UNIVERSITY OF CALIFORNIA

Santa Barbara

A. Studies In The Allylic Substitution Chemistry Of Copper Hydride

B. Stereoselective Silylcupration Of Conjugated Alkynes In Micellar Media

C. Palladium-Catalyzed Synthesis Of 1,3-Butadienes and [3]-[6]Dendralenes

D. Synthesis Of Small Molecule Underwater Adhesives Inspired By Mussels

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Roscoe T. H. Linstadt

Committee in Charge:

Professor Bruce Lipshutz, Chair

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March 2017

The dissertation of Roscoe T. H. Linstadt is approved.

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February 2017

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“Who wouldn’t that not make want to?”

-Tom Verlaine

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The work that is described herein would have been impossible were it not for the support of many people throughout the years.

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PUBLICATIONS

(1) N. A. Isley, R. T. H. Linstadt, E. D. Slack, B. H. Lipshutz "Copper-catalyzed hydrophosphinations of styrenes in water at room temperature" *Dalton. Trans.* **2014**, *43*, 13196.

(2) R. T. H. Linstadt, C. A. Peterson, D. J. Lippincott, C. I. Jette, B. H. Lipshutz "Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature" *Angew. Chem., Int. Ed.* **2014**, *53*, 4159.

(3) B. H. Lipshutz, M. Hageman, J. C. Fennewald, R. T. H. Linstadt, E. Slack, K. R. Voigtritter, "Selective oxidations of activated alcohols in water at room temperature" *Chem. Commun.* **2014**, *50*, 11378.

(4) N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou, B. H. Lipshutz, "Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis" *Org. Lett.* **2015**, *17*, 4734.

(5) B. K. Ahn, S. Das, R. T. H. Linstadt, Y. Kaufman, N. R. Martinez-Rodriguez, R. Mirshafian, E. Kesselman, Y. Talmon, B. H. Lipshutz, J. N. Israelachvili, J. H. Waite, "High-performance mussel-inspired adhesives of reduced complexity" *Nat. Commun*. **2015**, *6*, 8663.

(6) S. Das, B. H. Lee, R. T. H. Linstadt, K. Cunha, Y, Y. Kaufman, Z. A. Levine, B. H. Lipshutz, R. D. Lins, J-E. Shea, A. J. Heeger, B. K. Ahn "Molecularly-

smooth Self-Assembled Monolayer for High-Mobility Organic Field-Effect Transistors" *Nano Lett.*, **2016**, *16*, 6709.

(7) R. T. H. Linstadt, C. A. Peterson, C. I. Jette, Z. V. Boskovic, B. H. Lipshutz "Control of Chemo-, Regio-, and Enantioselectivity in Copper Hydride Reductions of Morita-Baylis-Hillman Adducts" *Org. Lett.* **2017**, *19*, 328.

(8) D. J. Lippincott, R. T. H. Linstadt, M. R. Maser, B. H. Lipshutz "Synthesis of Functionalized [3], [4], [5] and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates" *Angew. Chem., Int. Ed.* **2017**, *56*, 847.

ABSTRACT

A. Studies In The Allylic Substitution Chemistry Of Copper Hydride

B. Stereoselective Silylcupration Of Conjugated Alkynes In Micellar Media

C. Palladium-Catalyzed Synthesis Of 1,3-Butadienes and [3]-[6]Dendralenes

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Roscoe Thomas Hadley Linstadt

Copper hydride (CuH) has been shown to enable a number of selective 1,2- and 1,4-reductions when complexed with the appropriate ligand, yet the allylic substitution chemistry of CuH has been much less studied. This dissertation describes the further study of CuH to perform sequential reductions on Morita-Baylis-Hillman (MBH) adducts. Specifically: I) Selectivity in the S_N2' reduction of MBH adducts was shown to be highly dependant on the nature of the ligand used. II) The reaction of MBH alcohols was shown to involve an initial dehydrogenative silylation with PMHS, where both the oligomeric nature and electronics of the initially formed trialkoxysilyl ether intermediate are important in determining both the observed stereoselectivity, and efficiency of the substitution. III) MBH ketones could be employed in tandem S_N2'/1,2-reduction sequences to arrive at stereodefined allylic alcohols with central chirality.

Vinylsilanes are versatile intermediates in organic synthesis owing to numerous methods for their transformation into other functional groups that

proceed with high stereoretention. While there are numerous methods to synthesize stereodefined vinylsilanes from alkynes, many existing methods require the use of highly reactive moisture intolerant reagents and harsh reaction conditions, features that limit the functionality that can be accommodated. Even fewer of these existing methods are conducted under environmentally responsible conditions. The use of Suginome's reagent as a moisture tolerant source of nucleophilic silicon, small catalytic quantities of a simple copper(I) salt, and an aqueous solution of TPGS-750-M as an environmentally benign nonionic surfactant, is described herein as a highly effective combination of reagents that allows for the stereoselective silylcupration of conjugated alkynes giving access to a variety of (*E*)-β-silyl-substituted carbonyl derivatives under environmentally responsible conditions.

This dissertation also describes the application of substituted allenoates as electrophilic butadienyl coupling partners under palladium catalysis in aqueous micellar media. The substituted allenoates could then be transformed by the methods developed herein into a variety of 2-substituted butadienes, where the methods were then extended to provide entry into a variety of substituted [3]-[6]dendralenes. Specifically: I) Application of an additive based screen allowed for evaluation of functional group tolerance in the Pd-catalyzed coupling of substituted allenoates with boronic acids. II) Curiosity driven investigations to identify boron based sp^3 coupling reagents compatible with the conditions of micellar catalysis led to the identification of OBBD alkylborinate

reagents as stable and isolable coupling reagents, which was the applied to the synthesis of 2-alkyl 1,3-butadienes. III) An analogous vinylallenyl coupling partner that functions formally as an electrophilic [3]dendralene synthon was proposed, and a number of synthetic routes were examined to access this molecule. Optimization of the synthetic route allowed for access to multigram quantities of this material, where it was applied to the synthesis of variously substituted [3]-[6]dendralenes.

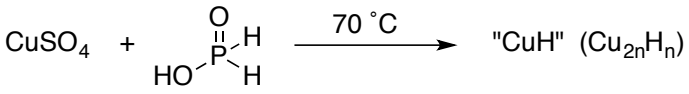
Efforts to understand the marine mussels mechanism of strong wet adhesion has been a subject of intense scientific investigation. Analysis of the peptide sequence of mfp-5, a mussel foot protein most correlated with interactions at the interface, revealed a high proportion of charged, hydrophobic, and catechol containing residues. Described in this dissertation is the synthesis of small molecule underwater adhesives by incorporation of these key features of mfp-5. These newly designed molecules formed adhesive bilayers underwater, and were shown to replicate and even exceed mfp-5's strong wet adhesive energy, while also being orders of magnitude smaller than both the native mussel proteins or existing biomimetic adhesive platforms. By systematically varying key portions of these small molecular adhesives, the adhesive bilayers could be transformed into molecularly uniform monolayers which were applied to the nanofabrication of organic electronic devices.

A) Studies In The Allylic Substitution Chemistry Of Copper Hydride

Copper Hydride: General Introduction and Background

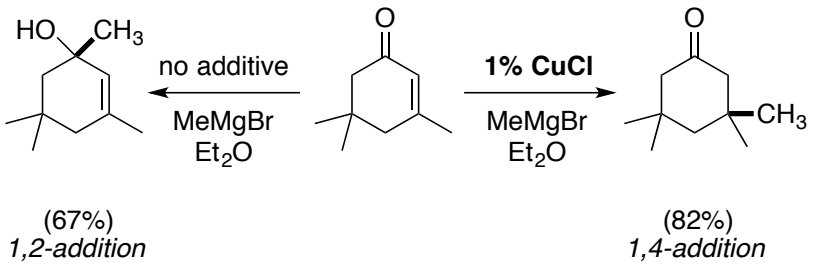
Copper hydride is among the oldest known metal hydrides, first prepared by Wurtz in 1845 at a time when the existence of such species was still treated as conjectural. By heating hypophosphorous acid with copper sulfate to 70 ˚C, Wurtz observed a gradual color change, from green to yellow, and finally red, at which point the solution began to evolve H_2 gas. The solution was cooled, filtered, and washed to give a polymeric red compound, that when analyzed corresponded to either Cu_8H_3 or Cu_2H (Scheme 1).[1] Later calorimetric studies found that Wurtz's material actually possessed a strong *negative* heat of formation, 5.1 kcal/mol, a property that was both unique among all known hydrides at the time, and which explained the explosive nature of the dry compound.[2] These studies were instrumental in the context of helping to give a systematic explanation of the existence of metal hydrides, although the seed that was planted with them would have to wait for over a century, and require many parallel developments before their full potential in synthetic organic chemistry could be realized. It would be the rise of organocopper chemistry that was to provide the fertile ground for these seminal reports to take root.

Scheme 1: Wurtz's synthesis of CuH (1845)



The development of organocopper chemistry, from the first isolation of Phenylcopper in 1923,[3] began in full force in 1936 with the pioneering work of Gilman on the preparation and reactivity of cuprate reagents,[4] and Kharasch who discovered that addition of copper salts to the reaction of Grignard reagents on unsaturated ketones switched the regioselectivity from a 1,2- to a 1,4-mode of addition.[5] Many further developments were to follow from these studies, and the study of cuprate reagents gave rise to mainstay reactions of modern synthetic chemistry. Carbocupration of alkynes would prove to be an immensely valuable tool in the preparation of substituted olefins,[6a-c] both allylic displacements and Michael additions,[7] mediated by cuprates would be renowned for their reliability, and the study of non-transferrable "dummy" ligands on copper would allow for greater gains in both reactivity and selectivity.[8] Notwithstanding the impressive advances achieved with the use of stoichiometric cuprate reagents, Kharasch's discovery is of special note, as it constitutes one of the earliest examples of copper (I) *catalysis* in the chemical literature (Scheme 2). To meet the grand challenges of preparing molecules in enantiopure form, with a minimum of waste, it would be catalysis that would come to the forefront of chemical inquiry and eventually dominate the field of organocopper chemistry, and in the context of this dissertation it is indeed copper catalysis that is the main focus.

Scheme 2: Kharasch's Discovery of Catalysis by a Cu(I) Salt (1941)



While Wurtz's copper hydride was explosive and kinetically unstable, the preparation and study of stable phosphine-ligated copper hydride complexes would finally enable the use of this metal hydride in synthesis.[9] The first transformation with these complexes was a Tischenko disproportionation of formaldehyde as reported by Caulton.[10] The major breakthrough was achieved by Stryker, who in a series of seminal reports, disclosed that $CuH(PAr_3)_n$ complexes could chemoselectively reduce unsaturated carbonyl compounds and alkynes.[11a-c] Equally important was the discovery that silanes, stannanes, and boranes could generate CuH by transmetalation obviating the necessity for high pressures of hydrogen.[12a-d] The importance of these discoveries was manifold: 1) A parallel to that of established organocopper (e.g. R-Cu) reagents was achieved suggesting that many of the reactivity modes already known to these species could now be harnessed to accommodate hydride as nucleophilic coupling partner. 2) The use of metalloid hydride precursors allowed for more convenient experimental set ups, and improved catalytic performance avoiding the need for stoichiometric quantities of copper and phosphine ligands 3) The use of phosphine-based ligands could not only be used to improve the stability of

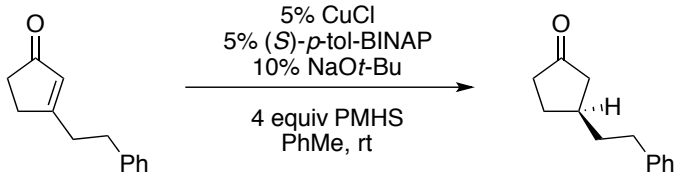
the active species, but alter the environment surrounding the metal and hence manipulate substrate recognition to alter chemo-, regio- and stereochemistry. It would be for these reasons that CuH reductions would develop into relatively mature methods for a number of transformations.

Copper hydride has a variety of mechanisms with which it can react with substrates. Most famously is the 1,4-reduction of enones/enoates as disclosed by Stryker, which was made into an accelerated catalytic variant by inclusion of a cyclic bis-phosphine BDP.[13] Asymmetric 1,4-reductions of a variety of β-β-disubstituted electron deficient substrates are possible, including ketones, nitriles, nitroalkenes, with small alterations in ligand choice, solvent, and temperature ultimately providing the requisite conditions necessary for high enantioselectivity. 1,2-reductions are also possible by manipulating the ligand, although for unsaturated ketones, 1,4-reduction pathways can be competitive. The high enantioselectivity observed for 1,4-reductions has been applied in total synthesis,[14a, b] with representative cases illustrated in Scheme 3. Regarding alkenes and alkynes, CuH can participate in a hydrocupration reaction with addition of CuH across the olefin/alkyne, where the resulting copper intermediate can be proteoquenched, or as recent studies have shown, participate in a second tandem nucleophilic coupling.[15a-c] In the presence of alcohols, CuH can react to produce hydrogen gas and a copper alkoxide, which can be silylated with silane, regenerating active CuH.[16] Additionally, copper hydride clusters can participate

in single electron redox chemistry, be used for hydrogen storage/evolution[17a, b] and transient CuH species are implicated in other transformations as well.[18]

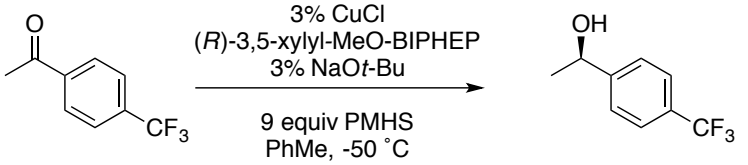
Scheme 3: Representative Examples of Enantioselective CuH Reductions

Asymmetric 1,4-Reductions:



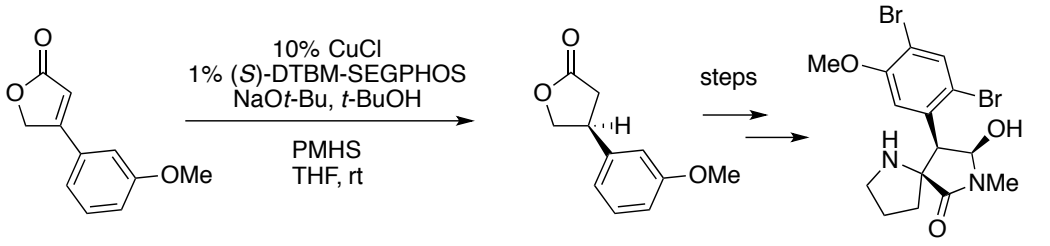
(86%), 94% *ee*
JACS **1999**, *121*, 9473

Asymmetric 1,2-Reductions:



(85%), 95% *ee*
JACS **2001**, *123*, 12817

Application to Total Synthesis:



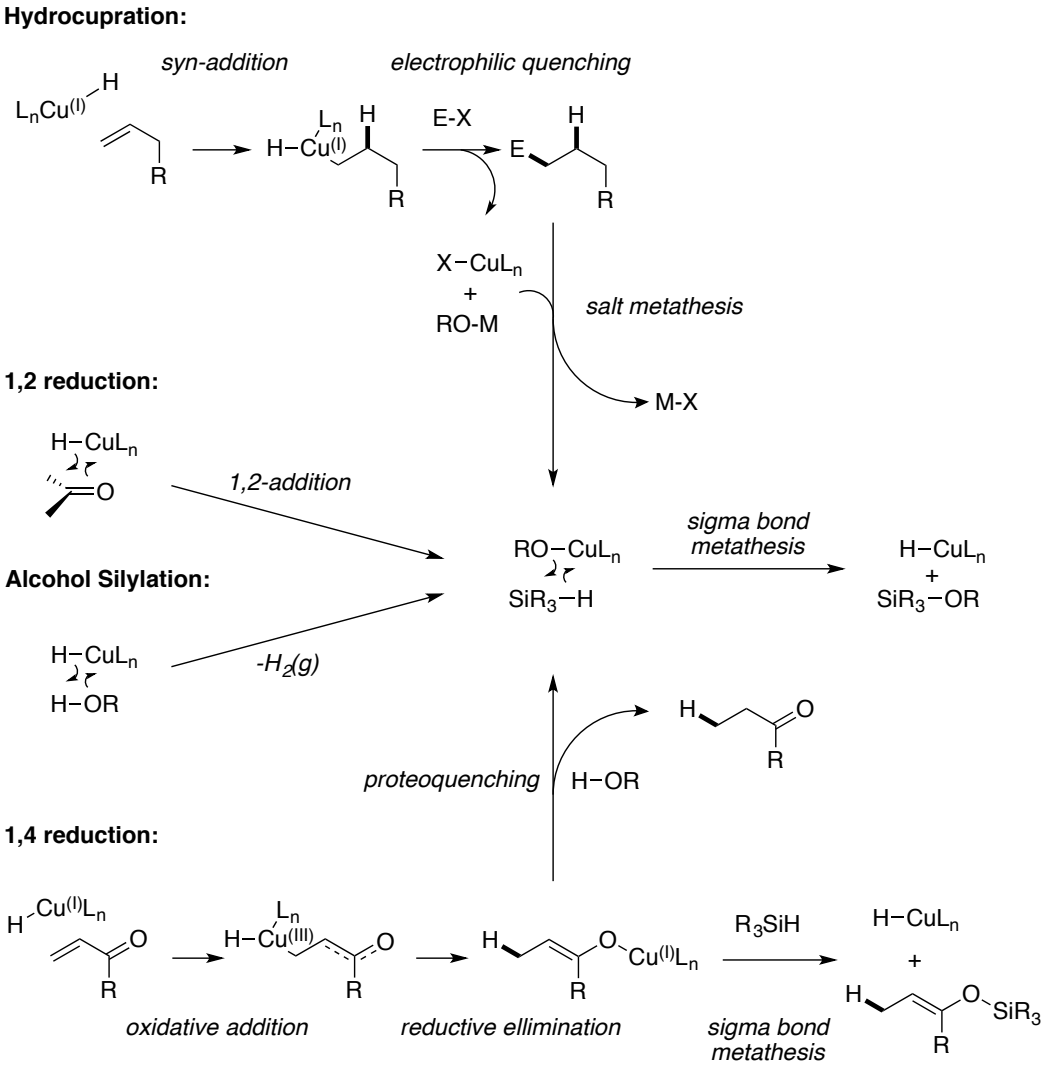
(72%), 98% *ee*)
20 gram scale

amathspiramide A
ACIE **2012**, *51*, 2505

As illustrated below, (Scheme 4) central to almost all catalytic CuH reactions is the regeneration of active CuH by sigma bond metathesis between a copper alkoxide and silane (although stannanes and boranes are occasionally encountered as well). While 1,4-reductions can be conducted without addition of

alcohols, their addition facilitates proteoquenching of the copper enolate to give product and soluble copper alkoxide which regenerates active CuH much faster than from metathesis with the O-Cu-enolate.

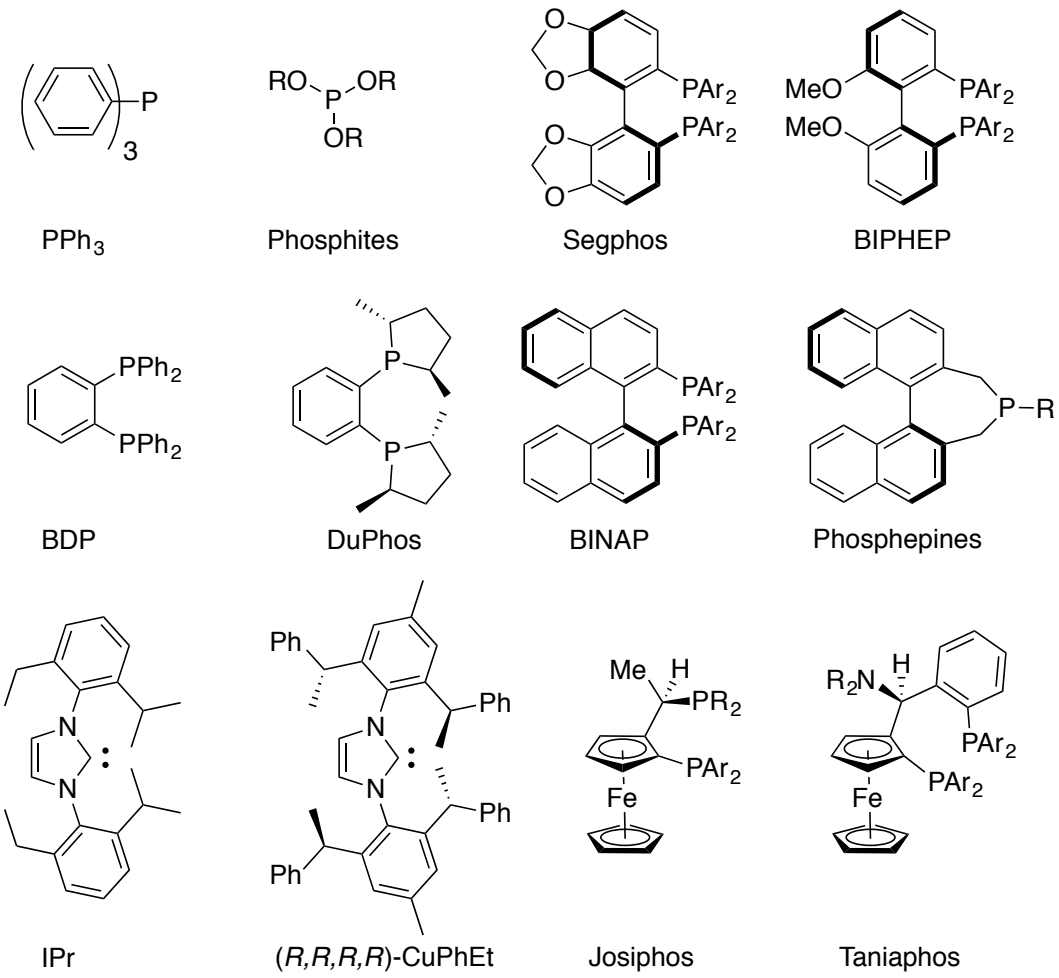
Scheme 4: General Mechanisms of CuH Reactions:



Much of the recent research in CuH and other Cu(I) chemistry has focused on identification of appropriate ligands to control both stereochemistry and regiochemistry of reductions. A large variety of ligating agents have been

employed, and a number of representative examples from the various classes are shown below (Figure 1).

Figure 1: Common Ligands Employed in CuH Reductions



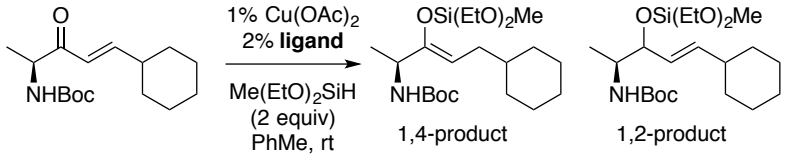
Ligand choice, bite angle, donicity, steric bulk, as well as the ligand-to-metal ratio can have a large impact on the regiochemical outcome of the Cu(I) couplings. To illustrate this, three examples from the literature involving CuH reductions are shown and discussed below (Scheme 5). Koskinen's study on the chemoselective 1,4-reductions of α-amino enones revealed that for these

substrates, using triisopropylphosphite as supprting ligand for Cu, provided the greatest selectivity for 1,4-reduction pathway over the 1,2-path.[19] The use of the triethylphosphite with similar electronics but a smaller cone angle (roughly 110˚ vs. 130˚) gave diminished selectivity where the use of bidentate BDP ligand in this case gave roughly equal amounts of the corresponding 1,2- and 1,4-products. In considering how reduction selectivity is contingent on the nature of the substrate, it should be noted that BDP was found to reduce other similar ketones lacking α-amino groups, with high 1,4-selectivity.[13]

The effect of added ligands on the regioselective reductions of enones was also investigated by Stryker.[20] He observed when conducting the reactions under high pressures of H_2, addition of equimolar Me_2PPh diverted the reaction from the standard 1,4-pathway to a 1,2-pathway, while addition of additional PPh_3 led to complete reduction of both olefin and carbonyl functionality. Recent research from the Lipshutz laboratory highlighted that enantioselective 1,2- or 1,4-reductions of β,β-disubstited enones were possible by switching between SEGPHOS or Josiphos ligand scaffolds.[21] The discriminating factor for the regiochemical preference of the bulky biaryl-bisphosphines such as SEGPHOS apparently is their ability to differentiate/stabilize the s-*cis* or s-*trans* conformation of the substrate. Much of the information regarding the behavior of these ligands is gained empirically, and it is difficult to select the appropriate ligand system for a given molecule *a-priori*. Less is known about the interplay between ligand structure, aggregation state, and reactivity of these copper hydrides. Crystal

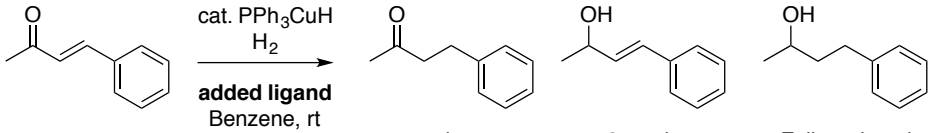
structures of the ligated complexes, when available, may not reflect the catalytically active species.

Scheme 5: Regiochemical Effects of Ligands on Reductions of α,β-Unsaturated Ketones:



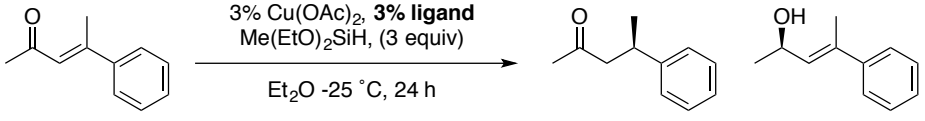
Ligand	Product Ratio (1,4:1,2)
PPh_3	79:8
BDP	42:43
$P(OEt)_3$	77:4
$P(O\textit{i}\text{-}Pr)_3$	95:3

J. Org. Chem. **2009**, *74*, 7598



PPh_3CuH	H_2	Added Phosphine	Time	Product Ratio
16%	1000 PSI	none	10 h	91:0:9
5%	500 PSI	6% Me_2PPh	18 h	0:92:8
16%	500 PSI	12% PPh_3	2 h	0:8:92

Tetrahedron. **2000**, *56*, 2789



Ligand	Product Ratio (1,4:1,2)	*ee* of major product
(*R*)-DTBM-SEGPHOS	2:98	97%
(*R,S*)-PPF-P(*t*-Bu)$_2$	95:5	99%

Tetrahedron. **2012**, *68*, 3410

References:

[1] Farber, E. *Chymia* **1962**, *8*, 165.

[2] Müller H.; Bradley, A. J.; *J. Chem. Soc*, **1926**, 1669.

[3] Reich, C. R.; *Hebd. Seances Acad. Sci.* **1923**, *177*, 322.

[4] Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas.* **1936**, *55*, 821.

[5] Kharasch, M. S.; P. O. Tawney, *J. Am. Chem. Soc.* **1941**, *63*, 2308.

[6] a) Normant J. F.; Bourgain, M.*Tetrahedron Lett.,* **1971**, *27*, 2583; b) Normant J. F.; Alexakis, A.; *Synthesis*, **1981**, 841; c) Müller, D. S.; Marek, I. *Chem. Soc. Rev.,* **2016**, *45*, 4552.

[7] Lipshutz, B. H.; Sengupta, S.; *Org. React*. **1992**, *41*, 135.

[8] Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

[9] Bezman, S. A.; Churchil, M. R.; Osborn, J. A.; Wormald, J. *J. Am. Chem. Soc.* **1971**, *93*, 2063.

[10] Goeden, G. V.; Caulton, K. G *J. Am. Chem. Soc.* **1981**, *103*, 7354.

[11] a) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Letters* **1988**, *29*, 3749; b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291; c) Brestensky, D. M.; Stryker, J. M. *Tet. Lett.* **1989**, *30*, 5677.

[12] a) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249; b) Llamas, T.; Arrayás, R. G.; Carretero, J. C.; *Angew. Chem., Int. Ed.* **2007**, *46*, 3329; c) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273; d) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.

[13] Baker, B. A.; Bošković, Z. B.; Lipshutz, B. H. *Org. Lett*. **2008**, *10*, 289.

[14] a) For a comprehensive review on reactions of CuH, see: Deutsch, C.; Krause, N. *Chem. Rev.* **2008**, *108*, 2916; b) For an application in total synthesis see: Chiyoda, K.; Shimokawa, J.; Fukuyama, T. *Angew. Chem., Int. Ed*. **2012**, *51*, 2505.

[15] a) Yang, Y.; Perry, I.B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787; b) Wang, Y-M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024; c) Pirnot, M. T.; Wang, Y-M.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 48.

[16] Ito, H.; Wantanabe, A.; Sawamura, M. *Org. Lett.* **2005**, *7*, 1869.

[17] a) Eberhart, M. S.; Norton, J. R.; Zuzek, A.; Sattler, W.; Ruccolo, S. *J. Am. Chem. Soc.* **2013**, *135*, 17262. b) Dhayal, R. S.; W. E.; Zyl, Liu, C. W. *Acc. Chem. Res*. **2016**, *49*, 86.

[18] Luo, H.; Ma, S. *Eur. J. Org. Chem.* **2013**, 3041.

[19] Pelss, A.; Kumpulainen, E. T. T.; Koskinen, A. M. P. *J. Org. Chem.* **2009**, *74*, 7598.

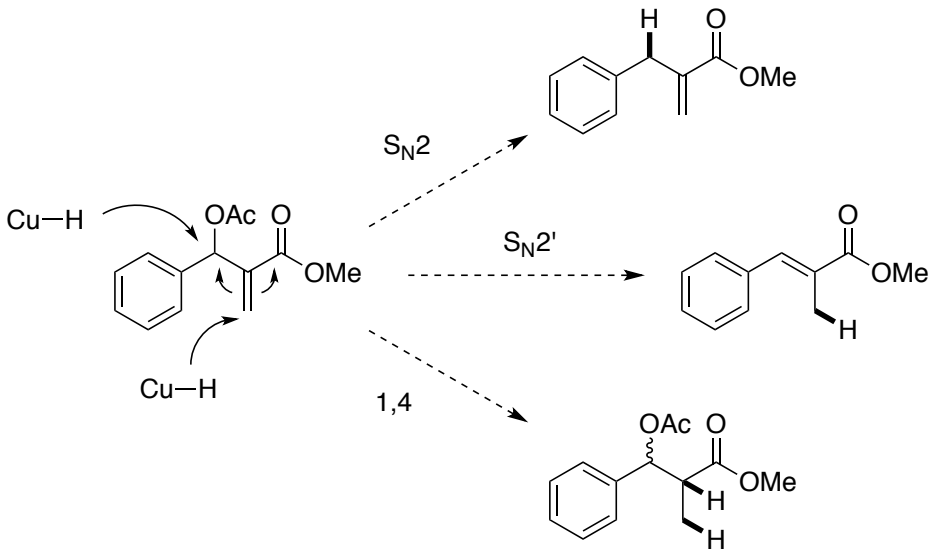
[20] Chen, J. X.; Daeuble, J. F.; Brestensky, D.M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153.

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

Copper Hydride Substitutions of Morita-Baylis-Hillman Adducts

In light of the regiochemical issues discussed earlier, we were enticed to study the reduction of MBH adducts[1a, b] with CuH to further understand relationships between substrate, ligand, and chemoselectivity. Additionally we had a longstanding interest in determining whether we could use CuH analogously to other organocopper reagents to perform allylic substitutions. Examining a simple MBH acetate, a number of questions regarding regiochemistry immediately become apparent.

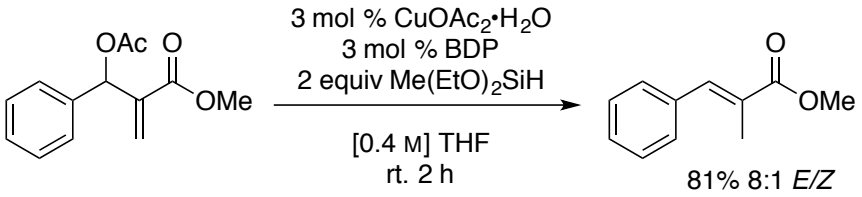
Figure 1. Initially Posed Questions of Regio- and Chemoselectivity



The presence of an allylic leaving group opens the question as to site selectivity in the reduction, where Cu can be envisaged to deliver hydride via an allylic substitution type mechanism to either site of the allylic system.

Furthermore alternative pathways are possible, in which a traditional 1,4-addition furnishes a copper enolate, which can either undergo *anti*-elimination to furnish an enoate, or be trapped as a silyl ketene acetal, and subsequently proteoquenched. Subjecting this MBH acetate to relatively standard CuH reduction conditions, gave rise to mainly an α-methyl substituted enoate, in a 8:1 *E/Z* isomeric ratio, with a small amount of overreduced product obtained as well (Scheme 1). This initial result suggested that allylic substitution, either as a direct, or stepwise (via addition/elimination pathway), was kinetically favored over simple 1,4-reduction, and the postulated direct S_N2' pathway was not operative.

Scheme 1. Initial Positive Result



With this preliminary result in hand this project was passed on to me, in which I had the unenviable task of improving both the *E/Z* ratio of the resulting enoates, and mitigating the overreduction pathway. This was to be accomplished for a number of reasons. Firstly, there are a variety of highly reliable methods to prepare α-β unsaturated esters,[2] and for any copper hydride method to be a viable alternative, the *E/Z* selectivity should be comparable or improved relative to the established olefination chemistry. Second, although allylic substitution chemistry with catalytic copper is well known for a variety of nucleophiles,[3a-d]

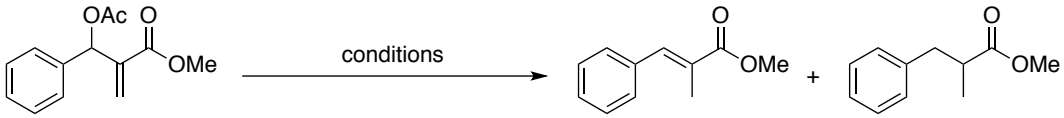
substitutions with hydride[4a-d] as the nucleophile are among the least explored. Finally, the factors ultimately responsible for such selectivity would lead to a more complete picture describing the relationships between ligated CuH, substrate, and selectivity.

The presence of overreduced product in the reaction mixture was viewed as the most problematic from the standpoint of purification, as R_f values were nearly identical, and only partial separations could be affected via standard chromatographic methods. At the same time, this problem was also viewed as the most tractable to solve. As the enoate was produced as the major product, and any overreduced material was necessarily produced in a second reduction of the initial product, the enoate was clearly the most kinetically favored product. Mitigating the subsequent reduction pathway by modulating the standard reaction parameters (e.g. amount of stochiometric reductant, solvent, temperature) to improve the rate of the initial substitution, seemed fully within the realm of possibility.

After extensive experimentation, it became clear that the solution to the problems of both *E/Z* selectivity and overreduction were not trivial. Any attempt to mitigate overreduction by adjusting reaction time (Table 1, entry 3), changing concentration (entry 4), or catalyst loading (entry 5), were unsuccessful. Likewise by changing silane reductant (entry 6), switching solvents (entry 7), or employing cryogenic temperatures (entry 8) either failed to give acceptable

amounts of product, or did not reduce the relative amounts of overreduced product.

Table 1. Optimization Conditions



A **B** **C**

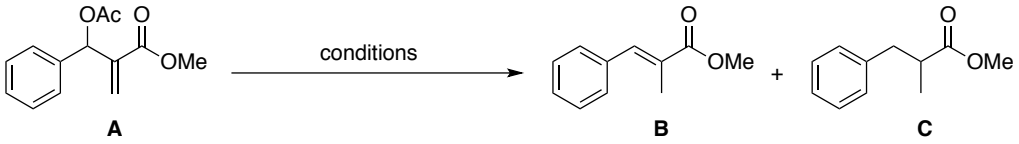
entry	$Cu(OAc)_2 \cdot H_2O$ (%)	Ligand (%)	Solvent	Silane	Temp (˚C)	Conc. [M]	Time (min)	%**A**	%**B**	%**C**
1	**0**	**0**	THF	DEMS 2 H- equiv	rt	[0.1]	18 hours	100	0	0
2	0	**BDP 3**	THF	DEMS 2 H- equiv	rt	[0.1]	3 days	100	0	0
3	**3**	**BDP 3**	THF	DEMS 2 H- equiv	rt	[0.1]	15	67.5	32	0.5
							30	46.5	52	1.5
							45	34	64	2
							60	20	76	4
							120	10	81	9
4	3	BDP 3	THF	DEMS 2 H- equiv	rt	**[0.05]**	120	36	61	3
5	**5**	**BDP 5**	THF	DEMS 2 H- equiv	rt	[0.1]	120	12	80	8
6	3	BDP 3	THF	**PMHS 5 H- equiv**	rt	[0.1]	60	7	75	18
7	3	BDP 3	**Toluene**	**PMHS 2 H- equiv**	rt	[0.1]	120	13	79	8
8	3	BDP 3	THF	DEMS 2 H- equiv	**-25 ˚C**	[0.4]	2 hours	57	42	1
							7 hours	23	73	4
							13 hours	13	80	7

[a] Conversions determined by GCMS of crude reaction mixture

In reevaluating the situation, a different approach to limit overreduction was envisaged. Since the initial substitution was already somewhat kinetically favored, improving the rate of substitution would potentially solve the problem of

overreduction. For many reactions, substitution rates are determined by the pK_a of the conjugate acid of the leaving group, and thus by switching to a more active leaving group in the MBH substrate, overreduction could potentially be remedied. A survey of several different leaving groups (e.g. -OBz, -OCO_2Me, etc…) at different temperatures, unfortunately did not give rise to the desired product with appropriate control of overreduction.

Table 2: Ligand Screening Reveals Ph-MeO-BIPHEP Prevents Overreduction



A **B** **C**

entry	$Cu(OAc)_2$ •H_2O (%)	Ligand (%)	Solvent	Silane	Temp (˚C)	Conc. [M]	Time (min)	%**A**	%**B**	%**C**
1	3	BDP (3)	THF	DEMS 2 H- equiv	rt	[0.4]	120	0	82	18
2	3	J002-1 (3)	THF	DEMS 2 H- equiv	rt	[0.4]	120	26	69	5
3	3	3,5 -*t*-Bu BIPHEP (3)	THF	DEMS 2 H- equiv	rt	[0.4]	120	79	21	0
4	3	(*R*)-DTBM SEGPHOS (3)	THF	DEMS 2 H- equiv	rt	[0.4]	120	77	22	1
5	3	**(*R*)-MeO-BIPHEP (3)**	THF	DEMS 2 H- equiv	rt	[0.4]	120	0	100	0
							480	0	95	5
6	3	**(*R*)-MeO-BIPHEP (3)**	THF	PMHS 4 H- equiv	rt	[0.4]	120	0	100	0
7	3	**(*R*)-MeO-BIPHEP (3)**	THF	DEMS 6 H- equiv	rt	[0.4]	120	0	100	0

[a] Conversions determined by GCMS of crude reaction mixture

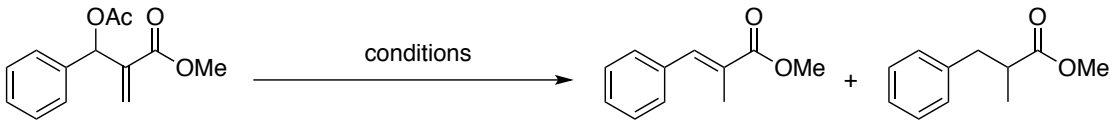
Several different ligands were evaluated at this stage (Table 2), yet representative ligands from the many of the commonly used families such as the SEGPHOS, JOSIEPHOS, and BIPHEP series performed poorly relative to BDP,[5] (entries 1-4) and employment of BDP was continued for a time.

At this stage it seemed like defeat was imminent, nearly every variable had been tested in multiple permutations, patience was running thin on all sides, and the decision was made to accept the imperfect results, and complete the study without either the problem of *E/Z* selectivity or overreduction solved. In a change of fortune, while locating chemicals to prepare additional substrates a BIPHEP derivative was located that had yet to be tested, and performed the reaction with it without any real hope of success, yet analysis of the reaction mixture showed that the enoate was produced without any observable overreduction in 100% conversion at two hours (entry 5). This result prompted a reevaluation of the situation. The use of (*R*)-Ph-MeO-BIPHEP apparently could completely mitigate overreduction even when employing excess reductant, or quadrupling the reaction time (entries 5-7)

It was clear from these results that overreduction resulted from subtler interactions between catalyst and substrate than originally anticipated, andthat in choosing representative ligands from the various families to screen with that an important variable had been untested. While 3,5-*t*-Bu-BIPHEP had given disappointing results earlier (entry 11), switching the sterics/electronics of the aryl groups on the phosphine to simple phenyl had solved the problem of

overreduction. On the other hand, this was not to be expected from prior results, as the simple phenyl groups on BDP were apparently not sufficient to control overreduction. This is likely due to the size of the chelate where BDP forms a 5-membered chelate with Cu, and BIPHEP forms a 7-membered chelate, and the resulting P-Cu-P angle differs significantly.

Table 3. Overreduction is Dependent on the Stereoelectronics of -PAr$_2$



A **B** **C**

entry	$Cu(OAc)_2$ •H_2O (%)	Ligand (%)	Solvent	Silane	Temp (˚C)	Conc. [M]	Time (min)	%**A**	%**B**	%**C**
1	3	**(*R*)-MeO-BIPHEP (3)**	THF	PMHS 4 H- equiv	rt	[0.4]	240	0	100	0
2	3	**(*R*)-Ph-SEGPHOS (3)**	THF	PMHS 4 H- equiv	rt	[0.4]	240	0	100	0
3	3	**(*R*)-BINAP (3)**	THF	PMHS 4 H- equiv	rt	[0.4]	240	0	100	0
4	3	**(*R*)-Ph-GARPHOS (3)**	THF	PMHS 4 H- equiv	rt	[0.4]	240	0	100	0

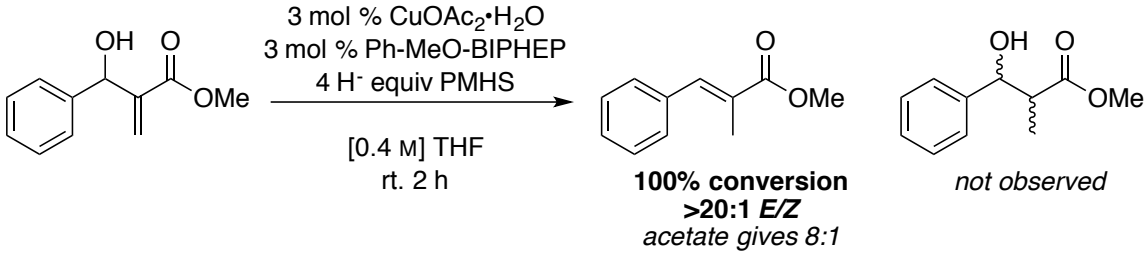
[a] Conversions determined by GCMS of crude reaction mixture

To test this hypothesis, several different biaryl bis-phosphines possessing only simple phenyl groups on phosphorus were tested, which differed only by varying amounts in the biaryl backbone. Somewhat surprisingly, all of these ligands were able to affect the desired transformation while also preventing overreduction. From these results it became clear that slight changes in the angle of the backbone for the bis-phosphines were inconsequential in changing

the amount of overreduction, and the presence of the simple phenyl substituents on phosphorus in combination with a 7-membered chelate on the copper center were the determining variables in shutting down overreduction.

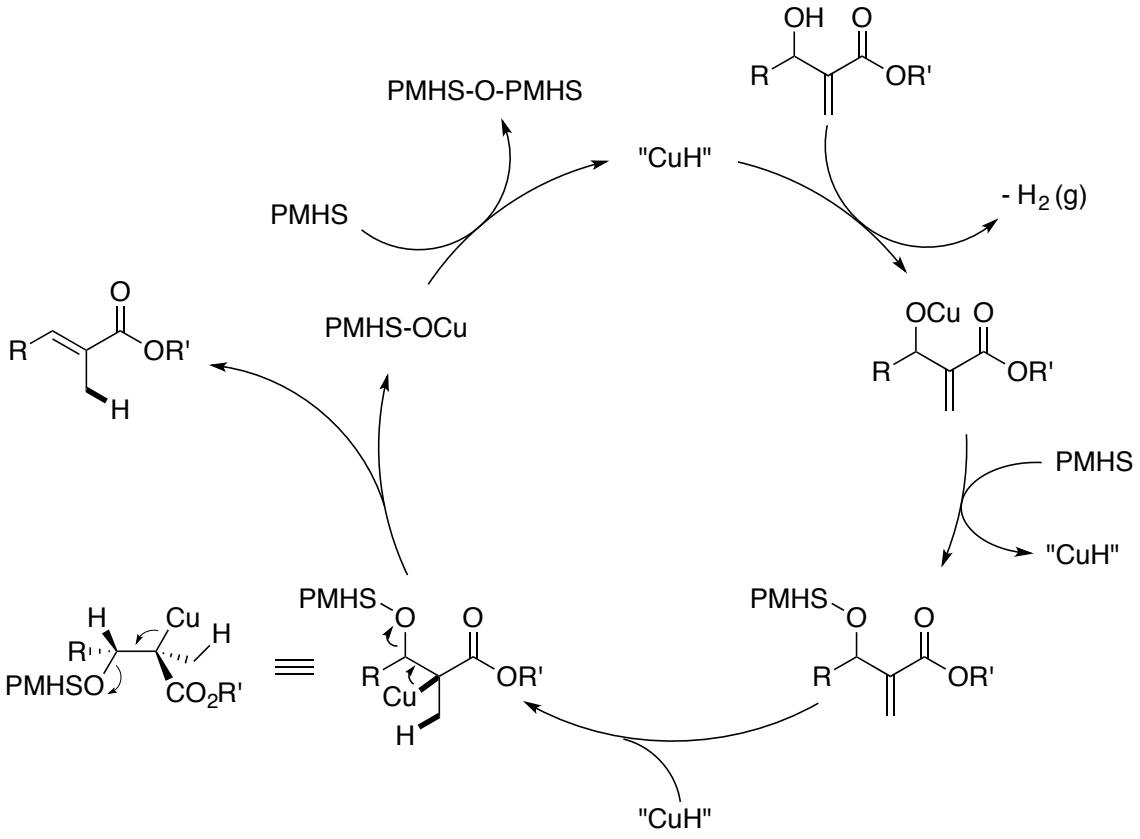
In another surprising turn of events, when the optimal conditions were tested upon the analogous MBH alcohol, it was anticipated that in the absence of a leaving group, that 1,4-reduction would predominate to give a mixture of diastereomeric alcohols. However, during the addition of the MBH alcohol to a solution of CuH, vigorous gas evolution was observed, and after a reaction time of two hours, usual workup, and isolation, the ester was obtained in nearly identical yield but greatly improved (>20:1) *E/Z* selectivity.

Scheme 2: MBH Alcohol/PMHS Improves Stereoselectivity



This exiting result implied that the reaction proceeded through an initial dehydrogenative silylation[6] at the alcohol to furnish an O-PMHS bound silyl ether, and subsequent S_N2' displacement or conjugate addition/elimination furnished the enoate. The size of the oligomeric[7] O-PMHS ether in this case presumably helps to force a selective anti-ellimination explaining the dramatically higher selectivity observed (Figure 2).

Figure 2. Proposed Reaction Mechanism

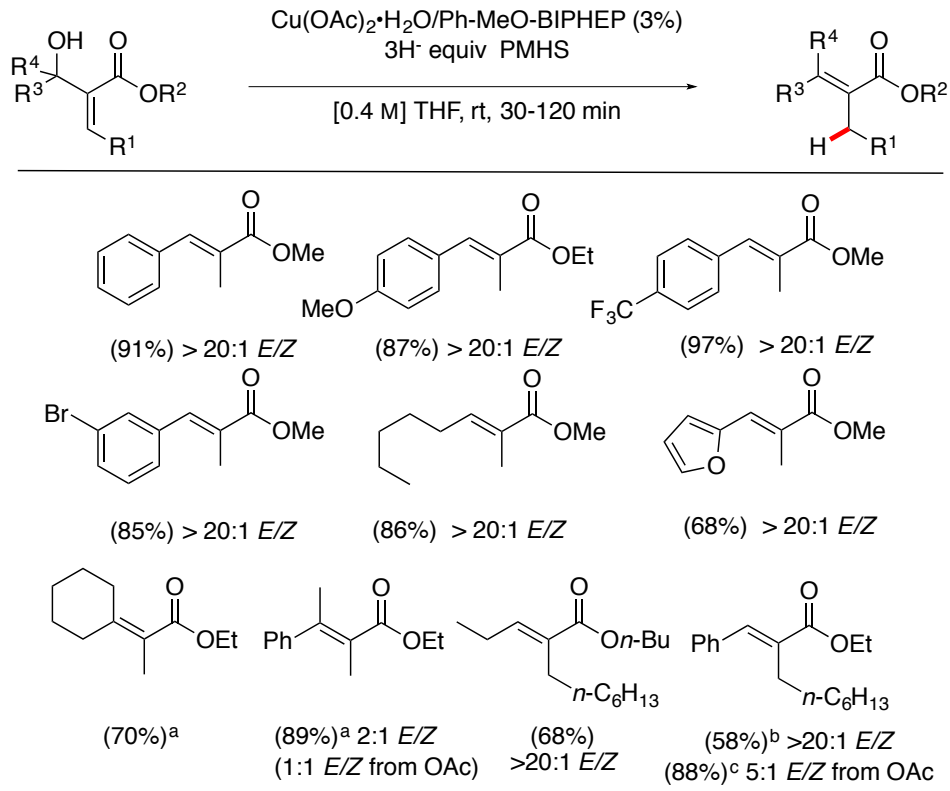


Both the effect of the BIPHEP ligand, and the use of MBH alcohols had now succeeded in solving the two main issues of overreduction and stereoselectivity that were originally confronted, and a brief survey of the scope substrates amenable to reduction was made. Indeed, a variety of simple MBH alcohols could be efficiently transformed to α-methyl-*E*-enoates as shown below (Scheme 3). Essentially the reaction appears to work for several simple aryl and alkyl MBH adducts, where only a 2-furyl adduct gave a diminished yield. As an

added bonus, unlike standard 1,4-hydrosilylation which produces a silyl enol ether (or silyl ketene acetal) which must be quenched with aqueous fluoride to liberate product prior to isolation, substitution produces a free enoate which is unbound with oligomeric PMHS, and reaction workup can be simplified by simply diluting the mixture with hexanes/Et_2O and filtering off the Cu catalyst and siloxane species through a short pad of silica. Either workup procedure could be used and both produced essentially identical material, although workup with fluoride took much longer and required multiple extractions to remove siloxane byproducts.

Although simple MBH alcohols worked effectively in the reaction, the products they afforded certainly were not very exciting, and accordingly the literature was searched for ways to prepare MBH adducts with further substitution. Thankfully, Ramachandran's DIBAL-H vinylalumination procedure[8] was found to be very reliable in preparing both MBH adducts with tertiary alcohols, but also those with β-substitution, a feature that normally fails to produce results in typical Lewis base mediated MBH reactions. Also, Ramachandran's method is notable in that it stands in contrast to the vast majority of literature on MBH reactions by actually providing reproducible results.

Scheme 3: CuH Reductions of MBH Alcohols to Form Enoates



Yields in parenthesis are isolated yields. *E/Z* selectivity determined by ^{1}HNMR
[a] Reaction time of 18 h. [b] Reaction time of 24 hours. [c] With 3 equiv of *t*-BuOH and reaction time of 72 h

Nearly a dozen other procedures were tested to provide the differentially substituted adducts, but none were as reliable as the aforementioned vinylalumination procedure.

Tertiary MBH alcohols could be employed as in the case of the educt derived from cyclohexanone, which forms a tetrasubstituted enoate in modest yield, with a remainder of the mass balance corresponding to the product of 1,4 reduction without displacement. The educt derived from acetophenone gave a tetrasubstituted enoate in 2:1 *E/Z* selectivity, which was a bit disappointing

considering that such high selectivities had been observed with the simpler enoates. Yet in testing the corresponding acetate, complete loss of selectivity was observed and the product was obtained in a 1:1 *E/Z* ratio. The use of the alcohol and, therefore, the PMHS leaving group, clearly provides an advantage. β-Substituted MBH adducts were next tested and although they were ultimately deemed functional, they required more attention and modification than other classes of MBH adducts.

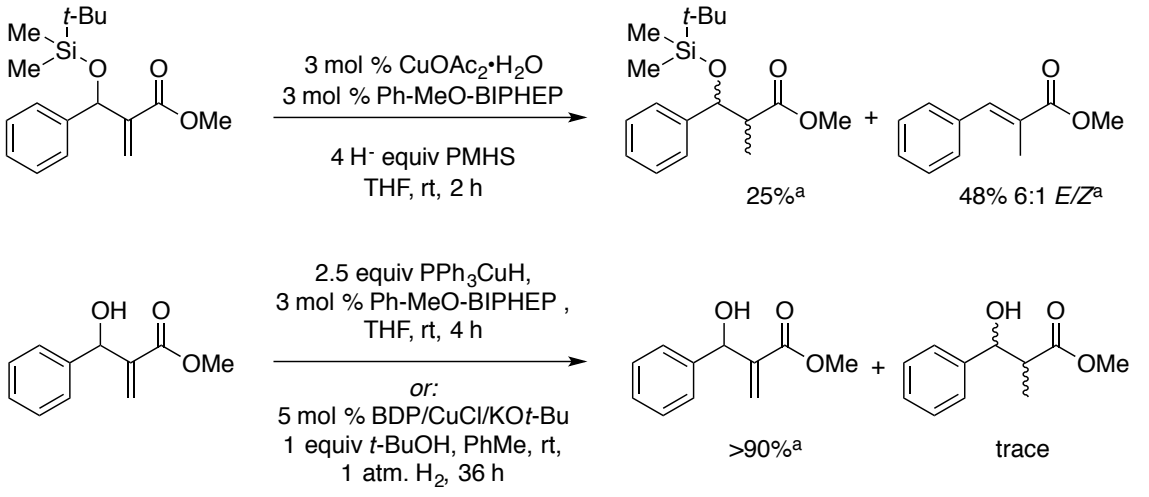
For instance, while reaction on a β-substituted educt derived from an aliphatic aldehyde was uneventful, the reaction on a similar system derived from an aromatic aldehyde was actually quite problematic. Apparently the geometry of the substrate was not a good fit for the ligand system and led to low levels of turnover, and incomplete reactions were always observed. However, this could be partially remedied by simply doubling the catalyst loading, affording the appropriate enoate in modest yield within 24 hours. As the overall rate of substitution was low, and hence the yield as well, it was questioned whether the acetate could be employed to improve this parameter. Surprisingly, the acetate actually reacted even more slowly than the corresponding alcohol, with low yields of product obtained after four days. By employing *t*-BuOH to accelerate catalyst regeneration, and elevated catalyst loading, complete reaction could be achieved within 72 hours at ambient temperature. At first glance this result may seem unsurprising but actually there are a number of features that merit discussion. Firstly, the low rate of reaction of the acetate compared to the alcohol is

surprising given that the catalyst has to perform twice the amount of work, both a silylation of the alcohol, and a nucleophilic displacement. This can be rationalized by considering that the greater bulk of the acetate decreases the initial rate of catalyst/substrate complexation and/or changes the lowest energy conformation of the substrate into one unfavorable for hydride delivery by the catalyst, where the steric bulk of the alcohol prior to silylation is smaller. Along similar lines once CuH has reacted at the alcohol to give the copper alkoxide, sigma bond metathesis with PMHS generates the O-PMHS leaving group and regenerates CuH. However this process is happening on the substrate itself, and such Cu-H is regenerated not from a soluble copper alkoxide in solution, but from the alkoxide on the substrate, and hence in close proximity to a reactive site on the enoate, the overall rate of substitution is higher with the alcohol. That *t*-BuOH could accelerate the reaction with the acetate was also puzzling, as this additive is usually employed in 1,4-reductions to facilitate proteoquenching of a copper enolate to give a soluble CuO*t*-Bu that can then react with silane in solution to regenerate active CuH. In the reaction with the acetate however, 1,4-addition to form a copper enolate would be rapidly followed by anti-elimination to give the substitution product, and no product of simple 1,4-reduction was observed; thus, the role of *t*-BuOH in this context is unclear. Other mechanisms of acceleration may be operative, for instance *t*-BuOH may modify the structure of the PMHS to facilitate more rapid hydride regeneration, or *t*-BuOH may be hydrogen bonding

with the substrate to lower activation barriers/change reactive conformation to allow for efficient reaction.

At the same time it became a point of interest to determine how and why the reaction was so efficient when employing PMHS. Silyl ethers are usually encountered in synthesis as non-labile protecting groups and are not normally employed as leaving groups. On the other hand, most silyl protecting groups are monoalkoxysilyl ethers, yet dehydrogenative silylation with PMHS would give rise to a trialkoxysilyl ether. It was then questioned whether the efficient substitution observed in the case of the MBH alcohols was a result of the activated nature of the MBH adducts, the bulk of the PMHS leaving group, and/or the electronics of the trialkoxysilyl ether intermediate.

Scheme 4. Mechanistic studies:



[a] Determined by TLC/GCMS of crude reaction mixture

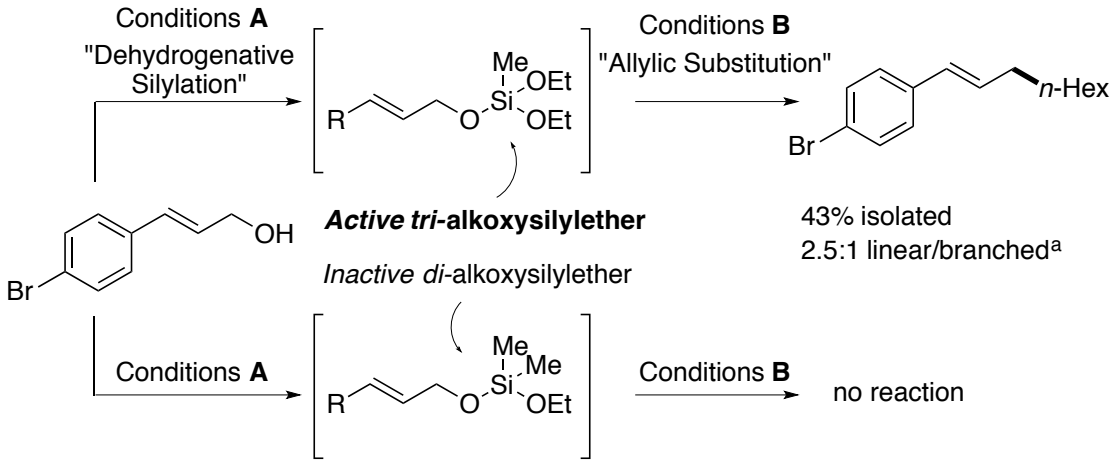
Accordingly, the TBS ether of the standard MBH adduct was prepared and tested, and it gave rise to a mixture of 1,4-reduction and S_N2' product with a

mixed *E/Z* ratio along with recovered starting material (Scheme 4, top). The diminished stereoselectivity suggested that despite the bulk of the TBS group, the much larger PMHS leaving group was required to enforce high *E*-selectivity, where the residual starting material and appearance of 1,4-reduction product was ascribed to the inefficiency of the trialkylsilyl ether to act as a leaving group. Likewise, MBH alcohol was subjected silane-free CuH reduction conditions, where workup and analysis showed no formation of the enoate (Scheme 4, bottom). This would suggest that the initially formed Cu alkoxide does not function as the leaving group in this reaction.

The previous experiments suggested that trialkoxysilyl ethers could constitute an unexplored class of leaving groups, and when prepared by a copper-catalyzed silylation of an alcohol, the copper catalyst could presumably mediate a further displacement with a nucleophile other than hydride. Allylic alcohols seemed attractive in this regard as copper catalyzed allylic alkylations are well known, many catalyst systems have been employed, and are amenable to a variety of nucleophiles.

Much experimentation was performed to this end, and while further optimization is required to develop this into a mature method for allylic alkylation, performing a dehydrogenative silylation using DEMS on *p*-bromocinnamyl alcohol affords an intermediate that is amenable to substitution. Subsequent treatment with Grignard reagent at low temperatures gave 43% of allylic alkylation product in a ca. 2.5:1 linear/branched ratio[9] (Scheme 5). By contrast, if *dimethyl*-

Scheme 5. Tandem Dehydrogenative Dilylation/Allylic Substitution



Conditions **A**) 6 mol % Xantphos/$Cu(OAc)_2 \cdot H_2O$, 1.25. equiv $(EtO)_2MeSiH$ or $EtO(Me)_2SiH$ [0.2 M] Et_2O, rt, 2h
Conditions **B**) 1.35 equiv *n*-HexMgBr, -78 ˚C to rt, overnight
[a] Determined by ^{1}HNMR of pure product

ethoxysilane was used as the silyl source, a dialkoxysilyl ether intermediate is obtained, and no reaction was observed with the Grignard reagent. On the whole, the aforementioned experiments were indicative that PMHS supplied both a leaving group of sufficient bulk to impart high *E*-selectivity, and gave a trialkoxysilyl ether with appropriate electronics for efficient substitution.

That so much trouble had been required to produce relatively simple enoates was difficult to digest, and for some time, the impression was that this project was an exercise in futility as most, if not all of these products could be prepared far easier using HWE based olefination chemistry. But in evaluating the relative merits of this the project several important differences become clear. An HWE approach to these enoates would require preparation of a phosphonoacetate ester, usually derived from bromination and Arbuzov reaction

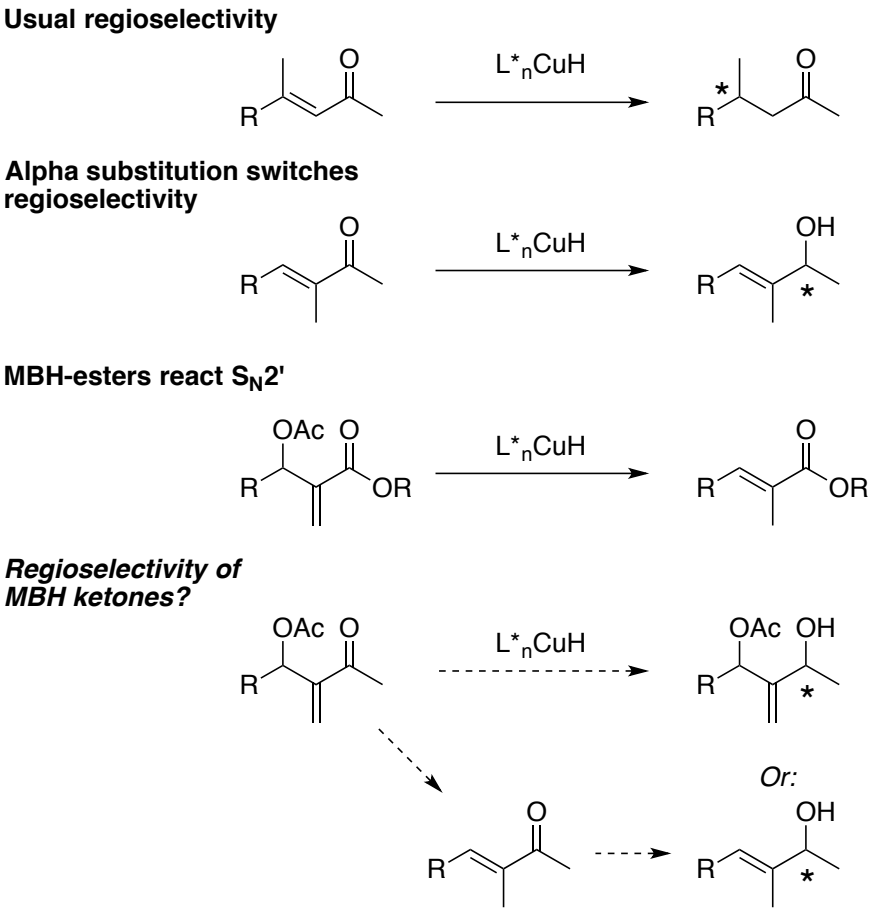
from an ester first, followed by a separate condensation step with stochiometric base. The advantages of an HWE approach clearly are the wealth of established conditions for condensations, the reliance on simple chemicals, and an established track record of reliability. The main disadvantages of the HWE approach is the necessity to prepare an appropriate phosphonate ester first, moderate to highly basic conditions, and variable *E/Z* selectivities. α-Substitution in HWE olefinations does not necessarily always give rise to an isomerically pure *E*-enoate[10] and variability is often observed depending on the nature of the base, solvent, and phosphonate ester, while the reaction may fail completely for the preparation of tetrasubstituted enoates. By contrast, the MBH adducts are prepared in a single step from simple acrylates and aldehydes using a catalytic amount of a Lewis base activator. The main advantage of the CuH method is the avoidance of highly basic conditions, high *E*-selectivities, and the ability to accommodate tri- and tetrasubstitution in the enoates, although these cases require a similarly harsh alumination procedure to afford the precursor MBH alcohol. The disadvantages of the CuH approach clearly are the reliance on the MBH reaction which can take extended times and experimentation to find appropriate conditions for substrates other than the simplest, as well as the necessity to employ a somewhat specialty copper catalyst. In light of this, the present method could in some circumstances offer advantages over traditional HWE chemistry, although many would likely be reluctant to test it unless failure of the HWE route was observed.

At this stage in the project, an important intellectual connection was made between the present work and previous work done in our group. While β,β-disubstituted enones react with CuH as anticipated in a 1,4-sense, our group had also shown that enones possessing α-substitution help to redirect CuH from a to a 1,2-reduction pathway to arrive at chiral allylic alcohols (Scheme 6).[11] The present work had also documented that MBH adducts react with allylic substitution to afford α-substituted enoates. Examining an MBH ketone then posed another question of regioselectivity (Scheme 6, bottom), where the α-substituent present in the MBH adduct could presumably direct CuH to a 1,2-pathway, or CuH could react as with the MBH esters in a preliminary allylic substitution to afford a second α-substituted enone which could be subsequently reduced in a 1,2-sense to afford a nonracemic allylic alcohol.

Since the BIPHEP series of ligands was used for both allylic reductions of MBH esters, and 1,2-reduction of α-substituted enones the answer to this question was not obvious. However, that the BIPHEP ligand discouraged 1,4-reduction for these enones in place of a 1,2-pathway helped to explain, in part, why no overreduction was observed in using the Ph-MeO-BIPHEP ligand for the MBH esters; the allylic displacement furnished an α-substituted enoate which was a poor match for 1,4-reduction of the analogous enones. Therefore if MBH ketones could be employed in the reaction analogously to the esters, then an alpha substituted enone would result which would then be asymmetrically

reduced in a 1,2-fashion, setting both the configuration of the double bond, and central chirality at the alcohol in a single pot.

Scheme 6: Question of Regioselectivity for MBH Ketones

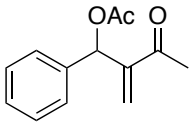
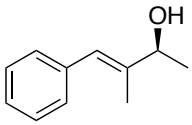
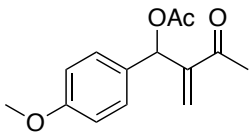
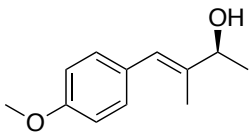
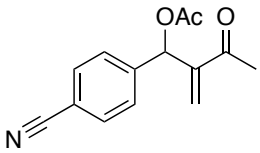
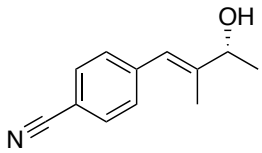
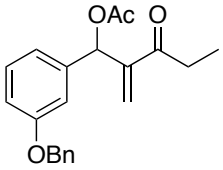
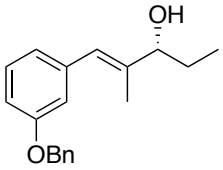
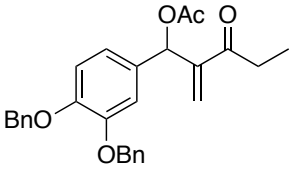
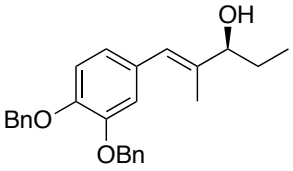


To reduce the number of possible pathways for CuH and encourage the desired tandem sequence, initially the acetates of MBH ketones were tested utilizing our previously developed conditions for asymmetric 1,2-reduction. While we had relied on the Ph-MeO-BIPHEP for the esters to control the reduction pathways for the esters, 3,5-xylyl-MeO-BIPHEP was required for asymmetric 1,2-

reduction but performed poorly with MBH esters, and it was not known from the outset if this would be a stumbling block for efficient tandem reactions.

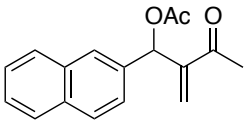
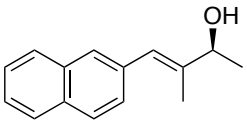
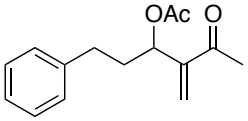
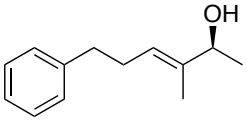
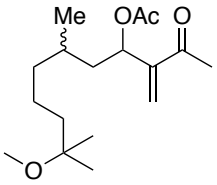
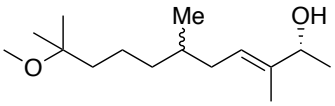
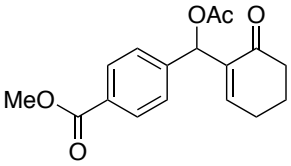
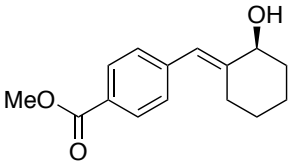
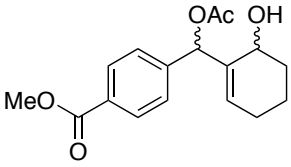
Subjecting a simple MBH acetate to previously developed conditions for 1,2-reduction cleanly afforded the chiral allylic alcohol resulting from sequential S_N2'/1,2-reduction, in both an excellent 92% yield and 93% *ee* (Table 4, entry 1).

Table 4: Tandem S_N2'/1,2-Reductions of MBH Acetates

Entry	Substrate	Ligand time (h)	Product	Yield[a] (% isolated)
1		**L3c** 24		(92%) 93% *ee* (91%)[b] 76% *ee*
2		**L3c** 24		(87%) 84% *ee*
3		***ent*-L3c** 24		(93%) 89% *ee*
4		***ent*-L3c** 24		(74%) 94% *ee*
5		**L3c** 24		(92%) 99% *ee*

[a] Conditions: 3 mol % $CuOAc_2$, 3 mol % **L3c**, 4 equiv DEMS, Et_2O [0.4 M], -25˚C, then quench NH_4F/MeOH. [b] Reaction conducted at rt. in aqueous TPGS-750-M using PMHS as H^- source
L3c = (*R*)-3,5-xylyl-MeO-BIPHEP, **L2** = (*R*)-DTBM-SEGPHOS

Table 4 (continued):

Entry	Substrate	Ligand time (h)	Product	Yield[a] (% isolated)
6		**L3c** 24		(91%) 89% ee
7		**L3c** 24		(87%) 83% *ee*
8		***ent*-L3c** 36		(70%) 22.1: 16.5: 1.5: 1 *dr* (88% *d.e.*)
9		**L3c** 24		(83%) 55% *ee*
10	------	**rac-L2** 24		(73%) 1.2:1 d.r.

[a] Conditions: 3 mol % $CuOAc_2$, 3 mol % **L3c**, 4 equiv DEMS, Et_2O [0.4 M], -25˚C, then quench NH_4F/MeOH. [b] Reaction conducted at rt. in aqueous TPGS-750-M using PMHS as H^- source
L3c = (*R*)-3,5-xylyl-MeO-BIPHEP, **L2** = (*R*)-DTBM-SEGPHOS

Therefore, for MBH ketones, allylic substitution is a faster process than 1,4-reduction, and preferred over initial 1,2-addition notwithstanding the presence of an α-substituent in the starting material.

The cryogenic temperatures employed and/or the nature of the ketone were satisfactory for controlling the *E*-selectivity, and no substantial amount of

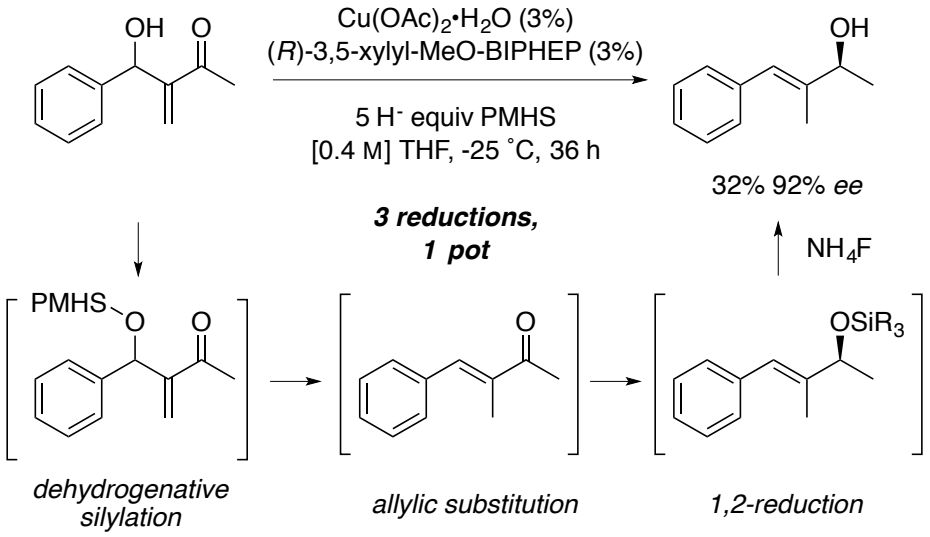
the corresponding *Z*-isomer was detected or isolated. While the reaction could be conducted in aqueous surfactant with similar yield, the ambient temperatures caused the *ee* to suffer. Owing to the success of the initial result, and the need to publish, the substrate scope was next examined. As illustrated in Table 4, the reaction is remarkably efficient and selective for both steps of the reduction sequence, and a few standout examples are discussed. The ethyl ketones with benzyloxy subtituents (entries 4, 5) gave remarkable enantioselectivity, the bis-derivative being obtained in essentially enantiopure form. By contrast, alkyl substituted acetate derived from hydrocinnamaldehyde (entry 7) gave a diminished yet still acceptable *ee*.

Reaction on a substrate containing an existing racemic center was successful (entry 8), suggesting that match/mismatch with the distal methyl group was not problematic. As discussed earlier, the s-*cis* conformation of enones has been suggested as an important factor in determining the 1,4/1,2-regioselectivity of CuH reductions, where DTBM-SEGPHOS was empirically determined to prefer 1,2-reductions for enones in the *s-cis* configuration. However employing a cyclic substrate locked in *s-trans* configuration, DTBM-SEGPHOS led to almost exclusive 1,2-reduction, to give a mixture of *syn*/*anti* diastereomers. (entry 9) In employing the structurally similar biaryl bis-phosphine, 3,5-xylyl-MeO-BIPHEP, differing slightly in overall stereoelectronics and bite angle, the reaction pathway reverted back to the S_N2'/1,2-reduction sequence affording the corresponding allylic alcohol, although with substantial reduction in enantioselectivity. It was

somewhat surprising with these two examples that the reaction path could be completely switched by relatively small changes in ligand structure, as this type of site selectivity scenario is more frequently observed in catalysis when the ligand scaffolds are switched (e.g., NHCs to phosphines). Clearly more subtle substrate-catalyst interactions dictate regiochemical outcomes in this chemistry, presumably a result of the close proximity of the reactive functionality.

With sets of conditions established to activate the alcohols of MBH esters for substitution, as well as effect tandem displacements/1,2-reductions for acetates of MBH ketones, the final question remaining was therefore obvious. Could the *in-situ* PMHS based leaving group be applied to the analogous ketones to effect a three-step targeted process, to the same allylic alcohols? Somewhat remarkably, the answer was affirmative and the expected allylic alcohol could be isolated (Scheme 6).

Scheme 6: Enantioselective Triple Reduction of an MBH Alcohol

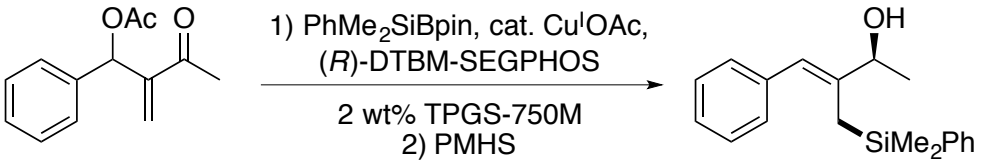


The yield was now substantially diminished, (32%) reflecting that other competitive reductive pathways were operative. However, it was the most significant product in the mixture obtained in identical *ee* (92%) and as exclusively an *E*-olefin. Moreover, the actual efficiency of the system was quite reasonable considering that three sequential reactions had been affected by a single catalyst (68% average yield per step) while concurrently controlling stereochemistry. This appeared to be the upper limit of the catalyst system, alterations in which influenced all three steps differently, and further attempts to improve upon this process were unsuccessful. For instance, if the yield of the initial silylation was low, the overall yield of the sequence would likely suffer. Attempts were made to remedy this by pretreatment of the alcohol with silane or HBpin to induce hydrogen evolution in the absence of copper, to activate the alcohol, yet offered no improvement. Pretreatment of MBH alcohol with one equivalent of HBpin at -25 ˚C was observed to lead to H_2 gas evolution, and once bubbling had ceased, an active solution of CuH/silane was added, where workup and analysis actually appeared to show a modified pathway shifting CuH to a 1,2-path affording a diastereomeric mixture of allylic diols as the major identifiable products. Even this compound was produced in low yield and separation from pinacol and other impurities was tedious and difficult, and was abandoned for the final publication.

During the course of this study, Suginome's silylborane [12] was found to also mediate allylic silylations of MBH acetates in water.[13] While we had

confirmed earlier that the tandem S_N2'/1,2-reductions of the acetates worked well in water, the enantioselectivity had suffered as a result of the higher ambient temperatures (Table 4, entry 1). If instead of hydride, a $PhMe_2Si$- residue was installed via S_N2' displacement, the larger size of the silyl residue could exert additional influence on the enantiotopic faces of the olefin where enantioselectivity for a subsequent 1,2-reduction might be improved. Thanks to much hard work by Carl Peterson, this goal was eventually realized. The conditions requisite for this to occur were determined to rely on an addition of $PhMe_2SiBpin$ to a solution of Cu(I)OAc/DTBM-SEGPHOS and MBH acetate in TPGS-750-M, and once the S_N2' silylation was complete, addition of a fresh solution of CuH in TPGS to the initial solution allowed for the desired tandem reaction to take place. (Scheme 7). While only one example, it is suggestive of a method to access stereodefined allylic silanes with pendant chiral alcohols.

Scheme 7: Tandem Allylic Silylation/ Asymmetric 1,2-Reduction



88% yield
86% *ee*

Several comments on this reaction are in order. Firstly the reaction must employ smaller TMS terminated PMHS oligomers with an average $M_n = 390$,[14] to function effectively in aqueous surfactant. The use of the standard higher oligomers, led to excessive foaming/clumping of the reaction mixture due to

reaction between siloxane and water, where although this reaction was likely occurring with the smaller oligomers, it did not interfere with the homogeneity of the reaction medium. Secondly, PMHS cannot directly be added to the solution once the initial silylation is complete, as it is very difficult to remove the $PhMe_2Si$ residue from copper once the initial MBH acetate is consumed, and CuH is generated very slowly unless a second portion of CuH is preformed in a different solution, and sequentially added. Quenching with NH_4F must be done quickly to avoid desilylation of the desired product. The BIPHEP ligand that had performed so admirably in the reductions of MBH acetates in solvent, led to no reduction of the silylated intermediate in surfactant, and DTBM-SEGPHOS was found to be singularly successful. If the reaction was performed in organic solvent, direct addition of PMHS to the mixture could be employed, so long as first a small quantity of methyl acrylate was added directly after the silylation was judged complete, in order to consume the remaining $PhMe_2SiBpin$, liberating free copper that could generate active CuH.

Conclusions:

MBH adducts, including those with β-substitution can be transformed into stereodefined enoates, or enantioenriched allylic alcohols by utilizing sequential selective reduction sequences, that take advantage of each of the three major modes of the reactivity of CuH (dehydrogenative silylation, 1,4-reduction, 1,2-reduction). Experimental evidence was obtained suggests that the sterics of the *in situ* generated PMHS based leaving group are important for high *E*-selectivity

in reductions MBH esters, while more generally, that the electronics of trialkoxysilyl ethers allows them to function as leaving groups. The stereo-electronics and ring size of the chelate of the bisphosphine ligand were both highly important in controlling reaction selectivities, and relatively small changes to the ligand were observed exert large influences on the reaction path. Finally, an interesting reduction cascade of a racemic MBH alcohol into an enantioenriched allylic alcohol and tandem allylic silylation/1,2-reduction in water were developed.

References:

[1] Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev*. **2010**, *110*, 5447; b) Basavaiah, D.; Venkateswara, K.; Reddy, R. *J. Chem. Soc. Rev*. **2007**, *36*, 1581.

[2] For instance Horner-Wadsworth-Emmons, or aldol condensaton reactions

[3] a) Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8513; b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856; c) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. J. *Am. Chem. Soc.* **2012**, *134*, 18573; d) Langlois, J.-B.; Alexakis, A. *Top. Organomet. Chem*. **2011**, *38*, 235.

[4] a) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett*., **2009**, *11*, 5010; b) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650. c) Simaan, S.; Marek, I. *Chem Comm.* **2009**, 292; d) Thanh Nguyen, T. N.; Thiel, N. O.; Pape, F.; Teichert, J. F. *Org. Lett.* **2016**, *18*, 2455.

[5] Baker, B. A.; Boškovic, Z. V.; Lipshutz, B. H. *Org. Lett*. **2008**, *10*, 289.

[6] Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett*. **2005**, *7*, 1869..

[7] Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1.* **1999**, 3381.

[8] Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310.

[9] Jackowski, O.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3346.

[10] Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

[11]) Moser, R.; Boskovic, Z. V.; Crowe, C. S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 7852.

[12] Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647.

[13] Xuan, Q.-Q.; Zhong, N.-J.; Ren, C.-L.; Liu, L.; Wang, D.; Chen, Y.-J.; Li, C.-J. *J. Org. Chem*. **2013**, *78*, 11076.

[14] average M_n = 390, CAS: 63148-57-2

[15] Linstadt, R. T. H.; Peterson, C. P.; Jette, C. I.; Boskovic, Z. V.; Lipshutz, B. H. *Org. Lett.*, **2017**, *19*, 328.

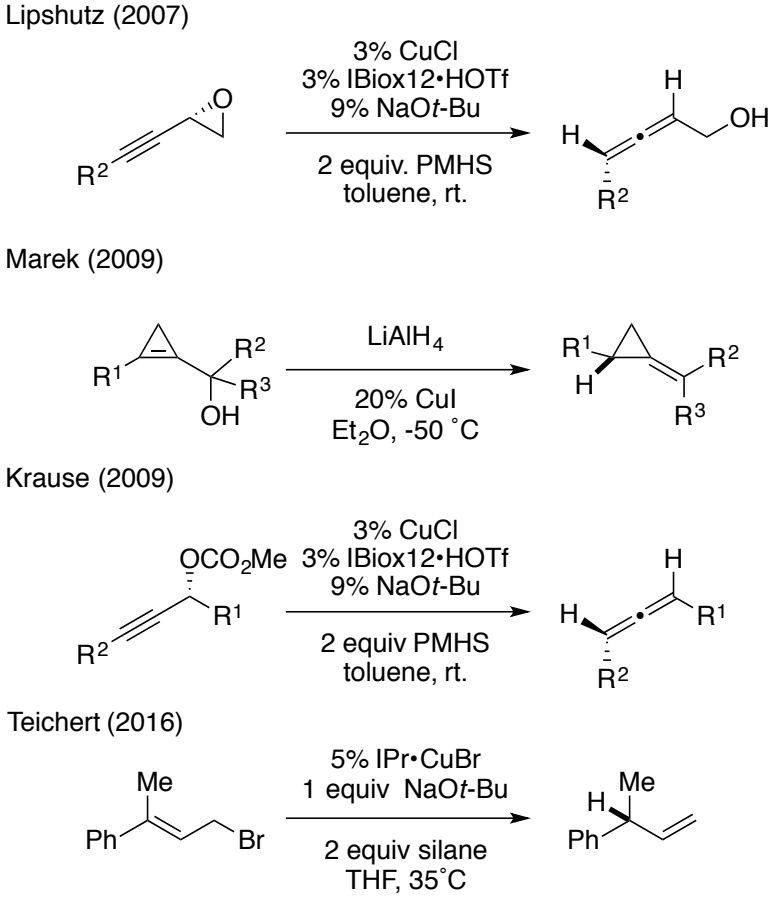
Copper Hydride Substitutions of Unactivated Allylic Systems

For a time it was a subject of interest in our group to develop an enantioselective CuH S_N2' reaction on allylic systems in the absence of an electronically biased substrate such as MBH adducts. This was because while substitutions mediated by copper are well known for silicon, boron, and carbon based nucleophiles the use of hydride has been far less investigated. CuH substitutions in the literature have been described for propargylic [1a, b] and cyclopropenyl systems,[2] yet only recently the first report of a system for Cu catalyzed S_N2' reduction of allylic systems has appeared,[3] while the asymmetric variant is apparently unknown (Scheme 1).

In working towards the goal of developing an enantioselective allylic substitution with CuH, a screening campaign was undertaken using substrates derived from geraniol to identify an appropriate set of conditions. At the time of undertaking this work, the 2016 Teichert report was unpublished. After some experimentation, it was eventually found that: 1) DTBM-SEGPHOS was singularly successful among phosphine ligands tested, with most others giving back recovered starting material. 2) Boc-carbonates were an acceptable leaving group, as substitution delivered product, CO_2 gas, and CuO*t*-Bu which could regenerate CuH from silane. 3) Aryl substituents on the olefin were problematic and led mainly to styrene reduction, suggesting that the aryl-substituent switches the regiochemistry of hydrocupration, the additional proton coming from adventitious water. (Scheme 2) Research from the Buchwald group has recently

taken advantage of the regioselectivity of this styrene hydrocupration to afford benzylic-Cu species which can be subsequently coupled with various electrophiles in a number of transformations.[4]

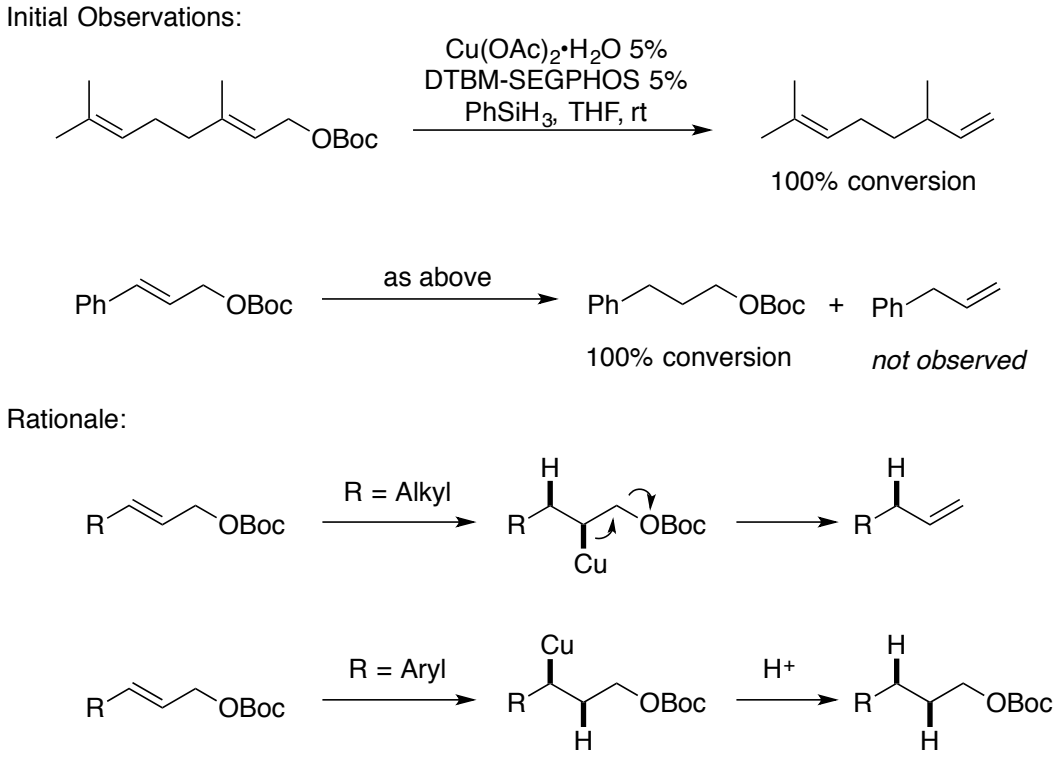
Scheme 1: Prior Art of CuH S_N2' Substitutions



The failure of cinnamates, to reduce effectively with substitution was a disadvantage synthetically, as reduction of the carbonates proceeded with a large reduction in mass making isolation problematic due to losses upon solvent removal. This was further accompanied with and additional decrease in polarity of the products, making separation from other nonpolar impurities difficult.

Relative to those possessing aryl moieties, very few allylic alcohols, or their precursor carbonyl compounds (when preparing the allylic alcohol by a HWE reaction/1,2-reduction sequence) that were possessed of both sufficient polarity and weight were commercially available to address these difficulties. Therefore the following route to the substrates was devised (Scheme 3).

Scheme 2: Discovery of a CuH S_N2' Substitution of Allylic Carbonates



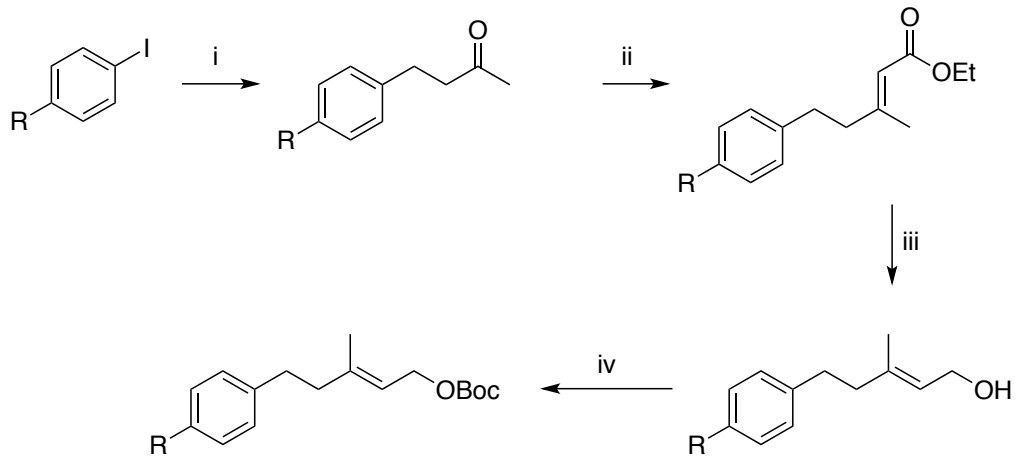
The sequence began from the appropriate aryl iodide, which was reacted in a Heck reaction with an allylic alcohol, where migratory insertion across the olefin and β-Hydride elimination of the hydrogen geminal to the alcohol afforded the corresponding 4-aryl 2-butanones. Use of allyl alcohol could be employed

instead of but 3-ene-2-ol, to arrive at the corresponding aldehydes, although this reaction was significantly messier. Standard HWE conditions (NaH, phosphonate, THF) afforded the corresponding enoates generally as ca. 80:20 mixture of *E/Z* isomers which were separable by flash chromatography. DIBAL-H reduction of the *E*-enoates afforded the allylic alcohols cleanly without the need for chromatography, although filtrations through a short pad of silica were routinely performed to assist in removal of Al impurities not removed in the aqueous workup. Finally, Boc-protection was accomplished by use of LiHMDS as a base in THF, the use of more standard conditions (cat. DMAP, Et_3N) giving low yields and producing a large amount of the symmetrical carbonate as a byproduct.

A number of substrates were prepared by this route, when the corresponding ketone or aldehyde substrate for HWE reaction was commercially unavailable. Unfortunately the yield of the subsequent substitutions for β,β-disubstituted substrates were uniformly low as given in the representative example below (Scheme 4). Further screening of phosphine ligands was fruitless, and only DTBM-SEGPHOS appeared to give any substantial amount of products, the reaction apparently requiring a highly bulky, electron rich ligand to achieve insertion of CuH across the olefin.

Scheme 3: Synthesis of Substrates

Synthetic Route:



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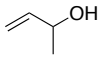
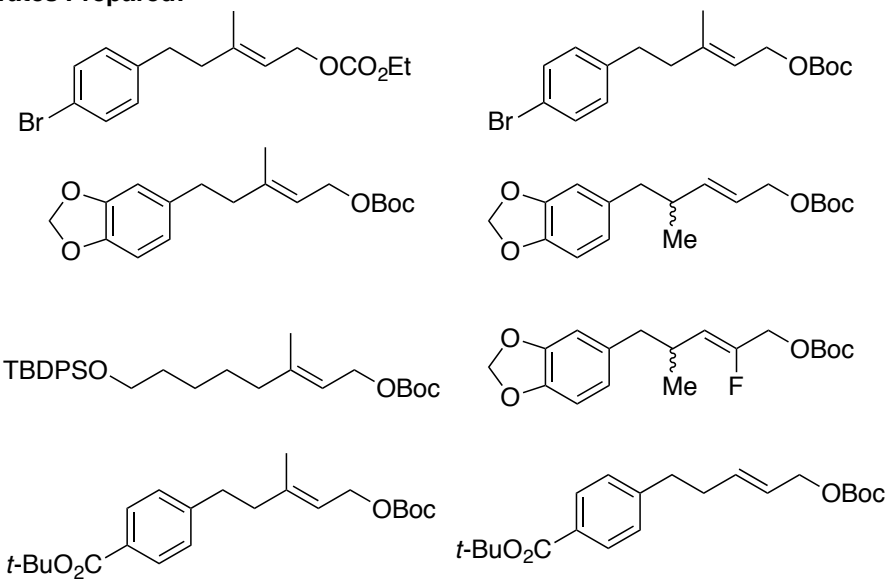
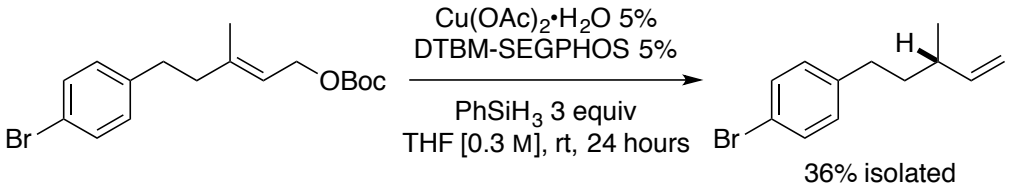
i) 1.5% $Pd(OAc)_2$, 10% Bu_4NCl, 1.5 equiv  2.5 equiv $NaHCO_3$, [0.33 M] H_2O, 80 ˚C, 18 h.
ii) NaH (1.15 equiv), triethylphosphonoacetate (1.15 equiv)., THF [0.2 M], 0 ˚C to rt, 18 h.
iii) 2.2 equiv DIBAL-H, DCM [0.2 M], 0˚C to rt, 4 h
iv) LiHMDS (1.05 equiv), Boc_2O (2 equiv),THF [0.2 M], -78 ˚C to rt, overnight.

Substrates Prepared:



Likewise, changing copper source, temperature, and silane were unable to improve the reaction yield for these β,β-disubstituted substrates. The Cu-catalyst appeared to decompose under these (less than optimal) reaction conditions, resulting in the precipitation of a copper(0) mirror on the sides of the reaction vessel. In cases when product could be obtained from substitution on β,β,-disubstituted material, the desired terminal olefin was contaminated with 10-20% of the corresponding overreduced alkane which was inseperable by chromatography, compounding difficulties already present regarding yield.

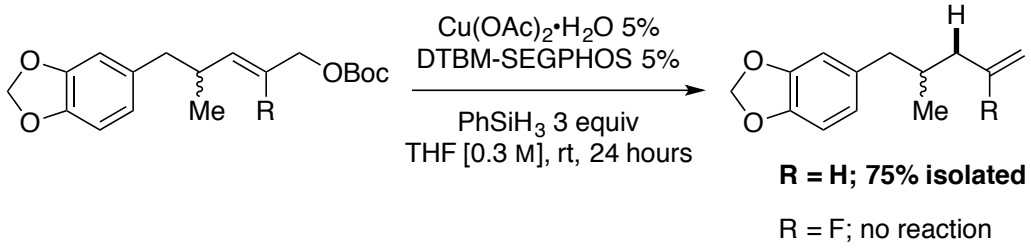
Scheme 4: CuH S_N2' reduction of a β,β-Disubstituted Allylic Carbonate



By contrast, in testing a β-monosubstituted allylic carbonate (Scheme 5), the reaction performed as expected, and the desired product could be isolated in synthetically useful yield. Performing the reaction with the analogous fluoro-olefin on the other hand completely shut down the reaction. Therefore, the low yields encountered earlier can be attributed to slow catalyst turnover as a result of steric encumbrance about the olefin, as opposed to problems associated with the catalyst/quality of Cu salt. Reactions with these β-monosubstituted derivatives afforded products of much higher purity than those from disubstituted

substrates, presumably because the higher efficiency of the reaction out-competes unproductive off-cycle pathways such as terminal olefin reduction.

Scheme 5: CuH S_N2' Reduction of a β-monosubstituted Allylic Carbonate



R = H; 75% isolated

R = F; no reaction

Since screening of our groups library of commonly used ligands for CuH reductions had shown that only DTBM-SEGPHOS was capable of producing any tangible product for β,β-disubstituted cases, and that in these low amounts of product there was consistently inseparable impurities from overreduction, the decision was made to abandon the project. The signs seemed to be all pointing towards a long and protracted ligand synthesis campaign, an endeavor I did not feel comfortable undertaking, considering that only one of our large supply of phosphine ligands provided any observable amount of conversion.

While incomplete, I view the asymmetric transformation as still possible. Important variables still untested include the use of NHC ligands on Cu, whose strong σ-donor characteristics may improve catalyst lifetime, and rate of the reaction. Examining the prior art in Scheme 1, most recent reports of CuH substitutions have relied on these types of ligands, which unfortunately were not available for testing at the time of the work. As chiral NHC ligands are not

generally commercially available, continuation of this research will require likely require the synthesis of a ligand library. While substitution upon the carbonate liberates CO_2 gas, in a sealed system this may pose a disadvantage, as CuH is known to reduce CO_2[5] and may cause off cycle reduction of this byproduct, consuming the stoichiometric silane reductant. On the other hand, substitution with carbonates is advantageous because it also produces CuO*t*-Bu which can regenerate CuH by direct metathesis with silane, obviating the need for stoichiometric alkoxide bases to produce the requisite Cu-alkoxide metathesis. The use of other leaving groups (e.g. Cl, Br, OTs, Phosphates) may improve the rate of substitution provided that an equivalent of a metal alkoxide (e.g. KO*t*-Bu) base is included to assist in regeneration of CuH. Additional obstacles to developing an enantioselective version of this process are that the olefinic products are of relatively low polarity, hindering chiral separations. Any of the materials produced from substitution must be further deriviatized by either hydroboration/oxidation, or ozonolysis to afford materials sufficient polarity that to allow separation *via* chiral HPLC for determination of *ee*. as the enantiomers of the direct product of the reaction are usually poorly resolved on chiral HPLC.

Conclusions

Attempts were made to develop an enantioselective allylic substitution with CuH. While the reaction is successful for β-monosubstituted alkenes, affording pure material in acceptable yields, β,β-disubstituted substrates were found to be possible, but highly problematic. Further development of this method was

hampered by the relatively time consuming 5-6 step procedures needed to prepare substrates of suitable weight and polarity, and the presence of inseparable overreduced byproduct. Additionally, the failure of nearly all ligand systems besides DTBM-SEGPHOS, was taken as a cautionary sign, to avoid a potentially large misadventure in ligand synthesis. On a more positive note, working on this project gave me lots of practice on working on larger scales than I was accustomed, and I was able to hone my techniques synthesizing the substrates.

References:

[1] a) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett*. **2009**, *11*, 5010; b) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650.

[2] Simaan, S.; Marek, I. *Chem Comm.* **2009**, 292.

[3] Thanh Nguyen, T. N.; Thiel, N. O., Pape, F.; Teichert, J. F. *Org. Lett.* **2016**, *18*, 2455.

[4] Wang, Y. M.; Buchwald, S.L. *J. Am. Chem. Soc*. **2016**, *138*, 5024.

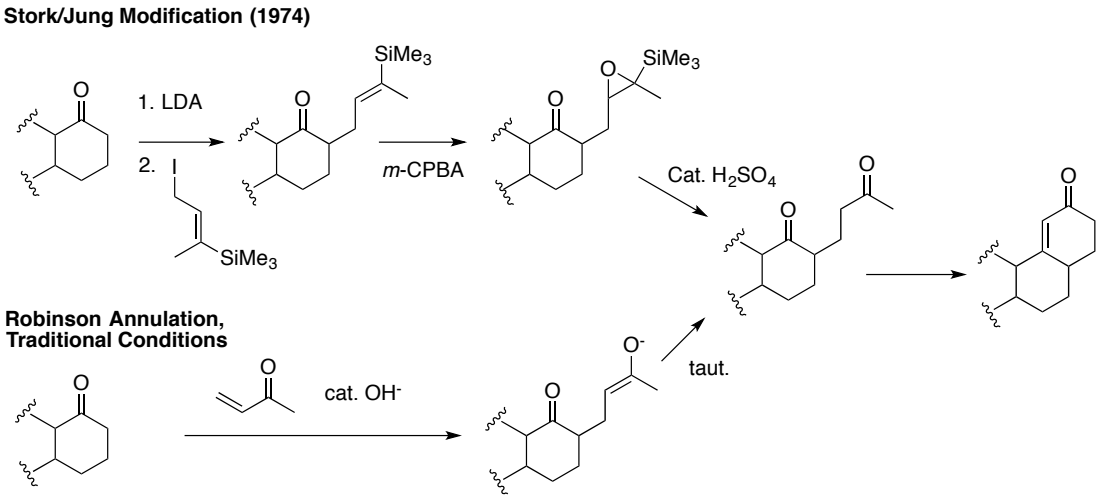
[5] Zhang, L.; Cheng, J.; Hou, Z. *Chem. Comm*. **2013**, *49*, 4782.

B) Stereoselective Silylcupration Of Conjugated Alkynes In Micellar Media

General Introduction and Overview of Vinylsilane Chemistry

Vinylsilanes have enjoyed a long history of use as synthetic intermediates in organic chemistry. Much of their popularity can be traced back to the work of Stork and Jung, who utilized them to great effect as an alternative to methyl-vinyl ketone in the Robinson Annulation (Figure 1).[1a, b]

Figure 1: Early Application of a Vinylsilane in Synthesis

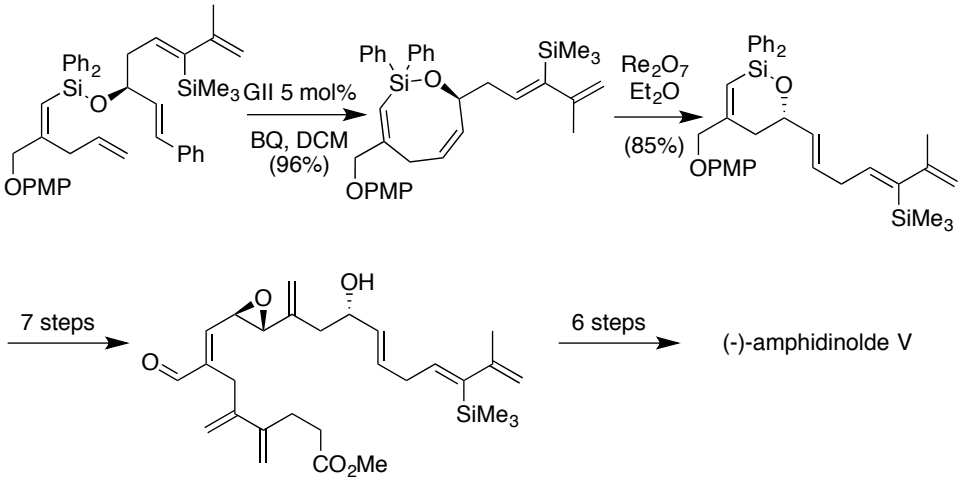


In this case, the use of an allyl iodide allowed for selective introduction of the vinylsilane functionality which could then be oxidatively transformed under mild conditions into the common diketone and subsequently cyclized, overcoming many of the difficulties (e.g. polymerzation of the vinyl ketone) associated with the traditional conditions employed in the Robinson annulation. Since Stork's report, many useful reactions have since been developed based on vinylsilanes, and have found use as synthetic lynchpins, allowing completion of a number of total syntheses (Figure 2). For instance, Lee and Volchkov[2] made creative use

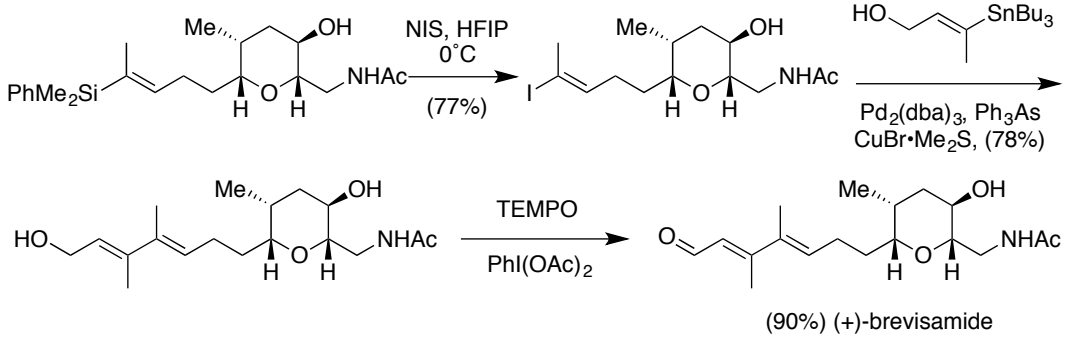
of a vinylsilane as a lynchpin in their total synthesis of (-)-amphidinolide V. In their study, the vinylsilane motif was used to construct a tether between two elaborated chains, in order to effect a ring closing metathesis, followed by a stereoselective rhenium catalyzed transposition of an allylic alcohol. The vinylsilane futher served to double as both an alcohol protective group and as a latent proton which was unmasked near the end of the synthesis. Equally

Figure 2: Recent Applications of Vinylsilanes in Total Synthesis

Lee and Volchkov (2013)



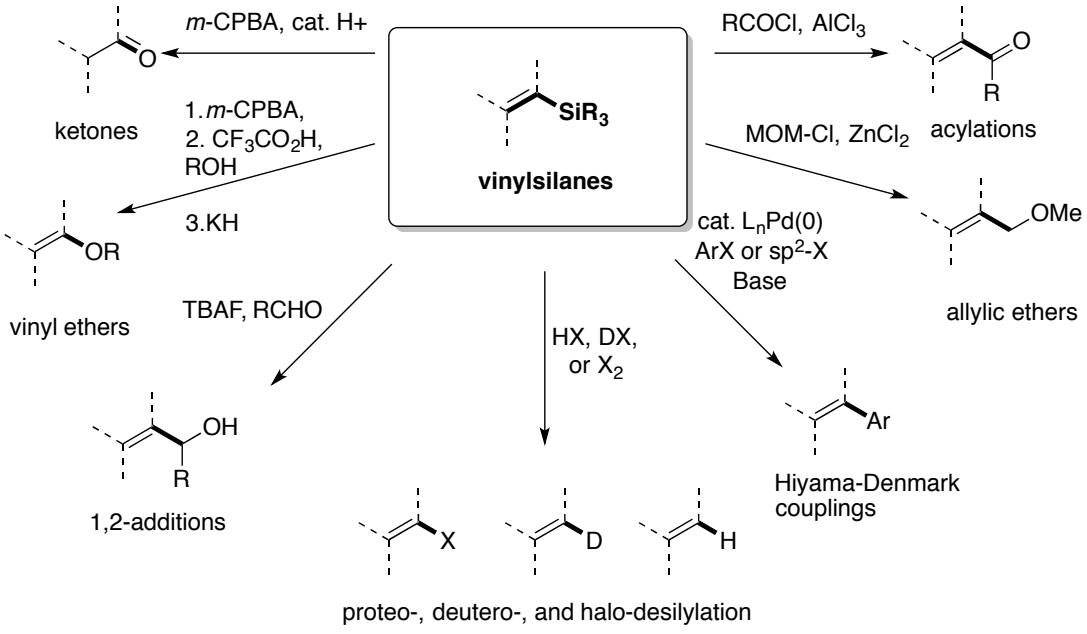
Zakarian (2011)



effective was the use of a vinylsilane as a masked iodide as demonstrated by Zakarian,[3a, b] where iododesilylation furnished a stereodefined vinyl iodide which was then subjected to Stille coupling to install the required diene in their total synthesis of brevisamide.

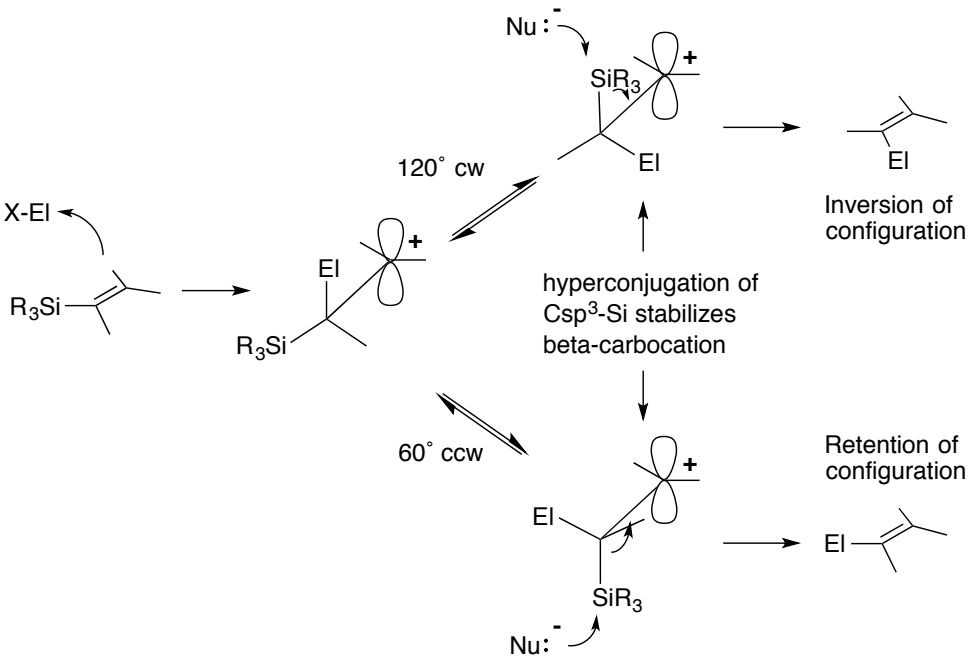
Notwithstanding these aforementioned examples, vinylsilanes can undergo many other reactions. Hiyama-Denmark couplings[4] allow for delivery of the vinyl group in Pd-catalyzed cross couplings, where fluoride furnishes a vinyl-carbanion which can participate in 1,2-additions to carbonyl compounds. Electrophilic substitution is by far the most common route for derivatization of these educts, where activation of the pi-system, followed by elimination of the silyl group furnishes the derivatized products.[5] Several transformations available to vinylsilanes are summarized in Figure 3.

Figure 3: Representative Reactions of Vinylsilanes



Many of the substitutions above are made more valuable by virtue of the fact that electrophilic substitution in these systems is regioselective, and proceed with retention of stereochemistry, where the configuration of the product is identical to the starting vinylsilane. Therefore, if one can synthesize a vinylsilane with stereochemical fidelity, it can in many cases be retained following derivatization. The high reactivity and selectivity of vinylsilanes for such electrophilic substitutions is usually ascribed to the "β-silicon effect" which is depicted in Figure 4.[6a, b]

Figure 4: Illustration of the β-Silicon Effect



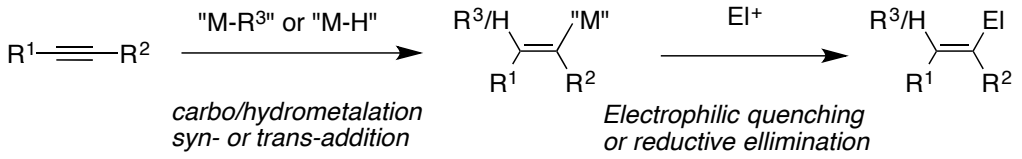
As illustrated above, the β-silicon effect is a hyperconjugative effect that explains observed regio- and stereochemical trends in these electrophilic substitution reactions. Addition to the electrophile produces a carbocation which

is stabilized β to the silicon atom by hyperconjugation with the Csp^3-Si bond. Subsequent addition of a nucleophile to the silicon atom liberates the substitution product. Erosion of stereochemical information can be traced back to the initially formed adduct with the electrophile where a low energetic barrier to rotation around the central C-C bond and subsequent elimination of Si produces the inverted stereoisomer. However, the full carbocation is not necessarily fully formed before C-C rotation, and rotation is likely already occurring along the path of least motion as the electrophile draws closer in proximity to the pi-system, so that stereochemical purity is usually preserved.

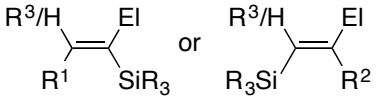
Considering the versatility of vinylsilane reagents, it should come as no surprise that they have attracted a large amount of interest as targets in there own right, and new methods to prepare them are continually appearing throughout the literature. Although a glance through the titles of these papers in the literature would seem to suggest that there are a large number of “novel” methods to prepare vinylsilanes, conceptually most of these methods center around two main strategies, either a metalation of an alkyne/allene or condensation of the appropriate nucleophile onto a carbonyl derivative (Figure 5).[5b]

Figure 5: General Approaches to Access Vinylsilanes

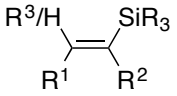
Vinylsilanes *via* hydrometalation or carbometalation:



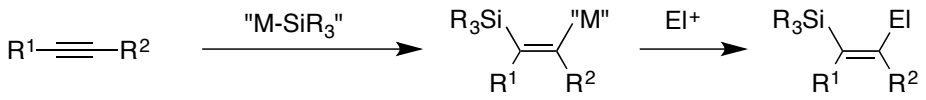
Metalation of a silylacetylene where R^1 or $R^2 = SiR_3$:

Product =  or

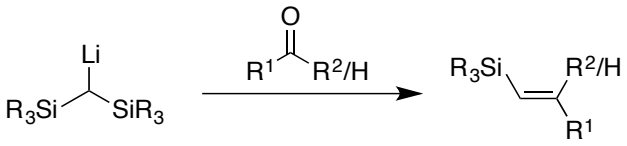
Metalation of a alkyne followed by trapping with Si where $R^1, R^2 \neq SiR_3$ and $El^+ = R_3Si\text{-}X$

Product = 

Vinylsilanes *via* silylmetalation:



Vinylsilanes *via* olefination:



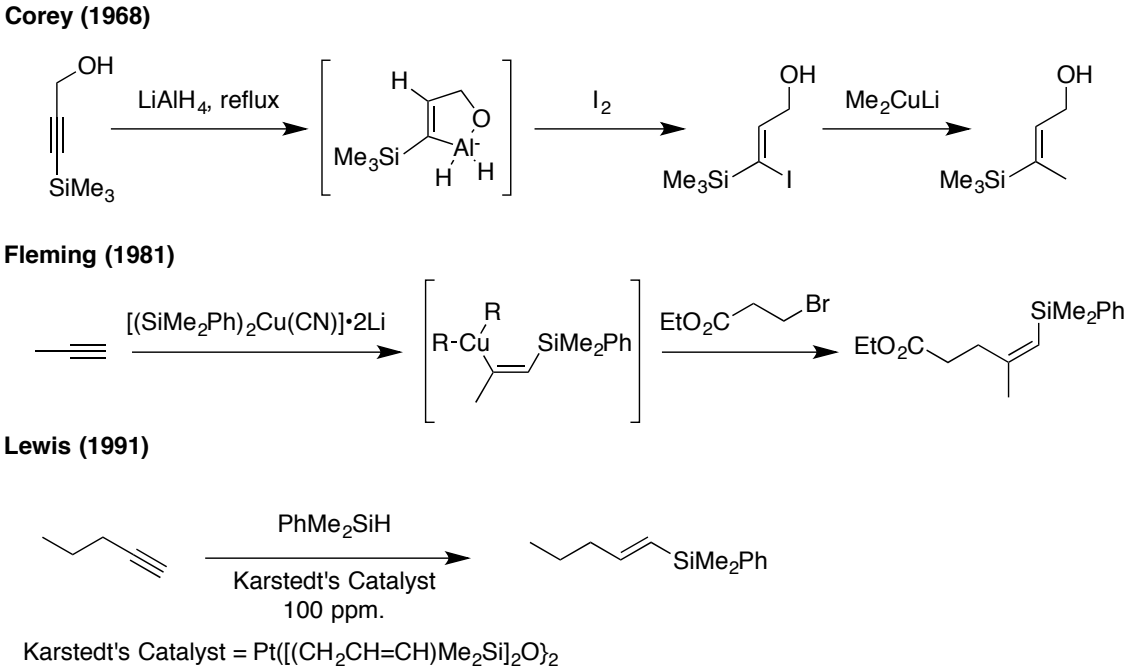
Of these two strategies metalation of a C-sp center on either an allene or alkyne is the most widely used. For instance, silylacetylenes are easily accessible from the corresponding silyl-halides and terminal alkynes, and can be selectively reduced to the corresponding (*E*)- or (*Z*)-vinylsilanes. Along similar lines, hydrometalation or carbometalation of an alkyne can be effected and the resulting vinylmetal species can be quenched with the appropriate silyl halide. In

the case of hydrosilylation, the vinylmetal species is quenched with additional silane or reductive elliminination furnishes the vinylsilane. If a silyl-metal reagent is employed, then addition of Si-M across the alkyne/allene forms the desired sp^2-Si bond and the resulting organometallic can be quenched with H^+ or a number of electrophiles to further elaborate the molecule. It is of note that many of the silylmetalation procedures are complementary with the other carbometalation procedures, as the addition of R-M or Si-M across the olefin proceed stereospecifically, so by switching the silylmetal reagent for the carbometalation reagent, and quenching with a silyl-electrophile the opposite regioisomer is produced. Also noteworthy is that the stereochemistry of the metalation reaction (*cis* or *trans*) is dependent on the metal used, and by proper selection of the metal, the stereochemistry can be altered appropriately.

Among the traditional approaches, the *trans* hydroalumination of siylacetylenes is a reliable procedure, accomplished by refluxing the appropriate silyl terminated alkyne with $LiAlH_4$.[7a-b] The intermediate vinylaluminum species can be quenched with H^+ to afford the *trans* vinyl-silane, although if additional substitution geminal to silicon is desired, quenching with I_2 can afford a vinyl-iodide which can be further derivatized. Fleming's silyllithium reagent $PhMe_2SiLi$ is a tremendously valuable source of nucleophilic silicon owing in part to the ease with which it is prepared compared with other silyllithiums.[8a-d] Much of Fleming's reagent value lies in that it can participate in metal permutation by transmetalation[9a-c] to tune its reactivity much like the analogous alkyllithium

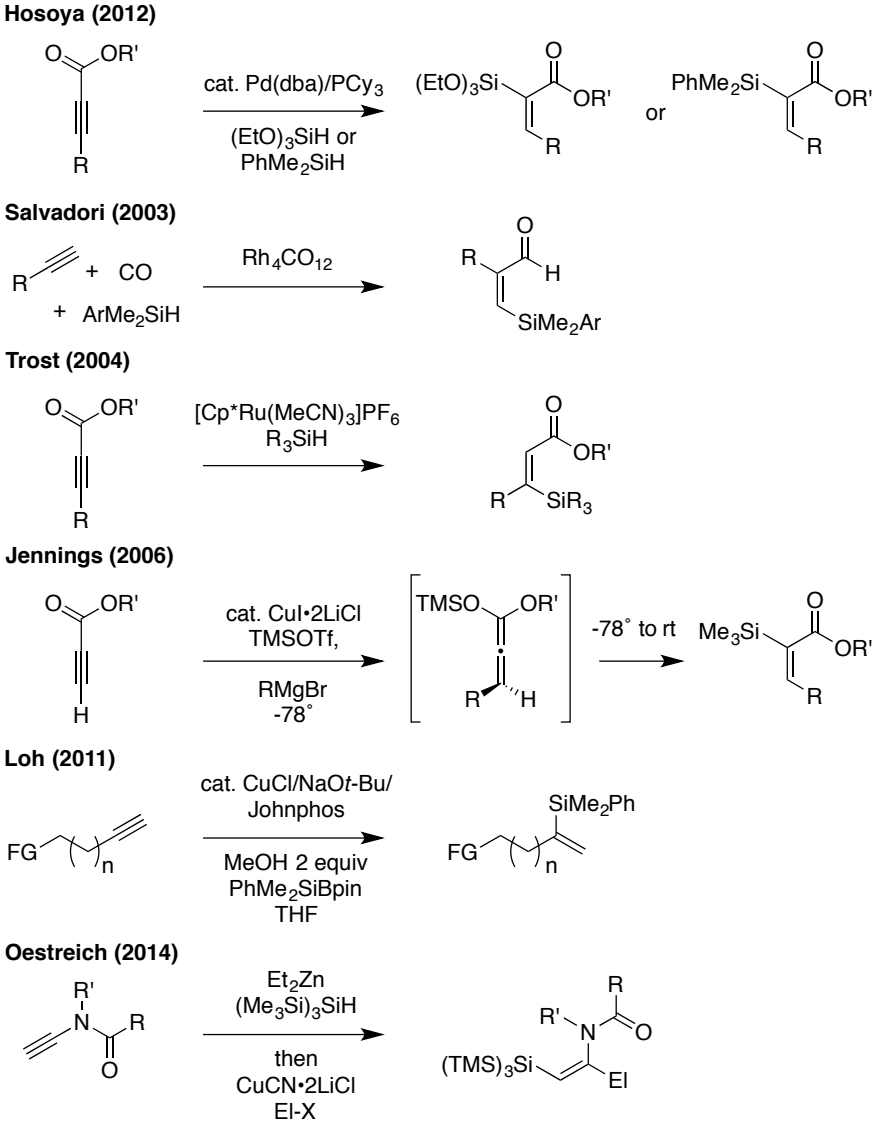
reagents. The use of 2 equiv of $PhMe_2SiLi$ in conjunction with CuCN gives rise to a higher order silylcuprate reagent, which can undergo a *syn*-silylcupration with alkynes, and the resulting vinylcuprate can be subsequently trapped with the appropriate electrophile. While this reaction, not unlike many of the other reactions based on cuprates, is valued for its selectivity, it requires both cryogenic conditions and results the generation of stochiometric amounts of metal waste; the disposal of which can render it economically, as well as environmentally, impractical on large scales.[10]

Figure 6: Traditional Methods to Access Vinylsilanes (pre-2000)



Since the 1990's, synthetic methodology development has shifted its focus away from solving the problem of simply addressing the *preparation* of a given molecule, towards an approach that more heavily favors addressing *how the*

Figure 7: Recent Methods to Access Vinylsilanes (2000-present)



molecule is prepared. New reactivity, improved selectivity, mitigating the use cryogenic or highly elevated temperatures, and reducing metal loading to catalytic levels, are all recognized as ideals to be strived for in the development and refinement of a synthetic method. In line with this broad push across the field, many recent developments have allowed for new and improved methods of

synthesizing vinylsilanes, and several standout methods from the literature are highlighted in Figure 7.[11a-h]

As illustrated above, most recent methods involve a metalation of an alkyne, where proper choice reactants and catalyst all help to control the regio- and stereochemistry of the product. Many of the conditions are made more mild relative to previous methods by avoiding large excesses of highly basic organometallic reagents. While α-silylation of enoates can be accomplished using palladium,[11a] or platinum[11g] catalysts, relatively few methods can access β-silylsubstituted enoates stereoselectively. In this regard Trost's cationic ruthenium system for the *trans*-hydrosilylation of activated alkynes to access (*Z*)-β silyl carbonyl derivatives stands out as an exception[11c] while similar educts could also be obtained by a rhodium catalyzed hydrosilylation/hydroformylation reaction.[11b]

Of particular note in all of the aforementioned procedures is Loh's method[11e] where Suginome's reagent is used as a source of nucleophilic silicon that can transmetalate to copper, much like $PhMe_2SiLi$, but under substantially milder conditions.[12] Although derived ultimately from the lithiated silane, the use of Suginome's reagent offers additional advantages over the organometallic, including isolability, thermal stability, and moisture tolerance. Owing to the weak character of the B-Si bond, transmetalation, which can be relatively slow for many boron nucleophiles, occurs quickly with this reagent. Additionally, many copper catalyzed reactions employing $PhMe_2SiBpin$ require the use of water or

alcoholic solvent for efficient transmetalation, and strict anhydrous conditions are not always required.[13] This aspect was viewed as particularly attractive, as our group has had an ongoing program of synthesis in aqueous media, and therefore the synthesis of Suginome's reagent was undertaken to evaluate potential silicon bond forming reactions in our surfactant platform.

References

[1] a) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684; b) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.

[2] Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324.

[3] a) Herrmann, A. T.; Martinez, S. R.; Zakarian, A.; *Org. Lett.* **2011**, *13*. 3636; b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

[4] S. E. Denmark, J. M. Kallemeyn, *J. Am. Chem. Soc.* **2006**, *128*, 15958.

