ENANTIOSELECTIVE METHODS FOR ALLYLIC SUBSTITUTION AND CONJUGATE ADDITION REACTIONS CATALYZED BY N-HETEROCYCLIC CARBENE–COPPER COMPLEXES

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KEVIN PATRICK MCGRATH

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Abstract

■ Chapter 1

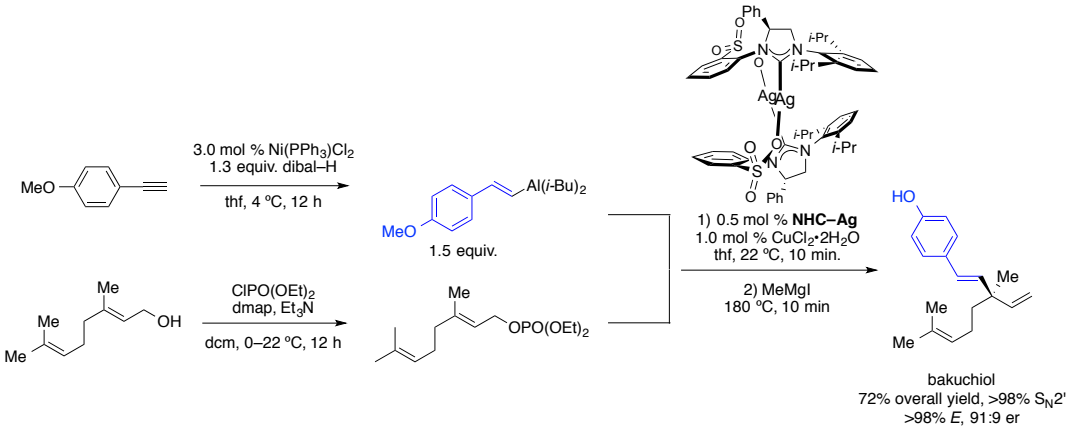
Catalytic Enantioselective Addition of Organoaluminum Reagents

Catalytic methods involving the enantioselective addition of both commercially available as well as *in situ* generated organoaluminum reagents are reviewed. An overview of additions to aldehydes, ketones, and imines is provided as well as the difficulties and limitations of such transformations. Furthermore, additions to unsaturation adjacent to a leaving group to form a new stereogenic center are examined. Finally, conjugate addition reactions wherein an organoaluminum reagent is added to an olefin adjacent to a carbonyl or nitro group are discussed.

■ Chapter 2

Synthesis of Quaternary Carbon Stereogenic Centers through Enantioselective Cu-Catalyzed Allylic Substitution with Alkenylaluminum Reagents

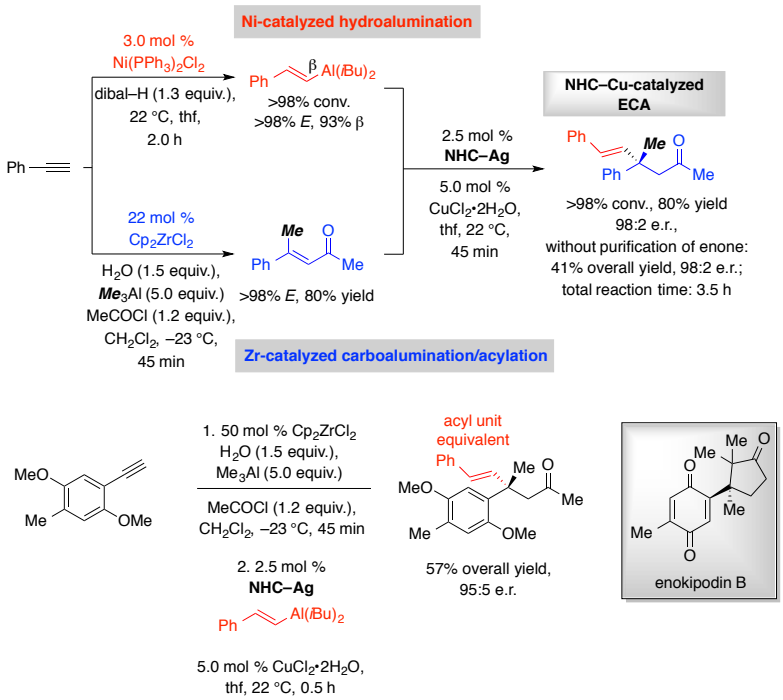
A method for the formation of 1,4-diene containing quaternary stereogenic centers through catalytic enantioselective allylic substitution is disclosed. The addition of alkyl- and aryl-substituted alkenylaluminum reagents to trisubstituted allylic phosphates is promoted by 0.5–2.5 mol % of a sulfonate-containing bidentate N-heterocyclic carbene–copper complex. Products containing a quaternary stereogenic center as well as a newly formed terminal olefin are obtained in up to 97% yield and 99:1 er with high site selectivity (>98:2 S_N2':S_N2). The requisite nucleophiles are generated in situ through hydroalumination of terminal alkynes. The utility of the method is demonstrated through a concise synthesis of natural product bakuchiol.



■ Chapter 3

A Multicomponent Ni-, Zr-, Cu-Catalyzed Strategy for Enantioselective Synthesis of Alkenyl-Substituted Quaternary Carbons

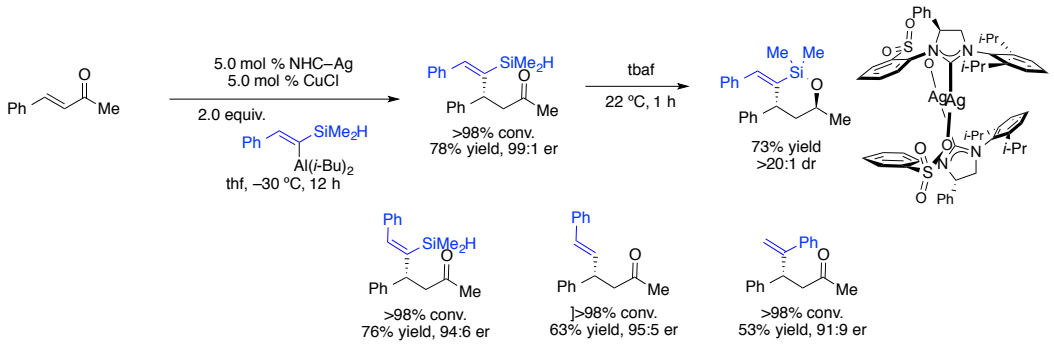
Despite the widespread use of conjugate addition in organic synthesis, few reports pertain to the addition of nucleophiles to acyclic systems and none in which the nucleophile is an alkene. Herein, we report the first examples of enantioselective conjugate addition of alkenylmetal reagents to trisubstituted enones to form all-carbon quaternary stereogenic centers. Alkenylaluminum nucleophiles are prepared through a site-selective Ni-catalyzed hydroalumination of terminal alkynes and the requisite E-trisubsituted enones are the products of a regioselective Zr-catalyzed carboalumination/acylation of a terminal alkyne. Products are obtained in up to 97% yield and 99:1 er. A model for enantioselectivity, supported by DFT calculations, is proposed.



■ Chapter 4

Formation of Tertiary Centers through Catalytic Enantioselective Conjugate Addition of Alkenylaluminum Reagents to Acyclic Enones

We have developed an enantioselective NHC–Cu catalyzed synthesis of tertiary centers in acyclic systems using in situ generated alkenylaluminum reagents, as current methods typically rely on Rh-catalysis at high temperatures with alkenyl boronic acids in protic solvents. Moreover, most examples include chalcone-derived substrates, which, while more reactive, often preclude further functionalization. With the current method, we are able to couple a variety of alkenyl nucleophiles with α,β-unsaturated ketones. *E*- or *Z*-silylalkenylaluminum reagents, derived from hydroalumination of silyl-protected alkynes, lead to products in good yields and high enantioselectivities. Additionally, both the α- and β-alkenylaluminum reagents participate in the reaction.



■ Chapter 5

Development of N-Heterocyclic Carbene–Cu Catalyzed Allylic Substitution of Diboryl Methane to Morita-Baylis-Hillman Derived Allylic Phosphates

We have developed a method for the coupling of a geminyl diboron reagent with Morita-Baylis-Hillman derived trisubstituted ester-containing allylic phosphates. With 10 mol % of an in situ generated NHC–Cu complex and 1.5 equivalents of the boron reagent, we are able to form the desired product in high regio- and enantioselectivity with a 2,5-di*tert*-butyl containing carbene. Simple aryl substituents as well as those containing a halogen or an electron-withdrawing group furnish the desired products in up to 85% yield and 98:2 er. Alkyl-containing substrates are also competent reaction partners, although longer chain aliphatics results in slightly diminished enantioselectivity. We are pursuing the application of this method to the synthesis of α-methylene lactones which can be further functionalized to natural products like tubulin polymerization inhibitor (–)-steganone and glaucoma medication (+)-pilocarpine.

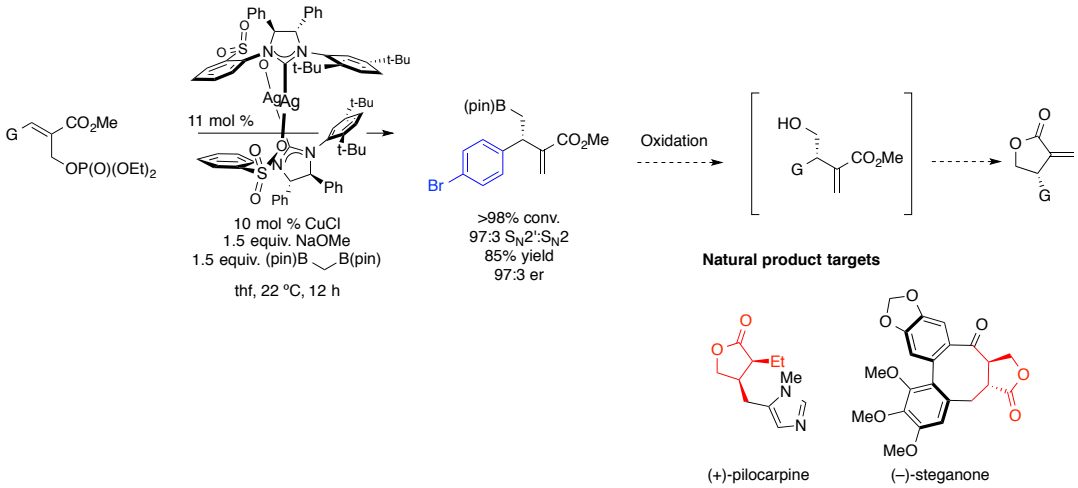

G
CO2Me
OP(O)(OEt)2
11 mol %
10 mol % CuCl
1.5 equiv. NaOMe
1.5 equiv. (pin)B B(pin)
thf, 22 °C, 12 h
(pin)B
CO2Me
Br
>98% conv.
97:3 SN2':SN2
85% yield
97:3 er
Oxidation
HO
G
CO2Me
Natural product targets
Et
Me
N
N
(+)-pilocarpine
MeO
MeO
MeO
(–)-steganone

Table of Contents

Chapter 1:

Catalytic Enantioselective Addition of Organoaluminum Reagents

1.1 Introduction

Additions of organometallic reagents to C–O, C–N, and C–C bonds to form new stereogenic centers are among the most fundamental C–C bond forming transformations. While organolithium and -magnesium compounds react readily with carbonyls and imines, control of enantioselectivity remains challenging, with the majority of transformations requiring extreme cryogenic temperatures and stoichiometric chiral ligands.[1] Moreover, the application of these reagents to allylic substitution and conjugate addition remains challenging due to their inherent reactivity and the need for high site selectivity.[2] Organozinc reagents have also received considerable interest due to their limited reactivity with aldehydes and ketones without the aid of a catalyst.[3] Despite the successes with such reagents, organozinc compounds are typically more expensive than the corresponding lithium or magnesium reagents especially dimethyzinc, which suffers from low reactivity in many catalytic systems.[4]

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(1) Luderer, M. R.; Basley, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. *Tetrahedron Asymm.* **2009**, *20*, 981–998.
(2) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.
(3)(a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; (c) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378; (d) Mauléon, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963; (e) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989; (f) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; (g) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629; (h) Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; (i) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; (j) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1097–1100. (k) Yamada, K.-I.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874–2886; (l) Matsumoto, Y.; Yamada, K-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581; (m) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804.
(4) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem, Soc.* **1989**, *111*, 4082–4036; (b) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260–14261; (c) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184.

Organoaluminum compounds often show reactivity that is in between that of organomagnesium reagents and organozincs. A range of simple trialkylaluminum reagents are commercially available and inexpensive (compared to alkylzincs). Additionally, organolithium reagents can react with aluminum halides to generate a variety of compounds. Organoaluminum compounds exhibit decreased Brønsted basicity relative to magnesium or lithium compounds and increased Lewis acidity due to the empty p-orbital on the aluminum center.[5] This chapter serves as an overview of catalytic enantioselective reactions of organoaluminum reagents, namely 1,2-addition, allylic substitution, and conjugate addition.

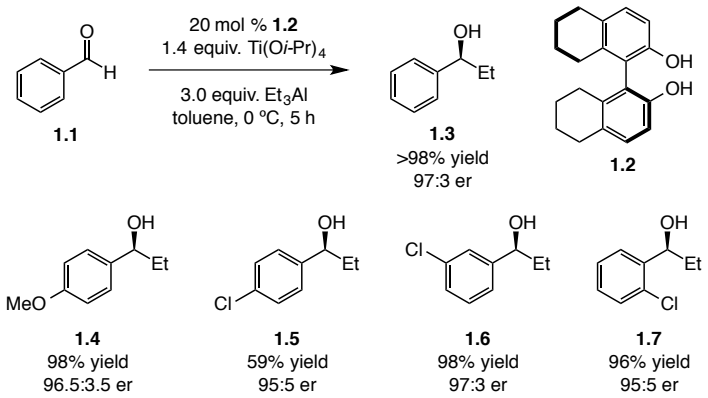
1.2 Catalytic Enantioselective 1,2-Addition of Organoaluminum Reagents

1.2.a. Addition to Aldehydes

Chan and co-workers published the first catalytic enantioselective addition of an organoaluminum reagent to an aldehyde in 1997.[6] As shown in Scheme 1.1, triethylaluminum was added to a selection of aryl aldehydes. Transformations are catalyzed by 20 mol % H_8-BINOL (**1.2**) and 1.4 equiv. of Ti(O*i*Pr)$_4$. The desired secondary alcohols are obtained in high yields and enantioselectivities regardless of the substitution on the aryl ring. Only a *para*-chloro substituent shows any marked decrease in conversion of the starting aldehyde. The authors note that the addition of Me_3Al results in significantly decreased enantioselectivity (70:30 er versus 97:3 er for **1.3**). Additionally, reactions with Al(*i*-Bu)$_3$ lead exclusively to the reduced product, presumably through a Meerwein-Ponndorf-Verley reduction mechanism.[7]

(5) von Zezschwitz, P. *Synthesis* **2008**, 1809–1831.
(6) Zhang, F.-Y.; Yip, C.-W.; Chan, A. S. C. *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081.
(7) Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796–14803.

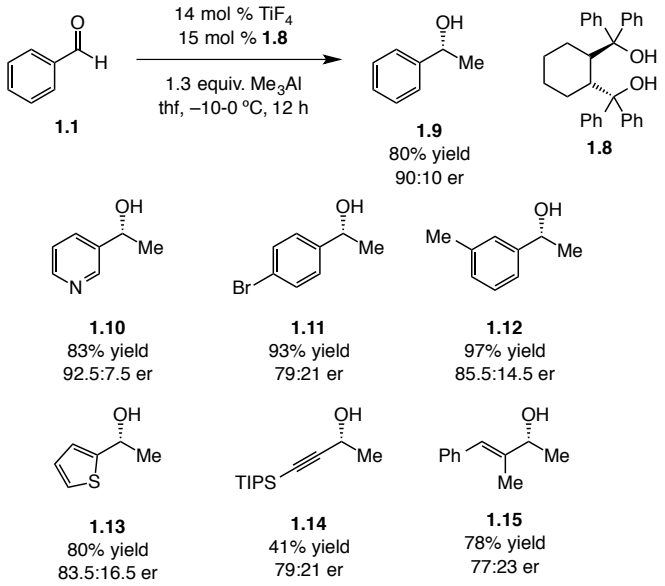
Scheme 1.1 Ti-Catalyzed Triethylaluminum Additions to Aryl Aldehydes



In 1998, Carreira and co-workers published a catalytic enantioselective additions of Me_3Al to aldehydes (Scheme 1.2).[8] Reactions are catalyzed by a chiral diol-ligated TiF_2 complex generated in situ through reaction of the diol with Me_3Al and subsequent addition of TiF_4. Reaction of aryl as well as alkenyl and alkynyl aldehydes generate the desired secondary alcohols in good yields and up to 90:10 er. While Et_3Al participates in the catalytic reactions, it is only with stoichiometric amounts of the catalyst that the product could be isolated in high enantiomeric purity. Aliphatic aldehydes lead to low yields as well as enantioselectivities due to their electron-rich nature (compared to acetophenone derivatives).

(8) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett*. **1998**, *39*, 9593–9596.

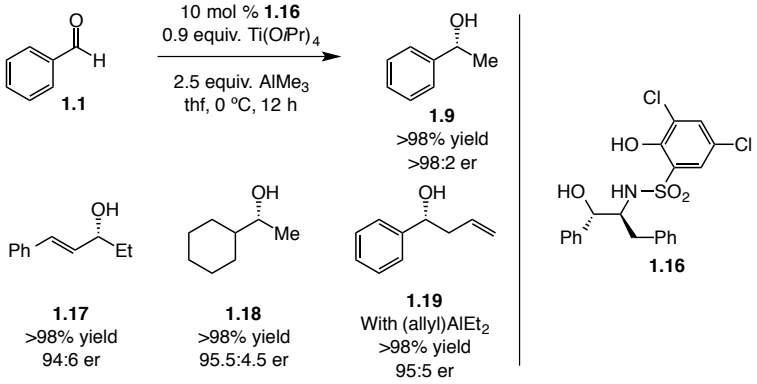
Scheme 1.2. Ti-Catalyzed Addition of Me_3Al to Aldehydes



The Gau laboratory published the addition of organoaluminum reagents to aldehydes catalyzed by $Ti(OiPr)_4$ and a chiral *N*-sulfonyl amino alcohol (Scheme 1.3).[9] Methyl and ethyl additions to simple aryl aldehydes proceed with high yields and enantioselectivity (up to >98:2 er). Moreover, both unsaturated and aliphatic aldehydes participate in the reaction to furnish the desired secondary alcohol with high enantiomeric purity. In addition to aliphatic nucleophiles, the authors also present the first Ti-catalyzed addition of an allylaluminum reagent to an aldehyde, which proceeds with complete group selectivity and 95:5 er.

(9) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun.* **2001**, 1546–1547.

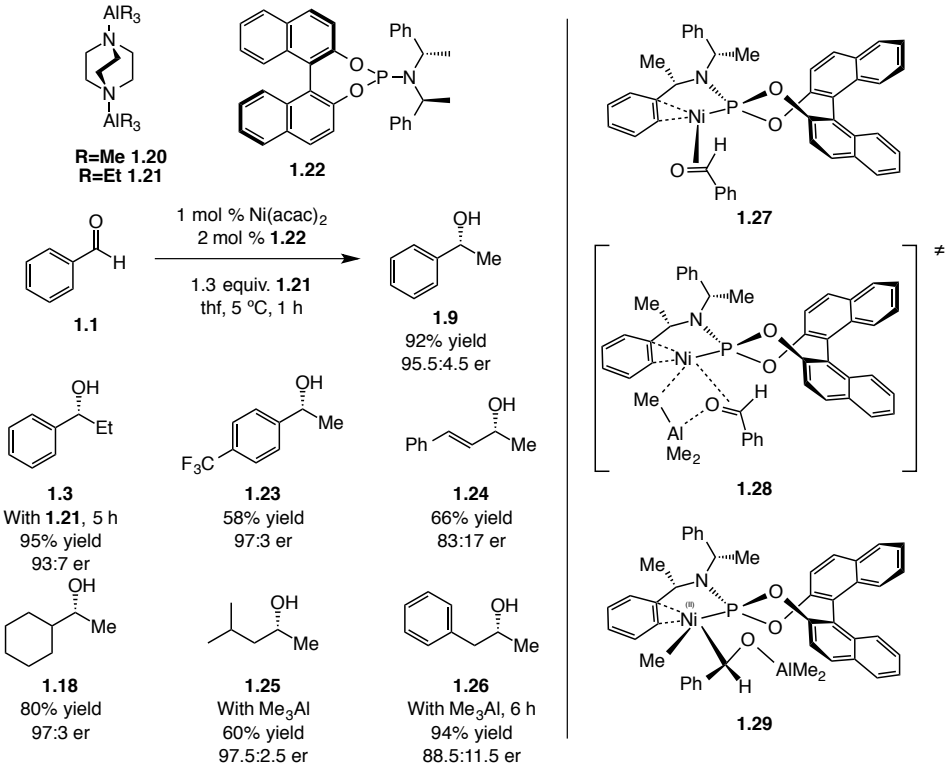
Scheme 1.3. Ti–Amino Alcohol Catalyzed Addition of Alkyl and Allyl Nucleophiles



Woodward and co-workers disclosed a phosphoramidite–Ni-catalyzed addition of methyl and ethyl nucleophiles through reaction of 1,4-diazabicyclo[2.2.2]octane (dabco) complexed Me_3Al and Et_3Al, respectively, with a variety of aldehydes (Scheme 1.4).[10] High enantioselectivity can be achieved for both methyl and ethyl addition to benzaldehyde (up to 95.5:4.5 er). Electron deficient aldehydes result in the most efficient and selective reactions (97:3 er). Furthermore, unlike Ti-catalyzed reactions, aliphatic aldehydes participate well in the reaction, although in some cases the presence of dabco results in α-deprotonation. The putative mechanism of the reaction involves two point ligation of nickel(0) to the phosphoramidite ligand through coordination of phosphorous as well as the pi-system of the adjacent aryl ring. The nickel center then coordinates the aldehyde in an η^2 fashion. Coordination of the aluminum reagent, which also serves as a Lewis acid to activate the aldehyde, is followed by oxidative addition to generate a Ni(II) complex and an aluminum alkoxide. Subsequent reductive elimination furnishes the desired product and regenerates the catalyst. The authors have suggested that the decreased enantioselectivity observed with an enal is due to competitive coordination of the alkene versus the aryl group of the ligand. Additionally, electron-rich aldehydes readily form benzylic cations in the presence of the aluminum reagent and lead to indiscriminant oxidative addition and therefore decreased enantioselectivity.

(10) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232–2234.

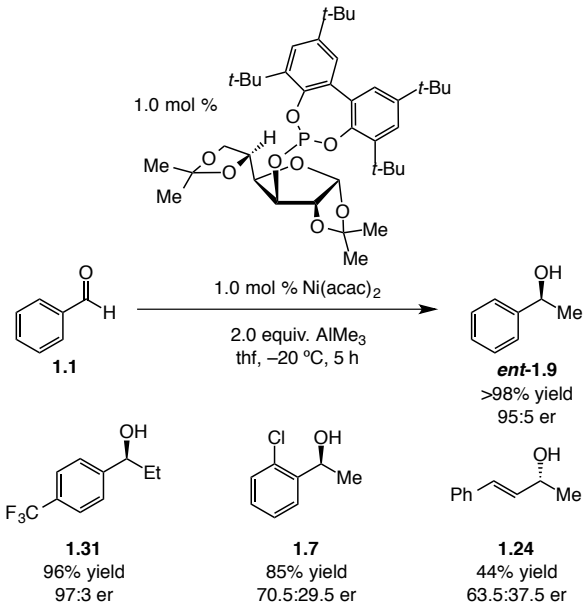
Scheme 1.4. Nickel-Catalyzed Addition of Alkylaluminum Reagents to Aldehydes



This method was further expanded upon through the use of a monophosphate ligand derived from (D)-glucose.[11] As shown in Scheme 1.5, a wider range of aldehydes participates in the reaction with high efficiency and enantioselectivity. Notably, both sterically hindered *ortho*-substituted aryl aldehydes and aliphatic aldehydes suffer from low enantioselectivity (63:37 to 70:30 er).

(11) (a) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159–8165. (b) Alegre, S.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2011**, *22*, 834–839.

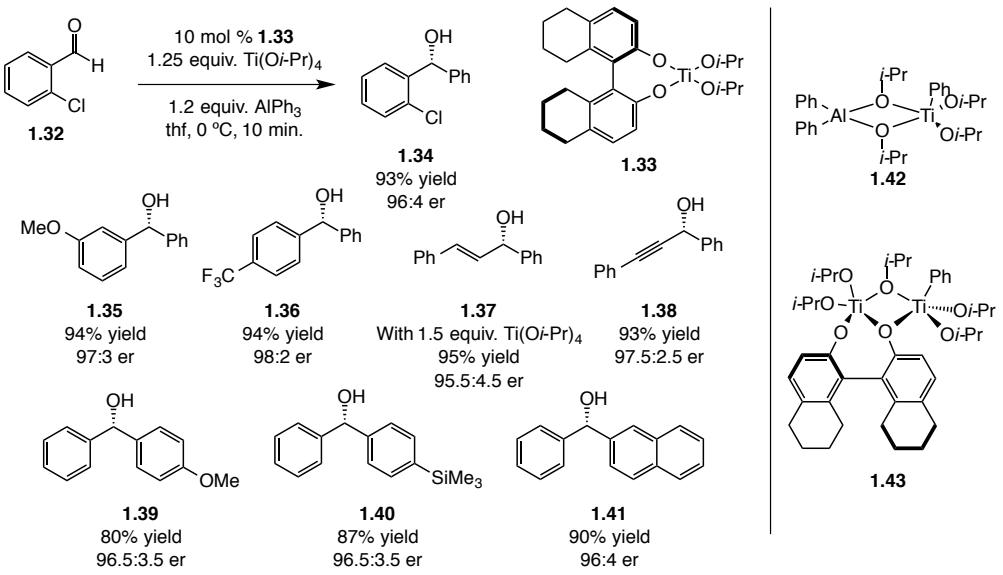
Scheme 1.5. Ni-Catalyzed Additions to Aldehydes With a Phosphorylated Glucose Derivative



Gau et al. disclosed the first additions of triarylaluminum reagents, generated from addition of aryl Grignard reagents to $AlCl_3$, in 2006 (Scheme 1.6).[12] Reactions are catalyzed by 10 mol % of a H_8-BINOL–Ti(O*i*Pr)$_2$ complex, **1.33**, and 1.25 equiv. Ti(O*i*Pr)$_4$. Sterically hindered aldehydes as well as those containing electron-withdrawing or electron-donating groups deliver the desired secondary alcohols in up to 94% yield and 98:2 er. Moreover, aryl nucleophiles can be added to unsaturated aldehydes with high enantioselectivity despite the sterically smaller substituents. Mechanistic studies indicate that complex **1.42**, generated from reaction of $AlPh_3$ and Ti(O*i*Pr)$_4$, transfers PhTi(O*i*Pr)$_3$ to the H_8-binol–Ti complex to form the catalytically active bimetallic complex, **1.43**. The method was expanded upon in 2009 with the more atom economic phenyl diethylaluminum. Reactions proceed with similar or slightly diminished enantioselectivity although high group selectivity is observed in most cases.[13]

(12) Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809.
(13) Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.*, **2009**, *74*, 3500–3505.

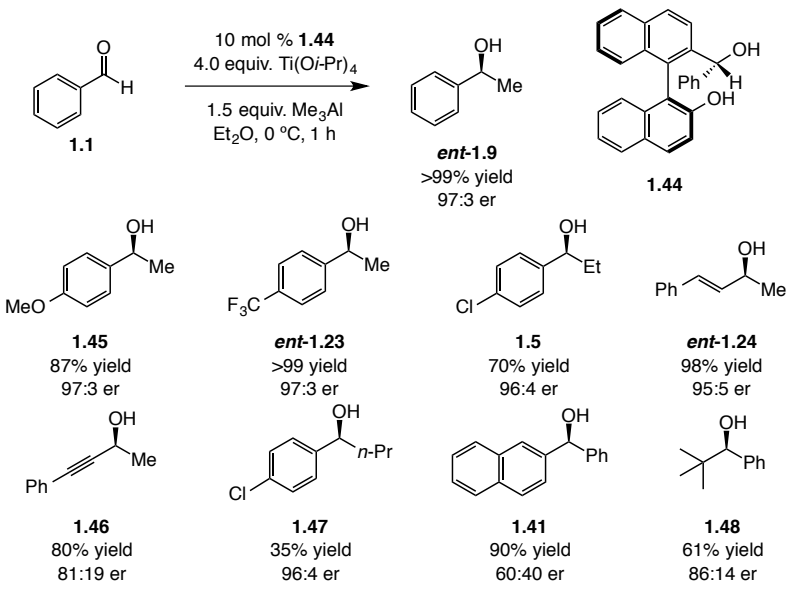
Scheme 1.6. Ti-Catalyzed addition of triarylaluminum reagents



In 2012, Yus reported the addition of a variety of alkyl- and arylaluminum reagents to aldehydes catalyzed by 10 mol % of a chiral BINMOL catalyst and excess Ti(O*i*-Pr)$_4$.[14] As shown in Scheme 1.7, additions of methyl and ethyl nucleophiles proceed to furnish the desired products in high yields and uniformly high enantioselectivities (up to >99% yield and up to 97:3 er). While cinnamaldehyde leads to a highly enantioselective product, an alkyne-containing substrate results in 81:19 er. Additionally, reactions of *n*-propyl and isobutyl nucleophiles are low yielding in part due to competitive reduction of the aldehydes. Additions of aryl nucleophiles are also less enantioselective than the corresponding alkyl additions.

(14) Fernández-Mateos, E; Maciá, B.; Yus, M. *Tetrahedron: Asymmetry* **2012**, 789–794.

Scheme 1.7. BINMOL–Ti-Catalyzed Addition of Organoaluminum Reagents to Aldehydes

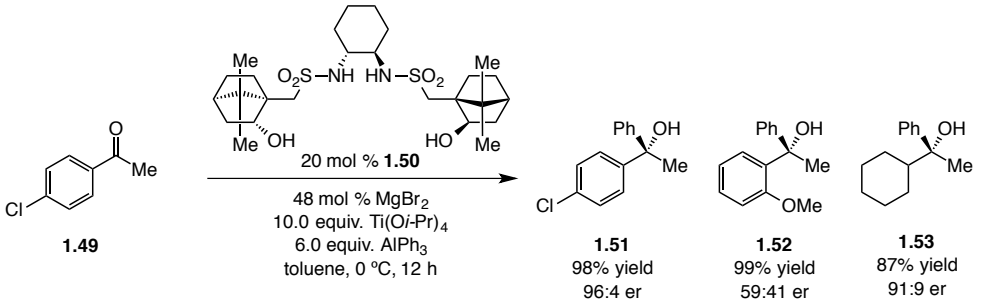


1.2.b. Additions to Ketones

In 2008, Gau and co-workers disclosed a method for the addition of triarylaluminum reagents to a variety of ketones (Scheme 1.8).[15] The reaction is catalyzed by 20 mol % of a C_2 symmetric camphor sulfonic acid derived ligand and 10 equivalents $Ti(OiPr)_4$. The authors found that the addition of substoichiometric amounts of $MgBr_2$ (originally an impurity from the synthesis of the organoaluminum) as an additive were necessary for both high yields and enantioselectivities. With 48 mol % $MgBr_2$, reaction of triphenylaluminum with substituted acetophenones lead to the desired tertiary alcohols in high yields and up to 96:4 er. Reaction with an acetophenone containing an *ortho* electron-donating group leads to lower enantioselectivity. Additionally, ketones with two aliphatic groups are less enantioselective, especially for straight chain aliphatics.

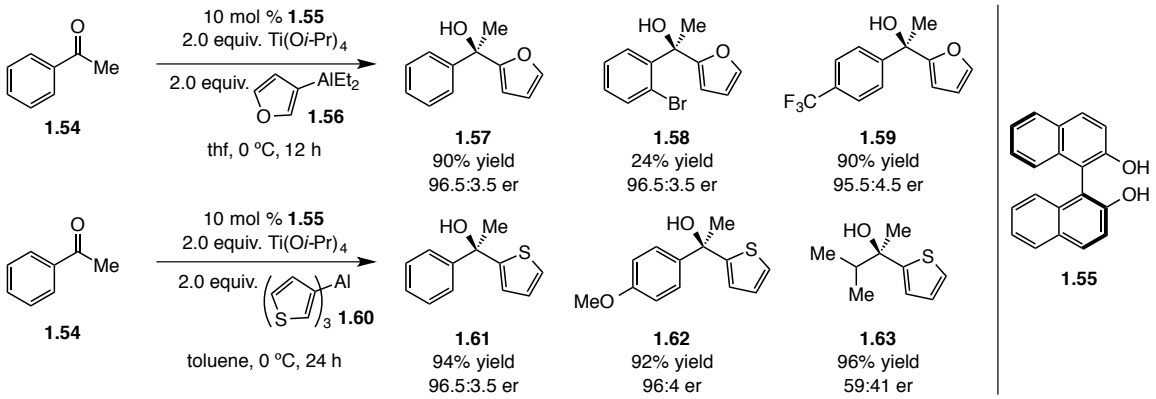
(15) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Adv. Synth. Catal.* **2008**, *350*, 1626–1634.

Scheme 1.8. Ti-Catalyzed Addition of Triarylaluminum Reagents to Ketones



The Gau group further explored aryl additions to ketones with the addition of 2-furyl diethylaluminum, generated from 2-furyllithium addition to diethylaluminum chloride, in order to generate furyl alcohols as intermediates for organic synthesis. As described in Scheme 1.9, the presence of 2.0 equivalents of Ti(O*i*Pr)$_4$ and 10-20 mol % (*S*)-BINOL, furyl addition to sterically hindered acetophenones proceeds with up to 96.5:3.5 er although yields are variable (24–90% yield). Both electron-withdrawing and electron-donating acetophenone derivatives lead to the corresponding alcohols efficiently. The same group published a similar method in 2009, adding Al(2-thienyl)$_3$ to aryl ketones in high enantioselectivity and yields. Reactions with aliphatic ketones, while efficient, furnished products in less than 60:40 er (Scheme 1.9).[16,17]

Scheme 1.9. Ti-BINOL Catalyzed Addition of Furyl and Thienyl Nucleophiles

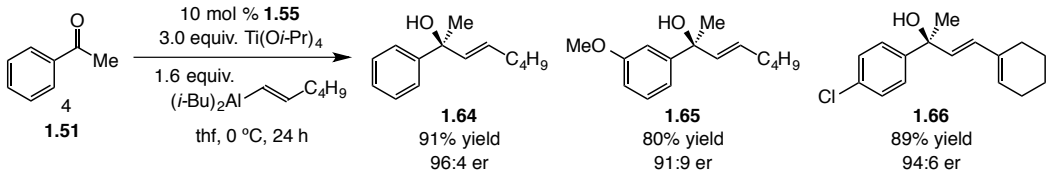


Under similar conditions for the aryl additions to ketones, the Gau group showed that additions of alkenylaluminum reagents, generated in situ through hydroalumination of terminal alkynes with dibal–H, to aryl- and alkenyl-substituted ketones proceed to

(16) Wu, K.-H.; Chaung, D.-W.; Chen, C.-A.; Gau, H.-M. *Chem. Commun.* **2008**, 2343–2345.
(17) Biradar, D. B.; Zhou, S.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386–3389.

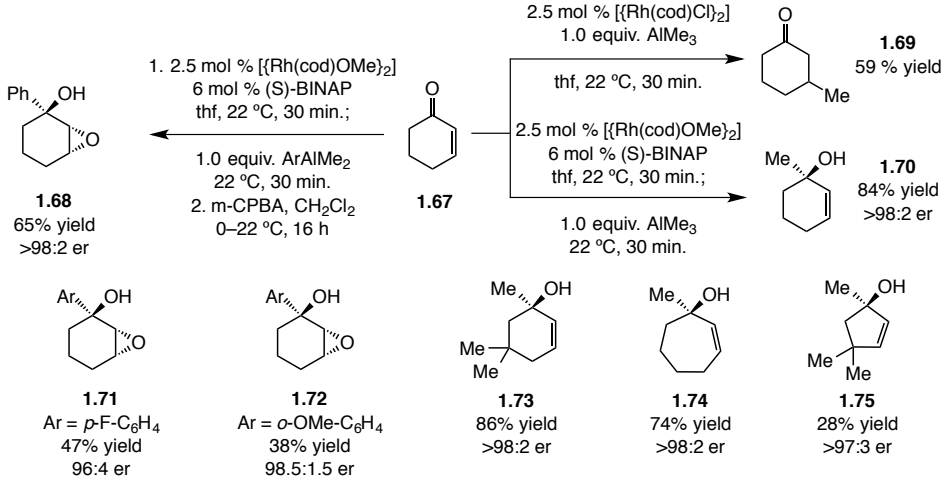
furnish products with up to 93% yield and 99:1 er. Reactions with electron-rich ketones are slightly less enantioselective (Scheme 1.10).[18]

Scheme 1.10. Ti-BINOL Catalyzed Addition of Alkenylaluminum Nucleophiles



In 2007, von Zezschwitz and co-workers disclosed the Rh-catalyzed 1,2 addition of alkyl- and arylaluminum reagents to a range of enones.[19] The authors showed that, with a Rh–BINAP complex, trimethylaluminum is added to cyclohexenone to form a tertiary alcohol (**1.70**) in 84% yield and >98:2 er (Scheme 1.11). In the absence of BINAP, the 1,4-addition product is formed in 59% yield. Reactions with 6- and 7-membered rings furnish the desired alcohols in high yields and enantioselectivities, whereas 5-membered rings resulted primarily in substrate decomposition. Arylaluminum reagents, generated from aryl Grignard addition to Me_2AlCl, are added selectively to cyclohexenone although the products were functionalized diastereoselectively to the corresponding epoxides due to product instability.

Scheme 1.11. Rh–BINAP Catalyzed Addition of Alkyl- and Arylaluminum Nucleophiles to Cyclic Enones



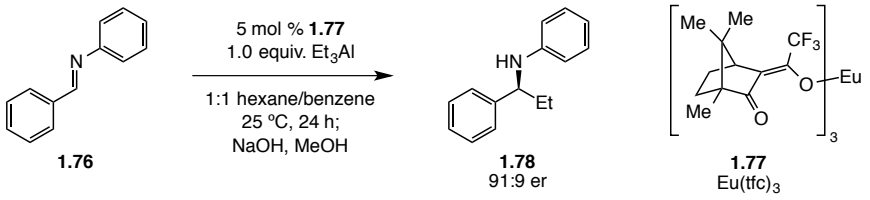
(18) Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499–502.

(19) (a) Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122–7124. (b) Kolb, A.; Zuo, W.; Siewert, J.; Harms, K.; von Zezschwitz, P. *Chem. Eur. J.* **2013**, *19*, 16366–16373.

1.2.c. Additions to imines and ketimines.

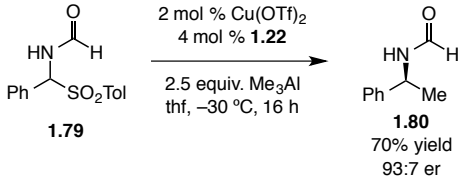
While pioneering work by Fujisawa and co-workers demonstrated the feasibility of Ni-catalyzed addition of trimethylaluminum to *N*-tosylbenzaldimine[20], Molander, Blum et al published the first enantioselective variant.[21] In the presence of a lanthanide catalyst, both Et_3Al and Me_3Al can be added to a variety of *N*-arylaldimines. A single enantioselective example is shown in which 5.0 mol % of Europium catalyst, $Eu(tfc)_3$, allows for the addition of Et_3Al to *N*-phenylbenzaldimine in 55 % yield and 91:9 er (Scheme 1.12). Replacing the lanthanide catalyst with a catalytic amount of a Lewis acid such as $SiMe_3Cl$, BF_3, $InCl_3$, or $ZnCl_2$ did not lead to formation of the desired product. The authors propose the intermediacy of an alkyl-lanthanide complex, which undergoes addition to the substrate.

Scheme 1.12. Europium-Catalyzed Addition of Alkylaluminums to Imines



In the course of investigating the addition of alkylzinc reagents to *N*-formylimines, Feringa reports a single example of trimethylaluminum addition.[22] The reaction is catalyzed by 4 mol % of a phosphoramidite ligand and 2 mol % $Cu(OTf)_2$ with 2.5 equivalents of Me_3Al. The desired product (**1.80**) is obtained in 70% yield and 93:7 er (Scheme 1.13).

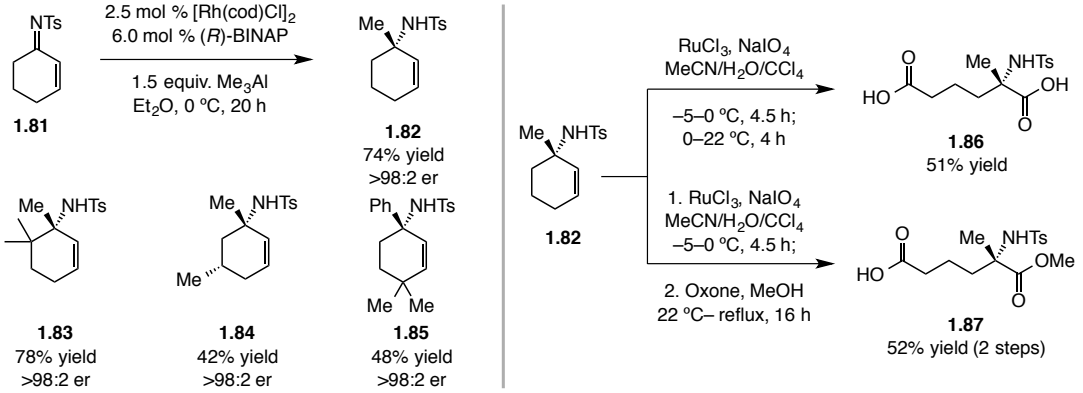
Scheme 1.13. Cu-Catalyzed Addition of Trimethylaluminum to *N*-Formylimines



(20) Ichiyanagi, T.; Kuniyama, S.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1998**, *27*, 1033–1034.
(21) Tsvelikhovsky, D.; Gelman, D.; Molander, G. A.; Blum J. *Org. Lett.* **2004**, *6*, 1995–1997.
(22) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940–947.

More recently, a Rh-catalyzed addition of organoaluminum reagents to *N*-tosyl ketimines derived from cyclohexenone has been published.[23] In the presence of 5.0 mol % of catalyst derived from $[Rh(cod)Cl]_2$ and (*R*)-BINAP, additions of both alkyl- as well as arylaluminum reagents proceed with high enantioselectivity (>98:2 er). Products can be functionalized through a Ru-catalyzed oxidative cleavage of the olefin in the presence of $NaIO_4$ to form di-acid **1.86** (Scheme 1.14).

Scheme 1.14. Rh-Catalyzed Addition of Alkyl- and Arylaluminum Reagents to *N*-Tosyl Ketimines



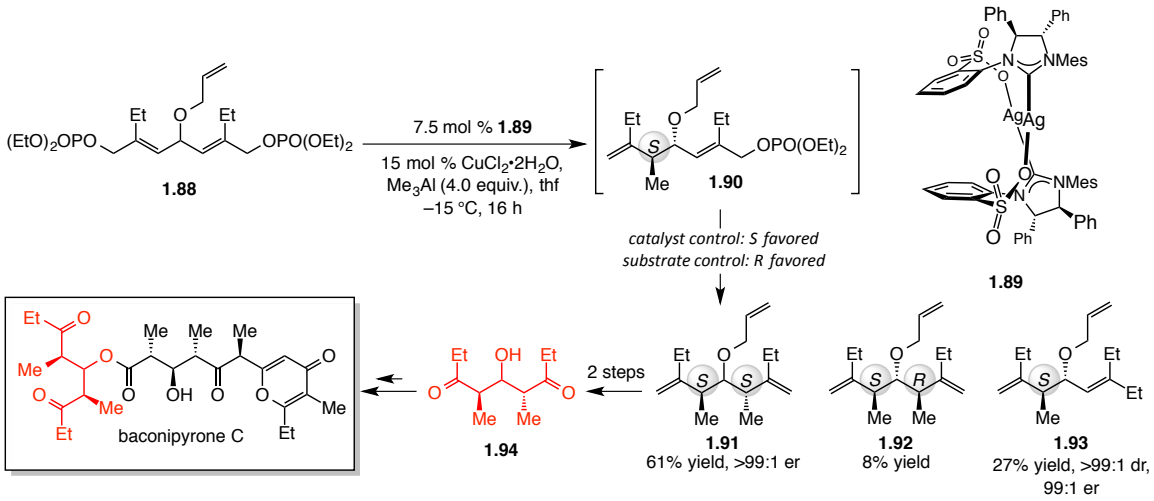
1.3 Catalytic Enantioselective Allylic Substitution with Organoaluminum Reagents

1.3.a. Addition of Alkyl and Aryl Nucleophiles

The first example of the addition of alkylaluminum reagents in enantioselective allylic substitution (EAS) was reported in the course of the total synthesis of siphonariid metabolite baconipyrone C.[24] One fragment of the molecule could come from a double allylic substitution of a symmetric allylic phosphate. Me_2Zn was found to be sluggish with super stoichiometric amounts of CuCN (10% conversion) and unreactive in the catalytic system with a model substrate. Upon switching to Me_3Al, with 15 mol % NHC–Cu complex, the desired *anti* product (**1.91**) could be obtained in 61% yield and >99:1 er. The critical second allylic substitution requires a highly catalyst controlled addition to obtain the desired diastereomer, as the substrate-controlled reaction produces the *syn* product (**1.92**).

(23) Hirner, S.; Kolb, A.; Westmeier, J.; Gebhardt, S.; Middel, S.; Harms, K.; von Zezschwitz, P. *Org. Lett.* **2014**, *16*, 3162–3165.
(24) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864.

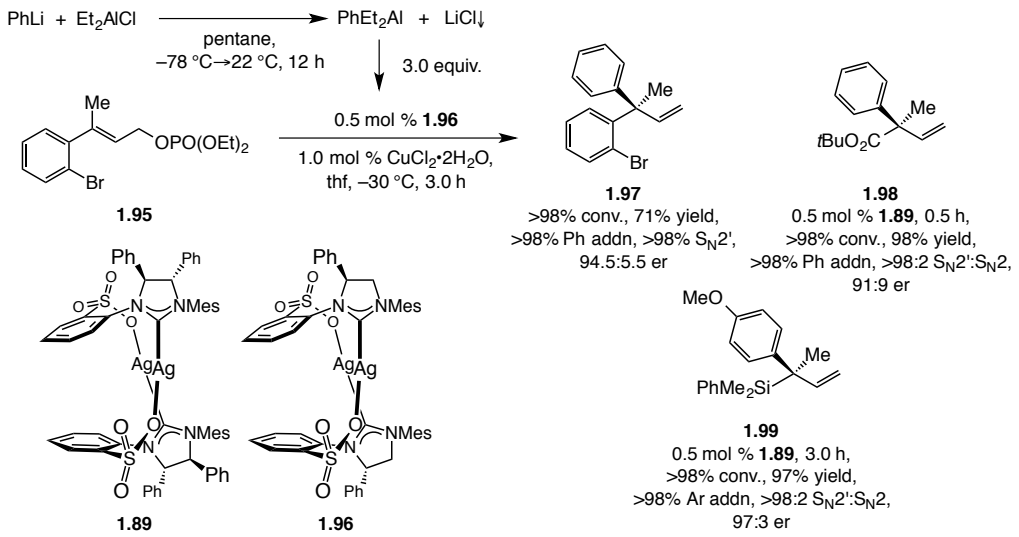
Scheme 1.15. Enantioselective Double Allylic Substitution in the Total Synthesis of Baconipyrone C



In addition to alkylaluminum reagents, a variety of mixed aryl(dialkyl)aluminum reagents have been examined in EAS reactions.[25] The only other method for EAS of aryl nucleophiles to generate quaternary stereocenters involves diarylzinc reagents, which, in addition to being less atom-economical, can be difficult to synthesize and purify.[26] The requisite nucleophiles can be formed in situ through reaction of commercially available aryllithium reagents with Et_2AlCl. The solution can be used directly in the reaction or after filtration of precipitated LiCl. Reactions proceed to full conversion in under three hours with selective transfer of the aryl unit and complete S_N2' selectivity. Products are obtained in up to 98% yield and 97:3 er (Scheme 1.16).

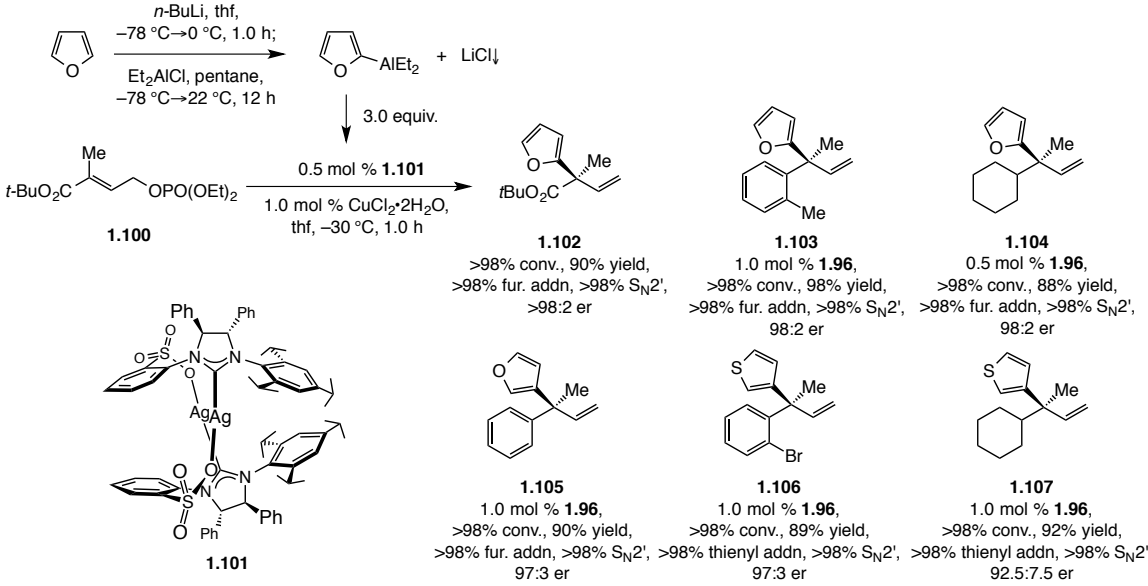
(25) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370–8374.
(26) (a) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558. For catalytic EAS reactions that involve arylmetals but deliver tertiary C–C bonds, see: (b) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393–3395; (c) Selim, K. B.; Yamada, K-i.; Tomioka, K. *Chem. Commun.* **2008**, 5140–5142; (d) Selim, K. B.; Matsumoto, Y.; Yamada, K-i.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733–8735; (e) Falciola, C. A.; Alexakis, A. *Chem. Eur. J.* **2008**, *14*, 10615–10627; (f) Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J. B.; Hajjaji, S. E.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 1205–1206.

Scheme 1.16. NHC–Cu-Catalyzed Allylic Substitution Reactions Starting with Aryllithium Reagents



As shown in Scheme 1.17, in the case of heteroaryl compounds, initial deprotonation, or lithium/halogen exchange, with *n*-butyllithium followed by addition to Et_2AlCl furnishes the required mixed aluminum nucleophiles. Reactions are similarly efficient with full conversion after one hour at –30 ºC with complete heteroaryl transfer (versus alkyl). High enantioselectivity can be obtained for substrates containing two alkyl groups at the β-position. Additionally, an ester-containing allylic phosphate is a competent reaction partner, in the presence of a sterically modified ligand containing a large 2,4,6-*tri*isopropyl *N*-aryl group, leading to the desired product in 90% yield and >98:2 er.

Scheme 1.17. NHC–Cu-Catalyzed Allylic Substitution Reactions of Heteroaryl Compounds

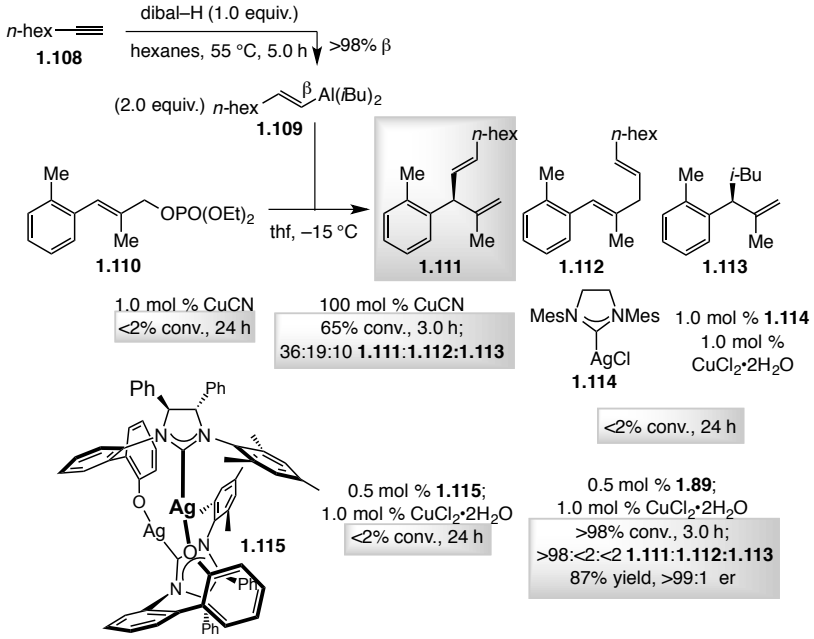


1.3.b. Addition of Alkenyl Nucleophiles

In 2007, the Hoveyda group disclosed the NHC–Cu catalyzed EAS of alkenylaluminum reagents with trisubstituted allylic phosphates to generate a variety of 1,4 diene-containing products.[27] Reactions are catalyzed by a Cu–carbene complex featuring a critical sulfonate bridge. As shown in Scheme 1.18, with stoichiometric CuCN in the absence of a ligand, 65% conversion is observed to a mixture of S_N2' (**1.111**) and S_N2 (**1.112**) products as well as isobutyl addition (**1.113**). Both monodentate and bidentate NHCs containing a phenoxy bridge (**1.114** and **1.115**, respectively) fail to promote the reaction. Reaction in the presence of 0.5 mol % of NHC–Ag dimer **1.89** and a copper salt furnish the desired product with complete site- and enantioselectivity in 87% yield.

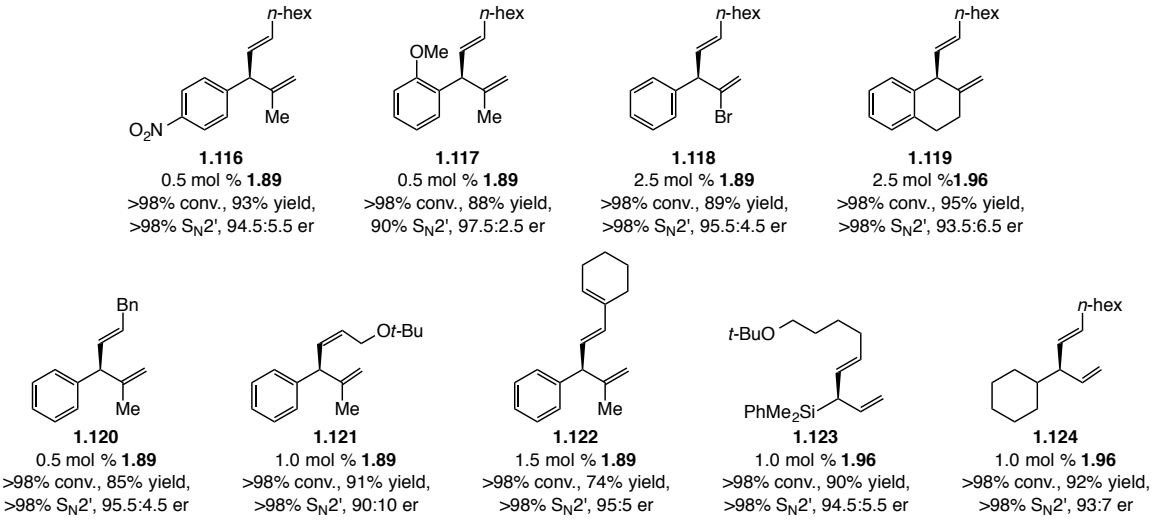
(27) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447.

Scheme 1.18. Screening of Reaction Conditions for Enantioselective Allylic Substitution of *in situ* Generated Alkenylaluminum Reagents



A range of allylic phosphates participates in the reaction including those containing electron-withdrawing and donating groups (4-NO_2- and 2-$OMeC_6H_5$, respectively). Moreover, the substitution pattern at the α-position can be varied to include a methyl, bromo, or even a cyclic substituent. The nucleophile can be varied to include not only straight chain aliphatics, but also benzyl, *tert*-butyl ether, and olefin-containing groups (Scheme 1.19).

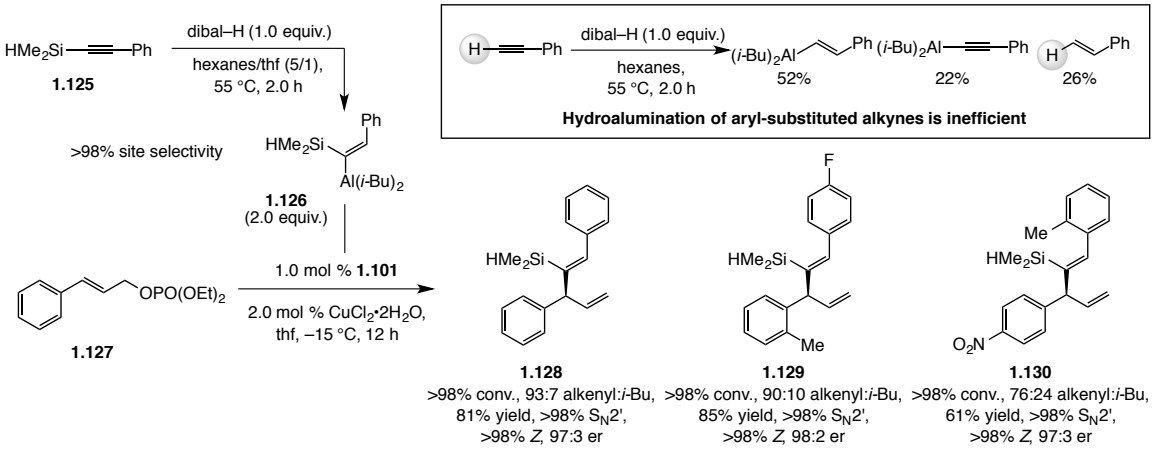
Scheme 1.19. Representative Substrate Scope for Alkenylaluminum Addition to Allylic Phosphates



While examining the hydroalumination of aryl-substituted alkynes, it was found that a statistical mixture of the desired alkenylaluminum reagent as well as the alkynylaluminum and styrene is formed.[28] The styrenylaluminum reagent is sufficiently basic to deprotonate the alkyne at a rate that is competitive with hydroalumination. To circumvent this problem, the alkyne was protected with a dimethylsilane group (Scheme 1.20). With 1.0 equivalent of dibal–H in a 5:1 mixture of hexanes and thf, the expected silyl-substituted alkenylaluminum is formed in >98% site selectivity. Reactions with disubstituted allylic phosphates in the presence of 2 mol % $CuCl_2 \bullet 2H_2O$ and 1 mol % NHC–Ag precursor **1.96** furnish products in high regioselectivity (>98% S_N2') and enantiselectivity (up 98:2 er) with full retention of the olefin geometry (>98% Z). Alkenylaluminum reagents bearing a dimethylsilane unit showed a higher propensity for vinyl transfer (versus *i*-Bu) than the corresponding trimethylsilane reagent.

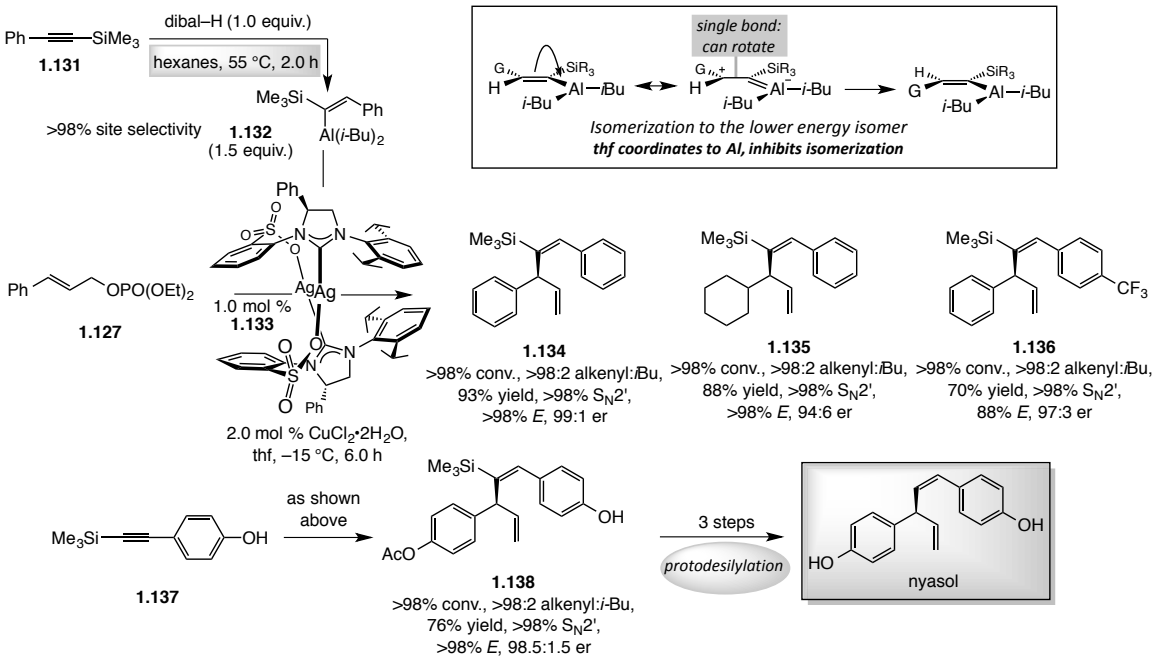
(28) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419–423.

Scheme 1.20. Hydroalumination of Silyl-Substituted Alkynes and Subsequent Allylic Substitution



Additionally, when the hydroalumination of a silyl-substituted aryl-alkyne is performed in the absence of a coordinating solvent, isomerization of the alkenyl reagent occurs to give the formal *trans* hydroalumination product. Without a solvent, such as thf, to coordinate to the empty p-orbital of the aluminum, isomerization occurs readily due to the steric repulsion of the aryl and silyl groups (Scheme 1.21). *E*-silyl-substituted alkenylaluminum reagents participate in allylic substitutions with disubstituted allylic phosphates catalyzed by 2 mol % of NHC–Cu complex derived from NHC–Ag precursor **1.133**. In these cases, trimethylsilyl-substituted reagents result in >98:2 alkenyl:*i*Bu addition and >98% S_N2' selectivity. Olefin isomeric purity is high (>98% E) in most cases except when *para* electron withdrawing groups are present which reduce the efficiency of isomerization. A concise synthesis of natural product nyasol highlights the utility of this method where, after protodesilylation, the *cis*-olefin is revealed.

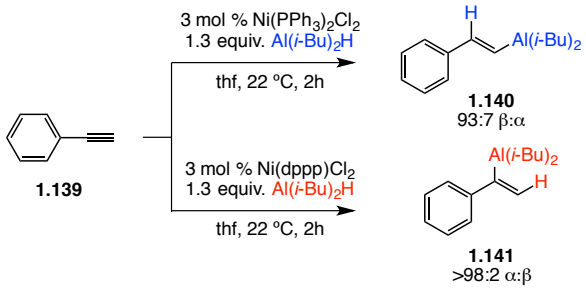
Scheme 1.21. Hydroalumination of Silyl-Substituted Alkynes and Addition of *E*-Alkenyl Nucleophiles



To address the problem of hydroalumination of aryl-substituted alkynes, Hoveyda and co-workers developed a Ni-catalyzed hydroalumination of terminal alkynes.[29] As shown in Scheme 1.22, with 3 mol % of monodentate $Ni(PPh_3)_2Cl_2$ and dibal-H, phenylacetylene undergoes hydroalumination in two hours at 22 ºC with 93:7 β:α selectivity and no detectable amount of the corresponding alkynylaluminum reagent is formed. The *in situ* generated alkenylaluminum reagents can participate in allylic substitution reactions to generate 1,4-dienyl products with high efficiency, site-, and enantioselectivity. By changing to a bidentate nickel salt, $Ni(dppp)Cl_2$, the α-isomer can be formed with complete site selectivity (>98:2 α:β).

(29) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

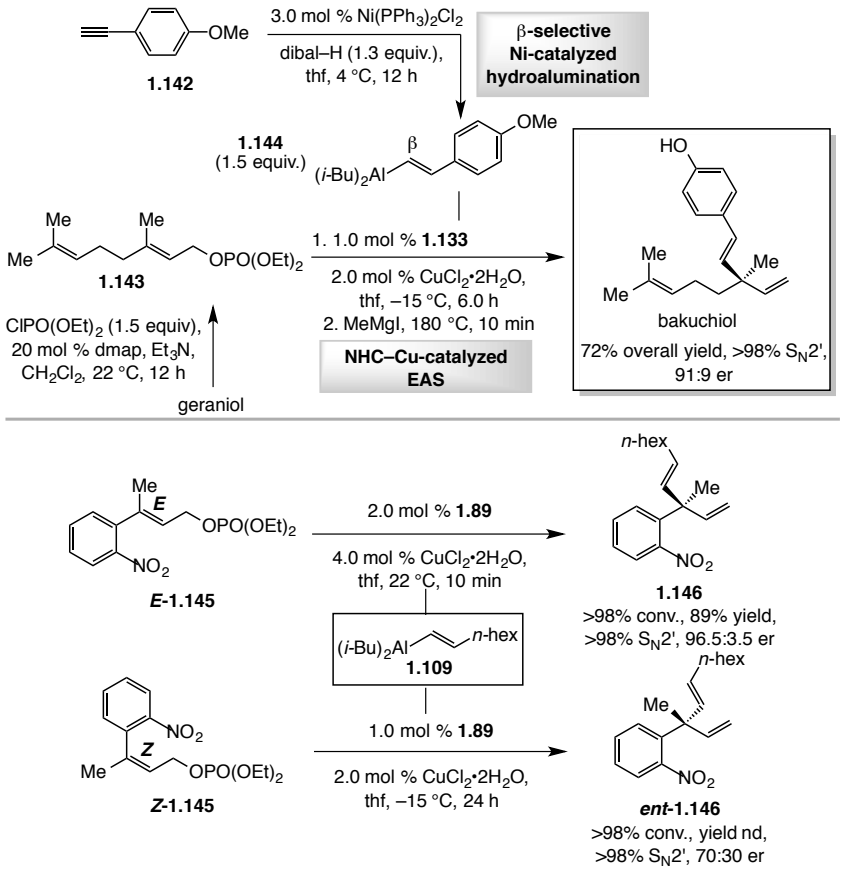
Scheme 1.22. Regioselective Ni-Catalyzed Hydroalumination of Terminal Alkynes



Both aryl- and alkyl-substituted alkenylaluminum reagents have been shown to be effective nucleophiles for EAS with trisubsituted allylic phosphates.[30] In the presence of 2.0 mol % of an NHC–Cu complex, *in situ* generated *para*-methoxy styrenylaluminum can be coupled with an allylic phosphate derived from geraniol to deliver the desired product with complete site selectivity in 72% overall yield and 91:9 er. Meroterpene bakuchiol can be accessed following treatment with MeMgI (Scheme 1.21). Additionally, it was found that the olefin geometry of the allylic phosphate was crucial for high enantioselectivity. While the *E*-isomer led to formation of the desired product in 10 minutes at 22 ºC in 89% yield and 96.5:3.5 er, the *Z*-isomer results in the opposite major enantiomer with decreased enantiopurity (70:30 versus 2:98) even at lower reaction temperatures.

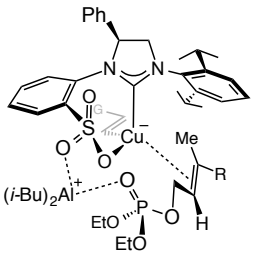
(30) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315–14320.

Scheme 1.23. Ni-Catalyzed Hydroalumination and Subsequent Allylic Substitution; Effect of Olefin Geometry on Enantioselectivity



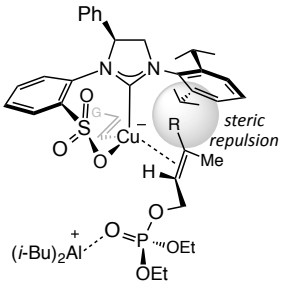
Based on this observation, the stereochemical model put forth involves chelation of the Lewis acidic aluminum counter ion to the equatorial oxygen of the sulfonate as well as the Lewis basic phosphate of the substrate. This chelation serves to raise the electrophilicity of the phosphate as well as organize the incipient transition state. The minor observed enantiomer would come from copper coordination to the opposite olefin face which would engender steric repulsion between the large aryl ring of the substrate and the *N*-aryl group. Additionally, due to geometric constraints, the aluminum chelation is not feasible which results in a less organized transition state (Scheme 1.24).

Scheme 1.24. Proposed Model for Enantioselectivity



1.147

Chelation of the Lewis acidic Al with pseudo-equatorial sulfonate oxygen and the substrate phophate unit, elevates alkene electrophilicity and induces transition state organization.



1.148

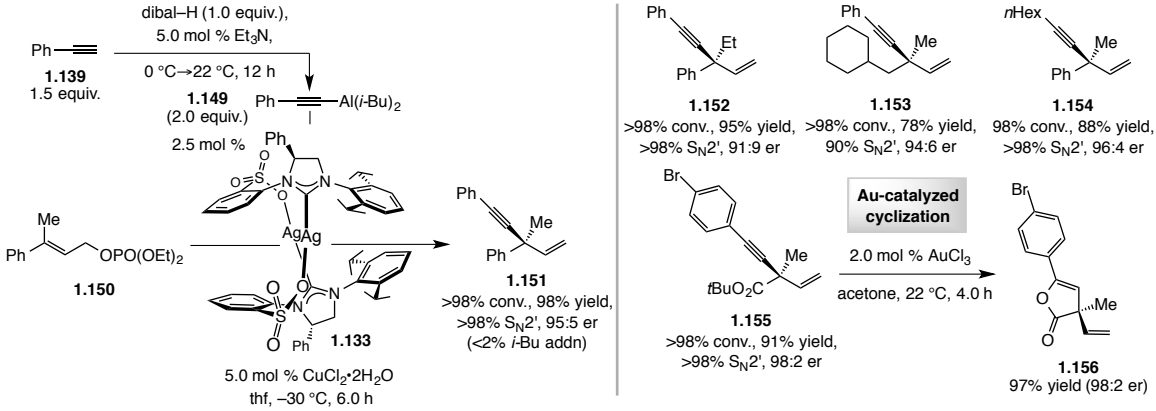
Bidentate Al chelation is no longer feasible due to geometric constraints; lower degree of transition state organization, reduced enantioselectivity.

1.3.c. Addition of Alkynyl Nucleophiles

In the course of studying the addition of alkenylaluminum reagents generated simply from hydroalumination with dibal-H, it was found that the undesired alkynylaluminum side product participated in the EAS reaction more efficiently than the corresponding alkenyl reagent. Based on reports by Micouin and co-workers,[31] the addition of 5 mol % Et_3N allows for clean *in situ* formation of diisobutyl(alkynyl)aluminum reagents. In the presence of 5.0 mol % of an *in situ* generated NHC–Cu complex, alkynyl nucleophiles can be coupled with a variety of trisubstituted allylic phosphates to generate all-carbon quaternary stereogenic centers in up to 98% yield and >98:2 er with exclusive S_N2' addition in most cases.[32] The utility of this method is demonstrated through the synthesis of γ-lactones by Au-catalyzed cyclization, molecules that cannot be accessed easily by other allylic substitution reactions (Scheme 1.25).

(31) (a) Binger, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 686; (b) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 2333–2336.
(32) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778–4781.

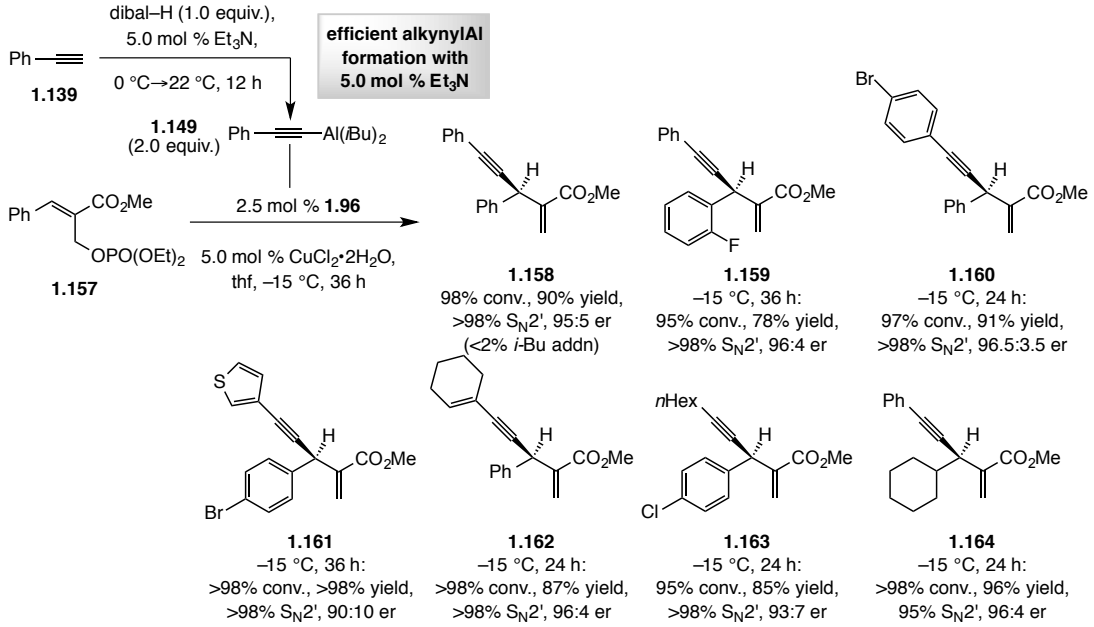
Scheme 1.25. NHC–Cu-Catalyzed Allylic Substitution of Alkynylaluminum Nucleophiles



Ester-containing trisubstituted allylic phosphates were examined for the formation of alkyne-containing tertiary stereogenic centers, as simple disubstituted allylic phosphates were less enantioselective (~75:25 er). A variety of aryl- and heteroaryl-substituted alkynes can be added efficiently with high site- and enantioselectivity.[33] Additionally, both alkene- and alkyl-containing alkynes participate in the reaction. Products are generated in 78–98% yield and 90:10–96.5:4.5 er (Scheme 1.26). Due to the mild reaction conditions, as little to no dibal-H remains after the formation of the alkynyl nucleophile, no byproducts arising from 1,2 or 1,4 addition to the α,β-unsaturated ester are formed. Additionally, no racemization of the relatively acidic stereogenic proton is observed.

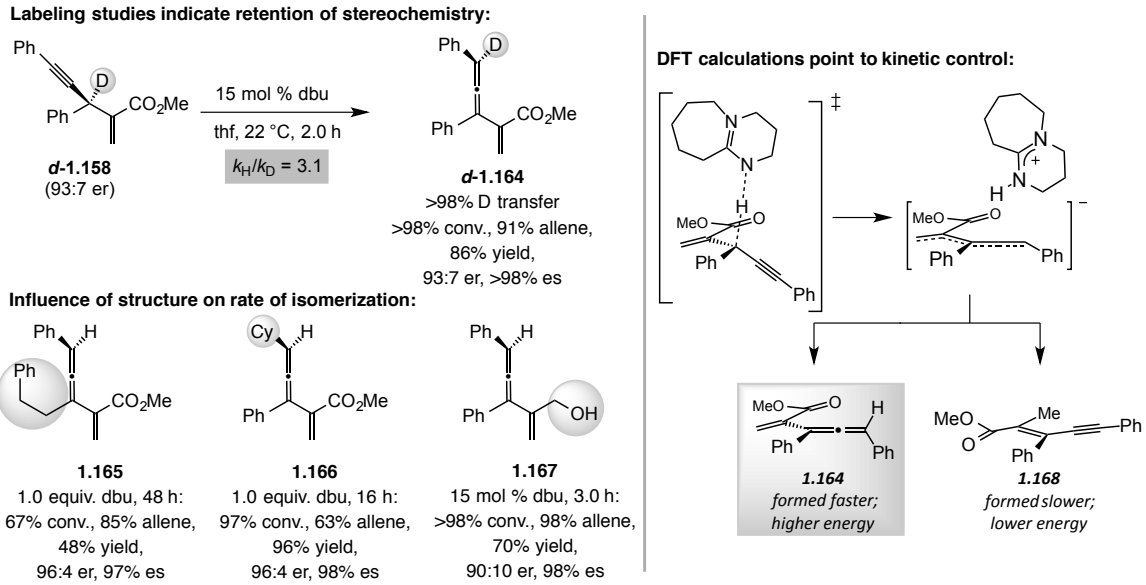
(33) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694–7699.

Scheme 1.26. Alkynylaluminum Addition to Morita-Baylis-Hillman-Derived Allylic Phosphates



It was found that, in the presence of 15 mol % 1,8-diazabicycloundec-7-ene (dbu), a Lewis-based catalyzed isomerization to the corresponding trisubstituted allene occurred with complete enantiospecificity (e.s.). As illustrated in Scheme 1.27, studies carried out with enantiomerically enriched deuterated substrate ***d*-1.158** showed >98% D incorporation in the newly formed allene. Additionally, a k_H/k_D value of 3.1 indicates that deprotonation is likely the rate-determining step. DFT calculations suggest a mechanism where dbu acts as a proton shuttle, first by deprotonating the propargylic position and then protonating the allenyl anion from the same face in an enantiospecific fashion. Substrates with a less acidic proton like those that contain an alkyl group at the stereogenic center or on the alkyne require one equivalent of dbu to achieve high conversion.

Scheme 1.27. Base-Catalyzed Stereospecific Isomerization of Alkynes to Allenes

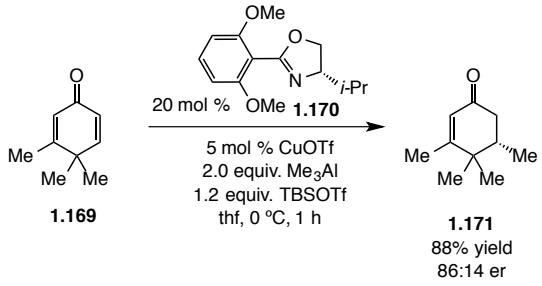


1.4 Catalytic Enantioselective Conjugate Addition of Organoaluminum Reagents

1.4.a. Addition of Alkylaluminum Reagents

The first catalytic enantioselective conjugate addition (ECA) of alkylaluminum reagents was disclosed in 1996 by Iwata. In the presence of 20 mol % of an aryloxazoline ligand and 5 mol % CuCl, the conjugate addition adduct is formed in 88% yield and 86:14 er when a stoichiometric Lewis acid, TBSOTf, is added (Scheme 1.28). [34]

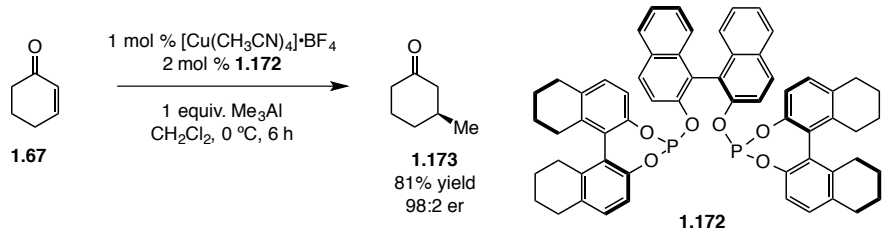
Scheme 1.28. Cu-Catalyzed Conjugate Addition of Trimethylaluminum with Stoichiometric Lewis Acid



(34) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1997**, *7*, 993–996.

Chan et al. disclosed the addition of Me_3Al to cyclohexenone catalyzed by a Cu–diphosphite complex (Scheme 1.29). The desired β-methyl cyclohexanone is obtained in 81% yield and 98:2 er. [35] The method was further expanded to the addition of triethylaluminum to cyclopentenone in up to 97:3 er with a modified diphosphite ligand.[36]

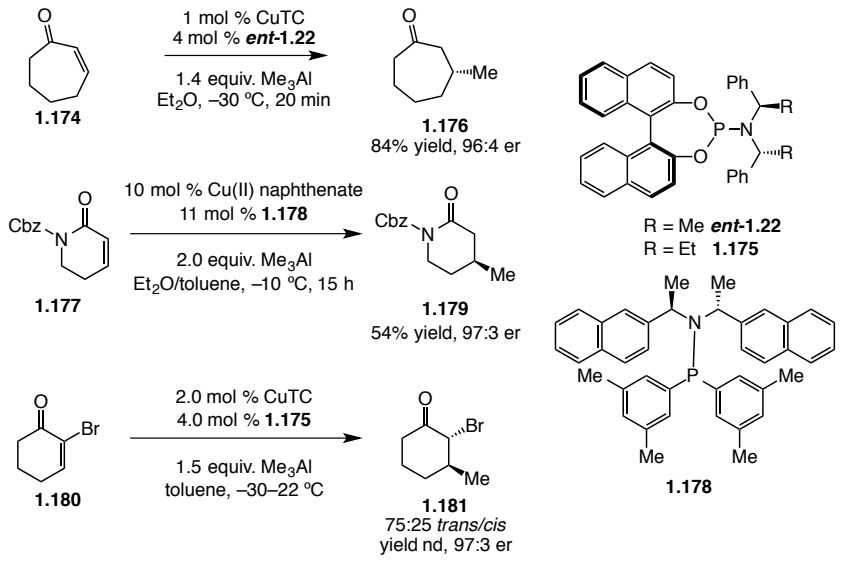
Scheme 1.29. Cu–Diphosphite Catalyzed Conjugate Addition to Cyclohexenone



Alexakis and co-workers disclosed a similar transformation for the addition to both trimethyl- and triethylaluminum to a number of enones (Scheme 1.30).[37] High enantioselectivities are obtained for both 6- and 7-membered rings. The same group has also disclosed examples of additions of alkylaluminum reagents to both *N*-protected unsaturated lactams[38] and α-halo cyclic enones[39] in the course of developing methods for the analogous additions of alkylzinc reagents.

(35) Liang, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1393–1396.
(36) Su, L.; Li, X.; Chan, W. L.; Jia, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 1865–1869.
(37) Alexakis, A.; Albrow, V.; Biswas, KM. d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843–2845.
(38) Cottet, P.; Müller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 828–831.
(39) Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600–7603.

Scheme 1.30. Cu-Catalyzed ECA of Alkyl Nucleophiles to Cyclic Enones



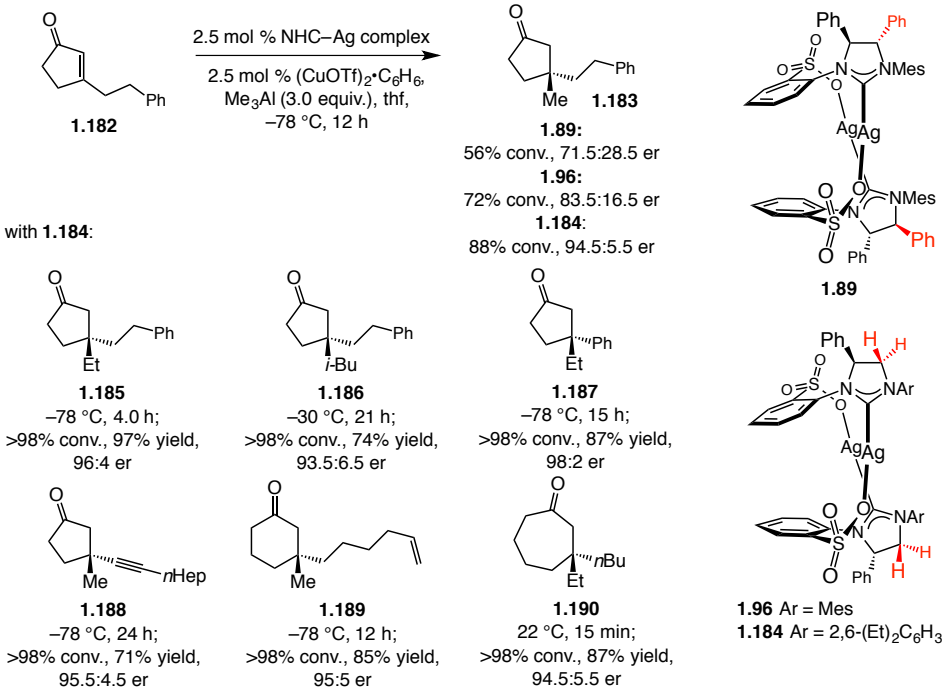
The formation of all-carbon quaternary stereogenic centers through conjugate addition is a particularly difficult problem due to the steric hindrance engendered in using trisubstituted enones. The increases Lewis acidity of trialkylaluminum reagents (versus organozinc or magnesium reagents) can better activate the substrate and facilitate the reaction. Alexakis and co-workers found that a biphenol-based phosphoramidite ligand in conjunction with a CuTC salt was optimal for the addition of trimethylaluminum to a variety of substrates. [40] The same group also developed a series of SimplePhos ligands, which have been found to be efficient for the addition of tri*n*-propyl and tri*n*-butylaluminum to trisubstituted cyclohexenone substrates.[41]

The Hoveyda group disclosed the addition of various trialkylaluminum reagents to a number of β-substituted enones (Scheme 1.31).[42] Enantioselectivities with *N*-heterocyclic carbene ligands were found to be higher for the very challenging β-substituted cyclopentenones than with the previously disclosed phosphoramidite ligands (up to 98:2 er). Both 6- and 7-memebered rings are competent partners for the reaction, delivering the desired products in up to 87% yield and 95:5 er. Through ligand

(40) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (b) M. Vuagnoux–d'Augustin, S. Kherli, A. Alexakis, *Synlett*, **2007**, 2057–2060. (c) M. Vuagnoux–d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647–9662.
(41) Palais, L.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 10473–10485.
(42) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.

optimization, the authors found that the removal of one phenyl group from the backbone of the ligand was crucial for obtaining high enantioselectivity; the reasoning being that the *N*-aryl group has greater freedom of rotation and is better able to accommodate the substrate.

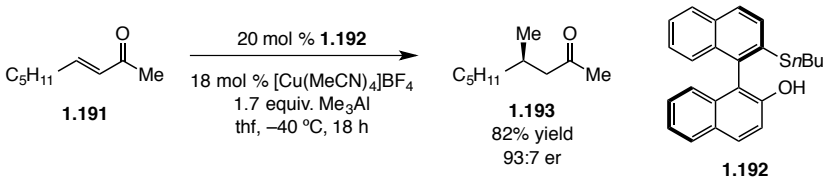
Scheme 1.31. NHC–Cu-Catalyzed Conjugate Addition of Alkylaluminum Reagents



One challenging area that remains underdeveloped is conjugate addition involving acyclic substrates, which are often more difficult due to their ability to react through either an s-*cis* or s-*trans* conformation. Pioneering work by Woodward and co-workers examined the addition of trimethylaluminum to acyclic alkyl substituted enones (Scheme 1.32).[43] The optimal ligand was found to be BINOL-derived thiol-containing **1.192**. The authors hypothesize that the soft sulfur coordinates the copper center while the hard donor oxygen binds the Lewis acidic aluminum cation. A range of alkyl-substituted enones participates in the reaction to generate the desired products in moderate yields and 90:10 to 96.5:3.5 er.

(43) Fraser, P. K.; Woodward, S. *Chem. Eur. J.* **2003**, *9*, 776–783.

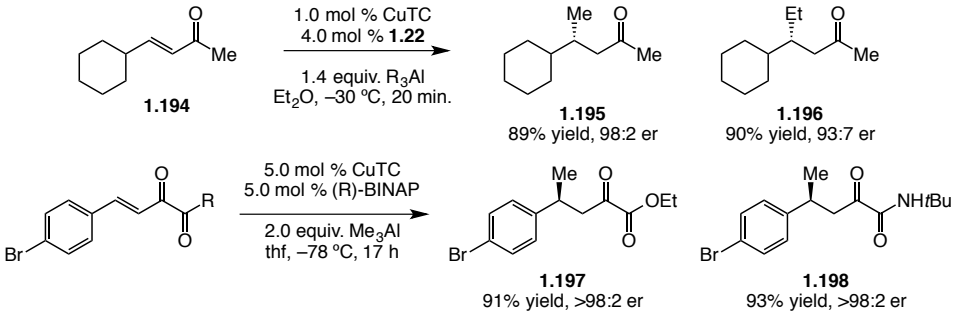
Scheme 1.32. Cu-Catalyzed Conjugate Addition to Acyclic Enones



Alexakis and co-workers found that with Feringa-type phosphoramidite ligands and a catalytic amount of CuTC, triethyl- and trimethylaluminum react with a variety of acyclic enones to deliver the products in good yields and enantioselectivities (Scheme 1.33).[36] Substrates containing α-branching groups (cyclohexyl, *tert*-butyl, *iso*-propyl) resulted in the highest observed enantioselectivities (92:8 to 98:2 er).

In addition to aliphatic ketones, the Alexakis group demonstrated that with CuTC and commercially available (*R*)-BINAP, trimethylaluminum is added to β,γ-unsaturated α-keto esters[44] and amides[45] with high enantioselectivity. A variety of aryl and alkyl substituents work well in the reaction although *ortho*-methoxy aryl groups lead to low yields and enantioselectivities. Products can be functionalized to access core structures for a variety of natural products (Scheme 1.33).

Scheme 1.33. BINAP–Cu-Catalyzed ECA to Acyclic Electrophiles

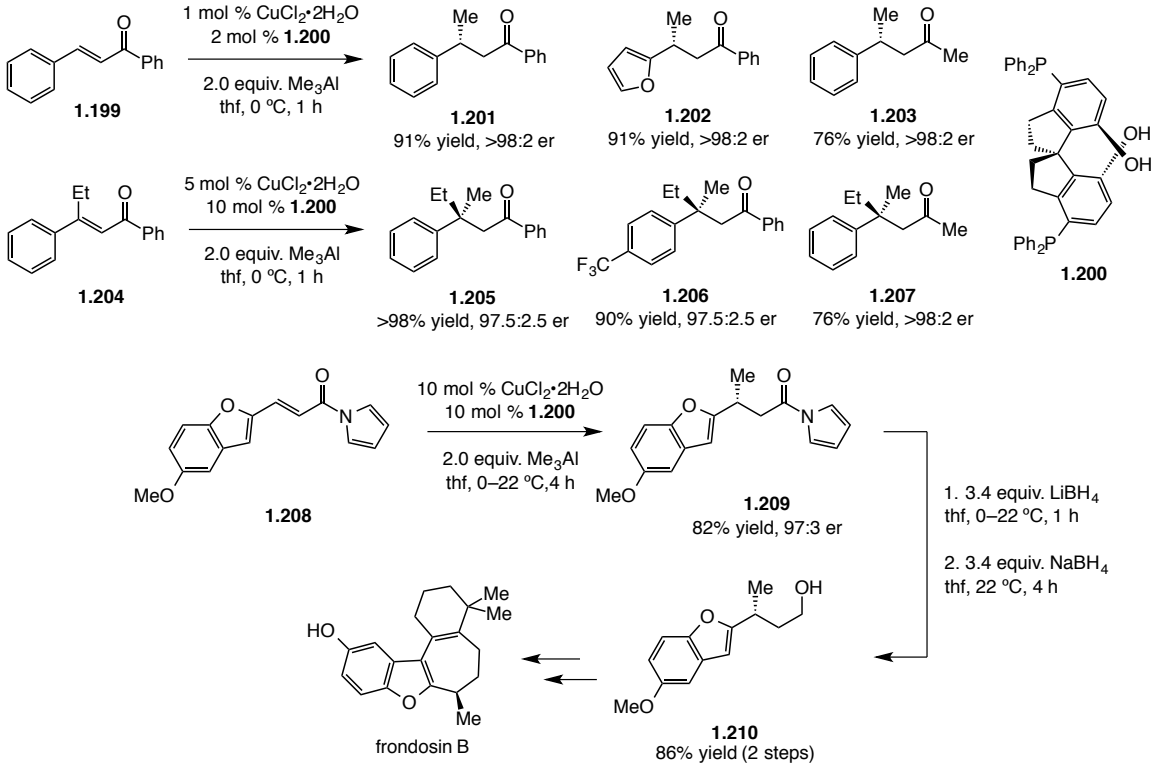


In 2014, the groups of Hoveyda and Shibata independently disclosed the addition of trialkylaluminum reagents to acyclic enone. The Shibata group found that in the presence of 1.0 mol % of a copper (II) salt and 2.0 mol % of a diol ligand, trimethylaluminum could be added efficiently and with high enantioselectivity to a number of chalcone derivatives to form the corresponding tertiary centers (Scheme

(44) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, 51, 794–797.
(45) Goncalves-Contal, S.; Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 12701–12704.

1.33).[46] Additionally, one example of addition to an unsaturated methyl ketone is shown. This method is also applicable to the formation of all-carbon quaternary stereogenic centers, although slightly higher catalyst loading is required for an efficient reaction. The authors demonstrate the utility of the method with the formal synthesis of a number of natural products including frondosin B through conjugate addition followed by reduction of an *N*-acyl pyrrole.

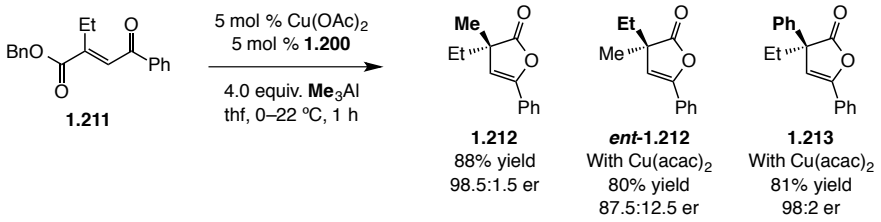
Scheme 1.34. Bidentate Diol–Cu-Catalyzed Addition of Alkylaluminum Reagents to Chalcone Derivatives



The Shibata group further expanded this method for the synthesis of α,α-disubstituted furanones where the *in situ* generated aluminum enolate undergoes intramolecular esterification.[47] Trimethyl-, triethyl-, and phenyldimethylaluminum are efficient nucleophiles, leading to the desired furanones in high yield and up to >98:2 er (Scheme 1.35).

(46) Endo, K.; Hamada, D.; Yakeishi, S.; Shibata, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 606–610.
(47) Endo, K.; Yakeishi, S.; Takayama, R.; Shibata, T. *Chem. Eur. J.* **2014**, *20*, 8893–8897.

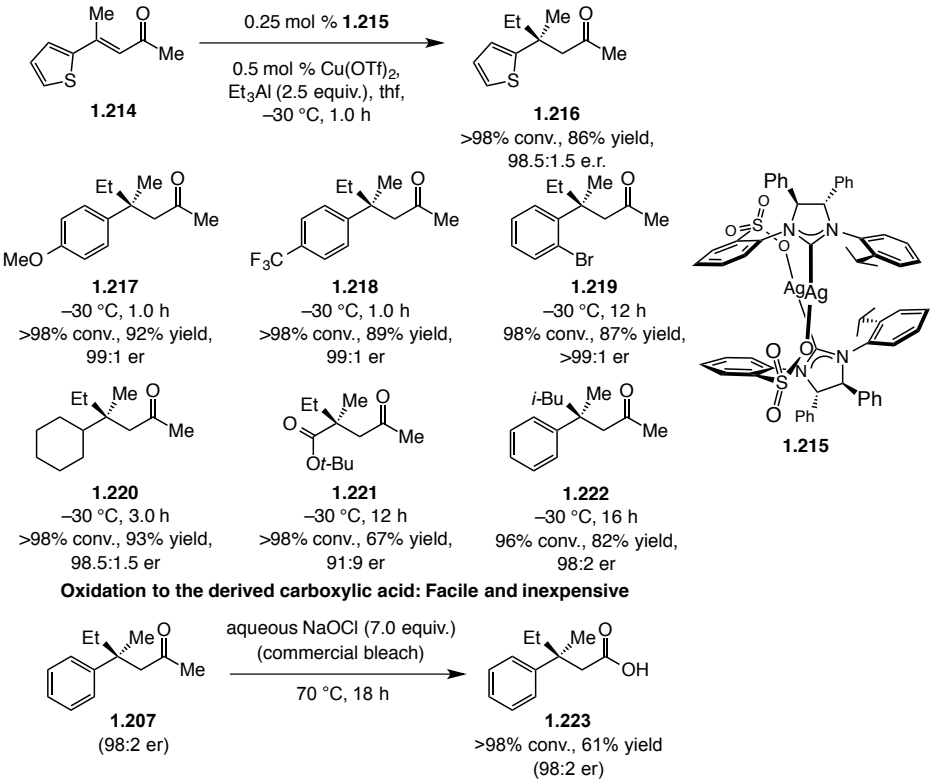
Scheme 1.35. Cu-Catalyzed Conjugate Addition with Disubstituted Furanones



The Hoveyda group reported that with as little as 0.5 mol % $Cu(OTf)_2$ and 0.25 mol % of an NHC–Ag dimer **1.199**, triethylaluminum reacts efficiently (1 h at –30 °C) with a variety of α,β-unsaturated ketones to form all-carbon quaternary stereogenic centers (Scheme 1.36) .[48] Sterically hindered aryl groups, alkyl substituents, as well as esters are tolerated in the reaction. Moreover, commercially available trimethyl- and tri*iso*butylaluminum work well in the reaction. The ketone products can be oxidized through reaction with commercial bleach (aq. NaOCl) to generate carboxylic acids in good yield and without loss of enantiomeric purity.

(48) Dabrowski, J. A.; Villaume, M. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8156–8159.

Scheme 1.36. NHC–Cu-Catalyzed Conjugate Addition of Alkylaluminum Reagents

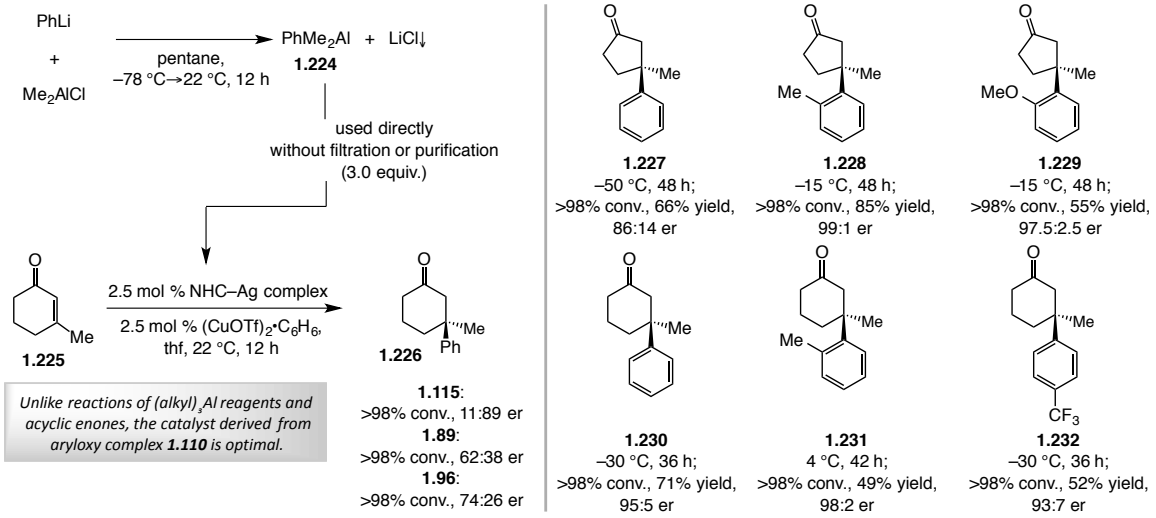


1.4.b. Catalytic enantioselective conjugate addition of arylaluminum nucleophiles

Although methods have been developed for the corresponding additions with aryl zinc and aryl Grignard reagents, the nucleophile scope is often limited to additions of simple phenyl or *para*-methoxybenzene groups. In 2008, both Hoveyda and Alexakis disclosed methods for the addition of dialkylarylaluminum reagents to β-substituted cyclic enones. Hoveyda shows that the addition of aryllithium reagents to dimethylaluminum chloride generated the requisite arylaluminum, which could be used in situ without purification or filtration.[49] Unlike additions of alkyl nucleophiles, a phenoxy-bridged carbene was found to be the optimal ligand in terms of enantioselectivity. Both 5- and 6- membered rings are competent substrates and a number of sterically hindered aryl group react efficiently. Additionally, both electron-rich and electron-poor aryl group are effectively transferred (Scheme 1.37).

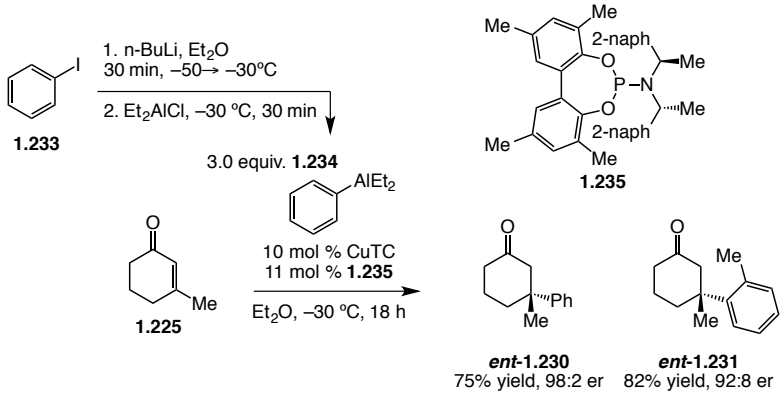
(49) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.

Scheme 1.37. NHC–Cu-Catalyzed Conjugate Addition of Dialkylarylaluminum Reagents to Cyclic Enones



Alexakis published a similar method for the addition of arylaluminum nucleophiles to 6-membered rings in the presence of a copper salt and phosphoramidite ligand (Scheme 1.38).[50] Initially, aryl reagents were generated through reaction of aryl boronic acids with excess triethylaluminum, but under the reaction conditions, 36% conversion to the corresponding ethyl addition was observed. As a result, lithium-halogen exchange with aryl iodides followed by addition to diethylaluminum chloride was chosen as the superior method. A range of aryl groups can be added to β-methylcyclohexenone including those with *ortho*-substituents as well as electronically modified groups.

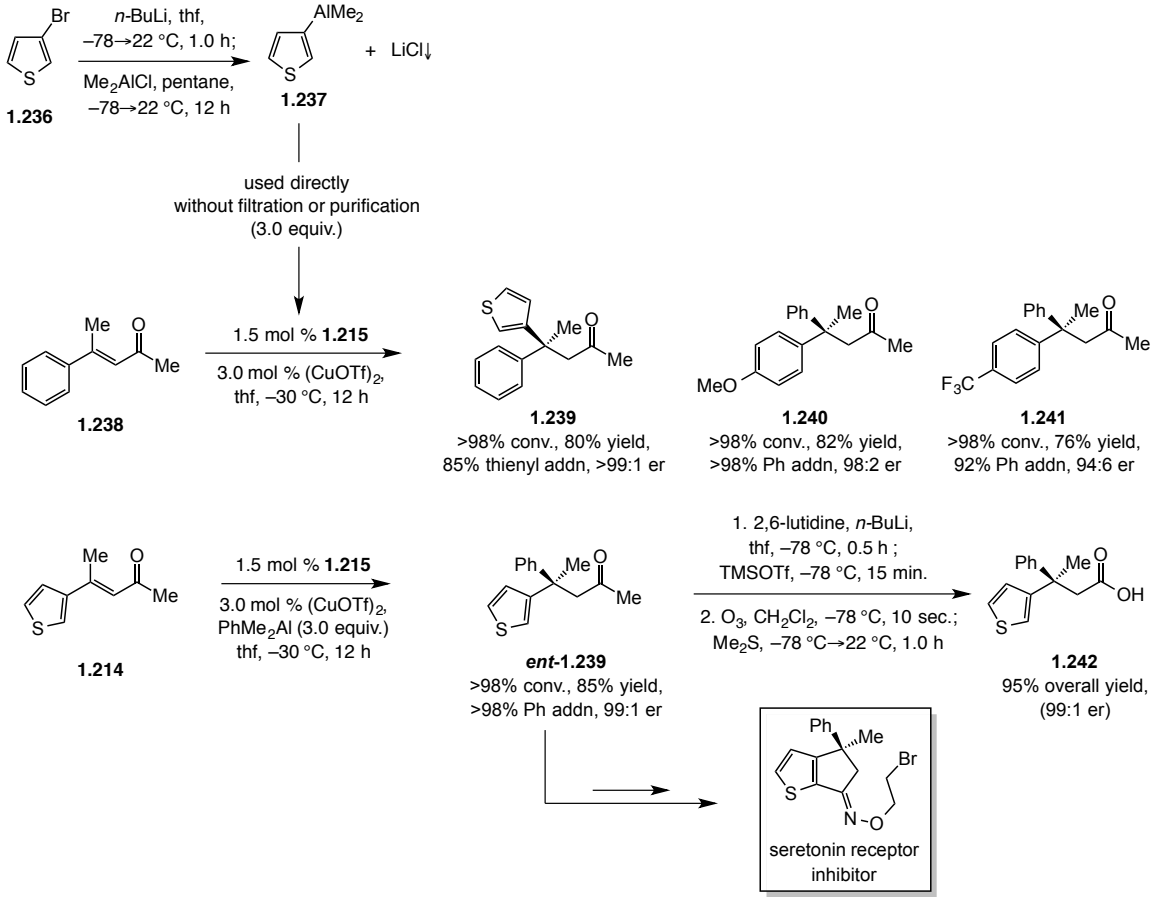
Scheme 1.38. Cu-Catalyzed ECA of Aryl Nucleophiles to Cyclic Enones



(50) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214.

In the course of developing the previously mentioned addition of trialkylaluminum reagents to acyclic enones, the Hoveyda group also disclosed the first examples of arylaluminum conjugate addition to the same class of substrates.[48] Lithium-halogen exchange of the requisite aryl bromide followed by addition to Me_2AlCl generates the desired arylaluminum, which can be added to the reaction without further purification. Electron deficient as well as electron rich aryl groups participate in the reaction to deliver the desired product in high yield and enantioselectivity (Scheme 1.39). In most cases, group selectivity, favoring aryl transfer, remains high (>92% Aryl vs Me), except in the case of *ortho*-substituted substrates. Formation of the kinetic silyl enol ether followed by ozonolyisis allows access to the corresponding carboxylic acids in high yield.

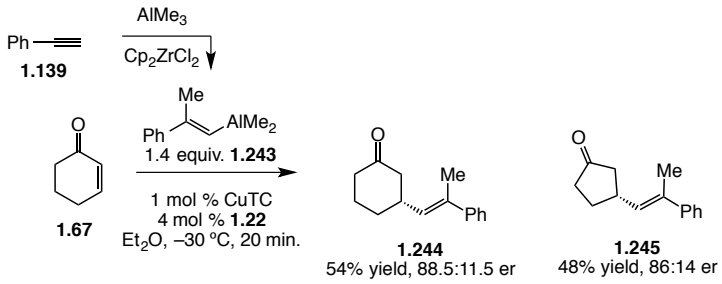
Scheme 1.39. NHC–Cu-Catalyzed ECA of Arylaluminum Reagents to Acyclic Enones



1.4.c. Catalytic enantioselective conjugate addition of alkenylaluminum nucleophiles

The first examples of enantioselective conjugate addition of alkenylaluminum reagents were published in 2005 by Woodward and Alexakis.[36] Zirconium catalyzed carboalumination of phenylacetylene with trimethylaluminum allows access to the desired dimethylalkenylaluminum reagent. Subsequent Cu-catalyzed conjugate addition to cyclohexenone and cyclopheptenone in the presence of CuTC and phosphoramidite **1.22** lead to the desired products in 88.5:11.5 and 86:16 er, respectively (Scheme 1.40).

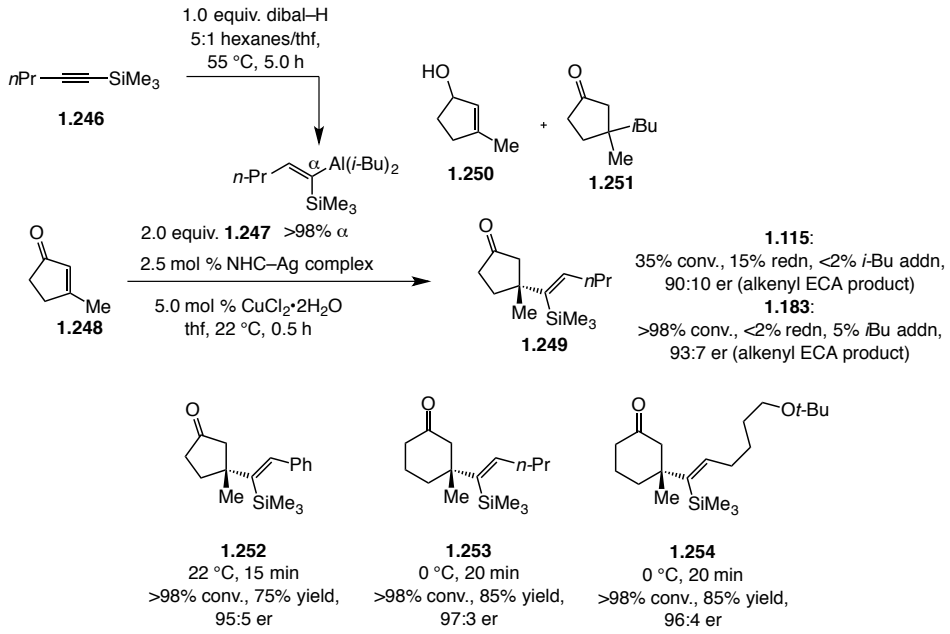
Scheme 1.40. ECA of Alkenylaluminum Reagents Derived from Zr-Catalyzed Carboalumination



While regioselectivity is typically an issue for the hydroalumination of internal alkynes, hydroalumination of silyl-protected alkynes proceeds with high selectivity for the formation of the α-silyl aluminum due to the stabilization of the carbon–aluminum bond through hyperconjugation with the adjacent silyl group. The Hoveyda group showed that a variety of silyl-alkenylaluminum reagents can be added to a number of cyclic enones.[51] Both β-substituted cyclohexenones and cyclopentenones can be coupled with aryl- or alkyl-containing aluminum reagents in the presence of a sulfonate-containing NHC–Cu complex (Scheme 1.41).

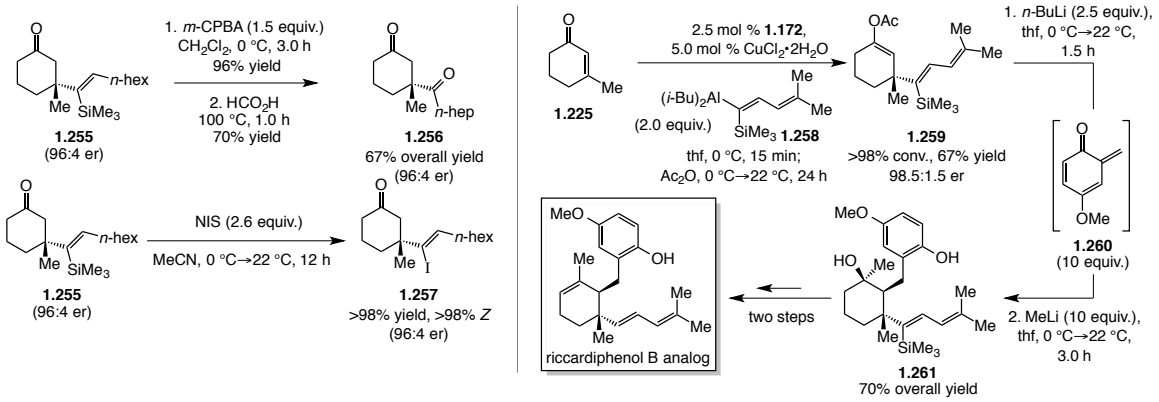
(51) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739.

Scheme 1.41. NHC–Cu-Catalyzed ECA of Silyl-Substituted Alkenylaluminum Reagents



The conjugate addition adducts have been functionalized in a variety of ways including a stereoretentive iodo-desilylation to form an alkenyl iodide with high *Z*-selectivity as well as an epoxidation/elimination sequence to generate the product of a formal acyl anion conjugate addition. Trapping the *in situ* generated aluminum enolate, the direct product of the conjugate addition, as the silyl enol ether, followed by reaction with an *ortho*-quinone methide, assembles the core structure of the riccardiphenol family of natural products in an expedient fashion (Scheme 1.42).

Scheme 1.42. Functionalizations of Alkenylsilanes and Synthesis of Riccardiphenol B Analog

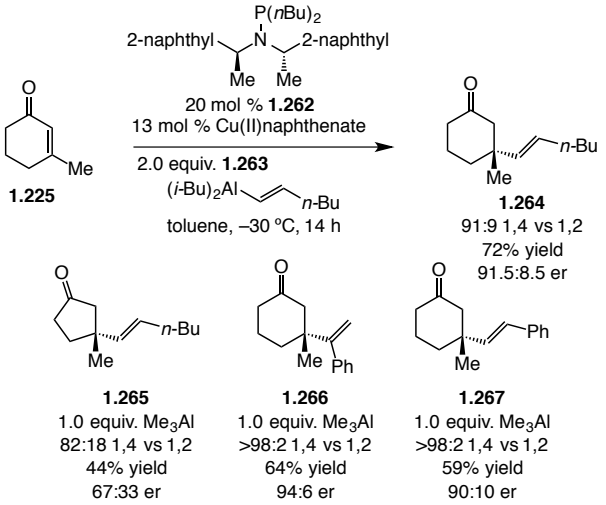


Alexakis and co-workers published a method in 2008 wherein the alkenylaluminum nucleophiles are accessed through lithium-halogen exchange of the corresponding alkenylbromide followed by addition to dimethyl- or diethylaluminum chloride, similar to the synthesis of arylaluminum reagents.[52] One drawback to this route is that synthesis of the alkenylbromide starting materials is often non-trivial and in certain cases actually proceeds through the intermediacy of an alkenylaluminum reagent. In the presence of CuTC and a phosphinamine ligand, a number of 1,1- and 1,2-disubstituted olefins can be synthesized. Enantioselectivities are decreased with substrates containing larger substituents (e.g. phenyl) or with cycloheptenone substrates.

The Alexakis group made use of a previously published Ni-catalyzed hydroalumination of terminal alkynes to generate both α- and β-alkenylaluminum reagents with high regioselectivity through judicious choice of nickel salt. Reactions, catalyzed by 13 mol % Cu salt and 20 mol % phosphinamine ligand, proceed to furnish the desired products in moderate to good yields and up to 94:6 er. [53] Reaction with a β-methylcyclopentenone substrate results in poor enantioselectivity (67:33 er) further highlighting the difficulty of reaction with this class of substrates (Scheme 1.43).

(52) Müller, D; Alexakis, A. *Chem. Eur. J.* **2013**, *19*, 15226 – 15239.
(53) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040–3043.

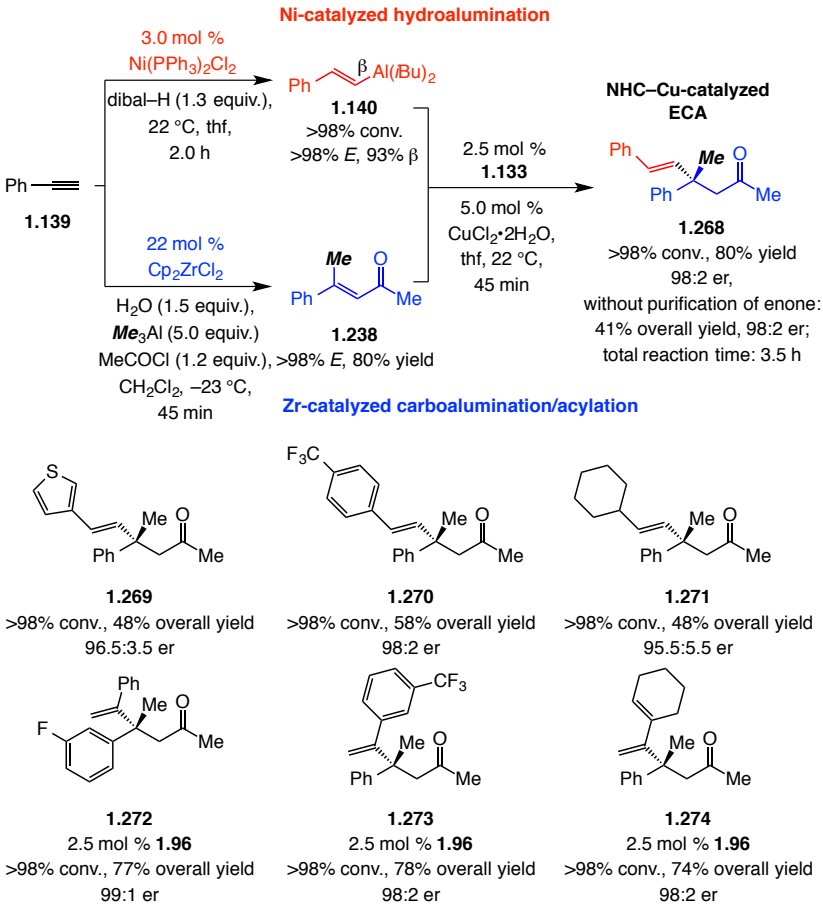
Scheme 1.43. Phosphinamine–Cu-Catalyzed ECA of Alkenylaluminum Reagents to Cyclic Enones



In 2014, the Hoveyda group disclosed the first ECA of alkenylaluminum reagents to trisubstituted acyclic enones.[54] The process consists of three concomitant catalytic reactions: (1) Ni-catalyzed hydroalumination of a terminal alkyne to generate either an α- or β-alkenylaluminum reagents (2) Zr-catalyzed carboalumination of a terminal alkyne and subsequent trapping with acetyl chloride to generate a stereo-defined trisubstituted enone (3) NHC–Cu catalyzed conjugate addition of the in situ generated alkenylaluminum reagent to generate an alkene-substituted all-carbon quaternary stereogenic center. A range of terminal alkynes have been shown to participate in both the hydro- and carboalumination reactions to generate a variety of partners which can be coupled through Cu-catalyzed cross coupling. β-Alkenylaluminum conjugate addition adducts are generated in up to 58% yield (for a two step carboalumination/conjugate addition sequence) and 98:2 er. The corresponding α-alkenylaluminum additions lead to products in up 76% overall yield and >99:1 er (Scheme 1.44).

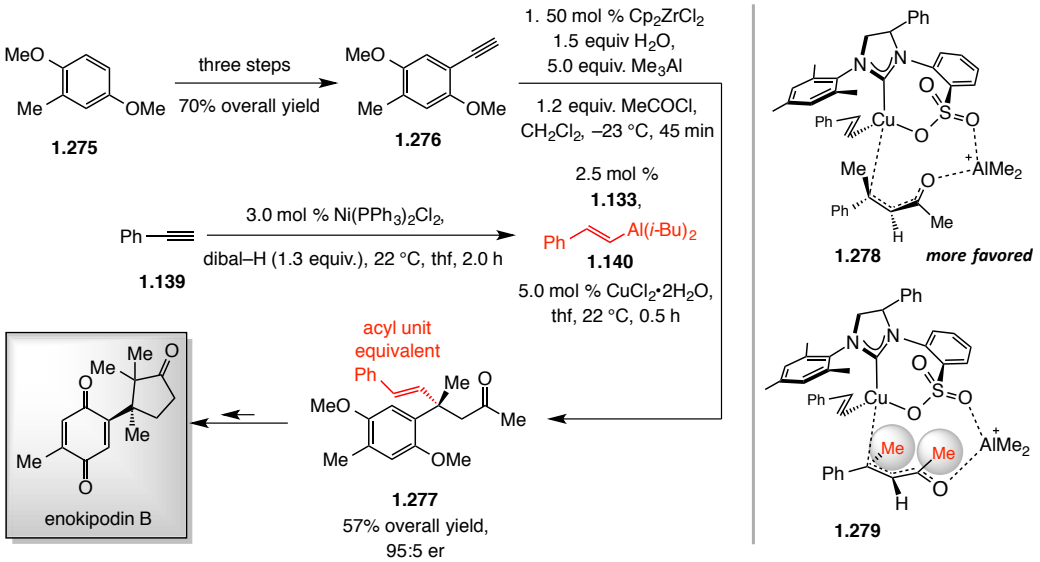
(54) McGrath, K. P.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 1910–1914.

Scheme 1.44. NHC–Cu-Catalyzed ECA of Alkenylaluminum Reagents to Acyclic Enones



The multi-component process has been applied to an efficient formal synthesis of antimicrobial natural product enokipodin B. DFT calculations support the proposed Al-bridge where the aluminum cation coordinates to the equatorially disposed sulfonate oxygen as well as the carbonyl of the enone. This coordination serves to organize the transition state as well as to activate the incoming electrophile. The major enantiomer forms through reaction of the enone in the s-*trans* conformation while minimizing steric interaction of the *N*-aryl ring and the substituents on the enone. Conversely, the minor enantiomer forms through reaction of the enone in the higher energy s-*cis* conformer while maintaining the stabilizing Al-bridge (Scheme 1.45).

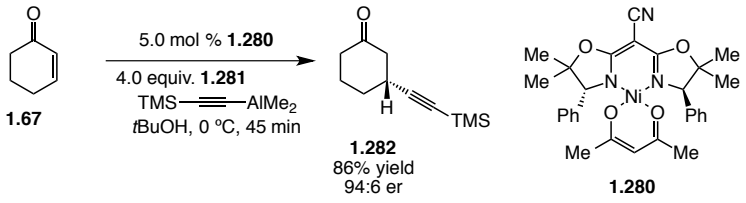
Scheme 1.45. Application of NHC–Cu-Catalyzed ECA to Synthesis of Enokipodin B



1.4.d. Catalytic Enantioselective Conjugate Addition of Alkynylaluminum Nucleophiles

Of all the organoaluminum nucleophiles, alkynylaluminum remains the most underutilized. While Schwartz first demonstrated the Ni-catalyzed conjugate addition of alkynylaluminum reagents to a number of enones over three decades ago, the first enantioselective variant of the reaction was disclosed by Corey in 2004.[55] In the presence of 5.0 mol % of a Ni(acac)–bisoxazoline complex trimethylsilyl dimethylaluminum acetylide reacts efficiently with cyclohexenone to generate the desired product in 86% yield and 94:6 er (Scheme 1.47).

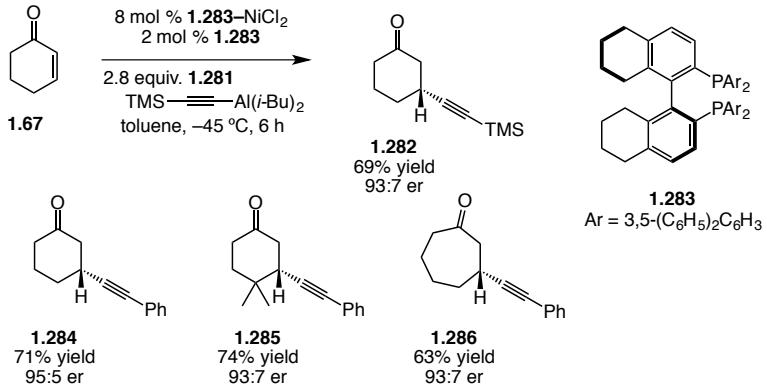
Scheme 1.47. Ni-Catalyzed ECA of Alkynylaluminum Reagents to Cyclohexenone



(55) Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385–3388.

The Corey group expanded the scope of alkyne conjugate addition in 2010 after discovering that Ni–bisphosphine complexes effectively catalyze the reaction.[56] With a binap-derived ligand, alkynyl nucleophiles are added with up to 74% yield and high enantioselectivity (92.5:7.5 to 95:5 er) to 6-,7-, and 8-membered rings as well geminyl-dimethyl substituted cyclohexenones. Both trimethylsilyl and aryl-substituted alkynes can be coupled in the reaction (Scheme 1.48).

Scheme 1.48. Ni-Catalyzed ECA of Alkynyl Nucleophiles to Cyclic Enones



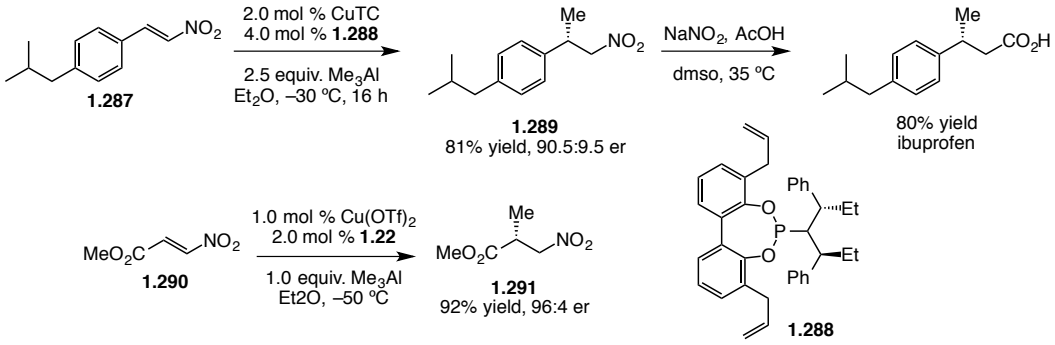
1.4.e. Catalytic enantioselective conjugate addition of alkylaluminum nucleophiles to other electrophiles

Both nitroolefins as well as nitro acrylates, highly activated conjugate acceptors, have been found to be suitable substrates for additions of trialkylaluminums. Moreover, the nitroalkane products can be converted into a variety of synthetically useful molecules.[57] Alexakis and co-workers found that with CuTC and a phosphoramidite ligand, trimethylaluminum could be added to a variety of nitroolefins containing both aryl and alkyl groups with moderate yield and up to 95.5:4.5 er.[58] A short synthesis of ibuprofen can be accomplished through oxidation of the nitroalkane to the corresponding carboxylic acid (Scheme 1.48). The Wendisch group showed that trialkylaluminum reagents in the presence of a BINOL-derived phosphoramidite ligand and a copper salt react with nitro acrylates to form ester-substituted tertiary stereogenic centers.[59] While

(56) Larionov, O. V.; Corey, E. J. *Org. Lett.* **2010**, *12*, 300–302.
(57) (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894; (b) Ono, N. In *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; Wiley-VCH: New York, 2001.
(58) Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *5*46,1529–1532.
(59) Eilitz, U.; Leβmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3095–3097.

methyl addition occurs with high enantioselectivity (96:4 er), both ethyl and isobutyl additions are less selective (83:17 and 63:27 er, respectively).

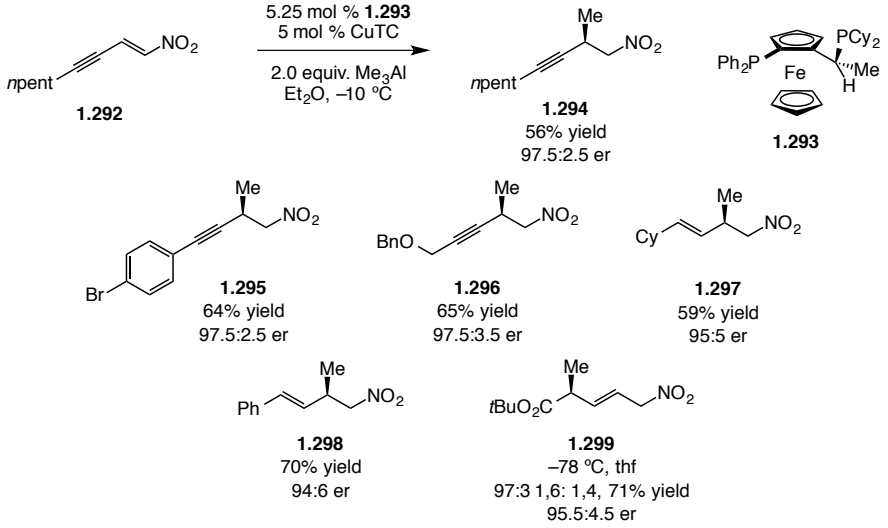
Scheme 1.48. Alkylaluminum Additions to Nitroolefins



More recently, the Alexakis group has demonstrated the regioselective addition of trimethylaluminum to nitro dienes[60] and nitro enynes.[61] As illustrated in Scheme 1.49, in the presence of a modified JosiPhos type ligand, exclusive 1,4 methyl addition is observed with a range of nitro enynes. With a nitro diene as substrate, the 1,4-addition product is isolated exclusively with high enantioselectivity for both aryl and alkyl substrates. Reactions with dienoates, carried out in thf at –78 ºC, generate the 1,6-adduct in >95% selectivity and >95:5 er. The observed change in regioselectivity may be a result of the decreased rate of reductive elimination of the Cu(III) intermediate at low temperatures, which would allow π-allyl isomerization to become competitive.

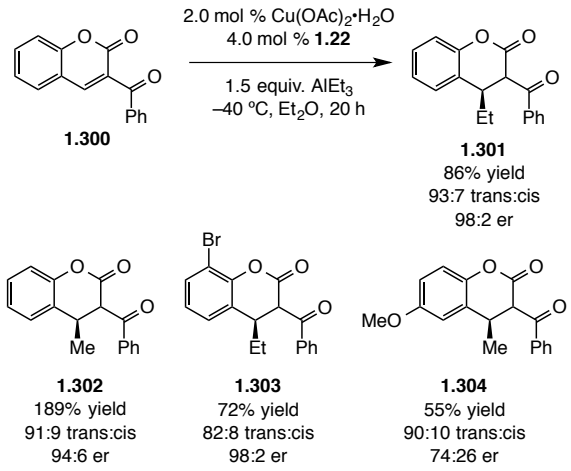
(60) Tissot, M.; Müller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 2770–2773.
(61) Tissot, M.; Alexakis, A. *Chem. Eur. J.* **2013**, *19*, 11352–11363.

Scheme 1.49. Phosphine–Cu-Catalyzed ECA with Nitro Dienes and Nitro Enynes



The Woodward group also examined the addition of trialkylaluminum reagents to a variety of 3-acylcoumarin derivatives.[62] In the presence of a biaryl phosphoramidite ligand, reactions proceed with high enantioselectivities and diasteroselectivities (90:10–>99:1 dr). Methyl addition (versus ethyl) results in lower selectivities in all cases examined (Scheme 1.50).

Scheme 1.50. Cu-Catalyzed Addition of Alkylaluminum Reagents to 3-Acylcoumarins



(62) Tang, X.; Blake, A. J.; Lewis, W.; Woodward, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1881–1891.

Chapter 2:

Synthesis of Quaternary Carbon Stereogenic Centers through Enantioselective Cu-Catalyzed Allylic Substitution with Alkenylaluminum Reagents

2.1 Introduction

Addition of an alkenyl nucleophile to a C-based electrophile to form a new stereogenic center allows for rapid access to a range of highly functionalized compounds. While the analogous reactions with carbonyls[1], imines[2], and α,β-unsaturated conjugate acceptors[3] have been disclosed, catalytic enantioselective allylic substitution (EAS) reactions[4], with alkenyl nucleophiles[5] are less prevalent. The majority of previous reports

(1) For examples of catalytic enantioselective alkenyl additions to carbonyls, see: (a) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593–1594. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443. (c) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539. (d) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138–4139. (e) Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 14052–14053. (f) Kerrigan, M. H.; Jeon, S.-J.; Chen, Y. K.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8434–8445. (g) Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499–502.

(2) For examples of catalytic enantioselective alkenyl additions to aldimines, see: (a) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941–3944. (b) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276. (c) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645. (d) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923. (e) Nakao, Y.; Takeda, M.; Chen, J.; Salvi, L.; Hiyama, T.; Ichikawa, Y.; Shintani, R.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 290–291.

(3) F or examples of catalytic enantioselective alkenyl conjugate additions to unsaturated carbonyls, see: (a) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97–99. (b) Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051–5055. (c) Otomaru, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2647–2651. (d) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874–3879. (e) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137–9143. (f) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662. (g) Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462. (h) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739. (i) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040–3043. (j) Müller, D.; Alexakis, A. *Org. Lett.* **2012**, *14*, 1842–1845. (k) Müller, D.; Alexakis, A. *Chem. Commun.* **2012**, *48*, 12037–12049. (l) Cottet, P.; Müller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 828–831. (m) Müller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 1594–1597.

(4) For reviews on allylic substitution reactions catalyzed by other transition metals and with "soft" nucleophiles, see: (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Oijima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 8E. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944. (c) Stanley, L. M.; Hartwig, J. F. *Acc. Chem. Res.* **2010**, *43*, 1461–1475. (d) Trost, B. M. *Org.*

deal primarily with alkyl metals reagents[6], and to a lesser extent aryl nucleophiles.[7] Even fewer are the examples that deal with the more challenging quaternary stereogenic centers[8] (versus tertiary centers). As such, a method in which easy-to-access alkenyl nucleophiles are coupled with allylic electrophiles to generate 1,4-dienes containing an all-carbon quaternary stereogenic center would be valuable, especially if such a method could be applied to the synthesis of important biologically active natural products (Scheme 2.1).

Process Res. Dev. **2012**, *16*, 185–194. (e) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147–3163.

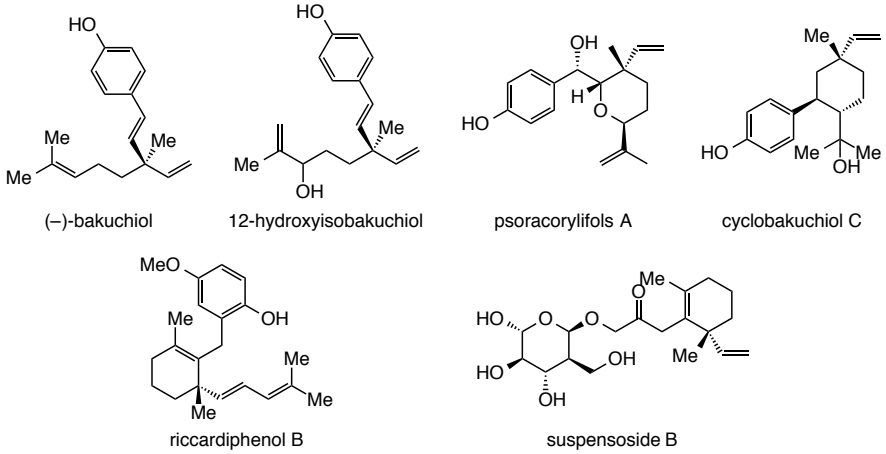
(5) For recent advances in enantioselective allylic substitution involving alkenyl metal reagents, see: (a) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447. (b) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315–14320. (c) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419–423. (d) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656–8659. (e) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994–997. For a related study involving additions of an allene group, see: (f) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493. For a related study involving additions of an propargyl group, see: (g) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137,* 8948–8964.

(6) For reviews on Cu-catalyzed allylic alkylation reactions that involve "hard" alkyl- or arylmetal-based reagents, see: (a) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785. (b) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435–4439. (c) Falciola, C. A.; Alexakis, A. Eur. *J. Org. Chem.* **2008**, 3765–3780. (d) Alexakis, A.; Bäckvall, J.-E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852. (f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (g) Langlois, J. -B.; Alexakis, A. *Topics in Organometallic Chemistry* **2012**, *38*, 235–268.

(7) For examples, see: (a) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558. (b) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393–3395. (c) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362. (d) Selim, K. B.; Yamada, K-i.; Tomioka, K. *Chem. Commun.* **2008**, 5140–5142. (e) Falciola, C. A.; Alexakis, A. *Chem. Eur. J.* **2008**, *14*, 10615–10627; (f) Selim, K. B.; Matsumoto, Y.; Yamada, K-I.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733–8735. (g) Polet, D.; Rathgeb, X.; Falciola, J C.; Langlois, A. B.; Hajjaji, S. E.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 1205–1206. (h) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370–8374. (i) ref. 5 (d).

(8) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623.

Scheme 2.1. Biologically Active Natural Products With Alkenyl-Substituted All-carbon Quaternary Stereogenic Centers



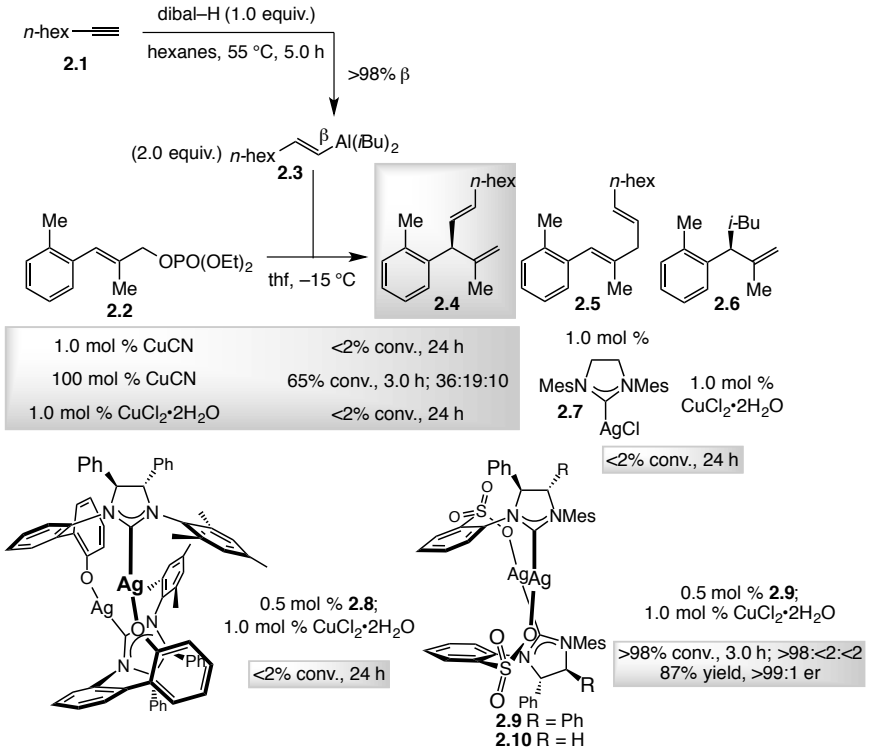
2.2 Background

Stemming from the application of N-Heterocyclic carbene (NHC)–Cu-catalyzed allylic substitution with alkylaluminum reagents to allylic phosphates in the course of the total synthesis of baconipyrone C,[9] the Hoveyda lab began exploring other types of readily available aluminum nucleophiles, specifically alkenylaluminum reagents. The addition of one equivalent of di*iso*butylaluminum hydride to a terminal olefin leads to the regiospecific addition of aluminum and the hydride across the triple bond.[10] The resulting *trans* 1,2-alkenylaluminum species can be used in subsequent reactions without any further purification. The first class of substrates that were examined was α,β-disubstituted allylic phosphates, which have been shown in the literature to be less reactive.[11] As described in Scheme 2.2, in the presence of either catalytic or stoichiometric CuCN, <2% conversion of the substrate was observed after 24 h.[5a] Additionally, catalytic $CuCl_2 \bullet 2H_2O$, in the presence or absence of an NHC–AgCl salt **2.7**, is ineffective at promoting the desired reaction. Ag-dimer **2.8**, which has been used for the addition of alkylzinc reagents, again did not lead to the desired product, **2.4**. Only

(9) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864.
(10) For a review on hydroaluminations of alkynes and alkenes, see: Eisch, J. J. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon, Oxford, 1991; Vol. 8, pp 733–766.
(11) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5995-5998.

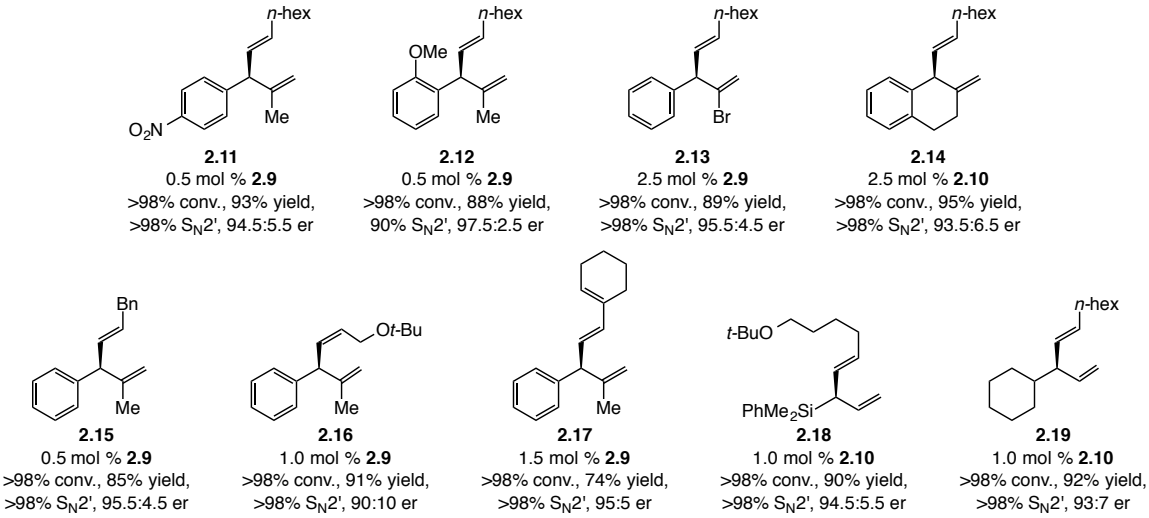
when a sulfonate-containing NHC–Ag salt **2.9** is added to the reaction is the desired product observed with complete site- (>98:2 S_N2':S_N2) group- (>98:2 alkenyl vs isobutyl transfer) and enantioselectivity (>99:1 er).

Scheme 2.2. NHC–Cu-Catalyzed Addition of Alkenylaluminum Reagents



As show in Scheme 2.3, a range of substrates is tolerated in the reaction including those containing electron-withdrawing as well as donating groups. Both β-methyl and bromide substrates lead to the desired product in high yields and enantioselectivities. A number of alkenylaluminum reagents with alkyl, aryl, ether, or olefin-containing groups participate in the reaction. Notably, the hydroalumination of *tert*-butyl protected propargyl alcohol results exclusively in the *Z*-alkenylaluminum reagent, which can be transferred with retention of olefin geometry. Simple disubstituted allylic phosphates can also be used in the reaction.

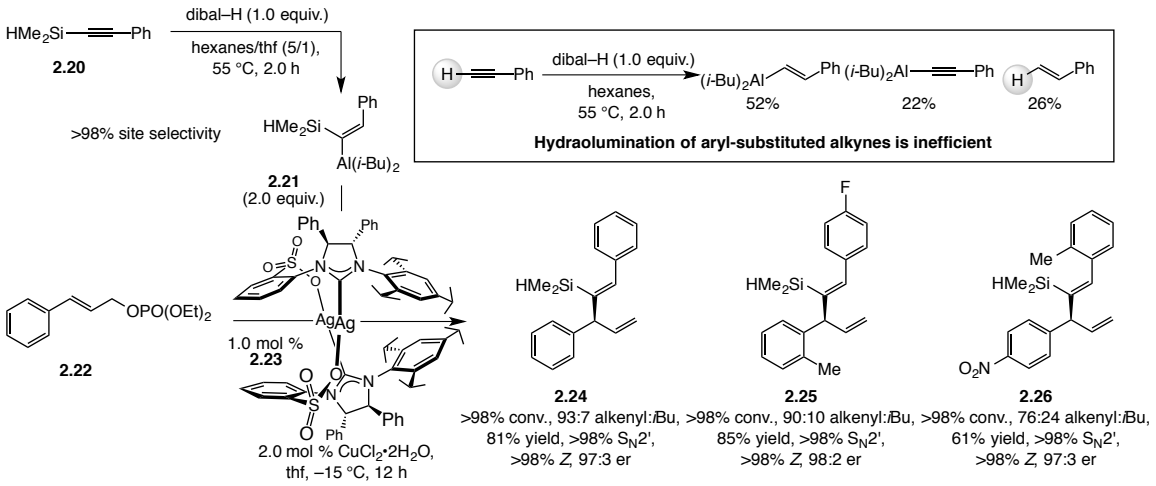
Scheme 2.3. Scope of NHC–Cu-Catalyzed Addition of Alkenylaluminum Reagents



In the course of developing the aforementioned reaction, it was found that while hydroalumination of a terminal alkyne bearing an alkyl group results in >90% conversion to the *trans* hydroalumination product, the same reaction with an aryl-containing alkyne results in a mixture of products. The initial styrenylaluminum generated in the reaction is basic enough to deprotonate the alkyne proton, leading to an alkynylaluminum species and an equivalent of styrene. Moreover, NHC–Cu-catalyzed allylic substitution with this mixture leads to both the alkenyl as well as the alkynyl addition products, which are inseparable.

The first solution that was examined was protection of the alkyne with a silyl group (Scheme 2.4).[5c] In a 5:1 solvent mixture of hexanes/thf, the desired silyl-substituted alkenylaluminum reagent is generated with complete regioselectivity as well as olefin geometry. In the presence of 2 mol % of NHC–Cu complex derived from NHC–Ag precursor **2.23**, *Z*-alkenylaluminum reagents can be added efficiently to disubstituted allylic phosphates with high S_N2' selectivity and enantioselectivity. Sterically hindered aluminum reagents, such as those containing a large *ortho*-methyl aryl group, lead to diminished group selectivity, with up to 24% isobutyl addition observed.

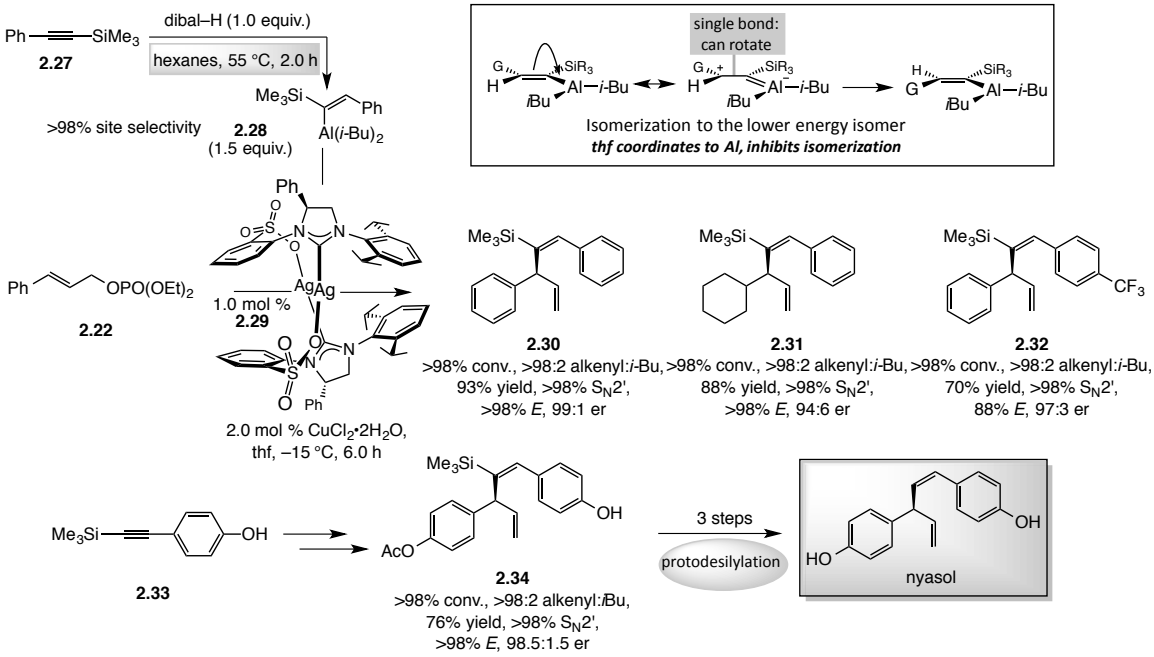
Scheme 2.4. NHC–Cu-Catalyzed EAS With *Z*-silylalkenylaluminum Nucleophiles



In addition to stopping adventitious alkyne deprotonation, the silyl group also allows for isomerization of the alkenylaluminum reagent. In the absence of a coordinating solvent, thf in the above reaction, complete isomerization of the alkenylaluminum species to the thermodynamically favored product is observed after two hours (Scheme 2.4). The isomerization is promoted by a number of factors: (1) the empty p-orbital on aluminum delocalizes the electron density of the adjacent olefin resulting in more single bond character (2) both the neighboring aryl group as well as the silicon group aid in stabilizing the forming carbocation which lowers the barrier to rotation (3) rotation around the C–C bond alleviates the steric repulsion of the sizable aryl and silyl groups and situates the aryl group *cis* to the longer carbon–aluminum bond. The empty p-orbital on aluminum is occupied in the presence of a coordinating solvent, which shuts down this isomerization and favors the kinetically formed *cis*-hydroalumination product.

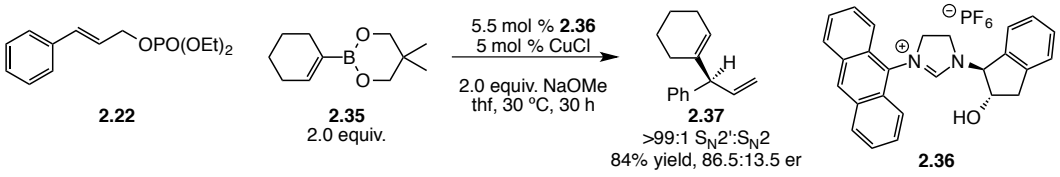
As shown in Scheme 2.5, despite the sterically large nature of the nucleophile, complete group selectivity is observed in the Cu-catalyzed allylic substitution of *E*-alkenylaluminum reagents. Products are generated in up to 93% yield and 99:1 er. Notably, diminished E-olefin selectivity is observed with aryl groups containing an electron-withdrawing *para*-CF_3 group. Presumably, the olefin isomerization is slowed down in the presence of an electron-withdrawing group, as the aryl group is less able to stabilize the incipient carbocation. This method can be applied to a concise synthesis of 1,4-diene containing natural product nyasol, where the *Z*-olefin is unmasked following protodesilylation.

Scheme 2.5. NHC–Cu-Catalyzed EAS With *E*-silylalkenylaluminum Nucleophiles



Given the incompatibility of aluminum reagents with ketones, aldehydes, and protic functional groups, a number of recent reports deal with the addition of the more functional group tolerant alkenyl boron reagents. The first of these was reported by Hayashi in 2008 wherein a number of arylboronic acid neopentyl glycol ester reagents are coupled to allylic phosphates in the presence of NHC–Cu complex derived from **2.36**.[5d] A single example of the addition of a cyclohexenyl nucleophile is reported in the study. With 5 mol % of bidentate NHC–Cu complex and 2.0 equivalents NaOMe, the desired product is formed with complete regioselectivity (S_N2' vs S_N2) and 86.5:13.5 er (Scheme 2.6).

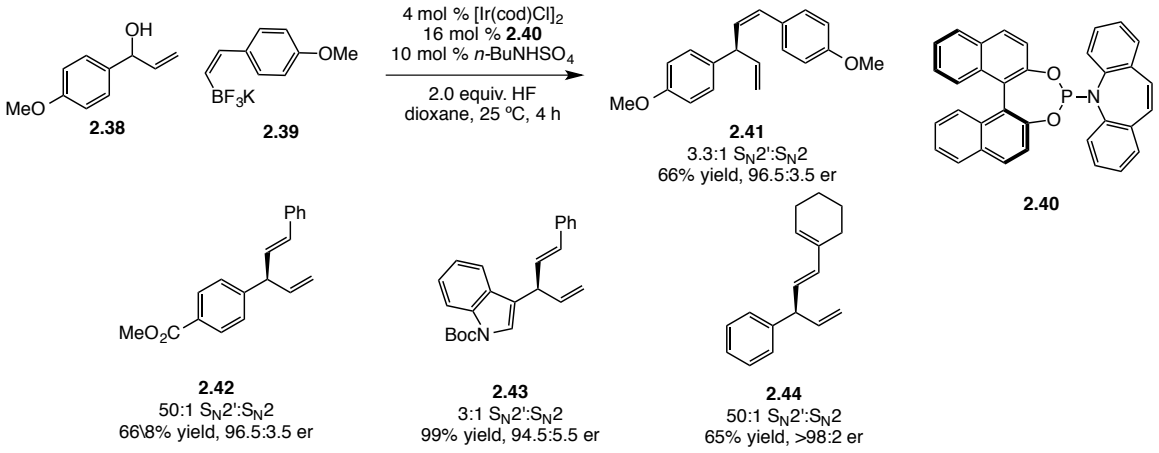
Scheme 2.6. NHC–Cu-Catalyzed Allylic Substitution With Alkenylboronic Esters



The Carreira group has also demonstrated that in the presence of an Ir–phosphoramidite complex a variety of alkenyl potassium trifluoroborate salts are coupled with racemic secondary allylic alcohols bearing an aryl group.[5e] Substrates are accessed in one step from the addition of vinyl Grignard to the requisite aldehyde. Reactions are

catalyzed by 8 mol % of the complex derived from $[Ir(cod)Cl]_2$ and phosphoramidite **2.40**. Products are obtained in moderate to good yields and high enantioselectivity, although site selectivity varies with the substrate (3:1–50:1 S_N2':S_N2). In addition to relatively high catalyst loading and variable selectivities, two equivalents of HF are needed to activate the alkenyl–BF_3K nucleophiles.

Scheme 2.7. Ir-Catalyzed EAS of Potassium Trifluoroborate Nucleophiles

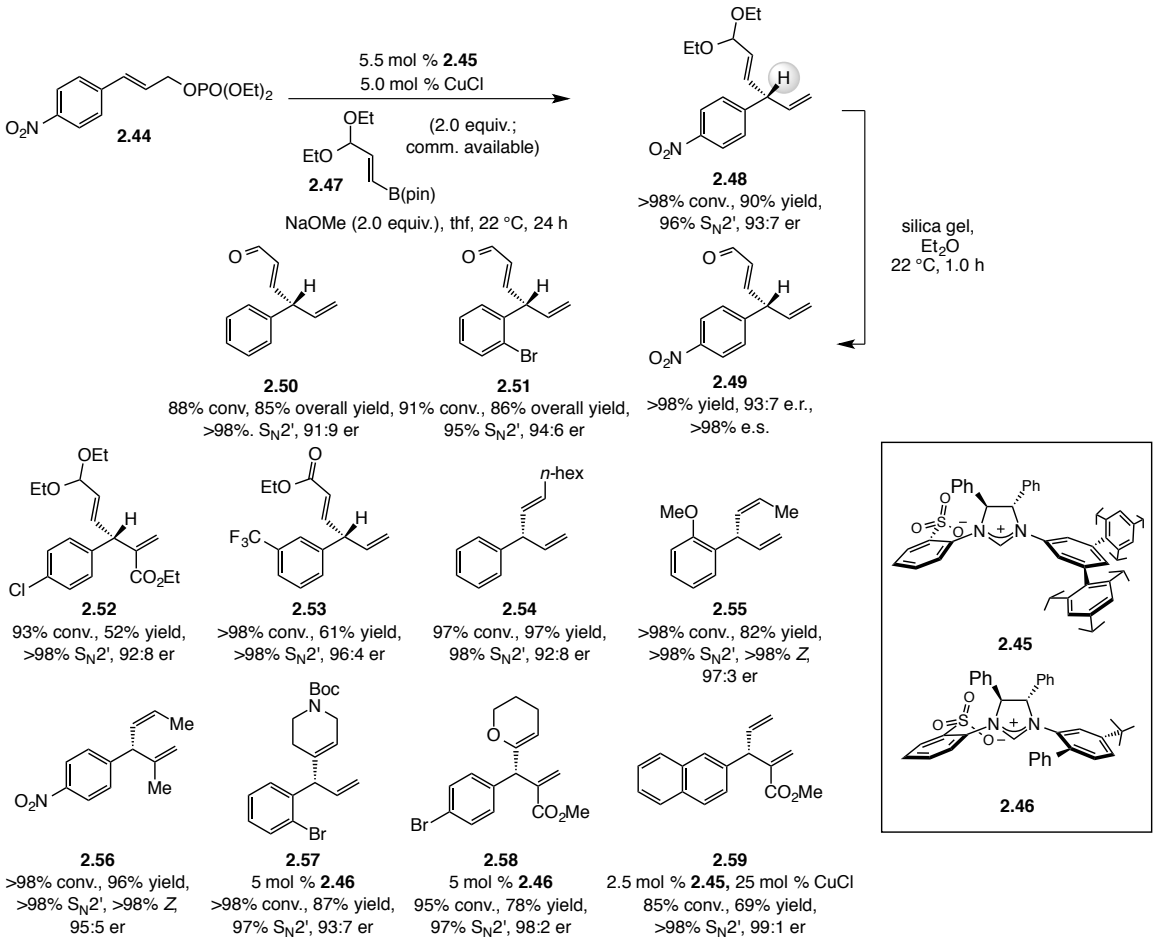


More recently, the Hoveyda laboratories disclosed the addition of a variety of alkenylboronic acid pinacol esters [alkenylB(pin)] to allylic phosphates to form tertiary centers.[12] Reactions are catalyzed by 5 mol % of an in situ generated sulfonate-containing NHC–Cu complex derived from imidazolinum salt **2.45**. As shown in Scheme 2.8, acetal-containing alkenylB(pin) reacts to form **2.48** in high yield and 93:7 er. Upon stirring with silica gel in Et_2O, the α,β-unsaturated aldehyde is generated in quantitative yield and without loss of enantiomeric purity. Nucleophiles containing unsaturated esters are also competent reaction partners generating the allylic substitution adducts in up to 95% yield and 96:4 er without any of the corresponding conjugate addition product observed. Both *trans*- as well as *cis*-alkenylB(pin) reagents can be coupled with a variety of allylic phosphates with complete retention of olefin geometry. Furthermore, heterocycle-containing nucleophiles, which could not be generated through hydroalumination of an alkyne, lead to desired products in up to 98% yield and 98:2 er (**2.57**–**2.58**). Sterically unhindered vinylB(pin) reacts with a number of Baylis-Hillman derived allylic

(12) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136,* 2149–2161.

phosphates to form 1,4-dienes containing an α,β-unsaturated ester in up to 69% yield and 99:1 er.

