Copper-Based N-Heterocyclic Carbene Complexes for Catalytic Enantioselective Conjugate Additions of Alkyl-, Aryl- and Vinyl-Based Nucleophiles to Form All-Carbon Quaternary Stereogenic Centers

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Boston College
The Graduate School of Arts and Sciences
Department of Chemistry

COPPER-BASED N-HETEROCYCLIC CARBENE COMPLEXES FOR CATALYTIC ENANTIOSELECTIVE CONJUGATE ADDITIONS OF ALKYL-, ARYL-, AND VINYL-BASED NUCLEOPHILES TO FORM ALL-CARBON QUATERNARY STEREOGENIC CENTERS

a dissertation
by
TRICIA LEE MAY

submitted in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
May 2011

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I was extremely fortunate to have Kevin Brown as a mentor when I began in the Hoveyda group. Starting in such an established group was a little frightening with limited research experience, but Kevin had seemingly unlimited patience and kindness for my questions and mistakes. Kevin has a sort of quiet leadership, guiding by his example of hard work and attentiveness. Most of the work in Chapters 2 and 3 of this thesis was performed in collaboration with Kevin and I am forever grateful for his guidance.

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My parents have always encouraged me to go after whatever I dreamed to do, even when it seemed impossible. Their support and love made this road possible. And I am incredibly lucky to have fantastic and supportive siblings, Laura and Danny.

Words fail me to express how supportive Curtis Dracka has been since day one of this journey. I love you more today than what I could have dreamed possible. I am so excited to start our next adventure in life.

Copper-Based N-Heterocyclic Carbene Complexes for Catalytic Enantioselective Conjugate Additions of Alkyl-, Aryl- and Vinyl-Based Nucleophiles to Form All-Carbon Quaternary Stereogenic Centers

TRICIA LEE MAY

Thesis Advisor: Professor Amir. H. Hoveyda

Abstract

■ Chapter 1

Enantioselective Conjugate Additions of Carbon Nucleophiles to Activated Olefins: Preparation of Enantioenriched Compounds Containing All-Carbon Quaternary Stereogenic Centers

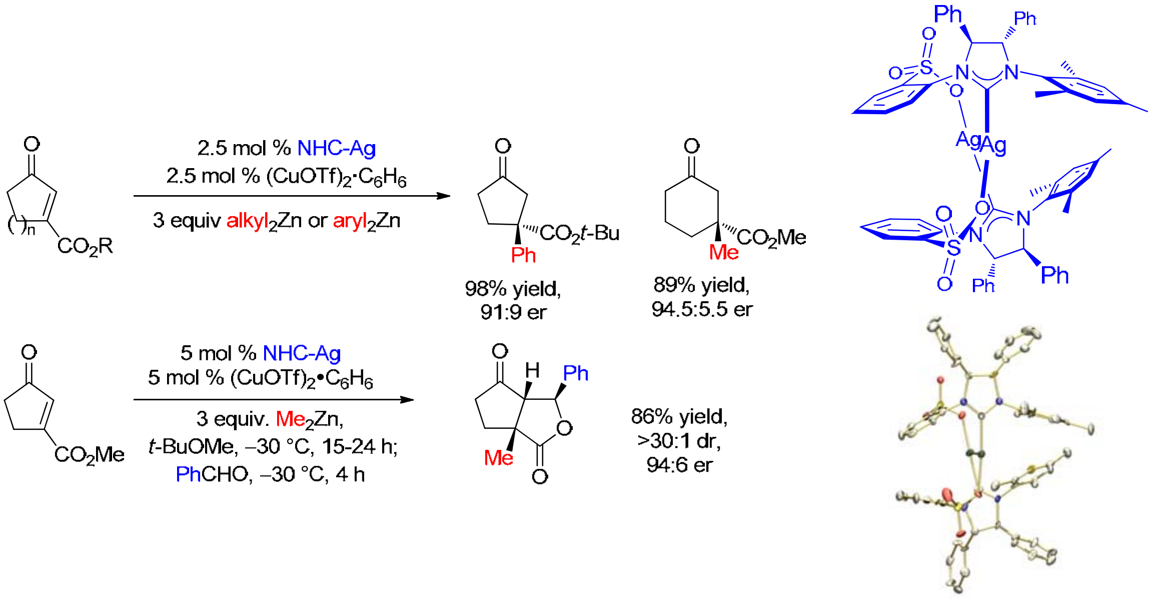
Methods for enantioselective conjugate addition of nucleophiles to activated olefins generating products containing all-carbon quaternary stereogenic centers are critically reviewed. Enantioselective conjugate addition has been shown to be a powerful and concise approach to construct carbon–carbon bonds to prepare compounds containing sterically hindered stereogenic centers and has seen great advances in the past several years. Owing to the difficult nature of additions to relatively unreactive conjugate acceptors, compared to additions generating tertiary stereogenic centers, and construction of a sterically-hindered bond, in many cases, new and active catalysts had to be

developed. The review discusses the areas where significant advances have been made as well as current limitations and future outlook.

■ Chapter 2

Development of New and Active Catalysts for Cu-Catalyzed Enantioselective Conjugate Addition of Alkyl- and Arylzinc Reagents

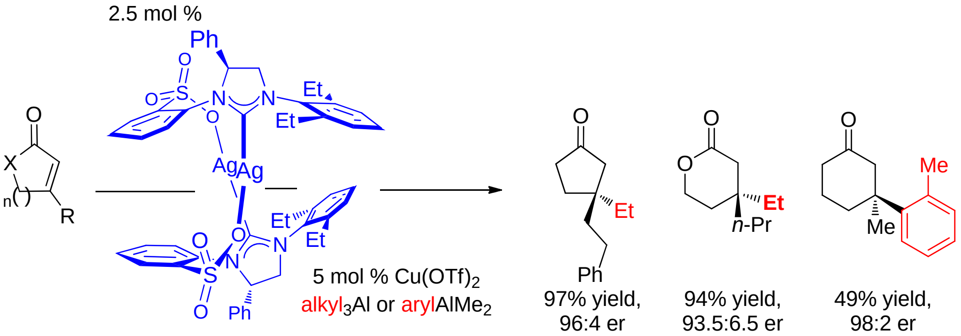
Through development of new chiral catalysts, we have found an active and enantiodiscriminating bidentate, sulfonate-containing NHC–Cu catalyst that effects enantioselective conjugate addition of alkyl- and arylzinc reagents on notoriously difficult trisubstituted cyclic enones. Products are prepared with high levels of selectivity and participate in a variety of further functionalizations. The enantioselective additions are efficient and practical, not requiring rigorously anhydrous or oxygen-free conditions.

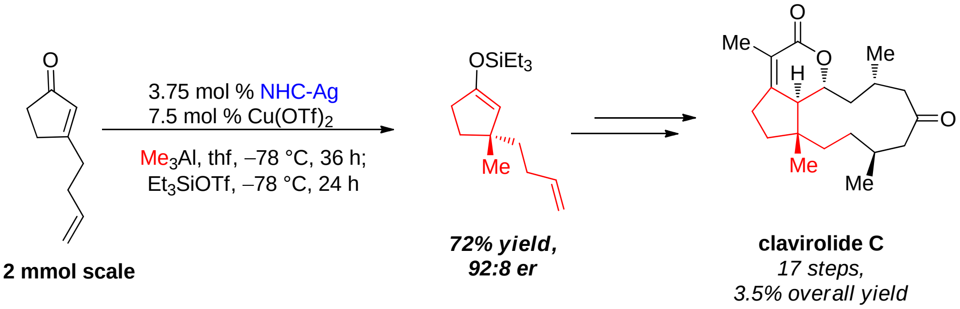

2.5 mol % NHC-Ag
2.5 mol % (CuOTf)2·C6H6
3 equiv alkyl2Zn or aryl2Zn
CO2R
CO2t-Bu
Ph
98% yield, 91:9 er
CO2Me
Me
89% yield, 94.5:5.5 er
5 mol % NHC-Ag
5 mol % (CuOTf)2•C6H6
3 equiv. Me2Zn, t-BuOMe, –30 °C, 15-24 h; PhCHO, –30 °C, 4 h
CO2Me
H
Ph
Me
86% yield, >30:1 dr, 94:6 er
Ag
Ag
Ph
Ph
N
S
O

■ Chapter 3

Cu-Catalyzed Enantioselective Conjugate Addition of Alkyl- and Arylaluminum Reagents to Trisubstituted Enones

Outlined in this chapter is the first effective solution for Cu-catalyzed enantioselective addition of alkyl and aryl nucleophiles to trisubstituted cyclopentenones generating products bearing a β-all-carbon quaternary stereogenic center. Products are obtained in up to 97% yield and 99:1 er, only requiring 5 mol % of an in situ generated Cu–NHC catalyst. The methodology was highlighted as one of the key steps in the total synthesis of clavirolide C. Not only five-membered rings, but six- and seven-membered rings serve as proficient partners in the enantioselective process. Moreover, in cases for the enantioselective aryl addition, in situ prepared Me_2AlAr can be used without purification, filtration, or isolation, only requiring the corresponding aryl halides. The additions have also been extended to trisubstituted unsaturated lactones and chromones.


2.5 mol %
Ph
O
O=S
N
N
Et
Et
O
Ag
Ag
Et
Et
O
O
N
N
S
O
Ph
O
X
n( )
R
5 mol % Cu(OTf)$_2$
alkyl$_3$Al or arylAlMe$_2$
O
Et
Ph
97% yield, 96:4 er
O
O
Et
n-Pr
94% yield, 93.5:6.5 er
O
Me
Me
49% yield, 98:2 er

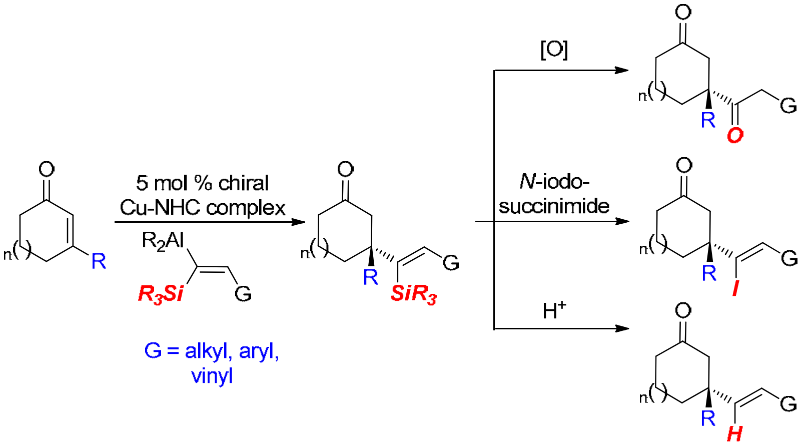

O
3.75 mol % NHC-Ag
7.5 mol % Cu(OTf)$_2$
Me$_3$Al, thf, –78 °C, 36 h;
Et$_3$SiOTf, –78 °C, 24 h
2 mmol scale
OSiEt$_3$
Me
72% yield, 92:8 er
O
Me
O
H
Me
O
Me
Me
clavirolide C
17 steps,
3.5% overall yield

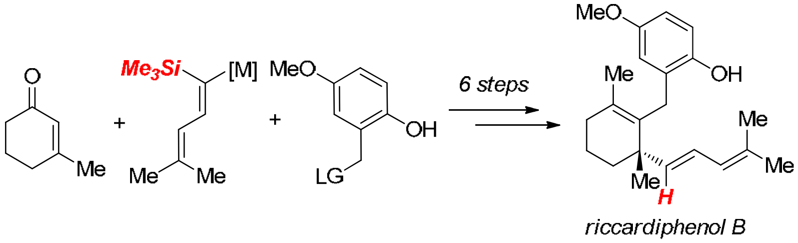
■ Chapter 4

Cu-Catalyzed Enantioselective Conjugate Addition of Vinylaluminum Reagents to Cyclic Trisubstituted Enones

An enantioselective protocol for the formation of *β,β*-disubstituted cyclic ketones containing a synthetically versatile vinylsilane is disclosed. Enantioselective conjugate addition of in situ prepared silyl-substituted vinylaluminum reagents to *α,β*-unsaturated ketones promoted by 5 mol % of chiral Cu–NHC complexes delivers desired products with high efficiency (up to 95% yield after purification) and enantioselectivities (up to

>98:<2 er). Several functionalizations utilizing the vinylsilanes, vicinal to an all-carbon quaternary stereogenic center, are shown, including an oxidative rearrangement, vinyl iodide formation and protodesilylation, accessing products not previously attainable. Furthermore, the enantioselective protocol is demonstrated as the key transformation in the total synthesis of riccardiphenol B.


5 mol % chiral
Cu-NHC complex
R_2Al
R_3Si
G
G = alkyl, aryl, vinyl
[O]
N-iodo-succinimide
H^+
R
SiR_3
O
I
H
n


Me_3Si
[M]
MeO
OH
LG
Me
6 steps
H
riccardiphenol B

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Chapter 1.

Enantioselective Conjugate Additions of Carbon Nucleophiles to Activated Olefins: Preparation of Enantioenriched Compounds Containing All-Carbon Quaternary Stereogenic Centers

1.1 Introduction

Catalytic enantioselective synthesis of compounds containing all-carbon quaternary stereogenic centers is a challenging and important objective in organic synthesis.[1] Steric and electronic repulsion between the four carbon substituents make the formation of quaternary stereogenic centers a difficult task even without the formidable task of rendering the process both catalytic and enantioselective. Much research has been dedicated to developing methods that allow access to all-carbon quaternary stereogenic centers. Some of the methods that has emerged for the synthesis of sterically congested compounds include enantioselective cycloadditions [cyclopropanations (2+1),[2] Diels-Alder (4+2)[3]], metal-catalyzed cross coupling reactions (Heck,[4] α-arylation[5]), and

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(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A.; Yamamoto, H., Eds; Springer: Berlin, Germany, 1999. (b) “Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters,” Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367. (c) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J.; Baro, A., Eds; Wiley-VCH, Weinheim, 2006.

(2) For a recent review and a lead reference, see: (a) “Recent Developments in Asymmetric Cyclopropanation,” Pellissier, H. *Tetrahedron*, **2008**, *64*, 7041–7095. (b) “Synthetic Studies on Nemorosone via Enantioselective Intramolecular Cyclopropanation,” Abe, M.; Saito, A.; Nakada, M. *Tetrahedron Lett*. **2010**, *51*, 1298–1302.

(3) For lead references, see: (a) “Highly Enantioselective Diels-Alder Reactions of Maleimides Catalyzed by Activated Chiral Oxazaborolidines,” Mukherjee, S.; Corey, E. J. *Org. Lett.* **2010**, *12*, 632–635. (b) “Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters by an Organocatalytic Diels-Alder Reaction of α-Substituted α,β-Unsaturated Aldehydes,” Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, 1956–1958.

enantioselective olefin metathesis reactions.[6] Other methodologies that has been extensively studied Hoveyda laboratories, which allows the efficient construction of all-carbon quaternary stereogenic centers, are enantioselective allylic substitution (EAS)[7] and conjugate addition (ECA) reactions.[8] The latter method, which is the subject of this review, has been shown to be a powerful and concise approach to construct carbon–carbon bonds and prepare compounds containing all-carbon quaternary stereogenic centers.

Catalytic enantioselective methods that prepare compounds with quaternary stereogenic centers are an important goal in organic synthesis. One such reason is that, in nature, many natural products and biologically active agents contain quaternary stereogenic centers (Scheme 1.1).[9] For example, guancastepene B has demonstrated

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(4) For a review, see: The Asymmetric Intramolecular Heck Reaction in Natural Product Synthesis, Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964.

(5) For lead references, see: (a) "Palladium-Catalyzed Enantioselective α-Arylation and α-Vinylation of Oxindoles Facilitated by an Axially Chiral P-Stereogenic Ligand," Talyor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901. (b) "Highly Chemo- and Enantioselective Synthesis of 3-Allyl-3-aryl Oxindoles via the Direct Palladium-Catalyzed α-Arylation of Amides," Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912–1915.

(6) For a review and a lead reference, see: (a) "Catalytic Enantioselective Olefin Metathesis in Natural Product Synthesis. Chiral Metal-Based Complexes that Deliver High Enantioselectivity and More," Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 34–44. (b) "H-Bonding as a Control Element in Stereoselective Ru-Catalyzed Olefin Metathesis," Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.

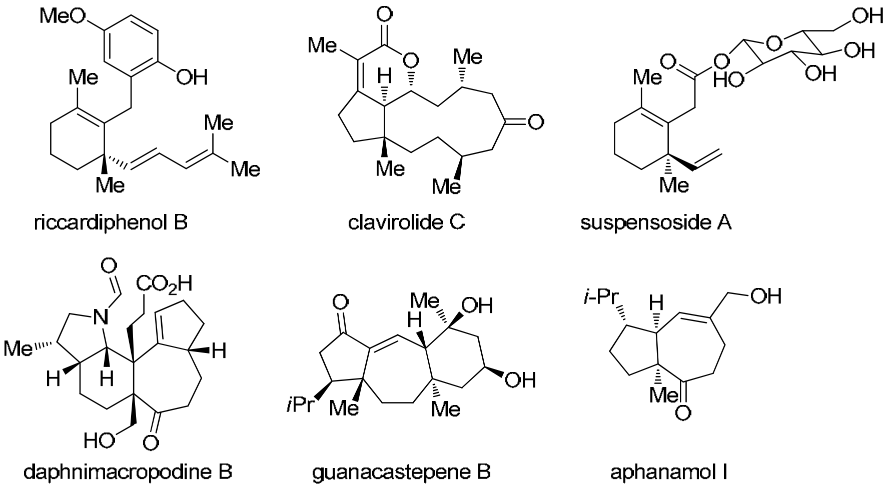
(7) For two recent reviews and a lead reference, see: (a) "Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions," Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pámies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (b) Spino, C. Copper-Mediated Asymmetric Allylic Alkylations. In *The Chemistry of Organocopper Compounds, Volume 1;* Rappoport, Z.; Marek, I., Eds. Wiley: Chichester, UK, 2009, pp 603–692. (c) "Synthesis of Quaternary Carbon Stereogenic Centers through Enantioselective Cu-Catalyzed Allylic Substitutions with Vinylaluminum Reagents," Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315–14320.

(8) For a recent reviews, see: (a) reference 7a. (b) "Recent Advances in Enantioselective Copper-Catalyzed 1,4 Addition," Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075. (c) "Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents," Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.

(9) For isolation accounts of the natural products shown in Figure 1, see: riccardiphenol B (a) "Sesquiterpene Derivatives and a Norsesquiterpenoid from the Liverworts *Riccardia Crassa* and *Porella Caespitans* var. *Setigera*," Toyota, M.; Asakawa, Y. *Phytochemistry* **1993**, *32*, 137–140. Clavirolide C (b) "Four Novel Diterpenoids: Clavirolides B, C, D, and E from the Chinese Soft Coral *Clavularia Viridis*," Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380–385. Suspensoside A (c) "Glucosylated Suspensosides, Water-Soluble Pheromone Conjugates from the Oral Secretions of Male *Anastrepha suspensa*," Walse, S. S.; Lu, F.; Teal, P. E. A. *J. Nat. Prod.* **2008**, *71*, 1726–1731. Daphnimacropodine B

promising activity against methicillin-resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus faecium*.[10] A concise, efficient and selective synthetic route to these natural products is of the utmost importance to secure enough material for biological testing or production as pharmaceuticals particularly when large quantities of the agents are limited or unavailable from the natural source. Furthermore, organic synthesis can provide unnatural analogues are that can give more stability or fine tuning of the biological activity). The synthesis of a complex target is also a useful probe to assess the generality and limitations of current methods.

Scheme 1.1. Representative Natural Products Containing an All-Carbon Quaternary Stereogenic Center



A synthesis target can also facilitate methodology progress; new approaches, reaction conditions, catalysts and ligands may be required to gain high efficiency and

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(d) "Daphnimacropodines A–D, Alkaloids from *Daphniphyllum macropodum*," Kong, N.-C.; He, H.-P.; Wang, Y.-H.; Mu, S.-Z.; Di, Y.-T.; Hao, X.-J. *J. Nat. Prod.* **2007**, *70*, 1348–1351. Guanacastepene B (e) "The Guanacastepenes: A Highly Diverse Family of Secondary Metabolites Produced by an Endophytic Fungus," Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901. Aphanamol I (f) "Structure of Aphanamol I and II," Nishizawa, M.; Inoue, A.; Hayashi, Y.; Sastrapradja, S.; Kosela, S.; Iwashita, T. *J. Org. Chem.* **1984,** *49*, 3660–3662.

(10) "Biological Activity of Guanacastepene, A Novel Diterpenoid Antibiotic Produced by an Unidentified Fungus CR115," Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–261.

selectivity in a synthesis-driven project.[11] For instance, ligands and catalysts that promote the formation of tertiary stereogenic centers are often not effective or selective for the preparation of the corresponding quaternary stereogenic centers (for examples, see Chapter 2). The development of active catalysts to help promote the difficult task of preparing sterically congested stereogenic centers while still delivering products with high selectivities (regio-, diastereo-, and/or enantioselectivities) is a daunting task. Nevertheless, if this objective is met, the developed catalysts could potentially find application in new projects and reactions. For instance, the new *N*-heterocyclic carbenes (NHCs) developed in our laboratories for the advancement of several Cu-catalyzed ECA projects (discussed in length later in this thesis) have led to several new enantioselective carbon–boron bond forming reactions (hydroboration of alkenes[12] and alkynes[13] and allylic boron substitutions[14]); these aforementioned reactions would not have been as fruitful if a new NHC had not been developed.

Enantioselective conjugate addition has proven to be a powerful method to construct carbon–carbon bonds starting with easily accessible starting materials. Hundreds of catalyst systems have been disclosed that have promoted additions to cyclohexenone;[15] however, enantioselective additions to tri- or tetra-substituted enones, to afford products containing all-carbon quaternary stereogenic centers, have been less extensively studied.[16] This review encompasses methods disclosed for the ECAs to

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(11) "Natural Products as Inspiration for the Development of Asymmetric Catalysis," Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(12) "Efficent Boron–Copper Additions of Aryl-Substituted Alkenes Promoted by NHC-Based Catalysts. Enantioselective Cu-Catalyzed Hydroboration Reactions," Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161.

(13) "Vicinal Diboronates in High Enantiomeric Purity through Tandem Site-Selective NHC–Cu-Catalyzed Boron–Copper Additions to Terminal Alkynes," Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235.

(14) "Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC–Cu-Catalyzed Substitution Reactions," Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

(15) For a review that primarily discusses the formation of tertiary stereogenic centers through ECA, see: "Recent Advances in Catalytic Enantioselective Michael Additions," Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196.

(16) There are several methods that form an all-carbon quaternary stereogenic center on the *nucleophile* (vs. a stereogenic center located on the electrophile) by enantioselective Michael additions. For examples, see: (a) "Catalytic Asymmetric Synthesis with Trans-Chelating Chiral Diphosphine Ligand TRAP:

activated electrophiles generating sterically hindered products β to an electron-withdrawing substituent (carbonyl, nitro, sulfone). The sections are divided by the type of nucleophile (alkyl, aryl, vinyl, cyanide) to various electrophiles. Critical evaluation is provided along with mechanistic details when needed.

1.2 Enantioselective Conjugate Additions of Alkyl Nucleophiles to Activated Olefins

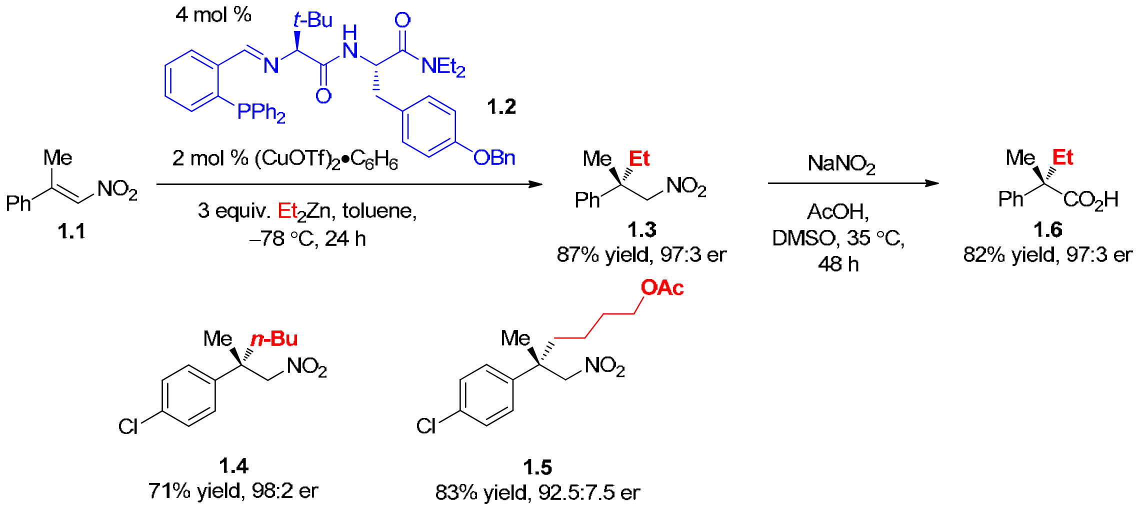
Most of the research disclosed for the formation of all-carbon quaternary stereogenic centers through ECA has centered on the addition of alkyl-based nucleophiles to activated alkenes. The first examples of the enantioselective additions involved alkylzinc reagents because they are mild nucleophiles (no uncatalyzed 1,2- or 1,4-additions) and functional-group tolerant and compatible. Later methods have began to explore more reactive and Lewis acidic nucleophiles (alkylaluminum and Grignard reagents) in an effort to increase the efficiency of some of the enantioselective additions. This review begins with ECAs of activated electrophiles (nitroalkenes, enones bearing electron-withdrawing groups) before discussing the more challenging substrates (alkyl- and aryl-substituted enones).

Rhodium-Catalyzed Asymmetric Michael Addition of α-Cyano Carboxylates," Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296. (b) "Asymmetric Michael Reaction of an α-Cyano Weinreb Amide Catalyzed by a Rhodium Complex with Trans-Chelating Chiral Diphosphine PhTRAP," Sawamura, M.; Hamashima, H.; Shinoto, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 6479–6482. (c) Catalytic Asymmetric Michael Reactions Promoted by the La-Na-BINOL Complex (LSB). Enantioface Selection on Michael Donors," Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron. Lett.* **1996**, *37*, 5561–5564. (d) "Direct Generation of Nucleophilic Chiral Palladium Enolate from 1,3-Dicarbonyl Compounds: Catalytic Enantioselective Michael Reaction with Enones," Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241. (e) "Highly Enantioselective Conjugate Additions to α,β-Unsaturated Ketones Catalyzed by a (Salen)Al Complex," Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317. (f) "Organocatalytic Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides," Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966–4970.

1.2.a Alkyl Additions to Activated Enones and Nitroalkenes

The first example of an enantioselective conjugate addition to generate an all-carbon quaternary stereogenic center was disclosed by our laboratory in 2005.[17] Cu-catalyzed ECA of alkylzinc reagents to trisubstituted nitroalkenes affords products in up to 99:1 er (Scheme 1.2). The addition is catalyzed by a chiral phosphine (**1.2**) that is easily prepared in five steps.[18] A variety of alkylzinc reagents are competent partners in this addition: long chained alkyl (Et, **1.3**, and *n*-Bu, **1.4**), methyl, as well as nucleophiles that contain a heteroatom (OAc, **1.5**). Nitroalkanes can be functionalized to yield a variety of enantiomerically enriched molecules; oxidation of **1.3** affords a carboxylic acid adjacent to a quaternary stereogenic center (**1.6**) in 82% yield.

Scheme 1.2. Cu-Catalyzed ECA of Alkylzinc Reagents to β,β-Disubstituted Nitroalkenes


4 mol %
t-Bu
H
N
O
N
NEt$_2$
O
PPh$_2$
1.2
OBn
Me
Ph
NO$_2$
1.1
2 mol % (CuOTf)$_2$•C$_6$H$_6$
3 equiv. Et$_2$Zn, toluene,
–78 °C, 24 h
Me
Et
Ph
NO$_2$
1.3
87% yield, 97:3 er
NaNO$_2$
AcOH,
DMSO, 35 °C,
48 h
Me
Et
Ph
CO$_2$H
1.6
82% yield, 97:3 er
Me
n-Bu
NO$_2$
Cl
1.4
71% yield, 98:2 er
OAc
Me
NO$_2$
Cl
1.5
83% yield, 92.5:7.5 er

Although this procedure is efficient and selective with Me, Ar-substituted nitroalkenes (i.e., **1.1**), the use of sterically more hindered electrophiles (for example *i*-Pr, Ph-substituted nitroalkene, **1.7**, Scheme 1.3) afford products with reduced reactivity and selectivity (Et_2Zn addition, following the conditions in Scheme 1.2 at 0 °C affords **1.9**

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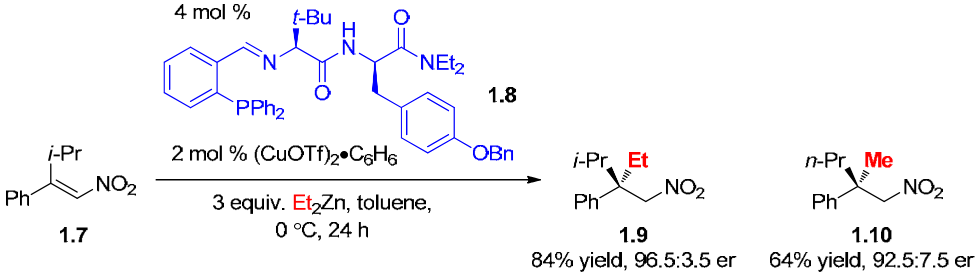
(17) "Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions," Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585.

(18) For a review of chiral peptide-based ligands in enantioselective alkylations, see: "Small Peptides as Ligands for Catalytic Asymmetric Alkylations of Olefins. Rational Design of Catalysts or of Searches that Lead to Them?," Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, *16*, 1779–1785.

with 53% conv, and 89.5:10.5 er). Since the phosphine-based ligands are modular and straightforward to prepare analogs, a short ligand screen elucidated a more effective ligand for the Cu-catalyzed ECA of alkylzinc additions to sterically hindered substrates. As shown in Scheme 1.3, substituting a in D-benzyl tyrosine affords products **1.9** and **1.10** in up to 84% yield and 96.5:3.5 er. The change in ligand structure from **1.2** to **1.8** gives a larger chiral binding pocket (D-benzyl tyrosine unit pointing away from the Cu-center that is bound between the imine and phosphine) and provides substrates that have a substituent larger than a methyl group to interact with a catalyst with a reduced steric environment.

Scheme 1.3. Cu-Catalyzed ECA of Alkylzinc Reagents to Sterically Hindered Nitroalkenes



Fillion and co-workers have disclosed a series of articles focused on additions to Meldrum's acid derived tetrasubstituted enones.[19] In their initial communication,[19a] the enantioselective alkylations are promoted by 10 mol % of a chiral phosphoramidite

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(19) (a) "Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Cu-Catalyzed Conjugate Addition of Dialkylzinc Reagents to 5-(1-Arylalkylidene) Meldrum's Acids," Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775. (b) "Asymmetric Cu-Catalyzed 1,6-Conjugate Addition of Dialkylzinc Reagents to 5-(3-Aryl-2-propenylidene) Meldrum's Acids," Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959. (c) "Asymmetric Synthesis of Carboxylic Acid Derivatives Having an All-Carbon α-Quaternary Center through Cu-Catalyzed 1,4-Addition of Dialkylzinc Reagents to 2-Aryl Acetate Derivatives," Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804. (d) "Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Conjugate Addition to Alkylidene and Indenylidene Meldrum's Acids," Wilsily, A.; Fillion, E. *J. Org. Chem.* **2009**, *74*, 8583–8594. (e) "Enantioselective Copper-Catalyzed Conjugate Addition of Dimethylzinc to 5-(1-Arylalkylidene) Meldrum's Acids," Wilsily, A.; Lou, T.; Fillion, E. *Synthesis* **2009**, 2066–2072. (f) "Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon-Carbon Bond-Forming Processes," Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454.

ligand, developed by Feringa and co-workers,[20] in the presence of $Cu(OTf)_2$ and 2 equiv. of the alkylzinc reagent and provide products in up to 98.5:1.5 er (Scheme 1.4). Various aromatic groups at the β-position of the activated enone are tolerated, including electron-rich and electron-poor substituents at the *para* position of the phenyl rings and heteroaromatic groups (i.e., product **1.14**). *Meta* substitution on the aryl ring leads to efficient alkylations, however, the enantioselectivities are diminished as compared to substitution at the *para* position (for example, product **1.15** is isolated in 93% yield and 89:11 er, Scheme 1.4). Ethylzinc, as well as butylzinc, are well tolerated in the reaction; however, Cu-catalyzed ECA of isopropylzinc affords products in reduced enantioselectivity (82.5:17.5 er) and methylzinc addition only provides <36% conv. Recently, a new catalyst system (modified phosphoramidite ligand and copper salt) has been developed that allows for the more efficient methyl alkylations (up to 68% yield, and 98.5:1.5 er).[19e] The utility of the enantiomerically enriched products was demonstrated by a Lewis acid catalyzed intramolecular Friedel-Crafts reaction to afford an indanone derivative **1.16** or hydrolysis of the Meldrum's acid product to yield a β,β-disubstituted pentanoic acid **1.17** (Scheme 1.4).

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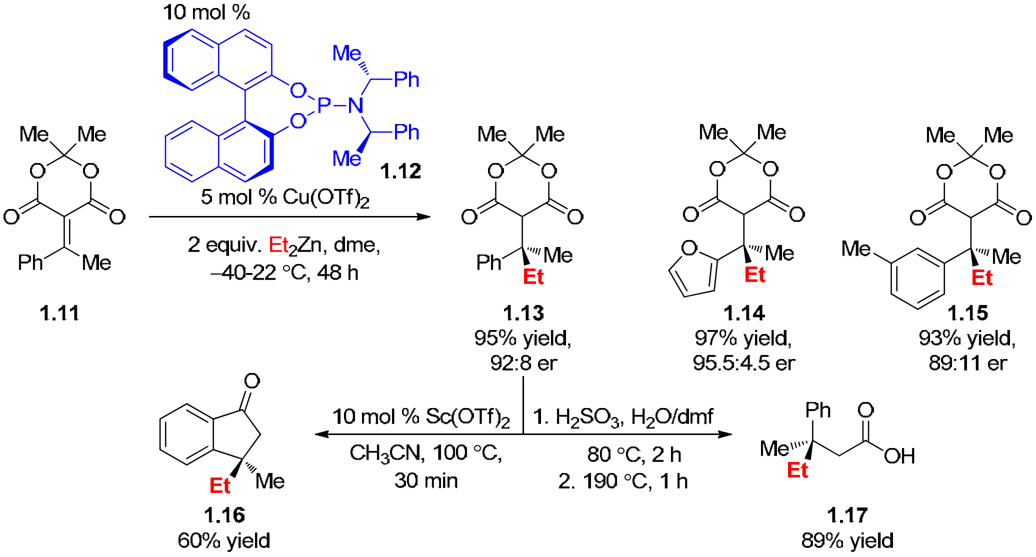
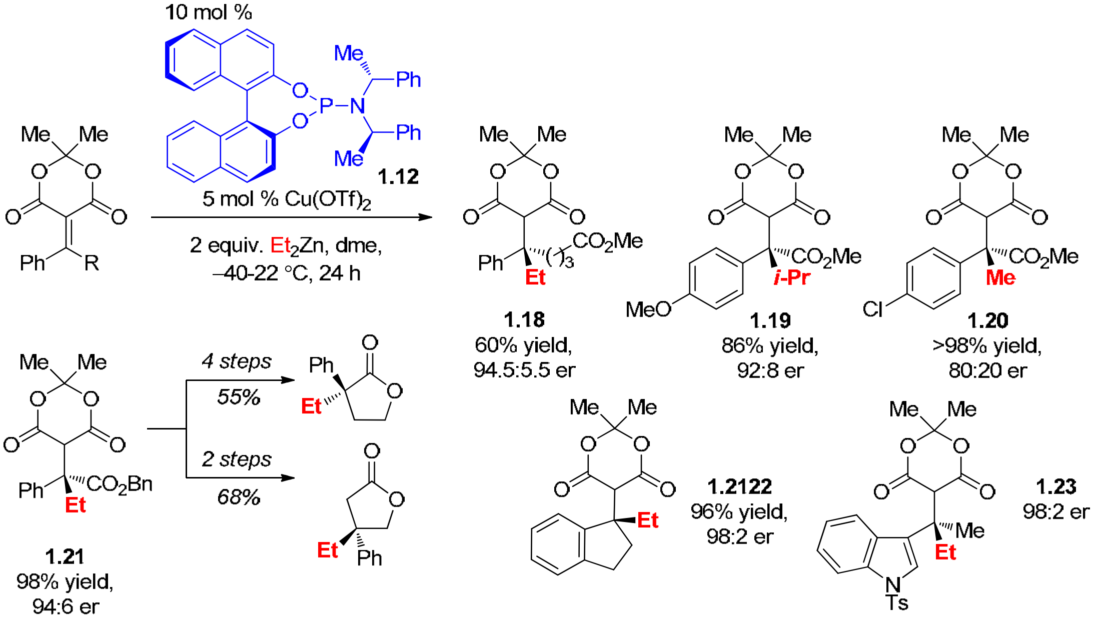
(20) (a) "Phosphoramidites: Marvellous Ligands in Catalytic Asymmetric Conjugate Addition," Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (b) "Phosphoramidites: Privileged Ligands in Asymmetric Catalysis," Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486–2528.

Scheme 1.4. Cu-Catalyzed ECAs of Alkylzinc Regents to Meldrum's Acid Derived Enones.


10 mol %
1.12
5 mol % Cu(OTf)$_2$
2 equiv. Et$_2$Zn, dme,
–40-22 °C, 48 h
1.11
1.13
95% yield,
92:8 er
1.14
97% yield,
95.5:4.5 er
1.15
93% yield,
89:11 er
10 mol % Sc(OTf)$_2$
CH$_3$CN, 100 °C,
30 min
1. H$_2$SO$_3$, H$_2$O/dmf
80 °C, 2 h
2. 190 °C, 1 h
1.16
60% yield
1.17
89% yield

Cu-catalyzed ECA of diakylzinc reagents (Et, Me, *i*-Pr, and *n*-Bu) to the expanded substrate scope provided products with an all-carbon quaternary stereogenic center bearing an ester group in high yields and enantioselectivities (Scheme 1.5, up to >98% yield, and 97:3 er).[19c] Similar trends were observed as above; the highest enantioselectivities were found with *p*-substituted aryl rings on the enone; the reaction of substrates with *m*-substitution delivers products with lower enantioselectivities. *o*-Substitution is tolerated on the β-ester containing enones (electron-withdrawing substituent lowers the LUMO of the enone), however, the selectivities of the products are moderate (66:34–90:10 er) and 1,4-hydride addition becomes competitive (up to 53% of the reaction material). Cu-catalyzed ECAs of indenylidene Meldrum's acid substrates are also suitable substrates (products **1.22** and **1.23**).[19d] Enantiomerically enriched lactones bearing an all-carbon quaternary stereogenic center at either the α- or β-position can be prepared, from the conjugate addition product **1.21** in four or two steps, respectively (Scheme 1.5).

Scheme 1.5. Expanded Substrate Scope for Cu-Catalyzed ECA of Alkylzinc Reagents to Meldrum's Acid Derived Substrates and Functionalizations of the Products


10 mol %
Me
Ph
O
P–N
O
Ph
Me
1.12
5 mol % Cu(OTf)2
2 equiv. Et2Zn, dme,
–40-22 °C, 24 h
Me
Me
O
O
O
O
Ph
R
Ph
Et
CO2Me
( )3
1.18
60% yield,
94.5:5.5 er
MeO
i-Pr
CO2Me
1.19
86% yield,
92:8 er
Cl
Me
CO2Me
1.20
>98% yield,
80:20 er
4 steps
55%
2 steps
68%
Ph
CO2Bn
Et
1.21
98% yield,
94:6 er
Et
Ph
O
1.2122
96% yield,
98:2 er
Me
Et
N
Ts
1.23
98:2 er

Professor Alexakis and co-workers disclosed a method for the Cu-catalyzed ECA of trialkylaluminum reagents to di-ester-substituted oxabicycles (**1.24**, Scheme 1.6).[21] As shown in Scheme 1.6, the reaction is promoted by 2 mol % of phosphoramidite **1.25** in the presence of 1 mol % of a Cu(I) salt; the reaction proceeds through an exo approach of the nucleophile generating the enolate **1.26**, which subsequently undergoes opening of the oxabicycle to afford the product **1.27** containing an all-carbon stereogenic center α to an alcohol as a single diastereomer. The enantioselective alkylation performs well with Me_3Al (**1.27**, 95% yield, 96.5:3.5 er). The method was also demonstrated on a substrate containing two methyl groups on the bridgehead carbons; the product **1.31**, which contains two adjacent quaternary stereogenic centers, is afforded in quantitative yield and in 96.5:3.5 er. Although this is the first ECA method developed to afford products containing all-carbon quaternary stereogenic centers on oxabicycles, the method is limited in scope; only oxabicycles are competent partners (norbornadiene substrates are

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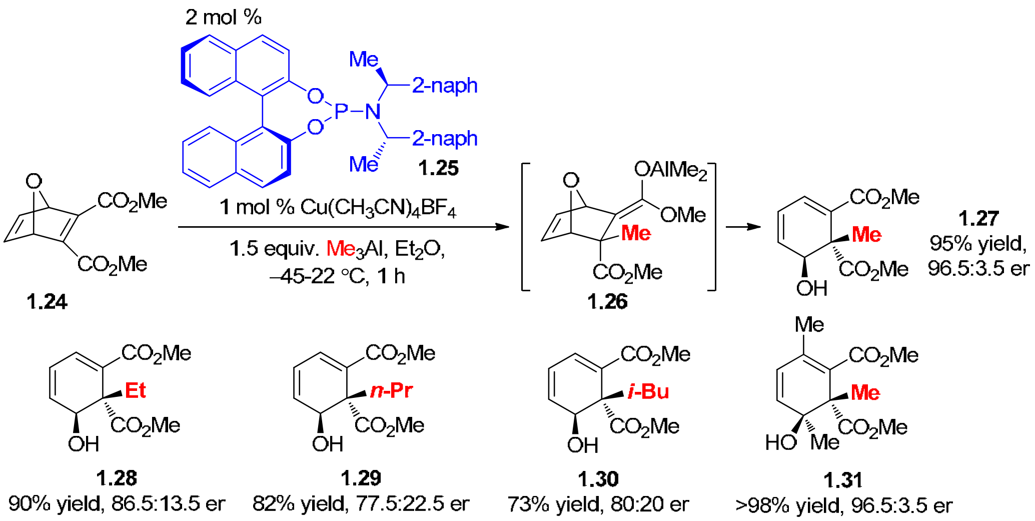
(21) "New Bifunctional Substrates for Copper-Catalyzed Asymmetric Conjugate Addition Reactions with Trialkylaluminum," Ladjel, C.; Fuchs, N.; Zhao, J.; Bernardinelli, G.; Alexakis, A. *Eur. J. Org. Chem.* **2009**, 4949–4955.

unreactive). Trimethylalumium is the only nucleophile examined that delivers products in >87.5:12.5 er; additions of other alkyl-based nucleophiles results in a significant decrease in the enantioselectivity of the products (Et, *n*-Pr, and *i*-Bu additions, 77.5:22.5–86.5:13.5 er, **1.28–1.30**).

Scheme 1.6. Cu-Catalyzed ECA of Alkylaluminum Reagents to Oxabicycles


2 mol %
Me
2-naph
O
P
N
O
2-naph
Me
1.25
1 mol % Cu(CH3CN)4BF4
1.5 equiv. Me3Al, Et2O,
–45-22 °C, 1 h
O
CO2Me
CO2Me
1.24
OAlMe2
OMe
Me
CO2Me
1.26
CO2Me
Me
CO2Me
OH
1.27
95% yield,
96.5:3.5 er
CO2Me
Et
CO2Me
OH
1.28
90% yield, 86.5:13.5 er
CO2Me
n-Pr
CO2Me
OH
1.29
82% yield, 77.5:22.5 er
CO2Me
i-Bu
CO2Me
OH
1.30
73% yield, 80:20 er
Me
CO2Me
Me
CO2Me
HO
Me
1.31
>98% yield, 96.5:3.5 er

Initial studies in our laboratories to investigate enantioselective additions to enones to generate all-carbon quaternary stereogenic centers centered on the use of the peptide-based phosphines as ligands in the presence of a copper salt. After a broad ligand screening including positional screening of different amino acids and a screening of different chelating groups on the C-terminus (phosphines, alcohols, amines) we found that Cu-catalyzed ECA of alkylzinc reagents to tetrasubstituted cyclic enones can be promoted by 2–5 mol % of an amino acid-based ligand bearing an anthranilic amide (**1.33**, Scheme 1.7) and air-stable CuCN.[22] For example, Cu-catalyzed ECA of Et_2Zn to enone **1.32**, promoted by **1.33** and CuCN, affords ketoester **1.34** in 89% yield and 91:9 er (Scheme 1.7). The addition is practical as undistilled toluene is used and the reaction can be performed under air (without excluding moisture). Various esters can be used on the substrate (Me, Et, *t*-Bu, Scheme 1.7) as well as several alkylzinc reagents [Et (**1.34**), *n*Bu

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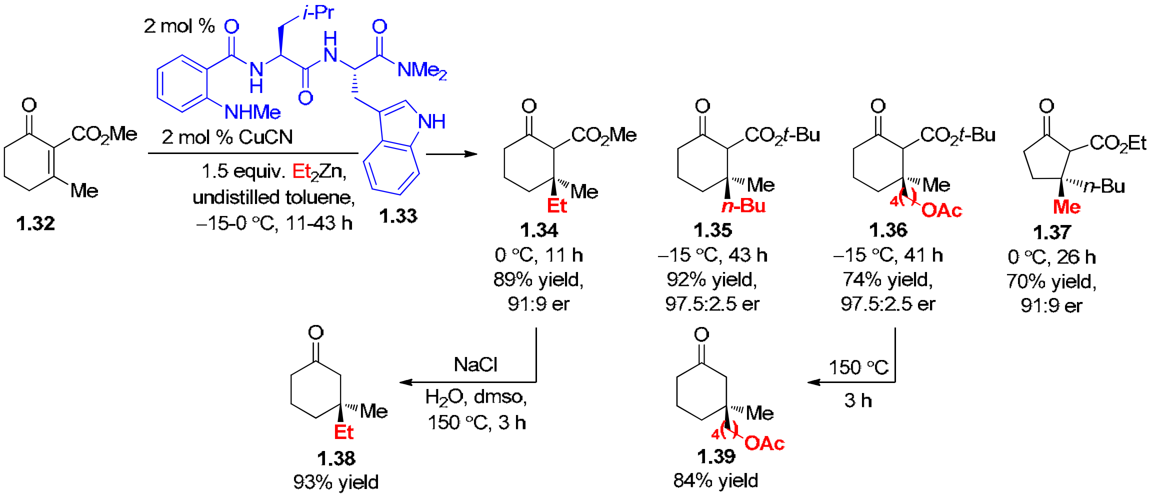
[22] "Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones," Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

(**1.35**), long-chained ester-containing groups (**1.36**), and *i*-Pr, and Me (**1.37**)] with enantioselectivities to six-membered ring enones above 91:9 er. Five-membered ring substrates are also efficient, however, products are isolated with slightly reduced enantioselectivities (product **1.37** is representative, 70% yield, 91:9 er, Scheme 1.7).[23] Although the method uses a readily available ligand, copper salt, and does not require rigorously dry materials, the substrate must contain an α-ester group. Under the conditions shown in Scheme 1.7, β-methylcyclohexenone is unreactive. The ester group presumably lowers the LUMO of the enone to facilitate the addition of the in situ prepared cuprate. Moreover, although various alkylzinc regents are commercially available, preparation of non-commercially available alkyl groups require Schlenk line or dry box techniques.[24] Alkylzinc reagents are, however, functional group tolerant (for example OAc in **1.36**, Scheme 1.7 is inert). Dialkylzinc reagents are more atom economical than trialkylaluminum reagents, but not as much as lithium or Grignard reagents. However, the latter nucleophiles can suffer from adventitious uncatalyzed background reactions.

Scheme 1.7. Cu-Catalyzed ECA of Dialkylzinc Reagents to Tetrasubstituted Enones



2 mol %
i-Pr
H
N
N
H
O
O
O
NMe2
NHMe
NH
CO2Me
Me
1.32
2 mol % CuCN
1.5 equiv. Et2Zn,
undistilled toluene,
–15-0 °C, 11-43 h
1.33
CO2Me
Me
Et
1.34
0 °C, 11 h
89% yield,
91:9 er
CO2t-Bu
Me
n-Bu
1.35
–15 °C, 43 h
92% yield,
97.5:2.5 er
CO2t-Bu
Me
4
OAc
1.36
–15 °C, 41 h
74% yield,
97.5:2.5 er
CO2Et
n-Bu
Me
1.37
0 °C, 26 h
70% yield,
91:9 er
NaCl
H2O, dmso,
150 °C, 3 h
Me
Et
1.38
93% yield
150 °C
3 h
Me
4
OAc
1.39
84% yield

---

[23] Five-membered ring enones are often less efficient and enantioselective substrates in ECA (further details and examples are shown below).

[24] "Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis," Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.

Several functionalizations are presented in the communication, including decarboxylation of the ester group by heating ketoester **1.34** in NaCl, H_2O and DMSO to afford **1.38** or a thermal decarboxylation to afford **1.39**. Procedures to prepare enantiomerically enriched tri- and tetra-substituted cyclohexenes are also straightforward in a two step process.

1.2.b Enantioselective Alkyl Conjugate Additions to Alkyl- and Aryl-Substituted Enones

Alexakis and co-workers disclosed the first example of ECA to β-alkyl cyclohexenones to generate all-carbon quaternary stereogenic centers in 2005[25] followed by a full paper account with an expanded substrate scope.[26] As shown in Scheme 1.8, the enantioselective alkylation is promoted by 4 mol % of Feringa's phosphoramidite ligand with 2 mol % of a Cu(I) salt; methyl and ethyl additions (from the corresponding two equiv. of trialkylaluminum reagents) to various enones are efficient and selective (up to 87% yield, 98.5:1.5 er, Scheme 1.8). Cu-catalyzed enantioselective conjugate addition of Et_3Al to β-methyl cycloheptenone proceeds with >95% conv and in 97.5:2.5 er, however, ketone **1.43** is isolated in only 58% yield.

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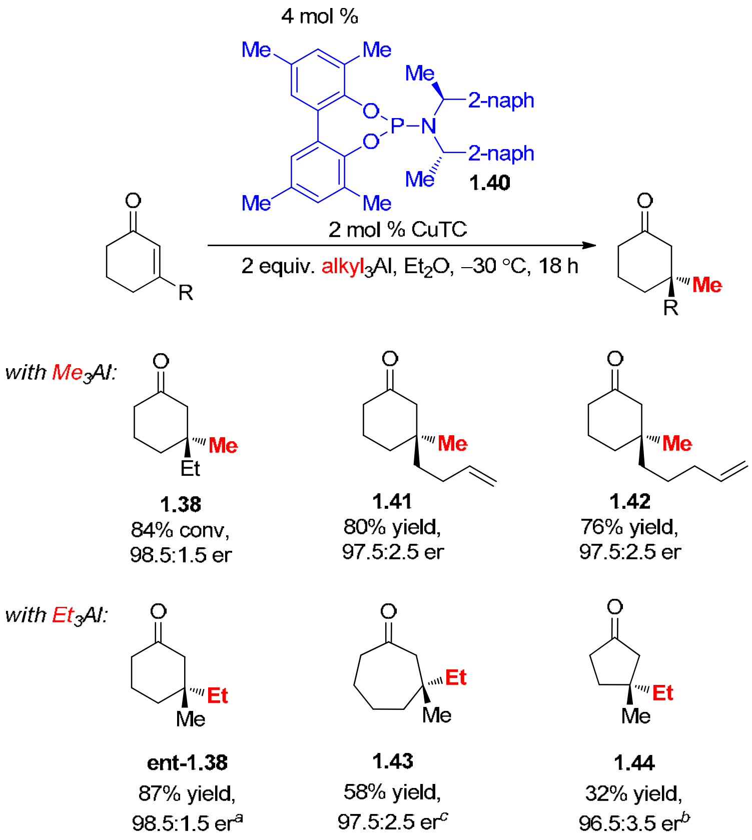
(25) "Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers," d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378.

(26) "Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminum Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers," Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662.

Scheme 1.8. Cu-Catalyzed ECA of Alkylzinc Reagents to Enones Promoted by a Phosphoramidite Ligand


4 mol %
Me
Me
Me
O
P–N
O
2-naph
2-naph
Me
Me
Me
Me
1.40
2 mol % CuTC
2 equiv. alkyl3Al, Et2O, –30 °C, 18 h
O
R
O
Me
R
with Me3Al:
Me
Et
1.38
84% conv,
98.5:1.5 er
Me
1.41
80% yield,
97.5:2.5 er
Me
1.42
76% yield,
97.5:2.5 er
with Et3Al:
Et
Me
ent-1.38
87% yield,
98.5:1.5 era
Et
Me
1.43
58% yield,
97.5:2.5 erc
Et
Me
1.44
32% yield,
96.5:3.5 erb

[a] 8 mol % **1.40**, 4 mol % $(CuOTf)_2{\bullet}C_6H_6$, –10 °C.
[b] 8 mol % **1.40**, 2 mol % $(CuOTf)_2{\bullet}C_6H_6$.
[c] Phosphoramidite **1.12** was used.

Although this procedure performs well for substituted cyclohexenones, the Cu-catalyzed ECA protocol is not as effective for additions to β-substituted cyclopentenones. As shown in Scheme 1.8, the ECA of Et_3Al to 3-methylcyclopentenone, promoted by a copper–phosphoramidite complex, affords cyclopentanone **1.44** in high selectivity (96.5:3.5 er) but only in 32% yield (>95% conv).[27] The enantioselective addition of less reactive Me_3Al (as compared to Et_3Al) to β-ethylcyclopentenone is inefficient, affording the desired product in 50% conv, 31% yield and 66.5:33.5 er (not shown).

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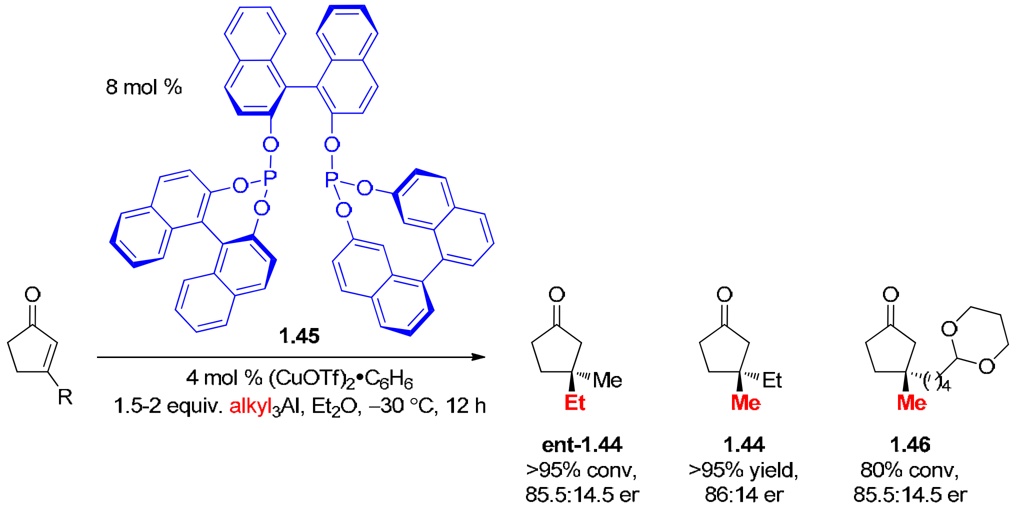
(27) "Enantioselective Copper-Catalyzed Conjugate Addition to 2- or 3-Substituted Cyclopent-2-en-1-ones: Construction of Stereogenic Quaternary Carbon Centers," Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, 2057–2060. For initial results, see: ref 24.

A follow up study investigated the Cu-catalyzed ECA reaction of β-substituted cyclopentenones promoted by a diphosphite ligand (Scheme 1.9).[27] The enantioselective additions were efficient (>80% conv at –30 °C overnight) but provided products with <87:13 er. One yield is reported for product **1.44** (>95% yield) while for products **ent-1.44** and **1.46**, only conversions are quoted. This class of enones are difficult substrates for ECA perhaps because of their relatively planar shape, while β-substituted cyclohexenones and cycloheptenones are bent, allowing for the Cu–ligand complex to have more steric interaction with the latter substrates. Regardless, more active and effective catalysts are needed for ECA of β-substituted cyclopentenones.

Scheme 1.9. Cu-Catalyzed ECA of Et$_3$Al and Me$_3$Al to β-Substituted Cyclopentenones Promoted by Diphosphite Ligand **1.45**



In 2007, the Alexakis group disclosed a new ligand **1.47**, a simplified version of the phosphoramidite ligands (Scheme 1.10).[28] Instead of a rigid binaphthal or biphenol unit, as found in ligands **1.25** or **1.40**, two aryl rings are used as ligands for the phosphine. The phosphinamine ligands allow for more flexibility around the phosphine center and can be synthesized in four steps. Interestingly, the modification should make the phosphine ligand not a strong of a Lewis base for copper (i.e., phosphites are stronger

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(28) "SimplePhos Monodentate Ligands: Synthesis and Application in Copper-Catalyzed Reactions," Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465.

σ-donors than the corresponding phosphines).[29] The phosphinamine **1.47**–copper complex has been shown to be effective in ECA of trialkylaluminum reagents to β-substituted enones in cases where the phosphoramidite **1.40**–copper complex only affords products in moderate levels of enantioselectivities (Scheme 1.10).[30]

As shown in entry 1, Scheme 1.10, Cu-catalyzed ECA of Me_3Al to 3-*i*-butylcyclohexenone in the presence of phosphoramidite ligand **1.40** and a Cu(I) salt affords the product **1.48** in 85% yield and 99:1 er; the phosphinamine ligand **1.47** is similarly effective for this transformation (90% conv, 98.5:1.5 er, no yield reported). Improvement can be seen in the ECA reactions when more difficult substrates are examined. For example, in entry 2, the enantioselective addition of Me_3Al to 3-phenylcyclohexenone, promoted by a Cu(I) salt and phosphoramidite ligand **1.40** only provides the desired product in 50% yield (70% conv) and 86:14 er. When the addition is promoted by new ligand phosphinamine **1.47** in the presence of a Cu(I) salt, the product is formed in 61% yield (74% conv) and 93.5:6.5 er. Both the conversion and yield are improved and the reaction proceeds in the presence of a more practical Cu(I) salt (CuTC vs., the moisture and air sensitive, CuOTf). Moreover, further improvements are observed when the Cu-catalyzed ECA is used to form ketones **1.50** and **1.51** the Cu–phosphoramidite complex (from **1.40**) affords the products in 20–93% conv and 80:20–83:17 er (entries 3–4, left column). When new phosphinamine ligand **1.47** is used in conjunction with a copper salt, the products are produced in 89–98% conv and up to 95.5:4.5 er (entries 3–4, right column).

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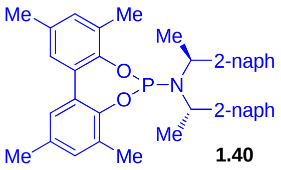
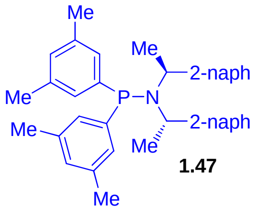
(29) "Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis," Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313–348.
(30) "Copper-Catalyzed Asymmetric Conjugate Addition with Chiral SimplePhos Ligands," Palais, L.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 10473–10485.

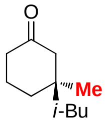
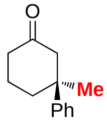
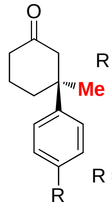
Scheme 1.10. Comparison of Phosphoramidite Ligand **1.40** and Phosphinamine **1.47** in Cu-Catalyzed ECA of Trialkylaluminum Reagents to β-Substituted Cyclohexenones



1.40



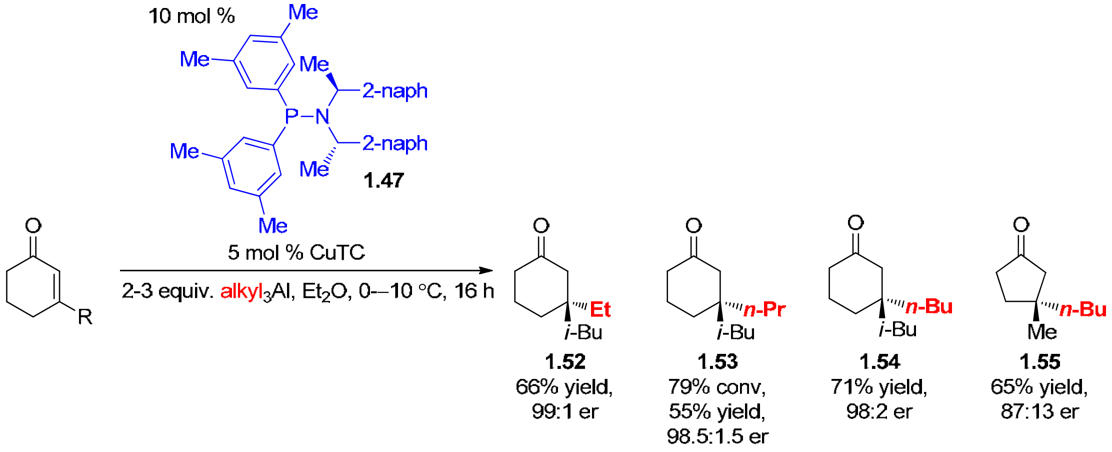
1.47

entry	product	**1.40** mol %, Cu mol %	conv (%)	yield (%)	er	**1.47** mol %, Cu mol %	conv (%)	yield (%)	er
1	 **1.48**	8 mol % **1.40**, 2 mol % $(CuOTf)_2•C_6H_6$	>95	85	99:1	10 mol % **1.47** 5 mol % $Cu(acac)_2$	90	nd	98.5:1.5
2	 **1.49**	8 mol % **1.40**, 2 mol % $(CuOTf)_2•C_6H_6$	70	50	86:14	10 mol % **1.47**, 5 mol % CuTC	74	61	93.5:6.5
3	 **1.50** R = CF_3	8 mol % **1.40**, 2 mol % $(CuOTf)_2•C_6H_6$	93	nd	83:17	8 mol % **1.47**, 2 mol % $(CuOAc)_2•H_2O$	>98	79	95.5:4.5
4	**1.51** R = OMe	8 mol % **1.40**, 2 mol % $(CuOTf)_2•C_6H_6$	20	nd	80:20	8 mol % **1.47**, 2 mol % $(CuOAc)_2•H_2O$	89	60	95:5

[a] Conditions: 2 equiv. of the alkyl$_3$Al at –30 °C for 16-18 h. nd = not determined. CuTC = copper thiocarboxylate.

Additional nucleophiles were examined in the Cu-catalyzed ECA reaction (Scheme 1.11). Cu-catalyzed ECA of Et_3Al, *n*-Pr_3Al, and *n*-Bu_3Al to sterically hindered 3-*i*-butylcyclohexenone, promoted by phosphinamine **1.47**, affords the conjugate addition adducts **1.52–1.54** in up to 99:1 er. Enantioselective additions to β-substituted cyclopentenones, however, still afford products with only moderate levels of enantioselectivity (**1.55**, 65% yield, 87:13 er).

Scheme 1.11. Cu-Catalyzed ECAs Promoted by Phosphinamine **1.47**


10 mol %
Me
Me
Me
2-naph
P–N
Me
2-naph
Me
Me
1.47
Me
O
R
5 mol % CuTC
2-3 equiv. alkyl₃Al, Et₂O, 0–-10 °C, 16 h
O
Et
i-Bu
1.52
66% yield, 99:1 er
O
n-Pr
i-Bu
1.53
79% conv, 55% yield, 98.5:1.5 er
O
n-Bu
i-Bu
1.54
71% yield, 98:2 er
O
n-Bu
Me
1.55
65% yield, 87:13 er

At this time, a general protocol for ECAs of nucleophiles to β-substituted cyclopentenones has not been achieved. Additionally, although the method and use of phosphine-based ligands Alexakis and co-workers has advanced the field for ECA of alkyl groups to β-substituted cyclohexenones, several deficiencies still remain that needs to be addressed. Functionalized trialkylaluminum reagents are difficult to prepare and if the alkyl group that will be transferred is expensive or precious (in the context of total synthesis for example), the other two groups on the aluminum will be wasted. An alternative to trialkylaluminum reagents for nucleophiles is dialkylzinc reagents. The latter nucleophiles are more atom economical and in some instances it is easier to prepare variants that are not commercially available; however, the dialkylzinc reagents that are commercially available are more expensive than trialkylaluminum reagents.[31] Moreover, high catalyst loadings are sometimes used, with multiple equivalents of ligand as compared to copper; phosphine-based ligands can dissociate from the metal, a characteristic that often necessitates excess ligand as compared to the metal to prevent uncatalyzed background reactions from occurring. As shown in the remaining examples in this subchapter, when N-heterocyclic carbenes (NHCs) are used as ligands for copper,

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(31) The following prices are from Strem in 2010: Me_3Al = \$104/mol. Me_2Zn = \$1380/mol. Et_3Al = \$33/mol. Et_2Zn = \$126/mol.

a 1:1 ligand:metal ratio can be used because of the tight binding that occurs.[32] Moreover, theoretical and experimental studies have elucidated that in many cases, NHCs are stronger electron donor ligands than phosphine-based ligands.[33]

As a follow up article to the Cu-catalyzed ECA of dialkylzinc reagents to activated tetrasubstituted enones,[22] investigations in our laboratories have focused on enantioselective additions of nucleophiles to unactivated enones that affords products containing all-carbon quaternary stereogenic centers. Initial results using a catalytic amount of chiral amino-acid based ligand (i.e., **1.33**, Scheme 1.7) and a copper salt with dialkylzinc or trialkylaluminum reagents to β-methylcyclohexenone only provided the desired product in <30% conv. It was evident that a more active catalyst must be developed to achieve effective ECA to sterically hindered cyclic enones. Since our group has demonstrated that chiral Cu–NHC complexes are efficient and selective catalysts for enantioselective allylic alkylation reactions,[34] which in some cases are more effective than the amino acid-based Cu catalysts, we investigated Cu–NHC complexes in the context of ECA reaction of β-substituted enones. As shown in Scheme 1.12, a Cu–NHC complex, prepared in situ from the bidentate Ag–NHC complex **1.56** and a Cu salt, promotes the ECA of diethylzinc to β-methylcyclohexenone to afford **ent-1.38** in 92%

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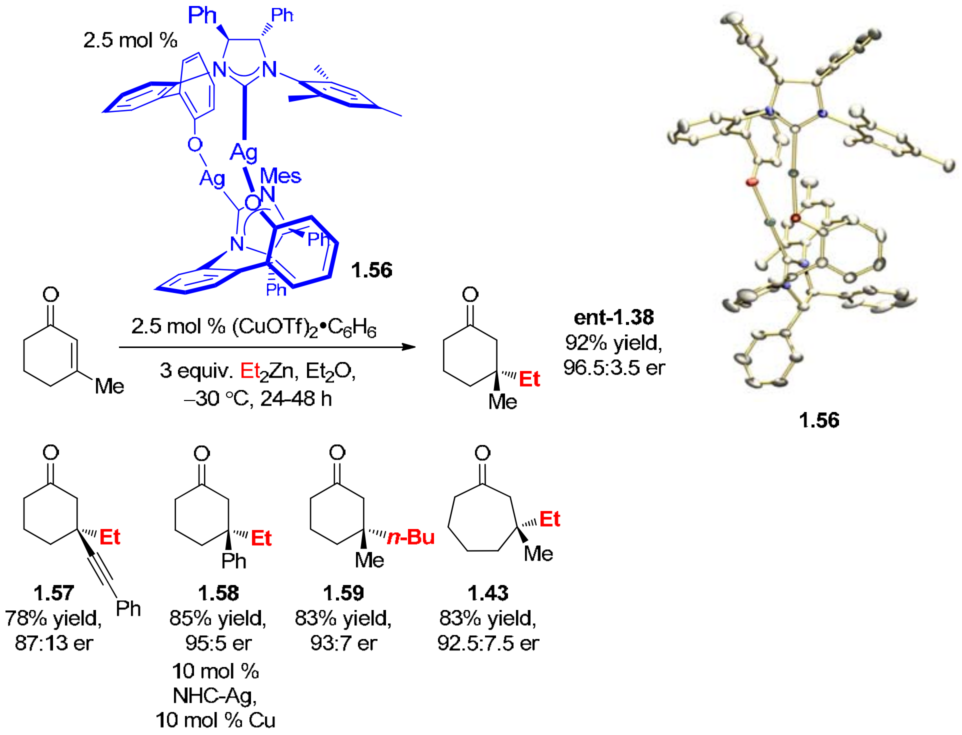
[32] *N-Heterocyclic Carbenes in Transition Metal Catalysis. Topics in Organometallic Chemistry 21;* Glorius, F., Ed.; Springer: New York, 2007.

[33] For representative studies that investigate the σ-donor abilities of phosphines vs. NHCs, see: (a) "Rhodium and Iridium Complexes of N-Heterocyclic Carbenes via Transmetallation: Structure and Dynamics," Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2003**, *22*, 1663–1667. (b) "Determination of N-Heterocyclic Carbene (NHC) Steric and Electronic Parameters using the [(NHC)Ir(CO)$_2$Cl] System," Kelly, R. A., III; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202–210. (c) "^{13}C NMR Spectroscopic Determination of Ligand Donor Strengths Using N-Heterocyclic Carbene Complexes of Palladium(II)," Huynh, H. V.; Han, Y.; Jothibasu, R.; Yang, J. A. *Organometallics* **2009**, *28*, 5395–5404.

[34] (a) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Nieto Oberhuber, C.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131. (b) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation," Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

yield and 96.5:3.5 er (Scheme 1.12).[35] The Ag–NHC complex **1.56** is air-stable and can be prepared on multi-gram scale, the structure of which is determined as a dimeric form by both solid (X-ray) and solution state (nOe) analyses suggest this conformation; however, we believe the active form of the catalyst (Cu–NHC) is monomeric, which is formed by transmetallation of the Ag–carbene to generate AgOTf as a byproduct). Moreover, a 1:1 ligand:metal ratio is used since the Cu–NHC complex does not dissociate when formed.

Scheme 1.12. Cu-Catalyzed ECA of Dialkylzinc Reagents to Enones Promoted by Bidentate NHC Complexes to Afford All-Carbon Quaternary Stereogenic Centers


2.5 mol %
Ph
Ph
N
N
O
Ag
Ag
Mes
N
O
N
Ph
Ph
1.56
O
Me
2.5 mol % (CuOTf)$_2$•C$_6$H$_6$
3 equiv. Et$_2$Zn, Et$_2$O,
–30 °C, 24-48 h
O
Et
Me
ent-1.38
92% yield,
96.5:3.5 er
1.56
O
Et
Ph
1.57
78% yield,
87:13 er
O
Et
Ph
1.58
85% yield,
95:5 er
10 mol %
NHC-Ag,
10 mol % Cu
O
n-Bu
Me
1.59
83% yield,
93:7 er
O
Et
Me
1.43
83% yield,
92.5:7.5 er

The Cu-catalyzed ECA protocol allows for the efficient and selective addition of ethyl groups to various β-substituted cyclohexenones including β-alkynyl substituted enones (**1.57**, 78% yield, 87:13 er) with >98% addition in the 1,4 pathway (vs. 1,6

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(35) "A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers through NHC–Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to β-Substituted Cyclic Enones," Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184.

addition through the conjugated alkyne) and sterically hindered β-phenyl substituted enones (**1.58**, 85% yield, 95:5 er) although higher catalyst loading much be used to insure complete conversion. Enantioselective addition of di-*n*-butylzinc to enones is also efficient as represented for **1.59** (83% yield, 93:7 er). Seven- and eight-membered ring enones are efficient substrates for the Cu–NHC catalyzed ECA method, however, lower enantioselectivities of the conjugate addition adducts are observed (**1.43** is representative, 92.5:7.5 er). This initial communication was the first example of ECA of alkylzinc reagents (and arylzinc reagents, see next section) to unactivated β-substituted enones; in some cases, however, high catalyst loadings must be used (up to 10 mol % NHC–Ag **1.56**) and β-substituted cyclopentenones are unreactive (<2% conv). These deficiencies have been addressed and solutions have been developed with new chiral bidentate Cu–NHC complexes (see chapters 2–4).

An alternative to zinc- and aluminum-based reagents are Grignard reagents, which are easily prepared and most are commercially available. These are intriguing nucleophiles if the catalyst can effectively compete with the Grignard reagents inherent reactivity towards 1,2 addition. As illustrated in Scheme 1.13, Alexakis, Mauduit and co-workers have investigated ECA of Grignard reagents, promoted by Cu–NHC complexes, to cyclic enones.[36] Various ligands, in combination with a copper salt, were screened including phosphoramidites, ferrocene-based ligands,[37] and NHCs. N-Heterocyclic carbene-based Cu catalysts afforded the conjugate addition products with the highest regio- and enantioselectivities (Scheme 1.13, >98% 1,4 addition). Both C_2-symmetric and bidenate C_1 symmetric Cu–NHC complexes, prepared in situ by deprotonation of the corresponding imidazolinium salts with the Grignard reagents in the presence of a copper

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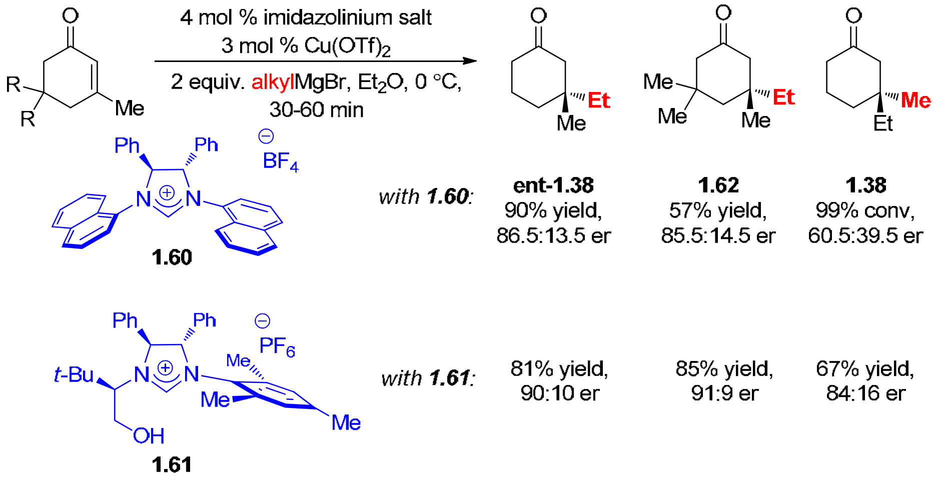
(36) (a) "Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers," Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (b) "Formation of Quaternary Chiral Centers by N-Heterocyclic Carbene–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Trisubstituted Cyclic Enones," Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. Eur. J.* **2010**, *16*, 9890–9904.

(37) "Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Cyclic Enones," Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acd. Sci. U. S. A.* **2004**, *101*, 5834–5838.

salt, promote the ECA of EtMgBr to 3-methylcyclohexenone affording **ent-1.38** in >80% yield and >86:14 er, however, the bidentate NHC–Cu complex, derived from **1.61** yields ketone **ent-1.38** in higher enantioselectivity (90:10 er, Scheme 1.13). The bidentate Cu–NHC complex is also more effective for ECAs of sterically hindered enones (to provide product **1.62**) and additions involving MeMgBr (product **ent-1.38**).

Scheme 1.13. ECA of Grignard Reagents to Cyclic Enones Promoted by Chiral Cu–NHC Complexes


4 mol % imidazolinium salt
3 mol % Cu(OTf)$_2$
2 equiv. alkylMgBr, Et$_2$O, 0 °C, 30-60 min
R
R
Me
O
Et
Me
Me
Me
Me
Et
Me
Et
Ph
Ph
BF$_4$
N
N
1.60
with 1.60:
ent-1.38
90% yield, 86.5:13.5 er
1.62
57% yield, 85.5:14.5 er
1.38
99% conv, 60.5:39.5 er
Ph
Ph
PF$_6$
t-Bu
N
N
Me
Me
Me
OH
1.61
with 1.61:
81% yield, 90:10 er
85% yield, 91:9 er
67% yield, 84:16 er

A range of β-substituted cyclohexenones participate in the enantioselective protocol (Scheme 1.14). Enones containing an appendant olefin (yielding **1.63**), β-substituted enones containing sterically hindered groups (*i*-Bu and phenyl, to afford **1.50** and **1.58**) and α,β,γ,δ-unsaturated enones (to deliver **1.64**) are effective in the Cu-catalyzed ECA reaction and are complete within 20 minutes at 0 °C.[38] Moreover, a variety of Grignard reagents are compatible in the Cu-catalyzed ECA reaction. Enantioenriched products are obtained in >87:13 er for addition involving long-chained alkyl groups (**1.59**), sterically hindered nucleophiles (**ent-1.48** and **1.65**), as well as cyclic Grignard reagents (**1.66** and **1.67**). The observed enantioselectivities of the products do

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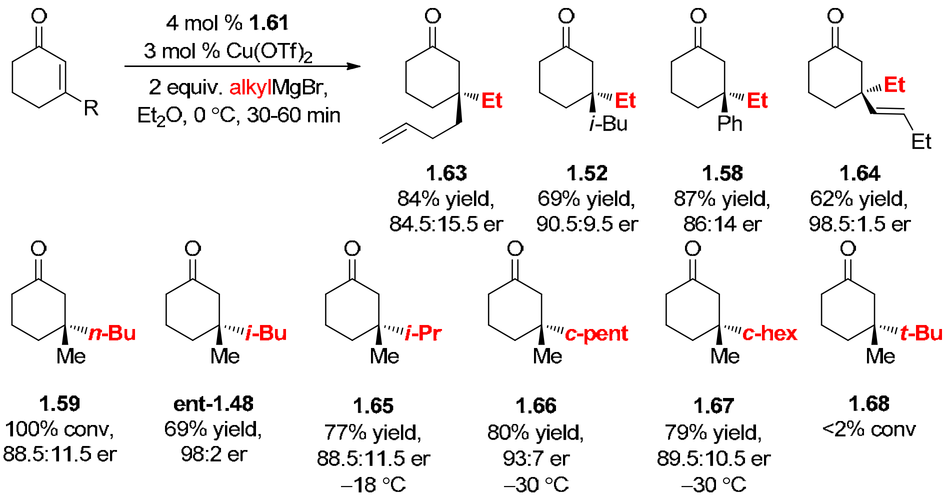
(38) For a more expanded scope of Cu-catalyzed ECA of Grignard reagents to α,β,γ,δ-unsaturated enones forming quaternary stereogenic centers, see: "Regiodivergent 1,4-versus 1,6-Asymmetric Copper-Catalyzed Conjugate Addition," Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122–9124.

not seem to be dependent on the relative size of the alkyl groups on the Grignard reagent (*n*-Bu addition and *i*-Pr addition both deliver products with 88.5:11.5 er, **1.59** and **1.65**); the enantioselective addition of the *i*-butyl group, however, affords the product with the highest enantioselectivity reported (98:2 er). Cu-Catalyzed ECA of *t*-butylMgBr to 3-methylcyclohexenone results in <2% conv.

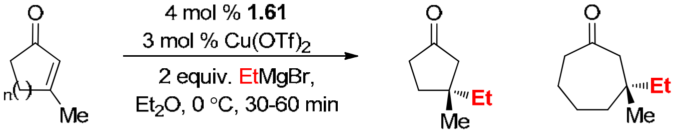
Scheme 1.14. Representative Substrate and Nucleophile Scope for Cu-Catalyzed ECA of Grignard Reagents to β-Substituted Cyclohexenones



R
4 mol % 1.61
3 mol % Cu(OTf)2
2 equiv. alkylMgBr,
Et2O, 0 °C, 30-60 min
Et
i-Bu
Et
Ph
Et
Et
Et
1.63
84% yield,
84.5:15.5 er
1.52
69% yield,
90.5:9.5 er
1.58
87% yield,
86:14 er
1.64
62% yield,
98.5:1.5 er
n-Bu
Me
i-Bu
Me
i-Pr
Me
c-pent
Me
c-hex
Me
t-Bu
Me
1.59
100% conv,
88.5:11.5 er
ent-1.48
69% yield,
98:2 er
1.65
77% yield,
88.5:11.5 er
−18 °C
1.66
80% yield,
93:7 er
−30 °C
1.67
79% yield,
89.5:10.5 er
−30 °C
1.68
<2% conv

Enantioselective addition of EtMgBr, catalyzed by the Cu–NHC complex derived from **1.61**, to 3-methylcyclopentenone delivers the product in 90% yield, however, in only 73:27 er (**1.44**, Scheme 1.15); additions to five-membered ring enones continues to be a difficult problem for enantioselective conjugate addition. Cycloheptanone **1.43** is accessed in 91:9 er (76% yield), which is comparable to the enantioinduction observed with additions of EtMgBr to β-substituted cyclohexenones. The magnesium enolate, generated in situ from the conjugate addition step before hydrolysis work-up, can be used to for further functionalizations; for example, treatment of the Mg-enolate of **1.38** with allyl iodide, with HMPA as a cosolvent, affords (3*R*)-2-allyl-3-ethyl-3-methylcyclohexanone in 70:30 dr (81% yield, 88:12 er, not shown).

Scheme 1.15. Cu-Catalyzed ECA of EtMgBr to β-Substituted Five- and Seven-Membered Ring Enones



1.44
90% yield,
73:27 er

1.43
76% yield
91:9 er

The Cu-catalyzed ECA of Grignard reagents to trisubstituted enones allows for the preparation of various enantioenriched quaternary carbon-containing compounds. The method described performs well with β-substituted cyclohexenones; however, perhaps with the development of new catalysts, enantioselectivities of the products can be improved since most of the products are obtained in 70–80% ee. Enantioselective additions to five-membered rings still continue to provided products with low enantioselectivities. An additional drawback is the requirement of slow addition of the enones over 15 minutes.

Tomioka and coworkers have also disclosed a Cu-catalyzed ECA method for Grignard reagents to trisubstituted enones.[39] The enantioselective additions are promoted by a C_2-symmetric bisphenoxy methyl ether containing NHC–Cu complex, prepared in situ by deprotonation of a chiral imidazolinium salt with excess Grignard reagent. Various Grignard reagents can be used in this ECA protocol and regioselectivities are high (>97% 1,4 addition). Enantioselectivities of the conjugate addition adducts, however, are moderate (<91:9 er) and the product of the enantioselective methyl addition (**1.38**) is only obtained in 59:41 er.

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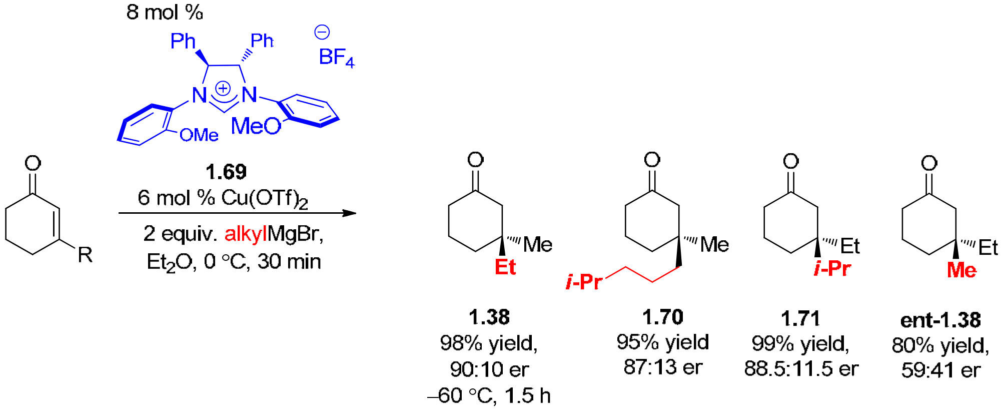
(39) "C_2 Symmetric Chiral NHC Ligand for Asymmetric Quaternary Carbon Constructing Copper-Catalyzed Conjugate Addition of Grignard Reagents to 3-Substituted Cyclohexenones," Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581.

Scheme 1.16. Cu-Catalyzed ECA of Grignard Reagents to Trisubstituted Enones Promoted by a C_2-Symmetric NHC Ligand


8 mol %
Ph
Ph
BF4
N
N
OMe
MeO
1.69
6 mol % Cu(OTf)2
2 equiv. alkylMgBr,
Et2O, 0 °C, 30 min
O
R
Me
Et
1.38
98% yield,
90:10 er
–60 °C, 1.5 h
Me
i-Pr
1.70
95% yield
87:13 er
Et
i-Pr
1.71
99% yield,
88.5:11.5 er
Et
Me
ent-1.38
80% yield,
59:41 er

1.2.c Conclusions and Remaining Goals for ECAs of Alkyl Groups to Enones Forming Quaternary Carbon Stereogenic Centers

Great strides have been made in the past several years involving protocols for the enantioselective conjugate additions of alkyl groups to activated enones to generate quaternary carbon stereogenic centers. Initial reports were centered on enantioselective additions to trisubstituted nitroalkenes and enones containing electron-withdrawing substituents (esters, oxabicycles). More recently, methods have been forthcoming involving additions of alkyl nucleophiles to trisubstituted enones without activating groups (alkyl and aryl groups). Complementary ECAs of alkylzinc, aluminum, and Grignard reagents have been developed. Most additions have addressed ECA additions to trisubstituted six-membered rings; products are afforded in up to 99:1 er. Enantioselective additions to five-membered ring enones, however, have not been as successful; investigations by our group and Alexakis and coworkers have found that β-substituted cyclopentenones are less reactive than β-substituted cyclohexenones and/or react with chiral catalysts to provide products with low to moderate levels of enantioselectivity (<90:10 er). There have been no examples of ECAs of nucleophiles to unactivated *acyclic* enones and only one addition centering on tetrasubstituted enones.[22] Development of new and active chiral catalysts that are efficient and selective for additions of various nucleophiles to β-substituted cyclopentenones was one of the goals when I began research in the Hoveyda laboratories.

1.3 Enantioselective Conjugate Additions of Aryl Nucleophiles to Enones

1.3.a Introduction

Enantioselective conjugate additions of aryl metals to activated alkenes to form all-carbon quaternary stereogenic centers have been less studied as compared to the corresponding reactions with alkyl metals, the first reaction was only disclosed in 2006.[35] It is noteworthy that additions of aryl metals may require significant optimization of conditions or the chiral catalyst that is used for alkyl additions since both the size and electronics of the nucleophile are considerably altered. For instance, the hybridization of the nucleophilic carbon is sp^2 vs. sp^3, the former is considered more basic and nucleophilic[40] and an aryl group is larger than a primary alkyl group (i.e., the A value of a phenyl group is 3.0 and a methyl group is 1.8).

Enantioenriched products that are obtained from the ECA reactions of aryl metals (i.e., **I**, Figure 1.1) can be elaborated into natural products, many of which contain all-carbon quaternary stereogenic centers with an aryl substituent.[41] Products, such as **I**, can be prepared through an enantioselective alkyl addition to an aryl-substituted enone; although this is a plausible pathway, the preparation of a quaternary stereogenic center on a hindered enone is a demanding task. Moreover, if the desired target contains two aryl substituents, the ECA of an alkyl nucleophile would not be a viable option. Therefore, an effective solution for ECA of an aryl nucleophile is an important strategy for organic synthesis.

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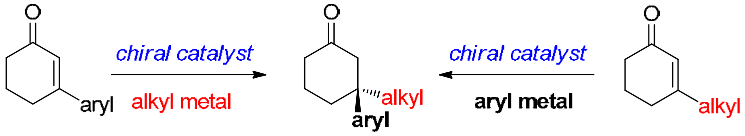
(40) For example, dialkylzinc reagents do not react with aldehydes without a catalyst; diarylzinc reagents, however, react with aldehydes uncatalyzed. See: "Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds," Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.

(41) (a) "Ketones from 'Mayur Pankhi': Some New Cuparene-Based Sesquiterpenoids," Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, *5*, 73–77. (b) "Laurene, A Sesquiterpene Hydrocarbon from *Laurencia* Species," Irie, T.; Suzuki, T.; Yasunari, Y.; Kurosawa, E.; Masamune, T. *Tetrahedron* **1969**, *25*, 459–468. (c) "Fredericamycin A, A New Antitumor Antibiotic. I. Production, Isolation and Physicochemical Properties," Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.(Tokyo)* **1981**, *34*, 1389–1401.

Figure 1.1. Two Ways of Preparing Conjugate Addition Product **I** with an Aryl-Containing All-Carbon Quaternary Stereogenic Center



I

With the exception of aryllithium and aryl Grignard reagents, other aryl-based nucleophiles are not as plentiful as alkyl-based nucleophiles. For example, there are only two commercially available arylzinc reagents, diphenylzinc and bis(pentafluoro)zinc. If a general method is to be developed, then one would also need to be able to access the nucleophiles quickly and efficiently. As is described in this chapter, aryl metal reagents that can be prepared in situ and used without isolation would be a practical advancement for ECA, as well as for other methods that require aryl nucleophiles.

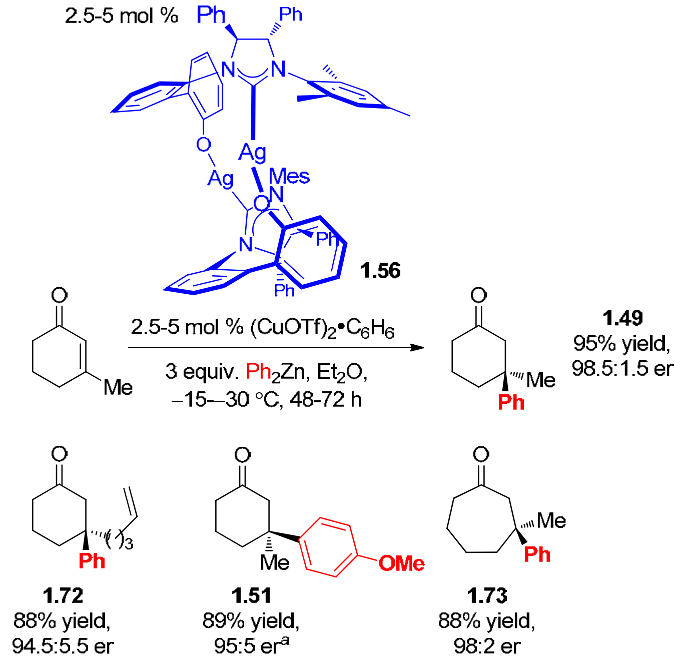
1.3.b Copper-Catalyzed Enantioselective Conjugate Addition of Aryl Grignard and Aryl Aluminum Reagents to Trisubstituted Enones

The first example of Cu-catalyzed ECA of an aryl metal to an electrophile generating a quaternary carbon stereogenic center is reported in 2006 from our laboratories.[35] A chiral Cu–NHC complex, generated in situ from **1.56** and a copper salt, efficiently and selectively promotes the conjugate addition of Ph_2Zn to 3-methylcyclohexenone affording **1.49** in 95% yield and 98.5:1.5 er. Electron-rich *p*-methoxyphenylzinc can also be utilized, product **1.51** is representative (89% yield, 95:5 er).[42] Trisubstituted cycloheptenones are also competent partners in the ECA protocol (**1.73**, 88% yield, 98:2 er).

---

(42) *p*-Methoxyphenylzinc is prepared from $ZnCl_2$ and the corresponding aryl lithium; the crude material is purified by sublimation. See: "Arylzinc Alkoxides: $[ArZnOCHPr^i_2]_2$ and $Ar_2Zn_3(OCHPr^i_2)_4$ When Ar = C_6H_5, *p*-$CF_3C_6H_4$, 2,4,6-$Me_3C_6H_2$ and C_6F_5," Chrisholm, M. H.; Gallucci, J. C.; Yin, H.; Zhen, H. *Inorg. Chem.* **2005**, *44*, 4777–4785.

Scheme 1.17. Cu-Catalyzed ECA of Arylzinc Reagents to Trisubstituted Enones


2.5-5 mol %
Ph
Ph
N
N
O
Ag
Ag
Mes
N
O
N
Ph
Ph
1.56
O
Me
2.5-5 mol % (CuOTf)$_2$•C$_6$H$_6$
3 equiv. Ph$_2$Zn, Et$_2$O,
–15–30 °C, 48-72 h
O
Me
Ph
1.49
95% yield,
98.5:1.5 er
O
( )3
Ph
1.72
88% yield,
94.5:5.5 er
O
Me
OMe
1.51
89% yield,
95:5 er^a
O
Me
Ph
1.73
88% yield,
98:2 er

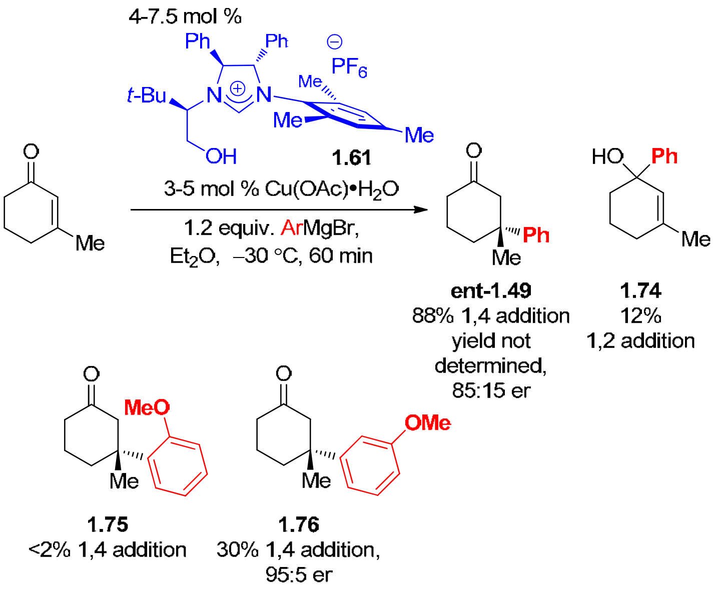
^{a} Reaction performed in toluene

Although the methodology put forth has demonstrated for the first time that arylzinc reagents can participate in ECA, catalyzed by a Cu–NHC complex, several deficiencies are noted. Trisubstituted cyclopentenones are unreactive under these current conditions, similar to additions of alkylzinc reagents, underscoring the difficulties associated with these substrates. The catalytic aryl additions are somewhat less efficient than the additions with alkylzinc reagents (examples in Scheme 1.17 vs. those in Scheme 1.12, longer reaction times are need for >90% conversion, 48–72 h vs. 6–48 h). Electron-deficient (p-CF$_3$C$_6$H$_4$)$_2$Zn, when used under the conditions described in Scheme 1.17 leads to <5% conv, probably due to the stabilization of the accumulated negative charge on the carbon that the electron-withdrawing substituent provides.

Similar to the report above regarding enantioselective addition of alkyl Grignard reagents to cyclic enones (cf. Scheme 1.13–1.15), Alexakis, Mauduit and co-workers have extended the ECA reaction, promoted by an in situ prepared Cu–NHC complex derived from **1.56**, to include additions of aryl Grignard reagents to cyclic enones.[36] As shown in Scheme 1.18, the enantioselective addition of PhMgBr to 3-

methylcyclohexenone proceeds to provide 88% of the 1,4-adduct **ent-1.49** (85:15 er, yield not reported) and 12% of the 1,2-addition product **1.74**. Although this is a promising reaction, other aryl Grignard reagents, under the Cu-catalyzed ECA conditions, react predominately to afford the 1,2-addition products (>70% 1,2-addition products). At this time, a catalyst has not been reported for efficient ECA of aryl Grignard reagents.[43]

Scheme 1.18. Cu-Catalyzed ECA of Aryl Grignard Reagents to Cyclic Enones


4-7.5 mol %
Ph
Ph
PF6
t-Bu
N
N
Me
Me
Me
OH
1.61
3-5 mol % Cu(OAc)•H2O
1.2 equiv. ArMgBr,
Et2O, –30 °C, 60 min
O
Me
O
Ph
Me
HO
Ph
Me
ent-1.49
88% 1,4 addition
yield not
determined,
85:15 er
1.74
12%
1,2 addition
O
MeO
Me
O
OMe
Me
1.75
<2% 1,4 addition
1.76
30% 1,4 addition,
95:5 er

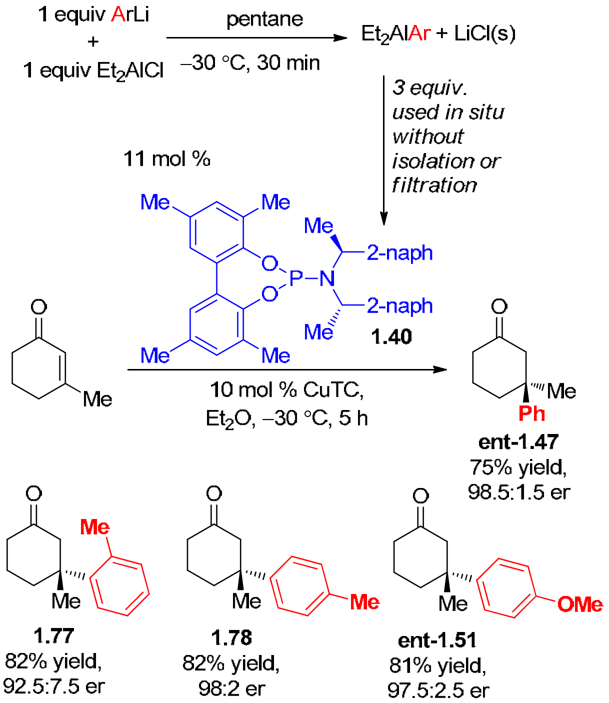
In an article that was disclosed shortly after our approach to Cu-catalyzed ECA of arylaluminum reagents (see Chapter 3), Alexakis and co-workers reported on a method for enantioselective conjugate addition with an arylaluminum reagent that is prepared and used in situ without isolation or purification.[44] The additions are catalyzed by phosphoramidite ligands in combination with a Cu(I) salt. As triphenylaluminum is the only commercial arylaluminum reagent available, and two phenyl groups per equivalent of Al used would be wasted, a procedure to prepare the aluminum reagents in situ is utilized; treatment of phenyllithium with Et_2AlCl affords diethylphenylaluminum. The ethyl groups on aluminum act as “dummy ligands” as the transfer of sp^2-hybridized groups on aluminum is significantly more facile than sp^3-hybridized ligands. The additions to β-substituted cyclohexenones, with a wide variety of substituted aryl groups, are efficient, providing products in up to 87% yield and 99:1 er (Scheme 1.19). Both electron-rich and electron-deficient aryl nucleophiles react to afford products in good yields and enantioselectivities; enantioselective addition of a sterically-hindered *o*-tolyl group affords **1.77** in a slightly decreased selectivity (92.5:7.5 er). The phosphinamine ligand **1.47**, found to promote ECA of trialkylaluminum reagents to β-substituted cyclohexenones in higher enantioselectivities than the phosphoramidite ligands (in some cases, cf. Scheme 1.10), are less effective as ligands in this process (following the conditions in Scheme 1.19, product **ent-1.49** is produced in 97:3 er).

---

[43] Tomioka and coworkers have reported one example of Cu-catalyzed ECA, promoted by a Cu–NHC complex, of PhMgBr to 3-methylcyclohexenone affording **1.49** in 48% yield and 67:33 er (see reference 39).

[44] "Copper-Catalyzed Asymmetric Conjugate Addition of Aryl Aluminum Reagents to Trisubstituted Enones: Construction of Aryl-Substituted Quaternary Centers," Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int Ed.* **2008**, *47*, 8211–8214.

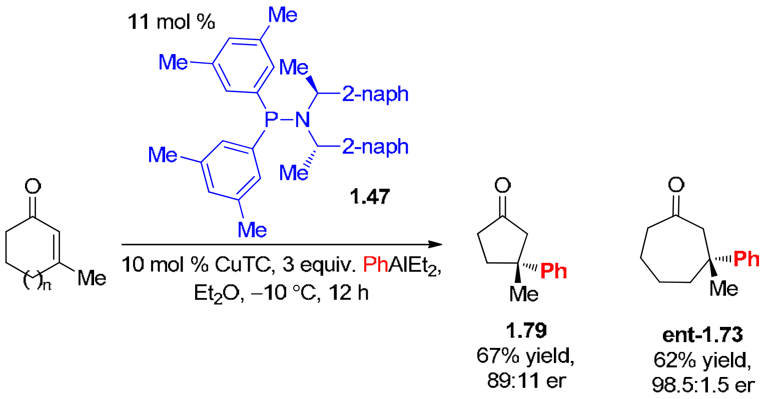
Scheme 1.19. Cu-Catalyzed ECA of Mixed Arylaluminum Reagents to Trisubstituted Enones


1 equiv ArLi
+
1 equiv Et2AlCl
pentane
–30 °C, 30 min
Et2AlAr + LiCl(s)
3 equiv. used in situ without isolation or filtration
11 mol %
Me
Me
Me
Me
O
O
P–N
Me
2-naph
Me
2-naph
1.40
O
Me
10 mol % CuTC,
Et2O, –30 °C, 5 h
O
Me
Ph
ent-1.47
75% yield,
98.5:1.5 er
O
Me
Me
1.77
82% yield,
92.5:7.5 er
O
Me
Me
1.78
82% yield,
98:2 er
O
Me
OMe
ent-1.51
81% yield,
97.5:2.5 er

Addition to the challenging five-membered ring enone requires the phosphinamine ligand **1.47**, longer reaction times and higher temperatures (Scheme

1.20); however, product **1.79** is isolated in 89:11 er. The seven-membered ring enone behaves similarly to the six-membered ring substrates. Although the results in Scheme 1.20 are promising, the generality of the reactions was not explored; the two products shown are the only non-six-membered ring products described. Moreover, relatively high catalyst loadings are required, but the inexpensive nature of a copper-based procedure and the use of in situ prepared nucleophiles make this process practical.

Scheme 1.20. Cu-Catalyzed ECA of Arylaluminum Reagents to Five- and Seven-Membered Ring Enones



1.3.c Rh-Catalyzed ECA of Aryl Nucleophiles to Trisubstituted Enones

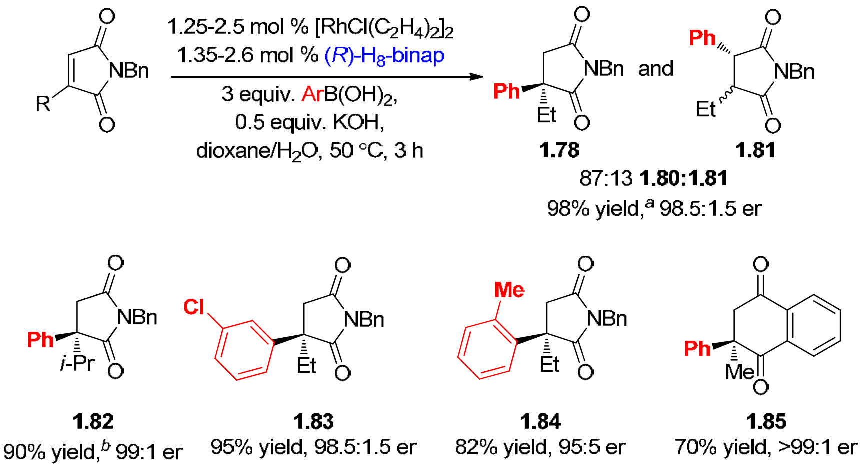
In addition to Cu-catalyzed enantioselective processes for generating all-carbon quaternary stereogenic centers through conjugate additions, there has been recent success with Rh-catalyzed additions of aryl nucleophiles. One of the earliest reports disclosed, from Hayashi and co-workers, describes a method for 1,4-addition of arylboronic acids to 3-substituted maleimides furnishing enantiomerically enriched succinimides.[45] The addition of phenylboronic acid to ethyl-substituted maleimide, catalyzed by a Rh(I) salt and (*R*)-H_8-binap, affords **1.80** in 98.5:1.5 er, along with 13% of the 1,4 addition product generating the tertiary stereogenic center (**1.81**, 98% yield combined, Scheme 1.21).

---

[45] "Rhodium-Catalyzed Asymmetric Construction of Quaternary Carbon Stereocenters: Ligand-Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides," Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629.

Interestingly, when the addition is catalyzed by a Rh chiral diene complex,[46] the regioselectivity shifts to afford ~20:80 ratio of **1.80**:**1.81**.

Scheme 1.21. Rh-Catalyzed ECA of Arylboronic Acids to Maleimides


1.25-2.5 mol % $[RhCl(C_2H_4)_2]_2$
1.35-2.6 mol % (*R*)-H_8-binap
3 equiv. ArB$(OH)_2$,
0.5 equiv. KOH,
dioxane/H_2O, 50 °C, 3 h
R
NBn
Ph
Et
and
1.78
1.81
87:13 **1.80:1.81**
98% yield,^{a} 98.5:1.5 er
i-Pr
Cl
Me
1.82
90% yield,^{b} 99:1 er
1.83
95% yield, 98.5:1.5 er
1.84
82% yield, 95:5 er
1.85
70% yield, >99:1 er

^{a} Combined yield.

The Rh-catalyzed ECA reaction can tolerate a bulky *i*-propyl substituent on the substrate, delivering succinimide **1.82** in excellent regioselectivity (97:3), yield (90%), and in 99:1 er (Scheme 1.21). Several arylboronic acids are demonstrated in the catalytic method, with the highest regioselectivities observed with sterically hindered nucleophiles (i.e., **1.84**, >98:2 regioselectivity, 82% yield, 95:5 er). One example of a quinone-based substrate also demonstrated high fidelity in the conjugate addition reaction (**1.85**).

A significant difference in Rh-catalyzed versus Cu-catalyzed ECA procedure is the presence of H_2O as a cosolvent. Since, there is a protic additive present during the course of the reaction; the in situ prepared boron (or rhodium enolate) is protonated, losing the valuable regioselectively formed enolate on the sterically more hindered side of the carbonyl moiety. Since the Cu-catalyzed ECA protocols do not have protic additives, the enolate can be further functionalized (i.e., formation of silyl enol ethers, enol acetates, or direct alkylation of the metal enolate with electrophiles). Moreover, Cu-based reagents are relatively inexpensive compared to Rh-based salts.[47]

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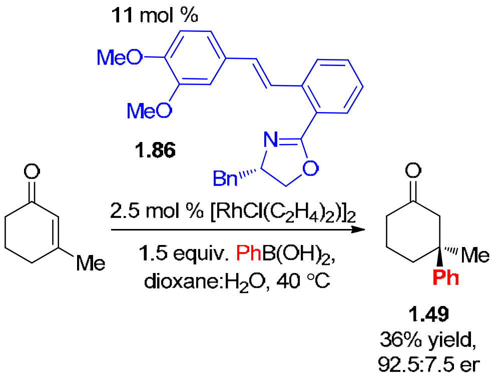
[46] For a recent review on diene ligands in catalysis, see: "Chiral Diene Ligands for Asymmetric Catalysis," Shintani, R.; Hayashi, T. *Aldrichim. Acta* **2009**, *42*, 31–38.

Glorius and coworkers have recently disclosed a Rh-catalyzed ECA reaction of phenylboronic acid to 3-methylcyclohexenone with a styrene oxazoline-based ligand (**1.86**).[48] Only one example is given, with ketone **1.49** afforded in 36% yield and 92.5:7.5 er.

Scheme 1.22. Rh-Catalyzed ECA of $PhB(OH)_2$ to 3-Methylcyclohexenone with Styrene Oxazoline-Based Catalyst



Professors Tamio Hayashi, Ryo Shintani and co-workers have disclosed two complementary articles on Rh-catalyzed ECA with arylborates and arylboroxines to trisubstituted enones.[49] The diene ligands **1.87** and **1.88** used in the active catalyst are electronically deficient, which facilitates the transmetallation and insertion steps in the catalytic cycle, improving the yields of the conjugate addition adducts. Diene **1.87** is prepared in one step through a stereoselective [4 + 2] cycloaddition;[50] diene **1.88**,

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(47) For example, $[RhCl(C_2H_4)_2]_2$ is $93,385/mol and CuOAc•$H_2O$ is $839/mol (prices are from Strem, 2010).

(48) "Olefin-Oxazolines (OlefOx): Highly Modular, Easily Tunable Ligands for Asymmetric Catalysis," Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143–1146.

(49) (a) "Sodium Tetraarylborates as Effective Nucleophiles in Rhodium/Diene-Catalyzed 1,4-Addition to β,β-Disubstituted α,β-Unsaturated Ketones: Catalytic Asymmetric Construction of Quaternary Carbon Stereocenters," Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589. (b) "Chiral Tetraflourobenzobarrelenes as Effective Ligands for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboroxines to β,β-Disubstituted α,β-Unsaturated Ketones," Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969–3971.

(50) (a) "Simple Chiral Diene Ligands Provide High Enantioselectivities in Transition-Metal-Catalyzed Conjugate Addition Reactions," Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387–4389.

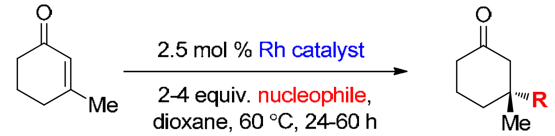
however, is prepared in five steps, including a HPLC resolution step.[51] The first account demonstrated the feasibility of a Rh-catalyzed enantioselective conjugate addition protocol with sodium tetraphenylborate affording cyclic ketones containing β-all-carbon stereogenic centers.[49a] Both six- and seven-membered ring enones react to afford products with high yields and selectivities (up to 83% yield and 99:1 er, entries 1, 3, and 4, Table 1.1). Additions catalyzed with a Rh(I) catalyst with diene **1.88** also promotes the formation of **ent-1.49**, from 3-methylcyclohexenone and $(PhBO)_3$, affording the product with a higher yield (99% yield, >99:1 er, entry 2). Only six-membered ring enones are demonstrated in the latter process and five-membered ring enones are not discussed (or examined) in either communication. Other electronically modified aryl nucleophiles can be used as shown in entries 5–9; the Rh-catalyzed ECA method with diene **1.88** is proficient in transferring a variety of *para*, *meta*, and *ortho*-substituted aryl groups providing products in enantiomeric purity (all cases >99:1 er).

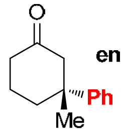
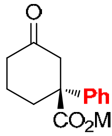
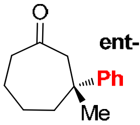
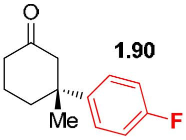
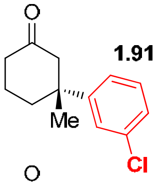
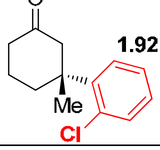
Although the enantioselective arylation with diene **1.87** seems to be more practical in terms of ligand preparation (one step vs. five steps for **1.88**), the latter protocol can be used to obtain cyclohexanones with outstanding levels of enantioselectivities. Moreover, the procedure with diene **1.88** and $(ArBO)_3$ does not require the use of a protic additive. Thus, the in situ generated boron enolate can potentially be used for further functionalizations. It remains to be investigated if either protocol can be extended to the more challenging five-membered ring enones. Multiple equivalence of the aryl group, also, is required for the ECA procedures (i.e., four aryl groups are used for each equivalent of Ar_4BNa and 2-4 equivalents are used per reaction).

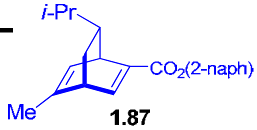
(b) "Electronic and Steric Tuning of Chiral Diene Ligands for Rhodium-Catalyzed Asymmetric Arylation of Imines," Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2008**, 4815–4817.

(51) "The Concise Synthesis of Chiral tfb Ligands and Their Application to the Rhodium-Catalyzed Asymmetric Arylation of Aldehydes," Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713–5715.

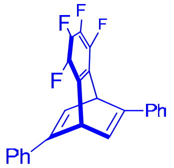
Table 1.1. Rh-Catalyzed ECA of Arylborates or Arylboroxines to Enones Promoted by Diene Ligands



entry	product	catalyst	nucleophile	yield (%)	er
1	 **ent-1.49**	$[RhCl((R)\text{-}\mathbf{1.87})]_2^{a}$	Ph_4BNa	83	99:1
2		$[RhOH((R,R)\text{-}\mathbf{1.88})]_2$	$(PhBO)_3$	99	>99:1
3	 **1.89**	$[RhCl((R)\text{-}\mathbf{1.87})]_2^{a}$	Ph_4BNa	80	99:1
4	 **ent-1.73**	$[RhCl((R)\text{-}\mathbf{1.87})]_2^{a}$	Ph_4BNa	75	94.5:5.5
5	 **1.90**	$[RhCl((R)\text{-}\mathbf{1.87})]_2^{a}$	Ph_4BNa	62	95.5:4.5
6		$[RhOH((R,R)\text{-}\mathbf{1.88})]_2$	$(PhBO)_3$	94	>99:1
7[b]	 **1.91**	$[RhCl((R)\text{-}\mathbf{1.87})]_2^{a}$	Ph_4BNa	84	97.5:2.5
8		$[RhOH((R,R)\text{-}\mathbf{1.88})]_2$	$(PhBO)_3$	85	>99:1
9	 **1.92**	$[RhOH((R,R)\text{-}\mathbf{1.88})]_2$	$(PhBO)_3$	87	>99:1



1.87



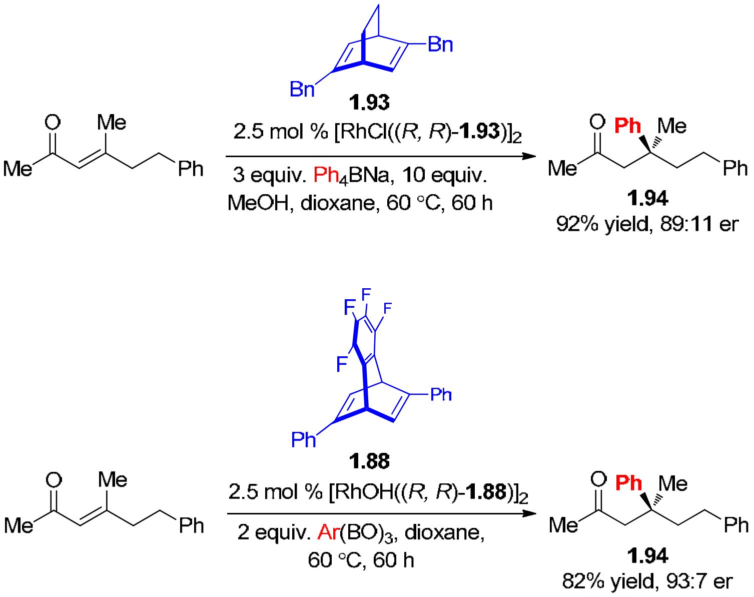
1.88

[a] Conditions include 10 equiv. of MeOH. [b] The reaction was performed at 90 °C with 5 mol % Rh

Further substrate screening elucidated that, for the first time, unactivated trisubstituted acyclic enones undergo enantioselective arylation promoted by a Rh-diene complex.[49] As shown in Scheme 1.23, Rh-catalyzed ECA of Ar_4BNa to the acyclic enone proceeds at 60 °C in 2.5 days to afford **1.94** in 92% yield and 89:11 er.[49a] Ligand **1.93** was found to promote the reaction with an increased enantioselectivity as compared to diene **1.87** (under the same conditions as described in the first equation in Scheme

1.23, the reaction promoted by [RhCl((*R*)-**1.87**)]$_2$ delivers **1.94** in 83:17 er). Subsequently, Hayashi and co-workers found that the Rh-catalyzed ECA of (PhBO)$_3$ to the acyclic enone, in the presence of **1.88**, affords the product **1.94** in an increased level of enantioselectivity (82% yield, 93:7 er).[49b] Only a total of three substrates are examined using the two procedures with arylation of only a phenyl group; generality of these two methods remains to be investigated. It should also be noted that long reaction times are needed (60 h); a more active catalyst may be needed to address efficiency.

Scheme 1.23. Rh-Catalyzed ECA of Arylborates and Arylboroxines to Trisubstituted Acyclic Enones


Bn
Bn
1.93
O
Me
Me
Ph
2.5 mol % [RhCl((R, R)-1.93)]2
3 equiv. Ph4BNa, 10 equiv.
MeOH, dioxane, 60 °C, 60 h
O
Ph
Me
Me
Ph
1.94
92% yield, 89:11 er
F
F
F
F
Ph
Ph
1.88
O
Me
Me
Ph
2.5 mol % [RhOH((R, R)-1.88)]2
2 equiv. Ar(BO)3, dioxane,
60 °C, 60 h
O
Ph
Me
Me
Ph
1.94
82% yield, 93:7 er

A recent report from Hayashi and Shintani investigates the reactivity and selectivity of unactivated trisubstituted enoates, an underrepresented substrates class due to the relatively low electrophilicity.[52] Diene ligand **1.95** in combination with a Rh(I) salt promotes the arylation of 2,6-dimethylphenyl ester with Ph$_4$BNa to afford **1.96** in 93% yield and in >99:1 er. Enantioselective arylations on simple methyl ester unsaturated enoates deliver products with reduced selectivities. The procedure can be used on a

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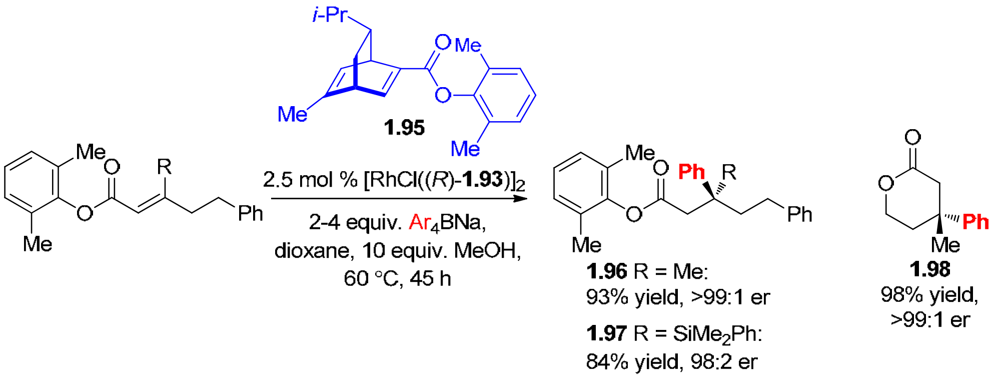
(52) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to β,β-Unsaturated Esters," Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350–352.

variety of trisubstituted unsaturated esters affording all products disclosed in higher than 98:2 er. Moreover, a Si-substituted unsaturated ester also was congruent in the addition; enantioenriched ester **1.97** is delivered in 84% yield and 98:2 er. Additionally, Rh-catalyzed ECA of Ph_4BNa to a β-substituted lactone affords lactone **1.98** in 98% yield and >99:1 er (Scheme 1.24). Although this is an impressive first account for additions to trisubstituted enoates, some drawbacks are noted. As before, the atom economy of the nucleophile is low, as multiple equivalence of the phenyl group is needed for one phenyl transfer and the additions require elevated reaction temperatures and prolonged times.

Scheme 1.24. Rh-catalyzed ECA with Ph_4BNa to Trisubstituted Enoates and Unsaturated Lactones



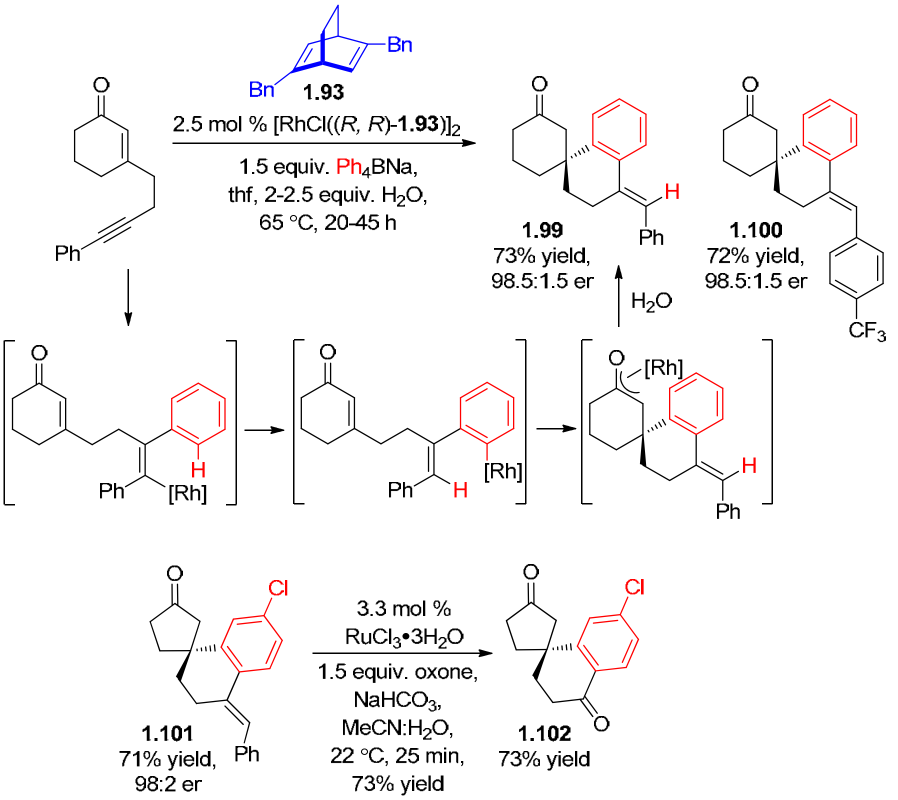
All of the protocols addressed thus far described only intermolecular ECA. Shintani, Hayashi and co-workers have recently addressed a perhaps more challenging approach, or at least an underrepresented tactic, involving the synthesis of enantiomerically enriched spirocycles by a three step process including aryl–Rh addition of an internal alkyne, a 1,4-rhodium shift and ECA of the in situ prepared metal–aryl reagent.[53] As shown in Scheme 1.25, a phenylrhodium complex, prepared in situ from Ph_4BNa and the chiral Rh(I) complex, undergoes insertion into the alkyne to give the alkenylrhodium intermediate. The rhodium species undergoes a 1,4-shift to provide an arylrhodium intermediate, which reacts with the enone moiety through a 1,4-addition

---

(53) "Rhodium-Catalyzed Asymmetric Synthesis of Spirocarbocycles: Arylboron Reagents as Surrogates of 1,2-Dimetalloarenes," Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795–3798.

process. Hydrolysis of the rhodium enolate delivers spirocycle **1.99** in 73% yield and 98.5:1.5 er. The authors observe a primary isotope effect ($k_H/k_D = 3.7$) and conclude that the 1,4-migration step may be the turnover-limiting step in the catalytic cycle. Notably, a Rh–phosphine complex ($[RhCl(binap)]_2$) leads to <5% of the desired product. Substitution of the aryl ring on the substrate is tolerated; product **1.100** is representative (72% yield, 98.5:1.5 er). Moreover, intramolecular additions to five-membered ring enones also proceed efficiently; product **1.101** is illustrative. The trisubstituted olefin can be cleaved under oxidation conditions with oxone (**1.102**, 73% yield, Scheme 1.25).

Scheme 1.25. Construction of Enantiomerically Enriched Spirocycles through an Arylrhodation, 1,4-Rhodium-Migration and ECA Sequence


Bn
Bn
1.93
2.5 mol % [RhCl((R, R)-1.93)]2
1.5 equiv. Ph4BNa,
thf, 2-2.5 equiv. H2O,
65 °C, 20-45 h
Ph
1.99
73% yield,
98.5:1.5 er
H
Ph
1.100
72% yield,
98.5:1.5 er
CF3
H2O
H
[Rh]
Ph
[Rh]
Ph
H
[Rh]
H
Ph
Cl
3.3 mol %
RuCl3•3H2O
1.5 equiv. oxone,
NaHCO3,
MeCN:H2O,
22 °C, 25 min,
73% yield
Cl
1.101
71% yield,
98:2 er
Ph
1.102
73% yield

Alexakis, Woodward and co-workers have disclosed a Rh-catalyzed ECA procedure that requires arylaluminum reagents, instead of the usual boron-based nucleophiles.[54] The nucleophile $ArAlMe_2$ is prepared in situ from an aryllithium reagent (or Grignard reagent) and Me_2AlCl. The in situ prepared arylaluminum reagent has also been successfully used in Cu-catalyzed ECA to cyclic enones (cf. Schemes 1.19–1.20).[44] The enantioselective additions are promoted by commercially available binap as a ligand for a Rh(I) complex. The products can be obtained from five-, six-, and seven-membered ring enones with high selectivities (up to >99:1 er, Scheme 1.26); however, the yields reported are rather low (35–73% yield) due to low conversions (product **ent-1.73** is formed in 86% conv) or what the authors state is product sensitivity during purification (product **1.79**).[55] Substituted aryl nucleophiles also participate in the enantioselective arylation, affording **1.77**, **1.78**, and **ent-1.51** in up to 99:1 er (Scheme 1.26). Rh-catalyzed ECA of Me_2AlPh to two acyclic trisubstituted enones were shown to provide products in 52–55% yield and 96.5:3.5–>97.5:2.5 er. The method described allows access to ketones bearing a β-all-carbon quaternary stereogenic center in high enantioselectivities; however, the yields are only moderate. Moreover, the Rh-catalyzed method, as of yet, can only be applied for additions of aryl groups (and potentially other groups not bearing a β-hydrogen) since Rh can undergo β-hydride elimination reactions (the Rh–H complex is catalytically unproductive).

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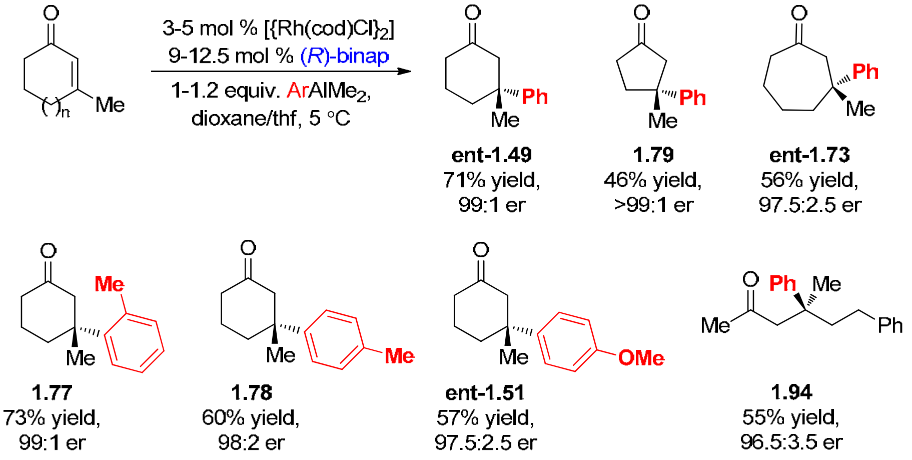
(54) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl Alanes to Trisubstituted Enones: Binap as an Effective Ligand in the Formation of Quaternary Stereocenters," Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769–7772.

(55) It should be noted that product **1.79** in our hands does not decompose under silica gel chromatography.

Scheme 1.26. Rh-Catalyzed ECA of Arylaluminum Reagents to Cyclic and Acyclic Trisubstituted Enones


O
Me
n
3-5 mol % [{Rh(cod)Cl}2]
9-12.5 mol % (R)-binap
1-1.2 equiv. ArAlMe2,
dioxane/thf, 5 °C
Ph
Me
ent-1.49
71% yield,
99:1 er
1.79
46% yield,
>99:1 er
ent-1.73
56% yield,
97.5:2.5 er
OMe
1.77
73% yield,
99:1 er
1.78
60% yield,
98:2 er
ent-1.51
57% yield,
97.5:2.5 er
1.94
55% yield,
96.5:3.5 er

1.3.d Conclusions and Remaining Goals for ECAs of Aryl Groups to Enones Forming Quaternary Carbon Stereogenic Centers

Enantioselective arylation of activated olefins has advanced significantly in the past several years. Cu- and Rh-catalyzed processes have enabled chemists to cross couple aryl units with olefins forming all-carbon quaternary stereogenic centers. The majority of accounts focus on cyclic trisubstituted enones; however, several disclosures demonstrated the feasibility of unsaturated heterocycles (lactones, maleimides) participating in ECA processes. Future directions may expand the scope of these reactions to include more examples of lactones, lactams, and acyclic trisubstituted α,β-unsaturated carbonyl units (ketones, esters, amides). Moreover, tetrasubstituted olefins have not been investigated, probably due to their inherent steric and decreased electrophilicity compared to trisubstituted enones.

With regards to nucleophile practicality, in situ prepared arylaluminum reagents are easy to handle and have the potential for preparation of various substitutions on the aryl rings. However, since the preparation requires the synthesis of the corresponding aryl Grignard or lithium reagents, functional groups on the arenes, such as ketones or esters, may not be tolerant. The arylaluminum reagents seem to be general as they have been used in both Cu- and Rh-catalyzed ECA protocols. Alternatively, boron-based nucleophiles have only been demonstrated in combination with Rh-catalyzed methods. The borates, boronic acids, and boroxines-based nucleophiles used in the Rh-catalyzed procedures generally require longer reaction times (3–60 h) and elevated temperatures (40–65 °C) as compared to the Cu-catalyzed reactions with arylaluminum and zinc reagents (1–72 h, –10 to –30 °C). Atom economy is low with regards to the borates (Ar_4BNa) and boroxines ($(ArOB)_3$) but offer more functional group tolerance than aryllithium and Grignard reagents. The products obtained from the current Rh-catalyzed procedures are isolated in outstanding levels of selectivity; further developments in both catalyst reactivity and substrate scope are sure to ensue.

1.4 Enantioselective Conjugate Additions of Vinyl Nucleophiles to Activated Olefins

1.4.a Introduction

As discussed in the previous sections, enantioselective conjugate addition to enones for the formation of all-carbon quaternary stereogenic centers is an important and flourishing topic in organic chemistry. Most disclosures, however, have as focused on alkyl additions (Section 1.2) and, less frequently, aryl additions (Section 1.3); enantioselective conjugate addition of vinyl nucleophiles to activated enones generating a quaternary stereogenic center has been met with only limited, albeit recent, success. Enantioselective vinyl additions represent a circumstance in which other disconnections can be problematic or proceed with other byproducts formed with the desired product. For example, as shown in Scheme 1.27, the ketone containing an all-carbon quaternary stereogenic center bearing a vinyl group can potentially be prepared through one of two ways. Pathway a, the representative reaction of the subject of this section, describes an ECA of a vinyl metal to a trisubstituted enone. This is a difficult task as there are few reports of vinyl metal reagents in catalytic enantioselective procedures to prepare quaternary stereogenic centers.[56] As compared to the enantioselective alkylation and arylations discussed in the previous sections, an enantioselective addition of a vinyl group is perhaps the most difficult; a vinyl nucleophile is smaller than the alkyl or aryl metal reagents,[57] making enantiodiscrimination by the catalyst more challenging.

On the other hand, the same molecule **II** can also be prepared through an enantioselective conjugate addition of an R group to an α,β,δ,γ-unsaturated ketone (pathway b). The route, however, can potentially lead to other products through a 1,6-addition of the doubly unsaturated enone (**III** and/or **IV**). In fact, the most electrophilic position of the α,β,δ,γ-unsaturated ketone should be at the 1,6-position of the enone (for steric and electronic reasons).[58] The following are enantioselective catalytic approaches employing pathway a as the strategy.

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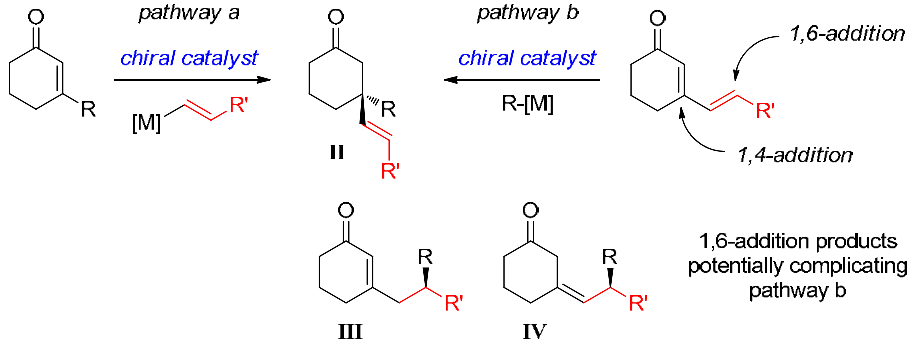
(56) The following references do not include ECA methods discussed further in the section. For procedures involving catalytic enantioselective additions of vinylzinc reagents to ketones, see: (a) “Catalytic Asymmetric Vinylation of Ketones,” Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539. (b) “Catalytic Asymmetric Vinylation and Dienylation of Ketones,” Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361. For a Ti-catalyzed enantioselective vinylation of vinylaluminum reagents to aryl ketones, see: (c) “Highly Enantioselective Vinyl Additions of Vinylaluminum to Ketones Catalyzed by a Titanium(IV) Catalyst of (*S*)-BINOL,” Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499–502. For enantioselective allylic substitution with vinylaluminum reagents to trisubstituted allylic phosphates, see: (d) Reference 7c. For enantioselective Rh-catalyzed reductive coupling of enynes to ketones, see: (e) “Enantioselective Reductive Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones via Rhodium-Catalyzed Asymmetric Hydrogenation: Mechanistic Insight into the Role of Brønsted Acid Additives,” Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449.

(57) For instance the A values of a methyl, phenyl and vinyl group are 1.7, 3.0, and 1.35, respectively. See, (a) “Table of Conformation Energies−1967,” Hirsch, J. A. *Topics in Stereochemistry* **1967**, *3*, 199–222. Although another report calculates the A value of a vinyl group to be closer to 1.68, only slightly smaller than a methyl group, see: (b) “Conformational Analysis. 40. Conformation of 1-Methyl-1-Phenylcyclohexane and Conformational Energies of the Phenyl and Vinyl Groups,” Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959–1962.

(58) For examples see: Krause, N.; Hoffmann-Röder, A. Copper-Mediated Addition and Substitution Reactions of Extended Multiple Bond Systems,” In *Modern Organocopper Chemistry;* Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 145–166.

Scheme 1.27. Methods to Prepare Enantiomerically Enriched Ketone **II** through Enantioselective Conjugate Additions Pathways a and b



1.4.b ECA of Vinyl Metals to Activated Olefins Generating All-Carbon Quaternary Stereogenic Centers

Professor Carretero and workers disclosed the first example of ECA of a vinyl reagent to an activated electrophile generating an all-carbon quaternary stereogenic center.[59] In their report, 5 mol % of a Rh(I) salt, in the presence of chiraphos, effectively promotes conjugate addition of three different alkenylboronic acids to two methyl-aryl substituted unsaturated pyridylsulfones generating products, such as **1.104** and **1.105**, in 41–71% yield and in 94:6–>99:1 er (Scheme 1.28). Low isolated yields are attributed to incomplete conversion (45–77% conv, 100 °C, 24 h). The authors note that even after prolonged reaction times or with additional equivalents of the vinyl boronic acid, increased conversions are not observed probably due to catalyst decomposition. The pyridylsulfone is essential for reactivity as the same addition with derived phenylsulfone substrate leads to <2% conversion. This suggests a bidentate chelation between the pyridylsulfone and the Rh-complex for organization and/or activation.

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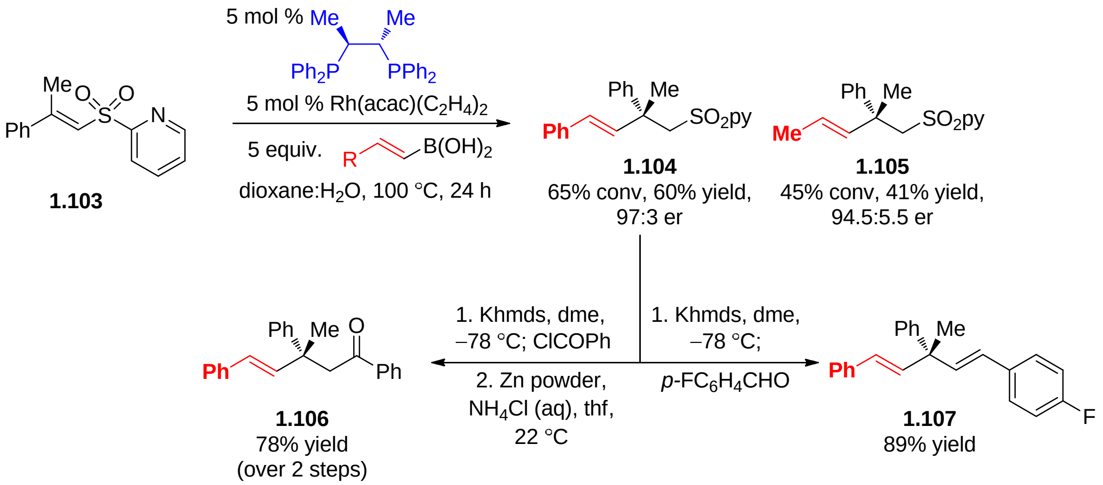
(59) "Enantioselective Construction of Stereogenic Quaternary Centres *via* Rh-Catalyzed Asymmetric Addition of Alkenylboronic Acids to α,β-Unsaturated Pyridylsulfones," Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963.

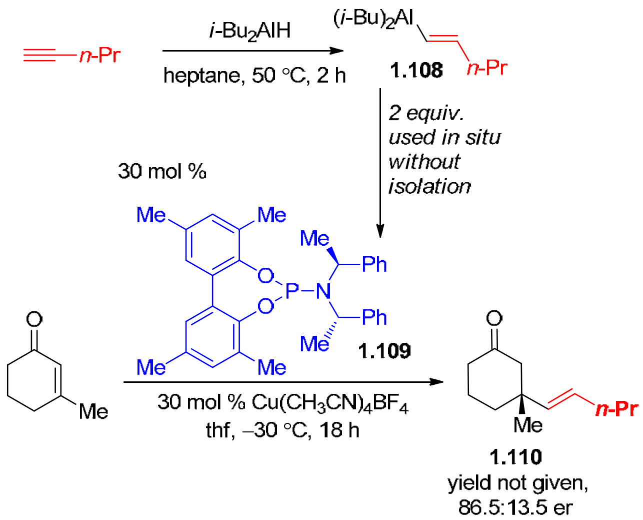
Scheme 1.28. Rh-Catalyzed ECA of Vinylboronic Acids to Trisubstituted Unsaturated Pyridylsulfones


1.103
5 mol % Me Me Ph2P PPh2
5 mol % Rh(acac)(C2H4)2
5 equiv. R B(OH)2
dioxane:H2O, 100 °C, 24 h
1.104
65% conv, 60% yield, 97:3 er
1.105
45% conv, 41% yield, 94.5:5.5 er
1. Khmds, dme, −78 °C; ClCOPh
2. Zn powder, NH4Cl (aq), thf, 22 °C
1. Khmds, dme, −78 °C;
p-FC6H4CHO
1.106
78% yield (over 2 steps)
1.107
89% yield

The synthetic utility of the enantiomerically enriched sulfones were demonstrated; α-deprotonation of **1.104** with Khmds and alkylation with benzoyl chloride, followed by desulfonylation with activated zinc powder affords the ketone **1.106** bearing a β-all carbon quaternary stereogenic center. Moreover, Julia-Kociensky olefination proceeds smoothly with **1.104** delivering **1.107** in 89% yield (Scheme 1.28). Although this account is an elegant solution to a standing problem of enantioselective addition of vinyl groups to activated olefins, some shortcomings exist. Conversions and, as a result, yields are moderate even at elevated temperatures and prolonged reaction times. Only two substrates are examined, therefore generality of the substrates cannot be determined.

Recently, limited success has been met with in situ prepared vinylaluminum reagents as nucleophiles in Cu-catalyzed ECA of trisubstituted cyclic enones. The Alexakis group published a single account in a full article describing their work in Cu-catalyzed ECA with aluminum-based nucleophiles.[26] The preparation of the vinylaluminum reagent **1.108** (Scheme 1.29) can be accomplished by treatment of 1-pentyne with 1 equiv. of i-Bu_2AlH in nonpolar solvents and the requisite vinylaluminum can be used without isolation or purification.[60] The addition is promoted by 30 mol % of a Cu(I)–phosphoramidite complex with 2 equiv. of **1.108** to provide **1.110** in 86.5:13.5 er (100% conv, yield not provided). Although this is a stimulating result, it is the only example provided with no variations of the substrate or nucleophile. Moreover, the efficiency of the reaction cannot be determined since no yields are provided. The enantioselectivity observed is moderate, and a large quantity of catalyst must be used to obtain the selectivity observed.

Scheme 1.29. Cu-Catalyzed ECA of a Vinylaluminum Reagent to 3-Methylcyclohexenone Promoted by Phosphoramidite **1.109**


n-Pr
i-Bu2AlH
heptane, 50 °C, 2 h
(i-Bu)2Al
1.108
n-Pr
2 equiv.
used in situ
without
isolation
30 mol %
Me
Me
Me
Ph
O
P–N
O
Ph
Me
1.109
Me
Me
O
Me
30 mol % Cu(CH3CN)4BF4
thf, –30 °C, 18 h
O
n-Pr
Me
1.110
yield not given,
86.5:13.5 er

The reaction outlined in Scheme 1.29 was subsequently improved by optimizing catalyst, copper salt, and solvent.[44] As shown in Scheme 1.30, sterically more hindered phosphoramidite **1.40** promotes the ECA of the *n*-butyl-substituted vinylaluminum reagent to 3-methylcyclohexenone to afford **1.111** in 93% yield and 91:9 er at –30 °C in 19 h. The reaction is more efficient than the former example as catalyst loading was able to be reduced to 10 mol % with sustained levels of selectivity; although only one example is provided.

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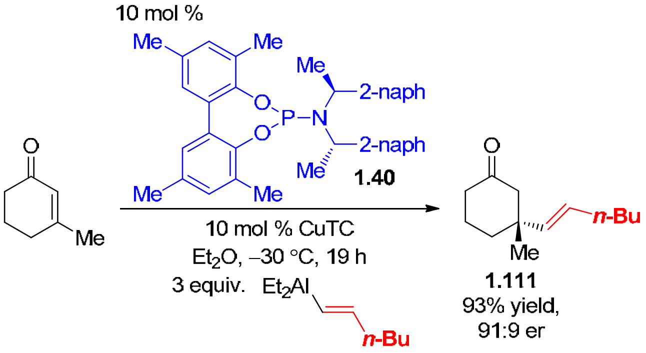
(60) "Syntheses Using Alkyne-Derived Alkenyl- and Alkynylaluminum Compounds," Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375–517.

Scheme 1.30. Cu-Catalyzed ECA of a Vinylaluminum Reagent to 3-Methylcyclohexenone Promoted by Phosphoramidite **1.40**



Attempts to improve the result in Scheme 1.30 with a phosphinamine based ligand (derivatives which were fruitful in Cu-catalyzed ECA of alkylaluminum reagents to trisubstituted enones, Schemes 1.10 and 1.11) did not lead to improvement (ketone **1.111**, 75:25 er, no yield provided).[30]

As a follow-up to the initial results put forth by Alexakis and co-workers in Schemes 1.29 and 1.30, an expanded disclosure has recently appeared.[61] The additions are catalyzed by a Cu(I)–phosphinamine complex, prepared in situ from CuTC and ligand **1.47**, with various internal and terminal alkyl- and aryl-substituted vinylaluminum reagents prepared from lithium halogen exchange of the corresponding vinyl halides and further reaction of the resulting vinyllithium with Me_2AlCl. Product **1.111** is produced in 50% yield and 88:12 er (Scheme 1.31), which is less efficient and selective than the addition that was reported previously (shown in Scheme 1.30). However, this procedure is extended to styrenyl addition to 3-methylcyclohexenone, delivering product **1.112** in an increased yield of pure desired product and selectivity (64% yield, 95.5:4.5 er, Scheme 1.31). The mixed vinylaluminum species selectively transfer the vinyl group over the other two methyl ligands; the methyl 1,4-addition products are less than 3% of the reaction mixture. When the more sterically hindered internal vinylaluminum species are used in the ECA protocol, the products are obtained in higher enantioselectivities (for

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(61) "Creation of Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Conjugate Addition of Alkenyl Alanes to α,β-Unsaturated Cyclic Ketones," Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett*, **2010**, 1694–1698.

example **1.113** and **1.114**, up to 98:2 er) but adventitious methyl addition occurred more readily (4% and 11%, respectively for **1.113** and **1.114**). The low yield of product **1.114** is attributed to an impurity in commercial α-bromostyrene, in which the corresponding vinylaluminum species is prepared from. This highlights a consequence of preparing internal vinylaluminum reagents from the vinylhalides; procedures to prepare these reagents require harsh conditions that can be intolerant of various acid-sensitive functional groups.[62] Moreover, only a handful of α-vinylhalides are commercially available, many of which contain the β-isomer contaminant. Difficult substrates, such as sterically hindered substituted cyclohexenones and 3-methylcyclopentenone led to reduced reactivity (up to 49% conv, Scheme 1.31); Me/vinyl addition ratios were not provided. Seven-membered ring enones were not investigated.

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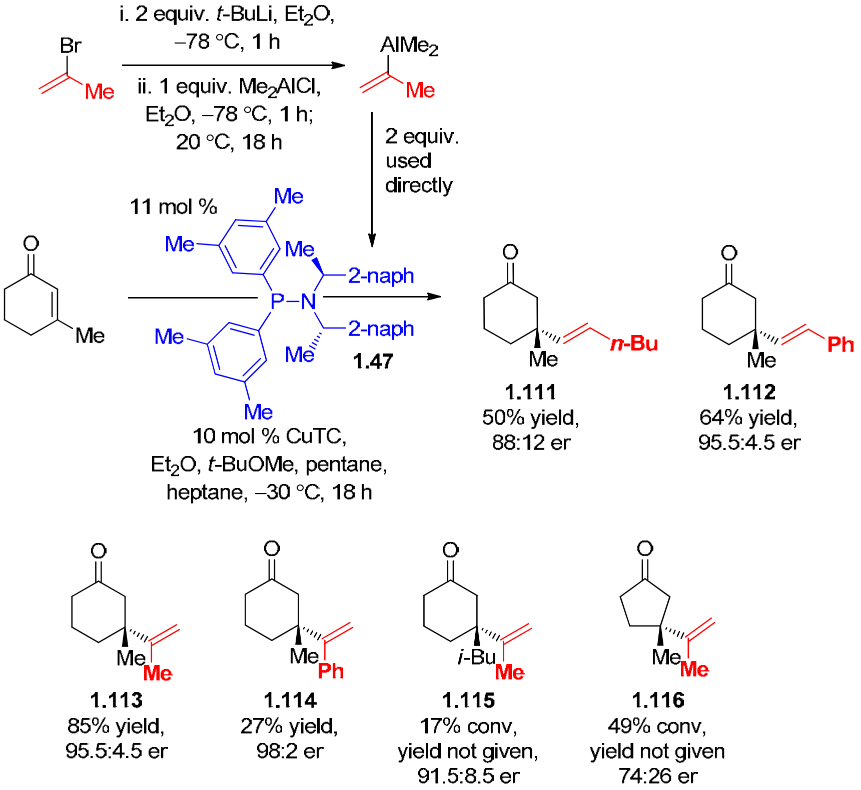
(62) For α-vinyl halide synthesis, see: (a) "Organic Synthesis using Haloboration Reaction. I. A Simple and Selective Synthesis of 2-Bromo- and 2-Iodo-1-Alkenes," Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734. (b) "Simple and Selective Method for Aldehydes (RCHO) → (*E*)-Haloalkenes (RCH=CHX) Conversion by Means of a CHX_3-$CrCl_2$ System," Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (c) "Stereoselective Synthesis of Internal Alkenyl Iodides from Alkynes via Addition of Hydrogen Iodide Generated in situ from a Chlorotrimethylsilane/Sodium Iodide/Water System," Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675–676. (d) "A Mild Synthesis of Vinyl Halides and *gem*-Dihalides Using Triphenyl Phosphite–Halogen-Based Reagent," Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216–2219. (e) "Highly Selective Hydroiodation of Alkynes Using an Iodine–Hydrophosphine Binary System," Kawaguchi, S-i.; Ogawa, A. *Org. Lett.* **2010**, *12*, 1893–1895.

Scheme 1.31. Cu-Catalyzed ECA of Terminal and Internal Vinylaluminum Reagents to Trisubstituted Cyclic Enones


Br
Me
i. 2 equiv. t-BuLi, Et_2O, –78 °C, 1 h
ii. 1 equiv. Me_2AlCl, Et_2O, –78 °C, 1 h; 20 °C, 18 h
$AlMe_2$
Me
2 equiv. used directly
O
Me
11 mol %
Me
Me
Me
P–N
2-naph
2-naph
Me
Me
Me
1.47
10 mol % CuTC, Et_2O, t-BuOMe, pentane, heptane, –30 °C, 18 h
O
Me
n-Bu
1.111
50% yield, 88:12 er
O
Me
Ph
1.112
64% yield, 95.5:4.5 er
O
Me
Me
1.113
85% yield, 95.5:4.5 er
O
Me
Ph
1.114
27% yield, 98:2 er
O
i-Bu
Me
1.115
17% conv, yield not given, 91.5:8.5 er
O
Me
Me
1.116
49% conv, yield not given 74:26 er

1.4.c Conclusions and Remaining Goals for ECAs of Vinyl Groups to Enones Forming Quaternary Carbon Stereogenic Centers

Enantioselective additions of vinyl metals remain an important and elusive goal in organic synthesis. If a general and practical method is developed, further functionalizations of the valuable olefin contained in the enantiomerically enriched conjugate adduct may lead to products that are not yet easily obtainable. Although the protocols put forth by Carretero, Alexakis and co-workers are the first examples of enantioselective vinyl additions to activated olefin partners, significant shortcomings still exist. A relatively small substrate generality and low to moderate yields of the desired products hamper the practicality of the methods. It is evident that more active catalysts must be developed to address this difficult but fruitful problem.

1.5 Enantioselective Conjugate Additions of Cyanide to Activated Electrophiles

A relatively new field, with limited disclosures, is ECA of cyanide to electrophiles. To date, there are only three publications detailing this process. Challenges surrounding this field include the small, linear nucleophile, which can be difficult to discriminate which face of the substrate the nucleophile approaches and, subsequently, adds to. A cyanide group is a stabilized nucleophile compared to an alkyl, aryl, or vinyl nucleophile. For instance, the pKa of a HCN in H_2O is 9.4 while methane, benzene, and ethylene are significantly higher (48, 43, and 50, respectively).[63]

The first publication in this area was in 2008 in which Professors Fochi, Ricci and co-workers describe the addition of cyanide, in the form of acetone cyanohydrins, with cinchona alkaloid **1.117** (Scheme 1.32).[64] The reactions are catalyzed by 10 mol % of the alkaloid **1.118** and the nitroalkanes bearing an all-carbon quaternary stereogenic center are isolated in moderate levels of selectivity (up to 86:14 er, not shown, with Me, 2-naphthyl-substituted nitroalkene). Notably, a substrate containing a furyl-substituent also undergoes enantioselective cyanide addition delivering **1.120** in 52% yield and 82.5:17.5 er (Scheme 1.32). Only aryl-substituted substrates were investigated and, although this represents a satisfactory first example, enantioselectivities and yields are moderate.

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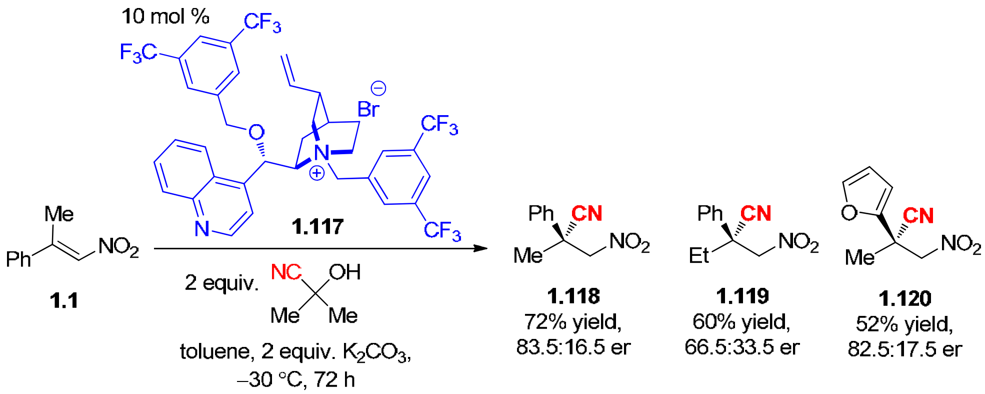
(63) Evans, D. A. pKa's of Inorganic and Oxo-Acids. evans.harvard.edu/pdf/evans_pKa_table.pdf (accessed January 5, 2011).

(64) "Organocatalyzed Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Conjugate Addition of Acetone Cyanohydrin," Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Synlett* **2008**, 1857–1861.

Scheme 1.32. Cinchona Alkaloid-Catalyzed Cyanide Addition to Trisubstituted Nitroalkenes


10 mol %
CF3
F3C
O
Br
CF3
N
N
CF3
Me
Ph
NO2
1.1
1.117
2 equiv.
NC
OH
Me
Me
toluene, 2 equiv. K2CO3,
–30 °C, 72 h
Ph
CN
Me
NO2
1.118
72% yield,
83.5:16.5 er
Ph
CN
Et
NO2
1.119
60% yield,
66.5:33.5 er
O
CN
Me
NO2
1.120
52% yield,
82.5:17.5 er

A disclosure from the Jacobsen laboratory focuses on cyanide additions to imides; investigations in this area determined that dinuclear salen–Al complexes (**1.121**, Scheme 1.33) catalyze enantioselective conjugate additions of TMSCN to disubstituted imides with rate differences several orders of magnitude greater than mononuclear salen–Al complexes.[65] With the new, more active catalysts in hand, product **1.122** is obtainable in 96:4 er, however, only in 38% yield (Scheme 1.33).

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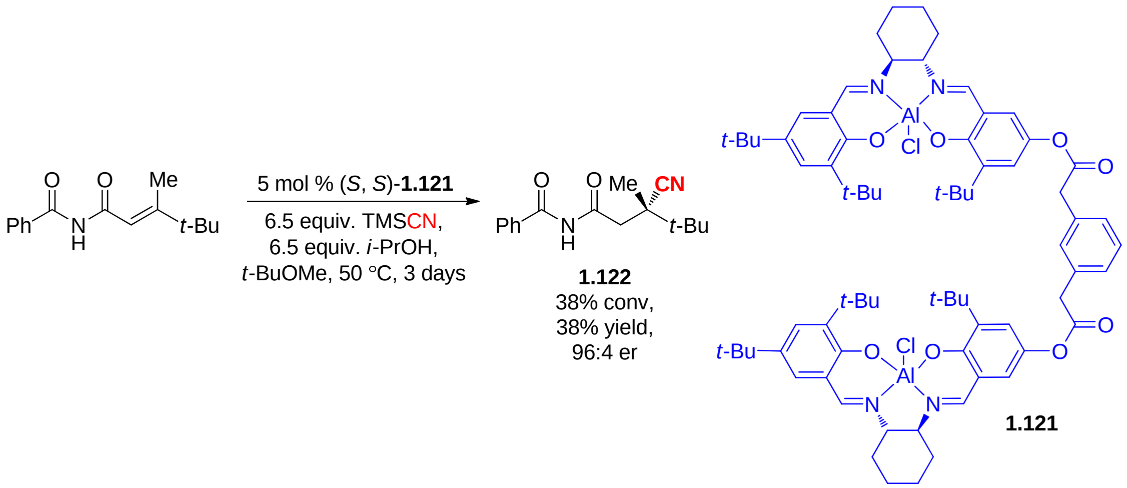
(65) "Dinuclear {(salen)Al} Complexes Display Expanded Scope in the Conjugate Cyanation of α,β-Unsaturated Imides," Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762–1765.

Scheme 1.33. Enantioselective Cyanide Addition Catalyzed by a Dinuclear Salen–Al Complex



Perhaps the most impressive disclosure in this area is by Shibasaki, Kanai and co-workers;[66] they found that a chiral diol ligand, in the presence of a Sr(II) salt, efficiently promotes the addition of cyanide, from TBSCN, to a variety of acyclic trisubstituted enones (Scheme 1.34). For example, phenyl ketone **1.124** bearing a β-all-carbon quaternary stereogenic center is produced, with only 0.5 mol % catalyst loading in 16 h at room temperature, in quantitative yield and 98.5:1.5 er. Methyl ketones are also afforded with sustained efficiency and selectivity (i.e., **1.125**, 98% yield, 94.5:5.5 er, Scheme 1.34). A variety of other trisubstituted enones with varying electronic and steric characters are also tolerated under the reaction conditions (for example **1.126** and **1.127**). The Sr-catalyzed ECA of TBSCN to a tetrasubstituted enone is tolerated with high efficiency and selectivity when the reaction is conducted at 50 °C for 2 h (**1.128**, 84% yield, >99:1 er). Moreover, the reaction is pertinent to synthetically useful *N*-acylpyrroles (**1.129**, >99% yield, 97.5:2.5 er).

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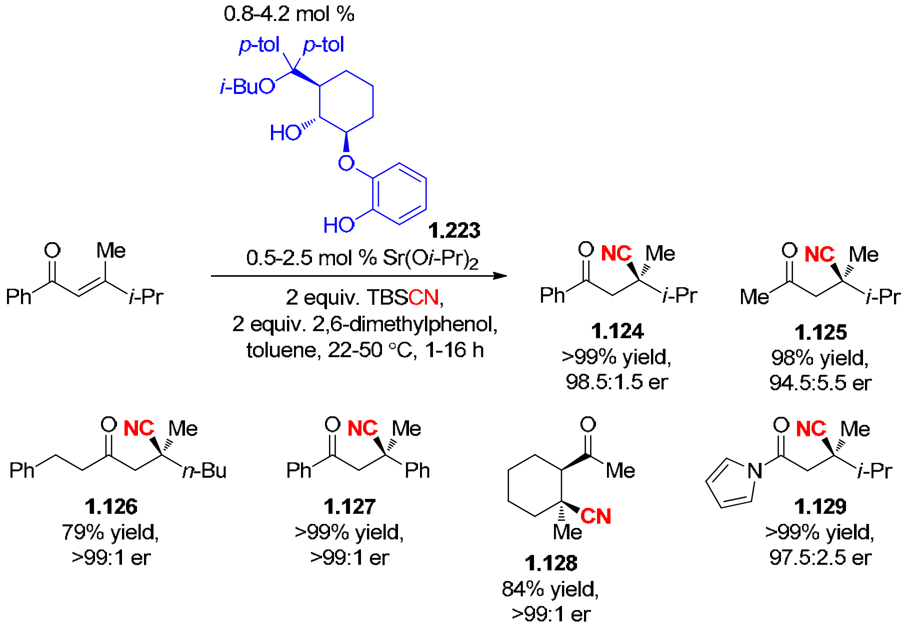
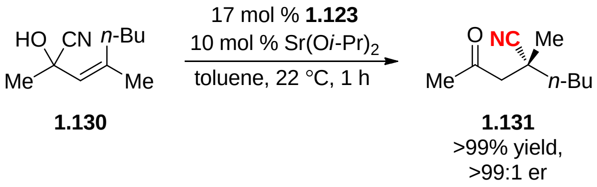
(66) "Catalytic Enantioselective Construction of *β*-Quaternary Carbons via a Conjugate Addition of Cyanide to *β,β*-Disubstituted *α,β*-Unsaturated Carbonyl Compounds," Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863.

Scheme 1.34. Sr-Catalyzed ECA of TBSCN to Tri- and Tetrasubstituted Enones


0.8-4.2 mol %
p-tol
p-tol
i-BuO
HO
O
HO
1.223
0.5-2.5 mol % Sr(Oi-Pr)2
2 equiv. TBSCN,
2 equiv. 2,6-dimethylphenol,
toluene, 22-50 °C, 1-16 h
O
Me
Ph
i-Pr
O NC Me
Ph
i-Pr
1.124
>99% yield,
98.5:1.5 er
O NC Me
Me
i-Pr
1.125
98% yield,
94.5:5.5 er
O NC Me
Ph
n-Bu
1.126
79% yield,
>99:1 er
O NC Me
Ph
Ph
1.127
>99% yield,
>99:1 er
O
Me
CN
Me
1.128
84% yield,
>99:1 er
O NC Me
N
i-Pr
1.129
>99% yield,
97.5:2.5 er

The authors note that 1,2-addition products are not observed, however, when racemic tertiary alcohol **1.130** is treated with the conditions found optimal in Scheme 1.34, the desired 1,4-adduct is formed in high yield and enantioselectivity. This suggests that the cyanohydrins (fromed by 1,2-addition) can equilibrate, under the catalytic conditions, to the starting enone and undergo an irreversible 1,4-addition reaction, yielding the desired **1.131.**

Scheme 1.35. Catalytic Enantioselective Rearrangement of Allyl Cyanide **1.130**


HO CN n-Bu
Me
Me
1.130
17 mol % 1.123
10 mol % Sr(Oi-Pr)2
toluene, 22 °C, 1 h
O NC Me
Me
n-Bu
1.131
>99% yield,
>99:1 er

1.6 Conclusions and Future Outlook

Enantioselective additions of carbon-based nucleophiles to electrophiles generating all-carbon quaternary stereogenic centers have seen great advances in the past several years. Owing to the difficult nature of additions to relatively unreactive conjugate acceptors, compared to additions generating tertiary stereogenic centers, and construction of a sterically-hindered bond, in many cases, new and active catalysts had to be developed. In fact, every example in this review has been published on or after 2005. With such a new field expanding yearly, it is exciting to see what innovative transformations the next five years will bring to the chemical community.

However, significant shortcomings still exist. For example, enantioselective additions of nucleophiles of any type to β-substituted cyclopentenones are inefficient, only moderately selective and have not been demonstrated on a broad scope of substrates. There have been only a handful of methods disclosed for additions to tetrasubstituted olefins and all of these accounts use electron-withdrawing substituents to render the substrate more electrophilic. Moreover, most of the substrates investigated are centered on cyclic enones. Recently, more accounts have used acyclic enones, but more work must be done in this area to address the generality of the scope.

With respect to the nucleophiles investigated, strides have been made in the area of enantioselective alkyl and aryl additions to conjugate acceptors. Cu-catalyzed methods have dominated enantioselective alkyl additions to prochiral electrophiles. Rh-catalyzed methods for alkyl additions, which have been recently exploited with regards to enantioselective aryl additions, have not been disclosed as of yet. This is likely due to the ability of the in situ prepared Rh-alkyl complex to undergo facile β-hydride elimination generating a Rh-H species. Nucleophiles that have been utilized for Cu-catalyzed ECA of alkyl groups include dialkylzinc, trialkylaluminum, and Grignard reagents. All three have both pros and cons related to them. Alkylzinc and alkylaluminum reagents are more functional group tolerate than Grignard reagents but the former are also less atom economical and more costly. Perhaps in the future, a protocol that encompasses an alkylmetal (or alkylmetal surrogate, such as an alkylsilane or alkylboronate) that is functional group tolerant, inexpensive, atom economical, easily modifiable to more complex derivatives and can be made efficiently will be developed.

Enantioselective aryl additions to activated olefins have had the benefit of both Cu- and Rh-catalyzed methods. The Cu-catalyzed ECA with arylaluminum reagents show great promise to be applicable to a range of enantiomerically enriched molecules. Since the nucleophile is prepared in situ and is also atom economical (one aryl group per aluminum reagent). While it seems that the Rh-catalyzed protocols have a larger range of substrates as of now, the more valuable Rh–metal and nucleophile (three to four aryl groups per boron reagent) may not be as practical in, for example, total synthesis of a complex natural product.

For the last two nucleophile subtypes, only a few disclosures have been put forth. While the methods are limited as of now, perhaps a more active class of catalysts will be developed to broaden the scope of the easily obtainable nucleophiles (vinylaluminum reagents, cyanohydrins, and silylcyanides), most pressingly, β-substituted cyclopentenones and medium ring enones. The enantiomerically enriched molecules containing an all-carbon quaternary stereogenic center bearing synthetically versatile vinyl or cyano group may be central to preparing biologically active agents.

Perhaps in the next decade of research, catalytic enantioselective conjugate addition methods will include some of the nucleophiles not yet addressed in the past few years, for example allyl, alkynyl, and propargyl additions. Development of methods including these nucleophiles will allow chemists to build enantiomerically enriched molecules through catalytic ECA in a practical, quick and simple manner.

Chapter 2.

Development of New and Active Catalysts for Cu-Catalyzed Enantioselective Conjugate Addition of Alkyl- and Arylzinc Reagents

2.1. Introduction

The design and synthesis of new chiral catalysts to promote enantioselective C–C bond formation is a crucial goal in organic synthesis.[1] Enantioselective conjugate addition (ECA) has proven to be a powerful method to prepare enantiomerically enriched compounds,[2] and such has been used as the key step in several syntheses of natural products.[3] Although studies toward the synthesis of tertiary stereogenic centers through ECA have been fruitful,[2] only recently have a growing number of disclosures focused on the more challenging formation of all-carbon quaternary stereogenic centers.[4]

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(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Berlin, Germany, 1999. (b) *New Frontiers in Asymmetric Catalysis;* Mikami, K.; Lautens, M., Eds; Wiley: Hoboken, NJ, 2007.