[5] a) Fleming, I.; Dunoguès, J.; Smithers R. in *Organic Reactions.* Wiley, New York, **2004**, 57-575; b) D. S. W. Lim, D. S. W.; Anderson, E. A. *Synthesis* **2012**, *44*, 983.

[6] a) Weirschke, S. G.; Chandresakar, J.; Jorgenson, W. L.; *J. Am. Chem. Soc.* **1985**, *107*, 1496; b) Lambert, J. B.; Wang, G-T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838.

[7] a) Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, *70*, 739; b) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

[8] a) Fleming, I.; Roberts, R. S.; Smith, S. C. *Tetrahedron Lett.* **1996**, *37*, 9395; b) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403; c) Lee, T. W.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3337; d) TMS-Li is infrequently encountered as it must be prepared in carcinogenic HMPA.

[9] a) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520; b) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701; c) Lithium Bis[dimethyl(phenyl)silyl]cuprate. *e-EROS Encyclopedia of Reagents for Organic Synthesis*. [Online]; Wiley & Sons, Posted April 15, 2001. http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rl054/full (accessed Oct 11, 2013).

[10] Lipshutz, B. H. *Acc. Chem. Res.* **1997**, *30*, 277.

[11] a) Sumida, Y.; Kato, T.; Yoshida, S.; Hosoya, T. *Org. Lett.* **2012**, *14,* 1552; b) Aronica, L. A.; Raffa, P.; Caporusso, A. M.; Salvadori, P. *J. Org. Chem.* **2003**, *68*, 9292; c) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942; d) Hendrix, A. J. M.; Jennings, M. P. *Org. Lett*. **2010**, *12*, 2750; e) P. Wang, X. L. Yeo, T. P. Loh. *J. Am. Chem. Soc.* **2011**, *133*, 1254; f) Romain, E.; Fopp, C.; Chemla F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Perez-Luna, A. *Angew. Chem., Int. Ed*. **2014**, *53*, 11333; g) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926; h) Martin, S. E. S.; Watson, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 13330.

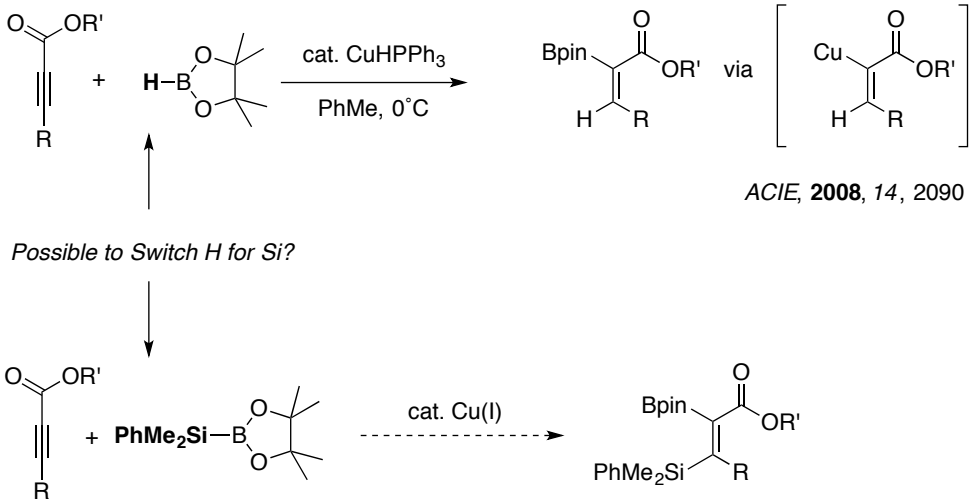
[12] For a recent review of silylboranes in synthesis, including copper catalysis, see: Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402.

[13] For instance, see: Calderone, J. A.; Santos, W. L. *Org. Lett.* **2012**, *14*, 2090.

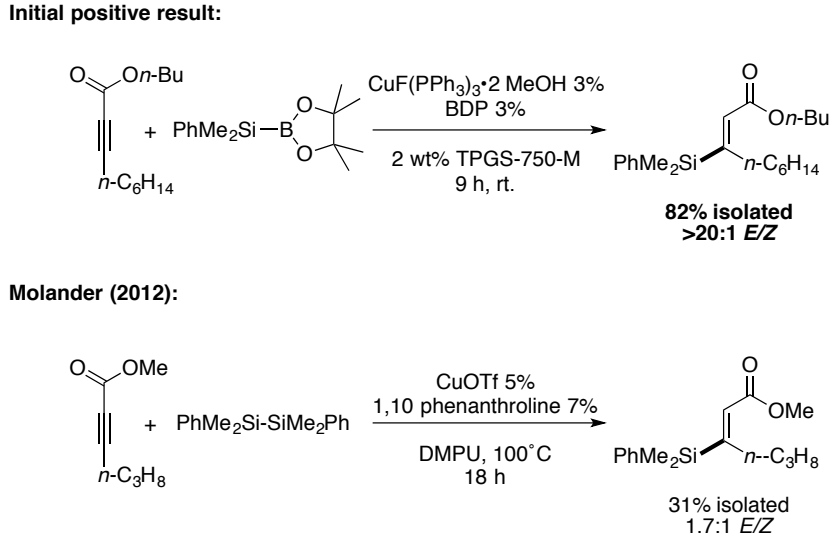
Stereoselective Silylcuprations of Electron Deficient Alkynes

Our group had previously demonstrated that CuH, generated from HBpin, could add hydride to the β-site of ynoates, via a *syn*-hydrocupration, where the intermediate α-cuprioenoate was then quenched with HBpin, affording an α-boryl-enoate and regenerating active CuH.[1] In teaching synthetic chemistry, students are often taught that silyl groups can be thought of as a "bulky proton", and so if HBpin was substituted for $PhMe_2SiBpin$ (Suginome's reagent), it was questioned whether the analogous silylboration reaction would take place (Figure 1)

Scheme 1: Initially Proposed Silylboration

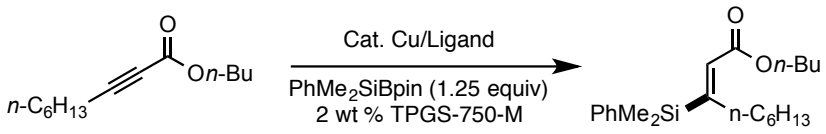


Scheme 2: Discovery of β-Silylation, Compared with Literature Conditions



A model reaction in aqueous TPGS-750-M[2] containing also ynoate, $PhMe_2SiBpin$, and the air stable copper(I) precatalyst ($CuF(PPh_3)_3$•2MeOH), gave somewhat surprisingly, none of the desired silylborylation product, but solely a β –silylenoate in 82% yield as exclusively the (*E*)-isomer (Figure 2, top). While the original idea had been to affect a double functionalization, the ability of the reaction to stereoselectively introducing silicon functionality seemed to merit further investigation. A literature search confirmed that there were no mild methods to affect this transformation with Cu, where the only catalytic method reported by Molander[3] to access (*E*)-isomeric products required high temperatures in DMPU, gave moderate yields and selectivities (Figure 2, bottom). Clearly, even the results from the initial reaction were substantially superior than the existing conditions, and bearing in mind the utility of vinylsilanes, it was then decided that the reaction be further investigated.

Table 1: Optimization of β-Silylcupration



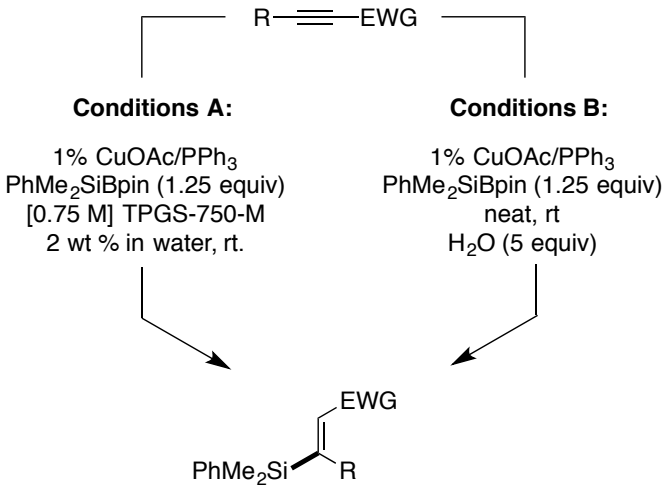
entry	Cu Source (mol %)	Ligand (mol %)	conc [M]	Time (h)	% conv.
1	None	BDP (3)	0.5	9	< 2%[b]
2	CuI (3)	BDP (3)	0.5	9	0%[a]
3	CuBr (3)	BDP (3)	0.5	9	0%[a]
4	$CuF(PPh_3)_3$•2MeOH (3)	BDP (3)	0.5	9	82%[a]
5	$Cu(OAc)_2$•H_2O (3)	BDP (3)	0.5	9	0%[a]
6	Cu(I)OAc (3)	none	0.5	1	44%[b]
7	Cu(I)OAc (3)	BDP (3)	0.5	1	100%[b]
8	Cu(I)OAc (3)	TMEDA (3)	0.75	6	98%[b]
9	Cu(I)OAc (1)	PPh_3 (1)	0.75	0.5	100%[b]
10	**Cu(I)OAc (1)**	**PPh_3 (1)**	**0.75**	**5 min**	**100%[b]**
11	**Cu(I)OAc (1)**	**PPh_3 (1)**	**Neat, 5 equiv H_2O**	**5 min**	**100%[b]**

All reactions were run under inert atmosphere of Argon [a] conversion monitored by GCMS.
[b] Conversion monitored by crude NMR

Initial studies with model ynoate ester and Suginome's reagent were performed in aqueous TPGS-750-M utilizing the air stable Cu(I) precatalyst ($CuF(PPh_3)_3$•2MeOH) initially reported by Gulliver[4] and later popularized by Riant,[5] in order to assure that catalytically active Cu(I) would be present in the reaction media, as well as BDP as supporting ligand. Further screening of the reaction conditions revealed that a copper(I) source is required and no reaction occurs without it (entries 1, 4, 5) Copper salts possessing a halide counterion

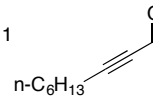
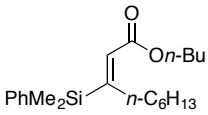
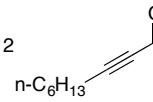
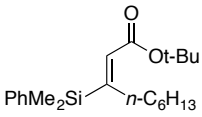
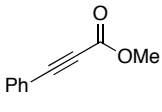
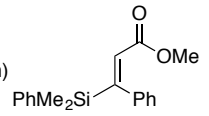
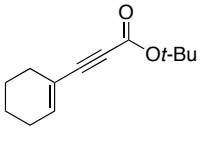
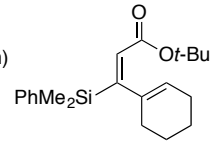
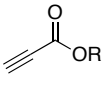
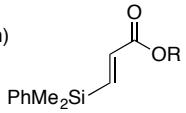
reacted much slower suggesting that an oxyanion counterion was needed for efficient transmetalation (entries 2, 3) In switching from BDP to the simpler and cheaper ligands PPh_3 and TMEDA along with Cu(I)OAc, the conversion could also be improved. Further reduction in catalyst loading, along with closer inspection of the reaction time revealed that the reaction was actually complete in five minutes, a testament to both the rapid rate of transmetalation, and the high concentration of reactants in the micellar cores (entries 8, 9, 10). Finally it was found that a model reaction could be conducted "neat" with five equivalents of H_2O allowing for further reductions in the aqueous waste stream. Clearly the conditions were about as optimal as they could be, and therefore conditions using either aqueous TPGS or "neat" were employed in examining the substrate scope, although the neat conditions were necessarily restricted to liquid substrates.

Scheme 3: Optimized Conditions



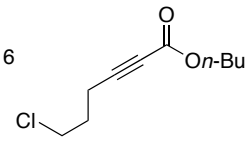
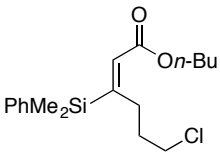
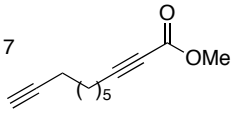
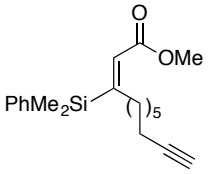
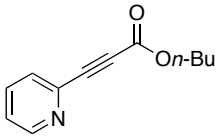
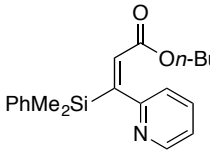
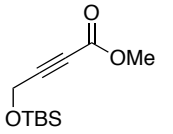
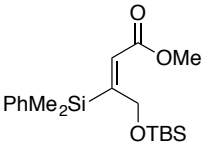
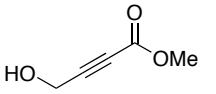
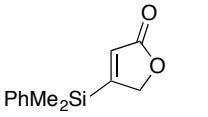
In examining the scope of this reaction for several acetylenic esters, a remarkably broad functional group tolerance was observed. Both aliphatic and aryl substituted alkynes reacted smoothly, accommodating bulky *t*-Butyl esters without difficulty (Table 2, entries 1, 2, 3). Extended conjugation was tolerated allowing access to a silyl-dienoate (entry 4), with no 1,6-addition observed. Simple ethyl, and octyl- propiolates could be used as substrates, while the yields were slightly diminished due to competitive double 1,4-addition (entry 5).

Table 2: Silylation of Ynoates

Entry	Substrate	Conditions, (time)	Product	Yield (% isolated)	*E/Z*
1		**A, B** (5 min)		95% (**A**) >95% (**B**)	> 20:1 > 20:1
2		**A, B** (5 min)		>95%	> 20:1
3		**A** (30 min)		>95%	> 20:1
4		**B** (30 min)		>95%	> 20:1
5		**A** (120 min)		R= Et, 75% R= *n*-oct, 82%	> 20:1 > 20:1

[a] with 2 equiv. $PhMe_2SiBpin$. Conditions **A:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ (1.25 equiv.), [0.75 M] TPGS-750-M, 2 wt.% in water, rt.
Conditions **B:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ (1.25 equiv.), 5 equiv. H_2O, neat, rt.

Table 2 (continued):

Entry	Substrate	Conditions, (time)	Product	Yield (% isolated)	*E/Z*
6		**A** (240 min)		72% (82%)[a]	> 20:1
7		**A** (30 min)		>95%	> 20:1
8		**A** (60 min)		82%	12:1
9		**A** (30 min)		88%	> 20:1
10		**A** (30 min)		70%	----

[a] with 2 equiv. $PhMe_2SiBpin$. Conditions **A:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ (1.25 equiv.), [0.75 M] TPGS-750-M, 2 wt.% in water, rt.
Conditions **B:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ (1.25 equiv.), 5 equiv. H_2O, neat, rt.

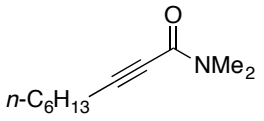
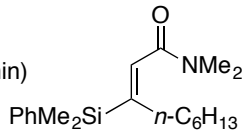
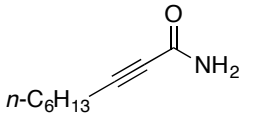
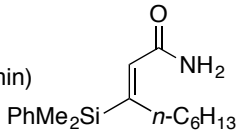
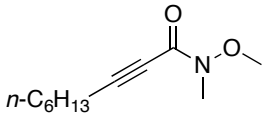
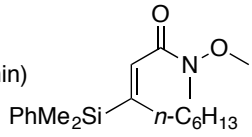
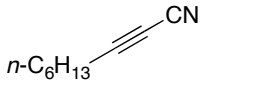
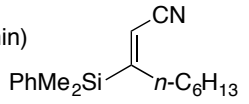
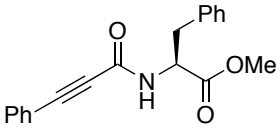
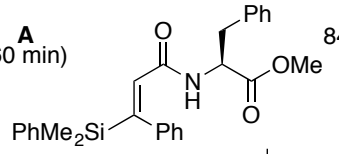
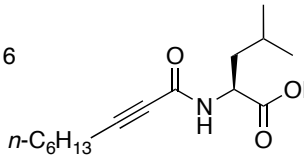
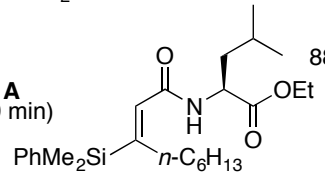
A primary chloride was tolerated as in the case of entry 6, however it did require a somewhat longer reaction time for unknown reasons. A terminal alkyne could be used as a substrate without major problems and the product was obtained in 75% yield where the remainder appeared to be a mixture of terminal alkyne addition products (entry 7). TBS protected propargyl alcohol coupled smoothly (entry 9) as well as the unprotected derivative which spontaneously

cyclized to the corresponding lactone (Entry 10).[6] Only an ynoate with a 2-pyridyl substituent gave diminished (*E*) selectivity (entry 8) whereas all other silylenoates were obtained in > 20:1 *E*/*Z* selectivity.

Owing to the success of this chemistry with acetylenic esters, we then sought to expand the utility of the chemistry to various other conjugated alkynes. Accordingly, a number of alkynes bearing electron withdrawing substituents were prepared and tested under the optimized conditions. Where a variety of electron withdrawing groups were accommodated under the optimized conditions (Table 3). Both a tertiary and primary amide could be reacted without issues (entries 1, 2), the reaction being tolerant of the N-H functionality. Silylation of a Weinreb amide (entry 3) occurred with > 90% yield, and was seen to be advantageous because it would allow for subsequent transformations into functionalized aldehydes and ketones. After some experimentation, the best yield was found to be obtained using 2 equiv of Suginome's reagent under the "neat" conditions, and subsequent quenching of the reaction mixture with bicarbonate. Silylation of this substrate initially forms an unidentified adduct that displays several extra peaks in ^{1}H-NMR and shows surprisingly none of the expected C=O stretching vibration by IR spectroscopy. Addition of aqueous sodium bicarbonate decomposes this unidentified adduct back to the desired product. An unsaturated nitrile was observed to be successful, with complete conversion in only 10 min (entry 4). Ynamides bearing a peptide linkage could also be used, requiring slightly more

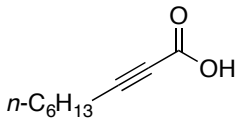
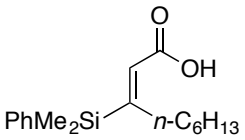
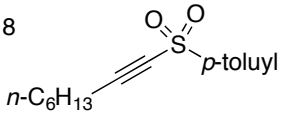
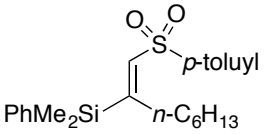
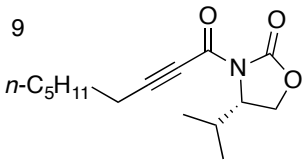
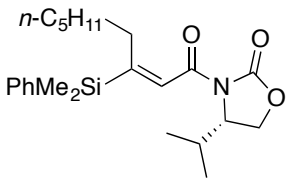
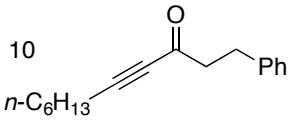
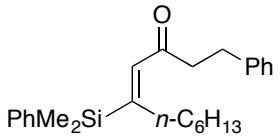
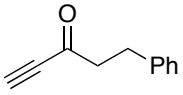
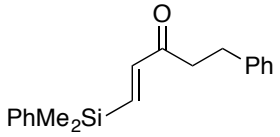
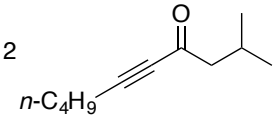
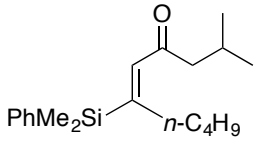
reagent to achieve complete conversion, while the mild reaction conditions avoided any isomerization of the chiral centers (entries 5, 6).

Table 3: Scope of Electron Withdrawing Groups:

Entry	Substrate	Conditions, (time)	Product	Yield (% isolated)	*E/Z*
1		**A** (30 min)		78%	>20:1
2		**A** (240 min)		85%[a]	>20:1
3		**B** (30 min)		90%[a]	>20:1
4		**A** (10 min)		>95%	>20:1
5		**A** (60 min)		84%[a]	>20:1
6		**A** (30 min)		88%[a]	>20:1

[a] with 2 equiv $PhMe_2SiBpin$. Conditions **A:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ 1.25 equiv, [0.75 M] TPGS-750-M, 2 wt % in water, rt.
Conditions **B:** 1% $CuOAc/PPh_3$, $PhMe_2SiBpin$ 1.25 equiv, 5 equiv H_2O, neat, rt.

Table 3 (continued):

Entry	Substrate	Conditions, (time)	Product	Yield (% isolated)	*E/Z*
7		**A** (30 min)		84%[a]	>20:1
8		**A** (360 min)		>95%	>20:1
9		**A** (30 min)		70% (*E*) 12% (*Z*)	
10		**C** (60 min)		91%	1:17
11		**D** (60 min)		65%	>20:1
12		**E** (120 min)		85%	1:8

[a] with 2 equiv $PhMe_2SiBpin$. Conditions **A:** 1% CuOAc/PPh_3, $PhMe_2SiBpin$ (1.25 equiv), [0.75 M] TPGS-750-M, 2 wt % in water, rt.
Conditions **B:** 1% CuOAc/PPh_3, $PhMe_2SiBpin$ 1.25 equiv, 5 equiv H_2O, neat, rt.
Conditions **C:** 2 equiv $PhMe_2SiBpin$, "on water" [0.3 M], 2% Cu(I)OAc, 2% P(4-F-C_6H_4)$_3$. Conditions **D:** $PhMe_2SiBpin$ (1 equiv), substrate (2 equiv) [0.75 M] TPGS-750-M, 2 wt % in water, 2% Cu(I)OAc/P(4-F-C_6H_4)$_3$
Conditions **E:** 1.25 equiv. $PhMe_2SiBpin$, 0 ˚C, [0.75 M] 2 wt % TPGS-750-M, 1% Cu(I)OAc/BDP

As these reactions were conducted at near neutral conditions, we questioned whether we might be able to silylate an acetylenic acid, a substrate

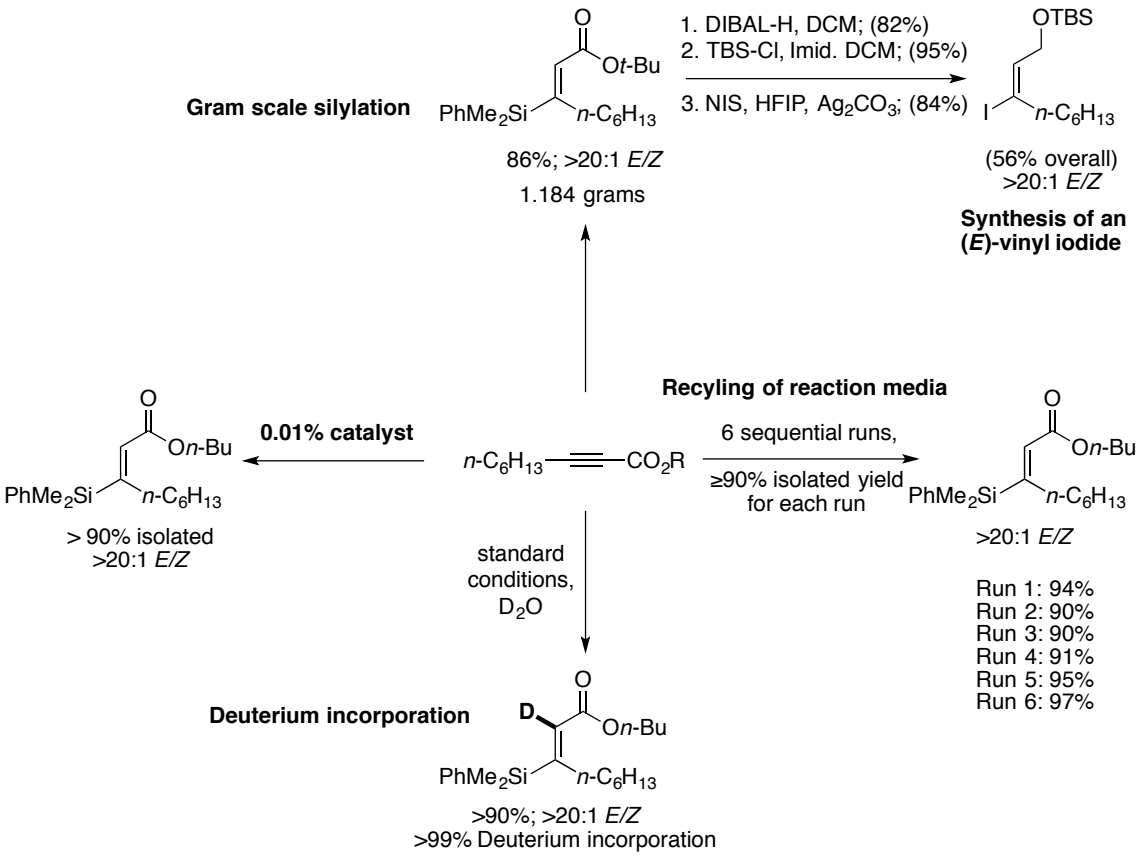
which would be precluded under basic conditions due to ionization of the acid. Subjecting an acid to the reaction conditions afforded the expected product in 84% yield and perfect (*E*)- selectivity, highlighting the beneficial effects of the neutral conditions employed (entry 7). In further examination of the scope of the transformation, we found that the reaction was not limited solely to carbonyl derivatives, where an acetylenic sulfone could be used to generate the expected product. (entry 8)

A substrate bearing a chiral imide auxillary was envisaged as an excellent test case as products of this type could be used in subsequent cycloaddition chemistry. Under the standard conditions 70% of the (*E*)-isomer was isolated along with 12% of the (*Z*)-isomer, both were easily separable by flash chromatography. The observation of the second (*Z*)-isomer here, not observed for the esters or amides, was ascribed to the higher withdrawing nature of the imide, lowering the energetic barrier of isomerization of the intermediate α-cuprio species to the O-Cu allenoate prior to proteoquenching.[1] We then turned our attention to examining ketones as substrates. A phenethyl ynone was tested under the standard conditions, however a disappointing 4:1 selectivity was observed. Further examination of the stereochemistry by NOESY revealed that in fact the (*Z*)-isomer was the major product. At this juncture the conditions were then reexamined to improve the stereoselectivity, and a combination of CuOAc/P(4-F-C_6H_4)$_3$ utilizing “on water” conditions allowed for an excellent 17:1 selectivity (entry 10). Slightly modified conditions were required for the isobutyl

ketone to be isolated in 8:1 selectivity (entry 12). Terminal ynone (entry 11) on the other hand was completely selective for the (*E*)-isomer, although it required an excess of substrate relative to reagent to improve the yield by mitigating competitive overaddition to the product.

Following the successful implementation of this method for a wide variety electron deficient alkynes, there were a number of other aspects of this chemistry we wished to address to further improve the utility as well as satisfying our own curiosity. Specifically; 1) The short reaction times for many of the substrates were indicative of a highly active catalyst, and further reductions in catalyst loading seemed to be not only possible but environmentally responsible by reducing metals in the waste stream. Thus we wished to ascertain the lower limit of catalyst required for this reaction. 2) TPGS and other surfactants offer the possibility of recycling of the aqueous reaction medium and catalysts for subsequent reactions following extraction of the product allowing for further reductions of the aqueous waste stream.[7a, b] Accordingly we wished to determine the upper limit of subsequent reactions that could be performed in a single solution of surfactant. 3) All the reactions conducted previously in this study were performed on scales of 0.1-0.4 mmol, but any truly useful methodology must be able to provide large quantities of product if necessary. Since the environmentally benign conditions involved in this chemistry realistically confer the most benefit on scale, we therefore wished to ascertain whether the chemistry could provide synthetically useful quantities of material for use in

Scheme 4: Further Applications of β-Silylations



multistep synthesis. 4) The α-proton in the products presumably come from proteoquenching of an intermediate copper species, therefore we wished to test to see if other electrophiles besides hydrogen could be incorporated at this position. Accordingly experiments were designed to address these concerns and the results are summarized in the following scheme.

Reaction with only 0.01 mol% (100 ppm) of Cu catalyst was successful, requiring eighteen hours for complete conversion, and a modest amount of extra precaution to seal the reaction mixture protecting it from atmospheric oxygen for the duration of the reaction. Likewise performing the reaction in TPGS dissolved

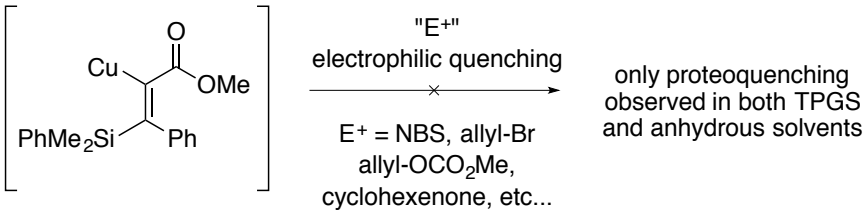
in deuterated water led to complete alpha deuterium incorporation, confirming that the proposed alpha copper species captures a proton from solvent to complete the reaction. Recycling of both the aqueous reaction media and catalyst was successful over six runs, with a simple in flask extraction, followed by addition of fresh substrate and silyl reagent with no decrease in yield or selectivity for each of the six cycles. By the sixth run the mixture became oversaturated with boron byproducts preventing adequate extraction and the mixture was filtered through silica to recover the product.

To address issues of scale and illustrate synthetic utility, performing silylation on 3.94 mmol of an ynoate afforded 1.184 grams of an (*E*)-β-silylenoate in 86% yield with the remainder of mass balance accounted for by unreacted starting material. Subsequent DIBAL-H reduction, and TBS protection proceeded in high yield, and this β-silyl allylic alcohol derivative was subjected to iododesilylation according to the Vilarrassa's[8] modification of Zakarian's[9] conditions, affording the desired vinyl iodide in 56% overall yield from the ynoate with complete retention of stereochemistry.

The inclusion of deuterium at the α-position implied that an intermediate α-Cu species is involved in quenching at this position. While quenching with Bpin from the reagent as initially proposed was unsuccessful, it still remained appealing to perform double functionalization by quenching with other electrophiles. This was examined with ynoates as substrates for several classes of electrophiles, in anhydrous solvent, yet only proteoquenching from

adventitious waster was observed. It still remains untested to see if the intermediate Cu species from reaction with ketones may be quenched with other electrophiles.

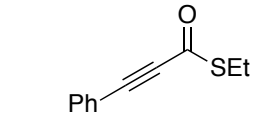
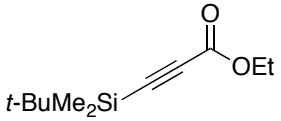
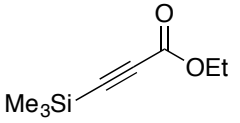
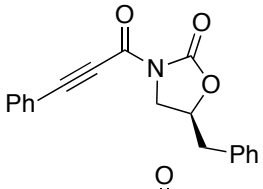
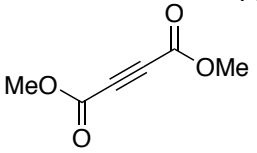
Scheme 5: Attempted Electrophilic Trapping



Although the reaction with most conjugated alkynes displayed remarkable breadth, several substrates tested were unsuccessful and the results are summarized below (Table 4).

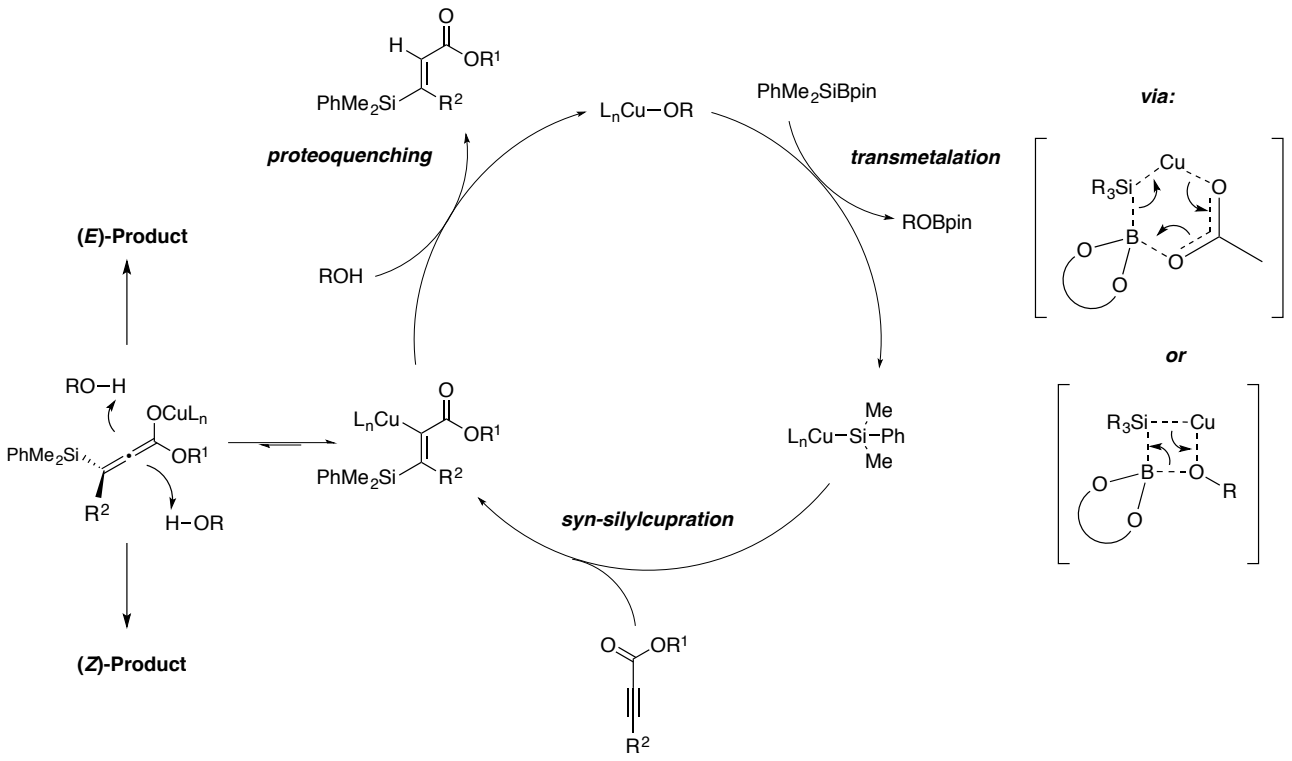
A few notes on validation of the reported stereo- and regioselectivity of the reaction are in order at this juncture. The β- selectivity for all products was confirmed by the presence of singlet's in the vinylic region of the ^{1}H-NMR spectrum for all compounds that possessed hydrogens at the allylic position, and then, by analogy for those without allylic hydrogens. The (*E*)-selectivity of the reaction was implicit in the formation of the lactone, and could also be confirmed by the *J*-coupling constants for compounds and derived from propiolate esters. Furthermore ^{1}H-^{1}H-NOESY spectra of several of the products showed the expected cross peaks indicative of (*E*) selectivity, and by analogy all the other esters were assigned (*E*)-stereochemistry. Additionally ^{1}H-^{1}H-NOESY spectra of the amides and other products were used to assign the reported stereochemistry.

Table 4: Unsuccessful Substrates

Unsuccessful substrates	Observations:
	Complex mixture HSEt addition compounds
	Complex mixture, decomposition
	Complex mixture, decomposition
	Substrate insoluble in TPGS
	Complex mixture of dimerization, double-addition, & oligomerization

Regarding the general mechanism for reactions with acetylenic esters a proposed mechanism is detailed below (Figure 2). In the proposed mechanism a ligated copper alkoxide undergoes transmetallation with Suginome's reagent to give a silyl-copper(I) species, which then undergoes *syn*-β-silylcupration with an acetylenic substrate giving an α-cuprio enoate. This species is subsequently proteoquenched regenerating the required copper alkoxide necessary for transmetalation and the cycle restarts. The high (*E*)-selectivity observed for acetylenic esters presumably is due to a high energetic barrier of isomerization to an O-Cu-allenoate, where proteoquenching from the two different faces of the

Figure 2: Proposed Mechanism For β-Silylcupration of Acetylenic Esters.



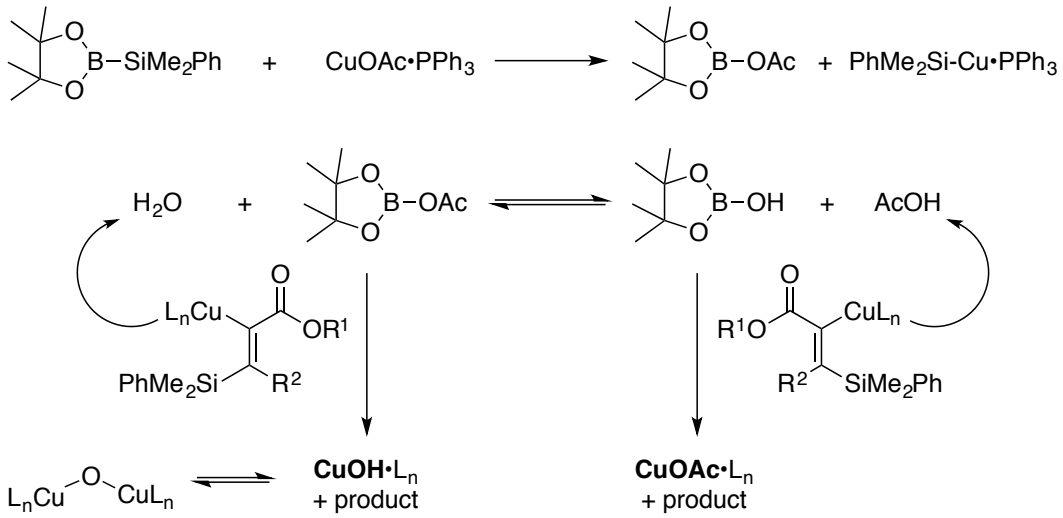
olefin either the (*E*)- or (*Z*)-product would be obtained.

Considering the transmetalation step, apparently the acetate is sufficiently basic enough to activate boron and sufficiently dissociable from copper to allow silicon to transmetalate. Transmetalation could be envisiaged to proceed *via* either a 6-centered transition state, or a 4-centered one, and both are shown here for reasons to be discussed below.

While the acetate likely facilitates the initial transmetallation, an acyloxyborate is produced, removing acetate from the catalytic cycle. Since the reaction is conducted in an excess of water, depending on the position of the equilibrium of the boron species present, proteoquenching of the intermediate

vinylcopper species would give a more basic copper hydroxide which is presumably in equilibrium with various ligated Cu_2O species, that is more poised to transmetalate in a 4-centered transition state. Therefore, it is possible that there are multiple copper species present in the reaction mixture, and the precise nature of the active catalyst/transmetalating species is not presently known.

Figure 3: Possible Speciation of Boron and Copper



Concurrent to the publication of this work, the group of Santos published their findings on a highly similar Cu-catalyzed β-silylation of similar substrates, mainly alkynyl aldehydes and esters.[10] However, it is interesting to note that they propose that the reaction is mediated by Cu(II) and not Cu(I) as we had indicated. While Santos' conditions do involve the use of a Cu(II) precatalyst, and open to atmosphere conditions, I view it as unlikely that Cu(II) is the actual nucleophilic source of silicon. Firstly, most, if not all nucleophilic Cu chemistry is

done with Cu(I), and Cu(II) salts when encountered, are often precatalysts that are reduced *in situ* to Cu(I) by the nucleophile, for instance in the case of Grignards.[11] The invoking of Cu(II) in Santos' conditions was justified on the grounds that Cu(II) salts were initially added to the reaction mixture, and the reaction was conducted open to air which could presumably oxidize any soluble Cu(I). The atmospheric conditions reported do not strictly imply though that any Cu(I) will be completely oxidized. As we demonstrated in our study, the reaction can be mediated by as little as 100 ppm of a Cu(I) salt, therefore traces of Cu(I) that are unoxidized may account for the reaction. Likewise in our optimization, we used the known air stable Cu(I) complex $CuF(PPh_3)_3$•2MeOH to avoid oxidation, and using Cu(II) acetate gives only trace coupling product within nine hours, compared to full conversion with Cu(I) acetate in less than ten minutes.

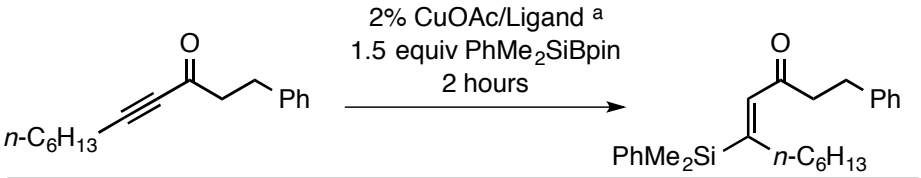
On the other hand Cu(I) salts have long been known to disproportionate in aqueous media to Cu^0 and Cu(II) rapidly.[12 a-c] Addition of coordinating ligands will disfavor this process and stabilize the +1 oxidation state, but the degree to which disproportionation is prevented depends on the nature of the counterion, solvent, and coordinating ligands.[13] Furthermore the precise mechanism by which Cu(II) would be reduced to Cu(I) under their conditions is not clear. Therefore, it remains possible that the reaction is mediated by Cu(II), or a mixture of oxidation states.

Understanding the factors governing the stereoselectivity for silylation of ynones required a number of experiments, before the optimized conditions

described earlier could be obtained. The model reaction on a ketone gave a disappointing 5:1 selectivity under standard conditions, with the (*Z*)-isomer being favored. This value could only be slightly elevated to 8.7:1 by running it in an ice bath, (Table 4, entries 1, 2). Addition of *t*-BuOH resulted in similar selectivity, whereas running it under neat conditions with ten equivalents of methanol gave diminished selectivity (entries 3, 4). Switching to "on water" conditions in which the reagents and catalyst were mixed in a biphasic system led to a surprising increase in selectivity to 15.9:1 (entry 5). This result implied that the overall polarity and extent of hydrogen bonding in the media was an important parameter for modulating selectivity. However, performing a similar reaction on water in the absence of PPh_3 diminished the selectivity back to 7.7:1 indicating that the overall level of hydrogen bonding was not the sole factor in determining the steroselectivity (entry 6).

Performing the reaction in a 1:1 mixture of nitromethane and water virtually erased any selectivity and a 1.5:1 ratio of isomers was obtained (entry 7). The addition of nitromethane reduces the extent of the hydrophobic effect by reducing the segregation of lipophilic and aqueous components while disrupting the network of hydrogen bonds near the lipophilic components. This could be interpreted to mean that a highly segregated solution in which the reaction takes part in the lipophilic organic microphase, the nonpolar character of which imparts

Table 4: Preliminary Optimization for Ynone Silylation

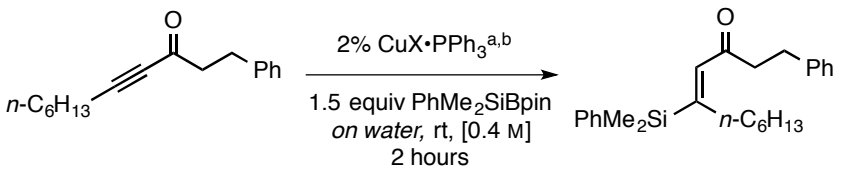


entry	Ligand (mol %)	additive	Temp.	Solvent	*Z/E* [b]
1	PPh_3 (2)	none	rt	2 wt % TPGS-750-M [0.75M]	5:1
2	PPh_3 (2)	none	**0 ˚C**	2 wt % TPGS-750-M [0.75M]	8.7:1
3	PPh_3 (2)	none	rt	**neat. 10 equiv MeOH**	3.8:1
4	PPh_3 (2)	**10 equiv *t*-BuOH**	rt	2 wt % TPGS-750-M [0.75M]	4.5:1
5	PPh_3 (2)	none	rt	**on H_2O [0.4M]**	15.9:1
6	**none**	none	rt	on H_2O [0.4M]	7.7
7	PPh_3 (2)	none	rt	**$MeNO_2/H_2O$ (1:1) [0.75M]**	1.5:1
8	**PPh_3 (4)**	none	rt	on H_2O [0.4M]	12.4:1
9	PPh_3 (2)	NaCl	**0 ˚C**	on sat. aq. NaCl [0.4M]	3.5:1

[a] Copper and ligand were first precomplexed in dry THF in the reaction vessel for 30-60 minutes, solvent was subsequently removed by blowing argon through the vial until there was no further change in mass, then water and reagents were added normally.
[b] reaction was worked up on silica gel and the *E/Z* ratio was determined by relative integrations of the alpha-vinyl protons in the crude NMR.

selectivity for “on water” conditions. Another interpretation is that by performing the reaction on water that the hydrophobic organization of lipophilic components near the water interface provides the correct orientation of reactants/intermediates required for proteoquenching with (*Z*)-selectivity. By running the reaction on a saturated solution of brine (entry 9), the segregation of

Table 5: Optimization of Copper Source and Counterion



entry	Cu source	*Z/E* [c]
1	**CuOAc**	**15.9:1**
2	CuOTf	12.5:1
3	CuCl	3.8:1
4	$CuF(PPh_3)_3$•2MeOH	5:1
5	CuCN	7.8:1
6	CuTC	9.2:1
7	**$Cu(SO_4)$•$2H_2O$**	**14:1**
8	$Cu(BF_4)_2$•x H_2O	7.8:1
9	$Cu(NO_3)_2$•2.5 H_2O	no rxn

[a] Copper and ligand were first precomplexed in dry THF in the reaction vessel for 30-60 minutes, solvent was subsequently removed by blowing argon through the vial until there was no further change in mass, then water and reagents were added normally.
[b] initial screening for esters revealed that Cu(II) is inactive under normal conditions. 2 equivalents of PPh_3 relative to copper were used for all Cu(II) salts to generate catalytically active Cu(I)
[c] reaction was worked up on silica gel and the *E/Z* ratio was determined by relative integrations of the alpha-vinyl protons in the crude NMR.

lipophilic molecules should be even more pronounced than on pure water, and if selectivity is derived from the reaction taking place in a highly nonpolar organic microphase, then a high selectivity should result. That only a 3.5:1 selectivity was observed indicated that this latter hypothesis is incorrect, and that the selectivity in the “on water” system comes largely from the organization of molecules at the interface, as NaCl will also disrupt the hydrogen bonding network there. With this insight, several copper salts possessing different

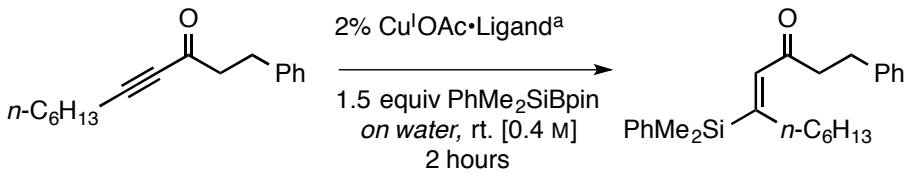
counterions capable of varying amounts of hydrogen bonding were subsequently tested (Table 5).

From this data, it becomes apparent that copper salts with hydrogen-bond donating counterions provided higher selectivity, (entries 1, 2, 6, 7) whereas counterions less capable of H-bonding (entries 3, 4, 5, 8) gave lower selectivity, with copper nitrate being the exception giving no reaction, presumably due to the oxidizing nature of the nitrate anion.

In the initial optimization it was additionally found that removing the ligand gave lower selectivity (Table 4, entries 5, 6) suggesting that coordination of copper also played a large role in determining the stereochemical outcome. Therefore, a small screen of phosphine ligands was undertaken so as to ascertain effects of ligand structure on stereochemistry as detailed in Table 6.

While PPh_3 gave product with and excellent 16:1 level of control, employing BDP as a cyclic analog diminished the selectivity by nearly half, indicating that a mono-coordinated copper species is desirable. By varying the electronics of the ligand, it was revealed that electron donating methoxy at the para- position diminished selectivity relative to PPh_3, and a withdrawing fluoro substituent increased the selectivity to between 10:1-18:1. While variability in the selectivity was noted in several of these runs the use of this ligand consistently gave higher selectivities than others. One interpretation of this result is that the more electron rich substituent helps to stabilize Cu at the α-position, slowing

Table 6: Optimization of Ligand

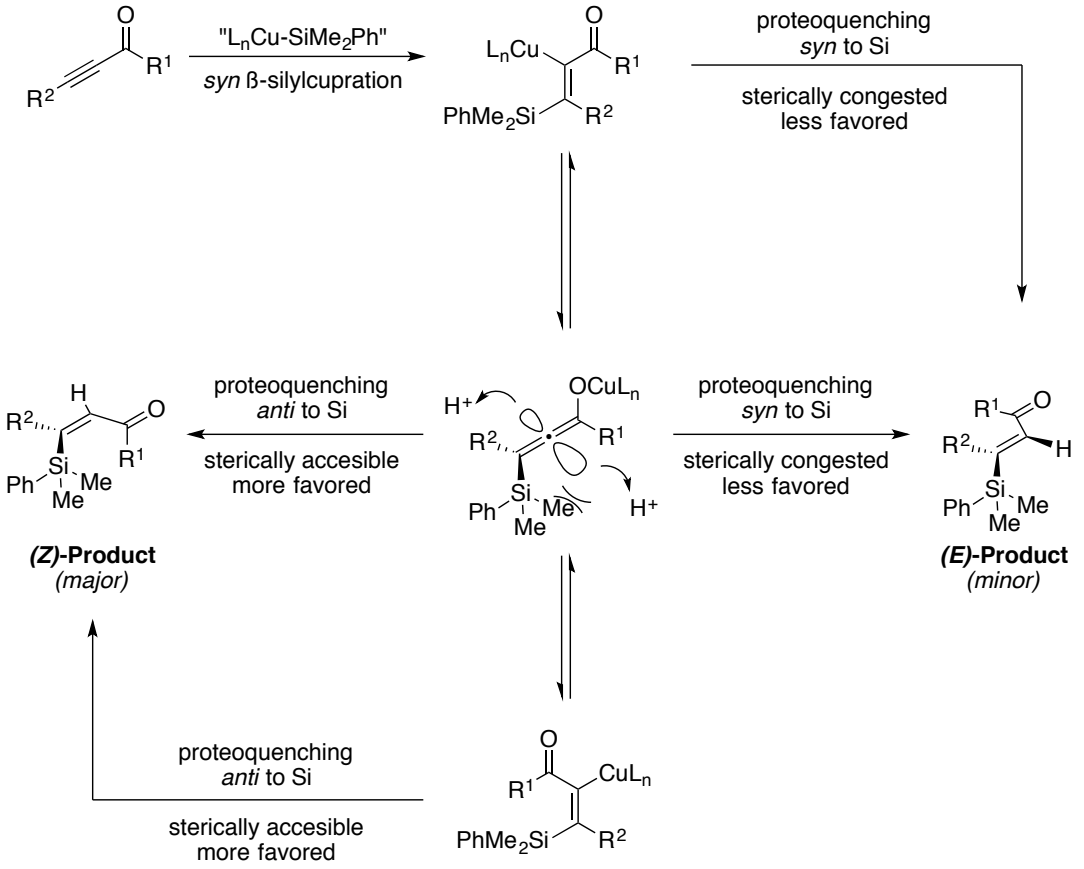


entry	Ligand	*Z/E* [b]
1	PPh_3	15.9:1 [c]
2	BDP	8.8:1
3	$P(C_6F_5)_3$	1:1
4	$P(4\text{-}MeOC_6H_4)_3$	5:1
5	**$P(4\text{-}F\text{-}C_6H_4)_3$**	**17:1** [d]
6	$P(4\text{-}F\text{-}C_6H_4)_3$	14:1 [e]

[a] Copper and ligand were first precomplexed in dry THF in the reaction vessel for 30-60 minutes, solvent was subsequently removed by blowing argon through the vial until there was no further change in mass, then water and reagents were added normally.
[b] reaction was worked up on silica gel and the *E/Z* ratio was determined by relative integrations of the alpha-vinyl protons in the crude NMR.
[c] Other runs of this reaction under identical conditions gave variable *E/Z* selectivities between 11:1-16:1
[d] Other runs of this reaction under identical conditions gave variable *E/Z* selectivities between 10:1-18:1 however the use of this ligand gave consistently higher selectivity than PPh_3
[e] Using 4 mol% ligand and 2 mol% $Cu(SO_4)_2 \cdot 2H_2O$

isomerization, and/or increasing the rate of proteoquenching from the initially formed α-Cu species. Switching the ligand to the pentafluorophenyl analog, although more electron deficient, also possesses a large cone angle of ca. 185˚ and gave product as a 1:1 mixture of stereoisomers. Further detailed studies on the how the Tolman parameters[14a-c] affect the selectivity were not undertaken and the results are only indicative of a general trend.

Figure 3: Mechanistic Rationale for (*Z*)-Selectivity with Alkynyl Ketones

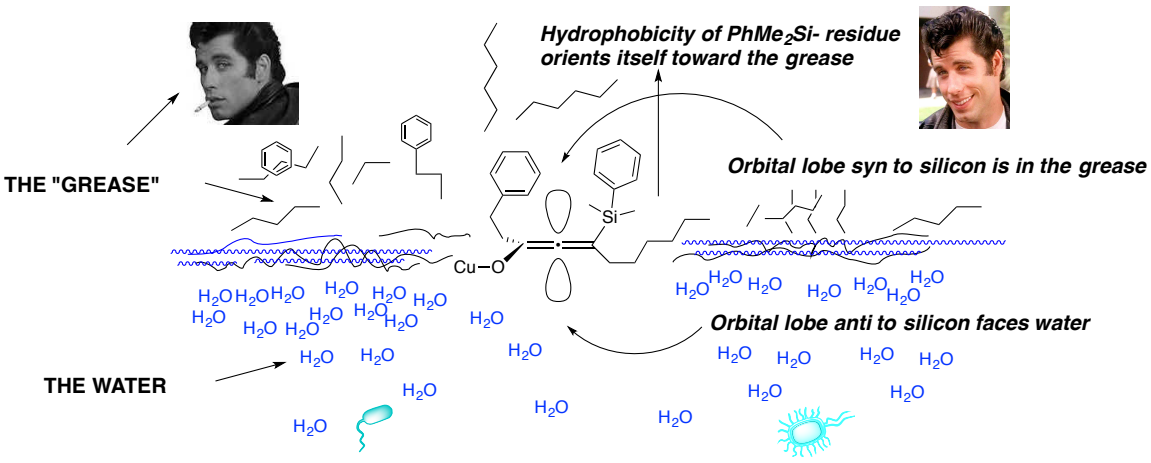


This switch in stereoselectivity for the ketones could be rationalized by considering that in contrast to other substrates that possess a high barrier of isomerization to the O-Cu-Allenoate, α-cuprio enones may preferentially exist in allenic form following insertion of the Si-Cu reagent across the alkyne. The allenic intermediate can proteoquench from either of the two faces of the central sp carbon, however, the high steric bulk of the $PhMe_2Si$- residue renders the necessary proton somewhat less accessible. Also plausible is that the allenoate intermediate re-isomerizes to the less congested (*Z*)-α-cuprio enone before proteoquenching to afford the (*Z*)-product. Presumably in the case of the

terminal ynone, the hydrogen atom is not a strong enough donor to stabilize the allene and undergoes no isomerization to the allene before proteoquenching

In fact the proposed allenyl intermediate actually helps to explain the higher selectivity for ketones utilizing “on water” conditions (Figure 4). If one considers not just the steric bulk of the $PhMe_2Si$- residue but also its attendant hydrophobicity, then when conducting the reaction in a biphasic system the O-Cu allenyl intermediate would likely orient itself such that the silyl residue faces away from the aqueous phase, while at the same time orienting the more sterically accessible lobe of the p-orbital towards the aqueous phase to allow proton capture affording the (*Z*)-isomer.

Figure 4: Hydrophobic Rationale for (*Z*)- Selectivity with Alkynyl Ketones



Conclusions & Outlook:

A highly selective copper catalyzed β-silylation of electron deficient alkynes was developed that allows access to isomerically pure (*E*)-β-silyl-carbonyl compounds.[15] The reaction takes place under environmentally responsible conditions in water at ambient temperatures, affords high yields of isomerically pure vinylsilane derivatives, and is compatible with a wide range of functionality. By taking advantage Suginome's reagent as a water stable source of nucleophilic silicon, reaction times are short, and low levels of catalyst are required. Additionally, recycling of both catalyst and reaction medium, possibilities for scale up, further derivatization, and reducing catalyst loading down to 100 ppm were demonstrated.

Crucially for me, our study highlighted that the main obstacle impeding further devolpment of organometallic chemistry in water is the ability of the pronucleophile to participate in transmetalation. Clearly if transmetalation occurs, the resulting copper species is nearly always of appreciable nucleophilicity to undergo subsequent chemistry, as seen in this study. As to be discussed subsequently in this dissertation, transmetalation of even simple alkyl groups from boron is actually quite difficult.

References

[1] Lipshutz, B. H.; Bošković, Z. V.; Aue, D. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10183.

[2] Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A. *J. Org. Chem.* **2011**, *76*, 4379.

[3] Iannazzo, L.; Molander, G. A.; *Eur. J. Org. Chem.* **2012**, 4923.

[4] Gulliver, D. J.; Levason, W.; Webster, M., *Inorg. Chim. Acta,* **1981**, *52*, 153.

[5] Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292.

[6] This lactonization was also observed in the analogous Cu-catalyzed addition of arylboronic acids to ynoates. See: Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Comm.* **2008**, 2010.

[7] (a) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1261. (b) Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack, E. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 10952.

[8] Sidera, M.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2011**, *13*, 4934.

[9] Ilardi, E. A.; C. E. Stivala, E.; Zakarian, A. *Org. Lett.* **2008,** *10*, 1727.

[10] Calderone, J. A.; Santos, W. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 4154.

[11] Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339.

[12] For selected recent examples see: a) Solari, E.; Latronico, M.; Blech, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35,* 4526; b) Berg, R.; Straub, B. F. *Beilstein J. Org. Chem.* **2013**, *9,* 2715; c) Cheng, B.; Yi, H.; He, C.; Liu, C.; Lei, A. *Organometallics* **2015**, *34*, 206.

[13] Tsarevsky, N. V.; Braunecker, W. A.; Matyjaszewski, K. *J. Organomet. Chem.* **2007**, *692,* 3212.

[14] (a) Chadwick A. Tolman, *Chem. Rev*. **1977**, *77*, 313; (b) Tolman, C. A.; Seidel, W. C.; Gosser, L. W. *J. Am. Chem. Soc.* **1974**, *96,* 53; (c) Chadwick A. Tolman. *J. Am. Chem. Soc.* **1970**, *92,* 2956.

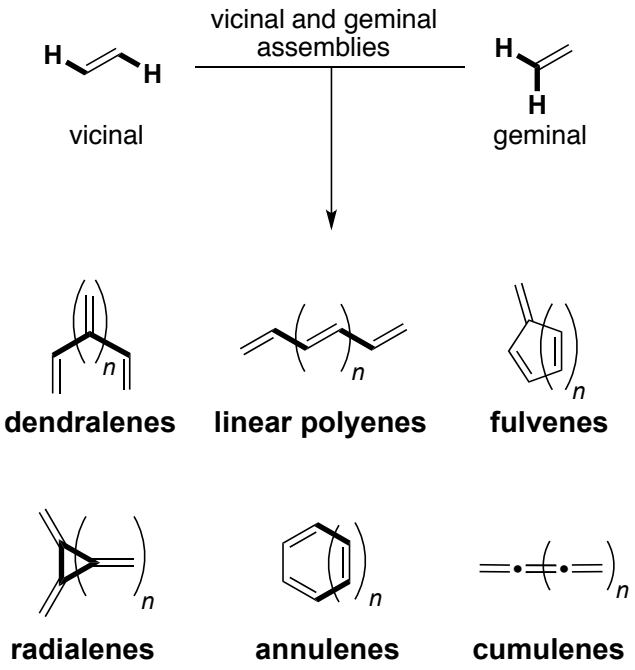
[15] Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4159.

C) Palladium-Catalyzed Synthesis of 1,3-Butadienes and [3]-[6] Dendralenes

General Introduction and Overview of 1,3-Butadiene, and Dendralene Chemistry

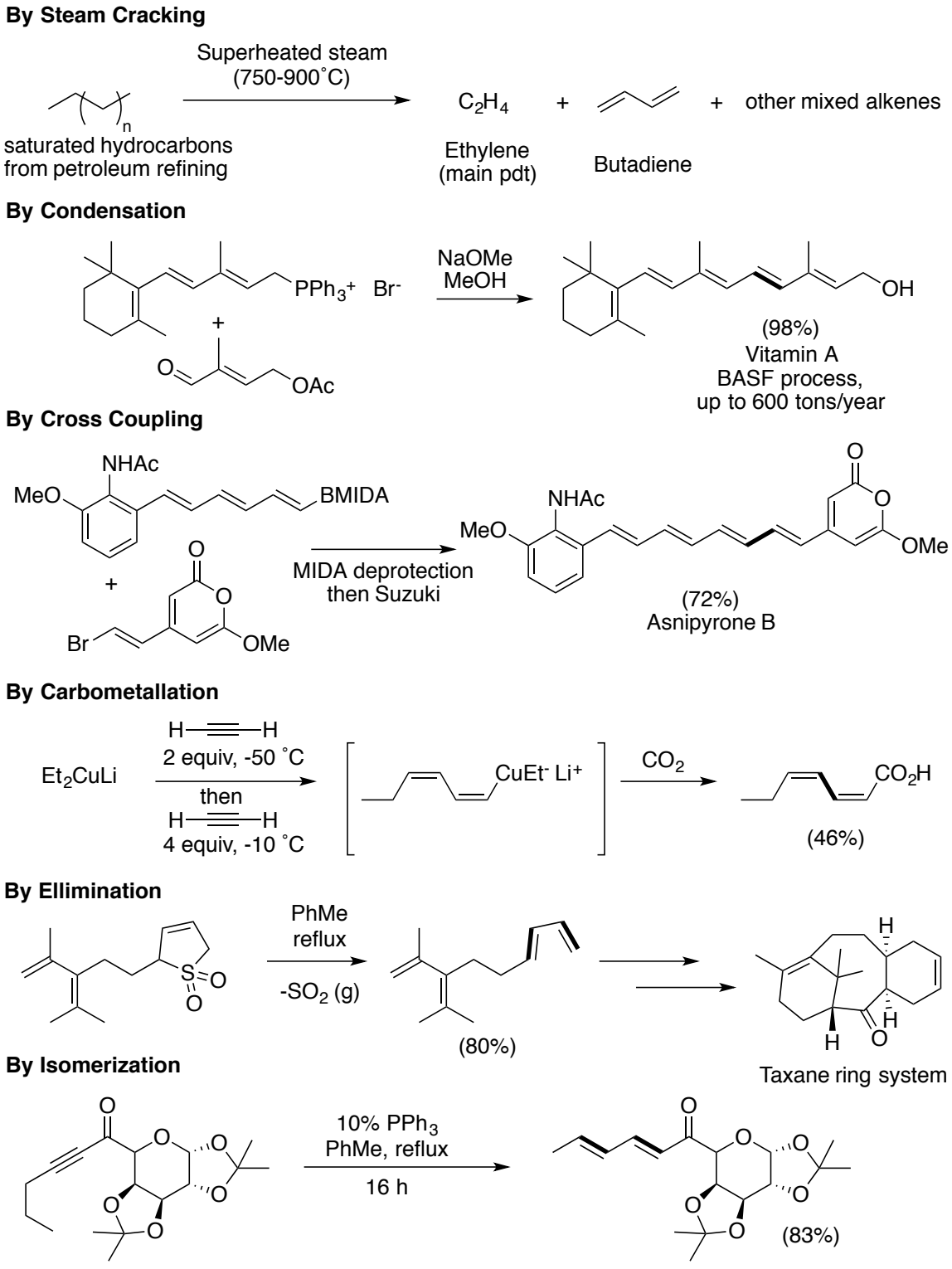
Linear conjugated alkenes are one of the fundamental classes of unsaturated hydrocarbons which are comprised from the various possible assemblies of ethylene units (Figure 1). 1,3-Butadiene is the simplest member of this class, and was first produced in small quantities by pyrolysis in 1863,[1] and its structure was identified a few years later in 1886.[2] Subsequent research on the polymerization of butadiene led to the discovery and refinement of the production of synthetic rubbers, helping in part to birth modern materials chemistry. Butadiene is now a commodity chemical produced annually in megaton quantities industrially as a byproduct of ethylene production.[3] In synthetic chemistry, 1,3-butadienes are almost universally recognized as versatile reagents for the Diels-Alder cycloaddition,[4] but react in many other valuable transformations.[5a-e] The higher linear homologs of ethylene, are found throughout nature acting as pigments, antibiotics, and chromophores, while many unnatural polyenes are encountered as conductive polymers.[6a-d] Owing to their numerous uses and properties, it should come as unsurprising that there exist a large number of synthetic methods to produce both 1,3-butadienes and the higher polyenes that control the peripheral substitution, as well as the number of ethylene units in their make-up.[7a-f]

Figure 1: Classes of Unsaturated Hydrocarbons Derived from Ethylene Units



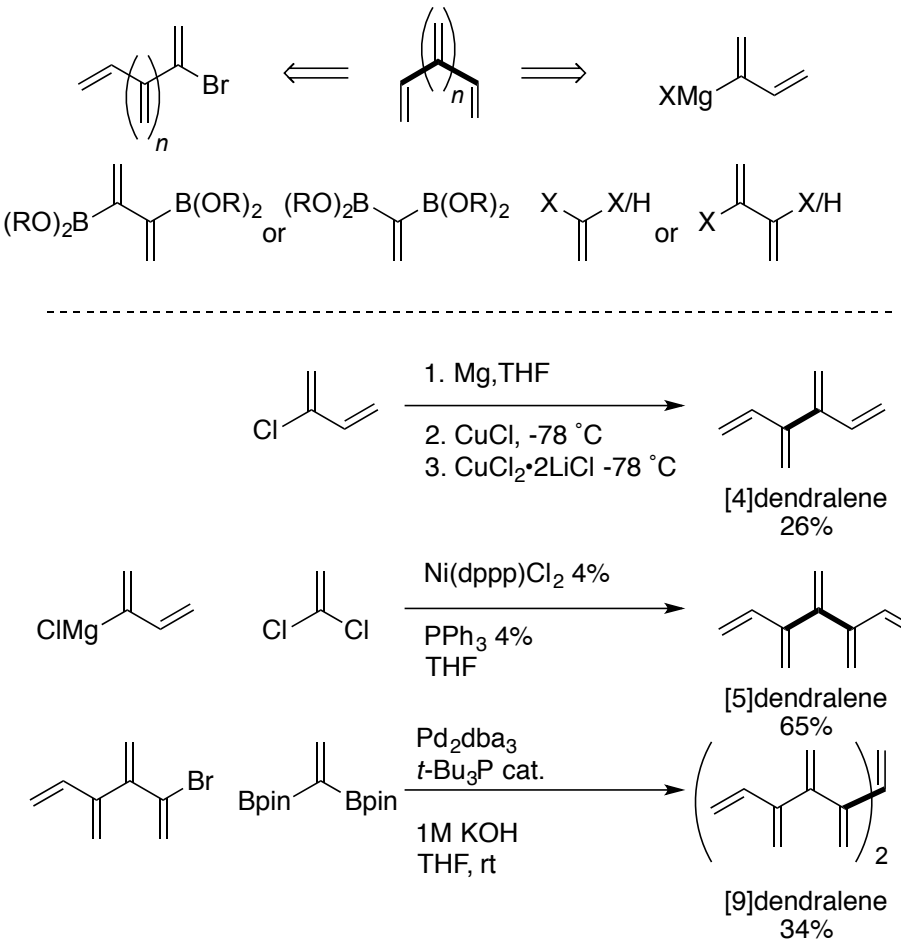
The literature regarding the synthesis of functionalized 1,3-butadienes and the higher linear polyenes is vast, and an exhaustive overview of methods for their preparation is well beyond the scope of the present discussion. Therefore, to better place the research of this dissertation in context, examples illustrative of a broader *class* of reactions that form 1,3-dienes or linear polyenes are shown and discussed above (Figure 2), where transformations that further append functionality to the polyenes are intentionally left out

Figure 2: General Methods For Synthesis of 1,3-Butadienes and Linear Polyenes



By contrast, the dendralenes, which are derived from repeated geminal assembly of ethylene units, are less frequently encountered in nature, and hence, less studied. For a period of time the dendralenes were molecules of curiosity, and while their synthesis had been accomplished in small quantities through pyrrolytic methods, the consensus was that they were too unstable to be prepared in both a useful quantity and time frame.[8] The early work of Hopf, [9a-d] and recently Sherburn[10a-c] has in large measure began to rectify this misconception, and allowed for impressive advances in the field, with homologs up to a [12]dendralene now synthesized,[11] and successful implementation of dendralenes as lynchpins in natural product synthesis.[12 a, b] Notwithstanding these achievements, a majority of the research on dendralenes has been directed towards identifying conditions that can afford the "parent" (e.g. unsubstituted) cases of these compounds. Insofar as their synthetic use is concerned, nearly all of the research has centered around their applications in diene-transmissive-Diels-Alder (DTDA) reactions. Methods that access unsymmetrical and substituted dendralene frameworks would offer even greater possibilities for structural diversity and elaboration, while similarly, other methods that regioselectively functionalize one of the olefinic centers would be of great value.

Figure 3: Sherburn's General Route to Dendralenes



References:

[1] Caventou, E. *Justus Liebigs Annalen der Chemie.* **1863**, *127*, 93.

[2] Armstrong, H. E.; Miller, A. K. *J. Chem. Soc.* **1886**, *49*, 74.

[3] Stevens, M. P. *Polymer Chemistry*; Oxford University Press: New York, **1990**.

[4] Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley: New York, **1990**.

[5] a) Nguyen, K. D.; Herkommer, D.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 14210; b) Wu, J. Y.; Stanzl, B. N. *J. Am. Chem. Soc.* **2010**, *132*, 13216; c) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 7577; d) Takao, K.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K. *J. Org. Chem.* **2004**, *69*, 8795; e) Saha, B.; RajanBabu, T. V. *Org. Lett.* **2006**, *8*, 4657.

[6] a) DellaGreca, M.; Marino, C. D.; Zarrelli, A.; D'Abrosca, B. *J. Nat. Prod*. **2004**, *67*, 1492; b) Hopf, H.; Kretschmer, O.; Naarman, H. *Angew. Chem***. 1989,** *101*, 1785; c) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.*, **1987**, *109*, 2821; d) Smith, J. H. C. *J. Am. Chem. Soc.* **1936**, *58*, 247.

[7] a) Morrow, N. L. *Env. Health. Persp.* **1990**, *86*, 7; b) Pommer, H.; Thieme, P. C. *Top. Cure Chem.* **1983,** *109,* 165; c) Woerly, E. M.; Roy, J.; Burke, M. D. *Nature Chem.* **2014**, *6*, 484; d) Furber, M.; Taylor, R. J. K.; Burford, S. C. *J.*

Chem. Soc. Perkin Trans. I **1986**, 1809; e) Winkler. J.; Houk, K. *J. Org. Chem.* **1997**, *62*, 2957; f) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.

[8] Sherburn, M. S. *Acc. Chem. Res.* **2015**, *48*, 1961.

[9] a) Hopf, H. *Angew. Chem., Int. Ed.* **1984**, *23*, 948; b) Hopf, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 705; c) Lehrich, F.; Hopf, H.; Grunenberg, J. *Eur. J. Org. Chem*. **2011**, 2705; d) Hopf, H.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298.

[10] a) Saglam, M. F.; Alborzi, A. R.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem*. **2016**, *81*, 1461; b) Payne, A. D.; Bojase, G.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4836; c) Payne, A. D.; Willis, A. C.; Sherburn, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12188.

[11] Saglam, M. F.; Fallon, T.; Paddon-Row, M. N.; Sherburn, M. S.; *J. Am. Chem. Soc.* **2016**, *138*, 1022.

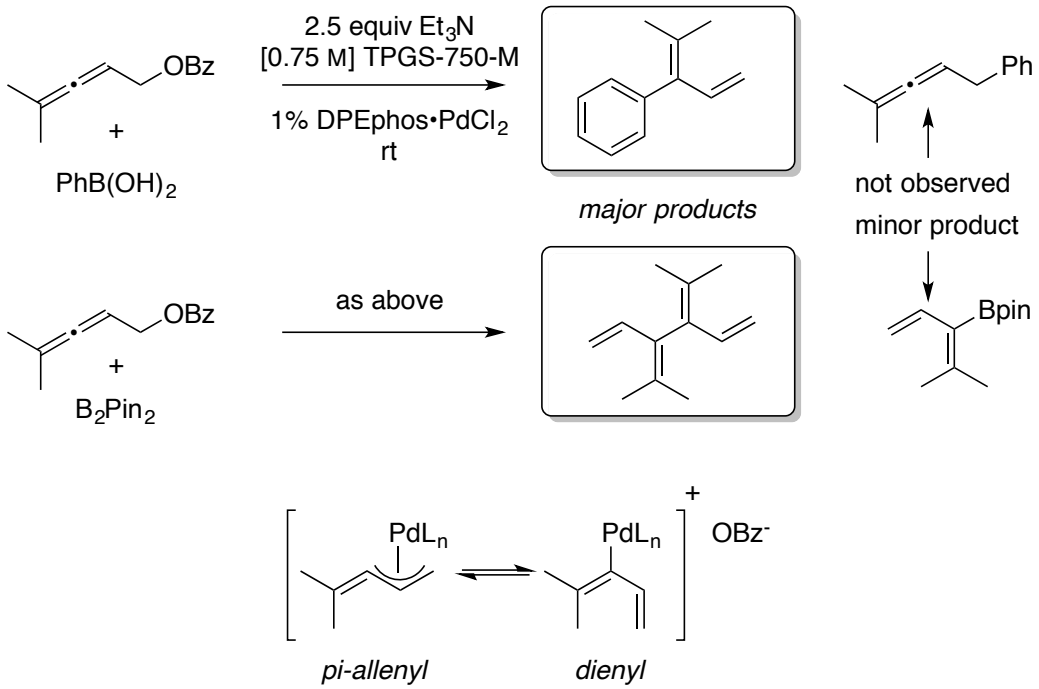
[12] a) Newton, C. G.; Drew, S. L.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N. Sherburn, M. S.; *Nat. Chem.* **2015**, *7*, 82; b) Lu, H-H; Pronin, S. V.; Antonova-Koch, Y.; Meister, S.; Winzeler, E. A.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 7268.

Synthesis of 1,3 Butadienes, and [3]-[6]Dendralenes Pd Catalyzed Reactions of Allenoates:

At the start of this project, my colleague Daniel J. Lippincott had become interested in the synthesis of allenes, and had been preparing allenic benzoates for use in Pd cross couplings in our aqueous surfactant platform. Initially the goal was to use these allenic substrates analogously to our group's previously published method of using allylic ethers in Suzuki-Miyaura couplings, in which it was anticipated that an allenyl appendage would be installed. However, it was quickly found that instead of the allene, 2-aryl-butadienes were produced instead. This process had, in fact, been described in an earlier report by Suzuki,[1] albeit under substantially harsher conditions. Using a diboron reagent in place of an aryl-boron coupling partner, only some of the expected 2-boryl-butadiene was produced, and a homocoupled product was produced as the major product, resulting from a second coupling of the initially formed boryl species with a second allenoate (Figure 1).

While Dan was highly disappointed with these results, I was actually very excited. The product was clearly a [4]dendralene, and only recently had I become aware of both their existence and the rather limited number of methods to prepare them. The only major routes to access dendralenes on preparative scale relied on large excess of organometallics reagents, low temperatures and were low yielding. Consequentially, the production of a [4]dendralene under the mild conditions of micellar catalysis seemed quite remarkable!

Figure 1: Initial Discovery of Pd-Catalyzed Couplings to Form Dienes and Dendralenes

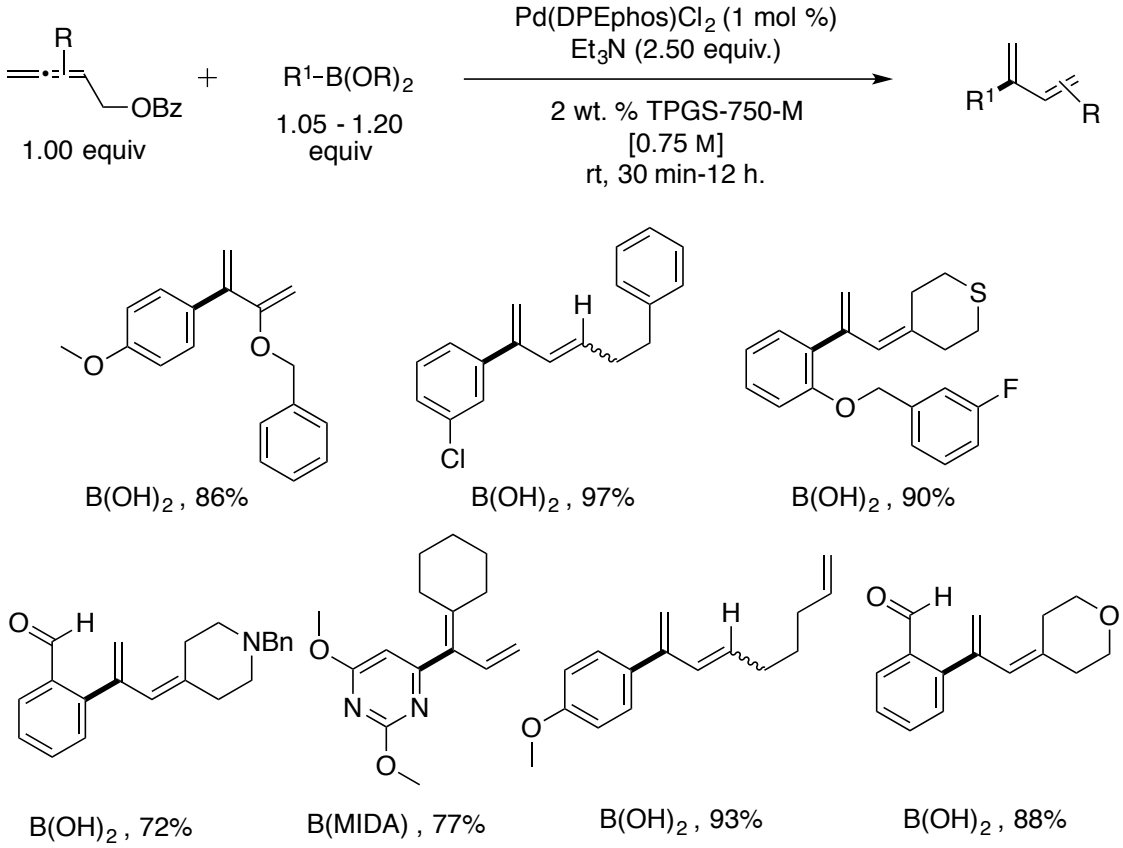


Once I had finished yelling this all over the lab, I managed to sit Dan down and argue persuasively that the allene product he initially wanted was old hat, and that synthesizing dendralenes was instead a much more interesting line of research. Thus, from a series of serendipitous observations, two new research projects were borne: leveraging micellar catalysis to improve Suzuki's method for preparing 2-substituted-1,3-butadienes, and using allenoates as an electrophilic diene synthon to construct dendralenes.

In fact, very little optimization was required to arrive at a final set of conditions for the preparation of the 2-substituted 1,3-butadienes. The reaction was so rapid at room temperature, that upon addition of the allenoate to the

reaction mixture a substantial amount of heat was evolved, an observation suggestive of the much higher reactivity of palladium pi-allenyl systems relative to the more commonly encountered pi-allyl. It was only a short time sooner that Dan was reporting that nearly every variety of aryl-boron coupling partners was successful. Indeed the reaction appeared to be a substantial improvement over Suzuki's existing method: 1% of Pd catalyst, ambient temperatures, aqueous reaction media, short (10-60 min) reaction times, and near stochoimetric levels (usually 1.00-1.05 equiv) of boron coupling partner were required. Several examples prepared by Dan are summarized below (Figure 2).

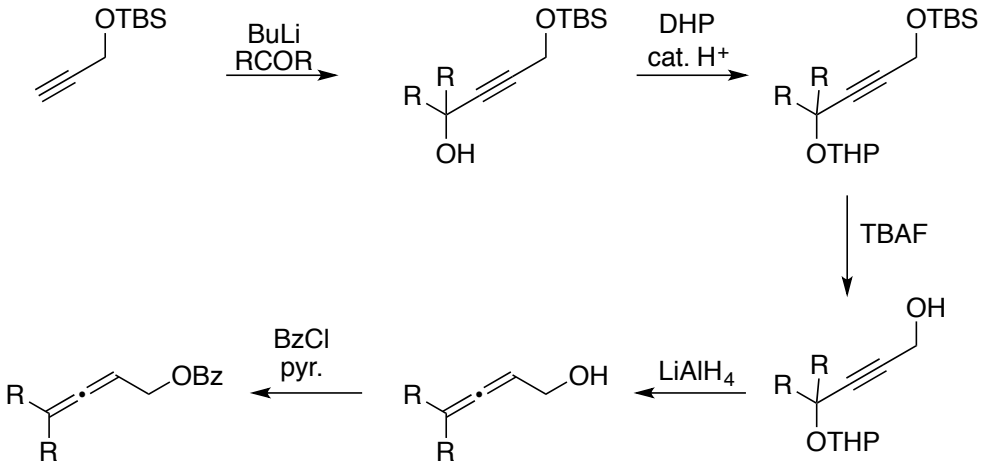
Figure 2: Selected Examples of Couplings with Allenoates



While apparently a successful method, in discussions with Dan, he had explained to me that it was difficult to ascertain the true level of functional group tolerance for this method from the various combinations of boron reagents and allenyl substrates on hand. It is true that the syntheses of allenes, are not difficult *per se*, they are, in fact, high yielding methods, but they can be relatively time consuming. Usually their synthesis requires between 3-6 manipulations from commercial materials to arrive at the desired product. Our preferred method relied on preparing an appropriate bis-propargyl alcohol derivative, and hydride displacement to form the allene, followed by conversion to the benzoate (Scheme 1). To incorporate more sensitive functionality on the allene such as ketones, amides, and other moieties that can interfere with Pd coupling chemistry or potentially give rise to side reactions, an additional set of functional group manipulations would be required, lengthening the synthesis by an additional 2-4 steps. While a valuable exercise in perfecting synthetic technique, it was also viewed as wasteful in some respects, and thus a more efficient means of evaluating the functional group tolerance was devised.

Glorius had described a method in which the functional group compatibility of a method was ascertained by performing a model reaction first without, and then in, the presence of various additives.[2] GC analysis of the final mixtures provides information on the amounts of product, reagents, and additive molecules. This data can then be used to infer if certain functionality is tolerated in the reaction, based on the functionality in the additive. Amount of additive remaining relative

Scheme 1: General Route to Allenic Substrates

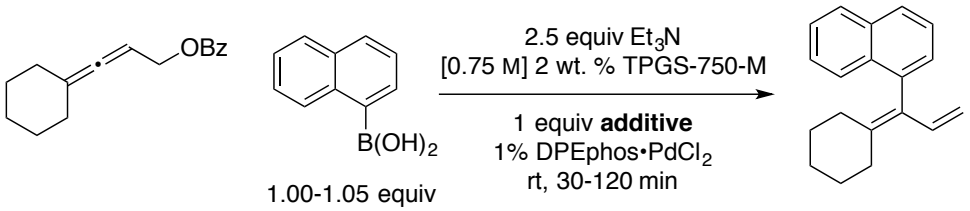


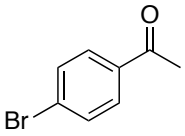
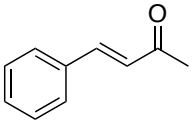
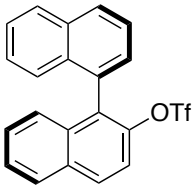
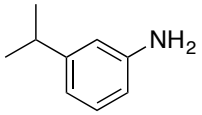
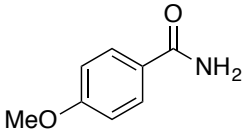
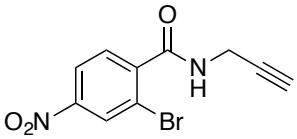
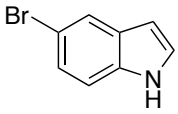
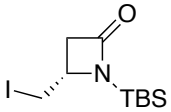
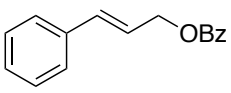
to a standard, and amounts of product and starting material relative to the amounts in the model reaction, can then be used to infer whether the functionality has a neutral, positive, or inhibitory effect on the reaction.

This type of additive-based testing seemed the best method to determine the true functional group tolerance of our reaction; additives containing different functionality that would otherwise require lengthly syntheses to install on the allenyl substrates could simply be added as small molecules on hand from the chemical inventory. Since column chromatography of the resulting 2-aryl-butadienes was usually trivial, I decided the best course of action was to simply avoid the hassle of a quantitative GC screen, and simply isolate both the product and additive by chromatography at the end of the reaction instead.

This screen was conducted upon reacting a simple allenoate with 1-naphthylboronic acid under the standard conditions for coupling (TPGS, Et_3N, $DPEphosPdCl_2$). Repeating the reaction again each time with one equivalent of

Table 1: Functional Group Compatibility Screening



Entry	Additive:	Additive (% recovered)	Product (% isolated)
1	*none*	----------	87%
2		91%	83%
3		91%	88%
4		95%	87%
5		89%	91%
6		95%	87%
7		69%	83%
8		93%	94%
9		86%	90%
10		88%	86%

an additive relative to the allenoate and isolation of product and additive gave the results that are summarized in Table 1.

The reaction appears to be tolerant of a wide range of functionality, with ketones, amides, and heteroaromatic substrates all tolerated and were recovered efficiently along with product nearly quantitatively. Particularly notable are the results from additives possessing a TBS β-lactam and an aliphatic iodide as well as an unsaturated ketone. The recovery of a cinnamyl benzoate with concurrent formation of the expected diene, demonstrates that the rates of reactivity of allylic systems and allenic systems with the Pd catalytic system differ largely. If the allenoate is excluded in this case, the expected pi-allyl coupling product is observed with complete conversion within 4-6 hours. Therefore the both the high rate of substitution and near stoichiometric levels of coupling partners contribute to the excellent selectivity observed in this case.

Use of OBBD borinates in couplings to form 2-alkyl 1,3 butadienes

For some time, I had become interested in performing alkyl-couplings in our aqueous surfactant platform. Alkyl couplings with organometallic reagents such as organolithiums or Grignards are commonly encountered in organic solvent, yet these reagents are for obvious reasons inaccessible in our aqueous chemistry. Their highly basic/reactive nature, and strict conditions for handling can be a disadvantage synthetically with regards to functional group tolerance and convenience of experimental set up. On the other hand, their highly reactive nature though is a distinct advantage with regards to rates of transmetallation, which is far slower with boron or tin reagents.[3a, b]

It was not obvious to me that there should be significant obstacles to performing valuable transition metal couplings that normally involve alkyl organometallics, such as carbocupration,[4] in our surfactant system. After all, as our research on β-silylcupration had shown, if the nucleophile could be transmetalated to Cu, from a water stable boron reagent, the resulting metal species should presumably react efficiently with the substrate within the micellar core.[5a, b] Therefore, if the appropriate boron reagent was available to deliver the group to the desired transition metal, many valuable sp^3 couplings should become possible under the mild, and green conditions of micellar catalysis.

A variety of alkyl-boron reagents were screened for a number of Pd and Cu catalyzed reactions under our aqueous conditions, however the use of

alkylboronic acids and their esters were inactive for attempted Cu catalyzed Michael additions, carbocuprations, or Pd catalyzed allylic couplings or Suzuki Miyaura couplings. Additionally varying the esters of the alkylboronic acids to various 5-, 6-, and 7-membered rings in an attempt to reduce the steric hindrance near the boron center were unable to produce any significant amount of coupling product. Switching to charged "ate" complexes such as BF_3K salts[6] or the triol-boronates[7] were similarly ineffective. Since transmetalation with B_2Pin_2 or $PhMe_2SiBpin$ can occur easily as a result of the weak character of the B-Si or B-B bond, and transmetalation of various arylboronic acids/esters is unproblematic, a different approach to facilitating transmetalation was needed. Research has shown that 9-BBN derivatives are effective coupling partners in Suzuki-Miyaura cross couplings,[8] and other reactions,[9] where the higher Lewis acidity of the trialkylborane relative to boronic esters is apparently sufficient to promote transmetalation and achieve subsequent coupling.

Considering 9-BBN derivates as alkyl coupling reagents, they possess a number of advantages and disadvantages. Among their attributes are their highly chemo and regioselective method of introduction, which proceeds with high selectivity for terminal olefins. The primary disadvantage to using 9-BBN derivatives as coupling agents is that since they are trialkyl boranes, they are pyrophoric in contact with oxygen, and may act as radical initiators.[10] These properties do not affect their water stability and they may be used under nominally aqueous or biphasic conditions; however, these properties usually

prevent their isolation and storage so that they are nearly always produced and used *in situ*. Another unfortunate downside to their use as coupling partners is the large amount of organic waste produced resulting from the borinic acid byproduct of transmetalation, where boronic acids give only the salts of boric acid. Interestingly, the use of *borinates* of intermediate reactivity between boranes and boronic acids, has been little explored in metal-catalyzed cross couplings.[11a, b] Therefore, it was hypothesized that by using alkylborinates, as coupling partners, the "sweet spot" between reactivity and oxidative stability might be found that would allow for both effective sp^3 coupling, and both isolation and storage of the reagent.

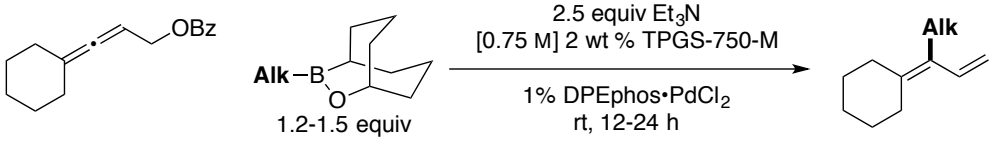
In fact, the group of Soderquist had previously reported the selective monooxidation of 9-BBN derivatives, accomplished with tertiary amine N-oxides to 9-oxa-10-borabicyclo-[3.3.2]decanes (OBBD's).[12] These new borinates are now possessed of sufficient oxidative stability to be handled in air for brief periods of time, permitting their isolation and storage in neat form. Furthermore their reduced Lewis acidity allows for formally only one equivalent of base required for coupling with these OBBDs, as the borinate and its corresponding byproduct of transmetallation do not appreciably absorb hydroxide from the reaction media to form an "ate" complex whereas the 9-BBN boranes require two.[13] These OBBD derivatives, therefore, seemed ideal candidates, for sp^3 couplings, and a batch was made for further testing.

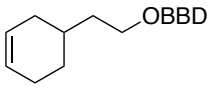
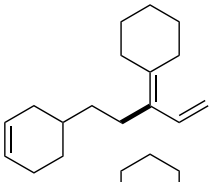
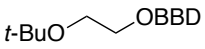
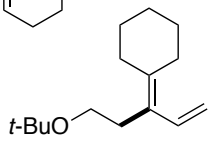
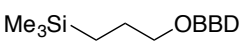
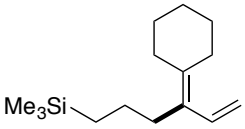
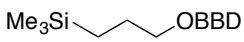
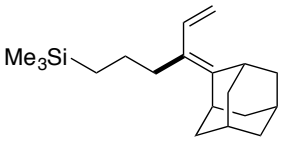
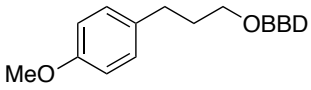
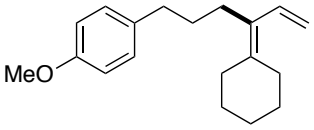
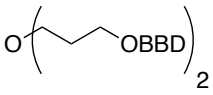
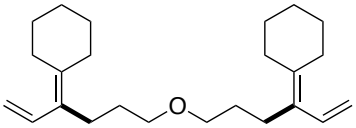
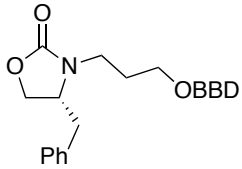
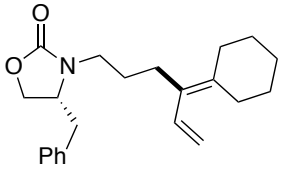
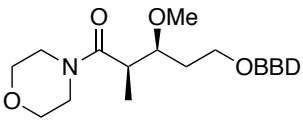
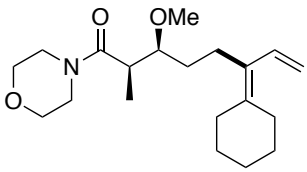
Indeed, subjecting a model OBBD borinate to aqueous Suzuki Miyaura coupling conditions with an aryl iodide afforded the expected coupling product in 70% yield. It was rather fortuitous at the time of this result that Dan had alerted me that alkylboronic acids performed poorly in the couplings with allenoates and consequentially I tested the OBBD derivatives in the diene coupling. Gratifyingly, the OBBD reagent was able to afford the expected alkyl coupling product in 54% yield, although a longer reaction time of 12 hours was required for complete conversion. Accordingly, several different OBBD derivatives were prepared and tested in the diene coupling. As the results in Table 2 indicate, the reaction was successful for several different OBBDs.

An OBBD derived from *t*-butyl vinyl ether was able to react within 48 hours, the longer reaction time presumably a consequence of greater steric hindrance near the boron center. While simple OBBDs gave products in moderate yields (entries 1-3), in switching to a heavier adamantyl derivative product could be isolated in 87% yield (entry 4), suggesting that in the previous examples, low yield was attributed to product volatility and losses on high-vacuum. Even a bis-borinate was able to react in the presence of excess allenoate (entry 6), affording the expected product of a double coupling. As stated earlier, one of the advantages of using the OBBD borinates, is that being derived directly from 9-BBN hydroboration, they take advantage of the high regio- and chemoselectivity associated with 9-BBN hydroboration, but can be isolated and stored neat for periods of time for use in subsequent coupling. To illustrate

this educts possessing both carbonyl functionality and asymmetric centers were subjected to 9-BBN hydroboration, followed by monooxidation to the OBBDs, which were isolated, and then tested in the coupling with dienes. A chiral oxazolidinone was prepared by allylation, then hydroboration/monooxidation and was coupled smoothly to afford the expected product in 93% yield (entry 7). To prepare a more involved substrate, more representative of applications in natural products synthesis, the use of an asymmetric aldol derived product seemed attractive. Particularly, I was interested to try Roush's recent method for preparing syn-aldol adducts, from an IPC-borane reductive aldol reaction.[14] Therefore, both fresh morpholino acrylamide, as well as $(^{\prime}\text{Ipc})_2\text{BH}$ were prepared, and then subjected to Roush's conditions. Using acrolein as the aldehyde afforded a diatereomericaly pure *syn*-aldol adduct bearing a terminal olefin, where subsequent methyl protection of the alcohol proceeded cleanly in 70% yield. Finally, hydroboration and monooxidation to the OBBD with NMO afforded the desired borinate coupling partner in nearly quantitative yield. Subjecting this aldol derived borinate to the coupling conditions, gave, as expected, the desired product in an acceptable 77% yield, with no erosion of the diastereomeric purity as evidenced by NMR (Scheme 2).

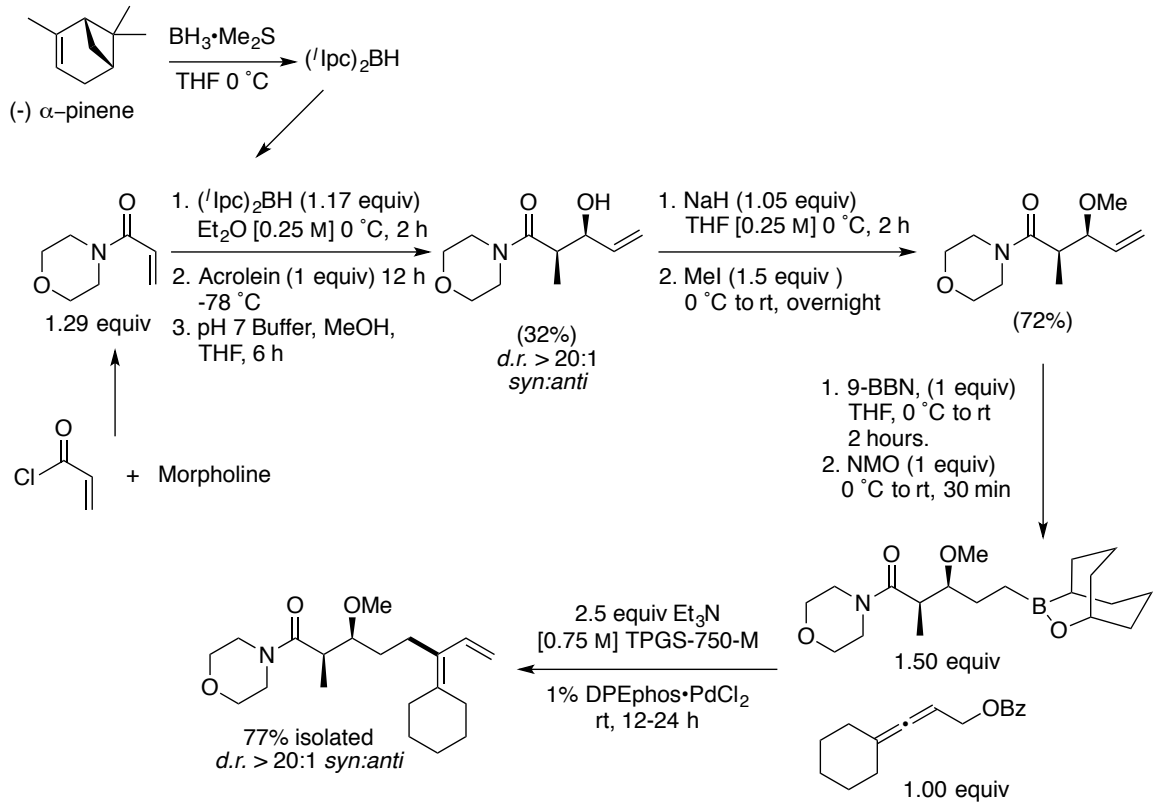
Table 2: Scope of Alkyl-OBBD Couplings With a Model Allenoate



Entry:	OBBD Borinate	Product	Yield (% isolated)
1			54%
2			64%[a]
3			65%
4			87%
5			94%
6			43%
7			93%
8			77%

All reactions conducted on a scale of 0.2-0.5 mmol, under Argon atmosphere and monitored by TLC. Reported yields are of pure material isolated by chromatography. [a] reaction time of 48 h

Scheme 2: Synthesis and Reaction of a Functionalized OBBD Coupling Partner With a Model Allenoate



While the present work was conducted primarily to expand the scope of nucleophiles accessible in coupling reactions to form dienes, this work is suggestive of a more generally applicable use of stable borinates to solve the problems associated with highly valuable sp^3 couplings in micellar media. Coupled with improved air stability, isolability, and established chemo- and regioselective methods for their introduction, I believe that these reagents will find further applications in the development of synthetic methods. In comparing the present method with existing methods for 1,3 diene synthesis, the present method offers the advantage of being conducted under both mild and aqueous

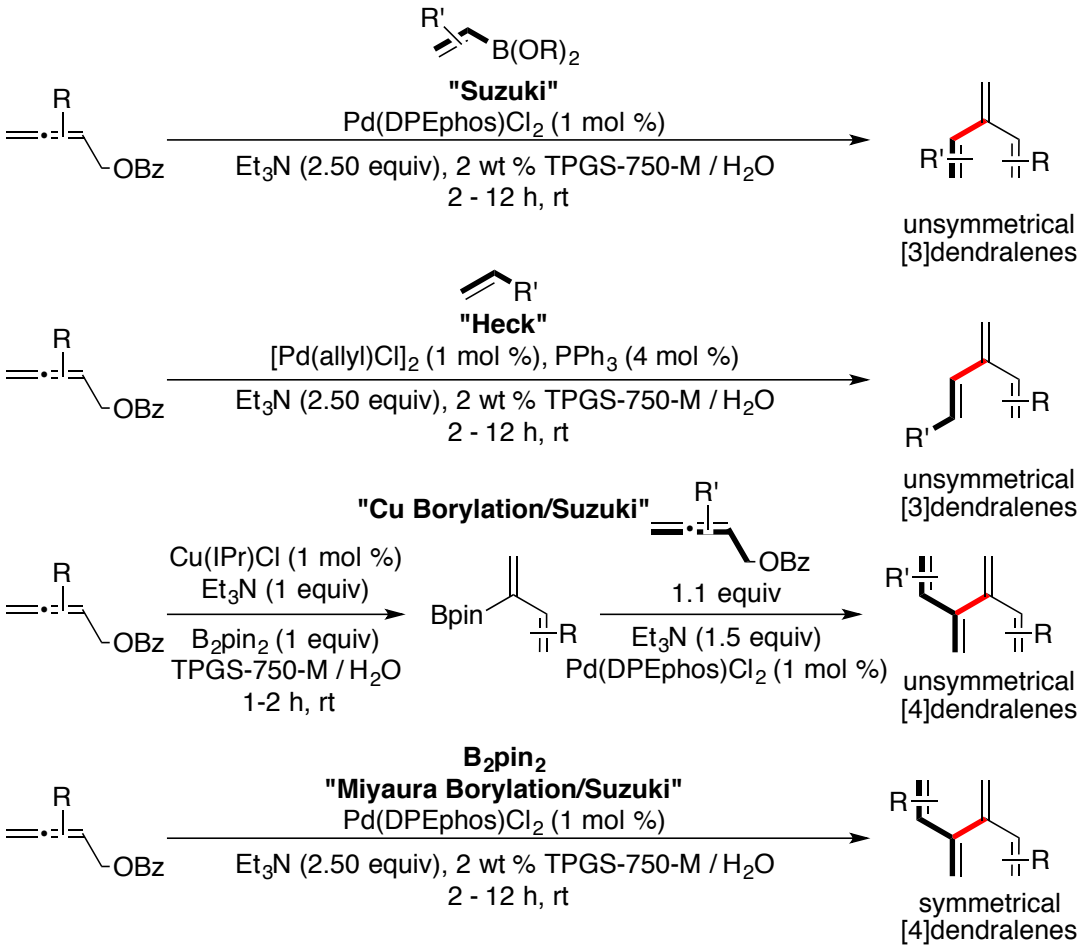
conditions at ambient temperatures. It also may provide for alternate bond disconnections when forming butadienes as it sets the diene while concurrently installing the 2-substituent which may require additional steps by existing methodology.

Synthesis of Vinyl-Allenoates and Applications to the Synthesis of [3]-[6]Dendralenes

Concurrently to my work in developing a robustness screen for the diene coupling and developing OBBD reagents for sp^3 couplings with allenoates, Dan had been pressing forward with the use of allenoates as electrophillic diene synthons. Importantly, he had developed four different methods to access [3]-[4]dendralenes: Suzuki-Miyaura coupling with vinylboron reagents afforded [3]dendralenes, Cu catalyzed borylation of an allenoate afforded a 2-boryl-butadiene which could be cross coupled in a second Suzuki Coupling with a second allenoate to form unsymmetrical [4] dendralenes, Pd-catalyzed borylation and subsequent homocoupling afforded symmetrical [4]dendralenes, and using the allenoate in combination with an activated olefin with catalytic Pd gave a Heck-type reaction to arrive at unsymmetrical [3]dendralenes. (Scheme 3) with selected examples highlighted in Figure 3.

The success of 1) the use of allenoates to form [3]-[4]dendralenes and 2) the use of OBBD coupling partners to effect a sp^3-sp^2 coupling to form 2-alkylbutadiene systems raised interesting questions as to how to expand on this chemistry to access the higher [5]-[6] dendritic oligomers and how to use the OBBD borinates to affect an sp^3-sp^2 coupling that would result in an alkylated dendralene. In considering that the previously employed allenyl benzoates were

Scheme 3: Methods to Access [3]-[4] Dendralenes From a Common Allenoate



functioning primarily as an electrophilic diene synthon, it was envisaged that by employing an analogous *vinyl allenoate*, an electrophilic [3]dendralene synthon would result (Figures 4, 5). Therefore, it was hypothesized that by employing the previously developed conditions for construction of dienes and [3]-[4]dendralenes, the use of a vinyl allenoate could provide for additional routes to: 1) alkyl substituted [3]dendralenes by employing the recently developed OBBD borinates, 2) differentially substituted [4] and [5]dendralenes by employing

borylated vinyl or dienyl species, 3) access to symmetrical [6]dendralenes by borylation and subsequent homocoupling.

Figure 3: Selected Examples of Dendralenes Prepared From Allenoates

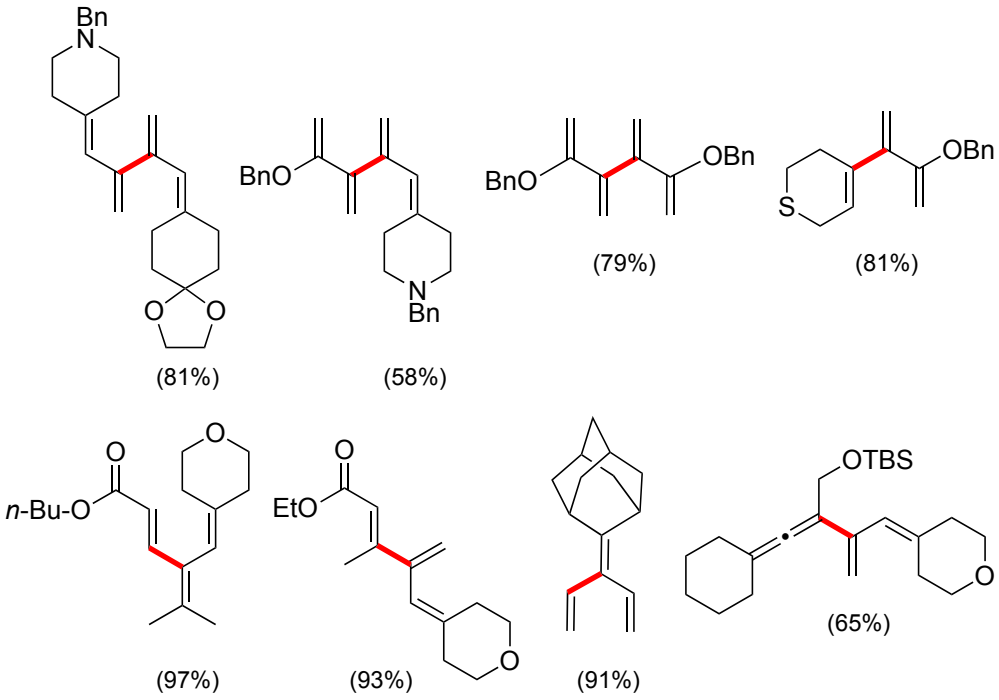


Figure 4: Simple, vs. Vinyl-Allenoate

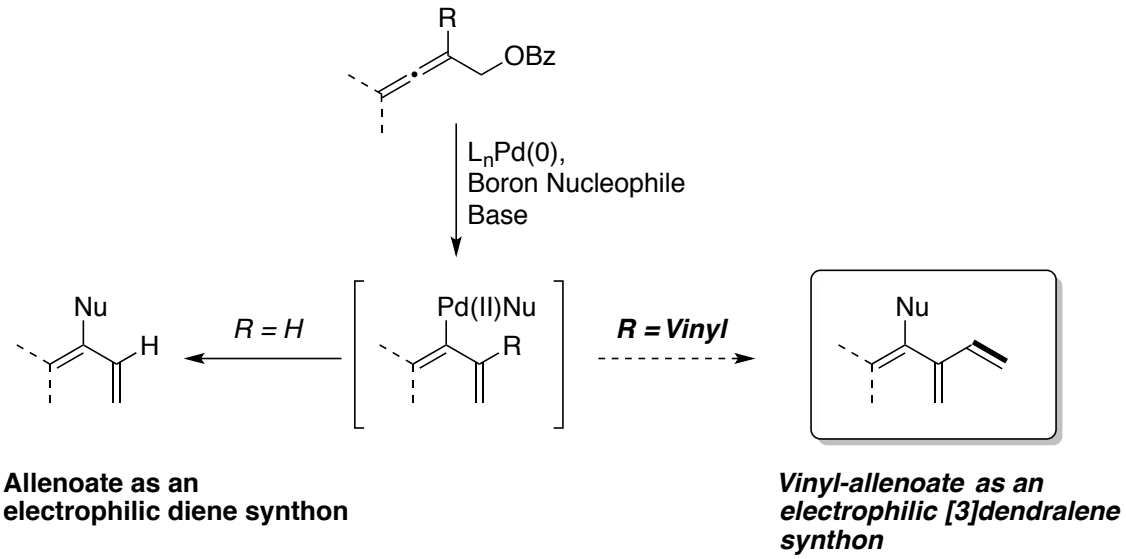
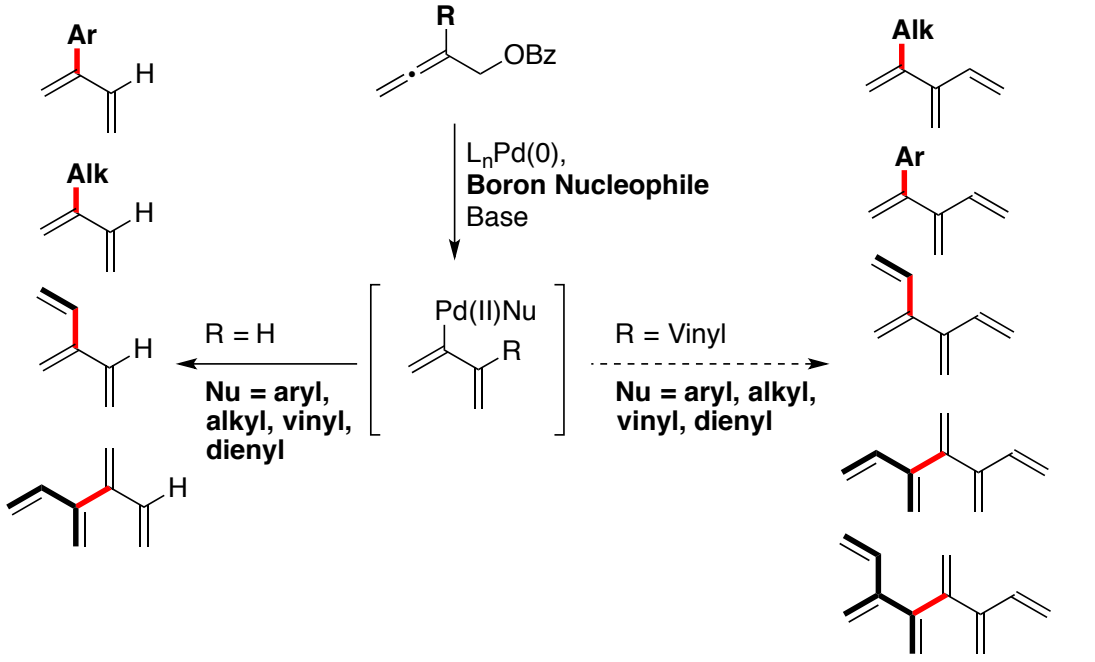


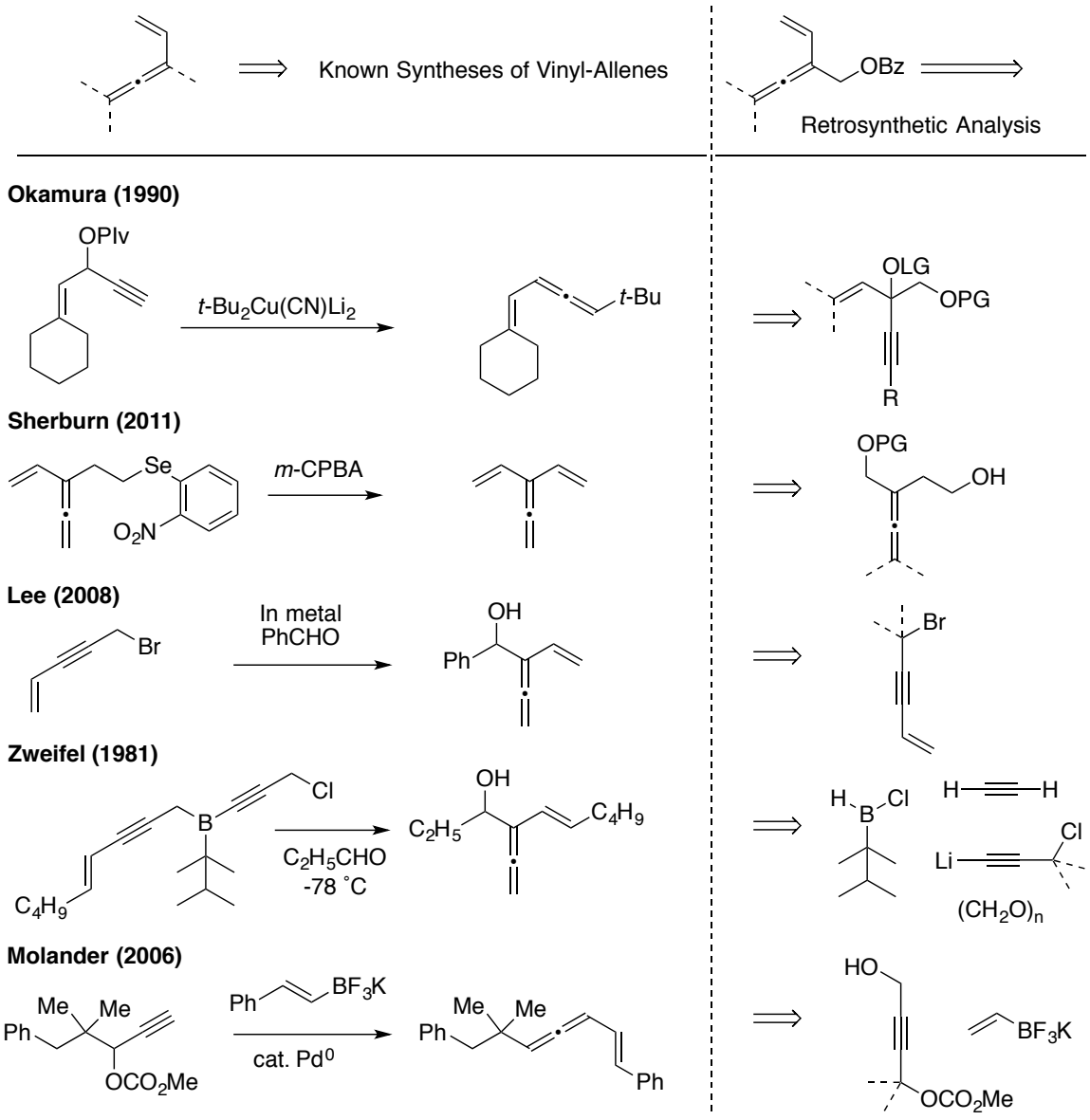
Figure 5: Products Obtained With a Standard Allenoate, vs. a Vinyl Allenoate



This hypothesis provided a substantial incentive to develop a synthetic route to a vinylallenyl benzoate, and therefore a search of the chemical literature was undertaken to assess viable routes to access such a scaffold, as well as to gain information regarding factors governing the stability of such species to better inform synthetic design. A desirable route would be able to accommodate substitution at a variety of positions, to reduce potential Diels-Alder side reactions of the vinylallenoate, and/or the resulting [3]dendralene formed from it's coupling. Routes that provide entry to vinylallenes, and particularly, vinylallenols are summarized in figure 6, as well as application of retrosynthetic analysis to assess applications to our desired target molecule.

As illustrated, there are a number of syntheses of vinyl allenes.[15 a-e] Okamura's route was attractive in that it used robust cuprate chemistry, however, retrosynthetic analysis showed that it would require preparation of a tertiary leaving group that was both propargylic and allylic, which could give undesired [1,3] sigmatropic shifts of the leaving group, and could potentially have competitive allylic/propargylic substitution if the ends of the olefin were uncapped. Additionally, when the ends of the olefin were capped, their study showed that the allylic hydrogens could engage in an undesired [1,5] hydride shift to form conjugated trienes. Sherburn's route relied on elimination of a selenoxide, although other elimination procedures could be potentially be performed. This route would require selective protection of one of two primary alcohols, and

Figure 6: Known Syntheses of Vinyl Allenes, and Retrosynthetic Analysis



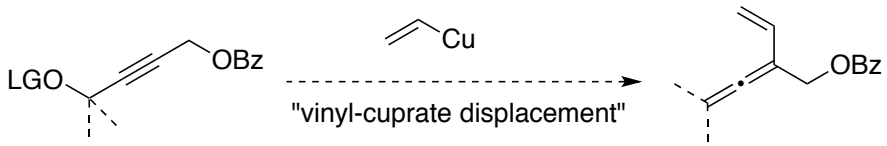
accommodating disubstitution at the end of the allene would require a gem-dibromocyclopropanation of the requisite tetrasubstituted olefin.

Lee's route seemed tenable, although again the main problem was the inability to accommodate substitution at the ends of the allene, and would require preparation of a tertiary propargylic bromide. Likewise, Zweifel's synthesis provides a route to the desired vinylallenols, but again, accommodating capping substituents at the ends of the allene would be impossible with this method as the the intermediate allenylborane would be unlikely to migrate to the required tertiary propargylic position upon warming. Finally, Molander's route involving cross coupling seemed within the realm of possibility, however vinyl allenols were not prepared by this method. Research from our group had shown that both allylic ethers and alcohols[16] could participate in pi-allyl Pd couplings. Considering our early observations that coupling with allenoates was rapid and quantitative, even accompanied in some cases with an exotherm, the higher reactivity of a vinyl-allenol or even as a protected ether, was viewed as a disadvantage as it could potentially lead to an undesired dendralene. All of the aforementioned syntheses required in excess of five steps, with the exception of Zweifel's route.

In light of these concerns, and in an effort to improve the step economy of the synthesis, a different approach to arriving at vinylallenoates was envisaged. If a vinylcuprate displacement[17] on a bis-propargylic substrate could be achieved, the desired vinylallenoate could be prepared in as few as 2-3 steps (Scheme 4). Furthermore, it was not known whether capping groups would be required at the end of the allene to improve stability; if they could be avoided then a wider variety of vinylallenoates could be prepared. Accordingly, initial tests involving cuprate

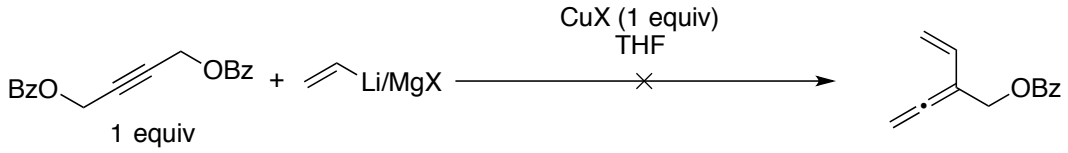
chemistry were performed on the bis-benzoate of 2-butyne-1,4-diol, a route that could potentially access the desired molecule in 2 synthetic operations!

Scheme 4: Proposed Synthesis of Vinyl-Allenoate



Accordingly the bis-benzoate was prepared without much fanfare and subjected to displacement under a variety of conditions (Table 3). As illustrated, in going from less reactive Cu species ($RCu{\cdot}MgX_2$) all the way to higher order cyanocuprates ($R_2Cu(CN)Li_2$), afforded none of the desired coupling product, the majority of cases giving back recovered starting material, and varying amounts of the mono-and diols upon workup. As most reactions were conducted at -78 ˚C with gradual warming to ambient temperature, it appears the cuprates primarily decomposed before the reaction could take place. Clearly although potentially a very effective two step route, the substrate would need to be modified with a more active leaving group to achieve displacement.

Table 3: Failure of Cuprates to Form Vinyl-Allenoates with Bis-Benzoates



Experimantal Conditions:	Organocopper Reagent
1) RMgX (1 equiv) added to CuI (1 equiv) @ -30 ˚C, stir 5 min, cool -78 ˚C, + 1 equiv. BF_3•Et_2O, stir 30 min, add to substrate @ -78 ˚C, gradually warm to rt.	**$RCu{\cdot}BF_3$**
2) RMgX (1 equiv) added to CuCl (1 equiv) @ -30 ˚C, then cannula into substrate @ -78 ˚C, warm gradually to rt.	**$RCu{\cdot}MgX_2$**
3) RMgX (1 equiv.) added to CuI•PPh_3 (1 equiv) @ -30 ˚C, stir for 2 hours then cannula into substrate @ -78 ˚C, warm gradually to rt.	**$RCu{\cdot}PPh_3$**
4) RMgX (1 equiv) added to CuCl•LiI (1 equiv) @ -30 ˚C, then cannula into substrate @ -78 ˚C, warm gradually to rt.	**RCu•LiX**
5) RMgX (1 equiv) added to CuCN•2LiCl (1 equiv) @ -78 ˚C, warm to rt 5 minutes, cool back to -78 ˚C, then add substrate as a THF solution @ -78 ˚C, warm gradually to rt.	**$[RCuCN]^-MgX^+$**
6) RMgX (1 equiv) added to CuCN (1 equiv) @ -78 ˚C, add solution of 2-thienyl lithium (1 equiv), warm to rt briefly until clear, cool back to -78 ˚C then add substrate as a THF solution @ -78 ˚C, warm gradually to rt.	**$[RCu(2\text{-thienyl})CN]^{2-}\ LiMgX^{2+}$**
7) RLi (1 equiv) added to CuCN (1 equiv) @ -40˚, stir until homogeneous (1-2 hours) cool -78˚, add 1 equiv. of BF_3•Et_2O, stir 30 min. add substrate, gradually warm to rt.	**$[RCuCN]^-\ Li^+{\cdot}BF_3$**
8) RLi (2 equiv) added to CuCN (1 equiv) @ -78˚, then graduall warm until homogeneous, recool to -78˚, add substrate @ -78˚C, warm gradually to rt.	**$[R_2CuCN]^{2-}\ 2\ Li^+$**
9) RLi (1 equiv) added to $[(2\text{-thienyl})CuCN]^-\ Li^+$ (1 equiv) @ -78˚, warm gradually to rt for a few minutes, then recool to -78˚, add substrate then gradually warm to rt.	**$[RCu(2\text{-thienyl})CN]^{2-}\ 2\ Li^+$**

Scheme 5: Preparation of Monochloride/mesylate Substrates

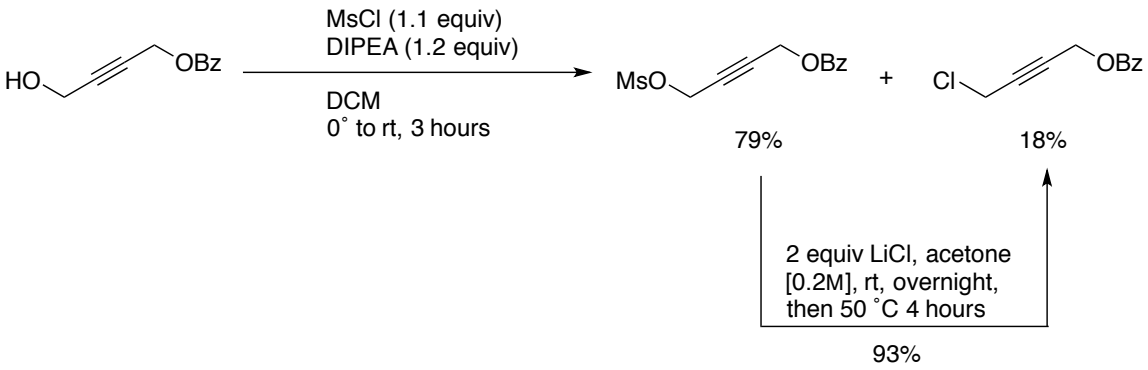
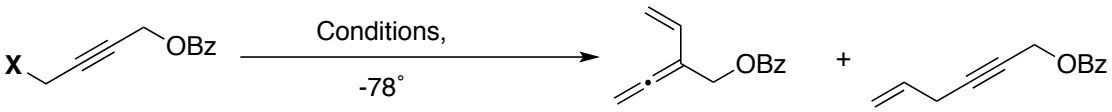


Table 4: Further Screening of Vinylcuprates to Form Vinylallenoates



X	Cu Source	M	Solvent	% product (S_N2':S_N2)	Notes
Cl	CuCN 1 equiv	Li 2 equiv	THF	nd, S_N2 only	with higher order cuprate $[R_2CuCN]^{2-}\bullet 2\ Li^+$
Cl	CuCN 1 equiv	Li 1 equiv	THF	no product	with lower order cuprate $[RCuCN]^-\bullet Li^+$
Cl	[(2-Thienyl)CuCN]$^-$ Li^+ 1 equiv	Li 1 equiv	THF	32%, S_N2' only	with mixed higher order cuprate $[RCu(2\text{-thienyl})CN]^{2-}\bullet 2\ Li^+$
OMs	CuCN•2LiCl 1 equiv	MgCl 1 equiv	THF	20% (1:3)	slower than with Cl as LG
OMs	CuCN•2LiCl 1 equiv	MgCl 1 equiv	Et_2O	40-50% (1:1)	Et_2O improves regioselectivity
Cl	CuCN•2LiCl 1 equiv	MgCl 1 equiv	Et_2O	45% (4:1)	32% pure vinyl-allene isolated
Cl	CuCN•2LiCl 0.1 equiv	MgCl 1.1 equiv	Et_2O	23%	ratio not determined

Subjecting the mono-benzoate to mesylation conditions afforded the desired product along with traces of the chloride, where a small quantity of the mesylate was saved, and the rest converted by standard methods to the chloride. (Scheme 5) With more reactive substrates in hand, cuprate conditions were re-examined to find optimal conditions for vinylallenoate formation (Table 4).