Scheme 2.8. NHC–Cu-Catalyzed EAS with AlkenylB(pin) Reagents to Form Tertiary Centers

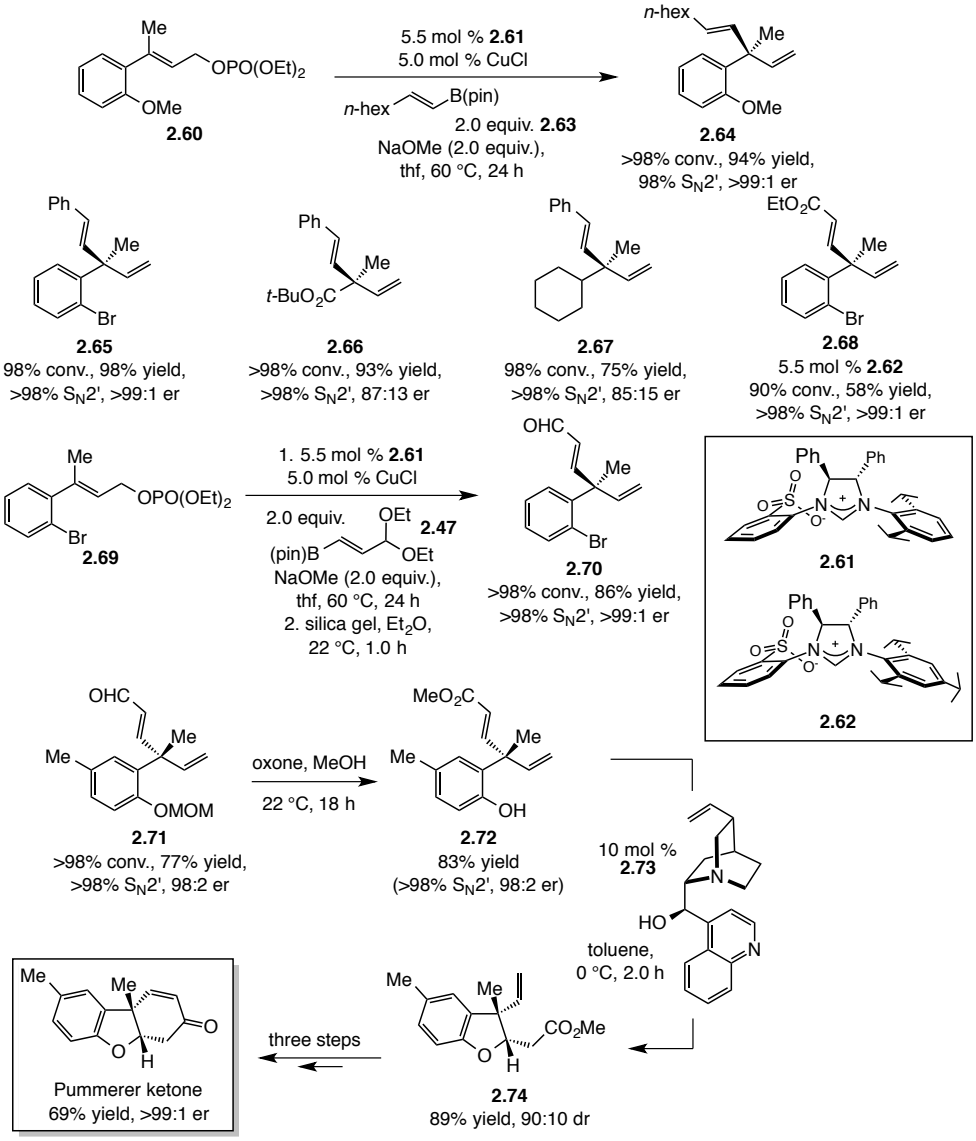


In addition to the formation of tertiary centers, Hoveyda and co-workers also disclosed the allylic substitution of allylic phosphates with alkenylB(pin) reagents to form all-carbon quaternary stereogenic centers.[13] As shown in Scheme 2.9, reactions are catalyzed by 5 mol % of the NHC–Cu complex derived from imidazolinum salt **2.61**. Both aryl- and alkyl-substituted alkenylB(pin) reagents are suitable coupling partners for the reaction with a variety of allylic phosphates, furnishing the desired dienes in 85:15 to >99:1 er. Additionally, unsaturated ester and acetal-containing reagents are stable under the reaction conditions and allow access to γ-substituted α,β-unsaturated esters and

(13) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51,* 6613–6617.

aldehydes. The utility of this method is highlighted through a concise enantioselective synthesis of Pummerer's ketone, an intermediate in the biosynthesis of morphine.

Scheme 2.9. NHC–Cu-Catalyzed EAS with AlkenylB(pin) Reagents to Form Quaternary Centers

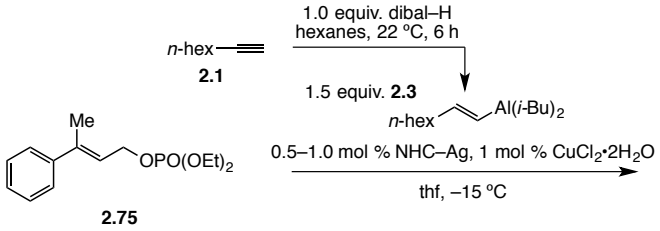


2.3 Catalytic Enantioselective Addition of Alkenyl Nucleophiles to Trisubstituted Allylic Phosphates

2.3.a. Screening of Reaction Conditions for the Addition of Alkyl-Substituted Alkenylaluminum Reagents

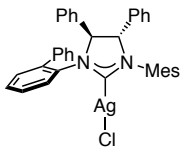
We set out to find a catalytic system that would allow for the coupling of trisubstituted allylic phosphates with alkenylmetals, more specifically with alkyl-substituted alkenylaluminum reagents, which have already proven to be competent reaction partners in allylic substitution. As shown in Table 2.1, NHC–Ag precursors containing a sulfonate chelate lead to high regioselectivity with the desired product isolated in 76–84% yield and up to 95:5 er. Monodentate NHC–Ag **2.77** leads to an inefficient reaction as well as low regioselectivity. Both phenoxy- as well as carboxylate-containing NHCs are inefficient with low to moderate enantioselectivity.

Table 2.1. Screening of NHC–Ag Complexes[(a)]

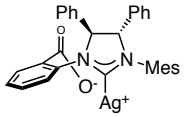


entry	NHC–Ag	time (h)	conv. (%)[(b)]	yield (%)[(c)]	$S_N2':S_N2$[(b)]	er[(d)]
1	**2.77**	120	58	nd	43:57	61:39
2	**2.8**	24	30	nd	>98:2	89.5:10.5
3	**2.9**	3	>98	76	>98:2	93.5:6.5
4	**2.10**	3	>98	84	>98:2	95:5
5	**2.29**	3	>98	80	>98:2	95:5
6	**2.78**	24	49	nd	71:29	53.5:46.5

(a) Reaction run under an atmosphere of N_2. (b) Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. (c) Yields of isolated and purified products. (d) Determined by HPLC analysis. nd = not determined



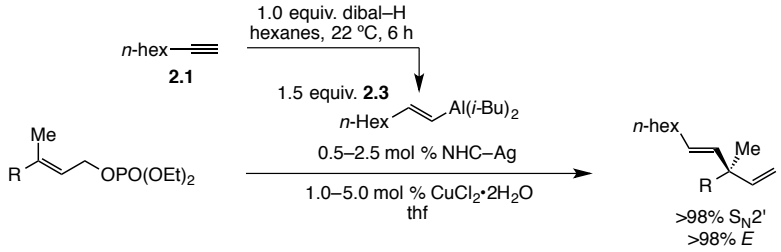
2.77



2.78

As shown in Table 2. 2, a range of allylic phosphates can be coupled with *n*-hexyl substituted alkenylaluminum, **2.3**, in the presence of 0.5–2.5 mol % **2.9** or **2.10** to furnish 1,4-dienes in 77–97% yield and 89:11–98:2 er. Reactions with aryl substituted allylic phosphates containing sterically hindered *ortho*-bromo, electron-withdrawing, or electron-donating groups can be run at room temperature to deliver the desired product in high yield with little diminution of enantioselectivity (Table 2.1, entries 1–2, 5–12). Alkyl-substituted allylic phosphates are run at –50 ºC to achieve the highest levels of enantioselectivity, although reaction at room temperature results in only a slight decrease in enantiopurity (Table 2.1, entries 13–14, 17–18). Silyl-substituted as well as carboxylic ester containing substrates are competent reaction partners, leading to the desired product in 82–85% yield and 91:9–95.5:4.5 er. (Table 2.1, entries 15–16).

Table 2.2. Substrate Scope for Addition of Alkenylaluminum **2.3**[(a)]



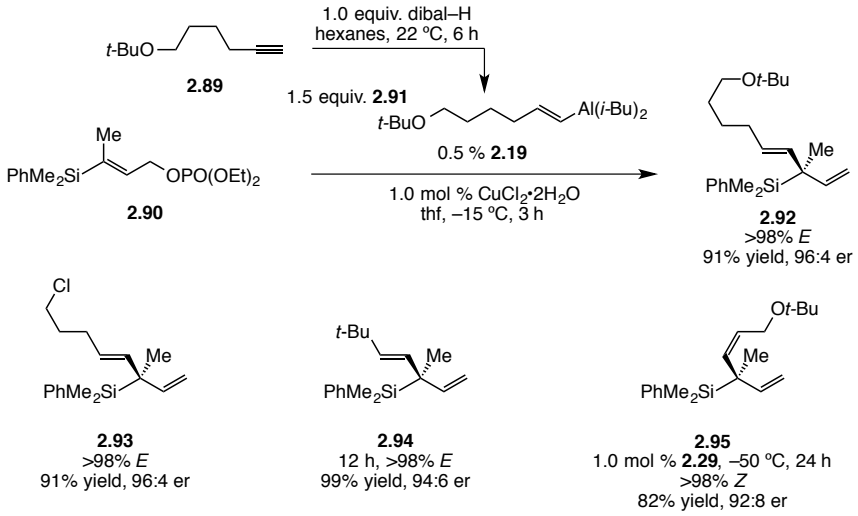
entry	Substrate (R)	NHC–Ag; mol %	Product	temp (ºC)	time (h)	yield (%)[(b)]	er[(c)]
1	Ph	**2.10**; 0.5	**2.79**	–15	3	84	95:5
2	Ph	**2.10**, 0.5	**2.79**	22	10 min	82	94:6
3	*o*-MeC_6H_4	**2.9**; 2.0	**2.80**	–15	3	87	96.5:3.5
4	*o*-$CF_3C_6H_4$	**2.9**; 2.5	**2.81**	–15	3	96	98:2
5	*o*-BrC_6H_4	**2.9**; 1.0	**2.82**	–15	3	87	98:2
6	*o*-BrC_6H_4	**2.9**; 1.0	**2.82**	22	10 min	92	96.5:3.5
7	*o*-$OMeC_6H_4$	**2.9**, 0.5	**2.64**	–15	3	86	98.5:1.5
8	*o*-$OMeC_6H_4$	**2.9**, 0.5	**2.64**	22	30 min	83	97.5:2.5
9	*o*-$NO_2C_6H_4$	**2.9**; 2.0	**2.83**	–15	3	97	97.5:2.5
10	*o*-$NO_2C_6H_4$	**2.9**; 2.0	**2.83**	22	10 min	89	96.5:3.5
11	*p*-$NO_2C_6H_4$	**2.9**, 0.5	**2.84**	–15	3	92	94.5:5.5
12	*p*-$NO_2C_6H_4$	**2.9**, 0.5	**2.84**	22	10 min	91	94.5:5.5
13	Cy	**2.9**; 2.0	**2.85**	–50	6	91	95:5
14	Cy	**2.9**, 0.5	**2.85**	22	10 min	93	93:7
15	$PhMe_2Si$	**2.9**, 0.5	**2.86**	–15	3	85	95.5:4.5
16	CO_2tBu	**2.10**, 0.5	**2.87**	–15	3	82	91:9
17[(d)]	$(CH_3)_2CH(CH_2)_2$	**2.9**, 1.0	**2.88**	–50	24	77	92.5:7.5
18	$(CH_3)_2CH(CH_2)_2$	**2.10**, 0.5	**2.88**	22	10 min	84	89:11

(a) Reaction run under an atmosphere of N_2. >98% conv. in all cases. (b) Yields of isolated and purified products. (c) Determined by HPLC analysis. (d) 91% conversion.

A number of other aliphatic alkynes undergo hydroalumination efficiently under standard conditions. *tert*-Butyl ether, halide, as well as sterically hindered *tert*-butyl substituted alkenylaluminum reagents lead to products in high yield and enantioselectivity, 82–99 % yield and 94:6–96:4 er, with complete retention of olefin configuration. Hydroalumination of *tert*-butyl protected propargyl alcohol leads to exclusive formation of the corresponding *Z*–alkenylaluminum reagent.[14] Reaction with silyl-substituted allylic phosphate **2.90** leads to allylsilane **2.95** in 82% yield and 92:8 er with retention of the *Z*-olefin.

(14) For directed (*Z*-selective) hydroalumination of terminal propargyl ethers, see: Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243–6246.

Scheme 2.10. Cu-Catalyzed EAS with Aliphatic Alkenylaluminum Reagents

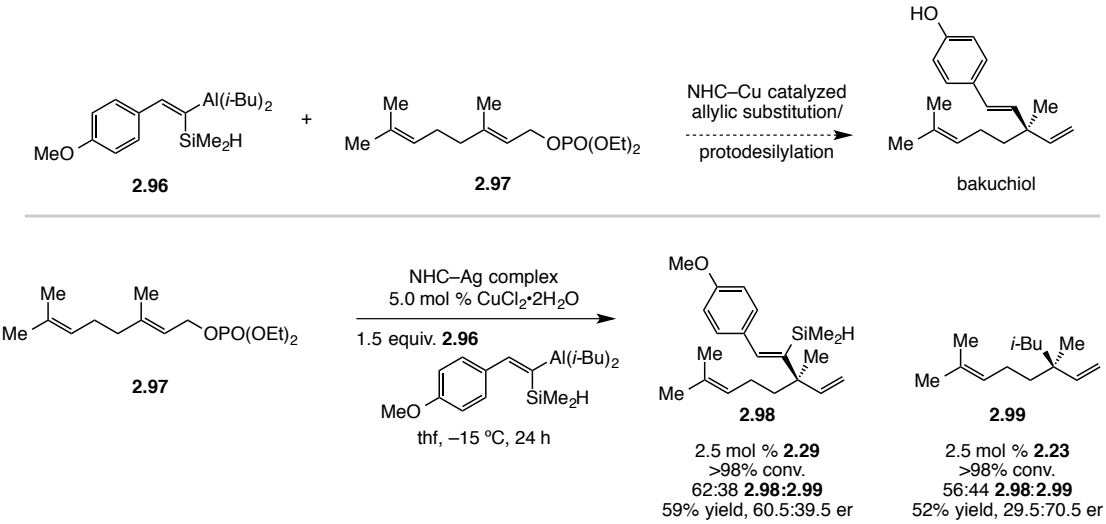


2.3.b Determining the Appropriate Nucleophile for the Formation of Quaternary Stereogenic Centers

Our interest in developing an enantioselective addition of alkenyl nucleophiles to form quaternary stereogenic centers stemmed from the retrosynthetic analysis of natural product bakuchiol.[15] EAS of a substituted styrenyl nucleophile to a geraniol-derived allylic phosphate would allow rapid access to the carbon framework of bakuchiol. We first began by assessing the viability of EAS with Si-substituted alkenylaluminum nucleophiles and trisubstituted allylic phosphates. As shown in Scheme 2.11, in the presence of NHC–Ag complexes **2.29** and **2.23**, which had proven optimal for reaction with disubstituted allylic phosphates, the reaction proceeds to give a mixture of both the desired alkenyl product as well as the corresponding *iso*butyl product. The increased steric bulk of the silyl group coupled with the larger allylic phosphate leads to decreased group selectivity. Additionally, the stabilizing effect of the alpha silyl group on the alkenyl anion likely retards its rate of transfer.

(15) For previous enantioselective syntheses of bakuchiol, see: (a) Takano, S.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett*. **1990**, *31*, 3325– 3326. (b) Du, X.-L.; Chen, H.-L.; Feng, H.-J.; Li, Y.-C. *Helv. Chim. Acta* **2008**, *91*, 371–378. (c) Esumi, T.; Shimizu, H.; Kashiyama, A.; Sasaki, C.; Toyota, M.; Fukuyama, Y. *Tetrahedron Lett*. **2008**, *49*, 6846–6849. (d) Bequette, J. P.; Jungong, C. S.; Novikov, A. V. *Tetrahedron Lett*. **2009**, *50*, 6963–6964.

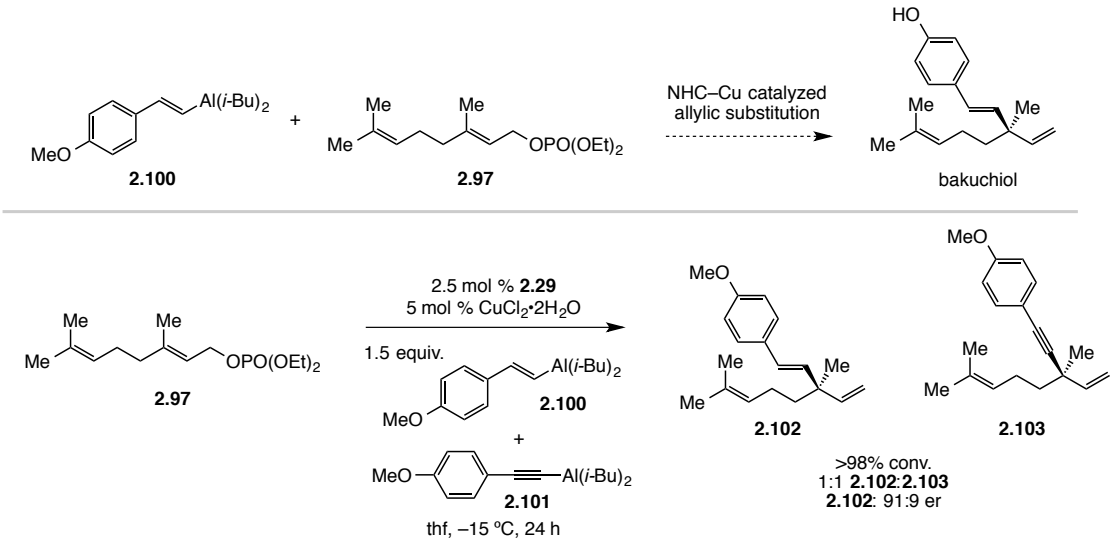
Scheme 2.11. Synthesis of Bakuchiol with Silyl-Substituted Alkenylaluminum Reagents



We moved on to examining the hydroalumination of aryl-substituted terminal alkynes, which, as discussed above, leads to a mixture of alkenyl- and alkynylaluminum reagents. Our hope was, given the commonly held belief that alkynes are "dummy ligands"[16] for copper, that the alkenyl group would transfer preferentially. As shown in Scheme 2.12, under the same reaction conditions used previously, a 50:50 mixture of **2.102** and **2.103** is obtained. As highlighted in the product distribution, where 1.5 equivalents of a 2:1 mixture of alkenyl:alkynyl reagents leads to a 1:1 mixture of products, the alkynyl group transfers faster than the corresponding alkenyl group. Despite the lack of group selectivity in the reaction, the desired alkenyl product is formed in 91:9 er.

(16) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, L. A. *Tetrahedron* **1984**, *40*, 5005–5038.

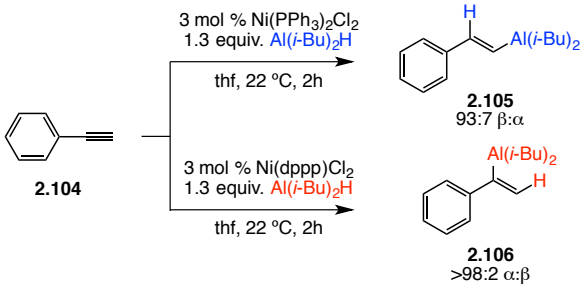
Scheme 2.12. Synthesis of Bakuchiol With Traditional hydroalumination of Aryl-Substituted Alkynes



In order to form the alkenylaluminum reagent in high purity, the rate of hydroalumination must be faster than the adventitious deprotonation. As such, we began to investigate catalysts that could effectively promote the desired hydroalumination. Eisch had reported that in the presence of catalytic $Ni(acac)_2$ the rate of hydroalumination for internal alkynes was increased dramatically (up to 60 times faster in certain cases). After extensive screening of commercially available Ni-salts, it was found that in the presence of 3.0 mol % $Ni(PPh)_3Cl_2$ the desired hydroalumination of phenylacetylene is complete in 3.0 hours at room temperature with 93:7 selectivity for the β-alkenylaluminum reagent without any of the alkynylaluminum byproduct.[17] Moreover, a Ni-catalyst with a bidentate phosphine ligand, $Ni(dppp)Cl_2$, leads to a complete reversal of regioselectivity, with the α-alkenylaluminum formed in >98:2 selectivity.

(17) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

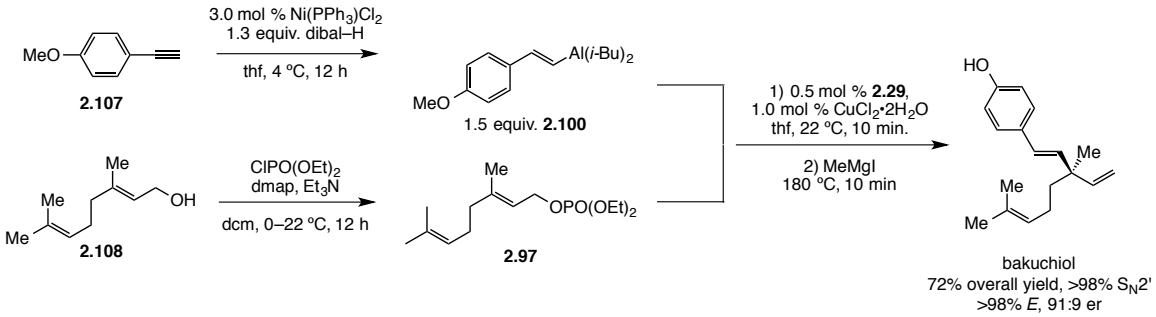
Scheme 2.13. Regioselective Ni-Catalyzed Hydroalumination of Terminal Alkynes



2.3.b. Synthesis of Bakuchiol

With a suitable procedure in hand, we turned our attention to the synthesis of natural product bakuchiol. In an expedient three-vessel procedure, bakuchiol can be synthesized from commercially available geraniol and 4-ethynylanisole. Phosphorylation of geraniol followed by subjection to EAS in the presence of 0.5 mol % NHC–Ag **2.29** with the appropriate *p*-methoxy substituted β-alkenylaluminum and demethylation with MeMgI lead to the natural product in 72% overall yield and 91:9 er. This route is significantly more expedient than previous syntheses of the same molecule, the shortest of which required 10 steps and lead to a 49% overall yield.[14]

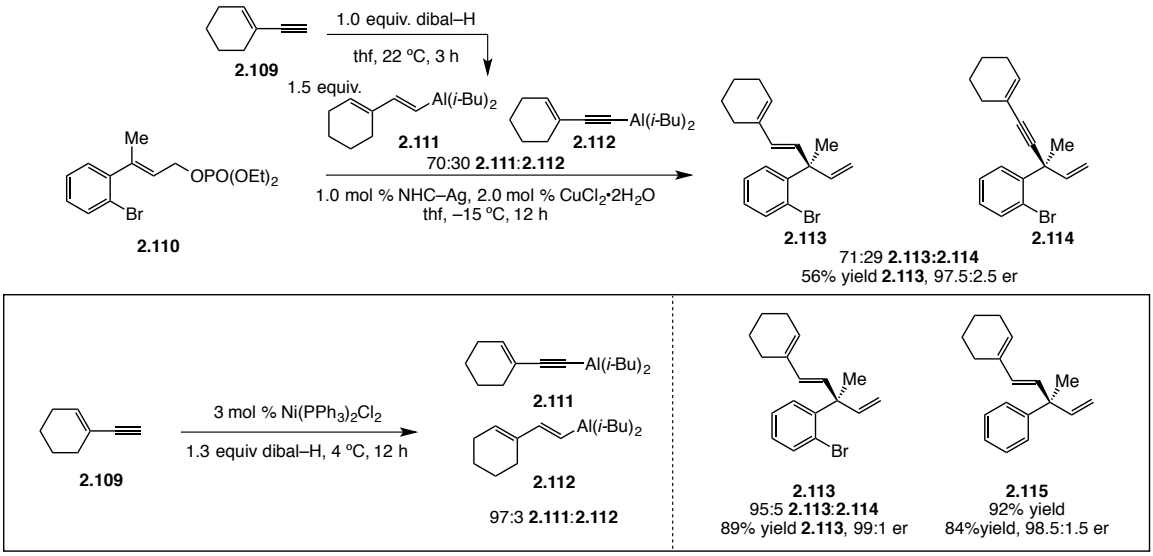
Scheme 2.14. Concise Total Synthesis of Bakuchiol



Another example that underscores the need for a catalytic hydroalumination procedure is the hydroalumination of cyclohexenyl-containing alkyne **2.109**. Under standard conditions with one equivalent of dibal–H, a 70:30 mixture of alkenyl- and alkynylaluminum reagents is generated. The pka of the enyne proton is sufficiently decreased relative to the corresponding cyclohexyl alkyne that the *in situ* generated alkenylaluminum reagent is able to deprotonate the more acidic proton to form the alkynylaluminum reagent. The ratio is reflected in the product distribution of the

subsequent NHC–Cu-catalyzed allylic substitution where the desired product can be obtained in 56% yield and 97.5:2.5 er. The cyclohexenyl alkyne undergoes hydroalumination efficiently (4 ºC, 12 h) in the presence of 3 mol % $Ni(PPh_3)_2Cl_2$ with minimal formation of the undesired alkynyl product. Subsequent EAS with an *ortho*-bromo aryl or phenyl substituted allylic phosphate generates products **2.113** and **2.115** in up to 92% yield and 99:1 er.

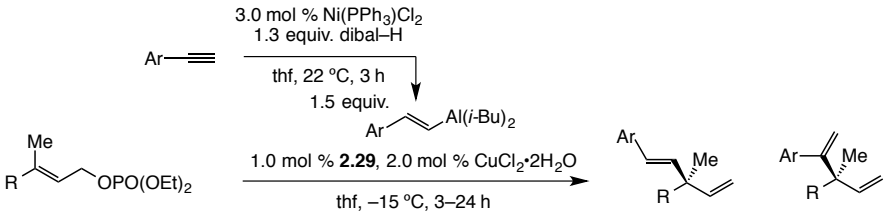
Scheme 2.15. Application of Ni-Catalyzed Hydroalumination to Enynes



To further highlight the utility of Ni-catalyzed hydroalumination, a number of aryl-substituted alkynes undergo site-selective Al–H addition in the presence of $Ni(PPh_3)_2Cl_2$ to form β-alkenylaluminum reagents which can be coupled with allylic phosphates to generate 1,4-dienes in 78–92% yield and 87:13–98:2 er (Table 2.3). Whereas the reaction of alkenylaluminum reagents generated from uncatalyzed processes lead to substantial formation of the derived alkyne-containing allylic substitution adduct, with the Ni-catalyzed procedure, in most cases, <2% alkynyl adduct is observed by ^1H NMR. Only cases where the alkyne contains a sterically hindered *ortho*-methyl aryl group is alkyne addition observed, most likely due to decreased rate of hydroalumination which allows deprotonation to be competitive. Again, only in cases where the alkenylaluminum reagent contains an electron withdrawing *para*-trifluoromethyl group is 13–15% of the corresponding α-alkenyl addition product observed. In all other cases, the

β-alkenyl product is formed in 92–>98% selectivity. Notably, the presence of the Ni catalyst does not have any deleterious effect on the Cu-catalyzed process.

Table 2.3. Scope of Aryl-Substituted Alkenylaluminum Additions[(a)]

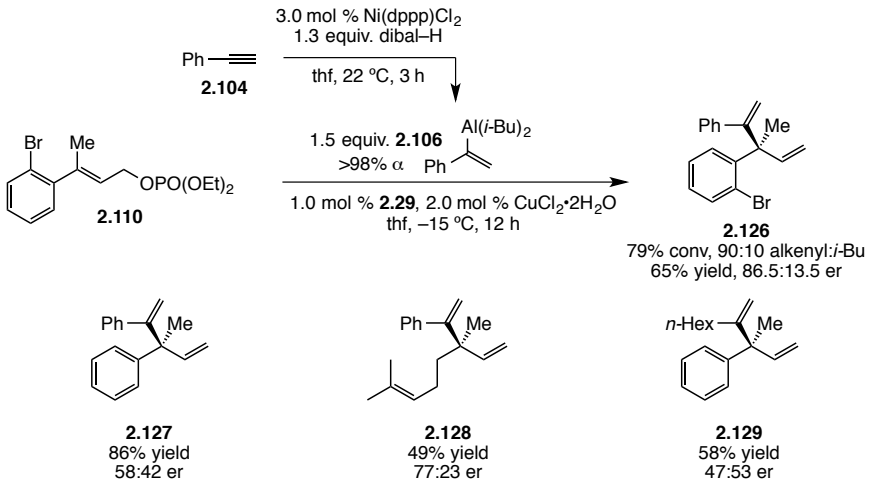


entry	Substrate (R)	Alkyne (Ar)	Product	time (h)	β:α[(b)]	yield (%)[(c)]	er[(d)]
1	Ph	Ph	**2.116**	3	95:5	78	96:4
2	Ph	*p*-$OMeC_6H_4$	**2.117**	6	>98:2	84	96.5:3.5
3	Ph	*p*-$CF_3C_6H_4$	**2.118**	3	87:13	82	94:6
4	Ph	*o*-MeC_6H_4	**2.119**	6	>98:2	88[(e)]	95:5
5	*o*-BrC_6H_4	Ph	**2.65**	3	96:4	81	98:2
6	*o*-MeC_6H_4	*p*-$OMeC_6H_4$	**2.120**	3	>98:2	82	98:2
7	*o*-$NO_2C_6H_4$	Ph	**2.121**	24	>98:2	92	98:2
8	*p*-$NO_2C_6H_4$	Ph	**2.122**	3	92:8	84	93:7
9	*p*-$CF_3C_6H_4$	*p*-$OMeC_6H_4$	**2.123**	3	>98:2	89	94:6
10	$(CH_3)_2CH(CH_2)_2$	Ph	**2.124**	3	93:7	81	90:10
11	$(CH_3)_2CH(CH_2)_2$	*p*-$CF_3C_6H_4$	**2.125**	3	85:15	79	87:13
12	$(CH_3)_2CH(CH_2)_2$	*o*-MeC_6H_4	**2.126**	6	>98:2	85[(e)]	91:9

(a) Reaction run under an atmosphere of N_2. (b) Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. (c) Yields of isolated and purified products. (d) Determined by HPLC analysis. (e) ~5-10% alkynylaluminum observed.

Following the observation of the α-alkenyl product in certain cases, we began to explore the addition of the pure α-alkenylaluminum reagents. As shown in Scheme 2.16, EAS reactions with the α-isomer, generated through hydroalumination in the presence of Ni(dppp)Cl_2, lead to formation of the desired product in low to moderate enantioselectivity with NHC–Ag **2.29**. With a sterically hindered *ortho*-bromo substrate, ~10% *iso*-butyl addition is observed presumably due to the more sterically encumbered α-nucleophile. Despite screening a number of NHC–Ag complexes, enantioselectivities could not be improved.

Scheme 2.16. Addition of α-Alkenylaluminum Reagents to Trisubstituted Allylic Phosphates



2.3.d. Insights into the Mechanism and Efficacy of Sulfonate-containing NHCs

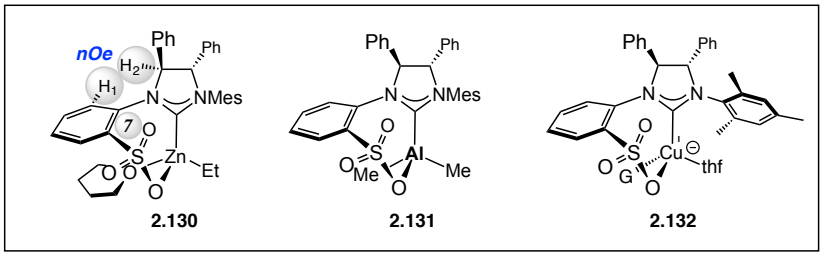
As shown in the catalyst screening data, the presence of a sulfonate-containing NHC is critically important for the efficiency of the reaction as well as the regio- and enantioselectivity. While we are unable to obtain a crystal structure of the NHC–Cu complex, the crystal structures of the analogous Zn- and Al-complexes have been reported.[18] While the NHC–Ag complex sits as a head-to-tail dimer where the sulfonate is situated *anti* to the backbone phenyl, in the monomeric Zn- and Al-complexes, the sulfonate sits *syn* to the phenyl on backbone. This change in orientation can be rationalized through examination of the chelate formed in the complex. Compared to the Ag-complex where the chelate ring size is much larger, in the Zn-complex a seven-membered chelate is formed. In order to minimize steric repulsion between the aryl group on the backbone and the *ortho* hydrogen of the N-aryl ring, the sulfonate sits *syn* to the aryl group, which is reflected in the observed nOe between the *ortho* hydrogen and the backbone hydrogen (Scheme 2.17, H_1 and H_2). Despite our inability to isolate the active NHC–Cu-complex, we assume that the analogous monomeric species forms in solution.

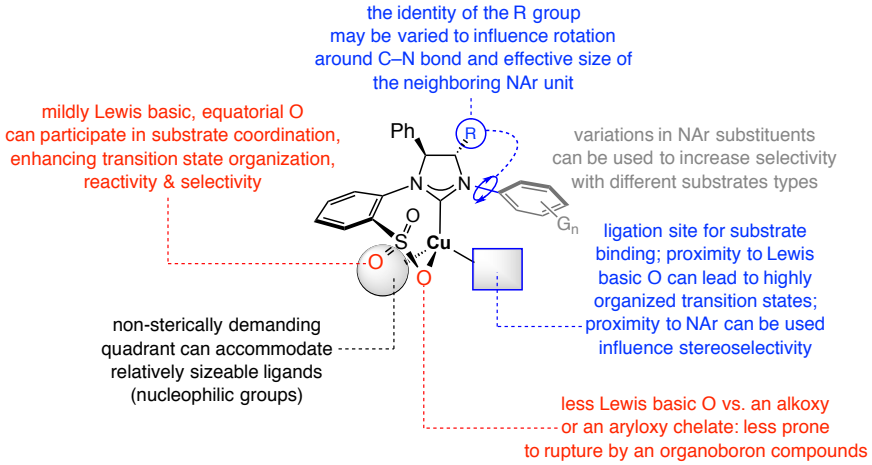
The structure of the catalyst gives rise to a number of attributes that merit mention; (1) the catalyst is relatively modular in that the group on the aryl group on the

(18) Lee, Y.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11625–11633.

backbone can be varied and/or removed entirely which affects the effective size and conformation of the neighboring N-aryl group; (2) the N-aryl group can be sterically modified, which can allow for an increase in enantioselectivity for a variety of substrates; (3) the tetrahedral Cu(I) center has two ligations sites, one located in the back, left quadrant which is relatively open and can accommodate a number of nucleophiles and one located in the front right quadrant in proximity to both the N-aryl group, which can influence its mode of binding, and the Lewis basic oxygen of the sulfonate, which can aid in substrate coordination; (4) the sulfonate provides a less Lewis basic oxygen chelate (versus a phenoxy or alkoxy chelate) as well as a Lewis basic oxygen situated in a pseudo equatorial position such that it can participate in substrate coordination and transition state organization.

Scheme 2.17. Unique Attributes of Sulfonate-containing Carbenes



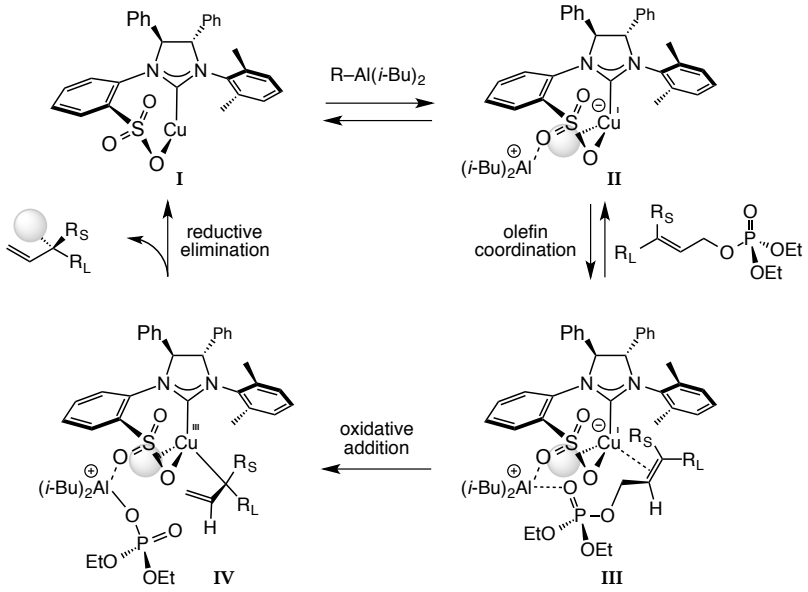


Based on the above considerations, the mechanism we put forth for the enantioselective allylic substitution consists of four major steps.[19] The initially formed

(19) For recent reports regarding the mechanism of non-catalytic allylic substitution reactions with alkyl- and allylcopper reagents, see: (a) Sofia, A.; Karlström, E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981–1989. (b) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863. (c) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244–

monomeric NHC–Cu complex reacts reversibly with the alkenylaluminum species to form a nucleophilic Cu(I) cuprate. This step is followed by olefin coordination of the substrate, where the large group, R_L, is pointed down and away from the N-aryl group, in addition, coordination of the Lewis basic oxygen of the phosphate with the aluminum cation serves to activate the substrate. Depending on the rate of olefin coordination, this step may be the enantio-determining step. The cuprate then irreversibly oxidatively adds to the substrate, kicking out the phosphate leaving group, to form a square planar Cu(III) intermediate. Again depending on the relative rates of the steps, this could be the enantio-determining step. Following the oxidative addition, the Cu(III) complex undergoes reductive elimination to reform the Cu(I) starting complex and release the product.

Scheme 2.18. Proposed Catalytic Cycle for Enantioselective Allylic Substitution.

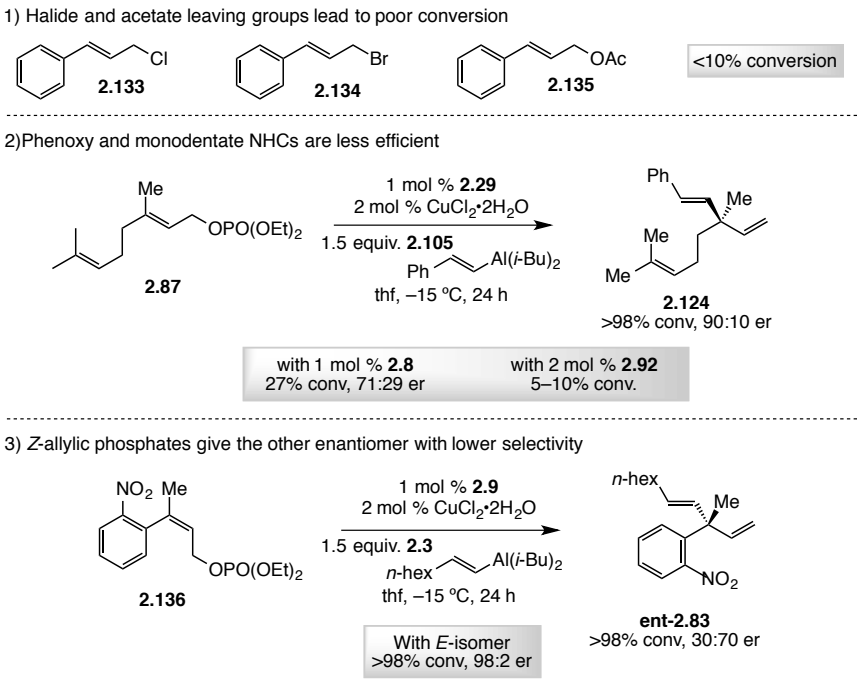


The attributes of the sulfonate-containing NHC–Cu-complexes are reflected in a number of experiments. Substrates containing a halide or acetate leaving group are ineffective in the EAS reaction (<10% conversion observed), which supports the proposal that coordination of the Lewis basic phosphate to the Al-cation serves to activate the substrate for addition. Moreover, without this chelation, the same degree of transition state preorganization is not possible leading to a higher barrier for oxidative addition. The ability of the proposed chelation to facilitate the reaction is again observed in the

11245. For a recent review on the mechanism of nucleophilic organocopper (I) reactions, see: (d) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339–2372.

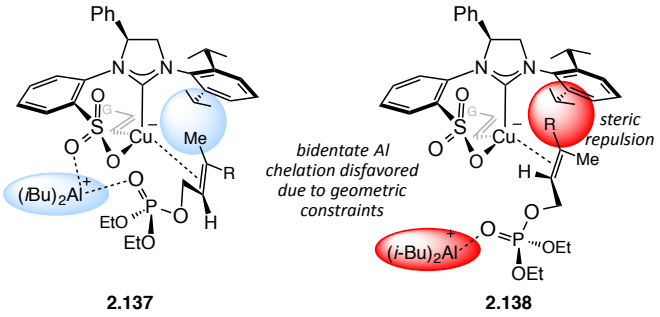
reactions catalyzed by complex **2.8** and **2.77**, the first containing a phenoxy-chelate and the second being a monodentate ligand. In both cases, minimal conversion to the desired product is observed. With a trisubstituted allylic phosphate containing a *Z*-olefin serving as the substrate, the desired product is formed in 70:30 er, with the major enantiomer being opposite to that observed with the *E*-allylic phosphate. In this case, the R_L group would be pointed toward the N-aryl group engendering an unfavorable steric interaction, thereby favoring the formation of the other enantiomer.

Scheme 2.19. Experimental Support for Proposed Mechanism



Based on the above observations, the model for enantioselectivity that we proposed is as follows: (1) the alkenyl nucleophile sits in the relatively open back left quadrant (2) the allylic phosphate approaches *syn* to the sulfonate such that the aluminum cation can bridge the pseudo equatorial sulfonate oxygen and the phosphate oxygen (3) to minimize steric interactions, the smaller methyl group of the allylic phosphate is pointed toward the N-aryl ring whereas the bulkier R group is pointed down and away (4) for the minor enantiomer, the copper center chelates the opposite face of the olefin such that the large R group points toward the N-aryl ring engendering steric repulsion (5) such a coordination disfavors the bridging chelation due to geometric constraints.

Scheme 2.20. Model for Observed Enantioselectivity



2.4 Conclusions

We have demonstrated that in conjunction with a protocol for the Ni-catalyzed hydroalumination of terminal alkynes, a variety of alkenylaluminum reagents can be coupled to allylic phosphates with high regioselectivity to form all-carbon quaternary stereogenic centers in high enantioselectivity. Products containing a 1,4-diene can be readily functionalized as demonstrated in a concise synthesis of natural product bakuchiol. Observations made over the course of the study have allowed us to develop a model for enantioselectivity and highlight the unique attributes of sulfonate-containing NHCs.

2.5 Experimental

General. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, n_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: *d* 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: *d* 77.16 ppm). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by analytical liquid chromatography (HPLC) on a Shimadzu chromatograph (Chiral Technologies Chiralpak AS (4.6 x 250 mm), Chiral Technologies Chiralcel OD (4.6 x 250 mm), Chiral Technologies Chiralcel OD-R (4.6 x 250 mm), Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm), or Chiral Technologies Chiralcel OD-H (4.6 x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher Inc.) in air.

n Reagents and Ligands:

3-(*tert*-Butoxy)prop-1-yne: Purchased from Acros and used after distillation from CaH_2 under N_2.

Chlorodiethylphosphate: Purchased from Aldrich and used as received.

5-Chloropent-1-yne: Purchased from Aldrich and used after distillation from CaH_2 under N_2.

Copper (II) chloride dihydrate: Purchased from Aldrich and used without further purification.

Di(*iso*-butyl)aluminum hydride (dibal-H, neat): Purchased from Aldrich and used as received.

4-Dimethylaminopyridine: Purchased from Advanced Chem Tech used as received.

3,3-Dimethylbut-1-yne: Purchased from Aldrich and used after distillation from CaH_2 under N_2.

1-Ethynylcyclohex-1-ene: Purchased from Aldrich and used after distillation from CaH_2 under vacuum.

1-Ethynyl-4-methoxybenzene: Purchased from Aldrich and used after distillation from CaH_2 under vacuum.

1-Ethynyl-2-methylbenzene: Purchased from Aldrich and used after distillation from CaH_2 under vacuum.

1-Ethynyl-4-(trifluoromethyl)benzene: Purchased from Aldrich and used after distillation from CaH_2 under vacuum.

1-Octyne: Purchased from Aldrich and used after distillation from CaH_2 under N_2.

Phenylacetylene: Purchased from Aldrich and used after distillation from CaH_2 under vaccum.

Tetrahydrofuran: Distilled under N_2 from sodium benzophenone ketyl.

Triethylamine: Purchased from Aldrich and distilled from CaH_2 under N_2.

Dichloromethane, diethyl ether, and hexanes: Purified by being passed through two alumina columns under a positive pressure of dry argon with a modified Advanced ChemTech purification system.

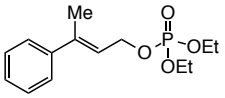
Alkyl-substituted alkenylaluminum reagents: Prepared according to a known literature procedure. [20]

Chiral NHC-Ag Complex 2.9: Prepared based on a previously reported procedure.[21]

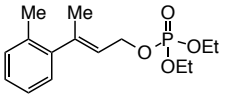
Chiral NHC-Ag Complex 2.10: Prepared based on a previously reported procedure.[22]

Chiral NHC-Ag Complex 2.29: Prepared based on a previously reported procedure.[23]

■ **Preparation of trisubstituted allylic phosphate substrates:** First, the requisite allylic alcohols were synthesized from the corresponding ketones by a two-step Horner-Wadsworth-Emmons olefination[24]/dibal–H reduction sequence.[25] Subsequently, allylic alcohols were converted to the corresponding allylic phosphates based on established methods.[26] Physical attributes of compounds, which have not been reported in the past, are presented below.



(*E*)-Diethyl (3-phenylbut-2-en-1-yl) phosphate. IR (neat): 2982 (w), 2908 (w), 1495 (w), 1478 (w), 1445 (w), 1391 (w), 1261 (m), 1165 (w), 1125 (w), 1100 (w), 1062 (w), 1004 (s), 969 (s), 879 (w), 821 (m), 758 (m), 696 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); d 7.42–7.39 (2H, m), 7.36–7.32 (2H, m), 7.30–7.28 (1H, m), 5.95 (1H, dt, *J* = 6.8, 1.2 Hz), 4.77 (2H, dd, *J* = 8.0, 7.6 Hz), 4.13 (4H, dq, *J* = 7.2, 1.2 Hz), 2.12 (3H, s), 1.36-1.32 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 142.5, 140.5, 128.5, 127.8, 126.0, 122.0 (d, *J* = 6.7 Hz), 64.5 (d, *J* = 5.2 Hz), 63.9 (d, *J* = 6.0 Hz), 16.35 (d, *J* = 3.0 Hz), 16.27; HRMS (ESI+): Calcd for $C_{14}H_{22}O_5P_1$ $[M+OH]^+$: 301.1205, Found: 301.1207.



(*E*)-Diethyl (3-(*o*-tolyl)but-2-en-1-yl) phosphate. IR (neat): 2982 (w), 2931 (w), 1486 (w), 1445 (w), 1381 (w), 1263 (w), 1263 (m), 1166 (w), 1103 (w), 1029 (s), 1009 (s), 977 (s), 881 (w), 827 (w), 761 (w), 729 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); d 7.28–7.22 (3H, m), 7.17–7.15 (1H, m), 5.63 (1H, dt, *J* =

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(23) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 419–423.

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(25) Clive, D. L. J.; Stoffman, E. J. L. *Chem. Commum.* **2007**, *21*, 2151–2153.

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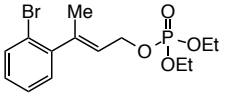
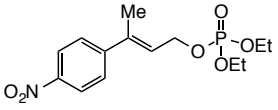
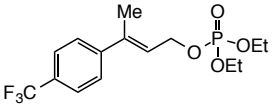
6.8, 1.2 Hz), 4.84 (2H, dd, *J* = 8.0, 7.6 Hz), 4.27–4.19 (4H, m), 2.37 (3H, s), 2.10 (3H, s), 1.47–1.43 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$), d 144.4, 142.5, 134.8, 130.5, 128.1, 127.4, 126.0, 124.0 (d, *J* = 6.7 Hz), 64.3 (d, *J* = 6.0 Hz), 64.0 (d, *J* = 5.9 Hz), 20.0, 18.7, 16.5 (d, *J* = 6.7 Hz); HRMS (ESI+): Calcd for $C_{15}H_{24}O_5P_1$ $[M+OH]^+$: 315.1361, Found: 315.1370.



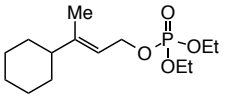
(*E*)-3-(2-Bromophenyl)but-2-enyl diethyl phosphate. IR (neat): 2983 (w), 2905 (w), 1468 (w), 1426 (w), 1378 (w), 1270 (m), 1166 (w), 1026 (s), 979 (s), 887 (w), 823 (w), 758 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); d 7.56–7.53 (1H, m), 7.29–7.24 (1H, m), 7.17–7.11 (2H, m), 5.59 (1H, dt, *J* = 5.2, 1.2 Hz), 4.74 (2H, dd, *J* = 6.8, 0.8 Hz), 4.14 (4H dq, *J* = 7.2, 0.8 Hz), 2.05–2.04 (3H, m), 1.37–1.34 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 145.1, 141.9, 132.9, 129.8, 128.8, 127.5, 125.2 (d, *J* = 6.7 Hz), 121.8, 63.9 (d, *J* = 6.7 Hz), 18.1, 16.3 (d, *J* = 6.7 Hz); HRMS (ESI+): Calcd for $C_{14}H_{21}Br_1O_5P_1$ $[M+OH]^+$: 379.0310, Found: 379.0332.



(*E*)-Diethyl (3-(4-nitrophenyl)but-2-en-1-yl) phosphate. IR (neat): 2984 (w), 2911 (w), 1595 (w), 1515 (m), 1444 (w), 1391 (w), 1369 (w), 1343 (s), 1263 (m), 1165 (w), 1106 (w), 1062 (w), 1005 (s), 974 (s), 853 (s), 818 (m), 747 (m), 695 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); d 8.21–8.17 (2H, m), 7.56–7.52 (2H, m), 6.07 (1H, dt, *J* = 6.4, 1.2 Hz), 4.78 (2H, dd, *J* = 6.4, 0.8 Hz), 4.18–4.10 (4H, m), 2.14–2.13 (3H, m), 1.37–1.33 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 148.9, 147.3, 138.2, 126.8, 125.9 (d, *J* = 6.7 Hz), 123.8, 64.1 (d, *J* = 4.5 Hz), 64.1 (d, *J* = 5.2 Hz), 16.3 (d, *J* = 4.5 Hz), 16.3 (d, *J* = 2.2 Hz); HRMS (ESI+): Calcd for $C_{14}H_{24}N_2O_6P$ $[M+NH_4]^+$: 347.1372, Found: 347.1379.

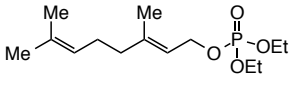


(*E*)-Diethyl (3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl) phosphate. IR (neat): 2986 (w), 2934 (w), 2910 (w), 1616 (w), 1445 (w), 1411 (w), 1394 (w), 1324 (s), 1265 (m), 1164 (m), 1115 (s), 1059 (m), 1006 (s), 975 (s), 847 (m), 819 (m), 749 (w), 724 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); d 7.60–7.57 (2H, m), 7.50–7.48 (2H, m), 6.00 (1H, dt, *J* = 5.6, 1.6 Hz), 4.79–4.75 (2H, m), 4.17–4.10 (4H, m), 2.12 (3H, s), 1.37–1.32 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 146.0, 139.1, 129.7 (q, *J* = 32.0 Hz), 128.8 (q, *J* = 82.1 Hz), 126.3, 125.4 (q, *J* = 3.8 Hz), 124.1 (d, *J* = 6.7 Hz), 64.2 (d, *J* = 5.3 Hz), 64.0 (d, *J* = 5.9 Hz), 17.8, 16.3 (d, *J* = 6.7 Hz); HRMS (ESI+): Calcd for $C_{15}H_{21}F_3O_5P_1$ $[M+OH]^+$: 369.1079, Found: 369.1084.

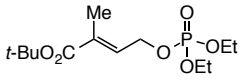


(*E*)-3-Cyclohexylbut-2-enyl diethyl phosphate. IR (neat): 2982 (w), 2925 (m), 2853 (w), 1663 (w), 1448 (w), 1392 (w), 1369 (w), 1261 (m), 1166 (w), 1098 (w), 1069 (w), 1024 (s), 1001 (s), 972 (s), 881

(w), 852 (w), 830 (w), 801 (m), 747 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); d 5.37 (1H, ddt, *J* = 6.8, 2.4, 1.2 Hz), 4.57 (2H, t, *J* = 7.6 Hz), 4.14–4.06 (4H, m), 1.87 (1H, t, *J* = 11.6 Hz), 1.77–1.69 (5H, m), 1.67 (3H, s), 1.35–1.30 (6H, m), 1.28–1.11 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 147.6, 117.4 (d, *J* = 6.7 Hz), 64.4 (d, *J* = 5.9 Hz), 63.7 (d, *J* = 5.2 Hz), 47.3, 31.7, 26.7, 26.4, 16.3 (d, *J* = 6.7 Hz), 15.0; HRMS (ESI+): Calcd for $C_{14}H_{28}O_5P_1$ $[M+OH]^+$: 307.1674, Found: 307.1681.



(*E*)-3, 7-Dimethylocta-2, 6-dienyl diethyl phosphate (10, Scheme 4). IR (neat): 2981 (w), 2912 (w), 1669 (w), 1444 (w), 1383 (w), 1261 (m), 1166 (w), 1100 (w), 1027 (s), 972 (s), 886 (w), 818 (m), 801 (m), 746 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); d 5.41–5.38 (1H, m), 5.10–5.06 (1H, m), 4.56 (2H, t, *J* = 7.6 Hz), 4.14–4.07 (4H, m), 2.13–2.02 (4H, m), 1.69 (6H, d, *J* = 10.0 Hz), 1.60 (3H, s), 1.35–1.31 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 142.7, 132.0, 123.8, 119.1 (d, *J* = 6.7 Hz), 64.2 (d, *J* = 5.2 Hz), 63.7 (d, *J* = 5.9 Hz), 39.6, 26.4, 25.8, 17.8, 16.6, 16.3 (d, *J* = 6.7 Hz); HRMS (ESI+): Calcd for $C_{14}H_{28}O_5P_1$ $[M+OH]^+$: 307.1674, Found: 307.1673.

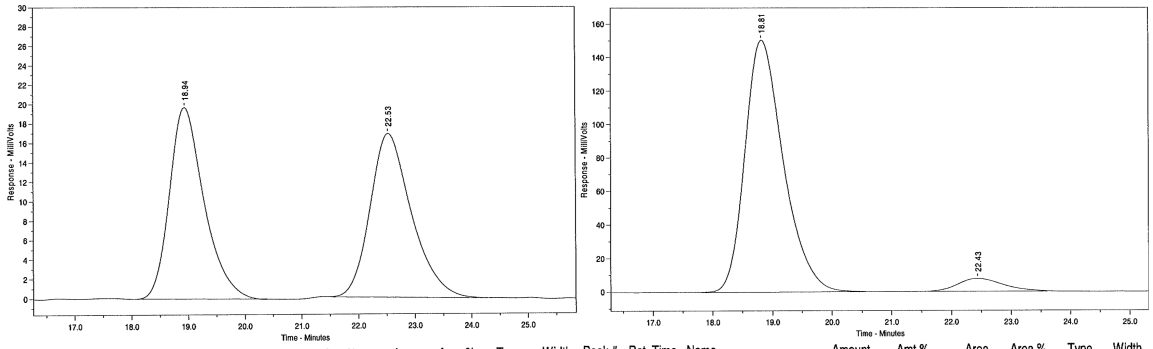


(*E*)-*tert*-Butyl 4-((diethoxyphosphoryl)oxy)-2-methylbut-2-enoate. IR (neat): 2980 (w), 2934 (w), 1708 (m), 1657 (w), 1479 (w), 1457 (w), 1392 (w), 1368 (w), 1333 (w), 1252 (m), 1171 (w), 1134 (m), 1100 (w), 1017 (s), 889 (w), 848 (w), 819 (w), 730 (w), 670 (w), 511 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 6.66–6.63 (1H, m), 4.68–4.63 (2H, m), 4.13–4.05 (4H, m), 1.78 (3H, s), 1.44 (9H, s), 1.33–1.28 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 166.4, 134.0 (d, *J* = 7.5 Hz), 132.2, 80.9, 64.0 (d, *J* = 6.0 Hz), 63.9 (d, *J* = 5.2 Hz), 28.1, 16.2 (d, *J* = 6.7 Hz), 12.9; HRMS (ESI+): Calcd for $C_{13}H_{26}O_6P_1$ $[M+H]^+$: 309.1467, Found: 309.1453.

■ **General Procedure for Cu-Catalyzed Enantioselective Allylic Substitutions with Alkyl-Substituted Alkenylaluminum Reagents (Table 2.1 and Scheme 2.10):** A 13 x 100 mm test tube equipped with a stir bar is charged with NHC–Ag complex **1a** (1.2 mg, 0.0010 mmol) in an N_2-filled glovebox. The vessel is sealed with a septum and removed from the glovebox. Tetrahydrofuran (1.0 mL) and a solution of $CuCl_2 \bullet 2H_2O$ (0.02M in thf, 100 mL, 0.002 mmol) are added to the test tube at 22 °C. The resulting blue solution is allowed to cool to –78 °C (dry ice/acetone bath), followed by the addition of the alkenylaluminum reagent (1.0 M in hexanes, 300 mL, 0.30 mmol) and a solution of (*E*)-diethyl (3-phenylbut-2-en-1-yl) phosphate (56.9 mg, 0.200 mmol) in thf (1.0 mL). The mixture is allowed to warm to –15 °C and sit in a freezer for 3 h, after which time, the reaction is quenched by the addition of a saturated aqueous solution of Rochelle's salt (2.0 mL) at –78 °C and the resulting mixture is allowed to warm to 22 °C and stir for one hour. The layers are separated, and the aqueous layer is washed with Et_2O (2.0 mL x 3). The combined organic layers are passed through a short plug of $MgSO_4$, and concentrated

under reduced pressure. The resulting yellow oil is purified by silica gel chromatography to give the product as colorless oil (39.8 mg, 0.164 mmol, 82% yield). **(*R*,*E*)-(3-Methylundeca-1,4-dien-3-yl)benzene (2.79, entry 1-2, Table 2.1).** IR (neat): 3083 (w), 2957 (m), 2925 (s), 2871 (m), 2854 (s), 1633 (w), 1599 (w), 1492 (m), 1460 (m), 1445 (m), 975 (m), 914 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (4H, m), 7.22-7.18 (1H, m), 6.09 (1H, dd, *J* = 17.6, 10.8 Hz), 5.67 (1H, dt, *J* = 15.6, 1.6 Hz), 5.43 (1H, dt, *J* = 15.6, 6.8 Hz), 5.12 (1H, dd, *J* = 10.8, 1.6 Hz), 5.02 (1H, dd, *J* = 17.2, 1.6 Hz), 2.09 (2H, dtd, *J* = 6.8, 6.8, 1.2 Hz), 1.49 (3H, s), 1.42–1.27 (8H, m), 0.90 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 146.0, 137.0, 129.1, 128.2, 127.3, 126.1, 112.4, 47.6, 32.9, 31.9, 29.7, 29.1, 25.9, 22.9, 14.3; HRMS (ESI+): Calcd for $C_{18}H_{27}$ $[M+H]^+$: 243.2113, Found: 243.2118. Elemental Analysis: Calcd for $C_{18}H_{26}$: C, 89.19; H, 10.81; Found: C, 89.35; H, 10.60. Optical Rotation: $[a]_D^{20}$ –5.31 (*c* 1.50, $CHCl_3$) for an enantiomerically enriched sample of 94.5:5.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (94.3:5.7 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



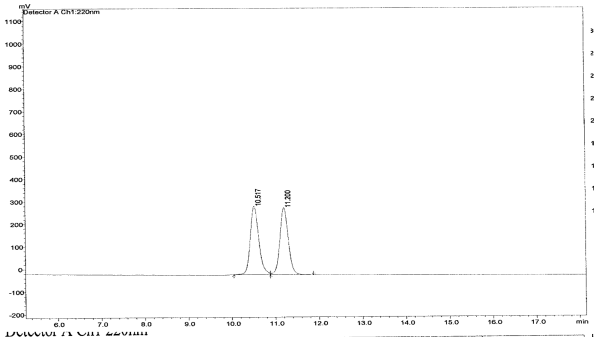
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	18.94		0.00	N/A	837687	49.408	BB	0.64
2	22.53		0.00	N/A	857748	50.592	BB	0.77

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	18.81		0.00	N/A	6736213	94.343	BB	0.68
2	22.43		0.00	N/A	403892	5.657	BB	0.80

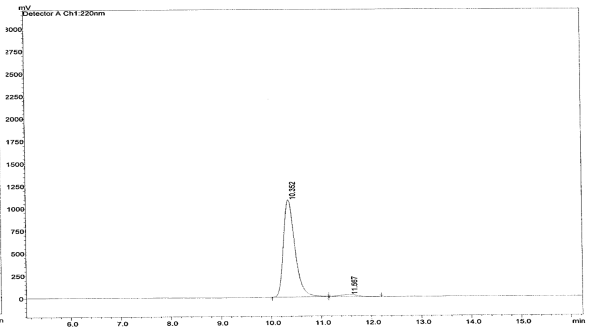
Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	18.94	49.4	1	18.81	94.3
2	22.53	50.6	2	22.43	5.7

(*R*,*E*)-1-Methyl-2-(3-methylundeca-1,4-dien-3-yl)benzene (2.80, entry 3, Table 2.1). IR (neat): 3014 (m), 2957 (m), 2853 (m), 1631 (w), 1485 (w), 1456 (m), 972 (m), 910 (m), 759 (s), 728 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.37 (1H, m), 7.17–7.12 (3H, m), 6.14 (1H, dd, *J* = 17.2, 10.4 Hz), 5.73 (1H, dt, *J* = 15.6, 1.6 Hz), 5.28 (1H, dt, *J* = 15.6, 6.8 Hz), 5.06 (1H, dd, *J* = 10.4, 1.2 Hz), 4.90 (1H, dd, *J* = 17.6, 1.2 Hz), 2.33 (3H, s), 2.05 (2H, dtd, *J* = 6.8, 6.8, 1.6 Hz), 1.53 (3H, s), 1.38–1.27 (8H, m), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 144.5, 137.6, 137.2, 132.4, 128.6, 127.6, 126.5, 125.6, 111.9, 48.1, 33.0, 31.9, 29.6, 29.1, 27.5, 22.9, 22.8, 14.3; HRMS (ESI+): Calcd for $C_{19}H_{29}$ $[M+H]^+$: 257.2269, Found: 257.2274. Optical Rotation: $[a]_D^{20}$ –7.58 (*c* 1.26, $CHCl_3$) for an enantiomerically enriched sample of 96.5:3.5 er.

Enantiomeric purity is determined by HPLC analysis in comparison with authentic racemic material (96.5:3.5 er shown; Chiralpak OD-H column, 99.8/0.2 hexanes/*i*-PrOH, 0.3 mL/min, 220 nm).



Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.517	4119220	303701	50.726	50.567
2	11.200	4001372	296892	49.274	49.433
Total		8120592	600593	100.000	100.000

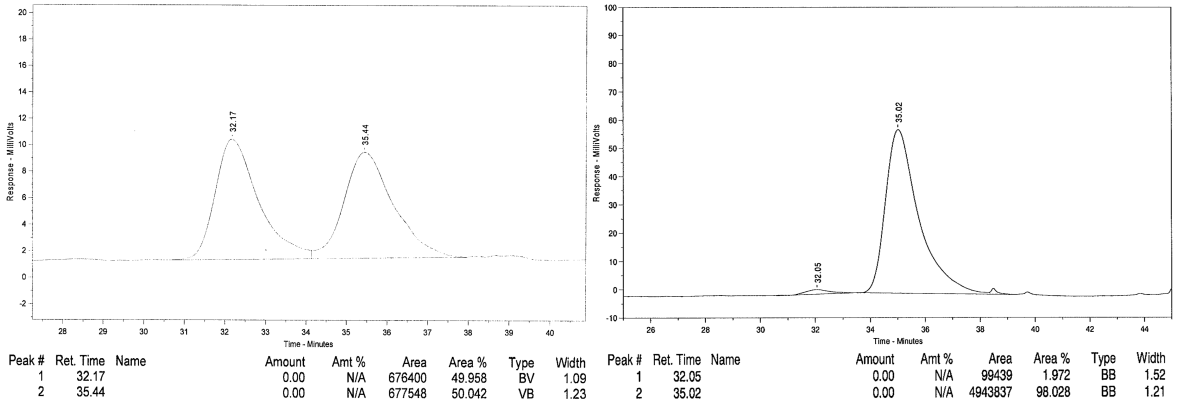


Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.352	17339090	1081398	96.505	97.712
2	11.567	627862	25325	3.495	2.288
Total		17966952	1106724	100.000	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	10.52	50.7	1	10.35	96.5
2	11.20	49.3	2	11.57	3.5

(*R*,*E*)-1-(3-Methylundeca-1,4-dien-3-yl)-2-(trifluoromethyl)benzene (2.81, entry 4, Table 2.1). IR (neat): 2957 (w), 2925 (w), 2855 (w), 1488 (w), 1304 (s), 1268 (m), 1166 (s), 1129 (s), 1034 (s), 912 (m), 765 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (1H, dd, *J* = 8.0, 1.6 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 7.46 (1H, dq, *J* = 8.0, 0.8 Hz), 7.35–7.31 (1H, m), 6.14 (1H, ddd, *J* = 17.6, 10.8, 0.8 Hz), 5.72 (1H, dd, *J* = 15.6, 0.8 Hz), 5.28 (1H, dt, *J* = 15.6, 6.8 Hz), 5.06 (1H, dd, *J* = 10.8, 0.8 Hz), 4.88 (1H, dd, *J* = 17.2, 0.8 Hz), 2.05 (2H, dtd, *J* = 6.8, 6.8, 1.2 Hz), 1.57 (3H, s), 1.38–1.26 (8H, m), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.9, 137.3, 131.4, 130.6, 129.2 (q, *J* = 30.7 Hz), 128.6, 128.6, 128.5, 124.7 (q, *J* = 272.8 Hz), 111.7, 48.7, 32.9, 31.9, 29.4, 29.1, 27.4, 22.8, 14.3; HRMS (ESI+): Calcd for $C_{19}H_{26}F_3$ $[M+H]^+$: 311.1987, Found: 311.1979. Optical Rotation: $[a]_D^{20}$ –13.3 (*c* = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (98.0:2.0 er shown; Chiralcel OD column, 99.5/0.5 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



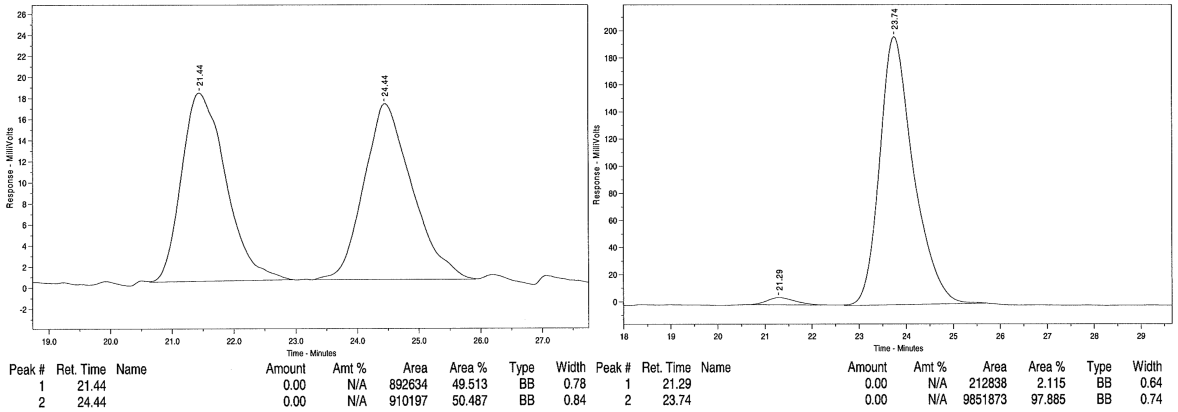
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	32.17		0.00	N/A	676400	49.958	BV	1.09
2	35.44		0.00	N/A	677548	50.042	VB	1.23

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	32.05		0.00	N/A	99439	1.972	BB	1.52
2	35.02		0.00	N/A	4943837	98.028	BB	1.21

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	32.17	50.0	1	32.05	2.0
2	35.44	50.0	2	35.02	98.0

(*R*,*E*)-1-Bromo-2-(3-methylundeca-1,4-dien-3-yl)benzene (2.82, entry 5-6, Table 2.1). IR (neat): 2956 (w), 2923 (m), 2853 (w), 1463 (m), 1431 (w), 1267 (w), 1019 (m), 987 (w), 966 (m), 944 (m), 754 (s), 734 (m), 724 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (1H, dd, *J* = 8.0, 1.2 Hz), 7.46 (1H, dd, *J* = 8.0, 1.6 Hz), 7.25 (1H, dt, *J* = 8.0, 0.8 Hz), 7.06 (1H, dq, *J* = 7.2, 0.8 Hz), 6.19 (1H, dd, *J* = 17.2, 10.8 Hz), 5.74 (1H, dt, *J* = 15.6, 0.8 Hz), 5.30 (1H, dt, *J* = 15.6, 6.8 Hz), 5.10 (1H, dt, *J* = 10.8, 0.9 Hz), 4.93 (1H, dd, *J* = 17.6, 0.8 Hz), 2.07 (2H, dtd, *J* = 7.2, 7.2, 1.6 Hz), 1.62 (3H, s), 1.39–1.26 (8H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 145.5, 136.4, 135.6, 129.8, 129.5, 128.0, 127.1, 124.0, 112.8, 48.8, 32.9, 31.9, 29.5, 29.1, 26.3, 22.8, 14.3. Elemental Analysis: Calcd for $C_{18}H_{25}Br_1$: C, 67.29; H, 7.84; Found: C, 67.34; H, 7.84. Optical Rotation: $[a]_D^{20}$ –9.71 (*c* = 1.12, $CHCl_3$) for an enantiomerically enriched sample of 96.5:3.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (97.9:2.1 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	21.44		0.00	N/A	892634	49.513	BB	0.78
2	24.44		0.00	N/A	910197	50.487	BB	0.84

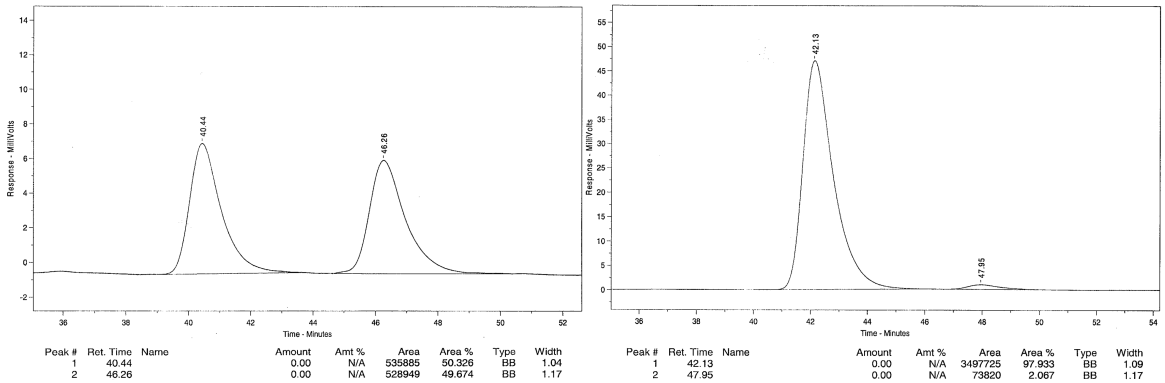
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	21.29		0.00	N/A	212838	2.115	BB	0.64
2	23.74		0.00	N/A	9851873	97.885	BB	0.74

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%

1	21.44	49.5	1	21.29	2.1
2	24.44	50.5	2	23.74	97.9

(*R*,*E*)-1-Methoxy-2-(3-methylundeca-1,4-dien-3-yl)benzene (2.64, entry 7-8, Table 2.1). IR (neat): 2956 (w), 2924 (m), 2853 (w), 1487 (m), 1461 (m), 1434 (m), 1241 (s), 1031 (m), 967 (w), 909 (m), 748 (s), 670 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d 7.27 (1H, dd, *J* = 7.6, 1.6 Hz), 7.21 (1H, dt, *J* = 7.6, 1.6 Hz), 6.91–6.86 (2H, m), 6.18 (1H, dd, *J* = 17.2, 10.4 Hz), 5.73 (1H, dt, *J* = 15.6, 1.2 Hz), 5.32 (1H, dt, *J* = 15.6, 6.0 Hz), 5.01 (1H, dd, *J* = 10.4, 1.6 Hz,), 4.91 (1H, dd, *J* = 17.2, 1.2 Hz), 3.76 (3H, s), 2.04 (2H, dt, *J* = 6.0, 6.0 Hz), 1.53 (3H, s), 1.35–1.27 (8H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): d 158.3, 146.3, 137.1, 135.7, 128.3, 127.9, 127.8, 120.5, 112.3, 111.2, 55.3, 46.5, 33.0, 32.0, 29.9, 29.1, 24.8, 22.9, 14.3; HRMS (ESI+): Calcd for $C_{19}H_{29}O_1$ $[M+H]^+$: 273.2218, Found: 273.2219. Optical Rotation: $[a]_D^{20}$ –3.36 (*c* 1.00, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (97.9:2.1 er shown; Chiralcel OD-R column, 99/1 hexanes/*i*-PrOH, 0.5 mL/min, 220 nm).

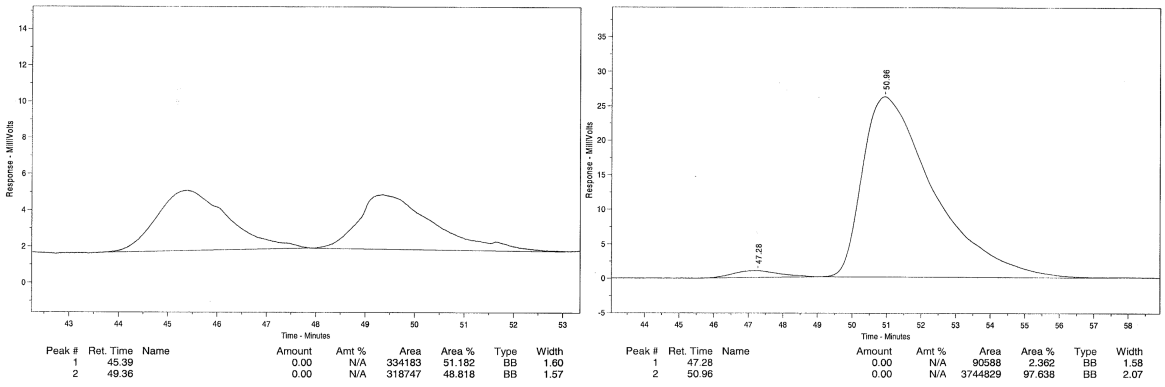


Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	40.44	50.3	1	42.13	97.9
2	46.26	49.7	2	47.95	2.1

(*R*,*E*)-1-(3-Methylundeca-1,4-dien-3-yl)-2-nitrobenzene (2.83, entry 9-10, Table 2.1). IR (neat): 2956 (w), 2925 (m), 2855 (w), 1531 (s), 1367 (m), 974 (w), 916 (w), 850 (w), 751 (s), 650 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d 7.53 (1H, dd, *J* = 7.2, 1.2 Hz), 7.47–7.39 (2H, m), 7.32 (1H, dt, *J* = 7.2, 1.2 Hz), 6.01 (1H, dd, *J* = 17.2, 10.6 Hz), 5.58 (1H, d, *J* = 16.4 Hz), 5.44 (1H, dt, *J* = 16.4, 6.0 Hz), 5.13 (1H, d, *J* = 10.6 Hz), 5.02 (1H, d, *J* = 17.6 Hz), 2.01 (2H, dt, *J* = 6.0, 6.0 Hz), 1.62 (3H, s), 1.40–1.24 (8H, m), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): d 151.3, 143.8, 139.3, 134.3, 131.2, 130.5, 130.2, 127.5, 124.4, 112.9, 47.4, 32.8, 31.9, 29.3, 29.2, 25.7, 22.9, 14.3; HRMS (ESI+): Calcd for $C_{18}H_{26}N_1O_2$ $[M+H]^+$: 288.1964, Found: 288.1961. Elemental Analysis: Anal Calcd for $C_{18}H_{25}N_1O_2$: C, 75.22; H, 8.77; N, 4.87; Found: C, 75.49; H, 9.04; N, 5.05.

Optical Rotation: $[a]_D^{20}$ +0.71 (*c* 1.00, $CHCl_3$) for an enantiomerically enriched sample of 97.5:2.5 er.

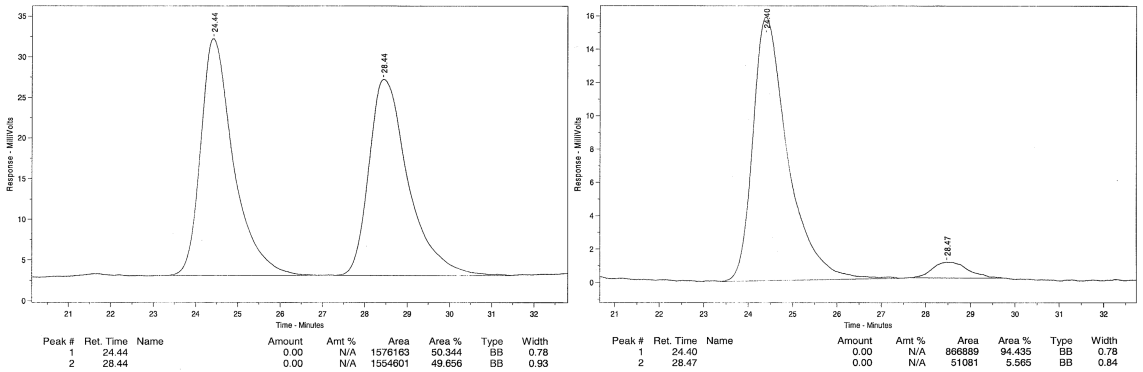
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (97.6:2.4 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	45.39	51.2	1	47.28	2.4
2	49.36	48.8	2	50.96	97.6

(*R*,*E*)-1-(3-Methylundeca-1,4-dien-3-yl)-4-nitrobenzene (2.84, entry 11-12, Table 2.1). IR (neat): 2956 (w), 2926 (m), 2855 (w), 1597 (w), 1518 (s), 1492 (w), 1459 (w), 1345 (s), 1216 (w), 1111 (w), 1014 (w), 1000 (w), 976 (w), 920 (w), 852 (m), 755 (s), 701 (m), 668 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 8.14 (2H, d, *J* = 6.8 Hz), 7.48 (2H, d, *J* = 9.2 Hz), 6.03 (1H, dd, *J* = 17.6, 10.6 Hz), 5.62 (1H, d, *J* = 15.6 Hz), 5.43 (1H, dt, *J* = 16.0, 6.8 Hz), 5.18 (1H, d, *J* = 10.6 Hz), 5.03 (1H, d, *J* = 17.6 Hz), 2.08 (2H, dt, *J* = 7.2, 7.2 Hz), 1.50 (3H, s), 1.43–1.27 (8H, m), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): d 155.0, 146.5, 144.6, 135.7, 130.7, 128.4, 123.5, 113.8, 48.0, 32.9, 31.9, 29.6, 29.1, 26.0, 22.9, 14.3; HRMS (ESI+): Calcd for $C_{18}H_{26}N_1O_2$ $[M+H]^+$: 288.1964, Found: 288.1949. Elemental Analysis: Anal Calcd for $C_{18}H_{25}N_1O_2$: C, 75.22; H, 8.77; N, 4.87; Found: C, 75.49; H, 8.90; N, 4.98. Optical Rotation: $[a]_D^{20}$ –7.54 (*c* = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 94.5:5.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (94.4:5.6 er shown; Chiralcel OD-R column, 98/2 hexanes/*i*-PrOH, 1.0 mL/min, 240 nm).

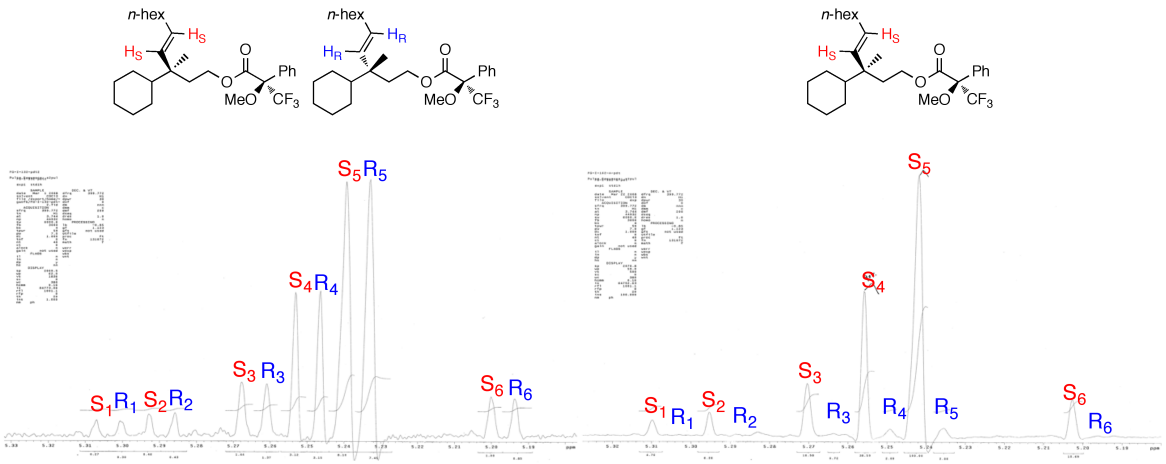


Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	24.44	50.3	1	24.40	94.4
2	28.44	49.7	2	28.47	5.6

(*S*,*E*)-(3-Methylundeca-1,4-dien-3-yl)cyclohexane (2.85, entry 13-14, Table 2.1). IR (neat): 2922 (s), 2852 (s), 1450 (m), 1000 (w), 973 (m), 910 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 5.82 (1H, dd, *J* = 17.6, 10.8 Hz), 5.40 (1H, dt, *J* = 15.6, 1.2 Hz), 5.28 (1H, dt, *J* = 15.6, 6.4 Hz), 4.97 (1H, dd, *J* = 10.8, 1.6 Hz), 4.89 (1H, dd, *J* = 17.6, 1.6 Hz), 2.01 (2H, dt, *J* = 6.4, 6.4 Hz), 1.75-1.69 (4H, m), 1.64–1.61 (1H, m), 1.36–1.19 (8H, m), 1.18–1.05 (4H, m), 1.01 (3H, s), 0.94–0.86 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 146.4, 137.0, 128.3, 111.6, 47.4, 45.3, 33.2, 31.9, 29.9, 29.2, 28.0, 27.4, 27.0, 22.9, 20.2, 14.3; HRMS (ESI+): Calcd for $C_{18}H_{33}$ $[M+H]^+$: 249.2582, Found: 249.2591. Elemental Analysis: Anal Calcd for $C_{18}H_{32}$: C, 87.02; H, 12.98; Found: C, 87.30; H, 13.26. Optical Rotation: $[a]_D^{20}$ –16.3 (*c* 1.00, $CHCl_3$) for an enantiomerically enriched sample of 93:7 er.

Site-selective hydroboration (9-BBN)/oxidation (H_2O_2) of the terminal alkene of the EAS product and generation of the derived Mosher ester, according to published procedures,[27] was performed first. Enantiomeric purity was determined by analysis of the ^1H NMR spectrum in comparison with that of authentic Mosher ester of racemic primary alcohol.[28] **(See ^1H NMR spectra for racemic and enantiomerically enriched Mosher esters in the Appendix, 94.9:5.1 er shown)**.

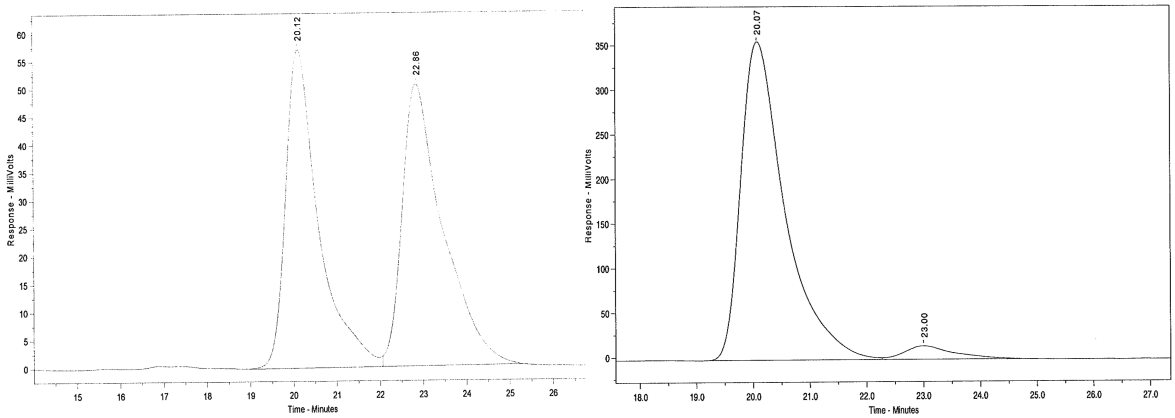
(27) Fujii, M.; Fukumura, M.; Hori, Y.; Hirai, Y.; Akita, H.; Nakamura, K.; Toriizukaa, K.; Idaa, Y. *Tetrahedron; Asymmetry* **2006**, *17*, 2292–2298.
(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.



Peak#	ppm	Area%	Peak#	ppm	Area%
S_4	5.253	99.51	S_4	5.254	100.0
R_4	5.246	100.0	R_4	5.247	5.42

(*R*,*E*)-Dimethyl(3-methylundeca-1,4-dien-3-yl)(phenyl)silane (2.86, entry 15, Table 1). IR (neat): 2956 (w), 2925 (w), 2856 (w), 1724 (w), 1427 (w), 1251 (w), 1117 (w), 1052 (w), 1026 (w), 998 (w), 829 (m), 811 (m), 790 (m), 773 (m), 698 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (2H, m), 7.39–7.31 (3H, m), 5.93 (1H, dd, *J* = 17.6, 10.8 Hz), 5.54 (1H, dt, *J* = 15.6, 1.2 Hz), 5.16 (1H, dt, *J* = 15.2, 7.2 Hz), 4.92 (1H, dd, *J* = 10.8, 1.2 Hz), 4.75 (1H, dd, *J* =17.2, 0.8 Hz), 2.03 (2H, dt, *J* = 6.8, 6.8 Hz), 1.36–1.23 (8H, m), 1.11 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz), 0.28 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 136.8, 135.0, 133.9, 129.2, 127.4, 126.8, 109.9, 36.2, 33.4, 32.0, 30.2, 29.1, 22.9, 17.9, 14.3, –5.8; HRMS (ESI+): Calcd for $C_{20}H_{33}Si_1$ $[M+H]^+$: 301.2352, Found: 301.2348. Optical Rotation: $[a]_D^{20}$ –3.56 (*c* 0.46, $CHCl_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.5:4.5 er shown; Chiralcel OD column, 99.5/0.5 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



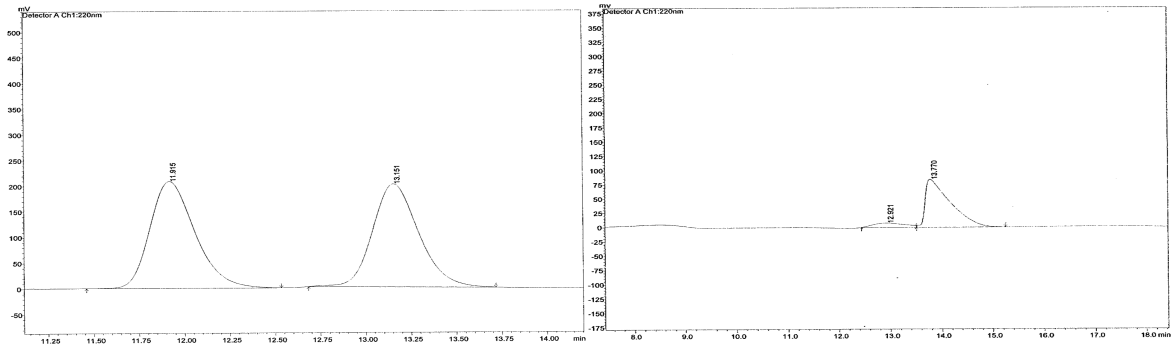
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	20.12		0.00	N/A	3039466	47.917	BV	0.72
2	22.86		0.00	N/A	3303744	52.083	VB	0.92

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	20.07		0.00	N/A	19301500	95.515	BV	0.78
2	23.00		0.00	N/A	906229	4.485	VB	0.86

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	20.12	47.9	1	20.07	95.5
2	22.86	52.1	2	23.00	4.5

(*R*,*E*)-*tert*-Butyl 2-methyl-2-vinyldec-3-enoate (2.87, entry 16, Table 1). IR (neat): 2958 (w), 2926 (m), 2855 (w), 1726 (s), 1456 (w), 1409 (m), 1250 (s), 1160 (s), 1123 (s), 971 (m), 915 (m), 850 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.04 (1H, dd, *J* = 18.0, 10.0 Hz), 5.60 (1H, dt, *J* = 16.0, 0.8 Hz), 5.47 (1H, dt, *J* = 15.6, 6.8 Hz), 5.08–5.04 (2H, m), 2.03 (2H, dtd, *J* = 7.6, 7.6, 0.8 Hz), 1.42 (9H, s), 1.37–1.24 (8H, m), 1.32 (3H, s), 0.87 (3H, t, *J* = 6.8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 141.7, 132.6, 130.3, 113.4, 80.7, 51.4, 32.8, 31.9, 29.5, 28.9, 28.1, 22.8, 21.6, 14.3; HRMS (ESI+): Calcd for $C_{17}H_{31}O_2$ $[M+H]^+$: 267.2324, Found: 267.2325. Optical Rotation: $[a]_D^{20}$ –11.4 (*c* 0.91, $CHCl_3$) for an enantiomerically enriched sample of 90:10 er.

Enantiomeric purity is determined by HPLC analysis in comparison with authentic racemic material (90.1:9.9 er shown; Chiralcel OD-H column, 99.8/0.2 hexanes/*i*-PrOH, 0.3 mL/min, 220 nm).



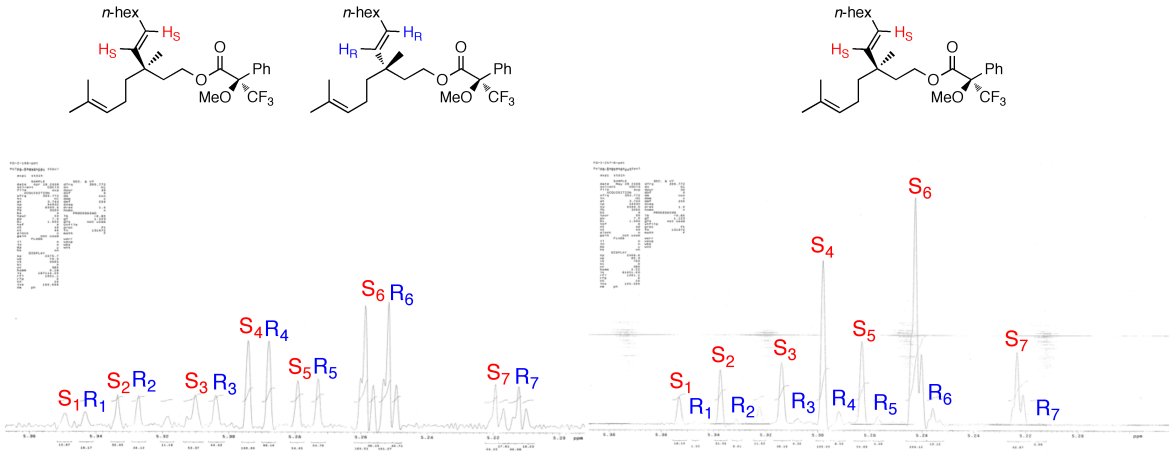
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.915	3599109	208131	50.400	50.959
2	13.151	3541926	200301	49.600	49.041
Total		7141035	408432	100.000	100.000

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.921	311759	7384	9.852	8.059
2	13.770	2852641	84240	90.148	91.941
Total		3164400	91625	100.000	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	11.92	50.4	1	12.92	9.9
2	13.15	49.6	2	13.77	90.1

(*R*,*E*)-2,6-Dimethyl-6-vinyltetradeca-2,7-diene (2.88, entry 17-18, Table 2.1). IR (neat): 2960 (m), 2923 (s), 2854 (m), 1634 (w), 1455 (m), 1376 (w), 1459 (w), 972 (s), 911 (s), 837 (w), 724 (w), 681 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 5.80 (1H, dd, *J* = 17.6, 10.8 Hz), 5.40–5.29 (2H, m), 5.09 (1H, tt, *J* = 7.2, 1.6 Hz), 4.97–4.91 (2H, m), 2.03–1.98 (2H, m), 1.89 (2H, dt, *J* = 6.8, 6.8 Hz), 1.67 (3H, s), 1.58 (3H, s), 1.38–1.27 (10H, m), 1.07 (3H, s), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): d 146.8, 137.3, 131.4, 128.1, 125.0, 111.3, 42.5, 41.9, 35.2, 34.2, 32.1, 31.3, 28.0, 23.7, 23.6, 23.0, 17.9, 14.6; HRMS (ESI+): Calcd for $C_{18}H_{33}$ $[M+H]^+$: 249.2582, Found: 249.2588. Optical Rotation: $[a]_D^{20}$ –8.37 (*c* 1.48, $CHCl_3$) for an enantiomerically enriched sample of 92.5:7.5 er.

Site-selective hydroboration (9-BBN)/oxidation (H_2O_2) of the terminal alkene of the EAS product and generation of the derived Mosher ester, according to published procedures,[9] was performed first. Enantiomeric purity was determined by analysis of the ^1H NMR spectrum in comparison with that of authentic Mosher ester of racemic primary alcohol.[8] **(See the ^1H NMR spectra for racemic and enantiomerically enriched Mosher esters in the Appendix, 92.2:7.8 er shown).**

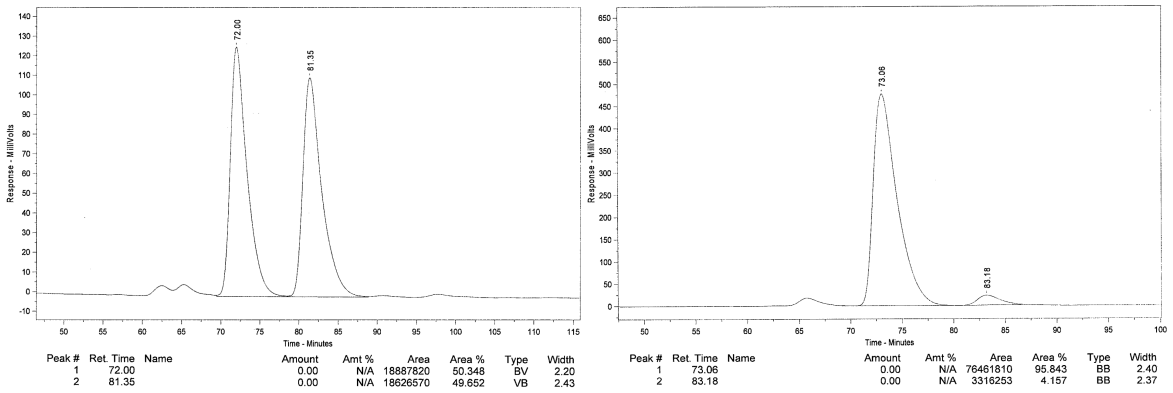


Peak#	ppm	Area%	Peak#	ppm	Area%
S_4	5.294	100.0	S_4	5.295	100.0
R_4	5.288	98.16	R_4	5.289	8.50

(*R*,*E*)-(9-(*tert*-Butoxy)-3-methylnona-1,4-dien-3-yl)dimethyl(phenyl)silane (2.92, Scheme 2.10). IR (neat): 2970 (m), 2927 (m), 2860 (w), 1621 (w), 1427 (w), 1361 (m), 1248 (m), 1198 (m), 1081 (m), 972 (m), 894 (m), 830 (s), 810 (s), 773 (s), 735 (s), 699 (s), 654 (m), 472 (m), 409 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.48–7.46 (2H, m), 7.36–7.32 (3H, m), 5.91 (1H, dd, *J* = 17.2, 10.8 Hz), 5.54 (1H, d, *J* = 15.6 Hz), 5.15 (1H, dt, *J* = 15.6, 7.2 Hz), 4.91 (1H, dd, *J* = 10.8, 1.2 Hz), 4.74 (1H, dd, *J* = 17.2, 1.2 Hz), 3.33 (2H, t, *J* = 7.6 Hz), 2.04 (2H, dt, *J* = 7.2, 7.2 Hz), 1.54–1.49 (2H, m), 1.43–1.39 (2H, m), 1.20 (9H, s), 1.10 (3H, s), 0.26 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): d 143.3, 136.8, 135.0, 134.1, 129.2, 127.5, 126.6, 110.0, 72.6, 61.7, 36.4, 33.3, 30.5, 29.9, 27.8, 26.9, 17.9, –5.8; HRMS (ESI+): Calcd for $C_{22}H_{36}O_1Si_1Na_1$ $[M+Na]^+$: 367.2433, Found:

367.2420. Optical Rotation: $[a]_D^{20}$ –0.11 (*c* 1.43, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

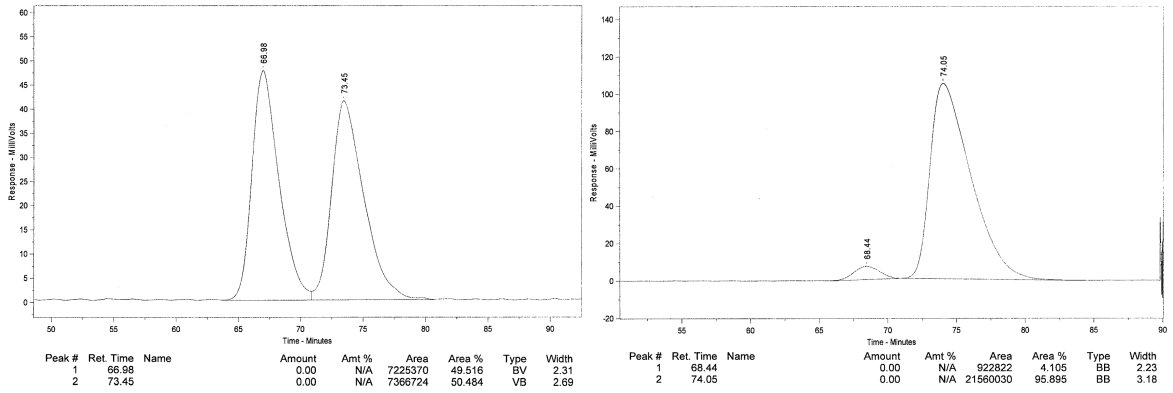
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.8:4.2 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 0.2 mL/min, 220 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	72.00	50.3	1	72.06	95.8
2	81.35	49.7	2	83.18	4.2

(*R*,*E*)-(8-Chloro-3-methylocta-1,4-dien-3-yl)dimethyl(phenyl)silane (2.93, Scheme 2.10). IR (neat): 2957 (w), 1621 (w), 1427 (w), 1247 (m), 1112 (m), 974 (m), 896 (m), 810 (s), 773 (s), 735 (s), 699 (s), 653 (s), 471 (m), 409 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.47–7.45 (2H, m), 7.37–7.33 (3H, m), 5.91 (1H, dd, *J* = 17.6, 11.2 Hz), 5.61 (1H, d, *J* = 15.2 Hz), 5.06 (1H, dt, *J* = 15.6, 6.4 Hz), 4.92 (1H, dd, *J* = 11.2, 1.2 Hz), 4.75 (1H, dd, *J* = 17.6, 1.2 Hz), 3.49 (2H, t, *J* = 6.8 Hz), 2.18 (2H, dt, *J* = 6.4, 6.4 Hz), 1.80 (2H, q, *J* = 7.2 Hz), 1.10 (3H, s), 0.27 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): d 143.0, 136.6, 135.8, 134.9, 129.3, 127.6, 124.4, 110.2, 44.7, 36.7, 32.7, 30.4, 17.9, –5.8, –5.8; HRMS (ESI+): Calcd for $C_{17}H_{25}Cl_1Si_1Na_1$ $[M+Na]^+$: 315.1312, Found: 315.1319. Optical Rotation: $[a]_D^{20}$ +0.92 (*c* 2.76, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

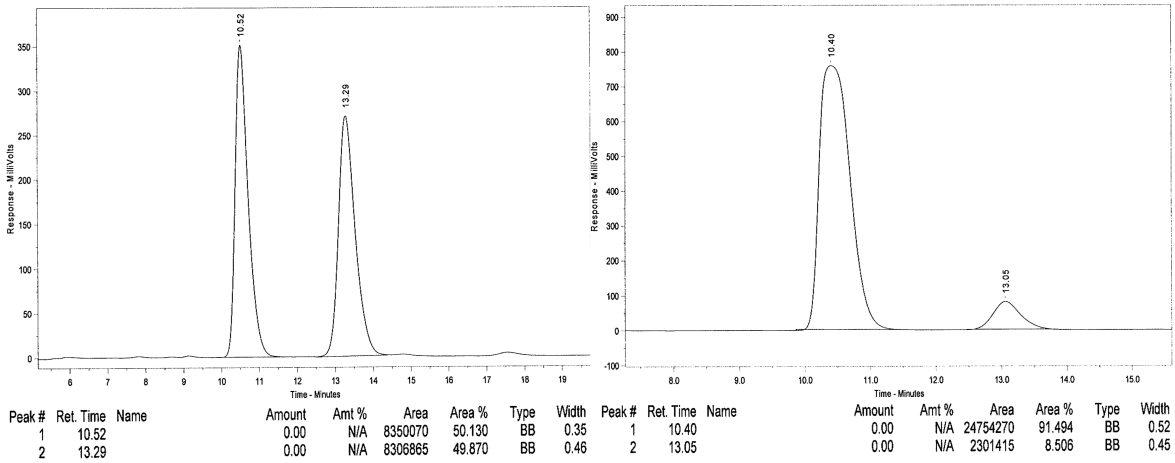
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.9:4.1 er shown; Chiralpak AS column, 99/1 hexanes/*i*-PrOH, 0.5 mL/min, 220 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	66.98	49.5	1	68.44	4.1
2	73.45	50.5	2	74.05	95.9

(*R*,*E*)-Dimethyl(phenyl)(3,6,6-trimethylhepta-1,4-dien-3-yl)silane (2.94, Scheme 2.10). IR (neat): 2956 (m), 1427 (w), 1247 (m), 1113 (m), 976 (m), 894 (m), 810 (s), 772 (s), 734 (s), 698 (s), 473 (m), 404 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.45 (2H, m), 7.36–7.32 (3H, m), 5.92 (1H, dd, *J* = 17.6, 10.8 Hz), 5.42 (1H, d, *J* = 16.0 Hz), 5.15 (1H, d, *J* = 16.0 Hz), 4.91 (1H, dd, *J* = 10.4, 1.2 Hz), 4.74 (1H, dd, *J* =17.2, 1.2 Hz), 1.09 (3H, s), 0.98 (9H, s), 0.25 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.4, 136.8, 134.9, 129.2, 128.6, 127.4, 109.8, 35.8, 33.3, 30.2, 17.8, –6.0; HRMS (ESI+): Calcd for $C_{18}H_{29}Si_1$ $[M+H]^+$: 273.2039, Found: 273.2027. Optical Rotation: $[a]_D^{20}$ +10.82 (*c* 3.58, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er.

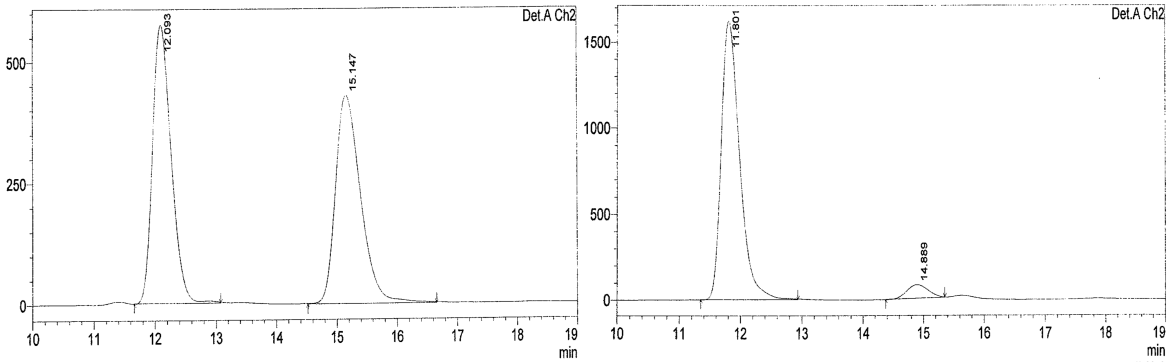
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (91.5:8.5 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	10.52	50.1	1	10.40	91.5
2	13.29	49.9	2	13.05	8.5

(*R*,*Z*)-(6-(*tert*-Butoxy)-3-methylhexa-1,4-dien-3-yl)dimethyl(phenyl)silane (2.95, Scheme 2.10). IR (neat): 2971 (m), 1363 (m), 1248 (m), 1196 (m), 1111 (m), 1069 (m), 892 (m), 808 (s), 773 (s), 735 (s), 700 (s), 654 (m), 474 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.53–7.51 (2H, m), 7.38–7.33 (3H, m), 6.04 (1H, dd, *J* = 17.2, 10.4 Hz), 5.47 (1H, d, *J* = 12.4 Hz), 5.40, (1H, dt, *J* = 11.6, 5.6 Hz), 4.97 (1H, d, *J* = 10.8 Hz), 4.81 (1H, dd, *J* = 17.6, 0.8 Hz), 3.87 (1H, dd, *J* = 11.2, 5.6 Hz), 3.77 (1H, ddd, *J* = 12.0, 6.0, 1.2 Hz), 1.25 (3H, s), 1.14 (9H, s), 0.32 (3H, s), 0.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): d 143.6, 136.4, 135.0, 133.9, 129.3, 127.9, 127.6, 110.3, 72.9, 58.8, 37.2, 27.8, 19.2, –5.9; HRMS (ESI+): Calcd for $C_{19}H_{30}O_1Si_1Na_1$ $[M+Na]^+$: 325.1964, Found: 325.1973. Optical Rotation: $[a]_D^{20}$ –26.78 (*c* 1.63, $CHCl_3$) for an enantiomerically enriched sample of 94.8:5.2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (94.8:5.2 er shown; Chiralcel OD-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



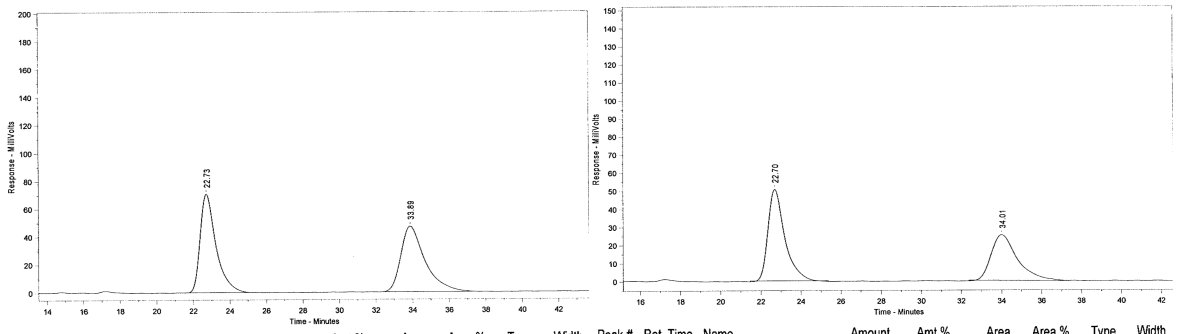
Peak#	Ret. Time	Area	Height	Area %
1	12.093	12146934	573358	49.406
2	15.147	12439114	429052	50.594
Total		24586047	1002410	100.000

Peak#	Ret. Time	Area	Height	Area %
1	11.801	33980596	1619852	94.790
2	14.889	1867747	78323	5.210
Total		35848343	1698175	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	12.09	49.4	1	11.80	94.8
2	15.15	50.6	2	14.89	5.2

(*R*,*Z*)-(1-(4-Methoxyphenyl)-3,7-dimethyl-3-vinylocta-1,6-dien-2-yl)trimethylsilane (2.98, Scheme 2.11). IR (neat): 2964 (w), 2929 (w), 2835 (w), 1609 (w), 1505 (s), 1464 (w), 1283 (w), 1244 (s), 1172 (m), 1038 (m), 911 (w), 835 (s), 763 (s), 679 (w), 646 (w), 573 (w), 514 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.20 (1H, s), 7.04 (2H, dd, *J* = 8.8, 1.2 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 5.95 (1H, dd, *J* = 17.6, 10.8 Hz), 5.14–5.09 (1H, m), 5.04–4.97 (2H, m), 3.80 (3H, s), 1.94 (2H, dt, *J* = 8.0, 8.0 Hz), 1.75–1.68 (4H, m), 1.60–1.50 (4H, m), 1.23 (3H, s), –0.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): d 158.5, 149.5, 148.2, 141.8, 134.1, 131.3, 129.9, 125.1, 113.2, 112.1, 55.4, 47.7, 39.9, 25.9, 25.7, 23.7, 17.9, 3.9; HRMS (ESI+): Calcd for $C_{22}H_{35}O_1Si_1$ $[M+H]^+$: 343.2457, Found: 343.2457.

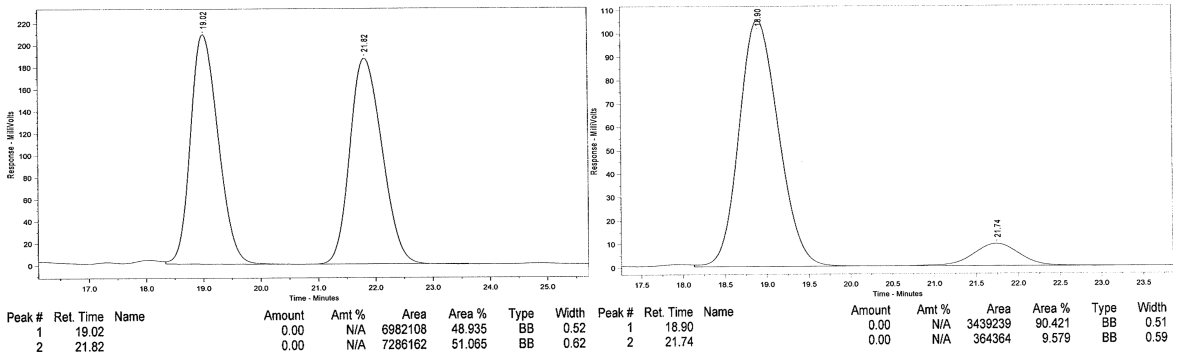
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (56.2:43.8 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	22.73	49.9	1	22.70	56.2
2	33.89	50.1	2	34.01	43.8

(*R*,*E*)-1-(3,7-Dimethyl-3-vinylocta-1,6-dien-1-yl)-4-methoxybenzene (2.102, Scheme 2.12). IR (neat): 2965 (m), 2916 (m), 1608 (m), 1510 (s), 1456 (w), 1280 (s), 1247 (m), 1037 (m), 970 (w), 913 (w), 815 (w), 527 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.29 (2H, m), 6.86–6.84 (2H, m), 6.27 (1H, d, *J* = 16.4 Hz), 6.07 (1H, d, *J* = 16.4 Hz), 5.89 (1H, dd, *J* = 17.2, 10.8 Hz), 5.14–5.10 (1H, m), 5.06–5.00 (2H, m), 3.81 (3H, s), 1.96 (2H, dt, *J* = 7.6, 7.6 Hz), 1.68 (3H, s), 1.59 (3H, s), 1.53–1.48 (2H, m), 1.21 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 146.2, 136.0, 131.4, 130.9, 127.3, 126.7, 124.9, 114.1, 112.0, 55.5, 42.7, 41.5, 25.8, 23.5, 23.4, 17.8; HRMS (ESI+): Calcd for $C_{19}H_{27}O_1$ $[M+H]^+$: 271.2062, Found: 271.2064. Optical Rotation: $[a]_D^{20}$ –25.16 (*c* 1.91, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er.

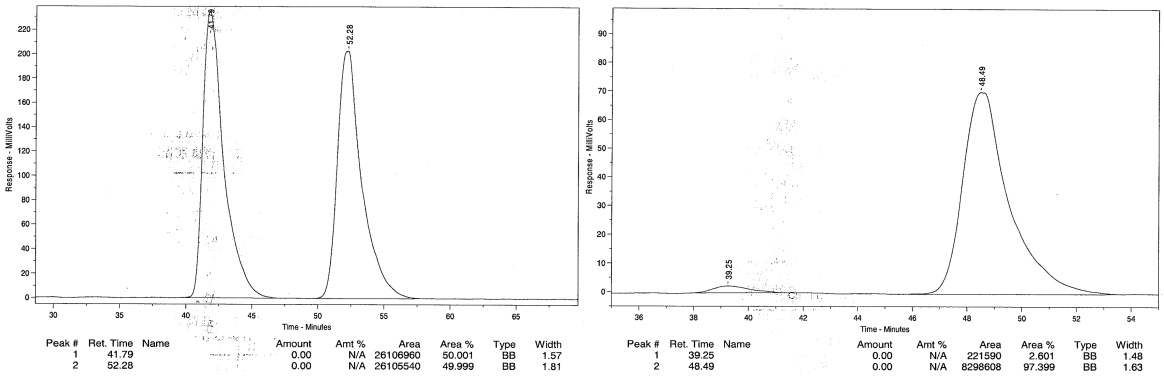
Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (90.4:9.6 er shown; Chiralcel OD-H column, 97/3 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm).



Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	19.02	48.9	1	18.90	90.4
2	21.82	51.1	2	21.74	9.6

(*R*,*E*)-1-Bromo-2-(1-(cyclohex-1-en-1-yl)-3-methylpenta-1,4-dien-3-yl)benzene (2.113, Scheme 2.15). IR (neat): 2925 (m), 1463 (m), 1018 (s), 963 (s), 911 (s), 791 (w), 756 (s), 645 (m), 454 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.58 (1H, dd, *J* = 8.0, 1.6 Hz), 7.46 (1H, dd, *J* = 8.0, 1.6 Hz), 7.26 (1H, dt, *J* = 7.6, 1.2 Hz), 7.08 (1H, dt, *J* = 8.0, 1.6 Hz), 6.22 (1H, dd, *J* = 17.2, 10.4 Hz), 5.92 (2H, s), 5.66–5.64 (1H, m), 5.13 (1H, dd, *J* = 10.8, 1.2 Hz), 4.97 (1H, dd, *J* = 17.6, 0.8 Hz), 2.22–2.18 (2H, m), 2.13–2.09 (2H, m), 1.70–1.65 (2H, m), 1.66 (3H, s), 1.63–1.59 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): d 145.9, 145.2, 135.9, 135.6, 132.9, 132.2, 129.7, 128.5, 128.1, 127.2, 124.0, 112.9, 48.7, 26.1, 26.0, 24.8, 22.83, 22.78; HRMS (ESI+): Calcd for $C_{18}H_{22}Br_1$ $[M+H]^+$: 317.0905, Found: 317.0906. Optical Rotation: $[a]_D^{20}$ –27.4 (*c* 1.29, $CHCl_3$) for an enantiomerically enriched sample of 97.5:2.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (97.4:2.6 er shown; Chiralcel OD column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



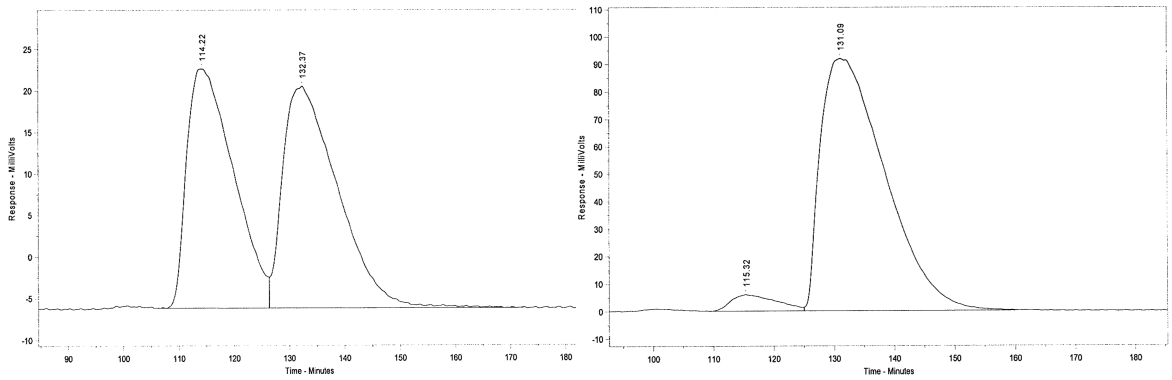
Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	41.79	50.0	1	39.25	2.6
2	52.28	50.0	2	48.49	97.4

■ **General Procedure for Catalytic Hydroalumination of Aryl-Substituted Terminal Alkynes with $Ni(PPh_3)_2Cl_2$ (Table 2, Scheme 2.16):** Commercial grade bis(triphenylphosphine)nickel dichloride ($Ni(PPh_3)_2Cl_2$, 19.6 mg, 0.0300 mmol) is placed in an oven-dried 13 x 100 mm test tube equipped with a stir bar. The vessel is sealed with a septum and purged with N_2 for approximately ten minutes. Tetrahydrofuran (thf, 1.0 mL) is added through a syringe, followed by dropwise addition of dibal–H (232 mL, 1.3 mmol) at 22 °C (gas evolution occurs as dibal–H is added). The resulting black solution is allowed to cool to 0 °C (ice bath) before phenylacetylene (110 mL, 1.0 mmol) is added slowly over five minutes (reaction is exothermic). The resulting black solution

is allowed to warm to 22 °C and stir for additional two hours and used without further purification.

■ **General Procedure for NHC–Cu-catalyzed Enantioselective Allylic Substitutions with Aryl-Substituted Alkenylaluminum Reagents (Table 2.2 and Scheme 2.15 and 2.16):** A 13 x 100 mm test tube equipped with a stir bar is charged with NHC–Ag complex **1c** (2.3 mg, 0.0020 mmol) in an N_2-filled glovebox. The vessel is sealed with a septum and removed from the glovebox. Tetrahydrofuran (1.0 mL) and a solution of $CuCl_2$•$2H_2O$ (0.02M in thf, 200 mL, 0.0040 mmol) are added to the test tube at 22 °C. The resulting blue solution is allowed to cool to –78 °C (dry ice/acetone), followed by the addition of the aryl-substituted vinylaluminum reagent (0.745 M in thf, 403 mL, 0.300 mmol) and a solution of (*E*)-diethyl (3-phenylbut-2-en-1-yl) phosphate (56.9 mg, 0.200 mmol) in thf (1.0 mL). The mixture is allowed to warm to –15 °C and sit in a freezer for three hours, after which time, the reaction is quenched by addition of a saturated aqueous solution of Rochelle's salt (2.0 mL) at –78 °C and the resulting mixture is allowed to warm to 22 °C and stir for one hour. The layers are separated, and the aqueous layer is washed with Et_2O (2.0 mL x 3). The combined organic layers are passed through a short plug of $MgSO_4$, and concentrated under reduced pressure. The resulting yellow oil is purified by silica gel chromatography to give the product as colorless oil (36.6 mg, 0.156 mmol, 78% yield). **(*R*,*E*)-(3-Methylpenta-1,4-diene-1,3-diyl)dibenzene (2.116, entry 1, Table 2.2).** IR (neat): 3082 (w), 3057 (w), 3025 (w), 2973 (w), 2917 (w), 2872 (w), 2849 (w), 1633 (w), 1598 (w), 1492 (m), 1445 (m), 1408 (w), 1368 (w), 1072 (w), 1029 (w), 971 (m), 916 (m), 748 (s), 694 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (4H, m), 7.28–7.22 (4H, m), 7.18–7.13 (2H, m), 6.39 (1H, d, *J* = 16.0 Hz), 6.29 (1H, d, *J* = 16.0 Hz), 6.09 (1H, dd, *J* = 17.6, 10.4 Hz), 5.11 (1H, dd, *J* = 10.8, 1.2 Hz), 5.00 (1H, dd, *J* = 17.6, 1.2 Hz), 1.55 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.2, 137.7, 137.3, 131.7, 128.7, 128.4, 128.2, 127.4, 127.3, 126.4, 113.2, 48.0, 25.7; HRMS (ESI+): Calcd for $C_{18}H_{19}$ $[M+H]^+$: 235.1487, Found: 235.1476. Optical Rotation: $[a]_D^{20}$ +33.80 (*c* 2.02, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.6:4.4 er shown; Chiralpak AS column, 99/1 hexanes/*i*-PrOH, 0.5 mL/min, 220 nm).



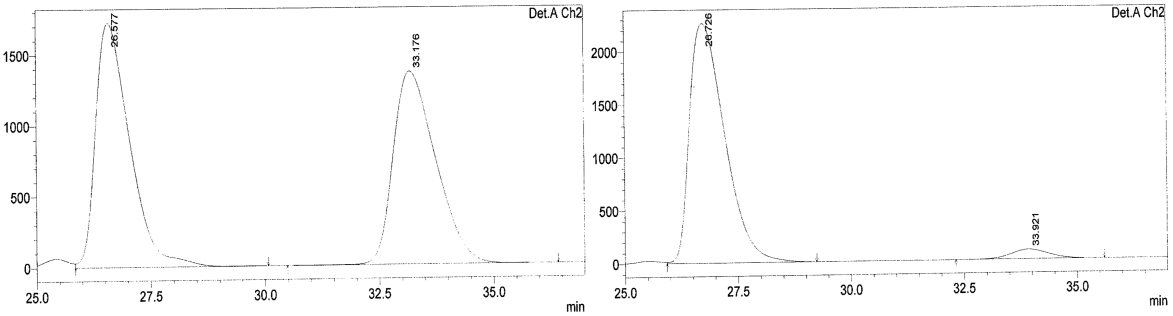
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	114.22		0.00	N/A	17014080	47.981	BV	9.66
2	132.37		0.00	N/A	18446020	52.019	VB	10.87

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	115.32		0.00	N/A	3135952	4.376	BV	9.13
2	131.09		0.00	N/A	68528960	95.624	VB	11.91

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	114.22	48.0	1	115.32	4.4
2	132.37	52.0	2	131.09	95.6

(*R*,*E*)-1-Methoxy-4-(3-methyl-3-phenylpenta-1,4-dien-1-yl)benzene (2.117, entry 2, Table 2.2). IR (neat): 3082 (w), 3056 (w), 3030 (w), 3021 (w), 2970 (w), 2933 (w), 2835 (w), 1607 (m), 1510 (s), 1443 (w), 1280 (w), 1246 (s), 1174 (m), 1034 (m), 972 (w), 917 (w), 808 (w), 762 (m), 700 (m), 533 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (6H, m), 7.22 (1H, tt, *J* = 6.4, 2.0 Hz), 6.88–6.84 (2H, m), 6.33 (2H, s), 6.17 (1H, dd, *J* = 17.6, 10.4 Hz), 5.18 (1H, dd, *J* = 10.4, 1.2 Hz), 5.07 (1H, dd, *J* = 17.2, 1.2 Hz), 3.81 (3H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 146.7, 145.4, 135.2, 130.4, 128.3, 127.6, 127.5, 127.4, 126.3, 114.1, 113.0, 55.5, 47.9, 25.8; HRMS (ESI+): Calcd for $C_{19}H_{21}O_1$ $[M+H]^+$: 265.1592, Found: 265.1590. Optical Rotation: $[a]_D^{20}$ +24.49 (*c* 1.16, $CHCl_3$) for an enantiomerically enriched sample of 96.5:3.5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.9:4.1 er shown; Chiralcel OD-H column, 97/3 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



Peak#	Ret. Time	Area	Height	Area %
1	26.577	89643798	1722114	50.446
2	33.176	88057866	1364330	49.554
Total		177701664	3086445	100.000

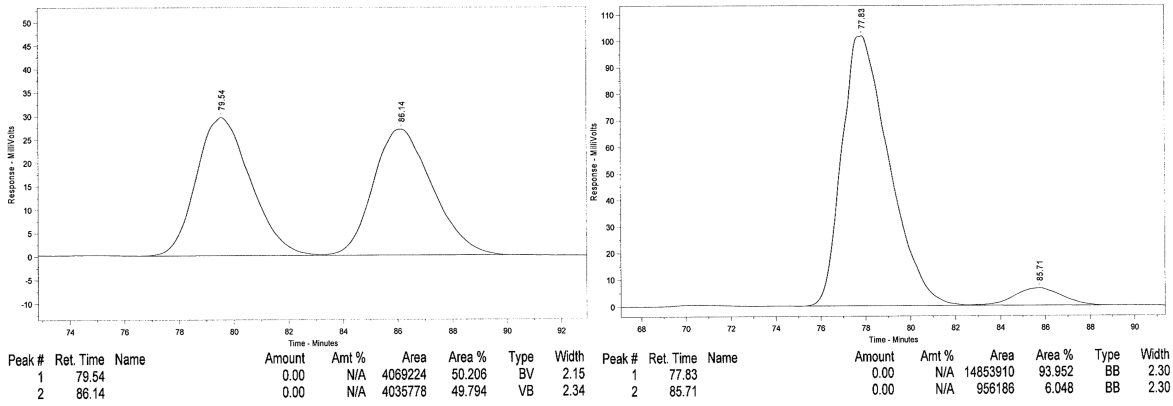
Peak#	Ret. Time	Area	Height	Area %
1	26.726	122902957	2263135	95.916
2	33.921	5233178	90344	4.084
Total		128136135	2353479	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	26.58	50.4	1	26.73	95.9

2	33.18	49.6	2	33.92	4.1

(*R*,*E*)-1-(3-Methyl-3-phenylpenta-1,4-dien-1-yl)-4-(trifluoromethyl)benzene (2.118, entry 3, Table 2). IR (neat): 2924 (m), 2854 (w), 1615 (w), 1323 (s), 1165 (m), 1125 (s), 1067 (s), 1016 (w), 975 (w), 919 (w), 815 (w), 762 (w), 699 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.38–7.32 (4H, m), 7.27–7.22 (1H, m), 6.57 (1H, d, *J* = 16.0 Hz), 6.40 (1H, d, *J* = 16.0 Hz), 6.17 (1H, dd, *J* = 17.6, 10.4 Hz), 5.22 (1H, dd, *J* = 10.8, 1.2 Hz), 5.09 (1H, dd, *J* = 17.6, 1.2 Hz), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 144.8 (q, *J* = 5.2 Hz), 141.2 (q, *J* = 1.5 Hz), 140.0 (q, *J* = 3.0 Hz), 132.1, 129.2 (q, *J* = 32.0 Hz), 128.5, 127.3, 127.1 (q, *J* = 3.8 Hz), 126.6 (q, *J* = 4.5 Hz), 125.7 (q, *J* = 10.4 Hz), 124.4 (q, *J* = 270.0 Hz), 113.6 (q, *J* = 3.0 Hz), 48.1, 25.6; HRMS (ESI+): Calcd for $C_{19}H_{18}F_3$ $[M+H]^+$: 303.1361, Found: 303.1373. Optical Rotation: $[a]_D^{20}$ –26.78 (*c* 2.47, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (94.0:6.0 er shown; Chiralcel OD-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	79.54		0.00	N/A	4069224	50.206	BV	2.15
2	86.14		0.00	N/A	4035778	49.794	VB	2.34

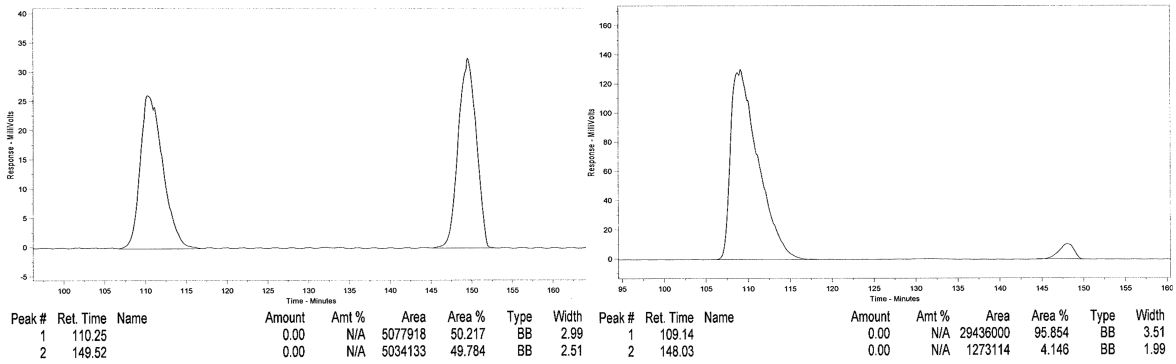
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	77.83		0.00	N/A	14853910	93.952	BB	2.30
2	85.71		0.00	N/A	956186	6.048	BB	2.30

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	79.54	50.2	1	77.83	94.0
2	86.14	49.8	2	85.71	6.0

(*R*,*E*)-1-Methyl-2-(3-methyl-3-phenylpenta-1,4-dien-1-yl)benzene (2.119, entry 4, Table 2.2). Spectra were recorded with samples containing 12% alkynyl adduct. IR (neat): 3059 (w), 3021 (w), 2958 (m), 2924 (m), 2854 (m), 1634 (w), 1600 (w), 1490 (m), 1459 (m), 1378 (w), 1029 (w), 951 (m), 916 (m), 747 (s), 698 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.46 (1H, m), 7.42–7.38 (2H, m), 7.37–7.32 (2H, m), 7.26–7.21 (2H, m), 7.19–7.14 (2H, m), 6.59 (1H, d, *J* = 16.0 Hz), 6.33 (1H, d, *J* = 16.0 Hz), 6.20 (1H, dd, *J* = 17.2, 10.4 Hz), 5.21 (1H, dd, *J* = 10.8, 1.2 Hz), 5.10 (1H, dd, *J* = 17.6, 1.2 Hz), 2.33 (3H, s), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 145.3, 138.8, 137.0, 135.5, 132.1, 130.3, 128.3, 127.4, 127.3, 126.4, 126.2, 125.8, 113.2, 48.1, 25.8,

20.0; HRMS (ESI+): Calcd for $C_{19}H_{21}$ $[M+H]^+$: 249.1643, Found: 249.1643. Optical Rotation: $[a]_D^{20}$ –29.53 (*c* 1.63, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (95.9:4.1 er shown; Chiralcel OD-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



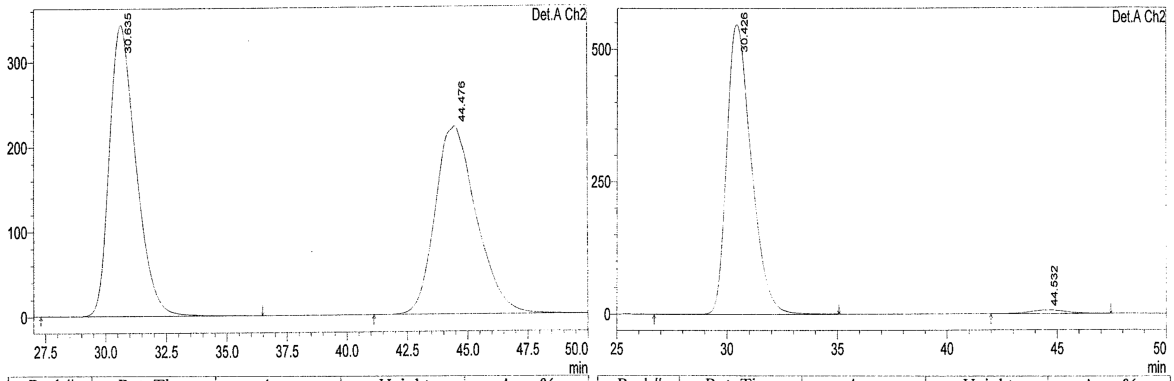
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	110.25		0.00	N/A	5077918	50.217	BB	2.99
2	149.52		0.00	N/A	5034133	49.784	BB	2.51

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	109.14		0.00	N/A	29436000	95.854	BB	3.51
2	148.03		0.00	N/A	1273114	4.146	BB	1.99

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	110.25	50.2	1	109.14	95.9
2	149.52	49.8	2	148.03	4.1

(*R*,*E*)-1-Bromo-2-(3-methyl-1-phenylpenta-1,4-dien-3-yl)benzene (2.65, entry 5, Table 2.2). IR (neat): 3080 (w), 3057 (w), 3024 (w), 2971 (w), 2918 (w), 2849 (w), 1630 (w), 1597 (w), 1491 (w), 1464 (w), 1427 (w), 1368 (w), 1018 (m), 963 (m), 912 (m), 746 (s), 690 (s), 646 (w), 458 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 7.61 (1H, dd, *J* = 8.0, 1.6 Hz), 7.51 (1H, dd, *J* = 7.6, 1.6 Hz), 7.38 (2H, dd, *J* = 8.4, 1.2 Hz), 7.32–7.27 (3H, m), 7.21 (1H, tt, *J* = 6.8, 2.0 Hz), 7.11, (1H, dt, *J* = 8.0, 2.0 Hz), 6.57 (1H, d, *J* = 16.0 Hz), 6.33–6.25 (2H, m), 5.19 (1H, dd, *J* = 10.4, 0.8 Hz), 5.04 (1H, dd, *J* = 17.6, 1.2 Hz), 1.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): d 145.4, 144.6, 137.9, 137.2, 135.6, 131.7, 129.7, 128.7, 128.5, 128.2, 127.2, 126.3, 123.9, 113.4, 49.0, 26.0; HRMS (ESI+): Calcd for $C_{18}H_{18}Br_1$ $[M+H]^+$: 313.0592, Found: 313.0589. Optical Rotation: $[a]_D^{20}$ –31.12 (*c* 0.91, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (98.2:1.8 er shown; Chiralcel OJ-H column, 95/5 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



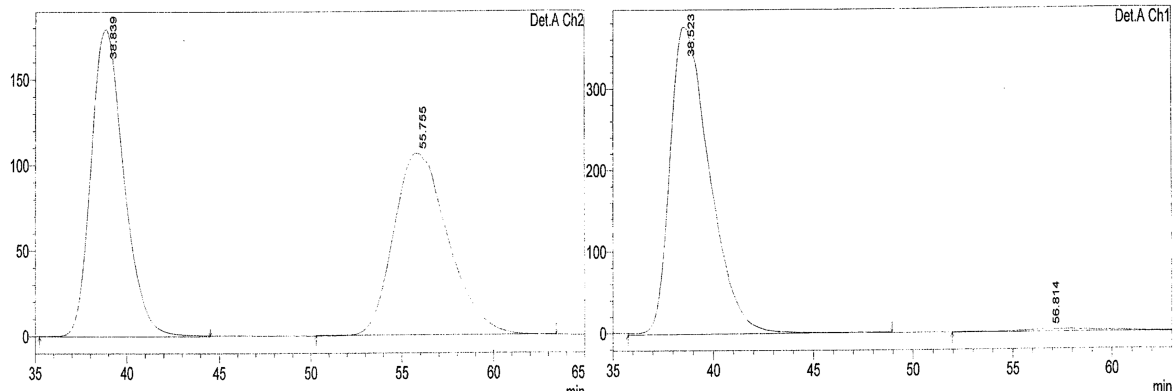
Peak#	Ret. Time	Area	Height	Area %
1	30.635	26267229	342739	50.004
2	44.476	26263306	221259	49.996
Total		52530535	563998	100.000

Peak#	Ret. Time	Area	Height	Area %
1	30.426	41880649	546331	98.173
2	44.532	779598	6637	1.827
Total		42660247	552968	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	30.64	50.0	1	30.43	98.2
2	44.48	50.0	2	44.53	1.8

(*R*,*E*)-1-(1-(4-Methoxyphenyl)-3-methylpenta-1,4-dien-3-yl)-2-methylbenzene (2.120, entry 6, Table 2). IR (neat): 3000 (w), 2968 (w), 2932 (w), 2835 (w), 1607 (m), 1510 (s), 1248 (s), 1175 (m), 1036 (m), 972 (w), 915 (w), 815 (w), 759 (w), 730 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.40 (1H, m), 7.29–7.25 (2H, m), 7.19–7.13 (3H, m), 6.85–6.80 (2H, m), 6.38 (1H, d, *J* = 16.0 Hz), 6.25–6.15 (2H, m), 5.11 (1H, dd, *J* = 10.8, 1.2 Hz), 4.95 (1H, dd, *J* = 17.2, 1.2 Hz), 3.80 (3H, s), 2.33 (3H, s), 1.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 145.4, 144.1, 137.4, 135.5, 132.3, 130.5, 127.5, 127.2, 126.9, 126.5, 125.6, 113.9, 112.3, 55.3, 48.2, 27.0, 22.6; HRMS (ESI+): Calcd for $C_{20}H_{21}O_1$ $[M+H]^+$: 277.1592, Found: 277.1598. Optical Rotation: $[a]_D^{20}$ –14.23 (*c* 1.07, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (98.1:1.9 er shown; Chiralcel OJ-H column, 95/5 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



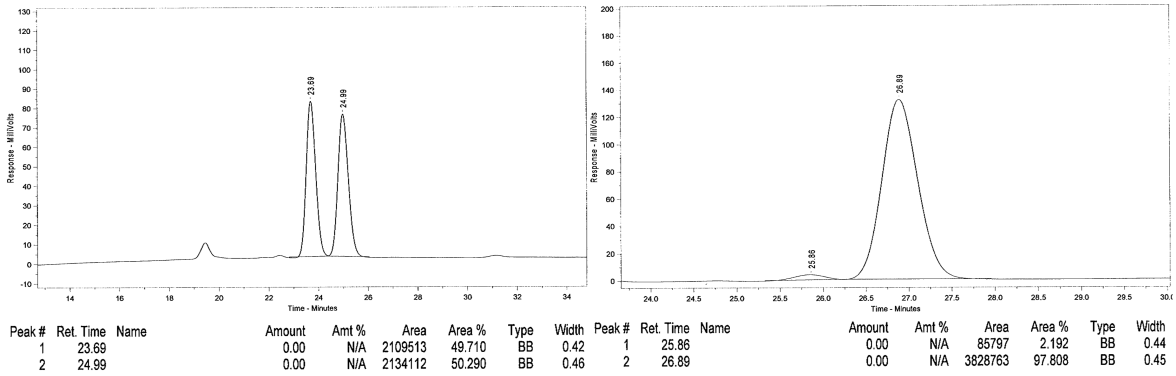
Peak#	Ret. Time	Area	Height	Area %
1	38.839	22537602	179456	50.954
2	55.755	21693733	106012	49.046
Total		44231335	285468	100.000

Peak#	Ret. Time	Area	Height	Area %
1	38.523	51401863	376815	98.122
2	56.814	983787	3129	1.878
Total		52385650	379944	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	38.84	51.0	1	38.52	98.1
2	55.76	49.0	2	56.81	1.9

(*R*,*E*)-1-(3-Methyl-1-phenylpenta-1,4-dien-3-yl)-2-nitrobenzene (2.122, entry 7, Table 2.2). IR (neat): 3082 (w), 3026 (w), 2925 (w), 2854 (w), 1528 (s), 1366 (s), 971 (m), 909 (s), 852 (m), 777 (m), 731 (s), 692 (s), 649 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, dd, *J* = 8.0, 1.2 Hz), 7.50–7.46 (2H, m), 7.38–7.29 (5H, m), 7.23 (1H, tt, *J* = 6.4, 1.6 Hz), 6.40 (1H, d, *J* = 16.4 Hz), 6.35 (1H, d, *J* = 16.4 Hz), 6.10 (1H, dd, *J* = 17.6, 10.4 Hz), 5.18 (1H, d, *J* = 10.8 Hz), 5.13 (1H, d, *J* = 17.6 Hz), 1.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 142.7, 138.8, 137.2, 134.8, 131.4, 130.4, 128.8, 128.7, 127.8, 127.6, 126.5, 124.5, 113.8, 47.7, 25.6; HRMS (ESI+): Calcd for $C_{18}H_{18}N_1O_2$ $[M+H]^+$: 280.1338, Found: 280.1327. Optical Rotation: $[a]_D^{20}$ –23.19 (*c* 1.71, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (97.8:2.2 er shown; Chiralcel OD-H column, 99.5/0.5 hexanes/*i*-PrOH, 0.5 mL/min, 220 nm).



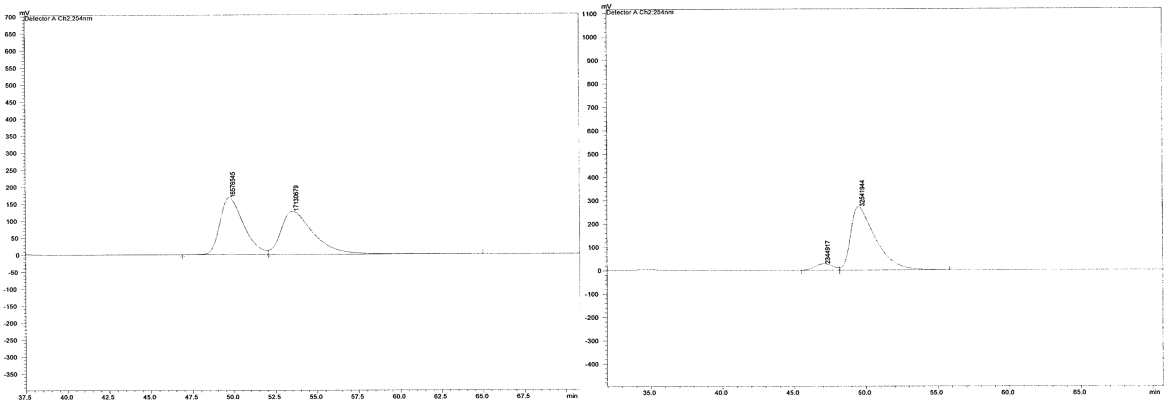
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	23.69		0.00	N/A	2109513	49.710	BB	0.42
2	24.99		0.00	N/A	2134112	50.290	BB	0.46

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	25.86		0.00	N/A	85797	2.192	BB	0.44
2	26.89		0.00	N/A	3828763	97.808	BB	0.45

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	23.69	49.7	1	25.86	2.2
2	24.99	50.3	2	28.89	97.8

(*R*,*E*)-1-(3-Methyl-1-phenylpenta-1,4-dien-3-yl)-4-nitrobenzene (2.122, entry 8, Table 2.2). IR (neat): 3082 (w), 3026 (w), 2974 (w), 2931 (w), 2852 (w), 1596 (m), 1514 (s), 1343 (s), 1111 (w), 1068 (w), 971 (m), 919 (m), 852 (s), 748 (s), 735 (s), 692 (s), 613 (w), 537 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.15 (2H, m), 7.55–7.52 (2H, m), 7.40–7.37 (2H, m), 7.34–7.31 (2H, m), 7.27–7.25 (1H, m), 6.44–6.35 (2H, m), 6.14 (1H, dd, *J* = 17.6, 10.8 Hz), 5.27 (1H, dd, *J* = 10.4, 0.8 Hz), 5.10 (1H, dd, *J* = 17.6, 0.8 Hz), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 146.6, 143.8, 137.0, 135.5, 129.5, 128.8, 128.4, 127.8, 126.5, 123.6, 114.5, 48.3, 25.8; HRMS (ESI+): Calcd for $C_{18}H_{18}N_1O_2$ $[M+H]^+$: 280.1338, Found: 280.1339. Optical Rotation: $[a]_D^{20}$ –20.37 (*c* 2.42, $CHCl_3$) for an enantiomerically enriched sample of 93:7 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (93.7:6.3 er shown; Chiralcel OJ-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



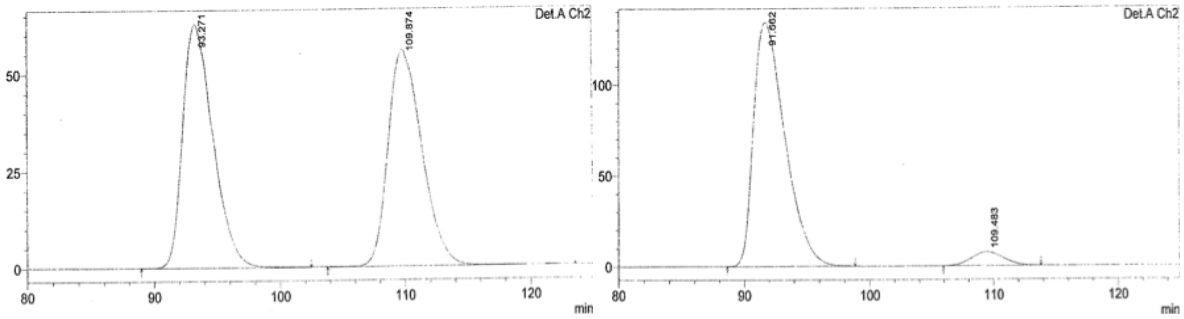
Peak#	Ret. Time	Area	Height	Area %	Height %
1	49.706	16576545	166872	49.178	56.845
2	53.528	17130679	126687	50.822	43.155
Total		33707225	293559	100.000	100.000

Peak#	Ret. Time	Area	Height	Area %	Height %
1	47.062	2344917	27231	6.721	9.125
2	49.485	32541944	271196	93.279	90.875
Total		34886861	298427	100.000	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	49.71	49.2	1	47.06	6.7
2	53.53	50.8	2	49.49	93.3

(*R*,*E*)-1-Methoxy-4-(3-methyl-3-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)benzene (2.123, entry 9, Table 2.2). IR (neat): 2957 (w), 2926 (w), 2854 (w), 1608 (w), 1511 (m), 1326 (s), 1248 (m), 1165 (m), 1123 (s), 1076 (m), 1036 (w), 1016 (w), 973 (w), 921 (w), 841 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 8.0 Hz), 7.48 (2H, d, *J* = 8.0 Hz), 7.34–7.30 (2H, m), 6.87–6.84 (2H, m), 6.32 (1H, d, *J* = 16.4 Hz), 6.26 (1H, d, *J* = 16.4 Hz), 6.13 (1H, dd, *J* = 17.2, 10.4 Hz), 5.22 (1H, dd, *J* = 10.8, 1.2 Hz), 5.07 (1H, dd, *J* = 17.6, 1.2 Hz), 3.81 (3H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 150.9, 144.6, 134.2, 130.1, 128.6 (q, *J* = 32.0 Hz), 128.4, 127.8, 127.6, 125.2 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 270.1 Hz), 114.2, 113.8, 55.5, 48.0, 25.8; HRMS (ESI+): Calcd for $C_{20}H_{20}F_3O_1$ $[M+H]^+$: 333.1466, Found: 333.1480. Optical Rotation: $[a]_D^{20}$ –22.91 (*c* 1.11, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (94.0:6.0 er shown; Chiralcel OD-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



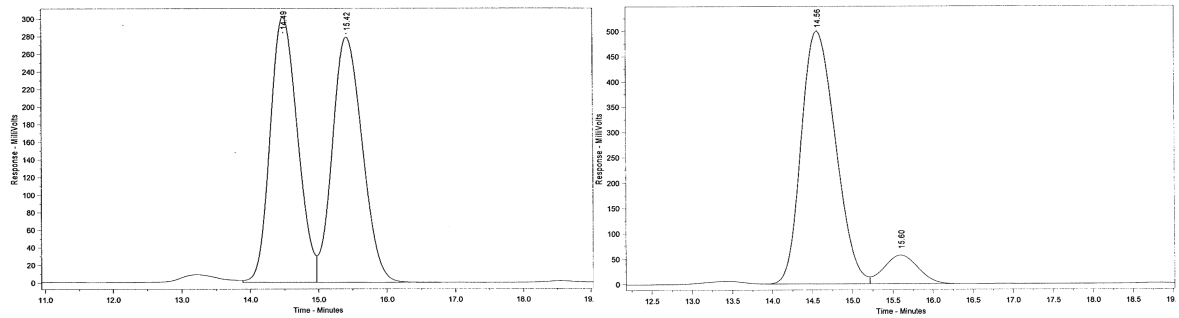
Peak#	Ret. Time	Area	Height	Area %
1	93.271	10594147	62857	50.263
2	109.874	10483365	55838	49.737
Total		21077512	118695	100.000

Peak#	Ret. Time	Area	Height	Area %
1	91.650	18888094	106429	93.976
2	109.481	1210681	6303	6.024
Total		20098775	112731	100.000

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	93.27	50.3	1	91.65	94.0
2	109.87	49.7	2	109.48	6.0

(*R*,*E*)-(3,7-Dimethyl-3-vinylocta-1,6-dien-1-yl)benzene (2.124, entry 10, Table 2.2). IR (neat): 3082 (w), 3059 (w), 3026 (w), 2966 (w), 2915 (w), 2854 (w), 1633 (w), 1598 (w), 1492 (w), 1447 (w), 1374 (w), 968 (m), 912 (m), 831 (w), 745 (s), 691 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.37 (2H, m), 7.33–7.29 (2H, m), 7.21 (1H, tt, *J* = 6.4, 1.6 Hz), 6.34 (1H, d, *J* = 16.8 Hz), 6.22 (1H, d, *J* = 16.0 Hz), 5.91 (1H, dd, *J* = 17.2, 10.8 Hz), 5.15–5.11 (1H, m), 5.08–5.02 (2H, m), 1.98 (2H, dt, *J* = 7.6, 7.6 Hz), 1.69 (3H, s), 1.60 (3H, s), 1.55–1.50 (2H, m), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 138.05, 138.03, 131.5, 128.6, 127.4, 127.1, 126.2, 124.9, 112.2, 42.8, 41.4, 25.8, 23.5, 23.4, 17.8; HRMS (ESI+): Calcd for $C_{18}H_{25}$ $[M+H]^+$: 241.1956, Found: 241.1945. Optical Rotation: $[a]_D^{20}$ +23.80 (*c* 1.83, $CHCl_3$) for an enantiomerically enriched sample of 90:10 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (89.9:10.1 er shown; Chiralcel OD-H column, 95/5 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	14.49		0.00	N/A	8407377	49.647	BV	0.44
2	15.42		0.00	N/A	8527098	50.353	VB	0.48

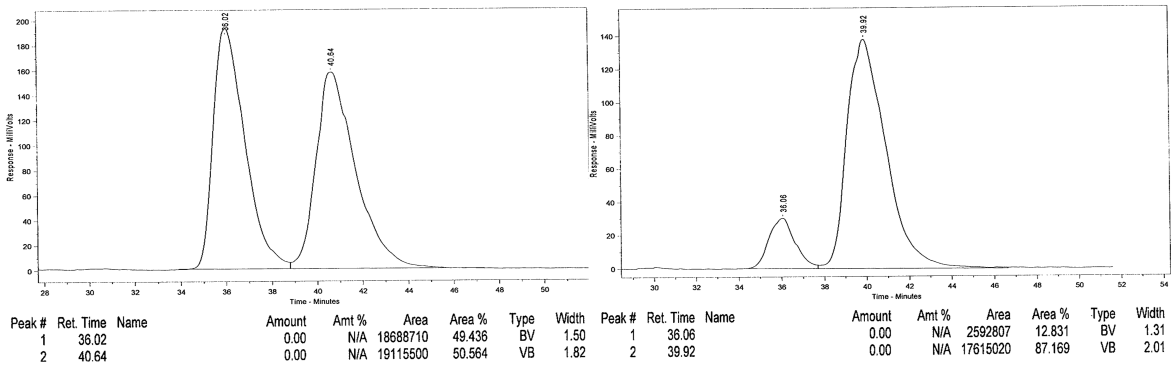
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	14.56		0.00	N/A	14871620	89.948	BV	0.47
2	15.60		0.00	N/A	1662039	10.052	VB	0.47

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	14.49	49.6	1	14.56	89.9

2	15.42	50.4	2	15.60	10.1

(*R*,*E*)-1-(3,7-Dimethyl-3-vinylocta-1,6-dien-1-yl)-4-(trifluoromethyl)benzene (2.125, entry 11, Table 2). IR (neat): 2969 (w), 2919 (w), 1616 (w), 1453 (w), 1413 (w), 1376 (w), 1323 (s), 1164 (m), 1124 (s), 1067 (m), 1016 (w), 973 (w), 916 (w), 817 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (2H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.4 Hz), 6.36 (1H, d, *J* = 16.0 Hz), 6.30 (1H, d, *J* = 16.0 Hz), 5.89 (1H, ddd, *J* = 17.2, 10.4, 0.8 Hz), 5.12–5.06 (2H, m), 5.03 (1H, dd, *J* = 17.2, 1.2 Hz), 1.96 (2H, dt, *J* = 7.2, 7.2 Hz), 1.68 (3H, s), 1.58 (3H, s), 1.55–1.50 (2H, m), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 141.5 (q, *J* = 1.4 Hz), 140.9, 131.7, 128.9 (q, *J* = 32.0 Hz), 126.4, 126.2, 125.6 (q, *J* = 3.7 Hz), 124.7, 124.4 (q, *J* = 270.1 Hz), 112.6, 43.0, 41.3, 25.8, 23.4, 23.3, 17.8; HRMS (ESI+): Calcd for $C_{19}H_{24}F_3$ $[M+H]^+$: 309.1830, Found: 309.1830. Optical Rotation: $[a]_D^{20}$ +13.68 (*c* 1.41, $CHCl_3$) for an enantiomerically enriched sample of 87:13 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (87.2:12.8 er shown; Chiralcel OJ-H column, 99/1 hexanes/*i*-PrOH, 0.5 mL/min, 220 nm).



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	36.02		0.00	N/A	18688710	49.436	BV	1.50
2	40.64		0.00	N/A	19115500	50.564	VB	1.82

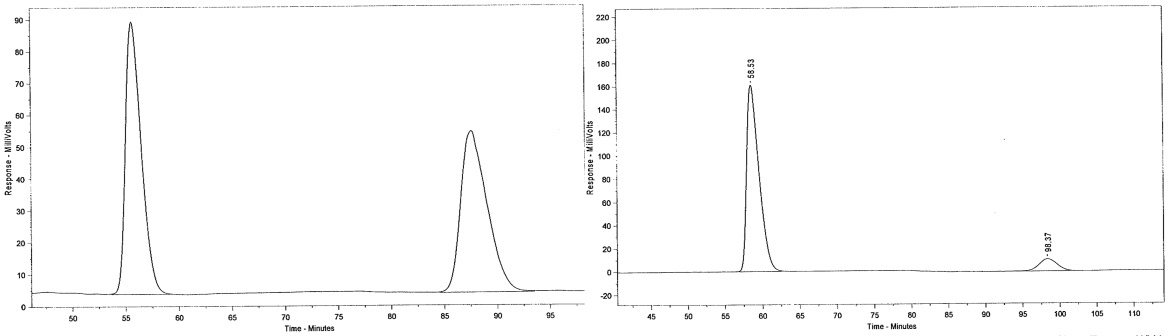
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	36.06		0.00	N/A	2592807	12.831	BV	1.31
2	39.92		0.00	N/A	17615020	87.169	VB	2.01

Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	36.02	49.4	1	36.06	12.8
2	40.64	50.6	2	39.92	87.2

(*R*,*E*)-1-(3,7-Dimethyl-3-vinylocta-1,6-dien-1-yl)-2-methylbenzene (2.126, entry 12, Table 2.2). Spectra are taken in the presence of 14% alkynyl adduct. IR (neat): 3019 (w), 2967 (m), 2921 (m), 2856 (w), 1636 (w), 1602 (w), 1511 (w), 1484 (w), 1457 (m), 1376 (w), 1248 (w), 1036 (w), 972 (m), 914 (m), 748 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.40 (1H, m), 7.20–7.11 (3H, m), 6.53 (1H, d, *J* = 16.4 Hz), 6.07 (1H, d, *J* = 16.4 Hz), 5.92 (1H, dd, *J* = 17.6, 10.8 Hz), 5.16–5.10 (1H, m), 5.08–5.02 (2H, m), 2.34 (3H, s), 1.98 (2H, dt, *J* = 7.6, 7.6 Hz), 1.69 (3H, s), 1.60 (3H, s), 1.53–1.50 (2H, m), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 143.6, 139.6, 137.4, 135.3, 132.1, 131.5, 130.2, 127.0, 126.2, 124.9, 112.2, 43.0, 42.4, 41.4, 25.8, 23.7, 23.4, 17.8; HRMS (ESI+): Calcd

for $C_{19}H_{27}$ [M+H]$^+$: 255.2113, Found: 255.2115. Optical Rotation: $[a]_D^{20}$ –23.46 (*c* 1.02, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er.