(2) (a) “Recent Advances in Catalytic Enantioselective Michael Additions,” Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (b) “Enantioselective Copper-Catalysed Conjugate Addition,” 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.

(3) For some representative natural products that have been prepared through Cu-catalyzed ECA, see: (a) “Catalytic Enantioselective Synthesis of Prostaglandin E_1 Methyl Ester Using a Tandem 1,4-Addition-Aldol Reaction to a Cyclopenten-3,5-dione Monoacetal,” Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841–5842. (b) “Enantioselective Total Synthesis of Erogorgiaene: Applications of Asymmetric Cu-Catalyzed Conjugate Additions of Alkyzincs to Acyclic Enones,” Cesati, R. R. III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96–101. (c) “An Iterative Catalytic Route to Enantiopure Deoxypropionate Subunits: Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Thioesters,” Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967. (d) “Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis,” Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906. (e) “Asymmetric Synthetic Access to the Hetisine Alkaloids: Total Synthesis of (+)-Nominine,” Peese, K. M.; Gin, D. Y. *Chem. Eur. J.* **2008**, *14*, 1654–1665.

(4) For ECA methods that access compounds containing all-carbon quaternary stereogenic centers, see: (a) “Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions,” Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am.*

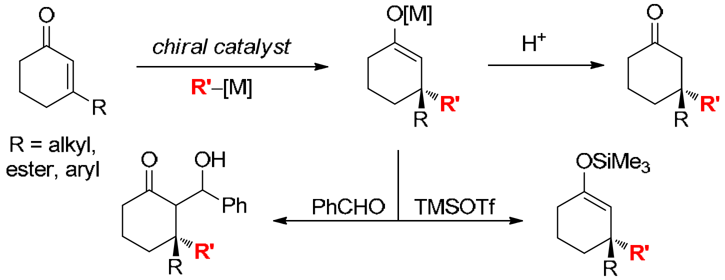
Chem. Soc. **2005**, *127*, 4584–4585. (b) “Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones,” Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989. (c) “Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers,” d’Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (d) “Enantioselective Construction of Stereogenic Quaternary Centres *via* Rh-Catalyzed Asymmetric Addition of Alkenylboronic Acids to α,β-Unsaturated Pyridylsulfones,” Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963. (e) “Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Cu-Catalyzed Conjugate Addition of Dialkylzinc Reagents to 5-(1-Arylalkylidene) Meldrum’s Acids,” Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775. (f) “A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers through NHC–Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to β-Substituted Cyclic Enones,” Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (g) “Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers,” Martin, D.; Kehrli, S.; d’Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (h) “Rhodium-Catalyzed Asymmetric Construction of Quaternary Carbon Stereocenters: Ligand-Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides,” Shintani, R.; Duan, W-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629. (i) “Asymmetric Cu-Catalyzed 1,6-Conjugate Addition of Dialkylzinc Reagents to 5-(3-Aryl-2-propenylidene) Meldrum’s Acids,” Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959. (j) “Enantioselective Copper-Catalyzed Conjugate Addition to 2- or 3-Substituted Cyclopent-2-en-1-ones: Construction of Stereogenic Quaternary Carbon Centers,” Vuagnoux-d’Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, 2057–2060. (k) “Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminum Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers,” Vuagnoux-d’Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662. (l) “SimplePhos Monodentate Ligands: Synthesis and Application in Copper-Catalyzed Reactions,” Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d’Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465. (m) “Organocatalyzed Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Conjugate Addition of Acetone Cyanohydrin,” Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Synlett* **2008**, 1857–1861. (n) “Dinuclear {(salen)Al} Complexes Display Expanded Scope in the Conjugate Cyanation of α,β-Unsaturated Imides,” Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762–1765. (o) “C_2 Symmetric Chiral NHC Ligand for Asymmetric Quaternary Carbon Constructing Copper-Catalyzed Conjugate Addition of Grignard Reagents to 3-Substituted Cyclohexenones,” Matsumoto, Y.; Yamada, K-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581. (p) “Copper-Catalyzed Asymmetric Conjugate Addition of Aryl Aluminum Reagents to Trisubstituted Enones: Construction of Aryl-Substituted Quaternary Centers,” Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int Ed.* **2008**, *47*, 8211–8214. (q) “C_2 Symmetric Chiral NHC Ligand for Asymmetric Quaternary Carbon Constructing Copper-Catalyzed Conjugate Addition of Grignard Reagents to 3-Substituted Cyclohexenones,” Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581. (r) “Regiodivergent 1,4- versus 1,6-Asymmetric Copper-Catalyzed Conjugate Addition,” Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122–9124. (s) “Asymmetric Synthesis of Carboxylic Acid Derivatives Having an All-Carbon α-Quaternary Center through Cu-Catalyzed 1,4-Addition of Dialkylzinc Reagents to 2-Aryl Acetate Derivatives,” Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804. (t) “Copper-Catalyzed Asymmetric Conjugate Addition with Chiral SimplePhos Ligands,” Palais, L.; Alexakis A. *Chem. Eur. J.* **2009**, *15*, 10473–10485. (u) “Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Conjugate Addition to Alkylidene and Indenylidene Meldrum’s Acids,” Wilsily, A.; Fillion, E. *J. Org. Chem.* **2009**, *74*, 8583–8594. (v) “Enantioselective Copper-Catalyzed Conjugate Addition of Diemethylzinc to 5-(1-Arylalkylidene) Meldrum’s Acids,” Wilsily, A.; Lou, T.; Fillion, E. *Synthesis* **2009**, 2066–2072. (w) “New Bifunctional Substrates for Copper-Catalyzed Asymmetric Conjugate Addition Reactions with Trialkylaluminium,” Ladjel, C.; Fuchs, N.; Zhao, J.; Bernardinelli, G.; Alexakis, A. *Eur. J.*

The research described herein focuses on catalysts that we have developed to promote Cu-catalyzed ECA of organozinc and aluminum-based nucleophiles to β-substituted cyclic enones, centering specifically on many of the limitations presented in recent publications. In particular, five-membered ring enones are often less efficient and enantioselective substrates in ECA.[5] Many of the latest protocols required to address this challenge required the preparation of new and active ligands.

Org. Chem. **2009**, 4949–4955. (x) "Sodium Tetraarylborates as Effective Nucleophiles in Rhodium/Diene-Catalyzed 1,4-Addition to β,β-Disubstituted α,β-Unsaturated Ketones: Catalytic Asymmetric Construction of Quaternary Carbon Stereocenters," Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589. (y) "Formation of Quaternary Chiral Centers by N-Heterocyclic Carbene–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Trisubstituted Cyclic Enones," Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. Eur. J.* **2010**, *16*, 9890–9904. (z) "Creation of Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Conjugate Addition of Alkenyl Alanes to α,β-Unsaturated Cyclic Ketones," Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett*, **2010**, 1694–1698. (aa) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl Alanes to Trisubstituted Enones: Binap as an Effective Ligand in the Formation of Quaternary Stereocenters," Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769–7772. (bb) "Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon-Carbon Bond-Forming Processes," Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454. (cc) "Olefin-Oxazolines (OlefOx): Highly Modular, Easily Tunable Ligands for Asymmetric Catalysis," Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143–1146. (dd) "Chiral Tetrafluorobenzobarrelenes as Effective Ligands for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboroxines to β,β-Disubstituted α,β-Unsaturated Ketones," Shintani, Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969–3971. (ee) "Rhodium-Catalyzed Asymmetric Synthesis of Spirocarbocycles: Arylboron Reagents as Surrogates of 1,2-Dimetalloarenes," Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795–3798. (ff) "Catalytic Enantioselective Construction of β-Quaternary Carbons via a Conjugate Addition of Cyanide to β,β-Disubstituted α,β-Unsaturated Carbonyl Compounds," Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863. (gg) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to β,β-Disubstitute, α,β-Unsaturated Esters," Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350–352.

(5) For a discussion on cyclopentenones in ECA, see: "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755–756.

Scheme 2.1. Metal Catalyzed Enantioselective Conjugate Addition



Enantioselective conjugate addition allows rapid access to products that contain all-carbon quaternary stereogenic centers adjacent to a metal enolate, which would be otherwise difficult to access from the requisite ketone (Scheme 2.1).[4f] The metal enolate can then be used for further functionalizations including the potential to access a variety of natural products (Scheme 2.2).[6] For example, clavirolide C was synthesized through Cu-catalyzed ECA of trimethylaluminum to a β-substituted cyclopentenone,[3d] highlighting the importance of a method that includes five-membered rings as substrates. Moreover, as illustrated by the CCR2 antagonist, nucleophiles and/or substrates that contain synthetically versatile substituents (i.e., other than simple primary alkyl groups, methyl or ethyl) would be imperative for application to natural products.

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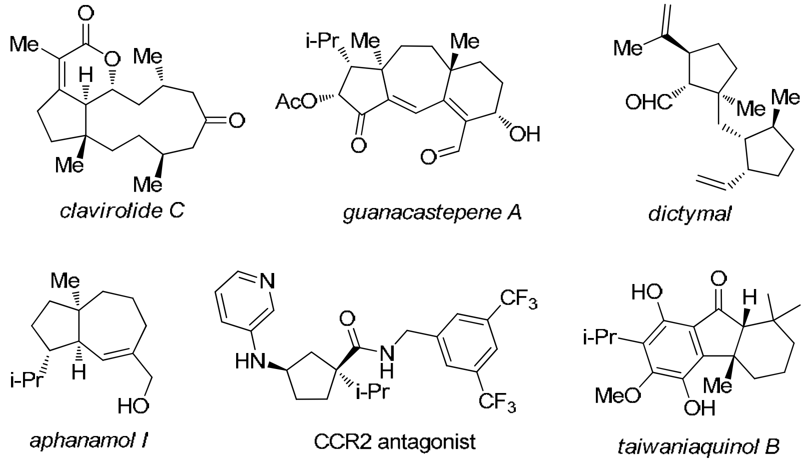
(6) For the isolation reports of the natural products depicted in Scheme 2.2, see: (a) "Four Novel Diterpenoids: Clavirolides B, C, D, and E from the Chinese Soft Coral Clavularia viridis," Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380–385. (b) "Guanacastepene, a Fungal-Derived Diterpene Antibiotic with a New Carbon Skeleton," Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117. (c) "Dictymal, a New Seco-fusicoccin Type Diterpene from the Brown Alga dictyota dichotoma," Segawa, M.; Enoki, N.; Ikura, M.; Hikichi, K.; Ishida, R.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 3703–3704. (d) "Structure of Aphanamols I and II," Nishizawa, M.; Inoue, A.; Hayashi, Y.; Sastrapradja, S.; Kosela, S.; Iwashita, T. *J. Org. Chem.* **1984**, *49*, 3660–3662. (e) Abbadie, C.; Lindia, J. A.; Wang, H. CCR-2 Antagonists for Treatment of Neuropathic Pain. Eur. Pat. Appl. WO2004110376, December 23, 2004. (f) "Uncommon Diterpenes with the Skeleton of Six-Five-Six Fused-Rings from *Taiwania cryptomerioides*," Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871–873.

Scheme 2.2. Natural and Biologically Active Products Containing All-Carbon Quaternary Stereogenic Centers



2.2. Chiral Amino Acid-based Ligands in Cu-Catalyzed Enantioselective Conjugate Additions of Alkylzinc Reagents to Enones

2.2.a. Ligand Screening and Condition Optimization

Previous work in our laboratories has focused on readily modifiable and easily prepared amino-acid based ligands.[7] A variety of these ligands have been shown to promote highly enantioselective Cu-catalyzed allylic alkylations of organozinc reagents to allyl phosphates[8] as well as conjugate additions to nitroalkenes[9] and various enones.[10]

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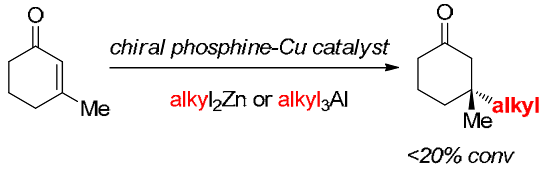
(7) "Small Peptides as Ligands for Catalytic Asymmetric Alkylations of Olefins. Rational Design of Catalysts or of Searches that Lead to Them?," Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, *16,* 1779–1785.

(8) (a) "Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Copper-Catalyzed Allylic Substitutions," Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456–1460. (b) "Cu-Catalyzed Asymmetric Allylic Allylations of Aromatic and Aliphatic Phosphates with Alkylzinc Reagents. An Effective Method for Enantioselective Synthesis of Tertiary and Quaternary Carbons," Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676–10681. (c) "Catalyltic Enantioselective Synthesis of Quaternary All-Carbon Stereogenic Centers. Preparation of α,α'-Disubstituted β,γ-Unsaturated Esters through Cu-Catalyzed Asymmetric Allylic Alkylations," Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 1255–1258.

(9) (a) "Cu-Catalyzed Enantioselective Conjugate Addition of Alkylzincs to Cyclic Nitroalkenes: Catalytic Asymmetric Synthesis of Cyclic α-Substituted Ketones," Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193. (b) "Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Aromatic and Aliphatic Acyclic Nitroalkenes," Mampreian, D. M.; Hoveyda, A. H.

While the amino acid-based ligands were found to be effective for conjugate additions of alkylzinc reagents to enones to form tertiary stereogenic centers, we found that transformations were sluggish when unactivated β-alkyl enones were used (eq. 1).[11] The poor efficiency was attributed to the increased steric hindrance at the electrophilic β-carbon, as well as the electron-donating character of the β-alkyl group rendering the substrate less reactive towards nucleophilic addition. While the Cu complexes of peptidic ligands, as of now, are not reactive enough to catalyze the ECA to β-alkyl unsaturated enones, we have found that they can promote Cu-catalyzed ECA to a class of electronically modified substrates, α-ester, β-alkyl unsaturated enones.[4f] The protocol furnishes products containing all-carbon quaternary stereogenic centers with good selectivities (83:17–97.5:2.5 er) and yields (64–>98%). We sought to expand this catalytic method further through alkylations of enones bearing an ester at the β-position. If the slow step in the process is the addition of the copper–alkyl complex to the substrate, then installing an electron-withdrawing substituent should facilitate this transformation by enhancing the electrophilicity of the substrate.



(1)

Org. Lett. **2004**, *6*, 2829–2832. (c) ref 4a. (d) "Cu-Catalyzed Asymmetric Conjugate Additions of Dialkyl- and Diarylzinc Reagents to Acyclic β-Silyl-α,β-Unsaturated Ketones. Synthesis of Allylsilanes in High Diastereo- and Enantiomeric Purity," Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 3187–3190.

(10) (a) ref 5. (b) "Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Acyclic Aliphatic Enones," Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779–781. (c) "Efficient Cu-Catlyzed Asymmetric Conjugate Additions of Alkylzincs to Trisubstituted Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362–13363. (d) "Cu-Catalyzed Enantioselective Conjguate Additions of Alkyl Zinc Reagents to Unsaturated *N*-Acyloxazolidinones Promoted by a Chiral Triamide Phosphane," Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276–1279. (e) ref. 4b. (f) "Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu–Peptide Complexes," Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310.

(11) Alkylaluminum reagents were found to decompose the amino acid-based ligands.

We began by examining the ability of Schiff base phosphine ligands to promote the Cu-catalyzed ECA of diethylzinc to enone **2.1**[12] (Table 2.1). Gratifyingly, phosphine ligand **2.3**, in the presence of $(CuOTf)_2•C_6H_6$, catalyzes the addition of Et_2Zn to enone **2.1** to provide the desired product in 98% conv and 77.5:22.5 er in 12 h at 0 °C (entry 1). Further investigation of modified ligands, which involved replacement of *tert*-leucine with glycine, decreased the enantioselectivity of **2.2** (ligand **2.4**, 37:63 er, entry 2). Installing a D-*p*-benzyl ether tyrosine unit (**2.5**, vs. L in **2.3**) results in a significant increase in enantioselectivity (91:9 er, entry 3). The Cu-catalyed ECA with ligand **2.5** can be performed at –30 °C for 12 h, furnishing ketone **2.2** with 94.5:5.5 er. Through further ligand optimization, glycine-containing phosphine ligand **2.6a** was identified to furnish the desired product in 94:6 er; however, the desired product is formed in only 33% yield (Scheme 2.3).

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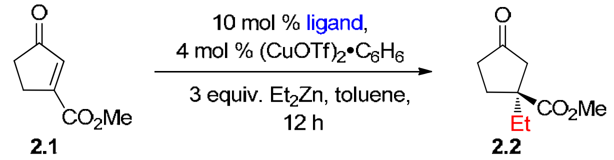
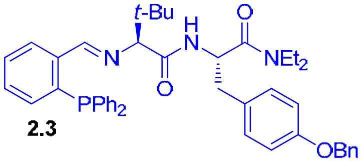
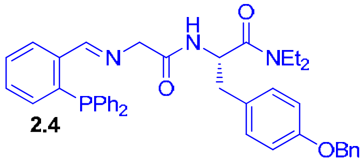
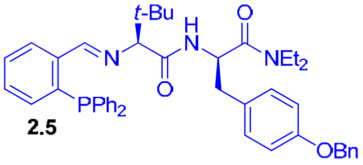
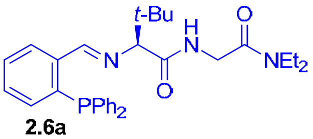
(12) For a Cr-mediated allylic oxidation procedure to prepare the unsaturated γ-ketoesters, see: (a) "Ring Expansions of [2 + 2] Photoadducts. Potential Applications in the Synthesis of Triquinane and Taxane Skeletons," Lange, G. L.; Decicco, C. P.; Willson, J.; Strickland, L. A. *J. Org. Chem.* **1989**, *54*, 1805–1810. Although other catalytic allylic oxidation methods have been reported (see below) to afford the cyclic enones, we found the highest purity of the products could be obtained with Cr-mediated allylic oxidation. For a detailed procedure on the preparation of the enones, see the experimental section. For Pd-catalyzed allylic oxidation, see: (b) "A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β-Enones to 1,4-Enediones," Yu, J-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. For Rh-catalyzed allylic oxidation, see: (c) "Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation," Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623.

Table 2.1. Cu-Catalyzed ECA of Et_2Zn to γ-Ketoesters Promoted by Amino Acid-Based Phosphine Ligands[a]



entry	ligand	temp (°C)	conv (%)[b]	er[c]
1	 **2.3**	0	98	77.5:22.5
2	 **2.4**	0	98	37:63
3	 **2.5**	0	98	91:9
4		–30	>98	94.5:5.5
5	 **2.6a**	0	98	90:10
6		–30	98	94:6

[a] Reactions performed under a N_2 atmosphere. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Enantiomeric ratios determined by GLC analysis; see the experimental section for details.

The low yield is attributed to Claisen condensation between the generated metal enolate and enone **2.1** to afford product **2.7** (either a zinc or copper enolate could mediate in this addition). At this time, it was unknown whether byproduct formation was from an adventitious background reaction or if the Cu–ligand complex was promoting the formation of **2.7**; we have previously studied Ag-catalyzed aldol reactions promoted by chiral amino-acid based ligands.[13]

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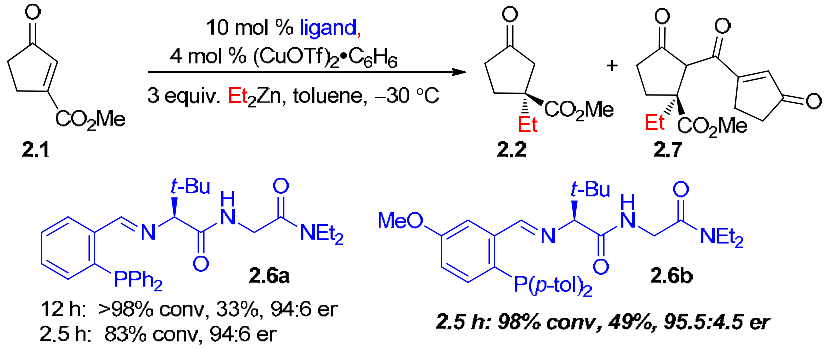
(13) "A Chiral Ag-Based Catalyst for Practical, Efficient, and Highly Enantioselective Additions of Enolsilanes to α-Ketoesters," Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532–6533.

Scheme 2.3. Improving Efficiency of the Cu-Catalyzed ECA through Ligand Optimization


10 mol % ligand,
4 mol % $(CuOTf)_2•C_6H_6$
3 equiv. Et_2Zn, toluene, –30 °C
CO_2Me
2.1
2.2
2.7
Et
CO_2Me
t-Bu
NEt_2
PPh_2
2.6a
MeO
P(*p*-tol)$_2$
2.6b
12 h: >98% conv, 33%, 94:6 er
2.5 h: 83% conv, 94:6 er
2.5 h: 98% conv, 49%, 95.5:4.5 er

We surmised that electronically modifying the Schiff base portion of the ligand could increase the overall rate of the alkylation, thus out competing the rate of the Claisen condensation such that there would be less of the enone **2.1** with which the metal enolate could react. To test this theory, Schiff base phosphine **2.6b** was synthesized[14] and found to promote the formation of the desired product **2.2** with increased efficiency (>98% conversion within 2.5 h) and yields (49% vs 33% with ligand **2.6a**). The increase in reactivity is due to the more electron rich phosphine, which, when bound to copper, increases the transferability of the alkyl group on copper (see mechanism discussion below).

2.2.b. ECA Promoted by Cu–2.6b Complex: Reaction Scope and Limitations

When the size of the ester unit on the substrate is increased (Me, *i*-propyl, *t*-butyl esters), the yield of the ECA reaction is increased (49%, 74%, 88%, respectively, Table 2.2, entries 1–3). The more sterically encumbered the substrate, the more the Claisen condensation pathway is suppressed. Furthermore, Cu-catalyzed ECA, promoted by the Cu complex of **2.6b**, of dimethylzinc to γ-ketoesters is efficient and selective (51–69% yield, ≥96:4 er, entries 4–5).

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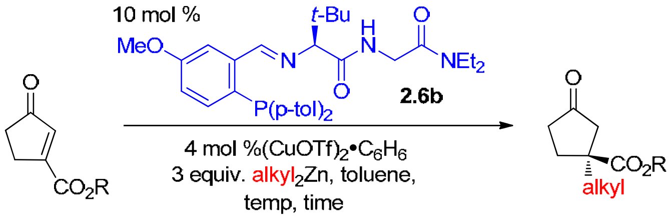
(14) For the synthesis of the corresponding aldehyde to prepare ligand **2.6b**, see: "Continuous Application of Chemzymes in a Membrane Reactor: Asymmetric Transfer Hydrogenation of Acetophenone," Laue, S.; Greiner, L.; Wöltinger, J.; Liese, A. *Adv. Synth. Catal.* **2001**, *343*, 711-720.

Table 2.2. Cu-Catalyzed ECA of γ-Ketoesters Promoted by a Phosphine-Based Ligand[a]

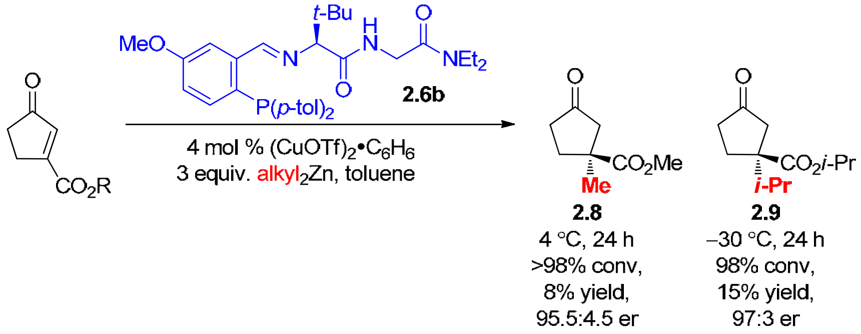


entry	R	alkyl$_2$Zn	temp (°C)	t (h)	conv (%)[b]	yield (%)[c]	er[d]
1	Me	Et$_2$Zn	–30	2.5	98	49	95.5:4.5
2	*i*-Pr	Et$_2$Zn	–30	6	98	74	95.5:4.5
3	*t*-Bu	Et$_2$Zn	–30	6	98	88	95.5:4.5
4	*i*-Pr	Me$_2$Zn	4	17	98	69	96:4
5	*t*-Bu	Me$_2$Zn	4	16	98	51	97:3

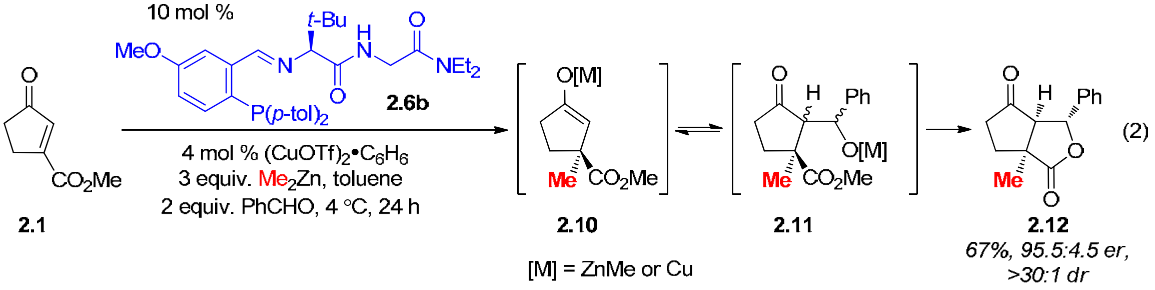
[a] Reactions performed under a N_2 atmosphere. [b] Conversions found by a combination of ^{1}H NMR and GLC analysis (β-dex). [c] Yields of isolated purified products. [d] Determined by GLC analysis, see experimental section for details.

Although the Cu-catalyzed additions of alkylzinc reagents perform well with certain substrates, there are some limitations with the current protocol. For example, Cu-catalyzed ECA of dimethylzinc to the Me-ester γ-ketoester substrate (**2.1**) delivers product **2.8** in 8% yield, although the selectivity observed is high (95.5:4.5 er, Scheme 2.4). The low yield is attributed to undesired Claisen condensation of the generated metal enolate with another molecule of γ-ketoester substrate (cf. **2.7**, Scheme 2.3). Similarly, Cu-catalyzed ECA of *i*-Pr$_2$Zn to the *i*-Pr-ester γ-ketoester affords product **2.9** in only 15% yield (97:3 er).

Scheme 2.4. Limitations of the Cu-Catalyzed ECA Protocol


MeO
t-Bu
H
N
O
NEt2
P(p-tol)2
2.6b
CO2R
4 mol % (CuOTf)2•C6H6
3 equiv. alkyl2Zn, toluene
CO2Me
Me
2.8
4 °C, 24 h
>98% conv,
8% yield,
95.5:4.5 er
CO2i-Pr
i-Pr
2.9
–30 °C, 24 h
98% conv,
15% yield,
97:3 er

Our group has shown previously that reactive Zn–enolates, in situ prepared from ECA additions, can be trapped via an intermolecular aldol reaction peforming the reaction in the presence of an aldehyde.[15] We were aware that that trapping of the Zn– or Cu–enolate in the current Cu-catalyzed ECA may prove to be more difficult considering an intermolecular aldol addition would need to occur with an enolate bearing a β-quaternary stereogenic center may not be as facile as with an enolate containing a β-tertiary carbon center. Nevertheless, when the Cu-catalyzed ECA of Me_2Zn to enone **2.1** is performed in the presence of three equivalents of benzaldehyde, the metal enolate **2.10** undergoes an aldol reaction followed by an esterification to furnish bicyclic lactone **2.12** in 67% yield and 95.5:4.5 er as a single diastereomer. We surmise that the initial aldol addition product **2.11** is not generated with high diastereoselectivity but the metal enolate **2.10** can presumably undergo aldol/retroaldol additions until the thermodynamically preferred diastereomer of the cyclized product is formed (eq. 2).


10 mol %
MeO
t-Bu
H
N
O
NEt2
P(p-tol)2
2.6b
CO2Me
2.1
4 mol % (CuOTf)2•C6H6
3 equiv. Me2Zn, toluene
2 equiv. PhCHO, 4 °C, 24 h
O[M]
Me
CO2Me
2.10
[M] = ZnMe or Cu
H
Ph
O[M]
2.11
2.12
67%, 95.5:4.5 er,
>30:1 dr
(2)

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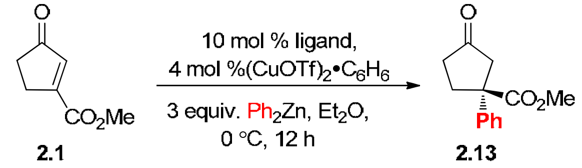
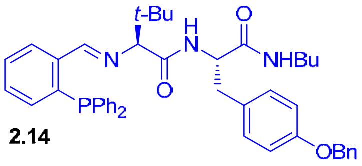
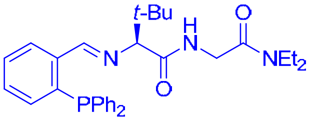
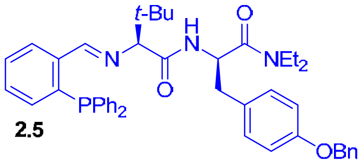
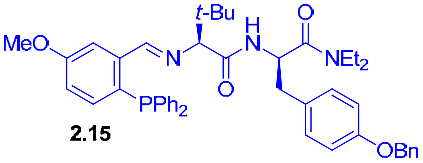
(15) (a) see ref. 10f. (b) "Conjugate Addition of Diorganozincs to α,β-Unsaturated Ketones Catalyzed by a Copper(I)-Sulfonamide Combined System," Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141–5144. (c) ref. 3a.

After determining that alkylzinc reagents can serve as effective nucleophiles in the Cu-catalyzed ECA protocol for γ-ketoesters, we next investigated if diphenylzinc could also be a competent partner. At this time, there were no examples of aryl nucleophiles in catalytic ECA reactions to form products containing quaternary stereogenic centers. As shown in Table 2.3, ligand **2.14**, containing L-*t*-leucine and L-benzyltyrosine units, along with a Cu(I) salt, promotes the ECA; however, the desired product **2.13** is isolated as a racemate (entry 1, Table 2.3). When the Cu-catalyzed enantioselective alkylation is carried out in the presence of ligand **2.6a**, **2.13** is isolated in 92.5:7.5 er (entry 2). Further ligand screening involving the diastereomer of **2.14** bearing L-*t*-leucine and D-benzyltyrosine residues promotes the addition with increased selectivity; product **2.13** is isolated in 95.5:4.5 er (94% conv) but only in 29% yield. The low yield is attributed to the reactive metal enolate undergoing subsequent reactions (cf. **2.7**, Scheme 2.3). In an effort to increase the rate of the alkylation, and therefore the yield of the product (a faster rate of reaction leaves less of the substrate for the resulting enolate to react with), we prepared more electron-rich phosphine ligand **2.15**. When the Cu-catalyzed ECA is promoted by the Cu–**2.15** complex, product **2.13** is isolated in 36% yield with sustained selectivity (96:4 er, entry 4). Despite this increase in rate, the yield could not be improved to synthetically useful levels.

Table 2.3. Ligand Optimization for Cu-Catalyzed ECA of Ph_2Zn to γ-Ketoester **2.1**[a]



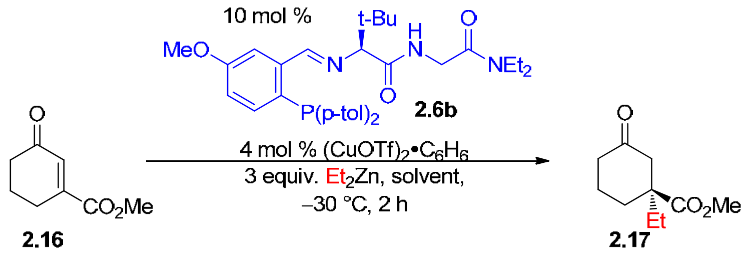
entry	ligand	conv (%)[b]	yield (%)	er[b]
1	 **2.14**	40	nd	50:50
2	 **2.6a**	50	nd	92.5:7.5
3	 **2.5**	94	29	95.5:4.5
4	 **2.15**	96	36	96:4

[a] Reactions carried out under an atmosphere of N_2. [b] Determined by GLC analysis with dodecane as an internal standard. nd = not determined.

It is noteworthy that the reactions in Table 2.3 were carried out with Et_2O as the solvent, which is different from the ECA of alkylzinc reagents which used toluene. When the reaction in entry 3 of Table 2.3 is instead performed in toluene at –15 °C, product **2.13** is formed in only 9% conv and 83.5:16.5 er. The low conversion is ascribed to the low solubility of Ph_2Zn in toluene at –15 °C. If the temperature is elevated to 22 °C to increase the solubility, full conversion is achieved, but **2.13** is isolated in 50:50 er. Furthermore, when tetrahydrofuran (thf) is used as the reaction solvent, using the same conditions in entry 3, Table 2.3, <2% conv of the conjugate adduct is formed (**2.1** is recovered). Attempts to further improve the yield of **2.13** were unsuccessful.

All studies thus far investigated additions to β-substituted cyclopentenones. Next, we studied whether the Cu-catalyzed ECA of alkyl- and arylzinc reagents could be extended to the corresponding six-membered ring enones. As shown in Table 2.4, using the conditions found optimal for catalytic enantioselective addition of Et_2Zn to the five-membered ring enone **2.1**, <2% conv to product **2.17** is formed (full recovery of **2.16**). Small changes in the ligand structure, however, led to considerable differences in reactivity; for example, all ligands screened that contained a *n*-butyl amide C-terminus (i.e., **2.14** vs. diethyl amide terminus of **2.66b**) led to full consumption of **2.16** with no detectable amount of **2.17**. Other solvents screened for the Cu-catalyzed ECA protocol include Et_2O, CH_2Cl_2, thf, dme, and dichloroethane (entries 2–6). The only conditions in which any **2.17** could be isolated is when CH_2Cl_2 is used as the reaction medium (entry 3). The addition leads to 28% conv after 2 h at –30 °C with **2.17** being formed in 95:5 er.

Table 2.4. Cu-Catalyzed ECA of Et_2Zn to β-Ester Cyclohexenone: Solvent Screen[a]

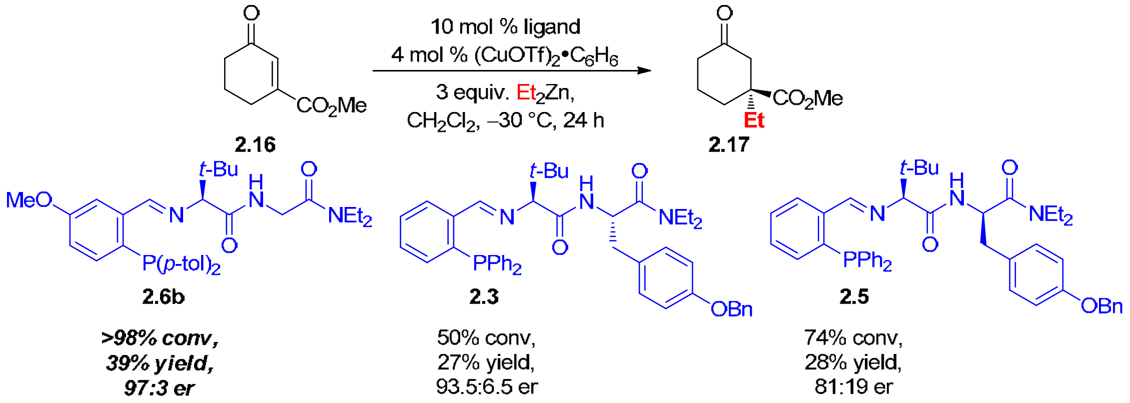


entry	solvent	conv (%)[b]	er[c]
1	toluene	<2[d]	nd
2	Et_2O	<2[d]	nd
3	CH_2Cl_2	28	95:5
4	thf	<2[e]	nd
5	dme	<2[e]	nd
6	$ClCH_2CH_2Cl$	<2[e]	nd

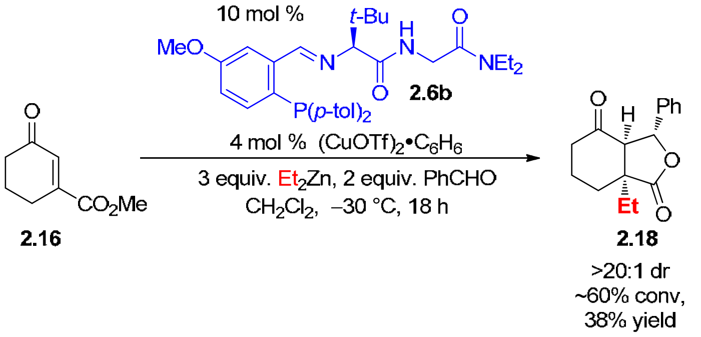
[a]Reactions performed under N_2 atm. [b]Determined by ^1H NMR analysis of the unpurified reaction mixture. [c]Determined by GLC analysis. [d]Recovered starting material. [e]Reactions proceed to <2% conv to desired product, however ^1H NMR analysis of the unpurified mixture showed multiple unidentified products. nd = not determined. thf = tetrahydrofuran. dme = dimethyoxyethane

To increase the conversion of the catalytic alkylation process, the reaction time was extended to 24 h (Scheme 2.5); full conversion is achieved; however, the yield after purification is only 39%. A select number of ligands were investigated with the new solvent system to gauge if the yield could be improved. Cu-catalyzed ECA of Et_2Zn to enone **2.16** in the presence of ligand **2.3** proceeds more slowly than with ligand **2.6b** (50% conv in 24 h), although similar levels of selectivities are observed (93.5:6.5 er). Furthermore, the ECA promoted by ligand **2.5** and a Cu(I) salt did not improve the reaction (74% conv, 28% yield, 81:19 er).

Scheme 2.5. Selected Ligand Screen for Cu(I)-Catalyzed ECA of Et_2Zn to **2.16**

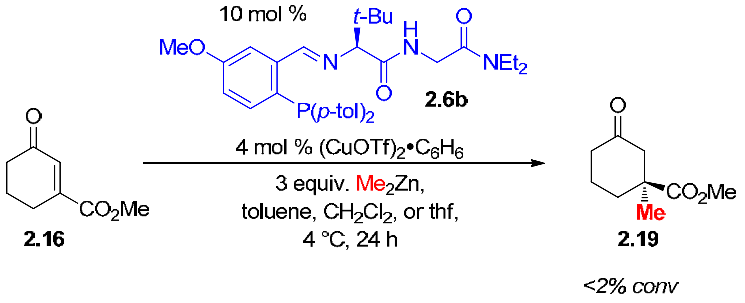

2.16
10 mol % ligand
4 mol % $(CuOTf)_2 \cdot C_6H_6$
3 equiv. Et_2Zn,
CH_2Cl_2, –30 °C, 24 h
2.17
2.6b
2.3
2.5
>98% conv,
39% yield,
97:3 er
50% conv,
27% yield,
93.5:6.5 er
74% conv,
28% yield,
81:19 er

To date, the by-products that arise during the course of the reaction, when enone **2.16** is employed as the substrate have not been identified. However, use of **2.1** as a substrate allows for the isolation of an oligomeric-product (cf. Scheme 2.3). We believe that the resulting Zn–enolate of **2.17** is not stable under the reaction conditions, leading to a diminished yield. In addition, if the reaction were to be performed in the presence of an aldehyde, the Zn–enolate could undergo an in situ aldol addition, trapping the reactive Zn–enolate to minimize degradation (cf. eq 2). As shown in eq 3, when enone **2.16** is subjected to Cu-catalyzed ECA of Et_2Zn with ligand **2.6b** in the presence of 2 equiv. of benzaldehyde, product **2.18** is isolated in 38% yield and >20:1 dr (~60% conv based on ^{1}H NMR analysis of the unpurified reaction mixture).


10 mol %
MeO
t-Bu
H
N
O
N
NEt2
O
P(p-tol)2
2.6b
4 mol % (CuOTf)2•C6H6
3 equiv. Et2Zn, 2 equiv. PhCHO
CH2Cl2, –30 °C, 18 h
O
CO2Me
2.16
O
H
Ph
O
Et
O
2.18
>20:1 dr
~60% conv,
38% yield

(3)

Attempts to use other alkylating reagents in the ECA reaction also proved unsuccessful. As illustrated in eq. 4, Cu-catalyzed ECA of Me_2Zn to enone **2.16** leads to <2% conv (full recovery of starting material) when toluene, thf, or CH_2Cl_2 is employed as the solvent. Although the Cu–peptide-based catalyst system efficiently furnishes some products with high enantioselectivities (Table 2.2), the substrate scope is limited to five-membered ring γ-ketoesters.


10 mol %
MeO
t-Bu
H
N
O
N
NEt2
O
P(p-tol)2
2.6b
4 mol % (CuOTf)2•C6H6
3 equiv. Me2Zn,
toluene, CH2Cl2, or thf,
4 °C, 24 h
O
CO2Me
2.16
O
CO2Me
Me
2.19
<2% conv

(4)

2.2.c. Working Transition State Model for the Cu-Catalyzed ECA of Dialkylzinc Reagents to Unsaturated γ-Ketoesters

The mode of addition to obtain the observed major enantiomer can be explained to proceed through the working transition state model illustrated in Scheme 2.6. This model is consistent with other enantioselective protocols with amino-acid based ligands.[16] The ligand, **2.6b**, coordinates with the Cu(I) salt through the imine nitrogen

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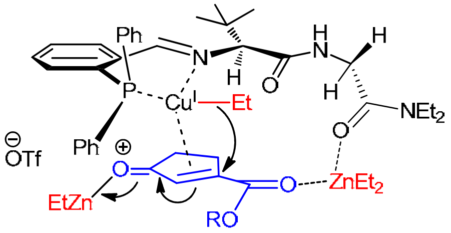
(16) For example, see: (a) "Mechanism of Enantioselective Ti-Catalyzed Strecker Reaction: Peptide-Based Metal Complexes as Bifunctional Catalysts," Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594–11599. (b) "A Highly Efficient and Practical Method for Catalytic Asymmetric Vinylogous Mannich (AVM) Reactions," Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233. (c) "Catalytic Asymmetric Alkylation of Ketoimines. Enantioselective Synthesis of *N*-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed

and phosphine. When the Cu–ligand complex is exposed to diethylzinc, the alkylcopper complex likely forms and forms a π-complex with the enone. As shown in Scheme 2.6, the enone is aligned to undergo a carbocupration. The substrate can be concomitantly activated by a Lewis acid interaction between the carbonyl and the alkylzinc species and by a zinc bridge between the β-ester moiety and the Lewis basic diethylamide unit in the ligand. Enhancing the Lewis basicity of the phosphine (comparing **2.6a** with **2.6b**) will increase the polarity of the Cu–alkyl bond and raise the nucleophilicity of the alkyl group; this is evident in the rate differences between ligands **2.6a** and **2.6b** (83% vs. 98% conv in 2.5 h, Scheme 2.3).

Scheme 2.6. Working Transition Model for Cu-Catalyzed ECA of Alkylzinc Reagents to γ-Ketoesters



In light of the prevalent limitations (six-membered ring substrates, aryl additions, and low to moderate yields of the conjugate adducts), we began to search for a more active and efficient catalyst for the formation of all-carbon quaternary stereogenic centers.

Additions to Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluroalkyl-Substituted Ketoimines," Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am Chem. Soc.* **2008**, *130*, 5530–5541. (d) "Aluminum-Catalyzed Asymmetric Alkylations of Pyridyl-Substituted Alkynyl Ketones with Dialkylzinc Reagents," Friel, D. K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 9942–9951.

2.3. Chiral NHC-Based Ligands in Cu-Catalyzed Enantioselective Conjugate Additions to Enones

2.3.a. Additions of Alkyl- and Arylzinc Reagents to γ-Ketoesters[17]

2.3.a.1. Initial Observations and Ligand Screening

N-Heterocyclic carbenes (NHCs) have been demonstrated to be powerful ligands for a variety of metal-catalyzed reactions.[18] Theoretical and experimental studies have elucidated that, in many cases, NHCs are stronger electron-donor ligands than phosphine-based ligands.[19] Moreover, NHC–metal complexes demonstrate a tight binding with various types of metals (a 1:1 ligand:metal ratio can be used with early and late transition metals) while phosphine-based ligands can dissociate from the metal, a characteristic that often necessitates the use of excess ligand in comparison to the metal.[20]

The design and synthesis of new chiral catalysts for enantioselective alkylations of activated olefins has been the subject of extensive studies in the Hoveyda laboratories. N-Heterocyclic carbenes have been the focal point for the design of new chiral catalysts.

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[17] "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100.

[18] For reviews on NHC-metal complexes, see: (a) "N-Heterocyclic Carbenes," Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162–2187. (b) "Chiral *N*-Heterocyclic Carbene-Transition Metal Complexes in Asymmetric Catalysis," Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951–961. (c) "Ag(I) N-Heterocyclic Carbenes Complexes: Synthesis, Structure, and Application," Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978–4008. (d) "N-Heterocyclic Carbenes in Late Transition Metal Catalysis," Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676. (e) "Understanding the M-(NHC) (NHC = N-Heterocyclic Carbene) Bond," Jacobsen, H.; Correa, A.; Poater, A.; Costablile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687–703. (f) "The Measure of All Rings–N-Heterocyclic Carbenes," Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940–6952.

[19] For representative studies that investigate the σ-donor abilities of phosphines vs. NHCs, see: (a) "Rhodium and Iridium Complexes of N-Heterocyclic Carbenes via Transmetalation: Structure and Dyamics," Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2003**, *22*, 1663–1667. (b) "Determination of N-Heterocyclic Carbene (NHC) Steric and Electronic Parameters using the [NHC)Ir$(CO)_2$Cl] System," Kelly, R. A., III; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202–210. (c) "^{13}C NMR Spectroscopic Determination of Ligand Donor Strengths Using N-Heterocyclic Carbene Complexes of Palladium(II)," Huynh, H. V.; Han, Y.; Jothibasu, R.; Yang, J. A. *Organometallics* **2009**, *28*, 5395–5404.

[20] *N-Heterocyclic Carbenes in Transition Metal Catalysis. Topics in Organometallic Chemistry 21;* Glorius, F., Ed.; Springer: New York, 2007.

The ease of synthesis of chiral variants as well as the new levels of reactivity displayed with those containing a bidentate linkage point (the point is discussed further below) makes the use of NHCs as ligands for metal-catalyzed enantioselective transformations attractive.

Inspired by the properties of NHCs which could potentially form an active Cu catalyst,[21] we investigated several bidentate NHC complexes (Chart 2.1) in promoting the Cu-catalyzed ECA of dialkylzinc reagents to γ-ketoesters (Table 2.5). The NHCs **2.20** and **2.21**, shown in Chart 2.1, were first probed in our group as ligands for Ru-catalyzed enantioselective olefin metathesis[22] and, subsequently, Cu-catalyzed enantioselective allylic alkylation.[23] The sulfonate-containing complex **2.22** was developed in our

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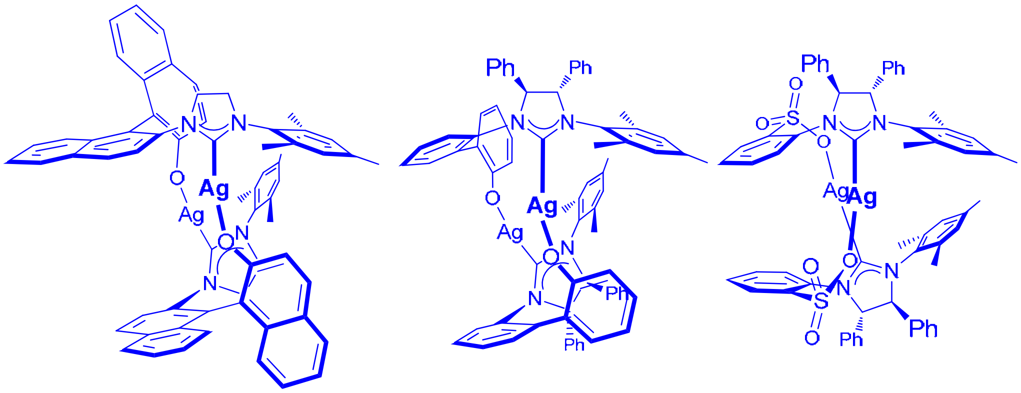
(21) In 1991, Woodward demonstrated how NHCs, as ligands for Cu, can greatly increase the rate of the conjugate addition reaction by acting as a strong σ-donor, stabilizing the Cu(III) intermediate, see: "Strong Ligand Accelerated Catalysis by an Arduengo-Type Carbene in Copper-Catalysed Conjugate Addition," Fraser, P. K.; Woodward, S. *Tetrahedron Lett.* **2001**, *42*, 2747–2749.

(22) For examples of the nobin-derived NHC complex (**2.20**) in Ru-catalyzed enantioselective olefin metathesis, see: (a) "A Recyclable Ru-Based Metathesis Catalyst," Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799. (b) "A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air," Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (c) "Chiral Ru-Based Complexes for Asymmetric Olefin Metathesis: Enhancement of Catalyst Activity through Steric and Electronic Modifications," Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003,** *125*, 12502–12508. (d) "Efficient Enantioselective Synthesis of Functionalized Tetrahydropyrans by Ru-Catalyzed Asymmetric Ring-Opening Metathesis/Cross-Metathesis (AROM/CM)," Gillingham, D. G.; Kataoka, O.; Garber, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004***,* *126*, 12288–12290. For examples of the binol-based NHC complex (**2.21**) in Ru-catalyzed enantioselective olefin metathesis, see: (e) "A Readily Available Chiral Ag-Based N-Hetereocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882. For a comparison study between Ru-based catalysts with ligands **2.20** and **2.21** and Mo-Based chiral catalysts, see: (f) "Comparison of Ru- and Mo-Based Chiral Olefin Metathesis Catalysts. Complementarity in Asymmetric Ring-Opening.Cross-Metathesis Reactions of Oxa- and Azabicycles," Cortez, G. A.; Baxter, C. A.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 2871–2874.

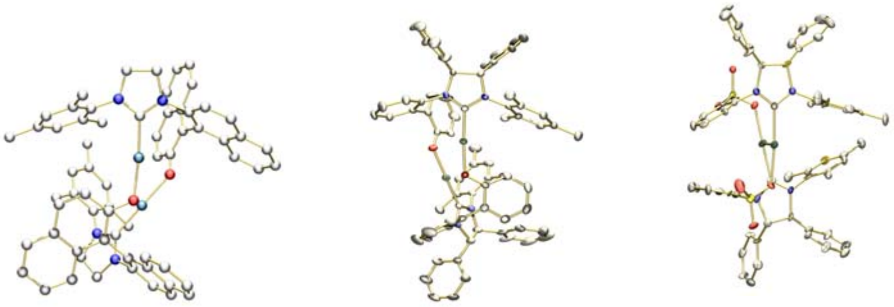
(23) For examples of the nobin-derived NHC complex (**2.20**) in Cu-catalyzed enantioselective allylic alkylation, see: (a) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131. (b) "Enantioselective Synthesis of Allylsilanes Bearing Tertiary and Quaternary Si-Substituted Carbons through Cu-Catalyzed Allylic Alkylations with Alkylzinc and Arylzinc Reagents," Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558. For examples of the binol-based NHC complex (**2.21**) in Cu-catalyzed enantioselective allylic alkylation, see: ref 22e and 23b. For examples of the nobin-derived NHC complex (**2.20**) in Mg-catalyzed enantioselective allylic alkylation, see: (c) "Lewis Base Activation of Grignard Reagents with *N*-Heterocyclic Carbenes. Cu-Free

laboratory as well; it was designed to be a less electron-donating ligand for a Ru-based complex (relative to the phenoxy-based linkages in NHCs **2.20** and **2.21**) to increase the activity of the propagating carbene. While attempts to prepare a Ru complex with sulfonate-complex **2.22** failed, Cu-based complexes with sulfonate-containing NHC **2.22** are exceptional catalysts for enantioselective alkylation and arylation reactions (discussed in Chapters 2, 3 and 4).

Chart 2.1. Chiral Bidentate Ag–NHC Complexes



2.20 **2.21** **2.22**



It is noteworthy that the studies carried out below are performed with the Ag–NHC complexes. The Ag–NHC complexes are air-stable pre-catalysts that can be prepared in quantitative yield from the corresponding imidazolinium salt by treatment with Ag_2O (see below for a detailed synthesis discussion). When the Ag–NHC complexes are exposed to a Cu salt (for example, $(CuOTf)_2$•C_6H_6), transmetallation occurs readily, forming the relatively air-sensitive Cu–NHC complex in situ along with

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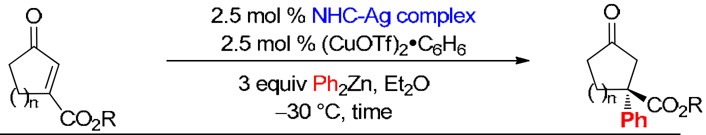
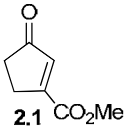
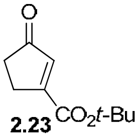
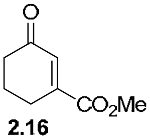
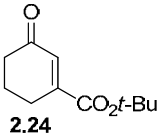
Catalytic Enantioselective Additions to γ-Chloro-α,β-Unsaturated Esters," Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604–15605.

AgOTf. The Ag–NHC complexes are also depicted as head-to-tail dimers, which is observed in both solution state (^{1}H NMR) and solid state (X-ray crystal structures, shown in Chart 2.1). However, we believe, due to steric considerations, the active Cu-catalyst is monomeric.

We began our investigations by examining the ability of the Cu–NHC complexes to promote ECA of Ph_2Zn to unsaturated five- and six-membered ring γ-ketoesters (Table 2.5). As shown in entries 1, 4, 7, and 10, additions promoted by the Cu–NHC complex of **2.20** do not lead to any product formation for the five-membered ring enones **2.1** and **2.23** (<2% conv) or <43% conv for the six-membered ring enones **2.16** and **2.24**. With phenoxy-containing complex **2.21**, the Cu-catalyzed ECA of Ph_2Zn to five-membered ring enones only leads to <26% conversion (entries 2 and 5) and, for the latter case, in a rather unselective process (62.5:37.5 er, entry 2). The six-membered ring enones are more reactive towards the phenoxy-based NHC–Cu catalyst; >98% conversions are achieved within 42 h and the products are obtained in 87:13–96.5:3.5 er (entries 8 and 11). Perhaps more notable are the yields of the conjugate addition products (57–82% yield). Claisen condensation products (e.g., **2.7**, Scheme 2.3) are not observed. Based on the aforementioned result, we believe the Claisen condensation product (metal enolate addition to ketoester **2.1**) is promoted by the peptide-based ligand through activations of the Cu– or Zn–enolate through complexation with the phosphine ligand. This ligand motif has been shown to promote Mukaiyama aldol reactions to α-keto esters.[13]

Table 2.5. ECAs Promoted by Cu(I)–NHC Complexes of Ph_2Zn to Unsaturated γ-Ketoesters[a]



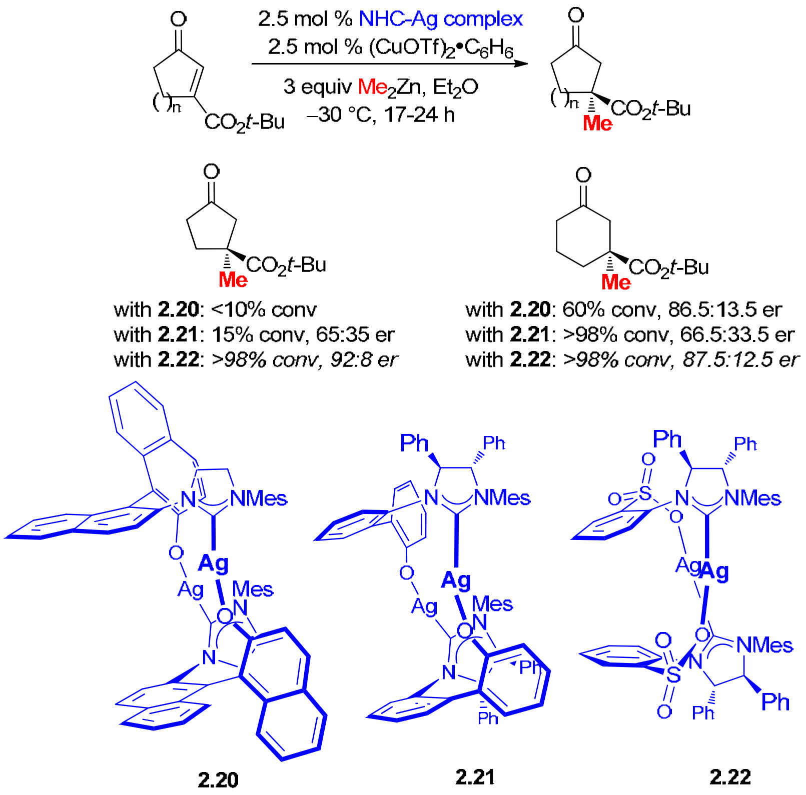
entry	substrate	NHC complex	time (h)	conv (%)[b]	yield (%)	er[c]
1	 **2.1**	**2.20**	15	<2	nd	nd
2		**2.21**	42	26	nd	62.5:37.5
3		**2.22**	42	>98	72	90.5:9.5
4	 **2.23**	**2.20**	15	<2	nd	nd
5		**2.21**	15	<2	nd	nd
6		**2.22**	42	>98	98	91:9
7	 **2.16**	**2.20**	21	43	nd	73:27
8		**2.21**	21	>98	82	96.5:3.5
9		**2.22**	18	>98	nd	41.5:58.5
10	 **2.24**	**2.20**	18	32	nd	58.5:41.5
11		**2.21**	42	>98	57	87:13
12		**2.22**	42	>98	90	41.5:58.5

[a]Reactions performed under a N_2 atmosphere. [b]Conversions determined by ^1H NMR and GLC analysis. [c]Determined by GLC analysis. nd = not determined.

The sulfonate-containing chiral NHC complex (**2.22**) promotes the Cu-catalyzed ECA with substantially higher conversions with the five-membered γ-ketoesters; as shown in entries 3 and 6, >98% conversion can be achieved at –30 °C in 42 h. The products are obtained in 72–98% yield and in up to 91:9 er. Reactions, promoted by the sulfonate-containing NHC ligand, are significantly more efficient than reactions promoted by chiral amino acid-based ligands (up to 36% yield, 96:4 er, Table 2.3). Although, the additions catalyzed by the NHC–Cu complex derived from **2.22** of Ph_2Zn to the six-membered rings are efficient (>98% conversion, entries 9 and 12), the products are obtained in lower selectivities than when the catalyst derived from **2.21** is used (41.5:58.5 er vs. 96.5:3.5–87:13 er).

A similar screen was performed for Me_2Zn addition to β-ester-containing five- and six-membered enones (Scheme 2.7).[24] With a similar trend to the results above, the sulfonate-containing NHC ligand promoted the Cu-catalyzed ECA with the highest efficiencies and selectivities, as compared to the phenoxy-based NHC ligands (from **2.20** and **2.21**). Complete conversions and selectivities from 87.5:12.5–92:8 are achieved.

Scheme 2.7. Cu-Catalyzed ECA of Me_2Zn to γ-Ketoesters: NHC Ligand Screen



with **2.20**: <10% conv
with **2.21**: 15% conv, 65:35 er
with **2.22**: *>98% conv, 92:8 er*

with **2.20**: 60% conv, 86.5:13.5 er
with **2.21**: >98% conv, 66.5:33.5 er
with **2.22**: *>98% conv, 87.5:12.5 er*

*2.3.a.2. Preparation of the Sulfonate-Containing Complex **2.22** and Comparison with the Phenoxy-Based NHC Complex **2.21***

Towards the synthesis of imidazolinium salt **2.29**, the requisite diamine **2.27** can be synthesized by two sequential Buchwald-Hartwig C–N cross coupling reactions[25] starting from commercially available *S*, *S*-diphenylethylenediamine (bromide **2.25** is prepared in one step,[26] Scheme 2.8). A second route was also developed that is more efficient (64% yield over two steps vs. 34% yield) but also only requires one Pd-mediated step (which can be costly if done on large scale).[27] The diamine **2.27** is synthesized by a Cu-catalyzed aminination procedure developed by Buchwald and co-workers[28] followed by a Pd-catalyzed C–N coupling reaction (Scheme 2.8). The next step is to prepare the imidazolinium salt **2.29**; we envisaged this process could occur through formation of the aminal followed by oxidation to afford the zwitterionic salt **2.29**.[29]

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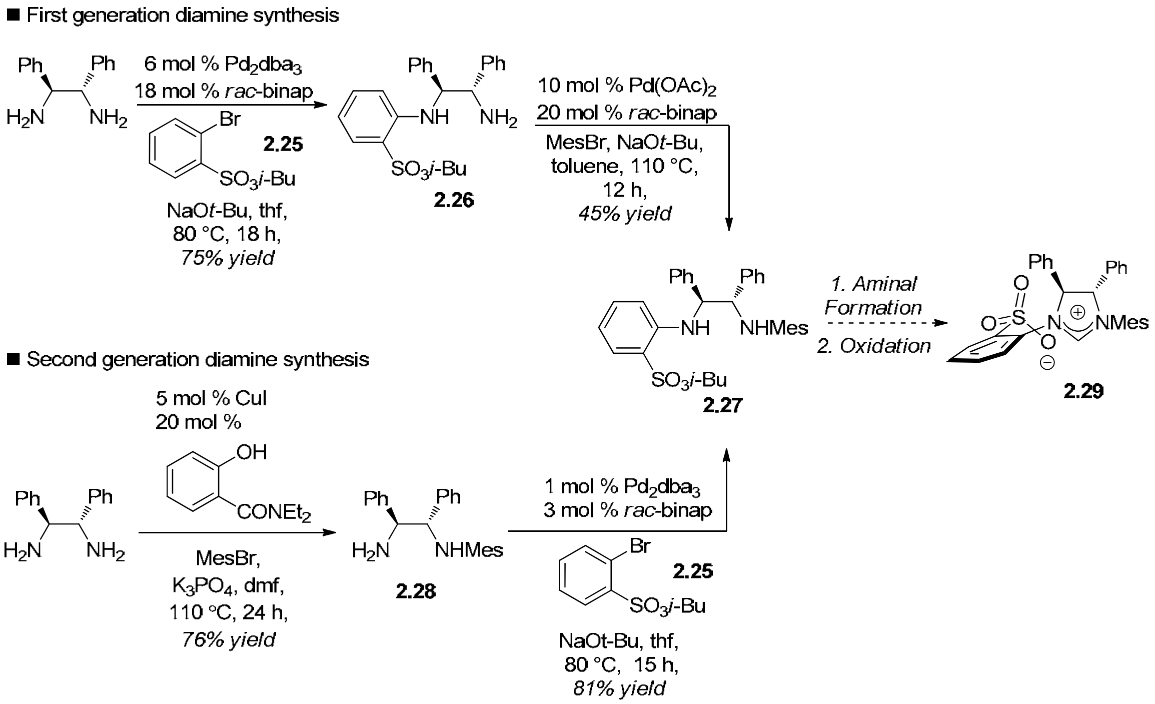
[24] Reactions performed by M. Kevin Brown.

[25] (a) "Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides," Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (b) "Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates," Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.*

Scheme 2.8. Synthesis of Diamine **2.27**


■ First generation diamine synthesis
Ph
Ph
H2N
NH2
6 mol % Pd2dba3
18 mol % rac-binap
Br
2.25
SO3i-Bu
NaOt-Bu, thf,
80 °C, 18 h,
75% yield
Ph
Ph
NH
NH2
SO3i-Bu
2.26
10 mol % Pd(OAc)2
20 mol % rac-binap
MesBr, NaOt-Bu,
toluene, 110 °C,
12 h,
45% yield
Ph
Ph
NH
NHMes
SO3i-Bu
2.27
1. Aminal Formation
2. Oxidation
Ph
Ph
O
O=S
N
⊕
NMes
O
⊖
2.29
■ Second generation diamine synthesis
5 mol % CuI
20 mol %
OH
CONEt2
Ph
Ph
H2N
NH2
MesBr,
K3PO4, dmf,
110 °C, 24 h,
76% yield
Ph
Ph
H2N
NHMes
2.28
1 mol % Pd2dba3
3 mol % rac-binap
Br
2.25
SO3i-Bu
NaOt-Bu, thf,
80 °C, 15 h,
81% yield

1998, *120*, 7369–7370. (c) "Palladium Catalysed Mono-*N*-Arylation of Enantiopure Diamines," Frost, C. G.; Mendonça, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1831–1834.

(26) (a) "Synthesis of Neophenylsulfonates using the Suzuki-Miyaura Reaction," Cho, C.-H.; Kim, C.-B.; Sun, M.; Park, K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1632–1636. (b) "Preparation of Unsymmetrical Terphenyls via the Nickel-Catalyzed Cross-Coupling of Alkyl Biphenylsulfonates with Aryl Grignard Reagents," Cho, C.-H.; Kim, I.-S.; Park, K. *Tetrahedron* **2004**, *60*, 4589–4599.

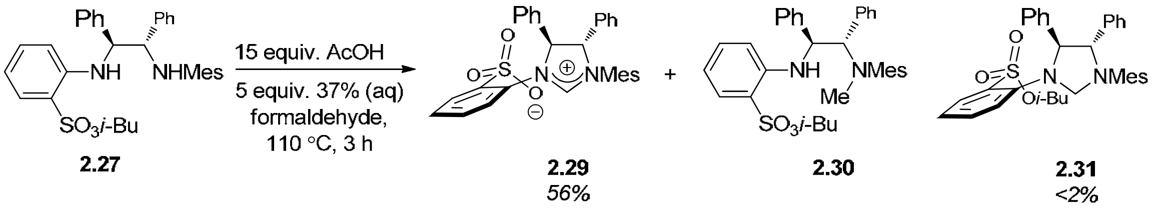
(27) This route was developed by Mikiko Akiyama.

(28) "Mild and Efficient Copper-Catalyzed Amination of Aryl Bromides with Primary Alkylamines," Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796.

(29) These investigations were carried out by Dr. Carl Baxter and M. Kevin Brown.

Following a procedure that Professors Roland, Alexakis and co-workers have developed for aminal formation (from 1,2-diamines containing N–alkyl substituents),[30] treatment of diamine **2.27** with AcOH and aqueous formaldehyde leads, not to the expected aminal **2.31**, but to a 58:42 mixture of desired imidazolinium salt **2.29** (56% yield after purification) and N–Me diamine **2.30** (<2% of the regioisomeric N–Me product was observed as determined by *n*O*e* analysis, Scheme 2.9). Several points are worthy of discussion related to Scheme 2.9. (1) When the cyclization is performed for 1 h (vs. 3 h in Scheme 2.9), a mixture of aminal, imidazolinium salt and N–Me diamine is present (33%, 27%, and 20%, respectively). Therefore, it is likely that the imidazolinium salt **2.29** and the N–methyl diamine **2.30** are derived from aminal **2.31**. (2) The aminal can be isolated in 72% yield when the cyclization is performed under dilute conditions (0.04 M solution in dioxane, 2% of imidazolinium salt **2.29** detected). (3) Furthermore, when aminal **2.31** is heated under acidic conditions (15 equiv of AcOH, no formaldehyde is used), a 1:1 ratio of **2.29** and **2.30** is afforded (80% conv).

Scheme 2.9. Cyclization of Diamine **2.27** Affords Unexpected Products



2.29:**2.30**:**2.31** = 58:42:<2

Based on the above studies, we proposed a mechanism to account for the products observed during the cyclization/oxidation process (Scheme 2.10). When diamine **2.27** is treated with formaldehyde and acetic acid, iminium **2.32** is formed, which is in equilibrium with aminal **2.31**. Elimination of a hydride on the methylene of **2.31**, assisted by the lone pair on nitrogen, affords reduction of iminium **2.32**, which leads to the formation of **2.30** and **2.33**. Elimination of 2-methylpropene from **2.33** affords the imidazolinium salt **2.29**. The mechanism outlined in Scheme 2.10 seems to account for the above observations: (1) When the cyclization is performed in a polar, dilute solvent (1,4-dioxane), only aminal **2.31** is observed, reducing the amount of hydride transfer due to increased solvation. (2) Based on the mechanism, a 1:1 mixture of **2.29** and **2.30** should be formed; however, **2.29** and **2.30** are observed as mixtures with an enrichment in the imidazolinium salt when the cyclization is performed in AcOH and formaldehyde (~60:40 **2.29**:**2.30**). However, when isolated and purified aminal **2.31** is treated with AcOH directly, a 1:1 mixture of **2.29** and **2.30** is formed. Therefore, we believe that the excess formaldehyde in solution (5 equiv used) is acting as a reducing agent for aminal **2.31**.

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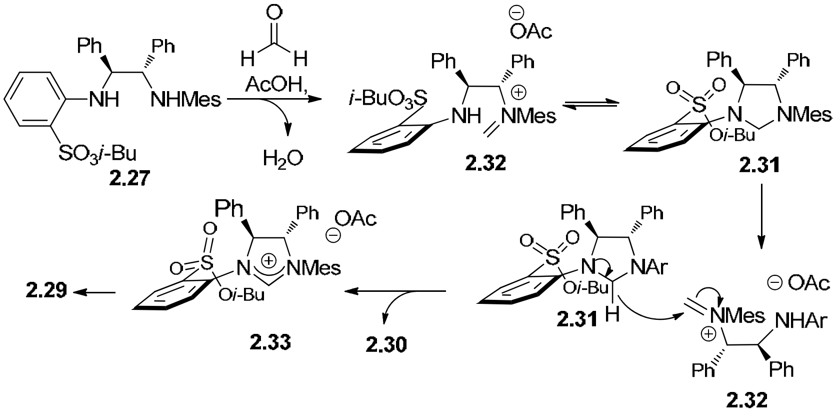
[30] (a) "A Practical and Efficient Synthesis of Enantiomerically Pure Di-*tert*-Butyl-Ethanediamine," Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228–230. (b) "Unusually Facile Palladium Catalysed Oxidation of Imidazolidines and Oxazolidines," Alexakis, A.; Aujard, I.; Pytkowicz, J.; Roland, S.; Mangeney, P. *J. Chem. Soc., Perkin Trans. 1*, **2001**, *631*, 949–951. (c) "Synthesis of Chiral Silver(I) Diaminocarbene Complexes from (*R*, *R*)-4,5-Di-*tert*-Butylimidazoline," Pytkowicz, J.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2001**, 157–163.

Scheme 2.10. Mechanism of the Cyclization of Diamine **2.27** Involving a Hydride Transfer



With a better understanding of the reaction mechanism, we sought to improve the yield for the formation of the imidazolinium salt by using a hydride acceptor that could compete with iminium **2.32**. Accordingly, when the cyclization is performed in the presence of Eschenmoser's salt (in place of formaldehyde),[31] the imidazolinium salt is formed in 79% yield (<2% N–Me amine **2.30** formed (Scheme 2.11). Thus, the sterically

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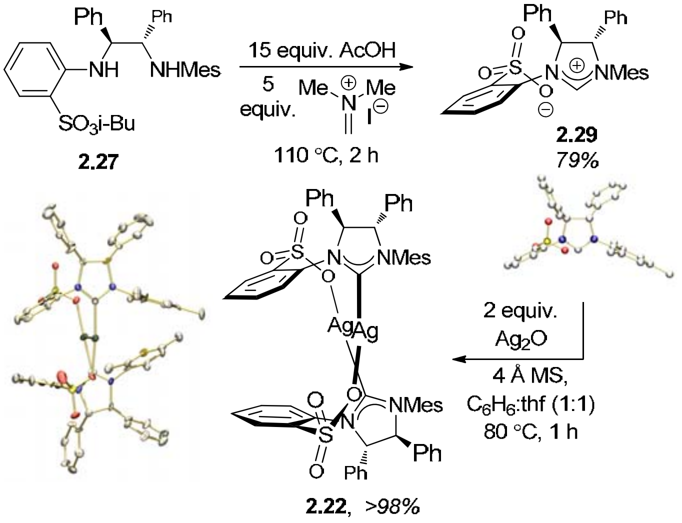
(31) "Dimethyl(methylene)ammonium Iodide," Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Eng.* **1971**, *10*, 330–331.

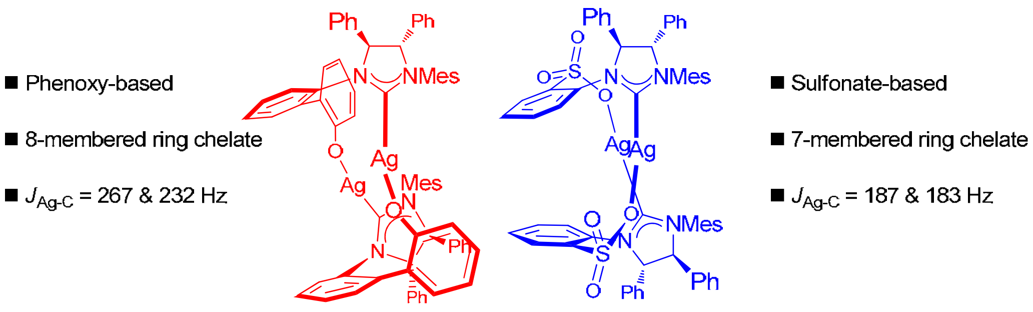
less hindered Eschenmoser's salt effectively competes with iminum **2.32**. Treatment of imidazolinium salt **2.29** with Ag_2O affords Ag–NHC complex **2.22** in >98% yield.

Scheme 2.11. Improved Synthesis of Imidazolinium Salt **2.29** and Preparation of Ag–NHC Complex **2.22**



With an efficient route to access the new sulfonate-containing NHC–Ag complex outlined, we next sought to understand why sulfonate-containing NHC **2.22** is significantly more active in Cu-catalyzed ECAs in some cases compared to the phenoxy-based NHC complexes **2.20** and **2.21** (cf. Table 2.5 and Scheme 2.7). Since the Cu(I)–NHC complexes derived form **2.21** and **2.22** are unstable, we were not able to study them in either solid or solution states; we instead analyzed the corresponding Ag–NHC complexes (Scheme 2.12). Thus, it is important to note that the values discussed below relate to the Ag complexes and thus conclusions on the characteristics of the Cu–NHC complexes are based on inferences from this data. The most apparent difference between the two complexes is the nature of the bidentate linkages; **2.21** contains a phenoxy-based binding component while complex **2.22** has a less basic sulfonate unit. The electronic difference between the two groups can perturb the monomeric Cu(I) complex. For example, Nakamura and co-workers have suggested, based on theoretical calculations, that an electron-withdrawing substituent on copper can help facilitate reductive elimination of the Cu(III) intermediate in the catalytic cycle (see Scheme 2.13 for a general mechanistic pathway for a Cu-catalyzed conjugate addition reaction).[32]

Scheme 2.12. Comparison Between the Phenoxy-based and Sulfonate-based NHC–Ag Complexes


■ Phenoxy-based
■ 8-membered ring chelate
■ $J_{Ag\text{-}C}$ = 267 & 232 Hz
Ph
Ph
N
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph
Ph
O
O=S
N
NMes
O
AgAg
O
O
NMes
N
S
O
Ph
Ph
■ Sulfonate-based
■ 7-membered ring chelate
■ $J_{Ag\text{-}C}$ = 187 & 183 Hz

2.21 **2.22**

Moreover, if the active catalyst is a monomeric Cu complex, the bidentate chelate in **2.21** and **2.22** forms rings of different size. The phenoxy-based carbene has an eight-membered ring size while the sulfonate-containing ligand would have a more geometrically constrained seven-membered ring; the latter structural attribute is thought to play an important role in what we surmise is the active catalyst (discussed in depth below). Another difference between the two catalysts is found in the respective C–Ag coupling constants from the ^{13}C NMR spectra. In the phenoxy-based complex **2.21**, the coupling constants are 267 and 232 Hz and for the sulfonate-containing complex **2.22**, they are appreciably smaller (187 and 183 Hz). The coupling constants between Ag and C can be a measure of the distance between the two nuclei. The larger the coupling constant, the smaller the distance between the two nuclei in solution state. The large coupling constant of phenoxy-containing NHC **2.21** can be interpreted to mean that the

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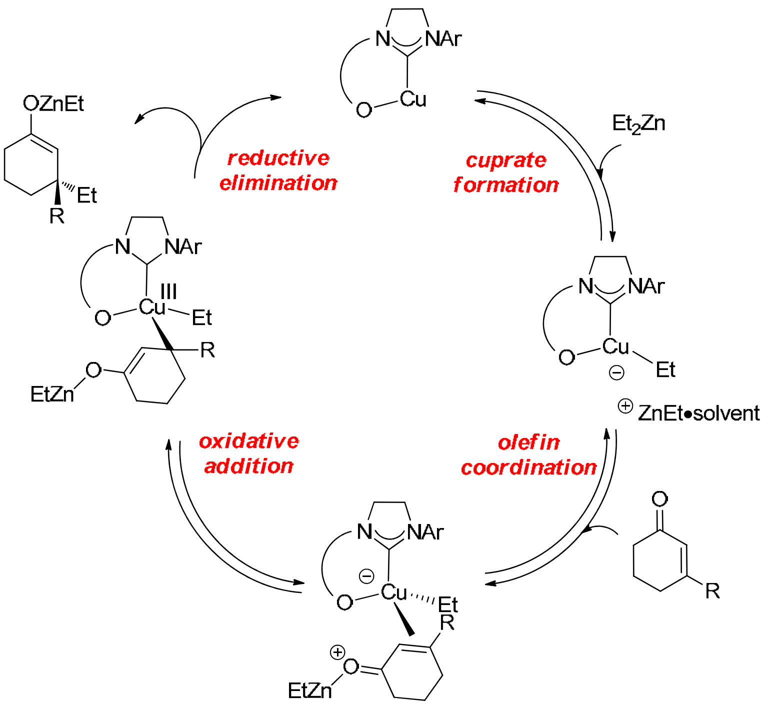
(32) (a) "Complexation of Lewis Acid with Trialkylcopper(III): On the Origin of BF_3-Acceleration of Cuprate Conjugate Addition," Nakamura, E.; Yamanaka, M.; Mori, S. *J. Am. Chem. Soc.* **2000**, *122*, 1826–1827. (b) "Thermodynamic and Kinetic Control in Selective Ligand Transfer in Conjugate Addition of Mixed Organocuprate Me(X)CuLi," Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 4697–4706.

NHC is a stronger donor than that on sulfonate-containing **2.22**.[33] This, again, is data that we are correlating from a dimeric Ag–NHC complex to a monomeric Cu–NHC complex.

Scheme 2.13. General Mechanistic Pathway for Cu–NHC-Catalyzed Conjugate Addition of Et_2Zn to an Enone



The differences between the two NHC ligands lie not only in their electronic attributes but also in their structure aspects. For example, if electronics were the only reason for the high activity and selectivity in the Cu-catalyzed ECA reaction, then a NHC that contains a more electron-withdrawing unit than a phenoxide should fare well. With this in mind, carboxylate-containing NHC complex **2.34** was prepared[34] and investigated in the Cu-catalyzed ECA reaction (Scheme 2.14). The Cu–NHC complex, prepared in situ from **2.34**, promotes the ECA of dimethylzinc to enone **2.1** affording **ent-2.8** in 71% conv and 60.5:39.5 er [compared with **2.21** (15% conv, 65:35 er) and **2.22** (>98% conv, 92:8 er)]. The lower efficiency observed with the carboxylate-containing ligand is in itself not particularly surprising since a carboxylate group is not as acidic as a sulfonate,

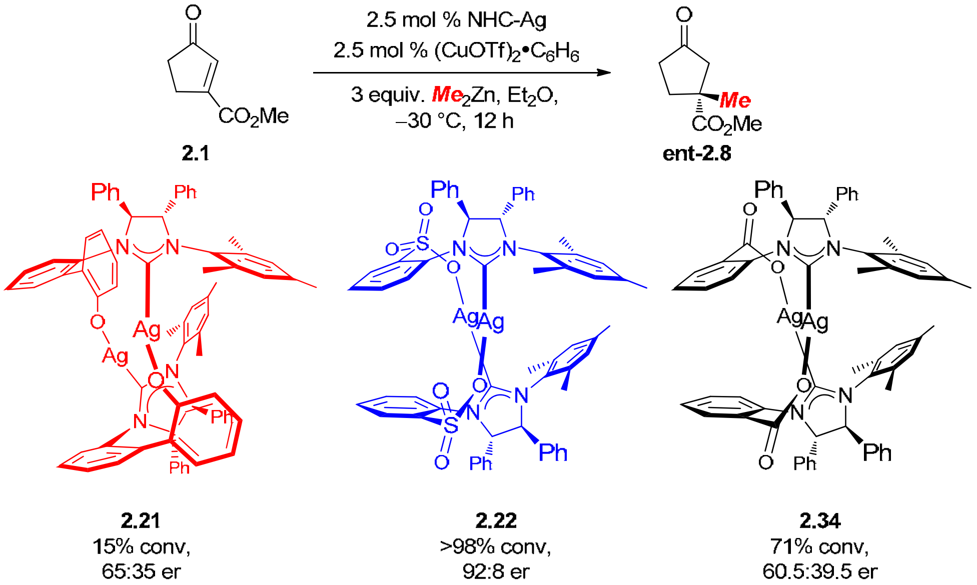
---

(33) Analysis of the X-ray crystal structures of complexes **2.21** and **2.22** reveals that the Ag-$C_{carbene}$ bond lengths are similar (2.068 and 2.087 Å, respectively).

(34) Kang-sang Lee prepared NHC-Ag complex **2.32**.

if the activity of the catalyst was caused entirely from the electronic component.[35] Perhaps more enlightening is that the selectivity of the product is notably lower (60.5:39.5 er) than the selectivity observed when the Cu–NHC catalyst prepared from **2.22** is used (92:8 er). This suggests that the two oxygen ligands (positioned pseudo-axial and -equatorial) on the sulfonate-containing ligand may play an important role in the catalytic cycle; this attribute is missing entirely in the phenoxy-based ligand and the pseudo-equatorial oxygen is omitted in the carboxylate-containing ligand. The difference in reactivity may allude to the equatorial oxygen of the sulfonate serving as a chelation site (a potential bifunctional catalyst).

Scheme 2.14. Comparison of Phenoxy-, Sulfonate- and Carboxylate-Containing NHC–Cu Catalysts


O
CO2Me
2.1
2.5 mol % NHC-Ag
2.5 mol % (CuOTf)2•C6H6
3 equiv. Me2Zn, Et2O,
–30 °C, 12 h
O
Me
CO2Me
ent-2.8
Ph
Ph
N
N
O
Ag
Ag
O
N
N
Ph
Ph
Ph
Ph
O
O=S
O
N
N
Ag
Ag
O
S
O
N
N
O
Ph
Ph
Ph
Ph
O
O
N
N
Ag
Ag
O
N
N
O
Ph
Ph
2.21
15% conv,
65:35 er
2.22
>98% conv,
92:8 er
2.34
71% conv,
60.5:39.5 er

At this time, we were fairly confident that the monomeric Cu–NHC complex derived from **2.21** is bidentate (dative bond between the phenoxy and Cu, Scheme 2.15); however, we were unclear if the sulfonate in **2.22** would be capable of forming a dative

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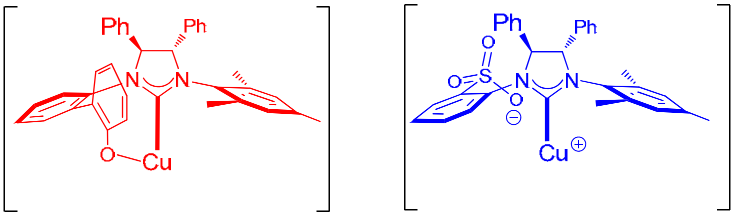
(35) For example, the pka of benzoic acid is 11.1, the pka of methylsulfonic acid is 1.6, and the pka of phenol is 18 (all values are in dmso). For original references, see: (a) "Ion-pair Association Constants in Dimethyl Sulfoxide," Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305. (b) "Nitrogen Acids. 1. Carboxamides and Sulfonamides," Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507–2508. (c) "Acidities and Hydrogen Bonding of Phenols in Dimethyl Sulfoxide," Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424–1427.

bond with copper. Perhaps, the complex existed as a zwitterionic salt (negatively charged sulfonate, Cu(I) formally cationic, Scheme 2.15). Based on (hand) molecular models, the bidentate Cu–NHC complex derived from **2.22** seems highly strained and unstable.

Scheme 2.15. Putative Cu–NHC Complexes Derived from **2.21** and **2.22**



2.3.a.3. Scope of Cu-Catalyzed ECA of Alkyl-and Arylzinc Additions to γ-Ketoesters Promoted by a Sulfonate-Containing NHC Ligand

With reactions promoted by the Cu–NHC catalyst, prepared in situ from a Cu(I) salt and complex **2.22**, a variety of cyclic ketones with a carboxylic ester-containing all-carbon quaternary stereogenic centers can be prepared with high enantiomeric purity (Scheme 2.16). Through optimization of the solvent medium, the reactions shown in Scheme 2.16 are performed in *t*-BuOMe (vs. Et_2O in Table 2.7); the rate of the enantioselective additions is slightly slower in *t*-BuOMe than with Et_2O but a sizeable increase in enantioselectivity is observed in *t*-BuOMe. For example, the product **2.36** is formed in >98% conversion after 42 h and in 95:5 er with *t*-BuOMe; when the reaction is performed in Et_2O, >98% conversion is observed after 15 h and **2.36** is afforded in 92:8 er. A few other observations are of note. (1) Both five- and six-membered unsaturated γ-ketoesters are competent partners in the Cu-catalyzed ECA reaction (53–98% yield, 80:20–97.5:2.5 er, Scheme 2.16). This marked the first general method for ECA of a nucleophile to β-substituted cyclopentenones. Additions to the corresponding seven-membered ring enones, however, are less efficient (**2.43–2.45**, Scheme 2.16); Cu-catalyzed ECA of Et_2Zn to a β-ester cycloheptenone affords **2.43** in >98% conv in 24 h (69% yield) in 77:23 er, which is generally a much lower selectivity observed than those observed for additions to the five- and six-membered ring enones. Moreover, enantioselective additions of Me_2Zn and Ph_2Zn to the seven-membered ring enone leads to <2% conversion. One explanation of the reduced electrophilicity of the seven-membered ring γ-ketoester has been put forth by Hirsch and co-workers;[36] medium ring enones bearing an electron withdrawing β-substituent tends to have reduced (and sometimes isomerizes to the β,γ-position) conjugation between the ketone and the olefin. (2) Primary alkyls (methyl, ethyl, and long chained alkyl groups), secondary alkyls (*i*-propyl), and aryl groups can be efficiently added to the trisubstituted enones. (3) Both methyl and sterically hindered *t*-butyl carboxylic esters can be used. (4) In all cases studied, except for Ph_2Zn addition to the six-membered ring γ-ketoesters (**2.37** and **2.38**), sulfonate-containing NHC–Cu complex (prepared in situ from **2.22**) delivers the products with the highest selectivities.

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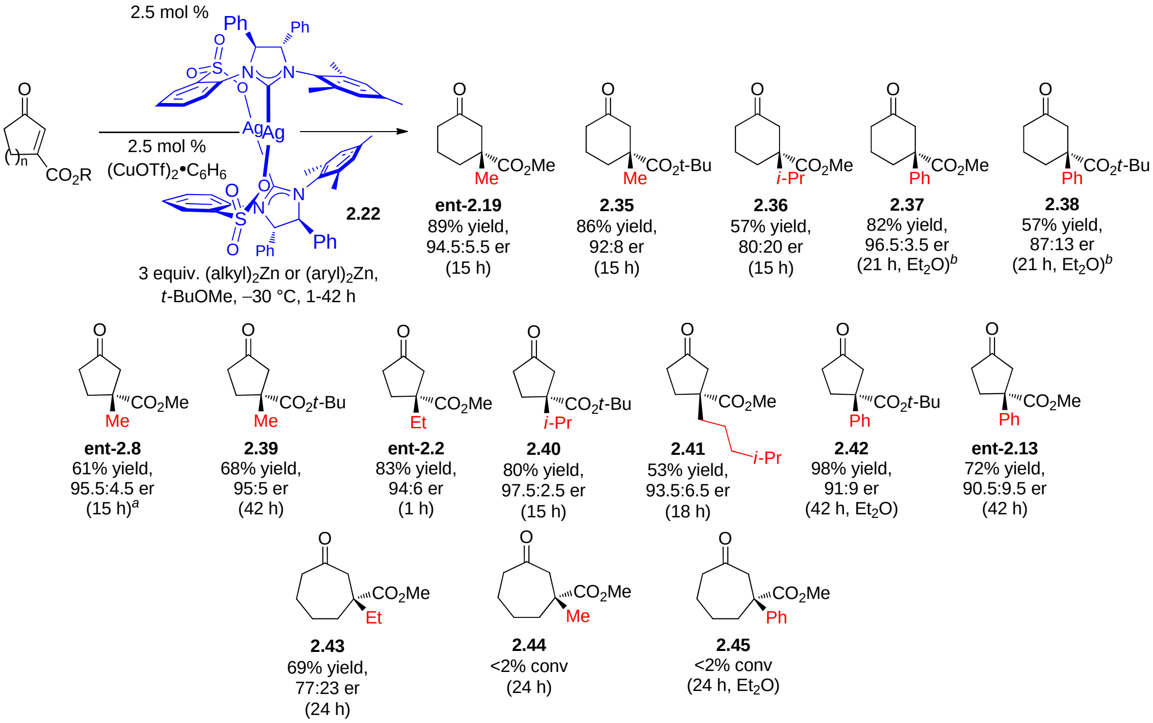
(36) (a) "Medium-Ring Systems. 5. Synthesis and Base-Catalyzed Isomerizations of Medium-Ring Cycloalkenones with Electron-Withdrawing Substituents," Mease, R. C.; Hirsch, J. A. *J. Org. Chem.* **1984**, *49*, 2925–2937. (b) "Medium-Ring Systems. 6. Synthesis and Isomerizations of Medium-Ring 3-Methylenecycloalkanones and 3-Methylcycloalkenones," Eskola, P.; Hirsch, J. A. *J. Org. Chem.* **1997**, *62*, 5732–5742.

Scheme 2.16. Substrate and Nucleophile Scope for Cu-Catalyzed ECA of Organozinc Reagents to γ-Ketoesters


2.5 mol %
2.22
2.5 mol %
(CuOTf)2•C6H6
3 equiv. (alkyl)2Zn or (aryl)2Zn,
t-BuOMe, –30 °C, 1-42 h
ent-2.19
89% yield,
94.5:5.5 er
(15 h)
2.35
86% yield,
92:8 er
(15 h)
2.36
57% yield,
80:20 er
(15 h)
2.37
82% yield,
96.5:3.5 er
(21 h, Et2O)b
2.38
57% yield,
87:13 er
(21 h, Et2O)b
ent-2.8
61% yield,
95.5:4.5 er
(15 h)a
2.39
68% yield,
95:5 er
(42 h)
ent-2.2
83% yield,
94:6 er
(1 h)
2.40
80% yield,
97.5:2.5 er
(15 h)
2.41
53% yield,
93.5:6.5 er
(18 h)
2.42
98% yield,
91:9 er
(42 h, Et2O)
ent-2.13
72% yield,
90.5:9.5 er
(42 h)
2.43
69% yield,
77:23 er
(24 h)
2.44
<2% conv
(24 h)
2.45
<2% conv
(24 h, Et2O)

[a] Reaction was performed with 5 mol % catalyst and 6 equiv. of Me_2Zn.
[b] Ag-NHC **2.21** was used (2.5 mol %).

While the method developed for Cu-catalyzed ECA of diorganozinc reagents to unsaturated cyclic γ-ketoesters allows access to products efficiently, only moderate selectivity is achieved in some cases. For example, Cu-catalyzed ECA of Et_2Zn to **2.16** only furnishes ketone **ent-2.7** with 75.5:24.5 er (Scheme 2.17). In an attempt to increase the enantioselectivity, we examined the reaction in the presence of a radical scavenger.[37] If the low selectivity is a result of an uncatalyzed alkylation occurring from the presence of adventitious radicals,[38] a scavenger should minimize the adverse effect of this

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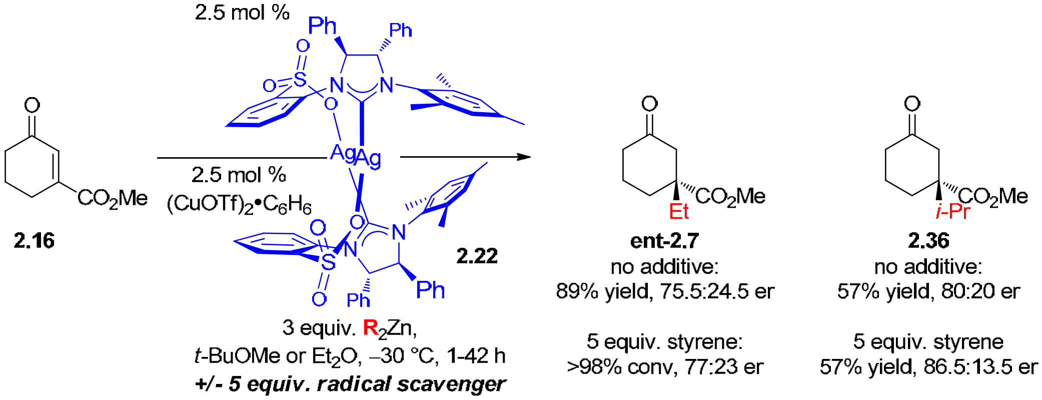
(37) "Asymmetric Conjugate Addiition to α-Halo Enones: Dramatic Effect of Styrene on the Enantioselectivity," Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600–7603.

(38) Feringa and co-workers have proposed that alkyl radicals could arise from the reaction of advantageous oxygen and Et_2Zn. The resulting zinc peroxide can catalyze nonstereoselective conjugate additions. For a proposed mechanism, see: "Remarkable O_2-Effect in 1,4-Additions of Diethylzinc to 6-Acyloxy-2*H*-pyran-3(6*H*)-ones and 6-Alkoxy-2*H*-pyran-3(6*H*)-ones," van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593–1595.

background reaction. As illustrated in Scheme 2.17, addition of 5 equiv. of styrene leads to minimal change in enantioselective formation of **ent-2.7** (75.5:24.5 er vs. 77:23 er). However, shown in Scheme 2.17, ketone **2.36** is afforded with an increased enantioselectivity with the addition of 5 equiv. of styrene (from 80:20 er to 86.5:13.5 er). Further increasing the equivalents of styrene (10 equiv) did not lead to an appreciable increase in selectivity (86:14 er).

Scheme 2.17. Cu-Catalyzed ECA of Alkylzinc Reagents to Unsaturated Cyclic γ-Ketoesters with a Radical Scavenger Additive



3 equiv. R_2Zn,
t-BuOMe or Et_2O, –30 °C, 1-42 h
+/- 5 equiv. radical scavenger

ent-2.7
no additive:
89% yield, 75.5:24.5 er

5 equiv. styrene:
>98% conv, 77:23 er

2.36
no additive:
57% yield, 80:20 er

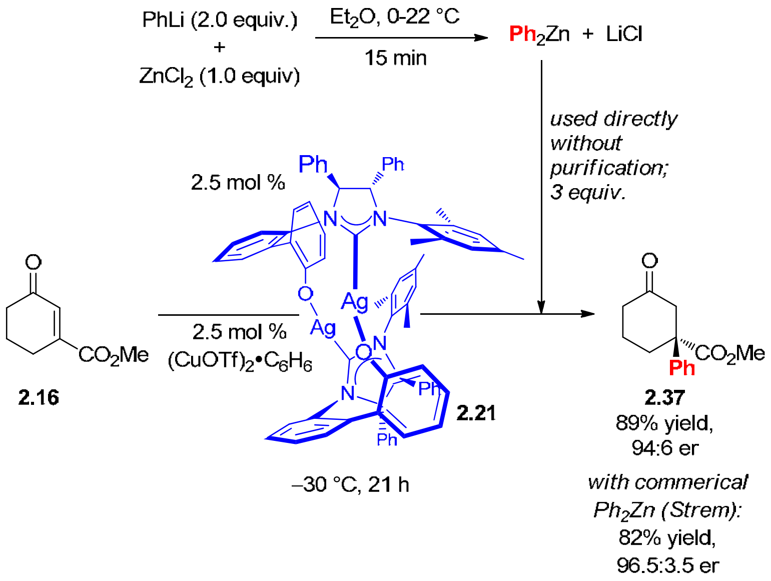
5 equiv. styrene
57% yield, 86.5:13.5 er

In an effort to render our protocol more practical, we set out to prepare the expensive diphenylzinc ($13,859/mol, Strem 2011) in situ. Inspired by a publication by Feringa and co-workers[39] and illustrated in Scheme 2.18, we are able to prepare diphenylzinc in situ from $ZnCl_2$ and PhLi in Et_2O. Using the freshly prepared Zn solution in the ECA reaction, product **2.37** can be prepared with the similar efficiency and selectivity as the reaction employing purchased Ph_2Zn (89% yield, 94:6 er vs. 82% yield, 96.5:3.5 er). This procedure negates isolation and purification of Ph_2Zn since the solution of Ph_2Zn can be used directly.

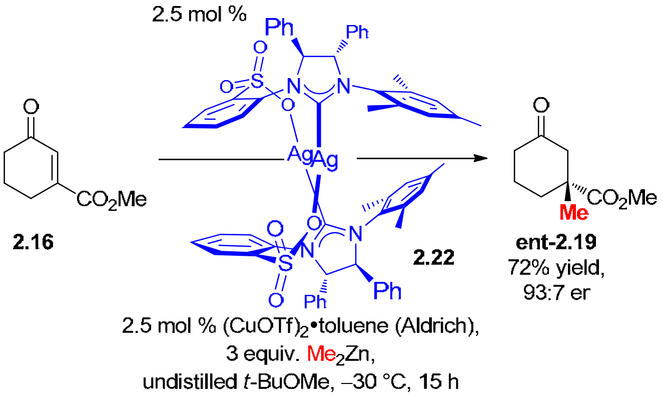
---

(39) (a) "Highly Enantioselective Cu-Catalysed Asymmetric 1,4-Addition of Diphenylzinc to Cyclohexenone," Peña, D.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836–1837. (b) "From Aryl Bromides to Enantioenriched Benzylic Alcohols in a Single Flask: Catalytic Asymmetric Arylation of Aldehydes," Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175–4178.

Scheme 2.18. In Situ Preparation of Ph_2Zn and its use in the Cu-Catalyzed ECA Reaction


PhLi (2.0 equiv.)
+
$ZnCl_2$ (1.0 equiv)
Et_2O, 0-22 °C
15 min
Ph_2Zn + LiCl
used directly without purification; 3 equiv.
2.5 mol %
Ph
Ph
N
N
O
Ag
Ag
O
N
N
Ph
Ph
2.21
2.5 mol %
$(CuOTf)_2•C_6H_6$
–30 °C, 21 h
O
CO_2Me
2.16
O
CO_2Me
Ph
2.37
89% yield,
94:6 er
with commerical Ph_2Zn (Strem):
82% yield,
96.5:3.5 er

The Cu-catalyzed ECA method is practical as rigorously dry and degassed materials do not have to be used. As depicted in eq (5), the reaction can be set up without the use of a N_2-filled glove box, with a commercial grade copper salt in undistilled solvent and the product is obtained with analogous efficiency and selectivities as the reaction performed under anhydrous conditions [72% yield, 93:7 er vs. 89% yield, 94.5:5.5 er, eq (5)].

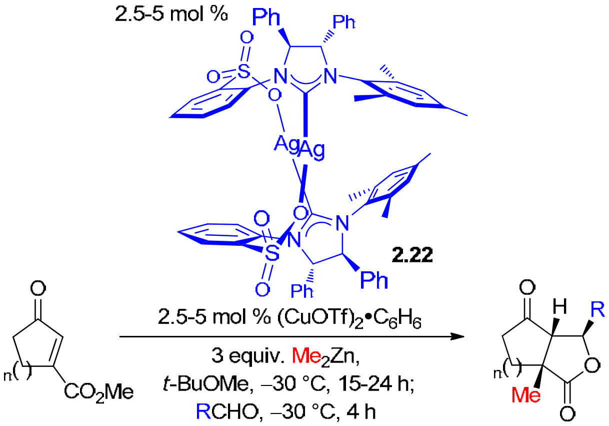

2.5 mol %
Ph
Ph
O
O=S
N
N
O
Ag
Ag
O
O
S
O
N
N
Ph
Ph
2.22
O
CO_2Me
2.16
O
CO_2Me
Me
ent-2.19
72% yield,
93:7 er
2.5 mol % $(CuOTf)_2$•toluene (Aldrich),
3 equiv. Me_2Zn,
undistilled *t*-BuOMe, –30 °C, 15 h

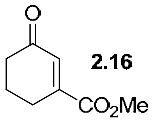
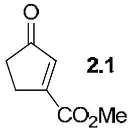
(5)

2.3.a.4. Functionalizations of the Enantiomerically Enriched Ketoesters Containing an All-Carbon Quaternary Stereogenic Centers

An attractive value of the enantiomerically enriched cyclic ketoesters, which we can prepare with high efficiency with the Cu-catalyzed ECA protocol, is the presence of the carboxylic ester moiety, a versatile handle for further manipulations. In light of the expanded substrate scope, provided by the NHC-based ligands, a tandem method for the synthesis of bicyclic lactones, through ECA followed by intermolecular aldol/esterification, is possible. When the Cu-catalyzed ECA is quenched with aromatic aldehydes, lactones are prepared with high enantiomeric and diastereomeric purity (up to 94.5:5.5 er and >30:1 dr, Table 2.6, entries 1 and 3). Aliphatic aldehydes are efficient in the cyclization; however, diastereomeric ratios are diminished (2–5:1 dr). As discussed above (cf. equation 2), we propose that the initial aldol reaction is not highly diastereoselective but the process is reversible (aldol/retroaldol) such that the reaction equilibrates to the thermodynamically preferred diastereomer of the cyclized product.

Table 2.6. One-Pot Formation of Bicyclic Lactones[a]



entry	substrate	aldehyde (2 equiv.)	product	catalyst loading (mol %)	yield[b] (%)	dr[c]	er[d] (%)
1	 **2.16**	PhCHO	**2.46a**	2.5	82	17:1	94.5:5.5
2		*n*-hexanal	**2.46b**	2.5	76	5:1	94.5:5.5
3	 **2.1**	PhCHO	**2.12**	5	86	>30:1	94:6
4		*n*-hexanal	**2.47**	5	76	2:1	95.5:4.5

[a]Reaction performed under N_2 atm. All reactions proceed to >98% conv. [b]Yields of purified products. [c]Determined by 400 MHz ^{1}H NMR analysis of the unpurified mixture. [d]Determined by GLC analysis, see the experimental section for details.

In the synthesis of (+)-eremantholide A by Tadano and co-workers (the enantiomer of (+)-eremantholide A is shown in Scheme 2.19), the bicyclic lactone intermediate **2.49** was prepared in 17 steps.[40] The tandem ECA/cyclization process could significantly streamline the synthesis of the natural product. For example, we have prepared bicyclic lactone **2.48** in 64% yield (2:1 dr, 95.5:4.5 er) in only two steps (synthesis of **2.1**[12] and tandem ECA/cyclization).

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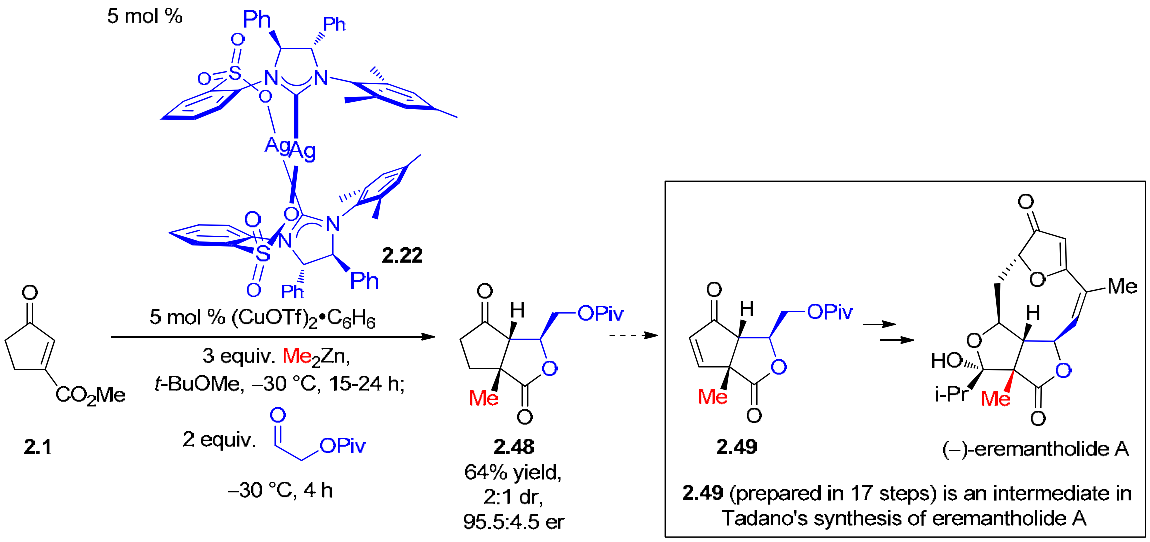
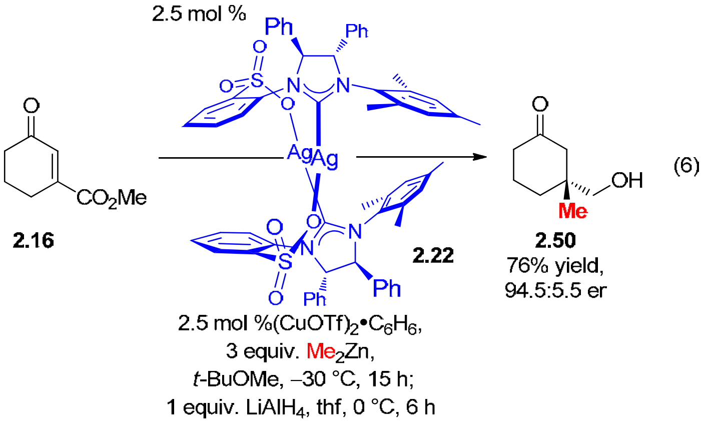
(40) "Novel Total Synthesis of (+)-Eremantholide A," Takao, K-i.; Ochiai, H.; Yoshida, K-i.; Hashizuka, T.; Koshimura, H.; Tadano, K-i; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179–8193.

Scheme 2.19. Preparation of Bicyclic Lactone: Potential Intermediate in the Synthesis of Eremantholide A


5 mol %
2.22
5 mol % (CuOTf)2•C6H6
3 equiv. Me2Zn,
t-BuOMe, –30 °C, 15-24 h;
2 equiv. OPiv
–30 °C, 4 h
2.1
2.48
64% yield,
2:1 dr,
95.5:4.5 er
2.49
(–)-eremantholide A
2.49 (prepared in 17 steps) is an intermediate in Tadano's synthesis of eremantholide A

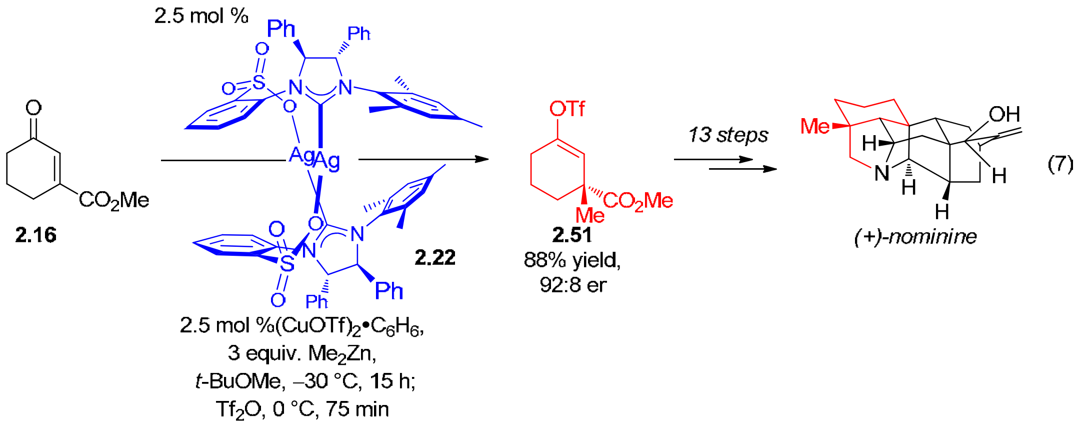
The preparation of enantiomerically enriched ketoalcohol **2.50** can be accomplished by chemoselective reduction of the ester by masking the more electrophilic ketone as the Zn–enolate. As illustrated in eq. 6, Cu-catalyzed ECA of Me_2Zn to **2.16** followed by treatment with $LiAlH_4$ in thf affords ketoalcohol **2.50** in 76% yield (94.5:5.5 er). The preparation of **2.50** otherwise would require a protection/deprotection sequence of the more reactive ketone moiety.[41]


2.5 mol %
2.22
2.16
2.50
76% yield,
94.5:5.5 er
(6)
2.5 mol %(CuOTf)2•C6H6,
3 equiv. Me2Zn,
t-BuOMe, –30 °C, 15 h;
1 equiv. LiAlH4, thf, 0 °C, 6 h

---

(41) For representative functionalizations of enolates derived from ECA processes, see: "Tandem Asymmetric Conjugate Addition–Silylation of Enantiomerically Enriched Zinc Enolates. Synthetic Importance and Mechanistic Implications," Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835–3837.

Professor David Gin and co-workers have employed the Cu-catalyzed ECA procedure toward the enantioselective synthesis of the naturally occurring alkaloid (+)-nominine (eq 7).[42] In the synthesis, they prepare enol triflate **2.51** through Cu-catalyzed ECA of Me_2Zn to enone **2.16**, promoted by the Cu–NHC catalyst generated from **2.22**, followed by trapping the Zn–enolate with Tf_2O. The enol triflate **2.51** is elaborated to (+)-nominine in 13 steps (total number of steps in the synthesis is 15). Further demonstrating the practicality of the current protocol as it can be performed on large scale without significant loss of efficiency or selectivity, and the products obtained are synthetically valuable.



2.3.b. Cu-Catalyzed ECA of Organozinc Reagents to β-Alkyl- and Aryl-Substituted Enones

Inspired by the unique reactivity that the sulfonate-containing NHC–Cu displays with β-ester-containing enones, we began to investigate a wider scope of α,β-unsaturated enones. We began by investigating the ECAs, promoted by in situ prepared Cu–NHC complexes, of organozinc reagents with β-substituted cyclopentenones, which, as discussed above, are often challenging substrates for ECA reactions.[43] Highlighting this difficultly, the Cu-catalyzed ECA, promoted by the Cu–NHC complex derived from **2.21**, of Et_2Zn or Ph_2Zn to 3-butylcyclopentenone leads to <2% conv (entries 1–2, Table 2.7).

---

[42] "Asymmetric Synthetic Access to the Hetisine Alkaloids: Total Synthesis of (+)-Nominine," Peese, K. M.; Gin, D. Y. *Chem. Eur. J.* **2008**, *14*, 1654–1665.

[43] These studies were investigated by Mikiko Akiyama.

In contrast, when the enantioselective addition is promoted by the sulfonate-containing Cu–NHC complex (derived from **2.22**), the addition proceeds to 30% conv (20% yield) and the product is obtained in 97.5:2.5 er (entry 2); longer reaction times do not improve conversions which is probably due to decomposition of the Cu–NHC complex. Although this result does not reach synthetically valuable levels of efficiency, it demonstrates that this class of enones is not especially prone to undergo ECA yet the sulfonate-containing Cu–NHC complex in these cases is more active than the complex derived from **2.21** and provides products with high enantiomeric purities. Additional organozinc nucleophiles can be utilized in NHC–Cu catalyzed ECA to unactivated enones. Arylzinc reagents are competent partners for the Cu-catalyzed ECA to β-substituted cyclopentenones (entries 4, 6–9); products are obtained in 35–71% yield and 95:5–97:3 er. Long-chained alkyl groups at the β-position of the enone are tolerated affording products in up to 97:3 er; although the efficiency of the reaction decreases (i.e., R = *n*-Bu: 30% conv vs R = Me: 70% conv, entries 3 and 5). Despite the low efficiencies in some cases, the yields of the products are similar to the observed conversions.[44]

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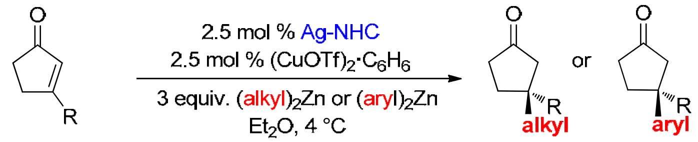
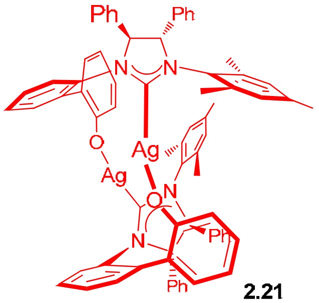
(44) For an expanded study of Cu-catalyzed ECA of these substrates with alkyl- and arylaluminum reagents (with high reactivity, >98% conv), see: Chapter 3.

Table 2.7. Cu-Catalyzed ECA of β-Substituted Cyclopentenones[a]

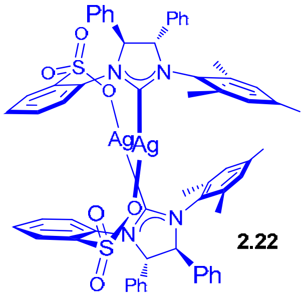


entry	R	Ag-NHC	Zn reagent	time (h)	conv (%)[b]	yield (%)[c]	er[d]
1[e]	*n*-Bu	**2.21**	Et_2Zn	48	<2	nd	nd
2[e]	*n*-Bu	**2.21**	Ph_2Zn	48	<2	nd	nd
3	*n*-Bu	**2.22**	Et_2Zn	24	30	20	97.5:2.5
4	*n*-Bu	**2.22**	Ph_2Zn	48	66	58	97:3
5	Me	**2.22**	Et_2Zn	24	70	52	95.5:4.5
6	Me	**2.22**	Ph_2Zn	48	78	71	97:3
7	Me	**2.22**	(p-$CF_3C_6H_4)_2Zn$	48	47	44	95:5
8	Me	**2.22**	(p-$OMeC_6H_4)_2Zn$	48	>98	35	95:5
9	Et	**2.22**	Ph_2Zn	48	67	62	96.5:3.5
10	CH_2CH_2Ph	**2.22**	Et_2Zn	24	47	23	96.5:3.5
11	Ph	**2.22**	Et_2Zn	48	25	20	96:6

[a]Reaction performed under N_2 atm. [b]Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c]Yield of isolated purified products. [d]Determined by GLC analysis, see experimental section for details. [e]Reaction performed at 22 °C. nd = not determined.



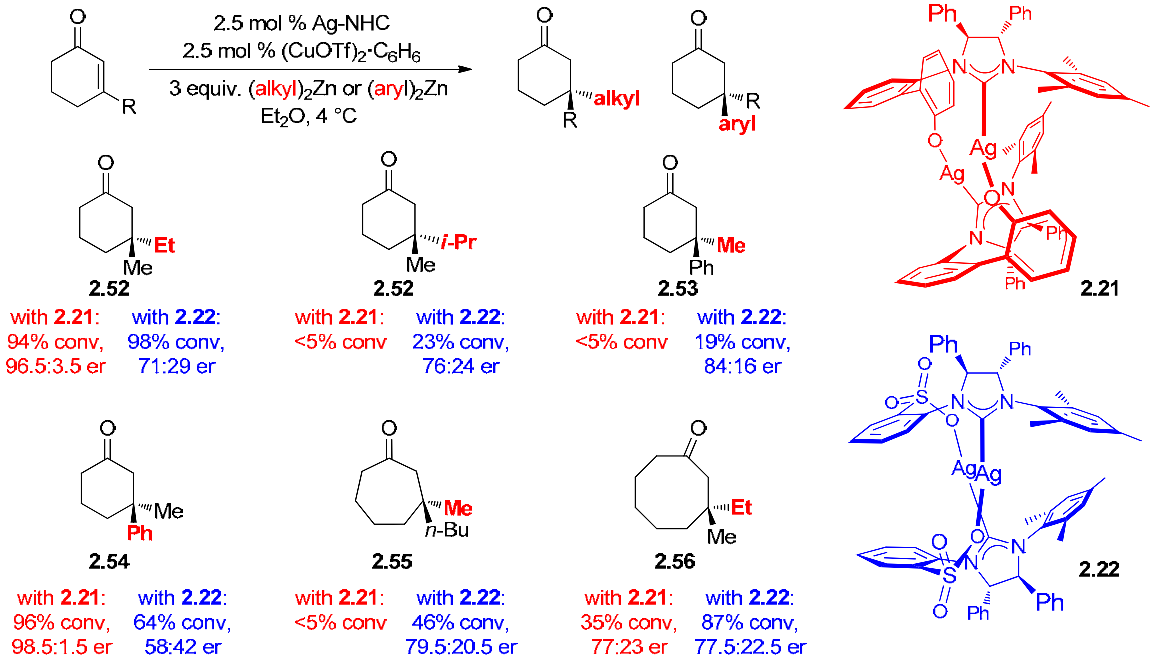
2.21



2.22

Continuing our investigations, we examined the behavior of larger ring enones in Cu-catalyzed ECAs of alkyl- and phenylzinc reagents, promoted by Cu–NHC complexes (Scheme 2.20). Several points are of note. (1) The phenoxy-containing Cu–NHC complex is less efficient than the sulfonate-containing Cu–NHC catalyst, similar to results obtained for the ECA of organozinc reagents to β-substituted cyclopentenones; for example, **2.56** is afforded in 35% conv with the phenoxy-containing NHC complex (**2.21**) and in 87% conv with complex **2.22**. (2) The sulfonate-containing Cu–NHC catalyst (with zinc reagents) is less effective in promoting conjugate addition to six-, seven-, and eight-membered ring activated enones than with the corresponding five-membered ring enones; the enantioselectivities of the products in these cases are significantly diminished in comparison (95:5–97.5:2.5 er vs. 58:24–84:16 er, Table 2.7 and Scheme 2.20). (3) We have previously demonstrated that the phenoxy-containing Cu–NHC catalyst is effective for alkyl- and arylzinc reagents to β-substituted cyclohexenones (and in some cases for β-substituted cyclohept- and cyclooctenones);[4f] although this catalyst is less efficient than the sulfonate-containing Cu catalyst (<5–96% conv vs. 23–98% conv), the conjugate addition products are obtained with higher enantioselectivities (76:24–98.5:1.5 er vs. 58:42–84:16 er).

Scheme 2.20. Cu-Catalyzed ECA of Alkyl- and Phenylzinc Reagents to β-Substituted Six-, Seven-, and Eight-Membered Ring Enones


O
R
2.5 mol % Ag-NHC
2.5 mol % (CuOTf)2·C6H6
3 equiv. (alkyl)2Zn or (aryl)2Zn
Et2O, 4 °C
O
alkyl
R
O
R
aryl
Ph
Ph
N
N
O
Ag
Ag
O
N
N
Ph
Ph
2.21
Et
Me
2.52
with 2.21: 94% conv, 96.5:3.5 er
with 2.22: 98% conv, 71:29 er
i-Pr
Me
2.52
with 2.21: <5% conv
with 2.22: 23% conv, 76:24 er
Me
Ph
2.53
with 2.21: <5% conv
with 2.22: 19% conv, 84:16 er
Ph
Ph
O
O=S
N
N
O
Ag
Ag
O
N
N
S
O
O
Ph
Ph
2.22
Me
Ph
2.54
with 2.21: 96% conv, 98.5:1.5 er
with 2.22: 64% conv, 58:42 er
Me
n-Bu
2.55
with 2.21: <5% conv
with 2.22: 46% conv, 79.5:20.5 er
Et
Me
2.56
with 2.21: 35% conv, 77:23 er
with 2.22: 87% conv, 77.5:22.5 er

2.2.d. Proposed Catalytic Cycle for Cu-Catalyzed ECA of Organozinc Reagents to Enones

Based on the experimental information we have gathered, we propose a catalytic cycle for Cu-catalyzed ECA, promoted a Cu complex with a sulfonate-containing NHC ligand, with organozinc reagents to cyclic enones affording products containing all-carbon quaternary stereogenic centers. Since efforts to characterize the active Cu(I)–NHC complex were unsuccessful, we inferred structural attributes of the NHC–Cu catalyst based on a recently secured X-ray crystal structure of the corresponding NHC–Zn–Et complex (Figure 2.1).[45] One of the surprising features of the sulfonate-containing

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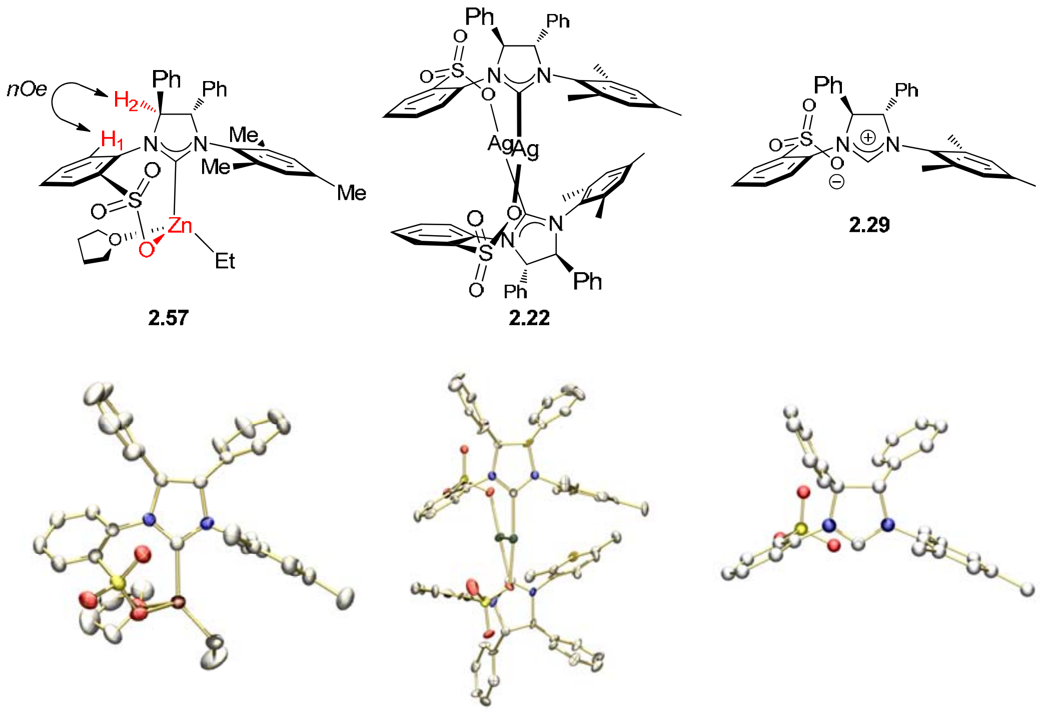
[45] "Stereogenic-at-Metal Zn- and Al-Based N-Heterocyclic Carbene (NHC) Complexes as Bifunctional Catalysts in Cu-Free Enantioselective Allylic Alkylations," Lee, Y.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11625–11633.

NHC-Zn complex is that the phenyl unit on the heterocycle is orientated *syn* to the *o*-substituted sulfonate, as seen through X-ray analysis in the solid state, as well as *nOe* analysis in solution state. This orientation is in contrast to that observed from the structural data obtained from X-ray of Ag–NHC complex **2.22** and imidazolinium salt **2.29**, which shows an anti relationship between the phenyl and the sulfonate group (Figure 2.1). We propose that when the NHC ligand is bidentate and monomeric on a metal (vs. dimeric for complex **2.22**), the aryl ring on the sulfonate has to significantly tilt to properly bind to the tetrahedral Zn or Cu center. To minimize the eclipsing interactions between H_1 and the Ph unit on the heterocycle (see **A'**, Scheme 2.21), the sulfonate flips and coordinates on the same side as the stereogenic phenyl group, placing H_1 and H_2 in close proximity (Figure 2.1).

Figure 2.1. Crystal Structures of the Sulfonate-Containing NHC–Zn, NHC–Ag, and Imidazolinium Salt



Therefore, based on the above solid and solution state data, we propose that the active Cu(I) catalyst **A** (Scheme 2.21) is structurally similar to the NHC–Zn complex **2.57** (Figure 2.1). Upon treatment with the diorganozinc reagent, a cuprate is formed (**B**).

Olefin coordination (**C**) on the least hindered quadrant of the cuprate, followed by oxidative addition to the square planer Cu(III) intermediate[46] (**D**) and reductive elimination affords the Zn–enolate and regenerates the active catalyst **A**. There are a few noteworthy points regarding the working transition state model. As discussed above, five-membered ring enones are typically less reactive than the six-membered ring analogs. This may be due to the equilibrium between **C** and **D** favoring the olefin coordination complex since theoretical studies by Nakamura support the instability of the Cu(III) intermediate **D**.[47] When the substrate is a six-membered ring enone, the enolate in transition state **D** can stabilize the Cu(III) complex, by acting as a strong donor ligand.[48] Perhaps, the donation from the more geometrically restrained five-membered ring enolate does not provide as much stabilization. Theoretical studies by Nakamura and kinetic studies by Feringa,[49] suggest that efficient catalysts for conjugate addition should thermodynamically stabilize the Cu(III) intermediate while allowing the complex to be kinetically labile to undergo reductive elimination. The bidentate nature of the sulfonate-containing NHC ligand allows for both; the soft and strong σ-donation of the NHC ligand stabilizes the Cu(III) intermediate while the hard donor ligand (the sulfonate moiety) lowers the kinetic barrier for reductive elimination.

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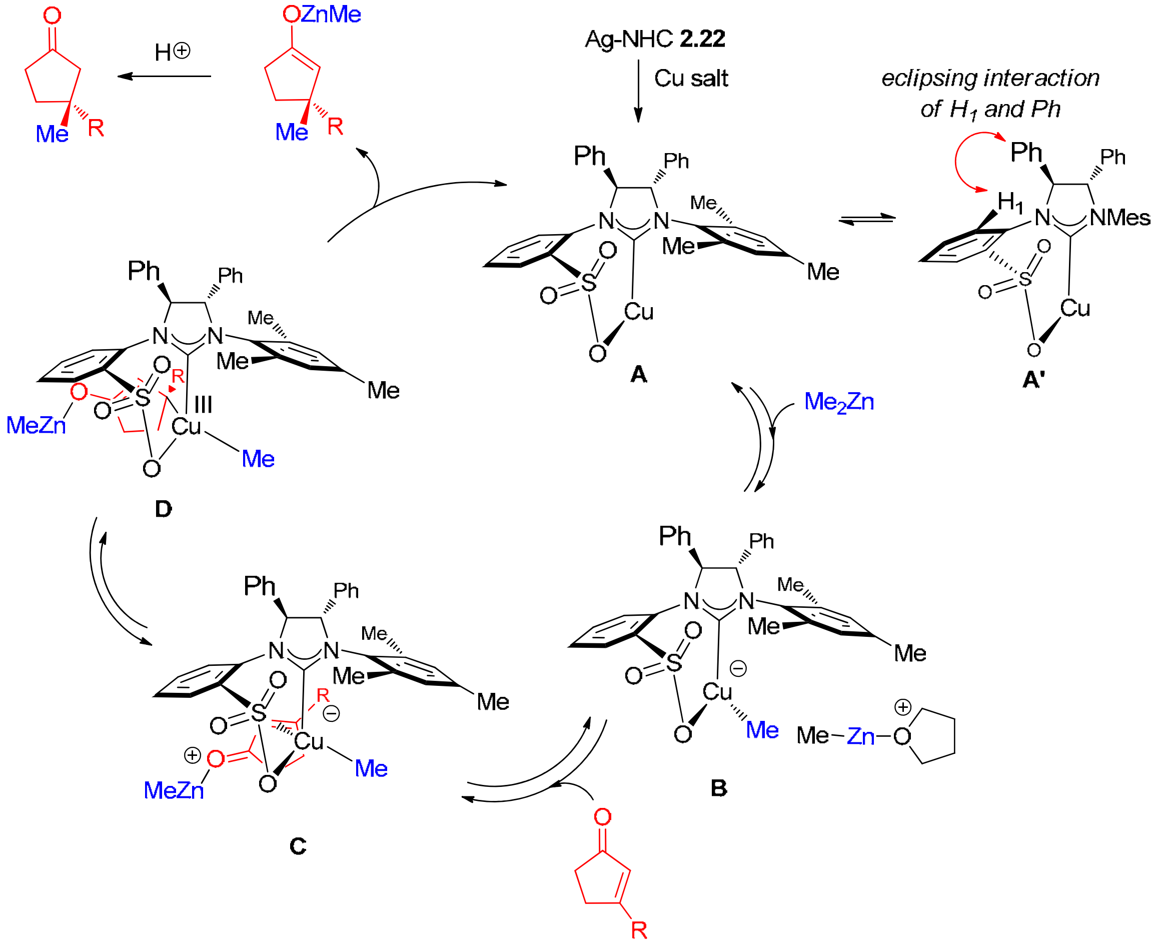
(46) For recent experimental studies detecting Cu(III) intermediates, see: (a) "Rapid Injection NMR in Mechanistic Organocopper Chemistry. Preparation of the Elusive Copper(III) Intermediate," Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208–7209. (b) "NMR-Detection of Cu(III) Intermediates in Substitution Reactions of Alkyl Halides with Gilman Cuprates," Gärtner, T.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 11362–11363.

(47) (a) ref 32a. (b) "Wherefore Art Thou Copper? Structures and Reaction Mechanisms of Organocuprate Clusters in Organic Chemistry," Nakamura, E.; Mori. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750–3771.

(48) "Mechanism and Regioselectivity of Reductive Elimination of π-Allylcopper (III) Intermediates," Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287–6293.

(49) "On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds," Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.

Scheme 2.21. Working Model for Cu-Catalyzed ECA of Organozinc Reagents


Ag-NHC **2.22**
Cu salt
eclipsing interaction of H1 and Ph
H⊕
OZnMe
Me
R
Ph
N
NMes
Cu
O
S
Me2Zn
Me–Zn–O
MeZn
A
A'
B
C
D

2.4. *Conclusions*

We have outlined an important and challenging objective in organic synthesis: enantioselective conjugate addition of carbon-based nucleophiles (discussed in this chapter, alkyl- and aryl-based nucleophiles) to trisubstituted cyclopentenones generating all-carbon quaternary stereogenic centers. At the start of this project, there were no effective and general approaches to this problem. Through development of new chiral catalysts, we have found an active and enantiodiscriminating bidentate, sulfonate-containing NHC-Cu catalyst that effects ECA on notoriously difficult trisubstituted cyclic enones. Products are prepared with high levels of selectivity and have participated in a variety of further functionalizations, including elaboration of the conjugate addition adduct toward the enantioselective synthesis of a complex alkaloid by Professor Gin and co-workers.

2.5. Experimentals

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, quint= quintet, 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. Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm)) or HPLC analysis (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 instrument analysis, the inlet and detector temperatures are set to 250 °C and runs were isothermal of the temperature given using ultra high purity helium as the carrier gas. Specific 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. 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 Catalysts:

Ag complexes 2.20 and 2.21 were prepared by previously reported methods.[22]

Acetic acid was purchased from Fisher and used as received.

Acetic anhydride was purchased from Aldrich and used as received.

2,2'-Azobisisobutyronitrile was purchased from Aldrich and used as received

Racemic-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (*rac*-binap) was purchased from Aldrich and used as received.

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

2-Bromobenzenesulfonyl chloride was purchased from Lancaster and purified by washing a benzene solution of the sulfonyl chloride with a 1.0 M aq solution of KOH (see below for details).

***t*-BuOH** was purchased from Aldrich and used as received.

Carbon disulfide was purchased from Aldrich and used as received.

Chloroform was purchased from Fisher and purified by distillation over $CaCl_2$ before use.

Chromium trioxide was purchased from Strem and used as received.

Copper iodide was purchased from Strem and was recrystallized from 3.5 M potassium iodide in water.

Copper (I) triflate benzene complex (2:1) (white solid) was prepared by previously reported methods.[50]

---

(50) "Cationic Olefin Complexes of Copper(I). Structure and Bonding in Group 1b Metal-Olefin Complexes," Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897.

Copper (I) triflate toluene complex (2:1) (brown solid) was purchased from Aldrich (99.99%) and used as received.

Copper (I) oxide (99.9%) was purchased from Strem and used as received.

Dicyclohexylcarbodiimide was purchased from Advanced Chem Tech and used as received.

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

Diisopropylzinc (1M in toluene) was purchased from Aldrich and used as received.

Dimethylformamide was purchased from Acros (99.8%, Acroseal) and used as received.

***N*,*N*-Diethylsalicylamide** was purchased from Aldrich and used as received.

Dimethylzinc (neat, 95%) was purchased from Strem and used as received.

Diphenylzinc (99%) was purchased from Strem (white solid) and used as received. Additionally, diphenylzinc can be prepared and purified (white solid) analogous to previously reported methods for the preparation of di-4-methoxyphenylzinc[4f] and used with similar levels of efficiency and selectivity. Diphenylzinc purchased from Aldrich (brown solid) was ineffective in the present Cu-catalyzed ECA.

(-)-(*S*,*S*)-Diphenylethylenediamine (99% purity) was purchased from Ivy Fine Chemicals and used as received.

4-Dimethylaminopyridine (dmap) was purchased from Advanced Chem Tech and used as received.

Iodomethane was purchased from Acros and used as received.

Lithium aluminum hydride (95%) was purchased from Strem and used as received.

Lithium hydroxide was purchased from Fisher and used as received.

$[(Me)_2CH(CH_2)_3]_2Zn$ was prepared by previously reported methods.[51]

Methyl 1-cyclopentene-1-carboxylate was purchased from Aldrich and used as received.

Methyl-1-cyclohexene-1-carboxylate was purchased from Aldrich and used as received.

***N*-Methyl-*N*-methylideneiminium iodide (Eschenmoser's salt)** was purchased from Aldrich and used as received.

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(51) "Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis," Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188 and references cited therein.

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

Tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$) was purchased from Strem Inc. and used as received.

Palladium (II) acetate (99.9+% purity) was purchased from Aldrich and used as received.

Phenyllithium (2.0 M in *n*-Bu_2O) was purchased from Acros and used as received.

Potassium Phosphate was purchased from Aldrich and used as received.

Pyridine was purchased from Aldrich and purified by distillation over KOH before use.

Silver nitrate (99%) was purchased from Aldrich and used as received.

Sodium *tert*-butoxide (98%) was purchased from Strem Inc. and used as received.

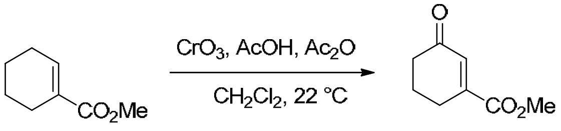
Sodium hydride was purchased from Strem Inc. and used as received.

Tri-*n*-butyltin hydride was purchased from Aldrich and used as received.

Triflic anhydride was prepared by distillation of triflic acid (Aldrich) over P_2O_5 (Aldrich).

Zinc (II) chloride (99.99%, ultradry), was purchased from Strem Inc. and used as received.

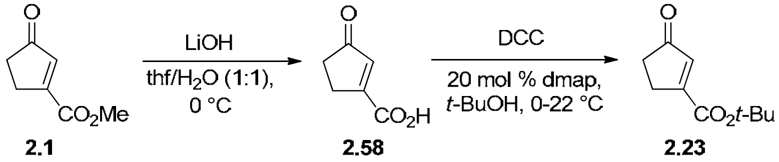
■ **Representative experimental procedures for the preparation of methyl ester substrates 2.1 and 2.16:**[12]



2.16

Methyl-3-oxocyclohex-1-enecarboxylate (2.16): To a 100 mL round bottom flask charged with CrO_3 (9.22 g, 60.7 mmol) was added AcOH (28.6 mL, 500 mmol) and Ac_2O (14.5 mL, 142 mmol). The dark red mixture was allowed to stir for 1 h at 22 °C. In a 250 mL round bottom flask equipped with an addition funnel was added methyl-1-cyclohexene-1-carboxylate (5.00 g, 35.7 mmol) and CH_2Cl_2 (71 mL). The solution of CrO_3 in AcOH/Ac_2O was transferred to the addition funnel and slowly added to the CH_2Cl_2 solution of methyl-1-cyclohexene-1-carboxylate over 1 h. (During the addition of CrO_3 to the substrate, the solution becomes black.) The mixture was allowed to stir for an additional 1 h, at which time the solution was allowed to cool to 0 °C and the reaction quenched upon addition of a 10 M aq solution of KOH (~80 mL) until pH ~ 8. The mixture was diluted with Et_2O (200 mL) and H_2O (200 mL). The organic layer was separated and the aqueous layer was washed with Et_2O (3 x 200 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (3 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a yellow oil, which was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/petroleum ether) and distilled under reduced pressure to yield 3.00 g (19.4 mmol, 54.3%) of **2.16** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.72 (1H, t, *J* = 2.0 Hz, CH), 3.82 (3H, s, OCH_3) 2.57 (2H, td, *J* = 6.0, 2.0 Hz), 2.45–2.42 (2H, m), 2.07–2.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 167.1, 149.0, 133.2, 52.7, 37.8, 25.0, 22.3.

■ **Representative experimental procedures for the preparation of *tert*-butyl ester substrates:**



3-Oxocyclopent-1-enecarboxylic acid (2.58): Lithium hydroxide (1.50 g, 64.0 mmol) was added to **2.1** (1.80 g, 12.8 mmol) dissolved in thf (180 mL) and H_2O (180 mL) at 0 °C. The mixture was allowed to stir for two minutes, at which time the reaction was quenched upon addition of a 0.5 M solution of aqueous HCl (100 mL) at 0 °C until pH < 4. The mixture was washed with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield 1.50 g (12.8 mmol, >98.0% yield) of the ketoacid **2.58** as a white solid, which was used directly in the subsequent reaction.

***tert*-Butyl-3-oxocyclopent-1-enecarboxylate (2.23):** To a solution of ketoacid **2.58** (206 mg, 1.64 mmol), dmap (39.0 mg, 0.320 mmol) and *t*-BuOH (235 μL, 2.46 mmol) dissolved in CH_2Cl_2 (15 mL) at 0 °C was added dropwise a solution of DCC (474 mg, 2.30 mmol) dissolved in CH_2Cl_2 (6.0 mL) through a syringe. The mixture was allowed to warm to 22 °C (during which time the mixture becomes brown) and stir for 15 h. At this time, the mixture was diluted with Et_2O (20 mL) and passed through a short column of Celite 545 (2 x 5 cm) layered on top of silica gel (2 x 10 cm) eluted with Et_2O (10 mL). The filtrate was concentrated in vacuo to afford a pale yellow oil, which was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/petroleum ether) then distilled under reduced pressure to yield 146 mg (0.784 mmol, 49.0%) of *tert*-butyl 3-oxocyclopent-1-enecarboxylate (**2.23**) as a clear oil. IR (neat): 2993 (m), 2945 (m), 1722 (s), 1721 (s), 1619 (m), 1443 (m), 1401 (m), 1377 (m), 1346 (m), 1249 (s), 1231 (s), 1153 (s), 1068 (m), 989 (w), 904 (w), 850 (w), 795 (w), 747 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.55 (1H, t, *J* = 2.0 Hz), 2.72–2.69 (2H, m), 2.41–2.39 (2H, m), 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 166.2, 163.4, 137.3, 82.4, 35.6, 27.9, 27.4; HRMS (CI+): Calcd for $C_{10}H_{15}O_3$: 183.1021, $[M+H]^+$, Found: 183.1018.

***tert*-Butyl-3-oxocyclohex-1-enecarboxylate:** IR (neat): 2984 (m), 2964 (m), 2875 (w), 1717 (s), 1690 (s), 1468 (w), 1387 (m), 1273 (s), 1165 (s), 1073 (m), 1029 (w), 975 (w), 905 (w), 851 (w), 742 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.65 (1H, t, *J* = 2.0 Hz), 2.52 (2H, dt, *J* = 6.0, 2.0 Hz), 2.41, (2H, dd, *J* = 8.0, 6.8 Hz), 2.02 (2H, tt, *J* = 6.0, 6.0 Hz), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 165.8, 151.1, 132.5, 82.4, 37.9, 28.1, 25.0, 22.4; HRMS (CI+): Calcd for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1177, Found: 197.1173.

■ **Phosphine-based ligand 2.6b** (prepared in accordance with reported procedures):[14] mp 68–75 °C; IR (neat): 3370 (br s), 2974 (m), 2930 (m), 2867 (m), 1683 (s), 1652 (s), 1583 (m), 1501 (s), 1463 (s), 1381 (m), 1274 (m), 1224 (m), 1073 (m), 1029 (m), 809 (m), 733 (m), 626 (w), 513 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (1H, d, *J* = 5.6 Hz), 7.72 (1H, t, *J* = 2.8 Hz), 7.63 (1H, t, *J* = 4.0 Hz), 7.14–7.01 (8H, m), 6.87–6.80 (2H, m), 4.00 (2H, dd, *J* = 4.0, 2.4 Hz), 3.90 (3H, s), 3.42 (1H, s), 3.38 (2H, dq, *J* = 7.2, 2.4 Hz), 3.25 (2H, q, *J* = 7.2 Hz), 2.33 (6H, d, *J* = 6.0 Hz), 1.16 (3H, t, *J* = 7.2 Hz), 1.11 (3H, t, *J* = 7.2 Hz), 0.85 (9H, s); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 171.8, 167.2, 160.7, 160.5, 160.4, 140.7, 140.5, 138.8, 138.8, 135.2, 135.2, 134.1, 134.0, 133.8, 133.5, 133.4, 129.8, 129.7, 129.6, 129.5, 129.5, 118.0, 112.1, 112.1, 84.0, 55.7, 41.1, 40.9, 40.5, 35.3, 27.3, 21.5, 21.5, 14.3, 13.2; Anal Calcd for $C_{34}H_{44}N_3O_3P$: C, 71.18; H, 7.73; N, 7.15; Found C, 71.18; H, 7.73; N, 7.32; Specific Rotation: $[\alpha]_D^{20}$ +30.6 (*c* = 0.266, $CHCl_3$).

■ **Representative procedure for Cu-catalyzed ECA of organozinc reagents promoted by peptide ligand 2.6b:** An oven-dried 13x100 mm test tube was charged with ligand **2.6b** (5.7 mg, 0.010 mmol) and $(CuOTf)_2{\cdot}C_6H_6$ (2.0 mg, 0.0040 mmol), weighed out in a N_2-filled glovebox. The test tube was sealed with a septum and wrapped with parafilm before removal from the glovebox. The test tube was allowed to cool to −30 °C in a dry ice/acetone bath and 1.6 mL of toluene was added to provide an orange solution. Diethylzinc (31 μL, 0.30 mmol) was added followed by isopropyl 3-oxocyclopent-1-enecarboxylate (17 mg, 0.10 mmol) in a solution of toluene (0.4 mL) and the reaction was transferred to a –30 °C cryocool. The resulting solution was allowed to stir for 12 hours before the reaction was quenched by addition of saturated NH_4Cl (1 mL) and H_2O (1 mL). The aqueous layer was washed with EtOAc (3 x 2 mL) and the combined organic layers were passed through a short plug of silica (1 cm x 1 cm) eluting with EtOAc (5 mL) and concentrated in vacuo to afford a yellow oil. Purification by silica gel chromatography (9:1 petroleum ether/ethyl acetate) provided (*S*)-isopropyl-1-ethyl-3-oxocyclopentanecarboxylate as a light yellow oil (14.4 mg, 0.074 mmol, 74% yield).

(*S*)-Methyl-1-ethyl-3-oxocyclopentanecarboxylate (Table 2.2, entry 1): IR (neat): 2953 (m), 2880 (w), 1734 (s), 1572 (w), 1543 (w), 1462 (m), 1373 (w), 1240 (m), 1203 (m), 1159 (m), 1139 (m), 1029 (m), 1001 (w); ^1H NMR ($CDCl_3$, 400 MHz): 3.67 (3H, s), 2.77 (1H, dt, *J* = 14.8, 1.6 Hz), 2.38–2.32 (1H, m), 2.26–2.18 (1H, m), 2.13–2.10 (2H, m), 1.95–1.85 (1H, m), 1.80–1.61 (3H, m), 1.53 (1H, dq, *J* = 15.2, 7.6 Hz) 0.81 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 209.4, 176.0, 52.2, 51.2, 47.6, 40.7, 33.4, 31.8, 22.2, 8.8; HRMS (EI+): Calcd for $C_{10}H_{16}O_3$ $[M+H]^+$: 184.1099, Found: 184.1097; Specific Rotation: $[\alpha]_D^{20}$ +49.6 (*c* = 0.286, $CHCl_3$) for a sample with 94:6 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 110 °C). T_{minor} = 44.458 min, T_{major} = 45.640 min.

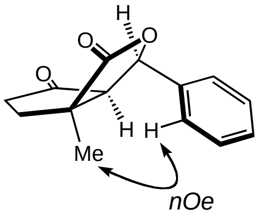
Claisen Condensation Byproduct: The side product characterized was isolated from ECA of Me_2Zn to **2.1**. For clarity, the side product derived from ECA of Et_2Zn to **2.1** was presented in the text. Two diastereomers are isolated. A) IR (neat): 2952 (br w), 2928 (br w), 1771 (s), 1743 (s), 1720 (s), 1437 (w), 1310 (m), 1272 (m), 1254 (m), 1203 (m), 1163 (m), 942 (m), 923 (m), 750 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.58 (1H, dt, *J* = 2.0, 0.8 Hz), 3.79 (3H, s), 2.81–2.73 (1H, m), 2.67–2.43 (4H, m), 2.32–2.22 (1H, m), 2.04–1.98 (1H, m), 1.88 (1H, ddd, *J* = 12.8, 11.6, 7.6 Hz), 1.57 (3H, s); HRMS (EI^+): Calcd for $C_{14}H_{17}O_5$ $[M+H]^+$: 265.10760; Found 265.10761.

B) IR (neat): 2953 (br w), 1771 (s), 1744 (s), 1722 (s), 1438 (w), 1305 (m), 1253 (m), 1226 (m), 1192 (m), 1134 (m), 1159 (m), 1054 (w), 950 (w), 751 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.39 (1H, t, *J* = 2.0 Hz), 3.78 (3H, s), 2.86–2.78 (1H, m), 2.71–2.63 (2H, m), 2.58–2.38 (4H, m), 2.34–2.24 (2H, m), 1.92 (1H, ddd, *J* = 13.2, 12.0, 8.4 Hz), 1.56 (3H, s); HRMS (EI^+): Calcd for $C_{14}H_{17}O_5$ $[M+H]^+$: 265.1076, Found 265.1063.

(*S*)-*tert*-Butyl 1-ethyl-3-oxocyclopentanecarboxylate (Table 2.2, entry 3): IR (neat): 2983 (m), 2940 (m), 2879 (w), 1747 (s), 1723 (s), 1472 (m), 1450 (m), 1380 (m), 1343 (m), 1252 (s), 1160 (s), 860 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.70 (1H, dd, *J* = 18.0, 1.2 Hz) 2.36–2.22 (3H, m), 2.02 (1H, d, *J* = 18.4 Hz), 1.86–1.77 (2H, m), 1.62–1.53 (1H, m), 1.42 (9H, s), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.5, 175.0, 81.3, 52.4, 47.2, 37.0, 32.7, 31.4, 28.1, 10.0; HRMS (EI^+): Calcd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1490, Found: 213.1484; Specific Rotation: $[\alpha]_D^{20}$ +63.7 (*c* = 1.69, $CHCl_3$) for a sample with 94:6 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 120 °C). T_{minor} = 36.180 min, T_{major} = 36.790 min.

(*S*)-*tert*-Butyl 1-methyl-3-oxocyclopentanecarboxylate (Table 2.2, entry 5): IR (neat): 2983 (m), 2946 (w), 2879 (w), 1759 (s), 1729 (s), 1613 (w), 1466 (w), 1368 (m), 1246 (m), 1160 (s), 1111 (m), 854 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.70 (1H, d, *J* = 18.0 Hz), 2.41–2.24 (3H, m), 2.06 (1H, d, *J* = 18.0 Hz), 1.91–1.82 (1H, m), 1.44 (9H, s), 1.33 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.6, 175.7, 81.3, 49.5, 47.2, 37.1, 34.1, 28.1, 24.1; HRMS (CI+): Calcd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1334, Found: 199.1333; Specific Rotation: $[\alpha]_D^{20}$ +57.5 (*c* = 0.893, $CHCl_3$) for a sample with 97:3 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 100 °C). T_{minor} = 65.151 min, T_{major} = 67.639 min.

6α-Methyl-3-phenyl-tetrahydro-5*H*-cyclopenta[*c*]furan-1,4-dione (2.12): >30:1 mixture of diastereomers, relative configuration determined by *nOe* correlation. IR (neat): 3068 (w), 3026 (m), 2978 (w), 2930 (w), 2877 (w), 1785 (s), 1749 (s), 1504 (w), 1462 (m), 1385 (w), 1343 (w), 1289 (m), 1265 (m), 1224 (m), 1170 (m), 1170 (s), 1062 (m), 1021 (m), 746 (m), 704 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.29 (5H, m), 5.53 (1H, d, *J* = 2.8 Hz), 2.76 (1H, d, *J* = 2.8 Hz), 2.57–2.49 (2H, m), 2.43–2.32 (1H, m), 2.01–1.93 (1H, m), 1.32 (3H, s); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.0, 180.7, 139.4, 129.1, 128.5, 124.6, 79.6, 62.4, 48.3, 37.8, 32.7, 23.3; HRMS (EI^+): Calcd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943; Found 230.0946; Specific Rotation: $[\alpha]_D^{20}$ +75.5 (*c* = 0.173, $CHCl_3$) for a sample with 95.5:4.5 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (Chiraldex GTA column, 15 psi, 140 °C). T_{major} = 86.7 min, T_{minor} = 96.8 min.

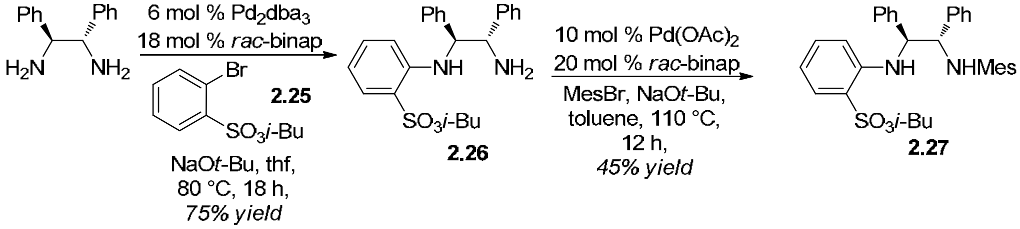


(*R*)-Methyl-3-oxo-1-phenylcyclopentanecarboxylate (Table 2.3, entry 4): IR (neat): 2962 (w), 2924 (m), 2848 (w), 1753 (s), 1734 (s), 1445 (w), 1249 (m), 1212 (m), 1162 (m), 752 (m), 695 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (5H, m), 3.64 (3H, s), 3.23 (1H, dd, *J* = 16.0, 2.0 Hz), 2.98–2.95 (1H, m), 2.62 (1H, d, *J* = 18.0 Hz), 2.35–2.32 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 175.0, 141.3, 129.0, 127.8, 126.6, 55.2, 53.1, 48.4, 37.2, 33.0; Elemental Analysis: Anal Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; Found C, 71.53; H, 6.68.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (Chiraldex GTA column, 15 psi, 140 °C). T_{major} = 44.3 min, T_{minor} = 41.5 min.

■ Preparation of Sulfonate-Containing Ag–NHC Complex 2.22

First Generation Diamine 2.27 Synthesis:

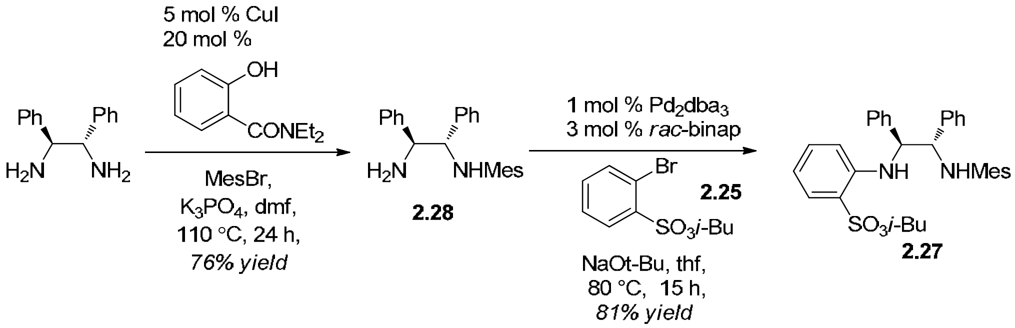

Ph
Ph
H2N
NH2
6 mol % Pd2dba3
18 mol % rac-binap
Br
2.25
SO3i-Bu
NaOt-Bu, thf,
80 °C, 18 h,
75% yield
Ph
Ph
NH
NH2
SO3i-Bu
2.26
10 mol % Pd(OAc)2
20 mol % rac-binap
MesBr, NaOt-Bu,
toluene, 110 °C,
12 h,
45% yield
Ph
Ph
NH
NHMes
SO3i-Bu
2.27

Isobutyl-2-bromobenzenesulfonate (2.25): (Prior to use in this reaction, commercially available 2-bromobenzenesulfonyl chloride was dissolved in benzene and washed with a 1.0 M aq solution of KOH. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo to afford the sulfonyl chloride as a clear oil). In two separate syringes, pyridine (4.56 mL, 55.9 mmol) and a solution of 2-bromobenzenesulfonyl chloride (6.49 g, 25.4 mmol) in $CHCl_3$ (13 mL) were added dropwise at the same time over 20 min to a solution of 2-methylpropanol (2.57 mL, 27.9 mmol) dissolved in $CHCl_3$ (13 mL) at 0 °C under a N_2 atmosphere. The solution was allowed to stir at 22 °C. After 20 h, the reaction was quenched upon addition of a 0.1 M aq solution of HCl (20 mL) and allowed to stir for five minutes. The $CHCl_3$ layer was separated and washed with a 0.1 M aq solution of HCl (20 mL), water (2 × 15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a clear oil, which was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 5.42 g (18.5 mmol, 72.8%) of sulfonate ester **2.25** as a clear oil. IR (neat): 2964 (m), 2926 (w), 2870 (w), 1573 (w), 1455 (w), 1362 (s), 1189 (s), 965 (m), 934 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10–8.09 (1H, m), 7.78–7.56 (1H, m), 7.50–7.44 (2H, m), 3.85 (2H, d, J = 6.6 Hz), 2.00 (1H, qt, J = 6.8, 6.6 Hz), 0.93 (6H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.9, 135.6, 134.6, 132.1, 127.6, 120.8, 77.2, 28.1, 18.7; HRMS (EI+): Calcd for $C_{10}H_{13}BrO_3S$ $[M]^+$: 291.9769, Found: 291.9773.

Isobutyl-2-((1*S*,2*S*)-2-amino-1,2-diphenylethylamino)benzenesulfonate (2.26): (–)-(*S*,*S*)-1,2-diphenylethylenediamine (1.00 g, 4.71 mmol), $Pd_2(dba)_3$ (258 mg, 0.283 mmol), *rac*-binap (528 mg, 0.848 mmol) and NaO*t*-Bu (815 mg, 8.48 mmol) were weighed out into an oven-dried 250 mL round bottom flask under a N_2 atmosphere in a glove box. The flask was removed from the glove box and fitted with a reflux condenser. A solution of **2.25** (1.38 g, 4.71 mmol) dissolved in thf (47 mL) was added through a syringe and the resulting mixture was allowed to stir at reflux (~80 °C) (the reaction mixture becomes deep red upon heating and remains this color for the length of the reaction). After 15 h, the mixture was allowed to cool to 22 °C and the volatiles were removed in vacuo affording a deep red oil. The deep red oil was then dissolved in toluene, loaded on top of a column containing silica gel, and purified by silica gel chromatography (100% petroleum ether (to elute toluene) → 50% Et_2O/petroleum ether) to afford 1.50 g (3.53 mmol, 74.9%) of **2.26** as a yellow solid. mp: 157–159 ^oC; IR (neat): 3364 (br), 2966 (w), 2874 (w), 1601 (m), 1504 (m), 1461 (m), 1167 (m), 978 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (1H, dd, *J* = 8.1, 1.7 Hz), 7.49 (2H, d, *J* = 8.1 H.), 7.44 (1H, d, *J* = 7.0 Hz) 7.35–7.22 (8H, m), 7.13 (1H, dd), 6.57 (1H, dd, *J* = 8.1, 7.2 Hz), 6.31 (1H, d, *J* = 8.1 Hz), 4.59 (1H, dd, *J* = 7.0, 3.5 Hz), 4.40 (1H, d, *J* = 3.5 Hz), 3.74 (1H, dd, *J* = 9.3, 6.8 Hz), 3.70 (1H, dd, *J* = 9.3, 6.6 Hz), 1.95 (1H, dddq, *J* = 6.8, 6.8, 6.8, 6.6 Hz), 1.51 (2H, br), 0.92 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 142.6, 140.7, 135.1, 130.8, 128.8, 128.4, 127.6, 127.6, 127.1, 126.8, 116.5, 115.1, 113.6, 76.3, 63.0, 61.2, 28.1, 18.8, 18.7; HRMS (EI+): Calcd for $C_{24}H_{29}N_2O_3S$ $[M+H]^+$: 425.1899, Found 425.1895; Specific Rotation: $[\alpha]_D^{25}$ –98.9 (*c* = 1.00, $CHCl_3$).

Isobutyl-2-((1*S*,2*S*)-2-(mesitylamino)-1,2-diphenylethylamino)benzenesulfonate (2.27): Diamine **2.26** (0.800 g, 1.88 mmol), $Pd(OAc)_2$ (42.0 mg, 0.188 mmol), *rac*-binap (234 mg, 0.376 mmol) and NaO*t*-Bu (272 mg, 2.83 mmol) were weighed out into an oven-dried 50 mL round bottom flask under a N_2 atmosphere in a glove box. The flask was removed from the glove box and fitted with a reflux condenser. A solution of 2-bromomesitylene (577 μL, 3.77 mmol) dissolved in toluene (19 mL) was added through a syringe and the resulting mixture was allowed to stir at 110 °C (the mixture becomes deep red upon heating and remains this color for the length of the reaction). After 18 h, the mixture was allowed to cool to 22 °C, loaded directly on top of a column containing silica gel and purified by silica gel column chromatography (100% petroleum ether (to elute toluene) → 20% Et_2O/petroleum ether) to afford a pale yellow solid, which was rinsed with petroleum ether to yield 441 mg (0.811 mmol, 43.1%) of diamine **2.27** as a white solid. mp: 164–166 °C; IR (neat): 3352 (m), 2962 (m), 2917 (w), 2861 (w), 1596 (s), 1350 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (1H, dd, *J* = 8.1, 1.7 Hz), 7.42 (1H, d, *J* = 4.5 Hz), 7.30–7.12 (9H, m), 7.07–7.04 (2H, m), 6.75–6.72 (3H, m), 6.57 (1H, d, *J* = 8.4 Hz), 4.97 (1H, dd, *J* = 7.0, 4.5 Hz), 4.57 (1H, d, *J* = 7.0 Hz), 3.88 (1H, dd, *J* = 9.3, 6.6 Hz), 3.78 (1H, dd, *J* = 9.3, 6.4 Hz), 3.65 (1H, br s), 2.20 (3H, s), 2.15 (6H, s), 2.01 (1H, dddq, *J* = 6.6, 6.4, 4.2, 4.0 Hz), 0.99 (3H, d, *J* = 4.0 Hz), 0.97 (3H, d, *J* = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.7, 140.9, 140.2, 140.1, 135.1, 131.1, 130.9, 129.8, 129.2, 128.4, 128.2, 128.1, 127.8, 127.6, 117.6, 115.8, 113.9, 76.2, 66.7, 62.0, 28.2, 20.5, 19.2, 18.8; HRMS (EI+): Calcd for $C_{33}H_{39}N_2O_3S$ $[M+H]^+$: 543.2681, Found 543.2680; Specific Rotation: $[\alpha]_D^{25}$ –94.4 (*c* = 0.100, $CHCl_3$).

Second Generation Diamine 2.27 Synthesis:

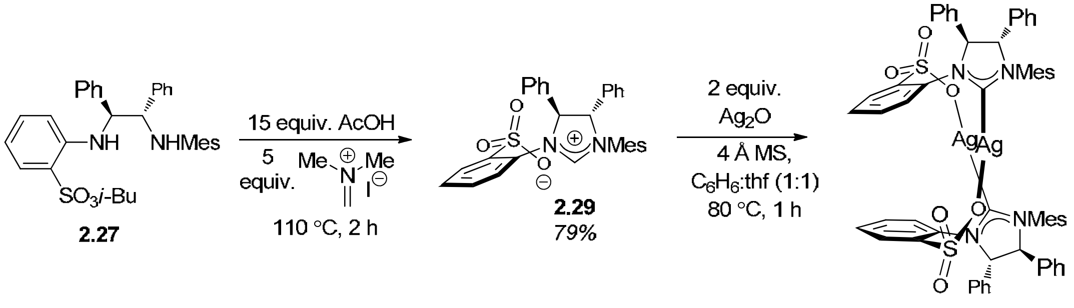

5 mol % CuI
20 mol %
OH
CONEt2
Ph
Ph
H2N
NH2
MesBr,
K3PO4, dmf,
110 °C, 24 h,
76% yield
Ph
Ph
H2N
NHMes
2.28
1 mol % Pd2dba3
3 mol % rac-binap
Br
2.25
SO3i-Bu
NaOt-Bu, thf,
80 °C, 15 h,
81% yield
Ph
Ph
NH
NHMes
SO3i-Bu
2.27

(1*S*, 2*S*)-*N*^{1}-Mestiyl-1,2-diphenylethane-1,2-diamine (2.28):[28] A flame-dried round bottom flask, equipped with a stir bar, was charged with (–)-(*S*,*S*)-1,2-diphenylethylenediamine (1.06 g, 5.00 mmol), CuI (48.0 mg, 0.250 mmol), *N*,*N*-diethylsalicylamide (193 mg, 1.00 mmol) and K_3PO_4 (2.10 g, 10.0 mmol). Dimethylformamide (2.5 mL) followed by mestyl bromide (750 μL, 5.00 mmol) were added through syringes and the solution was allowed to stir at 100 °C. After 24 h, the solution was allowed to cool to 22 °C and EtOAc (50 mL) and water (50 mL) were added. The layers were separated and the aqueous layer was washed with EtOAc (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. The oil was purified by silica gel chromatography (1:1 petroleum ether:Et_2O $\rightarrow$ 1:1 petroleum ether:Et_2O) to afford **2.28** (1.25 g, 3.77 mmol, 76%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (2H, d, *J* = 8.0 Hz), 7.27 (2H, t, *J* = 7.6 Hz), 7.23–7.14 (4H, m), 7.09 (2H, d, *J* = 7.6 Hz), 6.70 (2H, s), 4.59 (1H, d, *J* = 6.4 Hz), 4.47 (1H, d, *J* = 6.8 Hz), 2.80 (3H, br s), 2.18 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.1, 142.55, 142.0, 130.0, 129.8, 128.4, 128.3, 127.7, 127.7, 127.4, 127.2, 67.1, 61.4, 20.7, 19.7.

Isobutyl-2-((1*S*,2*S*)-2-amino-1,2-diphenylethylamino)benzenesulfonate (2.27): Diamine **2.28** (330 mg, 1.00 mmol), $Pd_2(dba)_3$ (9.00 mg, 0.010 mmol), *rac*-binap (19.0 mg, 0.030 mmol) and NaO*t*-Bu (173 mg, 1.80 mmol) were weighed out into an oven-dried round bottom flask under a N_2 atmosphere in a glove box. The flask was removed from the glove box and fitted with a reflux condenser. A solution of **2.25** (330 mg, 1.00 mmol) dissolved in thf (10.0 mL) was added through a syringe and the resulting mixture was allowed to stir at reflux (~80 °C) (the reaction mixture becomes deep red upon heating and remains this color for the length of the reaction). After 15 h, the mixture was allowed to cool to 22 °C and the volatiles were removed in vacuo affording a deep red oil. The deep red oil was then dissolved in toluene, loaded on top of a column containing silica gel, and purified by silica gel chromatography (100% petroleum ether (to elute toluene) $\rightarrow$ 50% Et_2O/petroleum ether) to afford 345 mg (0.635 mmol, 81%) of **2.27** as a yellow solid. mp: 164–166 ^{o}C; IR (neat): 3352 (m), 2962 (m), 2917 (w), 2861 (w), 1596 (s), 1350 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (1H, dd, *J* = 8.1, 1.7 Hz), 7.42 (1H, d, *J* = 4.5 Hz), 7.30–7.12 (9H, m), 7.07–7.04 (2H, m), 6.75–6.72 (3H, m), 6.57 (1H, d, *J* = 8.4 Hz), 4.97 (1H, dd, *J* = 7.0, 4.5 Hz), 4.57 (1H, d, *J* = 7.0 Hz), 3.88 (1H, dd, *J* = 9.3, 6.6 Hz), 3.78 (1H, dd, *J* = 9.3, 6.4), 3.65 (1H, br s), 2.20 (3H, s), 2.15 (6H, s), 2.01 (1H, ddqq, *J* = 6.6, 6.4, 4.2, 4.0 Hz), 0.99 (3H, d, *J* = 4.0 Hz), 0.97 (3H, d, *J* = 4.2 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.7, 140.9, 140.2, 140.1, 135.1, 131.1, 130.9, 129.8, 129.2, 128.4, 128.2, 128.1, 127.8, 127.6, 117.6, 115.8, 113.9, 76.2, 66.7, 62.0, 28.2, 20.5, 19.2, 18.8; HRMS (EI+): Calcd for $C_{33}H_{39}N_2O_3S$: 543.2681 $(M+H)^+$, Found 543.2680; Specific Rotation: $[\alpha]_D^{25}$ –94.4 (c = 0.100, $CHCl_3$).