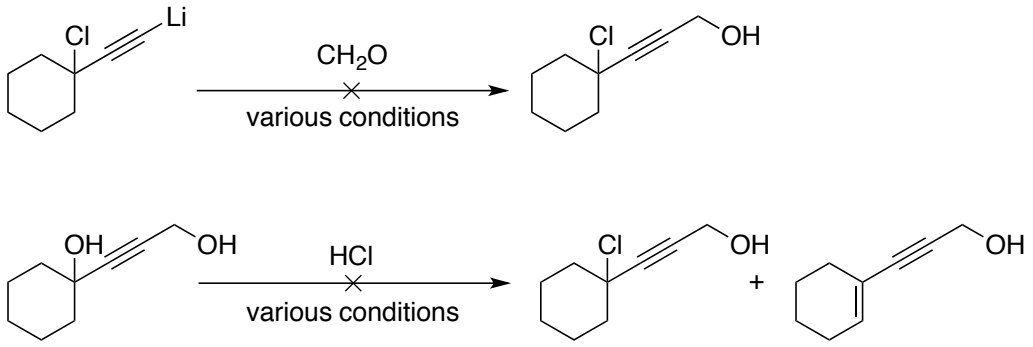
The second round of screening revealed that successful reaction was dependant upon several variables. Importantly, the reaction was much more efficient with the chloride relative to the mesylate, substituting ether for THF resulted in improved regioselectivity, and the Grignard reagent could be conveniently substituted for the organolithium without disadvantage. Separation for the undesired regioisomer afforded pure vinylallenoate which was subsequently tested under standard coupling conditions using an arylboronic acid. Unfortunately using this model vinylallenoate, coupling proceeded to give a variety of products, presumably due to facile Diels-Alder reaction between the allenoate and the [3]dendralene produced during the course of the reaction. Although isolation of a pure [3]dendralene was unsuccessful, this experiment provided useful information for substrate design, and efforts were subsequently undertaken to redesign a substrate that possessed a tertiary chloride to improve the regioselectivity of the reaction, as well as install the capping groups needed to prevent undesired Diels-Alder reactions.

Attempted preparation of several tertiary propargylic chloride substrates bearing the required alcohol or benzoate were unsuccessful, due to

decomposition to the undesired enyne, and low reactivity of various forms of formaldehyde with the corresponding lithium chloropropargyl acetylide (Figure 7).

Control experiments showed that lithiation of the propargylic chloride and trapping with other electrophiles, such as cyclohexanone were successful, however these products afforded material that was inactive under our cuprate coupling conditions. Additionally, installation of other leaving groups such as mesylates at the tertiary position were met with limited success, owing to an apparently facile elimination to the enyne.

Figure 7: Failure of Several Conditions to Prepare 3° Propargyl Chloride Substrate

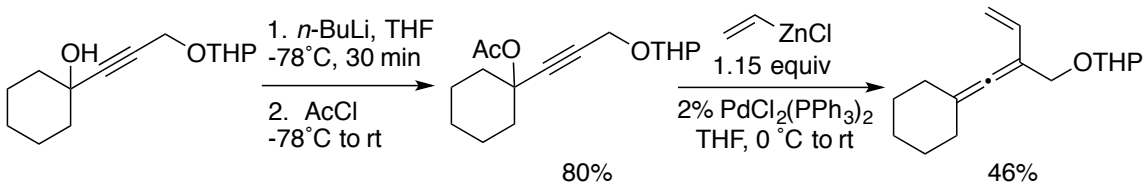


In the face of these difficulties it was fortunate that at this time, I was able to locate a reference in the literature that disclosed a preparation of highly similar vinylallenols, by Pd-catalyzed cross coupling of vinylzinc nucleophiles with propargylic electrophiles.[18a, b] While Pd chemistry had been avoided earlier due to perceived problems with a potential second substitution upon a free

vinylallenol or as its protected ether apparently the use of a less active $Pd(PPh_3)_4$ and proper choice of protecting group can suppress this pathway.

With now proper precedent to prepare a vinylallenol via cross coupling, the synthesis was replanned to use a tertiary propargylic acetate, with vinylzinc chloride and $Pd(PPh_3)_4$ to generate the desired vinylallene. Acylation of a THP protected propargyl alcohol proceeded cleanly in 80% yield, where subsequent Negishi coupling led to the desired vinylallene in 46% isolated yield (Scheme 6).

Scheme 6: First Generation Synthesis of a Vinylallene



While this initial route to the protected vinylallene was moderately successful, several features of these reactions merit further discussion. Although the acylation was high yielding, the yield could be substantially improved by switching to methyl chloroformate to arrive at the propargylic carbonate in 95% yield. Regarding the coupling, the zinc reagent was initially believed to require prior formation from the Grignard and anhydrous, $ZnCl_2$, however experimentation showed that the zinc reagent could be formed *in situ*, by simply adding the Grignard to a solution of $ZnCl_2$ and palladium catalyst prior to introduction of the substrate, avoiding the necessity of a preformed organozinc

solution. Adjusting the equivalents of organometallic did not improve yield, and only yields of up to 50% could be obtained. Additionally, while the reaction proceeded cleanly, after workup and column chromatography, several impurities close in R_f to the product became apparent. Even after THP deprotection and benzoylation, these impurities seemed to "follow" the material throughout the remainder of the synthesis. In rereading Molander's paper disclosing the preparation of vinylallenes by Suzuki coupling,[15e] it was noted that rigorous Pd removal was required at the end of the reactions. Apparently the vinylallene products complex with Pd(0) strongly and contributed to decomposition of the product. The solution given to this problem was to stir the reaction mixture with activated carbon under air for a period of time at the end of the reaction to oxidize and bind Pd to the charcoal surface. This was attempted, and did improve the purity profile of the product, yet the impurities seemed to persist in small amounts.

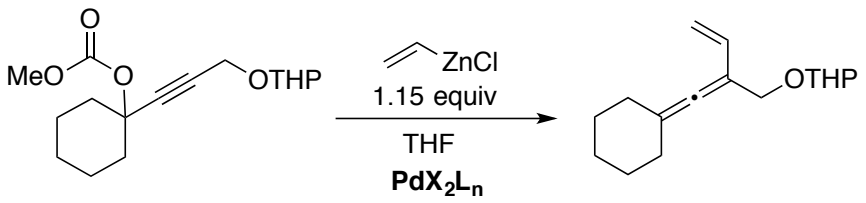
I recalled that recently a paper in OPRD had described a general solution to problems of trace metal removal from API's.[18] By using dithiocarbamate salts, which form insoluble adducts with various transition metals *irrespective of oxidation state*, they were able to remove residual transition metal residues from products produced in a number of coupling reactions to below 10 ppm in most cases. Thankfully the required dithiocarbamate salt was available to test it's metal removing capabilities. Upon quenching of excess organometallic with MeOH, a majority of the Mg and Zn salts could be precipitated from the reaction

mixture by addition of hexanes. This was done to avoid competitive binging of the chelator with Mg/Zn over the undesired Pd residues. Once these salts were nearly fully precipitated, the dithiocarbamate salt was then added to bind the palladium residues and the insoluble material could be filtered off. Treatment of the solution with additional portions of chelator and successive filtrations, afforded a material that was free from Pd residues, and the desired vinylallenes could now be obtained in high purity through the remainder of the synthesis.

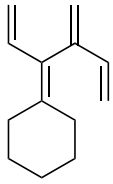
It seemed somewhat striking that the preferred ligand for the transformation was the lowly PPh_3. In many cases it seems that when scanning the literature for procedures, that Pd tetrakis is used by default, rather than having been determined to be the optimum ligand for the transformation. Accordingly I felt it best to test a small amount of more “modern” catalysts under these coupling conditions (Scheme 7)

As seen below, all other catalyst systems performed poorly relative to PPh_3, and it is surprisingly, the preferred ligand for this transformation. Of particular note is that DPEphos$PdCl_2$ gave none of the expected coupling product, instead producing exclusively the [4]dendralene in 50% yield. As approximately 50% of the starting material was recovered as well, the result suggested that this catalyst kinetically prefers reaction with the intermediate vinylallene over the propargyl substrate. This result helps to explain, in part, the high reactivity we had seen earlier employing this ligand with allenoates. Since a small quantity of the [4]dendralene was also isolated in the reaction conducted

Scheme 7: Survey of Ligands For Vinyl-Allene Formation *via* Pd Catalysis



Pd source 1 mol %	Conversion (TLC)
$PdCl_2(PPh_3)_2$	50%
$PdCl_2(PCy_3)_2$	0%
Handaphos $PdCl_2$ 0.1 mol %	0%
DPEphos $PdCl_2$	**trace**
$(P(o\text{-tol})_3)_2Pd^0$	0%
$(PPh_3)_4Pd^0$	**70-80%**



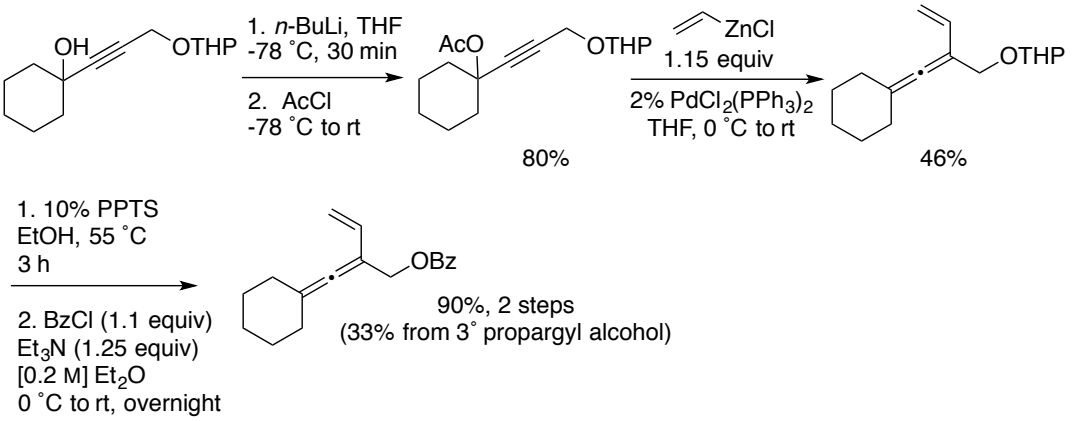
50% isolated
100% relative to RZnX

with PPh_3, it became prudent to switch this protecting group out for a less labile one such as TBS. The requirement for Pd tetrakis was somewhat of a disadvantage, as our supplies were low, and it is a relatively unstable catalyst; repeating the reaction with catalyst from a different batch gave a poorer result. This could be easily solved by using our rather large supply of $PdCl_2(PPh_3)_2$, with additional PPh_3, and simply adding a solution of DIBAL-H to produce the active Pd(0) for the reaction.

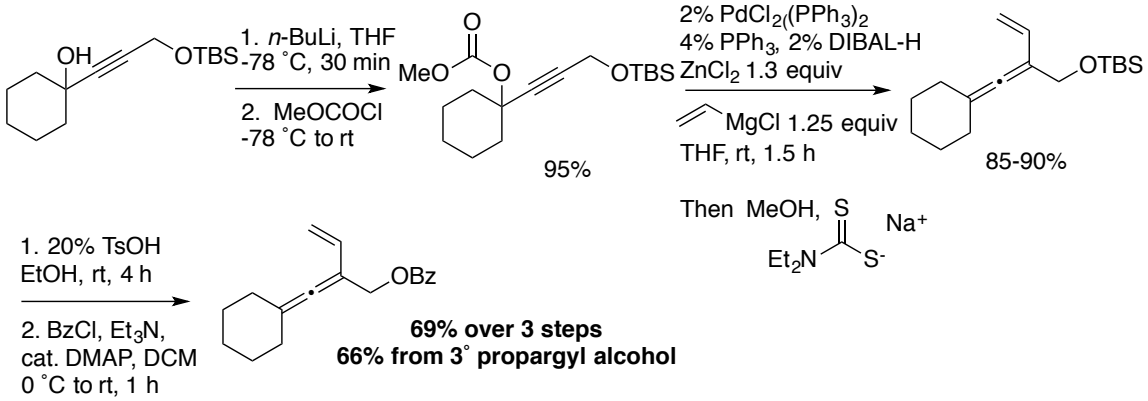
The results of these optimizations was that the overall yield of the final vinylallenoate could be doubled from to 33% to 66% over four steps from the tertiary propargyl alcohol (Scheme 8), allowing for easy access to multigram quantities of material.

Scheme 8: Comparison of First and Second Generation Routes to a Vinylallenoate

FIrst Generation Synthesis



Second Generation Synthesis

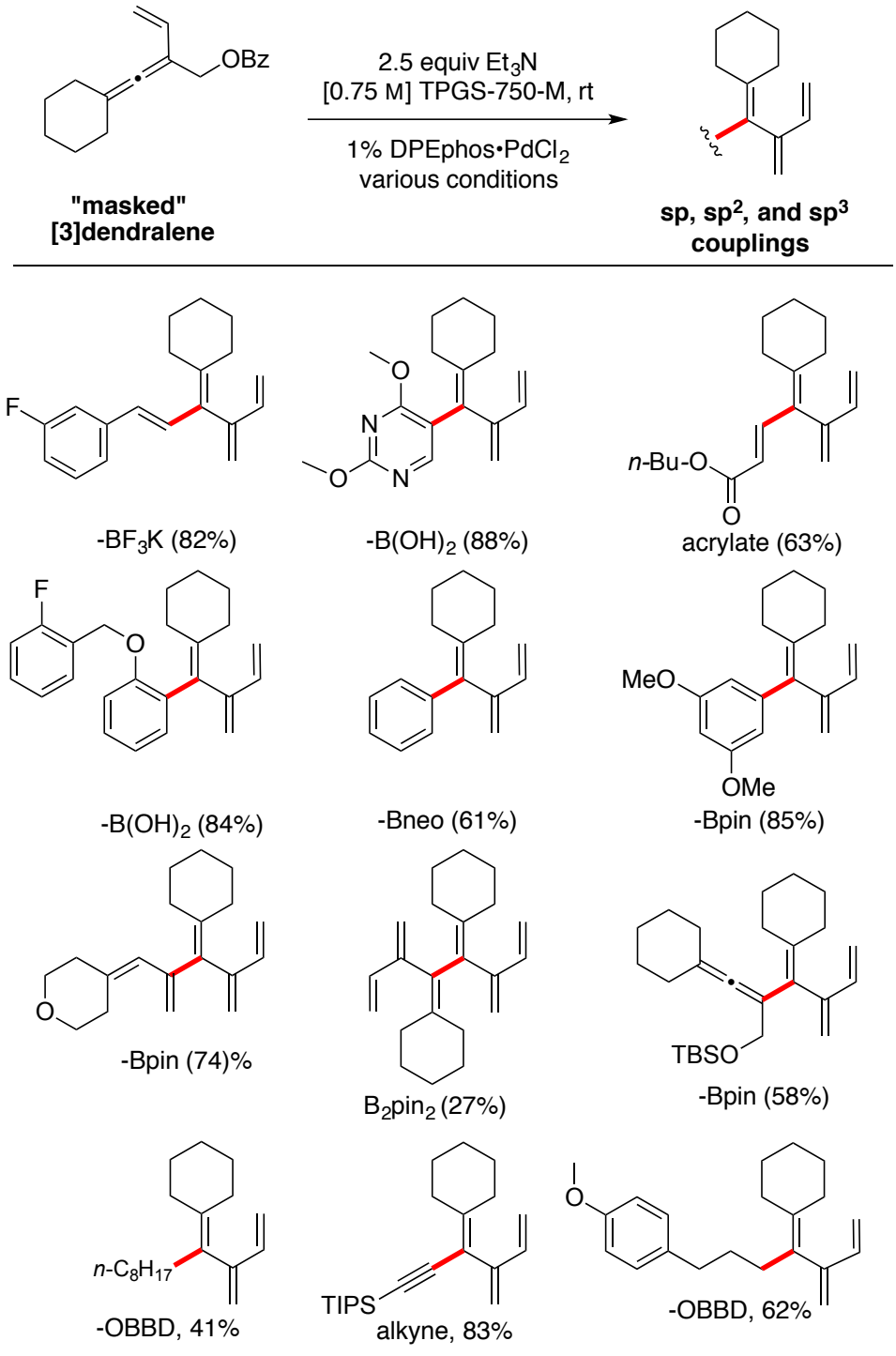


With gram quantities of vinylallenoate on hand, we could now test our original hypothesis to see if it functioned as electrophillic [3]dendralene synthon. Much to my relief, it coupled under every single one of our procedures (Figure 8). Aryl and heteroaryl moieties could be coupled without incident to arrive at [3]dendralenes, where the use of a vinyl-boron reagent reacted as expected to form an unsymmetrical [4]dendralene. Coupling with a borylated diene obtained

from copper catalyzed borylation, reacted to form the desired [5]dendralene. The OBBD-borinates reacted to effect an sp^3 coupling forming alkylated [3]dendralenes. Finally performing the reactions under B_2pin_2 homocoupling conditions allowed us to access a [6]dendralene with this vinylallenoate.

While all of this work employed the cyclohexyl-terminated allene, further studies will need to be conducted to ascertain the size and placement of substituents about the allene and vinyl unit to prevent undesired Diels-Alder reactions. Likewise, while the addition of substituents about the allene provides stability, further work will need to be done to accommodate substrates with monosubstitution at the allene terminus, as under the current conditions, these monosubstituted educts give variable *E/Z* ratios of coupling products.

Figure 8: [3]-[6]Dendralenes Prepared From a Vinyl Allenoate



Conclusions and Outlook

A general synthesis of 2-subsituted-1,3-butadienes from allenylbenzoates was developed, taking into account the principles of green chemistry.[20] This method offers a substantial improvement over existing methods with regard to environmental impact, and mildness of conditions. Performing an additive based screen, with isolation of additive and product, allowed for a quantitative measure of functional group tolerance for this method, without recourse to lengthly syntheses. Curiosity driven research into methods for aqueous sp^3-couplings led to the rediscovery of OBBD borinates as air tolerant alkyl-coupling reagents, where they were applied to the synthesis of substituted butadienes and dendralenes.

Serendipitous observation of homocoupled products under these conditions allowed for an intellectual connection with the syntheses of dendralenes. This was developed further into a mature method to access [3] and [4]dendralenes by a number of Cu- and Pd-catalyzed procedures. Examination of cuprate and Pd mediated methods to form vinylallenes led to the development of a scalable route that could access gram quantities of these educts that functioned formally as a “masked” [3]dendralene. Application of this vinyl-allenoate to the methods developed earlier in this project, allowed us to extend the technology to access [3] and [4]dendralenes with new substitution patterns, as well as extend the scope of the method to access unsymmetrical [5] and symmetrical [6]dendralenes.

Owing to the infancy of dendralene chemistry relative to that of linear polyenes, I am optimistic that the work we performed on these projects will be of interest and use to the synthetic community. I also hope that the investigations here on the use of OBBD sp^3 coupling partners will help to further the development of other alkyl coupling reactions in aqueous systems. Additionally, I would like to offer my deepest thanks to Dan for all his work on this project, I was able to learn quite a lot, and I had a great time all the while.

References:

[1] Moriya, T.; Furuuchi, T.; Miyaura, N.; Suzuki, A. *Tetrahedron* **1994**, *50*, 7961.

[2] Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.

[3] a) Lennox, A. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362; b) Lennox, A. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412; c) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998,** *120,* 8978.

[4] Normant J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, *27*, 2583.

[5] a) Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4159; b) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592.

[6] For a review of BF_3K salts in coupling reactions, see: Molander, G. A.; Sandrock, D, A. *Curr. Opin. Drug Discov. Devel.* **2009**, *12*, 811.

[7] Yamamoto, Y.; Takizawa, M.; Yu, X-Q.; Miyaura N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928.

[8] For a review of B-alkyl Suzuki couplings, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544; and references therein.

[9] For example: Ohmiya, H.; Yokobori, U,; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895.

[10] Zhang, Z-C.; Chung, T. C. M. *Macromolecules*, **2006**, *39*, 5187.

[11] For selected examples of borinates and borinic acids in cross coupling see: a) Winkle, D. D.; Schaab, K. M. *Org. Proc. Res. Dev.* **2001**, *5*, 450; b) Chen, X.; Ke, H.; Chen, Y.; Guan, C.; Zou, G. *J. Org. Chem.* **2012**, *77*, 7572.

[12] J. A. Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.

[13]Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

[14] Nuhant, P.; Allais, C.; Roush, W. R. *Angew. Chem., Int. Ed*. **2013**, *52*, 8703.

[15] Synthesis of vinyl-allenes: a) Wu, K-M.; M. Midland, M.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 4381; b) Katie M. Cergol, K. M.; Newton, C. G.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem*. **2011**, *123*, 10609; c) Park, J.; Kim, S. H.; Lee, P. H. *Org. Lett*. **2008**, *10*, 5067; d) Zweifel, G.; Pearson, N. R. *J. Org. Chem.* **1981**, *46*, 829; e) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563.

[16] Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103.

[17] *Modern Allene Chemistry* (Eds.: Krause, N.; Hashmi, S. K.), Wiley-VCH, Weinheim, **2004**.

[18] a) Feldman, K. S.; Antoline, J. F. *Tetrahedron,* **2013**, *69*, 1434; b) Ruitenberg, K.; Kleijn, H.; Elsevier, C. J.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1981**, *22*, 1451.

[19] Gallagher, W. P.; Vo, A. *Org. Process Res. Dev*. **2015**, *19*, 1369.

[20] Sheldon, R. A.; Arens, I. W. C. E.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, **2007**.

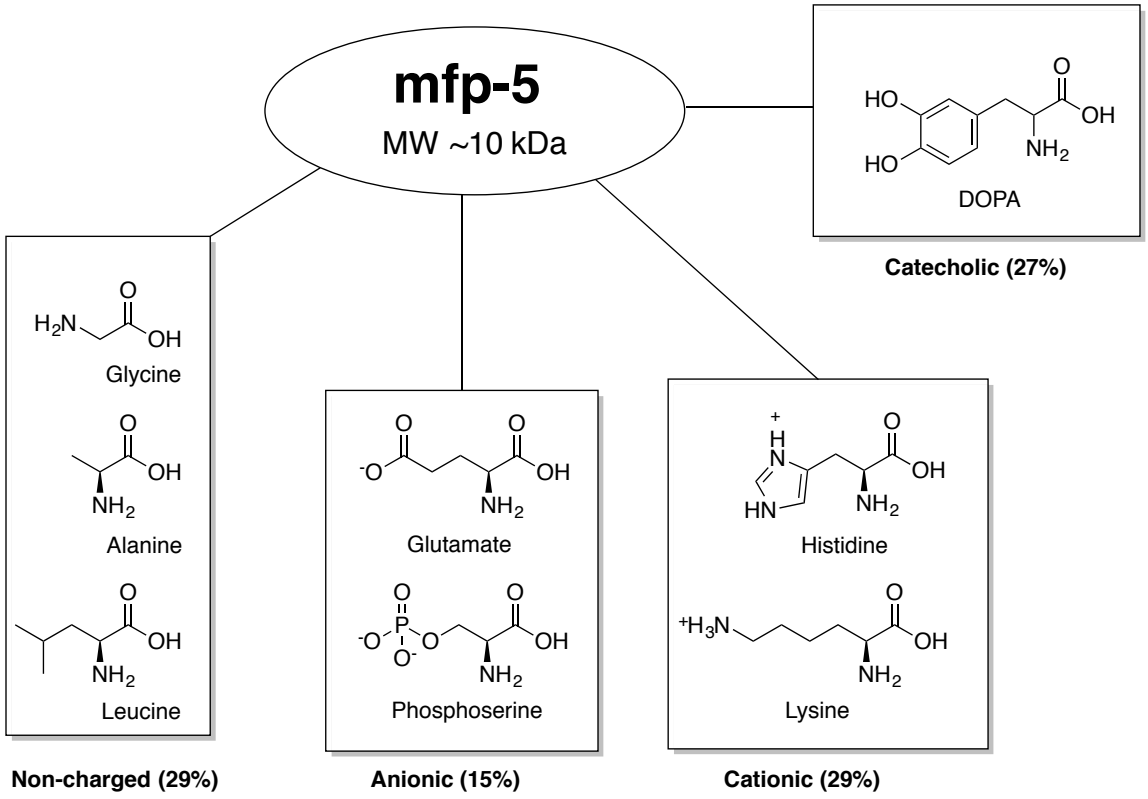
D) Synthesis Of Small Molecule Underwater Adhesives Inspired By Mussels

Synthesis of Small Molecule Underwater Adhesives

One of the longstanding challenges posed to scientists by nature is the engineering of robust adhesion in wet environments. Solutions to this problem are expected to have applications across a wide range of fields. For instance, applications can be envisioned to be applied in medical settings for the repair of damaged tissues, tendons, and as binders for use in dentistry.[1, 2] They may also be applied to anti-biofouling coatings for marine vessels, where attachment of marine organisms to the hulls incurs significant costs in the form of drag, and dry-docking of the vessels for hull cleaning.[3] Additionally, wet adhesion technologies may not be restricted to applications at large macromolecular scales, and can potentially be applied as primers for nanofabrication at scales <4 nm.

To understand the mechanisms by which wet adhesion is accomplished, the marine mussel has been the subject of intense scientific scrutiny over the past several decades.[1] Marine mussels must successfully adhere to rocks in intertidal zones and avoid being dislodged by strong tidal forces, crashing waves, and marine detritus. Adaptations allowing for attachment are present at both the large macromolecular scales (as in the byssal thread), and chemical adaptations at the nanoscale which corresponds with interactions between the organisms

Figure 1: Amino Acid Composition of mfp-5



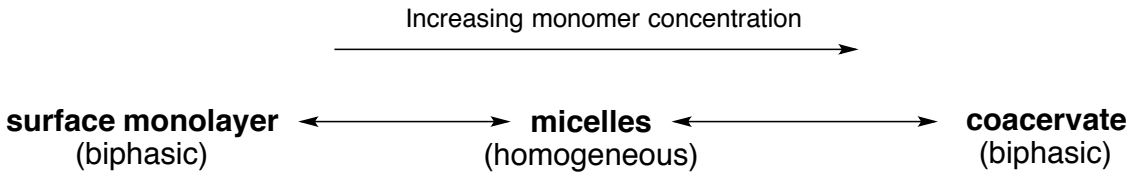
biomolecules and substrate at the interface. Analysis of mussel foot proteins (mfps) secreted at the interface, particularly mfp-5 and mfp-3, showed peptide sequences rich in cationic residues (lysine), anionic residues (phosphoserine), hydrophobic residues (glycine, alanine), and particularly the catecholic amino acid, 3,4-dihydroxy-phenylalanine (dopa) (Figure 1).[4] Both mfp-5 and mfp-3 are thought to function as adhesive primers. Other attributes of the mfps that help to promote adhesion include their apparent ability to dehydrate the surface of the substrate to allow for interfacial interactions between the proteins and the surface.[5] Complex coacervation of mfps is also thought to be an important

parameter for adhesion, and may help to form the basis of the delivery mechanism of the mfp primers to the surface.[6,7]

Since coacervation of mfps has been suggested as an important feature of mfps to deliver their payload of surface primers necessary for adhesion, it is important here to draw a distinction between coacervates and micelles. Micellization is the process by which molecules possessing both hydrophobic and hydrophillic regions may transition from a water insoluble monolayer to water soluble aggregates such as spheres, rods, and discs. With increasing monomer concentration, the surface tension decreases until the critical micelle concentration (cmc) is reached, at which point no further change in the surface tension is observed with additional monomer. This observed change in surface tension is the origin of the word “surfactant”, used to designate surface active molecules. Once the cmc is reached, addition of excess monomer does not change the surface tension further because the monomers are no longer incorporated into the initial water insoluble monolayer, and are instead driven into various water soluble aggregates termed micelles. Further increasing the concentration of monomers will continue to increase the number of micelles present in the medium for a time, until the increases in monomer can no longer be accommodated in a homogeneous single phase, and the phases separate to form one that is micelle poor, and another that is highly micelle rich with amorphous droplets termed coacervate droplets. The micelle rich phase may be

collected, and subsequently coalesce, to form a homogeneous dense micelle-rich fluid known as a coacervate.[8] (Figure 2)

Figure 2: Micelle and Coacervate Formation as a Function of Concentration

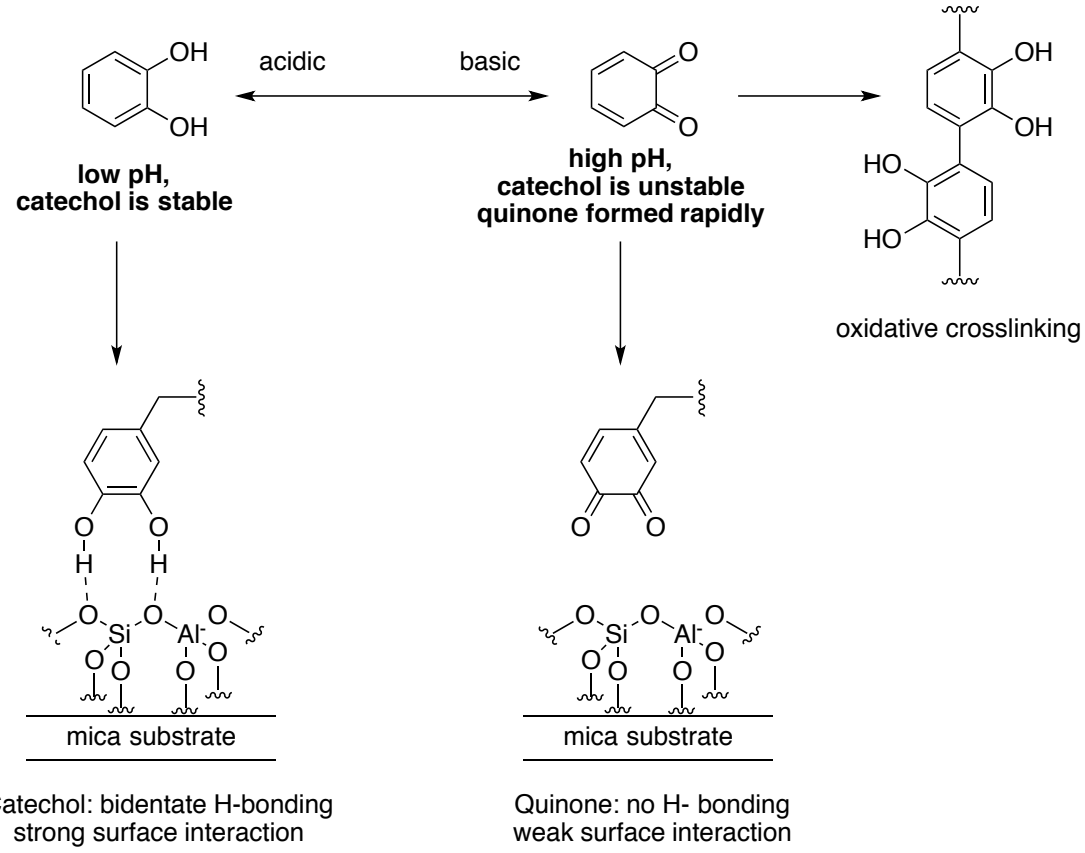


Mfps posess a high quantity of charged amino acid residues, and as such, they may be regarded as polyelectrolytes. The high charge densities present in the proteins help to drive their self-association into dense, fluid separated coacervates which help in turn to protect the dopa residues from oxidation, dehydrate the surface boundary, and help to spread the payload of adhesive primers across the surface.

The inclusion of Dopa into the mussel foot proteins has been suggested to promote adhesion by a variety of mechanisms. Cooperative hydrogen bonding between the catecholic functional groups and metal oxides in the substrate is a primary and highly important mechanism;[9] tyrosine residues are ineffectual at promoting surface adhesion. At acidic pH, the hydroxyl groups of the catechol exist in their phenolic form, which hydrogen bonds strongly to metal oxide surfaces. At basic pH, dissolved oxygen causes fast autooxidation to the quinones occur which bond much weaker to surfaces. Once in quinone form, the

molecules may then undergo oxidative crosslinking/polymerization with other catechol moieties [10] (Figure 3).

Figure 3: Oxidation of Catechols at High pH Inhibit Surface Adhesion

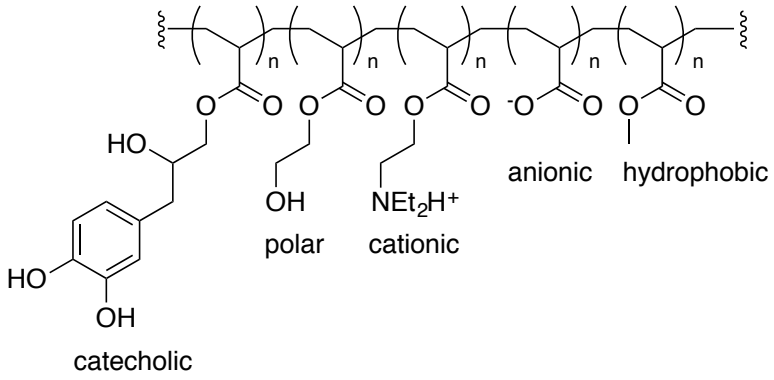


Therefore, it is unsurprising that mussels concurrently secrete acidic buffers and antioxidants along with the mfps to maintain phenolic form and oxidative stability of the catechol.[11] The oxidative crosslinking of other catecholic groups after initial adhesion to the surface may further help to solidify attachment of the mussel from the formation new covalent bonds, effectively “curing” the deposited adhesive.

Methods that can deliver strong and robust wet adhesion are highly valuable, yet practical applications continue to remain limited. Advances in scientific understanding of the mussel's mechanisms of surface attachment have given rise to a large number of biomimetic approaches. Peptide fragments of mfps have been investigated,[12] as well as polymeric peptides containing repeating units of Dopa/Lys to incorporate the catecholic and positively charged functionality found in mfps.[13] Catecholic molecules have been successfully incorporated into polysiloxanes for use in lithographic surface treatments, using a highly efficient synthesis derived from eugenol.[14] Of particular note is the synthesis of acrylate copolymers from monomers containing cationic, anionic, hydrophobic, and catecholic side chains, mimicking the composition of amino acids found in native mfps.[15] Until recently, the record for the highest strength of a bio-inspired or bio-derived underwater was held by a recombinant mfp-amyloid fusion protein[16] with an interaction energy of 20.9 mJ m^{-2}. All of the aforementioned approaches to mimicking the mussels adhesion have used large macromolecular platforms to supply the appropriate functionality, in the form of synthetic polypeptides, recombinant proteins, or polymers. Therefore, I was fortunate to enter a collaboration with Dr. Kollbe Ahn, and the Waite research group, in which we developed small molecule (MW < 500 Da) underwater adhesives that could both match the existing record for adhesive energy, and set a new record of ~50 mJ m^{-2}. At the time of publication this was the highest measured adhesive energy for an underwater catecholic adhesive.

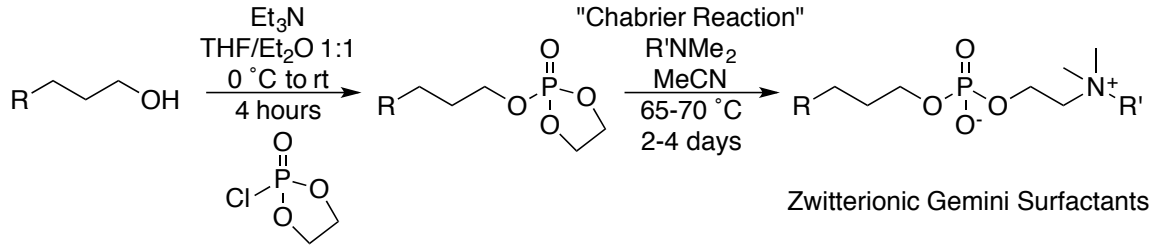
Dr. Kollbe Ahn had for some time been studying mussel foot proteins, and recently had achieved some success in mimicking the mussels mechanism of adhesion, by copolymerization of acrylate monomers containing four of the essential features of mfp-5: catecholic, anionic, cationic, and hydrophobic side chains.[15] Importantly, this research highlighted the effectiveness of hydrophobic side chains to shield the catecholic functionality from oxidation, but also the need to strike an appropriate hydrophobic/hydrophilic balance to achieve solubility and coacervation necessary for efficient spreading across the surface (Figure 4).

Figure 4: Example of a mfp-mimetic Copolymer Capable of Coacervation



In the pursuit of other platforms in which the translation of the mussels adhesive mechanisms could be accommodated, he had noted a report by Menger, who disclosed that zwitterionic gemini surfactants prepared by the Chabrier reaction[17] could form coacervates[18] (Scheme 1).

Scheme 1: Synthesis of Zwitterionic Geminis by the Chabrier Reaction



It was here that I was approached to synthesize analogs of these molecules to incorporate catechols, where now they would contain the four essential features of mfp-5 as well as presumably form coacervates necessary for attachment to the surface. In other words, the central hypothesis was to see if the key features of the mfps could be distilled down to their essence in a single molecule. As this approach relies on organic synthesis of small molecules, it would posess certain advantages over other platforms such as recombinant biotechnology and polymers, where application of such technology may not be able to cost effectively provide material on scale, as in the case of recombinant protein engineering, or provide molecularly well defined entities, as in the case of copolymers.

Several aspects of Menger's work are of particular note. The surfactants he prepared had exceedingly low cmc's even when compared to Gemini surfactants.[19] The methods by which they are synthesized also lends themselves to unsymmetrical derivatives that are difficult to obtain by other procedures. One particularly salient feature was the observation that geminis possessing different alkyl chain lengths off the nitrogen and phosphate can have

distinctly different properties when the alkyl chains are switched, where a "reversomer" in one case becoming a water soluble homogeneous solution from a water immiscible coacervate.

I had been largely unaware of the scientific efforts to understand and replicate the mussel's underwater adhesion prior to the beginning of this project. Therefore, my main contributions to this work were in the planning and execution of the synthesis, while my collaborators were involved in the study and analysis of the molecules by various techniques, whereby this information was passed back to me to refine the synthesis of derivatives.

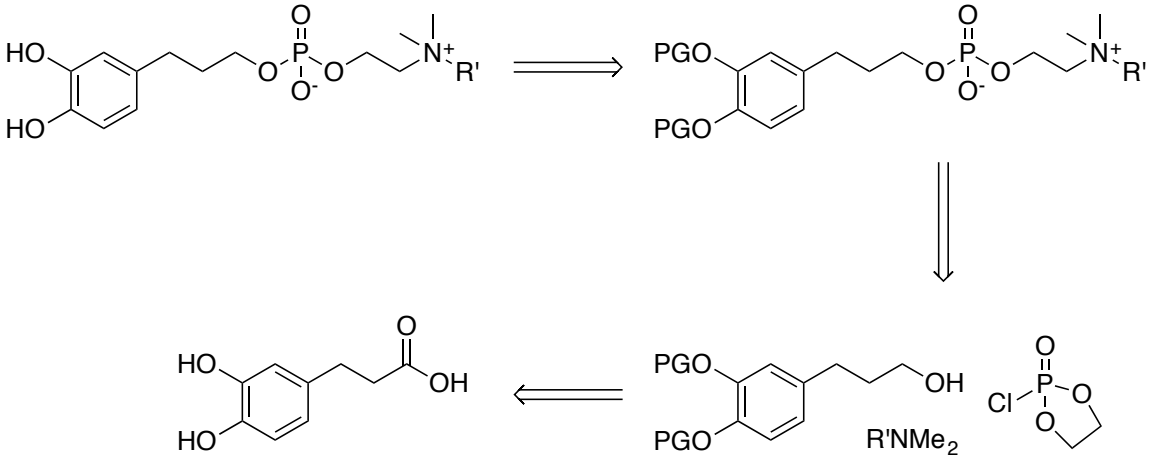
Concerning the synthetic design, the primary issue to be addressed was identification of an appropriate catecholic starting material, and choice of protecting group. The catecholic group owing to its high sensitivity would necessitate deprotection at the final stage of the synthesis to avoid polymerization during handling of the intermediates. The presence of the zwitterions presented an additional challenge, where reagents involved in catechol deprotection would need to be carefully selected, so as to avoid the presence of additional salts which could complicate purification of the product, which itself is also a salt. Additionally, the expected high polarity of the products and oxidative instability would necessitate a protective group that could be quantitatively removed, to avoid a tedious separation from unreacted starting material.

The byproduct of deprotection therefore should be able to be removed by washings or evaporation. Among the possible protective groups for phenols and catechols that fit this list of requirements, the only realistic choices were acetonides, acid cleavable ethers (e.g. MOM), cyclic orthoformates, and benzyl groups. Of these choices, benzyl was selected as the rest of the molecule was expected to be tolerant of hydrogenolysis conditions. The use of acids to effect removal of the others could potentially lead to the formation of an inclusion co-salt, or require undesirably high temperatures to remove trace acids; aqueous workups were to be avoided as the products were designed to be water soluble.

In considering the choice of starting materials, the catecholic moiety would have to be incorporated into the molecule with a tertiary dimethylamine to affect quaternization, or as an alcohol, that would be attached to form the phosphate. Since Menger's procedure relied on an excess of the tertiary amine, and the catecholic moiety was invariably the most costly, simple economics dictated linking of the catechol onto the phosphate, where excesses of simple tertiary amines could presumably be removed under vacuum to separate them from the zwitterion. However, there still was a need for flexibility in the synthesis to be able to switch the location of the catechol, as the reversomers could have very different properties. The only starting materials that satisfied these requirements were both caffeic acid, and it's dihydro derivative, where reduction of the carboxylic acid could furnish the required alcohol, and dimethylamide formation

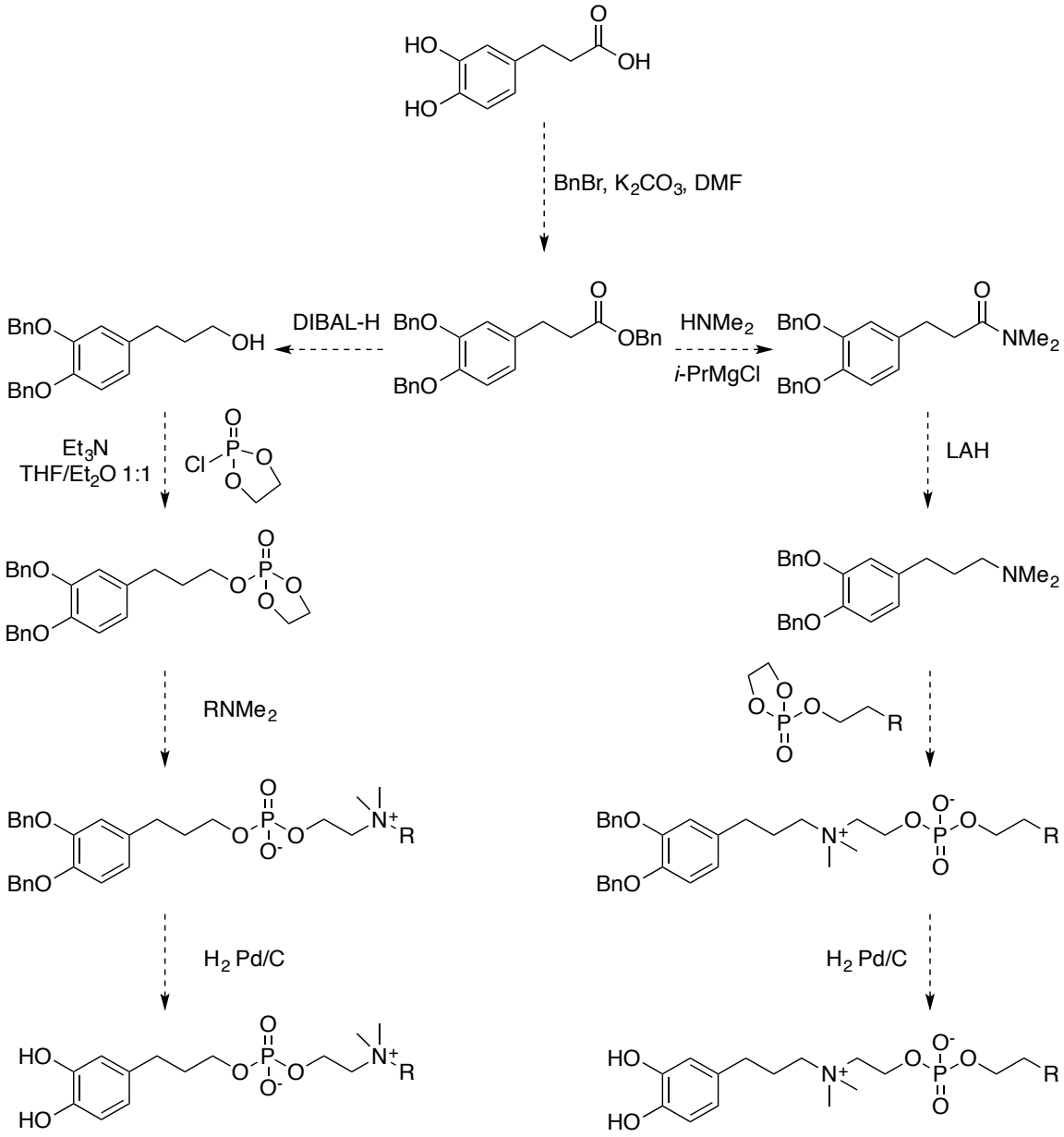
followed by reduction would deliver the required tertiary amine to synthesize the reversomer.

Scheme 2: Retrosynthetic Analysis



Accordingly the synthesis, was planned as follows. Triple benzylation could be achieved by standard means, where subsequent LAH or DIBAL-H reduction would furnish the desired alcohol. To arrive at the amide, the use of a magnesium-amide would be expected to lead to the corresponding amide, which could be reduced to the desired amine. Using Menger's method, the cyclic phosphate would be prepared from the alcohol, which would be further reacted by the Chabrier reaction to form the desired zwitterion. Finally, hydrogenolysis of the benzyl groups was expected to deliver the target molecules.

Scheme 3: Initially Planned Route to Zwitterionic Adhesives

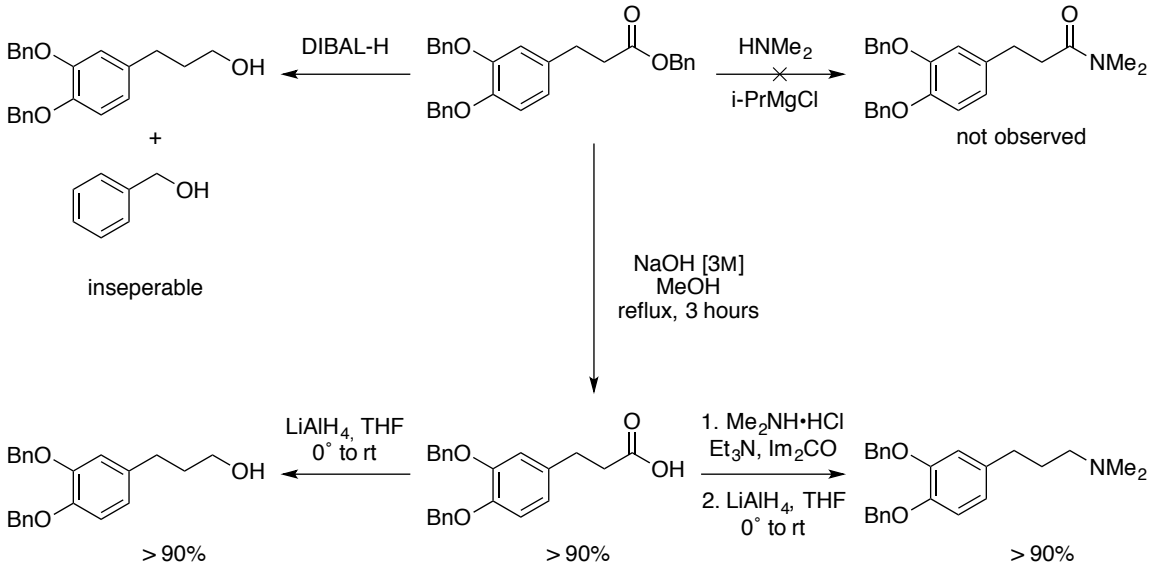


In subjecting the tribenzylated ester to standard DIBAL-H reduction conditions, it was somewhat unfortunate that both the desired alcohol, and the benzyl alcohol byproduct, had nearly identical R_f values and could not be

efficiently separated by chromatography. Distillation at reduced pressure was able to remove a majority of the benzyl alcohol, but due to presumably strong pi-stacking interactions, trace amounts always remained, even after extended distillation times. Accordingly, the sequence was modified to include a preliminary saponification of the benzyl ester, where separation of benzyl alcohol from the carboxylate salt became trivial. Acidification afforded the carboxylic acid which could now be reduced easily with $LiAlH_4$ in THF to the desired alcohol. After workup, the product was of sufficient purity that chromatography was unnecessary.

Since a large quantity of tribenzylated ester was still remaining on hand, attempts were made to directly convert it to the desired dimethylamide. The use of Bodroux conditions[20] (R_2NH, iPrMgCl, THF) unfortunately did not give the desired amide and a strange material was produced, that appeared to be an α-amino ketone, on the basis of IR stretching vibrations and, NMR spectroscopy. Therefore to, construct the required amine necessary for the synthesis of the reversomers, the remainder of tribenzylated material was saponified, subjected to standard peptide coupling conditions with carbonyldiimidazole (CDI, Im_2CO) as an activator, and the resulting amide was reduced the tetriary amine with $LiAlH_4$.

Scheme 4. Saponifaction of Benzyl Ester Improves Synthetic Route



The protected catecholic alcohol, could then be converted to the cyclic phosphate by Menger's method, where use of THF/Et_2O was required to assist in precipitation of the amine hydrochloride salt, which was then removed by a quick filtration over Celite. Dilution with additional Et_2O, and hexanes seemed to help in precipitating traces of soluble amine hydrochloride salts for filtration. As excess of triethylamine could potentially quaternize with the phosphate in the Chabrier reaction, DIPEA was substituted instead to reduce the chances of quaternization, and rigorous solvent removal to evaporate DIPEA with high vacuum was performed prior to quaternization.

Menger's procedure documented that between 2-4 days were required for complete quaternization in anhydrous MeCN at ca. 75 ˚C, however this was a distinct disadvantage experimentally, as prolonged refluxing would invariably lead to losses of solvent, introduction of adventitious water, and losses of volatile

amine over the course of 96 hours. Therefore, a more rigorously sealed system was desirable. Accordingly, the cyclic phosphate was dissolved in anhydrous acetonitrile, and added to a schlenk flask, along with the appropriate equivalents of amine. To avoid hazards of heating a closed system, vacuum was briefly applied before the valve was sealed, and the reaction could then be brought safely to the desired reaction temperature. In this case it was also deemed reasonable to leave the vacuum manifold active, despite the Schlenk valve being closed, so that any imperfections in the seal would lead to oxygen and moisture being removed, rather than being introduced into the reaction vessel.

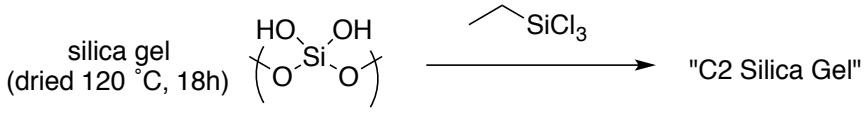
The procedure given for purification of these zwitterionic gemini surfactants was to recrystallize from a mixture of MeCN/Et_2O, and while effective reprecipitation could be achieved, analysis of the material showed the presence of several impurities. In the interest of expedience it was not desirable to set up a large solvent screen to identify the precise concentrations/volumes of solvent required for recrystallization. The product zwitterions additionally were far too polar for chromatography on regular silica gel, and therefore a different approach to purification was required. It was very fortunate that at this time, I had been a casual reader of various synthetic chemistry blogs on the internet that would occasionally post improved procedures and discuss various tricks to running reactions more efficiently.

Further searching around the internet showed that a few other graduate students had been having similar problems, with compounds of high polarity that

couldn't be effectively crystallized. Among the various suggestions given was the use of partially deactivated silica gel, as opposed to using a full blown preparatory scale reverse phase (C18) column. The discussion pointed to a paper that had prepared ethylated (C2) silica gel by reacting dry commercial gel with ethyl-trichlorosilane to mask the silanols.[21] Incorporation of the ethyl residues, rendered the resulting material much less polar than regular silica gel, yet the overall hydrophobicity of the material remained low enough so that it was not actually a reversed phase gel; compounds of low polarity still eluted first, and those of high polarity still eluted last. From my perspective this had the additional benefit of being able to use the various eluent systems that I was familiar with, rather than having to relearn and "get the feel" for how eluents behaved on a fully reversed C18 column.

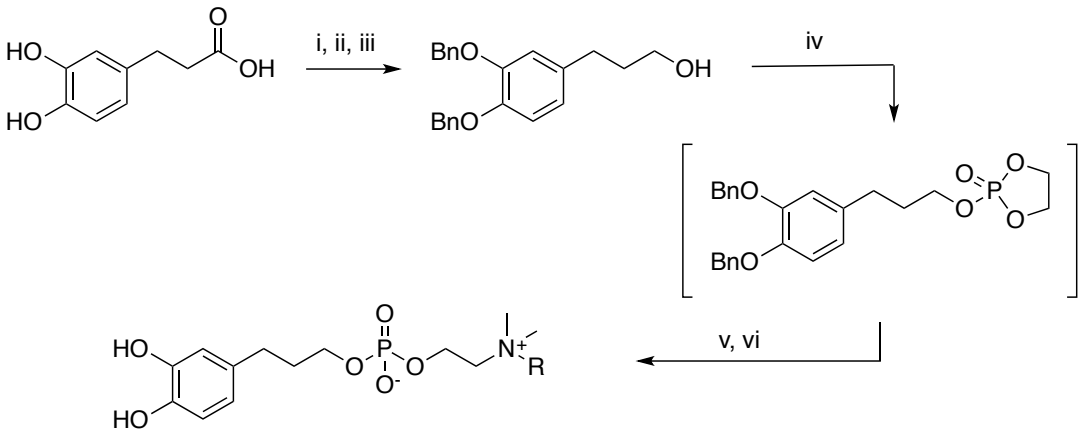
Preparation of C2 silica, by the reported procedure was effective (Scheme 5), and once filtered free from HCl and dried, could be packed into a column and eluted by standard gradient elution to purify the zwitterionic product, requiring a gradient of 0-100% MeOH/CH_2Cl_2, to fully elute. Commercial C2 silica, once it had shipped, was tested and was much more hydrophobic than the homemade material, although it still displayed the standard order of elution found in normal phase gels.

Scheme 5: Preparation of C2 Silica Gel



With the penultimate material now available in a pure state, the only remaining step was hydrogenolysis of the benzyl groups. Debenzylations proceeded slowly, requiring between 2-4 days for complete deprotection at 1 atm of hydrogen at ambient temperatures, and could not be effectively monitored by TLC. Therefore the reaction progress was monitored by filtration, concentration, and NMR analysis of aliquots withdrawn from the reaction. Unaware of it at the time, addition of acetic acid to the solvent has been successfully employed in hydrogenolysis of benylated catechols,[5] with complete reactions within 24 hours. This remains to be tested in future studies on these molecules, where an acidic solvent system may improve rates of deprotection and should permit filtrations of the solution in air, where the low pH of the solution protects the catechols from autooxidation.

Scheme 6: Final Route to Zwitterionic Small Molecule Adhesives

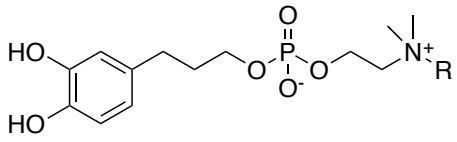


i) BnBr, DMF, K_2CO_3, 80˚C, 24h ii) NaOH, MeOH 100 ˚C 4h iii) $LiAlH_4$, THF, overnight iv) Ethylene chlorophosphate, DIPEA, Et_2O, 0˚, 4h v) $RNMe_2$, MeCN, 80˚C 2 days vi) H_2 (1 atm), Pd/C, CH_2Cl_2/MeOH 2-4 days.

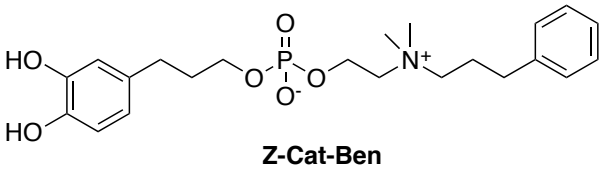
Since the commonly used Pd/C for hydrogenations is usually filtered off over Celite, and the catecholic products were expected to bind strongly to mineral oxide layers, a different means of catalyst removal would be needed. Explaining this problem to Dr. Sachin Handa, he quickly suggested that the use of a small PTFE filter be employed, where it's nonpolar/chemically inert characteristics would pose no problem with catechol/mineral binding. Thankfully this was highly successful at removing the Pd/C from the solution, and the final molecules could all be achieved in high purity, although variable yields were observed, presumably due to strong interaction of the molecules and carbon surface (Scheme 6). The first molecule prepared contained an octyl-group off of the nitrogen, and was termed Z-Cat-C8, to simply denote a zwitterionic catechol with an 8 carbon hydrophobic residue. This initial choice of chain length was simply dictated by an attempt to balance the 9 carbons present on the catecholic side of

the molecule. After I had delivered it to my collaborators for testing, I was surprised and amused to learn a few days later, that this compound was measured to have a higher interaction energy than the pure mussel protein mfp-5, and also was already on an airplane to Israel for microscopy studies. This positive result prompted the synthesis of several more derivatives by varying the length of the alkyl chain, reversing the ends, incorporation of aromatic residues, and incorporating catechol at both ends. A control substrate was also prepared that was identical in all respects, only lacking catechol functionality (Figure 5).

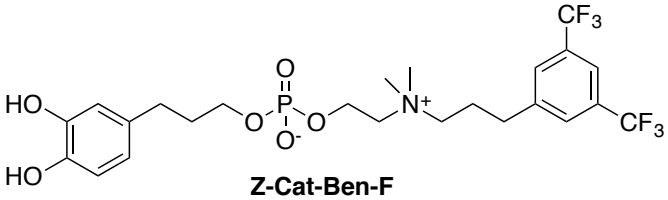
Figure 5: Library of Zwitterionic Gemini Surfactants Prepared



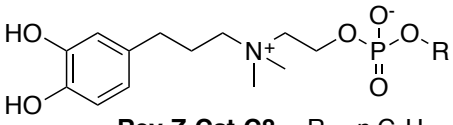
Z-Cat-C4 R = *n*-C_4H_9
Z-Cat-C6 R = *n*-C_6H_{13}
Z-Cat-C8 R = *n*-C_8H_{17}
Z-Cat-C10 R = *n*-$C_{10}H_{21}$
Z-Cat-C12 R = *n*-$C_{12}H_{25}$



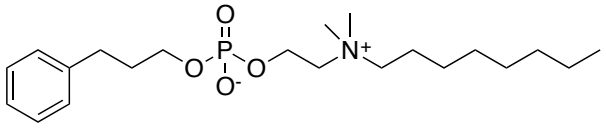
Z-Cat-Ben



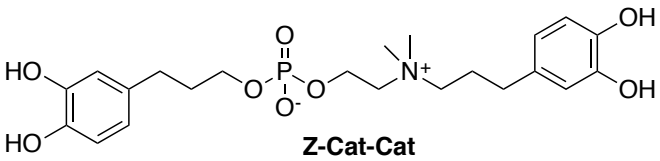
Z-Cat-Ben-F



Rev-Z-Cat-C8 R = *n*-C_8H_{17}



Z-Ben-C8



Z-Cat-Cat

This library of compounds was then passed on to my collaborators who performed adhesion testing, and a variety of other measurements to better understand the correlations with the physical properties. Specifically: 1) Underwater adhesion was measured on mica substrates using the surface force apparatus (SFA).[22] 2) Critical micelle concentrations were measured by surface tension, to provide a measure of the propensity of the molecules to self interact. 3) Cyclic voltammetry was used to measure the oxidation potential, to assess how changes in molecular structure protected the catechol moieties from oxidation. 4) AFM, Cryo-TEM, and optical microscopy were used to image solutions of the molecules as colloidal solutions, coacervates, and as adsorbed on various surfaces. When dissolved in degassed DI water at 0.5 mM concentration, both Z-Cat-C8 and Z-Cat-Ben displayed remarkably high adhesion energies between mica surfaces both of which were higher than native mfp-5 by nearly double (Table 1). Increasing the concentration to 5 mM (ca. 2 mg/mL for most of the molecules), a surprising concentration dependence was observed, with now Z-Cat-C4 and Z-Cat-Ben displaying the highest adhesion. The reason for this phenomenon is unknown, but may involve differences in the size and organization of the aggregates at different concentrations. The control molecule Z-Ben-C8 possessing no catecholic functionality displayed no adhesion to the mica surfaces forming a multilayer, where the other catecholic molecules rapidly absorbed to form bilayers. In examining the oxidation potential by cyclic voltammetry, it appears that at 5 mM, (above the CAC for all of the molecules)

both aggregation and hydrophobicity of the molecules helps to shield the catechol moieties from oxidation. My collaborators performed further studies on Z-Cat-C10, which was selected due to its low (0.003 mM) CAC. By preparing a highly concentrated solution of this, phase separation could be induced to obtain a coacervate, which could then be applied underwater to various surfaces to bind them together.

Table 1: Properties of Small Molecule Zwitterionic Adhesives

Compound	CAC	W_{ad} [0.5 mM]	W_{ad} [5 mM]	E_{ox}
Z-Ben-C8	1.4 mM	-------	0 mJ m^{-2}	-------
Z-Cat-C4	0.16 mM	6 mJ m^{-2}	19.4 ± 2.4 mJ m^{-2}	0.515 V
Z-Cat-C6	0.16 mM	6 mJ m^{-2}	9.6 ± 1.1 mJ m^{-2}	-------
Z-Cat-C8	0.013 mM	22 mJ m^{-2}	2.5 ± 0.3 mJ m^{-2}	0.582 V
Z-Cat-C10	0.003 mM	8 mJ m^{-2}	10.1 ± 2.3 mJ m^{-2}	0.600 V
Z-Cat-C10 - $NaIO_4$ oxidation, 12 h contact time: 50 mJ m^{-2}				
Z-Cat-Cat	0.7 mM	6 mJ m^{-2}	8.1 ± 1.3 mJ m^{-2}	0.594 V
Z-Cat-Ben	1.4 mM	18 mJ m^{-2}	18.7 ± 2.8 mJ m^{-2}	0.840 V
Z-Cat-Ben-F	-------	-------	4 mJ m^{-2}	0.597 V

CAC = Critical Aggregation Concentration. W_{ad} = Energy of adhesion
E_{ox} = Peak oxidation potential vs. Ag/AgCl.
For reference, mfp-5 is measured to have a W_{ad} of between 9-13 mJ m^{-2}
For reference, methyl-catechol is measured to have an E_{ox} of 0.455 V

Therefore, the compounds could mimic not just adhesion of the mfps but could also recreate their delivery mechanism by forming dense fluid separated coacervates. Other important experiments involved treating the adhered primer layers asymmetrically with periodate to affect oxidation to the quinone, applying compression, then measuring the resulting adhesion strength for different durations of compression. Although adhesion in this case decreased initially, it was observed to rebound after several hours of compressive contact, suggesting that crosslinking of the quinones was responsible for the rebound in adhesion. Asymmetrically oxidized Z-Cat-C10 by this method was measured to have an adhesion energy of ca. 50 mJ m^{-2} which was a new record for catechol mediated adhesion. A number of other tests were performed, documenting strong macroscale adhesion in both dry and wet conditions, where the adhesion was found to be greater than that of double sided scotch tape, adhesion of 100 nm silica beads to silicon wafers with Z-Cat-C10, documenting the ability to use these primers in nanofabrication.

Taken in the composite, our data showed that the strong wet adhesion and delivery mechanism of mussel foot proteins could be recreated in small molecules that are roughly two orders of magnitude smaller than existing biomolecular, or polymer platforms used in biomimetic adhesion.

Use of Zwitterionic Small Molecule Adhesives to form Surface Active Monolayers, and Applications in Nanofabrication

The decision to include a simple aryl-propyl residue, as in Z-Cat-Ben and Z-Cat-Ben-F was predicated by simple questions of structure and activity, as well as to potentially assess the affect of pi-stacking by asymmetrically coating two surfaces with each molecule. Once prepared, further study showed that Z-Cat-Ben and its 3,5-bis-CF_3 derivative actually possessed many highly valuable properties, not observed in the aliphatic series. Most importantly, in contrast to the other surface primers which formed bilayers, Z-Cat-Ben and Z-Cat-Ben-F appeared to deposit on surfaces as strongly bound self assembled monolayer (SAM), which was molecularly thin (0.5 nm) and completely uniform. Z-Cat-Ben also displayed the highest resistance to oxidation (E_{ox} = 0.84 V) of all of the zwitterions tested, the aromatic moieties providing a large degree of oxidative shielding, possibly a result of pi-stacking within the aggregates.

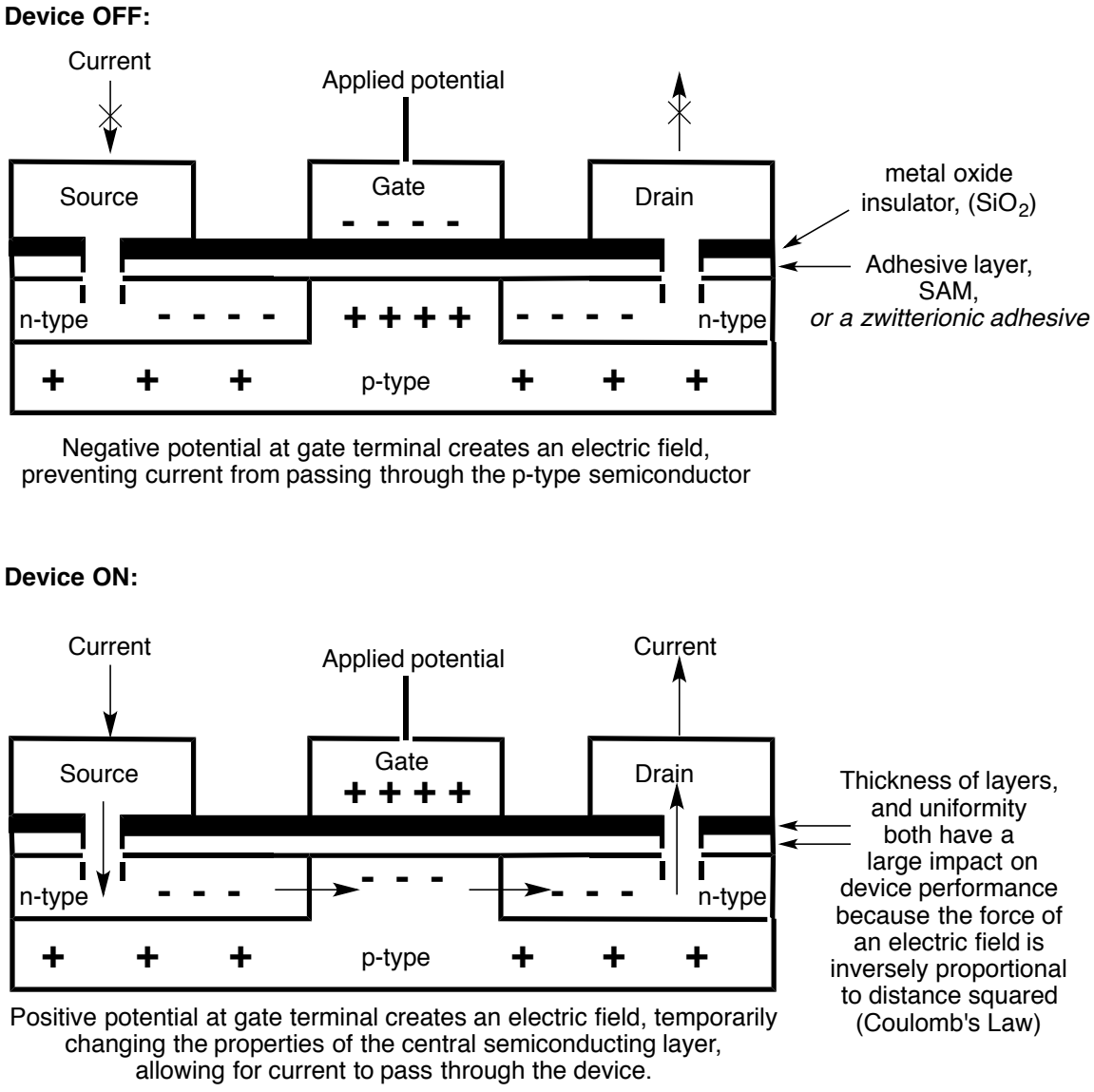
Z-Cat-Ben's strong adhesion, oxidative resistance, and quick self assembly to form defect free, nanometer thin monolayers were subsequently identified as potentially very useful properties for nanofabrication on metal oxide surfaces (SiO_2). Existing approaches that can use SAMs for nanofabrication are not yet practical, sulfur based SAMs are incompatible with oxide surfaces,[23] while silanization based methods and others require extended processing times, high temperatures, with excesses of toxic reagents/solvents, and do not form uniform monolayers.[24, 25] In order for organic-electronic devices to be realized as a viable

technology, methods of surface coating must be both rapid to allow high throughput processing, and yield uniform monolayers. Defects in the surface can cause failure of electronic devices, where transfer of charge across the boundary will render the device inoperable.[26, 27] Z-Cat-Ben, therefore, seemed an ideal candidate to test the newly minted small molecule surface primers in nanofabrications.

A field effect transistor, in its simplest form, is both a switch and an amplifier, and is one of the fundamental devices that allow for computers to operate. There is a source terminal and drain terminal through which current can flow, and a gate terminal between the two, used to switch the state of the transistor between on and off. The source and drain terminal are connected by a sandwich of semiconductor layers, in a p-n-p, or n-p-n arrangement. For example in a n-p-n type transistor, this means that the path between the source and drain consists of a p-type semiconductor where there fewer electrons available to conduct charge, sandwiched between two n-type semiconductors, where there are more “free” electrons available to conduct charge. The gate terminal is adhered above the middle p-type layer, but is insulated by a layer of metal oxide, preventing current from flowing through the gate. By applying a potential to the gate terminal, an electromagnetic field is produced, which temporarily changes the conductivity properties of the middle semiconducting layer, permitting current to flow through the sandwiched layers of semiconductors between the source and drain. Therefore, by adjusting the potential at the gate

terminal, it becomes possible to turn the flow of current on and off through the transistor (Figure 6).[28]

Figure 6: General Illustration of an n-p-n MOSFET Device



Since in a MOSFET (Metal Oxide Semiconductor Field Effect Transistor), the gate terminal is attached to the insulating oxide layer, and that the strength of an electromagnetic field is inversely proportional to distance squared (Coulomb's

Law), both a thinner oxide layer, and thinner binder used to attach the oxide to the gate terminal, will improve the efficiency of the device, by both increasing mobility of electrons in the semiconducting layers and reducing the potential needed to switch the on/off states at the gate terminal.[28]

Accordingly my collaborators were able to use Z-Cat-Ben and Z-Cat-Ben-F to construct organic field effect transistors, using the surface primers to adhere the insulating SiO_2 to organic conducting polymers and measuring their performance. The primers rapidly assembled a SAM on silicon wafers, where simple dipping in a 5 mM aqueous solution could coat the wafer in less than one minute. Therefore use of these primers reduces the environmental impact of SAM formation by obviating the need for high reaction temperatures, large quantities of organic solvent, or an excess surface modification reagents. Devices prepared with Z-Cat-Ben and particularly Z-Cat-Ben-F were then measured to have the highest charge mobility to date for organic field transistors, a testament to their strong adhesion, and molecularly thin characteristics. The higher charge mobility of Z-Cat-Ben-F was attributed to the repulsion residues of the CF_3 groups from one another, allowing for better contact between the insulating and semiconducting layers.

Conclusions:

By incorporation of the essential features of mfp-5 (fixed positive and negative charges, hydrophobic residues, catechols, coacervation) small molecules nearly two orders of magnitude smaller than the native proteins could be synthesized that displayed higher binding energies than mfp-5 while also mimicking the mussels delivery mechanism.[29] These molecules could be prepared in high purity by utilizing an underappreciated ethylated-silica adsorbent, which allows highly polar compounds to be purified by normal phase chromatography. By using benzyl protecting groups, the final catecholic zwitterions could be prepared without the need for any additional purification, or introduction of any salts or acids, where the use of PTFE filters was found to be convenient for separation of catalyst from the desired product. Using simple principles of molecular design and structure activity relationships, in going from simple alkyl residues to aryl, the zwitterionic adhesives could be transformed from bilayers to molecularly uniform monolayers that display remarkable resistance to oxidation. Dilute aqueous solutions of these aryl-containing adhesives could be used to bind substrates together by simple dip coating in times less than one minute, which allowed for both improved device properties, but also represents an environmentally responsible method for SAM formation.[30] In considering how relatively small changes in molecular structure can lead to large changes in physical properties for this class of molecules, I believe that there is a large body of knowledge waiting to be discovered with further studies of

these fascinating compounds. For instance, we have no good explanation as to why Z-Cat-C8 is a remarkable adhesive at 0.5 mM but is much less effective at 5 mM, where Z-Cat-Ben is equally effective at both concentrations, and Z-Cat-C4 is only effective at the higher concentration! Also puzzling is the reduced adhesion of the reversomer, Rev-Z-Cat-C8, relative to the normal compound. More generally, I believe that these projects exemplified how interdisciplinary collaborations should work. There remain a large number of problems that a practicing synthetic chemist may be unaware of if they remain focused within the "total-synthesis/synthetic-methods paradigm" that dominates most organic chemistry research labs. Yet a well trained organic chemist may be able to help his collaborators access many more interesting classes of compounds, unrelated to natural products or medicines that they couldn't synthesize on their own.

Finally I wish to offer my greatest thanks to Prof. Lipshutz, and Dr. Kollbe Ahn, for giving me this opportunity to broaden my horizons with this fascinating project.

References

[1] Lee, B. P.; Messersmith, P. B.; Israelachvili, J. N.; Waite, J. H. *Annu. Rev. Mater. Res.* **2011**, *41*, 99.

[2] Dolgin, E. *Nature Med.* **2013**, *19*, 124.

[3] Gittens, J. E.; Smith, T. J.; Suleiman, R.; Akid, R. *Biotechnology Advances*, **2013**, *31*, 1738.

[4] Danner, E. W.; Kan, Y. J.; Hammer, M. U.; Israelachvili, J. N.; Waite, J. H. *Biochemistry* **2012**, *51*, 6511.

[5] Maier, G. P.; Rapp, M. V.; Waite, J. H.; Israelachvili J. N.; Butler, A. *Science*, **2015**, *349*, 628.

[6] Stewart, R. J.; Wang, C. S.; Shao, H. *Adv. Colloid Interface Sci.* **2011**, *167*, 85.

[7] Winslow, B. D.; Shao, H.; Stewart, R. J.; Tresco, P. A. *Biomaterials*, **2010**, *31*, 9373.

[8] For a discussion of factors affecting formation of coacervates, see: Menger, F. M.; Sykes, B. M. *Langmuir,* **1998**, *14*, 4131; and references therein

[9] Anderson, T. H.; Yu, J.; Estrada, A, Y.; Hammer, M. U.; Waite, J. H.; Israelachvili, J. N. *Adv. Funct. Mater.* **2010**, *20*, 4196.

[10] Liu, B.; Burdine, L.; Kodadek, T. *J. Am. Chem. Soc.* **2006**, *128*, 15228.

[11] Martinez-Rodriguez, N. R.; Das, S.; Kaufman, Y.; Israelachvili, J. N.; Waite, J. H. *Biofouling*, **2015**, *31*, 221.

[12] Yamamoto, H. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 613.

[13] Statz, A. R.; Meagher, R. J.; Barron, A. E.; Messersmith, P. B. *J. Am. Chem. Soc.* **2005**, *127*, 7972.

[14] Heo, J.; Kang, T.; Jang, S. G.; Hwang, D. S.; Spruell, J. M.; Killops, K. L.; Waite, J. H.; Hawker, C. J. *J. Am. Chem. Soc.* **2012**, *134*, 20139.

[15] Seo, S.; Das, S.; Zalicki, P. J.; Mirshafian, R.; Eisenbach, C. D.; Israelachvili, J. N.; Waite, J. H.; Ahn, B. K. *J. Am. Chem. Soc*. **2015**, *137*, 9214.

[16] Zhong, C. Gurry, T.; Cheng, A. A.; Downey, J.; Deng, Z.; Stultz, C. M.; Lu, T. K. *Nat. Nanotechnol*. **2014**, *9*, 858.

[17] Thanh, T.; Chabrier, P. *Bull. Soc. Chem. Fr.* **1974**, *3*, 667.

[18] Peresypkin, A. V.; Menger, F. M. *Org. Lett*. **1999**, *1*, 1347.

[19] For a review of gemini surfactants, see: Menger, F. M.; Keiper, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1906.

[20] Bodroux, F. *Bull. Soc. Chim. France* **1905**, *33*, 831.

[21] For preparation of C2-silica gel, refer to the Supplementary Information of: Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

[22] Israelachvili, J.; et al*. Rep Prog Phys,* **2010**, *73*, 1.

[23] Vericat, C.; Vela, M. E.; Benitez, G.; Carro, P.; Salvarezza, R. C. *Chem. Soc. Rev.* **2010**, *39*, 1805.

[24] Gooding, J. J.; Ciampi, S. *Chem. Soc. Rev*. **2011**, *40*, 2704.

[25] Naik, V. V.; Crobu, M.; Venkataraman, N. V.; Spencer, N. D. *J. Phys. Chem. Lett.* **2013**, *4*, 2745.

[26] Luo, C.; Kyaw, A. K. K.; Perez, L. A.; Patel, S.; Wang, M.; Grimm, B.; Bazan, G. C.; Kramer, E. J.; Heeger, A. J. *Nano Lett*. **2014**, *14*, 2764.

[27] Das, S.; Donaldson, S. H., Jr.; Kaufman, Y.; Israelachvili, J. N. *RSC Adv*. **2013**, *3*, 20405.

[28] Horowitz, P.; Hill, W. *The Art of Electronics*, Cambridge University Press: New York, **1989**.

[29] Ahn, B. K.; Das, S.; Linstadt, R. T. H.; Kaufman, Y.; Martinez-Rodriguez, N. R.; Mirshafian, R.; Kesselman, E.; Talmon, Y.; Lipshutz, B. H.; Israelachvili, J. N.; Waite, J. H. *Nat. Commun*. **2015**, *6*, 8663.

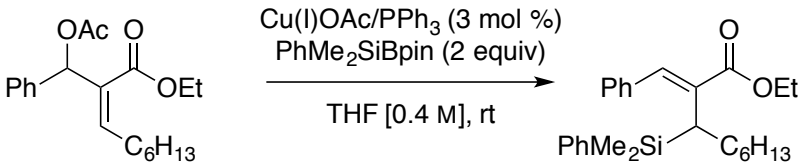
[30] Das, S.; Lee, B. H.; Linstadt, R. T. H.; Cunha, K.; Li, Y.; Kaufman, Y.; Levine, Z. A.; Lipshutz, B. H.; Lins, R. D.; Shea, J-E.; Heeger, A. J.; Ahn, B. K. *Nano Lett.*, **2016**, *16*, 6709.

Appendix: Selected Experimental Procedures, Notes, and Spectral Data

Boron and Silicon S_N2' Substitutions of β-substituted MBH-Adducts

Addition of Boron or Silicon Nucleophiles to MBH adducts with β-substitution has not been described, and remains an interesting and potentially enantioselective reaction.

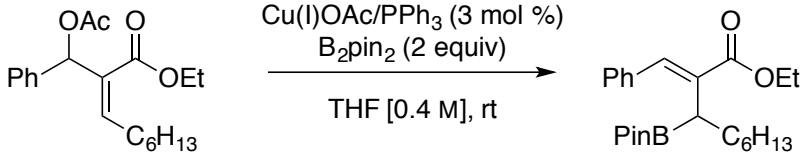
Ethyl-2-benzylidene-3-(dimethyl(phenyl)silyl)nonanoate



To a microwave vial fitted with a stir bar, septa, and Argon needle, was added 0.5 ml of THF (wet), 0.7 mg of Cu(I)OAc, and 1.3 mg PPh_3 and stirred until homogeneous. Suginome's Reagent (0.4 mmol) was added was added resulting in a dark red solution. β-substituted MBH acetate (0.2 mmol) was then introduced via syringe, and the reaction was stirred under Argon at ambient temperature until TLC indicated no further change. Once judged complete, the mixture was diluted with hexanes and filtered through a short plug of silica, whereupon volatiles were evaporated under reduced pressure and the residue was purified

by flash chromatography eluting 0-5% Et_2O/hexanes to afford the 65 mg (80%) of the title compound as a clear oil. R_f = 0.6 in 10% Et_2O/hexanes; Stain = UV/I_2/$KMnO_4$. See attached NMR for spectral data.

Ethyl-2-benzylidene-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonanoate



Prepared according to the procedure given above substituting Suginome's Reagent for B_2pin_2. Yield = 51 mg (64%). R_f = 0.16 in 5% Et_2O/hexanes; Stain = UV/I_2/$KMnO_4$. See attached NMR for spectral data.

Titration of commercial Vinylmagnesium Chloride:

Vinylmagnesium Chloride was titrated by the following modification of Watson & Easthams procedure: 1,10 phenanthroline was dissolved in anhydrous Xylenes to make a 1.5 mg/ml solution which served as indicator. 0.1 ml of the aforementioned 1,10 phenanthroline solution, and 0.9 ml of anhydrous xylenes were added to a dry 25 ml round bottom flask fitted with a septa, argon needle, stir bar and the flask was cooled to 0 ˚C in an ice bath. 1ml of the Grignard reagent in question was drawn into a syringe and the first few drops of RMgX solution was added to the indicator solution resulting in a brightly colored solution. The solution was stirred at 0 ˚C for 15 minutes, the absence of any

diminution in color indicated that the argon manifold was sufficiently anhydrous for subsequent work with organometallics. The remainder of the Grignard solution was added and let stir for a few minutes, then titrated dropwise at 0 ˚C with a [1 M] solution of 1-octanol in xylenes, whereupon the dissapearance of color indicated the endpoint had been reached.

Notes:

- Octanol was chosen as it is inherently a very anhydrous alcohol and showed minimal solubility problems of the resulting magnesium alkoxide. Additionally the use of a primary alcohol over a secondary alcohol in this case, while more exothermic, conveniently gave a more rapid color change near the endpoint, with less stirring time needed between drops.
- Switching the order of addition of RMgX/Octanol did not give as satisfactory an endpoint and adding the octanol solution last is recommended.
- Octanol and Xylenes were dried over activated 3 Å sieves overnight.
- A [1 M] solution of Octanol was prepared from 15 ml Octanol and 80 ml Xylenes
- As noted by other authors the organometallic content of the solution may not accurately reflect the true concentration of Vinyl Grignard as other metallated species may be present in the mixture. Therefore it is advisable to check the quality of Vinyl Grignard solutions upon recipt by

reacting with 1 equivalent of an aldehyde and checking the purity of the resulting allylic alcohol by ^{1}H NMR, GCMS, HPLC or other means.

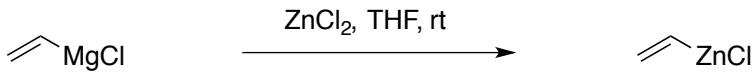
- Attempts to prepare Vinyl Magnesium Chloride in diethyl ether by evaporating the THF at 0 ˚C under high vaccum, and exchanging the solvent, led to polymerization of the Grignard reagent. Additionally attempts to prepare Vinylmagnesium Bromide in Diethyl ether as opposed to THF were completely unsuccessful, regardless of quality or method of activation of the magnesium surface, and commercial Vinylmagnesium Chloride from Acros was used in this study. This surprising result has been noted previously.
- Grignard reagent was stored at ambient temperature under argon, and no substantial degradation in quality or titre was noticed over the course of this study
- No difference in titre was noticed performing the titration at ambient temperature using a water bath

Preparation of [0.5 M] $ZnCl_2$ in THF:

Zinc Chloride was dried first superficially in an oven at 180 ˚C overnight, then transferred to a dry round bottom flask. The flask was placed under high vacuum with the aid of a dry ice/acetone trap and gently melted under low flame. The flask was let cool to allow solidification, and the process was repeated twice to

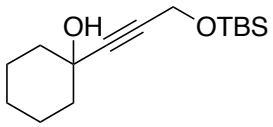
give anhydrous $ZnCl_2$. Once cooled the flask was backfilled with argon and brought into to a glovebox, along with a 100 ml volumetric flask, spatula, mortar and pestle, where the zinc chloride was ground to a fine powder and 6.816 g (50 mmol) were weighed out into the 100 ml volumetric flask. The volumetric flask containing the $ZnCl_2$ was fitted with a septa and brought out of the glovebox, and anhydrous THF was added via cannula to make the final volume 100 ml, the septa was briefly removed under argon to add a clean, dry, stirbar and the flask was stirred vigorously to give a [0.5 M] solution of $ZnCl_2$ in THF.

Vinyl Zinc(II) Chloride:



24 mmol of vinylmagnesium chloride in THF (15 ml, titrated to 1.6 M by the aforementioned method) was added via syringe to a dry 100ml round bottom flask fitted with stir bar, septa, and argon needle, and placed in a water bath. 24 mmol (48 ml, 0.5 M) of $ZnCl_2$ in THF was introduced slowly via syringe and the solution was stirred for 3 hours at ambient temperature to give a tan solution of Vinyl Zinc(II) Chloride (assumed to be 0.38 M) with some precipitate. Stirring was ceased to let the precipitate settle, and the supernatant could be then used directly in subsequent Negishi coupling. Alternatively the majority of the precipitated salts could be filtered off by means of a double-ended frit into a fresh 100 ml flask under argon.

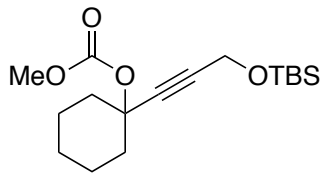
1-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol



To a dry 1L round bottom flask fitted with a septa, stir bar, and argon needle was added 17.714 grams (104 mmol, 1.04 equiv) of TBS-protected propargyl alcohol, and 500 ml anhydrous Et_2O. The solution was cooled with stirring to -78 ˚C in a dry ice/acetone bath whereupon 44 ml of *n*-BuLi [2.35 M] in hexanes (103.4 mmol, 1.034 equiv) was added dropwise over approx. 15 minutes, and the solution was stirred for 1 hour while maintaining temperature. 10.35 ml of freshly distilled Cyclohexanone (100 mmol, 1 equiv) was added slowly dropwise, and once the addition was complete the solution was stirred at -78 ˚C for an additional 1-2 hours, whereupon the cooling bath was removed and the flask was stirred while gradually warming to room temperature with slight yellowing of the solution. Once the solution reached ambient temperature, the septa was removed and the reaction was quenched by the cautious addition of 100 ml of a dilute pH 7 buffer solution. The mixture was stirred vigorously for a few minutes, then let settle before decanting the ether layer into a separatory funnel, with and additional 200 ml or so of ether used to rinse the reaction flask. The organic layer was extracted 2x with 50 ml water, 1x Brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude oil. The crude compound was then placed under high vacuum, and let sit for 3 days in this manner with periodic rotation of the flask to remove traces of cyclohexanone. Unreacted

cyclohexanone could not be satisfactorily removed by chromatography owing to the small differences in polarity, and if present, the use of a high vacuum manifold is recommended. Once traces of cyclohexanone were fully removed as indicated by TLC (R_f = 0.16, 10% Et_2O/Hexanes, yellow-green spots with Vanillin) the crude material was loaded with hexanes onto a flash column, and purified by gradient elution (0-2-5-25% Et_2O/Hexanes). Fractions containing the desired material were pooled, evaporated with Pentanes under reduced pressure, affording a clear viscous oil which gradually solidified into an amorphous white solid upon standing under high vacuum. Yield was 18 grams (67% of theoretical)

1-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclohexyl methyl carbonate

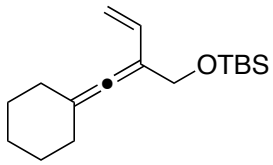


The title compound was prepared by an adaptation of a published procedure (*JOC*, **1970**, *35*, 1198)

A dry 250 ml round bottom flask fitted with a septa, stir bar, and argon needle, was charged with 8.215 g of the aforementioned tertiary alcohol (30.6 mmol, 1.02 equiv) and 130 ml of anhydrous THF and stirred at room temperature until complete dissolution. The flask was cooled with stirring to -78 ˚C, in a dry

ice/acetone bath and let stir for 10-15 minutes. 12.9 ml of *n*-BuLi 2.35 M in hexanes (30.3 mmol, 1.01 equiv) was then added slowly dropwise via syringe, and the solution was stirred for an additional 30 minutes while maintaining temperature. 2.318 ml of methyl chloroformate (30 mmol, 1.00 equiv) was added slowly dropwise via syringe, and the solution was stirred for an additional 1 hour at -78 ˚C. The cooling bath was then removed and let stir while warming to room temperature over the course of 2 hours. The septa was then removed and the reaction was quenched with 25 ml of sat. $NaHCO_3$ and 25 ml of water and stirred vigorously for 30 minutes to remove any traces of unreacted chloroformate, the stir bar was removed and the majority of the volatiles were removed under reduced pressure. The contents of the flask were then poured into a separatory funnel, and the flask was rinsed with two 100 ml portions of ether into the separatory funnel, and shaken. The layers were separated, and the ether layer was washed with a small quantity of water, saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to obtain a crude oil. The crude material was loaded on top of a silica column with hexanes, and purified by gradient elution (0-5-10-100% Et_2O/Hexanes). Fractions were pooled and evaporated with pentanes under reduced pressure, then let stand under high vacuum to afford the title compound as a clear viscous oil. Yield was 9.365 g (95.6% of theoretical)

***tert*-butyl((2-(cyclohexylidenemethylene)but-3-en-1-yl)oxy)dimethylsilane**



Vinyl allene was prepared from the preceding carbonate by substantial modifications of Vermeer's procedure (*Tet. Lett.* **1981**, *22*, 1451.)

A dry 500ml round bottom flask was fitted with a stirbar, septa, taken into a glovebox where 7.083 grams of $ZnCl_2$ (52 mmol, 1.3 equiv, **Note 1**), 561 mg of $PdCl_2(PPh_3)_2$ (0.8 mmol, 0.02 equiv), and 419 mg of PPh_3 (1.6 mmol, 0.04 equiv, **Note 2**), were added. The flask was sealed and removed from the glovebox, placed under a positive pressure of argon, 400 ml of anhydrous THF was added and the solution was stirred at ambient temperature until complete dissolution of all solids. 0.8 ml of a 1 M solution of DIBAL-H in hexanes (0.8 mmol, 0.02 equiv) was added slowly via syringe with stirring whereupon the solution turned from yellow to a dark brown (**Note 3**). The flask was then placed in a water bath to maintain ambient temperature, and 31.25 ml of a 1.6 M solution of Vinylmagnesium Chloride in THF (50 mmol, 1.25 equiv) was added slowly via syringe where there was a slight exotherm and formation of some precipitate (**Note 4**). After the addition was complete the solution was stirred at ambient temperature for an additional 15 minutes to ensure complete formation of the zinc reagent. 13.06 grams of the preceding propargyl carbonate (40 mmol, 1 equiv) was then added rapidly via syringe whereupon there was a slight exotherm

accompanied with some effervescence (Argon needle is still present to accommodate any pressure build up of CO_2) . The solution was let stir at ambient temperature for 1-1.5 hours or until TLC indicated complete conversion.

Proper quenching of the reaction mixture, precipitation of Mg/Zn salts, *and most importantly rapid removal of Palladium residues*, are essential to obtain the desired vinyl allene in high yield/purity. Incomplete removal of Pd residues before chromatography were found to substantially degrade desired product and make separation tedious. (**Note 5**)

3 ml of Methanol was then added via syringe to quench excess organometallics, and the solution was stirred for a few minutes, the septa was briefly removed and 4 grams of sodium diethydithiocarbamate trihydrate (NaDEDTC) was added in one portion, resealed and stirred for an additional 10 minutes. The 100 ml of hexanes was added with stirring resulting in the precipitation of a large amount of salts, and the solution was quickly filtered over a short pad of silica into a 1 L round bottom flask, and the residue in the reaction flask was rinsed through the pad with additional ether. An additional 4 grams of NaDEDTC, was added to the 1 L flask and the volatiles were removed under reduced pressure. The crude was resuspended in ether was added to the flask, and the contents were filtered over a second pad of silica. 4 more grams of sodium NaDEDTC, and 100 ml of DI water were added to the solution, and the solution was transferred to a separatory funnel, where it was shaken and the layers separated. The ether layer was washed with an additional portion of water, then brine, dried over

$MgSO_4$, filtered, and evaporated under reduced pressure to give a crude yellow oil with some yellow precipitate. The crude material was immediately taken up in hexanes and loaded onto a silica column and purified by gradient elution (0-1-2-5% Et_2O/Hexanes). Under these conditions the desired product was incompletely separated from traces of PPh_3, but could be used without disadvantage in the subsequent reaction. Pure fractions were combined and evaporated and weighed 6.8 grams (59.6% of theoretical). The mixed fractions containing product and traces of PPh_3 were evaporated to yield an additional 3.6 grams of material (31.6% of theoretical). Both samples were combined for the following reaction.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.22 (dd, J = 17.5 Hz, J = 10.5 Hz, 1H), 5.21 (d, J = 17.5 Hz, 1H), 4.99 (d, J = 11 Hz, 1H), 4.31 (s, 2H), 2.20-2.10 (m, 4H), 1.65-1.50 (m, 6H), 0.90 (s, 9H), 0.07 (s, 6H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 200.28, 134.52, 112.27, 104.37, 103.46, 62.52, 31.38, 27.64, 26.26, 26.06, 18.49, -5.05

CI-HRMS: Calculated for $C_{17}H_{31}OSi$: 279.2139. Found: 279.2133 $(M+H)^+$

Note 1: Although Vermeers protocol uses, and our initial experiments were performed with the preformed Zinc Reagent, it was found to be much more convenient to form the reagent *in situ*, with a slight excess of $ZnCl_2$ relative to RMgX, and 10-15 minutes of stirring sufficient to ensure complete formation of the organozinc.

Note 2: Vermeers protocol recommends the use of Palladium Tetrakis, however owing to the oxygen sensitivity/batch variability of Tetrakis more reliable results and cleaner reactions were obtained making it *in situ* from $PdCl_2(PPh_3)_2$ and PPh_3. Additionally, several other catalyst systems were examined, including $Pd(0)/(P(o\text{-}tol)_3)_2$, $Pd(0)/(PCy_3)_2$, Neolyst CX-31, 1000ppm Handaphos/$PdCl_2$, IPrCuCl, and DPEPhos/$PdCl_2$. Suprisingly PPh_3 is the preferred ligand for this transformation, with DPEPhos being the other ligand that gave any appreciable amount of product (*vida infra*). These results are in agreement with those of Molander who investigated the preparation vinylallenes from vinyl-BF_3K salts and found PPh_3 as the preferred ligand.

Note 3: DIBAL-H was used as to reduce Pd(II) to active Pd(0). While the Vinyl-organometallic could be used as well to reduce the palladium, reductive elimination from this complex furnishes a small amount of 1,3 butadiene which could potentially react with desired product and/or lead to side reactions and the use of DIBAL-H is recommended. Additionally the use of DIBAL-H is required when using different Grignard reagents such as MeMgCl, which did not reduce Pd(II) in the presence of $ZnCl_2$, for *in situ* RZnX formation.

Note 4: Exotherm present but is not vigorous even if the addition rate is rapid, and a water bath was employed.

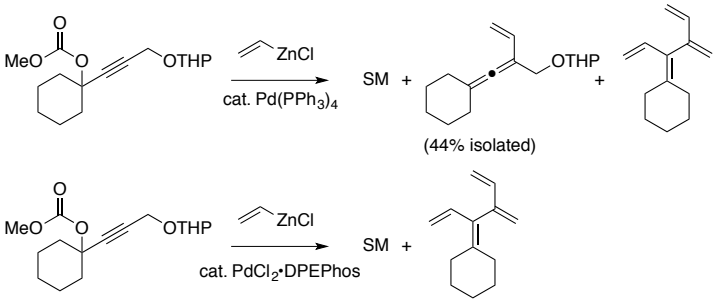
Note 5: As noted by Molander, if Palladium residues are not rapidly removed at the end of the reaction, the yield suffers substantially with the formation of

several byproducts similar in R_f to product, as well as some additional baseline impurities. Even several successive filtrations though silica gel at the end of the reaction are insufficient to remove soluble palladium species. Molander recommends the addition of activated charcoal (DARCO) and stirring under air for 30 minutes followed by filtration over celite, and while this procedure was successful at preventing the majority of sample degradation, separation was still tedious to remove trace impurities, which unfortunately could not be separated at a later stage in the synthesis. Therefore alternative methods were examined to remove the palladium residues presumable responsible for sample degradation.

Note 6: We were encouraged by a report detailing the use of sodium dithiocarbamate salts to remove metal residues, regardless of oxidation state, from organic mixtures to achieve 10 > ppm levels of Pd, Cu, and Fe in API's. (*Org. Process Res. Dev*. **2015**, *19*, 1369). Gratifyingly the use of three successive treatments with NaDEDTC combined with two silica filtrations, and an aqueous workup provided a crude material with substantially improved yield and impurity profile. While likely excessive, the procedure was not optimized to reduce the number of filtrations, or determine the minimum amount of NaDEDTC required for full Pd removal, and it was felt best to err on the side of caution to avoid laborious additional purification steps. We believe in addition to the documented uses in purification of wastewater and pharmaceutical intermediates, the use of thiocarbamate salts will prove advantageous for the

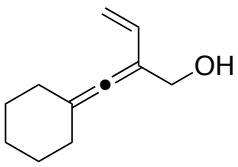
preparation of other highly unsaturated carbon structures when metal catalysis is required.

Note 7: Reaction of the analogous OTHP ether in place of the OTBS derivative gave in addition to anticipated product, unreacted starting material and a [4]-dendralene as the major side product as identified by ^{1}H-NMR. Switching the ligand to $PdCl_2$•DPEPhos actually led to the formation of the dendralene to the exclusion of the vinylallene. The catalyst $PdCl_2$•DPEPhos therefore kinetically favors reaction with the OTHP-vinylallene intermediate over the starting propargyl-carbonate.



Note 8: Attempts to install the vinyl unit on allenes via cuprates were low yielding. See below for additional details.

2-(cyclohexylidenemethylene)but-3-en-1-ol



The aforementioned vinyl-allene (10.4 grams) was dissolved in 200 ml of absolute EtOH in a 500 ml round bottom flask with a stir bar, followed by 1.384 grams of *p*-Toluenesulfonic acid monohydrate (7.28 mmol, 0.2 equiv, **Note 1**) and the solution was sealed with a septa and stirred for approx. 4 hours at room temperature until there was no further change as evidenced by TLC (**Note 2**). 10 mmol of solid $NaHCO_3$) was added along with 50ml or so of water to quench the reaction, and EtOH was removed under reduced pressure. The contents of the flask were poured into 200 ml of ether in a separatory funnel and the flask rinsed with additional ether and the layers were separated. The ether layer was washed sequentially with additional water, saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude allenyl alcohol which was purified further by flash chromatography gradient elution 0-5-10-20% Et_2O/Hexanes (**Note 3**), and evaporation of factions afforded of vinyl-allenol as a clear to slightly yellow oil with a pungent sweet odor. Yield was 5.86 grams (93% of theoretical) and was observed by NMR to contain ca. 5% of TBS-OH that co eluted with product. Product was stored under high vacuum in a dry round bottom flask overnight before being carried on to the next step.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.26 (dd, J = 18.5 Hz, J = 11 Hz, 1H), 5.14 (d, J = 18.5 Hz, 1H), 5.01 (d, J = 11 Hz, 1H), 4.23 (s, 2H), 2.18-2.14 (m, 4H), 1.65-1.50 (m, 7H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 198.15, 133.83, 112.21, 107.89, 104.16, 60.50, 31.59, 27.83, 26.12, 25.77

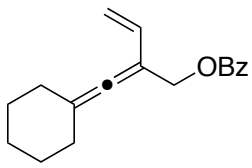
CI-HRMS: Calculated for $C_{11}H_{16}O$: 164.1201. Found: 164.1195 $(M+\bullet)^+$

Note 1: PTSA was found to be a convenient and efficient acid catalyst for this desilylation. The use of pyridinium p-toluenesulfonate (PPTS) as a milder acid catalyst had no benefit in terms of reaction cleanliness, and longer reaction times and/or heating was required. The use of Dowex 50-W as a heterogeneous acid catalyst, even at high loadings, gave a much slower reaction than PTSA.

Note 2: Residual starting material stains very intensely under UV/I_2 and trace amounts of starting material can appear as significant quantities, and a reaction time of ca. 4 hours is usually sufficient to desilylate the majority of substrate.

Note 3: 0-5% portion of the gradient is necessary to remove traces of starting material, and the residual PPh_3 present in the starting material.

2-(cyclohexylidenemethylene)but-3-en-1-yl benzoate



The flask containing approx. 33.8 mmol vinyl-allenol from the preceding step was backfilled with argon, removed from the manifold and quickly fitted with a dry stir bar, septa, and argon needle. 25.5 ml of anhydrous DCM was added via syringe, followed by 14.22 ml of anhydrous Et_3N (101.5 mmol, 3 equiv) and 68 mg DMAP (2 mg/mmol). The flask was cooled to 0 ˚C in an ice bath and stirred gently while the temperature was let equilibrate for 10 minutes. 5.9 ml of Benzoyl

Chloride (50.8 mmol, 1.5 equiv) was then added slowly dropwise via syringe over 10 minutes, during which time was accompanied by the formation of some white precipitate and a yellowing of the solution. The solution was stirred at 0 ˚C for an additional 15 minutes, and the cooling bath was removed and let stir while warming to ambient temperature for an additional 45 minutes. Once TLC indicated that the reaction was complete, the reaction was diluted with 200ml ether, and cautiously poured into 100 ml saturated $NaHCO_3$ in a 500ml round bottom flask, rinsing the reaction flask with additional ether. The biphasic solution was stirred vigorously at room temperature until TLC indicated that the excess Benzoyl Chloride had been completely quenched. The contents were then transferred to a separatory funnel, rinsing the flask with additional ether and the layers were separated. The organic layer was then washed sequentially with 70 ml water (ca. 2 ml/mmol), twice with 100 ml (10% w/w) aqueous $NaHSO_4$ (ca. 3 ml/mmol), 70 ml water, and finally 70 ml (2 ml/mmol) of sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude compound as a viscous yellow oil. The crude material was then evaporated twice with Pentanes to remove traces of Et_3N and Et_2O that interfered with subsequent chromatography, causing product to elute too rapidly. The crude material was loaded onto a flash column with hexanes, and purified by gradient elution 0-2% Et_2O/Hexanes. The fractions containing desired material were pooled, concentrated under reduced pressure, and trace volatiles were removed under high vacuum for several hours giving the pure vinyl-allenyl

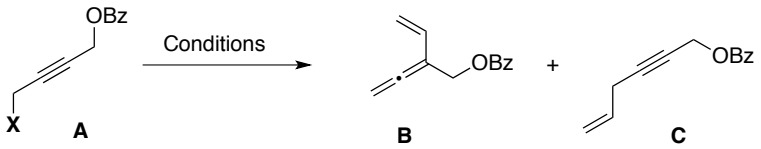
benzoate as a viscous, clear to slightly yellow oil. Yield was 7.4 grams (81% of theoretical.) Compound was stored under argon, protected from light, in vials tightly wrapped with parafilm.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 8.07-8.05 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.43 (m, 2H), 6.30 (dd, J = 18 Hz, J = 11 Hz, 1H), 5.21 (d, J = 17.5 Hz, 1H), 5.05 (d, J = 11 Hz, 1H), 4.98 (s, 2H), 2.17-2.08 (m, 4H), 1.62-1.42 (m, 6H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 201.24, 166.39, 134.02, 132.98, 130.56, 129.80, 128.41, 112.33 105.49, 99.06, 63.16, 31.15, 27.35, 26.05

CI-HRMS: Calculated for $C_{18}H_{19}O_2$: 267.1380. Found: 267.1405 $(M-H)^+$

Selected optimization conditions for vinylallenyl-benzoate formation *via* cuprates



Entry	M (equiv.)	X	Cu (equiv.)[a]	Solvent	Temp.	A	B	C	Method[b]
1	MgCl (1.00)[c]	OBz	CuI (1.00)	THF [0.2M]	-30˚C	100	0	0	(TLC)
2	--	--	CuI•PPh_3 (1.00)	--	--	100	0	0	(TLC)
3	--	--	CuBr•LiI (1.00)[d]	--	-30˚C to rt.	100	0	0	(TLC)
4	--	OMs	CuCN•2LiCl (1.00)	--	-78˚C	80	5	15	(GCMS)
5	--	--	--	Et_2O [0.2M]	--	0	25	25	(TLC)
6	**--**	**Cl**	**--**	**--**	**--**	**(45% iso. as 4:1 mixture of B:C)**			**(^{1}H-NMR)**
7	Li **(1.00)**	**--**	**[(2-Thienyl)CuCN]$^-$ Li$^+$ (1.00)**	**THF [0.2M]**	**--**	**(32% pure B isolated)[e]**			**(^{1}H-NMR)**
8	--	--	CuCN (1.00)	--	--	100	0	0	(TLC)
9	Li (2.00)	--	--	--	--	0	0	42	(^{1}H-NMR)
10	**MgCl (1.10)[c]**	**--**	**CuCN•2LiCl (0.10)[f]**	**Et_2O [0.2M]**	**-78˚C to rt.**	**(23% pure B isolated)[e]**			**(^{1}H-NMR)**

-- denotes no change from the variable given above.
Reactions were stirred until TLC indicated no further change in conversion (typically 2-18 hours).

[a] Reactions with stochiometric Cu were performed by first adding the indicated organometallic to the copper source, to form either "RCu" or the cuprate. Once reagent was fully formed the substrate was introduced last.

[b] Conversion as determined by TLC, GCMS, or ^{1}H-NMR. TLC values are approximate.

[c] Vinylmagnesium chloride was added as a [1.6M] solution in THF.

[d] With 1 equiv. BF_3•Et_2O to give formally RCu•BF_3 (Yammamoto's Reagent)

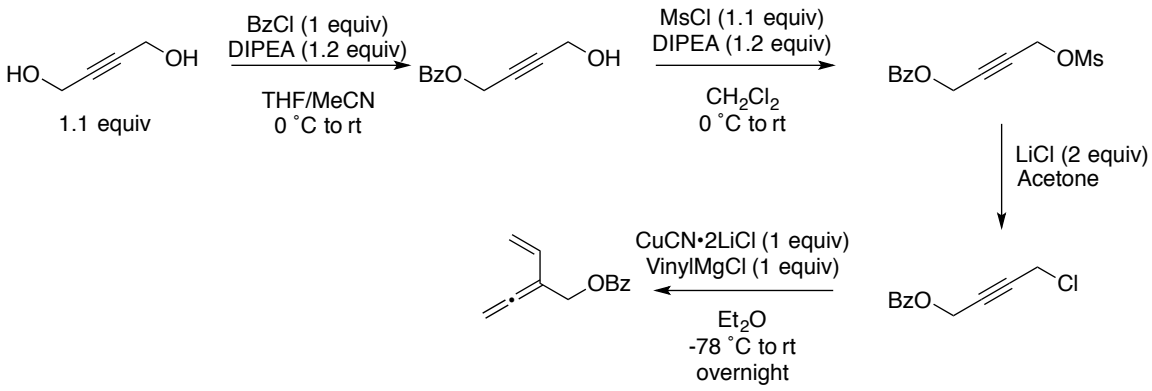
[e] Regioisomer **C** was present in small amounts as indicated by TLC and content was not determined. Yield refers to isolated amount of pure **B** after chromatography, mixed fractions containing **B**+**C** were discarded and not factored into the reported yield.

[f] RMgX was introduced last down the sides of the reaction vessel (1 drop/5 seconds) to a solution of copper catalyst and substrate at -78˚C.

Initially it was anticipated that desired vinylallenyl-benzoates could be formed via an S_N2' reaction of vinylcuprates with propargylic electrophiles. Extensive attempts to optimize the reaction were for the most part unsuccessful, and a sample of the many conditions tested are reported above. vinylallenyl-benzoates could only be formed from the corresponding chloride in low yield by either: the stochiometric mixed magnesio-cynaocuprate in ether (entry **6**), *via* the stochiometric mixed higher order cyanocuprate in THF (entry **7**), or using the grignard reagent with a catalytic amount of the soluble CuCN•2LiCl in ether (entry **10**). In general higher S_N2' selectivity was observed in Et_2O opposed to THF, yet vinylmagnesium reagents cannot be prepared in Et_2O (*vida supra*), and as a result, regioselectivity still suffers. These approaches were on the whole unsatisfactory as they generated a large amount of copper and cyanide waste, required cryogenic temperatures, overall yields were low, and chromatographic separation of regioisomeric product **C** was tedious. Therefore this route was abandoned in favor of the aforementioned Negishi coupling route which proved superior in all respects.

2-vinylbuta-2,3-dien-1-yl benzoate

Simple vinyl-allenoate could be synthesized by the following route:



To a dry 1 L flask fitted with a stir bar, septa, and argon needle was added 2-buyne-1,4 diol (recrystallized from boiling EtOAc, 220 mmol, 1.1 equiv), 240 mmol DIPEA, and 600 ml of THF. After stirring for 30 min, the diol had still not completely dissolved, whereupon anhydrous MeCN was added in 30 ml portions with stirring until the substrate had completely dissolved. The flask was cooled to 0 ˚C in an ice bath, and once fully cooled, 200 mmol (1 equiv) of BzCl was added dropwise over 2 hours via syringe. The cooling bath was removed and the flask was was brought slowly to room temperature. Once judged complete by TLC, the reaction mixture was diluted with hexanes to help precipitate the amine hydrochloride salt, which was filtered off over a short pad of Celite, and the volatiles were removed under reduced pressure. The residue was redissolved in ether, transferred to a separatory funnel and washed sequentially with water, 1N HCl, water, sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to afford crude material which was purified by flash chromatography 0-35%

EOAc/hexanes to give 28.9 grams (76%) of mono-benzoylated product as a clear oil, along with 6.8 grams of di-benzoylated material as a white solid. R_f = 0.3 in 35% EtOAc/hexanes; Stain = UV/I_2/$KMnO_4$.

7.6 grams (40 mmol, 1 equiv) of the preceding intermediate was dissolved in 50 ml of anhydrous DCM in a dry round bottom flask fitted with a stir bar, septa, and argon needle. 8.4 ml of anhydrous DIPEA (48 mmol, 1.2 equiv) was added to the mixture via syringe, and the flask was cooled to 0 ˚C in an ice bath, whereupon 3.4 ml of MsCl (44 mmol, 1.1 equiv), was added dropwise. The solution was stirred at 0 ˚C for 30 minutes, then the cooling bath was removed and the flask was gradually brought to room temperature over 3 hours. Usual workup and flash chromatography eluting 0-100% DCM/hexanes afforded 8.5 grams (79%) of the corresponding mesylate as an orange/yellow liquid. R_f = 0.6 in 100% DCM; Stain = UV/I_2/$KMnO_4$. About 1.5 grams (18%) of the corresponding chloride was also isolated: R_f = 0.82 in 100%DCM; Stain = UV/I_2/$KMnO_4$.

6.666 grams (24.85 mmol, 1 equiv) of the preceding mesylate was dissolved in 50 ml of anhydrous acetone, whereupon 2.119 g of anhydrous LiCl was added in one portion, and the septa was resealed and left to stir overnight. In the morning, a large amount of a voluminous white ppt was observed, which had hindered stirring, and TLC showed the reaction to be incomplete. An additional 20 ml or so of additional acetone was added and stirring was able to resume, and the mixture was then heated to 50 ˚C for 4 hours, whereupon TLC showed the reaction to be complete. The flask was diluted with hexanes to help precipitate the Lithium salts

which were filtered off over a short pad of Celite, and the volatiles were removed in vacuo. The resulting residue was purified by flash chromatography eluting 0-30% Et_2O/hexanes, which afforded 4.8 grams (92.5%) of the desired chloride as a viscous, oil with a pungent odor. R_f = 0.82 in 100% DCM; Stain = UV/I_2/$KMnO_4$.

20 mg (0.1 equiv) of either CuCN or CuCN•2LiCl (both are satisfactory) was added to a flame dried microwave vial fitted with a stir bar, septa, and argon needle, followed by 10 ml of anhydrous Et_2O. The slurry was cooled to -78 ˚C in a dry ice/acetone bath and let stir for 15 minutes. 416 mg (2 mmol, 1 equiv) of the preceding chloride was then added via syringe, and the solution was let stir for an additional 10 minutes. 1.2 ml of recently titrated Vinylmagnesium chloride (1.9 M in THF, 2.28 mmol, 1.14 equiv) was then added very slowly via syringe to the center of the vortex (1 drop/ 5 seconds). Once the addition was complete, additional dry ice was added to the cooling bath, and the mixture was left to stir overnight with warming of the bath. Approx. 12 hours later, the bath temperature was measured to be -50 ˚C and the reaction was quenched by dropwise addition of first 0.5 ml MeOH, then a 1:9 solution of NH_4Cl/NH_4OH, and the mixture was brought to room temperature. The contents were transferred to a separatory funnel, rinsing the flask with an additional 50 ml or so of Et_2O, and the layers were separated, and the aqueous phase was extracted 3x with Et_2O, and the combined organics were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford crude material. The crude material was purified by flash chromatography on 12 inches of pre-dried silica gel (130 ˚C overnight), with a

slow gradient of 0-1% Et_2O/Hexanes to separate the desired product from the undesired S_N2 regioisomer. Evaporation of only pure fractions afforded 90 mg (23%) of the desired product as a clear oil.

TLC: R_f = 0.6 in 4% Acetone/Hexanes, (desired, major regiosiomer), R_f = 0.52 (undesired, minor regiosiomer) Stain = UV/I_2/Vanillin

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 2H), 7.56 (td, *J* = 7.7, 1.3 Hz, 1H), 7.48 – 7.39 (m, 2H), 6.28 (ddd, *J* = 17.7, 10.9, 1.0 Hz, 1H), 5.29 (ddd, *J* = 17.7, 1.3, 0.6 Hz, 1H), 5.13 (ddd, *J* = 7.1, 5.8, 5.0 Hz, 1H), 5.09 – 5.04 (m, 2H), 5.01 (dt, *J* = 3.4, 1.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.42, 166.41, 133.13, 131.91, 130.24, 129.81, 128.49, 114.15, 100.97, 77.74, 62.46.

General procedure for Diene-coupling in presence of additives (Robustness Screen)

1-2 mg of $PdCl_2$DPEphos was added to a microwave vial fitted with a spin vane, septa, and argon needle, followed by 0.4 ml of a 2 wt % solution of TPGS-750-M, and the mixture was stirred vigorously until homogeneous. 0.05 ml of Et_3N was added via syringe and the mixture was left stirring while the other reagents were weighed out. Between 51.6-54.2 mg of naphthylboronic acid (0.300-0.315 mmol,1.00-1.05 equiv) was added as a solid, followed immediately by 0.3 mmol (1 equiv) of the appropriate additive and 0.3 mmol of the allenoate substrate as soon as possible, followed by the an additional 0.055 ml of Et_3N (total = 2.5

equiv). The reaction was left to stir for approx 30 minutes (reaction followed by TLC), and once complete, the mixture was diluted with EtOAc and the entire contents of the reaction vessel were filtered through a short plug of silica gel. Volatiles were removed under reduced pressure to afford a crude mixture of product and additive, which was purified by flash chromatography 0-100% EtOAc/hexanes, isolating both the desired product and additive. Yields obtained of product and recovered additive after removal of trace volatiles on high-vacuum were used then as a measure of the functional group tolerance of the reaction with respect to functionality in the additive.

General procedure for Diene-coupling with OBBD borinates

2 mg of $PdCl_2$DPEphos was added to a microwave vial fitted with a spin vane, septa, and argon needle, followed by 0.4 ml of a 2 wt % solution of TPGS-750-M, and the mixture was stirred vigorously until homogeneous. 0.050 ml of Et_3N was added via syringe and the mixture was left stirring while the other reagents were weighed out. Between 1.2-1.5 equiv of the appropriate OBBD was added neat as a liquid (highly viscous OBBD's were dissolved in the 2.5 equiv of Et_3N required) followed immediately by 0.3 mmol (1 equiv) of the allenoate substrate as soon as possible, followed by the an additional 0.055 ml of Et_3N (total = 2.5 equiv, omitted for viscous OBBD's). The reaction was left to stir for 12-24 h (reaction followed by TLC), and once complete, the mixture was diluted with

EtOAc and the entire contents of the reaction vessel were filtered through a short plug of silica gel. Volatiles were removed under reduced pressure to afford crude product, which was purified by flash chromatography or preparatory TLC.

General Methods for Dendralene Synthesis

Suzuki-Miyaura-mediated synthesis: General procedure '*A*'

Into a screw cap vial was measured the desired allenoate (1.00 equiv) followed by Pd(DPEphos)Cl_2 (≤1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in D.I. water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then 'a few drops' of Et_3N were added (to aid in reaction homogeneity, and possibly facilitating initial reduction of the Pd(II) catalyst to the active Pd(0) species) followed by addition of the boron coupling partner (1.05 – 1.25 equiv) either dropwise for oils or in one portion for solids, followed by the remainder of Et_3N (2.50 equiv total) with rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for ~ 2–12 h. Upon complete consumption of allenoate *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction and gently stirred for ~ 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

***Note:** The allenoate is usually added first *via* glass pipette capillary action. This is due to the highly viscous nature of most of the allenoates utilized in this research, making use of a microliter syringe cumbersome and the use of a disposable syringe/needle impractical due to substantial, yet unavoidable, transfer losses of valuable material. However, reactions are typically unaffected by the order of addition as long as the boronate coupling partner is added last because of eventual protodeborylation in an aqueous environment.

Heck-mediated synthesis: General procedure 'B'

To a screw cap vial was measured the desired allenoate (1.00 equiv), followed by $[Pd(allyl)Cl]_2$ (1 mol %) and PPh_3 (4 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in D.I. water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then 'a few drops' of Et_3N were added followed by addition of the olefin (1.05 – 1.25 equiv), followed by the remainder of Et_3N (2.50 equiv total); rinsing any residue from the wall of the vial into solution. The reaction was capped and heated to 45 ^oC for ~ 12–24 h. Upon complete consumption of allenoate *via* TLC analysis (see below), a small amount of EtOAc was added to the reaction and stirred for ~ 5 – 10 min (milky pale white to grey solution will eventually become clear to light yellow tinted). This mixture was directly passed through a short plug of Celite on top of silica with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

***Note:** Once all reagents have been added, the reaction may also be performed at room temperature if the sealed, full, reaction mixture is slowly heated *via* heat-gun, until the milky solution becomes transparently clear. After stirring for ~ 12 h this process is again performed, and on the following day the reaction should be complete. However, it is advised, if possible, to maintain 45 ˚C throughout for a more robust reaction.

Tandem borylation-Suzuki approach: **General procedure 'C'**

To a screw cap vial was measured the desired allenoate (1.00 equiv) followed by Cu(IPr)Cl (1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in D.I. water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt, Then a few drops of Et_3N were added followed by addition of B_2Pin_2 (1.10 equiv), in one portion, followed by the remainder of Et_3N (1.00 equiv total) rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for ca. 1-2 h. Upon complete consumption of allenoate *via* TLC analysis (see below) the reaction cap was removed, followed by sequential introduction of Pd(DPEphos)Cl_2 (≤1 mol %), the second allenoate (1.10 equiv) and more Et_3N (1.50 equiv total for this next step). The screw-cap was replaced and vigorous stirring was continued at rt for another 12 h. Once complete consumption of the allenic intermediate from the initial step (*i.e.,* the borylated 1,3-butadiene) was observed *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction after which it was stirred for ca. 5–10 min (milky pale yellow/orange solution will eventually become clear

yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

Palladium / B_2Pin_2 mediated homocoupling: General procedure 'D'

To a screw cap vial was measured the allenoate (1.00 equiv) followed by $Pd(DPEphos)Cl_2$ (≤1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in D.I. water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then, half of the Et_3N (0.75 mmol) was added followed by addition of B_2Pin_2 (0.75 equiv) in one portion, followed by the remainder of Et_3N (1.50 equiv total), rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for ca. 12–16 h. Upon complete consumption of allenoate *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction which was then stirred for ca. 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

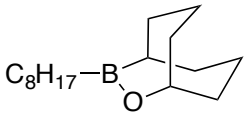
***Note:** Half of the triethylamine was added up front to assure that B_2Pin_2 immediately goes into solution upon addition. Otherwise, 'clumping' of B_2Pin_2 was observed, along with poor stirring and yields were diminished as a result.

Synthesis of -OBBD borinates

Prepared according to the method of Soderquist, substituting trimethylamine-N-oxide with NMO (*N*-methylmorpholine oxide). Once reactions were complete the residue was concentrated under reduced pressure, re-suspended in ether and filtered through a short plug of silica gel to remove traces of *N*-methylmorpholine. The resulting –OBBD derivatives were used without further purification, and stored in tightly wrapped vials with parafilm under argon.

Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.

10-Octyl-9-oxa-10-borabicyclo[3.3.2]decane



TLC: R_f =0.32 (100% pentanes), UV, I_2

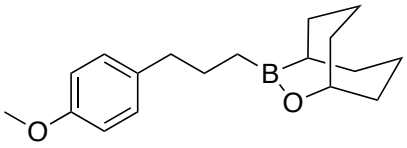
^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.73 – 4.15 (m, 1H), 1.92 – 1.19 (m, 25H), 0.91 – 0.85 (m, 3H), 0.85 – 0.71 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 73.4, 33.0, 32.1, 32.0, 29.8, 29.5, 26.2, 24.2, 22.9, 22.5, 14.3

IR: 2924, 2858, 1702, 1455, 1416 cm^{-1}

HRMS: (EI) calculated for $[C_{16}H_{31}{}^{11}BO_2]$: 266.2417 $[M+O]^+$, found 266.2423

10-(3-(4-Methoxyphenyl)propyl)-9-oxa-10-borabicyclo[3.3.2]decane



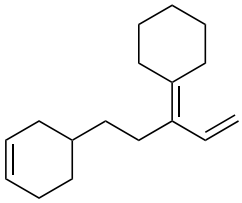
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.15 – 7.07 (d, *J* = 9.0 Hz, 2H), 6.87 – 6.80 (d, *J* = 8.5 Hz, 2H), 4.78 – 4.38 (m, 1H), 3.80 – 3.78 (bm, 3H), 2.60 – 2.48 (t, *J* = 7.8 Hz, 2H), 1.88 – 1.36 (m, 17H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 135.5, 129.5, 113.7, 73.5, 55.4, 38.2, 32.0, 26.5, 26.1, 22.5

IR: 2924, 2858, 1614, 1510, 1300, 1240 cm^{-1}

HRMS: (EI) calculated for $[C_{18}H_{27}{}^{10}BO_3]$: 301.2090 $[M+O]^+$, found 301.2097

4-(3-cyclohexylidenepent-4-en-1-yl)cyclohex-1-ene



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

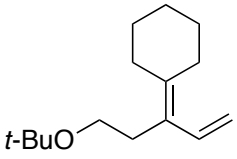
^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.82 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.67 (m, 2H), 5.17 (dd, *J* = 17, *J* = 1.5 Hz, 1H), 4.99 (dd, *J* = 11 Hz, *J* = 1 Hz, 1H), 2.37-2.21 (m, 6H), 2.19-2.11 (m, 1H), 2.09-2.01 (m, 2H), 1.84-1.65 (m, 2H), 1.62-1.50 (m, 7H), 1.35-1.19 (m, 3H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 140.15, 134.33, 128.91, 127.21, 126.76, 111.29, 36.69, 34.26, 32.08, 31.65, 30.32, 29.07, 28.66, 28.49, 27.14, 25.48, 25.09

IR: 3082, 3025, 2920, 2851, 1624, 1446, 1352, 1263, 1232, 984, 908, 890, 733, 652

EI-HRMS: Calculated for $C_{17}H_{26}$ 230.2035. Found: 230.2035 (M+•)

(5-(*tert*-butoxy)pent-1-en-3-ylidene)cyclohexane



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

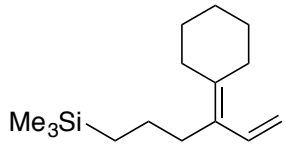
^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.83 (dd, *J* = 17, *J* = 11 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H) 5.00 (d, *J* = 11.5 Hz, 1H), 3.30 (t, *J* = 8 Hz, 2H), 2.54 (t, *J* = 8 Hz, 2H), 2.36-2.21 (m, 4H), 1.65-1.48 (m, 6H), 1.18 (s, 9H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 142.34, 134.37, 124.88, 111.55, 72.83, 61.05, 31.90, 30.39, 29.33, 28.76, 28.49, 27.73, 27.07

EI-HRMS: Calculated for $C_{15}H_{26}O$ 222.1984. Found: 222.1988 (M+•)

IR: 3093, 2973, 2925, 1726, 1627, 1445, 1361, 1272, 1195, 1072, 907, 892, 733,

(4-cyclohexylidenehex-5-en-1-yl)trimethylsilane



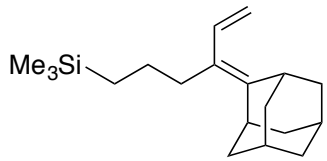
Purified by flash chromatography on silica gel eluting with 100% Hexanes.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.82 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.16 (dd, *J* = 17.5 Hz, *J* = 1.5 Hz, 1H), 5.00 (dd, *J* = 11.5 Hz, *J* = 1.5 Hz, 1H), 2.34 (t, *J* = 6 Hz, 2H), 2.28-2.21 (m, 4H), 1.61-1.52 (m, 6H), 1.40-1.31 (m, 2H), 0.57-0.50 (m, 2H), -0.03 (s, 9H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 140.36, 134.47, 128.91, 111.41, 31.81, 31.73, 30.34, 28.67, 28.53, 27.16, 24.19, 17.45, -1.50

EI-HRMS: Calculated for $C_{15}H_{28}Si$: 236.1960. Found: 236.1957 (M+•)

(4-(adamantan-2-ylidene)hex-5-en-1-yl)trimethylsilane



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.81 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.17 (dd, *J* = 17 Hz, *J* = 1.5 Hz, 1H), 4.97 (dd, *J* = 11 Hz, *J* = 1.5 Hz, 1H), 3.16 (s, 1H), 2.91

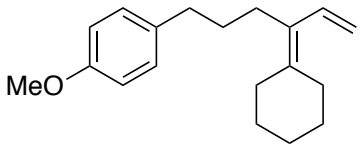
(s, 1H), 2.26 (m, 2H), 1.99-1.80 (m, 8H), 1.79-1.67 (m, 4H), 1.40-1.31 (m, 2H), 0.58-0.50 (m, 2H), -0.02 (s, 9H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 147.89, 134.1, 125.66, 111.10, 39.54, 39.38, 37.25, 34.12, 32.65, 31.35, 28.30, 24.31, 17.45, -1.50

EI-HRMS: Calculated for $C_{19}H_{32}Si$: 288.2273. Found: 288.2271 (M+•)

IR: 3083, 2951, 2907, 1627, 1476, 1246, 1107, 988, 888, 850, 832, 755, 739, 690

1-(4-cyclohexylidenehex-5-en-1-yl)-4-methoxybenzene



Purified by flash chromatography on silica gel eluting with 0-2% Ether/Hexanes.