Enantiomeric purity is determined by HPLC analysis of the derived primary alcohol (obtained from hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H_2O_2) in comparison with authentic racemic material (91.0:9.0 er shown; Chiralcel OD-H column, 99/1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm).



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	55.65		0.00	N/A	8753302	49.785	BB	1.57
2	87.62		0.00	N/A	8828987	50.215	BB	2.73

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	58.53		0.00	N/A	18541550	90.994	BB	1.78
2	98.37		0.00	N/A	1835078	9.006	BB	2.71

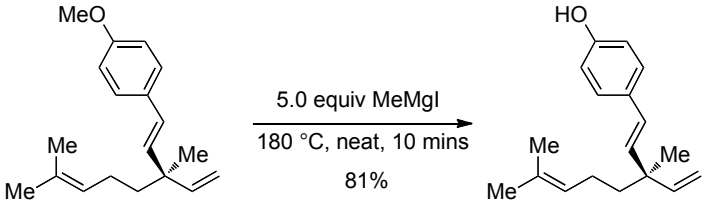
Peak#	Ret. Time	Area%	Peak#	Ret. Time	Area%
1	55.65	49.8	1	58.53	91.0
2	87.62	50.2	2	98.37	9.0

n Enantioselective Synthesis of *R*-(–)-bakuchiol (Scheme 7): Procedure for Demethylation of Bakuchiol Methyl Ether (Compound in entry 12, Table 2). A flame-dried 6-dram vial is charged with bakuchiol methyl ether (21.4 mg, 0.079 mmol) and a stir bar. The vial is sealed with a septum and purged with N_2 flow for 10 minutes. Freshly prepared MeMgI in diethyl ether (990 mL, 0.396 mmol) is added to the reaction vessel and solvent is carefully removed under reduced pressure. The resulting mixture is heated in a 180 °C oil bath for 10 minutes (white smoke generated as the reaction goes on and disappears in 10 minutes), after which time, it is allowed to cool to 22 °C and diluted with Et_2O (5 mL). A saturated solution of NH_4Cl is added to quench the reaction and layers are separated. The aqueous layer is washed with Et_2O (5 mL x 3) and the combined organic layers are dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a slightly yellow oil, which is subjected to silica gel chromatography (10:1 hexanes:ethyl acetate) to furnish the desired product as colorless oil (16.4 mg, 0.064 mmol, 81% yield). ***R*-(–)-Bakuchiol.** IR (neat): 3345 (br), 2966 (m), 2919 (m), 2862 (w), 1609 (m), 1511 (s), 1441 (m), 1374 (w), 1235 (m), 1171 (m), 970 (m), 914 (m), 813 (w), 527 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.24 (2H, m), 6.79–6.76 (2H, m), 6.25 (1H, d, *J* = 16.0 Hz), 6.06 (1H, d, *J* = 16.0 Hz), 5.88 (1H, dd, *J* = 17.2, 10.8 Hz), 5.13–5.09 (1H, m), 5.05–4.99 (2H, m), 4.74 (1H, br), 1.96 (2H, dt, *J* = 7.6, 7.6 Hz), 1.68 (3H, s), 1.58 (3H, s), 1.52–1.47 (2H, m), 1.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 146.1, 136.0, 131.5, 131.1, 127.5, 126.6, 125.0, 115.5, 112.0, 42.7, 41.4, 25.8, 23.5, 23.4, 17.8; HRMS (ESI+): Calcd for $C_{18}H_{25}O_1$ [M+H]$^+$: 257.1905, Found: 257.1903.

Optical Rotation: $[a]_D^{20}$ –23.81 (*c* 1.14, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er.

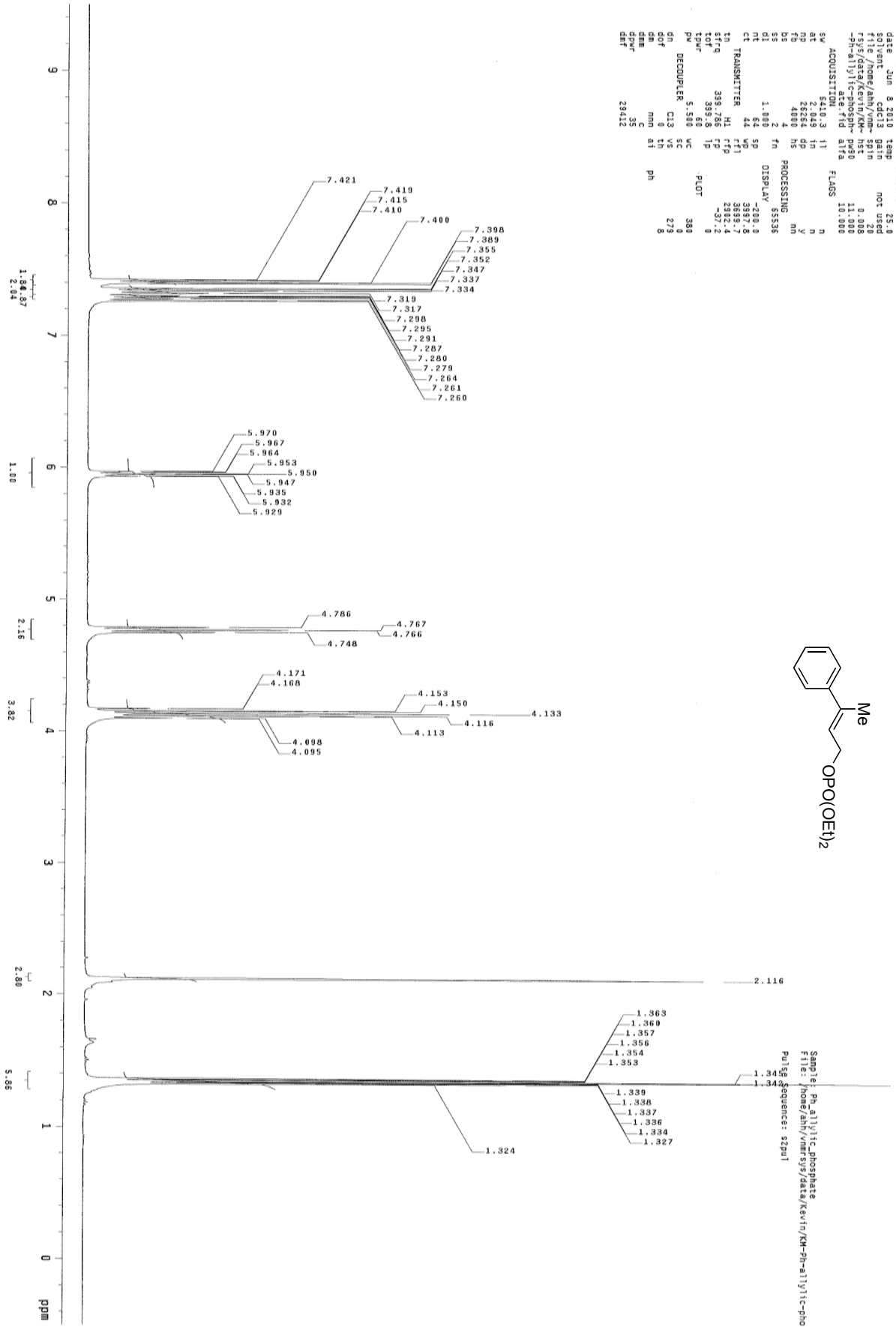
n Correlation of Stereochemistry: The stereochemical identity of bakuchiol derived from bakuchiol methyl ether in entry 12, Table 2 is determined to be *R*-(–)-bakuchiol by comparison with the data previously reported.[29] All the compounds generated in this study therefore are assigned as the *R* enantiomer by inference through analogy with bakuchiol methyl ether in entry 12, Table 2.

Scheme S1. Demethylation of R-(—)–Bakuchiol Methyl Ether and Stereochemistry Proof



R-(—)–bakuchiol methyl ether R-(—)–bakuchiol

(29) Du, X-L.; Chen, H-L.; Feng, H-J.; Li, Y-C. *Helv. Chim. Acta* **2008**, *91*, 371−378.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SAMPLE
date Jun 8 2010
solvent cdcl3
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-Ph-allylic_phosph
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at 2.049
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fb 4000
bs 4
ss 2
dl 1.000
dt 64
ct 44
tn H1
sfrq 399.786
tof 399.8
tpwr 60
pw 5.500
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dn C13
dof 0
dm nnn
dmm c
dmf 29412
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gain not used
spin 20
hst 0.038
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pl1 10.000
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in n
dp y
hs nn
PROCESSING
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DISPLAY
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rfp 2982.4
rp -37.2
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sc 0
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5.86
ppm
Me
OPO(OEt)2
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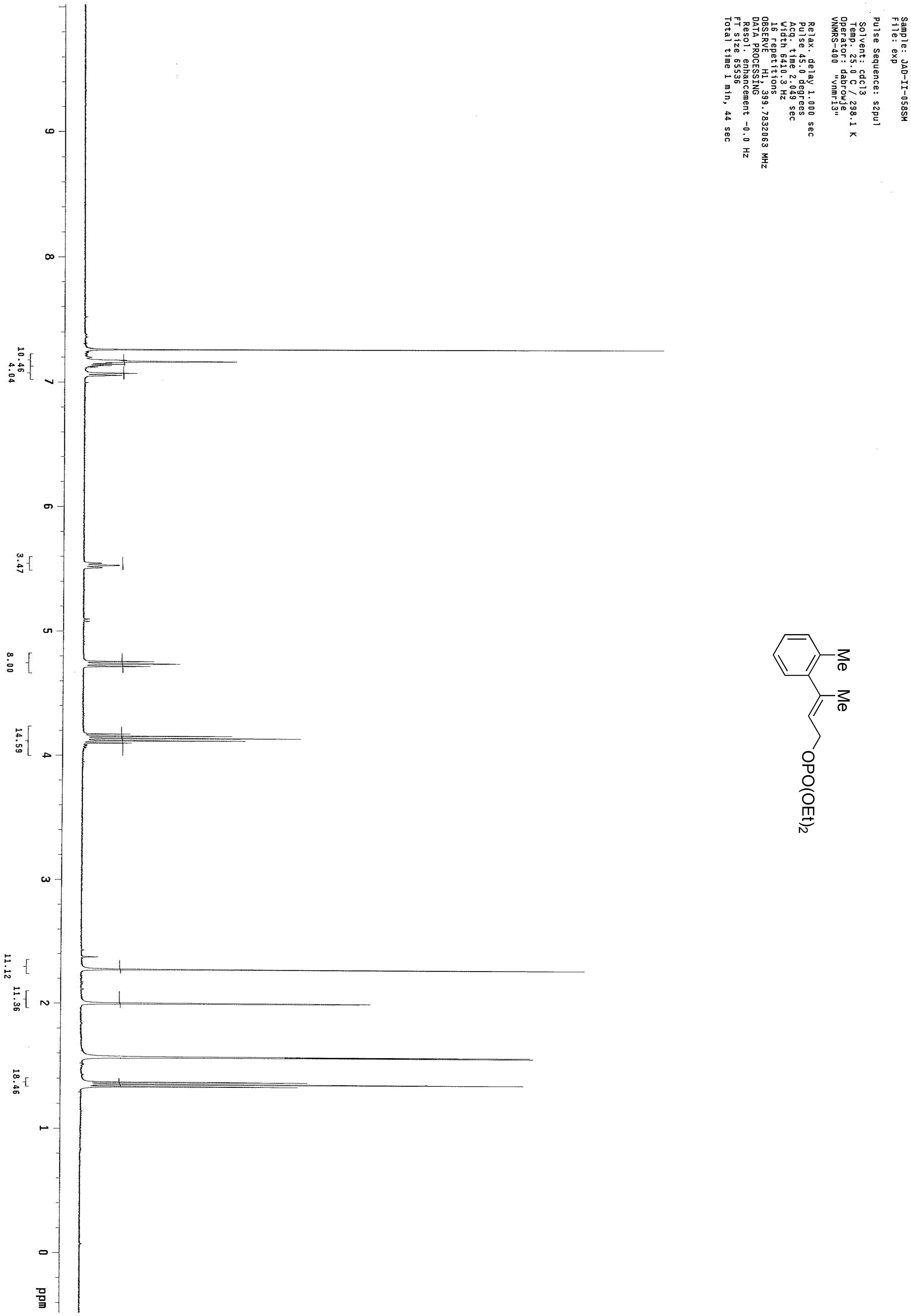
PulSeq Sequence: s2pul



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Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
16 repetitions
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DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 44 sec
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4.04
3.47
8.00
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11.12
11.36
18.46
9
8
7
6
5
4
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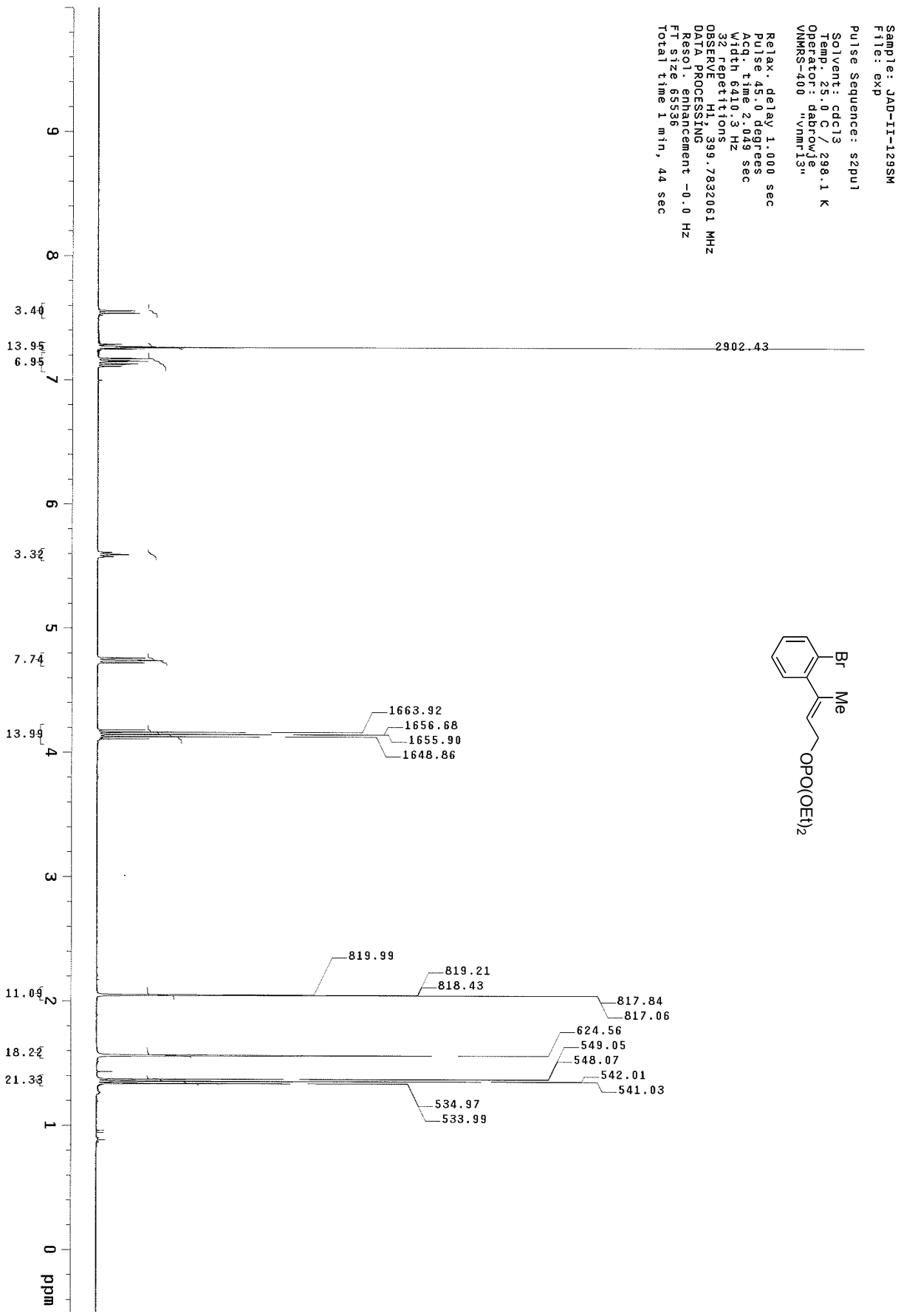
2
1
0
ppm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Pulse 45.0 degrees
Acq. time 2.049 sec
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32 repetitions
OBSERVE H1, 399.7832061 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
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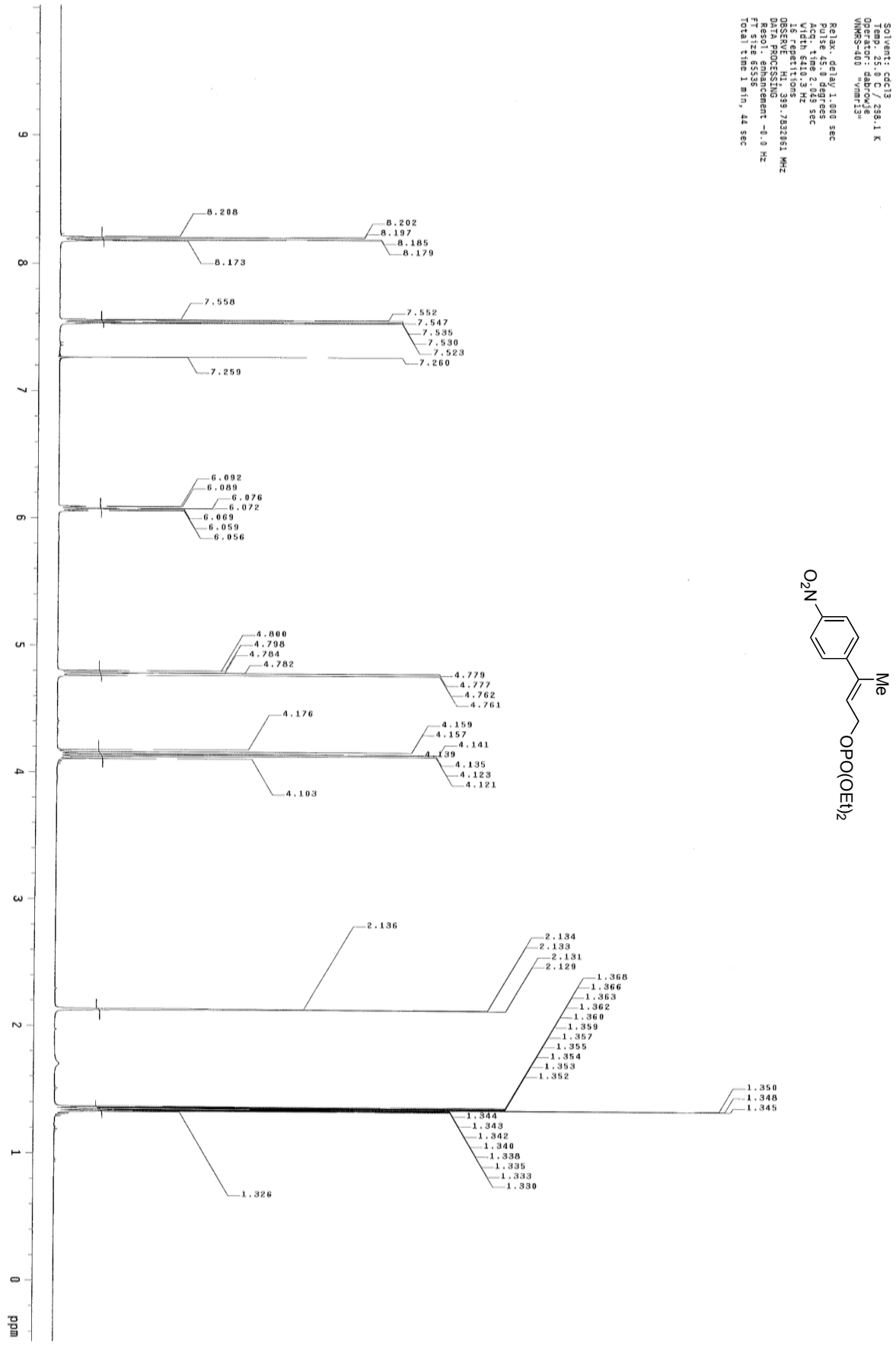
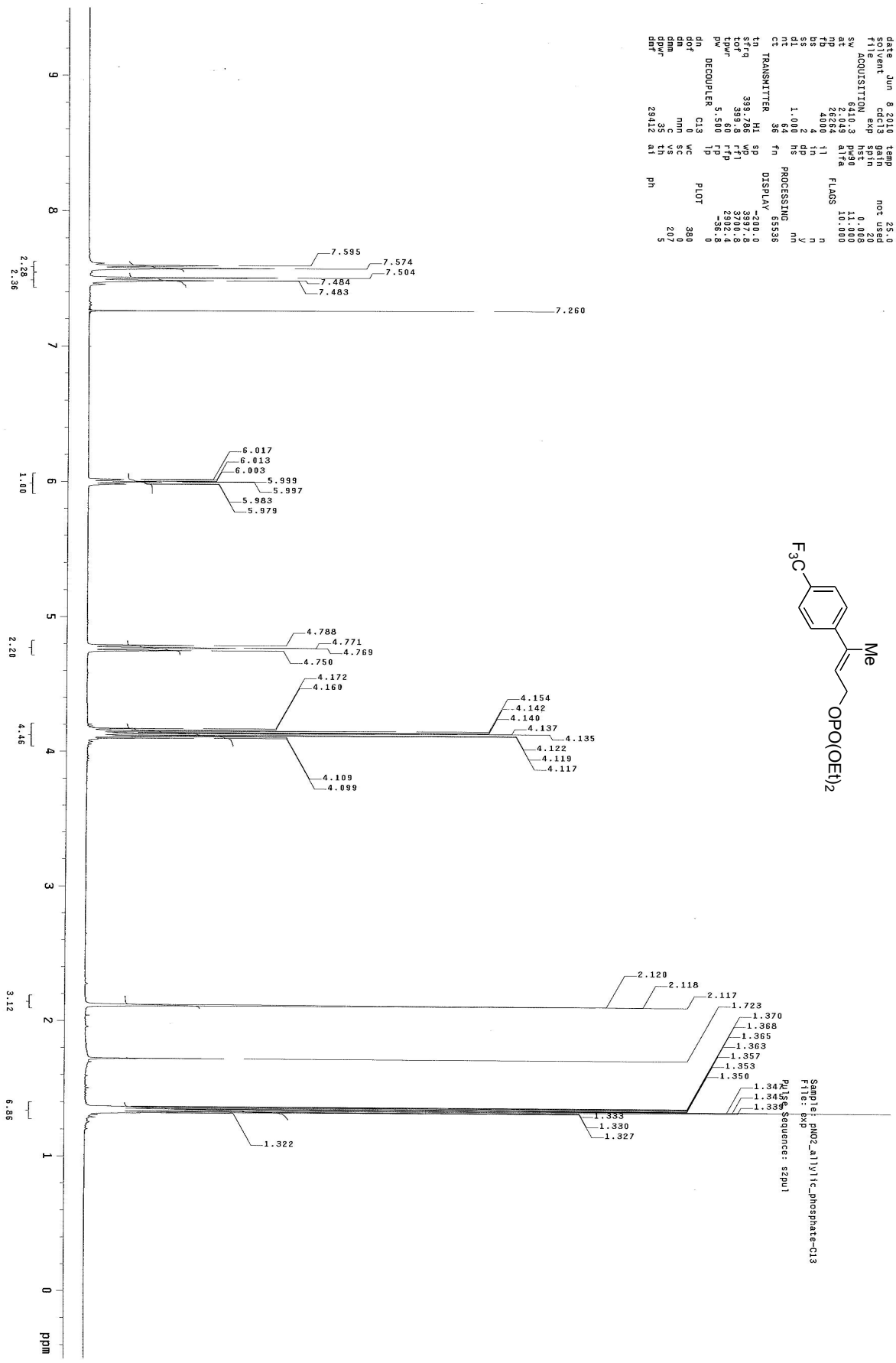
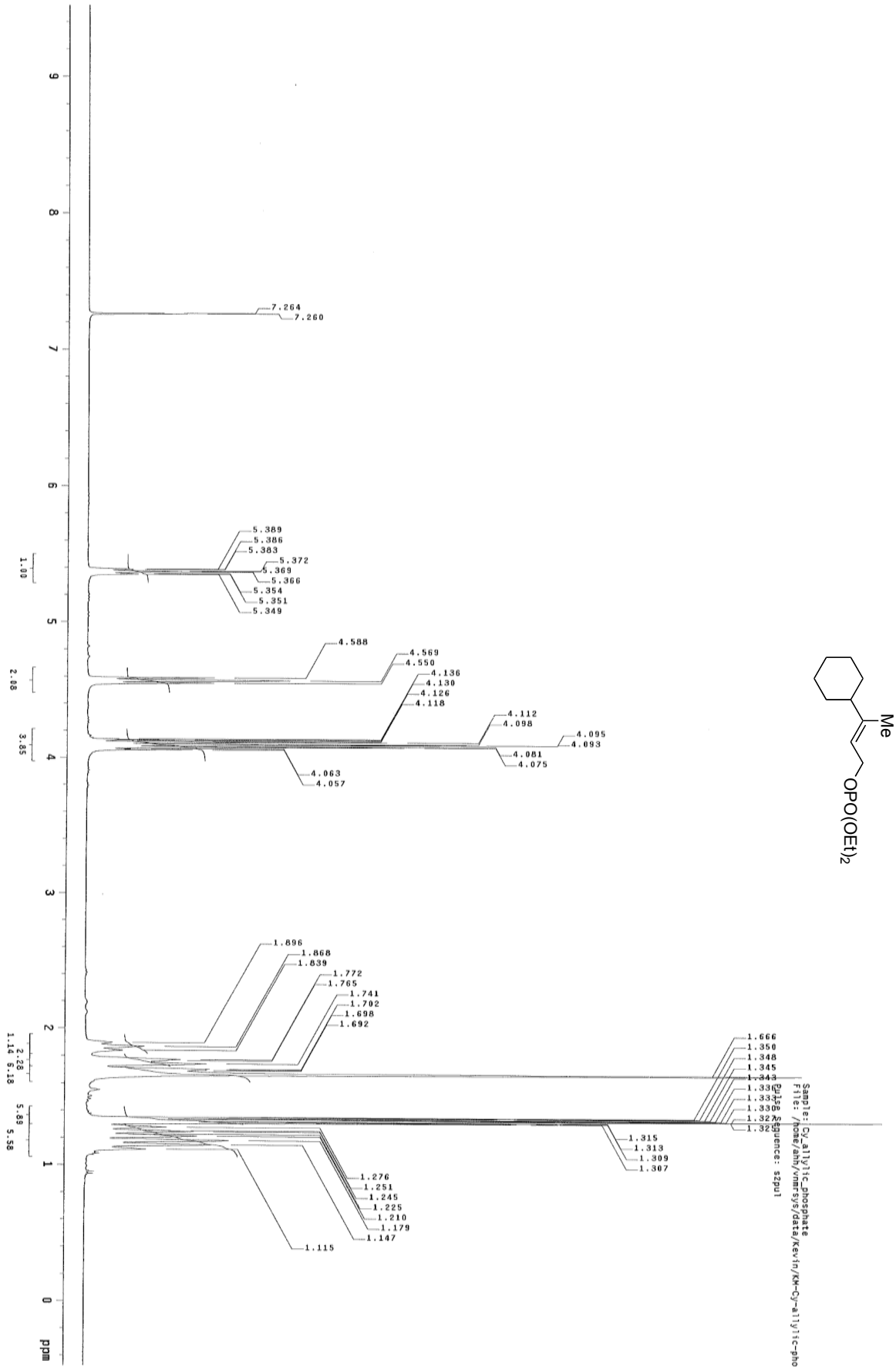
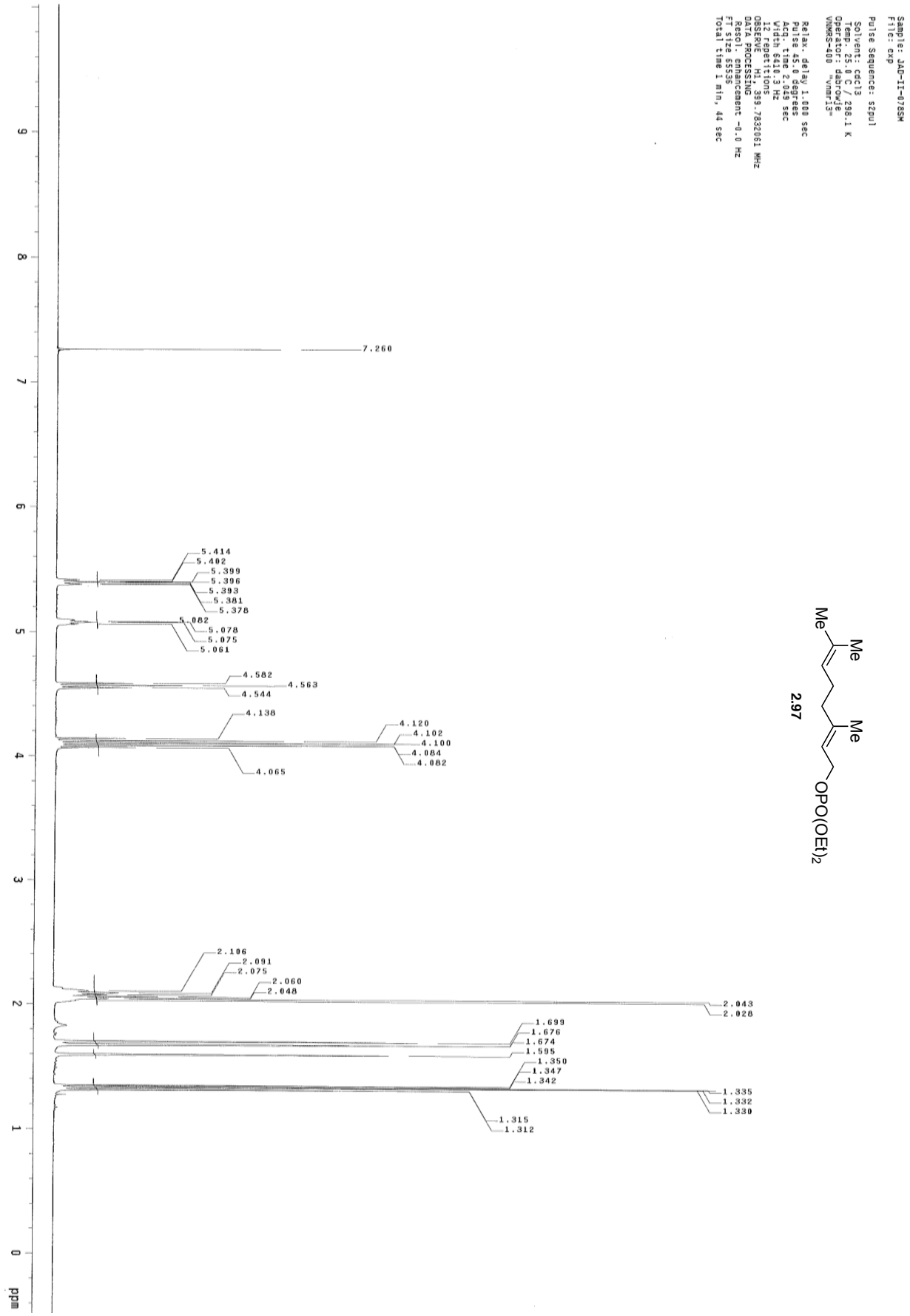
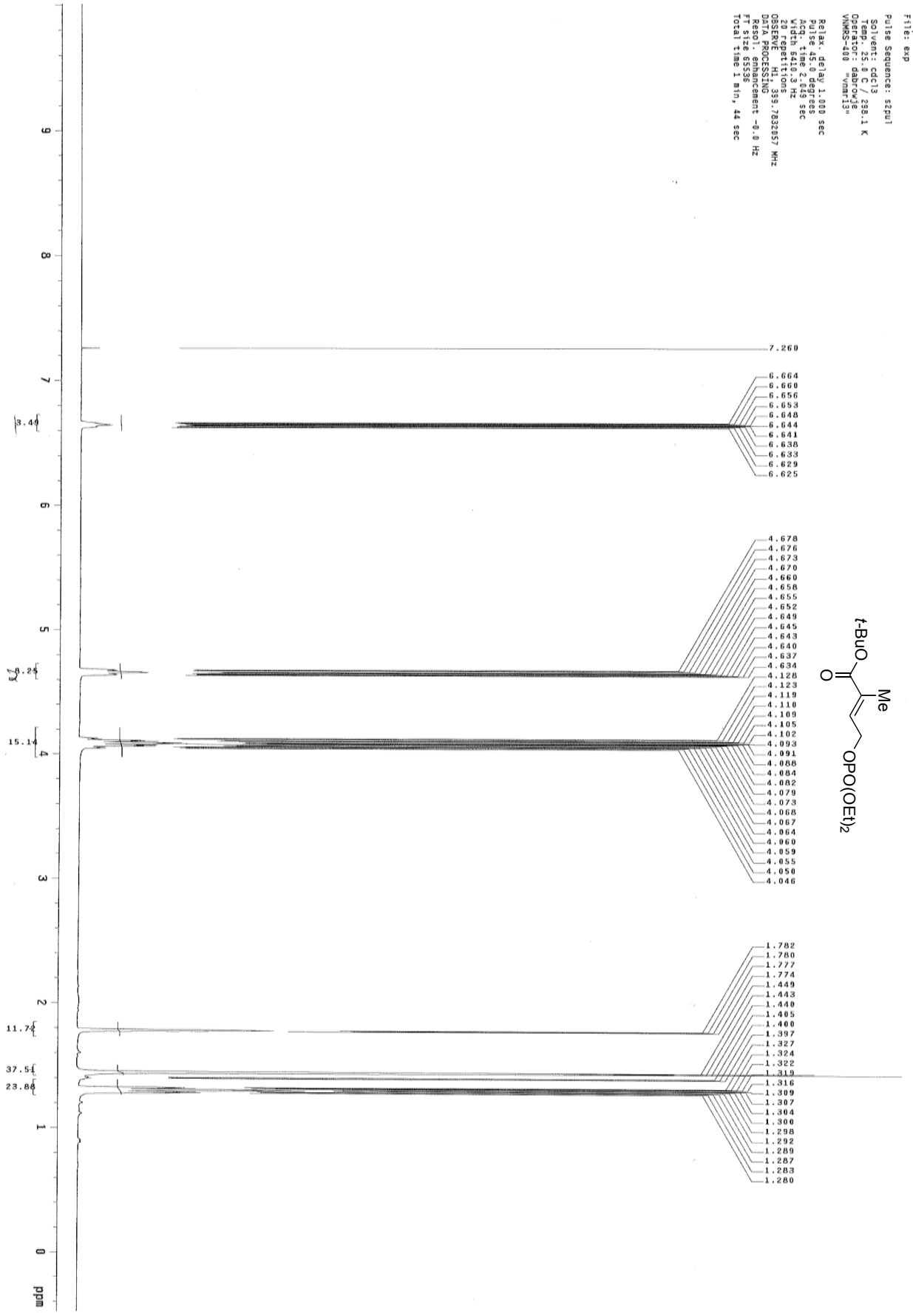
817.06
624.56
549.05
548.07
542.01
541.03
534.97
533.99
3.40
13.95
6.95
3.32
7.74
13.99
11.09
18.22
21.33
Br
Me
OPO(OEt)2
ppm

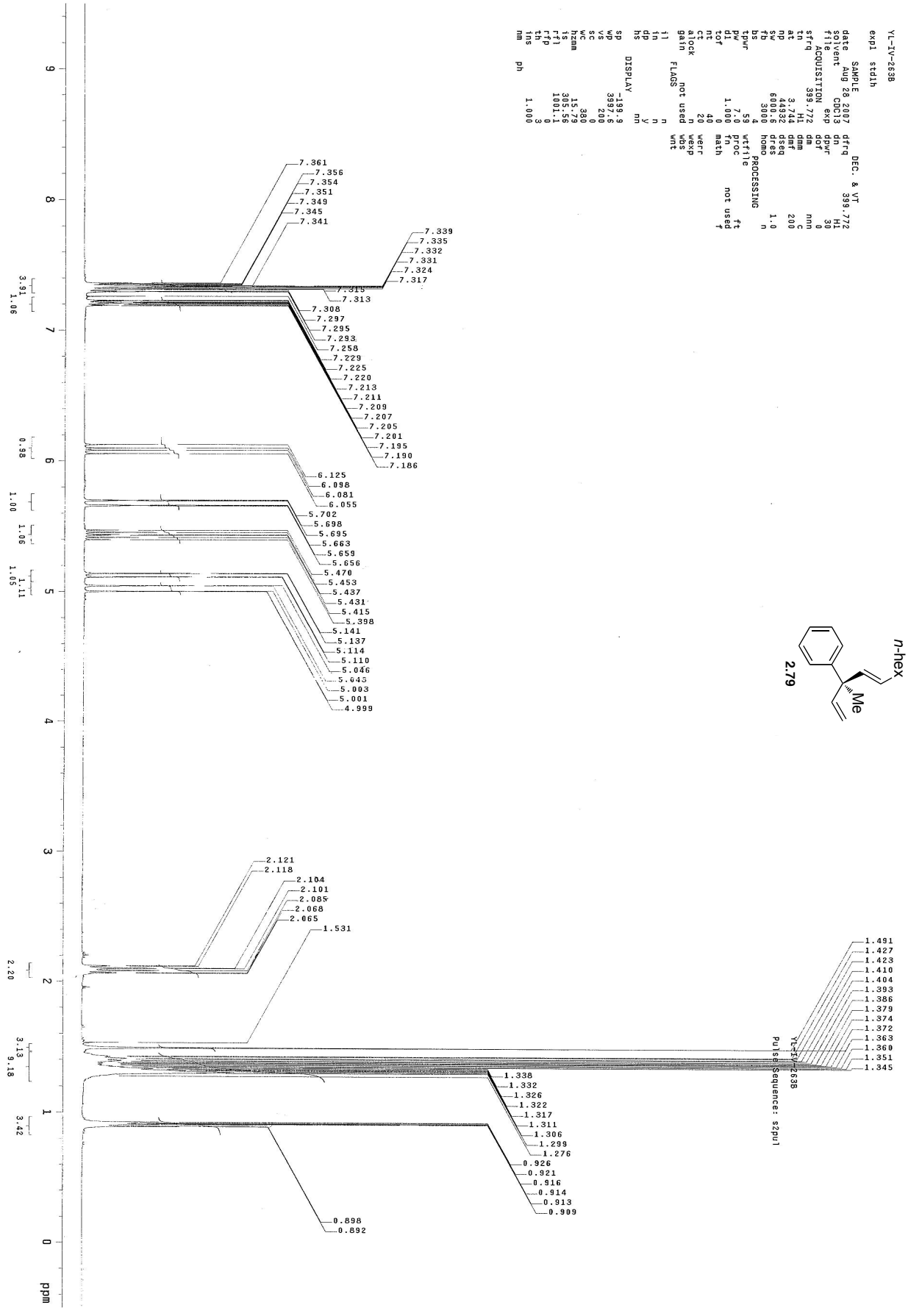

Sample: JAD-II-pNO2
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: dabrowje
VNMRS-400 "vnmr13"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7832061 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 44 sec
8.208
8.202
8.197
8.185
8.179
8.173
7.558
7.552
7.547
7.535
7.530
7.523
7.260
7.259
6.092
6.089
6.076
6.072
6.069
6.059
6.056
4.800
4.798
4.784
4.782
4.779
4.777
4.762
4.761
4.176
4.159
4.157
4.141
4.139
4.135
4.123
4.121
4.103
2.136
2.134
2.133
2.131
2.129
1.368
1.366
1.363
1.362
1.360
1.359
1.357
1.355
1.354
1.353
1.352
1.350
1.348
1.345
1.344
1.343
1.342
1.340
1.338
1.335
1.333
1.330
1.326
ppm
O2N
Me
OPO(OEt)2

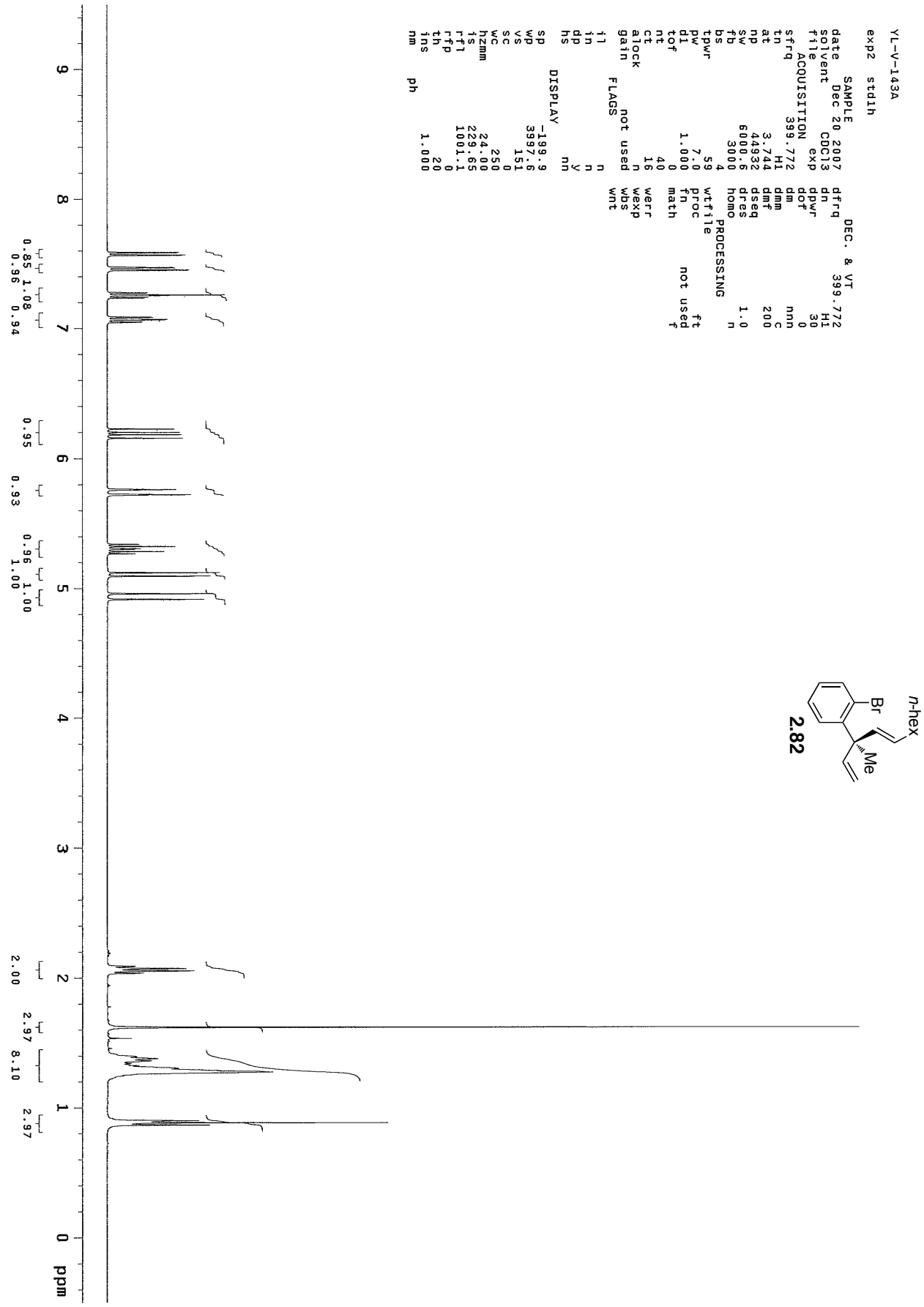

exp20 Proton
SAMPLE
Jun 8 2010
cdcl3
FLAGS
PROCESSING
DISPLAY
PLOT
DECOUPLER
TRANSMITTER
7.595
7.574
7.504
7.484
7.483
7.260
6.017
6.013
6.003
5.999
5.997
5.983
5.979
4.788
4.771
4.769
4.750
4.172
4.160
4.154
4.142
4.140
4.137
4.135
4.122
4.119
4.117
4.109
4.099
2.120
2.118
2.117
1.723
1.370
1.368
1.365
1.363
1.357
1.353
1.350
1.347
1.345
1.339
1.333
1.330
1.327
1.322
2.28
2.36
1.00
2.20
4.46
3.12
6.86
ppm
F3C
Me
OPO(OEt)2
Sample: pNO2_allylic_phosphate-C13
File: exp
Pulse Sequence: s2pul

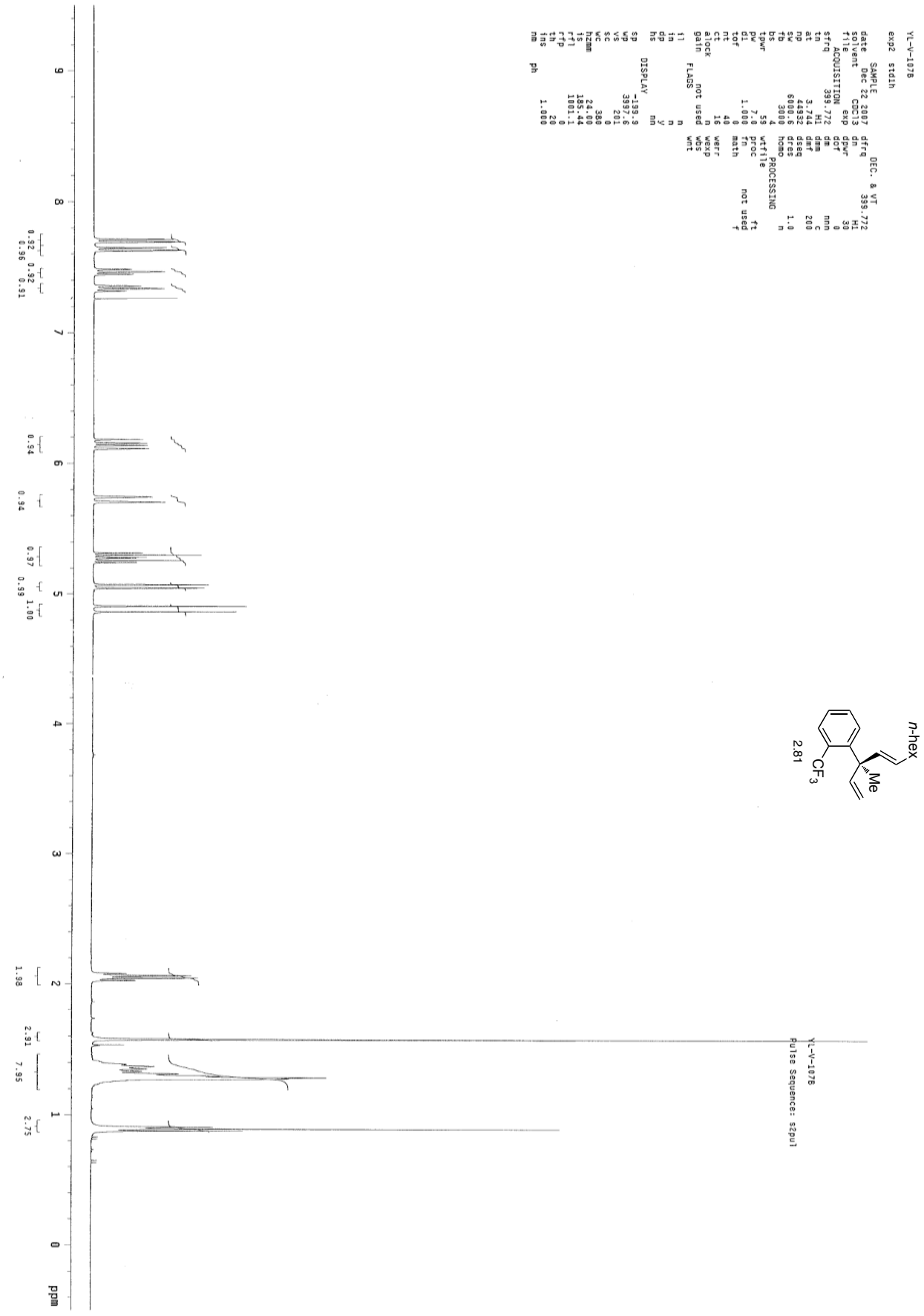

7.264
7.260
5.389
5.386
5.383
5.372
5.369
5.366
5.354
5.351
5.349
4.588
4.569
4.550
4.136
4.130
4.126
4.118
4.112
4.098
4.095
4.093
4.081
4.075
4.063
4.057
1.896
1.868
1.839
1.772
1.765
1.741
1.702
1.698
1.692
1.666
1.350
1.348
1.345
1.343
1.330
1.327
1.325
1.315
1.313
1.309
1.307
1.276
1.251
1.245
1.225
1.210
1.179
1.147
1.115
1.00
2.08
3.85
2.28
1.14
6.18
5.89
5.58
ppm
Me
OPO(OEt)2
Sample: Cy_allylic_phosphate
File: /home/anh/vnmrsys/data/Kevin/KM-Cy-allylic-pho
Pulse Sequence: s2pul

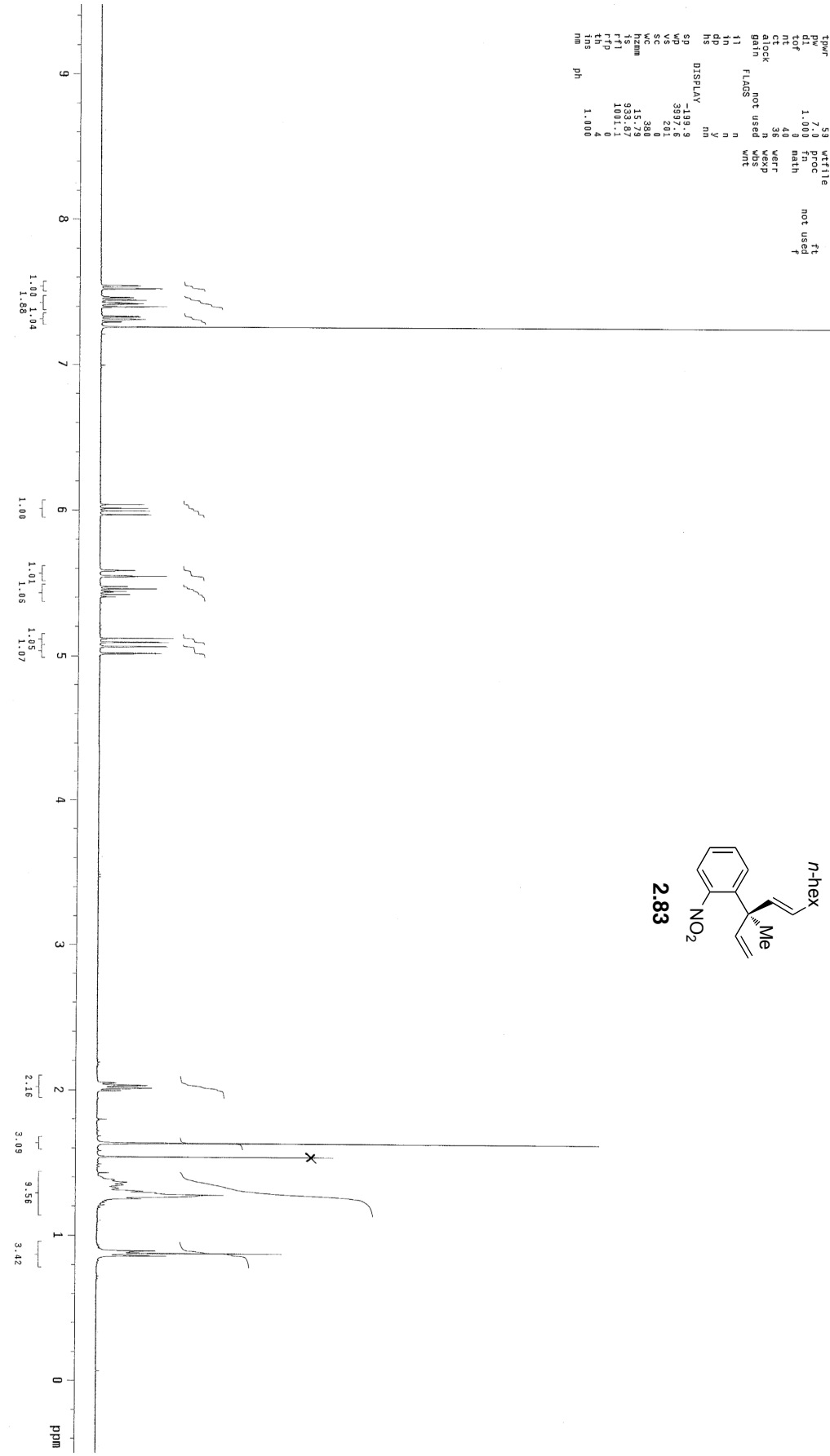

Sample: JAD-II-078SM
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Operator: dabrowje
VNMRS-400 "vnmrs"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.045 sec
Width 8410.3 Hz
1 repetitions
OBSERVE H1, 399.7832061 MHz
DATA PROCESSING
Resol. enhancement -0.1 Hz
FT size 65536
Total time 1 min, 44 sec
7.260
5.414
5.402
5.399
5.396
5.393
5.381
5.378
5.082
5.078
5.075
5.061
4.582
4.563
4.544
4.138
4.120
4.102
4.100
4.084
4.082
4.065
2.106
2.091
2.075
2.060
2.048
2.043
2.028
1.699
1.676
1.674
1.595
1.350
1.347
1.342
1.335
1.332
1.330
1.315
1.312
ppm
Me
Me
Me
OPO(OEt)2
2.97

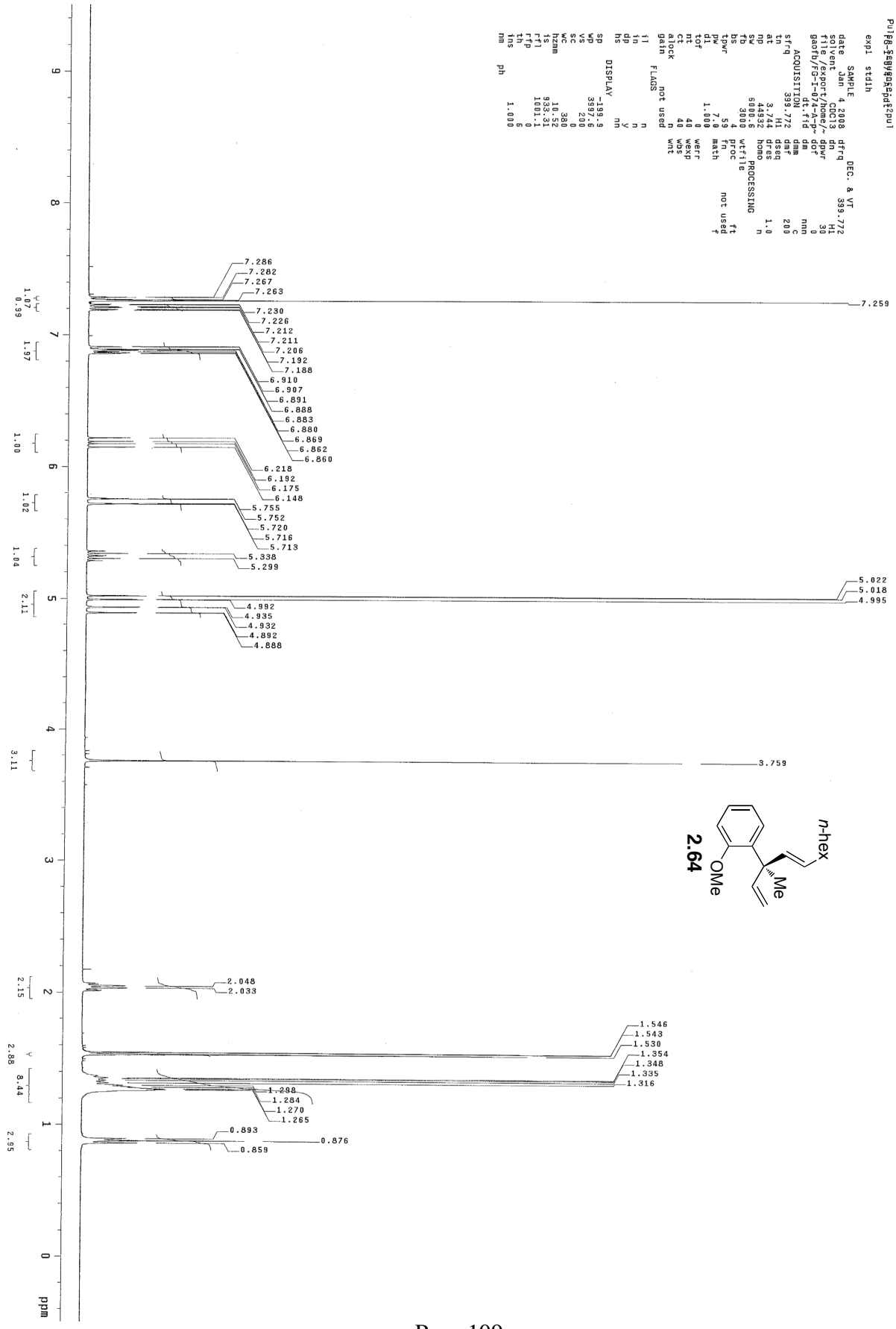

Sample: JAD-II-087SM
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Operator: dabrowse
VNMRS-400 "vnmrj3"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.045 sec
Width 6410.3 Hz
20 repetitions
OBSERVE H1, 399.7832057 MHz
DATA PROCESSING
Resol. enhancement -0.8 Hz
FT size 65536
Total time 1 min, 44 sec
7.260
6.664
6.660
6.656
6.653
6.648
6.644
6.641
6.638
6.633
6.629
6.625
4.678
4.676
4.673
4.670
4.660
4.658
4.655
4.652
4.649
4.645
4.643
4.640
4.637
4.634
4.128
4.123
4.119
4.110
4.109
4.105
4.102
4.093
4.091
4.088
4.084
4.082
4.079
4.073
4.068
4.067
4.064
4.060
4.059
4.055
4.050
4.046
1.782
1.780
1.777
1.774
1.449
1.443
1.440
1.405
1.400
1.397
1.327
1.324
1.322
1.319
1.316
1.309
1.307
1.304
1.300
1.298
1.292
1.289
1.287
1.283
1.280
3.40
2.24
15.14
11.72
37.51
23.80
ppm
t-BuO
O
Me
OPO(OEt)2

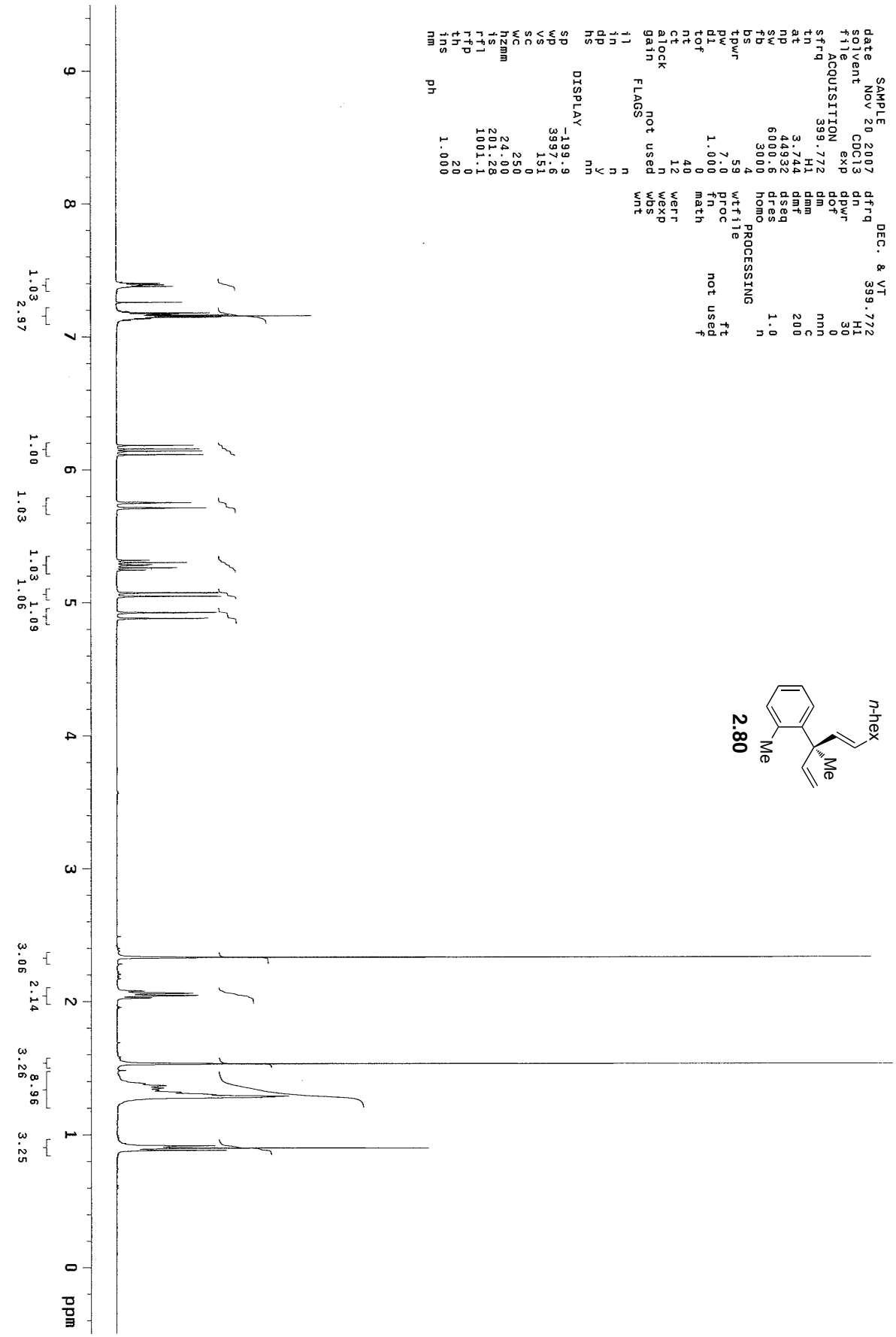

YL-IV-263B
expl stdih
SAMPLE
date Aug 28 2007
solvent CDCl3
file YL-IV-263B
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs 4
tpwr 59
pw 7.0
pw1 1.000
tof 0
nt 40
ct 20
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 200
sc 0
wc 300
hzcm 15.979
is 305.56
rfl 1001.1
rfp 0
th 3
ins 1
nm ph 1.000
dfrq
dn
dpwr
dof
dm
dmm
dmf
dseq
dres
homo
PROCESSING
wtfile
proc
ft
math
wnt
wbs
wexp
werr
DEC. & VT
399.772
H1
30
0
nnn
200
1.0
n
not used
f
7.361
7.356
7.354
7.351
7.349
7.345
7.341
7.339
7.335
7.332
7.331
7.324
7.317
7.315
7.313
7.308
7.297
7.295
7.293
7.258
7.229
7.225
7.220
7.213
7.211
7.209
7.207
7.205
7.201
7.195
7.190
7.186
6.125
6.098
6.081
6.055
5.702
5.698
5.695
5.663
5.659
5.656
5.470
5.453
5.437
5.431
5.415
5.398
5.141
5.137
5.114
5.110
5.046
5.043
5.003
5.001
4.999
2.121
2.118
2.104
2.101
2.085
2.068
2.065
1.531
1.491
1.427
1.423
1.410
1.404
1.393
1.386
1.379
1.374
1.372
1.363
1.360
1.351
1.345
1.338
1.332
1.326
1.322
1.317
1.311
1.306
1.299
1.276
0.926
0.921
0.916
0.914
0.913
0.909
0.898
0.892
3.91
1.06
0.98
1.00
1.06
1.11
1.05
2.20
3.13
9.18
3.42
ppm
n-hex
Me
2.79
YL-IV-263B
Pulse Sequence: s2pul

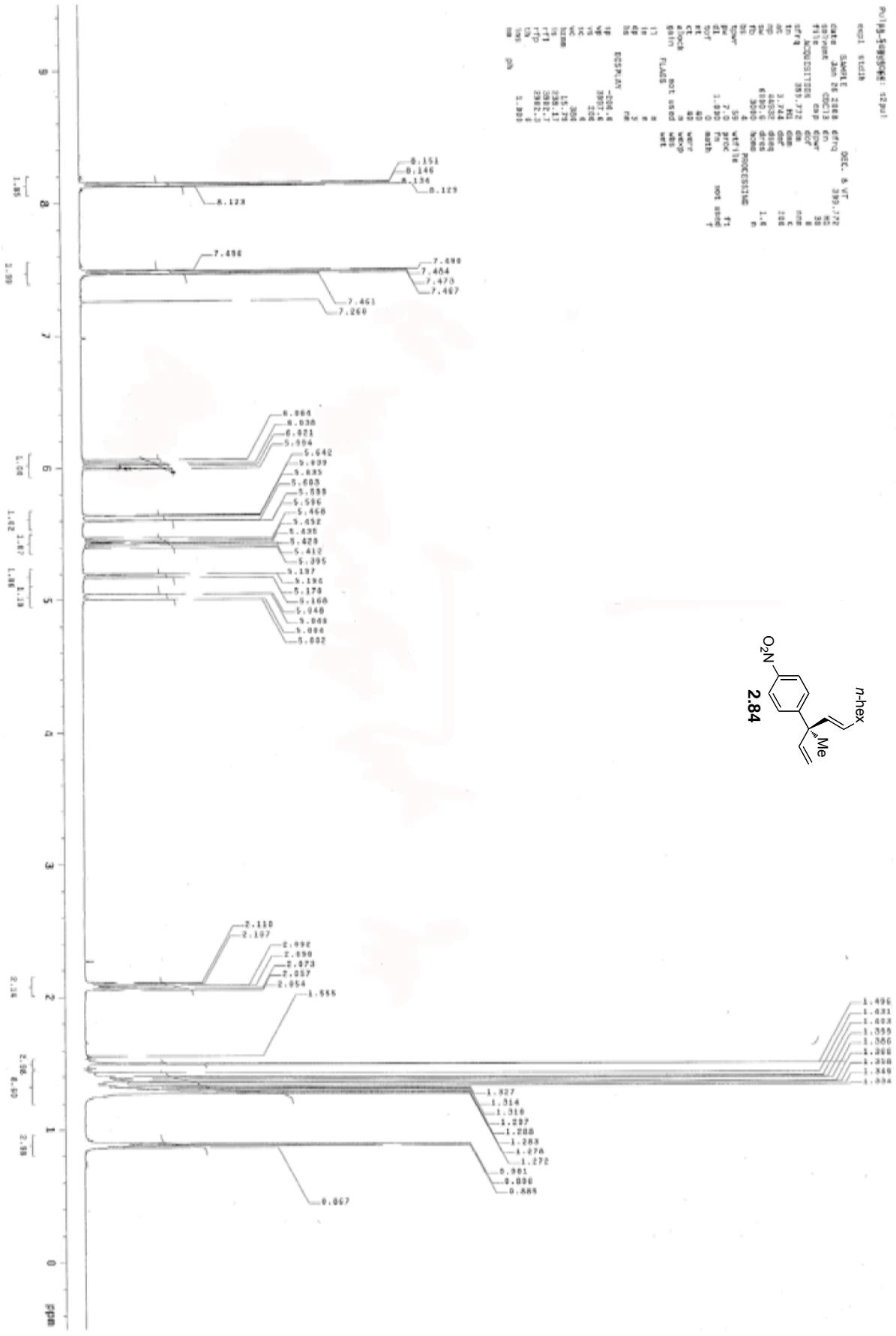

YL-V-143A
exp2 std1h
SAMPLE
date Dec 20 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs 4
tpwr 59
pw 7.0
d1 1.000
tof 0
nt 40
ct 16
alock n
gain FLAGS
not used
wnt
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 151
sc 0
wc 250
hzmm 24.00
is 229.65
rfl 1001.1
rfp 0
th 20
ins 1.000
nm
ph
DEC. & VT
dfrq 399.772
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
n-hex
Br
Me
2.82
9
8
7
6
5
4
3
2
1
0
ppm
0.85 1.08
0.96 0.94
0.95
0.93
0.96 1.00
1.00
2.00
2.97 8.10
2.97

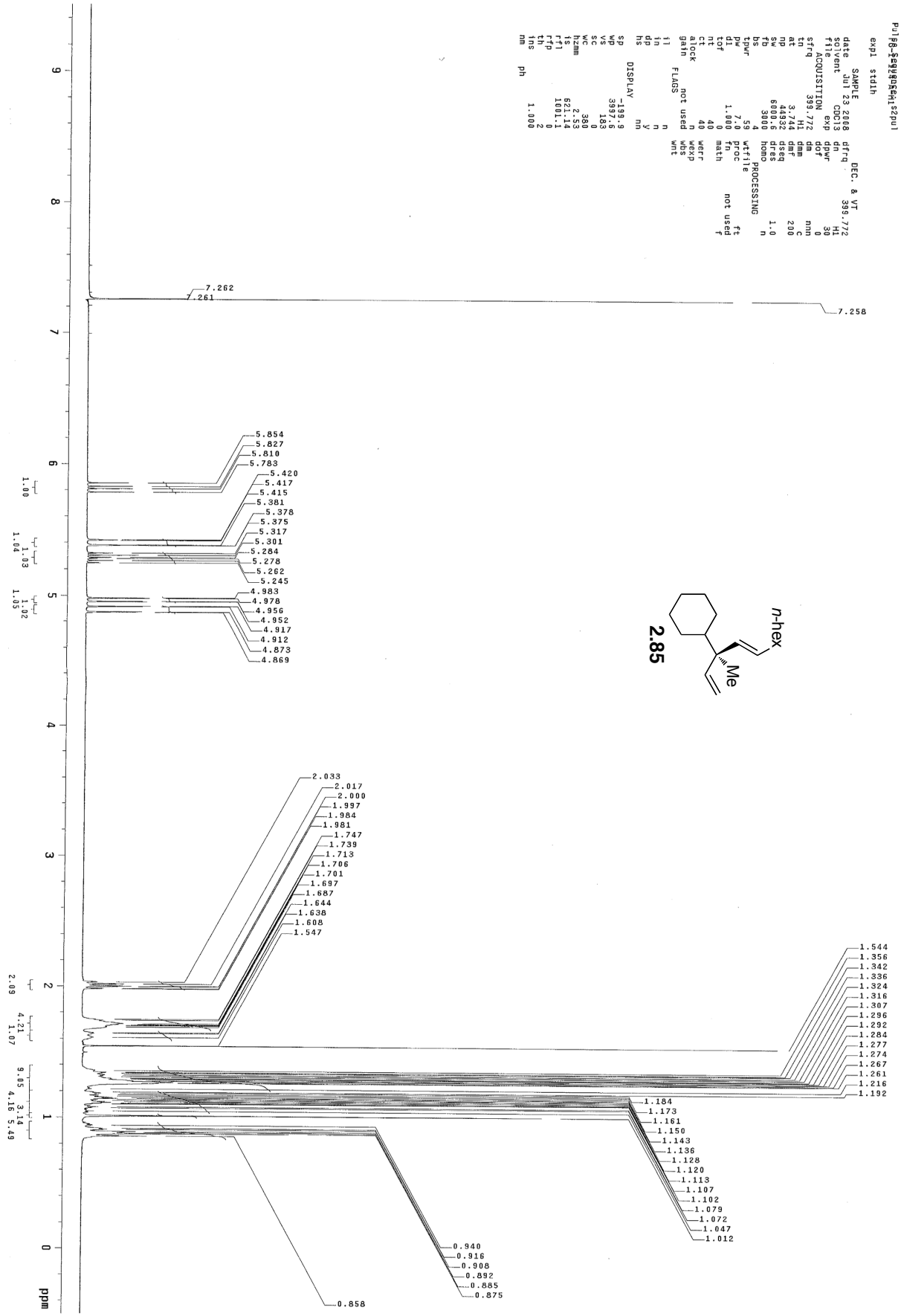

YL-V-107B
exp2 stdih
SAMPLE
date Dec 22 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 64932
sw 6009.6
fb 3008
bs 4
tpwr 59
pw 7.0
dl 1.000
tof 0
nt 16
ct 40
alock n
gain n
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 201
sc 0
wc 380
hzmm 24.00
is 185.44
rfl 1001.1
rfp 0
th 20
ins 1.000
nm ph
dfrq DEC. & vT
399.772
H1
30
0
nnn
c
200
1.0
n
PROCESSING
wtfile
proc ft
not used
fn not used
math f
werr
wexp
wbs
wnt
n-hex
Me
CF3
2.81
YL-V-107B
Pulse Sequence: s2pul
ppm
0.92 0.92
0.96 0.91
0.94
0.94
0.97 1.00
0.99
1.98
2.91 7.95
2.75

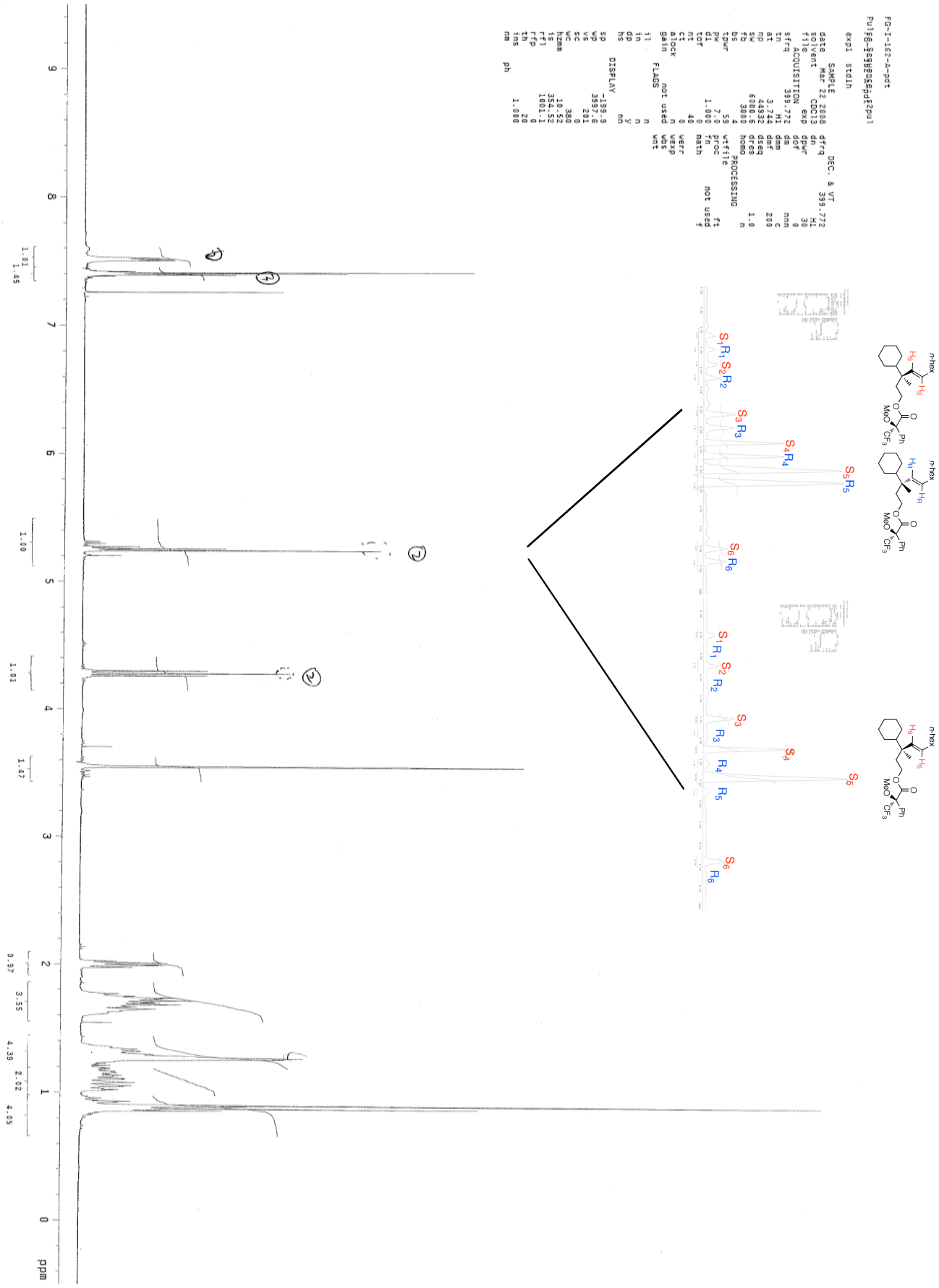

FG-I-102-A-pdt
Pulse Sequence: s2pul
exp1 std1h
SAMPLE
date Feb 1 2009
solvent CDCl3
file pdt
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3001
bs
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 40
ct 36
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 0
sc 201
wc 380
hzmm 15.79
rfl 933.87
rfp 1091.1
th 4
ins 1.000
nm ph
DEC. & VT
dfrq 399.772
dn H1
dpwr 50
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt
n-hex
Me
NO2
2.83
1.00
1.04
1.88
1.00
1.01
1.06
1.05
1.07
2.16
3.09
9.56
3.42
9
8
7
6
5
4
3
2
1
0
ppm

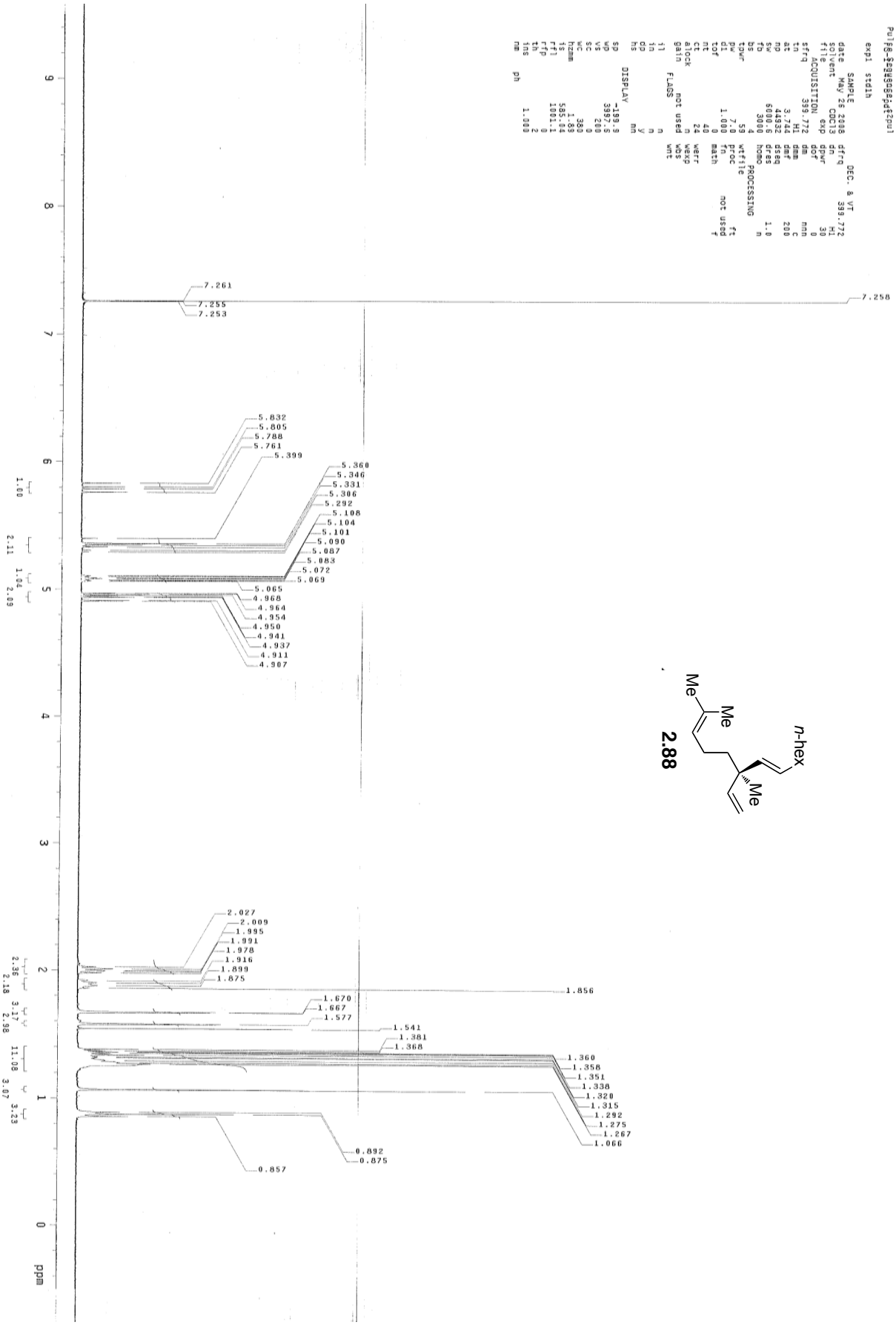

FG-I-074-A-pdt
7.286
7.282
7.267
7.263
7.259
7.230
7.226
7.212
7.211
7.206
7.192
7.188
6.910
6.907
6.891
6.888
6.883
6.880
6.869
6.862
6.860
6.218
6.192
6.175
6.148
5.755
5.752
5.720
5.716
5.713
5.338
5.299
5.022
5.018
4.995
4.992
4.935
4.932
4.892
4.888
3.759
2.048
2.033
1.546
1.543
1.530
1.354
1.348
1.335
1.316
1.298
1.284
1.270
1.265
0.893
0.876
0.859
ppm
n-hex
Me
OMe
2.64

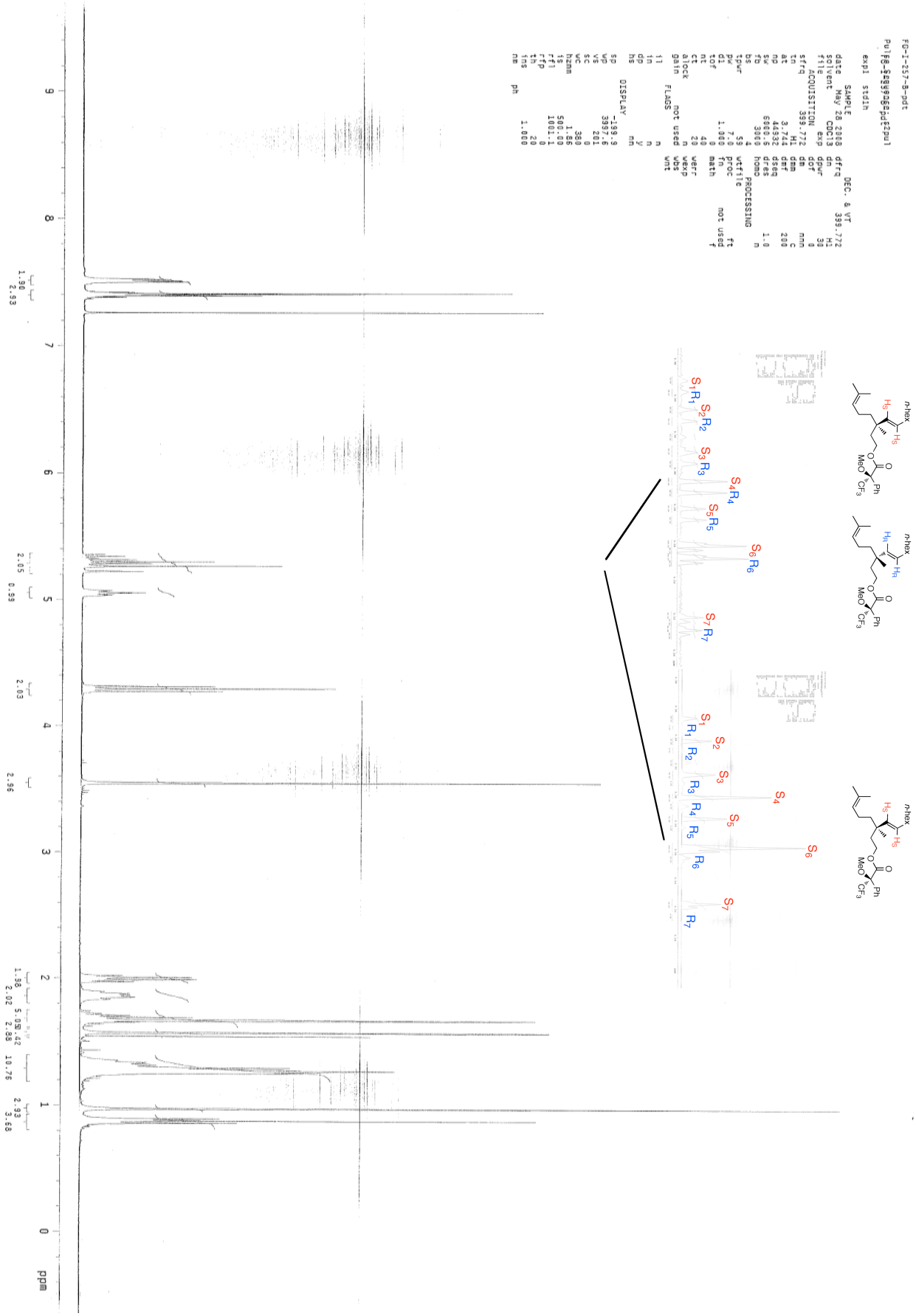

YL-V-103
exp2 stdih
SAMPLE
date Nov 20 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs 4
tpwr 59
pw 7.0
d1 1.000
tof 0
nt 40
ct 12
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 151
sc 0
wc 250
hzmm 24.00
is 201.28
rfl 1001.1
rfp 0
th 20
ins 1.000
nm ph
DEC. & VT
dfrq 399.772
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt
n-hex
Me
Me
2.80
9
8
7
6
5
4
3
2
1
0
ppm
1.03
2.97
1.00
1.03
1.03
1.06
1.09
3.06
2.14
3.26
8.96
3.25

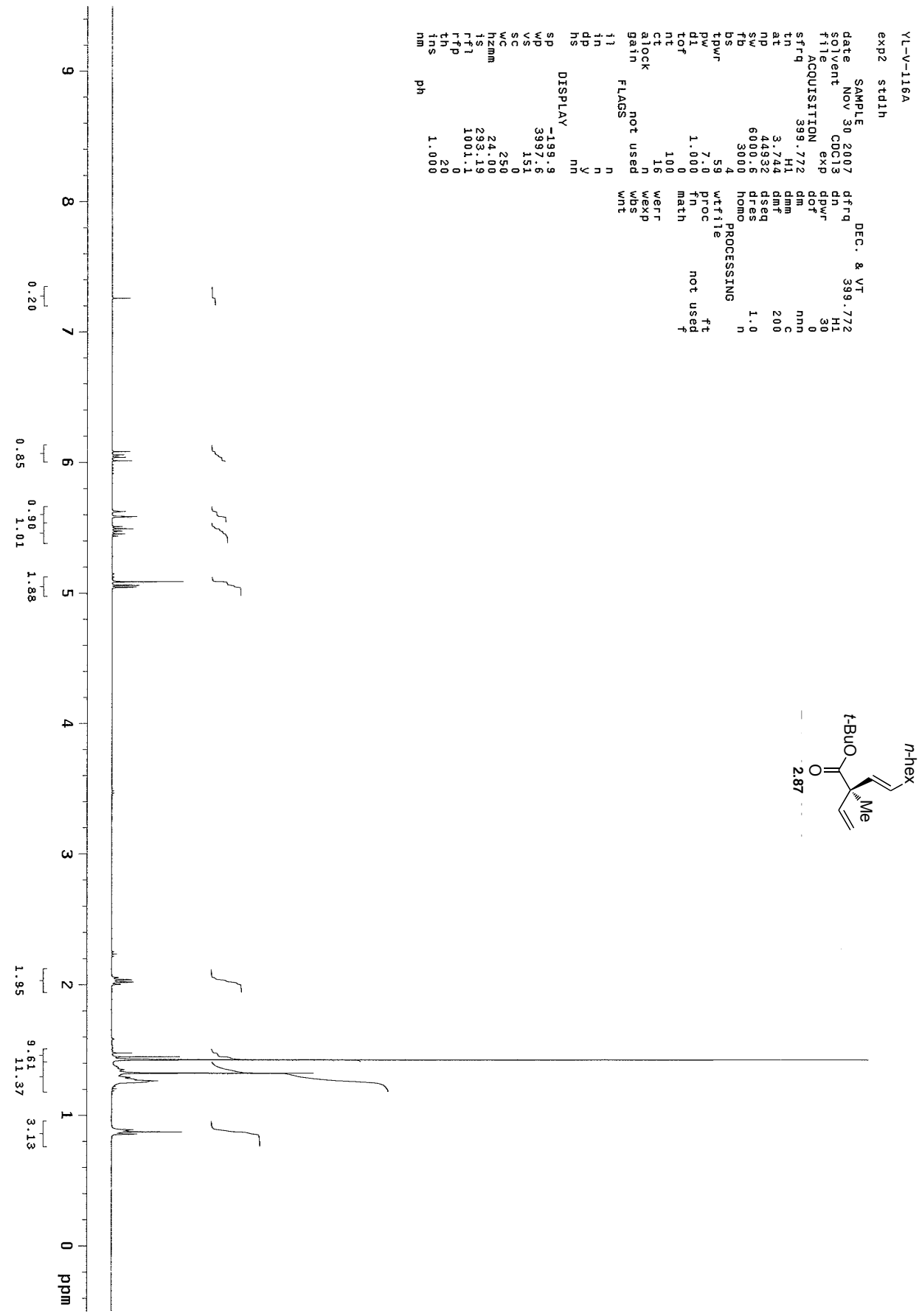

8.151
8.146
8.136
8.129
8.123
7.496
7.490
7.484
7.473
7.467
7.461
7.260
6.044
6.038
6.021
5.994
5.642
5.639
5.635
5.603
5.588
5.596
5.468
5.452
5.435
5.428
5.412
5.395
5.197
5.196
5.178
5.166
5.048
5.044
5.002
2.110
2.107
2.092
2.090
2.073
2.057
2.054
1.555
1.496
1.491
1.483
1.355
1.356
1.350
1.349
1.334
1.327
1.314
1.310
1.297
1.288
1.283
1.276
1.272
0.961
0.898
0.885
0.867
O2N
n-hex
Me
2.84

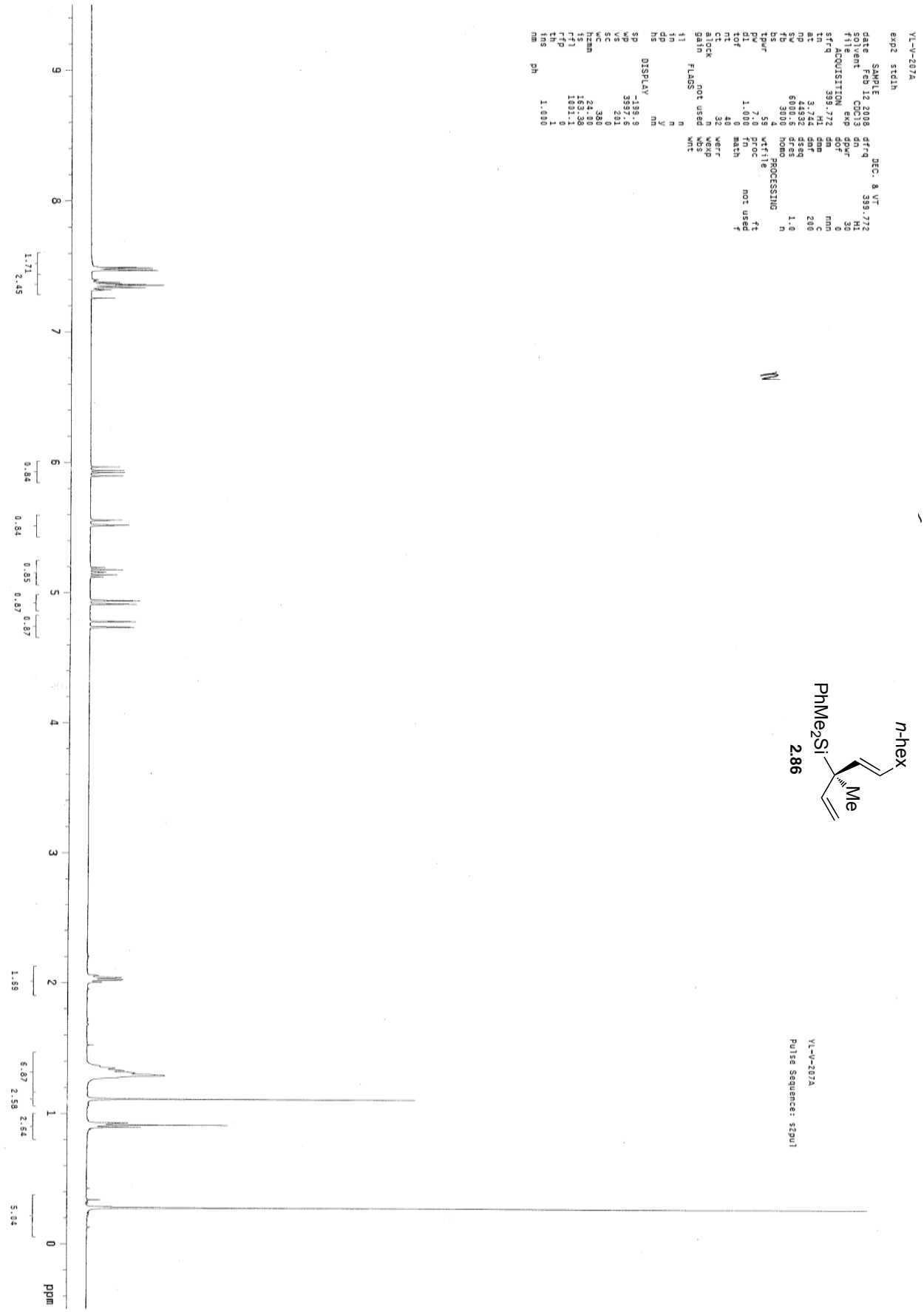

FG-I-124-A-H1
Pulse Sequence: s2pul
exp1 stdih
SAMPLE
date Jul 23 2008
solvent CDCl3
file
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 40
ct 40
alock n
gain 40
FLAGS not used
i1 n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 183
sc 0
wc 380
hzmm 2.53
rfl 621.14
rfp 1601.1
th 2
ins 1
nm
ph 1.000
DEC. & VT
dfrq 399.772
dn H1
dpwr 30
dof 0
dm nnn
dmm ccc
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
not used f
7.262
7.261
7.258
5.854
5.827
5.810
5.783
5.420
5.417
5.415
5.381
5.378
5.375
5.317
5.301
5.284
5.278
5.262
5.245
4.983
4.978
4.956
4.952
4.917
4.912
4.873
4.869
2.033
2.017
2.000
1.997
1.984
1.981
1.747
1.739
1.713
1.706
1.701
1.697
1.687
1.644
1.638
1.608
1.547
1.544
1.356
1.342
1.336
1.324
1.316
1.307
1.296
1.292
1.284
1.277
1.274
1.267
1.261
1.216
1.192
1.184
1.173
1.161
1.150
1.143
1.136
1.128
1.120
1.113
1.107
1.102
1.079
1.072
1.047
1.012
0.940
0.916
0.908
0.892
0.885
0.875
0.858
1.00
1.04
1.03
1.05
1.02
2.09
4.21
1.07
9.05
3.14
4.16
5.49
ppm
n-hex
Me
2.85

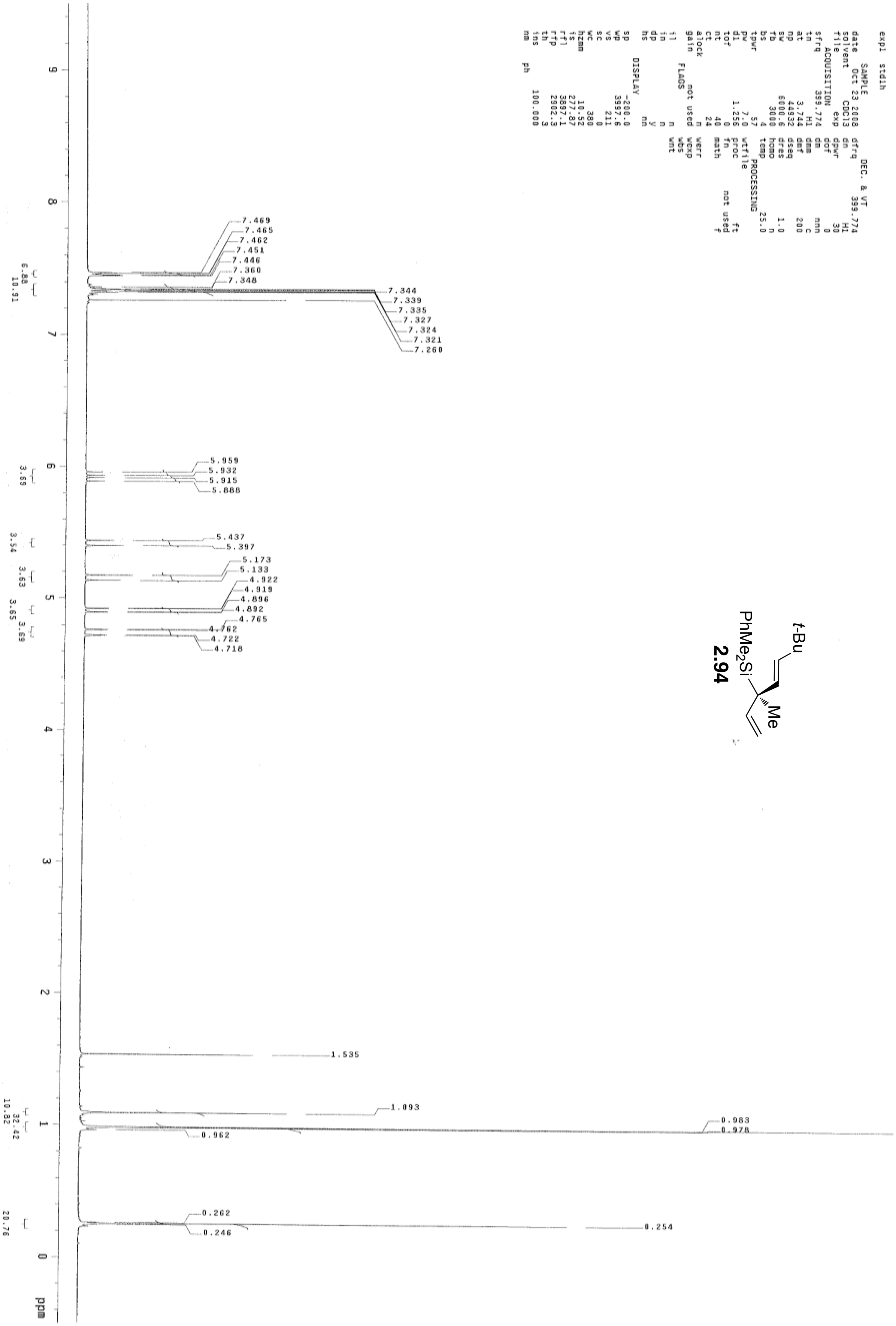

FG-I-162-A-pdt
Pulse Sequence: s2pul
exp1 stdih
SAMPLE
date Mar 22 2008
solvent CDCl3
file /ACQUISITION
sfrq 399.772 H1
tn H1
at 3.744
np 44932
sw 6000.6
fb 300.0
tpwr 59
pw 7.0
d1 1.000
tof 0
nt 40
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 201
sc 0
wc 380
hzmm 10.52
is 1001.52
rfl 1001.0
rfp 20
th 20
ins 1.000
nm
ph
DEC. & VT
dfrq 399.772
dn H1
dof 0
dm nnn
dmm c
dmf 200
homo 1.0
PROCESSING
wtfile n
ft
proc not used
math f
ppm
1.01
1.45
1.00
1.01
1.47
0.97
3.55
4.39
2.02
4.05
S1R1 S2R2
S3R3
S4R4
S5R5
S6R6
S1R1 S2R2
S3 R3
S4
S5
R4
R5
S6 R6
n-hex
MeO
Ph
CF3

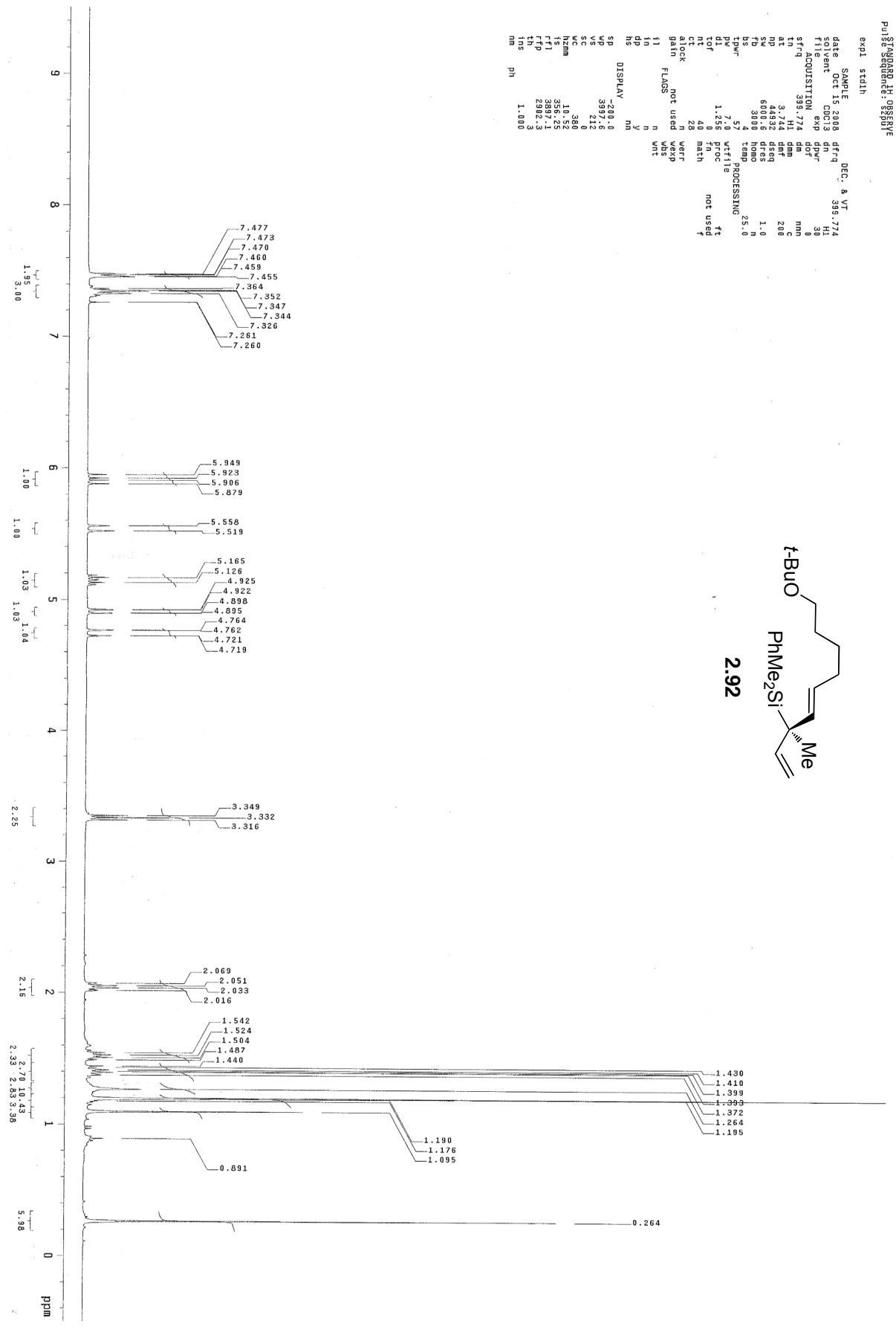

FG-I-243-S-pdt
Pulfg_1pguosspdt2pul
expl stdih
SAMPLE
date May 26 2008
solvent CDCl3
file expt
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 300.0
bs 59
tpwr 48
pw 7.0
dl 1.000
tof 0
nt 40
ct 24
alock werr
gain wet
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -189.9
wp 3997.5
vs 200
sc 0
wc 380
hzmm 1.89
alfa 585.1e4
flfl 1001.0
flfp 1
th 2
ins 1.000
ph
DEC. & VT
dfrq 399.772
dn H1
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo
PROCESSING
wtfile
proc ft
fn
not used
math
wexp
wnt
7.261
7.255
7.253
7.258
5.832
5.805
5.788
5.761
5.399
5.360
5.346
5.331
5.306
5.292
5.108
5.104
5.101
5.090
5.087
5.083
5.072
5.069
5.065
4.968
4.964
4.954
4.950
4.941
4.937
4.911
4.907
2.027
2.009
1.995
1.991
1.978
1.916
1.899
1.875
1.856
1.670
1.667
1.577
1.541
1.381
1.368
1.360
1.358
1.351
1.338
1.320
1.315
1.292
1.275
1.267
1.066
0.892
0.875
0.857
ppm
1.00
2.11
1.04
2.09
2.36
2.18
3.17
2.98
11.08
3.07
3.23
Me
Me
Me
n-hex
2.88

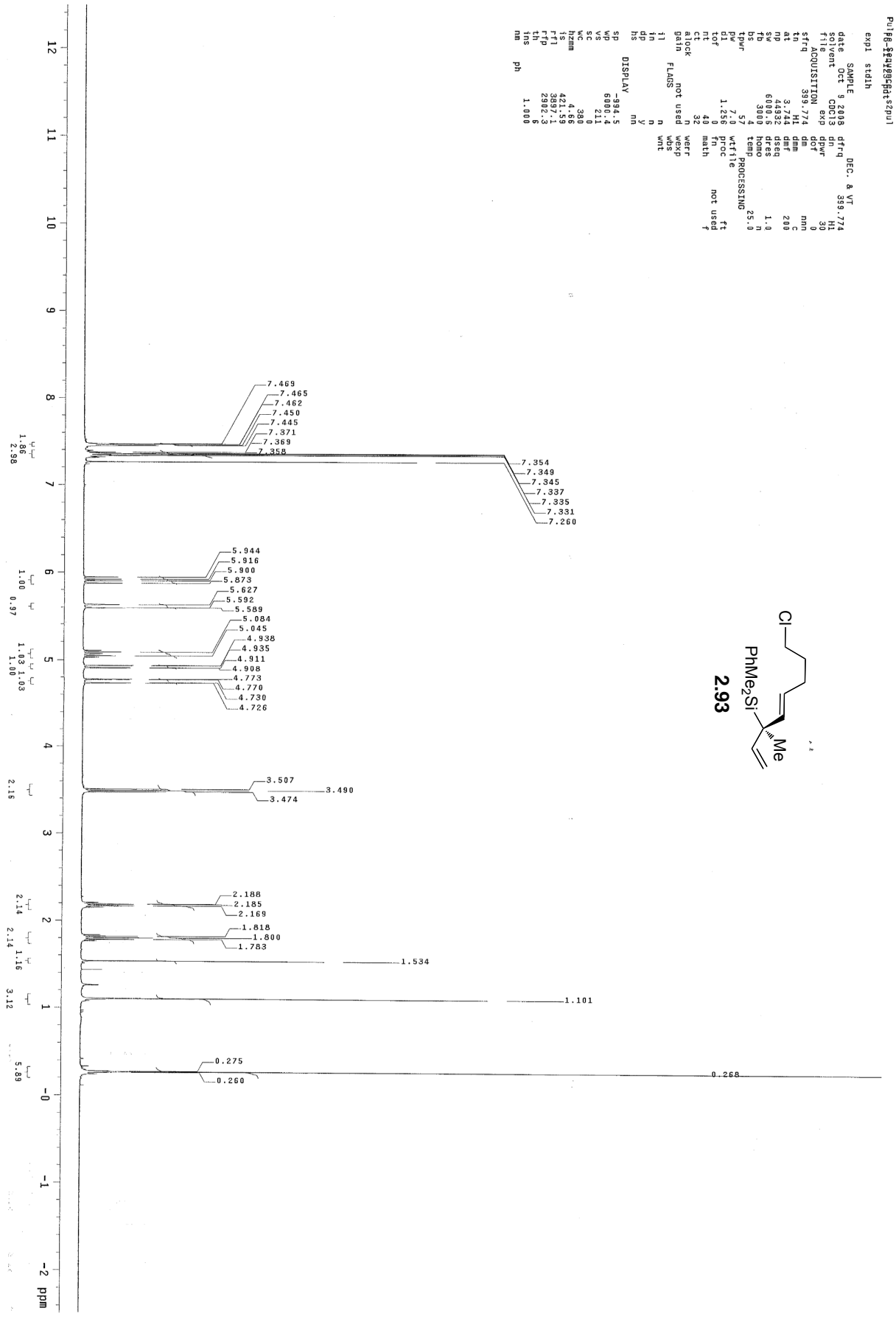

S1R1
S2R2
S3R3
S4R4
S5R5
S6R6
S7R7
S1
R1
S2
R2
S3
R3
S4
R4
S5
R5
S6
R6
S7
R7
n-hex
Ph
MeO
CF3
ppm

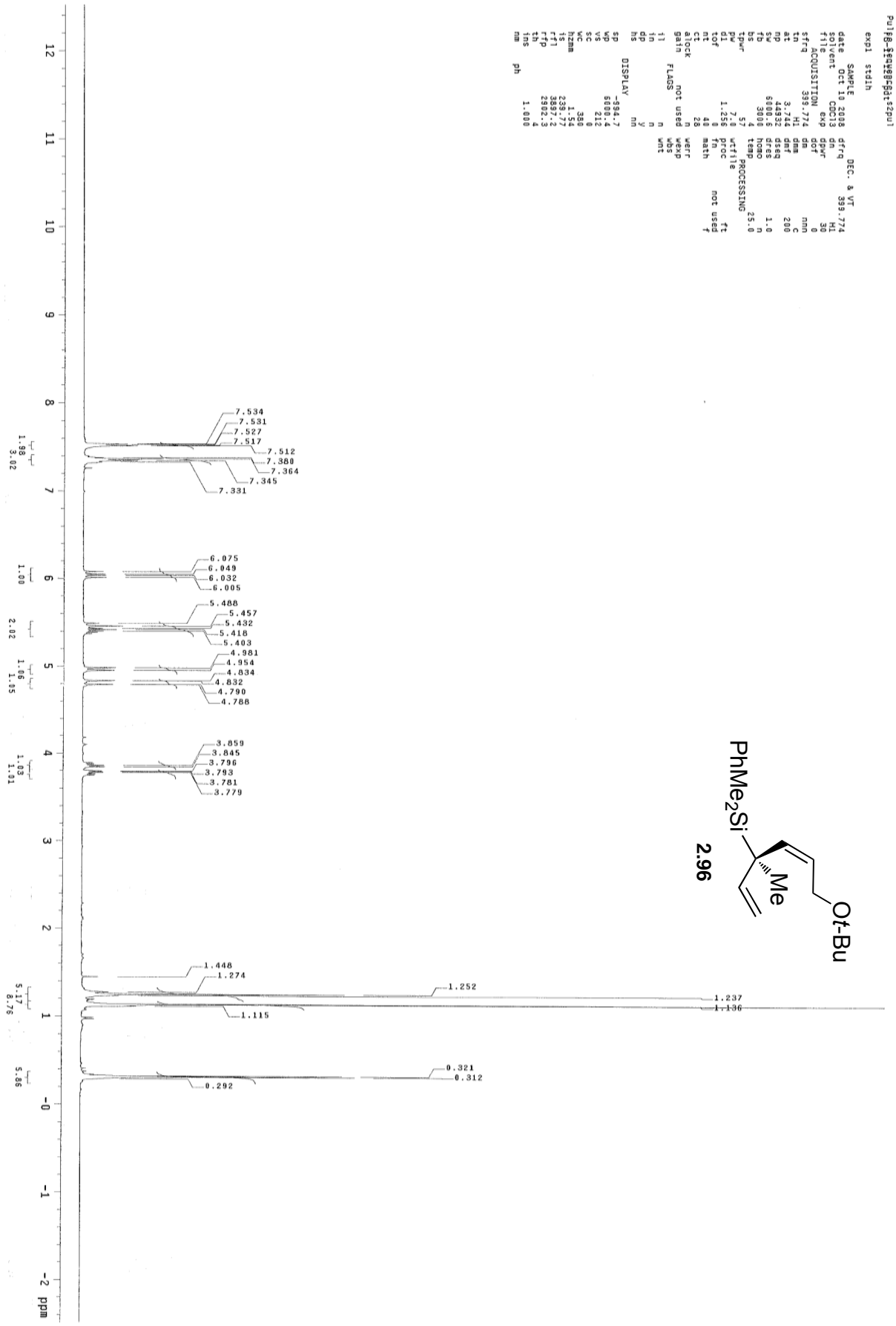

YL-V-116A
exp2 std1h
SAMPLE
date Nov 30 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 399.772
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs 4
tpwr 59
pw 7.0
d1 1.000
tof 0
nt 100
ct 16
alock n
gain wexp
FLAGS wbs
not used wnt
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 151
sc 0
wc 250
hzmm 24.00
is 293.19
rfl 1001.1
rfp 0
th 20
ins 1.000
nm ph
DEC. & VT
dfrq 399.772
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt
n-hex
t-BuO
Me
2.87
0.20
0.85
0.90
1.01
1.88
1.95
9.61
11.37
3.13
9
8
7
6
5
4
3
2
1
0
ppm

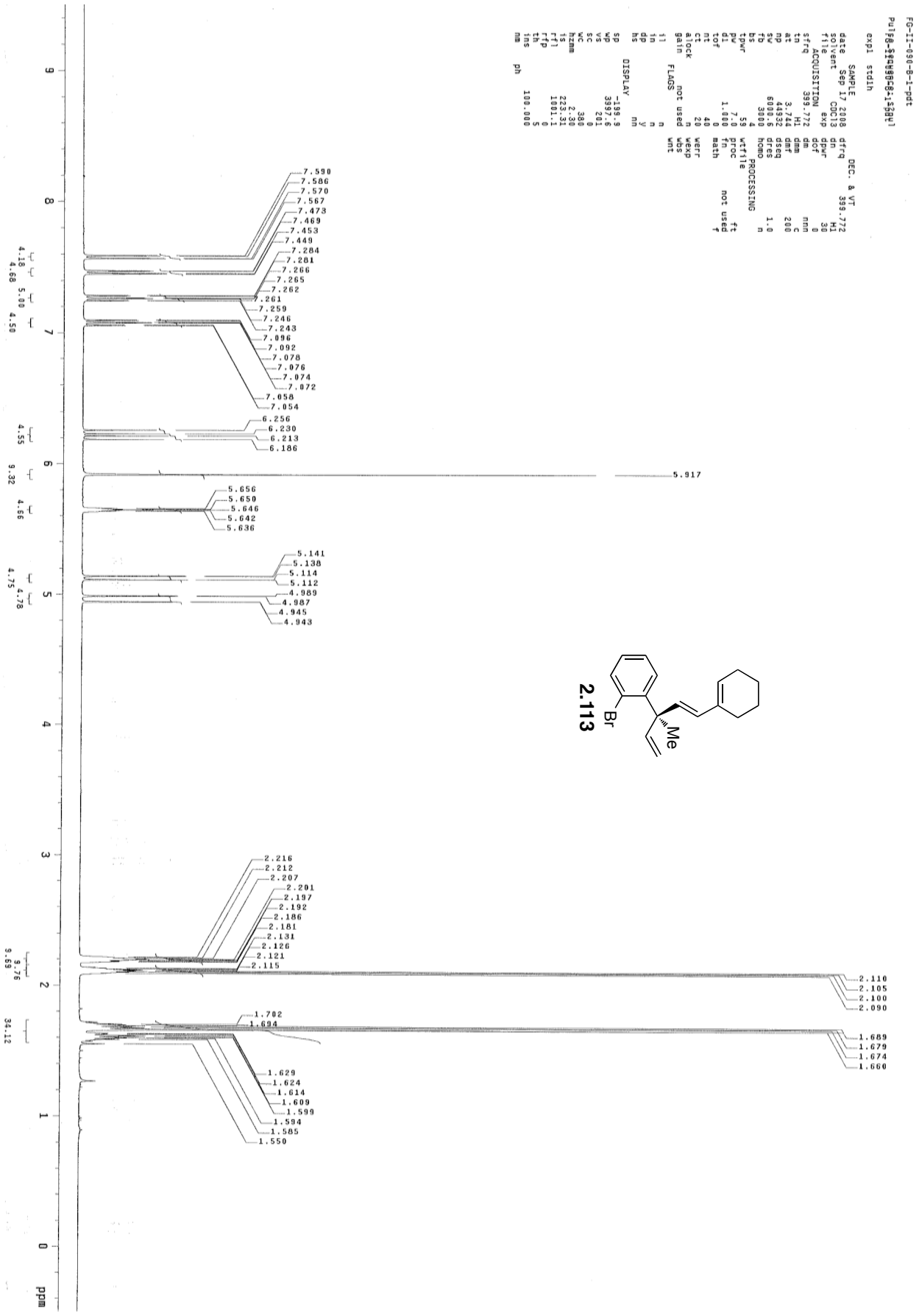

YL-V-207A
exp2 std1h
SAMPLE
date Feb 12 2008
solvent CDCl3
file ACQUISITION
sfrq 399.772 MHz
tn H1
at 3.744
np 44932
sw 6000.6
fb 3000
bs 54
tpwr 59
pw 7.10
pl1 1.00
tof 0
nt 40
ct 32
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -199.9
wp 3997.6
vs 201
sc 0
wc 380
hzmm 24.00
is 153.38
rfl 1001.4
rfp 0
th 1
ins 1
nm 1.000
ph
DEC. & VT
dfrq 399.772
dn H1
dof 30
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
ft
math not used
werr
wexp
wbs
wnt
n-hex
PhMe2Si
Me
2.86
YL-V-207A
Pulse Sequence: s2pul
ppm
1.71
2.45
0.84
0.84
0.85
0.87
0.87
1.89
6.87
2.58
2.64
5.04


FG-II-136-B-pdt
Pulse Sequence: s2pul
7.469
7.465
7.462
7.451
7.446
7.360
7.348
7.344
7.339
7.335
7.327
7.324
7.321
7.260
5.959
5.932
5.915
5.888
5.437
5.397
5.173
5.133
4.922
4.919
4.896
4.892
4.765
4.762
4.722
4.718
1.535
1.093
0.983
0.978
0.962
0.262
0.254
0.246
6.88
10.91
3.69
3.54
3.63
3.65
3.69
32.42
10.82
20.76
ppm
t-Bu
PhMe2Si
Me
2.94


STANDARD 1H OBSERVE
Pulse Sequence: szput
exp1 std1h
SAMPLE
date Oct 15 2008
solvent CDCl3
file exp
ACQUISITION
sfrq 399.774
tn H1
at 3.741
np 44932
sw 6000.6
fb 3000
bs 4
tpwr 57
pw 7.250
d1 1.000
tof 40
nt 28
ct n
alock werr
gain dseq
dres
homo
temp
PROCESSING
wtfile
proc
math
not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -200.0
wp 399.6
vs 2170
sc 0
wc 360
hzmm 10.52
is 356.25
rfl 3897.1
rfp 2902.3
th 3
ins 1
nm ph
DEC. & VT
dfrq 399.774
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
ft
not used f
7.477
7.473
7.470
7.460
7.459
7.455
7.364
7.352
7.347
7.344
7.326
7.261
7.260
5.949
5.923
5.906
5.879
5.558
5.519
5.165
5.126
4.925
4.922
4.898
4.895
4.764
4.762
4.721
4.719
3.349
3.332
3.316
2.069
2.051
2.033
2.016
1.542
1.524
1.504
1.487
1.440
1.430
1.410
1.399
1.393
1.372
1.264
1.195
1.190
1.176
1.095
0.891
0.264
1.95
3.00
1.00
1.00
1.03
1.03
1.04
2.25
2.16
2.70
10.43
2.33
2.83
3.38
5.98
ppm
t-BuO
PhMe2Si
Me
2.92

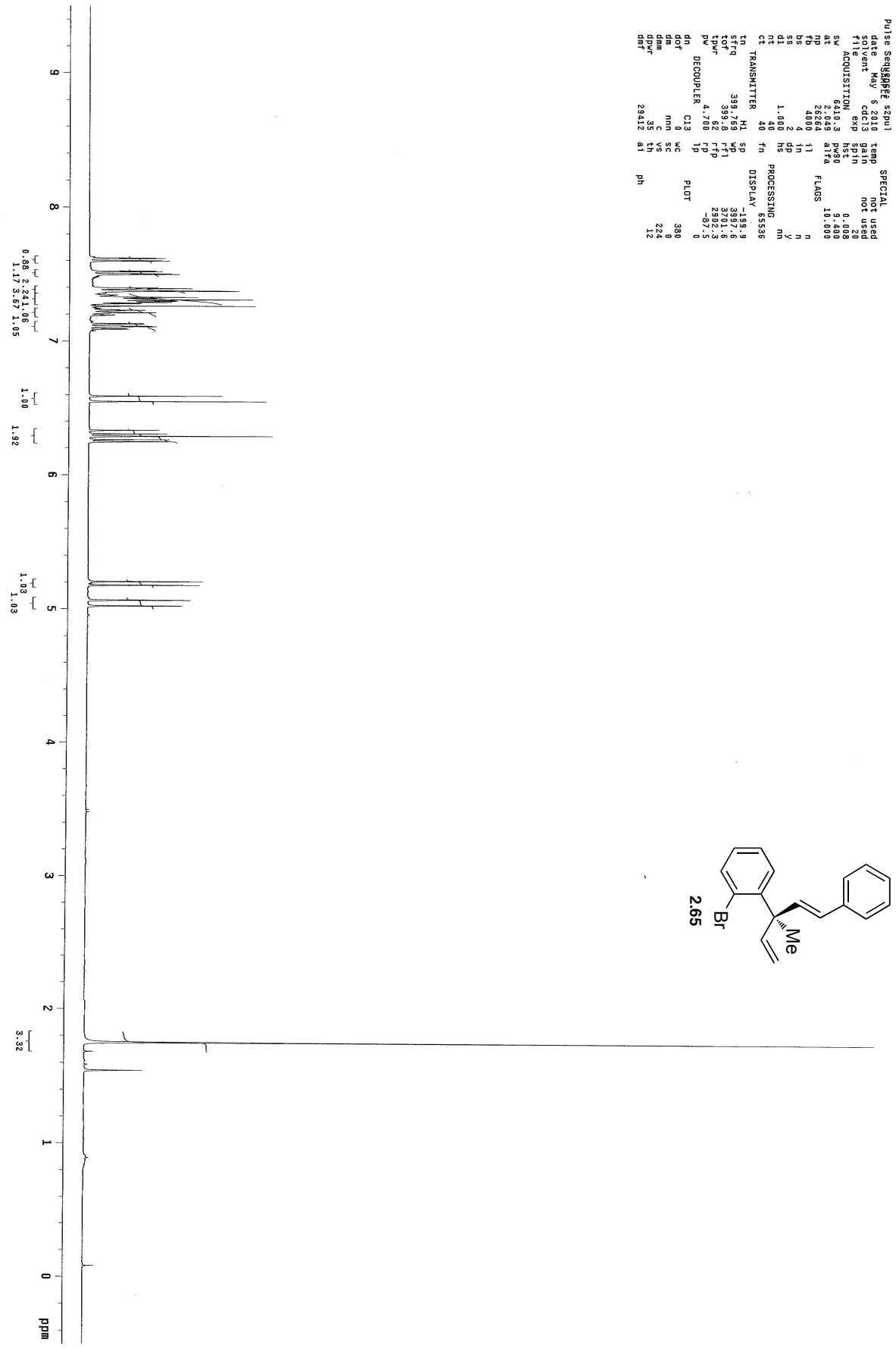

FG-II-123-pdt
Pulprog zgpg30
expl stdih
SAMPLE
date Oct 9 2013
solvent CDCl3
file exp
ACQUISITION
sfrq 399.774 MHz
tn H1
at 3.744 sec
np 44932
sw 6000.6 Hz
fb 300.0 Hz
bs 57
tpwr 57 dB
pw 7.0 usec
d1 1.256 sec
tof 0 Hz
nt 40
ct 32
alock n
gain n
FLAGS not used
il n
in n
dp y
hs nn
DISPLAY
sp -994.5 Hz
wp 6000.4 Hz
vs 211
sc 0
wc 380
hzmm 4.66
th 421.59
rfl 3851.1
rfp 2892.3
th 6
ins 1.000
nm
ph
DEC. & VT
dfrq 399.774 MHz
dn H1
dof 0 Hz
dm nnn
dmm c
dmf 200 Hz
dseq
dres 1.0
homo n
temp 25.0 C
PROCESSING
wtfile
proc ft
ft
fn not used
math f
wexp
wbs
wnt
7.469
7.465
7.462
7.450
7.445
7.371
7.369
7.358
7.354
7.349
7.345
7.337
7.335
7.331
7.260
5.944
5.916
5.900
5.873
5.627
5.592
5.589
5.084
5.045
4.938
4.935
4.911
4.908
4.773
4.770
4.730
4.726
3.507
3.490
3.474
2.188
2.185
2.169
1.818
1.800
1.783
1.534
1.101
0.275
0.260
0.268
1.86
2.98
1.00
0.97
1.03
1.00
2.16
2.14
2.14
1.16
3.12
5.89
Cl
PhMe2Si
Me
2.93
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2
ppm

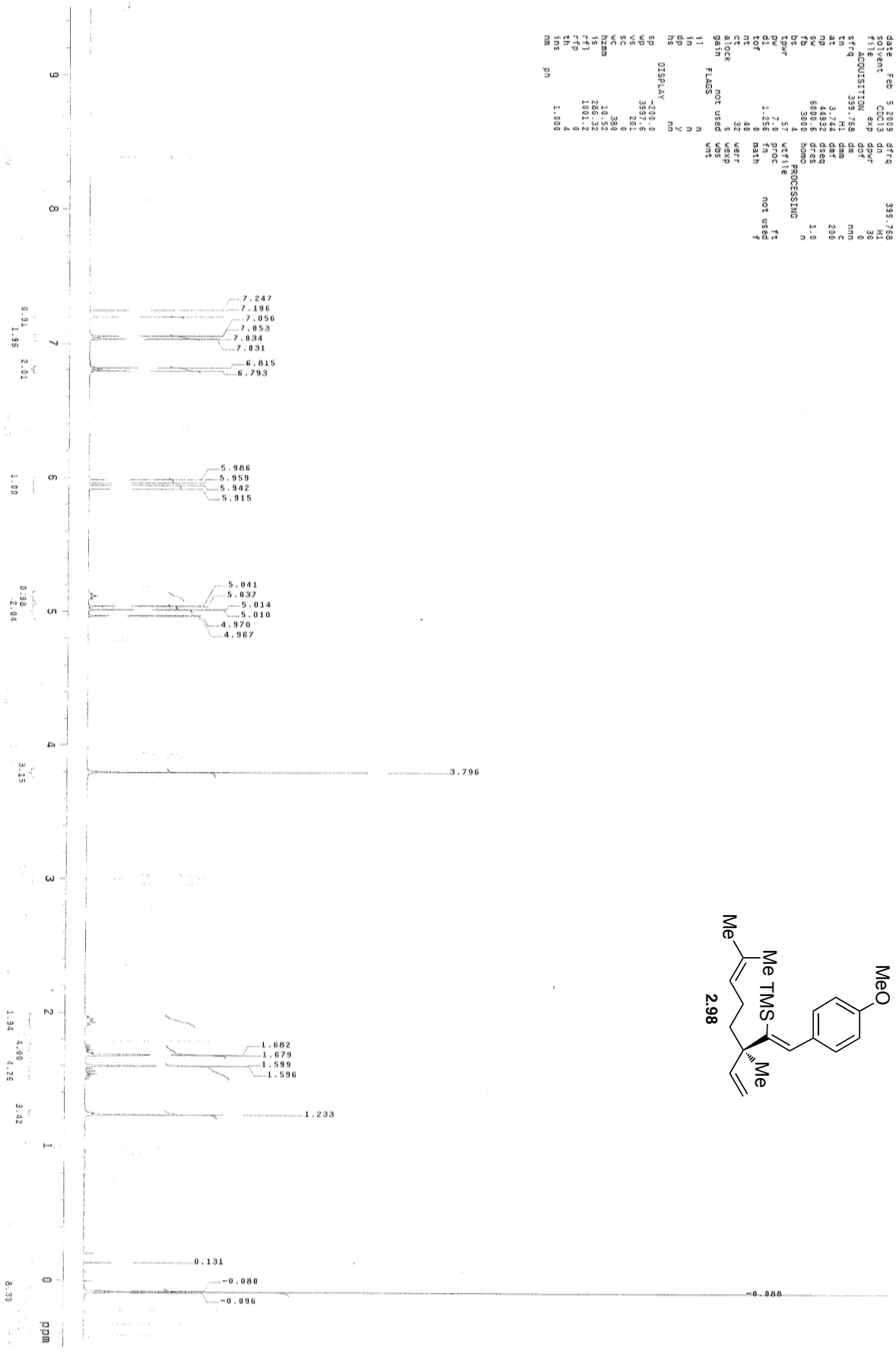

PhMe2Si
Me
Ot-Bu
2.96
7.534
7.531
7.527
7.517
7.512
7.380
7.364
7.345
7.331
6.075
6.049
6.032
6.005
5.488
5.457
5.432
5.418
5.403
4.981
4.954
4.834
4.832
4.790
4.788
3.859
3.845
3.796
3.793
3.781
3.779
1.448
1.274
1.252
1.237
1.136
1.115
0.321
0.312
0.292
ppm

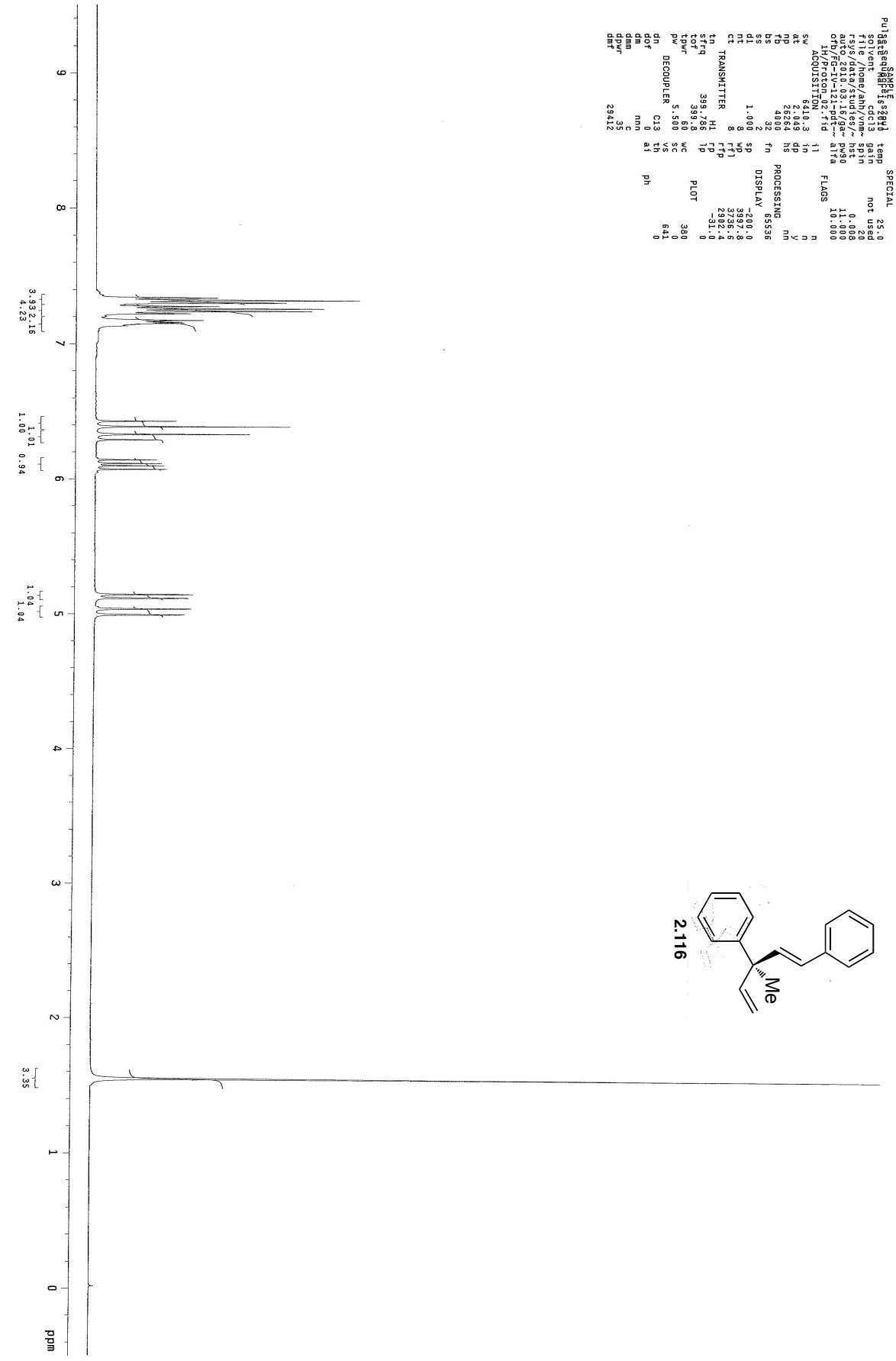

7.590
7.586
7.570
7.567
7.473
7.469
7.453
7.449
7.284
7.281
7.266
7.265
7.262
7.261
7.259
7.246
7.243
7.096
7.092
7.078
7.076
7.074
7.072
7.058
7.054
6.256
6.230
6.213
6.186
5.917
5.656
5.650
5.646
5.642
5.636
5.141
5.138
5.114
5.112
4.989
4.987
4.945
4.943
2.216
2.212
2.207
2.201
2.197
2.192
2.186
2.181
2.131
2.126
2.121
2.115
2.110
2.105
2.100
2.090
1.702
1.694
1.689
1.679
1.674
1.660
1.629
1.624
1.614
1.609
1.599
1.594
1.585
1.550
ppm

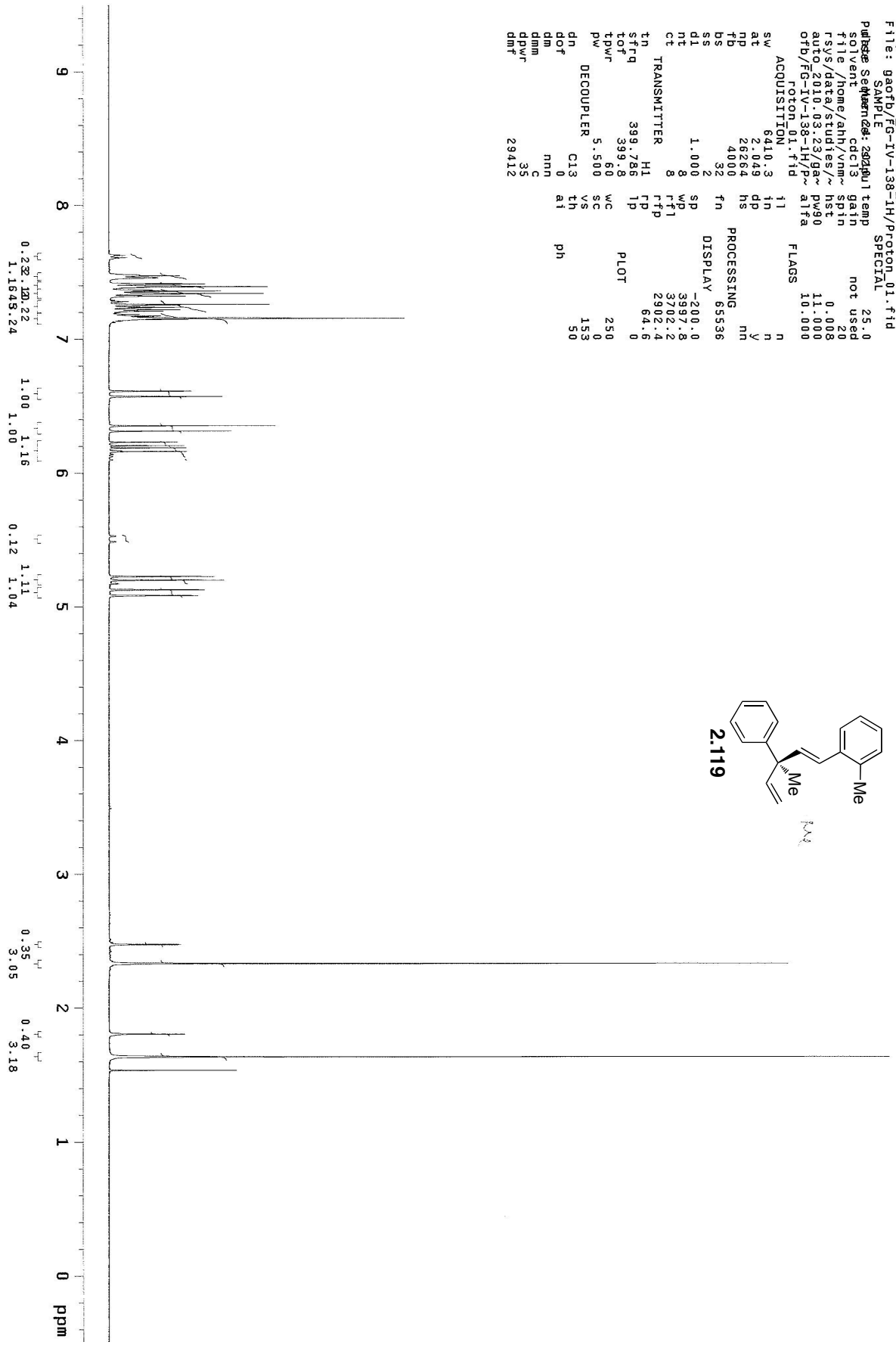
Br
Me

2.113


Sample: FG-IV-218-pdt
File: exp\Proton
Pulse Sequence: s2pul
date May 6 2010
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 2.049
np 26204
fb 400
bs 4
ss 2
d1 1.000
nt 40
ct
TRANSMITTER
tn H1
sfrq 399.763
tof 339.8
tpwr 62
pw 4.700
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dmf 35
dpwr
dmf 29412
SPECIAL
temp not used
gain not used
spin 20
0.008
pw90 9.400
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn 65536
DISPLAY
sp -197.9
wp 3701.6
rfl 3701.6
rfp 2902.3
rp -87.5
lp 0
PLOT
wc 380
sc 0
vs 224
th 12
ai
ph
0.88 2.24 1.06
1.17 3.67 1.05
1.00
1.92
1.03
1.03
3.32
Br
Me
2.65
9
8
7
6
5
4
3
2
1
0
ppm


7.247
7.196
7.056
7.053
7.034
7.031
6.815
6.793
5.986
5.959
5.942
5.915
5.041
5.037
5.014
5.010
4.970
4.967
3.796
1.682
1.679
1.599
1.596
1.233
0.131
-0.080
-0.096
-0.088
ppm
Me
Me TMS
Me
MeO
2.98


Sample: FG-IV-121-pdt-AH
Sample Id: FG-IV-121-pdt-AH
File: gabb/FG-IV-121-pdt-1H/Proton_02.fid
Pulse Sequence: s2pul
Solvent: CDCl3
File /home/ahb/vnmr spin
rsys/data/studies/ hst
auto_2010.03.16/ga pw90
orb/FG-IV-121-pdt pl1
1H/Proton_02.fid
ACQUISITION
sw 6410.3
at 2.043
np 26264
fb 4000
bs 32
ss 2
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.786
tof 399.8
tpwr 60
pw 5.500
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dmf 29412
SPECIAL
temp 25.0
gain 20
not used
0.008
11.000
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn 65536
DISPLAY
sp -200.0
wp 3997.8
rfl 3978.4
rfp 2232.4
lp -31.0
PLOT
wc 380
sc 0
vs 641
th 0
ph
INDEX FREQUENCY PPM HEIGHT
1 511.3 8.331 58.2
2 510.8 8.323 -27.2
3 510.3 8.315 573.2
3.93 2.16
4.23
1.01
1.00 0.94
1.04
1.04
3.35
Me
2.116
9
8
7
6
5
4
3
2
1
0
ppm