Cyclization of Diamine 2.27 and Ag–NHC Complex Formation



Imidazolinium Salt 2.29: Diamine **2.27** (1.60 g, 2.94 mmol) and *N*-methyl-*N*-methylideneiminium iodide (2.69 g, 5.00 mmol) were weighed out into a 75 mL heavy wall sealed tube. Acetic acid (2.55 mL, 15.0 mmol) was added, the vessel sealed, and the mixture allowed to stir at 110 °C (the yellow heterogeneous mixture becomes black and homogeneous upon heating). After 1 h, the mixture was allowed to cool to 22 °C and diluted with Et_2O (5 mL) and water (5 mL). The resulting mixture was basified by the *slow* addition of a saturated aqueous solution of K_2CO_3 until gas evolution ceased. Dichloromethane (10 mL) was added and the aqueous layer separated. The aqueous layer was washed further with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow solid. The yellow solid was purified by silica gel column chromatography (100% EtOAc → 2% MeOH/EtOAc → 5% MeOH/EtOAc) to afford imidazolinium salt **2.29** (1.05 g, 2.12 mmol, 72%) as a white solid. (Note: Separation of a yellow impurity by silica gel column chromatography can often be tedious. This solid can be obtained in white crystalline form by recrystallization from CH_2Cl_2:Et_2O, but is not required for effective formation of Ag complex **2.22**.) mp: 223–225 °C; IR (neat): 3058 (m), 2914 (m), 2861 (w), 1623 (s), 1579 (m), 1230 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (1H, s, NCHN), 8.23 (1H, dd, J = 7.9, 1.5 Hz), 7.67–7.64 (2H, m), 7.50–7.47 (2H, m), 7.43–7.41 (3H, m), 7.36–7.30 (4H, m), 7.10 (1H, td, J = 7.9, 1.5 Hz), 6.93 (1H, s), 6.73 (1H, s), 6.72 (1H, dd, J = 7.9, 1.5 Hz), 6.56 (1H, d, J = 11.8 Hz), 5.53 (1H, d, J = 11.8 Hz), 2.60 (3H, s), 2.23 (3H, s), 2.00 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 144.0, 140.4, 138.6, 135.0, 134.3, 131.5, 130.7, 130.5, 130.5, 130.3, 130.0, 129.9, 129.7, 129.6, 129.1, 129.1, 127.5, 76.2, 74.5, 21.0, 18.8, 18.5; HRMS (EI+): Calcd for $C_{30}H_{29}N_2O_3S$ $[M+H]^+$: 497.1899, Found 497.1886; Elemental Analysis: Anal Calcd for $C_{30}H_{28}N_2O_3S$: C 72.55; H 5.68; N 5.64; Found C 72.27; H 5.41; N 5.45; Specific Rotation: $[\alpha]_D^{25}$ –14.9 (c = 0.500, $CHCl_3$).

Preparation of Ag_2O: An aqueous solution of sodium hydroxide (20 mL, 2M, 40 mmol) was added to a solution of $AgNO_3$ (1.7g, 10 mmol) in H_2O (10 mL). A brown precipitate formed immediately, which was isolated by vacuum filtration. The solid was washed with 250 mL H_2O, 250 mL EtOH, and 250 mL acetone and repeated. The brown solid was dried overnight under vacuum (~0.5 mm Hg) over P_2O_5.

Ag Complex 2.22: Imidazolium salt **2.29** (100 mg, 0.201 mmol), Ag_2O (93.0 mg, 0.400 mmol) and oven-dried powdered <5 micron 4Å MS (ca. 50 mg) were weighed out into an oven-dried 10 mL round bottom flask. The flask was fitted with a reflux condenser and wrapped with aluminum foil to exclude light. Tetrahydrofuran (1.0 mL) followed immediately by benzene (1.0 mL) were added through a syringe resulting in a black heterogeneous mixture. The mixture was allowed to stir at 80 °C. After 1 h, the mixture was allowed to cool to 22 °C and filtered through a short plug of Celite 545 (4 x 1 cm) eluted with EtOAc (ca. 20 mL). The solution was then concentrated in vacuo to afford 119 mg (0.197 mmol, 98.0%) of Ag complex **2.22** as a white solid, which was stored under low light conditions. (Note: This material was obtained in crystalline form by recystallization from CH_2Cl_2:Et_2O bilayer, but recrystallization is not required for effective Cu-catalyzed ECA). mp: 247–249 °C (decomp); IR (neat): 3062 (w), 3026 (w), 2908 (w), 1608 (w), 1480 (s), 1455 (s), 1226 (s), 1201 (s), 1027 (m), 754 (s) cm^{-1}; ^{1}H

NMR ($CDCl_3$, 400 MHz): δ 8.27 (1H, br d, J = 7.3 Hz), 7.50–7.44 (2H, m), 7.32–6.95 (10H, m), 6.80 (2H, br s), 6.55 (1H, br d, J = 10.4 Hz), 6.33 (2H, br s), 5.18 (1H, br d, J = 10.4 Hz), 2.46 (3H, s), 2.29 (3H, s), 1.42 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.6 ($J_{C^{109}Ag}$ = 186.8 Hz, $J_{C^{107}Ag}$ = 182.5 Hz), 143.4, 138.6, 138.5, 136.5, 135.7, 135.2, 134.1, 131.1, 130.6, 130.0, 129.9, 129.6, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2, 76.5, 74.0, 68.6, 21.1, 19.0, 17.9; Specific Rotation: $[\alpha]_D^{25}$ –104 (c = 0.500, $CHCl_3$).

■ **Representative experimental procedure for Cu–NHC-catalyzed conjugate addition of *Me_2Zn* to unsaturated cyclic *γ*-ketoesters:** An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.30 mg, 2.50 μmol), under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before allowing to cool to –78 °C (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 °C (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 °C, methyl 3-oxocyclohex-1-enecarboxylate (**2.16**) (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe.[52] After 15 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/petroleum ether) to afford 15.1 mg of the desired product as a clear oil (0.0888 mmol, 88.8%).

■ **Representative experimental procedure for Cu–NHC-catalyzed conjugate addition of *Et_2Zn, $[(Me)_2CH(CH_2)_2]_2Zn$* and *i-Pr_2Zn* to unsaturated cyclic *γ*-**

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(52) Methyl 3-oxocyclopent-1-enecarboxylate (**2.1**) (white solid) was added as a solution in *t*-BuOMe (250 μL).

ketoesters: An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol) and $(CuOTf)_2\bullet C_6H_6$ (1.30 mg, 2.50 μmol), under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before allowing to cool to –30 °C (dry ice/acetone bath). Diethylzinc (30.7 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) followed by methyl 3-oxocyclopent-1-enecarboxylate (**2.1**) (14.0 mg, 0.100 mmol) dissolved in *t*-BuOMe (250 μL) were added through a syringe. (During the addition of Et_2Zn the mixture became dark brown.) After 1 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/ petroleum ether) to afford 14.9 mg of the desired product as a clear oil (0.0876 mmol, 87.6%).

■ **Representative experimental procedure for Cu–NHC-catalyzed conjugate addition of *Me₂Zn* to unsaturated cyclic γ-ketoesters *set up on a bench top and carried out in undistilled t-BuOMe*:** A 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol) and $(CuOTf)_2\bullet$toluene (1.30 mg, 2.50 μmol), weighed out on a bench top. The test tube was sealed with a septum and wrapped with parafilm before being purged with N_2 for five minutes. Undistilled *t*-BuOMe (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before allowing to cool to –78 °C (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 °C (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 °C, methyl 3-oxocyclohex-1-enecarboxylate (**2.16**) (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe. After 15 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/petroleum ether) to afford 12.3 mg of the desired product as a clear oil (0.0723 mmol, 72.3%).

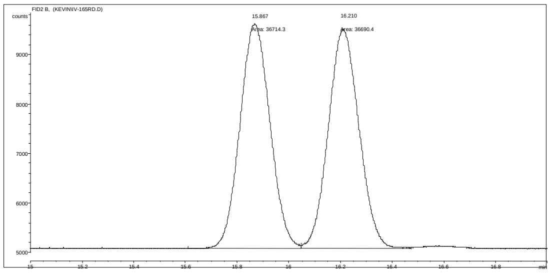
■ **Representative experimental procedure for Cu–NHC-catalyzed conjugate addition of *Ph_2Zn* to unsaturated cyclic γ-ketoesters:** An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol), $(CuOTf)_2{\bullet}C_6H_6$ (1.3 mg, 2.50 μmol), and Ph_2Zn (65.7 mg, 0.300 mmol), under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath) and Et_2O (1.0 mL) was added through a syringe. The resulting mixture was allowed to stir for 10 minutes. (During this time the mixture became dark brown.) At this time, a solution of methyl 3-oxocyclopent-1-enecarboxylate (**2.1**) (15.4 mg, 0.100 mmol) in Et_2O (500 μL) was added to the mixture through a syringe. After 42 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, to afford a yellow oil that was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 15.3 mg (0.0701 mmol, 70.1%) of the desired product as a clear oil.

■ **Representative experimental procedure for Cu–NHC-catalyzed conjugate addition of *in situ prepared Ph_2Zn* to unsaturated cyclic γ-ketoesters:** An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.21** (3.07 mg, 2.50 μmol) and

$(CuOTf)_2•C_6H_6$ (1.3 mg, 2.50 μmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath). Another oven-dried 13x100 mm test tube was charged with $ZnCl_2$ (0.124 g, 0.900 mmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. Diethyl ether (2.2 mL) was added through a syringe to the test tube containing $ZnCl_2$, first allowing the $ZnCl_2$ to dissolve and then allowing the mixture to cool to 0 °C. Phenyllithium (818 μL, 1.80 mmol, 2.20 M in *n*-Bu_2O) was added dropwise through a syringe to the test tube containing a solution of $ZnCl_2$ in Et_2O and allowed to stir at 22 °C for 15 minutes. During this time the solution of PhLi + $ZnCl_2$ becomes cloudy. The test tube, now containing a solution of Ph_2Zn and solid LiCl, was centrifuged for 15 minutes to assist with settling of the LiCl to the bottom of the test tube. At this time, 1.0 mL of the Ph_2Zn solution was added through a syringe to the test tube containing $(CuOTf)_2•C_6H_6$ and chiral Ag complex **2.21**, cooled to –30 °C (dry ice/acetone). The resulting mixture was allowed to stir for five minutes. A solution of methyl 3-oxocyclohex-1-enecarboxylate (**2.16**) (15.4 mg, 0.100 mmol) in Et_2O (500 μL) was added through a syringe. After 24 h at –30 °C (cryocool), the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, to afford a yellow oil that was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 19.0 mg (0.0820 mmol, 82.0%) of the desired product as a white solid.

(*R*)-Methyl-1-methyl-3-oxocyclohexanecarboxylate (ent-2.19): IR (neat): 2952 (m), 2877 (w), 1734 (s), 1462 (m), 1318 (w), 1208 (m), 1168 (m), 1139 (m), 1110 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.61 (3H, s), 2.66 (1H, dt, *J* = 14.8, 1.6 Hz), 2.31–2.24 (1H, m), 2.21–2.13 (1H, m), 2.11–2.02 (2H, m), 1.89–1.79 (1H, m), 1.73–1.60 (2H, m), 1.19 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.3, 176.6, 52.3, 50.0, 46.7, 40.3, 34.7, 24.8, 22.2; HRMS (EI+): Calcd for $C_9H_{14}O_3$: 170.094294, Found: 170.094668; Specific Rotation: $[\alpha]_D^{20}$ –17.7 (c = 1.66, $CHCl_3$) for an enantiomerically enriched sample of 89.5:10.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.7:5.3 er shown; β-dex column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area (%)
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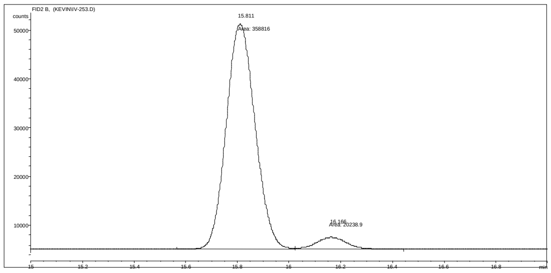
2	16.21	36690.4	4424.2	0.1382	49.964



#	Time	Area	Height	Width	Area (%)
1	15.811	358815.7	46138.6	0.1296	94.734
2	16.166	20238.9	2447.1	0.1378	5.265

Proof of absolute stereochemistry: Basic hydrolysis (LiOH (5.0 equiv), thf/H_2O (0.8 M/0.8 M) 0 °C → 22 °C, 30 minutes, 68% yield, unoptimized) of (*R*)-methyl 1-methyl-3-oxocyclohexanecarboxylate yielded (*R*)-1-methyl-3-oxocyclohexanecarboxylic acid. $[\alpha]_D^{20}$ –13.1 (c = 0.806, $CHCl_3$) for an enantiomerically enriched sample with 89.5:10.5 er. Literature: $[\alpha]_D^{22}$ –14.0 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample with 92.5:7.5 er in the *R* enantiomer.[53]

(*R*)-*tert*-Butyl-1-methyl-3-oxocyclohexanecarboxylate (2.35): IR (neat): 2978 (m), 2941 (m), 2884 (w), 1737 (s), 1469 (m), 1379 (m), 1327 (m), 1264 (m), 1232 (m), 1158 (s), 1132 (s), 848 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.67 (1H, dt, J = 14.4, 2.0 Hz), 2.39–2.31 (1H, m), 2.20 (1H, dddd, J = 16.0, 9.6, 6.4, 1.2 Hz), 2.11–2.05 (2H, m), 1.95–1.86 (1H, m), 1.82–1.68 (1H, m), 1.63 (1H, ddd, J = 14.0, 10.4, 4.0 Hz), 1.42 (9H, s), 1.21 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.6, 175.3, 81.3, 50.3, 47.1, 40.3, 34.9,

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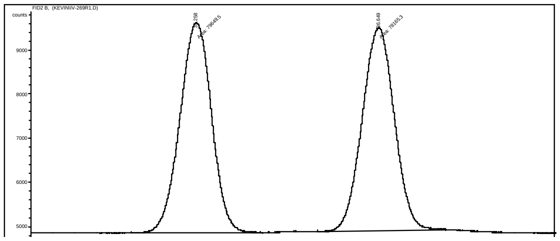
(53) "Formaldehyde Dialkylhydrazones as Neutral Formyl Anion Cyanide Equivalents: Nucleophilic Addition to Conjugated Enones," Díez, E.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E.; Vázquez, J. *J. Org. Chem.* **1997**, *62*, 5144–5155.

28.1, 25.2, 22.3; HRMS (CI+): Calcd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.149070, Found: 213.149254; Specific Rotation: $[\alpha]_D^{20}$ –19.6 (c = 1.25, $CHCl_3$) for an enantiomerically enriched sample with 92.5:7.5 er.

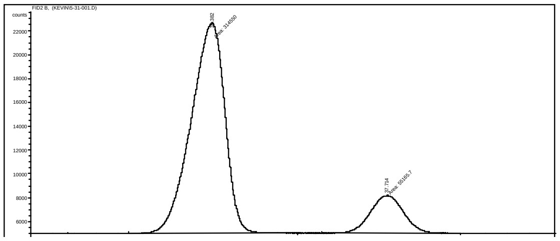
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 140 °C, t_{major} = 19.98 min, t_{minor} = 20.25 min).

***(R)*-Methyl-1-isopropyl-3-oxocyclohexanecarboxylate (2.36):** IR (neat): 2969 (m), 2877 (w), 1741 (s), 1567 (w), 1451 (m), 1382 (m), 1295 (m), 1242 (m), 1208 (m), 1167 (m), 1127 (m), 1092 (m), 988 (w), 889 (w), 750 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (3H, s), 2.70 (1H, dt, J = 14.8, 2.4 Hz), 2.40–2.33 (1H, m), 2.21–1.91 (5H, m), 1.75 (1H, dt, J = 12.8, 3.6 Hz), 1.58–1.46 (1H, m), 0.91 (3H, d, J = 6.8 Hz), 0.84 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.8, 176.1, 54.7, 52.1, 43.8, 40.6, 34.9, 31.9, 22.4, 18.2, 17.2; HRMS (EI+): Calcd for $C_{11}H_{18}O_3$ $[M]^+$: 198.1255, Found: 198.1263; Specific Rotation: $[\alpha]_D^{20}$ –23.8 (c = 0.673, $CHCl_3$) for an enantiomerically enriched sample with 85:15 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (84.9:15.1 er shown; β-dex column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area (%)
1	35.258	79649.5	4750.4	0.2794	50.546
2	36.649	78165.3	4595.4	0.2835	49.454

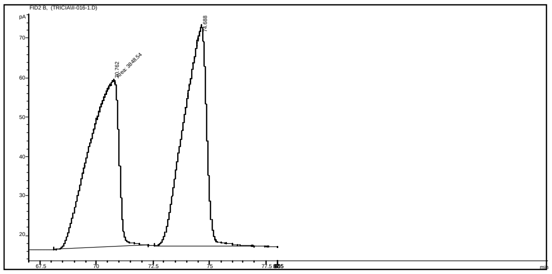


#	Time	Area	Height	Width	Area (%)
1	36.382	314549.9	17661.7	0.2968	84.851
2	37.714	55165.7	3147.9	0.2921	15.149

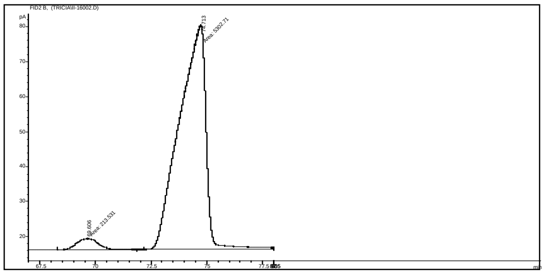
(*R*)-Methyl-3-oxo-1-phenylcyclohexanecarboxylate (2.37): mp: 96–98 °C; IR (neat): 2974 (m), 2961 (m), 2955 (m), 2879 (w), 1727 (s), 1495 (w), 1451 (m), 1325 (m), 1300 (m), 1249 (s), 1211 (s), 1155 (m), 1111 (m), 985 (w), 885 (w), 783 (w), 746 (m), 714 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (4H, m), 7.28–7.24 (1H, m), 3.64 (3H, s), 3.04 (1H, dt, J = 14.8, 1.6 Hz), 2.74 (1H, d, J = 14.8 Hz), 2.57–2.51 (1H, m), 2.42–2.24

(3H, m), 1.88–1.66 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 208.8, 174.9, 141.3, 129.1, 127.7, 126.2, 54.1, 52.8, 49.5, 40.5, 33.3, 21.7; HRMS (EI+): Calcd for $C_{14}H_{16}O_3$ $[M]^+$: 232.2750, Found 232.1096; Specific Rotation: $[\alpha]_D^{20}$ –4.61 (*c* = 0.700, CHCl$_3$) for an enantiomerically enriched sample with 96:4 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.1:3.9 er shown; chiral dex GTA column, 15 psi, 140 °C).

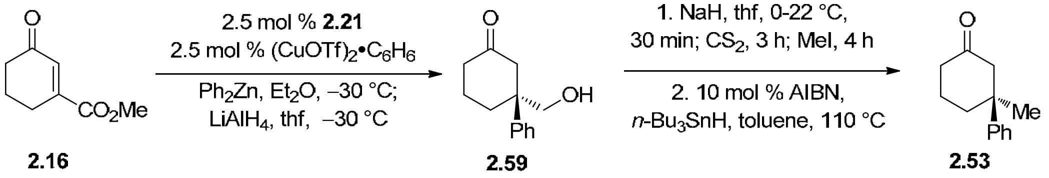


#	Time	Area	Height	Width	Area%
1	70.762	3848.5	42.3	1.5154	49.297
2	74.688	3958.2	56	1.1783	50.703



#	Time	Area	Height	Width	Area%
1	69.606	213.5	3.2	1.1166	3.871
2	74.713	5302.7	64	1.3818	96.129

Proof of absolute stereochemistry: The following sequence was carried out in order to obtain enantiomerically enriched material (*S*)-3-methyl-3-phenylcyclohexanone.



known absolute chemistry

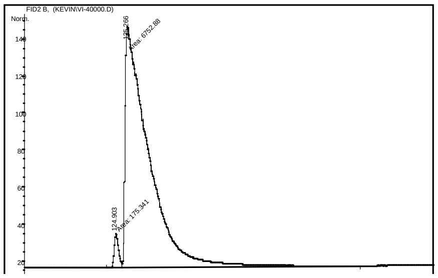
An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol), $(CuOTf)_2•C_6H_6$ (1.3 mg, 2.50 μmol), and Ph_2Zn (65.7 mg, 0.300 mmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath) and Et$_2$O (1.0 mL) was added through a syringe. The resulting mixture was allowed to stir for 10 minutes. (During this time the mixture became dark brown.) At this time, methyl 3-oxocyclohex-1-enecarboxylate (**2.16**) (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe. After 42 h at –30 °C, LiAlH$_4$ (18.9 mg, 0.500 mmol) was added as a solution in thf (500 μL) via cannula. After 10 minutes at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of sodium potassium tartrate (5 mL) and diluted with CH_2Cl_2 (5 mL). The mixture was allowed to warm to 22 °C and stir for 2 h before it was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford a clear oil. The clear oil was purified by silica gel chromatography (10% Et_2O/hexanes) to yield 9.6 mg of an inseparable mixture of ketoalcohol **2.59** and an unidentified compound (~25%). The mixture was carried on in the subsequent transformation.

Note: The following procedures are unoptimized. To a suspension of NaH (2.2 mg, 0.037 mmol, 60% dispersion in mineral oil) in thf (250 μL) at 0 °C was added ketoalcohol **2.59** (7.0 mg, 0.034 mmol) dissolved in thf (250 μL) via cannula. The mixture was allowed to warm to 22 °C and stir for 1 h. At this time, CS_2 (8.2 μL, 0.14 mmol) was added to the mixture through a syringe resulting in a yellow solution. The mixture was allowed to stir for 3 h until MeI (6.7 mL, 0.11 mmol) was added through a syringe. After 30 min, the reaction was quenched upon addition of H_2O (1 mL) and washed with $CHCl_3$ (2 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated, resulting in a yellow solid that was purified by silica gel chromatography (10% Et_2O/petroleum ether → 30% Et_2O/petroleum ether) to afford 2.6 mg of the desired xanthate contaminated with minor impurities. This material was carried on in the subsequent transformation.

2,2'-Azobisisobutyronitrile (0.10 mg, 0.84 μmol) was added to the xanthate (2.6 mg, 0.0084 mmol) and Bu_3SnH (5.6 mL, 0.21 mmol) dissolved in toluene (250 μL) in a screw cap vial. The vial was sealed with a cap and allowed to stir at 110 °C. After 1 h, the mixture was allowed to cool to 22 °C and was passed through a short plug of silica gel (4 cm x 1 cm) eluted with 50% Et_2O/petroleum ether. The volatiles were removed in vacuo, resulting in a clear oil that was purified by silica gel chromatography (25% Et_2O/petroleum ether) to afford **2.53** as a colorless oil. The ^1H NMR spectrum of 3-methyl-3-phenylcyclohexanone was identical to previously reported data.[4f] Based on the retention times from GLC chromatograms (illustrated below) of 3-methyl-3-

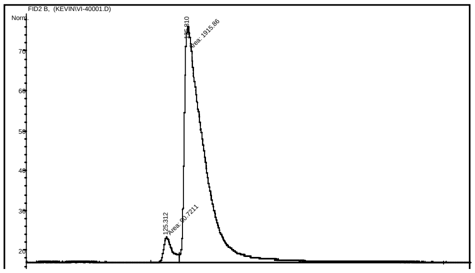
phenylcyclohexanone derived from reactions outlined in ref 4f (which was assigned *S* absolute stereochemistry), we assigned *R* absolute stereochemistry to the product **2.37**.

from ref 4f:



#	Time	Area	Height	Width	Area (%)
1	124.903	175.3	18.8	0.1556	2.528
2	125.266	6752.9	129.8	0.8671	97.47

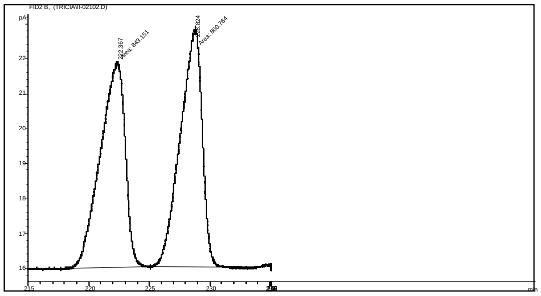
from ***2.16*** *(Scheme above)*

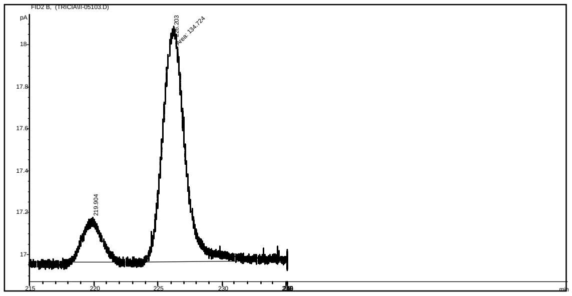


#	Time	Area	Height	Width	Area (%)
1	125.312	90.7	6.5	0.2326	4.520
2	125.81	1915.9	59.2	0.5391	95.48

(*R*)-*tert*-Butyl-3-oxo-1-phenylcyclohexanecarboxylate (2.38): IR (neat): 3062 (w), 2974 (w), 2936 (w), 2873 (w), 2363 (w), 2326 (w), 1722 (s), 1451 (m), 1369 (m), 1250 (m), 1162 (m), 1149 (m), 1111 (w), 847 (w), 771 (w), 696 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33−7.30 (4H, m), 7.25–7.23 (1H, m), 3.00 (1H, dd, *J* = 13.2, 1.6 Hz), 2.62 (1H, d, *J* = 15.2 Hz), 2.52–2.49 (1H, m), 2.43–2.36 (1H, m), 2.28–2.23 (2H, m), 1.86–1.78 (2H, m), 1.34 (9H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 209.1, 175.3, 142.1, 128.8, 127.3, 126.0, 81.8, 54.6, 49.9, 40.5, 33.2, 27.9, 21.7; HRMS (CI+): Calcd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1647, Found 275.1653; Specific Rotation: $[\alpha]_D^{20}$ –5.3 (*c* = 0.75, CHCl$_3$) for an enantiomerically enriched sample with 89.5:10.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (87.0:13.0 er shown; chiral dex GTA column, 15 psi, 120 °C).



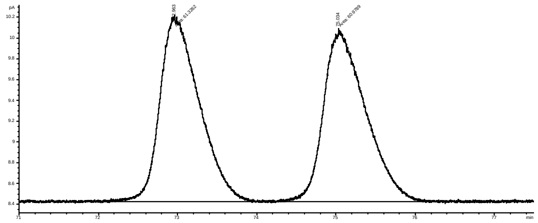


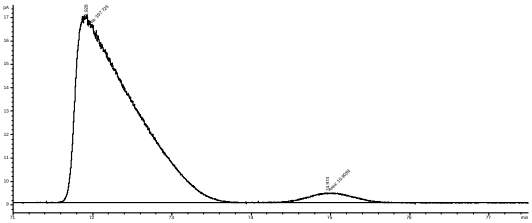
#	Time	Area	Height	Width	Area (%)
1	222.367	843.2	5.9	2.3859	49.483
2	228.824	860.8	6.9	2.0875	50.517

#	Time	Area	Height	Width	Area (%)
1	219.904	20.1	2.1E-1	1.5757	13.000
2	226.203	134.7	1.1	2.0044	87.000

(*R*)-Methyl-1-methyl-3-oxocyclopentanecarboxylate (ent-2.8): IR (neat): 2963 (m), 2929 (m), 2886 (w), 2750 (s), 1721 (s), 1475 (m), 1442 (m), 1413 (m), 1336 (m), 1244 (m), 1220 (s), 1177 (m), 1110 (m), 994 (w), 879 (w), 787 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.70 (3H, s), 2.74 (1H, d, J = 18.4 Hz), 2.41–2.27 (3H, m), 2.10 (1H, d, J = 18.4 Hz), 1.94–1.87 (1H, m), 1.36 (3H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 217.1, 177.0, 52.6, 49.4, 46.5, 36.9, 34.0, 24.1; HRMS (EI+): Calcd for $C_8H_{11}O_3$ $[M–H]^+$: 155.0708, Found: 155.0713; Specific Rotation: $[\alpha]_D^{20}$ –12.7 (c = 1.50, CHCl$_3$) for an enantiomerically enriched sample with 96:4 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.9:4.1 er shown; β-dex column, 15 psi, 90 °C).



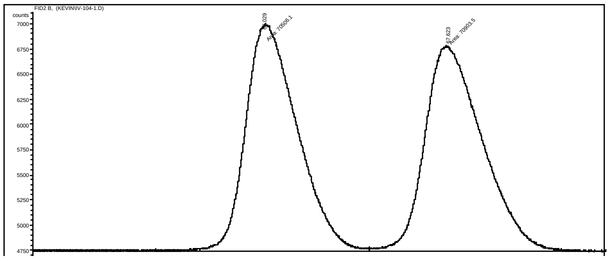


#	Time	Area	Height	Width	Area (%)
1	72.963	61.3	1.8	0.567	50.142
2	75.034	61	1.7	0.6099	49.858

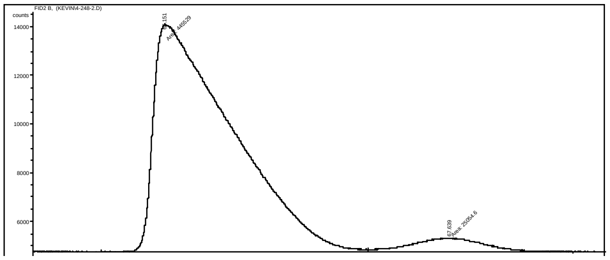
#	Time	Area	Height	Width	Area%
1	71.928	397.7	8	0.8242	95.923
2	74.973	16.9	4.2E-1	0.6733	4.077

(*R*)-*tert*-Butyl-1-methyl-3-oxocyclopentanecarboxylate (2.39): IR (neat): 2983 (m), 2946 (w), 2879 (w), 1759 (s), 1729 (s), 1613 (w), 1466 (w), 1368 (m), 1246 (m), 1160 (s), 1111 (m), 854 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.70 (1H, d, J = 18.0 Hz), 2.41–2.24 (3H, m), 2.06 (1H, d, J = 18.0 Hz), 1.91–1.82 (1H, m), 1.44 (9H, s), 1.33 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): 217.6, 175.7, 81.3, 49.5, 47.2, 37.1, 34.1, 28.1, 24.1; HRMS (CI+): Calcd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1334, Found: 199.1334; Specific Rotation: $[\alpha]_D^{20}$ –21.3 (*c* = 1.05, $CHCl_3$) for an enantiomerically enriched sample with 95:5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.7:5.3 er shown; β-dex column, 15 psi, 100 °C).



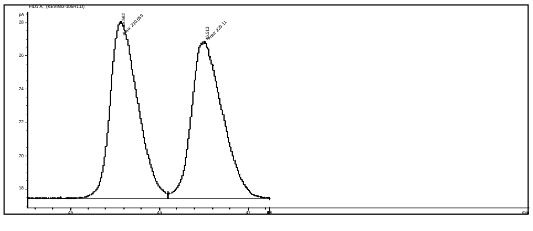
#	Time	Area	Height	Width	Area (%)
1	66.029	70506.1	2252.3	0.5217	49.859
2	67.623	70903.5	2040.2	0.5792	50.141



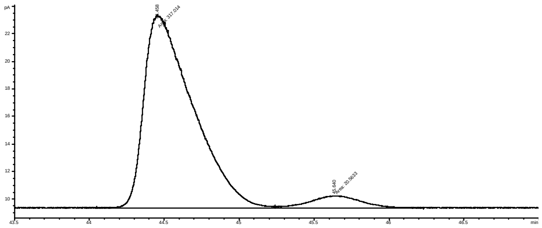
#	Time	Area	Height	Width	Area (%)
1	65.151	445508.2	9378.6	0.7917	94.675
2	67.639	25054.6	561.7	0.7434	5.325

(*R*)-Methyl-1-ethyl-3-oxocyclopentanecarboxylate (ent-2.2): IR (neat): 2977 (m), 2885 (w), 1759 (s), 1729 (s), 1466 (w), 1350 (w), 1258 (m), 1203 (m), 1166 (m), 995 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.68 (3H, s), 2.73 (1H, d, *J* = 18.4 Hz), 2.36 (1H, ddd, *J* = 8.4, 7.2, 1.2 Hz), 2.25 (2H, dd, *J* = 7.2, 7.2 Hz), 2.09 (1H, d, *J* = 18.4 Hz), 1.92–1.79 (2H, m), 1.68–1.59 (1H, m), 0.85 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.1, 176.3, 52.4, 51.8, 47.1, 36.9, 32.4, 31.3, 10.1; HRMS (EI+): Calcd for $C_9H_{14}O_3$ $[M]^+$: 170.0943, Found: 170.0941; Specific Rotation: $[\alpha]_D^{20}$ –45.1 (*c* = 0.286, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.9:6.1 er shown; β-dex column, 15 psi, 110 °C).



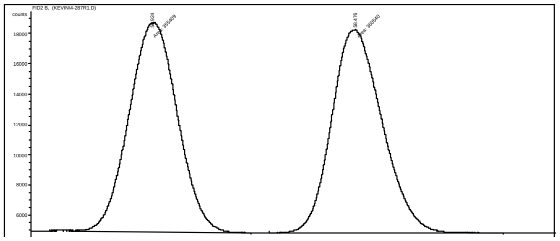
#	Time	Area	Height	Width	Area%
1	45.562	230.7	10.6	0.3611	50.168
2	46.513	229.1	9.4	0.4054	49.832



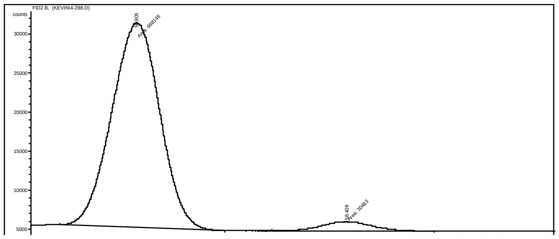
#	Time	Area	Height	Width	Area%
1	44.458	317	14	0.377	93.909
2	45.64	20.6	8.8E-1	0.3916	6.091

(*R*)-*tert*-Butyl-1-isopropyl-3-oxocyclopentanecarboxylate (2.40): IR (neat): 2975 (m), 2929 (w), 2877 (w), 1752 (s), 1718 (s), 1463 (w), 1376 (m), 1266 (m), 1156 (s), 854 (w), 675 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.75 (1H, d, *J* = 18.4 Hz), 2.42–2.36 (1H, m), 2.31–2.14 (2H, m), 2.06–1.95 (2H, m), 1.86 (1H, ddd, *J* = 13.2, 10.4, 10.4 Hz), 1.44 (9H, s), 0.95 (6H, dd, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.7, 174.7, 81.4, 56.2, 45.4, 37.5, 35.2, 30.8, 28.1, 18.7, 18.5; HRMS (CI+): Calcd for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1647, Found: 227.1644; Specific Rotation: $[\alpha]_D^{20}$ –100 (*c* = 0.893, $CHCl_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.6:4.4 er shown; β-dex column, 15 psi, 120 °C).



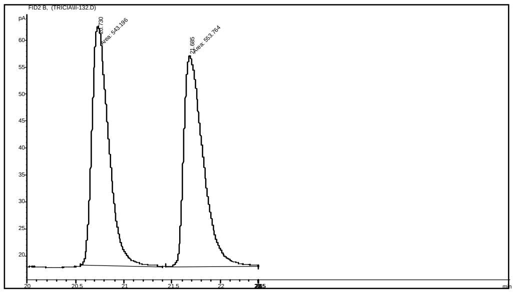
#	Time	Area	Height	Width	Area (%)
1	56.924	355409.4	13815.9	0.4287	49.599
2	58.476	360539.9	13413.4	0.448	50.400



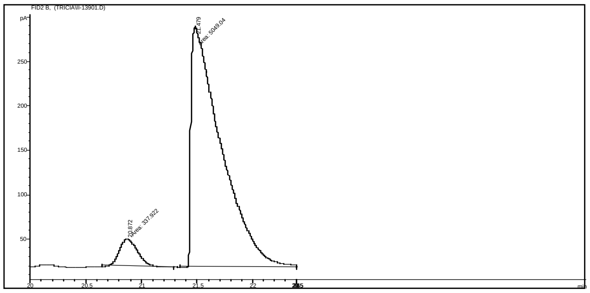
#	Time	Area	Height	Width	Area (%)
1	56.805	668145.7	26211	0.4248	95.618
2	58.409	30483	1143.6	0.4443	4.382

(*R*)-Methyl-1-(4-methylpentyl)-3-oxocyclopentanecarboxylate (2.41): IR (neat): 2955 (m), 2867 (w), 1747 (s), 1734 (s), 1457 (w), 1407 (w), 1388 (w), 1369 (w), 1338 (w), 1205 (m), 1155 (s), 985 (w), 872 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (3H, s), 2.79 (1H, dd, *J* = 18.4, 1.2 Hz), 2.43–2.36 (1H, m), 2.28 (2H, t, *J* = 8.8 Hz), 2.12 (1H, d, *J* = 18.4 Hz), 1.95–1.87 (1H, m), 1.83–1.76 (1H, m), 1.60–1.48 (2H, m), 1.26–1.12 (4H, m), 0.86 (3H, s), 0.84 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.1, 176.5, 52.4, 51.3, 47.6, 39.2, 38.8, 36.9, 32.9, 27.9, 23.6, 22.7, 22.7; HRMS (EI^+): Calcd for $C_{13}H_{22}O_3$ $[M]^+$: 226.1569, Found: 226.1569; Specific Rotation: $[\alpha]_D^{20}$ –30.8 (*c* = 0.647, $CHCl_3$) for an enantiomerically enriched sample with 93.5:6.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.7:6.3 er shown; chiral dex GTA column, 15 psi, 140 °C).



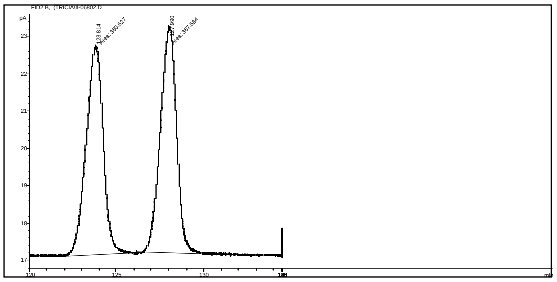
#	Time	Area	Height	Width	Area (%)
1	20.73	543.2	44.4	0.2039	49.518
2	21.685	553.8	39.3	0.2351	50.482



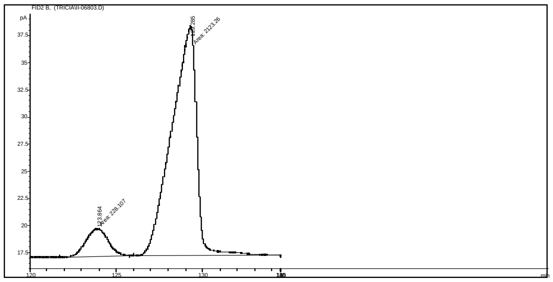
#	Time	Area	Height	Width	Area (%)
1	20.872	337.9	30.2	0.1864	6.273
2	21.479	5049	269.6	0.3122	93.727

(*R*)-*tert*-Butyl-3-oxo-1-phenylcyclopentanecarboxylate (2.42): mp: 69–74 °C; IR (neat): 2950 (m), 2930 (m), 1747 (s), 1722 (s), 1596 (w), 1501 (w), 1451 (w), 1394 (w), 1369 (m), 1148 (s), 847 (m), 702 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36–7.25 (5H, m), 3.20 (1H, dd, *J* = 18.0, 2.0 Hz), 2.96–2.90 (1H, m), 2.54 (1H, d, *J* = 18.0 Hz), 2.35–2.25 (3H, m), 1.33 (9H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 216.3, 173.5, 141.8, 128.8, 127.5, 126.6, 82.0, 55.9, 48.4, 37.3, 33.0, 27.9; HRMS (CI+): Calcd for $C_{16}H_{21}O_3$ [M+H]$^+$: 261.1492, Found 261.1491; Specific Rotation: $[\alpha]_D^{20}$ –7.11 (*c* = 0.780, CHCl$_3$) for an enantiomerically enriched sample with 89.5:10.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (90.3:9.7 er shown; chiral dex GTA column, 15 psi, 120 °C).



#	Time	Area	Height	Width	Area (%)
1	123.814	380.6	5.6	1.133	49.547
2	127.99	387.6	6.1	1.0667	50.453

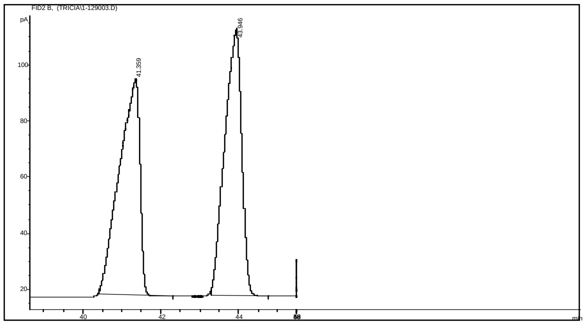


#	Time	Area	Height	Width	Area (%)
1	123.864	228.1	2.6	1.4718	9.701
2	129.285	2123.3	21.2	1.6727	90.299

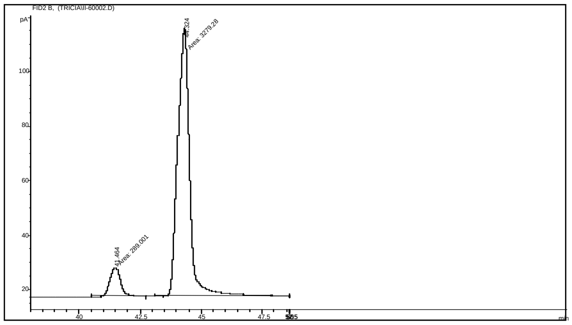
(*R*)-Methyl-3-oxo-1-phenylcyclopentanecarboxylate (ent-2.13): IR (neat): 2962 (w), 2924 (m), 2848 (w), 1753 (s), 1734 (s), 1445 (w), 1249 (m), 1212 (m), 1162 (m), 752 (m), 695 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36–7.24 (5H, m), 3.64 (3H, s), 3.23

(1H, dd, J = 16.0, 2.0 Hz), 2.98–2.95 (1H, m), 2.62 (1H, d, J = 18.0 Hz), 2.35–2.32 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 175.0, 141.3, 129.0, 127.8, 126.6, 55.2, 53.1, 48.4, 37.2, 33.0; Elemental Analysis: Anal Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; Found C, 71.53; H, 6.68; Specific Rotation: $[\alpha]_D^{20}$ –7.05 (c = 0.313, $CHCl_3$) for an enantiomerically enriched sample with 91.5:8.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (91.9:8.1 er shown; chiral dex GTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area (%)
1	41.359	2848.3	77.1	0.4342	49.748
2	43.946	2877.2	94.9	0.3579	50.252

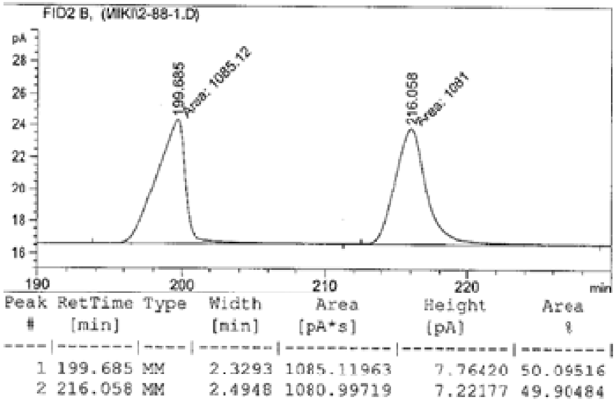


#	Time	Area	Height	Width	Area (%)
1	41.464	289	10.3	0.4693	8.099
2	44.324	3279.3	97.7	0.5593	91.901

■ **Experimental general procedure for Cu-catalyzed ECAs of Me_2Zn to enones/tandem aldol cyclization:** In a N_2-filled glove box, an oven-dried 5 mL vial equipped with a stir bar was charged with $(CuOTf)_2$•C_6H_6 (1.30 mg, 0.003 mmol) and NHC–Ag **2.22** (3.00 mg, 0.003 mmol). The vial was sealed with a septum, wrapped with parafilm and removed from the glove box. t-Butylmethylether (1 mL) was added and the solution was allowed to stir at 22 °C for 5 min (wrapped with aluminum foil). The vial was allowed to cool to –30 °C (dry ice/acetone bath) and Me_2Zn (21.0 μL, 0.300 mmol) (Caution! dialkylzinc reagents are pyrophoric!) was added through a syringe followed by the addition of enone **2.16** (15.6 mg, 0.100 mmol). The reaction was allowed to stir at –30 °C in a cryocool. After 24 h, benzaldehyde (20.0 μL, 0.200 mmol) was added and the solution was allowed to stir for 4 h, at which time the reaction was quenched by saturated aqueous solution of NH_4Cl (2 mL). The organic layers were separated and the aqueous layer was washed with Et_2O (3 x 2 mL). The combined organic layers were passed through a short plug of silica gel and concentrated under reduced pressure. The colorless oil was purified by silica gel chromatography (pentane/Et_2O = 9/1) to afford the desired product **2.46a** as a colorless oil (20.1 mg, 0.082 mmol, 82% yield).

(3*S*, 3a*S*, 7a*R*)-7a-methyl-3-phenylhexahydroisobenzofuran-1,4-dione (2.46a): IR (neat): 2967 (w), 2923 (m), 2851 (w), 1765 (s), 1702 (s), 1458 (m), 1450 (m), 1416 (m), 1383 (m), 1374 (m), 1351 (w), 1330 (m), 1294 (w), 1283 (w), 1260 (m), 1238 (m), 1223 (w), 1198 (w), 1166 (s), 1137 (m), 1113 (s), 1048 (w), 1030 (w), 1016 (w), 985 (m), 975 (s), 955 (s), 920 (m), 887 (m), 865 (m), 772 (s), 756 (w), 730 (w), 702 (s), 695 (s), 651 (m), 619 (w), 558 (s), 531 (w), 502 (m), 445 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.30 (5H, m), 5.75 (1H, d, *J* = 6.0 Hz), 2.87 (1H, d, *J* = 6.0 Hz), 2.62 (1H, ddd, *J* = 16.0, 8.4, 6.0 Hz), 2.48–2.41 (1H, m), 2.19 (1H, ddd, *J* = 14.0, 8.8, 3.6 Hz), 2.06–1.88 (2H, m), 1.79 (1H, ddd, *J* = 14.0, 7.6, 3.6 Hz), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 179.3, 138.7, 128.8, 129.5, 124.9, 78.1, 63.1, 46.8, 39.1, 31.5, 24.0, 21.1; HRMS (ES+): Calcd for $C_{15}H_{16}O_3Na$ $[M+Na]^+$: 267.0997, Found: 267.0992; Specific Rotation: $[\alpha]_D^{20}$ –30.6 (*c* = 0.71, $CHCl_3$) for an enantiomerically enriched sample of 92.5:7.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.4:5.6 er shown, chiral dex GTA column, 15 psi, 140 °C).



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   2 216.058 MM    2.4948 1080.99719    7.22177 49.90484
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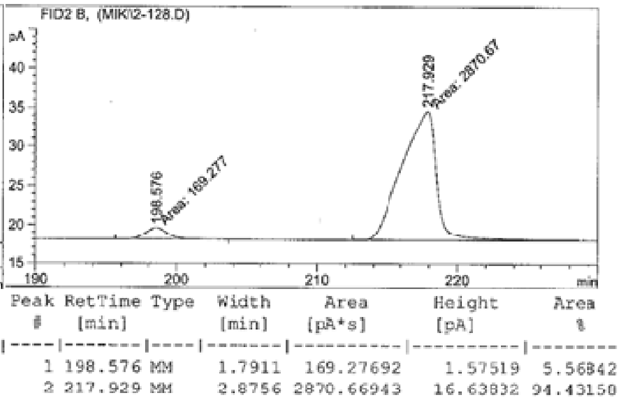

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Peak RetTime Type  Width     Area      Height     Area
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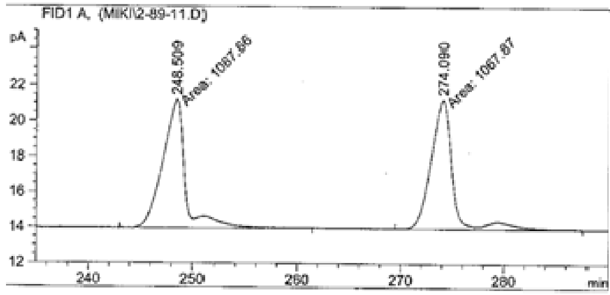
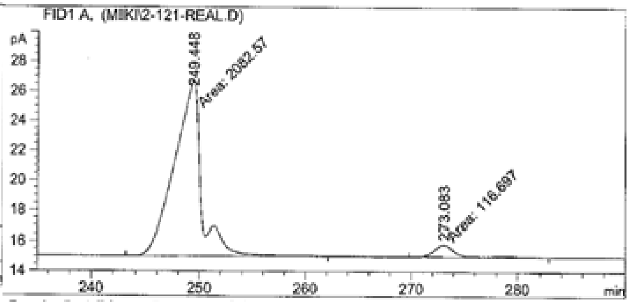
   1 198.576 MM    1.7911  169.27692    1.57519  5.56842
   2 217.929 MM    2.8756 2870.66943   16.63832 94.43150
```

7a-Methyl-3-pentyl-hexahydo-isobenzofuran-1,4-dione (2.46b): This product was characterized as a mixture with 5:1 dr. IR (neat): 2934 (m), 2871 (w), 1768 (s), 1708 (s), 1460 (m), 1381 (w), 1354 (w), 1336 (w), 1322 (w), 1288 (w), 1258 (w), 1238 (m), 1208 (w), 1168 (m), 1145 (m), 1123 (w), 1105 (m), 1046 (w), 1016 (m), 998 (m), 934 (m), 911 (w), 884 (w), 546 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64–4.57 (0.2H, m), 4.44 (1H, td, *J* = 8.4, 4.4 Hz), 2.56 (2H, d, *J* =8.8 Hz), 2.50–2.29 (2.2H, m), 2.04–1.88 (3.7H, m), 1.77–1.60 (3.2H, m), 1.56–1.49 (.5H, m), 1.35 (3.3H, s), 1.32–1.27 (6H, m), 0.89–0.86 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 179.4, 78.0, 61.7, 47.2, 38.6, 35.2, 31.3, 30.8, 25.1, 22.7, 22.4, 21.1, 13.9; HRMS (ESI+): Calcd for $C_{14}H_{23}O_3$ $[M+H]^+$: 230.1647, Found: 239.1646; Specific Rotation: $[\alpha]_D^{20}$ –53.2 (*c* = 0.650, $CHCl_3$) for an enantiomerically enriched sample of 94.5:5.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.7:5.3 er shown; β-dex column, 15 psi, 140 °C).





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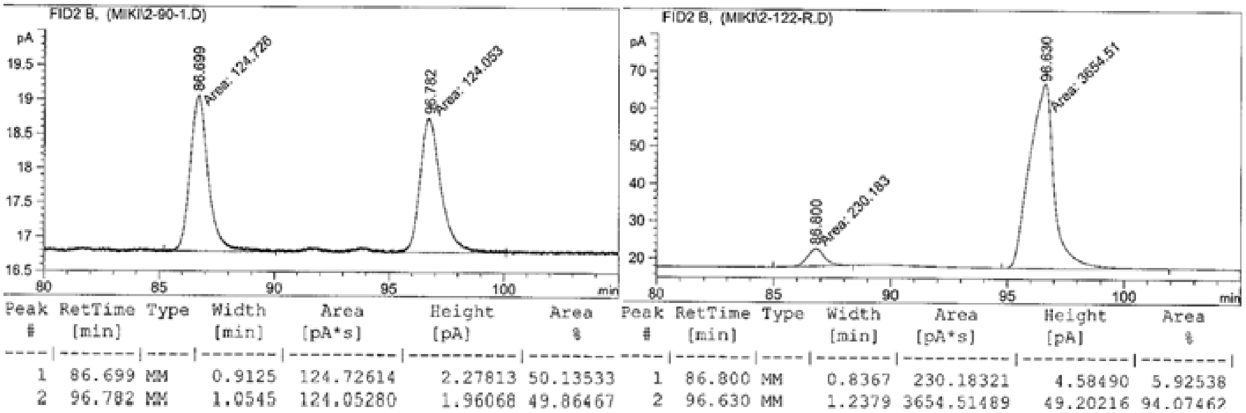
   1 249.448 MM    2.9678 2082.57275   11.69528 94.69382
   2 273.083 MM    2.3679  116.69724 8.21368e-1  5.30618
```

6a-Methyl-3-phenyl-tetrahydro-cyclopenta[c]furan-1,4-dione (2.12): IR (neat): 2971 (w), 2934 (w), 2876 (w), 1772 (s), 1742 (s), 1497 (w), 1452 (m), 1407 (w), 1379 (w), 1331 (w), 1281 (w), 1256 (w), 1215 (w), 1177 (w), 1157 (m), 1124 (m), 1058 (m), 1029 (m), 1001 (m), 911 (w), 737 (m), 698 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.31 (5H, m), 5.55 (1H, d, *J* = 2.8 H), 2.78 (1H, dd, *J* = 2.8, 0.8 Hz), 2.60–2.51 (2H, m), 2.44–2.34 (1H, m), 2.03–1.95 (1H, m), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.0, 180.5, 139.2, 128.9, 128.3, 124.4, 79.4, 62.2, 48.1, 37.6, 32.5, 23.1; HRMS (ESI+): Calcd for $C_{14}H_{15}O_3$ $[M+H]^+$: 231.1021, Found: 231.1018; Specific Rotation: $[\alpha]_D^{20}$ –134 (*c* = 0.410, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.1:5.9 er shown; chiral dex GTA column, 15 psi, 140 °C).



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Peak RetTime Type  Width      Area      Height      Area
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  1  86.699 MM     0.9125  124.72614    2.27813 50.13533
  2  96.782 MM     1.0545  124.05280    1.96068 49.86467
```

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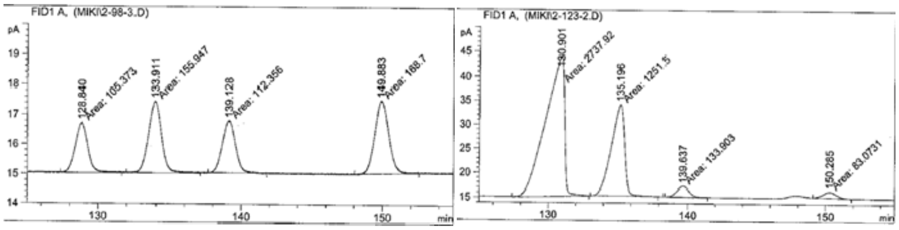
Peak RetTime Type  Width      Area      Height      Area
  #   [min]        [min]    [pA*s]       [pA]        %
----|-------|----|-------|----------|----------|--------|
  1  86.800 MM     0.8367  230.18321    4.58490  5.92538
  2  96.630 MM     1.2379 3654.51489   49.20216 94.07462
```

6a-Methyl-3-pentyl-tetrahydro-cyclopenta[c]furan-1,4-dione (2.47): This product was characterized as a mixture with 2:1 dr. IR (neat): 2954 (m), 2932 (m), 2861 (w), 1769 (s), 1741 (s), 2458 (m), 1410 (w), 1380 (w), 1351 (w), 1283 (w), 1198 (m), 1141 (m), 1113 (m), 1056 (w), 995 (m), 930 (w), 771 (w), 728 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.54 (0.6H, td, *J* = 8.4, 4.4 Hz), 4.44 (1H, ddd, *J* = 8.4), 2.55–2.11 (7.3H, m), 2.01–1.92 (1.5H, m), 1.84–1.63 (3.8H, m), 1.49 (3H, s), 1.47 (1.5H, s), 1.33–1.29 (8.9H, m), 0.90–0.87 (5.7H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 216.2, 214.4, 180.3, 79.9, 79.1, 69.3, 59.9, 56.7, 50.4, 48.4, 39.8, 37.7, 36.6, 35.4, 34.9, 33.0, 32.5, 32.0, 31.4, 31..2, 31.1, 25.9, 34.9, 32.5, 22.6, 22.4, 21.6, 17.2, 13.9. HRMS (ESI+): Calcd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1491, Found: 225.1490; Specific Rotation: $[\alpha]_D^{20}$ –148 (*c* = 0.660, CHCl$_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.5:4.5 er shown; β-dex column, 15 psi, 140 °C).



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Peak RetTime Type  Width     Area       Height     Area
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   2 133.911 MM    1.0693  155.94652    2.43073 28.75247
   3 139.128 MM    1.0588  112.35638    1.76862 20.71558
   4 149.883 MM    1.1378  168.70032    2.47122 31.10393
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Peak RetTime Type  Width     Area       Height     Area
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   2 135.196 MM    1.1061 1251.49658   18.85710 29.75229
   3 139.637 MM    1.0200  133.90253    2.18805  3.18331
   4 150.285 MM    1.0982   83.07314    1.26077  1.97493
```

■ Experimental procedure for Cu-catalyzed conjugate addition of *Me_2Zn* to unsaturated cyclic γ-ketoester 2.16 and in situ reduction with $LiAlH_4$

(*R*)-3-(hydroxymethyl)-3-methylcyclohexanone (2.50): An oven-dried 13x100 mm test tube was charged with chiral Ag complex **2.22** (3.02 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.30 mg, 2.50 μmol), under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before cooling to –78 °C (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 °C (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 °C, methyl 3-oxocyclohex-1-enecarboxylate (**2.16**) (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe. After 15 h at –30 °C, $LiAlH_4$ (4.00 mg, 0.100 mmol) dissolved in thf (1.0 mL) was added to the mixture via cannula. The solution was allowed to warm to 0 °C and stir for 6 h at which time the reaction was quenched upon addition of a saturated aqueous solution of sodium potassium tartrate (2.0 mL) and diluted with CH_2Cl_2 (2.0 mL). The resulting mixture was allowed to warm to 22 °C and stir for 2 h, after which time the reaction was washed with CH_2Cl_2 (4 x 2 mL). The combined organic layers were dried over $MgSO_4$ and filtered through filter paper. The volatiles were removed in vacuo resulting in a yellow oil, which was purified by silica gel column chromatography (50% Et_2O/petroleum ether) to afford 10.8 mg (0.0760 mmol, 76.0%) of the desired product as a clear oil. IR (neat): 3390 (br), 2955 (m), 2867 (m),

1703 (s), 1457 (w), 1420 (w), 1055 (m), 671 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (1H, d, *J* = 11.6 Hz), 3.36 (1H, d, *J* = 12.4 Hz), 2.36 (1H, d, *J* = 13.6 Hz), 2.32–2.23 (2H, m), 2.06 (1H, dt, *J* = 13.6, 1.6 Hz), 2.00–1.76 (3H, m), 1.52–1.47 (2H, m), 0.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 71.3, 50.1, 41.1, 32.8, 22.6, 22.2, 10.6; HRMS (EI+): Calcd for $C_8H_{14}O_2$ $[M]^+$: 142.0994, Found 142.0944.

■ **Experimental procedure for Cu-catalyzed conjugate addition of *aryl$_2$Zn* to β-substituted enones:**

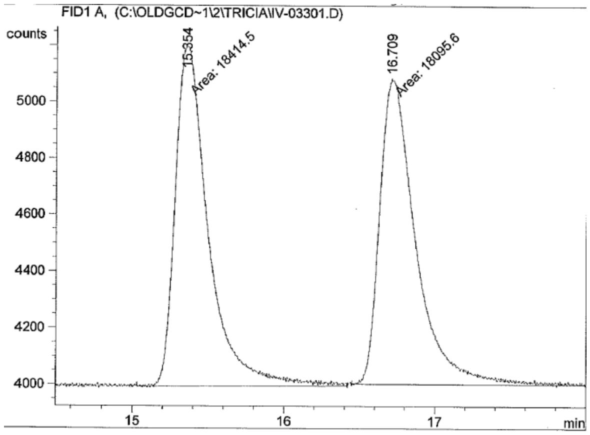
In a N_2-filled glove box, an oven-dried 5 mL vial was charged with $(CuOTf)_2•C_6H_6$ (5.00 mg, 0.010 mmol), NHC–Ag **2.22** (6.00 mg, 0.010 mmol) and diarylzinc (0.600 mmol). The vial was sealed with a septum, wrapped with parafilm and removed from the glove box. Diethylether (2 mL) was added and the solution was allowed to stir at 0 °C for 5 min (wrapped with aluminum foil) and then enone (0.200 mmol) was added. The reaction was allowed to stir for 48 h at 4 °C in a cold room, at which time the reaction was quenched by saturated aqueous solution of NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was washed with Et_2O (3 x 2 mL). The combined organic layers were passed through a short plug of silica gel and concentrated under reduced pressure. The colorless oil was purified by silica gel chromatography (pentane to pentane/Et_2O = 9/1) to afford the desired product.

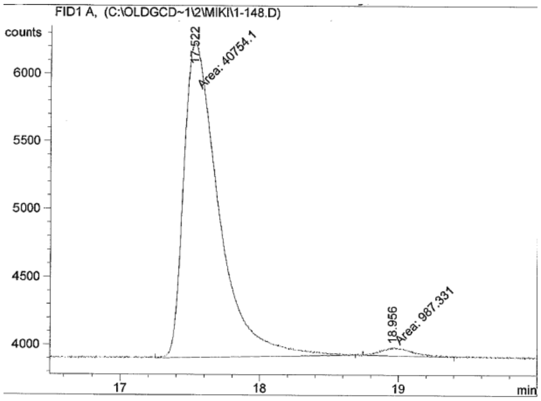
■ **Experimental procedure for Cu-catalyzed conjugate addition of *Et$_2$Zn* to β-substituted enones:**

In a N_2-filled glove box, an oven-dried 5 mL vial was charged with $(CuOTf)_2•C_6H_6$ (5.00 mg, 0.010 mmol) and NHC–Ag **2.22** (6.00 mg, 0.010 mmol). The vial was sealed with a septum, wrapped with parafilm and removed from the glove box. Diethylether (2 mL) was added and the solution was allowed to stir at 22 °C for 5 min (wrapped with aluminum foil). The vial was allowed to cool to 4 °C (ice bath) and Et_2Zn (61.0 μL, 0.600 mmol) (Caution! Dialkylzinc reagents are pyrophoric!) was added through a syringe followed by the addition of the enone (0.200 mmol). The reaction was allowed to stir for 24 h at 4 °C in a cold room, at which time the reaction was quenched by saturated aqueous solution of NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was washed with Et_2O (3 x 2 mL). The combined organic layers were passed through a short plug of silica gel and concentrated under reduced pressure. The colorless oil was purified by silica gel chromatography (pentane/Et_2O = 9/1) to afford the desired product.

(*R*)-3-Butyl-3-ethylcyclopentanone (Table 2.7, entry 3): IR (neat): 2958 (s), 2928 (s), 2860 (s), 2362 (m), 2341 (w), 1746 (s), 1498 (m), 1463 (m), 1379 (w), 1248 (w), 1172 (m), 1130 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (2H, t, *J* = 8.4 Hz), 2.05 (2H, s), 1.77 (2H, t, *J* = 7.6 Hz), 1.41 (2H, dq, *J* = 7.2, 0.8 Hz), 1.38–1.16 (6H, m), 0.90 (3H, dt, *J* = 7.2, 0.8 Hz), 0.84 (3H, dt, *J* = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.7, 51.0, 42.7, 37.1, 36.8, 33.0, 30.1, 26.6, 23.6, 14.3, 8.8; HRMS (EI+): Calcd for $C_{11}H_{21}O$ [M+H]$^+$: 169.159, Found: 169.159; Specific Rotation: $[\alpha]_D^{20}$ 0.74 (*c* = 0.81, $CHCl_3$) for an enantiomerically enriched sample with 97.5:2.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97.6:2.4 er shown; chiral dex GTA column, 15 psi, 110 °C).



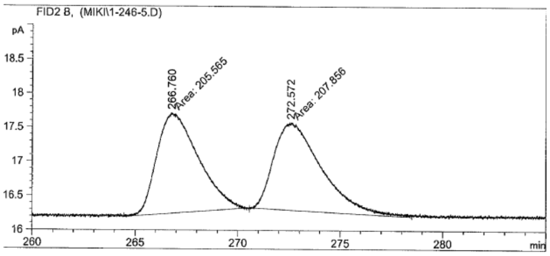


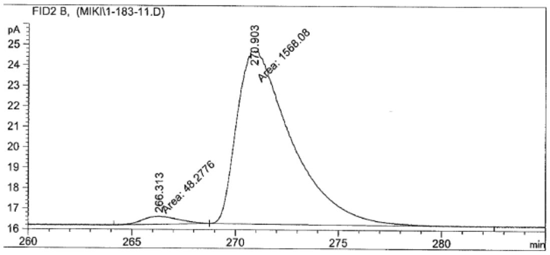
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	15.354	18414.5	1210.4	0.2536	50.44	1	17.522	40754.1	2329.4	0.2916	97.63
2	16.709	18095.6	1085.8	0.2778	49.56	2	18.956	987.33	65.031	0.2530	2.365

(*S*)-3-Butyl-3-phenylcyclopentanone (Table 2.7, entry 4): IR (neat): 2596 (m), 2927 (m), 2858 (m), 1740 (s), 1601 (w), 1497 (m), 1465 (m), 1445 (m), 1406 (m), 1378 (w), 1334 (w), 1158 (m), 1083 (w), 1033 (w), 866 (w), 768 (m), 752 (m), 729 (m), 700 (s) cm^{-}

^{1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35–7.31 (2H, m), 7.24–7.20 (3H, m), 2.67 (1H, d, J = 17.6 Hz), 2.51 (1H, d, J = 17.6 Hz), 2.37–2.21 (4H, m), 1.77–1.70 (1H, m), 1.65–1.58 (1H, m), 1.16 (2H, quint, J = 7.6 Hz), 1.02–0.94 (2H, m), 0.78 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 218.7, 146.3, 128.3, 126.3, 126.2, 50.7, 47.5, 41.7, 36.4, 34.4, 27.0, 23.0, 13.9; HRMS (ESI+): Calcd for $C_{15}H_{21}O$ [M+H]$^+$: 217.1592, Found: 217.1599; Specific Rotation: $[\alpha]_D^{20}$ 26.2 (c = 0.42, CHCl$_3$) for an enantiomerically enriched sample with 97:3 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97.0:3.0 er shown; chiral dex GTA column, 15 psi, 100 °C).

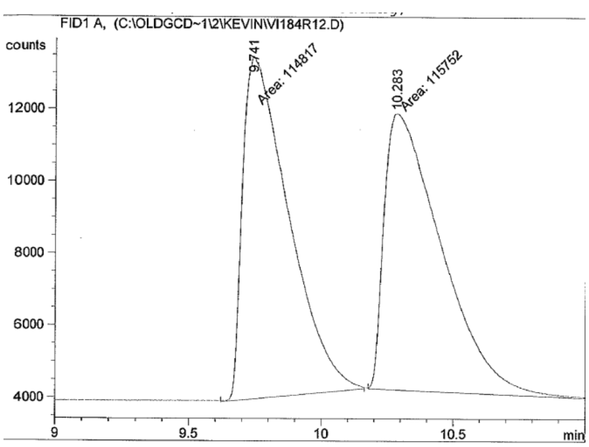


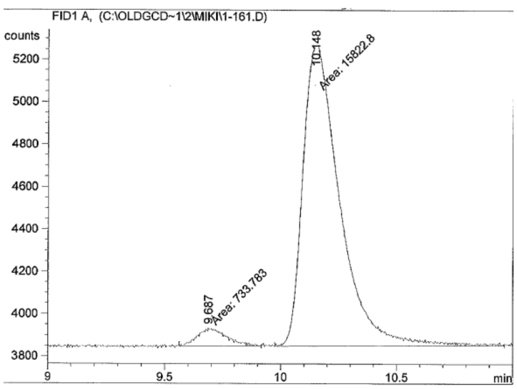


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	266.76	205.57	1.473	2.3257	49.723	1	266.31	48.278	4.126e-1	1.9500	2.987
2	272.57	207.86	1.286	2.6942	50.277	2	270.90	1568.08	8.468	3.0862	97.01

(*R*)-3-Ethyl-3-methylcyclopentanone (Table 2.7, entry 5): (This compound has been previously reported and spectra data matches those described.)^{4k} ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.31–2.26 (2H, m), 2.07 (1H, d, J = 18.0 Hz), 2.00 (1H, dt, J = 18.0, 0.8 Hz), 1.82–1.67 (2H, m), 1.44 (2H, q, J = 8.0 Hz), 1.03 (3H, s), 0.90 (3H, t, J = 7.2 Hz); Specific Rotation: $[\alpha]_D^{20}$ –21.0 (c = 1.19, CHCl$_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.6:4.4 er shown; chiral dex GTA column, 15 psi, 90 °C).

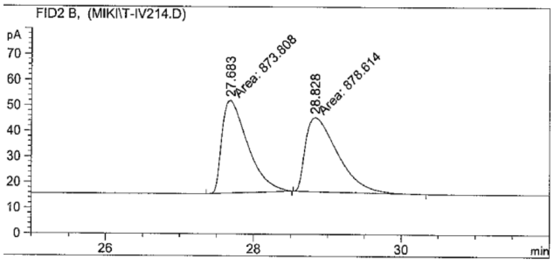




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	9.741	1.14817e5	9512.3	0.2012	49.80	1	9.687	733.78	87.291	0.1401	4.432
2	10.283	1.15752e5	7668.8	0.2516	50.20	2	10.148	15822.8	1422.9	0.1853	95.57

(*S*)-3-Methyl-3-phenylcyclopentanone (Table 2.7, entry 6): IR (neat): 3025 (w), 2961 (m), 2920 (m), 2873 (m), 1737 (s), 1501 (m), 1451 (m), 1409 (w), 1315 (w), 1277 (w), 1163 (m), 1079 (w), 1033 (w), 762 (w), 700 (m), 666 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.21 (5H, m), 2.66 (1H, d, *J* = 17.6 Hz), 2.48 (1H, dt, *J* = 17.6, 1.2 Hz), 2.44–2.35 (2H, m), 2.32–2.26 (2H, m), 1.39 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.8, 148.7, 128.8, 126.5, 125.7, 52.5, 44.0, 36.4, 36.0, 29.6; HRMS (EI+): Calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.11229, Found: 175.11161; Specific Rotation: $[\alpha]_D^{20}$ –10.1 (*c* = 1.03, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97.2:2.8 er shown; chiral dex GTA column, 15 psi, 120 °C).



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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  27.683 MM    0.4028  873.80847  36.15426 49.86288
   2  28.828 MM    0.5062  878.61438  28.92636 50.13712
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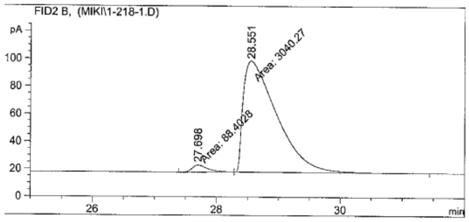

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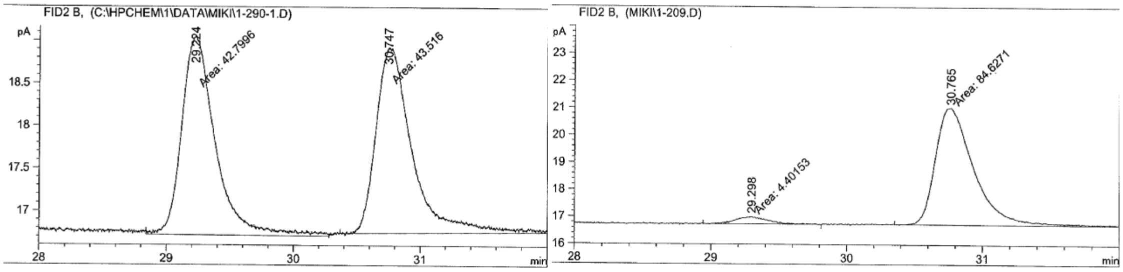
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  27.698 MM    0.2917   88.40279   5.05092  2.82557
   2  28.551 MM    0.6266 3040.26953  80.86738 97.17443
```

(*S*)-3-Methyl-3-(4-trifluromethylphenyl)cyclopentanone (Table 2.7, entry 7): IR (neat): 2662 (w), 1744 (s), 1618 (m), 1456 (w), 1409 (w), 1378 (m), 1328 (s), 1163 (m), 1121 (s), 1082 (w), 1067 (m), 1015 (w), 840 (m), 667 (w), 609 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (2H, dt, *J* = 8.0, 0.8 Hz), 7.40 (2H, dt, *J* = 8.0, 0.8 Hz), 2.64 (1H, d, *J* = 18.0 Hz), 2.51 (1H, dt, *J* = 18.0, 1.6 Hz), 2.47–2.38 (2H, m), 2.34–2.27 (2H, m), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 152.4, 125.9, 125.6, 125.5, 115.4, 51.9, 43.9, 36.5, 35.5, 29.2; Specific Rotation: $[\alpha]_D^{20}$ –15.4 (*c* = 0.94, $CHCl_3$) for an enantiomerically enriched sample with 95:5 er.

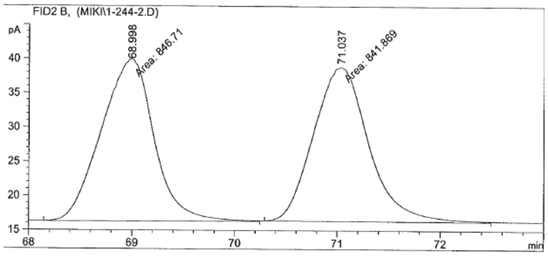
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.1:4.9 er shown; chiral dex GTA column, 15 psi, 130 °C).

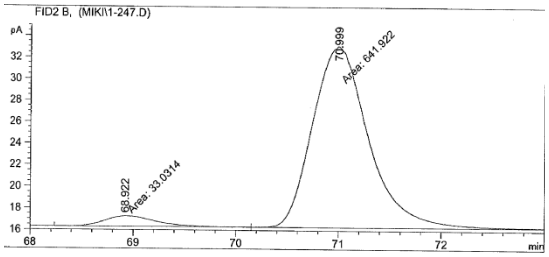


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	29.224	42.800	2.329	0.3063	49.59	1	29.298	4.402	2.72217e-1	0.2695	4.944
2	30.747	43.516	2.175	0.3334	50.41	2	30.765	84.63	4.300	0.3280	95.06

(*S*)-3-Methyl-3-(4-methoxyphenyl)cyclopentanone (Table 2.7, entry 8): IR (neat): 2955 (w), 2836 (w), 1736 (s), 1610 (w), 1579 (m), 1512 (w), 1462 (w), 1405 (w), 1376 (w), 1298 (s), 1247 (m), 1182 (w), 1157 (m), 1111 (w), 1079 (m), 1032 (w), 829 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.20 (2H, m), 6.89–6.86 (2H, m), 3.80 (3H, s), 2.62 (1H, d, *J* = 18.0 Hz), 2.46–2.33 (3H, m), 2.30–2.21 (2H, m), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.0, 158.2, 140.8, 126.7, 114.1, 55.5, 52.7, 43.4, 37.0, 36.3, 29.7; HRMS (ESI+): Calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229, Found: 205.122; Specific Rotation: $[\alpha]_D^{20}$ –5.63 (*c* = 0.21, $CHCl_3$) for an enantiomerically enriched sample with 95:5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.1:4.9 er shown; chiral dex GTA column, 15 psi, 130 °C).



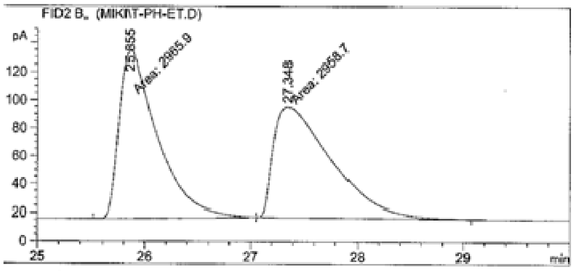


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	68.998	846.71	23.605	0.5978	50.143	1	68.922	33.031	9.8036e-1	0.5616	4.894
2	71.037	841.869	22.523	0.6230	49.86	2	70.999	641.92	16.83	0.6357	95.11

(*S*)-3-Ethyl-3-phenylcyclopentenone (Table 2.7, entry 9): IR (neat): 3063 (w), 3029 (w), 2970 (m), 2923 (m), 2877 (w), 1742 (s), 1602 (w), 1497 (w), 1442 (w), 1404 (w), 1374 (w), 1341 (w), 1290 (w), 1253 (w), 1159 (m), 758 (m), 700 (m), 670 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35–7.31 (2H, m), 7.23–7.21 (3H, m), 2.66 (1H, d, *J* = 18.0 Hz), 2.51 (1H, d, *J* = 17.6 Hz), 2.39–2.22 (4H, m), 1.76 (1H, dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz), 1.68 (1H, dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz), 0.66 (3H, dt, *J* = 7.2, 0.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 218.8, 146.1, 128.6, 126.7, 126.5, 50.5, 48.2, 36.6, 34.6, 34.0, 9.4; HRMS (ESI+): Calcd for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279, Found: 189.1276; Specific Rotation: $[\alpha]_D^{20}$ –10.4 (*c* = 0.77, CHCl$_3$) for an enantiomerically enriched sample with 96.5:3.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.6:3.4 er shown; chiral dex GTA column, 15 psi, 130 °C).

From entry 9:



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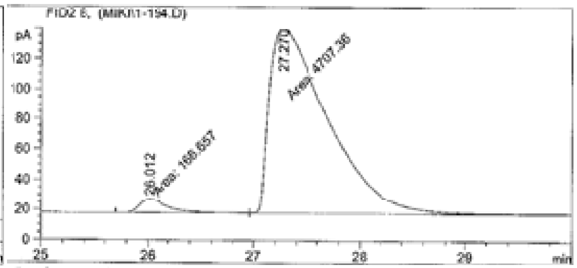
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]        [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  25.855 MM    0.4157 2965.90234  118.90854 50.06077
   2  27.348 MM    0.6265 2958.70190   78.70388 49.93923
```



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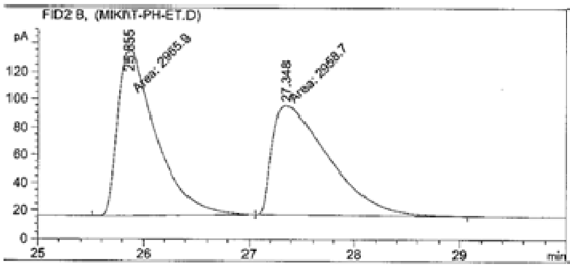
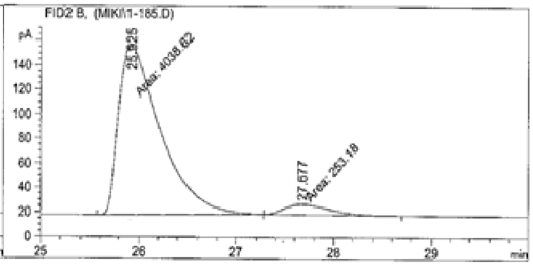
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]        [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  26.012 MM    0.2970  166.65739    9.35300  3.41930
   2  27.270 MM    0.6363 4707.35645  123.30732 96.58070
```

From entry 11:



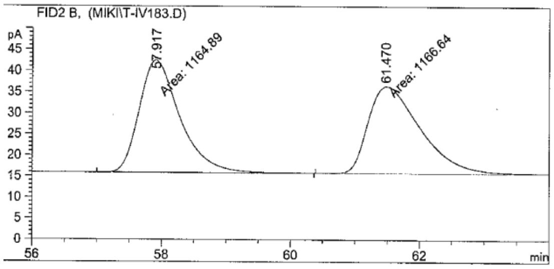
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]        [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  25.855 MM    0.4157 2965.90234  118.90854 50.06077
   2  27.348 MM    0.6265 2958.70190   78.70388 49.93923
```

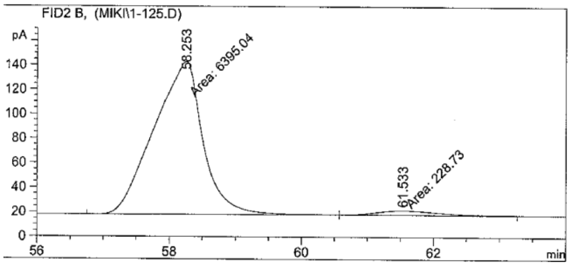


```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]        [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  25.925 MM    0.4898 4038.61572  137.42659 94.10083
   2  27.677 MM    0.5233  253.18018    8.06359  5.89917
```

(*R*)-3-Ethyl-3-phenethylcyclopentanone (Table 2.7, entry 10): IR (neat): 3393 (w), 3063 (w), 3028 (m), 2953 (s), 2928 (s), 2877 (m), 2873 (m), 1737 (s), 1602 (w), 1497 (m), 1450 (m), 1408 (m), 1383 (w), 1324 (w), 1286 (w), 1248 (m), 1155 (m), 1117 (w), 1075 (w), 1033 (w), 741 (m), 699 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31–7.25 (2H, m), 7.21–7.17 (3H, m), 2.63–2.48 (2H, m), 2.29 (2H, t, *J* = 8.0 Hz), 2.13 (2H, s), 1.86 (2H, dt, *J* = 8.0, 2.0 Hz), 1.70 (2H, dt, *J* = 6.8, 1.6 Hz), 1.53 (2H, q, *J* = 7.6 Hz), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 220.0, 142.6, 128.7, 128.4, 126.1, 50.9, 42.9, 39.7, 36.7, 33.1, 31.1, 29.9, 8.8; HRMS (EI+): Calcd for $C_{15}H_{21}O$ [M+H]$^+$: 217.1592, Found: 217.1591; Specific Rotation: $[\alpha]_D^{20}$ 3.27 (*c* = 0.51, CHCl$_3$) for an enantiomerically enriched sample with 95.5:4.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.5:3.5 er shown; chiral dex GTA column, 15 psi, 140 °C).





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Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1  57.917 MM    0.7296 1164.89392   26.60897 49.96249
   2  61.470 MM    0.9417 1166.64294   20.64861 50.03751
```

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
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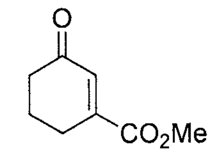
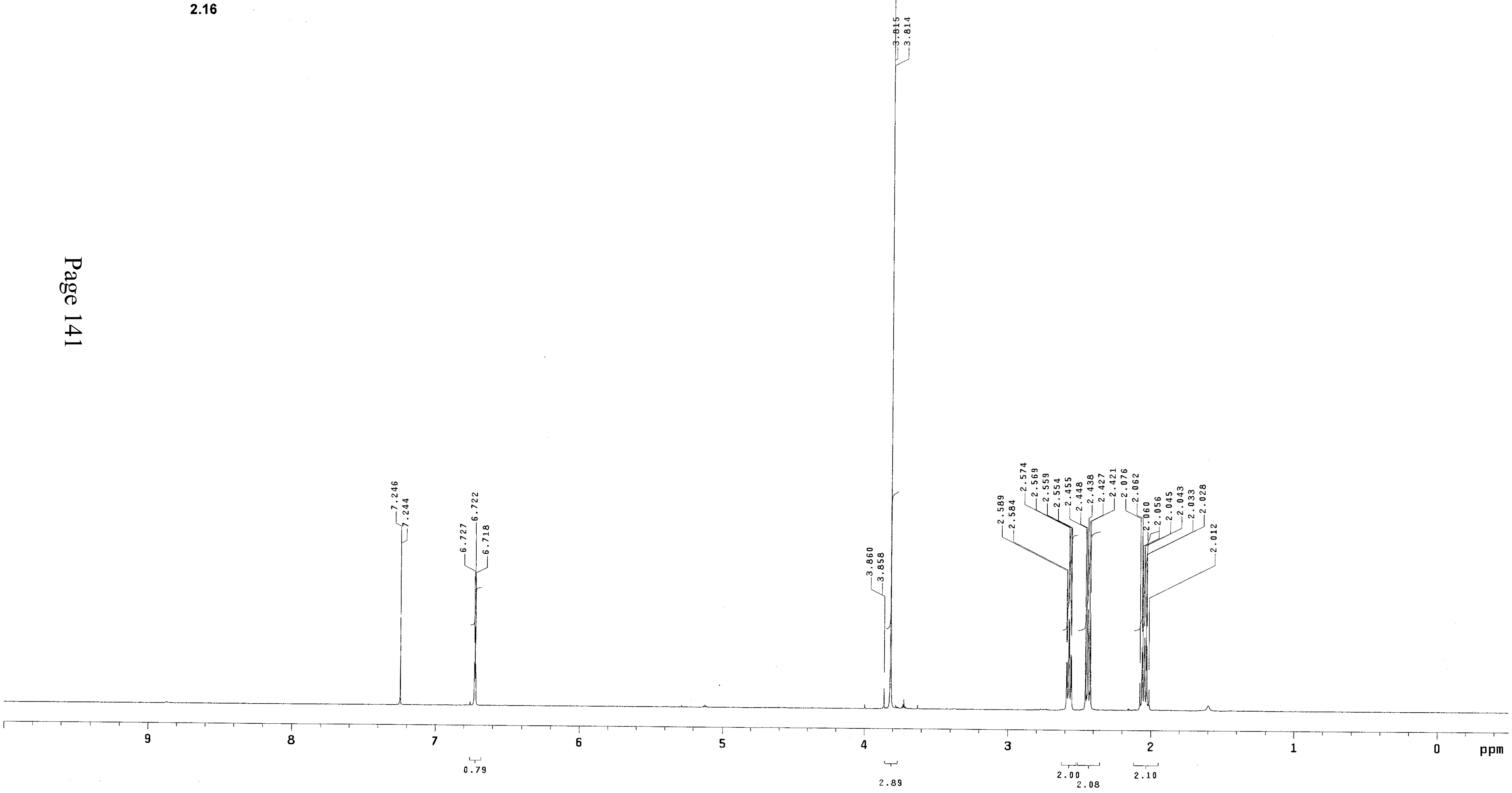
   2  61.533 MM    1.0598  228.72964    3.59690  3.45316
```



2.16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6.722
6.718
3.860
3.858
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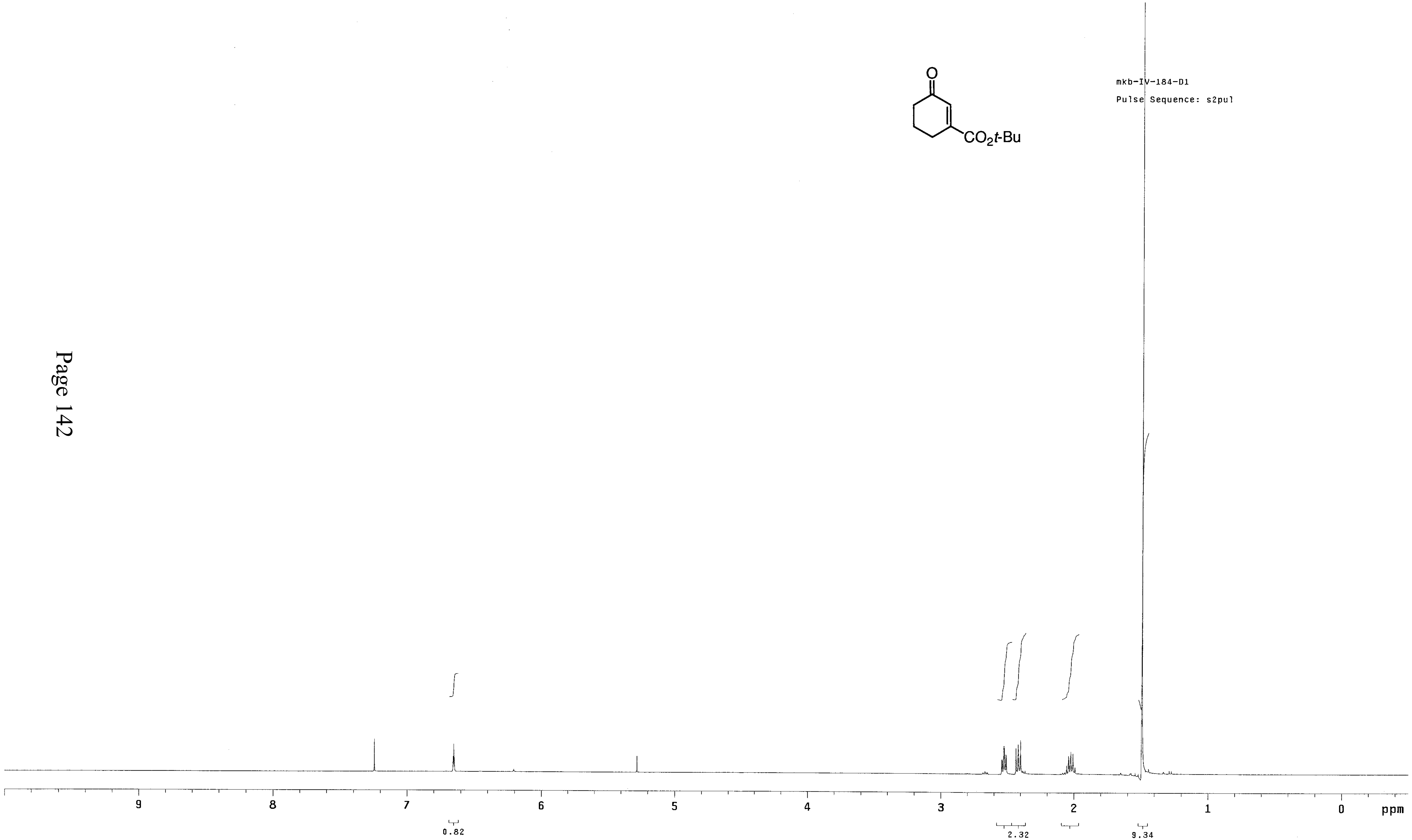
3.814
2.589
2.584
2.574
2.569
2.559
2.554
2.455
2.448
2.438
2.427
2.421
2.076
2.062
2.060
2.056
2.045
2.043
2.033
2.028
2.012
9
8
7
6
5
4
3
2
1
0
ppm
0.79
2.89
2.00
2.08
2.10


O
CO₂t-Bu
mkb-IV-184-D1
Pulse Sequence: s2pul
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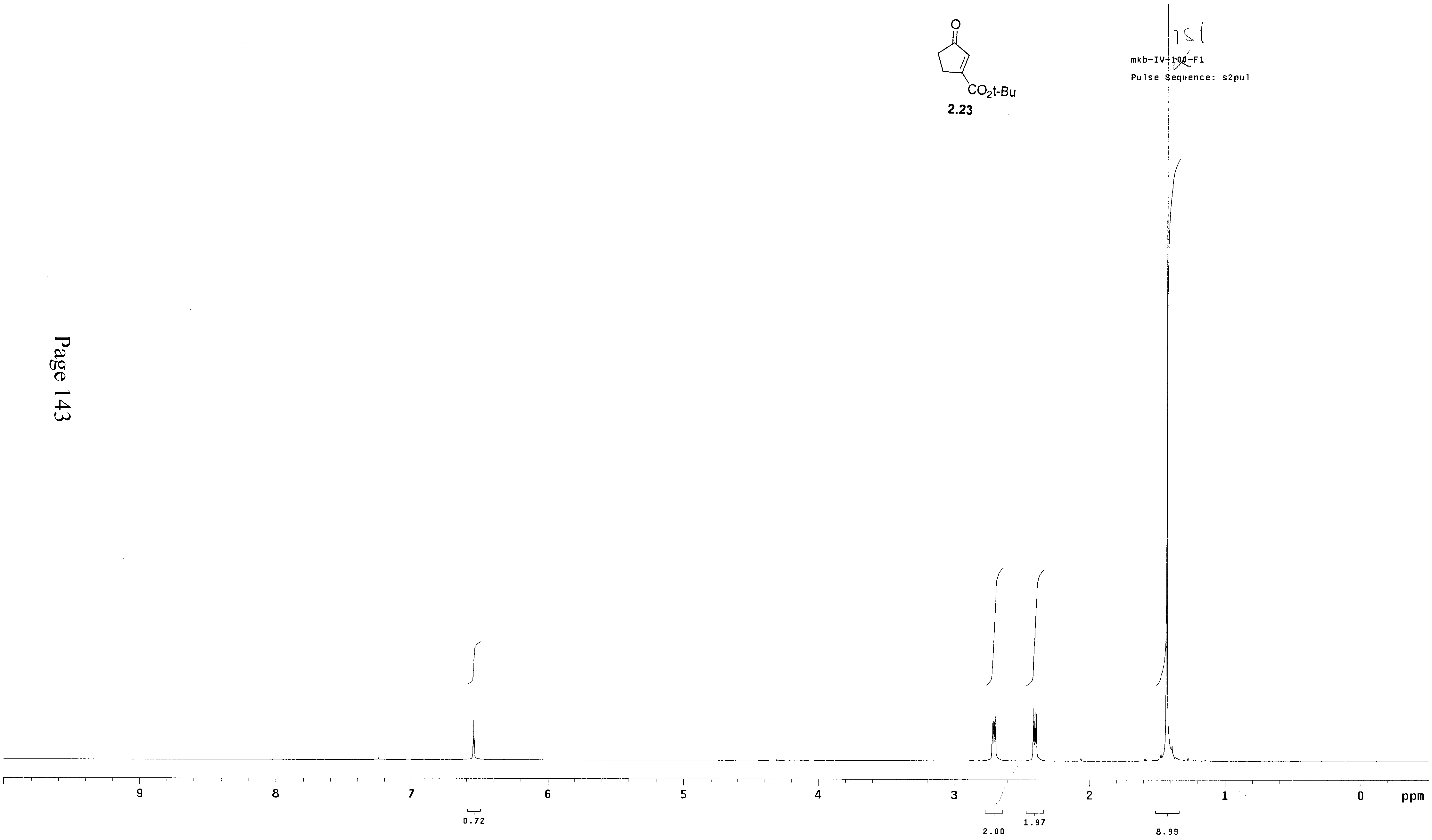
8
7
6
5
4
3
2
1
0
ppm
0.82
2.00
2.32
2.28
9.34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CO$_2$t-Bu
2.23
181
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Pulse Sequence: s2pul
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7
6
5
4
3
2
1
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ppm
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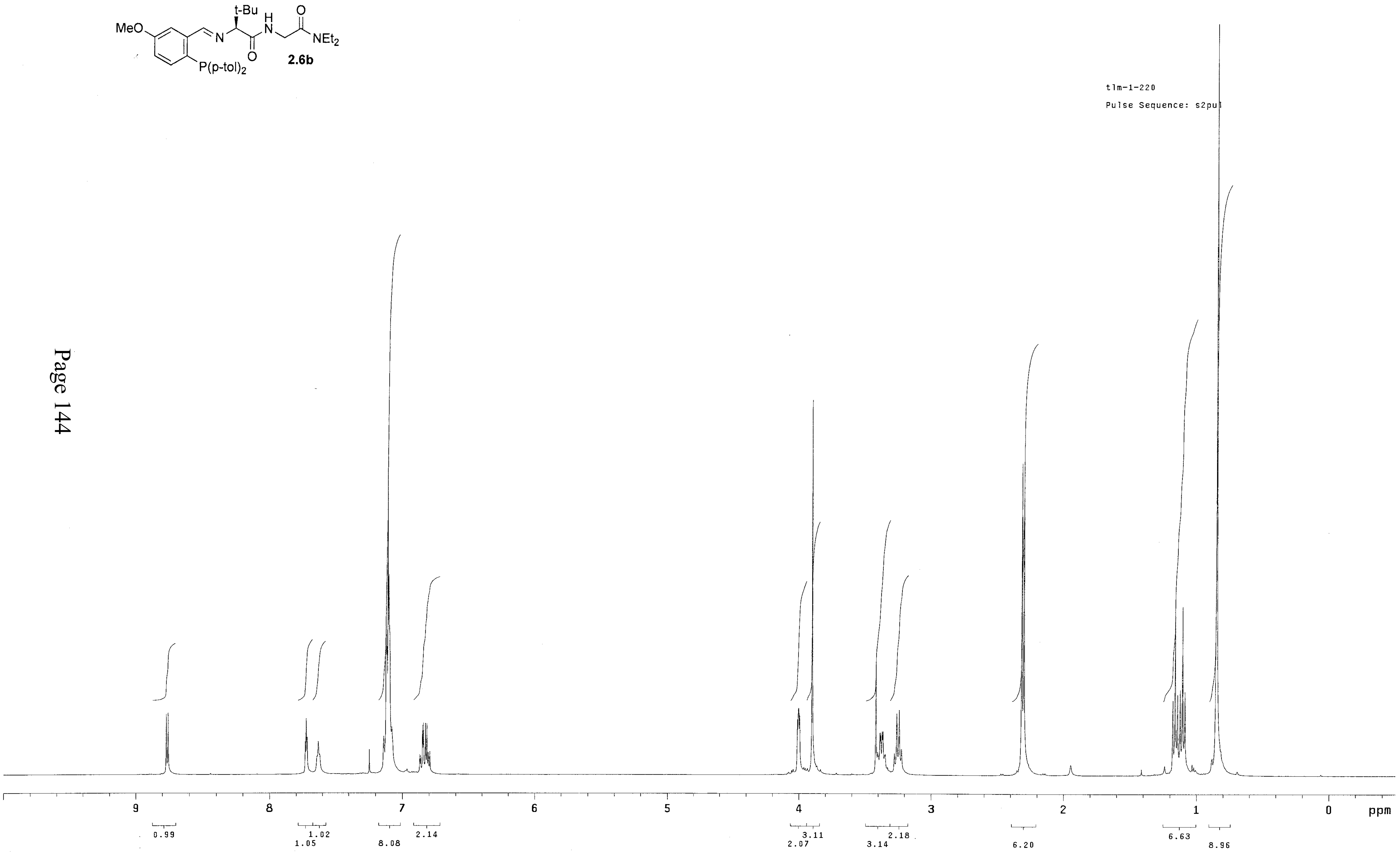
2.00
1.97
8.99


MeO
t-Bu
H
N
O
NEt2
P(p-tol)2
2.6b
tlm-1-220
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.05
1.02
8.08
2.14
2.07
3.11
3.14
2.18
6.20
6.63
8.96

```
CB-I-097

exp1  stdlh

      SAMPLE               DEC. & VT
date   Nov  7 2005  dfrq      `.399.774
solvent      CDC13  dn              H1
file           exp  dpwr            30
   ACQUISITION      dof              0
sfrq       399.774  dm             nnn
tn              H1  dmm              c
at           5.000  dmf            200
np           60006  dseq
sw          6000.6  dres           1.0
fb            3000  homo             n
bs               4  temp          25.0
tpwr            58      PROCESSING
pw            10.0  wtfile
d1           1.000  proc            ft
tof              0  fn        not used
nt              32  math             f
ct              16
alock            n  werr
gain      not used  wexp
      FLAGS         wbs
il               n  wnt
in               n
dp               y
hs              nn
     DISPLAY
sp          -200.1
wp          3997.7
vs              31
sc               0
wc             380
hzmm         10.52
is          373.07
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rfp         2902.3
th              20
ins        100.000
ai     ph
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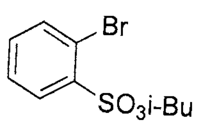
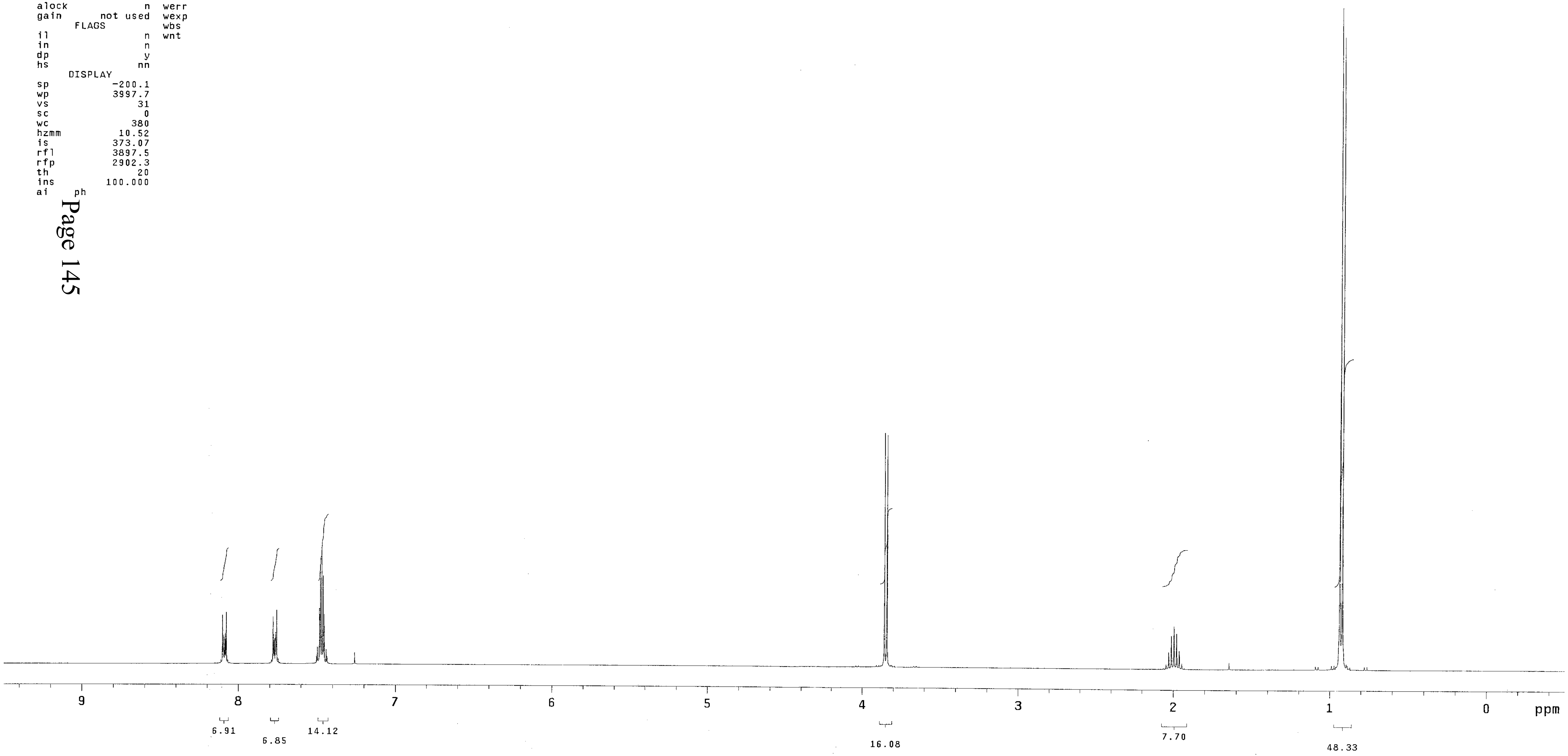
CB-I-097

Pulse Sequence: s2pul



2.25



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CB-I-098

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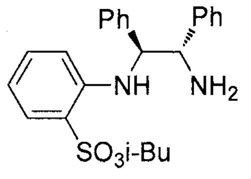
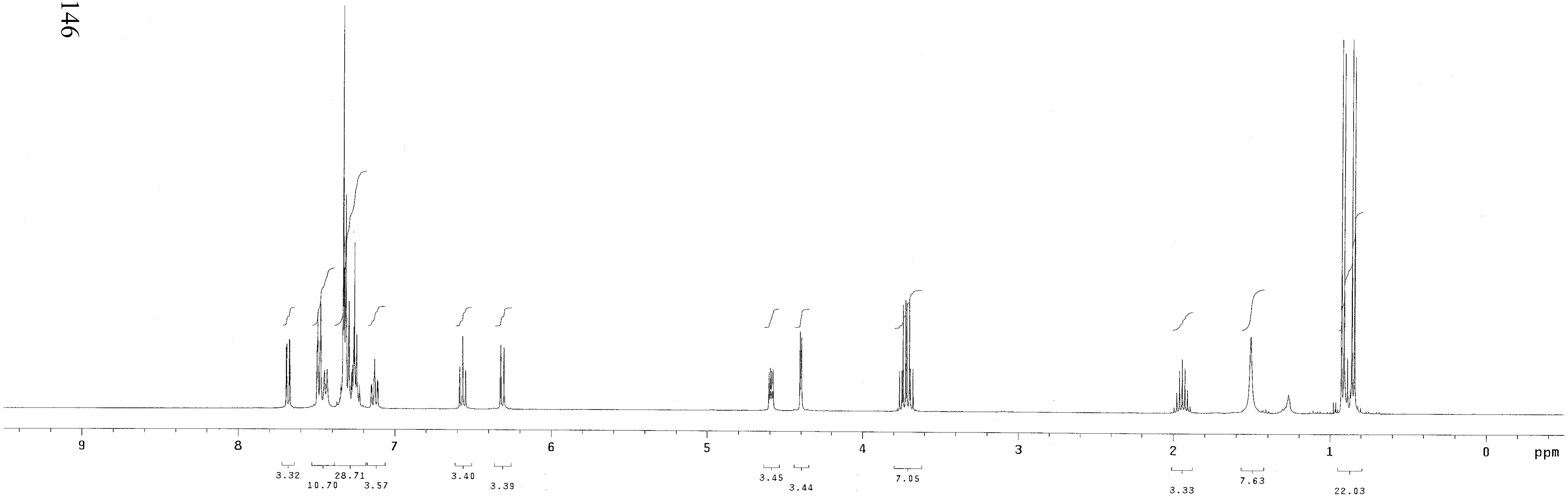
file            exp  dpwr               30
   ACQUISITION       dof                 0
sfrq        399.774  dm                nnn
tn               H1  dmm                 c
at            5.000  dmf               200
np            60006  dseq
sw           6000.6  dres              1.0
fb             3000  homo                n
bs                4  temp             25.0
tpwr             58        PROCESSING
pw             10.0  wtfile
d1            1.000  proc               ft
tof               0  fn           not used
nt               32  math                f
ct               20
alock             n  werr
gain       not used  wexp
      FLAGS          wbs
il                n  wnt
in                n
dp                y
hs               nn
     DISPLAY
sp           -200.1
wp           3997.7
vs               69
sc                0
wc              380
hzmm          10.52
is           341.56
rfl          3897.5
rfp          2902.3
th               20
ins         100.000
ai    ph
```

```
CB-I-098
Pulse Sequence: s2pul
```



2.26



```
CB-I-078b

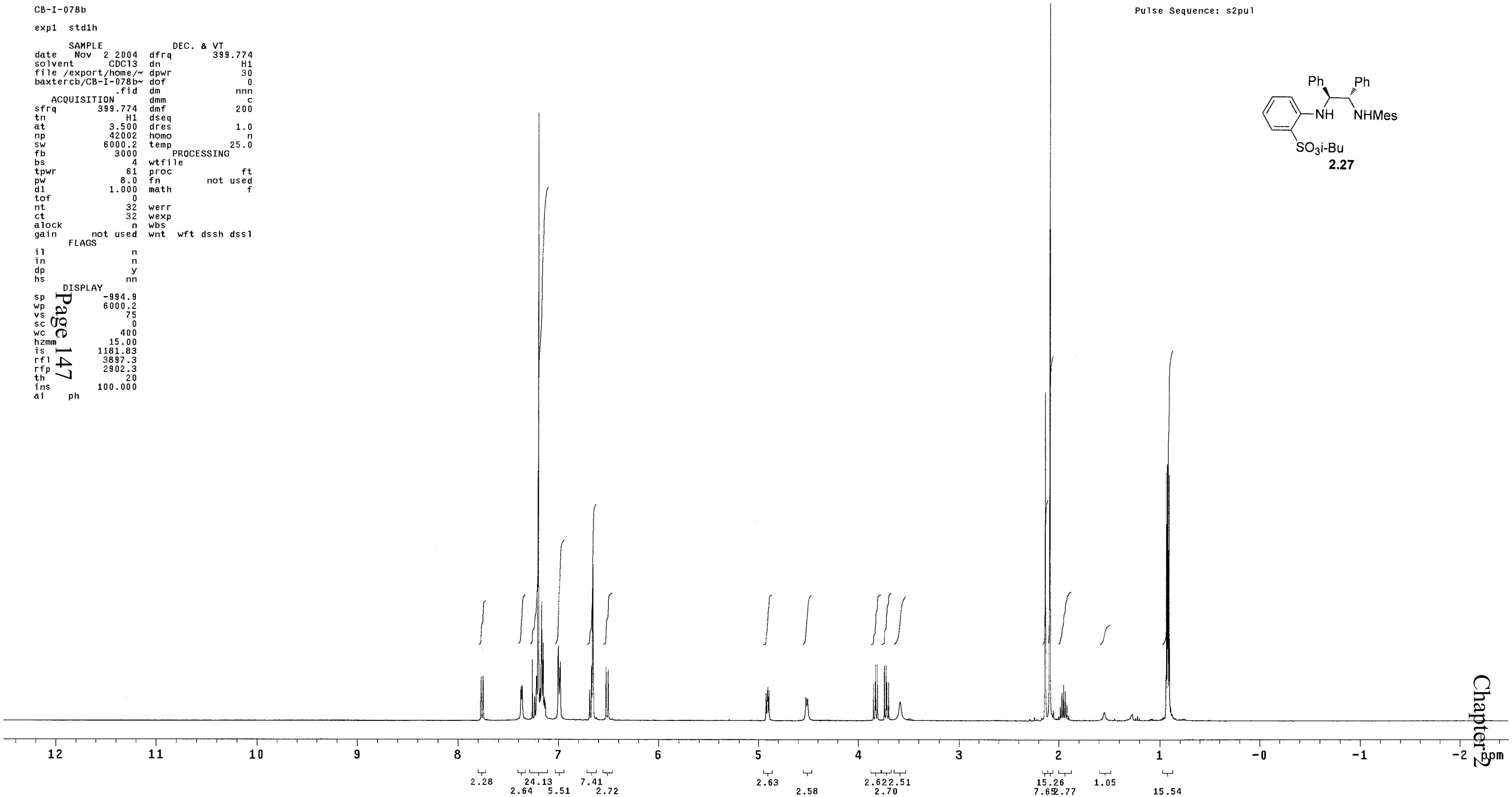
exp1  std1h

      SAMPLE                DEC. & VT
date   Nov  2 2004  dfrq       399.774
solvent      CDCl3  dn              H1
file /export/home/~ dpwr            30
baxtercb/CB-I-078b~ dof              0
              .fid  dm             nnn
   ACQUISITION      dmm              c
sfrq       399.774  dmf            200
tn              H1  dseq
at           3.500  dres           1.0
np           42002  homo             n
sw          6000.2  temp          25.0
fb            3000        PROCESSING
bs               4  wtfile
tpwr            61  proc            ft
pw             8.0  fn        not used
d1           1.000  math             f
tof              0
nt              32  werr
ct              32  wexp
alock            n  wbs
gain      not used  wnt  wft dssh dssl
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -994.9
wp          6000.2
vs              75
sc               0
wc             400
hzmm         15.00
is         1181.83
rfl         3897.3
rfp         2902.3
th              20
ins        100.000
ai     ph
```

CB-I-078b

Pulse Sequence: s2pul

2.27



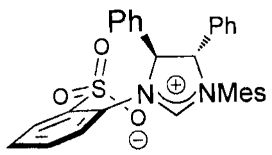
```
CB-I-107e

exp1  std1h

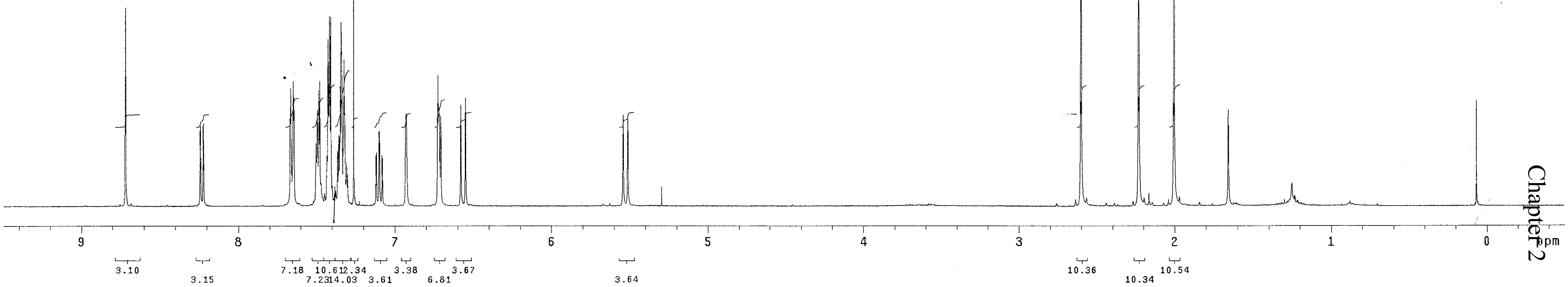
        SAMPLE              DEC. & VT
date    Jan 11 2005   dfrq        399.774
solvent       CDCl3   dn               H1
file            exp   dpwr             30
   ACQUISITION        dof               0
sfrq        399.774   dm              nnn
tn               H1   dmm               c
at            3.500   dmf             200
np            42002   dseq
sw           6000.2   dres            1.0
fb             3000   homo              n
bs                4   temp           25.0
tpwr             61         PROCESSING
pw              8.0   wtfile
d1            1.000   proc             ft
tof               0   fn         not used
nt               32   math              f
ct               32
alock             n   werr
gain       not used   wexp
      FLAGS           wbs
il                n   wnt   wft dssh dssl
in                n
dp                y
hs               nn
      DISPLAY
sp           -200.0
wp           3997.6
vs               80
sc                0
wc              400
hzmm           9.99
is           224.03
rfl          3898.0
rfp          2902.3
th               20
ins         100.000
ai   ph
```

CB-I-107e

Pulse Sequence: s2pul



2.29



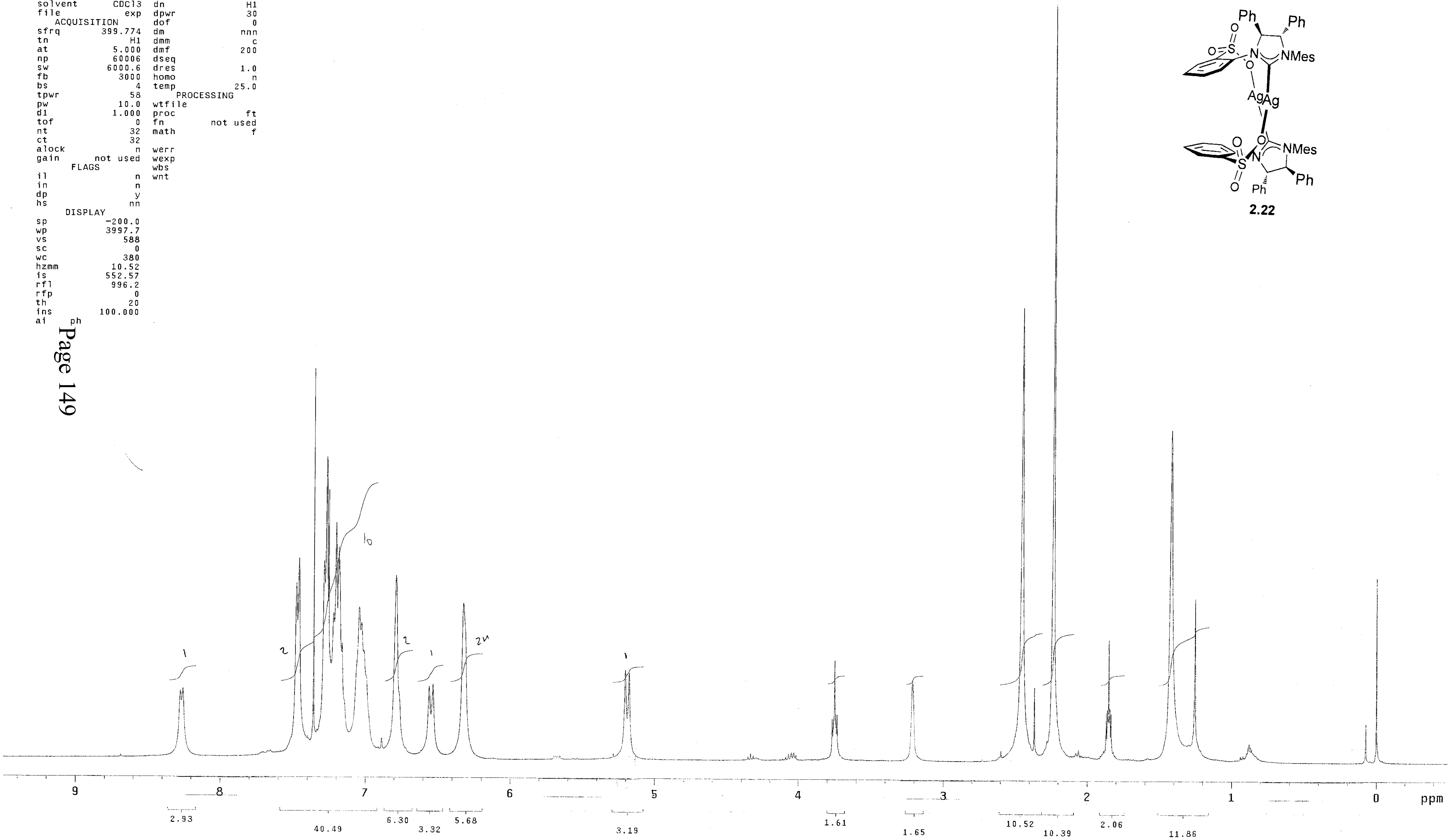
```
CB-I-300