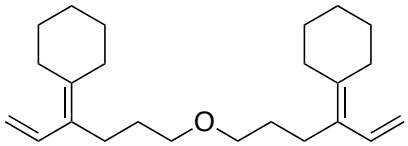
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.12 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 11.4 Hz, 2H), 6.82 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.08 (d, *J* = 16.2 Hz, 1H) 4.97 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 2.30 (m, 2H), 2.22 (t, *J* = 6 Hz, 2H), 1.69-1.65 (m, 2H), 1.64-1.50 (m, 6H)

^{13}C NMR (133MHz, $CDCl_3$) δ (ppm): 157.78, 140.49, 134.81, 134.26, 129.39, 128.51, 113.78, 111.43, 55.39, 35.37, 31.71, 31.51, 30.33, 28.67, 28.51, 27.15, 27.11

EI-HRMS: Calculated for $C_{19}H_{26}O$: 270.1984. Found: 270.1982 (M+•)

IR: 3088, 2923, 2859, 1721, 1612, 1511, 1451, 1270, 1243, 1175, 1038, 891, 826, 806, 712

(oxybis(hex-1-en-6-yl-3-ylidene))dicyclohexane



Reaction conducted with 5% catalyst, 1 equiv of the bis-OBBD borinate, and 2.4 equiv of the corresponding allenoate.

Purified by flash chromatography on silica gel eluting with 100% Hexanes.

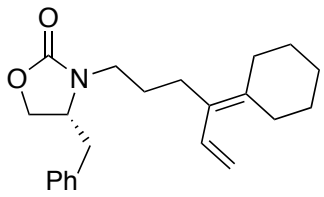
^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.82 (dd, *J* = 17.5 Hz, *J* = 11 Hz, 2H), 5.20 (dd, *J* = 17 Hz, *J* = 1 Hz, 2H), 4.99 (dd, *J* = 11 Hz, *J* = 1.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 4H), 2.37-2.31 (m, 8H), 2.29-2.24 (m, 4H), 1.67-1.61 (m, 4H), 1.60-1.50 (m, 12H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 140.67, 134.22, 128.24, 111.58, 70.75, 31.65, 30.35, 29.77, 28.65, 28.49, 27.13, 23.99

EI-HRMS: Calculated for $C_{24}H_{38}O$: 342.2923. Found: 342.2911 (M+•)

IR: 3093, 2924, 2852, 2251, 1624, 1447, 1115, 985, 906, 852, 731, 649

(*R*)-4-benzyl-3-(4-cyclohexylidenehex-5-en-1-yl)oxazolidin-2-one



Purified by flash chromatography eluting with 0-10-20-25% Ethyl Acetate/Hexanes.

Product co-eluted with the borabicyclodecanol formed during transmetallation.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.28-7.03 (m, 5H), 6.73 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 17.4 Hz 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.30 (br, s, 1H), 4.11-4.02 (m, 1H), 3.98-3.88 (m, 2H), 3.50-3.42 (m, 1H), 3.06-2.96 (m, 2H), 2.63-2.53 (m, 1H), 2.31-2.10 (m, 6H), 1.85-1.69 (m, 4H), 1.66-1.29 (m, 16H)

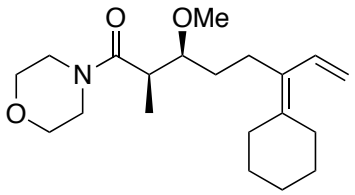
^{13}C NMR (133MHz, $CDCl_3$) δ (ppm): 158.10, 141.02, 135.67, 134.05,129.02, 129.01, 127.35, 127.25, 111.58, 71.03, 66.77, 56.04, 42.22, 38.56, 32.09, 31.68, 30.30, 28.59, 28.38, 27.12, 26.93, 26.29, 24.52, 22.06

ESI-HRMS: Calculated for $C_{22}H_{29}NNaO_2$: 362.2091. Found: 362.2094 ($M+Na^+$)

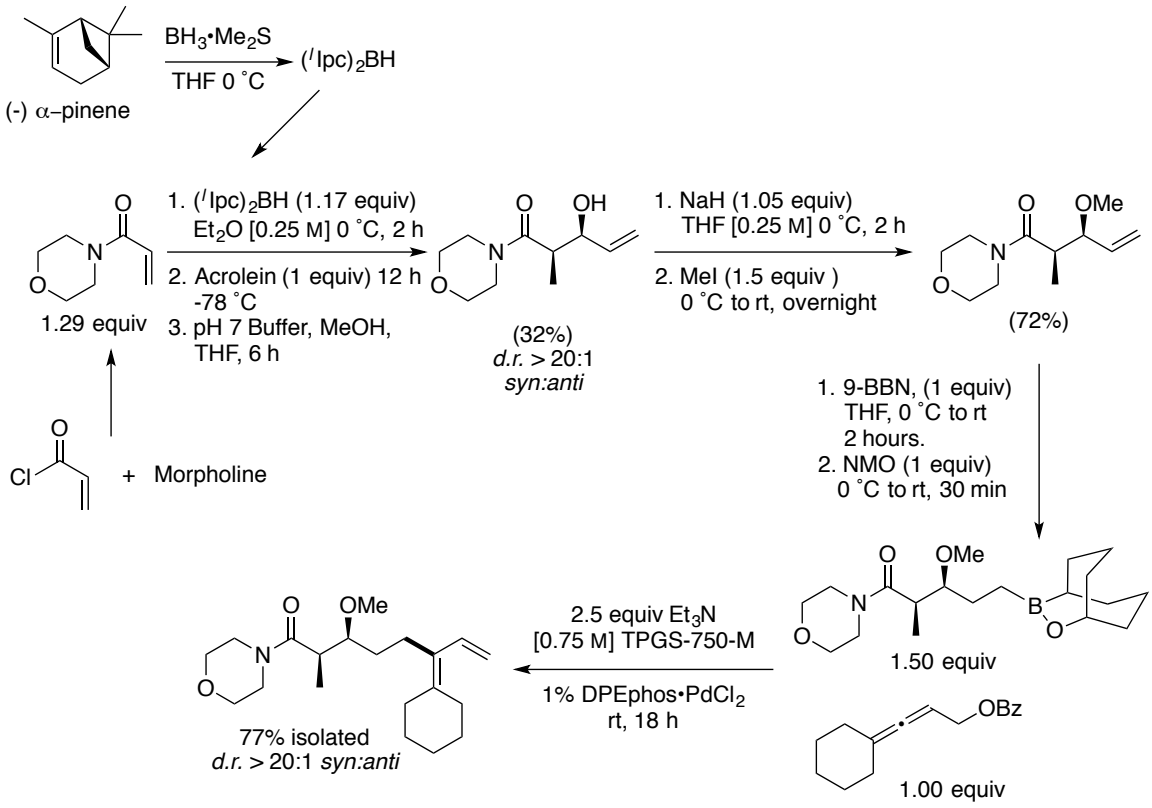
IR: 3092, 3029, 2922, 2854, 1746, 1450, 1412, 1386, 1340, 1300, 1251, 732, 700

TLC: 20:80 EA/Hexanes R_f = 0.3 Stain = UV/I_2/Vanillin

(2*R*,3*S*)-6-cyclohexylidene-3-methoxy-2-methyl-1-morpholinooct-7-en-1-one



The title compound was prepared according to the following route:



Syn-aldol adduct was prepared according to the method of Roush on a scale of 8.58 mmol using freshly prepared $(^{I}Ipc)_2BH$ and N-acryloyl morpholine. Flash chromatography eluting with 0-100% EtOAc/Hexanes gave 554 mg (32%) of the desired product as a viscous oil in greater than 20:1 *dr* as evidenced by ^1H NMR.

Nuhant, P.; Allais, C.; Roush, W. R. *Angew. Chem., Int. Ed*. **2013**, *52*, 8703.

TLC: R_f = 0.15 in 50% EtOAc/Hexanes; Stain = I_2

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.2, 10.6, 5.0 Hz, 1H), 5.33 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.16 (dt, *J* = 10.6, 1.5 Hz, 1H), 4.44 (ddd, *J* = 4.3, 2.8, 1.5 Hz, 1H), 4.33 (s, 1H), 3.74 – 3.35 (m, 8H), 2.63 (qd, *J* = 7.2, 2.7 Hz, 1H), 1.11 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.68, 137.73, 115.95, 72.33, 66.94, 66.79, 46.28, 41.94, 39.38, 10.66.

Methyl protection of the *syn*-aldol adduct was accomplished using NaH and methyl iodide in THF:

538 mg (2.7 mmol, 1 equiv) of the previously prepared aldol adduct was dissolved in ca 10 ml of anhydrous THF and cooled to 0 ˚C in an ice bath. 113.4 mg of NaH (60 wt % in mineral oil, 2.84 mmol, 1.05 equiv) was added cautiously in a single portion and the septa was resealed and argon needle re-inserted through the septum (argon line absorbs pressure from H_2 generated). After NaH had fully dissolved, and gas evolution ceased, 0.252 ml of methyl iodide (4.05 mmol, 1.5 equiv) was added dropwise, and the mixture was left to stir overnight with warming of the cooling bath. The reaction mixture was quenched with sat. NH_4Cl, diluted with Et_2O, and the layers were separated. The aqueous layer was extracted twice with additional Et_2O, and the combined organics were washed with dilute sodium sulfite, water, brine, dried over $MgSO_4$, filtered and evaporated, to afford crude compound, which was purified by passing through a

short plug of silica with 50% EtOAc, which afforded 415 mg (72%) of pure compound as evidenced by TLC, which was immediately subjected to the general procedure for OBBD formation, which gave crude OBBD adduct in quantitative yield. 158 mg (0.45 mmol, 1.5 equiv) of this crude OBBD derivative was then reacted under the general conditions given for Suzuki couplings to form dienes, employing a longer reaction time of 18 h. Usual workup afforded crude material which was purified by preparatory TLC with mobile phase of 50% Ethyl Acetate/hexanes, to afford 78.1 mg (77.6%) of the desired compound as a viscous oil.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.79 (dd, J = 17.5 Hz, J = 11 Hz, 1H), 5.16 (dd, J = 17.5 Hz, J = 1 Hz, 1H), 4.98 (dd, J =11 Hz, J = 1 Hz, 1H), 3.70-3.50 (m, 8H), 3.44 (s, 3H), 3.41 (dt, J = 7Hz, J = 2Hz, 1H), 2.85 (p, J = 7Hz, 1H), 2.36-2.17 (m, 6H), 1.70-1.39 (m, 12H), 1.21 (d, J = 7 Hz, 3H)

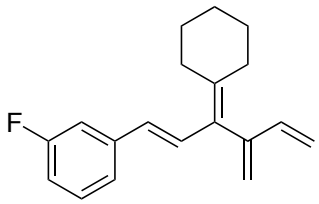
^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 173.58, 140.56, 134.17, 128.26, 111.49, 83.84, 71.06, 67.12, 67.01, 58.63, 46.36, 42.15, 39.64, 31.57, 30.32, 28.68, 28.45, 27.07, 26.40, 22.18, 15.21

IR: 3092, 2966, 2923, 2853, 2254,1638, 1430, 1227, 1115, 1098, 1069, 1032, 894, 731

ESI-HRMS: Calculated for $C_{20}H_{33}NNaO_3$: 358.2353. Found: 358.2350 ($M+Na^+$)

TLC: 20:80 EA/Hexanes R_f = 0.1 Stain = UV/I_2/Vanillin

(*E*)-1-(3-cyclohexylidene-4-methylenehexa-1,5-dien-1-yl)-3-fluorobenzene



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

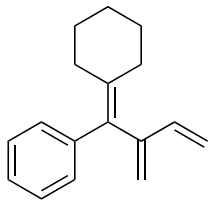
^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 7.32 (d, *J* = 13.5 Hz, 1H), 7.25 (q, *J* = 6 Hz, 1H), 7.14 (d, *J* = 6.5 Hz, 1H), 7.10 (d, *J* = 9 Hz, 1H), 6.87 (t, *J* = 7 Hz, 1H), 6.52 (dd, *J* = 14.5 Hz, *J* = 9 Hz, 1H), 6.35 (d, *J* = 13 Hz, 1H), 5.40 (s, 1H), 5.11 (d, *J* = 14 Hz, 1H) 5.07 (d, *J* = 8.5 Hz, 1H), 4.98 (s, 1H), 2.54 (t, *J* = 4.5 Hz, 2H), 2.16 (t, *J* = 5 Hz, 2H), 1.72-1.46 (m, 6H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 164.11, 162.49, 146.40, 143.46, 141.07, 141.02, 138.09, 126.92, 122.25, 122.24, 118.81, 116.14, 113.65, 113.51, 112.55, 112.41, 105.17, 33.61, 30.31, 28.79, 28.77, 27.03

IR: 3089, 3041, 2924, 2853, 1603, 1579, 1484, 1444, 1384, 1351, 1301, 1268, 1240, 1164, 1143, 1073, 1037, 986, 964, 951, 900, 867, 852, 816, 774, 726, 703, 681, 622, 561, 519

EI-HRMS: Calculated for $C_{19}H_{21}F$: 268.1627. Found: 268.1625 (M+•)

(1-cyclohexylidene-2-methylenebut-3-en-1-yl)benzene



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

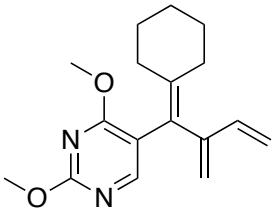
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.27-7.05 (m, 5H), 6.34 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 5.15 (s, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.98 (s, 1H), 2.16 (t, *J* = 4.8 Hz, 2H), 2.13 (t, *J* = 4.8 Hz, 2H), 1.57-1.44 (m, 6H)

^{13}C NMR (133MHz, $CDCl_3$) δ (ppm): 149.24, 141.64, 139.85, 182.40, 130.91, 129.10, 127.89, 126.24, 117.82, 116.51, 32.92, 31.56, 28.88, 28.86, 26.92

IR: 3079, 3019, 2921, 2851, 1804, 1583, 1490, 1442, 1385, 1264, 1230, 1107, 1072, 1031, 986, 894, 877, 853, 757, 699, 601, 555, 523

EI-HRMS: Calculated for $C_{17}H_{20}$: 224.1565. Found: 224.1562 (M+•)

5-(1-cyclohexylidene-2-methylenebut-3-en-1-yl)-2,4-dimethoxypyrimidine



Purified by flash chromatography eluting with 0-8% Et_2O/Hexanes

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 8.01 (s, 1H), 6.34 (dd, *J* = 17 Hz, *J* = 10.5 Hz, 1H), 5.32 (dd, *J* = 17.5 Hz, *J* = 1 Hz, 1H), 5.17 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.17 (m, 2H), 1.96 (m, 2H), 1.54 (m, 6H)

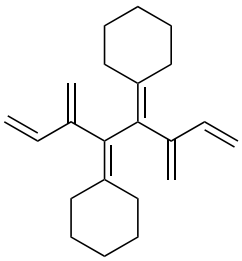
^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 168.41, 164.16, 157.95, 148.21, 143.57, 137.98, 121.04, 117.98, 116.12, 115.89, 54.72, 53.79, 32.29, 32.07, 28.56, 28.05, 26.66

IR: 3100, 2925, 2853, 1588, 1553, 1465, 1393, 1377, 1335, 1315, 1284, 1271, 1256, 1231, 1199, 1134, 1077, 1017, 988, 975, 899, 873, 853, 818, 797, 766, 740, 724, 675, 637, 600, 561, 460

EI-HRMS: Calculated for $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1674 (M^{+}•)

TLC: R_f = 0.3 in 10% Et_2O/Hexanes. Stain: UV/I_2/Vanillin

(3,6-dimethyleneocta-1,7-diene-4,5-diylidene)dicyclohexane



Purified by flash chromatography on silica gel eluting with 100% Hexanes.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 6.31 (dd, *J* = 17.4 Hz, *J* = 10.2 Hz, 2H), 5.14 (d, *J* = 17.4 Hz, 2H), 5.07 (s, 2H), 4.98 (d, *J* = 10.8 Hz, 2H), 2.49-1.87 (m, 8H), 1.76-1.33 (m, 12H)

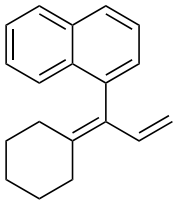
^{13}C NMR (133MHz, $CDCl_3$) δ (ppm): 148.41, 138.89, 137.26, 129.66, 117.38, 115.50, 32.26, 31.91, 28.17, 27.77, 26.93

IR: 3087, 3011, 2921, 2851, 1613, 1582, 1446, 1379, 1263, 1228, 1108, 1033, 980, 889, 853, 802, 753, 735, 528, 466

EI-HRMS: Calculated for $C_{22}H_{30}$: 294.2348. Found: 294.2352 (M+•)

TLC: R_f = 0.9 100% Hexanes. Stain = UV/I_2

1-(1-cyclohexylideneallyl)naphthalene



Purified by flash chromatography on silica gel eluting with 100% Hexanes. Longer (12-18 inch) columns were necessary to separate product from traces of proteodeborylated product.

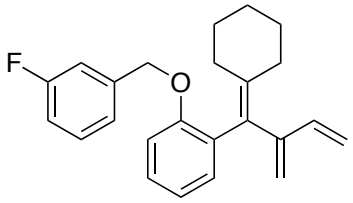
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 1H), 7.84 – 7.77 (m, 2H), 7.53 – 7.39 (m, 3H), 7.20 (ddd, *J* = 17.1, 8.7, 4.2 Hz, 2H), 4.97 (dd, *J* = 10.7, 1.7 Hz,

1H), 4.36 (dd, *J* = 17.1, 1.7 Hz, 1H), 2.84 – 2.46 (m, 2H), 1.88 – 1.72 (m, 4H), 1.60 (tt, *J* = 14.2, 7.0 Hz, 2H), 1.45 – 1.35 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.90, 138.33, 134.69, 133.78, 132.64, 130.51, 128.24, 127.37, 126.87, 126.23, 125.75, 125.68, 125.62, 115.61, 33.47, 30.28, 28.64, 28.44, 27.01.

EI-HRMS: Calculated for $C_{19}H_{20}$: 248.1565. Found: 248.1563 $(M+\bullet)^+$

1-(1-cyclohexylidene-2-methylenebut-3-en-1-yl)-2-((3-fluorobenzyl)oxy)benzene



Flash Chromatography Eluting 0-1% Et_2O/Hex

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 7.37-7.31 (m, 1H), 7.23-7.15 (m, 4H), 7.05-6.98 (m, 1H), 6.94-6.91 (m, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.43 (dd, *J* = 17.5 Hz, *J* = 10.5 Hz, 1H), 5.52 (dd, *J* = 17.5 Hz, *J* = 2 Hz, 1H), 5.21 (d, *J* = 2 Hz, 1H), 5.16 (d, *J* = 5 Hz, 1H), 5.10 (s, 2H), 5.09 (d, *J* = 10 Hz, 1H), 2.35-2.15 (m, 2H), 2.10-1.96 (m, 2H), 1.70-1.45 (m, 6H)

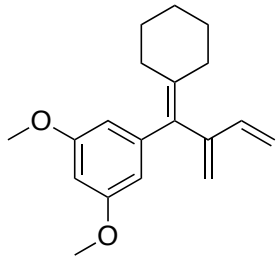
^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 164.12, 162.16, 155.47, 149.14, 140.79, 140.47, 140.41, 138.49, 131.44, 130.67, 130.08, 130.01, 127.74, 125.79, 122.29,

122.26, 120.78, 117.62, 116.04, 114.58, 114.41, 113.98, 113.80, 112.12, 69.11, 32.30, 32.19, 28.51, 28.08, 26.81

IR: 3084, 3012, 2924, 2852, 1617, 1592, 1489, 1443, 1379, 1235, 1193, 1162, 1138, 1117, 1052, 1033, 990, 899, 880, 830, 780, 749, 683, 520

EI-HRMS: Calculated for $C_{19}H_{20}$: Found: (M+•)

1-(1-cyclohexylidene-2-methylenebut-3-en-1-yl)-3,5-dimethoxybenzene



Purified by flash chromatography Eluting 2% Et_2O/Hexanes

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 6.43-6.37 (m, 1H), 6.41-6.39 (m, 2H), 6.33 (m, 1H), 5.32 (dd, *J* = 17 Hz, *J* = 1.5 Hz, 1H), 5.22 (d, *J* = 2 Hz, 1H), 5.12 (d, *J* = 10 Hz, 1H), 5.06 (m, 1H), 3.77 (s, 6H), 2.27 (m, 2H), 2.19 (m, 2H), 1.65-1.50 (m, 6H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 160.31, 148.99, 143.79, 140.03, 138.40, 130.73, 117.73, 116.45, 107.44, 98.13, 55.32, 32.88, 31.73, 28.85, 28.83, 26.87

IR: 3085, 3001, 2924, 2851, 1587, 1450, 1420, 1342, 1327, 1289, 1252, 1203, 1151, 1063, 1041, 1015, 991, 906, 871, 835, 783, 758, 730, 698, 649, 539

EI-HRMS: Calculated for $C_{19}H_{20}$: Found: (M+•)

General procedure for reduction of MBH adducts to form enoates.

All CuH reductions were performed on a scale of 0.5 mmol. To a flame dried conical microwave vial fitted with a spin vane under an argon atmosphere was added 3 mol % of finely powdered $Cu(OAc)_2•H_2O$, 3 mol % of (*R*)-MeO-BIPHEP, and the vial was resealed with a rubber septum, and anhydrous THF (0.4 M relative to substrate) was added and the mixture was stirred until homogeneous. Once homogeneous, 3 H^- equiv of PMHS was added via syringe (calculated based on 60 g mol^{-1} of effective hydride), whereupon there was a delayed onset of slight H_2 gas evolution, and the solution was stirred until a steady yellow/dark yellow solution of ligated CuH was obtained giving off no gas bubbles (time of induction period can vary, usually between 10-60 min). The appropriate MBH alcohol substrate was subsequently added. Liquid substrates were introduced via syringe. Solid substrates were added in one portion by briefly removing the septum and any residual substrate that adhered to the sides of the vial was rinsed into the reaction mixture with a small quantity of THF (never more than 10% of the initial volume added). Vigorous H_2 gas evolution was observed, and the solution was left to stir under argon. Once the indicated time had elapsed, the septum was removed and the reaction vessel was diluted to 2-4 x the initial volume with hexanes, the stir bar was removed, and the contents of the reaction

vessel were poured over a short pad of silica that had been wetted with hexanes and covered with a short layer of sand (**Notes 1, 2**). The mixture was rinsed through the pad of silica with ether into a round bottom flask, silica gel was added to the flask and the volatiles were removed under reduced pressure, and the crude mixture that had been adsorbed onto the silica was placed on top of a flash column, and purified by gradient elution, eluting usually with a ca. 0-40% Et_2O/hexanes or EtOAc/hexanes.

Note 1: Usual quenching of excess silane with NH_4F in methanol could be employed, but required an additional aqueous workup, and led occasionally to the presence of smaller siloxane oligomers that would co-elute on flash chromatography with the desired products. Filtration was found to be more efficient, and succeeded in removing the majority of siloxane byproducts. In cases where residual siloxane products were found to contaminate products after column chromatography, an additional aqueous workup was employed with aqueous NH_4F/Et_2O to remove these impurities.

Note 2: Simple filtration over a pad of silica and evaporation of solvents succeeded in removing most impurities, although column chromatography was performed regularly for all compounds. The purity of product obtained by simple filtration is depicted in the ^{1}H-NMR for Methyl (*E*)-2-methyl-3-phenylacrylate.

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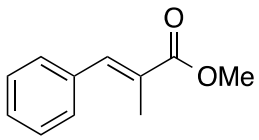
Methyl (*E*)-2-methyl-3-phenylacrylate



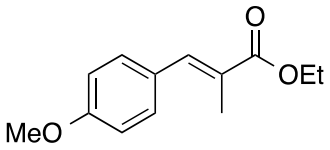
Performing the reaction on a scale of 0.5 mmol gave 81mg (91% isolated) as a clear viscous oil. *E/Z* > 20:1.

Reaction Time: 2 h.

Spectral data matches that of previously reported: *J. Am. Chem. Soc.* 2015, *137*, 8556–8563.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.44-7.28 (m, 5H), 3.82 (s, 3H), 2.13 (s, 3H)

Ethyl (*E*)-3-(4-methoxyphenyl)-2-methylacrylate



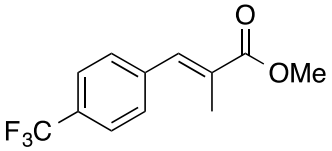
Performing the reaction on a scale of 0.5 mmol gave 96 mg (87% isolated) as a clear viscous oil. *E/Z* > 20:1.

Reaction Time: 2 h

Spectral data matches that of previously reported: *J. Am. Chem. Soc.* 2015, *137*, 3169–3172.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.39 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 9 Hz, 2H), 4.29 (q, *J* = 8 Hz, 2H), 3.84 (s, 3H), 2.13 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H)

Methyl (*E*)-2-methyl-3-(4-(trifluoromethyl)phenyl)acrylate



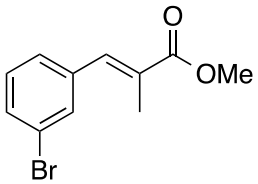
Performing the reaction on a scale of 0.5 mmol gave 122 mg (97% isolated) as a clear viscous oil *E/Z* > 20:1.

Reaction Time: 30 min.

Spectral data matches that of previously reported: *J. Am. Chem. Soc.* 2012, *134*, 11308–11311

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 2.11 (d, *J* = 1.5 Hz, 3H)

Methyl (*E*)-3-(3-bromophenyl)-2-methylacrylate



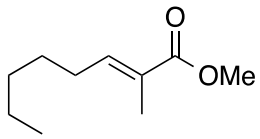
Performing the reaction on a scale of 0.5 mmol gave 108 mg (85% isolated) as a clear viscous oil. *E/Z* > 20:1.

Reaction Time: 2 h

Spectral data matches that of previously reported: *Tetrahedron* **2004**, *60*, 5793–5798.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.54 (s, 1H), 7.48 (dt, *J* = 1.5, 8 Hz, 1H), 7.34-7.27 (m, 2H), 3.84 (s, 3H), 2.12 (d, *J* = 1.5 Hz, 3H).

Methyl (*E*)-2-methyloct-2-enoate



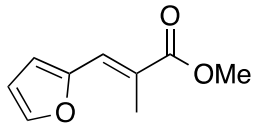
Performing the reaction on a scale of 1 mmol gave 146 mg (86% isolated) as a clear oil. *E/Z* > 20:1. Usual removal of trace solvents under high vacuum also led to slight loss of product owing to its volatility.

Reaction Time: 2 h

Spectral data matches that of previously reported: *J. Org. Chem.* **2012**, *77*, 9659–9667.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 1.5, 7.5 Hz, 1H), 3.73 (s, 3H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.83 (s, 3H), 1.47 (p, *J* = 7 Hz, 2H), 1.36-1.23 (m, 4H), 0.91 (t, *J* = 7 Hz, 3H).

Methyl (*E*)-3-(furan-2-yl)-2-methylacrylate



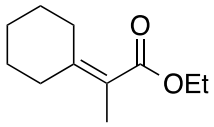
Performing the reaction on a scale of 0.5 mmol gave 57 mg (68% isolated) as a yellow viscous oil, that was prone to degradation over time. *E/Z* > 20:1.

Reaction Time: 2 h

Spectral data matches that of previously reported: *Chem Eur. J.* **2013**, *19*, 5854–5858.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.44 (s, 1H), 6.61 (d, *J* = 3.5 Hz, 1H), 6.50 (dd, *J* = 2, 3.5 Hz, 1H), 3.80 (s, 3H), 2.20 (s, 3H).

Ethyl 2-cyclohexylidenepropanoate



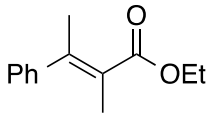
Performing the reaction on a scale of 0.5 mmol gave 64mg (70% isolated) as a clear viscous oil.

Reaction Time: 18 h

Spectral data matches that of previously reported: *Org. Lett.* 2002, *4*, 189–191.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (q, J = 7 Hz, 2H), 2.41 (m, 2H), 2.21 (m, 2H), 1.85 (s, 3H), 1.61-1.54 (m, 6H), 1.31 (t, J = 7 Hz, 3H).

Ethyl 2-methyl-3-phenylbut-2-enoate



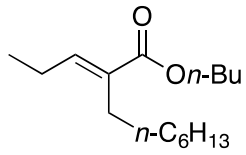
Performing the reaction on a scale of 0.5 mmol gave 91 mg (89% isolated) as a clear viscous oil and a 2:1 *E/Z* mixture of isomers. Reaction with the corresponding acetate gave the product in a 1:1 *E/Z* ratio.

Reaction Time: 18 h

Spectral data matches that of previously reported: *Org. Lett.* **2002**, *4*, 189–191.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5H, *Z*-isomer) 7.22-7.10 (m, 5H, *E*-isomer), 4.29 (q, J = 7 Hz, 2H, *Z*-isomer), 3.86 (q, J = 7 Hz, 2H, *E*-isomer), 2.26 (s, 3H, *Z*-isomer), 2.09 (s, 3H, *E*-isomer), 2.03 (s, 3H, *E*-isomer), 1.76 (s, 3H, *Z*-isomer), 1.36 (t, J = 7 Hz, 3H, *Z*-isomer), 0.83 (t, J = 7 Hz, 3H, *E*-isomer).

_n_-Butyl (_E_)-2-propylidenenonanoate (11)



Performing the reaction on a scale of 0.4mmol gave 69.5 mg (68% isolated) as a clear viscous oil. *E/Z* > 20:1.

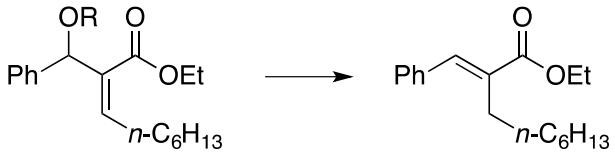
Reaction Time: 1.5 h

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (t, *J* = 7.5 Hz, 1H), 4.14 (t, *J* = 6.5 Hz, 2H), 2.28 (m, 2H), 2.21 (p, *J* = 7.5 Hz, 2H), 1.68 (m, 2H), 1.46-1.20 (m, 12H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.43, 143.82, 132.86, 64.34, 31.98, 30.94, 29.72, 29.59, 29.30, 26.87, 22.80, 21.98, 19.44, 14.25, 13.90, 13.55.

EI-HRMS Calculated for $C_{16}H_{30}O_2$ (M+•): 254.2246; Found: 254.2239.

Ethyl (_E_)-2-benzylidenenonanoate (12)



12

Procedure 1: (from the alcohol, R = H, scale = 0.4 mmol) To a flame dried microwave vial fitted with a rubber septum and triangular spin vane was added 4.8 mg $Cu(OAc)_2 \cdot H_2O$ (6 mol %), and 14 mg (*R*)-MeO-Biphep (6 mol %). The septum was re-applied and 2 mL of anhydrous THF was added via syringe and the solution was stirred at rt. Once the solution was homogeneous, 0.260 mL PMHS (4 H^- equiv) was added via syringe and the solution gradually turned from blue to dark yellow over 30-60 min with slight evolution of hydrogen gas. Once no further change in color was apparent, 116 mg (0.4 mmol) of substrate was added via syringe, whereupon evolution of hydrogen gas was observed. The mixture was left to stir at rt for 24 h, whereupon the contents of the vial were diluted with diethyl ether and filtered over a small plug of silica that had been pre-wetted with hexanes. Additional ether was flushed through the silica plug and the solvent was evaporated to afford crude product which was purified by flash chromatography to afford 63.4 mg of enoate as a colorless oil (58% isolated) with > 20:1 *E/Z* selectivity.

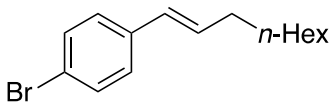
Procedure 2: (from the acetate, R = Ac) Prepared as above with 3 mol % catalyst, and 6H^- equiv PMHS. Following the addition of substrate, 3 equiv of *t*-BuOH was added and the mixture was left to stir at rt for 72 h. Workup as described above and flash chromatography afforded 97mg (88% isolated) of desired enoate as a 5:1 *E/Z* mixture.

The use of either DTBM-Biphep or DTBM-Segphos in place of Ph-MeO-Biphep in this case gave reduced yields and resulted in the formation of several byproducts.

Spectral data matches that of previously reported: *Org Lett*. **2005**, *7*, 1597-1600.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.64 (s, 1H), 7.42-7.29 (m, 5H), 4.29 (q, J = 7.2 Hz, 2H), 2.55 (m, 2H), 1.56 (p, J = 7.2 Hz, 2H), 1.38-1.20 (m, 11H), 0.89 (t, J = 7.2 Hz, 3H).

(*E*)-1-Bromo-4-(oct-1-en-1-yl)benzene



Dehydrogenative silylation/allylic alkylation tandem reaction:

Scale = 0.2 mmol. To a flame-dried 3 mL microwave vial equipped with a stir bar capped with a septum and placed under argon atmosphere, 6 mol % of finely powdered $Cu(OAc)_2 \cdot H_2O$ and 6 mol % Xantphos were added followed by 0.5 mL of diethyl ether and the mixture was stirred vigorously. Once the solution had achieved homogeneity, 1.35 equivalents of diethoxymethylsilane were introduced and the solution was stirred until no further color change was evident (CuH had fully formed). *p*-Bromocinnamyl alcohol (0.2 mmol, 1 equiv) was added whereupon gas evolution was observed and the reaction was allowed to stir at rt for 2 h (TLC indicated at this point no further change in conversion to silyl ether). The solution was then placed in a Dry Ice/acetone bath and allowed to cool to -78

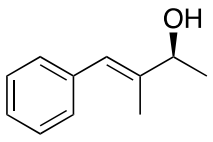
˚C. *n*-hexylMgBr (1.35 equiv, 1 M in Et_2O) was then introduced dropwise via syringe. The solution was stirred at this temperature briefly and the cooling bath was then removed and stirred while warming to rt for an additional 20 h. The reaction mixture was quenched by addition of 0.5 mL of 3 M NaOH and allowed to stir for 30 min. The product was then extracted with diethyl ether. Volatiles were removed via rotary evaporation, and the product was further purified by flash chromatography 0-5% Et_2O/hexanes, to afford 23mg (43%) as a pale yellow oil and a 2.5:1 mixture of linear/branched regioisomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 2H, major + minor), 7.22 (m, 2H, major), 7.06 (m, 2H, minor), 6.31 (d, *J* = 15.8 Hz, 1H, major), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1H, major), 5.96 – 5.81 (m, 1H, minor), 5.00 (ddt, *J* = 15.9, 13.4, 1.5 Hz, 2H, minor), 2.19 (td, *J* = 7.8, 1.1 Hz, 2H, major + minor), 1.75-1.25 (m, 10H, major + minor), 0.95 – 0.79 (m, 3H, major + minor).

General Procedure for reduction of MBH ketones:

The reduction of MBH acetates to chiral allylic alcohols were performed on scales of 0.2-0.5 mmol as described below.

(*S*)-(*E*)-3-Methyl-4-phenylbut-3-en-2-ol



A conical 5 mL microwave vial containing a conical stir bar was charged with fine powdered $Cu(OAc)_2 \cdot H_2O$ (3 mol %) and (*R*)-3,5-Xyl-MeO-Biphep (3 mol %). The vial was capped with a rubber septum and placed under an argon atmosphere, Et_2O (0.25 M) was added via syringe. At rt, either PMHS (4 H^- equiv) or DEMS (4H^- equiv.) (**Note 1**) was introduced, resulting in a yellow solution after 45 min. The vial was then placed into a pre-cooled acetone bath at -25 ˚C and stirred for an additional 10 min. Liquid substrates 0.4 mmol (1 equiv) were subsequently introduced via syringe (**Note 2**). After TLC confirmed full conversion (ca. 18-36 h) the reaction was quenched at -25 ˚C by dropwise addition of 0.5 ml sat. NH_4F/MeOH (**Note 3**). The reaction vial was taken out of the cooling bath and warmed to ambient temperature and stirred for 30-60 min. After filtration through SiO_2, the solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel.

Note 1: No substantial difference between the use of PMHS or DEMS was observed in either yield or observed enantioselectivity and either could be used in this study.

Note 2: Solid substrates added in one portion, and if residual solid was observed to adhere to the side of the vial, substrate was rinsed in with an additional 0.1 mL of anhydrous Et_2O. Highly viscous substrates were added dropwise as concentrated solution in anhydrous ether, never exceeding 1/5 the volume already present in the reaction vessel.

Note 3: Addition of methanolic NH_4F releases hydrogen gas. While not problematic when using DEMS as hydride source, when quenching reactions containing PMHS hydrogen gas evolution was occasionally concomitant with the formation of insoluble siloxane polymers which can lead to pockets of incompletely quenched solution above the mixture. To obtain the best yields, product must be fully liberated from the siloxane. In this case gentle scraping with a clean spatula and additional methanolic NH_4F can assist in breaking up the polymers. If aggregates persist, once the reaction vessel has reached ambient temperature the contents of the reaction vessel can be scraped then rinsed with ether into a larger flask and stirred vigorously with *aqueous* NH_4F until homogeneous.

TLC: 30% EtOAc/hexanes R_f = 0.3

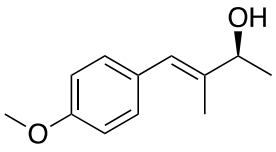
Flash chromatography eluting with 30% Et_2O/hexanes yielded 60 mg (92%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37-1.38 (d, 3H), 1.59 (s, 1H), 1.89 (s, 3H), 4.37-4.41 (q, 1H), 6.52 (s, 1H), 7.20-7.23 (m, 1H), 7.27-7.35 (m, 4H).

Spectra matches that of previously reported: Moser, R.; Boskovic, Z. V.; Crowe, C. S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 7852.

HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 0.9 mL/min, t_R = 9.42 and 10.67 min; 93% ee.

(*S*)-(*E*)-4-(4-Methoxyphenyl)-3-methylbut-3-en-2-ol



Performing the reaction according to the procedure above gave 67 mg (87%) as a pale yellow oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35-1.36 (d, 3H), 1.87-1.88 (m, 3H), 3.81 (s, 3H), 4.35-4.39 (q, 1H), 6.45 (s, 1H), 6.87-6.88 (m, 2H), 7.21-7.26 (m, 2H).

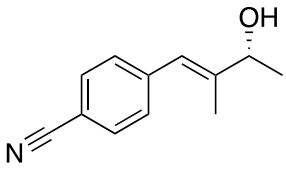
^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 21.9, 55.4, 74.0, 114.7, 124.2, 130.2, 130.3, 140.0, 158.3.

EI-HRMS: Calculated for $C_{12}H_{16}O_2$ (M+•): 192.1150; Found: 192.1155

Spectral data matches previously reported: Moser, R.; Boskovic, Z. V.; Crowe, C. S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 7852.

HPLC separation conditions: CHIRALCEL AD-H, 244 nm, 5% IPA/hexane, 1 mL/min, t_R = 12.97 and 14.39 min, 84% ee.

(*R*)-(*E*)-4-(3-Hydroxy-2-methylbut-1-en-1-yl)benzonitrile



Performing the reaction according to the procedure above with (*S*)-3,5-Xyl-MeO-Biphep above on gave 70 mg (93%) as a tan solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.53 (s, 1H), 4.37 (q, *J* = 6.4 Hz, 1H), 1.88 (t, *J* = 8.5 Hz, 4H), 1.36 (d, *J* = 6.4 Hz, 3H).

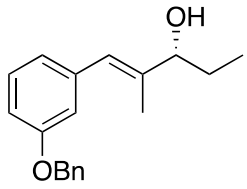
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.35, 142.69, 132.00, 129.59, 122.72, 119.15, 109.79, 103.84, 73.18, 22.05, 14.06.

IR: 3432, 2977,2227,1651, 1604, 1502, 1445, 1372, 1260, 1177, 1103, 1074, 1040, 965, 907, 877, 828, 788, 727, 647, 555 cm^{-1}

EI-HRMS: Calculated for $C_{12}H_{13}NO$ (M+•): 187.0997; Found: 187.0997

HPLC separation conditions: CHIRACEL AD-H, 265 nm, 3%IPA/hexane, 1.0 mL/min, t_R= 42.9 and 46.9 min; 89% ee.

(*R*)-(*E*)-1-(3-(Benzyloxy)phenyl)-2-methylpent-1-en-3-ol



Performing the reaction according to the procedure above with (*S*)-3,5-Xyl-MeO-Biphep gave 83 mg (74%) as a viscous pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.35 (dd, *J* = 4.8, 3.4 Hz, 1H), 7.26 (dd, *J* = 9.3, 6.4 Hz, 1H), 7.01 – 6.80 (m, 3H), 6.47 (s, 1H), 5.09 (s, 2H), 4.10 (t, *J* = 6.6 Hz, 1H), 1.84 (d, *J* = 1.3 Hz, 3H), 1.75 – 1.59 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

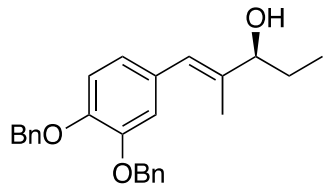
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.73, 140.55, 139.20, 137.21, 129.22, 128.71, 128.06, 127.58, 125.91, 121.97, 115.69, 113.06, 79.61, 70.13, 28.07, 13.33, 10.20.

IR: 3369, 3032, 2961, 2932, 2873, 1597, 1575, 1487, 1454, 1378, 1315, 1291, 1266, 1245, 1158, 1083, 1043, 1026, 988, 889, 873, 844, 765, 734, 694, 627, 590, 545, 499, 457 cm^{-1}

EI-HRMS: Calculated for $C_{19}H_{22}O_2$ (M+•): 282.1620; Found: 282.1607

HPLC separation conditions: CHIRACEL AD-H, 245 nm, 5% IPA/hexane, 1.0 mL/min, t_R =10.8 and 13.2 min; 94% ee

(*S*)-(*E*)-1-(3,4-bis(Benzyloxy)phenyl)-2-methylpent-1-en-3-ol



Performing the reaction according to the procedure above gave 143mg of **30** (92%) as a clear highly viscous oil

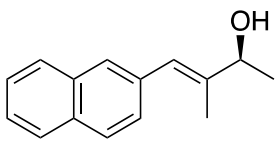
^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90-0.93 (t, 3H), 1.61-1.66 (m, 2H), 1.75 (s, 3H), 4.00-4.06 (m, 1H), 5.13-5.17 (m, 4H), 6.35 (s, 1H), 6.80-6.93 (m, 3H), 7.27-7.46 (m, 10H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 10.1, 13.0, 25.4, 27.9, 64.4, 71.3, 71.4, 79.6, 114.7, 116.3, 122.4, 125.5, 127.2, 127.3, 127.7, 127.8, 128.5, 131.2, 137.3, 138.8, 147.7, 148.4

EI-HRMS: Calculated for $C_{26}H_{28}O_3$ $(M)^+$: 388.2038; Found: 388.2038

HPLC separation conditions: Phenomenex Lux 5u Cellulose-2, 257 nm, 5% IPA/hexane, 0.7 mL/min, t_R = 52.85 and 88.04 min; 99 % ee.

(*S*)-(*E*)-3-Methyl-4-(naphthalen-2-yl)but-3-en-2-ol



Performing the reaction according to the procedure above gave 78 mg (91%) as a pale yellow oil

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72-7.81 (m, 4H), 7.40-7.52 (m, 3H), 6.68 (s, 1H), 4.42-4.46 (q, 1H), 1.97 (s, 3H), 1.41-1.42 (d, 3H)

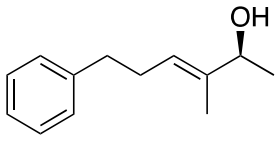
^{13}C NMR (150 MHz, $CDCl_3$) δ 142.24, 135.29, 133.44, 132.19, 127.98, 127.71, 127.69, 127.67, 127.57, 126.16, 125.78, 124.53, 73.80, 21.98, 13.72

IR: 3354, 3054, 2970, 2925, 2856, 1702, 1637, 1597, 1504, 1445, 1367, 1315, 1270, 1125, 1072, 1039, 971, 952, 898, 866 cm^{-1}

EI-HRMS: Calculated for $C_{15}H_{16}O$ (M+•): 212.1201; Found: 212.1209

HPLC separation conditions: Phenomenex Lux Cellulose-1, 242 nm, 2% IPA/hexane, 0.75 mL/min, t_R = 24.0 and 26.5 min; 88% ee.

(*S*)-(*E*)-3-Methyl-6-phenylhex-3-en-2-ol



Performing the reaction according to the procedure above gave 66 mg (87%) as a pale yellow oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.24 (d, 3H), 1.56 (s, 3H), 2.31-2.36 (q, 2H), 2.65-2.68 (t, 2H), 4.17-4.21 (q, 1H), 5.43-5.47 (t, 1H), 7.16-7.20 (m, 3H), 7.27-7.29 (m, 2H).

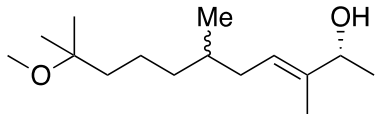
^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 21.6, 29.4, 35.7, 73.3, 124.0, 125.8, 128.2, 128.4, 139.3, 142.0.

IR: 3352, 3026, 2970, 2925, 2857, 1495, 1453, 1368, 1270, 1110, 1075, 1030, 855, 771, 747, 697 cm^{-1}

EI-HRMS: Calculated for $C_{13}H_{18}O$ (M+•): 190.1358; Found: 190.1355

HPLC separation conditions: Phenomenex Lux Cellulose-2, 210 nm, 1% IPA/hexane, 0.75 mL/min, t_R = 27.6 and 33.4 min; 83% ee.

(2*R*)-(*E*)-10-Methoxy-3,6,10-trimethylundec-3-en-2-ol



Reaction time: 36 hours. Performing the reaction according to the procedure above with (*S*)-3,5-Xyl-MeO-Biphep gave 68 mg (70%) as a pale yellow oil

Obtained as an inseparable mixture of *syn/anti* diastereomers.

TLC: R_f = 0.4 EtOAc/Hex 1:1, stain = I_2/Vanillin. The product alcohol has an almost identical R_f value with the starting material, and complete conversion is only distinguishable by color when staining sequentially with I_2 then vanillin.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (td, *J* = 7.3, 1.0 Hz, 1H), 4.21 (q, *J* = 6.4 Hz, 1H), 3.17 (s, 3H), 2.00 (dd, *J* = 14.1, 6.9 Hz, 1H), 1.85 (dd, *J* = 14.6, 7.4 Hz, 1H), 1.61 (d, *J* = 0.6 Hz, 3H), 1.50 (s, 2H), 1.45 – 1.28 (m, 5H), 1.27 – 1.23 (m, 4H), 1.12 (d, *J* = 5.0 Hz, 7H), 0.86 (dd, *J* = 6.7, 3.3 Hz, 3H).

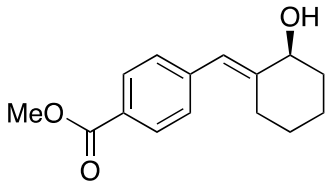
^{13}C NMR (125 MHz, $CDCl_3$) δ 139.24, 139.21, 124.08, 124.00, 74.78, 73.70, 73.66, 49.21, 40.29, 40.28, 37.46, 37.41, 34.99, 34.96, 34.26, 33.60, 33.58, 25.12, 25.11, 22.47, 21.84, 21.83, 21.53, 21.52, 21.32, 19.82, 14.19, 11.77, 11.71.

IR: 3440, 2969, 2936, 1738, 1461, 1379, 1364, 1239, 1187, 1153, 1080, 955, 890, 737, 544 cm^{-1}

HPLC: Chiracel AD-H, 206 nm, 1% IPA/hex, 1 mL/min, t_R = 13.3, 14.0, 15.4, and 25.3 min, dr: 22.1/16.5/1.5/1.

EI-HRMS: Calculated for $C_{14}H_{26}O$: 210.1984 ([M–CH_3OH]+•); Found: 210.1984.

Methyl (*S*)-(*E*)-4-((2-hydroxycyclohexylidene)methyl)benzoate (34)



Performing the reaction according to the procedure above gave 82 mg (83%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.56 (s, 1H), 4.30 – 4.20 (m, 1H), 3.91 (s, 3H), 2.83 – 2.66 (m, 1H), 2.16 – 1.97 (m, 2H), 1.87 (tdd, *J* = 9.5, 5.8, 3.6 Hz, 1H), 1.78 (s, 1H), 1.71 – 1.38 (m, 4H).

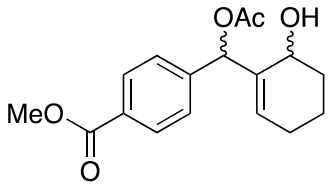
^{13}C NMR (125 MHz, $CDCl_3$) δ 167.18, 146.60, 142.82, 129.58, 129.01, 127.99, 119.98, 73.73, 52.16, 36.94, 27.49, 27.45, 23.49.

HPLC: Chiracel AD-H, 270 nm, 5% IPA/hex, 1 mL/min, t_R =16.7 and 20.0 min; 55% ee

EI-HRMS: Calculated for $C_{15}H_{18}O_3$: 246.1256 (M+•); Found: 246.1253

IR: 3442, 2932, 2858, 1720, 1607, 1436, 1280, 1179, 1113, 892, 751, 707 cm^{-1}

Methyl 4-(acetoxy(6-hydroxycyclohex-1-en-1-yl)methyl)benzoate



Reaction was performed according to the general procedure employing *racemic* DTBM SEGPHOS to avoid match/mismatch with the existing racemic center.

89 mg (73%) was obtained as a pale yellow oil, and as an inseparable mixture of *syn/anti* diastereomers.

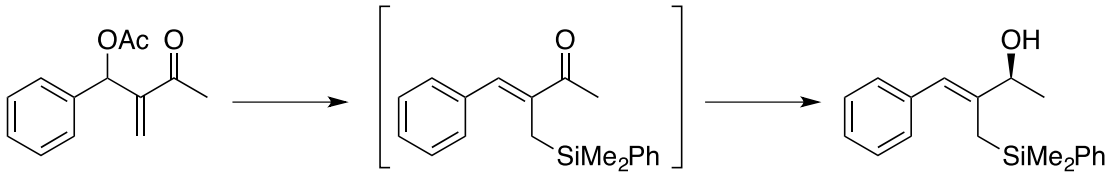
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H, major + minor), 7.42-7.32 (m, 2H, major + minor), 6.19 (m, 1H, minor), 5.87 (m, 1H, major), 5.36 (m, 1H, major), 5.31 (m, 1H, minor), 5.22-5.18 (m, 1H, major + minor), 3.90-3.87 (s, 3H, major + minor), 2.85-2.65 (m, 1H, major + minor), 2.27-1.95 (m, 3H, major + minor), 1.93 (s, 3H, major), 1.83-1.78 (m, 1H, major + minor), 1.70-1.55 (m, 3H, major + minor) 1.66 (s, 3H, minor).

^{13}C NMR (150 MHz, $CDCl_3$) δ 167.18, 146.59, 142.82, 129.60, 129.03, 128.03, 120.03, 73.78, 67.23, 52.18, 36.96, 27.51, 27.46, 23.50.

CI-HRMS (CH_4): Calculated for $C_{19}H_{25}O_5$: 333.1697 $(M+C_2H_5)^+$; Found: 333.1705

IR: 3474, 2949, 1722, 1610, 1436, 1371, 1278, 1239, 1191, 1109, 1018, 988, 923, 861, 768, 718 cm^{-1}

(*S*)-(*Z*)-3-((Dimethyl(phenyl)silyl)methyl)-4-phenylbut-3-en-2-ol



Performed on a scale of 0.4 mmol. A conical 5 mL microwave vial containing a conical stir bar was charged with fine powdered Cu(I)OAc (3 mol %) and (*R*)-DTBM-SEGPHOS (3 mol %). The vial was capped with a rubber septum and placed under an argon atmosphere. TPGS-750-M [1 M] was added via syringe. At rt, the liquid substrate was introduced via syringe followed subsequently by $PhMe_2SiBpin$ (1.25 equiv).

After TLC confirmed full conversion a second conical microwave vial containing a conical stir bar was charged with fine powdered Cu(I)OAc (3 mol%) and (*R*)-DTBM-SEGPHOS (3 mol %). The vial was capped with a rubber septum and placed under an argon atmosphere. TPGS-750-M [1 M] was added via syringe. PMHS (TMS terminated, average M_n = 390, 9 H^- equiv) was then added and let stir 15 min. This solution of preformed CuH was introduced to the previous microwave via syringe. After TLC confirmed full conversion, the reaction was quenched by the addition of 1 mL sat. NH_4F/H_2O. The reaction mixture was extracted with DCM (4 x), washed with $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel chromatography eluting with 30% Et_2O/hexanes yielded 104mg (88%) of pure **37** as a colorless oil in 87% *ee*.

Note: Care was taken while quenching this reaction with NH_4F and was not allowed to stir more than 30 min to prevent desilylation of the product.

TLC: 30% EtOAc/hexanes R_f = 0.24

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21-0.22 (d, 6H), 1.28-1.29 (d, 3H), 1.92-1.95 (m, 1H), 2.30-2.34 (m, 1H), 4.07-4.08 (m, 1H), 6.46 (s, 1H), 7.17-7.24 (m, 3H), 7.27-7.35 (m, 5H), 7.44-7.46 (m, 2H).

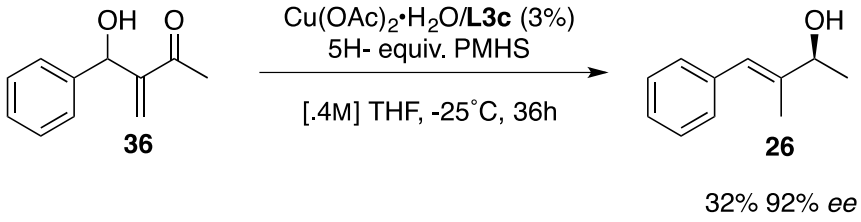
^{13}C NMR (125 MHz, $CDCl_3$) δ -1.9, -1.8, 18.7, 22.7, 72.7, 121.2, 126.2, 128.0, 128.3, 128.9, 129.3, 133.7, 138.5, 139.2, 144.6.

EI-HRMS: Calculated for $C_{19}H_{24}OSi$: 296.1596 (M+•); Found: 296.1587

HPLC separation conditions: Chiracel AD-H, 254 nm, 1% IPA/hexanes, 0.8 mL/min, t_R = 16.79 and 18.40 min; 87% ee.

IR: 3375, 3073, 3023, 2979, 2891, 1647, 1598, 1493, 1432, 1251, 1113, 1047, 838, 700

Reduction of a hydroxy MBH enone:

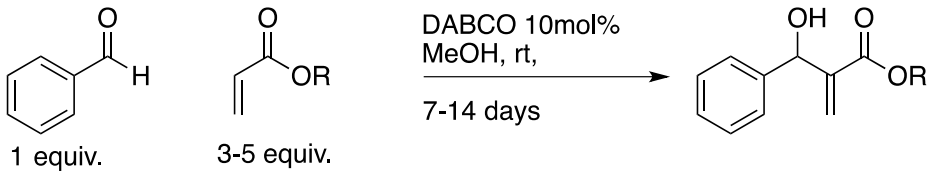


32% 92% *ee*

The reaction was performed according to the general procedure given above for the acetates, employing a slightly longer reaction time of 36 h, and 5 H^- equiv of PMHS. Several unidentified impurities were also formed in addition to the desired product, and purification required a longer 0-40% EtOAc/Hex (performed on a Biotage SP4 system) gradient over 20 CV's to give 21mg pure **26** in 32% yield. Enantioselectivity was identical to that obtained when employing the acetate (92% *ee*).

Synthesis of Substrates:

MBH adducts of esters were prepared according to the following scheme

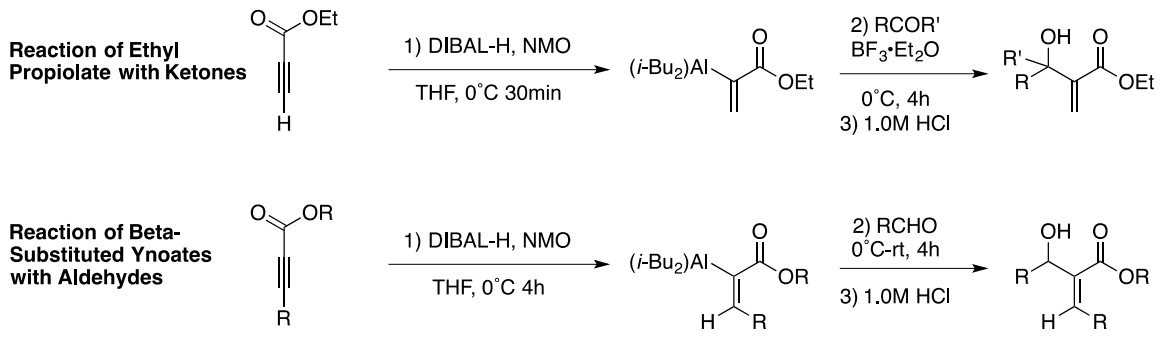


Methyl acrylate (3-5 equiv) was dissolved 0.1 M in MeOH (EtOH for ethyl acrylate), in an argon purged round bottom flask fitted with a septum and stir bar, followed by 1 equiv of aldehyde, and 10 mol % of DABCO. The septum was resealed, and the mixture was let stir for 7-14 days at rt. The reaction was then stopped by removing the stir bar and removing the volatiles under reduced pressure. The crude material was re-suspended in ether, and washed sequentially with dilute HCl, water, sat. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude compounds were then purified by flash chromatography (EtOAc/hex), volatiles were removed first by rotary evaporation, and then by high vacuum to afford pure MBH adducts. Pure MBH adducts were stored under argon-purged vials tightly wrapped with Parafilm and protected from light.

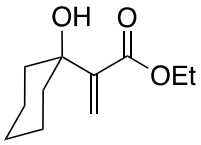
Preparation of tertiary MBH alcohols and b-substituted MBH alcohols by hydroalumination.

Adducts possessing either tertiary alcohols or β-substitution were prepared according to the method of Ramachandran:

Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310.



Ethyl 2-(1-hydroxycyclohexyl)acrylate

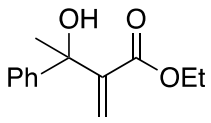


^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, *J* = 0.6 Hz, 1H), 5.73 (s, 1H), 4.29 – 4.16 (m, 2H), 3.71 (s, 1H), 2.33 (t, *J* = 6.8 Hz, 1H), 1.96 – 1.47 (m, 11H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.09, 146.62, 123.29, 72.05, 61.07, 42.13, 36.34, 25.86, 21.84, 14.26.

Clear oil.

Ethyl 3-hydroxy-2-methylene-3-phenylbutanoate

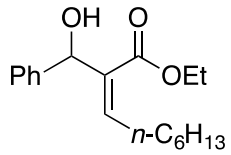


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.16 (m, 5H), 6.40 (d, *J* = 0.5 Hz, 1H), 5.95 (s, 1H), 4.59 (d, *J* = 1.0 Hz, 1H), 4.20 – 4.00 (m, 2H), 1.65 (d, *J* = 1.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

Spectral data matches that of previously reported: *J. Org. Chem.* **2003**, *68*, 9310–9316.

Pale yellow oil.

Ethyl (*Z*)-2-(hydroxy(phenyl)methyl)non-2-enoate



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 5H), 6.21 (t, *J* = 7.5 Hz, 1H), 5.40 (d, *J* = 7.2 Hz, 1H), 4.22 – 4.02 (m, 2H), 3.14 (dd, *J* = 7.3, 1.8 Hz, 1H), 2.58 – 2.42 (m, 2H), 1.51 – 1.39 (m, 2H), 1.37 – 1.21 (m, 9H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.94 – 0.83 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 167.44, 144.81, 142.37, 133.52, 128.41, 127.56, 126.34, 75.84, 60.60, 34.28, 31.77, 29.62, 29.30, 29.20, 22.72, 22.49, 14.21, 14.20.

Clear oil.

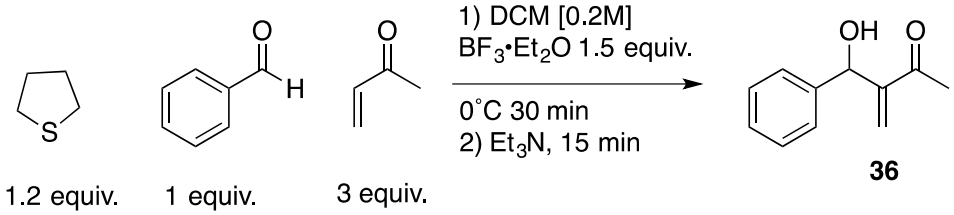
Spectral data matches that of previously reported: *Org. Lett.* 2008**,** *10*, 1649–1652.

Preparation of MBH enones:

Baylis-Hillman adducts of vinyl ketones were prepared according to the procedure given by Winn as described below.

Goodman, J. M.; Walsh, L. M.; Winn, C. L. *Tetrahedron Lett.* **2002**, *43*, 8219-8222.

3-(Hydroxy(phenyl)methyl)but-3-en-2-one



To a solution of aldehyde (1 equiv), methyl vinyl ketone (MVK), (3 equiv; **DANGER, Note 1**) and tetrahydrothiophene (1.2 equiv) in anhydrous DCM [0.2 M] at 0 ˚C was added $BF_3{\cdot}OEt_2$ (1.5 equiv). After stirring for 30 min at this temperature, Et_3N (1 equiv) was added to the mixture that was stirred for a further 15 min while warming to rt. The solution was washed with dilute HCl, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in*

vacuo to give the crude product which was purified by column chromatography (**Note 2**). The combined fractions were concentrated under reduced pressure to afford MBH ketones that were immediately carried on to the subsequent acylation step.

Note 1: MVK is a **highly toxic** molecule with a pungent odor and low vapor pressure, therefore care should be taken during rotary evaporation and handling of the crude compound to avoid inhalation. Performing rotary evaporation in a fume hood is highly recommended, as well as the segregation of all wastes that may contain traces of MVK.

Note 2: Some polymerization of the vinyl ketone was observed during the reaction as indicated by TLC which complicated a complete purification with flash chromatography. The use of acetone/hexanes mixtures was found on occasion to offer improved chromatographic separation for several of these compounds over the usual EtOAc/hexanes mixtures, although on occasion, a second chromatographic purification was deemed necessary. The presence of impurites that contaminated the desired product after chromatography was of no consequence during the subsequent acylation step, and the acetates could all be obtained in a state of high purity.

TLC: 30% EtOAc/hexanes R_f = 0.34

Flash chromatography eluting with a gradient of 5-40% EtOAc/hexanes yielded desired MBH alcohol as a colorless oil that gradually darkened over time.

Spectral data matches that previously reported: *Org. Lett.* 2011, *13*, 4076–4079.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.10-3.11 (d, *J* = 5.2 Hz, 1H), 5.61-5.62 (d, *J* = 5.2 Hz, 1H), 5.97 (s, 1H), 6.19 (s, 1H), 7.27-7.37 (m, 5H).

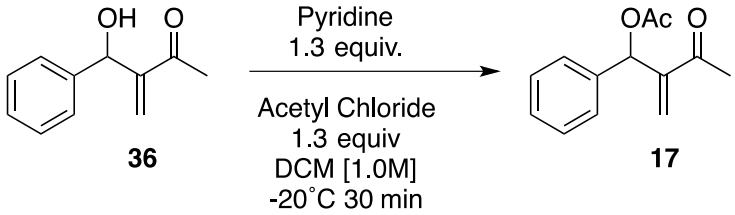
^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.7, 73.1, 126.7, 126.9, 127.8, 128.6, 141.7, 150.1, 200.5.

IR: 3419, 3031, 2922, 1670, 1627, 1453, 1364, 1313, 1242, 1191, 1038, 1025, 973, 953, 698 cm^{-1}

General procedure for acylation of MBH adducts:

Acylations on both MBH enones and enoates were carried out according to the procedure given below.

2-Methylene-3-oxo-1-phenylbutyl acetate



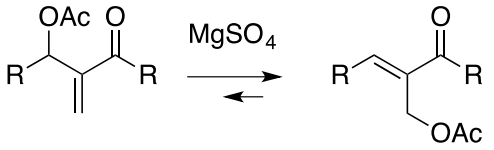
36 **17**

MBH alcohol **36** (1 equiv) in anhydrous DCM [1 M] at -20 ˚C (NaCl/ice bath) was added pyridine (1.3 equiv) (**Note 1**) followed by the dropwise addition of acetyl chloride (1.3 equiv). The solution was let stir 30 min while warming to rt. Water was added (equal to volume of DCM) to quench the reaction and let stir 5 min. The contents of the flask were rinsed into a separatory funnel with additional

DCM, the aqueous layer was separated, and the organic phase was washed sequentially with water (2 x), brine, dried over anhydrous Na_2SO_4, (**Note 2**) filtered, concentrated *in vacuo*, and purified by flash chromatography.

Note 1: 5 mol % DMAP was added for the less reactive/sterically congested tertiary alcohols.

Note 2: The higher Lewis acidity of $MgSO_4$ was found to lead to the formation of trace amounts of the [3,3] allylic rearrangement of the acetate for MBH ketones if let stand too long over the dessicant, and hence, the use of Na_2SO_4 is recommended. When MBH esters were employed as substrates this side reaction was not observed, either dessicant is suitable.



TLC: 20% EtOAc/hexanes R_f = 0.44

Flash chromatography eluting with a gradient of 0-10% EtOAc/hexanes yielded desired acetate as a colorless oil.

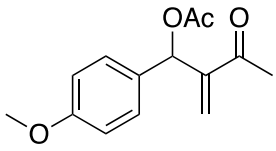
Spectral data matches that of previously reported: *Org. Lett.* **2004**, *6*, 1337–1339.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.31 (s, 3H), 6.07 (s, 1H), 6.22 (s, 1H), 6.74 (s, 1H), 7.28-7.37 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 26.2, 72.5, 125.2, 127.5, 128.2, 128.4, 138.2, 147.8, 169.4, 197.3.

IR: 3034, 1737, 1677, 1632, 1494, 1454, 1430, 1396, 1366, 1282, 1224, 1023, 994, 976, 951, 698 cm^{-1}

1-(4-Methoxyphenyl)-2-methylene-3-oxobutyl acetate

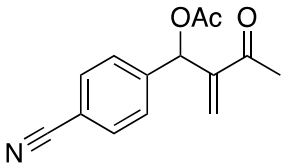


^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.30 (s, 3H), 3.78 (s, 3H), 6.06-6.07 (d, *J* = 1.6Hz, 1H), 6.69 (s, 1H), 6.84-6.86 (d, 2H), 7.28-7.30 (d, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 26.2, 55.2, 72.3, 113.8, 124.5, 128.9, 130.2, 147.9, 159.5, 169.4, 197.3.

Pale yellow oil.

1-(4-Cyanophenyl)-2-methylene-3-oxobutyl acetate



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.56 (m, 2H), 7.54 – 7.44 (m, 2H), 6.72 (s, 1H), 6.27 (s, 1H), 6.15 (d, *J* = 1.3 Hz, 1H), 2.32 (s, 3H), 2.14 – 2.09 (m, 3H).

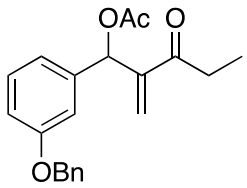
^{13}C NMR (125 MHz, $CDCl_3$) δ 197.15, 169.27, 147.12, 143.80, 132.40, 128.24, 126.20, 118.67, 112.19, 71.83, 26.13, 21.14.

EI-HRMS: Calculated for $C_{14}H_{13}NO_3$: 243.0895 (M+•) Found: 243.0905

IR: 3005, 2972, 2939, 2229, 1728, 1664, 1402, 1369, 1223, 1121, 1030, 1017, 1008, 978, 963, 948, 912, 863, 850, 829, 627, 603, 561, 512 cm^{-1}

Tan solid.

1-(3-(Benzyloxy)phenyl)-2-methylene-3-oxopentyl acetate



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.30 (m, 5H), 7.26 (dd, *J* = 11.3, 3.8 Hz, 1H), 7.00 (t, *J* = 4.8 Hz, 2H), 6.92 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 6.75 (s, 1H), 6.20 (s, 1H), 6.00 (d, *J* = 1.3 Hz, 1H), 5.06 (s, 2H), 2.80 – 2.59 (m, 2H), 2.11 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H).

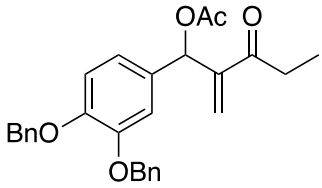
^{13}C NMR (125 MHz, $CDCl_3$) δ 200.13, 169.53, 158.91, 147.32, 139.98, 136.96, 129.61, 128.67, 128.09, 127.68, 124.15, 120.22, 114.54, 114.19, 72.62, 70.13, 31.37, 21.23, 8.05.

EI-HRMS: Calculated for $C_{21}H_{22}O_4$: 338.1518 (M+•); Found: 338.1524

IR: 3071, 3038, 2978, 2938, 1742, 1680, 1585, 1452, 1369, 1223, 1156, 1081, 1020, 978, 736, 696 cm^{-1}

Clear viscous oil.

1-(3,4-bis(Benzyloxy)phenyl)-2-methylene-3-oxopentyl acetate



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00-1.03 (t, 3H), 2.06 (s, 3H), 2.51-2.59 (m, 1H), 2.64-2.72 (m, 1H), 5.11-5.17 (m, 4H), 5.91 (d, 1H), 6.12 (s, 1H), 6.65 (s, 1H), 6.86-6.93 (m, 3H), 7.27-7.31 (m, 2H), 7.33-7.37 (m, 4H), 7.42-7.43 (m, 4H).

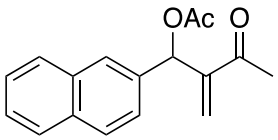
^{13}C NMR (125 MHz, $CDCl_3$) δ 8.1, 21.3, 31.5, 71.4, 71.5, 72.6, 114.7, 114.9, 121.2, 123.4, 127.4, 127.6, 127.9, 127.95, 128.6, 128.63, 131.5, 137.3, 137.4, 147.5, 148.8, 149.2, 169.5, 200.2.

IR: 2980, 2938, 2868, 2844, 1740, 1679, 1631, 1591, 1509, 1454, 1428, 1369, 1223, 1134, 1048, 1032, 1015, 853, 733, 695 cm^{-1}

EI-HRMS: Calculated for $C_{28}H_{28}O_5$ (M+•): 444.1937; Found: 444.1936

Clear highly viscous oil.

2-Methylene-1-(naphthalen-2-yl)-3-oxobutyl acetate



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.32 (s, 3H), 6.13 (s, 1H), 6.26 (s, 1H), 6.91 (s, 1H), 7.45-7.48 (m, 3H), 7.74-7.84 (m, 4H).

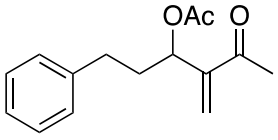
^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 26.2, 72.6, 125.0, 125.3, 126.2, 126.3, 126.8, 127.6, 128.1, 128.2, 133.1, 135.5, 147.8, 169.4.

IR: 3025, 1732, 1670, 1630, 1000, 1508, 1424, 1367, 1342, 1290, 1273, 1230, 1168, 1121, 1021, 998, 939, 864 cm^{-1}

EI-HRMS: Calculated for $C_{17}H_{16}O_3$ (M+•): 268.1099; Found: 268.1100

Clear viscous oil.

4-Methylene-5-oxo-1-phenylhexan-3-yl acetate



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87-1.95 (m, 1H), 2.00-2.05 (m, 1H), 2.06 (s, 3H), 2.33 (s, 3H), 2.60-2.71 (m, 2H), 5.68-5.71 (dd, J = 8.2, 4 Hz, 1H), 5.96 (s, 1H), 6.11 (s, 1H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H).

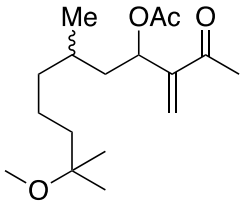
^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 26.0, 36.0, 71.2, 124.7, 125.9, 128.3, 128.4, 141.3, 148.2, 169.9, 197.8.

IR: 3027, 2929, 1738, 1676, 1632, 1603, 1496, 1454, 1431, 1368, 1229, 1121, 956, 877, 735, 699 cm^{-1}

ESI-HRMS: Calculated for $C_{15}H_{18}O_3$ $(M+Na)^+$: 269.1148; Found: 269.1143

Clear oil.

10-Methoxy-6,10-dimethyl-3-methylene-2-oxoundecan-4-yl acetate



Isolated as an inseparable mixture of syn/anti diastereomers.

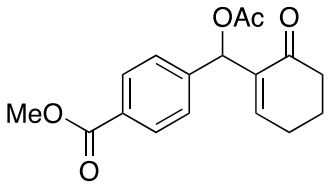
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (d, *J* = 5.8 Hz, 2H), 5.91 (d, *J* = 4.5 Hz, 2H), 5.71 (ddd, *J* = 12.6, 8.9, 3.1 Hz, 2H), 3.16 (s, 8H), 2.33 (s, 6H), 2.06 (d, *J* = 6.3 Hz, 7H), 1.64 – 1.17 (m, 21H), 1.12 (s, 18H), 0.92 (dd, *J* = 22.9, 6.5 Hz, 8H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.87, 197.86, 170.09, 170.07, 149.40, 149.30, 124.50, 124.16, 74.75, 74.73, 70.15, 69.83, 49.21, 42.44, 42.33, 40.18, 40.05, 38.20, 36.63, 30.00, 29.87, 26.22, 26.21, 25.18, 25.15, 25.12, 21.30, 21.28, 21.24, 20.99, 20.24, 19.08.

IR: 2958, 2939, 1741, 1679, 1463, 1366, 1230, 1080, 1023, 976, 875, 738, 606 cm^{-1}

Clear Oil.

Methyl 4-(acetoxy(6-oxocyclohex-1-en-1-yl)methyl)benzoate



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.96 (t, *J* = 4.1 Hz, 1H), 6.74 (s, 1H), 3.90 (s, 3H), 2.53 – 2.34 (m, 4H), 2.11 (d, *J* = 0.7 Hz, 3H), 2.03 – 1.88 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 196.87, 169.48, 166.87, 146.73, 144.15, 138.59, 129.84, 127.10, 71.23, 52.26, 38.38, 25.94, 22.57, 21.23.

EI-HRMS: Calculated for $C_{17}H_{18}O_5$: 302.1154 (M+•); Found: 302.1162

IR: 2952, 1741, 1718, 1672, 1434, 1369, 1277, 1223, 1193, 1171, 1102, 1017, 972, 746, 704, 526 cm^{-1}

Clear viscous oil.

Procedures for the preparation of racemic alcohols for HPLC analyses.

Racemic material to determine appropriate HPLC separation conditions was prepared by either of the following methods:

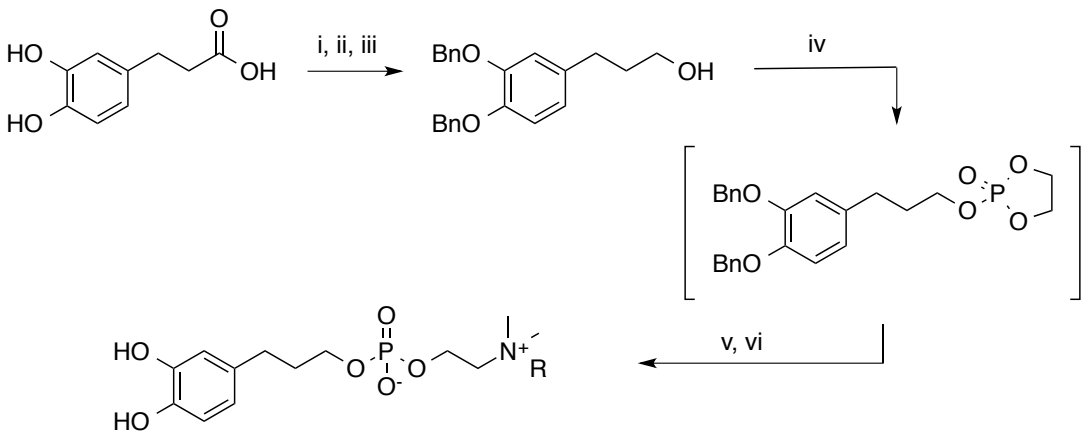
Method 1: Racemic material could be prepared according to the general procedure given above for the reduction of MBH ketones by employing racemic **L3c** or **L2**. Usual workup and flash chromatography afforded the desired racemic allylic alcohols that were used to determine HPLC separation conditions.

Method 2: Racemic material was prepared by CuH S_N2' reduction of the corresponding acetate employing only 1 H^- equiv of PMHS or DEMS to afford the corresponding *E*-enone, which was subsequently purified, and reduced to the racemic allylic alcohol by Luche reduction as described below:

A conical 5 mL microwave vial containing a conical stir bar was charged with finely powdered $CuOAc_2 \cdot H_2O$ (3 mol %) and BDP (3 mol %). The vial was capped with a rubber septum and placed under an argon atmosphere, Et_2O (0.25 M) was added via syringe. At rt, PMHS (1 H^- equiv) was introduced, resulting in a yellow solution after 45 min. Liquid substrate was subsequently introduced via syringe. After 2 h the reaction was quenched by the addition of sat. NH_4F/MeOH. After filtration through a short silica plug, the solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel to afford the desired unsaturated ketone. Freshly prepared unsaturated ketone was subsequently mixed with 1.1 equiv of $CeCl_3 \cdot 7H_2O$ in MeOH (0.4 M), and cooled

to 0 ˚C in an ice bath followed by portion-wise addition of solid $NaBH_4$ (1 equiv) and stirred until TLC indicated no further change. Usual workup and flash chromatography afforded the desired racemic allylic alcohols that were used to determine HPLC separation conditions.

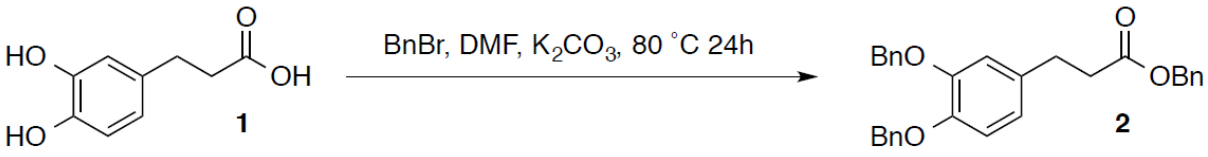
Synthesis of Small-Molecule Zwitterionic Adhesieves:



i) BnBr, DMF, K_2CO_3, 80˚C, 24h ii) NaOH, MeOH 100 ˚C 4h iii) $LiAlH_4$, THF, overnight iv) Ethylene chlorophosphate, Et_3N, Et_2O, 0˚, 4h v) $RNMe_2$, MeCN, 80˚C 2 days vi) H_2 (1atm), Pd/C, CH_2Cl_2/MeOH 2-4 days

Synthesis of Zwitterionic Adhesives:

Benzyl 3-(3,4-bis(benzyloxy)phenyl)propanoate:



Benzyl 3-(3,4-bis(benzyloxy)phenyl)propanoate was synthesized from 3-(3,4-dihydroxyphenyl)propanoic acid, purchased from Alfa Aesar, according to a previously described procedure with slight modifications. As the carboxylic acid contains potentially air sensitive catechol moieties, after opening, the bottle of carboxylic acid was purged with argon, and the cap tightly wrapped with parafilm until subsequent use. While the previously published procedure was observed to work well on scales < 5 grams, adequate stirring became problematic on the scales required for this work, and it is recommended that the procedure be performed with the largest possible football shaped stir bar that can fit into the flask. If stirring is observed to cease during the procedure due to caking of the base, one septa can be briefly removed while under positive Argon flow, and the solidified mass of K_2CO_3 at the bottom of the flask broken up gently with a dry metal spatula until stirring resumes, whereupon a fresh septa is added to the flask and the vessel stirred until completion on the reaction.

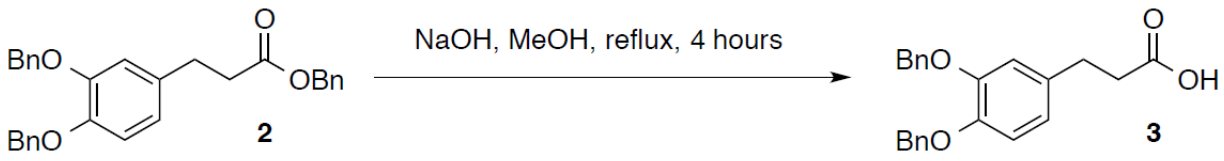
A flame dried 500 mL 3-necked round bottom flask was fitted with rubber septa and a large football shaped stir-bar and allowed to cool to ambient

temperature under positive argon flow. Subsequently, 20 grams (1 equiv, 109.8 mmol) of 3-(3,4-dihydroxyphenyl)propanoic acid was added, followed by 200 ml of anhydrous DMF with stirring. Once dissolved, 90.9 grams of anhydrous K_2CO_3 (6 equiv, 658.7 mmol) was added with stirring. Then, 58.678 mL of fresh benzyl bromide (4.5 equiv, 494 mmol) was added via syringe. The solution was placed in an oil bath set to 80 ˚C and stirred for 1 day at this temperature. After this time, no further reaction was observed by TLC, which also indicated the reaction was incomplete, and contained in addition to the desired product, a mixture of mono- and di-benzylated products. The reaction vessel was allowed to cool to room temperature. The reaction mixture was then poured through a large fritted glass funnel into a 2 L round bottom flask to remove solids, and the reaction vessel was rinsed 3x300 ml EtOAc through the frit. The solvent was then removed under reduced pressure with a rotary evaporator. To assist subsequent extraction, residual DMF was removed by 4 cycles of evaporation with toluene (500 ml). The crude residue was then redissolved in 1.5 L of Et_2O and washed 5x100 ml ice cold water, 1x500 ml Brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was then dry-loaded onto silica gel and purified by flash chromatography gradient elution 10-40% Et_2O/hexanes in a large (18 inch tall) glass column. Fractions containing the only desired product were identified by TLC at R_f = 0.31 (20:80 Et_2O:Hexanes, Stain = UV/Seebach's stain), pooled, and concentrated under reduced pressure to yield 17.42 grams of desired product. Fractions containing the two regioisomeric

dibenzylated products, in which the carboxylic acid and either the 3- or 4-hydroxyl was benzylated, were identified by TLC at R_f = 0.15 and 0.19 (20:80 Et_2O:Hexanes Stain = UV/Seebach's stain), pooled, concentrated under reduced pressure, and then resubjected to the reaction conditions to give an additional 20.56 grams of product, bringing the total amount of product to 37.98 grams in 76% isolated yield. The material was quickly checked for purity by ^{1}H-NMR and then carried on immediately to the next step. If the yield of the initial reaction is not deemed objectionable, after removal of solvent, rather than collecting partially benzylated material and resubjecting it to the reaction conditions, the product can be more rapidly purified by 2 successive filtrations over a 6-8 inch tall pad of basic Al_2O_3 (Acros, 50-200μm) eluting with 20% Et_2O/Hexanes.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 7.45-7.41 (m, 4H) 7.38-7.27 (m, 11H), 6.85 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2 Hz, 1H), 6.70 (dd, J = 2, 8.5 Hz, 1H) 5.12 (s, 2H), 5.10 (s, 2H), 5.09 (s, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H)

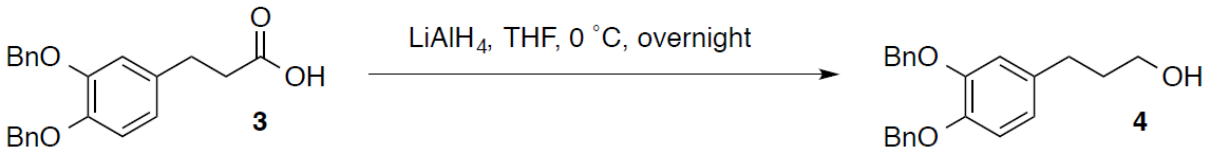
3-(3,4-bis(benzyloxy)phenyl)propanoic acid:



3-(3,4-bis(benzyloxy)phenyl)propanoic acid was synthesized in 88% isolated yield by saponification as previously described. Spectral data matches that of previously reported

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H), 7.46-7.41 (m, 4H), 7.38-7.33 (m, 4H), 7.32-7.27 (m, 2H), 6.87 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2 Hz, 1H), 6.73 (dd, J = 2, 8 Hz, 1H), 5.14, (s, 2H), 5.13 (s, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz)

3-(3,4-bis(benzyloxy)phenyl)propan-1-ol



3-(3,4-bis(benzyloxy)phenyl)propan-1-ol was synthesized from **3** in 89 % isolated yield by reduction with $LiAlH_4$. 7.24 grams of preceding acid (20 mmol, 1 equiv) were dissolved in 100 ml of anhydrous THF and cooled to 0 °C in an ice bath. 3.04 grams of $LiAlH_4$ (80 mmol, 4 equiv) was then added carefully in 4 portions. The reaction was left to stir overnight under argon while warming to ambient temperature. The reaction was then quenched cautiously according to the Feiser workup, diluted with 100 ml of Et_2O and the aluminum solids were

filtered off. The solution was then transferred to a separatory funnel, washed once with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford crude material. The crude material was subsequently purified on a pad of silica eluting with Et_2O. The compound was isolated as a clear viscous oil which gradually solidified over one week under high vacuum to a white wax. Over time, a slight pink coloration developed on the surface of the wax but this did not adversely purity as determined by ^{1}H-NMR or negatively affect subsequent steps. Attempts to prepare this compound directly from the reduction of the corresponding benzyl ester led to unsatisfactory levels of purity, as benzyl alcohol co eluted with product in flash chromatography, while bulb to bulb distillation was inefficient and took extended times to reach a satisfactory level of purity.

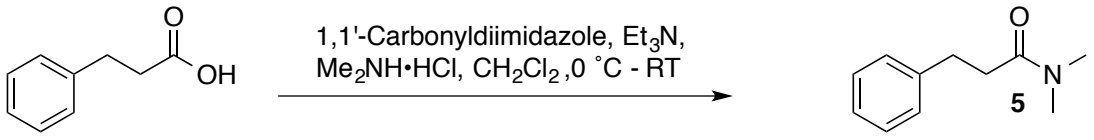
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.47-7.42 (m, 4H), 7.40-7.33 (m, 4H), 7.32-7.28 (m, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.71 (dd, J = 1.5, 8.1 Hz, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 3.62 (q, J = 6 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.84 (p, J = 7.2 Hz, 2H), 1.18 (t, J = 5.7 Hz, 1H).

General procedure for preparation of dimethylamides

Dimethylamides were conveniently prepared with 1-1' carbonyldiimidazole as peptide coupling reagent. A flame dried flask was fitted with a PTFE coated stir bar, rubber septa, and let cool to ambient temperature under positive argon

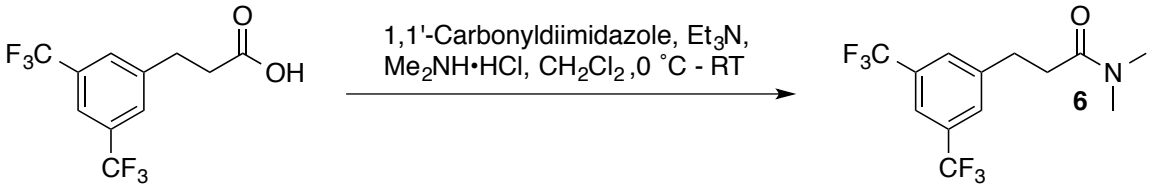
flow. 1 equiv. of the corresponding carboxylic acid, 4 equiv. of anhydrous Et_3N, and anhydrous CH_2Cl_2 [0.5 M] were added to the flask successively. The flask was cooled to 0 ˚C in an ice bath and stirred briefly, whereupon 1-1' carbonyldiimidazole (1.1 equiv) was added portionwise, (gas evolution) the cooling bath was then removed, and the solution was stirred for an additional 30 minutes while warming to ambient temperature. Finally Dimethylamine as the hydrochloride salt, (2 equiv), was added in one portion and the solution was stirred until TLC indicated completion. Upon completion the contents of the reaction vessel were transferred to a separatory funnel, diluted with CH_2Cl_2, and the organic layer was washed 2 x 1N HCl, 2 x sat. $NaHCO_3$, and dried over Na_2SO_4. The organic layer was filtered, evaporated under reduced pressure, and the crude residue was filtered once over a pad of basic Al_2O_3 eluting with EtOAc, evaporated again, and purified by flash chromatography gradient elution with 50-100% EtOAc/Hexanes. Dimethylamides were obtained in high purity as determined by TLC, and not fully characterized at this stage as they were carried immediately on to the next step. Yields were not optimized.

***N,N*-dimethyl-3-phenylpropanamide:**



Title compound was prepared in 84% isolated yield according to the general procedure from hydrocinnamic acid and carried immediately on to the next step.

3-(3,5-bis(trifluoromethyl)phenyl)-*N,N*-dimethylpropanamide (6):



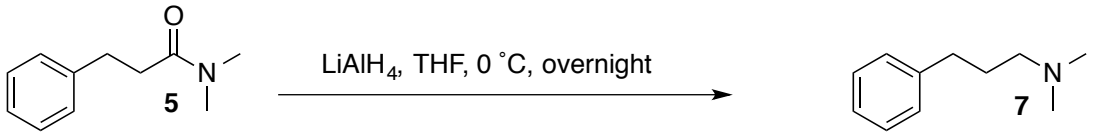
Title compound was prepared according to the general procedure in 77% isolated yield from 3,5-bis(trifluoromethyl)-hydrocinnamic acid (Aldrich) and carried immediately on to the next step.

General procedure for preparation of dimethylamines

Dimethylamines were prepared by reduction of dimethylamides with $LiAlH_4$. A flame dried flask was fitted with a PTFE coated stir bar, rubber septa, and let cool to ambient temperature under positive argon flow. 1 equiv. dimethylamide, anhydrous THF [0.2 M] was added, and the flask was placed in an ice bath and stirred for 10 minutes. $LiAlH_4$ (4 equiv) was then cautiously added to the flask portionwise, and the solution was left to stir under argon overnight with warming to ambient temperature. The reaction was quenched cautiously according to the Feiser workup, diluted with Et_2O, and the aluminum

solids were filtered off. The solution was then transferred to a separatory funnel, washed once with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford crude material. The crude residue was filtered over a short pad of basic Al_2O_3 eluting with Et_2O affording pure dimethylamines. Yields were not optimized.

***N,N*-dimethyl-3-phenylpropan-1-amine**

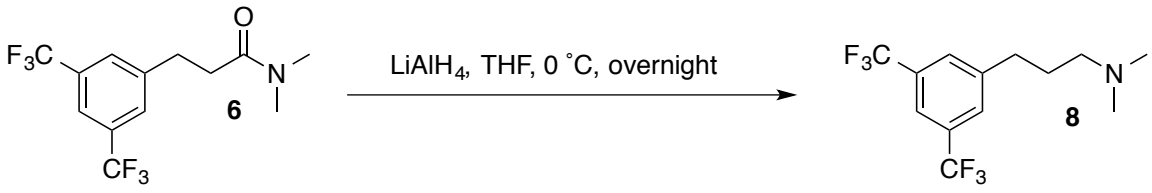


Title compound was obtained in 98% isolated yield from the preceding amide according to the general procedure.

Spectral data matches that of previously reported.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 2.65 (t, J = 7.8 Hz, 2H), 2.31 (t, J = 7.8 Hz, 2H), 2.23 (s, 6H), 1.82 (p, J = 7.8 Hz, 2H)

3-(3,5-bis(trifluoromethyl)phenyl)-*N,N*-dimethylpropan-1-amine:



Title compound was obtained 95% isolated yield from the preceding amide according to the general procedure.

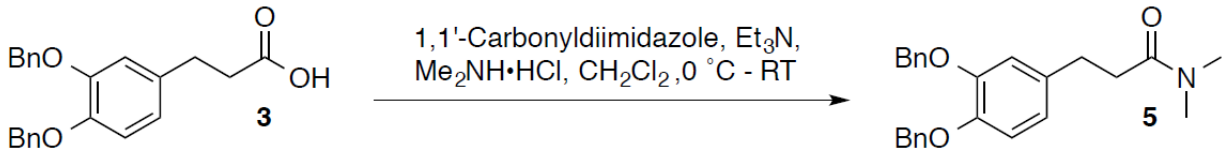
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.65 (s, 2H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 6H), 1.84 (p, *J* = 7.2 Hz, 2H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 144.81, 131.73, 131.51, 128.79, 58.60, 45.56, 33.23, 33.23, 29.13

FTIR (cm^{-1}): 2947, 2862, 2820, 2770, 1622, 1463, 1377, 1346, 1275, 1227, 1167, 1125, 1039, 971, 863, 843, 729, 706, 682, 517, 460

ESI-HRMS: Calculated for $C_{13}H_{16}F_6N^+$: 300.1181. Found: 300.1174 $(M+H)^+$

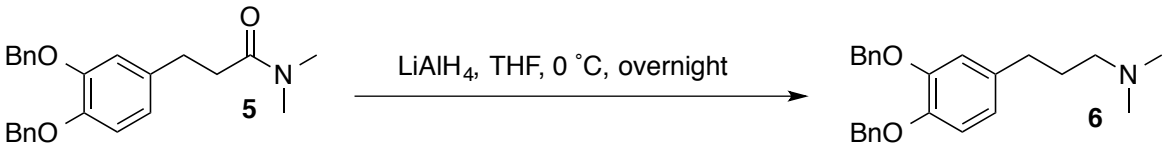
3-(3,4-bis(benzyloxy)phenyl-*N,N*-dimethylpropanamide



Prepared according to the procedure given above in 76% isolated yield, and carried immediately on to the next step.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.46-7.44 (t, *J* = 7.2 Hz, 4H), 7.37-7.34 (dd, *J* = 3, 7.2 Hz, 4H), 7.32-7.29 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.74 (dd, *J* = 1.8, 8.4 Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 2.93 (s, 3H), 2.88 (m, 5H), 2.54 (t, *J* = 8.4 Hz, 2H)

3-(3,4-bis(benzyloxy)phenyl)-*N,N*-dimethylpropan-1-amine



Prepared according to the general procedure in 87% isolated yield

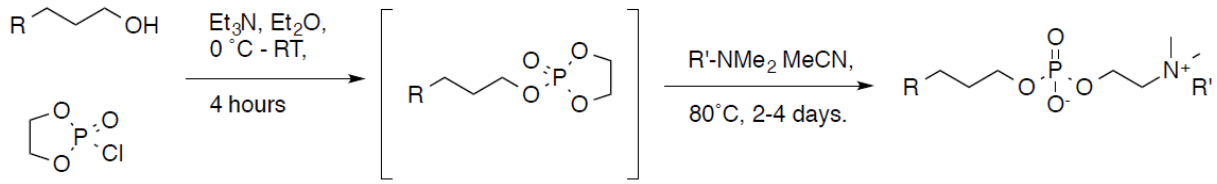
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 5.15 (s, 2H), 5.13 (s, 2H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 2.20 (s, 6H), 1.74 (p, *J* = 7.8 Hz, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 148.96, 147.67, 137.37, 137.20, 132.55, 128.46, 128.45, 127.82, 127.81, 127.40, 127.35, 121.29, 115.49, 115.42, 71.41, 71.27, 68.53, 62.04, 49.43, 31.50, 24.13

FTIR (cm^{-1}): 3088, 3058, 3031, 2939, 2857, 2814, 2763, 1605, 1588, 1509, 1454, 1423, 1379, 1261, 1221, 1158, 1134, 1067, 1016, 907, 847, 731, 694, 624, 605, 463

ESI-HRMS: Calculated for $C_{25}H_{30}NO_2^+$: 376.2271. Found: 376.2266 $(M+H)^+$

General procedure for the synthesis of benzyl-protected molecules by the Chabrier Reaction.



Benzyl-protected zwitterionic coacervates were prepared via the Chabrier-Reaction, according to a previously described procedure, with certain modifications, and no attempt was made to optimize yields. Ethylene chlorophosphate was purchased from Aesar, stored in a freezer, and used as received. In a typical procedure, a flame dried flask was fitted with a PTFE coated stir bar, rubber septa, and cooled under positive argon flow. Freshly prepared alcohol was added to the flask followed by anhydrous Et_2O [0.4 M],1.15 equiv Et_3N, and stirred under argon in an ice bath. 1.15 equiv ethylene chlorophosphate was then added semi-dropwise via syringe whereupon precipitation of the amine hydrochloride salt was observed to begin, and the flask was stirred for 10 minutes at 0 ˚C. The ice bath was then removed and the flask was allowed to warm to ambient temperature with stirring for 4 hours. Hexanes equal to the volume of Et_2O in the flask, was then added to assist in precipitation of the amine hydrochloride salt, and the contents of the flask were filtered quickly over a pad of basic celite into a fresh round bottom flask. The contents of the

reaction vessel was then rinsed once with hexanes, and once with Et_2O through the pad of basic celite, and volatiles were then removed under reduced pressure, and stored briefly in the round bottom flask under high vacuum while a second reaction vessel was prepared.

A schlenk-bomb type flask was fitted with a PTFE-coated stir bar, flame dried, fitted with two rubber septa, and allowed to cool to ambient temperature under positive argon flow. While the schlenk flask was cooling, the flask containing the phosphate ester was back-filled with argon, removed from the vacuum manifold, fitted with a rubber septa, and an argon needle was inserted into the septum. The appropriate amount of anhydrous MeCN (2-4 ml/ mmol alcohol) was then added to this flask via syringe, and swirled gently by hand until completely dissolved. At this point, the MeCN solution containing the phosphonate ester was transferred via syringe into the schlenk flask, and the round bottom was rinsed once with a minimal amount of MeCN into the schlenk flask. 2-4 equiv of the appropriate amine was then added to the schlenk flask, and the rubber septa was replaced with a schlenk valve coated with high-vacuum grease. The schlenk valve was closed, whereupon the second rubber septa containing an argon needle was replaced with a glass adaptor connected to the high vacuum manifold and placed under high vacuum. The schlenk valve was then cautiously opened and atmosphere was removed from the flask for 10 seconds to remove atmosphere from the flask, the schlenk valve was then closed

tightly, and the flask was refluxed under vacuum with stirring for 2-4 days at 80 ˚C in an oil bath (**Note 1**).

When the indicated time had been reached the flask was removed from the oil bath and allowed to cool to ambient temperature. The flask was then backfilled with argon, removed from the vacuum manifold and the schlenk valve was removed. As the inside neck of the flask contained residual vacuum grease from the schlenk valve, to avoid contamination with this potential impurity, rather than pouring, the reaction mixture was transferred via syringe into a round bottom flask and the reaction vessel was washed twice with CH_2Cl_2 into the round bottom flask. Volatiles were removed under reduced pressure and traces of solvents were removed by several rounds of evaporation with pentanes to give the crude, protected coacervates. The residue was then dissolved in a minimum amount of CH_2Cl_2 and loaded on top of a plastic column packed with bonded C2 reverse phase silica (**Note 2**). The column containing the crude residue was then capped and purified on a Biotage SP4 column chromatography system with gradient elution from 0-35% MeOH/CH_2Cl_2 (**Note 3**) collecting the set of UV active fractions (254nm, 10mAu threshold) eluting last. Concentration of these fractions afforded pure benzyl protected coacervates which were characterized by HRMS, FTIR, ^{1}H-, and ^{13}C-NMR prior to deprotection.

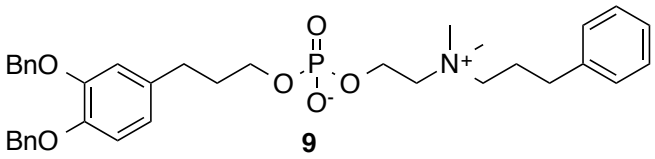
Note 1: A high quality schlenk valve is essential, as the vacuum manifold is active during the reaction even though the schlenk valve is closed, and a faulty valve will lead to evaporation of solvent over the course of the reaction.

Note 2: Although Menger's procedure documents the use of washing, and recrystallization to purify these compounds, in our hands recrystallization under the reported conditions led to only modest increases in purity, gave diminished yields and was highly dependent on the molecule being purified. As the last step of the synthesis (catalytic hydrogenolysis) was chosen to avoid the necessity of additional purification and introduction of additional impurities, and considering that catechols in their unprotected state are highly polar, and prone to oxidation/polymerization, an additional purification step following catechol-deprotection was deemed undesirable and considerably more difficult. Key to the success of this work was ensuring a high level of purity *prior to deprotection of the catechols* and thus it is recommended that purification of benzylated catechol intermediates be performed with C2-bonded reverse phase silica gel.

Note 3: "Reverse phase" C2 silica is technically a misnomer in this case as compounds of low polarity displayed low retention times eluting first, and compounds of high polarity displayed high retention times, eluting last. Gradient elution was performed starting with 0% MeOH/100% CH_2Cl_2 and the % of MeOH was increased over 10-25CV's to 35% MeOH/65% CH_2Cl_2. If cost of the reverse phase silica gel is of consideration, then C2 silica could be prepared readily by reacting the appropriate amount of ethyltrichlorosilane with standard grade silica gel (230 - 400 mesh) according to a previously described procedure.[1] However C2 silica prepared by this route was considerably more polar than the commercial material obtained from Analtech, and required longer and larger, 0-

100% MeOH/CH_2Cl_2 gradients to allow the desired product to elute. Both sources of C2 silica gel were used in this work and no substantial difference in the purity was observed with material purified with either source of C2 silica. To further reduce cost, the C2 silica from either source could be reused several times after use by flushing with 10-20 volumes of MeOH and storing the sealed columns wet with MeOH in a refrigerator. Before reuse, the columns were then flushed with 5-10 volumes of CH_2Cl_2 prior to loading crude compound. Without exception, in all cases the desired product was observed to elute last on the column, although on occasion the first few fractions of those that contained desired material also contained unidentified yellow-colored impurities, and these fractions were either discarded or separated, concentrated, and repurified according to the procedure.

Z-Cat-Ben-Bn



9

65% isolated yield.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.40 (t, J = 7.8 Hz, 4H), 7.32-7.18 (m, 8H), 7.15-7.10 (m, 3H), 6.80-6.76 (m, 2H), 6.65 (dd, J = 1.2, 8.4 Hz, 1H), 5.05 (s, 2H), 5.03 (s, 2H), 4.19 (m, 2H), 4.00 (m, 2H), 3.82 (q, J = 6 Hz, 2H), 3.64 (m, 2H),

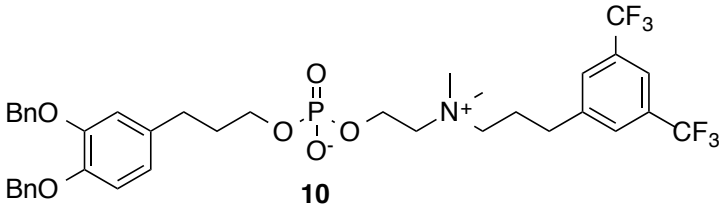
3.42 (m, 2H), 3.16 (s, 6H), 2.61 (t, J = 7.2 Hz, 2H), 2.56 (t, J = 7.8 Hz, 2H), 1.97 (p, J = 7.8 Hz, 2H), 1.84 (p, J = 7.2 Hz, 2H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.95, 147.28, 139.80, 137.57, 137.47, 135.63, 128.80, 128.51, 128.47, 127.81, 127.58, 127.43, 121.46, 116.06, 114.48, 71.58, 65.10, 64.85, 64.81, 64.18, 58.89, 51.77, 32.70, 32.17, 31.69, 24.60

FTIR (cm^{-1}): 3062, 3030, 2942, 2887, 1661, 1603, 1588, 1510, 1497, 1454, 1424, 1380, 1228, 1158, 1135, 1083, 1029, 1025, 968, 807, 733, 695, 621, 571, 534, 486.

ESI-HRMS: $C_{36}H_{44}NNaO_6P^+$: 640.2798. Found: 640.2794 $(M+Na)^+$

Z-Cat-(3,5-CF_3-Ph)-Bn



10

29% isolated yield.

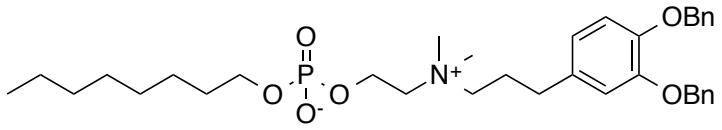
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.71-7.62 (m, 3H), 7.40-7.32 (m, 4H) 7.31-7.20 (m, 6H), 6.79-6.75 (m, 2H), 6.61 (dd, J = 1.2, 7.8 Hz, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 4.22 (m, 2H), 3.78 (m, 2H), 3.64 (m, 2H), 3.59 (m, 2H), 3.17 (s, 6H), 2.74 (t, J = 7.8 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 1.99 (m, 2H), 1.81 (p, J = 7.2 Hz, 2H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.94, 147.44, 142.77, 137.52, 137.47, 135.56, 131.81, 128.85, 128.57, 127.97, 127.92, 127.68, 127.51, 121.63, 116.45, 115.52, 71.82, 71.67, 64.95, 64.85, 51.84, 34.05, 32.05, 32.59, 32.54, 31.82, 31.58, 24.70

FTIR (cm^{-1}): 3071, 3034, 2944, 1588, 1510, 1455, 1425, 1381, 1277, 1228, 1169, 1126, 1080, 1039, 969, 896, 839, 807, 735, 696, 682, 536, 488, 461

ESI-HRMS: Calculated for $C_{38}H_{42}F_6NNaO_6P^+$: 776.2546. Found: 776.2557 $(M+Na)^+$

Reversed-Z-Cat-C_8-Bn



11

49% isolated yield.

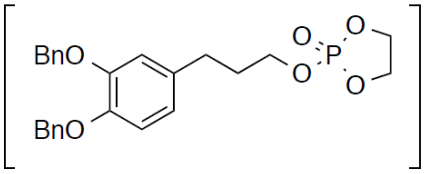
^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 7.48-7.40 (m, 4H), 7.37-7.25 (m, 6H), 6.88-6.82 (m, 1H), 6.78 (d, *J* = 1.5 Hz, 1H), 6.69 (dd, *J* = 1.5, 8 Hz, 1H), 5.16 (s, 2H), 5.11 (s, 2H), 4.24 (m, 2H), 3.84 (m, 2H), 3.69 (m, 2H), 3.41 (m, 2H), 3.22 (s, 6H), 2.59 (t, *J* = 7 Hz, 2H), 1.99-1.88 (m, 2H), 1.64-1.53 (m, 2H), 1.35-1.15 (m, 10H), 0.86 (t, *J* = 7 Hz, 3H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 149.10, 147.85, 137.44, 137.40, 132.94, 128.60, 127.94, 127.92, 127.50, 127.46, 121.34, 115.53, 71.54, 71.34, 65.72, 65.29, 64.28, 58.92, 51.88, 31.98, 31.77, 29.58, 29.46, 26.08, 24.75, 22.78, 14.24

FTIR (cm^{-1}): 3071, 3032, 2926, 2856, 1594, 1516, 1454, 1429, 1383, 1264, 1232, 1143, 1114, 1068, 1020, 975, 919, 798, 776, 733, 694, 595, 547

ESI-HRMS: Calculated for $C_{35}H_{50}NNaO_6P^+$: 634.3268 Found: 634.3246 $(M+Na)^+$

Phospholane Intermediate:

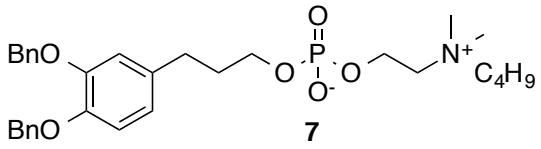


The cyclic phospholane intermediate in all cases was used immediately after preparation without further purification. However ^{1}H-NMR shifts of this crude material are included here for reference purposes and completeness of the supplementary information.

^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 7.46-7.42 (m, 4H) 7.38-7.33 (m, 4H), 7.32-7.28 (m, 2H), 6.87 (d, J = 6.5 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 1.5,

6.5 Hz, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 4.47 (m, 2H), 4.35 (m, 2H), 4.13 (dt, *J* = 2, 5 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 1.97 (p, *J* = 6 Hz, 2H)

Z-Cat-C_4-Bn



7

91% isolated yield.

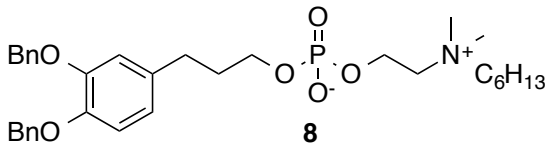
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.47-7.42 (m, 4H), 7.37-7.33 (m, 4H), 7.32-7.28 (m, 2H), 6.87-6.84 (m, 2H), 6.72 (dd, *J* = 7.8 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 4.26 (m, 2H), 3.88 (q, *J* = 7.2 Hz, 2H), 3.71 (m, 2H), 3.44 (m, 2H), 3.26 (s, 6H), 2.62 (t, *J* = 9 Hz, 2H), 1.91 (p, *J* = 9Hz, 2H), 1.66 (m, 2H), 1.38 (sex, *J* = 9 Hz, 2H), 0.95 (t, *J* = 9 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.91, 147.24, 137.55, 137.44, 135.70, 128.49, 128.48, 127.84, 127.79, 127.55, 127.41, 121.44, 116.05, 115.46, 71.58, 65.44, 64.71, 64.04, 58.93, 51.67, 32.75, 32.66, 31.70, 24.68, 19.67, 13.74

FTIR (cm^{-1}): 3031, 2937, 2875, 1588, 1510, 1454, 1424, 1380, 1247, 1158, 1135, 1087, 1064, 1042, 982, 937, 806, 731, 695, 623, 536, 486

HRMS: Calculated for $C_{31}H_{42}NaNO_6P^+$: 578.2642 Found: 578.2637 $(M+Na)^+$

Z-Cat-C_6-Bn



8

46% isolated yield.

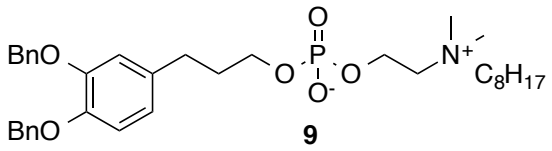
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.44-7.40 (m, 4H), 7.35-7.26 (m, 6H), 6.84-6.83 (m, 2H), 6.70-6.68 (m, 1H), 4.24 (m, 2H), 3.85 (q, *J* = 6 Hz, 2H), 3.69 (m, 2H), 3.39 (m, 2H), 3.24 (s, 6H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.88 (p, *J* = 7.2 Hz, 2H), 1.63 (m, 2H), 1.35-1.22 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.97, 147.31, 137.61, 137.51, 135.77, 128.54, 128.53, 127.88, 127.84, 127.60, 127.46, 121.50, 116.14, 115.53, 71.69, 71.64, 65.86, 64.26, 58.92, 53.20, 51.77, 50.46, 32.78, 31.75, 26.03, 22.84, 22.50, 14.01

FTIR (cm^{-1}): 3039, 2955, 2931, 2259, 2200, 1588, 1510, 1454, 1425, 1379, 1250, 1136, 1088, 1046, 967, 906, 807, 722, 696, 640, 599, 538, 487

HRMS: Calculated for $C_{33}H_{46}NaNO_6P^+$: 606.2955 Found: 606.2949 (M+Na)

Z-Cat-C_8-Bn



9

83% isolated yield.

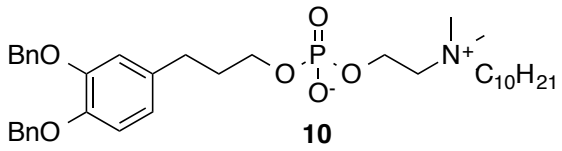
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.47-7.38 (m, 4H), 7.35-7.26 (m, 6H), 6.86-6.81 (m, 2H), 6.70 (dd, *J* = 1.8, 7.8 Hz, 1H), 5.10 (s, 2H), 5.09 (s, 2H), 4.25 (m, 2H), 3.86 (q, *J* = 6 Hz, 2H), 3.69 (m, 2H), 3.38 (m, 2H), 3.24 (s, 6H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.89 (p, *J* = 7.2 Hz, 2H), 1.62 (m, 2H), 1.33-1.17 (m, 12H), 0.86 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.98, 147.32, 137.63, 137.53, 135.80, 128.55, 128.54, 127.88, 127.84, 127.60, 127.46, 121.51, 116.16, 115.53, 71.70, 71.65, 65.90, 64.84, 64.80, 58.91, 51.79, 32.78, 32.73, 31.76, 29.29, 29.16, 26.40, 22.91, 22.69, 14.18

FTIR (cm^{-1}): 3071, 3034, 2926, 2856,1651, 1589, 1511, 1455, 1425, 1379, 1221, 1159, 1136, 1081, 1039, 972, 733, 695, 539, 491

ESI-HRMS: Calculated for $C_{35}H_{50}NNaO_6P^+$: 634.3268 Found: 634.3243 $(M+Na)^+$

Z-Cat-C_{10}-Bn



10

81% isolated yield.

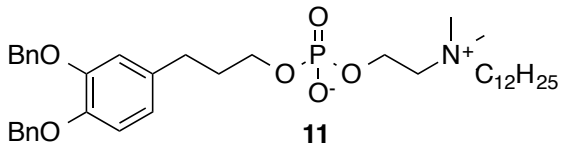
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.47-7.38 (m, 4H), 7.37-7.24 (m, 6H), 6.86-6.81 (m, 2H), 6.70 (dd, *J* = 1.8, 8.4 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 4.25 (m, 2H), 3.86 (q, *J* = 6 Hz, 2H), 3.70 (m, 2H), 3.38 (m, 2H), 3.24 (s, 6H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.88 (p, *J* = 7.2 Hz, 2H), 1.62, (m, 2H), 1.35-1.17 (m, 14H), 0.87 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.98, 147.32, 137.63, 137.53, 128.54, 128.53, 127.88, 127.83, 127.60, 127.45, 121.51, 116.15, 115.53, 71.69, 71.64, 65.88, 65.86, 64.85, 64.81, 58.98, 58.95, 51.77, 32.77, 32.71, 31.95, 31.75, 29.55, 29.51, 29.35, 22.92, 22.77, 14.18

FTIR (cm^{-1}): 3071, 3031, 2924, 2854, 1657, 1589, 1511, 1454, 1425, 1379, 1243, 1159, 1137, 1081, 1040, 1026, 967, 805, 789, 732, 695, 539, 489

ESI-HRMS: Calculated for $C_{37}H_{54}NNaO_6P^+$: 662.3581. Found: 662.3586 $(M+Na)^+$

Z-Cat-C_{12}-Bn



11

45% isolated yield.

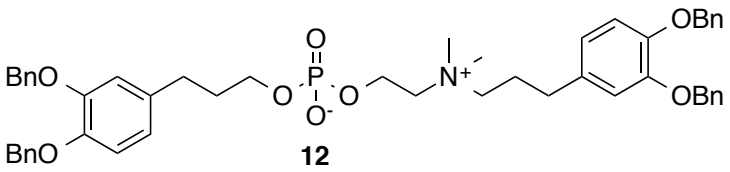
^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.40-7.32 (m, 4H), 7.29-7.24 (m, 4H), 7.23-7.19 (m, 2H), 6.78-6.75 (m, 2H), 6.63 (dd, *J* = 1.2, 8.4 Hz, 1H) 5.04 (s, 2H), 5.02 (s, 2H), 4.18 (m, 2H), 3.84 (m, 2H), 3.68 (m, 2H), 3.31 (m, 2H), 3.17 (s, 6H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.81 (p, *J* = 7.2 Hz, 2H), 1.61 (m, 2H), 1.29-1.06 (m, 16H), 0.81 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 148.98, 147.30, 137.61, 137.51, 135.76, 128.52, 128.51, 127.81, 127.58, 127.43, 121.47, 116.11, 115.52, 71.67, 71.61, 65.78, 64.81, 64.77, 64.25, 58.91, 51.74, 32.78, 32.73, 32.00, 31.75, 29.71, 29.62, 29.53, 29.43, 29.37, 26.41, 22.91, 22.78, 14.22

FTIR (cm^{-1}): 3071, 3028, 2923, 2853, 1589, 1512, 1455, 1425, 1378, 1227, 1137, 1084, 1040, 1026, 971, 721, 694, 492

ESI-HRMS: Calculated For $C_{39}H_{58}NNaO_6P^+$: 690.3894. Found: 690.3884 $(M+Na)^+$

Z-Cat-Cat-Bn



12

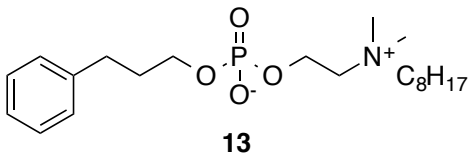
72% isolated yield. Samples of this compound were observed to degrade over time, and immediately after purification it was carried on to the next step.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.47-7.37 (m, 8H), 7.35-7.23 (m, 12H), 6.87-6.74 (m, 4H), 6.71-6.63 (m, 2H), 5.17-5.03 (m, 8H), 3.89 (s, 1H), 3.58 (m, 2H), 3.29 (m, 2H), 3.09-2.95 (m, 3H), 2.90-2.72 (m, 6H), 2.30-2.16 (m, 4H), 1.69-1.47 (m, 4H)

FTIR (cm^{-1}): 3031, 2941, 1588, 1510, 1454, 1425, 1380, 1259, 1218, 1159, 1136, 1078, 1011, 968, 848, 807, 733, 695, 466

HRMS: Calculated for $C_{50}H_{56}NNaO_8P^+$: 842.3636 Found: 852.3635 $(M+Na)^+$

Z-Ben-C_8



13

64% isolated yield.

^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.18-7.14 (m, 2H), 7.10-7.04 (m, 3H), 4.17 (m, 2H), 3.79 (q, *J* = 6.6 Hz, 2H), 3.38 (m, 2H), 3.21 (s, 6H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.85 (p, *J* = 7.2 Hz, 2H), 1.65-1.52 (m, 2H), 1.29-1.06 (m, 10H), 0.79 (t, *J* = 6.3 Hz, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 141.83, 128.32, 128.23, 125.66, 65.37, 64.65, 63.97, 63.90, 58.77, 52.86, 52.52, 32.57, 32.53, 32.07, 31.57, 29.15, 28.99, 26.26, 22.75, 22.47, 13.97

FTIR (cm^{-1}): 3029, 2924, 2854, 1604, 1496, 1468, 1453, 1378, 1246, 1093, 1063, 1034, 979, 947, 905, 826, 795, 752, 743, 699, 594, 540, 498, 485.

ESI-HRMS: Calculated for $C_{21}H_{38}NNaO_4P^+$: 422.2431. Found: 422.2430 $(M+Na)^+$

General procedure for deprotection of catechols by hydrogenolysis:

General Remarks**:** The oxidative stability of each of the zwitterionic coacervates containing unprotected catechols, either in the solid state, a solution in D_6-DMSO, or as a colloidal dispersion in water, was not known prior to undertaking this study and thus every effort was made to exclude atmospheric oxygen during all manipulations at all points after the catechols had been deprotected. Likewise, as purification of unprotected catechols was envisaged to be difficult and require application of purification techniques under inert atmosphere, every effort was

made to increase the purity of the intermediates immediately preceding the deprotection step and the final products were all obtained in satisfactory purity as determined by FTIR, ^{1}H-, and ^{13}C-NMR Spectroscopy.

In a typical procedure, A Schlenk-bomb type flask was fitted with a PTFE coated stir bar, flame dried, fitted with two rubber septa and allowed to cool to ambient temperature under positive argon flow. One septa was briefly removed, 10-20 wt% of Pd/C (5%Pd, Type 87L, dry, Aesar) relative to mass of substrate was added to the flask and the septa was resealed. A small quantity of CH_2Cl_2 (4-8ml) was added via syringe through the septa to rinse residual Pd on the sides of the flask to the bottom. A separate round bottom flask containing the desired amount of substrate was fitted with a rubber septa and argon needle, and vented briefly to purge air out. The vent needle was then removed, and the appropriate volume of a 1:1 v/v mixture of CH_2Cl_2/MeOH was added through the septa via syringe. The flask was then swirled by hand until the benzyl-protected coacervate had dissolved, and this solution containing the substrate was transferred via syringe to the schlenk flask. The interior of the round bottom flask was then rinsed with a small quantity of MeOH (4-8 ml), and transferred via syringe to the schlenk flask. The first septa over the threaded part of the flask was quickly removed and replaced with a schlenk valve coated with vacuum grease. The schlenk valve was closed, whereupon the second rubber septa was replaced with a glass adaptor connected to the high vacuum manifold and placed under high vacuum, which placed the antechamber before the schlenk valve

under vacuum, and the flask was stirred gently. The schlenk valve was then cautiously opened placing the contents of the flask under vacuum and the atmosphere was removed under vacuum for 2-3 minutes. Once this time had elapsed the schlenk valve was closed, the antechamber before the valve was backfilled with argon and the glass adaptor connecting the flask to the vacuum manifold was quickly replaced with a rubber septa. A hydrogen balloon (double ballooned) connected to a needle was placed through the septa and then a vent needle was placed though the septa to purge argon from the antechamber for 30 seconds whereupon it was subsequently removed. Then the schlenk valve was opened slowly to allow hydrogen into the reaction vessel. Stirring was continued for 2-4 days, with periodic replacement of the hydrogen balloon (fresh balloons were used with every replacement). (**Note 4**)

Once the indicated time had elapsed the schlenk valve was closed, and the remaining septa was replaced with a vacuum adaptor connected to a vacuum manifold and the antechamber before the schlenk valve was placed under vacuum. The schlenk valve was then cautiously opened placing the contents of the flask under vacuum and hydrogen gas was removed from the system in this manner for 5-10 minutes with stirring, whereupon there was concomitant bubbling and cooling of the flask due to slight solvent evaporation (Caution: opening the schlenk valve too quickly in this step will lead to solvent “bumping” into the vacuum manifold). During this time a separate round bottom flask was flame dried, fitted with a rubber septa, tared, and allowed to cool to ambient

temperature under positive argon flow. The schlenk flask was then backfilled with argon, and while under positive argon flow the schlenk valve was removed and quickly replaced with a rubber septa. A 30mL, luer lock, PTFE coated syringe was fitted with a long metal needle, and the syringe was filled and purged with argon 3x, whereupon it was inserted through the septa of the reaction vessel. The Pd/C was then separated from the reaction mixture as follows: (**Note 5**)

With the outlet of the syringe facing down, 25ml of the reaction mixture was pulled slowly up into the syringe, whereupon the needle was gently bent and the syringe was inverted so that the outlet of the syringe was now facing up. The needle was pulled above the level of solvent in the reaction mixture and a 5mL blanket of argon pulled into the syringe. Then, very quickly, the needle was removed from the flask with the syringe still inverted, and the metal needle was removed from the luer lock and quickly replaced with an Acrodisc 0.45μm PTFE membrane filter fitted with a fresh 18 gauge needle at the outlet. The empty round bottom flask, still fitted with septa and argon needle, was then inverted so that the neck of the flask was facing downward, and the needle attached to the membrane filter and syringe was placed though the septa of the inverted flask. The whole apparatus was inverted once more, so that the outlet of the syringe was facing down and the neck of the flask was facing up, and the solution was gently forced through the filter into the flask, removing the Pd/C from the solution. If more than 25mL of solution were present in the schlenk flask, then the procedure was repeated with fresh syringes, needles, and filters, until no more

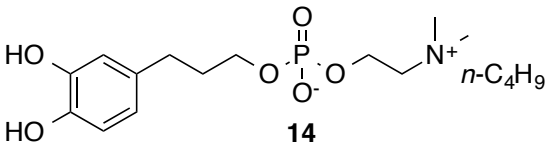
liquid remained in the flask. The septa was then quickly removed from round bottom flask containing product, and immediately placed on a rotavap to remove volatiles. Several subsequent rounds of evaporation first with CH_2Cl_2, then with pentanes helped to remove trace solvents from the products, and the flask was immediately placed under high vacuum afforded pure deprotected coacervates which were subject to further analysis and study. (**Note 6**) Pure coacervates were either stored in round bottom flasks under high vacuum, or in vials under an argon atmosphere and tightly wrapped with several layers of parafilm, until further study. Unfortunately the final products were not sufficiently stable under conditions of EI- or ESI-MS for accurate mass determination. However they were all characterized by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy, which confirmed that the anticipated products had been produced in high purity. The benzyl-protected coacervates were all sufficiently stable under conditions of ESI-HRMS for accurate mass determination and were characterized including this descriptor prior to hydrogenolysis.