Sample: FG-IV-138-1H
Sample ID: proton_00324_004
File: gaofb/FG-IV-138-1H/proton_01.fid
SAMPLE
Pulse Sequence: s2pul
solvent cdcl3
file /home/ahh/vnm~
rsys/data/studies/~
auto 2010-03-23/ga~
ofb/FG-IV-138-1H/p~
roton_01.fid
ACQUISITION
sw 6410.3
at 2.049
np 26264
fb 4000
bs 32
ss 2
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.786
tof 399.8
tpwr 60
pw 5.500
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 35
dmf 29412
SPECIAL
temp 25.0
gain not used
spin 20
hst 0.008
pw90 11.000
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn 65536
DISPLAY
sp -200.0
wp 3997.8
rfl 3702.2
rfp 2902.4
rp 64.6
lp 0
PLOT
wc 250
sc 0
vs 153
th 50
ph
Me
Me
2.119
9
8
7
6
5
4
3
2
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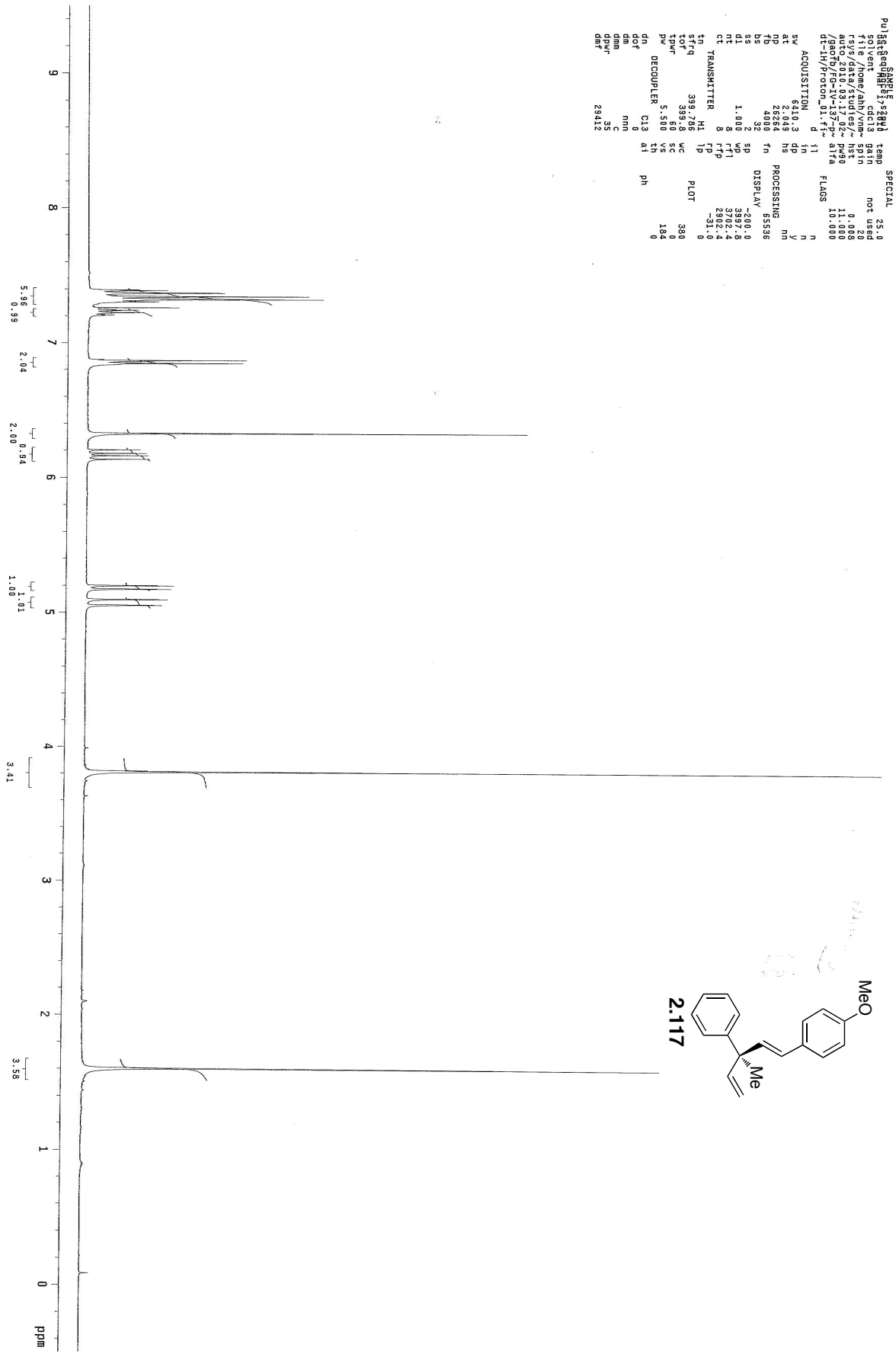
1.00
0.12 1.11
1.04
0.35
3.05
0.40
3.18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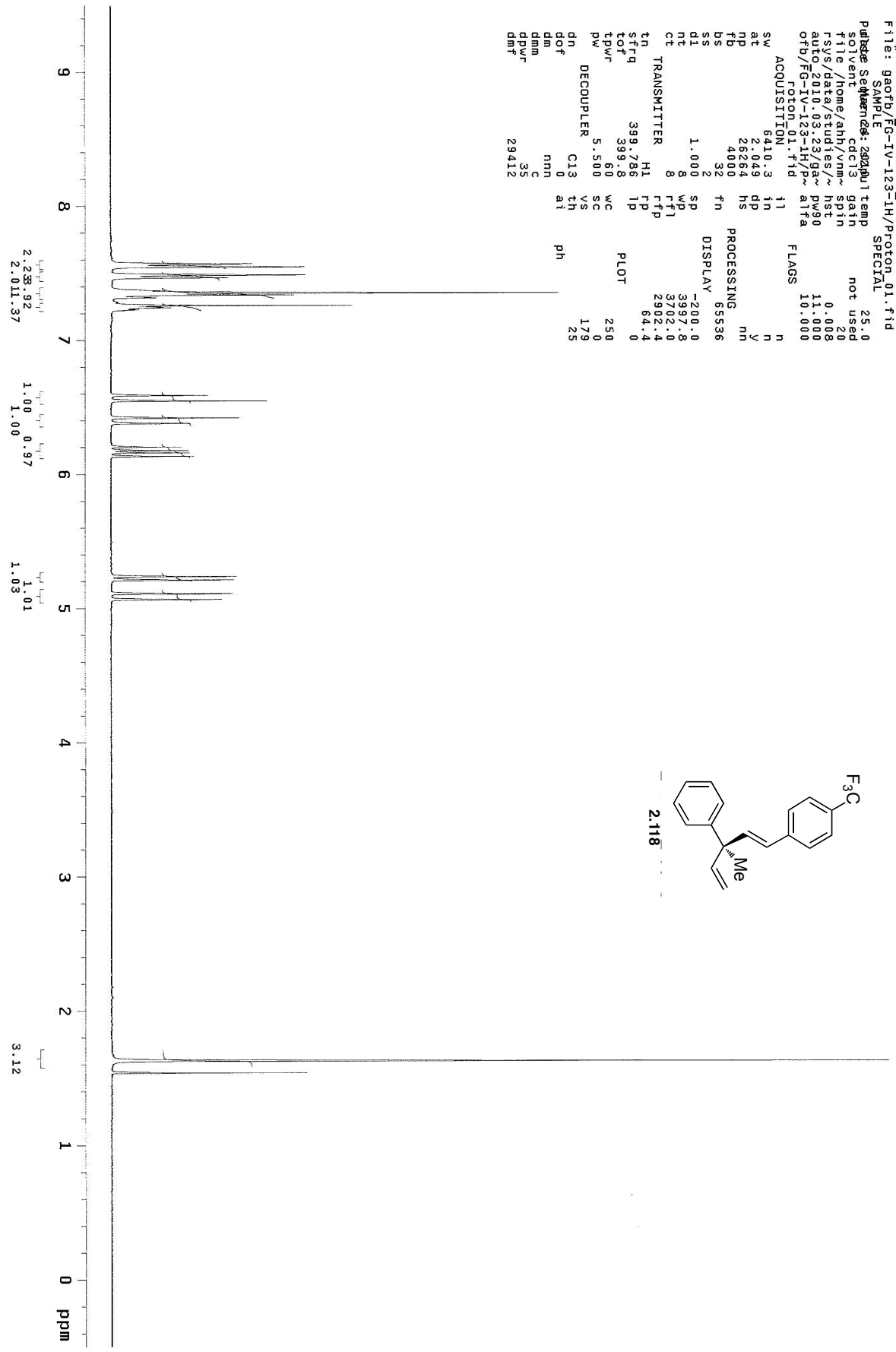
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nt 8
ct 8
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tof 399.8
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pw 5.500
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dmm c
dpwr 35
dmf 29412
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gain not used
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hst 0.008
pw90 11.000
alfa 10.000
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in n
dp y
hs nn
PROCESSING
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rfl 3702.0
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rp 64.4
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PLOT
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sc 0
vs 179
th 25
ai
ph
2.118
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8
7
6
5
4
3
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0.97
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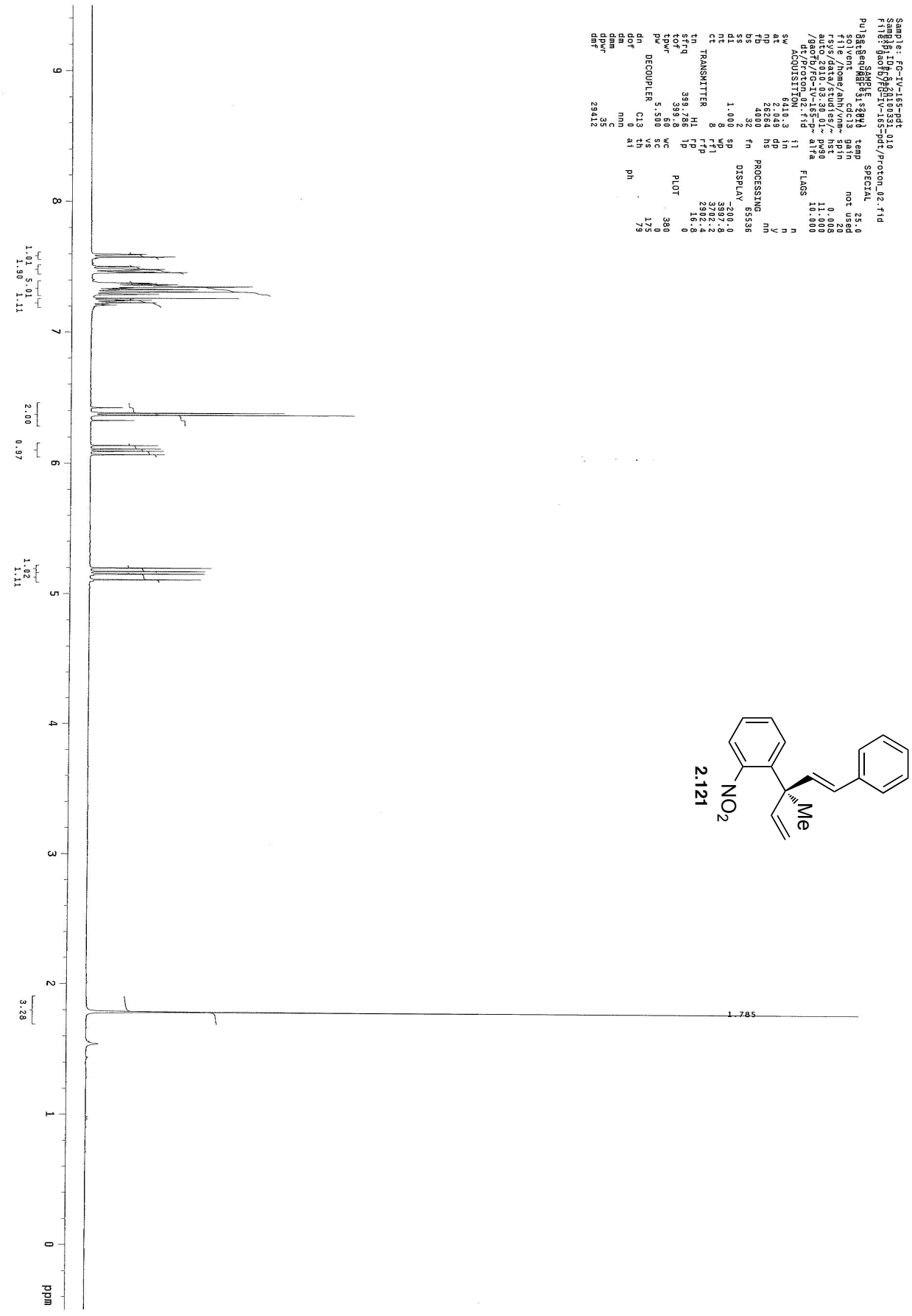
1.01
1.03
3.12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PLOT
DECOUPLER
TRANSMITTER
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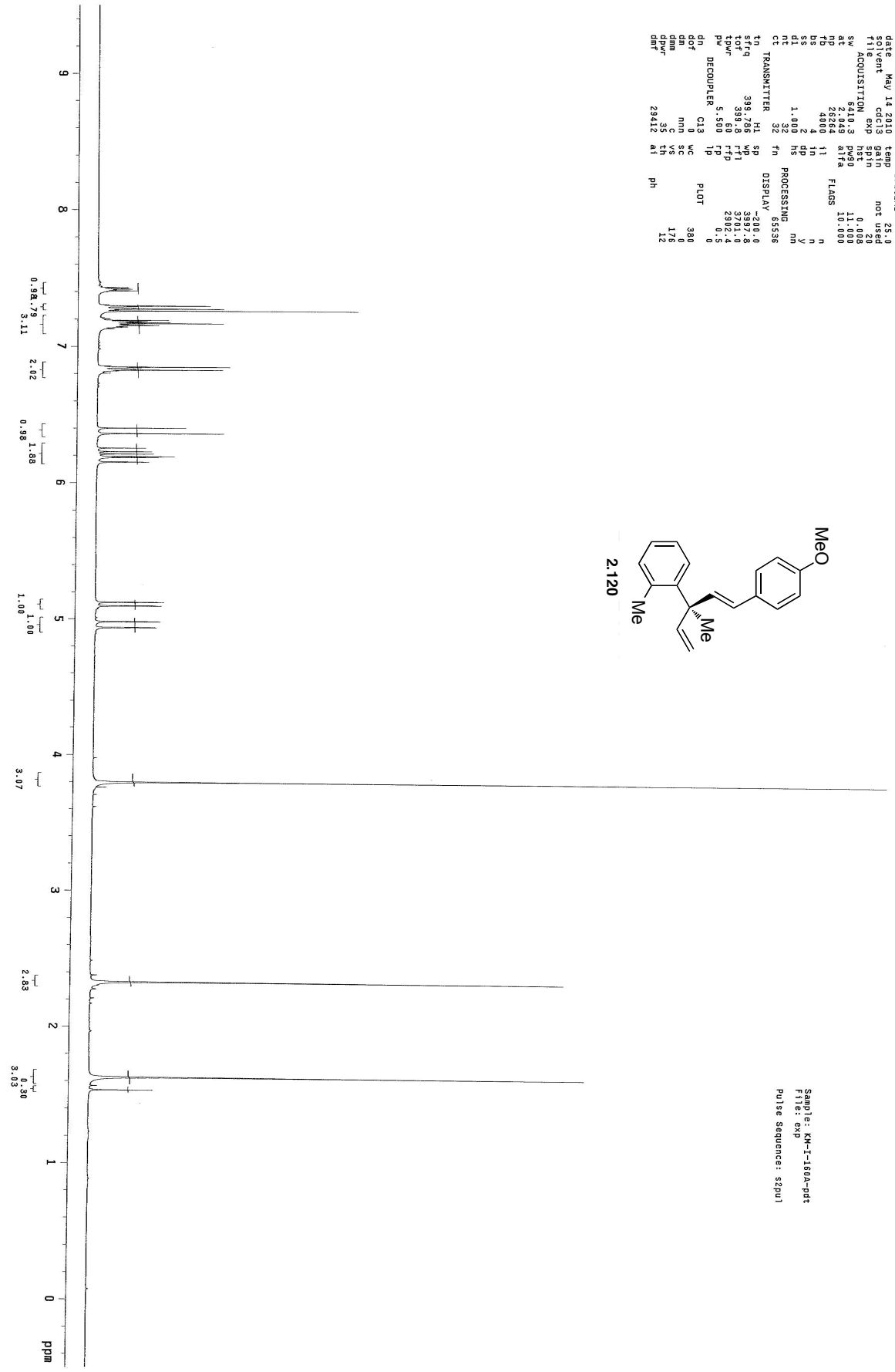
Me
ppm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d1 1.000
nt 32
ct 32
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sfrq 399.786
tof 399.8
tpwr 60
pw 5.500
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 35
dmf 29412
temp SPECIAL 25.0
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spin 20
nsp 0.088
pwSO 11.000
alfa 10.000
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dp y
hs nn
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PLOT
380
0
176
12
ph
MeO
Me
Me
2.120
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File: exp
Pulse Sequence: s2pul
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2.02
0.98
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1.00
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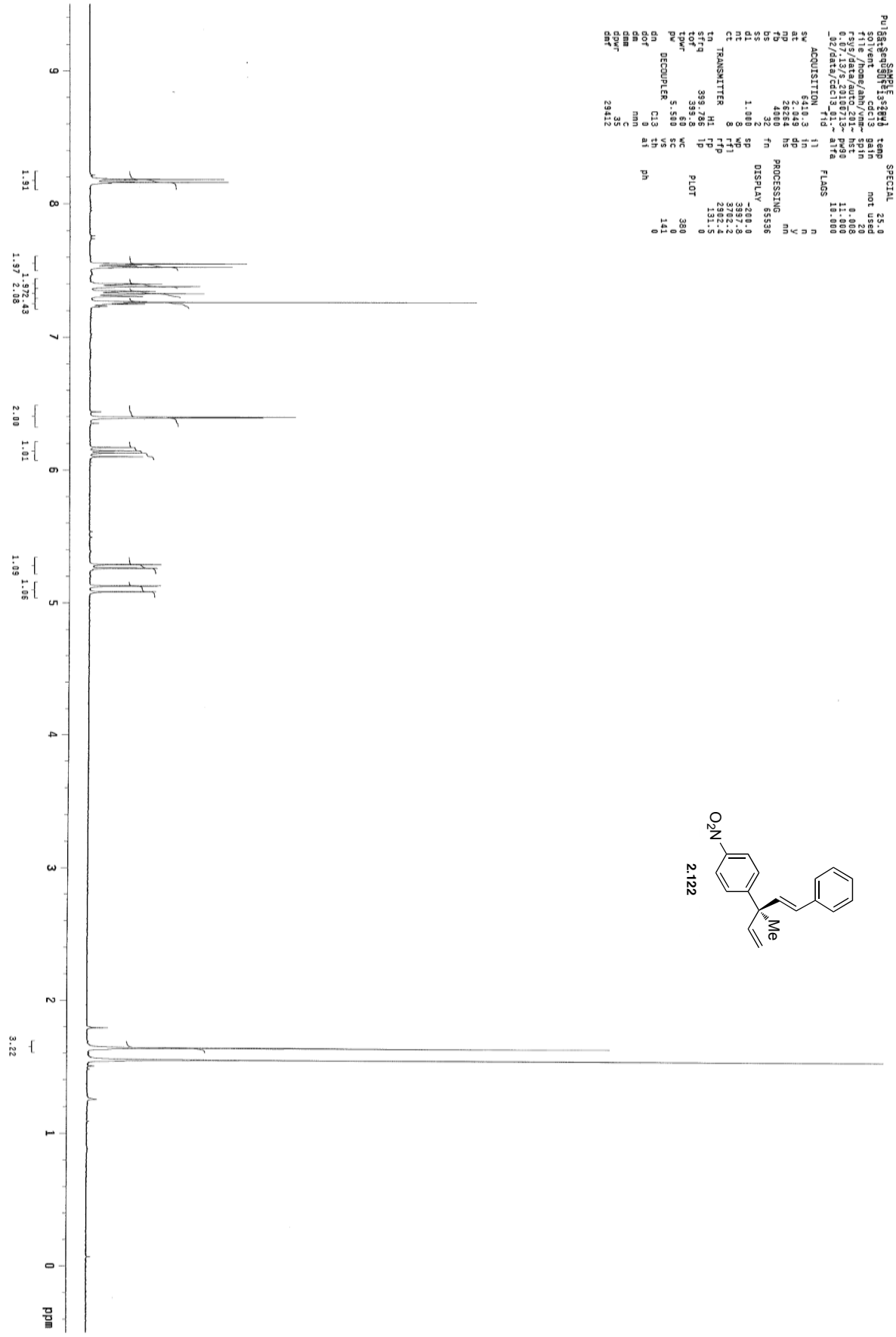
0.30
3.03
ppm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Ambient temperature
Pulse Sequence: s2pul
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0.07.13/s_20100713~ pw90 0.008
_02/data/cdcl3_01.~ alfa 11.000
FLAGS 10.000
ACQUISITION
sw 6210.3 fl n
at 2.949 in n
np 36254 dp y
fb 4000 hs nn
bs 32 fn 65536
ss 2 PROCESSING
d1 1.000 sp -200.0
nt 8 wp 3997.8
ct 8 rfl 3082.2
TRANSMITTER rfp 1082.4
tn H1 lp 191.5
sfrq 399.786 PLOT 0
tof 399.8 wc 380
tpwr 60 sc 0
pw 5.500 vs 141
DECOUPLER th 0
dn C13 ai
dof 0 ph
dm nnn
dmm c
dpwr 35
dmf 23412
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1.97 43
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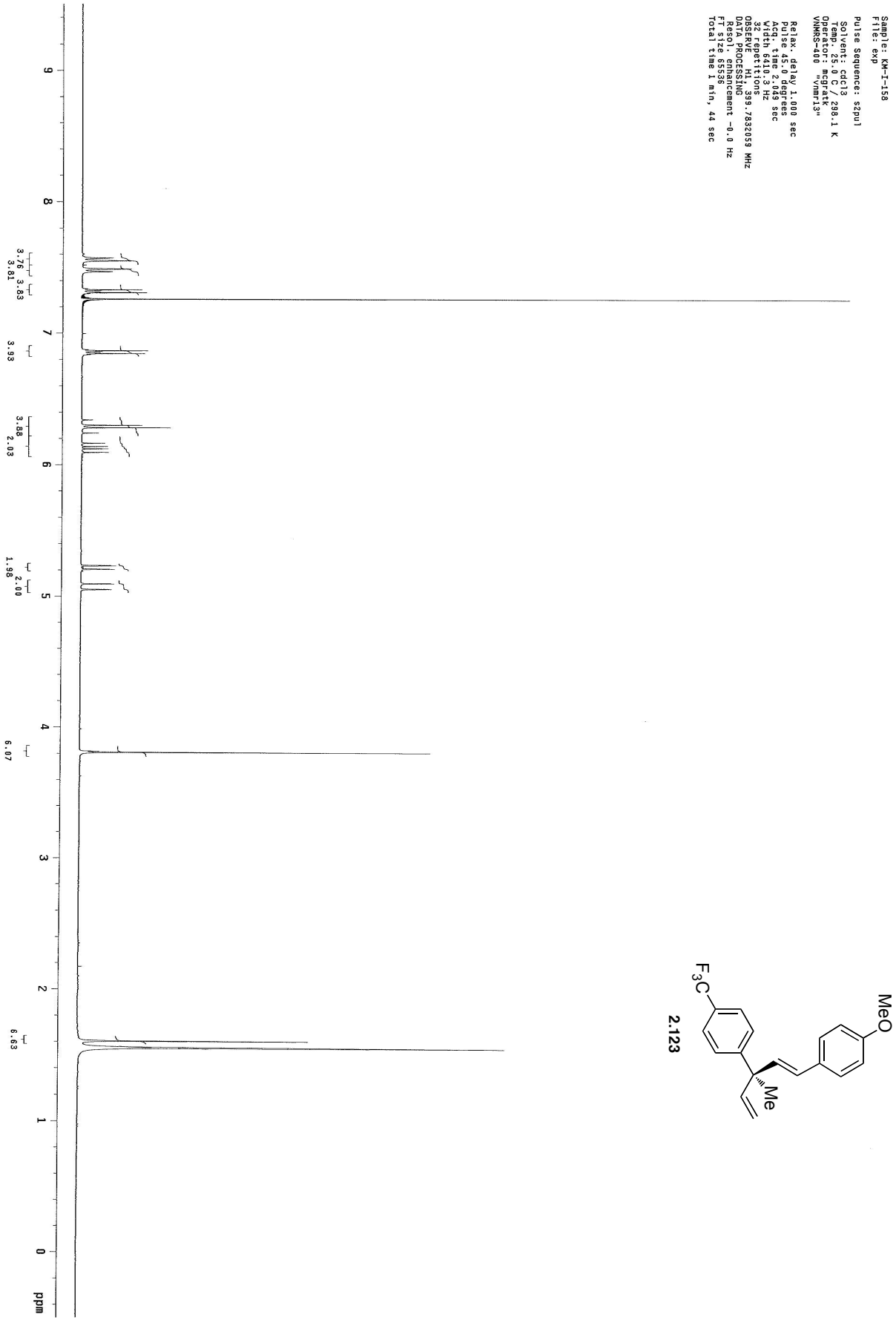
1.01
1.09
1.06
3.22
ppm
2.122
O_2N
Me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File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: mcgratk
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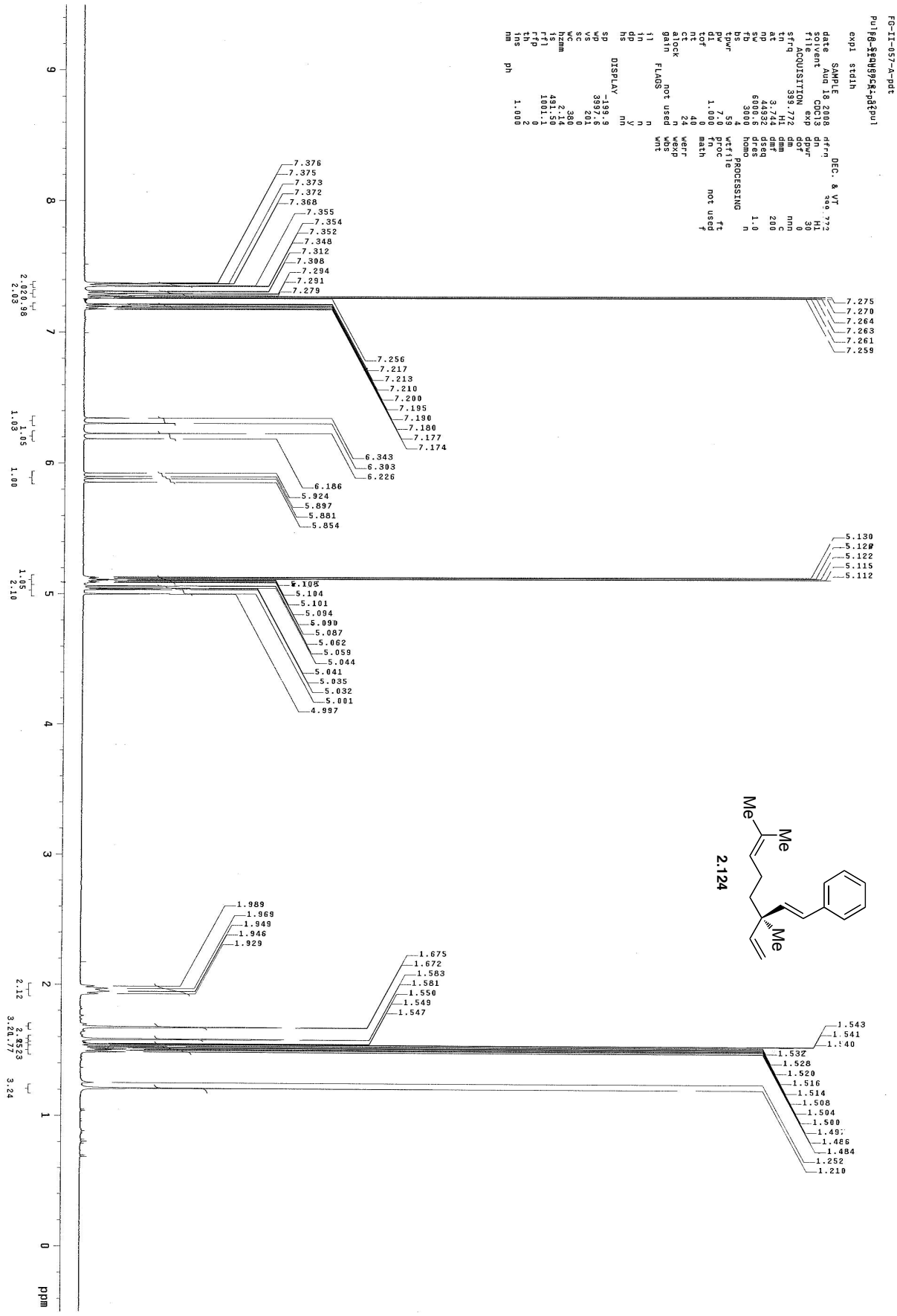
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.002 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.7832059 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 44 sec
3.76
3.81
3.83
3.93
3.88
2.03
1.98
2.00
6.07
6.63
ppm
F3C
MeO
Me
2.123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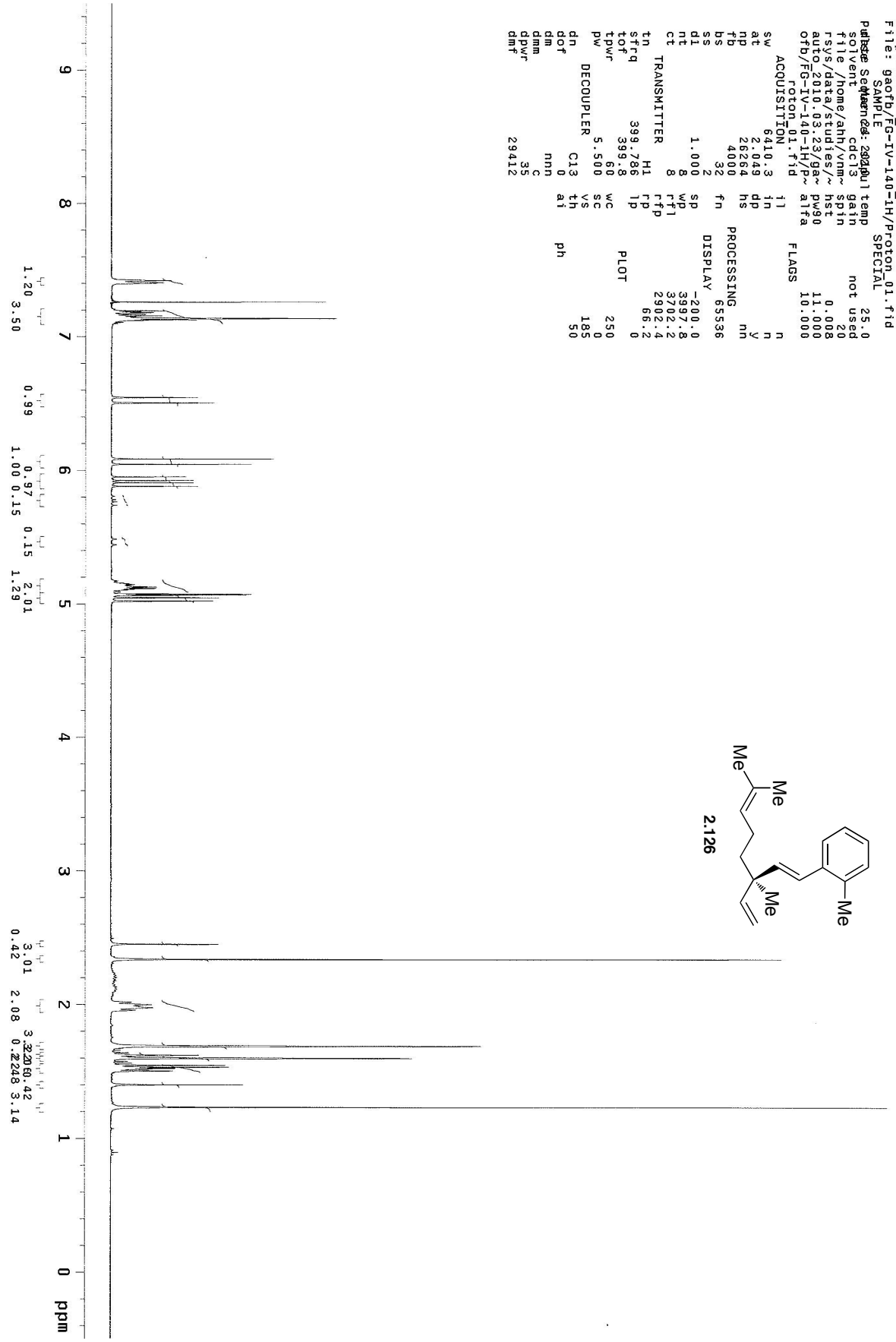
Me
Me
2.124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auto_2010.03.23/ga~
ofb/FG-IV-140-1H/p~
proton_01.fid
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np 26264
fb 4000
bs 32
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nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.786
tof 399.8
tpwr 60
pw 5.500
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 35
dmf 29412
temp 25.0
gain not used
spin 20
hst 0.008
pw90 11.000
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
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DISPLAY
sp -200.0
wp 3997.8
rfl 3702.2
rfp 2902.4
rp 66.2
lp 0
PLOT
wc 250
sc 0
vs 185
th 50
ai
ph
Me
Me
Me
Me
2.126
9
8
7
6
5
4
3
2
1
0
ppm
1.20
3.50
0.99
1.00
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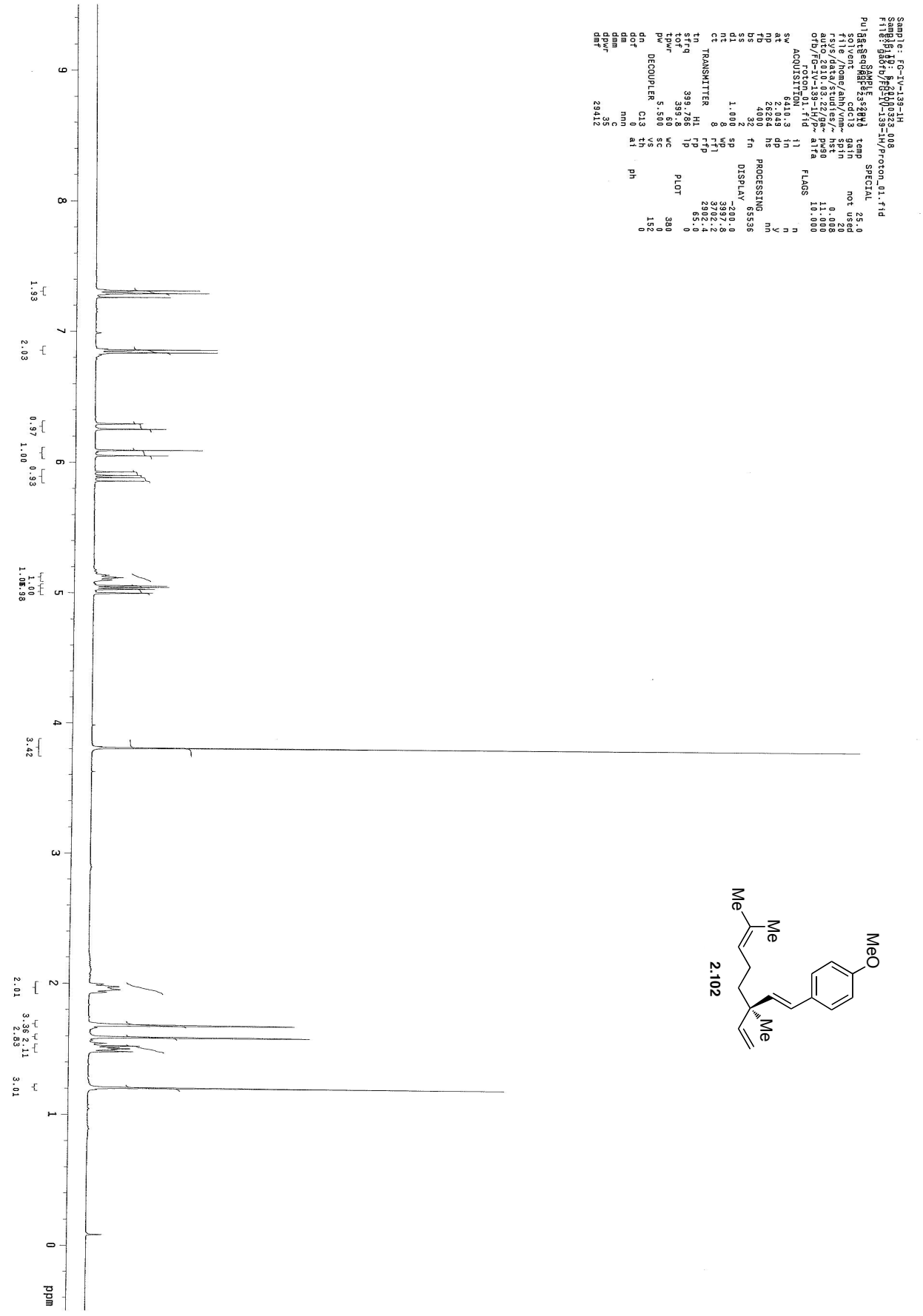
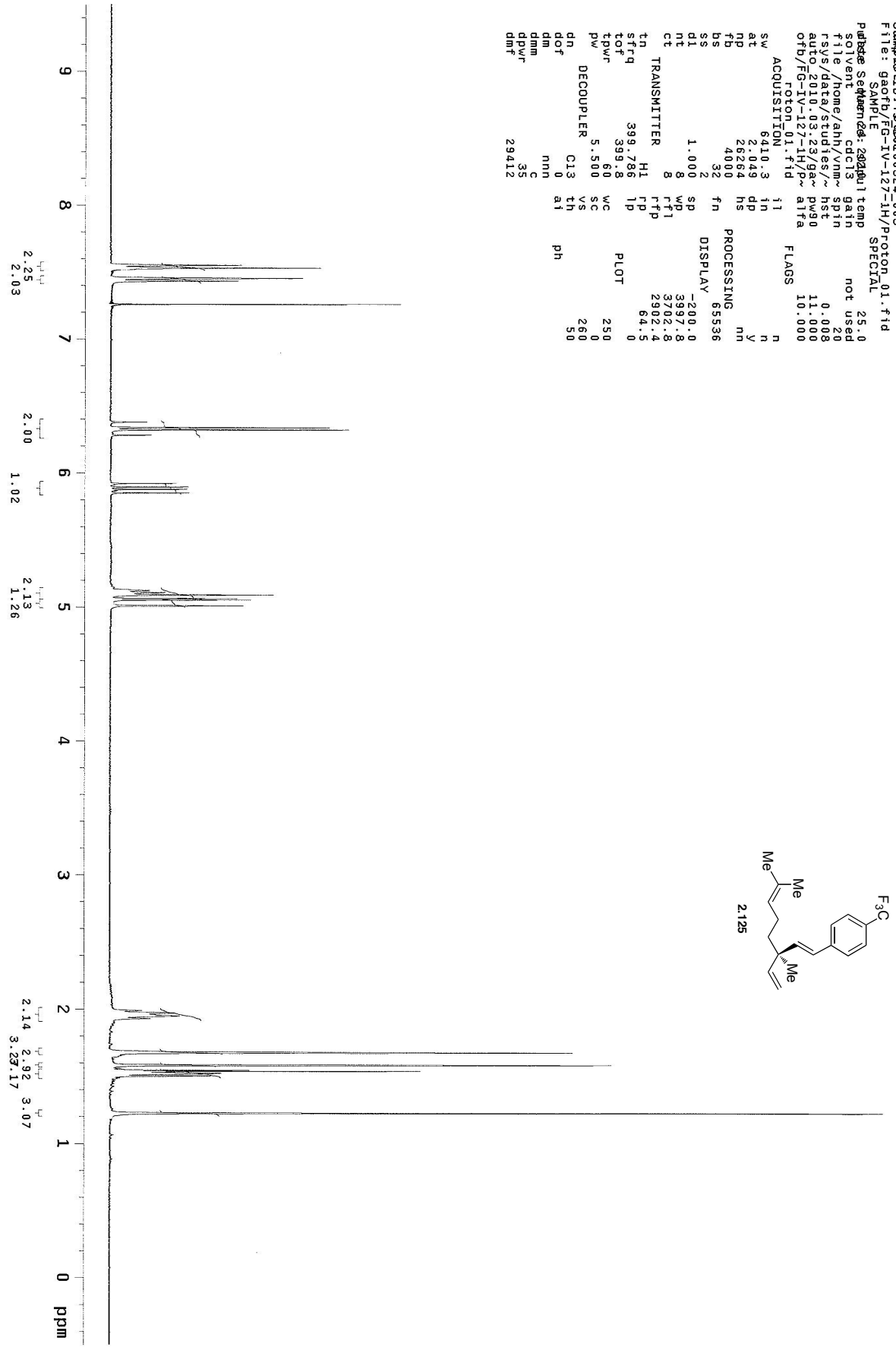
2.01
1.29
3.01
0.42
2.08
3.32
0.42
0.22
3.14


MeO
Me
Me
Me
2.102
ppm
1.93
2.03
0.97
1.00
0.93
1.10
1.06
0.98
3.42
2.01
3.36
2.11
2.83
3.01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Solvent: cdcl3
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SAMPLE
Pulse Sequence: s2pul
ACQUISITION
PROCESSING
DISPLAY
PLOT
TRANSMITTER
DECOUPLER
Me
Me
Me
F3C
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2.25
2.03
2.00
1.02
2.13
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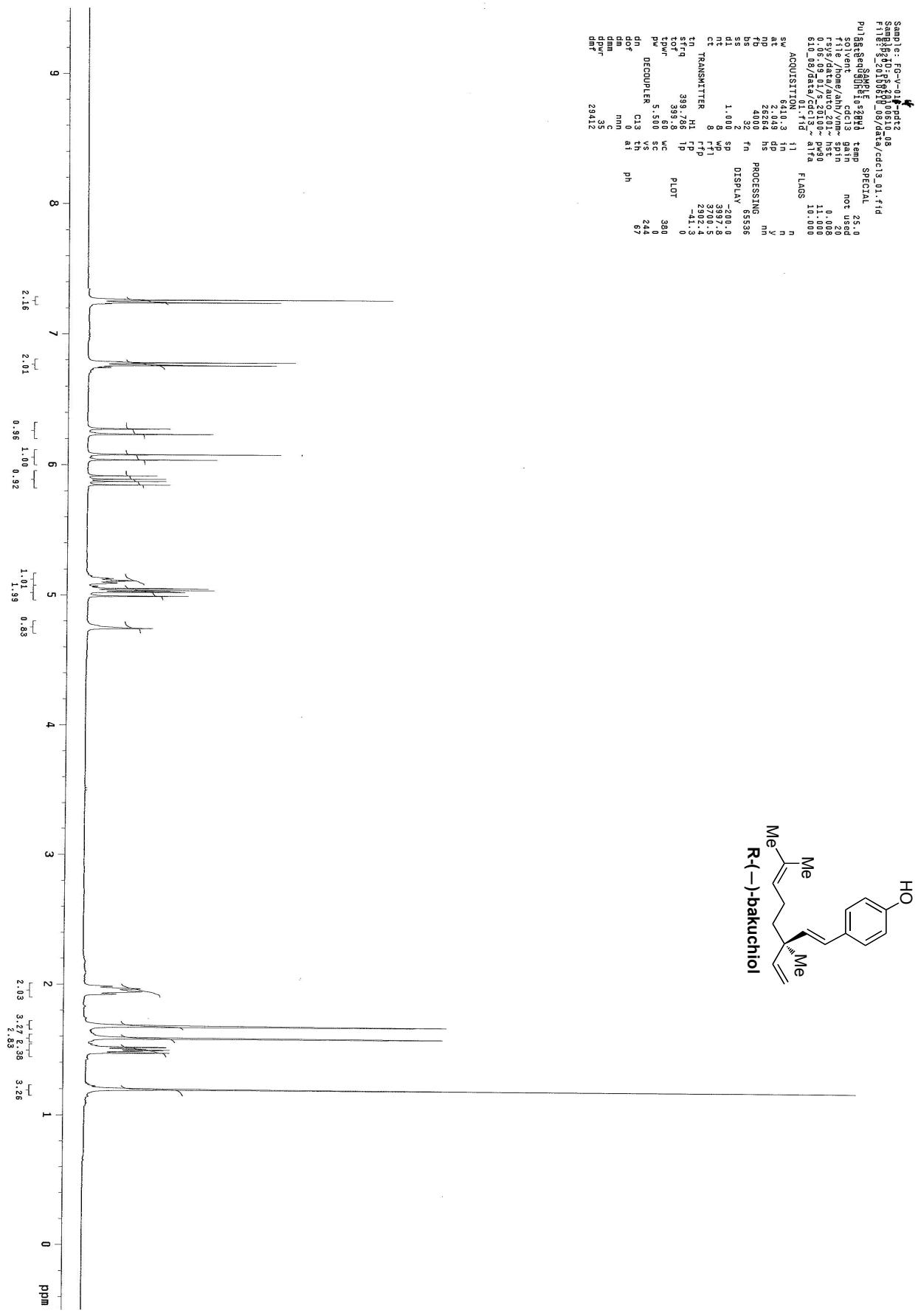
2.14
3.23
2.92
3.17
3.07
ppm


Me
Me
Me
HO
R-(−)-bakuchiol

Chapter 3:

A Multicomponent Ni-, Zr-, and Cu-Catalyzed Strategy for Enantioselective Synthesis of Alkenyl-Substituted Quaternary Carbons

3.1 Introduction

In the past two decades, a significant amount of progress has been made in the area of enantioselective Cu-catalyzed conjugate addition to enones for the formation of all-carbon quaternary stereogenic centers.[1] The majority of methods deal with the addition of alkyl organometallic reagents,[2] and to a lesser extent, aryl nucleophiles.[3] A limited number of reports focus on the addition of alkenyl nucleophiles to generate

(1) (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In Modern Organocopper Chemistry, Krause, N. Ed.; Wiley–VCH, Weinheim, 2002, pp. 224–258. (d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pámies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (e) Quasdorf, K. W.; Overman, L. E. *Nature*, **2014**, *516*, 181–191.

(2) (a) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989; (b) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378; (c) Lee, K.-s.; Brown, M. K.; Hird, A.W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; (d) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; (e) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100; (f) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362; (g) Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581; (h) Ladjel, C.; Fuchs, N.; Zhao, J.; Bernardinelli, G.; Alexakis, A. *Eur. J. Org. Chem.* **2009**, 4949–4955; (i) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. Eur. J.* **2010**, *16*, 9890–9904; (j) Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7995–7999. For related studies involving nitroalkanes as reagents, see: (k) Kwiatkowski, P.; Dudziński, K.; Łyźwa, D. *Org. Lett.* **2011**, *13*, 3624–3627.

(3) With Rh complexes and arylboronic acids, (a) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629; with Cu complexes and arylaluminum reagents, (b) Ref. 2f; (c) Hawner, C.; Li, C. K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214; with Rh complexes and sodium tetraarylborates, (d) Shintani, R.; Tsutsumi, R.Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589; with Rh complexes and triarylboroxines, (e) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969–3971; with Rh complexes and arylaluminum reagents, f) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769–7772; with Pd complexes and arylboronic acids, g) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902–6905; h) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. C.; Minnaard, A. J. *Chem. Eur. J.* **2012**, *18*, 6907–6914.

quaternary stereogenic centers and all such disclosures are with cyclic enones.[4] Moreover, additions involving acyclic α,β-unsaturated carbonyls are still underdeveloped[5] and the rare examples often involve highly activated substrates.[6,7] As such, a method for the formation of enantiomerically enriched alkenyl-substituted all-carbon quaternary stereogenic centers in acyclic systems would be of great interest.

3.2 Background

The first example of enantioselective conjugate addition (ECA) of alkenyl nucleophiles with acyclic substrates was published in 2005 by Carretero and co-workers.[7c] In the presence of 5.0 mol % of a Rh–phosphine complex, a range of alkenyl boronic acids can be added to trisubstituted pyridyl sulfones with high enantioselectivity. The resulting products can be functionalized through deprotonation and addition to a number of electrophiles. The authors report <2% conversion with the corresponding phenylsulfone, which suggests a crucial role for the pyridyl substrate that may involve a 2-point binding of the substrate to rhodium.

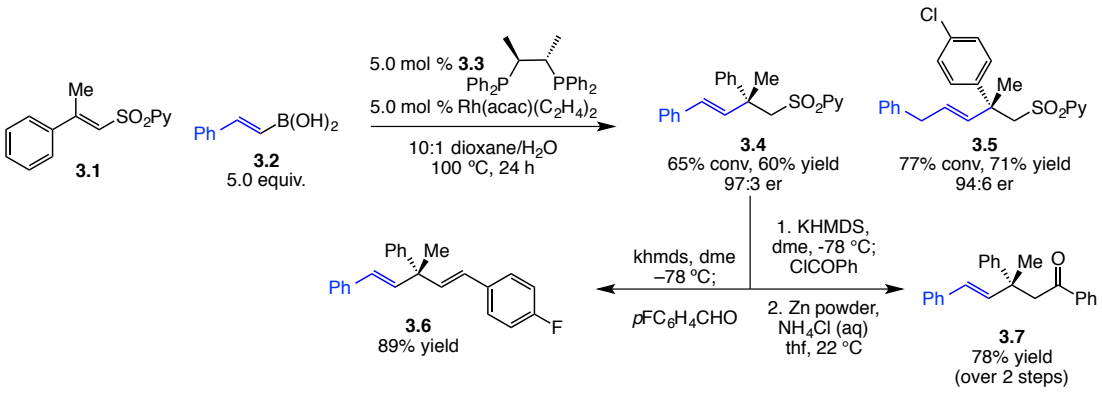
(4) (a) Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, 1694–1698; (b) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040–3043; For additions to β-substituted cyclopentenones and cyclohexenones, see: (c) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739; for isolated (single) cases of involving β-substituted cyclohexenones, see: (d) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662; (e) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214; (f) Palais, L.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 10473–10485.

(5) For a review on enantioselective synthesis of quaternary carbon stereogenic centers, see: Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623.

(6) For ECA of Me_3Al and Et_3Al to β,β-substituted acyclic enones, see: (a) Endo, K.; Hamada, D.; Shibata, Y. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 606–610; for reactions with alkyl- and arylaluminum reagents, see: (b) Dabrowski, J. A.; Villaume, M. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8156–8159.

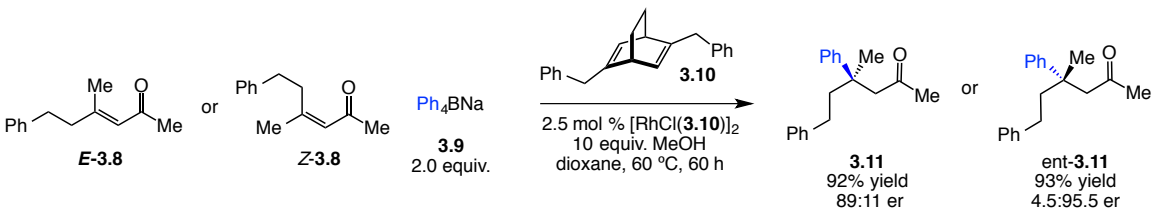
(7) For catalytic ECA of C-based nucleophiles to especially activated acyclic substrates affording all-carbon-substituted quaternary stereogenic centers, see: with alkylmetal reagents: a) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; b) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; c) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963; d) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804; e) Wilsily, A.; Fillion, E. *J. Org. Chem.* **2009**, *74*, 8583–8594; for studies involving nitroalkanes as nucleophiles, see: f) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575–5579; for catalytic ECA with a CN-based nucleophile, see: g) one example reported in: Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762–1765; h) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863.

Scheme 3.1. Rh-Catalyzed Addition of Alkenylboronic Acids to Pyridyl Sulfones



The Hayashi group disclosed the addition of sodium tetraarylborates to a number of substrates, including two examples to an acyclic enone.[3d] In the presence of 2.5 mol % of a dimeric Rh–diene complex and 10 equivalents of MeOH at elevated temperatures, aryl addition occurs in up to 95.5:4.5 er. *E*- and *Z*-olefin isomers lead to opposite enantiomers, which suggests that the catalyst binds to the opposite face of the olefin.

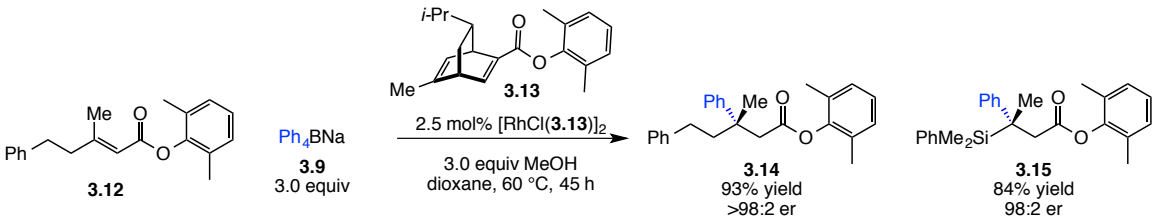
Scheme 3.2. Rh-Catalyzed Addition of Tetraarylboronates to Enones



Hayashi also disclosed the addition of aryl nucleophiles to α,β-unsaturated esters containing a large 2,6-dimethylphenoxide, a class of substrates that is particularly unreactive.[8] With an enantiomerically enriched diene and Rh(I) salt, the reaction proceeds to furnish the desired products in high yield and up to >98:2 er. Through screening, it was shown that the large ester group is necessary as all other groups examined delivered the product in lower enantioselectivity. Additionally, the reaction is not very atom economical as three equivalents of a tetraarylboronate are required to transfer a single aryl group.

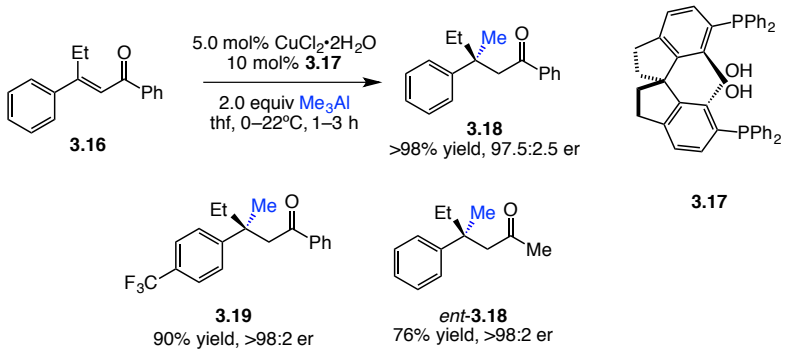
(8) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350–352.

Scheme 3.3. Rh-Catalyzed Addition of Tetraarylboronates to α,β-Unsaturated Enones



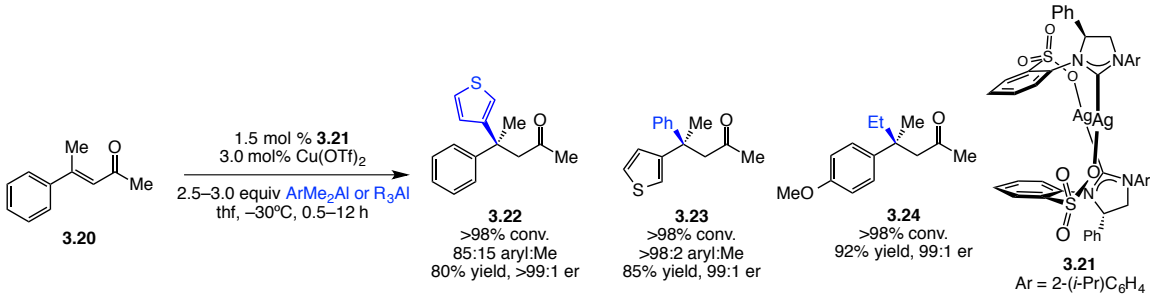
The Shibata group demonstrated that with a phosphine–Cu complex, trialkylaluminum reagents (Me_3Al in all but one example) are added to α,β-unsaturated chalcone derivatives as well as one example of addition to an unsaturated ketone.[6a] Reaction proceed in up to >98% yield and >98:2 er for a variety of electrophiles.

Scheme 3.4. Phosphine–Cu-Catalyzed Addition of Trialkylaluminum Reagents



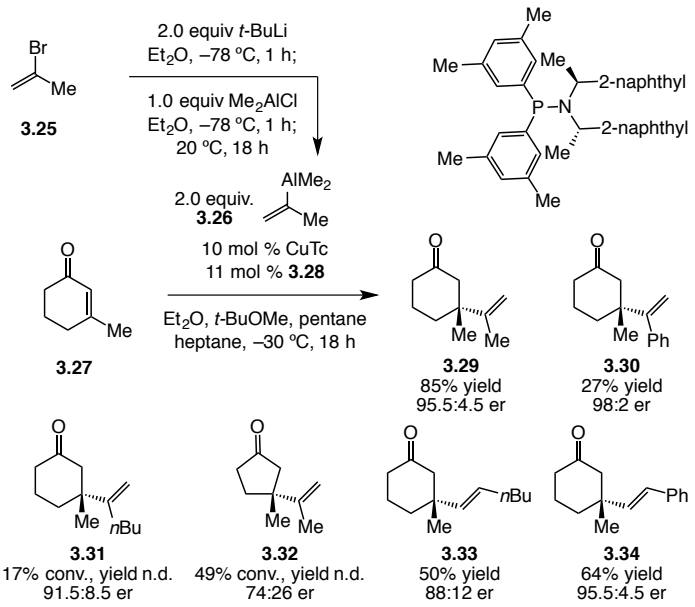
The Hoveyda group also disclosed the addition of both alkyl- as well as arylaluminum reagents to a range of acyclic enones catalyzed by 3.0 mol % of an NHC–Cu complex.[6b] Aryl nucleophiles, generated from addition of the requisite aryllithium to $AlMe_2Cl$, are transferred in 55:45 to >98:2 group selectivity and up to >99:1 er. Methyl, ethyl, and *iso*butylaluminum reagents all participate to form the desired products in high yields and enantioselectivities. Notably, reactions with sterically hindered enones, *ortho*-fluoro, are less efficient (88% conv.) and proceed with diminished group selectivity (55:45 Ar:Me).

Scheme 3.5. NHC–Cu-Catalyzed Addition of Aryl and Alkyl Nucleophiles to Enones



With the exception of three isolated examples,[4d,e,f] there are only a handful literature precedents for the addition of alkenyl nucleophiles to generate all-carbon quaternary stereogenic centers. The first was disclosed by Alexakis and co-workers where, following lithium/halogen exchange of the requisite alkenylbromide, addition of alkenyllithium species to Me_2AlCl generates the desired nucleophiles.[4a] With 10 mol % of a phosphoramidite–Cu-complex, six examples are shown where both 1,1- and *trans*-1,2-disubstituted aluminum reagents are added to β-methyl cyclohexenone in 27–85% yield and 88:12 to 95.5:4.5 er. α-Styrenyl as well as α-*n*-butylaluminum reagents lead to low yields of the desired products (**3.29** and **3.30**). One example of addition to a 5-membered ring substrate is shown but both conversion and enantioselectivity are moderate. In addition to the limited substrate scope, a limited number of alkenyl bromides are commercially available and their syntheses are often non-trivial.

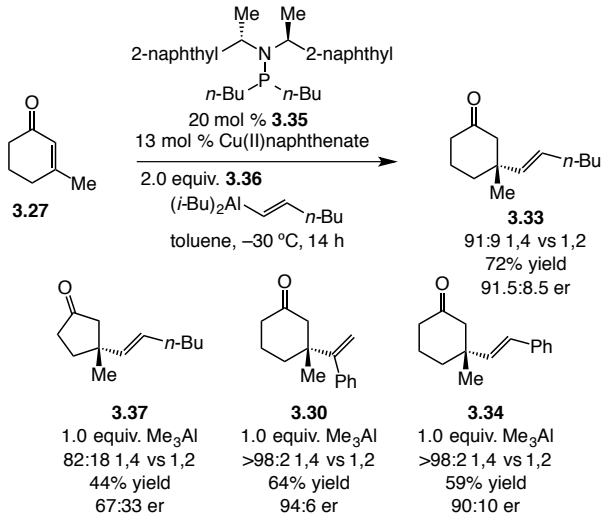
Scheme 3.6. Phosphoramidite–Cu-Catalyzed Conjugate Addition of Alkenylaluminum Reagents



The Alexakis group improved upon this method by taking advantage of a previously published Ni-catalyzed hydroalumination of terminal alkynes[9] to generate the desired alkenylaluminum nucleophiles.[4b] With a modified catalytic system derived from 13 mol % Cu(II)naphthenate and 20 mol % phosphoramidite **3.35**, ECA reactions proceed to generate the desired products in up to 72% yield and 94:6 er. Notably, reaction with cyclopentenone substrates still pose a problem with **3.37** isolated in 44% yield and 67:33 er. With the more nucleophilic *n*-alkyl substituted alkenylaluminum reagents, up to 20% of competitive 1,2-addition is observed, highlighting the need for efficient catalytic systems.

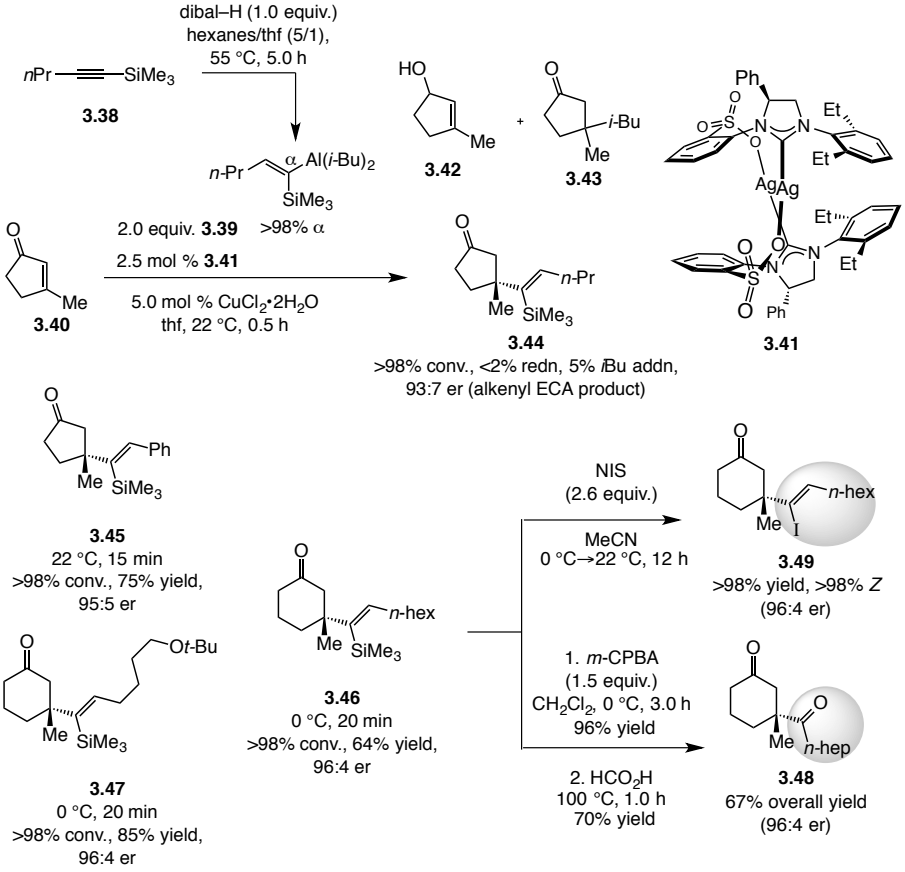
(9) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

Scheme 3.7. Phosphine–Cu-Catalyzed Alkenylaluminum Conjugate Addition



The Hoveyda group demonstrated that with a bidentate NHC–Cu complex derived from precatalyst **3.41**, silyl-substituted alkenylaluminum reagents can be coupled with a number of cyclopentenone and cyclohexenone substrates in 63–95% yield and up to 98.5:1.5 er.[4c] The authors note that addition to cycloheptenone substrates are inefficient (20–40% conversion) and the presence of a sterically hindered substituent (e.g. Ph) lead to reduced reaction rates (12 h vs. 20 min.) Conjugate addition adducts can be further functionalized through an epoxidation/elimination sequence to furnish diketone **3.48** or iodo-desilylation to generate Z-alkenyliodide **3.49** without loss of enantiomeric purity.

Scheme 3.8. NHC–Cu-Catalyzed Conjugate Addition of Silyl-Substituted Alkenylaluminum Reagents

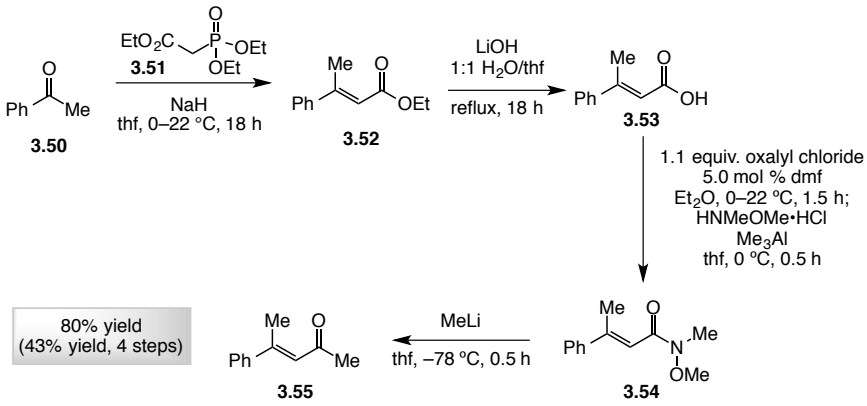


3.3. Zirconium-Catalyzed Carboalumination of Terminal Alkynes

Due to the limited number of examples for conjugate addition reaction that deliver all-carbon quaternary stereogenic centers in acyclic systems, we set out to establish a protocol to couple tri-substituted acyclic enones and alkenylaluminum nucleophiles through NHC–Cu-catalyzed conjugate addition. Our first goal was to determine the most expedient synthesis of the necessary enone substrates. As shown in Scheme 3.9, our first route required three to four steps over the course of two days in ~43% yield. Additionally, the Horner-Wadsworth-Emmons (HWE) results in a mixture of E/Z-olefin isomers (1:1–8:1 E/Z) that must be separated by silica gel chromatography. Other methods lead to the products in lower yield or indeterminate olefin geometry selectivity.[10]

[10] Synthesis of trisubstituted enones by established procedures is not straightforward. Horner– Emmons-type transformations are severely inefficient (vs. the derived carboxylic esters); for example, reaction with

Scheme 3.9. Synthesis of Trisubstituted Enones



We surmised that a more expedient synthesis could be achieved using carboalumination of a terminal alkyne. Based on work done by Negishi and co-workers and making use of a modified procedure by Wipf,[11] we found that with 22 mol % Cp_2ZrCl_2, carboalumination occurs efficiently at –23 ºC, and the intermediate alkenylaluminum can be trapped with acetyl chloride to form the desired α,β-unsaturated enone in >98% *E* selectivity and complete regioselectivity. Both Me_3Al and Et_3Al can be added across phenylacetylene to form enones **3.55** and **3.56** in 57–80% yield. The lower yield for **3.56** can be accounted for in part by the formation of the other regioisomer of enone. *para*-Methoxy and -bromo substitution lead to the desired enone in up to 63% yield. Electron-withdrawing groups at the *para* position lead to a sluggish reaction with ~15% conversion to the desired product observed. Additionally *meta* and *ortho* substituents lead to the desired enones in up to 88% yield (entry 4, 6, and 7). Moreover, aliphatic enones, which have the lowest *E*/*Z* selectivity in HWE reactions, can be formed in >98% *E*-selectivity and 61–80% yield (entry 8–12). Other acid chlorides can act as the trapping agents as show in entry 12 where a butenyl-substituted (versus methyl) enone is formed.

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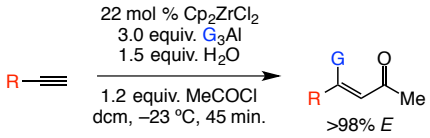
acetophenone under standard conditions (1.2 equiv NaH, 22ºC, 18 h) leads to <2% conversion to the desired enone. Another approach includes addition of a Grignard reagent to acetoacetone in the course of a day, followed by treatment with oxalic acid at reflux for 30 min; the stereoisomeric purity of the resulting enones has not been reported (Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369). Yet a different procedure calls for an acid chloride as the starting material, entails a three-step process that requires a total of 36 h, and generates the stereoisomerically pure α,β-unsaturated ketone in ca. 26% overall yield after purification (Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862 – 8863).

(11) (a) Negishi, E.; Kondakov, D. Y.; Chouiery, D.; Kasai, K.; Takahashi, T. *J. Am. Chem. Soc.* **1996**, *118*, 9577–9588; (b) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068–1071;

Table 3.1. Scope of Zr-Catalyzed Carboalumination[(a)]



entry	R	G	product	yield (%)[(b)]
1	C_6H_5	Me	**3.55**	80
2	C_6H_5	Et	**3.56**	57
3	*p*-$MeOC_6H_4$	Me	**3.57**	40
4	*o*-$MeOC_6H_4$	Me	**3.58**	80
5	*p*-BrC_6H_4	Me	**3.59**	63
6	*m*-FC_6H_4	Me	**3.60**	88
7	*o*-FC_6H_4	Me	**3.61**	60
8	C_6H_9	Me	**3.62**	62
9	C_6H_{11}	Me	**3.63**	61
10	CH_2Ph	Me	**3.64**	80
11	$(CH_2)_3OTBS$	Me	**3.65**	62
12[(c)]	C_6H_5	Me	**3.66**	64

[(a)] Reaction performed under atmosphere of N_2. [(b)] Yield of isolated and purified product. [(c)] 4-pentenoyl chloride used.

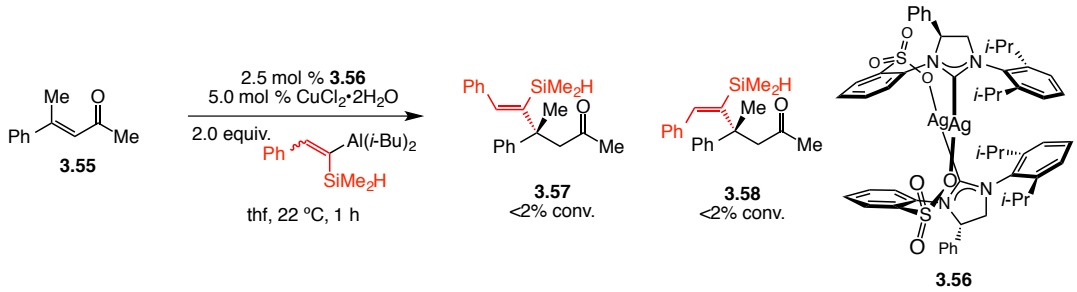
As compared to the previous route for the synthesis of trisubstituted enones, a carboalumination/acylation strategy has a number of notable advantages (1) reactions are complete in 45 minutes (versus ~2 days) (2) a single reaction produces the substrate (versus 3–4 steps) (3) the reaction is completely *E*-selective so there is no need for tedious separation of *E*- and Z-olefin isomers (4) the reaction is catalytic so there is less waste and only one purification is require (versus 2–3 purifications previously).

3.4. Cu-Catalyzed Conjugate Addition of Alkenylaluminum Nucleophiles to Acyclic Trisubstituted Enones

3.4.a. Catalyst Screening and Reaction Optimization

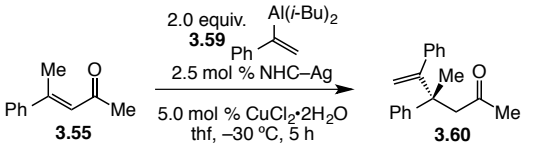
After establishing an expedient route to *E*-trisubstituted enones, we turned toward examining the NHC–Cu-catalyzed ECA of alkenyl nucleophiles. We began by examining the reaction of silyl-substituted alkenylaluminum reagents; previously[4c] the silicon group was found to be critical for high enantioselectivity with cyclic substrates. As shown in Scheme 3.10, with 5 mol % of an NHC–Cu complex derived from NHC–Ag **3.56**, both *E*- and *Z*-olefin isomers lead to <2% conversion to the desired product.

Scheme 3.10. NHC–Cu-Catalyzed Conjugate Addition to Acyclic Enones



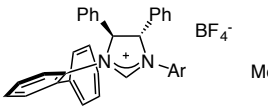
We then chose to look at monosubstituted alkenylaluminum reagents in hopes that decreasing the steric bulk of the nucleophile with the removal of the silyl group would allow the reaction to proceed. Additionally, both the α- and β-aluminum reagents are easily accessed through Ni-catalyzed hydroalumination of terminal alkynes in the presence of different Ni salts. After screening various ligands, we quickly realized that only sulfonate-containing NHC–Cu complexes are able to catalyze the transformation. As shown in Table 3.2, in the presence of 5.0 mol % of a C_1 or C_2 symmetric NHC, **3.61** and **3.62** respectively, <2% conversion to the desired product is observed. Additionally, with bidentate ligands containing an alkoxy or phenoxy chelate (**3.63** and **3.64**, respectively), the desired transformation does not proceed. NHC–Ag complexes with a diphenyl backbone and a sulfonate chelate lead to >98% conversion of the starting enone and 54–72% yield of the desired product in up to 97.5:2.5 er (Table 3.2, entries 5–6). Removal of one phenyl from the backbone, **3.67**, leads to an 84% yield of **3.60** and 99:1 er. Modification of the *N*-aryl group to 2,6-diethyl results in a decreased yield, and further increasing the size to 2,6-diisopropyl causes the reaction to shut down. A large α-alkenyl nucleophile in conjunction with a sterically larger *N*-aryl ring leaves little space for coordination of the substrate.

Table 3.2. Screening of Various NHC Precursors[a]



entry	NHC–Ag	conv. (%)[b]	yield (%)[c]	er[d]
1	**3.61**	<2	n.d.	n.d.
2	**3.62**	<2	n.d.	n.d.
3	**3.63**	<2	n.d.	n.d.
4	**3.64**	<2	n.d.	n.d.
5	**3.65**	>98	72	96:4
6	**3.66**	>98	54	97.5:2.5
7	**3.67**	>98	84	99:1
8	**3.41**	>98	41	98:2
9	**3.56**	<2	n.d.	n.d.

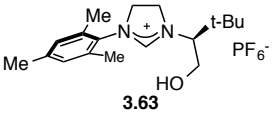
[a] Reaction performed under an atmosphere of N_2. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yield of isolated and purified product. [d] Determined by HPLC analysis.



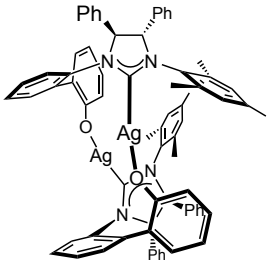
Ar

2-PhC$_6$H$_3$ **3.61**

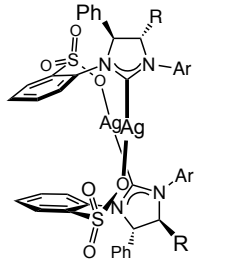
2,4,6-Me$_3$C$_6$H$_2$ **3.62**



3.63



3.64



R,	Ar	
Ph,	2,4,6-Me$_3$C$_6$H$_2$	**3.65**
Ph,	2,6-Et$_2$C$_6$H$_4$	**3.66**
H,	2,4,6-Me$_3$C$_6$H$_2$	**3.67**
H,	2,6-Et$_2$C$_6$H$_4$	**3.41**
H,	2,6-(*i*Pr)$_2$C$_6$H$_4$	**3.56**

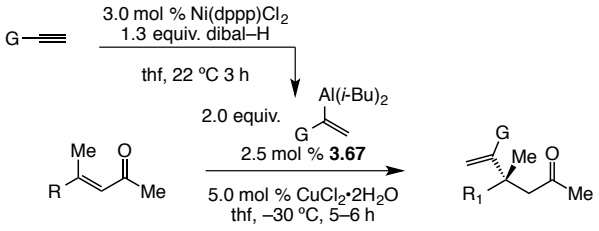
3.4.b. Scope of Conjugate Addition of α-Alkenylaluminum Reagents

After identifying the optimal catalyst for the addition of α-alkenylaluminum reagents, we turned our attention to increasing the scope of the reaction. As shown in Table 3.3, substitution on the *para* position with an electron-withdrawing trifluoromethyl, electron-donating methoxy group, or a bromide furnish the desired product, **3.68**–**3.70**, in up to 95% yield and 99:1 er (Table 3.3, entries 2–4). While a *meta* fluoro substituent results in an efficient reaction, an *ortho* fluoro group leads to diminished conversion, 88%, and 48% yield. (Table 3.3, entries 5–6). Both naphthyl and 3-thienyl substituents generate the product in high yield and enantioselectivity (Table 3.3, entries 7–8).

A variety of alkynes with other substitution patterns including halogen, methoxy, and trifluoromethyl substituents participate in the Ni-catalyzed hydroalumination to generate the desired alkenylaluminum reagents. As shown in Table 3.3, varying the aryl substituent leads to the desired conjugate addition adduct in uniformly high yields and enantioselectivity (entries 9–14). In addition to aryl-substituted enones, substrates with two aliphatic β-substituents are competent reaction partners although enantioselectivity is somewhat diminished with α-branched groups (92:8 vs. 98:2 er). Enantioselectivity decreases further as the substituent becomes less sterically hindered (Bn vs Cy); as a

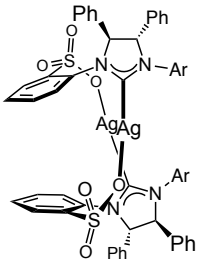
result, an NHC–Ag precursor with a larger N-aryl ring, **3.56**, is used to increase selectivity for **3.82** (79:21 er with **3.67** vs 97.5:2.5 er with **3.56**). A keto ester substrate also requires a more sterically encumbered NHC ligand to achieve high level of enantioselectivity. In this case **3.85** with a 2,4,6-triisopropyl N-aryl group allows for the formation of **3.84** in 97:3 er and 68% yield. Notably, no 1,4-addition to the α,β-unsaturated ester is observed.

Table 3.3. Scope of Addition of α-Alkenyl Nucleophiles [(a)]



entry	R	G	conv. (%)[(b)]	prod.	yield (%)[(c)]	er[(d)]
1	C_6H_5	C_6H_5	>98	**3.60**	84	99:1
2	*p*-$MeOC_6H_4$	C_6H_5	>98	**3.68**	85	97.5:2.5
3	*p*-BrC_6H_4	C_6H_5	>98	**3.69**	95	99:1
4	*p*-$CF_3C_6H_4$	C_6H_5	95	**3.70**	84	99:1
5	*m*-FC_6H_4	C_6H_5	>98	**3.71**	88	99:1
6	*o*-FC_6H_4	C_6H_5	88	**3.72**	48	99:1
7	2-naphthyl	C_6H_5	>98	**3.73**	90	98:2
8	3-thienyl	C_6H_5	>98	**3.74**	81	97:3
9	C_6H_5	*p*-$MeOC_6H_4$	>98	**3.75**	95	98:2
10	C_6H_5	*p*-$F_3CC_6H_4$	>98	**3.76**	80	97:3
11	C_6H_5	*m*-$F_3CC_6H_4$	>98	**3.77**	97	98:2
12	C_6H_5	*o*-FC_6H_4	>98	**3.78**	71	99:1
13	*p*-$MeOC_6H_4$	3-thienyl	>98	**3.79**	81	98:2
14	*p*-$CF_3C_6H_4$	*p*-$MeOC_6H_4$	95	**3.80**	78	98:2
15	Cy	C_6H_5	>98	**3.81**	83	92:8
16[(e)]	$CH_2C_6H_5$	C_6H_5	>98	**3.82**	85	97.5:2.5
17[(e)]	$(CH_2)_3OTBS$	C_6H_5	>98	**3.83**	87	95:5
18[(f)]	CO_2Me	C_6H_5	>98	**3.84**	68	97:3

[(a)] Reaction performed under an atmosphere of N_2. [(b)] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures. [(c)] Yield of isolated and purified product. [(d)] Determined by HPLC analysis.[(e)] **3.56** was used as the catalyst precursor. [(f)] **3.85** was used as the catalyst precursor.



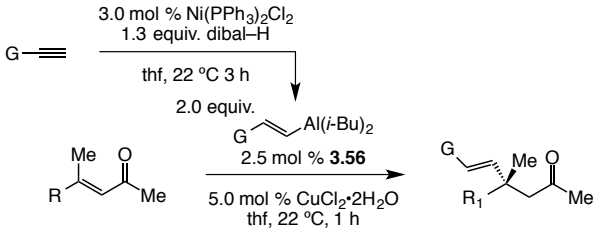
3.85
Ar = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$

3.4.c. Scope of Conjugate Addition of β-Alkenylaluminum Reagents

In addition to reactions with α-alkenyl nucleophiles, we also examined the reaction of β-alkenylaluminum reagents in our system. As shown in Table 3.4, in the presence of 5.0 mol % of NHC–Cu-complex derived from **3.56** at 22 ºC, styrenyl aluminum is coupled with a number of substrates to generate products **3.86–3.89** in 60–

80% yield and 95:5–98:2 er (Table 3.4, entries 1–4). Both electron-poor as well as electron-rich nucleophiles participate in the reaction to deliver conjugate addition adducts, **3.90** and **3.91,** respectively, in good yields and enantioselectivities. Unlike additions involving sterically encumbered α-alkenylaluminum reagents, a β-alkenyl nucleophile reacts efficiently (>98% conv. vs <2% conv.) with *ortho*-methoxy enone to generated **3.92** in 60% yield and 98:2 er. Heterocycles can be incorporated into either the nucleophile or electrophile to generate conjugate addition adducts in 54–57% yield and 96.5:3.6–98:2 er (Table 3.4, entries 8–9). While **3.95** containing a cyclohexyl group is generated in 97:3 er in the presence of NHC–Ag **3.85**, enantioselectivity drops for β-branched **3.96** (90.5:9.5 er).

Table 3.4. Scope of β-Alkenyl Nucleophiles[(a)]



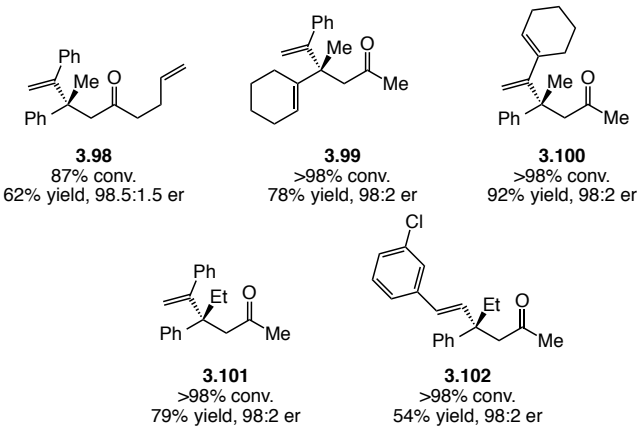
entry	R	G	conv. (%)[(b)]	prod	yield (%)[(c)]	er[(d)]
1	C_6H_5	C_6H_5	>98	**3.86**	80	98:2
2	*p*-$MeOC_6H_4$	C_6H_5	>98	**3.87**	75	98:2
3	*p*-BrC_6H_4	C_6H_5	>98	**3.88**	60	96:4
4	*p*-$CF_3C_6H_4$	C_6H_5	>98	**3.89**	67	95:5
5	C_6H_5	*p*-$MeOC_6H_4$	>98	**3.90**	60	96.5:3.5
6	C_6H_5	*p*-$F_3CC_6H_4$	>98	**3.91**	72	98:2
7	*o*-$MeOC_6H_4$	C_6H_5	>98	**3.92**	60	98:2
8	C_6H_5	3-thienyl	>98	**3.93**	54	96.5:3.5
9	3-thienyl	C_6H_5	>98	**3.94**	57	98:2
10[(e)]	Cy	C_6H_5	>98	**3.95**	51	97:3
11[(e)]	$CH_2C_6H_5$	C_6H_5	>98	**3.96**	55	90.5:9.5
12	C_6H_5	Cy	>98	**3.97**	60	94.5:5.5

[(a)] Reaction performed under an atmosphere of N_2. [(b)] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures. [(c)] Yields isolated and purified product. [(d)] Determined by HPLC analysis.[(e)] **3.85** was used as the catalyst precursor.

As shown in Scheme 3.11, in addition to reactions with substrates containing a methyl ketone, generated from trapping the carboalumination with acetyl chloride, product **3.98** containing a butenyl substituted ketone can be formed in good yield and high enantioselectivity. Additionally, both the carboalumination and Ni-catalyzed hydroalumination can be performed on enynes with selective addition to the terminal

alkyne as shown in the formation of **3.99** and **3.100**. The carboalumination can also be performed with triethylaluminum (vs. trimethylaluminum), which after NHC–Cu-catalyzed ECA results in quaternary stereogenic centers containing an ethyl group, **3.101** and **3.102**.

Scheme 3.11. Products Resulting from Reactions with an *n*-Alkyl Ketone, Enyne, or Et_3Al



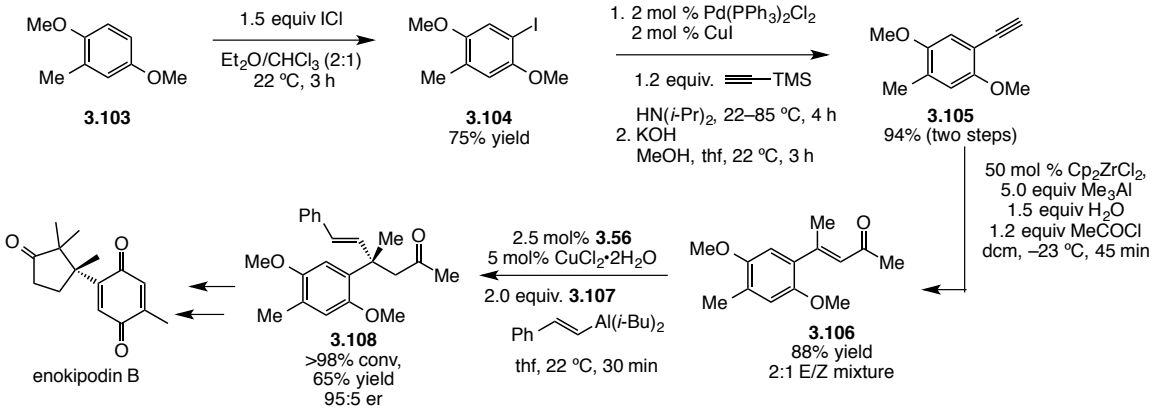
3.4.d. Formal Synthesis of Enokipodin B

In order to demonstrate the utility of the above method, we devised an expedient formal synthesis of antimicrobial agent enokipodin B.[12] The sequence begins with the iodination of **3.103** to form aryl iodide **3.104**, which is subsequently cross-coupled with trimethylsilylacetylene. After protodesilylation, terminal alkyne **3.105** is obtained in 71% yield over 3 steps. Carboalumination with Me_3Al in the presence of 50 mol % Cp_2ZrCl_2 furnishes the desired enone **3.106** as a 2:1 mixture of *E*/*Z* isomers. The low stereoselectivity of the Zr-catalyzed addition may be attributed to the electron-rich nature of the aryl group, which could stabilize an incipient benzylic carbocation and facilitate rotation around the C–C bond, Scheme 3.13. Fortunately, subjection of the enone mixture to NHC–Cu-catalyzed ECA results in formation of **3.108** in 65% yield and 95:5 er. Control experiments show that subjection of pure *E*- or pure *Z*-isomer lead to the same enantiomer of product in 95:5 er although the reaction of the *Z*-isomer occurs with diminished yield of the product. Therefore it appears that the *Z*-isomer either isomerizes to the *E*-isomer or reacts in a non-productive fashion before undergoing ECA. Compound

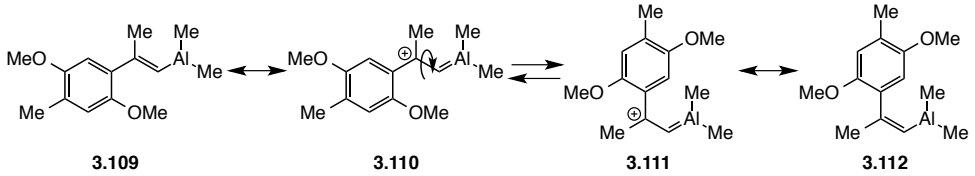
(12) (a) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441–1443; for an earlier enantioselective route to enokipodins, see: (b) Kuwahara, S.; Saito, M. *Tetrahedron Lett.* **2004**, *45*, 5047–5049.

3.108 has been elaborated into enokipodin B through conversion of the styrenyl moiety into the corresponding aldehyde followed by intramolecular cyclization with the ketone to form the desired cyclopentenone.

Scheme 3.12. Formal Synthesis of Enokipodin B



Scheme 3.13. Possible Mechanistic Explanation for Low Stereoselectivity

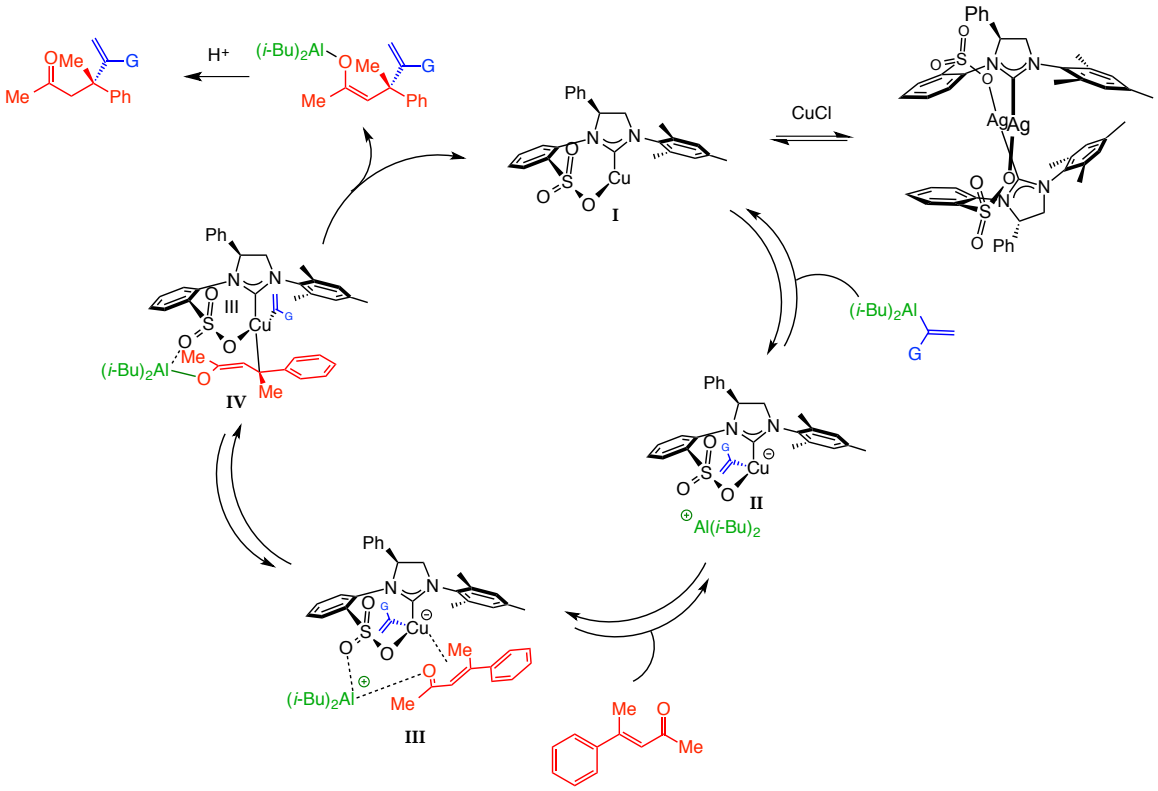


3.4.e. Proposed Mechanism and Model for Enantioselectivity

The mechanism proposed for the NHC–Cu-catalyzed ECA with alkenylaluminum reagents proceeds through four major steps.[13] (1) The in situ generated bidentate NHC–Cu complex **I** reacts with the alkenylaluminum reagents to form the Cu(I) cuprate **II** with concomitant association of the aluminum cation with the Lewis basic sulfonate oxygen. (2) Coordination of the substrate through the ketone oxygen to the aluminum cation serves to activate the substrate for addition as well as bring it into proximity with the Cu center at which point coordination of the olefin occurs, **III**. (3) Oxidative addition of the nucleophilic cuprate to the olefin generates the square planar Cu(III) complex **IV**. (4) Reductive elimination of the Cu(III) generates the new C–C bond, releases the product as the aluminum enolate, and regenerates the catalytically active Cu(I) species.

(13) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339–2372.

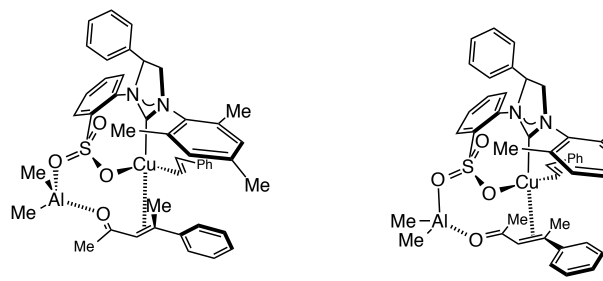
Scheme 3.14. Proposed Catalytic Cycle for NHC–Cu-Catalyzed Conjugate Addition



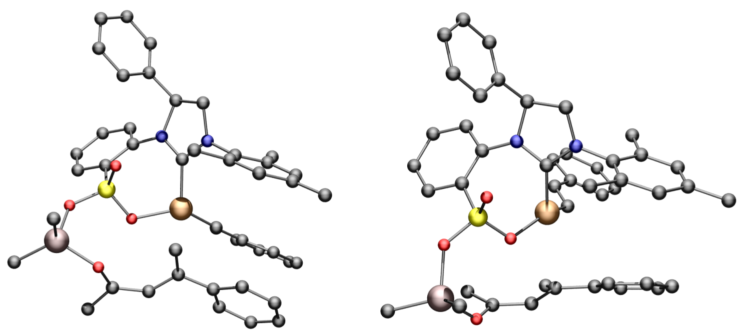
We carried out DFT calculations to gain insight into the structure of the transition states that lead to the major and minor enantiomers of the product. Transformations in which a Cu(III) complex is formed are 7–9 kcal/mol lower in energy than the mechanism in which the alkenyl group on the cuprate is directly added to the enone in a redox-neutral process (oxidative addition vs. direct addition). Additionally, transition state **3.113**, which leads to the major enantiomer, was found to be 1.6 kcal/mol lower in energy than the analogous transition state that forms the minor enantiomer, **3.114**. In order to form the minor enantiomer, which involves coordination of the substrate to the Lewis acidic aluminum as well as the Cu center, the substrate adopts a higher energy *s*-trans conformation (vs. *s*-cis in **3.113**) engendering $A_{1,3}$ strain between the ketone and the olefin substituents. Moreover, we found that structures in which the sulfonate is chelated to the Cu center anti to the Ph group on the backbone (vs. *syn* to the Ph in **3.113** and

3.114) are 4–6 kcal/mol higher in energy lending credence to the assumption that the Cu-complex chelates in the same fashion as the analogous Zn- and Al-complexes.[14]

Scheme 3.15. DFT Calculations of Transition States Leading to Major and Minor Enantiomers



3.113 **3.114**



3.5. Conclusions

We have developed the first enantioselective Cu-catalyzed conjugate addition of alkenyl nucleophiles to acyclic enones to generate all-carbon quaternary stereogenic centers. The requisite substrates are accessed through an efficient and stereoselective Zr-catalyzed carboalumination of terminal alkynes, which obviates the need for multi-step sequences and tedious separation of *E*- and *Z*-olefin isomers. Alkenyl nucleophiles are generated through a site-selective Ni-catalyzed hydroalumination of terminal alkynes where both α- and β-isomers can be accessed in high selectivity. Products are accessed in up to 95% yield and >98:2 er. A convenient formal synthesis of enokipodin B highlights the utility of the method. DFT calculations serve to bolster our mechanistic proposals and give insight into the various modes of substrate coordination.

(14) Lee, Y.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11625–11633.

3.6 Experimental

General. Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectrometry were performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiraldex CDB-DM column (30 m x 0.25 mm)) or by analytical liquid chromatography (HPLC) analysis on a Shimadzu chromatograph (Chiral Technologies Chiralcel OD-H (4.6 x 250 mm) and Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm)), in comparison with authentic racemic materials. For the GLC analysis, the inlet and detector temperatures are set to 250 °C and runs were isothermal of the temperature given with ultra high purity helium as the carrier gas. Specific rotations were measured on an ATAGO AP-300 Automatic Polarimeter. X-ray structure for **3.60** was obtained, as described in the cif file, with a Microfocus sealed Cu tube from Incote. It is well established that that aforementioned detector allows for the determination of absolute configuration of molecules that do not have a heavy atom.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and Hexanes were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) in air.

Reagents and Metal-based Complexes:

Acetyl Chloride was purchased from Aldrich and used as received.

2-Acetonaphthone was purchased from Aldrich and used as received.

2-Acetylthiophene was purchased from Aldrich and used as received.

Ag-complexes 1a[15], 1b[1], and 1c[16] were prepared by previously reported methods

Alkynes were purchased from Aldrich and distilled over CaH_2 prior to use, except 4'-bromophenylacetylene, which was used as received.

***n*-Butyllithium** was purchased from Strem (15% in Hexanes) and titrated before use.

Copper (II) chloride dihydrate was purchased from Aldrich and used as received.

***bis*-(Cyclopentadienyl)zirconium dichloride** was purchased from Strem and recrystallized from toluene prior to use.

Di-*iso*-butylaluminum hydride was purchased from Aldrich (neat) and used as received.

2,5-Dimethoxytoluene was purchased from Aldrich and used as received.

Iodine monochloride was purchased from Aldrich and used as received.

Ketones were purchased from Aldrich and used as received.

Methyl lithium was purchased from Acros and used as received.

***N,O*-Dimethylhydroxylamine hydrochloride** was purchased from Aldrich and used as received.

$Ni(dppp)Cl_2$ was purchased from Strem and used as received.

$Ni(PPh_3)_2Cl_2$ was purchased from Strem and used as received.

Sodium hydride (60% in oil) was purchased from Strem and used as received.

4-(Trifluoromethyl)acetophenone was purchased from Aldrich and used as received.

Trimethylaluminum was purchased from Aldrich (neat) and used as received.

Triethylaluminum was purchased from Aldrich (neat) and used as received.

Triethyl phosphonoacetate was purchased from Aldrich and used as received.

Preparation of unsaturated ketones: α,β-Unsaturated ketones were prepared either through a modified zirconocene-catalyzed carboalumination of the requisite terminal alkyne and trapping with the appropriate acid chloride[17] or from the requisite aryl ketone though a two-step Horner-Wadsworth-Emmons olefination/Weinreb amide formation. Subsequently, Weinreb amides were converted to methyl ketones by addition of MeLi.[18]

Representative procedure for zirconocene-catalyzed carboalumination/acylation: To a flame-dried round bottom flask equipped with a stir bar was added Cp_2ZrCl_2 (643 mg, 2.2 mmol) and dcm (50 mL). Me_3Al (2.9 mL, 30 mmol; USE CAUTION: PYROPHORIC) was added by syringe. The resulting solution was cooled to –23 ºC (dry ice/acetone bath) and H_2O (270 μL, 15 mmol) was added by syringe drop-wise (reaction is extremely vigorous). After stirring for 10 min, phenylacetylene (1.1 mL, 10 mmol) was

(15) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.
(16) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419–423.
(17) Wipf, P.; Lim, S. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1068–1071.
(18) Dabrowski, J. A.; Villaume, M. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, 52, 8156–8159

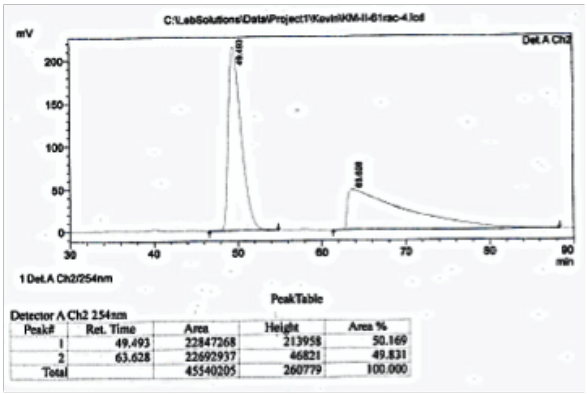
added. After the mixture was allowed to stir for 10 min, acetyl chloride (850 μL, 12 mmol) was added. The mixture was then allowed to stir for an additional 10 min at –22 ºC and warm to 22 ºC and again stir for an additional 10 min. The reaction was quenched upon drop-wise addition of a saturated aqueous solution of K_2CO_3 (reaction is vigorous, use vent needle) until gas evolution ceases. The mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was washed with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The desired product (**2a**) was isolated through silica gel chromatography (100% Hexanes then 20:1 Hexanes/Et_2O) as a light yellow solid (1.3 g, 8.0 mmol, 80% yield)

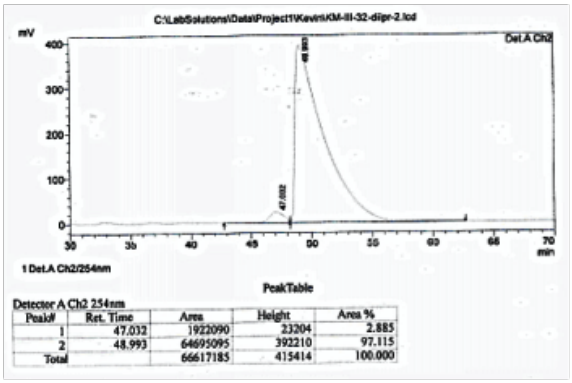
Representative Procedure for the Preparation of β-Alkenylaluminum Reagents: To a flame-dried round bottom flask equipped with a stir bar was added $Ni(PPh_3)_2Cl_2$ (39.4 mg, 0.06 mmol) and thf (1.3 mL). The solution was allowed to cool to 0 °C before the drop-wise addition of *i*-Bu_2AlH (0.46 mL, 2.6 mmol) and phenylacetylene (0.22 mL, 2.0 mmol). The dark brown solution was allowed to warm to 22 °C and stir for 2 h and then used without purification.

Procedure for Cu-catalyzed Enantioselective Conjugate Addition with a β-Alkenylaluminum Reagents: An oven-dried 1-dram vial was charged with NHC–Ag complex (2.84 mg, 2.50 mmol) and $CuCl_2•2H_2O$ (0.85 mg, 5.00 mmol) weighed under an N_2 atmosphere in a glove box. The vial was sealed with a cap with septum. Tetrahydrofuran (thf; 0.5 mL) was added with a syringe to the vial, and the resulting blue solution was allowed to stir for five minutes, followed by the addition of (*E*)-diisobutyl(styryl)aluminum (200 μL, 2.00 mmol, 1.0 M) and (*E*)-4-phenylpent-3-en-2-one (16.0 mg, 0.100 mmol) in thf (0.5 mL) through a syringe, sequentially, resulting in a brown solution. The mixture was allowed to stir at 22 ºC for 1 h, after which time, the reaction was quenched by the addition of a saturated aqueous solution of Rochelle's salt (1.0 mL). The layers are separated, and the aqueous layer was washed with Et_2O (3 x 2.0 mL). The combined organic layers were passed through a short plug of silica gel, and concentrated under reduced pressure. The resulting brown oil was purified by silica gel chromatography to give **3.86** as colorless oil (21.1 mg, 0.08 mmol, 80% yield).

(*S*,*E*)-4-Methyl-4,6-diphenylhex-5-en-2-one (3.86, entry 1, Table 3.4). IR (neat): 3802 (w), 3057 (w), 3025 (w), 2965 (w), 2926 (w), 1704 (m), 1599 (w) 1578 (w), 1494 (m), 1445 (m), 1356 (m), 1200 (w), 1157 (w), 1073 (w), 1030 (w), 970 (m), 913 (w), 843 (w), 764 (w), 749 (m), 696 (s), 541 (w), 494 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (8H, m), 7.24–7.20 (2H, m), 6.56 (1H, d, *J*= 16.4 Hz), 6.39 (1H, d, *J*= 16.4 Hz), 3.04 (1H, d, *J*= 14.4 Hz), 3.00 (1H, d, *J*= 14.4 Hz), 1.92 (3H, s), 1.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 146.5, 138.0, 137.4, 128.7, 128.5, 127.6, 127.5, 126.5, 126.5, 126.4, 54.5, 43.3, 32.2, 26.1; HRMS (ESI+): Calcd for $C_{19}H_{21}O_1$ [M+H$^+$]: 265.1592. Found: 265.1589. Specific Rotation $[\alpha]_D^{20}$ –19.3 (*c* 1.73, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with

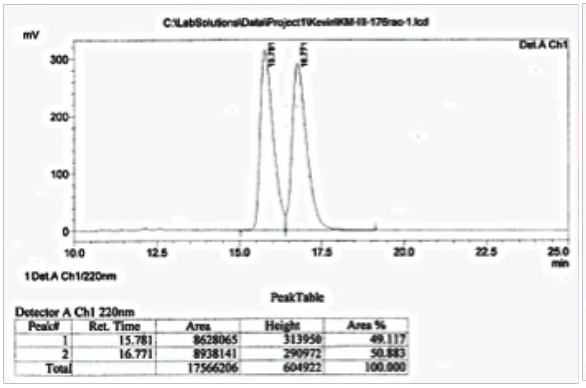
authentic racemic material; Chiracel OD-H, 99.5% Hexanes, 0.5% *i*PrOH, 1.0 mL/min, 254 nm.

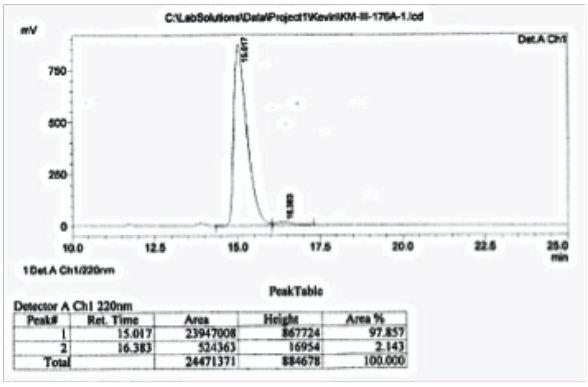




Retention Time	Area	Area %	Retention Time	Area	Area %
49.493	22847268	50.169	47.032	1922090	2.885
63.628	22692937	49.831	48.993	64695059	97.115

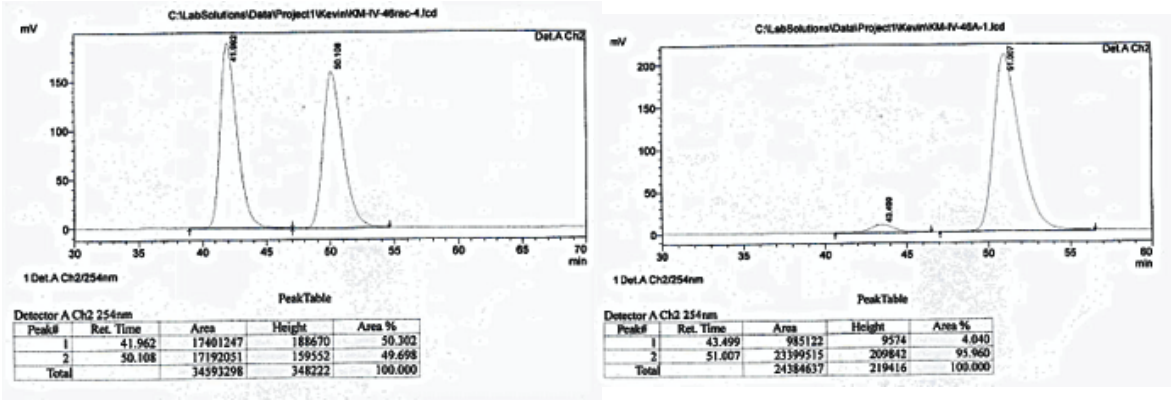
(*S*,*E*)-4-(4-Methoxyphenyl)-4-methyl-6-phenylhex-5-en-2-one (3.87, entry 2, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 3026 (w), 2998 (w), 2961 (w), 2933 (w), 2836 (w), 1703 (m), 1644 (w), 1609 (w), 1580 (w), 1511 (s), 1463 (w), 1447 (w), 1415 (w), 1357 (w), 1296 (w), 1249 (s), 1182 (m), 1123 (w), 1073 (w), 1032 (m), 971 (w), 915 (w), 830 (m), 805 (w), 751 (m), 720 (w), 695 (m) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.37 (2H, m), 7.33–7.26 (4H, m), 7.24–7.20 (1H, m), 6.87 (2H, m), 6.53 (1H, d, J = 16 Hz), 6.37 (1H, d, J = 16.4 Hz), 3.80 (3H, s), 2.98 (2H, ABq, $\delta\Delta_{AB}$= 0.06, J = 14.2), 1.92 (3H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 158.1, 138.5 138.4, 137.5, 128.7, 127.7, 127.4, 127.3, 126.4 113.8, 55.4, 54.7, 47.2, 32.2, 26.2; HRMS (ESI+): Calcd for $C_{20}H_{23}O_2$ [M+H$^+$]: 295.1698. Found: 295.1702. Specific Rotation $[\alpha]_D^{20}$ –18.1 (*c* 1.75, $CHCl_3$) for a sample of 98:2 er. Enantiomeric purity (98:2 er) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.





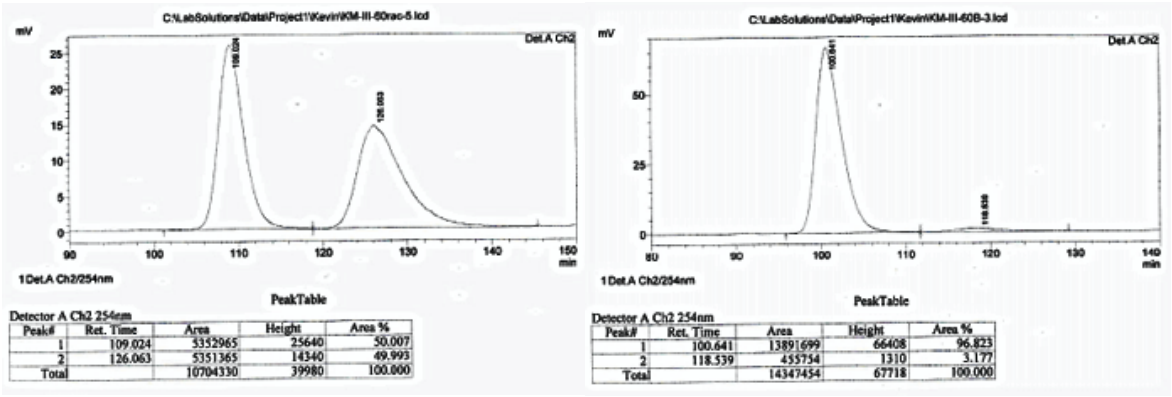
Retention Time	Area	Area %	Retention Time	Area	Area %
15.781	8628065	49.117	15.017	23947008	97.857
16.771	8938141	50.883	16.383	524363	2.143

(*S*,*E*)-4-(4-Bromophenyl)-4-methyl-6-phenylhex-5-en-2-one (3.88, entry 3, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 3080 (w), 3057 (w), 3024 (w), 2967 (w), 2929 (w), 1717 (s), 1599 (w), 1490 (s), 1447 (w), 1396 (w), 1357 (s), 1272 (w), 1156 (w), 1103 (w), 1081 (m), 1028 (w), 1007 (s), 970 (m), 914 (w), 824 (m), 751 (s), 718 (w), 694 (s), 669 (w), 541 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.42 (2H, m), 7.39–7.37 (2H, m), 7.32 (2H, t, *J* = 6.8 Hz), 7.25–7.21 (3H, m), 6.52 (1H, d, *J* = 16.4 Hz), 6.37 (1H, d, *J* = 16.0 Hz), 3.01 (2H, s), 1.98 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 145.7, 137.3, 137.2, 131.5, 128.8, 128.4, 128.0, 127.6, 126.4, 120.4, 54.2, 43.0, 32.1, 26.2; HRMS (ESI+): Calcd for $C_{19}H_{20}Br_1O_1$ $[M+H^+]$: 343.0698. Found: 343.0683. Specific Rotation $[\alpha]_D^{20}$ –16.9 (*c* 1.77, $CHCl_3$) for a sample of 96:4 e.r. Enantiomeric purity (96:4 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 98% Hexanes, 2% *i*PrOH, 1.0 mL/min, 254 nm.



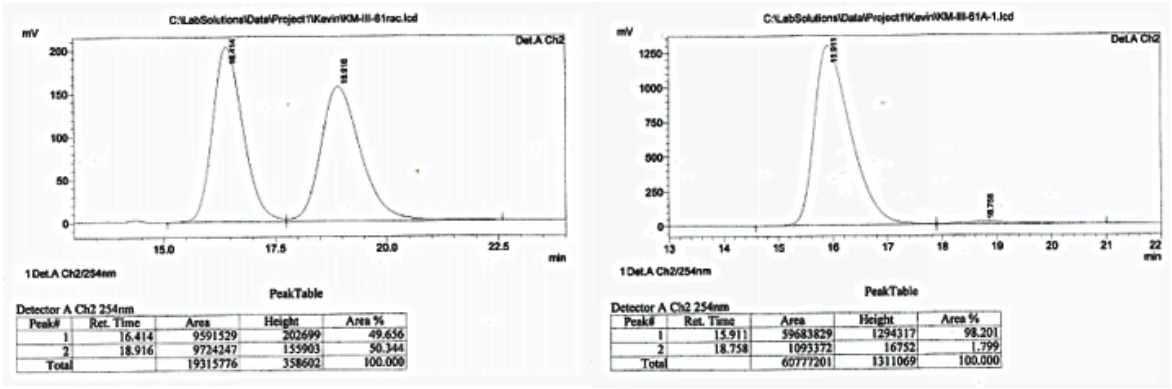
Retention Time	Area	Area %	Retention Time	Area	Area %
41.962	17401247	50.302	43.499	985122	4.040
50.108	17192051	49.698	51.007	23399515	95.960

(*S*,*E*)-6-(4-Methoxyphenyl)-4-methyl-4-phenylhex-5-en-2-one (3.90, entry 5, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 3031 (w), 2960 (w), 2930 (w), 2836 (w), 1704 (m), 1607 (m), 1577 (w), 1511 (s), 1494 (w), 1462 (w), 1444 (w), 1419 (w), 1356 (w), 1303 (w), 1281 (w), 1248 (s), 1175 (m), 1108 (w), 1073 (w), 1032 (m), 972 (w), 819 (w), 764 (w), 700 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.30 (6H, m), 7.21 (1H, app. tt, *J*= 7.2, 1.6 Hz), 6.87–6.83 (2H, m), 6.42 (1H, d, *J*= 16 Hz), 6.33 (1H, d, *J*= 16 Hz), 3.81 (3H, s), 3.03 (1H, dd, *J*= 14.4 Hz), 2.97 (1H, d, *J*= 14.8 Hz), 1.91 (3H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 159.2, 135.9, 130.2, 128.5, 127.5, 127.0, 126.6, 126.5, 115.2, 114.2, 55.5, 54.5, 43.2, 32.2, 26.2; HRMS (ESI+): Calcd for $C_{20}H_{23}O_2$ $[M+H^+]$: 295.1698. Found: 295.1699. Specific Rotation $[\alpha]_D^{20}$ –14.2 (*c* 1.28, $CHCl_3$) for a sample of 97:3 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



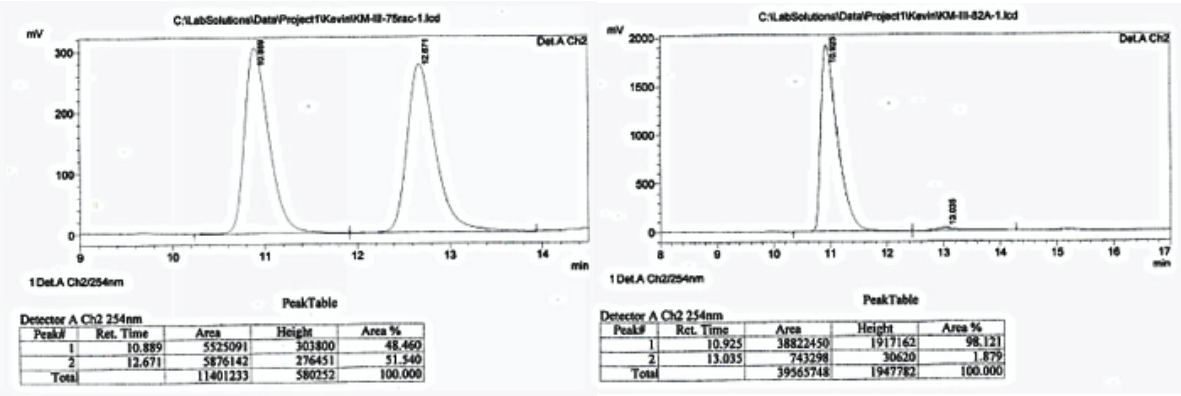
Retention Time	Area	Area %	Retention Time	Area	Area %
109.024	5352965	50.007	100.641	13891699	96.823
126.063	5351365	49.993	118.539	455754	3.177

(*S*,*E*)-4-Methyl-4-phenyl-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (3.91, entry 6, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 2969 (w), 1719 (w), 1646 (w), 1615 (w), 1495 (w), 1446 (w), 1414 (w), 1358 (w), 1325 (s), 1164 (m), 1121 (m), 1067 (m), 1030 (w), 1016 (w), 974 (w), 868 (w), 820 (w), 765 (w), 700 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.35 (2H, s), 7.34 (2H, s) 7.24 (1H, dt, J = 4.8, 4.0 Hz), 6.69 (1H, d, J = 16.4 Hz), 6.41 (1H, d, J = 16.4 Hz), 3.03 (2H, ABq, $\delta\Delta_{AB}$= 0.04 J = 7.1 Hz), 1.94 (3H, s), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 146.1, 141.0, 140.7, 129.2 (q, $J_{C\text{-}F}$ = 32 Hz), 128.6, 126.8 (q, $J_{C\text{-}F}$ = 250 Hz), 126.7, 126.6, 126.5, 126.5, 125.7 (q, $J_{C\text{-}F}$ = 12 Hz), 54.3, 43.4, 32.1, 26.1; HRMS (ESI+): Calcd for $C_{20}H_{20}F_3O_1$ [M+H^+]: 333.1466. Found: 333.1474. Specific Rotation $[\alpha]_D^{20}$ –18.5 (*c* 2.04, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 95% Hexanes, 5% *i*PrOH, 1.0 mL/min, 254 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
16.414	9591529	49.656	15.911	1294317	98.201
18.916	9724247	50.344	18.758	16752	1.799

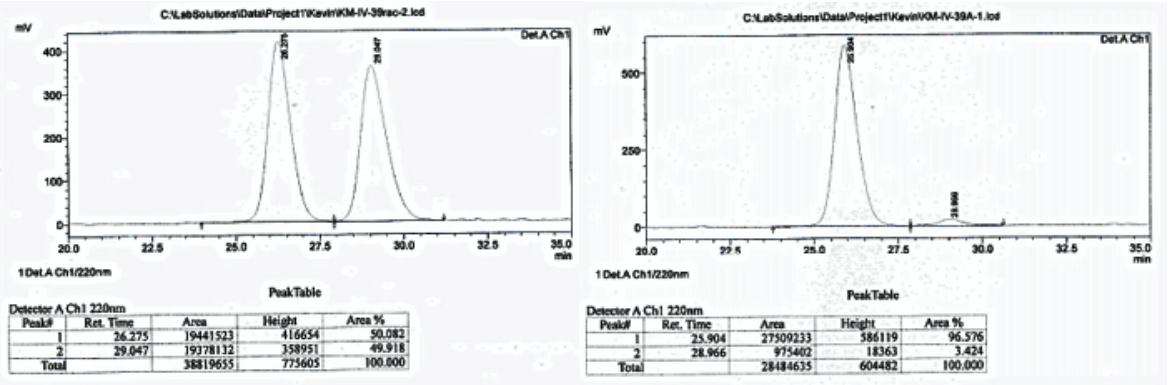
(*S*,*E*)-4-(2-Methoxyphenyl)-4-methyl-6-phenylhex-5-en-2-one (3.92, entry 7, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 3058 (w), 3023 (w), 2998 (w), 2963 (w), 2932 (w), 2835 (w), 1715 (m), 1703 (m), 1597 (w), 1579 (w), 1489 (m), 1462 (w), 1435 (w), 1356 (w), 1288 (w), 1238 (s), 1200 (w), 1179 (w), 1165 (w), 1122 (w), 1071 (w), 1049 (w), 1027 (m), 966 (w), 793 (w), 751 (s), 694 (m), 565 (w), 541 (w), 500 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.36 (2H, m), 7.31–7.28 (3H, m), 7.25–7.18 (2H, m), 6.94 (1H, dt, *J* = 1.2, 0.8 Hz), 6.89 (1H, dd, *J* = 8.8, 0.8 Hz), 6.74 (1H, d, *J* = 16 Hz), 6.30 (1H, d, *J* = 16.4 Hz), 3.82 (3H, s), 3.33 (1H, d, *J* = 14.8 Hz), 3.14 (1H, d, *J* = 14.8 Hz), 1.91 (3H, s), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 157.7, 138.6, 138.0, 134.2, 128.6, 128.3, 128.0, 127.1, 126.4, 126.3, 120.9, 111.9, 55.4, 52.9, 42.5, 31.6, 25.6; HRMS (ESI+): Calcd for $C_{20}H_{23}O_2$ [M+H$^+$]: 295.1698. Found: 295.1707. Specific Rotation $[\alpha]_D^{20}$ –55.2 (*c* 1.69, $CHCl_3$) for a sample of 98:2 er. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*-PrOH, 1.0 mL/min, 254 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
10.889	5525091	48.460	10.925	1917162	98.121
12.671	5876142	51.540	13.035	30620	1.879

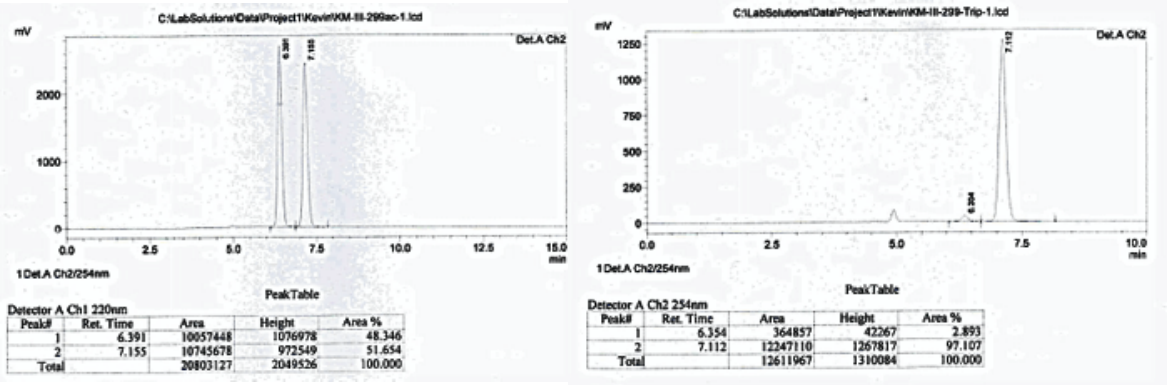
(*S*,*E*)-4-Methyl-4-phenyl-6-(thiophen-3-yl)hex-5-en-2-one (3.93, entry 8, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 3088 (w), 3057 (w), 3023 (w), 2967 (w), 2929 (w), 1703 (s), 1599 (w), 1494 (w), 1445 (w), 1414 (w), 1356 (m), 1306 (w), 1245 (w), 1206 (w), 1157 (w), 1079 (w), 1030 (w), 969 (w), 863 (w), 832 (w), 765 (s), 700 (s), 647 (w), 628 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (4H, m), 7.28–7.25 (1H, m), 7.24–7.20 (2H, m), 7.12 (1H, dd, *J* = 1.2, 2.8 Hz), 6.43 (1H, d, *J* = 16.4 Hz), 6.29 (1H, d, *J* = 16. Hz), 2.99 (2H, ABq, $\delta\Delta_{AB}$= 0.05, *J* = 14.8 Hz), 1.91 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 146.5, 140.0, 138.0, 128.5, 126.6, 126.5. 126.2, 125.1, 122.1, 121.6, 54.5 43.2, 32.1, 26.1; HRMS (ESI+): Calcd for $C_{17}H_{19}O_1S_1$ [M+H$^+$]: 271.1157. Found: 271.1158. Specific Rotation $[\alpha]_D^{20}$ –17.1 (*c* 1.46, $CHCl_3$) for a sample of 96.5:3.5 e.r. Enantiomeric purity (96.5:3.5 e.r.) was determined

by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
26.275	19441523	50.082	25.904	27509233	96.576
29.047	19378132	49.918	28.966	975402	3.424

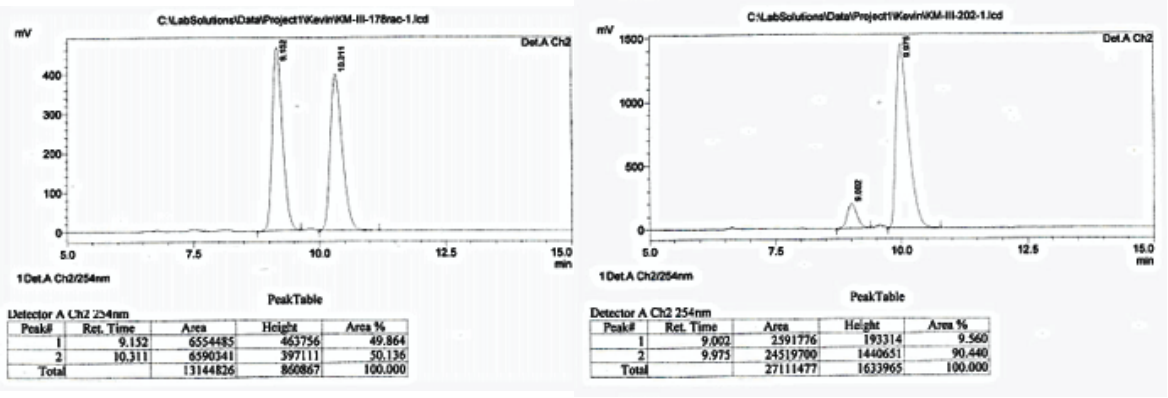
(*R*,*E*)-4-Cyclohexyl-4-methyl-6-phenylhex-5-en-2-one (3.95, entry 10, Table 3.4). The title compound was synthesized analogously to **3.86** except with 5 mol % 1b as catalyst precursor. IR (neat): 3024 (w), 2925 (s), 2852 (m), 1704 (s), 1600 (w), 1493 (w), 1448 (m), 1355 (m), 1269 (w), 1202 (w), 1181 (w), 1151 (w), 1072 (w), 1028 (w), 974 (w), 893 (w), 747 (m), 694 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.36 (2H, m), 7.32–7.28 (2H, m), 7.20 (1H, dt, *J* = 1.6, 7.6 Hz), 6.32 (1H, d, *J* = 16.4 Hz), 6.26 (1H, d, *J* = 16.4 Hz), 2.56 (2H, ABq, $\Delta\delta_{AB}$= 0.14, *J* = 14.4), 2.09 (3H, s) 1.79–1.63 (5H, m), 1.46 (1H, tt, *J* = 3.2, 12.0 Hz), 1.28–1.18 (2H, m), 1.16 (3H, s), 1.13–0.93 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 137.8, 128.7, 127.9, 127.2, 126.2, 52.8, 47.1, 42.1, 32.6, 28.1, 27.5, 27.13, 27.09, 26.7, 19.7; HRMS (ESI+): Calcd for $C_{19}H_{27}O_1$ [M+H$^+$]: 271.2062. Found: 271.2051. Specific Rotation $[\alpha]_D^{20}$ +70.6 (*c* 1.81, $CHCl_3$) for a sample of 97:3 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
6.391	10057448	48.346	6.354	364857	2.893

7.155	10745678	51.654	7.112	12247110	97.107

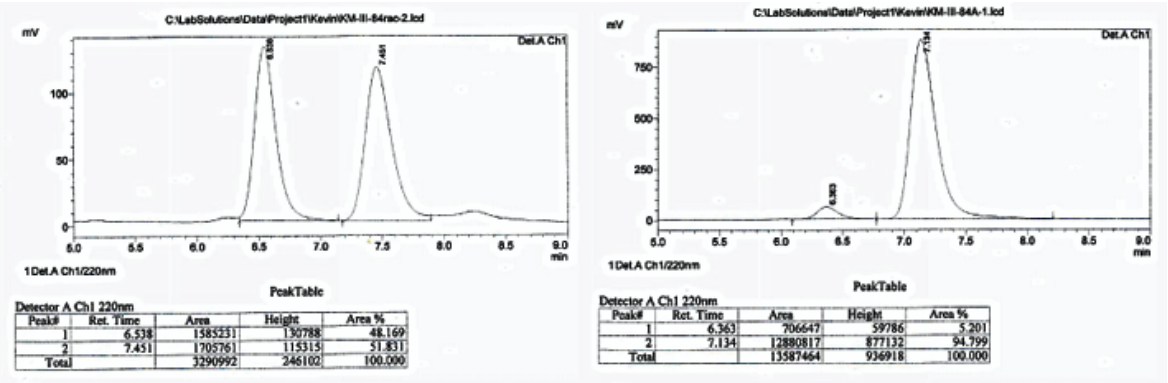
(*S*,*E*)-4-Benzyl-4-methyl-6-phenylhex-5-en-2-one (3.96, entry 11, Table 3.4). The title compound was synthesized analogously to **3.86** except with 5 mol % **1b** as catalyst precursor. IR (neat) 3082 (w), 3060 (w), 3026 (w), 2961 (w), 2920 (w), 1708 (s), 1600 (w), 1494 (m), 1452 (w), 1399 (w), 1357 (m), 1171 (w), 1124 (w), 1073 (w), 1030 (w), 972 (m), 914 (w), 845 (w), 736 (s), 695 (s), 638 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (4H, m), 7.27–7.17 (4H, m), 7.14–7.11 (2H, m), 6.36 (1H, d, *J* = 16.4 Hz), 6.23 (1H, d, *J* = 16.4 Hz), 2.88 (2H, app. t, *J* = 13.6), 2.52 (2H, ABq, $\Delta\delta_{AB}$= 0.13, *J* = 15.6), 2.09 (3H, s), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 138.0, 137.8, 137.6, 130.9, 128.7, 128.0, 127.6, 127.3, 126.4, 126.3, 52.9, 47.5, 40.0, 32.3, 23.9; HRMS (ESI+): Calcd for $C_{20}H_{26}N_1O_1$ [M+NH_4^+]: 296.2014. Found: 296.2015. Specific Rotation $[\alpha]_D^{20}$ –48.4 (*c* 0.33, $CHCl_3$) for a sample of 90.5:9.5 e.r. Enantiomeric purity (90.5:9.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD(H), 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
9.152	6554485	49.864	9.002	2591776	9.560
10.311	6590341	50.136	9.975	24519700	90.440

(*S*,*E*)-6-Cyclohexyl-4-methyl-4-phenylhex-5-en-2-one (3.97, entry 12, Table 3.4). The title compound was synthesized analogously to **3.86**. IR (neat): 2923 (m), 2850 (w), 1706 (m), 1600 (w), 1493 (w), 1446 (w), 1355 (w), 1181 (w), 1030 (w), 970 (w), 761 (w), 699 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.27 (4H, m), 7.21–7.17 (1H, m), 5.69 (1H, dd, *J* = 1.2, 15.6 Hz), 5.39 (1H, dd, *J* = 7.0, 15.8 Hz), 2.86 (2H, ABq, $\Delta\delta_{AB}$= 0.05, *J* = 13.8 Hz), 2.05–1.96 (1H, m), 1.88 (3H, s), 1.74–1.71 (4H, m), 1.68–1.63 (1H, m), 1.47 (3H, s), 1.32–1.19 (3H, m), 1.18–1.05 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 147.4, 135.3, 134.2, 128.3, 126.5, 126.2, 54.9, 42.7, 41.0, 33.4, 33.3, 32.3, 26.3, 26.2, 26.1; HRMS (ESI+): Calcd for $C_{19}H_{27}O_1$ [M+H^+]: 271.2062. Found: 271.2052. Specific Rotation $[\alpha]_D^{20}$ –29.1 (c 0.60 in $CHCl_3$) for a sample of 94.5:5.5 e.r. Enantiomeric purity (95:5 e.r.) was determined by HPLC analysis in comparison with

authentic racemic material; Chiracel OJ(H), 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



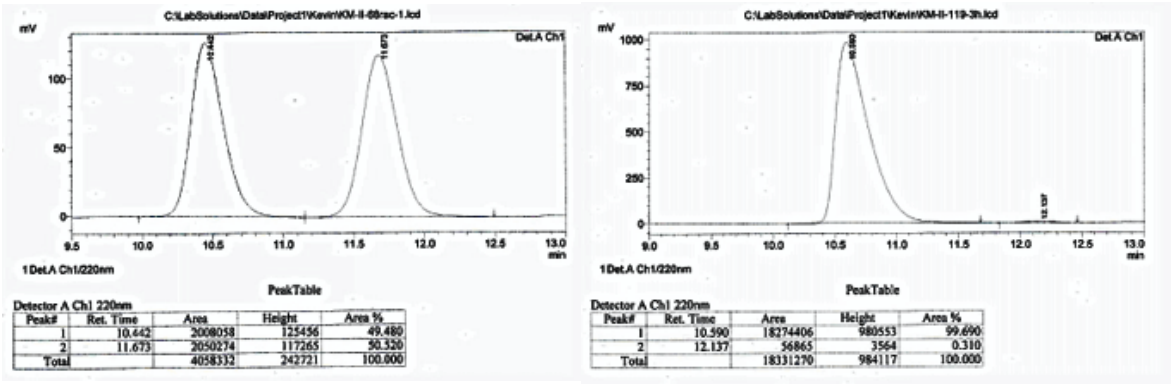
Retention Time	Area	Area %	Retention Time	Area	Area %
6.538	1585231	48.169	6.363	706647	5.201
7.451	1705761	51.831	7.134	12880817	94.799

Preparation of α-Alkenylaluminum Reagents. The necessary compounds were synthesized following the above-mentioned procedure used for preparation of β-alkenylaluminum species, except 3.0 mol % Ni(dppp)Cl_2 was used [vs 3.0 mol % Ni(PPh_3)$_2Cl_2$].

Procedure for NHC–Cu-catalyzed Enantioselective Conjugate Addition with an α-Alkenylaluminum Reagent. An oven-dried 1-dram vial was charged with NHC–Ag complex **1c** (2.64 mg, 2.50 mmol) and $CuCl_2$•$2H_2O$ (0.85 mg, 5.00 mmol) weighed under an N_2 atmosphere in a glove box. The vial was sealed with a cap with septum. Tetrahydrofuran (thf; 0.5 mL) was added with a syringe to the vial. The resulting blue solution was allowed to stir for five minutes and then cool to –78 °C (dry ice/acetone bath), followed by the addition of diisobutyl(1-phenylvinyl)aluminum (200 μL, 2.00 mmol, 1.0 M) and (*E*)-4-phenylpent-3-en-2-one (16.0 mg, 0.100 mmol) in thf (0.5 mL) through a syringe, sequentially, resulting in a brown solution. The mixture was allowed to warm to –30 °C and rest in a cryocool bath for 3.0 h, after which time, the reaction was quenched by the addition of a saturated aqueous solution of Rochelle's salt (1.0 mL) at –30 °C. The resulting mixture was then allowed to warm to 22 °C and stir for 30 min. The layers are separated, and the aqueous layer was washed with Et_2O (2.0 mL x 3). The combined organic layers were passed through a short plug of silica gel, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel chromatography to give the product as colorless crystals (21.1 mg, 0.08 mmol, 80% yield).

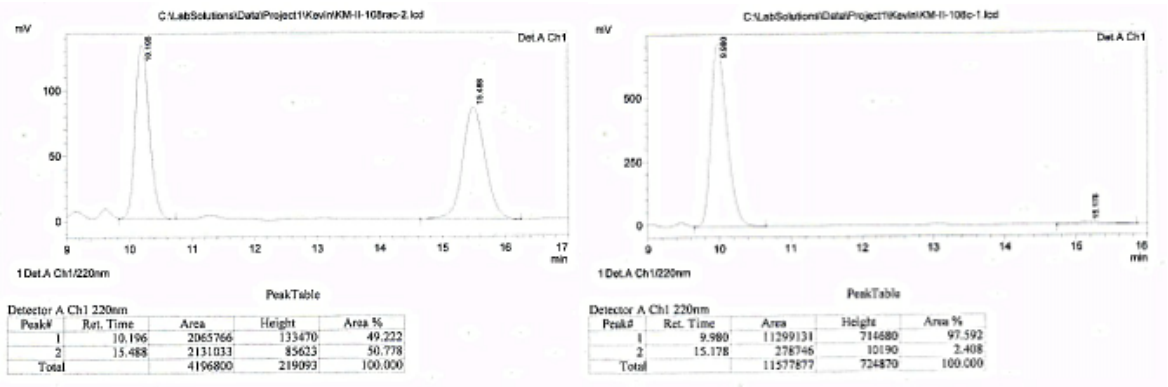
(*S*)-4-Methyl-4,5-diphenylhex-5-en-2-one (3.60, entry 1, Table 3.3). IR (neat): 3055 (w), 3023 (w), 2971 (w), 2925 (w), 1719 (m), 1703 (m), 1622 (w), 1599 (w), 1573 (m), 1491 (m), 1444 (m), 1417 (w), 1355 (m), 1300 (w), 1281 (w), 1156 (m), 1072 (w), 1029 (m), 1001 (w), 971 (w), 907 (w), 774 (m), 698 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

7.44–7.41 (2H, m), 7.37–7.33 (2H, m), 7.28–7.24 (1H, m), 7.17–7.13 (1H, m), 7.11–7.07 (2H, m) 6.76–6.74 (2H, m) 5.39 (1H, d, J = 1.2 Hz), 5.25 (1H, d, J = 0.8 Hz), 3.01 (2H, ABq, $\delta\Delta_{AB}$= 0.16, J_{AB} = 15.0 Hz) 1.76 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 155.4, 146.0, 142.4, 128.7, 128.6, 127.6, 127.0, 126.9, 126.6, 114.8, 53.2, 46.2, 32.0, 26.2; HRMS (ESI$^+$): Calcd for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587. Found: 265.1596. Specific Rotation $[\alpha]_D^{20}$ –22.4 (*c* 0.58, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (99:1 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



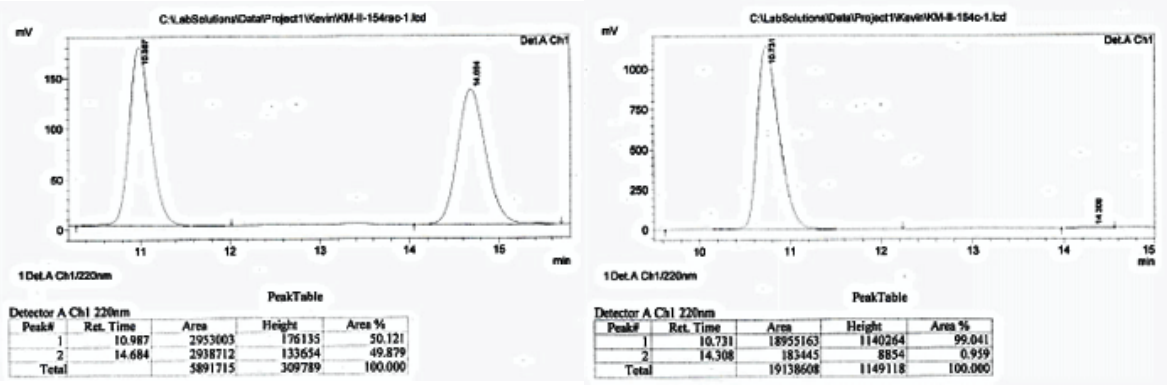
Retention Time	Area	Area %	Retention Time	Area	Area %
10.442	2008058	49.480	10.590	980553	99.690
11.673	2050274	50.520	12.137	3564	0.310

(*R*)-4-(4-Methoxyphenyl)-4-methyl-5-phenylhex-5-en-2-one (3.68, entry 2, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 2996 (w), 2933 (w), 2836 (w), 1718 (m), 1702 (m), 1677 (w), 1606 (m), 1592 (m), 1571 (w), 1509 (s), 1491 (w), 1462 (w), 1441 (w), 1415 (w), 1355 (m), 1291 (w), 1248 (s), 1180 (s), 1114 (w), 1073 (w), 1030 (s), 963 (w), 906 (m), 829 (s), 807 (w), 776 (m), 736 (w), 702 (s), 650 (w), 615 (w), 598 (w), 556 (m) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.30 (2H, m), 7.18–7.14 (1H, m), 7.12–7.08 (2H, m), 6.90–6.86 (2H, m), 6.77–6.75 (2H, m), 5.35 (1H, d, J = 0.8 Hz), 5.20 (1H, d, J = 0.8 Hz), 3.83 (3H, s), 2.97 (2H, ABq, $\delta\Delta_{AB}$= 0.19, J_{AB} = 14.8 Hz), 1.76 (3H, s), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 158.2, 155.7, 142.4, 137.8, 128.7, 128.1, 128.0, 127.0, 114.4, 113.8, 55.4, 53.4, 45.5, 32.1, 26.1; HRMS (ESI+): Calcd for $C_{22}H_{23}O_2$ $[M+H]^+$: 295.1693. Found: 295.1701. Specific Rotation $[\alpha]_D^{20}$ –32.3 (*c* 1.77, $CHCl_3$) for a sample of 97.5:2.5 e.r. Enantiomeric purity (97.5:2.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD(H), 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



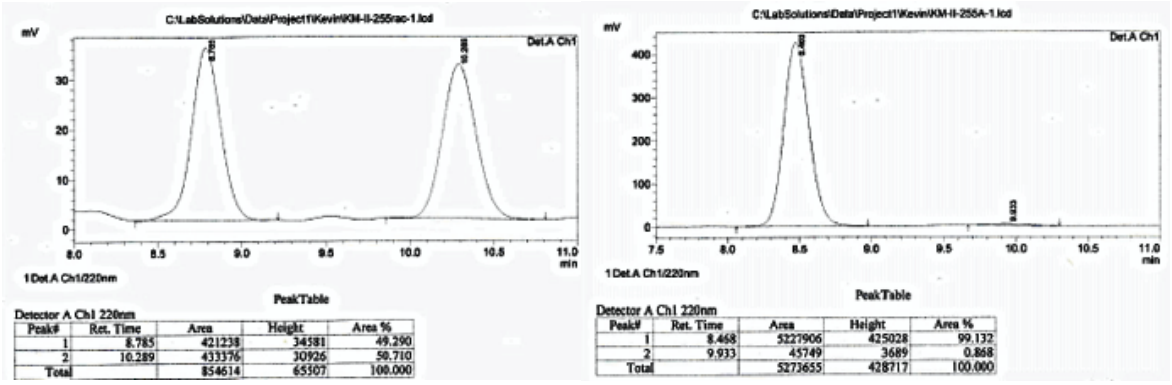
Retention Time	Area	Area %	Retention Time	Area	Area %
10.196	2065766	49.222	9.980	11299131	97.592
15.488	2131033	50.778	15.178	278746	2.408

(*R*)-4-(3-Fluorophenyl)-4-methyl-5-phenylhex-5-en-2-one (3.71, entry 5, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat) 3080 (w), 2976 (w), 1719 (m), 1612 (w), 1585 (m), 1486 (w), 1431 (w), 1356 (m), 1270 (w), 1235 (w), 1178 (w), 1163 (w), 1067 (w), 1029 (w), 1001 (w), 972 (w), 913 (m), 867 (w), 778 (s), 724 (w), 700 (s), 648 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (1H, m), 7.21–7.09 (5H, m), 6.98–6.93 (1H, m), 6.77–6.74 (2H, m), 5.39 (1H, s), 5.26 (1H, s), 2.99 (2H, ABq, $\delta\Delta_{AB}$= 0.11 J = 15.6 Hz), 1.81 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.8, 163.2 (d, J_{C-F} = 244 Hz), 154.9, 149.1 (d, J_{C-F} = 5.9 Hz), 142.0, 129.9 (d, J_{C-F} = 8.2 Hz), 128.6, 127.7, 127.2, 122.5 (d, J_{C-F} = 3.0 Hz), 115.2, 114.2 (d, J_{C-F} = 21.4 Hz), 113.5 (d, J_{C-F} = 20.9 Hz), 52.8, 46.1, 32.0, 26.3; HRMS (ESI+) Calcd for $C_{19}H_{20}FO$ $[M+H^+]$: 283.1498. Found: 283.1494. Specific Rotation $[\alpha]_D^{20}$ –18.0 (*c* 2.22, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (99:1 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
10.978	2953003	50.121	10.731	1140264	99.041
14.684	2938712	49.879	14.308	8854	0.959

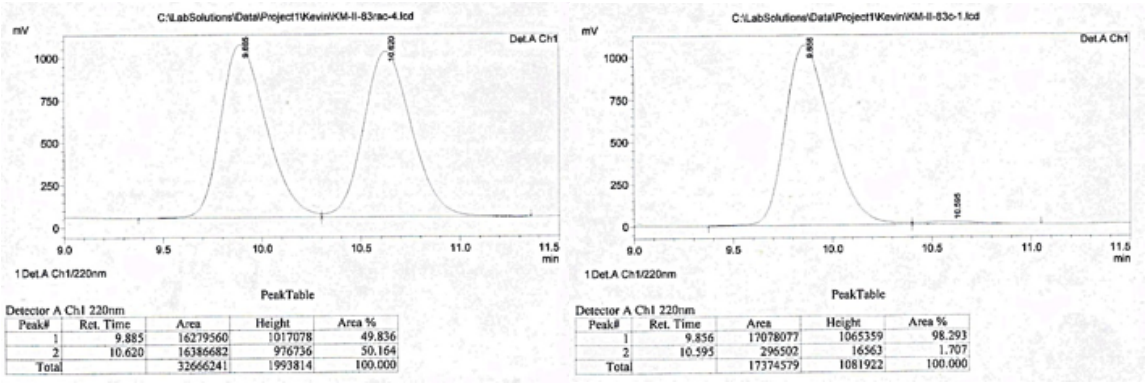
(*S*)-4-(2-Fluorophenyl)-4-methyl-5-phenylhex-5-en-2-one (3.72, entry 6, Table 3.3). The title compound was synthesized analogously to **3.60**, except the procedure was performed at –15 °C for 6.0 h. IR (neat): 3059 (w), 2978 (w), 1719 (m), 1703 (m), 1612 (w), 1575 (w), 1487 (m), 1445 (m), 1416 (w), 1356 (m), 1276 (w), 1212 (m), 1167 (w), 1119 (w), 1070 (w), 1037 (w), 1029 (w), 1001 (w), 970 (w), 942 (w), 910 (w), 856 (w), 815 (w), 754 (s), 702 (s), 669 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (1H, qd, J = 7.8, 1.6 Hz), 7.26–7.22 (1H, m), 7.20–7.15 (3H, m), 7.08 (1H, td, J = 7.6, 1.3 Hz), 7.01 (1H, ddd, J = 12.6, 8.0, 1.3 Hz), 6.96–6.94 (2H, m), 5.14 (1H, s), 5.07 (1H, s), 3.50 (1H, d, J = 15.5 Hz), 2.74 (1H, d, J = 15.5 Hz), 1.80 (3H, s), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 161.4 (d, J_{C-F} = 247.6 Hz), 155.7, 142.1, 132.5 (d, J_{C-F} = 10.5 Hz), 129.6 (d, J_{C-F} = 4.9 Hz), 129.0, 128.7 (d, J_{C-F} = 8.9 Hz), 127.6, 127.0, 124.0 (d, J_{C-F} = 3.6 Hz), 116.3 (d, J_{C-F} = 23.5 Hz), 114.7 (d, J_{C-F} = 2.1 Hz), 51.5 (d, J_{C-F} =5.0 Hz), 44.8 (d, J_{C-F} = 1.8 Hz), 31.8, 26.1; HRMS (ESI+) Calcd for $C_{19}H_{20}FO$ $[M+H]^+$: 283.1498. Found: 283.1494. Specific Rotation $[\alpha]_D^{20}$ –45.5 (*c* 1.36, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (99:1 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
8.785	421238	49.290	8.468	425028	99.132
10.289	433376	50.710	9.933	3689	0.868

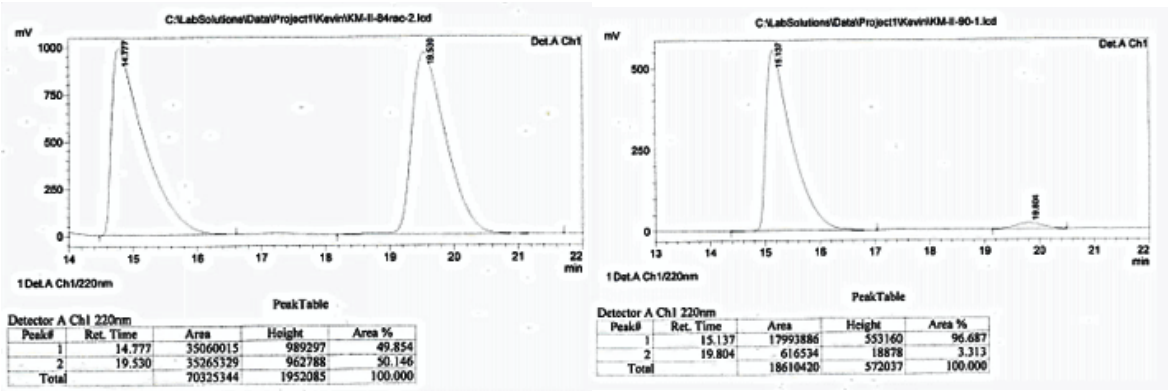
(*R*)-5-(4-Methoxyphenyl)-4-methyl-4-phenylhex-5-en-2-one (3.75, entry 9, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3088 (w), 3056 (w), 2997 (w), 2933 (w), 2836 (w), 1719 (m), 1703 (m), 1606 (m), 1573 (w), 1508 (s), 1461 (w), 1444 (m), 1417 (w), 1355 (m), 1287 (m), 1243 (s), 1178 (m), 1111 (m), 1074 (w), 1030 (m), 973 (w), 905 (m), 835 (m), 757 (m), 700 (s), 614 (w), 597 (m), 558 (m), 530 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.40 (2H, m), 7.37–7.32 (2H, m), 7.27–7.23 (1H, m), 6.70–6.61 (4H, m), 5.35 (1H, d, J = 0.8 Hz), 5.23 (1H, d, J = 0.8 Hz), 3.73 (3H, s), 3.00 (2H, ABq, $\delta\Delta_{AB}$= 0.14, J_{AB} = 15.2 Hz), 1.76 (3H, s), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 158.6, 154.7, 146.1, 134.7, 129.7, 128.6, 126.8, 126.5, 114.3, 113.0, 55.2, 53.1, 46.3, 32.0, 26.4; HRMS

(ESI+) Calcd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1698. Found: 295.1709. Specific Rotation $[\alpha]_D^{20}$ –18.5 (*c* 1.70, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 96% Hexanes, 4% *i*PrOH, 1.0 mL/min, 220 nm.



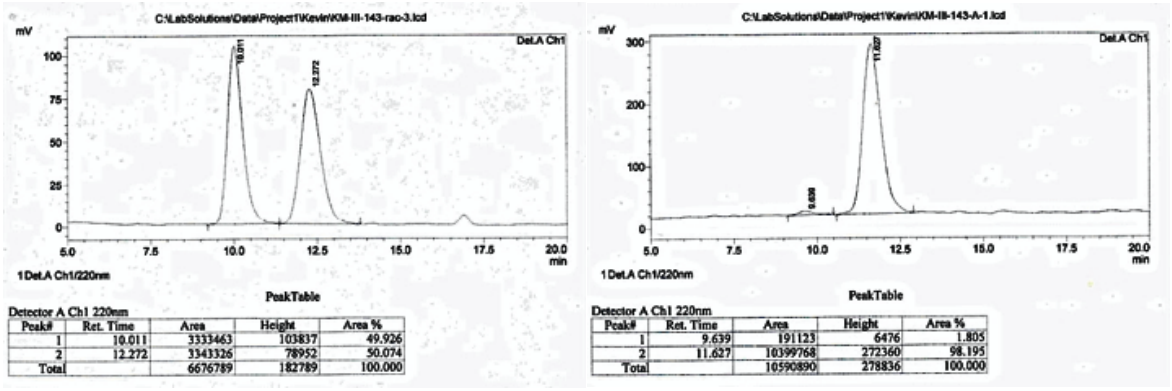
Retention Time	Area	Area %	Retention Time	Area	Area %
9.885	16279560	49.836	9.865	1065359	98.293
10.620	16386682	50.164	10.595	16563	1.707

(*S*)-4-Methyl-4-phenyl-5-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (3.76, entry 10, Table 3.3). The title compound was synthesized analogously to **3.60**, except the protocol was carried out at –15 °C for 5.0 h. IR (neat): 3058 (w), 2975 (w), 1721 (w), 1615 (w), 1493 (w), 1445 (w), 1403 (w), 1357 (w), 1324 (s), 1164 (m), 1122 (m), 1074 (w), 1064 (w), 1030 (w), 1016 (w), 973 (w), 912 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (6H, m), 7.30–7.27 (1H, m), 6.83, (2H, J = 8.0 Hz), 5.46 (1H, s), 5.25 (1H, s), 3.00 (2H, ABq, $\delta\Delta_{AB}$= 0.16, J_{AB} = 15.4 Hz), 1.81 (3H, s), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 154.4, 146.1, 145.3, 129.2 (q, J_{C-F} = 32.3 Hz), 128.9, 128.7, 126.9, 126.8, 124.5 (q, J_{C-F} = 3.7 Hz), 124.3 (q, J_{C-F} = 271 Hz), 115.6, 52.9, 46.0, 32.0, 25.8; HRMS (ESI+) Calcd for $C_{20}H_{20}F_3O$ $[M+H]^+$: 333.1466. Found: 333.1467. Specific Rotation $[\alpha]_D^{20}$ –25.7 (*c* 2.53, $CHCl_3$) for a sample of 97:3 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
14.777	3333463	49.926	15.137	17993886	96.687
19.530	3343326	50.074	19.804	616534	3.313

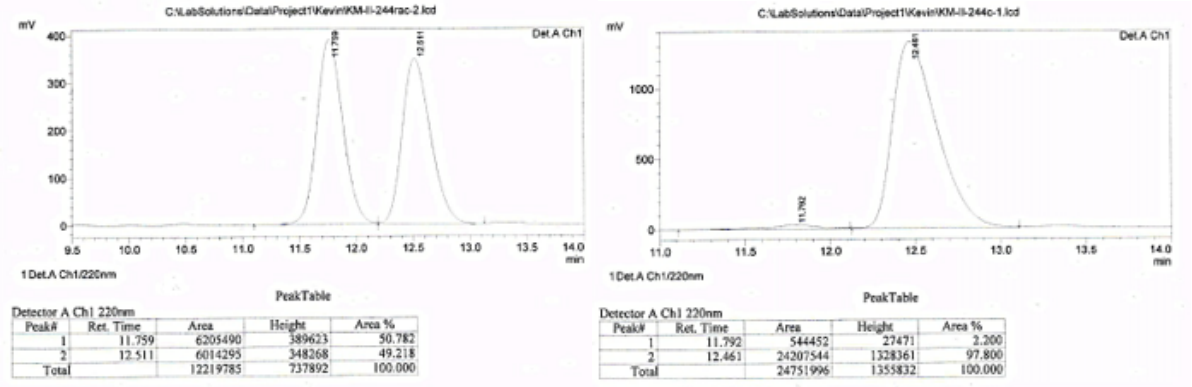
(*R*)-4-Methyl-4-phenyl-5-(3-(trifluoromethyl)phenyl)hex-5-en-2-one (3.77, entry 11, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3062 (w), 2970 (w), 2928 (w), 1721 (w), 1493 (w), 1445 (w), 1432 (w), 1357 (w), 1332 (s), 1263 (m), 1166 (s), 1125 (w), 1096 (w), 1072 (w), 909 (w), 808 (w), 768 (w), 730 (w), 701 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (5H, m), 7.19 (2H, dt, J = 8.0, 0.4 Hz), 6.94 (1H, app s), 6.88 (1H, app d, J = 7.2 Hz), 5.45 (1H, s), 5.23 (1H, s), 3.00 (2H, ABq, $\delta\Delta_{AB}$= 0.26, J_{AB} = 15.2 Hz), 1.82 (3H, s), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 154.4, 143.0, 131.9, 129.9 (q, J_{C-F} = 31.9 Hz), 128.7, 128.0, 126.9, 125.4 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 271 Hz), 123.8 (q, J_{C-F} = 3.6), 115.4, 52.8, 46.0, 32.0, 25.5; HRMS (ESI+) Calcd for $C_{20}H_{20}F_3O$ $[M+H]^+$: 333.1466. Found: 333.1471. Specific Rotation $[\alpha]_D^{20}$ –28.1 (*c* 3.2, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
10.011	3333463	49.926	9.639	6476	1.805
12.272	3343326	50.074	11.627	272360	98.195

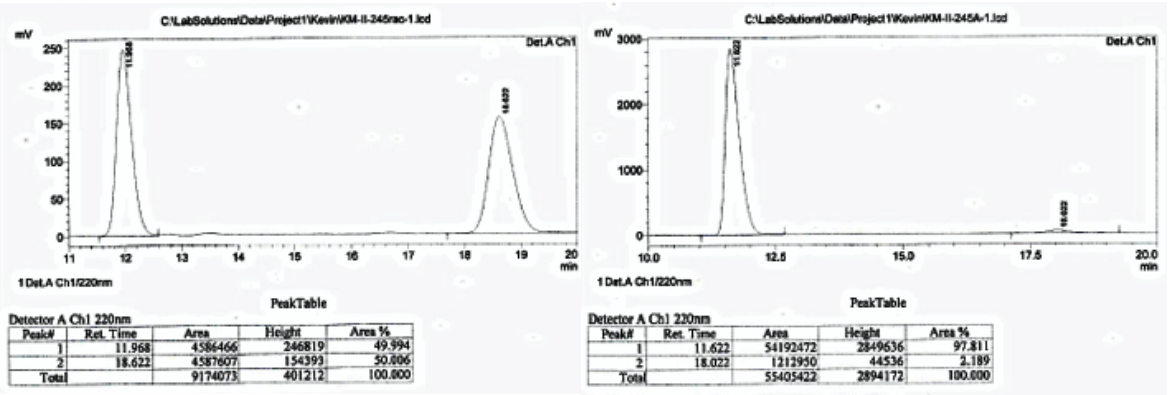
(*R*)-5-(2-Fluorophenyl)-4-methyl-4-phenylhex-5-en-2-one (3.78, entry 12, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3087 (w), 3060 (w), 3027 (w), 2978 (w), 2928 (w), 1721 (s), 1704 (s), 1630 (w), 1600 (w), 1577 (w), 1488 (s), 1446 (s), 1420 (w), 1357 (w), 1268 (w), 1215 (m), 1165 (w), 1126 (w), 1106 (w), 1072 (w), 1031 (w), 973 (w), 916 (w), 835 (w), 805 (w), 760 (s), 701 (s), 675 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (2H, m), 7.34–7.30 (2H, m), 7.25–7.21 (1H, m), 7.18–7.13 (1H, m), 7.01–6.97 (1H, m), 6.85–6.81 (1H, m), 6.48–6.43 (1H, m), 5.36 (1H, s), 5.11 (1H, s), 3.27 (1H, d, J = 14.8 Hz), 2.81 (1H, d, J = 14.8 Hz), 1.78 (3H, s), 1.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 160.0 (d, J_{C-F} = 243.3 Hz) 150.2, 144.7, 131.1 (d, J_{C-F} = 3.3 Hz), 129.3 (d, J_{C-F} = 16.4 Hz),

128.7 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.3, 127.4, 126.6, 123.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 116.5, 115.4 (d, $J_{C\text{-}F}$ = 23.8 Hz), 53.3, 46.5, 32.0, 23.9; HRMS (ESI+): Calcd for $C_{19}H_{20}F_1O_1$ $[M+H]^+$: 283.1498. Found: 283.1489. Specific Rotation $[\alpha]_D^{20}$ –37.5 (*c* 2.22, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 0.8 mL/min, 220 nm.



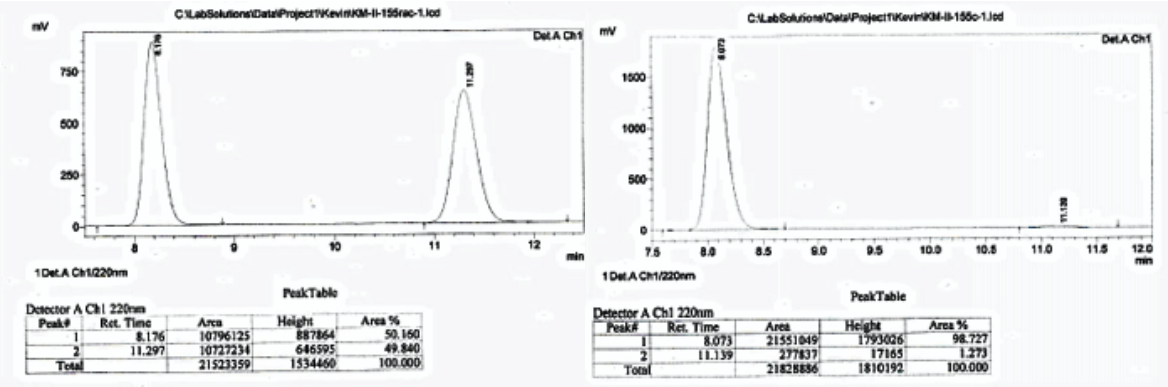
Retention Time	Area	Area %	Retention Time	Area	Area %
11.759	6205490	50.782	11.792	27471	2.200
12.511	6014295	49.218	12.461	1328361	97.800

(*R*)-4-(4-Methoxyphenyl)-4-methyl-5-(thiophen-3-yl)hex-5-en-2-one (3.79, entry 13, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3100 (w), 2962 (w), 2936 (w), 2835 (w), 1703 (m), 1608 (m), 1580 (w), 1509 (s), 1462 (m), 1441 (w), 1413 (w), 1355 (m), 1292 (m), 1249 (s), 1182 (s), 1114 (w), 1085 (w), 1033 (m), 975 (w), 905 (w), 867 (m), 830 (w), 797 (w), 740 (w), 717 (w), 692 (w), 630 (w), 551 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (2H, dd, *J* = 8.8, 3.2 Hz), 7.06 (1H, q, *J* = 4.8 Hz), 6.89 (2H, dd, *J* = 8.4, 3.2 Hz), 6.58 (1H, dd, *J* = 4.8, 0.8 Hz), 6.51 (1H, dd, *J* = 2.8, 1.2 Hz), 5.41 (1H, s), 5.35 (1H, s), 3.82 (3H, s), 2.98 (2H, ABq, $\delta\Delta_{AB}$= 0.08, J_{AB} = 14.0 Hz), 1.77 (3H, s), 1.57 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 158.3, 150.2, 142.3, 138.2, 128.6, 127.9, 124.2, 122.4, 114.0, 113.7, 55.4, 54.0, 45.7, 32.2, 26.5; HRMS (ESI+): Calcd for $C_{18}H_{21}O_2S_1$ $[M+H]^+$: 301.1262. Found: 301.1256. Specific Rotation $[\alpha]_D^{20}$= –28.9 (*c* 2.36, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



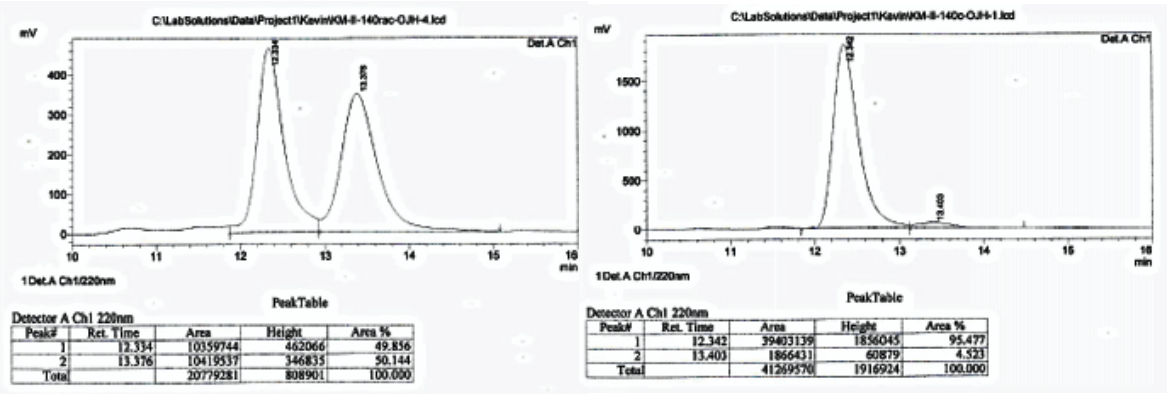
Retention Time	Area	Area %	Retention Time	Area	Area %
11.968	4586466	49.994	11.662	2849636	97.811
18.622	4587607	50.006	18.002	44536	2.189

(*S*)-4-(4-Bromophenyl)-4-methyl-5-phenylhex-5-en-2-one (3.69, entry 3, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3081 (w), 3052 (w), 2974 (w), 2935 (2), 1720 (s), 1622 (w), 1599 (w), 1572 (w), 1489 (s), 1465 (w), 1441 (w), 1416 (w), 1396 (w), 1357 (m), 1303 (m), 1272 (w), 1165 (w), 1126 (w), 1080 (m), 1029 (w), 1008 (s), 972 (w), 910 (m), 827 (m), 777 (m), 734 (w), 703 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (2H, m), 7.30–7.27 (2H, m), 7.20–7.15 (1H, m), 7.14–7.10 (2H, m), 6.77–6.74 (2H, m), 5.37 (1H, d, J = 0.8 Hz), 5.24 (1H, d, J = 0.4 Hz), 2.98 (2H, ABq, $\delta\Delta_{AB}$= 0.12, J_{AB} = 15.6 Hz), 1.81 (3H, s), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.8, 155.0, 145.3, 142.0, 131.6, 128.8, 128.6, 127.8, 127.2, 120.5, 115.2, 52.7, 45.9, 32.0, 26.2; HRMS (ESI+) Calcd for $C_{19}H_{20}O_1Br$ $[M+H]^+$: 343.0692. Found: 343.0683. Specific Rotation $[\alpha]_D^{20}$ –22.4 (*c* 1.25, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (99:1 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
8.176	10796125	50.160	8.073	1793026	98.727
11.297	10727235	49.840	11.139	17165	1.273

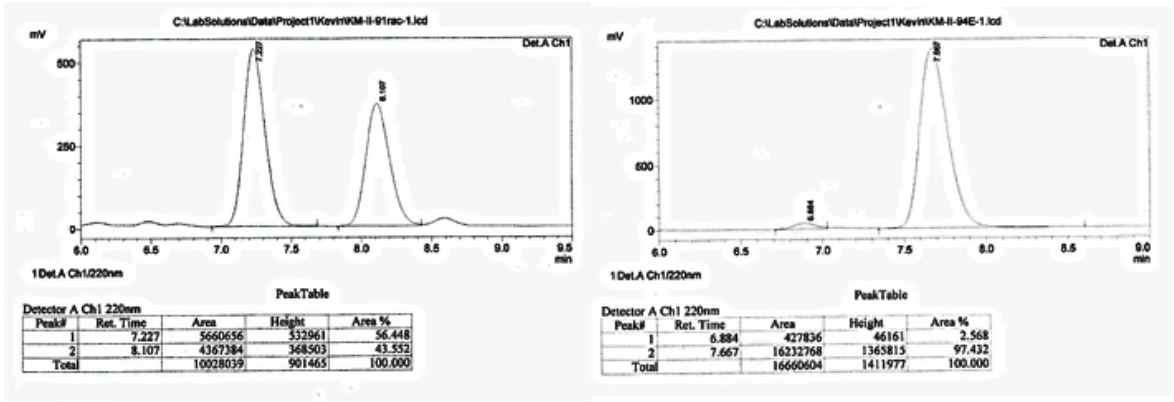
(*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-4-(1-phenylvinyl)heptan-2-one (3.83, entry 17, Table 3.3). The title compound was synthesized analogously to **3.60**, except that **1a** was used as catalyst precursor and the reaction time was 6.0 h. IR (neat): 2952 (m), 2928 (m), 2885 (w), 2856 (m), 1719 (m), 1619 (w), 1492 (w), 1471 (w), 1441 (w), 1387 (w), 1358 (m), 1253 (m), 1215 (w), 1163 (w), 1095 (s), 1042 (w), 1030 (w), 1006 (w), 939 (w), 906 (w), 833 (s), 813 (m), 773 (s), 704 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.24 (3H, m), 7.17– 7.15 (2H, m), 5.15 (1H, d, *J* = 1.2 Hz), 4.98 (1H, d, *J* = 1.2 Hz), 3.65–3.56 (2H, m), 2.57 (1H, d, *J* = 16.4 Hz), 2.42 (1H, d, *J* = 16 Hz), 2.30 (3H, s), 1.66–1.43 (4H, m), 1.24 (3H, s), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 154.8, 143.0, 128.9, 127.7, 126.7, 115.2, 63.6, 52.7, 41.6, 35.8, 32.2, 27.7, 26.1, 24.2, 18.5, –5.2; HRMS (ESI+): Calcd for $C_{22}H_{37}O_2Si$ [M+H$^+$]: 361.2557. Found: 361. 2568. Specific Rotation $[\alpha]_D^{20}$ –8.76 (*c* 1.14, $CHCl_3$) for a sample of 95.5:4.5 e.r. Enantiomeric purity (95.5:4.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 0.3 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
12.334	10359744	49.856	12.342	39403139	95.477
13.376	10419537	50.144	13.403	60879	4.523

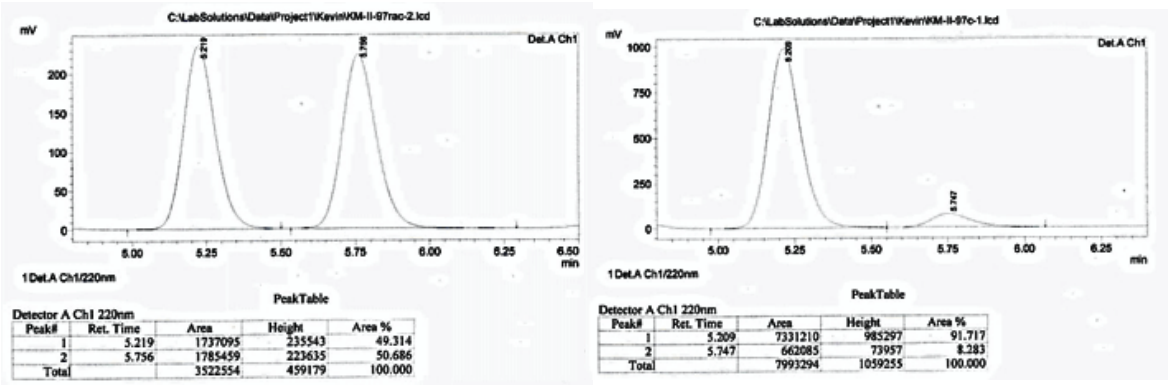
(*S*)-4-Benzyl-4-methyl-5-phenylhex-5-en-2-one (3.82, entry 16, Table 3.3). The title compound was synthesized analogously to **3.60**, except that **1a** was used as catalyst precursor and the reaction time was 6.0 h. IR (neat): 3082 (w), 3060 (w), 3027 (w), 2965 (w), 2927 (w), 1715 (m), 1623 (w), 1600 (w), 1573 (w), 1492 (w), 1453 (w), 1440 (w), 1400 (w), 1357 (m), 1261 (w), 1177 (w), 1121 (w), 1084 (w), 1073 (w), 1029 (w), 982 (w), 906 (w), 799 (w), 774 (m), 747 (m), 701 (s), 592 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.22 (6H, m), 7.19–7.13 (4H, m), 5.16 (1H, d, *J* = 1.0 Hz), 5.01 (1H, d, *J* = 1.0 Hz), 3.11 (1H, d, *J* = 13.2 Hz), 2.83 (1H, d, *J* = 13.1 Hz), 2.47 (2H, ABq, $\delta\Delta_{AB}$= 0.16 *J* = 17.4 Hz), 1.95 (3H, s), 1.19 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 155.9, 143.2, 138.4, 131.1, 129.1, 128.0, 127.7, 126.8, 126.4, 114.9, 51.0 46.2, 42.1, 31.8, 25.6; Calcd for $C_{20}H_{23}O$ [M+H$^+$]: 279.1749. Found: 279.1755. Specific Rotation $[\alpha]_D^{20}$ –16.9 (*c* 2.06, $CHCl_3$) for a sample of 97.5:2.5 e.r. Enantiomeric purity (97.5:2.5 e.r.) was

determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
7.227	5660656	56.448	6.884	46161	2.568
8.107	4367384	43.552	7.667	1365815	97.432

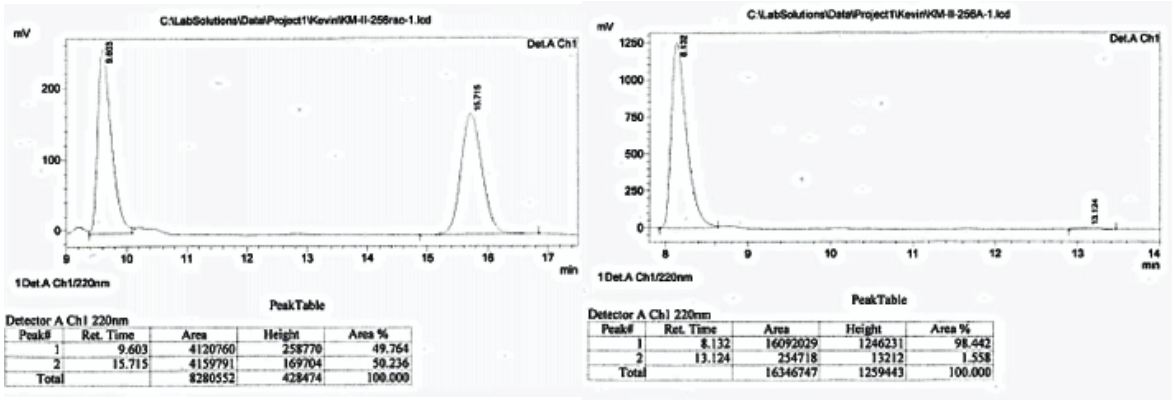
(*S*)-4-Cyclohexyl-4-methyl-5-phenylhex-5-en-2-one (3.81, entry 15, Table 3.3). The title compound was synthesized analogously to **3.60**, except the reaction time was 6.0 h. IR (neat): 3081 (w), 3052 (w), 2924 (s), 2851 (m), 1719 (s), 1687 (w), 1612 (w), 1574 (w), 1492 (w), 1448 (m), 1355 (s), 1269 (w), 1243 (w), 1173 (m), 1129 (w), 1073 (w), 1029 (w), 969 (w), 902 (m), 846 (w), 774 (m), 704 (s), 624 (w), 599 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.22 (3H, m), 7.14–7.12 (2H, m), 5.13 (1H, d, J = 1.6 Hz), 5.04 (1H, d, J = 1.2 Hz), 2.54 (2H, ABq, $\delta\Delta_{AB}$= 0.05 J = 16.8 Hz), 1.98 (3H, s), 1.88–1.69 (6H, m), 1.42 (1H, dt, J = 12, 2.8 Hz), 1.27–1.10 (2H, m), 1.20 (3H, s), 1.10–0.96 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 154.0, 143.4, 128.8, 127.5, 126.5, 116.3, 50.5, 44.9, 44.9, 32.0, 27.8, 27.7, 27.2, 26.9, 19.7; HRMS (ESI^+): Calcd for $C_{19}H_{27}O$ $[M+H^+]$: 271.2062. Found: 271.2074. Specific Rotation $[\alpha]_D^{20}$ –16.9 (*c* 1.66, $CHCl_3$) for a sample of 92:8 e.r. Enantiomeric purity (92:8 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %

5.219	1737095	49.314	5.209	7331210	91.717
5.756	1785459	50.686	5.747	73957	8.283

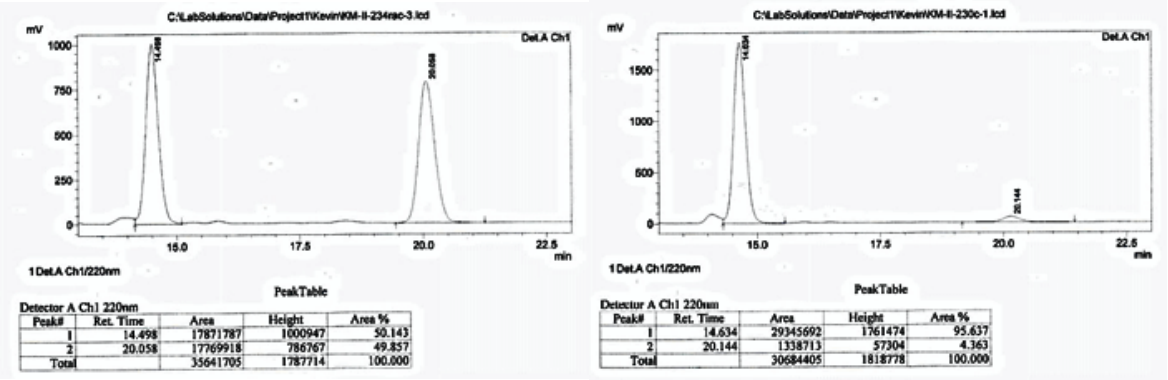
(*R*)-3-Methyl-2,3-diphenylnona-1,8-dien-5-one (3.98). The title compound was synthesized analogously to **3.60**, except the reaction was performed in the presence of 3.75 mol % **1b** as the catalyst precursor at –15 °C for 6.0 h. The desired product is inseparable from the starting material and is therefore characterized as an 85:15 mixture. IR (neat): 3079 (w), 3058 (w), 3022 (w), 2976 (w), 2937 (w), 1717 (m), 1685 (w), 1641 (w), 1600 (w), 1573 (w), 1491 (w), 1444 (w), 1409 (w), 1359 (w), 1282 (w), 1071 (w), 1029 (w), 999 (w), 909 (m), 777 (m), 767 (m), 701 (s) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.48 (0.35H, m, SM), 7.44–7.41 (2H, m), 7.39–7.32 (2.5H, m), 7.28–7.24 (), 7.18–7.13 (1H, m), 7.11–7.07 (2H, m), 6.77–6.75 (2H, m), 6.51 (0.15H, d, J = 1.2 Hz, SM), 5.92–5.82 (0.15H, m, SM), 5.69–5.59 (1H, m), 5.40 (1H, s), 5.27 (1H, s), 5.10–4.99 (0.33H, m), 4.92–4.87 (2H, m), 2.99 (2H, ABq, $\delta\Delta_{AB}$= 0.13 J = 15.2 Hz), 2.66 (0.32H, t, J = 7.2 Hz, SM), 2.55 (0.48H, d, J = 1.2 Hz, SM) 2.44–2.39 (0.32H, m, SM), 2.14–2.03 (4H, m), 1.61 (3H, s);); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 155.3, 146.2, 142.4, 137.3, 128.6, 128.5, 127.6, 127.0, 126.8, 126.5, 115.0, 114.9, 52.2, 46.2, 43.6, 27.6, 26.6; HRMS (ESI$^+$): Calcd for $C_{22}H_{25}O_1$ [M+H$^+$]: 305.1905. Found: 305.1913. Specific Rotation $[\alpha]_D^{20}$ –18.7 (*c* 1.60, $CHCl_3$) for a sample of 98.5:1.5 e.r. Enantiomeric purity (98.5:1.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 0.4 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
9.603	4120760	49.764	8.132	16092029	98.442
15.715	4159791	50.236	13.124	254718	1.558

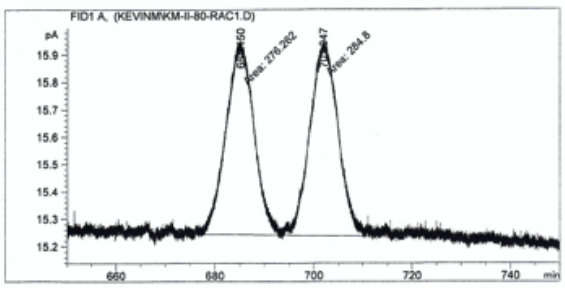
(*R*)-4-(Cyclohex-1-en-1-yl)-4-methyl-5-phenylhex-5-en-2-one (3.99). The title compound was synthesized analogously to **3.60**, except the reaction time was 5.0 h. IR (neat): 3080 (w), 3051 (w), 2925 (m), 2855 (w), 2835 (w), 1719 (m), 1704 (m), 1619 (w), 1598 (w), 1573 (w), 1490 (w), 1439 (w), 1354 (m), 1294 (w), 1178 (w), 1141 (w), 1073 (w), 1029 (w), 972 (w), 903 (m), 842 (w), 800 (w), 775 (m), 700 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (3H, m) 7.18–7.15 (2H, m), 5.53 (1H, t, J = 3.6 Hz), 5.17

(1H, d, J = 0.9 Hz), 5.12 (1H, d, J = 0.9 Hz), 2.70 (2H, ABq, $\delta\Delta_{AB}$= 0.15 J = 15.0 Hz), 2.11–2.09 (4H, m), 1.97 (3H, s), 1.63 (4H, m), 1.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 154.2, 142.7, 140.1, 128.7, 127.6, 126.9, 122.8, 115.2, 50.8, 47.1, 32.2, 25.9, 25.4, 24.2, 23.4, 22.5; HRMS (ESI$^+$): Calcd for $C_{19}H_{25}O$ [M+H$^+$]: 269.1905. Found: 269.1910. Specific Rotation $[\alpha]_D^{20}$ 3.9 (*c* 2.12, $CHCl_3$) for a sample of 96:4 e.r. Enantiomeric purity (96:4 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 0.4 mL/min, 220 nm.