exp1  stdlh

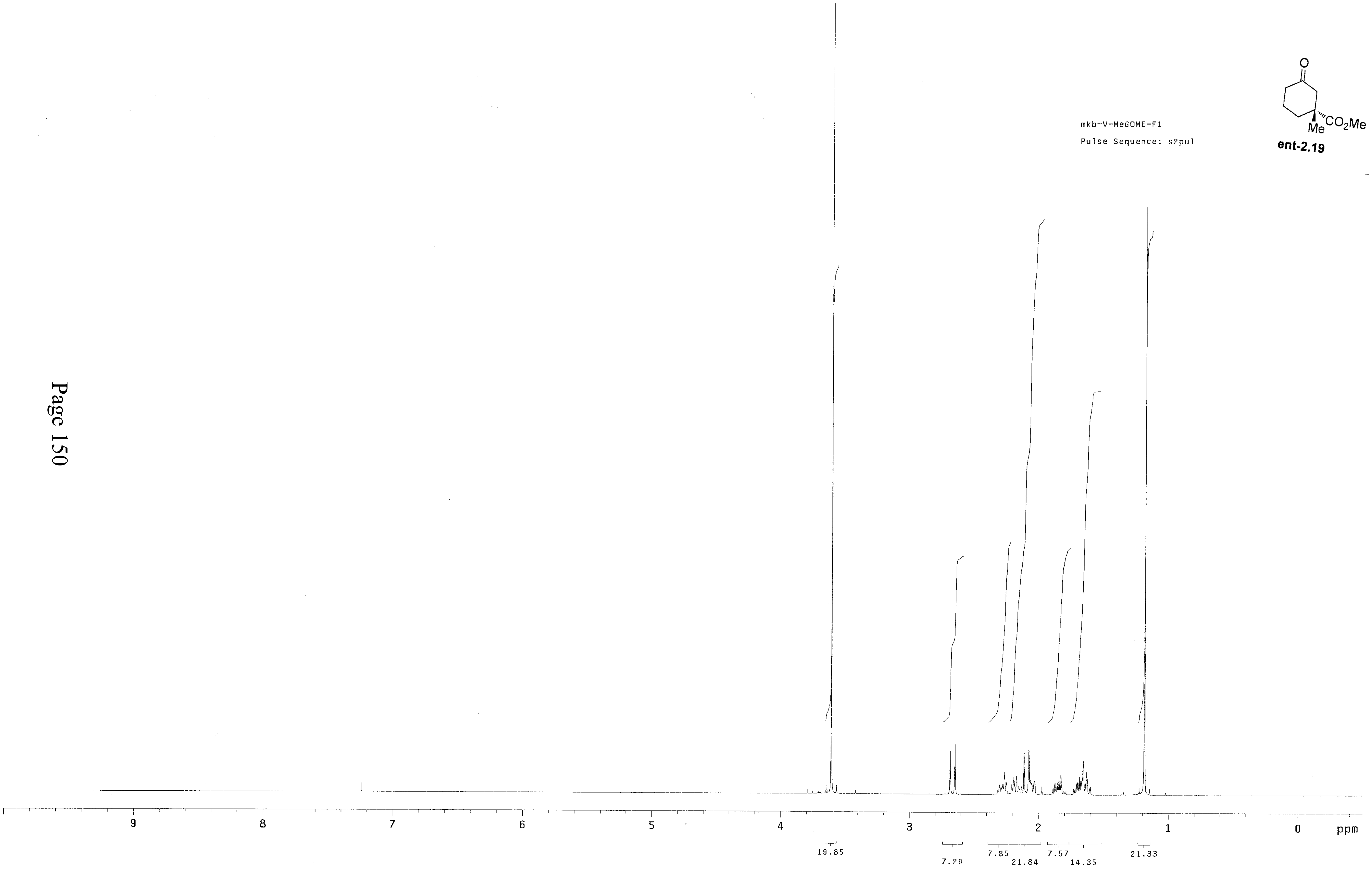
      SAMPLE               DEC. & VT
date   Jun 29 2005   dfrq         399.774
solvent       CDCl3  dn                H1
file            exp  dpwr              30
   ACQUISITION       dof                0
sfrq        399.774  dm               nnn
tn               H1  dmm                c
at            5.000  dmf              200
np            60006  dseq
sw           6000.6  dres             1.0
fb             3000  homo               n
bs                4  temp            25.0
tpwr             58      PROCESSING
pw             10.0  wtfile
d1            1.000  proc              ft
tof               0  fn          not used
nt               32  math               f
ct               32
alock             n  werr
gain       not used  wexp
      FLAGS          wbs
il                n  wnt
in                n
dp                y
hs               nn
     DISPLAY
sp           -200.0
wp           3997.7
vs              588
sc                0
wc              380
hzmm          10.52
is           552.57
rfl           996.2
rfp               0
th               20
ins         100.000
ai     ph
```

CB-I-300

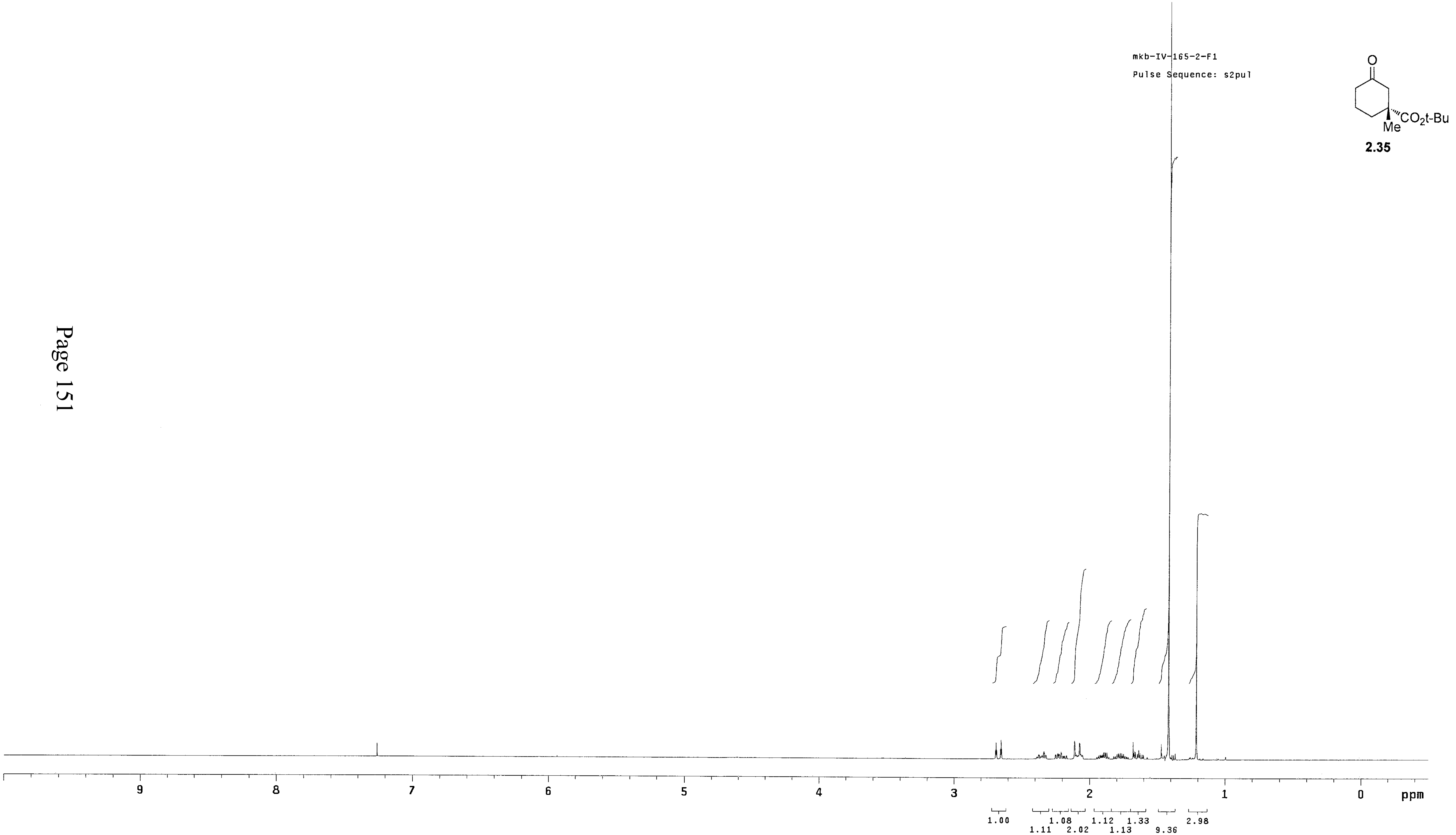
Pulse Sequence: s2pul

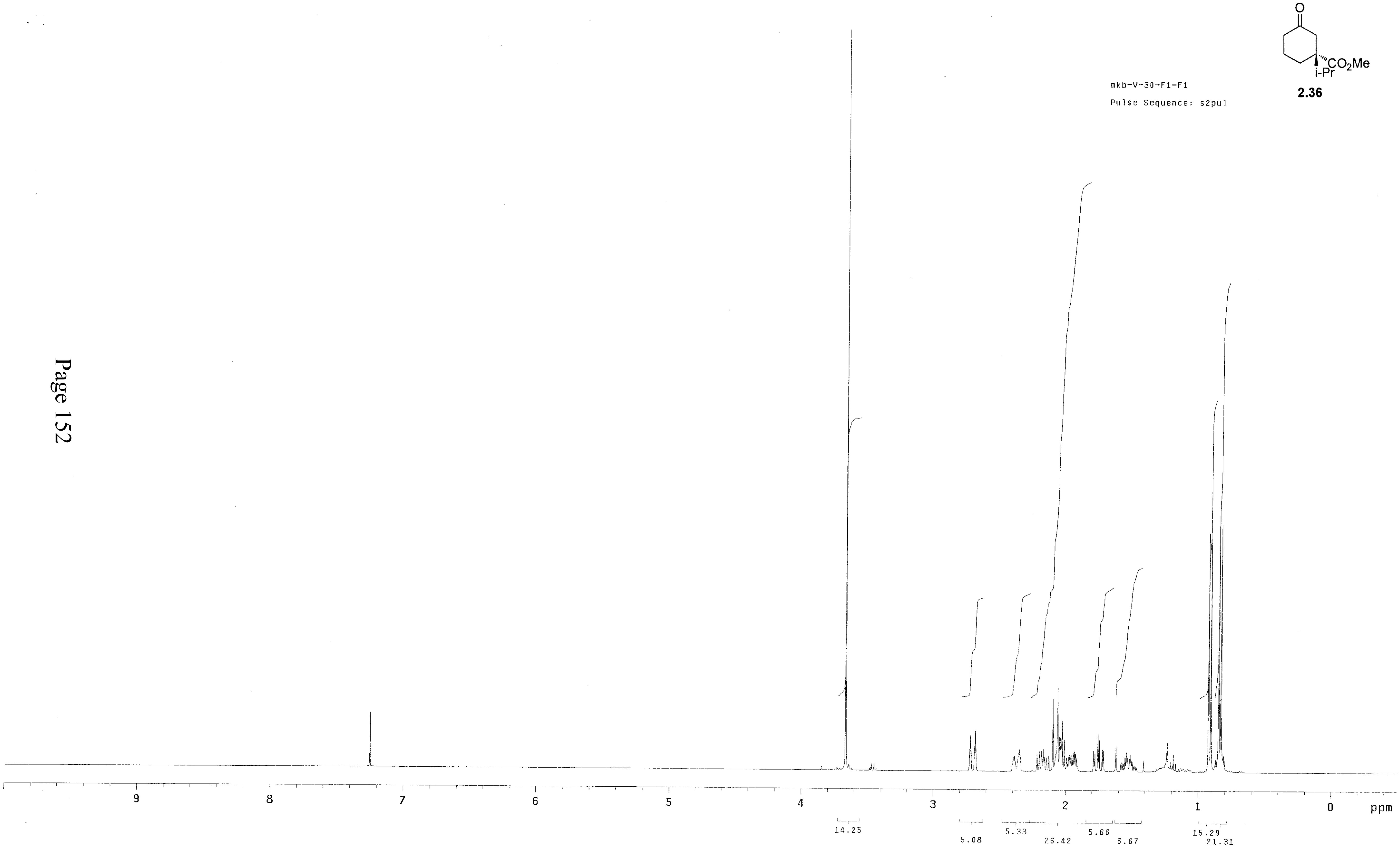


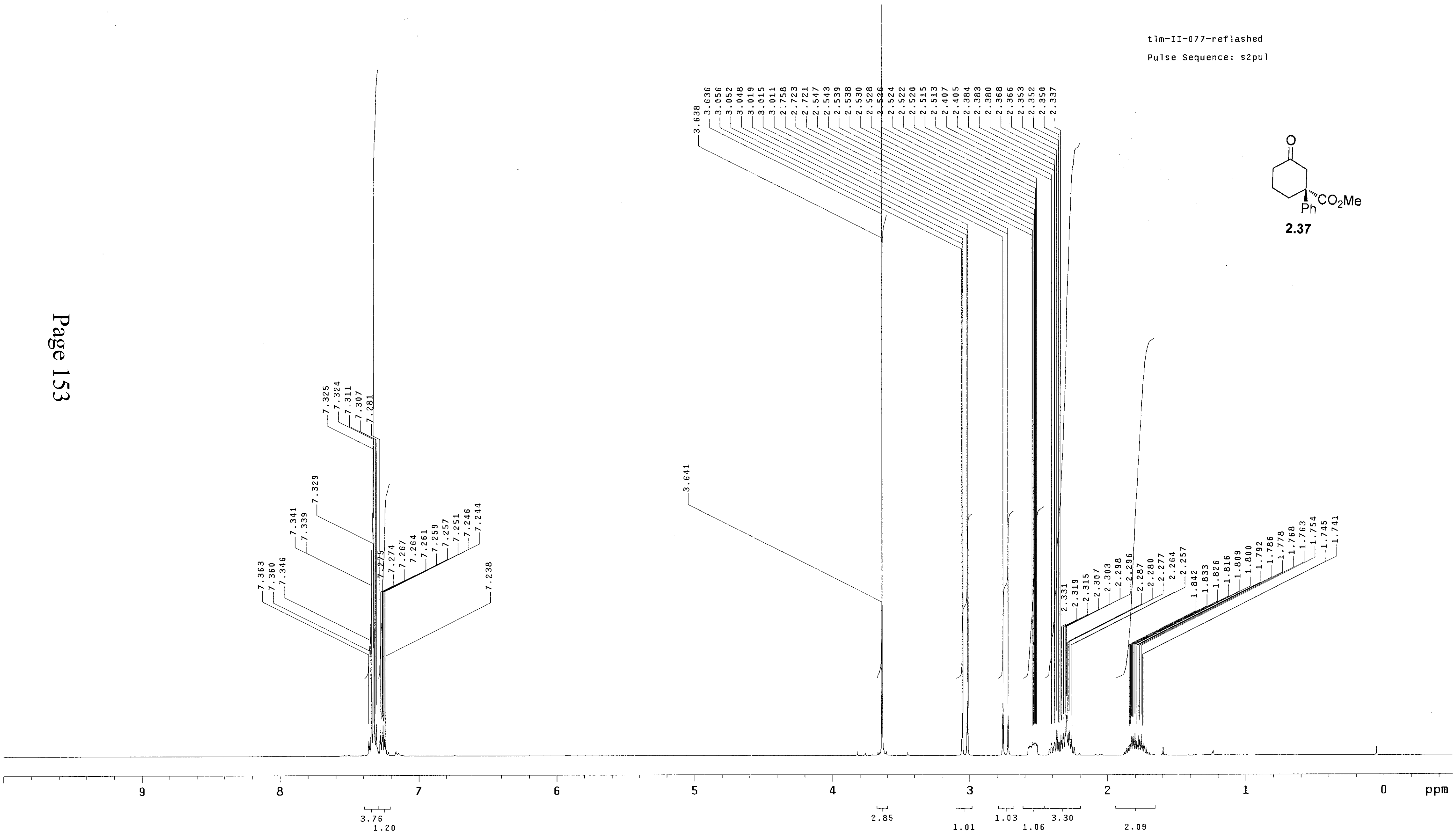
2.22

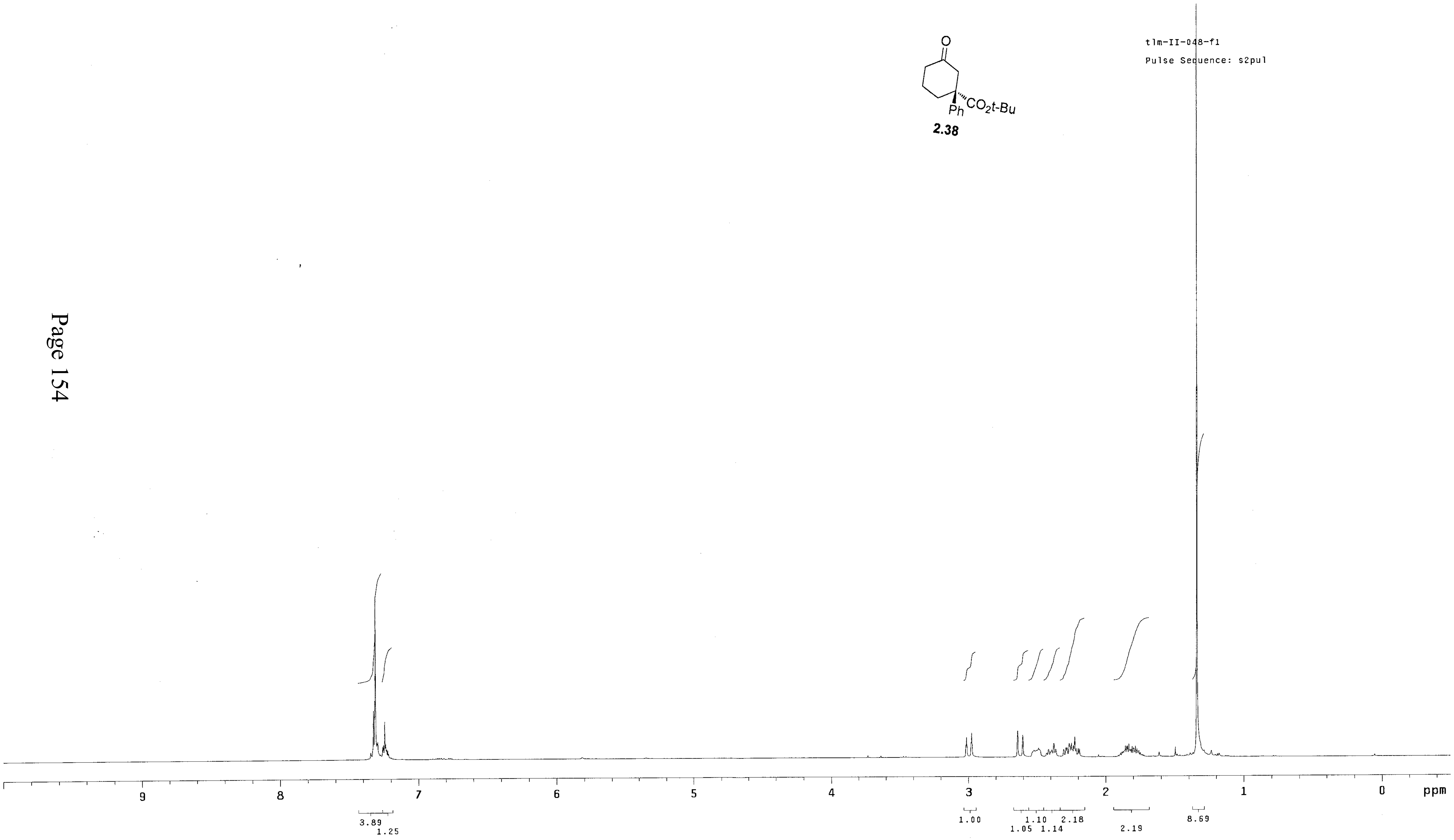

mkb-V-Me6OME-F1
Pulse Sequence: s2pul
O
CO2Me
Me
9
8
7
6
5
4
3
2
1
0
ppm
19.85
7.20
7.85
21.84
7.57
14.35
21.33

ent-2.19

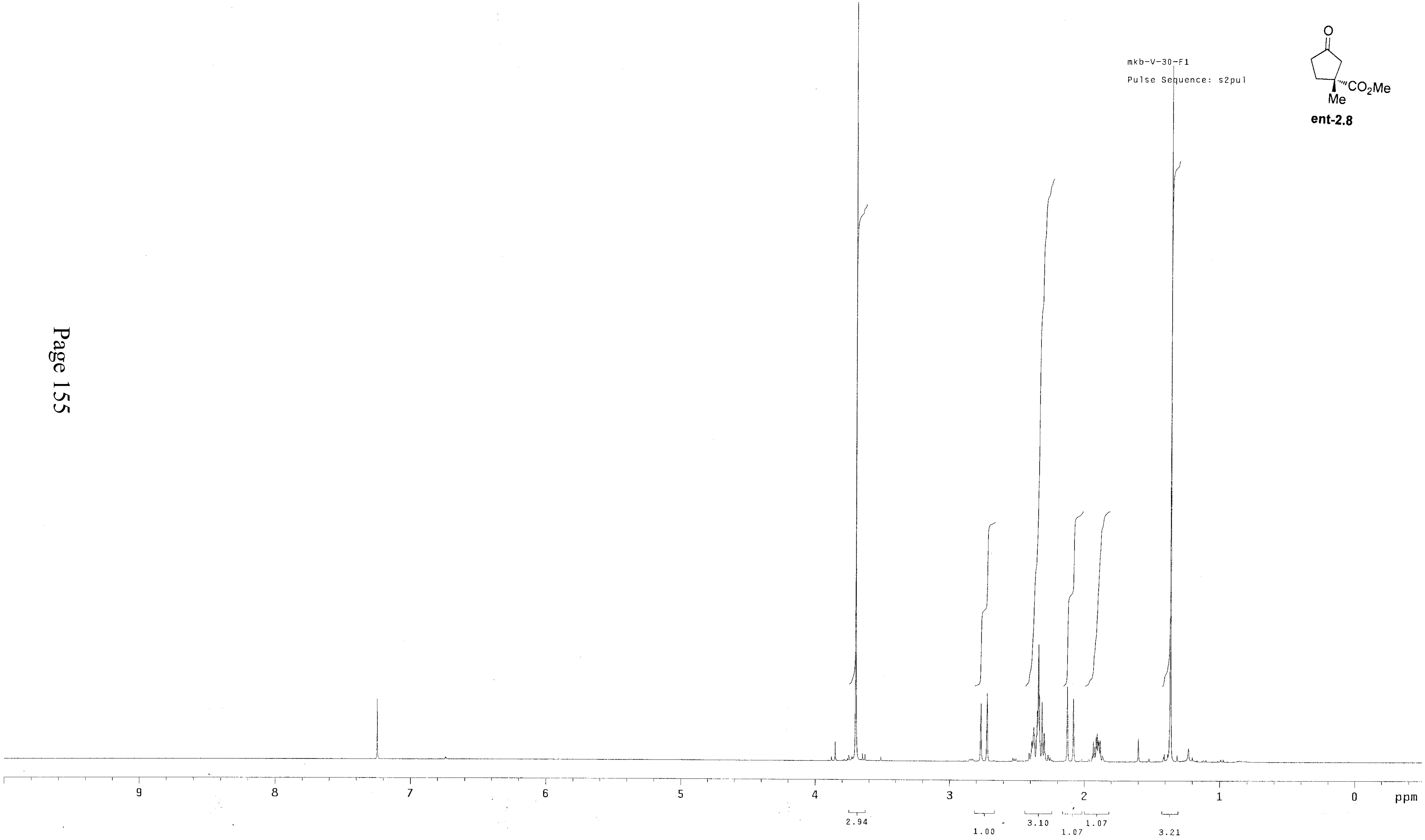

mkb-IV-165-2-F1
Pulse Sequence: s2pul
O
CO$_2$t-Bu
Me
2.35
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.11
1.08
2.02
1.12
1.13
1.33
9.36
2.98


2.36
mkb-V-30-F1-F1
Pulse Sequence: s2pul
O
CO2Me
i-Pr
9
8
7
6
5
4
3
2
1
0
ppm
14.25
5.08
5.33
26.42
5.66
6.67
15.29
21.31

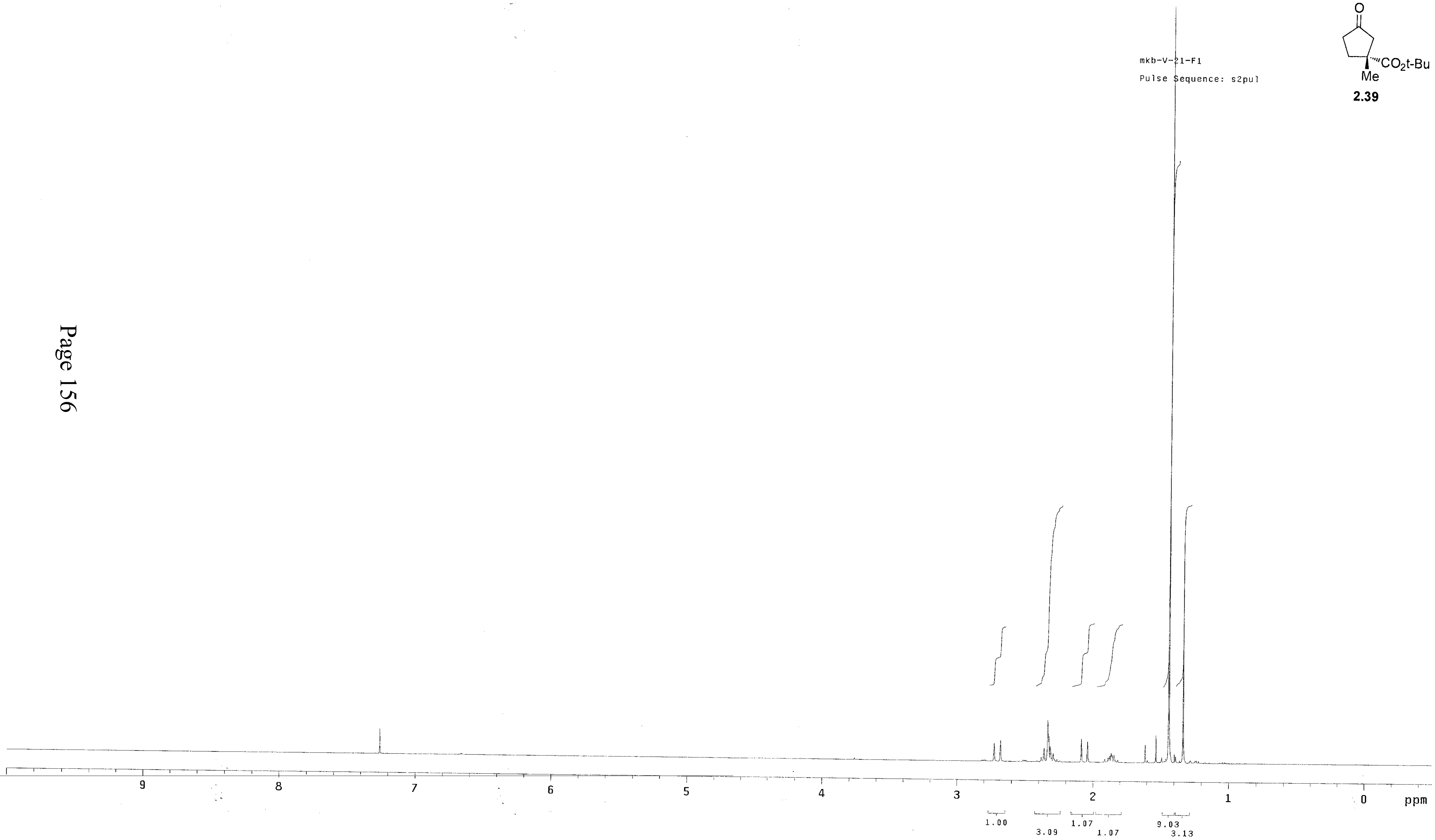

tlm-II-077-reflashed
Pulse Sequence: s2pul
O
CO2Me
Ph
2.37
3.638
3.636
3.056
3.052
3.048
3.019
3.015
3.011
2.758
2.723
2.721
2.547
2.543
2.539
2.538
2.530
2.528
2.526
2.524
2.522
2.520
2.515
2.513
2.407
2.405
2.384
2.383
2.380
2.368
2.366
2.353
2.352
2.350
2.337
7.325
7.324
7.311
7.307
7.281
7.363
7.360
7.346
7.341
7.339
7.329
7.275
7.274
7.267
7.264
7.261
7.259
7.257
7.251
7.246
7.244
7.238
3.641
2.331
2.319
2.315
2.307
2.303
2.298
2.296
2.287
2.280
2.277
2.264
2.257
1.842
1.833
1.826
1.816
1.809
1.800
1.792
1.786
1.778
1.768
1.763
1.754
1.745
1.741
9
8
7
6
5
4
3
2
1
0
ppm
3.76
1.20
2.85
1.01
1.03
1.06
3.30
2.09


O
CO2t-Bu
Ph
tlm-II-048-f1
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
3.89
1.25
1.00
1.10
2.18
1.05
1.14
2.19
8.69

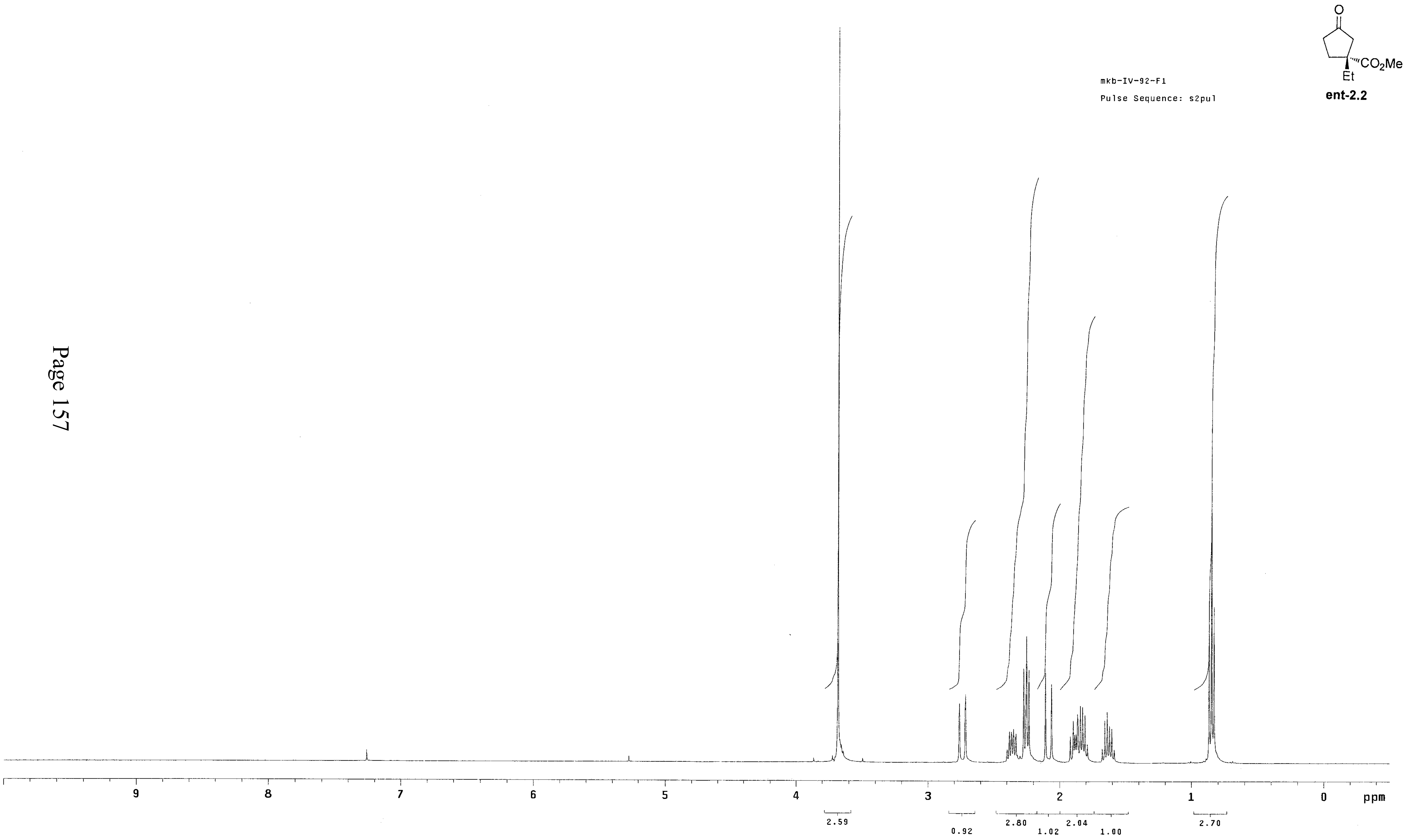
2.38


mkb-V-30-F1
Pulse Sequence: s2pul
O
CO$_2$Me
Me
9
8
7
6
5
4
3
2
1
0
ppm
2.94
1.00
3.10
1.07
1.07
3.21

ent-2.8

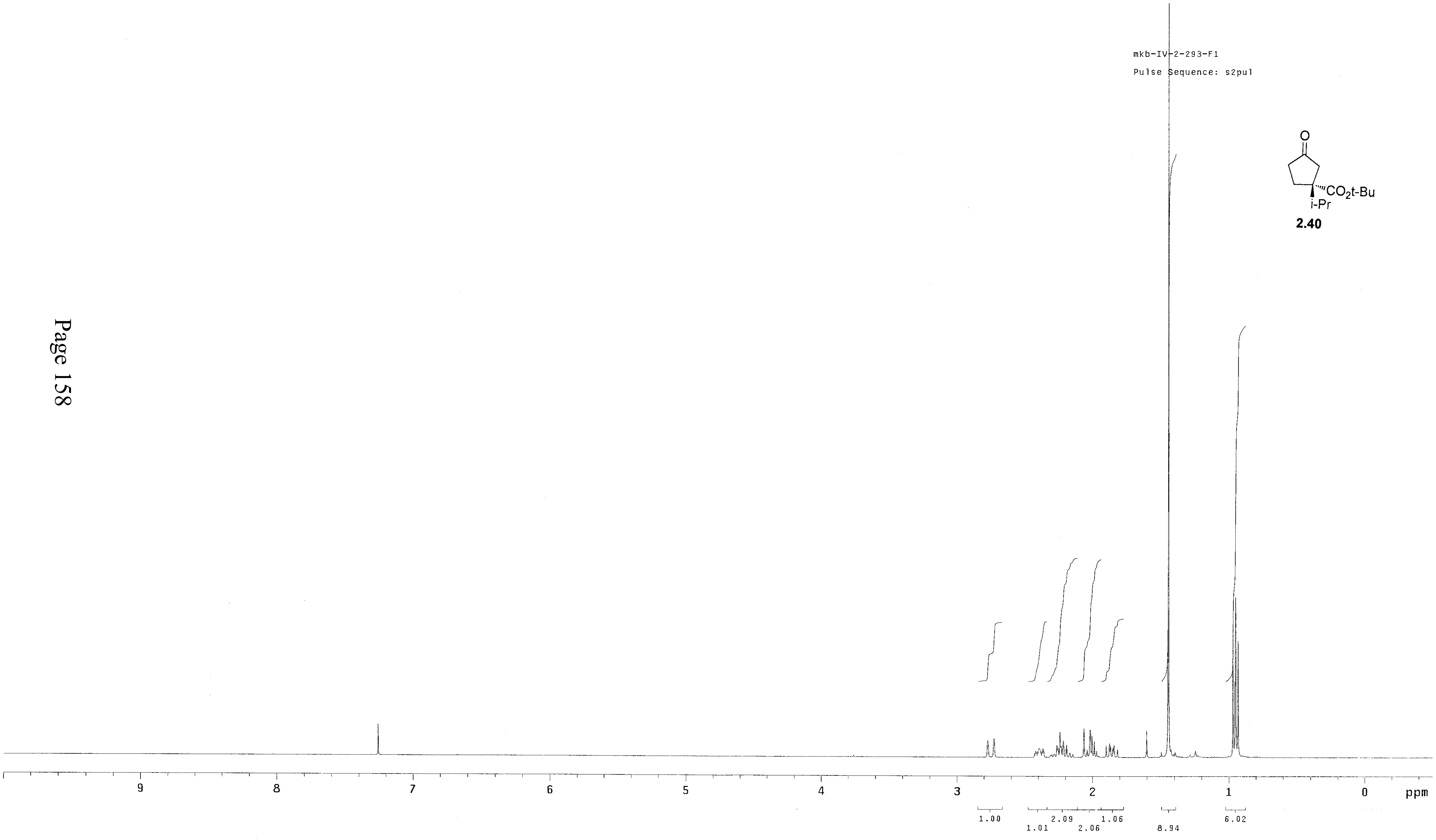

mkb-V-21-F1
Pulse Sequence: s2pul
O
CO$_2$t-Bu
Me
9
8
7
6
5
4
3
2
1
0
ppm
1.00
3.09
1.07
1.07
9.03
3.13

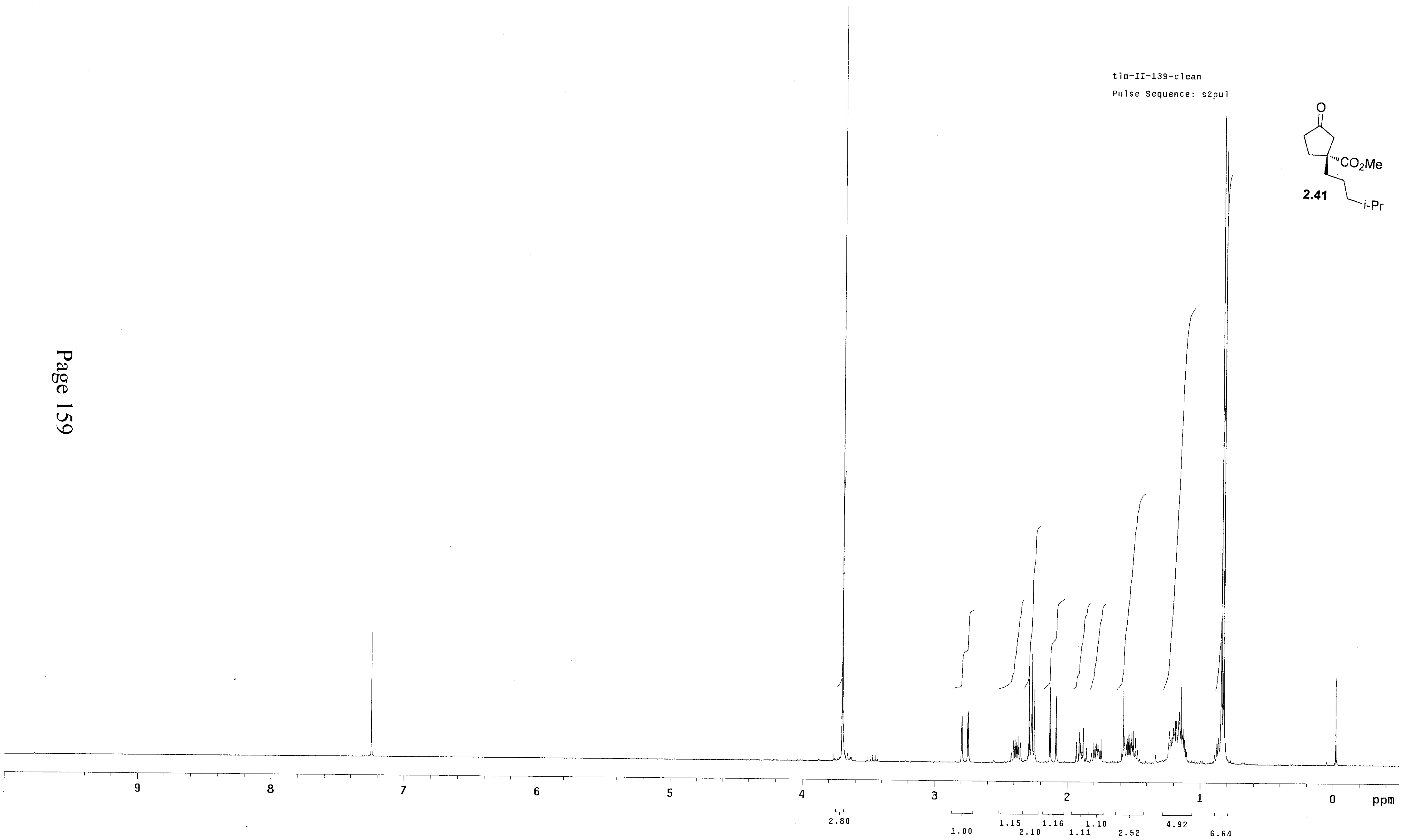
2.39

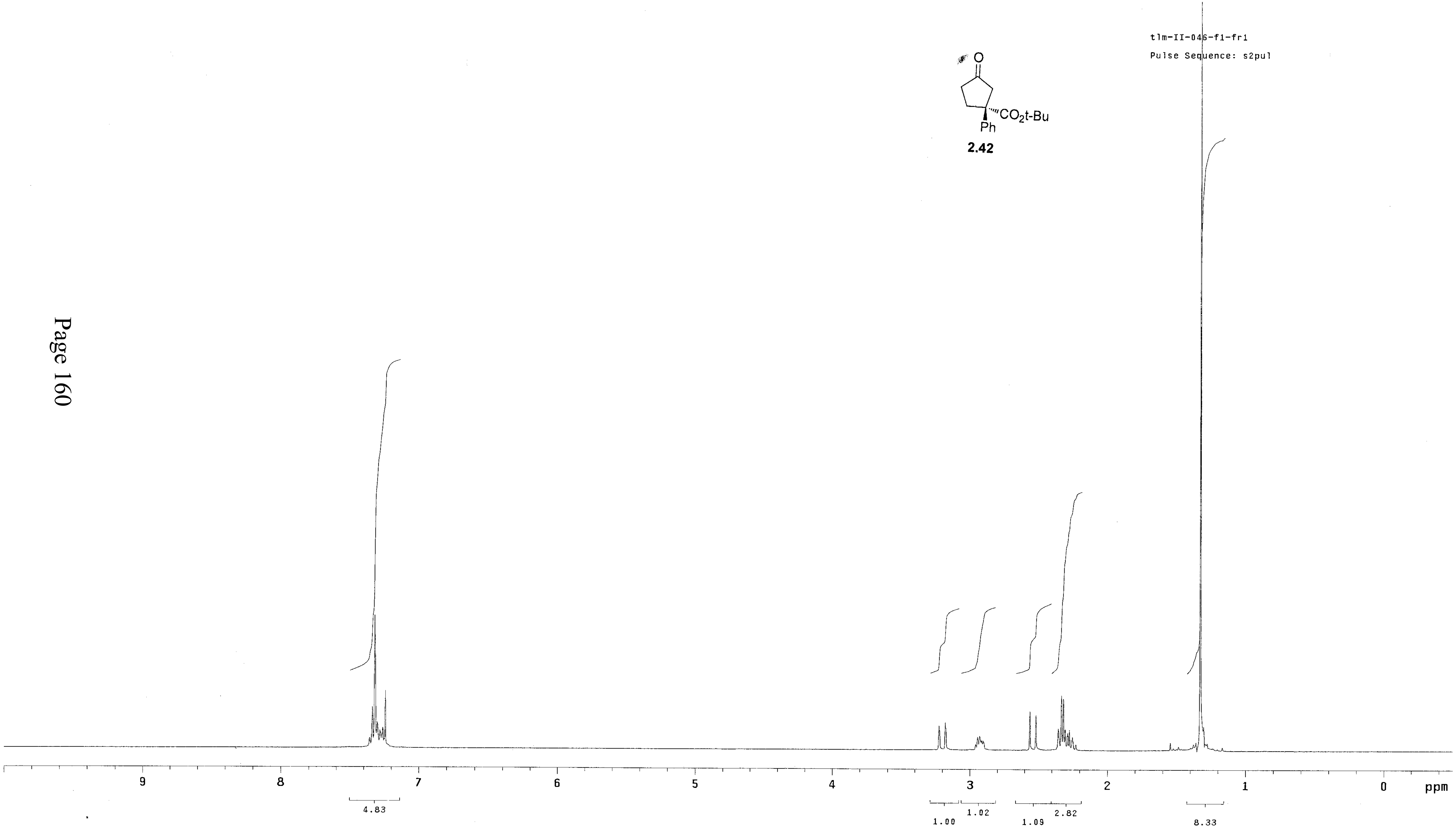

O
CO2Me
Et

ent-2.2

mkb-IV-92-F1
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
2.59
0.92
2.80
1.02
2.04
1.00
2.70

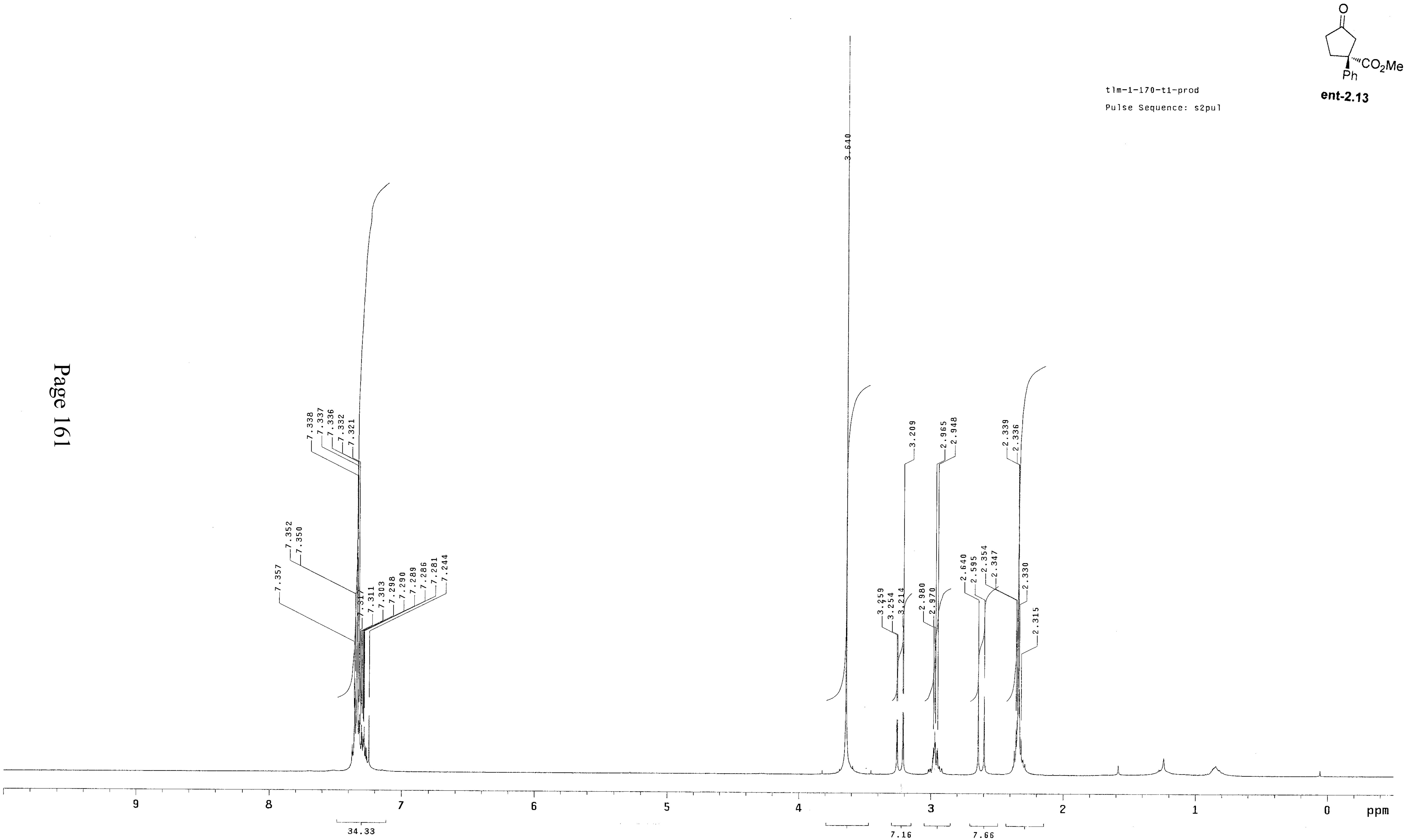

mkb-IV-2-293-F1
Pulse Sequence: s2pul
O
CO2t-Bu
i-Pr
2.40
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
2.09
2.06
1.06
8.94
6.02


tlm-II-139-clean
Pulse Sequence: s2pul
O
CO$_2$Me
2.41
i-Pr
9
8
7
6
5
4
3
2
1
0
ppm
2.80
1.00
1.15
2.10
1.16
1.11
1.10
2.52
4.92
6.64

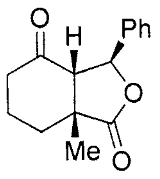


2.42

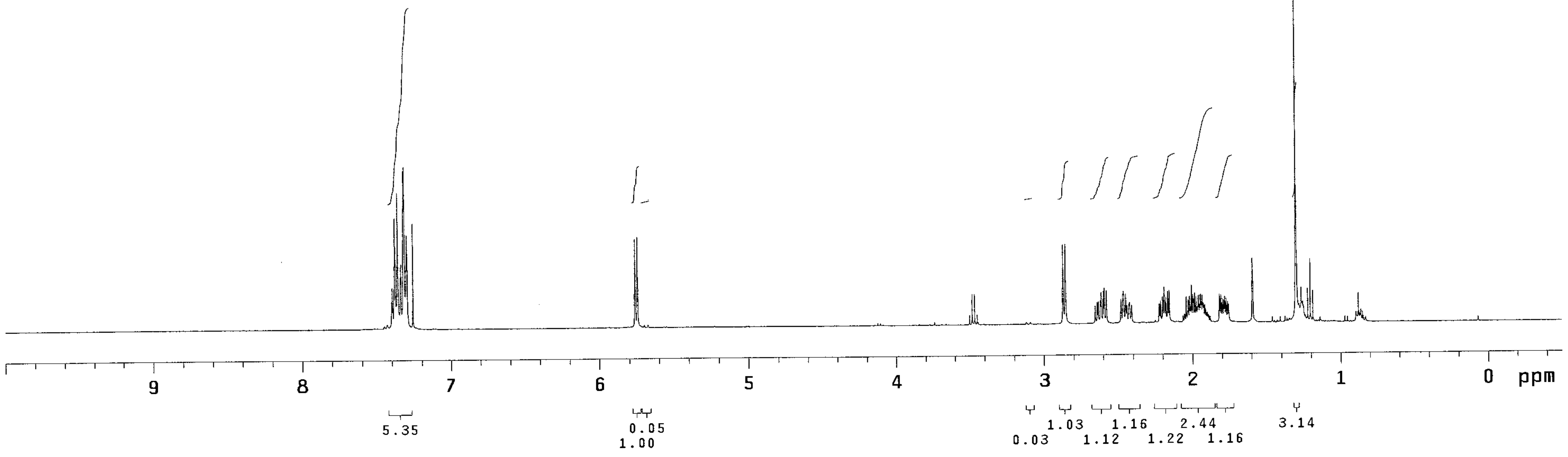
tlm-II-046-f1-fr1
Pulse Sequence: s2pul
O
CO2t-Bu
Ph
9
8
7
6
5
4
3
2
1
0
ppm
4.83
1.00
1.02
1.09
2.82
8.33

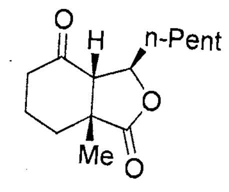

tlm-1-170-t1-prod
Pulse Sequence: s2pul
O
CO2Me
Ph
7.357
7.352
7.350
7.338
7.337
7.336
7.332
7.321
7.317
7.311
7.303
7.298
7.290
7.289
7.286
7.281
7.244
3.640
3.259
3.254
3.214
3.209
2.980
2.970
2.965
2.948
2.640
2.595
2.354
2.347
2.339
2.336
2.330
2.315
9
8
7
6
5
4
3
2
1
0
ppm
34.33
21.01
7.16
7.49
7.66
22.34

ent-2.13

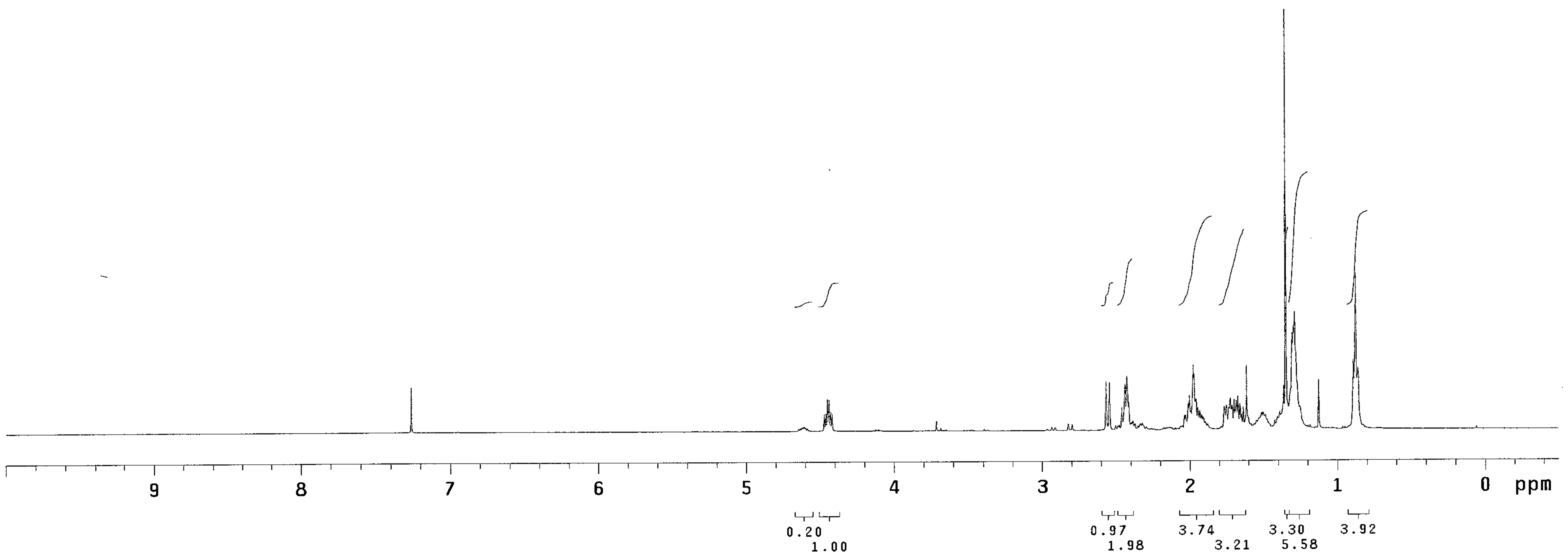

O
H
Ph
O
Me
O

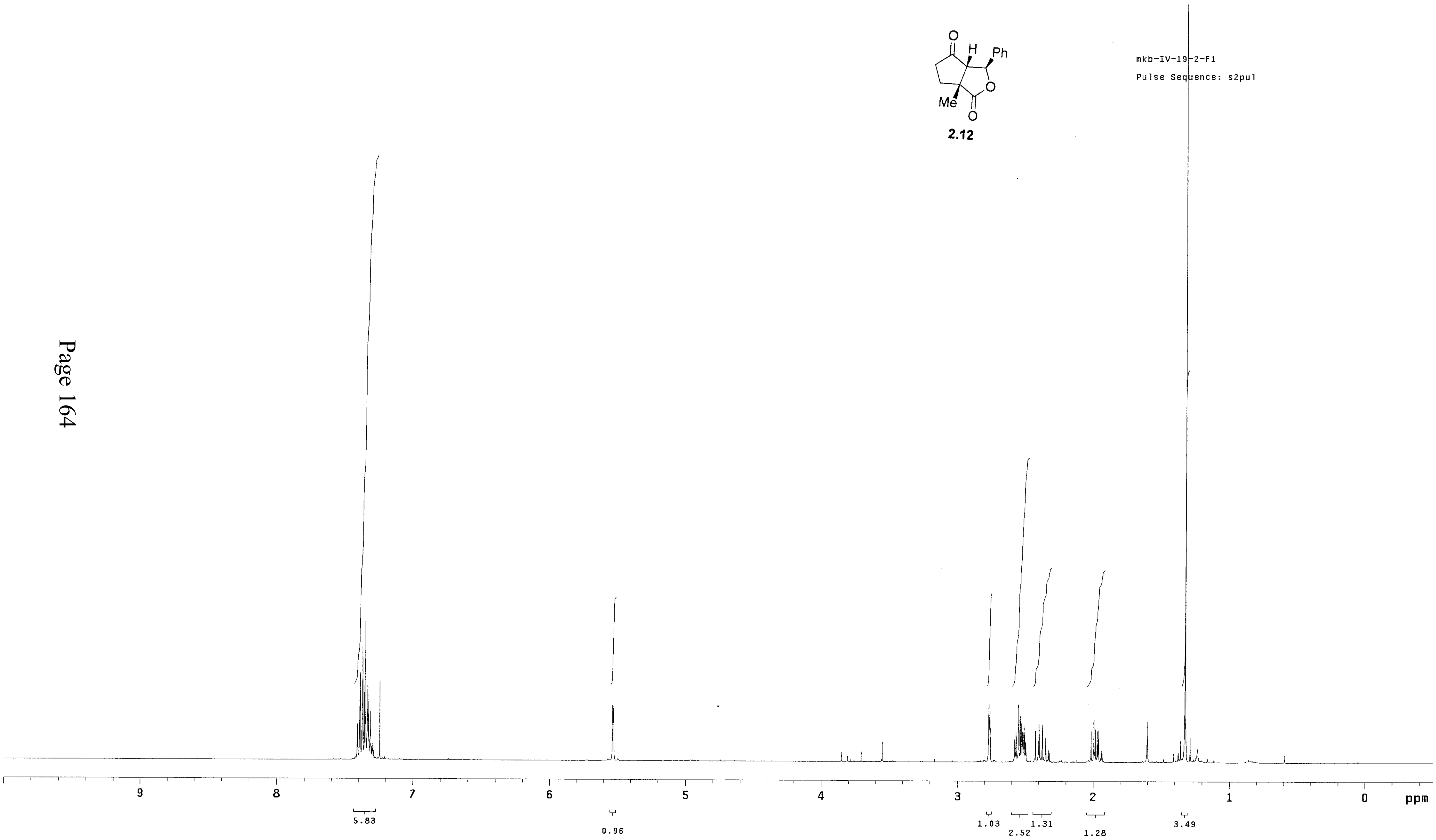
2.46a

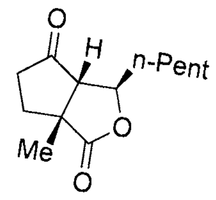

9
8
7
6
5
4
3
2
1
0
ppm
5.35
0.05
1.00
1.03
0.03
1.16
1.12
2.44
1.22
1.16
3.14


O
H
n-Pent
O
O
Me

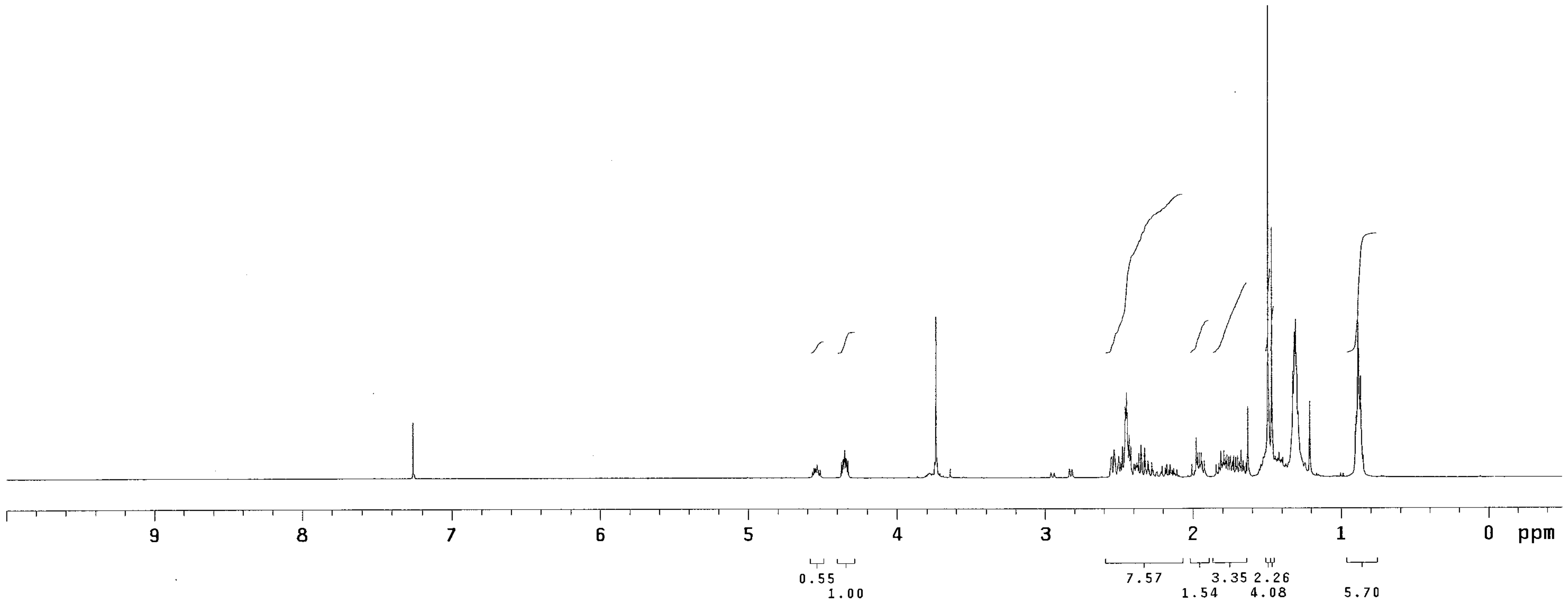
2.46b

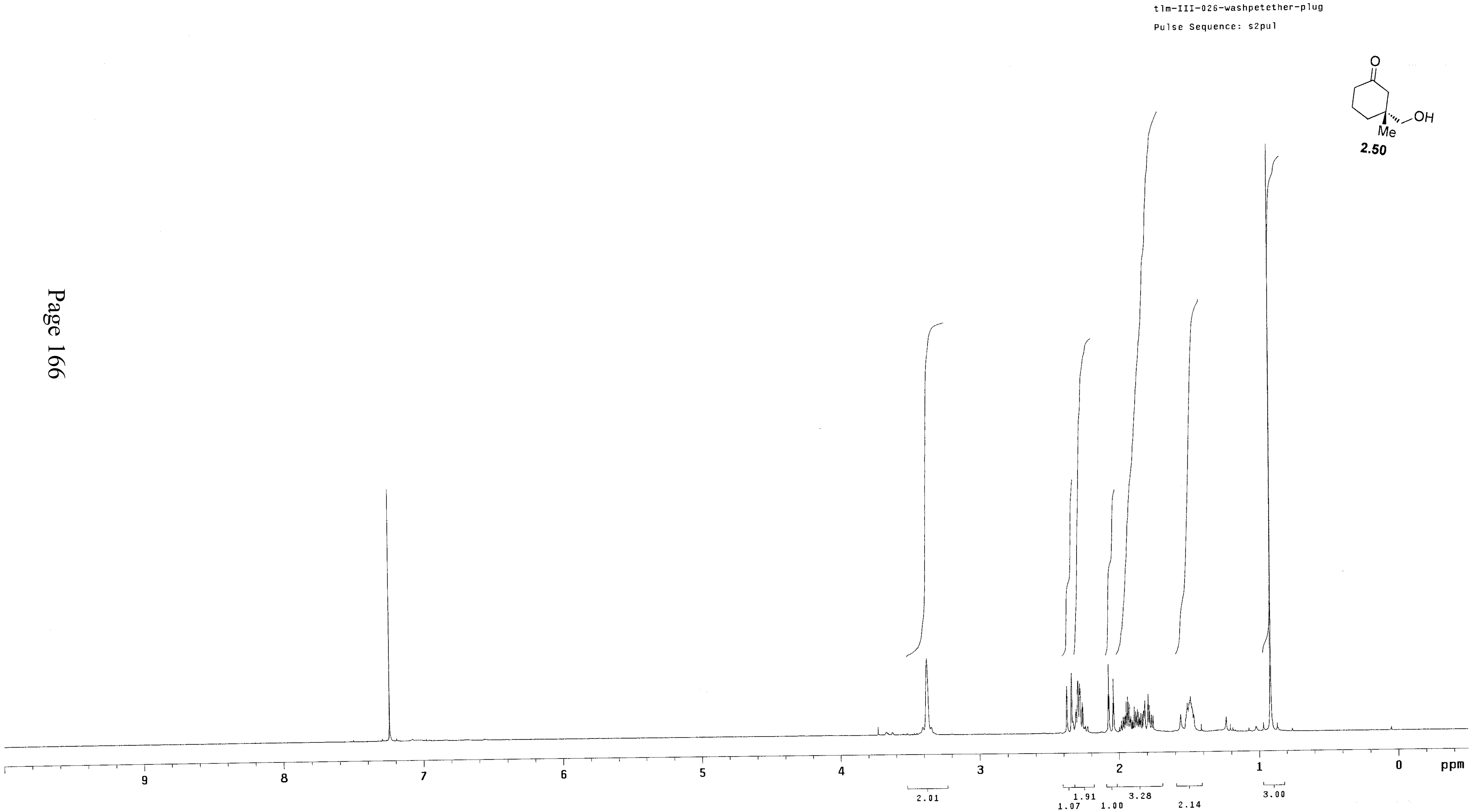

9
8
7
6
5
4
3
2
1
0
ppm
0.20
1.00
0.97
1.98
3.74
3.21
3.30
5.58
3.92


O
H
Ph
O
Me
O
2.12
mkb-IV-19-2-F1
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
5.83
0.96
1.03
2.52
1.31
1.28
3.49


O
H
n-Pent
O
Me
O

2.47




tlm-III-026-washpetether-plug
Pulse Sequence: s2pul
O
OH
Me
2.50
9
8
7
6
5
4
3
2
1
0
ppm
2.01
1.07
1.91
1.00
3.28
2.14
3.00

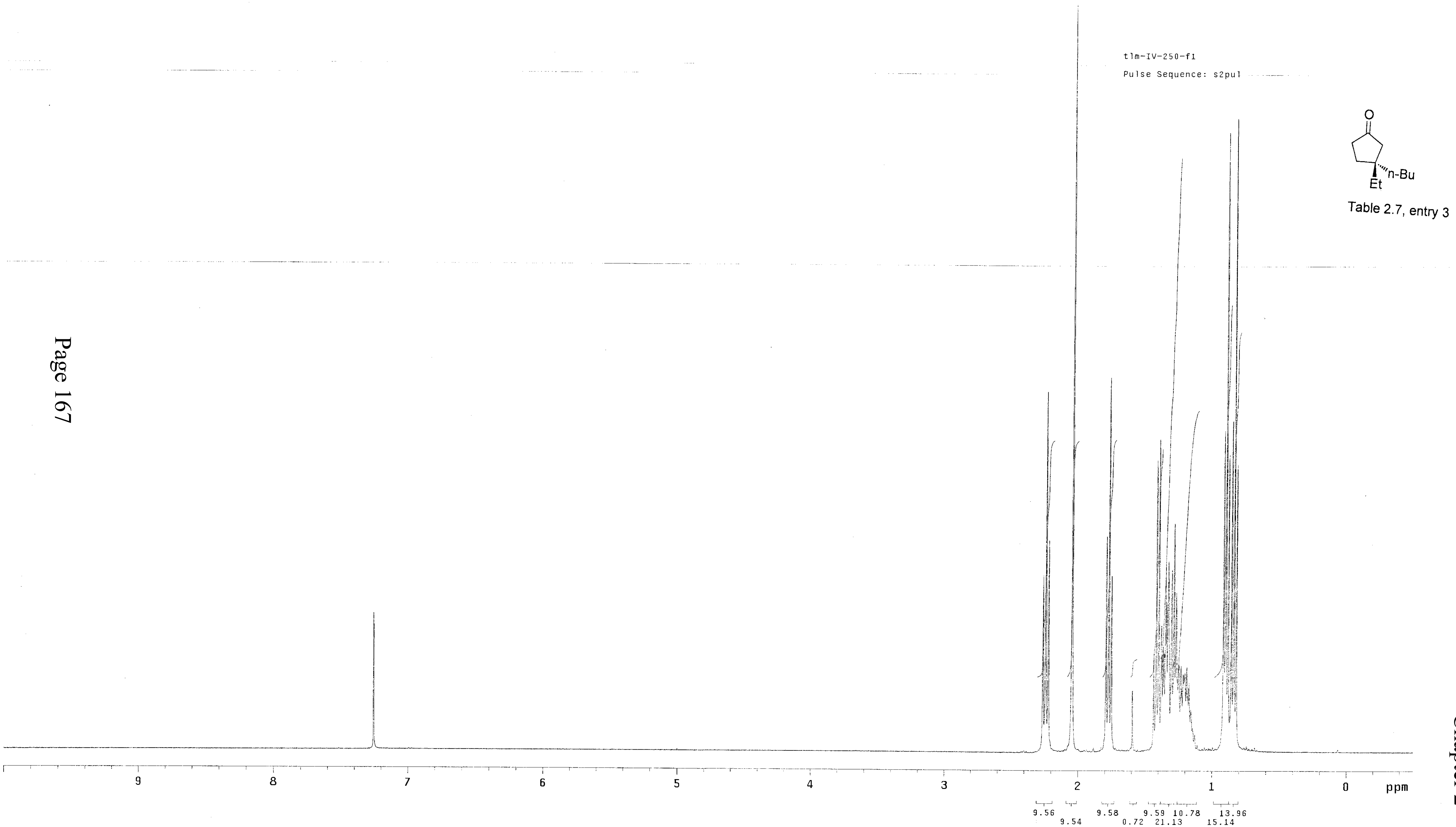


Table 2.7, entry 3

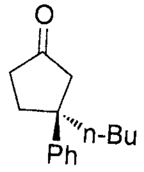
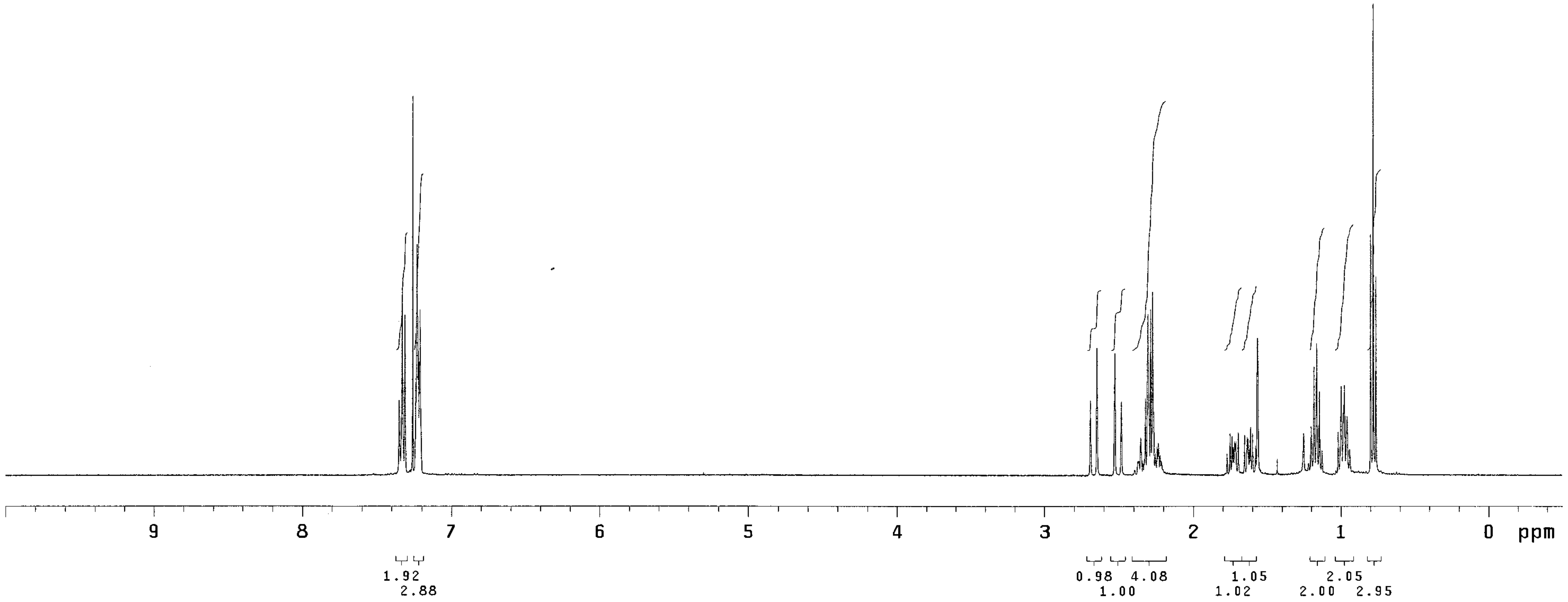


Table 2.7, entry 4



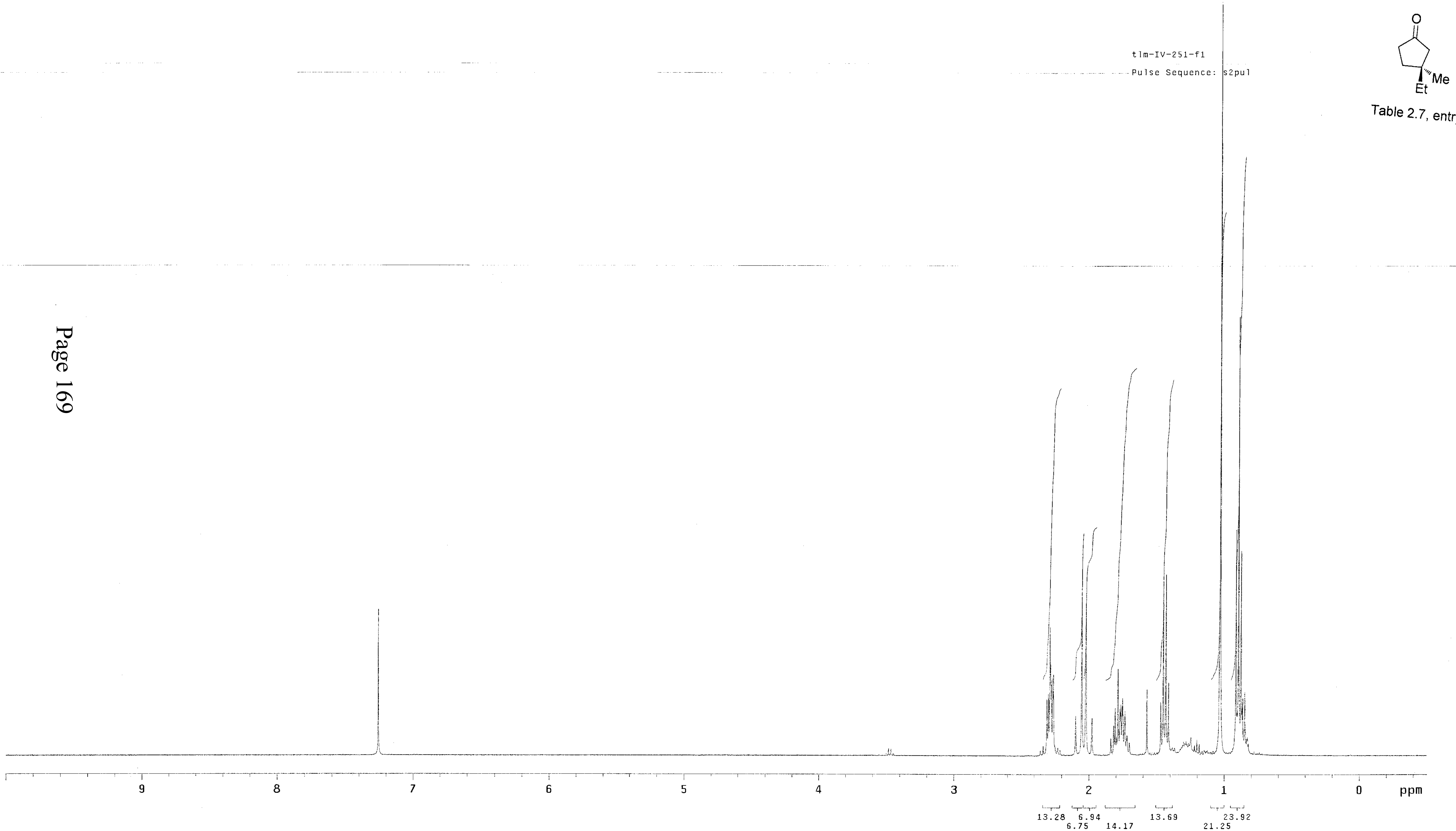


Table 2.7, entry 5

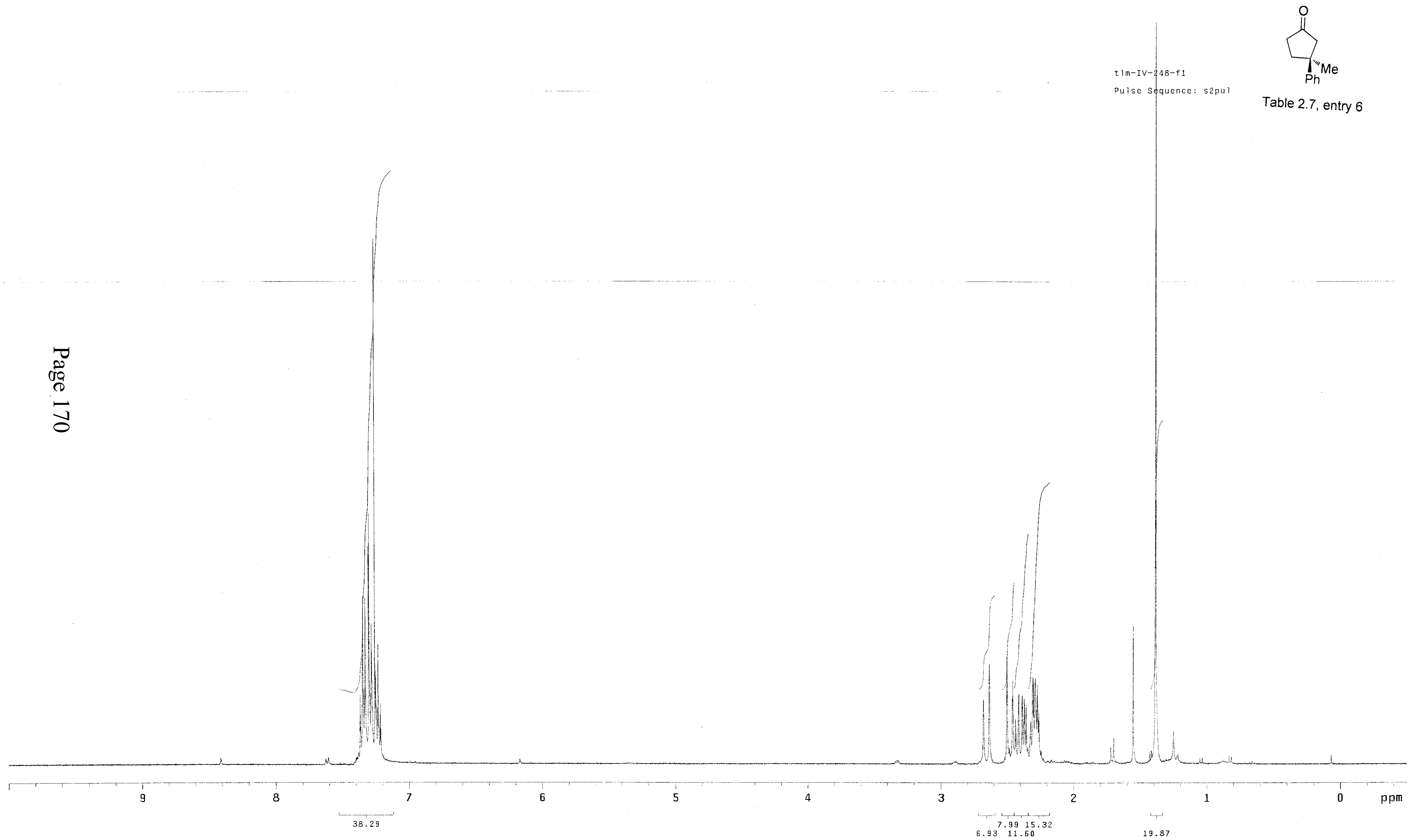


Table 2.7, entry 6

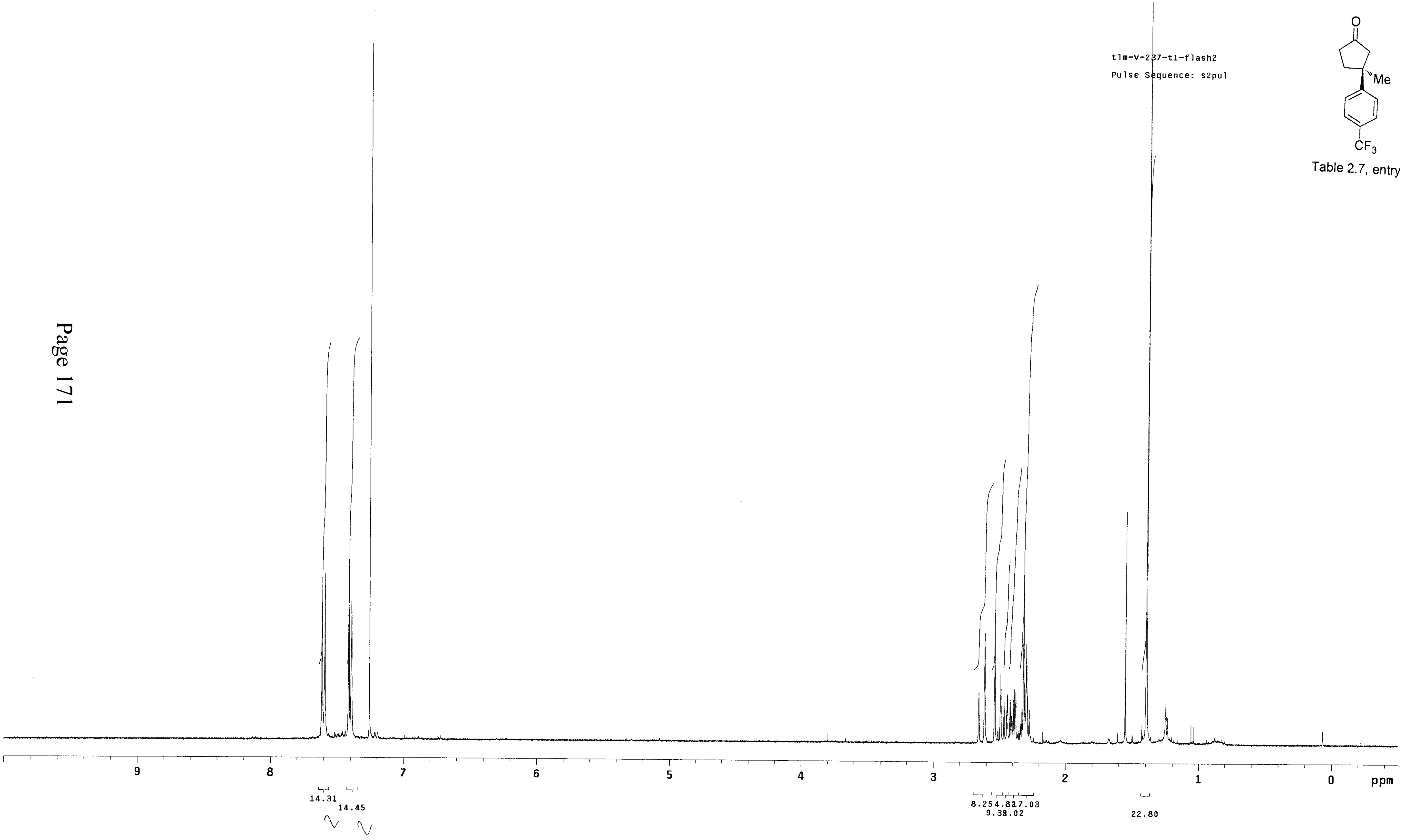


Table 2.7, entry 7

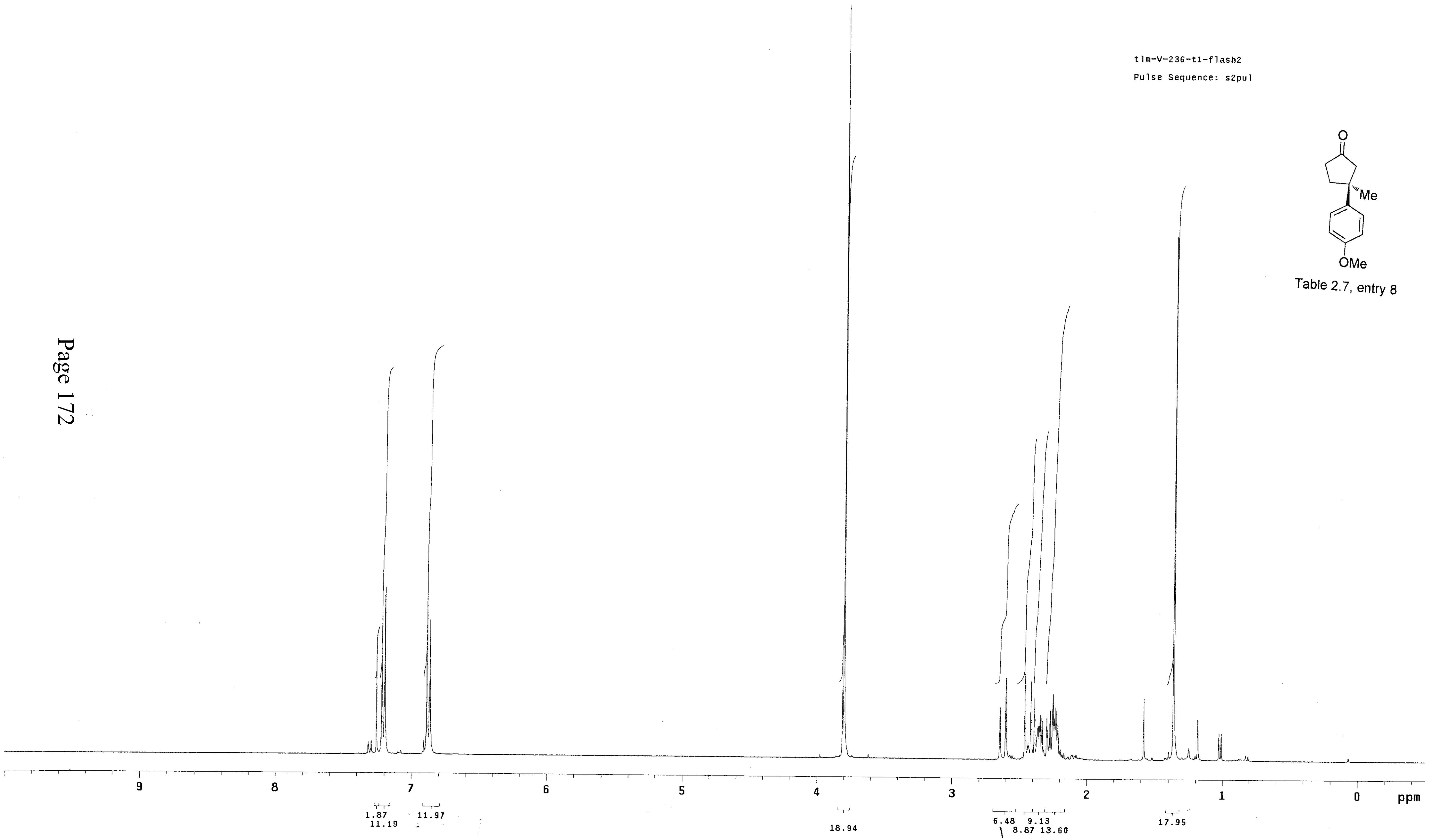


Table 2.7, entry 8

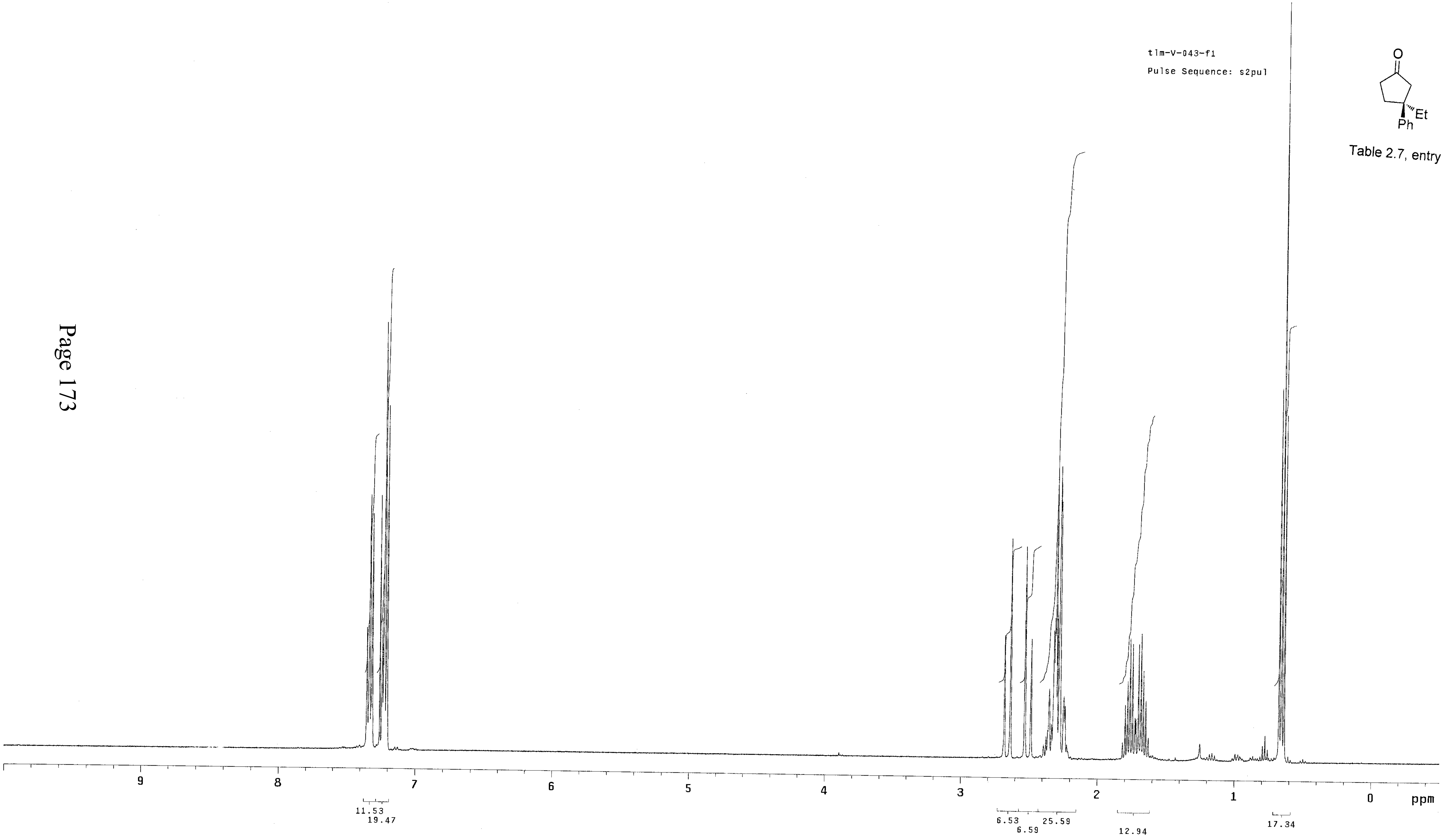


Table 2.7, entry 9

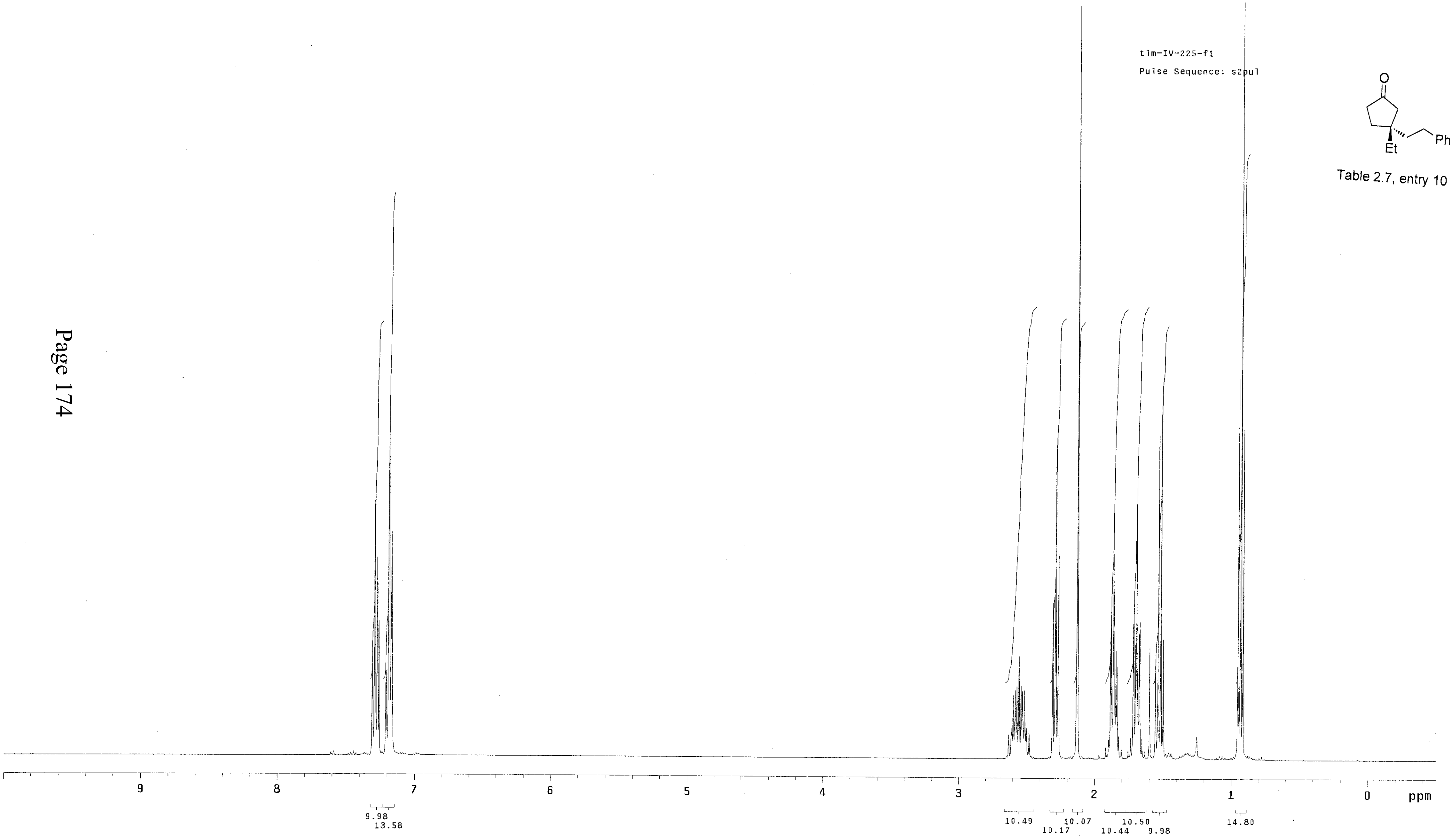


Table 2.7, entry 10

Chapter 3.

Cu-Catalyzed Enantioselective Conjugate Addition of Alkyl- and Arylaluminum Reagents to Trisubstituted Enones

3.1. Introduction

Conjugate addition reactions are a classic technique to build complexity starting from simple starting materials. Although the preparation of organocopper reagents dates back to 1859,[1] Gilman, in 1936, demonstrated that organocopper reagents react with a variety of electrophiles.[2] House and Corey were instrumental in extending the reaction scope to include α,β-unsaturated carbonyls[3] and applying the methods to natural product synthesis, most notably in context of steroids and prostaglandins.[4] A tremendous breadth of research surrounds the area of conjugate addition to electrophiles (enones, enoates, nitroalkenes, unsaturated sulfonones, etc) and quickly research turned to processes that are catalytic in copper.[5] The past four decades have focused on methods that are catalytic and enantioselective, delivering products that are enriched in one enantiomer.[6] Most

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(1) (a) Buckton, G. *Ann.* **1859**, *109*, 225. (b) Reich, R. *C. R. Hebd. Seances Acad. Sci.* **1923**, *177*, 322.

(2) "Relative Reactivities of Organometallic Compounds. XIII. Copper and Silver," Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 821–834.

(3) (a) *Modern Organocopper Chemistry*, Krause, N. Ed.; Wiley-VCH, Weinheim, 2002, pp. 224–258 and references cited therein. (b) "Conjugate Addition of Organocopper Reagents," Posner, G. H. *Org. React.* **1972**, *19*, 1–113.

(4) (a) "Prostaglandin Syntheses by Three-Component Coupling," Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847–876 and references cited therein. (b) "Enantioselective Synthesis of Steroids," Chapelon, A.-S.; Moraléda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, *63*, 11511–11616 and references cited therein.

(5) For the first observation that catalytic amounts of a copper salt can change the reactivity profile of Grignard reagents, see: "Factors Determining the Course and Mechanisms of Grignard Reactions. II. The Effect of Metallic Compounds on the Reaction between Isophorone and Methylmagnesium Bromide," Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308–2316.

(6) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Berlin, Germany, 1999. (b) *New Frontiers in Asymmetric Catalysis;* Mikami, K.; Lautens, M., Eds; Wiley: Hoboken, NJ, 2007 (c) "Recent Advances in Catalytic Enantioselective Michael Additions," Krause, N.;

research in the field of catalytic enantioselective conjugate addition (ECA) has centered on products that contain tertiary stereogenic centers, but in the past ten years, the more challenging objective of forming all-carbon quaternary stereogenic centers through such transformations has emerged.[7]

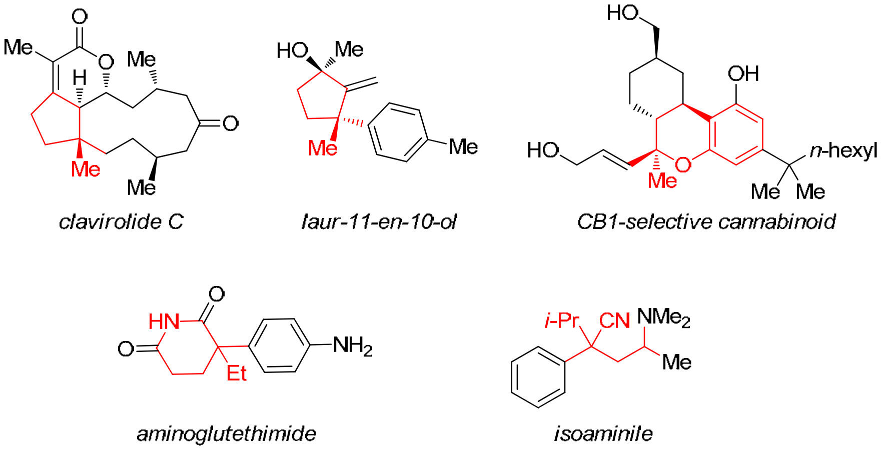
There are three considerable limitations for substrate classes in ECA methodology: additions to β-substituted cyclopentenones, trisubstituted unsaturated heterocycles (lactones, chromones, lactams), and trisubstituted acyclic enones. Outlined below is the current state of the art for each of the difficult and underrepresented enone classes. Choosing to study these difficult substrate classes is two-fold. One reason is to challenge the new catalysts we have developed in the Hoveyda laboratories and determine how effective and active they are for demanding reactions. For example, not much can be read about a catalyst when testing its ability on promoting the conjugate addition of diethylzinc to cyclohexenone when hundreds of catalyst systems have already been determined viable (>90% yield, >95:5 er).[6] Moreover, if the enantioselective additions to the aforementioned substrate classes are achievable with any type of nucleophile (alkyl, aryl, vinyl, etc), syntheses of biologically active molecules may become possible and/or more straightforward. Several compounds shown in Figure 3.1 are representative, each containing a cyclopentanone, heterocycle, or acyclic core.[8]

Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (d) "Enantioselective Copper-Catalysed Conjugate Addition," Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (e) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*, Krause, N. Ed.; Wiley-VCH, Weinheim, 2002, pp. 224–258.

(7) For a detailed review, see Chapter 1 of this thesis.

(8) For isolation account of clavirolide C, see: (a) "Four Novel Diterpenoids: Clavirolides B, C, D, and E from the Chinese Soft Coral *Clavularia viridis*," Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380–385. For the isolation account of laur-11-en-10-ol, see: (b) "Sesquiterpenes from the Red Alga *Laurencia tristicha*," Sun, J.; Shi, D.; Ma, M.; Li, S.; Wang, S.; Han, L.; Yang, Y.; Fan, X.; Shi, J.; He, L. *J. Nat. Prod.* **2005**, *68*, 915–919. For the synthesis and biological screen of the cannabinoid, see: (c) "Synthesis of Functionalized Cannabinoids," Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2000**, *65*, 6576–6582. Aminoglutethimide is a breast cancer drug marketed by Novartis. For a lead reference, see (d) "Aminoglutethimide-Induced Protein Free Radical Formation on Myeloperoxidase: A Potential Mechanism of Agranulocytosis," Siraki, A. G.; Bonini, M. G.; Jiang, J.; Ehrenshaft, M.; Mason, R. P. *Chem. Res. Toxicol.* **2007**, *20*, 1038–1045. Isoaminile is an antitussive agent. For a lead reference, see: (e) "Synthesis of Isoaminile Mediated by Enzymes," Antonietti, F.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Grande, V.; Malpezzi, L. *Synthesis* **2005**, 1148–1156.

Figure 3.1. Biologically Active Molecules that Contain an All-Carbon Quaternary Stereogenic Center



clavirolide C *laur-11-en-10-ol* *CB1-selective cannabinoid*

aminoglutethimide *isoaminile*

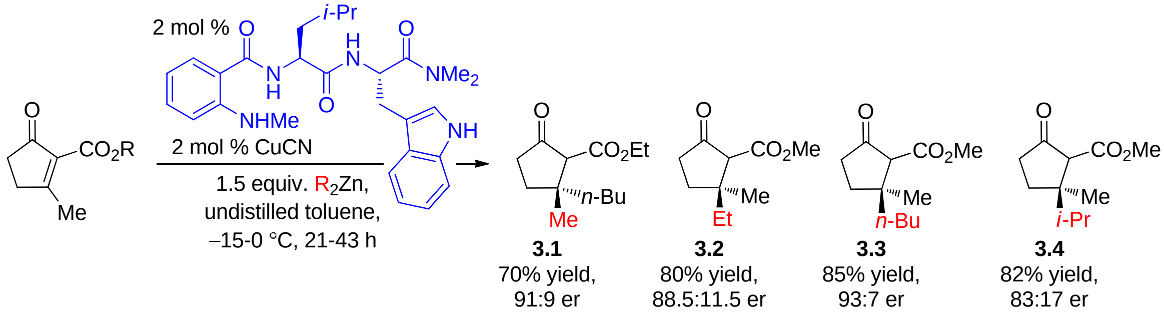
3.1.a Current Limitations in ECA Reactions: Trisubstituted Cyclopentenones

Although a sizeable amount of research has centered on ECA of activated olefins generating all-carbon quaternary stereogenic centers, several crucial limitations still exist. For example, ECA of nucleophiles to β-substituted cyclopentenones are relatively scarce, limited in scope of the electrophile and/or substrate, or afford products that are low yielding and/or have poor selectivity. A disclosure from our group was the first to include β-substituted cyclopentenones in the ECA method (Scheme 3.1).[9] It was found that a catalytic amount of air-stable CuCN and an amino acid-based ligand promotes ECA of alkylzinc reagents to tetrasubstituted cyclopentenones. Various nucleophiles were found to be competent, allowing methyl, ethyl, butyl, and *i*-propyl groups to be transferred and affording cyclopentanone products in up to 85% yield and 93:7 er. Although the method performs well, there are certain limitations. One such limitation is the substrate must contain an activating α-ester unit for reactivity. If β-methylcyclopentenone is used, <2% conv is observed.

---

(9) "Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones," Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

Scheme 3.1. Cu-Catalyzed ECA of Alkylzinc Reagents to Tetrasubstituted Cyclopentenones


2 mol %
i-Pr
NMe2
NHMe
NH
2 mol % CuCN
1.5 equiv. R2Zn,
undistilled toluene,
–15-0 °C, 21-43 h
CO2R
Me
CO2Et
n-Bu
Me
3.1
70% yield,
91:9 er
CO2Me
Me
Et
3.2
80% yield,
88.5:11.5 er
CO2Me
Me
n-Bu
3.3
85% yield,
93:7 er
CO2Me
Me
i-Pr
3.4
82% yield,
83:17 er

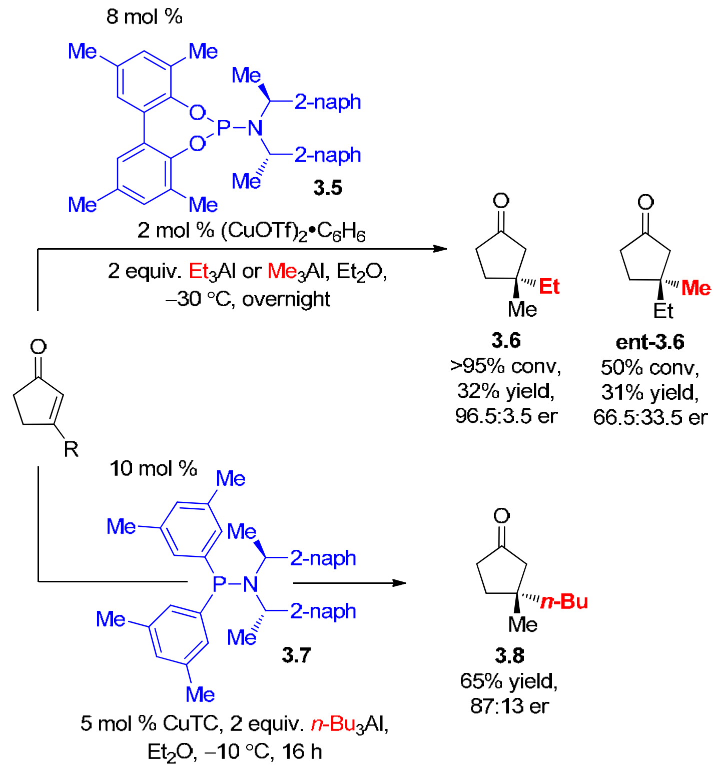
Alexakis and co-workers have also studied the Cu-catalyzed ECA of β-substituted cyclopentenones.[10] As shown in Scheme 3.2, phosphoramidite **3.5** in combination with a Cu(I) salt, promotes the ECA of Et_3Al to 3-methylcyclopentenone to afford **3.6** in high selectivity (96.5:3.5 er) but only in 32% yield. Extension of the protocol to addition of Me_3Al results in poor levels of efficiency and selectivity for the product **ent-3.6** (31% yield, 66.5:33.5 er). Modifications of the phosphoramidite ligand to a more flexible phosphinamine ligand **3.7** do not improve or extend the method.[11] The only two products disclosed (**3.8** and **3.6**) are obtained in <88:12 er.

---

(10) (a) "Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminum Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers," Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662. (b) "Enantioselective Copper-Catalyzed Conjugate Addition to 2- or 3-Substituted Cyclopent-2-en-1-ones: Construction of Stereogenic Quaternary Carbon Centers," Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, 2057–2060.

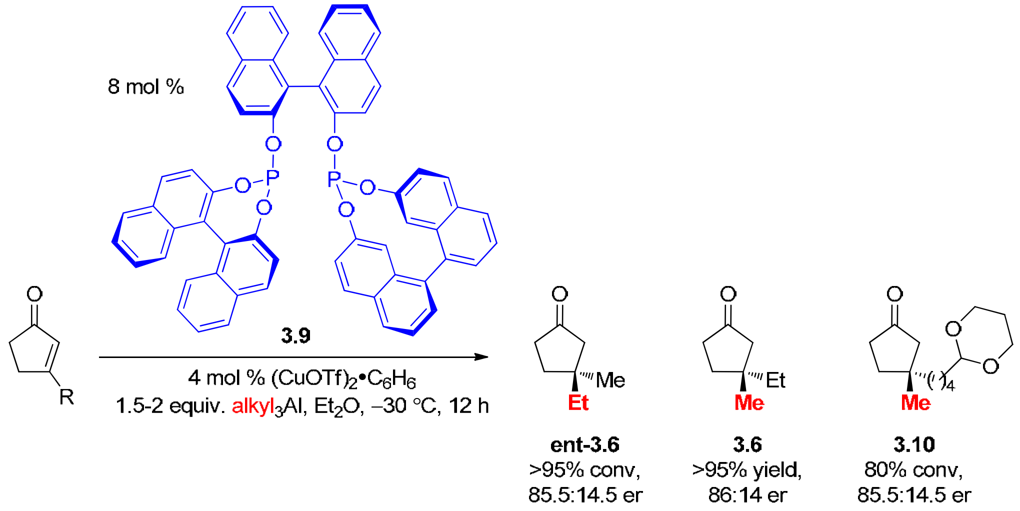
(11) "Copper-Catalyzed Asymmetric Conjugate Addition with Chiral SimplePhos Ligands," Palais, L.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 10473–10485.

Scheme 3.2. ECA of Alkylaluminum Reagents, Promoted by a Cu–Phosphine-Based Catalyst, of 3-Substituted Cyclopentenones

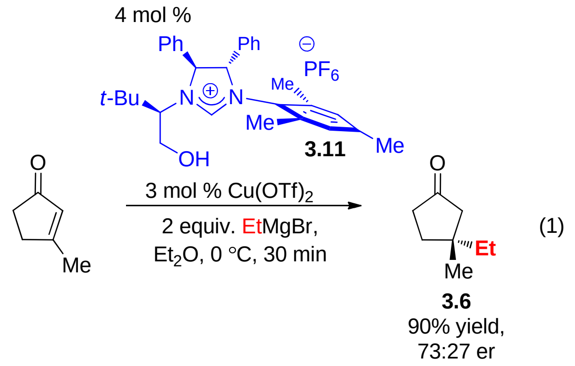

8 mol %
Me
Me
Me
2-naph
O
P–N
O
2-naph
Me
Me
Me
3.5
2 mol % (CuOTf)2•C6H6
2 equiv. Et3Al or Me3Al, Et2O,
–30 °C, overnight
O
Et
Me
3.6
>95% conv,
32% yield,
96.5:3.5 er
O
Me
Et
ent-3.6
50% conv,
31% yield,
66.5:33.5 er
O
R
10 mol %
Me
Me
Me
2-naph
P–N
2-naph
Me
Me
Me
3.7
5 mol % CuTC, 2 equiv. n-Bu3Al,
Et2O, –10 °C, 16 h
O
n-Bu
Me
3.8
65% yield,
87:13 er

Another ligand class was found to promote the ECAs of alkylaluminum reagents. Shown in Scheme 3.3, a diphosphite ligand with a Cu(I) salt promotes the addition of Et_3Al and Me_3Al, with limited success; only three substrates are probed and enantioselectivities are moderate (<86.5:13.5 er).[10b] A tetrasubstituted cyclopentenone (jasmone) is unreactive under the conditions in Scheme 3.3 (<2% conv).

Scheme 3.3. ECA of Alkylaluminum Reagents, Promoted by a Cu–Diphosphite Catalyst, to β-Substituted Cyclopentenones


8 mol %
3.9
4 mol % (CuOTf)2•C6H6
1.5-2 equiv. alkyl3Al, Et2O, –30 °C, 12 h
R
Me
Et
Et
Me
Me
ent-3.6
>95% conv,
85.5:14.5 er
3.6
>95% yield,
86:14 er
3.10
80% conv,
85.5:14.5 er

Alexakis and co-workers have also studied Cu-catalyzed ECA of Grignard reagents to enones to form products containing all-carbon quaternary stereogenic centers.[12] One example is provided to establish that 3-methylcyclopentenone can undergo ECA promoted by a Cu–NHC complex with EtMgBr (eq. 1). Product **3.6** is formed in 90% yield but in a low 73:27 er. Generality of this method was not further disclosed with respect to cyclopentenones as substrates.


4 mol %
Ph
Ph
PF6
t-Bu
OH
Me
Me
Me
3.11
3 mol % Cu(OTf)2
2 equiv. EtMgBr,
Et2O, 0 °C, 30 min
Me
Et
Me
(1)
3.6
90% yield,
73:27 er

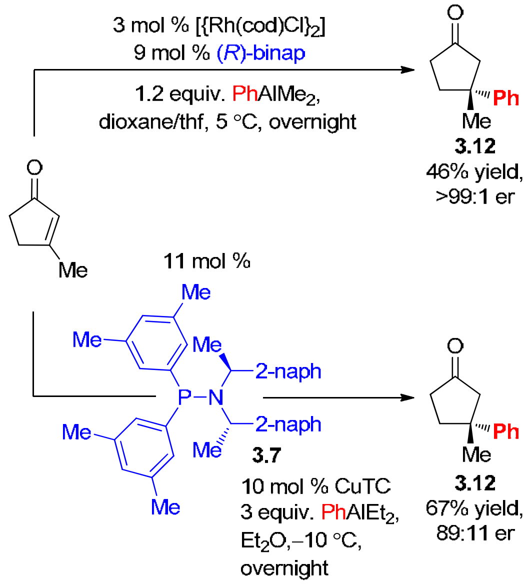
All the methods discussed until now are enantioselective alkyl additions; Alexakis and co-workers have also reported two results focusing on enantioselective aryl additions

---

(12) "Formation of Quaternary Chiral Centers by N-Heterocyclic Carbene–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Trisubstituted Cyclic Enones," Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. Eur. J.* **2010**, *16*, 9890–9904.

to 3-methylcyclopentenone (Scheme 3.4).[13] Only one example is provided in each disclosure and the products are obtained in 89:11–>99:1 er and 46–67% yield. The Rh-catalyzed process delivers **3.12** as a single enantiomer but the yield of the purified product is low (46%). Both results, however, are promising but the scope of the additions remains to be disclosed.

Scheme 3.4. Cu- and Rh-Catalyzed ECA of Dialkylphenylaluminum to 3-Methylcyclopentenone



3 mol % [{Rh(cod)Cl}$_2$]
9 mol % (*R*)-binap
1.2 equiv. PhAlMe$_2$,
dioxane/thf, 5 °C, overnight
O
Ph
Me
3.12
46% yield,
>99:1 er
O
Me
11 mol %
Me
Me
Me
2-naph
P–N
2-naph
Me
Me
Me
3.7
10 mol % CuTC
3 equiv. PhAlEt$_2$,
Et$_2$O, –10 °C,
overnight
O
Ph
Me
3.12
67% yield,
89:11 er

As discussed in Chapter 2 of this thesis, we found that Cu–NHC catalyzed ECA of alkyl- and arylzinc reagents perform well with a variety of β-ester-containing substrates.[14] When 3-alkyl or 3-arylcyclopentenones are used as substrates (electrophilic substrates), products with high enantioselectivities are afforded (>95:5 er) but low efficiencies are sometimes observed (25–>98% conv). Developing a catalyst system that

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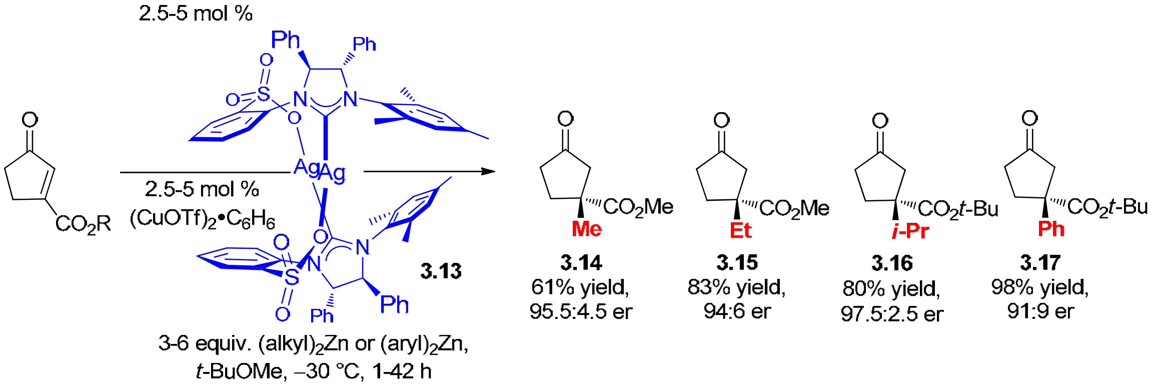
(13) (a) "Copper-Catalyzed Asymmetric Conjugate Addition of Aryl Aluminum Reagents to Trisubstituted Enones: Construction of Aryl-Substituted Quaternary Centers," Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int Ed.* **2008**, *47*, 8211–8214. (b) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl Alanes to Trisubstituted Enones: Binap as an Effective Ligand in the Formation of Quaternary Stereocenters," Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769–7772.

(14) "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100.

allows the direct enantioselective alkylation of less activated trisubstituted cyclopentenones was one of the goals of the studies in this chapter.

Scheme 3.5. Cu–NHC Catalyzed ECA of γ-Ketoesters


2.5-5 mol %
Ph
Ph
O
O=S
N
N
O
Ag
Ag
O
N
N
O
S
O
Ph
Ph
3.13
2.5-5 mol %
(CuOTf)$_2$•C$_6$H$_6$
O
CO$_2$R
3-6 equiv. (alkyl)$_2$Zn or (aryl)$_2$Zn,
t-BuOMe, –30 °C, 1-42 h
O
CO$_2$Me
Me
3.14
61% yield,
95.5:4.5 er
O
CO$_2$Me
Et
3.15
83% yield,
94:6 er
O
CO$_2$*t*-Bu
i-Pr
3.16
80% yield,
97.5:2.5 er
O
CO$_2$*t*-Bu
Ph
3.17
98% yield,
91:9 er

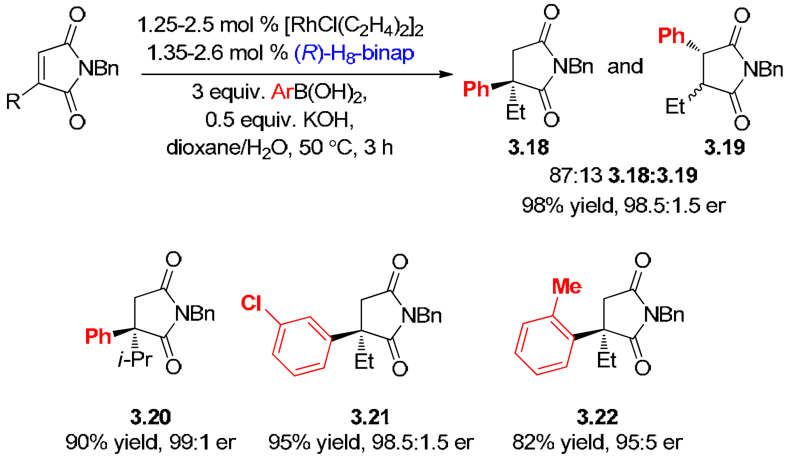
3.1.b Current Limitations in ECA Reactions: Trisubstituted Unsaturated Cyclic Heterocycles

Enantioselective conjugate addition of unsaturated heterocycles to afford products containing quaternary stereogenic centers also is an underdeveloped field of study; there are only two reports related to this topic. One example is by Hayashi and co-workers which describes a method for 1,4-addition of arylboronic acids to 3-substituted maleimides furnishing enantiomerically enriched succinimides.[15] Although this is an impressive first account for ECA of an unsaturated heterocycle, it has only been shown to be applicable for activated maleimides (and one example of a quinone-type substrate).

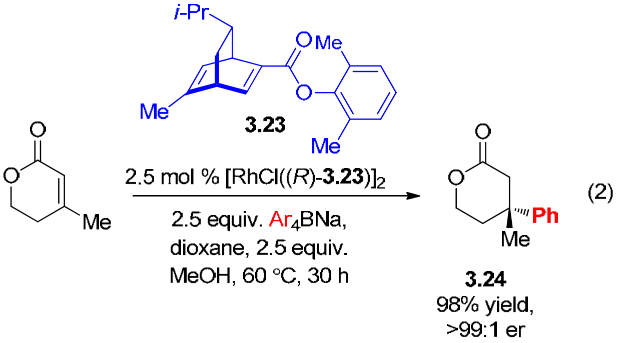
---

(15) "Rhodium-Catalyzed Asymmetric Construction of Quaternary Carbon Stereocenters: Ligand-Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides," Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629.

Scheme 3.6. Rh-Catalyzed ECA of Arylboronic Acids to Maleimides


1.25-2.5 mol % [RhCl(C2H4)2]2
1.35-2.6 mol % (R)-H8-binap
3 equiv. ArB(OH)2,
0.5 equiv. KOH,
dioxane/H2O, 50 °C, 3 h
NBn
R
Ph
Et
and
3.18
3.19
87:13 3.18:3.19
98% yield, 98.5:1.5 er
i-Pr
Cl
Me
3.20
90% yield, 99:1 er
3.21
95% yield, 98.5:1.5 er
3.22
82% yield, 95:5 er

A recent report from Hayashi and Shintani investigates the reactivity and selectivity of unactivated trisubstituted enoates and, in one example, shows the feasibility of trisubstituted unsaturated lactone (eq. 2).[16] The desired product **3.24** can be obtained in a high yield and enantioselectivity (98% yield, >99:1 er). Although this is a promising result, it remains to be explored if this a general approach.


i-Pr
Me
3.23
2.5 mol % [RhCl((R)-3.23)]2
2.5 equiv. Ar4BNa,
dioxane, 2.5 equiv.
MeOH, 60 °C, 30 h
Ph
3.24
98% yield,
>99:1 er
(2)

Furthermore, there have been no reports to date that include unsaturated chromones or lactams. The lack of data on these substrate classes are attributed to their low electrophility; for a general approach that allows the efficient and selective synthesis of the conjugate adducts, a highly active catalyst must be developed.

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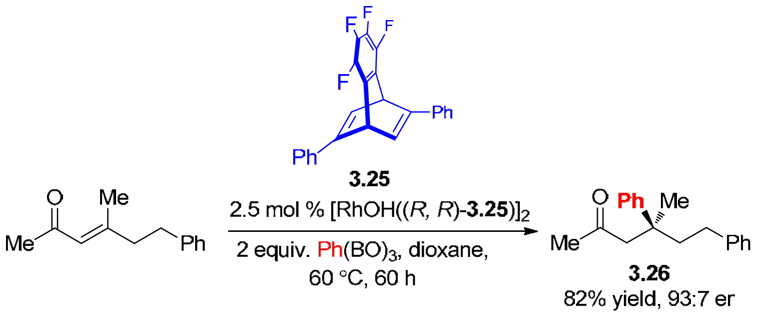
[16] "Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to β,β-Disubstituted α,β-Unsaturated Esters," Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350–352.

3.1.c Current Limitations in ECA Reactions: Trisubstituted Acyclic Enones

Reports on the ECA of non-activated trisubstituted acyclic enones are also scarce.[17] Only a few reports have been disclosed on these types of enones and all focus on enantioselective *aryl* additions with one report on enantioselective cyanide addition. Moreover, all involve either Rh- or Sr-catalyzed processes. There have been no reports on Cu-catalyzed enantioselective additions to non-activated trisubstituted acyclic enones.

Hayashi and co-workers have shown that acyclic enones are competent partners in the Rh-catalyzed ECA of $(PhBO)_3$. For example **3.26** is furnished in 82% yield and 93:7 er (eq. 3).[18] A similar protocol has been described for Rh-catalyzed ECA of Ph_4BNa (not shown),[19] although only three examples the ECA are provided in the two accounts.



(3)

Alexakis and Woodward have recently disclosed a Rh-catalyzed ECA protocol for arylaluminum reagents to trisubstituted enones (eq. 4).[13b] Two examples are provided and the products are isolated in 52–55% yield and in >96:4 er. Again, although the products can be obtained in high enantioselectivities (with moderate yields), the reaction scope was not probed.

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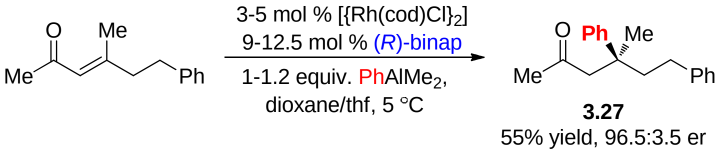
[17] There have been reports detailing ECA of nucleophiles to highly acyclic trisubstituted unsaturated electrophiles. For example, Fillion and co-workers have a series of papers involving Meldrum's acid derived enones; our group has an account with trisubstituted nitroalkenes, and Carretero and co-workers have disclosed an article on unsaturated pyridylsulfones. For lead references, see: (a) "Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon–Carbon Bond-Forming Processes," Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454. (b) "Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions," Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585. (c) "Enantioselective Construction of Stereogenic Quaternary Centres *via* Rh-Catalyzed Asymmetric Addition of Alkenylboronic Acids to α,β-Unsaturated Pyridylsulfones," Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963.

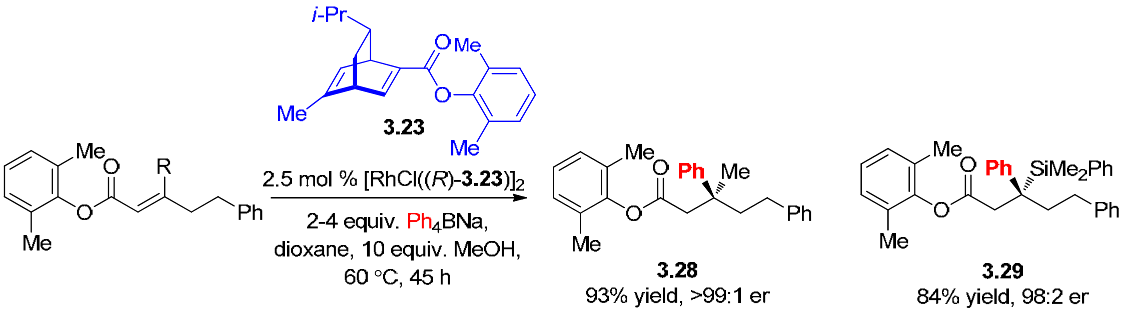
[18] "Chiral Tetrafluorobenzobarrelenes as Effective Ligands for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboroxines to β,β-Disubstituted α,β-Unsaturated Ketones," Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969–3971.

[19] "Sodium Tetraarylborates as Effective Nucleophiles in Rhodium/Diene-Catalyzed 1,4-Addition to β,β-Disubstituted α,β-Unsaturated Ketones: Catalytic Asymmetric Construction of Quaternary Carbon Stereocenters," Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589.



(4)

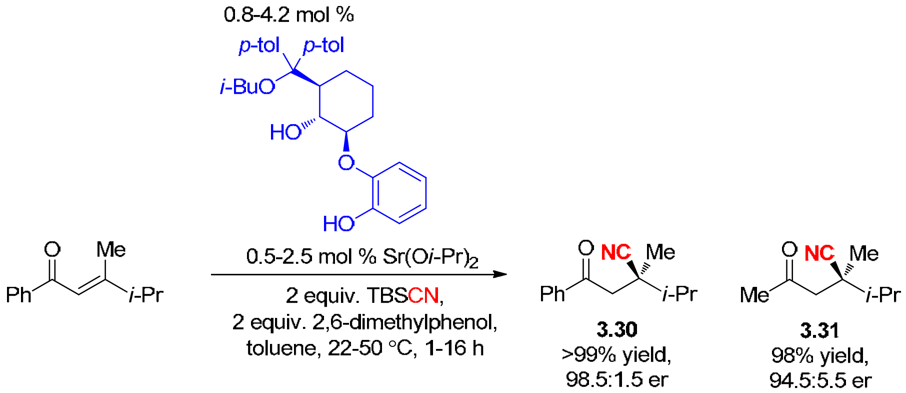
A recent report from Hayashi and Shintani investigates the reactivity and selectivity of unactivated trisubstituted enoates, an underrepresented substrate class due to the relatively low electrophilicity (eq. 4).[16] Diene ligand **3.23** in combination with a Rh(I) salt promotes the arylation of 2,6-dimethylphenyl ester with Ph_4BNa to afford **3.28** in 93% yield and in >99:1 er. The procedure can be used on a variety of trisubstituted unsaturated esters affording all products disclosed in higher than 98:2 er. Moreover, Si-substituted unsaturated ester also was congruent in the addition; enantioenriched ester **3.29** is delivered in 84% yield and 98:2 er. Although this is an impressive first account for additions to trisubstituted enoates, some drawbacks are noted. The atom economy of the nucleophile is low, as multiple equivalents of the phenyl group is needed for one phenyl transfer and the additions require elevated reaction temperatures and prolonged times. Interesting to note is that the ligand **3.23** used in the addition also contains a 2,6-dimethylphenylester, which could potentially undergo ECA with Ph_4BNa. It is not mentioned, however, if this does occur during the reaction conditions.



(4)

Lastly, Shibasaki has demonstrated that enantioselective cyanide additions to trisubstituted enones can be performed through a Sr-catalyzed procedure (Scheme 3.7).[20] A variety of other trisubstituted enones with varying electronic and steric characters are also tolerated under the reaction conditions.

Scheme 3.7. Sr-Catalyzed Enantioselective Cyanide Addition of Trisubstituted Acyclic Enones


0.8-4.2 mol %
p-tol
p-tol
i-BuO
HO
O
HO
O
Me
Ph
i-Pr
0.5-2.5 mol % Sr(Oi-Pr)2
2 equiv. TBSCN,
2 equiv. 2,6-dimethylphenol,
toluene, 22-50 °C, 1-16 h
O
NC
Me
Ph
i-Pr
3.30
>99% yield,
98.5:1.5 er
O
NC
Me
Me
i-Pr
3.31
98% yield,
94.5:5.5 er

As shown above, although there have been some initial studies published involving the more difficult substrate classes, general, practical and efficient methods for enantioselective additions of alkyl, aryl, and vinyl[21] groups are lacking. Discussed in this chapter is the progress our group has made for Cu-catalyzed ECA of alkyl- and arylmetals to cyclic enones to generate products bearing quaternary stereogenic centers, including and focusing on substrates that have been typically underrepresented in the chemistry literature.

---

(20) "Catalytic Enantioselective Construction of β-Quaternary Carbons via a Conjugate Addition of Cyanide to β,β-Disubstituted α,β-Unsaturated Carbonyl Compounds," Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863.

(21) Enantioselective conjugate addition of vinyl nucleophiles will be discussed in Chaper 4 of this thesis.

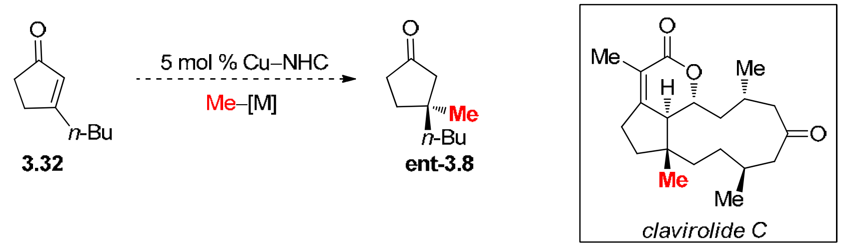
3.2. Cu-Catalyzed ECA of Alkylmetal Reagents to Trisubstituted Enones and Unsaturated Heterocycles

3.2.a Cu-Catalyzed ECA of Alkylaluminum Reagents to β-Substituted Cyclopentenones[22]

3.2.a.1. Initial Screening and Optimization[23]

We began our investigations with β-butylcyclopentenone (**3.32**) as the substrate for the Cu-catalyzed ECA reactions (Scheme 3.8). The interest in this substrate is two-fold. (1) As discussed above, β-substituted cyclopentenones are difficult substrates in ECA reactions to control both efficiency and selectivity. (2) If the conjugate adduct **ent-3.8** can be accessed in high yield and enantioselectivity, the all-carbon quaternary stereogenic center found in clavirolide C could possibly be formed through an ECA of a methyl nucleophile to a suitably functionalized β-substituted cyclopentenone.

Scheme 3.8. Cu–NHC Catalyzed ECA of an Alkylmetal to Enone **3.32**



We began by examining conditions found optimal for the Cu-catalyzed ECA of alkylzinc reagents to γ-ketoesters.[24] When the conjugate addition reaction of dimethylzinc to **3.32** is promoted by either the phenoxy-containing NHC–Cu complex

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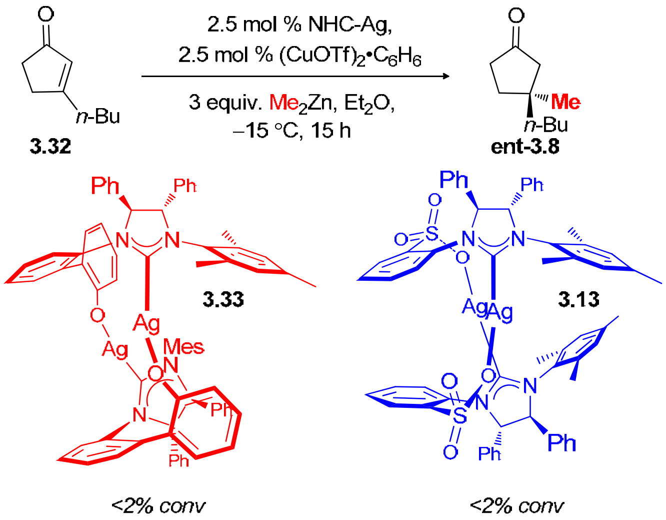
(22) "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl and Aryl Aluminum Reagents to Five-, Six- and Seven-Membered-Ring β-Substituted Cyclic Enones," May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.

(23) The initial screening was done by M. Kevin Brown.

(24) For full details, see Chapter 2 and reference 14.

(derived from NHC–Ag complex **3.33**)[25] or the sulfonate-containing NHC–Cu complex (derived from NHC–Ag complex **3.13**),[24] <2% conv is observed (Scheme 3.9). We surmised that if a more Lewis acidic nucleophile is used, then perhaps the efficiency would be increased.

Scheme 3.9. Cu–NHC Catalyzed ECA of Dimethylzinc to **3.32**



Switching the nucleophile to the more Lewis acidic trimethylaluminum,[26,27] the enantioselective addition now proceeds smoothly at –15 °C in 15 h (>98% conv) with both NHC complexes (**3.33** and **3.13**, Scheme 3.10). Product **ent-3.8** is afforded with higher enantioselectivity when the sulfonate-containing Cu–NHC is used (in situ prepared from **3.13**) in 73.5:26.5 er. Although this was a promising result, reaction medium optimization and catalyst screening were performed in an effort to increase the selectivity to synthetically useful levels (>90:10 er).

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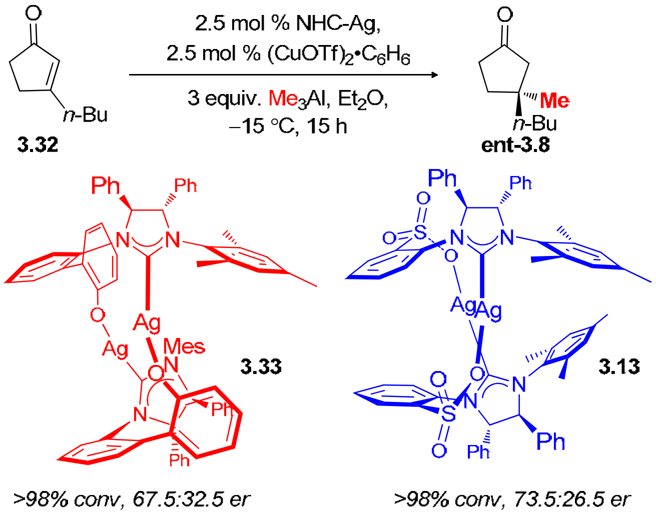
(25) "A Readily Available Chiral Ag-Based N-Hetereocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

(26) Trialkylaluminium reagents are also appreciably less expensive than the corresponding dialkylzinc reagents. The following prices are from Strem in 2010: Me$_3$Al = \$104/mol. Me$_2$Zn = \$1380/mol. Et$_3$Al = \$33/mol. Et$_2$Zn = \$126/mol.

(27) For a review on 1,2- and 1,4-additions with aluminum-based reagents, see: "Selectivity Control in 1,2- and 1,4-Additions of Aluminum Organyls to Carbonyl Compounds," von Zezschwitz, P. *Synthesis* **2008**, 1809–1831.

Scheme 3.10. Cu–NHC Catalyzed ECA of Trimethylaluminum to **3.32**



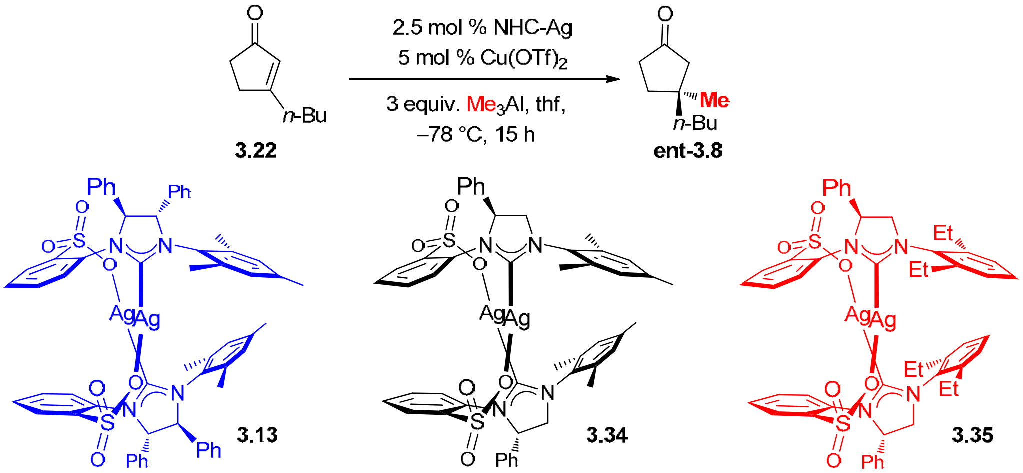
Optimization of the reaction medium led us to improve enantioselectivity of the **ent-3.8** to 80.5:19.5 er by changing the copper salt to Cu(OTf)$_2$, the solvent to thf, and lowering the temperature to –78 °C (Scheme 3.11). The use of a Cu(II) salt rendered the reaction more reproducible in terms of conversion[28,29] and changing the solvent to thf (vs. Et$_2$O) allowed the temperature to be reduced to –78 °C without significant loss of efficiency. For example, when the reaction shown in Scheme 3.10 is performed at –55 °C (2.5 mol % **3.13**, 2.5 mol % (CuOTf)•C$_6$H$_6$, Me$_3$Al, Et$_2$O, –55 °C, 15 h), the addition only proceeds to 70% conv (80:20 er); however, when the solvent medium is changed to thf, >98% conv is achieved even at –78 °C.

---

(28) We believe that the catalyst (the Cu(I)–NHC complex) decomposes under the reaction conditions over time. Starting with a copper(II) salt serves as a reservoir for the slow release of Cu(I). For a similar observation, see: "Synthesis of New Chiral 2,2'-Bipyridine Ligands and Their Application In Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation," Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Maghani, P.; Kočovsky, P. *J. Org. Chem.* **2003**, *68*, 4727–4742.

(29) For a proposed mechanism on the reduction of Cu(II) to Cu(I) in the presence of an alkylmetal, see: (a) "Electron-Transfer Mechanisms for Organometallic Intermediates in Catalytic Reactions," Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351–360. (b) "Interaction of Propagating Radicals with Copper (I) and Copper (II) Species," Matyjaszewski, K.; Woodworth, B. E. *Macromolecules* **1998**, *31*, 4718–4723. (c) Jukes, A. E. The Organic Chemistry of Copper. In *Advances in Organometallic Chemistry*, Volume 12; Stone, F. G. A.; West, R., Eds.; Academic Press, Inc: New York, NY, 1974, pp 215–322.

Scheme 3.11. Ligand Screening For Cu-Catalyzed ECA of Me_3Al to 3-Butylcyclopentenone



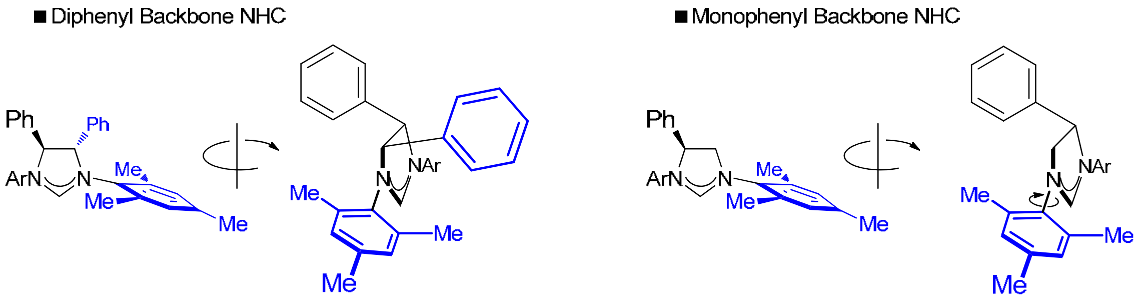
2.5 mol % NHC-Ag
5 mol % Cu(OTf)$_2$
3 equiv. Me$_3$Al, thf,
–78 °C, 15 h
O
n-Bu
Me
Ph
Et
O=S
N
O
Ag

3.22 **ent-3.8** **3.13** **3.34** **3.35**

>98% conv, 80.5:19.5 er *57% conv, 90:10 er* *72% conv, 94:6 er*

To further increase the enantioselectivity of the reaction, modifications of the ligand structure was probed. We surmised that removing one of the stereogenic phenyl groups on the backbone of the NHC would allow more freedom of rotation of the N–mesityl unit, presumably rendering one side of the ligand more sterically hindered (Scheme 3.12). Accordingly, when the ECA reaction is promoted by the in situ prepared NHC–Cu complex derived from the des-phenyl complex **3.34**, product **ent-3.8** is afforded with an increase in enantioselectivity (90:10 er, 57% conv, Scheme 3.11). Furthermore, modifying the ligand structure to include a more sterically bulky 2,6-diethylphenyl unit, in place of the mesityl, further increases the enantioselectivity of the product to 94:6 er (Scheme 3.11).

Scheme 3.12. Diphenyl vs. Monophenyl Backbone on NHC Ligands



■ Diphenyl Backbone NHC
■ Monophenyl Backbone NHC
Ph
ArN
N
Me
NAr

While we believe that the steric difference between complexes **3.13**, **3.34**, and **3.35** plays an important role for the enantiodiscrimination of the active Cu–NHC catalyst, altering the substituents on the backbone of the NHC ligand can also have subtle effects on the donor ability of the carbene. For instance, inferring bond lengths and angles from crystal structures of the imidazolinium salts (precursors of complexes **3.13** and **3.34)**, the C–C bond length on the heterocycle containing the diphenyl backbone is slightly longer than the C–C bond length of the heterocycle that bears the monophenyl backbone (1.556 Å vs. 1.546 Å, Scheme 3.13).[30] The bond length differences also affects the N–C–N angle; as shown in Scheme 3.13, the angle for the diphenyl backbone imidazolinium salt is 113.8° and the monophenyl backbone has a N–C–N angle of 111.8°. Although slight, the differences between the angles of the N–C–N can have an impact on the donor ability of the carbene by altering the hybridization of the orbitals on the carbene.[31,32] The more linear the N–C–N angle or, in other words, the more s character of the bonds, it is surmised that the carbene is a better σ-donor. The strain energy in the heterocyclic contributes to slightly higher energy of the carbene. Therefore, the Cu–NHC complex that contains a diphenyl backbone is a worse (albeit slightly) donor than the corresponding complex that contains a monophenyl backbone.

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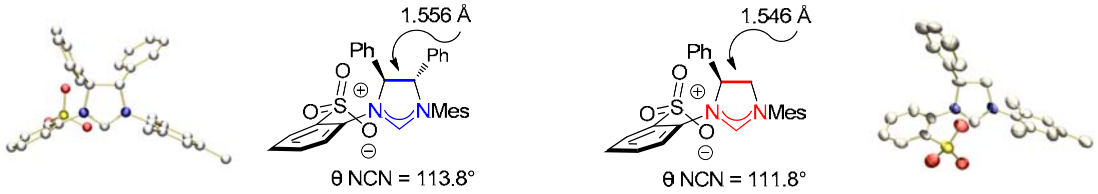
(30) The unit cell in the crystal structure of the imidazolinium salt bearing the monophenyl backbone shows four independent molecules. Two of the molecules in the cell have the sulfonate moiety and the phenyl group on the backbone of the heterocycle syn to each other. The other two molecules have the sulfonate and the phenyl group anti to each other. This is in contrast to the data observed with the crystal structure obtained from the imidazolinium salt that bears the two phenyl groups on the backbone; the only structure observed in the X-ray contained the sulfonate and the phenyl groups in an anti orientation. Regardless, we believe that the active bidentate Cu–NHC complexes derived from both ligands contains the sulfonate and the phenyl in a syn coordination. See the mechanism section for further elaboration.

(31) "Stable Carbenes," Bourissou, D.; Guerret, O.; Gabbaï, F.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.

(32) "Structures of Diarylcarbenes and Their Effect on the Energy Separation between the Singlet and Triplet States," Gilbert, B. C.; Griller, D.; Nazran, A. S. *J. Org. Chem.* **1985**, *50*, 4738–4742.

Scheme 3.13. Subtle Differences in Bond Angles and Bond Length Between the Diphenyl and Monophenyl Backbones Contained on the Imidazolinium Salts



3.2.a.2. Synthesis of Monophenyl Backbone Containing NHC Complexes

The synthesis of the Ag–NHC complex **3.35** is commenced with commercially available Boc-phenylglycinol (**3.36**, or prepared in one step[33] by Boc protection of phenylglycinol) in a six step sequence. Cyclization of **3.36** with thionyl chloride in the presence of imidazole and Et_3N affords the 1,2,3-oxathiazolidine 2-oxide **3.37** in 78% yield.[34] A Ru-catalyzed oxidation of **3.37** with sodium periodate affords the cyclic sulfamidate.[34] Nucleophilic displacement of the cyclic sulfamidate with the sodium salt of a Boc-protected aniline,[35] followed by acid-promoted hydrolysis of the carbamate protecting groups and the sulfamic acids affords diamine **3.40** in 77% yield.[34] Buchwald-Hartwig C–N cross coupling installs the sulfonate containing aryl group.[36,37] Cyclization

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(33) "Model Studies and First Synthesis of the Antifungal and Antibacterial Agent Cladobotryal," Clive, D. L. J.; Huang, X. *J. Org. Chem.* **2004**, *69*, 1872–1879.

(34) "Synthesis of the *kappa-agonist* CJ-15,161 *via* a Palladium-Catalyzed Cross-Coupling Reaction," Ghosh, A.; Sieser, J. E.; Caron, S.; Watson, T. J. N. *Chem. Commun.* **2002**, 1644–1645.

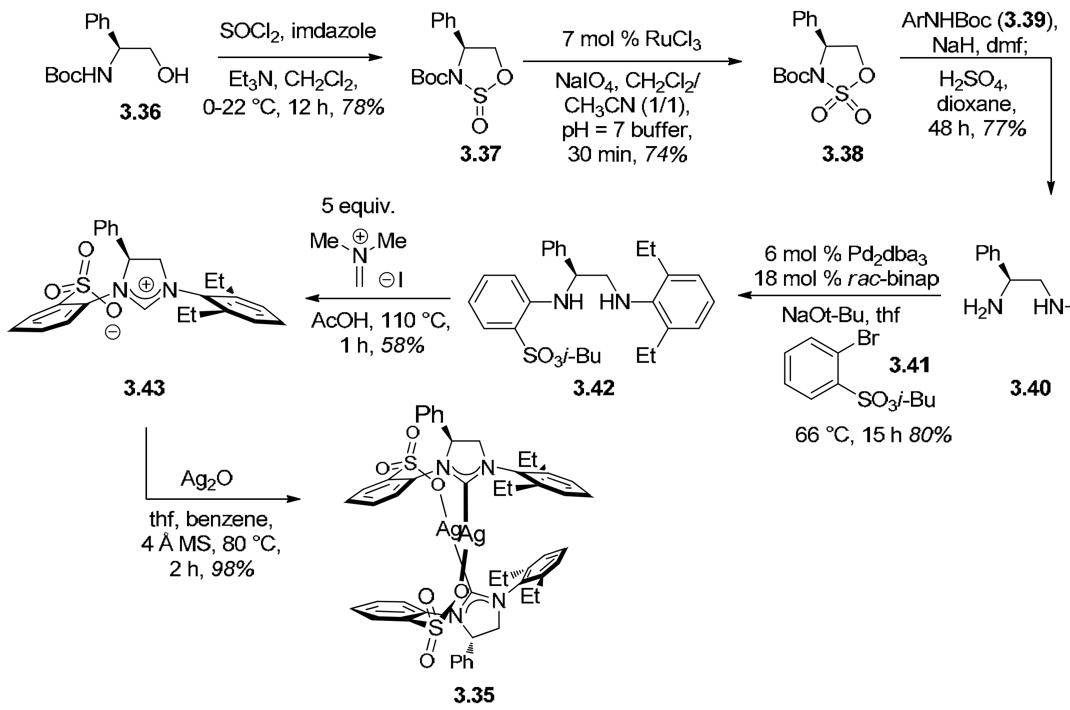
(35) For the synthesis of various Boc-protected anilines, see: "Catalyst-Free Chemoselective *N-tert*-Butyloxycarbonylation of Amines in Water," Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259–3262.

(36) (a) "Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides," Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (b) "Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates," Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370. (c) "Palladium Catalysed Mono-*N*-Arylation of Enantiopure Diamines," Frost, C. G.; Mendonça, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1831–1834.

(37) For the one step-preparation of aryl bromide **3.41**, see: (a) Synthesis of Neopentyl Biphenylsulfonates Using the Suzuki-Miyaura Reaction," Cho, C.-H.; Kim, C.-B.; Sun, M.; Park, K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1632–1636. (b) "Preparation of Unsymmetrical Terphenyls via the Nickel-Catalyzed Cross-Coupling of Alkyl Biphenylsulfonates with Aryl Grignard Reagents," Cho, C.-H.; Kim, I.-S.; Park, K. *Tetrahedron* **2004**, *60*, 4589–4599.

of the diaryl diamine **3.42** in the presence of Eschenmoser's salt[38] affords the zwitterionic imidazolinium salt **3.43**.[39] Treatment with Ag_2O quantitatively affords the NHC–Ag complex **3.35**. Complex **3.34** is prepared in an analogous route.

Scheme 3.14. Synthesis of Ag–NHC Complex **3.35**


Ph
BocHN
OH
3.36
SOCl2, imdazole
Et3N, CH2Cl2,
0-22 °C, 12 h, 78%
Ph
BocN
O
S
O
3.37
7 mol % RuCl3
NaIO4, CH2Cl2/
CH3CN (1/1),
pH = 7 buffer,
30 min, 74%
Ph
BocN
O
S
O
O
3.38
ArNHBoc (3.39),
NaH, dmf;
H2SO4,
dioxane,
48 h, 77%
Ph
Et
H2N
HN
Et
3.40
6 mol % Pd2dba3
18 mol % rac-binap
NaOt-Bu, thf
Br
3.41
SO3i-Bu
66 °C, 15 h 80%
Ph
Et
NH
HN
SO3i-Bu
Et
3.42
5 equiv.
Me
N
Me
I
AcOH, 110 °C,
1 h, 58%
Ph
O
O=S
N
N
Et
O
Et
3.43
Ag2O
thf, benzene,
4 Å MS, 80 °C,
2 h, 98%
Ph
O
O=S
N
N
Et
O
Et
Ag
Ag
Et
O
N
Et
O
S
N
O
Ph
3.35

3.2.a.3. Cu-Catalyzed ECA of Trialkylaluminum Reagents to Various β-Substituted Cyclopentenones

We next performed ligand screening with the three sulfonate-containing NHC complexes (**3.13**, **3.34**, **3.35**) in the Cu–NHC catalyzed ECA reactions with Et_3Al, Me_3Al, and *i*-Bu_3Al to various trisubstituted cyclopentenones (Table 3.1). Several points are noteworthy. (1) In most reactions, the new ligand bearing the sterically hindered 2,6-

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(38)"Dimethyl(methylene)ammonium Iodide," Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330–331.

(39) (a) Reference 14. (b) "Highly Site- And Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents," Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* .**2008**, *130*, 446–447.

diethylaryl group promotes the Cu-catalyzed ECA reaction to afford products with the highest selectivities (except entries 2, 4, 5, 7, and 11). However, the differences in enantioselectivities between the three catalysts are usually within 20% ee. This highlights an important attribute of having a family of ligands. The enantioselective additions can be tuned to obtain products with the highest selectivity. (2) The three nucleophiles examined all undergo highly selective enantioselective additions to a wide range of trisubstituted cyclopentenones. Although the Cu-catalyzed ECA of *i*-Bu_3Al to the enones are slower, products are obtained in >89:11 er; for example as shown in Table 3.1, entry 2, >98% conv is achieved at –78 °C within 12 h for ECA of Et_3Al to 3-butylcyclopentenone affording the product in up to 93:7 er, but the additions of *i*-Bu_3Al to the same substrate are performed at –30 °C for 24 hours for 73–>98% conv (entry 3). 3-Isobutyl-3-butylcyclopentanone is obtained in 96:4 er when the addition is catalyzed by the Cu–NHC catalyst derived from **3.35**. (3) The additions are the most efficient when $Cu(OTf)_2$ is used as the copper salt. When $CuCl_2•2H_2O$ is used, the additions are less effective; for example, as shown in entry 14, when the addition of Et_3Al to β-phenethylcyclopentenone is catalyzed by 5 mol % $CuCl_2•H_2O$ and 2.5 mol % **3.35**, the product is obtained in 41% conversion and 92:8 er. When the same conditions are used except with 5 mol % $Cu(OTf)_2$, >98% conv is achieved and the product is afforded in 96:4 er. (4) A variety of electronically and sterically diverse substrates can be used in the Cu–NHC catalyzed protocol. For example, β-alkylcyclopentenones (*n*-butyl, methyl, and phenethyl), an enone bearing an appendant olefin, a sterically hindered enone (3-phenylcyclopentenone) and an unsaturated γ-ketoester all serve as effective partners in the conjugate addition reaction. A caveat to the aforementioned statement is shown in entry 8; Cu-catalyzed ECA of *i*-Bu_3Al to the β-ester cyclopentenone predominately affords the product arising from 1,2-hydride addition to the carbonyl. This pathway likely occurs from a Meerwein-Ponndorf-Verley type process, the hydride source of which is from the *i*-Bu groups on the aluminum reagent.[40] An enone bearing an alkyne at

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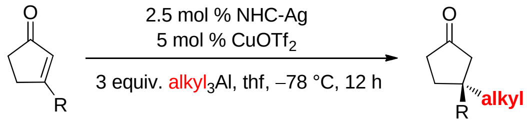
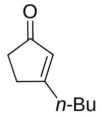
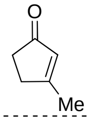
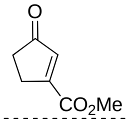
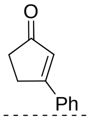
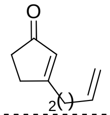
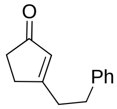
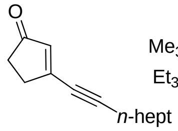
(40) For a review on Meerwein-Ponndorf-Verly Type reductions, see: “Selective Reduction of Carbonyl and Epoxy Compounds Using Aluminum, Boron and Other Metal Reagents. Comparison of Reducing

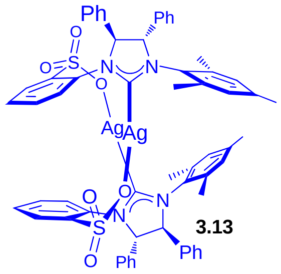
the β-position also undergoes facile ECA with Me_3Al affording the product in 95.5:4.5 er (entry 16); no products stemming from 1,6-addition into the alkyne are observed. However, when the addition is performed with Et_3Al, 14–21% of the 1,6-addition product is obtained (entry 17).

Characteristics between the Meerwein-Ponndorf-Verley Type Reduction and Metal Complex Hydrides Reduction: A Review," Cha, J. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 2162–2190.

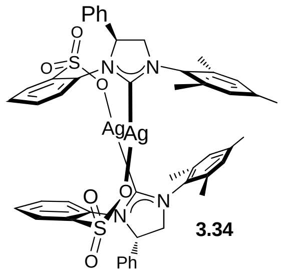
Table 3.1. Cu-Catalyzed ECA of Trialkylaluminum Reagents to β-Substituted Cyclopentenones: Ligand Screening


O
R
2.5 mol % NHC-Ag
5 mol % CuOTf$_2$
3 equiv. alkyl$_3$Al, thf, –78 °C, 12 h
O
R
alkyl

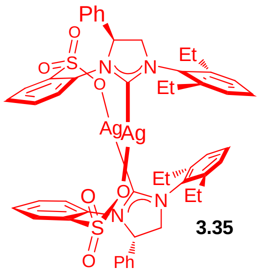
entry	substrate	alkyl$_3$Al	**3.13** conv (%)^a; er^b	**3.34** conv (%)^a; er^b	**3.35** conv (%)^a; er^b
1		Me$_3$Al	>98; 80.5:19.5	57; 90:10	**72; 94:6**
2		Et$_3$Al	>98; 88:12	**>98; 93:7**	>98; 92.5:7.5
3^e		*i*-Bu$_3$Al	>98, 89:11	73; 96:4	**78; 96:4**
4		Et$_3$Al	>98; 97.5:2.5	**>98; 98.5:1.5**	>98; 96:4
5^d		*i*-Bu$_3$Al	>98; 87:13	**>98; 94.5:5.5**	>98; 91.5:8.5
6		Me$_3$Al	>98; 50:50	>98; 58.5:41.5	**>98; 72:28**
7		Et$_3$Al	**>98; 94.5:5.5**	>98; 75.5:24.5	87; 65:35
8		*i*-Bu$_3$Al	32; nd^j	47; 87:13^d	94; nd^j
9^e		Me$_3$Al	52; 71:29	39; 81:19	**43;84.5:15.5**
10		Et$_3$Al	>98; 98:2	>98; 94.5:5.5	**>98; 98:2**
11		*i*-Bu$_3$Al	>98; 85.5:14.55	**>98; 89.5:10.5**	65; 87:13
12^c		Me$_3$Al	75; 74.5:25.5	97; 86:14	**84; 93:7**
13		Me$_3$Al	56; 71.5:28.5	72; 83.5:16.5	**88; 94.5:5.5**
14^f		Et$_3$Al	37; 97.5:12.5	41; 88.5:11.5	41; 92:8 (**98, 96:4**)^g
15^e		*i*-Bu$_3$Al	>98, 86.5:13.5	>98; 91:9	**>98; 93.5:6.5**
16		Me$_3$Al	94; 91:9	43; 93.5:6.5	**56; 95.5:4.5**
17		Et$_3$Al	>98, 62:38	>98; 75:25^h	**>98; 86:14^i**


Ph
Ph
O
O=S
O
N
N
Ag
Ag
O
O
N
N
S
O
Ph
Ph

3.13


Ph
O
O=S
N
N
O
Ag
Ag
O
O
N
N
S
O
Ph

3.34

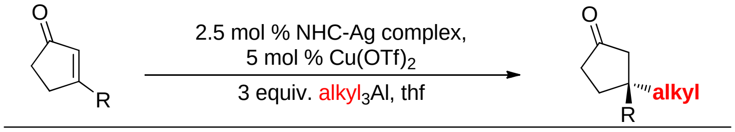

Ph
O
O=S
N
N
Et
Et
O
Ag
Ag
Et
Et
O
O
N
N
S
O
Ph

3.35

[a] Reactions performed under a N_2 atmosphere; conversions determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified mixture. [b] Enantioselectivities determined by GLC analysis. [c] Result by M. Kevin Brown; reaction was carried out for 36 h. [d] The reaction was performed at –30 °C and 5 mol % $CuCl_2$•$2H_2O$ was used. [e] The reaction was performed at –30 °C for 24 h. [f] 5 mol % $CuCl_2$•H_2O was used. [g] 5 mol % $CuOTf_2$ was used. [h] 86:14 desired:diene. [i] 79:21 desired:diene. [j] Only 1,2-reduced product is isolated (50:50 er). nd = not determined

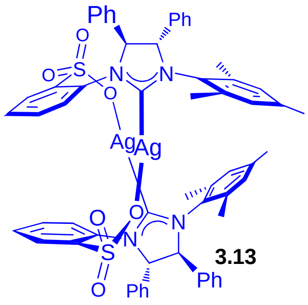
The full table with the optimized conditions, catalysts, and yields of the purified products are shown in Table 3.2. We have demonstrated that the Cu-catalyzed ECA protocol can be used to access a variety of β,β-disubstituted cyclopentanones in 34–97% yield and 72:28–98.5:1.5 er.

Table 3.2. Cu-Catalyzed ECA of Trialkylaluminum Reagents to β-Substituted Cyclopentenones: Scope of Nucleophiles and Enones[a]


O
R
2.5 mol % NHC-Ag complex,
5 mol % Cu(OTf)2
3 equiv. alkyl3Al, thf
O
alkyl
R

entry	substrate, R	alkyl$_3$Al	NHC-Ag	temp (°C)	time (h)	yield (%)[b]	er[c]
1	*n*-Bu	Me_3Al	**3.35**	–78	15	80	94:6
2	*n*-Bu	Et_3Al	**3.34**	–78	6	86	93:7
3	*n*-Bu	*i*-Bu_3Al	**3.35**	–30	24	34	96:4
4	Me	Et_3Al	**3.34**	–78	4	97	98.5:1.5
5	Me	*i*-Bu_3Al	**3.34**	–30	15	83	94.5:5.5
6	CO_2Me	Et_3Al	**3.13**	–78	6	76	94.5:5.5
7	CO_2Me	Me_3Al	**3.35**	–78	15	nd	72:28
8[d]	Ph	Me_3Al	**3.35**	–30	15	nd	84.5:15.5
9	Ph	Et_3Al	**3.35**	–78	15	87	98:2
10	CH_2CH_2Ph	Me_3Al	**3.35**	–78	24	71	94.5:5.5
11	CH_2CH_2Ph	Et_3Al	**3.35**	–78	4	97	96:4
12	CH_2CH_2Ph	*i*-Bu_3Al	**3.35**	–30	21	74	93.5:6.5
13[e]	1-nonyne	Me_3Al	**3.35**	–78	24	71	95.5:4.5

[a] Reactions performed under N_2; >98% conv in all cases except where noted. [b] Yields of isolated products. [c] Enantioselectivities determined by GLC analysis. [d] 42% conversion. [e] 5 mol % NHC and 10 mol % Cu salt is used to ensure complete conversion. nd = not determined.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N
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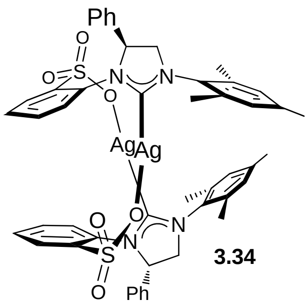
O
Ag
Ag
O
O
N
N
S
O
Ph
Ph

3.13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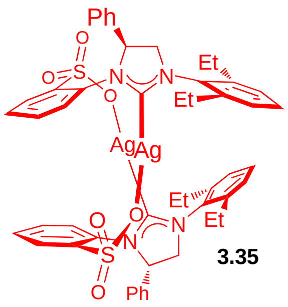
O
O=S
N
N
O
Ag
Ag
O
O
N
N
S
O
Ph

3.34


Ph
O
O=S
N
N
Et
Et
O
Ag
Ag
Et
Et
O
O
N
N
S
O
Ph

3.35

3.2.a.4. Application of the Cu–NHC Catalyzed ECA Method to the First Enantioselective Total Synthesis of Clavirolide C[41]

Based on the method developed for Cu–NHC catalyzed ECA of alkylaluminum reagents to trisubstituted cyclopentenones, we have been able to complete the first total

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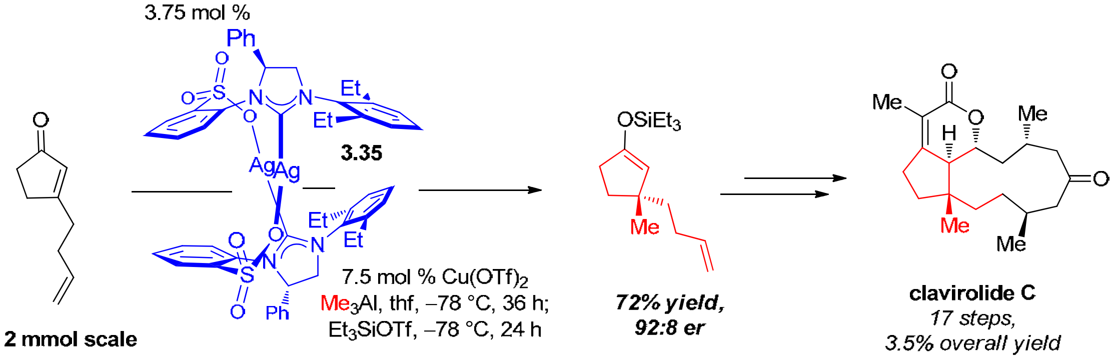
(41) "Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis," Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906.

synthesis of clavirolide C.[8a] In the first step of the sequence as shown in Scheme 3.15, ECA, promoted by the Cu–NHC catalyst prepared in situ from complex **3.35**, of Me_3Al to 3-butenylcyclopentenone followed by addition of Et_3SiOTf regioselectively affords the silyl enol ether bearing a β-all carbon quaternary stereogenic center found in the natural product. The addition requires 7.5 mol % of the active catalyst to achieve full conversion after 36 h. Strikingly, ECA of Me_3Al to 3-butylcyclopentenone (not containing a monosubstituted olefin) only requires 5 mol % of the Cu–NHC complex for 15 hours at –78 °C for full consumption of the starting material. We surmise that the difference in reactivities between the two substrates arises from the olefin in 3-butenylcyclopentenone chelating to a Cu complex, thus retarding the rate of the reaction. Completion of the synthesis requires ten additional steps with a longest linear sequence of 17 steps.

Scheme 3.15. Cu-Catalyzed ECA of Me_3Al to 3-Butenylcyclopentenone: Application in the First Total Synthesis of Clavirolide C

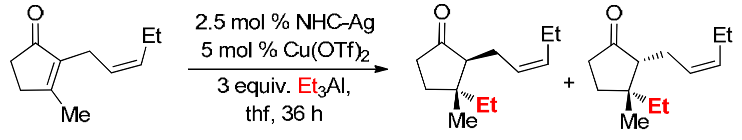


3.2.a.5. Cu-Catalyzed ECA of Et_3Al to a Tetrasubstituted Cyclopentenone

To test how effective our catalyst system is with even less reactive substrates, we investigated the Cu-catalyzed enantioselective addition protocol on a tetrasubstituted enone bearing no activating groups (such as an ester). There has been no accounts illustrating this type of addition to date; in fact, the only account that includes a non-activated tetrasubstituted enone reports that no conversion is observed [Cu-catalyzed ECA of Et_3Al, promoted by a diphosphite ligand (**3.9**, cf. Scheme 3.3), to jasmone (cf.

Table 3.3) at –30 °C].[10b] As shown in Table 3.3, Cu–NHC catalyzed ECA of Et_3Al to jasmone at –55 °C affords **3.44** and **3.45** in 40% conv and in 67:33 and 60:40 er, respectively (1:1 dr, entry 2). When the addition is performed at –78 °C, <2% conv is observed (entry 1). A temperature screen revealed that 72% conv can be reached at 22 °C after 36 h; however, the enantioselectivities of the two diastereomers are only moderate (52.5:47.5 er and 75:25 er, entry 5). When the ECA reaction is promoted by the Cu–NHC derived from **3.34**, the conjugate addition adducts are afforded with an increase in enantioselectivity (81.5:18.5 er and 83:17 er) but only in 19% conv. Further optimization will be needed to improve the efficiency and to increase the enantioselectivity; however, the initial results are promising.

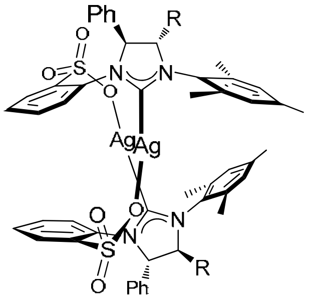
Table 3.3. Cu-Catalyzed ECA of Et_3Al to Jasmone: Initial Observations[a]



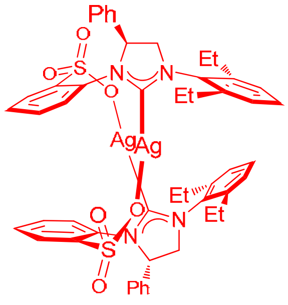
jasmone **3.44** **3.45**

entry	NHC-Ag	temp (° C)	conv (%)[b]	er (**3.44**)[c]	er (**3.45**)[c]	dr[d]
1	**3.13**	–78	<2	nd	nd	nd
2	**3.13**	–50	40	67:33	60:40	1:1
3	**3.13**	–30	55	61:39	60:40	1.2:1
4	**3.13**	4	62	58:42	59.5:40.5	1.3:1
5	**3.13**	22	72	52.5:47.5	75:25	1:3.3
6	**3.34**	–50	19	81.5:18.5	83:17	1:1
7	**3.35**	–50	66	69:31	71:29	1.1:1

[a] Reactions performed under N_2. [b] Conversions determined by analysis of the 400 MHz ^1H NMR spectra of the unpurified mixture. [c] Enantioselectivities determined by GLC analysis; enantiomeric ratio for both diastereomers shown. [d] Diastereomeric ratio determined by GLC analysis; it is unclear if the diastereomers isomerize during the thermal GLC run (80 °C, 240 min). The relative configuration of the diastereomers has not been rigorously proven. nd = not determined.



R = Ph: **3.13**
R = H: **3.34**

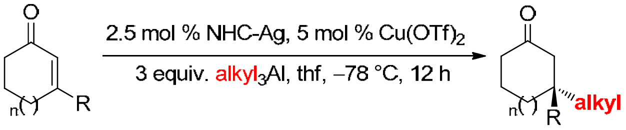


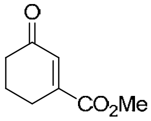
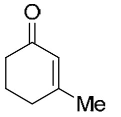
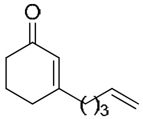
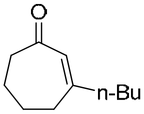
3.35

3.2.b Cu-Catalyzed ECA of Trialkylaluminum Reagents to β-Substituted Cyclohexenones and Cycloheptenones

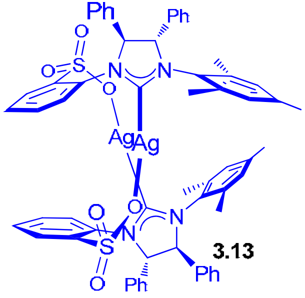
Since the Cu–NHC catalyzed protocol has proven to be highly efficient and selective for additions to trisubstituted cyclopentenones, we next, investigated how the system performs with larger cyclic enones. As shown in Table 3.4, various enones with Et_3Al, Me_3Al, and *i*-Bu_3Al were tested with the three new sulfonate-containing Cu–NHC complexes. As with the cyclopentenones discussed above, the des-phenyl version of the sulfonate-containing catalyst bearing a sterically hindered 2,6-diethylaryl group (in situ prepared from **3.35**) promotes the majority of the additions with the highest enantioselectivity (72:28–95:5 er vs 58.5:41.5–93:7 er). In some cases, the ECAs proceed faster and with higher selectivities at elevated temperature. For example, in entry 8, when the Cu-catalyzed ECA addition of Et_3Al to 3-butylcycloheptenone is promoted by the catalyst derived from **3.35**, >98% conv is achieved within 15 minutes to afford the desired product in 94.5:5.5 er. Whereas, when the addition is performed at –78 °C, twelve hours is required and the product is obtained in 92.5:7.5 er. This trend is also seen for Et_3Al addition to 3-methylcyclohexenone. When the addition is carried out at –78 °C, the product is obtained in 77.5:22.5 er (entry 4); however, when the ECA is performed at 4 °C, 3-ethyl-3-methylcyclohexanone is delivered in 81:19 er.

Table 3.4. Cu-Catalyzed ECA of Trialkylaluminum Reagents to Trisubstituted Six- and Seven-Membered Ring Enones


2.5 mol % NHC-Ag, 5 mol % Cu(OTf)$_2$
3 equiv. alkyl$_3$Al, thf, –78 °C, 12 h
R
n
alkyl

entry	substrate	alkyl$_3$Al	**3.13** conv (%)[a]; er[b]	**3.34** conv (%)[a]; er[b]	**3.35** conv (%)[a]; er[b]
1	 CO$_2$Me	Me$_3$Al	>98; 66:32	>98; 68:32	**>98; 72:28**
2		Et$_3$Al	**>98; 91.5:8.5**	83; 77:23	>98; 73:27
3[c]		*i*-Bu$_3$Al	>98; 64:36	>98; 58.5:41.5	nd
4[d]	 Me	Et$_3$Al	**>98; 77.5:22.5**	>98; 72.5:27.5	>98; 74:26
5		Me$_3$Al	>98; 88:12	>98; 91:9	**>98; 95:5**
6		Et$_3$Al	42; 65:35	35; 67:33	**55; 75:25**
7	 n-Bu	Me$_3$Al	>98; 85:15	>98; 90.5:9.5	**>98; 92.5:7.5**
8[e]		Et$_3$Al	>98; 89.5:10.5	>98; 93:7	**>98; 94.5:5.5**

[a] Reactions performed under a N_2 atmosphere; conversions determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified mixture. [b] Enantioselectivities determined by GLC analysis. [c] The reactions were performed at 4 °C for 15 min. [d] Reaction time = 3.5 h. [e] Reactions performed at 22 °C. nd = not determined


Ph
Ph
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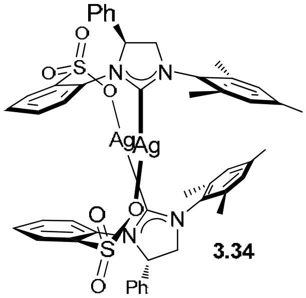
O=S
N
N
O
Ag
Ag
O
N
N
O
S
O
Ph
Ph

3.13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N
N
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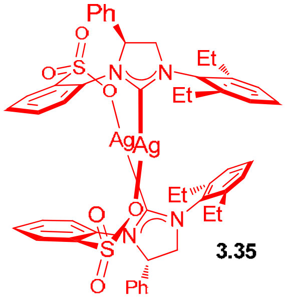
Ag
Ag
O
N
N
O
S
O
Ph

3.34

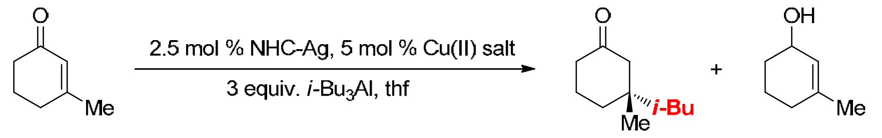

Ph
O
O=S
N
N
Et
Et
O
Ag
Ag
Et
Et
O
N
N
O
S
O
Ph

3.35

Cu-catalyzed ECA of *i*-Bu$_3$Al to 3-methylcyclohexenone, promoted by the Cu–NHC complex from **3.13** and Cu(OTf)$_2$ at –78 °C, affords a mixture of the desired product **3.46** and reduction product **3.47** (73:27, Table 3.5, entry 1). The latter product arises from a Meerwein-Ponndorf-Verley type reduction involving *i*-Bu$_3$Al and is isolated as a racemate.[40] Intriguingly, when the Cu–NHC complex is generated from

$CuCl_2$•$2H_2O$ [vs. $Cu(OTf)_2$], more of the desired product is formed (90:10 vs. 73:27 **3.46**:**3.47**), however, with a cost in efficiency (25% conv. vs. 47%, entries 2 and 1). Further examination revealed that **3.46** is formed in higher enantioselectivity when the reaction is conducted at elevated temperatures [42:58 er at –78 °C (entry 2) vs. 88.5:11.5 er at 22 °C (entry 9)]. Enantioselective conjugate addition catalyzed by the Cu–NHC catalyst derived from **3.35** delivers **3.46** with the highest enantioselectivity and with no formation of **3.47** (95:5 er, entry 11).

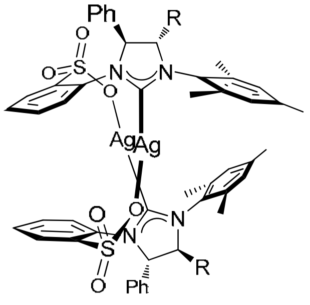
Table 3.5. Cu-Catalyzed ECA of *i*-Bu_3Al to 3-Methylcyclohexenone



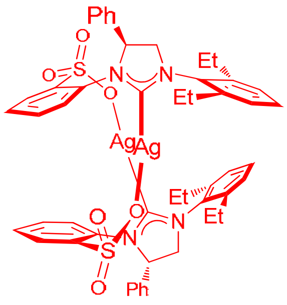
3.46 **3.47**

entry	temp (°C)	time (h)	NHC-Ag	Cu source	conv (%)^b	**3.46**:**3.47**^{b}	er (**3.46**)^c
1	–78	12	**3.13**	$CuOTf_2$	47	73:27	61.5:38.5
2	–78	12	**3.13**	$CuCl_2$•$2H_2O$	25	90:10	42:58
3	–60	12	**3.13**	$CuOTf_2$	>98	93:7	81.5:18.5
4	–30	12	**3.13**	$CuOTf_2$	>98	85:15	86.5:13.5
5	–30	12	**3.13**	$CuCl_2$•$2H_2O$	>98	>98:<2	85:15
6	4	0.25	**3.13**	$CuOTf_2$	>98	78:22	92:8
7	4	0.25	**3.13**	$CuCl_2$•$2H_2O$	>98	>98:<2	89:11
8	22	0.25	**3.13**	$CuOTf_2$	>98	87:13	93.5:6.5
9	22	0.08	**3.13**	$CuCl_2$•$2H_2O$	81	92:8	88.5:11.5
10	22	0.08	**3.34**	$CuCl_2$•$2H_2O$	82	94:6	95:5
11	*22*	0.25	***3.35***	*$CuCl_2$•$2H_2O$*	*>98*	*>98:<2*	*95:5*

^{a} Reactions performed under N_2. ^{b} Conversions and product ratios determined by analysis of the 400 MHz ^1H NMR spectra of the unpurified mixture. ^{c} Enantioselectivities determined by GLC analysis.



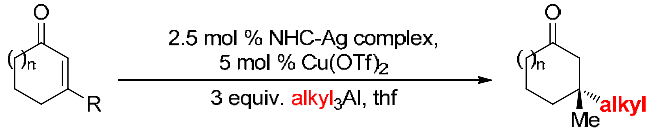
R = Ph: **3.13**
R = H: **3.34**



3.35

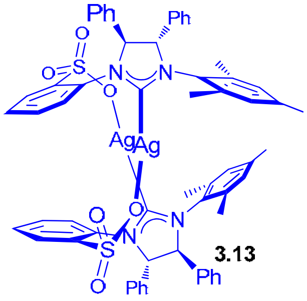
The optimized conditions for the Cu–NHC catalyzed ECAs of alkylaluminum reagents to six- and seven-membered ring enones are shown in Table 3.6. Additions to trisubstituted cyclohex- and cycloheptenones are not as selective as additions to the trisubstituted cyclopentenones but still afford products with appreciable levels of selectivities (81:19–95:5 er, 51–91% yield, Table 3.6 vs. 72:28–98.5:1.5 er, Table 3.2 for additions to β-substituted cyclopentenones). It is unknown as of yet why some additions afford products with higher enantioselectivities at higher temperatures (i.e., entries 1, 2 and 6), while others require low temperatures for optimal selectivity (entries 3–5).

Table 3.6. Cu-Catalyzed ECA of Trialkylaluminum Reagents to Six- and Seven-Membered Ring Enones: Optimized Conditions[a]

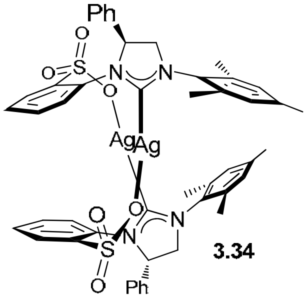


entry	substrate, R	n	alkyl$_3$Al	NHC-Ag	temp (°C)	time (h)	yield (%)[b]	er[c]
1	Me	1	Et_3Al	**3.13**	22	0.25	51	81:19
2	Me	1	*i*-Bu_3Al	**3.34**	22	0.25	89	95:5
3	CO_2Me	1	Et_3Al	**3.13**	–78	15	91	91.5:8.5
4	4-hexenyl	1	Me_3Al	**3.35**	–78	12	85	95:5
5	*n*-Bu	2	Me_3Al	**3.35**	–78	12	90	92.5:7.5
6	*n*-Bu	2	Et_3Al	**3.35**	22	0.25	87	94.5:5.5

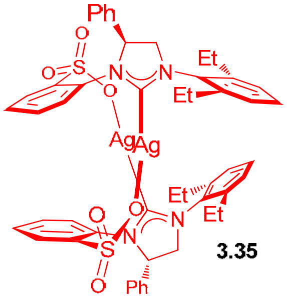
[a] Reactions performed under N_2; >98% conv in all cases. [b] Yields of isolated products. [c] Enantioselectivities determined by GLC analysis.



3.13



3.34

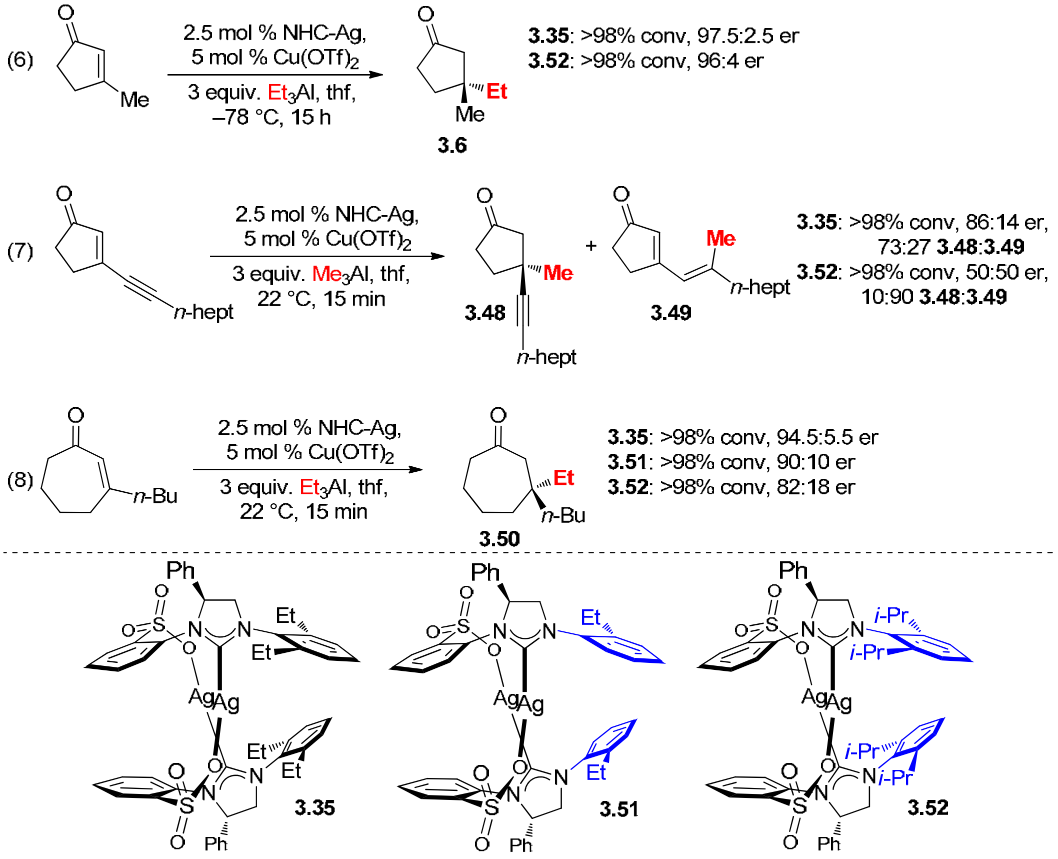


3.35

3.2.c Investigation of Sterically Modified NHC Complexes

Concurrently with determining the substrate and nucleophile scope for the Cu-catalyzed ECA of trialkylaluminum reagents to five-, six-, and seven-membered ring enones, we prepared sterically modified NHC complexes (**3.51** and **3.52**) to determine their catalytic activity and enantiodiscrimination for three test cases. One ligand structure contains a mono-ethyl aryl unit (**3.51**) and the other contains a di-*iso*-propyl aryl moiety (**3.52**) versus a 2,6-diethyl phenyl group found in the optimal complex (**3.35**, Scheme 3.16). As shown in eq 6, the catalyst derived from **3.52** containing the sterically bulky *i*-Pr groups promotes the ECA of Et_3Al to 3-methylcyclopentenone efficiently and with similar levels of selectivity as the diethyl aryl containing catalyst (96:4 vs 97.5:2.5 er). However, as illustrated in eq 7, when the Cu–NHC catalyst prepared from **3.52** is used to promote the addition of Me_3Al to the β-alkynyl cyclopentenone substrate, significant amounts of diene **3.49** is formed (90% of the reaction mixture attained from 1,6-addition to the alkyne unit and protonation of the enolate at the γ-position). Whereas, under the same conditions, the Cu–NHC catalyst from **3.35** promotes the addition and the desired 1,4-addition product is formed in 73% of the reaction mixture (27% of **3.49**) in 86:14 er. Moreover, both Cu–NHC ligands prepared from **3.51** and **3.52** promote the enantioselective addition of Et_3Al to 3-butylcycloheptenone efficiently (>98% conv after 15 min at 22 °C) but provide the conjugate addition product in lower enantioselectivities than with the diethylaryl containing NHC ligand (82:18–90:10 vs. 94.5:5.5 er, eq. 8).

Scheme 3.16. Sterically Modified NHC ligands for Cu-Catalyzed ECA


(6)
O
Me
2.5 mol % NHC-Ag,
5 mol % Cu(OTf)2
3 equiv. Et3Al, thf,
–78 °C, 15 h
O
Et
Me
3.6
3.35: >98% conv, 97.5:2.5 er
3.52: >98% conv, 96:4 er
(7)
O
n-hept
2.5 mol % NHC-Ag,
5 mol % Cu(OTf)2
3 equiv. Me3Al, thf,
22 °C, 15 min
O
Me
3.48
n-hept
+
O
Me
n-hept
3.49
3.35: >98% conv, 86:14 er,
73:27 3.48:3.49
3.52: >98% conv, 50:50 er,
10:90 3.48:3.49
(8)
O
n-Bu
2.5 mol % NHC-Ag,
5 mol % Cu(OTf)2
3 equiv. Et3Al, thf,
22 °C, 15 min
O
Et
n-Bu
3.50
3.35: >98% conv, 94.5:5.5 er
3.51: >98% conv, 90:10 er
3.52: >98% conv, 82:18 er
Ph
Et
Et
Ag
Ag
Et
Et
Ph
3.35
Ph
Et
Ag
Ag
Et
Ph
3.51
Ph
i-Pr
i-Pr
Ag
Ag
i-Pr
i-Pr
Ph
3.52

3.2.d Cu-Catalyzed ECA of Alkylaluminum Reagents to Trisubstituted Unsaturated Heterocycles[42]

Enantioselective conjugate additions to unsaturated lactones or chromones have predominately focused on the generation of tertiary stereogenic centers.[43] There is only

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(42) These studies were done in collaboration with Mikiko Akiyama.

(43) For Cu-catalyzed ECA protocols of additions to lactones, see: (a) "Catalytic Enantioselective Conjugate Addition of Grignard Reagents to Cyclic α,β-Unsaturated Carbonyl Compounds," Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843–3854. (b) "Conjugate Additon of Diethylzinc to α,β-Unsaturated Lactones Catalyzed by Copper–Phosphite Complexes," Yan, M.; Zhou, Z.-Y.; Chan, A. S. C. *Chem. Commun.* **2000**, 115–116. (c) "Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to α,β-Unsaturated Carbonyl Compounds Using Diphosphonites as Chiral Ligands," Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189–1191. (d) "Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Cyclic Enones," Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834–5838. (e) "Highly Enantioselective Copper-Catalyzed 1,4-Conjugate Addition of Diethylzinc to Cyclic Enones and α,β-

one study thus far that describes a Rh-catalyzed ECA with phenylborate to a trisubstituted lactone that generates an all-carbon quaternary stereogenic centers.[16,44] Studies involving ECA of disubstituted unsaturated lactones as substrates, in many cases, provided the desired products in low to moderate yields. It is likely that the metal enolate, formed from the conjugate addition, is unstable, decomposing to ketene or undergoing subsequent Michael additions to another molecule of starting lactone. This can be circumvented by performing the reaction in a solvent mixture with water in the case of Rh-catalyzed additions (protonating the Rh– or B–enolate) or trapping the reactive enolate in situ (with, for example, an aldehyde).

Continuing our efforts of examining substrates that are underrepresented in ECA reactions, we set out to investigate trisubstituted lactones in our Cu-catalyzed ECA reactions. As illustrated in Table 3.7, phenoxy-based NHC–Cu catalyst did not promote

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Unsaturated Lactones," Liang, L.; Yan, M.; Li, Y.-M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2575–2578. (f) "New Bidentate Alkoxy-NHC Ligands for Enantioselective Copper-Catalysed Conjugate Addition," Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921–924. (g) "Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes," Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310. For Rh-catalyzed ECAs, see: (h) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboron Reagents to α,β-Unsaturated Esters," Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047–4056. (i) "BINOL-Based Diphosphonites as Ligands in the Asymmetric Rh-Catalyzed Conjugate Addition of Arylboronic Acids," Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083–4085. (j) "Chiral [2.2.2] Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors," Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873–3876. (k) "Highly Enantioselective Rhodium-Catalyzed Conjugate Addition of Arylboronic Acids of Enones at Room Temperature," Martina, S. L. X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L. *Tetrahedron Lett.* **2005**, *46*, 7159–7163. (l) "Preparation of C_2-Symmetric Bicyclo[2.2.2]octa-2,5-diene Ligands and Their Use for Rhodium-Catalylzed Asymmetric 1,4-Addition of Arylboronic Acids," Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503–2508. (m) "A C_2-Symmetric Chiral Bis-Sulfoxide Ligands in a Rhodium-Catalyzed Reaction: Asymmetric 1,4-Addition of Sodium Tetraarylborates to Chromenones," Chen, J.; Chen, J.; Lang, F.; Zhang, X.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552–4553. For a Pd-catalyzed ECA protocol, see: (n) "Palladium-Catalyzed Enantioselective Conjugate Addition of Arylboronic Acids," Gini, F.; Hessen, B.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309–5312. (o) "Enantioselective Palladium-Catalysed Conjugate Addition of Arylsiloxanes," Gini, F.; Hessen, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 710–712.

(44) For a study regarding ECA of silyl-based nucleophiles to a trisubstituted lactone, see: (a) "Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes," Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900. For a Rh-catalyzed ECA procedure of aryl additions to unsaturated maleimides (generating products containing all-carbon quaternary stereogenic centers, see: (b) Reference 15.

the conjugate addition of Et_3Al to lactone **3.53** (entry 1).[45] In contrast, sulfonate-containing NHC–Cu catalyst, derived from **3.13**, promotes the ECA delivering the desired product **3.54** in 81% yield and 82.5:17.5 er. In contrast to previous studies involving additions to disubstituted lactones,[43] product **3.54** is afforded efficiently without the need to protonate (or further react) the metal enolate. The effective formation of the product might be due to the steric bulk of the metal enolate β to the all carbon quaternary stereogenic center, which could prevent the enolate from undergoing adventitious Michael additions. Alternatively, the Al–enolate may not be nucleophilic enough to proceed in further reactions. Ligand screening to optimize the selectivity of the reaction revealed that the des-phenyl catalyst, prepared in situ from **3.34**, promotes the addition delivering the product in 96% yield and 88.5:11.5 er (entry 3). Additionally, the sulfonate-containing NHC–Cu complex prepared from **3.35** was the most effective catalyst for the ECA; lactone **3.54** is prepared in 93.5:6.5 er and in 94% yield when the reaction is performed at –50 °C (entry 7). The more hindered 2,6-diisopropyl variant of the sulfonate NHC (**3.52**) only provides **3.54** in 77.5:22.5 er (entry 4).

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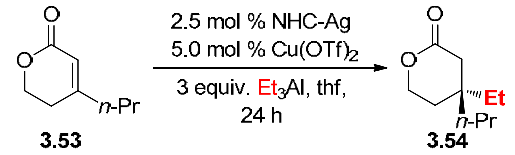
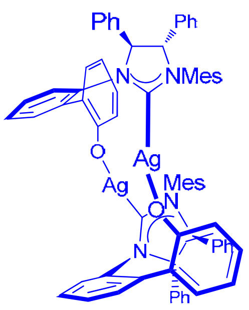
(45) Initial investigations were performed with the more Lewis-acidic Al-based nucleophiles; in all cases and catalysts screened, Cu-catalyzed ECA of alkylzinc reagents to lactones proceeds to <2% conv.

Table 3.7. Cu–NHC Catalyzed ECA of Et_3Al to Trisubstituted Unsaturated Lactone **3.53**[a]

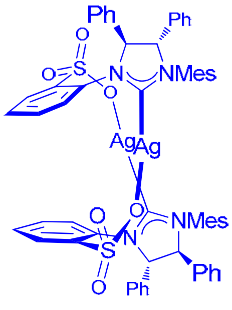

2.5 mol % NHC-Ag
5.0 mol % Cu(OTf)2
3 equiv. Et3Al, thf,
24 h
n-Pr
Et
n-Pr
3.53
3.54

entry	NHC-Ag	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]
1	**3.33**	–15	<2	nd	nd
2	**3.13**	–15	>98	81	82.5:17.5
3	**3.34**	–15	>98	96	88.5:11.5
4	**3.52**	–15	>98	88	77.5:22.5
5	**3.35**	–15	>98	88	90:10
6	**3.35**	–30	>98	93	91:9
7	**3.35**	–50	>98	94	93.5:6.5
8	**3.35**	–78	52	nd	95.5:4.5

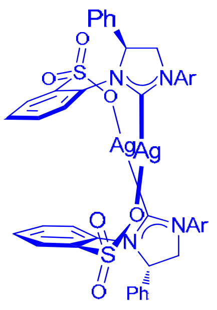
[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Yield of isolated purified products. [d] Determined by GLC analysis. nd = not determined


Ph
Ph
N
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph

3.33


Ph
Ph
O
O=S
N
NMes
O
Ag
Ag
O
O
NMes
N
S
O
Ph
Ph

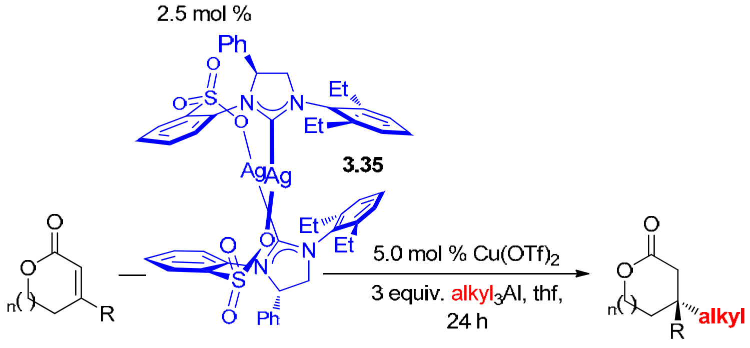
3.13


Ph
O
O=S
N
NAr
O
Ag
Ag
O
O
NAr
N
S
O
Ph

3.34 = Mes = 2,4,6-Me(C_6H_2)
3.35 = 2,6-Et(C_6H_3)
3.52 = 2,6-*i*-Pr(C_6H_3)

Enantioselective addition of Me_3Al to lactone **3.53** is selective as well; as shown in Table 3.8, the desired product can be obtained in 68% yield and 88.5:11.5 er (entry 2). Additions with Me_3Al are more sluggish (76–82% conv after 24 h) and need to be performed at –30 °C, as compared to reactions with Et_3Al (>98% conv, –50 °C, 24 h). Triisobutylaluminum also participates in the Cu-catalyzed ECA to afford the product in 88.5:11.5 er, however, the addition is slow (66% conv after 24 h at 22 °C, entry 3). Other substrates including a β-methyl substituted lactone (entries 4–5) as well as a more sterically-encumbered β-phenethyl unsaturated lactone are competent substrates (49–98% yield, 89:11–95.5:4.5 er). Five-membered ring unsaturated lactones were unreactive under the conditions explored in Table 3.8 (entries 8–9), even at elevated temperatures. Seven-membered ring unsaturated lactones also suffers from low reactivity. As shown in entry 10, Cu-catalyzed ECA of Et_3Al to the trisubstituted unsaturated ε-caprolactone only proceeds to 22% conv (11% yield) after 24 h at 22 °C. It is clear that more active catalysts must be developed to address the less reactive variants of unsaturated lactones.

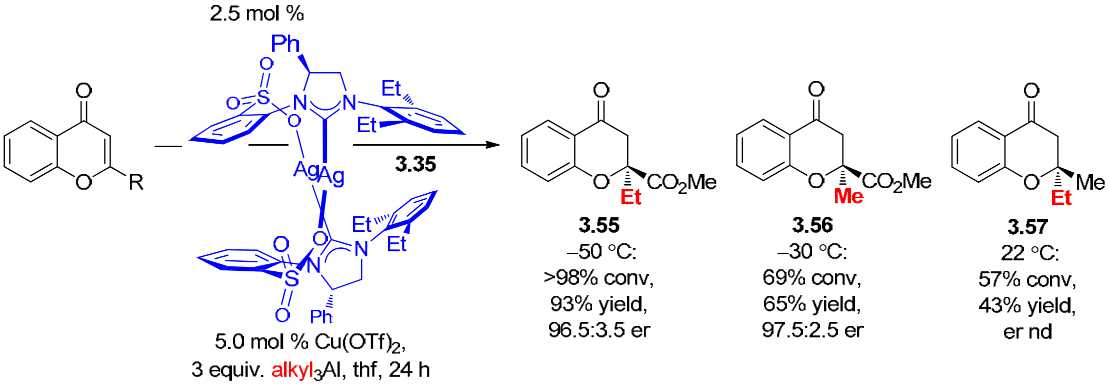
Table 3.8. Cu–NHC Catalyzed ECA of Trialkylaluminum Reagents to Trisubstituted Unsaturated Lactones[a]



entry	substrate (R)	n	(alkyl)$_3$Al	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]
1	*n*-Pr	1	Et_3Al	–50	>98	94	93.5:6.5
2	*n*-Pr	1	Me_3Al	–30	76	68	88.5:11.5
3	*n*-Pr	1	*i*-Bu_3Al	22	66	32	88.5:11.5
4	Me	1	Et_3Al	–50	>98	98	95.5:4.5
5	Me	1	*i*-Bu_3Al	–30	85	49	93:7
6	CH_2CH_2Ph	1	Et_3Al	–50	>98	86	93.5:6.5
7	CH_2CH_2Ph	1	Me_3Al	–30	82	55	89:11
8	*n*-Bu	0	Et_3Al	–30	<2	nd	nd
9	*n*-Bu	0	Me_3Al	22	<2	nd	nd
10	Me	2	Et_3Al	22	22	11	nd

[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Yield of isolated purified products. [d] Determined by GLC analysis. nd = not determined

The Cu-catalyzed ECA protocol is not limited to lactones. As shown in equation 8, a β-ester substituted chromone undergoes efficient alkylations with Et_3Al and Me_3Al, promoted by the sulfonate-containing NHC–Cu complex derived from **3.35**, to provide **3.55** and **3.56** in 65–93% yield and up to 97.5:2.5 er. However, when the Me-substituted chromone is used (vs. an ester), efficiency drops significantly; after 24 h at 22 °C only 57% conversion to **3.57** is observed (43% yield). This represents the first enantioselective conjugate additions to lactones and chromones to prepare products containing quaternary carbon stereogenic centers.



2.5 mol %
3.35
5.0 mol % Cu(OTf)$_2$,
3 equiv. alkyl$_3$Al, thf, 24 h

3.55
–50 °C:
>98% conv,
93% yield,
96.5:3.5 er

3.56
–30 °C:
69% conv,
65% yield,
97.5:2.5 er

3.57
22 °C:
57% conv,
43% yield,
er nd

(9)

Continuing our investigations of conjugate addition of heterocycles, we, next, studied the enantioselective alkylation of Et$_3$Al to a trisubstituted α,β-unsaturated γ-lactam (**3.58**, Table 3.9). Under a range of temperatures (–30–22 °C), the ECA of Et$_3$Al to lactam **3.58**, catalyzed by a sulfonate containing NHC–Cu complex, delivers no desired product **3.60** (entries 1–3, Table 3.9). A mixture of unidentifiable products is formed with no starting material (**3.58**) remaining. Changing to a more robust, albeit, less active protecting group (pmp, *p*-methoxyphenyl) on the lactam only leads to recoverable starting material after the Cu-catalyzed ECA of Et$_3$Al (entries 4–8). Both the phenoxy-containing Cu–NHC complex (formed from **3.33**) and a monodentate Cu–NHC complex (from **3.62**)[46] are also ineffective in catalyzing the enantioselective alkylation (entries 7–8).

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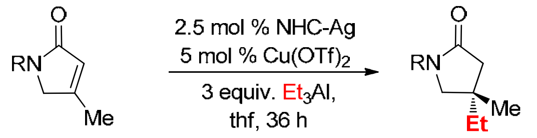
(46) *C*$_1$-symmetric monodentate NHCs have emerged as powerful ligands for a variety of Cu-catalyzed protocols in the Hoveyda group. For several examples, see: (a) "Monodentate Non-*C*$_2$-Symmetric Chiral *N*-Heterocyclic Carbene Complexes for Enantioselective Synthesis. Cu-Catalyzed Conjugate Additions of Aryl- and Alkenylsilylfluorides to Cyclic Enones," Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462. (b) "Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes," Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900. (c) "Enantioselective Synthesis of Boron-Substituted Quaternary Carbons by NHC–Cu-Catalyzed Boronate Conjugate Additions to Unsaturated Carboxylic Esters, Ketones, or Thioesters," O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (d) "Enantioselective Synthesis of Homoallylic Amines through Reactions of (Pinacolato)allylborons with Aryl-, Heteroaryl-, Alkyl- or Alkene-Substituted Aldimines Catalyzed by Chiral *C*$_1$-Symmetric NHC–Cu Complexes," Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, in press.

Table 3.9. Cu-Catalyzed ECA of Et_3Al to Trisubstituted Unsaturated Lactams[a]

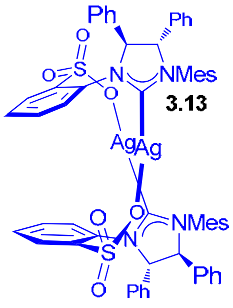

RN
O
Me
2.5 mol % NHC-Ag
5 mol % $Cu(OTf)_2$
3 equiv. Et_3Al,
thf, 36 h
RN
O
Me
Et

R = boc: **3.58**
R = pmp: **3.59**

R = boc: **3.60**
R = pmp: **3.61**

entry	R	NHC-Ag	temp (° C)	conv (%)[b]
1	boc	**3.13**	–30	<10[c]
2	boc	**3.13**	4	<10[c]
3	boc	**3.13**	22	<10[c]
4	pmp	**3.13**	–30	<10
5	pmp	**3.13**	4	<10
6	pmp	**3.13**	22	<10
7	pmp	**3.33**	22	<10
8[d]	pmp	**3.62**	22	<10

[a] Reactions performed under N_2. [b] Conversions determined by analysis of the 400 MHz ^1H NMR spectra of the unpurified mixture. [c] Complex mixture of unidentified prodcuts; <2% of starting material remaining. [d] 5 mol % of NHC-Ag. boc = *t*-butyl carbonyl. pmp = *p*-methoxyphenyl.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Ph
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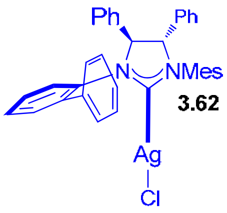
N
NMes
O
Ag
Ag
O
O
S
O
N
NMes
Ph
Ph

3.13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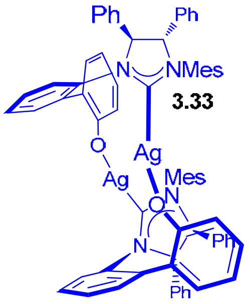
Ph
N
NMes
Ag
Cl

3.62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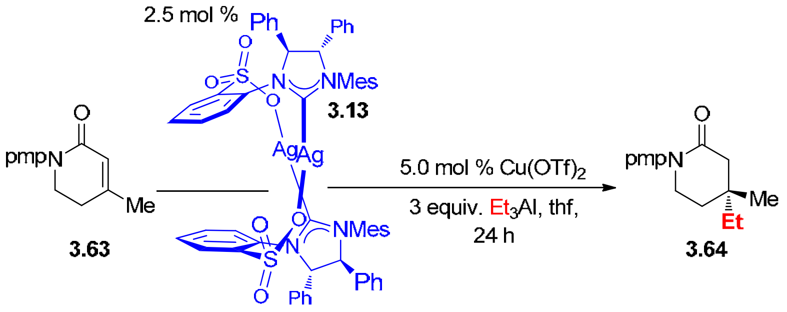
Ph
N
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph

3.33

Cu-catalyzed ECA of Et_3Al to a six-membered trisubstituted α,β-unsaturated lactam also proceeds sluggishly (entries 1–3, <12% conv). When the addition is performed at 4 °C, the alkylation proceeds to 50% conv affording **3.64** in a moderate 67.5:32.5 er. Clearly, a more active catalyst must be developed to efficiently catalyze the enantioselective additions to trisubstituted unsaturated heterocycles.

Table 3.10. Cu–NHC Catalyzed ECA of Et_3Al to Lactam **3.63**[a]



entry	temp (°C)	conv (%)[b]	er[c]
1	–50	<2	nd
2	–30	10	nd
3	–15	11	nd
4	4	50	67.5:32.5

[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Determined by GLC analysis. nd = not determined

3.2.e Cu-Catalyzed ECA of Alkylaluminum Reagents to Trisubstituted Acyclic Enones[47]

There are no reports thus far describing ECA of alkyl nucleophiles to acyclic trisubstituted enones.[48] To address this limitation, we have recently begun to study how the ligands developed and synthesized in our laboratories fare in Cu-catalyzed ECA of trialkylaluminum reagents to enone **3.65** (Table 3.11). When the enantioselective alkylation is promoted by the phenoxy-containing bidentate Cu–NHC complex derived from **3.33**, product **3.66** is afforded in 79% yield and in 83.5:16.5 er (entry 1). Similarly, the sulfonate-containing Cu–NHC catalysts also promote the ECA efficiently (>98% conv, 60–80% yield) and afford **3.66** in moderate levels of selectivity (77:23–82:18 er, entries (2–4). Lowering the temperature to –78 °C allows the formation of **3.66** with an

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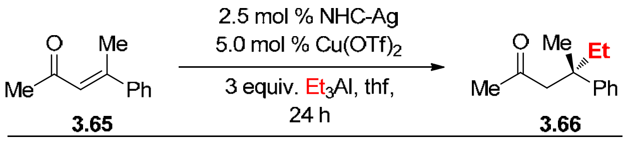
(47) This was done in collaboration with Matthew Villaume.

(48) There are three reports disclosing aryl nucleophiles to acyclic trisubstituted enones (with small substrate and nucleophile scope) and one describing the enantioselective addition of cyanide to acyclic enones. See, References 13b, 18, 19, and 20.

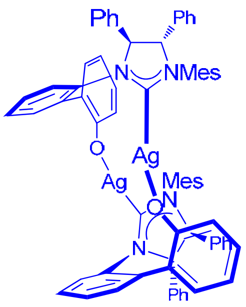
increase in enantioselectivity (90:10 er) without diminution in efficiency (>98% conv, entry 6).

Table 3.11. Cu-Catalyzed ECA of Et_3Al to Acyclic Enone **3.65**[a]


O
Me
Me
Ph
3.65
2.5 mol % NHC-Ag
5.0 mol % $Cu(OTf)_2$
3 equiv. Et_3Al, thf,
24 h
O
Me
Et
Me
Ph
3.66

entry	NHC-Ag	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]
1	**3.33**	–30	>98	79	83.5:16.5
2	**3.13**	–30	>98	80	77.5:22.5
3	**3.34**	–30	>98	62	82:18
4	**3.35**	–30	>98	60	77:23
5	**3.35**	–50	>98	nd	78:22
6	**3.35**	–78	>98	nd	90:10

[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Yield of isolated purified products. [d] Determined by GLC analysis. nd = not determined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Ph
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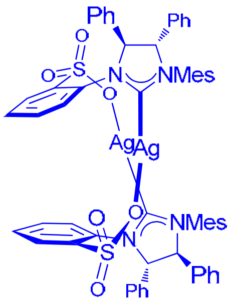
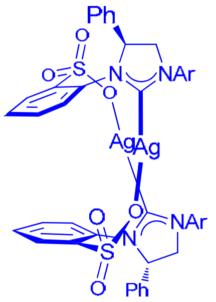
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph

3.33


Ph
Ph
O
O=S
N
NMes
O
AgAg
O
O
NMes
S
N
O
Ph
Ph

3.13


Ph
O
O=S
N
NAr
O
AgAg
O
O
NAr
S
N
O
Ph

3.34 = Mes = 2,4,6-Me(C_6H_2)
3.35 = 2,6-Et(C_6H_3)

Investigations are ongoing to determine the most effective catalysts (or catalysts) for the enantioselective addition to acyclic trisubstituted enones and initial results are promising. We will continue to pursue the aforementioned reaction scope with Et_3Al, Me_3Al and *i*-Bu_3Al. Concurrently, we are also interested in nucleophiles that are more practical, user-friendly, and could be extended to other transferable groups (than just Me, Et, and *i*-Bu). For example, alkylboranes are easy to prepare (hydroboration of an alkene) and easier to handle (not pyrophoric).[49] Efforts of extending our protocols to these areas are ongoing.

3.3. Cu-Catalyzed ECA of Arylmetal Reagents to Trisubstituted Enones[22]

Having developed an efficient protocol for enantioselective conjugate additions of alkylaluminum reagents to trisubstituted enones, we next turned our attention to enantioselective additions of arylaluminum-based nucleophiles. We decided not to pursue triarylaluminum reagents[50,51] as nucleophiles for two reasons. (1) Triarylaluminum reagents are not atom economical since two aryl groups are not transferred and wasted. This point is also valid when describing trialkylaluminum reagents, however, loss of a methyl group is not as acute as losing an aryl moiety. (2) Triphenylaluminum is the only arylaluminum reagent that is commercially available and the cost is prohibitively expensive ($43,000/mol, Strem).

To solve this problem, we drew inspiration from reports that prepare mixed dialkylarylaluminum reagents.[52] It has been established that sp^2-hybridized carbon

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(49) For a recent example of alkylboranes as nucleophiles in a Cu-catalyzed allylic substitution reaction, see: "Copper-Catalyzed γ-Selective Allyl–Alkyl Coupling between Allylic Phosphates and Alkylboranes," Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897.

(50) For initial accounts of the preparation and reactions with Ph_3Al, see: (a) "Organo-Aluminum Compounds. I. Preparation and Properties of Some Phenylaluminum Compounds," Mole, T. *Aust. J. Chem.* **1963**, *16*, 794–800 and references cited therein. (b) "Organo-Aluminum Compounds. III. Reactions of Triphenylaluminum with Carbonyl Compounds," Mole, T. *Aust. J. Chem.* **1963**, *16*, 807–813.

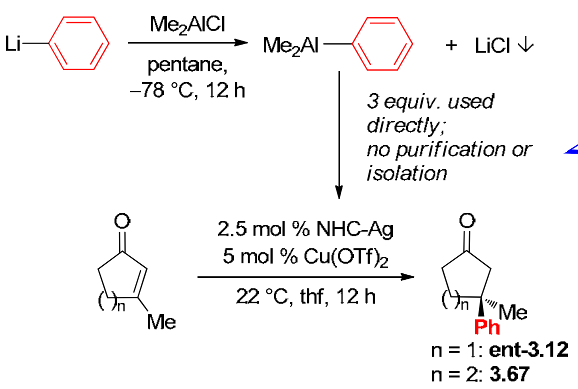
(51) For catalytic enantioselective reactions involving triarylaluminum reagents, see: (a) "Remarkably Efficient Enantioselective Titanium(IV)–(*R*)-H_8-BINOLate Catalyst for Arylations to Aldehydes by Triaryl(tetrahydrofuran)aluminum Reagents," Wu, K.-H.; Gau, H.-G. *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809. (b) "Highly Enantioselective Aryl Additions of [$AlAr_3$thf)] to Ketones Catalyzed by a Titanium(IV) Catalyst of (*S*)-Binol," Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5373–5376. (c) "Synthesis, Characterization, and Structures of Arylaluminum Reagents and Asymmetric Arylation of Aldehydes Catalyzed by a Titanium Complex of an N-Sulfonylated Amino Alcohol," Zhou, S.; Chuang, D.-W.; Chang, S.-J.; Gau, H.-M. *Tetrahedron: Asymmetry* **2009**, *20*, 1407–1412. (d) "Direct Asymmetric Catalytic Thienylaluminum Addition to Ketones: A Concise Approach to the Synthesis of (*S*)-Tiemonium Iodide," Biradar, D. B.; Zhou, S.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386–3389. (e) "$AlCl_3$ and BDMAEE: A Pair of Potent Reactive Regulators of Aryl Grignard Reagents and Highly Catalytic Asymmetric Arylation of Aldehydes," Fan, X.-Y.; Yang, Y.-X.; Zhuo, F.-F.; Yu, S.-L.; Li, X.; Guo, Q.-P.; Du, Z.-X.; Da, C.-S. *Chem. Eur. J.* **2010**, *16*, 7988–7991. (f) "Highly Enantioselective 3-Furylation of Ketones Using (3-Furyl)titanium Nucleophile," Zhou, S.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010**, *12*, 48–51.

(52) (a) "Ketone Synthesis via Palladium-Catalyzed Carbonylation of Organoaluminum Compounds," Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *Tetrahedron Lett.* **1985**, *26*, 4819–4822. (b) "Tris(pentafluorophenyl)alane: A Novel Aluminum Organyl," Belgardt, T.; Storre, J.; Roesky, H. W.;

substituents transfer more readily than sp^3-hybridized carbon groups.[39b] Accordingly, we can prepare the arylaluminum reagent by treatment of phenyllithium with one equivalent of commercially available Me_2AlCl ($320/mol, Aldrich) in pentane to afford a solution of Me_2AlPh; although the solution contains LiCl, the solution of Me_2AlPh can be used directly, without isolation, purification or filtration, in the Cu-catalyzed ECA of trisubstituted cyclic enones (Table 3.12). All of the bidentate NHC–Cu catalysts screened promote the ECA of Me_2AlPh efficiently (>98% conv at 22 °C after 12 h); the highest enantioinduction observed for both the five- and six-membered ring enones is when the addition is catalyzed by the phenoxy-containing NHC–Cu complex from **3.33** (entries 2 and 7). Cyclopentanone **ent-3.12** is formed in 73.5:26.5 er and cyclohexanone **3.67** is formed in 89:11 er. Interestingly, the sulfonate-containing Cu–NHC catalyst (in situ prepared from **3.13**, **3.34**, and **3.35**) affords the products as a racemate or slightly enriched in the opposite enantiomer as compared to the phenoxy-containing catalysts (50:50–26:74 er, entries 3–6 and 8–10). This is in contrast to the ECA reaction of *alkyl*aluminum reagents; the sulfonate-containing Cu–NHC catalysts promote the enantioselective additions with higher enantioinduction as compared to the phenoxy-containing bidentate NHC–Cu complexes (cf. Scheme 3.10).

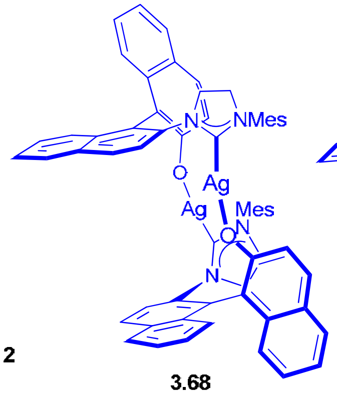
Noltemeyer, M.; Schmidt, H.-G. *Inorg. Chem.* **1995**, *34*, 3821–3822. (c) "New General Sulfinylating Process for Asymmetric Synthesis of Enantiopure Sulfinates and Sulfoxides," Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 1465–1468. (d) "Rhodium-Catalyzed Enantioselective 1,2-Addition of Aluminum Organyl Compounds to Cyclic Enones," Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122–7124. (e) "Palladium-Catalyzed Cross-Coupling Reaction of $AlArEt_2(THF)$ with Aryl Bromides," Shu, W.-T.; Zhou, S.; Gau, H.-M. *Synthesis* **2009**, 4075–4081. (f) "New Preparation and Reactions of Arylaluminum Reagents Using Barbier Conditions," Gao, H.; Knochel, P. *Synlett* **2009**, 1321–1325. (g) "Highly Enantioselective Arylation of Aldehydes and Ketones Using $AlArEt_2(THF)$ as Aryl Sources," Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500–3505.

Table 3.12. Cu–NHC-Catalyzed ECA of Arylaluminum Reagents, Prepared and Used In Situ, to 3-Methylcyclopentenone and 3-Methylcyclohexenone[a]

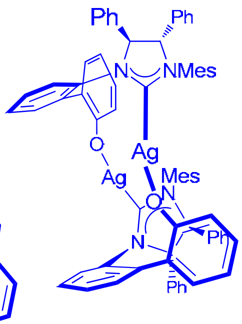

Li
Me_2AlCl
pentane,
–78 °C, 12 h
Me_2Al
+ LiCl ↓
3 equiv. used directly;
no purification or isolation
O
Me
( )n
2.5 mol % NHC-Ag
5 mol % Cu(OTf)$_2$
22 °C, thf, 12 h
O
( )n
Me
Ph
n = 1: **ent-3.12**
n = 2: **3.67**

entry	NHC-Ag	n	conv (%)[b]	er[c]
1	**3.68**	1	>98	68.5:31.5
2	**3.33**	1	>98	73.5:26.5
3	**3.13**	1	>98	50:50
4	**3.34**	1	>98	34:66
5	**3.35**	1	>98	46.5:53.5
6	**3.68**	2	>98	64:36
7	**3.33**	2	>98	89:11
8	**3.13**	2	>98	38:62
9	**3.34**	2	>98	26:74
10	**3.35**	2	>98	42.5:57.5

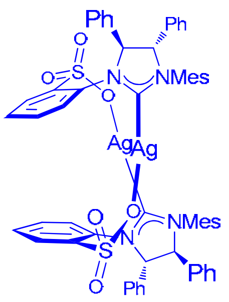
[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Determined by GLC analysis.


N
NMes
O
Ag
Ag
Mes
N
O
N

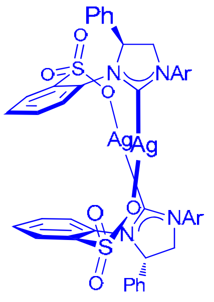
3.68


Ph
Ph
N
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph

3.33


Ph
Ph
O
O=S
N
NMes
O
Ag
Ag
O
NMes
O
S
O
N
Ph
Ph

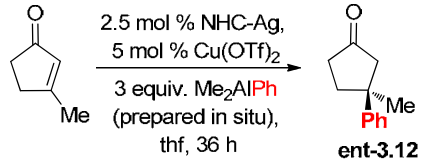
3.13


Ph
O
O=S
N
NAr
O
Ag
Ag
O
NAr
O
S
O
N
Ph

3.34 = Mes = 2,4,6-Me(C_6H_2)
3.35 = 2,6-Et(C_6H_3)

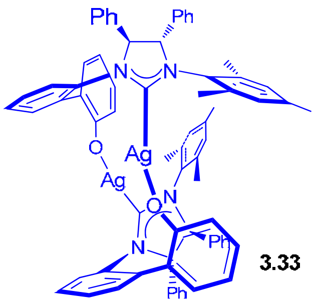
In an effort to increase the enantioselectivity of the conjugate addition products, the reaction was performed at a lower temperature. As shown in Table 3.13, when the addition catalyzed by Cu–NHC complex from **3.33** is carried out at –50 °C, **ent-3.12** is obtained with an increase in enantioselectivity without loss of efficiency (>98% conv, entry 3). Further decreasing the temperature to –78 °C results in only 26% conv to **ent-3.12**. Although the product **ent-3.12** can be obtained in 22:78 er with the sulfonate-containing catalyst when run at –15 °C (entry 4), the rate of enantioselective addition is significantly retarded when the temperature is reduced further (<2% conv at –30 °C). A steric modification of the phenoxy-containing NHC–Ag complex (**3.69**) was also prepared and examined in the enantioselective aryl addition to 3-methylcyclopentenone in an effort to increase the enantioselectivity of **ent-3.12**. As shown in entry 6 of Table 3.13, the reaction only proceeds to 66% conv and affords the cyclopentanone in 81:19 er.

Table 3.13. Temperature Screen for Cu-Catalyzed ECA of Me_2AlPh to 3-Methylcyclopentenone[a]

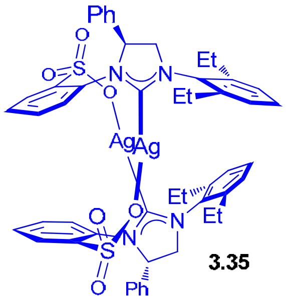


entry	NHC-Ag	temp (°C)	conv (%)[b]	er[c]
1	**3.33**	–15	>98	83:17
2	**3.33**	–30	>98	84.5:15.5
3	**3.33**	–50	>98	86:14
4	**3.35**	–15	24	22:78
5	**3.35**	–30	<2	nd
6	**3.69**	–50	66	81:19

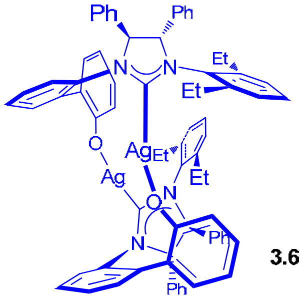
[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Determined by GLC analysis. nd = not determined.



3.33



3.35



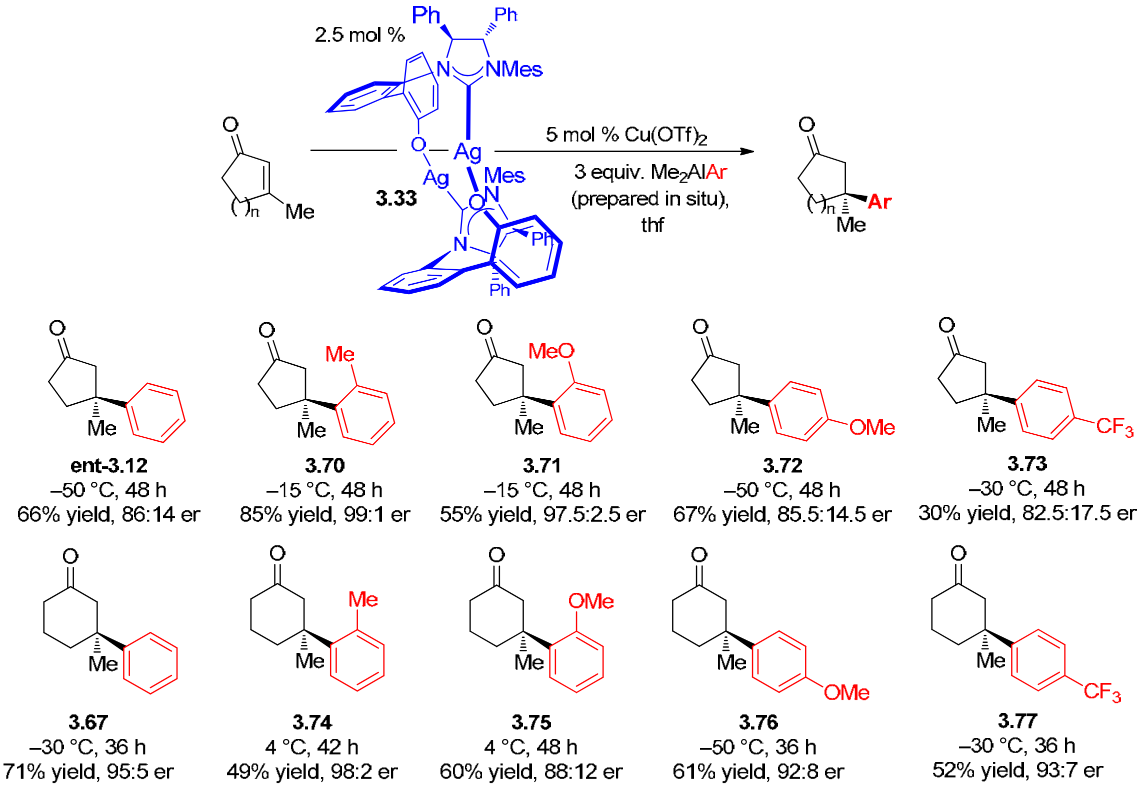
3.69

As the data in Scheme 3.17 illustrates, a series of arylaluminum reagents participate in the Cu-catalyzed ECA to five- and six-membered ring enones in up to 99:1 er. Both electron donating and electron withdrawing units on the aryl group are tolerated and the conjugate adducts are formed in 30–85% yield and 82.5:17.5–99:1 er. Enantioselectivities are highest when sterically hindered aryl groups are used (i.e., **3.70**, **3.71**, **3.74**, and **3.75**). Moreover, six-membered ring enones undergo the conjugate aryl addition reaction to produce products with higher enantioselectivities than the corresponding five-membered ring enones (88:12–98:2 er for six-membered ring products vs. 82.5:17.5–99:1 er for the five-membered ring products). It is important to note that in all cases examined, only aryl addition products are observed; there is no competitive addition stemming from the two methyl groups on aluminum. All cases shown in Scheme 3.17 proceed to >98% conv; however, the yields observed are moderate

(30–85%). This is partly due to difficulties arising from purifying biphenyl away from the desired product, which is a byproduct generated under the reaction conditions.

One advantage of using the in situ preparation of the mixed arylaluminum reagents is that a wide variety of aryl groups can be used; the only requirement is that the requisite lithium or Grignard reagent can be prepared. All of the arylaluminum reagents used in Scheme 3.17 are obtained by treatment of commercially available aryl bromides with *n*-BuLi (halogen/lithium exchange) followed by the addition of Me_2AlCl. The solution of Me_2AlPh can be stored under N_2 for more than two months and used in the catalytic ECA reactions without significant reduction in efficiency or enantioselectivity.

Scheme 3.17. Substrate and Nucleophile Scope for Enantioselective Conjugate Aryl Addition to Trisubstituted Cyclic Enones



ent-3.12
–50 °C, 48 h
66% yield, 86:14 er

3.70
–15 °C, 48 h
85% yield, 99:1 er

3.71
–15 °C, 48 h
55% yield, 97.5:2.5 er

3.72
–50 °C, 48 h
67% yield, 85.5:14.5 er

3.73
–30 °C, 48 h
30% yield, 82.5:17.5 er

3.67
–30 °C, 36 h
71% yield, 95:5 er

3.74
4 °C, 42 h
49% yield, 98:2 er

3.75
4 °C, 48 h
60% yield, 88:12 er

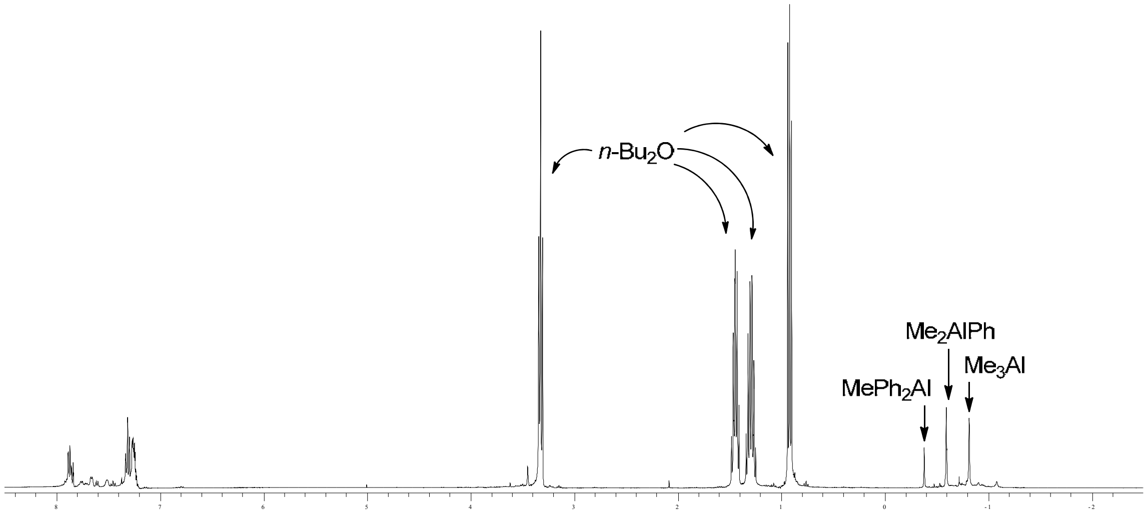
3.76
–50 °C, 36 h
61% yield, 92:8 er

3.77
–30 °C, 36 h
52% yield, 93:7 er

Although the arylaluminum reagent is prepared and used in the ECA reaction without filtration or purification, the reagent can be isolated. Filtration of the solid LiCl and removal of the solvent under anhydrous and air-free conditions affords a clear and colorless oil. Analysis of the ^{1}H NMR (400 MHz, $CDCl_3$) revealed that sample of

Me$_2$AlPh also contains MeAlPh$_2$ and Me$_3$Al, suggesting disproportionation under the reaction or isolation conditions (Scheme 3.18, *n*-Bu$_2$O is also present from the commercial solution of PhLi).[53] It is probable that the aluminum-based compounds are etherate complexes as the peaks (corresponding to the methyl groups on the aluminum) do not coalesce under the NMR timescale (22 °C). It is unclear what reagent (or reagents) is the active nucleophile in the ECA protocol (Me$_2$AlPh, MeAlPh$_2$). Based on analysis of the NMR spectra and steric considerations, we do not think that Ph$_3$Al is formed in the disproportionation pathway or the active reagent in the conjugate addition reaction. Interestingly, although Me$_3$Al is potentially present during the ECA reaction, and we know that Me$_3$Al can be used for effective Cu–NHC catalyzed ECA, we do not see 1,4-methyl addition products.

Scheme 3.18. ^{1}H NMR Spectra (400 MHz, CDCl$_3$) of the Disproportionation of Me$_2$AlPh



We also investigated the enantioselective addition of heteroaromatic groups to generate products containing all-carbon quaternary stereogenic centers (Scheme 3.19). Enantioselective addition of a pyridyl group, promoted by the Cu–NHC catalyst from

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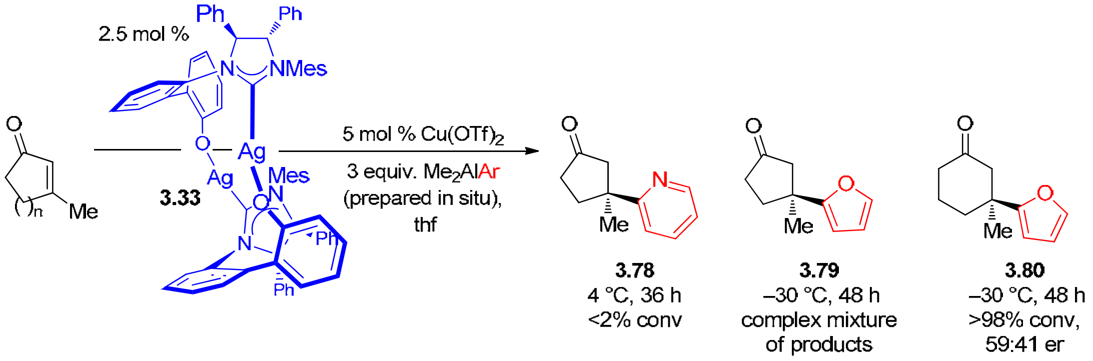
(53) For initial accounts of this observation, see: (a) "Organo-Aluminum Compounds. IV. Exchange Reactions Between Trialkylaluminums and Triphenylaluminums," Mole, T.; Surtees, J. R. *Aust. J. Chem.* **1964**, *17*, 310–314. (b) "Redistribution Reactions of Organoboranes and Organoalanes," Köster, R. *Ann. N. Y. Acad. Sci.* **1969**, *159*, 73–88. (c) "Redistribution Reactions of Organoaluminum Compounds," Mole, T. *Organometallic Reactions;* Wiley-Interscience: New York, 1970; Vol. 1, pp 1–54.

3.33, to 3-methylcyclopentenone leads to <2% conv to **3.78**; the low conversion may be due to the pyridyl chelating with copper, thus reducing productive catalytic activity. Enantioselective furyl addition was also attempted. When the addition is performed on 3-methylcyclopentenone (to form **3.79**), a complex mixture of products is formed. However, Cu-catalyzed ECA of furylaluminum to the six-membered ring enone proceeds efficiently at –30 °C (>98% conv) but **3.80** is formed in only 59:41 er.

Scheme 3.19. Cu-Catalyzed ECA of Heteroaromatic Nucleophiles to Trisubstituted Enones


2.5 mol %
Ph
Ph
NMes
N
O
Ag
Ag
Mes
N
O
N
Ph
Ph
3.33
O
( )n
Me
5 mol % Cu(OTf)$_2$
3 equiv. Me$_2$AlAr
(prepared in situ),
thf
O
N
Me
3.78
4 °C, 36 h
<2% conv
O
O
Me
3.79
–30 °C, 48 h
complex mixture
of products
O
O
Me
3.80
–30 °C, 48 h
>98% conv,
59:41 er

3.4. Proposed Catalytic Cycle for Cu-Catalyzed ECA of Alkyl- and Aryl-Aluminum Reagents to Enones

Similarly to the catalytic cycle shown in Chapter 2 for ECA of alkylzinc reagents to cyclic enones, we propose a process that has four distinct steps: cuprate formation (**B**), olefin coordination (**C**), oxidative addition (**D**)[54] and reductive elimination that regenerates the Cu–NHC complex (**A**) and the conjugate addition Al–enolate adduct (Scheme 3.20). We propose an Al-bridge between the sulfonate unit and the carbonyl of the enone (**C**); this activates the enone for efficient alkylation and organizes the

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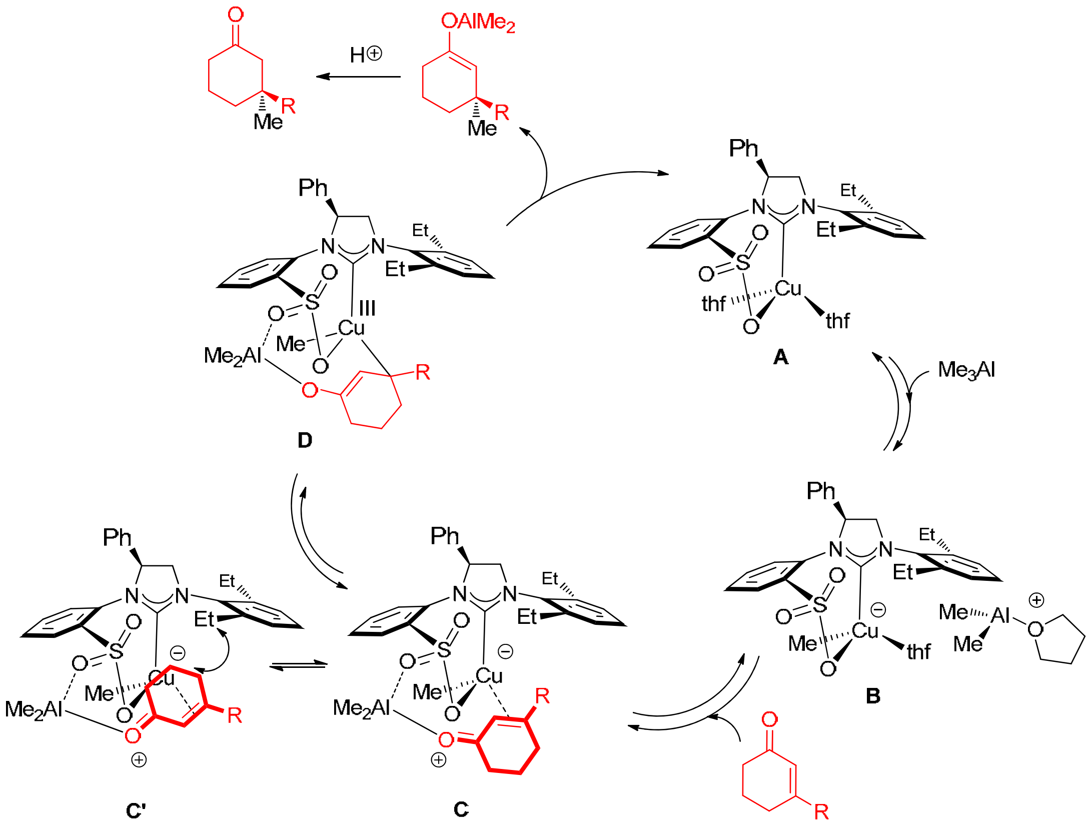
(54) For recent experimental studies detecting Cu(III) intermediates, see: (a) "Rapid Injection NMR in Mechanistic Organocopper Chemistry. Preparation of the Elusive Copper(III) Intermediate," Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208–7209. (b) "NMR-Detection of Cu(III) Intermediates in Substitution Reactions of Alkyl Halides with Gilman Cuprates," Gärtner, T.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 11362–11363.

intermediates for high selectivity. The large Ar group (2,6-diethylphenyl) forces the enone to coordinate through the least hindered side (**C**); coordination through mode **C'** is disfavored for steric reasons.

Scheme 3.20. Proposed Catalytic Cycle for Cu–NHC Catalyzed ECA of Alkylaluminum Reagents to Enones


O
H⊕
OAlMe$_2$
R
Me
R
Me
Ph
Et
Et
N
N
O
O=S
III
Cu
Me
Me$_2$Al
O
O
R
D
Ph
Et
Et
N
N
O
O=S
thf
Cu
thf
O
A
Me$_3$Al
Ph
Et
Et
N
N
O
O=S
⊖
Me
Cu
thf
O
Me
Al
⊕
O
Me
B
Ph
Et
Et
N
N
O
O=S
Me
Cu
⊖
Me$_2$Al
O
O
⊕
R
C'
Ph
Et
Et
N
N
O
O=S
⊖
Me
Cu
Me$_2$Al
O
O
⊕
R
C
O
R

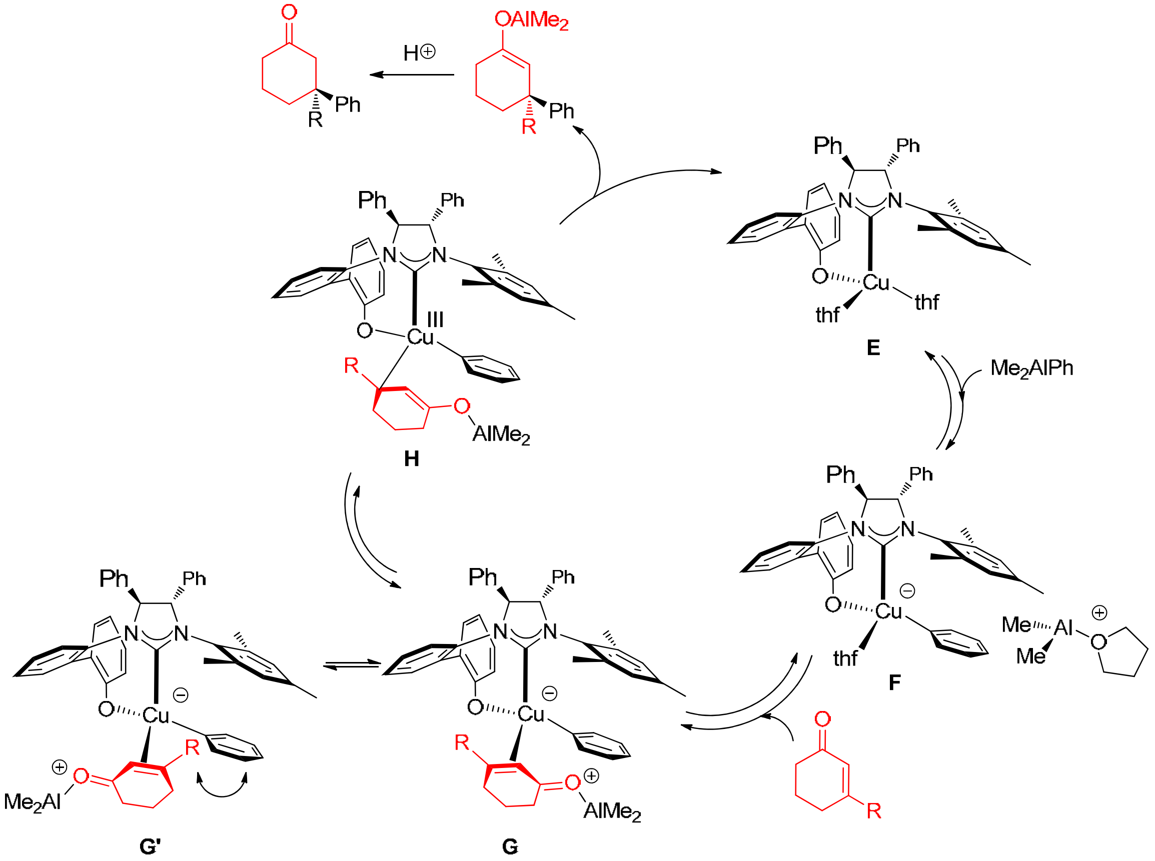
The proposed catalytic cycle for Cu-ECA of arylaluminums to enones is similar to that reported for Cu–NHC catalyzed ECA of arylzinc reagents to cyclic enones.[55] We propose that the Ag–NHC complex **3.33** transmetallates with the Cu source to form the active Cu–NHC complex **E**. When **E** is exposed to the arylaluminum reagent, cuprate **F** can be formed. Olefin coordination of the cuprate with the enone forms intermediate **G**. Oxidative addition to form the Cu(III) intermediate **H** followed by irreversible reductive

---

(55) "A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers through NHC-Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to β-Substituted Cyclic Enones," Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184.

elimination affords the Al–enolate and regenerates the active Cu–NHC catalyst **E**. The minor enantiomer can be potentially formed from intermediate **G'**; this intermediate is disfavored due to steric interactions between the Cu–aryl moiety and the group on the β-position of the enone (denoted by the R group in Scheme 3.21).

Scheme 3.21. Proposed Catalytic Cycle for Cu–NHC Catalyzed ECA of Arylaluminum Reagents to Enones


O
H⊕
OAlMe2
Ph
R
Ph
R
Ph
Ph
N
N
O
Cu
thf
thf
E
Me2AlPh
Ph
Ph
N
N
O
Cu
III
R
O
AlMe2
H
Ph
Ph
N
N
O
Cu
⊖
thf
F
Me
Al
⊕
O
Me
Ph
Ph
N
N
O
Cu
⊖
R
⊕
O
Me2Al
G'
Ph
Ph
N
N
O
Cu
⊖
R
O
⊕
AlMe2
G
O
R

3.5. Conclusions

Outlined in this chapter is the first effective solution for Cu-catalyzed enantioselective addition of alkyl and aryl nucleophiles to trisubstituted cyclopentenones generating products bearing a β-all-carbon quaternary stereogenic center. Products are obtained in up to 97% yield and 99:1 er, only requiring 5 mol % of an in situ generated Cu–NHC catalyst. The methodology was highlighted as one of the key steps in the total synthesis of clavirolide C. We have found, not only five-membered rings, but six- and seven-membered rings serve as proficient partners in the enantioselective process. The method can be performed on a synthetically useful scale (2 mmol of enone) with commercial copper sources and alkylaluminum reagents. Moreover, in cases for the enantioselective aryl addition, in situ prepared Me_2AlAr can be used without purification, filtration, or isolation, only requiring the corresponding aryl halides.

Enantioselective additions to trisubstituted unsaturated six-membered ring lactones and chromones also proceed efficiently to afford β,β-disubstituted lactones and chromones in up to 98% yield and 97.5:2.5 er. Currently there is only one Rh-catalyzed ECA with phenyl nucleophile in the addition to a trisubstituted unsaturated lactone[16]. Thus, this constitutes an advancement for the organic community. There are still some limitations that need to be addressed; for example, five-membered unsaturated lactones are inert under the reaction conditions and ECA of alkylaluminum reagents to trisubstituted unsaturated lactams are not efficient. Further investigations in our group are ongoing to develop more effective and active catalysts for these transformations.

3.6. Experimentals

General. Infrared (IR) spectra were recorded on a Nicolet 210 or a Bruker alpha spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H 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, s = septet, quint = quintet, 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. Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm), Betadex 120 column (30 m x 0.25 mm) or Chiraldex BDA column (30 m x 0.25 mm)) or HPLC analysis (Chiral Technologies Chiralcel OD, 4.6 x 250 mm and Chiral Technologies Chiralcel AS, 4.6 x 250 mm) in comparison with authentic racemic materials. The inlet and detector temperatures are set to 250 °C and runs were isothermal of the temperature given using ultra high purity helium as the carrier gas. Specific 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. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene, benzene and pentane 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 ketal immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air.

■ Reagents and Catalysts:

Acetonitrile was purchased from Aldrich and used as received.

Ag complexes 3.68,[56] **3.33,**[25] **and 3.13**[14] were prepared by previously reported methods.

Acetic acid was purchased from Fisher and used as received.

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(56) (a) "A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air," Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (b) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131

Racemic-2,2’-bis(diphenylphosphino)-1,1’-binapthyl (*rac*-binap) was purchased from Aldrich and used as received.

(*S*)-Boc-phenylglycinol can be purchased from BetaPharma or prepared[33] in one step from (*S*)-phenylglycinol (purchased from BetaPharma).

2-Bromoanisole was purchased from Aldrich and distilled from CaH_2 prior to use.

4-Bromoanisole was purchased from Aldrich and distilled from CaH_2 prior to use.

4-Bromobenzotrifluoride was purchased from Aldrich and distilled from CaH_2 prior to use.

2-Bromotoluene was purchased from Aldrich and distilled from CaH_2 prior to use.

2-Bromobenzenesulfonyl chloride was purchased from Lancaster and purified by washing a benzene solution of the sulfonyl chloride with a 1.0 M aq solution of KOH.

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

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

Copper (I) triflate benzene complex (2:1) (white solid) was prepared by previously reported methods.[57]

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

2,6-Diethylaniline was purchased from Aldrich and used as received.

1,4-Dioxane (99.8%, anhydrous) was purchased from Aldrich and used as received.

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

***N*, *N*-Dimethylformamide** (99.8%, Acroseal) was purchased from Acros was used as received.

Imidazole was purchased from Aldrich and used as received.

***cis*-Jasmone** was purchased from Aldrich and distilled over CaH_2 prior to use.

3-Methylcyclohexenone was purchased from Aldrich and distilled over CaH_2 prior to use.

3-Methylcyclopentenone was purchased from Aldrich and distilled over CaH_2 prior to use.

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(57) “Cationic Olefin Complexes of Copper(I). Structure and Bonding in Group 1b Metal–Olefin Complexes,” Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897.

***N*-Methyl-*N*-methylideneiminium iodide (Eschenmoser's salt)** was purchased from Aldrich and used as received.

pH = 7 buffer was prepared by mixing dibasic phosphate (Na_2HPO_4, 8.19 g) and monobasic phosphate (NaH_2PO_4, 5.84 g) and diluted to 1 L with distilled water.

Phenyllithium (2.0 M in *n*-Bu_2O) was purchased from Acros and titrated before use.

Ruthenium (III) chloride hydrate (40-45% Ru) was purchased from Strem and used as received.

Silver nitrate was purchased from Aldrich and used as received.

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

Sodium periodate was purchased from Aldrich and used as received.

Sodium *tert*-butoxide (98%) was purchased from Strem and used as received.

Sulfuric acid (concentrated, 18 M) was purchased from Fisher and used as received.

Thionyl chloride was purchased from Aldrich and used as received.

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

Triethylamine was purchased from Aldrich and distilled from CaH_2 prior to use.

Triisobutylaluminum (neat) was purchased from Strem and used as received.

Trimethylaluminum (neat) was purchased from Strem and used as received. We have found that old bottles (>1 year) of Me_3Al were not as effective for the ECA reactions (conversions suffered, enantioselectivities remained the same).

2,4,6-Trimethylaniline was purchased from Aldrich and used as received.

Tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$) was purchased from Strem and used as received.

■ Synthesis of Ag–NHC Complex 3.35:

(*S*)-Sulfamidate (3.38): To a solution of imidazole (4.54 g, 66.2 mmol), Et_3N (7.48 mL, 45.8 mmol) and $SOCl_2$ (1.62 mL, 22.3 mmol) in CH_2Cl_2 (170 mL) at –50 °C (dry ice/acetone bath) was added (*S*)-Boc-phenylglycinol (**3.36**) (3.96 g, 16.8 mmol) as a CH_2Cl_2 solution (43.8 mL) over 1.5 h through an addition funnel. The solution was allowed to warm to 4 °C (cold room) and stir for 12 h. The reaction was quenched through the addition of water (100 mL). The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford **3.37** as a white solid (3.67 g, 13.1 mmol, 78.4%).

Sulfamidite **3.37** (3.67 g, 13.1 mmol) and $RuCl_3 \cdot 2H_2O$ (0.190 g, 0.914 mmol) were dissolved in CH_2Cl_2 (26.1 mL) and CH_3CN (26.1 mL) and the resulting solution allowed to cool to 0 °C (ice bath). After 10 minutes, $NaIO_4$ (4.47 g, 20.9 mmol) and pH = 7 buffer (26.1 mL, 0.1 M aqueous solution of 1:1 Na_2HPO_4:NaH_2PO_4)[58] were added. The solution was allowed to stir at 0 °C for 20 min before allowing to warm to 22 °C over 5 min. The solution was filtered through a plug of Celite 545 (4 x 4 cm) eluted with CH_2Cl_2 (200 mL). The filtrate was diluted with water (100 mL) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was filtered through silica gel (4 x 4 cm) eluted with CH_2Cl_2 to afford **3.38** as a white solid (2.90 g, 9.69 mmol, 74%). m.p.: 144-150 °C; IR (neat): 2976 (w), 1723 (s), 1458 (w), 1368 (s), 1320 (s), 1309 (w), 1259 (w), 1227 (w), 1190 (s), 1150 (s), 1031 (w), 1006 (w), 996 (m), 959 (w), 927 (m), 851 (s), 834 (s), 797 (m), 779 (m), 763 (s), 723 (s), 704 (m), 661 (s), 604 (s), 574 (w), 528 (w), 498 (w), 456 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.35 (5H, m), 5.29 (1H, q, J = 4.4 Hz), 4.87 (1H, dd, J = 9.2, 8.0 Hz), 4.39 (1H, dd, J = 9.2, 4.0 Hz), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.4, 137.0, 129.3, 129.2, 126.2, 85.6, 71.9, 60.8, 27.9; Specific Rotation: $[\alpha]_D^{20}$ –45.6 (c = 1.17, $CHCl_3$).

***tert*-Butyl-2,6-diethylphenylcarbamate (3.39):**[35] To a solution of 2,6-diethylaniline (9.10 g, 61.0 mmol) in water (61.0 mL) was added $(Boc)_2O$ (14.8 g, 67.8 mmol) in one portion. After 48 h, a red semi-solid precipitated out of solution. The red solid was collected by vacuum filtration, washed with water (3 x 100 mL) and dried in a vacuum dessicator over P_2O_5 for 12 h to yield a light red solid (13.7 g, 54.9 mmol, 90%). m.p.:

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(58) The type of pH = 7 buffer used was found to be critical in order to achieve complete conversion in 30 min.

55-57 °C; IR (neat): 3296 (br), 2965 (m), 2932 (m), 2873 (w), 1687 (s), 1618 (w), 1591 (w), 1505 (s), 1458 (w), 1390 (m), 1364 (m), 1268 (m), 1244 (w), 1164 (m), 1054 (m), 1024 (m), 916 (w), 867 (w), 840 (w), 805 (w), 776 (w), 755 (w), 720 (w), 612 (w), 564 (w), 538 (m), 492 (w), 455 (w), 404 (w) cm^{-1}; this compound is isolated as a mixture of rotomers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23–7.09 (3H, m), 5.84 (1H, br s), 5.58 (0.2H, br s), 2.64 (4H, q, *J* = 7.6 Hz), 1.51 (9H, br s), 1.38 (0.3H, br s), 1.20 (6H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.6, 143.3, 133.0, 127.8, 126.5, 126.2, 118.5, 79.9, 28.6, 25.0, 24.5, 14.7, 13.3; HRMS (EI+): Calcd for $C_{15}H_{27}N_2O_2$ $[M+NH_4]^+$: 267.2073, Found: 267.2069.

(*S*)-*N*^{1}-(2,6-Diethylphenyl)-2-phenylethane-1,2-diamine (3.40): To a flame-dried flask was added NaH (60% dispersion in oil, 215 mg, 5.39 mmol) and DMF (11.0 mL). *tert*-Butyl-2,6-diethylphenylcarbamate (**3.39**) (1.19 g, 4.76 mmol) was added as a solid in one portion and the solution was allowed to stir until it turned clear (~15 min) at 22 °C. At this time, sulfonamide **3.38** (0.951 g, 3.17 mmol) was added as a solid in one portion and the resulting mixture was allowed to stir for 12 h. Dimethylformamide was removed under reduced pressure (~0.5 mm/Hg) with gentle heating (<60 °C). Dioxane (11.0 mL) was added followed by concentrated H_2SO_4 (0.480 mL, ~18 M). The solution was allowed to stir for 30 minutes before another portion of concentrated H_2SO_4 (1.90 mL, ~18 M) was added to the solution. The resulting solution was allowed to stir at 22 °C for 48 h. A saturated aqueous solution of Na_2CO_3 was then added until pH = ~10, CH_2Cl_2 (100 mL) was added and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (100 mL x 3) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a light yellow oil. The oil was passed through a short plug of silica gel (1:1 petroleum ether:Et_2O → 1:3 petroleum ether:Et_2O) to afford **3.40** (0.659 g, 2.46 mmol, 77.3%) as a yellow oil. IR (neat): 3363 (br), 3059 (w), 3033 (w), 2957 (s), 2932 (m), 2868 (m), 2366 (w), 2341 (w), 1733 (m), 1704 (w), 1594 (m), 1488 (m), 1450 (w), 1374 (w), 1269 (w), 1268 (w), 1248 (w), 1201 (w), 1159 (w), 1109 (w), 1058 (w), 1024 (w), 990 (w), 876 (w), 758 (s), 699 (w), 530 (w) cm^{-1}; (we have found that ^{1}H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.28 (5H, m), 7.01 (2H, d, *J* = 7.2 Hz), 6.92 (1H, dd, *J* = 6.4, 6.4 Hz), 4.15 (1H, q, *J* = 5.2 Hz), 3.11 (2H, dq, *J* = 11.6, 11.6 Hz), 2.57 (4H, q, *J* = 7.6 Hz), 2.62 (3H, br s), 1.17 (6H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 144.6, 136.7, 128.9, 127.7, 126.9, 126.6, 122.9, 57.6, 56.7, 24.6, 15.1; HRMS (EI+): Calcd for $C_{18}H_{25}N_2$ $[M+H]^+$: 269.2018, Found: 269.2018; Specific Rotation: $[\alpha]_D^{20}$ –17.7 (*c* = 1.33, $CHCl_3$) *[This specific rotation was taken with the R enantiomer of compound* ***3.40*** *(opposite enantiomer to what is shown above)].*

(*S*)-Isobutyl 2-(2-(2,6-diethylphenylamino)-1-phenylethylamino)benzenesulfonate (3.42): To a flame-dried round bottom flask in a N_2-filled glove box were added isobutyl-2-bromobenzenesulfonate (1.10 g, 3.75 mmol), Pd_2dba_3 (0.201 g, 0.219 mmol), NaO*t*-Bu (0.599 g, 6.57 mmol) and *rac*-binap (0.409 g, 0.657 mmol). The flask was equipped with a reflux condenser capped with a septum and removed from the glove box. A solution of diamine **3.40** (0.979 g, 3.75 mmol) in thf (36.5 mL) was added through a syringe and the resulting red solution was allowed to stir at 66 °C (oil bath) for 15 h. The mixture was allowed to cool to 22 °C and the reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl (30 mL). The layers were separated and the aqueous layer washed with CH_2Cl_2 (50 mL x 3). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a red oil. The oil was dissolved in toluene, loaded on top of a column containing silica gel, and purified by silica gel chromatography (100% petroleum ether (to elute toluene) → 90% petroleum ether /Et_2O) to afford **3.42** (1.73 g, 3.60 mmol, 99%) as a yellow solid (contains ~20% dehalogenated aryl sulfonate). IR (neat): 3380 (br), 3063 (w), 3029 (w), 2961 (s), 2932 (m), 2864 (m), 1602 (w), 1569 (m), 1509 (w), 1459 (w), 1450 (s), 1349 (w), 1269 (w), 1222 (w), 1184 (s), 1163 (s), 1109 (w), 1062 (w), 1024 (w), 973 (s), 952 (m), 843 (m), 813 (m), 573 (w), 522 (w) cm^{-1}; (we have found that ^{1}H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89–7.66 (2H, m), 7.52–6.97 (8H, m), 6.78 (1H, d, *J* = 3.2 Hz), 6.63 (1H, d, *J* = 8.0 Hz), 4.74 (1H, q, *J* = 6.0 Hz), 3.84 (1H, dd, *J* = 9.6, 6.4 Hz), 3.79 (1H, dd, *J* = 9.6, 6.8

Hz), 3.38 (1H, dd, *J* = 11.6, 4.4 Hz), 3.21 (1H, dd, *J* = 12.0, 6.0 Hz), 2.54 (2H, q, *J* = 7.6 Hz), 2.44 (2H, q, *J* = 7.6 Hz), 1.98 (1H, s, *J* = 6.8 Hz), 1.11 (6H, t, *J* = 7.6 Hz), 0.94 (3H, d, *J* = 3.2 Hz), 0.92 (3H, d, *J* = 3.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 146.0, 143.9, 140.3, 137.7, 135.4, 131.0, 129.2, 128.3, 128.1, 126.8, 126.6, 123.8, 115.9, 113.8, 76.5, 57.7, 56.2, 28.3, 24.2, 18.9, 15.1; HRMS (EI+): Calcd for $C_{28}H_{37}N_2O_3S$ $[M+H]^+$: 481.2525, Found: 481.2529; Specific Rotation: $[\alpha]_D^{20}$ –13 (*c* = 0.95, CHCl$_3$).