Note 4: As the high polarity of the products precluded the use of TLC or GC to monitor the progress of the reaction, reaction progress was monitored at 24h intervals by removal of a 0.5-1.0ml aliquot of the reaction mixture which was worked up by filtration according to the procedure and analyzed by NMR to determine completion of the reaction. In general, most reactions were incomplete after one day, and showed full conversion after two full days, although on occasion, up to 4 days were necessary for certain substrates.

Note 5: This procedure was devised on the basis of the expected high polarity of the products which would preclude removal of Pd/C by the usual filtration over celite, silica, or alumina, and thus a relatively inert and nonpolar PTFE filter was chosen to remove the Pd/C. The choice of the benzyl protecting group for catechols in this context is particularly noteworthy, as the only byproduct is toluene which can be removed by simple evaporation. Use of an acetonide or silicon based protecting group for the catechol, and subsequent removal with acid or fluoride respectively, was deliberately avoided as they would introduce other organic, or highly polar water-soluble impurities which would be difficult to remove from the desired product with conventional techniques. However this procedure gave variable isolated yields, presumably due to adsorption of the products onto the charcoal surface, and no attempt was made to optimize yields, although on occasion, additional washing of the reaction flask and PTFE filter with degassed MeOH was performed to assist in product recovery.

Note 6: Although azeotropic removal with pentanes, and gentle heating under high vacuum were successful at removing the majority of trace solvents from the pure coacervates, NMR spectra invariably contained some slight traces of solvents owing to the high propensity of the product molecules to self aggregate, trapping some residual solvents in the material.

Z-Cat-C_4:



14

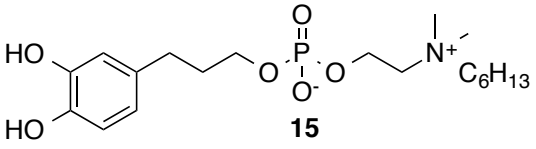
Reaction time = 2 days (48 hours) 88% isolated yield.

^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 9.67-8.74 (s, 1H), 9.67-8.74 (s, 1H) (overlapping), 6.76-6.58 (m, 2H), 6.46-6.37 (m, 1H), 4.06 (m, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.35 (m, 2H), 3.07 (s, 6H), 2.44 (t, *J* = 7.5 Hz, 2H),1.77-1.58 (m, 4H), 1.32-1.20 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm): 145.17, 143.29, 132.31, 118.63, 115.81, 115.51, 63.95, 63.83, 63.02, 58.19, 58.15, 50.74, 30.91, 23.76, 19.17, 13.50

FTIR (cm^{-1}): 3029, 2959, 1599, 1513, 1468, 1382, 1286, 1202, 1079, 1059, 1035, 977, 813, 768, 733, 634, 588, 535, 492

Z-Cat-C_6:



15

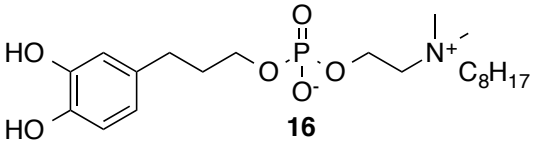
Reaction time = 2 days (48 hours) 74% isolated yield.

^{1}H NMR (600MHz, D_6-DMSO) δ (ppm): 9.79-8.80 (br, s, 1H), 9.79-8.80 (br, s, 1H) (overlapping), 6.69-6.58 (m, 2H), 6.44-6.33 (m, 1H), 4.04 (m, 2H), 3.69-3.60 (m, 2H), 3.51 (m, 2H), 3.32 (m, 2H), 3.06 (s, 6H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.77-1.56 (m, 4H), 1.33-1.16 (m, 8H), 0.90-0.78 (m, 3H)

^{13}C NMR (150MHz, D_6-DMSO) δ (ppm): 145.26, 143.38, 132.18, 118.50, 115.86, 115.57, 64.11, 63.88, 62.89, 58.25, 50.68, 32.45, 30.94, 30.68, 25.42, 21.98, 21.74, 13.83

FTIR (cm^{-1}): 3030, 2952, 1599, 1512, 1467, 1380, 1286, 1204, 1036, 966, 811, 765, 633, 537, 492

Z-Cat-C_8:



16

Reaction time = 2 days (48 hours) 93% isolated yield.

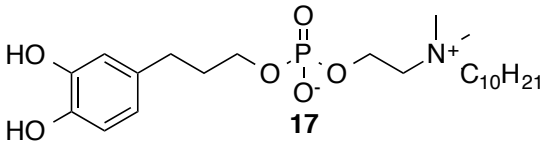
^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 9.14-8.43 (s, 1H), 9.14-8.43 (s, 1H) (overlapping), 6.45-6.40 (m, 2H), (dd, *J* = 2, 8 Hz, 1H), 3.85 (m, 2H), 3.48 (q, *J* = 6.5 Hz, 2H), 3.32 (m, 2H), 3.17 (m, 2H), 2.89 (s, 6H), 2.34 (m, 2H), 2.26 (t, *J* = 8 Hz, 2H), 1.58-1.42 (m, 4H), 1.15-1.01 (m, 12H), 0.70 (t, *J* = 7 Hz, 3H)

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm): 145.12, 143.23, 132.37, 118.58, 115.75, 115.44, 64.13, 63.65, 63.60, 63.08, 58.05, 58.01, 50.71, 31.16, 30.96, 28.48, 25.78, 22.03, 21.76, 13.93

FTIR (cm^{-1}): 3029, 2925, 2855, 1599, 1512, 1467, 1378, 1285, 1201, 1061, 1034, 973, 812, 769, 633, 590, 537, 494

MALDI-MS (aCHCA matrix, Low-Res): Calculated for $C_{21}H_{38}NO_6P$: 431.244 Found: 431.308

Z-Cat-C_{10}



17

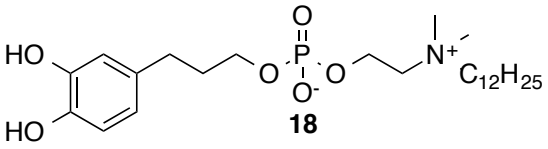
Reaction time = 2 days (48 hours) 79% isolated yield.

^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 9.83-8.55 (br, s, 1H), 9.83-8.55 (br, s, 1H) (overlapping), 6.64 (m, 2H), 6.39 (m, 1H), 4.07 (m, 2H), 3.70 (q, *J* = 6.5 Hz, 2H), 3.52 (m, 2H), 3.36 (m, 2H), 3.06 (s, 6H), 2.43 (t, *J* = 8 Hz, 2H), 1.76 (p, *J* = 7.5 Hz, 2H), 1.67 (m, 2H), 1.32-1.15 (m, 14H), 0.86 (t, *J* = 7 Hz, 3H)

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm):141.24, 139.38, 128.12, 114.49, 111.86, 111.57, 60.15, 59.92, 58.89, 54.25, 46.66, 28.44, 27.28, 26.90, 24.93, 24.87, 24.68, 24.56, 21.79, 18.09, 17.81, 9.93

FTIR (cm^{-1}): 3031, 2923, 2854, 1599, 1512, 1467, 1378, 1286, 1204, 1154, 1079, 1037, 967, 812, 770, 634, 591, 538, 492

Z-Cat-C_{12}



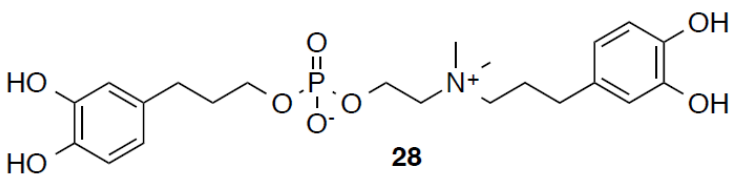
18

Reaction time = 2.5 days (60 hours) 77% isolated yield.

^{1}H NMR (600MHz, D_6-DMSO) δ (ppm): 9.12-8.27 (br, s, 1H), 9.12-8.27 (br, s, 1H) (overlapping), 6.48-6.36 (m, 2H), 6.22 (dd, *J* = 1.8, 7.8 Hz, 1H), 3.87 (m, 2H), 3.46 (q, *J* = 6 Hz, 2H), 3.31 (m, 2H), 3.15 (m, 2H), 2.87 (s, 6H), 2.32 (m, 4H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.56-1.37 (m, 4H), 1.14-0.99 (m, 16H), 0.68 (t, *J* = 7.2 Hz, 3H)

FTIR (cm^{-1}): 3034, 2922, 2852, 1696, 1599, 1512, 1466, 1444, 1378, 1286, 1202, 1079, 1036, 972, 812, 789, 634, 538, 495

Z-Cat-Cat



28

Hydrogenolysis of the Z-Cat-Cat-Bn was accomplished with a slightly higher catalyst loading (20wt% of Pd/C relative to mass of starting material) and extended reaction time (4 days) for complete deprotection, affording Z-Cat-Cat in 69% isolated yield. ^{1}H-NMR of the product compared to that of starting material showed complete debenzylation. Like it's precursor, Z-Cat-Cat was observed to be highly susceptible to degradation over time, and several unidentified impurities, albeit in low concentration relative to product, were apparent by ^{1}H- and ^{13}C-NMR even when the sample was analyzed within < 30 minutes of isolation. Attempts to increase the level of purity by either recrystallization or HPLC were unsuccessful and the compound was used "as is" for further study. It is recommended that extra care is taken to ensure that this compound be protected from atmospheric oxygen, and be used and analyzed immediately after isolation. Considering that the presence of trace impurities in this case did not give rise to improved or otherwise unexpected performance in adhesieve tests or other false positives and that all other zwitterionic adhesieves were obtained in higher purity, and several displayed higher adhesion, their presence in this case was not seen as problematic as it did not fundamentally affect the interpretation of the data or the broader conclusions of this work.

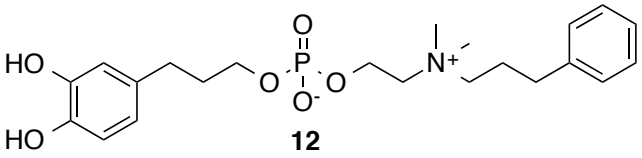
Reaction time = 4 days (96 hours) 69% isolated yield.

^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 10.44-8.23 (br, m, 4H), 6.81-6.54 (m, 4H), 6.49-6.34 (m, 2H), 4.04 (m, 1H), 3.75-3.62 (m, 2H), 3.56-3.46 (m, 2H), 3.42-3.36 (m, 1H), 3.35-3.21 (m, 2H), 3.03 (s, 6H), 2.47-2.36 (m, 4H), 1.98-1.86 (m, 2H), 1.77-1.67 (m, 2H).

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm): 145.59, 145.34, 145.10, 143.79, 143.74, 143.24, 132.37, 130.74, 130.22, 118.69, 115.84, 115.78, 115.64, 115.52, 115.37, 65.12, 63.88, 63.32, 58.28, 52.15, 50.79, 30.89, 24.12, 22.95

FTIR (cm^{-1}): 3045, 2954, 1600, 1522, 1473, 1375, 1286, 1196, 1081, 1040, 962, 877, 816, 790

Z-Cat-Ben



12

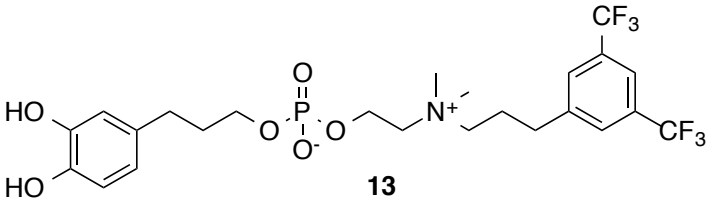
Reaction time = 2 days (48 hours) 74% isolated yield.

^{1}H NMR (600MHz, D_6-DMSO) δ (ppm): 9.37-9.10 (s, 1H), 9.01-8.76 (s, 1H), 7.34-7.17 (m, 5H), 6.67-6.58 (m, 2H), 6.40 (dd, *J* = 1.8, 7.8 Hz, 1H), 4.05 (m, 2H), 3.67 (q, *J* = 6 Hz, 2H), 3.52, (m, 2H), 3.41 (m, 2H), 3.08 (s, 6H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 2.03-1.95 (m, 2H), 1.74 (p, *J* = 7.2 Hz, 2H)

^{13}C NMR (150MHz, D_6-DMSO) δ (ppm): 145.17, 143.28, 140.46, 132.26, 128.35, 126.11, 118.62, 115.81, 115.76, 115.51, 115.47, 63.77, 63.72, 63.06, 50.91, 32.54, 32.49, 31.68, 30.95, 23.86

FTIR (cm^{-1}): 3027, 2950, 1600, 1513, 1454, 1382, 1286, 1202, 1155, 1117, 1067, 1034, 968, 813, 753, 701, 634, 571, 533, 491

Z-Cat-(3,5-CF_3-Ph)



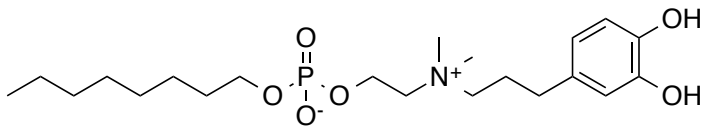
13

Reaction time = 3 days (72 hours) 39% isolated yield

^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 9.62-8.69 (br, s, 1H), 9.62-8.69 (br, s, 1H) (overlapping), 8.06 (s, 2H), 7.93 (s, 1H), 6.67-6.56 (m, 2H), 3.39 (dd, *J* = 2, 8 Hz, 1H), 4.08 (m, 2H), 3.69 (q, *J* = 6.5 Hz, 2H), 3.56 (m, 2H), 3.45 (m, 2H), 3.09 (s, 6H), 2.80 (t, *J* = 8 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.12-1.98 (m, 2H), 1.74 (p, *J* = 7 Hz, 2H)

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm): 145.15, 144.34, 143.26, 132.33, 130.30, 130.04, 129.78, 129.78, 129.49, 124.52, 122.35, 119.92, 118.60, 115.78, 115.49, 63.82, 62.77, 63.42, 62.98, 62.93, 58.22, 58.19, 51.01, 32.49, 32.43, 31.04, 30.90, 23.68

Reversed-Z-Cat-C_8



14

Reaction time = 2 days (48 hours) 42% isolated yield.

^{1}H NMR (500MHz, D_6-DMSO) δ (ppm): 10.69-8.45 (br, s, 1H), 10.69-8.45 (br, s, 1H) (overlapping), 6.75 (s, 1H), 6.34 (d, *J* = 8 Hz, 1H), 6.42 (d, *J* = 8 Hz, 1H), 4.07 (m, 2H), 3.78-3.64 (m, 2H), 3.61-3.47 (m, 2H), 3.39-3.27 (m, 2H), 3.06 (s, 6H), 2.43 (m, 2H), 2.00-1.83 (m, 2H), 1.56-1.44 (m, 2H), 1.33-1.15 (m, 10H), 0.86 (t, *J* = 6.5 Hz, 3H)

^{13}C NMR (125MHz, D_6-DMSO) δ (ppm): 145.52, 143.81, 130.36, 118.65, 115.77, 115.50, 64.54, 64.49, 63.87, 63.08, 58.35, 50.80, 31.27, 30.44, 28.10, 28.74, 25.43, 23.27, 22.10 13.95

FTIR (cm^{-1}): 3038, 2926, 2856, 1600, 1515, 1464, 1379, 1203, 1071, 971, 812, 727, 643, 491.

References for synthesis of coacervates:

1. Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22-23

2. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K.I. *Organometallics*, **2010**, *29*, 2176-2179

3. Garcia, G.; Rodriguez-Puyol, M.; Alajarin, R.; Serrano, I.; Sánchez-Alonso, P.; Griera M.; Vaquero, J. J.; Rodriguez-Puyol, D.; Álvarez-Builla, J.; Diez-Marqués, M. *J. Med. Chem*. **2009**, *52*, 7220–7227

4. Garcia, G.; Serrano, I.; Sánchez-Alonso, P.; Rodriguez-Puyol, M.; Alajarin, R.; Griera M.; Vaquero, J. J.; Rodriguez-Puyol, D.; Álvarez-Builla, J.; Diez-Marqués, M. *Eur. J. Med. Chem.* **2012**, *50*, 90-101

5. Hanada, S.; Tsutsumi, E.; Motoyama, Y.; Nagashima H. *J. Am. Chem. Soc.* **2009**, *131*, 15032-15040

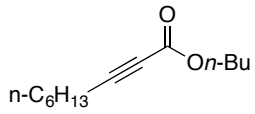
6. Thanh T.N.; Chabrier P. *Bull. Soc. Chem. Fr.* **1974**, *3-4*, 667-671

7. Peresypkin, A. V.; Menger, F. M. *Org. Lett.* **1999**, *1*, 1347-1350

Synthesis of Sugimoto's Reagent: $PhMe_2SiBpin$

$PhMe_2SiBpin$ was prepared according to the procedure outlined by Sugimoto. The procedure was observed to work well with lithium wire as opposed to lithium shot, and can be done conveniently performing the lithium halogen exchange for 6-8 hours at 0 ˚C as opposed to -5 ˚C for 18 h. Higher yields were observed when using HBpin as opposed to iPrOBpin. Old samples of HBpin and iPrOBpin led to unsatisfactory results and these reagents are best used fresh. The distillation of $PhMe_2SiBpin$ was performed in a bulb to bulb apparatus under high vacuum at 150 ˚C. Running the distillation under high vacuum at 125 ˚C led to longer distillation times by about 4-6 hours and gave lower yields presumably due to thermal decomposition. Running the reaction with old samples of HBpin and iPrOBpin were observed to generate up to 20% $PhMe_2Si$-O-Bpin as confirmed by GCMS and NMR which could not be separated from the desired compound by distillation. However samples that contained this impurity could be used in subsequent silylation without any disadvantage providing the mass of the impurity was taken into account in the corresponding molar equivalents calculation. $PhMe_2SiBpin$ was stored in a refrigerator in a parafilm wrapped vial under argon. Samples of the reagent stayed active for up to 6 weeks. Reagent was withdrawn from the vial under a blanket of argon. After some time the reagent was observed to turn from a clear liquid to a pale yellow color but this did not affect performance.

Butyl non-2-ynoate



Prepared according to the General Procedure:

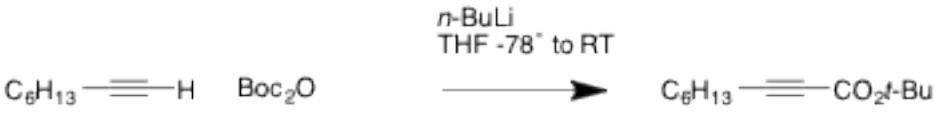
Flash chromatography gradient elution with 0-2% Et_2O/Hexanes yielded desired compound as a clear oil.

TLC: 2.5% Et_2O/Hexanes R_f: 0.55

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.87-0.90 (t, *J* = 7.1 Hz, 3H), 0.92-0.95 (t, *J* = 7.4 Hz, 3H), 1.24-1.34 (m, 4H), 1.36-1.44 (m, 4H), 1.55-1.60 (m, 2H), 1.62-1.68 (m, 2H), 2.31-2.33 (t, *J* = 7.2 Hz, 2H), 4.14-4.17 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.79, 14.15, 18.84, 19.19, 22.60, 27.66, 28.67, 30.59, 31.35, 65.78, 73.31, 89.66, 154.20

***t*-Butyl non-2-ynoate**



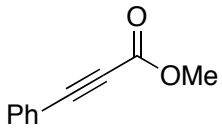
Prepared according to the General Procedure. Boc_2O was added as a [0.5 M] solution in THF. After work up and chromatography a significant amount of *t*-butanol remained and contaminated the compound. This could be removed by

several rounds of rotary evaporation with hexanes by azeotropic removal of the corresponding hexanes azeotrope.

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.89 (t, 3H), 1.29 (m, 4H), 1.39 (m, 2H), 1.49 (s, 9H), 1.56 (m, 2H), 2.29 (t, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 14.16, 18.8, 22.6, 27.5, 27.7, 28.2, 28.7, 31.4, 74.6, 83.0, 87.2, 153.1

Methyl 3-phenylpropiolate



Prepared according to the General Procedure.

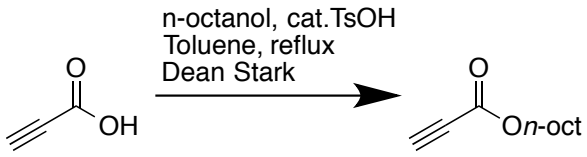
TLC: 5% Et_2O/Hexanes R_f = 0.31

Flash chromatography gradient elution with 5% EtOAc/Hexanes yielded **3** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.57-7.59 (m, 2H), 7.36-7.47 (m, 3H), 3.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 154.61, 133.14, 130.83, 128.72, 119.68, 86.64, 80.50, 52.94

***n*-octyl propiolate**

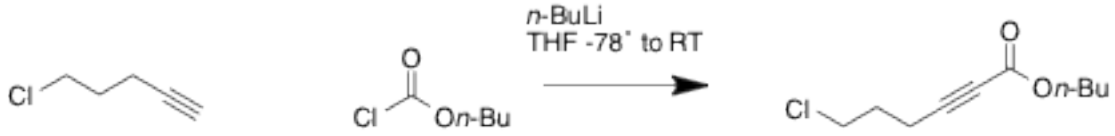


5b

A solution of 1-octanol (0.869 mL, 5.5 mmol, 1.1 equiv.), propiolic acid (0.308 mL, 5 mmol, 1 equiv.), and p-toluenesulfonic acid monohydrate (95.11 mg, 0.5 mmol, 0.1 equiv.) in toluene (20 mL) was allowed to reflux overnight in a Dean Stark apparatus. The solvent was removed by rotovap, and the product was further purified by flash chromatography.

^{1}H NMR (500 MHz, $CDCl_3$): 4.20 (t, 2H), 2.86, (s, 1H), 1.70 (m, 2H), 1.30 (m, 10H), 0.90 (t, 3H)

Butyl 6-chlorohex-2-ynoate



Prepared according to a modification of the general procedure. Extended times for lithiation of the alkyne were observed to lead to side products. The compound could be prepared in low yield with the following unoptimized procedure.

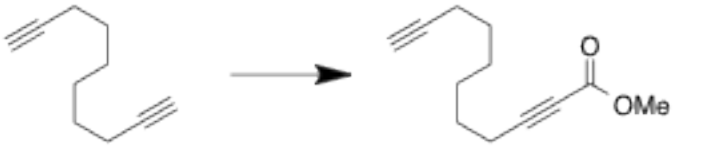
To a solution of 5-chloro-1-pentyne (0.5 mL, 4.7 mmol, 1 equiv) in 9.4 ml THF at -78 °C was added *n*-BuLi (2.30 ml, 5.2 mmol, 1.1 equiv, [2.2 M] in hexane)

dropwise. The solution was allowed to stir for 10 minutes. *n*-Butyl-chloroformate (0.732 ml, 5.66 mmol, 1.2 equiv) was then added and the cooling bath removed and solution was allowed to warm to room temperature. Saturated ammonium chloride was subsequently added and the layers separated. The aqueous layer was washed twice with Et_2O and organic extracts combined and washed once with brine, then dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The resulting crude product was further purified by flash chromatography, affording 279 mg (29.2%) of a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.94 (t, J = 7.2 Hz, 3H), 1.45 (sex, J = 7.4 Hz, 2H), 1.69 (p, J = 7.1 Hz, 2H), 2.08 (p, J = 6.6 Hz, 2H), 2.57 (t, , J = 7 Hz, 2H), 3.65 (t, J = 6.4 Hz, 3H), 4.18 (t, J = 6.8 Hz, 2H)

.

Methyl undeca-2,10-diynoate



methyl undeca-2,10-diynoate

Extended stirring at low temperature or brief warming during the lithiation of the diyne was observed to cause vigorous polymerization and is not advised. The compound could be prepared in low yield by the following unoptimized procedure:

1 ml (6.24 mmol) 1,9 decadiyne was dissolved in 12.5 ml dry THF and cooled to -78 ˚C. 1.2 ml *n*-BuLi [2.2 M] in hexanes was then added dropwise, and the solution was stirred for 10 minutes. After 10 minutes 1.2 equivalents of methyl chloroformate were added dropwise and the solution was stirred for 60 minutes at -78 ˚C, then let warm to room temperature. Usual workup and flash chromatography yielded 300 mg (24.9%) of Ynoate as a clear oil.

TLC: 10% EtOAc/Hexanes R_f = 0.39, Stain $KMnO_4$,

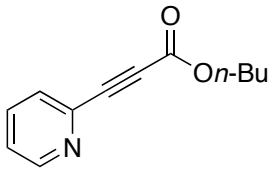
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.39-1.63 (m, 8H), 1.94 (t, J = 3.5 Hz, 1H), 2.19 (dt, J = 9, 3.5 Hz, 2H), 2.34 (t, J = 9 Hz, 2H), 3.76 (s, 3H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 18.45, 18.73, 27.48, 28.20, 28.31, 28.39, 52.69, 68.43, 73.07, 84.55, 89.82, 154.38.

ESI-HRMS: Calcd. For $C_{12}H_{16}O_2$: 192.1150. Found: 215.1041 $(M+Na)^+$

IR: 3295, 2938, 2861, 2235, 2116, 1710, 1434, 12498, 1074, 752, 632.

Butyl 3-(pyridin-2-yl)propiolate



Prepared according to the General Procedure:

Flash chromatography eluting with 20% EtOAc/Hexanes yielded desired compound as a yellow oil.

TLC: 30% EtOAc/Hexanes R_f = 0.4, Stain: UV/$KMnO_4$

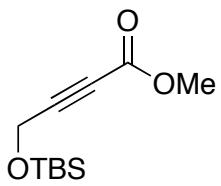
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J* = 7.4 Hz, 3H), 1.39-1.46 (sex, 2H), 1.65-1.71 (p, J = 14.5 Hz, 2H), 4.23-4.25 (t, *J* = 6.6 Hz, 2H), 7.33-7.36 (ddd, 1H), 7.58-7.60 (dt, 1H), 7.70-7.73 (dt, 1H), 8.64-8.66 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.75, 19.15, 30.53, 66.31, 79.36, 83.87, 124.72, 128.66, 136.44, 140.76, 150.65, 153.75

IR: 2961, 2874, 2228, 1706, 1581, 1565, 1462, 1430, 1293, 1280, 1195, 907, 778, 726

ESI-HRMS: Calcd. For $C_{12}H_{13}NO_2$: 203.0946. Found: 226.0850 $(M+Na)^+$

Methyl 4-((tert-butyldimethylsilyl)oxy)but-2-ynoate



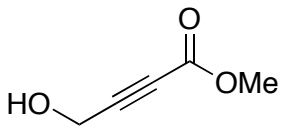
Prepared according the General Procedure.

Flash chromatography eluting with 10% EtOAc/Hexanes yielded product as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.13 (s, 6H), 0.90 (s, 9H), 3.78 (s, 3H), 4.43 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -5.09, 18.37, 25.85, 51.52, 52.86, 76.49, 86.31, 153.89

Methyl 4-hydroxybut-2-ynoate



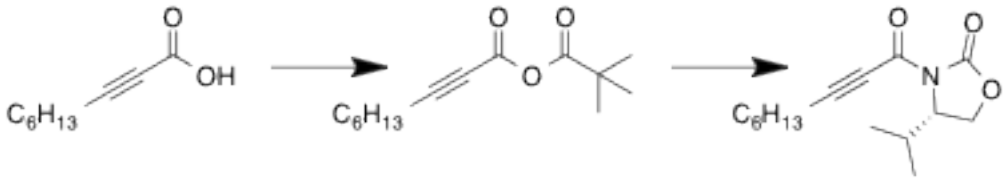
To a solution of THP protected ynoate (367 mg, 1.85 mmol) in MeOH:H_2O (9:1, 10 mL) at 23 ˚C was added TsOH·H_2O (36 mg, 0.185 mmol), the mixture was allow to stir overnight. The reaction was quenched with sat. aq. $NaHCO_3$, and the MeOH was removed in vacuo. The mixture was extracted with Et_2O (4x), and the combined organic layers were washed with brine then dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography gradient elution with 20-30% EtOAc/Hexanes yielded desired product as a colorless oil.

TLC: 30% EtOAc/Hexanes R_f = 0.29. Stain = UV/$KMnO_4$

Spectral data matches that of previously reported by Larock

Larock, R. C.; Liu, C. L. *J. Org. Chem.* **1983**, 48, 2251-2158.

(*S*)-4-isopropyl-3-(non-2-ynoyl)oxazolidin-2-one



Alkynyl oxazolidinone was prepared according to the method of Evans.

Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063.

TLC: 20% EtOAc/Hexanes R_f = 0.23, stained with CAM

Flash chromatography gradient elution with 10-20% EtOAc/Hexanes yielded 71% of desired oxazolidinone.

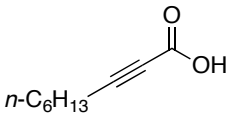
^{1}H NMR (500 MHz, CDCl3) δ (ppm): 0.85-0.90 (m, 6H), 0.93, (d, *J* = 10 Hz, 3H), 1.29 (m, 4H), 1.43 (m, 2H), 1.63 (m, 2H), 2.39 (m, 1H), 2.43 (t, *J* = 5 Hz, 2H) 4.21 (dd, *J* = 5, 10 Hz, 1H), 4.25 (t, *J* = 10Hz, 1H), 4.41 (dt, *J* = 5, 10 Hz, 1H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 14.15, 14.85, 18.10, 19.48, 22.58, 26.60, 27.56, 28.61, 28.66, 31.35, 58.68, 63.35 73.66, 150.98, 152.69

ESI-HRMS: Calcd. For $C_{15}H_{23}NO_3$: 265.1678. Found: 288.1570 $(M+Na)^+$

IR: 2958, 2930, 2860, 2227, 1789, 1659, 1486, 1465, 1385, 1364, 1311, 1198, 1086, 1051, 772, 717, 670, 594, 533.

Non-2-ynoic acid



To a solution of 1-octyne (13.5 mmol) in 40 mL of dry THF at -78 ˚C was added *n*-BuLi (13.5 mmol). The solution was stirred at -78 ˚C for 30 min. The reaction mixture was warmed to 0 ^{o}C and a balloon of CO_2 gas was bubbled through and vigorously stirred for 30 min. Then conc. HCl (10 mL), water (10 mL) and Et_2O (30 mL) was added. The aqueous layer was discarded and the organic layer was extracted with NaOH (1M; 3 x 20 mL). The aqueous extracts were acidified with conc. HCl, extracted with Et_2O (3 x 20 mL), washed with water and brine, dried with $MgSO_4$ and concentrated. The resulting oil was purified by bulb to bulb distillation (170 ˚C at 3 millibar) to afford (1.63 g, 78.2% yield) as a clear oil.

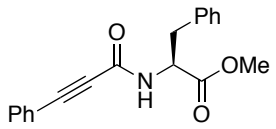
Spectral data matches that of previously reported.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88-0.91 (t, *J* = 7.0 Hz, 3H), 1.25-1.35 (m, 4H), 1.37-1.43 (m, 2H), 1.56-1.62 (p, 2H), 2.34-2.37 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.14, 18.92, 22.58, 27.49, 28.63, 31.31, 72.70, 93.01, 158.36

IR: 2930, 2860, 2653, 2236, 1681, 1458, 1408, 1379, 1275, 1072, 889, 754, 723, 604

Methyl (3-phenylpropioloyl)-*L*-phenylalaninate



To a solution of phenyl propiolic acid (1.18 mmol) in dry DCM (15 ml) at 0 ˚C was added dry Et_3N (1.18 mmol). The reaction mixture was stirred for 10 min at 0 ˚C followed by the addition of isobutyl chloroformate (1.3 mmol) was added dropwise and let stir for 15 min. A separate solution of *L*-phenylalanine methyl ester HCl (2.36 mmol) in dry DCM (40 ml) was added dry Et_3N (2.36 mmol) which was stirred for 15 min. This solution was added dropwise to the solution of phenyl propiolic acid, warmed to room temperature and stirred overnight. To the reaction mixture was added water (20 mL) and subsequently washed with DCM (3x). The organic layer was washed with water (2 x 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated by rotary evaporation.

The resulting solid was purified by recrystallization in DCM to afford (271.6 mg, 63.7% yield) as pale yellow crystals.

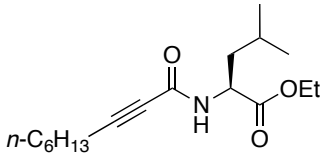
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.15-3.25 (dq, *J* = 13.9, 5.6 Hz, 2H), 3.76 (s, 3H), 4.96-5.00 (m, 1H), 6.38-6.39 (d, *J* = 7.6 Hz, 1H), 7.13-7.15 (m, 2H), 7.25-7.44 (m, 6H), 7.53-7.55 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 37.91, 52.69, 82.68, 85.68, 120.13, 127.43, 128.67, 128.82, 129.47, 130.37, 132.78, 135.58, 152.84, 171.41

IR: 3293, 2946, 2216, 1739, 1632, 1529, 1490, 1454, 1350, 1318, 1299, 1228, 1211, 1171, 757, 704, 689, 677

ESI-HRMS: Calcd. For $C_{19}H_{17}NO_3$: 307.1208. Found: 330.1090 $(M+Na)^+$

Ethyl non-2-ynoyl-*L*-leucinate



To a solution of non-2-ynoic acid (2 mmol) in DCM (20 mL) cooled to 0 ^oC was added Et_3N (2 mmol, 1 equiv) followed by dropwise addition of isobutyl chloroformate (2.2 mmol, 1.1 equiv). The reaction was monitored by TLC. A second solution of *L*-Leucine ethyl ester HCl (2 mmol) in DCM (20 mL) was added Et_3N (4 mmol, 2 equiv) This solution was transferred via syringe dropwise to the solution of mixed anhydride at 0 ˚C. The cooling bath was removed and reaction was let stir overnight. Reaction was quenched with water (20 mL) and subsequently extracted with DCM (3x 30ml). The organic layer was washed with water (2 x 30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography with 1:10:89 Et_3N:EtOAc:Hexanes afforded pure product as a yellow oil.

TLC: 10% EtOAc/Hexanes R_f: 0.17

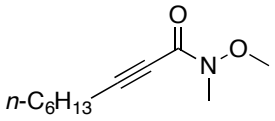
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.87-0.90 (t, *J* = 7.0 Hz, 3H), 0.93-0.95 (m, 6H), 1.25-1.33 (m, 8H), 1.36-1.42 (m, 2H), 1.51-1.60 (m, 3H), 1.63-1.72 (m, 2H), 2.27-2.30 (t, *J* = 7.2 Hz, 2H), 4.17-4.21 (q, *J* = 7.1 Hz, 2H), 4.62-4.67 (m, 1H), 6.10-6.11 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.16, 14.28, 18.78, 22.18, 22.60, 22.91, 24.98, 27.82, 28.71, 31.37, 41.88, 51.09, 61.63, 75.34, 88.51, 153.20, 172.64

IR: 3286, 2957, 2932, 2870, 2237, 1736, 1633, 1527, 1467, 1369, 1335, 1271, 1224, 1196, 1154, 1029

ESI-HRMS: Calcd. For $C_{17}H_{29}NO_3$: 295.2147. Found: 318.2042 $(M+Na)^+$

_N_-methoxy-_N_-methylhex-2-ynamide



To a flame-dried RBF, under argon, was added solid Weinreb hydrochloric salt (1 equi.) and the RBF was degassed (x 3), and dry THF was added to ~1M and the solution was brought to -20 ˚C. Methyl hex-2-ynoate (1.5 equiv) was then added dropwise to the solution, "neat," and the mixture was allowed to stir for about 20 minutes. At -20 ˚C, a [2M] solution of isopropyl-Magnesium chloride (1.5 equiv), in THF, was added dropwise and the solution was allowed to stir for 30 minutes at which point it was raised from the cold bath and allowed to warm to room temperature over the course of 1.5 hours. The solution was quenched with

saturated NH_4Cl and transferred to a separatory funnel with ether. The aqueous layer was extracted twice with ether, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification via column chromatography (15% EtOAc: hexanes) afforded pure *N*-methoxy-*N*-methylhex-2-ynamide as a yellow oil.

Product TLC R_f = 0.28 in (2:1) EtOAc: hexanes (stain: $KMnO_4$).

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 1.01-1.04 (t, *J* = 7.25 Hz, 3H), 1.59-1.65 (m, 2H), 2.35-2.37 (t, *J* = 7.0 Hz, 2H), 3.23 (bs, 3H), 3.77 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 13.406, 20.887, 21.239, 32.299, 61.999, 73.268, 93.453, 154.685.

IR: 3492.5, 2966.6, 2935, 2877.1, 2235.5, 1714.9, 1641.2, 1415, 1383.5, 973.3, 720.85, 584.11

1-methyl-4-(oct-1-yn-1-ylsulfonyl)benzene

To a dilute solution of sodium p-toluenesulfinate water was added a concentrated solution of iodine (1 equiv) in toluene. The reaction was stirred for about one hour at room temperature while covered in foil to avoid contact with light. The reaction mixture was then transferred to a sep. funnel via water and washed twice with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was then washed with hexanes and decanted to remove iodine, until the decantant remained clear. The solid was applied to high-vacuum for 30 minutes, after which the solid was sealed

under argon, wrapped in foil and stored in the freezer until use (Product is only stable for a short time at room-temperature, thus it is prepared directly before its subsequent use). Pure 4-methylbenzenesulfonyl iodide was isolated as yellow crystals.

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 2.43 (s, 3H), 7.18-7.38 (m, 2), 7.71 (m, 2H).

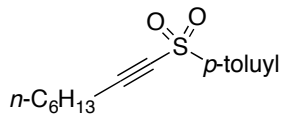
(*E*)-1-((2-iodooct-1-en-1-yl)sulfonyl)-4-methylbenzene

A 0.25 M solution of freshly prepared 4-methylbenzenesulfonyl iodide (2.29 mmol, 1.1 equiv) and 1-octyne (2.08 mmol, 1 equiv) in dry ether was stirred at room temperature, exposed to ambient light, overnight. The solution was concentrated *in vacuo* and the crude orange solid/oil mixture was purified via column chromatography (5% ether: hexanes) to afford β-iodo sulfone in 92%, 587mg, isolated yield.

Product TLC R_f = 0.44 in 20% ether: hexanes.

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.88-0.99 (t, *J* = 6.6 Hz, 3H), 1.25-1.35 (m, 6H), 1.44-1.55 (m, 2H), 2.45 (s, 3H), 3.0-3.03 (t, *J* = 7.6 Hz, 2H), 7.0 (s, 1H), 7.35-7.37 (d, *J* = 8.0 Hz, 2H), 7.78-7.79 (d, *J* = 8.0 Hz, 2H).

1-methyl-4-(oct-1-yn-1-ylsulfonyl)benzene



A solution of (*E*)-1-((2-iodooct-1-en-1-yl)sulfonyl)-4-methylbenzene (1.92 mmol, 1 equiv) in dry acetone was refluxed overnight with anhydrous K_2CO_3 (2.0 mmol, 2 equiv). The crude solution was transferred to a separatory funnel and washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified via column chromatography (10% ether: hexanes) to afford pure 1-methyl-4-(oct-1-yn-1-sulfonyl)benzene as a colorless oil 50% isolated, and 40% recovered starting material.

Product TLC R_f=0.38 in 20% ether: hexanes (UV, $KMnO_4$, I_2).

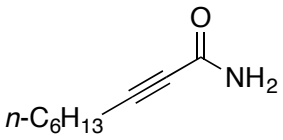
^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.848-0.88 (m, 3H), 1.22-1.32 (m, 6H), 1.50-1.56 (m, 2H), 2.32-2.35 (t, *J* = 7.25 Hz, 2H), 2.45 (s, 3H), 7.35-7.36 (d, *J* = 8.0 Hz, 2H), 7.87-7.88 (d, *J* = 8.5 Hz, 2H).

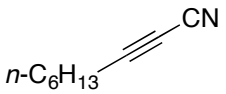
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 13.911, 18.902, 21.667, 22.338, 26.915, 28.362, 31.002, 78.402, 97.420, 127.208, 129.859, 139.238, 145.065.

ESI-HRMS: Calculated for $[C_{15}H_{20}O_2S + Na^+]^+$: 264.118. Found: 287.1066, $[M+Na^+]^+$.

IR: 2956, 2929.7, 2861.4, 2198.7, 1599.1, 1331, 1157.4, 1089, 678.78 cm^{-1}

Non-2-ynamide and Non-2-ynenitrile





Methyl non-2-ynoate was synthesized according to the general procedure.

Product TLC R_f=0.32 in 2% ether: hexanes (stain= I_2, $KMnO_4$).

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.87-0.89 (t, *J* = 7.0 Hz, 3H), 1.24-1.34 (m, 4H), 1.38-1.40 (m, 2H), 1.55-1.59 (m, 2H), 2.30-2.33 (t, *J* = 7.0 Hz, 2H), 3.75 (s, 3H).

Non-2-ynamide

To a sealed tube containing a solution of Methyl non-2-ynoate in methanol (~0.125 M)was added aqueous NH_4OH (~100 equiv) and the tube was sealed and teflon tapped immediately. The reaction was allowed to stir at room temperature for about 6 hours. The solution was applied to a rotary evaporator to remove methanol and the viscous crude mixture was transferred to a separatory funnel with water, and extracted (x3) with EtOAc. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was solubilized in a minimal amount of ether, then hexanes was added slowly, 10 volumes relative to ether. The crude solution was sealed with parafilm and stored at 5 ˚C overnight. The precipitate was filtered and the obtained crystals washed with cold hexanes. After solvent

removal under high-vacuum, amide was obtained as flaky clear crystals. (Ref. Smith, E. *J. Chem. Soc.* **1992,** *17*, 2163)

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.87-0.89 (t, *J* = 7.0 Hz, 3H), 1.24-1.33 (m, 4H), 1.37-1.41 (m, 2H), 1.52-1.58 (m, 2H), 2.27-2.30 (t, *J* = 7.25 Hz, 2H), 5.70 (s, 1H), 6.01 (s, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 14.00, 18.60, 22.45, 27.63, 28.52, 31.20, 74.85, 89.08, 155.24.

ESI-HRMS: Calculated for [$C_9H_{15}NO$]: 153.115. Found: 176.1041, [$M+Na^+$]$^+$.

IR: 3311.29, 3143.13, 2931.57, 2857.51, 2241.64, 1651.64, 1608.52, 1465.20, 1391.64, 1130.34, 702.85, 590.53, 563.27, 476.42 cm^{-1}

Non-2-ynenitrile

To a solution of preceding amide and dry DMSO in dry DCM at -78 ˚C was added a solution of oxalyl chloride (0.385 mmol, 1.4 equiv) in dry DCM; the reaction was allowed to stir for 30 minutes. Then dry triethylamine (0.825 mmol, 3.0 equiv) was added to the solution (still at -78 ˚C) and the reaction was allowed to stir for 30 minutes. At this point the reaction progress was checked via TLC, if full conversion was not achieved then the RBF was raised out of dry ice/ acetone bath and routinely monitored via TLC. When complete the reaction was quenched, at -78 ˚C, with water and allowed to warm to room temperature with stirring. The crude mixture was transferred to a separatory funnel via water and

extracted (3x) with EtOAc. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification via column chromatography (2% ether: hexanes) afforded nitrile **29** as a colorless oil, 75% isolated yield.

Product TLC R_f=0.49 in 10% ether: hexanes (stain: $KMnO_4$). This product is highly volatile; thus care should be taken to avoid extended periods of time on either the rotary evaporator or high-vacuum.

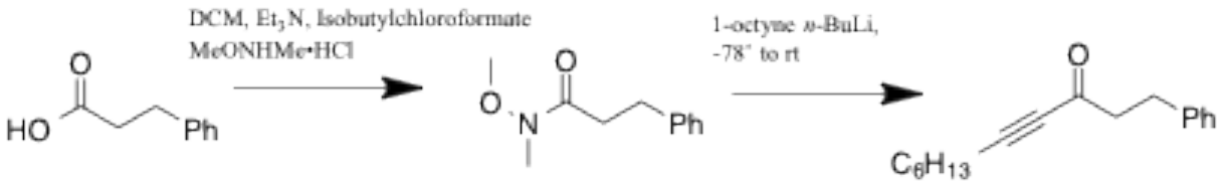
^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm): 0.87-0.90 (t, *J* = 7.2 Hz, 3H), 1.24-1.33 (m, 4H), 1.36-1.41 (m, 2H), 1.56-1.60 (m, 2H), 2.33-2.35 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 13.92, 18.81, 22.36, 26.99, 28.37, 31.03, 55.23, 87.47, 105.30.

ESI-HRMS: Calculated for $C_9H_{13}N$: 135.105. Found: 134.0971, $[M-H]^+$.

IR: 2956, 2929.7, 2861.4, 2314.4, 2261.8, 2156.6, 1457.1, 1420.3, 726.11, 499.96 cm^{-1}

1-phenylundec-4-yn-3-one



10 mmol of Hydrocinnamic acid was dissolved in 50 ml of dry Dichloromethane in a 250 ml RBF and the solution was cooled to 0 ˚C with an ice bath. 1.53 ml (11 mmol) of dry Triethylamine was added through the septa via syringe and the solution was stirred for 10 minutes. 1.37 ml of isobutylchloroformate was added to the solution dropwise and following the addition the solution was further stirred for 30 minutes. In a separate flask 975.4 mg (10 mmol) of MeONHMe•HCl was dissolved in 50 ml of dry dichloromethane in a 100 ml RBF and 3.06 ml (22 mmol) of dry triethylamine was added and the solution was stirred for 10 minutes at ambient temperature. After 30 minutes, the solution containing MeONHMe•HCl was transferred dropwise via cannula to the solution of the mixed anhydride. The solution was stirred until the temperature of the ice bath reached room temperature and the reaction was quenched by addition of H_2O. The layers were separated, and the aqueous layer was washed 2 times with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered through a short silica pad, and concentrated under rotary evaporation. The crude compound was purified by flash chromatography in a 4 cm outer diameter column filled with 18 cm of silica, eluting with 30-35% Ethyl Acetate/Hexanes. Concentration yielded 1.851 grams (95.8%) of pure Weinreb amide as a clear oil.

TLC: 35% EtOAc/Hexanes R_f = 0.375.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.74 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 7 Hz, 2H), 3.18 (s, 3H), 3.61 (s, 3H), 7.19-7.30 (m, 5H).

To prepare the ynone, 579.74 mg (3 mmol) of Weinreb amide was dissolved in 30 ml of dry THF, and cooled to -78 ˚C with a dry ice acetone bath. In a separate flask, 0.487 ml (3.3 mmol) of 1-octyne was dissolved in 30 ml THF, and cooled to -78 ˚C. 1.25 ml (3 mmol) of *n*-BuLi (2.2 M in hexanes) was added dropwise to the solution of 1-octyne and the solution was stirred for 15 minutes at -78˚, then at 0˚ for 30 minutes, then recooled to -78 ˚C. The solution containing lithiated alkyne was then transferred dropwise via cannula to the solution of Weinreb Amide. Once the addition was complete the cooling bath was removed and allowed to come to room temperature. Once the flask was felt to be at room temperature, the reaction was quenched with saturated aqueous ammonium chloride, stirred for 10 minutes, and then diluted with Et_2O. The contents of the flask were transferred to a seperatory funnel and rinsed with ether. The layers were separated and washed with Et_2O twice and the combined organic extracts were washed with a small amount of water, brine, dried over sodium sulfate, filtered and concentrated by rotary evaporation. Flash chromatography eluting with 0-5% Et_2O/Hexanes yielded 692 mg (95.2%) of the pure product.

Use of an excess of *n*-BuLi relative to 1-Octyne was observed to lead to the corresponding butyl-phenethyl-ketone which could not be efficiently separated

from the desired product by either column chromatography or bulb to bulb distillation; the reaction is best performed using a slight excess of 1-Octyne.

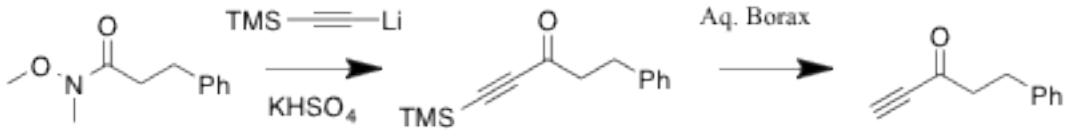
TLC: 10% Et_2O/Hexanes R_f = 0.38. Stain: $KMnO_4$ or Vanillin.

^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 0.89 (t, *J* = 7.2 Hz, 3H), 1.27-1.34 (m, 4H), 1.40 (p, *J* = 7.8 Hz, 2H), 1.56 (p, *J* = 7.2 Hz, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 7.19-7.21 (m, 3H), 7.27-7.35 (m, 2H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 14.132, 19.085, 22.587, 27.774, 28.650, 30.111, 31.320, 47.102, 80.952, 95.107, 126.341, 128.440, 128.630, 140.500, 187.252,

IR: 3091, 3028, 2929, 2858, 1672, 1604, 1454, 1158, 1029, 747, 697, 560 487.

5-phenylpent-1-yn-3-one



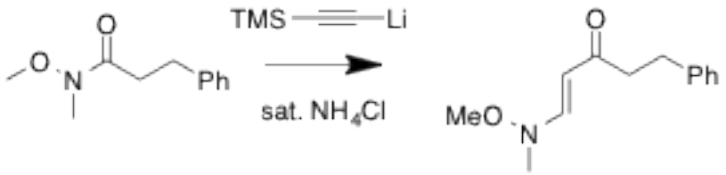
To a solution of TMS-acetylene (4.4 ml, 30.6 mmol, 1.53 equiv) in THF (150 ml) at -78 °C under argon, *n*-BuLi (12.0 ml, 29 mmol, [2.41 M] in hexanes, 1.45 equiv) was added dropwise. The solution was allowed to stir for 30 minutes, after which it was warmed to 0°C briefly and then cooled back down to -78 °C. A

solution of the weinreb amide (3.58 g, 20 mmol, 1 equiv) in THF (150 ml) was then added via cannula. The solution was then immediately warmed to -10 °C and allowed to stir for 1 hr. The solution was then poured into cold $KHSO_4$ (1 M, 150 ml) and let stir for another hour. The quenched solution was then concentrated by rotary evaporation, and the remaining aqueous layer was extracted with Et_2O (2x 150 ml), and the organic layer was washed once with 1M $KHSO_4$ (150 ml), then sat. $NaHCO_3$ (150 ml) and brine (150 ml). It was then further dried over Na_2SO_4, filtered, and the solvent was removed by rotary evaporation. The crude product was further purified by column chromatography and was then used immediately in the subsequent deprotection.

TMS protected ynone was deprotected according to the method of Walton and Waugh. Aqueous borax (13.2 ml, 0.135 mmol, 0.01 M) was then added to a solution of crude 5-phenyl-1-(trimethylsilyl)pent-1-yn-3-one (1.99 g, 8.65 mmol, 1 equiv) in methanol (108 ml). The mixture was allowed to stir for 5 minutes, which was then quenched with cold dilute HCl. The aqueous layer was extracted with DCM (2 x 100 ml) then dried over Na_2SO_4. The crude product was further purified by flash chromatography (10% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.95 (m, 2H), 3.02 (m, 2H), 3.23 (s, 1H), 7.22 (m, 2H), 7.31 (m, 2H),

$KHSO_4$ or $NaHSO_4$ are necessary for quenching in the first step. Substituting with saturated ammonium chloride was observed to yield the undesired beta enamino ketone as the major product



General procedures for Silylcupration:

As with all reactions performed using surfactants, stirring is a very important parameter to ensure complete solubilization of the reagents and complete conversion. Care must be taken to ensure that the solution is vigorously stirred and also to minimize splashing on the sides of the reaction vessel, as once on the sides of the vessel it may be difficult to achieve complete conversion.

Conditions A: (Surfactant)

1 equiv ynoate [0.75 M] in 2 wt% TPGS-750-M, 1 mol% Cu(OAc)/PPh_3, 1.25 equiv $PhMe_2SiBpin$.

General procedure: To an argon purged 5ml conical microwave vial, fitted with a rubber septa under positive argon flow, with a triangular spin vane, was added 0.25 mg (1 mol%) Cu(I)OAc and 0.5 mg (1 mol%) PPh_3. The flask was recovered with the septa with attached argon line and was purged of air with additional argon for two minutes by inserting a vent needle through the septa, after two minutes the vent needle was removed. 0.267 ml of degassed TPGS-

750-M, 2 wt% solution in water was then added to the vial and the vial was clamped a few cm above a stir plate and stirred as vigorously as possible without splashing for 5 minutes. A reddish/yellow color is usually observed upon the addition of the surfactant solution to the copper. 0.2 mmol of the corresponding Ynoate was then added via syringe and vigorously stirred for 5 more minutes. 65.6 mg (1.25 equiv) of Sugimoto's reagent $PhMe_2SiBpin$ was then added via syringe and the reaction let stir at room temperature for 5-30 minutes. In many cases the reaction is complete at this time, but all reactions were monitored by TLC to determine complete conversion. The reaction was quenched by pouring the mixture on to a short pad of silica. The vial was rinsed with a minimum amount of solvent (usually Et_2O or EtOAc) and the pad was flushed with sufficient solvent to elute product. If so desired, the crude mixture can be poured directly on top of a silica column, rinsed with hexanes, and purified immediately by flash chromatography. Rotary evaporation afforded crude product which was then purified by flash chromatography, usually eluting with Et_2O/Hexanes mixtures. Starting material and product are oftentimes of similar polarity so it is advantageous to ensure complete consumption of starting material before quenching.

General conditions B: (Neat)

1 equiv. ynoate, 5 equiv H_2O 1 mol% $Cu(OAc)/PPh_3$, 1.25 equiv $PhMe_2SiBpin$.

Same as conditions **A** but with 5 equivalents of water as opposed to surfactant solution. Does not work with solid substrates.

Conditions C: (Ynones - On Water)

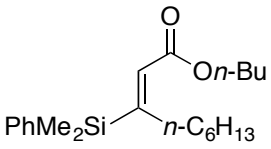
1 equiv ynone [0.4 M] on water 1 mol % CuOAc•(4-F-$C_6H_4)_3P$, 1.5 equiv $PhMe_2SiBpin$.

Best results are achieved when the copper and ligand are precomplexed first in solvent, followed by solvent removal prior to addition of surfactant solution. *E*-beta-silyl-enones with a second beta substituent are sensitive to isomerization and must be purified and used immediately after the reaction. Neat samples stored in the fridge, or NMR samples in deuterated chloroform were noticed to isomerize over time and it is suggested that the products be analyzed and used immediately after the reaction.

2 mol% Copper(I) Acetate and P(4-F-$C_6H_4)_3$ were added to a 5 ml flame dried conical microwave vial fitted with a triangular spin vane under a positive flow of argon. 0.5 ml of dry THF was added via syringe and the solution was stirred for 30 minutes at RT. THF was then removed by reinserting the argon and vent needle through the septa and letting evaporate under positive argon flow until the mass of the vial no longer changed.. Once evaporation was complete, 0.5 ml degassed DI water was added and the solution was vigorously stirred to remove

most of the ligand complex that had caked to the side of the vial. Ynone was then added to the vial followed by 1.5 equiv $PhMe_2SiBpin$ and the reaction was left stirring at rt for 2 hours. The reaction was quenched by diluting with Et_2O or EtOAc and poured immediately onto a short pad of silica where it was flushed through, concentrated, and purified immediately by flash chromatography usually eluting 0-3% Et_2O/Hexanes.

(*E*)-butyl 3-(dimethyl(phenyl)silyl)non-2-enoate



Prepared according to General Procedure **A** or **B**

Flash chromatography with 1% Et_2O/Hexanes yielded (94%, procedure **A**) or (98%, procedure **B**) of product as a clear oil.

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.42 (s, 6H), 0.82-0.85 (t, J = 7.1 Hz, 3H), 0.92-0.95 (t, J = 7.4 Hz, 3H), 1.22-1.28 (m, 8H), 1.36-1.43 (m, 2H), 1.61-1.66 (m, 2H), 2.59-2.62 (m, 2H), 4.09-4.11 (t, J = 6.7 Hz, 2H), 7.30-7.40 (m, 3H), 7.49-7.52 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.07, 13.89, 14.20, 19.40, 22.73, 29.87, 29.97, 30.93, 31.69, 31.82, 63.92, 103.89, 128.03, 129.51, 134.18, 136.87, 164.32, 165.67.

IR: 2956, 2929, 2858, 1715, 1587, 1459, 1427, 1379, 1249, 1216, 1147, 1112, 1088, 998, 909, 832, 815, 699.

Recycle Study

Prepared according to General Procedure **A** with the following modification.

All reactions run on 0.1 mmol scale. The reaction was worked up by addition via syringe of 0.2 mL hexane while remaining under argon atmosphere. The reaction was let stir for 30 seconds and was subsequently let settle for an additional 30 seconds until two separate layers formed. The hexane was removed via syringe. The extraction was performed a second time with 0.3 mL hexane. The organic extracts were combined and subsequently purified by flash chromatography. A second addition of ynoate (1 equiv) was added and let stir 5 min, followed by addition of $PhMe_2SiBpin$ (1.25 equiv). The reaction was let stir 30 min. followed by extraction outlined previously. This was performed five times. The sixth reaction was pipetted onto a pad of silica and worked up according to the general procedure.

Procedure for reaction using 0.01 mol % catalyst

Prepared according to General Procedure **A** with the following modifications:

Due to the low amount of copper in the reaction, to prevent oxidation of the catalyst all starting materials were purged under vacuum and backfilled with argon 4-5 times. Surfactant solution, TPGS-750M (2 wt %), was thoroughly

degassed with argon bubbling while stirring prior to use. 0.01 mol % $CuOAc/PPh_3$ were introduced into the reaction vessel by serial dilutions of a stock solution in THF. The appropriate volume of dilute $CuOAc/PPh_3$ was then transferred to the reaction vessel and evaporated under a positive flow of argon until the mass of the vial no longer changed. 0.13 ml of freshly degassed 2 wt% TPGS-750M solution was added via syringe and the solution was let stir 15 min under a positive argon flow. Ynoate (1 equiv) was added via syringe and let stir 5 min followed by addition of $PhMe_2SiBpin$ (1.25 equiv). The argon needle was removed and the septa was securely sealed with parafilm and stirred vigorously for 16 hours followed by standard workup.

_t_-Butyl (_E_)-3-(dimethyl(phenyl)silyl)non-2-enoate

Prepared according to general procedure **B**

Flash Chromatography gradient elution 0-2% Et_2O/Hexanes gave quantitative yield of *t*-Butyl (*E*)-3-(dimethyl(phenyl)silyl)non-2-enoate as a clear oil. Single Isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.41 (s, 6H), 0.84 (t, *J* = 7.5 Hz, 3H), 1.14-1.27 (m, 8H), 1.48 (s, 9H), 2.57 (t, *J* = 8 Hz, 2H), 5.98 (s, 1H), 7.34-7.39 (m, 3H), 7.50-7.52 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -3.012, 14.192, 22.707, 28.365, 29.925, 31.485, 31.746, 80.192, 127.987, 129.427, 130.214, 134.209, 137.132, 161.43, 165.37

ESI-HRMS: Calcd. For $C_{21}H_{34}O_2Si$: 346.2328. Found: 369.2226 $(M+Na)^+$

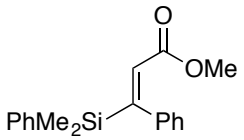
IR: 3075, 2956, 2928, 2857, 1712, 1598, 1456, 1428, 1366, 1249, 1214, 1146, 832, 816, 773, 731, 699.

Procedure for Gram scale reaction:

4.8 mg CuOAc (1 %) and 10.4 mg PPh_3 (1%) were added to an argon purged 25 ml RBF fitted with a rubber septa. 5.26 ml of degassed 2 wt% TPGS-750-M solution was added and the solution was observed to turn a reddish orange color immediately. The solution was stirred vigorously for 15 minutes whereupon 830 mg (3.94 mmol) of *t*-butyl non-2-ynoate was added via syringe and the solution was stirred vigorously until homogeneous. 1.36 grams of $PhMe_2SiBpin$ was then added dropwise and the solution was observed to exotherm slightly. After 15 minutes the reaction was poured onto a wide pad of silica and worked up according to the usual procedure. Flash chromatography eluting 0-2%

Et_2O/Hexanes gave 1.184 grams (86%) of pure *t*-butyl (*E*)-3-(dimethyl(phenyl)silyl)non-2-enoate as a clear oil. In addition, 91.3 mg (11%) of starting material was also recovered pure.

Methyl (*E*)-3-(dimethyl(phenyl)silyl)-3-phenylacrylate



Prepared according to General Procedure **A**

Flash chromatography gradient elution with 1-2% Et_2O/Hexanes yielded 98% of pure product as a colorless oil.

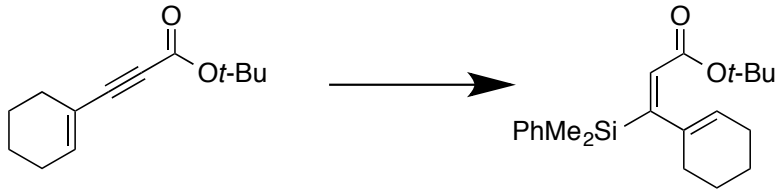
TLC: 10% Et_2O/Hexanes R_f: 0.37 Stain: UV/$KMnO_4$

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.38 (s, 6H), 3.50 (s, 3H), 6.21 (s, 1H), 6.82-6.84 (m, 2H), 7.19-7.25 (m, 3H), 7.36-7.37 (m, 3H), 7.46-7.48 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.69, 51.10, 125.86, 126.13, 127.74, 127.92, 128.75, 129.59, 134.21, 135.58, 140.96, 162.11, 165.47

IR: 3023, 2952, 1732, 1713, 1594, 1490, 1428, 1349, 1249, 1195, 1163, 1113, 1032, 942, 860, 831, 809, 779, 696.

***Tert*-butyl (*E*)-3-(cyclohex-1-en-1-yl)-3-(dimethyl(phenyl)silyl)acrylate**



Preppared according to general procedure **B** on 0.4 mmol scale. Flash chromatography through a short (3 inch) silica column yielded 131 mg (95.6% isolated)

R_f = 0.55 in 10% EtOAc/Hexanes; Stain: UV/$KMnO_4$

^{1}H NMR (500 MHz, CDCl3) δ (ppm): 0.40 (s, 6H), 1.45 (s, 9H), 1.54 (m, 4H), 1.84 (br, m, 2H), 2.00 (br, m, 2H), 5.09 (m, 1H), 5.87 (s, 1H), 7.33-7.37 (m, 3H), 7.50-7.52 (m, 2H)

^{13}C NMR (125MHz, CDCl3) δ (ppm): -3.14, 22.12, 22.87, 25.19, 28.32, 29.11, 80.34, 120.28, 127.85, 129.39, 130.06, 134.31, 136.94, 138.58, 160.51, 165.66

ESI-HRMS: Calcd. For $C_{21}H_{30}O_2Si$: 342.2015. Found: 365.1900 $(M+Na)^+$

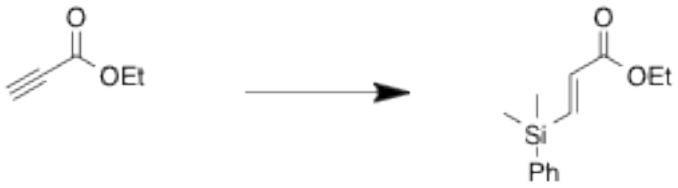
IR: 3070, 2929, 2834, 2210, 1718, 1704, 1588, 1427, 1390, 1349, 1247, 1145, 985, 808, 699.

E stereochemistry was confirmed by ^{1}H-^{1}H NOESY (600MHz, $CDCl_3$) (See attached spectra)

Key observations supporting the assignment were as follows:

1) Methyl groups on silicon gave a strong cross peak with the alpha-vinyl proton
2) The ring vinyl and the allylic ring protons gave a strong cross peak with t-buyl protons.
3) The absence of Silicon methyl's coupling to the *t*-butyl protons which would be expected for the *Z* isomer
4) The absence of coupling between the silicon phenyl protons and *t*-butyl protons

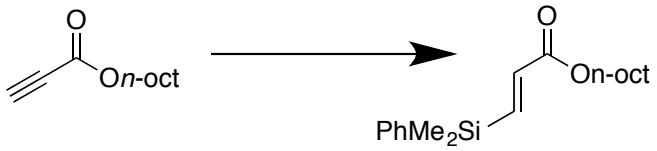
Ethyl (*E*)-3-(dimethyl(phenyl)silyl)acrylate



Prepared according to General Procedure **A** in 75% isolated yield as a single isomer.

^{1}H NMR (500 MHz $CDCl_3$) δ (ppm): 0.42 (s, 6H), 1.30 (t, *J* = 12.5 Hz, 3H), 4.20 (q, *J* = 7 Hz, 2H), 6.29 (d, *J* = 19 Hz, 1H), 7.34-7.40 (m, 4H), 7.50-7.52 (m, 2H).

***n*-octyl (*E*)-3-(dimethyl(phenyl)silyl)acrylate**



In a microwave vial under Argon atmosphere, copper (I) acetate (0.5 mg, 0.004 mmol, 0.02 equiv), triphenylphosphine (1.1 mg, 0.004 mmol, 0.02 equiv), were added to 266.67 μL of TPGS-750M**.** *n*-octyl propiolate (36.45 mg, 0.2 mmol, 1 equiv) was subsequently added followed immediately by dropwise addition of $PhMe_2SiBpin$ (0.25 mmol, 1.25 equiv The solution was allowed to stir for 2 hours. After which the reaction was diluted with CH_2Cl_2 and filtered through a pad of SiO_2. The solvent was removed by rotovap and the resulting crude product was further purified by flash chromatography, affording 50.4mg (80%) of product as a colorless oil.

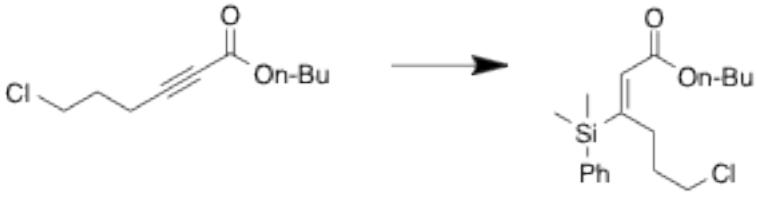
^{1}H NMR (500 MHz, $CDCl_3$): 7.52-7.34 (m, 6H), 6.29 (d, 1H), 4.15 (t, 2H), 1.69 (q, 2H), 1.38-1.26 (m, 10H), 0.90 (t, 3H), 0.42 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 166.01, 147.41, 136.60, 135.52, 133.99, 129.64, 128.13, 65.00, 31.93, 30.47, 29.85, 29.37, 29.31, 28.79, 26.09, 22.78, 14.23, -3.02.

IR: 2956, 2925, 2856, 1725, 1430, 1304, 1249, 1221, 1165, 839, 996, 840, 817, 730, 698

EI-HRMS calcd for $C_{19}H_{30}O_2Si$ [M^+]=318.2015, found 303.1784 [M-CH_3] $^+$

Butyl (*E*)-6-chloro-3-(dimethyl(phenyl)silyl)hex-2-enoate



Prepared according to general procedure **A**

Stirred for 240 min. Usual workup and flash chromatography gradient elution 0-2% Et_2O/Hexanes yielded 82% of a colorless oil. Use of 5 mol% catalyst and 2 equiv. $PhMe_2SiBpin$ gave 82% isolated yield.

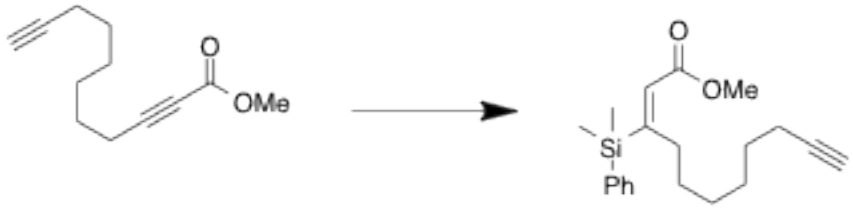
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.46 (s, 6H), 0.95 (t, J = 9 Hz, 3H), 1.43 (sex, J = 9.5 Hz, 2H), 1.66 (p, J = 8.5 Hz, 2H), 1.78 (m, J = 8 Hz, 2H), 2.75 (t, J = 10 Hz 2H), 3.48 (t, J = 8.5 Hz, 2H), 4.11 (t, J = 8.5 Hz, 2H), 6.12 (s, 1H), 7.51-7.36 (m, 5H),

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -3.24, 13.88, 19.37, 29.18, 30.89, 32.57, 45.33, 64.10, 128.17, 129.08, 129.73, 134.17, 136.30, 162.81, 165.41

ESI-HRMS: Calcd. For $C_{18}H_{27}ClO_2Si$: 338.1469. Found: 361.1353 $(M+Na)^+$

IR: 3076, 2958, 2873, 1712, 1602, 1428, 1250, 1178, 1153, 1113, 1027, 833, 814, 775, 732, 699, 569, 469.

Methyl (*E*)-3-(dimethyl(phenyl)silyl)undec-2-en-10-ynoate



Prepared according to General Procedure **A**

TLC: 10% EtOAc/Hexanes R_f = 0.41 (product), 0.47 (impurity), Stain: UV/$KMnO_4$

Usual workup and flash chromatography gradient elution with 0-0.5% Et_2O/Hexanes yielded 98 mg (75%) of product. Eluting with Ethyl Acetate/Hexanes mixtures gave poor separations.

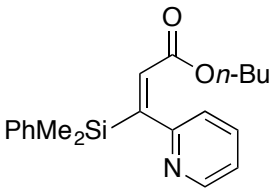
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.43 (s, 6H), 1.23-1.35 (br, m, 6H), 1.45 (p, *J* = 7.5 Hz, 2H), 1.92, (t, *J* = 7.5 Hz, 1H), 2.13 (dt, *J* = 2.5, 7 Hz, 2H), 2.63 (t, *J* = 8.5 Hz, 2H), 3.69 (s, 3H), 6.07 (s, 1H), 7.32-7.40 (m, 3H), 7.47-7.57 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -3.13, 18.49, 28.51, 28.53, 29.61, 29.65, 31.71, 51.07, 68.17, 84.9, 127.59, 128.07, 129.58, 134.16, 136.68, 165.18, 165.76.

EI-HRMS: Calcd. For $C_{20}H_{28}O_2Si$: 328.1859. Found: 313.1638 $(M\text{-}CH_3)^+$

IR: 3306, 3070, 2935, 2858, 2122, 1718, 1602, 1428, 1346, 1249, 1193, 1170, 1112, 1044, 833, 817, 775, 732, 631, 468.

Butyl (*E*)-3-(dimethyl(phenyl)silyl)-3-(pyridin-2-yl)acrylate



Prepared according to General Procedure **A**

TLC: 40% EtOAc/Hexanes R_f: 0.3, Stain: UV/$KMnO_4$

Flash chromatography elution with 20% EtOAc/Hexanes yielded 82% of product as a yellow oil in a 12:1 *E/Z* ratio as determined according to the relative integrations of vinyl protons, providing sample was worked up, purified, and analyzed immediately.

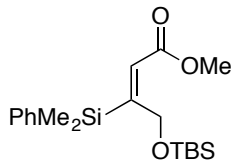
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.42 (s, 6H), 0.79-0.82 (t, *J* = 7.4 Hz, 3H), 1.10-1.18 (sex, 2H), 1.31-1.37 (p, 2H), 3.88-3.90 (t, *J* = 6.6 Hz, 2H), 6.06 (s, *Z* (minor) isomer, 0.09H), 6.25 (s, *E* (major) isomer, 1H), 6.83-6.85 (d, *J* = 7.9 Hz, 1H), 7.08-7.11 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 8.55-8.56 (ddd, *J* = 4.9, 1.7, 1.1 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.29, -3.27, 13.78, 19.14, 29.43, 30.51, 63.93, 64.36, 121.10, 121.72, 121.78, 128.07, 129.72, 130.66, 130.73, 134.10, 134.37, 135.51, 135.53, 135.77, 149.06, 160.18, 160.33, 165.30

IR: 3069, 2958, 2873, 1708, 1583, 1562, 1463, 1427, 1381, 1346, 1248, 1170, 1114, 1024, 834, 813, 792, 775, 699

ESI-HRMS: Calcd. For $C_{20}H_{25}NO_2Si$: 339.1655. Found: 362.1561 $(M+Na)^+$

Methyl (*E*)-4-((tert-butyldimethylsilyl)oxy)-3-(dimethyl(phenyl)silyl)but-2-enoate



Prepared according to General Procedure **A**

Flash chromatography gradient elution with 0-5% Et_2O/Hexanes yielded 88% of product as a yellow oil.

TLC: 10% Et_2O/Hexanes R_f: 0.53

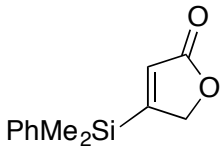
^1H NMR (500 MHz, $CDCl_3$) δ (ppm): -0.04 (s, 6H), 0.47 (s, 6H), 0.82 (s, 9H), 3.67 (s, 3H), 4.97 (d, J = 2.4 Hz, 2H), 5.87 (t, J = 2.4 Hz, 1H), 7.32-7.35 (m, 3H), 7.48-7.50 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -5.52, -1.57, 18.58, 26.19, 51.29, 65.73, 125.68, 127.86, 127.86, 129.12, 134.15, 138.11, 165.89, 157.60

IR: 2952, 2929, 2886, 2856, 1716, 1603, 1428, 1070, 1178, 833, 814, 775

EI-HRMS: For $C_{19}H_{32}O_3Si_2$: 364.1890. Found: 364.1884 (M+·)

4-(dimethyl(phenyl)silyl)furan-2(5H)-one



Prepared according to General Procedure **A**

Flash chromatography gradient elution with 5-20% EtOAc/Hexanes yielded 70% of product as a colorless oil.

TLC: 15% EtOAc/Hexanes R_f: 0.24

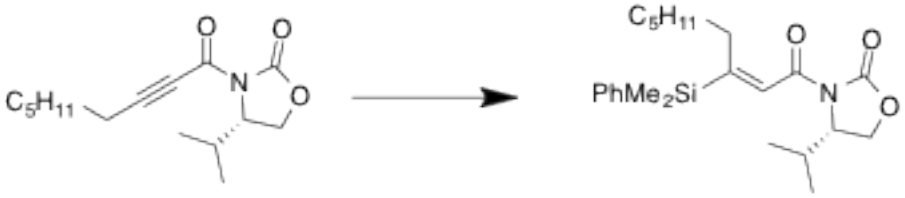
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.53 (s, 6H), 4.87 (d, *J* = 2.1 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 1H), 7.39-7.49 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.42, 75.64, 128.55, 129.27, 130.44, 133.77, 134.16, 174.01

IR: 3070, 2959, 1777, 1743, 1339, 1428, 1245, 1164, 1111, 1056, 998, 833, 805, 780, 735, 780

ESI-HRMS: Calcd. For $C_{12}H_{14}O_2Si$: 218.0763. Found: 218.0766 (M+·)

(*S*,*E*)-3-(3-(dimethyl(phenyl)silyl)non-2-enoyl)-4-isopropyloxazolidin-2-one



Prepared according to general procedure **A**

TLC 10% EtOAc/Hexanes R_f: 0.29 (major, *E* isomer), 0.36 (minor, *Z* isomer)

Staining with Seebach's Stain.

Flash chromatography gradient elution 10-20% Et_2O/Hexanes yielded 70% of *E* silylated oxazolidinone as a clear viscous oil. 12% of the corresponding *Z* isomer was also isolated.

Chromatography using EtOAc/Hexanes caused isomers to elute with together.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.46 (s, 6H), 0.83 (t, J = 10 Hz, 3H), 0.90 (d, J = 5 Hz, 3H), 0.93 (d, J = 5 Hz, 3H), 1.11-1.30 (m, 8H), 2.41 (m, 1H), 2.52 (m, 2H). 4.21 (dd, J = 10, 5 Hz, 1H), 4.26 (t, J = 10 Hz, 1H), 4.48 (dt, J = 10, 5 Hz, 1H), 7.21 (s, 1H), 7.34-7.38 (m, 3H), 7.53-7.56 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -3.12, -3.06, 14.20, 14.89, 18.23, 22.69, 28.64, 29.69, 29.88, 31.67, 32.45, 58.42, 63.42, 128.00, 128.27, 129.47, 134.25, 136.92, 154.02, 164.37, 164. 41

IR: 3070, 3054, 2957, 2927, 2856, 1776, 1679, 1587, 1486, 1464, 1427, 1384, 1372, 1299, 1242, 1199, 1112, 1022, 997, 971, 833, 813, 774, 732, 700, 632, 568, 469

ESI-HRMS: Calcd. For $C_{23}H_{35}NO_3Si$: 401.2386. Found: 424.2266 $(M+Na)^+$

***Z* - isomer:**

TLC: 10% EtOAc/Hexanes R_f = 0.36

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 0.47 (d, *J* = 9 Hz, 6H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 1.26 (m, 6H), 1.43 (m, 2H), 2.03 (m, 1H), 2.35 (t, *J* = 7.8 Hz, 2H), 4.08 (s, 3H), 7.29 (m, 3H), 7.42 (s, 1H), 7.50 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -1.45, -1.27, 14.21, 14.68, 18.07, 22.71, 28.34, 29.24, 29.51, 31.75, 39.42, 58.18, 63.35, 127.48, 128.56, 132.10, 134.00, 139.14, 154.05, 164.32, 165.74

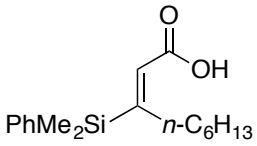
IR: 3072, 2958, 2927, 2858, 1777, 1678, 1581, 1486, 1464, 1429, 1384, 1372, 1300, 1245, 1203, 1142, 1109, 1064, 1036, 976, 909, 836, 816, 774, 730, 701, 669, 647, 473.

ESI-HRMS: Calcd. For $C_{23}H_{35}NO_3Si$: 401.2386. Found: 424.2286 $(M+Na)^+$

Absolute configuration was determined for both compounds based on comparison of ^{1}H-^{1}H NOESY for both isomers. *E* stereochemistry was suggested by a strong cross peak of the silicon methyl's with the vinyl proton and the absence of a cross peak between the vinyl proton and allylic protons. Conversely, the *Z* isomer showed a strong cross peak between the vinyl and allylic protons and the absence of coupling between the silicon methyl's and the vinyl proton

^{1}H NMR of the Z isomer showed a puzzling singlet at 4.08 ppm integrating to 3 hydrogens, and the notable absence of the characteristic multiplets of the oxazolidone ring in the 4-4.5ppm region. This would seem to suggest some sort of fragmentation/rearrangement resulting in the formation of an N, or O-Methyl bond with concomitant opening of the oxazolidone ring, but this possibility is ruled out on the basis of several observations: 1) R_f values and staining are very similar by TLC 2) The chirality is still intact as evidenced by the presence of diastereotopic doublets at 0.47 ppm, 0.73 ppm and 0.80 ppm. 3) HRMS confirms product is of the same mass as the *E* isomer. 4) GHSQC spectrum revealed that the apparent singlet results from the hydrogens of 2 carbons at 58.18 ppm and 63.35 ppm respectively, which are substantially similar to the shifts observed for the ring carbons adjacent to N, and O in the *E* isomer at 58.42, and 63.42 ppm. 5) IR stretches are almost identical for both compounds 6) 2D NOESY confirms that the geometry of the minor product is most likely the (*Z*) - isomer.

(*E*)-3-(dimethyl(phenyl)silyl)non-2-enoic acid



Prepared according to General Procedure **A**

Flash chromatography with 10% EtOAc/Hexanes yielded 84% of product as a colorless oil.

TLC: 10% EtOAc/Hexanes Rf: 0.23

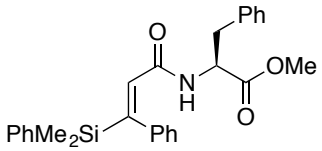
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.44 (s, 6H), 0.83-0.85 (t, *J* = 7.0 Hz, 3H), 1.17-1.28 (m, 8H), 2.62-2.65 (m, 2H), 6.08 (s, 1H), 7.35-7.40 (m, 3H), 7.54-7.55 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.16, 14.18, 22.64, 29.69, 29.84, 31.52, 31.91, 127.12, 127.84, 128.09, 129.38, 129.62, 133.14, 134.17, 136.49

IR: 2955, 2928, 2857, 1687, 1601, 1458, 1427, 1288, 1249, 1233, 819, 775, 730, 697

ESI-HRMS: Calcd. For $C_{17}H_{26}O_2Si$: 290.1702. Found: 313.1599 (M+Na)

Methyl (*E*)-(3-(dimethyl(phenyl)silyl)-3-phenylacryloyl)-*L*-phenylalaninate



Prepared according to General Procedure **A** using 2 equivalents of $PhMe_2SiBpin$ and strirred for 1 hour.

TLC: 20% EtOAc/Hexanes R_f: 0.14

Flash chromatography elution with 20% EtOAc/Hexanes yielded 84% of product as a yellow oil, and 15% recovered staring material.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.36 (d, *J* = 1.6 Hz, 6H), 2.70-2.79 (dq, *J* = 13.9, 6.1 Hz, 2H), 3.53 (s, 3H), 4.65-4.69 (dt, *J* = 7.5, 6.1 Hz, 1H), 5.60-5.62 (d, *J*

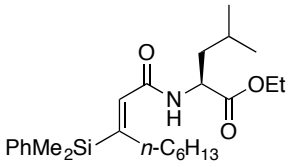
= 7.5 Hz, 1H), 6.24 (s, 1H), 6.81-6.84 (m, 4H), 7.18-7.24 (m, 6H), 7.33-7.44 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.58, -3.56, 37.89, 52.16, 53.45, 126.59, 126.97, 126.99, 128.05, 128.51, 128.77, 129.21, 129.72, 133.66, 134.35, 135.72, 135.96, 139.82, 154.63, 165.52, 171.61.

ESI-HRMS: Calcd. For $C_{27}H_{29}NO_3Si$: 443.1917. Found: 466.1807 $(M+Na)^+$

IR : 3409, 3027, 2953, 1742, 1650, 1601, 1581, 1496, 1428, 1359, 1248, 1173, 1112, 1074, 935, 832, 811, 735.

Ethyl (*E*)-(3-(dimethyl(phenyl)silyl)non-2-enoyl)-*L*-leucinate



Prepared according to General Procedure **A**

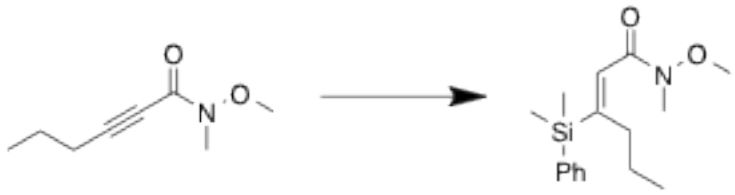
Flash chromatography elution with 20% EtOAc/Hexanes yielded 88% of product as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.41 (s, 6H), 0.81-0.84 (t, *J* = 7.1 Hz, 3H), 0.94-0.96 (t, *J* = 5.8 Hz, 6H), 1.13-1.24 (m, 6H), 1.26-1.29 (t, *J* = 7.1Hz, 6H), 1.51-1.57 (m, 2H), 1.62-1.67 (m, 2H), 2.57-2.60 (m, 2H), 4.16-4.21 (q, J = 7.1 Hz, 2H), 4.65-4.67 (dt, *J* = 8.7, 5.1 Hz, 1H), 5.77-5.79 (d, *J* = 8.4 Hz, 1H), 5.99 (s, 1H), 7.34-7.39 (m, 3H), 7.49-7.52 (m, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): -2.96, 14.21, 14.30, 22.23, 22.72, 22.93, 25.04, 29.91, 30.13, 31.59, 31.72, 42.10, 50.56, 61.44, 128.02, 129.45, 131.00, 134.23, 137.15, 158.37, 165.95, 173.46.

ESI-HRMS: Calcd. For $C_{25}H_{41}NO_3Si$: 431.2846. Found: 454.2751 $(M+Na)^+$

(*E*)-3-(dimethyl(phenyl)silyl)-*N*-methoxy-*N*-methylhex-2-enamide



Prepared According to General procedure **B** using 2 equivalents of $PhMe_2SiBpin$. The reaction was quenched with 50% sat. aq. $NaHCO_3$ and stirred for 15 minutes, before being poured onto a pad of silica and further purified. Flash chromatography gradient eluting 0-20% EtOAc/Hexanes yielded 96% as a yellow oil.

TLC 20% EtOAc/Hexanes R_f: 0.39 Stain: $KMnO_4$, CAM

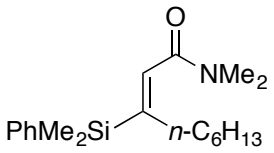
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.43 (s, 6H), 0.88 (t, *J* = 7.5 Hz, 3H), 1.37 (sex, *J* = 3 Hz, 2H), 2.54 (t, *J* = 2.5 Hz, 2H), 3.18 (s, 3H), 3.57 (s, 3H), 6.44 (w, br, s, 1H), 7.33-7.44 (m, 3H), 7.50-7.55 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -2.881, 14.687, 23.425, 29.826, 33.91, 61.446, 127.947, 128.474 (br, w), 129.368, 134.147, 137.472, 158.819 (br, w), 167.521.

IR: 3074, 2958, 2932, 2870, 1650, 1596, 1462,1427, 1406, 1375, 1248, 1112, 998, 832, 813, 772, 773, 700, 468.

ESI-HRMS: Calcd. For $C_{16}H_{25}NO_2Si$: 291.1655 Found: 314.1541 $(M+Na)^+$

(*E*)-3-(dimethyl(phenyl)silyl)-N,N-dimethylnon-2-enamide



Prepared according to General Procedure **A**

Flash chromatography gradient elution with 5-20% EtOAc/Hexanes yielded 78% of desired product as a colorless oil.

TLC: 10% EtOAc/Hexanes R_f: 0.2

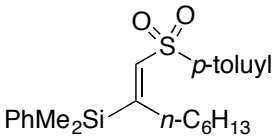
^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.42 (s, 6H), 0.81-0.84 (t, *J* = 7.1 Hz, 3H), 1.10-1.31 (m, 8H), 2.17-2.18 (d, *J* = 3.3 Hz, 1H), 2.27-2.30 (m, 2H), 2.94-2.96 (d, *J* = 6.5 Hz, 6H), 6.19 (s, 1H), 7.33-7.38 (m, 3H), 7.51-7.53 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -2.64, 14.21, 22.69, 29.43, 29.69, 29.75, 31.65, 32.25, 34.50, 37.85, 127.97, 129.32, 133.29, 134.12, 137.73, 150.81, 168.91.

IR: 2954, 2926, 2855, 1703, 1634, 1488, 1457, 1427, 1389, 1247, 1146, 1112, 1051, 998, 832, 813, 772, 732, 700

ESI-HRMS: Calcd. For $C_{19}H_{31}NOSi$: 317.5410. Found: 340.2066 $(M+Na)^+$

(*E*)-dimethyl(phenyl)(1-tosyloct-1-en-2-yl)silane



Prepared according to general procedure **A** stirring for 6 hours. The reaction was filtered through a short plug of silica. Purification via column chromatography eluting with 20% ether: hexanes afforded product in 99% isolated yield.

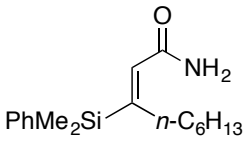
^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.40 (s, 6H), 0.82-0.85 (t, *J* = 7.0 Hz, 3H), 1.07-1.13 (m, 2H), 1.15-1.23 (m, 6H), 2.44 (s, 3H), 2.60-2.63 (t, *J* = 7.25 Hz, 2H), 6.46 (s, 1H), 7.31-7.42 (m, 7H), 7.77-7.78 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): -3.14, 14.02, 21.60, 22.47, 29.48, 29.68, 30.32, 30.71, 31.37, 127.34, 128.03, 129.74, 129.75, 133.93, 135.45, 136.94, 139.37, 144.00, 161.39.

ESI-HRMS: Calculated for $[C_{23}H_{32}O_2SSi]^+$: 400.189. Found: 423.1773, $[M+Na^+]^+$.

IR: 3045, 2955.1, 2928.7, 2854.6, 1595.4, 1315, 1288.6, 1145.7, 817.7, 706.6 cm^{-1}

(*E*)-3-(dimethyl(phenyl)sily)non-2-enamide



Prepared according to general procedure **A** using 2 equivalents of $PhMe_2SiBpin$ and stirring for 6.5 hours. The reaction was quenched with 50% sat. aq. $NaHCO_3$, stirred for 10 minutes and filtered through a short plug of silica. Purification via column chromatography afforded product 76.8 mg, 85% isolated yield.

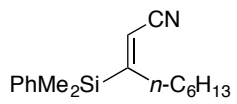
^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.41 (s, 6H), 0.82-0.85 (t, J = 7.0, 3H), 1.17-1.33 (m, 8H), 2.59-2.62 (t, J = 7.75 Hz, 2H), 5.41 (s, 1H), 5.48 (s, 1H), 6.00 (s, 1H), 7.34-7.38 (m, 3H), 4.49-7.51 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): -3.05, 14.05, 22.54, 29.71, 29.84, 31.40, 31.48, 127.88, 129.33, 130.08, 134.04, 136.92, 159.34, 168.14.

ESI-HRMS: Calculated for $[C_{17}H_{27}NOSi]$: 289.186. Found: 312.1747, $[M+Na^+]^+$.

IR: 3482, 3350.5, 3198, 2956, 2929.7, 2856.1, 1662.3, 1630.7, 1604.4, 1246.8, 1115.3, 810.26, 699.81 cm^{-1}

(*E*)-3-(dimethyl(phenyl)silyl)non-2-enenitrile



Prepared according to general procedure **A**. The reaction was filtered through a short plug of silica. Purification via column chromatography eluting with 2% ether: hexanes afforded product in 96% isolated yield.

TLC 2% Ether: Hexanes R_f:0.26 Stain: I_2, $KMnO_4$.

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 0.45 (s, 6H), 0.85-0.87 (t, *J* = 7.0 Hz, 3H), 1.16-1.30 (m, 6H), 1.31-1.38 (m, 2H), 2.47-2.50 (t, *J* = 7.75 Hz, 2H), 5.50 (s, 1H), 7.37-7.46 (m, 3H), 7.46-7.49 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): -3.36, 14.01, 22.46, 29.12, 29.25, 31.37, 35.29, 107.74, 115.96, 128.14, 129.87, 133.92, 135.19, 171.81.

ESI-HRMS: Calculated for $[C_{17}H_{25}NSi]^+$: 271.176. Found: 294.1643, $[M+Na^+]^+$.

IR: 3071.7, 2956, 2929.7, 2861.4, 2214.5, 1467.7, 1430.9, 1252, 1115.3, 815.52, 778.7, 736.63, 699.81, 478.93 cm^{-1}

(*E*)-5-(dimethyl(phenyl)silyl)-1-phenylundec-4-en-3-one

Prepared according to general procedure **C**.

TLC: 20% Et_2O/Hexanes R_f: 0.69, blue spots when staining with p-anisaldehyde. Starting material stains brown.

Flash chromatography gradient elution with 0-2% Et_2O/Hexanes yielded 91% of (*E*)-5-(dimethyl(phenyl)silyl)-1-phenylundec-4-en-3-one as a clear oil in a 17:1 E/Z ratio as determined according to relative integrations of vinyl protons, providing sample was worked up, purified, and analyzed immediately, as the product was observed to isomerize over time.

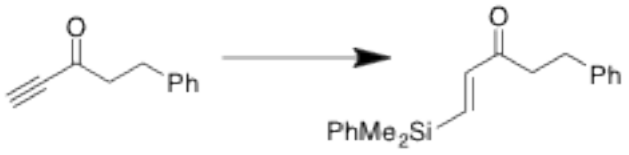
^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm): 0.38 (s, 6H), 0.85 (t, J = 6 Hz, 3H), 1.18-1.33 (m, 8H), 2.24 (t, J = 2 Hz, 2H), 2.69 (t, J = 5.5 Hz, 2H), 2.76 (t, J = 6 Hz, 2H), 6.38 (s, *Z* (minor) isomer, 0.06H), 6.74 (s, *E* (major) isomer, 1H), 7.07-7.37 (m, 8H), 7.46-7.51 (m, 2H)

^{13}C NMR (125MHz, CD_2Cl_2) δ (ppm): -1.88, 13.88, 22.61, 29.12, 29.65, 29.87, 31.63, 39.21, 44.54, 125.91, 127.36, 128.32, 128.35, 128.37, 133.79, 138.15, 138.15, 139.55, 141.47, 163.28 198.96

IR: 3074, 3026, 2955, 2927, 2856, 1686, 1572, 1497, 1454, 1406, 1361, 1245, 1110, 814, 775, 735, 666, 559, 473

EI-HRMS: Calcd. For $C_{25}H_{34}OSi$: 378.2379. Found: 363.2143 $(M\text{-}CH_3)^+$

(*E*)-1-(dimethyl(phenyl)silyl)-5-phenylpent-1-en-3-one



In a 3ml flame-dried microwave vial under argon, copper(I) acetate (0.25 mg, 2%) and tris(*p*-fluoro-triphenylphosphine) (0.65 mg, 2%) were stirred for 30 minutes in THF (0.1 ml), after which a vent needle was inserted and the THF was allowed to evaporate over 1 h. TPGS-750-M was immediately added to the vial followed by 5-phenylpent-1-yn-3-one (31.6 mg, 0.2 mmol, 2 equiv) and $PhMe_2SiBpin$ (26.22 mg, 0.1 mmol, 1 equiv) both added dropwise. The resulting mixture was allowed to stir for 1 h. It was then diluted with Et_2O and filtered through a pad of silica. The product was purified by flash chromatography (0.5-2% Et_2O/Hexanes), yielding 58.8 mg (61%) of a colorless oil. *J* coupling of 14 Hz for vinyl protons confirms product is only the *E* -isomer.

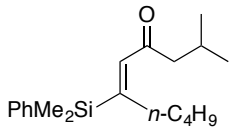
^1H NMR (500 MHz, CD_2Cl_2) δ (ppm): 0.45 (s, 6H), 2.83 (t, 2H), 2.91 (t, 2H), 6.54 (d, J = 14 Hz, 1H), 6.97 (d, J = 14 Hz, 1H), 7.12-7.59 (m, 10H)

^{13}C NMR (125MHz, CD_2Cl_2) δ (ppm): 200.0, 148.8, 142.3, 141.1, 139.7, 133.8, 128.9, 128.6, 128.5, 127.8, 126.2, 44.8, 30.5, 29.9.

IR: 3067, 3026, 2954, 2083, 1694, 1603, 1578, 1427, 1372, 1245, 1111, 1096, 817, 696

EI-HRMS Calcd. for $C_{19}H_{22}OSi$: 294.1440, Found: 279.1201 $(M\text{-}CH_3)^+$

(*E*)-6-(dimethyl(phenyl)silyl)-2-methyldec-5-en-4-one



Prepared according to General Procedure **A** using BDP in place of PPh_3 as the ligand. The metal and ligand were stirred at room temperature for 10 min followed by stirring at 0 ˚C for 5 min. The substrate was then added and stirred at 0 ˚C for 1 hr. The reaction was removed from the cooling bath and allowed to warm to room temperature and monitored by TLC.

Flash chromatography with 1% Et_2O/Hexanes yielded 85% of product as a colorless oil (*E/Z* 8:1).

TLC: 1% Et_2O/Hexanes R_f: 0.28

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.45 (s, 6H), 0.82-0.85 (m, 9H), 1.19-1.35 (m, 4H), 1.19-1.35 (m, 1H), 2.22-2.26 (m, 4H), 6.37 (s, *Z* (minor) isomer, 0.12H), 6.71-6.72 (s, *E* (major) isomer, 1H), 7.28-7.38 (m, 3H), 7.49-7.53 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -2.99, -1.64, 13.95, 22.62, 22.71, 25.15, 31.93, 31.98, 39.10, 52.25, 53.47, 127.48, 128.02, 128.49, 129.49, 133.96, 134.17, 135.66, 138.52, 139.55, 163.83, 200.0.

IR: 3069, 2956, 2930, 2871, 1684, 1571, 1465, 1427, 1404, 1365, 1244, 1153, 1109, 1062, 1030, 998, 815, 775, 735, 700, 666.

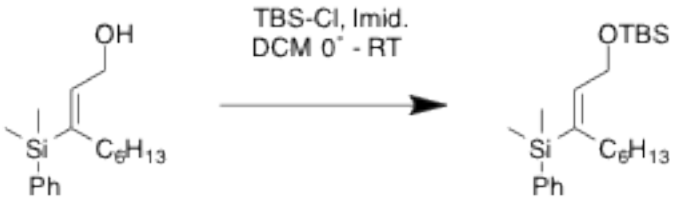
EI-HRMS: Calcd. For $C_{19}H_{30}OSi$: 302.2066. Found: 287.1840 $(M\text{-}CH_3)^+$

(*E*)-3-(dimethyl(phenyl)silyl)non-2-en-1-ol

To a flame dried, argon purged 25 ml RBF, 618.5 mg (1.6 mmol) *t*-Butyl (*E*)-3-(dimethyl(phenyl)silyl)non-2-enoate was dissolved in 10 ml dry DCM and the flask was placed in a room temperature water bath on a stir plate. 0.628 ml (3.52 mmol) neat DIBAL-H was then added cautiously dropwise over 10 minutes and the solution was let to stir for 4 hours at room temperature. To a second 250 ml RBF open to air was added 50 ml of benchtop DCM and the contents of the first flask were poured into the second and rinsed with DCM. The flask was then cooled to 0 ˚C with an ice bath and a saturated aqueous solution of potassium sodium tartarate (Rochelle salt) was then added cautiously dropwise. The cooling bath was removed and the flask was left stirring until most of the aluminum solids had dissolved (about 30 minutes). Once the majority of the

solids had dissolved both aqueous and organic liquids were filtered into a separatory funnel, rinsing the filter paper and remaining solids with a liberal amount of DCM. The layers were separated, and aqueous layer was washed 3x with DCM. The organic extracts were combined, washed with a small amount of DI water, brine, and dried over sodium sulfate. The solution was then passed through a short pad of silica eluting with Ethyl Acetate and concentrated under rotary evaporation, and purified by flash chromatography to give 82% (*E*)-3-(dimethyl(phenyl)silyl)non-2-en-1-ol as a clear viscous oil. Product was not characterized at this stage and carried immediately on to the next step

(*E*)-*tert*-butyl((3-(dimethyl(phenyl)silyl)non-2-en-1-yl)oxy)dimethylsilane (50)



To a flame dried argon purged 25 ml 221 mg (0.8 mmol) (*E*)-3-(dimethyl(phenyl)silyl)non-2-en-1-ol, and 8 ml dry DCM, were added. The flask was cooled to 0 ˚C with an ice bath and after 10 minutes, 163.8 mg (2.4 mmol) imidazole was added and the solution stirred briefly. 132.6 mg (0.88 mmol) TBS-Cl was added and the solution was left in the ice bath to stir and slowly warm to

RT overnight. The reaction was quenched with 8 ml of DI water and stirred briefly. The contents of the flask were

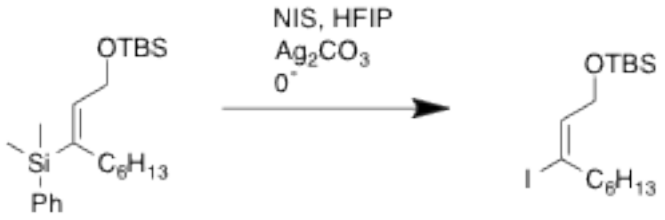
then diluted with DCM, poured into a separatory funnel and the flask was rinsed with DCM. The layers were separated, and the aqueous layer was washed 3x with DCM. The combined organic extracts were washed with sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residue was then passed through a short pad of silica eluting with 20% Et_2O/Hexanes to yield 302 mg (96.6%) of pure (*E*)-*tert*-butyl((3-(dimethyl(phenyl)silyl)non-2-en-1-yl)oxy)dimethylsilane as a clear oil.

TLC: 5% Et_2O/Hexanes R_f = 0.6 Staining with CAM

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.06 (s, 6H), 0.35, (s, 6H), 0.84 (t, *J* = 7 Hz, 3H), 0.89 (s, 9H), 1.19 (m, 8H), 2.05 (m, 2H), 4.32 (d, *J* = 5.5 Hz, 2H), 5.89 (t, *J* = 5.5 Hz, 1H), 7.30-7.40 (m, 3H), 7.47-7.54 (m, 2H)

^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): -4.878, -2.691, 14.118, 18.254, 22.698, 26.123, 29.660, 30.114, 30.477, 31.700, 60.811, 105.152, 127.770, 128.957, 134.142, 138.797, 140.141, 142.151

(*E*)-*tert*-butyl((3-iodonon-2-en-1-yl)oxy)dimethylsilane



To a flame dried conical microwave vial fitted with a rubber septum and triangular spin vane under argon was added 0.8 ml Hexafluoroisopropanol and 78.1 mg (0.2 mmol) (*E*)-*tert*-butyl((3-(dimethyl(phenyl)silyl)non-2-en-1-yl)oxy)dimethylsilane via syringe. The vial was cooled to 0 ˚C in an ice bath. 16.5 mg (0.24 mmol) of Ag_2CO_3 was then added to the vial and stirred for an additional 10 minutes at 0 ˚C. 67.2 mg (0.3 mmol) N-iodosuccinimide was then added to the vial, which was then wrapped in aluminum foil, and placed back in the ice bath. The reaction was monitored by TLC, and upon complete consumption of starting material the reaction was quenched with DI water, diluted with DCM. The layers were quickly separated and aqueous layer washed 3x with DCM. Combined organic extracts were then diluted with DCM, placed into a seperatory funnel, and shaken with sat. aq. sodium thiosulfate until color disappeared. The layers were separated, and the organic was washed with a small quantity of dilute HCl, sat. $NaHCO_3$, dried over sodium bicarbonate, filtered, and concentrated under rotary evaporation. The crude was then purified by flash chromatography eluting with 100% Hexanes to yield 64 mg (83.7%) of (*E*)-*tert*-butyl((3-iodonon-2-en-1-yl)oxy)dimethylsilane as a clear oil.

TLC: 5% Et_2O/Hexanes $R_f = 0.73$, Staining with Vanillin gave purple spots

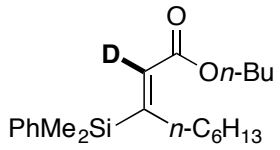
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 0.07 (s, 6H), 0.89 (m, 12H), 1.28 (m, 6H), 1.49 (m, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 4.13 (d, *J* = 6 Hz, 2H), 6.311 (t, *J* = 7.2 Hz, 1H)

^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): -5.034, 14.220, 18.481, 22.730, 26.046, 28.203, 29.398, 39.314, 60.991, 106.127, 140.764

IR: 2954, 2927, 2856, 1631, 1462, 1372, 1253, 1095, 1005, 938, 909, 833, 811, 774, 734, 667

EI-HRMS: Calcd. For $C_{15}H_{31}IOSi$: 382.1189 Found: 382.1197

Butyl (*E*)-3-(dimethyl(phenyl)silyl)non-2-enoate-2-D



Prepared according to General Procedure **A** or **B** with the following modification. The reaction was run on 0.1 mmol scale (0.75 M) in TPGS-750M (in 2 wt% D_2O) or D_2O (degassed). The reaction was worked up according to the general procedure.

Flash chromatography with 1% Et_2O/Hexanes yielded (92%, procedure **A**) or (97%, procedure **B**) of α-deuterated product as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.43 (s, 6H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.15-1.29 (m, 8H), 1.36-1.43 (m, 2H), 1.61-1.66 (m, 2H), 2.59-

2.62 (t, J = 8.1 Hz, 2H), 4.09-4.11 (t, J = 6.8 Hz, 2H), 6.06 (s, 1H), 7.34-7.40 (m, 3H), 7.49-7.51 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): -3.06, 13.89, 14.20, 19.40, 22.73, 29.87, 29.97, 30.93, 31.69, 31.87, 63.93, 128.03, 128.08, 129.5, 134.18, 136.88, 164.38, 165.70

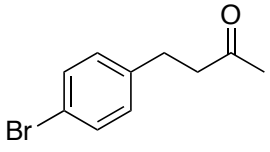
IR: 2956, 2929, 2858, 1716, 1600, 1249, 1166, 1112, 832, 814, 774, 731, 699

ESI-HRMS: Calcd. For $C_{21}H_{33}DO_2Si$: 347.2391. Found: 370.2274 $(M+Na)^+$

Experimental Data for CuH S_N2'

Allylic carbonates for use in subsequent CuH S_N2' displacements were prepared from Aryl Iodides according to the following general procedure as given below for (*E*)-5-(4-bromophenyl)-3-methylpent-2-en-1-yl *tert*-butyl carbonate. When the appropriate ketone/aldehyde substrate for HWE reaction was commercially available, the initial Heck reaction could be avoided, and the synthesis commenced with HWE reaction.

4-(4-bromophenyl)butan-2-one:

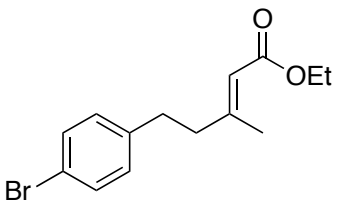


A 100ml round bottom flask fitted with a strong stir bar and septa/argon needle was charged with 80mg $Pd(OAc)_2$, 560mg Bu_4NCl, 4.2 grams of $NaHCO_3$, 2.15 grams of but-3-ene-2-ol, 5.66 grams of 4-Bromo-1-Iodobenzene, 60 ml of degassed DI water was then added via syringe and the septa was replaced with a reflux condenser, and the flask was placed in an oil bath preheated to 80˚C and stirred with heating overnight. The mixture was cooled to ambient temperature, and poured into a separatory funnel containing 200 ml of ether, rinsing the reaction vessel with additional ether. The funnel was then shaken vigorously for a few minutes and the layers were separated. The organic layer was washed with additional water, brine, and then transferred to an Erlenmeyer flask where it was swirled with a small quantity of activated charcoal to remove Pd-black. The charcoal was filtered off, and the organics were further dried over Na_2SO_4, filtered, and evaporated to afford a crude material. Flash chromatography eluting sequentially with 0-20-30-40% Et_2O/Hexanes, afforded 3.77 grams (83%) the desired product as a white solid.

TLC: R_f= 0.2 in 20% Et_2O/Hexanes. Stain = UV/Vanillin

^{1}HNMR (500MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H)

Ethyl (*E*)-5-(4-bromophenyl)-3-methylpent-2-enoate



To a dry 100 ml flask fitted with a strong stir bar, septa/argon needle, was added 40 ml of anhydrous THF, followed by 9.35 mmol (1.1 equiv) of NaH as a 60% dispersion in mineral oil. The mixture was stirred at ambient temperature for 10 minutes, cooled to 0˚ C, whereupon 9.77 mmol (1.15 equiv) of triethylphosphonoacetate was added slowly dropwise with concomitant evolution of hydrogen gas. The mixture was then brought to ambient temperature slowly, heated to 50˚ C for 30 minutes to ensure complete deprotonation, and then cooled back to ambient temperature. 1.93 grams (8.5 mmol, 1 equiv) of the preceding ketone was then added in one portion and the mixture was left to stir at ambient temperature overnight. Upon completion, the phosphonate byproduct had precipitated from the reaction mixture as a viscous dark brown oil. Et_2O was then added to assist in precipitation of this salt, and the solvent was decanted from the salts through a paper funnel into a 250 ml round bottom flask, and the solvents were removed in vacuo. The residue was resuspended in ether, placed into a separatory funnel, and washed sequentially with water, sat. bicarbonate, dried over $MgSO_4$, filtered, and evaporated to afford crude material as an *E/Z* mixture. The crude was then purified by flash chromatography, eluting with a slow, 0-5% Et_2O/Hexanes gradient to separate *E/Z* isomers. Concentration of

only fractions containing exclusively the *E* isomer afforded 2.056 g (81%) of the corresponding *E*-isomer as a colorless oil. Approx. 500mg (19%) of the *Z*-isomer was also isolated as a colorless oil

TLC: $R_f = 0.6$ (*E*-isomer), $R_f = 0.75$, (*Z*-isomer). Solvent = 20% Et_2O/hexanes, Stain= UV/$KMnO_4$,

Spectral data for the *E*-Isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 5.65 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.74 (dd, *J* = 9.2, 6.8 Hz, 2H), 2.48 – 2.33 (m, 2H), 2.19 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 4H).

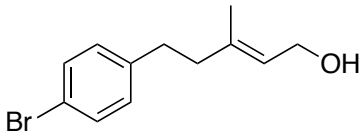
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.79, 158.36, 140.12, 131.66, 130.18, 120.02, 116.45, 59.73, 42.54, 33.44, 19.01, 14.46.

Spectral data for the *Z*-isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.70 (d, *J* = 1.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.88 (dd, *J* = 9.4, 6.7 Hz, 2H), 2.74 (dd, *J* = 9.4, 6.7 Hz, 2H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.31, 159.06, 140.73, 131.48, 130.39, 119.83, 117.01, 59.69, 35.42, 34.06, 25.57, 14.48.

(*E*)-5-(4-bromophenyl)-3-methylpent-2-en-1-ol



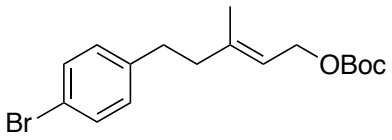
1.188 grams (4 mmol) of the preceding *E*-enoate was dissolved in ca. 10-20 ml anhydrous DCM, in a dry round bottom flask fitted with a stir bar and septa/argon needle. The flask was cooled to 0˚C in an ice bath whereupon 1.568 ml (8.8 mmol, 2.2 equiv) of neat DIBAL-H was added slowly dropwise via syringe. Once the addition was complete, the cooling bath was removed and the mixture slowly brought to ambient temperature, with stirring for an additional 4 hours. The flask was recooled to 0˚ C and excess DIBAL-H was destroyed by slow dropwise addition of Acetone, then Acetone/Water 9:1. The mixture was diluted with additional DCM, poured into a separatory funnel, and shaken with a saturated solution of Rochelle salt to remove aluminum salts, and the DCM layer was drained off. The solvent was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude alcohol. The crude material was essentially pure by TLC, but could be purified by quick passage through a short plug of silica eluting with 100% Et_2O to remove additional Al-impurities. Concentration afforded 900mg (88%) of desired product as a clear, viscous oil, which was carried immediately on to the next step.

TLC: R_f= 0.08 10% Et_2O/hexanes

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.40 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 5.41 (td, *J* = 7, 1Hz, 1H), 4.15 (d, *J* = 7 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 8 Hz, 2H) 1.71 (s, 3H)

^{13}C-NMR (126MHz, $CDCl_3$) δ: 140.988, 138.761, 131.483, 130.254, 124.321, 119.698, 59.450, 41.241, 33.809, 16.525

(*E*)-5-(4-bromophenyl)-3-methylpent-2-en-1-yl *tert*-butyl carbonate



Method 1 (with LiHMDS in THF): 527 mg of LiHMDS (3.15 mmol, 1.05 equiv) was weighed out in a glove box and added a dry 50 ml round bottom flask, fitted with a stir bar. The flask was sealed with a rubber septa, removed from the glove box, and placed under an atmosphere of argon. About 15 ml of anhydrous THF was added to the flask and the solution was stirred at ambient temperature to dissolve the LiHMDS. Once dissolved, the flask was cooled to 0 ˚C in an ice bath and 765.5 mg of the preceding allylic alcohol (3 mmol, 1 equiv), was added slowly via syringe. The cooling bath was removed and the mixture was stirred at ambient temperature for 30 minutes to ensure complete deprotonation. The flask was then cooled to -78 ˚C in a dry ice/acetone bath, and let equilibrate at this temperature for 10 minutes whereupon 1.309 g of Boc_2O (6 mmol, 2 equiv) was

added dropwise as a concentrated solution in anhydrous THF (**Note 1**). The cooling bath was removed and the mixture was stirred while warming to ambient temperature. Once TLC indicated the reaction was complete, the reaction mixture was diluted with Et_2O, and quenched with sat. aq. $NaHCO_3$ and stirred vigorously for 10-20 minutes. The Mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted 2x with additional ether. The organic extracts were combined, washed with brine, dried over $MgSO_4$ (**Note 2**), filtered and concentrated under reduced pressure. The crude residue was dissolved in Hexanes, and loaded onto a silica gel column, and purified by gradient elution 0-10% Et_2O/hexanes. Concentration of the appropriate fractions by rotary evaporation, and drying under high vacuum afforded 930 mg (93%) of the desired carbonate as a clear oil, contaminated with ca. 1 equiv of *t*-BuOH

TLC: R_f 0.52, 10% Et_2O/hexanes, Stain = UV/$KMnO_4$

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.38 (d, *J* = 7 Hz, 2H), 7.03 (d, *J* = 7 Hz, 2H), 5.37 (td, *J* = 7, 1Hz, 1H), 4.15 (d, *J* = 6 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.31 (t, *J* = 7 Hz, 2H) 1.73 (s, 3H), 1.47 (s, 9H)

Note 1 (Alternatively the Boc_2O can also be added as a solid in a single portion by quickly removing the septa, adding anhydride, and resealing, with no

substantial change in yield. Chloroformates were added dropwise as a neat liquid at -78˚) .

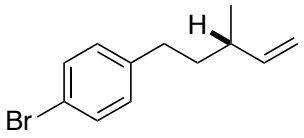
Note 2: Substituting $CaCl_2$ for $MgSO_4$ resulted in more efficient removal of *t*-BuOH, but required longer times to effect efficient drying of the solution.

Note 3: Substituting NaH for LiHMDS gave inferior results, while BuLi could be employed for substrates without halogens (Li-X/exchange observed)

Method 2 (with 3˚ amine base in DCM): 1 equiv. of the preceding allylic alcohol was dissolved in anhydrous DCM [0.2 M], in a dry round bottom flask fitted with a stir bar, septa/argon needle. 1.1 equiv of either DIPEA or Et_3N (Both acceptable), was added via syringe, and the flask was cooled to 0˚C in an ice bath. 1.1 equiv Boc-anhydride was then added dropwise as a concentrated solution in anhydrous DCM, and once the addition was complete the flask was allowed to warm to ambient temperature and stirred overnight. Once TLC indicated complete conversion, the contents of the reaction vessel were stirred vigorously for several minutes with a 40% aqueous solution of Me_2NH (1 ml/mmol substrate) to decompose excess Boc-anhydride. The mixture was poured into a separatory funnel and diluted with ether until the organic layer remained on top. The layers were separated, and the aqueous layer was extracted twice more with additional ether, the organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated to afford crude compound. Flash chromatography eluting 0-10% Et_2O/Hexanes afforded the desired carbonate in ca. 40-50% isolated

yield. These conditions also produced the corresponding symmetrical carbonate (R_f = 0.38 in 10% Et_2O/hex) as a byproduct.

1-bromo-4-(3-methylpent-4-en-1-yl)benzene



2 mg of $Cu(OAc)_2 \cdot H_2O$, and 11.8 mg of (*R*)-DTBM-SEGPHOS, (5 mol %) were added to a flame dried vial fitted with a spin vane, septa, and argon needle. 0.666 ml of anhydrous THF was added and the solution was stirred until homogeneous. 0.074 ml of Phenylsilane (3 equiv) was added via syringe, and slight gas evolution was observed while the color changed to a dark brown/yellow. Once no further color change was observed, 71 mg of the corresponding carbonate (0.2 mmol) was added via syringe and the solution was left to stir at ambient temperature for 24 hours. At this time, no further change was noted by TLC, and the reaction was quenched by cautious slow addition of 1 ml sat. aq. NH_4F resulting in gas evolution, and the solution was stirred at ambient temperature for 1 hour. The organics were extracted 3 x 5 ml ether, combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford ca. 100 mg of crude material. The crude was dissolved in hexanes, loaded onto a silica column, and eluted with 100% hexanes, where concentration of the appropriate fractions and drying under high

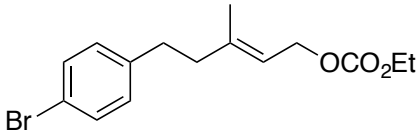
vacuum afforded 17 mg (35%) of product as a ca. 5:1 mixture of the desired product and the corresponding saturated hydrocarbon (from reduction of the terminal olefin). Clear to slightly pale yellow oil.

TLC: R_f = 0.9, stain = UV/$KMnO_4$, 5% Et_2O /hexanes

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.39 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 5.72 (ddd, *J* = 17, 10.5, 7.5, Hz, 1H) 4.99 (dddd, *J* = 10.5, 5, 1.8, 1 Hz, 2H), 2.64-2.47 (m, 2H), 2.25-2.00 (m, 1H), 1.59 (td, *J* = 8.2, 7.1 Hz, 2H), 1.03 (d, *J* = 6.5 Hz, 3H)

^{13}C-NMR (126MHz, $CDCl_3$) δ: 144.297, 141.820, 131.445, 130.313, 119.437, 113.388, 38.340, 37.509, 33.122, 20.434

(*E*)-5-(4-bromophenyl)-3-methylpent-2-en-1-yl ethyl carbonate

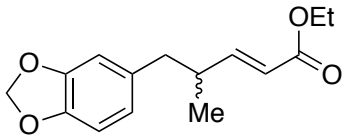


Prepared according from the corresponding alcohol and ethyl chloroformate with LiHMDS as described above for Boc-carbonates.

Scale: 3 mmol. Yield: 930mg, (95%)

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.37 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 5.36 (td, *J* = 7, 1Hz, 1H), 4.62 (d, *J* = 7 Hz, 2H), 4.18 (q, *J* = 7 Hz, 2H), 2.78-2.58 (m, 2H), 2.43-2.19 (m, 2H), 1.74 (s, 3H), 1.30 (t, *J* = 7 Hz 9H)

Ethyl (*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-methylpent-2-enoate



Prepared from the corresponding commercially available aldehyde, via HWE reaction as described above.

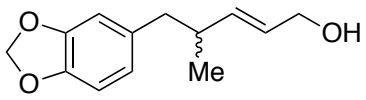
Scale: 32 mmol. Flash chromatography eluting with 0-10% Et_2O/Hexanes gradient, afforded 6.4 grams (76%) of the *E* isomer as a colorless oil.

TLC: R_f = 0.3 (*E* isomer, major) 0.4 (*Z* isomer, minor) 10% Et_2O/Hexanes. Stain = UV/Seebach's stain

^{1}H-NMR (600MHz, $CDCl_3$) δ: 6.92, (dd, *J* = 15.7, 7.2 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.92 (s, 2H), 5.74 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.18 (q ,*J* = 7.1 Hz, 2H), 2.67 (dd, *J* = 13.1, 6.3 Hz, 1H), 2.52 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H)

^{13}C-NMR (133MHz, $CDCl_3$) δ: 166.907, 153.526, 147.669, 146.015, 133.498, 122.144, 120.106, 109.503, 108.216, 100.948, 60.353, 42.251, 38.523, 18.792, 14.709

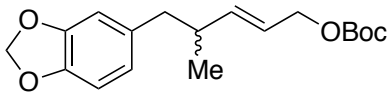
(*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-methylpent-2-en-1-ol



Prepared according to the general procedure given above for DIBAL-H reduction of enoates on a scale of 25 mmol. Usual workup and removal of solvents in vacuo afforded essentially pure compound which was further purified by passing through a short pad of silica eluting with EtOAc afforded 4.2 grams (76%) of pure product as a clear viscous oil.

^{1}H-NMR (500MHz, $CDCl_3$) δ: 6.71 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 5.76-5.40 (m, 2H), 4.07 (m, 2H), 2.59 (dd, *J* = 12.9, 6.4 Hz, 1H), 2.43 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H)

(*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl *tert*-butyl carbonate

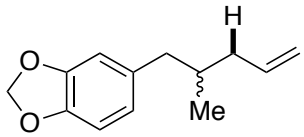


Prepared according to the general procedure for Boc protection with LiHMDS on a scale of 5 mmol. Usual workup and flash chromatography elution 0-10% Et_2O/Hexanes afforded 1.528 grams (95%) of carbonate as a clear oil containing ca. 1 equiv. of *t*-BuOH by NMR

TLC: R_f = 0.35, 10% Et_2O/Hexanes. Stain = UV/Seebach's stain.

^{1}H-NMR (500MHz, $CDCl_3$) δ: 6.71 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.91 (s, 2H), 5.74 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.52 (dt, *J* = 15.5, 6.5 Hz, 1H) 4.48 (d, *J* = 6.5 Hz, 2H), 2.66-2.54 (m, 1H), 2.41 (dt, *J* = 10.6, 7.9 Hz, 2H), 1.48 (s, 9H), 0.98 (d, *J* = 6.4 Hz, 3H)

5-(2-methylpent-4-en-1-yl)benzo[*d*][1,3]dioxole



Prepared according to the general procedure for CuH allylic reductions as described above on a scale of 0.5 mmol, with 6 mol% of *R*/*S*-DTBM-SEGPHOS and 5 mol % of $Cu(OAc)_2 \cdot H_2O$. Reaction time = 20 hours. The use of DEMS (6H- equiv) could be employed in place of the usual 3 equiv. $PhSiH_3$ with comparable results. Several grades of PMHS from various suppliers, including

(M_n 390, TMS terminated) were tested and afforded inferior results relative to $PhSiH_3$ or DEMS, either in solvent or aqueous surfactants.

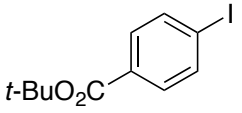
Yield: 77mg (75%) isolated as a colorless oil.

TLC: R_f= 0.86, 5% Et_2O/Hexanes.

^{1}H NMR (600 MHz, cdcl$_3$) δ 6.71 (d, *J* = 7.9 Hz, 1H), 6.63 (s, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.91 (s, 2H), 5.83 – 5.72 (m, 1H), 5.01 (dd, *J* = 7.7, 6.9 Hz, 2H), 2.61 – 2.51 (m, 1H), 2.32 – 2.23 (m, 1H), 2.09 (dt, *J* = 12.7, 6.2 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.74 (dh, *J* = 13.7, 6.7 Hz, 1H), 0.84 (d, *J* = 6.4 Hz, 3H).

^{13}C-NMR (125MHz, $CDCl_3$) δ: 147.535, 145.644, 137.449, 135.293, 122.075, 116.088, 109.622, 108.060, 100.838, 42.932, 40.986, 35.246, 19.278

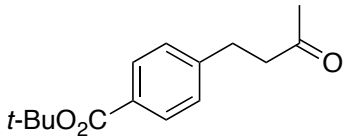
***tert*-butyl 4-iodobenzoate**



Prepared from 4-iodobenzoic acid, and 1.2 equiv oxalyl chloride in DCM with cat. DMF. Once the acid chloride was fully formed, solvent, HCl, and excess oxalylchloride were removed under vacuum affording crude acid chloride which was redissolved in anhydrous THF, cooled to 0 ˚C, where 1.3 equiv of NaO*t*-Bu was added slowly as a [1 M] solution in anhydrous THF. Removal of THF in vacuo afforded crude product which was purified by passing through a short pad

of silica eluting with 10% Et_2O/Hexanes, to afford 11.873 grams of the title compound (97%).

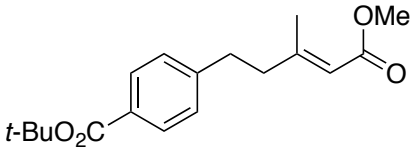
tert-butyl 4-(3-oxobutyl)benzoate



Prepared according to the general procedure given earlier for Heck reactions on a scale of 20 mmol. Workup and flash chromatography eluting 0-20% Et_2O/Hexanes afforded 4.25 grams (85%) of the desired product as a colorless oil.

TLC: R_f = 0.15, 20% Et_2O/Hexanes, product stains green/blue with vanillin

tert-butyl (_E_)-4-(5-methoxy-3-methyl-5-oxopent-3-en-1-yl)benzoate



Prepared via a modified HWE reaction on a scale of 16 mmol.

1.2 equiv of LiHMDS was dissolved in anhydrous THF (ca [0.1 M] with respect to ketone) under argon and 1.2 equiv of trimethylacetylphosphonate was added

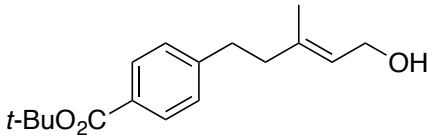
slowly via syringe at rt. The mixture was stirred for 30 minutes at ambient temperature, then 16 mmol of ketone substrate (1 equiv) was added slowly and the mixture was stirred overnight. The reaction was quenched with $NaHCO_3$, diluted with DCM, poured into a separatory funnel, shaken, and the aqueous layer was extracted 3x with DCM. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and solvents were evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gradually eluting with 0-30% Et_2O/Hexanes over about 15 column volumes to separate the isomers. Fractions were combined, evaporated, and dried under high vacuum to afford 3.78 grams (78%) of the desired *E*-isomer as a colorless oil.