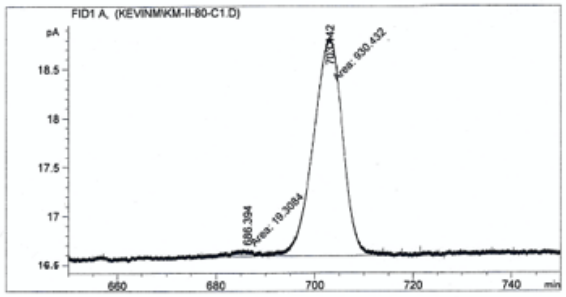


Retention Time	Area	Area %	Retention Time	Area	Area %
14.498	17871787	50.143	14.634	1761474	95.637
20.058	17769918	49.857	20.144	57304	4.363

(*R*)-5-(Cyclohex-1-en-1-yl)-4-methyl-4-phenylhex-5-en-2-one (3.100). The title compound was synthesized analogously to **3.60**, except the reaction was performed at –15 °C for 6.0 h. IR (neat): 3086 (w), 3057 (w), 3022 (w), 2926 (m), 2856 (w), 2835 (w), 1721 (m), 1704 (m), 1615 (w), 1599 (w), 1493 (w), 1445 (m), 1355 (m), 1301 (w), 1274 (w), 1246 (w), 1188 (w), 1161 (w), 1137 (w), 1076 (w), 1030 (w), 1001 (w), 973 (w), 900 (m), 854 (w), 804 (w), 767 (m), 700 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (2H, m), 7.29–7.25 (2H, m), 7.20–7.15 (1H, m), 5.27–5.24 (1H, m), 5.11 (1H, d, J = 1.2 Hz), 5.04 (1H, d, J = 1.2 Hz), 2.98 (2H, ABq, $\delta\Delta_{AB}$= 0.04, J_{AB} = 14.3 Hz), 1.93–1.88 (2H, m), 1.82 (3H, s), 1.66–1.64 (2H, m), 1.57 (3H, s), 1.47–1.41 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 157.5, 146.8, 138.8, 128.3, 126.5, 126.3, 126.2, 111.6, 53.6, 45.8, 32.1, 30.0, 26.4, 25.6, 23.1, 22.1; HRMS (ESI$^+$): Calcd for $C_{19}H_{25}O$ [M+H]$^+$: 269.1905. Found: 269.1907. Specific Rotation $[\alpha]_D^{20}$ –41.4 (*c* 1.78, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by GLC analysis in comparison with authentic racemic material; CDB-DM column, 15 psi, 110 ºC.



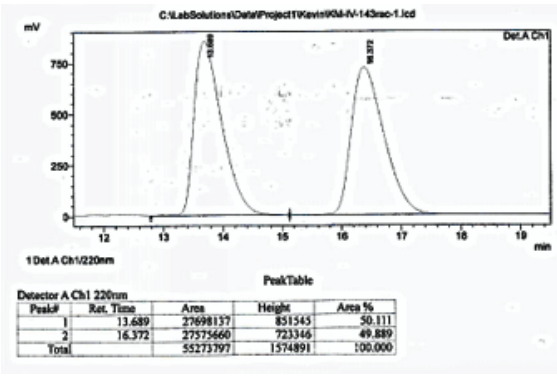
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	685.150	MF	6.4566	276.26230	7.13127e-1	49.23918
2	701.947	FM	6.6584	284.79959	7.12883e-1	50.76082

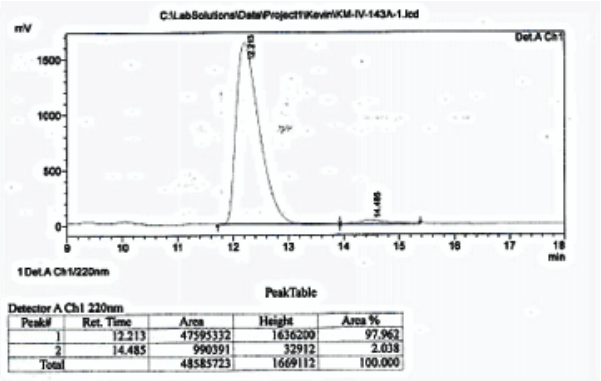


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	686.394	MF	4.0070	19.30844	8.03112e-2	2.03302
2	703.142	FM	6.9159	930.43188	2.24226	97.96698

Retention Time	Area	Area %	Retention Time	Area	Area %
685.150	276.262	49.239	686.394	19.308	2.033
701.947	284800	50.761	703.142	930432	97.967

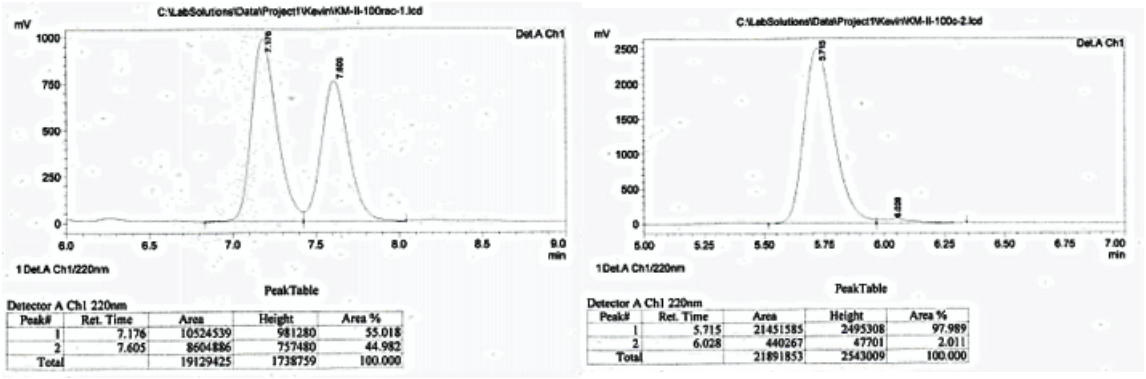
(*S*,*E*)-6-(3-Chlorophenyl)-4-ethyl-4-phenylhex-5-en-2-one (3.102). The title compound was synthesized analogously to **3.86**. IR (neat): 3057 (w), 3027 (w), 2966 (w), 2933 (w), 2878 (w), 1704 (m), 1593 (w), 1564 (w), 1493 (w), 1474 (w), 1460 (w), 1445 (w), 1425 (w), 1378 (w), 1356 (w), 1254 (w), 1195 (w), 1164 (w), 1093 (w), 1028 (w), 996 (w), 975 (w), 881 (w), 777 (m), 761 (m), 732 (w), 699 (s) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (1H, s), 7.35–7.28 (4H, m), 7.25–7.18 (4H, m), 6.50 (1H, d, J = 16.4 Hz), 6.35 (1H, d, J = 1.6 Hz), 3.01 (2H, ABq, $\delta\Delta_{AB}$= 0.03, J = 14.8 Hz), 2.06 (2H, ABX_3, J = 6.8, 14.0 Hz), 1.87 (3H, s), 0.82 (3H, t, J = 7.3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 144.8 139.4, 138.5, 134.7, 129.9, 128.5, 127.3, 126.6, 126.3, 124.6, 50.8, 47.1, 32.3, 30.5, 8.9; HRMS (ESI+): Calcd for $C_{20}H_{22}Cl_1O_3$ [M+H$^+$]: 313.1359. Found: 313.1367. Specific Rotation $[\alpha]_D^{20}$ –24.2 (c 0.55, $CHCl_3$) for a sample of 96:4 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



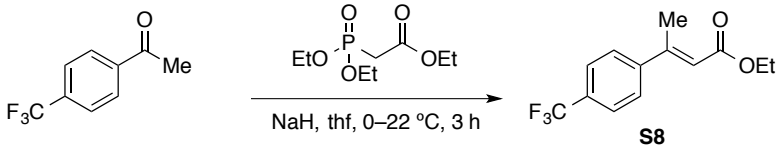


Retention Time	Area	Area %	Retention Time	Area	Area %
13.689	27698137	50.111	12.213	47595332	97.962
16.372	27575660	49.889	14.485	990391	2.038

(*R*)-4-Ethyl-4,5-diphenylhex-5-en-2-one (3.101). The title compound was synthesized analogously to **3.60**, except reaction time was 5.0 h. IR (neat): 3056 (w), 3023 (w), 2965 (w), 2937 (w), 2879 (w), 1702 (m), 1619 (w), 1598 (w), 1572 (w), 1491 (w), 1444 (w), 1416 (w), 1378 (m), 1355 (w), 1293 (w), 1188 (w), 1164 (w), 1125 (w), 1075 (w), 1028 (w), 1001 (w), 967 (w), 902 (m), 845 (w), 804 (w), 767 (m), 698 (s), 617 (w), 599 (w), 562 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.40 (2H, m), 7.37–7.32 (2H, m), 7.28–7.24 (1H, m), 7.16–7.12 (1H, m), 7.08–7.04 (2H, m), 6.68–6.65 (2H, m), 5.46 (1H, d, J = 0.8 Hz), 5.31 (1H, d, J = 0.8 Hz), 2.98 (2H, ABq, $\delta\Delta_{AB}$= 0.47 J_{AB} = 14.6 Hz), 2.08 (2H, ABX_3, J = 7.2, 13.6 Hz), 1.69 (3H, s), 0.78 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 154.6, 144.8, 142.5, 129.6, 128.5, 127.6, 127.5, 127.1, 126.6, 115.8, 49.6, 48.0, 32.2, 27.4, 8.7; HRMS (ESI^+): Calcd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1749. Found: 279.1753. Specific Rotation $[\alpha]_D^{20}$ –22.2 (*c* 0.45, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



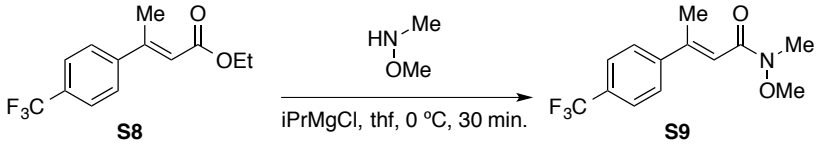
Retention Time	Area	Area %	Retention Time	Area	Area %
7.176	10524539	55.018	5.715	21451585	97.989
7.605	8604886	44.982	6.028	47701	2.011



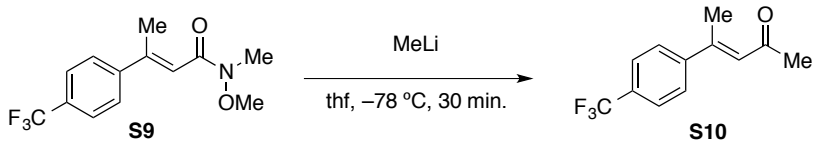
S8

Alternative Synthesis of α,β-Unsaturated Ketones. To a solution of sodium hydride (0.7 g, 29 mmol) in thf (40 mL) was added triethylphosphonoacetate (5.4 mL, 27.5 mmol) slowly at 0 ºC. After the mixture was allowed to stir for 30 min., 4-trifluoromethylacetophenone (4.5 g, 24 mmol) was added and the resulting solution was allowed to stir at 22 ºC for 3.0 h. The reaction was quenched upon addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was washed with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in*

vacuo to yield **S1** as a 3:1 *E*/*Z* mixture of olefins. The desired product was isolated through silica gel chromatography (100% hexanes→20:1 hexanes/Et_2O) as light yellow oil (1.41 g, 5.5 mmol, 23% yield).



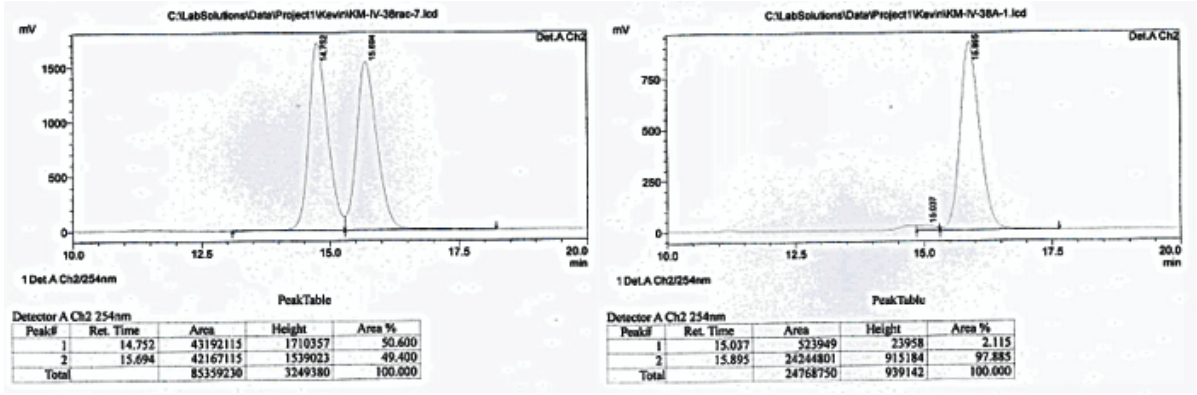
Representative procedure for synthesis of α,β-unsaturated Weinreb Amides. To a solution of **S1** (1.45g, 5.6 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.1 g, 11.2 mmol) in thf (28 mL) was added isopropylmagnesium chloride (22 mL, 1.2 M, 25.3 mmol) at 0 ºC. The resulting mixture was allowed to stir for 30 minutes. The reaction was quenched upon addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was washed with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to furnish **S2** as yellow oil. The unpurified mixture was used directly in the following step.



Representative Procedure for Synthesis of α,β-Unsaturated Ketones. To a solution of S2 (1.41 g, 5.2 mmol) in thf (52 mL) at –78 ºC was added MeLi slowly (5.5 mL, 1.6 M). The resulting mixture was allowed to stir at –78 ºC for 30 min before addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous layer was washed with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to furnish **S3** as yellow oil. The desired product was isolated through silica gel chromatography (100% hexanes→20:1 hexanes/Et_2O) as light yellow oil (680 mg, 3.0 mmol, 58% yield).

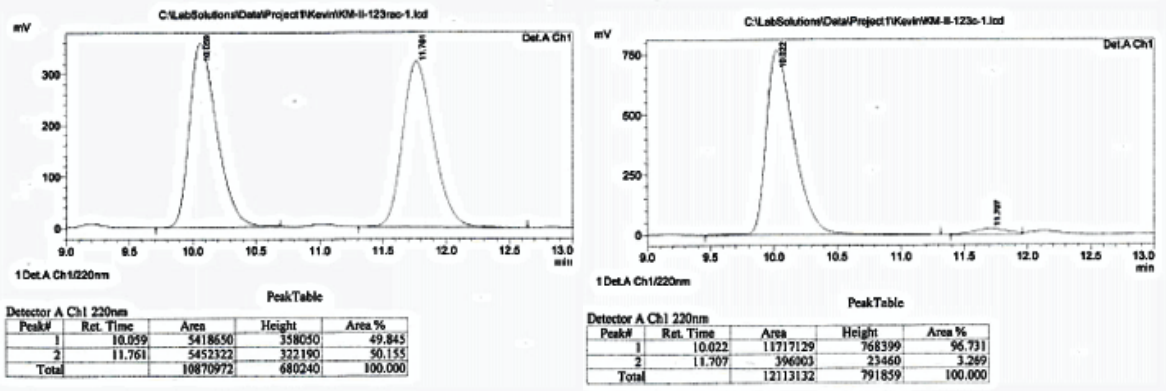
(*S*,*E*)-4-Methyl-6-phenyl-4-(thiophen-2-yl)hex-5-en-2-one (3.94, entry 9, Table 3.4). The requisite enone was prepared following the above three-step procedure; 2-acetylthiophene was used as the starting ketone was obtained as a 3:1 *E*/*Z* mixture in ca. 10% yield, and the α,β-unsaturated ketone was isolated in 63% yield after alkylation. The title compound is synthesized analogously to **3.60**. IR (neat): 3058 (w), 3025 (w), 2968 (w), 2932 (w), 1704 (m), 1599 (w), 1578 (w), 1494 (w), 1447 (w), 1356 (m), 1235 (w), 1198 (w), 1157 (w), 1073 (w), 1054 (w), 1030 (w), 968 (m), 914 (w), 849 (w), 828 (w), 751 (m), 693 (s), 595 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.37 (2H, m), 7.33–7.29 (2H, m), 7.23 (1H, dt, *J* = 1.2, 8.0 Hz), 7.19 (1H, dd, *J* = 1.2, 4.8 Hz), 6.96 (1H, dd,

J = 3.6, 5.2 Hz), 6.90 (1H, dd, *J* = 1.2, 3.6 Hz), 6.58 (1H, d, *J* = 16.4 Hz), 6.40 (1H, d, *J* = 16.0 Hz), 3.02 (2H, ABq, $\delta\Delta_{AB}$= 0.03, *J* = 14.4 Hz), 2.00 (3H, s), 1.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.8, 152.4, 137.2, 137.2, 128.7, 127.8, 127.6, 126.8, 126.6, 123.8, 123.5, 55.8, 42.0, 32.1, 27.1; HRMS (ESI+): Calcd for $C_{17}H_{19}O_1S_1$ [M+H$^+$]: 271.1157. Found: 271.1166. Specific Rotation $[\alpha]_D^{20}$ –23.7 (*c* 1.60, $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 85% Hexanes, 15% *i*PrOH, 1.0 mL/min, 254 nm.



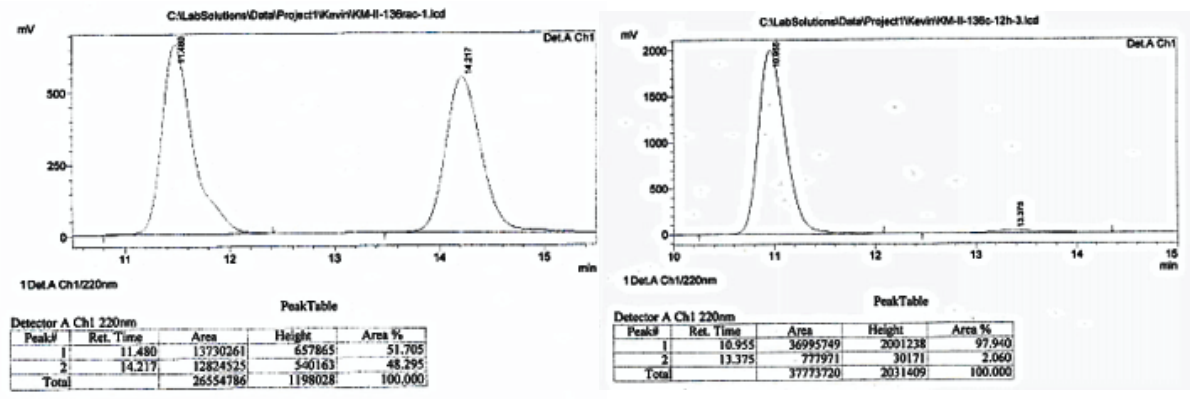
Retention Time	Area	Area %	Retention Time	Area	Area %
14.752	43192115	50.600	15.037	523949	2.115
15.694	42167115	49.400	15.895	24244801	97.885

(*S*)-4-Methyl-5-phenyl-4-(thiophen-2-yl)hex-5-en-2-one (3.74, entry 8, Table 3.3). The requisite substrate was synthesized analogously to that of **10**; the title compound was synthesized analogously to **3.60**, except reaction time was 5.0 h. IR (neat): 2970 (w), 2926 (w), 1720 (m), 1623 (w), 1598 (w), 1573 (w), 1490 (w), 1437 (w), 1356 (m), 1299 (w), 1235 (w), 1183 (w), 1166 (w), 1080 (w), 1054 (w), 1028 (w), 970 (w), 908 (m), 849 (w), 830 (w), 776 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.22 (1H, m), 7.20–7.14 (3H, m), 6.96 (1H, ddd, *J* = 5.1, 3.6, 0.5 Hz), 6.90–6.87 (3H, m), 5.41 (1H, s), 5.18 (1H, s), 3.04 (2H, s), 1.86 (3H, s), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 155.3, 153.2, 142.0, 128.7, 127.7, 127.2, 126.8, 124.2, 124.0, 114.6, 53.8, 44.5, 31.7, 27.9; HRMS (ESI+): Calcd for $C_{17}H_{19}SO$ [M+H]$^+$: 271.1157. Found: 271.1167. Specific Rotation $[\alpha]_D^{20}$ –25.4 (*c* 1.34, $CHCl_3$) for a sample of 97:3 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



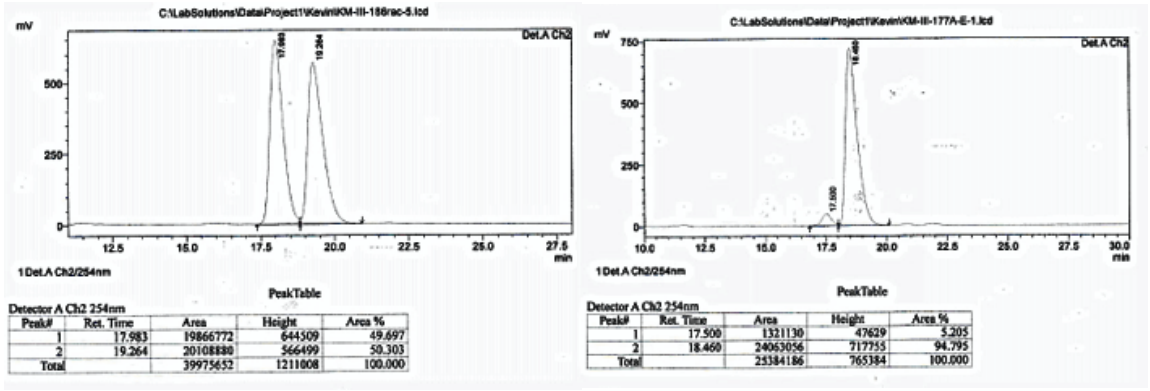
Retention Time	Area	Area %	Retention Time	Area	Area %
10.059	5418650	49.845	10.022	768399	96.731
11.761	5452322	50.155	11.707	23460	3.269

(*R*)-4-Methyl-4-(naphthalen-2-yl)-5-phenylhex-5-en-2-one (3.73, entry 7, Table 3.3). The requisite substrate was synthesized by the above three-step procedure, except 2-acetonaphthone was used as the starting ketone (77% conv., ca. 10% yield, 5:1 *E*/*Z*). The enone was obtained in 81% yield after alkylation. The title compound was synthesized analogously to **3.60**, except reaction time was 5.0 h. IR (neat): 3056 (w), 3018 (w), 2972 (w), 2934 (w), 1719 (s), 1624 (w), 1598 (w), 1504 (w), 1491 (w), 1464 (w), 1440 (w), 1414 (w), 1355 (m), 1299 (w), 1275 (w), 1184 (w), 1161 (w), 1129 (w), 1184 (w), 1161 (w), 1129 (w), 1068 (w), 1029 (w), 969 (w), 949 (m), 909 (m), 857 (m), 820 (m), 778 (m), 738 (m), 703 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.83 (2H, m), 7.82–7.79 (1H, m), 7.76 (1H, d, *J* = 2.0) 7.66 (1H, dd, *J* = 8.0, 2.0 Hz), 7.51–7.47 (2H, m), 7.13 (1H, tt, *J* = 7.2, 1.2), 7.07–7.03 (2H, m), 6.78–6.75 (2H, m), 5.47 (1H, d, *J* = 0.8 Hz), 5.32 (1H, d, *J* = 0.8 Hz), 3.20 (1H, d, *J* = 14.8 Hz), 3.02 (1H, d, *J* = 15.2 Hz) 1.76 (3H, s), 1.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 155.0, 143.4, 142.3, 133.5, 132.3, 128.6, 128.32, 128.30, 127.7, 127.6, 127.0, 126.2, 126.0, 125.8, 125.1, 115.4, 53.0, 46.4, 32.1, 26.4; HRMS (ESI^+): Calcd for $C_{23}H_{23}O$ [$M+H^+$]: 315.1749. Found: 315.1734. Specific Rotation $[\alpha]_D^{20}$ –25.1 (*c* 2.79 in $CHCl_3$) for a sample of 98:2 e.r. Enantiomeric purity (98:2 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



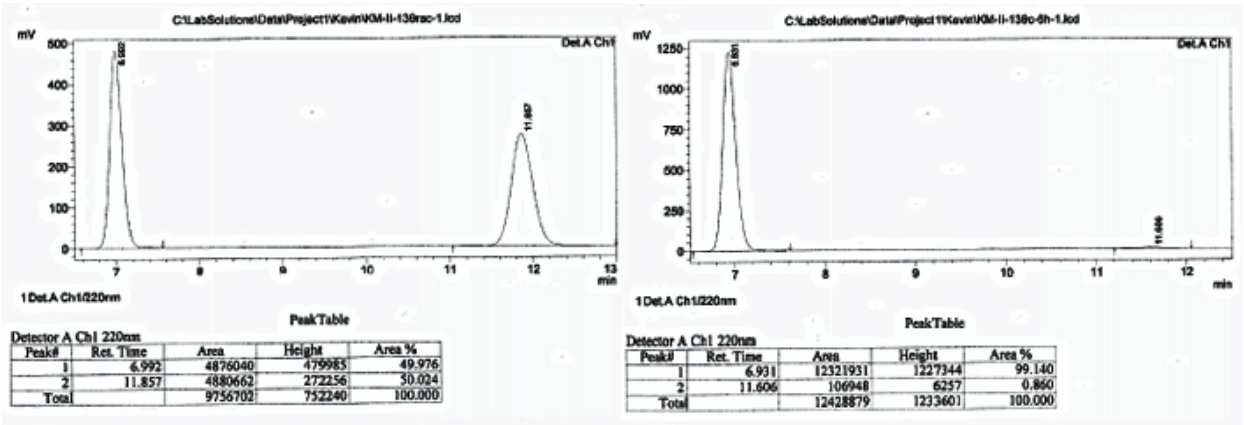
Retention Time	Area	Area %	Retention Time	Area	Area %
11.480	13730261	51.705	10.955	2001238	97.940
14.217	12824525	48.295	13.375	30171	2.060

(*S*,*E*)-4-Methyl-6-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (3.89, entry 4, Table 3.4). The requisite substrate (**S10**) was synthesized by the above three-step procedure. The title compound was synthesized analogously to **3.60**. IR (neat): 3026 (w), 2969 (w), 1718 (m), 1617 (w), 1495 (w), 1448 (w), 1410 (w), 1358 (w), 1325 (s), 1164 (m), 1118 (s), 1078 (m), 1015 (m), 970 (w), 840 (m), 752 (m), 721 (m), 659 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.56 (2H, m), 7.47–7.45 (2H, m), 7.40–7.38 (2H, m), 7.34 (2H, m), 7.26 –7.22 (1H, m), 6.55 (1H, d, J = 16.3 Hz), 6.40 (1H, d, J = 16.3 Hz), 3.07 (2H, ABq, $\delta\Delta_{AB}$= 0.02, J = 16.0 Hz), 2.01 (3H, s), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 150.87, 150.85, 137.1, 137.0, 128.8, 128.3, 127.7, 127.1 (q, J_{C-F} = 280.5), 126.9, 126.5, 125.4 (q, J_{C-F} = 3.7 Hz), 53.9, 43.1, 31.2, 26.2; HRMS (ESI+): Calcd for $C_{20}H_{20}F_3O_1$ [M+H$^+$]: 333.1466. Found: 333.1464. Specific Rotation $[\alpha]_D^{20}$ –17.7 (c = 1.22, $CHCl_3$) for a sample of 95:5 e.r. Enantiomeric purity (95:5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
17.983	19866772	49.697	17.500	1321130	5.205
19.264	20108880	50.303	18.460	24063056	94.795

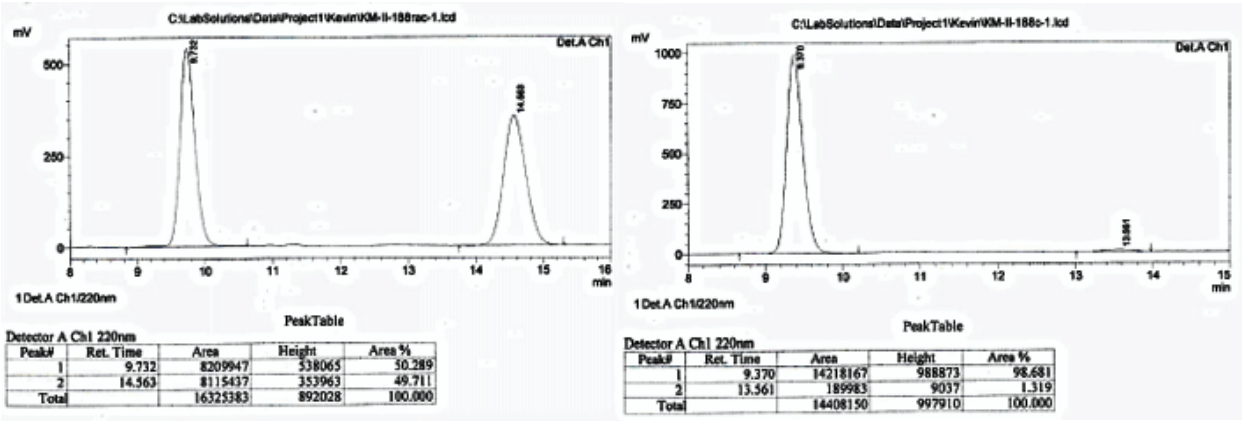
(*S*)-4-Methyl-5-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (3.70, entry 4, Table 3.3). The requisite enone (**S10**) was synthesized by the above three-step procedure. The title compound was synthesized analogously to **3.60**, except reaction time is 6.0 h. IR (neat): 2976 (w), 1720 (w), 1616 (w), 1573 (w), 1492 (w), 1409 (w), 1358 (w), 1324 (s), 1164 (m), 1114 (s), 1076 (m), 1029 (w), 1015 (m), 928 (w), 911 (m), 841 (m), 776 (m), 702 (m), 625 (w), 602 (m), 560 (w), 524 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.20–7.16 (1H, m), 7.14–7.10 (2H, m), 6.74–6.72 (2H, m), 5.40 (1H, s), 5.28 (1H, s), 3.03 (2H, ABq, $\delta\Delta_{AB}$= 0.10, J_{AB} = 15.6 Hz), 1.84 (3H, s), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 154.7, 150.5, 150.4 141.9, 128.6, 127.8, 127.3, 127.2, 125.4 (q, J_{C-F} = 3.7 Hz), 124.4 (q, J_{C-F} = 270.4 Hz), 115.6, 52.6, 46.3, 32.0, 26.4; HRMS (ESI+): Calcd for $C_{20}H_{20}F_3O$ $[M+H^+]$: 333.1466. Found: 333.1459. Specific Rotation $[\alpha]_D^{20}$ –11.4 (*c* 0.88, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (99:1 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
6.992	4876040	49.976	6.931	1227344	99.140
11.857	4880662	50.024	11.606	6257	0.860

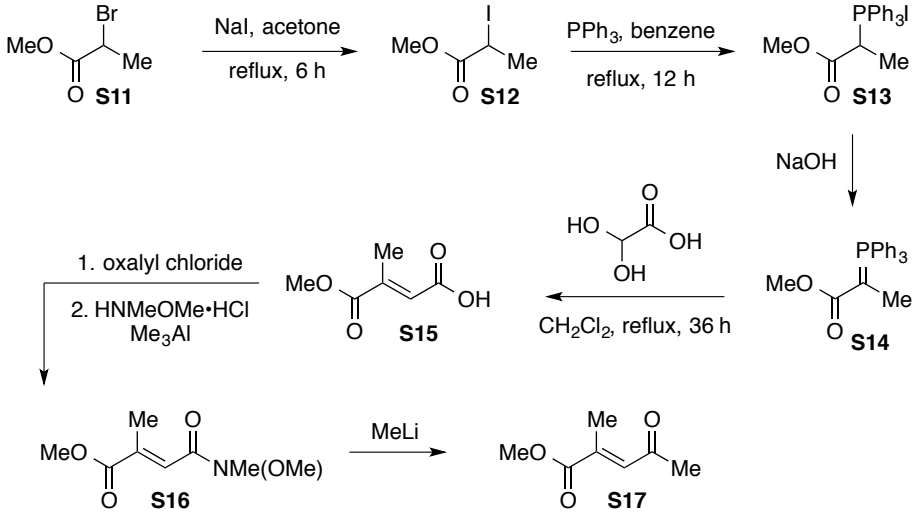
(*S*)-5-(4-Methoxyphenyl)-4-methyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (3.80, entry 14, Table 3.3). The requisite enone (**S10**) was synthesized by the above three-step procedure. The title compound was synthesized analogously to **3.60**, except reaction was performed at –15 °C for 6.0 h. IR (neat): 2939 (w), 2838 (w), 1720 (m), 1608 (m), 1573 (w), 1509 (m), 1463 (w), 1443 (w), 1409 (w), 1358 (w), 1326 (s), 1288 (w), 1245 (m), 1164 (m), 1120 (s), 1077 (m), 1065 (m), 1033 (m), 1015 (m), 974 (w), 910 (w), 837 (m), 778 (w), 757 (w), 743 (w), 675 (w), 641 (w), 612 (w), 572 (w), 528 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.0 Hz), 6.66 (4H, s), 5.37 (1H, d, J = 0.8 Hz), 5.26 (1H, d, J = 0.8 Hz), 3.74 (3H, s), 3.02 (2H, ABq, $\delta\Delta_{AB}$ = 0.07, J_{AB} = 16.0 Hz), 1.84 (3H, s), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 158.8, 154.0, 150.6, 134.2, 129.6, 127.3, 125.5 (q, J = 3.7 Hz), 115.1, 55.3, 52.5,

46.4, 32.0, 26.6; HRMS (ESI+): Calcd for $C_{21}H_{22}F_3O_2$ $[M+H]^+$: 363.1572. Found: 363.1578. Specific Rotation $[\alpha]_D^{20}$ –13.2 (c 2.55, $CHCl_3$) for a sample of 99:1 e.r. Enantiomeric purity (98.5:1.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
9.732	8209947	50.289	9.370	14218167	98.681
14.563	8115437	49.711	13.561	189983	1.319

Synthesis of Ester-Containing Enone Substrate 16:



Methyl 2-iodopropanoate (S12). To a round bottomed flask equipped with a stir bar and reflux condenser was added NaI (8.2 g, 54.5 mmol) and 2-bromopropionic methyl ester (5.6 mL, 50 mmol, **S11**) followed by acetone (50 mL). The flask was sealed and purged with N_2 and allowed to reflux for 6.0 h. The mixture was allowed to cool to 22 °C and H_2O was added to dissolve the resulting white precipitate. The layers were separated and the aqueous layer was washed with Et_2O. The combined organic phase was washed with a 10% solution of of aqueous $Na_2S_2O_3$. The organic layer was then dried over $MgSO_4$ and

concentrated in vacuo. The resulting residue was purified through silica gel chromatography (20:1 hexanes/Et_2O), affording the desired product as yellow oil (8.0 g, 37.4 mmol, 75% yield).

(1-Methoxy-1-oxopropan-2-yl)triphenylphosphonium iodide (S13). To a flame-dried flask equipped with a stir bar and fitted with a reflux condenser was added **S12** (8.0 g, 37.4 mmol) and PPh_3 (11.8 g, 44.8 mmol) followed by benzene (40 mL). The mixture was allowed to stir at 90 ºC under N_2 atm. After 12 h, the solution was allowed to warm 22 °C and the resulting solid was collected by vacuum filtration, washed with Et_2O, and dried under high vacuum to furnish the product as yellow/brown solid (17.0 g, 35.7 mmol, 96% yield).

Methyl 2-(triphenyl-λ^5-phosphanylidene)propanoate (S14). To a round bottom flask was added **S13** (17.0 g, 37.4 mmol) followed by slow addition of a 2.0 M solution of NaOH (18 mL). The mixture was allowed to stir for 6.0 h before the resulting solid was collected (vacuum filtration) and washed with H_2O. The product was dried in a P_2O_5 dessicator for 12 h and used without further purification (11.9 g, 34.2 mmol, 96% yield).

(*E*)-4-Methoxy-3-methyl-4-oxobut-2-enoic acid (S15). To a flask equipped with a stir bar and fitted with a reflux condenser was added **S14 (**11.9 g, 34.2 mmol), glyoxylic acid monohydrate (4.76 g, 49.3 mmol) and dcm (55 mL). The solution was allowed to reflux for 36 h, after which it was allowed to cool to 22 °C. Solvent removal in vacuo afforded a product mixture of 97:3 *E*/*Z* ratio. The desired product was isolated through silica gel chromatography (10:1 hexanes/EtOAc→5:1 hexanes/EtOAc) as white solid (3.83 g, 26.6 mmol, 78% yield)

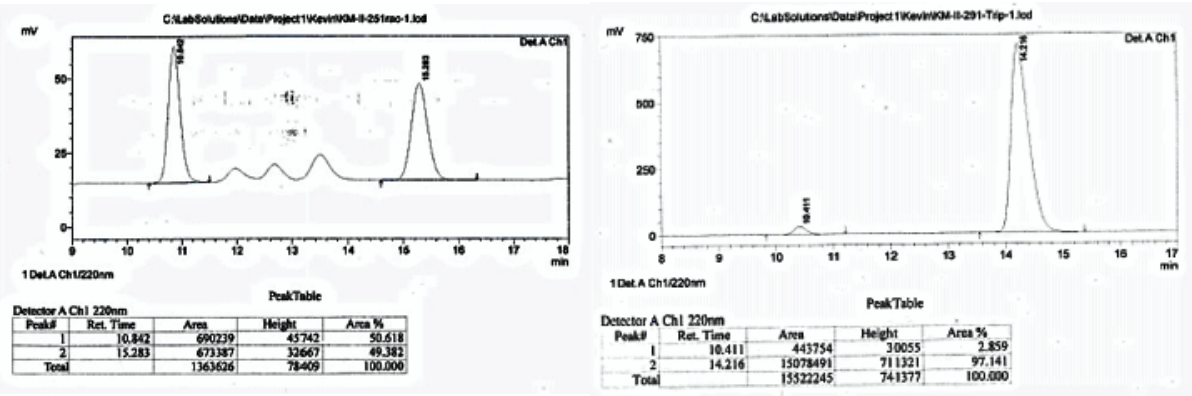
Methyl (*E*)-4-(methoxy(methyl)amino)-2-methyl-4-oxobut-2-enoate (S16). To a flame-dried round bottom flask equipped with a stir bar under N_2 was added **S15** (800 mg, 5.6 mmol) and Et_2O (56 mL). Oxalyl chloride (530 µL, 6.1 mmol) was then added drop-wise at 0 ºC followed by slow addition of dmf (21 µL, 0.30 mmol). The mixture was allowed to warm to 22 ºC and was then concentrated in vacuo and the resulting residue was used without further purification.

To a round bottom flask under N_2 was added N,O–dimethylhydroxylamine hydrochloride (1.63 g, 16.7 mmol) and thf (18.5 mL). Me_3Al (1.6 mL, 16.7 mmol) was subsequently introduced slowly at 0 ºC. The resulting mixture was allowed to stir for 15 min. at 0 ºC, after which it was allowed to warm to 22 ºC for 15 min. The solution was cooled to –20 ºC and acid chloride was added as a solution in thf. The resulting mixture was allowed to warm to 0 ºC in an ice bath and stir for an additional 30 min; a 0.5 N solution of HCl (CH_2Cl_2) was added and the mixture was allowed to stir for 30 min. at 22 ºC. The layers were separated and the aqueous phase was washed with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified through silica gel

chromatography (100% hexanes→10:1 hexanes/EtOAc→5:1 hexanes/EtOAc) affording the desired product as light yellow oil (875 mg, 4.67 mmol).

Methyl (*E*)-2-methyl-4-oxopent-2-enoate (S17). To a round bottom flask equipped with a stir bar was added **S16** (400 mg, 2.1 mmol) and thf (21 mL). MeLi (2.7 mL, 1.2M) was added slowly at –78 ºC and the resulting mixture was allowed to stir at –78 ºC for 30 min. The reaction was quenched upon addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous layer was washed with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified through silica gel chromatography (100% hexanes→9:1 hexanes/Et_2O) to furnish the desired product as off-white solid (194 mg, 1.37 mmol, 65 % yield)

(*S*)-Methyl 2-methyl-4-oxo-2-(1-phenylvinyl)pentanoate (3.84, entry 18, Table 3.3). The requisite substrate was synthesized by the above-mentioned procedure. The title compound was synthesized analogously to **3.60**, except **1b** was used as the catalyst precursor and the reaction time was 6.0 h. IR (neat): 2994 (w), 2948 (w), 1718 (s), 1626 (w), 1599 (w), 1574 (w), 1492 (w), 1433 (w), 1403 (w), 1359 (w), 1291 (w), 1266 (w), 1234 (m), 1209 (m), 1163 (m), 1113 (m), 1085 (w), 1029 (w), 1000 (w), 914 (w), 819 (w), 775 (w), 738 (s), 704 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (3H, m), 7.11–7.09 (2H, m), 5.29 (1H, d, J = 0.5 Hz), 5.07 (1H, d, J = 0.4 Hz), 3.66 (3H, s), 3.16 (1H, d, J = 17.8 Hz), 2.68 (1H, d, J = 17.6 Hz), 2.06 (3H, s), 1.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 175.3, 152.1, 141.2, 128.7, 128.0, 127.4, 115.8, 52.2, 50.8, 49.5, 30.9, 22.7; HRMS (ESI+): Calcd for$C_{15}H_{19}O_3$ [M+H$^+$]: 247.1334. Found: 247.1328. Specific Rotation $[\alpha]_D^{20}$ –29.9 (*c* 1.17, $CHCl_3$) for a sample of 97:3 e.r. Enantiomeric purity (97:3 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	Area %	Retention Time	Area	Area %
10.842	690239	50.618	10.411	443754	2.859
15.283	673387	49.382	14.216	15078491	97.141

Formal Synthesis of Enokipodin B

Iodination of 2,5-dimethoxytoluene: In a flame-dried 25mL round-bottom flask was added 2,5-dimethoxytoluene (1.0 mL, 6.89 mmol, **19**) and Et_2O (7.0 mL). To the resulting solution was added ICl (1.68 g, 10.3 mmol) as a solution in $CHCl_3$ (1.4 mL) in the span of 30 minutes. The mixture was allowed to stir for 3 h at 22 ºC, after which it was diluted with Et_2O and washed with 10% $Na_2S_2O_3$ (10 mL x 3), $NaHCO_3$ (3 x 10 mL), and 10% $Na_2S_2O_3$ (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford a light purple solid. The product was dissolved in hot MeOH. Upon cooling, the precipitate was collected and washed with cold MeOH to furnish the desired product as a white solid (1.46g, 5.25 mmol, 76% yield).[19] Spectra are in good agreement with previously reported compounds. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (1H, s), 6.74 (1H, s), 3.84 (3H, s), 3.78 (3H, s), 2.19 (3H, s).

Pd-Catalyzed Cross Coupling of Aryl Iodide/Removal of Silyl Ether: In a glove-box under an N_2 atm., a flame-dried round-bottom flask was charged with the aryl iodide (600 mg, 2.16 mmol), $(PPh_3)_2PdCl_2$ (30.2 mg, 0.043 mmol), and CuI (8.2 mg, 0.043 mmol). The flask was then equipped with a reflux condenser, sealed with a septum, and removed from the glovebox. The mixture was charged with di*iso*propylamine (6.2 mL), followed by the addition of trimethylsilylacetylene (367 μL, 2.6 mmol) over 10 minutes. The resulting mixture was allowed to stir at 22 ºC for 2 h and then allowed to reflux (at ~90 ºC) for an additional 2 h. After cooling, the solution was passed through a plug of silica gel, eluting with Et_2O, and concentrated in vacuo. The resulting ^{1}H NMR spectrum was in agreement with that reported previously. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (1H, s), 6.67 (1H, s), 3.83 (3H, s), 3.78 (3H, s), 2.21 (3H, s), 0.27 (9H, s). The unpurified mixture was then dissolved in thf (37 mL), followed by the addition of a 20% aqueous solution of KOH (1.3 mL) and MeOH (19 mL). The mixture was allowed to stir for 3 h at 22 ºC, after which it was diluted with H_2O and washed with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to afford a brown solid. Purification by silica gel chromatography (100% Hexanes→10:1 Hexanes/Et_2O) furnished 368 mg of 1-ethynyl-2,5-dimethoxy-4-methylbenzene (**20**) as white solid (2.09 mmol, 97% yield).[20] The 1H NMR spectrum proved to be in agreement with the previously reported data. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (1H, s), 6.71 (1H, s), 3.86 (3H, s), 3.78 (3H, s), 3.28 (1H, s), 2.23 (3H, s).

Synthesis of Trisubstituted Enone: Zirconocene dichloride (214 mg, 0.732 mmol) and CH_2Cl_2 (8 mL) were added to a flame-dried flask equipped with a stir bar. Trimethylaluminum (702 μL, 7.32 mmol) (CAUTION! Flammable) was added slowly to the mixture, resulting in a clear yellow mixture. The solution was cooled to –23 ºC prior to the drop-wise addition of H_2O (40 μL, 2.2 mmol) (CAUTION! Reaction generates a

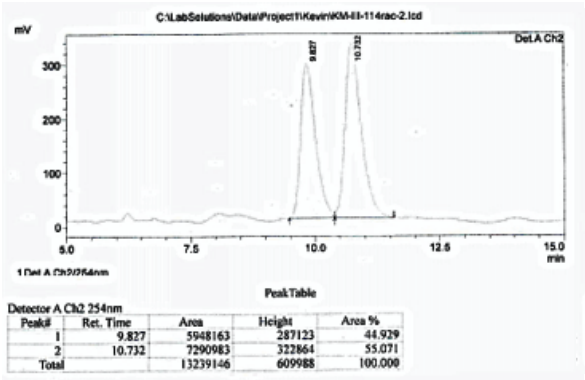
[19] M. W. Reed, A. Wald, R. B. Meyer, *J. Am. Chem. Soc.* **1998**, *120*, 9729–9734.

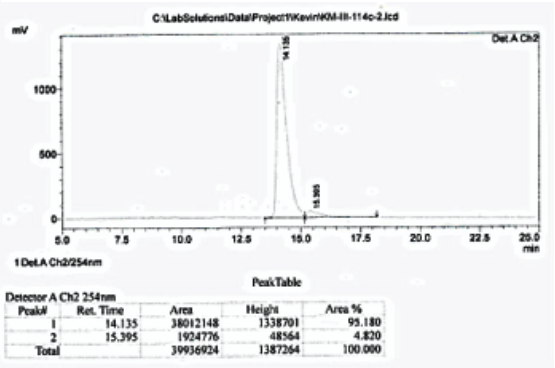
[20] R. Shukla, S. V. Lindeman, R. Rathore, *Org. Lett.* **2007**, *9*, 1291–1294.

significant amount of flammable gas. Vent as necessary). The mixture was allowed to stir for 10 min, followed by the slow addition of the alkyne substrate (258 mg, 1.46 mmol) as a solution in CH_2Cl_2 (5 mL). The resulting mixture was allowed to stir for 10 minutes before addition of acetyl chloride (125 μL, 1.76 mmol). The mixture was allowed to stir for an additional 10 min before being allowed to warm to 22 °C, at which point the mixture is allowed to stir for an additional 10 min. The reaction is quenched upon dropwise addition of a saturated solution of K_2CO_3 until evolution of gas ceased. The aqueous layer was washed with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a yellow oil that was purified by silica gel chromatography (100% Hexanes→20:1 Hexanes/Et_2O→9:1 Hexanes/Et_2O) to afford 302 mg of (*E*)-4-(2,5-dimethoxy-4-methylphenyl)pent-3-en-2-one as a 2:1 mixture of olefin isomers (1.29 mmol, 88% yield).

(*E*)-4-(2,5-Dimethoxy-4-methylphenyl)pent-3-en-2-one (3.106). IR (neat): 2996 (w), 2933 (w), 2849 (w), 1683 (m), 1598 (m), 1500 (m), 1465 (w), 1397 (m), 1375 (w), 1280 (w), 1210 (s), 1174 (w), 1042 (s), 961 (w), 856 (w), 807 (w), 695 (w), 604 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (1H, s), 6.63 (1H, s), 6.30 (1H, d, *J* = 0.8 Hz), 3.80 (3H, s), 3.77 (3H, s), 2.46 (3H, d, *J* = 1.2 Hz), 2.26 (3H, s), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 155.1, 151.7, 150.3, 130.9, 127.9, 126.6, 114.8, 111.4, 55.4, 56.2, 32.2, 20.5, 16.4; HRMS (ESI+): Calcd for $C_{14}H_{19}O_3$ [M+H$^+$]: 235.1334. Found: 235.1345.

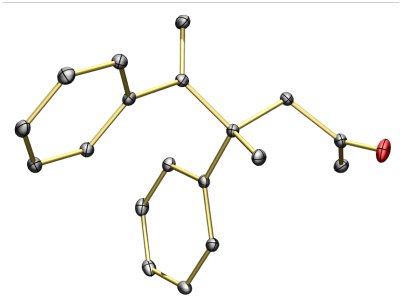
(*R*,*E*)-4-(2,5-Dimethoxy-4-methylphenyl)-4-methyl-6-phenylhex-5-en-2-one (3.108). The title compound was synthesized analogously to **3.86**. IR (neat): 2933 (w), 2844 (w), 1702 (w), 1599 (m), 1503 (w), 1465 (w), 1392 (m), 1372 (w), 1356 (w), 1210 (s), 1045 (m), 1003 (w), 967 (w), 866 (w), 802 (w), 751 (w), 725 (w), 695 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (2H, d, *J* = 6.0 Hz), 7.29 (2H, t, *J* = 6.0 Hz), 7.19 (1H, t, *J* = 6.0 Hz), 6.80 (1H, s), 6.72 (1H, d, *J* = 12.8 Hz), 6.70, (1H, s), 6.30 (1H, d, *J* = 12.8 Hz), 3.77 (3H, s), 3.76 (3H, s), 3.33 (1H, d, *J* = 12.0 Hz), 3.11 (1H, d, *J* = 12.0 Hz), 2.20 (3H, s), 1.92 (3H, s), 1.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.3, 151.7, 151.5, 138.7, 138.1, 132.2, 128.6, 127.1, 126.4, 126.3, 125.8, 115.4, 111.5, 56.3, 56.1, 53.0, 42.6, 31.6, 25.7, 16.1; HRMS (ESI+): Calcd for $C_{22}H_{26}O_3$ [M+H$^+$]: 338.1882. Found: 338.1887 Specific Rotation $[\alpha]_D^{20}$ –78.6 (c 2.06, $CHCl_3$) for a sample of 95.5:4.5 e.r. Enantiomeric purity (95.5:4.5 e.r.) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OD(H), 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.





Retention Time	Area	Area %	Retention Time	Area	Area %
9.827	5948163	44.929	9.623	28607707	95.549
10.732	7290983	55.071	10.622	1332497	4.451

X-RAY CRYSTAL STRUCTURE of ECA PRODUCT 3.60



X-ray Structure of 4a

***Table 1*: Crystal data and structure refinement for (*S*)-4-methyl-4,5-diphenylhex-5-en-2-one**

Identification code	C19H20O	
Empirical formula	C19 H20 O	
Formula weight	264.35	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.5997(2) Å	a= 90°.
	b = 7.9511(2) Å	b= 90°.
	c = 28.4791(7) Å	g = 90°.
Volume	1494.44(7) Å ^{3}	
Z	4	
Density (calculated)	1.175 Mg/m^3	
Absorption coefficient	0.542 mm^{-1}	
F(000)	568	
Crystal size	0.18 x 0.06 x 0.04 mm^3	
Theta range for data collection	3.10 to 67.73°.	
Index ranges	-7<=h<=3, -9<=k<=9, -33<=l<=34	
Reflections collected	12852	
Independent reflections	2669 [R(int) = 0.0217]	
Completeness to theta = 67.73°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9786 and 0.9087	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2669 / 0 / 182	
Goodness-of-fit on F^2	1.057	

Final R indices [I>2sigma(I)]	R1 = 0.0272, wR2 = 0.0725
R indices (all data)	R1 = 0.0273, wR2 = 0.0726
Absolute structure parameter	0.1(3)
Extinction coefficient	na
Largest diff. peak and hole	0.216 and -0.132 e. Å $^{-3}$

Table 2: **Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å ^{2}x 10^3) for $C_{19}H_{20}O$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor**

	x	y	z	U(eq)
C(1)	2965(2)	7223(1)	9102(1)	21(1)
C(2)	2878(2)	9103(1)	8972(1)	21(1)
C(3)	4019(2)	10287(1)	9165(1)	29(1)
C(4)	1294(2)	9624(1)	8624(1)	22(1)
C(5)	1238(2)	9002(1)	8164(1)	25(1)
C(6)	-208(2)	9568(2)	7848(1)	27(1)
C(7)	-1637(2)	10748(1)	7984(1)	28(1)
C(8)	-1614(2)	11361(1)	8440(1)	30(1)
C(9)	-166(2)	10803(1)	8756(1)	26(1)
C(10)	3822(2)	6206(1)	8689(1)	20(1)
C(11)	5572(2)	6762(1)	8460(1)	24(1)
C(12)	6325(2)	5916(2)	8073(1)	29(1)
C(13)	5362(2)	4479(2)	7909(1)	31(1)
C(14)	3667(2)	3878(1)	8142(1)	28(1)
C(15)	2902(2)	4742(1)	8528(1)	23(1)
C(16)	4368(2)	6997(1)	9538(1)	24(1)
C(17)	4488(2)	5216(2)	9727(1)	26(1)
C(18)	6303(2)	4183(1)	9597(1)	30(1)
C(19)	799(2)	6678(2)	9230(1)	26(1)
O(1)	3199(2)	4687(1)	9992(1)	43(1)

Table 3: **Bond lengths [Å] and angles [º] for Compound 3.60**

C(1)-C(10)	1.5360(14)
C(1)-C(19)	1.5370(16)
C(1)-C(2)	1.5412(14)
C(1)-C(16)	1.5579(15)
C(2)-C(3)	1.3245(17)
C(2)-C(4)	1.5009(15)
C(3)-H(3A)	0.9500
C(3)-H(3B)	0.9500
C(4)-C(9)	1.3963(16)
C(4)-C(5)	1.3994(15)
C(5)-C(6)	1.3865(16)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.3848(17)
C(6)-H(6)	0.9500
C(7)-C(8)	1.3879(17)
C(7)-H(7)	0.9500
C(8)-C(9)	1.3869(17)
C(8)-H(8)	0.9500
C(9)-H(9)	0.9500
C(10)-C(15)	1.3913(15)
C(10)-C(11)	1.3972(16)
C(11)-C(12)	1.3838(17)
C(11)-H(11)	0.9500
C(12)-C(13)	1.3880(18)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.3853(19)
C(13)-H(13)	0.9500
C(14)-C(15)	1.3897(16)
C(14)-H(14A)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.5180(16)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-O(1)	1.2119(15)

C(17)-C(18)	1.4986(18)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800

C(10)-C(1)-C(19)	112.04(9)
C(10)-C(1)-C(2)	109.88(8)
C(19)-C(1)-C(2)	107.21(9)
C(10)-C(1)-C(16)	109.30(9)
C(19)-C(1)-C(16)	109.40(9)
C(2)-C(1)-C(16)	108.97(9)
C(3)-C(2)-C(4)	118.32(10)
C(3)-C(2)-C(1)	124.65(10)
C(4)-C(2)-C(1)	116.92(9)
C(2)-C(3)-H(3A)	120.0
C(2)-C(3)-H(3B)	120.0
H(3A)-C(3)-H(3B)	120.0
C(9)-C(4)-C(5)	118.21(10)
C(9)-C(4)-C(2)	119.12(9)
C(5)-C(4)-C(2)	122.66(10)
C(6)-C(5)-C(4)	120.66(11)
C(6)-C(5)-H(5A)	119.7
C(4)-C(5)-H(5A)	119.7
C(7)-C(6)-C(5)	120.53(10)
C(7)-C(6)-H(6)	119.7
C(5)-C(6)-H(6)	119.7
C(6)-C(7)-C(8)	119.41(10)
C(6)-C(7)-H(7)	120.3
C(8)-C(7)-H(7)	120.3
C(9)-C(8)-C(7)	120.27(11)
C(9)-C(8)-H(8)	119.9
C(7)-C(8)-H(8)	119.9
C(8)-C(9)-C(4)	120.91(10)

C(8)-C(9)-H(9)	119.5
C(4)-C(9)-H(9)	119.5
C(15)-C(10)-C(11)	118.09(10)
C(15)-C(10)-C(1)	122.21(10)
C(11)-C(10)-C(1)	119.70(10)
C(12)-C(11)-C(10)	120.97(11)
C(12)-C(11)-H(11)	119.5
C(10)-C(11)-H(11)	119.5
C(11)-C(12)-C(13)	120.23(12)
C(11)-C(12)-H(12A)	119.9
C(13)-C(12)-H(12A)	119.9
C(14)-C(13)-C(12)	119.51(11)
C(14)-C(13)-H(13)	120.2
C(12)-C(13)-H(13)	120.2
C(13)-C(14)-C(15)	120.04(11)
C(13)-C(14)-H(14A)	120.0
C(15)-C(14)-H(14A)	120.0
C(14)-C(15)-C(10)	121.09(11)
C(14)-C(15)-H(15)	119.5
C(10)-C(15)-H(15)	119.5
C(17)-C(16)-C(1)	114.93(9)
C(17)-C(16)-H(16A)	108.5
C(1)-C(16)-H(16A)	108.5
C(17)-C(16)-H(16B)	108.5
C(1)-C(16)-H(16B)	108.5
H(16A)-C(16)-H(16B)	107.5
O(1)-C(17)-C(18)	121.64(11)
O(1)-C(17)-C(16)	120.54(11)
C(18)-C(17)-C(16)	117.73(10)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(1)-C(19)-H(19A)	109.5

C(1)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(1)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. **Anisotropic displacement parameters (Å ^{2}x 10^3) for compound 3.60. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	23(1)	20(1)	19(1)	1(1)	0(1)	-2(1)
C(2)	24(1)	20(1)	19(1)	-1(1)	1(1)	0(1)
C(3)	35(1)	21(1)	31(1)	2(1)	-8(1)	-1(1)
C(4)	24(1)	20(1)	22(1)	2(1)	1(1)	-3(1)
C(5)	28(1)	23(1)	23(1)	1(1)	1(1)	1(1)
C(6)	32(1)	27(1)	21(1)	1(1)	-2(1)	-2(1)
C(7)	27(1)	26(1)	31(1)	5(1)	-7(1)	-2(1)
C(8)	28(1)	26(1)	34(1)	0(1)	0(1)	5(1)
C(9)	29(1)	24(1)	24(1)	-1(1)	1(1)	0(1)
C(10)	22(1)	20(1)	18(1)	3(1)	-2(1)	2(1)
C(11)	23(1)	23(1)	25(1)	3(1)	0(1)	1(1)
C(12)	28(1)	31(1)	28(1)	7(1)	6(1)	8(1)
C(13)	42(1)	30(1)	22(1)	-1(1)	2(1)	15(1)
C(14)	39(1)	22(1)	25(1)	-2(1)	-8(1)	5(1)
C(15)	25(1)	20(1)	23(1)	2(1)	-4(1)	0(1)
C(16)	32(1)	22(1)	20(1)	-1(1)	-4(1)	-1(1)
C(17)	33(1)	26(1)	20(1)	2(1)	-4(1)	-2(1)
C(18)	34(1)	23(1)	32(1)	1(1)	-6(1)	-2(1)
C(19)	26(1)	27(1)	24(1)	2(1)	5(1)	-3(1)
O(1)	44(1)	44(1)	40(1)	20(1)	11(1)	2(1)

Table 5. **Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound 3.60**

	x	y	z	U(eq)
H(3A)	3823	11432	9082	35
H(3B)	5034	9991	9387	35
H(5A)	2201	8184	8068	29
H(6)	-219	9143	7536	32
H(7)	-2624	11135	7766	34
H(8)	-2593	12167	8535	35
H(9)	-168	11228	9068	31
H(11)	6254	7734	8572	28
H(12A)	7505	6319	7919	35
H(13)	5861	3912	7639	37
H(14A)	3027	2875	8038	34
H(15)	1732	4326	8683	27
H(16A)	5751	7369	9452	29
H(16B)	3878	7745	9792	29
H(18A)	7513	4656	9747	44
H(18B)	6475	4193	9255	44
H(18C)	6107	3023	9705	44
H(19A)	-83	6814	8956	39
H(19B)	295	7376	9488	39
H(19C)	806	5495	9327	39

Table 6. **Torsion angles [º] for compound 3.60**

C(10)-C(1)-C(2)-C(3)	-111.93(12)
C(19)-C(1)-C(2)-C(3)	126.09(12)
C(16)-C(1)-C(2)-C(3)	7.79(15)
C(10)-C(1)-C(2)-C(4)	72.00(12)
C(19)-C(1)-C(2)-C(4)	-49.98(12)
C(16)-C(1)-C(2)-C(4)	-168.27(9)
C(3)-C(2)-C(4)-C(9)	-56.19(15)
C(1)-C(2)-C(4)-C(9)	120.13(11)
C(3)-C(2)-C(4)-C(5)	122.44(12)
C(1)-C(2)-C(4)-C(5)	-61.23(14)
C(9)-C(4)-C(5)-C(6)	1.15(16)
C(2)-C(4)-C(5)-C(6)	-177.50(10)
C(4)-C(5)-C(6)-C(7)	-0.62(17)
C(5)-C(6)-C(7)-C(8)	-0.13(17)
C(6)-C(7)-C(8)-C(9)	0.31(18)
C(7)-C(8)-C(9)-C(4)	0.25(18)
C(5)-C(4)-C(9)-C(8)	-0.97(16)
C(2)-C(4)-C(9)-C(8)	177.73(11)
C(19)-C(1)-C(10)-C(15)	-13.17(14)
C(2)-C(1)-C(10)-C(15)	-132.23(10)
C(16)-C(1)-C(10)-C(15)	108.25(11)
C(19)-C(1)-C(10)-C(11)	166.13(9)
C(2)-C(1)-C(10)-C(11)	47.07(13)
C(16)-C(1)-C(10)-C(11)	-72.45(12)
C(15)-C(10)-C(11)-C(12)	2.39(16)
C(1)-C(10)-C(11)-C(12)	-176.94(10)
C(10)-C(11)-C(12)-C(13)	-0.89(17)
C(11)-C(12)-C(13)-C(14)	-1.39(17)
C(12)-C(13)-C(14)-C(15)	2.11(17)
C(13)-C(14)-C(15)-C(10)	-0.57(16)
C(11)-C(10)-C(15)-C(14)	-1.66(15)
C(1)-C(10)-C(15)-C(14)	177.65(10)
C(10)-C(1)-C(16)-C(17)	-63.85(12)
C(19)-C(1)-C(16)-C(17)	59.15(13)

C(2)-C(1)-C(16)-C(17)	176.06(10)
C(1)-C(16)-C(17)-O(1)	-82.94(13)
C(1)-C(16)-C(17)-C(18)	100.42(12)

Symmetry transformations used to generate equivalent atoms:

DFT Calculations

Transition state leading to the major enantiomer (3.113)

#p bp86/6-31G* freq scrf(solvent=thf)

Cartesian coordinates (Angstroms):

N	1.866	-1.630	0.545
C	2.381	-3.000	0.163
C	1.607	-3.239	-1.154
N	0.529	-2.223	-1.088
C	0.736	-1.275	-0.151
C	2.467	-0.917	1.615
C	2.750	0.480	1.594
S	2.202	1.516	0.230
O	2.603	0.907	-1.063
O	2.874	2.895	0.475
Cu	-0.500	0.155	0.220
O	0.705	1.693	0.459
C	-2.132	-0.400	0.953
C	-2.329	-0.729	2.265
Al	2.450	4.476	-0.573
C	3.077	5.948	0.601
C	3.172	4.299	-2.406
C	-0.388	4.317	0.106
C	-1.078	2.084	-2.019
C	-1.911	2.452	-0.812
H	2.243	-3.059	-2.041
H	1.188	-4.255	-1.220
H	-2.994	-0.549	0.277
H	4.180	6.033	0.539
H	2.666	6.928	0.289
H	2.825	5.816	1.670
H	4.275	4.215	-2.403
H	2.780	3.414	-2.940
H	2.923	5.187	-3.020
H	-0.013	2.274	-1.845
H	-1.225	1.032	-2.321
H	-1.379	2.712	-2.884
C	-0.301	5.370	1.191
O	0.609	4.243	-0.743
H	-1.230	5.449	1.776
H	0.526	5.130	1.884
H	-0.067	6.355	0.748
C	-3.557	-1.239	2.906

C	-4.751	-1.526	2.194
C	-5.887	-2.018	2.850
C	-5.872	-2.241	4.240
C	-4.700	-1.963	4.964
C	-3.564	-1.472	4.306
H	-4.783	-1.358	1.112
H	-6.794	-2.231	2.272
H	-6.763	-2.626	4.750
H	-4.670	-2.131	6.047
H	-2.653	-1.258	4.880
H	-1.494	-0.606	2.977
C	-0.535	-2.221	-2.059
C	-0.349	-1.570	-3.301
C	-1.394	-1.638	-4.245
C	-2.583	-2.344	-3.994
C	-2.720	-2.998	-2.754
C	-1.712	-2.959	-1.775
C	0.935	-0.843	-3.639
H	-1.264	-1.129	-5.208
H	-3.639	-3.560	-2.540
C	-1.891	-3.675	-0.455
C	-3.317	1.984	-0.776
C	-3.934	1.464	-1.944
C	-5.290	1.106	-1.954
C	-6.070	1.239	-0.794
C	-5.471	1.722	0.383
C	-4.120	2.083	0.394
H	-3.357	1.364	-2.867
H	-5.739	0.727	-2.879
H	-7.129	0.960	-0.803
H	-6.058	1.806	1.305
H	-3.669	2.415	1.333
C	3.403	1.103	2.672
C	3.813	0.355	3.782
C	3.553	-1.023	3.815
C	2.892	-1.644	2.749
H	3.595	2.177	2.619
H	4.332	0.847	4.610
H	3.858	-1.624	4.678
H	2.688	-2.717	2.796
H	0.778	-0.157	-4.490
H	1.324	-0.259	-2.788
H	1.730	-1.553	-3.939
C	-3.681	-2.423	-5.035
H	-3.756	-3.441	-5.460
H	-4.667	-2.184	-4.598
H	-3.497	-1.725	-5.869
H	-2.832	-4.249	-0.449

```
H  -1.065  -4.380  -0.251
H  -1.920  -2.954   0.383
C   3.889  -3.086   0.017
H   2.042  -3.727   0.926
C   4.609  -2.095  -0.683
C   5.995  -2.220  -0.853
C   6.676  -3.336  -0.336
C   5.964  -4.325   0.361
C   4.577  -4.196   0.541
H   4.024  -4.968   1.090
H   4.083  -1.217  -1.076
H   6.488  -5.195   0.772
H   6.547  -1.440  -1.391
H   7.759  -3.431  -0.473
C  -1.552   3.519   0.042
H  -2.300   3.806   0.787
---------------------------------
```

SCF Done: E(RB-P86) = -4435.28285560 A.U. after 27 cycles

	1	2	3
	A	A	A
Frequencies --	-56.5303	11.5731	14.6515
Red. masses --	8.2320	5.5608	5.6026

Zero-point correction= 0.798860 (Hartree/Particle)
Thermal correction to Energy= 0.855213
Thermal correction to Enthalpy= 0.856157
Thermal correction to Gibbs Free Energy= 0.703468
Sum of electronic and zero-point Energies= -4434.483995
Sum of electronic and thermal Energies= -4434.427642
Sum of electronic and thermal Enthalpies= -4434.426698
Sum of electronic and thermal Free Energies= -4434.579388

Item	Value	Threshold	Converged?
Maximum Force	0.000008	0.000450	YES
RMS Force	0.000002	0.000300	YES

Transition state leading to the minor enantiomer (3.114)

#p bp86/6-31G* freq scrf(solvent=thf)

Cartesian coordinates (Angstroms):

N	1.464	-1.755	0.188
C	1.688	-3.197	-0.190
C	0.826	-3.279	-1.472
N	-0.065	-2.097	-1.342
C	0.365	-1.210	-0.427
C	2.159	-1.153	1.266
C	2.596	0.202	1.251
S	2.361	1.268	-0.196
O	2.873	0.582	-1.407
O	3.172	2.535	0.176
Cu	-0.533	0.368	0.205
O	0.888	1.677	-0.241
C	-1.943	-0.150	1.311
C	-1.858	-0.815	2.500
Al	3.028	4.379	-0.390
C	4.272	5.304	0.844
C	3.268	4.447	-2.353
C	0.363	4.134	0.706
C	-2.332	2.917	1.997
C	-1.904	2.935	0.545
H	1.442	-3.186	-2.386
H	0.242	-4.211	-1.531
H	-2.964	0.032	0.921
H	5.325	5.044	0.623
H	4.189	6.405	0.746
H	4.098	5.064	1.910
H	4.298	4.168	-2.649
H	2.581	3.761	-2.884
H	3.082	5.463	-2.754
H	-3.079	3.720	2.165
H	-2.795	1.958	2.276
H	-1.504	3.101	2.690
C	0.724	3.912	2.157
O	1.247	4.762	-0.044
H	0.131	4.568	2.820
H	0.537	2.868	2.462
H	1.788	4.146	2.319
C	-2.962	-1.285	3.361
C	-4.334	-1.097	3.050
C	-5.342	-1.565	3.901
C	-5.018	-2.235	5.096
C	-3.666	-2.430	5.425
C	-2.657	-1.962	4.570
H	-4.608	-0.574	2.126
H	-6.394	-1.406	3.632
H	-5.810	-2.598	5.762

H	-3.394	-2.948	6.352
H	-1.604	-2.118	4.836
H	-0.861	-1.041	2.915
C	-1.153	-1.901	-2.266
C	-0.918	-1.233	-3.491
C	-1.987	-1.135	-4.403
C	-3.252	-1.686	-4.134
C	-3.442	-2.353	-2.907
C	-2.411	-2.478	-1.960
C	0.441	-0.670	-3.849
H	-1.818	-0.619	-5.356
H	-4.421	-2.792	-2.680
C	-2.643	-3.210	-0.658
C	-2.917	2.501	-0.452
C	-4.270	2.288	-0.074
C	-5.245	1.937	-1.020
C	-4.900	1.774	-2.370
C	-3.561	1.955	-2.763
C	-2.588	2.310	-1.823
H	-4.573	2.429	0.967
H	-6.283	1.798	-0.696
H	-5.663	1.504	-3.108
H	-3.270	1.808	-3.808
H	-1.550	2.421	-2.153
C	3.281	0.744	2.353
C	3.565	-0.047	3.474
C	3.164	-1.391	3.489
C	2.471	-1.933	2.400
H	3.607	1.785	2.309
H	4.106	0.386	4.321
H	3.382	-2.024	4.355
H	2.148	-2.977	2.432
H	0.346	0.099	-4.634
H	0.954	-0.221	-2.983
H	1.107	-1.459	-4.250
C	-4.388	-1.558	-5.127
H	-4.930	-2.513	-5.246
H	-5.129	-0.809	-4.788
H	-4.025	-1.241	-6.119
H	-3.688	-3.555	-0.587
H	-1.991	-4.100	-0.565
H	-2.431	-2.561	0.211
C	3.143	-3.578	-0.388
H	1.241	-3.840	0.593
C	4.021	-2.747	-1.115
C	5.349	-3.144	-1.331

```
C    5.813   -4.374   -0.830
C    4.944   -5.202   -0.103
C    3.616   -4.803    0.121
H    2.940   -5.450    0.694
H    3.669   -1.781   -1.493
H    5.298   -6.159    0.297
H    6.026   -2.489   -1.890
H    6.850   -4.681   -1.002
C   -0.827    3.715    0.073
H   -0.808    3.932   -1.000
---------------------------------
```

SCF Done: E(RB-P86) = -4435.28032748 A.U. after 29 cycles

	1	2	3
	A	A	A
Frequencies --	-46.8842	14.9417	17.3903
Red. masses --	7.5699	5.0247	5.5488

Zero-point correction= 0.799051 (Hartree/Particle)
Thermal correction to Energy= 0.855376
Thermal correction to Enthalpy= 0.856321
Thermal correction to Gibbs Free Energy= 0.703528
Sum of electronic and zero-point Energies= -4434.481276
Sum of electronic and thermal Energies= -4434.424951
Sum of electronic and thermal Enthalpies= -4434.424007
Sum of electronic and thermal Free Energies= -4434.576800

Item	Value	Threshold	Converged?
Maximum Force	0.000009	0.000450	YES
RMS Force	0.000003	0.000300	YES

Direct transfer transition state leading to the major enantiomer

#p bp86/6-31G* freq scrf(solvent=thf)

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---------------------------------
Cartesian coordinates (Angstroms):
---------------------------------
N    2.506   -1.108    0.978
C    3.369   -2.342    0.868
C    2.516   -3.220   -0.080
N    1.204   -2.534   -0.060
C    1.231   -1.305    0.500
C    3.002    0.042    1.649
C    2.823    1.385    1.208
```

```
S    1.771    1.809  -0.191
O    2.065    0.907  -1.337
O    2.128    3.290  -0.518
Cu  -0.271  -0.180   0.442
O    0.362    1.763   0.366
C   -2.145  -0.099   0.650
C   -2.457    0.679   1.740
Al   1.158   4.314  -1.849
C    1.230    6.150  -1.095
C    1.942    3.955  -3.632
C   -1.624    3.569  -1.192
C   -1.430    0.652  -2.307
C   -2.530    1.164  -1.399
C   -2.560    2.539  -1.016
H    2.928  -3.230  -1.106
H    2.423  -4.259   0.274
H   -2.773  -0.991   0.468
H    2.268    6.536  -1.148
H    0.599    6.864  -1.658
H    0.922    6.210  -0.034
H    3.011    4.240  -3.673
H    1.879    2.888  -3.915
H    1.429    4.532  -4.426
H   -0.454    1.056  -2.016
H   -1.384  -0.448  -2.309
H   -1.620    0.991  -3.347
C   -1.970    4.950  -0.669
O   -0.477    3.438  -1.822
H   -3.477    2.875  -0.525
H   -2.995    5.002  -0.270
H   -1.268    5.238   0.135
H   -1.859    5.701  -1.472
C   -3.437    0.431   2.806
C   -4.285  -0.708   2.826
C   -5.220  -0.891   3.852
C   -5.332    0.050   4.893
C   -4.497    1.181   4.894
C   -3.564    1.367   3.866
H   -4.207  -1.448   2.023
H   -5.867  -1.776   3.843
H   -6.062  -0.099   5.696
H   -4.575    1.921   5.699
H   -2.915    2.252   3.869
```

H	-1.932	1.646	1.840
C	0.030	-3.112	-0.658
C	-0.102	-3.127	-2.067
C	-1.229	-3.766	-2.619
C	-2.204	-4.385	-1.816
C	-2.030	-4.361	-0.418
C	-0.922	-3.740	0.183
C	0.927	-2.476	-2.968
H	-1.345	-3.777	-3.710
H	-2.776	-4.845	0.224
C	-0.763	-3.719	1.686
C	-3.856	0.474	-1.494
C	-4.107	-0.454	-2.536
C	-5.369	-1.047	-2.697
C	-6.416	-0.742	-1.814
C	-6.182	0.161	-0.762
C	-4.925	0.755	-0.604
H	-3.317	-0.701	-3.250
H	-5.533	-1.745	-3.527
H	-7.401	-1.207	-1.938
H	-6.982	0.397	-0.051
H	-4.759	1.421	0.248
C	3.409	2.455	1.909
C	4.198	2.224	3.042
C	4.390	0.908	3.485
C	3.801	-0.160	2.798
H	3.246	3.472	1.543
H	4.656	3.067	3.569
H	4.995	0.703	4.374
H	3.954	-1.178	3.163
H	0.491	-2.250	-3.955
H	1.312	-1.537	-2.535
H	1.795	-3.141	-3.143
C	-3.426	-5.032	-2.433
H	-3.753	-5.914	-1.855
H	-4.277	-4.324	-2.454
H	-3.237	-5.350	-3.472
H	-1.587	-4.264	2.177
H	0.191	-4.177	2.007
H	-0.760	-2.678	2.059
C	4.774	-2.076	0.361
H	3.423	-2.825	1.863
C	5.002	-1.204	-0.724

```
C    6.303   -1.013   -1.214
C    7.387   -1.693   -0.632
C    7.166   -2.560    0.450
C    5.865   -2.746    0.946
H    5.695   -3.420    1.795
H    4.161   -0.659   -1.170
H    8.006   -3.089    0.914
H    6.471   -0.327   -2.052
H    8.402   -1.542   -1.017
---------------------------------
```

SCF Done: E(RB-P86) = -4435.27203360 A.U. after 29 cycles

	1	2	3
	A	A	A
Frequencies --	-173.3027	13.9884	17.1949
Red. masses --	7.1728	5.4562	6.0309

Zero-point correction= 0.798924 (Hartree/Particle)
Thermal correction to Energy= 0.855126
Thermal correction to Enthalpy= 0.856071
Thermal correction to Gibbs Free Energy= 0.704385
Sum of electronic and zero-point Energies= -4434.473110
Sum of electronic and thermal Energies= -4434.416907
Sum of electronic and thermal Enthalpies= -4434.415963
Sum of electronic and thermal Free Energies= -4434.567649

Item	Value	Threshold	Converged?
Maximum Force	0.000003	0.000450	YES
RMS Force	0.000001	0.000300	YES

Direct transfer transition state leading to the minor enantiomer

#p bp86/6-31G* freq scrf(solvent=thf)

```
---------------------------------
Cartesian coordinates (Angstroms):
---------------------------------
N   -2.326    0.420    0.562
C   -3.434    1.345    0.982
C   -2.970    2.653    0.299
N   -1.519    2.408    0.108
C   -1.184    1.104    0.205
C   -2.326   -0.959    0.901
C   -1.786   -1.966    0.049
S   -1.237   -1.629   -1.655
```

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O  -2.317  -0.888  -2.351
O  -1.023  -3.049  -2.254
Cu   0.499   0.280   0.012
O   0.112  -0.939  -1.609
C   1.939   0.019   1.227
C   1.680  -0.877   2.250
Al   0.611  -3.778  -2.991
C   0.018  -5.610  -3.468
C   1.329  -2.586  -4.406
H  -3.465   2.799  -0.680
H  -3.144   3.543   0.923
H   2.541   0.905   1.511
H  -0.740  -5.602  -4.275
H   0.863  -6.227  -3.832
H  -0.428  -6.153  -2.612
H   0.651  -2.580  -5.282
H   1.453  -1.535  -4.087
H   2.314  -2.936  -4.771
C   1.946  -0.743   3.682
C   2.573   0.399   4.252
C   2.822   0.474   5.627
C   2.447  -0.583   6.479
C   1.820  -1.719   5.937
C   1.573  -1.796   4.561
H   2.865   1.231   3.602
H   3.310   1.363   6.041
H   2.642  -0.519   7.555
H   1.523  -2.547   6.591
H   1.083  -2.684   4.143
H   1.205  -1.836   1.978
C  -0.623   3.444  -0.336
C  -0.564   3.776  -1.709
C   0.288   4.830  -2.095
C   1.063   5.544  -1.164
C   0.974   5.183   0.195
C   0.139   4.141   0.634
C  -1.391   3.041  -2.742
H   0.343   5.098  -3.158
H   1.570   5.729   0.936
C   0.070   3.766   2.098
C  -1.785  -3.311   0.460
C  -2.328  -3.684   1.697
C  -2.893  -2.705   2.525
C  -2.888  -1.361   2.130
H  -1.376  -4.066  -0.214
H  -2.323  -4.737   1.997
H  -3.333  -2.979   3.490
H  -3.308  -0.603   2.796
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H  -0.966   3.178  -3.750
H  -1.445   1.959  -2.533
H  -2.431   3.420  -2.774
C   1.990   6.655  -1.610
H   1.708   7.044  -2.603
H   1.984   7.497  -0.895
H   3.035   6.298  -1.678
H   0.693   4.444   2.704
H  -0.963   3.812   2.487
H   0.426   2.732   2.261
C  -4.828   0.890   0.597
H  -3.383   1.480   2.081
C  -5.092   0.322  -0.667
C  -6.401  -0.043  -1.015
C  -7.459   0.158  -0.111
C  -7.201   0.721   1.149
C  -5.890   1.080   1.502
H  -5.690   1.514   2.490
H  -4.267   0.147  -1.368
H  -8.018   0.876   1.862
H  -6.595  -0.491  -1.995
H  -8.480  -0.128  -0.387
C   2.771  -1.971  -0.936
C   3.435  -0.986  -0.133
C   4.391  -1.385   0.983
C   3.838   0.261  -0.885
C   5.170   0.731  -0.855
C   5.562   1.847  -1.616
C   4.632   2.522  -2.418
C   3.298   2.073  -2.451
C   2.914   0.964  -1.691
C   2.492  -3.321  -0.701
C   3.029  -4.164   0.440
O   1.710  -4.004  -1.520
H   2.326  -1.592  -1.861
H   5.318  -1.805   0.543
H   4.675  -0.514   1.596
H   3.965  -2.140   1.654
H   5.923   0.216  -0.252
H   6.603   2.186  -1.576
H   4.936   3.396  -3.005
H   2.551   2.601  -3.053
H   1.865   0.640  -1.691
H   4.127  -4.098   0.524
H   2.605  -3.848   1.411
H   2.747  -5.214   0.269
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```

SCF Done: E(RB-P86) = -4435.26905482 A.U. after 28 cycles

	1	2	3
	A	A	A
Frequencies --	-215.9049	10.7284	11.6324
Red. masses --	7.4985	5.3857	5.8344

Zero-point correction= 0.797926 (Hartree/Particle)
Thermal correction to Energy= 0.854591
Thermal correction to Enthalpy= 0.855535
Thermal correction to Gibbs Free Energy= 0.700311
Sum of electronic and zero-point Energies= -4434.471129
Sum of electronic and thermal Energies= -4434.414464
Sum of electronic and thermal Enthalpies= -4434.413520
Sum of electronic and thermal Free Energies= -4434.568744

Item	Value	Threshold	Converged?
Maximum Force	0.000013	0.000450	YES
RMS Force	0.000002	0.000300	YES

#p bp86/6-31G* freq scrf(solvent=thf)

Cartesian coordinates (Angstroms):

N	-1.566	1.824	0.167
C	-2.144	2.763	1.208
C	-1.018	2.741	2.271
N	-0.142	1.627	1.822
C	-0.479	1.132	0.618
C	-2.338	1.425	-0.967
C	-2.911	0.131	-1.095
S	-2.655	-1.115	0.190
O	-1.212	-1.602	0.062
O	-3.583	-2.275	-0.256
Cu	0.291	-0.341	-0.350
O	-3.031	-0.538	1.504
C	1.558	0.231	-1.599
C	2.912	0.385	-1.598
Al	-3.591	-4.154	0.188
C	-3.794	-4.358	2.146
C	-4.939	-4.891	-1.065
C	-0.976	-4.111	-1.057
C	1.548	-2.847	-2.574
C	1.361	-3.043	-1.084
C	-1.409	-3.965	-2.497

O	-1.846	-4.631	-0.218
C	3.756	1.060	-2.604
C	3.238	1.738	-3.739
C	4.085	2.361	-4.664
C	5.482	2.333	-4.490
C	6.016	1.669	-3.372
C	5.166	1.045	-2.448
C	1.008	1.255	2.608
C	2.254	1.877	2.347
C	3.337	1.562	3.187
C	3.212	0.664	4.264
C	1.957	0.072	4.493
C	0.838	0.354	3.686
C	2.428	2.846	1.200
C	-0.503	-0.276	3.992
C	2.553	-2.844	-0.219
C	3.860	-2.883	-0.768
C	4.996	-2.780	0.050
C	4.861	-2.607	1.436
C	3.571	-2.538	1.996
C	2.439	-2.660	1.185
C	-3.677	-0.211	-2.221
C	-3.903	0.737	-3.229
C	-3.352	2.021	-3.112
C	-2.574	2.358	-1.995
C	4.403	0.337	5.140
C	-2.504	4.148	0.701
C	-1.527	5.009	0.156
C	-1.878	6.291	-0.290
C	-3.209	6.734	-0.191
C	-4.187	5.886	0.351
C	-3.835	4.598	0.791
C	0.282	-3.750	-0.523
H	-3.053	2.273	1.601
H	-0.447	3.687	2.296
H	-1.405	2.544	3.284
H	1.038	0.697	-2.465
H	3.495	-0.050	-0.770
H	-4.791	-4.022	2.491
H	-3.686	-5.415	2.456
H	-3.042	-3.778	2.712
H	-5.962	-4.583	-0.772
H	-4.797	-4.573	-2.115
H	-4.928	-5.998	-1.059
H	2.256	-2.029	-2.771
H	1.940	-3.775	-3.040
H	0.610	-2.593	-3.083
H	-0.660	-4.374	-3.195

```
H   -2.361   -4.494   -2.653
H   -1.556   -2.899   -2.756
H    2.153    1.778   -3.893
H    3.653    2.878   -5.530
H    6.142    2.823   -5.214
H    7.102    1.637   -3.219
H    5.593    0.527   -1.579
H    4.307    2.039    2.995
H    1.837   -0.625    5.333
H    2.304    2.335    0.227
H    1.689    3.667    1.237
H    3.433    3.299    1.222
H   -1.033   -0.592    3.079
H   -0.379   -1.151    4.651
H   -1.171    0.434    4.518
H    3.995   -3.028   -1.844
H    5.992   -2.835   -0.403
H    5.747   -2.518    2.073
H    3.445   -2.377    3.072
H    1.446   -2.582    1.643
H   -4.103   -1.215   -2.289
H   -4.507    0.467   -4.100
H   -3.515    2.766   -3.898
H   -2.127    3.352   -1.911
H    5.000    1.238    5.362
H    4.090   -0.113    6.098
H    5.079   -0.383    4.641
H   -0.488    4.669    0.065
H   -1.110    6.947   -0.715
H   -3.481    7.738   -0.536
H   -5.226    6.222    0.432
H   -4.601    3.936    1.212
H    0.353   -3.989    0.544
---------------------------------
```

SCF Done: E(RB-P86) = -4435.27538330 A.U. after 29 cycles

	1	2	3
	A	A	A
Frequencies --	-51.7972	12.8599	14.0834
Red. masses --	8.3884	5.7370	5.6638

Zero-point correction= 0.798363 (Hartree/Particle)
Thermal correction to Energy= 0.855033
Thermal correction to Enthalpy= 0.855977
Thermal correction to Gibbs Free Energy= 0.701721
Sum of electronic and zero-point Energies= -4434.477021
Sum of electronic and thermal Energies= -4434.420350

Sum of electronic and thermal Enthalpies= -4434.419406
Sum of electronic and thermal Free Energies= -4434.573662

Item	Value	Threshold	Converged?
Maximum Force	0.000006	0.000450	YES
RMS Force	0.000001	0.000300	YES

#p bp86/6-31G* freq scrf(solvent=thf)

Cartesian coordinates (Angstroms):

N	-0.255	2.631	0.394
C	0.500	3.637	1.222
C	0.829	2.780	2.464
N	0.740	1.402	1.916
C	0.038	1.331	0.765
C	-1.167	3.084	-0.598
C	-2.431	2.488	-0.895
S	-2.978	0.972	-0.100
O	-2.143	-0.131	-0.737
O	-4.443	0.770	-0.577
Cu	-0.219	-0.264	-0.303
O	-2.878	1.117	1.373
C	1.283	-0.574	-1.387
C	2.392	-1.361	-1.376
Al	-5.450	-0.849	-0.190
C	-5.999	-0.851	1.710
C	-6.819	-0.850	-1.626
C	-3.400	-2.628	-1.299
C	-1.465	-2.393	1.179
C	-1.069	-2.853	-0.207
C	-4.157	-2.916	-2.578
O	-4.080	-2.101	-0.306
C	3.531	-1.345	-2.317
C	3.629	-0.456	-3.419
C	4.731	-0.485	-4.281
C	5.778	-1.405	-4.076
C	5.701	-2.295	-2.992
C	4.595	-2.264	-2.129
C	1.228	0.288	2.696
C	2.569	-0.139	2.524
C	3.039	-1.189	3.333
C	2.232	-1.804	4.308
C	0.917	-1.333	4.469
C	0.396	-0.280	3.692
C	3.482	0.506	1.507

C	-1.000	0.235	3.966
C	0.183	-3.641	-0.332
C	0.684	-4.084	-1.587
C	1.785	-4.941	-1.674
C	2.446	-5.372	-0.510
C	2.001	-4.910	0.738
C	0.894	-4.054	0.826
C	-3.295	3.052	-1.850
C	-2.953	4.232	-2.519
C	-1.726	4.844	-2.228
C	-0.855	4.279	-1.291
C	2.778	-2.909	5.187
C	1.754	4.189	0.548
C	2.495	3.436	-0.384
C	3.681	3.953	-0.931
C	4.139	5.226	-0.553
C	3.402	5.984	0.373
C	2.215	5.469	0.918
C	-2.038	-2.992	-1.233
H	-0.181	4.464	1.483
H	0.086	2.909	3.272
H	1.835	2.980	2.862
H	1.267	0.199	-2.189
H	2.493	-2.122	-0.585
H	-5.138	-0.759	2.397
H	-6.687	-0.014	1.939
H	-6.533	-1.784	1.977
H	-7.599	-0.096	-1.400
H	-6.425	-0.611	-2.631
H	-7.337	-1.825	-1.703
H	-2.333	-1.726	1.151
H	-1.752	-3.274	1.790
H	-0.635	-1.899	1.717
H	-3.547	-3.460	-3.316
H	-5.066	-3.505	-2.359
H	-4.496	-1.969	-3.038
H	2.824	0.266	-3.602
H	4.777	0.215	-5.124
H	6.640	-1.425	-4.752
H	6.506	-3.019	-2.817
H	4.540	-2.966	-1.287
H	4.073	-1.532	3.197
H	0.273	-1.788	5.233
H	4.503	0.099	1.593
H	3.122	0.317	0.480
H	3.539	1.601	1.638
H	-1.591	-0.519	4.511
H	-0.967	1.141	4.603

```
H  -1.539   0.501   3.043
H   0.219  -3.735  -2.514
H   2.138  -5.265  -2.659
H   3.305  -6.049  -0.578
H   2.511  -5.224   1.656
H   0.563  -3.727   1.816
H  -4.248   2.556  -2.047
H  -3.640   4.664  -3.253
H  -1.432   5.768  -2.738
H   0.104   4.765  -1.095
H   3.541  -3.508   4.658
H   3.261  -2.495   6.092
H   1.978  -3.589   5.526
H   2.136   2.448  -0.692
H   4.245   3.358  -1.657
H   5.062   5.629  -0.982
H   3.747   6.982   0.666
H   1.640   6.067   1.636
H  -1.701  -3.495  -2.144
---------------------------------
```

SCF Done: E(RB-P86) = -4435.27590057 A.U. after 29 cycles

	1	2	3
	A	A	A
Frequencies --	-69.8779	7.6312	15.6726
Red. masses --	9.7292	5.6470	5.7061

Zero-point correction= 0.799244 (Hartree/Particle)
Thermal correction to Energy= 0.855198
Thermal correction to Enthalpy= 0.856142
Thermal correction to Gibbs Free Energy= 0.705758
Sum of electronic and zero-point Energies= -4434.476657
Sum of electronic and thermal Energies= -4434.420702
Sum of electronic and thermal Enthalpies= -4434.419758
Sum of electronic and thermal Free Energies= -4434.570143

Item	Value	Threshold	Converged?
Maximum Force	0.000009	0.000450	YES
RMS Force	0.000003	0.000300	YES

#p bp86/6-31G* freq scrf(solvent=thf)

Cartesian coordinates (Angstroms):

```
N  -2.412  -0.619  -0.092
C  -3.496  -1.295  -0.905
C  -2.650  -2.282  -1.750
N  -1.255  -1.832  -1.506
C  -1.152  -0.897  -0.541
C  -2.697   0.484   0.769
C  -2.343   1.824   0.452
S  -1.560   2.253  -1.132
O  -0.115   1.786  -1.089
O  -1.568   3.805  -1.150
Cu   0.392   0.089  -0.031
O  -2.394   1.686  -2.220
C   1.535  -0.302   1.423
C   2.494  -1.287   1.539
Al  -0.120   5.042  -0.793
C   1.284   4.873  -2.186
C  -1.105   6.751  -0.593
C   1.112   3.627   1.518
C   3.243   1.553   2.595
C   2.722   1.639   1.168
C   1.894   2.745   0.770
H  -2.773  -3.329  -1.418
H  -2.896  -2.227  -2.823
H   0.972  -0.097   2.359
H   0.936   5.320  -3.138
H   2.207   5.415  -1.900
H   1.574   3.830  -2.406
H  -1.580   7.065  -1.542
H  -1.906   6.703   0.169
H  -0.426   7.574  -0.291
H   2.431   1.471   3.333
H   3.896   0.679   2.727
H   3.817   2.469   2.840
C   0.988   3.656   3.030
O   0.379   4.556   0.920
H   1.829   2.912  -0.308
H   0.579   2.706   3.419
H   1.961   3.821   3.522
H   0.307   4.471   3.316
C   2.728  -2.206   2.654
C   1.941  -2.219   3.839
C   2.215  -3.114   4.879
C   3.279  -4.031   4.774
C   4.068  -4.038   3.609
C   3.795  -3.142   2.568
H   1.104  -1.518   3.937
H   1.592  -3.102   5.781
H   3.488  -4.731   5.590
```

H	4.899	-4.746	3.514
H	4.415	-3.152	1.663
H	3.187	-1.430	0.694
C	-0.141	-2.456	-2.170
C	0.580	-3.477	-1.502
C	1.637	-4.098	-2.190
C	1.985	-3.736	-3.507
C	1.240	-2.726	-4.138
C	0.170	-2.072	-3.495
C	0.235	-3.884	-0.087
H	2.202	-4.890	-1.683
H	1.494	-2.432	-5.165
C	-0.619	-1.003	-4.221
C	3.676	1.194	0.091
C	5.072	1.195	0.303
C	5.958	0.851	-0.733
C	5.469	0.493	-1.998
C	4.080	0.481	-2.221
C	3.202	0.827	-1.188
H	5.479	1.486	1.277
H	7.038	0.866	-0.544
H	6.161	0.219	-2.802
H	3.679	0.187	-3.197
H	2.117	0.787	-1.347
C	-2.651	2.870	1.338
C	-3.325	2.604	2.539
C	-3.689	1.288	2.857
C	-3.370	0.240	1.982
H	-2.370	3.891	1.076
H	-3.565	3.428	3.218
H	-4.211	1.068	3.794
H	-3.630	-0.792	2.233
H	0.844	-4.746	0.230
H	0.423	-3.054	0.619
H	-0.829	-4.165	0.013
C	3.147	-4.406	-4.211
H	3.094	-4.265	-5.304
H	4.113	-3.988	-3.870
H	3.175	-5.490	-4.004
H	-0.028	-0.581	-5.052
H	-1.547	-1.416	-4.663
H	-0.918	-0.181	-3.550
C	-4.597	-1.952	-0.091
H	-3.938	-0.515	-1.551
C	-4.316	-2.998	0.814
C	-5.349	-3.605	1.543
C	-6.679	-3.180	1.372
C	-6.967	-2.142	0.472

```
C  -5.930  -1.530  -0.252
H  -6.157  -0.717  -0.952
H  -3.282  -3.331   0.960
H  -8.000  -1.803   0.334
H  -5.116  -4.413   2.245
H  -7.486  -3.657   1.939
---------------------------------
```

SCF Done: E(RB-P86) = -4435.26897115 A.U. after 29 cycles

	1	2	3
	A	A	A
Frequencies --	-180.8768	8.8800	12.0296
Red. masses --	6.8538	5.9558	5.6236

Zero-point correction= 0.798103 (Hartree/Particle)
Thermal correction to Energy= 0.854741
Thermal correction to Enthalpy= 0.855685
Thermal correction to Gibbs Free Energy= 0.700651
Sum of electronic and zero-point Energies= -4434.470868
Sum of electronic and thermal Energies= -4434.414230
Sum of electronic and thermal Enthalpies= -4434.413286
Sum of electronic and thermal Free Energies= -4434.568320

Item	Value	Threshold	Converged?
Maximum Force	0.000005	0.000450	YES
RMS Force	0.000001	0.000300	YES

#p bp86/6-31G* freq scrf(solvent=thf)

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Cartesian coordinates (Angstroms):
---------------------------------
H  -5.016  -2.532  -3.135
H  -4.280  -3.483  -1.832
C  -4.720  -2.498  -2.070
H  -5.624  -2.351  -1.458
C  -3.698  -1.401  -1.858
O  -2.568  -1.486  -2.505
C  -3.996  -0.342  -0.978
H  -4.938  -0.466  -0.436
H  -1.722   0.570  -2.215
C  -3.233   0.825  -0.683
H  -2.850   1.924  -2.488
```

C	-2.267	1.377	-1.716
H	-4.828	0.330	1.519
C	-4.697	1.398	1.319
C	-3.855	1.810	0.254
H	-1.549	2.086	-1.275
C	-5.330	2.328	2.150
H	-5.968	1.976	2.968
C	-3.666	3.203	0.075
H	-3.032	3.569	-0.737
C	-5.139	3.708	1.948
C	-4.301	4.138	0.908
H	-5.633	4.437	2.599
H	-4.142	5.208	0.735
N	2.624	-0.334	0.311
C	4.018	-0.002	-0.161
C	3.901	1.538	-0.322
N	2.436	1.775	-0.256
C	1.736	0.692	0.140
C	2.172	-1.665	0.582
C	1.315	-2.375	-0.302
S	0.973	-1.771	-1.985
O	0.238	-0.460	-1.910
O	0.013	-2.867	-2.548
Cu	-0.098	0.316	0.117
O	2.275	-1.748	-2.703
C	-1.725	-0.395	0.740
C	-2.059	-0.226	2.064
Al	-1.573	-2.614	-3.591
C	-1.139	-1.582	-5.225
C	-2.262	-4.473	-3.702
C	-2.641	-1.200	2.996
C	-2.984	-2.527	2.620
C	-3.549	-3.415	3.542
C	-3.785	-3.012	4.870
C	-3.451	-1.704	5.264
C	-2.889	-0.814	4.340
C	1.872	3.085	-0.446
C	1.564	3.883	0.683
C	1.048	5.173	0.461
C	0.845	5.683	-0.836
C	1.155	4.857	-1.932
C	1.669	3.557	-1.765
C	1.763	3.364	2.090

C	1.971	2.687	-2.966
C	0.852	-3.657	0.041
C	1.234	-4.247	1.256
C	2.093	-3.560	2.125
C	2.549	-2.276	1.791
C	0.325	7.090	-1.045
C	5.135	-0.460	0.760
C	5.249	0.026	2.080
C	6.297	-0.399	2.909
C	7.251	-1.314	2.427
C	7.146	-1.803	1.115
C	6.092	-1.379	0.289
H	4.145	-0.484	-1.148
H	4.314	1.886	-1.283
H	4.412	2.083	0.492
H	-2.004	-1.371	0.297
H	-1.915	0.771	2.513
H	-0.424	-2.125	-5.873
H	-2.040	-1.384	-5.839
H	-0.686	-0.601	-4.990
H	-1.548	-5.114	-4.256
H	-2.414	-4.948	-2.714
H	-3.227	-4.534	-4.241
H	-2.802	-2.856	1.591
H	-3.807	-4.433	3.225
H	-4.225	-3.711	5.590
H	-3.632	-1.377	6.294
H	-2.632	0.207	4.651
H	0.799	5.797	1.329
H	0.986	5.229	-2.950
H	1.476	4.127	2.832
H	1.155	2.458	2.271
H	2.816	3.087	2.282
H	1.558	3.135	-3.884
H	3.060	2.563	-3.123
H	1.544	1.676	-2.847
H	0.201	-4.190	-0.656
H	0.864	-5.244	1.513
H	2.398	-4.012	3.075
H	3.190	-1.717	2.477
H	-0.252	7.172	-1.982
H	-0.322	7.411	-0.211
H	1.158	7.816	-1.111

```
H    4.506    0.734    2.466
H    6.371   -0.016    3.932
H    8.071   -1.644    3.073
H    7.884   -2.516    0.732
H    6.011   -1.763   -0.735
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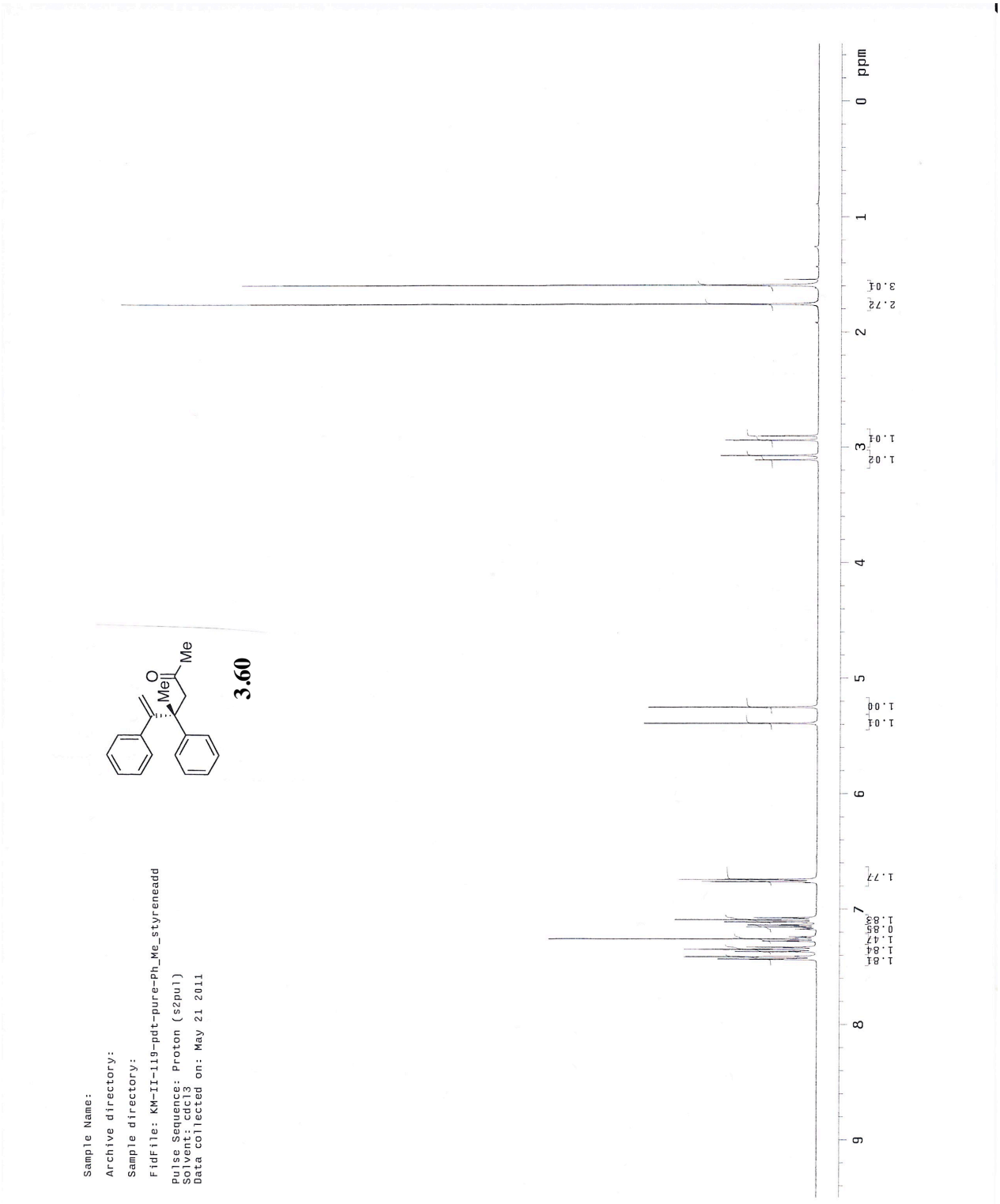
```

SCF Done: E(RB-P86) = -4435.26864532 A.U. after 26 cycles

	1	2	3
	A	A	A
Frequencies --	-171.9249	9.0241	13.8128
Red. masses --	7.2469	5.8268	5.7826

Zero-point correction= 0.798858 (Hartree/Particle)
Thermal correction to Energy= 0.855477
Thermal correction to Enthalpy= 0.856421
Thermal correction to Gibbs Free Energy= 0.701389
Sum of electronic and zero-point Energies= -4434.469787
Sum of electronic and thermal Energies= -4434.413169
Sum of electronic and thermal Enthalpies= -4434.412225
Sum of electronic and thermal Free Energies= -4434.567256

Item	Value	Threshold	Converged?
Maximum Force	0.000007	0.000450	YES
RMS Force	0.000002	0.000300	YES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Data collected on: May 21 2011
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O
Me
ppm
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1
2
3
4
5
6
7
8
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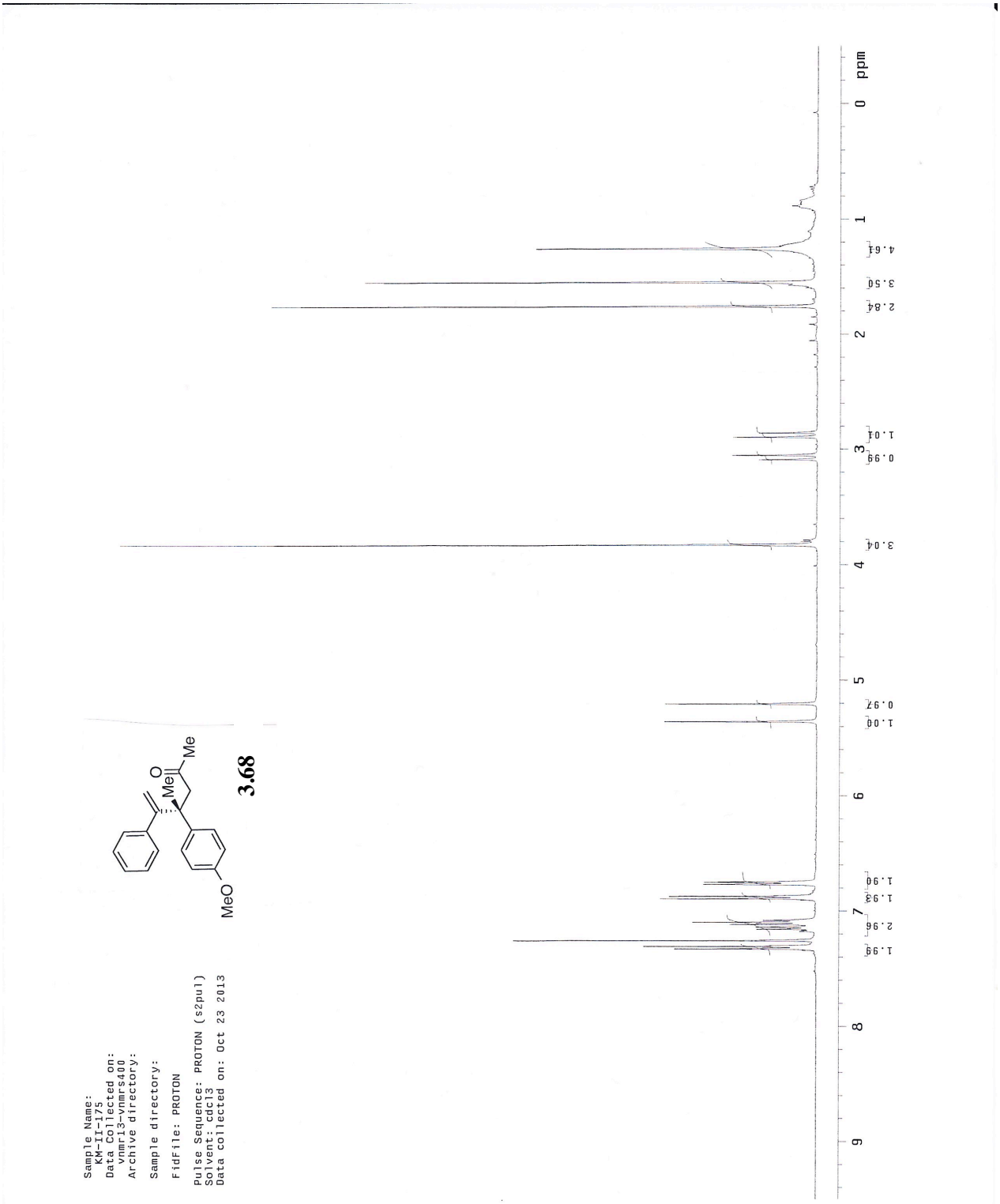
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Me
MeO
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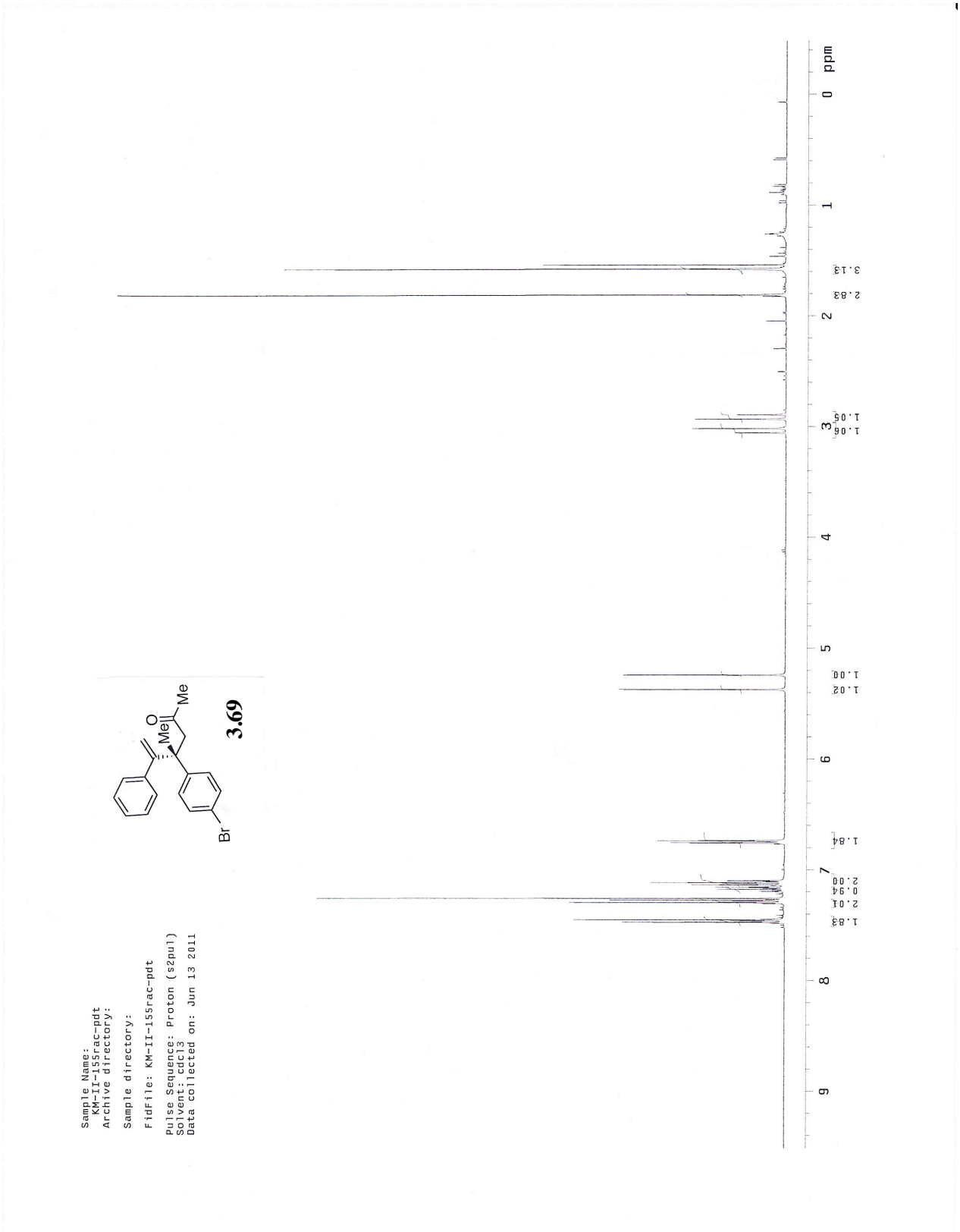
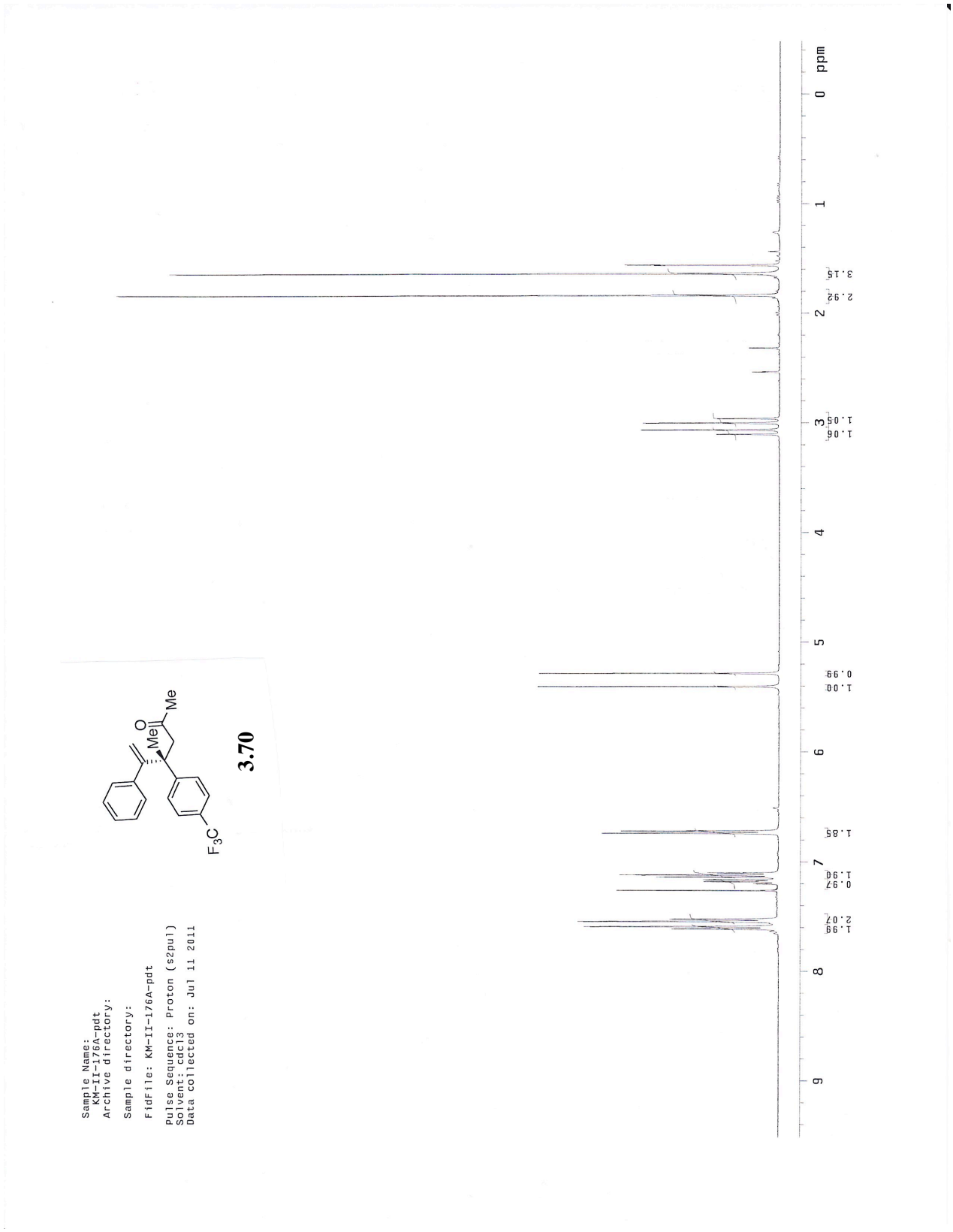
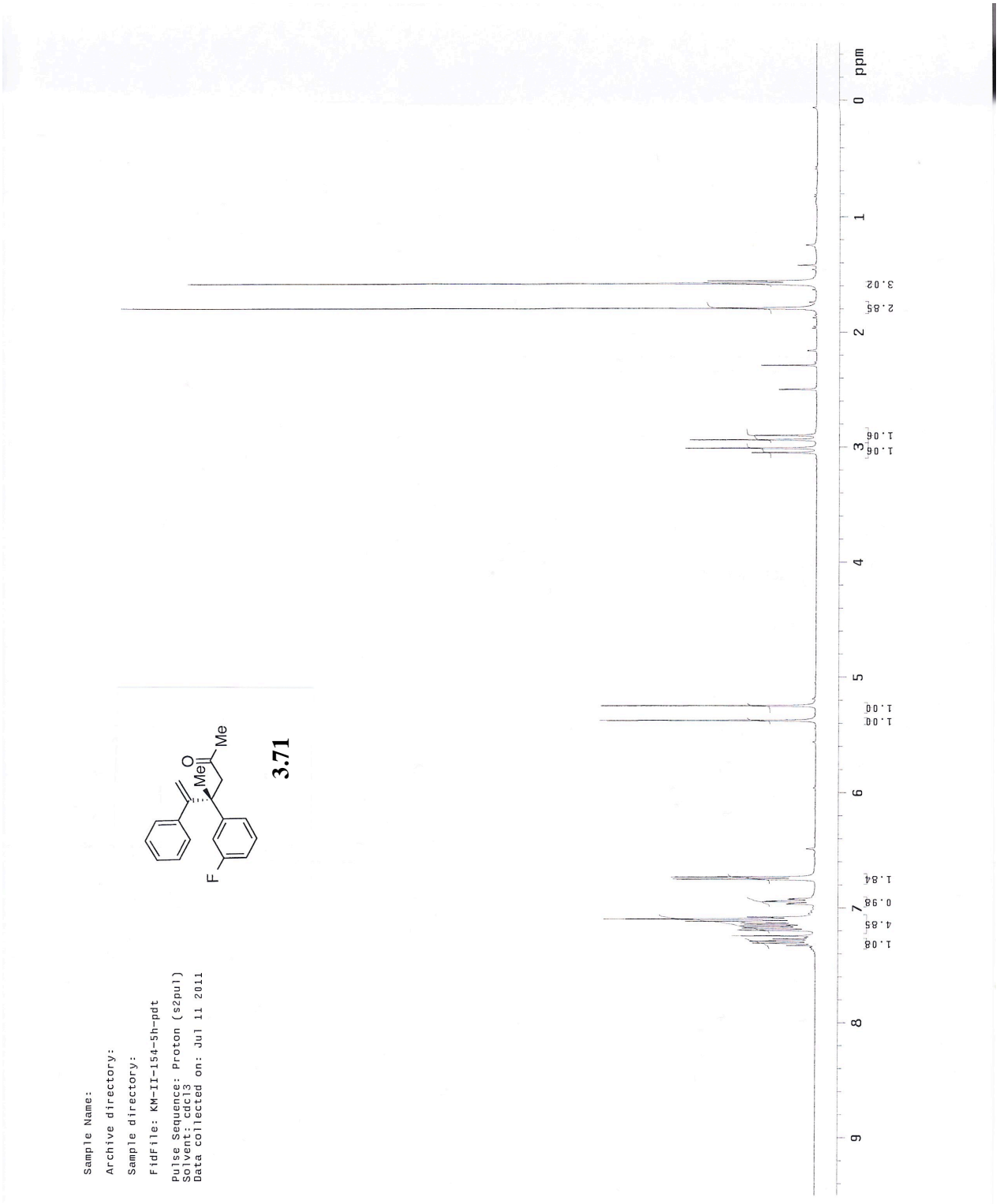
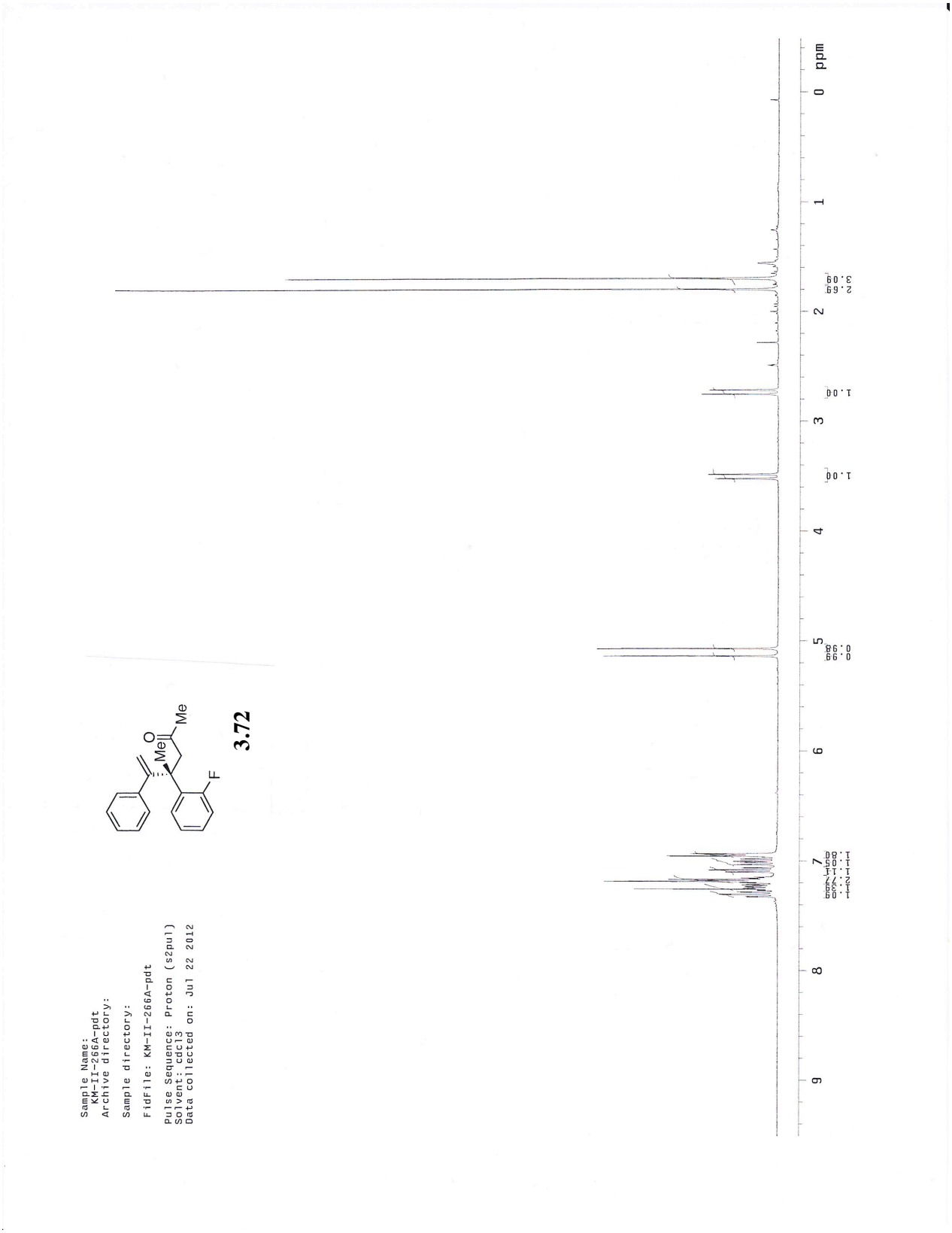
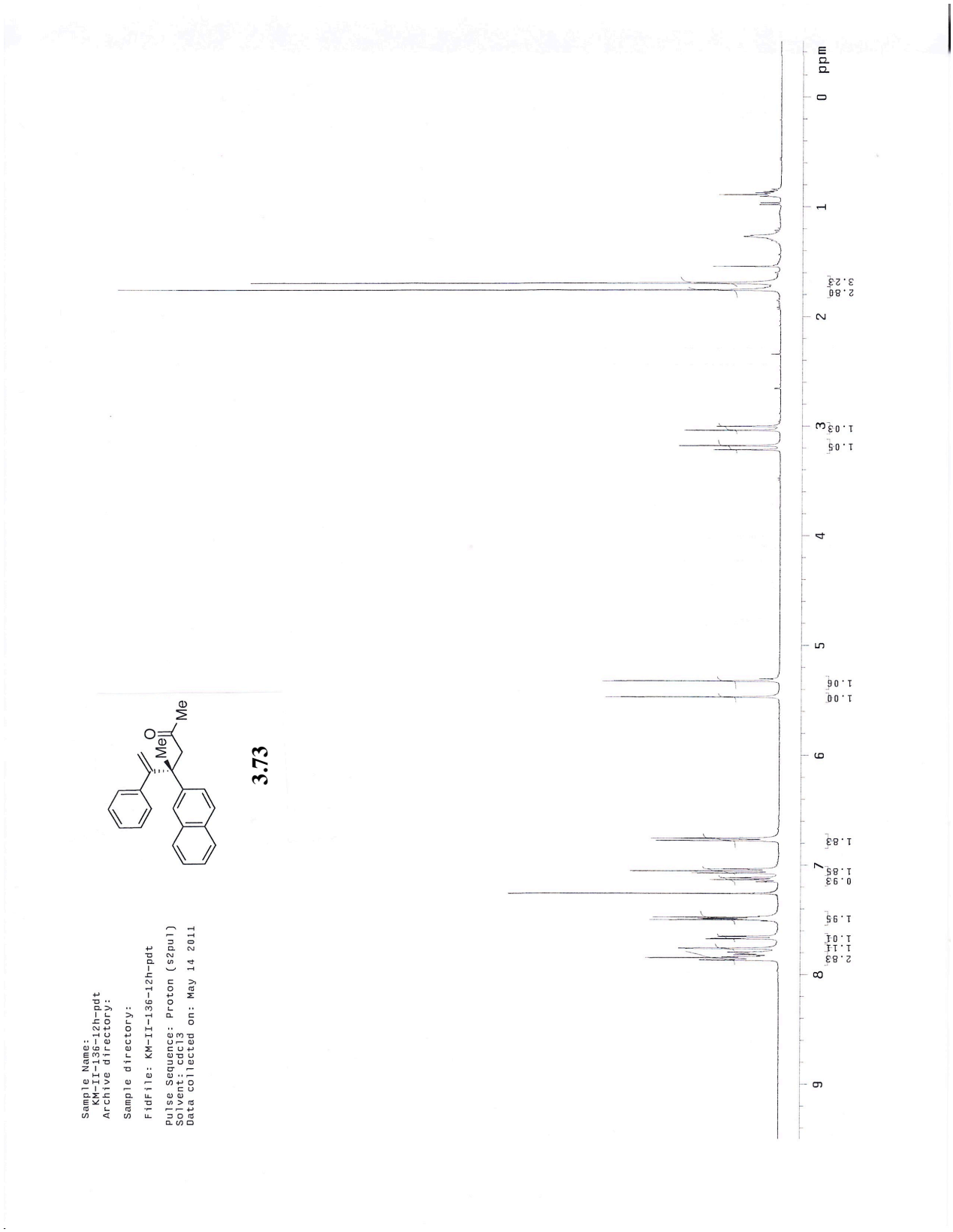
1.90
1.93
2.96
1.99

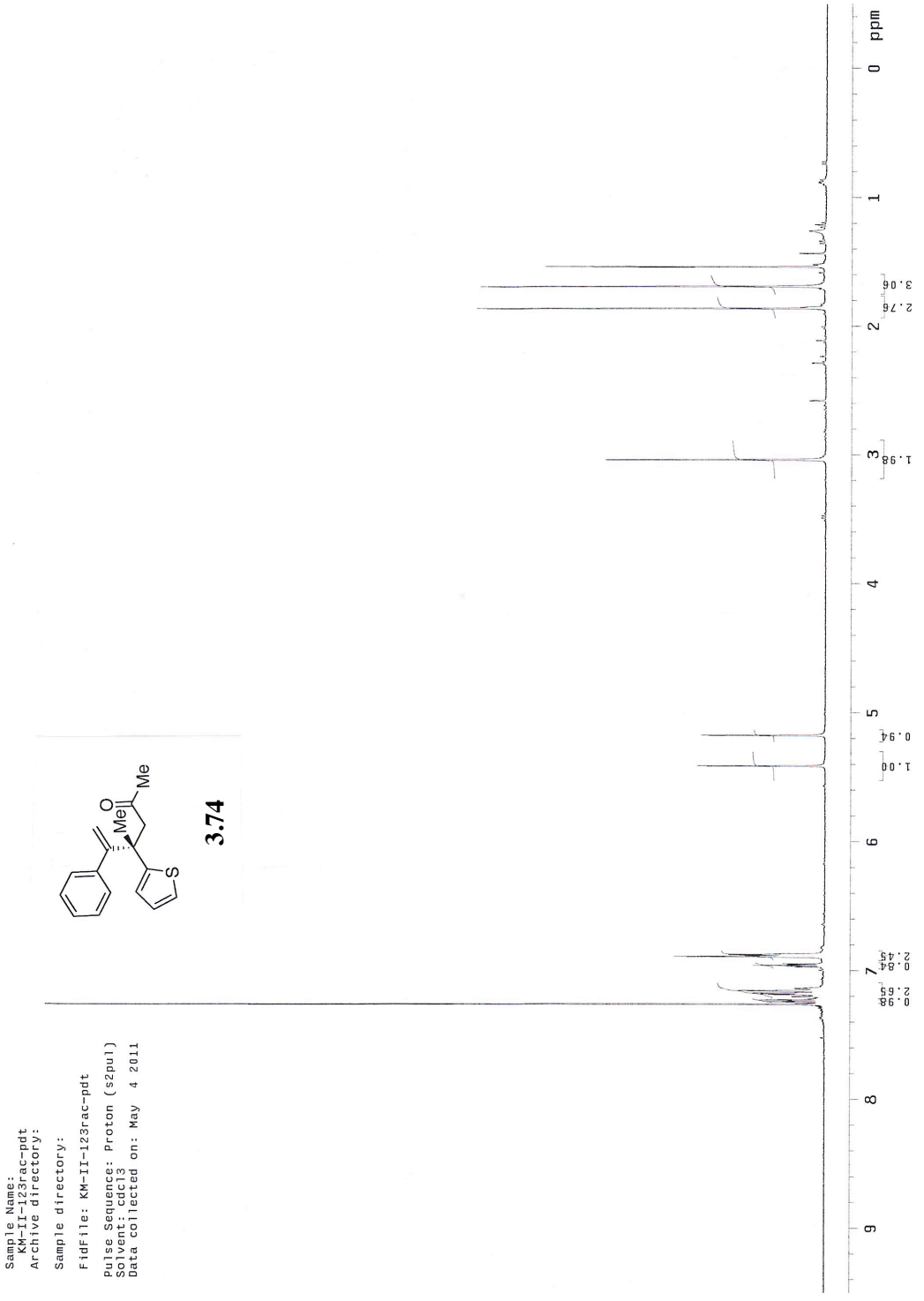

Sample Name:
KM-II-155rac-pdt
Archive directory:
Sample directory:
FidFile: KM-II-155rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2011
O
Me
Me
Br
3.69
ppm
0
1
2
3
4
5
6
7
8
9
3.13
2.83
1.05
1.06
1.00
1.02
1.84
1.83
2.01
0.94
2.00

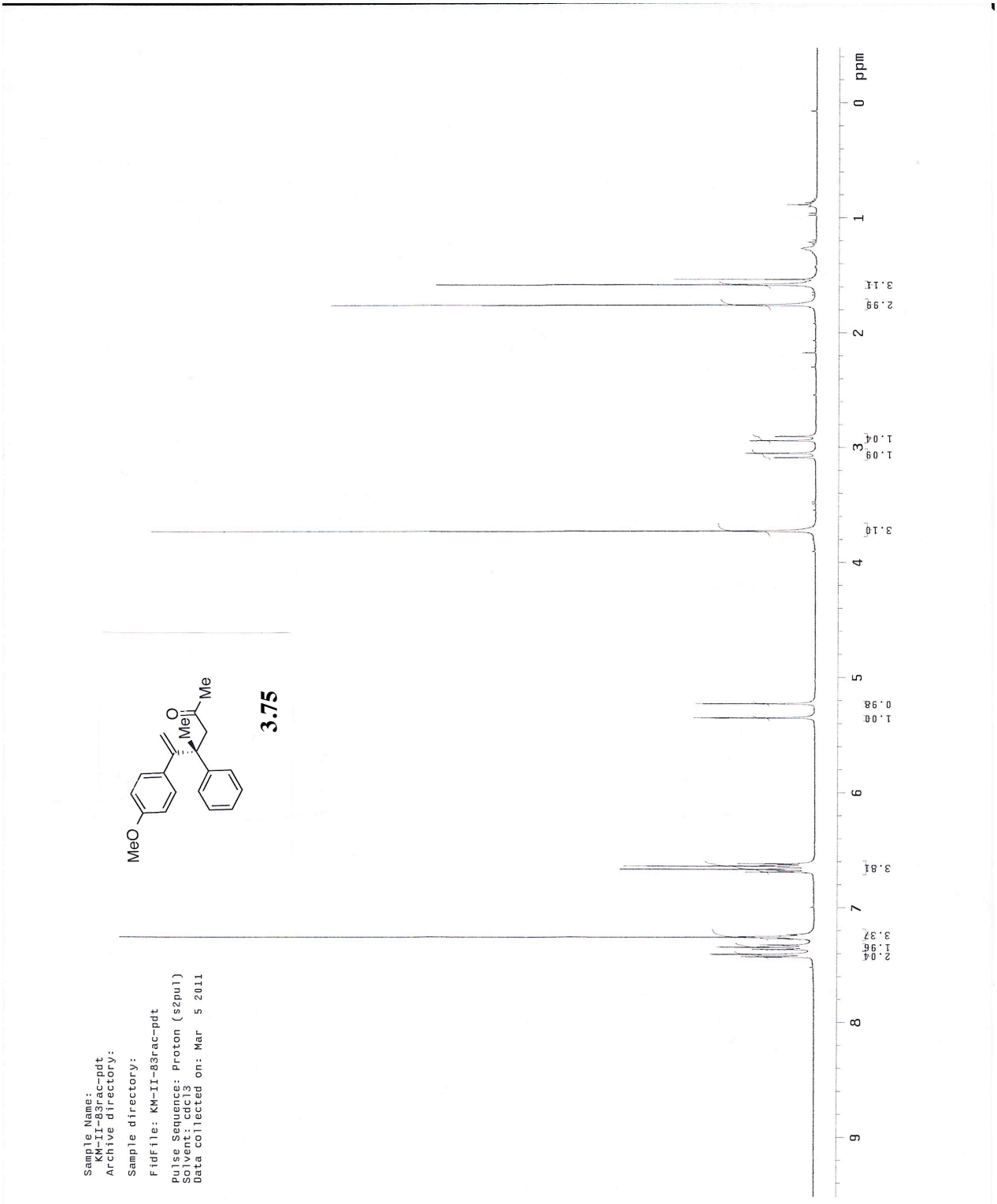

Sample Name:
KM-II-176A-pdt
Archive directory:
Sample directory:
FidFile: KM-II-176A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011
O
Me
Me
F3C
3.70
ppm
0
1
2
3
4
5
6
7
8
9
3.15
2.92
1.06
1.05
1.00
0.99
1.85
0.97
1.90
1.99
2.07

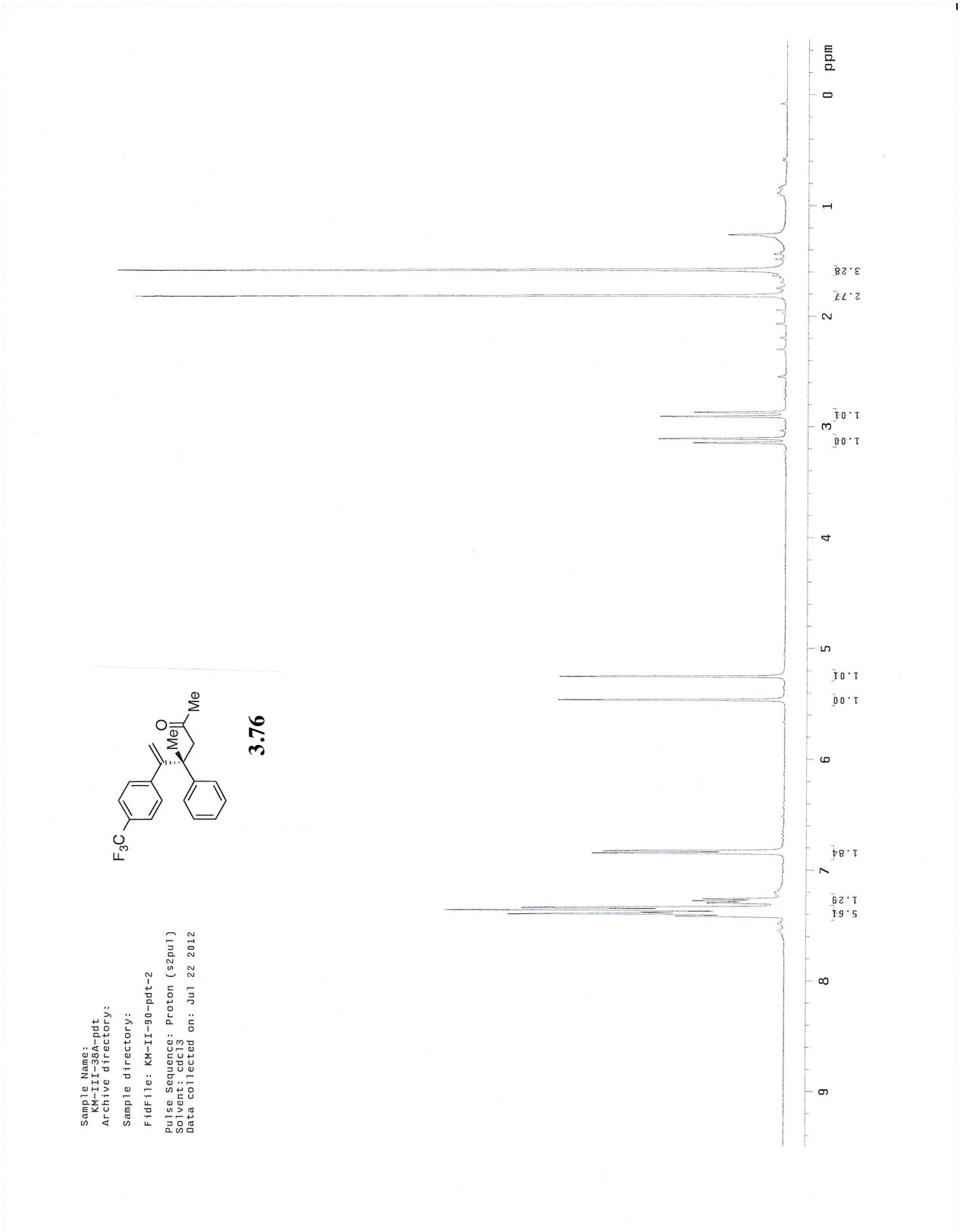

Sample Name:
Archive directory:
Sample directory:
FidFile: KM-II-154-5h-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011
Me
O
Me
F
3.71
ppm
0
1
2
3
4
5
6
7
8
9
3.02
2.85
1.06
1.06
1.00
1.00
1.84
0.98
4.85
1.08

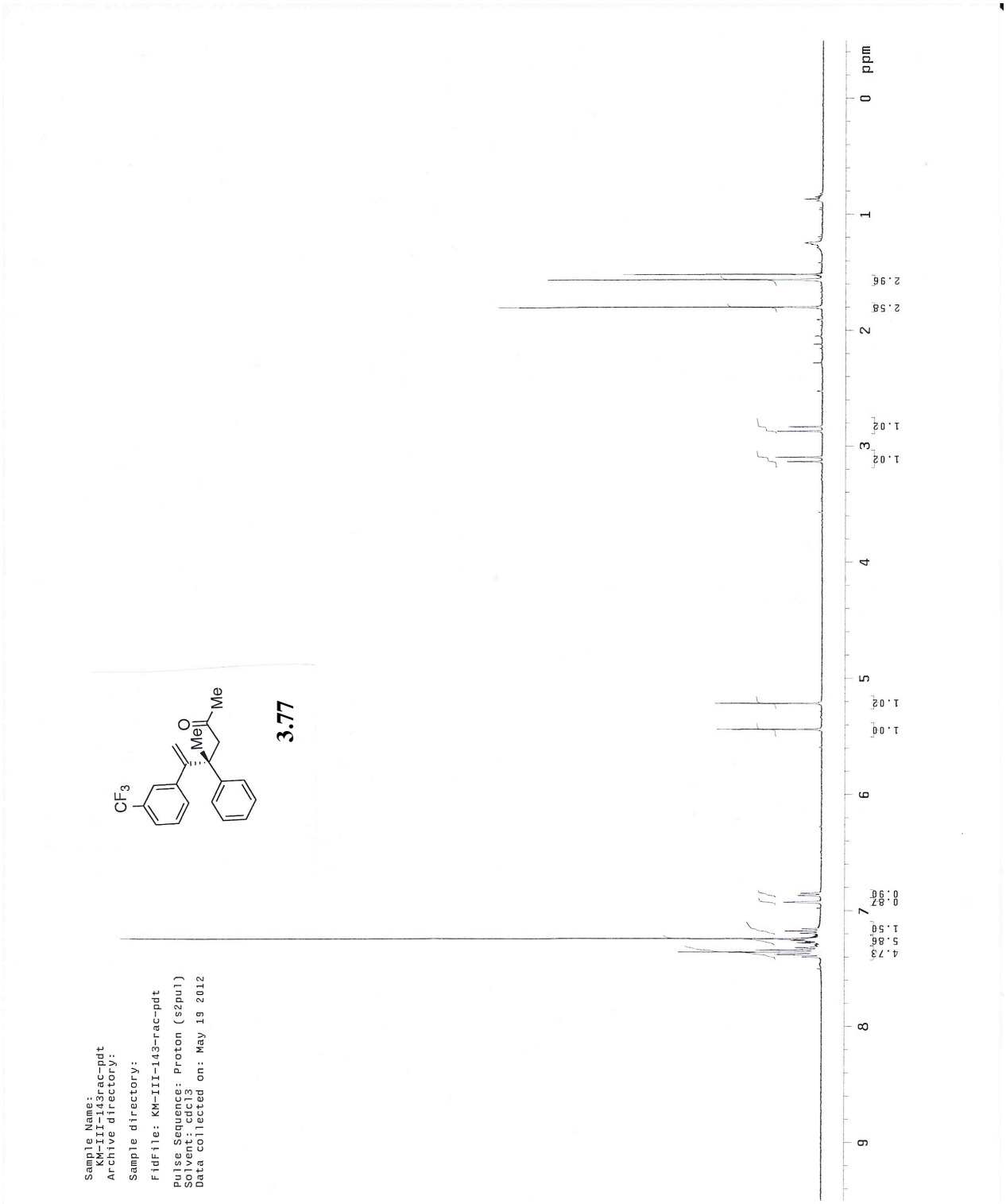

Sample Name:
KM-II-266A-pdt
Archive directory:
Sample directory:
FidFile: KM-II-266A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2012
O
Me
Me
F
3.72
ppm
0
1
2
3
4
5
6
7
8
9
3.09
2.69
1.00
1.00
0.96
0.96
1.00
1.00
1.00
1.00
1.00
1.00

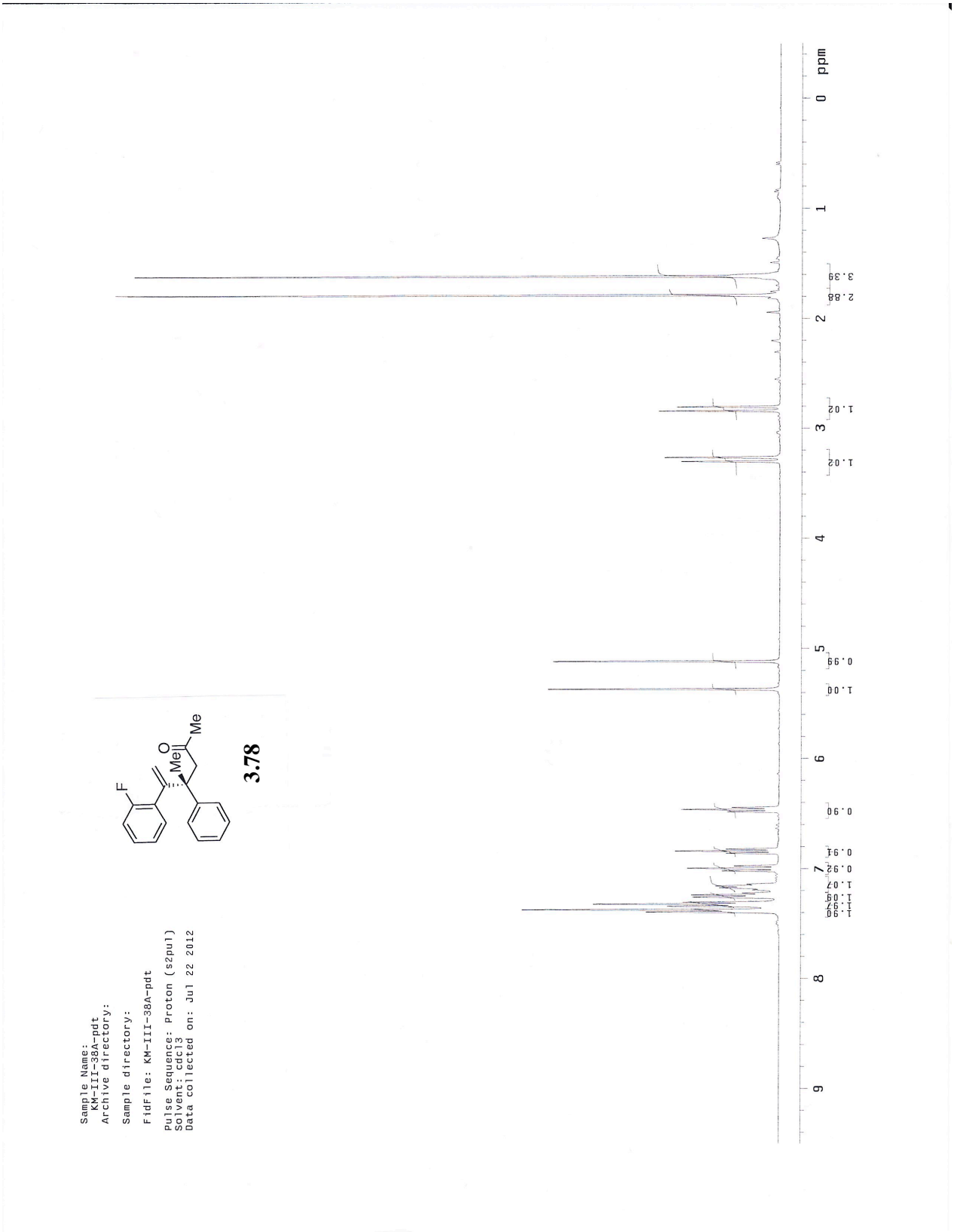

Sample Name:
KM-II-136-12h-pdt
Archive directory:
Sample directory:
FidFile: KM-II-136-12h-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: May 14 2011
3.73
Me
O
MeO
ppm
0
1
2
3
4
5
6
7
8
9
2.84
3.24
1.03
1.05
1.00
1.06
1.83
0.93
1.85
1.95
2.83
1.11
1.01

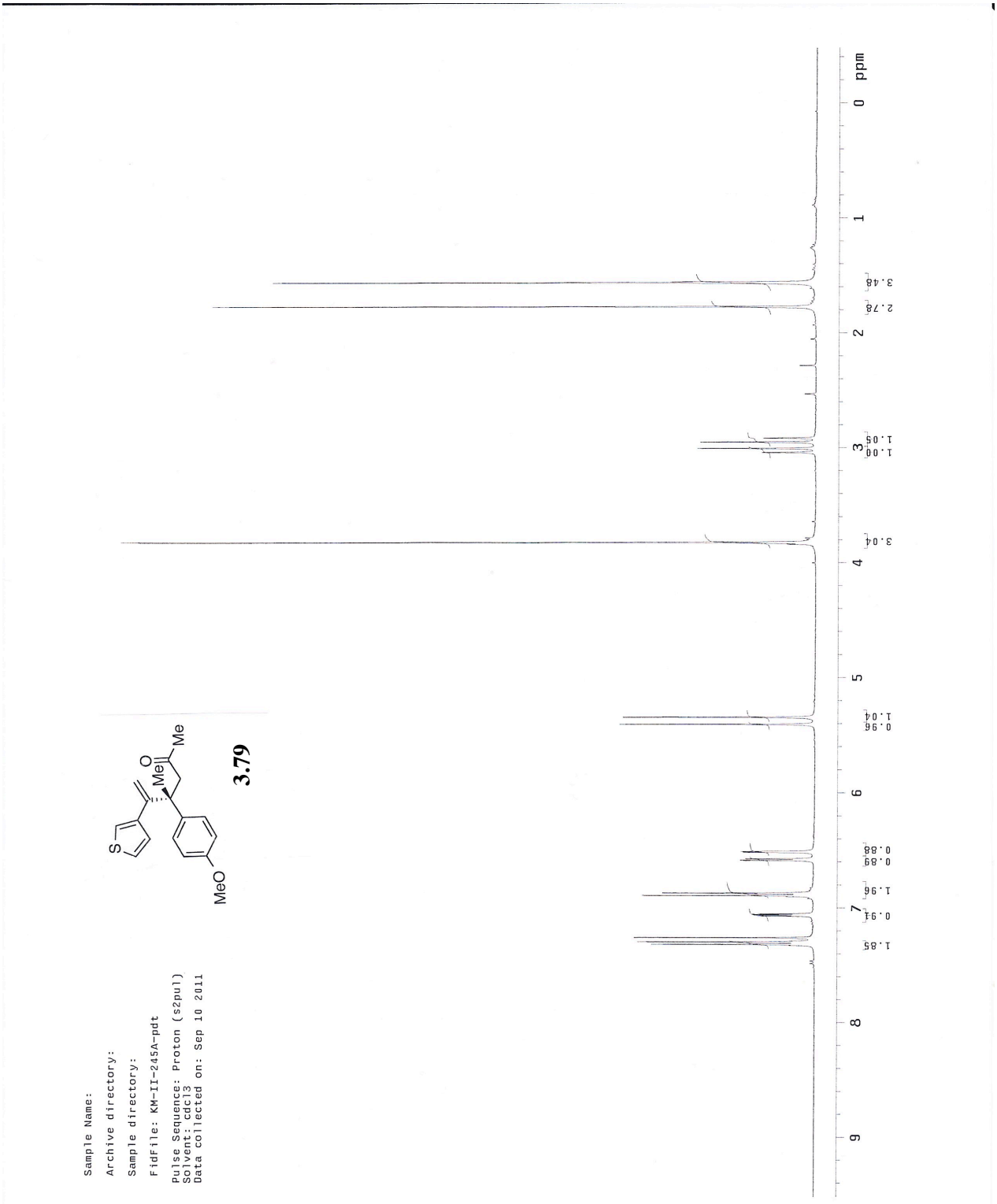

Sample Name:
KM-II-123rac-pdt
Archive directory:
Sample directory:
FidFile: KM-II-123rac-pdt
Pulse Sequence: Proton (S2pul)
Solvent: cdcl3
Data collected on: May 4 2011
Me
O
Me
S
3.74
ppm
0
1
2
3
4
5
6
7
8
9
1.98
3.06
2.76
1.00
0.94
2.68
2.44
2.65