Imdizolium Salt 3.43: Diamine **3.42** (4.66 g, 9.71 mmol) and *N*-methyl-*N*-methylideneiminium iodide (8.98 g, 48.5 mmol) were weighed out into a 75 mL heavy wall sealed tube. Acetic acid (1.04 mL, 145 mmol) was added, the vessel sealed, and the mixture allowed to stir at 110 °C (the yellow heterogeneous mixture becomes black and homogeneous upon heating). After 1 h, the mixture was allowed to cool to 22 °C and diluted with Et$_2$O (5 mL) and water (5 mL). The resulting mixture was basified by the *slow* addition of a saturated aqueous solution of K$_2$CO$_3$ until gas evolution ceased. Dichloromethane (10 mL) was added and the aqueous layer separated. The aqueous layer was washed further with CH$_2$Cl$_2$ (2 × 10 mL) and the combined organic layers dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford a yellow solid. The yellow solid was purified by silica gel column chromatography (100% EtOAc → 2% MeOH/EtOAc → 5% MeOH/EtOAc) to afford imidazolinium salt **3.43** (2.10 g, 4.83 mmol, 50%) as a white solid. (Note: Separation of a yellow impurity by silica gel column chromatography can often be tedious. This solid can be obtained in white crystalline form by recrystallization from CH$_2$Cl$_2$:Et$_2$O, but is not required for effective formation of Ag complex **3.35**.) m.p.: 251–252 °C; IR (neat): 3051 (m), 2965 (w), 2933 (m), 2874 (w), 1612 (w), 1583 (w), 1457 (m), 1430 (m), 1310 (w), 1282 (w), 1266 (w), 1236 (w), 1200 (m), 1139 (m), 1091 (w), 1054 (w), 1021 (w), 956 (w), 890 (w), 865 (w), 806 (w), 758 (s), 735 (w), 717 (w), 704 (s), 684 (w), 650 (m), 612 (m), 580 (m), 565 (m), 538 (w), 523 (w), 492 (w), 446 (m), 427 (w), 405 (m) cm^{-1}; (we have found that ^{1}H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.64 (1H, s), 8.19 (1H, dd, *J* = 8.0, 1.2 Hz), 7.49–7.45 (5H, m), 7.43 (1H, t, *J* = 7.6 Hz), 7.34 (1H, dt, *J* = 7.6, 1.2 Hz), 7.31–7.21 (2H, m), 7.10 (1H, dt, *J* = 7.2, 1.2 Hz), 6.61 (1H, dd, *J* = 7.6, 0.8 Hz), 6.25 (1H, dd, *J* = 12.4, 9.6 Hz), 4.86 (1H, t, *J* = 12.0 Hz), 4.16 (1H, dd, *J* = 11.6, 9.2 Hz), 3.11 (1H, dq, *J* = 7.6, 7.2 Hz), 2.98 (1H, dq, *J* = 7.2, 7.2 Hz), 2.89–2.73 (2H, m), 1.37 (3H, t, *J* = 7.6 Hz), 1.34 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 144.3, 143.6, 140.8, 136.1, 131.6, 131.2, 130.8, 130.4, 130.2, 130.0, 129.9, 129.9, 128.6, 127.9, 127.2, 127.1, 68.6, 60.4, 24.5, 23.8, 15.7, 15.1; HRMS (ESI+): Calcd for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1742, Found: 435.1732; Specific Rotation: $[\alpha]_D^{20}$ –126 (*c* = 0.65, $CHCl_3$).

Preparation of Ag_2O: An aqueous solution of sodium hydroxide (20 mL, 2M, 40 mmol) was added to a solution of $AgNO_3$ (1.7g, 10 mmol) in H_2O (10 mL). A brown precipitate formed immediately, which was isolated by vacuum filtration. The solid was washed with 250 mL H_2O, 250 mL EtOH, and 250 mL acetone and repeated. The brown solid was dried overnight under vacuum (~0.5 mm Hg) over P_2O_5.

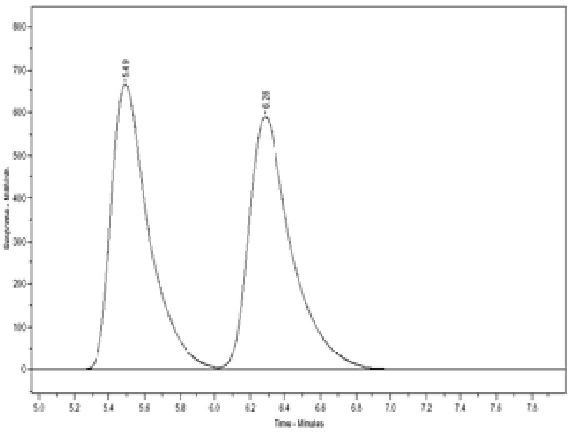
NHC-Ag complex 3.35: Imidazolium salt **3.43** (100 mg, 0.201 mmol), Ag_2O (93.0 mg, 0.400 mmol) and oven-dried <5 micron 4Å molecular sieves (ca. 50 mg) were weighed out into an oven-dried 10 mL round bottom flask fitted with a reflux condenser, and wrapped with aluminum foil. Tetrahydrofuran (1.0 mL) followed immediately by benzene (1.0 mL) were added through a syringe resulting in a black heterogeneous mixture, which was allowed to stir at 80 °C. After 2 h, the mixture was allowed to cool to 22 °C and filtered through a short plug of Celite 545 (4 x 1 cm) eluted with EtOAc (ca. 20 mL). The solution was concentrated in vacuo to afford 119 mg (0.197 mmol, 98%) of Ag complex **3.35** as a white solid, which was stored under low light conditions. (Note: This material was obtained in crystalline form by recrystallization from CH_2Cl_2:Et_2O bilayer, but recrystallization is not required for effective Cu-catalyzed ECA.) m.p. = 167–170 °C (decomp); IR (neat): 3443 (br), 3062 (w), 2964 (m), 2928 (m), 2871 (w), 1769 (w), 1625 (w), 1590 (w), 1573 (w), 1480 (w), 1467 (w), 1443 (s), 1373 (w), 1272 (s), 1228 (w), 1198 (s), 1167 (w), 1136 (s), 1089 (w), 1053 (w), 1020 (s), 905 (w), 869 (w), 804 (w), 757 (w), 726 (w), 699 (s), 661 (s), 608 (s), 564 (s), 548 (m), 466 (w), 407 (w) cm $^{-1}$; (We have found that ^{1}H NMR peaks of this compound can be concentration dependent and can shift +/– 0.2 ppm.) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (1H, br s), 7.27–7.18 (6H, m), 7.05 (2H, d, *J* = 8.0 Hz), 6.86 (1H, br s), 6.73 (1H, br s), 6.23–6.16 (2H, m), 4.34 (1H, t, *J* = 7.2 Hz), 3.71 (1H, t, *J* = 8.4 Hz), 2.62–2.28 (4H, m), 1.28 (3H, t, *J* = 7.2 Hz), 0.941 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.7, 205.8, 143.5, 143.3, 141.4, 139.4, 136.8, 135.5, 130.7, 130.6, 130.6, 129.5, 129.0, 128.7, 128.6, 128.3, 127.8, 126.3, 68.4, 61.5, 24.7, 23.5, 15.9, 15.5; HRMS (EI+): Calcd for $C_{25}H_{25}N_2O_3NaSAg$ $[M+Na]^+$: 563.0535, Found: 563.0536; Specific Rotation: $[\alpha]_D^{20}$ –64 (*c* = 0.82, $CHCl_3$) *(This specific rotation was taken with the R enantiomer of compound* ***3.35*** *(opposite enantiomer to what is shown above)).*

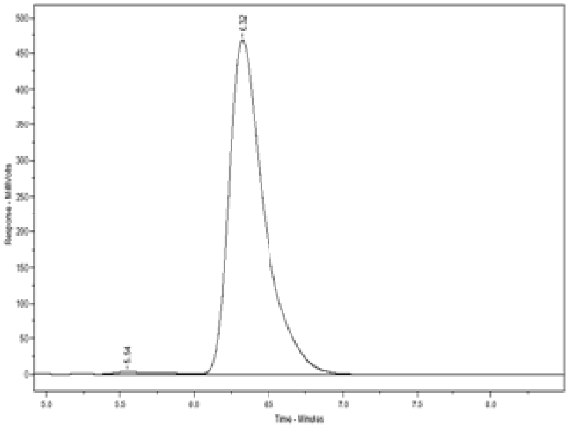
(*S*)-N-Mesityl-2-phenylethane-1,2-diamine: IR (neat): 3368 (bs), 3059 (m), 3025 (m), 2918 (bs), 2854 (m), 2725 (w), 1601 (m), 1484 (s), 1451 (s), 1374 (m), 1303 (m), 1265 (s), 1232 (s), 1154 (m), 1026 (m), 855 (m), 740 (s), 702 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (1H, s), 7.37 (3H, s), 7.29 (1H, ddd, *J* = 13.6, 8.4, 4.4 Hz), 6.81 (2H, s), 4.11 (1H, dd, *J* = 7.6, 5.2 Hz), 3.18 (1H, dd, *J* = 12.0, 5.2 Hz), 3.08 (1H, dd, *J* = 12.0, 8.0 Hz), 2.30 (2H, bs), 2.23 (3H, s), 2.20 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.3, 143.2, 131.2, 129.6, 129.4, 128.6, 127.3, 126.3, 56.3, 56.0, 20.5, 18.2; HRMS (EI+): Calcd for $C_{17}H_{23}N_2$ $[M+H]^+$: 255.1861, Found 255.1869; Specific Rotation: $[\alpha]_D^{20}$ +11.3 (*c* = 2.03, $CHCl_3$).

(*S*)-Isobutyl-2-(2-(mesitylamino)-1-phenylethylamino)benzenesulfonate: IR (neat): 3371 (w), 2966 (m), 2923 (w), 2868 (w), 1733 (w), 1602 (m), 1573 (w), 1509 (w), 1484 (m), 1467 (s), 1450 (m), 1349 (s), 1298 (w), 1180 (s), 1163 (s), 1121 (w), 1092 (w), 978 (m), 940 (m), 910 (w), 847 (w), 817 (w), 746 (s), 699 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (1H, dd, *J* = 8.0, 1.6 Hz), 7.39–7.33 (4H, m), 7.30–7.23 (2H, m), 6.97 (1H, d, *J* = 6.4 Hz), 6.69 (2H, s), 6.68 (1H, dt, *J* = 7.2, 0.8 Hz), 6.51 (1H, d, *J* = 8.4 Hz), 4.70 (1H, ddd, *J* = 6.4, 6.4, 4.4 Hz), 3.83 (1H, dd, *J* = 9.2, 6.4 Hz), 3.78 (1H, dd, *J* = 9.2, 6.4 Hz), 3.35 (1H, dd, *J* = 12.0, 4.0 Hz), 3.20 (1H, dd, *J* = 12.4, 6.4 Hz), 3.02 (1H, bs), 2.21 (3H, s), 2.12 (6H, s), 1.97 (1H, sep, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 2.8 Hz), 0.92 (3H, d, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 142.1, 140.1, 135.2, 132.1, 130.8, 130.6, 129.4, 128.9, 127.7, 126.3, 116.8, 115.6, 113.6, 76.2, 57.2, 54.6, 28.0, 20.6, 18.6, 17.8;

HRMS (EI+): Calcd for $C_{27}H_{34}N_2O_3SNa$ $[M+Na]^+$: 489.2188, Found: 489.2183; Specific Rotation: $[\alpha]_D^{20}$ –43.0 (*c* = 2.28, $CHCl_3$).

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (98.9:1.1 er shown; chiralpak OD column (25 cm x 0.46 cm), 90/10 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).





Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	5.49		0.00	N/A	9773754	49.310	BV	0.21
2	6.28		0.00	N/A	10047270	50.690	VB	0.25

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %	Type	Width
1	5.54		0.00	N/A	87348	1.121	BV	0.35
2	6.32		0.00	N/A	7706958	98.879	VB	0.24

Imidazolinium Salt (precursor to Ag–NHC 3.34): mp: 189-191 °C; IR (neat): 3447 (b), 1636 (s), 1471 (w), 1244 (m), 1197 (m), 1142 (w), 1101 (w),1087 (w), 860 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.93 (1H, s), 7.92 (1H, dd, *J* = 7.6, 1.2 Hz), 7.46–7.45 (2H, m), 7.37–7.30 (3H, m), 7.10 (1H, dt, *J* = 6.4, 1.2 Hz), 6.94 (1H, dt, *J* = 8.0, 1.6 Hz), 6.90 (1H, bs), 6.86 (1H, bs), 6.71 (1H, dd, *J* = 7.6, 0.8 Hz), 6.26 (1H, dd, *J* = 12.4, 9.2 Hz), 4.74 (1H, t, *J* = 12.4 Hz), 3.98 (1H, dd, *J* = 11.6, 9.6 Hz), 2.43 (3H, bs), 2.29 (6H, bs); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.4, 143.3, 140.4, 136.9, 136.5, 135.3, 130.9, 130.5, 130.3, 130.0, 129.8, 129.4, 129.4, 128.5, 127.1, 68.0, 59.0, 21.3, 18.4, 18.0; HRMS (EI+): Calcd for $C_{24}H_{24}N_2O_3SNa$ $[M+Na]^+$: 443.1405, Found: 443.1398; Specific Rotation: $[\alpha]_D^{20}$ +144 (*c* = 1.00, $CHCl_3$).

Ag–NHC 3.34: mp: 240 °C (decomp); IR (neat): 3468 (b), 3067 (w), 3033 (w), 2944 (w), 2923 (w), 1640 (m), 1607 (m), 1590 (m), 1569 (m), 1484 (s), 1438 (s), 1265 (s), 1210 (s), 1142 (m), 1092 (m), 1024 (s), 1007 (w), 902 (m), 847 (m), 771 (m), 729 (s), 699 (s), 611 (m), 564 (m), 522 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.18 (1H, d, *J* = 7.2 Hz), 7.30–7.23 (5H, m), 6.80 (2H, s), 6.73 (1H, t, *J* = 7.6 Hz), 6.62 (1H, s), 6.25 (1H, d, *J* = 7.2 Hz), 6.13–6.09 (1H, m), 4.31–4.25 (1H, m), 3.70–3.65 (1H, m), 2.30 (3H, s), 2.27 (3H, s), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5 ($C_{carbene}$, d, *J* = 185.5 Hz), 143.3, 139.9, 137.4, 137.2, 135.8, 135.5, 135.1, 130.7, 130.2, 129.5, 129.0, 128.6, 128.4, 128.3, 68.1, 60.2, 21.4, 18.8, 18.0; Elemental Analysis: Anal Calcd for $C_{24}H_{23}AgN_2O_3S$: C, 54.66; H, 4.40; N, 5.31; Found: C, 54.75; H, 4.83; N, 5.02; Specific Rotation: $[\alpha]_D^{20}$ +70.1 (*c* = 0.727, $CHCl_3$).

■ **Preparation of unsaturated enones:** *α,β*-Unsaturated carbonyls are commercially available (3-methylcyclopentenone and 3-methylcyclohexenone, Aldrich) or can be prepared according to published procedures.[59]

3-(Non-1-ynyl)cyclopent-2-enone :[60] IR (neat): 2930 (s), 2859 (w), 2214 (m), 1718 (w), 1670 (w), 1598 (w), 1455 (w), 1428 (w), 1345 (w), 1324 (w), 1299 (m), 1183 (m), 1133 (w), 1090 (w), 1052 (w), 1021 (w), 963 (w), 886 (s), 842 (w), 748 (w), 723 (w), 611 (s), 564 (w), 493 (w), 459 (w), 415 (s) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.13 (1H, s), 2.42–2.34 (6H, m), 2.00 (2H, quintet, *J* = 6.4 Hz), 1.55 (2H, quintet, *J* = 6.8 Hz), 1.42–1.35 (2H, m), 1.34–1.27 (4H, m), 0.89 (3H, t, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.4, 145.0, 132.0, 102.8, 80.7, 37.5, 31.5, 31.1, 28.7, 28.5, 22.8, 22.7, 20.0, 14.2; HRMS (EI+): Calcd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1592, Found: 205.1596.

■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *trialkylaluminum* reagents to unsaturated enones:** An oven-dried 13x100 mm test tube was charged with Ag complex **3.35** (2.71 mg, 2.50 μmol), $Cu(OTf)_2$ (1.64 mg, 5.00

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(59) a) reference 10a. b) “Synthesis of β-Alkyl Cyclopentenones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Addition,” Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798. c) “Organocatalytic Transfer Hydrogenation of Cyclic Enones,” Tuttle, J. B.; Ouellet, S. G.; MacMillian, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662–12663.

(60) “A Copper-Free Palladium Catalyzed Cross Coupling Reaction of Vinyl Tosylates with Terminal Acetylenes,” Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673–6676.

μmol) and 3-methylcyclopentenone[61] (18.6 mg, 0.100 mmol) weighed out under a N_2 atmosphere. The test tube was sealed with a septum and wrapped with parafilm. Tetrahydrofuran (1.0 mL) was added through a syringe and the resulting solution allowed to stir for five minutes before allowing to cool to –78 °C (dry ice/acetone bath). Triethylaluminum (41.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting brown solution transferred to a –78 °C cryocool. After 4 h, the reaction was quenched upon addition of a saturated aqueous solution of sodium potassium tartrate (2 mL). After allowing the mixture to warm to 22 °C and stir for 30 min, it was washed with Et_2O (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with Et_2O. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether → 20% Et_2O/petroleum ether) to afford 19.7 mg of (*S*)-3-ethyl-3-phenethylcyclopentanone as a clear oil (0.091 mmol, 91%).

(*S*)-3-Butyl-3-methylcyclopentanone (Table 3.2, entry 1): IR (neat): 2953 (w), 2924 (s), 2852 (m), 2358 (m), 2337 (m), 1746 (m), 1459 (w), 1385 (w), 1219 (w), 1160 (w), 771 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30–2.26 (2H, m), 2.08 (1H, d, *J* = 18.0 Hz), 2.01 (1H, dd, *J* = 18.0, 0.8 Hz), 1.84–1.71 (2H, m), 1.41–1.35 (2H, m), 1.32–1.19 (4H, m), 1.04 (3H, s), 0.91 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.5, 52.5, 41.8, 39.7, 37.0, 35.5, 27.2, 25.3, 23.6, 14.3; HRMS (EI+): Calcd for $C_{10}H_{19}O$ $[M+H]^+$: 155.1436, Found: 155.1436; Specific Rotation: $[\alpha]_D^{20}$ –17 (*c* = 0.27, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.8:6.2 er shown; CDGTA column, 15 psi, 110 °C).

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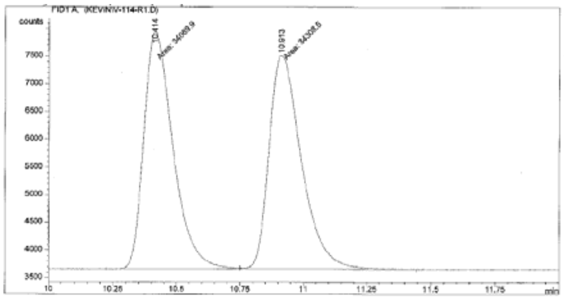
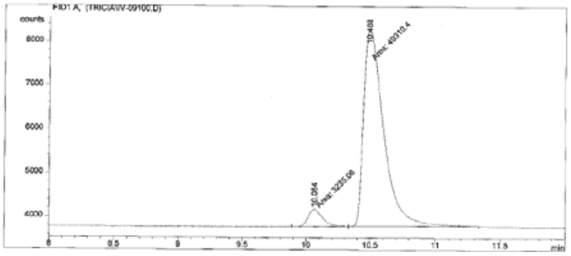
[61] Enones 3-phenethylcyclopentenone, 3-phenylcyclopentenone, and methyl 3-oxocyclopent-1-enecarboxylate are solids and are added to the reaction under N_2 after the addition of $Cu(OTf)_2$ and NHC–Ag (for ease of setting up reactions). All other substrates are oils and were added (neat) to the reaction after the addition of the aluminum reagent through a syringe. The order of addition has no effect on the outcome of the reaction.

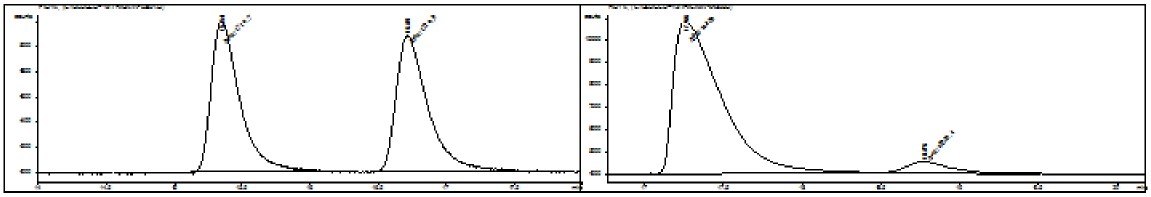




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	10.414	3.4089e4	4300.328	0.1321	49.840	1	10.064	3235.055	404.018	0.1335	6.156
2	10.913	3.4308e4	3860.631	0.1481	50.159	2	10.488	4.9314e4	4527.871	0.1815	93.843

(*S*)-3-Butyl-3-ethylcyclopentanone (Table 3.2, entry 2): IR (neat): 2958 (s), 2928 (s), 2860 (s), 2362 (m), 2341 (w), 1746 (s), 1498 (m), 1463 (m), 1379 (w), 1248 (w), 1172 (m), 1130 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.24 (2H, t, *J* = 8.4 Hz), 2.05 (2H, s), 1.77 (2H, t, *J* = 7.6 Hz), 1.41 (2H, dq, *J* = 7.2, 0.8 Hz), 1.38–1.16 (6H, m), 0.90 (3H, dt, *J* = 7.2, 0.8 Hz), 0.84 (3H, dt, *J* = 7.6, 1.2 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 220.7, 51.0, 42.7, 37.1, 36.8, 33.0, 30.1, 26.6, 23.6, 14.3, 8.8; HRMS (EI+): Calcd for $C_{11}H_{21}O$ [M+H]$^+$: 169.1592, Found: 169.1590; Specific Rotation: $[\alpha]_D^{20}$ +1.0 (*c* = 0.73, CHCl$_3$) for an enantiomerically enriched sample of 93:7 er.

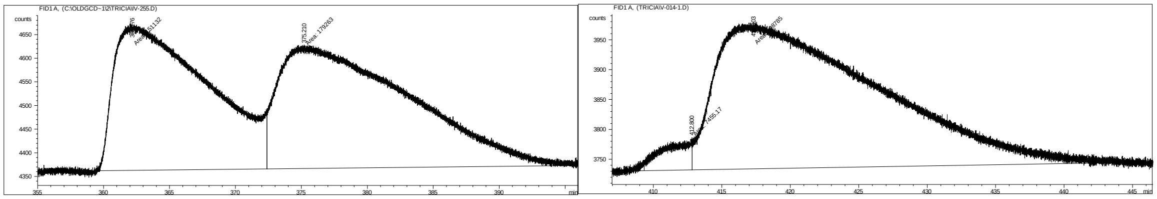
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.4:6.6 er shown; CDGTA column, 15 psi, 110 °C; the GC trace was taken with the *R* enantiomer of product prepared by using the *R* enantiomer of ligand).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	15.354	17115.7	1190.8	0.2395	49.673	1	17.266	143308.9	6831.2	0.3496	93.355
2	16.709	17340.9	1076.9	0.2684	50.327	2	18.776	10200.4	496.7	0.3423	6.645

(*S*)-3-Butyl-3-*i*-butylcyclopentanone (Table 3.2, entry 3): IR (neat): 2953 (s), 2932 (s), 2869 (m), 1737 (s), 1467 (w), 1404 (w), 1387 (w), 1362 (w), 1273 (w), 1168 (m), 1138 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.24–2.20 (2H, m), 2.11 (1H, d, *J* = 18.4 Hz), 2.06 (1H, d, *J* = 18.0 Hz), 1.90–1.83 (1H, m), 1.78–1.63 (2H, m), 1.41–1.35 (3H, m), 1.32–1.17 (5H, m), 0.94–0.89 (9H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 220.8, 52.4, 47.3, 42.9, 37.1, 36.4, 34.1, 26.8, 25.2, 24.9, 24.8, 23.6, 14.3; HRMS (EI+): Calcd for $C_{13}H_{25}O$ [M+H]$^+$: 197.1905, Found: 197.1908; Specific Rotation: $[\alpha]_D^{20}$ +21.9 (*c* = 0.573, CHCl$_3$) for an enantiomerically enriched sample of 96:4 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.4:3.6 er shown; CDGTA column, 15 psi, 70 °C; the GC trace was taken with the *R* enantiomer of product prepared by using the *R* enantiomer of ligand).

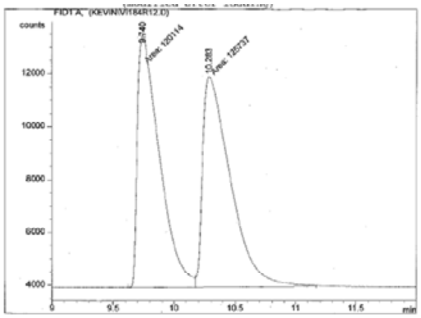


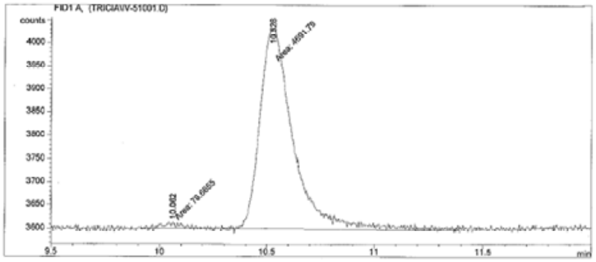
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	362.176	151131.6	312.6	8.0569	45.743	1	412.8	7455.2	55	2.2572	3.615
2	375.21	179262.6	262	11.4028	54.257	2	417.303	198785.3	245.6	13.4873	96.385

(*R*)-3-Ethyl-3-methylcyclopentanone (Table 3.2, entry 4): (This compound has been previously reported and spectra data matches those described.)[10a] ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.31–2.26 (2H, m), 2.07 (1H, d, *J* = 18.0 Hz), 2.00 (1H, dt, *J* = 18.0, 0.8 Hz), 1.82–1.67 (2H, m), 1.44 (2H, q, *J* = 8.0 Hz), 1.03 (3H, s), 0.90 (3H, t, *J* = 7.2 Hz); Specific Rotation: $[\alpha]_D^{20}$ –31.3 (*c* = 1.69, CHCl$_3$) for an enantiomerically enriched sample of 97.5:2.5 er *(This specific rotation was taken with the S enantiomer of product prepared by using the R enantiomer of ligand.)*

Stereochemistry Proof: Previous reported rotation: $[\alpha]_D^{20}$ +55.0 (*c* = 1.41, CHCl$_3$) for an enantiomerically enriched sample of 96.5:3.5 er of the *R* enantiomer.[10a]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (98.4:1.6 er shown; CDGTA column, 15 psi, 110 °C; the GC trace was taken with the *S* enantiomer of product prepared by using the *R* enantiomer of ligand)).

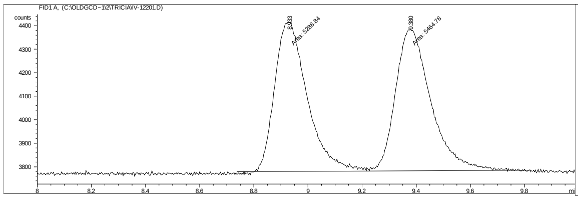


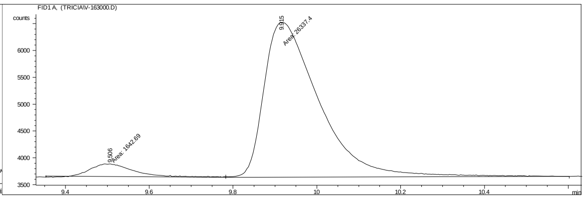


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	9.740	1.20114e5	9561.746	0.2094	48.8563	1	10.062	76.6655	14.3219	0.0892	1.607
2	10.288	1.15737e5	7964.659	0.2631	51.1436	2	10.528	4691.950	433.9506	0.1802	98.392

(*S*)-3-Isobutyl-3-methyl-cyclopentanone (Table 3.2, entry 5): IR (neat): 2954 (s), 2871 (m), 1741 (s), 1466 (w), 1405 (w), 1380 (w), 1366 (w), 1267 (w), 1174 (w), 1136 (w), 501 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23–2.25 (2H, m), 2.07 (2H, s), 1.82–1.70 (3H, m), 1.39 (1H, dd, *J* = 5.6, 1.6 Hz), 1.31 (1H, dd, *J* = 6.8, 1.6 Hz), 1.05 (3H, s), 0.94 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.5, 53.4, 51.4, 40.0, 36.7, 25.2, 25.2, 25.1, 24.7; HRMS (ESI+): Calcd for $C_{10}H_{19}O$ [M+H]$^+$: 155.1436, Found: 155.1437; Specific Rotation: $[\alpha]_D^{20}$ –36.7 (*c* = 1.95, $CHCl_3$) for a 95.5:4.5 er sample. *(This specific rotation was taken with the R enantiomer of product prepared by using the R enantiomer of ligand.)*

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.1:5.9 er sample below: CDGTA column, 15 psi, 110 °C; the GC trace was taken with the *R* enantiomer of product prepared by using the *R* enantiomer of ligand)).



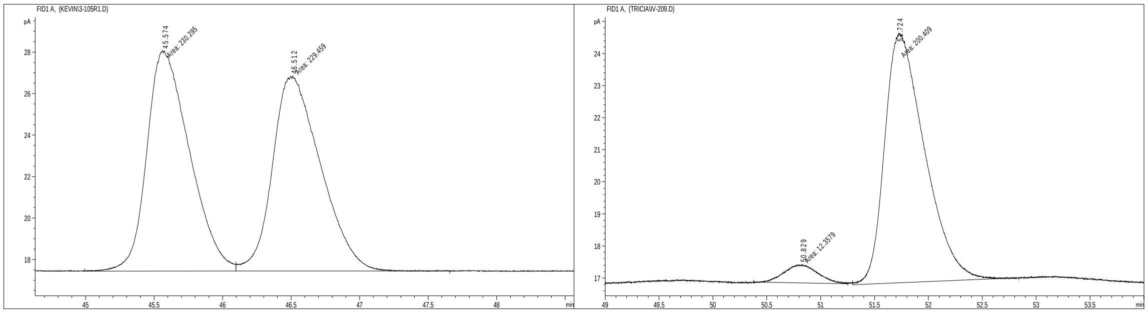


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	8.933	5288.8	636.3	0.1385	49.182	1	9.506	1642.7	234	0.117	5.871
2	9.38	5464.8	604.2	0.1508	50.818	2	9.915	26337.4	2891.1	0.1518	94.129

(*S*)-Methyl-1-ethyl-3-oxocyclopentanecarboxylate (Table 3.2, entry 6): (This compound has been previously reported and spectra data matches those described.)[14] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.68 (3H, s), 2.73 (1H, d, *J* = 18.4 Hz), 2.36 (1H, ddd, *J* = 8.4, 7.2, 1.2 Hz), 2.25 (2H, dd, *J* = 7.2, 7.2 Hz), 2.09 (1H, d, *J* = 18.4 Hz), 1.92–1.79 (2H, m), 1.68–1.59 (1H, m), 0.85 (3H, t, *J* = 7.6 Hz); Specific Rotation: $[\alpha]_D^{20}$ +43 (*c* = 0.89, $CHCl_3$) for an enantiomerically enriched sample of 94.5:5.5 er.

Stereochemistry Proof: Previously reported specific rotation: $[\alpha]_D^{20}$ –45.1 (*c* = 0.286, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er of the *R* enantiomer.[14]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.2:5.8 er shown; β-dex column, 15 psi, 90 °C).

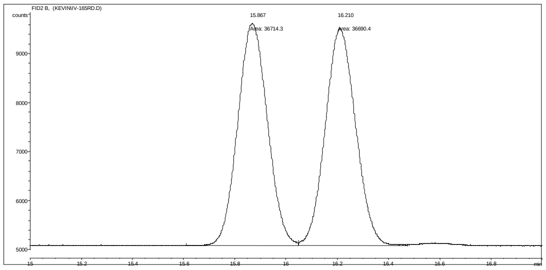


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	45.574	230.3	10.6	0.3607	50.091	1	50.829	12.4	5.8E-1	0.3531	5.808
2	46.512	229.5	9.4	0.4061	49.909	2	51.724	200.4	7.8	0.4288	94.192

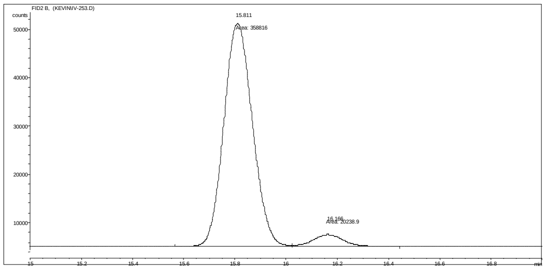
(*S*)-Methyl-1-methyl-3-oxocyclohexanecarboxylate (Table 3.2, entry 7): IR (neat): 2952 (m), 2877 (w), 1734 (s), 1462 (m), 1318 (w), 1208 (m), 1168 (m), 1139 (m), 1110 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.61 (3H, s), 2.66 (1H, dt, *J* = 14.8, 1.6 Hz), 2.31–2.24 (1H, m), 2.21–2.13 (1H, m), 2.11–2.02 (3H, m), 1.89–1.79 (1H, m), 1.73–1.60 (2H, m), 1.19 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.3, 176.6, 52.3, 50.0, 46.7, 40.3,

34.7, 24.8, 22.2; HRMS (EI+): Calcd for $C_9H_{14}O_3$: 170.0943, Found: 170.0947; Specific Rotation: $[\alpha]_D^{20}$ –17.7 (*c* = 1.66, $CHCl_3$) for an enantiomerically enriched sample of 89.5:10.5 er. *(This specific rotation was taken with the R enantiomer of product prepared by using the R enantiomer of ligand.)*

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.7:5.3 er shown; β-dex column, 15 psi, 140 °C; the GC trace was taken with the *R* enantiomer of product prepared by using the *R* enantiomer of ligand).



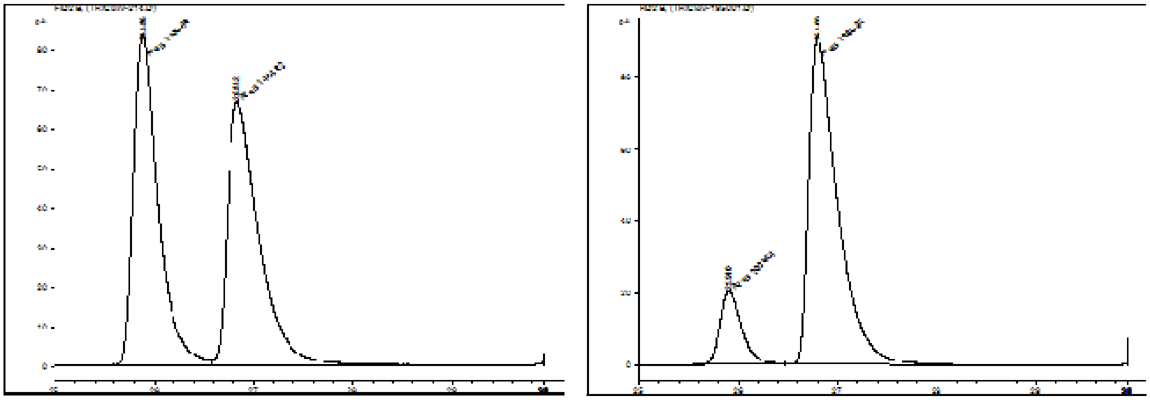
#	Time	Area	Height	Width	Area (%)
1	15.867	36714.3	4530.7	0.1351	50.035
2	16.21	36690.4	4424.2	0.1382	49.964



#	Time	Area	Height	Width	Area (%)
1	15.811	358815.7	46138.6	0.1296	94.734
2	16.166	20238.9	2447.1	0.1378	5.265

(*S*)-3-Methyl-3-phenylcyclopentanone (Table 3.2, entry 8, ent-3.12): IR (neat): 3025 (w), 2961 (m), 2920 (m), 2873 (m), 1737 (s), 1501 (m), 1451 (m), 1409 (w), 1315 (w), 1277 (w), 1163 (m), 1079 (w), 1033 (w), 762 (w), 700 (m), 666 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.21 (5H, m), 2.66 (1H, d, *J* = 17.6 Hz), 2.48 (1H, dt, *J* = 17.6, 1.2 Hz), 2.44–2.35 (2H, m), 2.32–2.26 (2H, m), 1.39 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.8, 148.7, 128.8, 126.5, 125.7, 52.5, 44.0, 36.4, 36.0, 29.6; HRMS (EI+): Calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, Found: 175.1116; Specific Rotation: $[\alpha]_D^{20}$ –22 (*c* = 0.57, $CHCl_3$) for an enantiomerically enriched sample of 86:14 er.

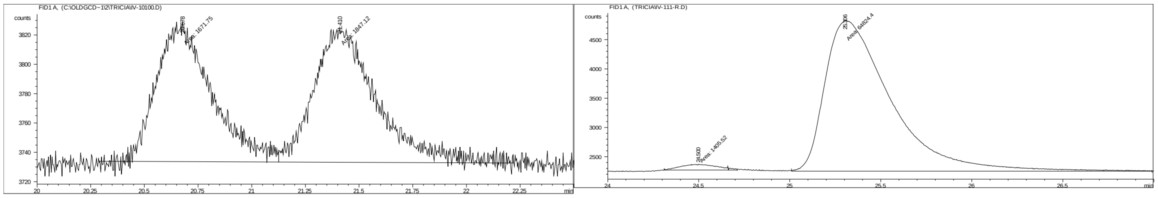
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (86.4:13.6 er shown; CDGTA column, 15 psi, 120 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	25.886	1409.5	83.6	0.2809	49.381	1	25.91	292.7	20.2	0.2416	13.593
2	26.832	1444.8	66.4	0.3628	50.619	2	26.8	1860.3	91.7	0.3379	86.407

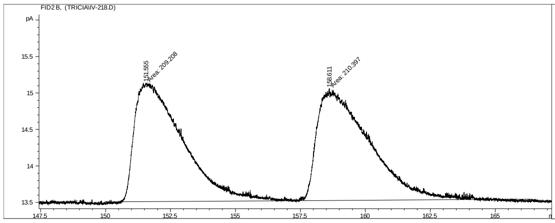
(*S*)-3-Ethyl-3-phenylcyclopentanone (Table 3.2, entry 9): IR (neat): 3063 (w), 3029 (w), 2970 (m), 2923 (m), 2877 (w), 1742 (s), 1602 (w), 1497 (w), 1442 (w), 1404 (w), 1374 (w), 1341 (w), 1290 (w), 1253 (w), 1159 (m), 758 (m), 700 (m), 670 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35–7.31 (2H, m), 7.23–7.21 (3H, m), 2.66 (1H, d, *J* = 18.0 Hz), 2.51 (1H, d, *J* = 17.6 Hz), 2.39–2.22 (4H, m), 1.76 (1H, dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz), 1.68 (1H, dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz), 0.66 (3H, dt, *J* = 7.2, 0.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 218.8, 146.1, 128.6, 126.7, 126.5, 50.5, 48.2, 36.6, 34.6, 34.0, 9.4; HRMS (ESI+): Calcd for $C_{13}H_{17}O$ [M+H]$^+$**:** 189.1279, Found: 189.12760; Specific Rotation: $[\alpha]_D^{20}$ +13.7 (*c* = 1.09, CHCl$_3$) for a 98:2 er sample.

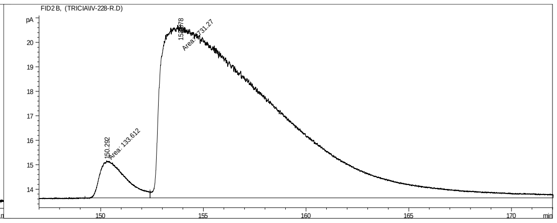
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97.9:2.1 sample below; CDGTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	20.678	1671.8	96.3	0.2894	47.508	1	24.5	1405.5	104.9	0.2233	2.122
2	21.41	1847.1	92.1	0.3343	52.492	2	25.306	64824.4	2574.4	0.4197	97.878

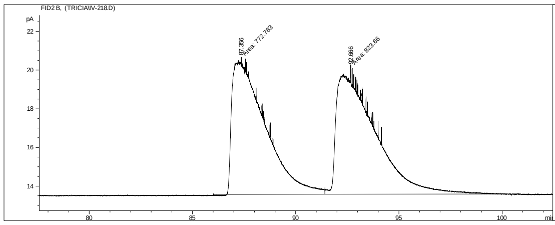
(*S*)-3-Methyl-3-phenethylcyclopentanone (Table 3.2, entry 10): IR (neat): 3035 (w), 2949 (m), 2928 (m), 2873 (w), 1742 (s), 1653 (w), 1602 (w), 1561 (w), 1535 (w), 1493 (m), 1459 (m), 1404 (w), 1379 (w), 1307 (w), 1257 (w), 1176 (m), 1163 (m), 1113 (w), 1024 (w), 771 (w), 750 (m), 700 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.26 (2H, m), 7.21–7.17 (3H, m), 2.71–2.55 (2H, m), 2.35–2.30 (2H, m), 2.15 (1H, d, *J* = 18.0 Hz), 2.08 (1H, dd, *J* = 18.0, 0.4 Hz), 1.90–1.83 (2H, m), 1.74 (2H, dd, *J* = 9.2, 8.0 Hz), 1.15 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.8, 142.6, 128.7, 128.5, 126.1, 52.4, 44.2, 29.9, 37.0, 35.5, 31.6, 25.1; HRMS (EI+): Calcd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436, Found: 203.1433; Specific Rotation: $[\alpha]_D^{20}$ –41 (*c* = 0.72, $CHCl_3$) for an enantiomerically enriched sample of 94.5:5.5 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.3:4.7 er shown; CDGTA column, 15 psi, 120 °C).

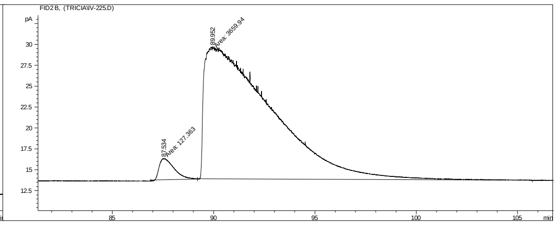




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	151.555	209.2	1.6	2.1469	49.858	1	150.292	133.6	1.5	1.4729	4.664
2	158.611	210.4	1.5	2.2828	50.142	2	153.878	2731.3	7.1	6.4164	95.336

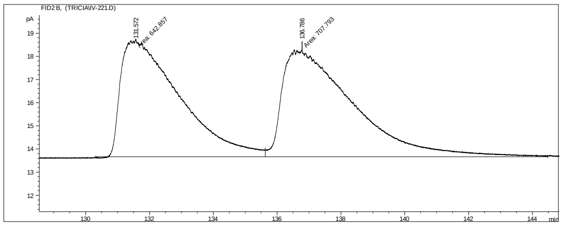
(*S*)-3-Ethyl-3-phenethylcyclopentanone (Table 3.2, entry 11): IR (neat): 3393 (w), 3063 (w), 3028 (m), 2953 (s), 2928 (s), 2877 (m), 2873 (m), 1737 (s), 1602 (w), 1497 (m), 1450 (m), 1408 (m), 1383 (w), 1324 (w), 1286 (w), 1248 (m), 1155 (m), 1117 (w), 1075 (w), 1033 (w), 741 (m), 699 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.25 (2H, m), 7.21–7.17 (3H, m), 2.63–2.48 (2H, m), 2.29 (2H, t, *J* = 8.0 Hz), 2.13 (2H, s), 1.86 (2H, dt, *J* = 8.0, 2.0 Hz), 1.70 (2H, dt, *J* = 6.8, 1.6 Hz), 1.53 (2H, q, *J* = 7.6 Hz), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.0, 142.6, 128.7, 128.4, 126.1, 50.9, 42.9, 39.7, 36.7, 33.1, 31.1, 29.9, 8.8; HRMS (EI+): Calcd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1592, Found: 217.1591; Specific Rotation: $[\alpha]_D^{20}$ +3.1 (*c* = 1.3, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.6:3.4 er shown; CDGTA column, 15 psi, 140 °C).

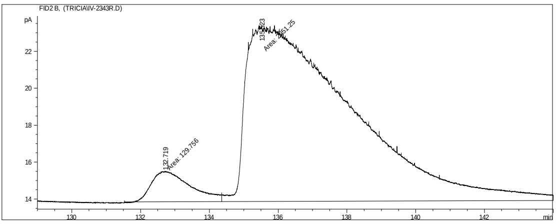




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	87.356	772.8	7.1	1.8097	48.407	1	87.534	127.4	2.6	0.8296	3.363
2	92.666	823.7	6.6	2.0657	51.593	2	89.952	3659.9	15.8	3.8564	96.637

(*S*)-3-Isobutyl-3-phenethylcyclopentanone (Table 3.2, entry 12): IR (neat): 3079 (w), 3058 (w), 2957 (s), 2923 (s), 2868 (m), 1742 (w), 1708 (w), 1640 (w), 1594 (m), 1497 (m), 1455 (m), 1408 (w), 1383 (w), 1366 (w), 1168 (m), 1075 (w), 741 (m), 695 (m), 665 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31–7.26 (2H, m), 7.21–7.16 (3H, m), 2.64–2.51 (2H, m), 2.27 (2H, t, *J* = 7.6 Hz), 2.19 (1H, d, *J* = 18.0 Hz), 2.14 (1H, d, *J* = 18.0 Hz), 1.99–1.91 (1H, m), 1.88–1.74 (2H, m), 1.71 (2H, dd, *J* = 10.0, 8.8 Hz), 1.50 (1H, dd, *J* = 14.4, 5.2 Hz), 1.39 (1H, dd, *J* = 14.4, 6.4 Hz), 0.99 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz)**:** δ 220.0, 142.5, 128.7, 128.4, 126.2, 52.3, 47.0, 43.1, 39.7, 36.4, 34.2, 31.2, 25.3, 25.0, 24.9; HRMS (EI+): Calcd for $C_{17}H_{25}O$ [M+H]$^+$: 245.1905, Found: 245.1903; Specific Rotation: $[\alpha]_D^{20}$ +18.6 (*c* = 1.45, CHCl$_3$) for an enantiomerically enriched sample of 96:4 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94.1:5.9 er shown; CDGTA column, 15 psi, 140 °C).



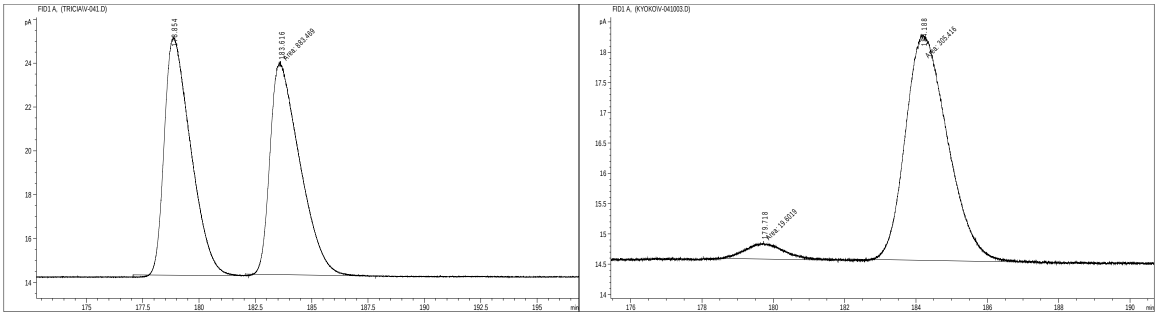


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%

1	131.572	642.9	5.1	2.1098	47.596	1	132.719	129.8	1.6	1.3137	5.949
2	136.786	707.8	5	2.359	52.404	2	135.523	2051.2	9.6	3.5775	94.051

(*S*)-3-Methyl-3-(non-1-ynyl)cyclopentanone (Table 3.2, entry 13): IR (neat): 2953 (s), 2928 (s), 2857 (m), 2214 (w), 1716 (s), 1671 (s), 1590 (m), 1455 (w), 1428 (w), 1346 (m), 1324 (m), 1299 (m), 1237 (m), 1133 (m), 887 (w) cm $^{-1}$; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.44 (1H, dt, *J* = 13.6, 2.0 Hz), 2.37–2.33 (1H, m), 2.22 (1H, dd, *J* = 13.6, 1.2 Hz), 2.21–2.06 (4H, m), 1.96–1.85 (2H, m), 1.63–1.59 (1H, m), 1.45–1.19 (8H, m), 1.29 (3H, s), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 210.0, 84.0, 83.9, 54.8, 40.8, 38.2, 36.4, 31.5, 29.9, 29.1, 28.6, 23.1, 22.8, 18.8, 14.3; HRMS (EI+): Calcd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1905, Found: 221.1895; Specific Rotation: $[\alpha]_D^{22}$ –1.4 (*c* = 1.4, CHCl$_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

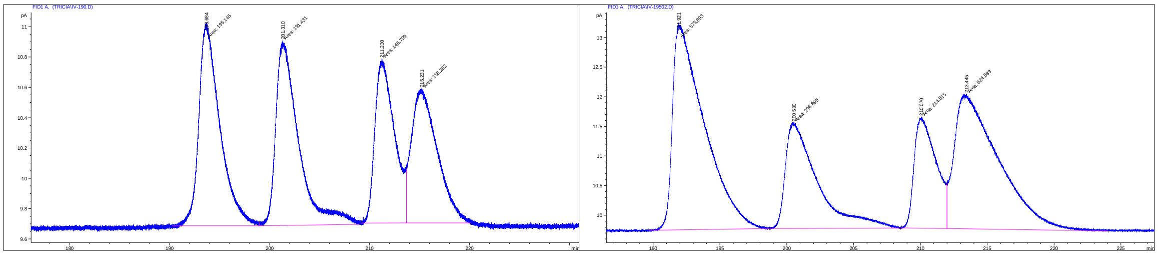
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94:6 er sample below: *β*-dex column, 15 psi, 120 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	178.854	880.3	10.9	1.3496	49.909	1	179.718	19.6	3E-1	1.1018	6.031
2	183.616	883.5	9.7	1.5146	50.091	2	184.188	305.4	3.7	1.3663	93.969

(3*R*)-3-Ethyl-3-methyl-2-((*Z*)-pent-2-en-1-yl)cyclopentanone (3.44 and 3.45): (This compound is characterized as a 1:1 mixture of diastereomers.) ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.48–5.33 (5H, m), 2.32–2.19 (4H, m), 2.17–1.91 (6H, m), 1.71–1.61 (3H, m), 1.54–1.22 (3H, m), 1.29–1.22 (2H, m), 1.11 (3H, s), 0.98–0.81 (18H m); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 220.4, 132.4, 132.3, 127.7, 127.6, 61.9, 59.5, 42.9, 42.4, 35.0, 35.0, 34.0, 32.1, 31.1, 26.4, 25.9, 22.8, 22.4, 20.7, 19.7, 14.3, 8.8, 8.6; HRMS (ESI+): Calcd for $C_{13}H_{23}O$ $[M+H]^+$: 195.17489, Found: 195.17489**.**

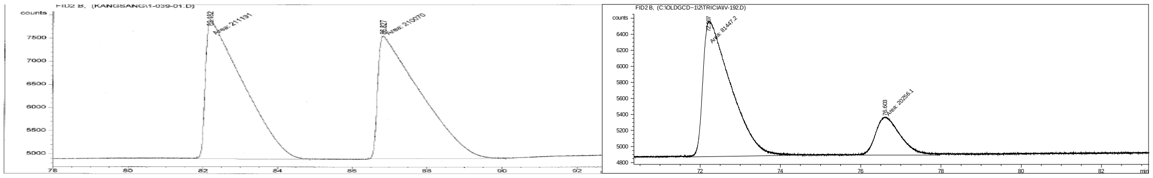
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material [66:34 er and 71:29 er shown below (1:1.3 dr): CDBDA column, 15 psi, 80 °C].



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	193.684	195.1	1.3	2.431	28.218	1	191.921	573.9	3.5	2.7362	35.648
2	201.31	191.4	1.2	2.6165	27.681	2	200.53	296.9	1.8	2.7712	18.442
3	211.23	146.7	1.1	2.2603	21.214	3	210.07	214.5	1.9	1.9083	13.325
4	215.231	158.3	8.8E-1	2.9815	22.887	4	213.445	524.6	2.3	3.8445	32.585

(*R*)-3-Ethyl-3-methylcyclohexanone (Table 3.6, entry 1): (This compound has been previously reported and spectra data matches those described.)[55] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (2H, dd, *J* = 6.8, 6.8 Hz), 2.18 (1H, d, *J* = 13.6 Hz), 2.09 (1H, d, *J* = 13.6 Hz), 1.90–1.83 (2H, m), 1.66–1.50 (2H, m), 1.35–1.29 (2H, m), 0.90 (3H, s), 0.84 (3H, t, *J* = 7.6 Hz).

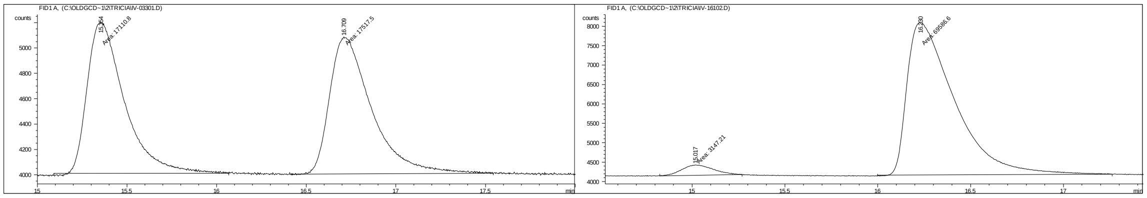
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (80.1:19.9 shown below; β-dex column, 80 °C, 15 psi).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	82.182	2.11191e5	3035.643	1.1595	50.13298	1	72.207	72.207	1693.6	0.8015	80.083
2	86.827	2.1007e5	2667.8967	1.3123	49.86702	2	76.603	20256.1	474.1	0.7121	19.917

(*S*)-3-Isobutyl-3-methylcyclohexanone (Table 3.6, entry 2): IR (neat): 2949 (s), 2873 (s), 2848 (m), 1716 (s), 1463 (w), 1421 (w), 1379 (w), 1358 (w), 1311 (w), 1290 (m), 1222 (m), 1176 (w), 1083 (w), 775 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.28–2.25 (2H, m), 2.21 (1H, d, *J* = 13.6 Hz), 2.10 (1H, dt, *J* = 13.6, 1.6 Hz), 1.94–1.79 (2H, m), 1.74–1.62 (2H, m), 1.59–1.52 (1H, m), 1.21 (2H, t, *J* = 4.8 Hz), 0.94 (3H, s), 0.93 (3H, d, *J* = 0.8 Hz), 0.91 (3H, d, *J* = 1.2 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 212.7, 54.5, 51.2, 41.3, 39.6, 36.7, 25.7, 25.6, 25.5, 24.1, 22.4; HRMS (EI+): Calcd for $C_{11}H_{21}O$ [M+H]$^+$: 169.1592, Found: 169.1596; Specific Rotation: $[\alpha]_D^{20}$ −1.1 (*c* = 0.76, CHCl$_3$) for an enantiomerically enriched sample of 95.5:4.5 er.

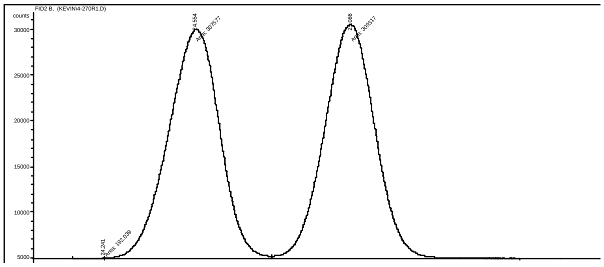
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.7:4.3 er shown; CDGTA column, 15 psi, 110 °C).

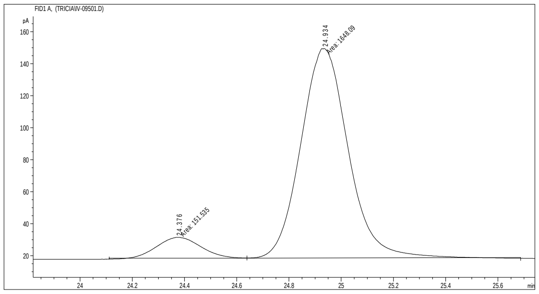


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	15.354	17110.8	1192.6	0.2391	49.413	1	15.017	3147.2	268	0.1957	4.327
2	16.709	17517.5	1081.6	0.2699	50.587	2	16.23	69586.6	3937.7	0.2945	95.673

(*S*)-Methyl-1-ethyl-3-oxocyclohexanecarboxylate (Table 3.6, entry 3): IR (neat): 2953 (m), 2880 (w), 1734 (s), 1572 (w), 1543 (w), 1462 (m), 1373 (w), 1240 (m), 1203 (m), 1159 (m), 1139 (m), 1029 (m), 1001 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.67 (3H, s), 2.77 (1H, dt, *J* = 14.8, 1.6 Hz,), 2.38–2.32 (1H, m), 2.26–2.18 (1H, m), 2.13–2.10 (2H, m), 1.95–1.85 (1H, m), 1.80–1.61 (3H, m), 1.53 (1H, dq, *J* = 15.2, 7.6 Hz) 0.81 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 209.4, 176.0, 52.2, 51.2, 47.6, 40.7, 33.4, 31.8, 22.2, 8.8; HRMS (EI+): Calcd for $C_{10}H_{16}O_3$ [M+H]$^+$: 184.1100, Found: 184.1097; Specific Rotation: $[\alpha]_D^{20}$ +19 (*c* = 1.1, CHCl$_3$) for an enantiomerically enriched sample of 91.5:8.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (91.6:8.4 shown; β-dex column, 15 psi, 140 °C).





#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	24.554	307577.2	25085.4	0.2044	49.885	1	24.376	151.5	13.1	0.1934	8.420
2	25.086	309317.2	25659.1	0.2009	50.114	2	24.934	1648.1	131	0.2097	91.580

(*S*)-3-Methyl-3-(pent-4-enyl)cyclohexanone (Table 3.6, entry 4): IR (neat): 3076 (w), 2933 (m), 2874 (w), 1710 (s), 1640 (w), 1459 (m), 1425 (m), 1380 (w), 1352 (m), 1312 (m), 1288 (m), 1148 (w), 1076 (w), 1047 (w), 993 (w), 909 (w), 776 (m), 737 (w), 641 (w), 552 (w), 508 (w), 477 (m), 425 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (1H, dddd, *J* = 13.2, 10.4, 6.8, 6.8 Hz), 4.99 (1H, dq, *J* = 17.2, 1.6 Hz), 4.94 (1H, dddd, *J* = 10.0, 2.0, 1.2, 1.2 Hz), 2.27 (2H, t, *J* = 6.4 Hz), 2.18 (1H, d, *J* = 13.6 Hz), 2.10 (1H, dd, *J* = 13.2, 0.4 Hz), 2.02 (2H, q, *J* = 7.2 Hz), 1.85 (2H, quintet, *J* = 6.0 Hz), 1.66–1.50 (2H, m), 1.41–1.20 (4H, m), 0.91 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.6, 138.9, 114.9, 54.0, 41.3, 38.8, 36.1, 34.5, 29.9, 25.3, 23.0, 22.4; HRMS (EI+): Calcd for $C_{12}H_{21}O$ $[M+H]^+$: 181.1592, Found: 181.1599; Specific Rotation: $[\alpha]_D^{20}$ –0.385 (*c* = 1.13, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er

Stereochemistry Proof: Previously reported specific rotation: $[\alpha]_D^{20}$ –1.6 (*c* = 1.7, $CHCl_3$) for a 96.5:3.5 er of the *S* enantiomer.[62]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.2:4.8 er shown; CDGTA column, 15 psi, 110 °C).

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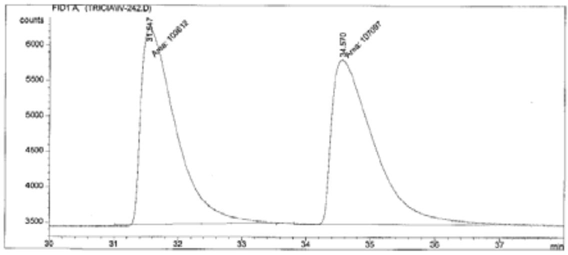
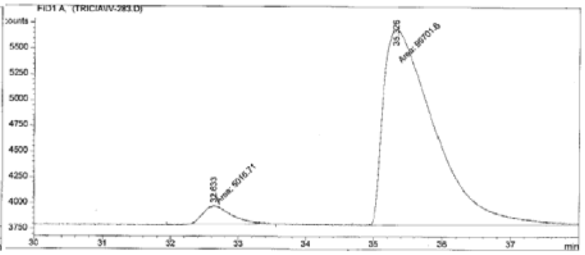
(62) "Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers," d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378.



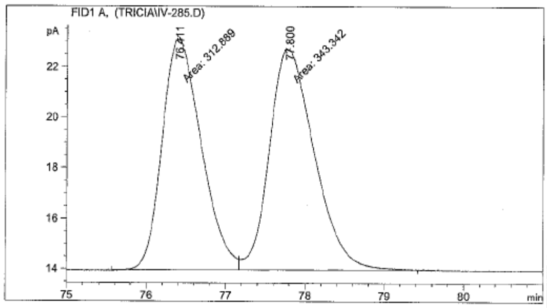


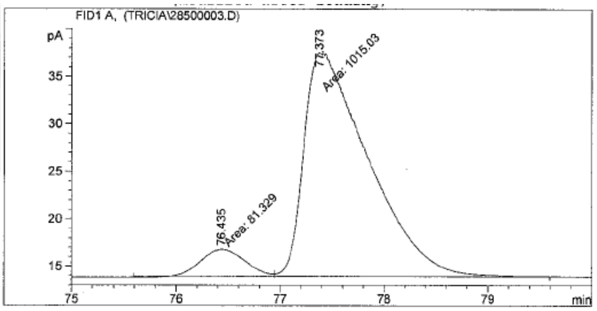
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	31.547	1.03612e5	2785.032	0.6201	49.17305	1	32.633	5016.70508	182.785	0.4575	4.79067
2	34.570	1.07097e5	2334.463	0.7646	50.82695	2	35.326	9.97016e4	1904.69	0.8724	95.20933

(*S*)-3-Butyl-3-methylcycloheptanone (Table 3.6, entry 5): (This compound has been previously reported and spectra data matches those described.)[55] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (1H, d, *J* = 12.4 Hz), 2.41–2.35 (3H, m), 1.77–1.57 (5H, m), 1.52–1.47 (1H, m), 1.23–1.17 (6H, m), 0.90–0.86 (6H, m); Specific Rotation: $[\alpha]_D^{20}$ –5.5 (*c* = 1.3, $CHCl_3$) for a 92.5:7.5 er sample.

Stereochemistry Proof: Previously reported optical rotation: $[\alpha]_D^{20}$ +10.0 (*c* = 1.00, $CHCl_3$) for a 88.5:11.5 er of the *R* enantiomer.[55]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (92.6:7.4 er shown; β-dex column, 15 psi, 90 °C).



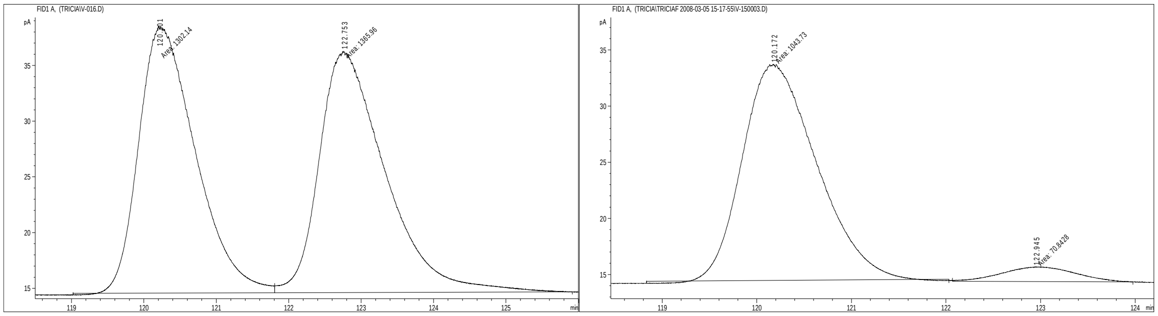


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	76.411	312.88910	9.22212	0.5655	47.22212	1	76.435	81.32899	2.86775	0.4727	7.41807
2	77.800	343.34183	8.77507	0.6521	52.32028	2	77.373	92.58193	23.60205	0.7168	92.58193

(*S*)-3-Butyl-3-ethylcycloheptanone (Table 3.6, entry 6): (This compound has been previously reported and spectra data matches those described.)[55] ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.43 (2H, s), 2.39 (2H, t, *J* = 6.2 Hz), 1.77–1.72 (2H, m), 1.64–1.60 (2H, m), 1.57–1.53 (2H, m), 1.34–1.13 (8H, m), 0.88 (3H, t, *J* = 7.0 Hz), 0.79 (3H, t, *J* = 7.6 Hz); Specific Rotation: $[\alpha]_D^{20}$ +2.9 (*c* = 1.0, CHCl$_3$) for a 89.5:10.5 sample.

Stereochemistry Proof: Previously reported specific rotation: $[\alpha]_D^{20}$ +5.98 (*c* = 1.00, CHCl$_3$) for a 88:12 er sample of the *S* enantiomer.[55]

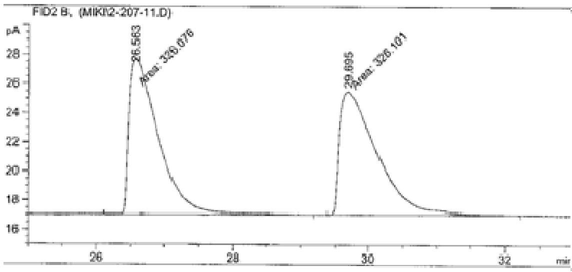
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.6:6.4 shown; β-dex column, 15 psi, 110 °C; the GC trace was taken with the *R* enantiomer of product prepared by using the *R* enantiomer of ligand).

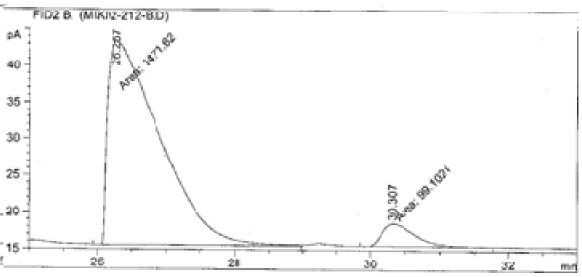


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	120.201	1302.1	24	0.9054	48.804	1	120.172	1043.7	19.2	0.9038	93.644
2	122.753	1366	21.7	1.0512	51.196	2	122.945	70.8	1.3	0.9042	6.356

(*R*)-4-Ethyl-4-propyltetrahydro-2*H*-pyran-2-one (Table 3.8, entry 1): IR (neat): 2960 (m), 2931 (m), 2873 (m), 1736 (s), 1462 (m), 1384 (m), 1256 (m), 1227 (m), 1202 (w), 1174 (w), 1040 (w), 1070 (m), 1024 (w), 820 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.29–4.27 (2H, m), 2.31 (2H, s), 1.68 (2H, t, *J* = 6.0 Hz), 1.40 (2H, q, *J* = 7.6 Hz), 1.34–1.20 (4H, m), 0.92 (3H, t, *J* = 7.0 Hz), 0.84 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.5, 66.1, 40.9, 40.7, 35.3, 32.6, 31.1, 16.4, 14.6, 7.6; HRMS (EI+): Calcd for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1385, Found: 171.1383; Specific Rotation: $[\alpha]_D^{20}$ –2.64 (*c* =0.83, CHCl$_3$) for an enantiomerically enriched sample of 93.5:6.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.7:6.3 er shown; CDGTA column, 15 psi, 140 °C).

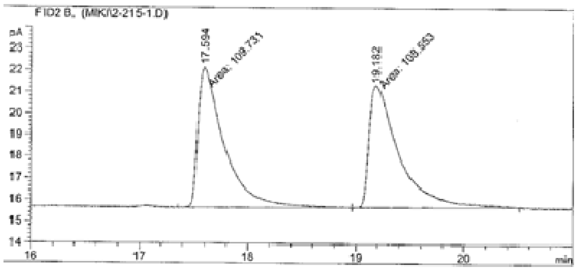


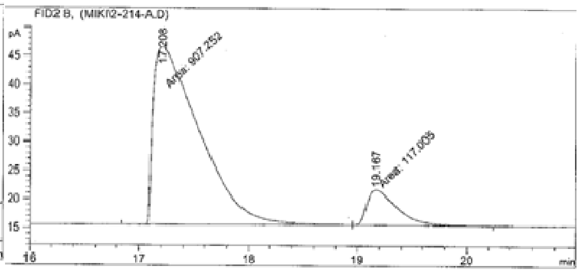


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	26.563	326.1	10.6473	0.5104	49.998	1	26.257	1471.6	27.9464	0.8776	93.691
2	29.695	326.1	8.4699	0.6417	50.001	2	30.307	99.1021	3.0466	0.5421	6.309

(*R*)-Methyl-4-propyl-tetrahydro-2*H*-pyran-2-one (Table 3.8, entry 2): IR (neat): 2958 (m), 2932 (m), 2873 (m), 1738 (s), 1459 (w), 1404 (w), 1385 (w), 1258 (m), 1229 (m), 1171 (w), 1141 (w), 1071 (m), 993 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.34–4.32 (2H, m), 2.36 (1H, d, *J* = 16.4 Hz), 2.27 (1H, d, *J* = 16.4 Hz), 1.75 (1H, dt, *J* = 14.4, 6.4 Hz), 1.62 (1H, dt, *J* = 14.4, 5.6 Hz), 1.32–1.28 (4H, m), 1.04 (3H, s), 0.94–0.91 (3H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.9, 66.3, 44.5, 43.0, 34.4, 32.6, 26.0, 16.7, 14.6; HRMS (EI+): Calcd for $C_9H_{17}O_2$ $[M+H]^+$: 157.1229, Found: 157.1233; Specific Rotation: $[\alpha]_D^{20}$ –2.20 (*c* = 0.27, CHCl$_3$) for an enantiomerically enriched sample of 88.5:11.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material 88.6:11.4 er; CDGTA column, 15 psi, 140 °C).

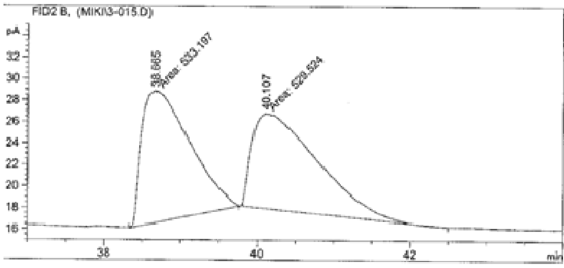


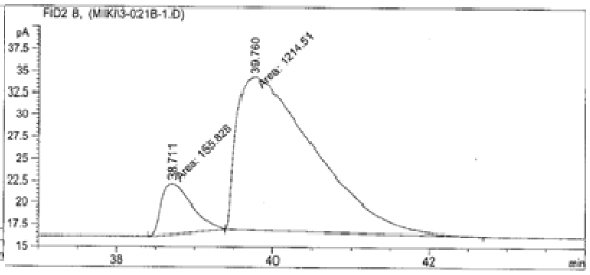


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	17.594	109.73	6.509	0.2810	50.270	1	17.208	907.25	31.097	0.4862	88.577
2	19.182	108.55	5.656	0.3199	49.730	2	19.167	117.01	6.116	0.3188	11.423

(*S*)-4-Isobutyl-4-propyl-tetrahydro-2*H*-pyran-2-one (Table 3.8, entry 3): IR (neat): 2956 (m), 2931 (m), 2871 (m), 1741 (s), 1467 (m), 1404 (w), 1386 (w), 1366 (w), 1259 (m), 1228 (m), 1120 (m), 1167 (w), 1074 (m), 974 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31–4.28 (2H, m), 2.35 (2H, d, J = 1.6 Hz), 1.71 (2H, t, J = 6.0 Hz), 1.72–1.63 (1H, m), 1.40–1.22 (6H, m), 0.95 (6H, d, J = 6.4 Hz), 0.92 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 66.1, 47.7, 42.1, 41.2, 36.0, 33.6, 25.2, 25.1, 23.9, 16.6, 14.6; HRMS (EI+): Calcd for $C_{12}H_{26}O_2$ $(M+H)^+$: 199.1698, Found: 199.1696; Specific Rotation: $[\alpha]_D^{20}$ –2.91 (c = 0.41, $CHCl_3$) for an enantiomerically enriched sample of 88.5:11.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (88.6:11.4 er shown; CDGTA column, 15 psi, 140 °C).

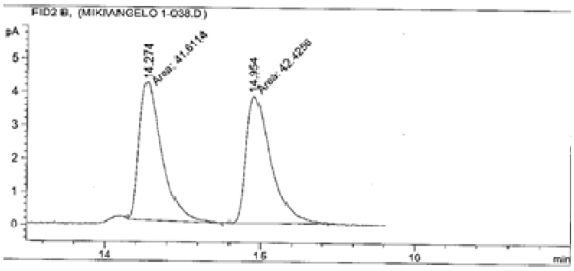


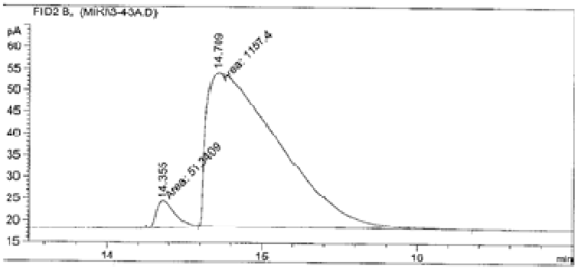


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	38.665	533.20	12.379	0.7179	50.173	1	38.711	155.83	5.8322	0.4453	11.371
2	40.107	529.52	8.9036	0.9912	49.827	2	39.760	1214.51	17.5193	1.1554	88.629

(*S*)-4-Ethyl-4-methyl-tetrahydro-2*H*-pyran-2-one (Table 3.8, entry 4): IR (neat): 2964 (m), 2881 (m), 1733 (s), 1485 (w), 1461 (m), 1403 (m), 1385 (m), 1311 (w), 1256 (m), 1223 (m), 1174 (m), 1141 (m), 1061 (m), 1041 (w), 1005 (w), 990 (w), 922 (w), 819 (w), 789 (w), 655 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34–4.31 (2H, m), 2.34 (1H, d, J = 16.4 Hz), 2.27 (1H, dd, J = 16.4, 1.2 Hz), 1.77–1.70 (1H, m), 1.61 (1H, dddd, J = 14.4, 6.0, 5.2, 0.8 Hz), 1.39 (2H, q, J = 7.4 Hz), 1.03 (3H, s), 0.88 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 66.3, 42.6, 34.4, 33.9, 32.6, 25.4, 7.8; HRMS (EI+): Calcd for $C_8H_{15}O_2$ $[M+H]^+$: 143.1072, Found: 143.1068; Specific Rotation: $[\alpha]_D^{20}$ –2.79 (c = 0.93, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.8:4.2 er shown; CDGTA column, 15 psi, 140 °C).

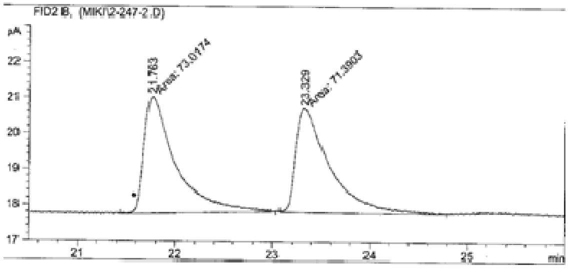


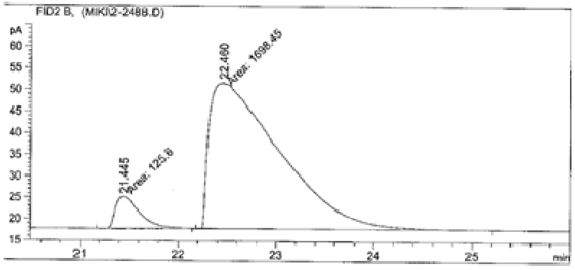


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	14.247	41.61	4.1316	0.1679	49.515	1	14.355	51.34	6.158	0.1390	4.247
2	14.954	42.43	3.8185	0.1852	50.484	2	14.709	1157.40	35.599	0.5429	95.753

(*S*)-4-Isobutyl-4-methyl-tetrahydro-2*H*-pyran-2-one (Table 3.8, entry 5): IR (neat): 2955 (m), 2928 (m), 2871 (m), 1737 (s), 1465 (w), 1404 (w), 1386 (w), 1366 (w), 1312 (w), 1256 (m), 1228 (m), 1171 (m), 1070 (m), 994 (w), 975 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.36–4.33 (2H, m), 2.37 (1H, d, *J* = 16.8 Hz), 2.30 (1H, dd, *J* = 16.8, 0.8 Hz), 1.81–1.72 (1H, m), 1.72–1.62 (2H, m), 1.29 (2H, d, *J* = 5.6 Hz), 1.08 (3H, s), 0.95 (6H, dd, *J* = 6.8, 0.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.8, 66.3, 51.0, 43.7, 35.0, 33.1, 26.0, 25.2, 25.1, 24.1; HRMS (EI+): Calcd for $C_{10}H_{19}O_2$ [M+H]$^+$: 171.1385, Found: 171.1393; Specific Rotation: $[\alpha]_D^{20}$ –1.92 (*c* = 0.31, CHCl$_3$) for an enantiomerically enriched sample of 93:7 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.1:6.9 er shown; CDGTA column, 15 psi, 140 °C).



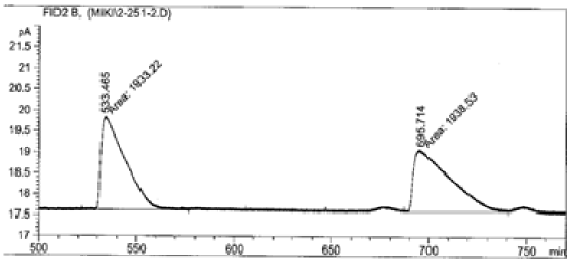


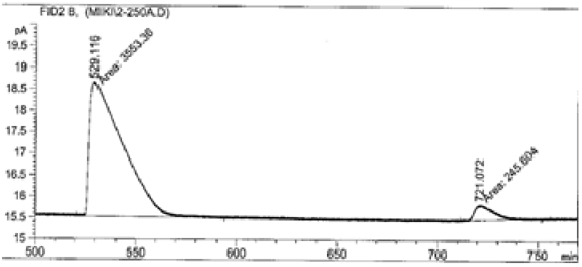
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	21.763	73.017	3.2742	0.3605	50.563	1	21.445	125.60	7.4526	0.2809	6.886

2	23.329	71.390	2.9108	0.4000	49.437	2	22.460	1698.45	33.921	0.8345	93.114

(*R*)-Ethyl-4-phenethyl-tetrahydro-4*H*-pyran-2-one (Table 3.8, entry 6): IR (neat): 2964 (m), 2931 (m), 2861 (w), 1737 (s), 1603 (w), 1495 (w), 1455 (w), 1404 (w), 1386 (w), 1257 (m), 1229 (m), 1184 (w), 1110 (w), 1071 (m), 1030 (w), 755 (m), 700 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (2H, m), 7.22–7.16 (3H, m), 4.34–4.31 (2H, m), 2.57–2.53 (2H, m), 2.40 (2H, s), 1.77 (2H, t, *J* = 6.0 Hz), 1.69–1.64 (2H, m), 1.52 (2H, q, *J* = 7.6 Hz), 0.93 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 141.7, 128.5, 128.2, 126.0, 66.0, 40.9, 40.5, 35.5, 32.7, 30.9, 29.7, 7.6; HRMS (EI+): Calcd for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1542, Found: 233.1530; Specific Rotation: $[\alpha]_D^{20}$ –14.7 (*c* = 0.900, $CHCl_3$) for an enantiomerically enriched sample of 93.5:6.5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.5:6.5 er shown; CDGTA column, 15 psi, 140 °C).



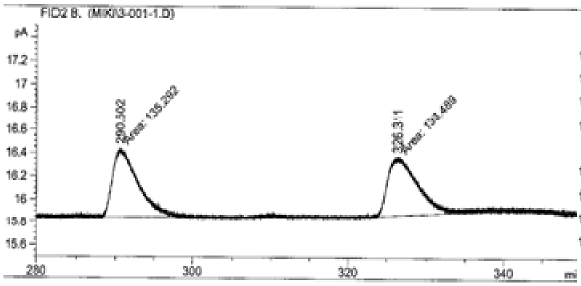


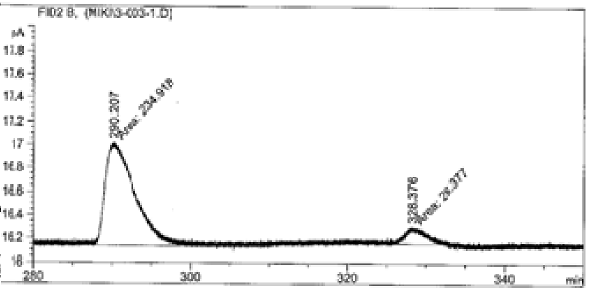
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	533.465	1933.22	2.2300	14.4517	49.931	1	529.116	3553.36	3.1515	18.7922	93.535
2	695.714	1938.53	1.4933	21.6359	50.069	2	721.072	245.60	3.7250e-1	10.9887	6.465

(*R*)-Methyl-4-phenethyl-tetrahydro-4*H*-pyran-2-one (Table 3.8, entry 7): IR (neat): 2925 (m), 2859 (m), 1730 (s), 1603 (w), 1495 (w), 1455 (m), 1404 (m), 1385 (m), 1257 (m), 1225 (m), 1117 (w), 1075 (m), 1032 (w), 745 (m), 700 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (2H, m), 7.22–7.16 (3H, m), 4.39–4.36 (2H, m), 2.63–2.58 (2H, m), 2.43 (1H, d, *J* = 16.4 Hz), 2.36 (1H, dd, *J* = 16.4, 0.8 Hz), 1.84 (1H, dt, *J* = 14.4, 6.4 Hz), 1.73 (1H, t, *J* = 5.6 Hz), 1.69–1.65 (2H, m), 1.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 141.7, 128.5, 128.2, 126.0, 66.2, 44.2, 42.9, 34.4, 32.7, 30.1, 25.9; HRMS (EI+):

Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1385, Found: 219.1389; Specific Rotation: $[\alpha]_D^{20}$ –10.0 (*c* = 0.80, $CHCl_3$) for an enantiomerically enriched sample of 89:11 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (89.2:10.8 er shown; CDGTA column, 15 psi, 140 °C).

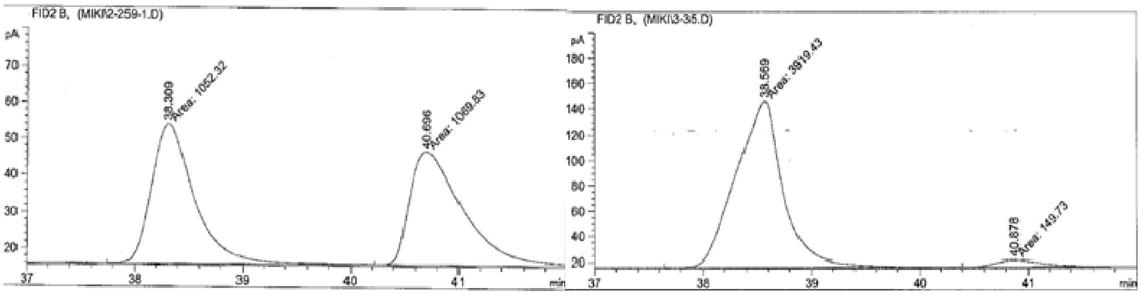




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	290.602	135.29	5.9757e-1	3.7734	50.33	1	290.207	234.92	8.86035e-1	4.4189	89.22
2	326.311	133.48	5.0896e-1	4.3713	49.66	2	328.377	28.377	1.52429e-1	3.1027	10.77

(*S*)-Methyl 2-ethyl-4-oxochroman-2-carboxylate (3.55): IR (neat): 2976 (w), 2954 (w), 1750 (m), 1737 (m), 1695 (s), 1609 (m), 1578 (w), 1462 (s), 1439 (w), 1322 (m), 1305 (m), 1232 (m), 1120 (m), 1177 (m), 1128 (m), 1117 (m), 1096 (w), 1029 (m), 998 (m), 965 (w), 767 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, ddd, *J* = 8.0, 2.0, 0.4 Hz), 7.51 (1H, ddd, *J* = 8.4, 7.2, 2.0 Hz), 7.09 (1H, ddd, *J* = 8.4, 1.2, 0.4 Hz), 7.02 (1H, ddd, *J* = 8.0, 7.2, 0.8 Hz), 3.68 (3H, s), 3.15 (1H, d, *J* =16.8 Hz), 2.90 (1H, d, *J* = 16.8 Hz), 2.06 (2H, q, *J* = 7.6 Hz), 1.04 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 171.6, 160.2, 136.4, 126.7, 121.7, 120.5, 118.1, 84.5, 52.8, 43.8, 31.1, 7.7; HRMS (EI+): Calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 235.0970, Found: 235.0970; Specific Rotation: $[\alpha]_D^{20}$ –62.7 (*c* = 0.96, $CHCl_3$) for an enantiomerically enriched sample of 96.5:3.5 er.

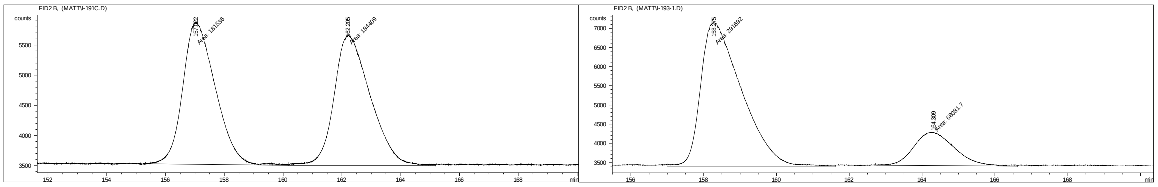
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.3:3.7 er shown; CDGTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	38.309	1052.32	38.2187	0.4589	49.587	1	38.569	3919.43	129.7522	0.5035	96.320
2	40.696	1069.83	30.8347	0.5783	50.413	2	40.878	149.730	5.1603	0.4836	3.680

(*S*)-Methyl 2-methyl-4-oxochroman-2-carboxylate (3.56): IR (neat): 2990 (w), 2955 (w), 1737 (s), 1692 (s), 1659 (w), 1606 (s), 1578 (m), 1460 (s), 1399 (w), 1377 (w), 1325 (m), 1302 (s), 1236 (s), 1188 (s), 1152 (m), 1129 (s), 1108 (s), 1089 (m), 1051 (w), 1023 (w), 978 (m), 959 (m), 902 (m), 893 (m), 837 (m), 826 (m), 762 (s), 724 (w), 677 (w), 582 (m), 553 (m), 518 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (1H, dd, *J* = 7.6, 1.6 Hz), 7.51 (1H, ddd, *J* = 8.4, 7.2, 1.6 Hz), 7.08–7.01 (2H, m), 3.68 (3H, s), 3.21 (1H, d, *J* = 16.8 Hz), 2.88 (1H, d, *J* = 16.8 Hz), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 172.0, 160.1, 136.4, 126.8, 121.8, 120.3, 118.1, 81.4, 53.0, 45.6, 24.8; HRMS (ESI+): Calcd for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, Found: 221.0819; Specific Rotation: $[\alpha]_D^{20}$ –68.7 (*c* = 0.69, $CHCl_3$) for an enantiomerically enriched sample of 97.5:2.5 er.

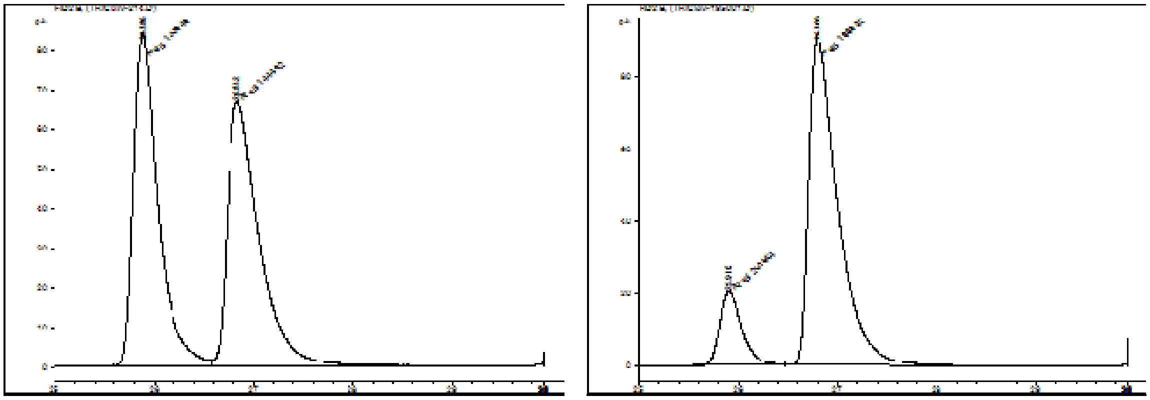
(*S*)-4-Methyl-4-phenylhexan-2-one (3.66): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.31 (4H, m), 7.21–7.17 (1H, m), 2.88 (1H, d, *J* = 14.4 Hz), 2.59 (1H, d, *J* = 14.4 Hz), 1.92–1.82 (1H, m), 1.76 (3H, s), 1.75–1.64 (1H, m), 1.41 (3H, s), 0.68 (3H, t, *J* = 7.2 Hz).
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (81.1:18.9 er shown; β-dex column, 15 psi, 100 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	157.022	181535.9	2358.8	1.2827	49.608	1	158.275	291691.9	3766.4	1.2908	81.077
2	162.205	184408.5	2170.3	1.4162	50.392	2	164.309	68081.7	869.2	1.3055	18.923

(*S*)-3-Methyl-3-phenylcyclopentanone (ent-3.12): IR (neat): 3025 (w), 2961 (m), 2920 (m), 2873 (m), 1737 (s), 1501 (m), 1451 (m), 1409 (w), 1315 (w), 1277 (w), 1163 (m), 1079 (w), 1033 (w), 762 (w), 700 (m), 666 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.37–7.21 (5H, m), 2.66 (1H, d, *J* = 17.6 Hz), 2.48 (1H, dt, *J* = 17.6, 1.2 Hz), 2.44–2.35 (2H, m), 2.32–2.26 (2H, m), 1.39 (3H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 218.8, 148.7, 128.8, 126.5, 125.7, 52.5, 44.0, 36.4, 36.0, 29.6; HRMS (EI+): Calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, Found: 175.1116; Specific Rotation: $[\alpha]_D^{20}$ –22 (*c* = 0.57, CHCl$_3$) for an enantiomerically enriched sample of 86:14 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (86.4:13.6 er shown; CDGTA column, 15 psi, 120 °C).

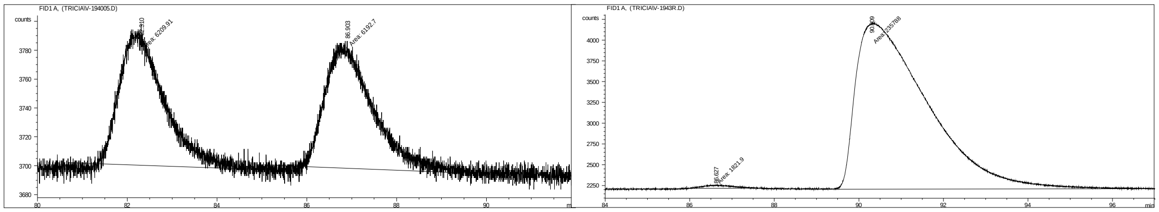


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	25.886	1409.5	83.6	0.2809	49.381	1	25.91	292.7	20.2	0.2416	13.593
2	26.832	1444.8	66.4	0.3628	50.619	2	26.8	1860.3	91.7	0.3379	86.407

(*S*)-3-Methyl-3-(*o*-tolyl)cyclopentanone (3.70): IR (neat): 2958 (w), 2928 (w), 1741 (s), 1489 (w), 1458 (w), 1404 (w), 1382 (2), 1285 (w), 1262 (w), 1183 (w), 1160 (w), 1136 (w), 1117 (w), 1057 (w), 997 (w), 763 (m), 750 (w), 727 (m), 461 (w), 435 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25–7.24 (1H, m), 7.21–7.15 (3H, m), 2.75 (1H, d, *J* =

17.6 Hz), 2.60 (1H, d, *J* = 17.8 Hz), 2.52–2.45 (1H, m), 2.45 (3H, s), 2.43–2.35 (3H, m), 1.38 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.1, 146.7, 135.8, 132.8, 126.7, 126.4, 126.3, 53.2, 44.7, 36.3, 36.1, 26.7, 22.8; HRMS (EI+): Calcd for $C_{13}H_{17}O$ $[M+H]^+$: 189.1280, Found: 189.1281;Specific rotation: $[\alpha]_D^{20}$ –106 (*c* = 0.48, $CHCl_3$) for a 99:1 er sample.

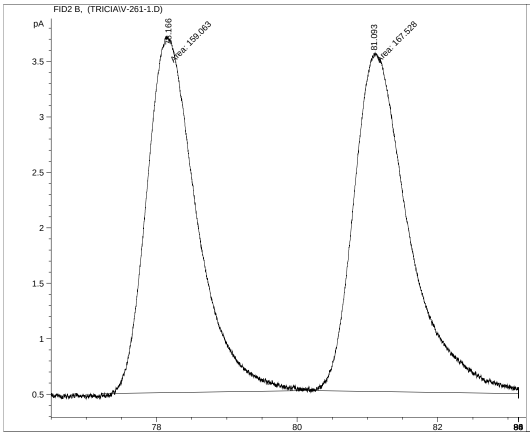
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (99.2:0.8 er shown; CDGTA column, 15 psi, 120 °C).

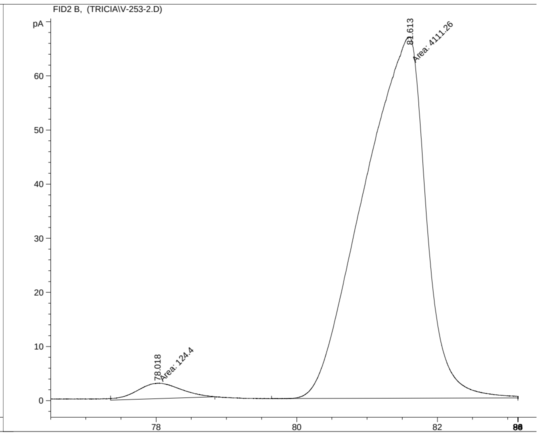


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	82.31	6096.1	97.3	1.1441	50.985	1	86.627	1821.9	43.6	0.696	0.767
2	86.903	5860.5	87.6	1.1144	49.015	2	90.309	235787.5	2002.7	1.9622	99.233

(*S*)-3-Methyl-3-(2-methoxyphenyl)cyclopentanone (3.71): IR (neat): 2955 (w), 1740 (s), 1698 (w), 1683 (w), 1598 (w), 1580 (w), 1558 (s), 1541 (w), 1521 (w), 1507 (w), 1490 (w), 1457 (w), 1436 (w), 1405 (s), 1295 (w), 1262 (s), 1238 (w), 1179 (w), 1156 (w), 1140 (s), 1121 (w), 1073 (w), 1053 (w), 1027 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.20 (2H, m), 6.96–6.89 (2H, m), 3.83 (3H, s), 2.68 (1H, d, *J* = 18.4 Hz), 2.60 (1H, d, *J* = 18.0 Hz), 2.42–2.31 (4H, m), 1.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.3, 157.9, 136.4, 127.9, 126.5, 120.7, 111.6, 55.2, 52.5, 42.9, 36.6, 35.1, 26.4; HRMS (EI+): Calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229, Found: 205.1219; Specific Rotation: $[\alpha]_D^{20}$ +27 (*c* = 1.1, $CHCl_3$) for a 97.5:2.5 er sample.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97.1:2.9 shown: CDGTA column, 15 psi, 120 °C).

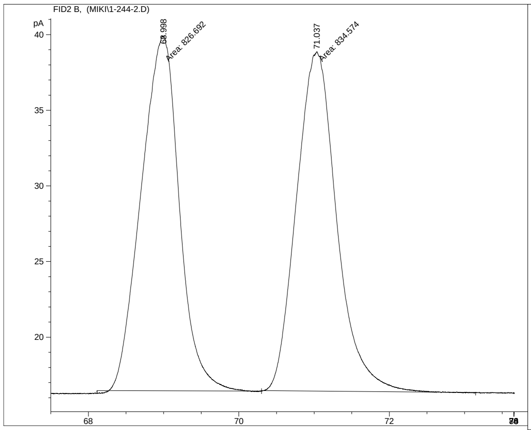


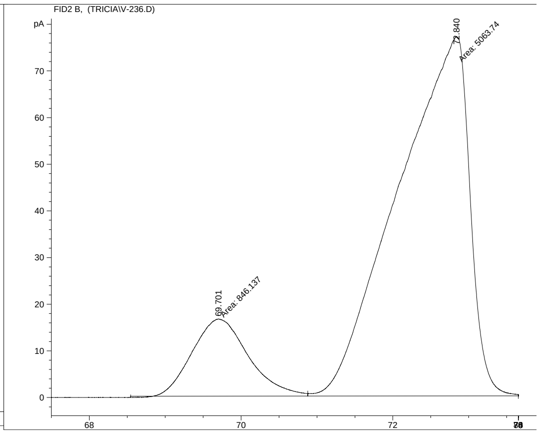


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	78.166	159.1	3.2	0.827	48.704	1	78.018	124.4	2.9	0.7229	2.937
2	81.093	167.5	3	0.9161	51.296	2	81.613	4111.3	66.8	1.0257	97.063

(*S*)-3-Methyl-3-(4-methoxyphenyl)cyclopentanone (3.72): IR (neat): 2955 (w), 2836 (w), 1736 (s), 1610 (w), 1579 (m), 1512 (w), 1462 (w), 1405 (w), 1376 (w), 1298 (s), 1247 (m), 1182 (w), 1157 (m), 1111 (w), 1079 (m), 1032 (w), 829 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.22–7.20 (2H, m), 6.89–6.86 (2H, m), 3.80 (3H, s), 2.62 (1H, d, *J* = 18.0 Hz), 2.46–2.33 (3H, m), 2.30–2.21 (2H, m), 1.36 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 219.0, 158.2, 140.8, 126.7, 114.1, 55.5, 52.7, 43.4, 37.0, 36.3, 29.7; HRMS (EI+): Calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229, Found: 205.1229; Specific Rotation: $[\alpha]_D^{20}$ –4.0 (*c* = 0.93, CHCl$_3$) for a 85.5:14.5 er sample.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (85.7:14.3 shown; CDGTA column, 120 °C, 15 psi).

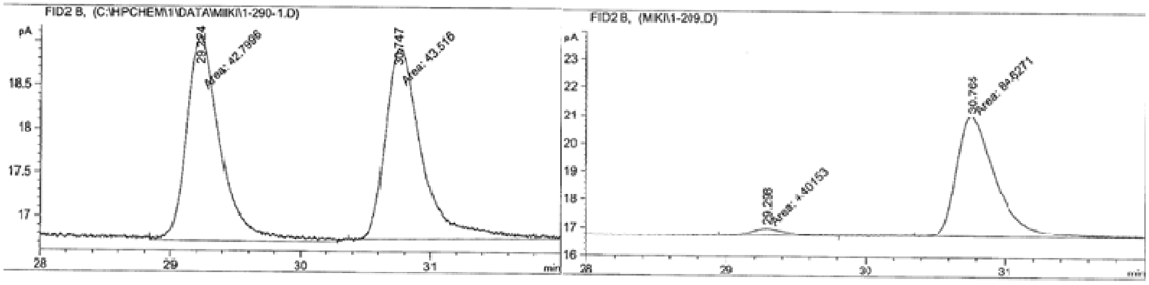




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	68.998	826.7	23.4	0.5878	49.763	1	69.701	846.1	16.5	0.8534	14.317
2	71.037	834.6	22.5	0.6193	50.237	2	72.840	5063.7	77	1.0956	85.683

(*S*)-3-Methyl-3-(4-trifluromethyl-phenyl)cyclopentanone (3.73): IR (neat): 2962 (w), 1744 (s), 1618 (w), 1456 (w), 1409 (w), 1378 (w), 1329 (s), 1163 (m), 1121 (s), 1081 (w), 1068 (w), 1015 (w), 840 (m), 667 (w), 608 (w); ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 2.64 (1H, d, *J* = 18.0 Hz), 2.51 (1H, dd, *J* = 18.0, 0.8 Hz), 2.47–2.38 (2H, m), 2.34–2.27 (2H, m), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 152.4, 125.9, 125.6, 125.5, 115.4, 51.9, 43.9, 36.5, 35.5, 29.2; HRMS (ESI+): Calcd for $C_{13}H_{14}F_3O$ $[M+H]^+$: 243.1000, Found 243.0997; Specific Rotation: $[\alpha]_D^{20}$ –15.4 (*c* = 0.940, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.1:4.9 er shown; CDGTA column, 15 psi, 130 °C).

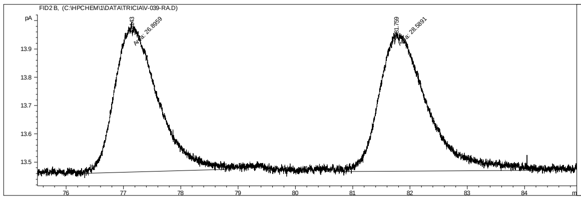


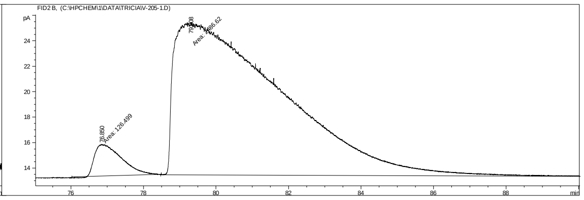
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	29.224	42.800	2.329	0.3063	49.59	1	29.298	4.402	2.7221e-1	0.2695	4.944
2	30.747	43.516	2.175	0.3334	50.41	2	30.765	84.63	4.300	0.3280	95.060

(*S*)-3-Methyl-3-phenylcyclohexanone (3.67): (This compound has been previously reported and spectra data matches those described.)[55] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.31 (2H, m), 7.26–7.19 (3H, m), 2.88 (1H, d, *J* = 14.4 Hz), 2.44 (1H, dd, *J* = 14.4, 0.4 Hz), 2.32 (2H, t, *J* = 6.4 Hz), 2.22–2.16 (1H, m), 1.96–1.83 (2H, m), 1.71–1.61 (1H, m), 1.32 (3H, s); Specific Rotation: $[\alpha]_D^{20}$ +36.0 (*c* = 1.08, $CHCl_3$) for a 95:5 er sample.

Stereochemistry Proof: Previously reported specific rotation: $[\alpha]_D^{20}$ +70.1 (*c* = 1.00, $CHCl_3$) for a 98.5:1.5 er sample for the *S* enantiomer.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material 95.2:4.8 er shown: CDGTA column, 15 psi, 120 °C).

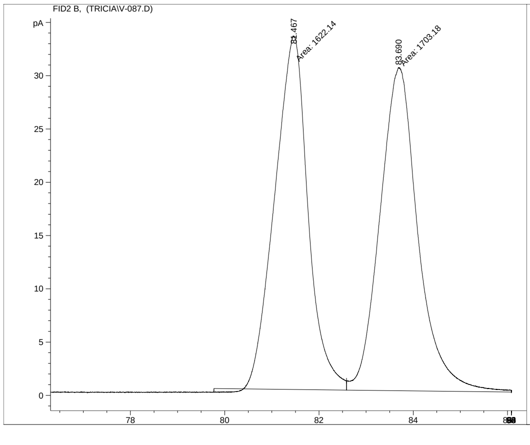


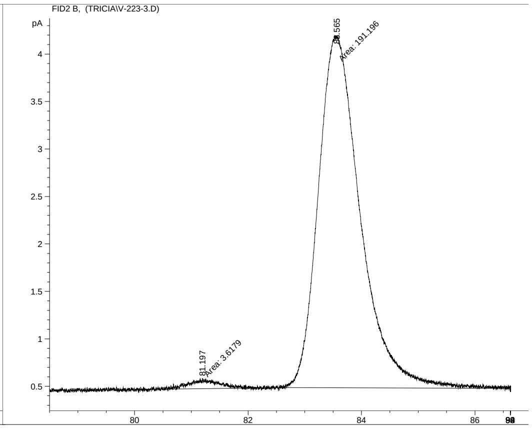


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	77.143	26.9	5.3E-1	0.8459	48.474	1	76.850	126.5	2.5	0.8426	4.841
2	81.759	28.6	4.9E-1	0.9702	51.526	2	79.308	2486.6	12	3.4545	95.159

(*S*)-3-Methyl-3-*o*-tolylcyclohexanone (3.74): IR (neat): 2955 (m), 2930 (m), 2871 (w), 1709 (w), 1598 (w), 1488 (w), 1451 (m), 1382 (w), 1350 (w), 1315 (w), 1287 (w), 1226 (m), 1167 (w), 1108 (m), 1078 (s), 1059 (w), 982 (w), 950 (w), 884 (w), 846 (w), 755 (s), 727 (s), 684 (w), 565 (w), 547 (w), 525 (w), 478 (w), 461 (w), 422 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.23 (1H, m), 7.16–7.11 (3H, m), 3.00 (1H, d, *J* = 14.4 Hz), 2.53 (3H, s), 2.50–2.45 (2H, m), 2.31 (2H, t, *J* = 6.4 Hz), 1.97–1.84 (2H, m), 1.64–1.55 (1H, m), 1.42 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 144.5, 135.9, 133.6, 127.3, 126.7, 126.4, 55.3, 44.4, 41.0, 36.2, 27.5, 23.6, 22.1; HRMS (EI+): Calcd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436, Found: 203.1441; Specific Rotation: $[\alpha]_D{}^{20}$ +32 (*c* = 0.71, $CHCl_3$) for a 95.5:4.5 er sample.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (98.1:1.9 er shown: β-dex column, 15 psi, 110 °C).

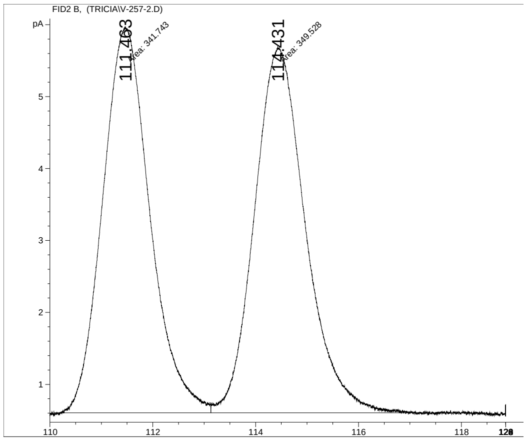


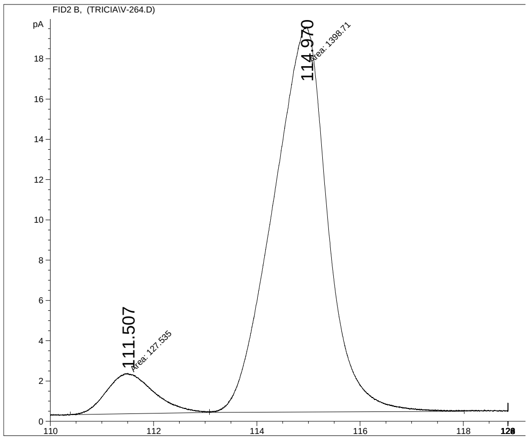


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	81.467	1622.1	33.2	0.8151	48.782	1	81.197	3.6	1.1E-1	0.563	1.857
2	83.69	1703.2	30.3	0.9361	51.218	2	83.565	191.2	3.7	0.8595	98.143

***(S)*-3-Methyl-3-(2-methoxyphenyl)cyclohexenone (3.75):** IR (neat): 2953 (m), 2930 (m), 2870 (w), 2836 (w), 1706 (w), 1597 (w), 1579 (w), 1490 (m), 1462 (m), 1434 (m), 1376 (m), 1349 (w), 1314 (w), 1287 (s), 1237 (w), 1180 (w), 1128 (w), 1084 (m), 1057 (s), 1025 (w), 963 (w), 950 (w), 795 (s), 753 (w), 695 (w), 536 (w), 478 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.24–7.20 (2H, m), 6.92–6.88 (2H, m), 3.83 (3H, s), 3.04 (1H, d, *J* = 14.4 Hz), 2.60–2.54 (1H, m), 2.45 (1H, d, *J* = 14.4 Hz), 2.31 (2H, t, *J* = 6.8 Hz), 1.91–1.79 (2H, m), 1.70–1.60 (1H, m), 1.40 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 212.6, 158.1, 135.0, 128.0, 127.6, 120.8, 112.0, 55.1, 53.6, 43.0, 41.2, 35.2, 26.5, 22.4; HRMS (EI+): Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1385, Found: 219.1387; Specific Rotation: $[\alpha]_D^{20}$ +38 (*c* = 0.85, CHCl$_3$) for a 88:12 er sample.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (91.6:8.4 sample below; CDGTA column, 120 °C, 15 psi).





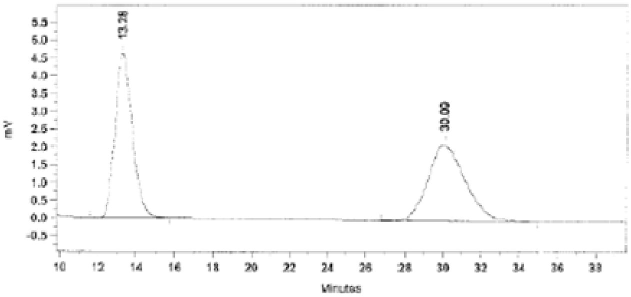
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	111.465	343	5.4	1.0643	49.321	1	111.507	127.5	2	1.0653	8.356
2	114.429	352.4	5.1	1.1502	50.679	2	114.97	1398.7	19.1	1.2187	91.644

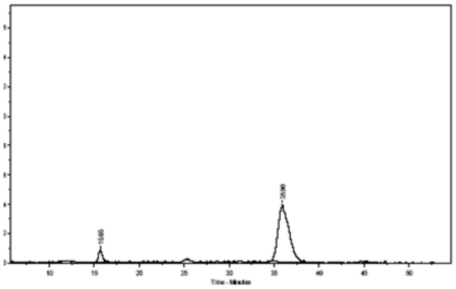
(*S*)-3-Methyl-3-(4-methoxyphenyl)cyclohexanone (3.76): (This compound has been previously reported and spectra data matches those described.)[55] ^{1}H NMR (CDCl$_3$, 400

MHz): δ 7.23 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 3.79 (3H, s), 2.85 (1H, d, J = 14.4 Hz), 2.41 (1H, d, J = 14.0 Hz), 2.30 (2H, t, J = 7.2 Hz), 2.19–2.12 (1H, m), 1.92–1.82 (2H, m), 1.70–1.62 (m, 1H), 1.30 (3H, s); Specific Rotation: $[\alpha]_D^{20}$ +35 (c = 0.76, $CHCl_3$) for an enantiomerically enriched sample of 88.5:11.5 er.

Stereochemistry Proof: Previously reported specific rotation: $[\alpha]_D^{20}$ +51.7 (c = 0.960, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er of the *S* enantiomer.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (92.2:7.8 er shown; chiralpak AS column, 254 nm, 95:5 hexanes:*i*-PrOH, 1 ml/min).

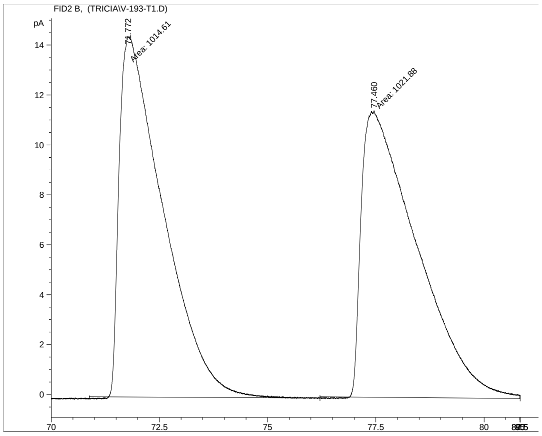


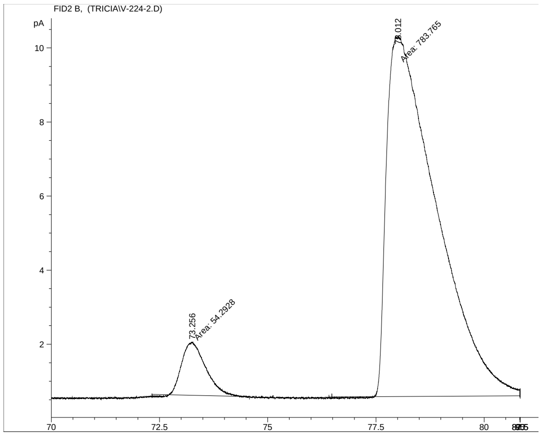


#	Time	Area	Area%	#	Time	Area	Area%
1	13.282	288783.6	49.612	1	15.65	27446	7.850
2	30.087	293300.6	50.388	2	35.90	322196	92.150

(*S*)-3-Methyl-3-(4-(trifluromethyl)phenyl)cyclohexanone (3.77): IR (neat): 2960 (w), 2875 (w), 1711 (w), 1618 (m), 1456 (w), 1409 (w), 1328 (w), 1228 (w), 1200 (w), 1165 (w), 1118 (w), 1081 (w), 1067 (w), 1014 (w), 840 (w), 608 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (2H, dt, J = 8.4, 0.8 Hz), 7.44 (2H, dd, J = 9.2, 0.8 Hz), 2.88 (1H, dd, J = 14.0, 1.2 Hz), 2.47 (1H, dd, J = 14.4, 0.8 Hz), 2.35–2.31 (2H, m), 2.23–2.17 (1H, m), 1.99–1.85 (2H, m), 1.69–1.60 (1H, m), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 151.6, 128.8 (q, J = 32.3 Hz), 126.3, 125.7, 124.3 (q, J = 270.2 Hz), 53.0, 43.3, 40.9, 38.0, 30.0, 22.1; HRMS (EI+): Calcd for $C_{14}H_{16}F_3O$ $[M+H]^+$: 257.1153, Found: 257.1150; Specific Rotation: $[\alpha]_D^{20}$ +40 (c = 0.85, $CHCl_3$) for a 90.5:9.5 er sample.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.5:6.5 er shown: CDGTA column, 15 psi, 120 °C).





#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	71.772	1014.6	14.4	1.1704	49.822	1	73.256	54.3	1.4	0.628	6.478
2	77.46	1021.9	11.5	1.4833	50.178	2	78.012	783.8	9.7	1.3437	93.522

3.7. X-Ray Crystal Structure Data

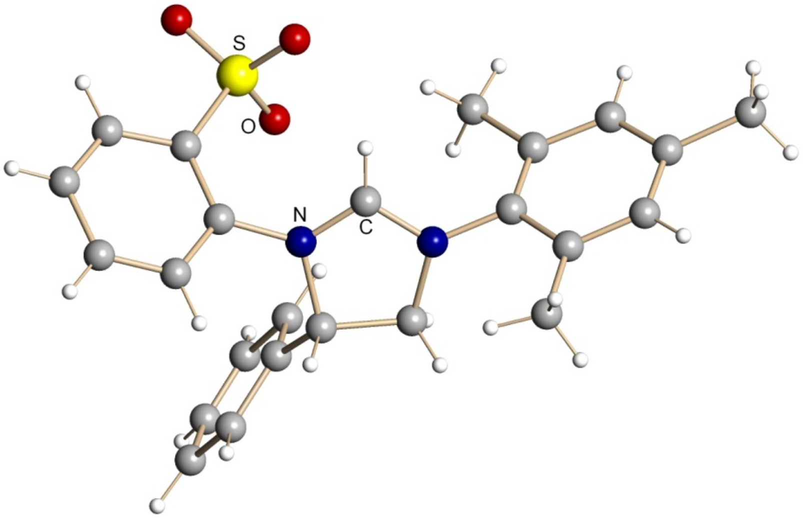


Figure 1. Molecular structure of $C_{24}H_{24}N_2O_3S$. Only one of the four crystallographically independant molecules was shown. Solvent molecules are removed for clarity.

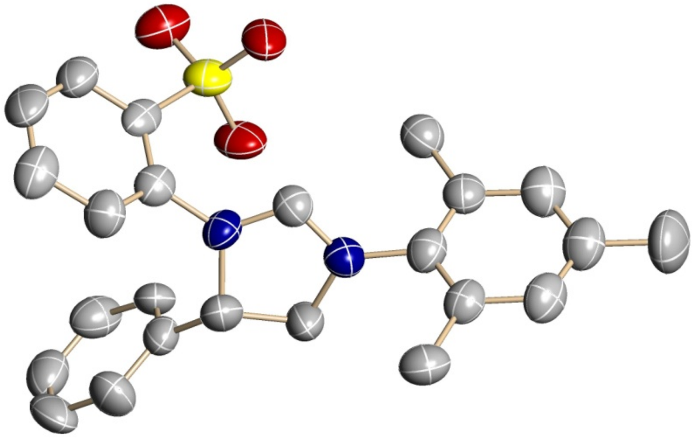


Figure 2. Molecular structure of $C_{24}H_{24}N_2O_3S$. Only one of the four crystallographically independant molecules was shown. Non-Hydrogen atomes are represented by thermal ellipsoids. Hygrogen atoms and solvent molecules are removed for clarity.

Table 1. Crystal data and structure refinement for $C_{24}H_{24}N_2O_3S$.

Identification code	$C_{24}H_{24}N_2O_3S$	
Empirical formula	$C_{24}\ H_{24.50}\ N_2\ O_{3.25}\ S$	
Formula weight	425.02	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P\ 2_1$	
Unit cell dimensions	a = 13.358(7) Å	α= 90°.
	b = 21.033(11) Å	β= 103.260(5)°.
	c = 16.121(9) Å	γ = 90°.
Volume	4409(4) $Å^3$	
Z	8	
Density (calculated)	1.281 Mg/m^3	
Absorption coefficient	0.176 mm^{-1}	
F(000)	1796	
Crystal size	0.35 x 0.25 x 0.04 mm^3	
Theta range for data collection	2.25 to 25.36°.	
Index ranges	-16<=h<=16, -25<=k<=25, -19<=l<=19	
Reflections collected	27675	
Independent reflections	15236 [R(int) = 0.0953]	
Completeness to theta = 25.36°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9930 and 0.9411	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15236 / 4 / 1024	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0844, wR2 = 0.1704	
R indices (all data)	R1 = 0.2084, wR2 = 0.2188	
Absolute structure parameter	-0.03(11)	
Extinction coefficient	noref	

Largest diff. peak and hole	0.820 and -0.288 e.Å^{-3}

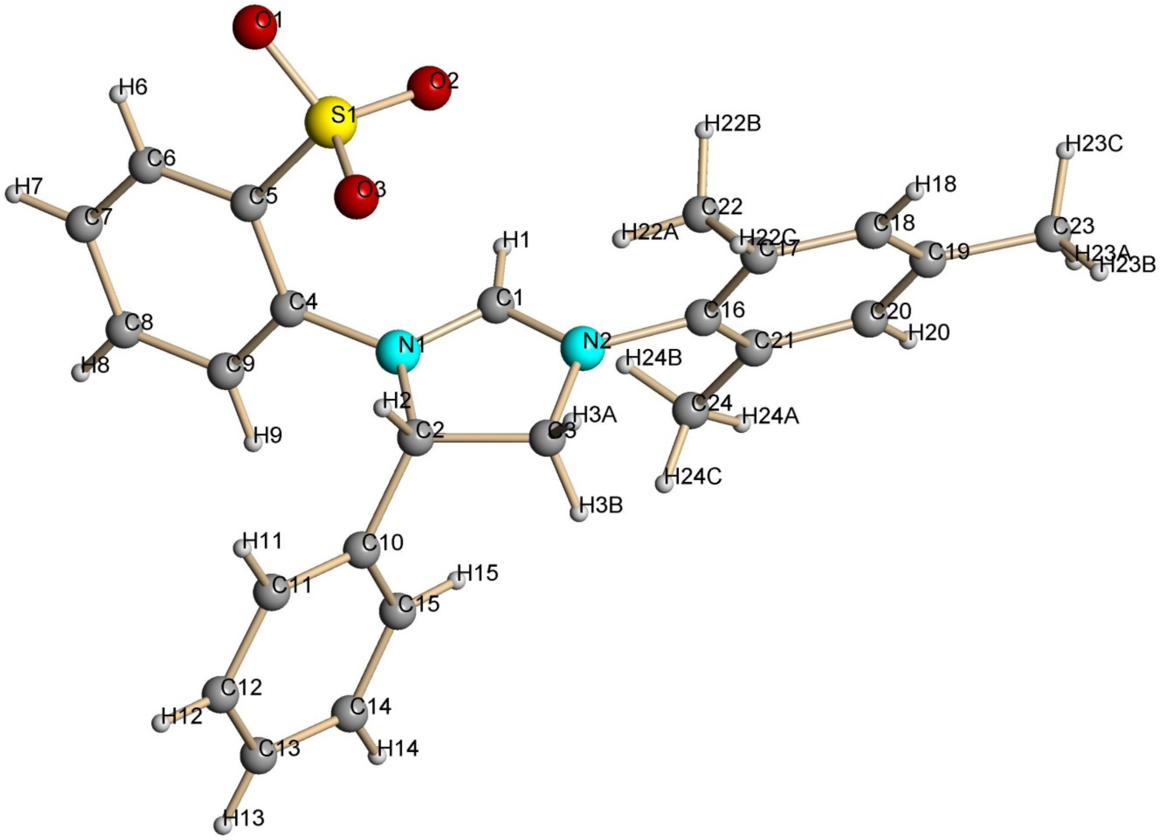

O1
H6
O2
S1
H22B
H23C
H7
C6
C5
O3
H18
C22
C23
C7
H22A
H22C
C17
C18
C19
H23A
H23B
H1
C1
C4
C16
C20
C8
N1
N2
C21
H20
H8
C9
H24B
H2
C24
H24A
H3A
C2
C3
H9
H24C
H3B
H11
C10
H15
C11
C15
C12
C14
H12
C13
H14
H13

Table 2. Selected bond lengths [Å] and angles [°] for $C_{24}H_{24}N_2O_3S$.

S(1)-O(2)	1.429(6)
S(1)-O(3)	1.432(6)
S(1)-O(1)	1.471(6)
S(1)-C(5)	1.774(10)
N(1)-C(1)	1.328(10)
N(1)-C(4)	1.437(10)
N(1)-C(2)	1.485(9)

N(2)-C(1)	1.316(10)
N(2)-C(3)	1.445(10)
N(2)-C(16)	1.483(10)
C(2)-C(10)	1.499(12)
C(2)-C(3)	1.546(11)
C(4)-C(9)	1.384(11)
C(4)-C(5)	1.408(11)
C(5)-C(6)	1.363(12)
C(6)-C(7)	1.361(13)
C(7)-C(8)	1.400(13)
C(8)-C(9)	1.362(12)
C(10)-C(11)	1.353(13)
C(10)-C(15)	1.418(13)
C(11)-C(12)	1.372(14)
C(12)-C(13)	1.400(16)
C(13)-C(14)	1.408(16)
C(14)-C(15)	1.370(15)
C(16)-C(21)	1.359(12)
C(16)-C(17)	1.424(12)
C(17)-C(18)	1.390(12)
C(17)-C(22)	1.458(12)
C(18)-C(19)	1.366(12)
C(19)-C(20)	1.395(12)
C(19)-C(23)	1.516(12)
C(20)-C(21)	1.408(11)
C(21)-C(24)	1.494(12)

O(2)-S(1)-O(3)	113.4(4)
O(2)-S(1)-O(1)	113.8(4)
O(3)-S(1)-O(1)	113.9(4)
O(2)-S(1)-C(5)	104.5(4)
O(3)-S(1)-C(5)	106.4(4)
O(1)-S(1)-C(5)	103.6(4)
C(1)-N(1)-C(4)	122.8(7)

C(1)-N(1)-C(2)	111.5(7)
C(4)-N(1)-C(2)	124.6(6)
C(1)-N(2)-C(3)	111.8(7)
C(1)-N(2)-C(16)	123.1(7)
C(3)-N(2)-C(16)	124.7(6)
N(2)-C(1)-N(1)	111.4(7)
N(1)-C(2)-C(10)	112.0(7)
N(1)-C(2)-C(3)	101.0(6)
C(10)-C(2)-C(3)	115.7(7)
N(2)-C(3)-C(2)	104.0(6)
C(9)-C(4)-C(5)	120.8(8)
C(9)-C(4)-N(1)	118.4(8)
C(5)-C(4)-N(1)	120.7(8)
C(6)-C(5)-C(4)	117.3(9)
C(6)-C(5)-S(1)	121.9(7)
C(4)-C(5)-S(1)	120.8(7)
C(7)-C(6)-C(5)	123.1(9)
C(6)-C(7)-C(8)	118.9(9)
C(9)-C(8)-C(7)	120.1(10)
C(8)-C(9)-C(4)	119.8(9)
C(11)-C(10)-C(15)	117.2(10)
C(11)-C(10)-C(2)	122.6(9)
C(15)-C(10)-C(2)	119.9(9)
C(10)-C(11)-C(12)	123.9(12)
C(11)-C(12)-C(13)	118.1(12)
C(12)-C(13)-C(14)	120.3(12)
C(15)-C(14)-C(13)	118.7(13)
C(14)-C(15)-C(10)	121.6(11)
C(21)-C(16)-C(17)	123.8(8)
C(21)-C(16)-N(2)	121.1(8)
C(17)-C(16)-N(2)	115.1(8)
C(18)-C(17)-C(16)	115.9(8)
C(18)-C(17)-C(22)	120.5(9)
C(16)-C(17)-C(22)	123.5(8)

C(19)-C(18)-C(17)	122.2(9)
C(18)-C(19)-C(20)	120.1(8)
C(18)-C(19)-C(23)	122.7(9)
C(20)-C(19)-C(23)	117.2(9)
C(19)-C(20)-C(21)	120.2(9)
C(16)-C(21)-C(20)	117.8(9)
C(16)-C(21)-C(24)	121.7(9)
C(20)-C(21)-C(24)	120.6(9)

Symmetry transformations used to generate equivalent atoms:

Table 3. Selected torsion angles [°] for $C_{24}H_{24}N_2O_3S$.

C(3)-N(2)-C(1)-N(1)	2.4(10)
C(16)-N(2)-C(1)-N(1)	175.6(8)
C(4)-N(1)-C(1)-N(2)	170.2(7)
C(2)-N(1)-C(1)-N(2)	1.5(10)
C(1)-N(1)-C(2)-C(10)	-128.0(8)
C(4)-N(1)-C(2)-C(10)	63.6(10)
C(1)-N(1)-C(2)-C(3)	-4.3(9)
C(4)-N(1)-C(2)-C(3)	-172.8(8)
C(1)-N(2)-C(3)-C(2)	-5.0(9)
C(16)-N(2)-C(3)-C(2)	-178.1(8)
N(1)-C(2)-C(3)-N(2)	5.3(8)
C(10)-C(2)-C(3)-N(2)	126.4(8)
C(1)-N(1)-C(4)-C(9)	108.7(9)
C(2)-N(1)-C(4)-C(9)	-84.1(10)
C(1)-N(1)-C(4)-C(5)	-69.2(11)
C(2)-N(1)-C(4)-C(5)	98.0(9)
C(9)-C(4)-C(5)-C(6)	-0.9(12)
N(1)-C(4)-C(5)-C(6)	176.9(7)
C(9)-C(4)-C(5)-S(1)	-179.0(6)
N(1)-C(4)-C(5)-S(1)	-1.2(10)
O(2)-S(1)-C(5)-C(6)	-111.5(7)

O(3)-S(1)-C(5)-C(6)	128.3(7)
O(1)-S(1)-C(5)-C(6)	8.0(8)
O(2)-S(1)-C(5)-C(4)	66.5(7)
O(3)-S(1)-C(5)-C(4)	-53.7(7)
O(1)-S(1)-C(5)-C(4)	-174.0(6)
C(4)-C(5)-C(6)-C(7)	-0.2(13)
S(1)-C(5)-C(6)-C(7)	177.9(7)
C(5)-C(6)-C(7)-C(8)	1.4(14)
C(6)-C(7)-C(8)-C(9)	-1.4(13)
C(7)-C(8)-C(9)-C(4)	0.4(13)
C(5)-C(4)-C(9)-C(8)	0.8(12)
N(1)-C(4)-C(9)-C(8)	-177.1(7)
N(1)-C(2)-C(10)-C(11)	-112.9(9)
C(3)-C(2)-C(10)-C(11)	132.1(9)
N(1)-C(2)-C(10)-C(15)	60.9(10)
C(3)-C(2)-C(10)-C(15)	-54.1(11)
C(15)-C(10)-C(11)-C(12)	5.8(15)
C(2)-C(10)-C(11)-C(12)	179.8(9)
C(10)-C(11)-C(12)-C(13)	-4.4(17)
C(11)-C(12)-C(13)-C(14)	2.1(17)
C(12)-C(13)-C(14)-C(15)	-1.7(17)
C(13)-C(14)-C(15)-C(10)	3.3(16)
C(11)-C(10)-C(15)-C(14)	-5.2(14)
C(2)-C(10)-C(15)-C(14)	-179.4(9)
C(1)-N(2)-C(16)-C(21)	-67.8(10)
C(3)-N(2)-C(16)-C(21)	104.5(10)
C(1)-N(2)-C(16)-C(17)	112.6(9)
C(3)-N(2)-C(16)-C(17)	-75.1(10)
C(21)-C(16)-C(17)-C(18)	-2.3(12)
N(2)-C(16)-C(17)-C(18)	177.3(6)
C(21)-C(16)-C(17)-C(22)	174.1(8)
N(2)-C(16)-C(17)-C(22)	-6.3(11)
C(16)-C(17)-C(18)-C(19)	2.2(12)
C(22)-C(17)-C(18)-C(19)	-174.3(8)

C(17)-C(18)-C(19)-C(20)	-1.6(13)
C(17)-C(18)-C(19)-C(23)	-179.1(8)
C(18)-C(19)-C(20)-C(21)	0.9(12)
C(23)-C(19)-C(20)-C(21)	178.6(7)
C(17)-C(16)-C(21)-C(20)	1.7(12)
N(2)-C(16)-C(21)-C(20)	-177.9(7)
C(17)-C(16)-C(21)-C(24)	-178.4(7)
N(2)-C(16)-C(21)-C(24)	2.0(11)
C(19)-C(20)-C(21)-C(16)	-1.0(12)
C(19)-C(20)-C(21)-C(24)	179.2(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sad2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	7244(2)	4699(1)	8021(2)	54(1)
O(1)	6350(4)	5114(3)	7709(4)	69(2)
O(2)	6982(4)	4047(3)	8102(4)	59(2)
O(3)	8058(4)	4785(3)	7588(4)	64(2)
N(1)	9219(4)	4236(3)	9239(4)	41(2)
N(2)	9446(5)	3326(3)	8654(4)	43(2)
C(1)	8881(6)	3644(4)	9081(6)	48(2)
C(2)	10117(6)	4366(4)	8866(5)	45(2)
C(3)	10296(6)	3703(4)	8511(6)	52(2)
C(4)	8655(6)	4713(4)	9579(6)	43(2)
C(5)	7728(6)	4959(4)	9084(6)	49(2)
C(6)	7212(7)	5388(4)	9465(7)	58(3)
C(7)	7551(7)	5580(4)	10287(8)	60(3)
C(8)	8484(7)	5339(5)	10765(7)	60(3)
C(9)	9026(7)	4909(4)	10413(6)	50(2)
C(10)	11006(7)	4636(4)	9511(6)	56(1)
C(11)	11345(7)	5238(5)	9466(8)	70(2)
C(12)	12154(9)	5499(6)	10048(9)	95(2)
C(13)	12614(8)	5134(7)	10761(9)	97(3)
C(14)	12269(9)	4511(6)	10854(9)	100(2)
C(15)	11462(8)	4278(5)	10246(7)	72(2)
C(16)	9290(6)	2642(4)	8442(6)	44(2)
C(17)	8930(6)	2505(4)	7559(6)	42(2)
C(18)	8822(6)	1864(5)	7345(6)	49(2)
C(19)	9015(6)	1395(4)	7946(6)	46(2)
C(20)	9357(6)	1549(4)	8806(6)	46(2)
C(21)	9491(6)	2190(4)	9060(6)	45(2)
C(22)	8626(7)	2993(5)	6908(6)	67(3)
C(23)	8914(8)	694(5)	7719(7)	73(3)

C(24)	9843(8)	2359(5)	9981(6)	66(3)
S(2)	6684(2)	2644(1)	9922(2)	48(1)
O(4)	7296(4)	3222(3)	10114(4)	50(2)
O(5)	5806(4)	2640(3)	10297(4)	56(2)
O(6)	7300(5)	2077(3)	10073(4)	61(2)
N(3)	4953(5)	3540(3)	8849(5)	41(2)
N(4)	4776(5)	4394(3)	9598(5)	43(2)
C(25)	5416(7)	3990(4)	9361(6)	42(2)
C(26)	3786(6)	3649(4)	8614(7)	55(3)
C(27)	3689(6)	4177(4)	9250(6)	51(2)
C(28)	5425(6)	3080(4)	8384(6)	40(2)
C(29)	6206(6)	2656(4)	8813(6)	43(2)
C(30)	6603(6)	2251(4)	8283(6)	45(2)
C(31)	6296(6)	2248(4)	7418(6)	45(2)
C(32)	5503(7)	2662(4)	7020(7)	56(3)
C(33)	5082(7)	3064(4)	7510(6)	48(2)
C(34)	3177(7)	3067(4)	8657(7)	56(1)
C(35)	2441(7)	2892(4)	7904(8)	70(2)
C(36)	1762(9)	2340(6)	7913(10)	95(2)
C(37)	1900(8)	2093(6)	8710(10)	97(3)
C(38)	2542(9)	2216(6)	9419(9)	100(2)
C(39)	3276(7)	2773(5)	9396(7)	72(2)
C(40)	5057(6)	4863(4)	10246(6)	39(2)
C(41)	4798(6)	5512(4)	10011(7)	47(2)
C(42)	5079(7)	5963(4)	10653(7)	50(3)
C(43)	5563(7)	5829(4)	11472(7)	49(2)
C(44)	5779(7)	5189(4)	11672(6)	52(3)
C(45)	5517(6)	4712(4)	11073(6)	48(2)
C(46)	4266(7)	5683(4)	9134(6)	61(3)
C(47)	5913(7)	6329(4)	12147(7)	69(3)
C(48)	5775(7)	4018(4)	11328(6)	61(3)
S(3)	3207(2)	6940(1)	5131(2)	62(1)
O(7)	3999(5)	7095(3)	4695(4)	72(2)
O(8)	2843(5)	6295(3)	4957(4)	74(2)

O(9)	2368(6)	7394(4)	5035(5)	103(3)
N(5)	5126(5)	6170(3)	6062(5)	43(2)
N(6)	5195(5)	5385(3)	5169(5)	47(2)
C(49)	4710(7)	5636(5)	5692(6)	50(2)
C(50)	5972(6)	6369(4)	5639(6)	47(2)
C(51)	6167(6)	5757(4)	5200(7)	61(3)
C(52)	4682(7)	6581(4)	6585(6)	43(2)
C(53)	3803(7)	6953(4)	6232(6)	49(2)
C(54)	3430(7)	7344(4)	6794(7)	53(2)
C(55)	3872(8)	7354(5)	7647(7)	58(3)
C(56)	4695(8)	6993(4)	7959(7)	56(3)
C(57)	5083(7)	6586(4)	7419(6)	48(2)
C(58)	6870(7)	6654(4)	6228(7)	56(1)
C(59)	7197(7)	7278(4)	6091(7)	70(2)
C(60)	8004(9)	7539(6)	6678(9)	95(2)
C(61)	8523(8)	7199(7)	7338(9)	97(3)
C(62)	8256(9)	6596(7)	7484(9)	100(2)
C(63)	7427(8)	6302(5)	6916(7)	72(2)
C(64)	4890(6)	4849(4)	4591(6)	47(2)
C(65)	5178(7)	4239(5)	4883(7)	55(3)
C(66)	4875(7)	3746(4)	4283(7)	49(2)
C(67)	4390(8)	3846(5)	3456(8)	57(3)
C(68)	4154(7)	4466(5)	3200(7)	62(3)
C(69)	4378(7)	4985(5)	3767(6)	54(2)
C(70)	5709(8)	4098(5)	5790(7)	70(3)
C(71)	4157(7)	3317(5)	2839(7)	75(3)
C(72)	4074(8)	5660(4)	3448(7)	67(3)
S(4)	1735(2)	4905(1)	7068(2)	65(1)
O(10)	743(4)	5163(3)	7102(4)	73(2)
O(11)	2565(4)	5364(3)	7333(4)	72(2)
O(12)	1939(5)	4295(3)	7476(5)	79(2)
N(7)	727(5)	5723(4)	5453(5)	53(2)
N(8)	476(6)	6651(4)	5990(5)	54(2)
C(73)	1130(8)	6198(5)	5943(6)	54(3)

C(74)	-341(8)	5875(5)	4987(7)	68(3)
C(75)	-570(7)	6408(5)	5584(6)	68(3)
C(76)	1265(7)	5162(5)	5301(6)	54(3)
C(77)	1726(6)	4759(4)	5971(6)	50(2)
C(78)	2258(8)	4246(5)	5777(7)	67(3)
C(79)	2302(7)	4134(5)	4924(9)	76(3)
C(80)	1826(8)	4495(5)	4273(8)	73(3)
C(81)	1292(7)	5052(5)	4468(7)	66(3)
C(82)	-1073(7)	5321(4)	4861(7)	53(2)
C(83)	-1159(7)	4955(5)	5539(7)	67(3)
C(84)	-1792(8)	4405(5)	5438(8)	75(3)
C(85)	-2333(9)	4269(6)	4649(10)	83(4)
C(86)	-2283(7)	4642(7)	3951(8)	85(4)
C(87)	-1626(9)	5184(6)	4065(7)	77(3)
C(88)	665(8)	7254(5)	6458(7)	64(3)
C(89)	452(7)	7811(5)	6005(7)	55(3)
C(90)	584(8)	8385(5)	6462(8)	67(3)
C(91)	936(9)	8400(6)	7314(9)	77(3)
C(92)	1181(8)	7820(6)	7753(8)	75(3)
C(93)	1044(7)	7237(5)	7327(7)	57(3)
C(94)	55(8)	7837(5)	5037(7)	75(3)
C(95)	1058(10)	9013(5)	7823(9)	108(4)
C(96)	1297(8)	6619(5)	7827(6)	66(3)
O(13S)	4344(5)	4669(4)	7172(5)	76(2)

Table 5. Bond lengths [Å] and angles [°].

S(1)-O(2)	1.429(6)
S(1)-O(3)	1.432(6)
S(1)-O(1)	1.471(6)
S(1)-C(5)	1.774(10)
N(1)-C(1)	1.328(10)
N(1)-C(4)	1.437(10)
N(1)-C(2)	1.485(9)
N(2)-C(1)	1.316(10)
N(2)-C(3)	1.445(10)
N(2)-C(16)	1.483(10)
C(2)-C(10)	1.499(12)
C(2)-C(3)	1.546(11)
C(4)-C(9)	1.384(11)
C(4)-C(5)	1.408(11)
C(5)-C(6)	1.363(12)
C(6)-C(7)	1.361(13)
C(7)-C(8)	1.400(13)
C(8)-C(9)	1.362(12)
C(10)-C(11)	1.353(13)
C(10)-C(15)	1.418(13)
C(11)-C(12)	1.372(14)
C(12)-C(13)	1.400(16)
C(13)-C(14)	1.408(16)
C(14)-C(15)	1.370(15)
C(16)-C(21)	1.359(12)
C(16)-C(17)	1.424(12)
C(17)-C(18)	1.390(12)
C(17)-C(22)	1.458(12)
C(18)-C(19)	1.366(12)
C(19)-C(20)	1.395(12)
C(19)-C(23)	1.516(12)
C(20)-C(21)	1.408(11)

C(21)-C(24)	1.494(12)
S(2)-O(6)	1.437(6)
S(2)-O(5)	1.438(6)
S(2)-O(4)	1.460(6)
S(2)-C(29)	1.755(10)
N(3)-C(25)	1.312(10)
N(3)-C(28)	1.455(10)
N(3)-C(26)	1.535(10)
N(4)-C(25)	1.322(10)
N(4)-C(40)	1.425(10)
N(4)-C(27)	1.502(10)
C(26)-C(34)	1.479(12)
C(26)-C(27)	1.537(11)
C(28)-C(33)	1.379(11)
C(28)-C(29)	1.425(12)
C(29)-C(30)	1.395(11)
C(30)-C(31)	1.360(11)
C(31)-C(32)	1.407(12)
C(32)-C(33)	1.364(11)
C(34)-C(39)	1.322(13)
C(34)-C(35)	1.424(13)
C(35)-C(36)	1.474(14)
C(36)-C(37)	1.358(16)
C(37)-C(38)	1.289(15)
C(38)-C(39)	1.533(15)
C(40)-C(45)	1.371(12)
C(40)-C(41)	1.436(11)
C(41)-C(42)	1.391(12)
C(41)-C(46)	1.475(13)
C(42)-C(43)	1.361(13)
C(43)-C(44)	1.398(12)
C(43)-C(47)	1.510(12)
C(44)-C(45)	1.382(12)
C(45)-C(48)	1.534(12)

S(3)-O(7)	1.436(6)
S(3)-O(8)	1.447(7)
S(3)-O(9)	1.453(7)
S(3)-C(53)	1.771(9)
N(5)-C(49)	1.334(10)
N(5)-C(52)	1.426(10)
N(5)-C(50)	1.508(10)
N(6)-C(49)	1.288(10)
N(6)-C(64)	1.460(10)
N(6)-C(51)	1.508(10)
C(50)-C(58)	1.475(12)
C(50)-C(51)	1.521(11)
C(52)-C(57)	1.328(11)
C(52)-C(53)	1.418(12)
C(53)-C(54)	1.397(12)
C(54)-C(55)	1.366(12)
C(55)-C(56)	1.336(13)
C(56)-C(57)	1.402(12)
C(58)-C(63)	1.397(13)
C(58)-C(59)	1.417(12)
C(59)-C(60)	1.376(14)
C(60)-C(61)	1.336(17)
C(61)-C(62)	1.353(16)
C(62)-C(63)	1.407(15)
C(64)-C(69)	1.378(12)
C(64)-C(65)	1.390(12)
C(65)-C(66)	1.413(12)
C(65)-C(70)	1.501(13)
C(66)-C(67)	1.358(13)
C(67)-C(68)	1.382(13)
C(67)-C(71)	1.478(13)
C(68)-C(69)	1.412(12)
C(69)-C(72)	1.531(13)
S(4)-O(12)	1.439(7)

S(4)-O(10)	1.444(6)
S(4)-O(11)	1.459(6)
S(4)-C(77)	1.793(10)
N(7)-C(73)	1.309(11)
N(7)-C(76)	1.431(11)
N(7)-C(74)	1.486(11)
N(8)-C(73)	1.306(11)
N(8)-C(88)	1.468(12)
N(8)-C(75)	1.491(11)
C(74)-C(82)	1.505(13)
C(74)-C(75)	1.552(13)
C(76)-C(81)	1.372(12)
C(76)-C(77)	1.400(12)
C(77)-C(78)	1.368(12)
C(78)-C(79)	1.409(14)
C(79)-C(80)	1.332(14)
C(80)-C(81)	1.442(13)
C(82)-C(87)	1.357(13)
C(82)-C(83)	1.362(13)
C(83)-C(84)	1.420(14)
C(84)-C(85)	1.342(15)
C(85)-C(86)	1.386(15)
C(86)-C(87)	1.424(15)
C(88)-C(89)	1.375(13)
C(88)-C(93)	1.376(13)
C(89)-C(90)	1.404(13)
C(89)-C(94)	1.531(14)
C(90)-C(91)	1.347(14)
C(91)-C(92)	1.411(15)
C(91)-C(95)	1.516(15)
C(92)-C(93)	1.398(14)
C(93)-C(96)	1.526(13)

O(2)-S(1)-O(3)	113.4(4)

O(2)-S(1)-O(1)	113.8(4)
O(3)-S(1)-O(1)	113.9(4)
O(2)-S(1)-C(5)	104.5(4)
O(3)-S(1)-C(5)	106.4(4)
O(1)-S(1)-C(5)	103.6(4)
C(1)-N(1)-C(4)	122.8(7)
C(1)-N(1)-C(2)	111.5(7)
C(4)-N(1)-C(2)	124.6(6)
C(1)-N(2)-C(3)	111.8(7)
C(1)-N(2)-C(16)	123.1(7)
C(3)-N(2)-C(16)	124.7(6)
N(2)-C(1)-N(1)	111.4(7)
N(1)-C(2)-C(10)	112.0(7)
N(1)-C(2)-C(3)	101.0(6)
C(10)-C(2)-C(3)	115.7(7)
N(2)-C(3)-C(2)	104.0(6)
C(9)-C(4)-C(5)	120.8(8)
C(9)-C(4)-N(1)	118.4(8)
C(5)-C(4)-N(1)	120.7(8)
C(6)-C(5)-C(4)	117.3(9)
C(6)-C(5)-S(1)	121.9(7)
C(4)-C(5)-S(1)	120.8(7)
C(7)-C(6)-C(5)	123.1(9)
C(6)-C(7)-C(8)	118.9(9)
C(9)-C(8)-C(7)	120.1(10)
C(8)-C(9)-C(4)	119.8(9)
C(11)-C(10)-C(15)	117.2(10)
C(11)-C(10)-C(2)	122.6(9)
C(15)-C(10)-C(2)	119.9(9)
C(10)-C(11)-C(12)	123.9(12)
C(11)-C(12)-C(13)	118.1(12)
C(12)-C(13)-C(14)	120.3(12)
C(15)-C(14)-C(13)	118.7(13)
C(14)-C(15)-C(10)	121.6(11)

C(21)-C(16)-C(17)	123.8(8)
C(21)-C(16)-N(2)	121.1(8)
C(17)-C(16)-N(2)	115.1(8)
C(18)-C(17)-C(16)	115.9(8)
C(18)-C(17)-C(22)	120.5(9)
C(16)-C(17)-C(22)	123.5(8)
C(19)-C(18)-C(17)	122.2(9)
C(18)-C(19)-C(20)	120.1(8)
C(18)-C(19)-C(23)	122.7(9)
C(20)-C(19)-C(23)	117.2(9)
C(19)-C(20)-C(21)	120.2(9)
C(16)-C(21)-C(20)	117.8(9)
C(16)-C(21)-C(24)	121.7(9)
C(20)-C(21)-C(24)	120.6(9)
O(6)-S(2)-O(5)	114.5(4)
O(6)-S(2)-O(4)	112.6(4)
O(5)-S(2)-O(4)	112.7(4)
O(6)-S(2)-C(29)	104.2(4)
O(5)-S(2)-C(29)	106.7(4)
O(4)-S(2)-C(29)	105.0(4)
C(25)-N(3)-C(28)	127.3(7)
C(25)-N(3)-C(26)	110.7(7)
C(28)-N(3)-C(26)	120.6(7)
C(25)-N(4)-C(40)	125.3(7)
C(25)-N(4)-C(27)	109.4(7)
C(40)-N(4)-C(27)	123.6(6)
N(3)-C(25)-N(4)	113.7(8)
C(34)-C(26)-N(3)	113.8(7)
C(34)-C(26)-C(27)	115.8(8)
N(3)-C(26)-C(27)	100.3(7)
N(4)-C(27)-C(26)	104.2(6)
C(33)-C(28)-C(29)	121.1(8)
C(33)-C(28)-N(3)	117.5(8)
C(29)-C(28)-N(3)	121.4(8)

C(30)-C(29)-C(28)	115.1(8)
C(30)-C(29)-S(2)	120.9(7)
C(28)-C(29)-S(2)	124.0(7)
C(31)-C(30)-C(29)	124.2(8)
C(30)-C(31)-C(32)	118.9(9)
C(33)-C(32)-C(31)	119.2(9)
C(32)-C(33)-C(28)	121.5(9)
C(39)-C(34)-C(35)	123.6(9)
C(39)-C(34)-C(26)	119.1(10)
C(35)-C(34)-C(26)	117.1(9)
C(34)-C(35)-C(36)	120.1(11)
C(37)-C(36)-C(35)	111.1(12)
C(38)-C(37)-C(36)	132.9(14)
C(37)-C(38)-C(39)	115.6(12)
C(34)-C(39)-C(38)	116.6(10)
C(45)-C(40)-N(4)	122.4(8)
C(45)-C(40)-C(41)	120.3(8)
N(4)-C(40)-C(41)	117.2(8)
C(42)-C(41)-C(40)	116.4(9)
C(42)-C(41)-C(46)	122.3(9)
C(40)-C(41)-C(46)	121.2(9)
C(43)-C(42)-C(41)	124.5(9)
C(42)-C(43)-C(44)	116.8(9)
C(42)-C(43)-C(47)	123.7(9)
C(44)-C(43)-C(47)	119.4(10)
C(45)-C(44)-C(43)	122.2(9)
C(40)-C(45)-C(44)	119.7(8)
C(40)-C(45)-C(48)	120.3(9)
C(44)-C(45)-C(48)	119.9(9)
O(7)-S(3)-O(8)	111.7(4)
O(7)-S(3)-O(9)	115.8(5)
O(8)-S(3)-O(9)	112.3(5)
O(7)-S(3)-C(53)	105.9(4)
O(8)-S(3)-C(53)	105.2(4)

O(9)-S(3)-C(53)	104.8(5)
C(49)-N(5)-C(52)	126.1(7)
C(49)-N(5)-C(50)	108.1(7)
C(52)-N(5)-C(50)	123.7(6)
C(49)-N(6)-C(64)	128.7(8)
C(49)-N(6)-C(51)	109.0(8)
C(64)-N(6)-C(51)	122.3(7)
N(6)-C(49)-N(5)	114.7(8)
C(58)-C(50)-N(5)	113.9(7)
C(58)-C(50)-C(51)	116.2(7)
N(5)-C(50)-C(51)	101.7(6)
N(6)-C(51)-C(50)	102.5(6)
C(57)-C(52)-C(53)	120.4(8)
C(57)-C(52)-N(5)	118.5(8)
C(53)-C(52)-N(5)	121.0(8)
C(54)-C(53)-C(52)	116.8(8)
C(54)-C(53)-S(3)	120.9(8)
C(52)-C(53)-S(3)	122.3(7)
C(55)-C(54)-C(53)	121.7(9)
C(56)-C(55)-C(54)	119.8(9)
C(55)-C(56)-C(57)	120.2(10)
C(52)-C(57)-C(56)	120.8(9)
C(63)-C(58)-C(59)	119.2(10)
C(63)-C(58)-C(50)	120.2(8)
C(59)-C(58)-C(50)	120.6(9)
C(60)-C(59)-C(58)	118.9(11)
C(61)-C(60)-C(59)	121.1(13)
C(60)-C(61)-C(62)	122.1(13)
C(61)-C(62)-C(63)	119.9(13)
C(58)-C(63)-C(62)	118.7(10)
C(69)-C(64)-C(65)	123.8(9)
C(69)-C(64)-N(6)	117.3(8)
C(65)-C(64)-N(6)	118.8(8)
C(64)-C(65)-C(66)	115.6(9)

C(64)-C(65)-C(70)	122.9(9)
C(66)-C(65)-C(70)	121.3(9)
C(67)-C(66)-C(65)	123.7(9)
C(66)-C(67)-C(68)	117.7(10)
C(66)-C(67)-C(71)	121.5(10)
C(68)-C(67)-C(71)	120.7(11)
C(67)-C(68)-C(69)	122.5(10)
C(64)-C(69)-C(68)	116.6(9)
C(64)-C(69)-C(72)	123.5(9)
C(68)-C(69)-C(72)	119.9(9)
O(12)-S(4)-O(10)	113.5(4)
O(12)-S(4)-O(11)	113.8(4)
O(10)-S(4)-O(11)	112.5(4)
O(12)-S(4)-C(77)	104.9(4)
O(10)-S(4)-C(77)	107.6(4)
O(11)-S(4)-C(77)	103.6(4)
C(73)-N(7)-C(76)	125.3(8)
C(73)-N(7)-C(74)	110.8(7)
C(76)-N(7)-C(74)	123.5(8)
C(73)-N(8)-C(88)	128.5(8)
C(73)-N(8)-C(75)	107.2(8)
C(88)-N(8)-C(75)	123.7(8)
N(8)-C(73)-N(7)	113.8(9)
N(7)-C(74)-C(82)	114.8(8)
N(7)-C(74)-C(75)	98.4(8)
C(82)-C(74)-C(75)	115.4(9)
N(8)-C(75)-C(74)	102.8(8)
C(81)-C(76)-C(77)	123.2(9)
C(81)-C(76)-N(7)	115.7(9)
C(77)-C(76)-N(7)	121.1(9)
C(78)-C(77)-C(76)	117.5(9)
C(78)-C(77)-S(4)	118.3(8)
C(76)-C(77)-S(4)	124.0(7)
C(77)-C(78)-C(79)	119.6(10)

C(80)-C(79)-C(78)	123.7(10)
C(79)-C(80)-C(81)	117.5(11)
C(76)-C(81)-C(80)	118.4(10)
C(87)-C(82)-C(83)	120.7(9)
C(87)-C(82)-C(74)	119.2(10)
C(83)-C(82)-C(74)	120.1(9)
C(82)-C(83)-C(84)	121.7(10)
C(85)-C(84)-C(83)	117.3(11)
C(84)-C(85)-C(86)	122.2(12)
C(85)-C(86)-C(87)	119.4(11)
C(82)-C(87)-C(86)	118.6(11)
C(89)-C(88)-C(93)	123.1(10)
C(89)-C(88)-N(8)	118.3(9)
C(93)-C(88)-N(8)	118.6(10)
C(88)-C(89)-C(90)	117.9(10)
C(88)-C(89)-C(94)	123.5(9)
C(90)-C(89)-C(94)	118.5(10)
C(91)-C(90)-C(89)	121.8(11)
C(90)-C(91)-C(92)	118.6(11)
C(90)-C(91)-C(95)	122.7(12)
C(92)-C(91)-C(95)	118.7(12)
C(93)-C(92)-C(91)	121.6(11)
C(88)-C(93)-C(92)	116.9(11)
C(88)-C(93)-C(96)	123.1(10)
C(92)-C(93)-C(96)	119.9(10)

Symmetry transformations used to generate equivalent atoms:

Table 6. Anisotropic displacement parameters ($Å^2 x 10^3$)for sad2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	37(1)	51(2)	72(2)	5(1)	11(1)	1(1)
O(1)	32(3)	65(4)	107(5)	19(4)	7(3)	6(3)
O(2)	47(4)	42(4)	87(5)	-1(3)	13(3)	-11(3)
O(3)	45(4)	83(5)	66(4)	3(4)	18(3)	4(4)
N(1)	26(4)	34(4)	64(5)	-6(4)	12(3)	7(3)
N(2)	39(4)	33(4)	58(5)	-2(4)	15(4)	1(3)
C(1)	31(5)	57(6)	55(6)	16(5)	11(5)	11(5)
C(2)	40(5)	42(5)	54(6)	9(5)	9(4)	0(4)
C(3)	44(5)	42(5)	74(7)	-18(5)	20(5)	-5(4)
C(4)	43(5)	25(5)	64(7)	10(5)	22(5)	0(4)
C(5)	17(4)	41(5)	95(7)	13(5)	27(5)	1(4)
C(6)	32(5)	51(6)	92(8)	4(6)	15(6)	-3(5)
C(7)	49(7)	37(6)	103(9)	-1(6)	33(6)	-10(5)
C(8)	51(6)	60(7)	65(7)	-3(6)	7(5)	-11(5)
C(9)	47(5)	39(5)	66(7)	-2(5)	21(5)	3(4)
C(10)	54(3)	42(3)	78(4)	4(3)	24(3)	4(3)
C(11)	46(4)	50(4)	116(5)	-14(3)	22(4)	0(3)
C(12)	59(4)	77(5)	150(8)	-29(6)	24(5)	2(4)
C(13)	43(4)	109(6)	145(7)	-48(6)	35(4)	-14(4)
C(14)	80(5)	113(7)	111(6)	-14(5)	30(5)	-5(5)
C(15)	63(4)	70(4)	91(5)	0(4)	36(4)	-14(3)
C(16)	24(4)	37(5)	77(7)	-2(5)	23(4)	-7(4)
C(17)	37(5)	43(6)	46(6)	-6(5)	8(4)	-5(4)
C(18)	42(5)	50(6)	56(6)	-11(6)	15(5)	-3(5)
C(19)	41(5)	49(6)	52(7)	-12(5)	18(5)	6(4)
C(20)	39(5)	29(5)	73(7)	3(5)	21(5)	0(4)
C(21)	42(5)	46(6)	49(6)	2(5)	15(4)	9(4)
C(22)	58(6)	71(7)	71(7)	11(6)	15(6)	-8(5)
C(23)	74(7)	54(7)	101(9)	-14(6)	42(6)	3(5)

C(24)	70(7)	72(7)	56(7)	10(6)	15(5)	18(5)
S(2)	49(1)	39(1)	58(2)	7(1)	18(1)	4(1)
O(4)	50(4)	49(4)	51(4)	5(3)	14(3)	-3(3)
O(5)	55(4)	51(4)	68(4)	10(3)	29(3)	-3(3)
O(6)	61(4)	42(4)	68(5)	7(3)	-6(3)	14(3)
N(3)	33(4)	33(4)	58(5)	-2(4)	12(4)	6(3)
N(4)	39(4)	20(4)	75(5)	-5(4)	24(4)	5(3)
C(25)	49(5)	23(5)	56(6)	0(4)	16(5)	1(4)
C(26)	27(5)	54(6)	85(7)	0(5)	14(5)	3(4)
C(27)	39(5)	34(5)	86(7)	-10(5)	23(5)	-5(4)
C(28)	42(5)	22(5)	66(7)	-9(4)	31(5)	-11(4)
C(29)	32(5)	27(5)	78(7)	-9(5)	27(5)	-5(4)
C(30)	36(5)	45(6)	54(6)	15(5)	13(5)	6(4)
C(31)	43(5)	31(5)	65(7)	-5(5)	19(5)	-1(4)
C(32)	57(6)	43(6)	72(7)	-7(6)	20(5)	-9(5)
C(33)	62(7)	26(5)	58(7)	0(5)	19(6)	2(4)
C(34)	54(3)	42(3)	78(4)	4(3)	24(3)	4(3)
C(35)	46(4)	50(4)	116(5)	-14(3)	22(4)	0(3)
C(36)	59(4)	77(5)	150(8)	-29(6)	24(5)	2(4)
C(37)	43(4)	109(6)	145(7)	-48(6)	35(4)	-14(4)
C(38)	80(5)	113(7)	111(6)	-14(5)	30(5)	-5(5)
C(39)	63(4)	70(4)	91(5)	0(4)	36(4)	-14(3)
C(40)	27(4)	33(5)	62(7)	2(5)	21(4)	4(4)
C(41)	37(5)	41(6)	70(7)	10(5)	25(5)	-3(4)
C(42)	41(6)	40(6)	77(8)	-10(6)	28(6)	-2(4)
C(43)	39(5)	46(6)	66(8)	-16(5)	24(5)	6(4)
C(44)	54(6)	45(6)	58(7)	-1(5)	13(5)	17(5)
C(45)	44(5)	35(5)	70(7)	-2(5)	24(5)	1(5)
C(46)	71(7)	36(5)	81(8)	18(5)	32(6)	7(5)
C(47)	55(6)	51(6)	110(9)	-20(6)	37(6)	-9(5)
C(48)	70(7)	42(6)	72(7)	15(5)	16(6)	4(5)
S(3)	52(2)	74(2)	59(2)	3(2)	14(1)	18(2)
O(7)	71(5)	95(6)	55(4)	17(4)	29(4)	10(4)
O(8)	65(5)	84(5)	70(5)	-14(4)	8(4)	-17(4)

O(9)	79(5)	128(7)	95(6)	-7(5)	8(4)	62(5)
N(5)	42(4)	29(4)	59(5)	-2(4)	16(4)	-6(3)
N(6)	51(5)	38(4)	56(5)	2(4)	19(4)	6(4)
C(49)	46(6)	57(7)	51(6)	4(5)	20(5)	9(5)
C(50)	39(5)	43(5)	62(6)	3(5)	17(5)	-4(4)
C(51)	33(5)	54(6)	99(8)	-6(6)	19(5)	-2(4)
C(52)	57(6)	35(5)	40(6)	-5(4)	21(5)	-1(5)
C(53)	52(6)	45(6)	50(6)	5(5)	14(5)	-1(5)
C(54)	50(6)	47(6)	61(7)	-5(5)	15(5)	-5(5)
C(55)	60(7)	49(6)	74(8)	-14(6)	35(6)	2(5)
C(56)	80(7)	36(6)	58(7)	0(5)	26(6)	-11(5)
C(57)	52(6)	54(6)	41(7)	0(5)	14(5)	-1(5)
C(58)	54(3)	42(3)	78(4)	4(3)	24(3)	4(3)
C(59)	46(4)	50(4)	116(5)	-14(3)	22(4)	0(3)
C(60)	59(4)	77(5)	150(8)	-29(6)	24(5)	2(4)
C(61)	43(4)	109(6)	145(7)	-48(6)	35(4)	-14(4)
C(62)	80(5)	113(7)	111(6)	-14(5)	30(5)	-5(5)
C(63)	63(4)	70(4)	91(5)	0(4)	36(4)	-14(3)
C(64)	51(5)	35(6)	58(7)	-11(5)	17(5)	3(4)
C(65)	53(6)	52(7)	64(7)	2(6)	22(5)	-1(5)
C(66)	59(6)	28(5)	66(8)	1(5)	27(6)	-7(4)
C(67)	53(6)	51(7)	73(8)	0(6)	29(6)	-10(5)
C(68)	48(6)	67(8)	67(7)	-11(6)	3(5)	-4(5)
C(69)	58(6)	51(6)	52(7)	2(5)	13(5)	-3(5)
C(70)	81(8)	53(7)	77(8)	1(6)	19(6)	16(5)
C(71)	54(7)	70(8)	103(9)	-4(7)	25(6)	-7(6)
C(72)	91(8)	40(6)	68(7)	-2(5)	11(6)	6(5)
S(4)	43(2)	82(2)	68(2)	4(2)	8(1)	5(1)
O(10)	38(4)	105(6)	77(5)	-3(4)	17(3)	14(4)
O(11)	35(4)	81(5)	94(5)	-18(4)	3(3)	-1(3)
O(12)	64(4)	68(5)	106(6)	27(4)	25(4)	8(4)
N(7)	45(5)	45(5)	74(6)	-9(4)	22(4)	7(4)
N(8)	46(5)	59(5)	58(5)	-5(4)	14(4)	-10(4)
C(73)	50(6)	58(7)	59(7)	-6(6)	23(5)	3(6)

C(74)	65(7)	67(7)	64(7)	6(6)	1(5)	17(6)
C(75)	59(7)	68(7)	74(7)	-24(6)	6(6)	11(5)
C(76)	44(6)	60(7)	59(7)	1(6)	17(5)	-11(5)
C(77)	30(5)	37(5)	85(7)	1(5)	16(5)	-10(4)
C(78)	65(7)	64(7)	72(8)	-7(6)	14(6)	9(6)
C(79)	46(6)	66(8)	113(11)	-12(8)	12(7)	19(5)
C(80)	69(7)	59(8)	105(10)	-2(7)	50(7)	-6(6)
C(81)	74(7)	64(7)	65(7)	-7(6)	26(6)	1(6)
C(82)	51(6)	45(6)	63(7)	-10(6)	14(5)	-1(5)
C(83)	51(6)	68(8)	66(8)	-15(6)	-18(5)	14(6)
C(84)	60(7)	76(8)	84(9)	10(7)	9(7)	-4(6)
C(85)	61(8)	68(8)	124(12)	-17(9)	31(8)	6(6)
C(86)	44(7)	118(11)	77(9)	-28(8)	-17(6)	8(7)
C(87)	89(8)	84(8)	52(8)	-10(6)	3(6)	-3(7)
C(88)	57(7)	67(8)	72(8)	-16(7)	27(6)	3(6)
C(89)	56(6)	51(7)	64(7)	0(6)	27(5)	0(5)
C(90)	74(7)	53(7)	80(9)	-2(6)	29(6)	-8(5)
C(91)	76(8)	70(9)	93(10)	-6(8)	40(7)	0(6)
C(92)	69(7)	77(9)	87(9)	6(7)	30(6)	-10(6)
C(93)	47(6)	51(7)	73(8)	-2(6)	15(5)	1(5)
C(94)	59(6)	81(8)	84(8)	9(6)	14(6)	16(6)
C(95)	128(12)	55(8)	149(13)	-27(8)	44(10)	-9(7)
C(96)	59(7)	73(7)	64(7)	-5(6)	12(5)	-3(5)
O(13S)	43(4)	84(5)	100(6)	-15(4)	13(4)	8(4)

Table 7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sad2.

	x	y	z	U(eq)
H(1)	8303	3472	9255	57
H(2)	9910	4672	8383	54
H(3A)	10287	3727	7896	62
H(3B)	10962	3523	8820	62
H(6)	6587	5560	9141	70
H(7)	7162	5873	10533	72
H(8)	8739	5477	11336	72
H(9)	9656	4744	10738	60
H(11)	11002	5496	9005	84
H(12)	12396	5914	9970	114
H(13)	13160	5308	11183	116
H(14)	12590	4258	11328	120
H(15)	11201	3867	10319	86
H(18)	8606	1749	6762	58
H(20)	9500	1221	9221	55
H(22A)	8746	3414	7171	100
H(22B)	7895	2945	6637	100
H(22C)	9034	2947	6477	100
H(23A)	9083	440	8242	109
H(23B)	9388	587	7358	109
H(23C)	8207	603	7412	109
H(24A)	9935	1971	10326	98
H(24B)	9327	2631	10150	98
H(24C)	10499	2588	10072	98
H(25)	6142	4022	9544	50
H(26)	3587	3826	8024	66
H(27A)	3257	4531	8961	62
H(27B)	3383	4011	9711	62

H(30)	7122	1958	8543	54
H(31)	6612	1971	7089	54
H(32)	5265	2661	6418	67
H(33)	4540	3340	7242	58
H(35)	2387	3130	7396	84
H(36)	1291	2179	7425	114
H(37)	1429	1763	8752	116
H(38)	2560	1978	9923	120
H(39)	3776	2900	9887	86
H(42)	4922	6396	10508	60
H(44)	6118	5079	12238	63
H(46A)	4140	5298	8783	91
H(46B)	4696	5977	8895	91
H(46C)	3609	5888	9140	91
H(47A)	6246	6124	12686	104
H(47B)	5318	6574	12226	104
H(47C)	6404	6615	11968	104
H(48A)	6104	3997	11937	92
H(48B)	6244	3848	10997	92
H(48C)	5141	3766	11214	92
H(49)	4104	5454	5805	60
H(50)	5685	6691	5190	57
H(51A)	6266	5841	4619	74
H(51B)	6778	5530	5533	74
H(54)	2853	7609	6578	63
H(55)	3595	7618	8018	69
H(56)	5019	7012	8548	67
H(57)	5640	6310	7652	58
H(59)	6864	7512	5601	84
H(60)	8196	7968	6613	114
H(61)	9096	7387	7717	116
H(62)	8628	6371	7968	120
H(63)	7250	5873	6999	86
H(66)	5018	3320	4468	59

H(68)	3830	4546	2620	75
H(70A)	5827	3640	5859	106
H(70B)	5277	4242	6169	106
H(70C)	6370	4322	5932	106
H(71A)	3814	3483	2278	112
H(71B)	3703	3011	3030	112
H(71C)	4798	3105	2800	112
H(72A)	3727	5645	2843	101
H(72B)	4692	5924	3524	101
H(72C)	3607	5841	3774	101
H(73)	1832	6211	6238	65
H(74)	-327	6063	4420	81
H(75A)	-1003	6747	5256	82
H(75B)	-919	6236	6015	82
H(78)	2596	3966	6215	81
H(79)	2693	3782	4807	91
H(80)	1838	4390	3703	87
H(81)	966	5335	4029	79
H(83)	-785	5071	6093	80
H(84)	-1832	4145	5911	89
H(85)	-2764	3904	4567	99
H(86)	-2683	4537	3401	102
H(87)	-1576	5444	3594	92
H(90)	421	8774	6162	80
H(92)	1444	7826	8353	90
H(94A)	-51	8281	4853	113
H(94B)	-599	7607	4875	113
H(94C)	559	7639	4761	113
H(95A)	1326	8917	8428	163
H(95B)	388	9223	7746	163
H(95C)	1538	9294	7624	163
H(96A)	1147	6257	7436	98
H(96B)	880	6588	8252	98
H(96C)	2028	6615	8115	98

H(131)	4900(40)	4790(50)	7500(60)	114
H(132)	3930(60)	4930(40)	7290(70)	114

Table 8. Torsion angles [°].

C(3)-N(2)-C(1)-N(1)	2.4(10)
C(16)-N(2)-C(1)-N(1)	175.6(8)
C(4)-N(1)-C(1)-N(2)	170.2(7)
C(2)-N(1)-C(1)-N(2)	1.5(10)
C(1)-N(1)-C(2)-C(10)	-128.0(8)
C(4)-N(1)-C(2)-C(10)	63.6(10)
C(1)-N(1)-C(2)-C(3)	-4.3(9)
C(4)-N(1)-C(2)-C(3)	-172.8(8)
C(1)-N(2)-C(3)-C(2)	-5.0(9)
C(16)-N(2)-C(3)-C(2)	-178.1(8)
N(1)-C(2)-C(3)-N(2)	5.3(8)
C(10)-C(2)-C(3)-N(2)	126.4(8)
C(1)-N(1)-C(4)-C(9)	108.7(9)
C(2)-N(1)-C(4)-C(9)	-84.1(10)
C(1)-N(1)-C(4)-C(5)	-69.2(11)
C(2)-N(1)-C(4)-C(5)	98.0(9)
C(9)-C(4)-C(5)-C(6)	-0.9(12)
N(1)-C(4)-C(5)-C(6)	176.9(7)
C(9)-C(4)-C(5)-S(1)	-179.0(6)
N(1)-C(4)-C(5)-S(1)	-1.2(10)
O(2)-S(1)-C(5)-C(6)	-111.5(7)
O(3)-S(1)-C(5)-C(6)	128.3(7)
O(1)-S(1)-C(5)-C(6)	8.0(8)
O(2)-S(1)-C(5)-C(4)	66.5(7)
O(3)-S(1)-C(5)-C(4)	-53.7(7)
O(1)-S(1)-C(5)-C(4)	-174.0(6)
C(4)-C(5)-C(6)-C(7)	-0.2(13)
S(1)-C(5)-C(6)-C(7)	177.9(7)
C(5)-C(6)-C(7)-C(8)	1.4(14)
C(6)-C(7)-C(8)-C(9)	-1.4(13)
C(7)-C(8)-C(9)-C(4)	0.4(13)
C(5)-C(4)-C(9)-C(8)	0.8(12)

N(1)-C(4)-C(9)-C(8)	-177.1(7)
N(1)-C(2)-C(10)-C(11)	-112.9(9)
C(3)-C(2)-C(10)-C(11)	132.1(9)
N(1)-C(2)-C(10)-C(15)	60.9(10)
C(3)-C(2)-C(10)-C(15)	-54.1(11)
C(15)-C(10)-C(11)-C(12)	5.8(15)
C(2)-C(10)-C(11)-C(12)	179.8(9)
C(10)-C(11)-C(12)-C(13)	-4.4(17)
C(11)-C(12)-C(13)-C(14)	2.1(17)
C(12)-C(13)-C(14)-C(15)	-1.7(17)
C(13)-C(14)-C(15)-C(10)	3.3(16)
C(11)-C(10)-C(15)-C(14)	-5.2(14)
C(2)-C(10)-C(15)-C(14)	-179.4(9)
C(1)-N(2)-C(16)-C(21)	-67.8(10)
C(3)-N(2)-C(16)-C(21)	104.5(10)
C(1)-N(2)-C(16)-C(17)	112.6(9)
C(3)-N(2)-C(16)-C(17)	-75.1(10)
C(21)-C(16)-C(17)-C(18)	-2.3(12)
N(2)-C(16)-C(17)-C(18)	177.3(6)
C(21)-C(16)-C(17)-C(22)	174.1(8)
N(2)-C(16)-C(17)-C(22)	-6.3(11)
C(16)-C(17)-C(18)-C(19)	2.2(12)
C(22)-C(17)-C(18)-C(19)	-174.3(8)
C(17)-C(18)-C(19)-C(20)	-1.6(13)
C(17)-C(18)-C(19)-C(23)	-179.1(8)
C(18)-C(19)-C(20)-C(21)	0.9(12)
C(23)-C(19)-C(20)-C(21)	178.6(7)
C(17)-C(16)-C(21)-C(20)	1.7(12)
N(2)-C(16)-C(21)-C(20)	-177.9(7)
C(17)-C(16)-C(21)-C(24)	-178.4(7)
N(2)-C(16)-C(21)-C(24)	2.0(11)
C(19)-C(20)-C(21)-C(16)	-1.0(12)
C(19)-C(20)-C(21)-C(24)	179.2(8)
C(28)-N(3)-C(25)-N(4)	170.7(7)

C(26)-N(3)-C(25)-N(4)	4.7(10)
C(40)-N(4)-C(25)-N(3)	169.8(7)
C(27)-N(4)-C(25)-N(3)	4.3(10)
C(25)-N(3)-C(26)-C(34)	-135.4(8)
C(28)-N(3)-C(26)-C(34)	57.5(11)
C(25)-N(3)-C(26)-C(27)	-11.0(9)
C(28)-N(3)-C(26)-C(27)	-178.1(7)
C(25)-N(4)-C(27)-C(26)	-11.2(9)
C(40)-N(4)-C(27)-C(26)	-176.9(7)
C(34)-C(26)-C(27)-N(4)	135.4(8)
N(3)-C(26)-C(27)-N(4)	12.5(8)
C(25)-N(3)-C(28)-C(33)	-122.4(9)
C(26)-N(3)-C(28)-C(33)	42.4(10)
C(25)-N(3)-C(28)-C(29)	58.2(11)
C(26)-N(3)-C(28)-C(29)	-137.0(8)
C(33)-C(28)-C(29)-C(30)	1.9(11)
N(3)-C(28)-C(29)-C(30)	-178.7(6)
C(33)-C(28)-C(29)-S(2)	-179.9(6)
N(3)-C(28)-C(29)-S(2)	-0.5(10)
O(6)-S(2)-C(29)-C(30)	-12.2(7)
O(5)-S(2)-C(29)-C(30)	-133.8(6)
O(4)-S(2)-C(29)-C(30)	106.4(7)
O(6)-S(2)-C(29)-C(28)	169.7(6)
O(5)-S(2)-C(29)-C(28)	48.1(7)
O(4)-S(2)-C(29)-C(28)	-71.7(7)
C(28)-C(29)-C(30)-C(31)	0.5(12)
S(2)-C(29)-C(30)-C(31)	-177.7(7)
C(29)-C(30)-C(31)-C(32)	-2.3(13)
C(30)-C(31)-C(32)-C(33)	1.5(13)
C(31)-C(32)-C(33)-C(28)	0.9(13)
C(29)-C(28)-C(33)-C(32)	-2.7(12)
N(3)-C(28)-C(33)-C(32)	177.9(7)
N(3)-C(26)-C(34)-C(39)	62.1(12)
C(27)-C(26)-C(34)-C(39)	-53.5(11)

N(3)-C(26)-C(34)-C(35)	-123.7(9)
C(27)-C(26)-C(34)-C(35)	120.8(9)
C(39)-C(34)-C(35)-C(36)	-2.3(14)
C(26)-C(34)-C(35)-C(36)	-176.3(8)
C(34)-C(35)-C(36)-C(37)	4.7(14)
C(35)-C(36)-C(37)-C(38)	-6(2)
C(36)-C(37)-C(38)-C(39)	4(2)
C(35)-C(34)-C(39)-C(38)	-0.2(14)
C(26)-C(34)-C(39)-C(38)	173.6(8)
C(37)-C(38)-C(39)-C(34)	0.0(15)
C(25)-N(4)-C(40)-C(45)	-59.1(11)
C(27)-N(4)-C(40)-C(45)	104.4(9)
C(25)-N(4)-C(40)-C(41)	123.7(8)
C(27)-N(4)-C(40)-C(41)	-72.9(9)
C(45)-C(40)-C(41)-C(42)	2.7(11)
N(4)-C(40)-C(41)-C(42)	-180.0(7)
C(45)-C(40)-C(41)-C(46)	-177.6(8)
N(4)-C(40)-C(41)-C(46)	-0.2(11)
C(40)-C(41)-C(42)-C(43)	-0.8(12)
C(46)-C(41)-C(42)-C(43)	179.5(8)
C(41)-C(42)-C(43)-C(44)	-0.4(13)
C(41)-C(42)-C(43)-C(47)	176.5(8)
C(42)-C(43)-C(44)-C(45)	-0.2(12)
C(47)-C(43)-C(44)-C(45)	-177.2(8)
N(4)-C(40)-C(45)-C(44)	179.5(7)
C(41)-C(40)-C(45)-C(44)	-3.3(12)
N(4)-C(40)-C(45)-C(48)	1.6(12)
C(41)-C(40)-C(45)-C(48)	178.8(7)
C(43)-C(44)-C(45)-C(40)	2.1(12)
C(43)-C(44)-C(45)-C(48)	179.9(8)
C(64)-N(6)-C(49)-N(5)	-172.2(8)
C(51)-N(6)-C(49)-N(5)	5.1(10)
C(52)-N(5)-C(49)-N(6)	172.2(8)
C(50)-N(5)-C(49)-N(6)	8.5(10)

C(49)-N(5)-C(50)-C(58)	-143.4(8)
C(52)-N(5)-C(50)-C(58)	52.4(11)
C(49)-N(5)-C(50)-C(51)	-17.6(9)
C(52)-N(5)-C(50)-C(51)	178.2(8)
C(49)-N(6)-C(51)-C(50)	-15.9(10)
C(64)-N(6)-C(51)-C(50)	161.6(7)
C(58)-C(50)-C(51)-N(6)	143.4(8)
N(5)-C(50)-C(51)-N(6)	19.1(9)
C(49)-N(5)-C(52)-C(57)	107.1(10)
C(50)-N(5)-C(52)-C(57)	-91.6(10)
C(49)-N(5)-C(52)-C(53)	-69.9(11)
C(50)-N(5)-C(52)-C(53)	91.4(10)
C(57)-C(52)-C(53)-C(54)	3.5(13)
N(5)-C(52)-C(53)-C(54)	-179.6(7)
C(57)-C(52)-C(53)-S(3)	-177.4(7)
N(5)-C(52)-C(53)-S(3)	-0.5(11)
O(7)-S(3)-C(53)-C(54)	123.6(7)
O(8)-S(3)-C(53)-C(54)	-117.9(8)
O(9)-S(3)-C(53)-C(54)	0.6(9)
O(7)-S(3)-C(53)-C(52)	-55.5(8)
O(8)-S(3)-C(53)-C(52)	63.0(8)
O(9)-S(3)-C(53)-C(52)	-178.4(7)
C(52)-C(53)-C(54)-C(55)	-1.7(13)
S(3)-C(53)-C(54)-C(55)	179.2(7)
C(53)-C(54)-C(55)-C(56)	1.2(14)
C(54)-C(55)-C(56)-C(57)	-2.3(14)
C(53)-C(52)-C(57)-C(56)	-4.7(14)
N(5)-C(52)-C(57)-C(56)	178.3(7)
C(55)-C(56)-C(57)-C(52)	4.2(14)
N(5)-C(50)-C(58)-C(63)	60.3(11)
C(51)-C(50)-C(58)-C(63)	-57.5(12)
N(5)-C(50)-C(58)-C(59)	-121.5(9)
C(51)-C(50)-C(58)-C(59)	120.8(9)
C(63)-C(58)-C(59)-C(60)	-5.2(14)

C(50)-C(58)-C(59)-C(60)	176.6(9)
C(58)-C(59)-C(60)-C(61)	4.6(16)
C(59)-C(60)-C(61)-C(62)	-2.9(19)
C(60)-C(61)-C(62)-C(63)	1.8(18)
C(59)-C(58)-C(63)-C(62)	4.1(14)
C(50)-C(58)-C(63)-C(62)	-177.6(9)
C(61)-C(62)-C(63)-C(58)	-2.5(16)
C(49)-N(6)-C(64)-C(69)	93.7(11)
C(51)-N(6)-C(64)-C(69)	-83.3(10)
C(49)-N(6)-C(64)-C(65)	-89.8(11)
C(51)-N(6)-C(64)-C(65)	93.2(10)
C(69)-C(64)-C(65)-C(66)	-2.4(13)
N(6)-C(64)-C(65)-C(66)	-178.7(7)
C(69)-C(64)-C(65)-C(70)	-178.2(9)
N(6)-C(64)-C(65)-C(70)	5.6(13)
C(64)-C(65)-C(66)-C(67)	4.0(13)
C(70)-C(65)-C(66)-C(67)	179.8(9)
C(65)-C(66)-C(67)-C(68)	-2.1(13)
C(65)-C(66)-C(67)-C(71)	175.5(8)
C(66)-C(67)-C(68)-C(69)	-1.5(14)
C(71)-C(67)-C(68)-C(69)	-179.1(8)
C(65)-C(64)-C(69)-C(68)	-0.8(13)
N(6)-C(64)-C(69)-C(68)	175.5(7)
C(65)-C(64)-C(69)-C(72)	-179.3(9)
N(6)-C(64)-C(69)-C(72)	-3.0(12)
C(67)-C(68)-C(69)-C(64)	2.9(13)
C(67)-C(68)-C(69)-C(72)	-178.5(9)
C(88)-N(8)-C(73)-N(7)	-178.3(9)
C(75)-N(8)-C(73)-N(7)	10.4(11)
C(76)-N(7)-C(73)-N(8)	-178.9(8)
C(74)-N(7)-C(73)-N(8)	7.9(11)
C(73)-N(7)-C(74)-C(82)	-144.1(9)
C(76)-N(7)-C(74)-C(82)	42.6(12)
C(73)-N(7)-C(74)-C(75)	-21.0(10)

C(76)-N(7)-C(74)-C(75)	165.6(8)
C(73)-N(8)-C(75)-C(74)	-23.0(10)
C(88)-N(8)-C(75)-C(74)	165.2(8)
N(7)-C(74)-C(75)-N(8)	25.0(9)
C(82)-C(74)-C(75)-N(8)	147.6(8)
C(73)-N(7)-C(76)-C(81)	-120.2(10)
C(74)-N(7)-C(76)-C(81)	52.2(12)
C(73)-N(7)-C(76)-C(77)	59.9(12)
C(74)-N(7)-C(76)-C(77)	-127.7(9)
C(81)-C(76)-C(77)-C(78)	2.5(13)
N(7)-C(76)-C(77)-C(78)	-177.6(8)
C(81)-C(76)-C(77)-S(4)	178.1(7)
N(7)-C(76)-C(77)-S(4)	-2.1(11)
O(12)-S(4)-C(77)-C(78)	-24.4(8)
O(10)-S(4)-C(77)-C(78)	-145.5(7)
O(11)-S(4)-C(77)-C(78)	95.2(7)
O(12)-S(4)-C(77)-C(76)	160.1(7)
O(10)-S(4)-C(77)-C(76)	39.0(8)
O(11)-S(4)-C(77)-C(76)	-80.3(7)
C(76)-C(77)-C(78)-C(79)	-1.5(13)
S(4)-C(77)-C(78)-C(79)	-177.3(7)
C(77)-C(78)-C(79)-C(80)	-1.8(16)
C(78)-C(79)-C(80)-C(81)	4.0(16)
C(77)-C(76)-C(81)-C(80)	-0.4(14)
N(7)-C(76)-C(81)-C(80)	179.7(8)
C(79)-C(80)-C(81)-C(76)	-2.8(14)
N(7)-C(74)-C(82)-C(87)	-127.2(10)
C(75)-C(74)-C(82)-C(87)	119.5(10)
N(7)-C(74)-C(82)-C(83)	51.5(12)
C(75)-C(74)-C(82)-C(83)	-61.9(12)
C(87)-C(82)-C(83)-C(84)	2.6(15)
C(74)-C(82)-C(83)-C(84)	-176.1(9)
C(82)-C(83)-C(84)-C(85)	-2.0(15)
C(83)-C(84)-C(85)-C(86)	0.2(16)

C(84)-C(85)-C(86)-C(87)	1.0(17)
C(83)-C(82)-C(87)-C(86)	-1.2(15)
C(74)-C(82)-C(87)-C(86)	177.4(9)
C(85)-C(86)-C(87)-C(82)	-0.5(16)
C(73)-N(8)-C(88)-C(89)	121.0(11)
C(75)-N(8)-C(88)-C(89)	-69.0(12)
C(73)-N(8)-C(88)-C(93)	-59.0(13)
C(75)-N(8)-C(88)-C(93)	110.9(11)
C(93)-C(88)-C(89)-C(90)	-3.2(14)
N(8)-C(88)-C(89)-C(90)	176.8(8)
C(93)-C(88)-C(89)-C(94)	178.5(9)
N(8)-C(88)-C(89)-C(94)	-1.5(14)
C(88)-C(89)-C(90)-C(91)	1.9(15)
C(94)-C(89)-C(90)-C(91)	-179.7(9)
C(89)-C(90)-C(91)-C(92)	0.3(16)
C(89)-C(90)-C(91)-C(95)	-178.4(10)
C(90)-C(91)-C(92)-C(93)	-1.5(15)
C(95)-C(91)-C(92)-C(93)	177.2(10)
C(89)-C(88)-C(93)-C(92)	2.0(14)
N(8)-C(88)-C(93)-C(92)	-177.9(8)
C(89)-C(88)-C(93)-C(96)	-178.9(9)
N(8)-C(88)-C(93)-C(96)	1.2(14)
C(91)-C(92)-C(93)-C(88)	0.3(14)
C(91)-C(92)-C(93)-C(96)	-178.8(9)

Symmetry transformations used to generate equivalent atoms:

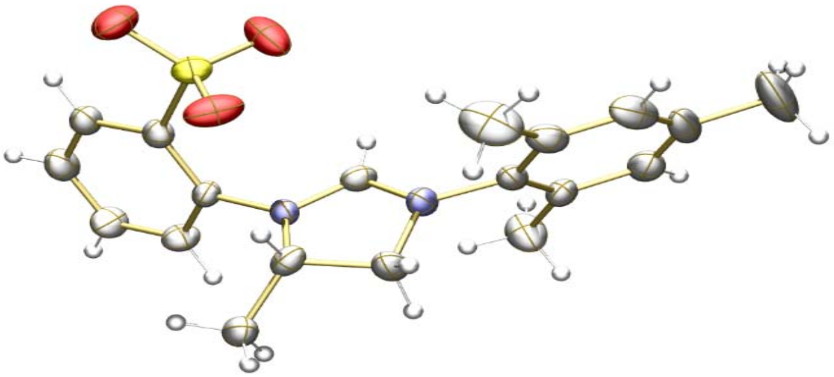


Table 1. Crystal data and structure refinement for sad.

Identification code	C19H22N2O3S	
Empirical formula	C19 H22 N2 O3 S	
Formula weight	358.45	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 12.072(4) Å	α= 90°.
	b = 11.684(4) Å	β= 107.969(4)°.
	c = 13.125(4) Å	γ = 90°.
Volume	1760.9(10) Å^3	
Z	4	
Density (calculated)	1.352 Mg/m^3	
Absorption coefficient	0.205 mm^{-1}	
F(000)	760	
Crystal size	0.10 x 0.07 x 0.04 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Index ranges	-14<=h<=14, -13<=k<=13, -15<=l<=15	

Reflections collected	12145
Independent reflections	6084 [R(int) = 0.0323]
Completeness to theta = 25.00°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9919 and 0.9798
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6084 / 1 / 451
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0483, wR2 = 0.1093
R indices (all data)	R1 = 0.0619, wR2 = 0.1175
Absolute structure parameter	0.04(9)
Extinction coefficient	na
Largest diff. peak and hole	0.277 and -0.256 e.Å^{-3}

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

	x	y	z	U(eq)
S(1)	8631(1)	5427(1)	7991(1)	32(1)
O(1)	9003(3)	4999(2)	9067(2)	49(1)
O(2)	7537(2)	6019(3)	7729(3)	54(1)
O(3)	8705(3)	4593(3)	7208(2)	52(1)
N(1)	9574(2)	7408(3)	9612(2)	25(1)
N(2)	8306(3)	7573(3)	10488(2)	32(1)
C(1)	9656(3)	6516(3)	7931(3)	29(1)
C(2)	10093(3)	6540(4)	7074(3)	33(1)
C(3)	10862(3)	7365(4)	6995(3)	40(1)
C(4)	11193(4)	8216(4)	7761(3)	40(1)
C(5)	10762(3)	8222(3)	8621(3)	34(1)
C(6)	9998(3)	7377(3)	8704(3)	26(1)
C(7)	10180(3)	6863(3)	10670(3)	31(1)
C(8)	9403(3)	7277(4)	11319(3)	37(1)
C(9)	8509(3)	7689(3)	9560(3)	30(1)
C(10)	11444(3)	7173(3)	11119(3)	37(1)
C(11)	7245(3)	7883(4)	10687(3)	29(1)
C(12)	6923(3)	9024(3)	10669(3)	32(1)
C(13)	5859(3)	9259(4)	10836(3)	40(1)
C(14)	5151(4)	8408(5)	11025(3)	48(1)
C(15)	5538(4)	7292(5)	11061(3)	49(1)
C(16)	6575(3)	7002(4)	10912(3)	38(1)
C(17)	7655(4)	9962(4)	10452(4)	50(1)
C(18)	4007(4)	8683(6)	11193(4)	81(2)
C(19)	6962(5)	5777(4)	10977(5)	68(2)
S(2)	6494(1)	9496(1)	6988(1)	31(1)
O(4)	6227(3)	9735(2)	5859(2)	42(1)
O(5)	7632(2)	9000(2)	7443(2)	43(1)
O(6)	6255(2)	10438(3)	7603(2)	44(1)

N(3)	5604(2)	7353(3)	5492(2)	26(1)
N(4)	6826(2)	7191(3)	4576(2)	29(1)
C(20)	5493(3)	8388(3)	7086(3)	26(1)
C(21)	5040(3)	8457(4)	7937(3)	37(1)
C(22)	4261(4)	7638(4)	8060(3)	42(1)
C(23)	3903(3)	6770(4)	7327(3)	42(1)
C(24)	4362(3)	6683(4)	6483(3)	34(1)
C(25)	5172(3)	7480(3)	6382(3)	25(1)
C(26)	4819(3)	7334(3)	4358(3)	31(1)
C(27)	5688(3)	7227(4)	3731(3)	42(1)
C(28)	6680(3)	7283(3)	5527(3)	28(1)
C(29)	4067(4)	8389(4)	4092(3)	48(1)
C(30)	7934(3)	7065(3)	4371(3)	27(1)
C(31)	8362(3)	5968(3)	4324(3)	30(1)
C(32)	9442(3)	5886(4)	4160(3)	34(1)
C(33)	10065(3)	6839(3)	4029(3)	31(1)
C(34)	9574(3)	7907(4)	4023(3)	31(1)
C(35)	8496(3)	8053(3)	4188(3)	32(1)
C(36)	7720(4)	4921(4)	4485(3)	42(1)
C(37)	11253(3)	6711(4)	3893(3)	46(1)
C(38)	7946(4)	9218(4)	4150(4)	50(1)

Table 3. Bond lengths [Å] and angles [°] for sad.

S(1)-O(1)	1.433(3)
S(1)-O(2)	1.435(3)
S(1)-O(3)	1.439(3)
S(1)-C(1)	1.793(4)
N(1)-C(9)	1.308(5)
N(1)-C(6)	1.435(4)
N(1)-C(7)	1.497(4)
N(2)-C(9)	1.322(5)
N(2)-C(11)	1.431(4)
N(2)-C(8)	1.474(5)
C(1)-C(2)	1.383(5)
C(1)-C(6)	1.398(5)
C(2)-C(3)	1.364(6)
C(3)-C(4)	1.382(6)
C(4)-C(5)	1.381(5)
C(5)-C(6)	1.379(5)
C(7)-C(10)	1.500(5)
C(7)-C(8)	1.528(5)
C(11)-C(12)	1.387(6)
C(11)-C(16)	1.395(6)
C(12)-C(13)	1.396(6)
C(12)-C(17)	1.489(6)
C(13)-C(14)	1.382(6)
C(14)-C(15)	1.381(7)
C(14)-C(18)	1.499(6)
C(15)-C(16)	1.367(6)
C(16)-C(19)	1.500(6)
S(2)-O(5)	1.439(3)
S(2)-O(4)	1.444(3)
S(2)-O(6)	1.445(3)
S(2)-C(20)	1.803(4)
N(3)-C(28)	1.288(5)

N(3)-C(25)	1.427(4)
N(3)-C(26)	1.498(4)
N(4)-C(28)	1.317(4)
N(4)-C(30)	1.450(4)
N(4)-C(27)	1.476(5)
C(20)-C(25)	1.381(5)
C(20)-C(21)	1.389(5)
C(21)-C(22)	1.386(6)
C(22)-C(23)	1.373(6)
C(23)-C(24)	1.387(5)
C(24)-C(25)	1.386(5)
C(26)-C(29)	1.506(6)
C(26)-C(27)	1.526(5)
C(30)-C(31)	1.390(5)
C(30)-C(35)	1.397(6)
C(31)-C(32)	1.389(5)
C(31)-C(36)	1.497(5)
C(32)-C(33)	1.384(6)
C(33)-C(34)	1.381(6)
C(33)-C(37)	1.506(5)
C(34)-C(35)	1.394(5)
C(35)-C(38)	1.508(6)
O(1)-S(1)-O(2)	113.0(2)
O(1)-S(1)-O(3)	113.42(19)
O(2)-S(1)-O(3)	114.2(2)
O(1)-S(1)-C(1)	106.30(18)
O(2)-S(1)-C(1)	104.11(18)
O(3)-S(1)-C(1)	104.68(18)
C(9)-N(1)-C(6)	124.0(3)
C(9)-N(1)-C(7)	110.3(3)
C(6)-N(1)-C(7)	124.2(3)
C(9)-N(2)-C(11)	125.0(3)
C(9)-N(2)-C(8)	109.1(3)

C(11)-N(2)-C(8)	125.1(3)
C(2)-C(1)-C(6)	118.4(4)
C(2)-C(1)-S(1)	119.5(3)
C(6)-C(1)-S(1)	122.1(3)
C(3)-C(2)-C(1)	121.1(4)
C(2)-C(3)-C(4)	120.2(4)
C(5)-C(4)-C(3)	120.1(4)
C(6)-C(5)-C(4)	119.4(4)
C(5)-C(6)-C(1)	120.8(3)
C(5)-C(6)-N(1)	117.8(3)
C(1)-C(6)-N(1)	121.4(3)
N(1)-C(7)-C(10)	114.1(3)
N(1)-C(7)-C(8)	100.0(3)
C(10)-C(7)-C(8)	115.4(3)
N(2)-C(8)-C(7)	103.1(3)
N(1)-C(9)-N(2)	112.6(3)
C(12)-C(11)-C(16)	122.4(4)
C(12)-C(11)-N(2)	120.1(4)
C(16)-C(11)-N(2)	117.5(4)
C(11)-C(12)-C(13)	116.9(4)
C(11)-C(12)-C(17)	122.2(4)
C(13)-C(12)-C(17)	121.0(4)
C(14)-C(13)-C(12)	122.5(4)
C(15)-C(14)-C(13)	117.6(4)
C(15)-C(14)-C(18)	121.0(5)
C(13)-C(14)-C(18)	121.4(5)
C(16)-C(15)-C(14)	123.0(4)
C(15)-C(16)-C(11)	117.6(4)
C(15)-C(16)-C(19)	120.7(4)
C(11)-C(16)-C(19)	121.7(4)
O(5)-S(2)-O(4)	112.70(18)
O(5)-S(2)-O(6)	113.88(17)
O(4)-S(2)-O(6)	113.93(17)
O(5)-S(2)-C(20)	104.85(17)

O(4)-S(2)-C(20)	105.64(17)
O(6)-S(2)-C(20)	104.68(17)
C(28)-N(3)-C(25)	126.7(3)
C(28)-N(3)-C(26)	110.9(3)
C(25)-N(3)-C(26)	122.4(3)
C(28)-N(4)-C(30)	125.7(3)
C(28)-N(4)-C(27)	110.1(3)
C(30)-N(4)-C(27)	124.1(3)
C(25)-C(20)-C(21)	118.9(4)
C(25)-C(20)-S(2)	124.1(3)
C(21)-C(20)-S(2)	117.0(3)
C(22)-C(21)-C(20)	120.2(4)
C(23)-C(22)-C(21)	120.4(4)
C(22)-C(23)-C(24)	119.8(4)
C(25)-C(24)-C(23)	119.6(4)
C(20)-C(25)-C(24)	120.9(3)
C(20)-C(25)-N(3)	122.0(3)
C(24)-C(25)-N(3)	117.1(3)
N(3)-C(26)-C(29)	111.7(3)
N(3)-C(26)-C(27)	102.0(3)
C(29)-C(26)-C(27)	114.0(4)
N(4)-C(27)-C(26)	103.4(3)
N(3)-C(28)-N(4)	113.6(3)
C(31)-C(30)-C(35)	123.2(3)
C(31)-C(30)-N(4)	118.6(3)
C(35)-C(30)-N(4)	118.2(3)
C(32)-C(31)-C(30)	116.8(4)
C(32)-C(31)-C(36)	121.1(4)
C(30)-C(31)-C(36)	122.1(3)
C(33)-C(32)-C(31)	122.4(4)
C(34)-C(33)-C(32)	118.6(3)
C(34)-C(33)-C(37)	120.8(4)
C(32)-C(33)-C(37)	120.6(4)
C(33)-C(34)-C(35)	122.0(4)

C(34)-C(35)-C(30)	116.9(4)
C(34)-C(35)-C(38)	121.8(4)
C(30)-C(35)-C(38)	121.3(3)

Symmetry transformations used to generate equivalent atoms:

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	36(1)	28(1)	30(1)	0(1)	6(1)	-4(1)
O(1)	72(2)	38(2)	29(2)	6(1)	5(2)	-19(2)
O(2)	36(2)	44(2)	85(2)	9(2)	19(2)	1(1)
O(3)	65(2)	46(2)	47(2)	-16(2)	21(2)	-12(2)
N(1)	22(2)	29(2)	23(2)	1(1)	7(1)	3(1)
N(2)	28(2)	47(2)	22(2)	0(2)	10(1)	1(2)
C(1)	29(2)	30(2)	29(2)	2(2)	9(2)	5(2)
C(2)	32(2)	42(2)	25(2)	1(2)	11(2)	3(2)
C(3)	36(2)	56(3)	33(2)	4(2)	15(2)	1(2)
C(4)	41(2)	42(3)	41(3)	0(2)	19(2)	-9(2)
C(5)	39(2)	30(2)	32(2)	-1(2)	10(2)	-5(2)
C(6)	28(2)	27(2)	23(2)	-2(2)	9(2)	3(2)
C(7)	40(2)	29(2)	23(2)	-1(2)	9(2)	6(2)
C(8)	29(2)	57(3)	25(2)	3(2)	6(2)	3(2)
C(9)	33(2)	36(2)	20(2)	0(2)	6(2)	-2(2)
C(10)	34(2)	40(2)	34(2)	-5(2)	8(2)	5(2)
C(11)	25(2)	44(2)	18(2)	-1(2)	6(2)	0(2)
C(12)	33(2)	39(2)	24(2)	-4(2)	10(2)	2(2)
C(13)	36(2)	51(3)	30(2)	-1(2)	4(2)	13(2)
C(14)	30(2)	94(4)	20(2)	7(2)	10(2)	8(3)
C(15)	43(3)	72(3)	30(2)	12(2)	11(2)	-17(3)
C(16)	33(2)	50(3)	27(2)	5(2)	4(2)	-4(2)
C(17)	48(3)	36(2)	71(3)	2(2)	25(2)	0(2)
C(18)	34(3)	158(6)	55(3)	36(4)	21(2)	25(3)
C(19)	66(4)	44(3)	89(4)	13(3)	16(3)	-6(3)
S(2)	35(1)	27(1)	29(1)	0(1)	4(1)	-1(1)
O(4)	60(2)	33(2)	31(2)	1(1)	12(1)	-10(1)
O(5)	31(2)	42(2)	52(2)	14(1)	5(1)	-1(1)
O(6)	56(2)	31(2)	40(2)	-10(1)	9(1)	-3(2)

N(3)	24(2)	28(2)	26(2)	-4(1)	7(1)	-4(1)
N(4)	22(2)	38(2)	27(2)	-3(2)	6(1)	2(1)
C(20)	25(2)	28(2)	25(2)	4(2)	5(2)	5(2)
C(21)	34(2)	46(2)	32(2)	-8(2)	9(2)	4(2)
C(22)	42(3)	59(3)	31(2)	0(2)	20(2)	5(2)
C(23)	37(2)	48(3)	46(3)	6(2)	21(2)	-6(2)
C(24)	29(2)	36(2)	40(2)	-5(2)	14(2)	-2(2)
C(25)	26(2)	26(2)	25(2)	3(2)	9(2)	7(2)
C(26)	25(2)	44(2)	26(2)	-10(2)	9(2)	-6(2)
C(27)	26(2)	73(3)	27(2)	-7(2)	7(2)	-5(2)
C(28)	30(2)	23(2)	31(2)	-2(2)	10(2)	-1(2)
C(29)	42(3)	64(3)	34(2)	-1(2)	8(2)	13(2)
C(30)	25(2)	36(2)	22(2)	-4(2)	9(2)	1(2)
C(31)	26(2)	40(2)	25(2)	3(2)	9(2)	-1(2)
C(32)	35(2)	42(2)	27(2)	-1(2)	14(2)	7(2)
C(33)	27(2)	45(2)	20(2)	4(2)	9(2)	1(2)
C(34)	23(2)	39(2)	32(2)	1(2)	7(2)	-3(2)
C(35)	31(2)	37(2)	29(2)	-3(2)	9(2)	-3(2)
C(36)	43(2)	46(2)	37(2)	3(2)	14(2)	0(2)
C(37)	29(2)	65(3)	45(3)	12(2)	15(2)	6(2)
C(38)	39(2)	35(3)	77(3)	-1(2)	22(2)	-2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for sad.

	x	y	z	U(eq)
H(2B)	9855	5973	6531	39
H(3B)	11172	7355	6411	48
H(4A)	11717	8798	7695	48
H(5A)	10991	8804	9150	41
H(7A)	10109	6013	10591	37
H(8A)	9279	6665	11794	45
H(8B)	9744	7953	11758	45
H(9A)	7944	7948	8924	36
H(10A)	11870	6869	10652	55
H(10B)	11763	6844	11837	55
H(10C)	11524	8008	11161	55
H(13A)	5612	10032	10820	49
H(15A)	5063	6699	11195	58
H(17A)	8364	9638	10355	75
H(17B)	7865	10495	11059	75
H(17C)	7216	10372	9801	75
H(18A)	3639	7975	11326	121
H(18B)	3497	9060	10552	121
H(18C)	4137	9195	11810	121
H(19A)	6377	5290	11140	103
H(19B)	7708	5695	11544	103
H(19C)	7053	5544	10290	103
H(21A)	5266	9067	8436	45
H(22A)	3972	7678	8655	51
H(23A)	3343	6230	7398	50
H(24A)	4122	6080	5976	41
H(26A)	4314	6637	4239	37
H(27A)	5552	6518	3297	51

H(27B)	5638	7893	3252	51
H(28A)	7308	7297	6176	33
H(29A)	3532	8399	4521	71
H(29B)	3619	8382	3329	71
H(29C)	4562	9072	4252	71
H(32A)	9765	5148	4137	40
H(34A)	9982	8562	3902	38
H(36A)	6977	5146	4583	63
H(36B)	8190	4508	5121	63
H(36C)	7572	4424	3855	63
H(37A)	11462	5898	3924	69
H(37B)	11828	7124	4468	69
H(37C)	11243	7027	3199	69
H(38A)	8468	9802	4017	74
H(38B)	7811	9374	4835	74
H(38C)	7203	9236	3573	74

Table 6. Torsion angles [°] for sad.

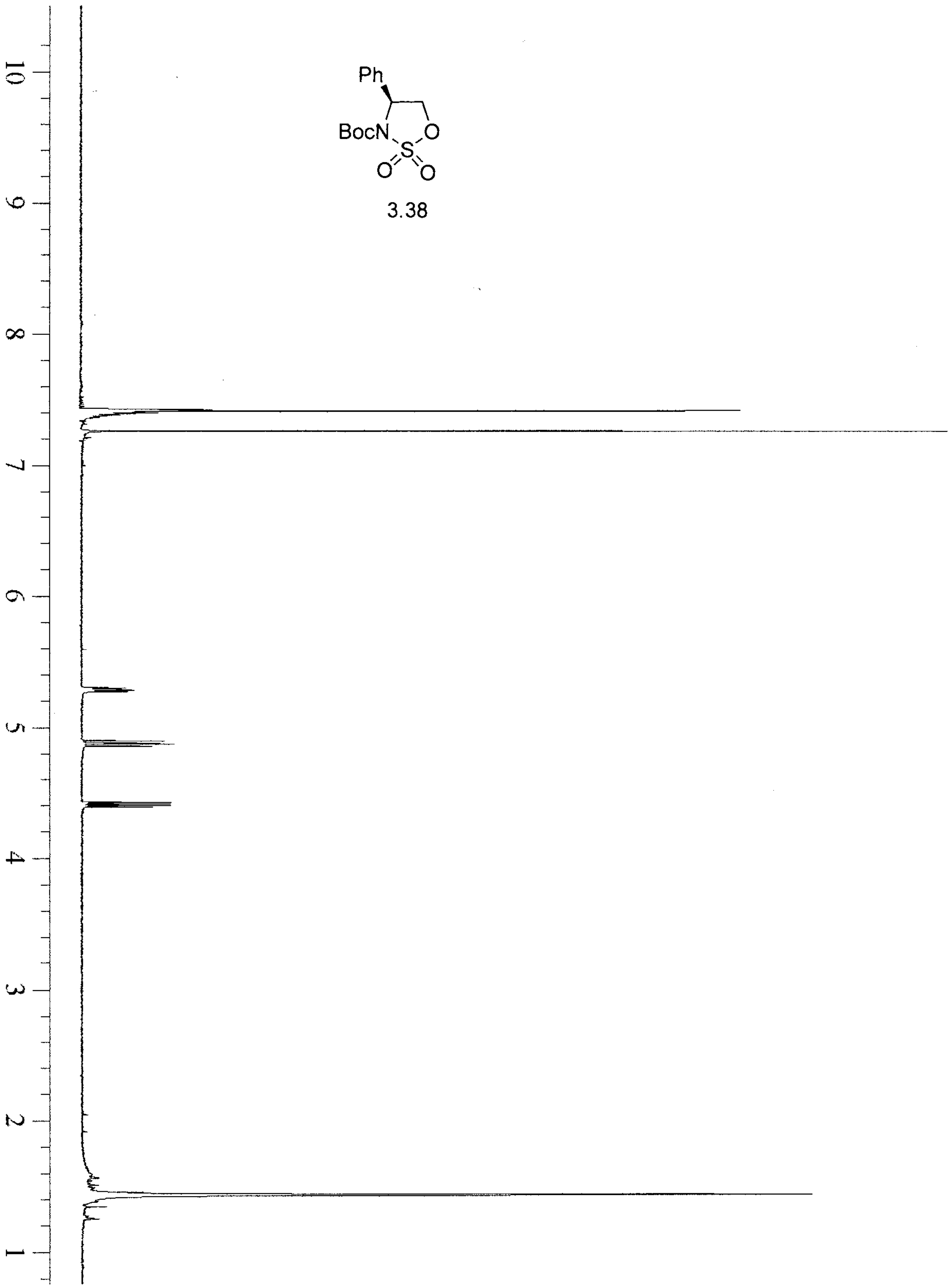
O(1)-S(1)-C(1)-C(2)	134.7(3)
O(2)-S(1)-C(1)-C(2)	-105.8(3)
O(3)-S(1)-C(1)-C(2)	14.4(4)
O(1)-S(1)-C(1)-C(6)	-47.8(3)
O(2)-S(1)-C(1)-C(6)	71.7(3)
O(3)-S(1)-C(1)-C(6)	-168.1(3)
C(6)-C(1)-C(2)-C(3)	1.6(6)
S(1)-C(1)-C(2)-C(3)	179.1(3)
C(1)-C(2)-C(3)-C(4)	-1.9(6)
C(2)-C(3)-C(4)-C(5)	1.2(6)
C(3)-C(4)-C(5)-C(6)	-0.3(6)
C(4)-C(5)-C(6)-C(1)	0.1(6)
C(4)-C(5)-C(6)-N(1)	179.6(4)
C(2)-C(1)-C(6)-C(5)	-0.7(5)
S(1)-C(1)-C(6)-C(5)	-178.2(3)
C(2)-C(1)-C(6)-N(1)	179.8(3)
S(1)-C(1)-C(6)-N(1)	2.3(5)
C(9)-N(1)-C(6)-C(5)	108.0(4)
C(7)-N(1)-C(6)-C(5)	-87.5(4)
C(9)-N(1)-C(6)-C(1)	-72.5(5)
C(7)-N(1)-C(6)-C(1)	92.1(4)
C(9)-N(1)-C(7)-C(10)	-142.8(3)
C(6)-N(1)-C(7)-C(10)	50.8(5)
C(9)-N(1)-C(7)-C(8)	-19.0(4)
C(6)-N(1)-C(7)-C(8)	174.7(3)
C(9)-N(2)-C(8)-C(7)	-17.7(4)
C(11)-N(2)-C(8)-C(7)	172.4(4)
N(1)-C(7)-C(8)-N(2)	20.8(4)
C(10)-C(7)-C(8)-N(2)	143.7(3)
C(6)-N(1)-C(9)-N(2)	175.4(3)
C(7)-N(1)-C(9)-N(2)	9.0(5)
C(11)-N(2)-C(9)-N(1)	176.0(4)

C(8)-N(2)-C(9)-N(1)	6.0(5)
C(9)-N(2)-C(11)-C(12)	-67.5(5)
C(8)-N(2)-C(11)-C(12)	100.9(5)
C(9)-N(2)-C(11)-C(16)	113.5(4)
C(8)-N(2)-C(11)-C(16)	-78.2(5)
C(16)-C(11)-C(12)-C(13)	-3.0(6)
N(2)-C(11)-C(12)-C(13)	178.0(3)
C(16)-C(11)-C(12)-C(17)	178.6(4)
N(2)-C(11)-C(12)-C(17)	-0.4(6)
C(11)-C(12)-C(13)-C(14)	0.7(6)
C(17)-C(12)-C(13)-C(14)	179.1(4)
C(12)-C(13)-C(14)-C(15)	1.0(6)
C(12)-C(13)-C(14)-C(18)	-179.5(4)
C(13)-C(14)-C(15)-C(16)	-0.5(7)
C(18)-C(14)-C(15)-C(16)	180.0(4)
C(14)-C(15)-C(16)-C(11)	-1.7(6)
C(14)-C(15)-C(16)-C(19)	179.0(5)
C(12)-C(11)-C(16)-C(15)	3.5(6)
N(2)-C(11)-C(16)-C(15)	-177.5(3)
C(12)-C(11)-C(16)-C(19)	-177.2(4)
N(2)-C(11)-C(16)-C(19)	1.8(6)
O(5)-S(2)-C(20)-C(25)	-79.9(3)
O(4)-S(2)-C(20)-C(25)	39.4(4)
O(6)-S(2)-C(20)-C(25)	159.9(3)
O(5)-S(2)-C(20)-C(21)	99.1(3)
O(4)-S(2)-C(20)-C(21)	-141.7(3)
O(6)-S(2)-C(20)-C(21)	-21.1(3)
C(25)-C(20)-C(21)-C(22)	-1.3(6)
S(2)-C(20)-C(21)-C(22)	179.7(3)
C(20)-C(21)-C(22)-C(23)	-1.8(6)
C(21)-C(22)-C(23)-C(24)	2.7(6)
C(22)-C(23)-C(24)-C(25)	-0.5(6)
C(21)-C(20)-C(25)-C(24)	3.5(6)
S(2)-C(20)-C(25)-C(24)	-177.5(3)

C(21)-C(20)-C(25)-N(3)	-179.9(3)
S(2)-C(20)-C(25)-N(3)	-0.9(5)
C(23)-C(24)-C(25)-C(20)	-2.7(6)
C(23)-C(24)-C(25)-N(3)	-179.4(4)
C(28)-N(3)-C(25)-C(20)	57.7(5)
C(26)-N(3)-C(25)-C(20)	-119.6(4)
C(28)-N(3)-C(25)-C(24)	-125.6(4)
C(26)-N(3)-C(25)-C(24)	57.1(5)
C(28)-N(3)-C(26)-C(29)	-121.8(4)
C(25)-N(3)-C(26)-C(29)	56.0(5)
C(28)-N(3)-C(26)-C(27)	0.4(4)
C(25)-N(3)-C(26)-C(27)	178.1(3)
C(28)-N(4)-C(27)-C(26)	-1.1(4)
C(30)-N(4)-C(27)-C(26)	178.5(3)
N(3)-C(26)-C(27)-N(4)	0.4(4)
C(29)-C(26)-C(27)-N(4)	120.9(4)
C(25)-N(3)-C(28)-N(4)	-178.8(3)
C(26)-N(3)-C(28)-N(4)	-1.2(4)
C(30)-N(4)-C(28)-N(3)	-178.1(3)
C(27)-N(4)-C(28)-N(3)	1.5(5)
C(28)-N(4)-C(30)-C(31)	89.8(5)
C(27)-N(4)-C(30)-C(31)	-89.7(5)
C(28)-N(4)-C(30)-C(35)	-92.7(5)
C(27)-N(4)-C(30)-C(35)	87.7(5)
C(35)-C(30)-C(31)-C(32)	4.6(6)
N(4)-C(30)-C(31)-C(32)	-178.1(3)
C(35)-C(30)-C(31)-C(36)	-177.7(4)
N(4)-C(30)-C(31)-C(36)	-0.4(6)
C(30)-C(31)-C(32)-C(33)	-1.1(6)
C(36)-C(31)-C(32)-C(33)	-178.8(4)
C(31)-C(32)-C(33)-C(34)	-2.4(6)
C(31)-C(32)-C(33)-C(37)	177.7(4)
C(32)-C(33)-C(34)-C(35)	2.7(6)
C(37)-C(33)-C(34)-C(35)	-177.5(4)

C(33)-C(34)-C(35)-C(30)	0.5(6)
C(33)-C(34)-C(35)-C(38)	-178.2(4)
C(31)-C(30)-C(35)-C(34)	-4.4(6)
N(4)-C(30)-C(35)-C(34)	178.3(3)
C(31)-C(30)-C(35)-C(38)	174.4(4)
N(4)-C(30)-C(35)-C(38)	-2.9(6)

Symmetry transformations used to generate equivalent atoms: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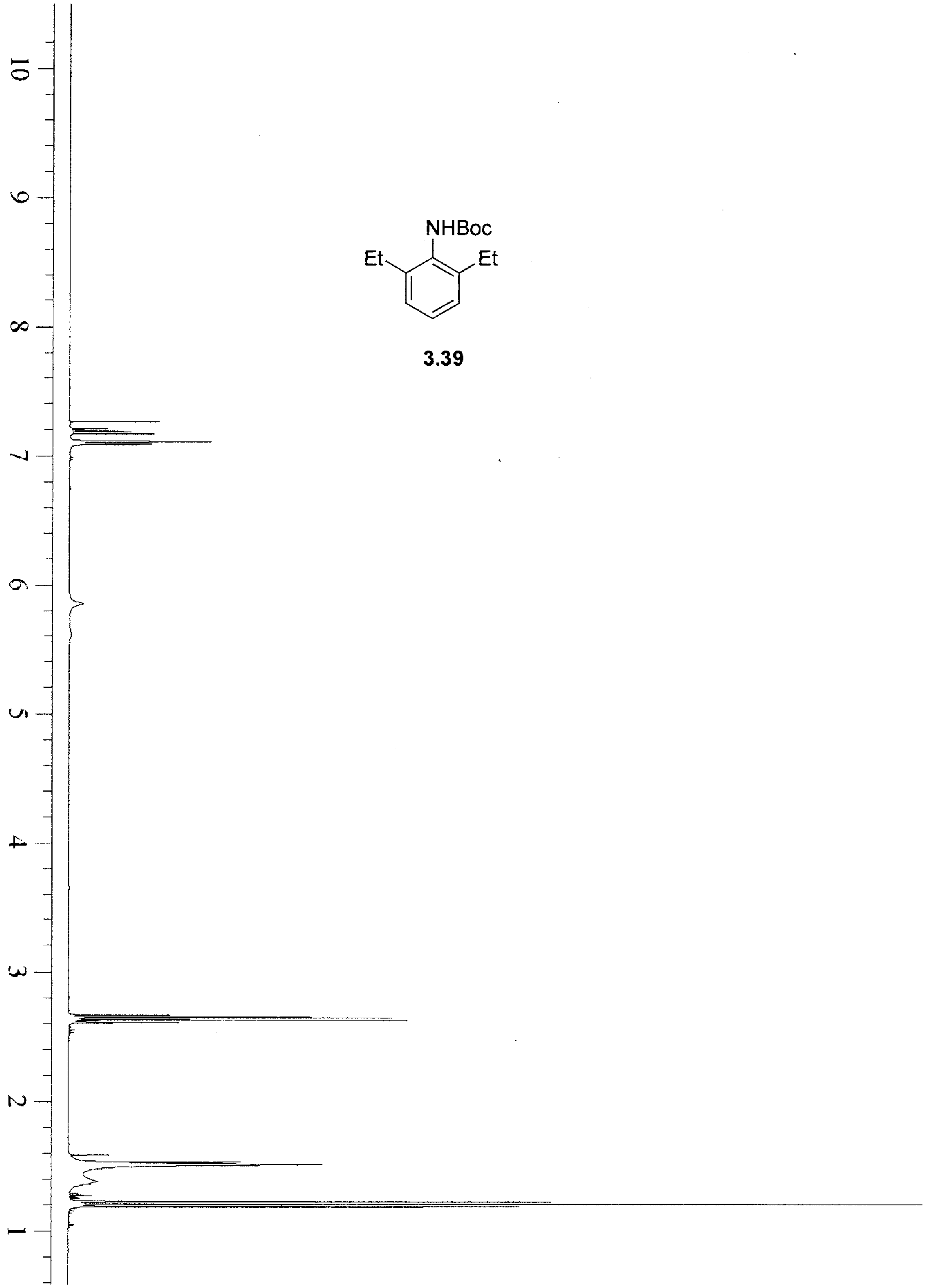

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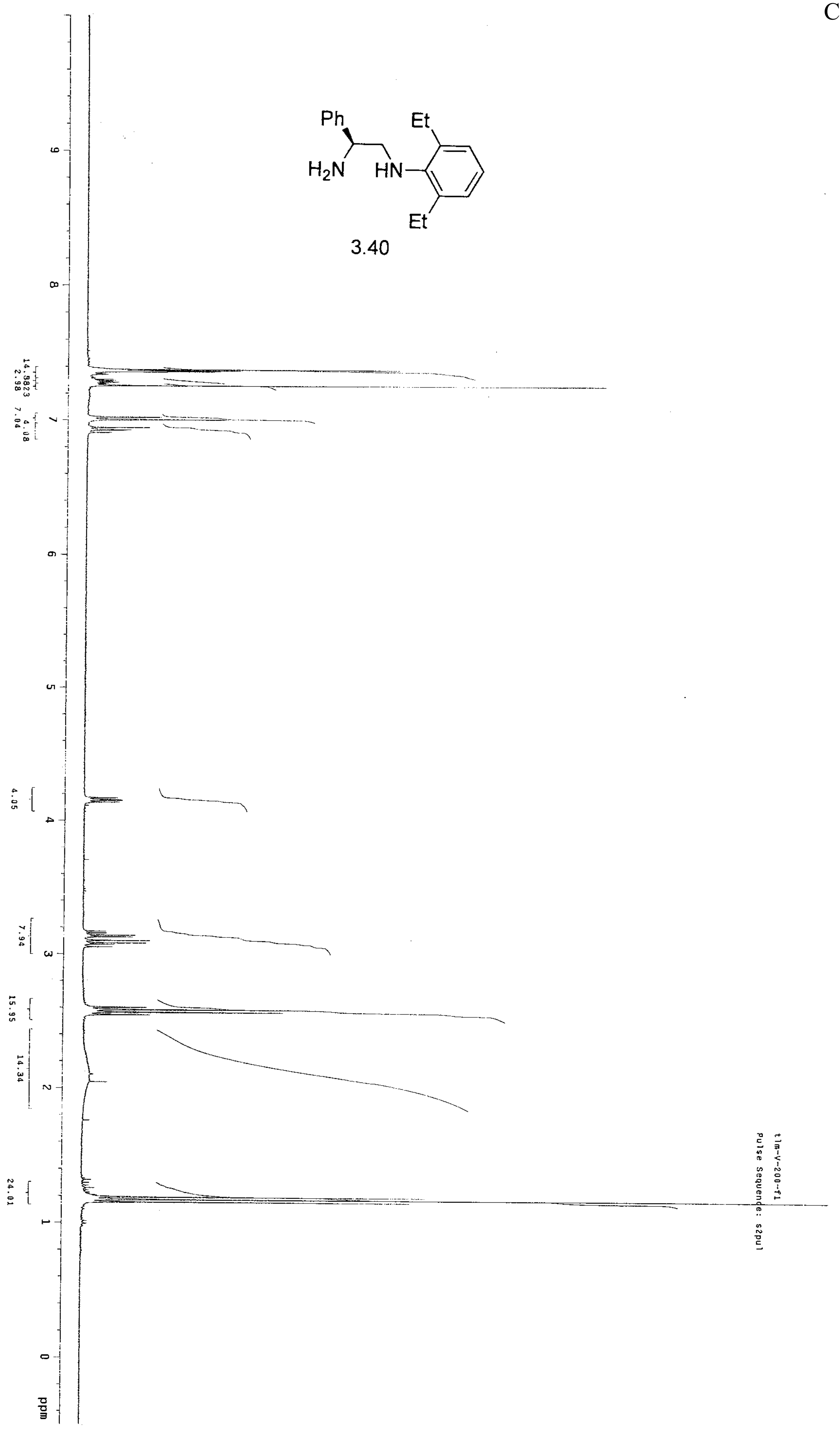
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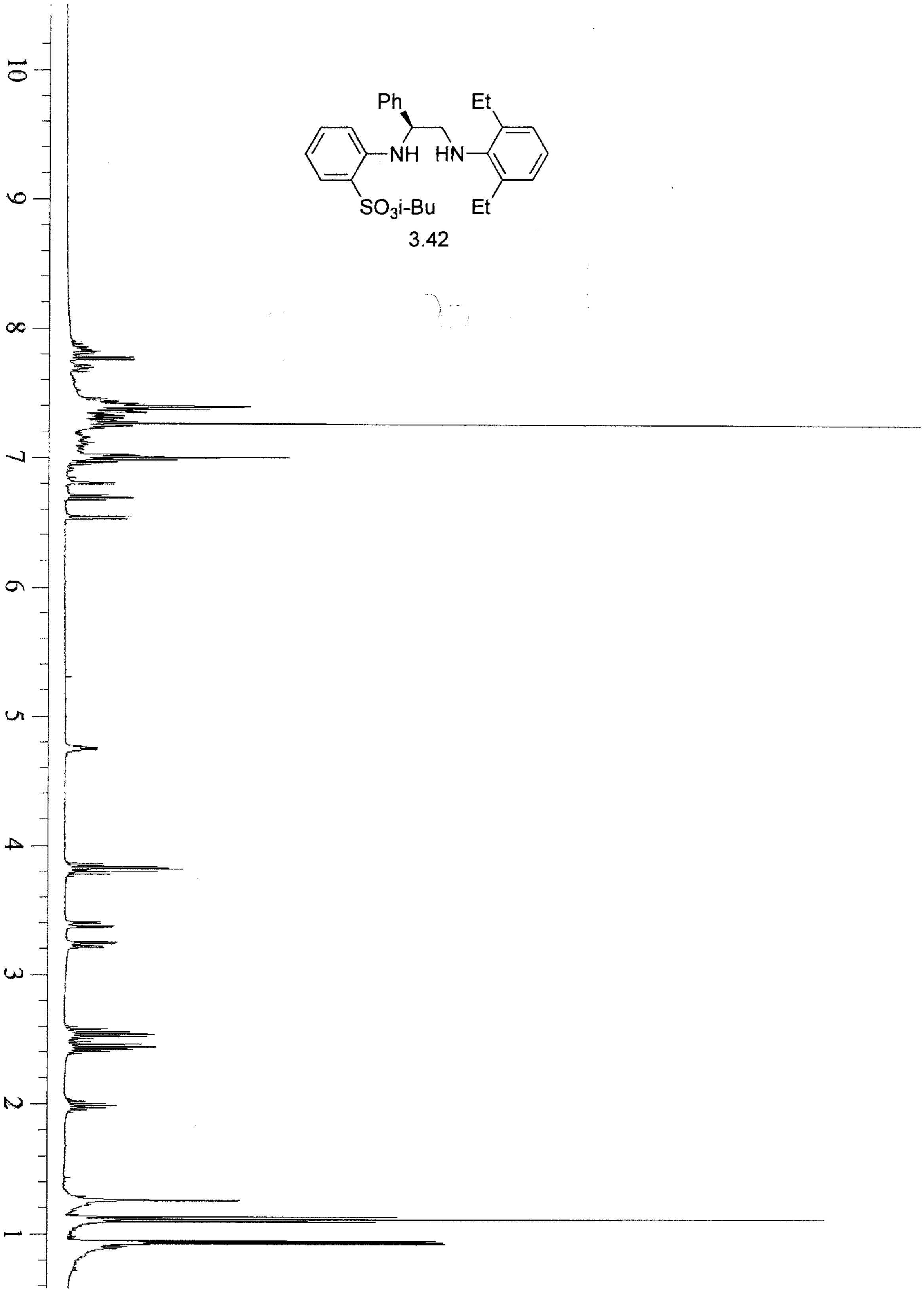

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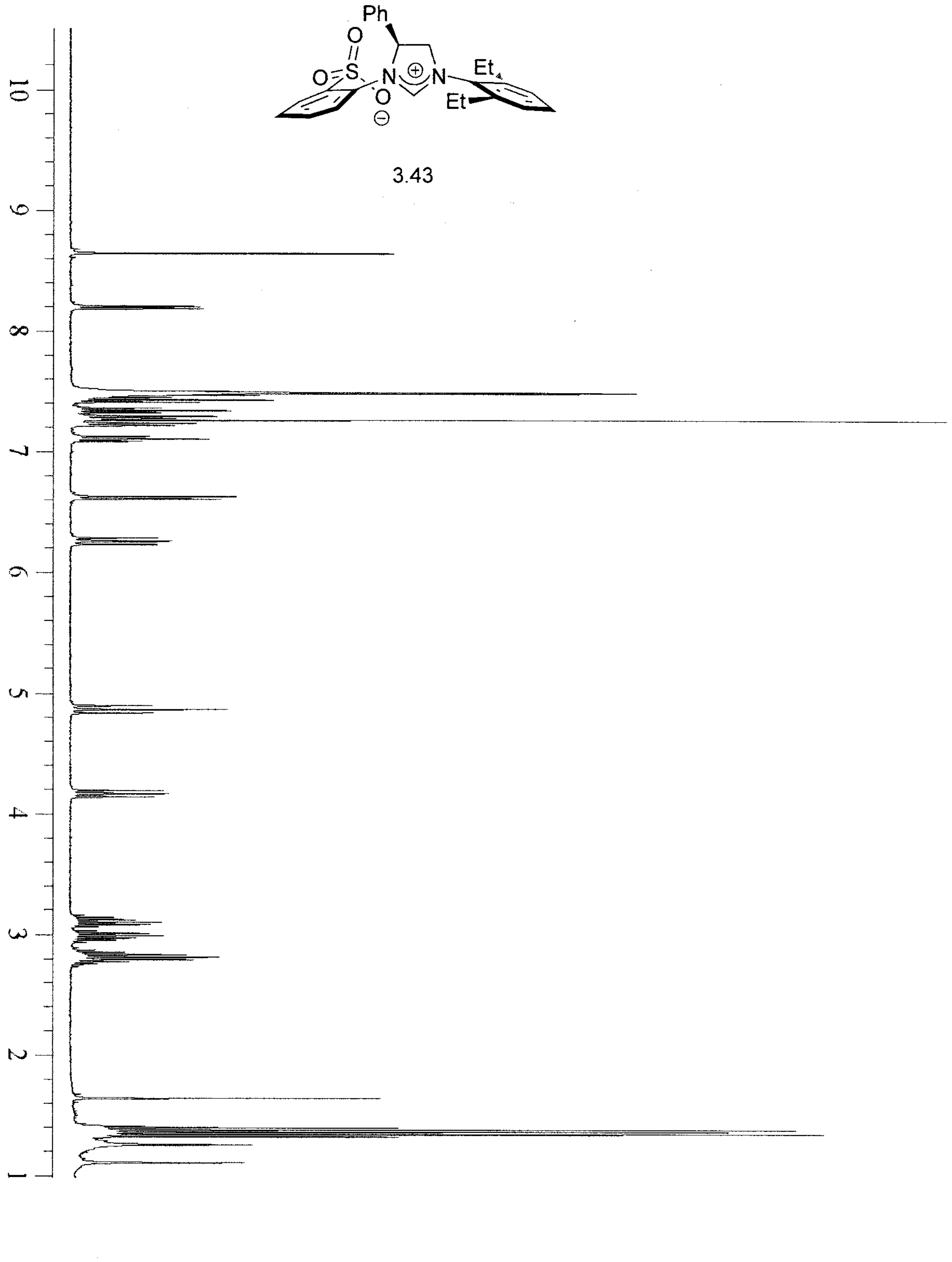

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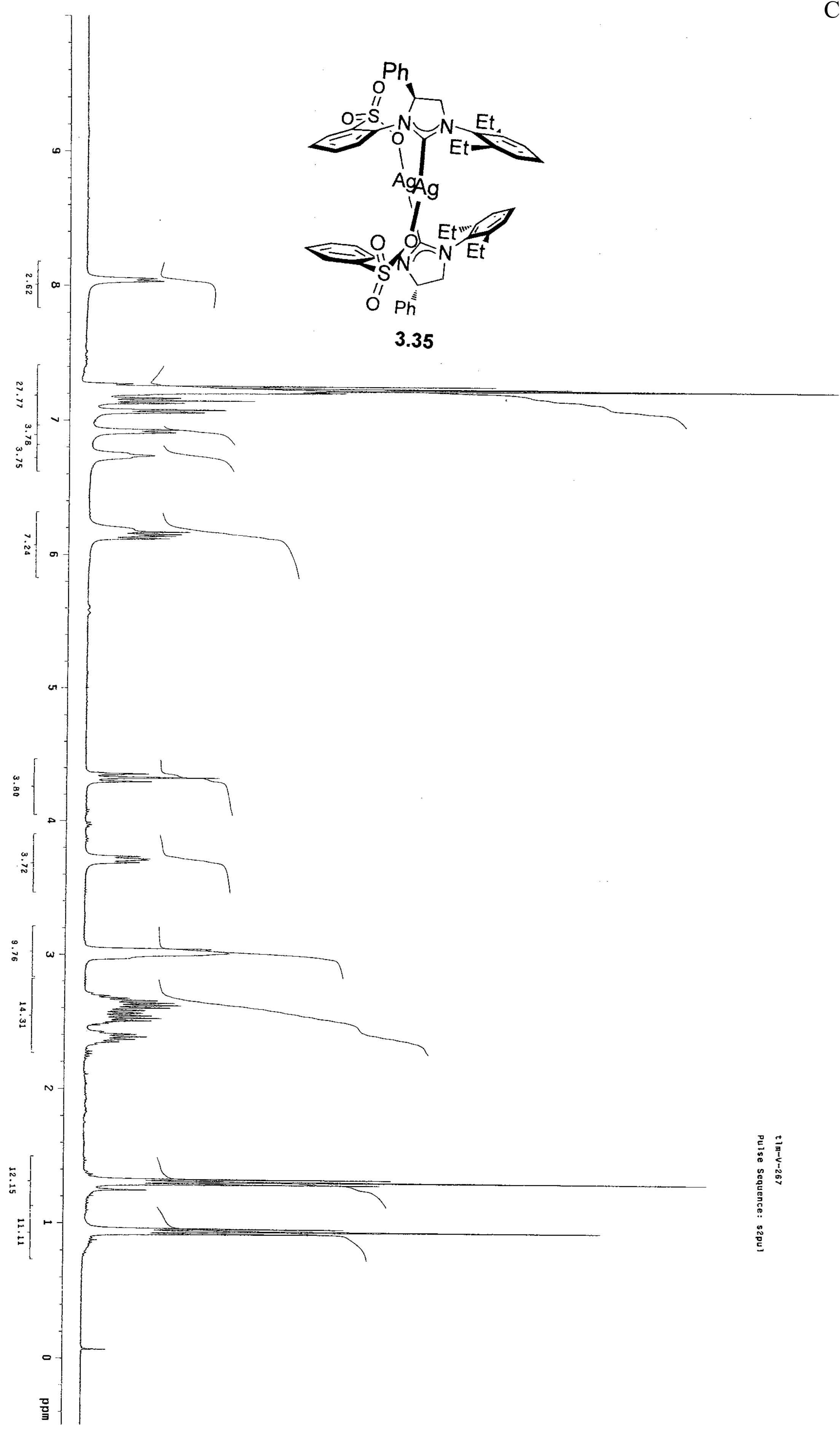
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2
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ppm
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3.78
3.75
7.24
3.80
3.72
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12.15
11.11
Ph
O
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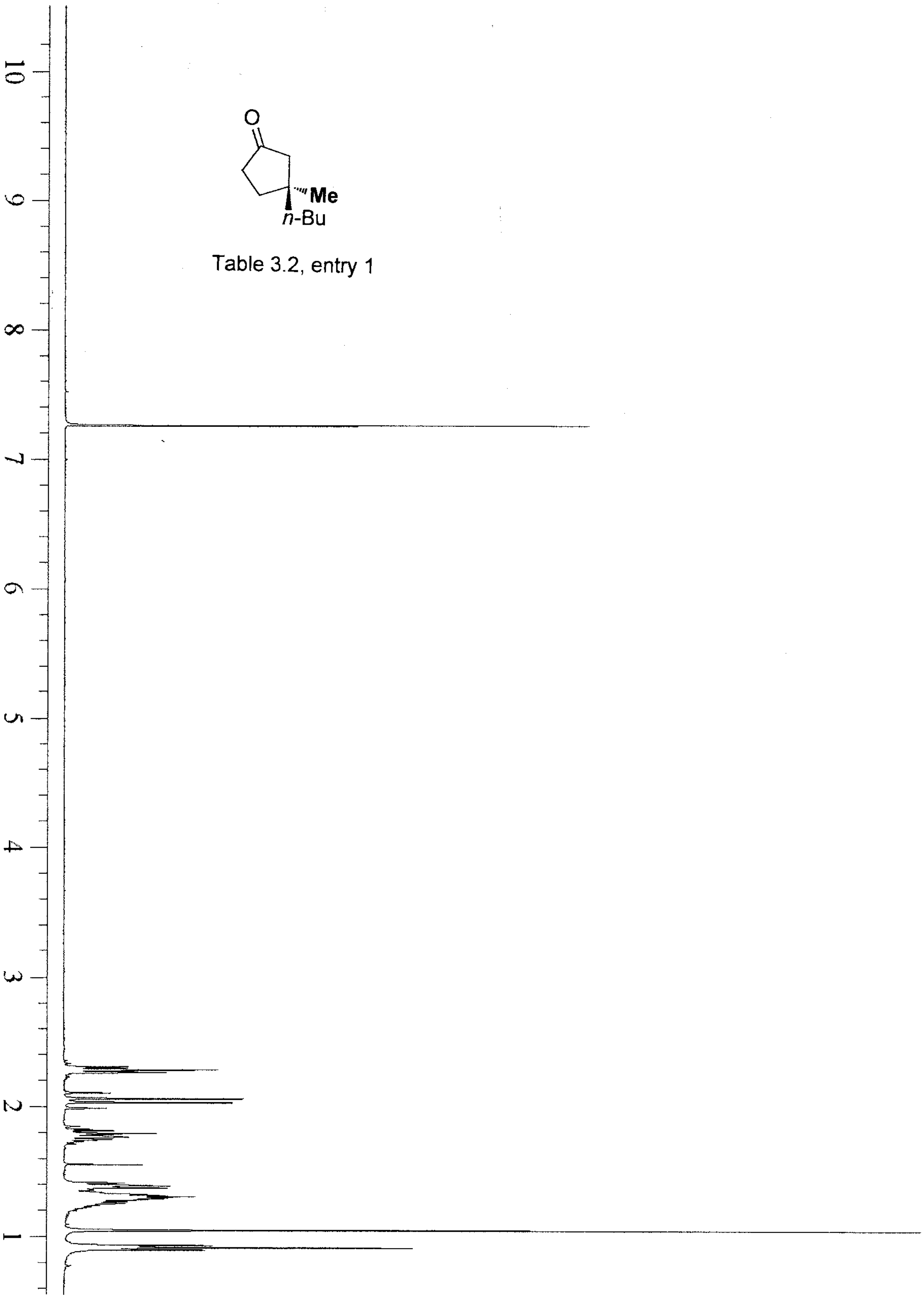
Et
Ag
Ag
Et
Ph

3.35



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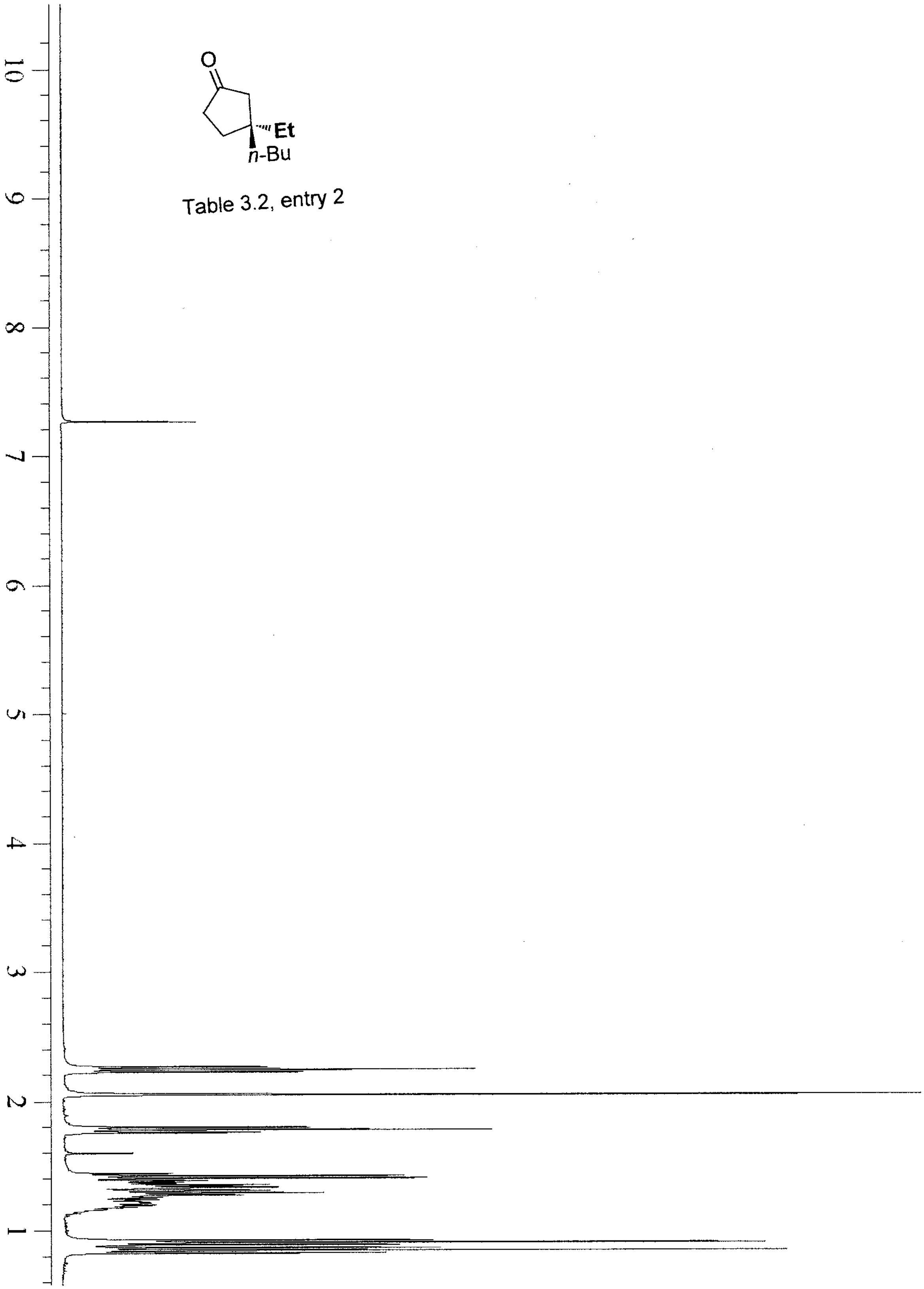

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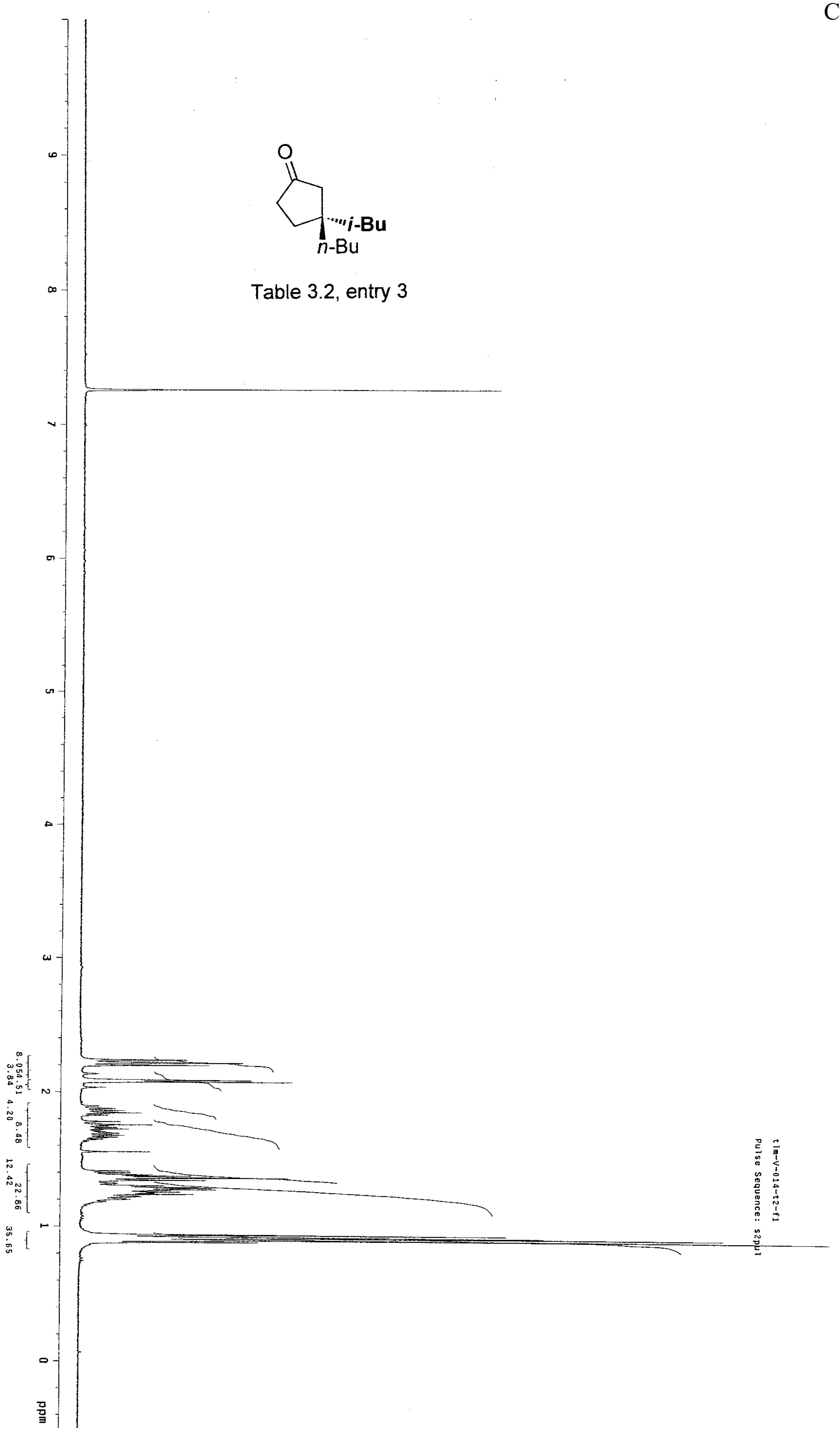

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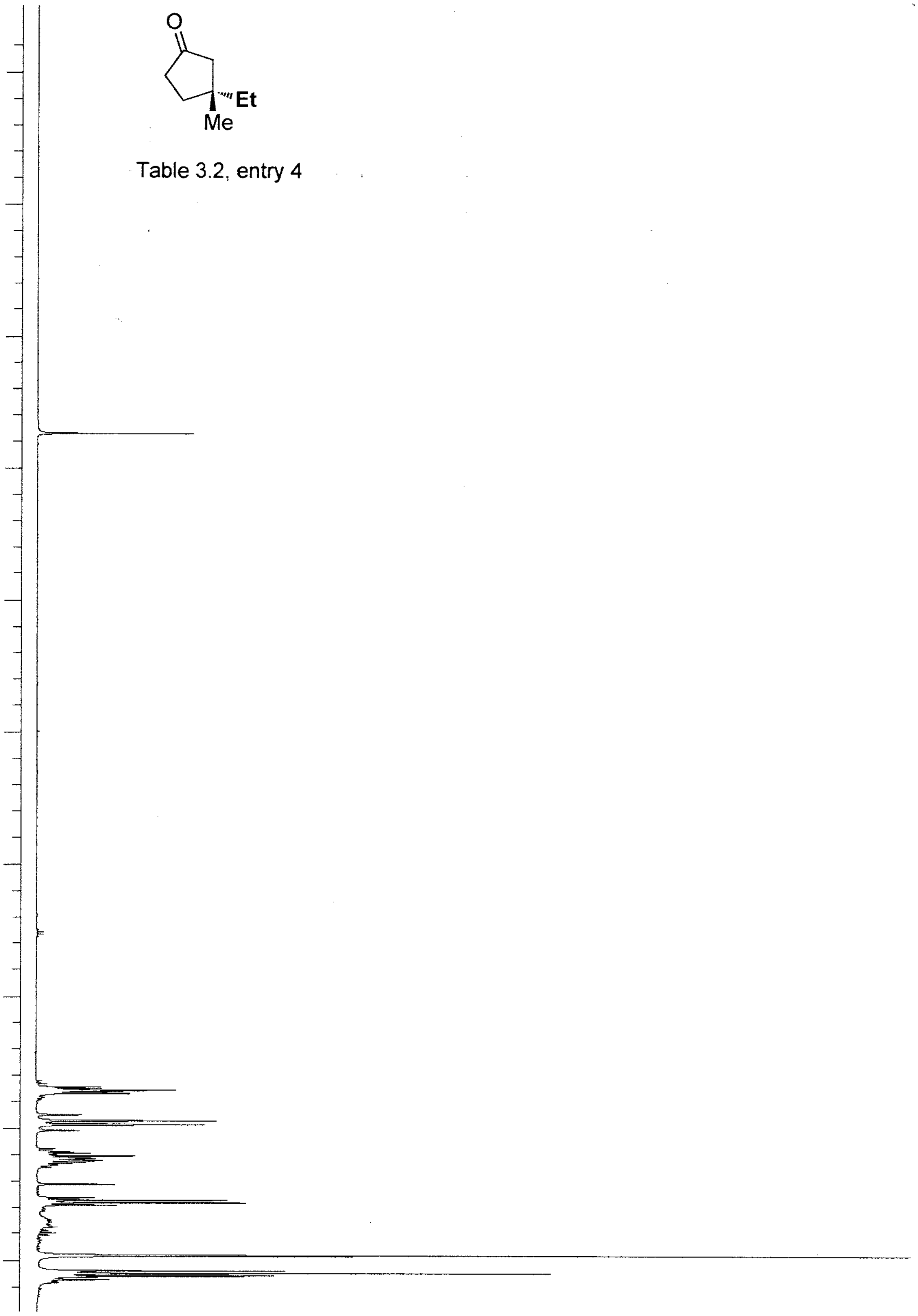

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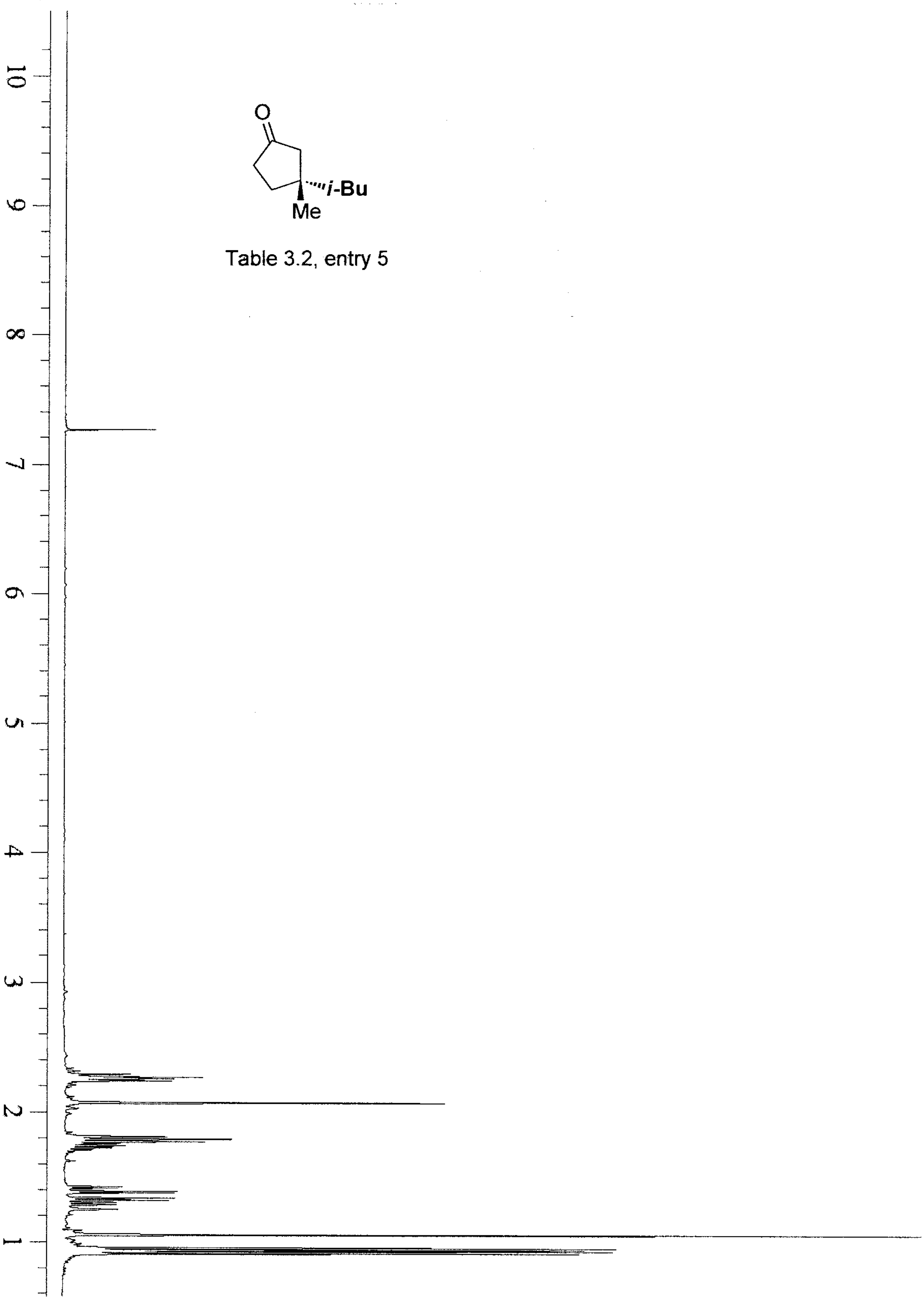

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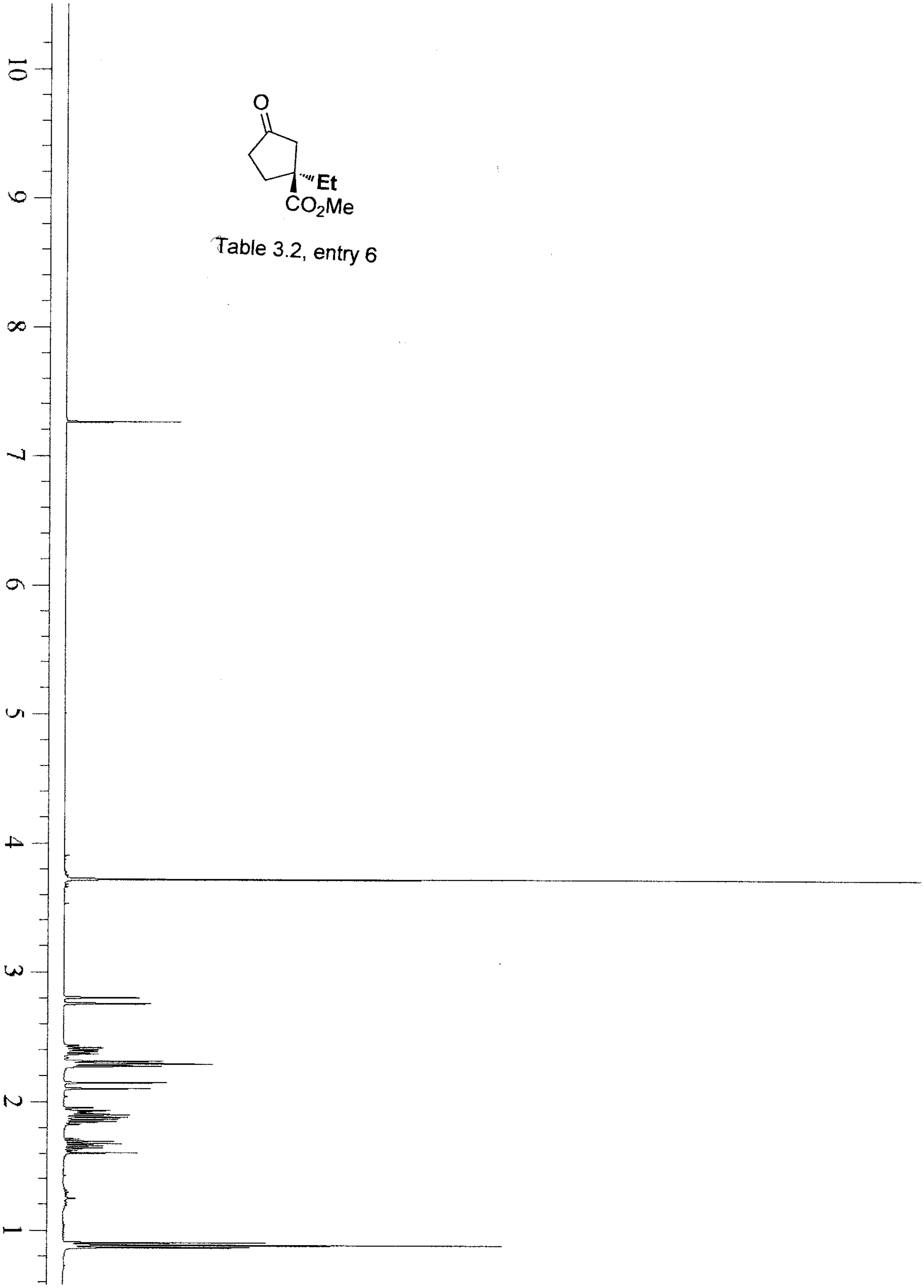

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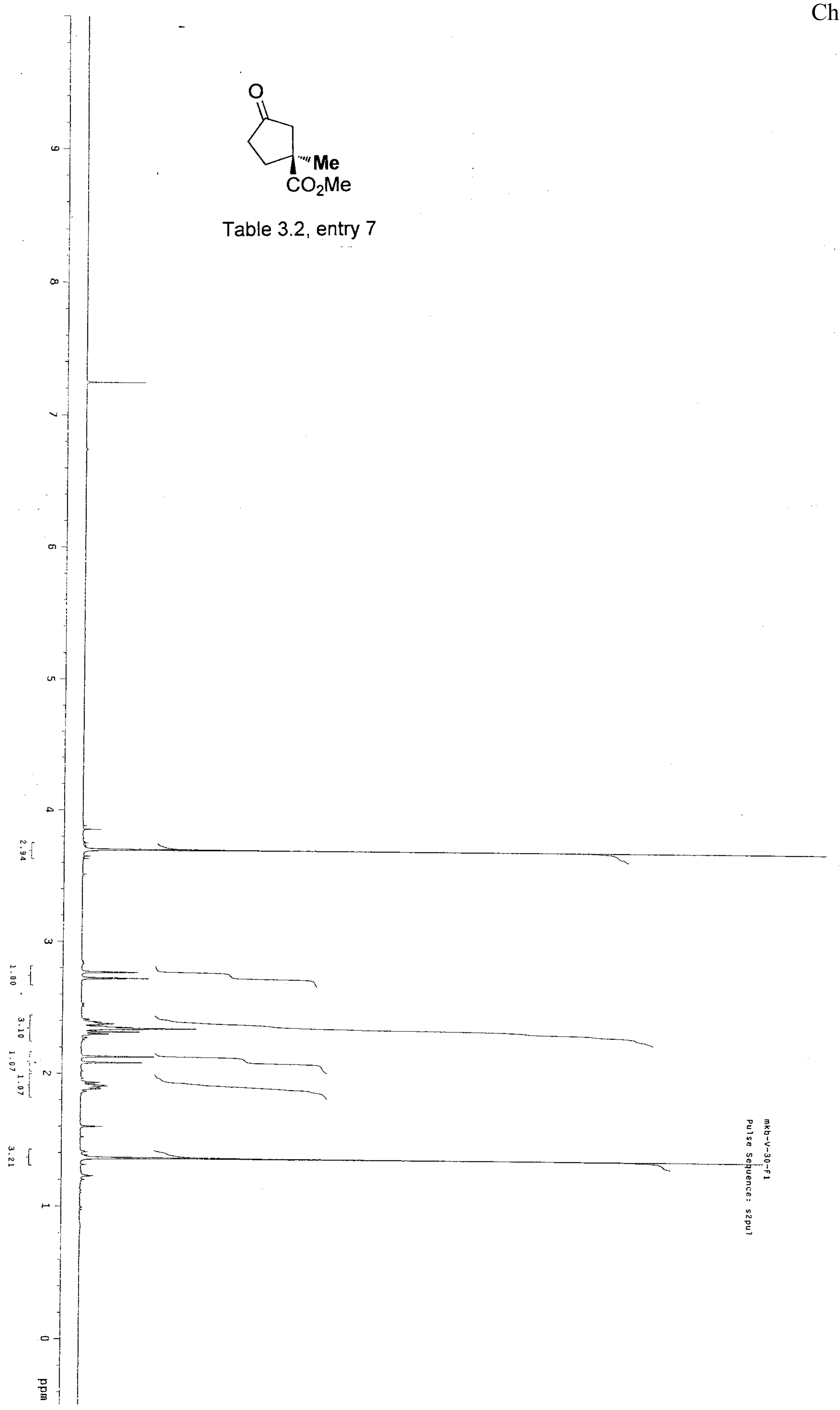

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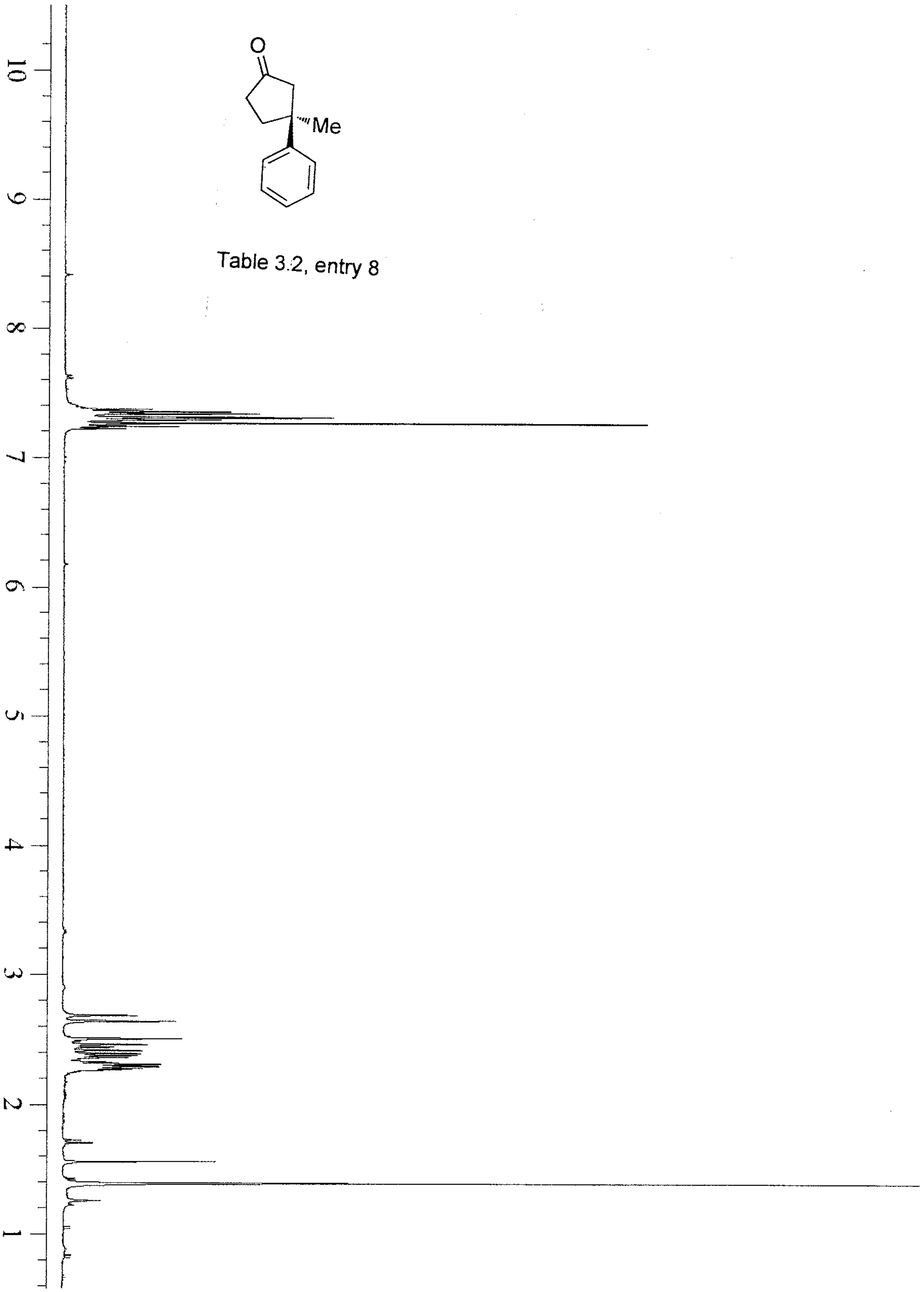
O
Me
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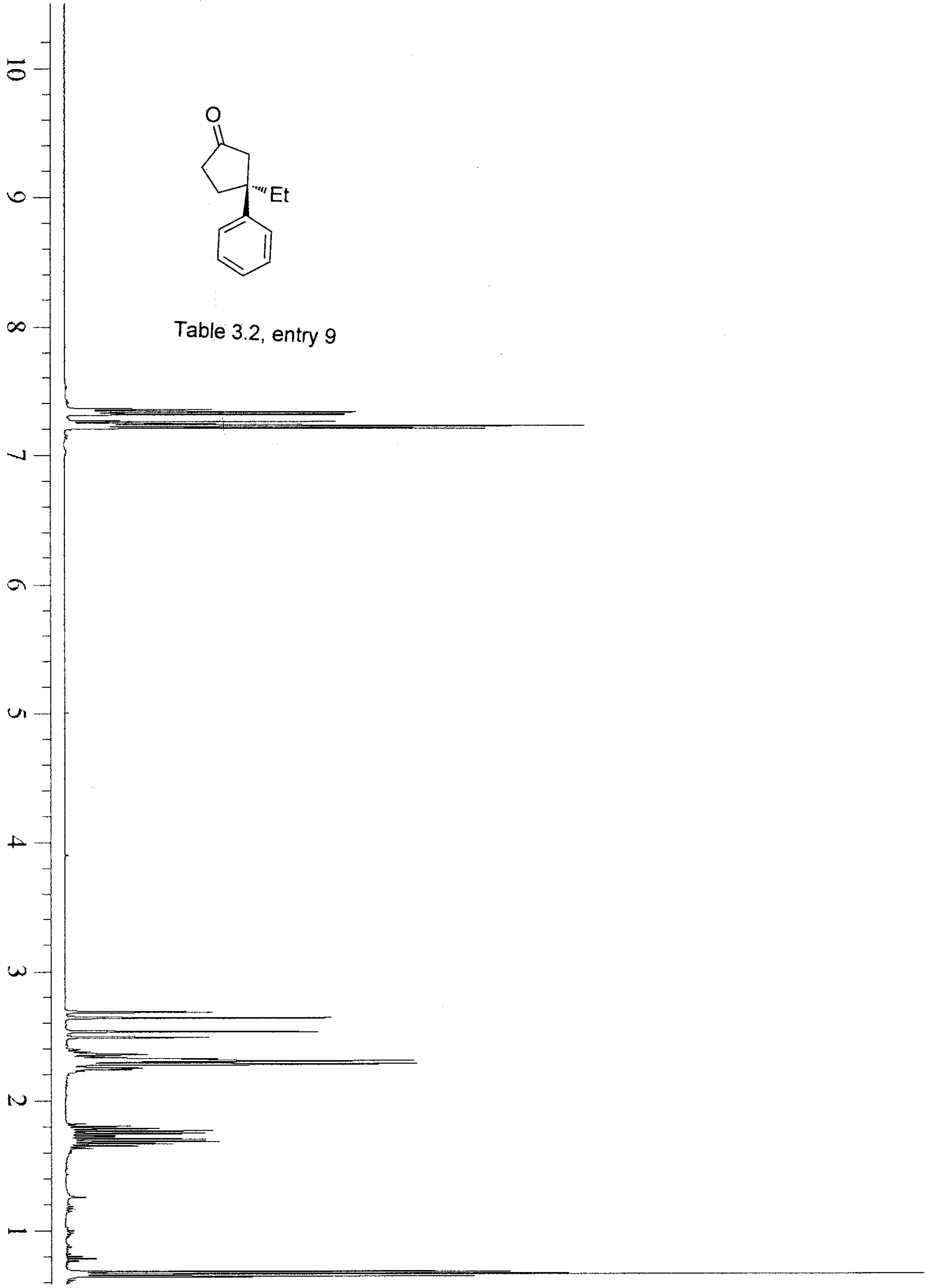
7
6
5
4
3
2
1



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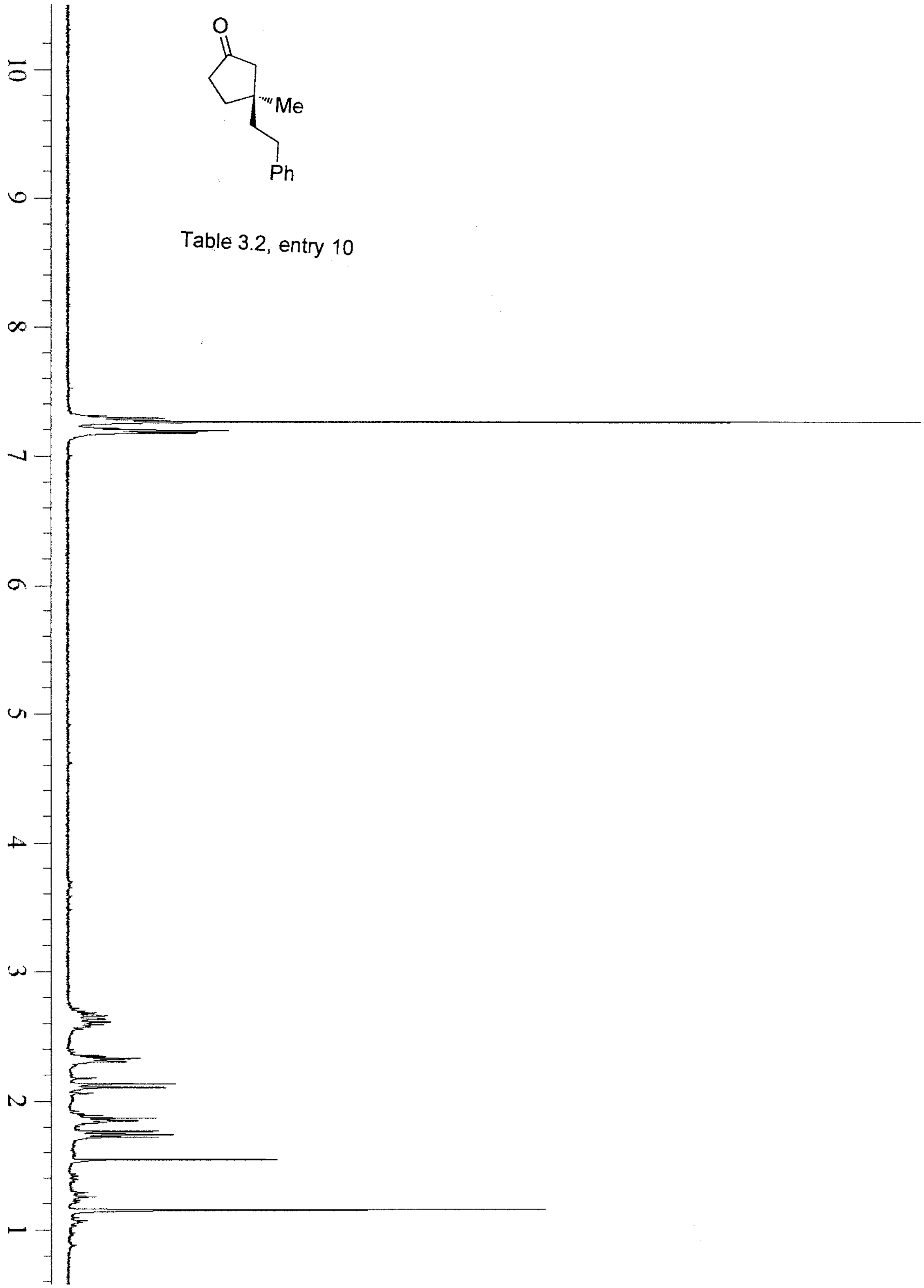
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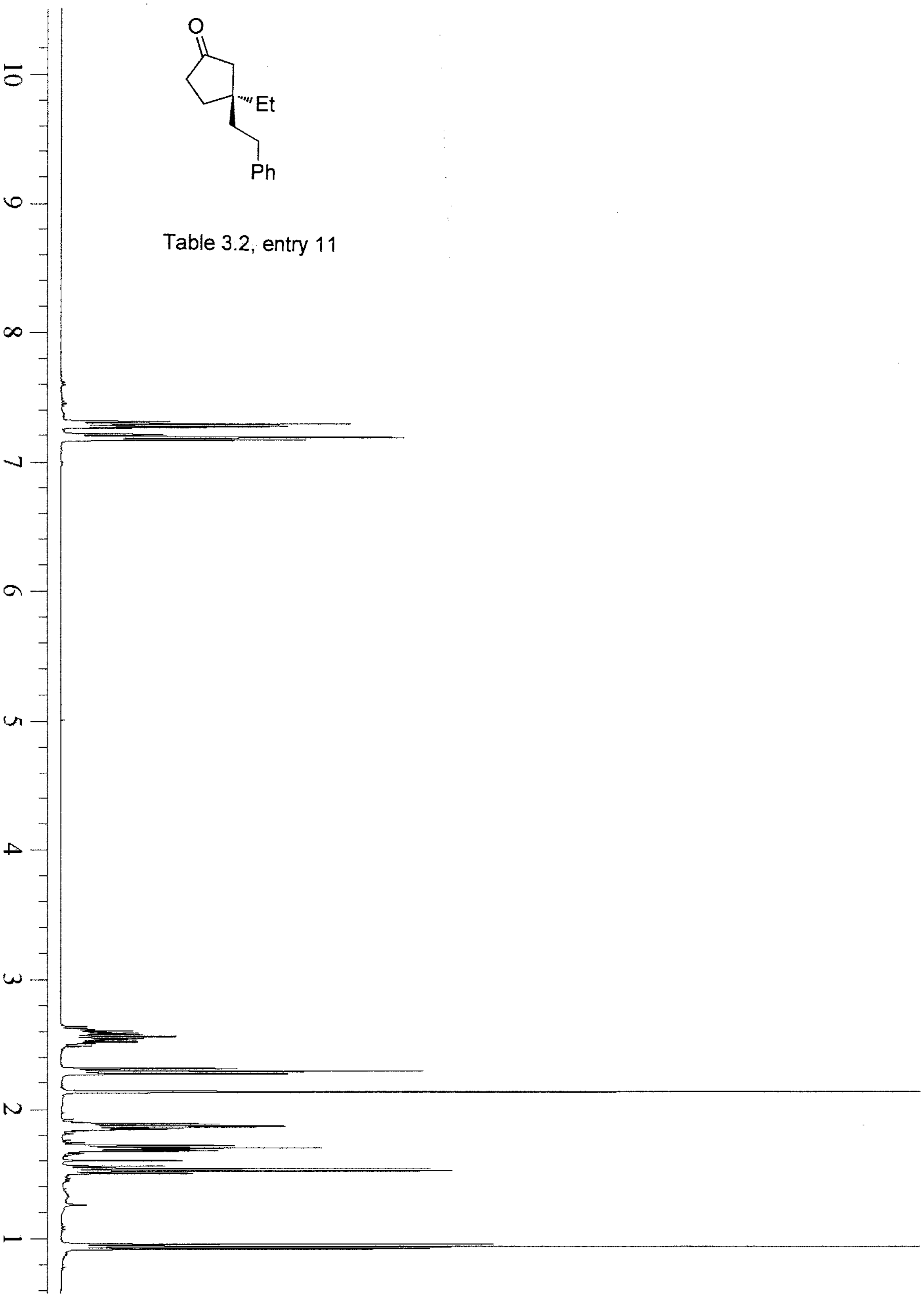

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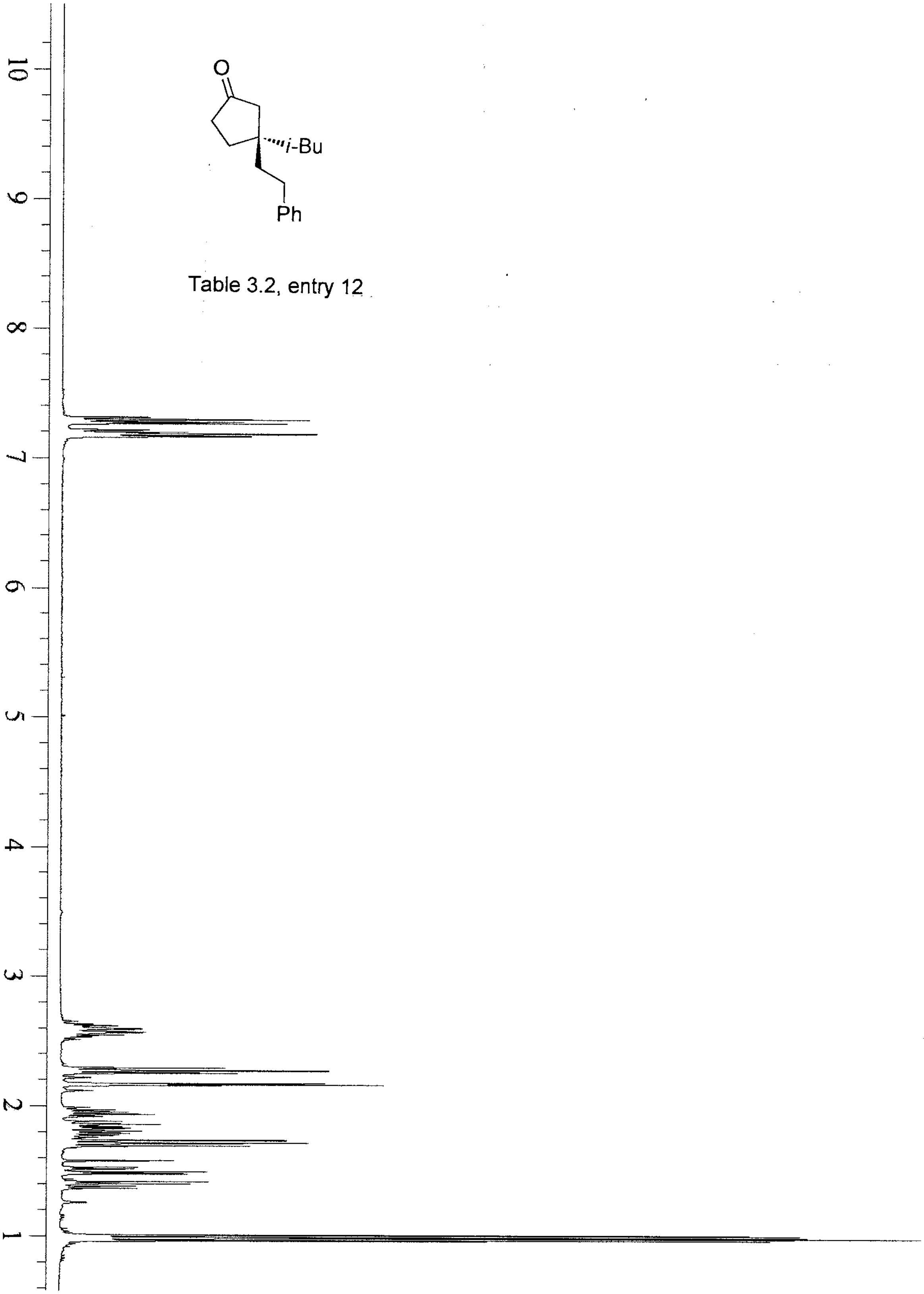

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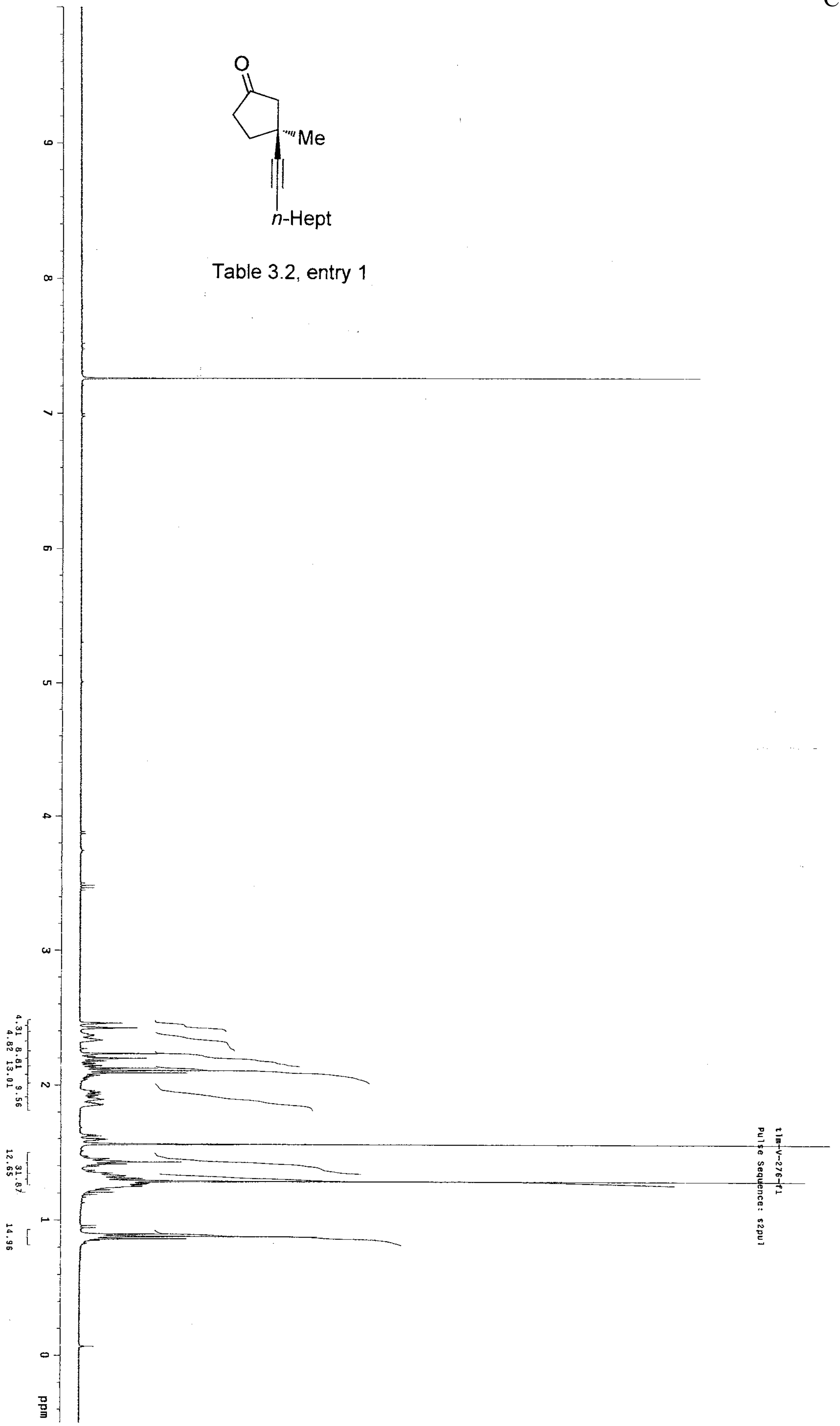
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Me
n-Hept
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6
5
4
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0
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12.65
31.87
14.96
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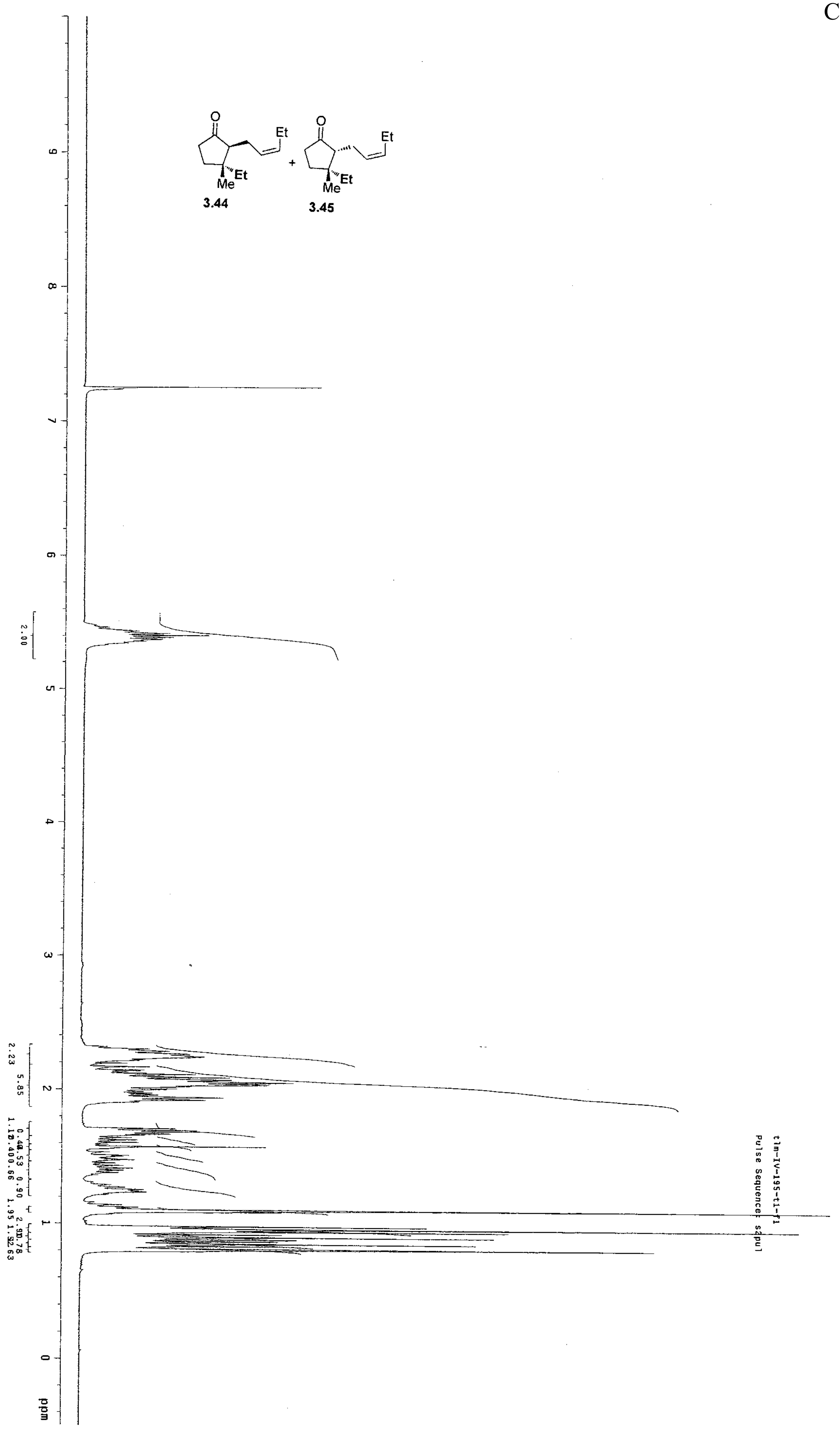
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3.45
Et
Me
O
+
tlm-IV-195-t1-f1
Pulse Sequence: s2pul
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8
7
6
5
4
3
2
1
0
ppm
2.00
2.23
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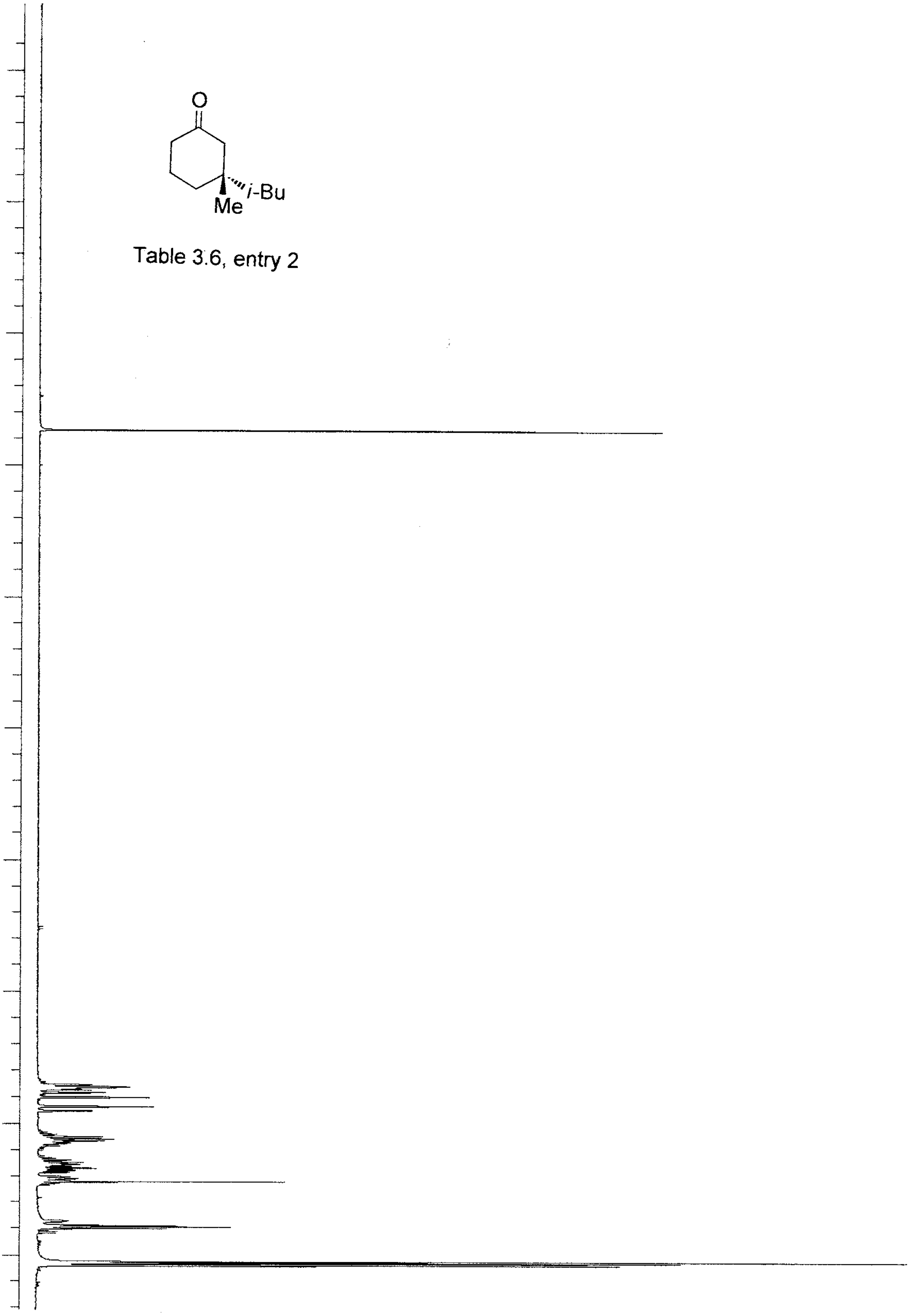
0.40
0.53
0.90
2.51
0.78
1.12
1.40
0.66
1.95
1.52
2.63



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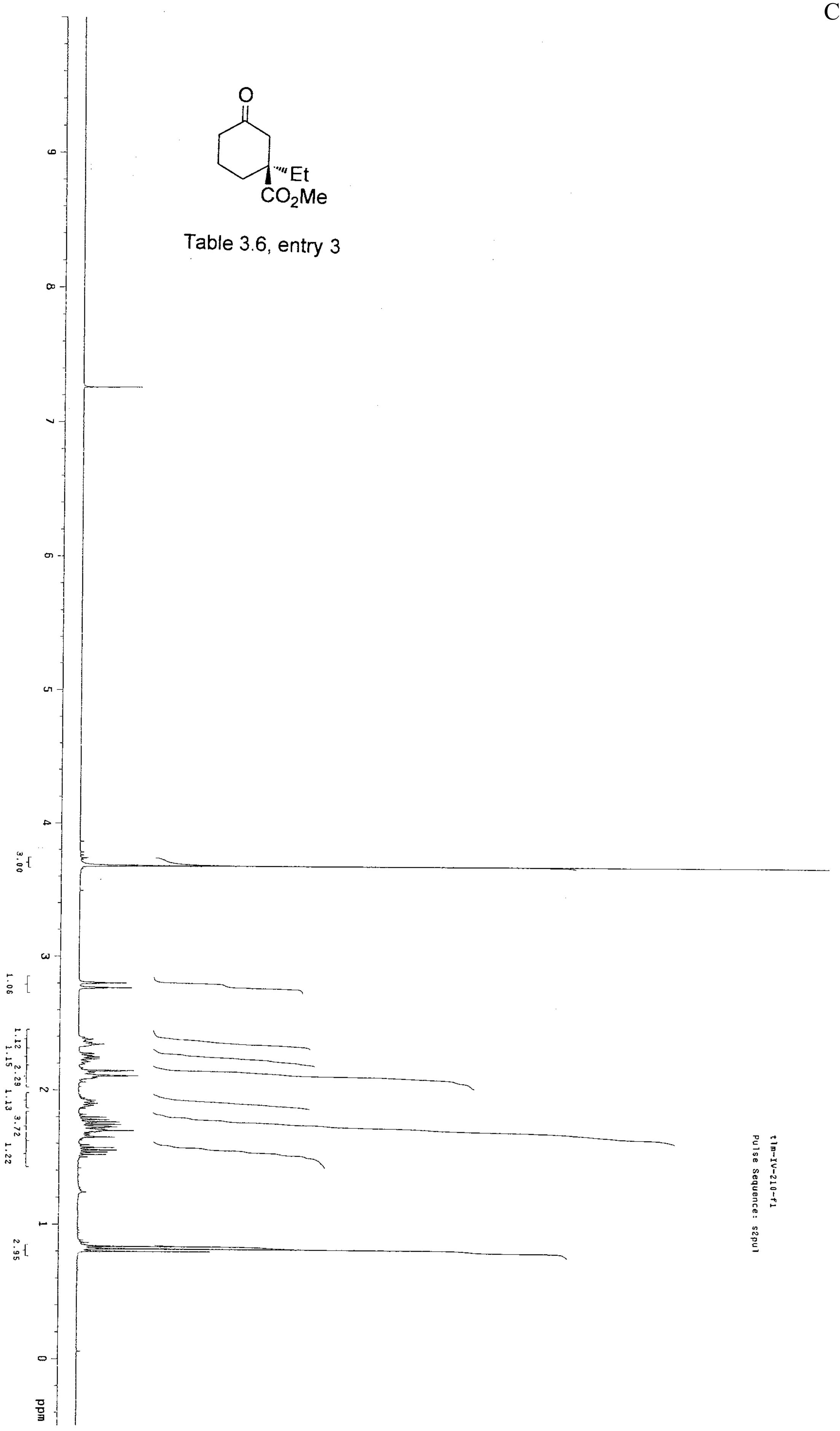
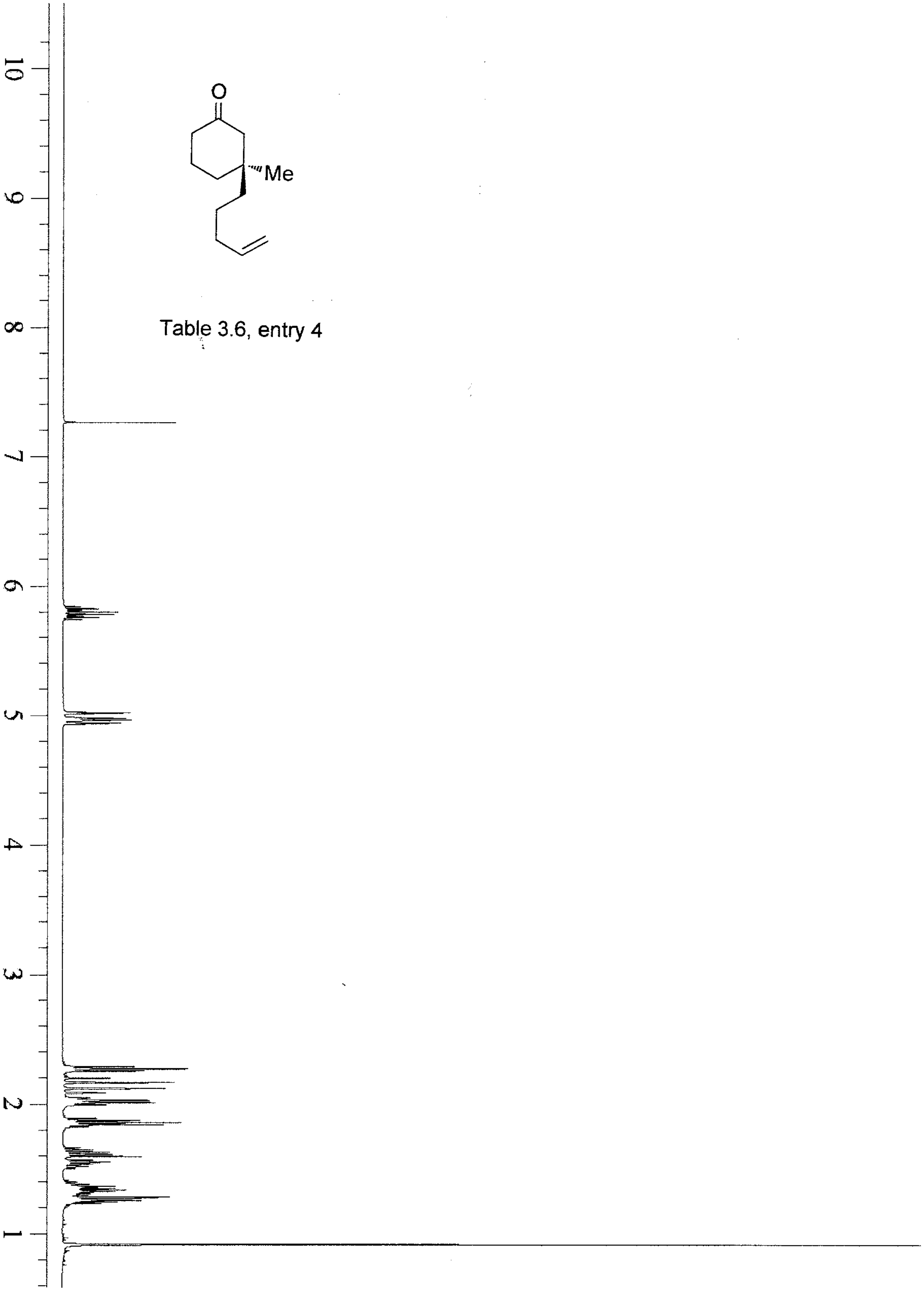


Table 3.6, entry 3



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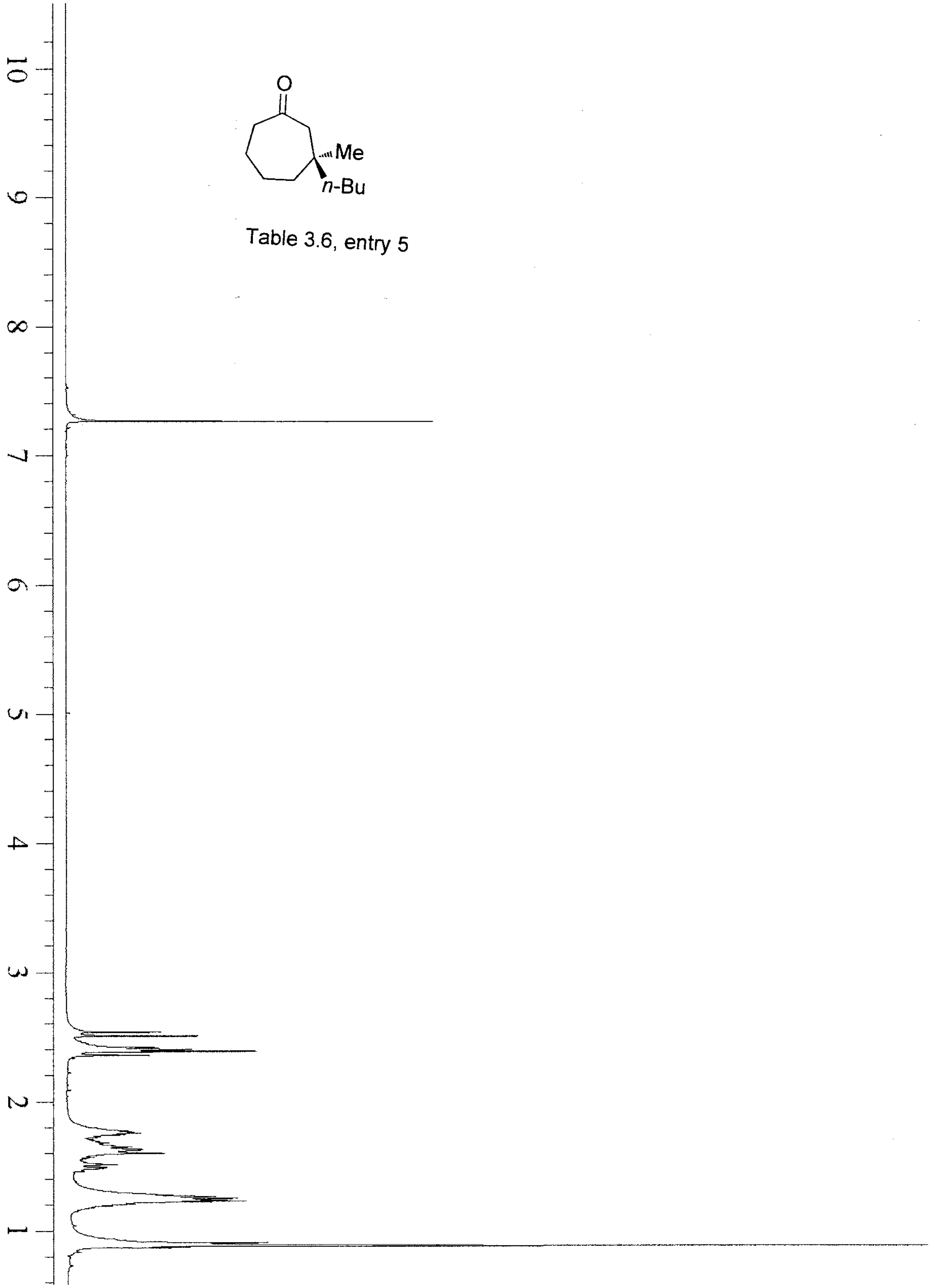

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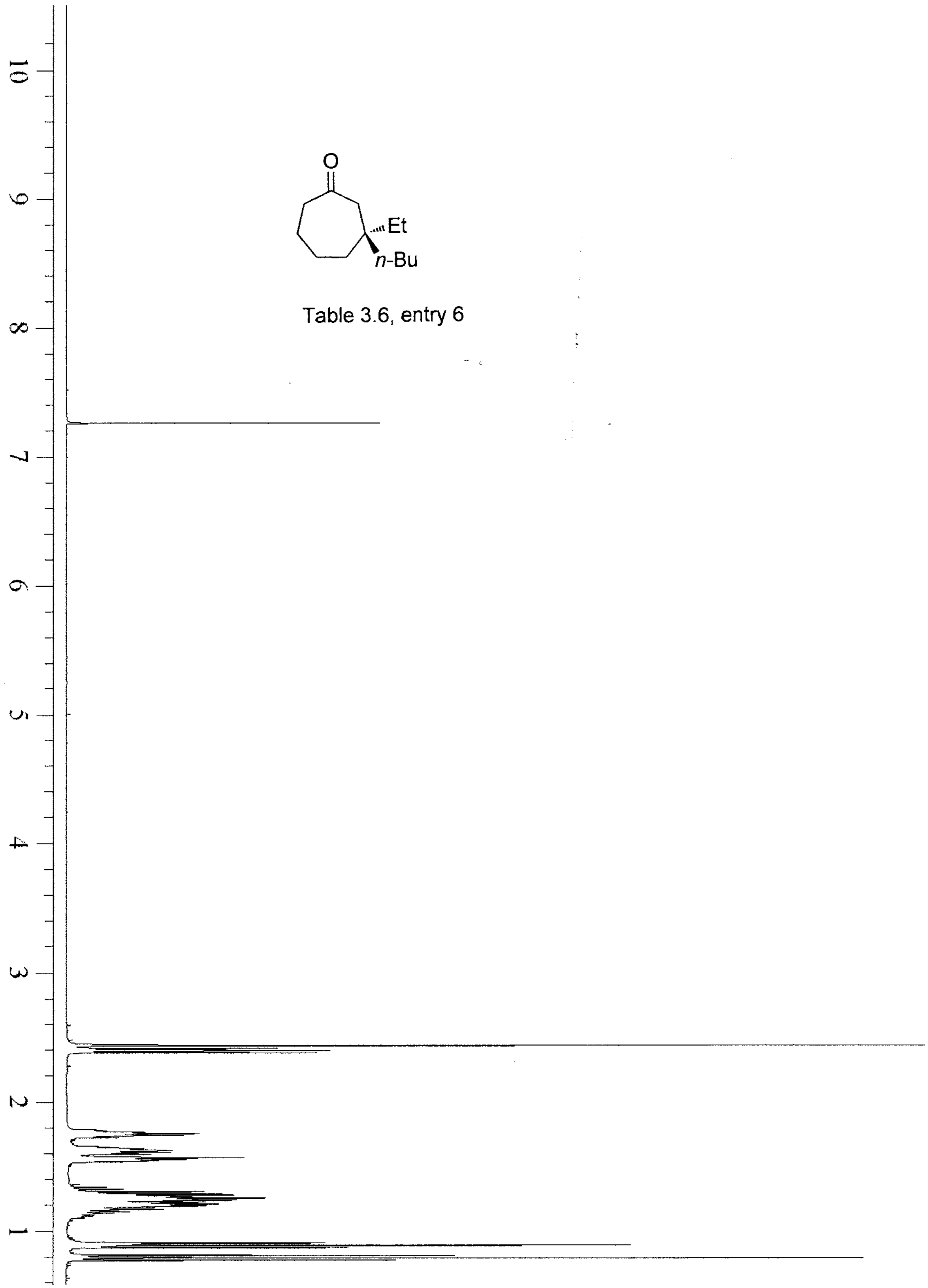

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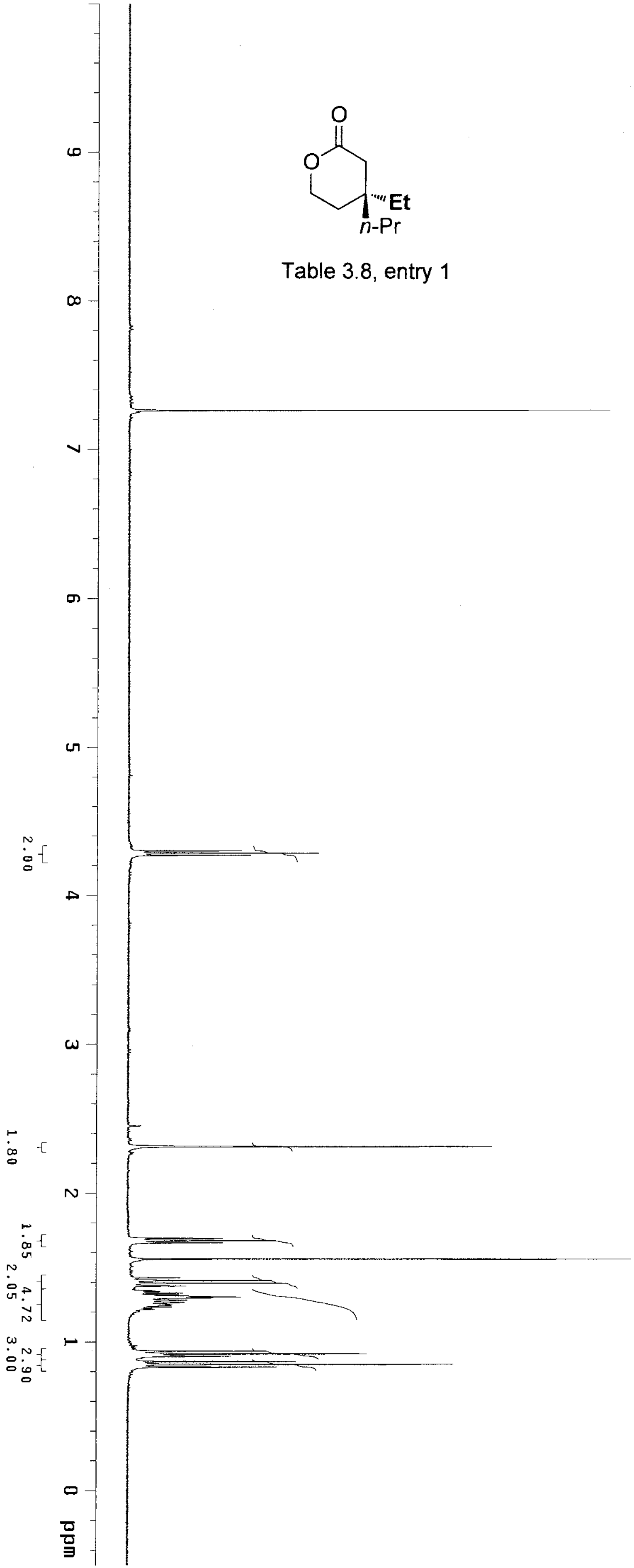

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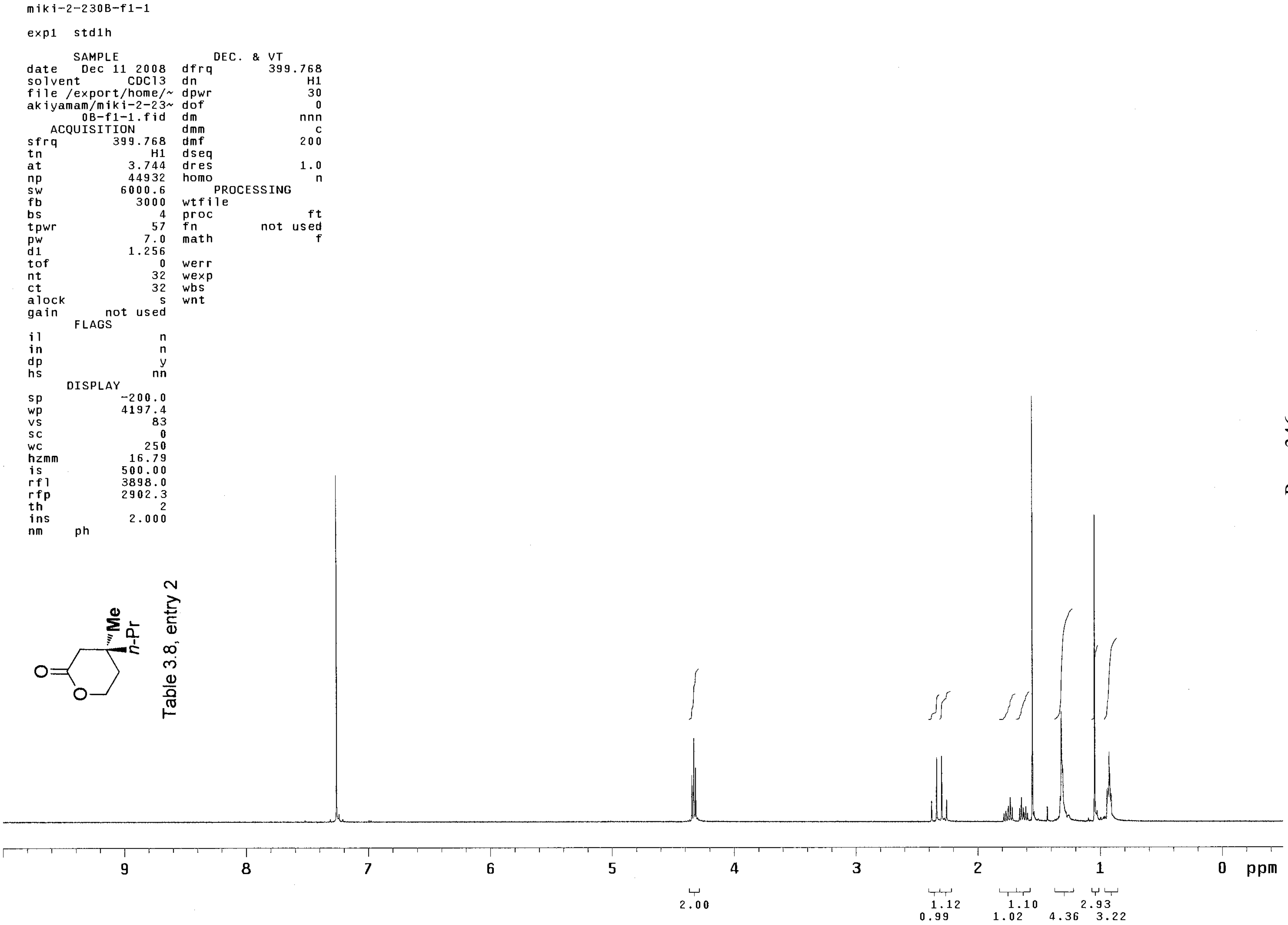

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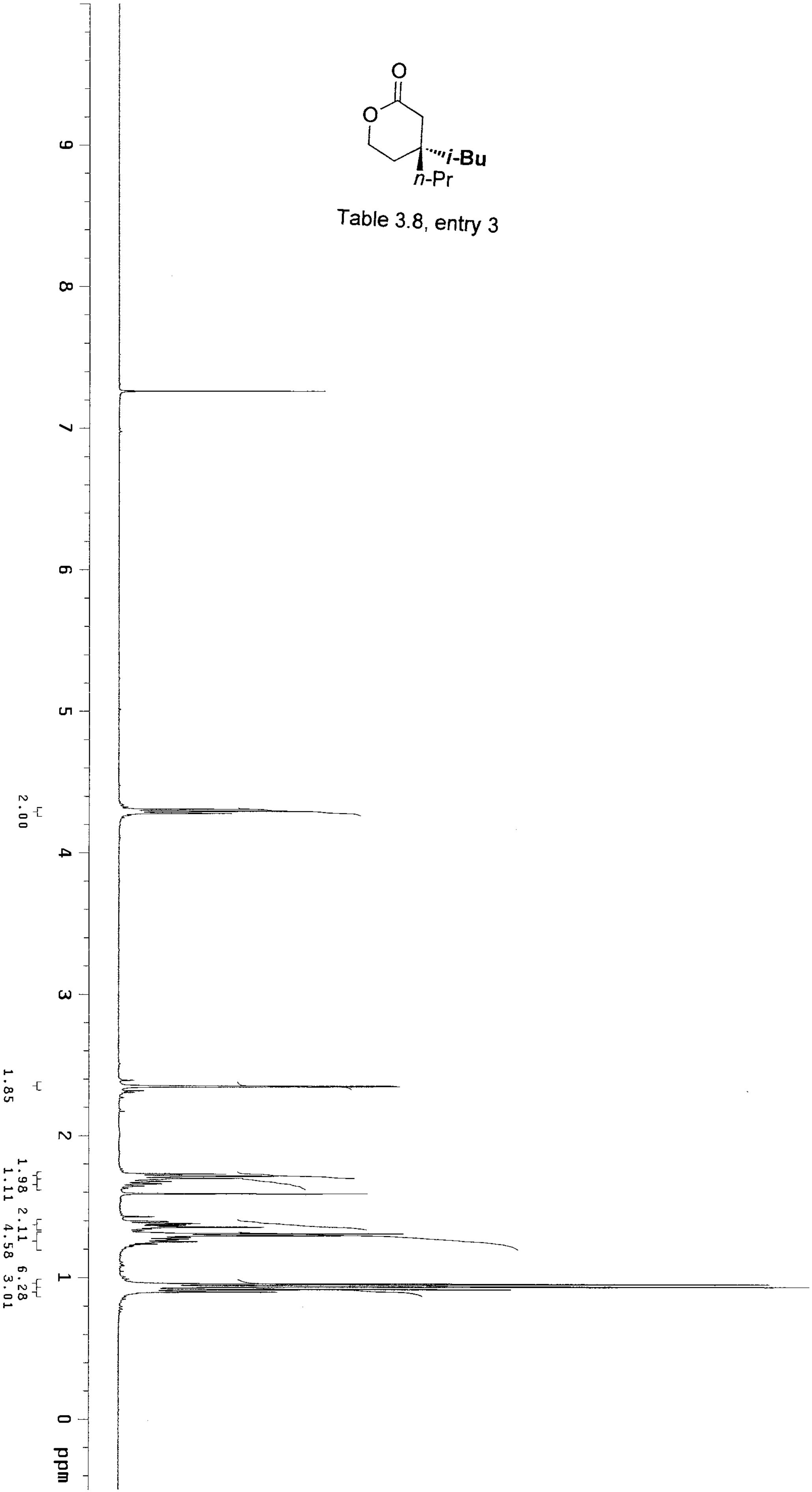
file /export/home/~ dpwr              30
akiyamam/miki-2-23~ dof                0
        0B-f1-1.fid dm               nnn
   ACQUISITION      dmm                c
sfrq        399.768 dmf              200
tn               H1 dseq
at            3.744 dres             1.0
np            44932 homo               n
sw           6000.6       PROCESSING
fb             3000 wtfile
bs                4 proc              ft
tpwr             57 fn          not used
pw              7.0 math               f
d1            1.256
tof               0 werr
nt               32 wexp
ct               32 wbs
alock             s wnt
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
       DISPLAY
sp           -200.0
wp           4197.4
vs               83
sc                0
wc              250
hzmm          16.79
is           500.00
rfl          3898.0
rfp          2902.3
th                2
ins           2.000
nm    ph
```