TLC: R_f = 0.41 (*E*- isomer, major, desired), 0.5 (*Z*- isomer), 20% Et_2O/Hexanes, Stain = UV/$KMnO_4$

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.91 (d, *J* = 8Hz, 2H), 7.21 (d, *J* = 8Hz, 2H), 5.66 (s, 1H), 3.68 (s, 3H), 2.89-2.76 (m, 2H), 2.51-2.39 (m, 2H) 2.20 (s, 3H), 1.59 (s, 9H)

^{13}C-NMR (125MHz, $CDCl_3$) δ: 167.18, 165.86, 158.76, 145.96, 130.20, 129.81, 128.28, 116.05, 80.99, 51.03, 42.35, 33.97, 28.37, 22.50, 19.05, 14.22

***tert*-butyl (*E*)-4-(5-hydroxy-3-methylpent-3-en-1-yl)benzoate**



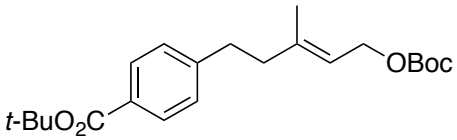
To a flame dried 250ml round bottom flask, fitted with a stir bar, septa/argon needle, was added anhydrous DCM [0.1 M] and 2.427 g (7 mmol, 1 equiv) of the preceding diester and stirred at rt briefly before cooling the flask to -78 ˚C in a dry ice/acetone bath. The mixture was stirred at -78 ˚C for 15 minutes whereupon 2.49 ml of neat DIBAL-H (2 equiv) was added very slowly dropwise to the center of the vortex (addition rate 1 drop/3-4 seconds). Once the addition was complete, the mixture was left to stir at -78 ˚C for 4 hours, then warmed to ambient temperature. Usual workup, and flash chromatography eluting 10-100% Et_2O/Hexanes afforded 1.040 grams (55%) of the desired compound as a clear viscous oil along with 430mg (20%) unreacted starting material, and 380 mg (26%) of the corresponding allylic alcohol/aromatic aldehyde as a side product.

TLC: R_f = 0.55 (starting material), 0.16 (desired product), 0.07 (allylic alcohol/aromatic aldehyde side product) 50% Et_2O/Hexanes. Stain = UV/Seebach's stain.

^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.91 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8Hz, 2H), 5.42 (td, *J* = 7, 1 Hz, 1H), 4.15 (d, *J* = 7 Hz, 2H), 2.80 (t, *J* = 8 Hz, 2H), 2.34 (t, *J* = 7 Hz, 2H) 1.72 (s, 3H), 1.59 (s, 9H)

^{13}C-NMR (125MHz, $CDCl_3$) δ: 165.951, 146.980, 138.763, 129.907, 129.657, 128.355, 124.370, 80.902, 59.466, 41.111, 34.411, 28.373, 22.492, 16.531, 14.216

tert-butyl (_E_)-4-(5-((_tert_-butoxycarbonyl)oxy)-3-methylpent-3-en-1-yl)benzoate

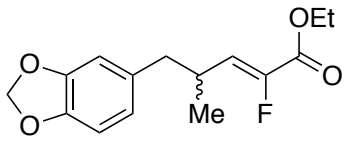


Prepared according to the general procedure on a scale of 3.13 mmol. Usual workup and flash chromatography eluting 0-20% Et_2O/Hexanes afforded 1 gram (85%) of the desired product as a clear oil.

TLC: R_f = 0.6, 50% Et_2O/Hexanes. Stain = UV/Seebach's stain

^{1}H-NMR (600MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8Hz, 2H), 5.38 (t, *J* = 7 Hz, 1H), 4.57 (d, *J* = 7 Hz, 2H), 2.79 (t, *J* = 8.1 Hz, 2H), 2.34 (t, *J* = 8.1 Hz, 2H) 1.75 (s, 3H), 1.59 (s, 9H), 1.48 (s, 9H)

ethyl (*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)-2-fluoro-4-methylpent-2-enoate



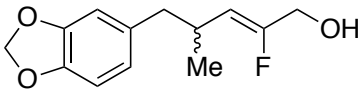
Prepared according to the general procedure using the Fluoro-HWE reagent, on a scale of 16 mmol. Usual workup and flash chromatography eluting 0-10% Et_2O/Hexanes afforded 3 grams (66%) of the desired product as a colorless oil.

TLC: R_f = 0.5 (top spot, major), 10% Et_2O/Hexanes. Stain = UV/Seebach's stain

^{1}H-NMR (600MHz, $CDCl_3$) δ: 6.71, (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.1 Hz, 1H), 6.59 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.92 (s, 2H), 5.72, (dd, *J* = 21.8, 10.6 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.57-3.43 (m, 1H), 2.56 (m, 2H), 1.33 (t, *J = 7.1* Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H)

^{13}C-NMR (133MHz, $CDCl_3$) δ: 161.116, 160.879, 147.620, 147.340, 146.010, 145.663, 133.372, 128.450, 128.342, 122.188, 109.626, 108.149, 100.925, 61.501, 43.216, 43.200, 32.381, 32.348, 20.207, 14.267

(*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)-2-fluoro-4-methylpent-2-en-1-ol



Prepared according to the general procedure on a scale of 9.27 mmol. Aqueous workup with Rochelle salt, and removal of solvents afforded essentially pure product, which was further purified by passage through a small pad of silica

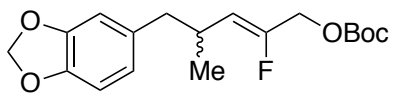
eluting with DCM. Evaporation of DCM in vacuo, and removal of trace solvents under high vacuum afforded 1.968 grams (89%) of the desired product as a clear viscous oil.

TLC: R_f = 0.28, 100% DCM. Stain = UV/Seebach's stain

^{1}H-NMR (600MHz, $CDCl_3$) δ: 6.73, (d, *J* = 7.9 Hz, 1H), 6.61 (s, 1H), 6.56 (dd, *J* = 7.8, 1 Hz, 1H), 5.92 (s, 2H), 4.99 (dd, *J* = 21, 10.5 Hz, 1H), 3.96 (m, 2H) 2.62 (dd, *J* = 13, 4.9 Hz, 1H), 3.57-3.43 (m, 1H), 2.52 (m, 1H), 2.39 (dd, *J* = 13.1, 9 Hz, 1H) 1.07 (s, 3H)

^{13}C-NMR (133MHz, $CDCl_3$) δ: 158.417, 156.764, 147.684, 146.009, 134.059, 122.159, 114.073, 113.952, 109.768, 108.204, 101.023, 57.697, 57.495, 43.972, 43.955, 33.917, 33.862, 21.787, 21.773

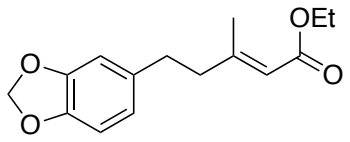
(*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)-2-fluoro-4-methylpent-2-en-1-yl *tert*-butyl carbonate



Prepared on a scale of 1.9 grams (8 mmol) of the preceding alcohol. Usual workup and flash chromatography eluting 0-20% Et_2O/Hexanes afforded 2.632

grams (97%) of the desired product contaminated with ca. 1 equiv of *t*-BuOH as determined by ^{1}H-NMR.

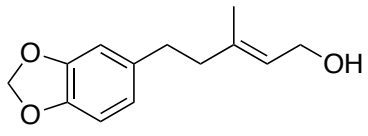
Ethyl (*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-3-methylpent-2-enoate



Prepared according to the general procedure from the commercially available ketone on a scale of 20 mmol. Usual workup and flash chromatography eluting 0-20% Et_2O/Hexanes afforded 3.956 grams (74%) of the desired compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 – 6.70 (m, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.64 – 6.58 (m, 1H), 5.92 (d, *J* = 5.5 Hz, 2H), 5.67 (d, *J* = 1.2 Hz, 1H), 4.15 (dt, *J* = 14.3, 5.4 Hz, 2H), 2.74 – 2.63 (m, 2H), 2.43 – 2.35 (m, 2H), 2.19 (d, *J* = 1.1 Hz, 3H), 1.31 – 1.22 (t, 3H).

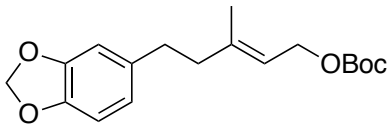
(*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-3-methylpent-2-en-1-ol



Prepared according to the general procedure on a scale of 5 mmol. Usual workup and filtration over a short pad of silica eluting with 100% Et_2O afforded 990 mg (90%) of the desired compound as a clear viscous oil.

TLC: R_f = 0.13 (top spot, major), 30% Et_2O/Hexanes. Stain = UV/Seebach's stain

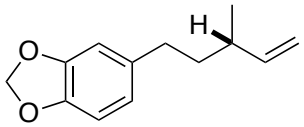
(*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-3-methylpent-2-en-1-yl *tert*-butyl carbonate



The compound was synthesized by deprotonation of the preceding alcohol with 1 equiv *n*-BuLi in THF at -78 ˚C followed by addition of 1 equiv of Boc_2O at -78 ˚C. with warming to ambient temperature. The reaction was worked up by quenching with $NaHCO_3$, poured into a separatory funnel and extracted with ether. The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford crude compound. Flash chromatography eluting 0-10% Et_2O/Hexanes afforded the desired compound as a colorless oil.

TLC: R_f = 0.5 (top spot, major), 10% Et_2O/Hexanes. Stain = UV/Seebach's stain

5-(3-methylpent-4-en-1-yl)benzo[*d*][1,3]dioxole

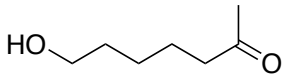


Prepared according to the general procedure given for CuH reductions of allylic carbonates on a scale of 0.2 mmol where usual workup and flash chromatography afforded 6.5 mg of the desired product in 16% yield. Separation from impurities proved difficult and the resulting spectral data showed the presence of several unidentified impurities. The presence of an additional doublet in the ^{1}H-NMR at δ: 0.97 ppm was attributed to the presence of the corresponding overreduced product (via reduction of the terminal olefin) although the NMR data is inconclusive.

TLC: R_f = 0.8 5% Et_2O/Hexanes. Stain = UV/$KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.6 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.91 (s, 2H), 5.72 (ddd, *J* = 17.7, 10.3, 7.7 Hz, 1H), 4.98 (ddd, *J* = 10.1, 2.3, 1.4 Hz, 2H), 2.58 – 2.43 (m, 2H), 2.18 – 2.08 (m, 1H), 1.63 – 1.51 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H),

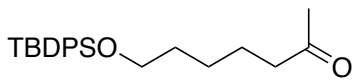
7-hydroxyheptan-2-one



7-hydroxyheptan-2-one was prepared from caprolactone. 20 mmol (1 equiv) of caprolactone, was slurried with 2.32 g (24 mmol, 1.2 equiv) of HN(OMe)Me•HCl and 280mg of NaOMe (5 mmol, 0.25 equiv) in anhydrous THF [0.05M]. The slurry was cooled to -10 ˚C in an ice/salt bath. MeMgBr ([3 M] in THF, 53.3 ml, 160 mmol, 8 equiv.) was added dropwise maintaining the temperature below 0˚C. Once the addition was complete, the solution was stirred at 0 ˚C for 2 hours, then at ambient temperature for 8 hours. The reaction was quenched with 200 ml 1N HCl, and stirred for 2 hours, the THF was evaporated in vacuo, and the resulting liquid was extracted in a separatory funnel 5x with DCM. The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford crude compound. Flash chromatography eluting 50-100% Et_2O/Hexanes afforded 1.8 grams (69%) of 7-hydroxyheptan-2-one as a clear oil, which was carried directly on to the next step.

TLC: R_f = 0.28, 100% Et_2O. Stain = Seebach's stain

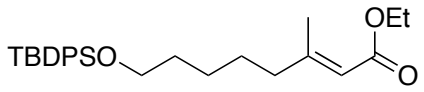
7-((*tert*-butyldiphenylsilyl)oxy)heptan-2-one



1.8 grams of 7-hydroxyheptan-2-one (10 mmol, 1 equiv) and 2.045 grams of imidazole (30mmol, 3 equiv.) was dissolved in 100 ml anhydrous DCM, and the mixture was cooled to 0˚C. 2.6ml TBDPS-Cl (11 mmol, 1.1 equiv) was then added slowly via syringe, and the mixture was stirred overnight with warming to ambient temperature. Workup with sat. $NaHCO_3$, extraction, and drying of solvent afforded crude compound that was purified by passing though a short pad of silica with 50% Et_2O/Hexanes afforded 3.2 grams (87%) of the desired product as a colorless oil which was carried directly on to the next step.

TLC: R_f = 0.9, 100% Et_2O. Stain = UV/Seebach's stain

Ethyl (*E*)-8-((*tert*-butyldiphenylsilyl)oxy)-3-methyloct-2-enoate



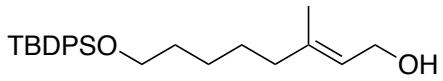
Performed according to the general procedure with 4.5 equiv of NaH and 4.5 equiv of HWE reagent on a scale of 8.1 mmol. Usual workup and flash chromatography eluting with 0-10% Et_2O/Hexanes afforded 1.41 grams (39%) of the desired product as a mixture of *E/Z* isomers.

TLC: R_f = 0.42, 10% Et_2O/Hexanes. Stain = UV/Seebach's stain

^1H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.60 (m, 5H), 7.48 – 7.31 (m, 5H), 5.69 – 5.59 (m, 1H), 4.17 – 4.08 (m, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.14 (d, *J* = 1.0 Hz,

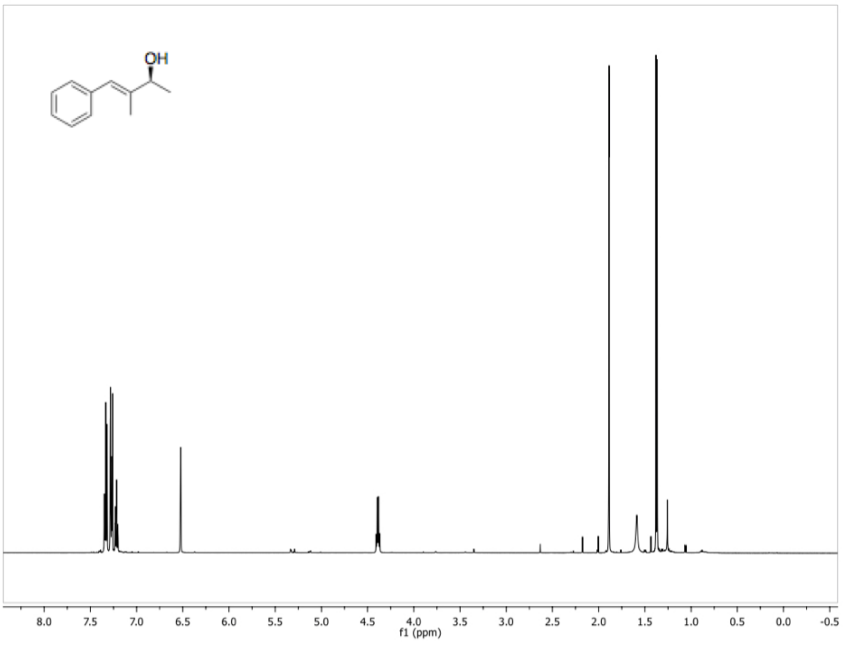
3H), 2.13 – 2.08 (m, 2H), 1.60 – 1.51 (m, 2H), 1.49 – 1.40 (m, 2H), 1.36 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H).

(*E*)-8-((*tert*-butyldiphenylsilyl)oxy)-3-methyloct-2-en-1-ol



Prepared according to the general procedure with 1.036 g (2.36 mmol) of the corresponding enoate. Usual workup and flash chromatography eluting with 0-35% Et_2O/Hexanes afforded 913 mg (97%) of the desired compound as a colorless oil.

TLC: R_f = 0.21, 30% Et_2O/Hexanes. Stain = UV/Seebach's stain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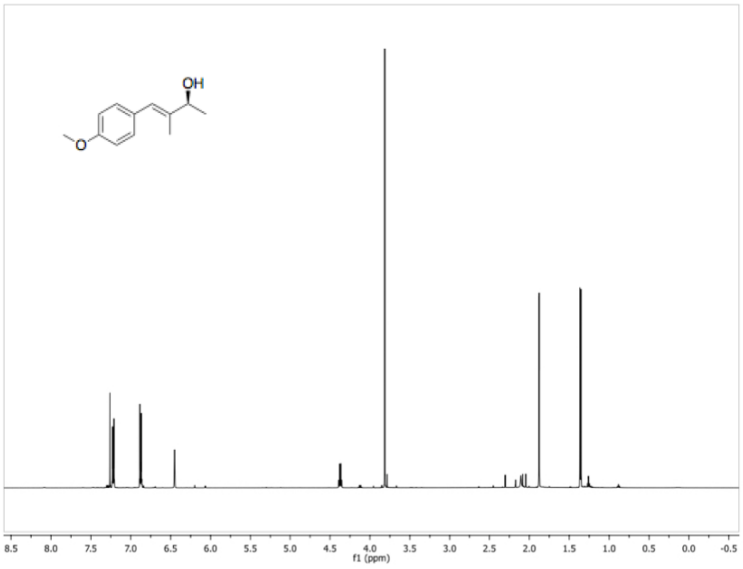
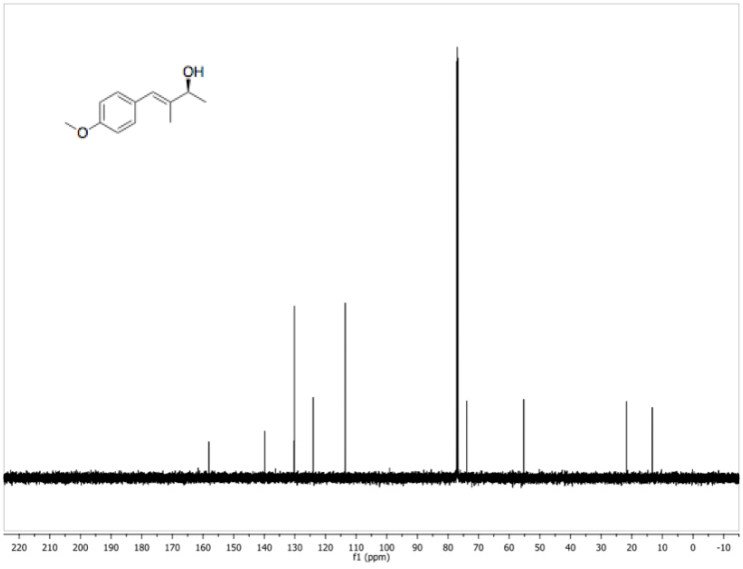
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OH
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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O
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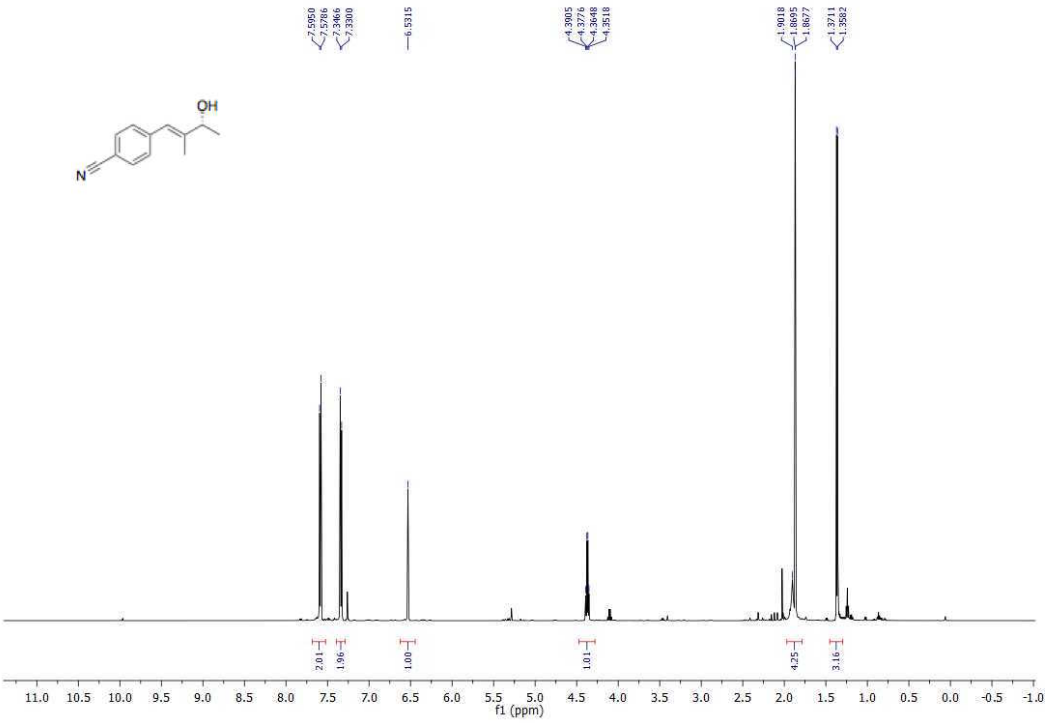
f1 (ppm)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7.5766
7.3966
7.3800
6.5315
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4.3776
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4.3518
1.9018
1.8695
1.8677
1.3711
1.3582
OH
N
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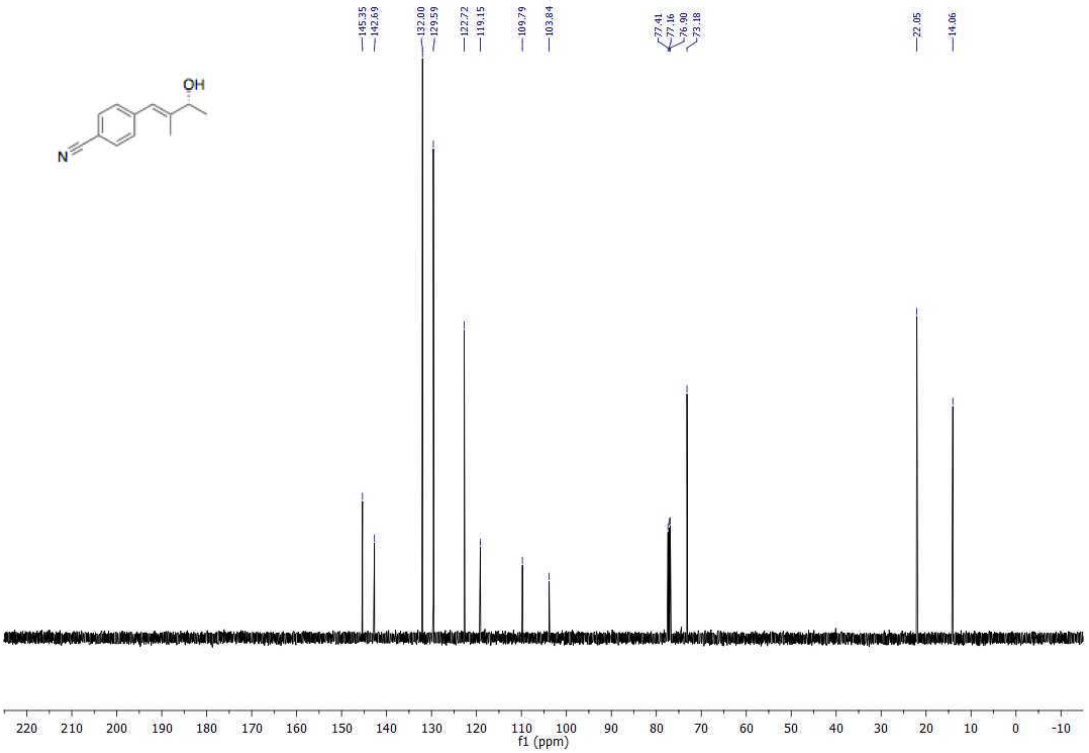
1.96
1.00
1.01
4.25
3.16
f1 (ppm)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119.15
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103.84
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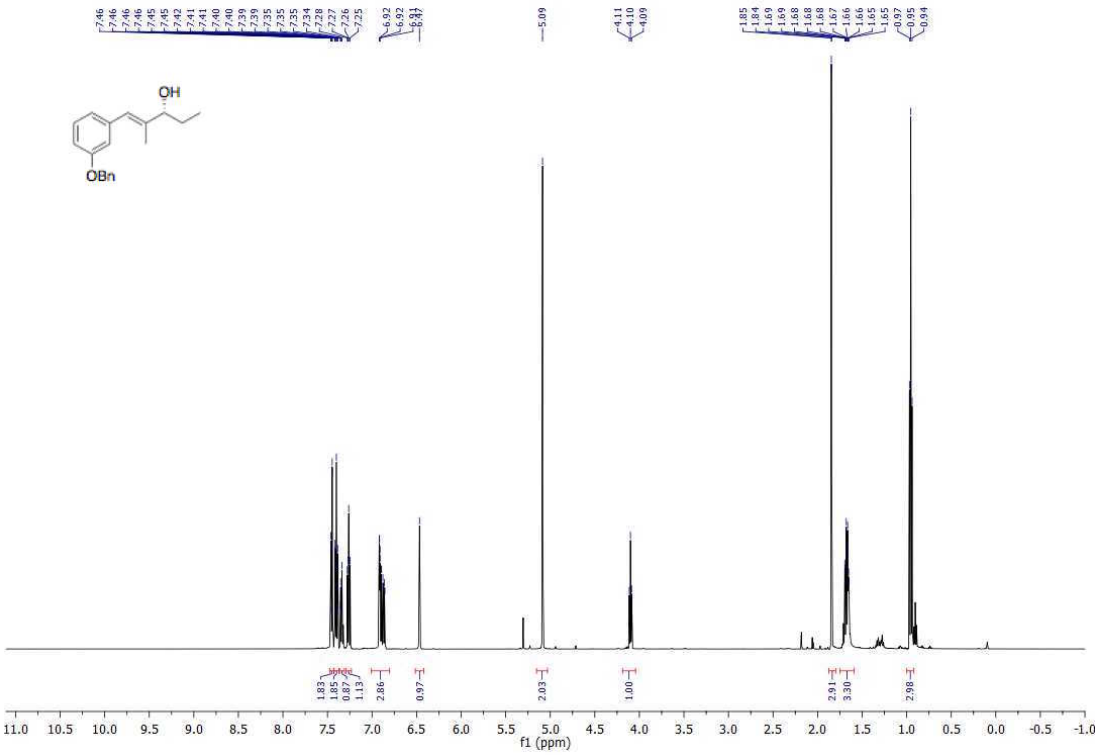
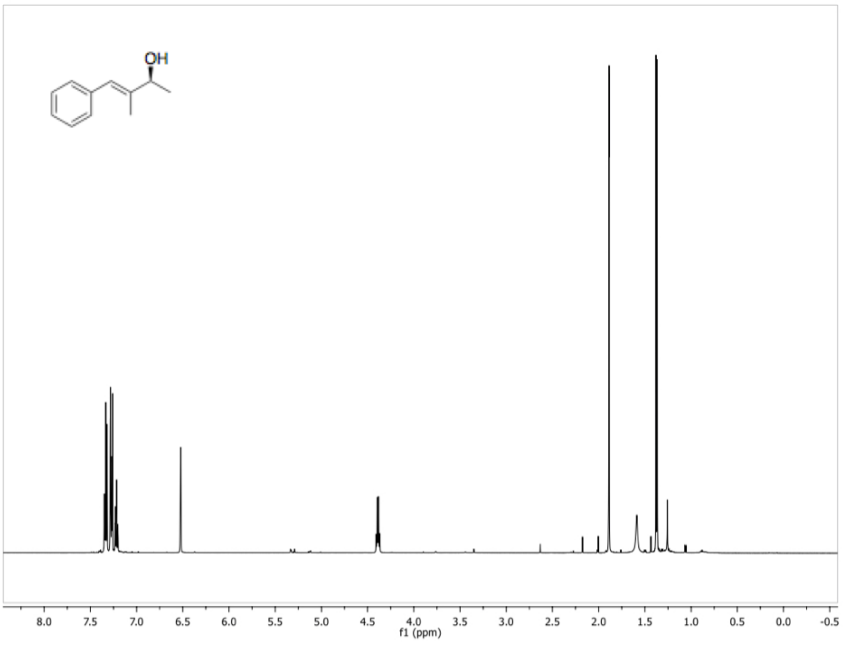
77.16
76.90
73.18
22.05
14.06
OH
N
f1 (ppm)


OH
OBn
f1 (ppm)


OH
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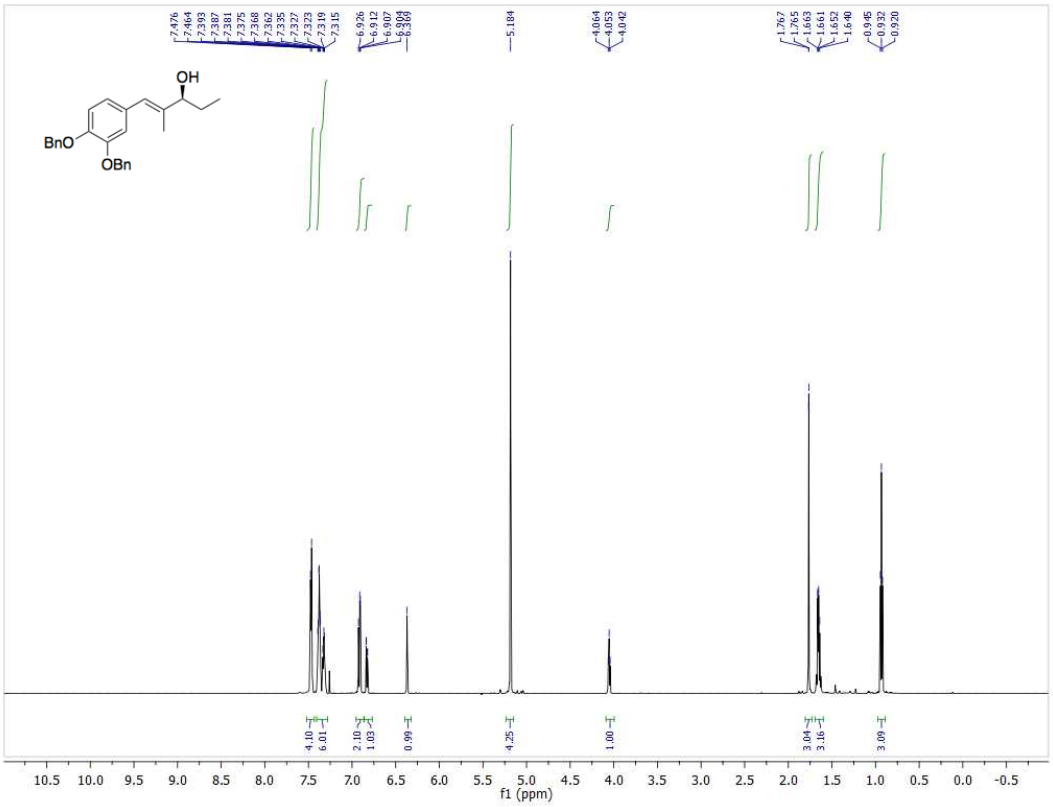
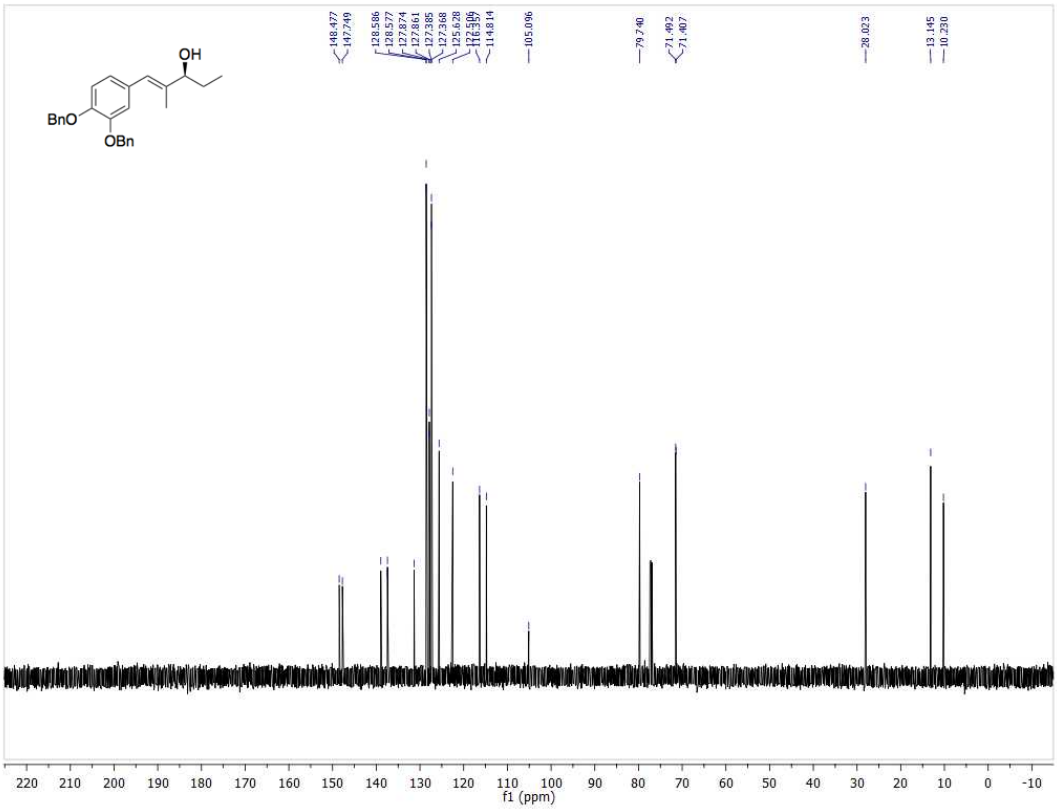
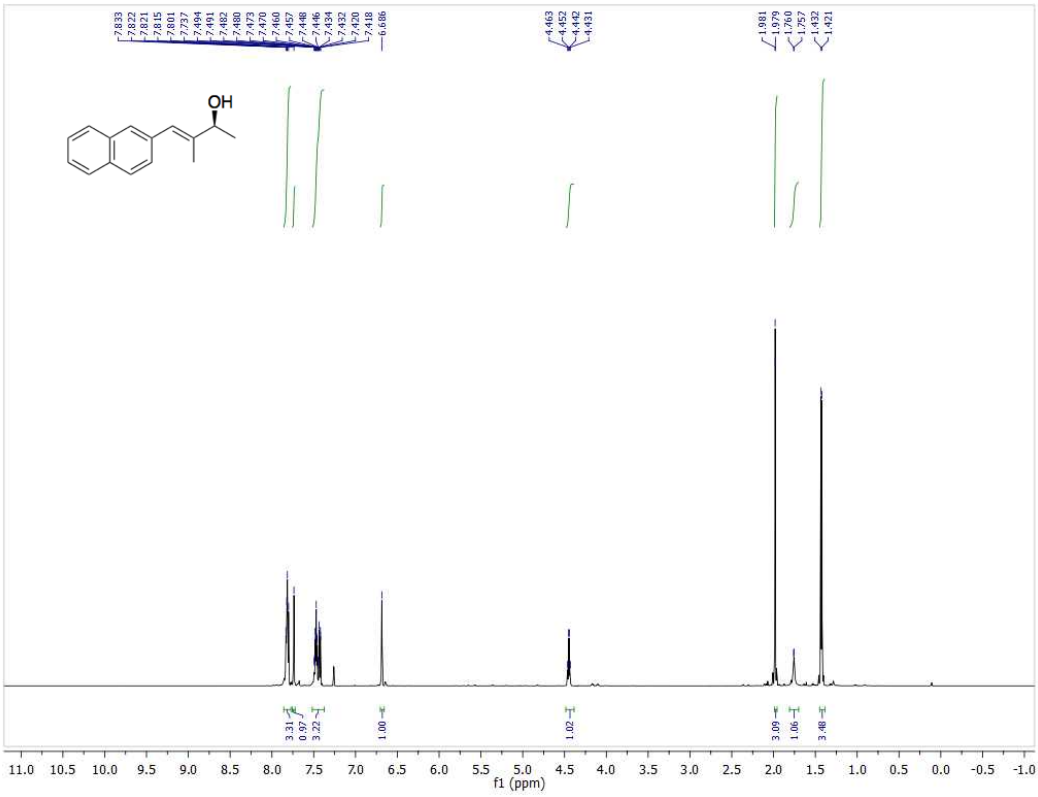
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OH
BnO
OBn
f1 (ppm)


OH
BnO
OBn
f1 (ppm)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7.815
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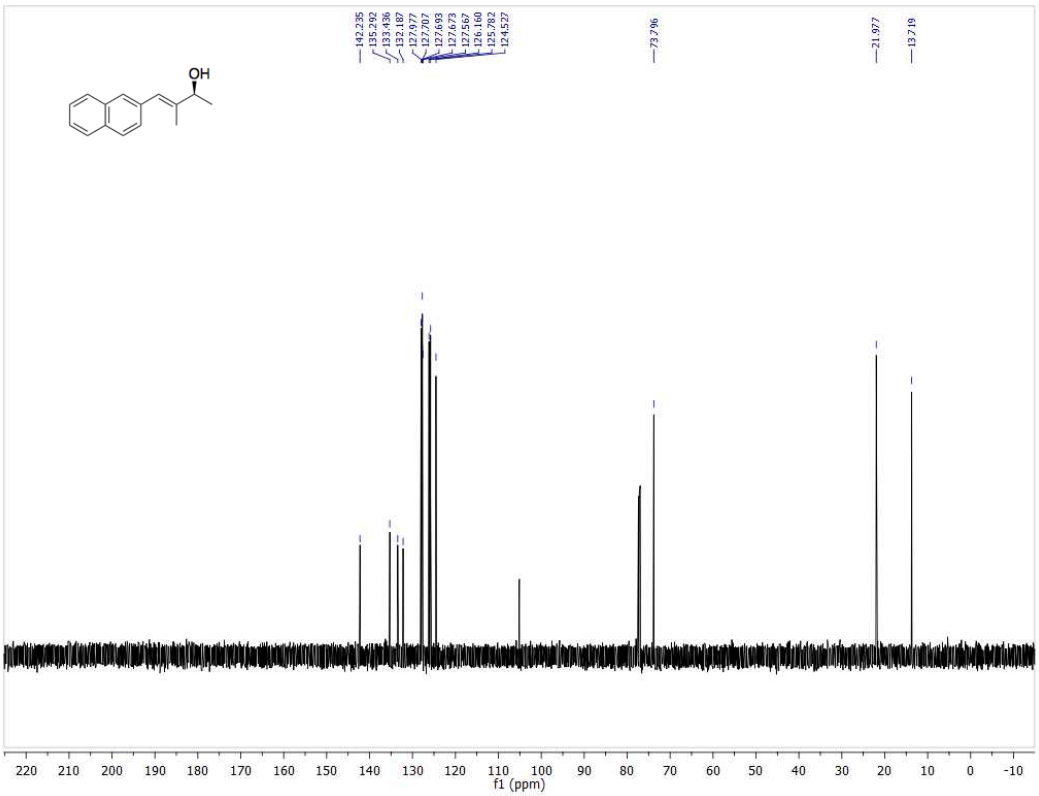
7.446
7.434
7.432
7.420
7.418
6.686
4.463
4.452
4.442
4.431
1.981
1.979
1.760
1.757
1.432
1.421
3.31
0.97
3.22
1.00
1.02
3.09
1.06
3.48
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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127.693
127.673
127.567
126.160
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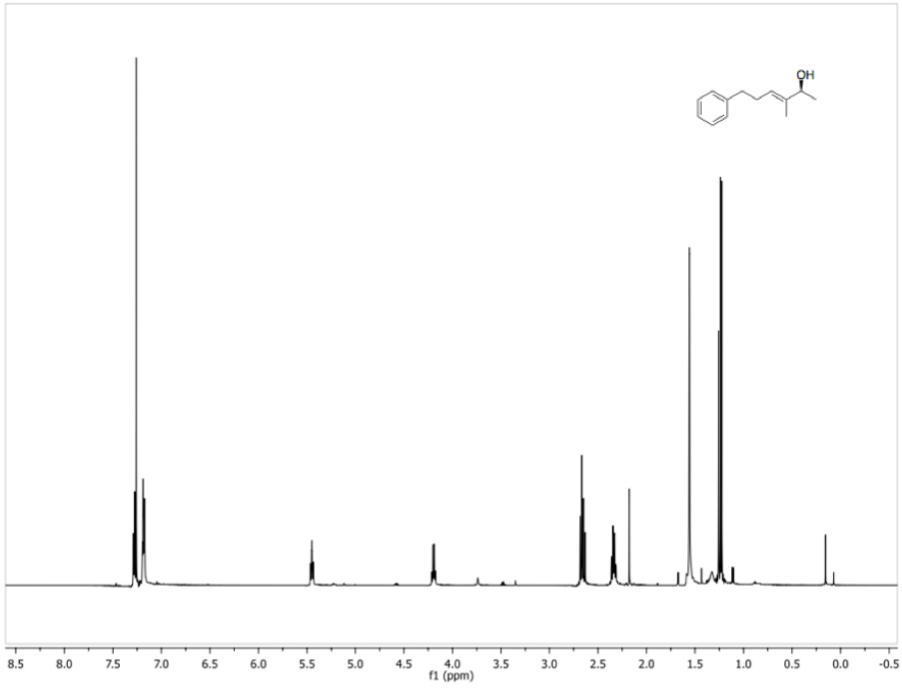
124.527
73.796
21.977
13.719
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
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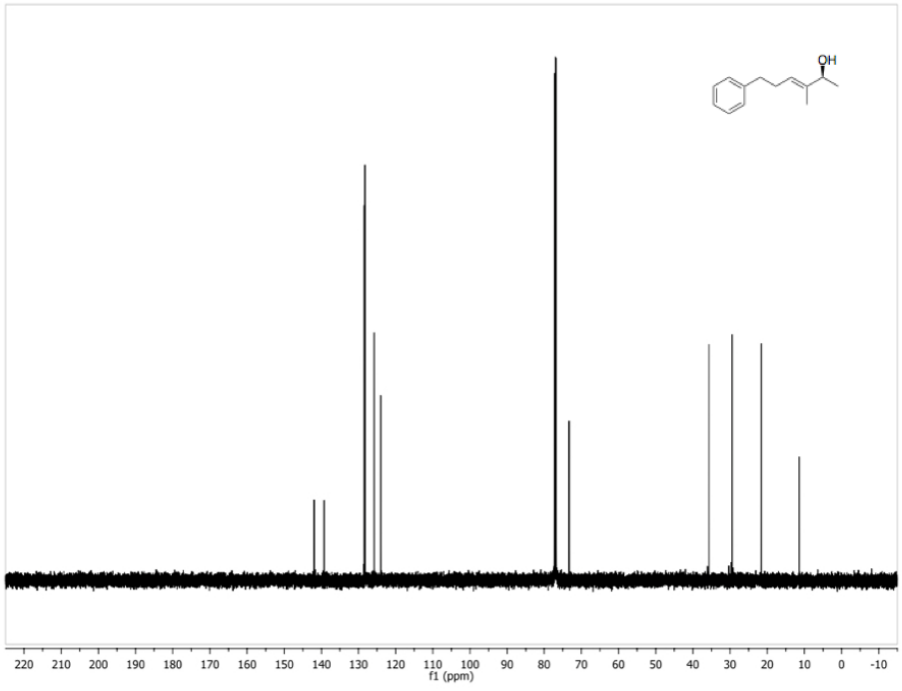
f1 (ppm)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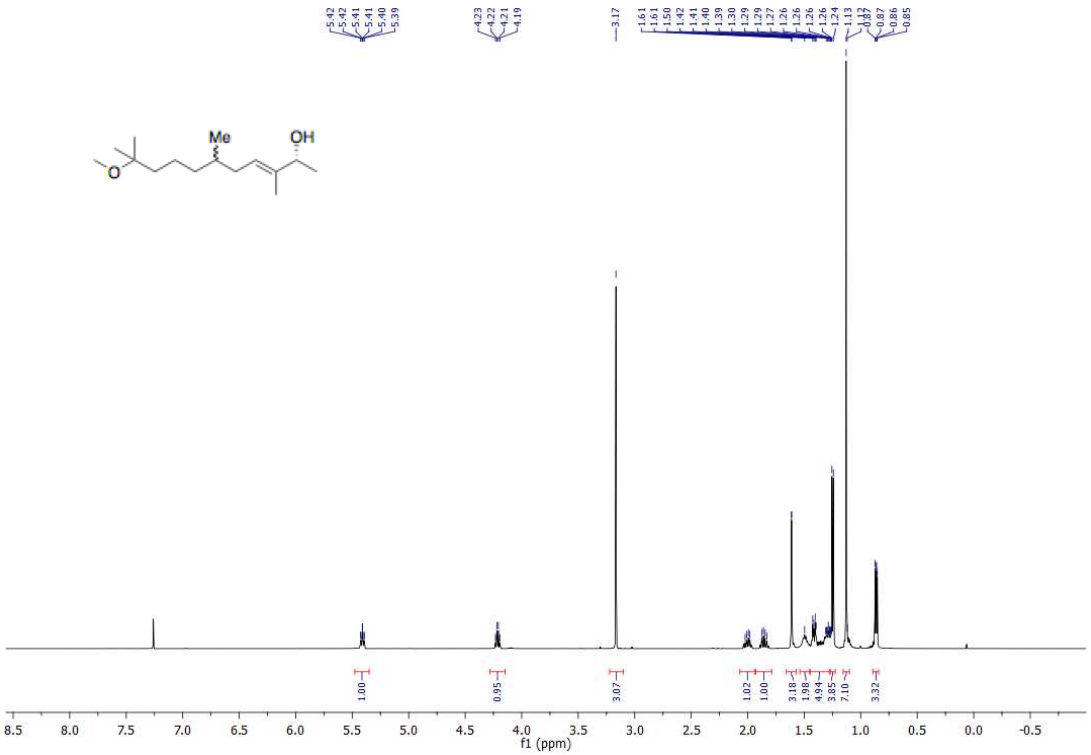
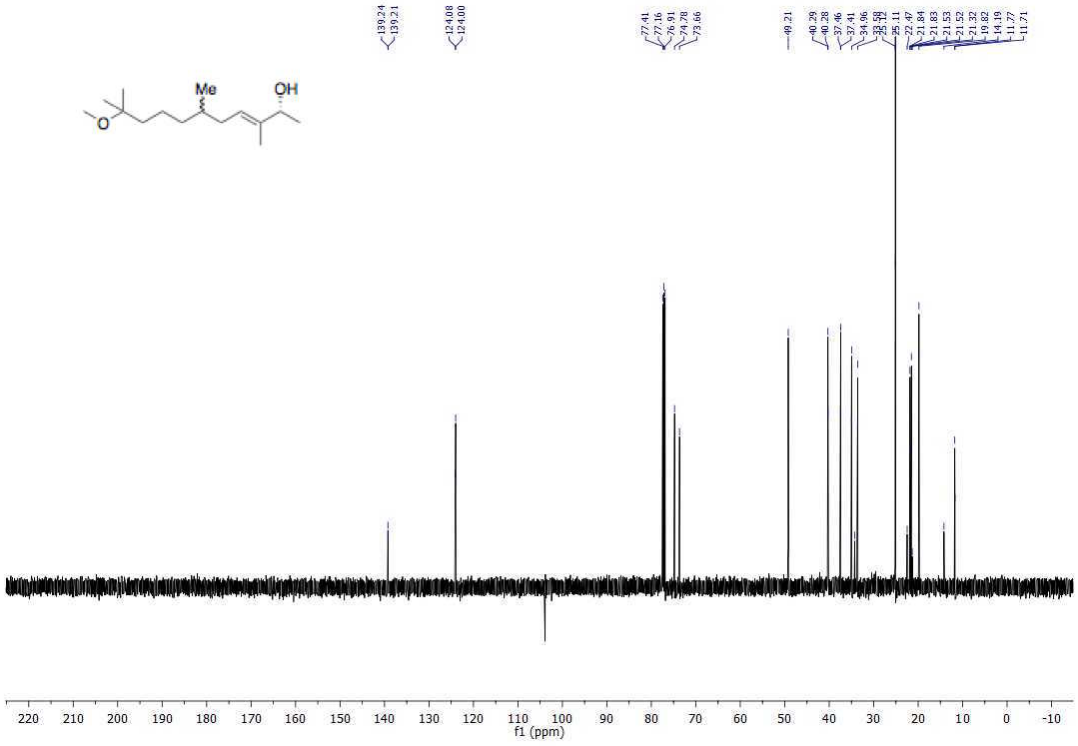
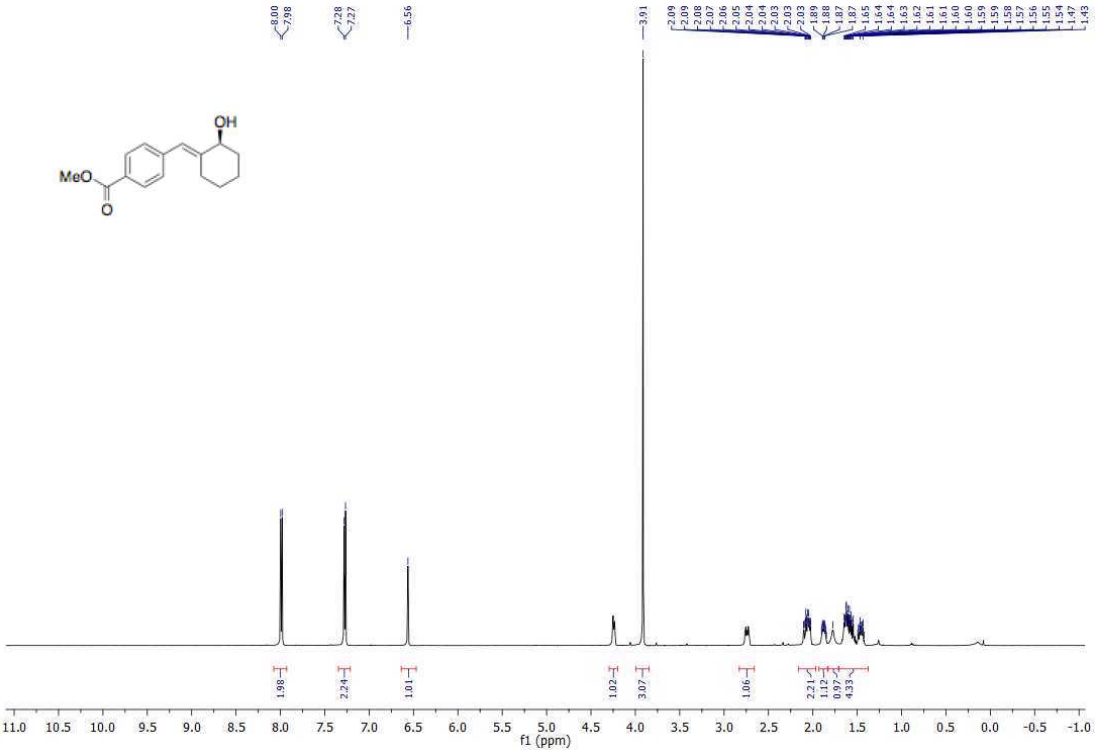
f1 (ppm)


Me
OH
O
f1 (ppm)


Me
OH
O
f1 (ppm)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MeO
O
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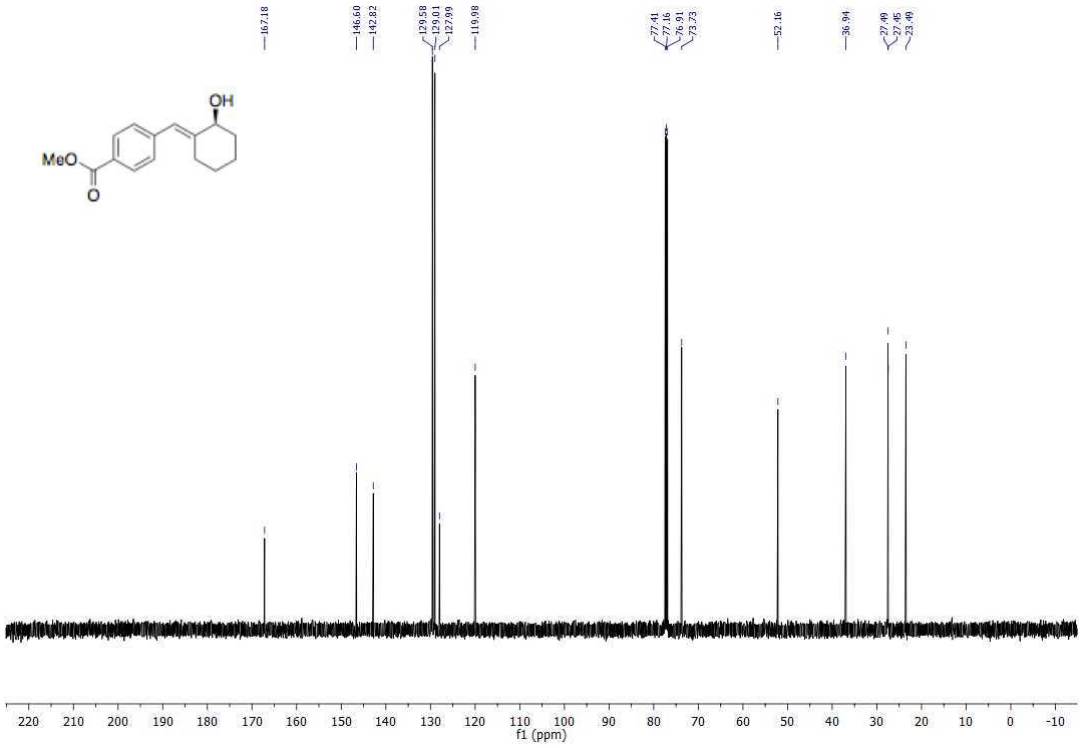
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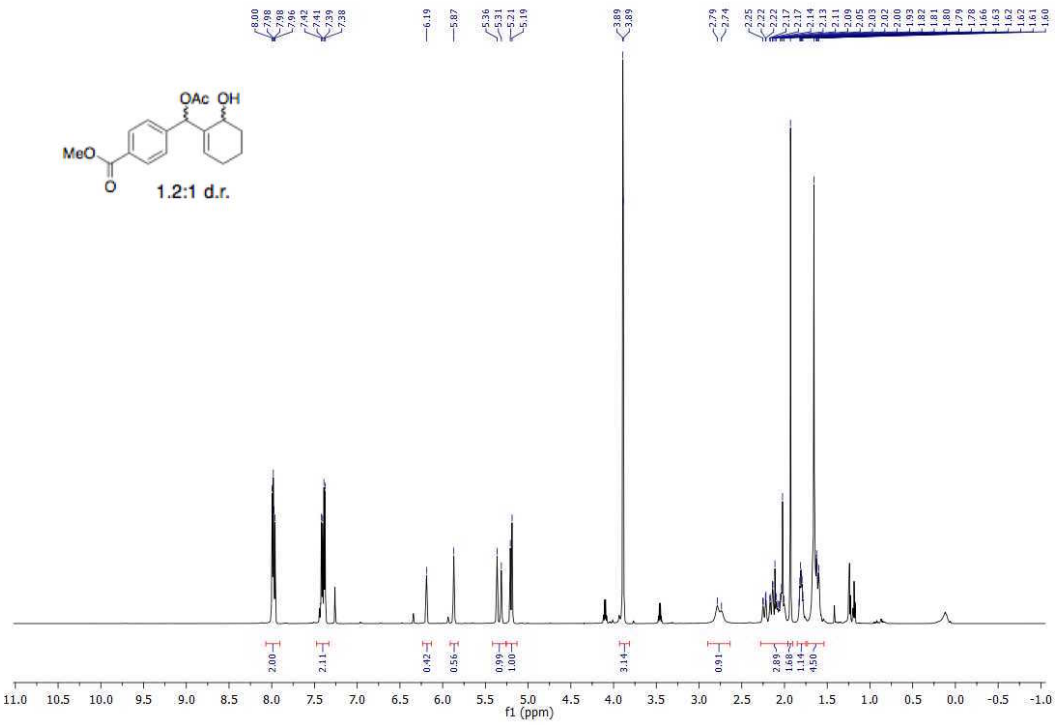
MeO
O
f1 (ppm)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MeO
O
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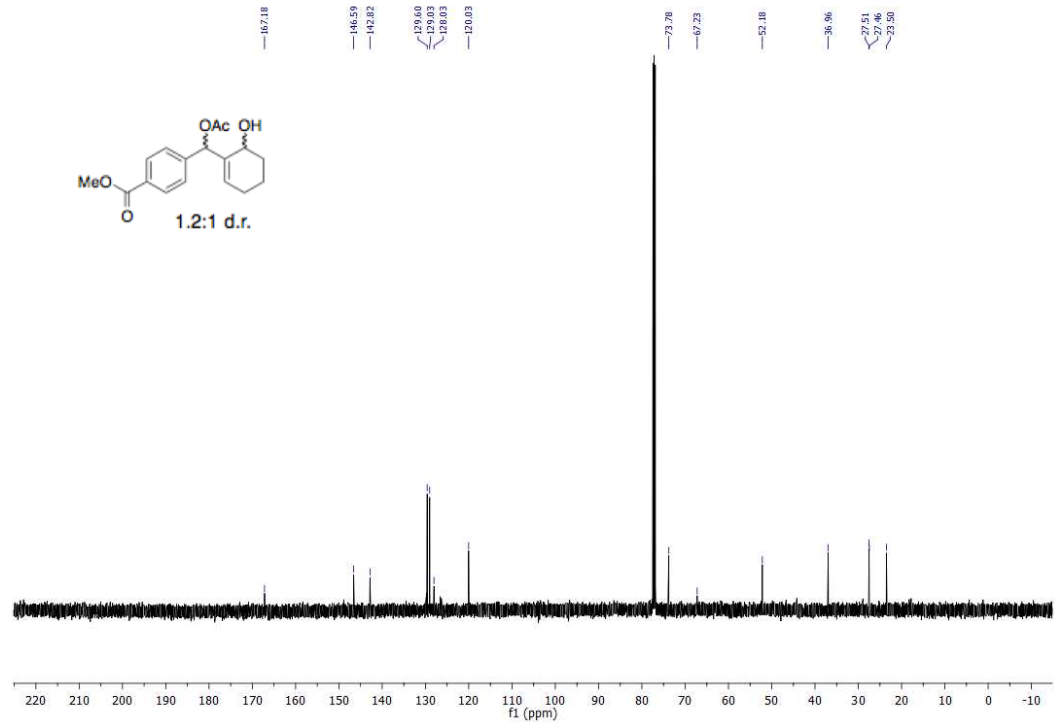
f1 (ppm)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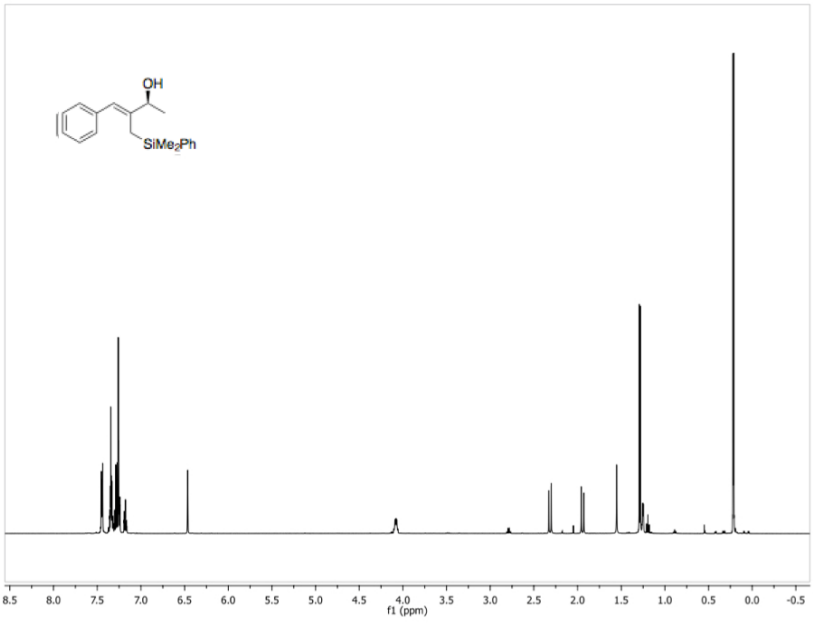
MeO
O
1.2:1 d.r.
f1 (ppm)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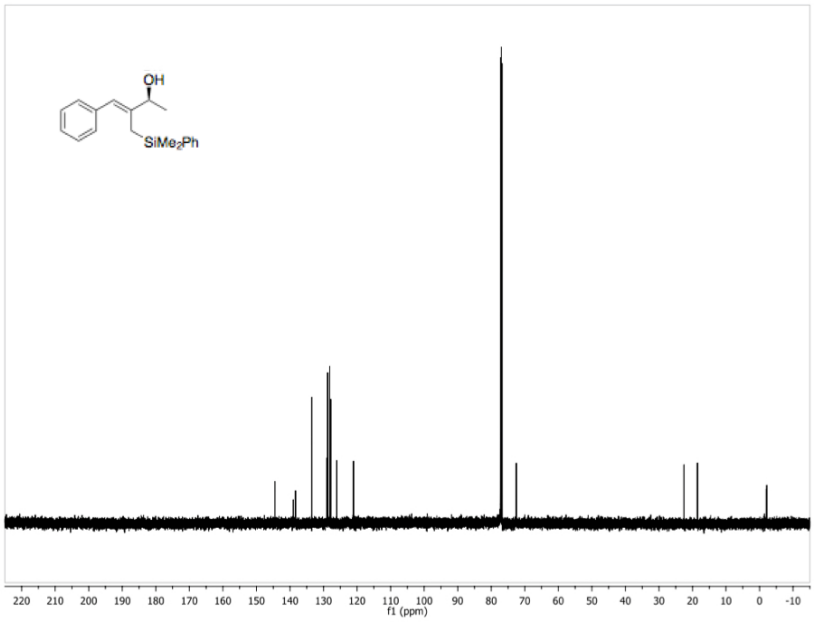
f1 (ppm)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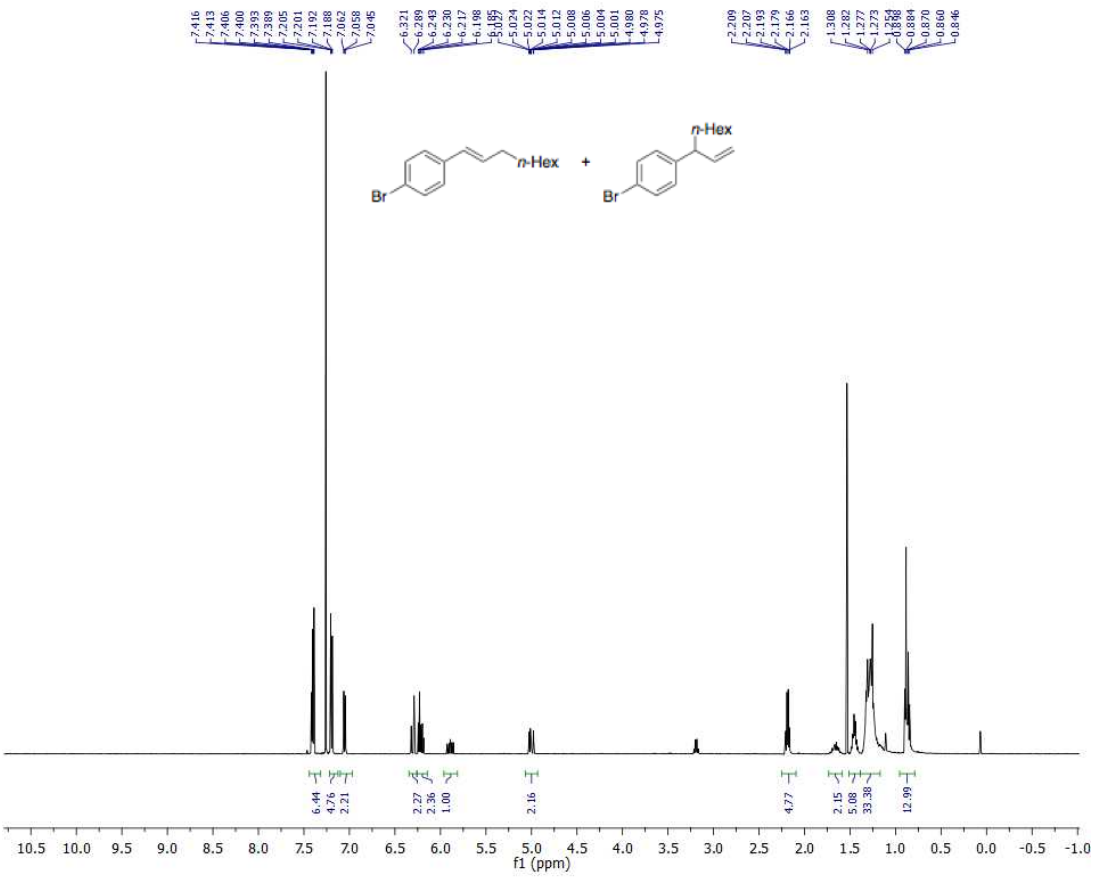
f1 (ppm)


n-Hex
Br
+
n-Hex
Br
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2.36
1.00
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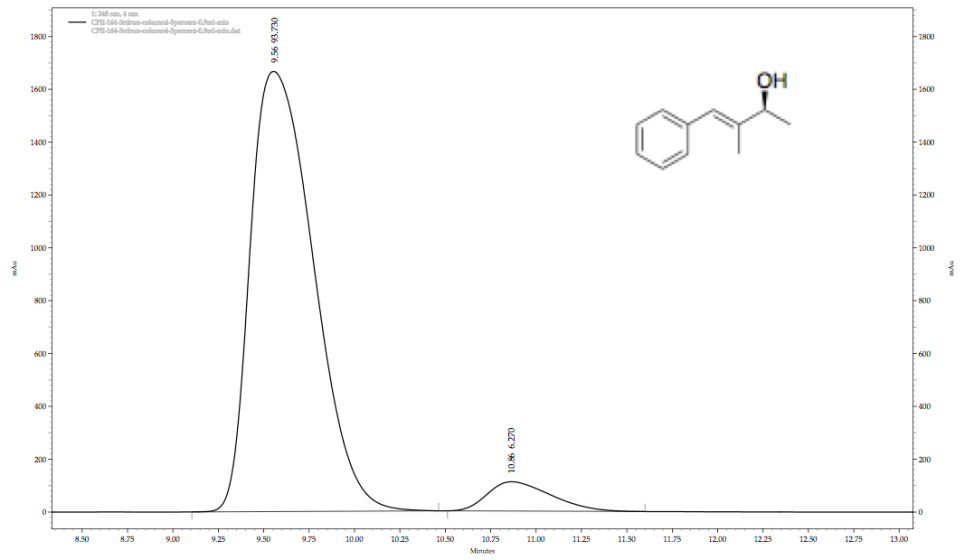
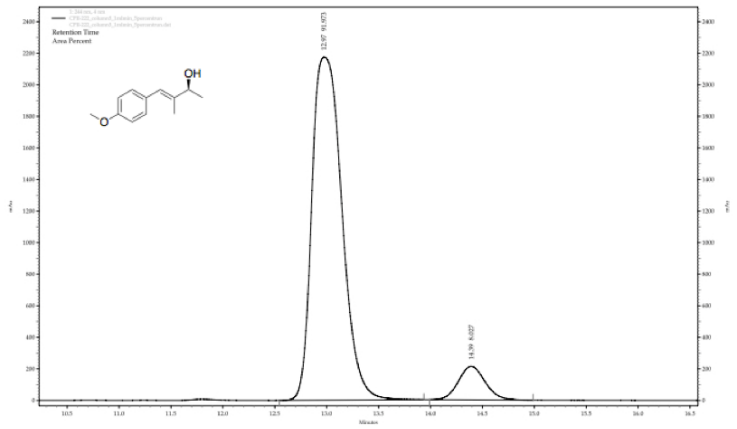
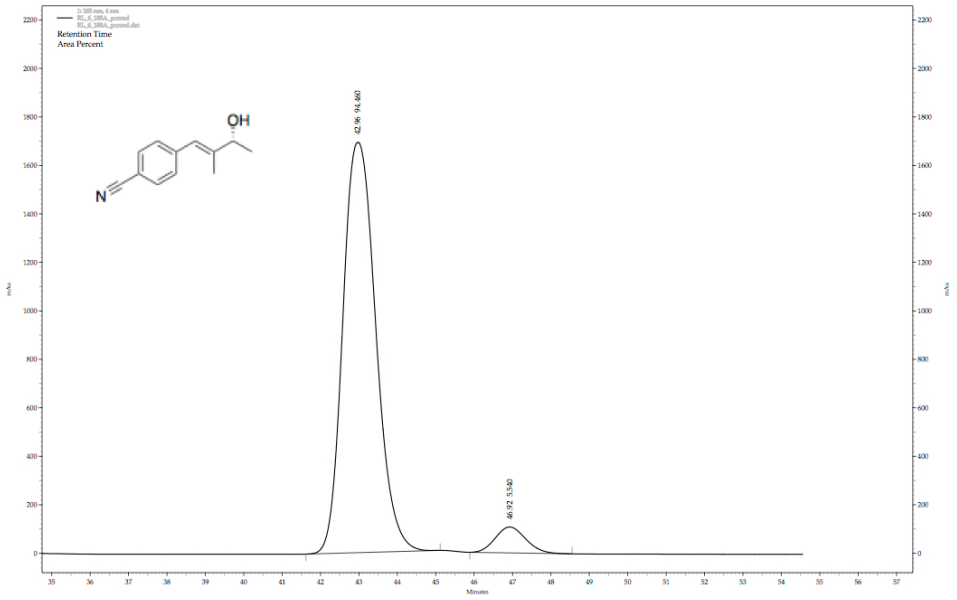
4.77
2.15
5.08
33.38
12.99
f1 (ppm)



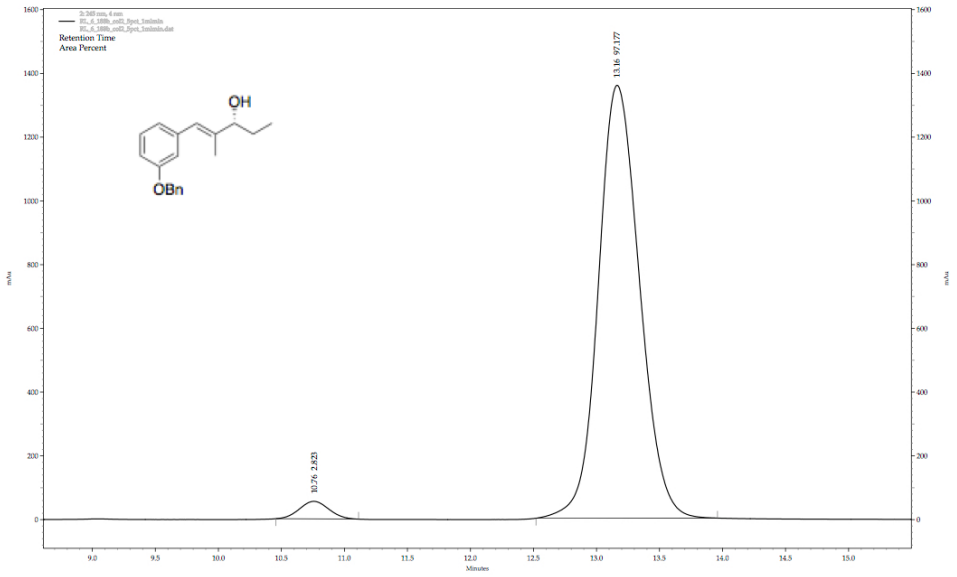
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CPII-164-3rdrun-column4-5percent-0.9ml-min.dat, 1: 248 nm, 4 nm



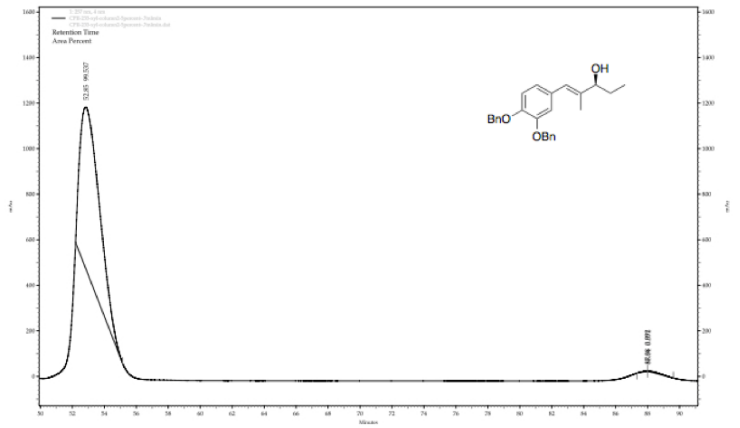
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CPII-222_column5_1mlmin_5percentrun.dat, 1: 244 nm, 4 nm



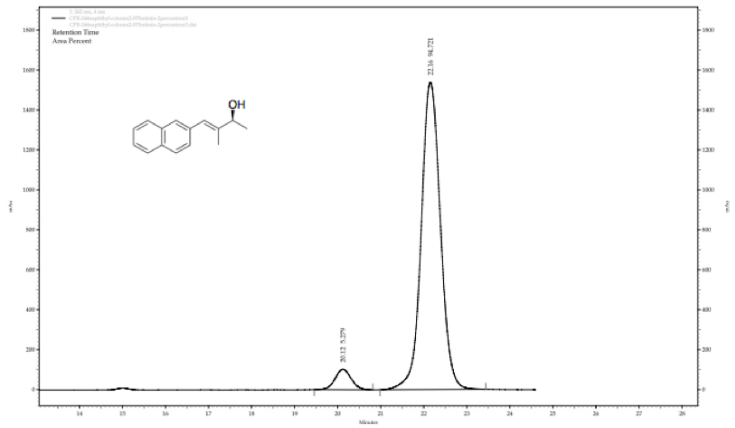
C:\EZStart\Projects\Default\Data\Roscoe\RL_6_188A_pcnred.dat, 1: 265 nm, 4 nm



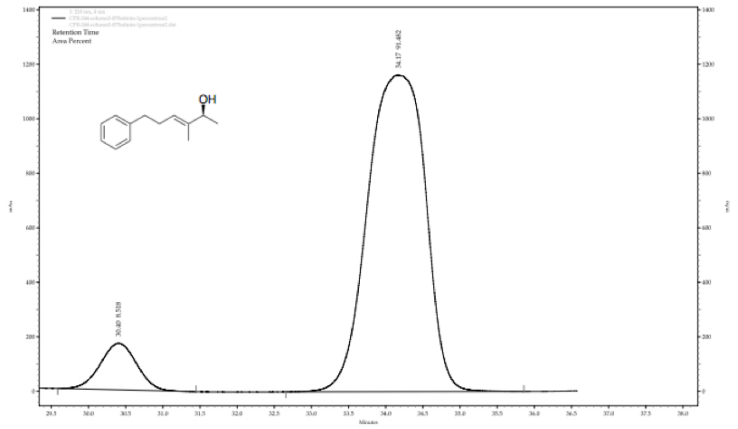
—— C:\EZStart\Projects\Default\Data\Roscoe\RL_6_188b_col2_5pct_1mlmin.dat, 2: 245 nm, 4 nm



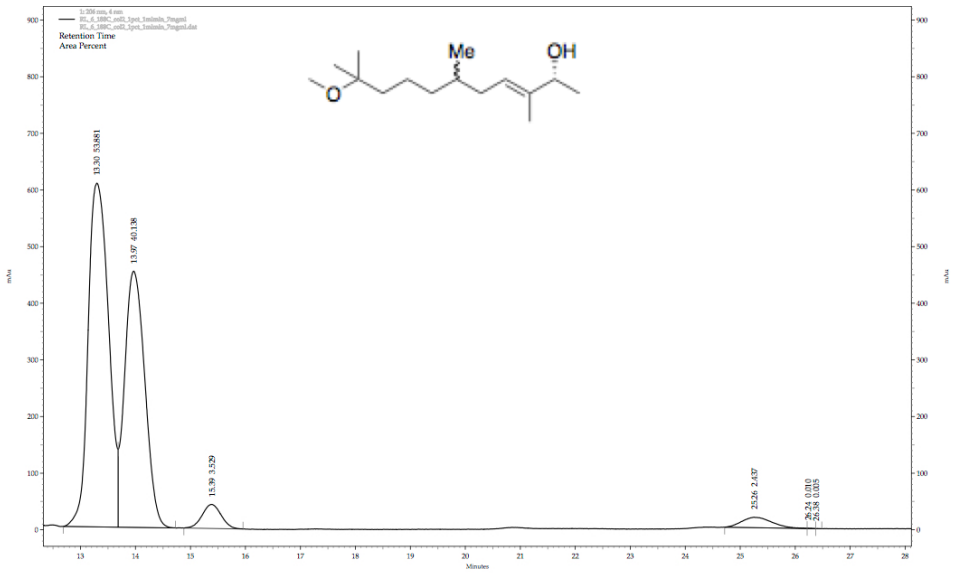
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CPII-233-xyl-column2-5percent-.7mlmin.dat, 1: 257 nm, 4 nm



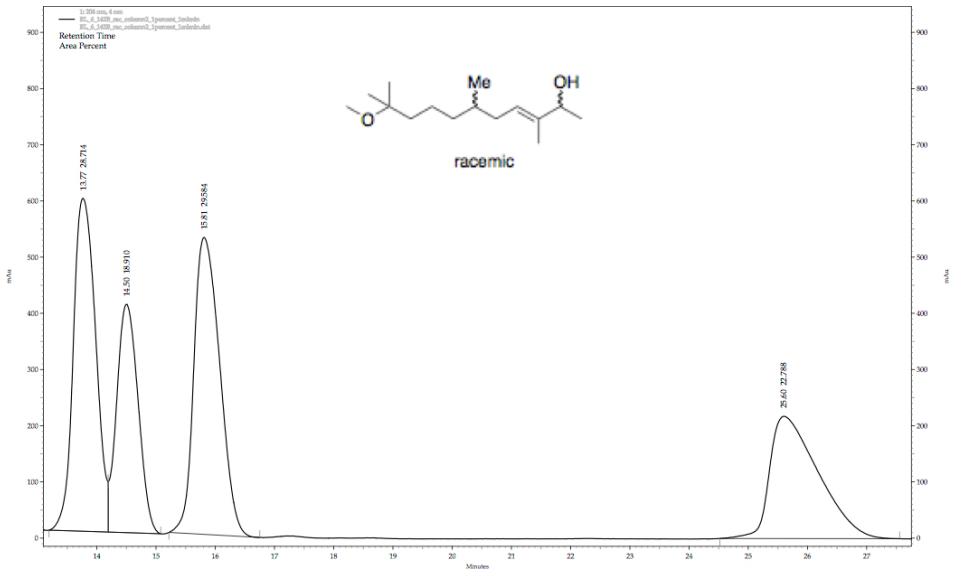
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CPII-244naphthyl-column2-075mlmin-2percentrun3.dat, 1: 242 nm, 4



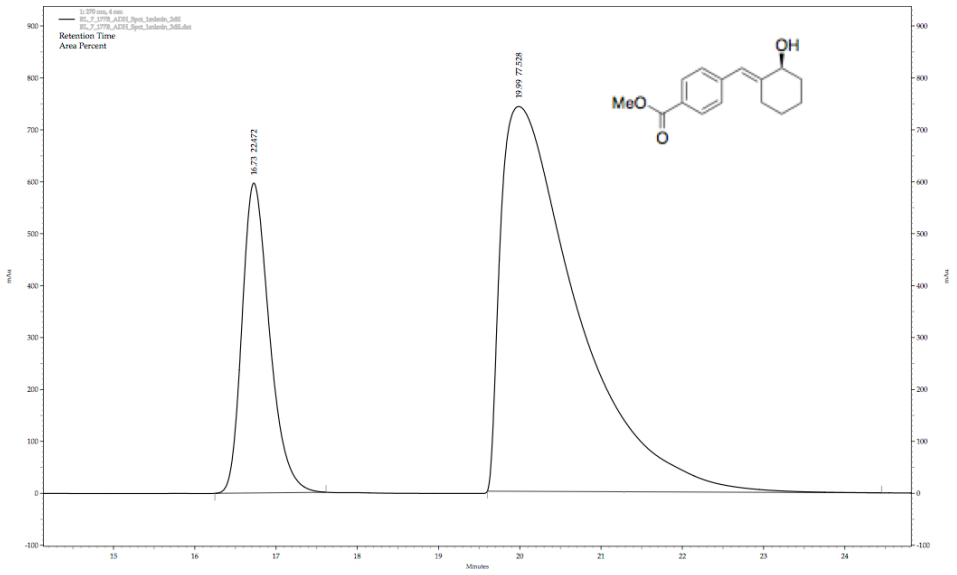
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CPII-244-column3-075mlmin-1percentrun2.dat, 1: 210 nm, 4 nm



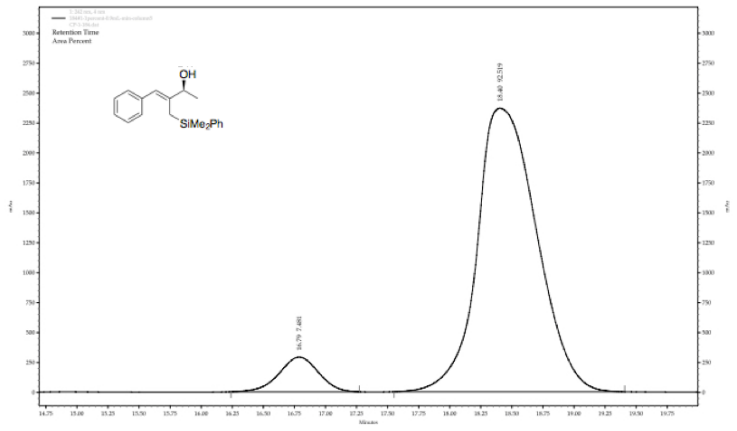
—— C:\EZStart\Projects\Default\Data\Roscoe\RL_6_188C_col2_1pct_1mlmin_7mgml.dat, 1: 206 nm, 4 nm



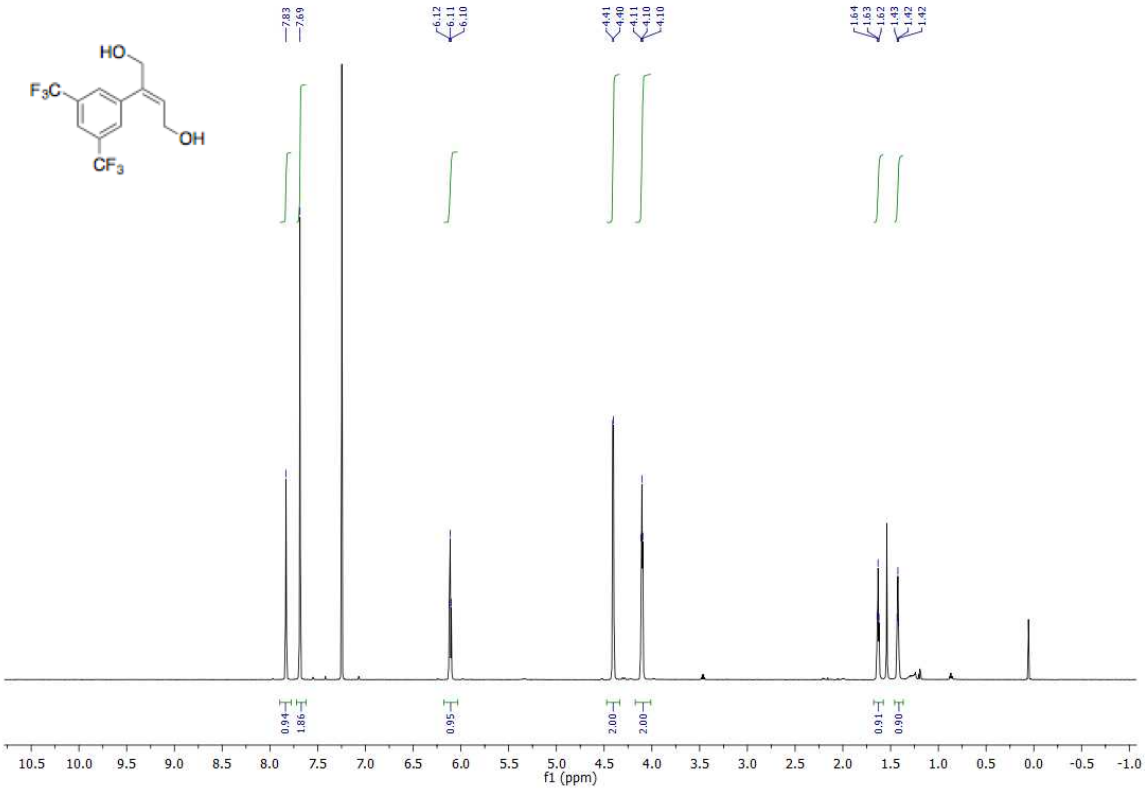
—— C:\EZStart\Projects\Default\Data\Roscoe\RL_6_142B_rac_column2_1percent_1mlmin.dat, 1: 206 nm, 4 nm

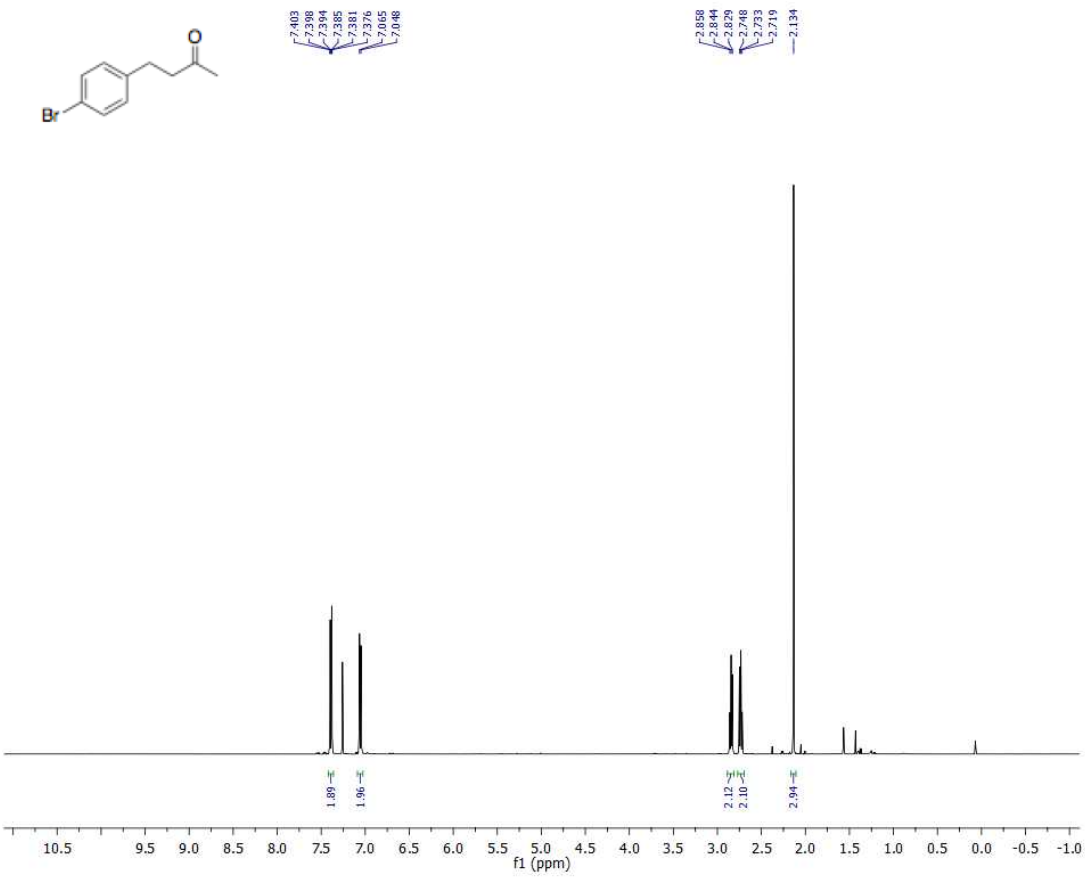


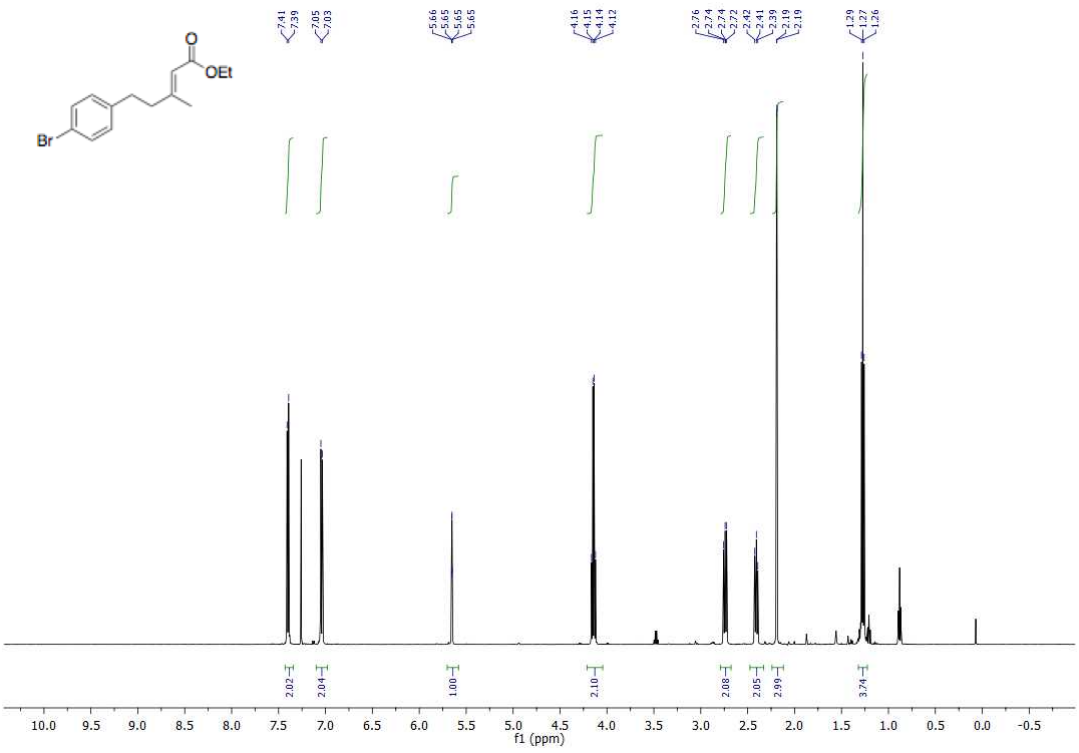
—— C:\EZStart\Projects\Default\Data\Roscoe\RL_7_177B_ADH_5pct_1mlmin_2dil.dat, 1: 270 nm, 4 nm

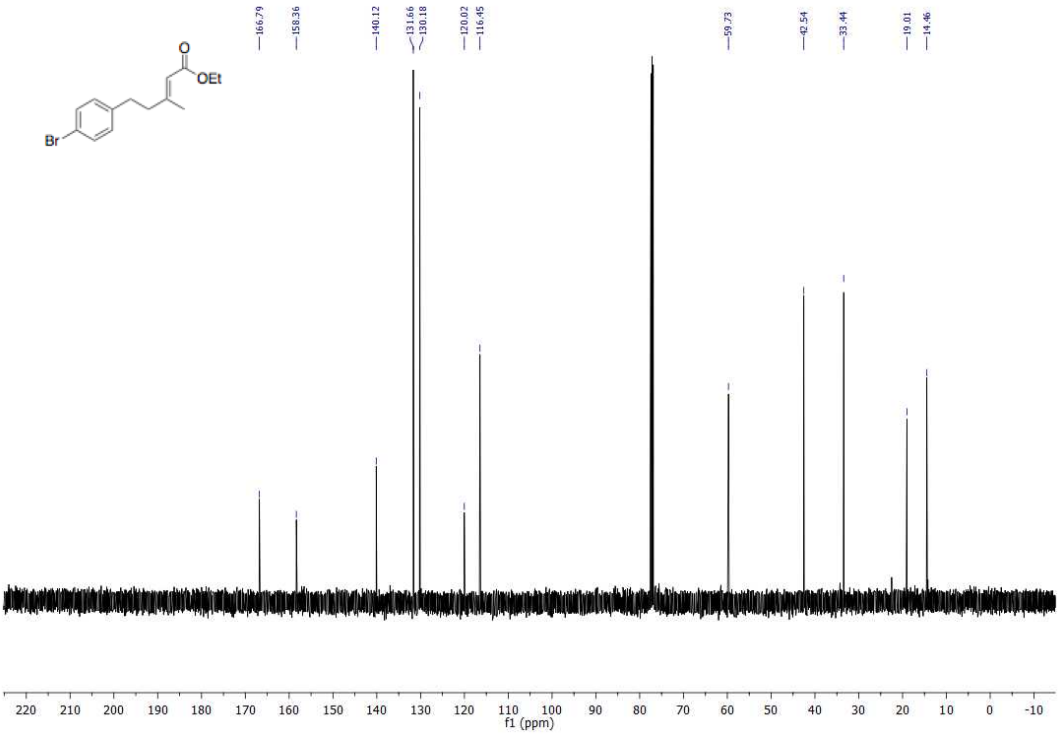


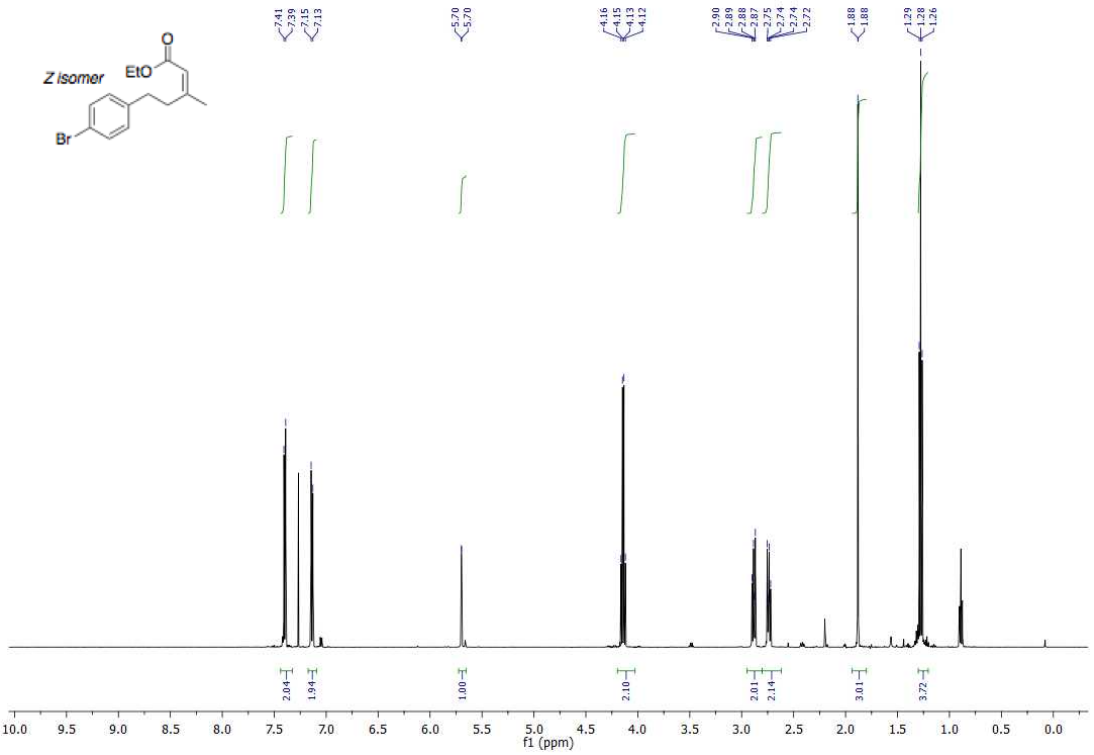
—— C:\EZStart\Projects\Default\Data\RASTASOLJA!\CP-1-184.dat, 1: 242 nm, 4 nm

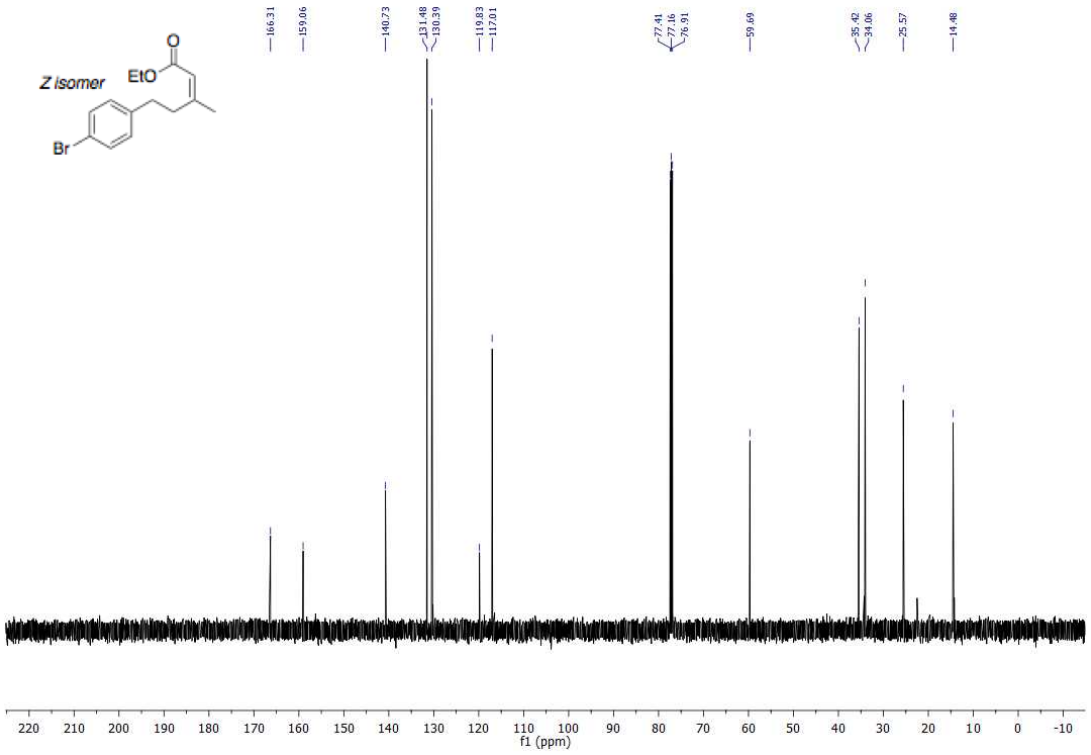

HO
F3C
OH
CF3
7.83
7.69
6.12
6.11
6.10
4.41
4.40
4.11
4.10
4.10
1.64
1.63
1.62
1.43
1.42
1.42
0.94
1.86
0.95
2.00
2.00
0.91
0.90
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

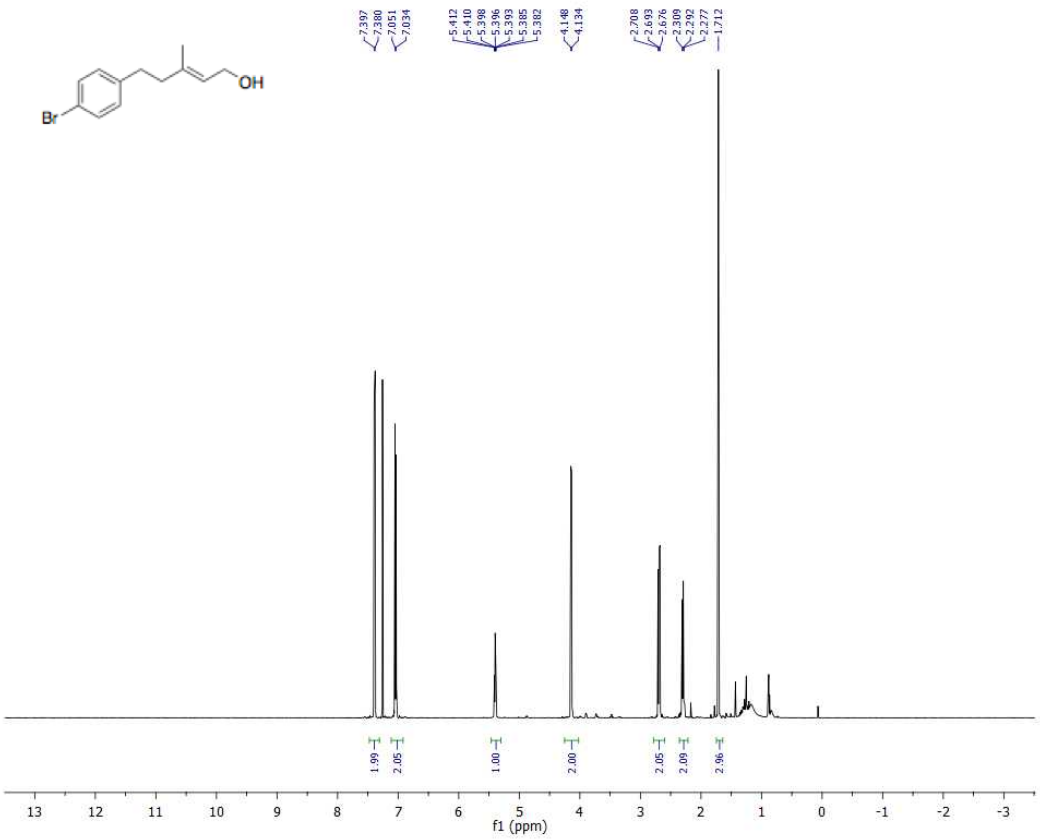

Br
O
7.403
7.398
7.394
7.385
7.381
7.376
7.065
7.048
2.858
2.844
2.829
2.748
2.733
2.719
2.134
1.89
1.96
2.12
2.10
2.94
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

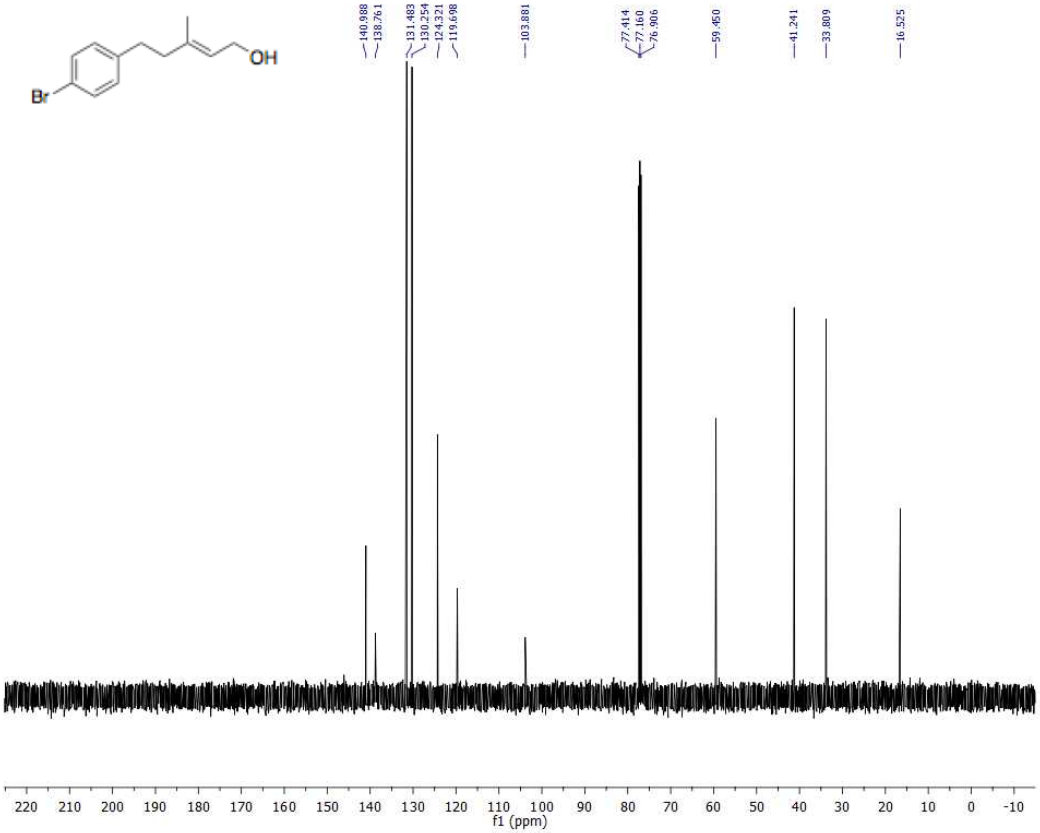

O
OEt
Br
7.41
7.39
7.05
7.03
5.66
5.65
5.65
5.65
4.16
4.15
4.14
4.12
2.76
2.74
2.74
2.72
2.42
2.41
2.39
2.19
2.19
1.29
1.27
1.26
2.02
2.04
1.00
2.10
2.08
2.05
2.99
3.74
f1 (ppm)

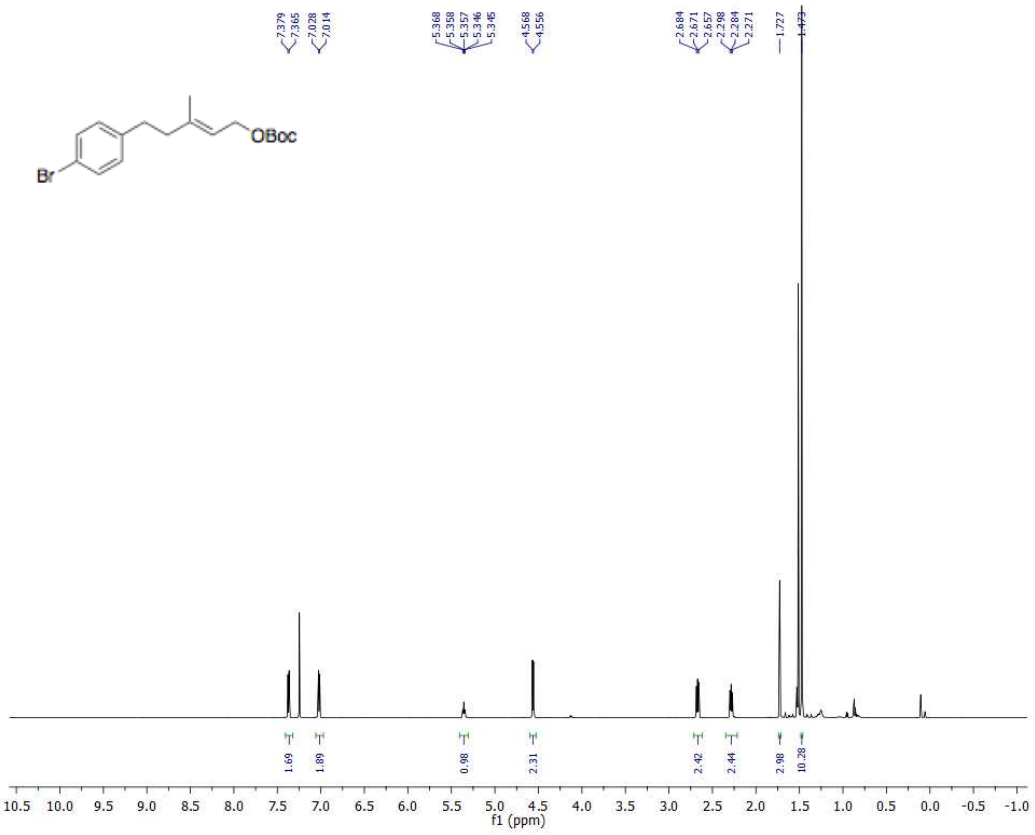

O
OEt
Br
166.79
158.36
140.12
131.66
130.18
120.02
116.45
59.73
42.54
33.44
19.01
14.46
f1 (ppm)

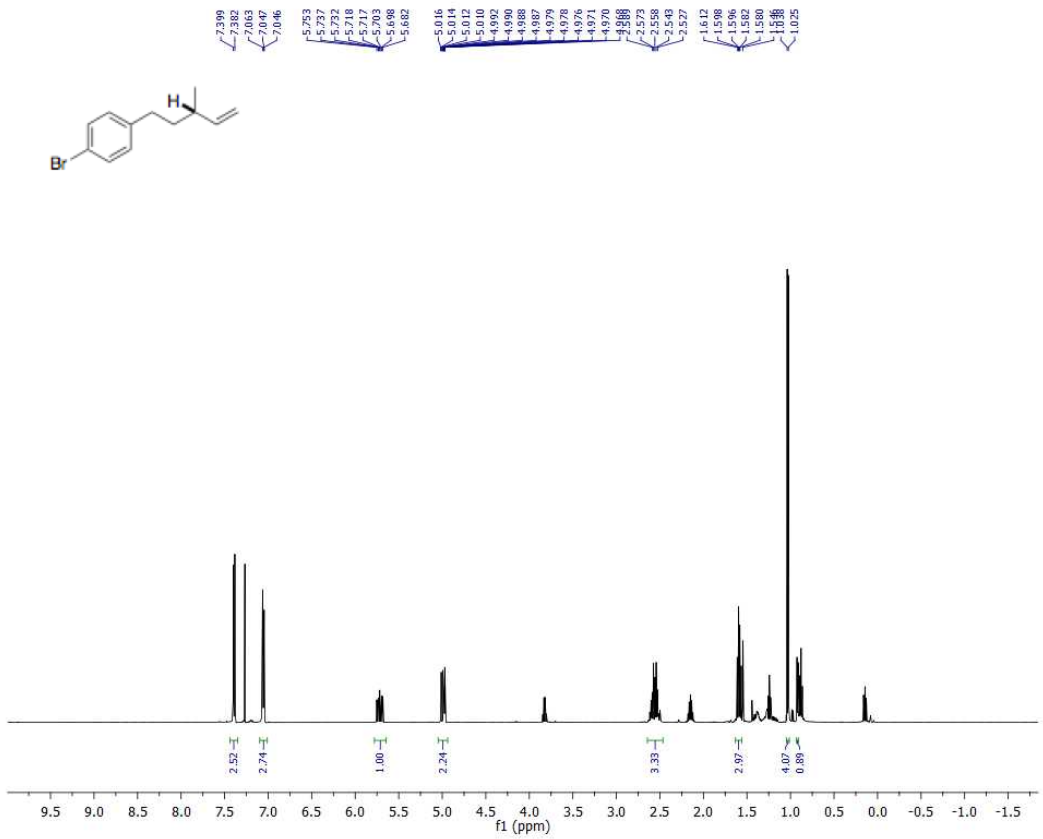

Z isomer
EtO
O
Br
7.41
7.39
7.15
7.13
5.70
5.70
4.16
4.15
4.13
4.12
2.90
2.89
2.88
2.87
2.75
2.74
2.74
2.72
1.88
1.88
1.29
1.28
1.26
2.04
1.94
1.00
2.10
2.01
2.14
3.01
3.72
f1 (ppm)

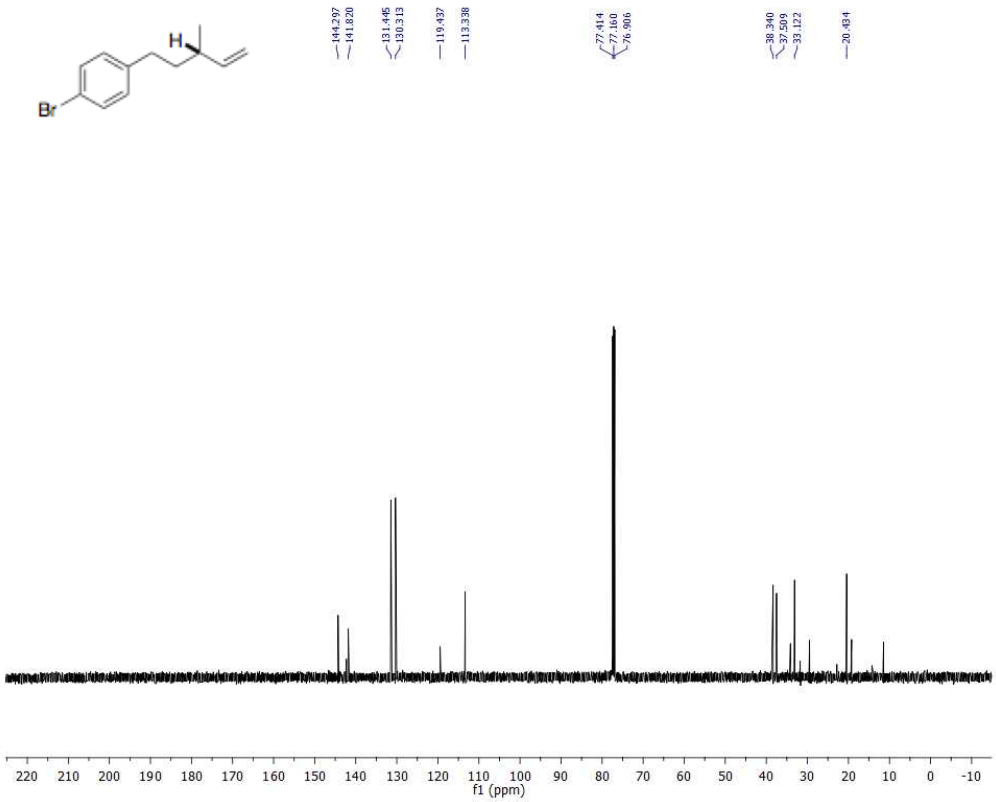

Z isomer
EtO
O
Br
166.31
159.06
140.73
131.48
130.39
119.83
117.01
77.41
77.16
76.91
59.69
35.42
34.06
25.57
14.48
f1 (ppm)

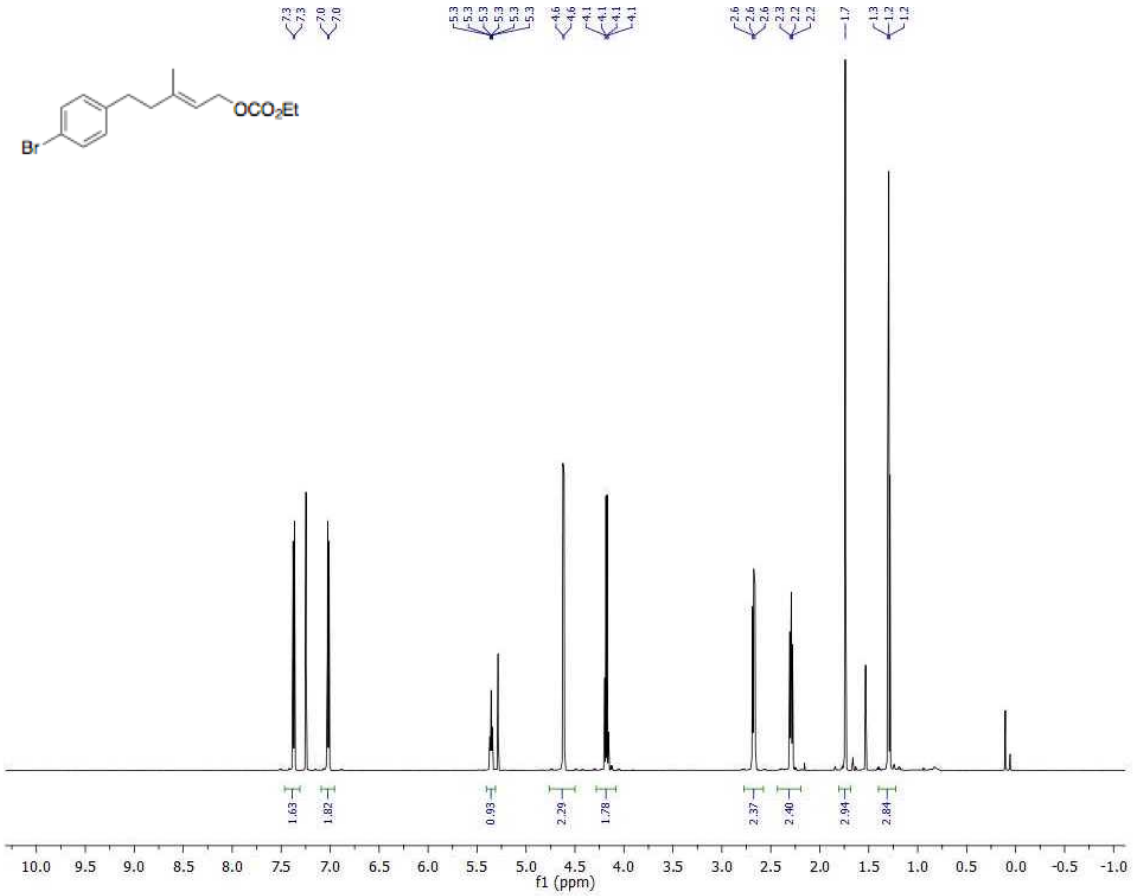

Br
OH
7.397
7.380
7.051
7.034
5.412
5.410
5.398
5.396
5.393
5.385
5.382
4.148
4.134
2.708
2.693
2.676
2.309
2.292
2.277
1.712
1.99
2.05
1.00
2.00
2.05
2.09
2.96
f1 (ppm)

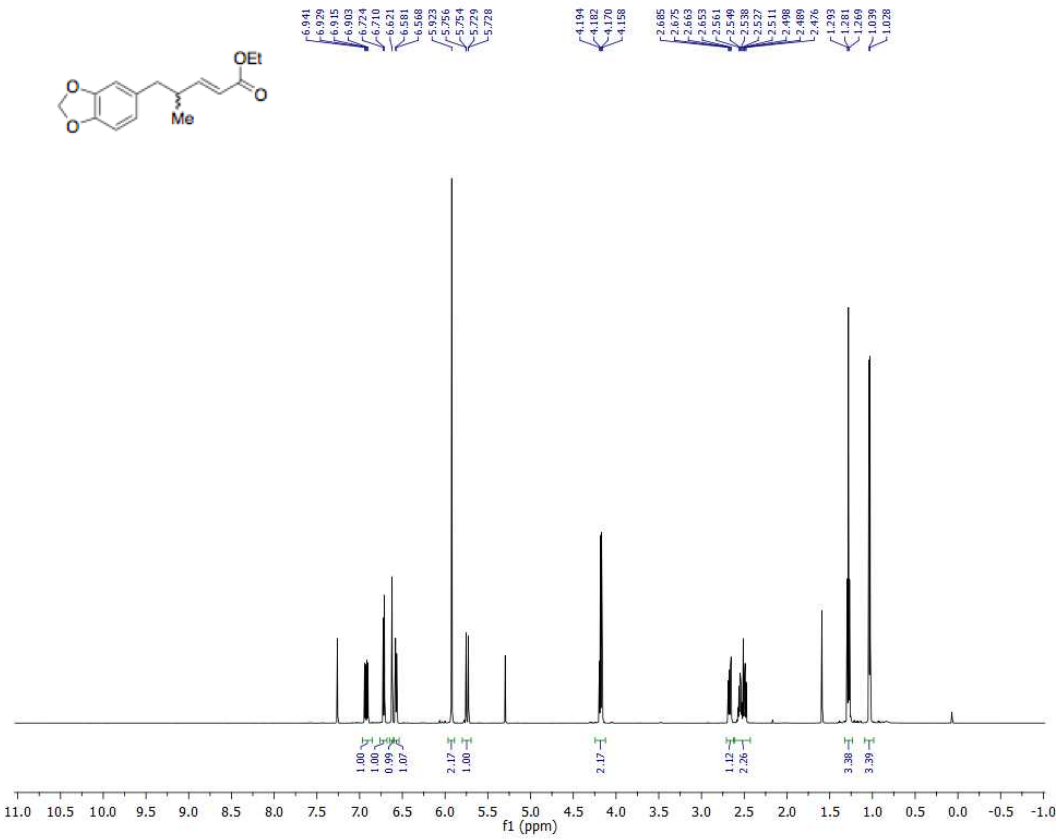

Br
OH
140.988
138.761
131.483
130.254
124.321
119.698
103.881
77.414
77.160
76.906
59.460
41.241
33.809
16.525
f1 (ppm)

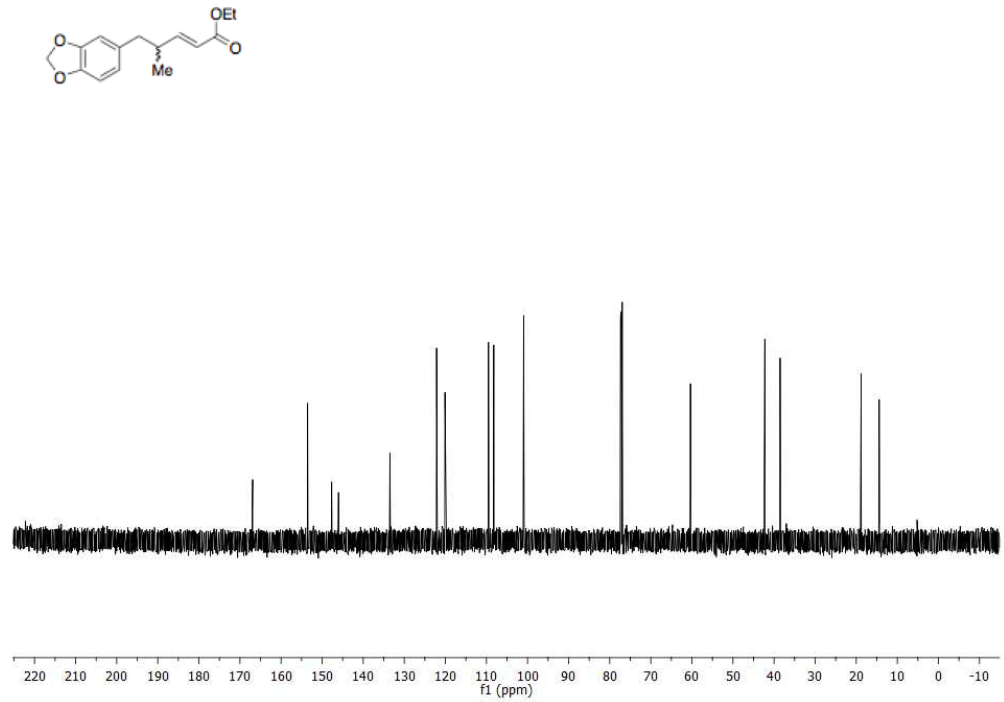

7.379
7.365
7.028
7.014
5.368
5.358
5.357
5.346
5.345
4.568
4.556
2.684
2.671
2.657
2.298
2.284
2.271
1.727
1.473
OBoc
Br
1.69
1.89
0.98
2.31
2.42
2.44
2.98
10.28
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

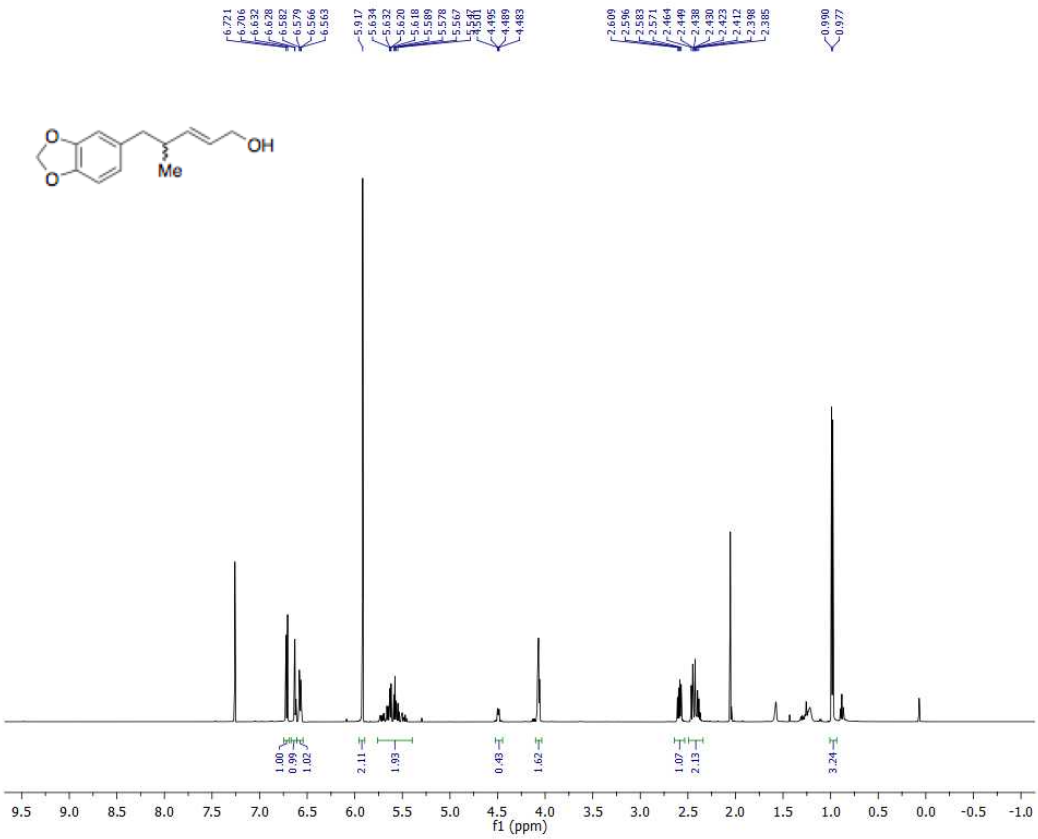

7.399
7.382
7.063
7.047
7.046
5.753
5.737
5.732
5.718
5.717
5.703
5.698
5.682
5.016
5.014
5.012
5.010
4.992
4.990
4.988
4.987
4.979
4.978
4.976
4.971
4.970
2.573
2.558
2.543
2.527
1.612
1.598
1.596
1.582
1.580
1.025
Br
2.52
2.74
1.00
2.24
3.33
2.97
4.07
0.89
f1 (ppm)

