 (t, J = 7.6 Hz, 9H); 0.87 (t, J = 7.2 Hz, 3H); 0.76 (q, J = 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 137.9, 115.0, 57.4, 34.0, 21.1, 11.9, 9.8, 7.9, 6.6, 4.6; IR (neat) 2958, 2877, 1712, 1660, 1235, 1169, 1125, 1005; HRMS (ESI+) for $C_{15}H_{30}O_2Si$ [M+H]: calculated: 271.2093, found: 271.2095.



6-methyl-4-(triphenylsilyloxy)hept-5-en-3-one (Table 5.4, entry 5): Purified on SiO_2 (10% diethyl ether/hexanes, stain in CAM) to afford a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (bd, J = 6.6 Hz, 6H); 7.46-7.37 (m, 9H); 5.21-5.18 (m, 1H); 4.93 (d, J = 9.0 Hz, 1H); 2.60 (dq, J = 18.4, 7.4 Hz, 1H); 2.44 (dq, J = 18.3, 7.3 Hz, 1H); 1.64 (d, J = 1.2, 3H); 1.41 (d, J = 1.2 Hz, 3H); 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 210.5, 138.3, 135.4, 134.0, 130.0, 127.8, 122.5, 77.2, 30.8, 25.7, 18.4, 7.3; IR (neat) 974, 2917, 1731, 1618, 1428, 1156, 1115, 710, 698, 506; HRMS (ESI+) for $C_{26}H_{28}O_2Si$ [M+H]: calculated: 401.1905, found: 401.1920.