Table 3.8, entry 2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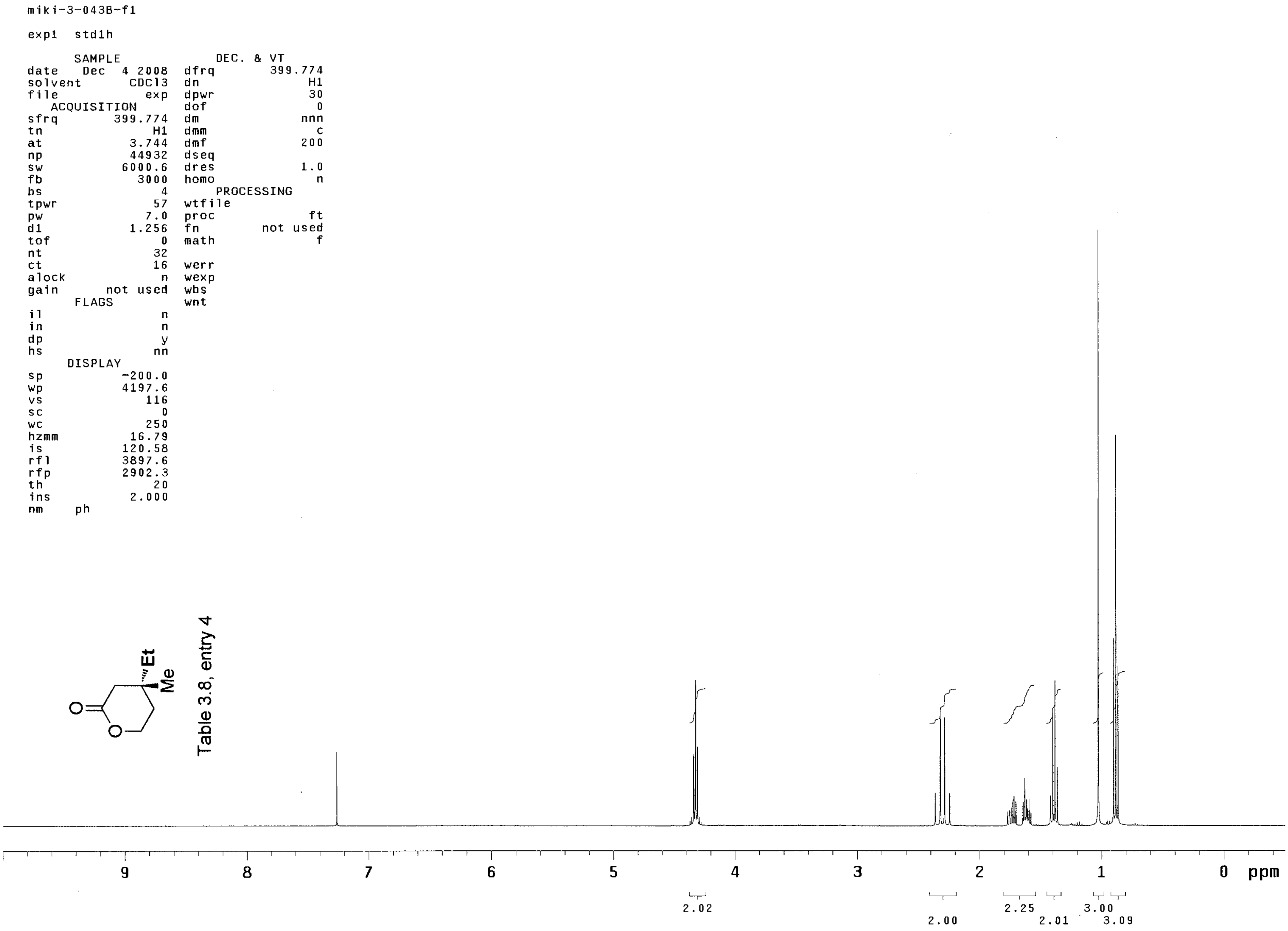

```
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file           exp  dpwr            30
   ACQUISITION      dof              0
sfrq       399.774  dm             nnn
tn              H1  dmm              c
at           3.744  dmf            200
np           44932  dseq
sw          6000.6  dres           1.0
fb            3000  homo             n
bs               4      PROCESSING
tpwr            57  wtfile
pw             7.0  proc            ft
d1           1.256  fn        not used
tof              0  math             f
nt              32
ct              16  werr
alock            n  wexp
gain      not used  wbs
      FLAGS         wnt
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -200.0
wp          4197.6
vs             116
sc               0
wc             250
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rfp         2902.3
th              20
ins          2.000
nm    ph
```