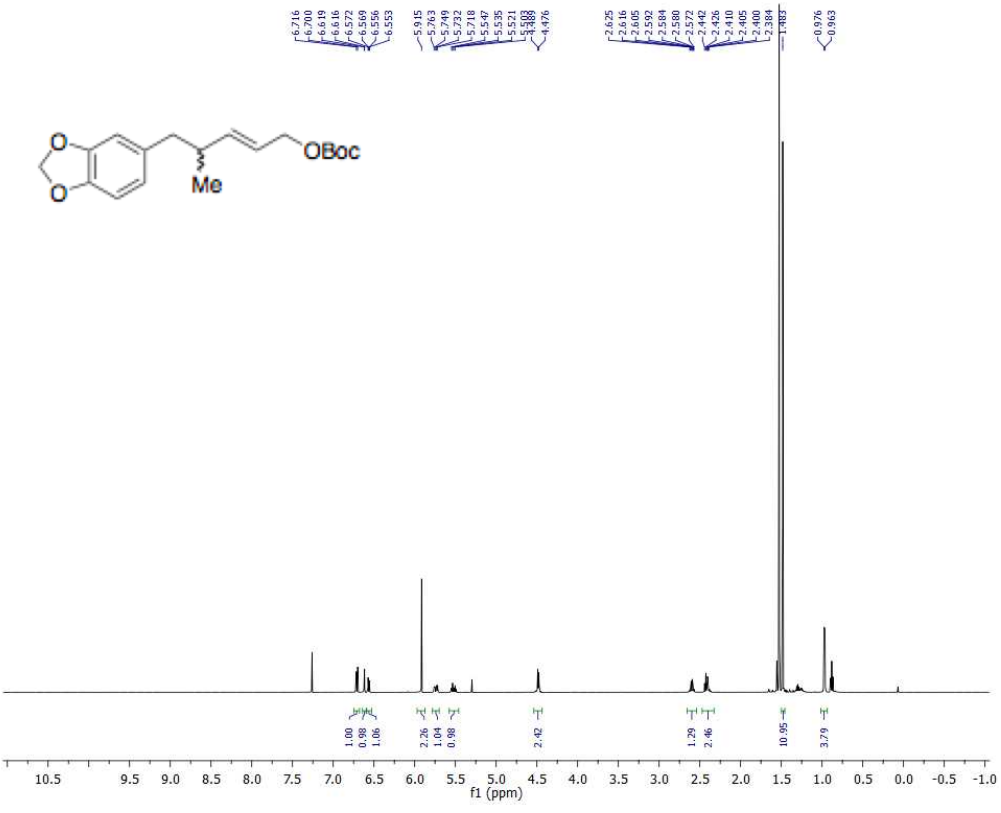

144.297
141.820
131.445
130.313
119.437
113.338
77.414
77.160
76.906
38.340
37.599
33.122
20.434
Br
f1 (ppm)

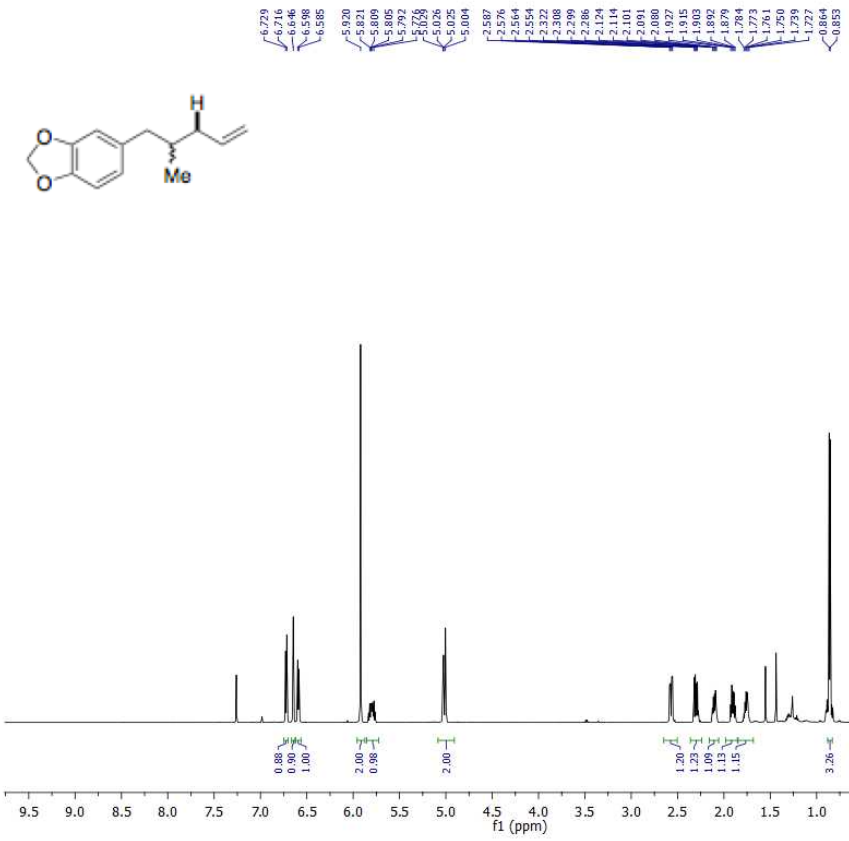

Br
OCO2Et
f1 (ppm)

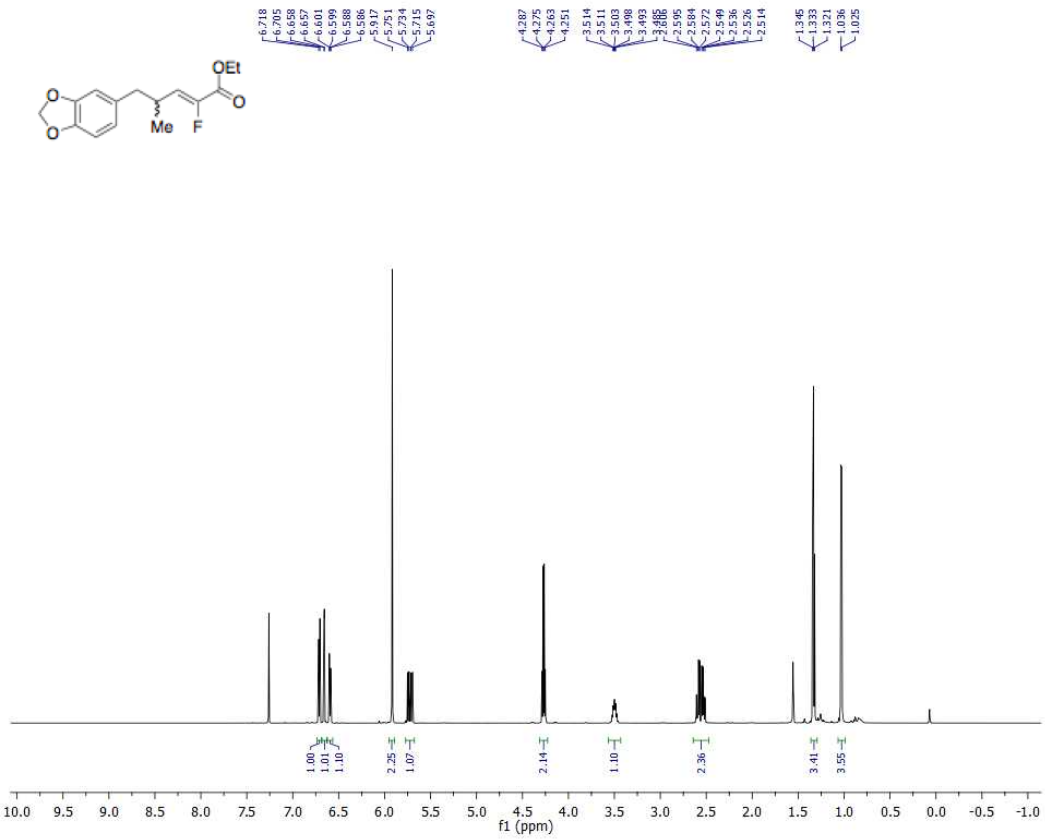

6.941
6.929
6.915
6.903
6.724
6.710
6.621
6.581
6.568
5.923
5.756
5.754
5.729
5.728
4.194
4.182
4.170
4.158
2.685
2.675
2.663
2.653
2.561
2.549
2.538
2.527
2.511
2.498
2.489
2.476
1.293
1.281
1.269
1.099
1.028
OEt
O
O
O
Me
1.00
1.00
0.99
1.07
2.17
1.00
2.17
1.12
2.26
3.38
3.39
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

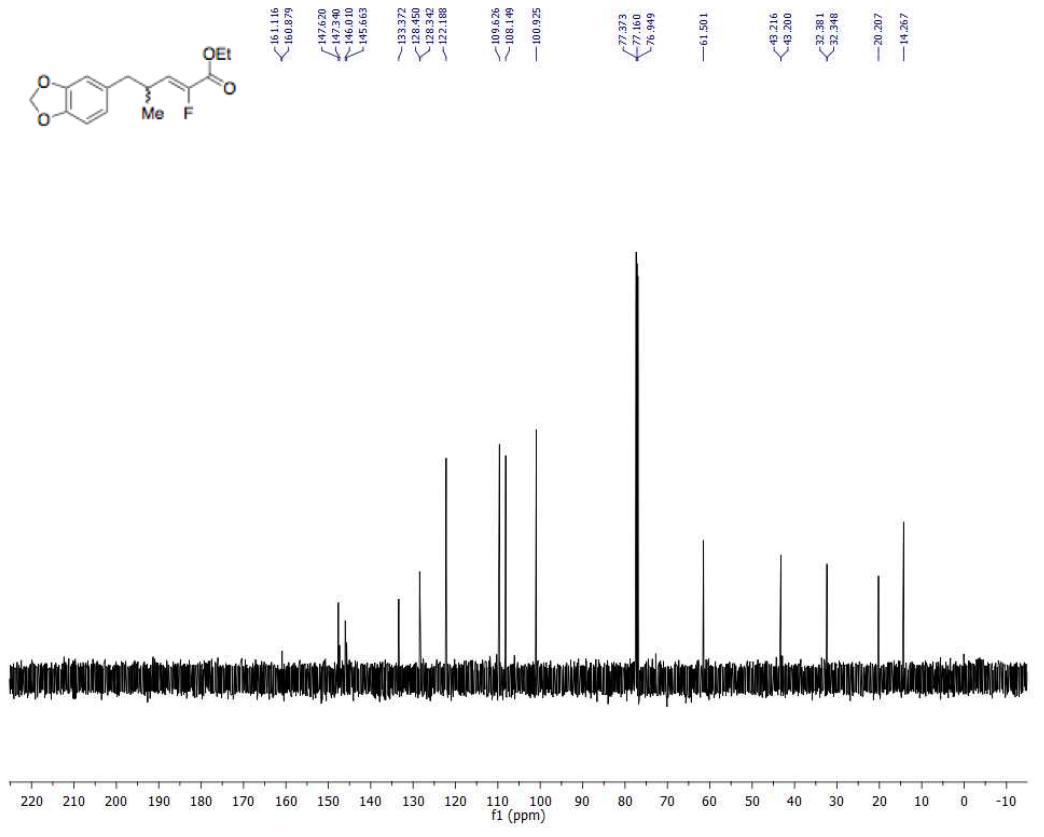

166.907
153.526
147.669
146.015
133.498
122.144
120.106
109.503
108.216
100.948
77.323
77.162
76.950
60.353
42.251
38.523
18.792
14.409
OEt
O
O
O
Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

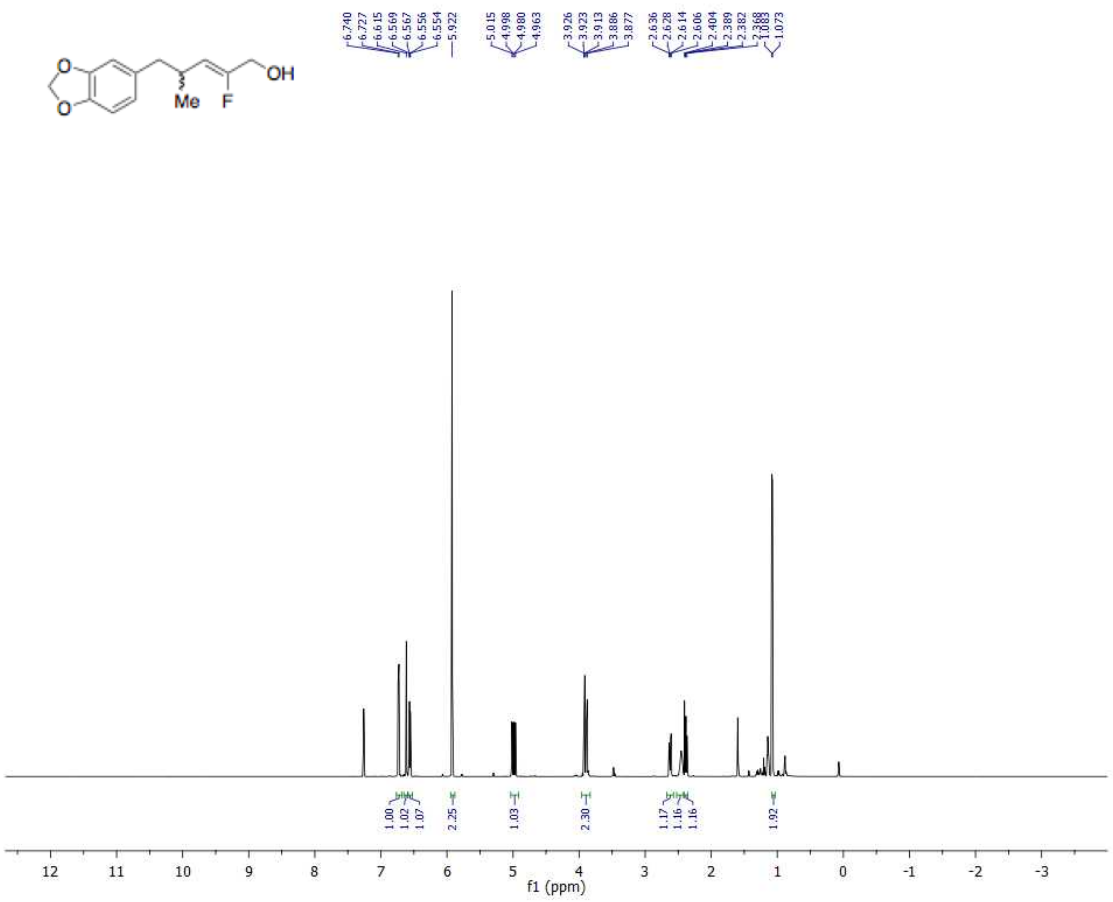

OH
Me
f1 (ppm)

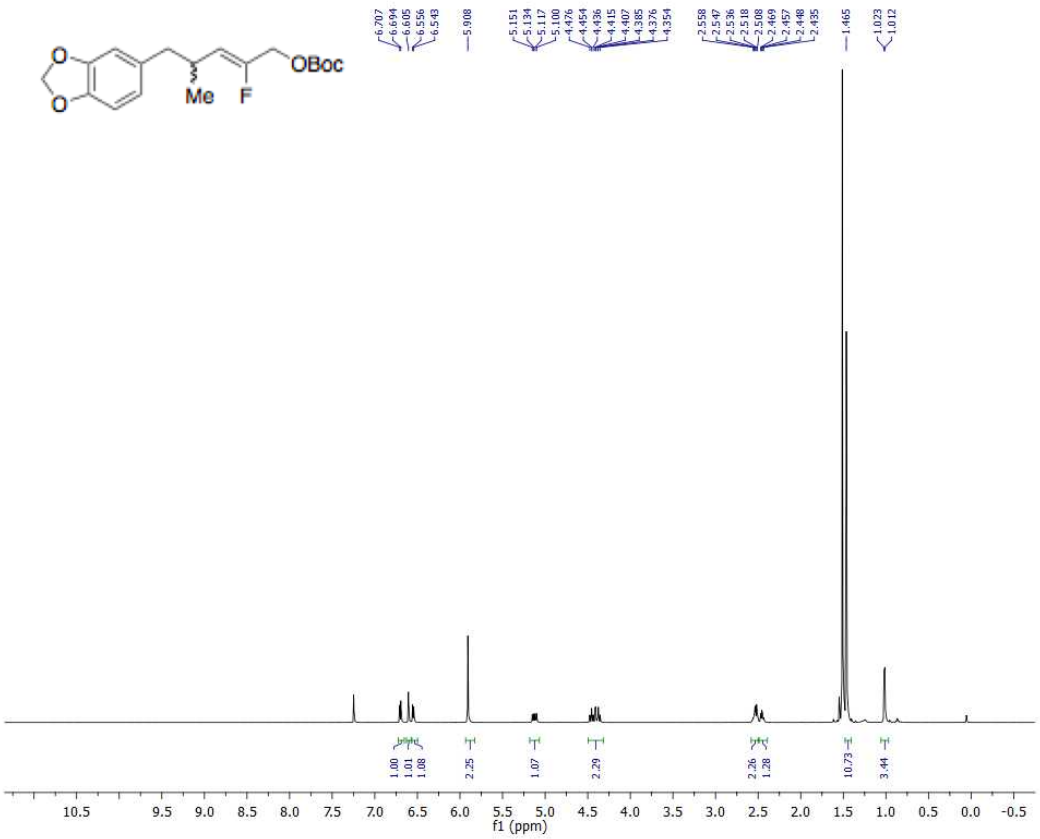

OBoc
Me
f1 (ppm)

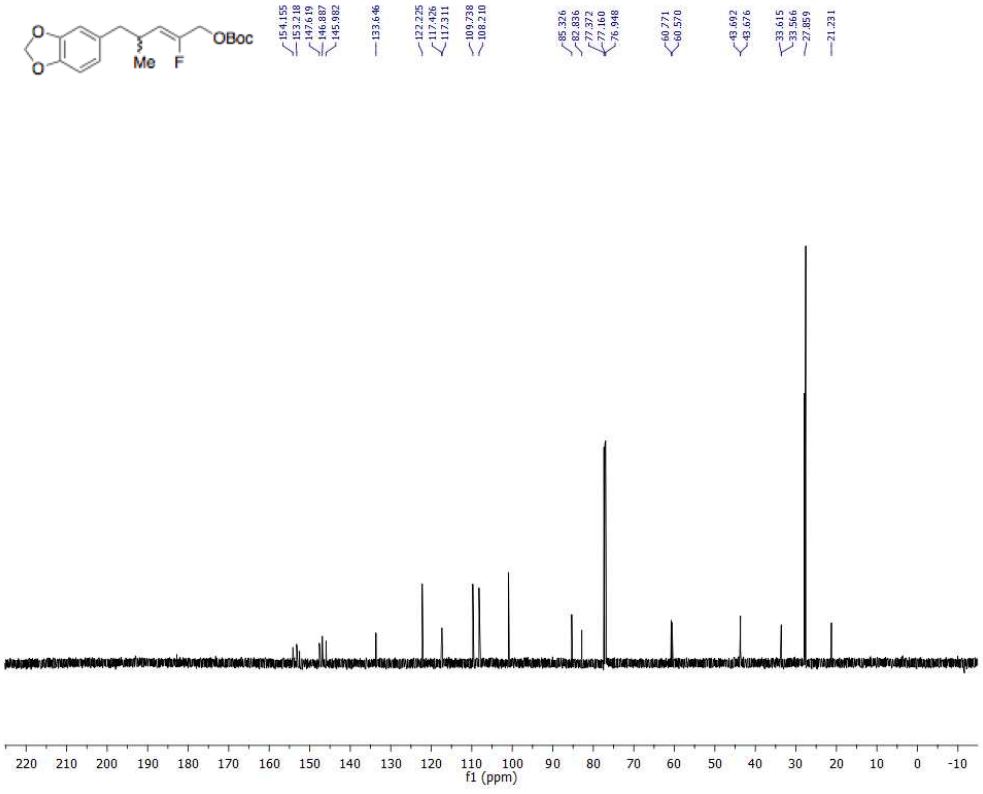

6.729
6.716
6.646
6.598
6.585
5.920
5.821
5.809
5.805
5.792
5.026
5.025
5.004
2.587
2.576
2.564
2.554
2.322
2.308
2.299
2.286
2.124
2.114
2.101
2.091
2.080
1.927
1.915
1.903
1.892
1.879
1.784
1.773
1.761
1.750
1.739
1.727
0.864
0.853
H
O
O
Me
0.88
0.90
1.00
2.00
0.98
2.00
1.20
1.23
1.09
1.13
1.15
3.26
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
147.535
145.644
137.449
135.293
122.075
116.088
109.622
108.060
100.838
77.373
77.161
76.949
62.932
40.986
35.246
19.278
H
O
O
Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

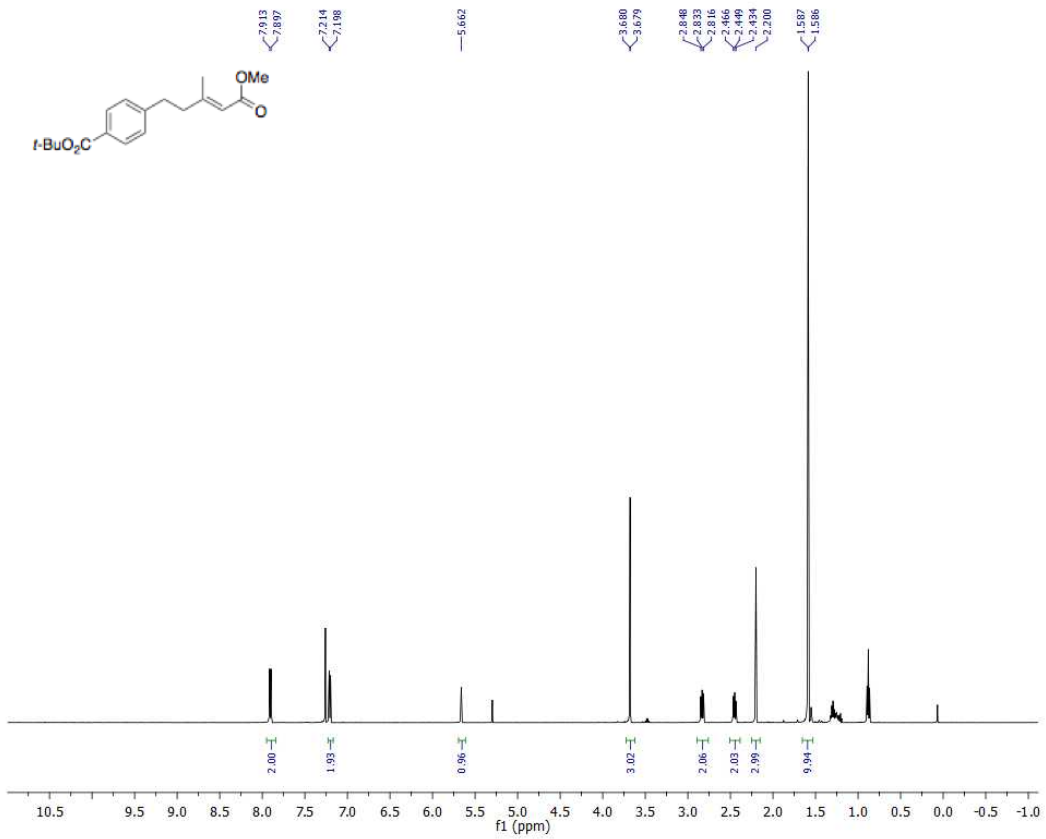

OEt
O
O
Me
F
f1 (ppm)


OEt
O
O
Me
F
f1 (ppm)


6.740
6.727
6.615
6.569
6.567
6.556
6.554
5.922
5.015
4.998
4.980
4.963
3.926
3.923
3.913
3.886
3.877
2.636
2.628
2.614
2.606
2.404
2.389
2.382
1.088
1.073
OH
Me
F
1.00
1.02
1.07
2.25
1.03
2.30
1.17
1.16
1.16
1.92
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


OBoc
Me
F
f1 (ppm)


OBoc
Me
F
f1 (ppm)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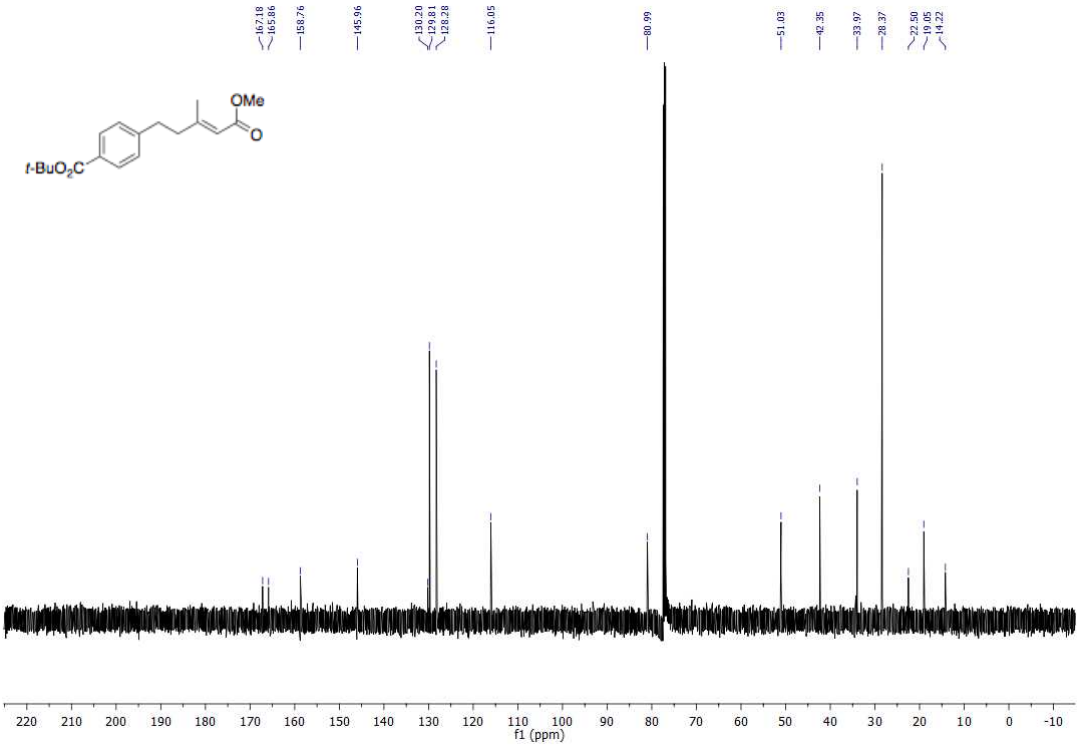
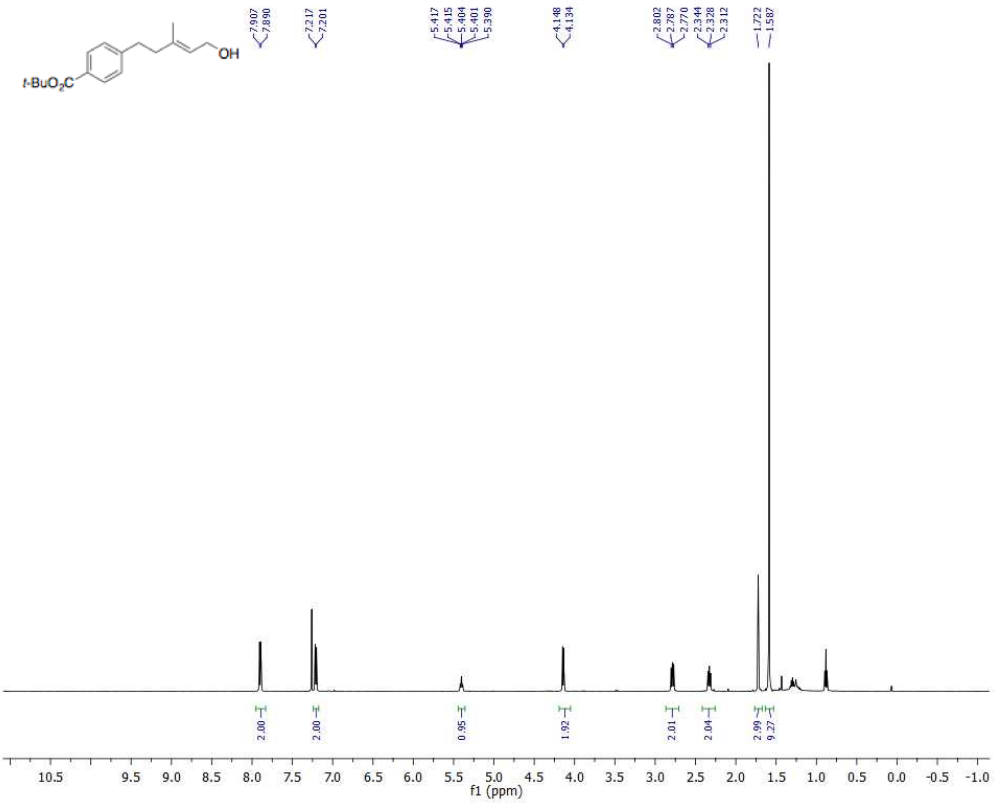
7.897
7.214
7.198
5.662
3.680
3.679
2.848
2.833
2.816
2.466
2.449
2.434
2.200
1.587
1.586
OMe
O
t-BuO2C
2.00
1.93
0.96
3.02
2.06
2.03
2.99
9.94
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


167.18
165.86
158.76
145.96
130.20
129.81
128.28
116.05
80.99
51.03
42.35
33.97
28.37
22.50
19.05
14.22
OMe
O
t-BuO2C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.890
7.217
7.201
5.417
5.415
5.404
5.401
5.390
4.148
4.134
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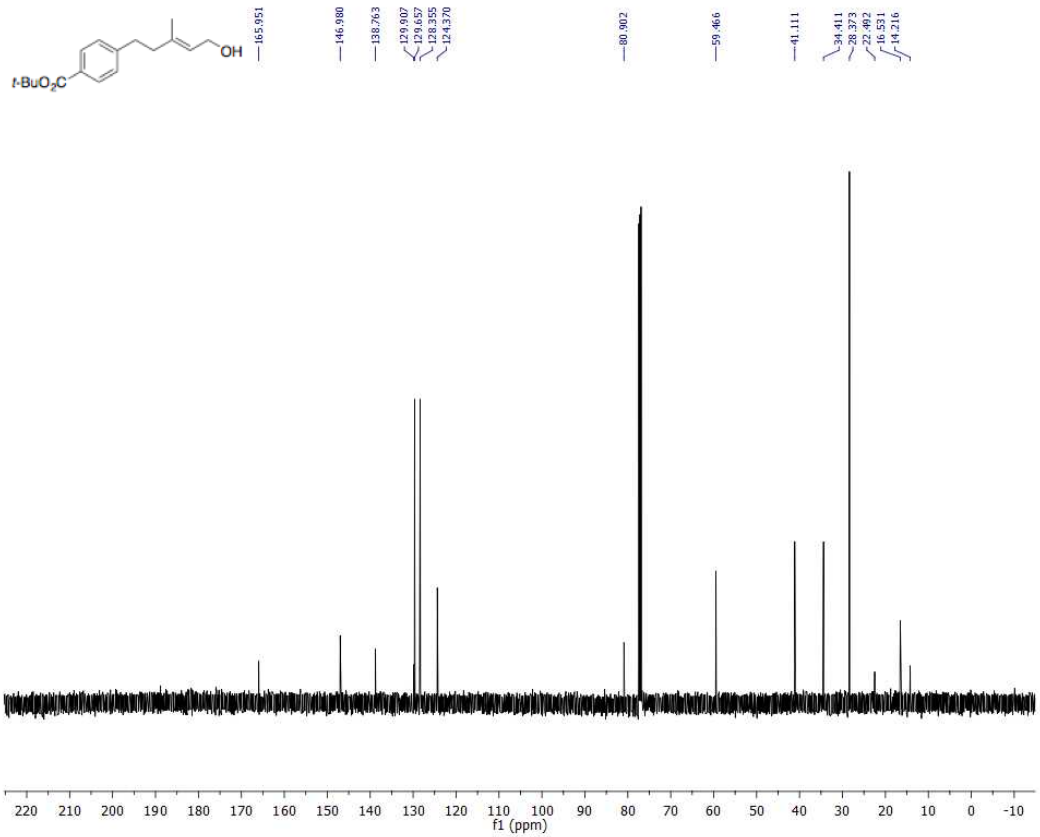
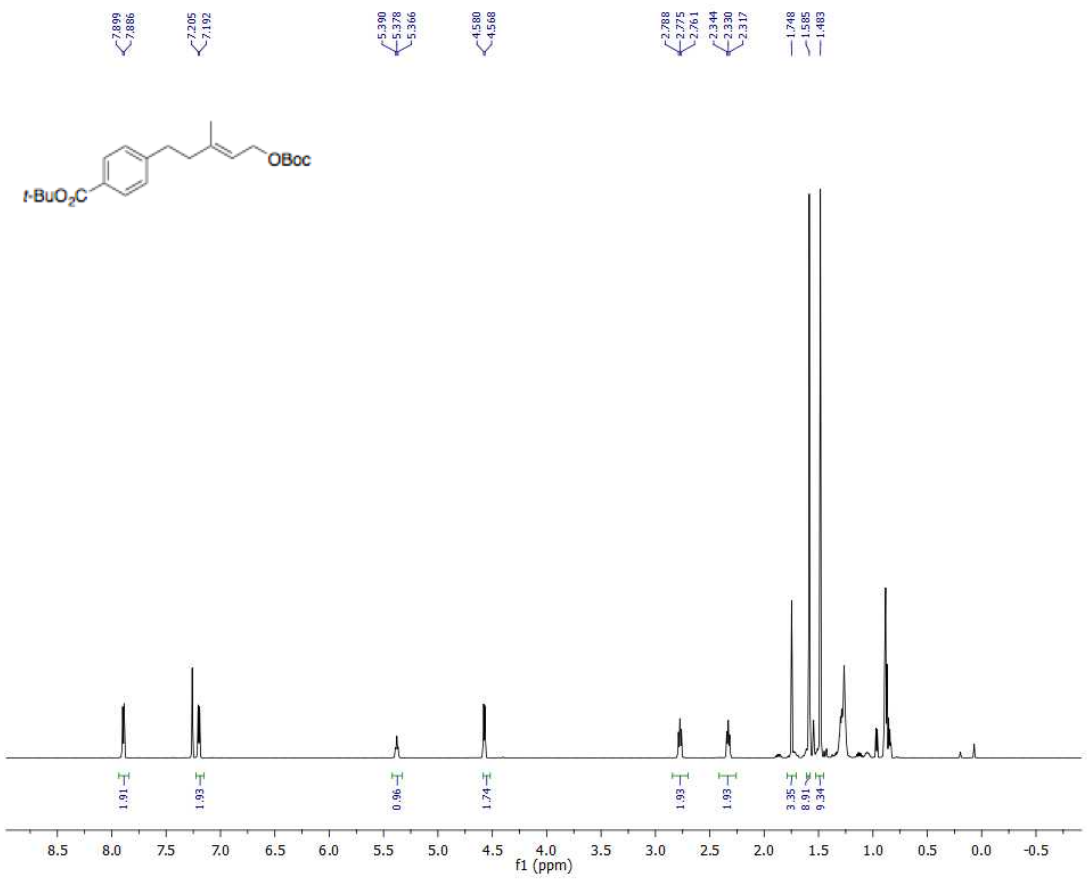
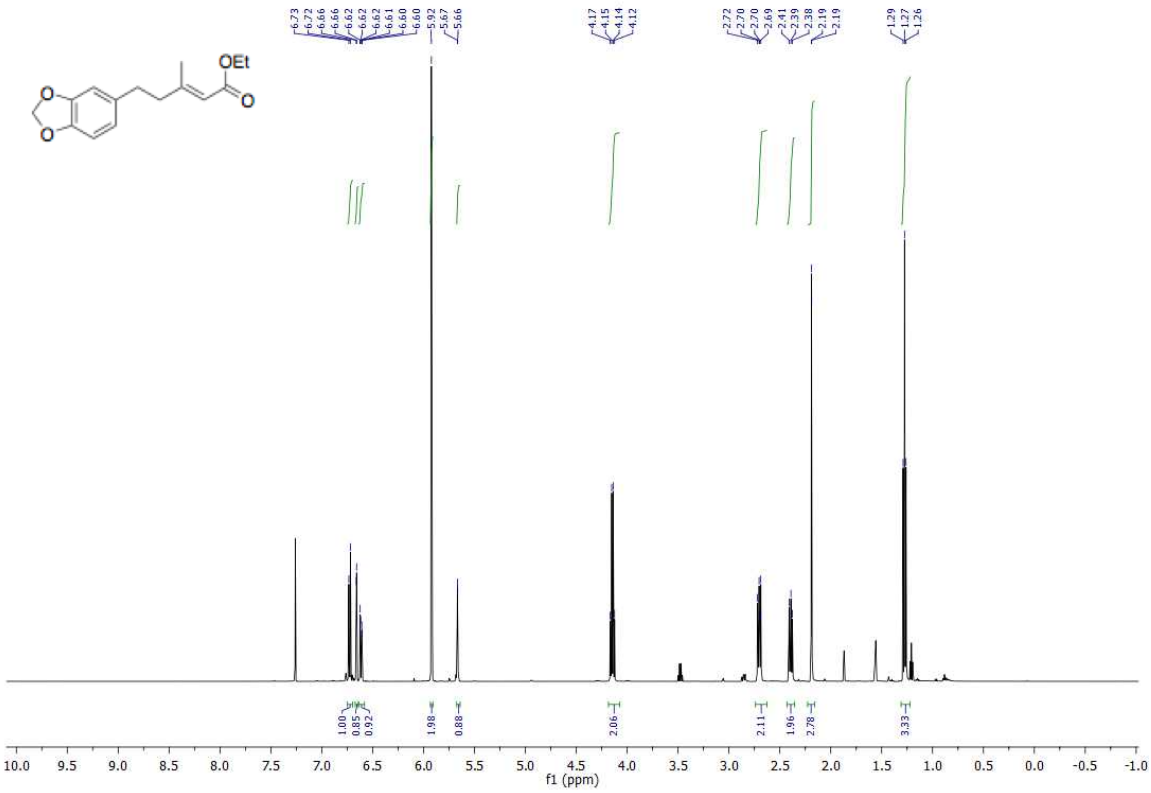
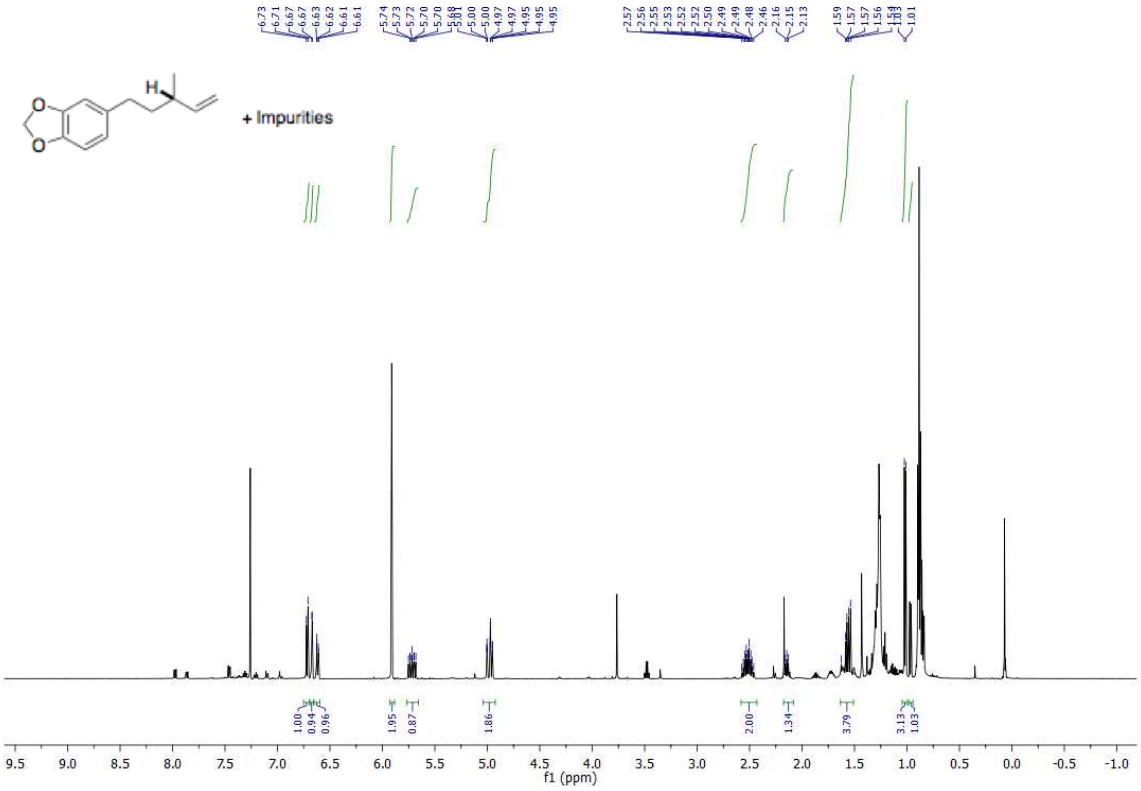
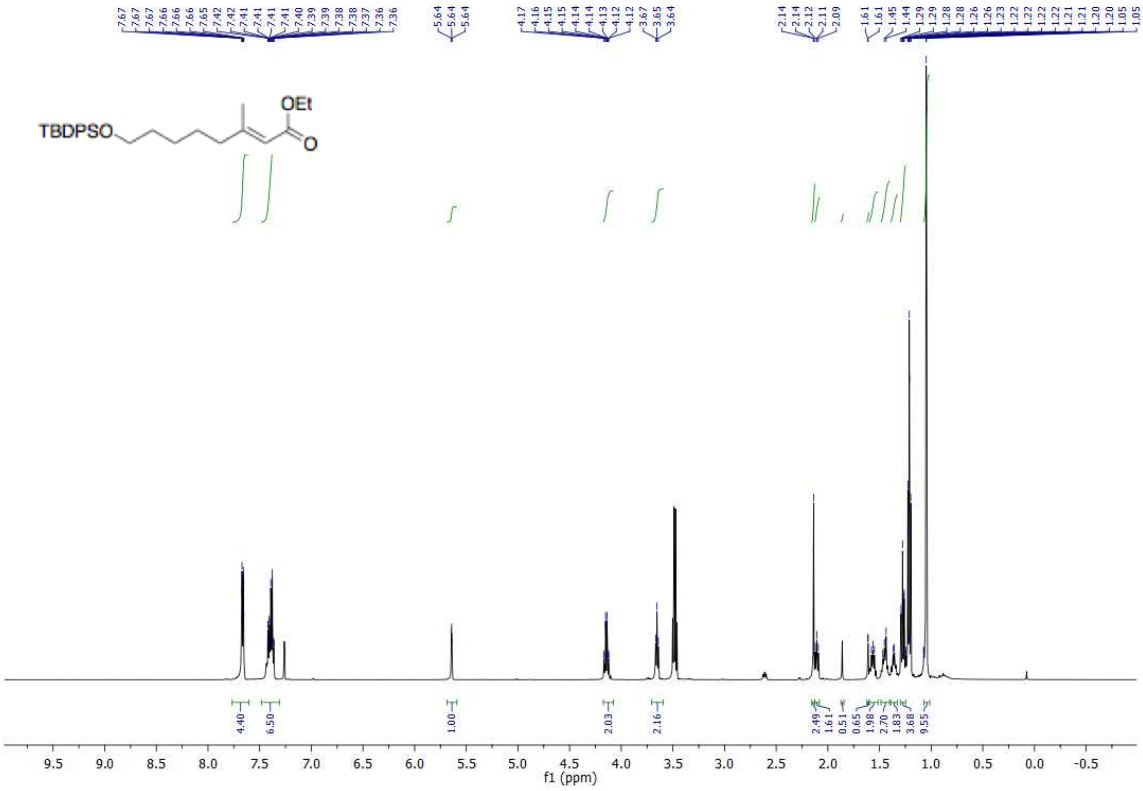
2.787
2.770
2.344
2.328
2.312
1.722
1.582
OH
t-BuO2C
2.00
2.00
0.95
1.92
2.01
2.04
2.99
9.27
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

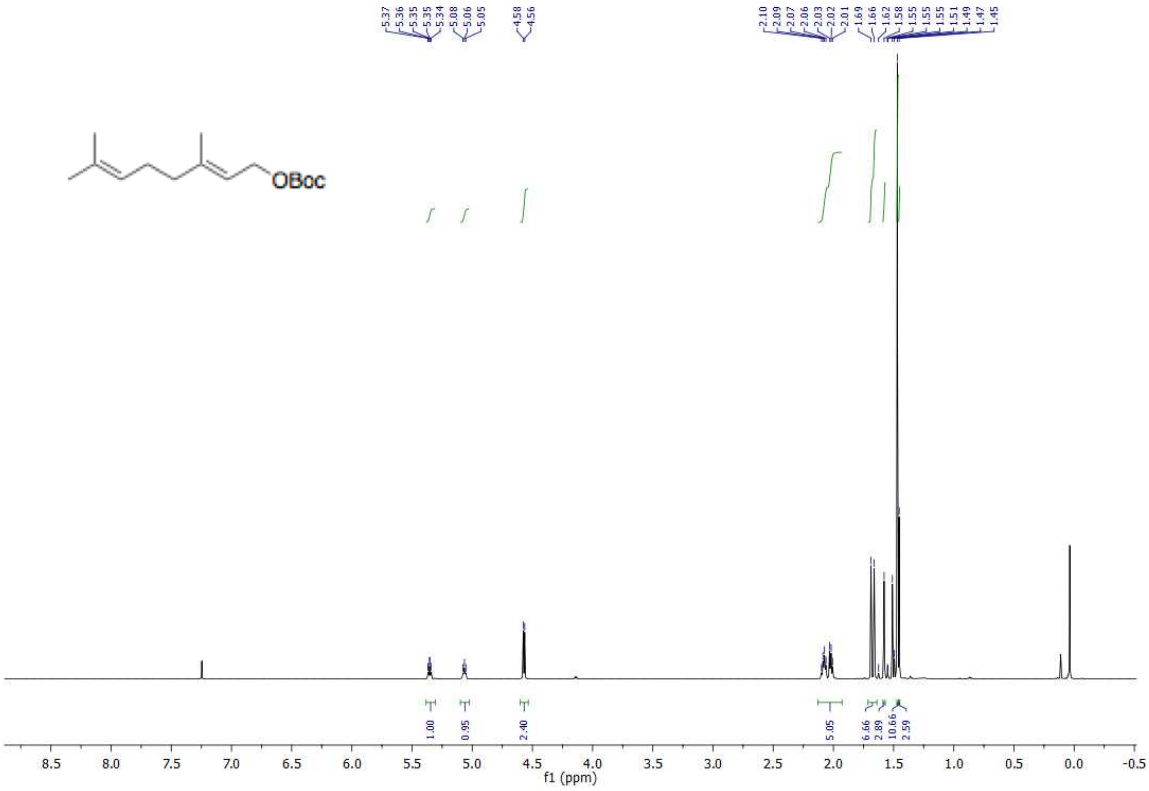

165.951
146.980
138.763
129.907
129.657
128.355
124.370
80.902
59.466
41.111
34.411
28.373
22.492
16.531
14.216
OH
t-BuO2C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

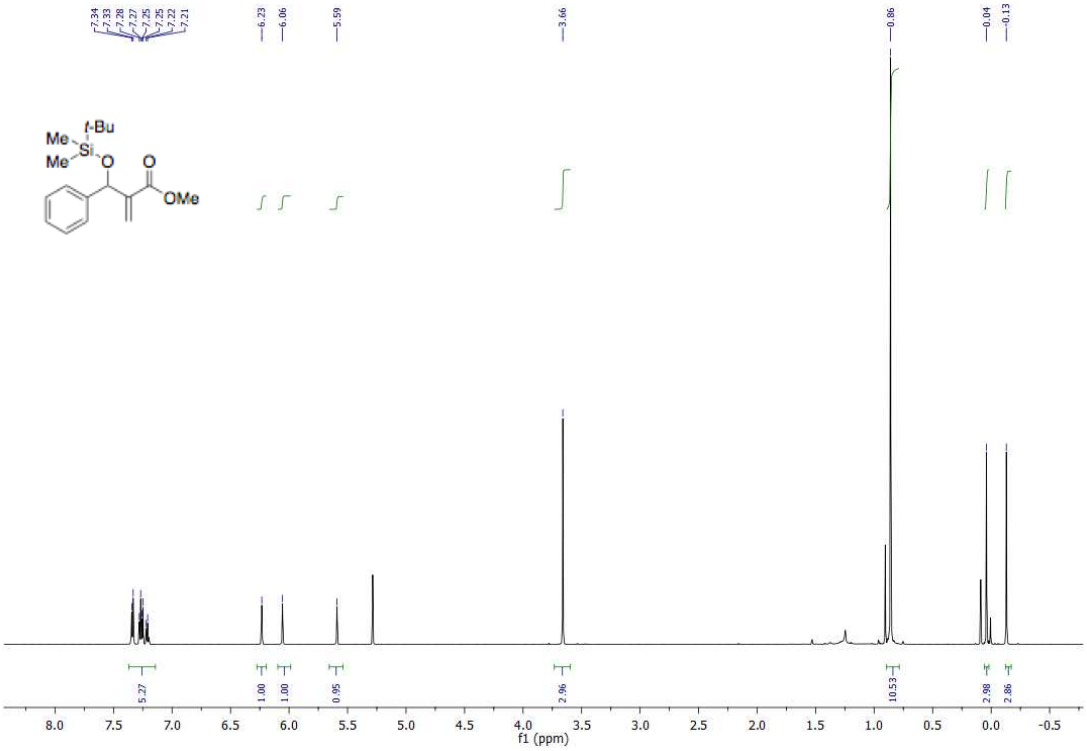

7.899
7.886
7.205
7.192
5.390
5.378
5.366
4.580
4.568
2.788
2.775
2.761
2.344
2.330
2.317
1.748
1.585
1.483
OBoc
t-BuO2C
1.91
1.93
0.96
1.74
1.93
1.93
3.35
8.91
9.34
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

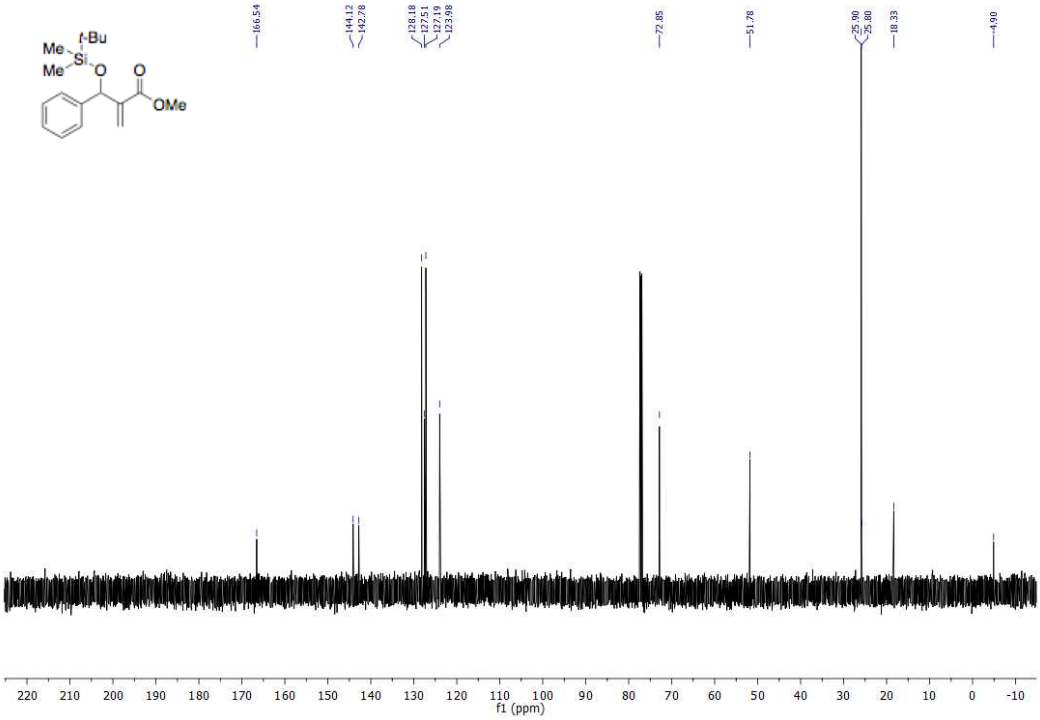

OEt
O
O
O
6.73
6.72
6.66
6.66
6.62
6.62
6.62
6.61
6.60
6.60
5.92
5.67
5.66
4.17
4.15
4.14
4.12
2.72
2.70
2.70
2.69
2.41
2.39
2.38
2.19
2.19
1.29
1.27
1.26
1.00
0.85
0.92
1.98
0.88
2.06
2.11
1.96
2.78
3.33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

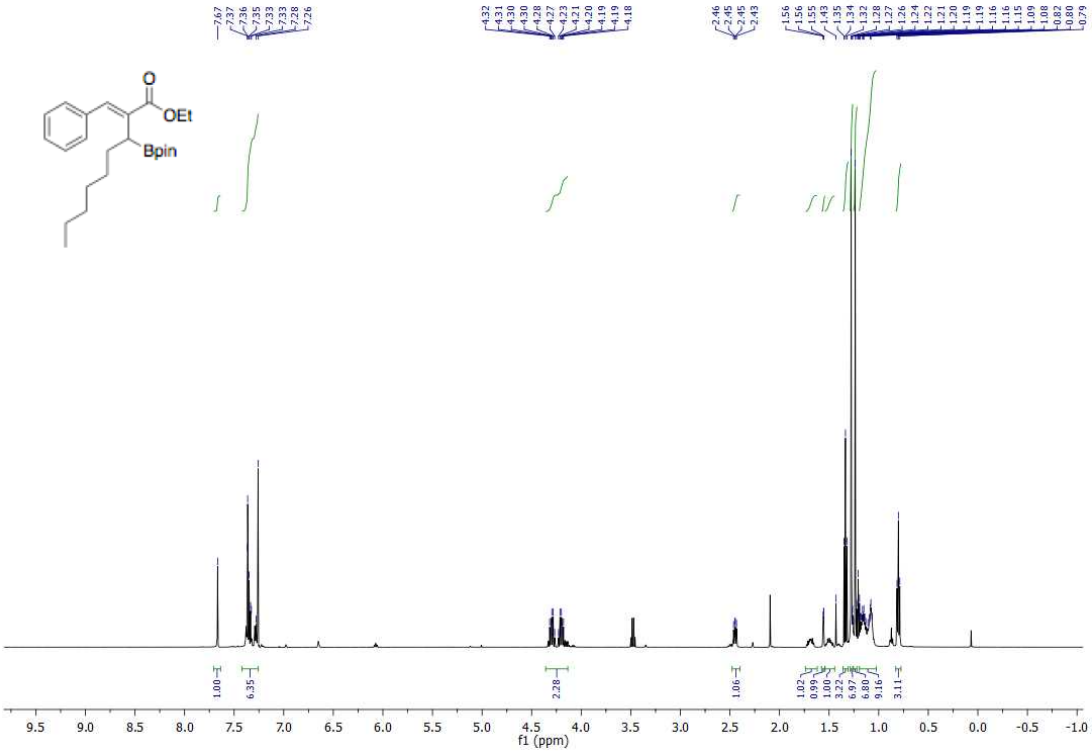

+ Impurities
f1 (ppm)

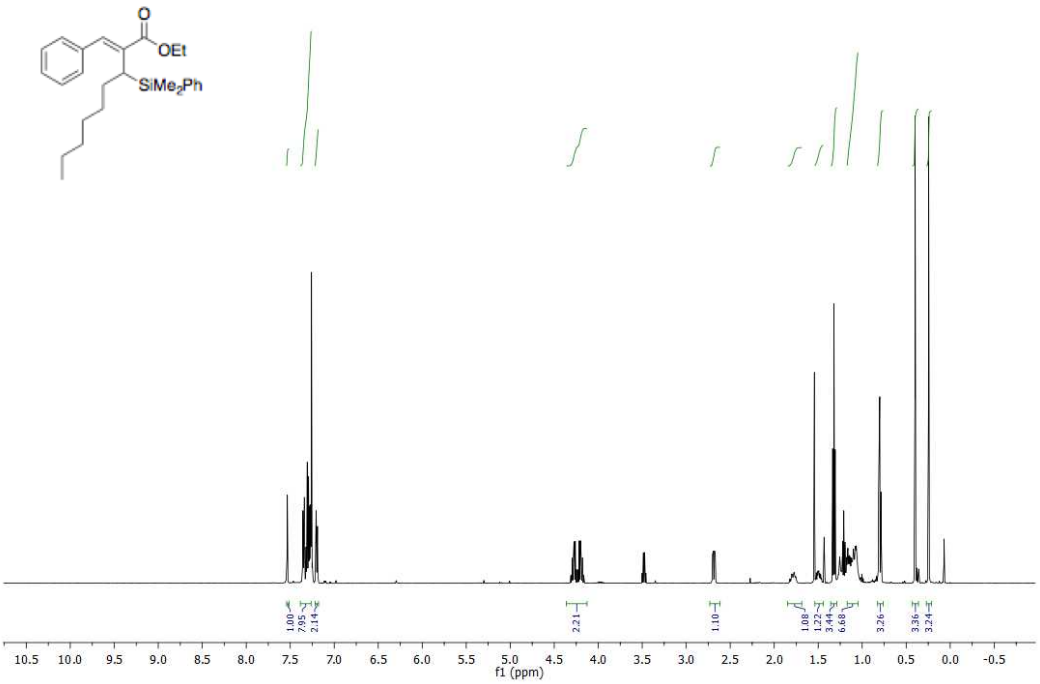

TBDPSO
OEt
O
f1 (ppm)

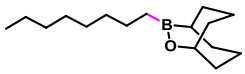

OBoc
5.37
5.36
5.35
5.35
5.34
5.08
5.06
5.05
4.58
4.56
2.10
2.09
2.07
2.06
2.03
2.02
2.01
1.69
1.66
1.62
1.58
1.55
1.55
1.55
1.51
1.49
1.47
1.45
1.00
0.95
2.40
5.05
6.66
2.89
10.66
2.59
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

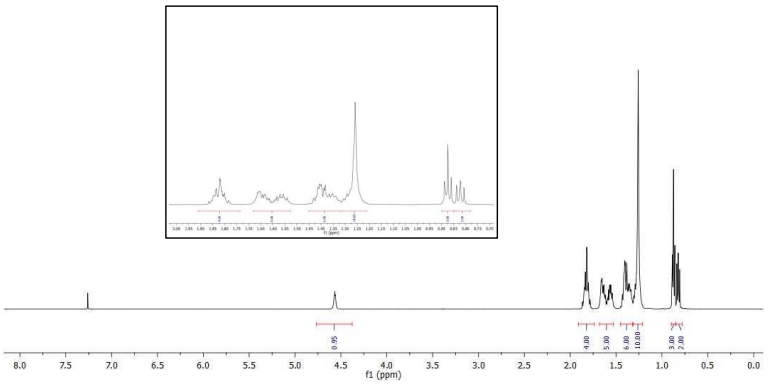

7.34
7.33
7.28
7.27
7.25
7.25
7.22
7.21
6.23
6.06
5.99
3.66
0.86
0.04
0.13
t-Bu
Me
Si
Me
O
O
OMe
5.27
1.00
1.00
0.95
2.96
10.53
2.98
2.86
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


166.54
144.12
142.78
128.18
127.51
127.19
125.98
72.05
51.78
25.90
25.80
18.33
-4.90
t-Bu
Me
Si
Me
O
O
OMe
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
OEt
Bpin
f1 (ppm)


O
OEt
SiMe2Ph
f1 (ppm)


B
O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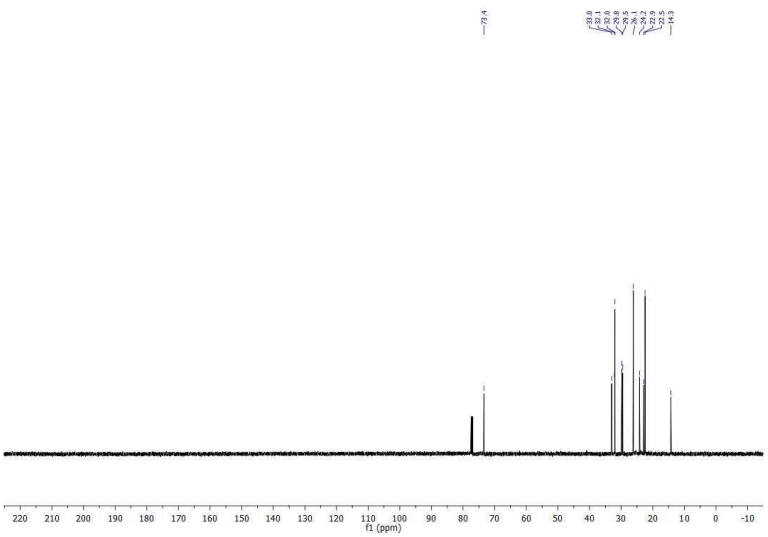
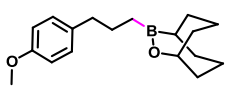
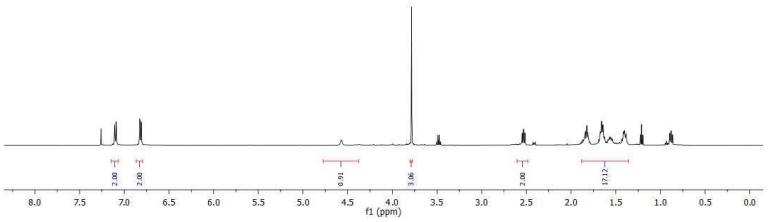
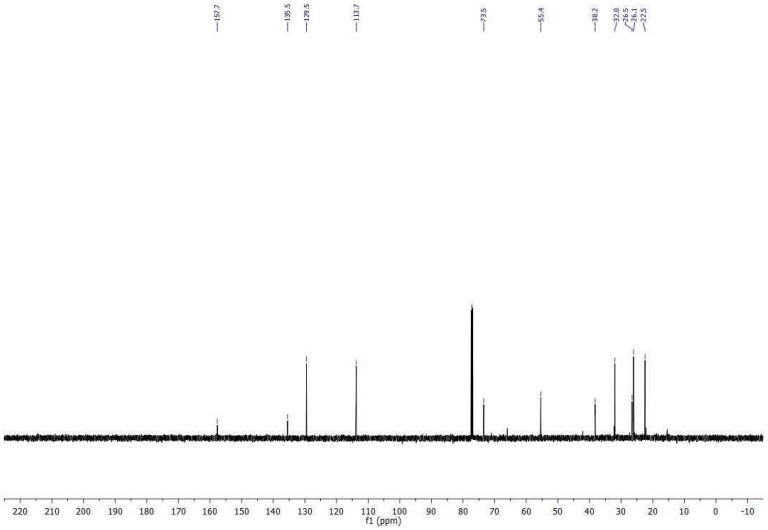
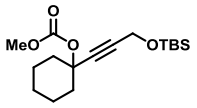
4.00
5.00
6.00
10.00
3.00
2.00
f1 (ppm)

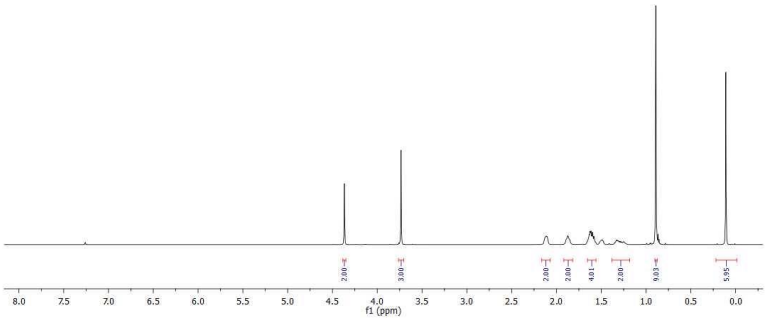

79.4
33.0
32.1
32.0
30.8
29.5
26.1
24.2
23.9
23.5
14.4
f1 (ppm)

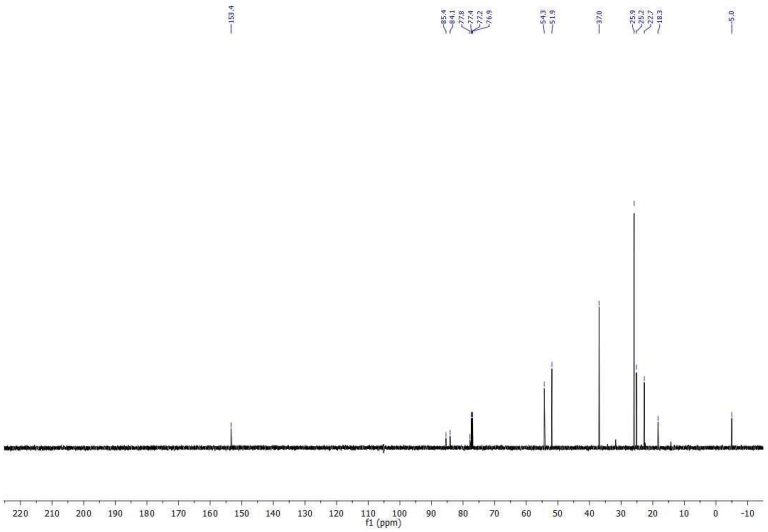

B
O
O

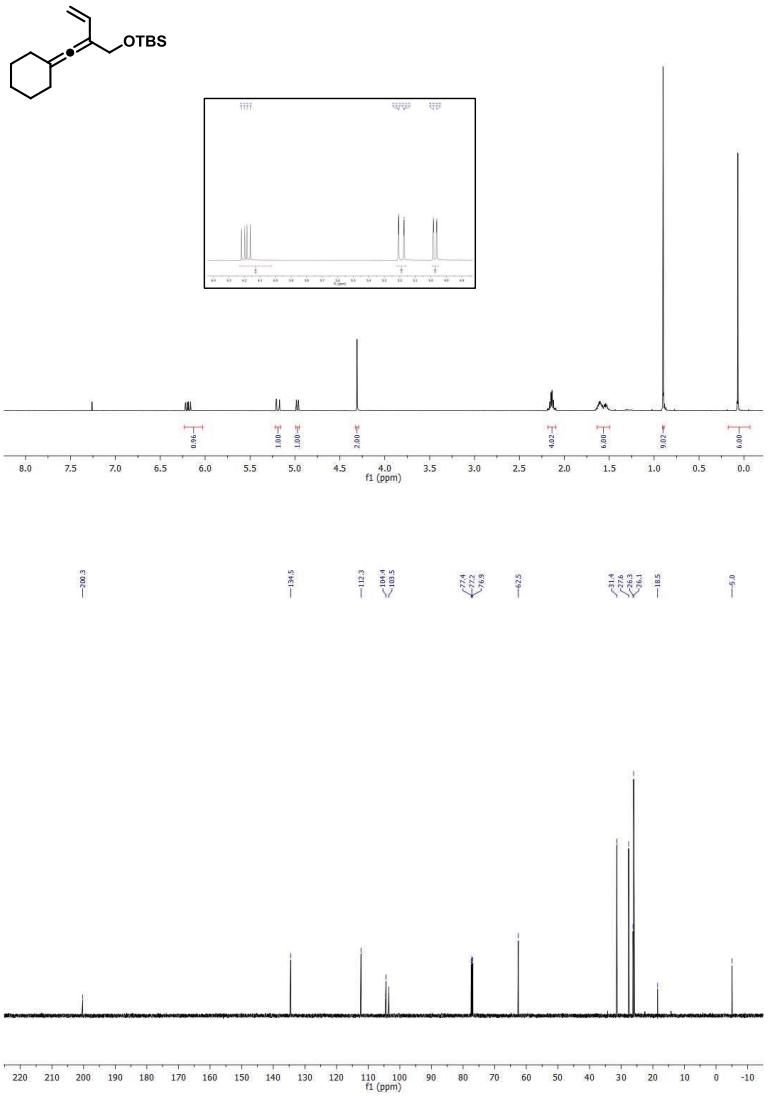

2.00
2.00
0.91
3.00
2.00
17.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

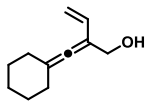

157.7
135.5
129.5
113.7
73.5
55.4
38.2
32.8
26.5
26.1
22.5
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

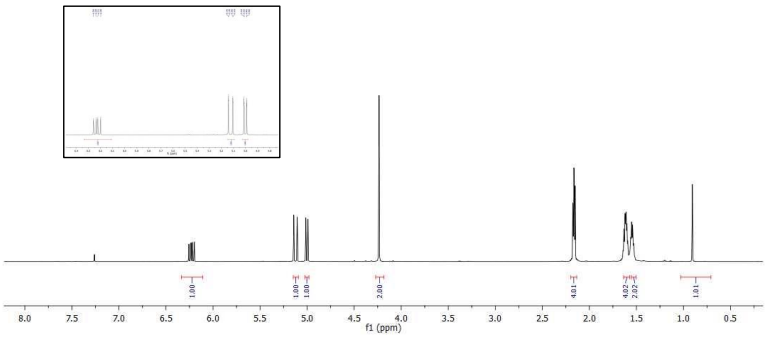

MeO
O
O
OTBS

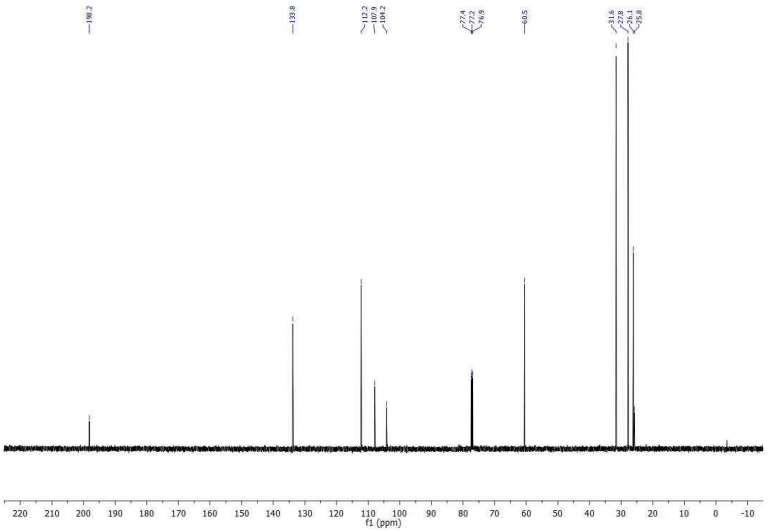

2.00
3.00
2.00
2.00
4.01
2.00
9.03
5.95
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

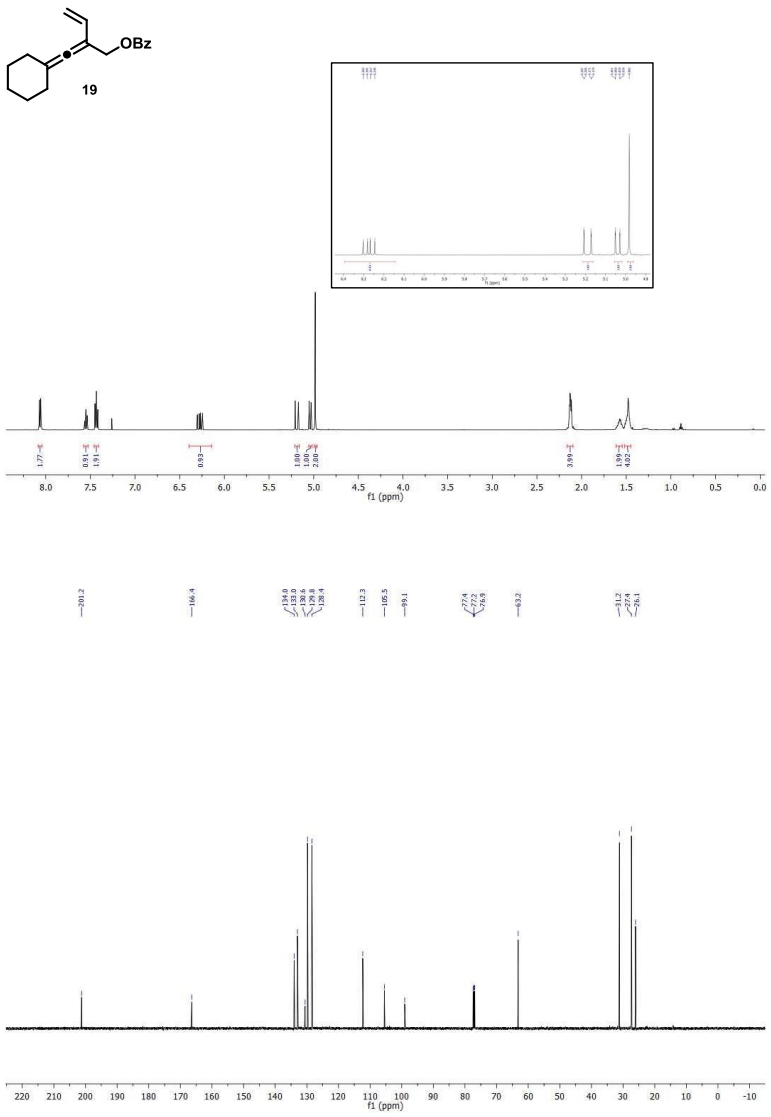

153.4
85.4
84.1
77.8
77.4
77.2
76.6
54.3
51.9
37.0
25.9
25.2
22.7
18.3
-5.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

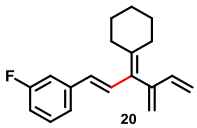

OTBS
0.96
1.00
1.00
2.00
4.02
6.00
9.02
6.00
f1 (ppm)
200.3
134.5
112.3
108.4
103.5
77.4
77.2
76.9
62.5
31.4
29.6
29.5
26.1
18.5
-5.0
f1 (ppm)


OH

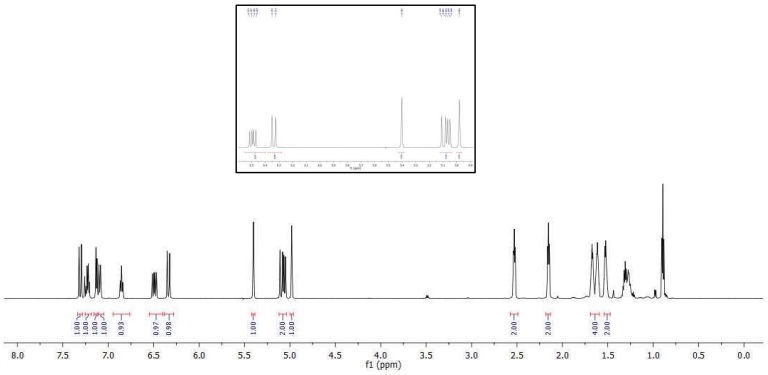

1.00
1.00
1.00
2.00
4.01
4.02
2.02
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

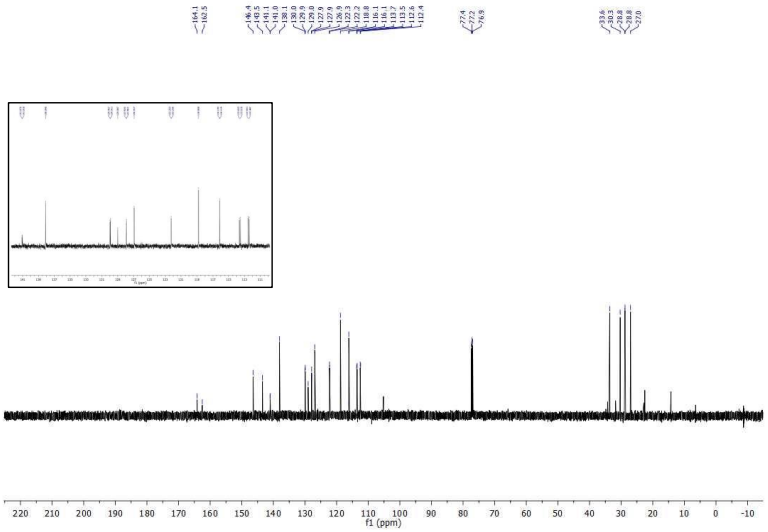

198.2
133.8
112.2
107.9
104.2
77.4
77.2
76.9
60.5
31.6
29.8
29.1
25.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

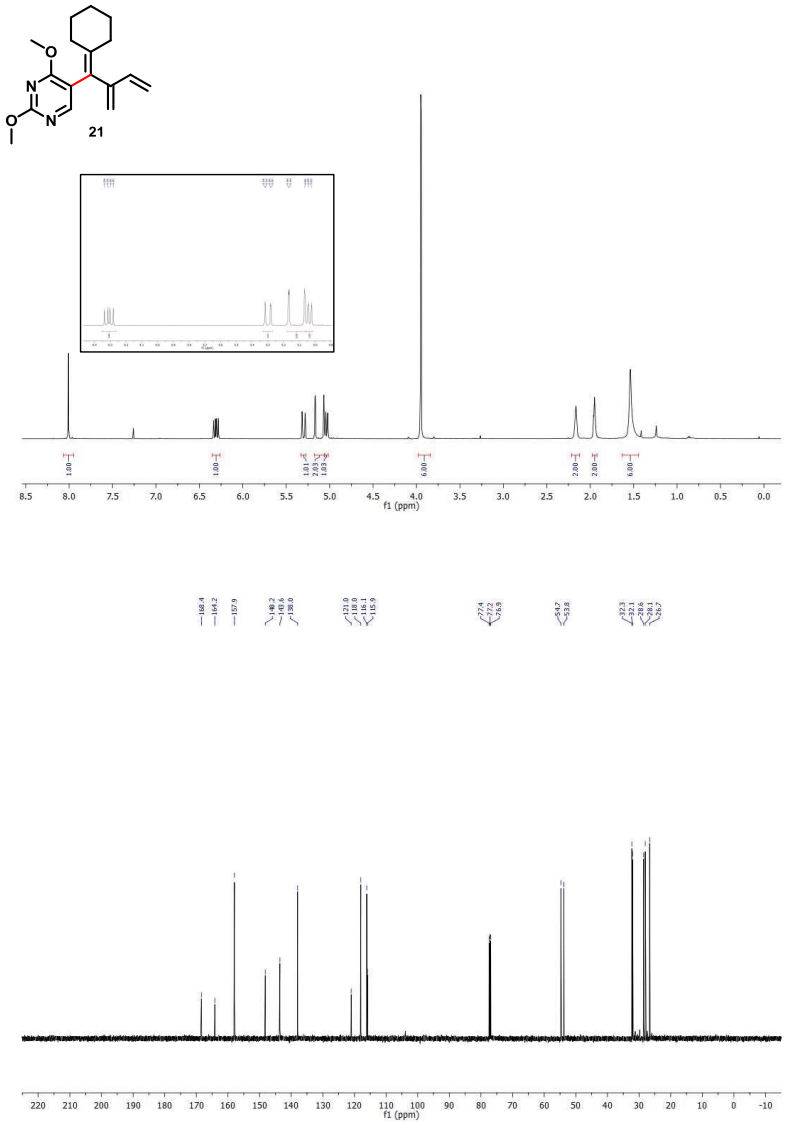

OBz
19
f1 (ppm)
f1 (ppm)


F

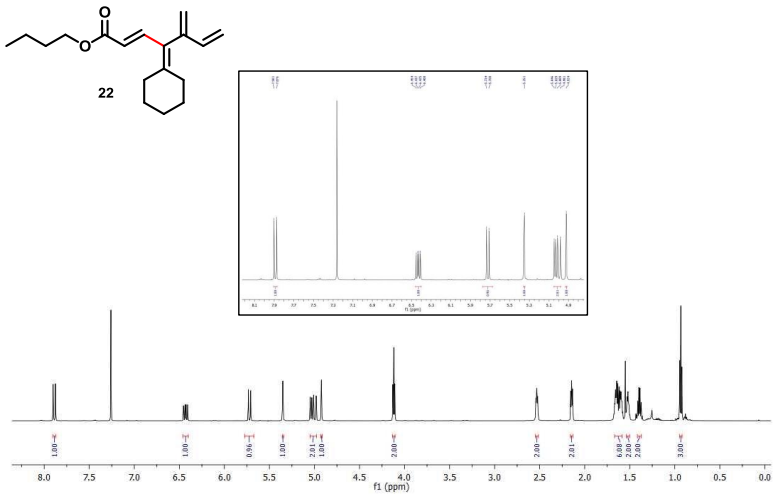
20

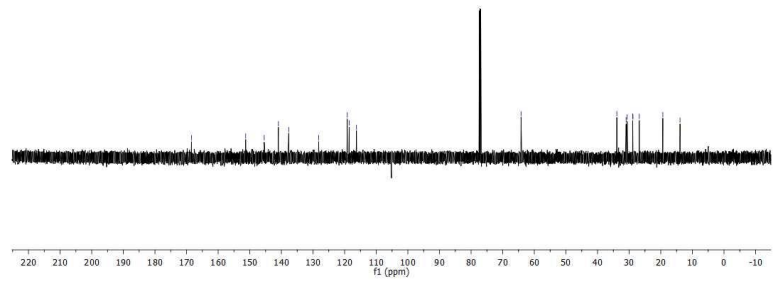

1.00
1.00
1.00
1.00
0.91
0.67
0.86
1.00
2.00
1.00
2.00
2.00
4.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

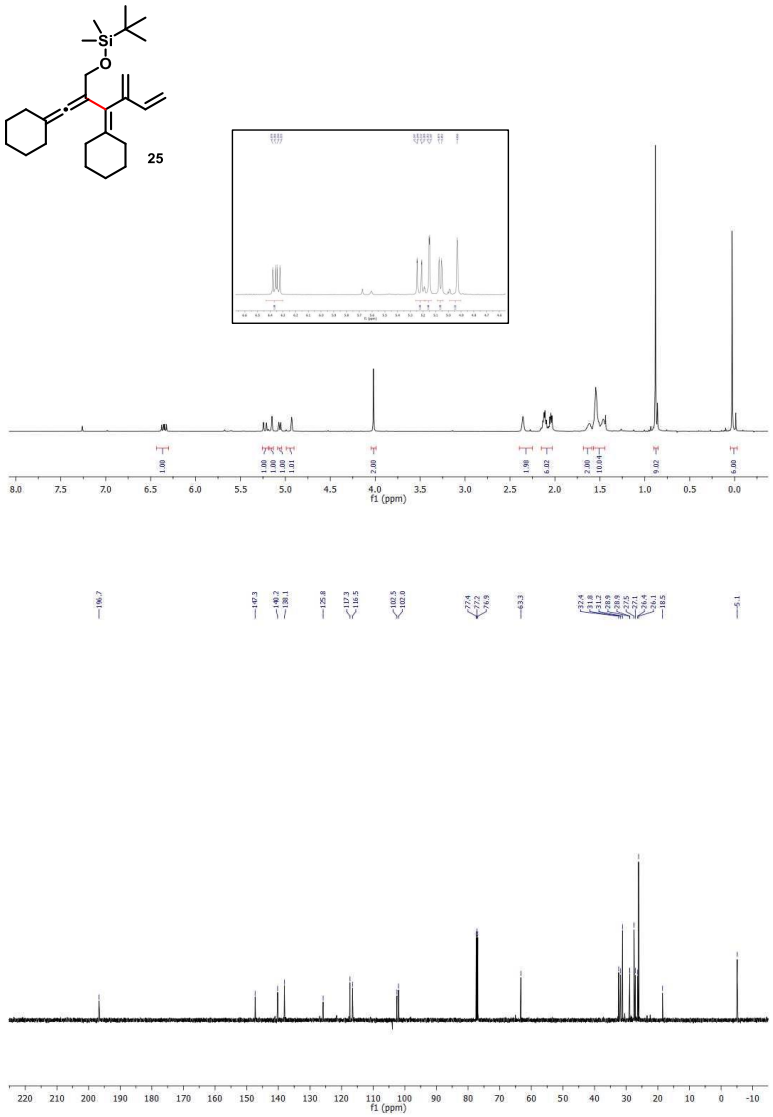

164.1
162.5
146.4
140.5
141.1
141.0
138.1
138.0
129.9
129.8
127.9
127.2
125.9
125.3
122.2
119.8
116.1
116.0
113.5
112.6
112.4
77.4
77.2
76.9
33.6
30.3
28.8
28.8
27.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

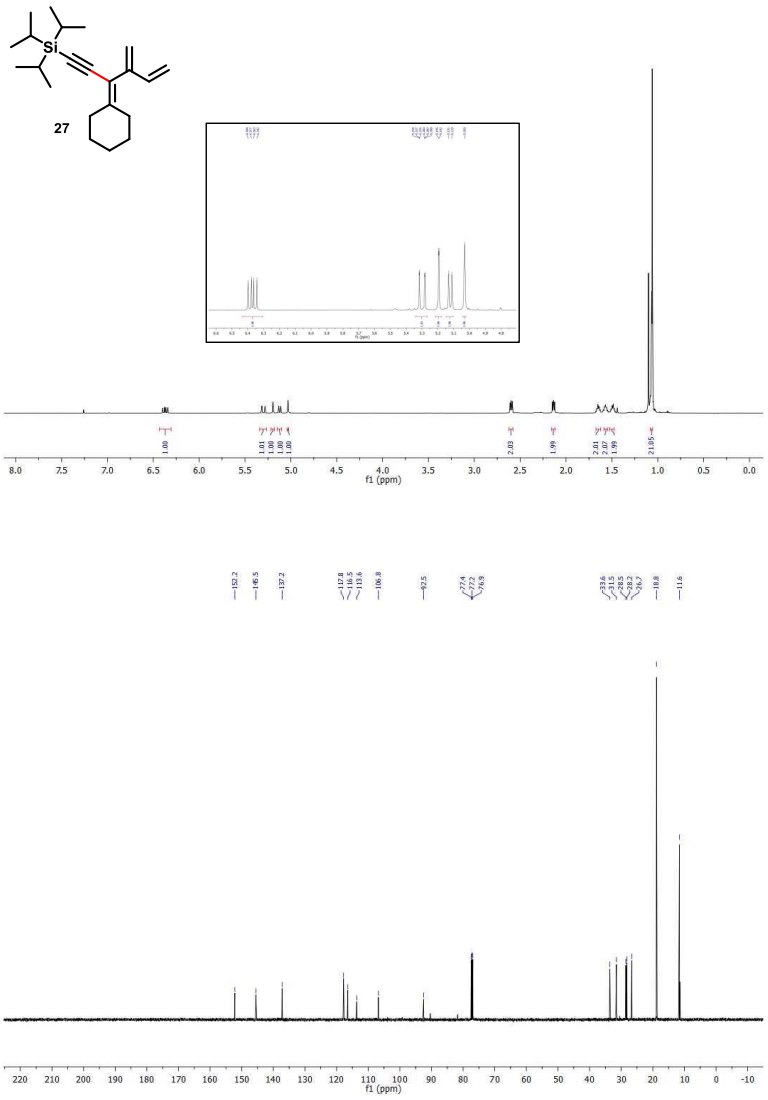


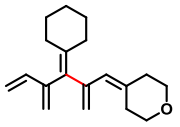
S182


22
f1 (ppm)

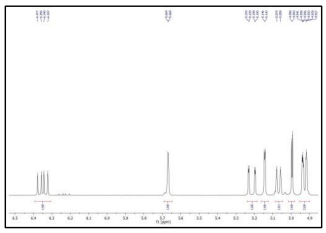

f1 (ppm)

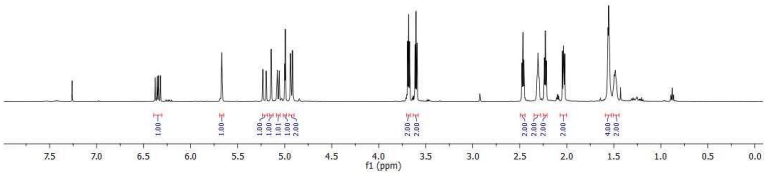

Si
O
25
f1 (ppm)

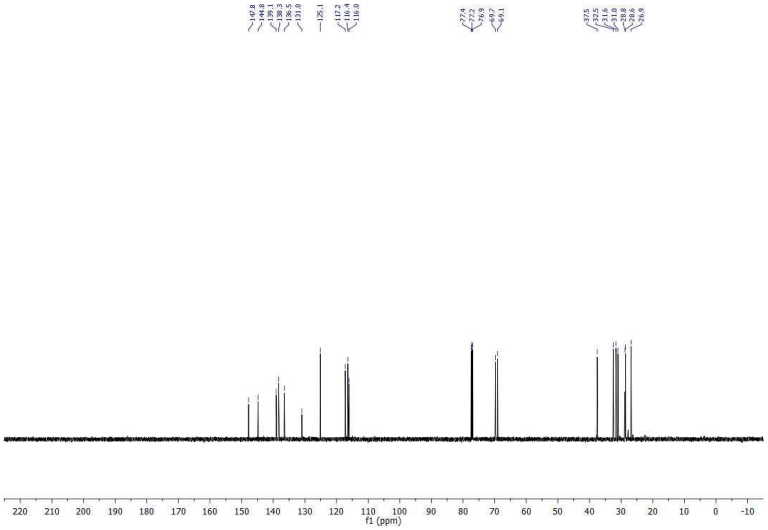

27
Si
f1 (ppm)
f1 (ppm)

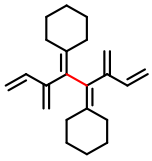


23

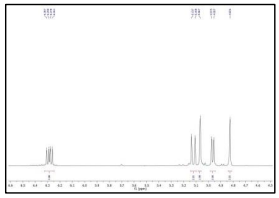


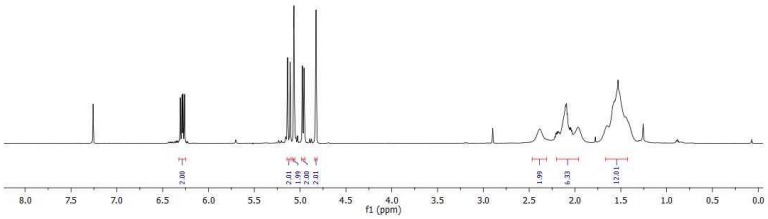




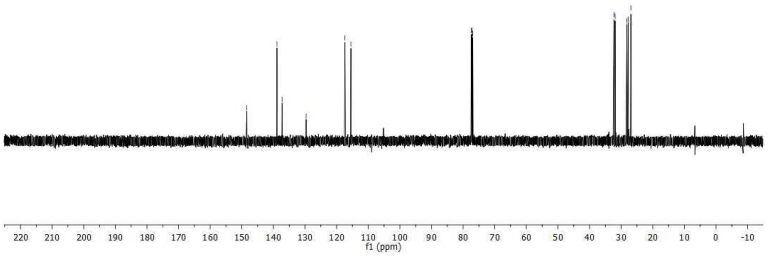


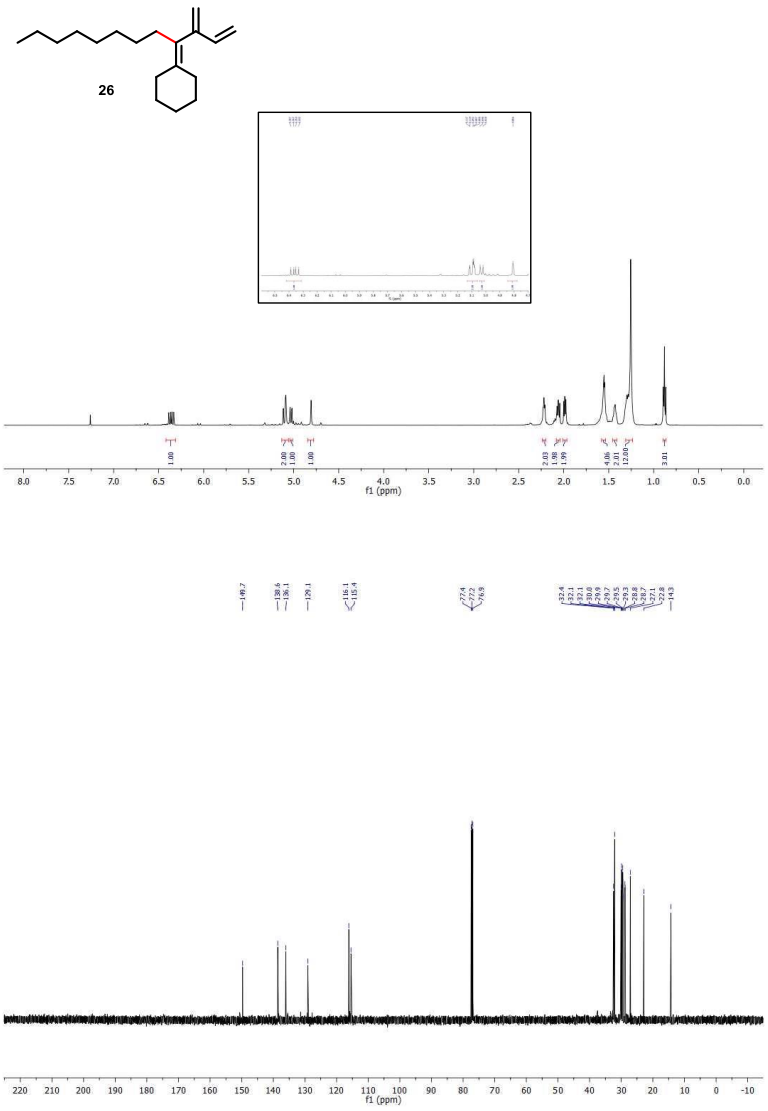
24

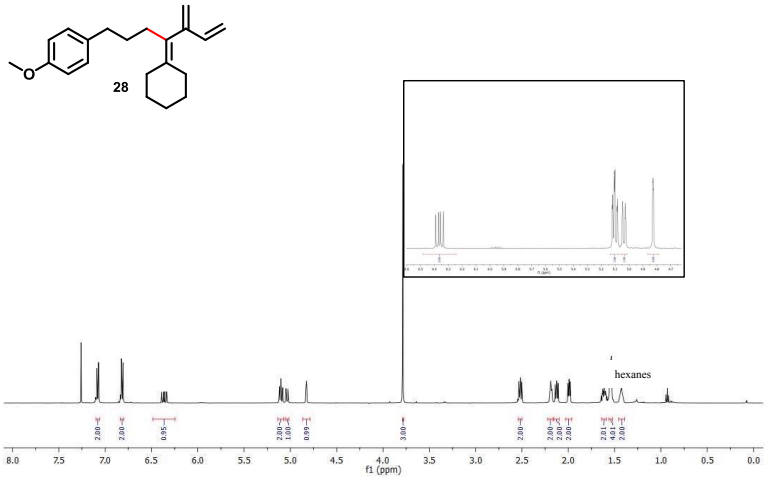


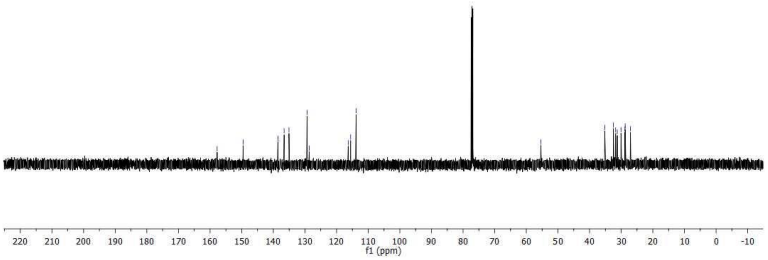

2.00
2.01
1.00
1.98
2.01
1.99
6.33
12.01
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

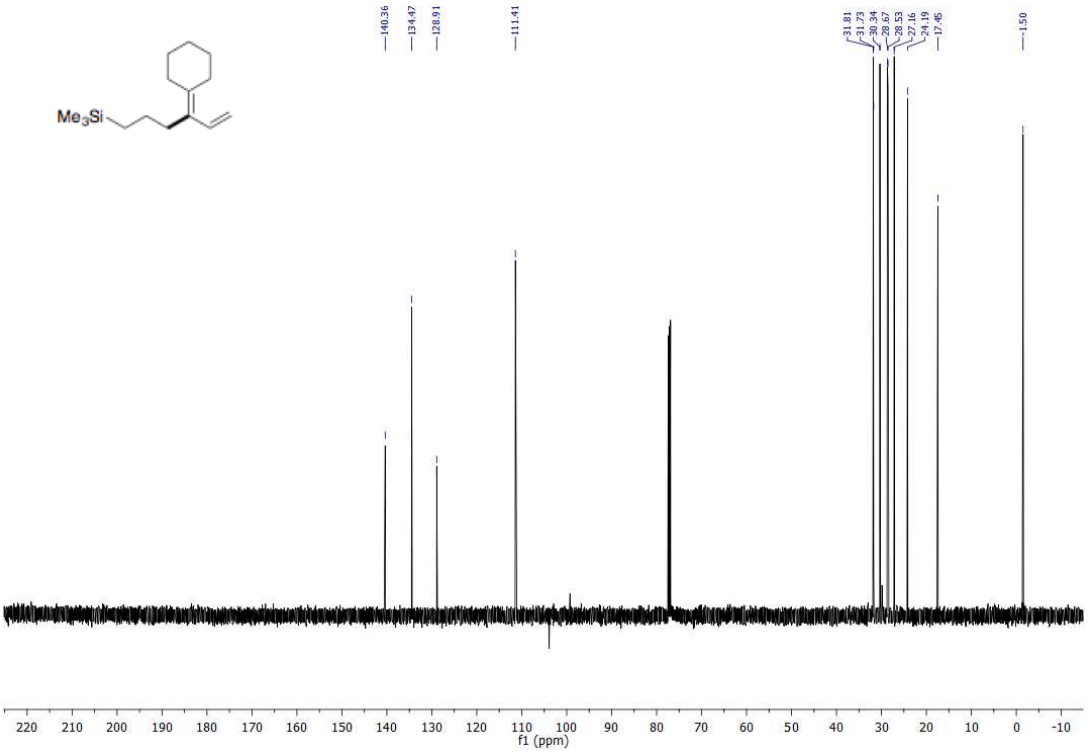

148.4
138.9
137.3
129.7
117.4
115.5
77.4
77.2
76.9
32.3
31.9
28.2
26.8
26.9

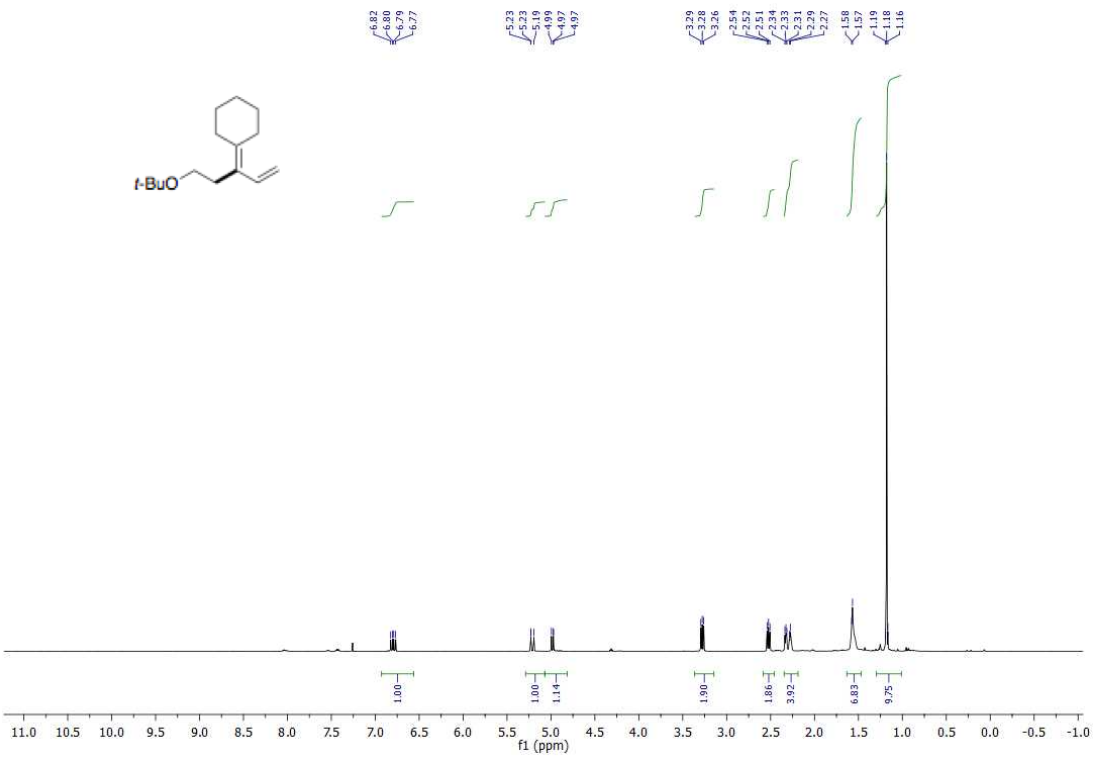

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

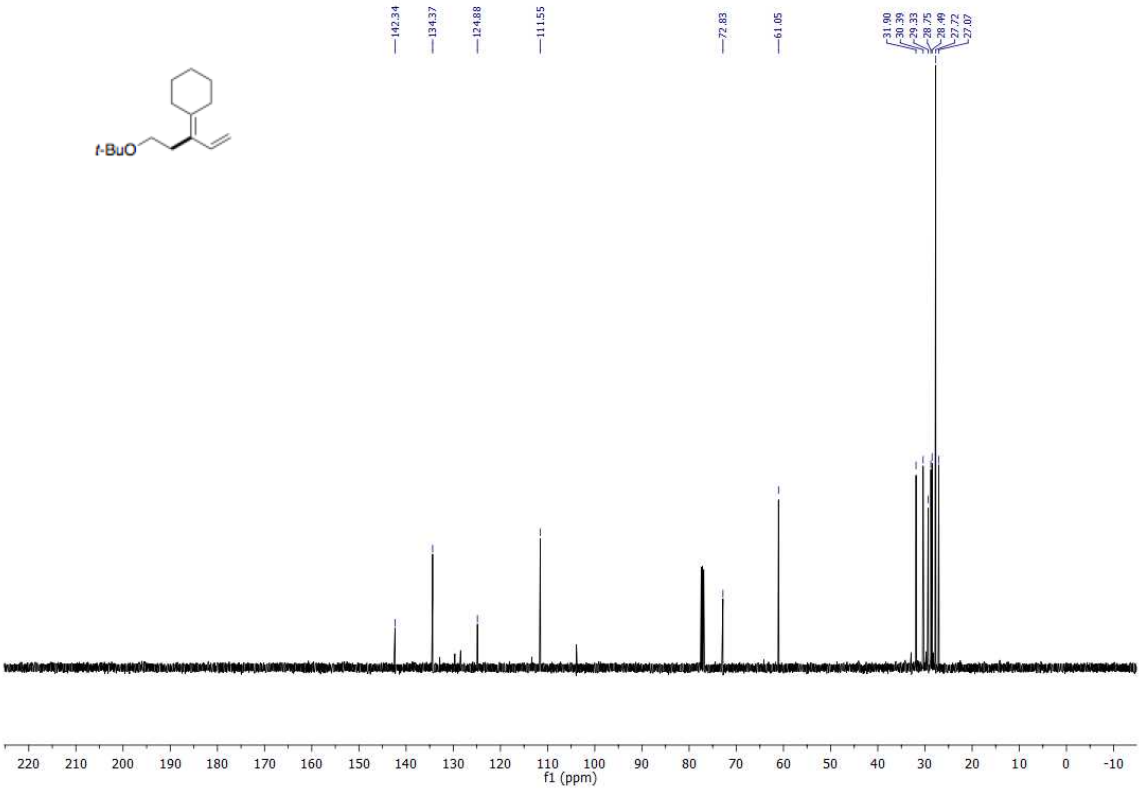

26
f1 (ppm)
f1 (ppm)

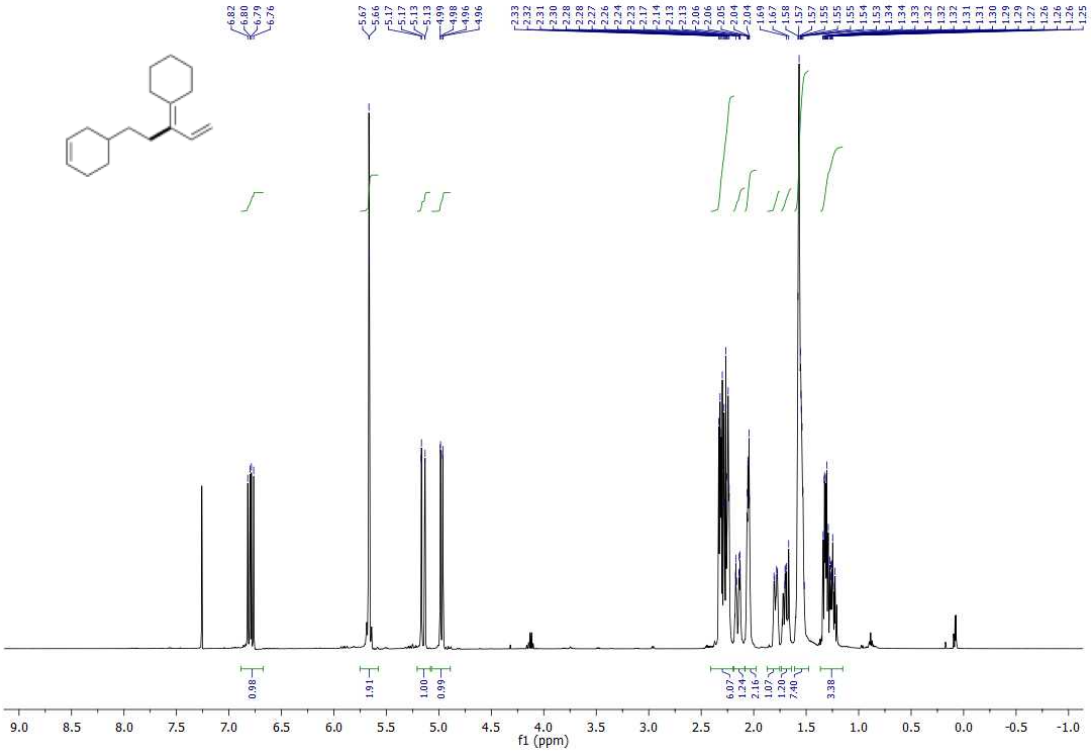

28
hexanes
f1 (ppm)

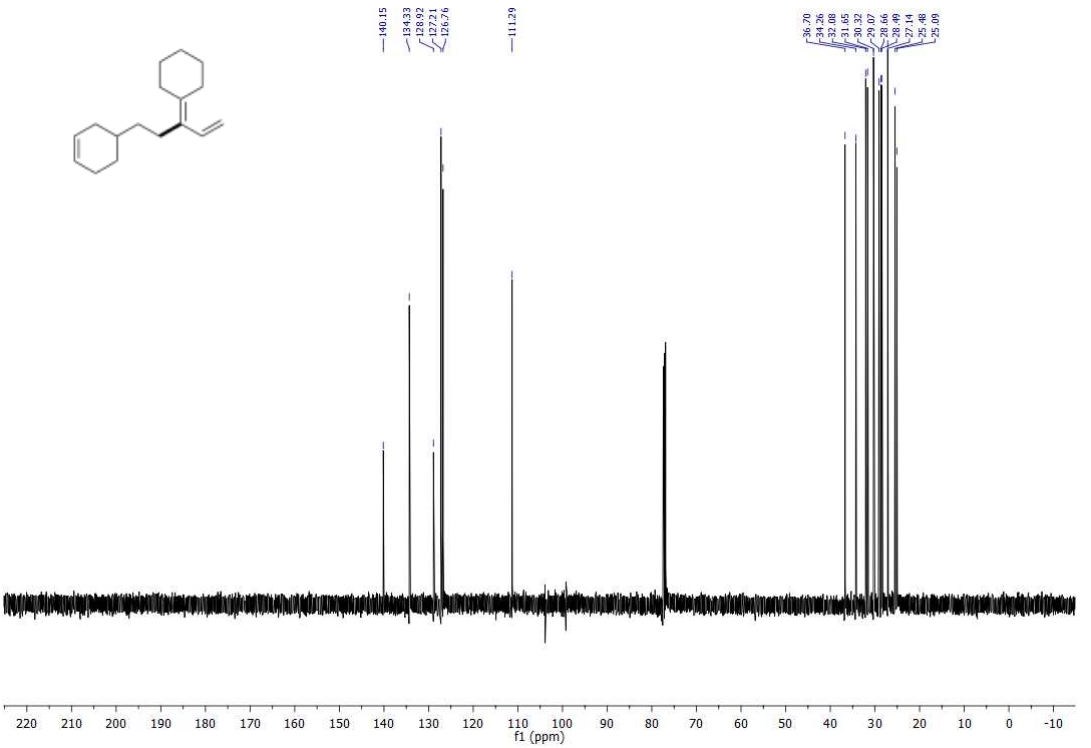

f1 (ppm)

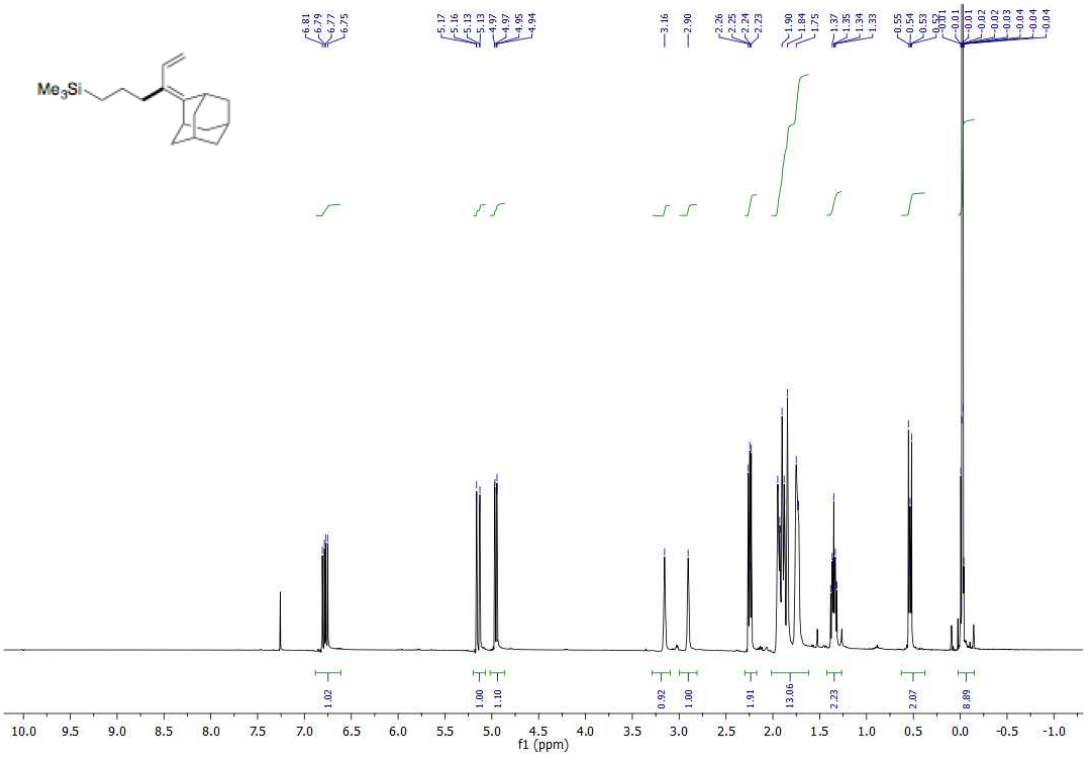

Me3Si
140.36
134.47
128.91
111.41
31.81
31.73
30.34
28.67
28.53
27.16
24.19
17.46
1.50
f1 (ppm)

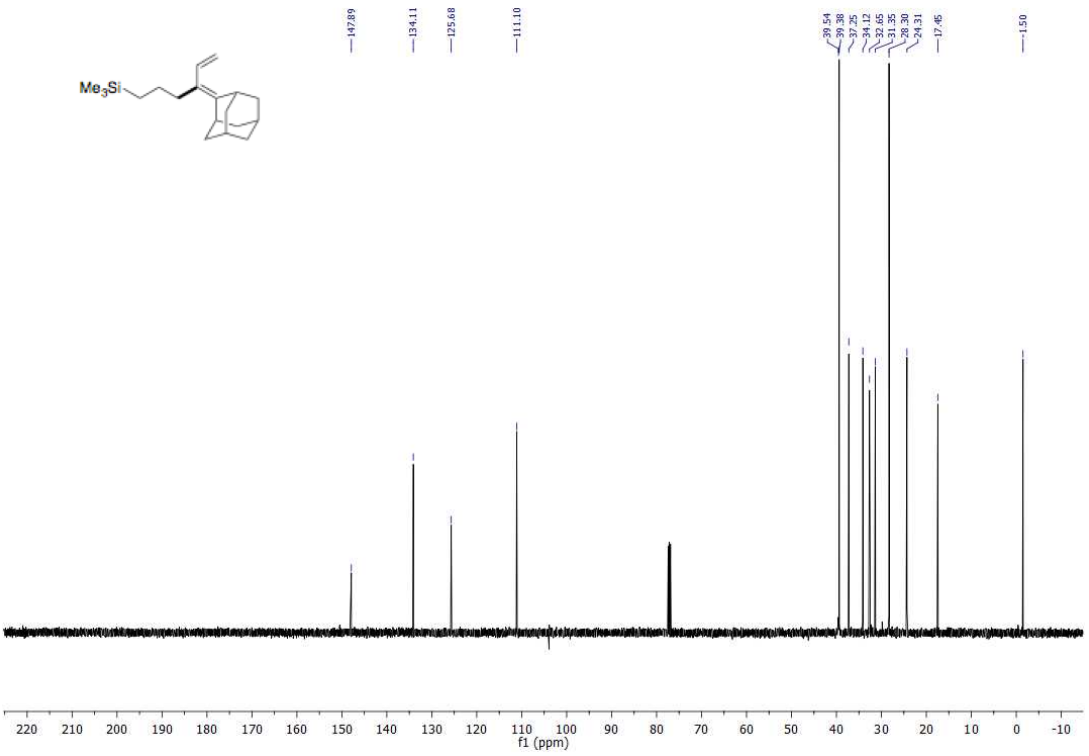

t-BuO
6.82
6.80
6.79
6.77
5.23
5.23
5.19
4.99
4.97
4.97
3.29
3.28
3.26
2.54
2.52
2.51
2.34
2.33
2.31
2.29
2.27
1.58
1.57
1.19
1.18
1.16
1.00
1.00
1.14
1.90
1.86
3.92
6.83
9.25
f1 (ppm)

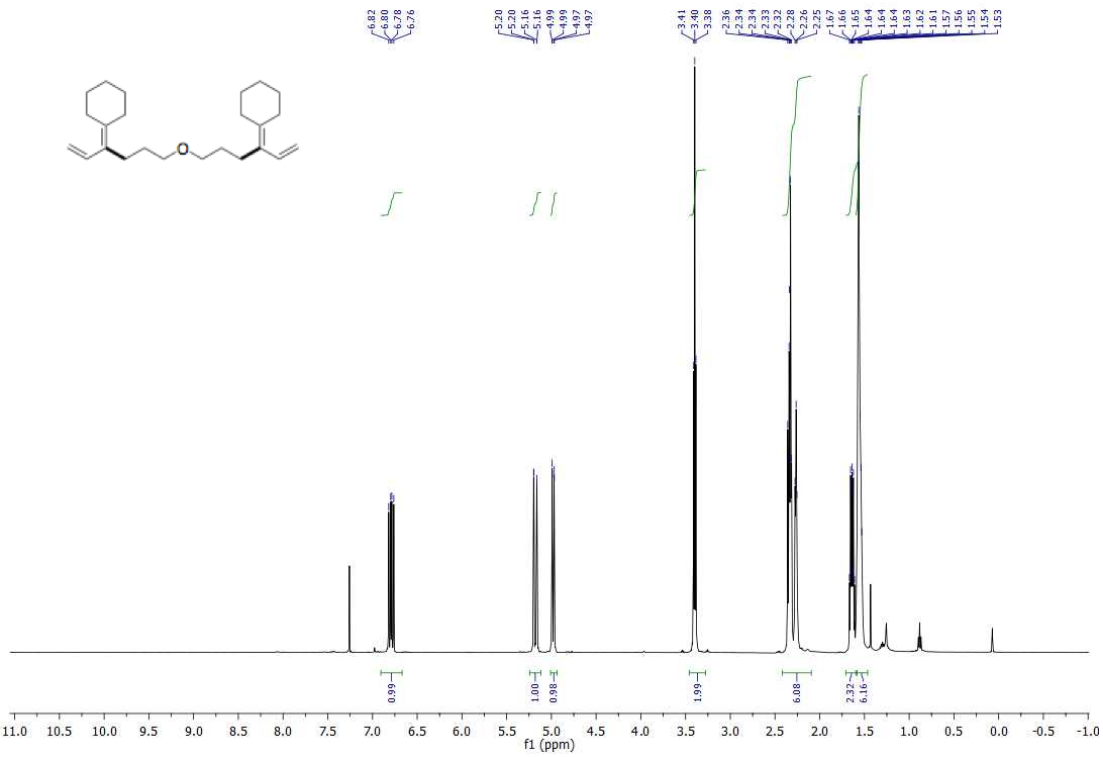

t-BuO
142.34
134.37
124.88
111.55
72.83
61.05
31.90
30.39
29.33
28.75
28.49
27.72
27.07
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

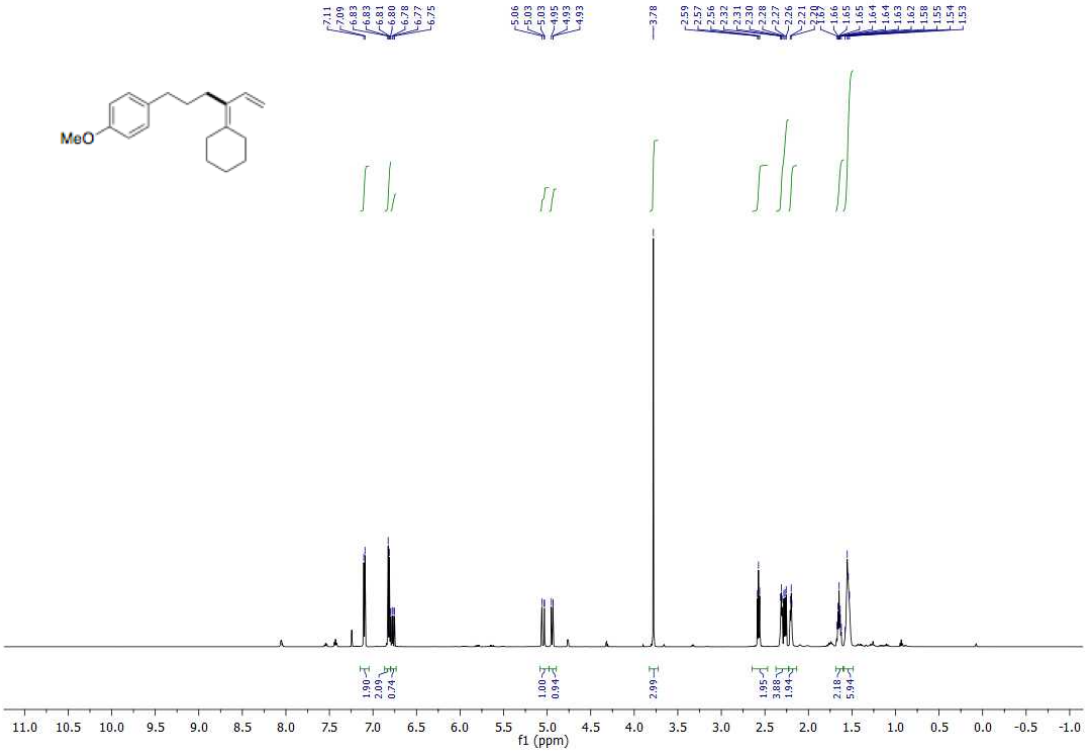

6.82
6.80
6.79
6.76
5.67
5.66
5.17
5.13
4.99
4.98
4.96
4.96
2.33
2.32
2.31
2.30
2.28
2.28
2.27
2.26
2.24
2.23
2.17
2.14
2.13
2.06
2.06
2.05
2.04
2.04
1.69
1.67
1.58
1.57
1.55
1.55
1.55
1.54
1.53
1.34
1.34
1.33
1.32
1.32
1.32
1.31
1.31
1.30
1.29
1.29
1.27
1.26
1.26
1.25
0.98
1.91
1.00
0.99
6.07
1.94
2.14
1.07
1.20
7.40
3.38
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

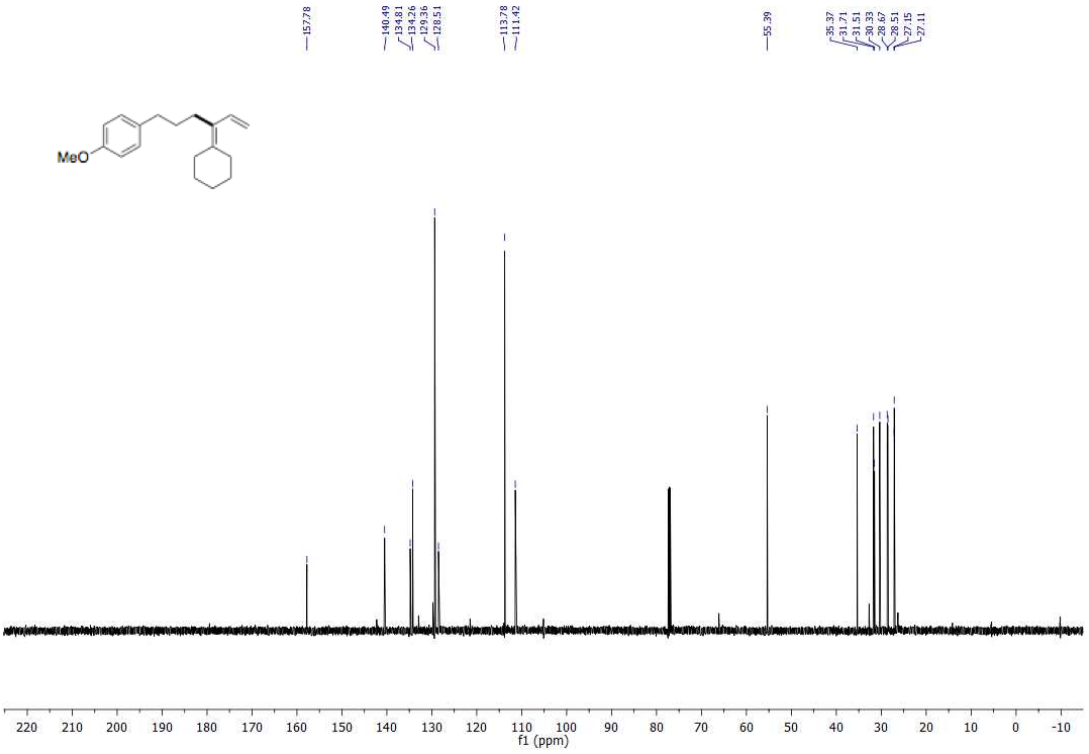

140.15
134.33
128.92
127.21
126.76
111.29
36.70
34.26
32.08
31.65
30.32
29.07
28.66
28.40
27.14
25.48
25.09
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

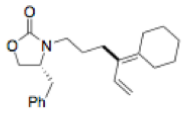

Me3Si
6.81
6.79
6.77
6.75
5.17
5.16
5.13
5.13
4.97
4.96
4.95
4.94
3.16
2.90
2.26
2.25
2.24
2.23
1.90
1.84
1.75
1.37
1.35
1.34
1.33
0.55
0.54
0.53
0.52
0.01
0.01
0.01
0.02
0.03
0.03
0.04
0.04
0.04
1.02
1.00
1.10
0.92
1.00
1.91
13.06
2.23
2.07
8.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

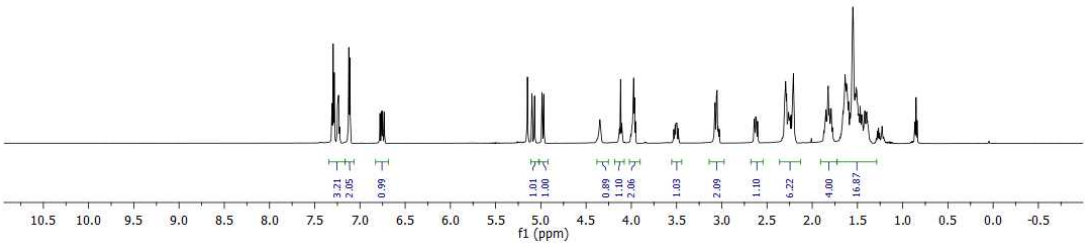

Me3Si
147.89
134.11
125.68
111.10
39.54
39.38
37.26
34.12
32.65
31.35
28.30
24.31
17.46
1.50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

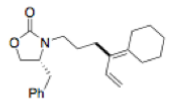

6.82
6.80
6.78
6.76
5.20
5.20
5.16
5.16
4.99
4.99
4.97
4.97
3.41
3.40
3.38
2.36
2.34
2.34
2.33
2.32
2.28
2.26
2.25
1.67
1.66
1.65
1.64
1.64
1.64
1.63
1.62
1.61
1.57
1.56
1.55
1.54
1.53
O
0.99
1.00
0.98
1.99
6.08
2.32
6.16
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


MeO
7.11
7.09
6.83
6.83
6.81
6.80
6.78
6.77
6.75
5.06
5.03
5.03
4.95
4.93
4.93
3.78
2.59
2.57
2.56
2.32
2.31
2.30
2.28
2.27
2.26
2.21
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.62
1.58
1.55
1.54
1.53
1.00
2.00
0.74
1.00
0.94
2.99
1.95
3.88
1.94
2.18
5.94
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