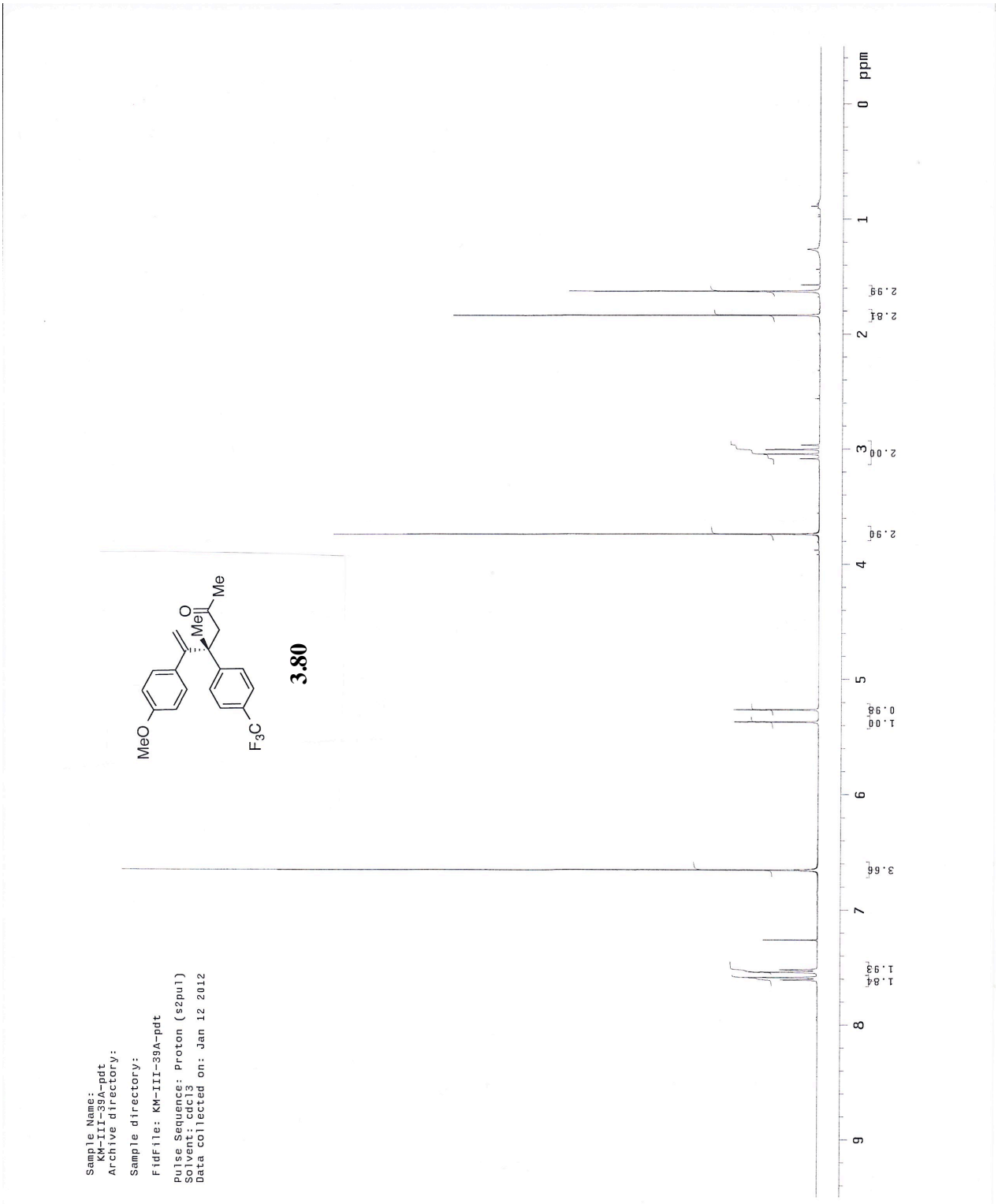

Sample Name:
KM-II-83rac-pdt
Archive directory:
Sample directory:
FidFile: KM-II-83rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 5 2011
MeO
O
MeO
Me
3.75
ppm
0
1
2
3
4
5
6
7
8
9
3.11
2.99
1.09
1.04
3.10
1.00
0.98
3.81
2.04
1.96
3.37

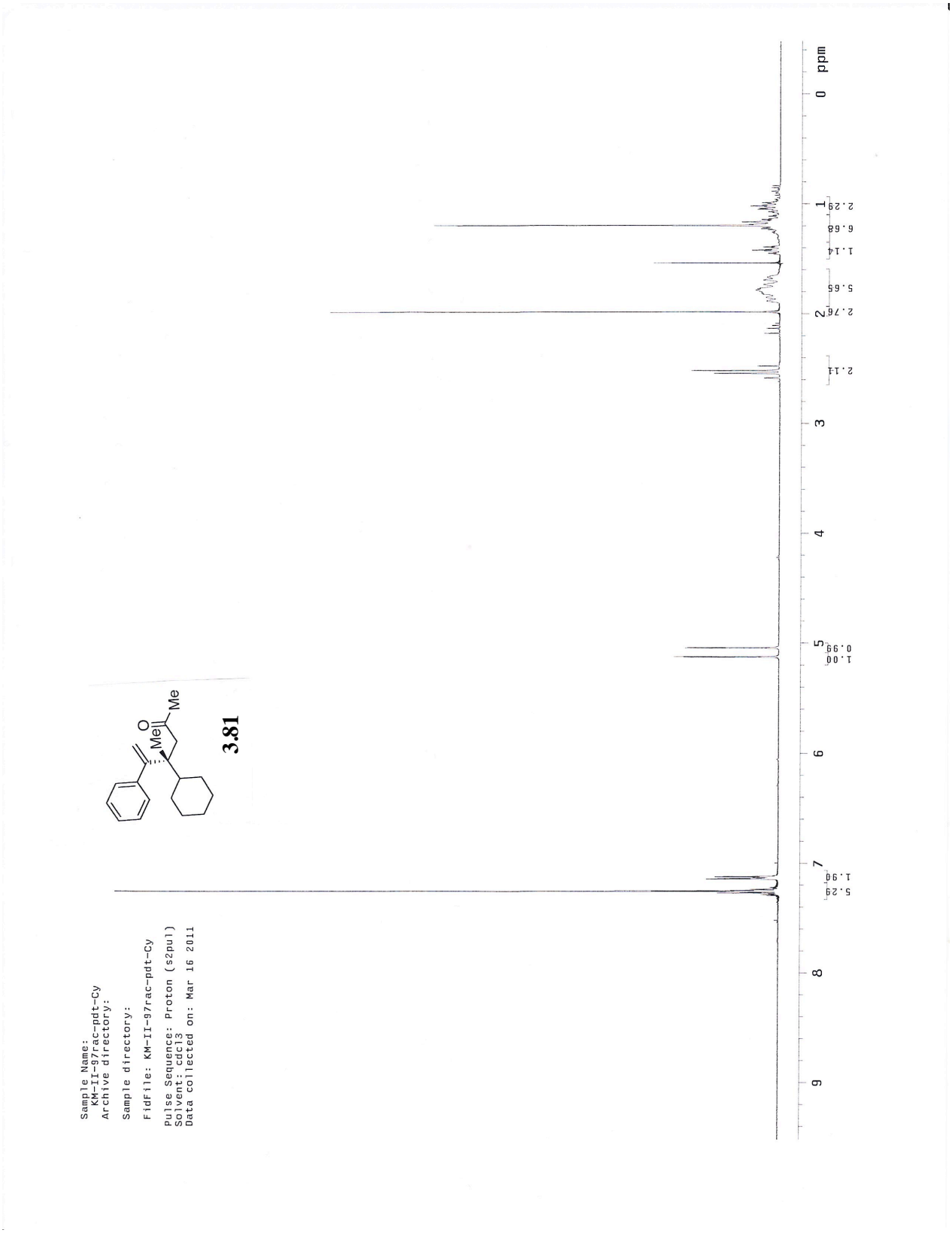

Sample Name:
KM-II-38A-pdt
Archive directory:
Sample directory:
FidFile: KM-II-90-pdt-2
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2012
3.76
Me
O
Me
F3C
ppm
0
1
2
3
4
5
6
7
8
9
3.28
2.77
1.01
1.00
1.01
1.00
1.84
1.29
5.61

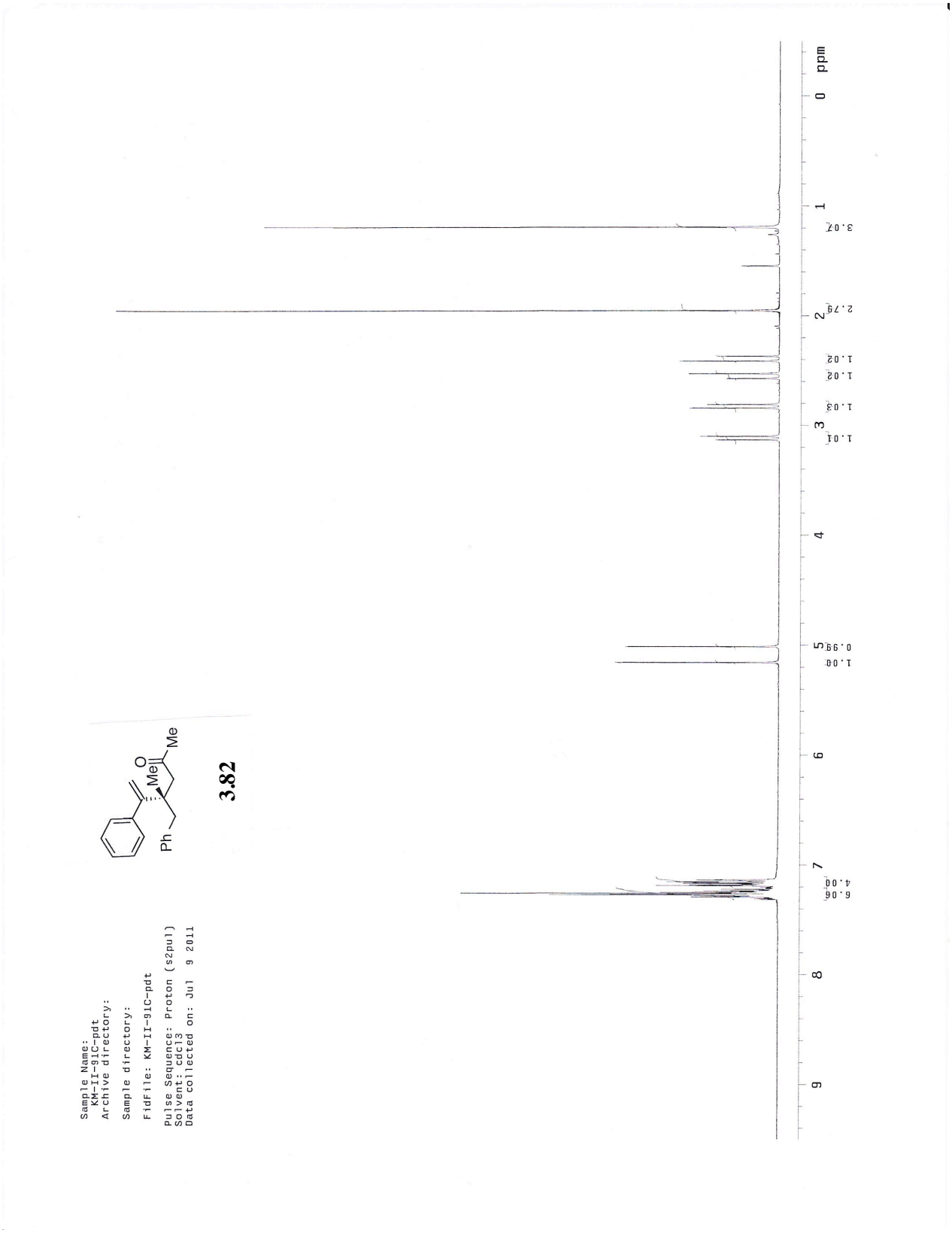

Sample Name:
KM-II-143rac-pdt
Archive directory:
Sample directory:
FidFile: KM-III-143-rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: May 19 2012
CF3
Me
O
Me
3.77
ppm
0
1
2
3
4
5
6
7
8
9
2.96
2.58
1.02
1.02
1.02
1.04
0.87
0.90
1.56
5.86
4.73

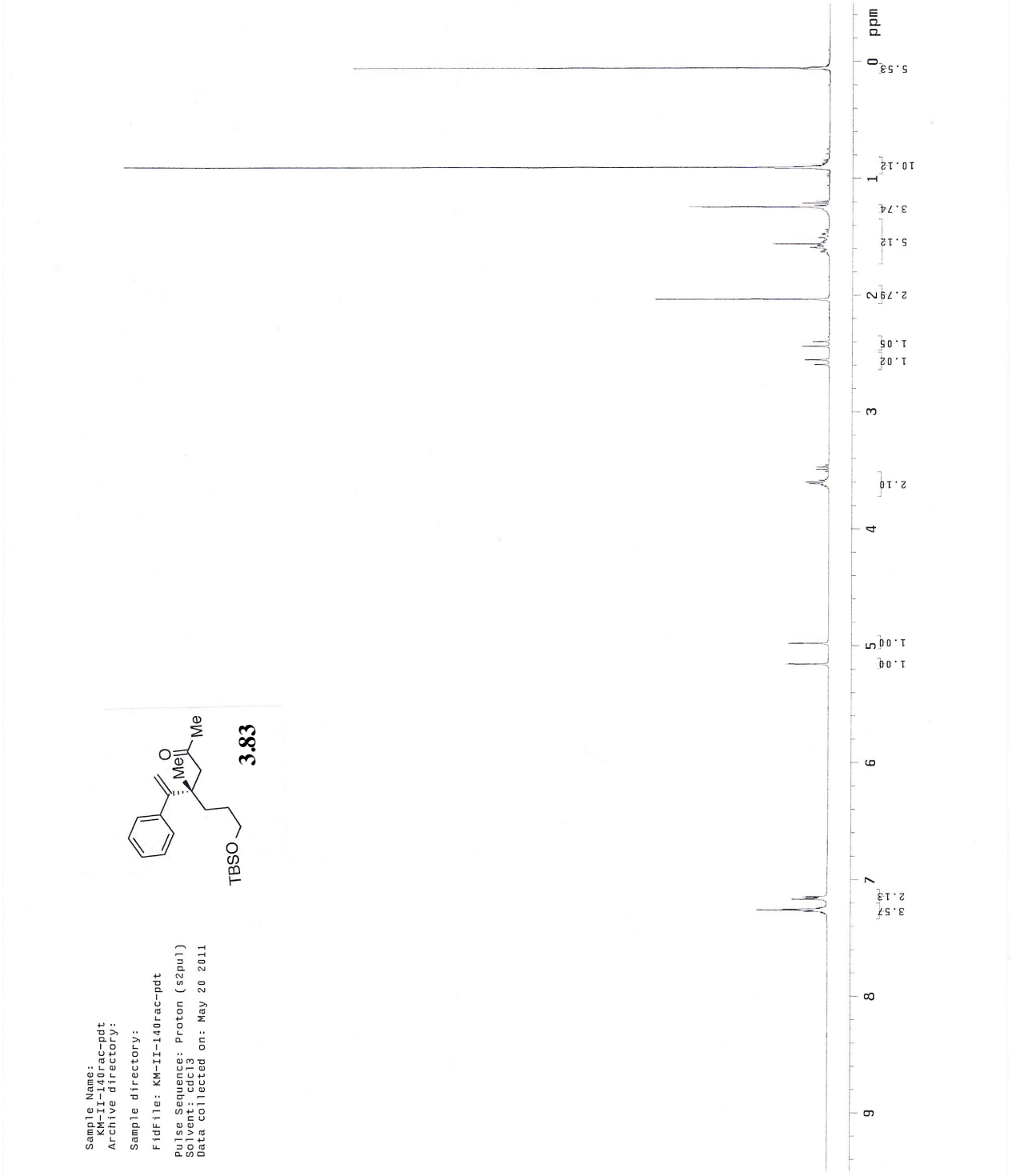

Sample Name:
KM-III-38A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-38A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2012
F
O
Me
Me
3.78
ppm
0
1
2
3
4
5
6
7
8
9
3.39
2.88
1.02
1.02
0.99
1.00
0.90
0.91
0.92
1.07
1.09
1.97
1.90

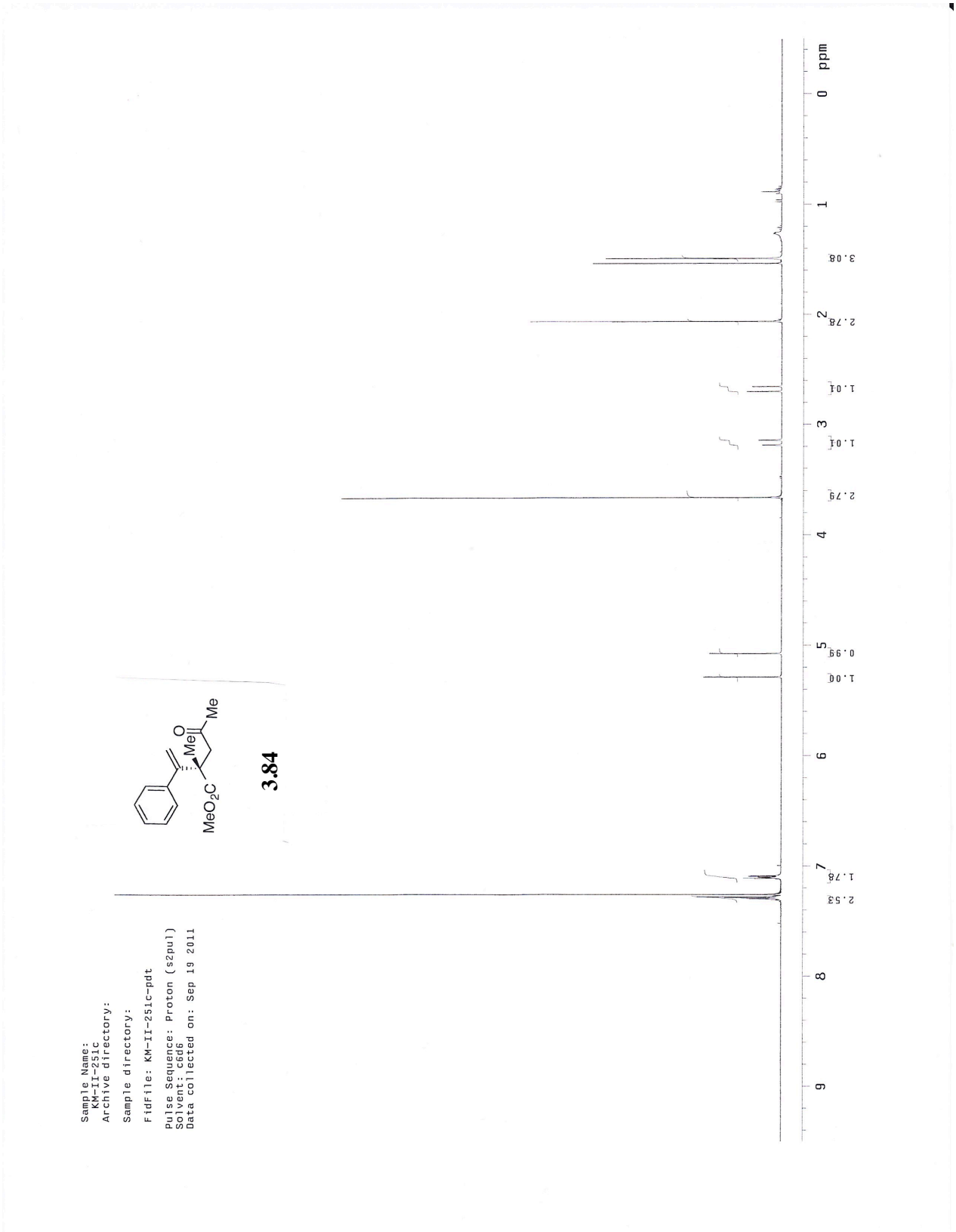

Sample Name:
Archive directory:
Sample directory:
FidFile: KM-II-245A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Sep 10 2011
3.79
Me
O
MeO
S
ppm
0
1
2
3
4
5
6
7
8
9
3.48
2.78
1.00
1.05
3.04
0.96
1.04
0.89
0.88
1.96
0.91
1.85

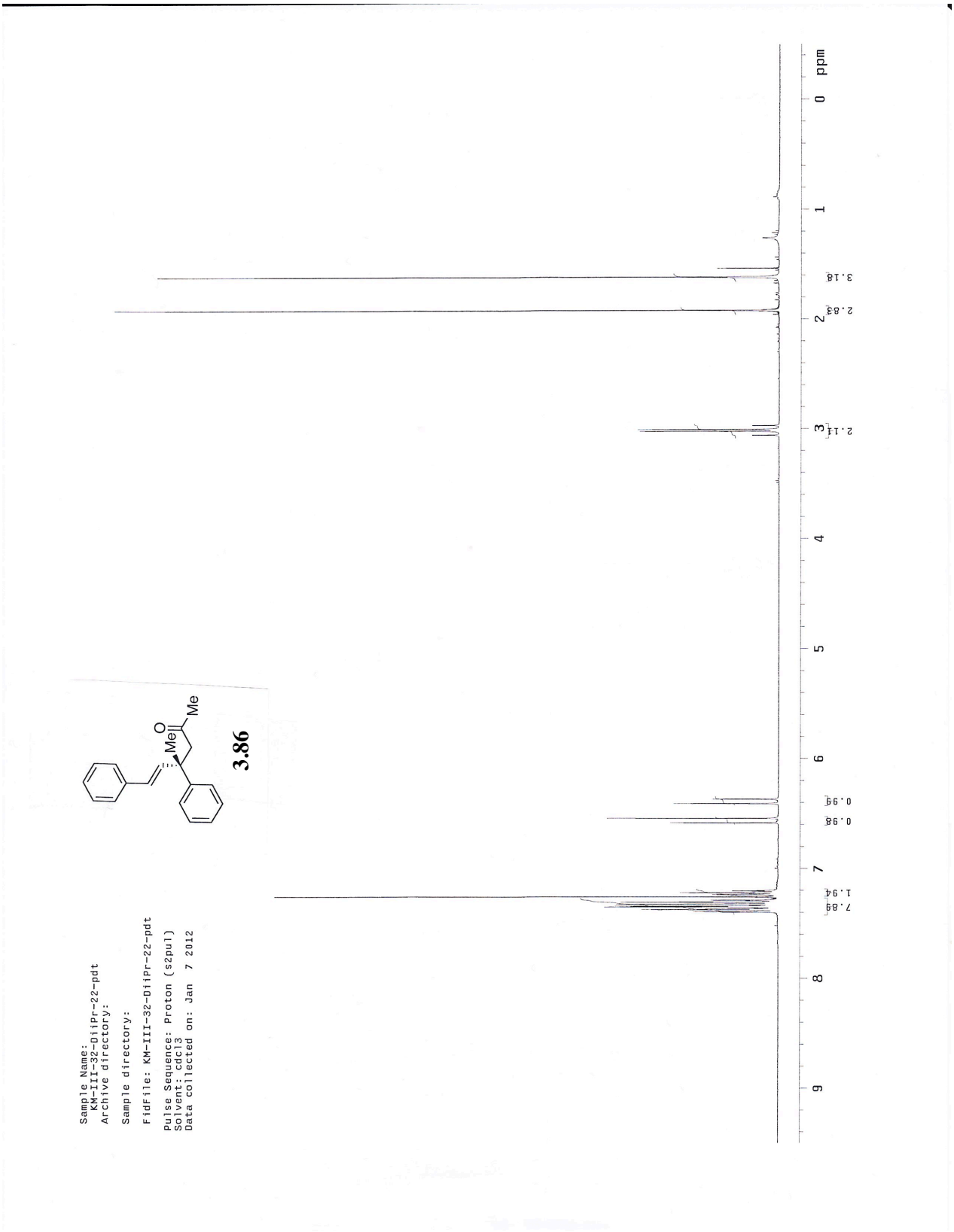

Sample Name:
KM-III-39A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-39A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 12 2012
MeO
O
Me
Me
F3C
3.80
ppm
0
1
2
3
4
5
6
7
8
9
2.99
2.81
2.00
2.94
1.00
0.98
3.66
1.93
1.84

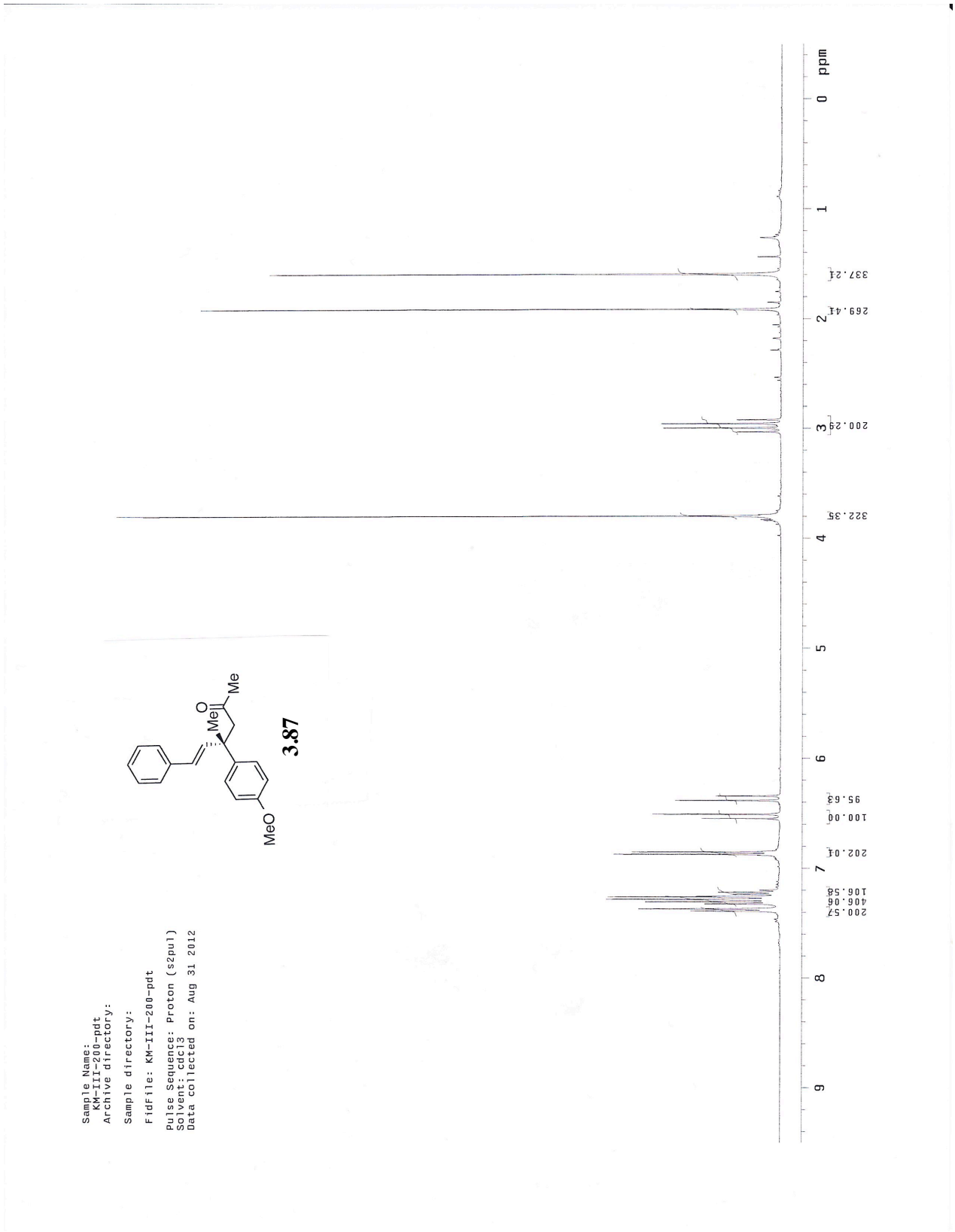

Sample Name:
KM-II-97rac-pdt-Cy
Archive directory:
Sample directory:
FidFile: KM-II-97rac-pdt-Cy
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 16 2011
Me
O
Me
Me
3.81
ppm
0
1
2
3
4
5
6
7
8
9
2.29
6.68
1.14
5.65
2.76
2.11
1.00
0.99
5.29
1.90

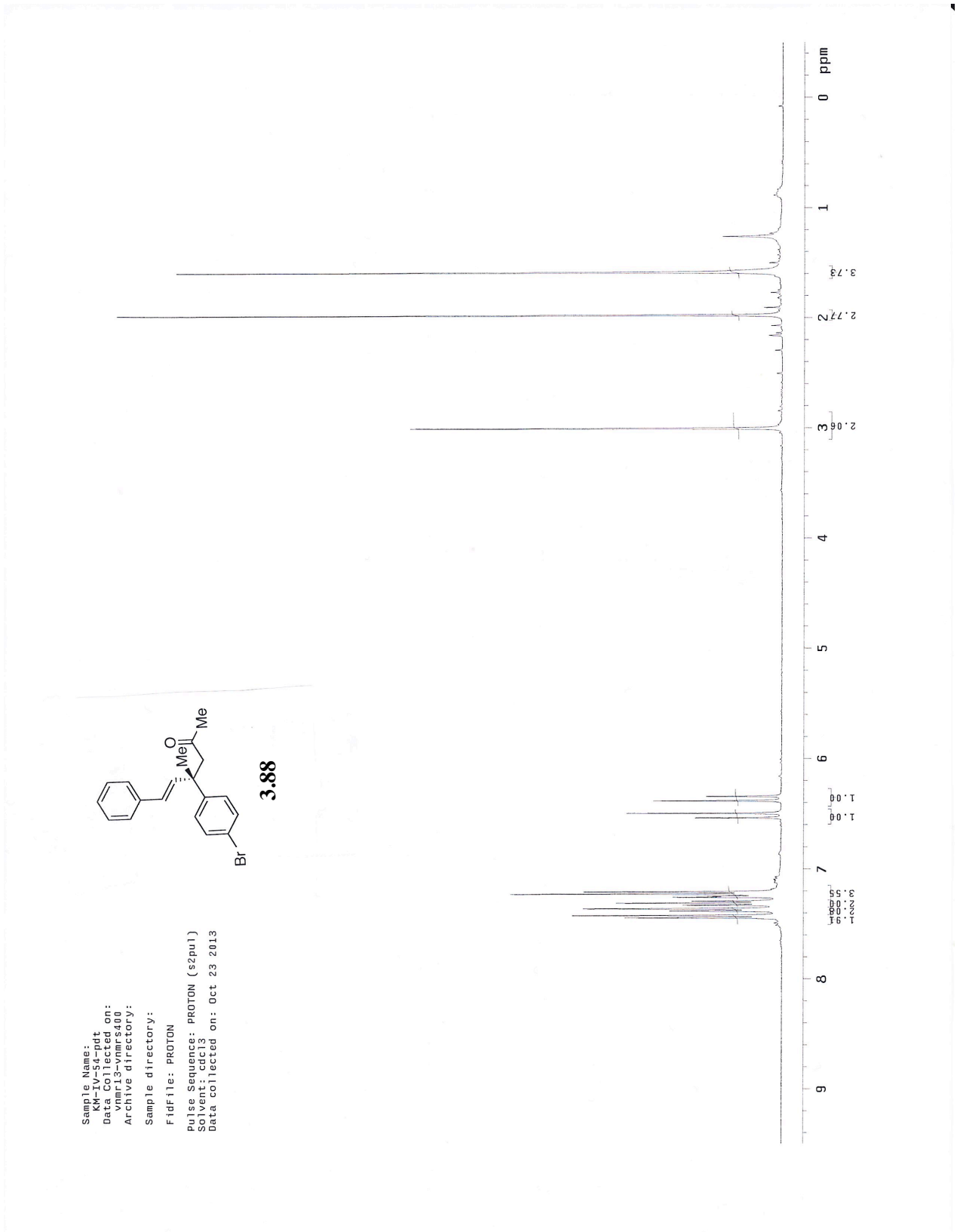

Sample Name:
KM-II-91C-pdt
Archive directory:
Sample directory:
FidFile: KM-II-91C-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 9 2011
O
Me
Me
Ph
3.82
ppm
0
1
2
3
4
5
6
7
8
9
3.07
2.79
1.02
1.02
1.03
1.01
1.00
0.99
6.06
4.00

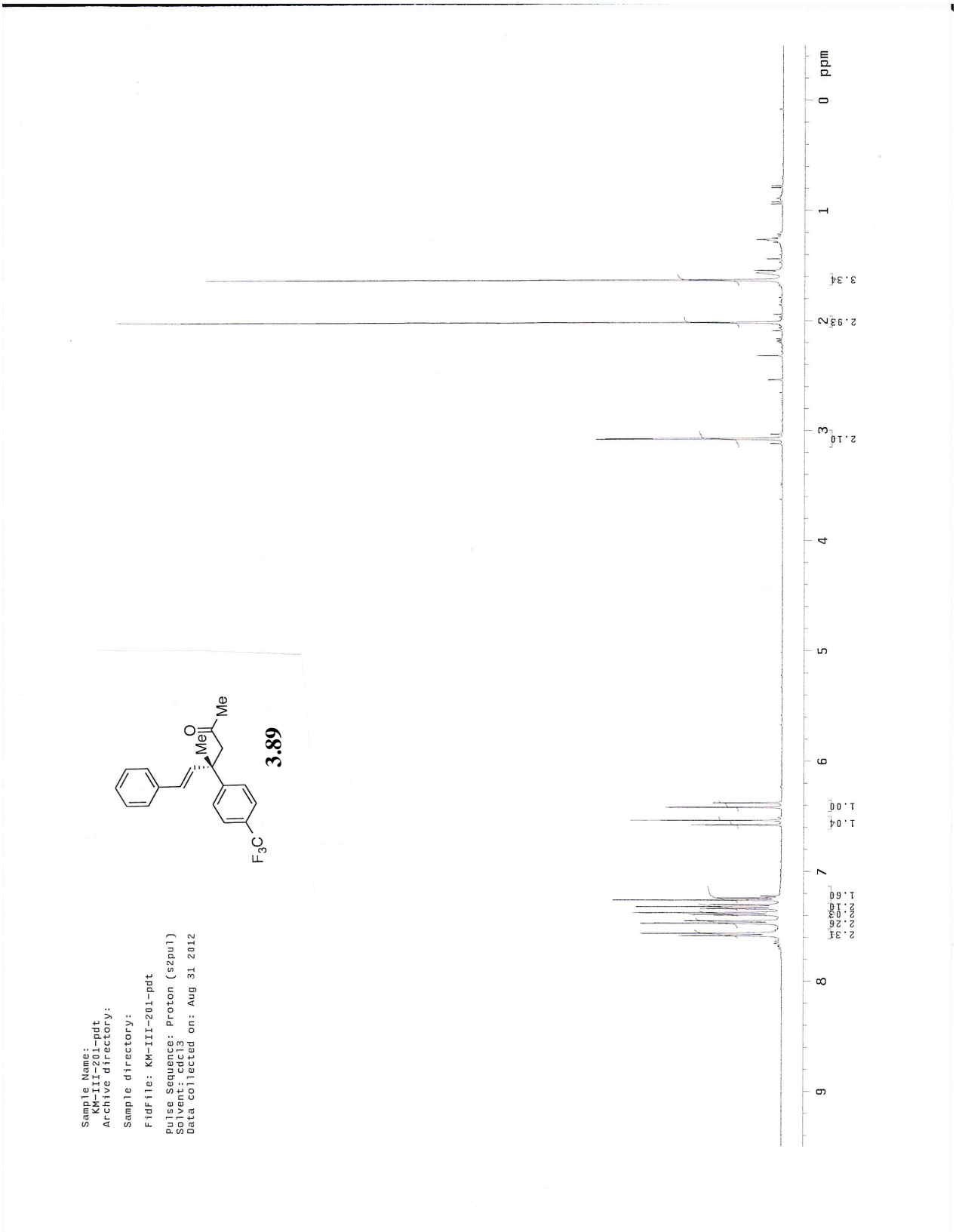

Sample Name:
KM-II-140rac-pdt
Archive directory:
Sample directory:
FidFile: KM-II-140rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: May 20 2011
TBSO
Me
Me
O
3.83
ppm
5.53
10.12
3.74
5.12
2.79
1.02
1.05
2.10
1.00
1.00
3.57
2.13

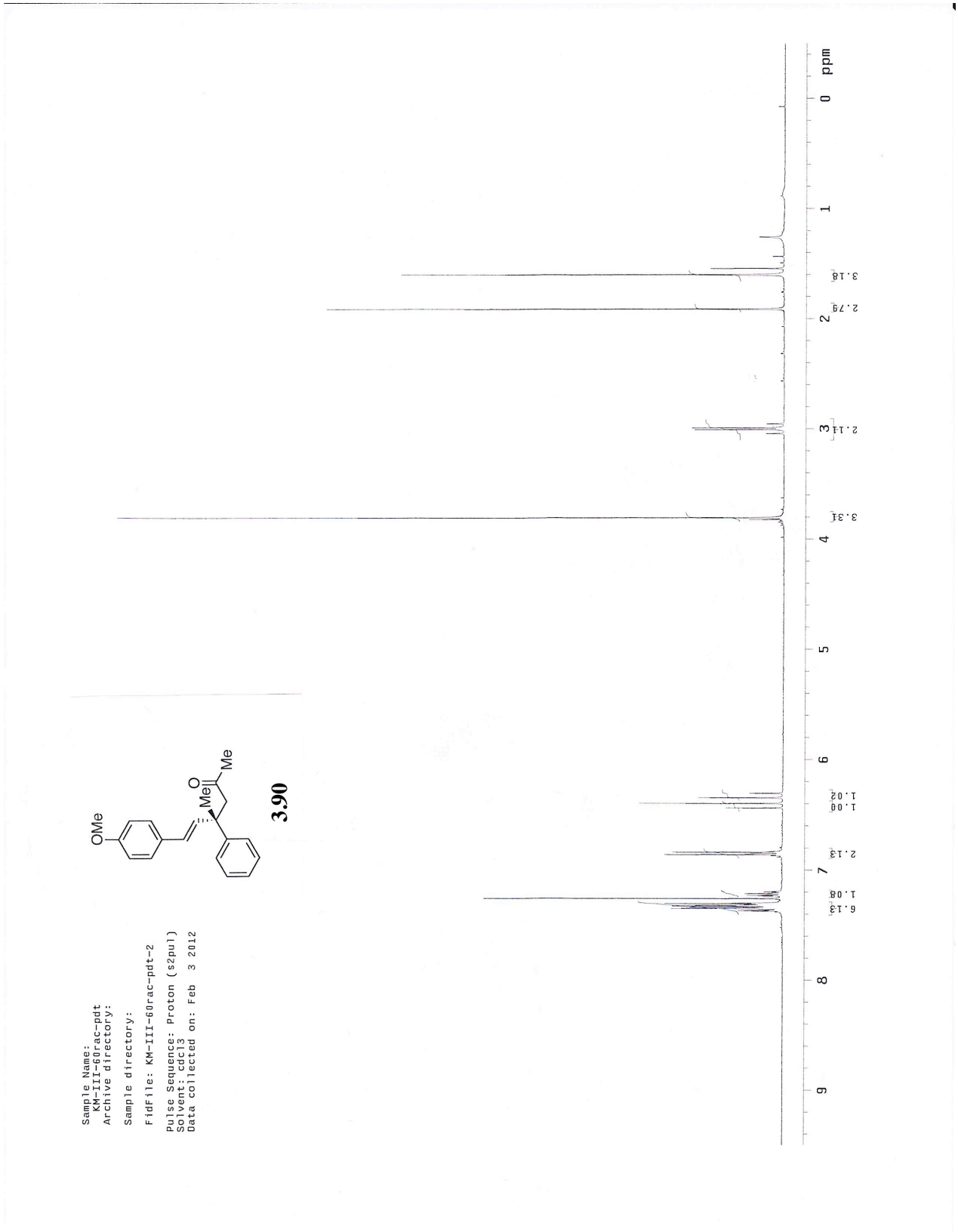

Sample Name:
KM-II-251c
Archive directory:
Sample directory:
FidFile: KM-II-251c-pdt
Pulse Sequence: Proton (s2pul)
Solvent: C6D6
Data collected on: Sep 19 2011
MeO2C
Me
Me
O
3.84
ppm
0
1
2
3
4
5
6
7
8
9
2.53
1.78
1.00
0.99
2.79
1.01
1.01
2.78
3.08

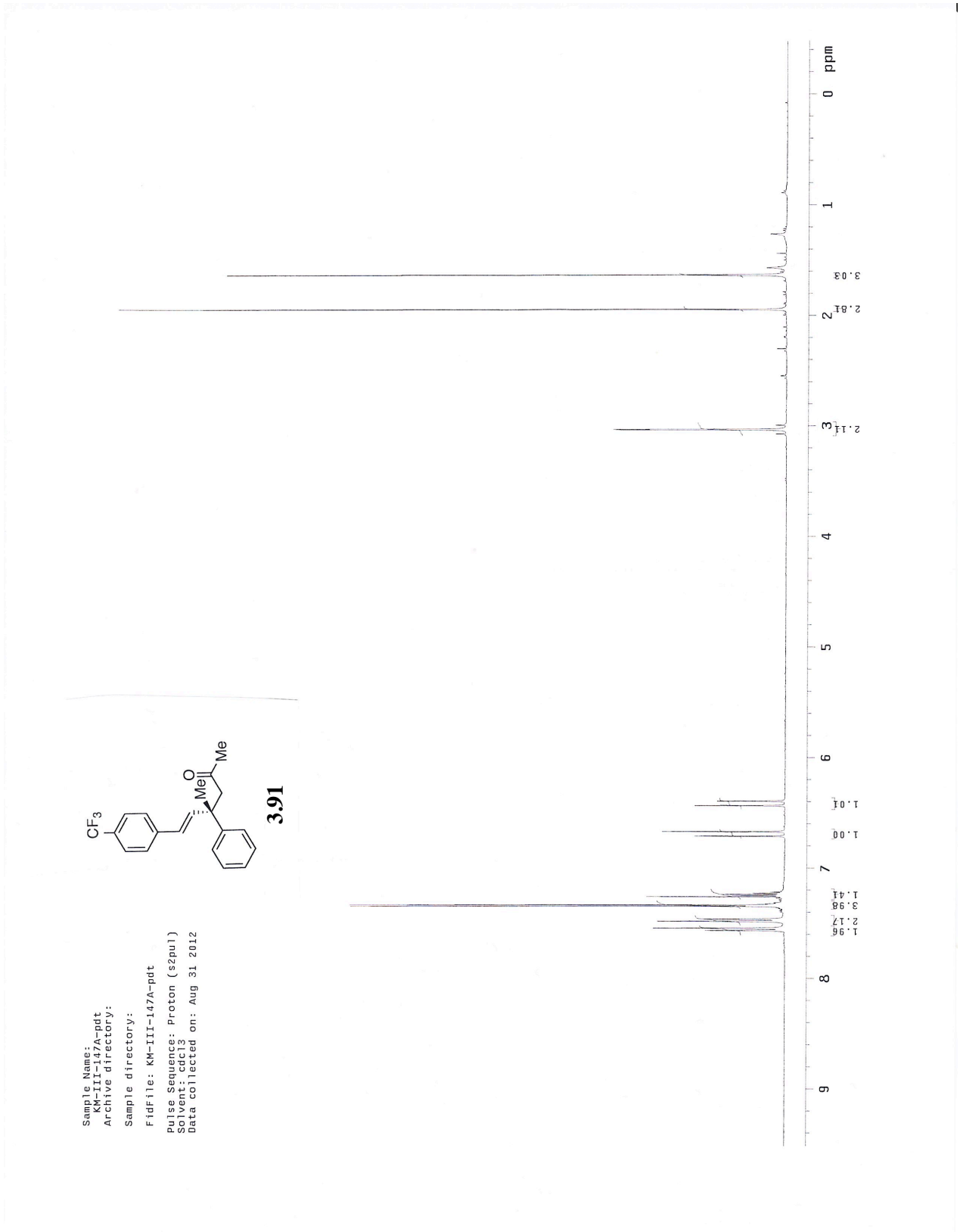

Sample Name:
KM-III-32-DiiPr-22-pdt
Archive directory:
Sample directory:
FidFile: KM-III-32-DiiPr-22-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 7 2012
Me
O
Me
Me
3.86
ppm
3.18
2.83
2.11
0.99
0.98
1.94
7.89

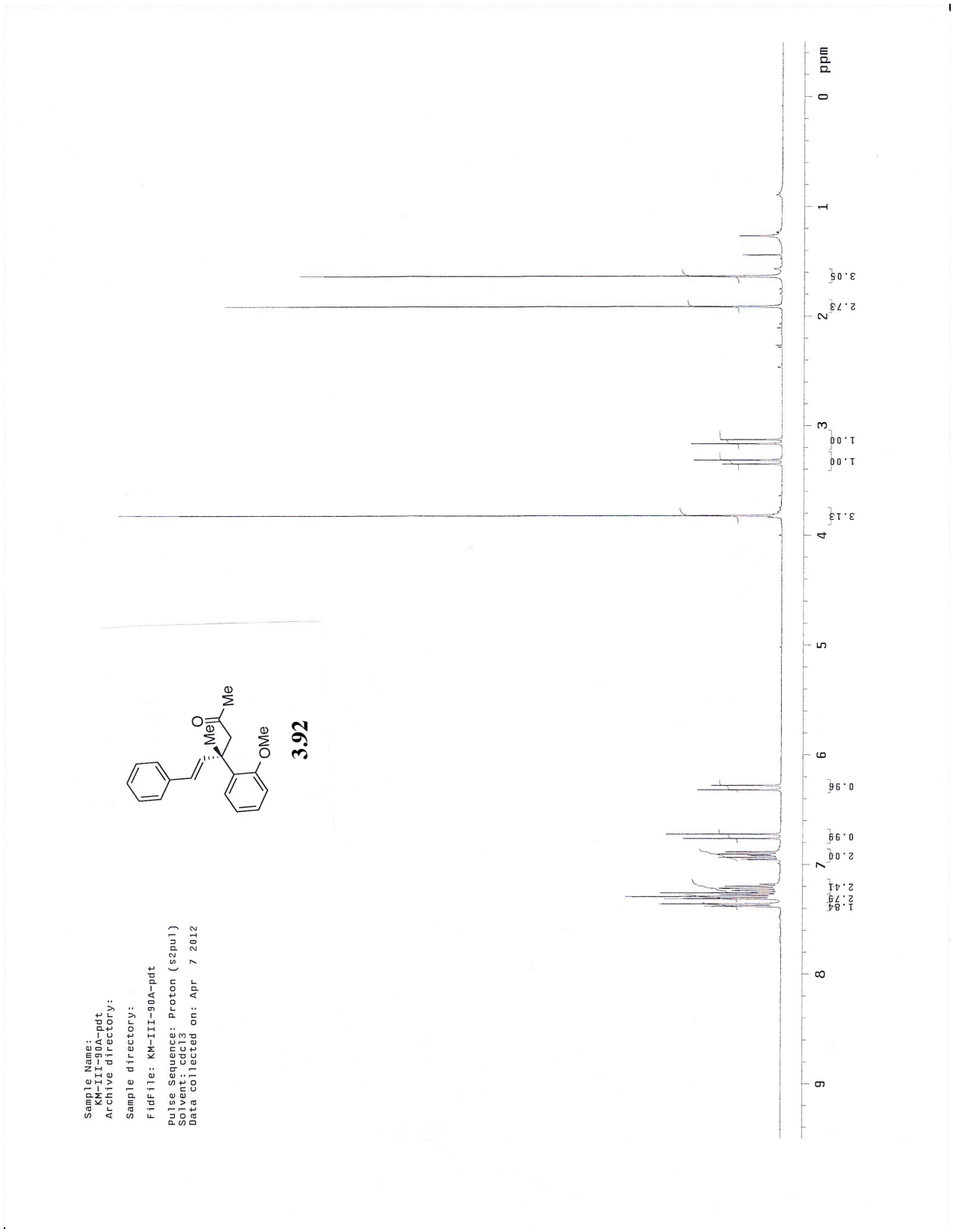

Sample Name:
KM-III-200-pdt
Archive directory:
Sample directory:
FidFile: KM-III-200-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2012
Me
O
Me
MeO
3.87
ppm
337.21
269.41
200.29
322.35
95.63
100.00
202.01
200.57
406.06
106.58

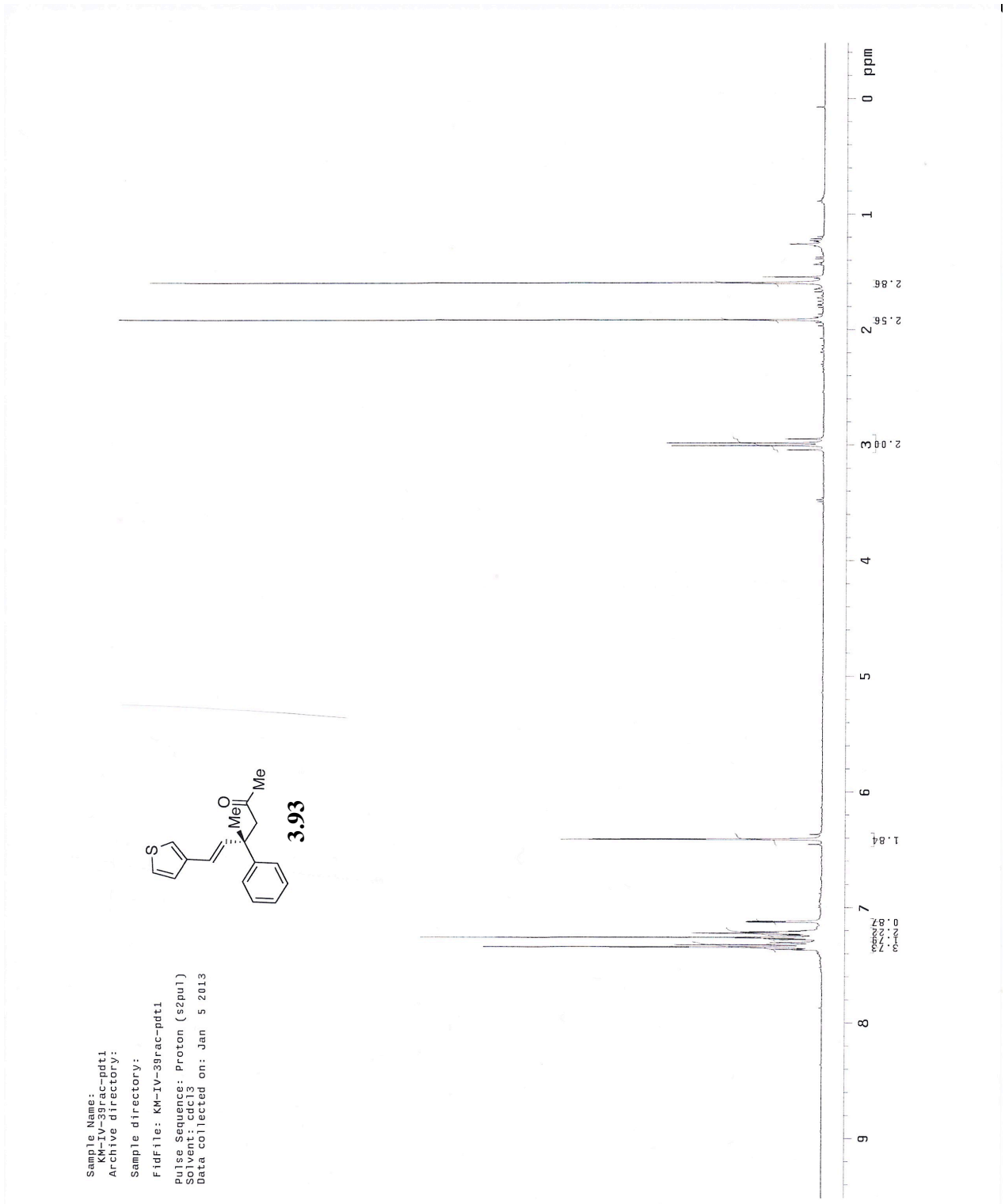

Sample Name:
KM-IV-54-pdt
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 23 2013
O
Me
Me
Br
3.88
ppm
0
1
2
3
4
5
6
7
8
9
3.74
2.77
2.06
1.00
1.00
3.55
3.00
1.91

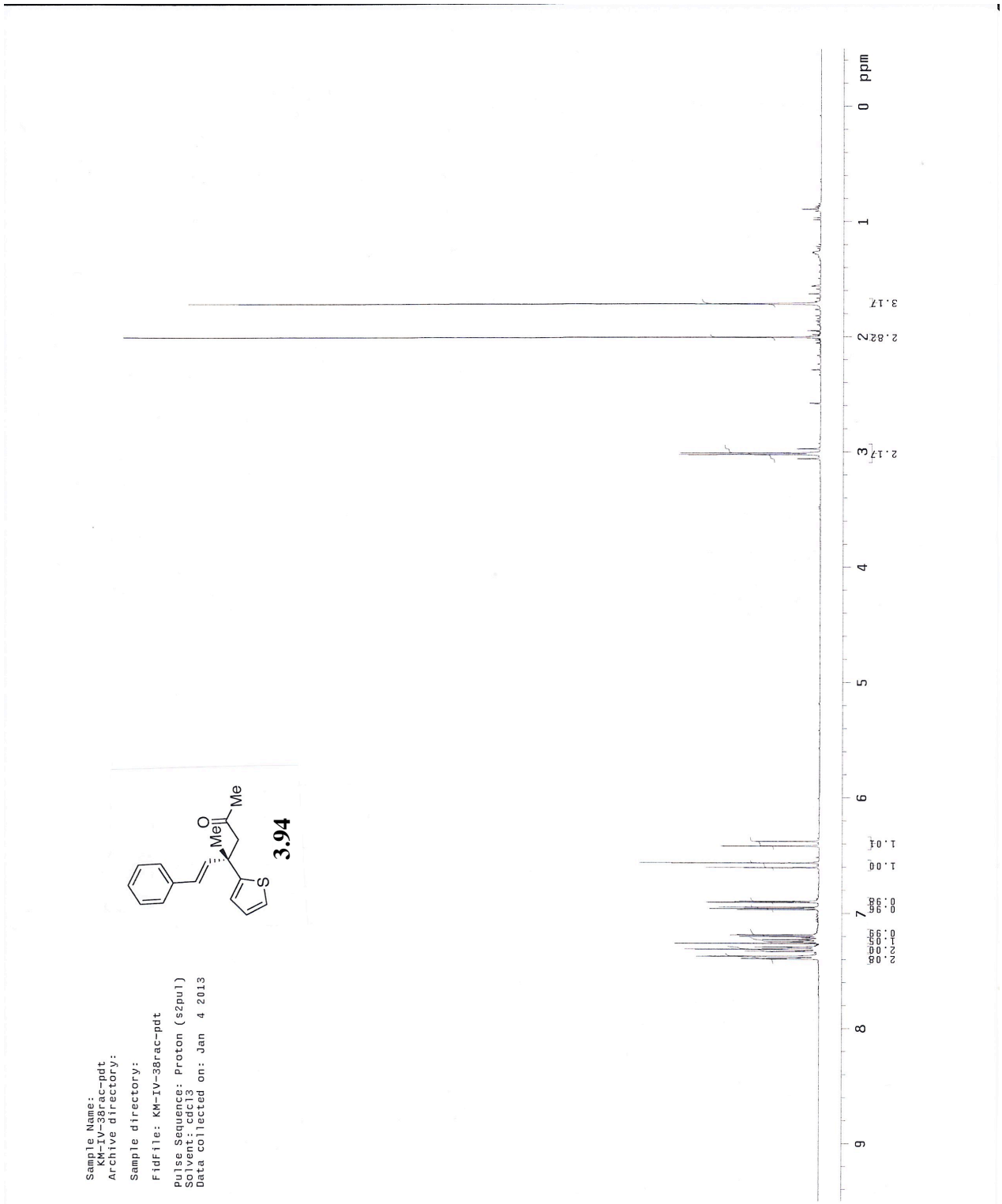

Sample Name:
KM-III-201-pdt
Archive directory:
Sample directory:
FidFile: KM-III-201-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2012
Me
O
Me
F3C
3.89
ppm
0
1
2
3
4
5
6
7
8
9
3.34
2.93
2.10
1.00
1.04
1.60
2.31
2.28
2.26
2.14

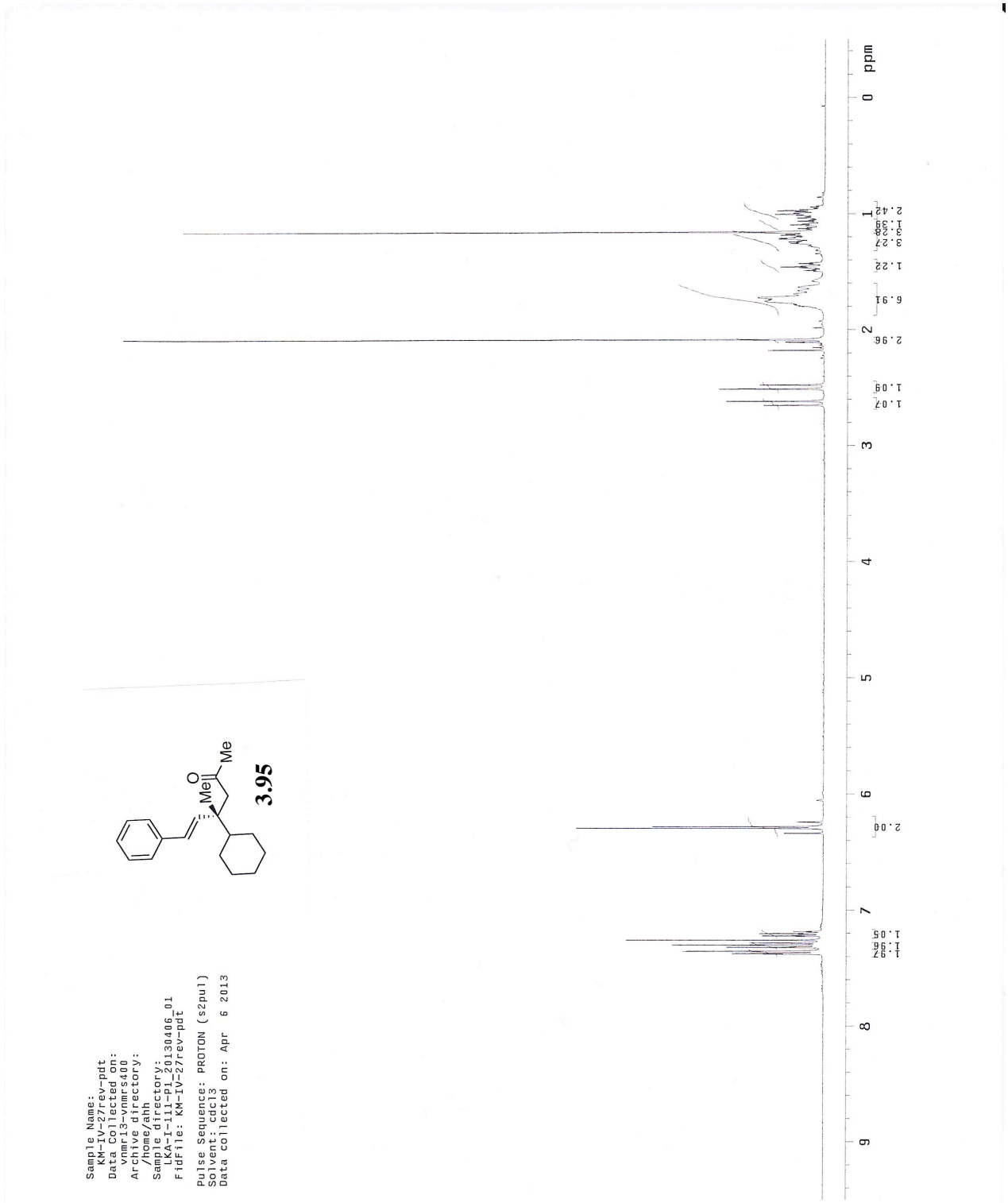

Sample Name:
KM-III-60rac-pdt
Archive directory:
Sample directory:
FidFile: KM-III-60rac-pdt-2
Pulse Sequence: Proton (S2pul)
Solvent: cdcl3
Data collected on: Feb 3 2012
OMe
Me
O
Me
3.90
ppm
0
1
2
3
4
5
6
7
8
9
6.13
1.08
2.13
1.00
1.02
3.31
2.11
2.79
3.18


Sample Name:
KM-III-147A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-147A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2012
CF3
O
Me
Me
3.91
ppm
0
1
2
3
4
5
6
7
8
9
3.03
2.81
2.11
1.01
1.00
1.96
2.17
3.98
1.41


Sample Name:
KM-III-90A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-90A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Apr 7 2012
Me
O
Me
OMe
3.92
ppm
3.05
2.73
1.00
1.00
3.13
0.96
0.99
2.00
2.41
2.79
1.84


Sample Name:
KM-IV-39rac-pdt1
Archive directory:
Sample directory:
FidFile: KM-IV-39rac-pdt1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 5 2013
S
O
Me
Me
3.93
ppm
2.86
2.56
2.00
1.84


Sample Name:
KM-IV-38rac-pdt
Archive directory:
Sample directory:
FidFile: KM-IV-38rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 4 2013
O
Me
Me
S
3.94
ppm
0
1
2
3
4
5
6
7
8
9
3.17
2.82
2.17
1.01
1.00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KM-IV-27rev-pdt
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vnmr13-vnmrs400
Archive directory:
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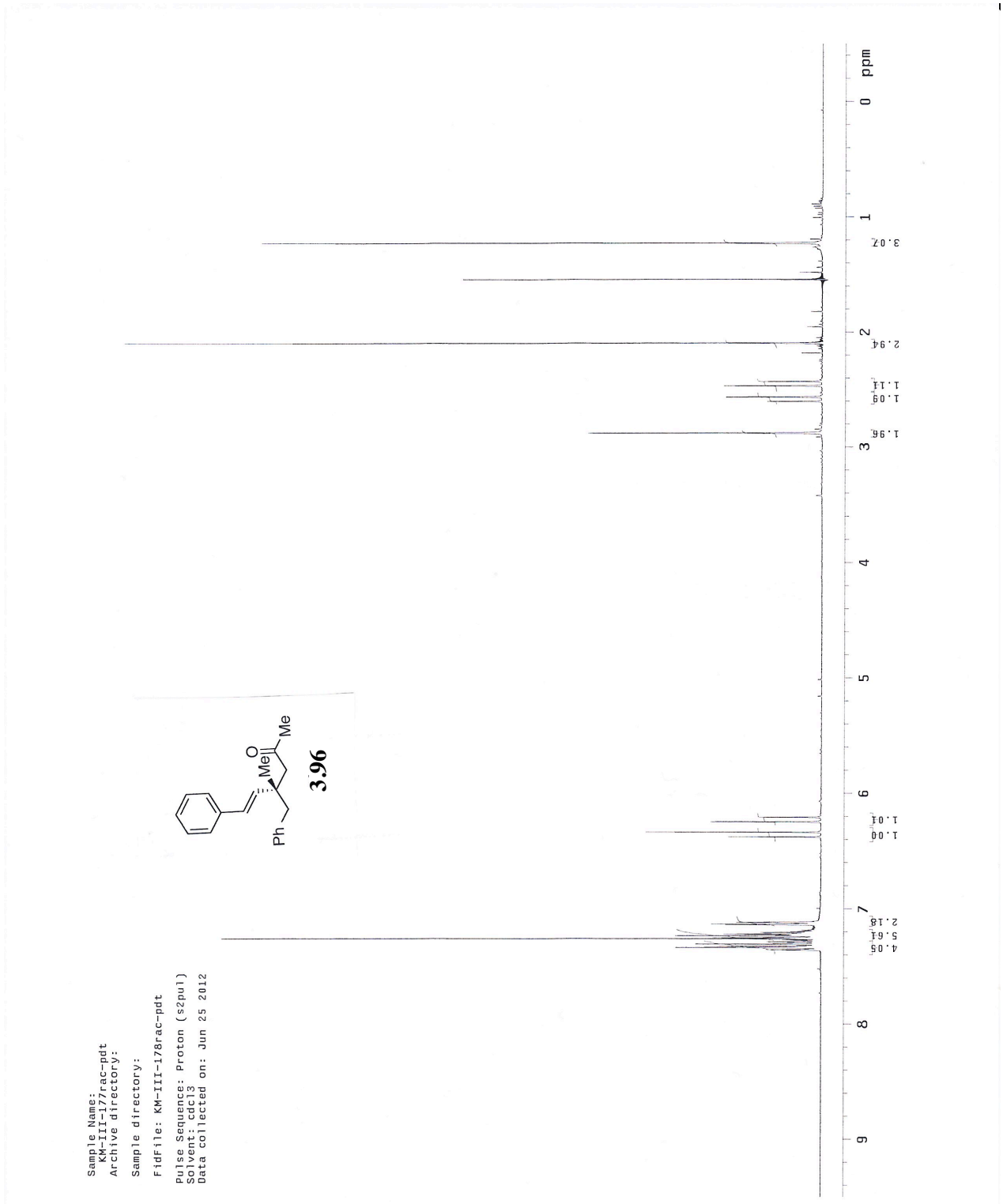
Sample directory:
LKA-I-111-P1_20130406_01
FidFile: KM-IV-27rev-pdt
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 6 2013
O
Me
Me
3.95
ppm
0
1
2
3
4
5
6
7
8
9
2.42
1.39
3.27
1.22
6.91
2.96
1.09
1.07
2.00
1.97
1.96
1.05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Archive directory:
Sample directory:
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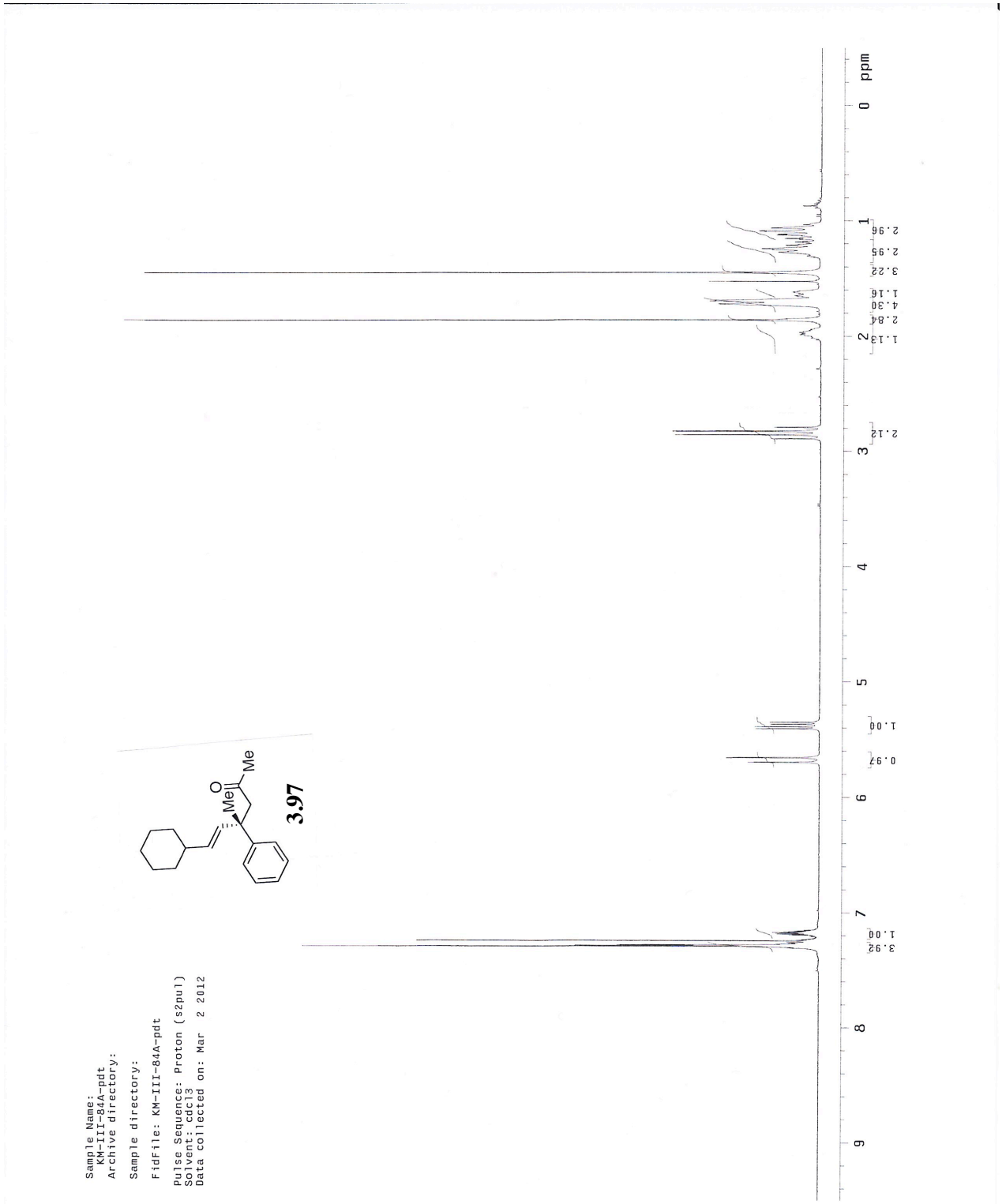
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jun 25 2012
Me
O
Me
Ph
3.96
ppm
3.07
2.94
1.09
1.11
1.96
1.00
1.01
4.05
5.61
2.18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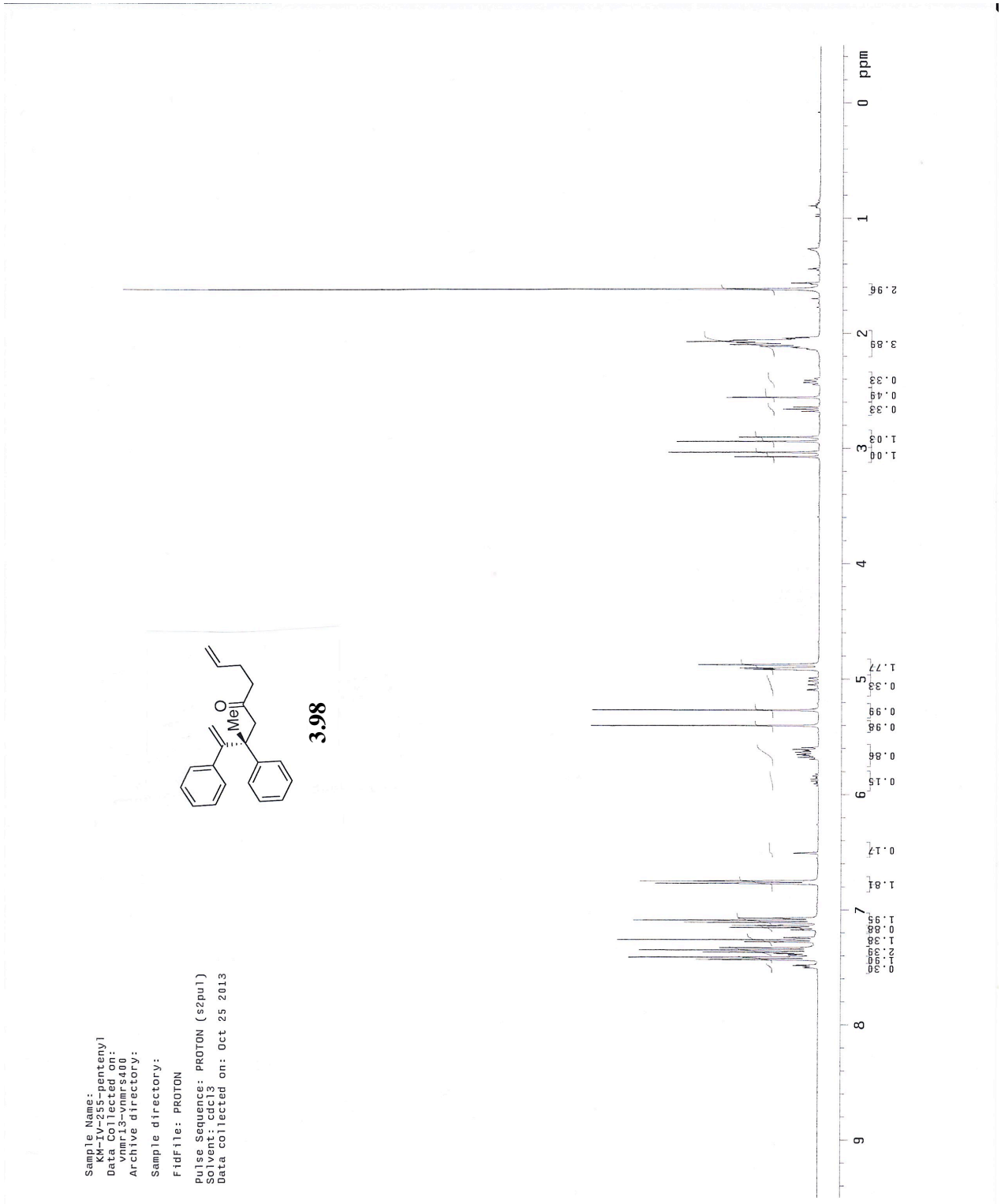
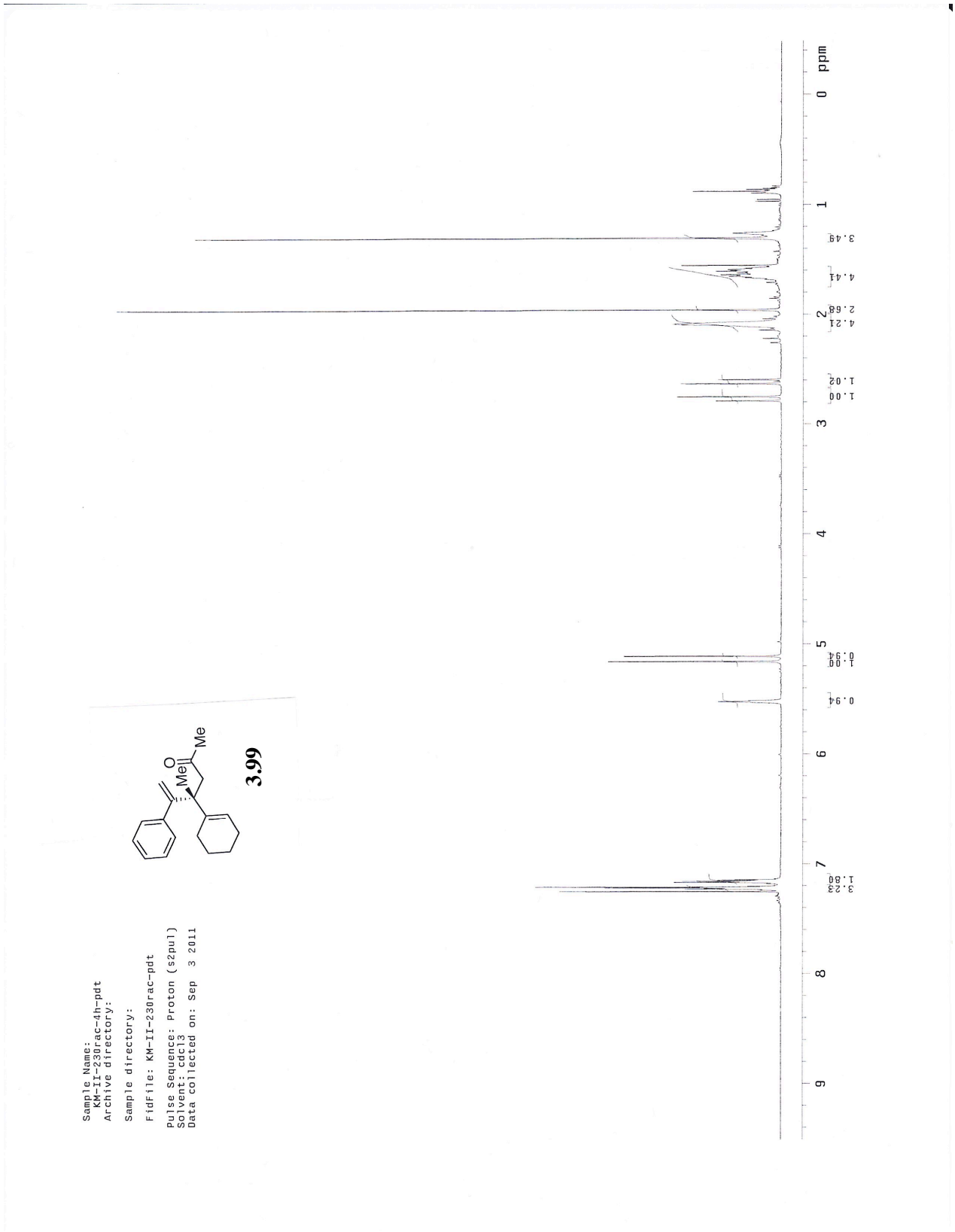
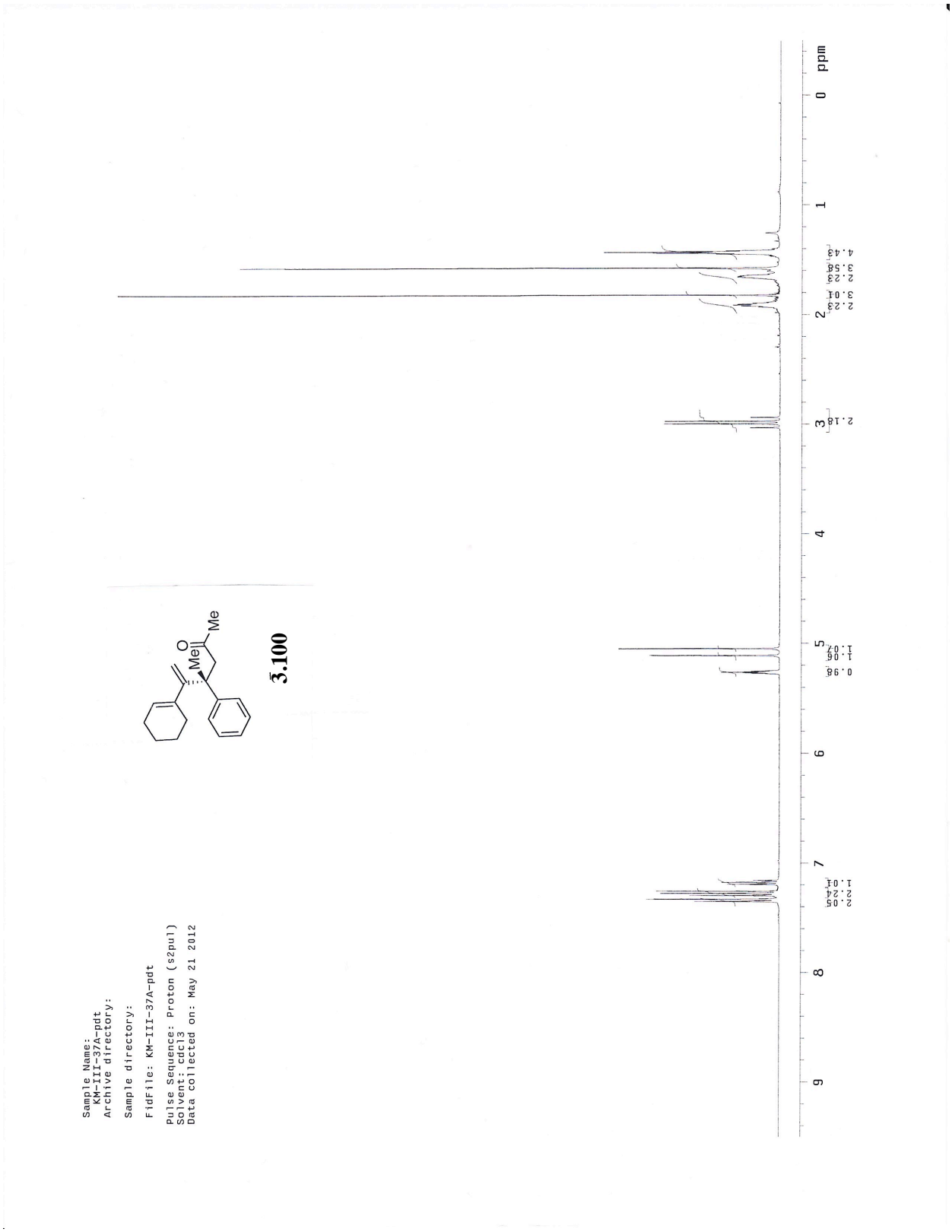
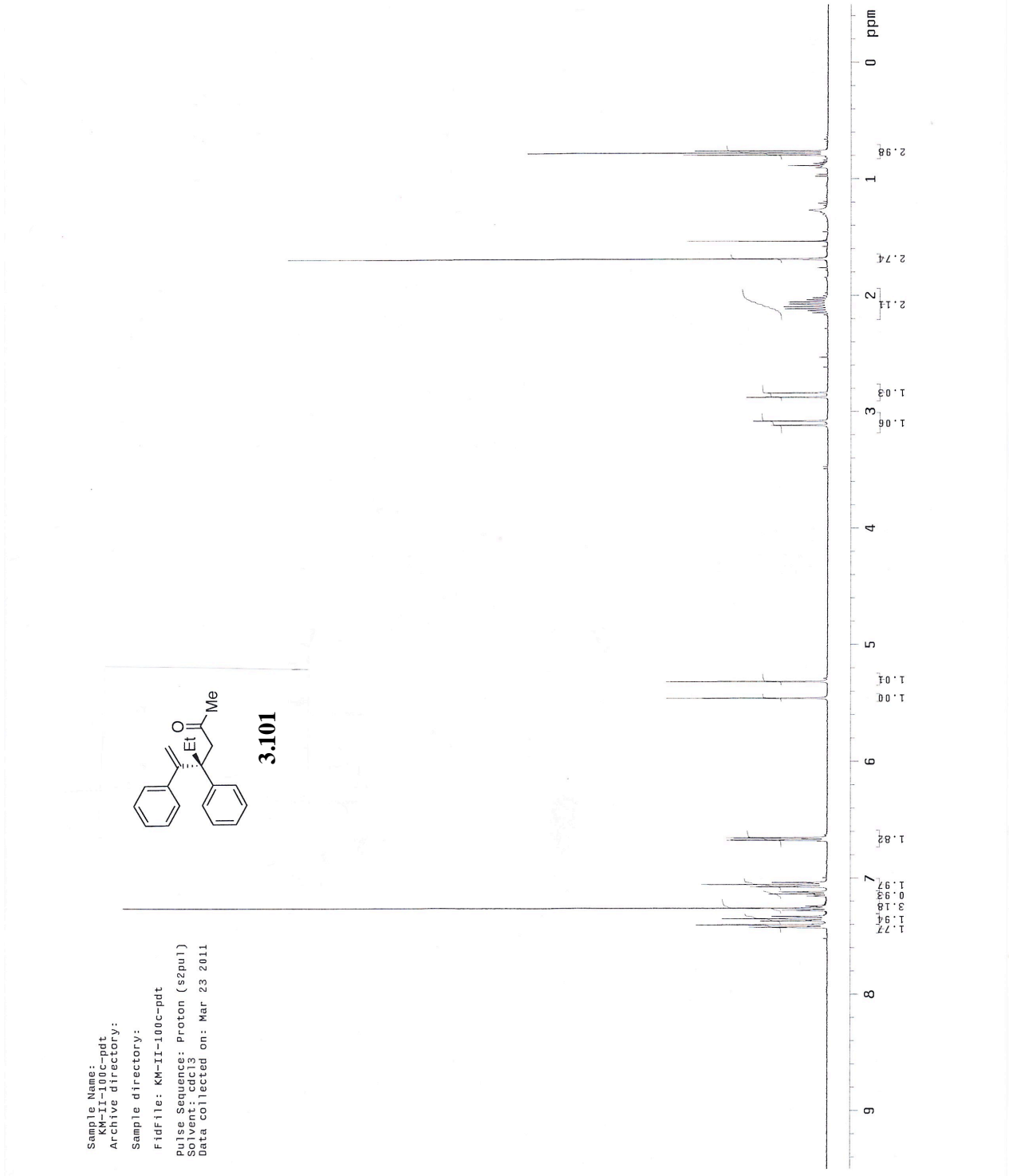
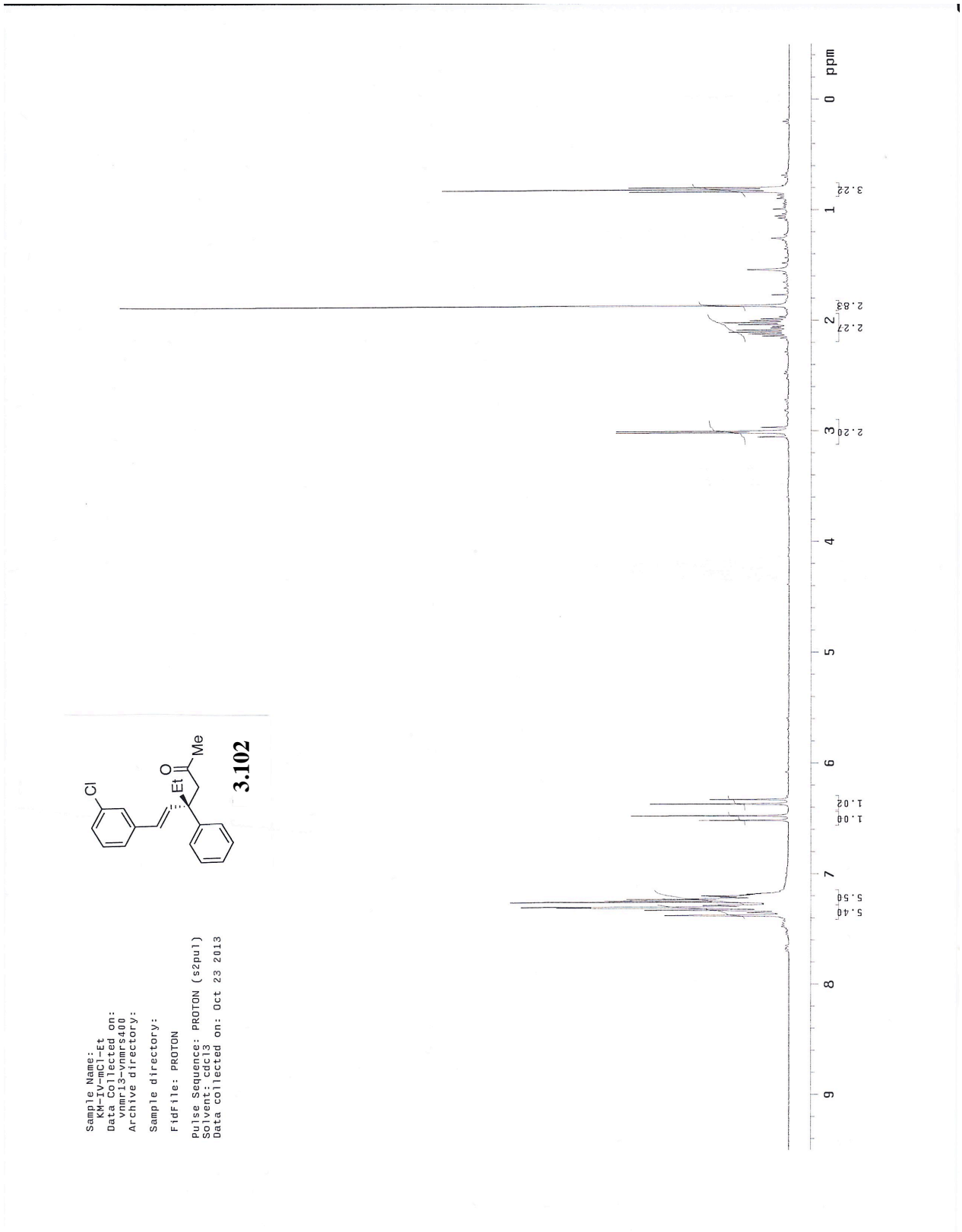
KM-III-84A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-84A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 2 2012
Me
O
Me
3.97
ppm
0
1
2
3
4
5
6
7
8
9
2.96
2.95
3.22
1.16
4.30
2.84
1.13
2.12
1.00
0.97
3.92
1.00

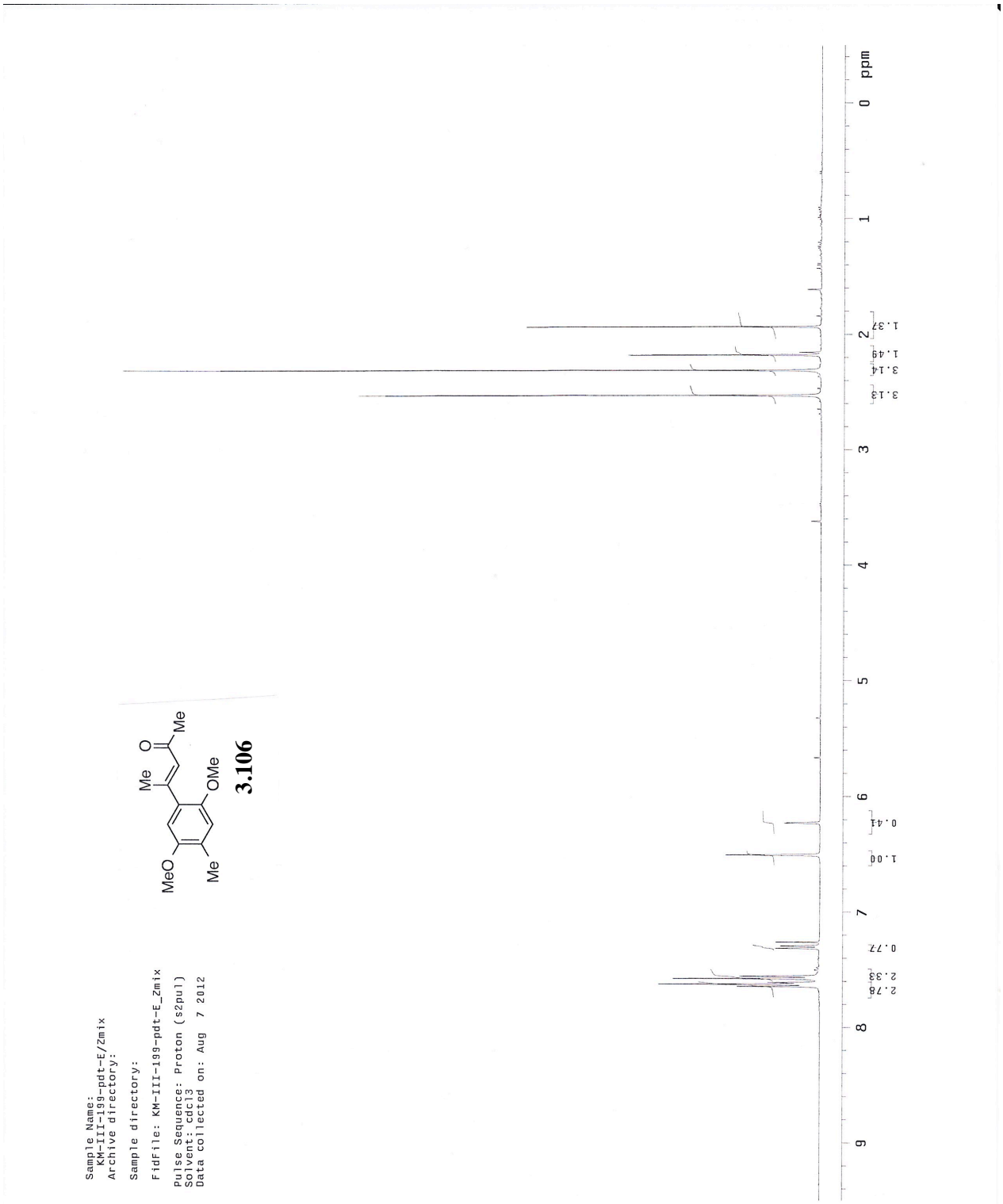

Sample Name:
KM-IV-255-pentenyl
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 25 2013
MeO
3.98
ppm
0
1
2
3
4
5
6
7
8
9
2.96
3.89
0.33
0.49
0.33
1.03
1.00
1.77
0.33
0.99
0.98
0.86
0.15
0.17
1.81
1.95
0.88
1.33
2.33
1.99
0.33

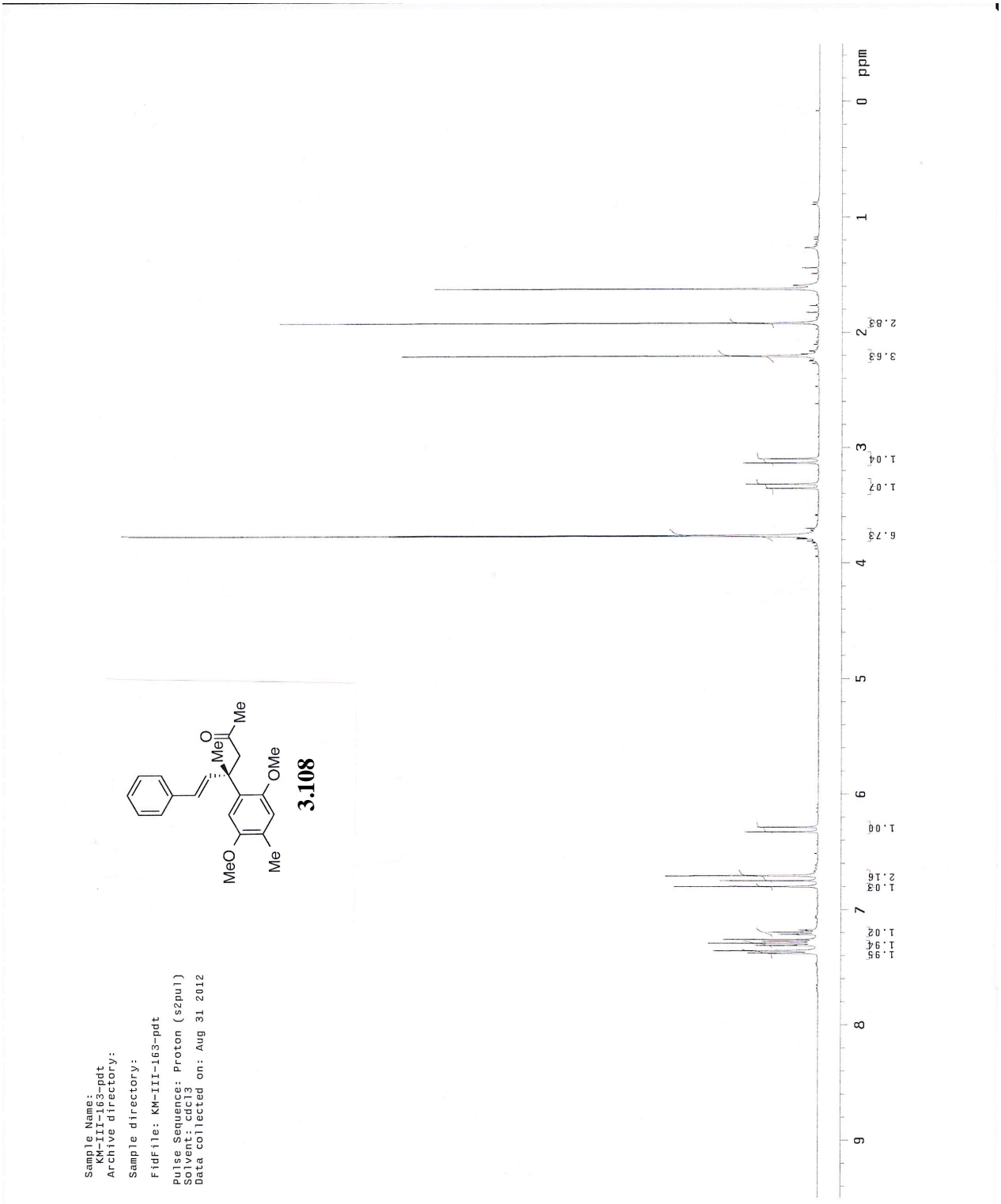

Sample Name:
KM-II-230rac-4h-pdt
Archive directory:
Sample directory:
FidFile: KM-II-230rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Sep 3 2011
O
Me
Me
3.99
ppm
0
1
2
3
4
5
6
7
8
9
3.49
4.41
2.68
4.21
1.00
1.02
1.00
0.94
0.94
3.23
1.00


Sample Name:
KM-III-37A-pdt
Archive directory:
Sample directory:
FidFile: KM-III-37A-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: May 21 2012
O
Me
Me
3.100
ppm
0
1
2
3
4
5
6
7
8
9
4.43
3.58
2.23
3.01
2.23
2.18
0.98
1.06
1.07
2.05
2.24
1.01


Sample Name:
KM-II-100c-pdt
Archive directory:
Sample directory:
FidFile: KM-II-100c-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 23 2011
Et
O
Me
3.101
ppm
0
1
2
3
4
5
6
7
8
9
2.98
2.74
2.11
1.03
1.06
1.01
1.00
1.82
1.77
1.94
3.18
0.93
1.97


Sample Name:
KM-IV-mCl-Et
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 23 2013
Cl
Et
O
Me
3.102
ppm
0
1
2
3
4
5
6
7
8
9
3.22
2.83
2.27
2.20
1.04
1.02
5.56
5.40


Sample Name:
KM-III-199-pdt-E/Zmix
Archive directory:
Sample directory:
FidFile: KM-III-199-pdt-E_Zmix
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 7 2012
MeO
Me
Me
O
Me
OMe
3.106
ppm
0
1
2
3
4
5
6
7
8
9
1.37
1.49
3.14
3.13
0.41
1.00
0.77
2.33
2.78


Sample Name:
KM-III-163-pdt
Archive directory:
Sample directory:
FidFile: KM-III-163-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2012
Me
O
Me
OMe
MeO
Me
3.108
ppm
0
1
2
3
4
5
6
7
8
9
1.95
1.94
1.02
2.16
1.00
6.73
1.07
1.04
3.63
2.83

Chapter 4:

Enantioselective *N*-Heterocyclic Carbene–Copper-Catalyzed Conjugate Addition of Alkenyl Nucleophiles to Acyclic Enones

4.1 Introduction

Formation of C–C bonds, especially those that generate a new stereogenic center, is essential for the construction of structurally complex organic molecules. As such, a significant amount of effort has been spent on the development of Cu-catalyzed conjugate addition of organometallic reagents to electron deficient olefins.[1] The majority of publications deal with the addition of alkylzinc[2], -aluminum[3], or -magnesium[4] nucleophiles to cyclic enones. The corresponding acyclic enones[5] have received less

(1) For recent reviews see: (a) Mauduit, M.; Blasé, H.; Crévisy, C.; Denicourt-Nowicki, A. in *Comprehensive Organic Synthesis II, Vol. 4*; Knochel, P.; Molander, G. A., Eds.; Elsevier: Amsterdam, (2) (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779–781; (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (c) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199–2203; (d) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518–3521; (e) Hajra, A.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2006**, *8*, 4153–4155; (f) Endo, K.; Ogawa, M.; Shibata, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 2410–2413; (g) Endo, K.; Takayama, R.; Shibata, T. *Synlett* **2013**, *24*, 1155–1159; (h) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699–3702; (i) Lega, M.; Margalef, J.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron: Asymmetry* **2013**, *24*, 995–1000; (j) Yu, H.; Xie, F.; Ma, Z.; Liu, Y.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 1941–1947; (k) Zhang, L.; Yang, G.; Shen, C.; Arghib, S.; Zhang, W. *Tetrahedron Lett.* **2011**, *52*, 2375–2378; (l) Hobuβ, D.; Baro, A.; Axenov, K. V.; Laschat, S.; Frey, W. *Eur. J. Inorg. Chem.* **2011**, 384–392; (m) Dohi, K.; Kondo, J.; Yamada, H.; Arakawa, R.; Sakaguchi, S. *Eur. J. Org. Chem.* **2012**, 7143–7152; (n) Magrez-Chiquet, M.; Morin, M. S. T.; Wencel-Delord, J.; Amraoui, S. D.; Baslé, O.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Chem.-Eur. J.* **2013**, *19*, 13663–13667.
(3) (a) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843–2845; (b) Fraser, P. K.; Woodward, S. *Chem.-Eur. J.* **2003**, *9*, 776–783; (c) Endo, K.; Hamada, D.; Yakeishi, S.; Shibata, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 606–610; (d) Endo, K.; Yakeishi, S.; Takayama, R.; Shibata, T. *Chem.-Eur. J.* **2014**, *20*, 8893–8897.
(4) (a) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. J. *Am. Chem. Soc.* **2004**, *126*, 12784–12785; (b) Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503–16510; (c) van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994–7002; (d) Maciá, B.; Fernández-Ibáñez, M. A.; Mršić, N.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron Lett.* **2008**, *49*, 1877–1880; (e) Palais, L.; Alexakis, A. *Tetrahedron Asymmetry* **2009**, *20*, 2866–2870.
(5) (a) Garcia-Ruiz, V.; Woodward, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2177–2180; b) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843–2845; (c) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry*

attention, in part, due to their diminished reactivity (versus cyclic enones) given the inherent lack of ring strain as well as their ability to undergo s-*cis*/s-*trans* interconversion on a comparable timescale as conjugate addition. In order to achieve high enantioselectivity, a catalytic system must preferentially react with one conformation or form the same enantiomer from either conformation. As a result, a method in which acyclic enones react with readily available nucleophiles, ideally ones that can be functionalized more easily than simple alkyl chains, to deliver a range of products with high enantioselectivity would be of value.

4.2 Background

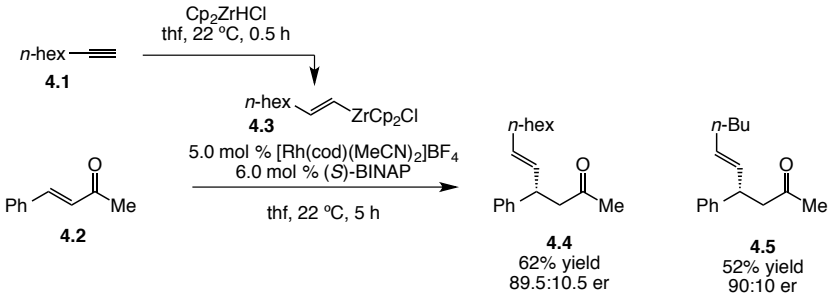
A limited number of publications deal with the addition of alkenyl nucleophiles to acyclic enones to form tertiary centers. Inoue and co-workers demonstrated that in the presence of 5.0 mol % of a chiral Rh complex, alkenylzirconium nucleophiles, generated through hydrozirconation of alkynes with Schwartz reagent, undergo conjugate addition to acyclic enones to generate **4.4** and **4.5** in 52–62% yield and 90:10 er.[6] One drawback of this method is the use of Schwartz reagent, which, while commercially available, is expensive[7] as well as air, moisture, and light sensitive.

2005, *16*, 3143–3146; (d) Mata, Y.; Diéguez, M.; Pàmies, O.; Biswas, K.; Woodward, S. *Tetrahedron: Asymmetry,* **2007**, *18*, 1613–1617; (e) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794–797.

(6) (a) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97–99; (b) Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051–5055.

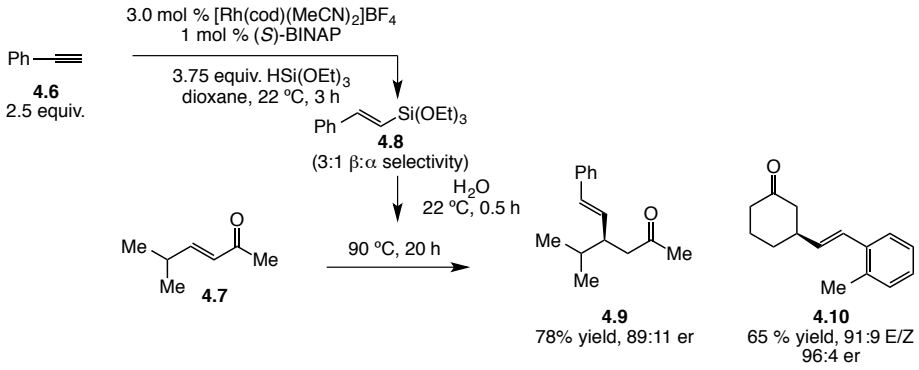
(7) Schwartz reagents (Cp_2ZrHCl) sold by Aldrich is $3.67/mmol whereas dibal–H ($Al(i\text{-}Bu)_2$) is $0.22/mmol.

Scheme 4.1. Rh-Catalyzed Conjugate Addition of Alkenylzirconium Reagents



The Hayashi group published a sequential one-pot Rh-catalyzed hydrosilylation/conjugate addition.[8] In the presence of a BINAP–Rh complex, hydrosilylation of a terminal alkyne generates alkenylsilane **4.8** in 3:1 β:α selectivity. After addition of H_2O and enone **4.7**, at 90 °C for 20 h, conjugate addition occurs to produce **4.9** in 78% yield and 89:11 er. Only one example is given for addition to an acyclic enone. With more sterically hindered alkynes, the hydrosilylation also generates the *Z*-alkenylsilane, which undergoes conjugate addition at a comparable rate to the E-alkenylsilane and is inseparable from the desired product.

Scheme 4.2. One-Pot Rh-Catalyzed Conjugate Addition of Alkenylsilanes

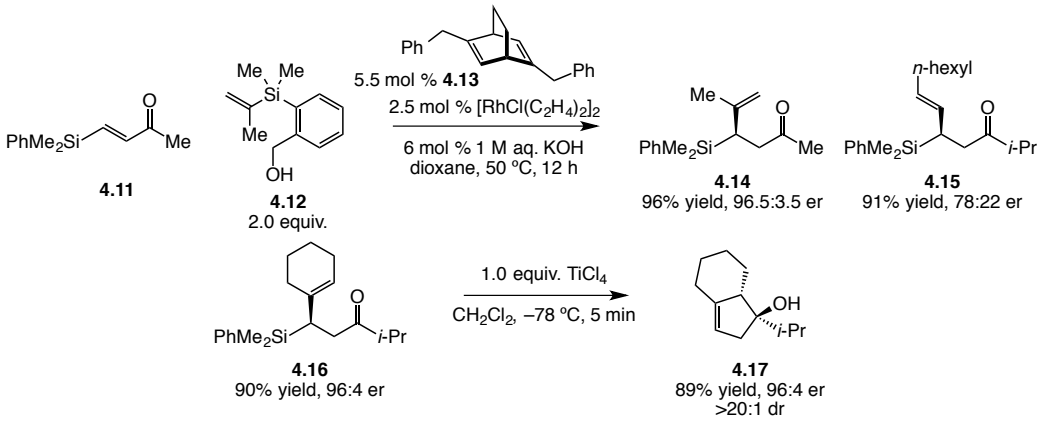


The Hiyama group showed that with a Rh–diene complex generated from diene **4.13**, a number of substituted alkenylsilanes containing a hydroxymethyl phenyl group could be coupled with β-silyl enones.[9] The highest enantioselectivities are achieved for nucleophiles containing an α-substituted olefin such as those in **4.14** and **4.16**. Reaction of a β-substituted alkenylsilane generates **4.15** in 91% yield and 78:22 er. Reaction with a

(8) Otomaru, Y.; Hayashi, T. *Tetrahedron Asymm.* **2004**, *15*, 2647–2651.
(9) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2007**, *9*, 4643–4645.

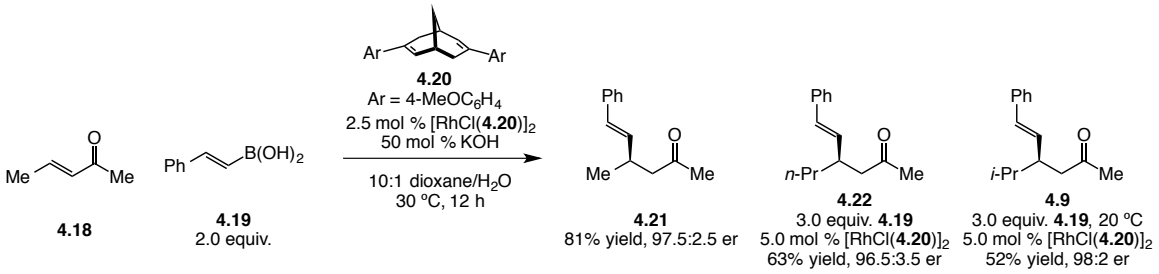
Lewis acid, $TiCl_4$, results in intramolecular allylation of the ketone to generate bicycle **4.17** in 80% yield as a single diastereomer.

Scheme 4.3. Rh–Diene-Catalyzed Addition of Alkenylsilanes



The Hayashi group demonstrated that with a Rh-diene complex of **4.20**, styrenyl boronic acid **4.19** reacts with alkyl-substituted acyclic enones with high enantioselectivity.[10] With 5.0 mol% catalyst and 50 mol % KOH in a 10:1 dioxane/H_2O mixture, ketone **4.21** is generated in 81% yield and 97.5:2.5 er. With longer chain and branch aliphatic substituents, 3.0 equiv. **4.19** and 10 mol % catalyst are needed to form **4.22** and **4.9** in moderate yield and up to 98:2 er. One drawback of this method is that alkenylboronic acids are often unstable and typically require strong base and protic conditions for reaction. Furthermore, rhodium is one of the most rare transition metals and as such is more expensive than first row transition metals like copper, nickel, and iron.

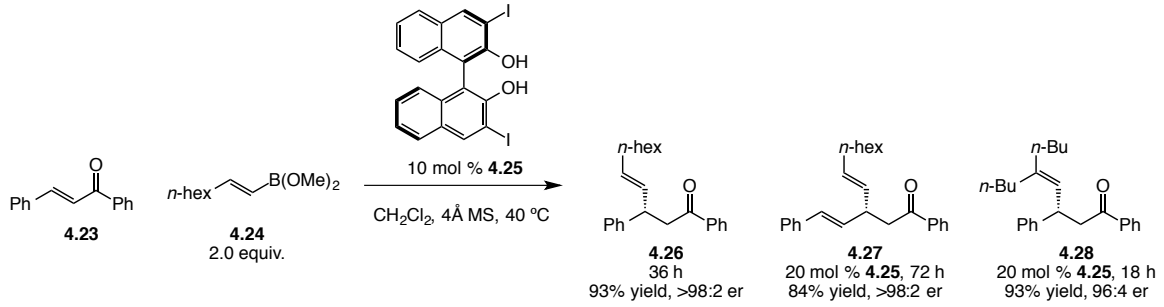
Scheme 4.4. Rh-Catalyzed Conjugate Addition of Alkenyl Boronic Acids



(10) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.-X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869–873.

Chong and co-workers demonstrated the conjugate addition of alkenylboronic esters without the need for precious metals.[11] In the presence of 10–20 mol % of substituted BINOL-derivative **4.25**, alkenyl boronic ester **4.24** is coupled with chalcone **4.23** in 93% yield and >98:2 er. 1,4-diene **4.27** is formed in 72 h with 20 mol % **4.25** in 84% yield and >98:2 er. Other alkenyl nucleophiles participate in the reaction to form the desired conjugate addition adducts like **4.28** in high enantioselectivity. The authors propose that the BINOL catalyst displaces the methoxide groups of the boron to generate methanol and a chiral alkenylboron species, which then transfers the alkenyl unit to the enone.

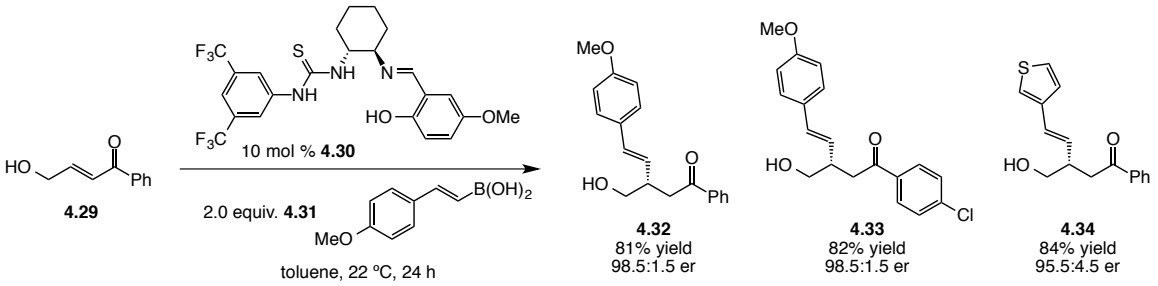
Scheme 4.5. Alkenyl Boronic Acid Methyl Ester Addition to Enones Catalyzed by a BINOL-derivative



Takemoto published a method where a bifunctional thiourea catalyst is effective for the conjugate addition of alkenylboronic acids to acyclic enones containing a hydroxyl methyl substituent.[12] Reactions with a number of α,β-unsaturated aryl ketones react with boronic acid **4.31** to generate the desired product in up to 82% yield and 98.5:1.5 er. Other aryl- and heterocycle-containing alkenyl nucleophiles participate in the reaction. The two groups on the catalyst are key for reactivity as the authors proposed that the thiourea moiety activates the ketone through hydrogen bonding and the electron rich phenol serves to activate the alkenyl boronic acid. Furthermore the hydroxyl methyl group is necessary to coordinate to the boronic acid and orient the nucleophile.

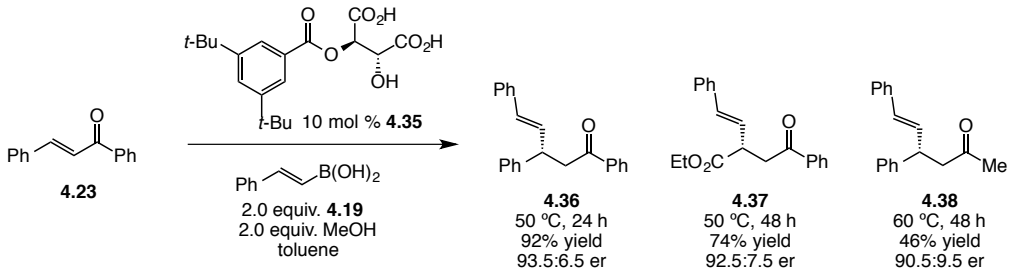
(11) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908–4909.
(12) Inokuma, T.; Takasu, K.; Sakaeda, T.; Takemoto, Y. *Org. Lett.* **2009**, *11*, 2425–2428.

Scheme 4.6. Bifunctional Thiourea Catalyst for the Addition of Alkenyl Boronic Acids



The Nakajima group disclosed an acyl tartaric acid catalyst **4.35** for the addition of alkenylboronic acids to chalcone derivatives.[13] In the presence of 10 mol % **4.35** with 2.0 equiv. MeOH for 24-48 h, boronic acid **4.19** is coupled with chalcone in 92% yield and 93.5:6.5 er. Substrates with other aryl groups or an ester substituent deliver the desired product with similarly high enantioselectivity. Reaction with phenyl butenone to generate **4.38** is less efficient (48 h, 60 °C versus 24 h, 50 °C) with the product formed in 46% yield and 90.5:9.5 er.

Scheme 4.7. Addition of Boronic Acids Catalyzed by an Acylated Tartaric Acid

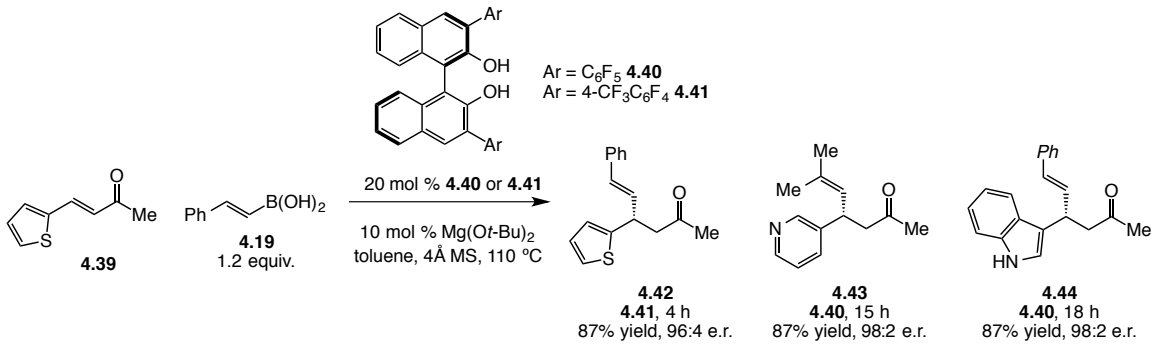


May published a method for the addition of alkenyl boronic acids to a range of heterocycle-substituted enones.[14] Thiophene containing enone **4.39** reacts with boronic acid **4.19** in the presence of 20 mol % **4.41** to form conjugate addition adduct **4.42** in 87% yield and 96.4 er. The reaction is also tolerant of pyridyl groups as well as unprotected indoles, **4.43** and **4.44** respectively. In an analogous fashion to Chong, the authors propose that the BINOL catalyst reacts with the boronic acid to form a chiral alkenylboron and release water. $Mg(O\textit{t}\text{-}Bu)_2$ accelerates the rate of the reaction by acting

(13) Sugiura, M.; Tokudomi, M.; Nakajima, M. *Chem. Commun.* **2010**, *46*, 7799–7800.
(14) (a) Lundy, B. J.; Jansone-Popova, S.; May, J. A. *Org. Lett.* **2011**, *13*, 4958–4961; (b) Le, P. Q.; Nguyen, T. S.; May, J. A. *Org. Lett.* 2012, *14*, 6104–6107.

as a proton shuttle to release the catalyst and quench the boron enolate formed after the addition.

Scheme 4.8. Addition of Alkenyl Boronic Acids to Heterocycle-Containing Enones



Based on the above studies, our goals for developing an enantioselective alkenyl conjugate addition to acyclic enones were (1) Find an active catalytic system that avoids the need for expensive rhodium complexes, ideally a Cu-based catalyst with an easily modifiable chiral ligand (2) Find a class of stable nucleophiles that can be readily accessed and allow for the addition of a variety of alkenyl groups.

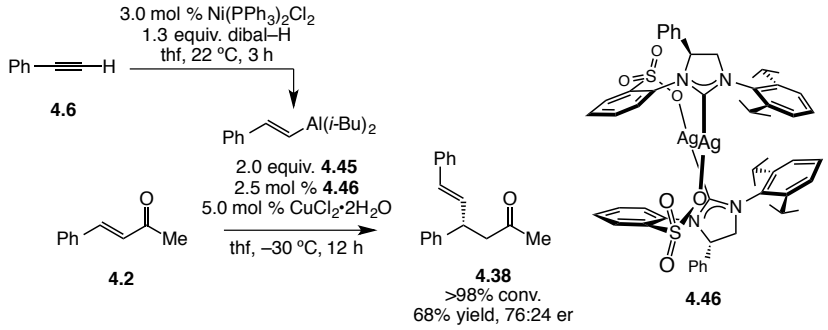
4.3 Enantioselective Conjugate Addition of Alkenylaluminum Nucleophiles to Acyclic Enones

4.3.a Addition of Si-Substituted Alkenylaluminum Reagents

Following our success with the formation of quaternary stereogenic centers bearing an alkenyl unit,[15] we turned our attention to additions to disubstituted enones. We began by examining the addition of β-styrenylaluminum **4.45**, generated from Ni-catalyzed hydroalumination of **4.6**,[16] to enone **4.2**. As shown in Scheme 4.9, the reaction proceeds to form the desired product **4.38** in 68% yield although the enantioselectivity is moderate, 76:24 er (versus 98:2 er for the analogous reaction with a trisubstituted enone).

(15) McGrath, K. P.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 1910–1914.
(16) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

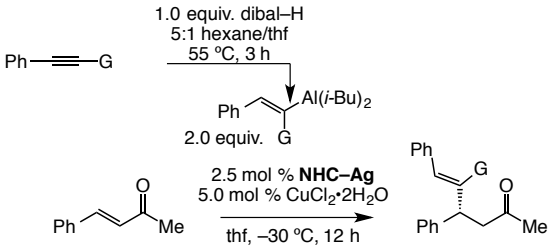
Scheme 4.9. Initial Addition of β-Alkenylaluminum to Phenyl Butanone



As we had observed previously that substitution on the olefin is often critical to achieve high enantioselectivity,[17] we began to look at silyl-substituted alkenylaluminum reagents. As shown in Table 1, the identity of the chiral catalyst as well as silyl group are important to obtain the desired product in high yield and enantioselectivity. We began with trimethylsilyl-substituted phenylacetylene, which in the presence of dibal–H undergoes hydroalumination to furnish the Z-alkenylaluminum species. In the presence of an NHC with a small N-aryl group, **4.47**, the desired conjugate addition adduct is formed in 84% yield and 76.5:13.5 er. Unfortunately, increasing the size of the N-aryl substituent from mesityl to 2,6-diisopropylphenyl, **4.46**, leads to diminished group transfer selectivity with 16% isobutyl addition observed. NHC–Ag precursor **4.48** leads to 27% isobutyl addition although the desired product is obtained in 92.5:7.5 er. With large N-aryl groups, the rate of transfer of the large alkenylsilane is decreased enough that transfer of the small isobutyl group becomes competitive. In order to decrease the size of our nucleophile, we switched to a smaller dimethylsilane-substituted alkenylaluminum. With **4.48**, the desired product is obtained in 75% yield and 89.5:10.5 er without any of the isobutyl addition product observed. Changing the sterics of the N-aryl to a 3,5-di*tert*butylphenyl group resulted in severely diminished enantioselectivity, 60:40 er. Increasing to larger 3,5-substitutents in **4.50** leads to the product in 76% yield and 94:6 er.

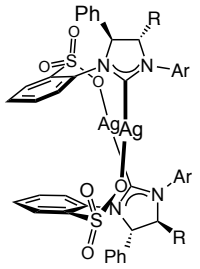
(17) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739.

Table 4.1. Effect of NHC Precursor and Silicon Substituent Reactivity



entry	G	NHC–Ag	conv. (%)[b]	yield (%)[c]	er[d]
1	$SiMe_3$	**4.47**	>98	84	76.5:13.5
2	$SiMe_3$	**4.46**	>98	36[e]	83.5:16.5
3	$SiMe_3$	**4.48**	>98	40[f]	92.5:7.5
4	$SiMe_2H$	**4.48**	>98	75	89.5:10.5
5	$SiMe_2H$	**4.49**	>98	n.d.	60:40
6	$SiMe_2H$	**4.50**	>98	76	94:6

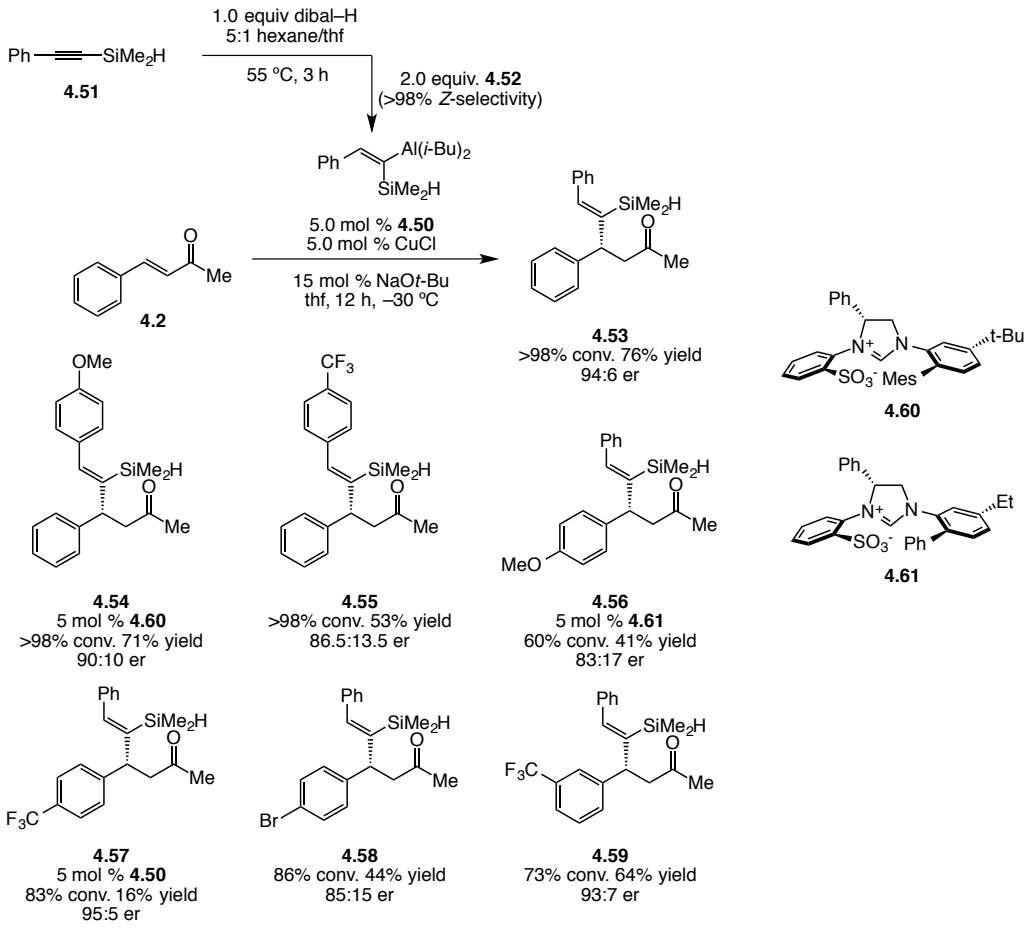
[a]Reactions were performed under N_2 atmosphere. [b] Determined by anaylsis of 400 MHz ^1H NMR of unpurified mixtures. [c] Yield of isolated and purified product. [d] Determined by HPLC analysis. [e] 16% *i*-Bu addition observed [f] 27% *i*-Bu addition observed nd = not determined



4.47 R= H, Ar = 2,4,6-$Me_3C_6H_2$
4.48 R= Ph, Ar = 2,4,6-*i*-$Pr_3C_6H_2$
4.49 R= Ph, Ar = 3,5-(*t*-Bu)$_2C_6H_3$
4.50 R= Ph, Ar = 3,5-(2,4,6-*i*-$Pr_3C_6H_2$)C_6H_3

After establishing an optimal nucleophile as well as NHC–Ag precursor, we moved on to explore the scope of the addition of Z-alkenylaluminum reagents. As illustrated in Scheme 4.10, nucleophiles with either electron donating or electron withdrawing groups react efficiently to deliver the desired products in 71 and 53% yield and 90:10 and 86.5:13.5 er respectively. In the case of **4.54**, imidazolinium salt **4.60** was determined to be optimal. A range of substrates is coupled with Z-alkenylaluminum **4.52** to furnish products in up to 64% yield and 95:5 er. Reactivity with an electron rich enone is diminished and as such only 60% conversion is achieved to generate **4.56** in the presence of **4.61**. Increased conversion is observed for a *para*-CF_3 containing enone, yet **4.57** is isolated in 16% yield. The product with a *para*-Br aryl group, **4.58,** is obtained in 44% yield and 85:15 er, while *meta*-CF_3-containing **4.59** is generated in 64% yield and 93:7 er.

Scheme 4.10. Addition of *Z*-Alkenylsilanes to Acyclic Enones

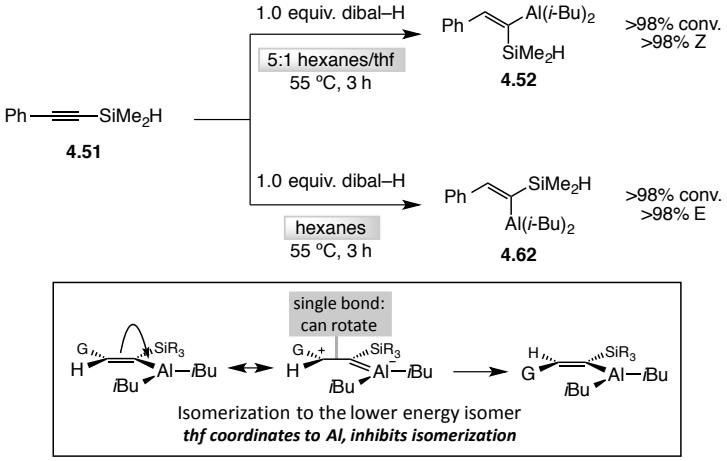


After examining the addition of *Z*-alkenylaluminum reagents, we moved on to look at the corresponding *E*-alkenylaluminum reagents. In addition to directing the hydroalumination[18], the silyl group allows for isomerization of the alkenylaluminum reagent under slightly different reaction conditions: the absence or presence of tetrahydrofuran (thf), a coordinating solvent. Without thf, the kinetically formed *Z*-alkenylaluminum, from *cis* addition of Al–H across the alkyne, is able to isomerize to the thermodynamically more stable *E*-alkenylaluminum reagent. The isomerization is promoted by a number of factors: (1) the empty p-orbital on aluminum delocalizes the electron density of the adjacent olefin resulting in more single bond character (2) both the

[18] For a review regarding stereoselective synthesis through the use of Si-containing compounds, see: (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. For related examples, see: (b) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520–3526; (c) Eisch, J. J.; Rhee, S-G. *J. Am. Chem. Soc.* **1975**, *97*, 4673–4682.

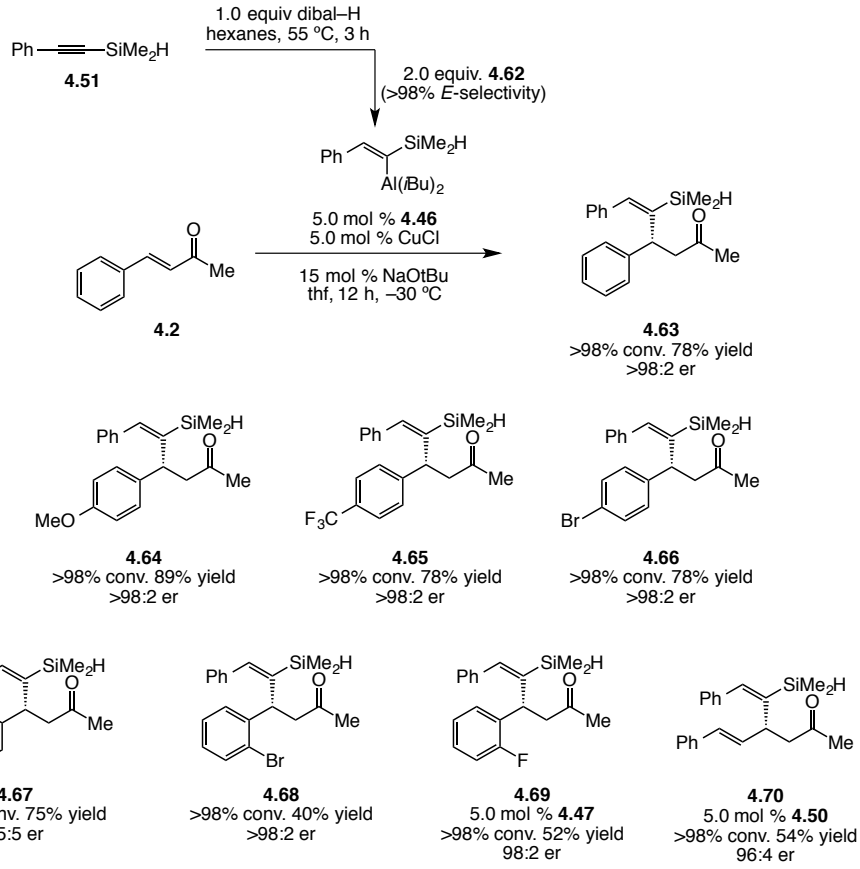
neighboring aryl group as well as the silicon group aid in stabilizing the forming carbocation which lowers the barrier to rotation (3) rotation around the C–C bond alleviates the steric repulsion of the sizable aryl and silyl groups and situates the aryl group *cis* to the longer carbon–aluminum bond. The empty p-orbital on aluminum is occupied in the presence of a coordinating solvent, which shuts down this isomerization and favors the kinetically formed *cis*-hydroalumination product.

Scheme 4.11. Solvent Effects on Product Formation in Hydroalumination



As shown in Scheme 4.12, E-alkenylaluminum reagent is coupled with enone **4.2** in the presence of 5.0 mol % of NHC–Cu complex derived from **4.46**. **4.63** is formed in 78% yield and >98:2 er. Products containing either an electron-rich *p*-methoxy phenyl or electron-poor *p*-trifluoromethyl phenyl group, **4.64** and **4.65** respectively, are formed in up to 89% yield and >98:2 er. Halogen-containing substrates are coupled to alkenylaluminum **4.62** in 40–78% yield and 95:5–>98:2 er. Substitution at the *ortho* position leads to a less efficient reaction and therefore lower yield of **4.68**. A smaller *ortho* substituent, fluorine, in conjunction with NHC precursor **4.47** leads to olefin-containing compound **4.69** in 52% yield and 98:2 er. Additionally, 1,4-diene **4.70** is formed in 54% yield and 96:4 er.

Scheme 4.12. Conjugate Addition of *E*-Alkenylsilanes to Acyclic Enones

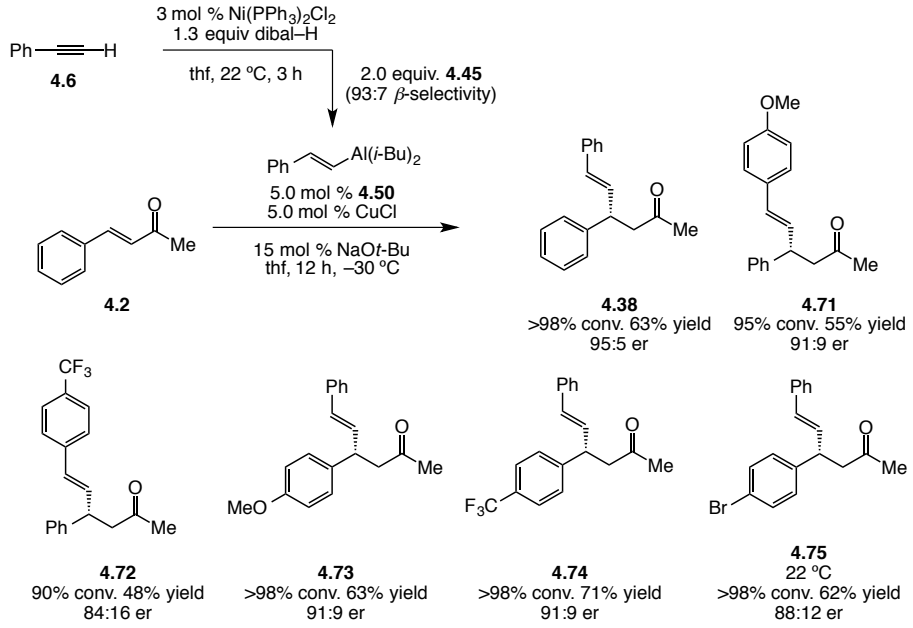


4.3.b. Addition of Nucleophiles Derived from Terminal Olefins

After examining silyl-substituted nucleophiles, we returned to our investigations of alkenylaluminum reagents generated from Ni-catalyzed hydroalumination of terminal alkynes. As mentioned above, in the presence of NHC–Ag complex **4.46**, styrenylaluminum **4.45** is coupled with enone **4.2** with moderate enantioselectivity (76:24 er). Increasing the size of the N-aryl group to tri*iso*propyl phenyl generates **4.38** in 56% yield and 81:19 er. Further steric modification leads to NHC–Ag **4.50**, which furnished **4.38** in 63% yield and 95:5 er. Reactions with an electron-deficient nucleophile are less efficient leading to **4.72** in 48% yield and 84:16 er. Conversely, an electron-rich nucleophile results in formation of **4.71** in 55% yield and increased enantioselectivity, 91:9 er. The electronic nature of the enone also has a pronounced effect on the enantioselectivity of the transformation where an electron-rich enone results in **4.73** in 80:20 er whereas electron-poor or halogen-containing enones lead to **4.74** and **4.75** in

88:12 and 91:9 er, respectively. Coupling partners that slow down either the oxidative addition (an electron rich enone is less prone to addition) or the reductive elimination or transmetalation (an electron poor olefin would transfer less readily to the Cu-center as well as stabilizing the Cu(III) intermediate thereby slowing down reductive elimination) lead to decreased enantioselectivity presumably due to the reversible nature of the steps in conjugate addition.

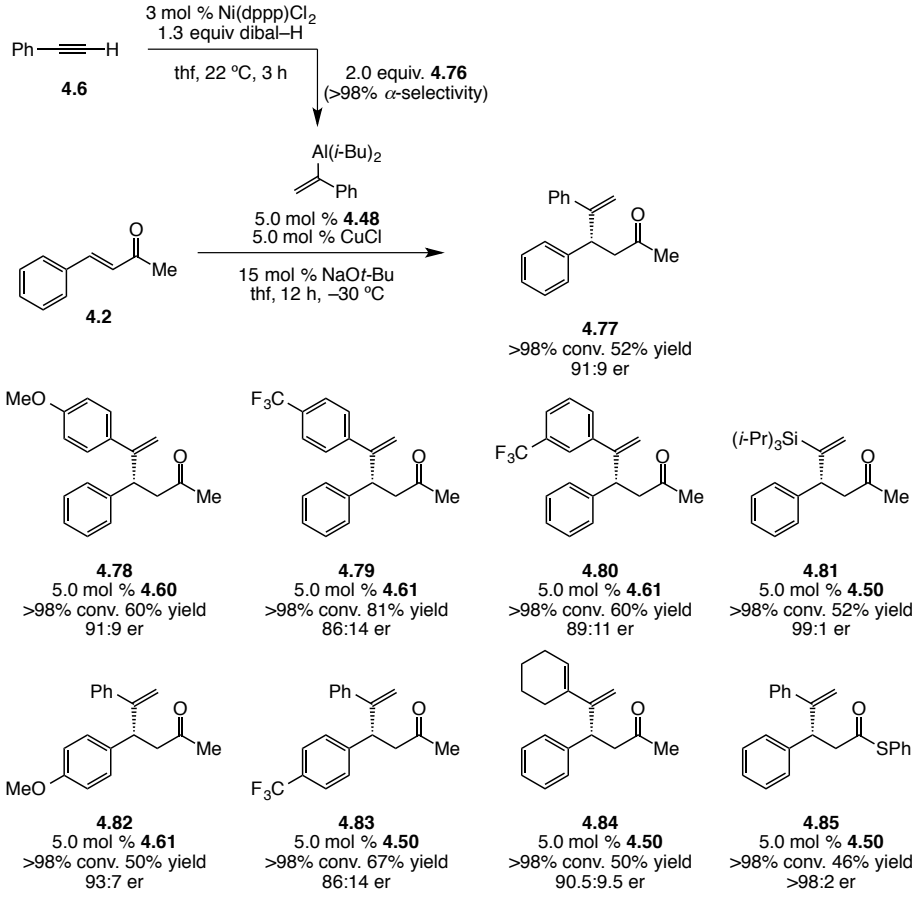
Scheme 4.13. Enantioselective Conjugate Addition of β-Alkenylaluminum Reagents



We also examined the addition of α-alkenylaluminum reagents which can be generated in >98% selectivity through $Ni(dppp)Cl_2$ catalyzed hydroalumination. In the presence of 5.0 mol % NHC–Cu complex derived from imidazolinium salt **4.48**, α-styrenylaluminum **4.76** is coupled with enone **4.2** in 52% yield and 91:9 er. Similar results are obtained for electron-rich *p*-methoxy styrenylaluminum with which **4.78** is obtained in 60% yield and 91:9 er with imidazolinium salt **4.60**. Electron poor nucleophiles react efficiently to generate **4.79** and **4.80** in 60–81% yield and 86:14–89:11 er. While a *p*-OMe-containing enone leads to **4.82** in 50% yield and 93:7 er with **4.61,** a *p*-CF_3-containing enone results in formation of **4.83** in 86:14 er in the presence of **4.50**. Both tri*iso*propylsilane- as well as cyclohexene-substituted nucleophiles are competent reaction partners, furnishing the desired products in 99:1 and 90.5:9.5 er respectively.

Additionally, an α,β-unsaturated thioester can serve as the electrophile leading to the formation of **4.85** in 46% yield and >98:2 er.

Scheme 4.14. Conjugate Addition of α-Alkenylaluminum Reagents



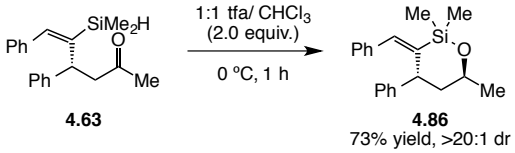
4.3.c Functionalization of Alkenylsilane Products

As has been demonstrated in the past, alkenylsilanes can be converted into a variety of useful function groups including alkenyliodides, ketones (through an epoxidation/elimination sequence), or simple alkenes through protodesilylation.[8] Our initial interest was in the protodesilylation of **4.63** to reveal the Z-alkene,[19] a product that is not readily available through most conjugate addition methods. Upon subjection of the alkenylsilane to trifluoroacetic acid at 0 °C, we did not observe the protodesilylation but instead the product of a 1,5-hydride shift to product siloxane **4.86**. The anti conformation

(19) For a similar transformation involving allylic substitution see: Akiyama, K.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *49*, 419–423.

of the product was determined through a NOESY experiment as no nOe exists between the two protons at the stereogenic centers.

Scheme 4.15. Intramolecular Ketone Reduction Through 1,5-Hydride Shift

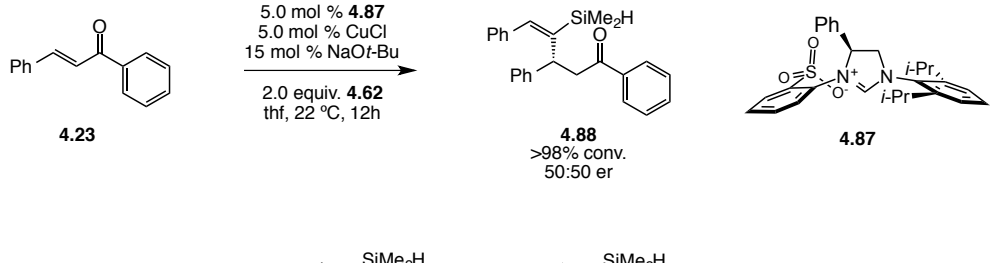


4.63 **4.86**
73% yield, >20:1 dr

4.3.d Diastereoselective Conjugate Addition to α,β-Unsaturated N-Acyl Oxazolidinones

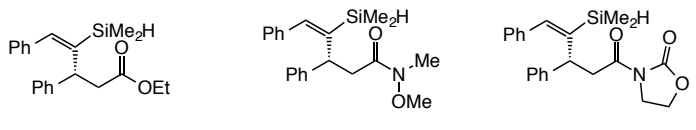
In an effort to expand the scope of additions of *E*-alkenysilanes, we investigated a variety of unsaturated carbonyls. As shown in Scheme 4.16, while reaction with **4.23** is efficient, resulting in >98% conversion to desired product **4.88**, no enantioselectivity is observed. Reaction with either an α,β-unsaturated ester or Weinreb amide lead to <2% conversion of the starting material. We surmised that donation of the oxygen or nitrogen lone pair into the carbonyl increases the barrier to 1,4-addition, so we examined a substrate containing an oxazolidinone where the nitrogen lone pair would be less donating. Complete conversion to the desired product is observed, and **4.91** is obtained in 90% yield, but again the product is racemic.

Scheme 4.16. NHC–Cu-Catalyzed Addition of *E*-Alkenylsilanes to Chalcone and Unsaturated Esters and Amides



4.23 **4.88**
>98% conv.
50:50 er

4.87



4.89
<2% conv.

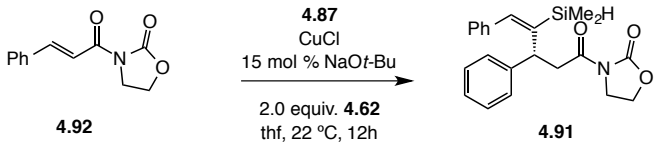
4.90
<2% conv.

4.91
>98% conv.
90% yield
50:50 er

Further examination of the reaction of **4.92** with *E*-alkenylaluminum **4.62** revealed that although full conversion is achieved at 22 °C, decreasing the temperature to

–30 ºC, the optimal temperature for the previously discussed unsaturated ketones, leads to <5% conversion to the desired **4.91** (Table 4.2, entries 1-2). Additionally, as shown in Table 4.2, entry 3, in the absence of imidazolinium salt **4.87**, only ~18% conversion to the desired product is observed. Furthermore, addition of **4.62** to oxazolidinone **4.92**, in the absence of both **4.87** and CuCl, does not lead to any reaction.

Table 4.2. Examination of Reaction Conditions for ECA with **4.92**[a]

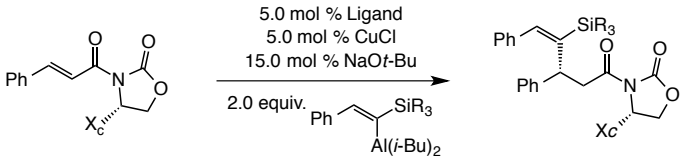


entry	**4.87** (mol %)	CuCl (mol %)	conv. (%)[b]
1	5	5	>98
2[c]	5	5	<5
3	0	5	18
4	0	0	<5

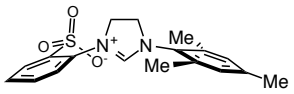
[a] Reactions were performed under N_2 atmosphere. [b] Determined by anaylsis of 400 MHz ^{1}H NMR of unpurified mixtures. [c] Reaction performed at –30 ºC

Following the above findings, we moved on to examine the reaction of an enone containing an enantiomerically enriched phenylglycinol-derived *N*-acyl oxazolidinone, **4.93**. As shown in Table 4.3, reaction of **4.93** with **4.62** in the presence of 5 mol % of NHC–Cu complex derived from **4.87** leads to >98% conversion to the desired product as a 53:47 mixture of diastereomers. Surprisingly, achiral sulfonate-containing imidazolinium **4.95**, leads to a highly diastereoselective reaction, with **4.94** obtained in 95% yield and 95:5 dr. As shown in entry 3, reaction in the presence of monodentate C_2-symmetric **4.96** leads to 90% conversion to the desired product in 82:18 dr. Additionally, in the absence of a ligand, reaction of **4.62** with 5.0 mol % CuCl leads to 90:10 dr. Modifying the nucleophile to a trimethylsilyl-containing olefin (versus dimethylsilane) results in a slight increase in diastereoselectivity (only one diastereomer observed by ^{1}H NMR) and >98% yield in the presence of **4.95**. In the absence of the NHC–Cu complex, ~4% conversion to the desired product is observed. With a modified chiral auxiliary containing a benzyl-substituted stereogenic center, the reaction with **4.95** is less efficient (46% conversion) although diastereoselectivity remains high.

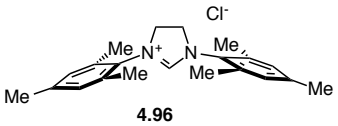
Table 4.3. Ligand Screening for Diastereoselective Conjugate Addition[a]



entry	X_c	SiR_3	Ligand	conv (%)[b]	yield (%)[c]	d.r.[b]
1	Ph	$SiMe_2H$	**4.87**	>98	nd	53:47
2	Ph	$SiMe_2H$	**4.95**	>98	95	95:5
3	Ph	$SiMe_2H$	**4.96**	~90	nd	82:18
4	Ph	$SiMe_2H$	–	>98	nd	90:10
5	Ph	$SiMe_3$	**4.95**	>98	98	>98:2
6	Ph	$SiMe_3$	–	4	nd	nd
7	Bn	$SiMe_3$	**4.95**	46	nd	>98:2
8	Bn	$SiMe_3$	–	<2	nd	nd



4.95

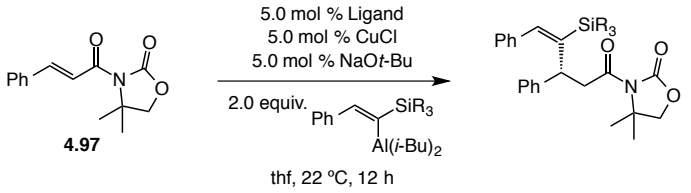


4.96

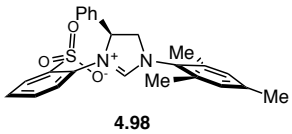
[a] Performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [c] Yield of isolated and purified product. *nd* = not determined

As shown in Table 4.4, in an attempt to decrease the chelation between the substrate and the catalyst, we explored the reaction of enone **4.97** containing a dimethyl-substituted *N*-acyl oxazolidinone. As shown in entry 1, in the presence of chiral imidiazolinium salt **4.87** containing a sterically encumbered 2,6-di*iso*propyl aryl group, <2% conversion to the desired product is observed. With the achiral variant of the ligand, **4.95**, 70% conversion was obtained, but as a 56:44 mixture of alkene addition to conjugate hydride reduction. The sterically larger dimethyl auxiliary slows down the desired conjugate addition such that insertion of the catalyst into the Si–H bond to form a copper hydride becomes competitive. Changing to a trimethylsilyl group to obviate the conjugate reduction side product results in <2% conversion with **4.87** as well as with the smaller **4.98**. With achiral ligand **4.95**, only 27% conversion to the desired product is observed although none of the undesired reduction product is present.

Table 4.4. Optimization of Reaction Conditions for Dimethyl-Substituted *N*-Acyl Oxazolidinone[a]



entry	SiR_3	Ligand	conv (%)[b]	Alkene:H[b]
1	$SiMe_2H$	**4.87**	<2	nd
2	$SiMe_2H$	**4.95**	70	56:44
3	$SiMe_3$	**4.87**	<2	nd
4	$SiMe_3$	**4.98**	<2	nd
5	$SiMe_3$	**4.95**	27	>98:2

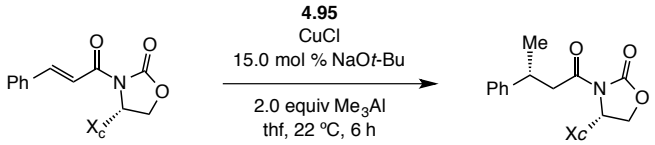


4.98

[a] Performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^1H NMR of unpurified mixtures. *nd* = not determined

In addition to addition of alkenylsilanes, we also examined the reaction with commercially available trimethylaluminum. As shown in Table 4.5, in the absence of the NHC–Cu complex derived from 4.95, <2 % conversion is observed for any chiral auxiliary (Table 4.5, entries 1, 4, and 7). With 5 mol % CuCl, only 13–15% conversion is observed and the diastereoselectivity is minimal (~57:43 dr). With a phenyl-substituted auxiliary and 5 mol % of NHC–Cu catalyst, 65% conversion to the desired product is observed and 60:40. A benzyl-substituted auxiliary leads to 90% conversion and 83:17 dr with the desired product isolated in 71% yield and >20:1 dr. An *iso*propyl auxiliary results in 96% conversion and 91% yield of the conjugate addition adduct in 81:19 dr (diastereomers are not separable by column chromatography).

Table 4.5. Optimization of Reaction Conditions for Methyl Addition to Unsaturated *N*-Acyl Oxazolidinone[a]

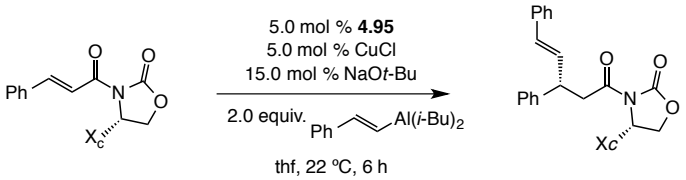


entry	X_c	**4.95** (mol %)	CuCl (mol %)	conv (%)[b]	yield (%)[c]	d.r.[b]
1	Ph	0	0	<2	nd	nd
2	Ph	0	5	13	nd	56:44
3	Ph	5	5	65	nd	60:40
4	Bn	0	0	<2	nd	nd
5	Bn	0	5	15	nd	57:43
6	Bn	5	5	90	71[d]	83:17
7	*i*-Pr	0	0	<2	nd	nd
8	*i*-Pr	0	5	15	nd	57:43
9	*i*-Pr	5	5	96	91[e]	81:19

[a] Performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [c] Yield of isolated and purified product. [d] Product isolated in >20:1 dr. [e] Product isolated in 80:20 dr. *nd* = not determined

We examined similar reaction conditions for the addition of a styrenyl nucleophile generated from Ni-catalyzed hydroalumination of phenylacetylene. 43–56% conversion to the conjugate addition product occurs in the absence of any catalyst with low diastereoselectivity (50:50–60:40). Similar conversion and diastereoselectivity is observed with 5.0 mol % CuCl (Table 4.6, entries 2, 5, 8). Although increased conversion is observed for reactions with NHC–Cu complex derived from **4.95** (57–80% conversion), diastereoselectivity does not improve (up to 60:40 dr). Clearly ligand modification as well as modified reaction conditions are necessary to achieve a highly diastereoselective reaction.

Table 4.6. Optimization of Reaction Conditions for β-Styrenyl Addition to Unsaturated *N*-Acyl Oxazolidinone[a]

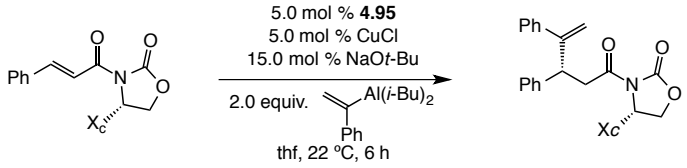


entry	X_c	**4.95** (mol %)	CuCl (mol %)	conv (%)[b]	yield (%)[c]	d.r.[b]
1	Ph	0	0	56	nd	nd
2	Ph	0	5	55	nd	60:40
3	Ph	5	5	80	42	60:40
4	Bn	0	0	43	nd	60:40
5	Bn	0	5	66	nd	nd
6	Bn	5	5	80	30	nd
7	*i*-Pr	0	0	47	nd	60:40
8	*i*-Pr	0	5	88	nd	50:50
9	*i*-Pr	5	5	57	28	50:50

[a] Performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [c] Yield of isolated and purified product. nd = not determined

We also investigated the addition of the sterically larger α-styrene nucleophiles with a variety of unsaturated *N*-acyl oxazolidinones. As shown in Table 4.7, no conversion is observed for the uncatalyzed addition of the nucleophiles to phenyl-substituted auxiliary. In the presence of NHC–Cu complex derived from **4.95**, 50 % conversion to the desired product is observed in >95:5 dr. 42% uncatalyzed addition occurs with the benzyl-containing substrate in 75:25 dr. With the NHC–Cu complex, 50 % conversion is observed with a reversal of diastereoselectivity (33:67 dr). Finally, with the isopropyl variant, a highly diastereoselective background reaction is observed (50% conversion, >95:5 dr). The reaction catalyzed by the copper complex of **4.95** is more efficient (70 % conversion in 6 h), but the diastereoselectivity drops sharply (40:60 dr). The NHC–Cu-catalyzed addition of α-styrenyl nucleophiles to phenyl-substituted auxiliaries merits further examination.

Table 4.7. Optimization of Reaction Conditions for β-Styrenyl Addition to Unsaturated *N*-Acyl Oxazolidinone[a]



entry	X_c	**4.95** (mol %)	CuCl (mol %)	conv (%)[b]	d.r.[b]
1	Ph	0	0	<2	nd
2	Ph	0	5	33	nd
3	Ph	5	5	50	>95:5
4	Bn	0	0	42	75:25
5	Bn	0	5	25	nd
6	Bn	5	5	50	33:67
7	*i*-Pr	0	0	50	>95:5
8	*i*-Pr	0	5	35	50:50
9	*i*-Pr	5	5	70	40:60

[a] Performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR of unpurified mixtures. [c] Yield of isolated and purified product. *nd* = not determined

4.4 Conclusions

We have developed the first Cu-catalyzed enantioselective conjugate addition of alkenyl nucleophiles to acyclic enones. Reactions are catalyzed by 5.0 mol % of an *in situ* generated NHC–Cu complex and nucleophiles are formed through hydroalumination of both terminal and internal alkynes. Both *E*- and *Z*-silyl-substituted alkenylaluminum reagents are competent reaction partners as well as α- and β-alkenylaluminum reagents, which are generated through Ni-catalyzed hydroalumination. Products are generated in up to 89% yield and >98:2 er. Moreover, we have found that the use of a chiral auxiliary in conjunction with an achiral NHC–Cu complex leads to an efficient and highly diastereoselective conjugate addition of alkenylsilanes.