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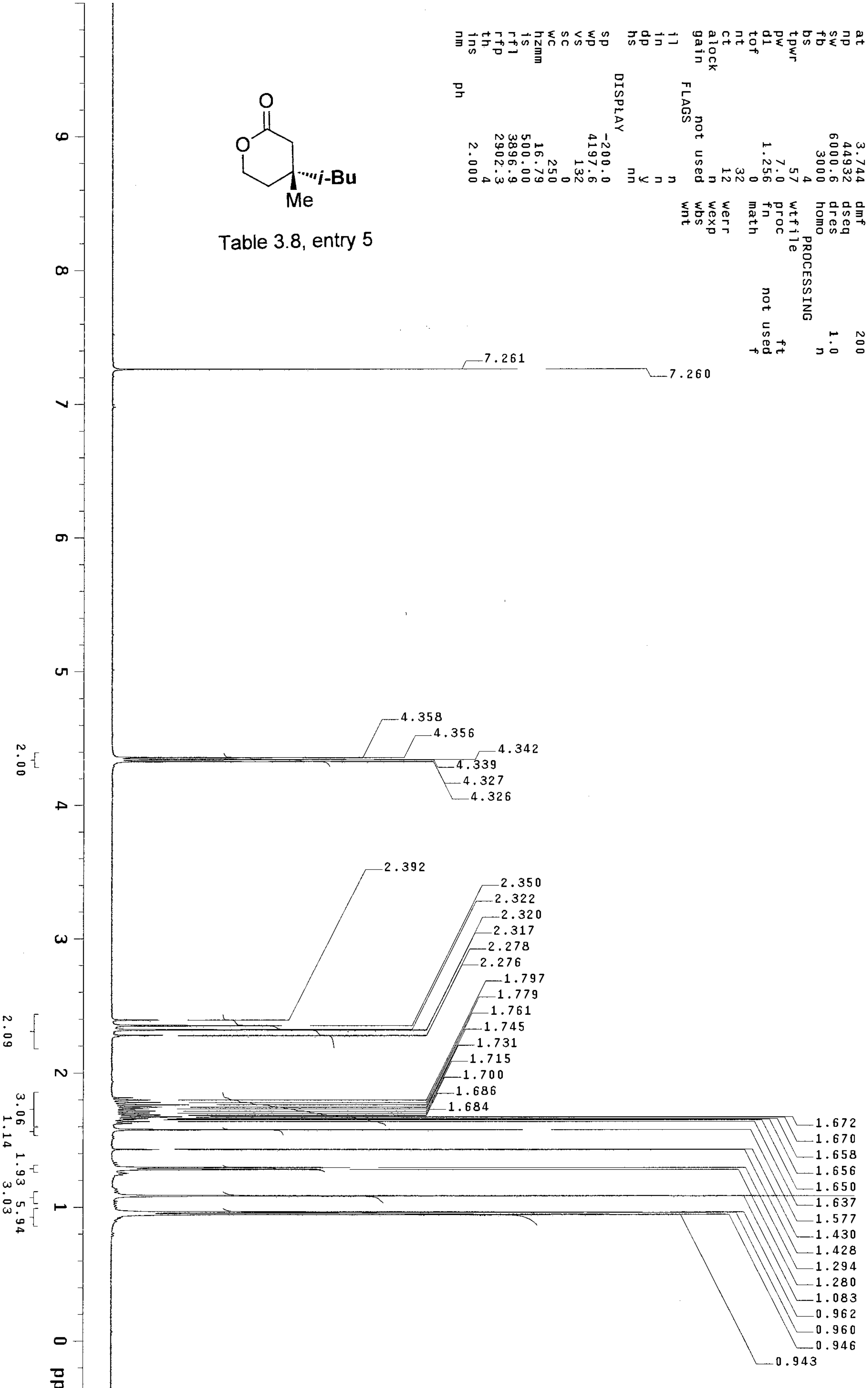

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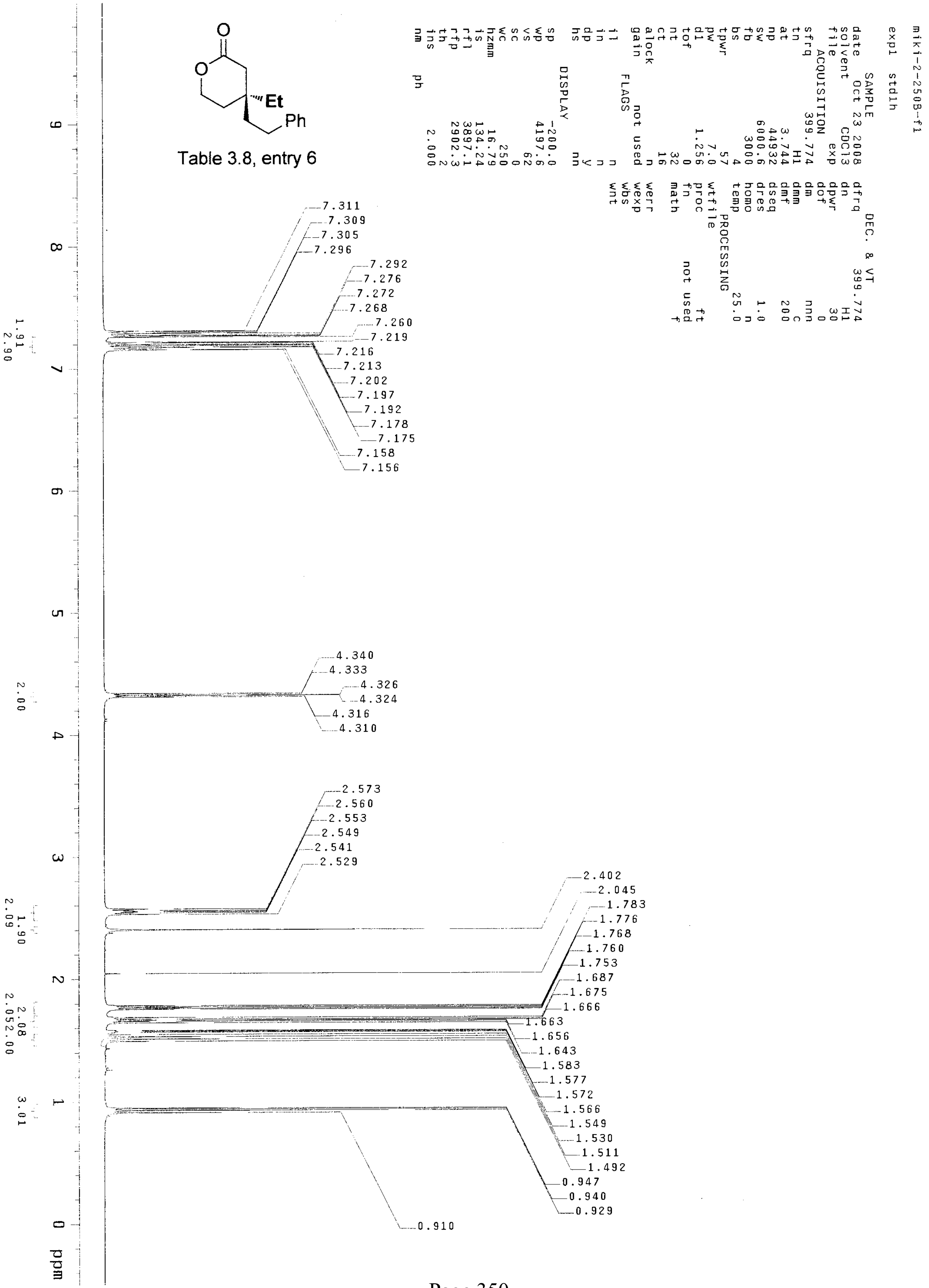

Table 3.8, entry 6

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solvent          CDCl3     dn                H1
file               exp     dpwr              30
       ACQUISITION         dof                0
sfrq           399.774     dm               nnn
tn                  H1     dmm                c
at               3.744     dmf              200
np               44932     dseq
sw              6000.6     dres             1.0
fb                3000     homo               n
bs                   4     temp            25.0
tpwr                57          PROCESSING
pw                 7.0     wtfile
d1               1.256     proc              ft
tof                  0     fn          not used
nt                  32     math               f
ct                  16
alock                n     werr
gain          not used     wexp
         FLAGS             wbs
il                   n     wnt
in                   n
dp                   y
hs                  nn
         DISPLAY
sp              -200.0
wp              4197.6
vs                  62
sc                   0
wc                 250
hzmm             16.79
is              134.24
rfl             3897.1
rfp             2902.3
th                   2
ins              2.000
nm                  ph
```

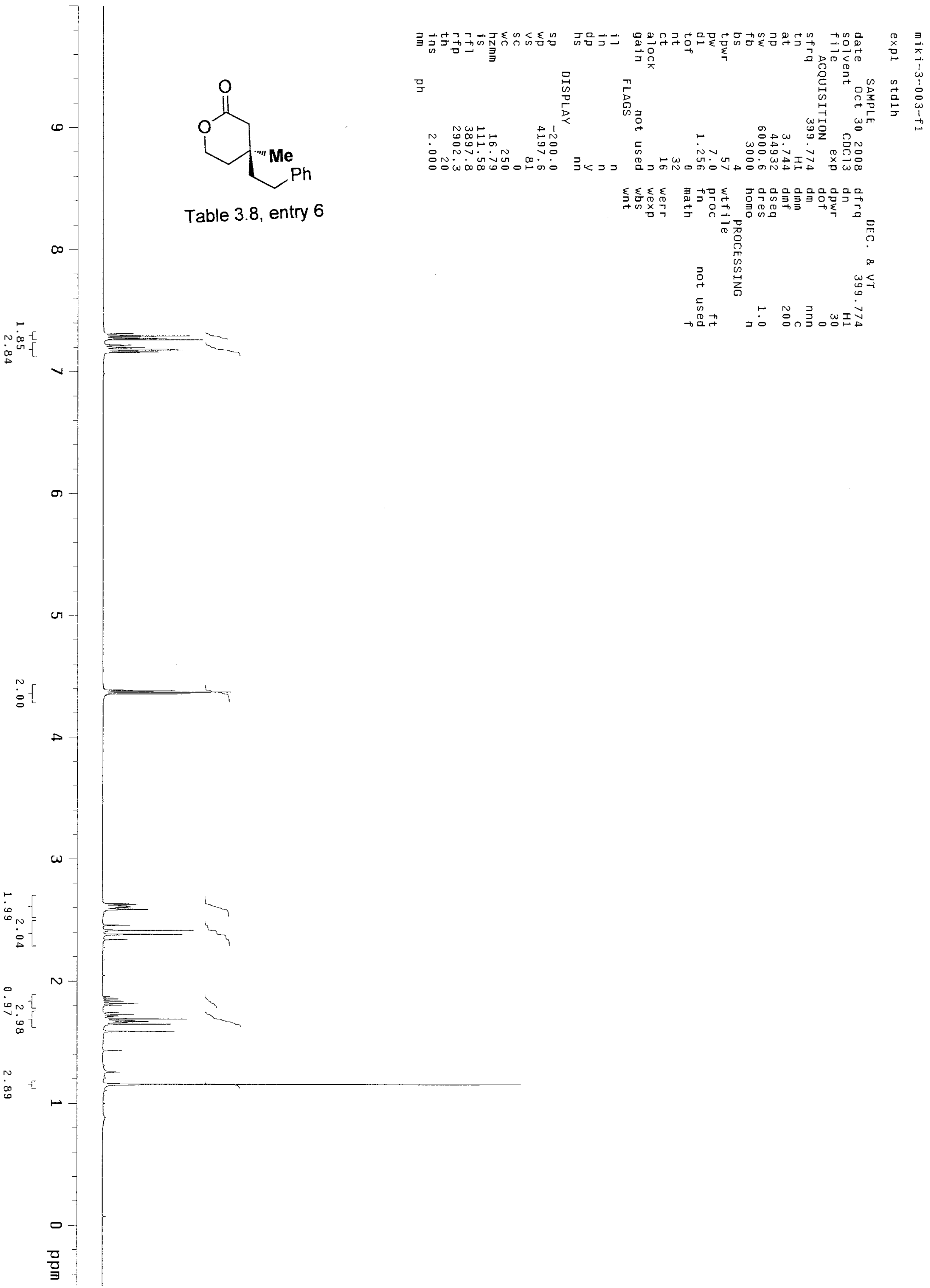
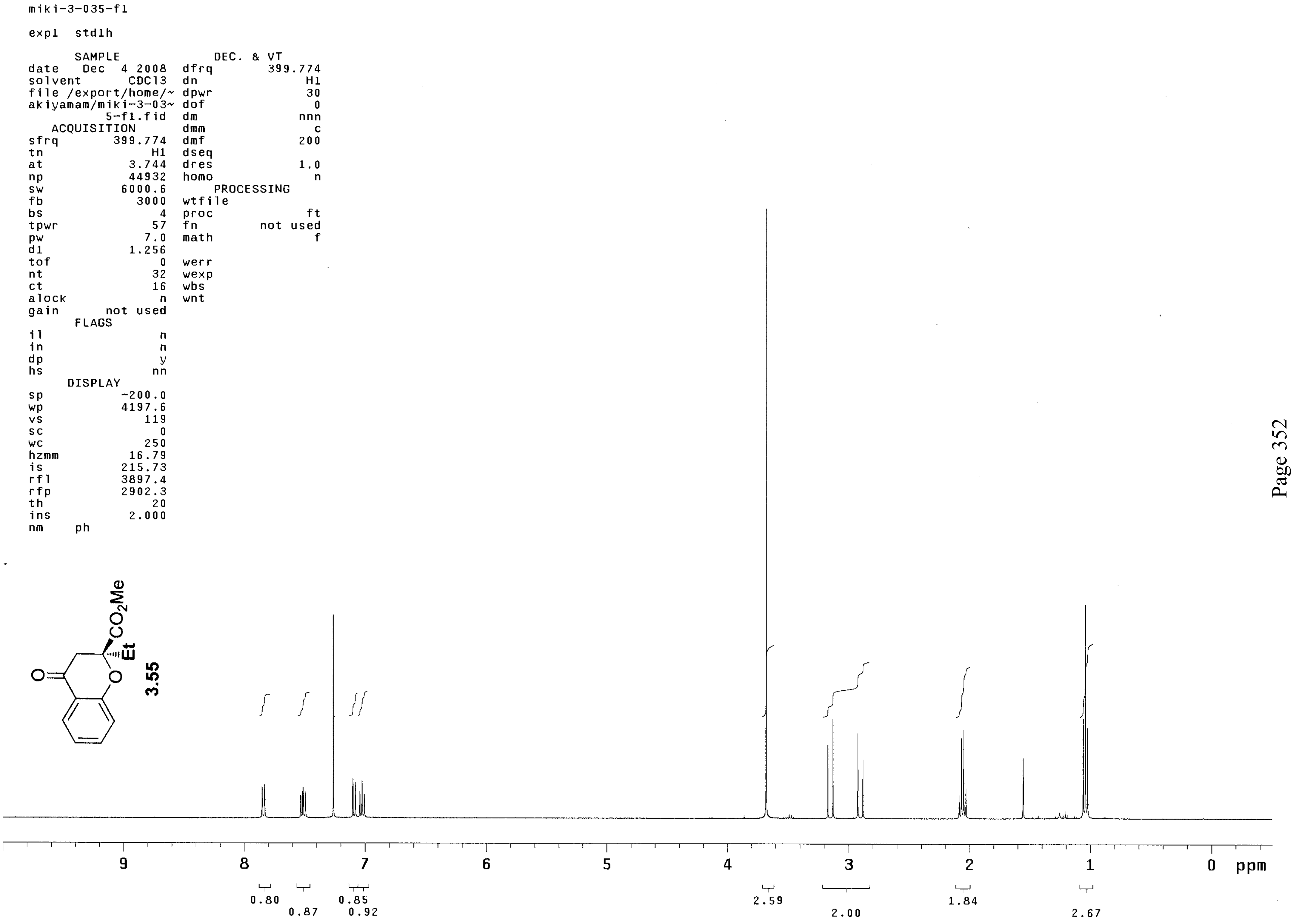


Table 3.8, entry 6



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file /export/home/~ dpwr             30
akiyamam/miki-3-03~ dof               0
          5-f1.fid  dm              nnn
   ACQUISITION      dmm               c
sfrq       399.774  dmf             200
tn              H1  dseq
at           3.744  dres            1.0
np           44932  homo              n
sw          6000.6      PROCESSING
fb            3000  wtfile
bs               4  proc             ft
tpwr            57  fn         not used
pw             7.0  math              f
d1           1.256
tof              0  werr
nt              32  wexp
ct              16  wbs
alock            n  wnt
gain      not used
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -200.0
wp          4197.6
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sc               0
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rfl         3897.4
rfp         2902.3
th              20
ins          2.000
nm    ph
```

3.55

O
O
CO2Me
Et
9
8
7
6
5
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3
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1
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ppm
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0.85
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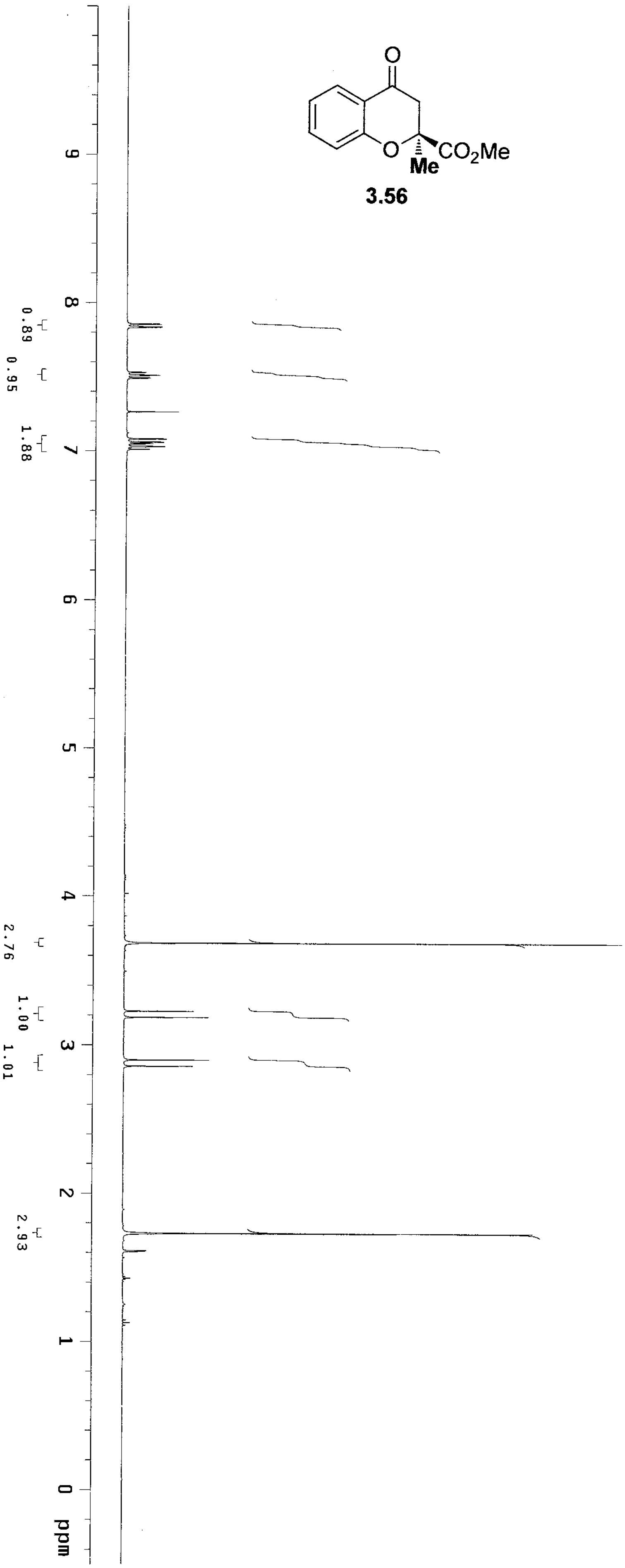
2.00
1.84
2.67



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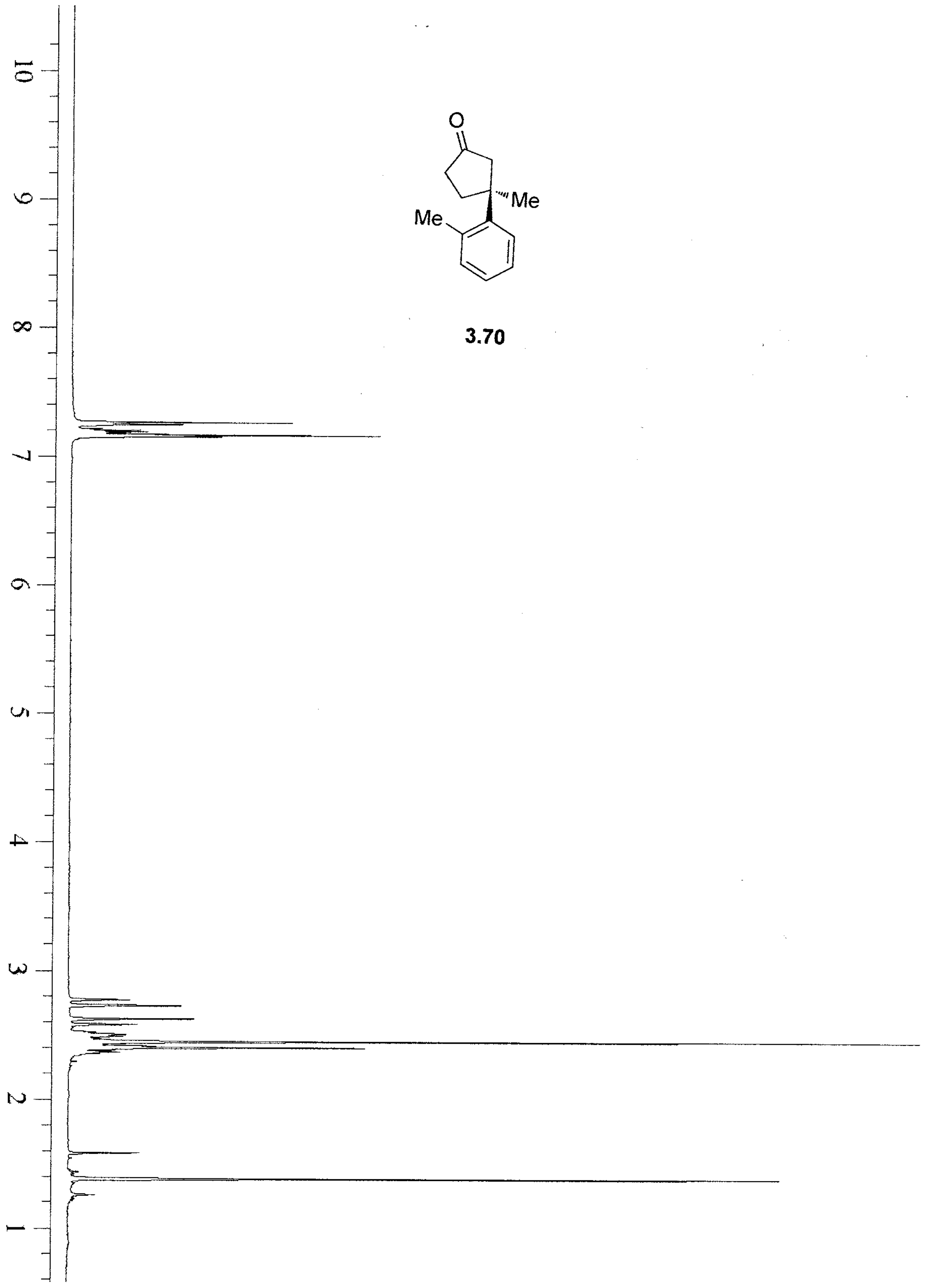

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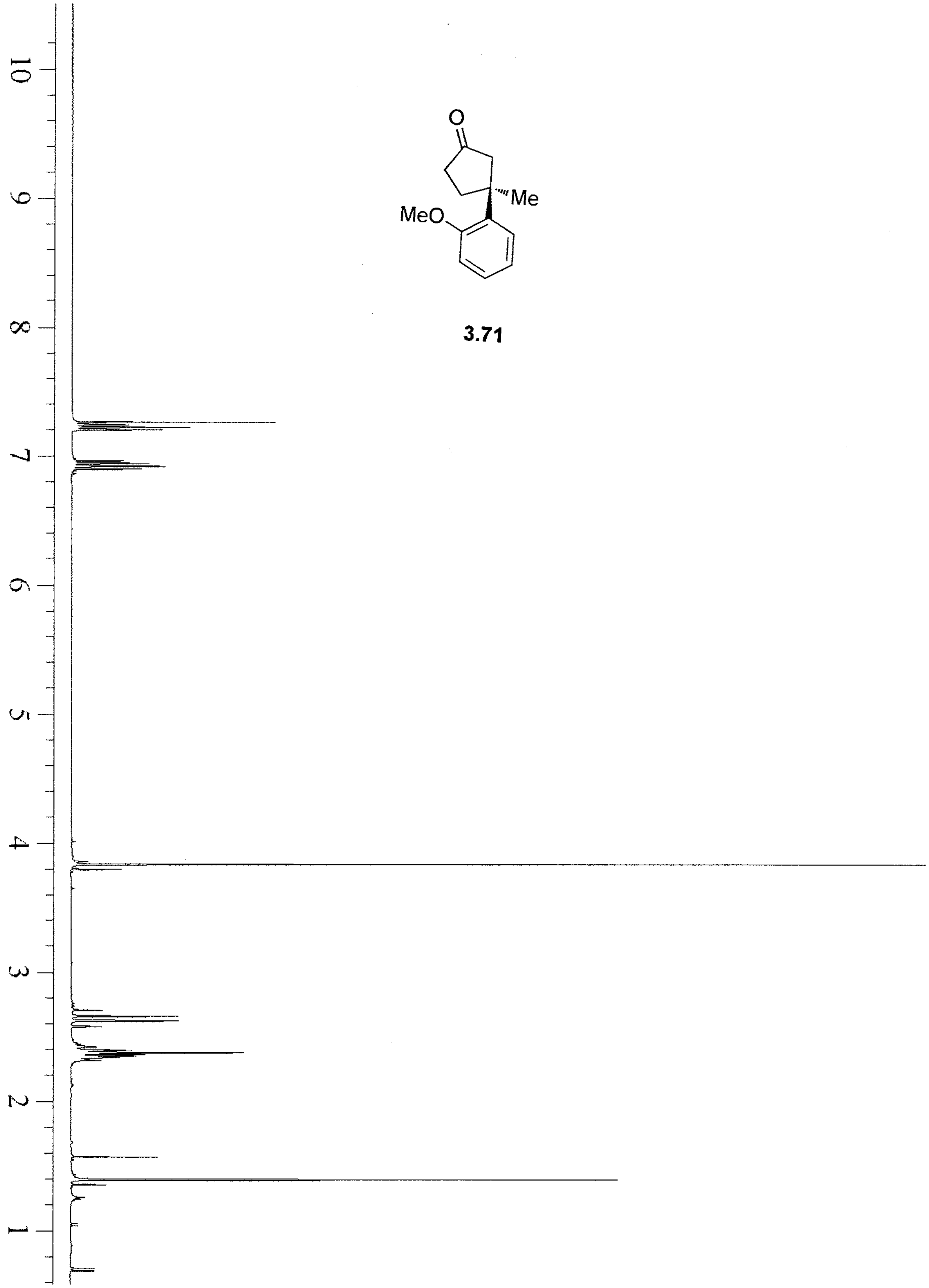

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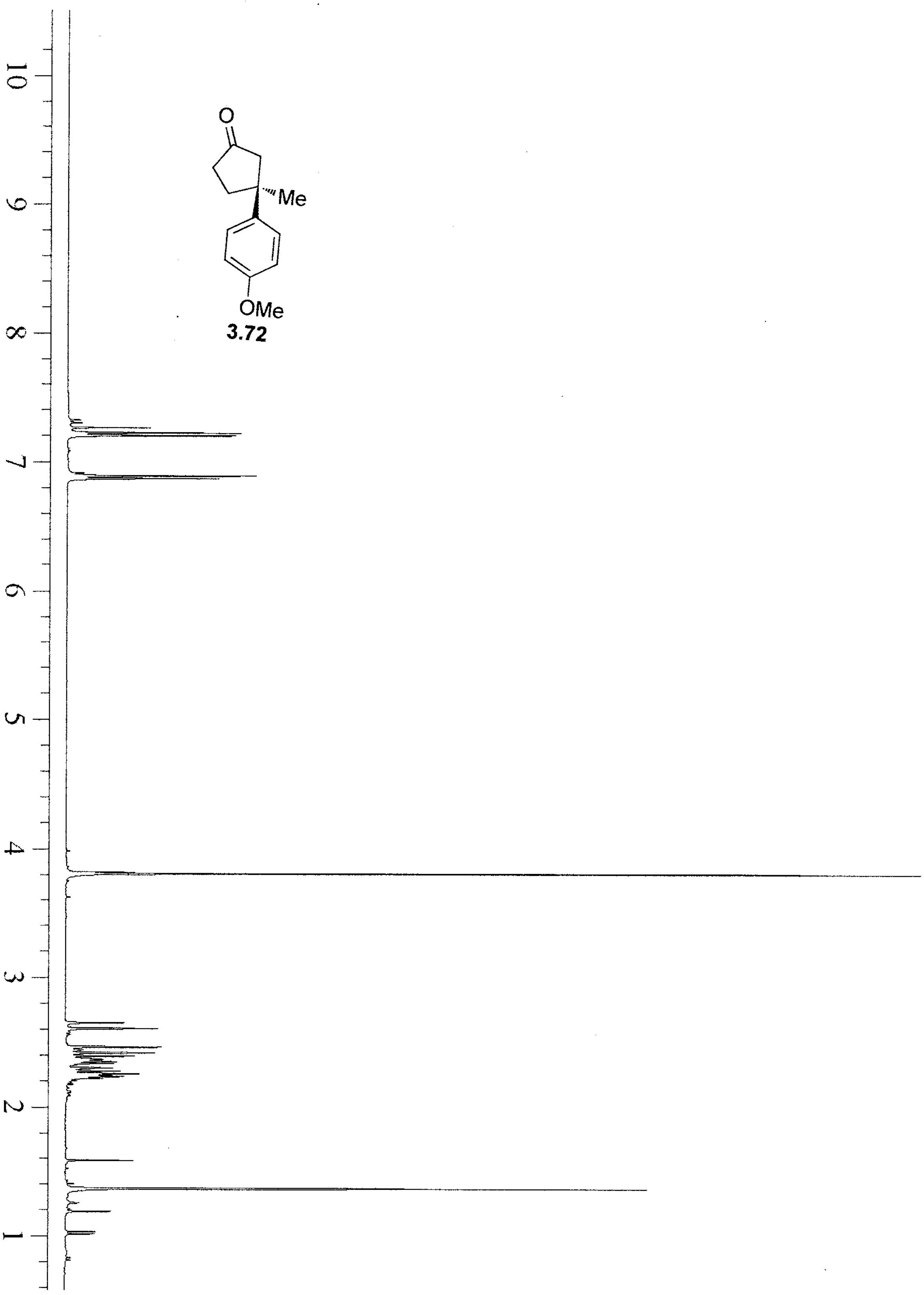
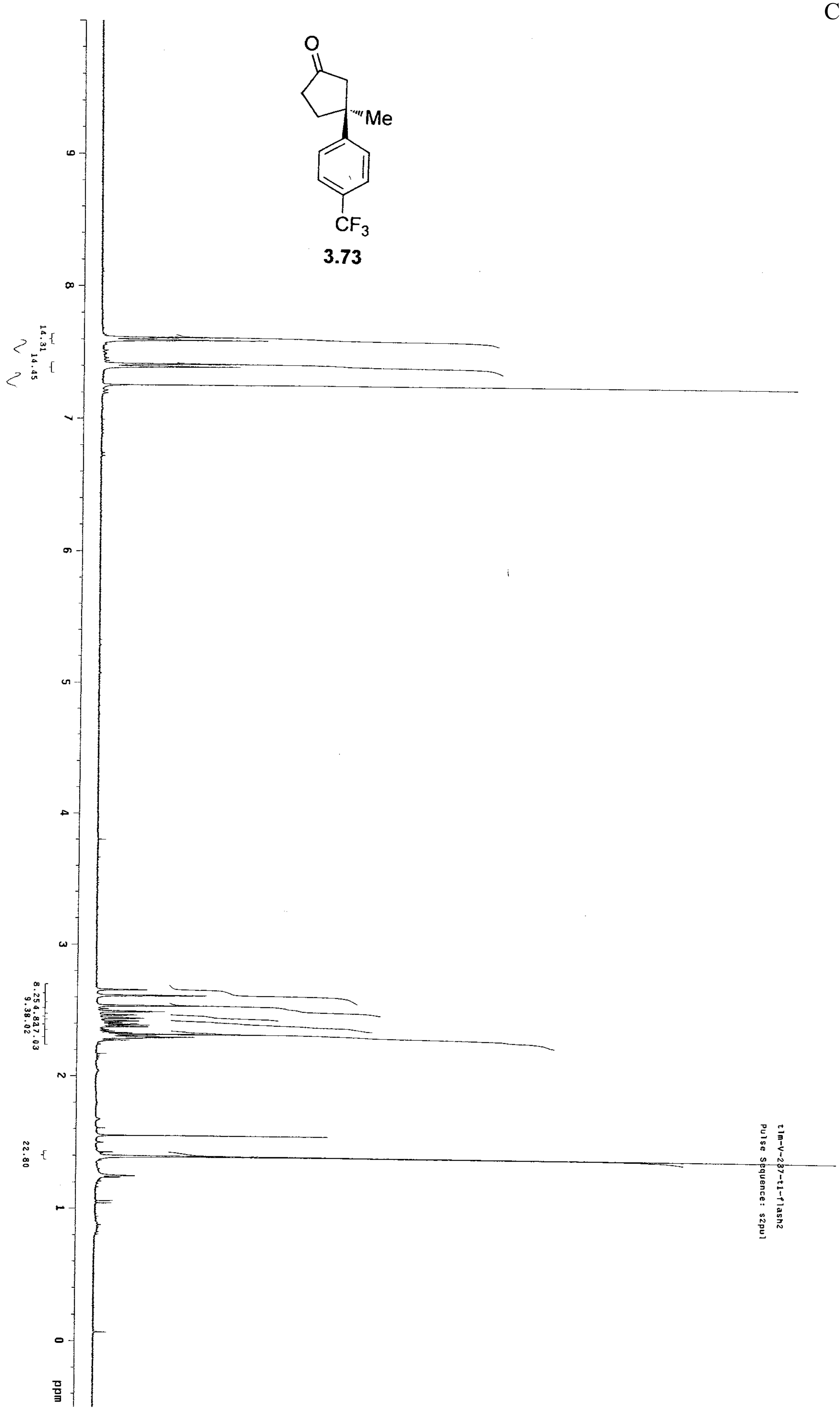
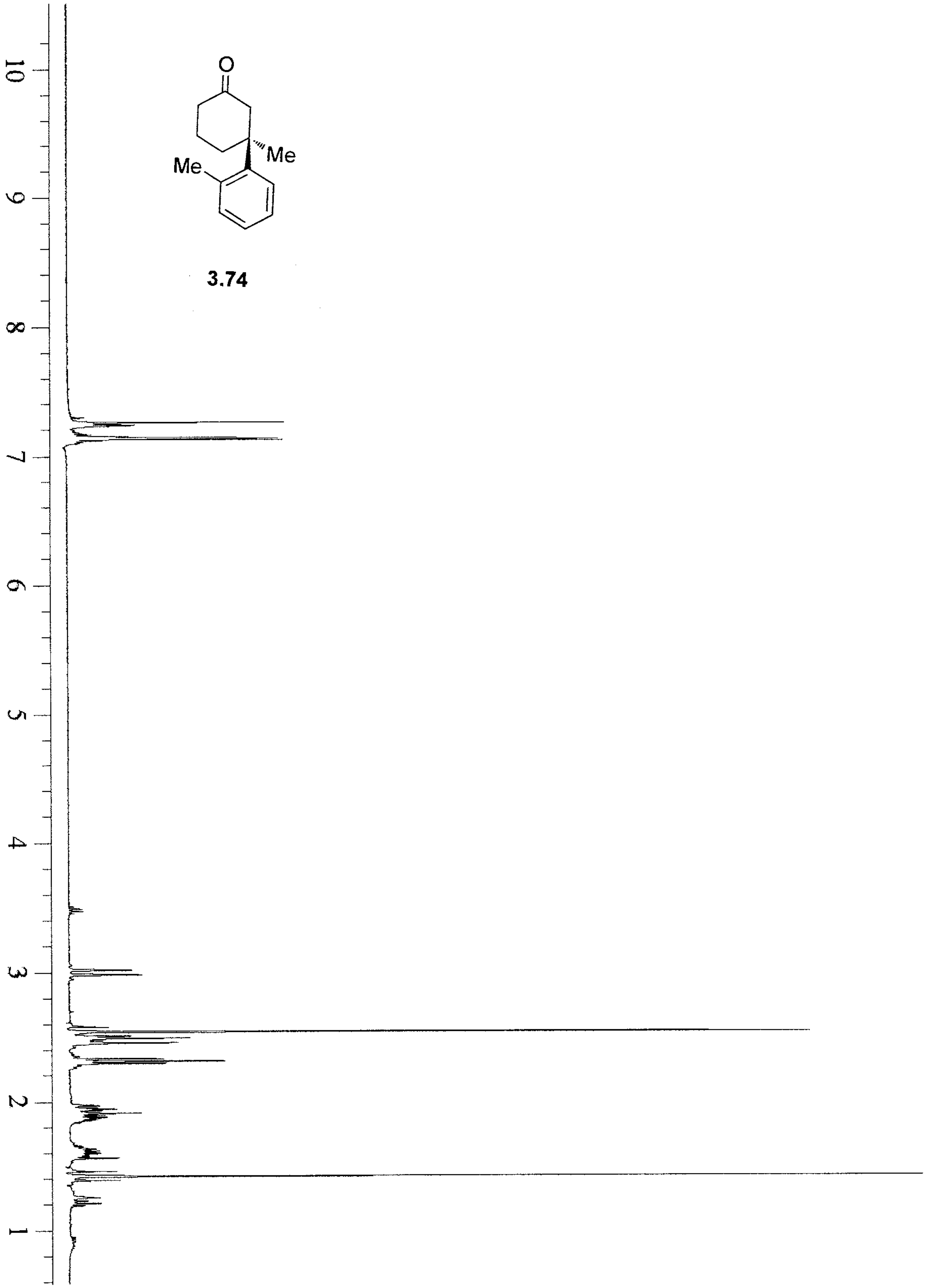


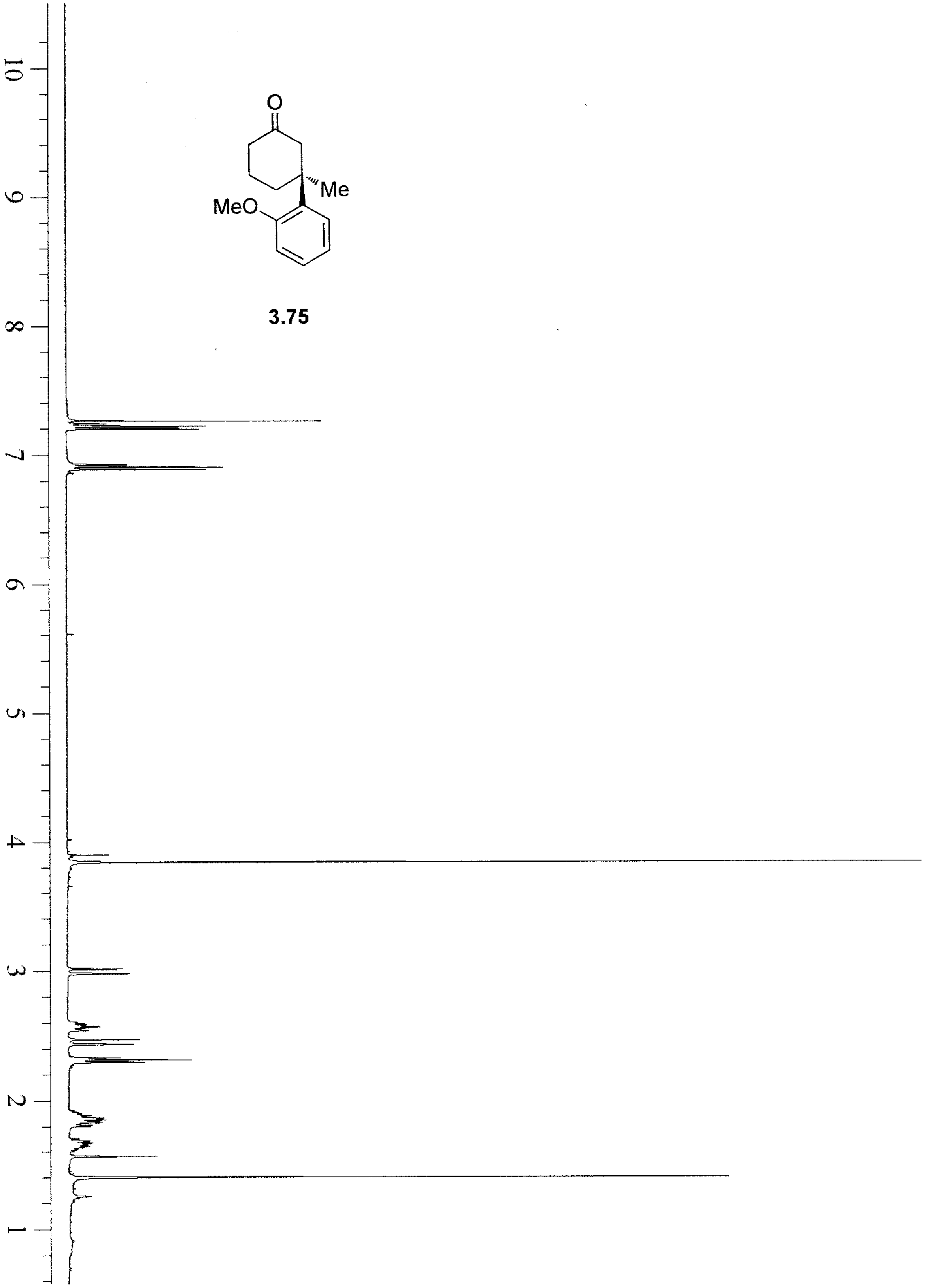
3.72


O
Me
CF3
9
8
7
6
5
4
3
2
1
0
ppm
14.31
14.45
8.25
4.82
7.03
9.38.02
22.80
tlm-V-287-t1-flash2
Pulse Sequence: s2pul

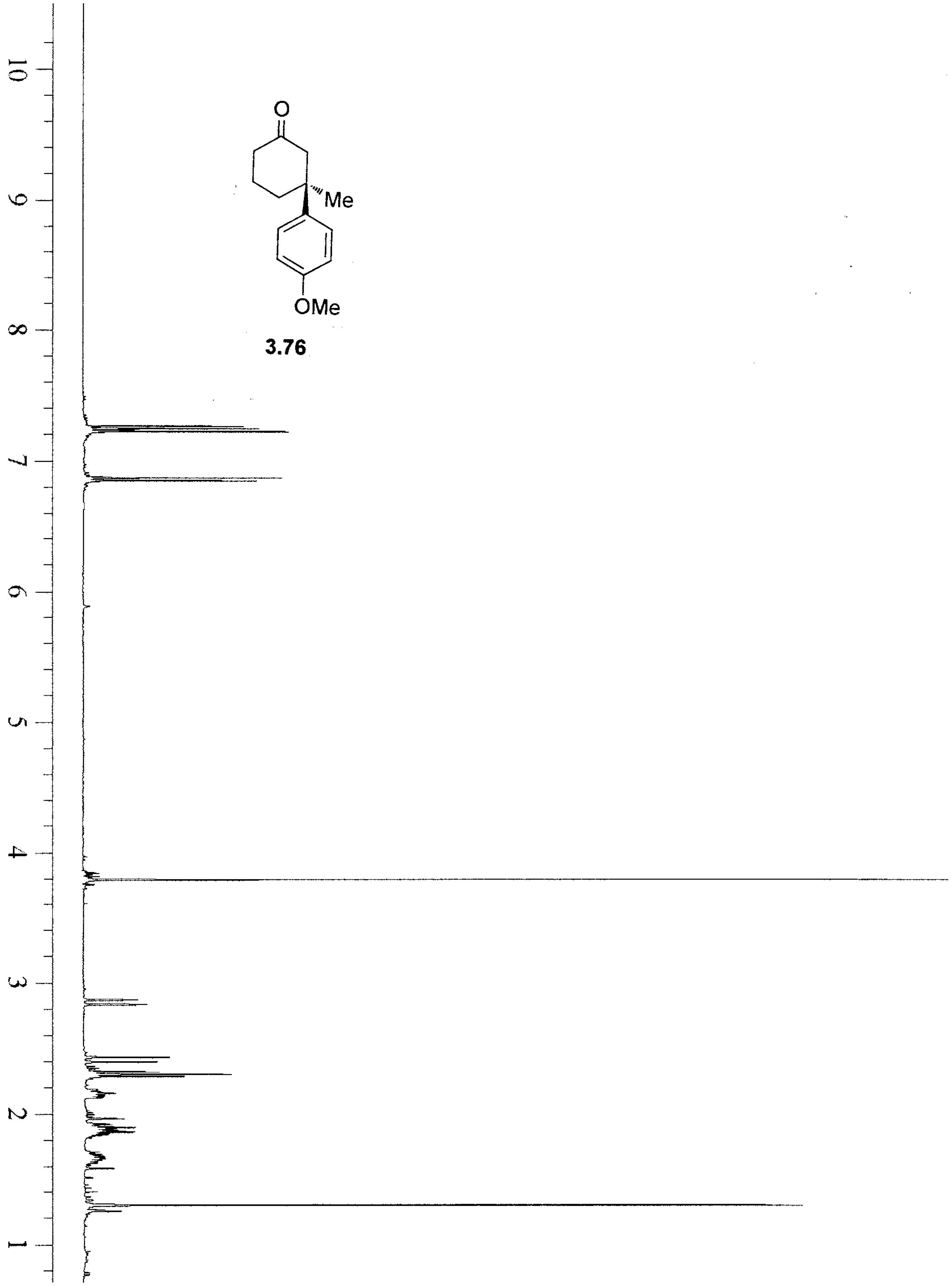
3.73



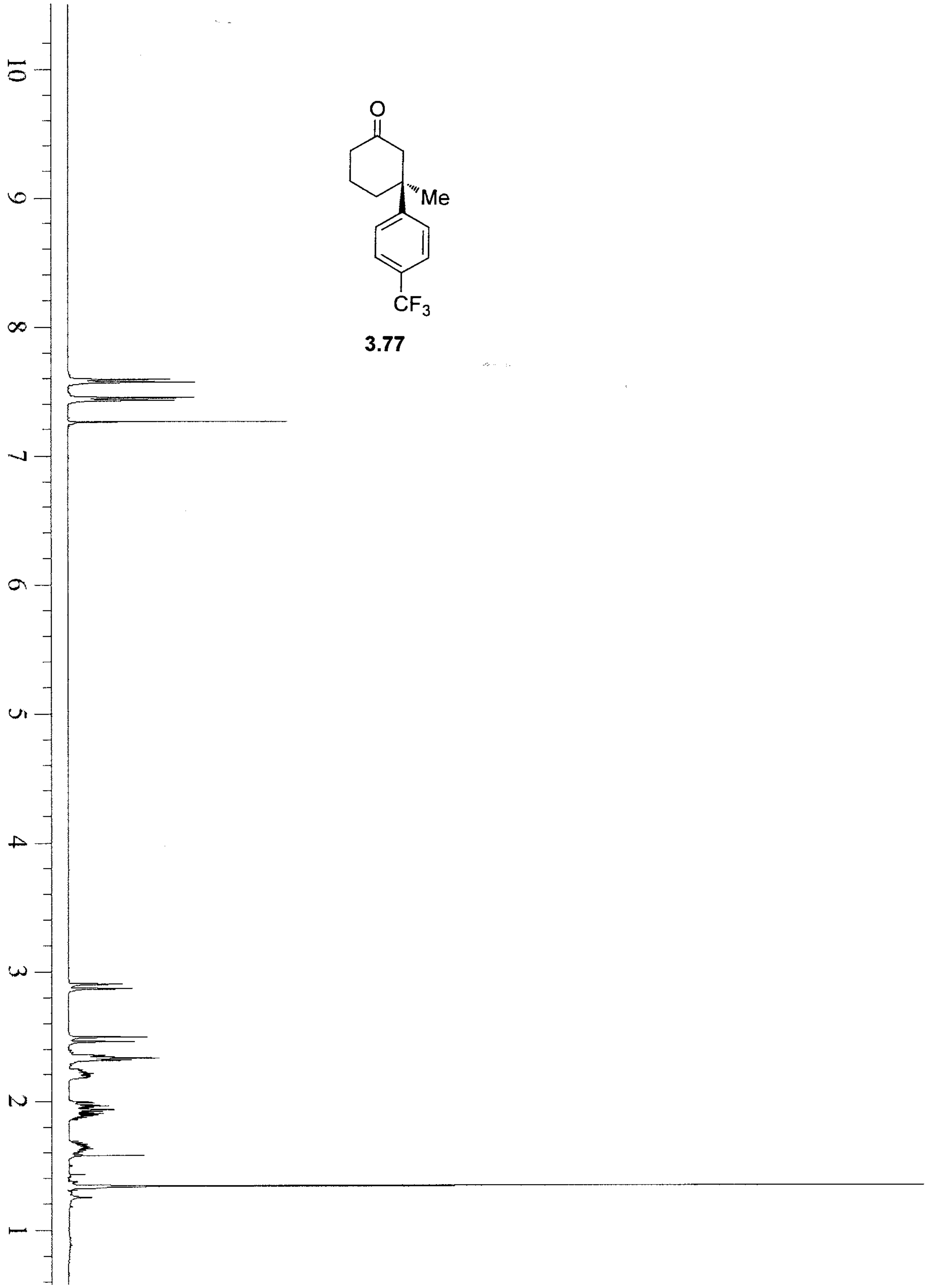
3.74



3.75



3.76



3.77

Chapter 4.

Cu-Catalyzed Enantioselective Conjugate Addition of Vinylaluminum Reagents to Cyclic Trisubstituted Enones

4.1. Introduction

Cu-catalyzed enantioselective conjugate addition to enones for the formation of all-carbon quaternary stereogenic centers is an important and flourishing topic in organic chemistry.[1] Most disclosures, however, have focused on alkyl additions and, less frequently, aryl additions; enantioselective conjugate addition of vinyl nucleophiles to enones generating a quaternary stereogenic center has been met with only limited success.[2] Enantioselective vinyl addition is an important and critical goal in organic synthesis. One such reason is that, in nature, many natural products and biologically active agents contain quaternary stereogenic centers that bear a vinyl group (Figure 4.1). For example, sesquiterpene riccardiphenol B,[3] suspensoside A[4] and daphnimacropodine

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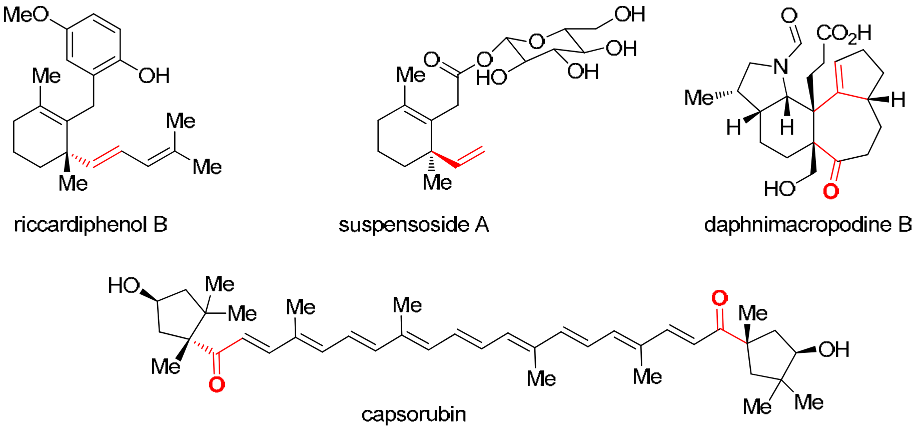
(1) (a) “Recent Advances in Catalytic Enantioselective Michael Additions,” Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (b) “Enantioselective Copper-Catalysed Conjugate Addition,” Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem*. **2002**, 3221–3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*, Krause, N. Ed.; Wiley–VCH, Weinheim, 2002, pp. 224–258.

(2) (a) “Enantioselective Construction of Stereogenic Quaternary Centres *via* Rh-Catalyzed Asymmetric Addition of Alkenylboronic Acids to α,β-Unsaturated Pyridylsulfones,” Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963. (b) “Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminum Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers,” Vuagnoux-d’Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662. (c) “Copper-Catalyzed Asymmetric Conjugate Addition of Aryl Aluminum Reagents to Trisubstituted Enones: Construction of Aryl-Substituted Quaternary Centers,” Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int Ed.* **2008**, *47*, 8211–8214. (d) “Copper-Catalyzed Asymmetric Conjugate Addition with Chiral SimplePhos Ligands,” Palais, L.; Alexakis, A. *Chem. Eur. J.* **2009**, *15*, 10473–10485. (e) “Creation of Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Conjugate Addition of Alkenyl Alanes to α,β-Unsaturated Cyclic Ketones,” Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, 1694–1698.

(3) “Sesquiterpene Derivatives and a Norsesquiterpenoid from the Liverworts *Riccardia Crassa* and *Porella Caespitans* var. *Setigera*,” Toyota, M.; Asakawa, Y. *Phytochemistry* **1993**, *32*, 137–140.

B[5] all bear a quaternary carbon stereogenic center containing an olefin. A vinyl group is also synthetically versatile; further functionalizations of the olefin can allow access to ketones (Wacker oxidation[6]), long-chained alkyl groups (reduction[7]), secondary alcohols (hydroboration,[8] epoxidation/epoxide opening), and amines (hydroamination[9]), among others. Moreover, the quaternary carbon stereogenic carbon bearing a carbonyl moiety found in daphnimacropodine B[5] and capsorubin[10] could potentially be prepared by further elaboration of the conjugate vinyl addition adduct.

Figure 4.1. Natural Products Containing All-Carbon Quaternary Stereogenic Centers Bearing a Vinyl Group or Functionalizations of the Corresponding Olefin



riccardiphenol B

suspensoside A

daphnimacropodine B

capsorubin

Enantioselective vinyl additions represent a circumstance in which other disconnections are not as straightforward. For example, as shown in Scheme 4.1, the ketone containing an all-carbon quaternary stereogenic center bearing a vinyl group can

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(4) "Glucosylated Suspensosides, Water-Soluble Pheromone Conjugates from the Oral Secretions of Male *Anastrepha suspensa*," Walse, S. S.; Lu, F.; Teal, P. E. A. *J. Nat. Prod.* **2008**, *71*, 1726–1731.

(5) "Daphnimacropodines A–D, Alkaloids from *Daphniphyllum macropodum*," Kong, N.-C.; He, H.-P.; Wang, Y.-H.; Mu, S.-Z.; Di, Y.-T.; Hao, X.-J. *J. Nat. Prod.* **2007**, *70*, 1348–1351.

(6) "The Wacker Reaction and Related Alkene Oxidation Reactions," Takacs, J. M.; Jiang, X-t. *Curr. Org. Chem.* **2003**, *7*, 369–396.

(7) Genet, J.-P. Reduction of Functionalized Alkenes. In *Modern Reduction Methods;* Andersson, P. G.; Munslow, I. J., Eds. Wiley-VCH: Weinheim, 2008; pp 3–38.

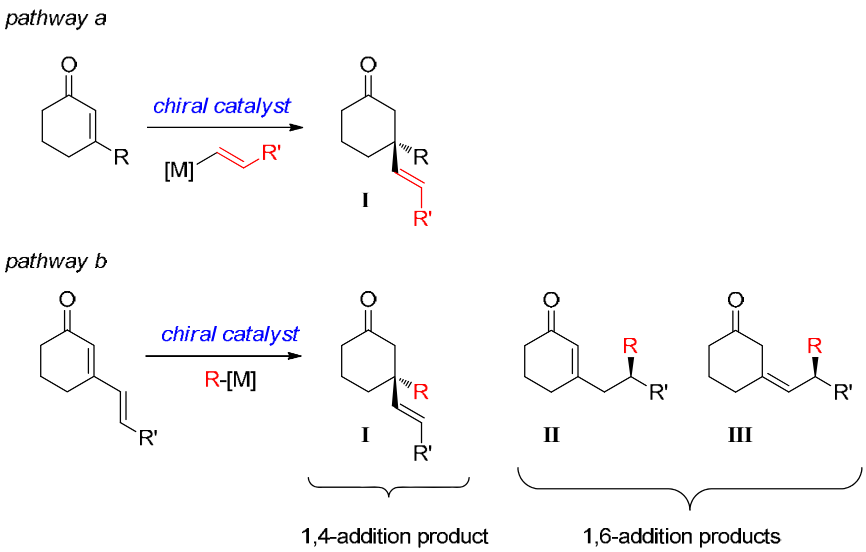
(8) Dhillon, R. S. *Hydroboration and Organic Synthesis: 9-Borabicyclo [3.3.1] Nonane (9-BBN)*; Springer: New York, 2007.

(9) "Hydroamination: Direct Addition of Amines to Alkenes and Alkynes," Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.

(10) "Cycloviolaxanthin (= (3*S*, 5*R*, 6*R*, 3'*S*, 5'*R*, 6'*R*)-3,6:3',6'-Diepoxy-5,6,5',6'-tetrahydro-β,β-carotene-5,5'-diol), a Novel Carotenoid from Red Paprika (*Capsicum annuum*)," Deli, J.; Mólnar, P.; Tóth, G.; Baumeler, A.; Eugster, C. H. *Helv. Chim. Acta* **1991**, *74*, 819–824.

potentially be prepared through one of two ways. Pathway a illustrates an enantioselective conjugate addition (ECA) of a vinyl metal to a trisubstituted enone. This is a difficult task as there are few reports of vinyl metal reagents in catalytic enantioselective procedures to prepare quaternary stereogenic centers. As compared to the enantioselective alkylations and arylations discussed in the previous sections, an enantioselective addition of a vinyl group is perhaps the most difficult; a vinyl nucleophile is smaller than the alkyl or aryl metal reagents,[11] making enantiodiscrimination by the catalyst more challenging.

Scheme 4.1. Preparation of Vinyl-Containing All-Carbon Quaternary Stereogenic Centers Through Enantioselective Conjugate Addition



On the other hand, the same molecule **I** can also be prepared through an enantioselective conjugate addition of an R group to an α,β,δ,γ-unsaturated ketone (pathway b).[12] The route, however, can potentially lead to other products through a 1,6-

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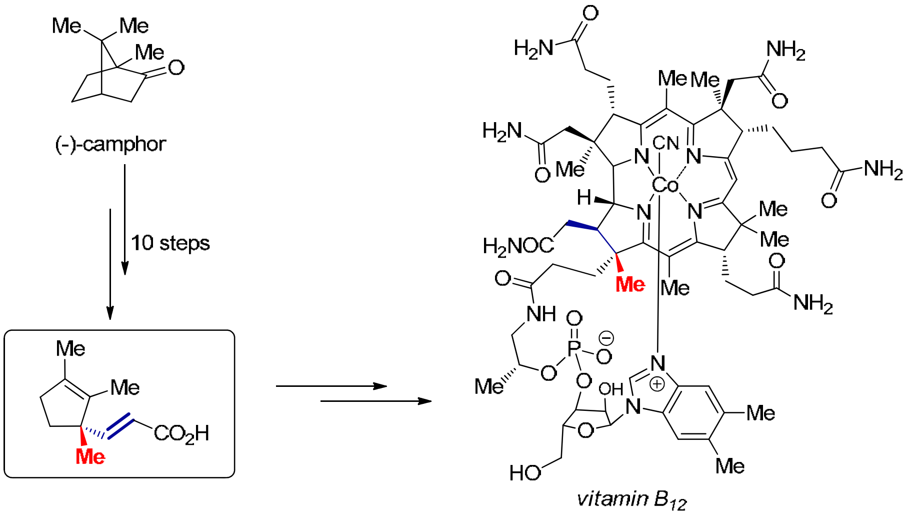
[11] For instance the A-values of a methyl, phenyl and vinyl group are 1.7, 3.0, and 1.35, respectively. See, (a) "Table of Conformation Energies–1967," Allinger, N. L.; Eliel, E. L.; Hirsch, J. A. *Topics in Stereochemistry* **1967**, *1*, 199–222. Another report calculates the A value of a vinyl group to be closer to 1.68, only slightly smaller than a methyl group, see: (b) "Conformational Analysis. 40. Conformation of 1-Methyl-1-Phenylcyclohexane and Conformational Energies of the Phenyl and Vinyl Groups," Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959–1962.

[12] For a report regarding pathway b, see: "Regiodivergent 1,4 versus 1,6-Asymmetric Copper-Catalyzed Conjugate Addition," Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122–9124.

addition to the doubly unsaturated enone (**II** and/or **III**). In fact, additions of cuprates to α,β,δ,γ-unsaturated ketones predominately afford products arising from the 1,6-addition pathway.[13] A general, effective and practical method for ECA of a vinyl nucleophile to activated enones would provide an easy route to products similar to **I**.

In the classic synthesis of vitamin B_{12} by Woodward and Eschenmoser in 1973, one of the intermediates in the synthesis bears a cyclopentanone containing a quaternary carbon stereogenic center bearing an appendant olefin (Scheme 4.2);[14] the intermediate is prepared in ten steps from commercially available (−)-camphor. The intermediate shown in Scheme 4.2 could potentially be prepared through conjugate addition of a vinyl nucleophile to a substituted cyclopentenone in a catalytic, enantioselective fashion which would shorten the route.

Scheme 4.2. Synthesis of Vitamin B_{12} by Woodward and Eschenmoser



There have been only four reports disclosing catalytic enantioselective conjugate addition of vinyl nucleophiles to activated olefins. Professor Carretero and co-workers disclosed the first example of ECA of a vinyl reagent to an activated electrophile generating an all-carbon quaternary stereogenic center.[2a] In their report, 5 mol % of a Rh(I) salt, in the presence of chiraphos, effectively promotes conjugate addition of three different alkenylboronic acids to two methyl-aryl substituted unsaturated pyridylsulfones to generate products, such as **4.2** and **4.3**, in 41–71% yield and in 94:6–>99:1 er (Scheme 4.3). Low to moderate yields are attributed to incomplete conversion (45–77% conv, 100 °C, 24 h). The authors note that even after prolonged reaction times or additional equivalents of the vinyl boronic acid, increased conversions are not observed perhaps due to catalyst decomposition. The pyridylsulfone is essential for reactivity as the same addition with derived phenylsulfone substrate leads to <2% conversion. This suggests a two point chelation between the pyridylsulfone and the Rh complex for organization and/or activation.

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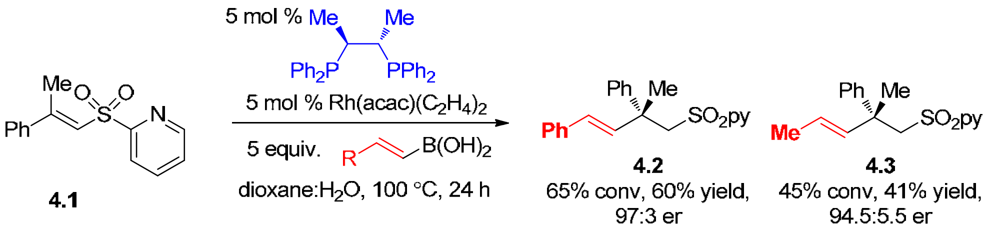
[13] For examples see: Krause, N.; Hoffmann-Röder, A. Copper-Mediated Addition and Substitution Reactions of Extended Multiple Bond Systems," In *Modern Organocopper Chemistry;* Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 145–166.

[14] (a) "Recent Advances in the Chemistry of Natural Products," Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519–547. (b) "Recent Advances in the Chemistry of Natural Products," Woodward, R. B. *Pure. Appl. Chem.* **1971**, *25*, 283–304. (c) "The Total Synthesis of Vitamin B_{12}," Woodward, R. B. *Pure Appl. Chem.* **1973**, *33*, 145–178.

Scheme 4.3. Rh-Catalyzed ECA of Vinylboronic Acids to Pyridylsulfones: Carretero and Co-Workers



The Alexakis group has published the first examples of Cu-catalyzed enantioselective vinyl addition to 3-methylcyclohexenone. The preparation of vinylaluminum reagent **4.4** (Scheme 4.4) can be accomplished by treatment 1-hexyne with one equivalent of i-Bu$_2$AlH in heptane and the requite vinylaluminum can be used without isolation or purification.[15] The enantioselective addition is promoted by 10 mol % of a Cu(I)–phosphoramidite complex with 2 equivalents of **4.4** to provide **4.6** in 91:9

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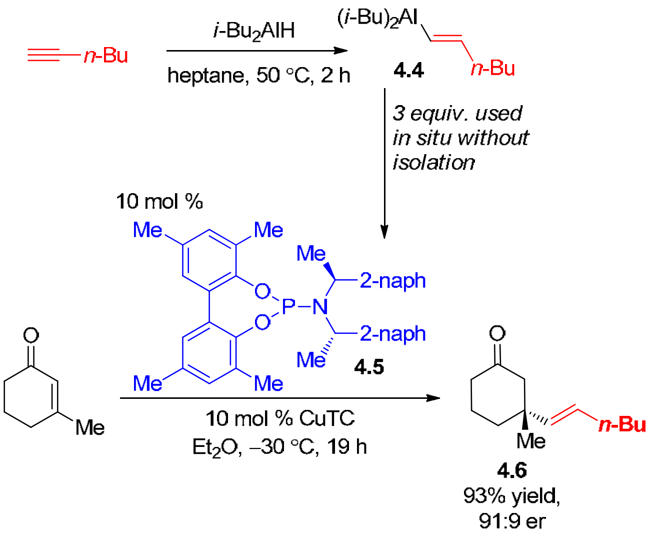
[15] "Syntheses Using Alkyne-Derived Alkenyl- and Alkynylaluminum Compounds," Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375–517.

er (93% yield).[2c] This is the only example disclosured thus the scope of the nucleophile and substrate cannot be determined.[16]

Scheme 4.4. Cu-Catalyzed ECA of a Vinylaluminum Reagent to 3-Methylcyclohexenone: Alexakis and Co-Workers



As a follow-up to the initial results put forth by Alexakis and co-workers in Scheme 4.4, an expanded disclosure has recently appeared.[2e] The additions are catalyzed by a Cu(I)–phosphinamine complex, prepared in situ from CuTC and ligand **4.7**, with various internal and terminal alkyl- and aryl-substituted vinylaluminum reagents prepared from lithium halogen exchange of the corresponding vinyl halides and subsequent reaction with Me_2AlCl. Product **4.6** is produced in 50% yield and 88:12 er (Scheme 4.5), which is less efficient and selective than the addition that was reported previously (shown in Scheme 4.4). In addition, procedure is extended to styrenyl addition to 3-methylcyclohexenone, delivering product **4.11** with increased yield of pure desired product and selectivity (64% yield, 95.5:4.5 er, Scheme 4.5). The mixed vinylaluminum species selectively transfers the vinyl group over the methyl ligands; the methyl 1,4-addition products are less than 3% of the reaction mixture. When the more sterically

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(16) The Alexakis group has also published two other examples of Cu-catalyzed ECA of vinylaluminum reagents to 3-methylcyclohexenone; the additions are promoted by 30 mol % phosphine-based Cu catalysts. The examples provided in the papers afford the products in 75:25 er and 86.5:13.5 er. No yields are reported. See: references 2b and 2d.

hindered internal vinylaluminum species are used in the ECA protocol, the products are obtained in higher enantioselectivities (for example, **4.8** and **4.9**, up to 98:2 er) but adventitious methyl addition occurred more readily (4% and 11%, respectively). The low yield of product **4.9** is attributed to an impurity in commercial α-bromostyrene, in which the corresponding vinylaluminum species is prepared from. This highlights a consequence of preparing internal vinylaluminum reagents from the vinyl halides; procedures to prepare these reagents require harsh conditions that can be intolerant of various acid-sensitive functional groups.[17] Moreover, only a handful of α-halide olefins are commercially available, many of which contain the *trans* isomer contaminant. Difficult substrates, such as sterically hindered-substituted cyclohexenones and 3-methylcyclopentenone led to reduced reactivity (up to 49% conv); methyl/vinyl addition ratios were not provided. Seven-membered ring enones were not investigated.

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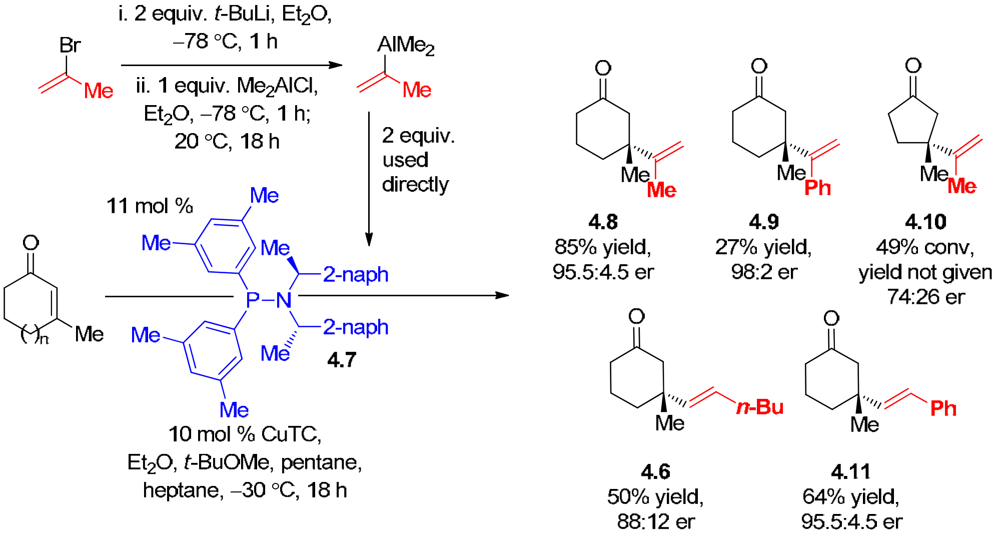
(17) For α-vinyl halide synthesis, see: (a) "Organic Synthesis using Haloboration Reaction. I. A Simple and Selective Synthesis of 2-Bromo- and 2-Iodo-1-Alkenes," Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734. (b) "Simple and Selective Method for Aldehydes (RCHO) → (*E*)-RCH=CHX Conversion by Means of a CHX_3-$CrCl_2$ System," Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (c) "Stereoselective Synthesis of Internal Alkenyl Iodides from Alkynes via Addition of Hydrogen Iodide Generated *in situ* from a Chlorotrimethylsilane/Sodium Iodide/Water System," Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675–676. (d) "A Mild Synthesis of Vinyl Halides and *gem*-Dihalides Using Triphenyl Phosphite–Halogen-Based Reagents," Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216–2219. (e) "Highly Selective Hydroiodation of Alkynes Using an Iodine–Hydrophosphine Binary System," Kawaguchi, S-i.; Ogawa, A. *Org. Lett.* **2010**, *12*, 1893–1895.

Scheme 4.5. Cu-Catalyzed ECA of Vinylaluminum Reagents to Trisubstituted Cyclic Enones: Alexakis and Co-Workers


Br
Me
i. 2 equiv. t-BuLi, Et2O, –78 °C, 1 h
ii. 1 equiv. Me2AlCl, Et2O, –78 °C, 1 h; 20 °C, 18 h
AlMe2
Me
2 equiv. used directly
11 mol %
Me
Me
Me
2-naph
P–N
2-naph
Me
Me
Me
4.7
Me
10 mol % CuTC, Et2O, t-BuOMe, pentane, heptane, –30 °C, 18 h
O
n
Me
O
Me
Me
4.8
85% yield, 95.5:4.5 er
O
Me
Ph
4.9
27% yield, 98:2 er
O
Me
Me
4.10
49% conv, yield not given 74:26 er
O
Me
n-Bu
4.6
50% yield, 88:12 er
O
Me
Ph
4.11
64% yield, 95.5:4.5 er

Based on the above studies, our goals for developing a Cu-catalyzed enantioselective vinyl addition method were as follows: (1) Find an active catalyst that promotes the conjugate addition of readily available and practical vinyl nucleophiles to a variety of activated enones, starting with trisubstituted cyclic enones. Although six-membered ring enones will be studied, special emphasis will be given to trisubstituted cyclopentenones, as additions to these substrates have proven to be difficult. (2) Another Be able to further functionalize the conjugate addition products into synthetically valuable molecules. Accordingly, we were interested in preparing riccardiphenol B (Figure 4.1) through an enantioselective vinyl addition to a trisubstituted cyclohexenone.

4.2. Cu-Catalyzed ECA of Vinylaluminum Reagents (Derived from Hydroalumination with i-Bu$_2$AlH to 1-Octyne) to Trisubstituted Cyclic Enones

We began by examining several in situ generated Cu–*N*-heterocyclic carbenes (Cu–NHCs), prepared by transmetallation of the corresponding Ag–NHC complexes (Table 4.1) with air-stable and commercially available $CuCl_2$•$2H_2O$, in the reaction of 3-methylcyclohexenone and vinylaluminum **4.12**, prepared from hydroalumination of 1-

octyne.[15] We chose to begin with vinylaluminum reagents since the preparation of these reagents are facile and can be used in situ without purification or isolation. As shown in Table 4.1, naphthol- and phenoxy-based Cu–NHC complexes (from **4.15**[18] and **4.16**,[19] respectively) promote the conjugate addition reaction to afford **4.13** in 59.5:40.5 er and 77:23 er (entry 1 and 2); however, a significant amount of 1,2-hydride addition to the enone is occurs to form allylic alcohol **4.14** (63% and 30%, respectively). The reduction presumably comes from a Meerwein-Ponndorf-Verley type reduction.[20] When a sulfonate-based bidenate NHC complex is used (**4.17**),[21] the Cu-catalyzed ECA of **4.12** to 3-methylcyclohexenone delivers the desired product **4.13** in 71.5:28.5 er with <2% **4.14** (entry 3). Sterically modified Cu–NHC catalyst (from **4.18**)[22] also promotes effective conjugate addition of **4.12** to 3-methylcyclohexenone (75% conv, <2% **4.14**) affording cyclohexanone in slightly reduced enantioselectivity (67:33 er, entry 4). The in situ prepared monodentate Cu–NHC catalyst (from **4.19**)[23] did not promote the addition (<2% conv, entry 5).

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(18) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131.

(19) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

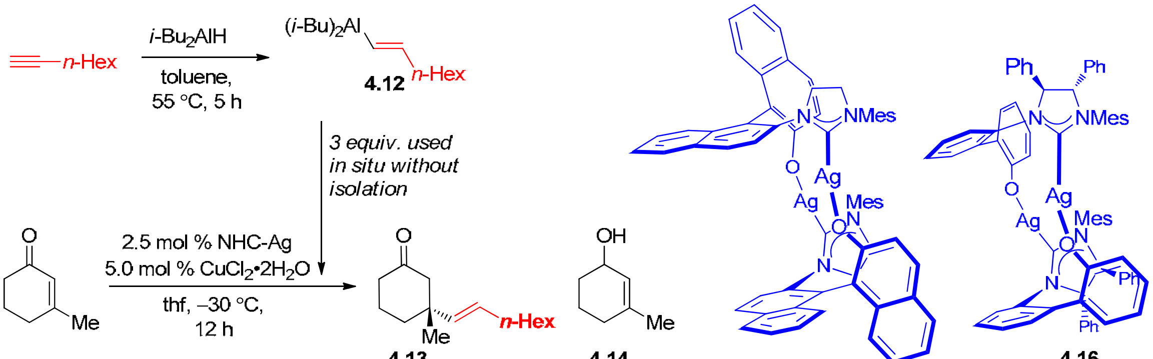
(20) For a review on Meerwein-Ponndorf-Verely Type reductions, see: "Selective Reduction of Carbonyl and Epoxy Compounds Using Aluminum, Boron and Other Metal Reagents. Comparison of Reducing Characteristics between the Meerwein-Ponndorf-Verley Type Reduction and Metal Complex Hydrides Reduction: A Review," Cha, J. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 2162–2190.

(21) "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100.

(22) (a) "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl and Aryl Aluminum Reagents to Five-, Six- and Seven-Membered-Ring β-Substituted Cyclic Enones," May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362. (b) "Highly Site- And Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents," Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447.

(23) (a) "Monodentate Non-C_2-Symmetric Chiral *N*-Heterocyclic Carbene Complexes for Enantioselective Synthesis. Cu-Catalyzed Conjugate Additions of Aryl- and Alkenylsilylfluorides to Cyclic Enones," Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462. (b) "Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes," Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900. (c) "Enantioselective

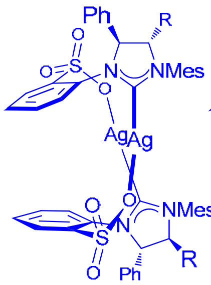
Table 4.1. Cu-Catalyzed ECA of Vinylaluminum Reagent **4.12** to 3-Methylcyclohexenone: NHC Screen[a]


n-Hex
i-Bu2AlH
toluene, 55 °C, 5 h
(i-Bu)2Al
4.12
n-Hex
3 equiv. used in situ without isolation
O
Me
2.5 mol % NHC-Ag
5.0 mol % CuCl2•2H2O
thf, –30 °C, 12 h
O
Me
n-Hex
OH
Me
Ph
Ph
N
NMes
O
Ag
Ag
Mes
N
O
N
Ph
Ph

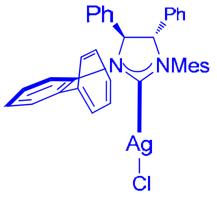
4.13 **4.14** **4.15** **4.16**

entry	NHC-Ag	conv (%)[b]	**4.13**:**4.14**[b]	er(**4.13**)[c]
1[d]	**4.15**	72	37:63	59.5:40.5
2	**4.16**	69	70:30	77:23
3	**4.17**	>98	>98:<2	71.5:28.5
4	**4.18**	75	>98:<2	67:33
5	**4.19**	<2	nd	nd

[a] Reaction performed under N_2 atm. [b] Determined by 400 MHz ^{1}H NMR analysis of the unpurified mixture. [c] Determined by GLC analysis. [d] Reaction performed for 40 h. nd = not determined. Compound **4.14** is isolated as a racemate.


Ph
R
O
O=S
N
NMes
O
Ag
Ag
O
O
NMes
N
S
O
Ph
R

4.17: R = Ph
4.18: R = H


Ph
Ph
N
NMes
Ag
Cl

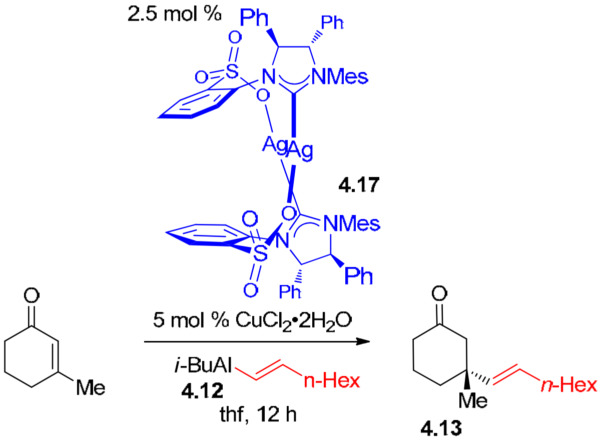
4.19

Mes = 2,4,6-Me(C_6H_2)

Further investigations revealed that the ECA of vinylaluminum reagent **4.12** to 3-methylcyclohexenone, promoted by the Cu–NHC complex of **4.17** exclusively affords **4.13** regardless of the reaction temperature with similar levels of enantioselectivity (71.5:28.5–73:27 er, Table 4.2). The desired product is isolated in 84–98% yield. When the reaction is performed at –78 °C, however, only 5% conversion is achieved.

Synthesis of Boron-Substituted Quaternary Carbons by NHC–Cu-Catalyzed Boronate Conjugate Additions to Unsaturated Carboxylic Esters, Ketones, or Thioesters," O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (d) "Enantioselective Synthesis of Homoallylic Amines through Reactions of (Pinacolato)allylborons with Aryl-, Heteroaryl-, Alkyl- or Alkene-Substituted Aldimines Catalyzed by Chiral C_1-Symmetric NHC–Cu Complexes," Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, asap.

Table 4.2. Cu-Catalyzed ECA of Vinylaluminum **4.12** to 3-Methylcyclohexenone: Temperature Screen[a]



entry	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]
1	22	>98	84	71.5:28.5
2	4	>98	98	72.5:27.5
3	–15	>98	97	72:28
4	–30	>98	93	72:28
5	–50	>98	nd	73:27
6	–78	5	nd	72:28

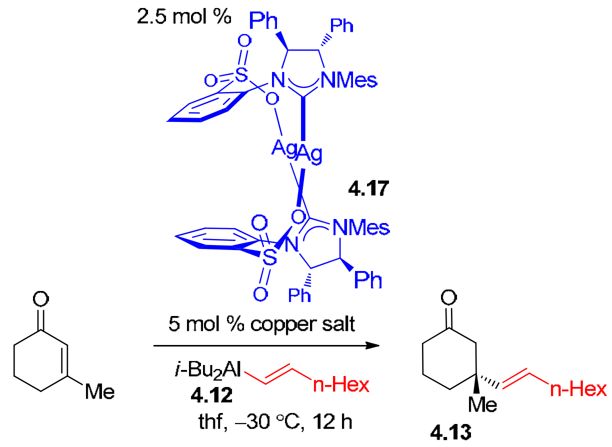
[a] Reactions performed under N_2. [b] Determined by ^{1}H NMR analysis. [c] Yields of isolated products. [d] Enantioselectivities determined by GLC analysis. nd = not determined.

Examination of various copper salts for the Cu-catalyzed ECA of octenylaluminum led us to discover that when the addition is promoted by $CuBr_2$, **4.13** is afforded in 77:23 er (entry 2, Table 4.3). Interestingly, both Cu(I) and Cu(II) salts are efficient in catalyzing the conjugate addition reaction with similar levels of selectivity (69.5:30.5–77:23 er), with the exception of CuCN (<2% conv, entry 8). We surmise that the active catalyst is a Cu(I) complex; Cu(II) salts, in the presence of the vinylaluminum reagent, are reduced to Cu(I).[24]

---

(24) For a proposed mechanism on the reduction of Cu(II) to Cu(I) in the presence of an alkylmetal, see: (a) "Electron-Transfer Mechanisms for Organometallic Intermediates in Catalytic Reactions," Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351–360. (b) "Interaction of Propagating Radicals with Copper (I) and Copper

Table 4.3. Cu-Catalyzed ECA of Vinylaluminum **4.12** to 3-Methylcyclohexenone: Copper Salt Screen[a]



entry	Cu salt	conv (%)[b]	yield (%)[c]	er[d]	entry	Cu salt	conv (%)[b]	yield (%)[c]	er[d]
1	$CuCl_2$•$2H_2O$	>98	93	71.5:28.5	6	CuI	82	78	69.5:30.5
2	$CuBr_2$	>98	48	77:23	7	CuCl	>98	nd	73:27
3	$CuOTf_2$	>98	51	73:27	8	CuCN	<2	nd	nd
4	$CuOAc_2$	>98	91	72:28	9[e]	$(CuOTf)_2$•C_6H_6	>98	91	72:28
5	CuTFAA	>98	nd	72.5:27.5	10	CuTC	>98	nd	72:28

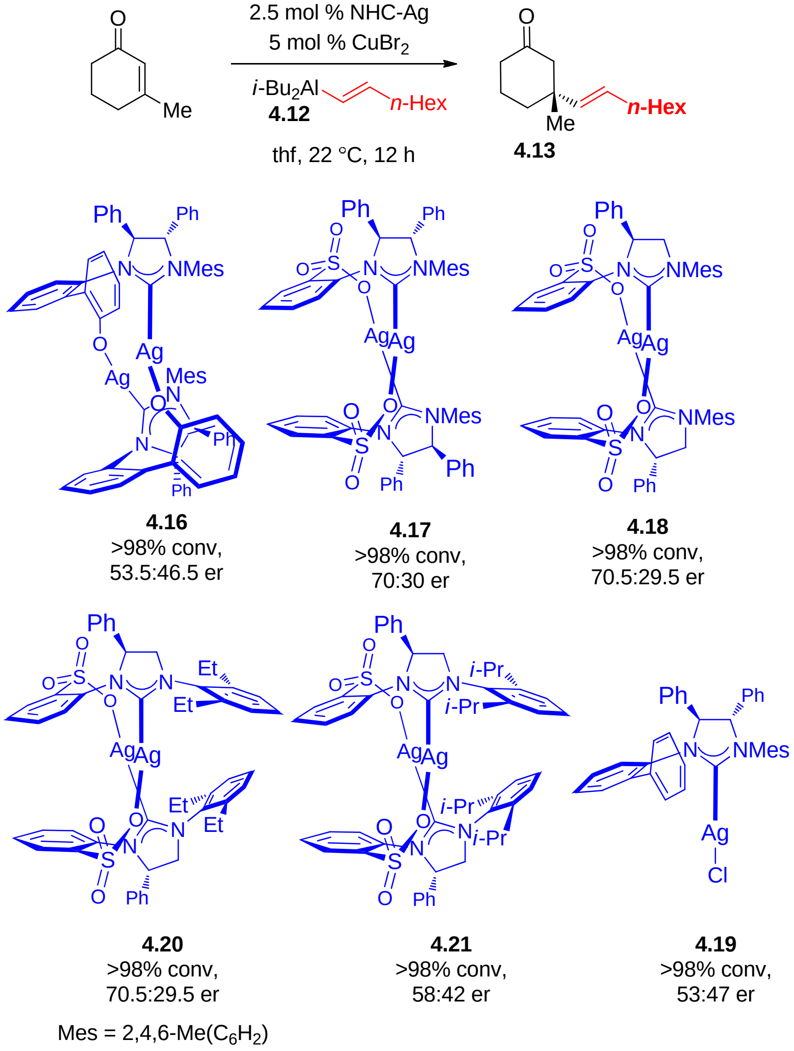
[a] Reactions performed under N_2. [b] Determined by ^1H NMR analysis. [c] Yields of isolated products. [d] Enantioselectivities determined by GLC analysis. [e] 2.5 mol % of the copper salt was used. nd = not determined. TFAA = Trifluroacetylacetonate. TC = thiophenecarboxylate.

Since the addition is slightly more enantioselective when $CuBr_2$ is used, another catalyst screen was investigated using the optimized conditions. As shown in Scheme 4.6, all of the Cu–NHC catalysts screened promote the addition with full consumption of starting material after 12 h at –30 °C. Only the sulfonate-containing NHC–Cu complexes promote the enantioselective addition with appreciable levels of selectivity (from **4.17**, **4.18**, and **4.20**, up to 70.5:29.5 er). If the sulfonate-containing Cu–NHC catalyst bears a large N–Ar group (2,6-diisopropylphenyl in **4.21**), the enantioselectivity of **4.13** drops to 58:42 er. When the catalysts derived from the phenoxy-containing bidentate NHC (**4.16**)

(II) Species," Matyjaszewski, K.; Woodworth, B. E. *Macromolecules* **1998**, *31*, 4718–4723. (c) Jukes, A. E. The Organic Chemistry of Copper. In *Advances in Organometallic Chemistry*, Volume 12; Stone, F. G. A.; West, R., Eds.; Academic Press, Inc: New York, NY, 1974, pp 215–322.

or monodentate NHC **4.19** are used, product **4.13** is obtained in essentially racemic form (<54:46 er).

Scheme 4.6. Catalyst Screening for Cu-Catalyzed ECA of **4.12** to 3-Methylcyclohexenone


2.5 mol % NHC-Ag
5 mol % CuBr₂
i-Bu₂Al n-Hex
4.12
thf, 22 °C, 12 h
Me
n-Hex
4.13
4.16
>98% conv,
53.5:46.5 er
4.17
>98% conv,
70:30 er
4.18
>98% conv,
70.5:29.5 er
4.20
>98% conv,
70.5:29.5 er
4.21
>98% conv,
58:42 er
4.19
>98% conv,
53:47 er
Mes = 2,4,6-Me(C6H2)

Cu-catalyzed ECA of vinylaluminum reagent **4.12** to 3-methylcyclopentenone also occurs efficiently to afford **4.22** in >98% conv after 12 h at –30 °C in 78% yield, albeit with moderate selectivity (75:25 er, Scheme 4.7).[25] Furthermore, unsaturated γ-ketoesters can be used as substrates to afford products **4.23** and **4.24** in moderate to low

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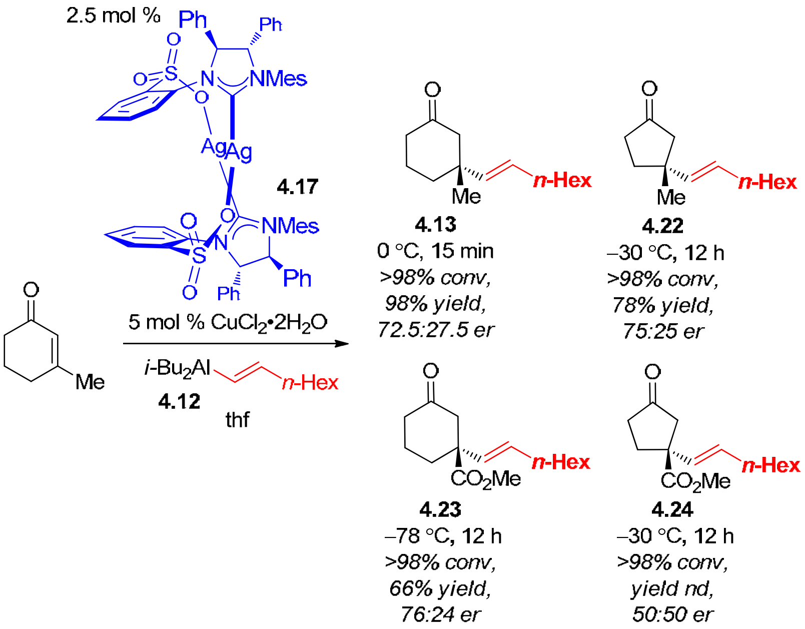
(25) Result done in collaboration with Kevin McGrath.

levels of selectivity (76:24 and 50:50 er, respectively); however, significant quantities of the 1,2-reduction of the ketone are formed in each case (26% and 50%).

Scheme 4.7. Substrate Scope for Cu-Catalyzed ECA of Vinylaluminum **4.12** to Five- and Six-Membered Ring Enones

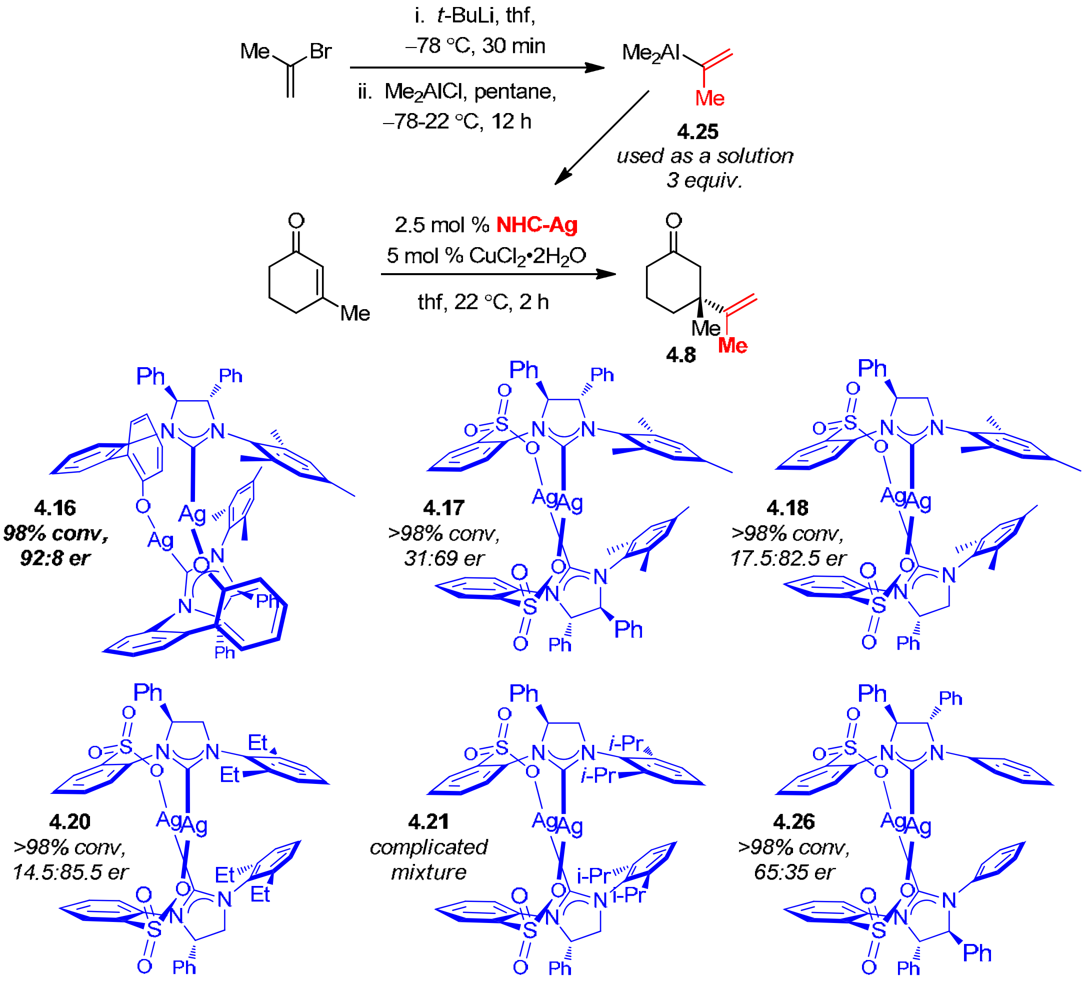

2.5 mol %
Ph
Ph
NMes
AgAg
4.17
NMes
Ph
Ph
5 mol % CuCl2•2H2O
i-Bu2Al
n-Hex
4.12
thf
Me
Me
n-Hex
4.13
0 °C, 15 min
>98% conv,
98% yield,
72.5:27.5 er
Me
n-Hex
4.22
–30 °C, 12 h
>98% conv,
78% yield,
75:25 er
CO2Me
n-Hex
4.23
–78 °C, 12 h
>98% conv,
66% yield,
76:24 er
CO2Me
n-Hex
4.24
–30 °C, 12 h
>98% conv,
yield nd,
50:50 er

Although we were able to promote the enantioselective addition of the easily and in situ prepared vinylaluminum reagent to 3-methylcyclohexenone affording **4.13** in high yield (98%), the enantioselectivity is moderate. We, next, decided to probe sterically and electronically different nucleophiles to gauge their effect in the ECA reactions.

4.3. Cu-Catalyzed ECA of Internal Vinylaluminum Reagents to Trisubstituted Cyclic Enones

We began by examining the ability of different Cu–NHC catalysts to promote the enantioselective addition of 2-propenylaluminum reagent **4.25** to 3-methylcyclohexenone. Dimethyl-(2-propenyl)aluminum is prepared by vinyl lithium (from the corresponding vinyl bromide) addition of Me_2AlCl (Scheme 4.8; the reagent is prepared and used in the ECA reaction in situ without isolation or purification). The phenoxy-containing bidentate Cu–NHC catalyst derived from **4.16** promotes the addition affording **4.8** in 92:8 er (>98% conv); this constitutes a marked improvement in enantioselectivity compared to the analogous enantioselective octenyl addition (cf. Scheme 4.7, 72.5:27.5 er). Furthermore, the sulfonate-containing Cu–NHC complexes (from **4.17**, **4.18**, and **4.20**) also promote the ECA of **4.25** to the six-membered ring enone, affording the product in >98% conv at 22 °C after 2 h in 69:31–85.5:14.5 er.

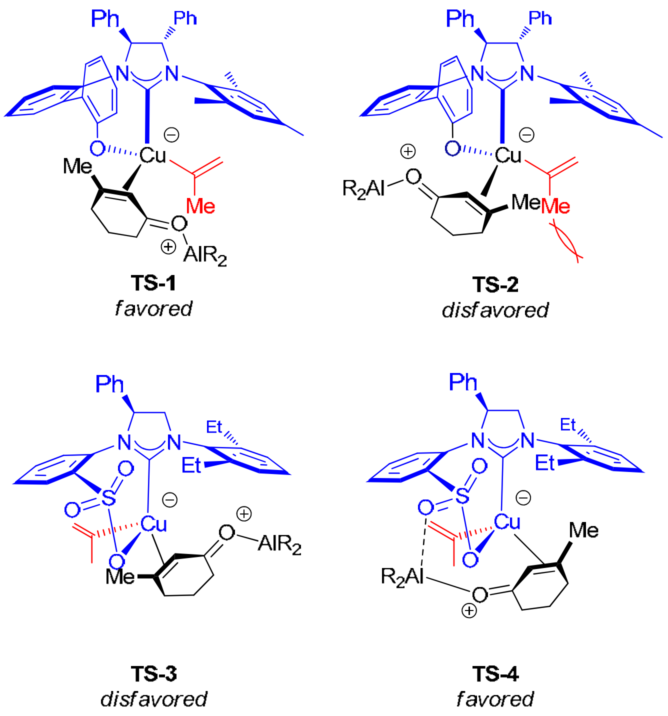
Scheme 4.8. Cu-Catalyzed ECA of 2-Propenylaluminum to 3-Methylcyclohexenone: NHC Screening


Me
Br
i. t-BuLi, thf,
–78 °C, 30 min
ii. Me2AlCl, pentane,
–78-22 °C, 12 h
Me2Al
Me
4.25
used as a solution
3 equiv.
O
Me
2.5 mol % NHC-Ag
5 mol % CuCl2•2H2O
thf, 22 °C, 2 h
O
Me
Me
4.8
4.16
98% conv,
92:8 er
4.17
>98% conv,
31:69 er
4.18
>98% conv,
17.5:82.5 er
4.20
>98% conv,
14.5:85.5 er
4.21
complicated
mixture
4.26
>98% conv,
65:35 er
Ph
Ag
N
O
S
Et
i-Pr

It is noteworthy that the sulfonate-containing NHC catalysts promote the additions affording **4.8** with the opposite sense of selectivity compared to the phenoxy-containing Cu–NHC complex. The aforementioned result potentially can be explained by different approaches of the enone to the in situ prepared NHC–cuprate complex

(Scheme 4.9). We surmise that approach of the enone towards the phenoxy-containing cuprate is predominately based on sterics; the enone approaches and forms an olefin coordination complex on the least hindered face of the cuprate (**TS-1**). In the sulfonate-containing complex, we believe that the substrate has pre-organization by forming a chelate between the sulfonate-oxygen with an aluminum ion as the bridging Lewis acid (**TS-4**).

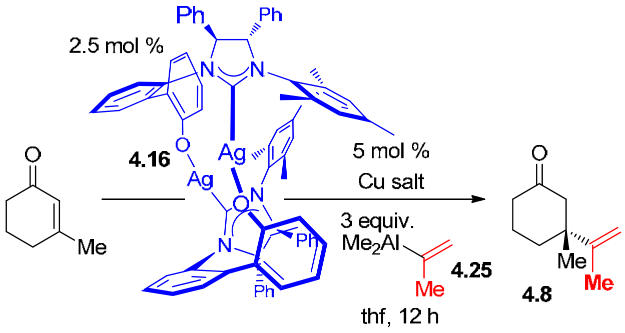
Scheme 4.9. Transition States for Cu-Catalyzed ECA


Ph
Ph
N
N
O
Cu
⊖
Me
Me
⊕
O
AlR$_2$
TS-1
favored
Ph
Ph
N
N
⊕
R$_2$Al
O
Cu
⊖
Me
Me
TS-2
disfavored
Ph
N
N
Et
Et
O
O
S
⊖
Cu
O
Me
⊕
O
AlR$_2$
TS-3
disfavored
Ph
N
N
Et
Et
O
O
S
⊖
Cu
O
Me
R$_2$Al
O
⊕
TS-4
favored

A temperature profile shows that Cu-catalyzed ECA of 2-propenylaluminum (**4.25**) to 3-methylcyclohexenone, promoted by a phenoxy-containing Cu–NHC catalyst, affords the cyclohexanone **4.8** in higher selectivities with decreased reaction temperatures (Table 4.4, entries 1–5). High selectivity is observed at –30 °C and –50 °C (up to 96.5:3.5 er), however, the transformation is less efficient (28–67% conv, entries 4 and 5). Enantioselective vinyl additions with Cu(OTf)$_2$ as the copper source, which in some cases has been shown to improve reactivity compared to the use of $CuCl_2•2H_2O$,[26] does not exhibit a significance difference in efficiency (57% conv vs. 67% conv, entries 7 and 4).

It is also noteworthy that 1,2-reduction or methyl addition products are not observed under the conditions examined for the enantioselective addition of 2-propenylaluminum (Scheme 4.8 and Table 4.4), contrary to some of the reactions investigated with diisobutyloctenylaluminum (cf. Table 4.1). One difference is that the ligands on the aluminum reagent is methyl (vs. *i*-butyl), which cannot undergo Meerwein-Ponndorf-Verley type reductions.

Table 4.4. Cu and Temperature Screen for Cu-Catalyzed ECA of 2-Propenylaluminum to 3-Methylcyclohexenone



entry	Cu salt	temp (°C)	conv (%)^{b}	er^{c}
1	$CuCl_2•2H_2O$	22	>98	91.5:8.5
2	$CuCl_2•2H_2O$	4	83	93:7
3	$CuCl_2•2H_2O$	–15	74	94.5:5.5
4	$CuCl_2•2H_2O$	–30	67	96:4
5	$CuCl_2•2H_2O$	–50	28	96.5:3.5
6	$Cu(OTf)_2$	–15	80	95.5:4.5
7	$Cu(OTf)_2$	–30	57	96:4
8	$Cu(OTf)_2$	–50	39	97:3
9	$Cu(OTf)_2$	–78	21	97.5:2.5

^{a} Reactions performed under N_2. ^{b} Determined by ^{1}H NMR analysis. ^{c} Enantioselectivities determined by GLC analysis.

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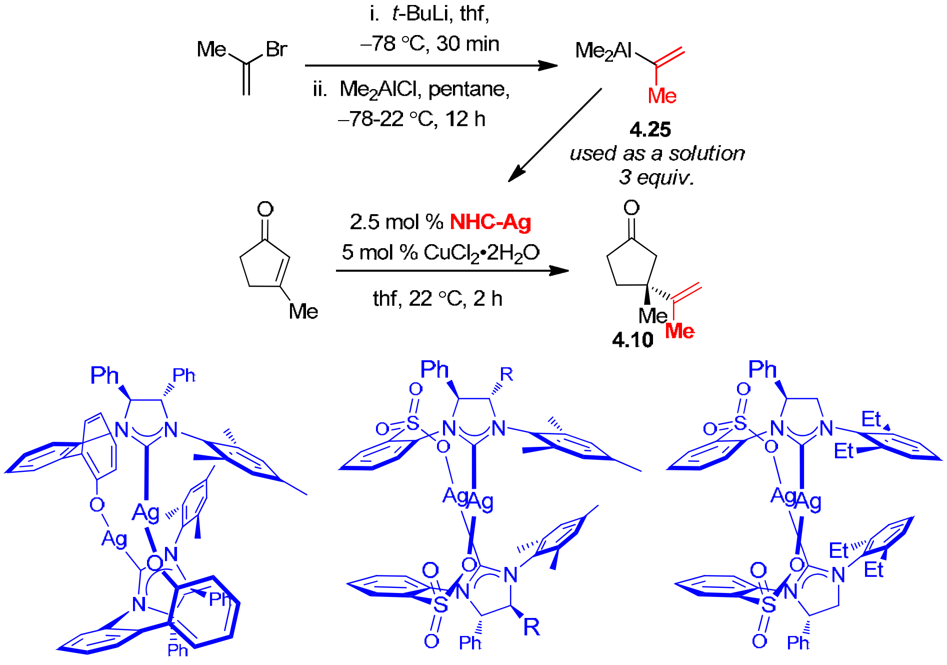
[26] "Enantioselective Synthesis of Allylsilanes Bearing Tertiary and Quaternary Si-Substituted Carbons through Cu-Catalyzed Allylic Alkylations with Alkylzinc and Arylzinc Reagents," Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558.

Selective vinyl additions are also effective with five-membered ring enones. Cu-catalyzed ECA of 2-propenylaluminum **4.25** to 3-methylcyclopentenone delivers cyclopentanone **4.10** in 90:10 er when promoted by the phenoxy-bearing Cu–NHC (from **4.16**). Similar to the observations regarding additions to the six-membered ring enone, the Cu–NHC catalysts derived from the sulfonate-containing NHC–Ag complexes **4.17**, **4.18**, ad **4.20**, afford the desired product **4.10** with lower enantioselectivities (60.5:39.5–78:22 er, Scheme 4.10). No products arising from reduction or methyl addition are observed.

Scheme 4.10. Catalyst Screen for Cu–NHC Catalyzed ECA of **4.25** to 3-Methylcyclopentenone


Me
Br
i. *t*-BuLi, thf,
–78 °C, 30 min
ii. Me_2AlCl, pentane,
–78-22 °C, 12 h
Me_2Al
Me
4.25
used as a solution
3 equiv.
O
Me
2.5 mol % NHC-Ag
5 mol % $CuCl_2•2H_2O$
thf, 22 °C, 2 h
O
Me
Me
4.10
Ph
Ph
N
N
O
Ag
Ag
O
N
N
Ph
Ph
Ph
R
O
O=S
N
N
O
Ag
Ag
O
O
S
O
N
N
Ph
R
Ph
O
O=S
N
N
Et
Et
O
Ag
Ag
Et
Et
O
O
S
O
N
N
Ph

4.16
>98% conv,
90:10 er

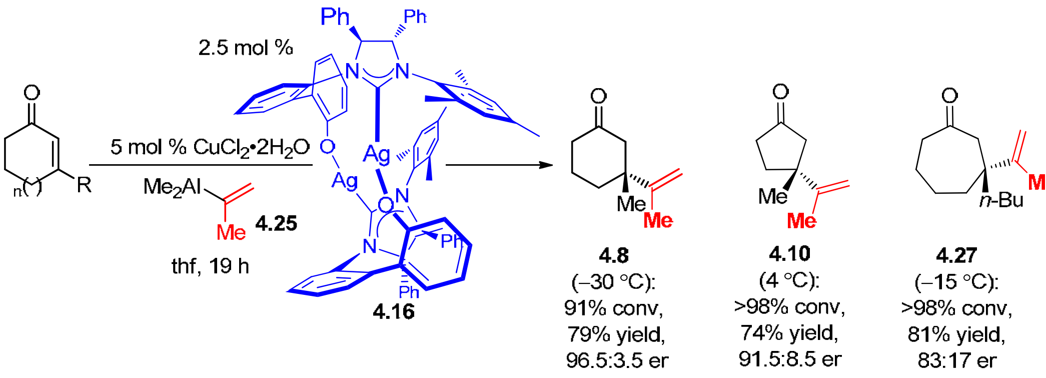
R = Ph: **4.17**
48% conv,
39.5:60.5 er

R = H: **4.18**
45% conv,
25:75 er

4.20
57% conv,
22:78 er

Extending the reaction times allows for isolation of the desired products from additions to the five- and six-membered ring enone in 74–79% yield (Scheme 4.11) in 91–>98% conv. High selectivities of the products are obtained (91.5:8.5–96.5:3.5 er). Compared to the disclosure by Alexakis and co-workers (cf. Scheme 4.5), the Cu-catalyzed ECA of propenyl the group to 3-methylcyclopentenone can be obtained with high efficiency (>98% conv and 91.5:8.5 er vs. 49% conv and 74:26 er). The seven-membered ring enone also undergoes effective enantioselective addition of the 2-propenyl group (>98% conv, 81% yield), however, the enantioselectively is only moderate (83:17 er).

Scheme 4.11. Cu-Catalyzed ECA of 2-Propenylaluminum to Five-, Six-, and Seven-Membered Ring Enones



4.8 (–30 °C): 91% conv, 79% yield, 96.5:3.5 er

4.10 (4 °C): >98% conv, 74% yield, 91.5:8.5 er

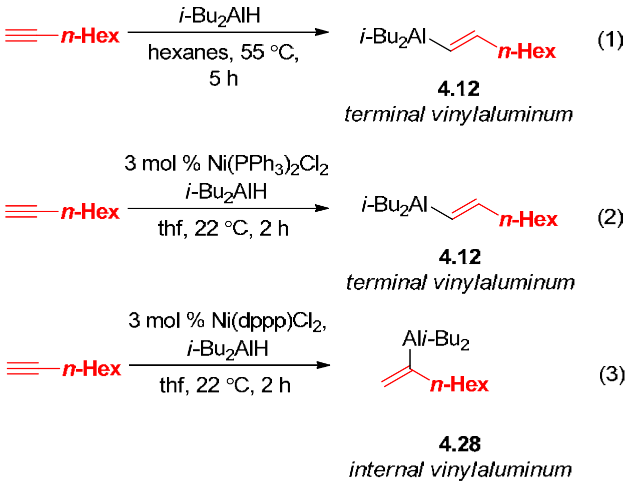
4.27 (–15 °C): >98% conv, 81% yield, 83:17 er

We, next, wanted to extend this method to include other internal vinyl groups, however, obtaining the vinylhalide precursors is not straightforward; procedures to prepare vinylhalides require harsh conditions and only a handful of α-halide olefins are commericallly available (and are sometimes contaminated with by-products that are difficult to purify).[17] Concurrently with this project, our group was interested in practical methods for hydroalumination of alkynes; however, no procedures were known, at the time, to afford *internal* vinylaluminum reagents (i.e., **4.28**, eq. 3). Hydroalumination of termial alkynes (for example 1-octyne) reacts with *i*-Bu_2AlH to exclusively afford terminal vinylaluminum products (**4.12**, eq. 1). We found that when the transformation is catalyzed by 3 mol % of $Ni(PPh_3)_2Cl_2$, the addition occurs more readily (95% conv within 2 h at 22 °C, delivering **4.12** in 95% conv with complete selectivity for the terminal vinylaluminum reagent.[27] When the reaction is performed in the absence of catalyst (eq 1), the addition requires elevated temperatures for 5 h (55 °C). More

---

(27) "α-Selective Ni-Catalyzed Hydroalumination of Aryl- and Alkyl-Substituted Terminal Alkynes: Practical Syntheses of Internal Vinyl Aluminums, Halides, or Boronates," Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

importantly however, when a bidentate phosphine ligand on Ni is used, a complete reversal in regioselectivity is observed; internal vinylaluminum reagent **4.28** is formed as the elusive product (<2% **4.12**).



4.12
terminal vinylaluminum

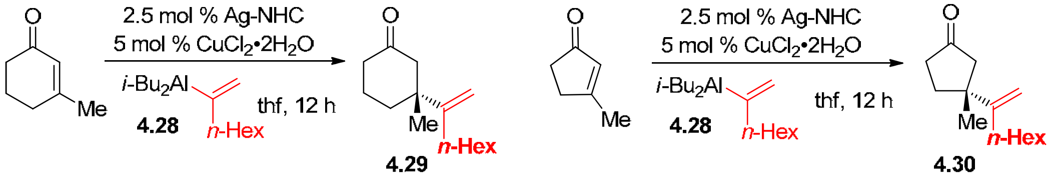
4.12
terminal vinylaluminum

4.28
internal vinylaluminum

With a practical and facile route to access internal vinylaluminum reagents, we investigated how they perform in the Cu–NHC catalyzed ECA reactions. As shown in the left portion of Table 4.5, we investigated how the phenoxy- and a sulfonate-bearing Cu–NHC catalysts perform at varying temperatures in the addition of **4.28** to 3-methylcyclohexenone. Both catalysts are effective in catalyzing the additions, however the Cu catalyst derived from **4.20** delivers **4.29** in the highest enantioselectivity (92:8 er, entry 8) at –15 °C; cyclohexanone **4.29** is prepared in 96% yield with no production of reduction or alkyl addition products.

The five-membered ring enones also are competent partners in the enantioselective addition of internal vinylaluminum reagents. Similar to the results found with the six-membered ring enones, both of the bidentate Cu–NHC complexes effect conjugate addition, however, the sulfonate-containing NHC–Cu complex can deliver **4.30** in 85% yield and 91:9 er at –50 °C (entry 21). Lowering the temperature to –78 °C allows for the formation of **4.30** in a slightly higher enantioselectivity but with a drop in efficiency (20% conv, 20% yield, 91.5:8.5 er, entry 22).

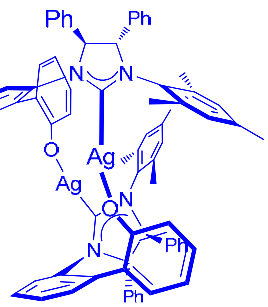
Table 4.5. Cu-Catalyzed ECA of Internal Vinylaluminum Reagents to Five- and Six-Membered Ring Enones: Catalyst and Temperature Screen[a]


2.5 mol % Ag-NHC
5 mol % $CuCl_2•2H_2O$
i-Bu_2Al
thf, 12 h
Me
4.28
n-Hex
Me
n-Hex
4.29
2.5 mol % Ag-NHC
5 mol % $CuCl_2•2H_2O$
i-Bu_2Al
thf, 12 h
Me
4.28
n-Hex
Me
n-Hex
4.30

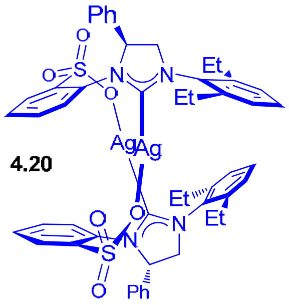
entry	Ag-NHC	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]	entry	Ag-NHC	temp (°C)	conv (%)[b]	yield (%)[c]	er[d]
1	**4.16**	22	>98	51	18:82	12	**4.16**	22	>98	nd	19:81
2	**4.16**	0	72	31	20:80	13	**4.16**	0	>98	18	14:86
3	**4.16**	–30	66	49	18:82	14	**4.16**	–30	70	nd	11:89
4	**4.16**	–50	61	nd	15:85	15	**4.16**	–50	20	nd	5:95
5	**4.16**	–78	<5	nd	nd	16	**4.16**	–78	<2	nd	nd
6	**4.20**	22	>98	62	89:11	17	**4.20**	22	>98	63	83:17
7	**4.20**	0	>98	>98	91:9	18	**4.20**	0	>98	83	85:15
8	**4.20**	–15	>98	96	92:8	19	**4.20**	–15	>98	>98	nd
9	**4.20**	–30	>98	96	91:9	20	**4.20**	–30	>98	>98	89.5:10.5
10	**4.20**	–50	>98	>98	90:10	21	**4.20**	–50	94	85	91:9
11	**4.20**	–78	27	21	87:13	22	**4.20**	–78	20	20	91.5:8.5

[a] Reactions performed under N_2. [b] Determined by ^1H NMR analysis. [c] Yields of isolated products. [d] Enantioselectivities determined by GLC analysis. nd = not determined.

4.16

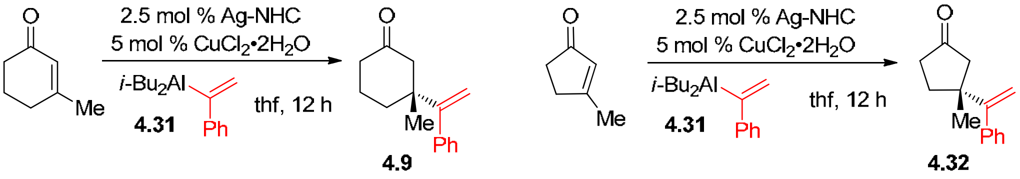

Ph
Ph
N
N
O
Ag
Ag
N
O
N
Ph
Ph

4.20


Ph
O
O=S
O
N
N
Et
Et
Ag
Ag
Et
O
O
N
Et
O
S
N
O
Ph

A similar screen was also conducted for the ECA of α-styrenyl aluminum **4.31** to five- and six-membered ring enones. In this particular case, the additions that are promoted by the phenoxy-containing Cu–NHC complex (entries 1–5 and 12–16) afford the products in the highest enantioselectivities (81:19–96:4 er) versus additions promoted by the sulfonate containing Cu–NHC complex (entries 6–11 and 17–18, 73:28–82:18 er). To achieve complete conversion to **4.9**, a more concentrated reaction is needed (0.2 M thf vs. 0.1 M thf, entry 4).

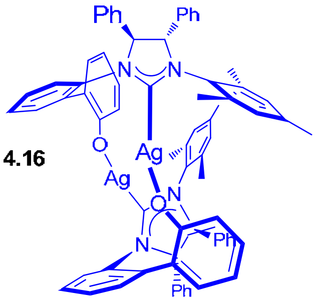
Table 4.6. Cu-Catalyzed ECA of Internal Vinylaluminum Reagents to Five- and Six-Membered Ring Enones: Ligand and Temperature Screen[a]



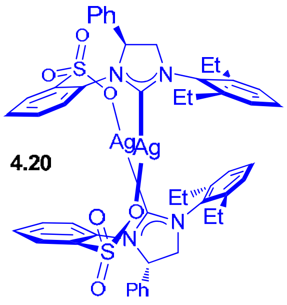
entry	Ag-NHC	temp (°C)	time (h)	conv (%)^b	yield (%)^c	er^d
1	**4.16**	22	0.25	72	50	nd
2	**4.16**	0	0.25	47	30	12:88
3	**4.16**	–30	12	89	62	9:91
4^e	**4.16**	–50	36	>98	79	4:96
5	**4.16**	–78	12	<5	nd	nd
6	**4.20**	22	0.25	>98	92	81:19
7	**4.20**	4	36	>98	94	81.5:18.5
8	**4.20**	–15	36	>98	>98	82:18
9	**4.20**	–30	36	>98	>98	82:18
10	**4.20**	–50	36	>98	90	73:28
11	**4.20**	–78	36	16	nd	nd
12	**4.16**	22	0.25	57	32	19:81
13	**4.16**	0	0.25	37	26	15:95
14	**4.16**	–30	12	77	50	12:88
15	**4.16**	–50	12	40	40	9:91
16	**4.16**	–78	12	<5	nd	nd
17	**4.20**	22	0.25	>98	91	74:26
18	**4.20**	0	0.33	>98	96	77:23

[a] Reactions performed under N$_2$; 0.1 M solutions. [b] Determined by ^{1}H NMR analysis. [c] Yields of isolated products. [d] Enantioselectivities determined by GLC analysis. nd = not determined. [e] Reaction performed with a 0.2 M solution of thf.

4.16

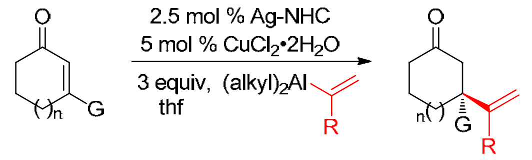


4.20



Cu-catalyzed ECA of internal vinylaluminum reagents to trisubstituted enones are efficient and selective as shown in Scheme 4.12 (up to 85% yield and 98:2 er). Both aryl-substituted and alkyl-substituted vinyl groups are competent nucleophiles allowing access to products containing all-carbon quaternary stereogenic centers.

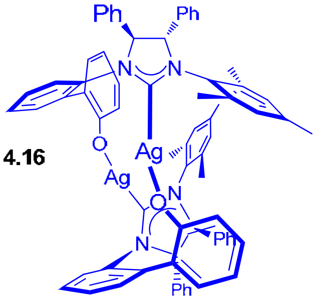
Scheme 4.12. Nucleophile and Substrate Scope for Cu-Catalyzed ECA of Internal Vinylaluminum Reagents[a]



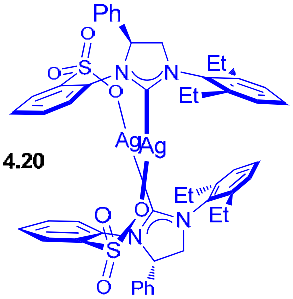
entry	n	G	R	Ag-NHC	temp (°C)	time (h)	conv (%)^b	yield (%)^c	er^d
1	0	Me	Me	**4.16**	4	19	>98	74	91.5:8.5
2	0	Me	Ph	**4.16**	–50	36	85	61	98:2
3	0	Me	*n*-Hex	**4.20**	–50	12	94	85	9:91
4	1	Me	Me	**4.16**	–30	19	91	79	96.5:3.5
5^e	1	Me	Ph	**4.16**	–50	36	>98	79	96:4
6	1	Me	*n*-Hex	**4.20**	–15	12	94	84	8:92
7	2	*n*-Bu	Me	**4.16**	–15	19	>98	81	83:17

[a] Reactions performed under N_2; 0.1 M solutions. [b] Determined by ^1H NMR analysis. [c] Yields of isolated products. [d] Enantioselectivities determined by GLC analysis. nd = not determined. [e] Reaction performed with a 0.2 M solution of thf.

4.16



4.20



As shown in eq 4 and 5, ozonolysis can be performed on the vinyl addition products to afford diketones in 80–>98% yield. The diketones **4.33** and **4.34** constitute a difficult (and unprecedented) enantioselective acyl anion addition to an enone.[28]

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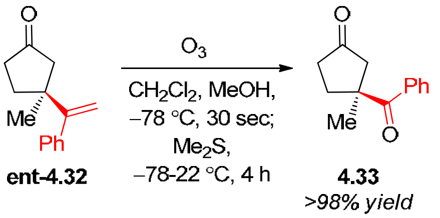
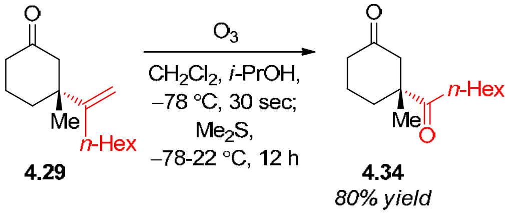
(28) For a recent review on acyl anion additions, see: (a) "Advances in Acyl Anion and Homoenolate Catalysis," Johnson, J. S. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 691–703. For a recent example (non-enantioselective), see: (b) "Pd-Catalyzed Carbonylative Conjugate Addition of Dialkylzinc Reagents to Unsaturated Carbonyls," Custar, D. W.; Le, H.; Morken, J. P. *Org. Lett.* **2010**, *12*, 3760–3763.


O
Me
Ph
ent-4.32
O3
CH2Cl2, MeOH,
–78 °C, 30 sec;
Me2S,
–78-22 °C, 4 h
O
Ph
Me
O
4.33
>98% yield

(4)


O
Me
n-Hex
4.29
O3
CH2Cl2, i-PrOH,
–78 °C, 30 sec;
Me2S,
–78-22 °C, 12 h
O
n-Hex
Me
O
4.34
80% yield

(5)

4.4. *Cu-Catalyzed ECA of Si-Substituted Vinylaluminum Reagents to Trisubstituted Cyclic Enones*[29]

4.4.a Optimization of Cu-Catalyzed ECA of Si-Substituted Vinylaluminums to Trisubstituted Cyclic Enones

Simultaneously with the above studies utilizing internal vinylaluminum reagents in enantioselective additions to cyclic enones, we were interested in other nucleophiles that could be used for further functionalizations to allow access to products not otherwise easily obtainable. We found that stereo- and regiochemically pure silyl-substituted vinylaluminum reagents can be prepared from hydroalumination of silyl acetylenes (Scheme 4.13);[30,31] the hydroalumination proceeds to afford exclusively the *Z*-olefin isomer and are conformationally stable when thf is included in the solvent mixture.[31] The origin of selectivitiy in the hydroalumination stems from the inherent electronic character of silicon. Through hyperconjugation of the low lying Si–C σ*-bond, silicon is capable of stabilizing α-anions and β-cations.[32]

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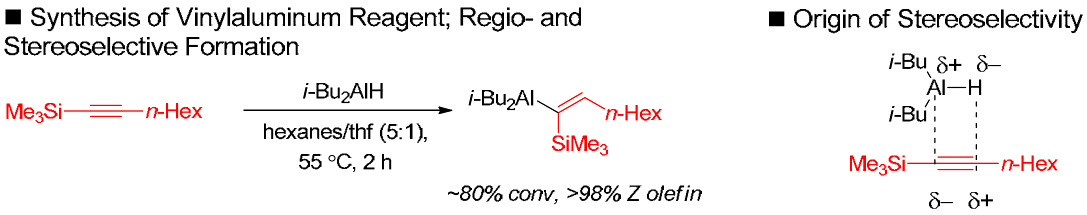
[29] "Formation of Vinyl- Vinylhalide- or Acyl-Substituted Quaternary Carbon Stereogenic Centers through NHC–Cu-Catalyzed Enantioselective Conjugate Additions of Si-Containing Vinylaluminums to *β*-Substituted Cyclic Enones," May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739.

[30] "Organometallic Compounds of Group III. XIX. Regiospecificity and Stereochemistry in the Hydralumination of Unsymmetrical Acetylenes. Controlled Cis or Trans Reduction of 1-Alkynyl Derivatives," Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520–3526.

[31] For a recent Cu-catalyzed enantioselective allylic substitution method for Si-substituted vinylaluminum reagents that generate products containing tertiary stereogenic centers, see: "Stereoisomerically Pure Trisubstituted Vinylaluminum Reagents and their Utility in Copper-Catalyzed Enantioselective Synthesis of 1,4-Dienes Containing *Z* or *E* Alkenes," Akiyama, K.; Gao, F; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419–423.