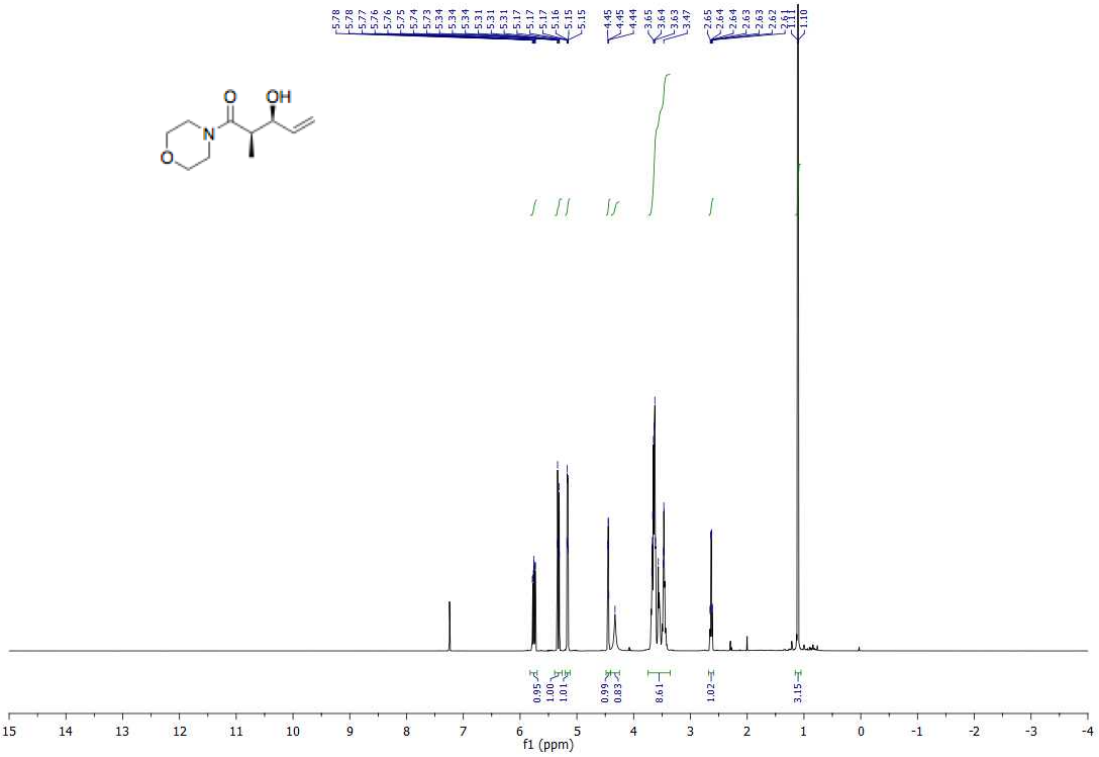

MeO
157.78
140.49
134.81
134.26
129.36
128.51
113.78
111.42
55.39
35.37
31.71
31.51
30.33
28.87
28.51
27.15
27.11
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

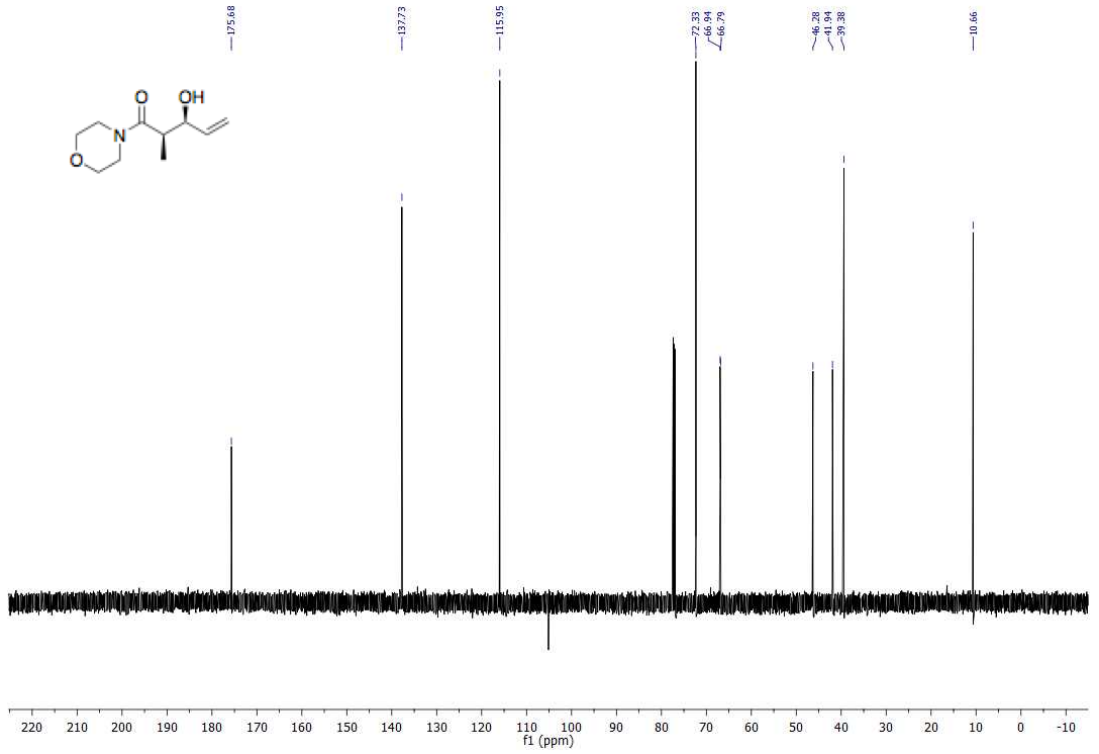

O
O
N
Ph

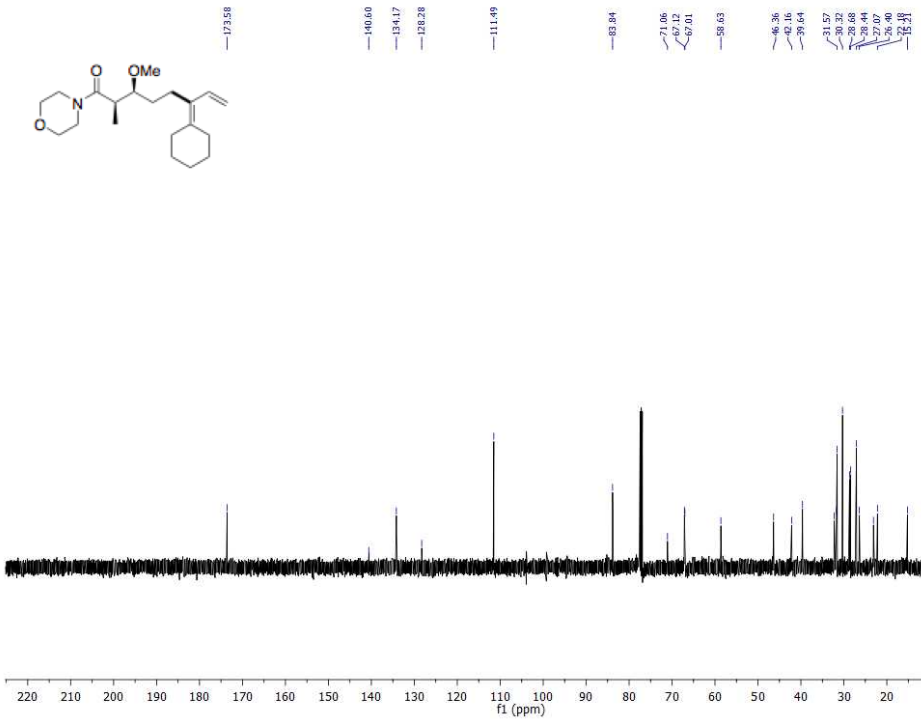

3.21
2.05
0.99
1.01
1.00
0.89
1.10
2.06
1.03
2.09
1.10
6.22
4.00
16.87
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

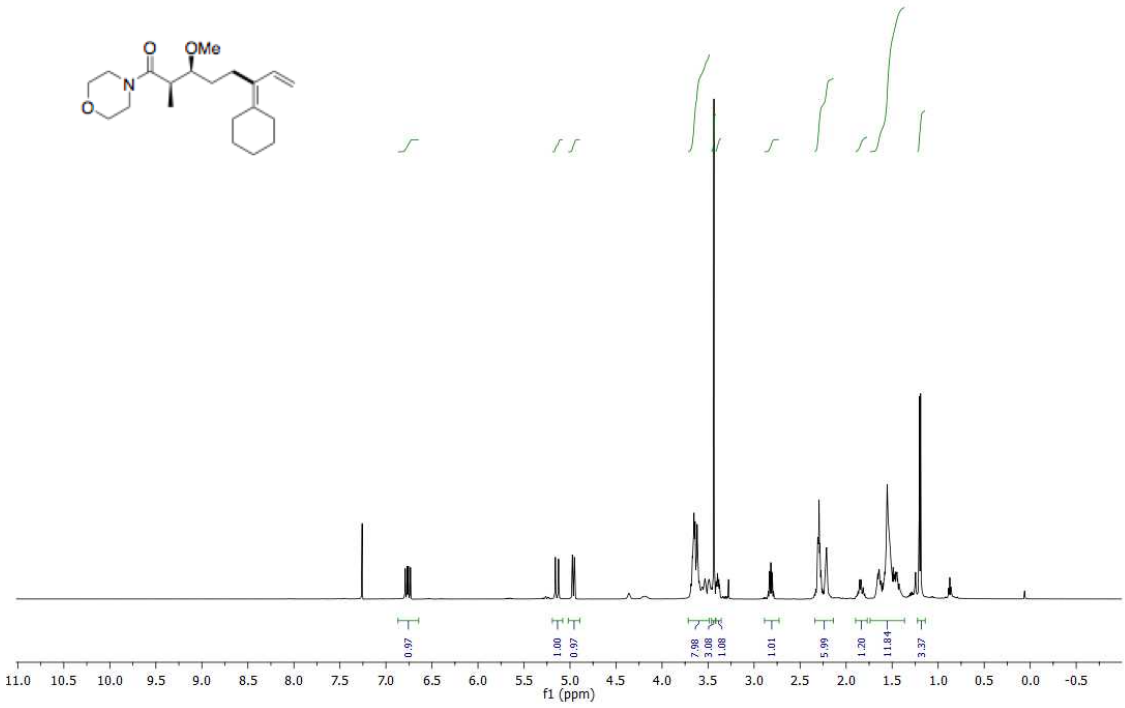

O
O
N
Ph

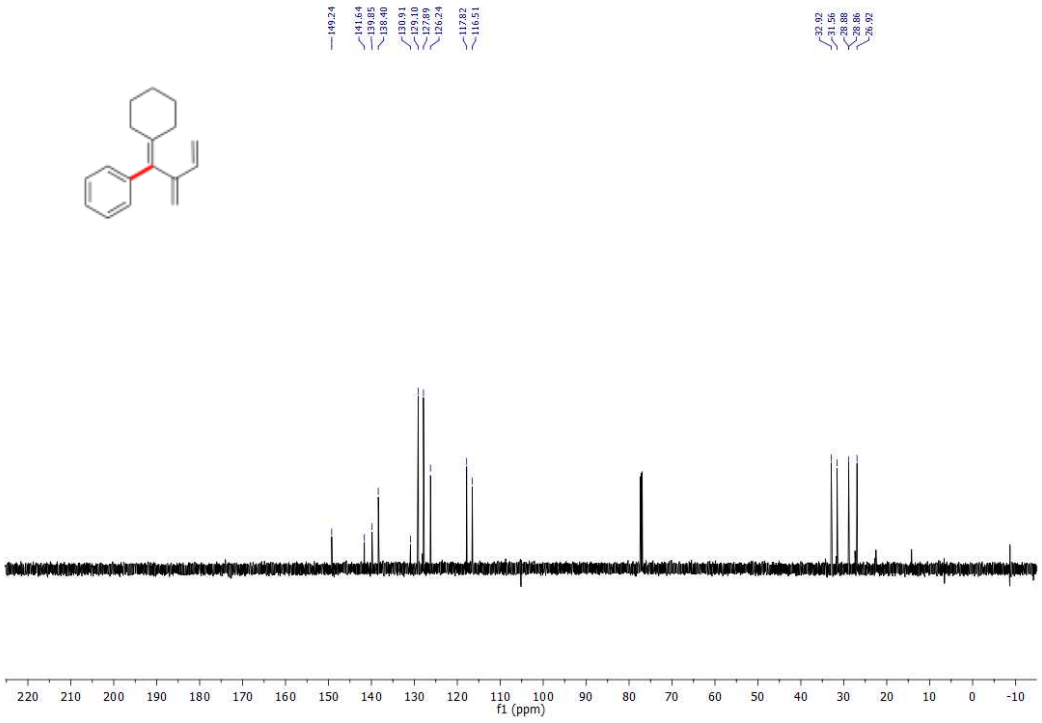
158.10
141.02
135.87
134.65
129.01
127.35
127.25
111.58
71.03
66.77
56.04
42.22
39.56
37.00
31.68
30.30
28.59
28.38
27.12
26.94
26.29
24.52
22.06
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

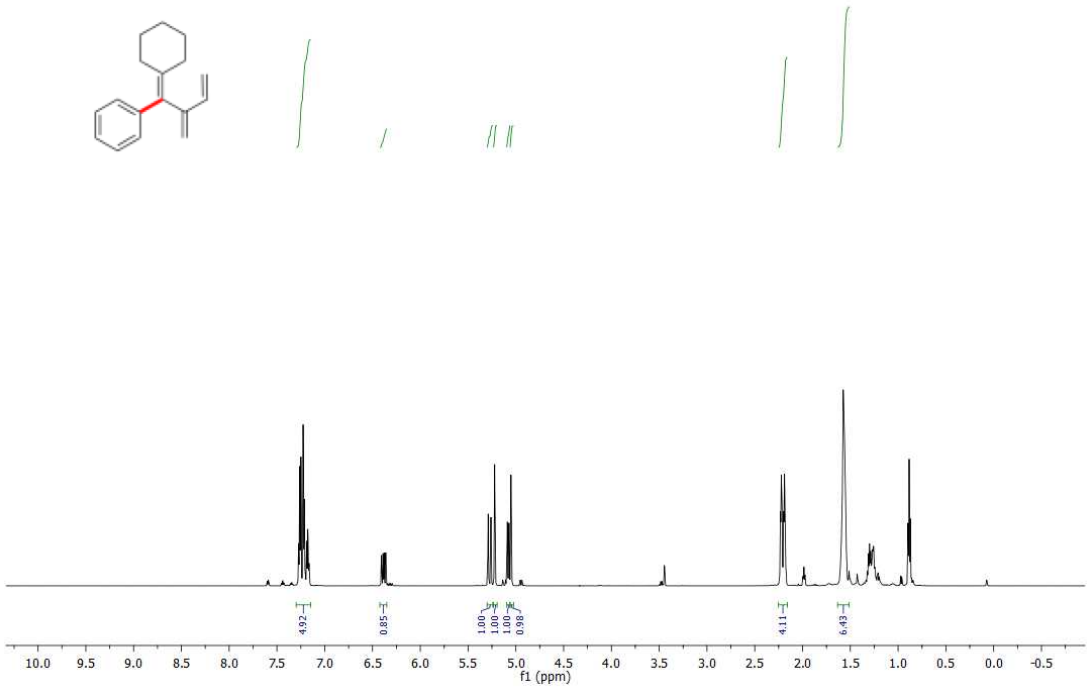

O
OH
N
O
f1 (ppm)

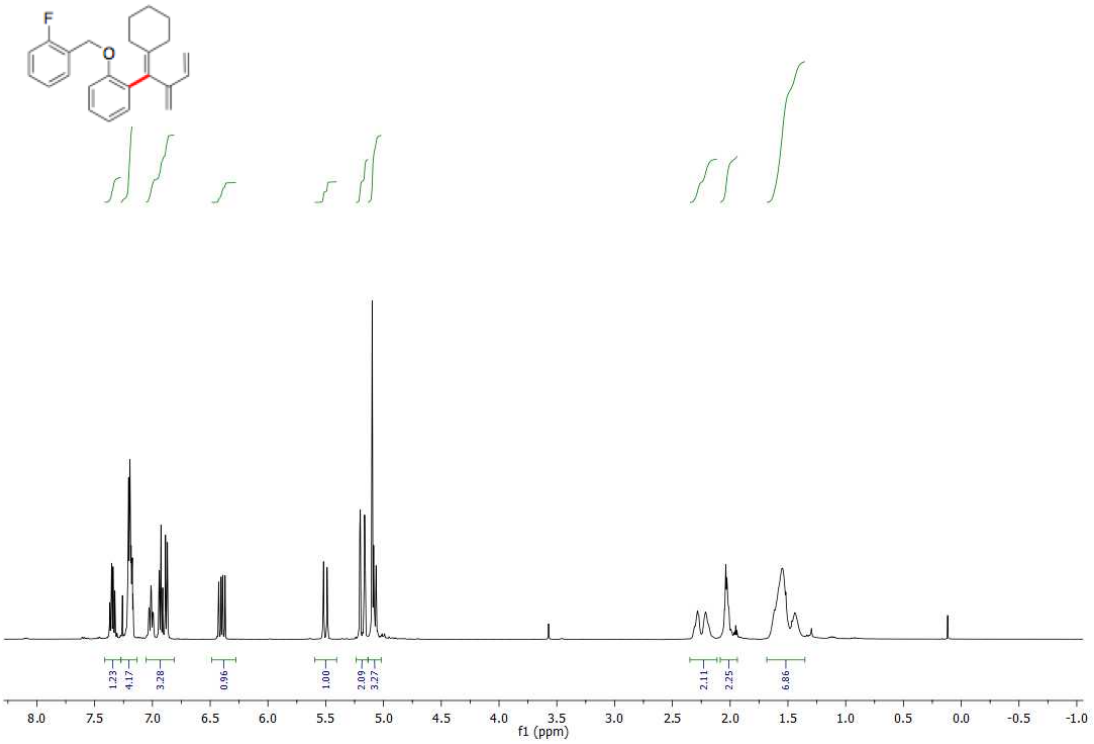

175.68
137.73
115.95
72.33
66.94
66.79
46.28
41.94
39.38
10.66
O
OH
N
O
f1 (ppm)

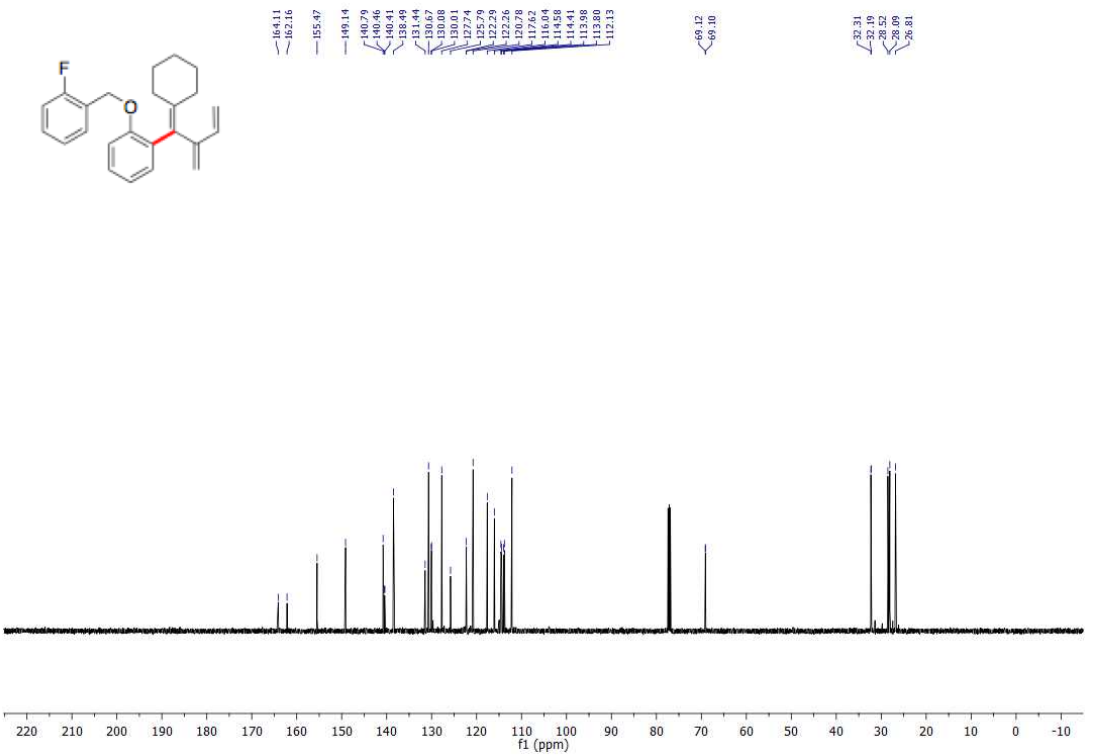

173.58
140.60
134.17
128.28
111.49
83.84
71.06
67.12
67.01
58.63
46.36
42.16
39.64
31.57
30.32
28.68
28.44
27.07
26.40
15.48
15.23
OMe
O
N
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

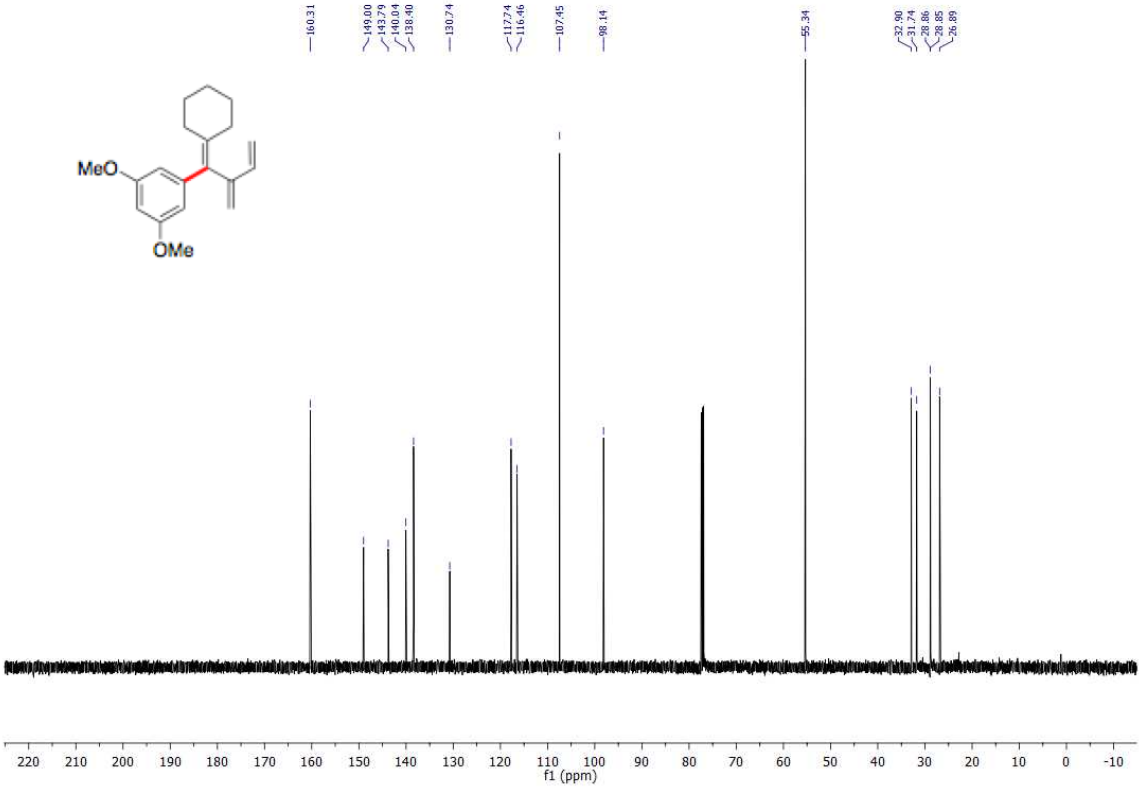

OMe
O
N
O
0.97
1.00
0.97
7.98
3.08
1.08
1.01
5.99
1.20
11.84
3.37
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

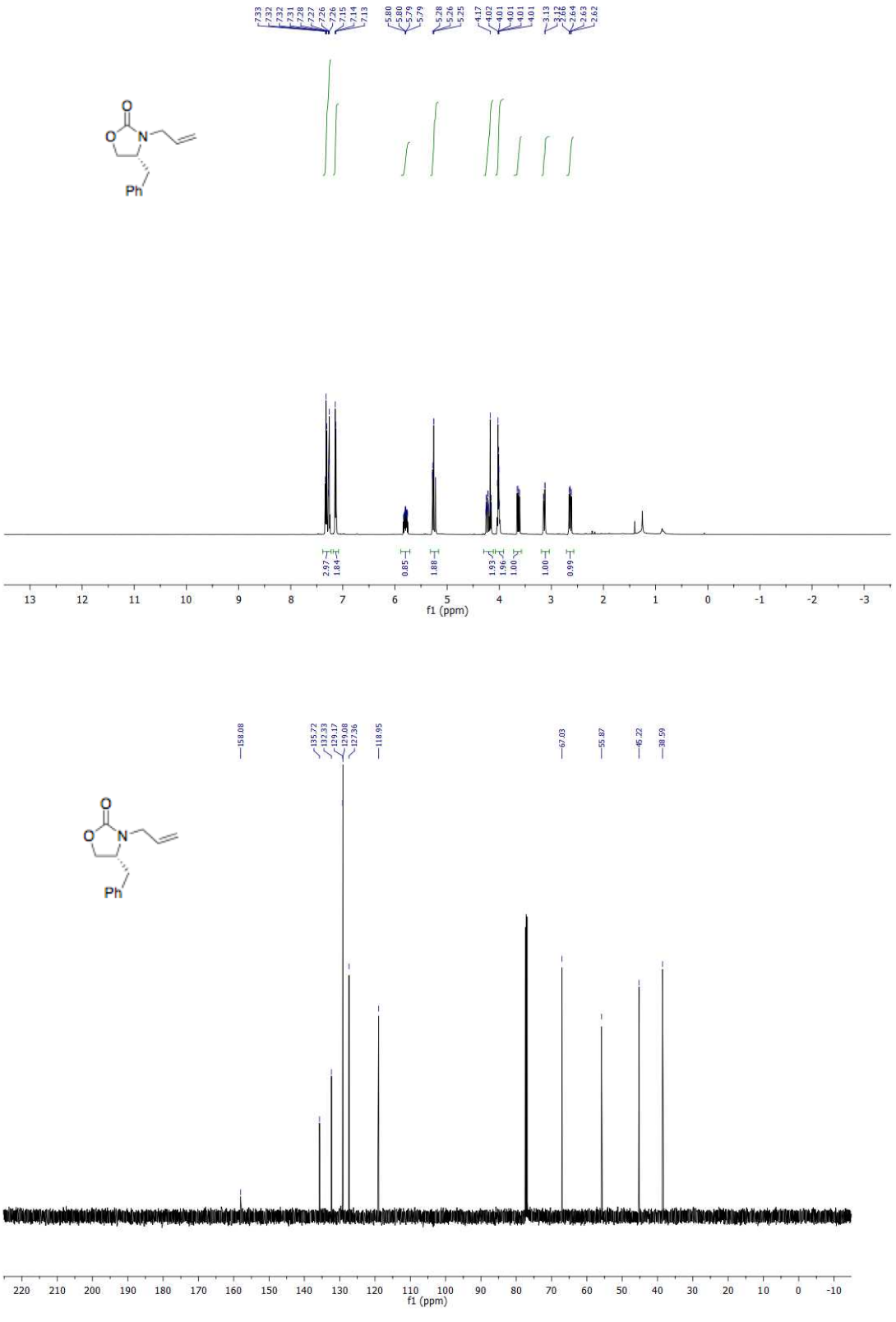

149.24
141.64
139.85
138.40
130.91
129.10
127.89
126.24
117.82
116.51
32.92
31.56
28.88
28.86
26.92
f1 (ppm)

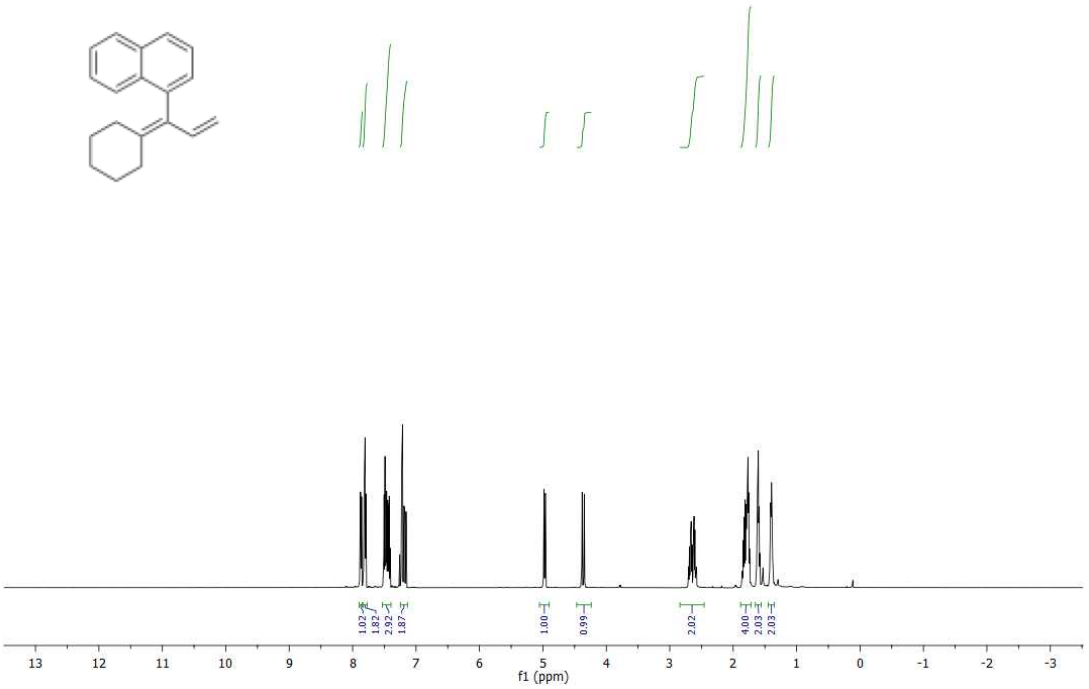

4.92
0.85
1.00
1.00
1.00
0.98
4.11
6.43
f1 (ppm)

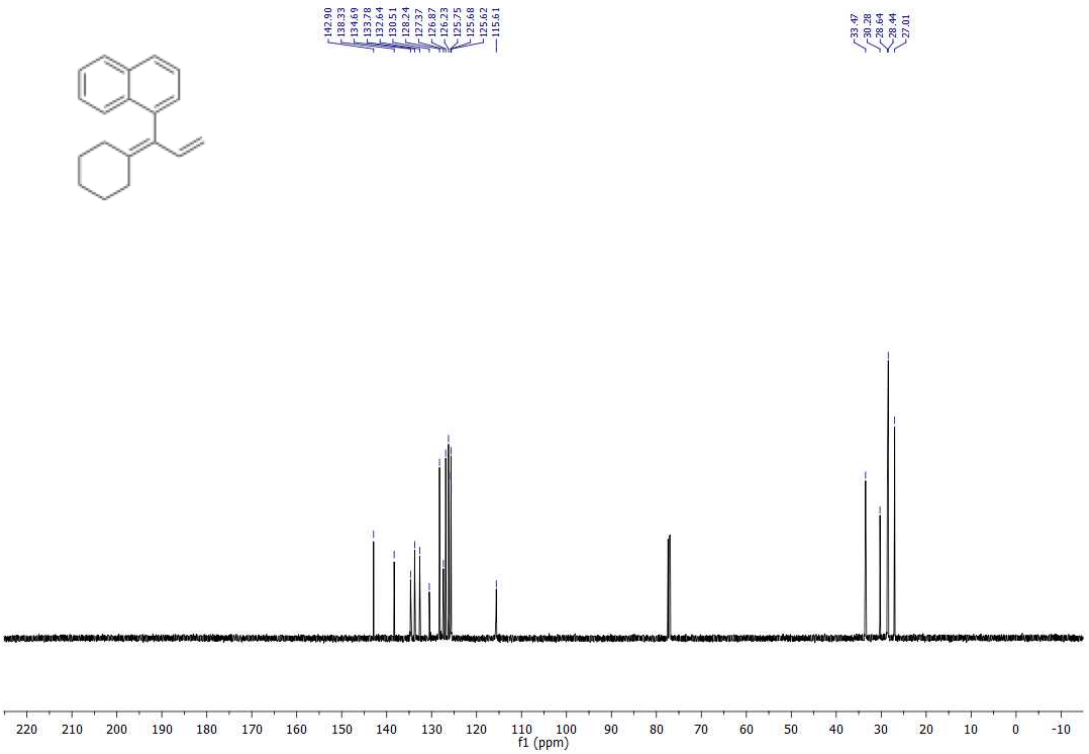

F
O
1.23
4.17
3.28
0.96
1.00
2.09
3.27
2.11
2.25
6.86
f1 (ppm)

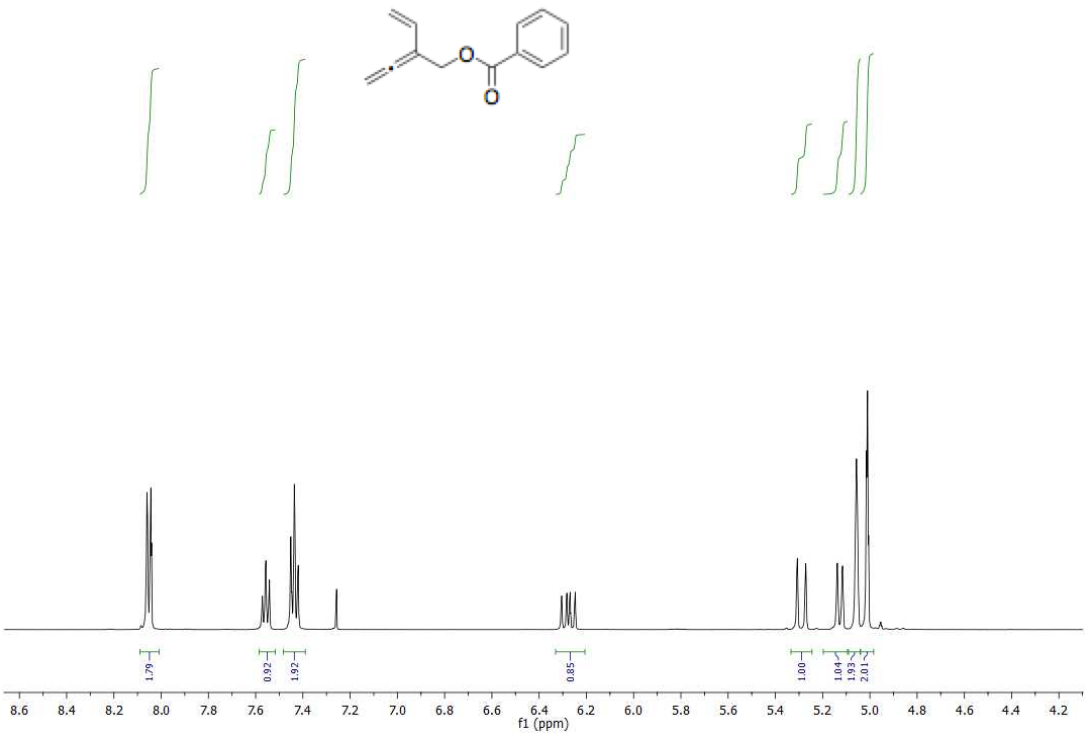

F
O
164.11
162.16
155.47
149.14
140.79
140.46
140.41
138.49
131.44
130.67
130.08
130.01
127.74
125.79
122.29
122.26
120.78
117.62
116.04
114.58
114.41
113.98
113.80
112.13
69.12
69.10
32.31
32.19
29.53
28.09
26.81
f1 (ppm)

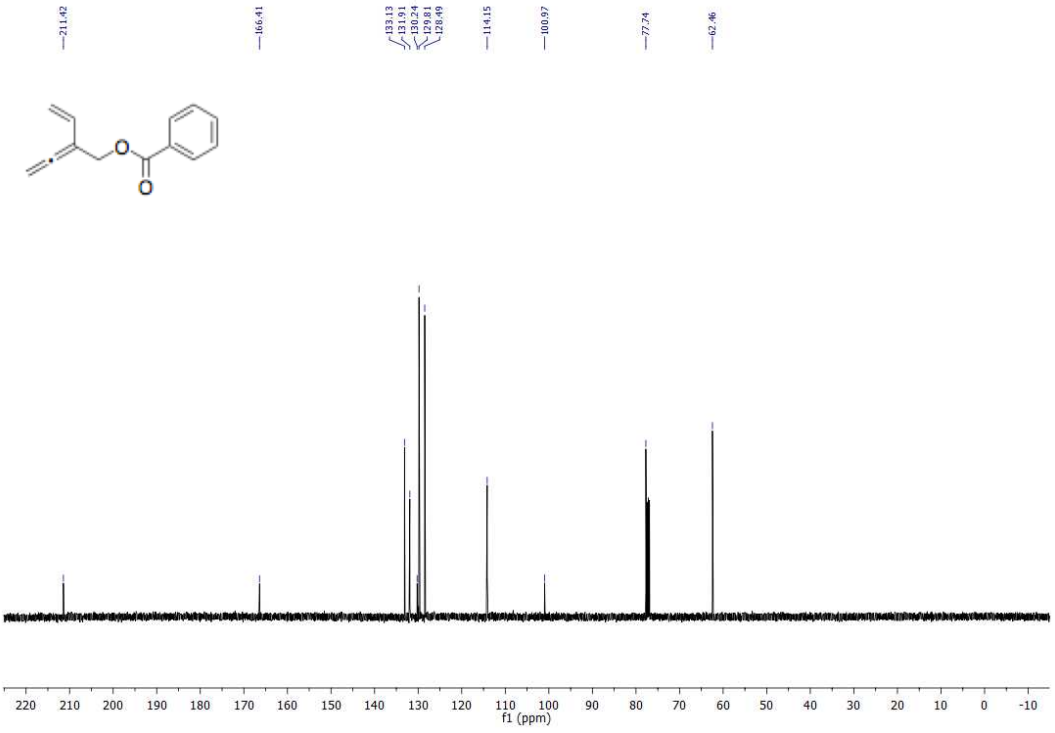

160.31
149.00
143.79
140.04
138.40
130.74
117.74
116.46
107.45
98.14
55.34
32.90
31.74
28.86
28.05
26.89
MeO
OMe
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.33
7.32
7.32
7.31
7.28
7.27
7.26
7.26
7.15
7.14
7.13
5.80
5.80
5.79
5.79
5.28
5.26
5.25
4.17
4.02
4.01
4.01
4.01
4.01
3.13
3.12
3.08
2.64
2.63
2.62
O
O
N
Ph
2.97
1.84
0.85
1.88
1.93
1.96
1.00
1.00
0.99
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)
158.08
135.72
133.33
129.17
129.08
127.36
118.95
67.03
55.87
45.22
38.59
O
O
N
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


1.02
1.82
2.92
1.87
1.00
0.99
2.02
4.00
2.03
2.03
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

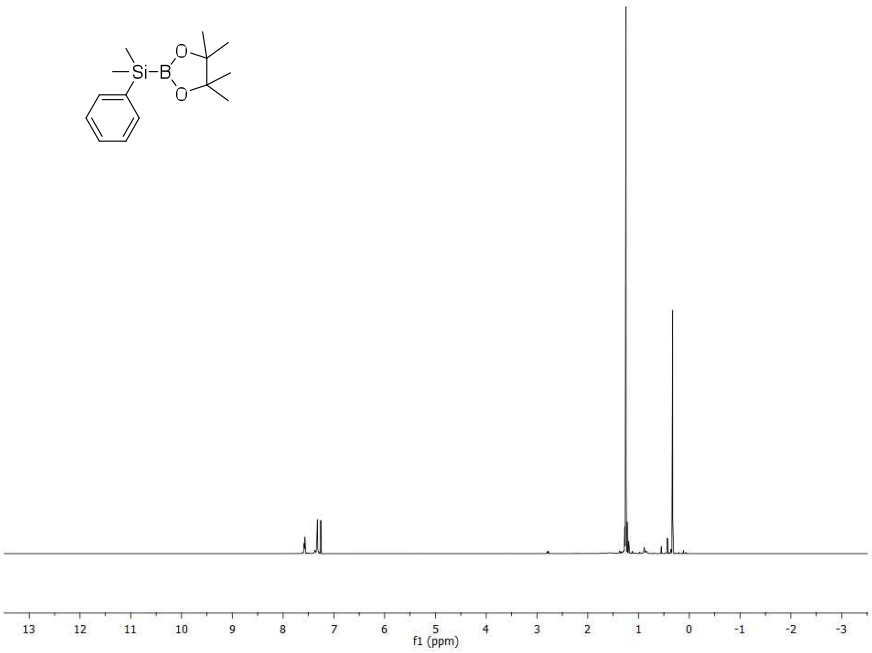

142.90
138.33
134.69
133.78
132.64
130.51
128.24
127.37
126.87
126.23
125.75
125.68
125.62
115.61
33.47
30.28
28.64
28.44
27.01
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

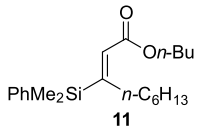

O
O
1.79
0.92
1.92
0.85
1.00
1.04
1.93
2.01
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2
f1 (ppm)


211.42
166.41
133.13
131.91
130.24
129.81
128.49
114.15
100.97
77.74
62.46
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

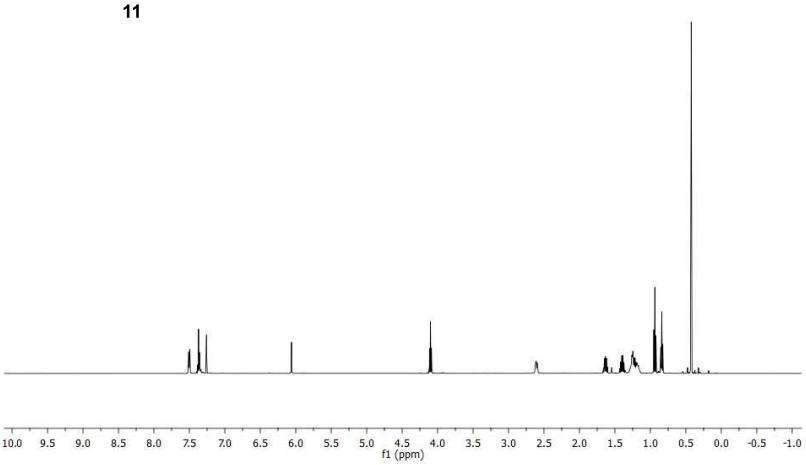
Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature

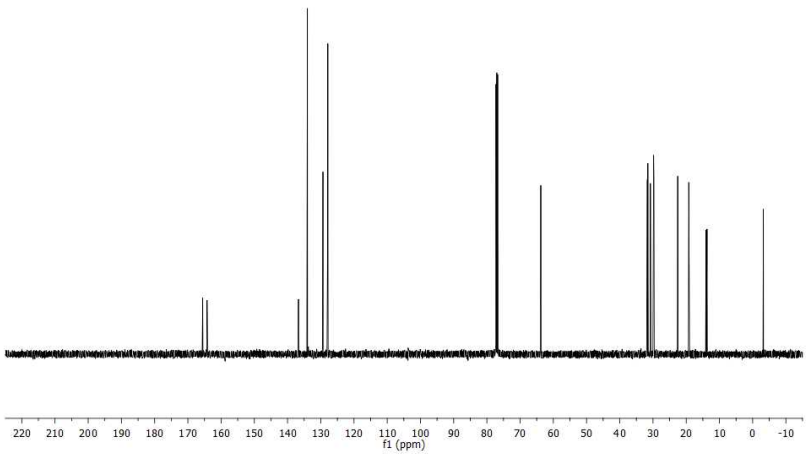
NMR Spectra:

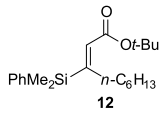



O
O*n*-Bu
PhMe$_2$Si
n-C$_6$H$_{13}$

11

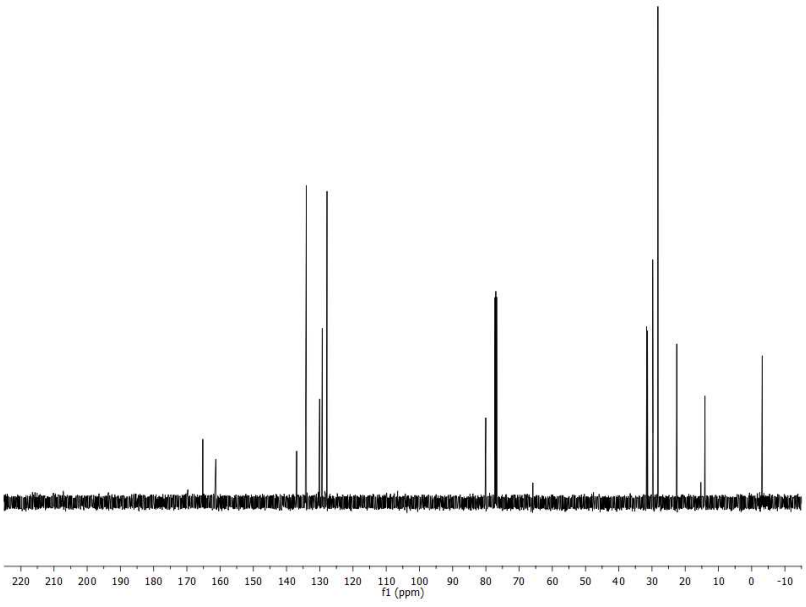

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

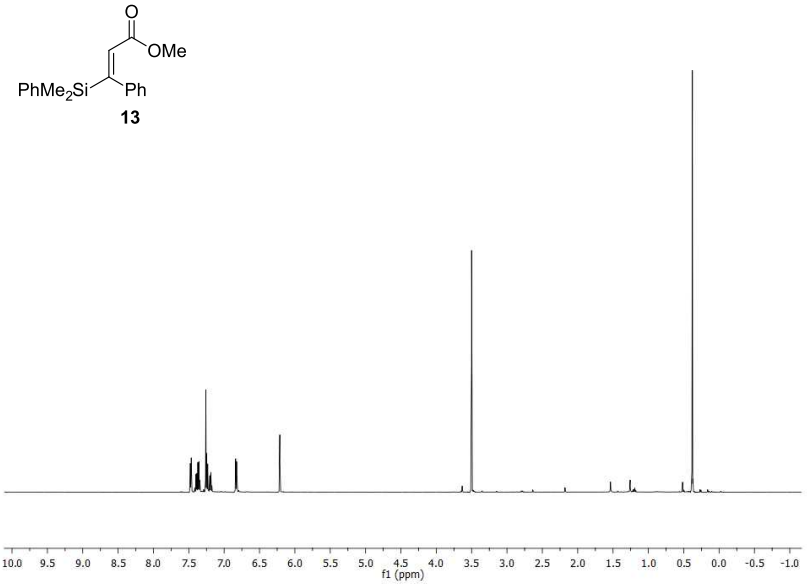

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

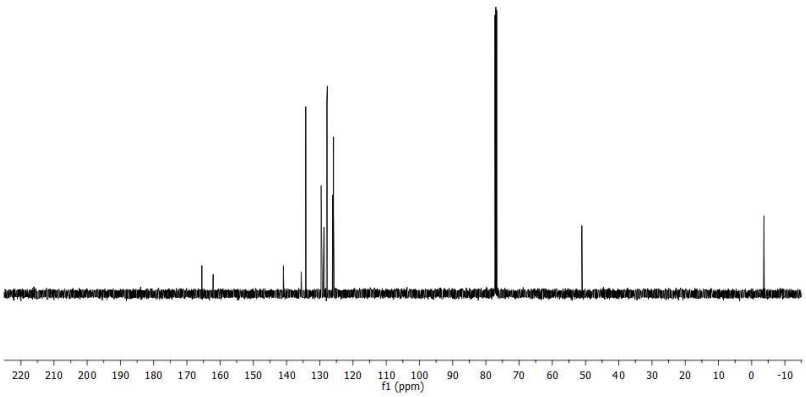

O
Ot-Bu
PhMe2Si
n-C6H13

12

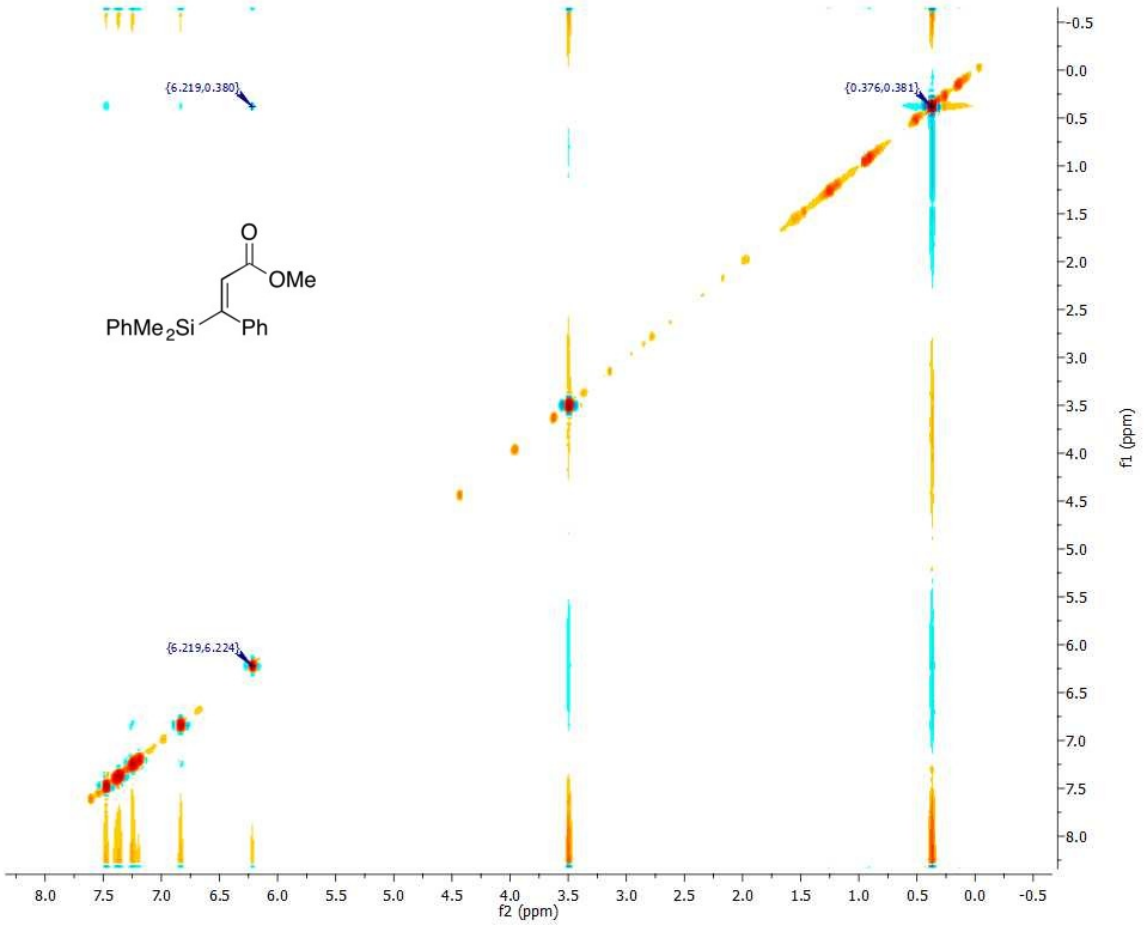
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

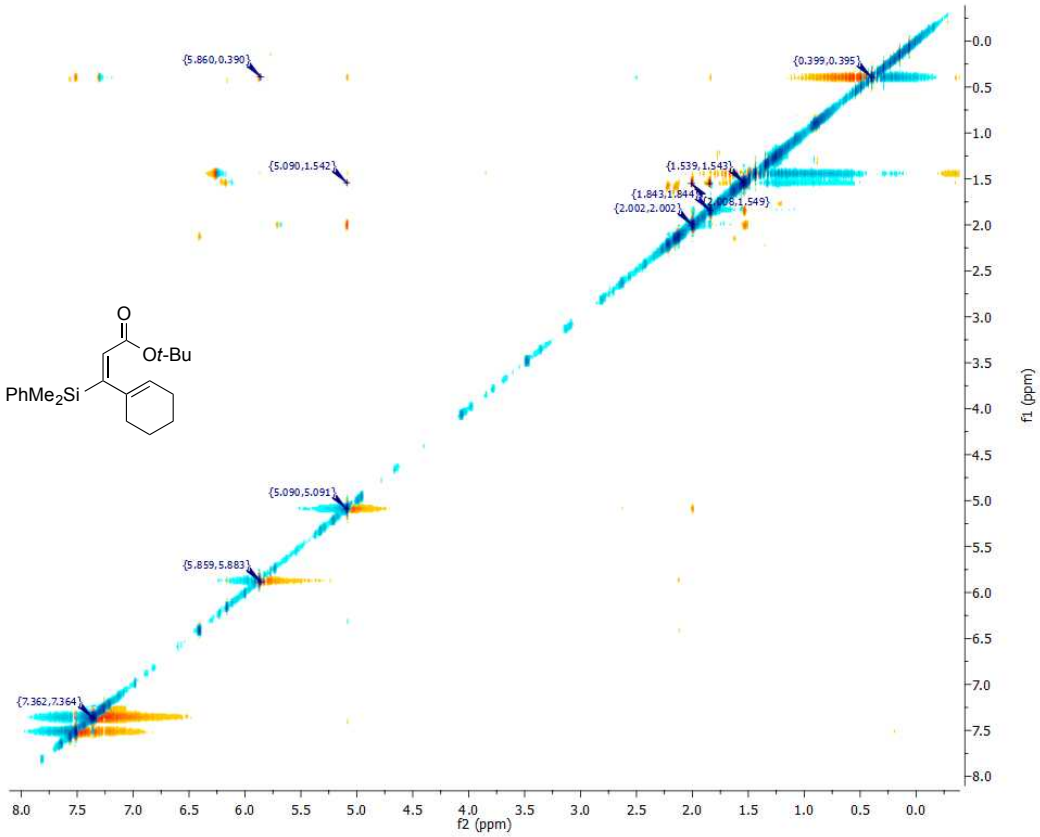

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

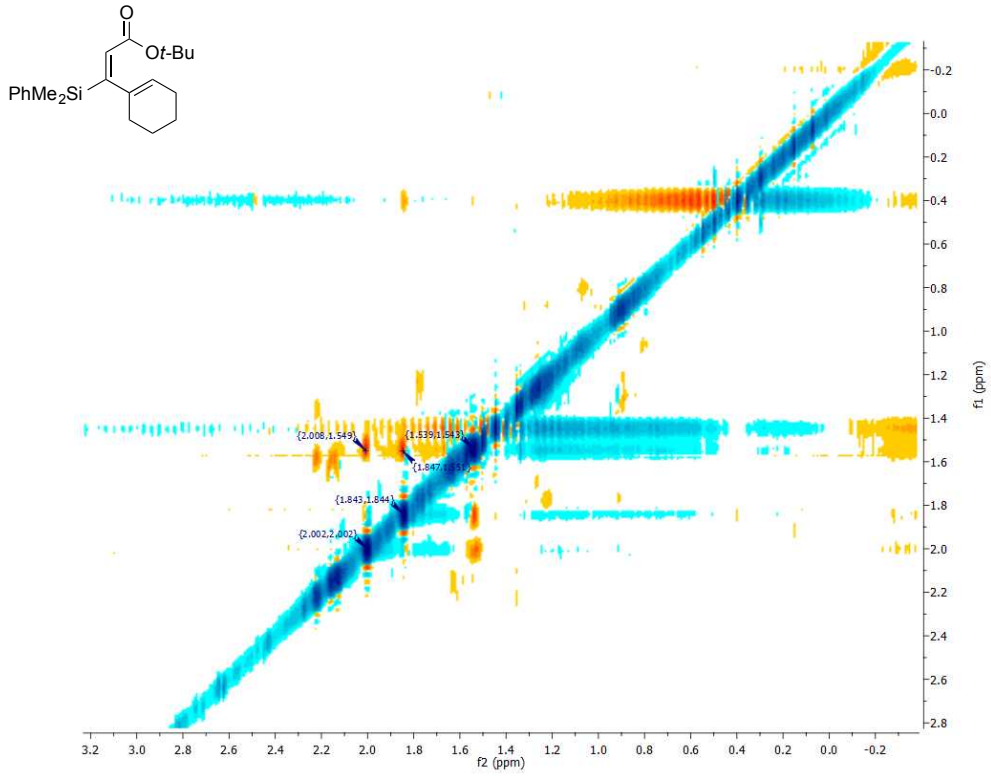

O
OMe
PhMe2Si
Ph
13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

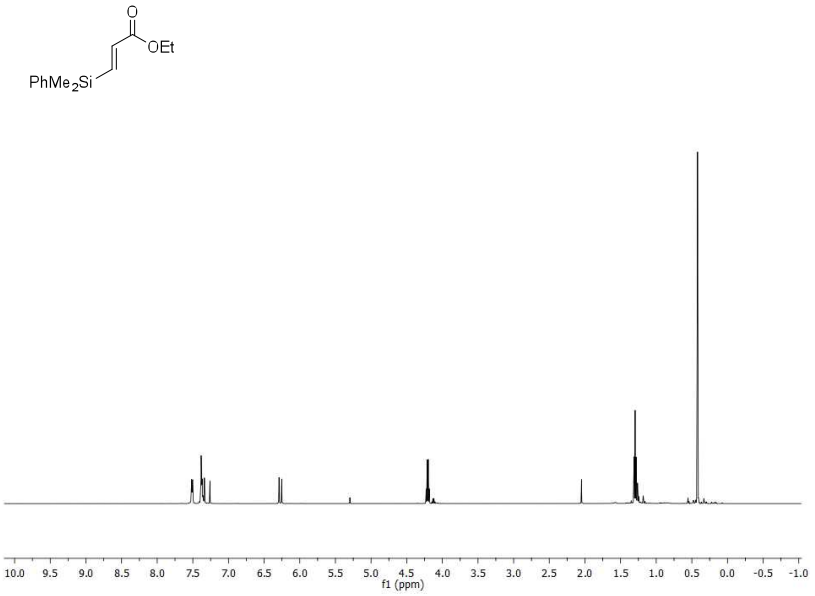

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

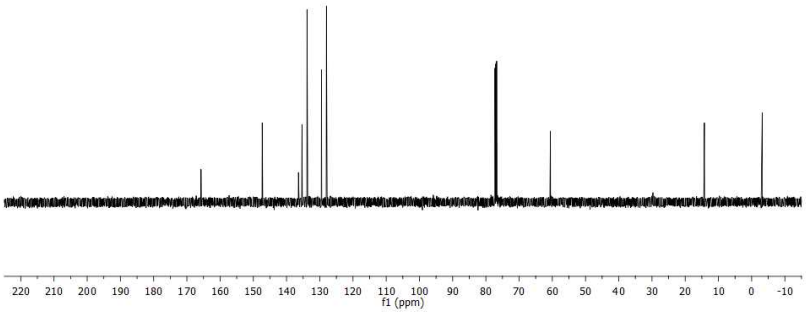
1

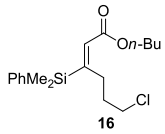



{5.860,0.390}
{0.399,0.395}
{5.090,1.542}
{1.539,1.543}
{1.843,1.844}
{2.002,2.002}
{2.008,1.549}
O
Ot-Bu
PhMe2Si
{5.090,5.091}
{5.859,5.883}
{7.362,7.364}
f2 (ppm)
f1 (ppm)

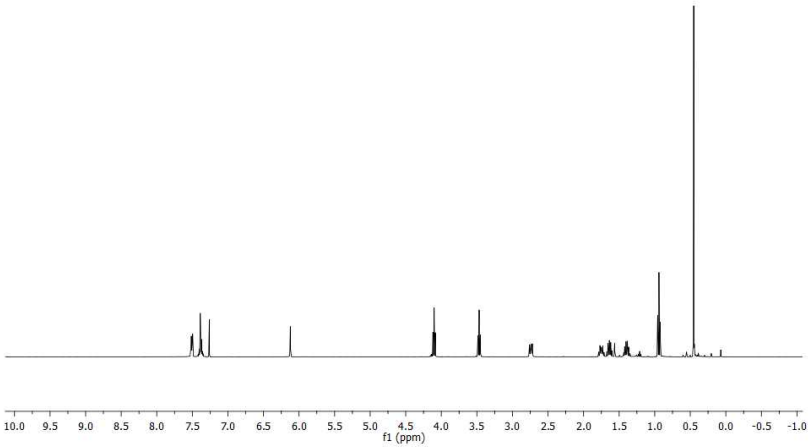

O
Ot-Bu
PhMe2Si
{2.008,1.549}
{1.539,1.543}
{1.847,1.851}
{1.843,1.844}
{2.002,2.002}
f1 (ppm)
f2 (ppm)

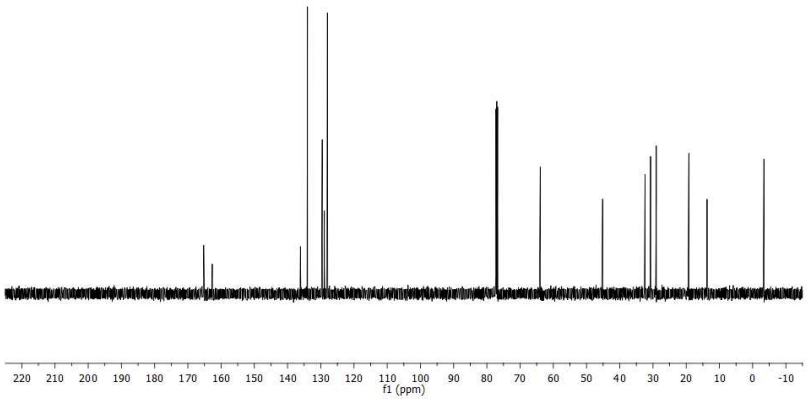

O
OEt
PhMe2Si
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

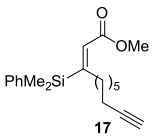

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O*n*-Bu
PhMe$_2$Si
Cl

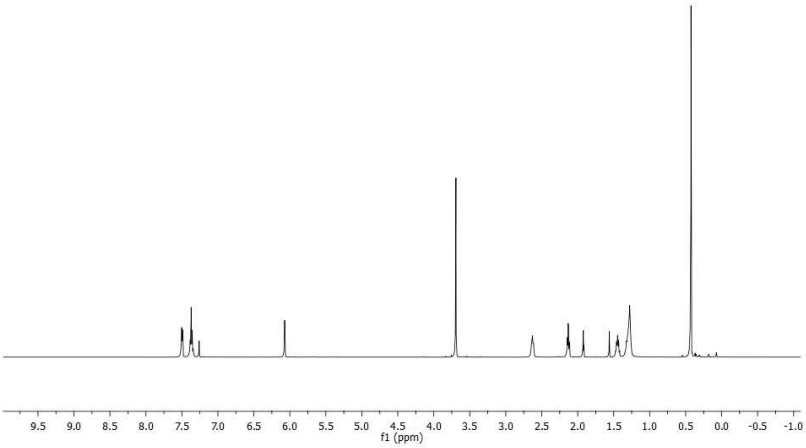
16

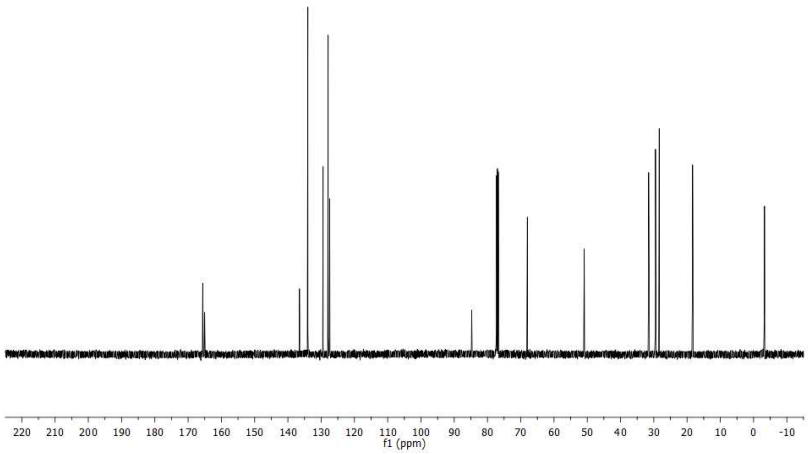

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

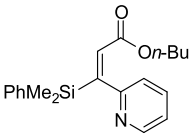

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OMe
PhMe2Si
5

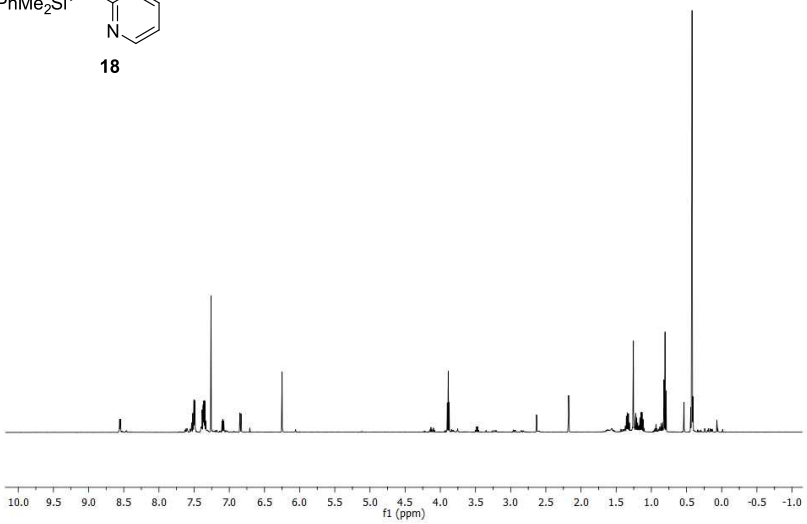
17

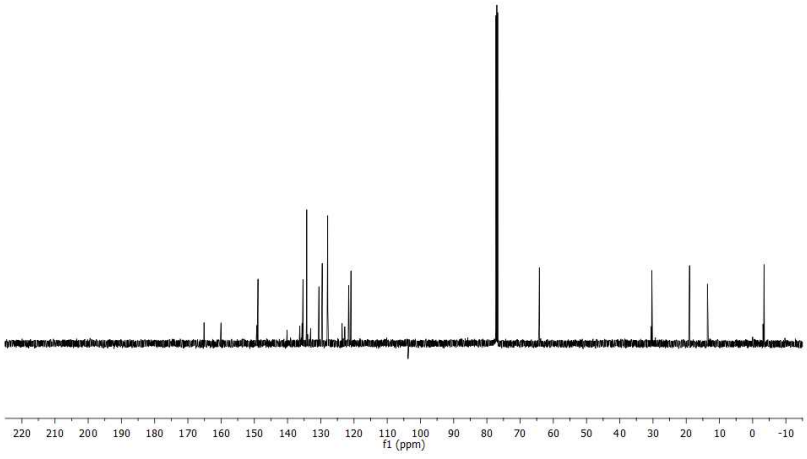

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

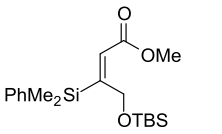

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O*n*-Bu
PhMe$_2$Si
N

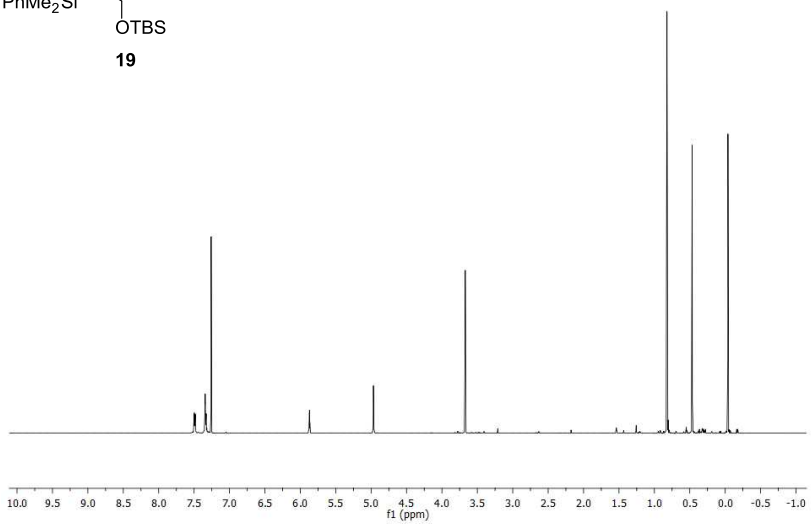
18

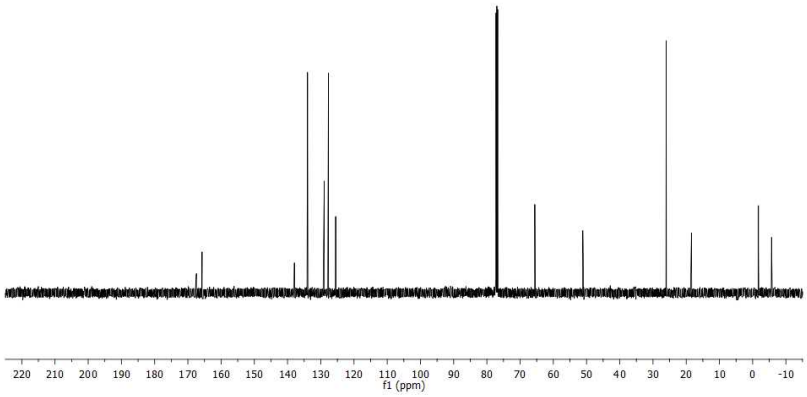

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

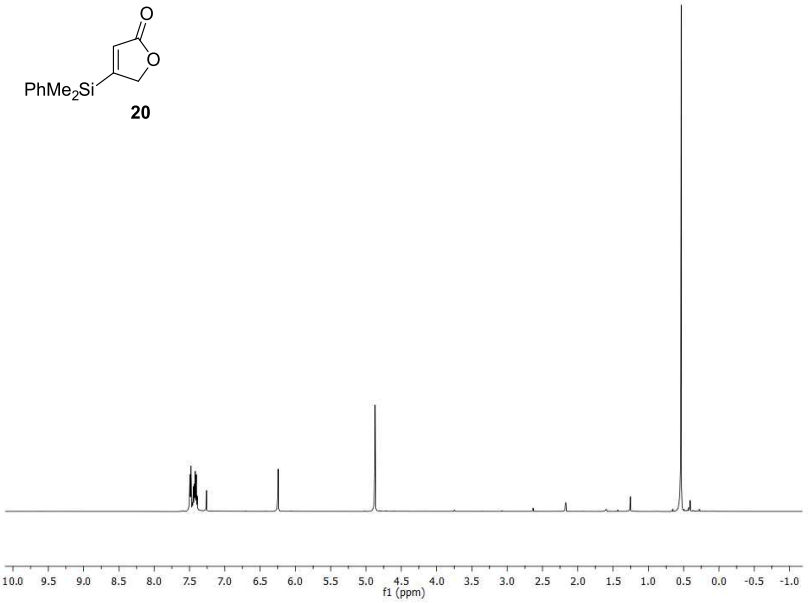

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OMe
PhMe2Si
OTBS

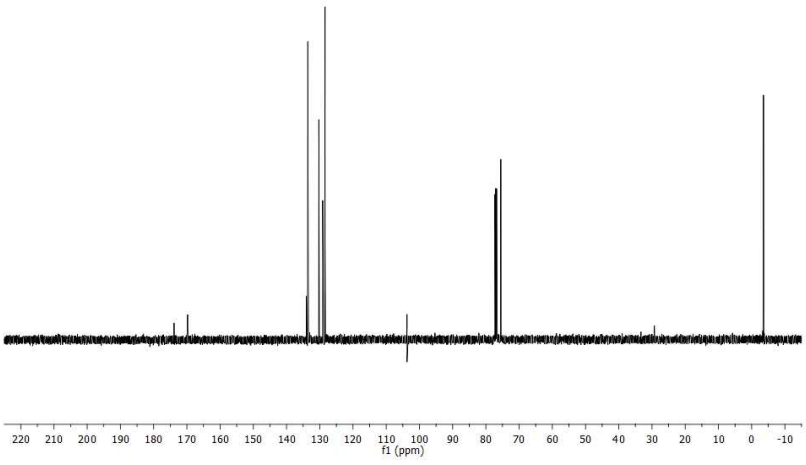
19


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

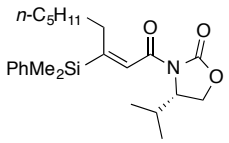

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
PhMe2Si
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

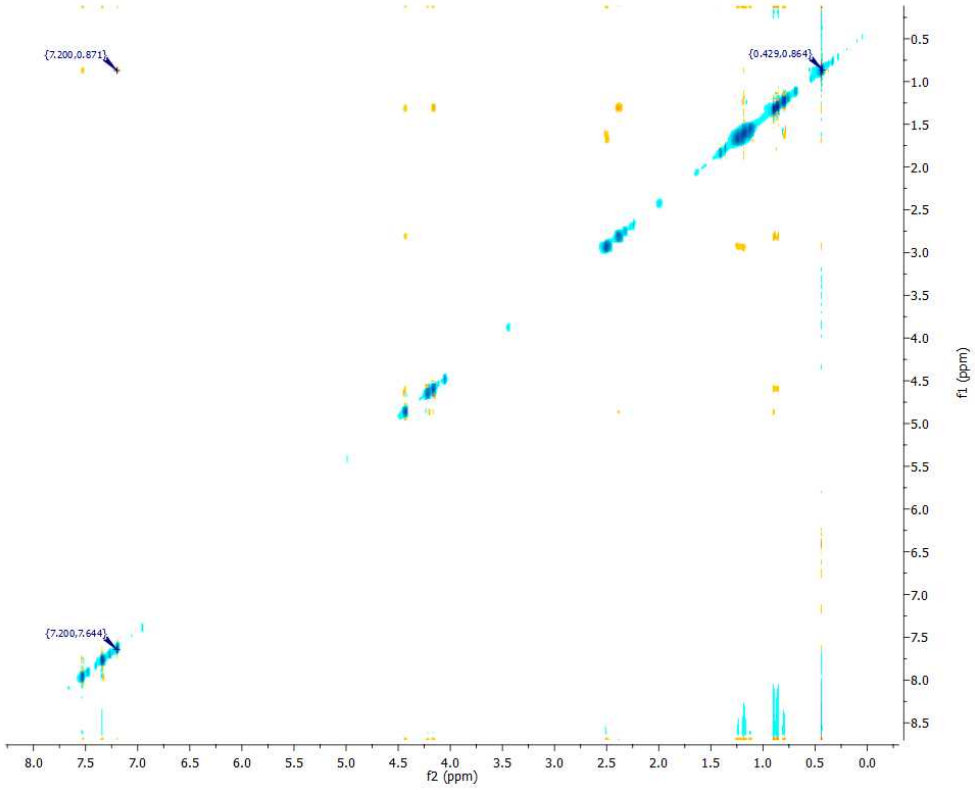
20

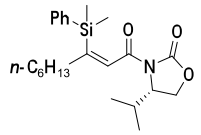

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2D-NOESY 1H-1H 600MHz:

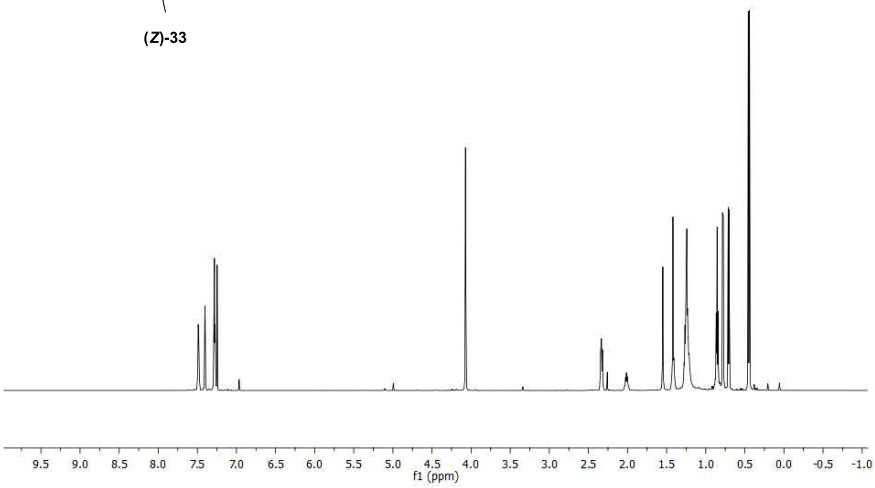


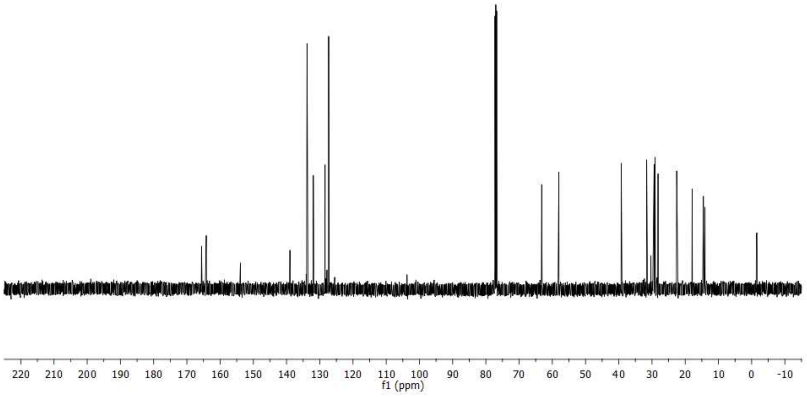
***(E)*-33**



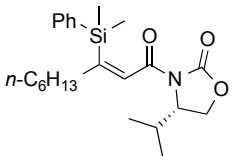

Ph
Si
O
O
N
O
n-C6H13

(*Z*)-33

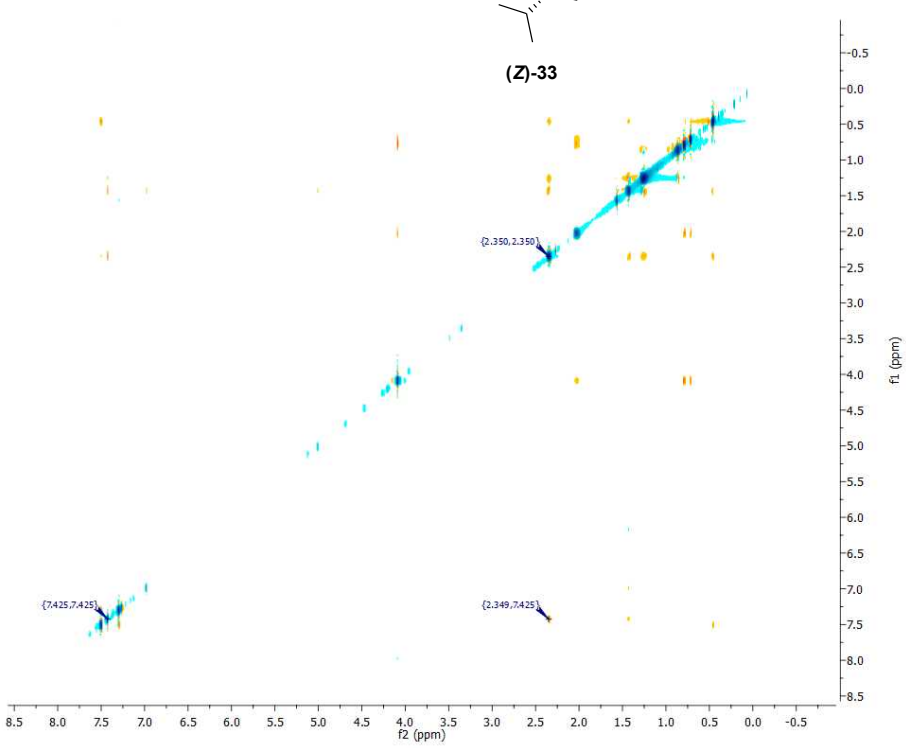

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

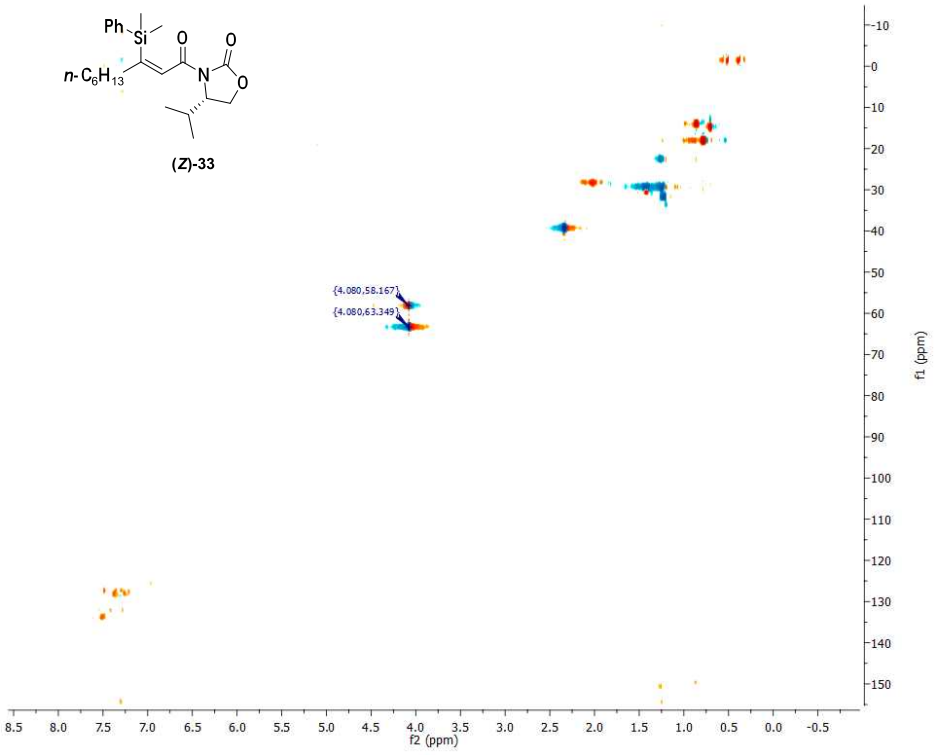

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

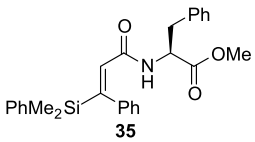
2D NOESY 1H-1H 600MHz:



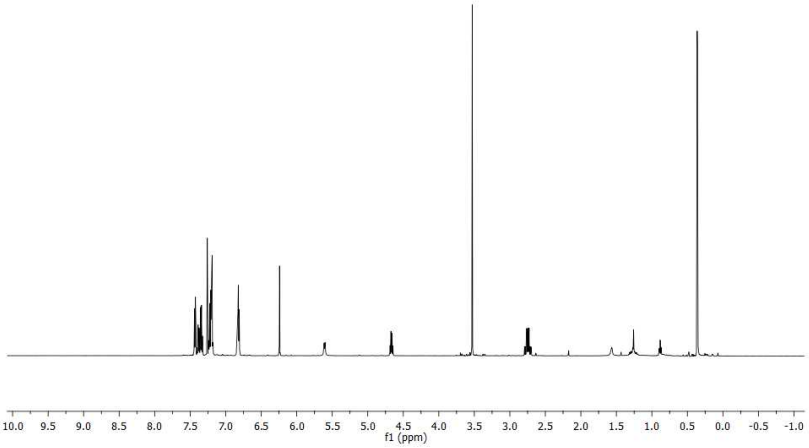
(*Z*)-33

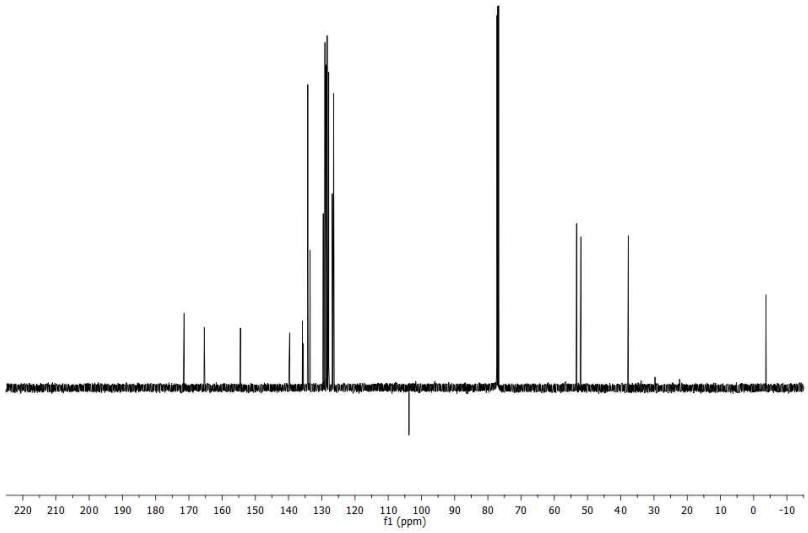


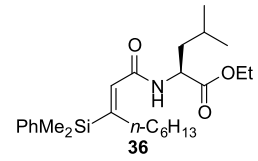

Ph
Si
O
O
N
O
n-C6H13
(Z)-33
{4.080,58.167}
{4.080,63.349}
f1 (ppm)
f2 (ppm)


Ph
O
N
H
OMe
O
PhMe2Si
Ph

35

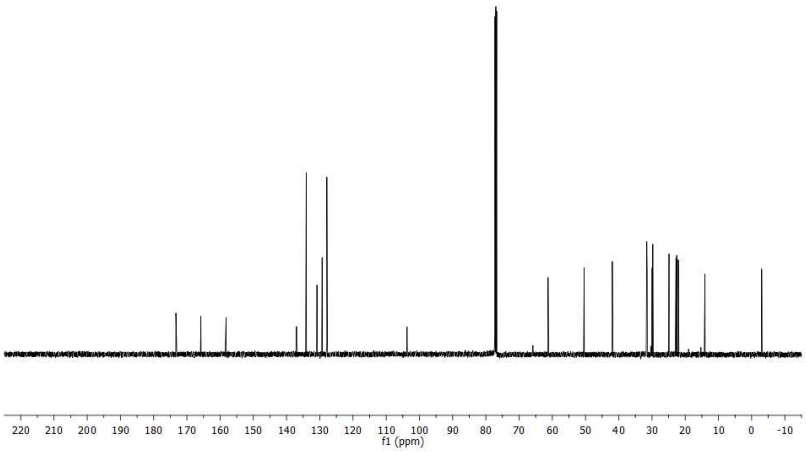

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

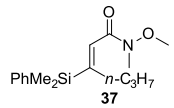

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
N
H
OEt
O
PhMe2Si
n-C6H13

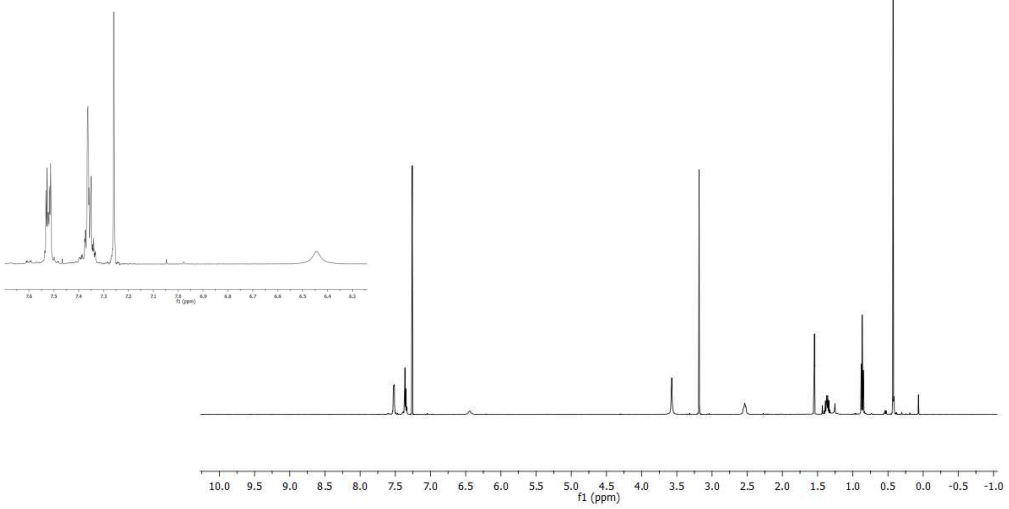
36

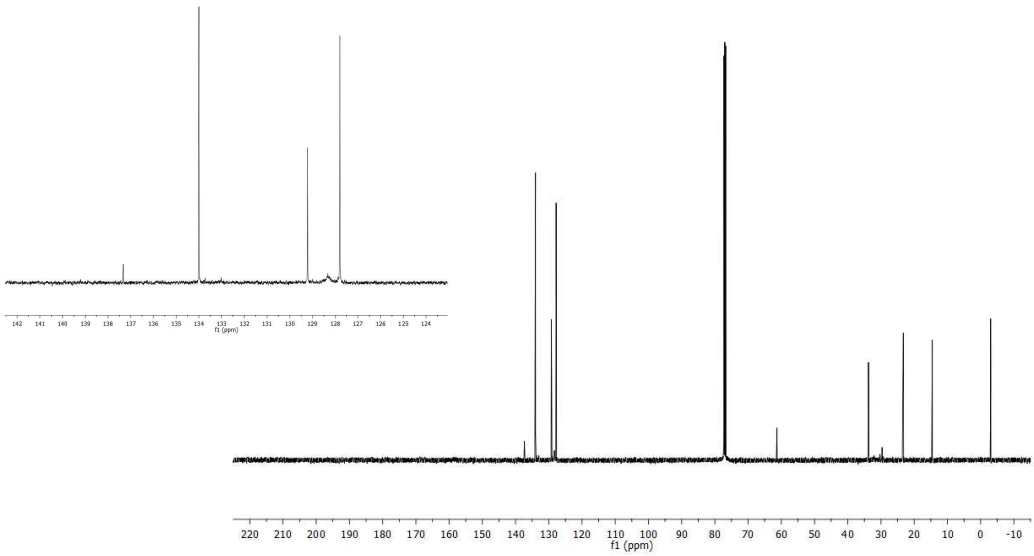
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

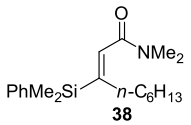

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
N
O
PhMe2Si
n-C3H7

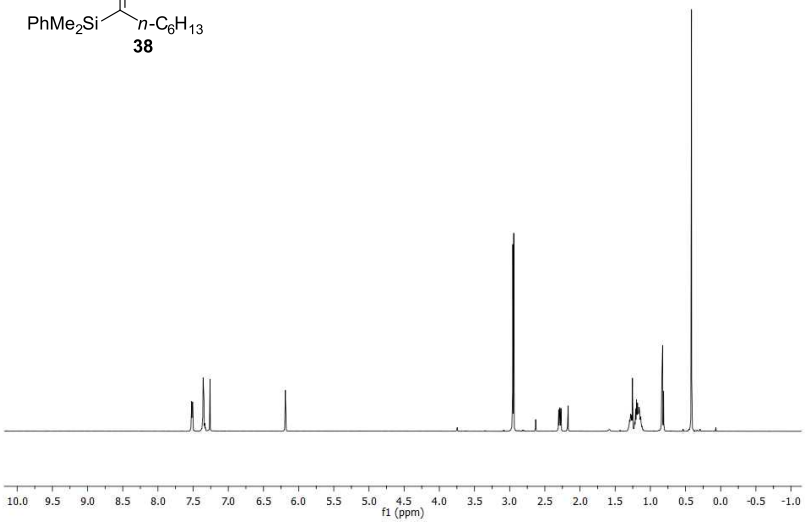
37

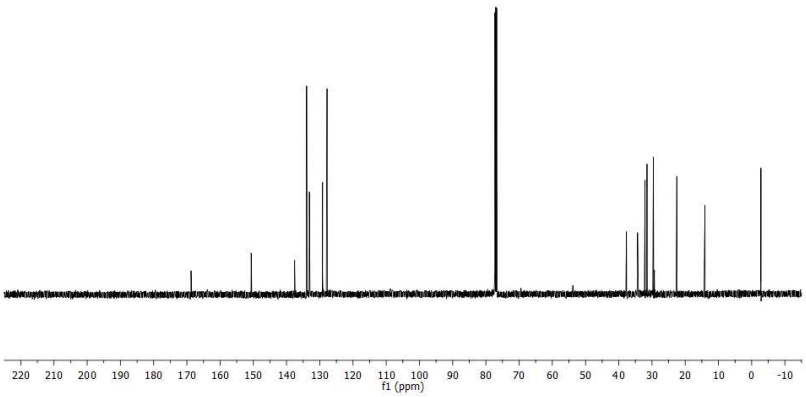

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

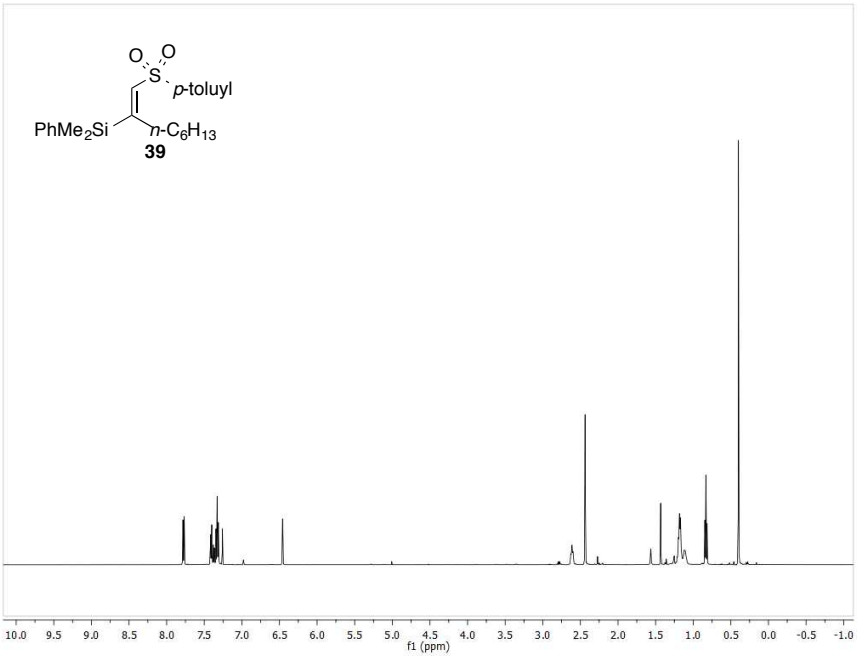

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

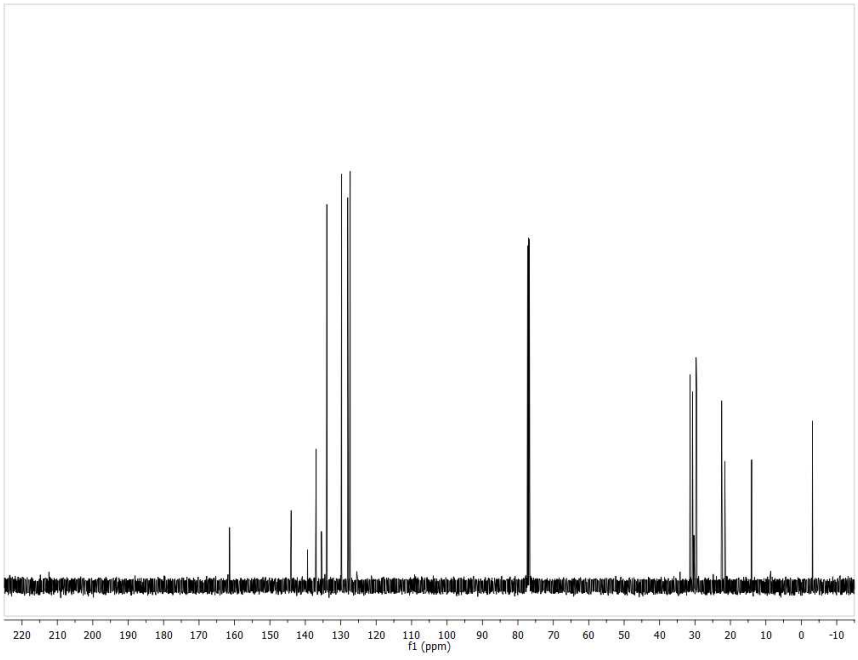

O
NMe2
PhMe2Si
n-C6H13

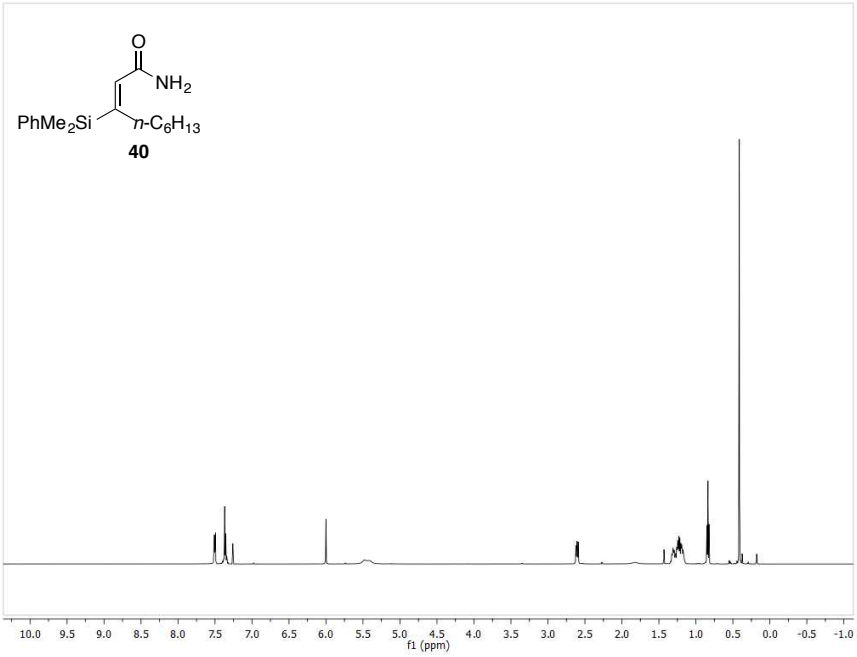
38

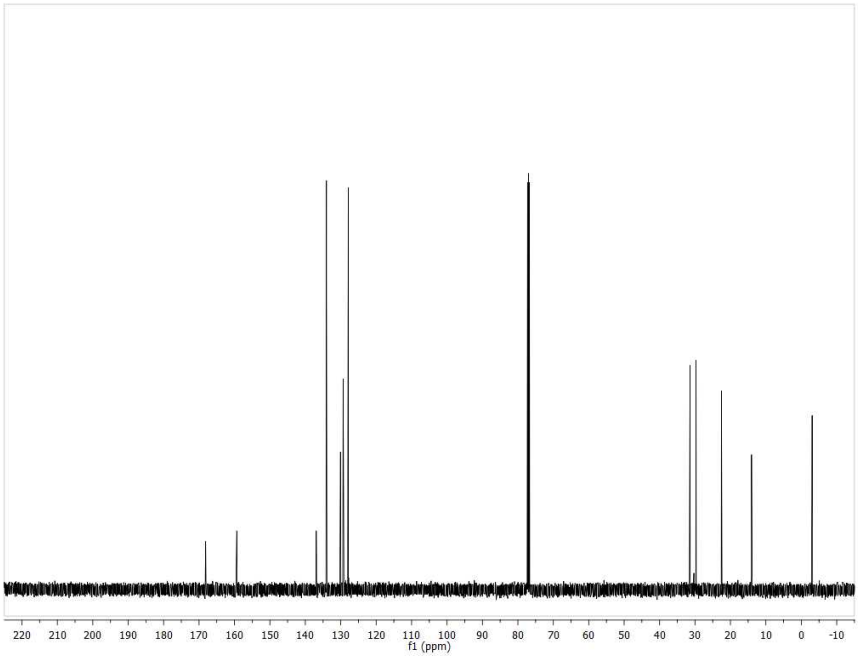

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

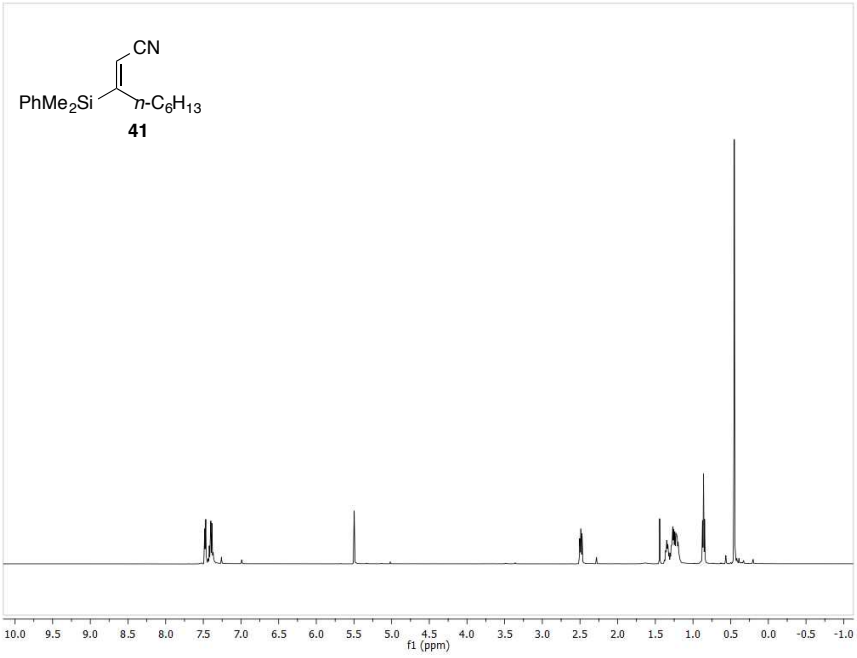

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

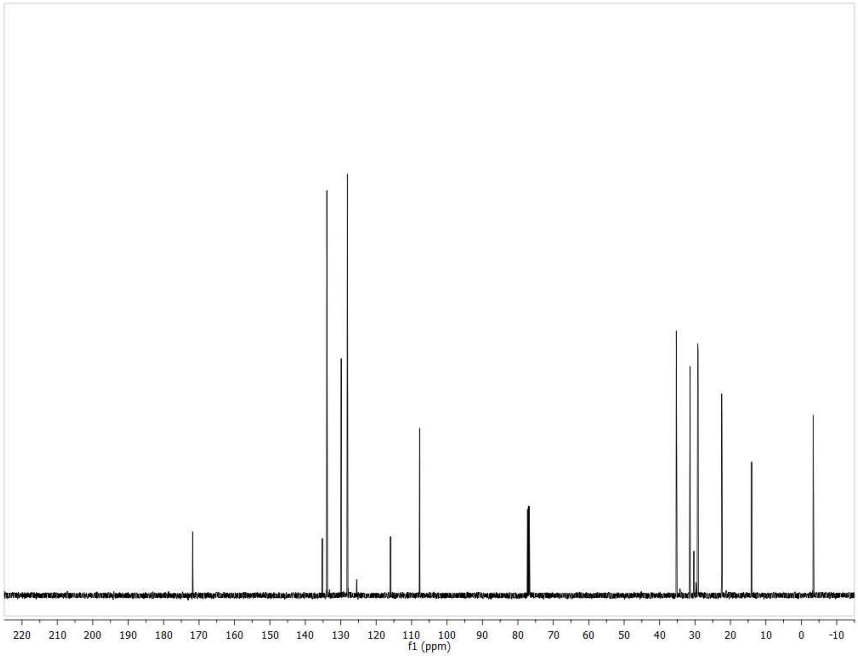

O
O
S
p-toluyl
PhMe2Si
n-C6H13
39
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

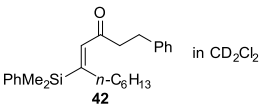

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
NH2
PhMe2Si
n-C6H13
40
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

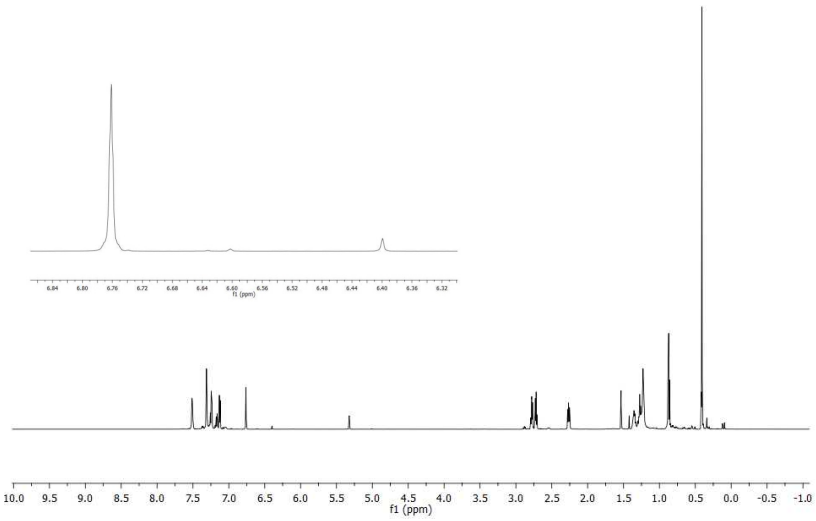

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

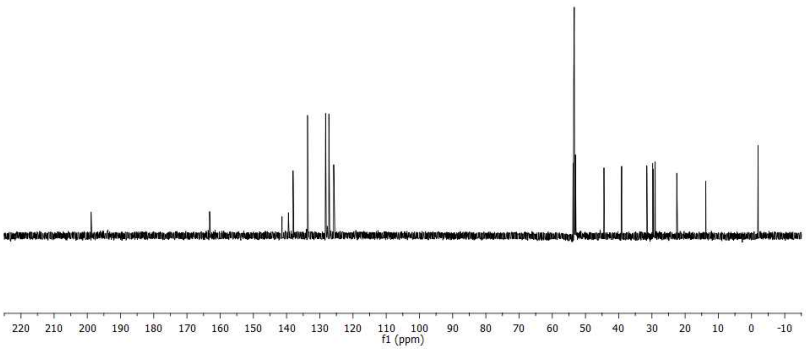

CN
PhMe2Si
n-C6H13
41
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

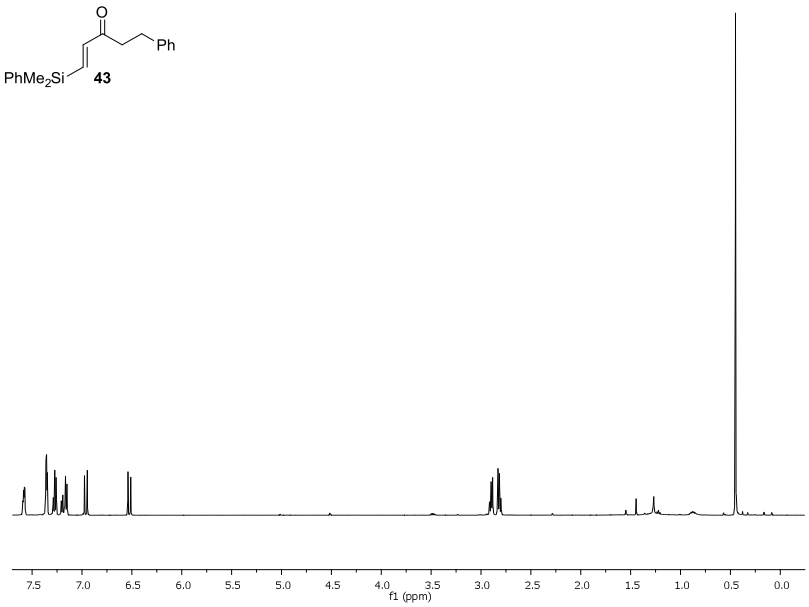

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

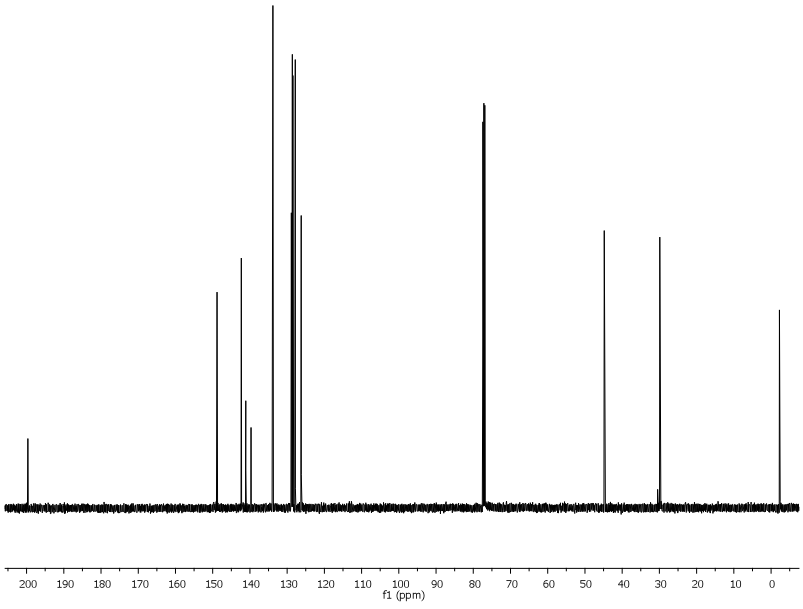

O
Ph
PhMe2Si
n-C6H13

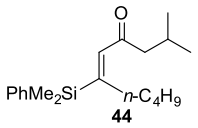
42 in CD_2Cl_2


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

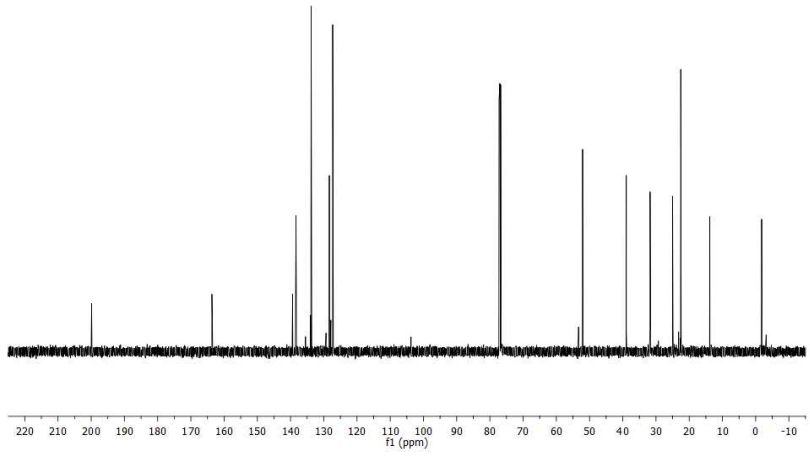

O
Ph
PhMe2Si
43
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

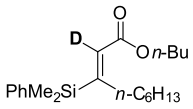

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
PhMe2Si
n-C4H9

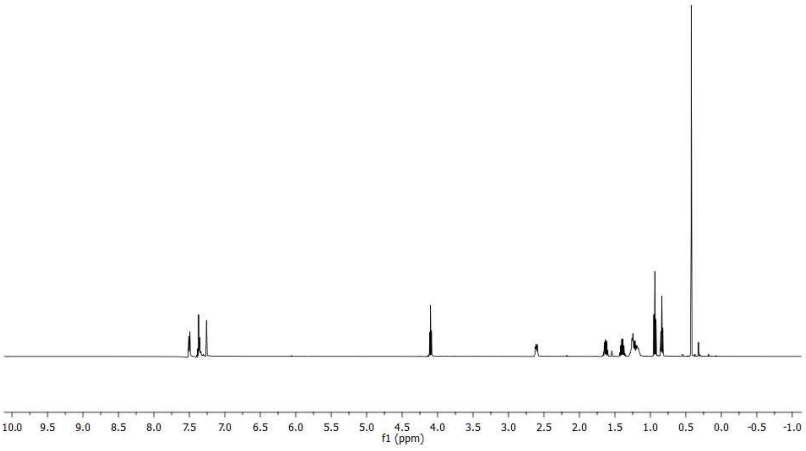
44

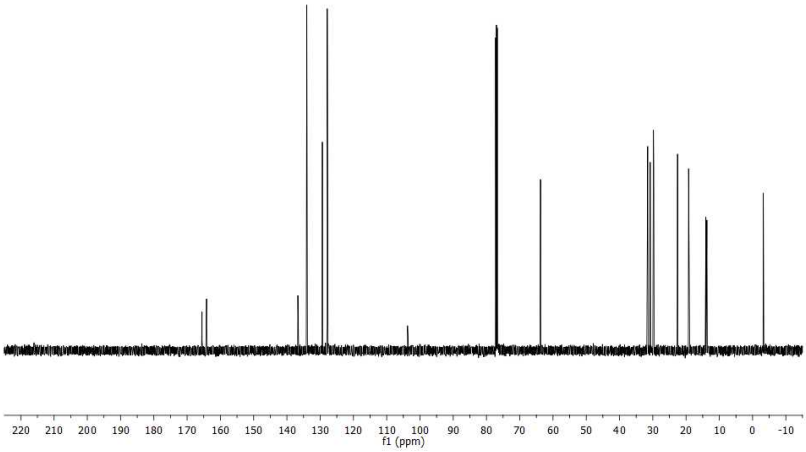
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

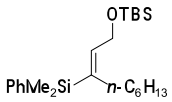

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
D
O n-Bu
PhMe2Si
n-C6H13

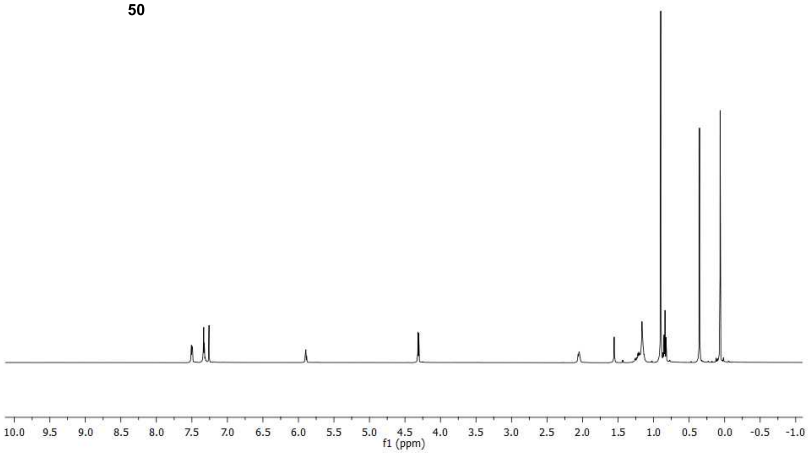
45


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OTBS
PhMe2Si
n-C6H13

50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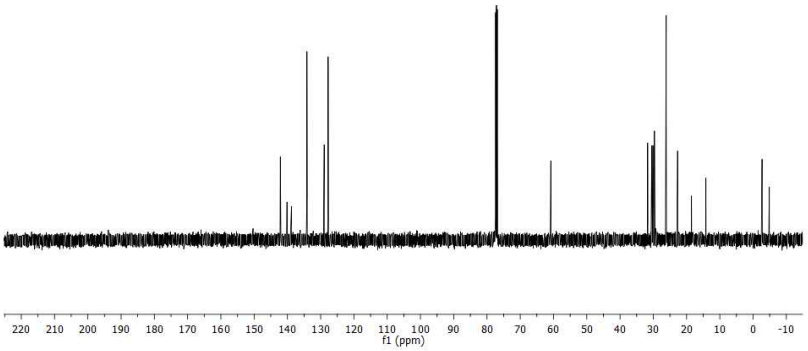
f1 (ppm)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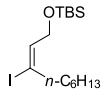
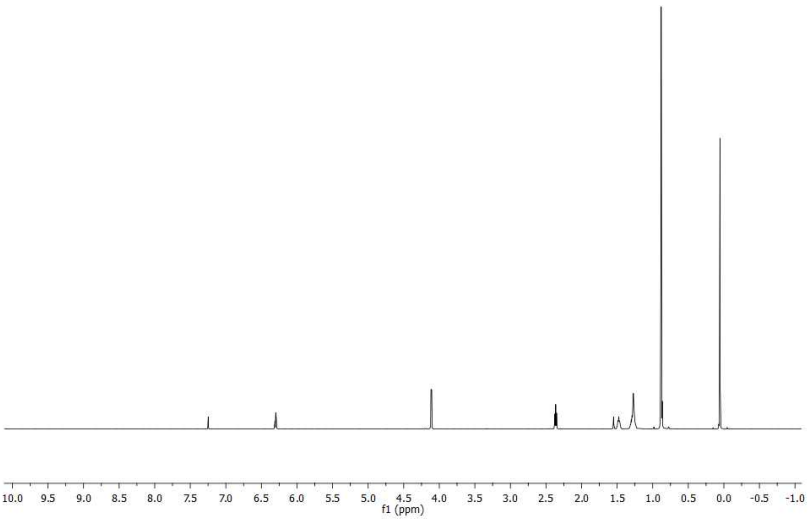
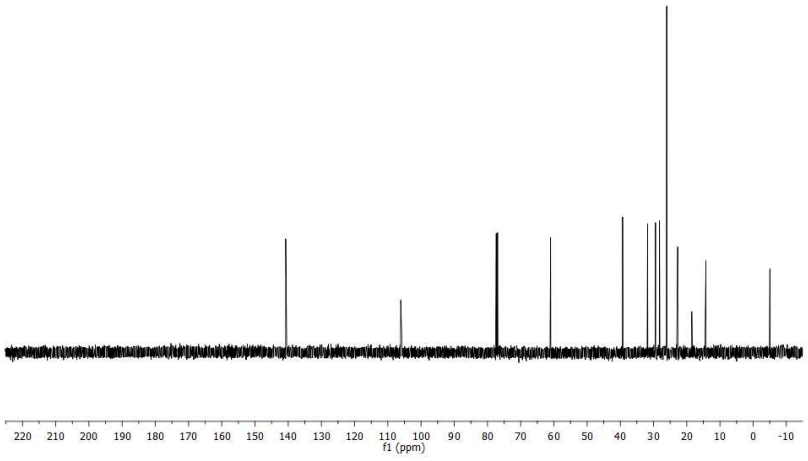
f1 (ppm)


OTBS
I
n-C6H13

51


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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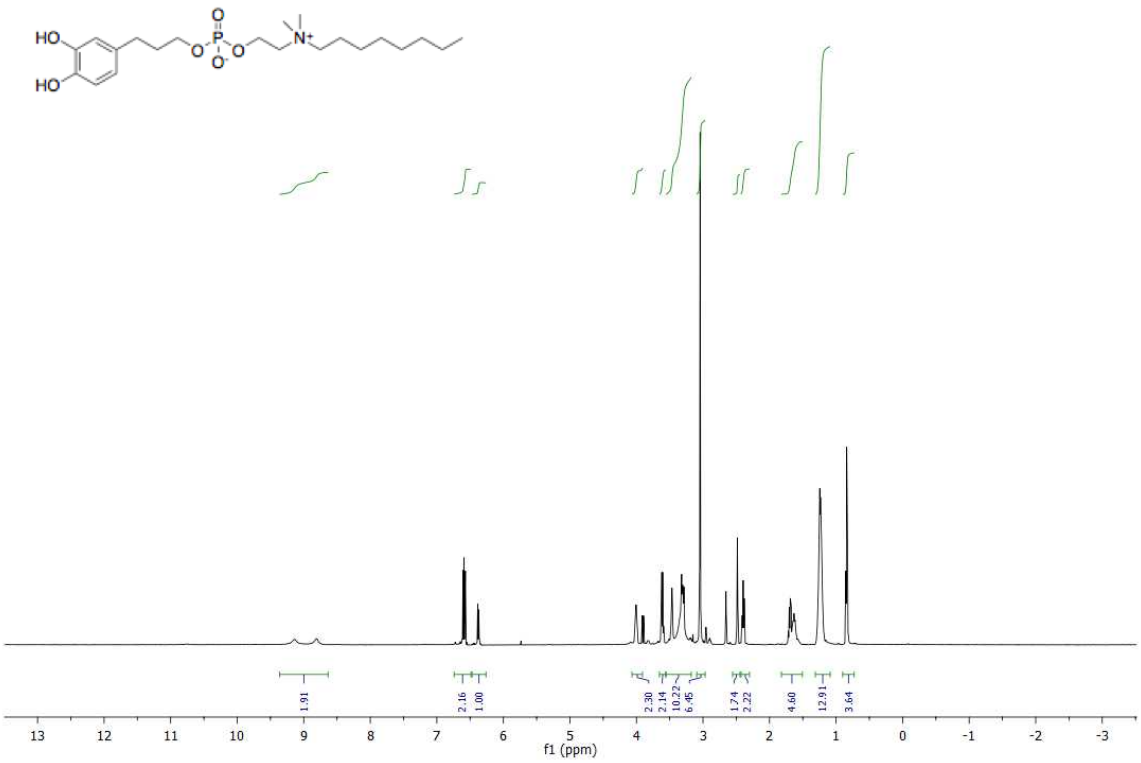
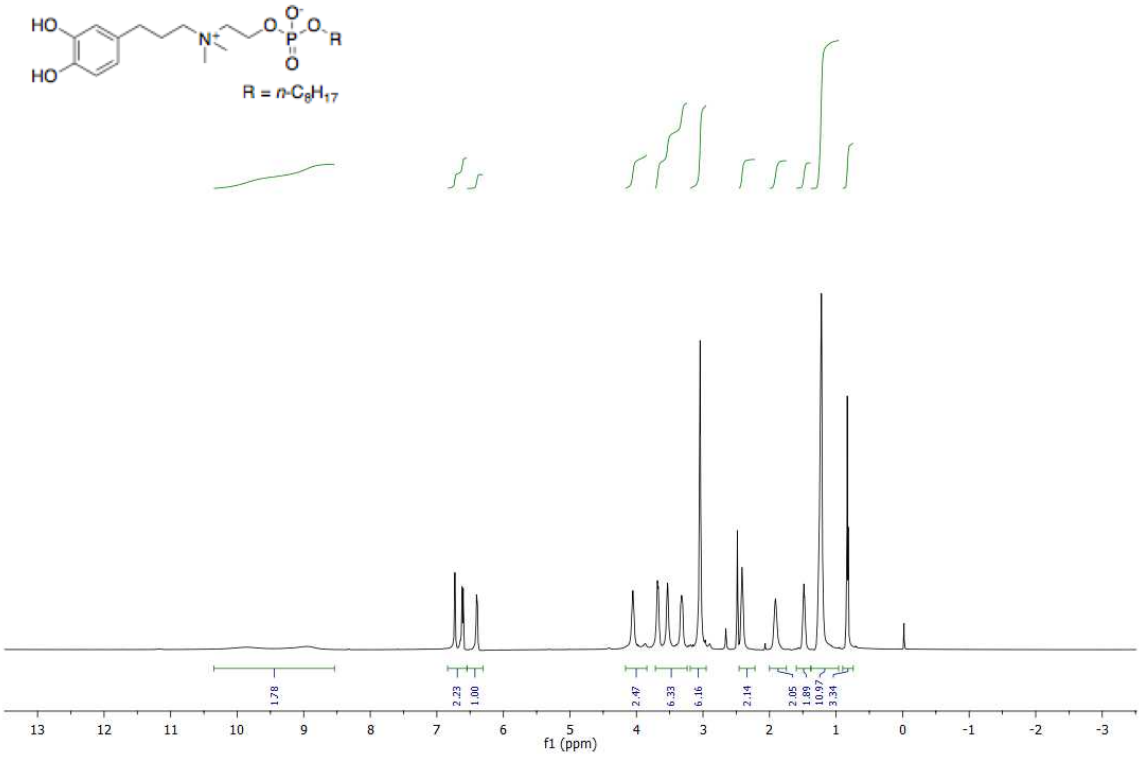
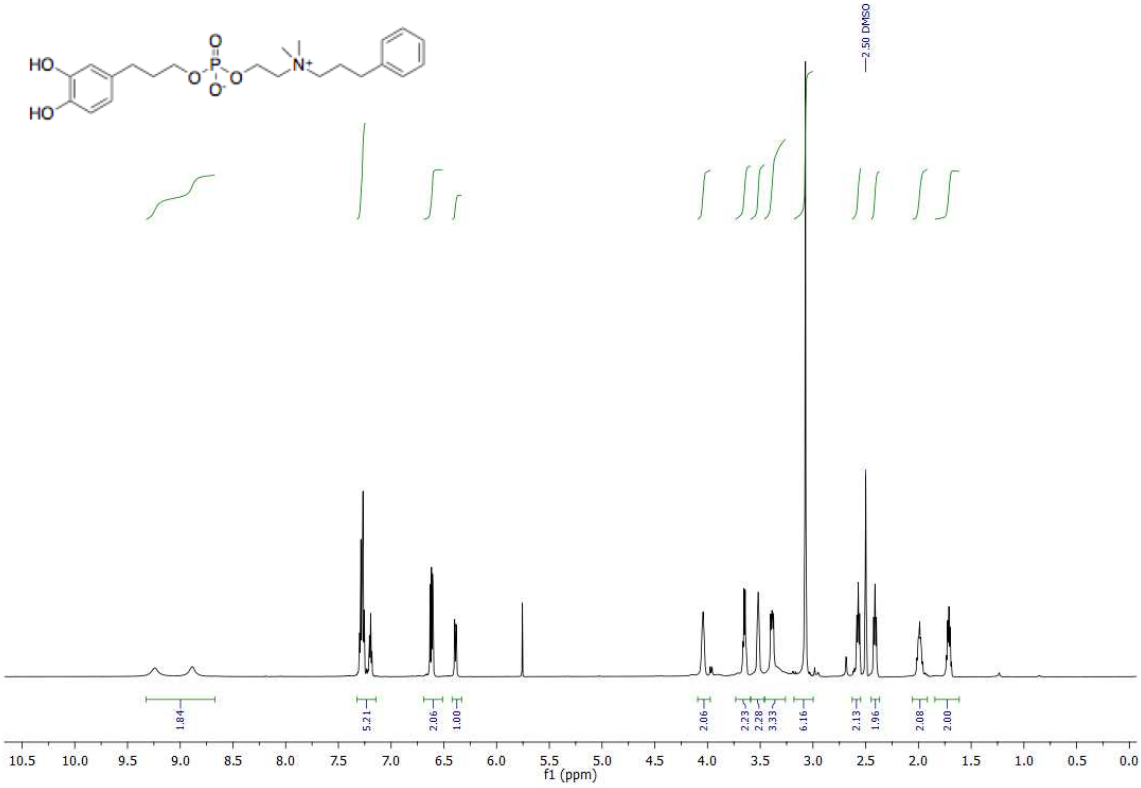
f1 (ppm)


HO
HO
O
P
O
O
O
N+
1.91
2.16
1.00
2.30
2.14
10.22
6.45
1.74
2.22
4.60
12.91
3.64
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


HO
HO
N+
O
O
P
O
O-
O
R
R = n-C8H17
1.78
2.23
1.00
2.47
6.33
6.16
2.14
2.05
1.89
10.97
3.34
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


HO
HO
O
O
O
O
N+
2.50 DMSO
1.84
5.21
2.06
1.00
2.06
2.23
2.28
3.33
6.16
2.13
1.96
2.08
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)