4.5 Experimentals

■ **General.** Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, λ_{max} in cm^{-1}. Bands are characterized as strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete protondecoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility at Boston College. Enantiomeric ratios were determined by HPLC analysis (Chiral Technologies Chiralcel OD(H) (4.6 x 250 mm), Chiral Technologies Chiralcel OJ(H) (4.6 x 250 mm) Chiral Technologies Chiralcel AD(H) (4.6 x 250 mm)) or GC analysis (Chiraldex CDGTA 30 m x 0.25 mm) in comparison with authentic racemic materials. Specific rotations were measured on an ATAGO AP-300 Automatic Polarimeter. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and hexanes were purified through a copper oxide and alumina column; Et_2O was purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) in air.

■ **Solvents, Reagents & Catalysts:**

[1,3-Bis(diphenylphosphino)propane]dichloronickel(II) was purchased from Strem and used as received.

Bis(triphenylphosphine)nickel(II) dichloride was purchased from Strem and used as received.

2-Bromobenzaldehyde was purchased from Aldrich and used as received.

3-Bromobenzaldehyde was purchased from Aldrich and used as received.

4-Bromobenzaldehyde was purchased from Aldrich and used as received.

***n*-Butyllithium** was purchased from Strem (15% in hexanes) and titrated before use.

Chlorodimethylsilane was purchased from Aldrich and used as received.

Chlorotrimethylsilane was purchased from Aldrich and used as received.

Cinnamaldehyde was purchased from Aldrich and used as received.

Copper(I) Chloride was purchased from Strem and used as received.

Copper(II) chloride dihydrate was purchased from Aldrich and used as received.

Cyclohexanecarboxaldehyde was purchase from Aldrich and used as received.

2-Cyclohexen-1-one was purchase from Aldrich and was distilled over CaH_2 prior to use.

2-Cyclopent-1-one was purchase from Aldrich and was distilled over CaH_2 prior to use.
Diisobutylaluminum hydride was purchase from Aldrich and used as received.
4-Ethynylanisole was purchase from Aldrich and was distilled over CaH_2 prior to use.
1-Ethynylcyclohexene was purchase from Aldrich and was distilled over CaH_2 prior to use.
3-Ethynyl-α,α,α-trifluorotoluene was purchase from Aldrich and was distilled over CaH_2 prior to use.
4-Ethynyl-α,α,α-trifluorotoluene was purchase from Aldrich and was distilled over CaH_2 prior to use.
2-Fluorobenzaldehyde was purchase from Aldrich and used as received.
NHC–Ag complexes and immidazolinium salts (2.5-2.8, 2.35, 2.37, 2.46, and 2.47)[32] were prepared according to published procedures.
NHC–Ag complexes and imidazolinium salts (2.9-2.12, 2.23, and 2.36)[33] were prepared according to published procedures.
NHC–Ag complexes (2.13-2.15)[34] were prepared according to published procedures.
***p*-Anisaldehyde** was purchased from Aldrich and used as received.
Phenylacetylene was purchase from Aldrich and was distilled over CaH_2 prior to use.
4-Phenyl-3-buten-2-one (2.22) was purchased from Aldrich and used as received.
Sodium *tert*-butoxide was purchased from Strem and used as received.
Trifluoroacetic acid was purchased from Aldrich and used as received.
2-(Trifluoromethyl)benzaldehyde was purchased from Aldrich and used as received.
3-(Trifluoromethyl)benzaldehyde was purchased from Aldrich and used as received.
4-(Trifluoromethyl)benzaldehyde was purchased from Aldrich and used as received.
(Triisopropylsilyl)acetylene was purchase from Aldrich and distilled over CaH_2 prior to use.
1-(Triphenylphosphoranylidene)-2-propanone was purchased from Aldrich and used as received.

■ Representative Procedure for the Synthesis of Enone Substrates:
To a flame-dried round bottom flask equipped with a stir bar, a solution of 1-(triphenylphosphoranylidene)-2-propanone (3.06 g, 9.6 mmol) in benzene (80 mL) and then 2-fluorobenzaldehyde (842 μL, 5.00 mmol) was added. The resulting mixture refluxed overnight. After cooling to 22 °C, the solution was concentrated and washed with pentane to remove triphenyphosphine, which was filtered off. The remaining material was concentrated and the product was isolated by silica gel chromatography (100% hexanes → 5:1 Hexanes/Et2O) to produce a white solid (0.93 g, 5.6 mmol, 70%).

■ Representative Procedure for the Synthesis of Silyl-Substituted Alkynes:

(32) Brown, K. M.; May, T. L; Baxter, C. A; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100.
(33) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2010**, *49*, 419−423.
(34) Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900.

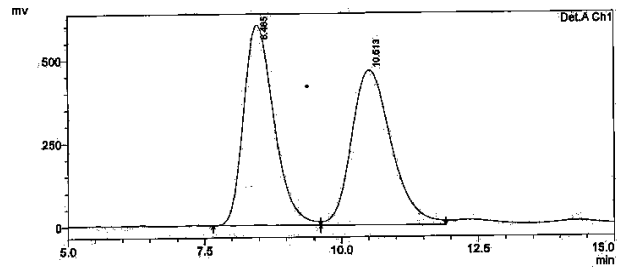
To a flame-dried 100 mL round bottom flask was added phenylacetylene (2.0 mL, 18.2 mmol) and thf (30 mL). The solution was cooled to –78 ºC, and *n*-butyllithium (1.6 M, thf, 13.6 mL, 21.9 mmol) was added dropwise. After 2 h, as solution of chlorodimethylsilane (2.6 mL, 27.3 mmol) in thf (23 mL) was added and allowed to stir for 36 h, slowly warming to 22 ºC. The reaction was quenched upon addition of a saturated solution of NH_4Cl. Layers were separated and the aqueous layer was washed with Et_2O. Combined organic layers were dried over $MgSO_4$, filtered and concentrated. Dimethyl(phenylethynyl)silane was isolated by silica gel chromatography (100% hexanes) as a clear liquid (2.41 g, 15.0 mmol, 83%).

■ **Representative Procedure for the Synthesis of Silyl-Substituted-*E*-Alkenylaluminum Reagents:** A flame-dried round bottom flask fitted with a reflux condenser was equipped with a stir bar and was charged with hexanes (1.3 mL). Dibal-H (356 μL, 2.0 mmol) was added dropwise to the solution at 22 ºC. Dimethyl(phenylethynyl)silane (354 μL, 2.0 mmol) was then added dropwise and the resulting solution was allowed to warm to 55 ºC (oil bath) for 3 h and then cooled to 22 ºC, producing a solution of (E)-(1-(dimethylsilyl)-2-phenylvinyl)diisobutylaluminum. The resulting solution was used without further purification.

■ **Representative Procedure for NHC–Cu Copper Catalyzed Conjugate Addition with Alkenylaluminum Reagents:** To an flame-dried 1 dram vial equipped with a magnetic stir bar, was charged with imidazolinium salt **2.37** (4.3 mg, 0.005 mmol), sodium *tert*-butoxide (1.4 mg, 0.015 mmol), and copper(I) chloride (0.5 mg, 0.005 mmol) under a N_2 atmosphere in a glovebox. The reaction was sealed with a septum cap and removed from the glovebox. thf (0.5 mL) was added and the resulting solution was allowed to stir for 15 minutes prior to addition of (*Z*)-(1-(dimethylsilyl)-2-phenylvinyl)diisobutylaluminum solution (200 μL, 0.2 mmol). The solution was allowed to cool to –78 ºC (dry ice acetone bath) and a solution of 4-phenyl-3-buten-2-one, **2.22**, (17.6 mg, 0.1 mmol) in thf (0.5 mL) was added by syringe, and the reaction was allowed to stir for 12 h at –30 ºC. The reaction was subsequently quenched upon addition of a saturated solution of sodium potassium tartrate (Rochelle's salt) after allowing the mixture to warm to 22 ºC. The solution was washed with Et_2O. Organic layers were combined and passed through a short plug of silica gel, eluting with Et_2O. The resulting elutant was concentrated and purified by silica gel chromatography (100% hexanes → 20:1 hexanes:Et_2O) to produce a clear oil (22.1 mg, 0.065 mmol, 62%).

(R,E)-5-(dimethylsilyl)-4,6-diphenylhex-5-en-2-one (4.63). IR (neat): 3058 (w), 3026 (w), 2956 (w), 2118 (w), 1711 (s), 1599 (w), 1492 (w), 1419 (w), 1356 (w), 1248 (m), 1159 (w), 1072 (w), 1020 (w), 887 (s), 837 (m), 762 (s), 750 (s), 698 (s), 658 (w), 635 (w), 570 (w), 519 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.36 (2H, m), 7.33–7.23 (5H, m), 7.21–7.14 (3H, m), 6.95 (1H, s), 4.87–4.83 (1H, dd, *J* = 6.9, 8.0 Hz), 4.12–4.09 (1H, sept., *J* = 4.0 Hz), 3.22 (1H, dd, *J* = 8.4, 16.0 Hz), 2.82 (1H, dd, *J* = 6.8, 16.4 Hz), 2.01 (3H, s), 1.00 (3H, d, *J* = 3.6 Hz), -0.16 (3H, d, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3, 145.2, 142.2, 139.9, 138.0, 128.6, 128.5, 127.8, 127.3, 126.6, 47.7, 41.3, 30.0, -2.5, -2.9; HRMS (DART): Calcd for $C_{20}H_{24}OSi$

$[M+NH_4^+]$: 307.1518. Found: 307.1579; specific rotation: $[\alpha]_D^{20}$ -214.1 (c = 0.35, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r. Enantiomeric purity (>99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OJ-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

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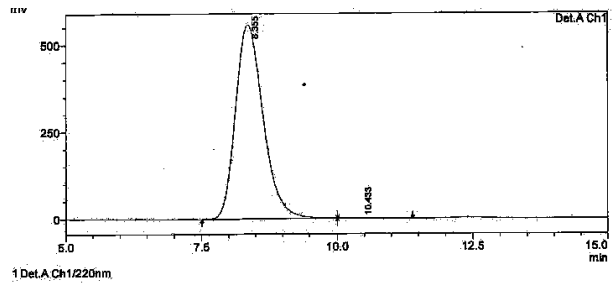
2	10.513	23662504	463204	50.360
Total		46986552	1062540	100.000



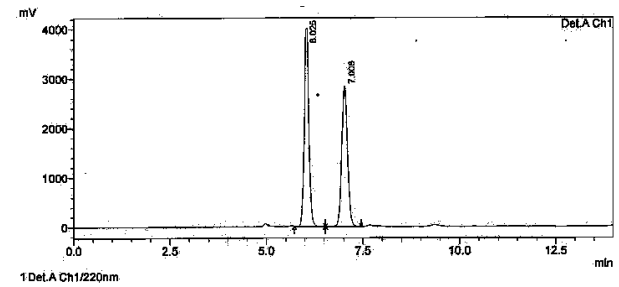
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.355	19816456	556858	99.729
2	10.433	53810	1402	0.271
Total		19870265	558260	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
8.465	23324048	49.540	8.355	19816456	99.729
10.513	23662504	50.360	10.433	53810	0.271

(R,E)-5-(dimethylsilyl)-6-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.65). IR (neat): 2959 (w), 2119 (w), 1718 (m), 1618 (w) 1414 (w), 1358 (w), 1326 (s), 1250 (w), 1163 (m), 1117 (s), 1070 (m), 1016 (w), 889 (s), 837 (w), 770 (w), 698 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.50 (2H, d, *J* = 8.0 Hz), 7.39–7.35 (2H, m), 7.30–7.21 (5H, m), 6.97 (1H, s), 4.90–4.86 (1H, m), 4.12–4.07 (1H, m), 3.23 (1H, dd, *J* = 8.8, 16.8 Hz), 2.87 (1H, dd, *J* = 6.0, 16.8 Hz), 2.06 (3H, s), 0.12 (3H, d, *J* = 4.0 Hz), -0.14 (3H, d, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 146.5, 144.0, 140.6, 137.6, 128.7 (q, J_{C-F} = 32.0 Hz), 128.5, 128.2, 128.3, 127.9, 127.3, 126.9 (q, J_{C-F} = 270.1 Hz), 125.2 (q, J_{C-F} = 3.7 Hz), 47.2,40.9, 30.0, -2.7, -3.0; HRMS (DART): Calcd for $C_{21}H_{24}F_3OSi$ $[M+H^+]$: 377.1549. Found: 377.1556; specific rotation: $[\alpha]_D^{20}$ -240.4 (c = 3.00, $CHCl_3$) for an enantiomerically enriched sample of 99:1 e.r. Enantiomeric purity (99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
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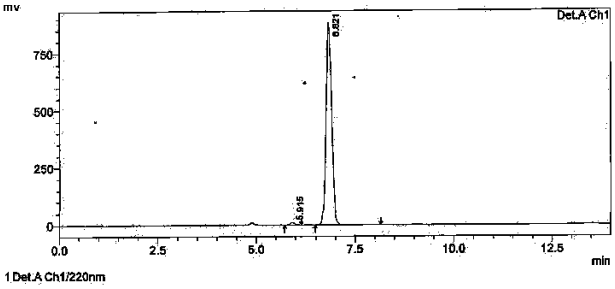
2	7.006	29732234	2834174	47.308
Total		62848149	6817099	100.000



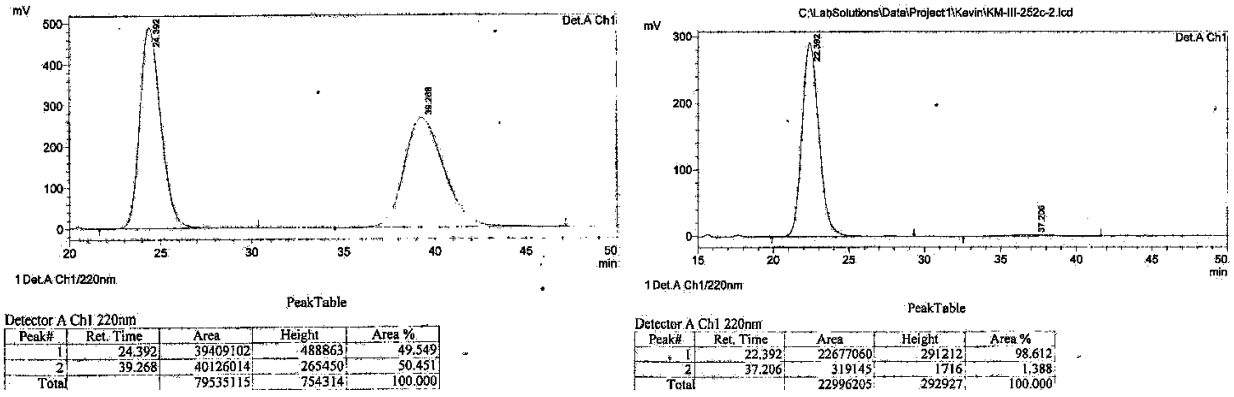
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	5.915	84262	9792	0.945
2	6.821	8835109	884081	99.055
Total		8919371	893874	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
6.025	33115914	52.692	5.915	84262	0.945
7.006	29732234	47.308	6.821	8835109	99.055

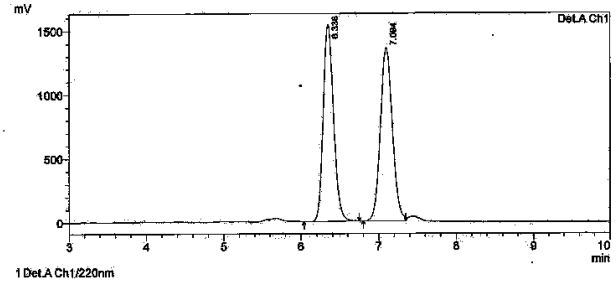
(R,E)-5-(dimethylsilyl)-4-(4-methoxyphenyl)-6-phenylhex-5-en-2-one (4.64). IR (neat): 3059 (w), 2995 (w), 2955 (w), 2900 (w), 2835 (w), 2116 (w), 1709 (m), 1608 (w), 1582 (w), 1510 (s), 1492 (w), 1463 (w), 1443 (w), 1420 (w), 1356 (w), 1305 (w), 1247 (s), 1178 (m), 1159 (w), 1035 (m), 883 (s), 832 (s), 763 (s), 737 (s), 698 (s), 542 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.37 (2H, m), 7.36–7.25 (3H, m), 7.07–7.04 (2H, m), 6.92 (1H, s), 6.82–6.78 (2H, m), 4.78 (1H, dd, *J* = 6.8, 8.8 Hz), 4.11–4.08 (1H, m), 3.78 (3H, s), 3.17 (1H, dd, *J* = 8.8, 16.0 Hz), 2.80 (1H, dd, *J* = 6.4, 16.0 Hz), 1.99 (3H, s), 0.10 (3H, d, *J* = 4.0 Hz), -0.14 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3, 173.6, 158.1, 145.4, 139.3, 137.9, 134.0, 128.6, 128.4, 128.3, 127.0, 113.7, 55.2, 47.8, 40.4, 29.8, -2.7, -3.0; HRMS (DART): Calcd for $C_{21}H_{27}O_2Si$ $[M+H^+]$: 339.1780. Found: 339.1797; specific rotation: $[\alpha]_D^{20}$ –248.3 (*c* 1.69, $CHCl_3$). Enantiomeric purity (99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OJ-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	% Area	Retention Time	Area	% Area
24.392	39409102	49.549	22.392	22677060	98.612
39.268	40126014	50.451	37.206	319145	1.388

(R,E)-4-(4-bromophenyl)-5-(dimethylsilyl)-6-phenylhex-5-en-2-one (4.66). IR (neat): 2960 (w), 2147 (w), 1714 (m), 1488 (m), 1358 (w), 1249 (w), 1159 (w), 1075 (w), 1009 (m), 889 (s), 838 (m), 766 (m), 698 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.39–7.36 (4H, m), 7.30–7.26 (3H, m), 7.02–6.99 (2H, m), 6.95 (1H, s), 4.80–4.76 (1H, m), 4.13–4.07 (1H, m), 3.18 (1H, dd, *J* = 8.8, 16.4 Hz), 2.83 (1H, dd, *J* = 8.0, 16.8 Hz), 2.04 (3H, s), 0.13 (3H, d, *J* = 3.6), -0.11 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 144.4, 141.3, 140.2, 137.7, 131.4, 129.3, 128.5, 128.3, 128.3, 127.2, 120.2, 47.3, 40.6, 29.9, -2.6, -3.0; HRMS (DART): Calcd for $C_{20}H_{24}BrOSi$ $[M+H^+]$: 387.0780. Found: 387.0781; specific rotation: $[\alpha]_D^{20}$ –335.9 (*c* 1.98, $CHCl_3$). Enantiomeric purity (99:1) was determined by HPLC analysis in comparison with

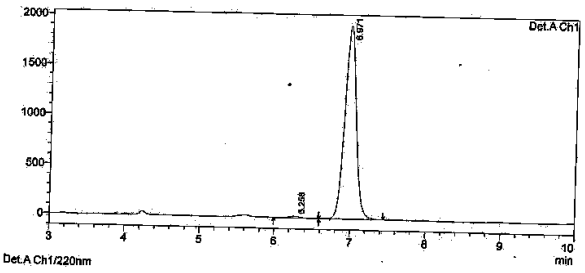
authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.338	14397340	1539133	49.579
2	7.094	14641793	1357531	50.421
Total		29039133	2896663	100.000



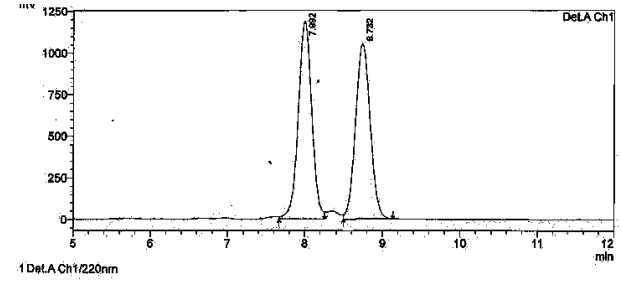
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.256	165858	18628	0.805
2	6.971	20432978	1928289	99.195
Total		20598836	1946917	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
6.338	14397340	49.579	6.256	165858	0.805
7.094	14641793	50.421	6.971	20432978	99.195

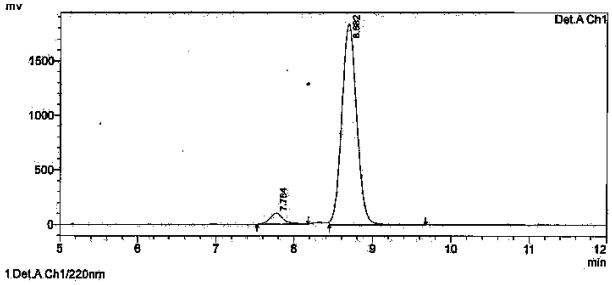
(R,E)-4-(3-bromophenyl)-5-(dimethylsilyl)-6-phenylhex-5-en-2-one (4.67). IR (neat): 2956 (w), 2118 (w), 1714 (m), 1592 (w), 1565 (w), 1474 (w), 1421 (w), 1357 (w), 1248 (w), 1159 (w), 1074 (w), 1026 (w), 886 (s), 837 (m), 765 (s), 697 (s), 670 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.36 (2H, m), 7.33–7.36 (5H, m), 7.16–7.11 (1H, m), 7.07–7.05 (1H, m), 6.97 (1H, s), 4.83–4.80 (1H, m), 4.13–4.09 (1H, m), 3.19 (1H, dd, *J* = 8.4, 16.8 Hz), 2.83 (1H, dd, *J* = 6.4, 16.8 Hz), 2.05 (3H, s), 0.13 (3H, d, *J* = 3.6 Hz), -0.10 (3H, d, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 144.9, 144.4, 140.6, 137.8, 131.0, 130.0, 129.7, 128.6, 128.4, 127.4, 126.3, 122.7, 47.4, 40.9, 30.1, -2.5, -2.9; HRMS (DART): Calcd for $C_{20}H_{24}BrOSi$ [M+H$^+$]: 387.0780. Found: 387.0770; specific rotation: $[\alpha]_D^{20}$ -386.3 (c = 1.05, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r. Enantiomeric purity (95:5) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.992	14537199	1187092	50.920
2	8.732	14011741	1054595	49.080
Total		28548941	2241686	100.000



PeakTable

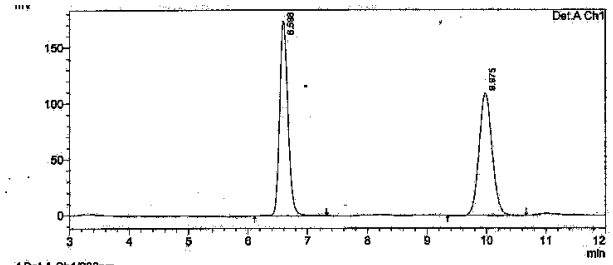
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.764	1196906	99684	4.629
2	8.682	24662080	1839940	95.371
Total		25858986	1939625	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
7.992	14537199	50.920	7.764	1196906	4.629

8.732	14011741	49.080	8.682	24662080	95.371

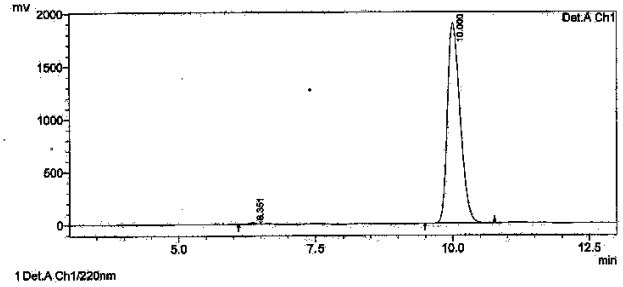
(R,E)-4-(2-bromophenyl)-5-(dimethylsilyl)-6-phenylhex-5-en-2-one (4.68). IR (neat): 2955 (w), 2925 (m), 1854 (w), 2118 (w), 1713 (s), 1568 (w), 1437 (w), 1357 (w), 1280 (m), 1158 (w), 1023 (m), 889 (s), 837 (m), 752 (s), 697 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53–7.50 (1H, m), 7.39–7.32 (5H, m), 7.29–7.23 (2H, m), 7.09–7.05 (1H, m), 6.97 (1H, s), 5.02–4.98 (1H, m), 4.09–4.05 (1H, m), 3.26 (1H, dd, *J* = 10.4, 16.9 Hz), 2.81 (1H, dd, *J* = 6.0, 17.2 Hz), 1.97 (3H, s), 0.072 (3H, d, *J* = 3.6 Hz), -0.19 (3H, d, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 142.5, 141.5, 141.0, 138.2, 133.6, 128.6, 128.5, 128.4, 127.4, 127.3, 126.2, 48.3, 42.3, 29.5, -3.0; HRMS (DART): Calcd for $C_{20}H_{24}BrOSi$ [M+H$^+$]: 387.0780. Found: 387.0764; specific rotation: $[\alpha]_D^{20}$ -64.6 (c = 1.26, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r. Enantiomeric purity (>99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.598	1702503	174370	50.394
2	9.975	1675876	109276	49.606
Total		3378379	283647	100.000



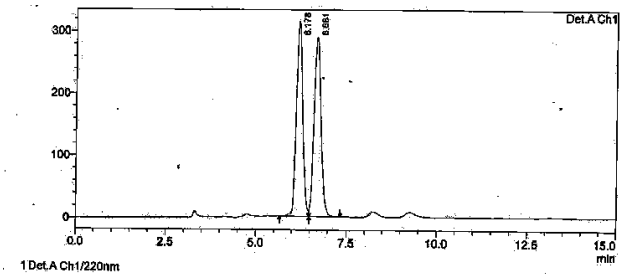
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.351	140406	12770	0.457
2	10.000	30574569	1895859	99.543
Total		30714976	1908629	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
6.598	1702503	50.394	6.351	140406	0.457
9.975	1675876	49.506	10.000	30574569	99.543

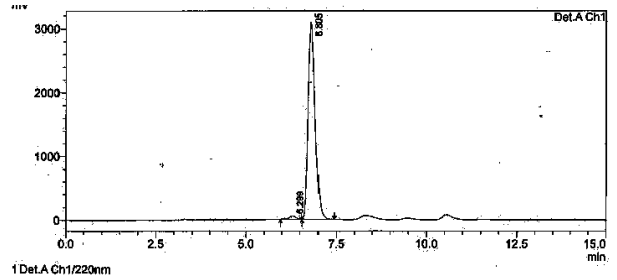
(R,E)-5-(dimethylsilyl)-4-(2-fluorophenyl)-6-phenylhex-5-en-2-one (4.69). IR (neat): 3062 (w), 2958 (w), 2902 (w), 2118 (w), 1715 (m), 1584 (w), 1489 (m), 1454 (w), 1419 (w), 1357 (w), 1249 (w), 1229 (m), 1160 (w), 1106 (w), 889 (s), 838 (m), 757(s), 700 (m) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.37 (2H, t, *J* = 6.8 Hz), 7.31–7.25 (2H, m), 7.22–7.17 (2H, m), 7.05 (1H, t, *J* = 7.6 Hz), 6.99–6.94 (2H, m), 5.01–4.97 (1H, dd, *J* = 6.4, 10.0 Hz), 4.08–4.06 (1H, m), 3.22 (1H, dd, *J* = 9.6, 16.4 Hz), 2.73 (1H, dd, *J* = 6.0, 16.4 Hz), 1.95 (3H, s), 0.09 (3H, d, *J* = 4.0 Hz), 0.17 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 161.6 (d, J_{C-F} = 245.2), 143.4, 140.8, 138.1, 129.1 (d, J_{C-F} = 13.7 Hz), 128.4 (d, J_{C-F} = 15.2 Hz), 128.3, 127.2, 124.0, 115.7 (d, J_{C-F} = 22.0), 47.4, 36.0, 29.6, -2.9, -3.0; HRMS (DART): Calcd for $C_{20}H_{23}FOSi$ [M+H$^+$]: 327.1580. Found: 327.1566; specific rotation: $[\alpha]_D^{20}$ -512.5 (c = 0.23, $CHCl_3$) for an enantiomerically enriched sample of 98:2 e.r. Enantiomeric purity (98:2) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.178	3867664	313287	49.912
2	6.681	3881377	288661	50.088
Total		7749041	601948	100.000



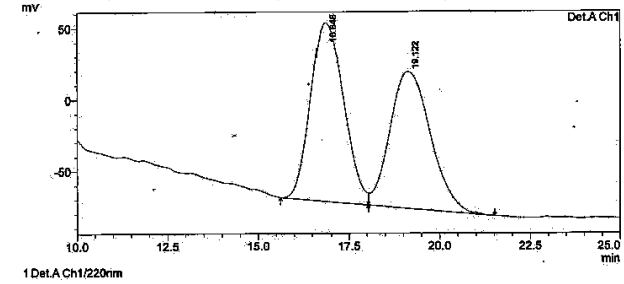
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	6.299	787536	54613	1.865
2	6.805	41433202	3094669	98.135
Total		42220738	3149283	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
6.178	3867664	49.912	6.299	787536	1.865
6.681	3881377	50.088	6.805	41433202	98.135

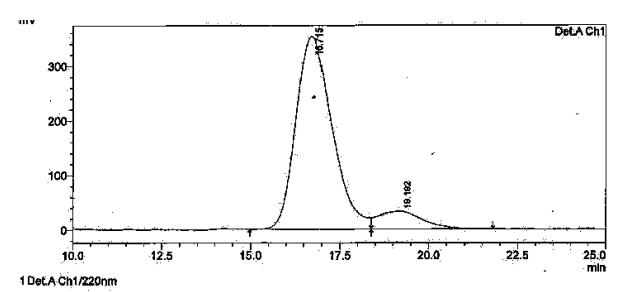
(R,E)-5-(dimethylsilyl)-6-phenyl-4-((E)-styryl)hex-5-en-2-one (4.70). IR (neat): 3059 (w), 3024 (w), 2957 (w), 2117 (w), 1713 (m), 1598 (w), 1492 (w), 1446 (w), 1418 (w), 1357 (w), 1249 (w), 1159 (w), 1071 (w), 1029 (w), 967 (w), 887 (s), 836 (m), 766 (m), 748 (w), 695 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.18 (10H, m), 6.96 (1H, s), 6.34 (1H, d, J = 16.4 Hz), 6.24 (1H, dd, J = 6.0, 16.0 Hz), 4.34–4.27 (1H, m), 2.82 (1H, dd, J = 8.4, 16.0 Hz), 2.70 (1H, dd, J = 6.8, 16.0 Hz), 2.03 (3H, s), 0.30 (3H, d, J = 3.2 Hz), 0.28 (3H, d, J = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 148.4, 143.4, 140.7, 137.9, 137.4, 131.8, 130.6, 128.7, 128.5, 128.5, 127.4, 127. 3, 126.3, 48.5, 40.2, -1.8, -2.5; HRMS (DART): Calcd for $C_{22}H_{26}OSi$ [M+H$^+$]: 335.1838. Found: 335.1831; specific rotation: $[\alpha]_D^{20}$ -6.1 (c = 1.63, $CHCl_3$) for an enantiomerically enriched sample of 90:10 e.r. Enantiomeric purity (90:10) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OJ-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	16.848	7898069	124709	51.409
2	19.122	7465054	95486	48.591
Total		15363122	220195	100.000



PeakTable

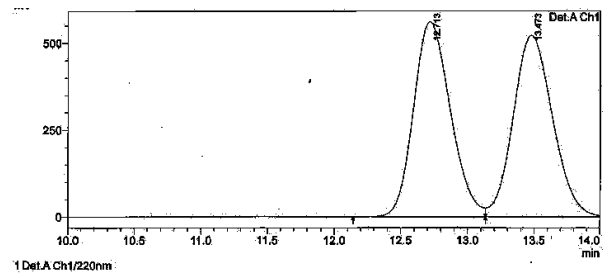
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	16.715	24641624	352345	89.681
2	19.192	2835277	32608	10.319
Total		27476901	384953	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
16.848	7898069	51.409	16.715	24641624	89.681
19.122	7465054	48.591	19.192	2835277	10.319

■ **Representative Procedure for the Synthesis of Silyl-Substituted-*Z*-Alkenylaluminum Reagents:** A flame-dried round bottom flask fitted with a reflux condenser was equipped with a stir bar and was charged with hexanes (1.1 mL) and thf (217 μL). Dibal-H (356 μL, 2.0 mmol) was added dropwise to the solution at 22 ºC. Dimethyl(phenylethynyl)silane (354 μL, 2.0 mmol) was then added dropwise and the resulting solution was allowed to warm to 55 ºC (oil bath) for 3 h and then cooled to 22 ºC, producing a solution of (Z)-(1-(dimethylsilyl)-2-phenylvinyl)diisobutylaluminum. The resulting solution was used without further purification.

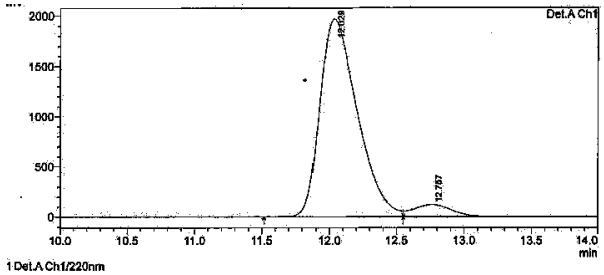
(R,Z)-5-(dimethylsilyl)-4,6-diphenylhex-5-en-2-one (4.53). IR (neat): 3025 (w), 2958 (w), 2900 (w), 2122 (w), 1716 (s), 1599 (w), 1492 (m), 1452 (w), 1444 (w), 1417 (w), 1355 (w), 1248 (m), 1072 (w), 1029 (w), 893 (s), 893 (m), 966 (m), 750 (s), 699 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.32 (1H, m), 7.32–7.31 (2H, m), 7.30–7.25 (5H, m), 7.25–7.19 (3H, m), 4.29–4.25 (1H, m), 4.02–3.98 (1H, m), 3.09 (1H, dd, *J* = 6.8 Hz, 15.6 Hz), 2.96 (1H, dd, 8.0, 16.0 Hz), 2.10 (3H, s), -0.07 (3H, d, *J* = 4.0 Hz), -0.23 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 144.1, 142.6, 141.0, 139.4, 128.6, 128.4, 128.4, 127.9, 127.1, 126.6, 49.2, 47.1, 30.8, -2.9, -3.1; HRMS (DART): Calcd for $C_{20}H_{25}OSi$ $[M+H^+]$: 309.1675. Found: 309.1689; specific rotation: $[\alpha]_D^{20}$ –22.5 (c 1.12, $CHCl_3$). Enantiomeric purity (94:6) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	12.713	10784635	560022	49.859
2	13.473	10845831	521340	50.141
Total		21630466	1081362	100.000



PeakTable

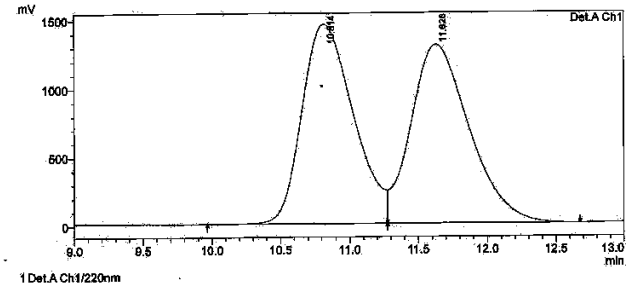
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	12.029	37941643	1968078	94.220
2	12.757	2327606	118757	5.780
Total		40269249	2086835	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
12.713	30784635	49.859	12.029	37941647	94.220
13.473	30845831	50.141	12.757	2327606	5.780

(R,Z)-5-(dimethylsilyl)-6-(4-methoxyphenyl)-4-phenylhex-5-en-2-one (4.54). IR (neat): 2956 (w), 2903 (w), 2129 (w), 1714 (s), 1607 (m), 1507 (s), 1452 (w), 1355 (w), 1287 (w), 1247 (s), 1174 (m), 1158 (w), 1033 (m), 891 (s), 837 (s), 763 (s), 701 (s), 542 (w), 525 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.32–7.14 (8H, m), 6.86–6.83 (2H, m), 4.27–4.24 (1H, m), 4.06–4.01 (1H, m), 3.81 (3H, s), 3.07 (1H, dd, *J* = 7.2, 15.6 Hz), 2.95 (1H, dd, *J* = 7.6, 15.6 Hz), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3, 158.7, 142.6, 142.4, 140.6, 131.7, 129.7, 128.2, 126.4, 113.1, 55.1, 49.1, 47.0, 30.6, -3.0, -3.2; HRMS (DART): Calcd for $C_{18}H_{19}O$ $[M+H^+]$: 339.1780. Found: 339.1791; specific rotation: $[\alpha]_D^{20}$ –20.1 (c = 1.69, $CHCl_3$) for an enantiomerically

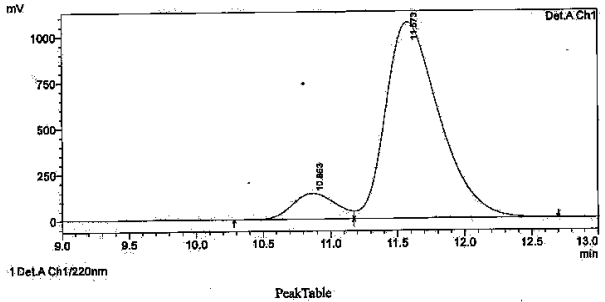
enriched sample of 90:10 e.r. Enantiomeric purity (90:10) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.814	37493431	1453109	49.506
2	11.626	38242338	1301815	50.494
Total		75735770	2754923	100.000



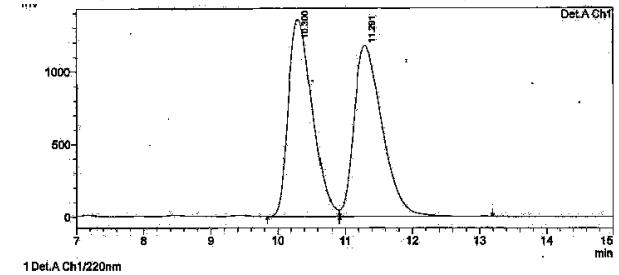
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.863	3126374	139925	9.602
2	11.573	29432758	1064664	90.398
Total		32559132	1204589	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
10.814	37493431	49.506	10.863	3126574	9.602
11.626	38242338	50.494	11.573	29432758	90.398

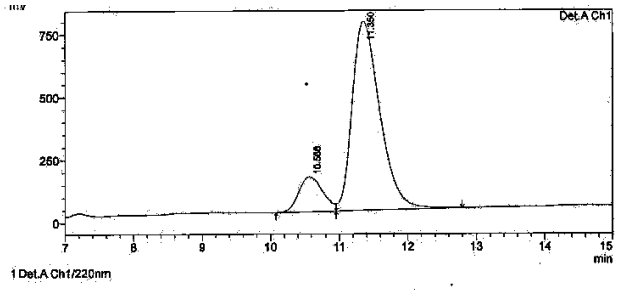
(R,Z)-5-(dimethylsilyl)-4-phenyl-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.55). IR (neat): 3027 (w), 2129 (w), 1717 (w), 1408 (w), 1356 (w), 1323 (s), 1252 (w), 1162 (m), 1123 (m), 1066 (m), 1018 (w), 883 (m), 837 (w), 168 (w), 701 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.56 (2H, d, J = 8.0 Hz), 7.33–7.29 (4H, m), 7.26–7.21 (4H, m), 4.31–4.27 (1H, m), 4.00–3.96 (1H, m), 3.08 (1H, dd, J = 6.8, 16.4 Hz), 2.97 (1H, dd, J = 8.0, 16.0 Hz), 2.10 (3H, s), -0.05 (3H, d, J = 4.0 Hz), -0.23 (3H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 145.8, 142.2, 141.3, 138.6, 128.3 (q, J_{C-F} = 31.9 Hz), 128.0, 127.7, 127.5, 126.0, 124.0 (app. d, J_{C-F} = 3.1 Hz), 123.3 (q, J_{C-F} = 270.2 Hz), 48.2, 46.2, 29.9, -3.8, -4.1; HRMS (DART): Calcd for $C_{21}H_{24}F_3OSi$ [M+H^+]: 377.1549. Found: 377.1566; specific rotation: $[\alpha]_D^{20}$ +4.9 (c = 1.64, $CHCl_3$) for an enantiomerically enriched sample of 86.5:13.5 e.r. Enantiomeric purity (86.5:13.5) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.300	33694498	1354038	49.640
2	11.291	34182683	1171964	50.360
Total		67877180	2526002	100.000



PeakTable

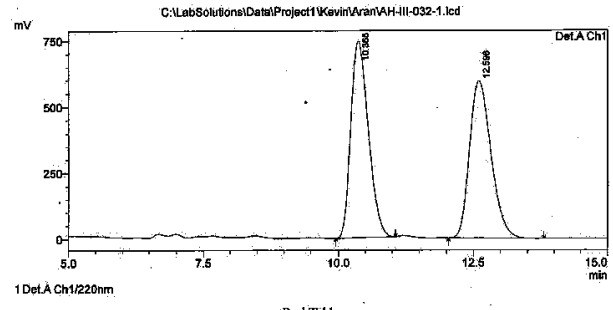
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.566	3308380	138463	13.486
2	11.350	21224363	750470	86.514
Total		24532742	888933	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area

10.300	33694498	49.640	10.566	3308380	13.486
11.291	34182683	50.360	11.350	21224363	86.514

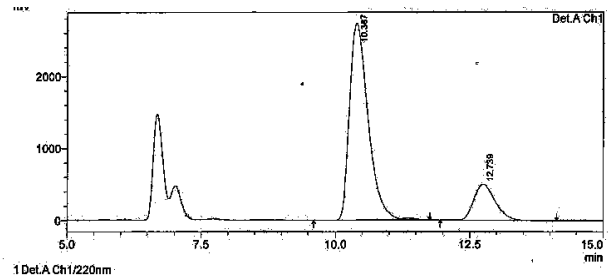
(R,Z)-5-(dimethylsilyl)-4-(4-methoxyphenyl)-6-phenylhex-5-en-2-one (4.56). IIR (neat): 2956 (w), 2160 (w), 1715 (m), 1609 (w), 1510 (s), 1492 (w), 1463 (w), 1443 (w), 1356 (w), 1302 (w), 1249 (s), 1177 (w), 1157 (w), 1035 (w), 893 (s), 834 (m), 771 (w), 754 (w), 700 (w), 549 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.16 (7H, m), 6.86–6.82 (3H, m), 4.23–4.19 (1H, m), 4.01–3.97 (1H, m), 3.80 (1H, s), 3.04 (1H, dd, *J* = 6.4, 15.6 Hz), 2.93 (1H, dd, *J* = 8.4, 15.6 Hz), 2.08 (3H, s), -0.07 (3H, d, *J* = 4.0 Hz), -0.22 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 158.4, 144.6, 140.7, 139.6, 134.7, 129.5, 128.7, 128.0, 127.2, 114.0, 55.4, 49.5, 46.6, 31.0, -2.7, -2.9; HRMS (DART): Calcd for $C_{21}H_{25}O_2Si$ [M+H$^+$]: 337.1624. Found: 337.1634; specific rotation: $[\alpha]_D^{20}$ -2.7 (c = 0.75, $CHCl_3$) for an enantiomerically enriched sample of 83:17 e.r. Enantiomeric purity (83:17) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.365	16883846	741107	50.670
2	12.596	16437997	593601	49.330
Total		33321443	1334709	100.000



PeakTable

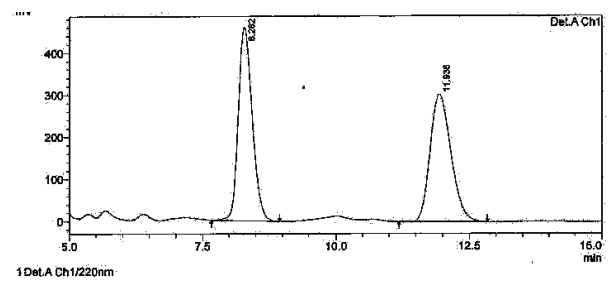
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.387	66530865	2731597	82.823
2	12.739	13798206	499624	17.177
Total		80329071	3231221	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
10.365	16883846	50.670	10.387	66530865	82.823
12.596	16437997	49.330	12.739	13798206	17.177

(R,Z)-5-(dimethylsilyl)-6-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.57). IR (neat): 2959 (w), 2124 (w), 1717 (m), 1617 (w), 1417 (w), 1358 (w), 1324 (s), 1250 (w) 1162 (m), 1120 (s), 1068 (s), 1017 (m), 893 (s), 837 (m), 770 (m), 751 (m), 699 (m) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.58–7.52 (3H, m), 7.40 (3H, d, *J* = 8.4 Hz), 7.34–7.26 (2H, m), 7.22–7.20 (2H, m), 4.36 (1H, app. t, *J* = 7.2 Hz), 4.02–3.99 (1H, m), 3.12 (1H, dd, *J* = 6.8, 16.8 Hz), 2.98 (1H, dd, *J* = 8.0, 16.0 Hz), 2.13 (3H, s), -0.07 (3H, d, *J* = 3.6 Hz), -0.20 (3H, d, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 147.2, 143.7, 142.2, 139.2, 128.9, 128.7, 128.6 (q, J_{C-F} = 32.7), 128.1, 128.0, 127.5, 125.5, 124.4 (q, J_{C-F} = 271.2 Hz), 49.0, 46.8, 30.9, -2.7, -3.0; HRMS (DART): Calcd for $C_{21}H_{24}F_3OSi$ [M+H$^+$]: 377.1549. Found: 377.1539; specific rotation: $[\alpha]_D^{20}$ –22.9 (c = 0.61, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r. Enantiomeric purity

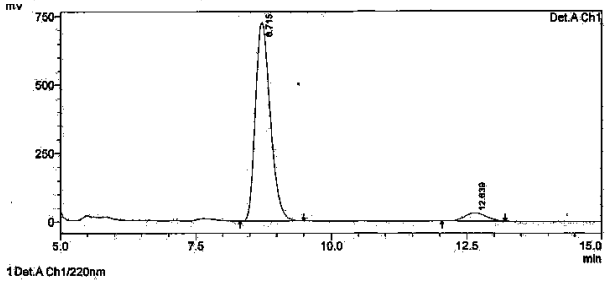
(95:5) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.282	8371787	459599	50.592
2	11.936	8175819	302105	49.408
Total		16547606	761704	100.000



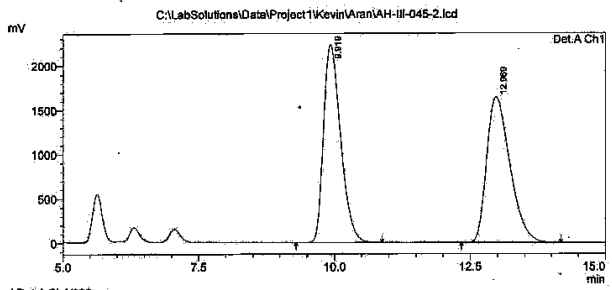
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.715	13917307	723062	94.711
2	12.639	777214	28716	5.289
Total		14694521	751777	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
8.282	8371787	50.592	8.715	13917307	94.711
11.936	8175819	49.408	12.639	777214	5.289

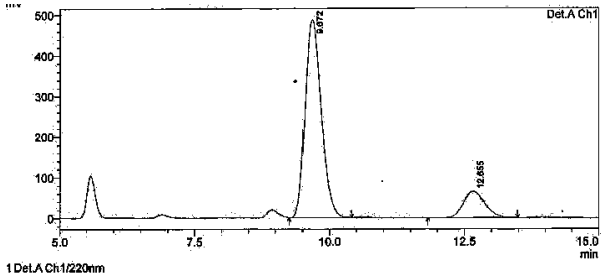
(R,Z)-4-(4-bromophenyl)-5-(dimethylsilyl)-6-phenylhex-5-en-2-one (4.58). IR (neat): 2956 (w), 2926 (w), 2901 (w), 2128 (w), 1717 (s), 1592 (w), 1573 (w), 1488 (m), 1443 (w), 1404 (w), 1303 (w), 1158 (w), 1072 (w), 1029 (m), 895 (s), 835 (m), 791 (m), 769 (m), 699 (m), 515 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.42 (2H, m), 7.33–19 (6H, m), 7.16–7.14 (2H, m), 4.26–4.22 (1H, m), 4.01–3.97 (1H m), 3.06 (1H, dd, J = 6.8, 16.4 Hz), 2.93 (1H, dd, J = 8.4, 16.4 Hz), 2.11 (3H, s), -0.08 (3H, d, J = 4.0 Hz), -0.20 (3H, d, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 143.9, 142.0, 141.7, 139.3, 131.7, 130.3, 128.7, 128.1, 127.4, 120.6, 49.1, 46.6, 31.0, -2.7, -2.9; HRMS (DART): Calcd for $C_{20}H_{24}BrOSi$ $[M+H^+]$: 387.0780. Found: 387.0770; specific rotation: $[\alpha]_D^{20}$ -6.0 (c = 0.67, $CHCl_3$) for an enantiomerically enriched sample of 85:15 e.r. Enantiomeric purity (85:15) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.919	49106995	2227994	50.104
2	12.969	48902242	1637281	49.896
Total		98009237	3865276	100.000



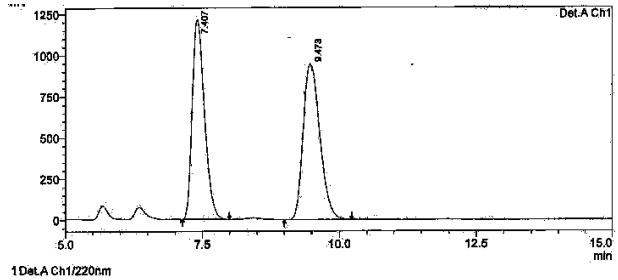
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.672	10034157	487382	84.886
2	12.655	1786589	64870	15.114
Total		11820747	552251	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
9.919	49106995	50.104	9.672	10034157	84.886
12.969	48902242	49.896	12.655	1786589	15.114

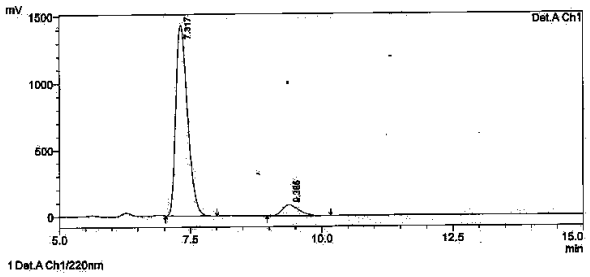
(R,Z)-5-(dimethylsilyl)-6-phenyl-4-(3-(trifluoromethyl)phenyl)hex-5-en-2-one (4.59). IR (neat): 2960 (w), 2924 (w), 2126 (w), 1718 (m), 594 (w), 1574 (w), 1492 (w), 1444 (w), 1419 (w), 1358 (w), 1329 (s), 1250 (w), 1163 (s), 1125 (s), 1096 (m), 895 (m),837 (w), 801 (w), 770 (w), 753 (w), 701 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53–7.41 (2H, m), 7.34–7.26 (7H, m), 7.24 (1H, d, J = 8.4 Hz), 4.36 (1H, app. t, J = 7.6 Hz), 4.00–3.96 (1H, m), 3.13 (1H, dd, J = 6.4, 16.4 Hz), 2.98 (1H, dd, J = 8.0, 16.8 Hz), 2.14 (3H, s), -0.91 (3H, d, J = 4.0 Hz), -0.23 (3H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 144.1, 143.7, 142.2, 139.2, 132.1, 130. 9 (q, J_{C-F} = 31.9 Hz), 129.0, 128.7, 128.1, 127.3 (q, J_{C-F} = 305.1 Hz), 127.5, 125.2 (app. d), 123.7 (app. d), 49.0, 46.8, 30.9, -2.8, -3.0; HRMS (DART): Calcd for $C_{21}H_{24}F_3OSi$ [M+H$^+$]: 377.1549. Found: 377.1561; specific rotation: $[\alpha]_D^{20}$ -8.5 (c = 1.41, $CHCl_3$) for an enantiomerically enriched sample of 93:7 e.r. Enantiomeric purity (93:7) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.407	19003959	1213407	49.524
2	9.473	19369592	942803	50.476
Total		38373550	2156210	100.000



PeakTable

Detector A Ch1 220nm

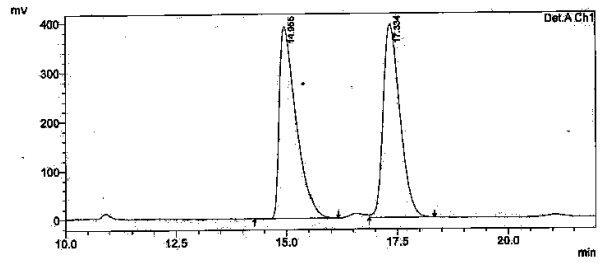
Peak#	Ret. Time	Area	Height	Area %
1	7.317	22334766	1429354	92.805
2	9.385	1731532	82360	7.195
Total		24066298	1511715	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
7.407	19003959	49.524	7.317	22334766	92.805
9.473	19369592	50.476	9.385	1731532	7.195

■ **Representative Procedure for the Ni-catalyzed Synthesis of *α*-Alkenylaluminum Reagents:** To a flame-dried test tube equipped with a stir bar was added Ni(dppp)Cl_2 (32.5 mg, 0.03 mmol). The test tube was sealed with a septa and purged under N_2 for 10 minutes. Then thf (1.3 mL) was added followed by dropwise addition of dibal-H (463 μL, 1.3 mmol) at 22 ºC, resulting in a black solution. The reaction mixture was then cooled to 0 ºC in an icebath and phenylacetylene (220 μL, 1.00 mmol) was added dropwise. The solution was allowed to warm to 22 ºC and stir for 2 h. The resulting solution was used without further purification.

(R)-4,5-diphenylhex-5-en-2-one (4.77). (neat): 3026 (w), 3922 (w), 1714 (s), 1625 (w), 1600 (w), 1492 (w), 1452 (w), 1443 (w), 1420 (w), 1355 (w), 1233 (w), 1158 (w), 1112 (w), 1027 (w), 903 (w), 777 (m), 753 (w), 698 (s), 556 (w), 518 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.30–7.27 (2H, m), 7.25–7.22 (6H, m), 7.21–7.20 (2H, m), 7.18–7.14 (1H, m), 5.35 (1H, s), 5.06 (1H,

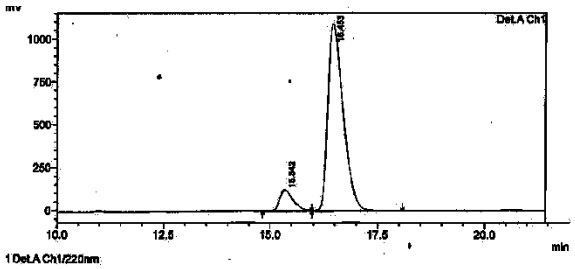
s), 4.48-4.45 (1H, m), 3.00 (1H, dd, *J* = 7.2, 16.8 Hz), 2.90 (1H, dd, *J* = 7.6, 16.4 Hz), 2.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 150.9, 142.0, 141.8, 128.5, 128.1, 128.0, 127.4, 126.8, 126.6, 113.2, 49.2, 45.4, 30.6; HRMS (DART): Calcd for $C_{18}H_{19}O$ [M+H$^+$]: 251.1436. Found: 251.1436; specific rotation: $[\alpha]_D^{20}$ -68.7 (c = 1.60, $CHCl_3$) for an enantiomerically enriched sample of 91:9 e.r. Enantiomeric purity (91:9) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	14.955	10340199	390051	49.820
2	17.334	10415116	393797	50.180
Total		20755315	783848	100.000



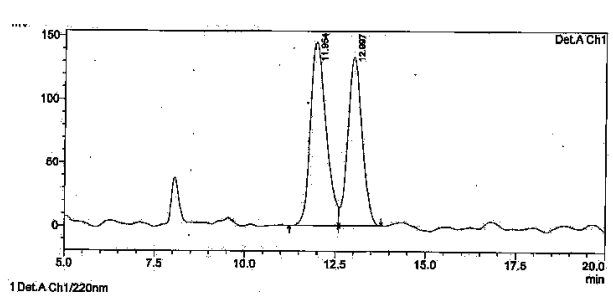
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	15.342	2702242	121841	8.957
2	16.453	27468267	1091390	91.043
Total		30170508	1213231	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
14.955	10340199	49.820	15.342	2702242	8.957
17.334	10415116	50.180	16.453	27468267	91.043

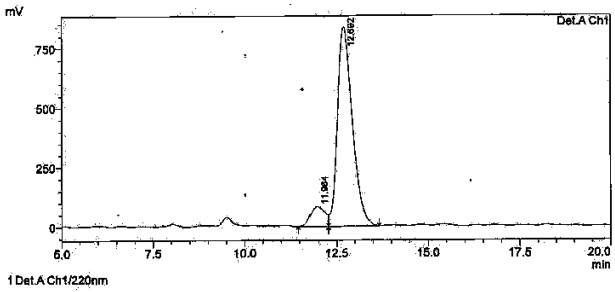
(R)-5-(4-methoxyphenyl)-4-phenylhex-5-en-2-one (4.78). IR (neat): 3086 (w), 3060 (w), 3029 (w), 3001 (w), 2957 (w), 2836 (w), 1714 (s), 1607 (m), 1511 (s), 1453 (w), 1356 (w), 1293 (w), 1248 (s), 1179 (m), 1159 (w), 1031 (m), 898 (w), 836 (m), 755 (m), 701 (m), 607 (w) cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.29-7.25 (6H, m), 7.21-7.16 (1H, m), 6.81-6.78 (2H, m), 5.35 (1H, s), 5.04 (1H, s), 4.50-4.46 (1H, m), 3.04 (1H, dd, *J* = 6.8, 16.8 Hz), 2.93 (1H, dd, *J* = 8.0,16.8 Hz), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 159.2, 150.3, 142.4, 134.3, 128.6, 128.1, 128.0, 126.7, 113.7,112.1, 55.4,49.4, 45.5, 30.8; HRMS (DART): Calcd for $C_{19}H_{21}O_2$ [M+H$^+$]: 281.1541. Found: 281.1531; specific rotation: $[\alpha]_D^{20}$ -84.2 (c = 1.40, $CHCl_3$) for an enantiomerically enriched sample of 91:9 e.r. Enantiomeric purity (91:9) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 96 % hexanes, 4 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	11.954	4201630	144208	53.304
2	12.997	3680746	132437	46.696
Total		7882375	276645	100.000



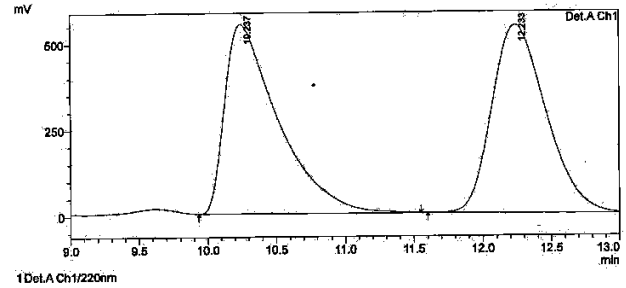
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	11.964	2268790	82902	8.644
2	12.692	23979377	836222	91.356
Total		26248166	919123	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
11.954	4201630	53.304	11.964	2268790	8.644
12.997	3680746	46.606	12.692	23979377	91.356

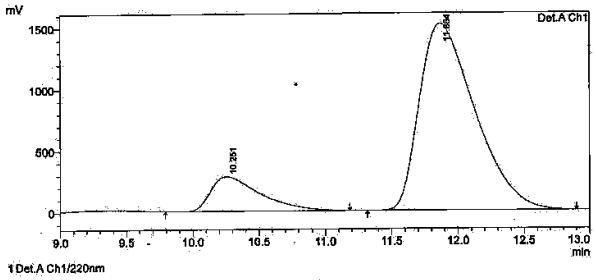
(R)-4-phenyl-5-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.79). IR (neat): 3061 (w), 3028 (w), 2928 (w), 1718 (m), 1616 (w), 1493 (w), 1453 (w), 1359 (w), 1325 (s), 1164 (m), 1129 (s), 1067 (m), 1016 (w), 911 (w), 849 (m), 754 (w), 700 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.28-7.16 (6H, m), 5.42 (1H, s), 5.21 (1H, s), 4.45 (1H, m), 3.06 (1H, dd, J = 7.6, 16.8 Hz), 2.93 (1H, dd, J = 7.6, 17.2 Hz), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 150.0, 145.6, 141.7, 129.6 (q, $J_{C\text{-}F}$ = 31.9 Hz), 128.8, 128.0, 127.3, 127.0, 125.3 (app. d, $J_{C–F}$ = 3.1 Hz), 124.3 (q, $J_{C–F}$ = 270.2 Hz), 114.7, 49.23, 45.4, 30.8, 29.9; HRMS (DART): Calcd for $C_{19}H_{18}F_3O$ $[M+H^+]$: 319.1310. Found: 319.1304; specific rotation: $[\alpha]_D^{20}$ -72.1 (c = 1.83, $CHCl_3$) for an enantiomerically enriched sample of 86:14 e.r. Enantiomeric purity (86:14) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 93 % hexanes, 7 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.237	14906960	549084	49.932
2	12.233	14947402	544410	50.068
Total		29854362	1093494	100.000



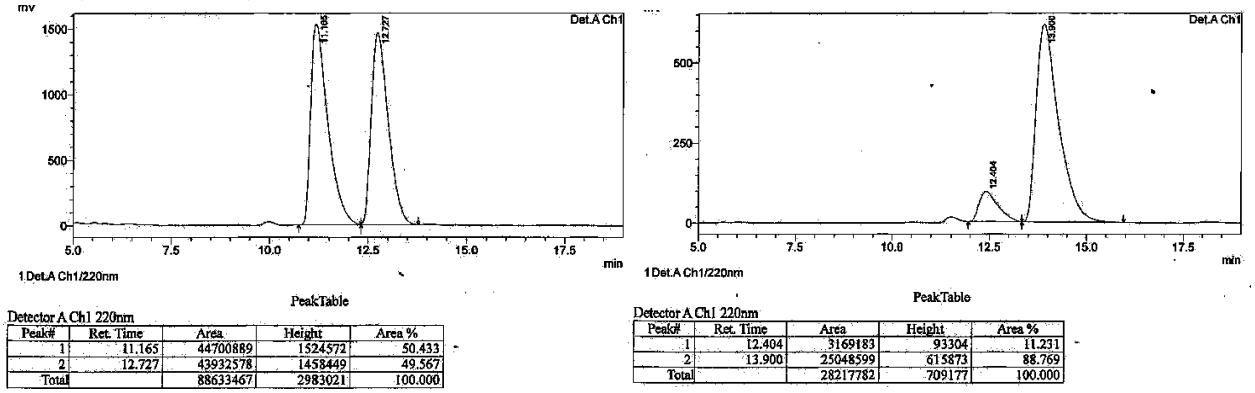
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.251	7330096	282427	14.274
2	11.864	44023506	1516829	85.726
Total		51353603	1799256	100.000

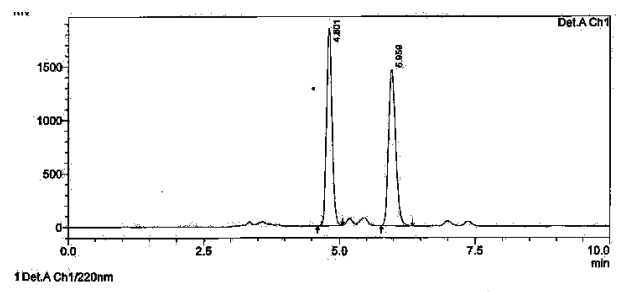
Retention Time	Area	% Area	Retention Time	Area	% Area
10.237	14906960	49.932	10.251	7330096	14.274
12.233	14947402	50.068	11.864	44023506	85.726

(R)-4-phenyl-5-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.80). IR (neat): 3063 (w), 3028 (w), 2922 (w), 1716 (m), 1491 (w), 1436 (w), 1357 (w), 1331 (s), 1257 (w), 1163 (s), 1123 (s), 1074 (m), 903 (w), 807 (w), 754 (w), 721 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, s), 7.46 (2H, d, *J* = 8.0 Hz), 7.35 (1H, t, *J* = 7.6 Hz), 7.28–7.15 (6H, m), 5.42 (1H, s), 5.20 (1H, s), 4.48–4.44 (1H, m), 3.06 (1H, dd, *J* = 7.6, 16.8 Hz), 2.94 (1H, dd, *J* = 7.2, 16.8 Hz), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 150.0, 142.7, 141.6, 130.3, 130.7 (q, J_{C-F} = 31.9 Hz), 128.8, 128.0, 127.0, 124.3 (app. d, J_{C-F} = 3.0 Hz), 124.0 (q, J_{C-F} = 271.0 Hz), 123.8 (app. d, J_{C-F} = 3.0 Hz), 114.4, 49.2, 45.4, 30.8; HRMS (DART): Calcd for $C_{19}H_{18}F_3O$ [M+H$^+$]: 319.1320. Found: 319.1315; specific rotation: $[\alpha]_D^{20}$ -86.5 (c = 0.63, $CHCl_3$) for an enantiomerically enriched sample of 89:11 e.r. Enantiomeric purity (89:11) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 93 % hexanes, 7 % *i*-PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	% Area	Retention Time	Area	% Area
11.165	44700889	50.433	12.404	3169183	11.231
12.727	43932578	49.567	13.900	25048599	88.769

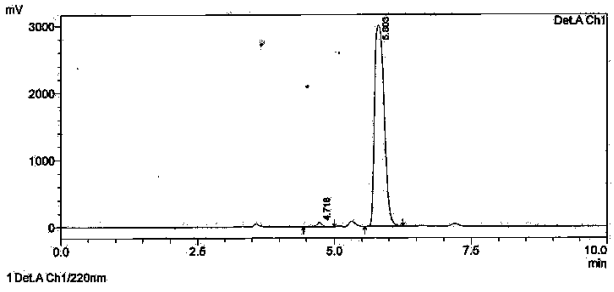
(R)-4-phenyl-5-(triisopropylsilyl)hex-5-en-2-one (4.81). IR (neat): 2943 (m), 2891 (w), 2865 (s), 1719 (s), 1463 (w), 1453 (w), 1384 (w), 1161 (w), 1016 (w), 924 (w), 882 (s), 753 (m), 700 (s), 676 (s) 639 (m), 545 (w), 511 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.29–7.17 (6H, m), 5.99 (1H, s), 5.60 (1H, s), 4.16–4.13 (1H, m), 2.98–2.86 (2H, m), 2.02 (3H, s), 1.17–1.06 (12H, m), 0.84 (9H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 149.4, 142.9, 128.7, 128.4, 127.6 126.6, 50.6, 45.4, 31.1, 18.9, 18.4, 11.3; HRMS (DART): Calcd for $C_{21}H_{35}OSi$ [M+H$^+$]: 331.2457. Found: 331.2448; specific rotation: $[\alpha]_D^{20}$ -149.8 (c = 0.52, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r. Enantiomeric purity (>99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	4.801	13120185	1847564	49.606
2	5.959	13328758	1457746	50.394
Total		26448943	3305310	100.000



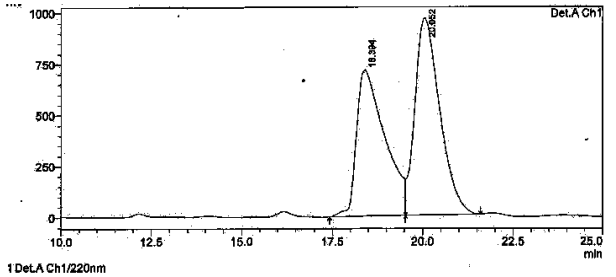
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	4.718	406731	62554	1.100
2	5.803	36574397	2989123	98.900
Total		36981128	3051677	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
4.801	13120185	49.606	4.718	406731	1.100
5.959	13328758	50.394	5.803	36574397	98.900

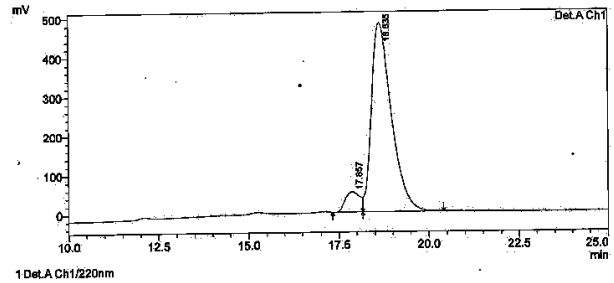
(R)-4-(4-methoxyphenyl)-5-phenylhex-5-en-2-one (4.82). IR (neat): 2955 (w), 2908 (w), 2835 (w), 1714 (s), 1609 (w), 1510 (s), 1494 (w), 1442 (w), 1356 (w), 1301 (w), 1248 (s), 1177 (m), 1158 (w), 1030 (m), 904 (w), 833 (m), 807 (w), 779 (m), 702 (s), 551 (w), 526 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.29 (2H, m), 7.27–7.21 (3H, m), 7.19–7.14 (2H, m), 6.80–6.78 (2H, m), 5.35 (1H, s), 5.07 (1H, s), 4.43 (1H, app. t, J = 7.2 Hz), 3.76 (3H, s), 2.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3, 158.3, 151.4, 142.0, 134.1, 129.1, 128.3, 127.5, 127.0, 114.0, 113.1, 55.3, 49.4, 44.8, 30.8; HRMS (DART): Calcd for $C_{19}H_{21}O_2$ [M+H$^+$]: 281.1542. Found: 281.1550; specific rotation: $[\alpha]_D^{20}$ -85.6 (c = 1.05, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r. Enantiomeric purity (97:3) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	18.394	38987656	712635	45.845
2	20.052	46054671	960923	54.155
Total		85042327	1673558	100.000



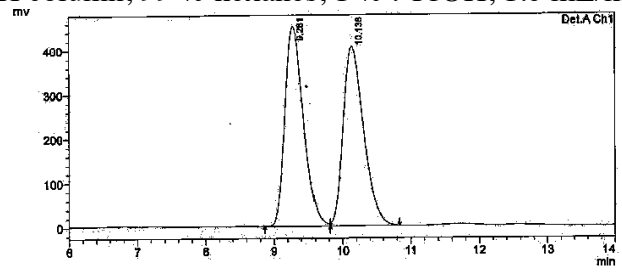
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	17.857	1457369	50504	7.311
2	18.635	18477257	481048	92.689
Total		19934625	531552	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
18.394	38987656	45.845	17.857	1457369	7.311
20.052	46054671	54.155	18.635	18477257	92.689

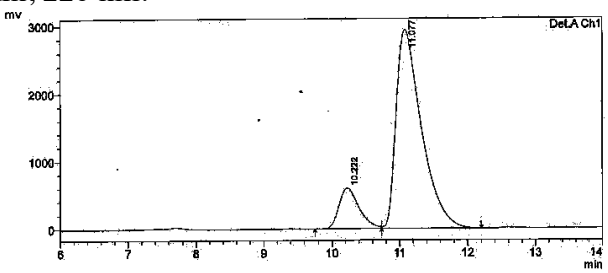
(R)-5-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.83). IR (neat): 3063 (w), 2919 (w), 1718 (m), 1617 (w), 1418 (w), 1357 (w), 1324 (s), 1162 (m), 1120 (m), 1018 (w), 906 (w), 843 (w), 779 (w), 705 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (2H, d, *J* = 6.0 Hz), 7.36 (2H, d, *J* = 6.8 Hz), 7.31–7.21 (6H, m), 5.41 (1H, s), 5.09 (1H, s), 4.48 (1H, app. t, *J* = 5.6 Hz), 3.07 (1H, dd, *J* = 4.8, 16.0 Hz), 2.93 (1H, dd, *J* = 6.0, 13.6 Hz), 2.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 150.5, 146.4, 141.4, 129.0 (q, J_{C-F} = 31.8 Hz), 128.5, 128.5, 127.8, 126.9, 124.2 (q, J_{C-F} = 271 Hz), 125.6 (q, J_{C-F} = 3.8 Hz), 113.9, 48.9, 45.1, 30.7; HRMS (DART): Calcd for $C_{19}H_{18}F_3O$ $[M+H^+]$: 319.1310. Found: 319.1305; specific rotation: $[\alpha]_D^{20}$ -53.1 (c = 1.92, $CHCl_3$) for an enantiomerically enriched sample of 86:14 e.r. Enantiomeric purity (86:14) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	9.281	8518874	450960	49.999
2	10.136	8519230	405188	50.001
Total		17038104	856148	100.000



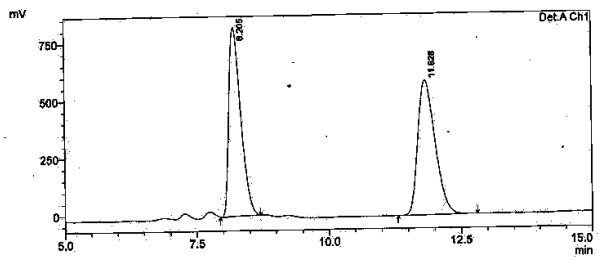
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.222	12510154	599427	14.112
2	11.077	76140590	2934769	85.888
Total		88650744	3534195	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
9.281	8518874	49.999	10.222	1251427	14.112
10.136	8519230	50.001	11.077	76140590	85.888

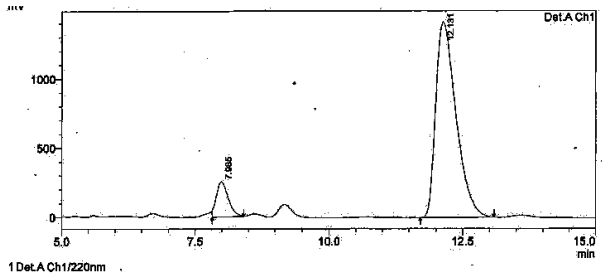
(R)-5-(cyclohex-1-en-1-yl)-4-phenylhex-5-en-2-one (4.84). IR (neat): 3027 (w), 2927 (s), 2858 (w), 2834 (w), 1716 (s), 1601 (w), 1493 (w), 1451 (w), 1433 (w), 1356 (m), 1158 (w), 894 (w), 851 (w), 751 (w), 701 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.15 (6H, m), 5.89 (1H, app. s), 5.18 (1H, s), 4.83 (1H, s), 4.33 (1H, app. t, *J* = 7.2 Hz), 2.95 (1H, dd, *J* = 7.2, 16.4 Hz), 2.84 (1H, dd, *J* = 8.0, 16.8 Hz), 2.06 (3H, s), 1.64–1.57 (2H, m), 1.52–1.46 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 150.9, 143.5, 136.1, 128.5, 127.8, 126.4, 125.6, 109.5, 50.1, 43.0, 30.7, 27.0, 25.9, 23.0, 22.2; HRMS (DART): Calcd for $C_{18}H_{23}O$ $[M+H^+]$: 255.1849. Found: 255.1742; specific rotation: $[\alpha]_D^{20}$ -86.9 (c = 1.10, $CHCl_3$) for an enantiomerically enriched sample of 90.5:9.5 e.r. Enantiomeric purity (90.5:9.5) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 0.4 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	8.205	12917061	824145	49.255
2	11.828	13307962	584483	50.745
Total		26225023	1408628	100.000



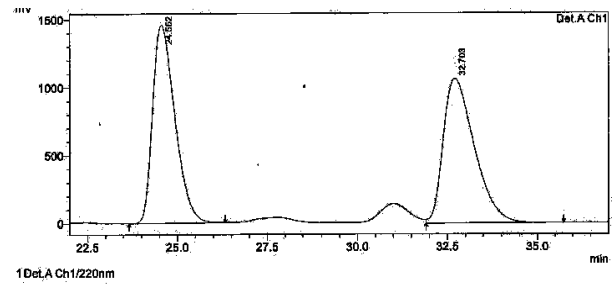
PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	7.985	3944367	254625	9.610
2	12.131	37101449	1412841	90.390
Total		41045816	1667466	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
8.205	12917061	49.255	7.985	3944367	9.610
11.828	13307962	50.745	12.131	37101449	90.390

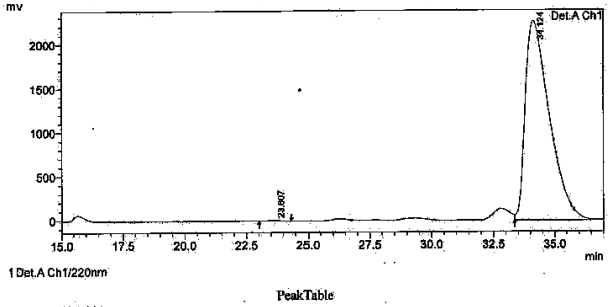
S-phenyl (R)-3,4-diphenylpent-4-enethioate (4.85). IR (neat): 3059 (w), 3027 (w), 2920 (w), 1703 (m), 1615 (m), 1576 (w), 1494 (w), 1478 (w), 1478 (w), 1441 (w), 1327 (w), 1031 (m), 1019 (m), 998 (m), 904 (w), 885 (w), 767 (m), 746 (s), 699 (s), 689 (s), 572 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.56 (1H, m), 7.51–7.49 (1H, m), 7.46–7.40 (2H, m), 7.38–7.35 (2H, m), 7.31–7.17 (10H, m), 5.44 (1H, s), 5.21 (1H, s), 4.57-4.53 (1H, app. t, J = 7.6 Hz), 3.27 (1H, dd, J = 7.2, 15.6 Hz), 313 (1H, dd, J = 7.6, 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 141.7, 130.9, 129.5, 129.4, 129.3, 129.2, 128.7, 128.3, 128.2, 127.6, 127.0, 127.0, 124.3, 113.9, 49.2, 46.7; HRMS (DART): Calcd for $C_{23}H_{21}OS$ $[M+H^+]$: 345.1313. Found: 345.1320; specific rotation: $[\alpha]_D^{20}$ -159.5 (c = 1.19, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r. Enantiomeric purity (>99:1) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 0.4 mL/min, 220 nm.



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	24.552	62690184	1457697	49.572
2	32.703	63773624	1062875	50.428
Total		126463808	2520572	100.000



PeakTable

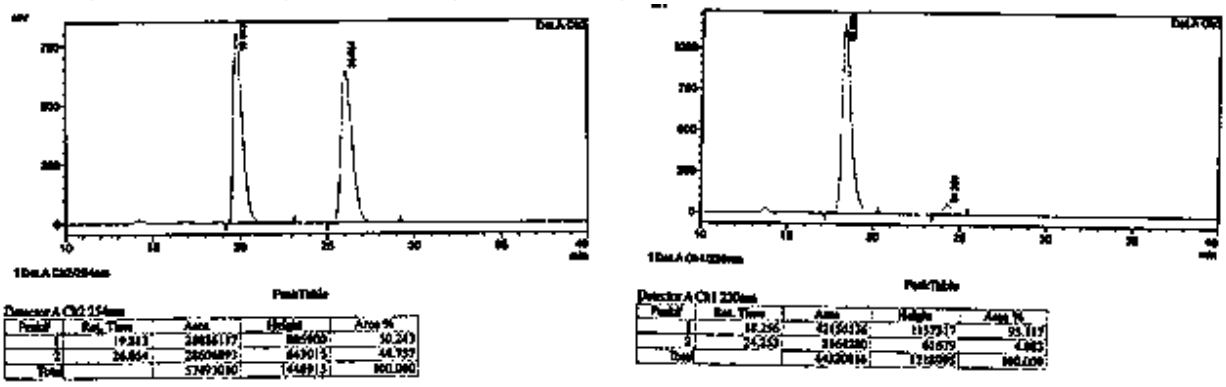
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	23.607	339887	9071	0.217
2	34.124	155962553	2261621	99.783
Total		156302439	2270692	100.000

Retention Time	Area	% Area	Retention Time	Area	% Area
24.552	62690184	49.572	23.607	339887	0.217
32.703	63773624	50.428	34.124	155962553	99.783

■ **Representative Procedure for the Ni-catalyzed Synthesis of *β*-Alkenylaluminum Reagents:** To a flame dried test tube equipped with a stir bar was added $Ni(PPh_3)_2Cl_2$ (39.2 mg, 0.03 mmol). The test tube was sealed with a septa and purged under N_2 for 10 minutes. Then thf (1.0 mL) was added followed by dropwise addition of dibal-H (463 μL, 1.3 mmol) at 22 ºC, resulting in a black solution. The reaction mixture was then cooled to 0 ºC in an icebath and phenylacetylene (220 μL, 1.00 mmol) was added dropwise. The solution was allowed to warm to 22 ºC and stir for 2 h. The resulting solution was used without further purification.

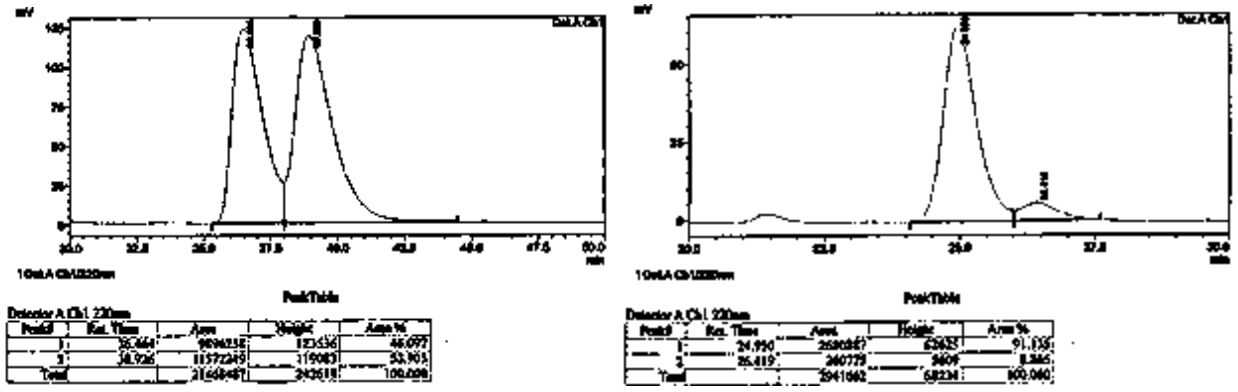
(S,E)-4,6-diphenylhex-5-en-2-one (4.38). IR (neat): 3082 (w), 3058 (w), 3026 (w), 2926 (w), 1714 (s), 1599 (w), 1493 (m), 1452 (w), 1357 (m), 1158 (m), 745 (s), 695 (s), 491 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.34–7.29 (5H, m), 7.28–7.24 (3H, m), 7.23–7.18 (2H, m), 6.39 (1H, d, *J* = 16.0 Hz), 6.32 (1H, dd, *J* = 6.4, 16.0 Hz), 4.114.06 (1H, m), 2.98 (1H, dd, *J* = 7.6, 16.4 Hz), 2.93 (1H, dd, *J* = 7.2, 16.4 Hz), 2.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 143.1, 137.2, 132.5, 130.2, 128.9, 128.6, 127.8, 127.5, 126.8, 126.4, 49.6, 44.1, 30.9; HRMS (DART): Calcd for $C_{18}H_{19}O$ $[M+H^+]$: 251.1436. Found: 251.1447; specific rotation: $[\alpha]_D^{20}$ -53.4 (c = 1.01, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r. Enantiomeric purity (95:5) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel AD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	% Area	Retention Time	Area	% Area
19.813	28886117	50.243	18.256	42156536	95.117
26.054	28606893	49.757	24.253	2164280	4.883

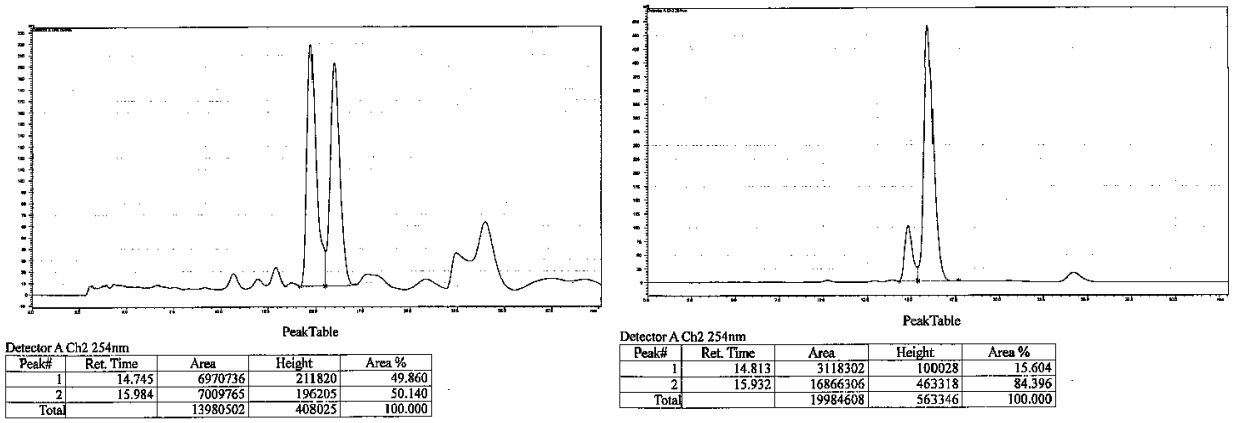
(S,E)-6-(4-methoxyphenyl)-4-phenylhex-5-en-2-one (4.71). IR (neat): 3001 (w), 2924 (m), 2854 (w), 1714 (m), 1606 (m), 1510 (s), 1453 (w), 1357 (w), 1298 (w), 1247 (s), 1175 (m), 1158 (w), 1031 (m), 967 (w), 829 (w), 757 (w), 701 (m), 525 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (2H, t, *J* = 15.6 Hz), 7.26–7.19 (6H, m), 6.81 (2H, d, *J* = 8.4 Hz), 6.32 (1H, d, *J* = 16.0 Hz), 6.18 (1H, dd, *J* = 7.6, 16.0 Hz), 4.05 (1H, dd, *J* = 6.8, 14.4 Hz), 3.78 (3H, s), 2.96 (1H, dd, *J* = 7.6, 16.4 Hz), 2.90 (1H, dd, *J* = 4.0, 13.6 Hz), 2.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 159.2, 143.3, 130.3, 130.0, 129.5, 128.8, 127.8, 127.5, 126.8, 114.0, 55.4, 49.7, 44.2, 30.9; HRMS (DART): Calcd for $C_{19}H_{21}O_2$ $[M+H^+]$: 281.1541. Found: 281.1538; specific

rotation: $[\alpha]_D^{20}$ -14.5 (c = 1.10, $CHCl_3$) for an enantiomerically enriched sample of 91:9 e.r. Enantiomeric purity (91:9) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel AD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	% Area	Retention Time	Area	% Area
36.464	9896238	46.097	24.950	2680887	91.135
38.926	11572249	53.903	26.419	260775	8.865

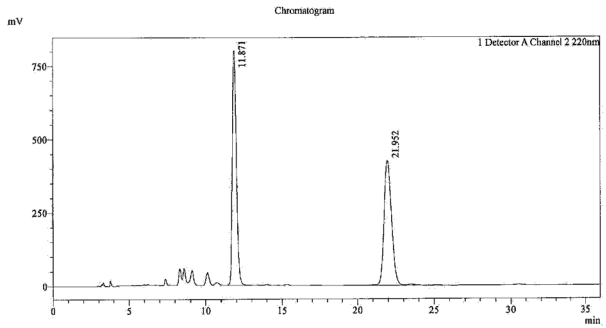
(S,E)-4-phenyl-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.72). IR (neat): 3030 (w), 2926 (w) 1718 (m), 1648 (w), 1494 (w), 1453 (w), 1414 (w), 1358 (w), 1324 (s), 1162 (m), 1120 (s), 1067 (s), 1016 (w), 969 (w), 953 (w), 849 (w), 830 (w), 760 (w), 700 (m), 544 (w) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.53–7.48 (2H, m), 7.41 (2H, d, *J* = 8.4 Hz), 7.36–7.32 (2H, m), 7.27–7.18 (3H, m), 6.47–6.37 (2H, m), 4.46 (1H, app. t, *J* = 7.2 Hz), 4.14–4.09 (1H, m), 3.09–2.90 (2H, m), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 143.6, 140.7, 135.3, 129.3 (q, J_{C-F} = 31.9 Hz), 129.0, 127.8, 127.0, 126.5, 126.5 (q, J_{C-F} = 231.5 Hz), 125.6 (app. d, J_{C-F} = 3.8 Hz), 49.3, 44.0, 30.9; HRMS (DART): Calcd for $C_{19}H_{18}F_3O$ $[M+H^+]$: 319.1310. Found: 319.1316; specific rotation: $[\alpha]_D^{20}$ -27.2 (c = 1.54, $CHCl_3$) for an enantiomerically enriched sample of 84:16 e.r. Enantiomeric purity (84:16) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Retention Time	Area	% Area	Retention Time	Area	% Area
14.745	6970736	49.860	14.813	3118302	15.604

15.984	7009765	50.140	15.943	16866306	84.396

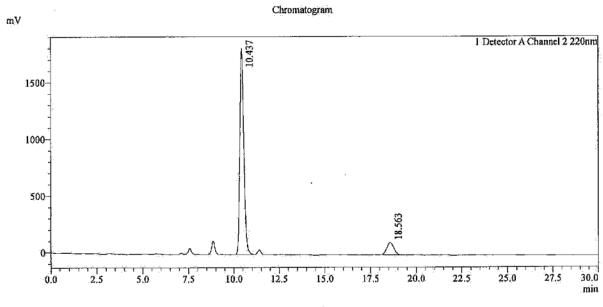
(*S*,*E*)-6-phenyl-4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (4.74). IR (neat) 3027 (w), 2923 (w), 2854 (w), 1717 (w), 1618 (w), 1495 (w), 1448 (w), 1418 (w), 1360 (w), 1324 (s), 1240 (w), 1162 (m), 1114 (s), 1068 (m), 1017 (w), 966 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 8.0 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.35–7.27 (5H, m) 7.24–7.19 (m, 1H), 6.39 (d, 2H, J = 16.4 Hz), 6.28 (dd, 1H, J = 6.8, 16.0 Hz), 4.18 (q, 1H, J = 7.2 Hz), 3.01 (dd, 1H, J = 7.2, 16.8 Hz), 2.95 (dd, 1H, J = 6.8, 16.8 Hz), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 147.3, 136.9, 131.4, 130.9, 129.1 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.7, 128.2, 127.7, 126.4, 125.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.3 (q, $J_{C\text{-}F}$ = 270.2 Hz), 49.2, 43.7, 30.9; HRMS (DART): Calcd for $C_{19}H_{18}F_3O$ [M+H$^+$]: 319.1310. Found: 319.1309. Specific rotation $[\alpha]^{20}$ –18.2 (*c* 1.92, $CHCl_3$) for a sample of 90:10 er. Enantiomeric purity (90:10) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time	Peak Start	Peak End	Area	Area%
1	11.871	11.225	13.350	14324818	49.501
2	21.952	19.292	25.992	14613859	50.499
Total				28938678	100.000



Peak Table

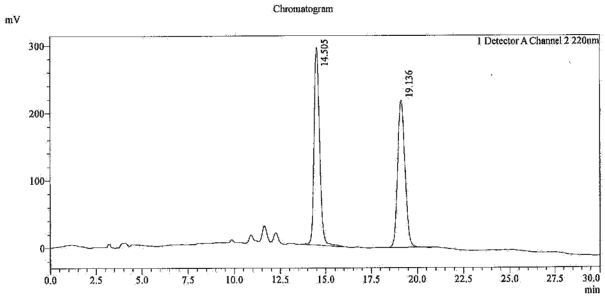
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	10.437	28903051	1819580	90.384
2	18.563	3075123	110489	9.616
Total		31978173	1930069	

Retention Time	Area	% Area	Retention Time	Area	% Area
11.871	14324818	49.501	10.437	28903051	90.384
21.952	14613859	50.499	18.563	3075123	9.616

(*S*,*E*)-4-(4-methoxyphenyl)-6-phenylhex-5-en-2-one (4.73). IR (neat) 3028 (w), 3003 (w), 2956 (w), 2936 (w), 2907 (w), 2836 (w), 1715 (m), 1610 (w), 1583 (w), 1511 (s), 1463 (w), 1448 (w), 1421 (w), 1359 (w), 1302 (w), 1248 (s), 1178 (w), 1158 (w), 1112 (w), 1033 (w), 1033 (w), 967 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 3H), 7.27–7.26 (m, 2H), 7.21–7.17 (m, 3H), 6.88–6.85 (m, 2H), 6.38–6.28 (m, 2H), 4.04 (q, 1H, J = 7.2 Hz), 3.80 (s, 3H), 2.95 (dd, 1H, J = 7.2, 16.0 Hz), 2.89 (dd, 1H, J = 7.2, 16.0 Hz), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 158.4, 137.3, 135.1, 132.8, 129.8, 128.7, 128.6, 127.4, 126.3, 114.2, 55.4, 49.7, 43.3, 30.9; HRMS (DART): Calcd for $C_{19}H_{21}O_2$ [M+H$^+$]: 281.1542. Found: 281.1536. Specific rotation $[\alpha]^{20}$ –38.6 (*c* 0.97, $CHCl_3$) for a sample of 91:9 er. Enantiomeric purity (91:9) was determined

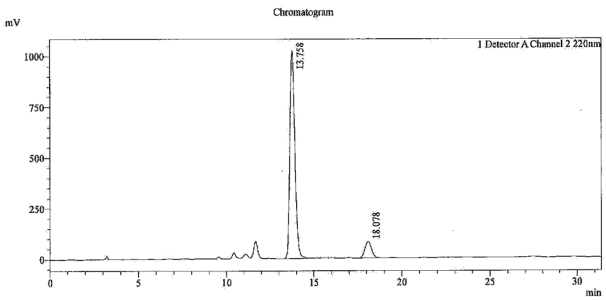
by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	14.505	6283931	293208	50.675
2	19.136	6116427	218633	49.325
Total		12400358	511841	



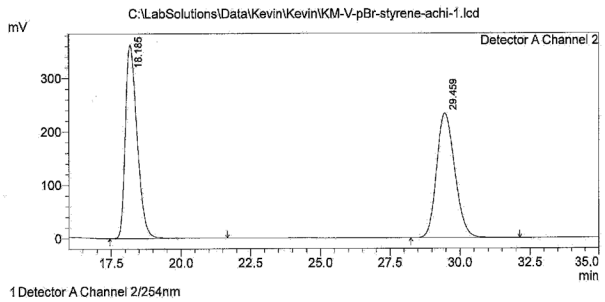
Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	13.758	20650282	1023656	90.746
2	18.078	2105801	80336	9.254
Total		22756083	1103992	

Retention Time	Area	% Area	Retention Time	Area	% Area
14.505	6283931	50.675	13.758	20650282	90.746
19.136	6116427	49.325	18.078	2105801	9.254

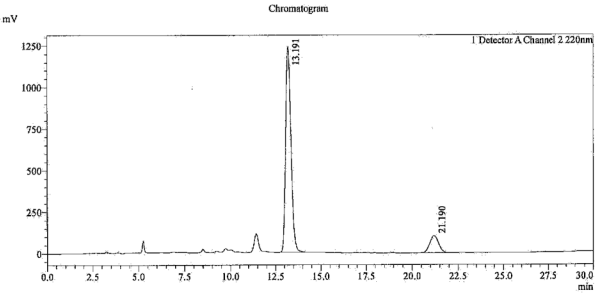
(*S*,*E*)-4-(4-bromophenyl)-6-phenylhex-5-en-2-one (4.75). IR (neat) 3057 (w), 3026 (w), 2922 (w), 1715 (s), 1598 (w), 1487 (m), 1447 (w), 1405 (w), 1358 (w), 1308 (w), 1231 (w), 1179 (w), 1158 (w), 1106 (w), 1072 (m), 1009 (w), 966 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.33–7.25 (m, 5H), 7.24–7.19 (m, 1H), 7.16–7.13 (m, 2H), 6.36 (d, 1H, *J* = 16.0 Hz), 6.27 (dd, 1H, *J* = 6.8, 15.6 Hz), 4.06 (q, 1H, *J* = 6.8 Hz), 2.96 (dd, 1H, *J* = 6.8, 16.4 Hz), 2.89 (dd, 1H, *J* = 6.8, 16.4 Hz), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 142.1, 137.0, 131.9, 131.8, 130.5, 129.6, 128.7, 127.6, 126.4, 49.3, 43.4, 30.9; HRMS (DART): Calcd for $C_{18}H_{18}BrO$ [M+H$^+$]: 329.0541. Found: 329.0538. Specific rotation $[\alpha]^{20}$ –25.0 (*c* 0.50, $CHCl_3$) for a sample of 87:13 er. Enantiomeric purity (87:13) was determined by HPLC analysis in comparison with authentic racemic material. Chiracel OD-H column, 99 % hexanes, 1 % *i*-PrOH, 1.0 mL/min, 220 nm.



PeakTable

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Area %
1	18.185	10578806	362775	50.033
2	29.459	10564728	233638	49.967
Total		21143534	596413	100.000



Peak Table

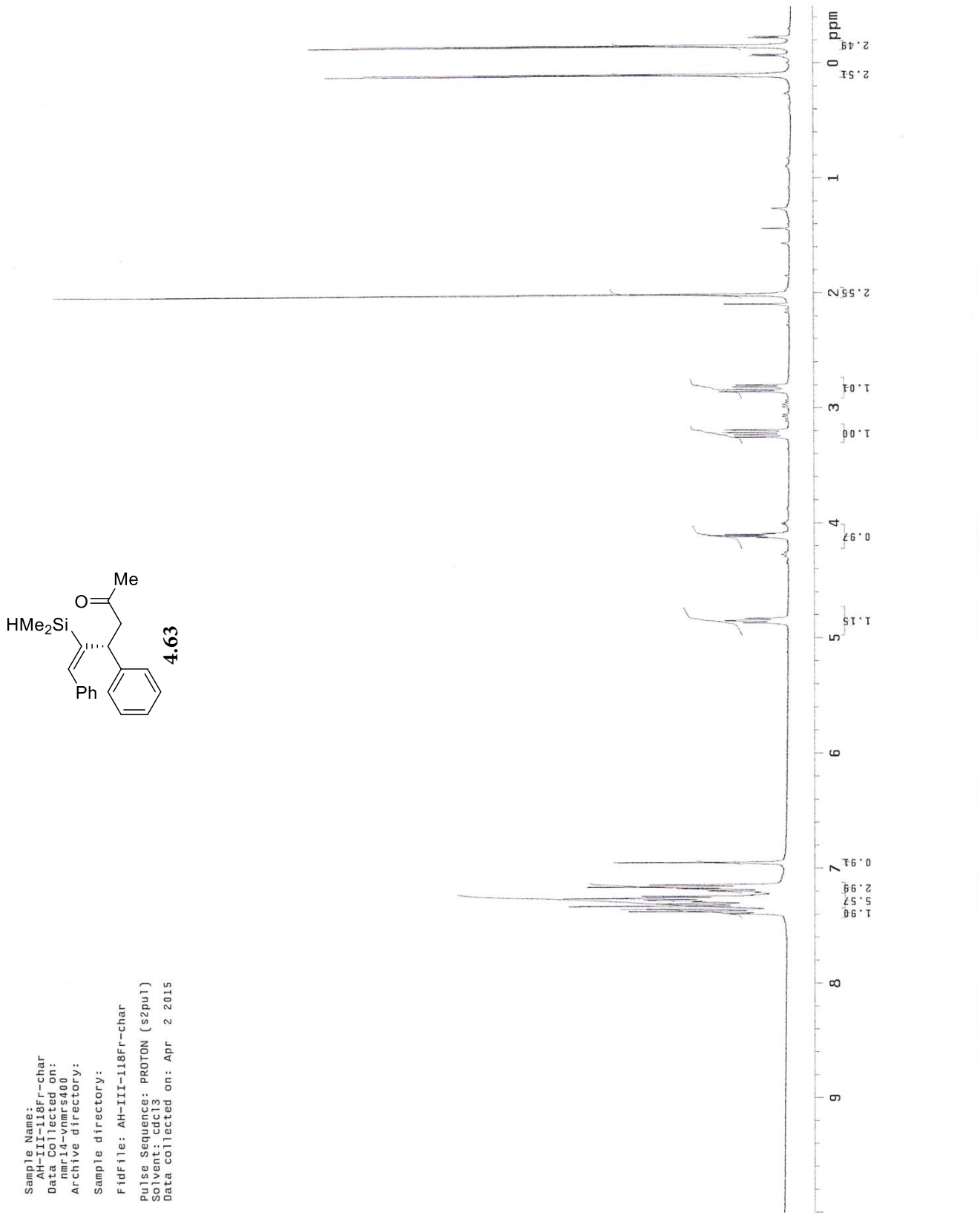
Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	13.191	25412951	1237298	87.937
2	21.190	3486252	103598	12.063
Total		28899203	1340896	

Retention Time	Area	% Area	Retention Time	Area	% Area
18.185	10578806	50.033	13.191	1237298	87.937
29.459	10564728	49.967	21.190	103598	12.063

■ **Representative Procedure for Hydride Transfer Under Protodesilylation Conditions:** To a 1 dram vial containing a solution of conjugate addition product, **2.25**, (68.4 mg, 0.22 mmol) in $CHCl_3$ (1.7 mL) at 0 ºC was added trifluoroacetic acid (1.18 mL, 0.06 M). The reaction was allowed to stir for 1 minute after which it was diluted with Et_2O and quenched by addition of a saturated solution of $NaHCO_3$ until pH was neutral. The aqueous layer was washed with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil, which was purified by silica gel chromatography (100% hexanes → 20:1 hexanes:Et_2O → 9:1 hexanes:Et_2O) to produce a clear oil (50.0 mg, 0.16 mmol, 73%).

(4R,6S)-3-((E)-benzylidene)-2,2,6-trimethyl-4-phenyl-1,2-oxasilinane (4.86). IR (neat): 3059 (w), 3025 (w), 2966 (w), 2930 (w), 2908 (w), 2871 (w), 1598 (w), 1493 (w), 1445 (w), 1374 (w), 1251 (m), 1120 (m), 1074 (w), 1045 (m), 1031 (w), 975 (s), 867 (w), 826 (s), 781 (s), 760 (m), 745 (w), 698 (s), 685 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.33 (4H, m), 7.26–7.11 (6H, m), 6.93 (1H, s), 4.39 (1H, app. s), 3.96–3.92 (1H, m), 2.19–2.14 (1H, m), 1.92–1.85 (1H, m), 1.16 (3H, d, *J* = 6.0 Hz), 0.40 (3H, s), 0.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 128.9, 128.7, 128.3, 128.2, 127.3, 126.3, 65.8, 43.8, 43.1, 25.1, 1.7, 1.6; HRMS (DART): Calcd for $C_{20}H_{25}OSi$ [$M+H^+$]: 309.1675. Found: 309.1686; specific rotation: $[\alpha]_D^{20}$ -35.7 (c = 0.56, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r. Diasteriomeric purity (>98:2) and relative stereochemistry were determined by ^1H NMR and NOESY NMR.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Ph
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Archive directory:
Sample directory:
FidFile: AH-III-118Fr-char
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015
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1.00
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1.15
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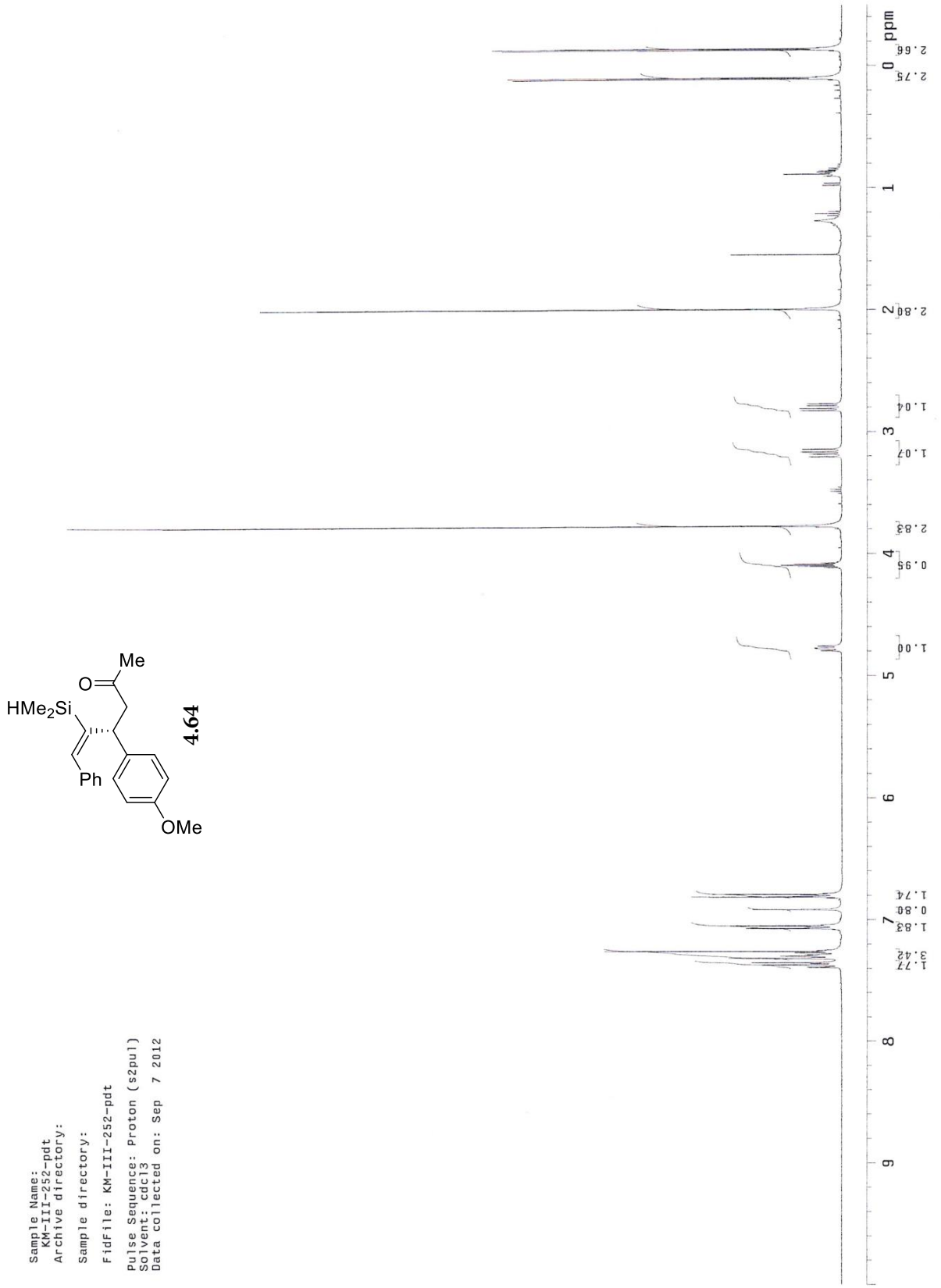
2.99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Ph
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Solvent: cdcl3
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1.74
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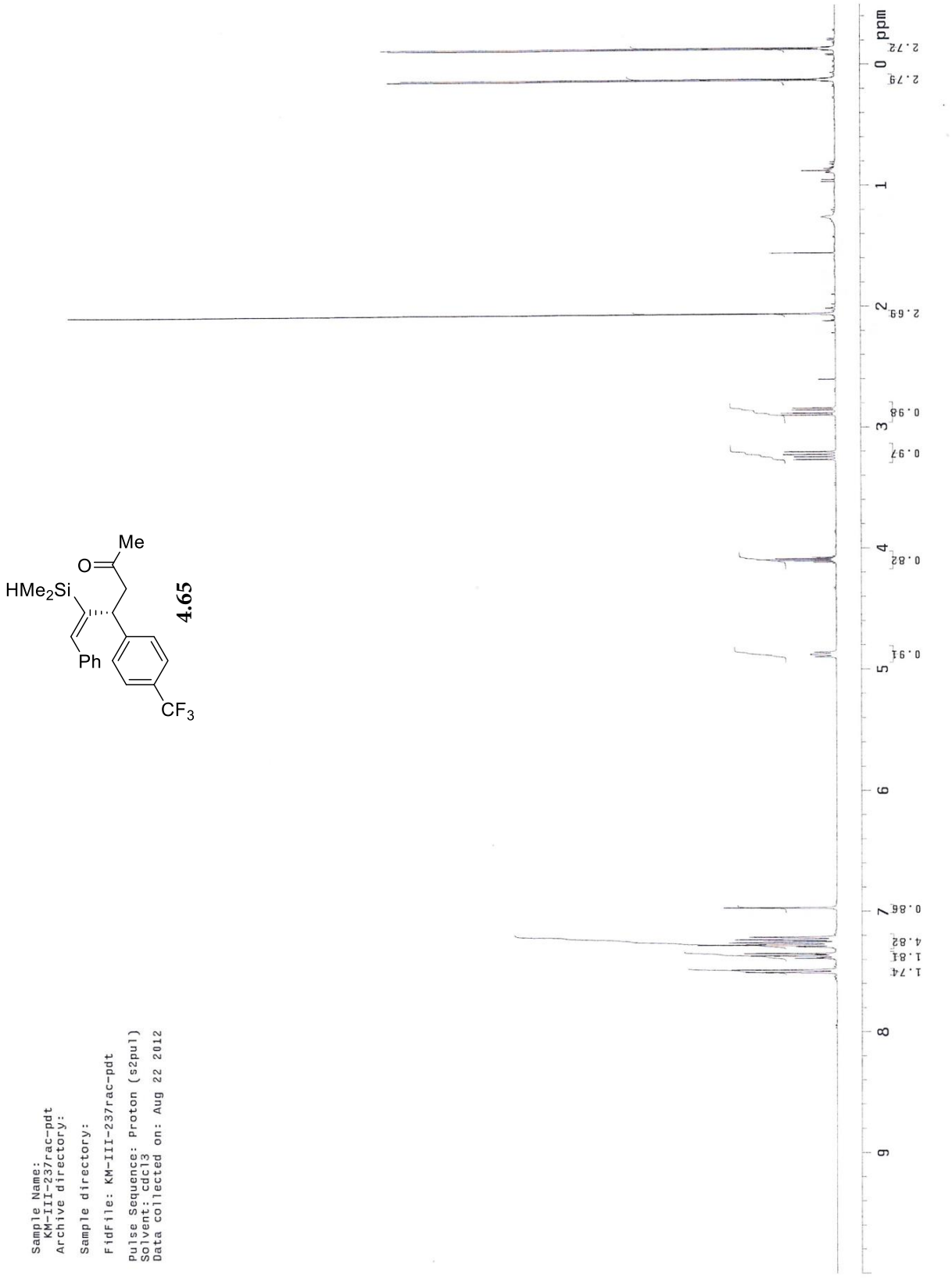
1.83
3.42
1.77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Ph
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ppm
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0.97
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0.86
4.82
1.81
1.74
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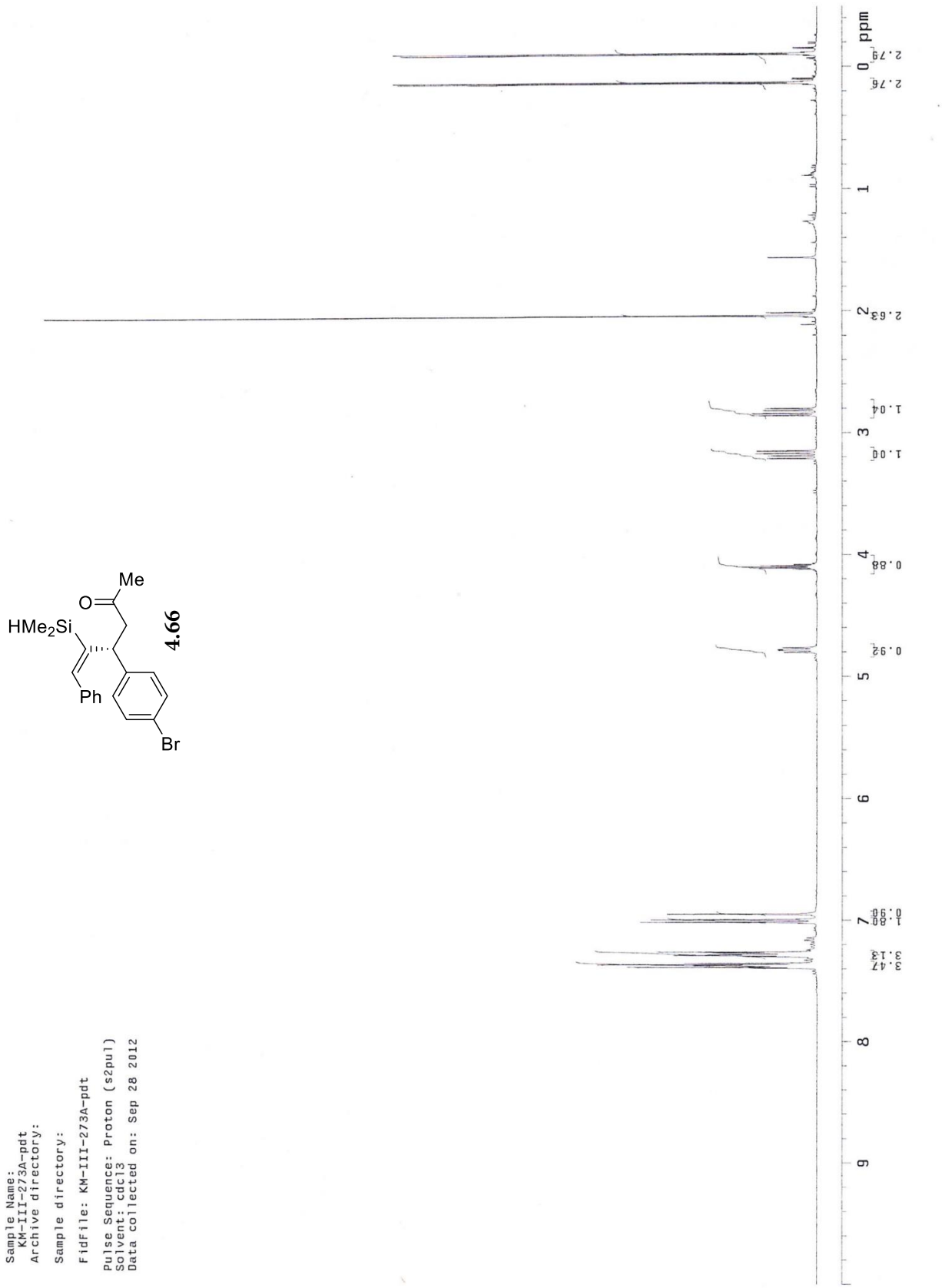
Data collected on: Aug 22 2012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O
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Ph
Br
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ppm
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2.63
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1.00
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1.80
0.98
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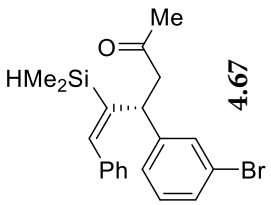

4.67


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File: exp

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 Solvent: cdcl3
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Operator: ahh
VNMRS-500  "nmr15"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 8012.8 Hz
 24 repetitions
OBSERVE H1, 499.8808018 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 3 min, 21 sec
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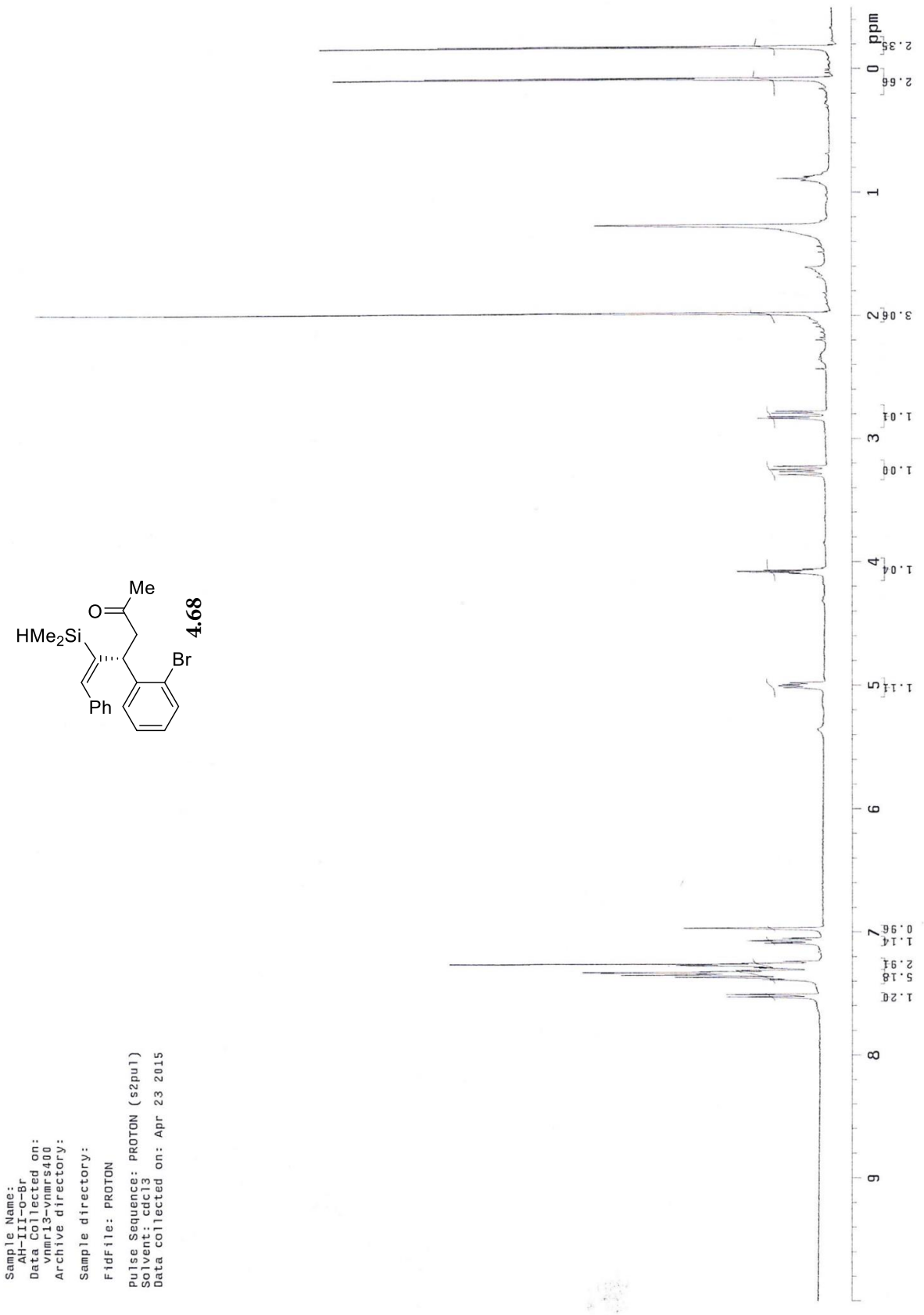
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Br
Ph
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ppm
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1.04
1.11
0.96
1.14
2.91
5.18
1.20
Sample Name:
AH-III-o-Br
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
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Pulse Sequence: PROTON (s2pul)
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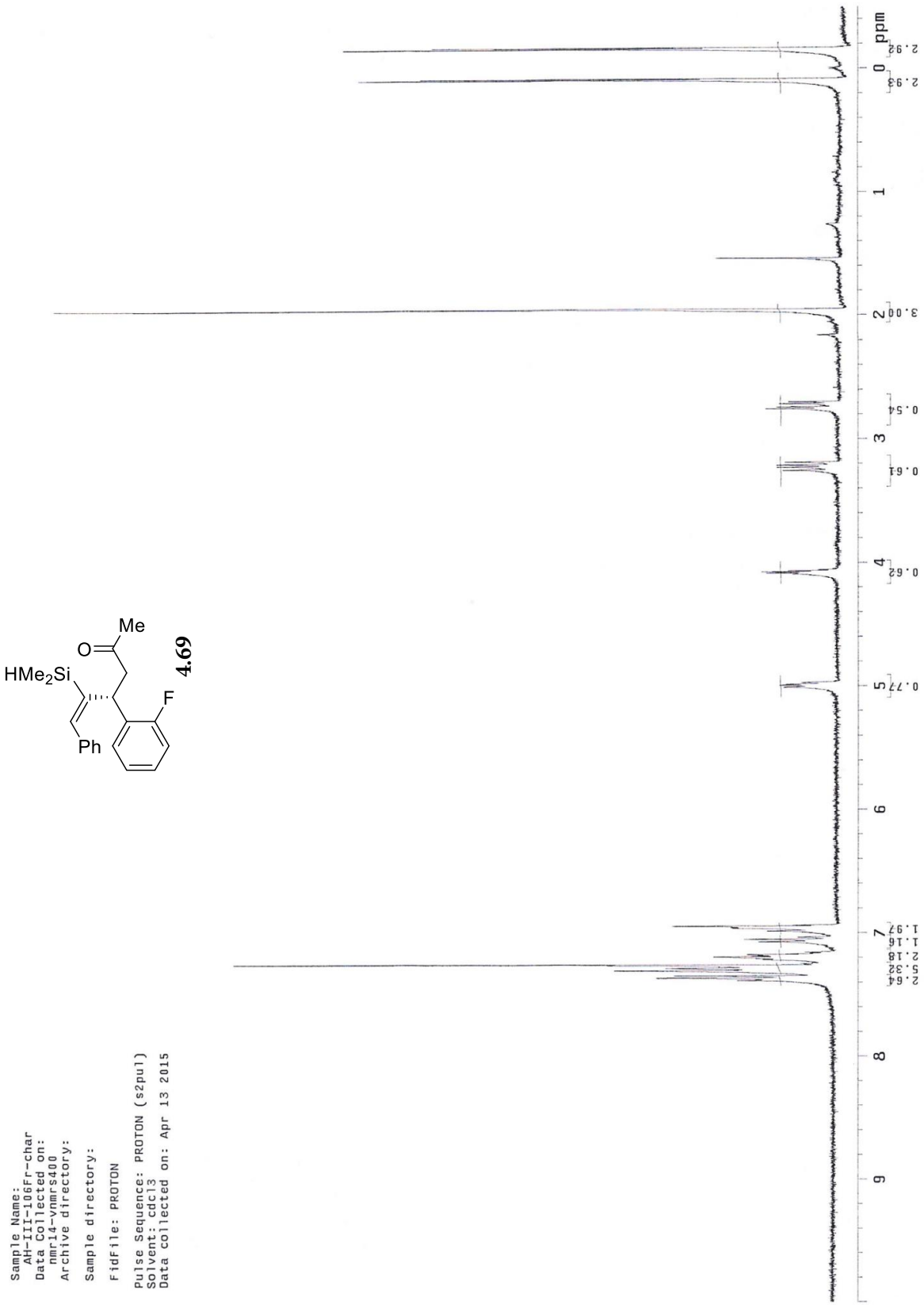
Data collected on: Apr 23 2015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Ph
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Archive directory:
Sample directory:
Fidfile: PROTON
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Solvent: cdcl3
Data collected on: Apr 13 2015
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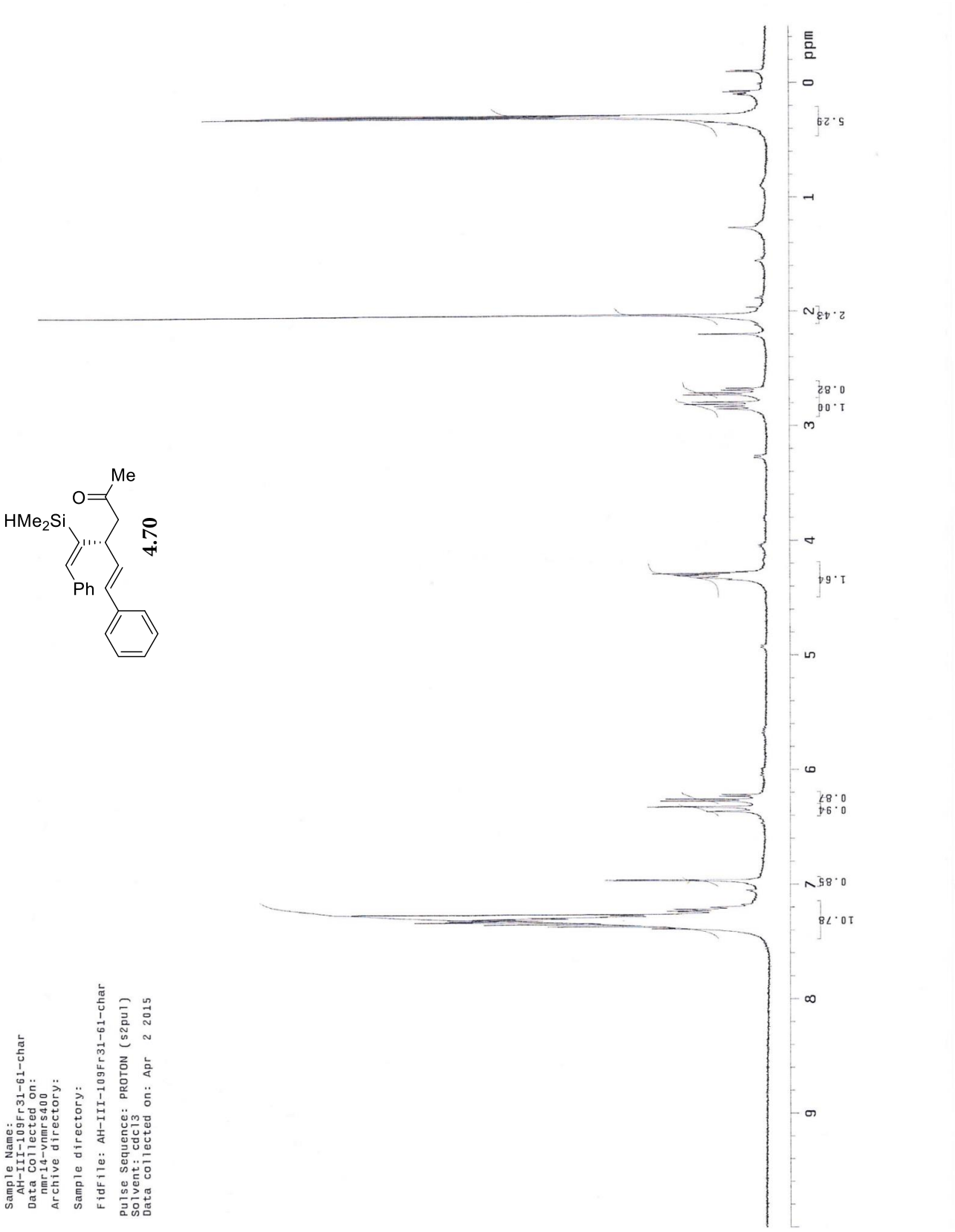
2.18
5.32
2.64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Archive directory:
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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015
ppm
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4
5
6
7
8
9
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1.00
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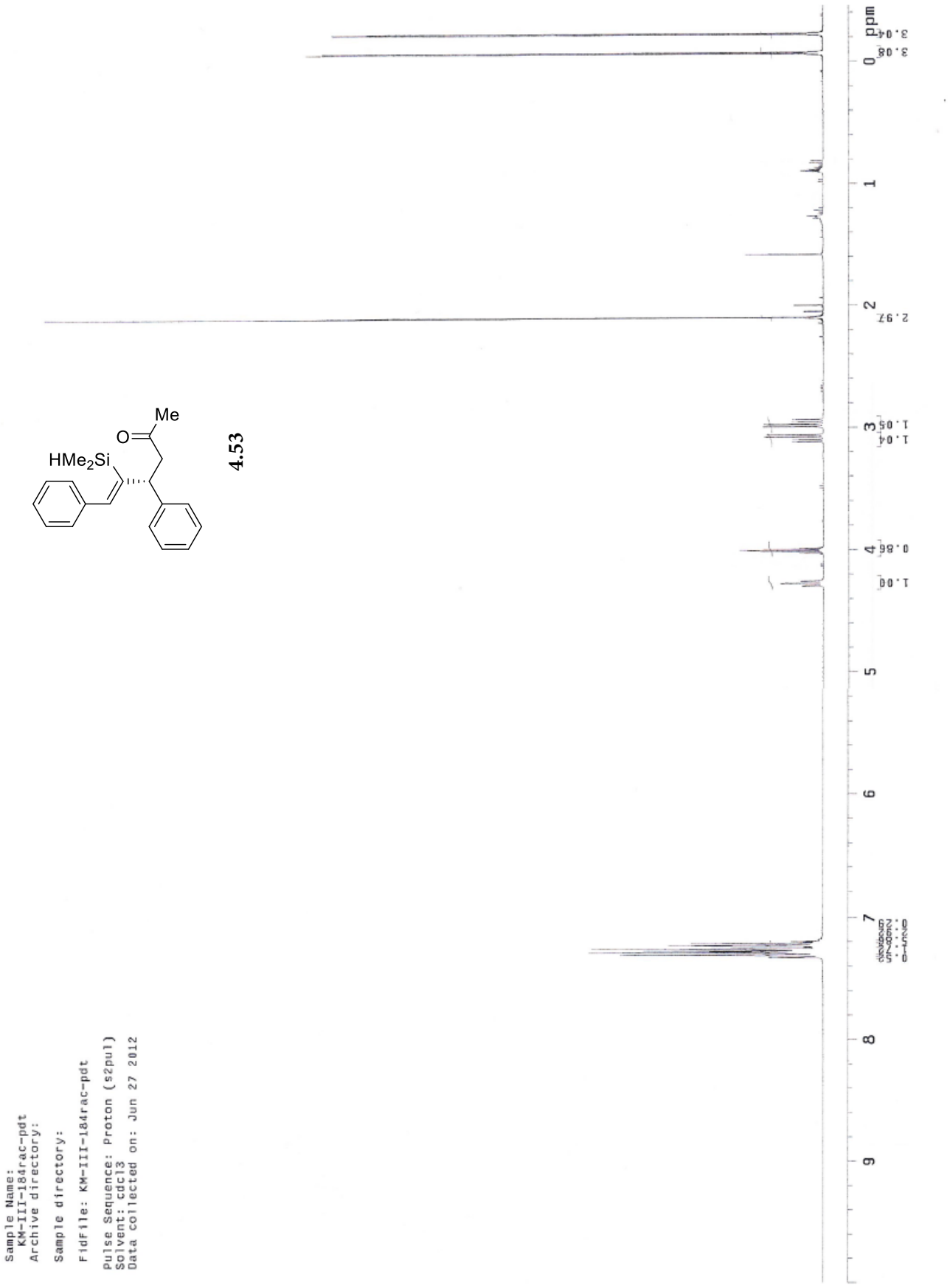
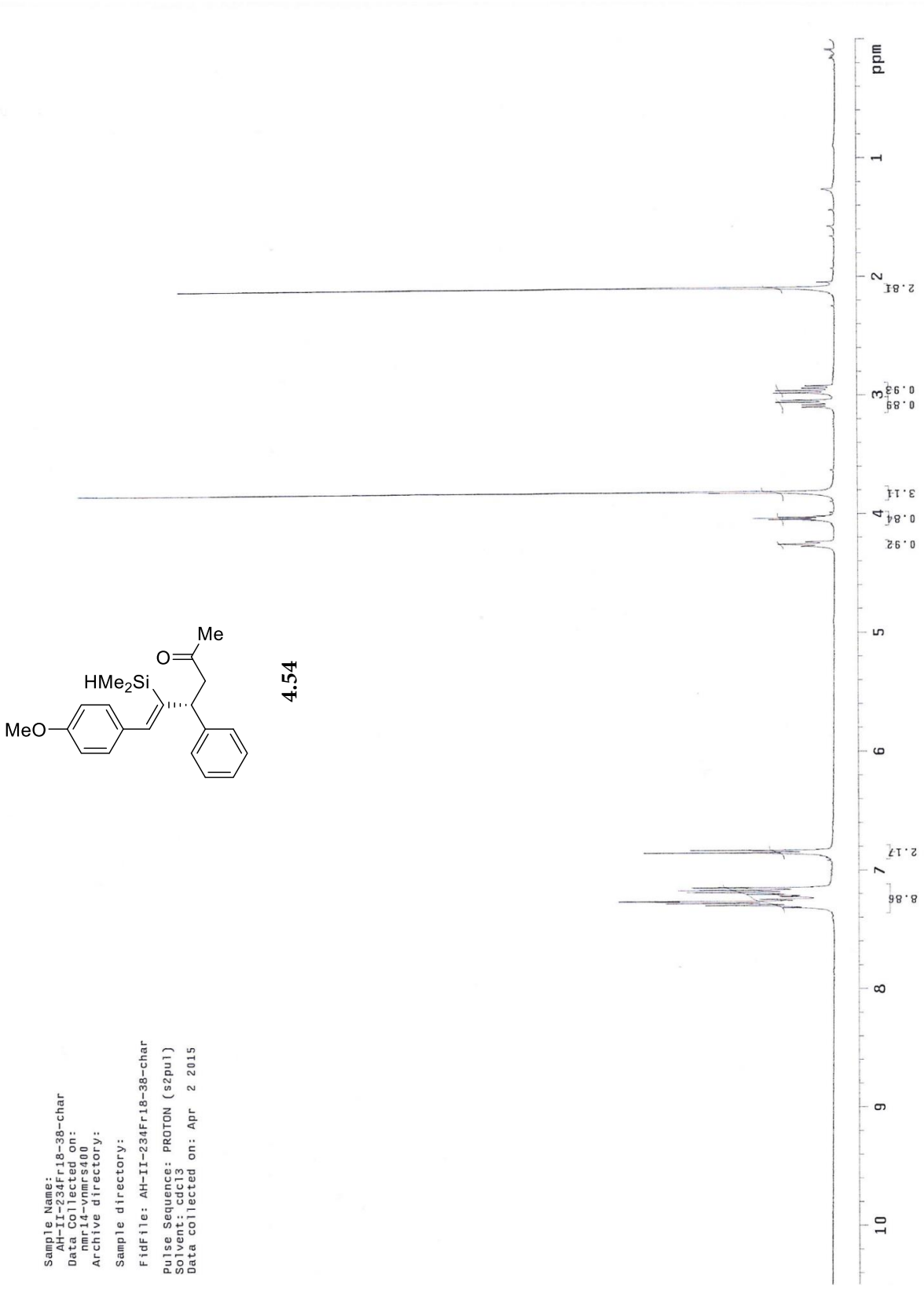
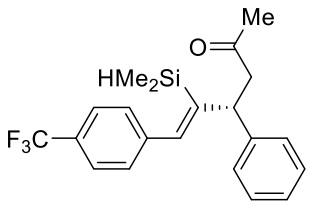
0.87
0.94
0.85
10.78

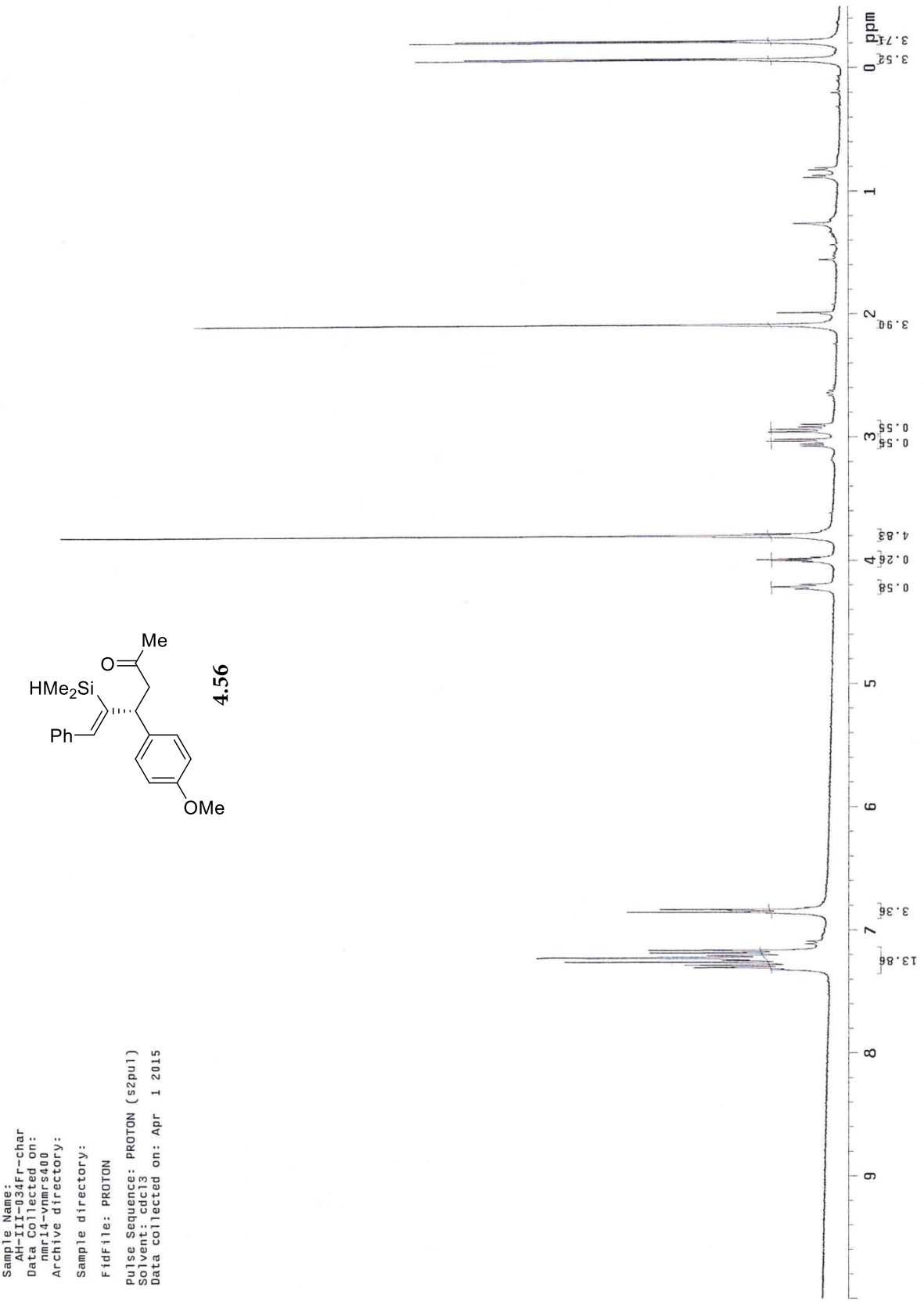

Me
O
HMe2Si
4.53
Sample Name:
KM-III-184rac-pdt
Archive directory:
Sample directory:
FidFile: KM-III-184rac-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jun 27 2012
ppm
3.04
3.08
2.97
1.05
1.04
0.86
1.00

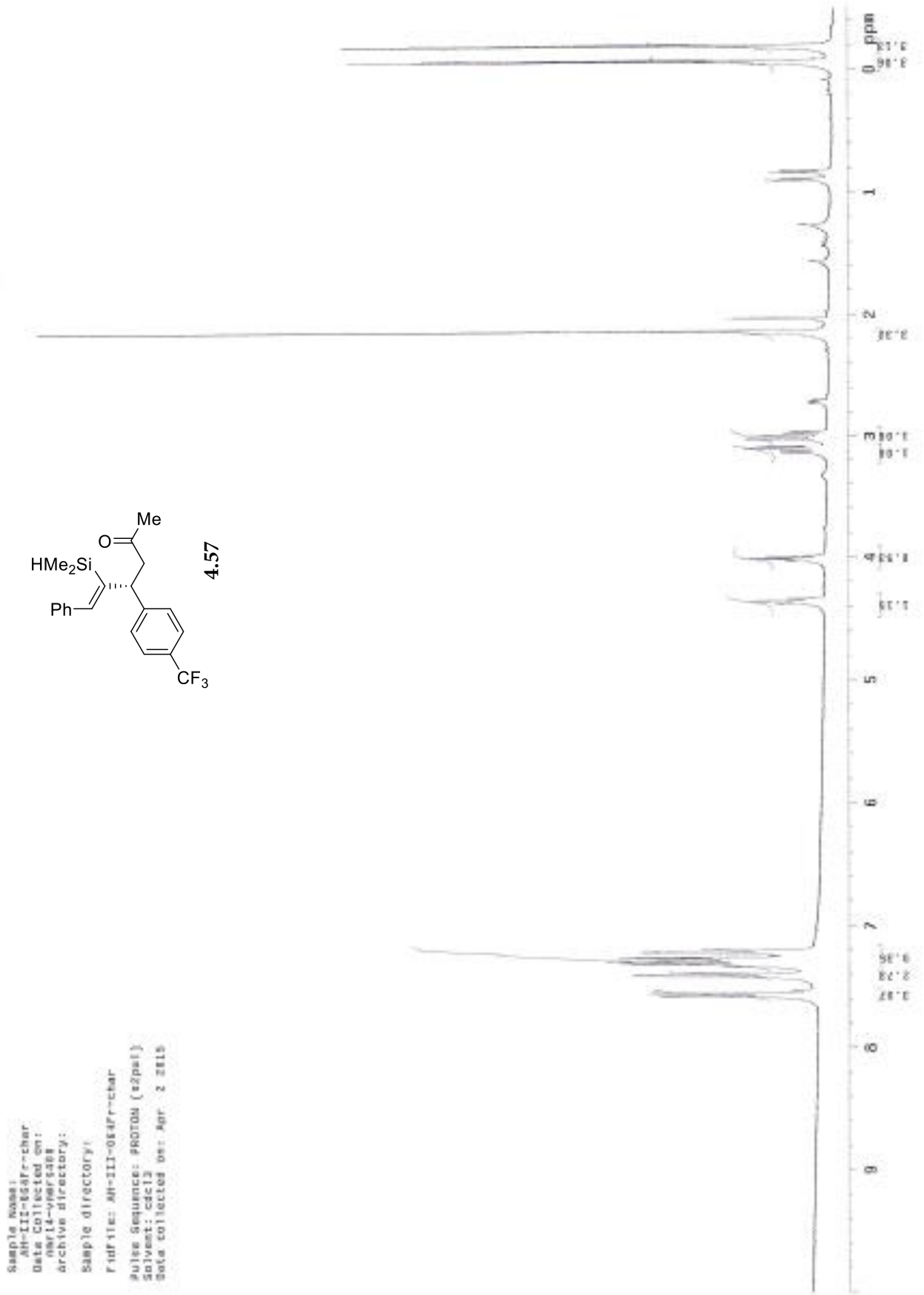

Me
O
HMe2Si
MeO
4.54
ppm
1
2
3
4
5
6
7
8
9
10
2.81
0.93
0.89
3.11
0.84
0.92
2.17
8.86
Sample Name:
AH-II-234Fr18-38-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: AH-II-234Fr18-38-char
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015

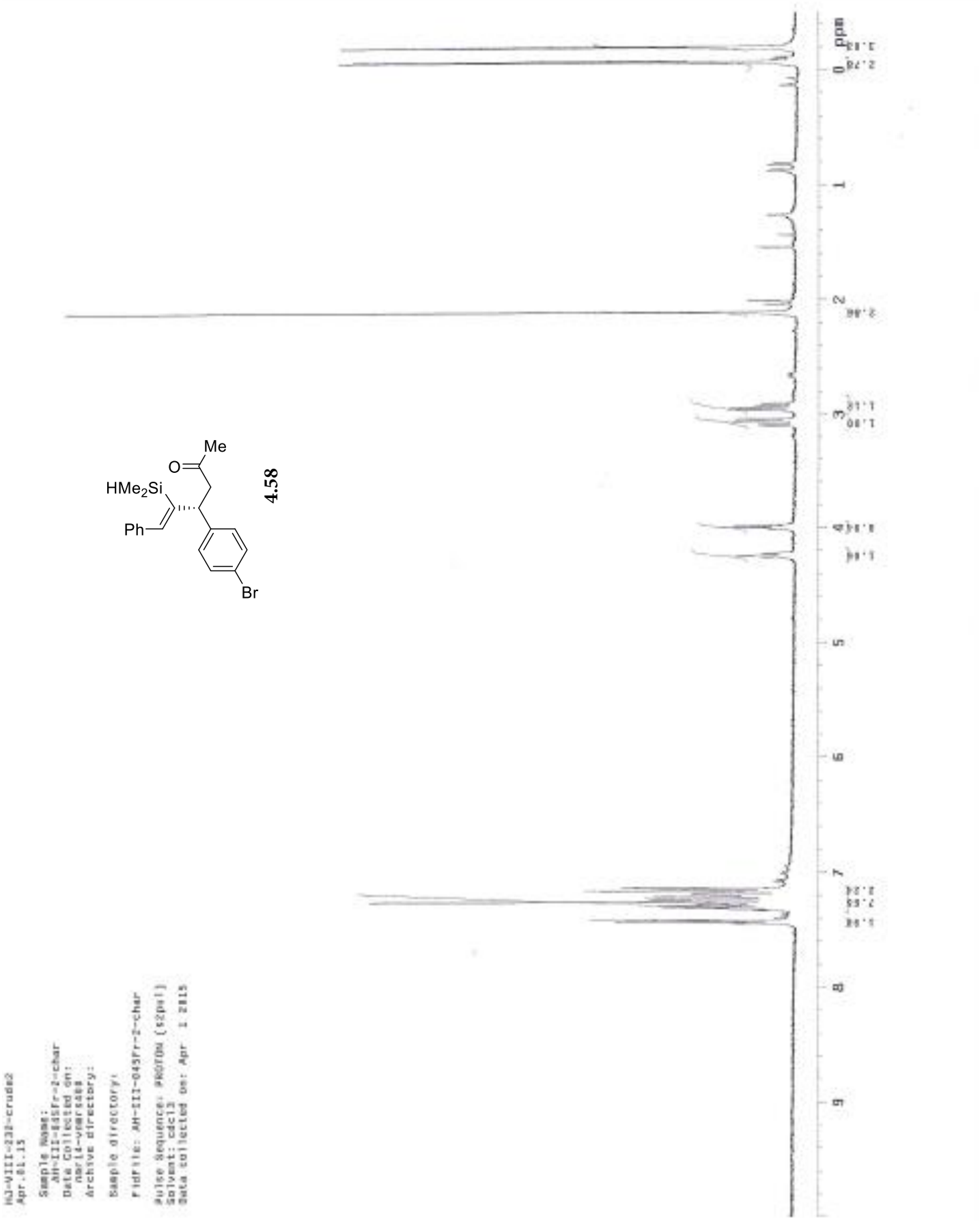

Me
O
HMe2Si
F3C

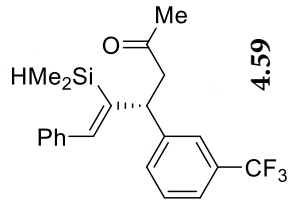
4.55

ppm
MJ-VIII-232-crude2
Apr.01.15
Sample Name:
AH-II-244Pr-char
Data Collected on:
mar14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2015

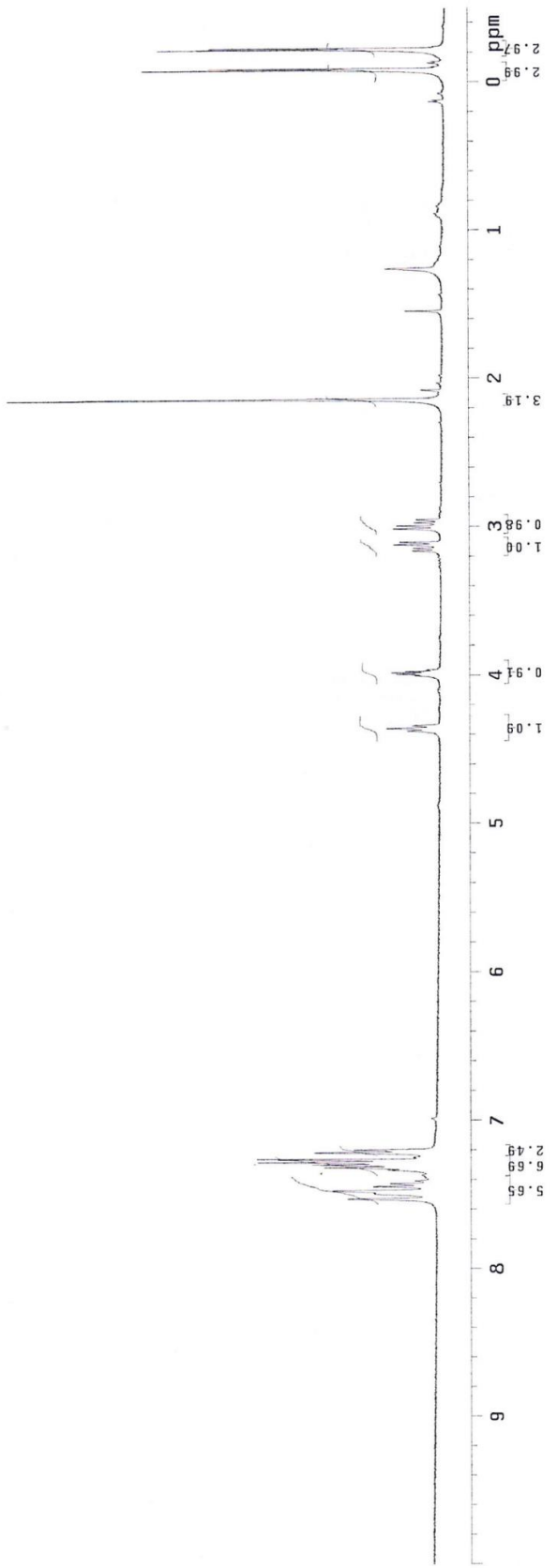

Sample Name:
AH-III-034Fr-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2015
Me
O
HMe2Si
Ph
OMe
4.56
ppm
3.71
3.52
3.90
0.55
0.55
4.83
0.26
0.58
3.36
13.86


Me
O
HMe2Si
Ph
CF3
4.57
Sample Name:
AH-III-66Fr-char
Data Collected on:
nmr14-ymr5488
Archive directory:
Sample directory:
FidFile: AH-III-66Fr-char
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015
ppm


Me
O
HMe2Si
Ph
Br
4.58
ppm
0
1
2
3
4
5
6
7
8
9
HJ-VIII-232-crude2
Apr.01.15
Sample Name:
AH-III-045Fr-2-char
Data Collected on:
nmr14-vnmrs600
Archive directory:
Sample directory:
Fidfile: AH-III-045Fr-2-char
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2015



4.59

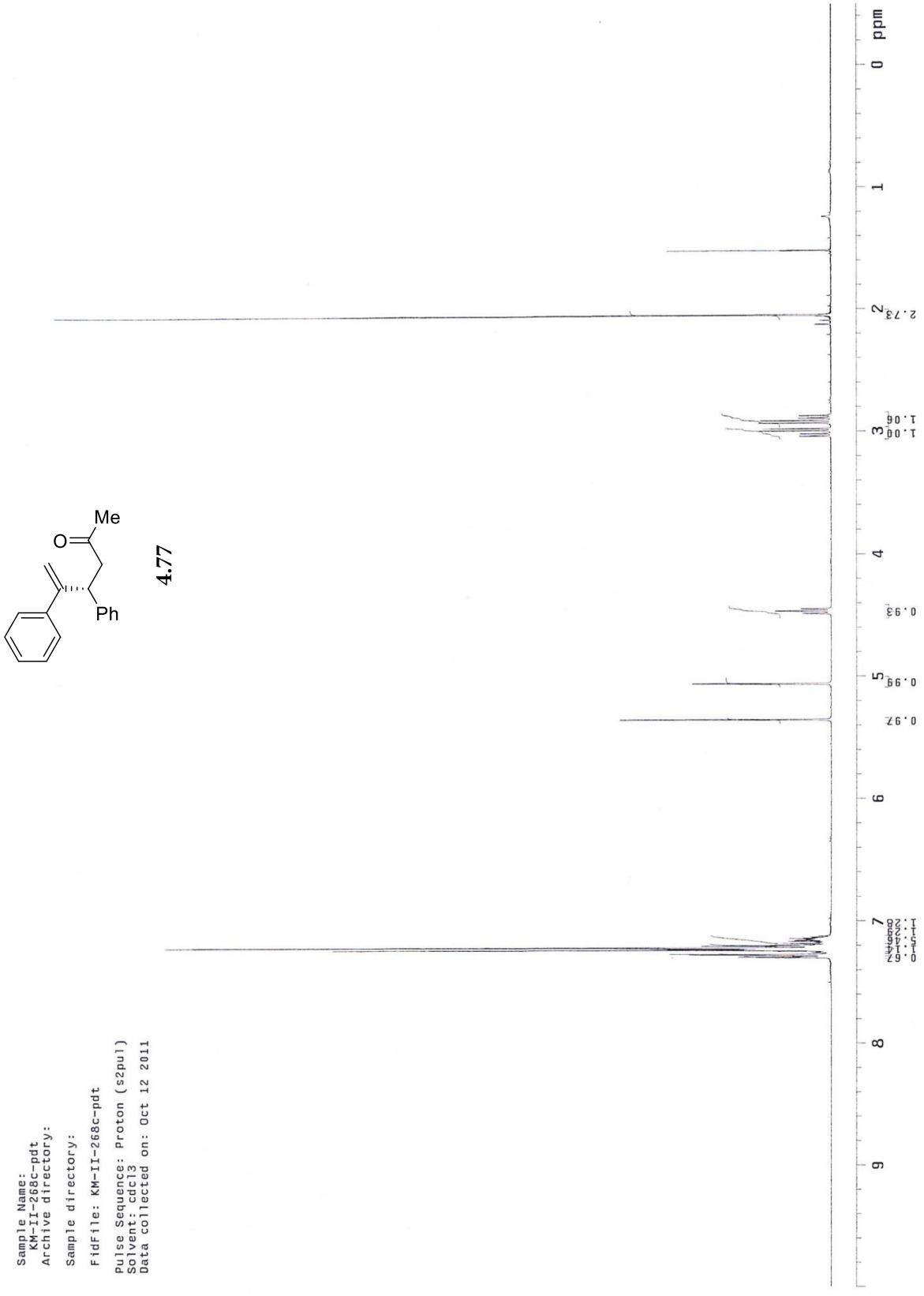


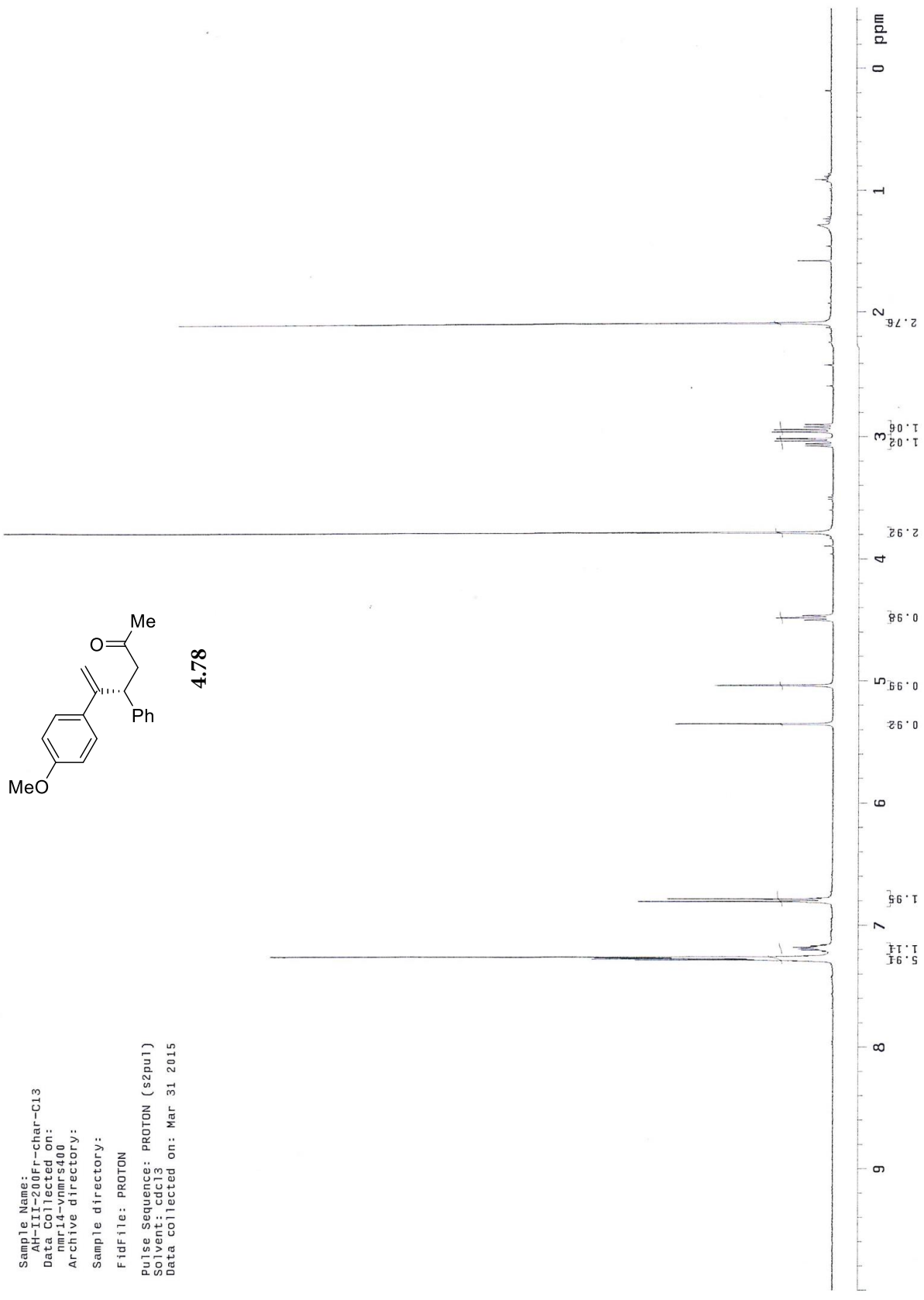
Sample Name:
AH-III-048Fr-char
Data Collected on:
nmr14-vnmrs400
Archive directory:

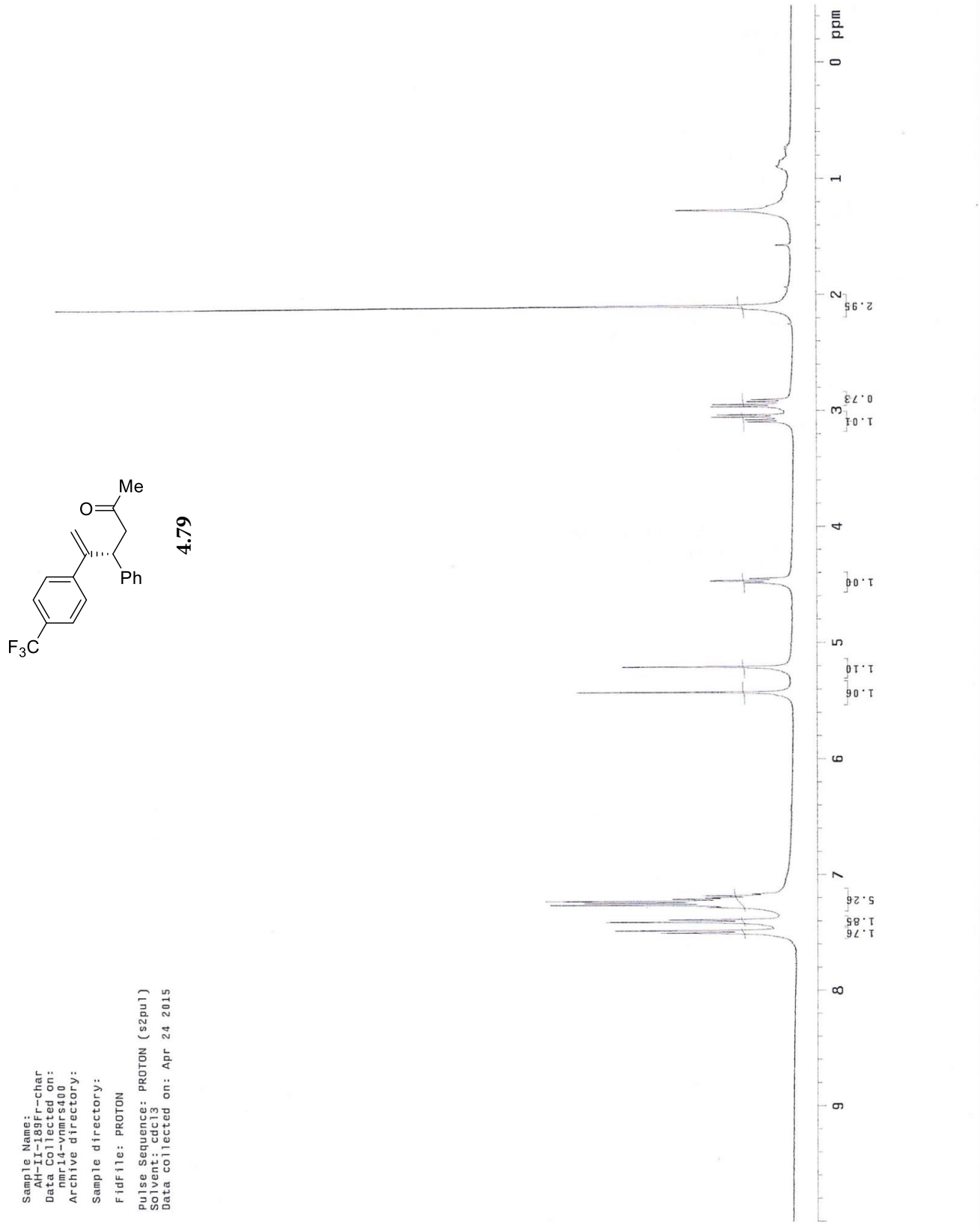
Sample directory:

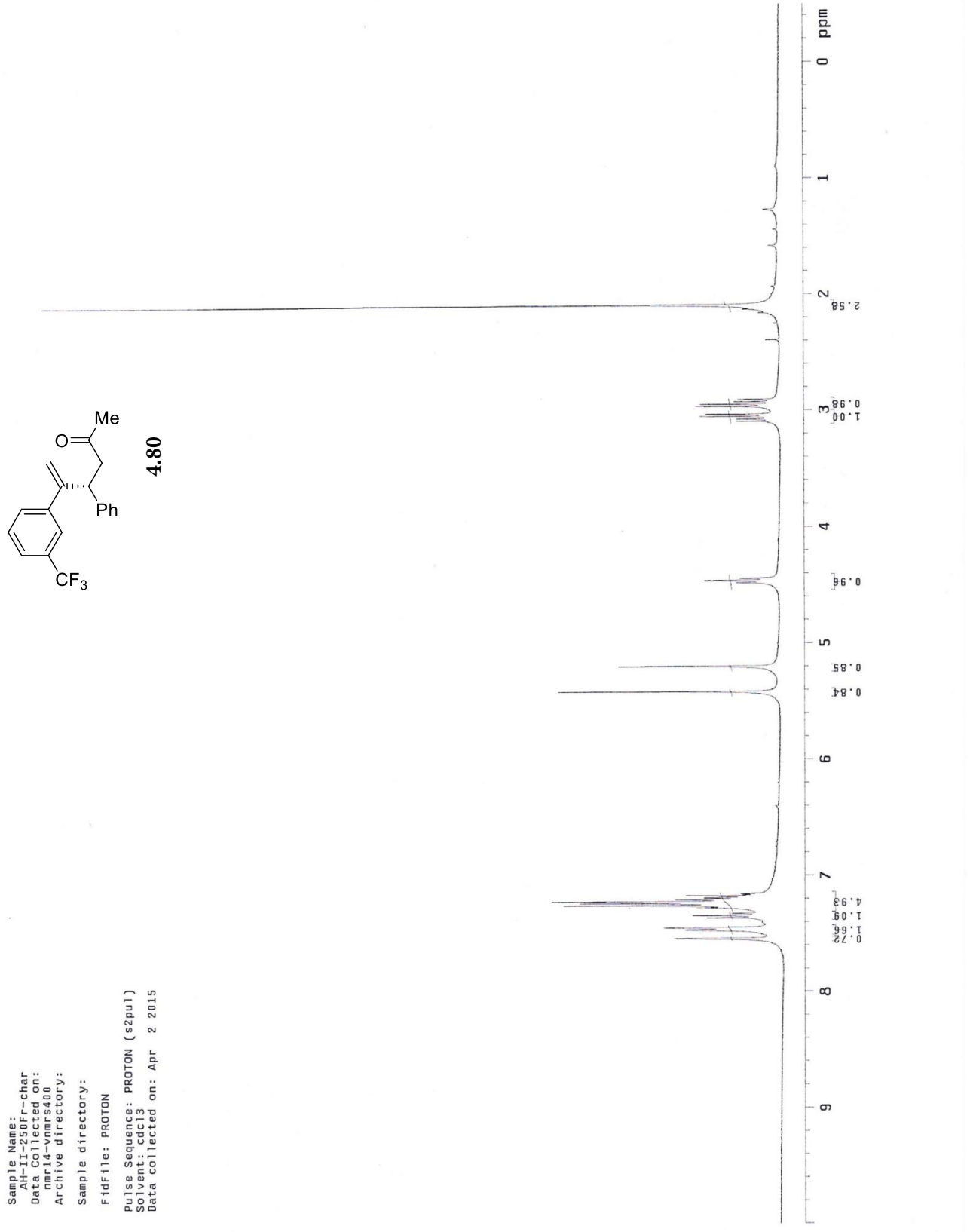
FidFile: AH-III-048Fr-char

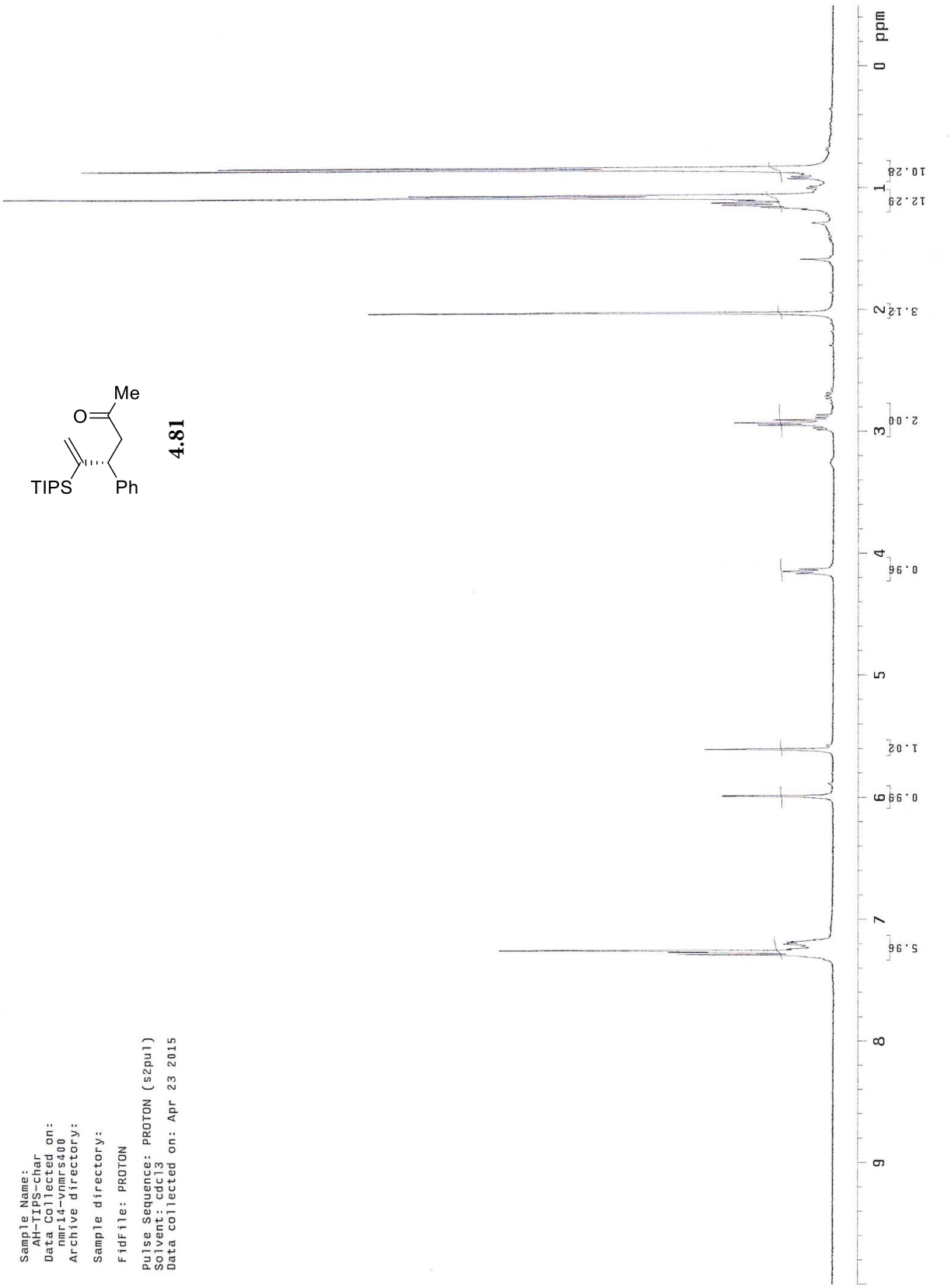
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015

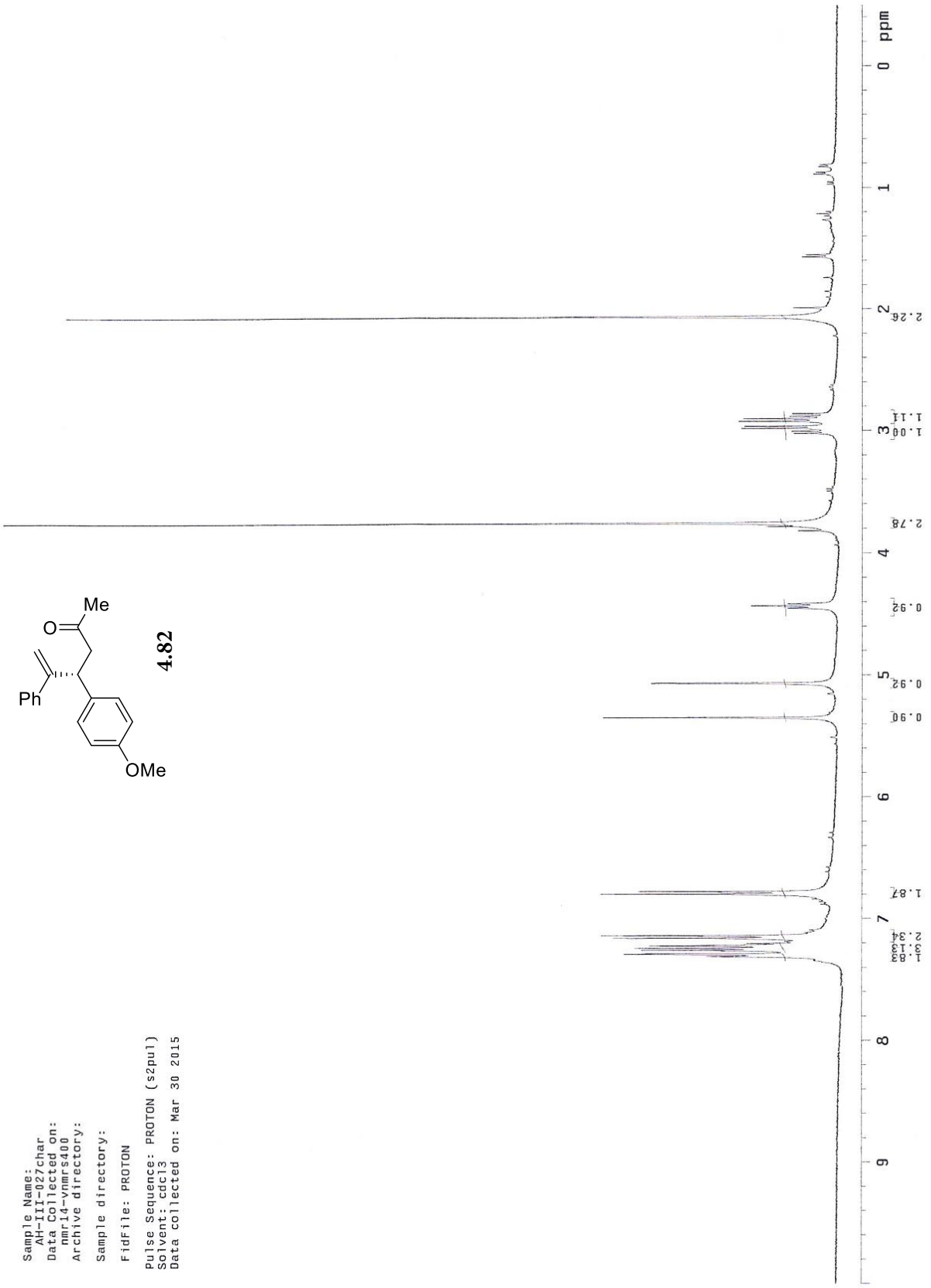

Me
O
Ph
4.77
Sample Name:
KM-II-268c-pdt
Archive directory:
Sample directory:
FidFile: KM-II-268c-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 12 2011
ppm
0
1
2
3
4
5
6
7
8
9
2.73
1.06
1.00
0.93
0.99
0.97

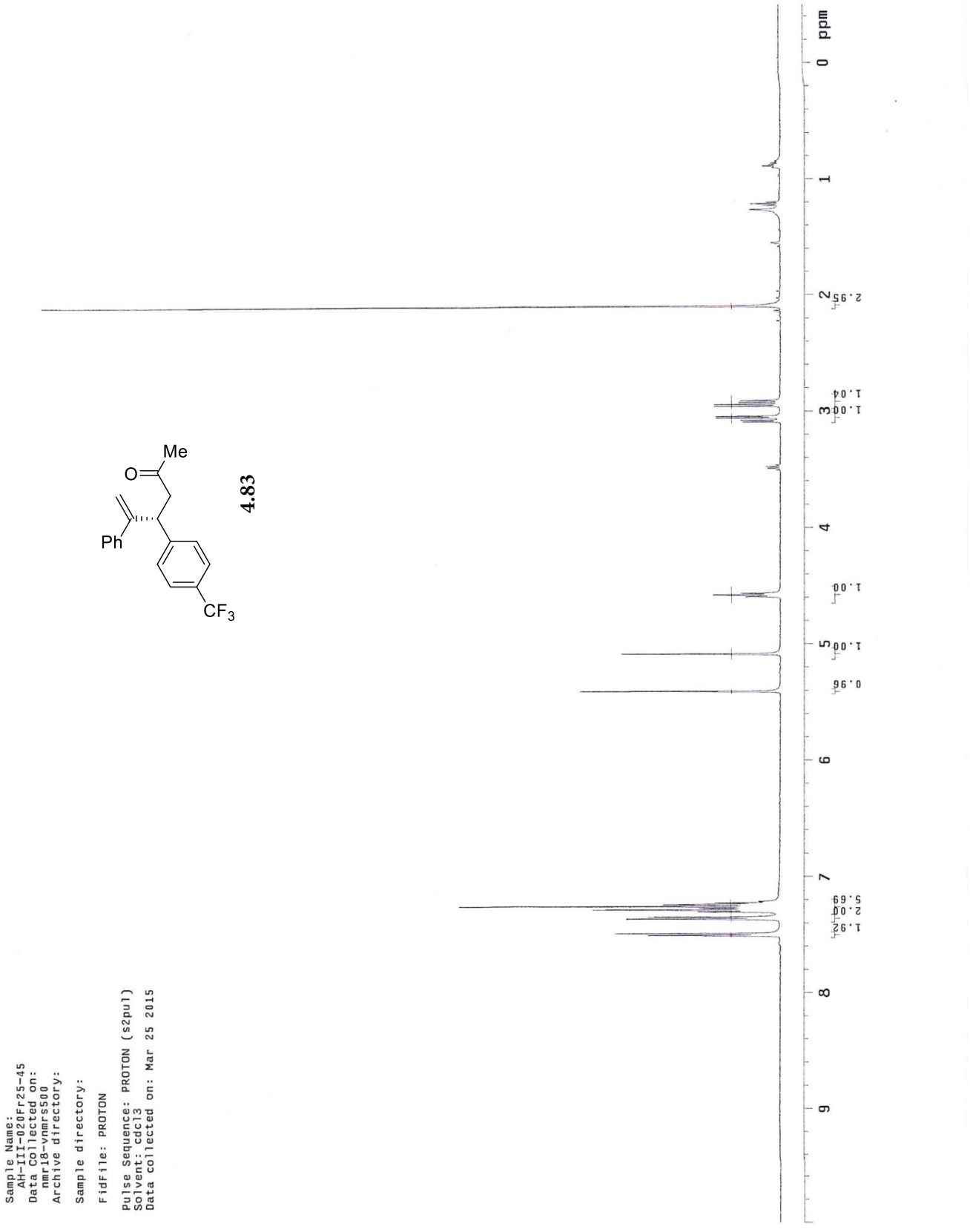

Me
O
Ph
MeO
4.78
Sample Name:
AH-III-200Fr-char-Cl3
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 31 2015
ppm
0
1
2
3
4
5
6
7
8
9
2.76
1.06
1.02
2.92
0.98
0.99
0.92
1.95
5.91
1.14

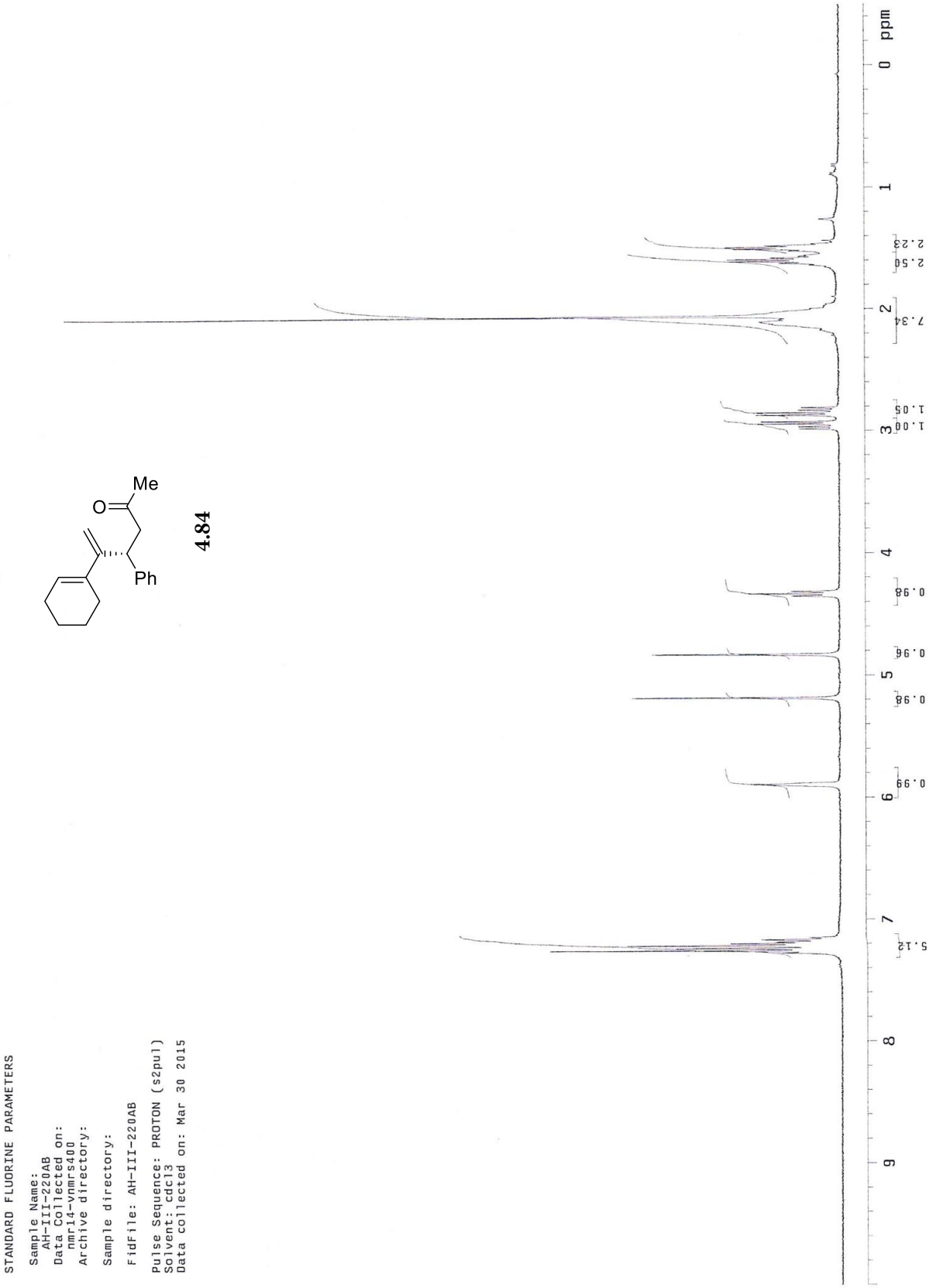

Me
O
Ph
F3C
4.79
Sample Name:
AH-II-189Fr-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 24 2015
ppm
0
1
2
3
4
5
6
7
8
9
2.95
0.73
1.01
1.00
1.10
1.06
5.26
1.85
1.76

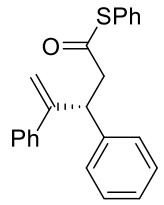

Me
O
Ph
CF3
4.80
Sample Name:
AH-II-250Fr-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015
ppm
2.58
1.00
0.98
0.96
0.85
0.84
0.72
1.66
1.09
4.93


Me
O
TIPS
Ph
4.81
Sample Name:
AH-TIPS-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 23 2015
ppm
10.28
12.29
3.12
2.00
0.96
1.02
0.99
5.96


Me
O
Ph
OMe
4.82
Sample Name:
AH-III-027char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 30 2015
ppm
0
1
2
3
4
5
6
7
8
9
2.26
1.11
1.00
2.78
0.92
0.92
0.90
1.87
3.14
2.34
1.88

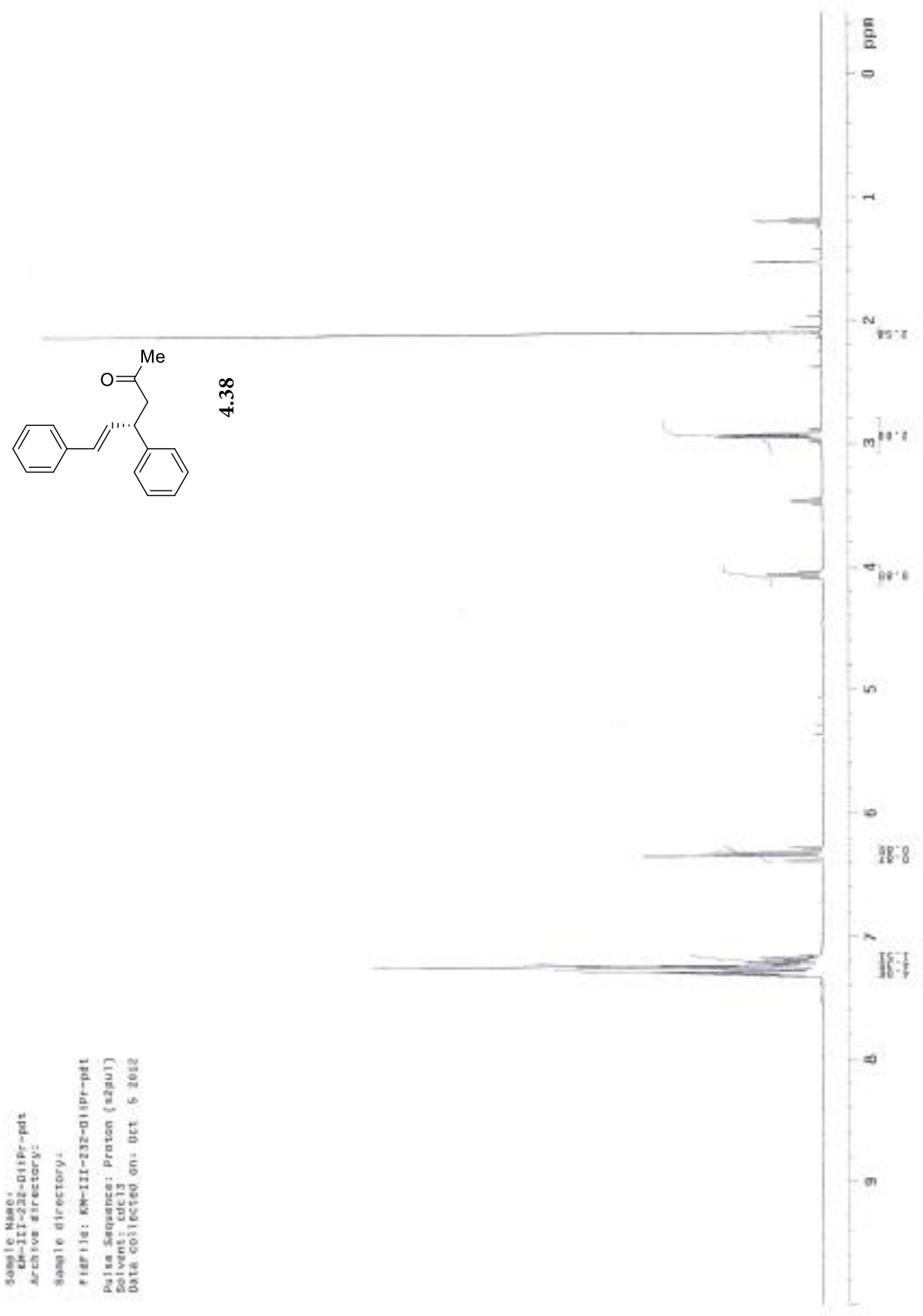

Me
O
Ph
CF3
4.83
Sample Name:
AH-III-020Fr25-45
Data Collected on:
nmr18-vnmrs500
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 25 2015
ppm
0
1
2
3
4
5
6
7
8
9
2.95
1.04
1.00
1.00
1.00
0.96
1.92
2.00
5.69

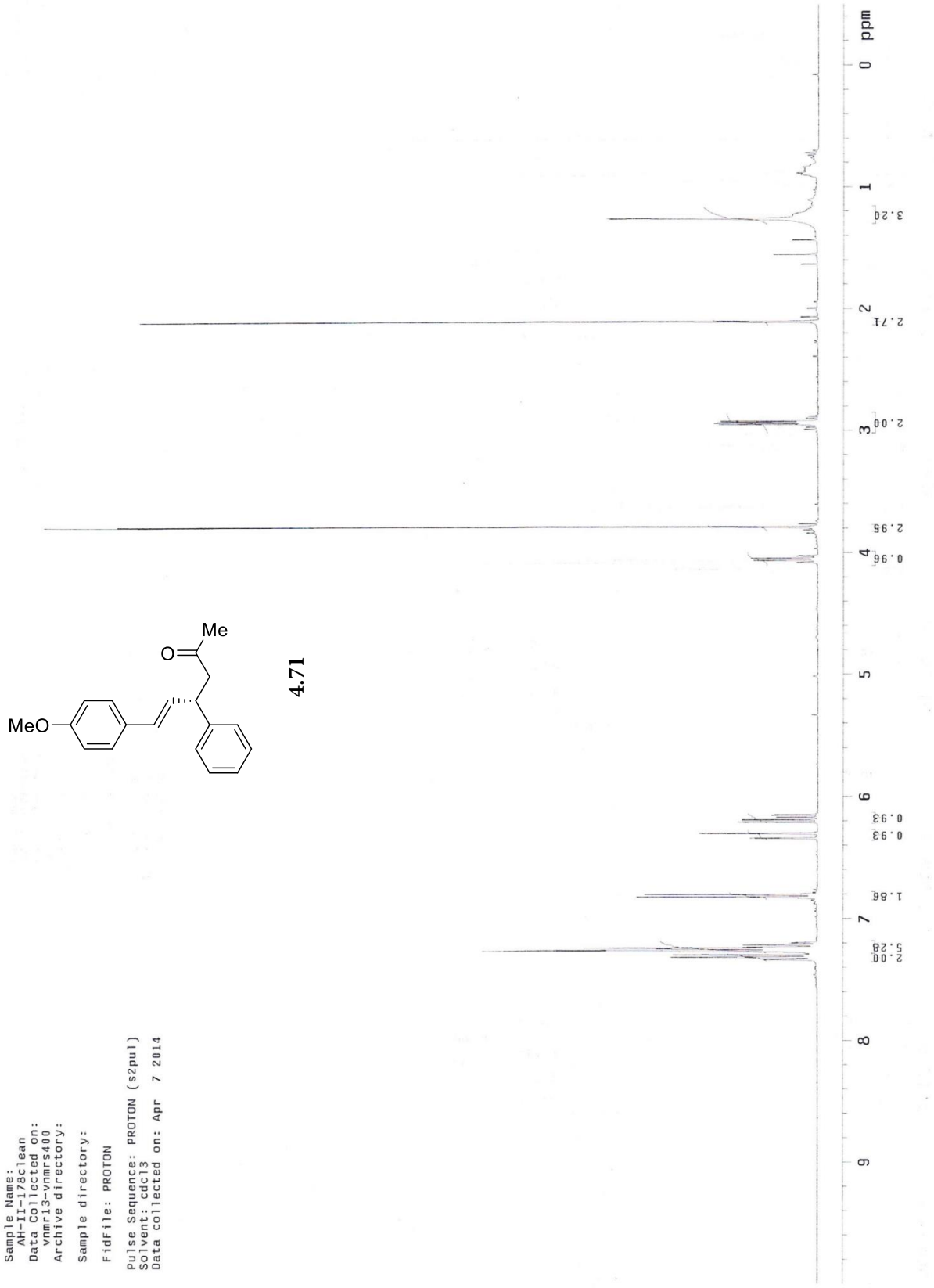

STANDARD FLUORINE PARAMETERS
Sample Name:
AH-III-220AB
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: AH-III-220AB
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 30 2015
Me
O
Ph
4.84
ppm
0
1
2
3
4
5
6
7
8
9
2.23
2.50
7.34
1.05
1.00
0.98
0.96
0.98
0.99
5.12

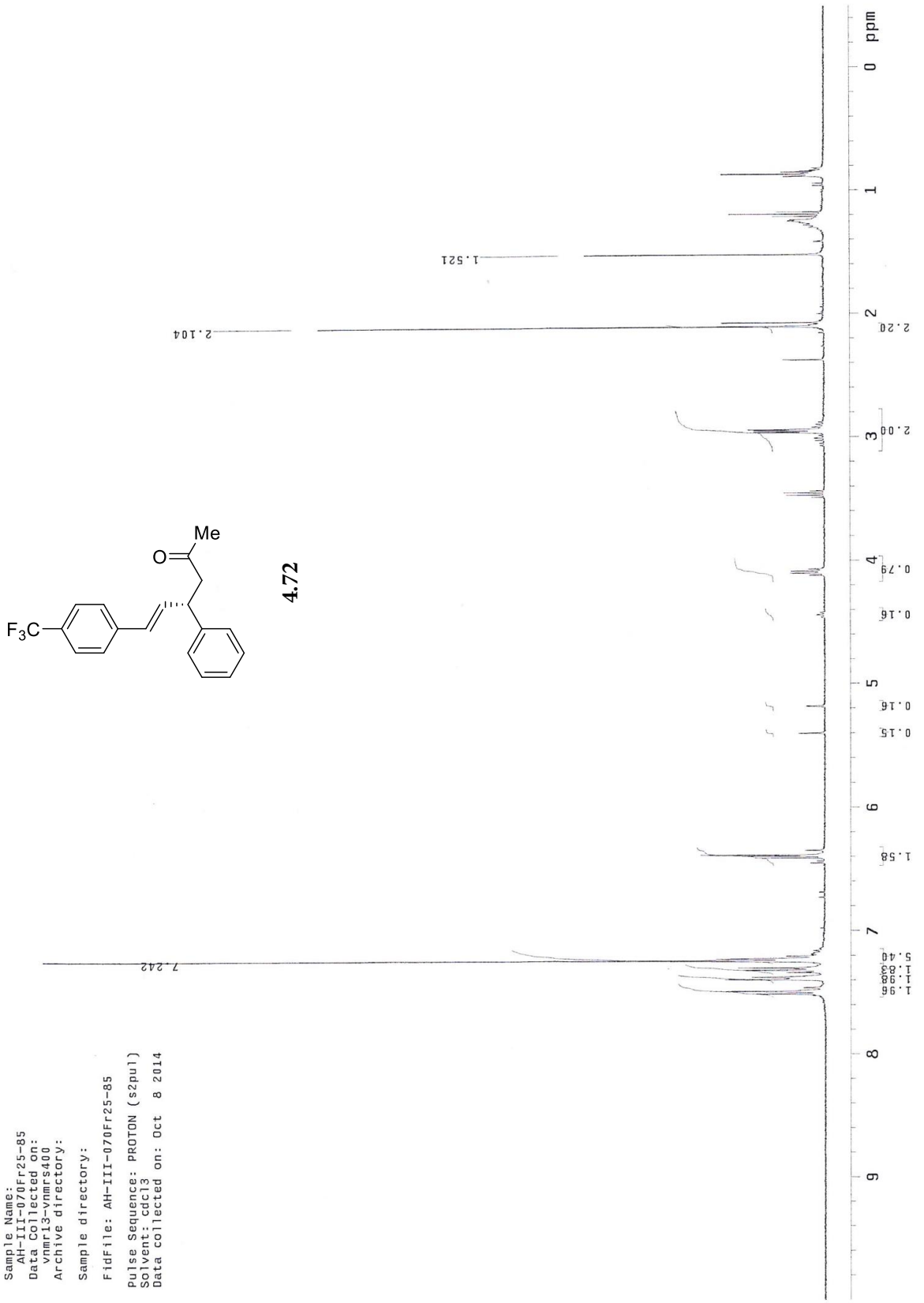

SPh
O
Ph

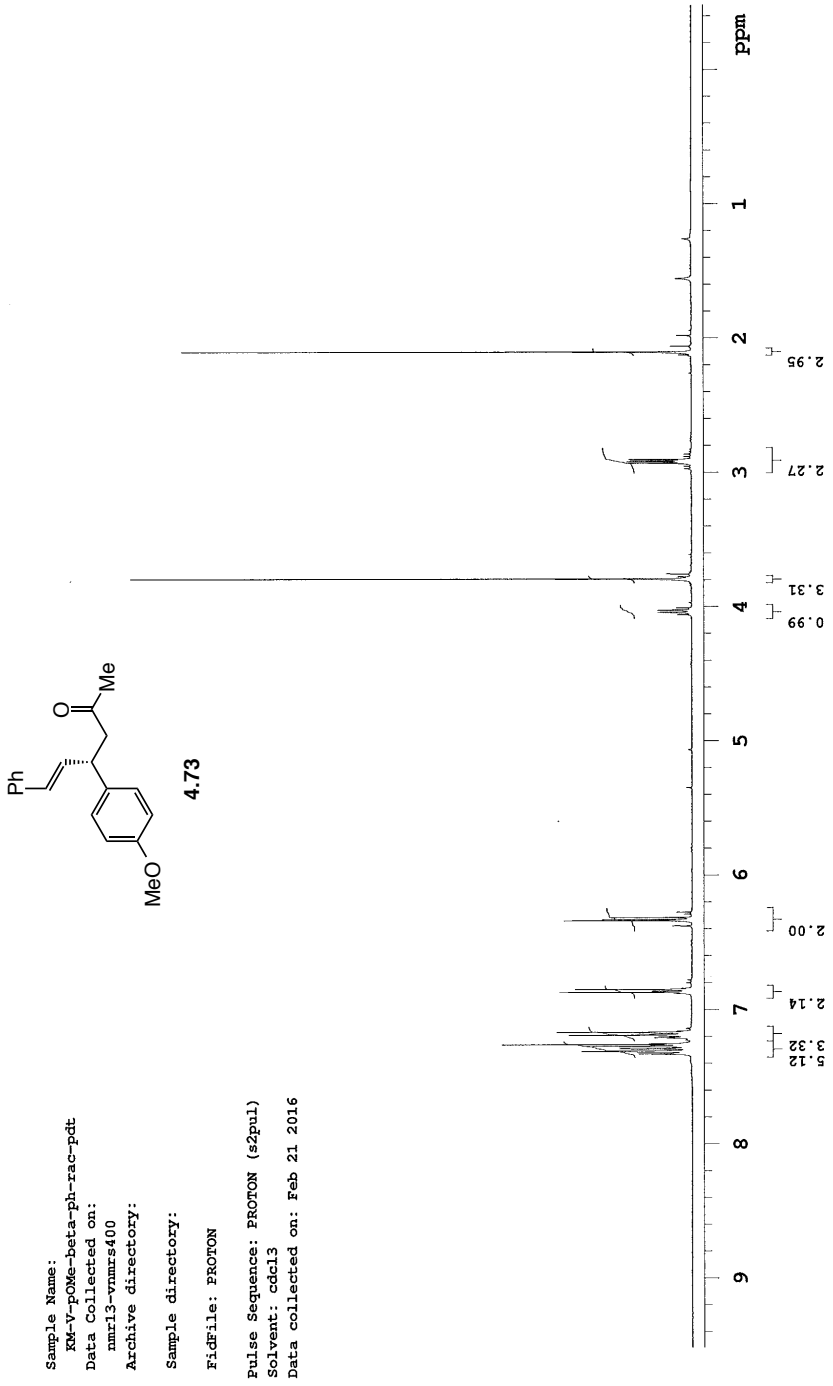
4.85

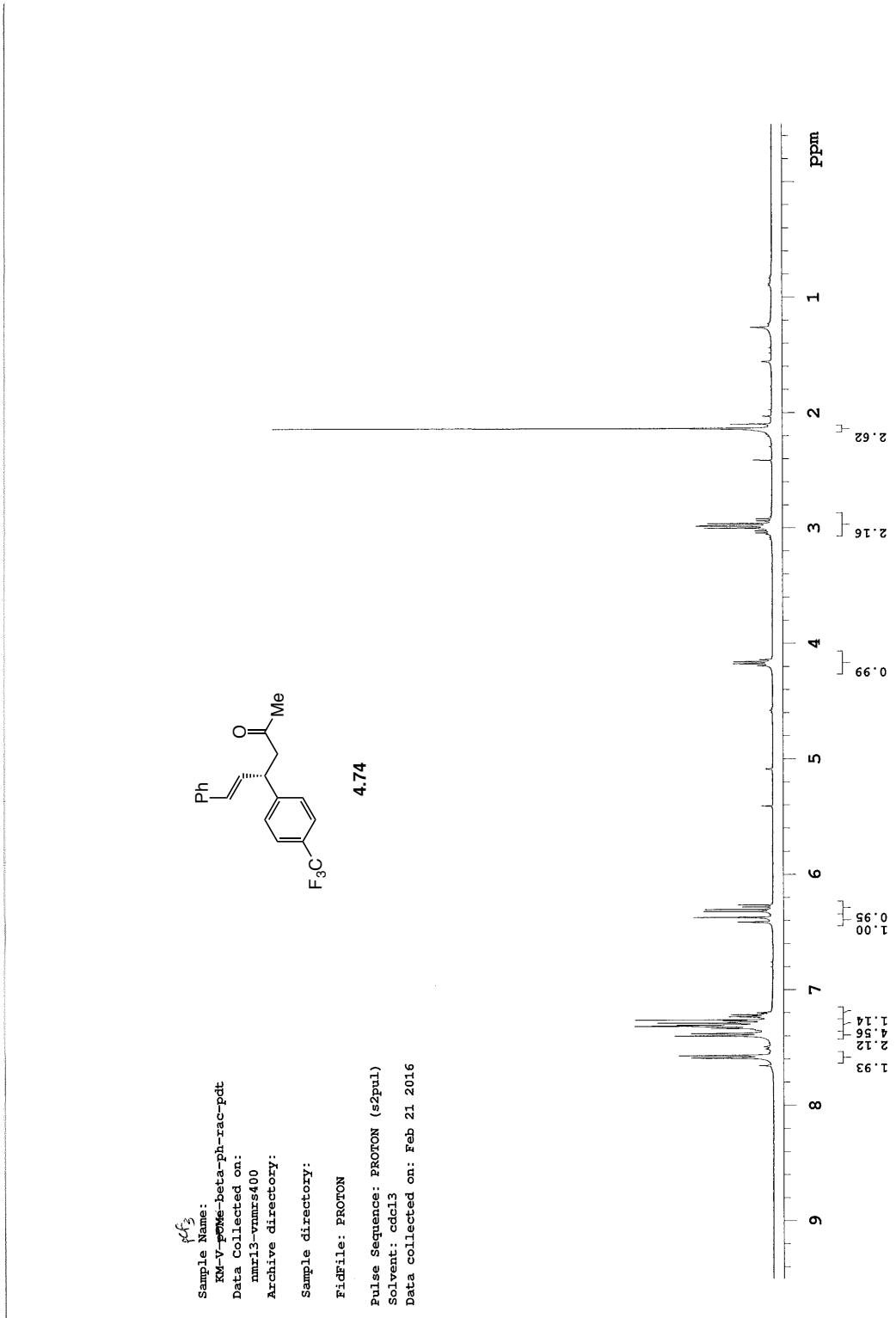
Sample Name:
AH-III-292Fr-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2015
ppm
0 1 2 3 4 5 6 7 8 9
0.90
1.00
0.85
0.77
0.80
0.46
10.98
0.44

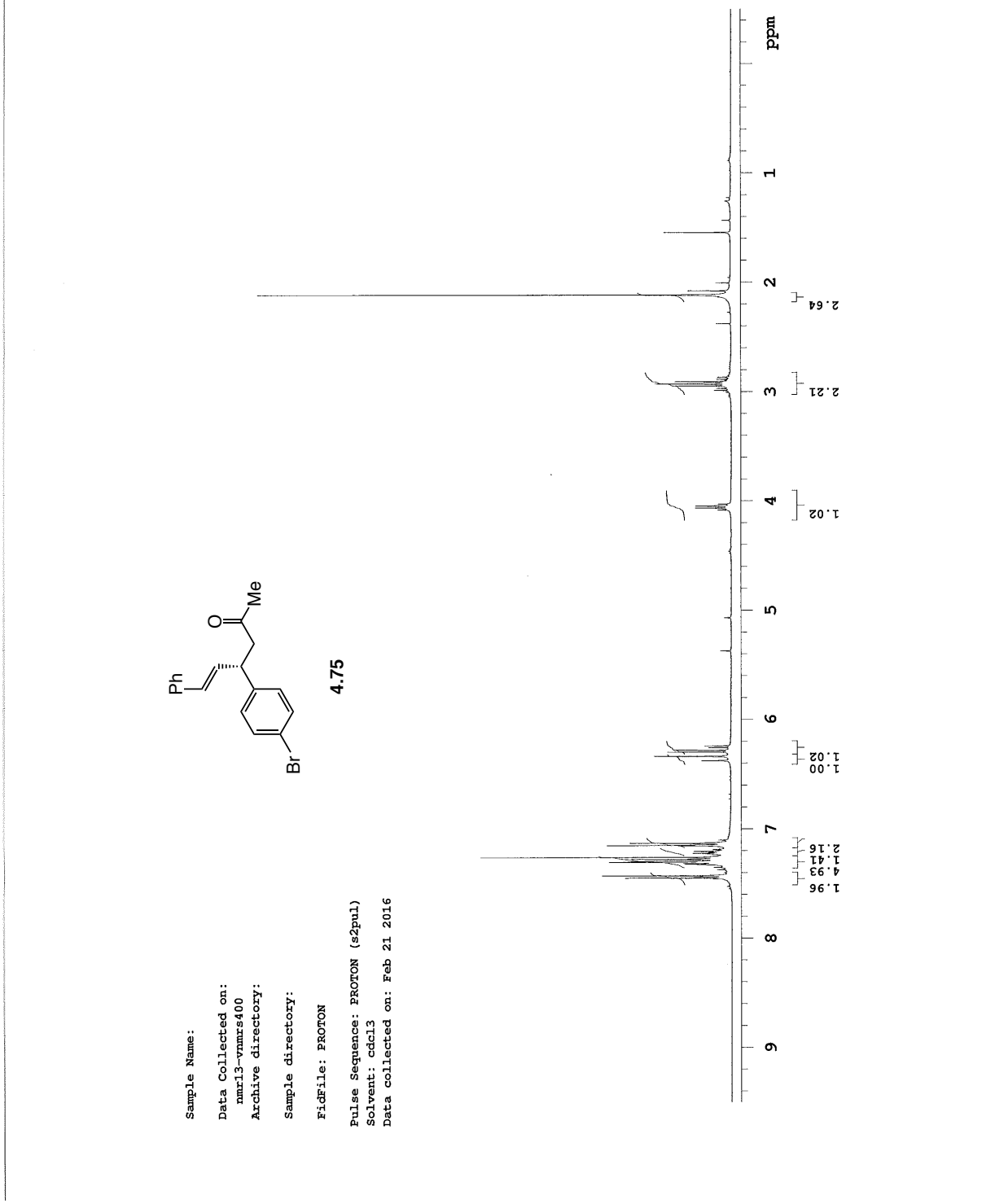

Me
O
4.38
Sample Name:
KN-III-232-DiPr-pdt
Archive directory:
Sample directory:
Filefile: KN-III-232-DiPr-pdt
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 5 2012
ppm
0
1
2
3
4
5
6
7
8
9

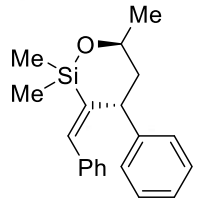

Me
O
MeO
4.71
Sample Name:
AH-II-178clean
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 7 2014
ppm
3.20
2.71
2.00
2.95
0.96
0.93
0.93
1.86
2.00
5.28


Me
O
F3C
4.72
Sample Name:
AH-III-070Fr25-85
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: AH-III-070Fr25-85
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 8 2014
7.242
2.104
1.521
ppm


Sample Name:
KM-V-pOMe-beta-ph-rac-pdt
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2016
Ph
O
Me
MeO
4.73
ppm
2.95
2.27
3.31
0.99
2.00
2.14
5.12
3.32

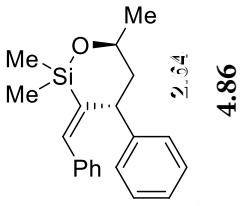

Sample Name:
KM-V-pOMe-beta-ph-rac-pdt
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2016
Ph
O
Me
F3C
4.74
ppm
1.93
2.12
4.56
1.14
1.00
0.95
0.99
2.16
2.62


Sample Name:
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2016
Ph
O
Me
Br
4.75
ppm
1.96
4.93
1.41
2.16
1.00
1.02
1.02
2.21
2.64


Me
O
Me
Si
Me
Ph

4.86

Sample Name:
AH-III-205Fr12-14-char
Data Collected on:
nmr14-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2015
ppm
0
1
2
3
4
5
6
7
8
9
3.68
2.85
2.90
1.14
1.00
0.96
0.96
1.02
8.88
4.06



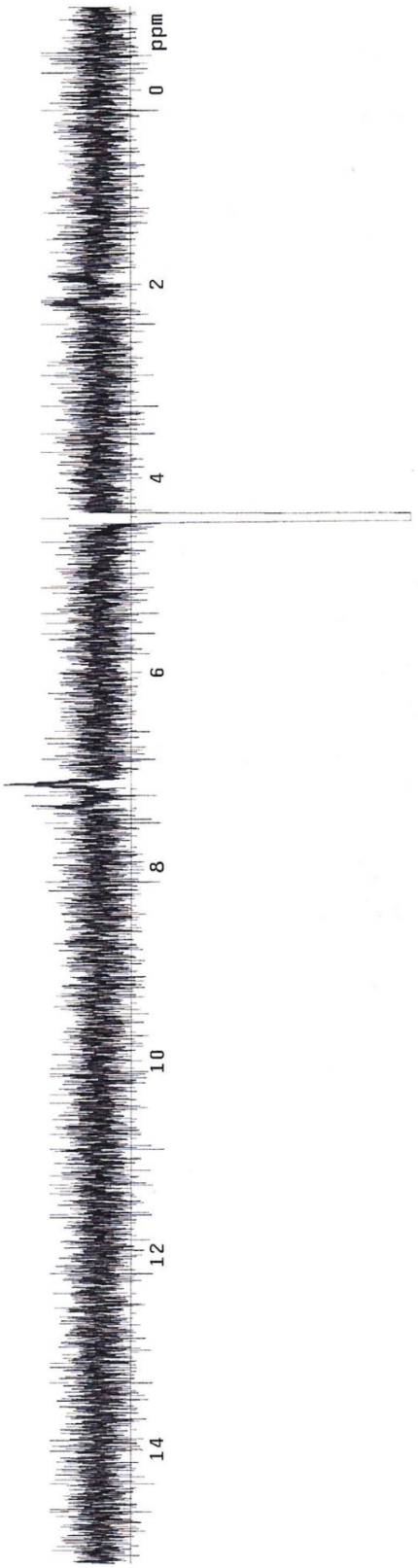
4.86

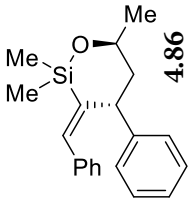
Sample Name:
AH-III-205Fr10-11-char-NOE
Data Collected on:
vnmr13-vnmrs400
Archive directory:

Sample directory:

FidFile: NOESY1D

Pulse Sequence: NOESY1D
Solvent: cdcl3
Data collected on: Apr 21 2015





4.86

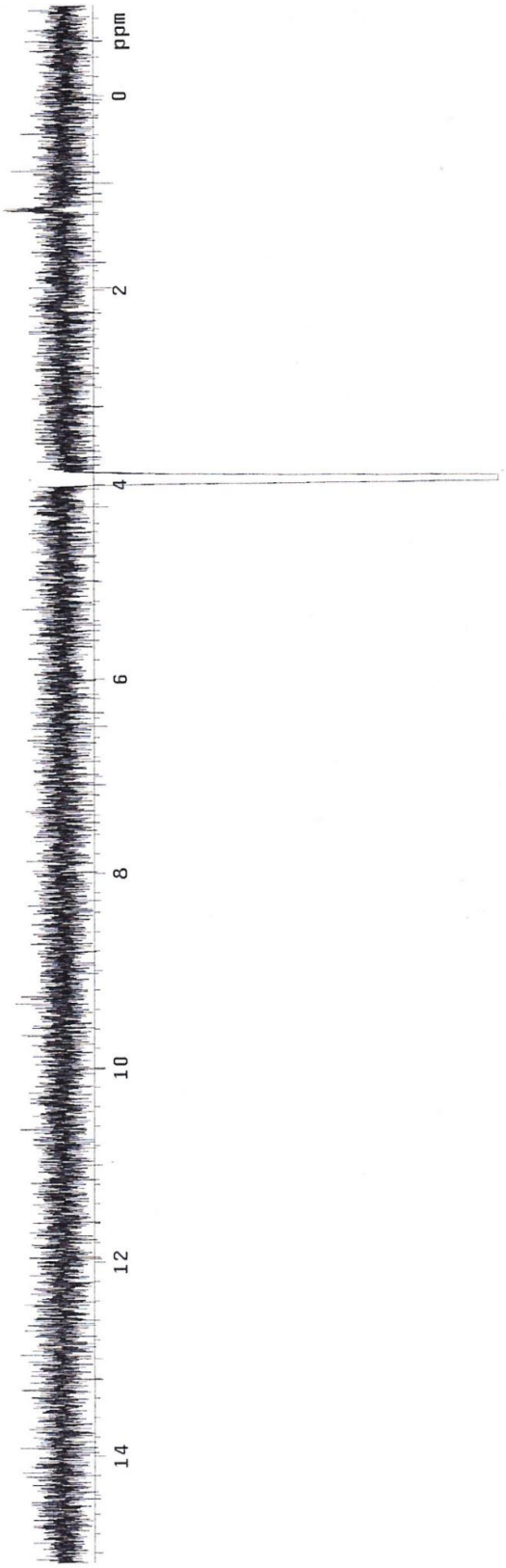
Selective band center: 3.92 (ppm); width: 46.3 (Hz)

Sample Name:
AH-III-205Fr10-11-char-NOE-2
Data Collected on:
vnmr13-vnmrs400
Archive directory:

Sample directory:

FidFile: NOESY1D

Pulse Sequence: NOESY1D
Solvent: cdcl3
Data collected on: Apr 21 2015



Chapter 5:

N-Heterocyclic Carbene–Copper Complexes as Catalysts for Allylic Substitution with Diborylmethane to Trisubstituted Allylic Phosphates

5.1 Introduction

Catalytic enantioselective allylic substitution (EAS) is a valuable process in organic synthesis as it allows for the formation of a new stereogenic center as well as a transposed olefin. Although significant progress has been made in this area for the addition of organometallic nucleophiles (Mg-, Zn-, and Al-based)[1], such reagents are often air and moisture sensitive, sufficiently basic and/or nucleophilic to limit their functional group tolerance (carboxylic esters and ketones), and reaction often require cryogenic temperatures to achieve high stereoselectivity.

More recently, additions of the more functional group tolerant and widely available organoboron reagents have been disclosed.[2,3] Reactions with alkyl-substituted

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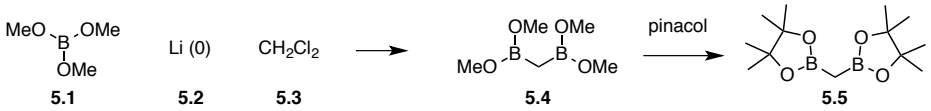
(1) For reviews on catalytic enantioselective allylic substitution (EAS) reactions with "hard" organometallic reagents, see: (a) Hoveyda, A. H.; Hird, A.W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785; (b) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435–4439; (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852; (d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, 108, 2796–2823; (e) Baslé, O.; Denicourt-Nowicki, A.; Crévisy, C.; Mauduit. M. in *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014, 85–125.
(2) Hall, D. G. *Boronic Acids*, Wiley-VCH: Weinheim, 2005.
(3) For addition of alkylboron reagents, see: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897; (b) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 18573–18576; (c) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 8982–8987; (d) Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4954–4958. For addition of arylboronic acid reagents, see: For copper-catalyzed reactions, see: (e) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216–3218; (f) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656–8659; (g) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354–2367; For palladium-catalyzed reactions, see: (h) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277; (i) Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3344–3347; (j) Makida, Y.; Ohmiya, H.; Sawamura, M. *Chem. Asian J.* **2011**, *6*, 410–414. For rhodium-catalyzed reactions, see: (k) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569–4572; (l) Yu, B.; Menard, F.; Isono, N.; Lautens, M. *Synthesis* **2009**, 853–859; (m) Menard, F.; Perez, D.;

organoboron compounds are limited to the more reactive alkyl-9-BBN (9-BBN = 9-borabicyclononane) derivatives. As such, a method in which the more stable alkylB(pin) (pin = pinacolato) reagents could be used would be of great value, even more so if the product of such a reaction contained a modifiable boron as well.[4]

5.2 Background

One class of reagents that has recently seen increased interest is multiborylated alkanes, more specifically *geminyl* diborylmethane and its substituted variants. The first synthesis of diborylmethane was reported by Matteson in 1982 where dichloromethane and Li(0) react with trimethoxyboron to generate the tetramethoxy diborylmethane followed by the addition of pinacol to form the pinacolato boron species.[5] Since then, a variety of methods have been developed to generate such diboryl compounds including Cu-catalyzed hydroboration of boryl-substituted olefins[6] as well as diboration of alkynes[7].

Scheme 5.1. Synthesis of Methylene Diboron



5.1 **5.2** **5.3** **5.4** **5.5**

Following pioneering work by Matteson and Pelter,[8] Shibata and co-workers demonstrated the utility of geminyl diboron compounds in organic synthesis.[9] As show in

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Roman, D. S.; Chapman, T. M.; Lautens, M. *J. Org. Chem.* **2010**, *75*, 4056–4068; (n) H. Kiuchi, D. Takahashi, K. Funaki, T. Sato, S. Oi, *Org. Lett.* **2012**, 14, 4502–4505. For addition of allylboron reagents, see: (o) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686–10688 (p) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716–9719; (q) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778–16781. For addition of allenylboron, see: (r) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493. For addition to alkenylboron reagents, see: (s) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656–8659; (t) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6613–6617; (u) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149–2161. For addition of propargylboron reagents, see: (v) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948–8964. For addition of alkynylboron reagents, see: (w) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532–7535.

(4) For a multicomponent reaction involving allylic substitution of an allyl–Cu reagent to form an alkenylboron containing product, see: Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367–374.

(5) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20–28.

(6) (a) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894–899. (b) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989–3992.

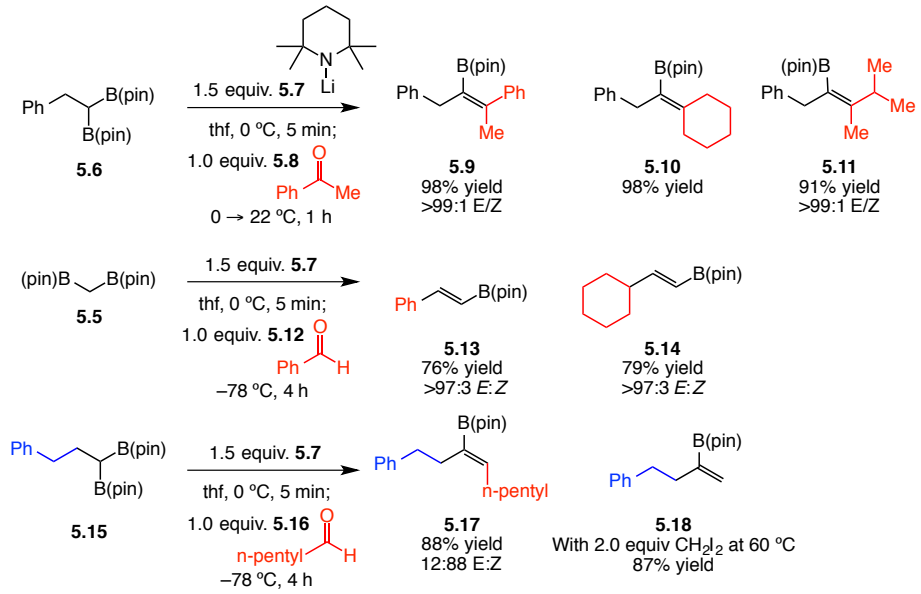
(7) Lee, S.; Li, D.; Yun, J. *Chem. Asian J.* **2014**, *9*, 2440–2443.

(8) (a) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. *J. Am. Chem. Soc.* **1975**, *97*, 5608–5609; (b) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25–37; (c) Matteson, D. S.; Moody, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 3196–3197; (d) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron* **1993**, *49*,

the Scheme 5.2, deprotonation of diboron **5.6** with LiTMP (TMP = tetramethylpiperdine) followed by addition to a ketone results in the formation of a new tetrasubstituted alkenylB(pin) with high *E*-selectivity. In all cases, except where chelation of a Lewis basic nitrogen is present, the larger group on the ketone is *syn* to the B(pin) in the product.

The Morken group demonstrated that this strategy could be applied to reactions with aldehydes with methylene diboron **5.5** to form disubstituted olefins and substituted diboron **5.15** to form trisubstituted alkenyl boron compounds.[10]

Scheme 5.2. Wittig-type Olefination with Substituted *Geminyl* Diboron



The Shibata group demonstrated that the Suzuki cross coupling of diboron reagents, unlike other alkylboron compounds, which suffer from slow transmetalation as well as β-hydride elimination or protodeboration, proceeds at room temperature without the need for a large excess of the boron reagent.[11] Additionally, the second B(pin) substituent does not undergo further cross coupling even in the presence of excess

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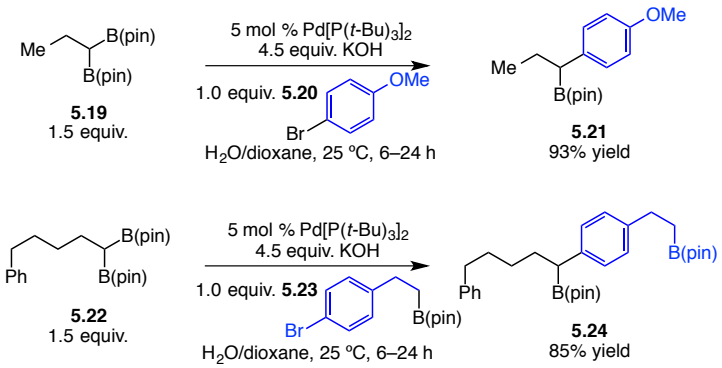
7077–7103.
(9) Endo, K.; Hirokami, M; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469–3472.
(10) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708–1711.
(11) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033–11035; (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, 13, 3368–3371; (c) Endo, K.; Sakamoto, A.; Ohkubo, T.; Shibata, T. *Chem. Lett.* **2011**, *40*, 1440–1442; (d) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826–4831; (d) Endo, K.; Ishioka, T.; Ohkubo, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 7223–7231.

aryliodide. As shown in the reaction of **5.22** with **5.23**, the aryl bromide is selectively cross coupled versus the alkylB(pin).

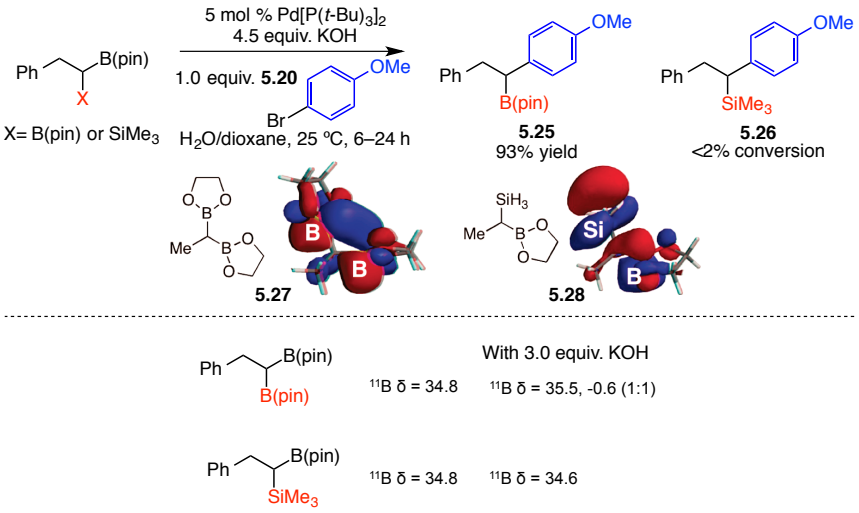
Scheme 5.3. Suzuki Cross Coupling with Diboron Reagents



The authors propose that the transmetalation is able to occur at lower temperatures in part due to the ability of the B(pin) moiety to stabilize the α-C–Pd bond through hyperconjugation.[12] To probe this stabilizing effect, the analogous boro-silyl reagent was subjected to the same cross coupling conditions, but <2% conversion to the desired product was observed. Additionally, reaction with the vicinal diboron reagents also results in <2% conversion. DFT calculations were used to create a LUMO map for both the diboron and borosilane reagents. As shown in Scheme 5.4, the LUMO of **5.27** is distributed across the B–C–B bonds whereas in **5.28**, the LUMO is delocalized around the boron and silicon atoms. The distribution of the LUMO in **5.27** lowers its energy and allows for a more facile formation of the boronate species, which then participates in transmetalation. ^{11}B NMR of 5.X and 5.X point to the formation of a boronate species of 5.X with 3.0 equiv. KOH (1:1 signals at 35.5 and –0.6 ppm) whereas with 5.X only one signal is 34.6 ppm is observed, indicating that the boronate is not formed.

(12) (a) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Org. Lett.* **2001**, *3*, 3137–3140; (b) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 14344–14345. (c) Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 15688–15701.

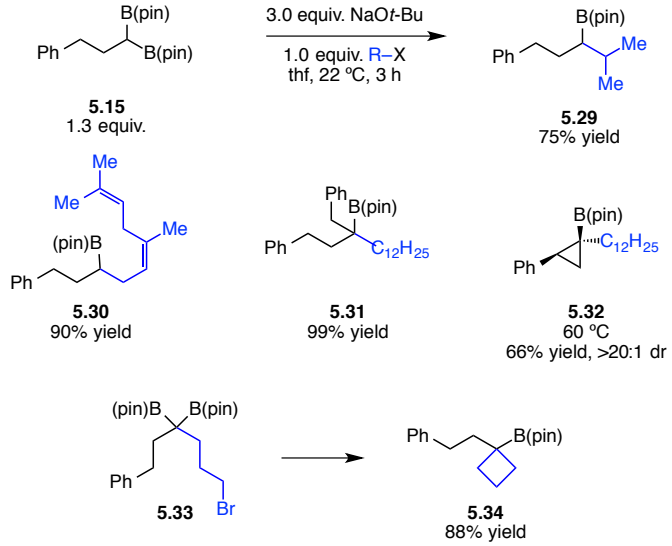
Scheme 5.4. Factors Affecting Transmetalation of *Geminyl* Disubstituted Reagents



The Morken group demonstrated that a deborylation/alkylation could be performed with a diboron reagent in the presence of NaOt-Bu and an alkylhalide.[13] As shown in Scheme 5.5, with 3.0 equivalents of NaO*t*-Bu, substituted diboron compounds can be couple with a variety of aliphatic, allylic, and benzylic halides to generate the desired products in high yields. Based on mechanistic experiments with an isotopically labeled reagent, the authors conclude, after mass spectrum analysis, that the reaction is most likely occurring through an α-boryl anion as nonspecific reaction of both B(pin) groups occurs.

(13) Hong, K; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581–10584.

Scheme 5.5. Deborylative Alkylation of *Geminyl* Diboron Reagents

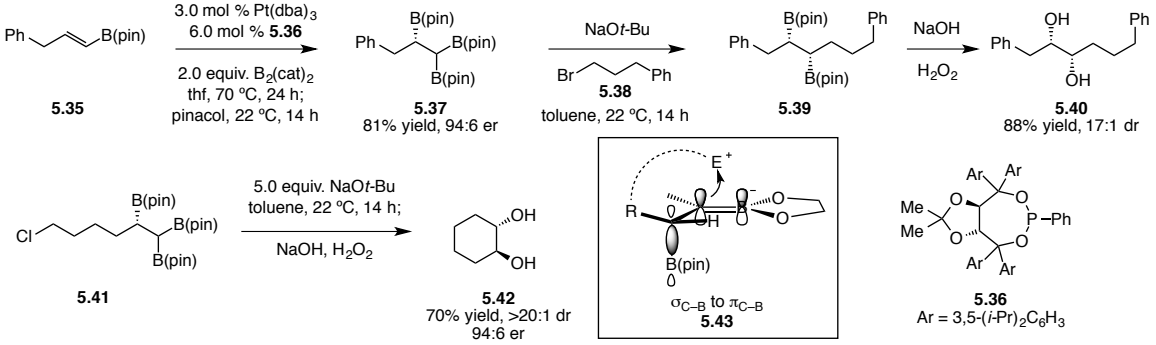


The Fu group also demonstrated that in the presence of 0.1–3.0 equiv. CuI and 3.0–8.0 equivalents of LiO*t*-Bu at elevated temperatures diborylmethane reagents are coupled with a variety of alkyl halides and tosylates.[14] Products are generated in 41–89% yield.

The Morken group was also able to demonstrate that following enantioselective diboration of alkenyl boronic acid pinacol esters the deborylative alkylation of the *tris*boronate products occurs with high diastereoselectivity.[15] In the presence of 3.0 mol % $Pt(dba)_3$ and 6.0 mol % of chiral phosphite ligand **5.36**, a range of alkyl-substituted alkenylB(pin) substrates undergo diboration with $B_2(cat)_2$ in 67–82% yield and up to 95:5 er. Aryl- as well as α-branched aliphatic substituents lead to diminished conversion as well as enantioselectivity. Deborylative/alkylation occurs in the prensence of NaO*t*-Bu in toluene at room temperature with both primary and secondary alkyl halides. Intramolecular alkylation provides access to *anti*-diols in good yields and high diastereoselectivty.

(14) Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. *Org. Lett.* **2014**, *16*, 6342–6345.
(15) Coombs, J.R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.

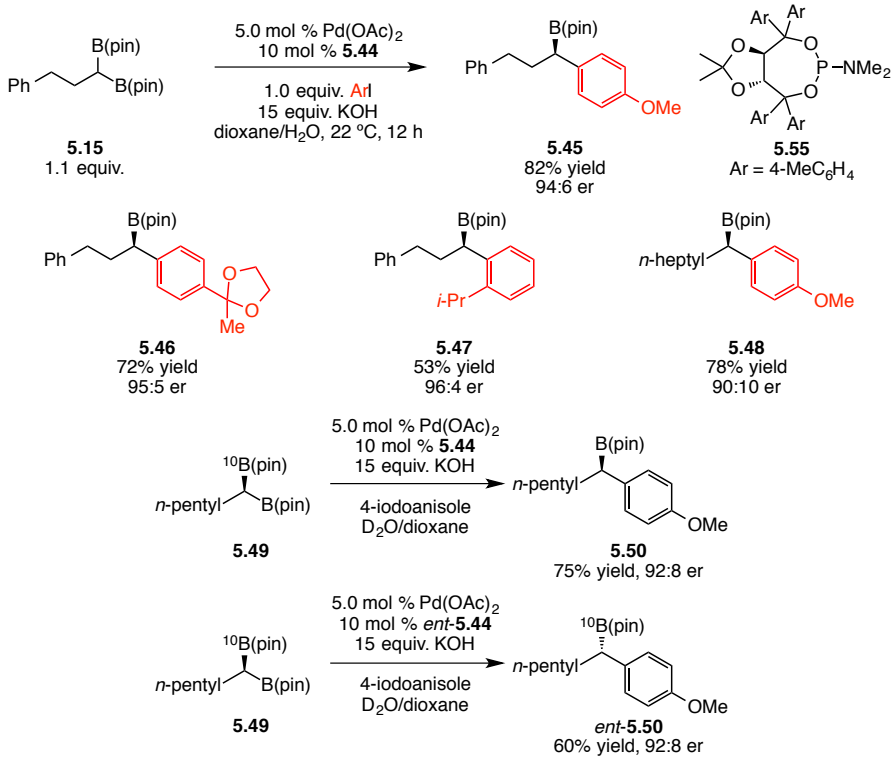
Scheme 5.6. Synthesis and Reaction of Trisboronate Compounds



Morken and co-workers demonstrated the first enantioselective cross coupling of symmetric germinal diboron compounds.[16] The reaction, catalyzed by 5.0 mol % $Pd(OAc)_2$ and 10 mol % of phosphite ligand **5.55** with 15 equiv. KOH, allows for the enantioselective cross coupling of diboron reagents with a range of aryl halide in up to 92% yield and 96:4 er. A short formal synthesis of pharmaceutical tolterodine serves to highlight the utility of this method. The authors proposed that the transmetalation occurs with inversion in a stereospecific fashion. With an enantioenriched (98:2 er) isotopically labeled ^{11}B reagent, reaction of (S)-**5.49** leads to **5.50** with phosphite **5.44** while in the presence of *ent*-**5.44**, *ent*-**5.50** is formed.

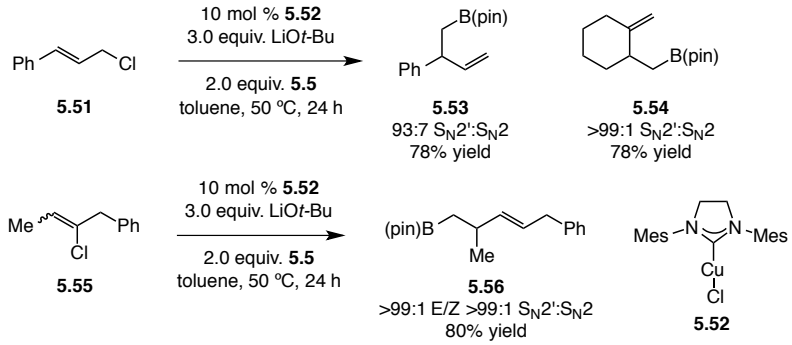
(16) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537.

Scheme 5.7. Enantioselective Cross Coupling of Diboron Reagents with Aryl Halides



More recently, Cho and co-workers disclosed the NHC–Cu-catalyzed allylic substitution of geminyl diboron reagents.[17] Reaction of allylic chlorides and diboron reagents, catalyzed by NHC–Cu complex **5.52**, occur at 50 ºC in toluene to afford racemic primary alkylB(pin) products in 55–86% yield. Notably racemic secondary allylic chlorides react to deliver the product in high *E*-selectivity for the newly formed olefin.

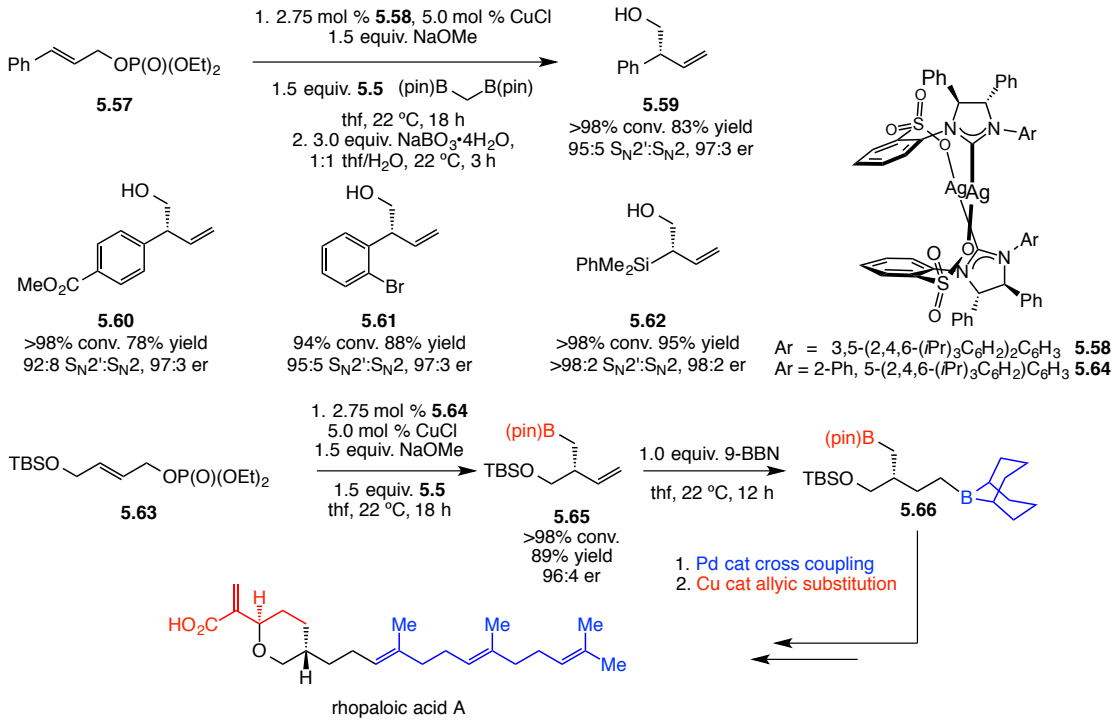
Scheme 5.8. NHC–Cu-catalyzed Allylic Substitution with Methylene Diboron



(17) Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498–1501.

The Hoveyda group disclosed the first catalytic enantioselective allylic substitution of diborylmethane to allylic phosphates.[18] With NHC–Ag **5.58** as the catalyst precursor, a range of aryl- and alkyl-substituted allylic phosphates can be coupled in an S_N2' selective fashion to deliver the desired products in 62–95% yield and 85:15–99:1 er. Formal synthesis of rhopaloic acid A highlights the utility of this method where after 9-BBN hydroboration of the terminal olefin, selective cross coupling of the two alkyl boron substituents can be achieved.

Scheme 5.9. Enantioselective Allylic Substitution of Methylene Diboron



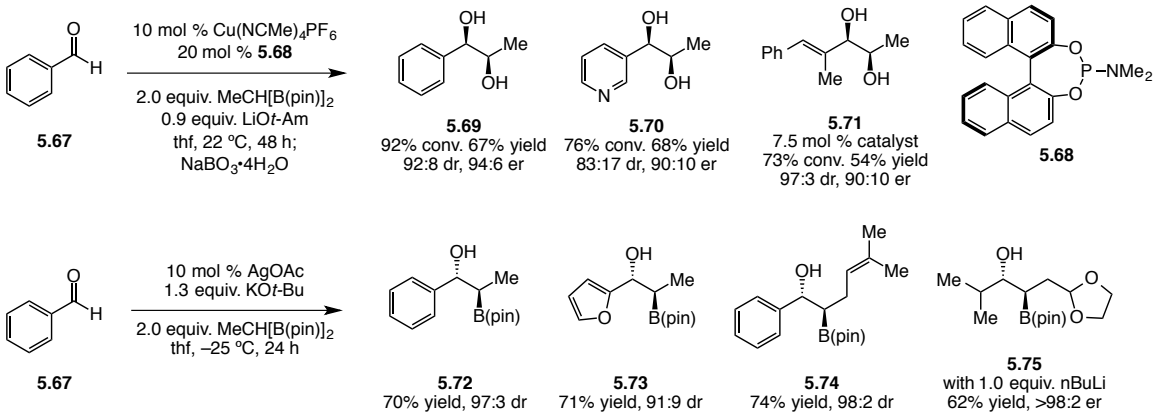
The Meek group demonstrated that in the presence of a phosphine–Cu catalyst, a substituted methylene diboron reacts with benzaldehyde to furnish syn-diol **5.69**.[19] Reaction proceed with high enantioselectivity and diastereoselectivity for a number of aryl-subsituted aldehydes. Cinnamaldhyde-derived aldehydes lead to decreased diastereoselectivity in the absence of α-branching. Based on NMR studies, the authors propose that, unlike in reactions with NaOt-Bu, in the presence of LiO*t*-Bu, ~20%

(18) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, Early View
(19) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176–6179.

conversion to the boronate is observed without any of the free α-boryl anion observed by Morken and co-workers.

The same group also disclosed a Ag-catalyzed addition of diboron reagents to access *anti*-addition products.[20] In addition to aryl-substituted aldehydes, aliphatic aldehydes are competent reaction partners. To circumvent competitive deprotonation of the aldehyde, the diboron reagent was activated with 1.0 equiv. nBuLi, which allowed for the formation of **5.75** in 62% yield and >98:2 dr.

Scheme 5.10. *Syn*- and *anti*-Diol Formation through Cu- or Ag-Catalyzed Additions to Aldehydes



5.3. Enantioselective Allylic Substitution of Diboryl Methane

5.3.a. Catalyst Screening and Reaction Optimization

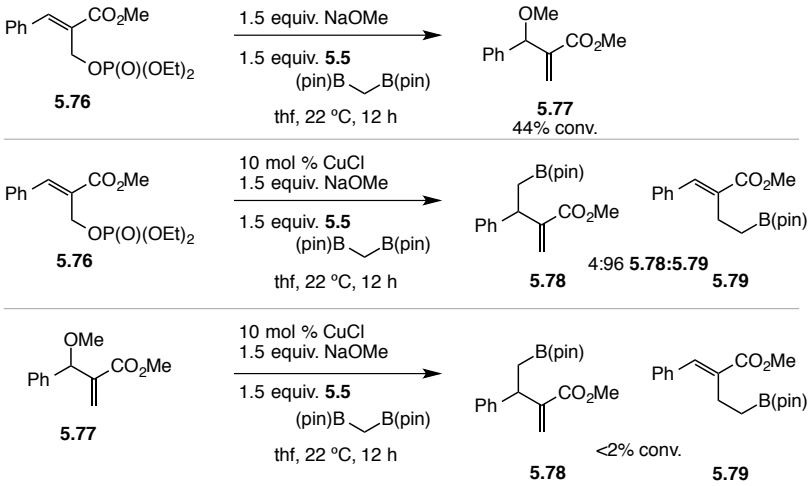
Given the abundance of natural products with important and varied biological activities that a contain an α-methylene γ-butyrolactone unit[21], we reasoned that such a motif could be accessed rapidly through lactonization of alcohol 5.X which could come from the allylic substitution of a methylB(pin) nucleophiles to an ester-containing trisubstituted allylic phosphate[22].

We began by evaluating the reactivity of methylenediboron **5.5** with allylic phosphate **5.76** in the presence of 1.5 equivalents NaOMe. After 12 h at 22 ºC, 44%

(20) Joannous, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14141–14145.
(21) (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451; (b) Janecka, A.; Wyrębska, A.; Gach, K.; Fichna, J.; Janecki, T. *Drug Discovery Today*, **2012**, *17*, 561–572.
(22) (a) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694–7699; (b) ref. 3(u).

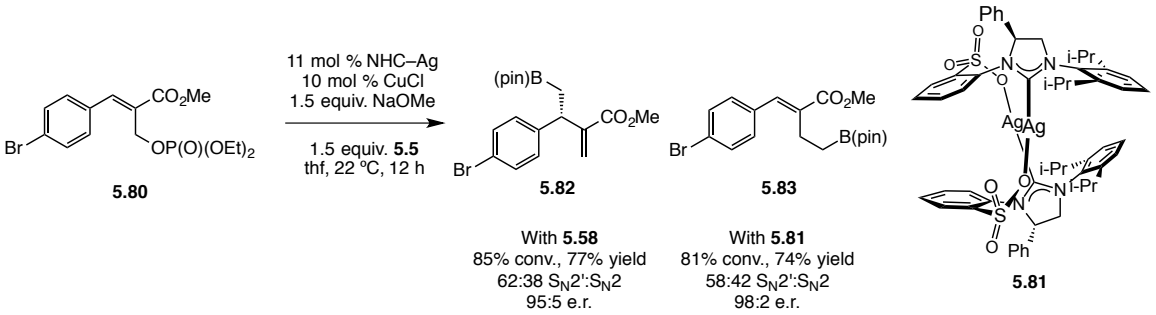
conversion of **5.76** to allylic ether **5.77** is observed. Under the same conditions, but with 10 mol % CuCl, 67% conversion to a 4:96 mixture of **5.78** and **5.79** is formed. Given the lack of **5.77** in equation 2, we hypothesized that it may be a competent electrophile and lead to the formation of **5.79**. Subjection of allylether **5.77** to the CuCl reaction results in no observable formation of **5.78** or **5.79**.

Scheme 5.11. Initial Screening of Reactivity of **5.5** with Trisubstituted Allylic Phosphates



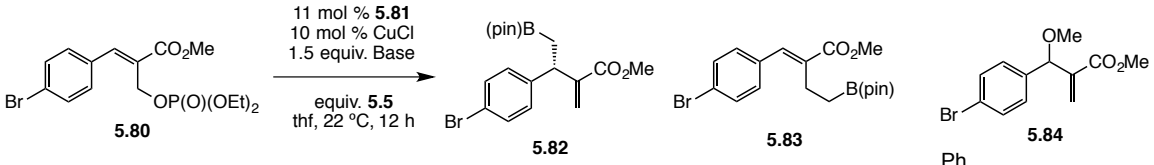
We began examining chiral NHCs as ligands for the enantioselective EAS, beginning with NHC–Ag complex **5.81**, which was the optimal catalyst precursor for reaction with disubstituted allylic phosphates. Under the reaction conditions with 11 mol % **5.81** and 10 mol % CuCl to ensure complete complexation, 85% conversion is observed to a 62:38 S_N2':S_N2 mixture with a 77% yield of the regioisomers and **5.82** formed in 95:5 er. With NHC–Ag complex **5.81**, 81% conversion of **5.80** to a 58:42 mixture of S_N2':S_N2 products is observed and the mixture of products is isolated in 74% yield and 98:2 er.

Scheme 5.12. Initial Screening of NHC–Ag Precursors

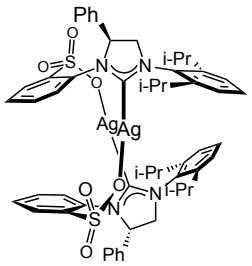


Given the high enantioselectivity achieved with **5.81**, we examined the ratio of reagents to improve the conversion and regioselectivity. With 1.0 equivalents **5.5**, competitive methoxide addition leads to a 44:7:49 mixture of **5.82**:**5.83**:**5.84**. Reaction in the presence of 2.0 equivalents **5.5** results a 21:79 mixture of **5.82**:**5.83**. Increased diboron reagents leads to increased S_N2 reaction, indicating that the diboron reagent may be able to add to the substrate without direct reaction with the NHC–Cu complex. The nature of the base, which is necessary to activate the diboron reagents for transmetalation, was also examined. Reaction in the presence of 1.5 equiv. NaO*t*-Bu (versus NaOMe) leads to >98% conversion to **5.83** exclusively. Reaction with 1.5 equiv. NaOPh leads to decomposition of the substrate with no discernable conversion to product. Changing to the counterion to LiOMe results in ~20% conversion of **5.80** to **5.82** exclusively. Reaction in the presence of KOMe leads to >98% conversion **5.80** to a 13:87 mixture of S_N2':S_N2. Increased nucleophilicity of the base leads to increased S_N2 product. One explanation may be that the more nucleophlic bases result in increased formation of the reactive boronate, which is able to displace the phosphate leaving group.

Table 5.1. Effect of Base and Equivalents of **5.5** on Allylic Substitution[(a)]



entry	equiv. **5.5**; base	conv. (%)[(b)]	**5.82:5.83:5.84**
1	1.0; NaOMe	80	44:7:48
2	1.5; NaOMe	81	58:42:0
3	2.0: NaOMe	87	21:79:0
4	1.5; LiOMe	20	>98:<2:0
5	1.5; KOMe	>98	13:87:0
6	1.5; NaO*t*-Bu	>98	<2:>98:0
7	1.5; NaOPh	<2	n.d.

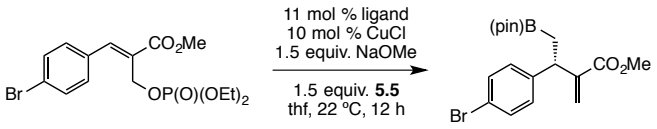


5.81

[(a)] Reactions run under N_2 atmosphere. [(b)] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. n.d. = not determined

Further screening of NHC–Ag catalyst precursors is shown in Table 5.1. Decreasing the sterics of the N-aryl group to a mesityl or 2-Me,6-*i*-PrC_6H_3 (vs 2,6-(*i*-Pr)$_2C_6H_3$) results in 86:14 and 70:30 S_N2':S_N2 selectivity respectively although the enantioselectivity drops to 79:21 and 89:11 er. Increasing the sterics of the N-aryl group leads to increased S_N2 selectivity. **5.86** with a diphenyl backbone and a single isopropyl group at the 2-position leads to high regioselectivity (97:3 S_N2':S_N2) and moderate enantioselectivity, 86:14 er. In an effort to increase the enantioselectivity, we removed one of the phenyl groups from the backbone, which should allow for a higher freedom of rotation of the N-aryl unit, therefore increasing its effective size. Unfortunately, the regioselectivity of the reaction decreased to 84:16 S_N2':S_N2, while the enantioselectivity remained the same. Based on the above screening, we tested NHC–Ag **5.92** with a 2,5-(*t*-Bu)$_2C_6H_3$ N-aryl group and a diphenyl backbone; >98% conversion with 97% S_N2' selectivity is observed and the desired alkylboron is obtained in 85% yield and 97:3 er.

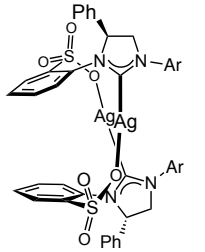
Table 5.2. Screening of NHC–Ag Complexes[(a)]



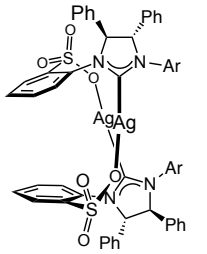
5.80 **5.82**

entry	ligand	conv. (%)[b]	$S_N2':S_N2$[b]	yield (%)[c]	er[d]
1	**5.85**	90	84:16	80	79:21
2	**5.81**	81	58:42	74	98:2
3	**5.86**	95	84:16	90	86:14
4	**5.87**	85	15:85	nd	nd
5	**5.58**	85	62:38	77	95:5
6	**5.88**	89	97:3	86	86:14
7	**5.89**	82	6:94	nd	nd
8	**5.90**	>98	70:30	50	89:11
9	**5.91**	75	10:90	nd	nd
10	**5.92**	>98	97:3	85	97:3
11	**5.93**	90	3:97	nd	nd
12	**5.94**	67	8:92	nd	nd

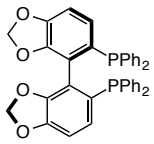
[a]Reactions were performed under N_2 atmosphere. [b] Determined by anaylsis of 400 MHz ^{1}H NMR of unpurified mixtures. [c]Yield of isolated and purified products. [d]Determined by HPLC analysis. nd = not determined



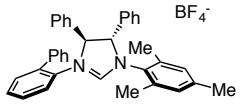
5.85 Ar = 2,4,6-$Me_3C_6H_2$
5.81 Ar = 2,6-$iPr_2C_6H_3$
5.86 Ar = 2-$iPrC_6H_4$



5.87 Ar = 2,4,6-$iPr_3C_6H_2$
5.58 Ar = 3,5-(2,4,6-$iPr_3C_6H_2$)C_6H_3
5.88 Ar = 2-$iPrC_6H_4$



5.93



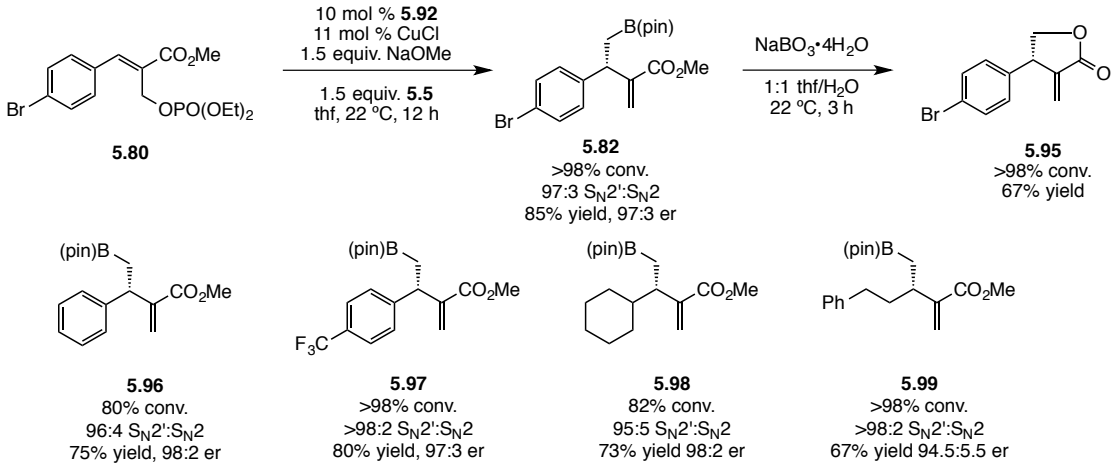
5.94

5.89 Ar = 2-PhC_6H_4
5.90 Ar = 2-Ph,6-MeC_6H_3
5.91 Ar = 2-iPr,6-MeC_6H_3
5.92 Ar = 2,5-(tBu)$_2C_6H_3$

5.3.b. Scope of Addition of Methylene Diboron to Morita-Baylis-Hillman type Allylic Phosphates

After determining the optimal ligand, we moved on to examining the scope of the reaction. Phenyl-substituted allylic phosphate is converted to 5.96 in 80% conversion and 96:4 $S_N2':S_N2$ selectivity with 75% yield and 98:2 er. Addition of an electron withdrawing group, *para*-trifluoromethyl, allows for the formation of **5.97** in 80% yield and >98:2 $S_N2':S_N2$. α-Branched cyclohexyl-containing **5.98** is generated in 73% yield and 95:5 $S_N2':S_N2$ with 98:2 er. While high regioselectivity (>98:2 $S_N2':S_N2$) is achieved for the formation of **5.99**, the enantioselectivity drops slightly to 94.5:5.5 er. Following oxidation of **5.82** with $NaBO_3•H_2O$, spontaneous lactonization occurs and **5.95** is formed in 67% yield.

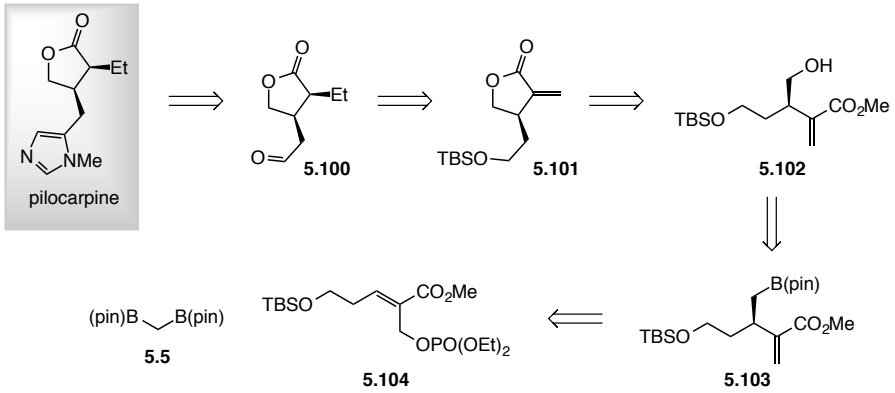
Scheme 5.13. Scope of NHC–Cu-Catalyzed EAS



5.3.c. Proposed Route to Pilocarpine

In order to demonstrate the utility of our method, we devised the syntheses of several lactone-containing natural products. As shown in Scheme 5.14, pilocarpine[23], used for the treatment of glaucoma, can be synthesized from aldehyde **5.100** which can be generated from **5.101** following a methyl conjugate addition and oxidation. **5.101** is synthesized from acyclic alcohol **5.102** which is the oxidized product of alkylB(pin) **5.103**.

Scheme 5.14. Retrosynthetic Analysis of Pilocarpine

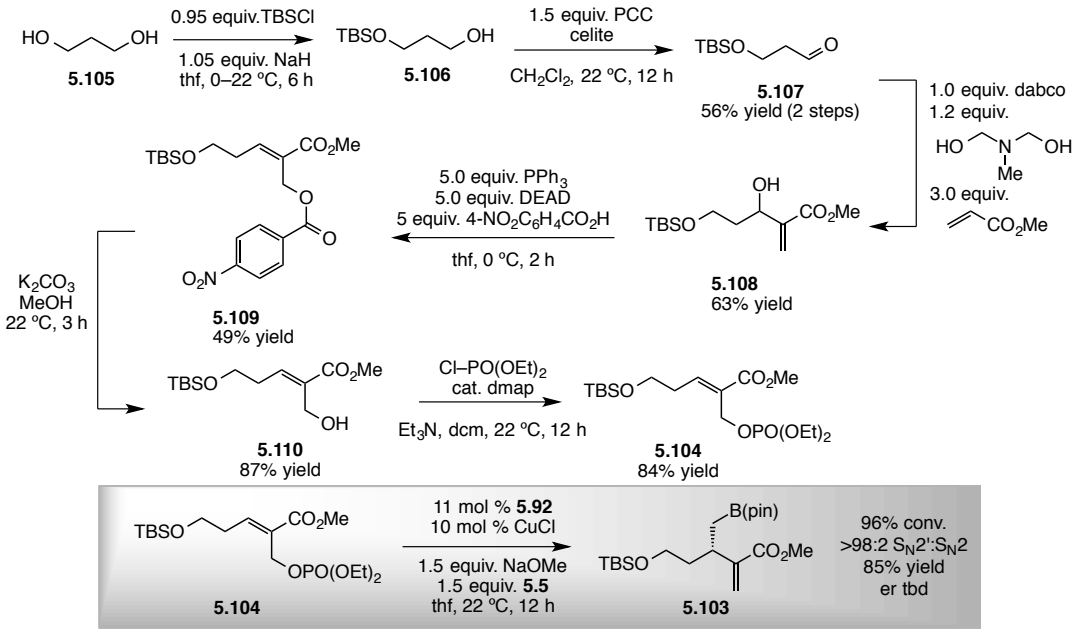


In a forward sense, our synthesis begins with silyl protection of commercially available propane diol, **5.105**, and subsequent PCC oxidation to afford **5.107** in 56%

(23) (a) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198–8199; (b) Wang, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 5213-5216; (c) Horne, D. A.; Fugmann, B.; Yakushijin, K.; Buchi, G. *J. Org. Chem.* **1993**, *58*, 62-64; (c) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713.

yield over 2 steps. Morita-Baylis-Hillman with methyl acrylate catalyzed by dabco leads to secondary alcohol **5.108**. Under Mitsunobu conditions, allylic displacement of the alcohol with nitro benzoic acid forms **5.109** in 49% yield. Saponification and phosphorylation generate the desired allylic phosphate in 73% yield (over two steps). Under our optimized reaction conditions with 11 mol % **5.92** and 10 mol % CuCl, **5.104** is formed in 85% yield and >98:2 S_N2':S_N2. The remainder of the synthesis, which involves concomitant oxidation/cyclization followed by methyl conjugate addition and deprotection/oxidation is ongoing.

Scheme 5.15. Synthesis of Pilocarpine Precursor



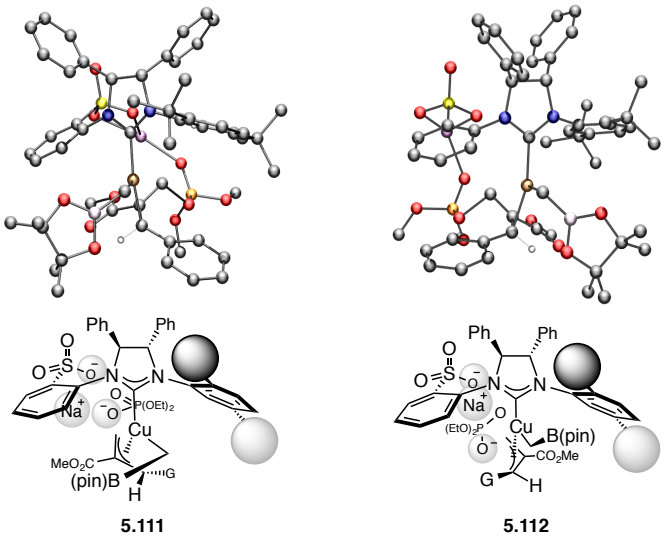
5.3.d. DFT Calculations and Proposed Model for Enantioselectivity

In order to better understand the high level of enantioselectivity observed in the reaction, DFT calculations were performed. Based on our previous system for NHC–Cu-catalyzed addition of propargyl boron reagents to allylic phosphates, we examined a model where the sulfonate-containing NHC acts as a monodentate ligand.[24] In such a model, the sulfonate sits such that it is *anti* to the adjacent phenyl group on the backbone to minimize steric interaction. The sulfonate coordinates to a sodium cation, which then coordinates to the Lewis basic oxygen of the allylic phosphate. In the transition state that forms the major enantiomer, the substrate approaches from below the catalyst with the

[24] See ref. 3v.

phosphate in the back right and the large substituent (phenyl) in the front right. As such, the large B(pin) group sits in the relatively open front left, pointed away from the *ortho t*-Bu group of the N-aryl ring. In order to form the minor enantiomer, the Cu-center coordinates the other face of the olefin, which situates the large group in the front left. In order to minimize steric repulsion with the large group, the B(pin) moiety sits in the front right in close proximity to the *ortho t*-Bu group. The calculated $\Delta\Delta G^{\neq}$ for the two transition states is 2.6 kcal/mol.

Scheme 5.16. Model for enantioselectivity based on DFT calculations



5.111 **5.112**

5.4. Conclusions

We have developed a method for the allylic substitution of diboryl methane to a variety of trisubstituted allylic phosphates to generate tertiary centers. Reactions are catalyzed by an NHC–Cu complex derived from a 2,5-di*tert*-butylphenyl containing imidazolinium salt. Products are generated in up to 85% yield and 98:2 er. Products can be oxidized to rapidly form α-methylene lactones, a motif found in a number of natural products. We have begun efforts toward a synthesis of natural product pilocarpine. Through DFT calculations, we have devised a working stereochemical model to account for the high levels of enantioselectivity observed.

5.5 Experimental

General. Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectrometry were performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiraldex CDB-DM column (30 m x 0.25 mm)) or by analytical liquid chromatography (HPLC) analysis on a Shimadzu chromatograph (Chiral Technologies Chiralcel OD-H (4.6 x 250 mm) and Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm)), in comparison with authentic racemic materials. For the GLC analysis, the inlet and detector temperatures are set to 250 °C and runs were isothermal of the temperature given with ultra high purity helium as the carrier gas. Specific rotations were measured on an ATAGO AP-300 Automatic Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and Hexanes were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with Ar and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) in air.

■Reagents and Metal-based Complexes:

Allylic phosphates[1] were prepared following previously reported methods.

Bis[(pinacolato)boryl]methane[2] was prepared following previously reported methods.

Copper (I) Chloride was purchased from Strem and used as received.

Lithium methoxide was purchased from Strem and used as received.

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(1) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694–7699.
(2) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537.

NHC–Ag complexes[3] were prepared following previously reported methods.

Potassium methoxide was purchased from Strem and used as received.

Sodium methoxide was purchased from Strem and used as received.

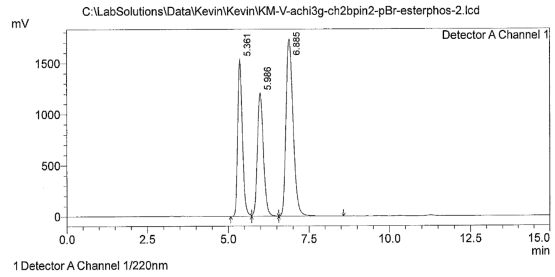
Sodium phenoxide was purchased from Alfa Aesar and used as received.

Sodium *tert*-butoxide was purchased from Strem and used as received.

Representative Procedure for Cu-catalyzed Allylic Substitution with 5.5: An oven-dried 1-dram vial was charged with NHC–Ag complex (7.4 mg, 0.011 mmol), CuCl (1.0 mg, 0.01 mmol), and NaOMe (8.4 mg, 0.15 mmol) weighed under an N_2 atmosphere in a glove box. The vial was sealed with a cap with septum. Tetrahydrofuran (thf; 0.5 mL) was added with a syringe to the vial, and the resulting blue solution was allowed to stir for five minutes, followed by the addition of a solution of diboron reagent **5.5** (40.2 mg, 0.15 mmol) in thf (0.5 mL) through a syringe resulting in a brown solution. The mixture was allowed to stir at 22 ºC for five min, after which time, a solution of allylic phosphate **5.80** (35.6 mg, 0.1 mmol) in thf (0.5 mL) was added. The reaction was allowed to stir at 22 ºC for 12 h after which the crude mixture was passed though a short plug of silica gel and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel chromatography to give **5.82** as colorless oil (33.5 mg, 0.085 mmol, 85% yield).

Methyl-(*S*)-3-(4-bromophenyl)-2-methylene-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (5.82). IR (neat): 2977 (w), 2931, (w), 1721 (w), 1627 (w), 1485 (w), 1467 (w), 1438 (w), 1367 (m), 1317 (s), 1269 (m), 1214 (w), 1141 (s), 1098 (w), 1072 (w), 1036 (w), 1010 (s), 967 (m), 890 (w), 845 (m), 817 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.33 (2H, m), 7.12–7.09 (2H, m), 6.26 (1H, s), 5.68 (1H, s), 4.11 (1H, t, J = 8 Hz), 3.62 (3H, s), 1.35–1.23 (2H, m), 1.11 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 145.0, 143.7, 131.3, 129.7, 123.9, 120.0, 83.4, 83.1, 51.9, 41.6, 24.9; HMRS (ESI^+): Calcd for $C_{18}H_{25}BBrO_4$ $[M+H^+]$: 395.1029 m/z. Found: 395.1023 m/z. Specific rotation $[\alpha]^{20}$ –37.0 (*c* 0.81, $CHCl_3$) for a sample of 98:2 er. Enantiomeric purity (98:2 er) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.

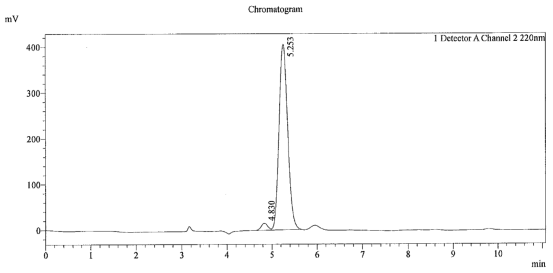
(3) (a) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 419–423.



PeakTable

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	5.361	15708815	1538004	27.210
2	5.986	15826422	1208345	27.414
3	6.885	26196186	1732738	45.376
Total		57731423	4479087	100.000



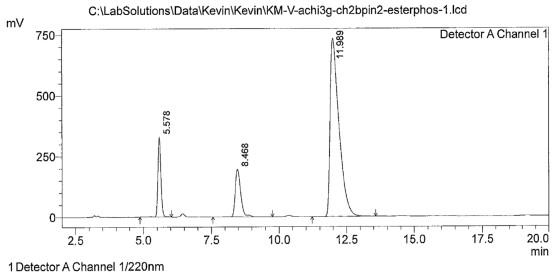
Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time	Area	Height	Conc.
1	4.830	153111	15342	2.774
2	5.253	5365817	405171	97.226
Total		5518928	420513	

Retention Time	Area	Area %	Retention Time	Area	Area %
5.361	15708815	49.813	4.830	153111	2.774
5.986	15826422	50.187	5.253	5365817	97.226

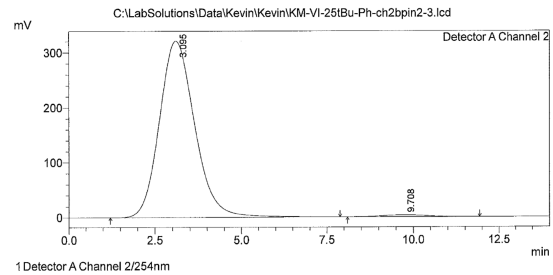
Methyl-(*S*)-2-methylene-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate-3-*d* (5.96). IR (neat): 2978 (w), 2931 (w), 1722 (m), 1626 (w), 1493 (w), 1437 (w), 1389 (w), 1359 (m), 1320 (m), 1272 (w), 1212 (w), 1143 (s), 1111 (w), 1082 (w), 1059 (w), 1006 (w), 986 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.21 (m, 4H), 7.17–7.12 (m, 1H), 6.25 (d, 1H, *J* = 0.8 Hz), 5.68 (d, 1H, *J* = 0.8 Hz), 3.65 (s, 3H), 1.39–1.28 (m, 2H), 1.11 (d, 12H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 145.4, 144.5, 128.3, 127.9, 126.2, 123.6, 83.351.9, 31.6, 24.9, 24.8, 24.7; HMRS (ESI^+): Calcd for $C_{18}H_{25}DBO_4$ $[M+H^+]$: 318.1987 m/z. Found: 318.2003 m/z. Specific rotation $[\alpha]^{20}$ –53.7 (*c* 2.0, $CHCl_3$) for a sample of 98.2 er. Enantiomeric purity (98:2 er) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



PeakTable

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	5.578	2607559	329442	11.698
2	8.468	2717194	195876	12.190
3	11.989	16966225	732589	76.113
Total		22290978	1257908	100.000



PeakTable

Detector A Channel 2 254nm

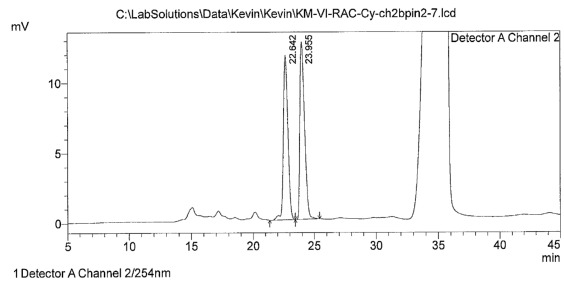
Peak#	Ret. Time	Area	Height	Area %
1	3.095	22679042	320998	98.749
2	9.708	287234	3176	1.251
Total		22966277	324174	100.000

Retention Time	Area	Area %	Retention Time	Area	Area %
5.578	2607559	48.766	3.095	22679042	98.749
8.468	2717194	51.234	9.708	287234	1.251

Methyl-(*S*)-2-methylene-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(4-(trifluoromethyl)phenyl)butanoate (5.97). IR 2979 (w), 1722 (w), 1617 (w), 1439 (w), 1369 (w), 1322 (s), 1278 (w), 1262 (w), 1191 (w), 1161 (m), 1143 (m), 1124 (m), 1068

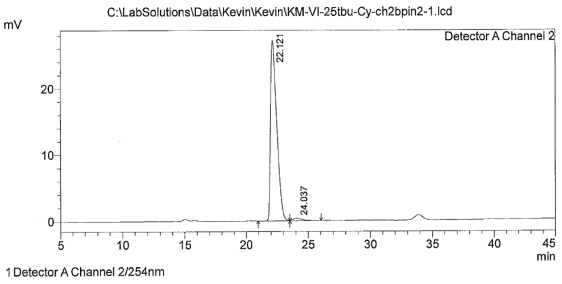
(m), 1019 (w), 968 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 8.4 Hz), 7.35 (d, 1H, J = 8.4 Hz), 6.32 (s, 1H), 5.74 (s, 1H), 4.22 (t, 1H, J = 8.4 Hz), 3.65 (s, 3H), 1.34 (dq, 2H, J = 8.0, 14.6 Hz), 1.11 (s, 6H), 1.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 148.7, 144.4, 128.4 (q, $J_{C–F}$ = 32 Hz), 128.1, 125.1 (q, $J_{C–F}$ = 3.8 Hz), 124.5 (q, $J_{C–F}$ = 270 Hz), 124.1, 83.3, 51.8, 41.9, 24.7, 24.6, 24.6; HRMS (ESI^+): Calcd for $C_{19}H_{25}BF_3O_4$ [M+H^+]: 385.1798. Found: 385.1803. Specific rotation $[\alpha]^{20}$ –58.4 (*c* 2.43, $CHCl_3$).

Methyl-(*S*)-3-cyclohexyl-2-methylene-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (5.98). IR 2978 (w), 2924 (w), 2851 (w), 1719 (m), 1623 (w), 1437 (w), 1364 (m), 1320 (m), 1268 (w), 1227 (w), 1200 (w), 1143 (s), 1001 (w), 967 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.48 (s, 1H), 3.73 (s, 3H), 2.71 (dt, 1H, J = 6.0, 10.8 Hz), 1.72–1.59 (5H, m), 1.39–1.30 (m, 1H), 1.26–1.05 (m, 5H), 1.18 (s, 6H), 1.16 (s, 6H), 0.98–0.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 145.2, 124.4, 83.1, 51.8, 43.0, 41.8, 31.3, 29.7, 26.71, 26.69, 26.68, 25.0, 24.7; HRMS (ESI^+): Calcd for $C_{18}H_{32}BO_4$ [M+H^+]: 323.2394. Found: 323.2302. Specific rotation $[\alpha]^{20}$ –1.31 (*c* 1.91, $CHCl_3$) for a sample of 98:2 er. Enantiomeric purity (98:2 er) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OZ-H, 99.5% Hexanes, 0.5% *i*PrOH, 1.0 mL/min, 254 nm.



PeakTable
Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Area %
1	22.642	301777	11730	46.948
2	23.955	341013	12638	53.052
Total		642790	24368	100.000



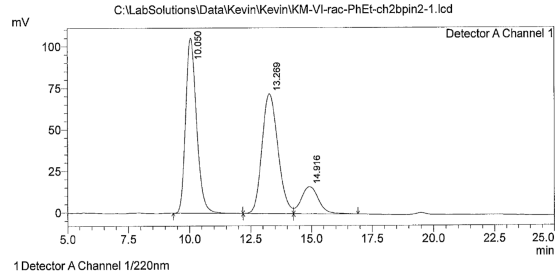
PeakTable
Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Area %
1	22.121	972811	27208	97.960
2	24.037	20256	418	2.040
Total		993067	27626	100.000

Retention Time	Area	Area %	Retention Time	Area	Area %
22.642	301777	46.948	22.121	972811	97.960
23.935	341013	53.052	24.037	20256	2.040

Methyl-(*S*)-2-methylene-5-phenyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl) pentanoate (5.99). IR 3025 (w), 2977 (w), 2926 (w), 2855 (w), 1719 (m), 1625 (w), 1496 (w), 1454 (w), 1437 (w), 1369 (m), 1321 (m), 1269 (m), 1197 (m), 1143 (s), 1107 (w), 1030 (w), 1004 (w), 968 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 7.17–7.14 (m, 3H), 6.20 (s, 1H), 5.58 (s, 1H), 3.75 (s, 3H), (app pent, 1H, J = 7.2 Hz), 2.55 (app t, 2H, J = 8.0 Hz), 1.92–1.83 (m, 1H), 1.80–1.71 (m, 1H), 1.21 (s, 6H), 1.20 (s, 6H), 1.08 (dq, J = 6.8, 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 145.7, 142.8, 128.5, 128.4, 125.7, 124.0, 83.2, 51.8, 38.7, 36.6, 33.7, 24.9; HRMS (ESI^+):

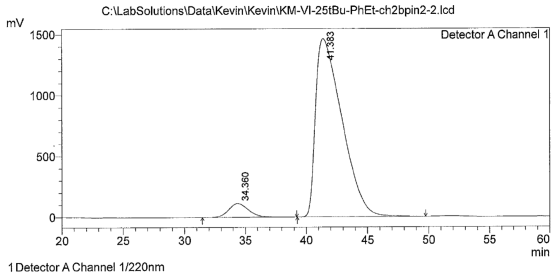
Calcd for $C_{20}H_{30}BO_4$ [M+H$^+$]: 345.2247. Found: 345.2247. Specific rotation $[\alpha]^{20}$ –25.7 (*c* 1.36, $CHCl_3$) for a sample of 94.5:5.5 er. Enantiomeric purity (94.5:5.5 er) was determined by HPLC analysis in comparison with authentic racemic material; Chiracel OJ-H, 99% Hexanes, 1% *i*PrOH, 1.0 mL/min, 254 nm.



PeakTable

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	10.050	3282514	105453	44.437
2	13.269	3298602	72270	44.654
3	14.916	805849	16285	10.909
Total		7386965	194008	100.000



PeakTable

Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Height	Area %
1	34.360	13135227	113746	5.645
2	41.383	219560847	1463112	94.355
Total		232696074	1576859	100.000

Retention Time	Area	Area %	Retention Time	Area	Area %
10.050	3282514	49.878	34.360	13135227	5.645
13.269	3298602	50.122	41.383	219560847	94.355

Methyl-(*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylene-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pentanoate (5.103). IR 2978 (w), 2953 (w) 2929 (w), 2856 (w), 1721 (m), 1471 (w), 1437 (w), 1369 (w), 1320 (w), 1255 (w), 1216 (w), 1198 (w), 1143 (s), 1098 (m), 1005 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.55 (s, 1H), 3.73 (s, 3H), 3.56 (app t, 2H, *J* = 6.8 Hz), 2.91 (app pent, 1H, *J* = 8.0 Hz) 1.84–1.75 (m, 1H), 1.74–1.65 (m, 1H), 1.20 (s, 6H), 1.196 (s, 6H), 1.04 (dq, 2H, *J* = 6.8, 15.6 Hz). 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 145.5, 124.0, 83.1, 61.6, 51.7, 39.5, 33.8, 26.1, 24.9, 24.9, 18.4, -5.2; HRMS (ESI$^+$): Calcd for $C_{20}H_{40}BO_5Si$ [M+H$^+$]: 399.2738. Found: 399.2738. Specific rotation $[\alpha]^{20}$ –6.8 (*c* 2.95, $CHCl_3$).

Methyl-(*E*)-5-((*tert*-butyldimethylsilyl)oxy)-2-(((diethoxyphosphoryl)oxy)methyl) pent-2-enoate (5.104). IR 2955 (w), 2930 (w), 2857 (w), 1720 (m), 1472 (w), 1437 (w), 1391 (w), 1323 (w), 1245 (m), 1215 (w), 1166 (w), 1140 (w), 1098 (w), 1007 (s), 878 (w), 834 (m), 776 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, 1H, *J* = 8.0 Hz), 4.81 (d, 2H, *J* = 6.8 Hz), 4.10 (app pent, 4H, *J* = 6.8 Hz), 3.78 (s, 3H), 3.73 (t, 2H, *J* = 6.4 Hz), 2.58 (q, 2H, *J* = 6.4 Hz), 1.35–1.30 (m, 6H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 147.0, 128.9, 66.1, 63.9, 63.8, 61.5, 60.9, 60.8, 52.1, 32.4, 25.9, 25.8, 18.4, 16.3, 16.2, –5.3; HRMS (ESI$^+$): Calcd for $C_{17}H_{36}O_7PSi$ [M+H$^+$]: 4111.1968. Found: 411.1963.

DFT Calculations

`Transition state leading to the major enantiomer (5.111)`

```
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```

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 Cartesian coordinates (Angstroms):
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H  -1.515   3.752   1.164
C  -0.777   0.919   0.162
C  -1.594   0.876  -2.167
C  -2.754   0.080  -2.093
C  -0.943   1.030  -3.418
C  -3.277  -0.535  -3.239
H  -3.259  -0.044  -1.130
C  -1.491   0.428  -4.564
C  -2.657  -0.346  -4.482
H  -4.183  -1.143  -3.156
H  -0.972   0.559  -5.518
H  -3.071  -0.805  -5.386
S   0.604   1.969  -3.660
O   1.219   1.393  -4.919
O   1.477   1.655  -2.458
O   0.227   3.416  -3.776
Cu  -0.668  -1.004   0.405
C  -2.507   3.660  -1.231
C  -2.557   4.704  -2.176
C  -3.703   3.232  -0.620
C  -3.779   5.323  -2.489
H  -1.635   5.017  -2.676
C  -4.924   3.845  -0.937
H  -3.681   2.409   0.103
C  -4.965   4.896  -1.870
H  -3.803   6.134  -3.225
H  -5.847   3.499  -0.457
H  -5.919   5.375  -2.118
N  -1.155   1.543  -0.979
N  -0.553   1.858   1.115
C  -0.018  -2.881   0.392
C   0.565  -3.426   1.646
C  -0.292  -4.142   2.523
C   1.938  -3.337   1.985
C   0.197  -4.716   3.703
C   2.422  -3.923   3.166
C   1.557  -4.604   4.038
H  -0.488  -5.263   4.362
H   3.492  -3.858   3.394
H   1.942  -5.058   4.958
C   0.675  -2.135  -0.651
C   1.713  -1.192  -0.410
H   2.646  -2.864   1.298
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O   4.487  -0.449  -2.336
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O   3.458  -2.080  -0.489
Na   3.190   0.601  -3.800
H  -1.349  -4.252   2.258
C   4.625  -4.324  -2.182
H   4.651  -4.968  -3.073
H   5.514  -4.522  -1.557
H   3.712  -4.529  -1.597
C   7.176  -1.636  -1.387
H   7.981  -1.780  -0.651
H   7.310  -2.346  -2.223
H   7.205  -0.603  -1.774
C   0.103   1.605   2.383
C  -0.526   1.683   3.657
C   1.497   1.361   2.272
C   0.342   1.463   4.758
C   2.339   1.179   3.379
C   1.711   1.226   4.642
H   2.297   1.090   5.557
H   1.913   1.368   1.262
H   1.714   3.151  -0.795
H   3.712   4.596  -0.467
C   1.696   3.936  -0.029
C   2.823   4.753   0.155
C   0.543   4.132   0.760
C   2.815   5.771   1.125
H   3.696   6.408   1.262
C   0.541   5.157   1.726
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H  -0.355   5.321   2.337
H   1.649   6.768   2.664
C  -2.144  -1.379   1.640
H   1.913  -0.891   0.620
H   1.936  -0.445  -1.174
B  -3.246  -2.307   1.062
O  -3.327  -3.680   1.305
O  -4.296  -1.857   0.258
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C  -4.392  -4.227   0.454
C  -3.711  -4.801  -0.800
H  -4.444  -5.271  -1.480
H  -2.988  -5.576  -0.491
H  -3.158  -4.024  -1.354
C  -5.104  -5.340   1.229
H  -5.483  -4.983   2.200
H  -4.403  -6.171   1.417
H  -5.954  -5.738   0.646
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H  -5.161  -2.983  -2.025
H  -6.478  -1.972  -1.358
H  -6.627  -3.751  -1.349
C  -6.337  -2.680   1.244
H  -5.894  -2.700   2.255
H  -7.154  -3.421   1.204
H  -6.771  -1.678   1.081
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C   4.358   0.932   1.813
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C   4.547   2.224   3.955
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C  -2.985   2.242   2.876
C  -2.060   3.218   4.962
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H  -1.494   3.078   5.899
H  -3.109   3.435   5.234
H  -2.802   3.221   2.405
H  -4.014   2.274   3.277
H  -2.954   1.464   2.099
C  -2.563   0.740   4.823
H  -2.578  -0.162   4.187
H  -3.598   0.947   5.152
H  -1.965   0.511   5.721
H   3.962   0.049   1.281
H   5.460   0.850   1.802
H   4.089   1.839   1.242
H   4.277   3.164   3.441
H   5.646   2.114   3.919
H   4.251   2.319   5.015
H   3.806  -1.178   3.557
H   4.035  -0.269   5.077
H   5.390  -0.428   3.927
C   0.280  -2.490  -2.053
O  -0.684  -3.196  -2.353
O   1.146  -1.997  -2.982
C   0.859  -2.405  -4.345
H   1.634  -1.928  -4.959
H  -0.142  -2.059  -4.646
H   0.913  -3.502  -4.432
H  -2.559  -0.392   1.892
H  -1.661  -1.812   2.533
H  -0.820  -3.510  -0.015
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 SCF Done:  E(RB-P86) =  -5641.26711795     A.U. after    1
cycles
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Frequencies --  -220.3318           7.8223           16.7697
 Red. masses --    9.0463           5.6596            5.0791

 Zero-point correction=                           1.118232
(Hartree/Particle)
 Thermal correction to Energy=                    1.195869
 Thermal correction to Enthalpy=                  1.196813
 Thermal correction to Gibbs Free Energy=         1.000850
 Sum of electronic and zero-point Energies=         -5640.148886
 Sum of electronic and thermal Energies=            -5640.071249
 Sum of electronic and thermal Enthalpies=          -5640.070304
 Sum of electronic and thermal Free Energies=       -5640.266268

         Item               Value     Threshold  Converged?
 Maximum Force            0.000004     0.000450     YES
 RMS     Force            0.000000     0.000300     YES
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Transition state leading to the minor enantiomer (5.112)

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 Cartesian coordinates (Angstroms):
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C   1.584   4.109   2.320
C   2.238   4.511   3.491
C   3.410   3.857   3.910
C   2.074   3.027   1.540
C   3.267   2.391   1.964
C   3.922   2.806   3.134
C   1.358   2.689   0.282
C   1.678   1.620  -0.651
C   2.235   0.362  -0.291
O   4.191   0.479  -0.407
P   4.973  -0.522  -1.302
O   4.287  -1.769  -1.834
O   5.601   0.410  -2.501
O   6.292  -1.053  -0.464
C   6.391  -0.255  -3.515
C   7.119  -0.074   0.210
C   1.517   1.986  -2.095
O   0.931   2.987  -2.510
O   2.159   1.117  -2.921
C   2.191   1.521  -4.313
H   0.687   4.641   1.984
H   1.838   5.350   4.072
H   3.927   4.177   4.822
H   3.722   1.611   1.348
H   4.852   2.306   3.431
H   0.938   3.568  -0.220
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H   2.162  −0.471  −0.992
H   2.280   0.081   0.762
H   6.743   0.533  −4.199
H   5.779  −0.985  −4.071
H   7.260  −0.768  −3.066
H   7.946  −0.632   0.674
H   6.543   0.456   0.987
H   7.526   0.659  −0.509
H   2.679   0.693  −4.843
H   2.777   2.449  −4.420
H   1.172   1.690  −4.693
C  −1.621  −2.341   1.917
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N  −0.707  −1.165   1.746
C  −0.941  −0.436   0.626
N  −1.987  −0.992  −0.038
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C  −3.711  −0.421  −3.333
C  −2.744  −0.938  −4.195
C  −1.492  −1.369  −3.712
C  −1.299  −1.261  −2.326
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C   0.882  −2.299  −3.966
C  −0.225  −1.130  −5.899
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C   0.341  −0.908   2.692
C   1.492  −1.732   2.797
C   2.463  −1.446   3.773
C   2.308  −0.358   4.644
C   1.169   0.453   4.549
C   0.192   0.172   3.583
S   1.782  −3.215   1.772
O   1.470  −2.813   0.342
O   0.879  −4.283   2.320
O   3.255  −3.529   1.920
C  −2.349  −2.332   3.253
C  −2.188  −3.421   4.131
C  −2.861  −3.451   5.363
C  −3.696  −2.385   5.735
C  −3.852  −1.287   4.871
C  −3.183  −1.262   3.639
C  −2.600  −3.493  −0.173
C  −1.431  −4.119  −0.655
C  −1.519  −5.316  −1.383
C  −2.769  −5.909  −1.632
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C  −3.847  −4.102  −0.416
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H  −3.573  −1.981   0.978
Cu  −0.055   1.282   0.394
C  −1.273   2.452   1.411
B  −1.714   3.690   0.579
O  −2.597   3.660  −0.501
O  −1.256   4.983   0.842
C  −2.935   5.051  −0.839
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C  −4.269   5.363  −0.138
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C  −2.071   7.223   0.354
C  −0.536   6.009  −1.227
H  −4.659  −0.100  −3.775
H  −2.982  −1.013  −5.262
H  −0.369  −1.611  −1.869
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H  −5.370   1.143   0.739
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H  −6.098   1.991  −1.277
H  −5.632   1.383  −2.879
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H  −6.197  −1.057  −2.168
H  −6.795  −0.351  −0.637
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H   1.592  −2.730  −4.695
H   0.775  −3.023  −3.139
H   0.179  −0.145  −5.607
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H  −0.348  −3.888  −5.822
H  −2.010  −3.245  −5.681
H   3.347  −2.088   3.828
H   3.077  −0.150   5.395
H   1.033   1.303   5.225
H  −0.712   0.781   3.513
H  −1.522  −4.244   3.845
H  −2.728  −4.307   6.034
H  −4.220  −2.406   6.697
H  −4.495  −0.448   5.158
H  −3.303  −0.396   2.976
H  −0.448  −3.679  −0.444
H  −0.603  −5.794  −1.749
H  −2.832  −6.846  −2.197
H  −4.914  −5.761  −1.316
H  −4.760  −3.644  −0.016
```

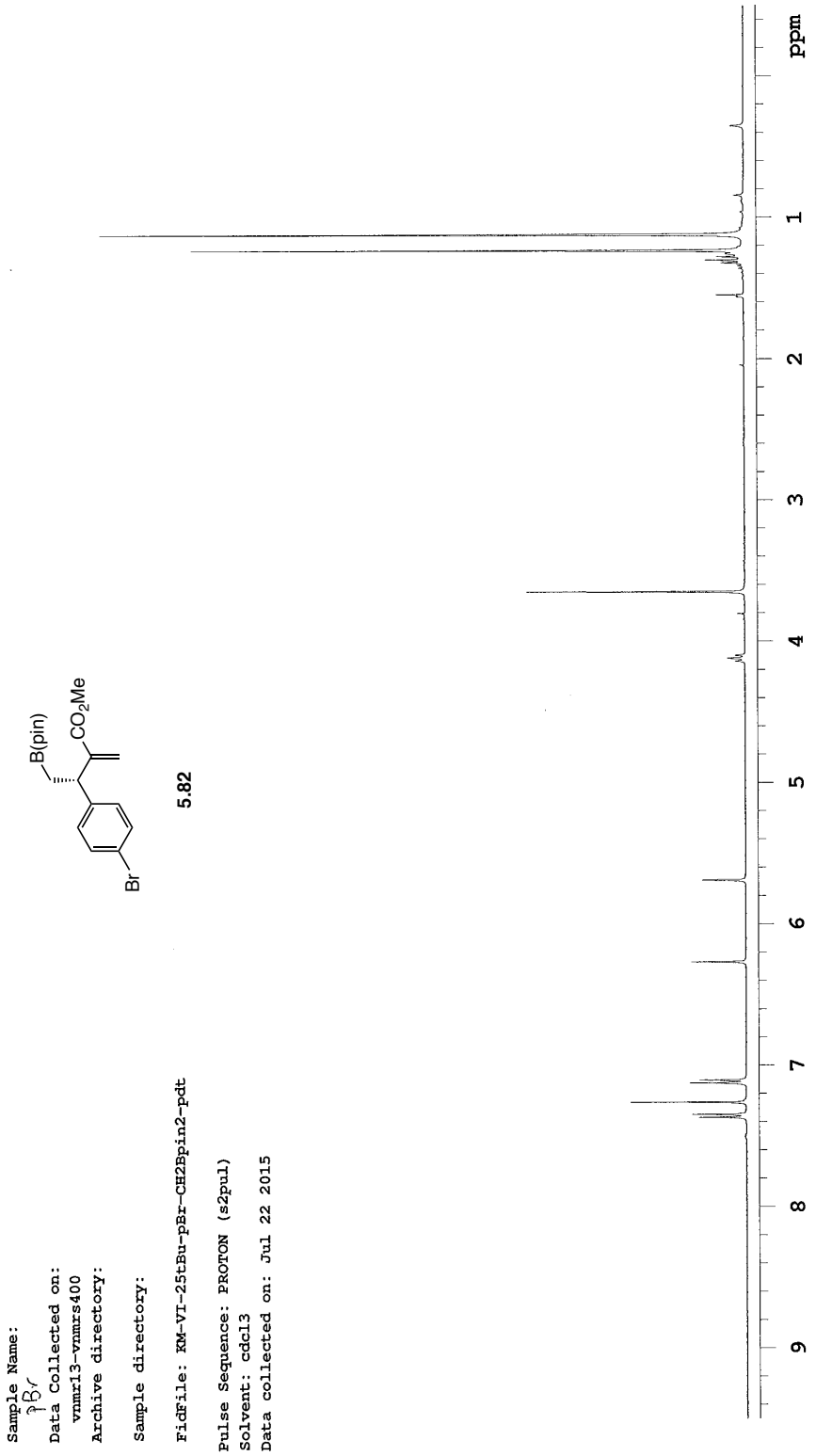
```
H  -2.121   1.810   1.705
H  -0.725   2.761   2.316
H  -4.175   5.283   0.959
H  -5.030   4.637  -0.471
H  -4.629   6.377  -0.386
H  -2.206   4.786  -2.888
H  -3.264   6.212  -2.655
H  -3.968   4.573  -2.689
H  -2.806   7.134   1.169
H  -2.485   7.893  -0.421
H  -1.163   7.701   0.762
H  -0.240   5.041  -1.665
H   0.332   6.421  -0.683
H  -0.783   6.706  -2.048
Na   3.671  -3.435  -0.461
---------------------------------

 SCF Done:  E(RB-P86) =  -5641.26022444     A.U. after    1
cycles

Frequencies --  -227.8799          5.1526         13.5713
 Red. masses --     9.7689         4.6543          4.3964

 Zero-point correction=                           1.117430
(Hartree/Particle)
 Thermal correction to Energy=                    1.195397
 Thermal correction to Enthalpy=                  1.196341
 Thermal correction to Gibbs Free Energy=         0.998078
 Sum of electronic and zero-point Energies=         -5640.142794
 Sum of electronic and thermal Energies=            -5640.064827
 Sum of electronic and thermal Enthalpies=          -5640.063883
 Sum of electronic and thermal Free Energies=       -5640.262147

         Item               Value     Threshold  Converged?
 Maximum Force            0.000002     0.000450     YES
 RMS     Force            0.000000     0.000300     YES
```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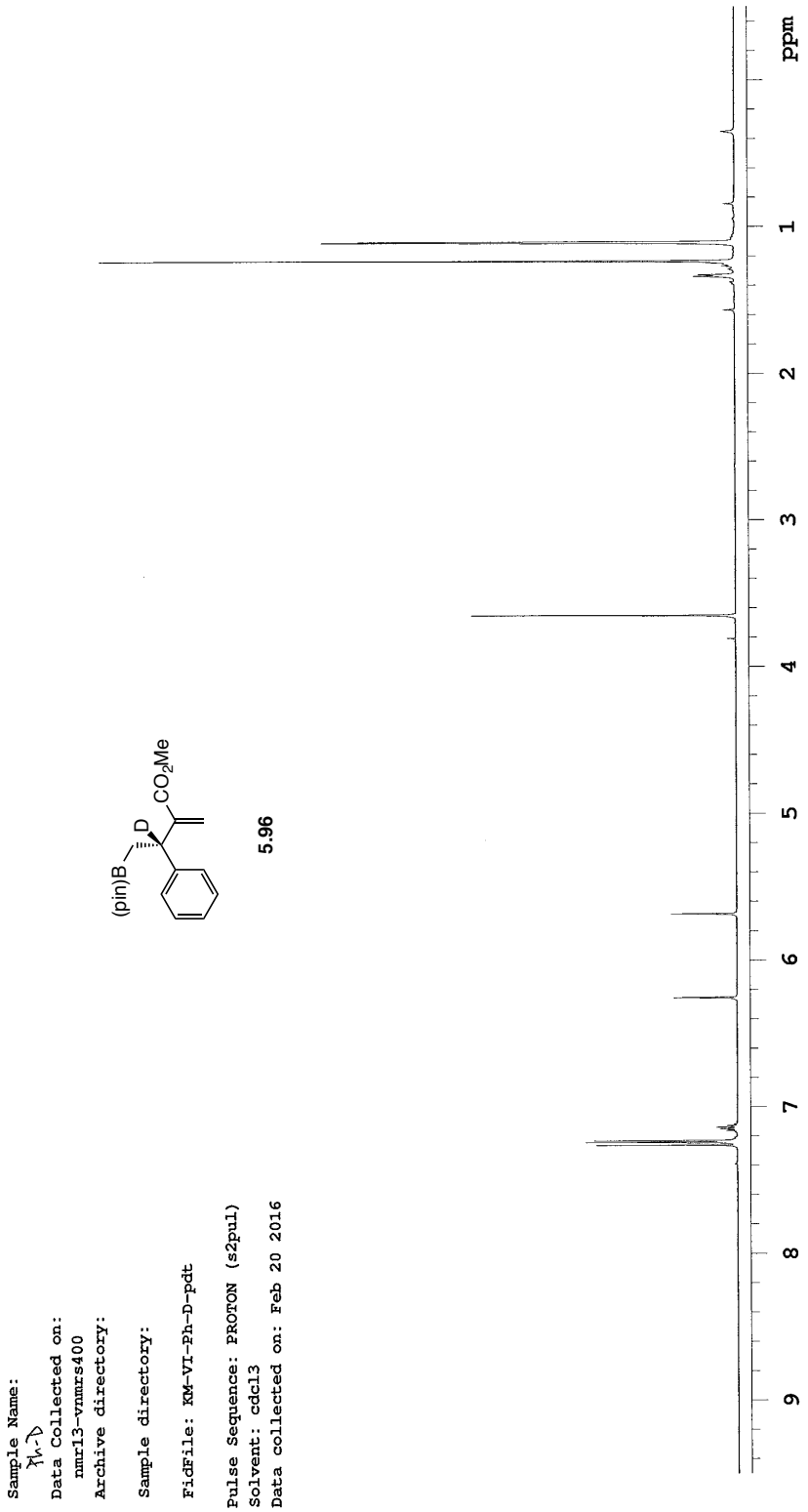
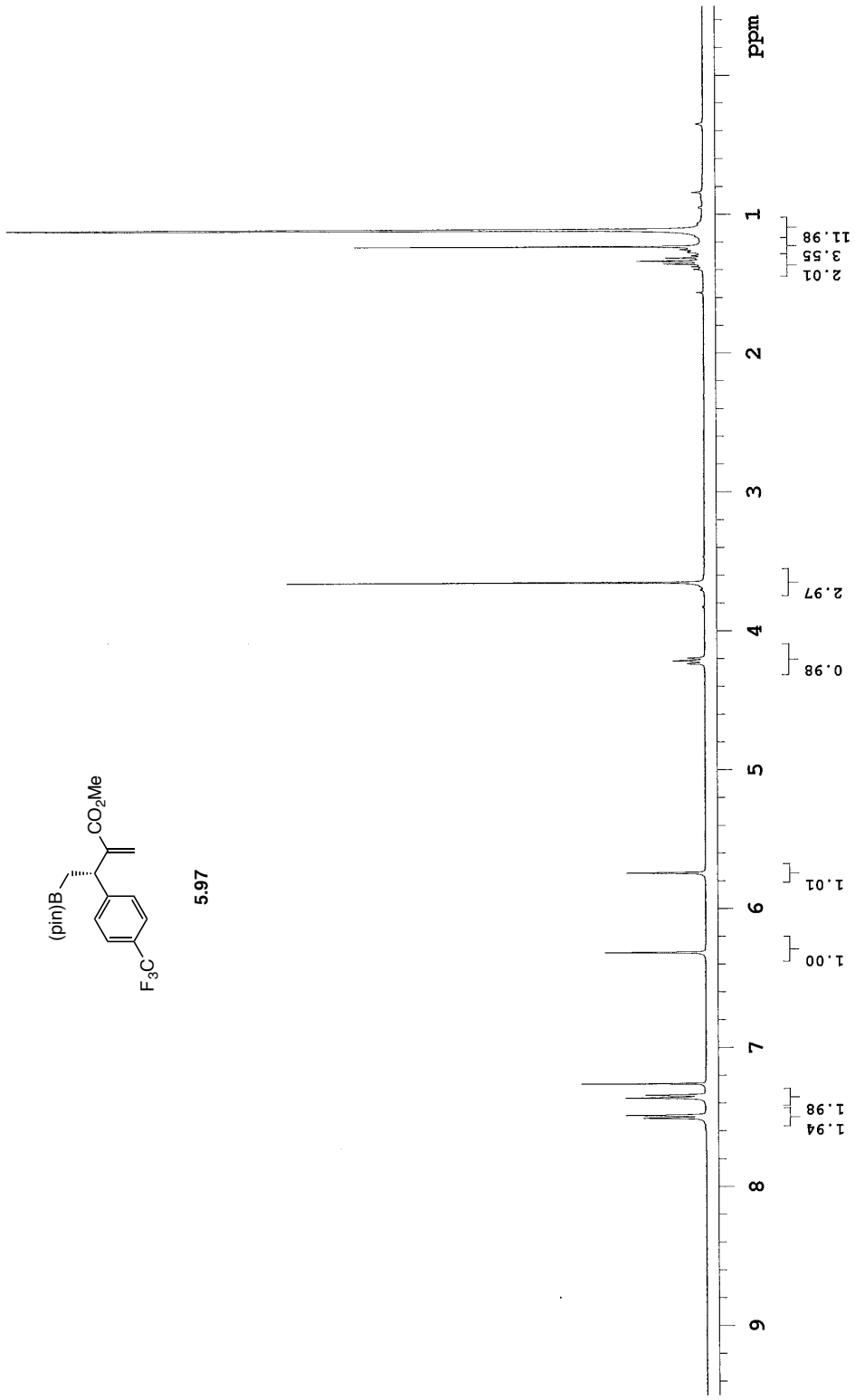
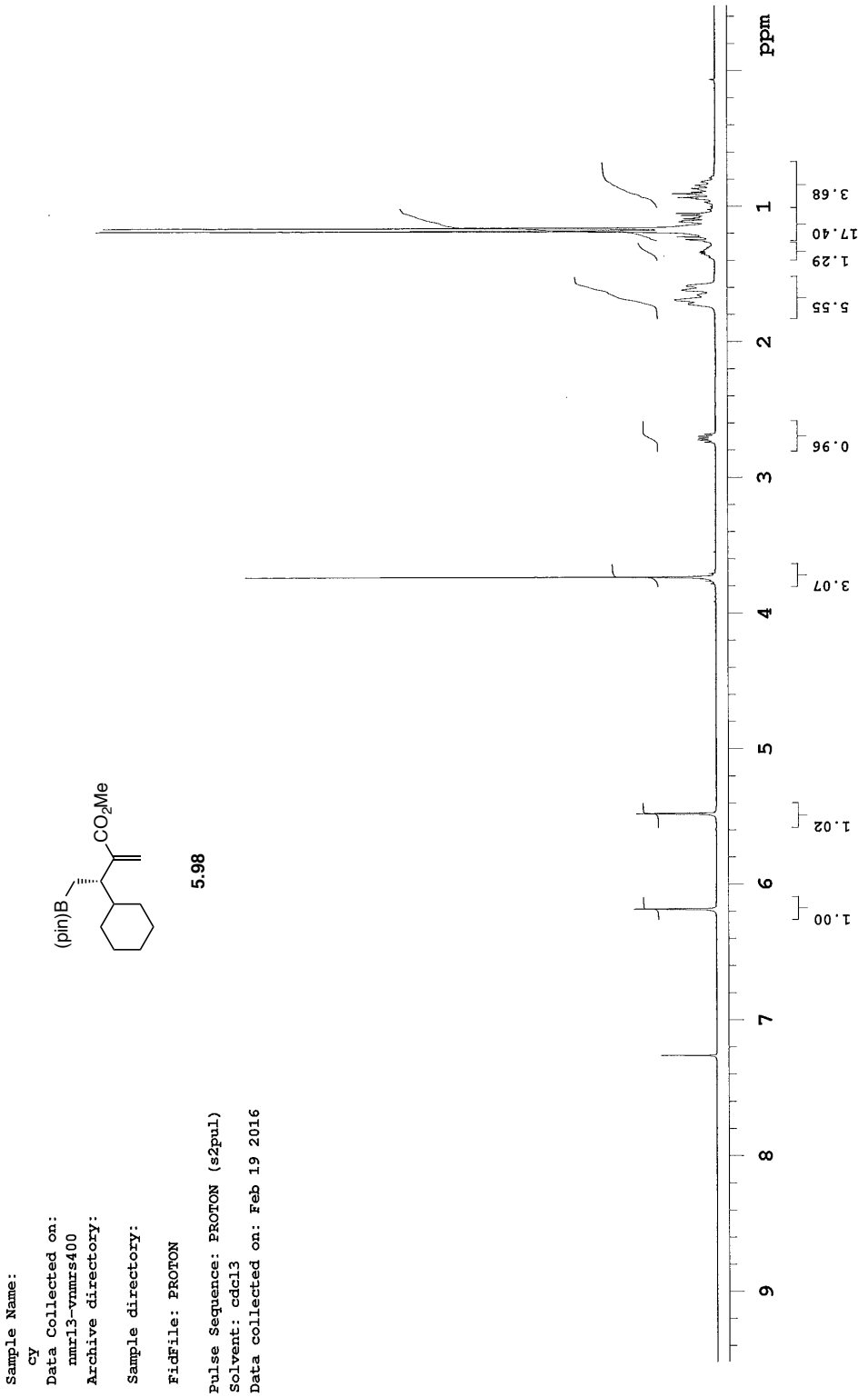
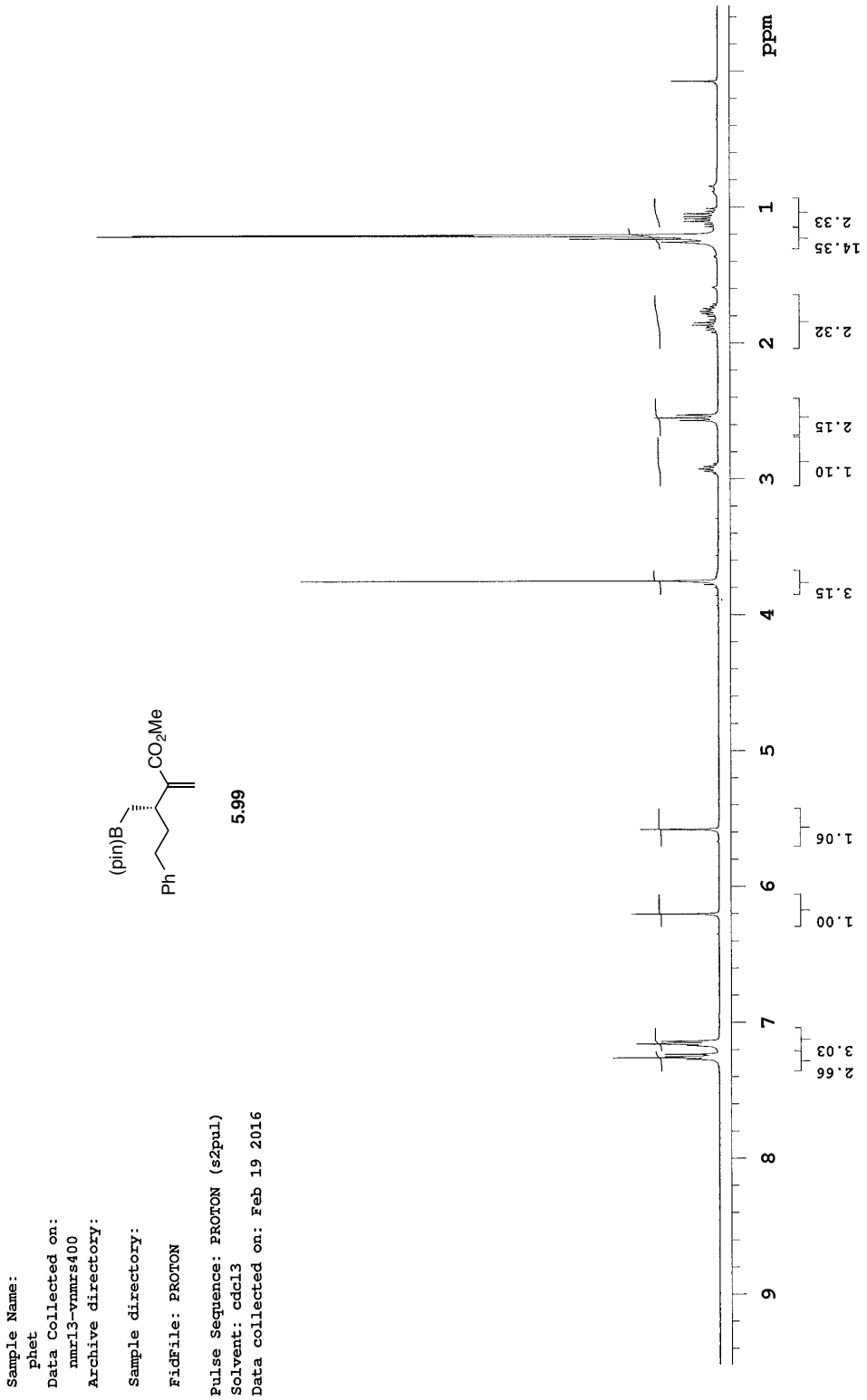
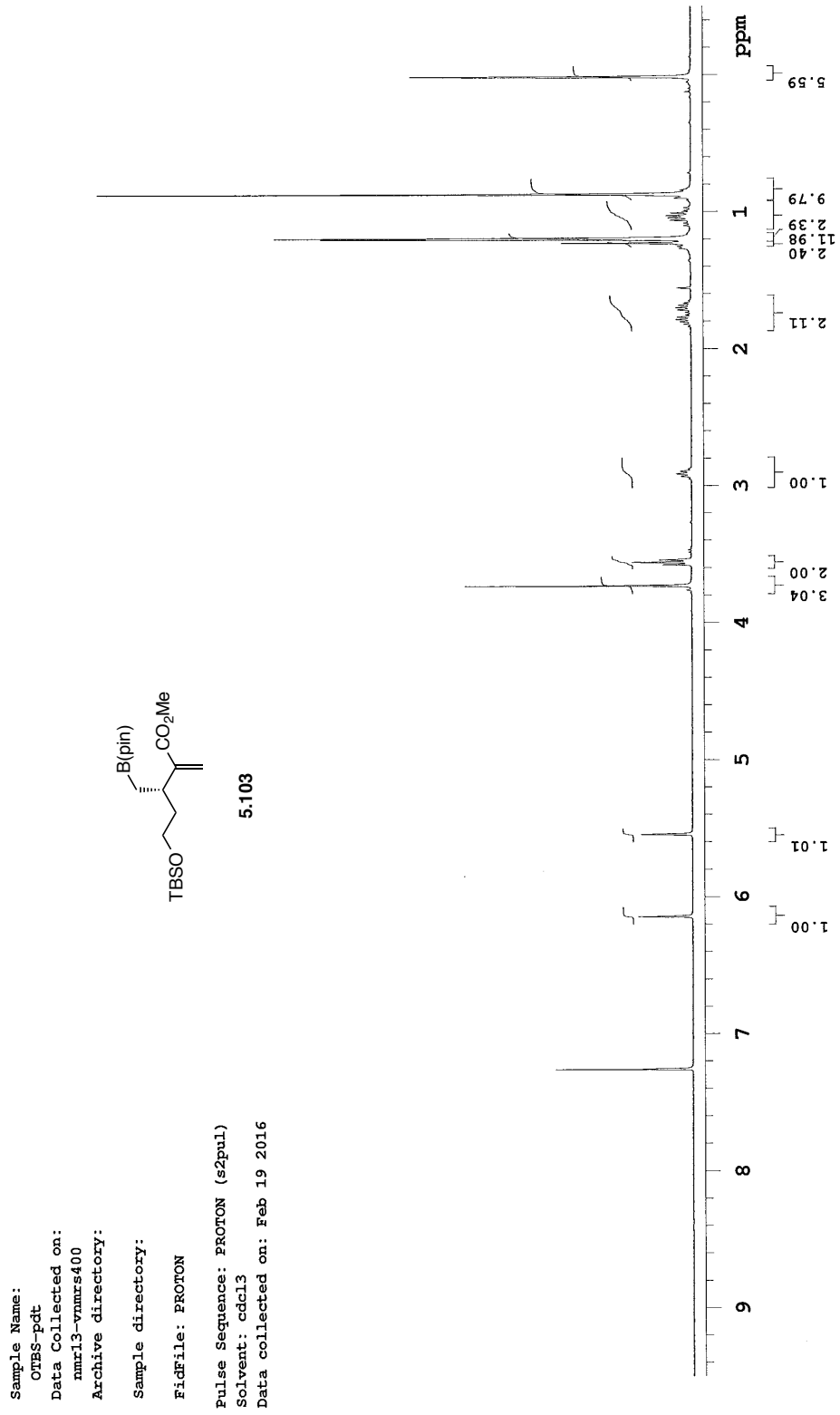
pBr
Data Collected on:
vnmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: KM-VI-25tBu-pBr-CH2Bpin2-pdt
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2015
B(pin)
CO2Me
Br
5.82
ppm
9
8
7
6
5
4
3
2
1

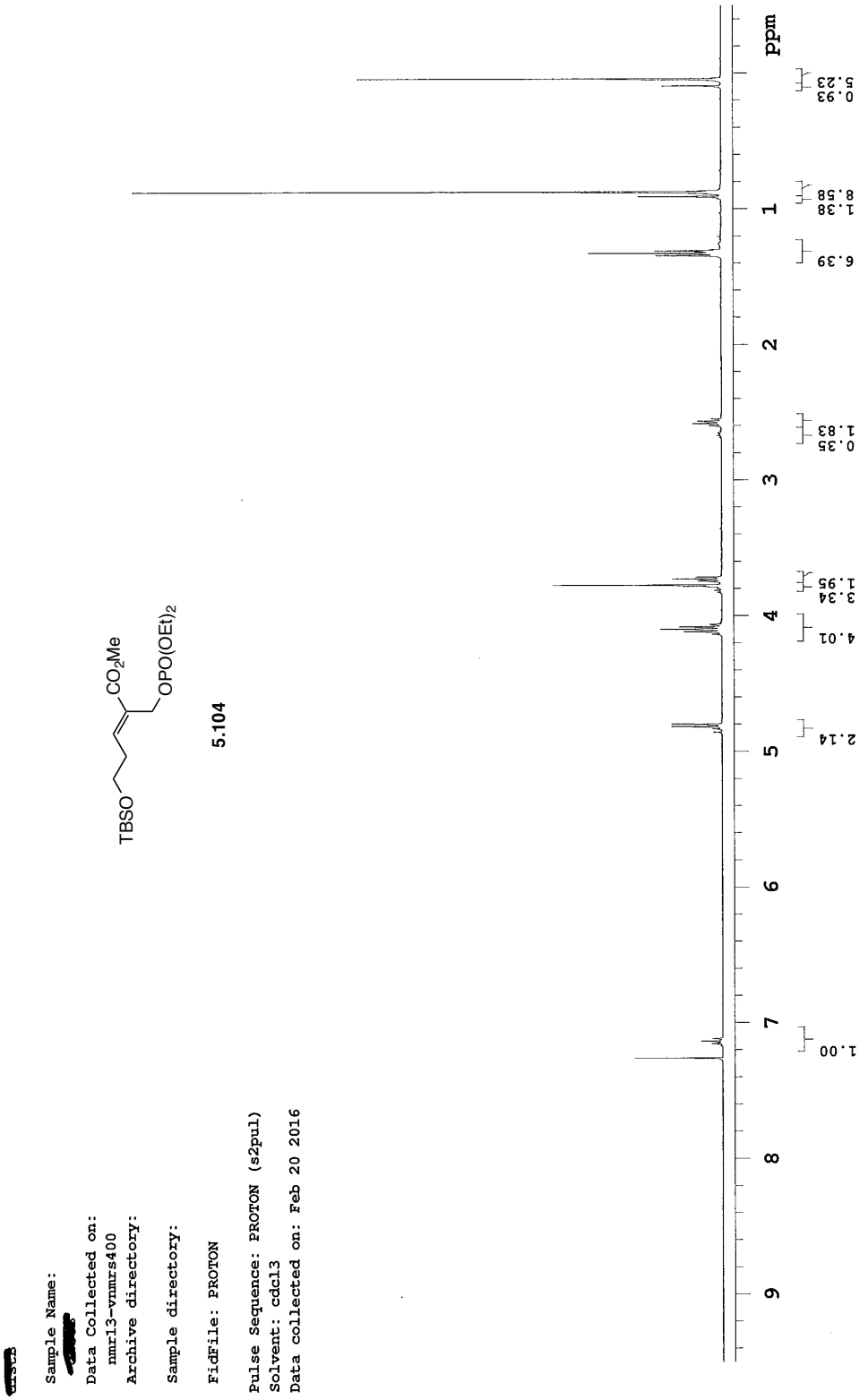

Sample Name:
Ph-D
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: KM-VI-Ph-D-pdt
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 20 2016
(pin)B
D
CO2Me
5.96
ppm
1
2
3
4
5
6
7
8
9


ppm
1
2
3
4
5
6
7
8
9
11.98
3.55
2.01
2.97
0.98
1.01
1.00
1.98
1.94
5.97
(pin)B
CO2Me
F3C


Sample Name:
cy
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 19 2016
(pin)B
CO2Me
5.98
ppm
1.00
1.02
3.07
0.96
5.55
1.29
17.40
3.68


Sample Name:
phet
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 19 2016
(pin)B
CO2Me
Ph
5.99
ppm
2.66
3.03
1.00
1.06
3.15
1.10
2.15
2.32
14.35
2.33


Sample Name:
OTBS-pdt
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 19 2016
B(pin)
CO2Me
TBSO
5.103
ppm
5.59
9.79
2.39
11.98
2.40
2.11
1.00
2.00
3.04
1.01
1.00


Sample Name:
Data Collected on:
nmr13-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 20 2016
TBSO
CO2Me
OPO(OEt)2
5.104
ppm
1.00
2.14
4.01
3.34
1.95
0.35
1.83
6.39
1.38
8.58
0.93
5.23