Scheme 4.13. Synthesis and Origin of Selectivity of Si-Substituted Vinylaluminum Reagents


■ Synthesis of Vinylaluminum Reagent; Regio- and Stereoselective Formation
Me_3Si—≡—n-Hex
i-Bu_2AlH
hexanes/thf (5:1), 55 °C, 2 h
i-Bu_2Al
n-Hex
$SiMe_3$
~80% conv, >98% Z olefin
■ Origin of Stereoselectivity
i-Bu
δ+ δ–
Al—H
i-Bu
Me_3Si
n-Hex
δ– δ+

Since the reactivity of silyl-substituted aluminum reagents have not been studied extensively, we investigated their inherent reactivity toward aldehydes. As shown in Scheme 4.14, when benzaldehyde is treated with dienylaluminum reagent (prepared from the cooresponding silylacetylene and used without isolation or purification), allylic alcohol **4.35** is isolated in 34% yield; benzyl alcohol and 3-methyl-1-phenylbutan-1ol are formed predominately (66%). The reduction product is formed from a Meerwein-Ponndorf-Verley type reduction (Scheme 4.14). Hydrocinnamaldehyde and cinnamaldehyde behave similarly, only affording <21% vinyl addition. Silyl-substituted vinylaluminum reagents are not nucleophilic in character; the hyperconjugation of the Al–C σ-bond to the low lying Si–C σ*-bond can stabilize the adjacent δ-negative charge on the sp^2 carbon and decrease the transferability of the vinyl group. Therefore, the addition of the other substituents on Al (the *i*-Bu groups) becomes competitive.

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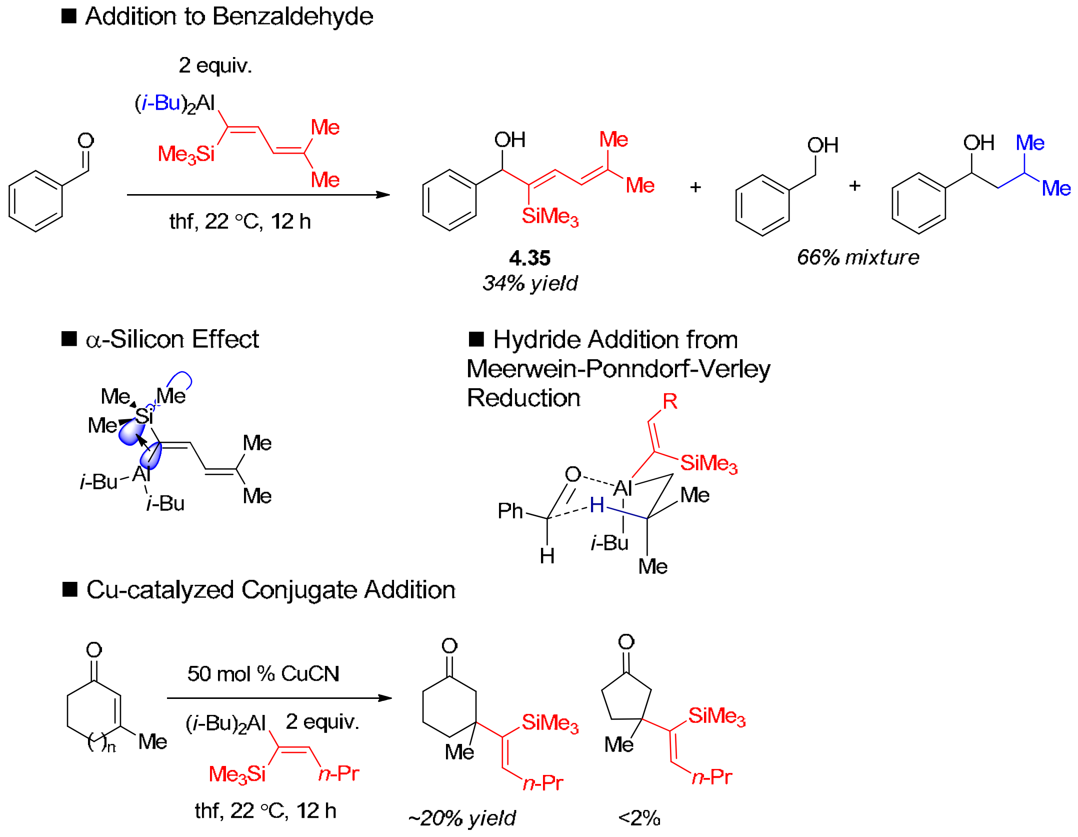
(32) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley: New York, 2000.

Scheme 4.14. Additions of Si-Substituted Vinylaluminum Reagents to Aldehydes


■ Addition to Benzaldehyde
2 equiv.
(i-Bu)₂Al
Me₃Si
Me
Me
thf, 22 °C, 12 h
OH
Me
Me
SiMe₃
+
OH
+
OH
Me
Me
4.35
34% yield
66% mixture
■ α-Silicon Effect
Me
Me
Me
Si
i-Bu
Al
i-Bu
Me
Me
■ Hydride Addition from Meerwein-Ponndorf-Verley Reduction
R
SiMe₃
O
Al
Me
Ph
H
H
i-Bu
Me
■ Cu-catalyzed Conjugate Addition
O
( )n
Me
50 mol % CuCN
(i-Bu)₂Al 2 equiv.
Me₃Si
n-Pr
thf, 22 °C, 12 h
O
SiMe₃
Me
n-Pr
~20% yield
O
SiMe₃
Me
n-Pr
<2%

Moreover, when the Si-substituted vinylaluminum reagents are used in the presence of 50 mol % of CuCN (a typical procedure to prepare racemate conjugate addition products), only 20% yield of the cyclohexanone bearing a β-all-carbon quaternary stereogenic center is afforded and <2% of the five-membered ring product is observed (Scheme 4.14). This highlights an important objective if silyl-substituted vinylaluminum reagents are used in the catalytic enantioselective conjugate addition. The catalyst must be highly active to overcome the low reactivity associated with the vinylaluminum reagents.

We began by examining the efficiency and selectivity of several in situ generated Cu–NHCs, prepared by transmetallation of the corresponding Ag–NHC complexes with an air stable and readily available $CuCl_2{\bullet}2H_2O$ salt, to promote the reaction of 3-methylcyclopentenone and a silyl-substituted vinylaluminum reagent (**4.36**). As shown in Table 4.13, naphthol- and phenoxy-based Cu–NHC complexes are not effective in promoting the conjugate addition reaction (<21% desired product **4.37** formation, entries 1 and 2). When a sulfonate-based bidenate NHC ligand is used (**4.17**), the Cu-catalyzed ECA of the vinylaluminum reagent to 3-methylcyclopentenone delivers **4.37** in 80:20 er, along with allylic alcohol **4.39** (85:15 **4.37**:**4.39**, entry 3). Sterically modified sulfonate-containing Cu–NHC catalysts (prepared from **4.18** and **4.20**) promote the conjugate addition of vinylaluminum **4.36** to the enone with an increased level of enantioselectivity (90:10 to 93:7 er, entries 4–5) compared to **4.17** (80:20 er).[33] These initial results highlight the unique reactivity that the sulfonate-containing ligands possess: catalyzing a difficult transformation with a deactivated nucleophile within 15 minutes to deliver a product with a sterically encumbered all-carbon quaternary stereogenic center. Increasing the sterics on the N–Ar unit to a 2,6-diisopropylphenyl group (**4.21**) results in a sharp decrease in the selectivity of **4.37** (52:48 er) along with a significant amount of *i*-Bu addition (product **4.38**, entry 6). When the addition is promoted by mondentate Cu–NHC complexes (prepared from **4.19** and **4.40**) the reaction is not efficient (15–31% conv vs. >98% conv in entries 3–5), however it does promote the addition with appreciable levels of selectivity (83:17 er).

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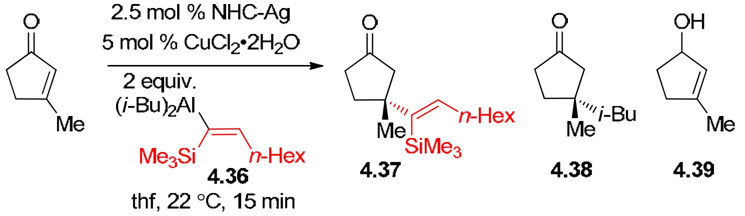
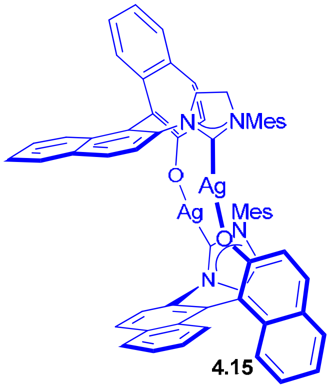
[33] The *i*-butyl addition product **4.38** is formed through a Cu–NHC catalyzed pathway and isolated in 89:11 er. See, reference 22a.

Table 4.13. Cu-Catalyzed ECA of Si-Substituted Vinylaluminum **4.36** to 3-Methylcyclopentenone: NHC Ligand Screening[a]

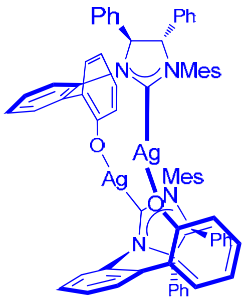

O
Me
2.5 mol % NHC-Ag
5 mol % $CuCl_2•2H_2O$
2 equiv.
$(i\text{-Bu})_2Al$
Me_3Si
n-Hex
4.36
thf, 22 °C, 15 min
O
Me
n-Hex
$SiMe_3$
4.37
O
Me
i-Bu
4.38
OH
Me
4.39

entry	Ag-NHC	conv (%)[b]	**4.37**:**4.38**:**4.39**[b]	er (**4.37**)[c]
1	**4.15**	8	<2:<2:08	nd
2	**4.16**	35	20:<2:15	10:90
3	**4.17**	>98	85:<2:15	80:20
4	**4.18**	>98	86:05:09	90:10
5	**4.20**	>98	95:05:<2	93:7
6	**4.21**	70	46:21:03	52:48
7	**4.19**	31	28:<2:03	17:83
8	**4.40**	15	04:<2:11	nd

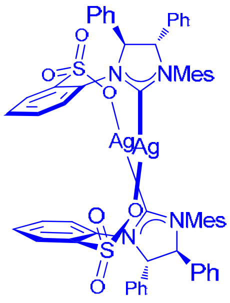
[a] Reactions performed under a N_2 atmosphere using a 0.1M solution. [b] Conversions and ratios determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Enantiomeric ratios determined by GLC analysis. nd = not determined.


N
NMes
O
Ag
Ag
Mes
O
N
N

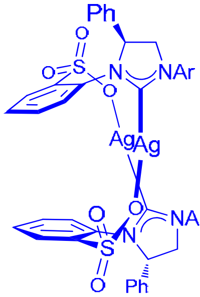
4.15


Ph
Ph
N
NMes
O
Ag
Ag
Mes
O
N
N
Ph
Ph

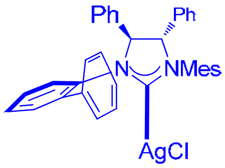
4.16


Ph
Ph
O
O=S
N
NMes
O
AgAg
O
NMes
O
S
N
O
Ph
Ph

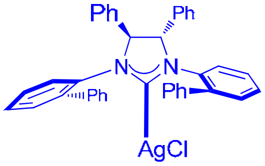
4.17


Ph
O
O=S
N
NAr
O
AgAg
O
NAr
O
S
N
O
Ph

4.18 = Mes
4.20 = 2,6-Et(C_6H_3)
4.21 = 2,6-*i*-Pr(C_6H_3)


Ph
Ph
N
NMes
AgCl

4.19


Ph
Ph
N
N
Ph
Ph
AgCl

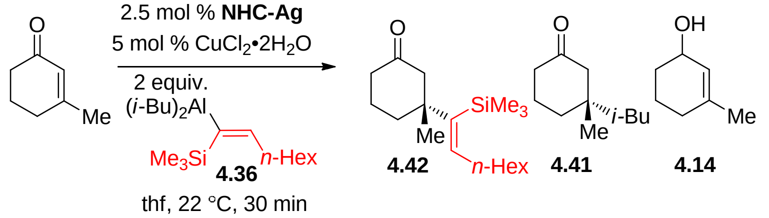
4.40

Mes = 2,4,6-Me(C_6H_2)

A similar catalyst screen was performed for the conjugate addition of Si-substituted vinylaluminum reagent **4.36** to a β-substituted cyclohexenone (Table 4.14).

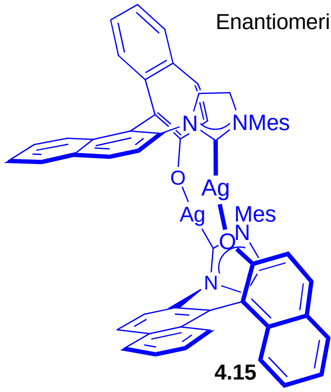
The naphthol- and binol-derived Cu–NHC catalysts are ineffective in the formation of **4.42** (entries 1 and 2); <6% of the desired product is formed. When the Cu–NHC catalysts prepared from the sulfonate-containing NHC complexes **4.17**, **4.18**, and **4.20** are used, however, the up to 68% of the reaction mixture is the desired product, with varying amounts of the *i*-Bu addition and 1,2-reduction products (**4.41** and **4.14**, entries 3–5). Most notably, the conjugate addition adduct is formed in 96:4 er (entry 5).

Table 4.14. Cu-Catalyzed ECA of **4.36** to 3-Methylcyclohexenone: NHC Screen[a]

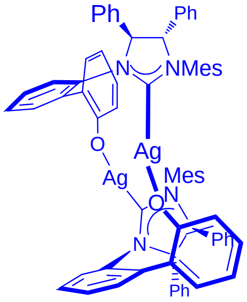

O
Me
2.5 mol % **NHC-Ag**
5 mol % $CuCl_2$•$2H_2O$
2 equiv.
$(i\text{-Bu})_2Al$
Me_3Si
n-Hex
4.36
thf, 22 °C, 30 min
O
$SiMe_3$
Me
n-Hex
4.42
O
i-Bu
Me
4.41
OH
Me
4.14

entry	Ag-NHC	conv (%)[b]	**4.42**:**4.41**:**4.14**[b]	er (**4.42**)[c]
1	**4.15**	7	<2:<2:7	nd
2	**4.16**	44	5:<2:39	48:52
3	**4.17**	>98	62:24:14	90:10
4	**4.18**	>98	68:29:3	92:8
5	**4.20**	>98	67:33:<2	96:4
6	**4.21**	>98	58:29:13	36.5:63.5

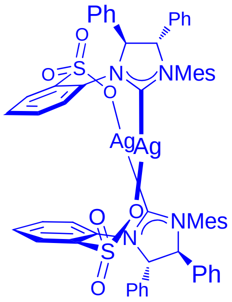
[a] Reactions performed under a N_2 atmosphere using a 0.1M solution. [b] Conversions and ratios determined by 400 MHz ^{1}H NMR analysis of the unpurified mixture. [c] Enantiomeric ratios determined by GLC analysis. nd = not determined.


N
NMes
O
Ag
Ag
Mes
O
N
N

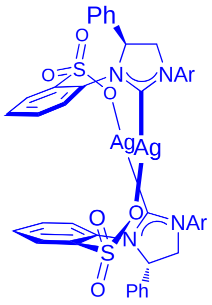
4.15


Ph
Ph
N
NMes
O
Ag
Ag
Mes
O
N
N
Ph
Ph

4.16


Ph
Ph
O
O=S
N
NMes
O
Ag
Ag
O
O
NMes
N
S
O
Ph
Ph

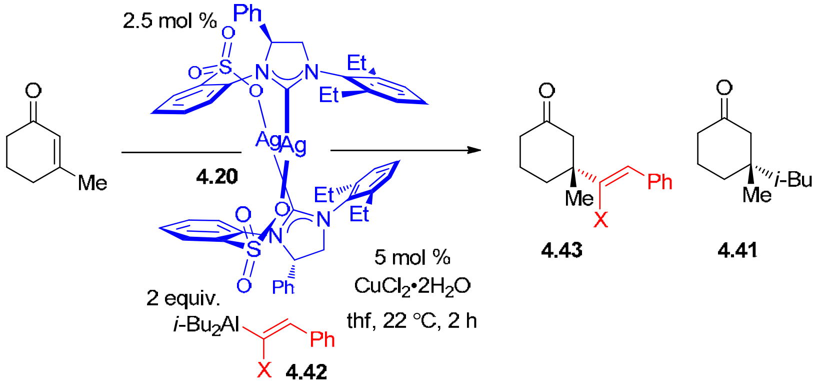
4.17


Ph
O
O=S
N
NAr
O
Ag
Ag
O
O
NAr
N
S
O
Ph

4.18 = Mes = 2,4,6-Me(C_6H_2)
4.20 = 2,6-Et(C_6H_3)
4.21 = 2,6-*i*-Pr(C_6H_3)

Although the enantioselective addition of Si-substituted vinylaluminum reagent **4.36** to 3-methylcyclohexenone affords **4.42** in high enantioselectivity (96:4 er), 33% of the product mixture containes *i*-Bu addition product **4.41**. We surmised that changing the substituents on silicon would affect its ability to stabilize the α-anionic character. A more electron-rich silicon should destabilize the adjacent δ- character and the vinyl group should transfer to Cu faster than the *i*-Bu group. To test this explanation, we prepared several electronically modified vinylaluminum reagents (Table 4.15) prepared from hydroalumination of silylphenylacetylenes. A few points are noteworthy. (1) Cu-catalyzed ECA of vinylaluminum reagents derived from phenylsilylacetylene (Table 4.15) generally provides a lower ratio of desired product to *i*-Bu addition product than studies done with aluminum reagent **4.36** (Table 4.14). This could be due to the extra stabilization of the anionic character on the sp^2 carbon that the phenyl substituent on **4.43** provides. (2) Cu-catalyzed ECA of Me_3Si-containing vinylaluminum to 3-methylcyclohexenone furnishes the desired product **4.44a** in a 58:42 ratio with **4.41** (entry 1). If the silyl group is changed to Me_2PhSi, the ratio of products drops to an 11:89 mixture of **4.44h**:**4.41** (entry 8); thus, changing a methyl to a electron-withdrawing phenyl group significantly favors the transfer of an *i*-Bu group over the vinyl group. Moreover, if the phenyl group is made to be more electron-donating by the presence of a para-methoxy group (vinyl aluminum **4.43c**, entry 3), then the ratio of **4.44c**:**4.41** increases to 52:48. Therefore, the ratio of products formed can be controlled by *altering the electronic nature of the silicon group*. The size of the silyl groups also plays an important role; although a $SiEt_3$ group should be a slightly better electron-donating group than $SiMe_3$, the ratio of vinyl to *i*-Bu addition products are higher when the smaller $SiMe_3$ group is used (58:42 vs. 28:72, entries 1 vs. 4).

Table 4.15. Examination of Different Silicon Groups on the Vinylaluminum Reagent[a]



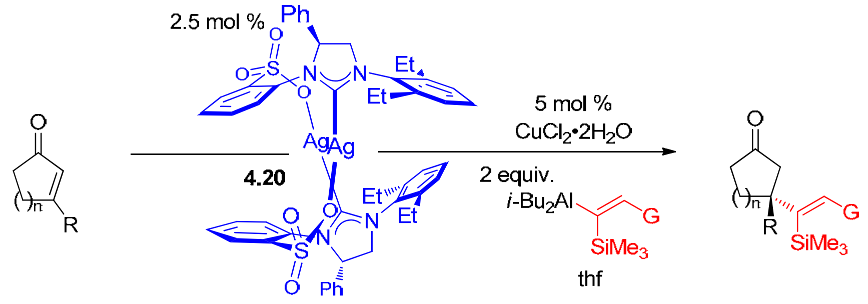
entry	X	conv (%)[b]	**4.43**:**4.41**[b]
1	Me_3Si, **a**	>98	58:42
2	Me_2HSi, **b**	>98	58:42
3	$Me_2(PMP)Si$, **c**	>98	52:48
4	Et_3Si, **d**	>98	28:72
5	$Me_2(PDMA)Si$, **e**	90	18:82
6	*i*-Pr_3Si, **f**	>98	13:87
7	Me_2*t*-BuSi, **g**	>98	11:89
8	Me_2PhSi, **h**	>98	11:89

[a] Reactions performed under a N_2 atmosphere.
[b] Conversions determined by 400 MHz ^1H NMR analysis of the unpurified mixture. PMP = dimethylparamethoxyphenylsilyl. PDMA = dimethylparadimethylaminophenysilyl.

4.4.b Substrate and Nucleophile Scope of Cu–NHC Catalyzed ECA of Si-Substituted Vinylaluminum Reagents to Cyclic Enones

As shown in Table 4.15, a variety of *β*-substituted cyclopentenones and cyclohexenones are efficient partners for Cu-catalyzed ECA of in situ prepared silyl-substituted vinylaluminum reagents. It is noteworthy that these reactions are performed at 0–22 °C and proceed to >98% conversion within only 15–20 minutes affording ketones containing all-carbon quaternary stereogenic centers with 92.5:7.5–98.5:1.5 er. Only 5–33% of *i*-Bu conjugate addition products are observed. Several points are noteworthy: (1) Various silyl-substituted vinylaluminums are efficient partners in the ECA reaction; alkyl-substituted (entries 1–4 and 7–10) and ether-containing vinylaluminum reagents (entries 4 and 10) deliver products in 63–95% yield and up to 97:3 er. Silyl-substituted styrenyl aluminum reagents (entries 5 and 11) can also be used in the ECA reaction, furnishing products with high enantioselectivities (95:5–98.5:1.5 er) but generally provides a lower ratio of desired product to the *i*-Bu addition product than studies performed with alkyl-substituted aluminum reagents (85:15 vs. 67:33, entries 9 and 11). The increase in *i*-Bu addition could be due to the extra stabilization of the δ–negative charge that the conjugated phenyl substituent provides (vinyl group less nucleophilic). Accordingly, when *p*-methoxystyrenylaluminum reagent is used, the five- and six-membered ring ketones are isolated in higher ratios (78:22 vs. 67:33 and 92:8 vs. 90:10 vinyl:*i*-Bu product, entries 5–6 and 11–12). (2) Additions to cyclopentenones generally deliver products in a higher vinyl addition to *i*-Bu addition ratio vs. the corresponding cyclohexenone additions (90:10–95:5 vs. 67:33–96:4). (3) The Cu-catalyzed ECA can be performed with lower catalyst loadings than described in Table 4.16; for example, with 0.5 mol % **4.20** and 1.0 mol % $CuCl_2 \cdot 2H_2O$, the processes in entries 3 and 9 proceed to >98% conv in 1.5 h to afford products with the same level of enantioselectivity in 68% and 85% yield, respectively. (4) Catalytic additions to β-substituted cyclohepetenones are inefficient; only 20–40% conversion to the desired product is formed.

Table 4.16. Cu–NHC Catalyzed ECA of Vinylaluminum Reagents to Cyclic Enones[a]

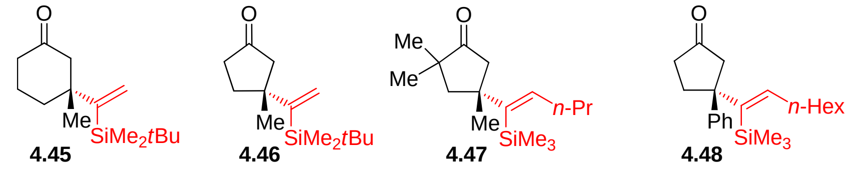


entry	substrate (R)	n	G	temp (°C)	time (min)	vinyl:*i*-Bu addition[b]	yield of vinyl prod (%)[c]	er[d]
1	Me	1	*n*-Hex	22	15	91:9	91	94:6
2	CH_2CH_2Ph	1	*n*-Hex	22	15	95:5	95	95.5:4.5
3	Me	1	*n*-Pr	22	15	95:5	76	93:7
4	Me	1	$(CH_2)_4OtBu$	0	15	95:5	80	92.5:7.5
5	Me	1	Ph	22	15	90:10	75	95:5
6	Me	1	*p*-OMe(C_6H_4)	22	20	92:8	67	94:6
7	Me	2	*n*-Hex	0	20	71:29	64	96:4
8	4-hexenyl	2	*n*-Pr	0	20	80:20	63	96:4
9	Me	2	*n*-Pr	0	20	85:15	85	97:3
10	Me	2	$(CH_2)_4OtBu$	0	20	96:4	85	96:4
11	Me	2	Ph	0	20	67:33	50	98.5:1.5
12	Me	2	*p*-OMe(C_6H_4)	0	20	78:22	66	98.5:1.5

[a] Reactions performed under a N_2 atmosphere with 0.1 M solutions. [b] Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [c] Yields of isolated purified products. [d] Enantiomeric ratios determined by HPLC or GLC analysis.

As shown in Scheme 4.15, enantiomerically enriched ketones containing dimethyl-*t*-butylsilyl group can also be prepared (60–71% yield, 92.5:7.5–95:5 er, **4.45** and **4.46**). Highly enantioselective synthesis of **4.47** can be accomplished, which bears a gem-dimethyl group at the C2’ position (70% yield, >98:<2 er); comparing this result with the enone that does not contain the dimethyl groups (Table 4.16, entry 3) demonstrates that higher enantioselectivity is observed with sterically demanding enones (93:7 vs. >98:<2 er). Relatively large β-substituents on the enone can be used; product **4.48** is afforded in 48% yield and 89:11 er, however, longer reaction time is needed (12 h).

Scheme 4.15. Variations in Substrates and Nucleophiles for Cu-Catalyzed ECA[a]



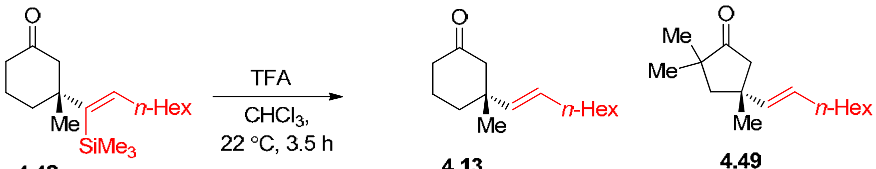
4.45	**4.46**	**4.47**	**4.48**
80:20 vinyl:*i*-Bu	95:5 vinyl:*i*-Bu	95:5 vinyl:*i*-Bu	84:16 vinyl:*i*-Bu
71% yield,	60% yield,	70% yield	48% yield
95:5 er	92.5:7.5 er	>98:<2 er	89:11 er
(22 °C, 20 min)	(22 °C, 20 min)	(0 °C, 20 min)	(22 °C, 12 h)

[a] Same conditions shown in Table 4.16 were used except where noted.

4.4.c Functionalizations of the Enantiomerically Enriched Products bearing a Vinylsilane

We next investigated functionalizations that could be performed on the enantiomerically enriched vinylsilane products.[34] As shown in Scheme 4.16, facile protodesilylation occurs upon treatment of the vinylsilane with trifluroacetic acid (TFA) to deliver disubstituted olefins with >98% *E* olefin isomer with no diminution in enantioselectivity; products **4.13** and **4.49** are representative.[35]

Scheme 4.16. Protodesilyation of the Vinylsilane Group



4.42

4.13
>98% *E*, 76% yield,
94:6 e.r.

4.49
>98% *E*, >98% yield,
98.5:1.5 e.r

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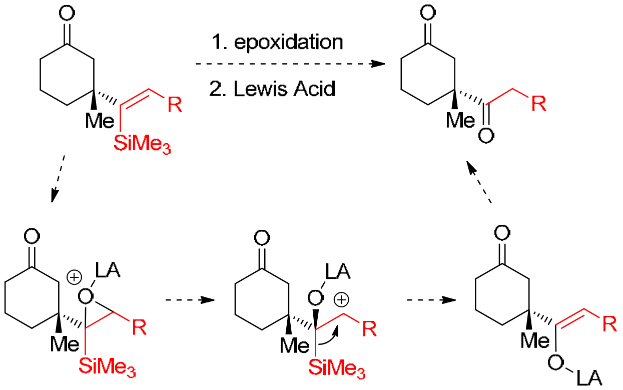
(34) For excellent reviews on the synthetic utility of vinylsilanes, see: (a) "The Electrophilic Substitution of Allylsilanes and Vinylsilanes," Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575. (b) "Vinyl-, Propargyl-, and Allenylsilicon Reagents in Asymmetric Synthesis: A Relatively Untapped Resource of Enviromentally Benign Reagents," Curtis-Long, M. J.; Aye, Y. *Chem Eur. J.* **2009**, *15*, 5402–5416.

(35) (a) Reference 31. (b) "Stereoselective Cyclization of (2-Bromophenyl)- and (2-Iodophenyl)alkynes Catalyzed by Palladium(0) Complexes," Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846–4849 (c) "Total Syntheses of (±)-Axamide-1 and (±)-Axisonitrile-1 via 6-*Exo-dig* Radical Cyclization," Kuo, Y.-L.; Dhanasekaran, M.; Sha, C.-K. *J. Org. Chem.* **2009**, *74*, 2033–2038. (d) "Ring-Closing Metathesis of Allylsilanes as a Flexible Strategy Toward Cyclic Terpenes. Short Syntheses of Teucladiol, Isoteucladiol, Poitediol, and Dactylol and an Attempted Synthesis of Caryophyllene," Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010**, *75*, 6908–6922.

The electron-rich silyl-substituted olefins, found in the conjugate addition products, are known to undergo facile epoxidation and, upon treatment with a Lewis acid, undergo a rearrangement to afford a ketone (net electrophilic substitution).[36] If this transformation occurs, then the product would constitute an equivalent of an enantioselective acyl anion addition (currently not known for the preparation of all-carbon quaternary stereogenic centers).[28]

Scheme 4.17. Potential Oxidative Rearrangement to Afford Enantiomerically Enriched Diketones



Epoxidation of **4.42** occurs cleanly to afford the α,β-epoxysilane **4.50** in 96% yield with the inconsequential formation of a 3:2 mixture of diastereomers. When the

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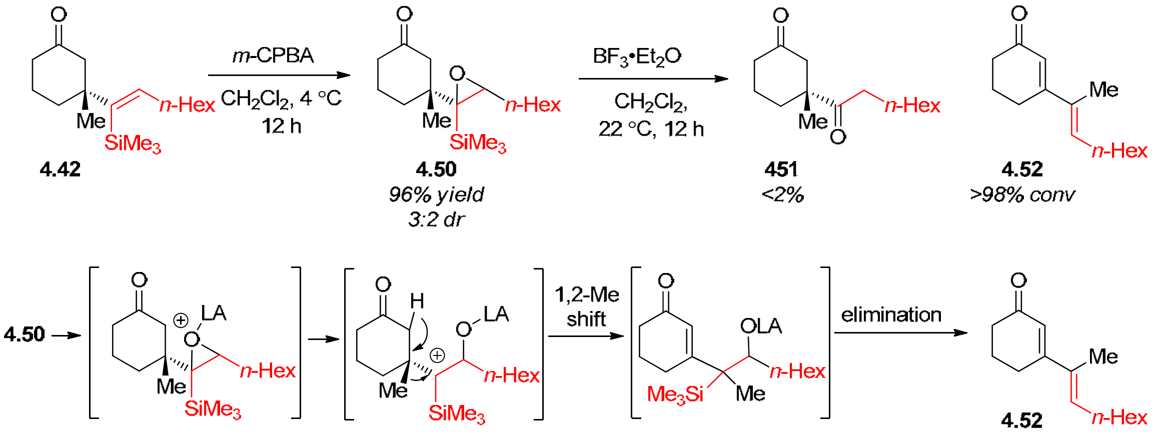
(36) For examples of the oxidation rearrangement, see: (a) "New Synthesis of Aldehydes *via* Vinylsilanes," Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080–2081. (b) "Vinylsilanes as Carbonyl Precursors. Use in Annelation Reactions," Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684. (c) "Thermal Rearrangement of Epoxysilanes," Bassindale, A. R.; Brook, A. G.; Chen, P.; Lennon, J. *J. Organomet. Chem.* **1975**, *94*, C21–C25. (d) "Pyrolytic Rearrangements of α,β-Epoxysilanes to Silyl Enol Ethers," Hudrlik, P. F.; Wan, C.-N.; Withers, G. P. *Tetrahedron Lett.* **1976**, *17*, 1449–1452. (e) "Magnesium Bromide Induced Rearrangements of α,β-Epoxysilanes," Hudrlik, P. F.; Misra, R. N.; Withers, G. P.; Hudrlik, A. M.; Rona, R. J.; Arcoleo, J. P. *Tetrahedron Lett.* **1976**, *17*, 1453–1456. (f) Hydrolytic Ring-Opening of α,β-Epoxysilanes to α,β-Dihydroxysilanes," Hudrlik, P. F.; Arcoleo, J. P.; Schwartz, R. H.; Misra, R. N.; Rona, R. J. *Tetrahedron Lett.* **1977**, *18*, 591–594. (g) "Conversion of α,β-epoxysilanes to Silyl Enol Ethers; An Unprecedented Stereochemical Result," Hudrlik, P. F.; Schwartz, R. H.; Kulkarni, A. K. *Tetrahedron Lett.* **1979**, *20*, 2233–2236. (h) "Chemistry of Diorganocuprates Containing Functionalized Ligands. 2. Methodology for Conjugate Addition of Synthetic Equivalents of Enolates and Acyl Anions," Boeckman, R. K., Jr.; Bruza, K. J. *J. Org. Chem.* **1979**, *44*, 4781–4788. (i) "Stereospecific Rearrangement of 2,2-Disubstituted Vinylsilane Epoxides to the Silyl Enol Ethers of 2,2-Disubstituted Aldehydes," Fleming, I.; Newton, T. W. *J. Chem. Soc. Perkin Trans. 1* **1984**, 119–123. (j) "Free Radical Cyclizations in Alkaloid Synthesis: (+)–Heliotridine and (+)–Hastanecine," Choi, J.-K.; Hart, D. J. *Tetrahedron* ***1985***, *41*, 3959–3971.

rearrangement of **4.50** is induced with BF_3•Et_2O,[36h] the desired product **4.51** is not formed, but >98% conv to diene **4.52** occurs (Scheme 4.18). We surmise that the diene comes from opening of the epoxide placing the carbocation on the carbon adjacent to the quaternary stereogenic center; although the silicon substituent should better electronically stabilize the opening of the epoxide where the cation is β to the trimethylsilyl unit (cf. Scheme 4.17), the steric bulk of the adjacent quaternary carbon may override in this case. A 1,2-methyl shift can then occur followed by a Peterson elimination to afford **4.52**.

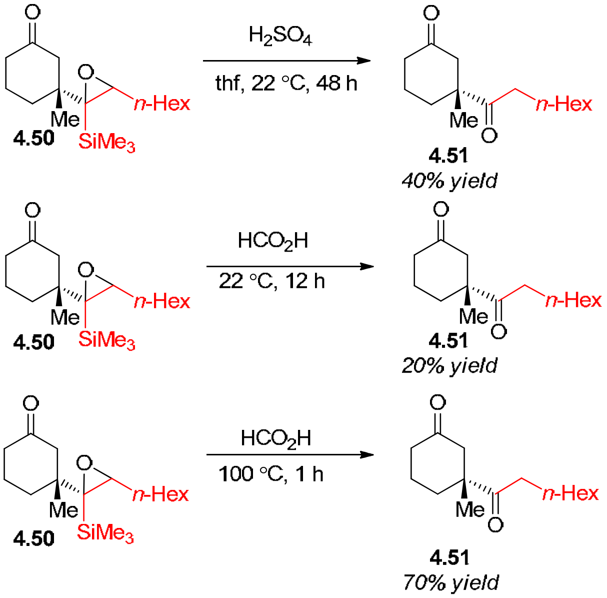
Scheme 4.18. Epoxidation and BF_3•Et_2O Induced Rearrangement of **4.42**



4.42
m-CPBA
CH2Cl2, 4 °C
12 h
4.50
96% yield
3:2 dr
BF3•Et2O
CH2Cl2,
22 °C, 12 h
451
<2%
4.52
>98% conv
Me
n-Hex
SiMe3
4.50
LA
H
1,2-Me shift
OLA
Me3Si
elimination
4.52

As shown in Scheme 4.19, when sulfuric acid is used to induce the rearrangement, the desired diketone **4.51** is isolated in 40% yield, along with other unidentified decomposition products. If a mild acid is used (aqueous formic acid),[36j] the desired product is formed in 20% yield, however with 80% conversion to diene **4.52**. If the acid-mediated rearrangement is conducted at elevated temperatures, the desired product is afforded in a synthetically useful 70% yield (~28% of **4.52** is also formed).

Scheme 4.19. Acid-Mediated Rearrangements



It is known that halides stereoselectively react with vinylsilanes to afford the corresponding vinylhalides.[37] For example, when a vinylsilane reacts with I_2, the vinyliodide is formed and the olefin isomer obtained is a net retention from the starting olefin isomer (Scheme 4.20); the addition is thought to occur with the elimination of in situ prepared iodonium compound. Moreover, when the vinylsilane is treated with Br_2, bromination occurs. Upon treatment with a base (or KF), elimination occurs to yield the vinylbromide with net inversion of the olefin isomer.

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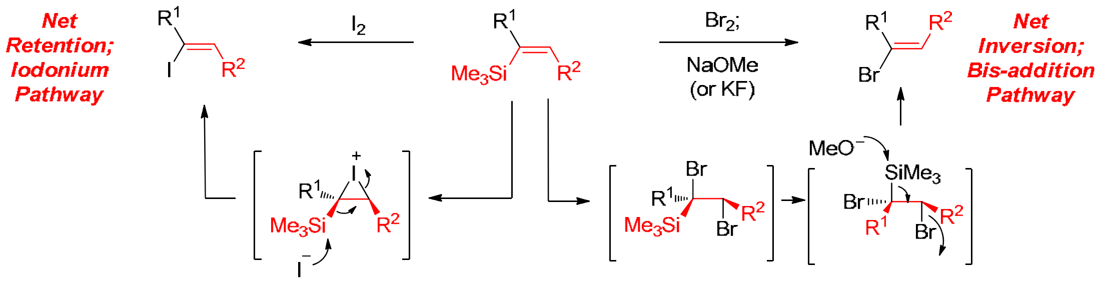
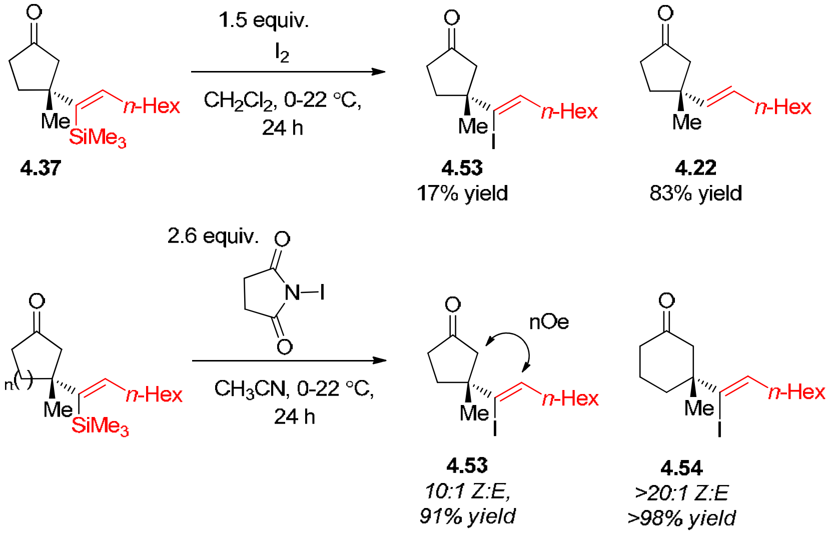
(37) For several lead references discussing halogenations of vinylsilanes, see: (a) "The Stereospecific Synthesis of Vinyl Halides using a Vinylsilane as the Synthetic Precursor," Miller, R. B.; Reichenbach, T. *Tetrahedron Lett.* **1974**, *15*, 543–546. (b) "A Highly Stereoselective Synthesis of Vinyl Bromides and Chlorides via Disubstituted Vinylsilanes," Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424–4431. (c) "A New Synthesis of Substituted Vinylsilanes and Vinyl Iodides," Huynh, C.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *20*, 1073–1076. (d) "Silicon in Organic Synthesis. Stereoselective Synthesis of Some Insect Sex Pheromones," Chan, T. H.; Koumaglo, K. *J. Organomet. Chem.* **1985**, *285*, 109–119. (d) "A Mild Preparation of Vinyliodides from Vinylsilanes," Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647–8650. (e) "Efficient and General Synthetic Approach to Pentasubstituted Conjugated Dienes Using Site-Selective Coupling of Cuprates with 1,4-Diiodo-1,3-Alkadienes as the Key Reaction," Nakajima, R.; Delas, C.; Takayama, Y.; Sato, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3023–3025. (f) Iodine/Palladium Approaches to the Synthesis of Polyheterocyclic Compounds," Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658.

Scheme 4.20. Stereoselective Synthesis of Vinylhalides


Net Retention; Iodonium Pathway
I2
Br2; NaOMe (or KF)
Net Inversion; Bis-addition Pathway
R1
R2
I
Me3Si
Br
MeO−
SiMe3

When vinylsilane **4.37** is treated with I_2 (CH_2Cl_2, 0→22 °C, 24 h), the desired vinyliodide is formed (**4.53**) in a low 17% yield; protodesilyation product **4.22** is the major product isolated (83% yield, Scheme 4.21). It is inferred that the protodesilyated product is formed from advantageous HI present during the reaction. When *N*-iodosuccinimide is used as the iodide source, clean formation of **4.53** is achieved (91% yield) as a 10:1 mixture of *Z*:*E* olefin isomers (Scheme 4.21) as determined by nOe analysis. Similar reaction with the six-membered ring containing vinylsilane affords vinyliodide **4.54** in quantitative yield as a single olefin isomer. Notably, products **4.53** and **4.54** cannot be prepared in a direct manner through an ECA protocol and can serve

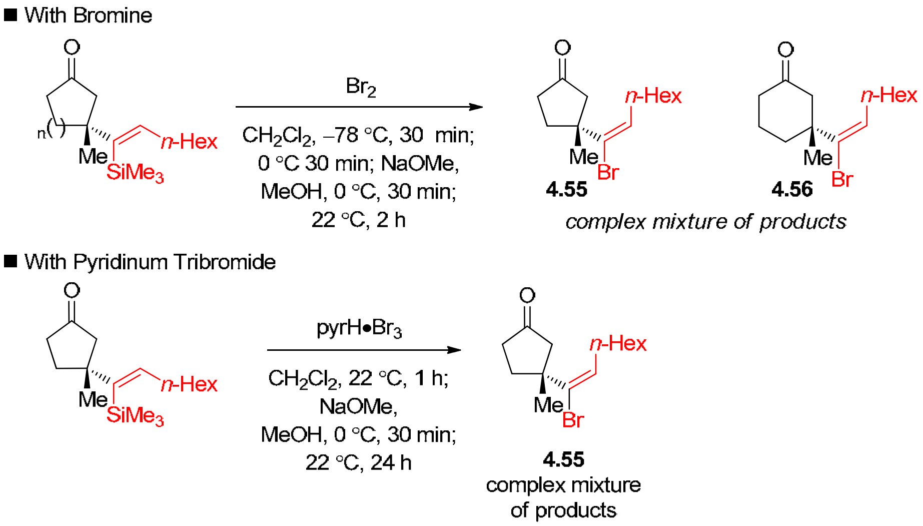
Scheme 4.21. Vinyliodide Formation


1.5 equiv. I2
CH2Cl2, 0-22 °C, 24 h
4.37
4.53
17% yield
4.22
83% yield
2.6 equiv.
N–I
CH3CN, 0-22 °C, 24 h
nOe
n-Hex
Me
SiMe3
I
4.53
10:1 Z:E, 91% yield
4.54
>20:1 Z:E
>98% yield

as synthetically useful intermediates.[38]

We, next, attempted to prepare vinylbromide containing compounds with *E*-olefin geometry. When either the five- or six-membered ring vinylsilane is treated with Br_2 followed by NaOMe, the desired products **4.55** and **4.56** are formed but contaminated with other byproducts including protodesilyation products (Scheme 4.22). When the bromination is conducted with pyridinum tribromide, the formation of **4.55** is still complicated with protodesilyation. Further screening is still need to efficiently convert the vinylsilanes adjacent to a quaternary stereogenic center to vinylbromides without competing pathways leading to desilylation products.

Scheme 4.22. Vinylbromide Formation


■ With Bromine
O
n( )
Me
n-Hex
SiMe3
Br2
CH2Cl2, –78 °C, 30 min; 0 °C 30 min; NaOMe, MeOH, 0 °C, 30 min; 22 °C, 2 h
O
n-Hex
Me
Br
4.55
O
n-Hex
Me
Br
4.56
complex mixture of products
■ With Pyridinum Tribromide
O
Me
n-Hex
SiMe3
pyrH•Br3
CH2Cl2, 22 °C, 1 h; NaOMe, MeOH, 0 °C, 30 min; 22 °C, 24 h
O
n-Hex
Me
Br
4.55
complex mixture of products

Vinylsilanes are known to react with acid chlorides in the presence of Lewis acids.[39] With this in mind, treatment of **4.42** with $AlCl_3$ or $TiCl_4$ and AcCl was pursued,

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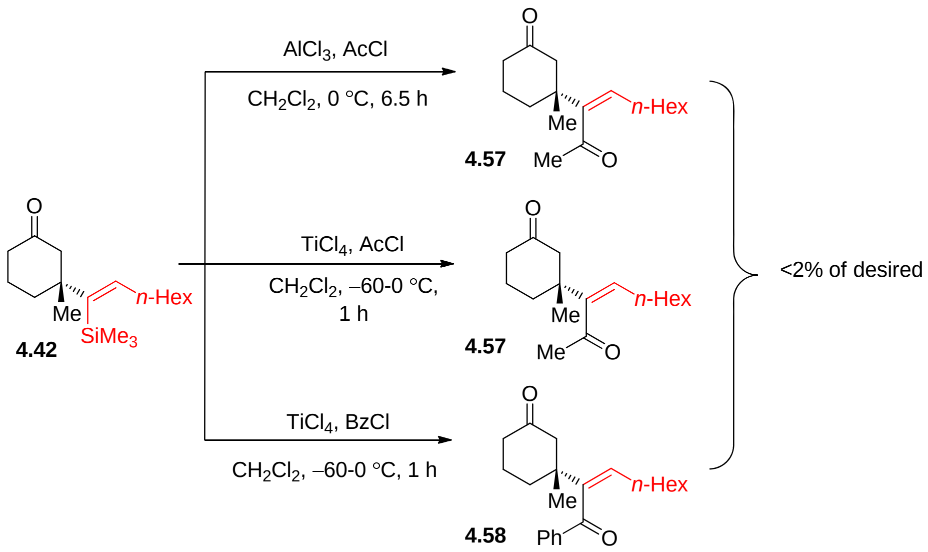
(38) For representative cross-coupling protocols involving sterically hindered vinyl iodides, see: (a) “Synthesis of 2(3*H*)-Furanones via Electrophilic Cyclization,” Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662–2667. (b) “Pd-Catalyzed Alkylation of Halogen-Substituted Steroids with Organozinc Compounds,” Latyshev, G. V.; Lukashev, N. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2008**, *44*, 785–790. (c) “The Synthesis of 13α-Androsta-5,16-Diene Derivatives with Carboxylic Acid, Ester and Carboxamido Functionalities at Position-17 via Palladium-Catalyzed Carbonylation,” Ács, P.; Takács, A.; Szilágyi, A.; Wölfling, J.; Schneider, G.; Kollár, L. *Steroids* **2009**, *74*, 419–423.

(39) (a) “Silanes in Organic Synthesis. 8. Preparation of Vinylsilanes from Ketones and Their Regiospecific Cyclopentenone Annulation,” Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017–3028. (b) “A New and Short Synthesis of Dehydroelsholtzione (Naginata Ketone) and Isoegomaketone,” Pillot, J.-P.; Bennetau, B.; Dunogues, J.; Calas, R. *Tetrahedron Lett.* **1980**,

however, the reaction only leads to protodesilylation of the starting material, most likely due to HCl formation during the reaction (Scheme 4.23); diketone **4.57** is not formed. In an effort to prevent ketene formation of acylchloride during the course of the reaction, the Friedal–Crafts reaction was also investigated with BzCl as the electrophile; however, no desired product is formed.

Scheme 4.23. Friedel–Crafts Reaction of Vinylsilanes with Acid Chlorides



4.5. Enantioselective Synthesis of Riccardiphenol B through Cu-Catalyzed ECA of Si-Substituted Dienylaluminum Reagent to 3-Methylcyclohexenone

With an efficient and selective method developed for Cu–NHC catalyzed ECA of Si-substituted vinylaluminum reagents to trisubstituted cyclic enones, we sought to demonstrate the protocol in the context of total synthesis. As shown in Scheme 4.24, we thought that we could access the naturally occurring sesquiterpene, isolated from a Japanese collection of *Riccardia crassa*,[3] by ECA of a dienylaluminum reagent to 3-methylcyclohexenone. Addition of the regioselectively formed metal enolate to a

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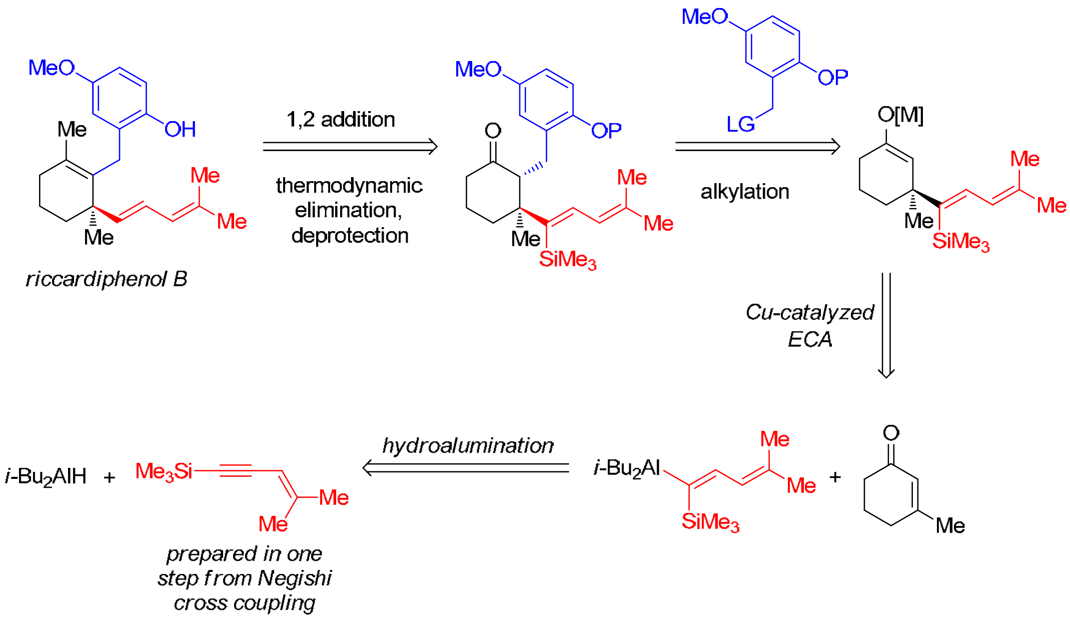
21, 4717–4720. (c) "Friedel–Crafts Reactions of Some Vinylsilanes," Fleming, I.; Pearce, A. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2485–2489.

substituted electrophilic benzyl group followed by 1,2-methyl addition, thermodynamic elimination, and deprotection of the phenol should afford riccardiphenol B.

Scheme 4.24. Retrosynthesis of Riccardiphenol B


MeO
OH
Me
Me
Me
Me
riccardiphenol B
1,2 addition
thermodynamic elimination, deprotection
MeO
OP
O
Me
Me
Me
SiMe3
MeO
OP
LG
alkylation
O[M]
Me
Me
Me
SiMe3
Cu-catalyzed ECA
hydroalumination
i-Bu2AlH +
Me3Si
Me
Me
prepared in one step from Negishi cross coupling
i-Bu2Al
Me
Me
SiMe3
+
O
Me

Although riccardiphenol B has not been evaluated for biological activity, a close family member of the terpene family (riccardiphenol C) has shown mild cytotoxicity to BSC−1 cells and was slightly active against *B. subtilis*.[40] Moreover, a synthetic analog of riccardiphenol B was found to be active against human cancer lines in vitro.[41] There has been one synthesis of riccardiphenol B by Tori and co-workers;[42] the chiral-auxiliary-based synthesis has twelve steps and a 0.004% overall yield.

Dienylaluminum reagent **4.59** is prepared from hydroalumination (with *i*-Bu$_2$AlH) of the corresponding enyne and used in situ without purification or isolation (Scheme

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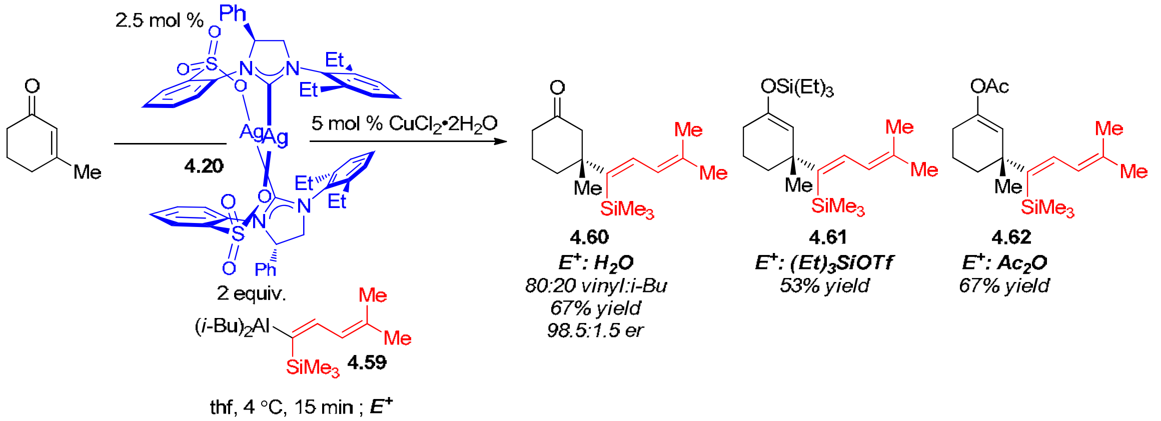
(40) "Sesquiterpene/Quinol from a New Zealand Liverwort, *Riccardia crassa*," Perry, N. B.; Foster, L. M. *J. Nat. Prod.* **1995**, *58*, 1131–1135.

(41) "Design, Synthesis and Biological Evaluation of Novel Riccardiphenol Analogs," Kumar, S. K.; Amador, M.; Hidalgo, M.; Bhat, S. V.; Khan, S. R. *Bioorg. Med. Chem.* **2005**, *13*, 2873–2880.

(42) "Total Synthesis and Absolute Configuration of Riccardiphenols A and B, Isolated from the Liverwort *Riccardia crassa*," Tori, M.; Hamaguchi, T.; Sagawa, K.; Sono, M.; Asakawa, Y. *J. Org. Chem.* **1996**, *61*, 5362–5370.

4.25).[43] Cu-catalyzed reaction of **4.59** with 3-methylcyclohexenone, promoted by a sulfonate-containing NHC complex at 4 °C, furnishes **4.60** in 98.5:1.5 er in 67% yield. The resulting regioselective Al–enolate can be directly converted to versatile silyl enol ether **4.61** (53% yield) or enol acetate **4.62** (67% yield) in one pot by the addition of Et_3SiOTf or Ac_2O, respectively.

Scheme 4.25. Preparation of Diene-Containing Cyclohexanone


O
Me
2.5 mol %
Ph
O
O=S
N
N
Et
Et
O
Ag Ag
4.20
Et
Et
O
N
N
S
O
O
Ph
2 equiv.
(i-Bu)2Al
Me
Me
SiMe3
4.59
thf, 4 °C, 15 min ; E+
5 mol % CuCl2•2H2O
O
Me
Me
Me
SiMe3
4.60
E+: H2O
80:20 vinyl:i-Bu
67% yield
98.5:1.5 er
OSi(Et)3
Me
Me
Me
SiMe3
4.61
E+: (Et)3SiOTf
53% yield
OAc
Me
Me
Me
SiMe3
4.62
E+: Ac2O
67% yield

With an efficient method in hand for the enantioselective conjugate addition step, we investigated the feasibility of the alkylation of the metal enolate with a functionalized benzyl bromide leading to **4.64** (Scheme 4.26). Treatment of the in situ generated Al–enolate (from the ECA reaction) with electron-rich benzyl bromide **4.63**[41] (prepared in four steps) results in <2% of the alkylation product **4.64**; the only product recovered is **4.59** from protonation of the Al–enolate. This is not surprising as Al–enolates are not especially nucleophilic.[2b] We, next, investigated the Li–enolate **4.65** in the alkylation; treatment of silyl enol ether **4.61** with *n*-butyllithium, to form the lithium enolate, followed by treatment with 7 equivalents of **4.63** does not deliver the desired alkylation product; only hydrolyzed ketone **4.60** is formed (Scheme 4.26). Conducting the alkylation with HMPA or at elevated temperatures does not improve the reaction.

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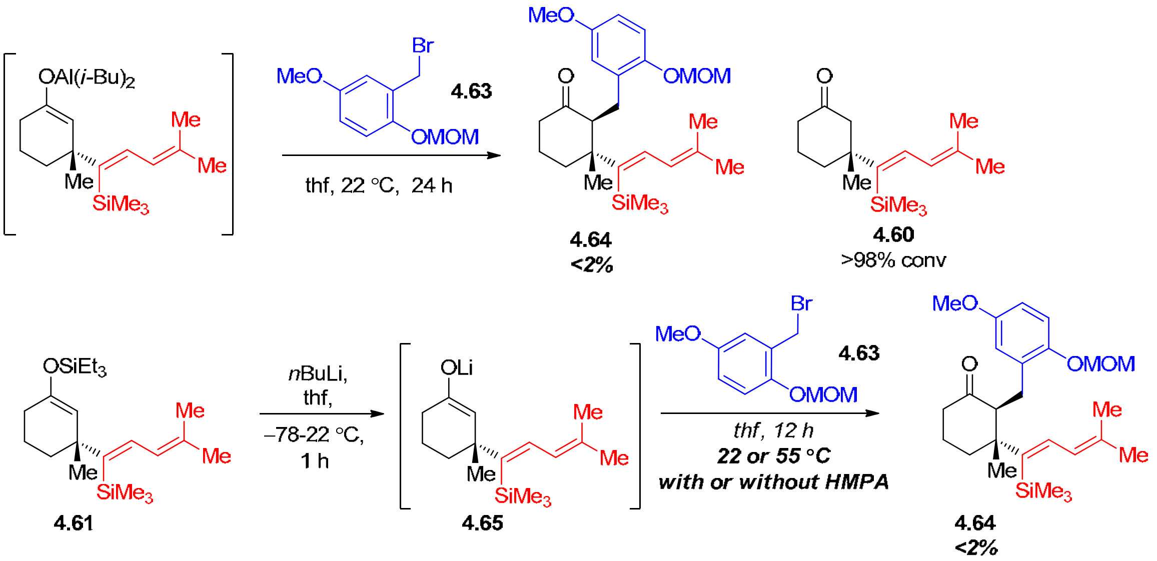
(43) "A Concise and Efficient Novel Synthesis of Cleviolide," Rossi, R.; Bellina, F.; Biagetti, M. *Synth. Commun.* **1999**, *29*, 3415–3420.

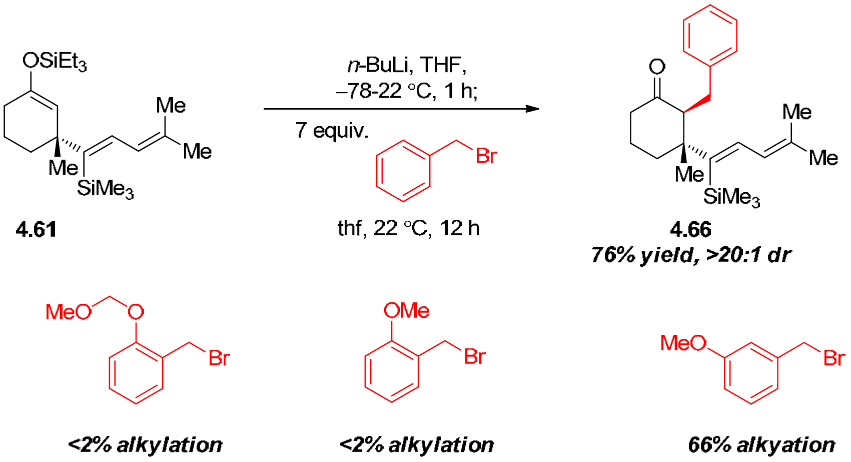
Moreover, when Zn- or Cu-enolates are involved, only hydrolyzed product **4.60** is isolated.

Scheme 4.26. Alkylation of the Al– or Li–Enolate with Benzyl Bromide **4.63**


OAl(*i*-Bu)$_2$
Me
Me
Me
SiMe$_3$
MeO
Br
OMOM
4.63
thf, 22 °C, 24 h
4.64
<2%
4.60
>98% conv
OSiEt$_3$
4.61
*n*BuLi,
thf,
–78-22 °C,
1 h
OLi
4.65
thf, 12 h
22 or 55 °C
with or without HMPA
4.64
<2%

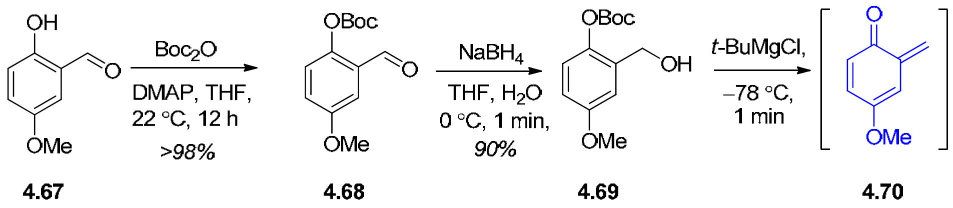
In an effort to establish which reaction component (nucleophile or electrophile) is the cause of the complete lack of reactivity, we investigated whether other electrophiles might react with the lithium enolate **4.65**. As shown in Scheme 4.27, when the lithium enolate generated from **4.61**, is treated with 7 equivalents of benzyl bromide, ketone **4.66** is isolated in 74% yield (>20:1 dr). When *o*-substituted benzyl bromides are used, there is <2% alkylation (Scheme 4.27). Moreover, when 3-methoxy benzyl bromide is subjected to the alkylation conditions, a 3:2 mixture of the desired product and hydrolyzed lithium enolate (**4.60**) is observed. The above results suggest that subtle steric modifications of the electrophile can cause a significant decrease in the efficiency of the benzyl addition.

Scheme 4.27. Alkylation with Various Benzyl Bromides


OSiEt3
Me
Me
Me
SiMe3
4.61
n-BuLi, THF,
–78-22 °C, 1 h;
7 equiv.
Br
thf, 22 °C, 12 h
O
Me
Me
Me
SiMe3
4.66
76% yield, >20:1 dr
MeO
O
Br
OMe
Br
MeO
Br
<2% alkylation
<2% alkylation
66% alkyation

Based on the data summarized in Scheme 4.27, it appears that enolate **4.65** generated from **4.61** does not have the propensity to undergo alkylation. Next, we pursued the use of a more reactive electrophilic partner. We hypothesized that if we could generate an *o*-quinone methide, alkylation would occur more efficiently. Moreover, use of the quinone does not require a separate deprotection step to unmask the phenol. The *o*-quinone precursor is prepared in two steps (Boc protection of **4.67** followed by $NaBH_4$ reduction of the corresponding salicylaldehyde **4.68**) according to a procedure by Pettus and coworkers (Scheme 4.28).[44] Treatment of benzyl alcohol **4.69** with *t*-BuMgCl at –78 °C for one minute leads to the formation of a cyclic carbonate that spontaneously rearranges to form *o*-quinone methide **4.70**.

Scheme 4.28. Preparation of *o*-Quinone Methide **4.70**


OH
O
OMe
4.67
Boc2O
DMAP, THF,
22 °C, 12 h
>98%
OBoc
O
OMe
4.68
NaBH4
THF, H2O
0 °C, 1 min,
90%
OBoc
OH
OMe
4.69
t-BuMgCl,
–78 °C,
1 min
O
OMe
4.70

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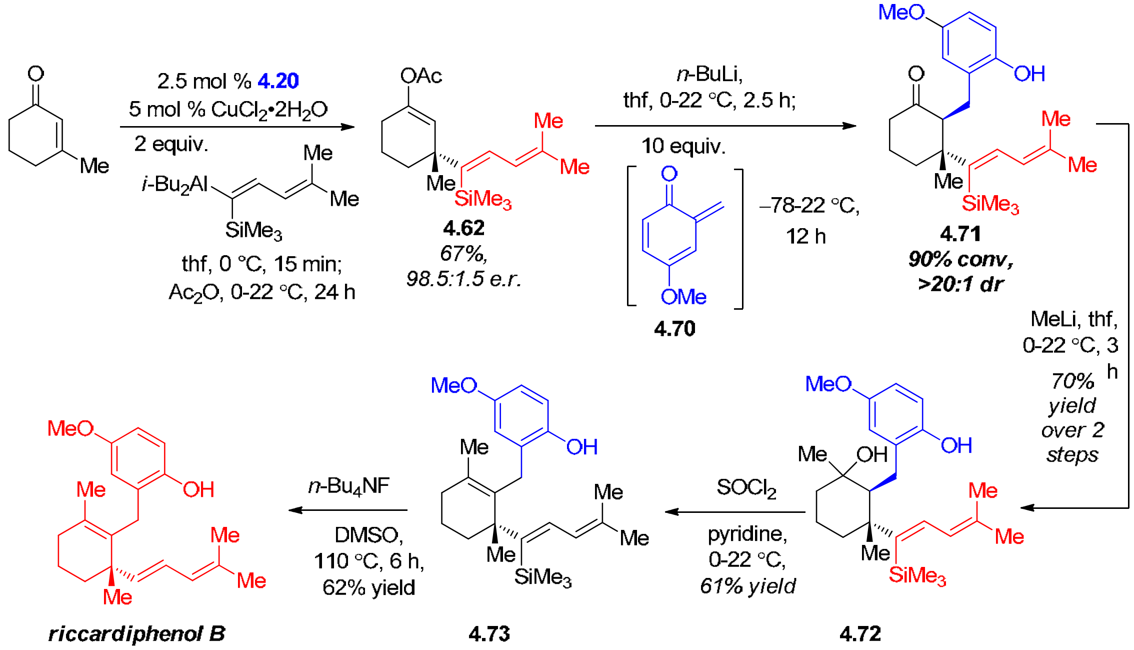
[44] "A Mild Anionic Method for Generating *o*-Quinone Methides: Facile Preparations of *Ortho*-Functionalized Phenols," Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435–3441.

The addition of the in situ prepared lithium enolate from **4.62** to 10 equivalents of the *o*-quinone methide **4.70** delivers the alkylation product **4.71** in 90% conversion and >20:1 dr; the stereochemical identity of **4.71** is projected on the basis of steric factors and has not been rigorously determined. Treatment of **4.71** with MeLi delivers the 1,2 addition product with 70:30 dr in a 70% yield over two steps. Elimination of the tertiary alcohol with $SOCl_2$ in pyridine affords tetrasubstituted olefin **4.73**.[42] Desilylation of **4.73** with tetrabutylammonium fluoride delivers the target molecule in 62% yield, which constitutes the first total synthesis of riccardiphenol B through the use of catalytic, enantioselective methods (six-step longest linear sequence).

Scheme 4.28. Completion of the Total Synthesis of Riccardiphenol B



2.5 mol % 4.20
5 mol % CuCl₂•2H₂O
2 equiv.
i-Bu₂Al
SiMe₃
thf, 0 °C, 15 min;
Ac₂O, 0-22 °C, 24 h
OAc
4.62
67%,
98.5:1.5 e.r.
n-BuLi,
thf, 0-22 °C, 2.5 h;
10 equiv.
4.70
–78-22 °C,
12 h
4.71
90% conv,
>20:1 dr
MeLi, thf,
0-22 °C, 3 h
70% yield over 2 steps
4.72
SOCl₂
pyridine,
0-22 °C,
61% yield
4.73
n-Bu₄NF
DMSO,
110 °C, 6 h,
62% yield
riccardiphenol B
MeO
OH
Me
OMe

4.6. Conclusions

We have developed an efficient and practical preparation of enantiomerically enriched β,β-substituted ketones containing 1,1-disubstituted olefins and synthetically versatile vinylsilanes. The protocol allows the preparation of molecules that are difficult to access by other means. The method is highlighted by the total synthesis of riccardiphenol B, the first catalytic, enantioselective synthesis of this compound. The current protocol underlines the effectiveness of the bidenate sulfonate-containing NHC complexes as a proficient chiral promoter.

4.7. 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. Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm)) or HPLC analysis (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 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. 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 Catalysts:

Acetonitrile was purchased from Aldrich (anhydrous, 99.8%) and used as received.

Acetic anhydride was purchased from Aldrich and used as received.

Ag-complexes 4.15[18] **and 4.16**[19] were prepared by previously reported methods.

Ag-complex 4.17[21] was prepared by previously reported methods with the exception of the procedure for the formation of the imidazolinium salt.[22b]

Ag-complex 4.18,[22b] **4.20,**[22a] **and 4.21**[31] were prepared by previously reported methods.

Ag-complex 4.19 and 4.41 were prepared by previously reported methods.[23]

2-Bromoprop-1-ene was purchased from Aldrich and distilled from CaH_2 prior to use.

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

***t*-Butyllithium** was purchased from Strem (16% in pentane) and titrated before use.

***t*-Butylmagnesium chloride** was prepared from *t*-BuCl (Aldrich) and magnesium turnings (Strem).

***m*-Chloroperbenzoic acid** was purchased from Aldrich and recrystallized before use.

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

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

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

Dimethylaminopyridine was purchased from Advanced Chem Tech and used as received.

Dimethylsulfoxide was purchased from Aldrich (anhydrous) and used as received.

Di-*t*-butyldicarbonate was purchased from Aldrich and used as received.

Formic acid was purchased from Aldrich (95-97%) and used as received.

2-Hydroxy-5-methoxybenzaldehyde was purchased from Aldrich and used as received.

***N*-Iodosuccinimide** was purchased from Aldrich and used as received.

Methyl lithium was purchased from Acros and titrated before use.

Phenylacetylene was purchased from TCI America and distilled from CaH_2 prior to use.

Pyridine was distilled from KOH prior to use.

Sodium borohydride was purchased from Aldrich and used as received.

Thionyl chloride was purchased from Aldrich and distilled prior to use.

Tetrabutylammonium fluoride ($3H_2O$) was purchased from Aldrich and used as received under a dry atmosphere.

Trifluroacetic acid was purchased from Acros (99%) and used as received.

Preparation of unsaturated enones: α,β-Unsaturated carbonyls are commercially available (3-methylcyclopentenone and 3-methylcyclohexenone, Aldrich, distilled over CaH_2) or can be prepared according to published procedures.[45]

Preparation of Terminal Vinylaluminum Reagents: prepared according to published procedures.[22b]

Preparation of silylacetylenes: Prepared according to published procedures.[46]

■ **Representative procedure for the preparation of silyl-substituted vinylaluminum reagents:** To a flame-dried round bottom flask equipped with a stir bar was added hexanes (1.31 mL) and thf (0.263 mL). The solution was allowed to cool to 0 °C before the drop-wise addition of *i*-Bu_2AlH (0.351 mL, 1.97 mmol) and trimethyl(4-methylpent-3-en-1-yn-1-yl)silane (0.410 mL, 1.97 mmol). The clear solution was allowed to warm to 55 °C and stir for 2 h and was used without purification.

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(45) (a) Reference 2b. (b) “Synthesis of β-Alkyl Cyclopentanones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Reduction,” Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798. (c) “Organocatalytic Transfer Hydrogenation of Cyclic Enones,” Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662–12663.

(46) “The Stereochemistry of Organometallic Compounds: XXXVI. Regio- and Stereo-Chemical Control in the Nickel-Catalysed Hydrocyanation of Silylalkynes,” Fitzmaurice, N. J.; Jackson, W. R.; Perlmetter, P. *J. Organomet. Chem.* **1985**, *285*, 375–381.

■ **Representative experimental procedure for the preparation of vinylaluminum reagents with vinyllithium and Me_2AlCl:** 2-Bromoprop-1-ene (0.856 mL, 10.0 mmol) and thf (4 mL) were added through a syringe to a flame-dried round bottom flask equipped with a stir bar. The solution was allowed to cool to –78 °C (dry ice/acetone bath). *t*-Butyllithium (12.1 mL, 20.0 mmol, 1.65 M, CAUTION, REAGENT IS PYROPHORIC) was added through a syringe and the solution was allowed to stir at –78 °C for 15 min. Pentane (4 mL) followed by Me_2AlCl (0.929 mL, 10.0 mmol, CAUTION, REAGENT IS PYROPHORIC) was added through a syringe and the solution was allowed to warm to 22 °C and stir for 12 h. The resulting mixture was a clear yellow solution (0.498 M) containing LiCl solid that had precipitated out of solution. The solution was allowed to stand for 30 min to assist with settling of solid LiCl.

■ **Representative experimental procedure for the preparation of vinylaluminum reagents by Ni-catalyzed hydroalumination of alkynes:**[27] To a flame-dried round bottom flask equipped with a stir bar was added $NiCl_2$(dppp) (81.3 mg, 0.150 mmol) and thf (5 mL). The red heterogeneous solution was allowed to cool to 0 °C before the dropwise addition of *i*-Bu_2AlH (0.934 mL, 5.25 mmol). The solution turned to a dark brown homogenous solution. Phenylacetylene (0.464 mL, 5.00 mmol) was added dropwise and the solution was allowed to warm to 22 °C and stir for 2 h.

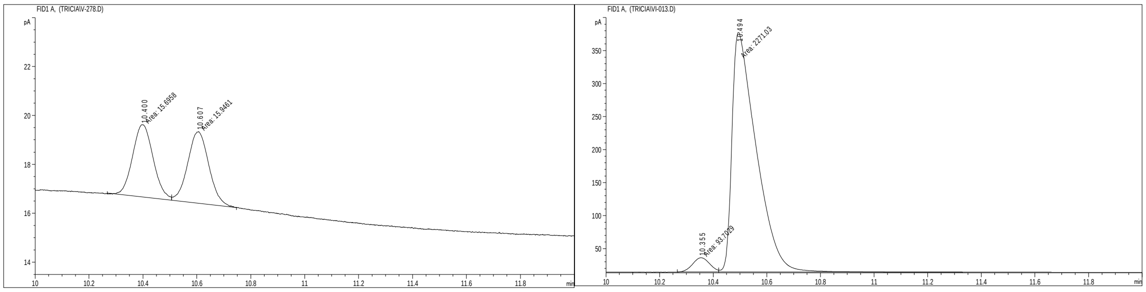
■# **Representative procedure for NHC–Cu-catalyzed conjugate addition of vinylaluminum reagents to unsaturated enones.** An oven-dried 4 dram vial was charged with NHC–Ag complex **4.20** (2.70 mg, 5.00 μmol) and $CuCl_2•2H_2O$ (0.850 mg, 5.00 μmol) weighed under a N_2 atmosphere in a glove box. The vial was sealed with a cap with septum. Tetrahydrofuran (1.0 mL) was added through a syringe to the vial and the resulting blue solution was allowed to stir for five min. The aluminum reagent ((*E*-di-*i*-butyl(1-trimethylsilyl)pent-1-en-1-yl)aluminum) (160 μL, 2.00 mmol, 1.25 M) (CAUTION! Flammable!) and 3-methylcyclopentenone 9.90 μL, 0.100 mmol) were added through a syringe, sequentially, resulting in a brown solution. The solution was allowed to stir at 22 °C for 15 min after which the reaction was quenched upon addition of a saturated aqueous solution of sodium potassium tartrate (2 mL). The solution was washed with Et_2O (2 x 1 mL) and passed through a short plug of silica gel (2 cm x 1 cm) and eluted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil that was purified by silica gel chromatography (5% Et_2O/hexanes→10% Et_2O/hexanes) to afford 18.1 mg of (*R*,*Z*)-3-methyl-3-(1-(trimethylsilyl)pent-1-en-1-yl)cyclopentanone as a clear oil (0.076 mmol, 76% yield).

■# **Representative procedure for protodesilylation of vinylsilanes**. Trifluoroacetic acid (550 μL) was added to a solution of (*R*,*Z*)-2,2,4-trimethyl-4-(1-(trimethylsilyl)pent-1-en-1-yl)cyclopentanone (8.80 mg, 0.033 mmol) in $CHCl_3$ (550 μL) at 22 °C under air. The solution was allowed to stir for 12 h after which it was diluted with Et_2O (2 mL). The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (~4 mL, until neutral pH is observed). The aqueous layer was washed with Et_2O (3 x 2 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil that was purified by silica gel chromatography (5% Et_2O/hexanes→10% Et_2O/hexanes) to afford 6.40 mg of (*R*,*E*)-2,2,4-trimethyl-4-(pent-1-en-1-yl)cyclopentanone as a clear oil (0.033 mmol, >98% yield).

(*S*)-3-Methyl-3-(prop-1-en-2-yl)cyclohexanone (4.8): IR (neat): 2958 (m), 2930 (m), 2871 (w), 2856 (w), 1715 (s), 1637 (w), 1454 (m), 1377 (w), 1350 (w), 1315 (w), 1291 (w), 1258 (m), 1225 (w), 1081 (w), 901 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.83 (1H, dd, *J* = 1.2, 1.2 Hz), 4.74 (1H, s), 2.60 (1H, ddd, *J* = 14.4, 1.6, 1.6 Hz), 2.34–2.19 (3H, m), 2.19 (1H, d, *J* = 14.8 Hz), 1.95–1.87 (1H, m), 1.87–1.73 (1H, m), 1.72 (3H, s), 1.62–1.56 (1H, m), 1.09 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.8, 150.0, 112.0, 52.6, 43.9, 40.9, 34.9, 26.9, 22.0, 19.2; HRMS (EI+): Calcd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1279, Found: 153.1286; Specific Rotation: $[\alpha]_D^{24}$ +29.7 (*c* = 0.800, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

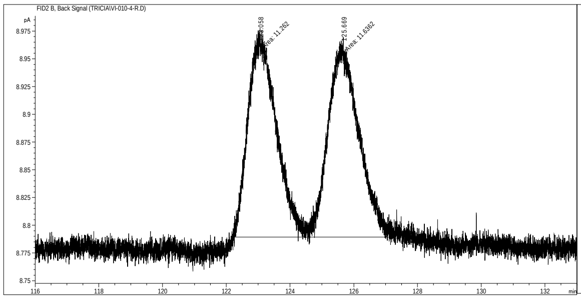
Stereochemistry Proof: Previous reported specific rotation: $[\alpha]_D^{20}$ −62.5 (*concentration not given,* $CHCl_3$) for an enantiomerically enriched sample of 95.5:4.5 er of the *R* enantiomer.[2e]

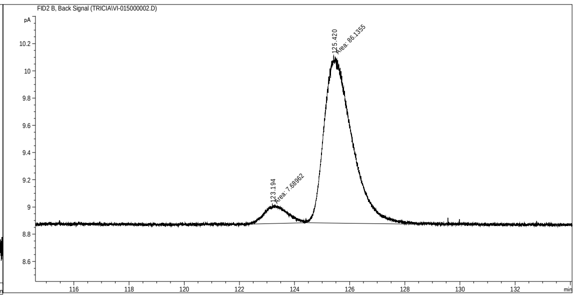
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.1:3.9 er shown; β-dex column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	10.400	15.7	3.0	0.0886	49.604	1	10.355	92.5	21.3	0.0725	3.910
2	10.607	15.9	2.9	10.0909	50.396	2	10.494	2272.1	362.5	0.1045	96.090

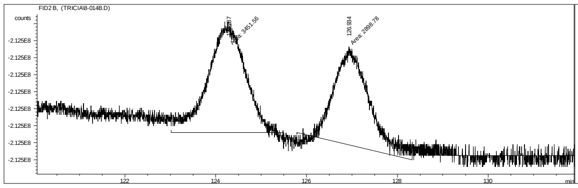
(*S*)-3-Methyl-3-(prop-1-en-2-yl)cyclopentanone (4.10): IR (neat): 2961 (m), 2875 (w), 1743 (s), 1703 (w), 1640 (w), 1617 (w), 1455 (w), 1406 (w), 1376 (w), 1251 (w), 1163 (m), 1109 (w), 892 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.79 (1H, dd, *J* = 1.2, 1.2 Hz, 4.72 (1H, dd, *J* = 1.2, 0.8 Hz), 2.42 (1H, d, *J* = 17.6 Hz), 2.32–2.28 (2H, m), 2.13 (1H, dd, *J* = 17.2, 1.2 Hz), 2.08–2.02 (1H, m), 1.91–1.82 (1H, m), 1.79 (3H, dd, *J* = 12, 0.8 Hz), 1.19 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.1, 150.7, 109.6, 51.3, 45.0, 36.8, 33.9, 25.7, 19.6; Specific Rotation: $[\alpha]_D^{24}$ –11.1 (*c* = 0.480, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (91.8:8.2 er shown; α-dex column, 15 psi, 50 °C).

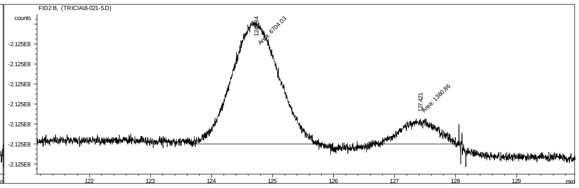




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	123.058	11.3	0.19	0.9891	49.183	1	123.194	7.7	0.14	0.9141	8.196
2	125.669	11.6	0.18	1.0721	50.817	2	125.420	86.1	1.2	1.1646	91.804

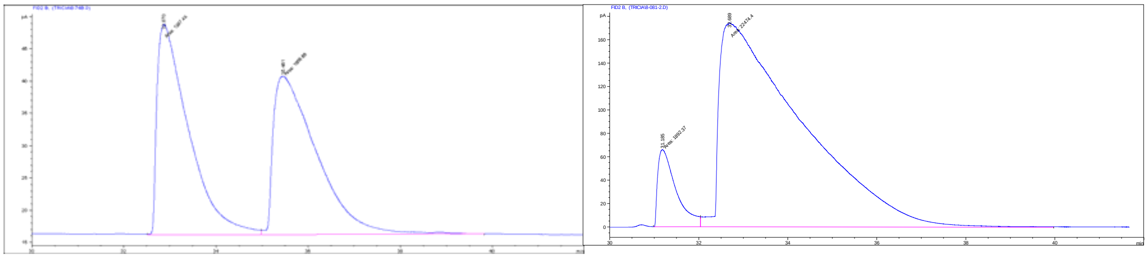
(*S*)-3-Butyl-3-(prop-1-en-2-yl)cycloheptenone (4.27): IR (neat): 2930 (s), 2860 (m), 1693 (s), 1635 (w), 1452 (m), 1408 (w), 1378 (w), 1348 (w), 1334 (w), 1290 (w), 1253 (w), 1185 (w), 894 (s), 517 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.83 (1H, dd, *J* = 1.6, 1.6 Hz), 4.63 (1H, s), 2.73 (1H, dd, *J* = 14.4, 1.6 Hz), 2.42 (1H, d, *J* = 14.0 Hz), 2.83–2.32 (2H, m), 1.93–1.89 (1H, m), 1.74–1.64 (2H, m), 1.63 (3H, s), 1.60–1.40 (3H, m), 127–1.20 (3H, m), 1.16 (3H, t, *J* = 7.2 Hz), 0.80 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 214.7, 148.6, 112.9, 52.6, 44.5, 44.4, 40.5, 39.7, 26.0, 25.7, 24.3, 23.3, 19.7, 14.2; HRMS (EI+): Calcd for $C_{14}H_{25}O$ $[M+H]^+$: 209.1905, Found: 209.1905; specific Rotation: $[\alpha]_D^{24}$ +37.5 (*c* = 1.12, $CHCl_3$) for an enantiomerically enriched sample of 83:17 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (83.1:16.9 er shown; β-dex column, 15 psi, 100 °C).





#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	124.287	3451.6	64.4	0.893	54.352	1	124.734	6704	124.2	0.8998	83.126
2	126.934	2898.8	57.9	0.8349	45.648	2	127.421	1360.9	30.5	0.7431	16.874

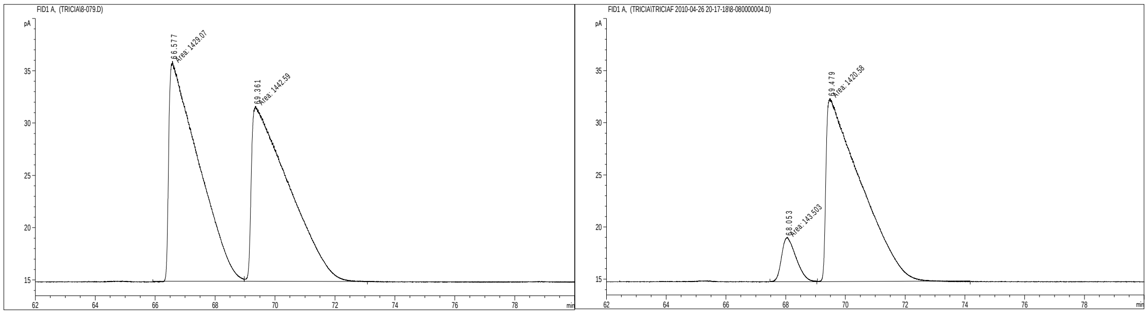
(*S*)-3-Methyl-3-(oct-1-en-2-yl)cyclohexanone (4.29): IR (neat): 2955 (m), 2929 (s), 2858 (m), 1714 (s), 1634 (w), 1457 (m), 1423 (w), 1377 (w), 1350 (w), 1289 (m), 1226 (w), 1080 (w), 903 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.85 (2H, s), 2.60 (1H, dd, *J* = 14.0, 1.2 Hz), 2.33–2.17 (3H, m), 2.00–1.90 (3H, m), 1.86–1.68 (2H, m), 1.62–1.60 (1H, m), 1.47–1.41 (2H, m), 1.36–1.26 (6H, m), 1.08 (3H, s), 0.89 (3H, t, *J* = 5.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 211.9, 154.3, 109.7, 52.9, 44.4, 40.1, 35.0, 32.0, 30.8, 29.6, 29.1, 26.9, 22.8, 22.0, 14.2; HRMS (EI+): Calcd for $C_{15}H_{27}O$ [M+H]$^+$: 223.2062, Found: 223.2064; Specific Rotation: $[\alpha]_D^{24}$ +25.2 (*c* = 1.42, CHCl$_3$) for an enantiomerically enriched sample of 92:8 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (92.2:7.8 er shown; CDGTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	32.87	1557.5	32.7	0.7946	49.219	1	31.185	1892.4	66	0.4779	7.766
2	35.461	1606.9	24.5	1.092	50.781	2	32.689	22474.4	174.4	2.1483	92.234

(*S*)-3-Methyl-3-(oct-1-en-2-yl)cyclopentanone (4.30): IR (neat): 2956 (m), 2926 (s), 2856 (m), 1745 (s), 1637 (w), 1588 (w), 1465 (m), 1406 (w), 1377 (w), 1249 (w), 1160 (w), 895 (w), 725 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.81 (1H, s), 4.81 (1H, s), 2.41 (1H, d, *J* = 17.6 Hz), 2.31–2.27 (2H, m), 2.13 (1H, d, *J* = 17.6 Hz), 2.07–2.01 (3H, m), 1.91–1.85 (1H, m), 1.49–1.43 (2H, m), 1.36–1.25 (6H, m), 1.17 (3H, s), 0.89 (3H, t, *J* = 6.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 219.2, 155.0, 107.7, 51.5, 45.5, 36.7, 34.0, 32.0, 31.7, 29.5, 28.9, 26.2, 22.8, 14.2; HRMS (EI+): Calcd for $C_{14}H_{25}O$ [M+H]$^+$: 209.1905, Found: 209.1903; Specific Rotation: $[\alpha]_D^{24}$ –10.0 (*c* = 1.04, CHCl$_3$) for an enantiomerically enriched sample of 91:9 er. Enantiomeric purity was determined by

GLC analysis in comparison with authentic racemic material (90.8:9.2 er shown; CDM-DM column, 15 psi, 120 °C).

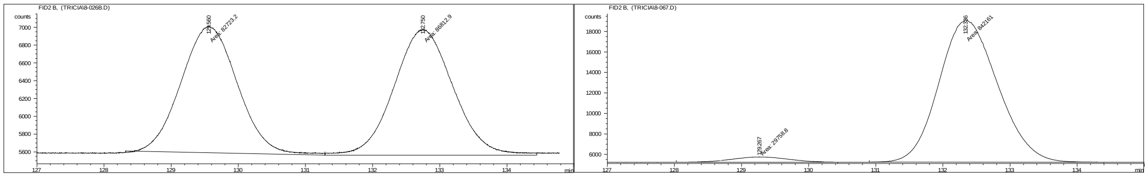


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	66.577	1429.1	21	1.132	49.765	1	68.053	143.5	4.2	0.5631	9.175
2	69.361	1442.6	16.7	1.4366	50.235	2	69.479	1420.6	17.6	1.3458	90.825

(*S*)-3-Methyl-3-(1-phenylvinyl)cyclohexanone (4.9): IR (neat): 2956 (m), 2872 (w), 1707 (s), 1625 (w), 1491 (w), 1441 (w), 1421 (w), 1399 (w), 1375 (w), 1349 (w), 1289 (w), 1226 (m), 1135 (w), 1074 (w), 1028 (w), 951 (w), 909 (m), 773 (m), 703 (s), 676 (w), 636 (w), 614 (w), 571 (w), 538 (m), 503 (m), 440 (w), 420 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.23 (3H, m), 7.11–7.08 (2H, m), 5.18 (1H, d, *J* = 0.8 Hz), 4.91 (1H, d, *J* = 1.2 Hz), 2.66 (1H, d, *J* = 14.0 Hz), 2.32–2.22 (3H, m), 1.96–1.79 (3H, m), 1.63–1.57 (2H, m), 1.13 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.6, 156.4, 142.2, 129.2, 127.7, 126.9, 115.1, 52.8, 44.2, 40.9, 35.0, 26.7, 22.2; HRMS (EI+): Calcd for $C_{15}H_{19}O$ $[M+H]^+$: 215.1436, Found: 215.1438; Specific Rotation: $[\alpha]_D^{24}$ +32.2 (*c* = 0.980, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

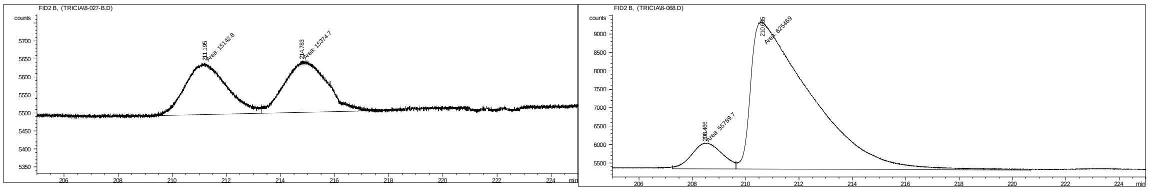
Stereochemistry Proof: Previous reported specific rotation: $[\alpha]_D^{20}$ −35.7 (*concentration not given,* $CHCl_3$) for an enantiomerically enriched sample of 97:3 er of the *R* enantiomer.[2d]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96.6:3.4 er shown; β-dex column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	129.56	82723.2	1424.2	0.9681	48.794	1	129.267	29758.8	511.7	0.9693	3.413
2	132.75	86812.9	1414.3	1.023	51.206	2	132.336	842161.3	13874.3	1.0117	96.587

(*S*)-3-Methyl-3-(1-phenylvinyl)cyclopentanone (4.32): IR (neat): 2959 (w), 2873 (w), 1741 (s), 1627 (w), 1598 (w), 1573 (w), 1492 (w), 1441 (w), 1405 (w), 1375 (w), 1280 (w), 1249 (w), 1231 (w), 1208 (w), 1165 (m), 1120 (w), 1074 (w), 1028 (w), 980 (w), 906 (m), 877 (w), 812 (w), 774 (w), 812 (w), 774 (w), 752 (m), 702 (w), 672 (w), 613 (w), 599 (w), 567 (w), 524 (w), 492 (w), 404 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.30–7.22 (3H, m), 7.14–7.12 (2H, m), 5.16 (1H, d, *J* = 0.8 Hz), 4.94 (1H, d, *J* = 0.8 Hz), 2.48 (1H, d, *J* = 17.2 Hz), 2.30–2.26 (2H, m), 2.19–2.11 (2H, m), 1.87–1.81 (1H, m), 1.23 (3H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 218.6, 156.4, 142.3, 128.7, 128.0, 127.1, 113.7, 51.9, 45.1, 36.6, 34.5, 26.6; HRMS (EI+): Calcd for $C_{14}H_{17}O$ [M+H]$^+$: 201.1279, Found: 201.1285; Specific Rotation: $[\alpha]_D^{24}$ –11.3 (*c* = 0.733, CHCl$_3$) for an enantiomerically enriched sample of 92:8 er. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (91.8:8.2 er shown; β-dex column, 15 psi, 120 °C).



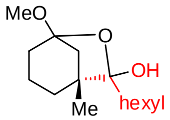
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	211.195	15142.8	145	1.741	49.620	1	208.466	55789.7	702.4	1.3238	8.189
2	214.783	15374.7	143.6	1.7838	50.380	2	210.635	625469.2	3995.4	2.6091	91.81

■ **Representative experimental procedure for the ozonolysis of 1,1-disubstituted olefins:** Ozone was bubbled through a solution of (*S*)-3-methyl-3-(1-phenylvinyl)cyclopentanone (11.5 mg, 0.058 mmol) in CH_2Cl_2 (0.442 mL) and MeOH (0.143 mL) at –78 °C for 30 seconds (until a blue color persisted). Nitrogen was bubbled through the solution until the solution was clear and colorless. Dimethylsulfide (0.0210 mL, 0.288 mmol) was added through a syringe and the solution was allowed to warm to 22 °C and stir for 4 h. The solution was concentrated to afford a clear, colorless oil that was purified by silica gel chromatography (20% Et_2O/hexanes) to afford 11.6 mg of (*S*)-3-benzoyl-3-methylcyclopentanone as a clear oil (0.058 mmol, >98%, yield).

(*S*)-3-Benzoyl-3-methylcyclopentanone (4.33): IR (neat): 2960 (w), 2925 (m), 2875 (m), 2850 (w), 2176 (w), 1672 (s), 1474 (s), 1458 (m), 1405 (m), 1263 (w), 1245 (w), 1228 (w), 1202 (m), 1168 (w), 965 (m), 715 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86–7.83 (2H, m), 7.56–7.52 (1H, m), 7.45–7.43 (2H, m), 2.95 (1H, d, *J* = 18.0 Hz), 2.64–2.57 (1H, m), 2.40–2.34 (3H, m), 2.20–2.13 (1H, m), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 216.9, 204.4, 136.0, 132.5, 128.9, 128.6, 51.9, 50.0, 36.6, 33.7, 25.6; HRMS (ESI^+): Calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1072; Found: 203.1070; Specific Rotation: $[\alpha]_D^{25}$ –22.1 (c = 0.773, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er.

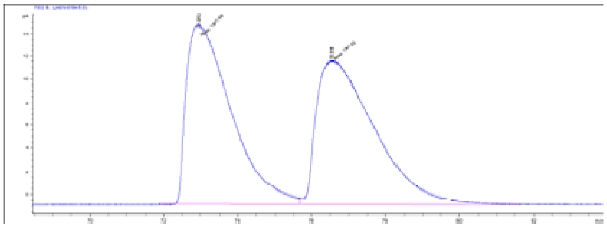
(*R*)-3-Heptanoyl-3-methylcyclohexanone (4.34): *This compound was prepared analogous to the above compound except i-PrOH was used instead of MeOH.* IR (neat): 2955 (m), 2928 (m), 2857 (w), 1702 (s), 1459 (m), 1407 (w), 1377 (w), 1352 (w), 1316 (w), 1293 (w), 1227 (m), 1120 (w), 1059 (w), 996 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.67 (1H, dt, *J* = 14.4, 1.2 Hz), 2.52–2.38 (2H, m), 2.35–2.20 (2H, m), 2.10 (1H, dt, *J* = 14.4, 1.2 Hz), 2.04–1.97 (1H, m), 1.93–1.82 (1H, m), 1.78–1.67 (2H, m), 1.58–1.50 (2H, m), 1.29–1.23 (6H, m), 1.20 (3H, s), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 213.9, 210.0, 52.2, 49.6, 40.5, 36.8, 33.6, 31.8, 29.1, 23.8, 23.6, 22.7, 22.1, 14.3; HRMS (ESI^+): Calcd for $C_{14}H_{25}O_2$ $[M+H]^+$: 225.1855; Found: 225.1861; Specific Rotation: $[\alpha]_D^{25}$ –0.948 (c = 0.633, $CHCl_3$) for an enantiomerically enriched sample of 92:8 er.

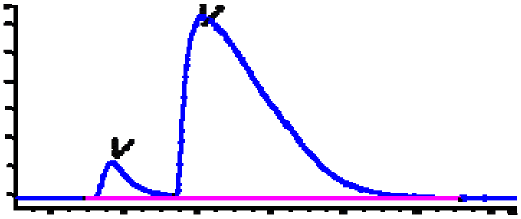
When MeOH is used in the above reaction, there is 20% yield of the compound shown below:



IR (neat): 3414 (br m), 2956 (m), 2927 (s), 2873 (w), 2855 (w), 1702 (w), 1460 (m), 1378 (w), 1352 (m), 1309 (m), 1209 (w), 1173 (s), 1149 (s), 1136 (s), 1101 (m), 1074 (w), 1050 (w), 984 (w), 934 (w), 907 (w), 877 (w), 858 (w), 816 (w), 760 (w), 726 (w), 676 (w), 609 (w), 556 (w), 519 (w), 490 (w), 457 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.29 (3H, s), 2.72 (1H, s), 2.33–2.22 (1H, m), 2.11 (1H, dt, *J* = 14.4, 2.8 Hz), 2.09–2.05 (2H, m), 1.82–1.69 (4H, m), 1.58–1.47 (4H, m), 1.30–1.19 (6H, m), 1.02 (3H, s), 0.88 (3H, t, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.9, 99.8, 77.4, 48.9, 42.9, 41.3, 35.3, 34.8, 31.8, 30.5, 29.4, 25.2, 24.3, 22.8, 21.2, 14.2; Specific Rotation: $[\alpha]_D^{25}$ +74.6 (c = 0.393, $CHCl_3$) for an enantiomerically enriched sample of 92:8 er.

(*R,Z*)-3-Methyl-3-(1-trimethylsilyl)oct-1-enyl)cyclopentanone (Table 4.16, entry 1): IR (neat): 2956 (m), 2925 (m), 2855 (w), 1745 (s), 1597 (w), 1459 (w), 1406 (w), 1375 (w), 1307 (w), 1250 (m), 1174 (w), 1116 (w), 837 (m), 762 (w), 691 (w), 632 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90 (1H, t, *J* = 7.4 Hz), 2.35–2.20 (4H, m), 2.16–2.10 (2H, m), 2.08–2.00 (1H, m), 1.98–1.91 (1H, m), 1.38–1.24 (8H, m), 1.14 (3H, s), 0.88–0.85 (3H, m), 0.20 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.6, 145.7, 140.5, 52.8, 46.8, 36.5, 35.3, 32.1, 31.9, 30.2, 29.2, 27.6, 22.7, 14.2, 3.0; HRMS (ESI^{+}): Calcd for $C_{17}H_{33}OSi$ $[M+H]^{+}$: 281.2301, Found: 281.2306; Specific Rotation: $[\alpha]_D^{20}$ –8.86 (*c* = 0.953, $CHCl_3$) for an enantiomerically enriched sample of 95.5:4.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above): **(*R,E*)-3-Methyl-3-(oct-1-enyl)cyclopentanone (4.22):** IR (neat): 2956 (m), 2925 (s), 2855 (m), 1744 (s), 1459 (w), 1406 (w), 1377 (w), 1251 (w), 1220 (w), 1162 (w), 972 (w), 880 (w), 724 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46–5.30 (2H, m), 2.30–2.21 (2H, m), 2.04–1.90 (3H, m), 1.80–1.73 (1H, m), 1.37–1.20 (10H, m), 1.18 (3H, s), 0.88–0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.6, 137.2, 128.0, 51.7, 41.6, 36.9, 35.8, 32.7, 31.8, 29.6, 28.9, 26.6, 22.7, 14.2; HRMS (ESI+): Calcd for $C_{14}H_{25}O$ $[M+H]^+$: 209.1905, Found: 209.1903. Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.6:6.4 er shown; CDGTA column, 15 psi, 105 °C).

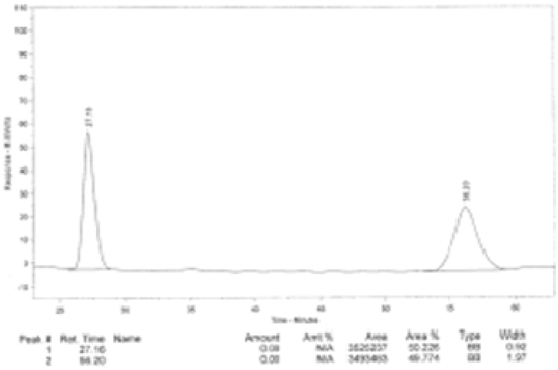


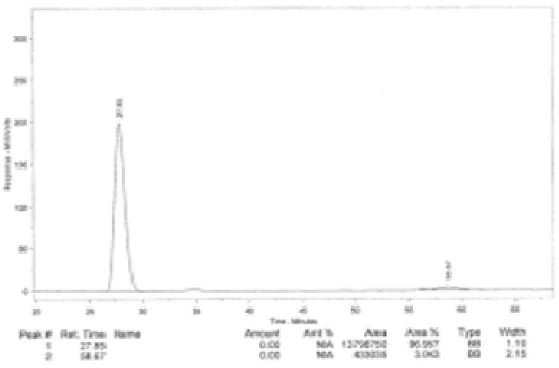


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	73.952	1301.5	15.7	1.3841	49.133	1	73.649	340	6.4	0.8861	6.427
2	76.546	1347.4	12.4	1.8101	50.867	2	76.051	4949.8	32.2	2.5603	93.573

(*R*,*Z*)-3-Phenethyl-3-(1-trimethylsilyl)oct-1-enyl)cyclopentanone (Table 4.16, entry 2): IR (neat): 3063 (w), 3026 (w), 2956 (m), 2925 (m), 2856 (m), 1744 (s), 1599 (w), 1496 (w), 1455 (w), 1405 (w), 1378 (w), 1250 (m), 1165 (w), 838 (m), 758 (w), 699 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28–7.09 (5H, m), 5.90 (1H, t, J = 7.4 Hz), 2,49–2.34 (3H, m), 2.26–1.98 (7H, m), 1.93–1.85 (1H, m), 1.78–1.68 (1H, m), 1.42–1.23 (8H, m), 0.90–0.86 (3H, m), 0.26 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.0, 143.3, 142.6, 142.5, 128.7, 128.4, 126.0, 51.5, 50.9, 41.4, 36.1, 33.7, 32.4, 32.1, 32.0, 30.4, 29.4, 22.8, 14.3, 3.2; HRMS (ESI+): Calcd for $C_{24}H_{39}OSi$ $[M+H]^+$: 371.2770, Found: 371.2784; Specific Rotation: $[\alpha]_D^{20}$ +12.9 (c = 0.980, $CHCl_3$) for an enantiomerically enriched sample of 95.5:4.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above): **(*R*,*E*)-3-(Oct-1-enyl)-3-phenethylcyclopentanone:** IR (neat): 3026 (w), 2955 (m), 2924 (s), 2853 (m),

1743 (s), 1603 (w), 1496 (w), 1456 (m), 1406 (w), 1378 (w), 1272 (w), 1161 (m), 1072 (w), 1030 (w), 974 (w), 748 (w), 699 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.38–7.35 (2H, m), 7.29–7.24 (3H, m), 5.50–5.49 (2H, m), 2.74–2.68 (1H, m), 2.63–2.57 (1H, m), 2.50 (1H, d, *J* = 17.5 Hz), 2.37–2.27 (2H, m), 2.20–2.09 (4H, m), 1.97–1.85 (3H, m), 1.46 (2H, q, *J* = 5.5 Hz), 1.40–1.33 (6H, m), 0.98 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 219.0, 142.5, 134.9, 130.4, 128.6, 128.6, 128.4, 126.0, 49.6, 45.7, 43.5, 36.5, 34.4, 32.9, 31.8, 29.6, 28.9, 22.8, 14.2; HRMS (ESI$^+$): Calcd for $C_{21}H_{34}ON$ $[M+NH_4]^+$: 316.2640, Found: 316.2640. Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (97:3 er shown; OD-C column, 99:1 [hexanes:*i*-PrOH], 0.5 mL/min, 220 nm).

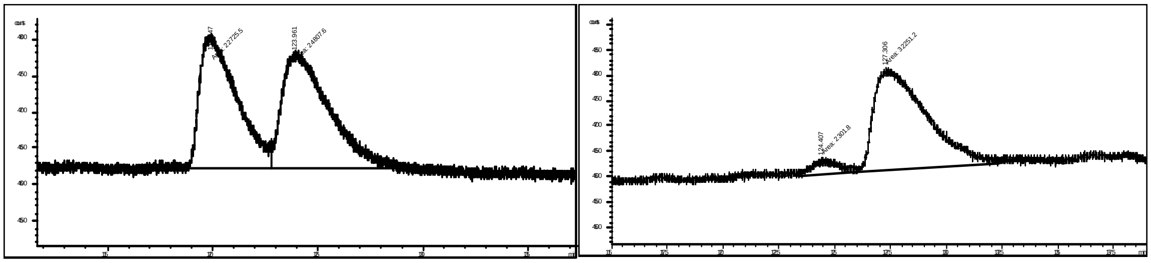




Retention Time	Area	Area %	Retention Time	Area	Area%
27.16	3532537	50.226	27.85	13798750	96.957
56.20	3493463	49.774	58.67	433035	3.043

(*R*,*Z*)-3-Methyl-3-(1-(trimethylsilyl)pent-1-en-1-yl)cyclopentanone (Table 4.16, entry 3): IR (neat): 2956 (m), 2929 (m), 2871 (w), 2162 (w), 1743 (s), 1596 (w), 1457 (w), 1406 (w), 1376 (w), 1250 (s), 1176 (w), 1113 (w), 989 (w), 904 (w), 836 (s), 761 (m), 690 (w), 678 (s), 645 (w), 631 (w), 554 (w), 469 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.90 (1H, dd, *J* = 7.6, 7.6 Hz), 2.33 (1H, d, *J* = 17.2 Hz), 2.25–2.21 (2H, m), 2.16–2.09 (3H, m), 2.03–2.01 (2H, m), 1.37 (2H, q, *J* = 7.6 Hz), 1.14 (3H, s), 0.89 (3H, t, *J* = 7.2 Hz), 0.20 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 219.7, 146.0, 140.3, 52.8, 46.8, 36.5, 35.3, 34.0, 27.6, 23.4, 13.9, 3.0; HRMS (ESI+):

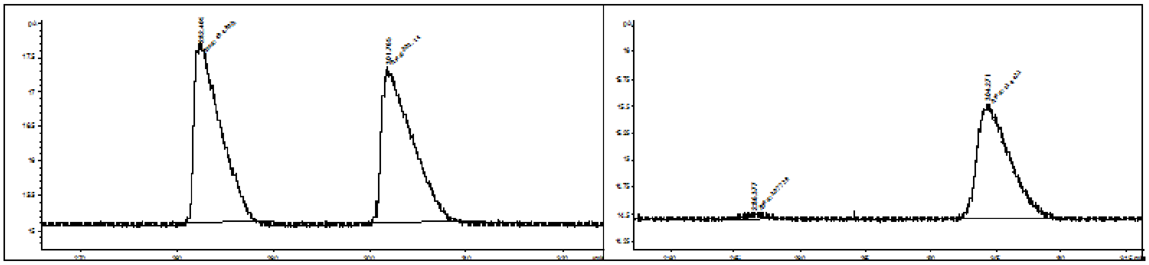
Calcd for $C_{14}H_{27}OSi$ $[M+H]^+$: 239.1831, Found: 239.1823; Specific Rotation: $[\alpha]_D^{20}$ –17.7 (*c* = 1.10, $CHCl_3$) for an enantiomerically enriched sample of 93:7 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure, described above). **(*R,E*)-3-Methyl-3-(pent-1-en-1-yl)cyclopentanone:** IR (neat): 2957 (m), 2927 (m), 2871 (w), 1743 (s), 1457 (w), 1405 (w), 1377 (w), 1259 (w), 1162 (w), 972 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.47 (1H, d, *J* = 15.6 Hz), 5.40–5.33 (1H, m), 2.32–2.25 (2H, m), 2.05 (1H, d, *J* = 17.6 Hz), 2.01–1.91 (4H, m), 1.83–1.78 (1H, m), 1.37 (2H, q, *J* = 7.6 Hz), 1.18 (3H, s), 0.88 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.6, 137.4, 127.7, 51.7, 41.6, 36.9, 35.8, 34.8, 26.7, 22.7, 13.7; HRMS (ESI+): Calcd for $C_{11}H_{19}O$ $[M+H]^+$: 167.1436, Found: 167.1438; Specific Rotation: $[\alpha]_D^{20}$ +38.9 (*c* = 0.146, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (93.3:6.7 er shown; CDGTA column, 15 psi, 70 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	119.947	22725.5	187.5	2.0195	47.810	1	124.407	2301.8	34.7	1.1041	6.662
2	123.961	24807.6	164.7	2.5103	52.190	2	127.306	32251.2	204.4	2.6295	93.338

(*R,Z*)-3-(6-*tert*-Butoxy-1-(trimethylsilyl)hex-1-enyl)-3-methylcyclopentanone (Table 4.16, entry 4): IR (neat): 2972 (m), 2932 (m), 2868 (w), 1744 (s), 1597 (w), 1460 (w), 1406 (w), 1391 (w), 1362 (w), 1251 (m), 1198 (m), 1174 (w), 1083 (m), 1018 (w), 838 (m), 763 (w), 692 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.92 (1H, t, *J* = 7.5 Hz), 3.33

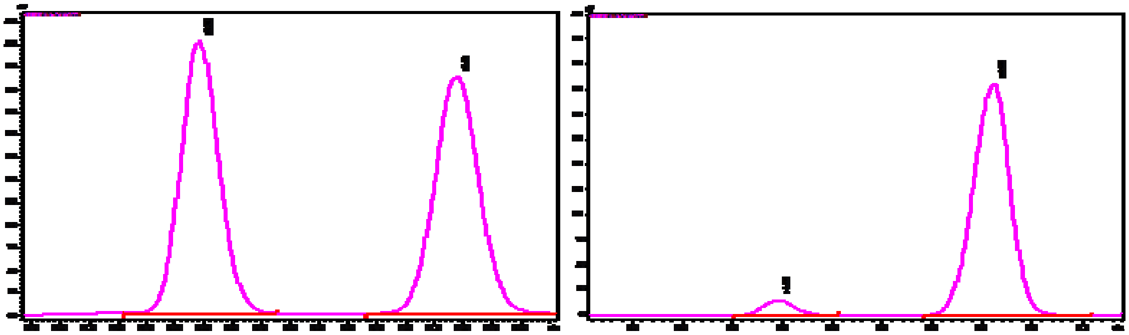
(2H, t, *J* = 6.4 Hz), 2.33 (1H, d, *J* = 17.4 Hz), 2.26–2.14 (5H, m), 2.09–1.92 (2H, m), 1.57–1.50 (2H, m), 1.44–1.37 (2H, m), 1.18 (9H, s), 1.15 (3H, s), 0.22 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.6, 146.0, 140.2, 72.6, 61.6, 52.7, 46.8, 36.4, 35.3, 31.9, 30.6, 27.7, 27.6, 27.0, 3.0; HRMS (ESI$^+$): Calcd for $C_{19}H_{37}O_2Si_1$ $[M+H]^+$: 325.2563, Found: 325.2562; Specific Rotation: $[\alpha]_D^{20}$ –19.0 (*c* = 0.513, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from deprotection of the *t*-butyl ether group (by the same procedure for protodesilylation, except 9.5 equiv of trifluroacetic acid used; 95.8:4.2 er shown; CDB/DM column, 15 psi, 90 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	282.405	495	2.6	3.143	49.590	1	286.377	8.1	6.6E-2	2.041	4.196
2	301.765	503.1	2.3	3.7209	50.410	2	304.271	184.4	1.1	2.8979	95.804

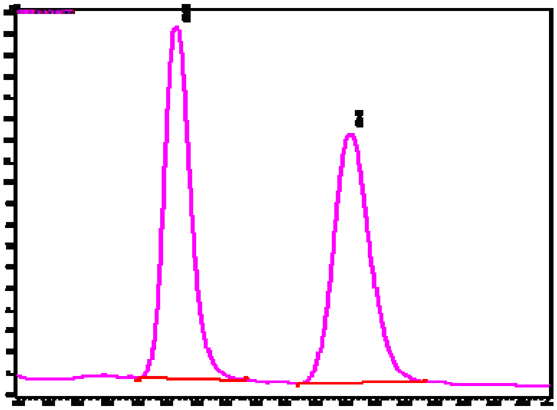
(*R*,*Z*)-3-Methyl-3-(2-phenyl-1-(trimethylsilyl)vinyl)cyclopentanone (Table 4.16, entry 5): IR (neat): 2954 (m), 2895 (w), 1741 (s), 1583 (w), 1490 (w), 1442 (w), 1405 (w), 1375 (w), 1249 (s), 1174 (m), 1096 (w), 1071 (s), 1029 (m), 916 (w), 835 (s), 752 (s), 700 (s), 640 (w), 580 (w), 562 (w), 541 (w), 500 (w), 465 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.24 (4H, m), 7.12 (2H, d, *J* = 7.2 Hz), 2.50 (1H, d, *J* = 17.6 Hz), 2.39–2.33 (3H, m), 2.26–2.12 (2H, m), 1.30 (3H, s), –0.04 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.2, 151.2, 140.9, 140.8, 128.7, 128.0, 127.0, 52.9, 47.4, 36.4, 35.6, 27.7, 3.3; HRMS (ESI$^+$): Calcd for $C_{17}H_{25}OSi$ $[M+H]^+$: 273.1675, Found: 273.1679; Specific Rotation: $[\alpha]_D^{26}$ –36.5 (c = 0.593, $CHCl_3$) for an enantiomerically enriched sample of

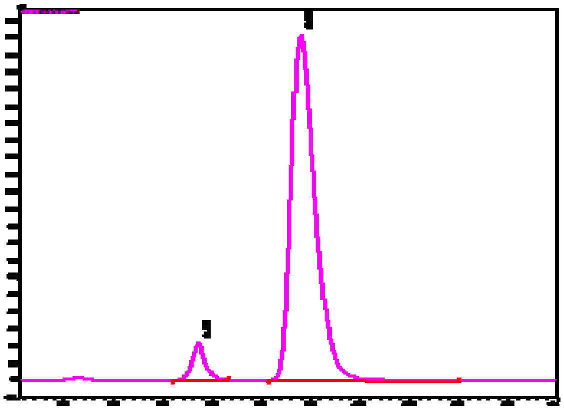
94:6 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (94.8:5.2 er shown; OD-H column, 99% [hexanes:*i*-PrOH], 1.0 mL/min, 254 nm).



#	Time	Area	Height	Area%	#	Time	Area	Height	Area%
1	15.203	702581	30086	49.485	1	14.449	334425	15510	5.199
2	17.441	717211	26312	50.515	2	16.605	6098486	231411	94.801

(*R*,*Z*)-3-(2-(4-Methoxylphenyl)-1-(trimethylsilyl)vinyl)-3-methylcyclopentanone (Table 4.16, entry 6): IR (neat): 2952 (w), 1739 (s), 1608 (m), 1585 (w), 1505 (w), 1463 (w), 1405 (w), 1374 (w), 1282 (w), 1244 (s), 1172 (m), 1123 (w), 1105 (w), 1033 (m), 934 (w), 834 (s), 762 (m), 679 (w), 635 (w), 576 (w), 550 (w), 516 (w), 494 (w), 410 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (1H, s), 7.05–7.02 (2H, m), 6.82 (2H, d, *J* = 8.8 Hz), 3.81 (3H, s), 2.48 (1H, d, *J* = 17.2 Hz), 2.37–2.31 (3H, m), 2.24–2.07 (2H, m), 1.28 (3H, s), –0.3 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz: δ 219.3, 158.7, 150.7, 140.6, 133.1, 129.8, 113.3, 55.4, 53.0, 47.4, 36.4, 35.7, 27.7, 3.4; HRMS (ESI^{+}): Calcd for $C_{18}H_{27}O_2Si$ $[M+H]^+$: 303.1780, Found: 303.1781; Specific Rotation: $[\alpha]_D^{26}$ –32.1 (*c* = 0.807, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (94.2:5.8 er shown; OJ-H column, 99:1 [hexanes:*i*-PrOH], 1.0 mL/min, 254 nm).

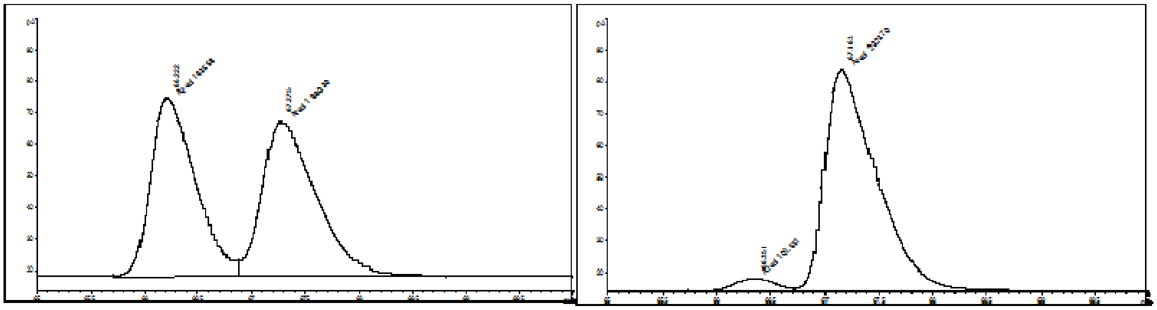




#	Time	Area	Height	Area%	#	Time	Area	Height	Area%
1	22.286	1033504	16706	50.488	1	21.784	1072161	22215	5.849
2	28.149	1013512	11860	48.512	2	26.965	18331165	201825	94.151

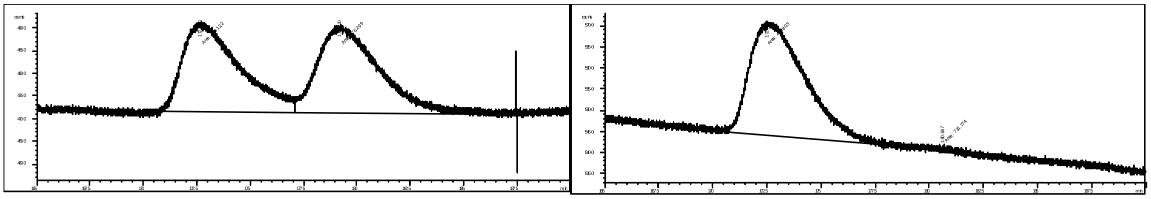
(*R*,*Z*)-3-Methyl-3-(1-(trimethylsilyl)oct-1-en-1-yl)cyclohexanone (Table 4.16, entry 7): IR (neat): 2954 (m), 2924 (m), 2854 (w), 1712 (s), 1456 (w), 1420 (w), 1376 (w), 1314 (w), 1284 (w), 1249 (s), 1225 (m), 883 (w), 834 (s), 762 (m), 725 (w), 690 (w), 676 (w), 646 (w), 533 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.88 (1H, t, *J* = 7.2 Hz), 2.62 (1H, d, *J* = 14.0 Hz), 2.31–2.08 (4H, m), 2.00–1.95 (1H, m), 1.83–1.66 (2H, m), 1.60 (1H, ddd, *J* = 13.2, 9.6, 3.2 Hz), 1.34–1.22 (9H, m), 1.10 (3H, s), 0.88 (3H, t, *J* = 6.8 Hz), 0.23 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 212.3, 145.1, 142.2, 54.3, 46.0, 41.0, 36.3, 32.3, 31.9, 30.1, 29.2, 28.3, 22.7, 22.0, 14.2, 3.5; HRMS (ESI+): Calcd for $C_{18}H_{35}OSi$ [M+H]$^+$: 295.2457, Found: 295.2461; Specific Rotation: $[\alpha]_D^{20}$ +33.1 (*c* = 1.33, CHCl$_3$) for an enantiomerically enriched sample of 96:4 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above): **(*R*,*E*)-3-Methyl-3-(oct-1-en-1-yl)cyclohexanone (4.13):** IR (neat): 2955 (m), 2925 (s), 2854 (m), 1713 (s), 1454 (w), 1423 (m), 1377 (w), 1349 (w), 1314 (w), 1286 (w), 1249 (w), 1225 (w), 1078 (w), 974 (m), 885 (m), 838 (m), 763 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.38–5.25 (2H, m), 2.42 (1H, dt, *J* = 14.0, 1.2 Hz), 2.35–2.17 (1H, m), 2.14 (1H, d, *J* = 14.4 Hz), 1.98 (2H, d, *J* = 6.8 Hz), 1.95 (1H, d, *J* = 6.4

Hz), 1.86–1.79 (1H, m), 1.71–1.59 (2H, m), 1.31–1.23 (9H, m), 1.04 (3H, s), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.8, 137.6, 128.9, 52.5, 41.0, 40.9, 37.3, 32.9, 31.8, 29.6, 28.9, 28.2, 22.8, 22.3, 14.2; HRMS (ESI+): Calcd for $C_{15}H_{27}O$ $[M+H]^+$: 223.2061, Found: 223.2068; Specific Rotation: $[\alpha]_D^{20}$ +15.2 (*c* = 0.253, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis (95.8:4.2 er shown; CDGTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	66.222	1635.6	56.3	0.4844	49.488	1	66.351	101.6	4	0.4204	4.187
2	67.275	1669.4	48.6	0.5722	50.512	2	67.163	2323.8	69.6	0.5568	95.813

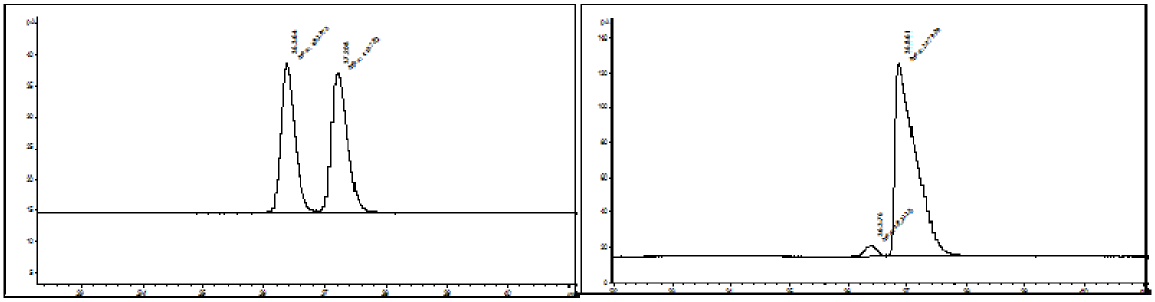
(*R*,*Z*)-3-(Hex-4-en-1-yl)-3-(1-(trimethylsilyl)pent-1-en-1-yl)cyclohexenone (Table 4.16, entry 8): IR (neat): 2955 (m), 2932 (m), 2869 (w), 1710 (s), 1641 (w), 1594 (w), 1460 (m), 1351 (w), 1315 (w), 1282 (s), 1250 (m), 1227 (w), 991 (w), 910 (m), 838 (s), 762 (w), 661 (w), 678 (w), 646 (w), 531 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83–5.70 (2H, m), 5.02–4.92 (2H, m), 2.70 (1H, ddd, *J* = 14.4, 2.0, 2.0 Hz), 2.30–2.25 (1H, m), 2.20–1.92 (6H, m), 1.73–1.58 (4H, m), 1.43–1.13 (6H, m), 0.89 (3H, t, *J* = 7.2 Hz), 0.22 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.2, 144.6, 143.2, 138.9, 114.9, 52.9, 51.9, 49.7, 46.6, 41.2, 40.0, 35.9, 34.3, 31.6, 21.5, 13.9, 3.5; HRMS (ESI+): Calcd for $C_{19}H_{35}OSi$ $[M+H]^+$: 307.2457, Found: 307.2447; Specific Rotation: $[\alpha]_D^{27}$ +50.2 (*c* = 0.860, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above (98.5:1.5 er shown; CDGTA column, 15 psi, 110 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	172.69	35612.2	199.1	2.981	48.623	1	172.49	47680.3	269.7	2.9465	98.488
2	179.22	37629.9	193.5	3.2403	51.377	2	180.667	731.8	18.7	0.6515	1.512

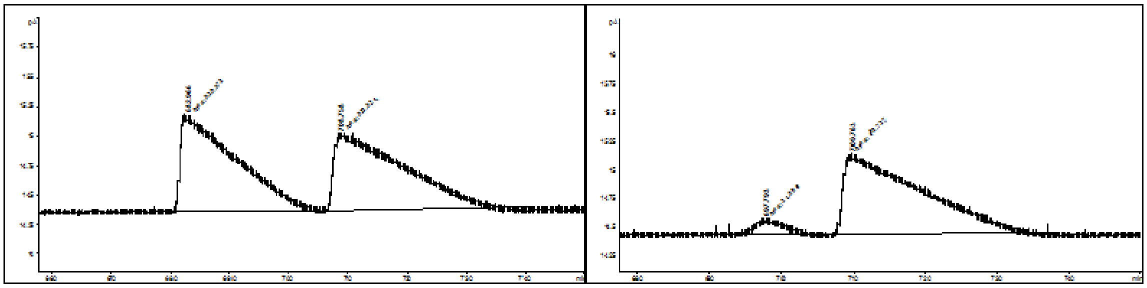
(*R*,*Z*)-3-Methyl-3-(1-(trimethylsilyl)pent-1-en-1-yl)cyclohexanone (Table 4.16, entry 9): IR (neat): 2956 (s), 2931 (m), 2871 (w), 1712 (s), 1595 (w), 1455 (w), 1420 (w), 1377 (w), 1349 (w), 1315 (w), 1284 (w), 1249 (w), 1224 (s), 1077 (w), 909 (w), 837 (s), 763 (w), 691 (w), 676 (w), 676 (w), 647 (w), 531 (w), 482 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.87 (1H, t, *J* = 7.2 Hz), 2.61 (1H, ddd, *J* = 14.4, 1.4, 1.4 Hz), 2.29–2.22 (1H, m), 2.20–2.05 (4H, m), 2.00–1.93 (1H, m), 1.87–1.55 (3H, m), 1.35 (2H, q, *J* = 6.8 Hz, 1.09 (3H, s), 0.87 (3H, t, *J* = 7.2 Hz), 0.21 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 212.3, 145.5, 142.1, 54.4, 46.1, 41.1, 36.3, 34.1, 28.3, 23.3, 22.1, 13.9, 3.6; HRMS (ESI+): Calcd for $C_{15}H_{29}OSi$ [M+H]$^+$: 253.1988, Found: 253.1978; Specific Rotation: $[\alpha]_D^{20}$ +38.6 (*c* = 1.41, CHCl$_3$) for an enantiomerically enriched sample of 97:3 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above): **(*R*,*E*)-3-Methyl-3-(pent-1-en-1-yl)cyclohexanone:** (This compound has been previously reported and spectra data match those described.)^{2b} ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.37–5.25 (2H, m), 2.41 (1H, ddd, *J* = 14.0, 1.6, 1.6 Hz), 2.29–2.07 (3H, m), 1.96 (1H, d, *J* = 6.0 Hz), 1.92 (1H, d, *J* = 7.2 Hz), 1.88–1.78 (2H, m), 1.70–1.63 (1H, m), 1.63–1.54 (1H, m), 1.33 (2H, q, *J* = 7.2 Hz), 1.03 (3H, s), 0.84 (3H, t, *J* = 7.6 Hz); HRMS (ESI+): Calcd for $C_{12}H_{21}O$ [M+H]$^+$: 181.1592, Found: 181.1591; Specific Rotation: $[\alpha]_D^{20}$ +27.0 (*c* = 0.933, CHCl$_3$) for an enantiomerically enriched sample of 95.5:4.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97:3 er shown; CDGTA column, 15 psi, 140 °C).

Proof of Absolute Stereochemistry: Previous reported specific rotation: $[\alpha]_D^{20}$ –30.7 (*c* = 1.1, $CHCl_3$) for an enantiomerically enriched sample of 86.5:13.3 er of the *R* enantiomer.[2b]



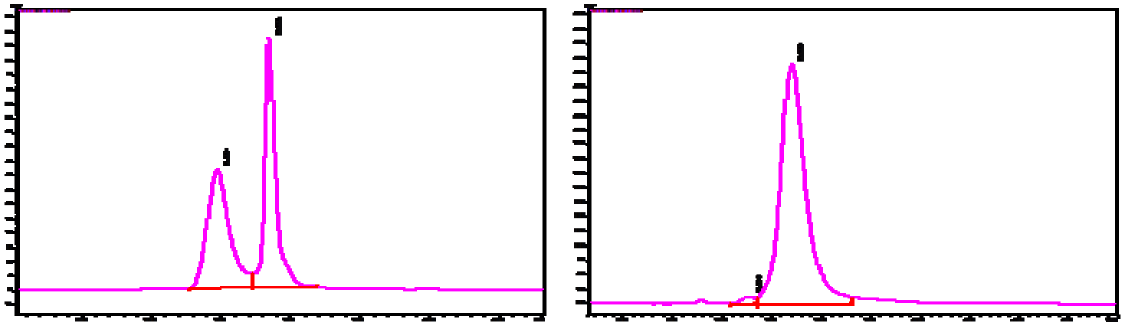
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	36.364	404	24.3	0.2773	49.282	1	36.376	86.3	6.2	0.231	3.122
2	37.208	415.8	22.6	0.3065	50.718	2	36.861	2679.1	110.8	0.4028	96.878

(*R*,*Z*)-3-(6-*tert*-Butoxy-1-(trimethylsilyl)hex-1-enyl)-3-methylcyclohexanone (Table 4.16, entry 10): IR (neat): 2971 (s), 2934 (m), 2866 (w), 1713 (s), 1595 (w), 1454 (w), 1421 (w), 1390 (w), 1362 (m), 1315 (w), 1284 (w), 1250 (m), 1226 (w), 1199 (w), 950 (w), 838 (s), 764 (w), 692 (w), 677 (w), 648 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.88 (1H, t, *J* = 7.4 Hz), 3.32 (2H, t, *J* = 6.6 Hz), 2.62 (1H, d, *J* = 14.1 Hz), 2.30–2.12 (5H, m), 1.99–1.94 (1H, m), 1.85–1.66 (2H, m), 1.64–1.58 (1H, m), 1.55–1.48 (2H, m), 1.43–1.33 (2H, m), 1.18 (9H, s), 1.10 (3H, s), 0.23 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.3, 145.6, 141.9, 72.6, 61.6, 54.3, 46.1, 41.1, 36.3, 32.1, 30.6, 28.1, 27.7, 27.0, 22.1, 3.6; HRMS (ESI^+): Calcd for $C_{20}H_{39}O_2Si$ $[M+H]^+$: 339.2719, Found: 339.2714; Specific Rotation: $[\alpha]_D^{20}$ +27.4 (*c* = 0.440, $CHCl_3$) for an enantiomerically enriched sample of 94:6 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained by deprotection of the *t*-butyl ether group (by the same procedure for protodesilylation except 11 equiv of trifluroacetic acid was used, 94:6 er shown; CDB/DM column, 15 psi, 105 °C).



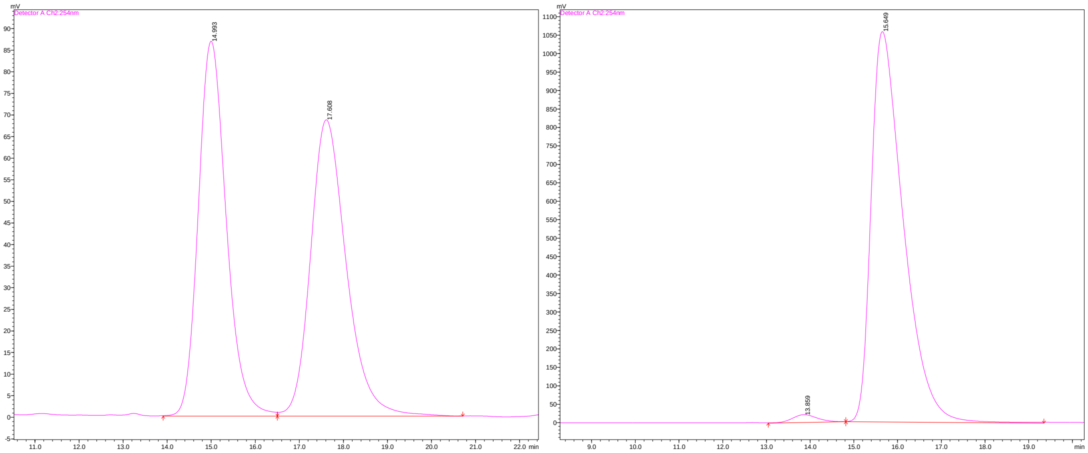
#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	682.966	530.6	8.2E-1	10.809	50.335	1	697.793	31.7	1.3E-1	3.9197	5.975
2	708.758	523.5	6.5E-1	13.4792	49.665	2	709.763	498.7	7.1E-1	11.7623	94.025

(*R*,*Z*)-3-Methyl-3-(2-phenyl-1-(trimethylsilyl)vinyl)cyclohexanone (Table 4.16, entry 11): IR (neat): 2950 (m), 1789 (w), 1712 (s), 1443 (w), 1419 (w), 1314 (w), 1282 (m), 1248 (w), 1225 (w), 1071 (w), 839 (s), 764 (w), 751 (m), 700 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28–7.20 (4H, m), 7.09–7.07 (2H, m), 2.72 (1H, d, *J* = 14.0 Hz), 2.38–2.25 (3H, m), 2.10–2.03 (1H, m), 1.93–1.86 (2H, m), 1.82–1.76 (1H, m), 1.21 (3H, s), –0.05 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 211.9, 150.6, 141.0, 140.6, 128.7, 127.9, 126.8, 54.5, 46.6, 41.1, 36.4, 27.4, 22.2, 4.0; HRMS (ESI$^+$): Calcd for $C_{18}H_{27}OSi$ $[M+H]^+$: 287.1831, Found: 287.1834; Specific Rotation: $[\alpha]_D^{26}$ +46.1 (c = 0.620, CHCl$_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (98.3:1.7 er shown; OJ-H column, 99.5:0.5 [hexanes:*i*-PrOH], 0.5 mL/min, 254 nm).



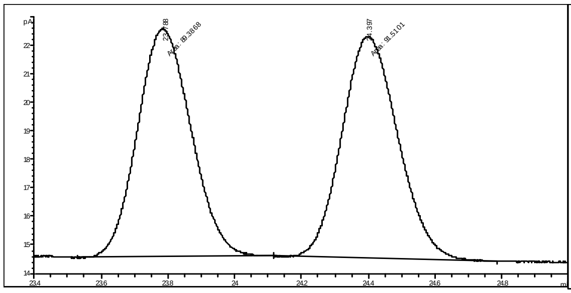
#	Time	Area	Height	Area%	#	Time	Area	Height	Area%
1	22.346	2289380	40976	49.991	1	21.293	64480	1351	1.672
2	24.232	2290213	86453	50.009	2	23.489	3792489	41715	98.328

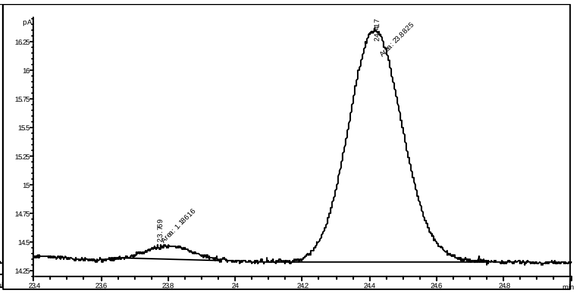
(*R*,*Z*)-3-(2-(4-Methoxyphenyl)-1-(trimethylsilyl)vinyl)-3-methylcyclohexanone (Table 4.16, entry 12): IR (neat): 2951 (m), 1710 (s), 1609 (m), 1505 (s), 1463 (w), 1420 (w), 1314 (w), 1281 (m), 1246 (s), 1173 (w), 1035 (w), 878 (s), 764 (m), 677 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.19 (1H, s), 7.03 (2H, d, *J* = 8.4 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 3.83 (3H, s), 2.75 (1H, d, *J* = 14.4 Hz), 2.41–2.22 (3H, m), 2.12–2.06 (1H, m), 1.96–1.78 (3H, m), 1.24 (3H, s), 0.00 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): 212.0, 158.7, 150.3, 141.4, 133.3, 129.9, 111.3, 55.3, 54.6, 46.6, 41.1, 36.5, 27.5, 22.2, 4.1; HRMS (ESI$^+$): Calcd for $C_{19}H_{29}O_2Si$ $[M+H]^+$: 317.1937, Found: 317.1929; Specific Rotation: $[\alpha]_D^{26}$ +54.2 (*c* = 0.933, CHCl$_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (98.5:1.5 er shown; OJ-H column, 99:1 [hexanes:*i*-PrOH], 1.0 mL/min, 254 nm).



#	Time	Area	Height	Area%	#	Time	Area	Height	Area%
1	14.995	3882570	88862	50.634	1	13.859	847742	21129	1.541
2	17.607	3785308	69369	49.366	2	15.649	54173443	1057630	98.459

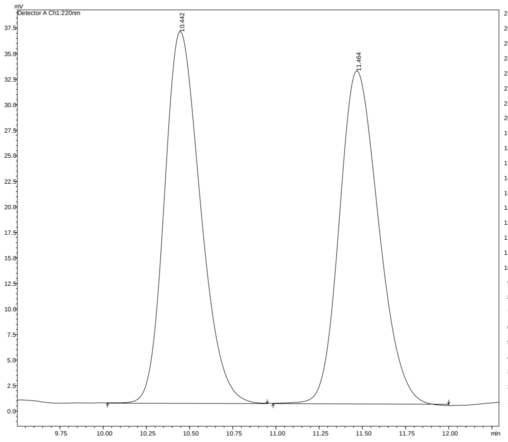
(*R*)-3-1-(*tert*-Butyldimethylsilyl)vinyl)-3-methylcyclohexanone (4.45): IR (neat): 2957 (s), 2931 (s), 2883 (m), 2856 (m), 1713 (s), 1463 (m), 1420 (m), 1389 (w), 1375 (w), 1361 (w), 1348 (w), 1314 (m), 1286 (w), 1252 (w), 1228 (w), 1008 (w), 936 (w), 877 (w), 833 (s), 823 (s), 770 (m), 677 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (1H, s), 5.43 (1H, s), 2.56 (1H, d, J = 13.6 Hz), 2.27–2.23 (2H, m), 2.18 (1H, d, J = 14.0 Hz), 1.89–1.77 (3H, m), 1.68–1.63 (1H, m), 1.08 (3H, s), 0.88 (9H, s), 0.18 (3H, s), 0.15 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.3, 186.9, 126.8, 53.8, 45.4, 41.1, 36.5, 27.7, 27.2, 22.1, 17.6, –1.4, –1.5; HRMS (ESI+): Calcd for $C_{15}H_{29}OSi$ $[M+H]^+$: 253.1988, Found: 253.1992; Specific Rotation: $[\alpha]_D^{30}$ +7.76 (c = 0.687, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95.3:4.7 er shown; β-dex column, 15 psi, 120 °C).

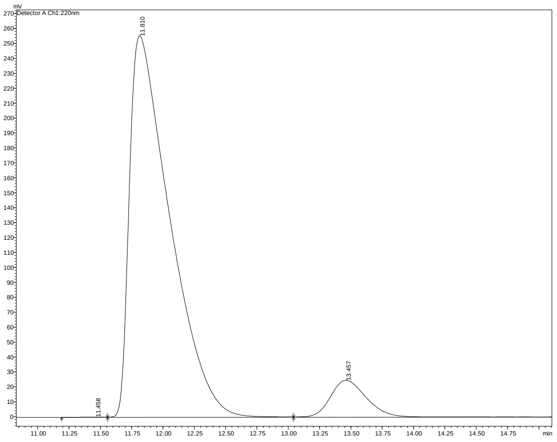




#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	23.788	89.4	8	0.1857	49.498	1	23.769	1.2	1.3E-1	0.1468	4.732
2	24.397	91.5	7.8	0.1952	50.502	2	24.417	23.9	2	0.196	95.268

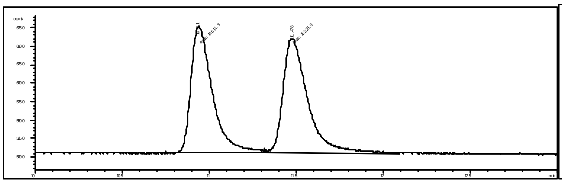
(*R*)-3-1-(*tert*-Butyldimethylsilyl)vinyl)-3-methylcyclopentanone (4.46): IR (neat): 2959 (s), 2929 (m), 2893 (w), 2857 (m), 1744 (s), 1463 (w), 1405 (w), 1254 (m), 928 (w), 834 (m), 823 (s), 770 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.74 (1H, s), 5.42 (1H, s), 2.38 (1H, d, *J* = 17.6 Hz), 2.29–2.24 (2H, m), 2.18 (1H, d, *J* = 18.0 Hz), 2.11–2.03 (1H, m), 1.98–1.92 (1H, m), 1.17 (3H, s), 0.89 (9H, s), 0.15 (3H, s), 0.14 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.4, 156.6, 125.7, 52.4, 46.3, 36.5, 35.2, 27.9, 27.6, 17.5, –2.1, –2.2; HRMS (ESI+): Calcd for $C_{14}H_{27}OSi$ $[M+H]^+$: 239.1831, Found: 239.1839; Specific Rotation: $[\alpha]_D^{27}$ –36.0 (*c* = 0.253, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (94.6:7.4 er shown; OD-H column, 99.9:0.1 [hexanes:*i*-PrOH], 1.0 mL/min, 220 nm).

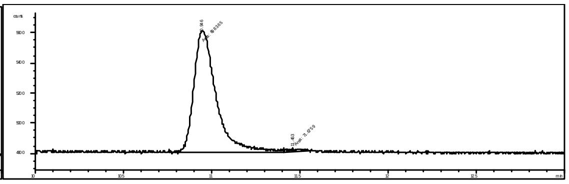




#	Time	Area	Height	Area%	#	Time	Area	Height	Area%
1	10.442	528207	36392	50.615	1	11.810	5749925	2255738	92.637
2	11.464	515364	32613	49.385	2	13.457	456998	24167	7.363

(*R*,*Z*)-2,2,4-Trimethyl-4-(1-(trimethylsilyl)pent-1-en-1-yl)cyclopentanone (4.47): IR (neat): 2958 (m), 2930 (w), 2870 (w), 1739 (s), 1597 (w), 1560 (m), 1413 (w), 1378 (w), 1358 (w), 1308 (s), 1250 (w), 1223 (w), 1176 (w), 1124 (w), 1067 (w), 904 (w), 835 (s), 761 (w), 690 (w), 679 (w), 643 (w), 624 (w), 495 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.56 (1H, dd, *J* = 7.6, 7.6 Hz), 2.67 (1H, d, *J* = 16.8 Hz), 2.27 (1H, d, *J* = 10.0 Hz), 2.16–2.07 (2H, m), 2.01 (1H, d, *J* = 13.2 Hz), 1.91 (1H, d, *J* = 13.2 Hz), 1.36 (2H, q, *J* = 7.2 Hz), 1.16 (3H, s), 1.10 (3H, s), 1.03 (3H, s), 0.89 (3H, t, *J* = 7.6 Hz), 0.21 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 223.5, 146.8, 139.7, 51.7, 51.3, 44.5, 44.0, 34.0, 29.7, 28.2, 27.3, 23.3, 14.0, 3.1; HRMS (ESI+): Calcd for $C_{16}H_{31}OSi$ $[M+H]^+$: 267.2144, Found: 267.2146; Specific Rotation: $[\alpha]_D^{33}$ +2.46 (*c* = 0.620, CHCl$_3$) for an enantiomerically enriched sample of 98:2 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above): **(*R*,*E*)-2,2,4-Trimethyl-4-(pent-1-en-1-yl)cyclopentanone (4.49):** IR (neat): 2958 (m), 2928 (m), 2868 (w), 1739 (s), 1459 (m), 1411 (w), 1379 (m), 1261 (w), 1168 (w), 1114 (w), 1068 (w), 973 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.48 (1H, d, *J* = 15.6 Hz), 5.39–5.32 (1H, m), 2.53 (1H, dd, *J* = 17.2, 1.2 Hz), 2.20 (1H, d, *J* = 17.2 Hz), 2.00–1.92 (3H, m), 1.76 (1H, d, *J* = 13.6 Hz), 1.36 (2H, q, *J* = 7.2 Hz), 1.17 (3H, s), 1.10 (3H, s), 1.07 (3H, s), 0.87 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 223.6, 139.0, 127.3, 52.0, 50.4, 45.2, 38.6, 34.8, 28.8, 27.5, 27.3, 22.7, 13.8; HRMS (ESI+): Calcd for $C_{13}H_{23}O$ [M+H]$^+$: 195.1749, Found: 195.1744; Specific Rotation: $[\alpha]_D^{33}$ +23.0 (*c* = 0.573, CHCl$_3$) for an enantiomerically enriched sample of 99:1 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (99:1 er shown; CDGTA column, 15 psi, 120 °C).



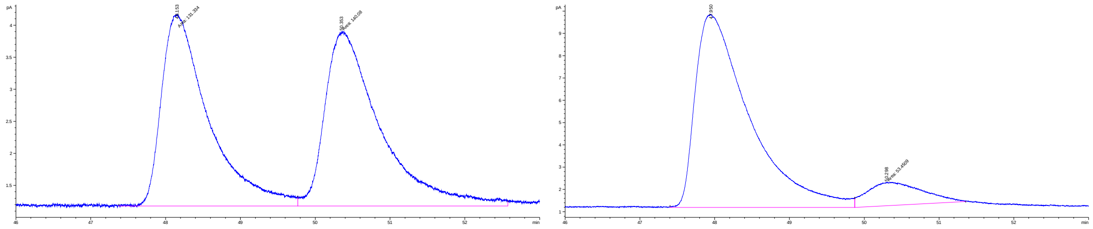


#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	10.941	14611.3	1713.3	0.1421	49.498	1	10.946	6983.6	807.2	0.1442	98.984
2	11.478	15325.9	1546.7	0.1651	50.502	2	11.463	71.7	23.6	0.0506	1.016

(*R*,*Z*)-3-Phenyl-3-(1-trimethylsilyl)oct-1-enyl)cyclopentanone (4.48): IR (neat): 3029 (m), 2956 (s), 2924 (m), 2854 (m), 1745 (s), 1684 (w), 1600 (w), 1462 (w), 1458 (w), 1445 (w), 1405 (w), 1249 (m), 1147 (w), 1033 (w), 837 (s), 761 (m), 700 (m), 467 (w), 456 (w), 424 (w), 404 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.35–7.17 (5H, m), 6.17 (1H, t, *J* = 7.6 Hz), 2.72 (1H, d, *J* = 18.0 Hz), 2.50 (1H, d, *J* = 17.6 Hz), 2.39–2.20 (4H, m), 1.48–1.42 (2H, m), 1.40–1.19 (8H, m), 0.91 (3H, t, *J* = 6.8 Hz), –0.12 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 218.5, 145.6, 143.3, 141.2, 128.4, 126.8, 126.5, 54.1, 52.2, 36.4, 34.4, 32.2, 32.0, 30.3, 28.5, 22.8, 14.2, 1.9; HRMS (ESI+): Calcd for $C_{22}H_{35}OSi$ [M+H]$^+$: 343.2457, Found: 343.2465; Specific Rotation: $[\alpha]_D^{20}$ –10.1 (*c* = 0.445, CHCl$_3$)

for an enantiomerically enriched sample of 89:11 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the protodesilylated product (see protodesilylation procedure above) followed by ozonolysis[47] to furnish a previously reported compound. **(*R*)-Methyl-3-oxo-1-phenylcyclopentanecarboxylate:** IR (neat): 2962 (w), 2924 (m), 2848 (w), 1753 (s), 1734 (s), 1445 (w), 1249 (m), 1212 (m), 1162 (m), 752 (m), 695 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (5H, m), 3.64 (3H, s), 3.23 (1H, dd, J = 16.0, 2.0 Hz), 2.98–2.95 (1H, m), 2.62 (1H, d, J = 18.0 Hz), 2.35–2.32 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 175.0, 141.3, 129.0, 127.8, 126.6, 55.2, 53.1, 48.4, 37.2, 33.0; elemental analysis: Anal Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47, Found C, 71.53; H, 6.68.; Specific Rotation: $[\alpha]_D^{20}$ +3.01 (c = 0.233, $CHCl_3$) for an enantiomerically enriched sample of 89:11 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.)

Proof of Absolute Stereochemistry: Previous reported specific rotation: $[\alpha]_D^{20}$ –7.05 (c = 0.313, $CHCl_3$) for an enantiomerically enriched sample of 91.5:8.5 er for the *R* enantiomer of product.[21] Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (89.1:10.9 er shown; CDGTA column, 15 psi, 140 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	48.153	131.3	3	0.7349	48.389	1	47.950	436.8	8.7	0.8405	89.097
2	50.353	140.1	2.7	0.8584	51.611	2	50.298	53.5	1	0.8535	10.903

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(47) "Oxidative Cleavage of Mono-, Di-, and Trisubstituted Olefins to Methyl Esters through Ozonolysis in Methanolic Sodium Hydroxide," Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.

■ **Representative procedure for the oxidation/rearrangement of vinylsilanes**:[36j] A solution of *m*-chloroperbenzoic acid (0.0180 g, 0.102 mmol) in CH_2Cl_2 (0.291 mL) was added to a stirred solution of vinylsilane **11** (0.020 g, 0.068 mmol) in CH_2Cl_2 (0.235 mL) at 0 °C (ice bath). The clear, colorless solution was allowed to stir for three hours (until disappearance of starting material as viewed by TLC analysis). The reaction was quenched by the addition of a 20% aqueous solution of $NaSO_3H$ (2 mL) and the mixture was diluted with CH_2Cl_2 (2 mL). The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ (2 mL), brine (2 mL), dried over $MgSO_4$, filtered and concentrated to afford a clear, colorless oil that was purified by silica gel chromatography (5% Et_2O/hexanes → 10% Et_2O/hexanes) to afford 20.6 mg of (3*R*)-3-((2*S*)-3-hexyl-2-(trimethylsilyl)oxiran-2-yl)-3-methylcyclohexanone as a clear oil (0.066 mmol, 98% yield, 3:2 mixture of diastereoisomers).

(3*R*)-3-((2*S*)-3-Hexyl-2-(trimethylsilyl)oxiran-2-yl)-3-methylcyclohexanone (4.50): *This data relates to a 3:2 mixture of diastereomers.* IR (neat): 2956 (s), 2928 (s), 2872 (w), 2857 (m), 1712 (s), 1458 (m), 1422 (w), 1378 (w), 1315 (w), 1285 (w), 1251 (w), 1224 (w), 841 (s), 761 (w), 682 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.90 (1H, dd, *J* = 7.6, 4.8 Hz), 2.82 (0.7H, dd, *J* = 7.2, 4.8 Hz), 2.32 (1H, d, *J* = 14.0 Hz), 2.28–2.20 (4H, m), 2.03 (1H, dt, *J* = 14.4, *J* = 1.6 Hz), 1.98–1.90 (1H, m), 1.88–1.79 (4.3H, m), 1.61–1.53 (2.2H, m), 1.52–1.37 (6.2H, m), 1.35–1.20 (11H, m), 1.04 (3H, s), 1.00 (2H, s), 0.86 (4.8H, t, *J* = 6.0 Hz), 0.21 (9H, s), 0.21 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.1, 63.0, 62.5, 60.4, 57.9, 50.0, 49.8, 43.8, 43.6, 41.0, 40.6, 33.8, 32.7, 31.9, 30.1, 29.3, 27.4, 27.3, 24.2, 23.7, 22.7, 21.9, 21.7, 14.2, 2.3; HRMS (ESI^+): Calcd for $C_{18}H_{35}O_2Si$ $[M+H]^+$: 311.2406, Found: 311.2398.

A solution of the epoxide (0.015 g, 0.048 mmol) in formic acid (0.127 mL) was heated under reflux (100 °C) in a sealed vial. After 1 h, the clear, colorless solution was allowed to cool to 22 °C and concentrated under vacuum to afford a clear, colorless oil that was purified by silica gel chromatography (10% Et_2O/hexanes) to afford 8.00 mg of (*R*)-3-methyl-3-octanoylcyclohexanone as a clear oil (0.034 mmol, 70% yield).

(*R*)-3-Methyl-3-octanoylcyclohexanone (4.51): IR (neat): 2926 (w), 2856 (m), 1703 (s), 1459 (m), 1408 (w), 1378 (w), 1358 (w), 1316 (w), 1535 (w), 1226 (w), 1049 (w), 1010 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.69 (1H, dd, *J* = 14.0, 1.2 Hz), 2.52–2.34 (2H, m), 2.36–2.18 (2H, m), 2.11 (1H, dd, *J* = 14.8, 1.2 Hz), 2.05–1.99 (1H, m), 1.94–1.83 (1H, m), 1.79–1.66 (1H, m), 1.56–1.53 (2H, m), 1.30–1.26 (4H, m), 1.31–1.23 (6H, m) 1.21 (3H, s), 0.87 (3H, t, *J* = 5.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 213.5, 210.0, 52.1, 59.5, 40.4, 36.7, 33.5, 31.8, 29.4, 29.3, 23.8, 23.5, 22.8, 22.0, 14.2; HRMS (ESI$^+$): Calcd for $C_{15}H_{27}O_2$ [M+H]$^+$: 239.2011, Found: 239.2020; Specific Rotation: $[\alpha]_D^{28}$ –3.12 (*c* = 0.320, CHCl$_3$) for an enantiomerically enriched sample of 96:4 er.

■ **Representative procedure for the iodination of vinylsilanes:**[36j] To a solution of (*R,Z*)-3-methyl-3-(1-trimethylsilyl)oct-1-enyl)cyclopentanone (20.0 mg, 0.071 mmol) in CH$_3$CN (0.071 mL) at 0 °C (ice bath) was added N-iodosuccinimide (42.0 mg, 0.185 mmol) in one portion. The brown, heterogeneous solution was allowed to warm and stir at 22 °C for 12 h while the solution gradually turned light brown and homogenous. The solution was diluted with Et$_2$O (1 mL) and washed with 10% aqueous Na$_2$S$_2$O$_3$ (2 mL x 3). The organic layers were collected and dried over MgSO$_4$, filtered and concentrated to afford a yellow oil that was purified by silica gel chromatography (10% Et$_2$O/hexanes) to afford 22.5 mg of (*R*, *Z*)-3-(1-iodooct-1-en-1-yl)-3-methylcyclopentanone as a clear oil (0.065 mmol, 91% yield, 10:1 *Z*:*E*).

***(R,Z)*-3-(1-iodooct-1-en-1-yl)-3-methylcyclopentanone (4.53):** IR (neat): 2957 (w), 2925 (m), 2855 (w), 1745 (s), 1460 (w), 1405 (w), 1376 (w), 1251 (w), 1171 (w), 1127 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.51 (1H, t, *J* = 6.8 Hz), 2.60 (1H, d, *J* = 17.6 Hz), 2.36–2.31 (2H, m), 2.30–2.21 (1H, m), 2.19–2.13 (2H, m), 2.00–1.93 (1H, m), 1.43–1.38 (2H, m), 1.32–1.29 (7H, m), 1.28 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 217.2, 133.7, 121.2, 53.0, 49.2, 37.3, 36.8, 36.4, 31.8, 29.0, 28.4, 27.5, 22.7, 14.2; Specific Rotation: $[\alpha]_D^{25}$ –2.15 (*c* = 0.260, CHCl$_3$) for an enantiomerically enriched sample of 94:6 er.

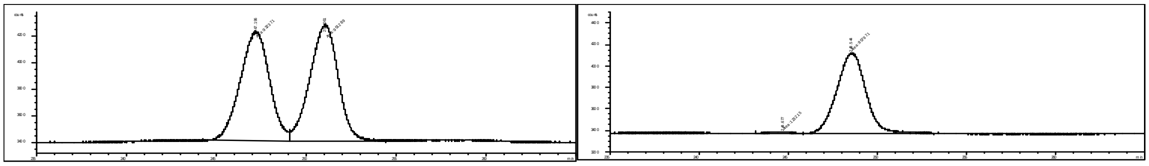
***(R,Z)*-3-(1-iodooct-1-en-1yl)-3-methylcyclohexanone (4.54):** IR (neat): 2955 (m), 2925 (s), 2854 (m), 1714 (s), 1454 (m), 1421 (w), 1376 (w), 1313 (w), 1285 (s), 1226 (w), 932 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84 (1H, d, *J* = 12.0 Hz), 6.19 (1H, d, *J* = 11.6 Hz), 4.64 (1H, s), 1.94 (2H, dd, *J* = 6.4 Hz, 6.4 Hz), 1.79 (3H, s), 1.75 (3H, s), 1.30-1.24 (2H, m), 1.15 (3H, s), 0.99-0.94 (11H, m), 0.70-0.62 (6H, m), 0.23 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.7, 149.1, 136.4, 135.5, 124.6, 114.3, 43.9, 35.6, 30.0, 29.7, 26.8, 19.7, 18.1, 6.9, 5.3, 3.6; HRMS (ESI$^+$): Calcd for $C_{22}H_{43}OSi_2$ [M+H]: 379.2852, Found: 349.1023; Specific Rotation: $[\alpha]_D^{25}$ +36.3 (*c* = 0.773, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

■ Total Synthesis of Riccardiphenol B

Synthesis of Enol Acetate (4.62): An oven-dried 4 dram vial was charged with Ag complex **4.20** (50.0 mg, 46.0 μmol) and $CuCl_2•2H_2O$ (16.0 mg, 92.0 μmol) weighed out under a N_2 atmosphere in a glove box. The vial was sealed with a cap with septum. Tetrahydrofuran (18.4 mL) was added through a syringe to the vial and the resulting blue solution was allowed to stir for five min. The aluminum reagent (3.70 mL, 4.60 mmol, 1.25 M) (CAUTION! Flammable) and 3-methylcyclopentenone 208 μL, 1.84 mmol) were added, sequentially, through a syringe resulting in a brown solution. The mixture was allowed to stir at 0 °C for 15 min before acetic anhydride (868 μL, 9.2 mmol) was added through a syringe. The solution was allowed to warm to 22 °C and stir for 12 h. The reaction was quenched upon addition of a saturated aqueous solution of sodium bicarbonate (30 mL) and passed through a short plug of Celite (3 x 5 in) eluting with Et_2O (20 mL). The layers were separated and the aqueous layer was washed with Et_2O (3 x 30 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated to a yellow oil that was purified by silica gel chromatography (100% hexanes) to afford 378 mg of (*R,Z*)-3-methyl-3-(4-methyl-1-(trimethylsilyl)penta-1,3-dien-1-yl)cyclohex-1-en-1yl acetate as a clear oil (1.23 mmol, 67% yield).

(*R,Z*)-3-Methyl-3-(4-methyl-1-trimethylsilyl)penta-1,3-dien-1-yl)cyclohex-1-en-1-yl acetate (4.62): IR (neat): 2932 (w), 2868 (w), 1751 (s), 1686 (w), 1452 (m), 1362 (w), 1262 (m), 1249 (s), 1210 (w), 1152 (w), 1134 (w), 1112 (w), 1080 (w), 1046 (w), 1007 (w), 983 (w), 967 (w), 918 (w), 900 (w), 834 (s), 760 (m), 689 (w), 679 (w), 660 (w), 612 (w), 602 (w), 541 (w), 487 (w), 458 (w), 438 (w), 416 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.92 (1H, d, *J* = 12.0 Hz), 6.17 (1H, ddd, *J* = 11.6, 0.8 Hz), 5.13 (1H, s), 2.11 (3H, s), 2.08–2.03 (2H, m), 1.78 (6H, s), 1.76–1.24 (4H, m), 1.20 (3H, s), 0.26 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 147.2, 146.9, 137.8, 136.7, 124.3, 124.3, 43.8, 35.1, 28.8, 26.9, 26.8, 21.3, 19.2, 18.0, 3.4; HRMS (ESI+): Calcd for $C_{18}H_{31}O_2Si$ $[M+H]^+$: 307.2093, Found: 307.2101; Specific Rotation: $[\alpha]_D^{24}$ –122 (*c* = 0.833, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.)

(*R*,*Z*)-3-Methyl-3-(4-methyl-1-trimethylsilyl)penta-1,3-dien-1-yl)cyclohexanone (4.60): IR (neat): 2953 (m), 2870 (m), 1710 (s), 1448 (w), 1376 (m), 1315 (w), 1284 (w), 1249 (s), 1224 (m), 1202 (w), 975 (w), 906 (w), 882 (w), 851 (s), 834 (s), 761 (m), 691 (w), 678 (w), 655 (w), 609 (w), 535 (w), 488 (w), 440 (w), 421 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (1H, d, *J* = 11.2 Hz), 6.14 (1H, ddd, *J* = 12.0, 2.8, 1.2 Hz), 2.69 (1H, d, *J* = 14.4 Hz), 2.30–2.00 (4H, m), 1.79 (3H, s), 1.79 (3H, s), 1.74–1.60 (3H, m), 1.15 (3H, s), 0.26 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.2, 145.9, 137.6, 135.9, 123.9, 54.5, 47.0, 41.1, 36.5, 28.6, 26.8, 22.2, 18.0, 3.6; HRMS (ESI+): Calcd for $C_{16}H_{29}OSi$ $[M+H]^+$: 265.1988, Found: 265.1987; Specific Rotation: $[\alpha]_D^{33}$ +13.7 (*c* = 1.14, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.) Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (98.5:1.5 er shown; β-dex column, 15 psi, 120 °C).



#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
1	247.196	93237.1	822.2	1.89	49.498	1	244.677	1232.2	17.4	1.1827	1.416
2	251.061	95128.9	879	1.8037	50.502	2	248.544	85797.1	756.1	1.8911	98.584

Silyl Enol Ether (4.61): IR (neat): 2953 (m), 2932 (m) 2876 (m), 1657 (m), 1455 (w), 1361 (w), 1263 (w), 1248 (w) 1198 (w), 1187 (m), 1116 (s), 1086 (w), 1054 (w), 1004 (w), 971 (w), 914 (w), 891 (w), 835 (s), 792 (m), 758 (s), 730 (w), 677 (w), 612 (w), 470 (w), 443 (w), 417 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.84 (1H, d, *J* = 12.0 Hz), 6.19 (1H, d, *J* = 11.6 Hz), 4.64 (1H, s), 1.94 (2H, dd, *J* = 6.4, 6.4 Hz), 1.79 (3H, s), 1.75 (3H, s), 1.30–1.24 (2H, m), 1.15 (3H, s), 0.99–0.94 (11H, m), 0.70–0.62 (6H, m), 0.23 (9H, s). ^{13}C NMR ($CDCl_3$,100 MH): δ 149.7, 149.1, 136.4, 135.5, 124.6, 114.3, 43.9, 35.6, 30.0, 29.7, 26.8, 19.7, 18.1, 6.9, 5.3, 3.6. HRMS (EI+): Calcd for $C_{22}H_{43}OSi_2$ $[M+H]^+$: 379.2852. Found: 379.2860; Specific Rotation: $[\alpha]_D^{33}$ +19.1 (*c* = 0.820, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.)

(2*S*,3*R*)-2-Benzyl-3-methyl-3-((*Z*)-4-methyl-1-(trimethylsilyl)penta-1,3-dien-1-yl)cyclohexanone (4.66): IR (neat): 3085 (w), 3061 (w), 3028 (s), 2950 (s), 2923 (s), 2862 (m), 1701 (s), 1638 (w), 1602 (w), 1555 (w), 1495 (w), 1453 (m), 1376 (m), 1317 (w), 1283 (w), 1251 (s), 1185 (w), 1153 (w), 1097 (w), 1075 (w), 1031 (w), 974 (w), 852 (s), 838 (s), 754 (m), 744 (m), 701 (s), 663 (w), 612 (w), 556 (w), 495 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz,): δ 7.29–6.97 (5H, m), 6.52 (1H, d, *J* = 11.5 Hz), 5.85 (1H, d, *J* = 11.5 Hz), 3.21 (1H, d, *J* = 13.5 Hz), 2.96 (1H, d, *J* = 13.5 Hz), 2.82 (1H, d, *J* = 13.5 Hz), 2.78 (1H, dd, *J* = 15.0, 2.0 Hz), 2.40 (3H, dd, *J* = 19.0, 17.5 Hz), 2.04–2.01 (1H, m), 1.87–1.81 (1H, m), 1.78 (3H, s), 1.76 (3H, s), 1.52–1.50 (2H, m), 1.03 (3H, s), 0.94 (9H, s);. HRMS (EI+): Calcd for $C_{23}H_{35}OSi$ $[M+H]^+$: 355.2457, Found: 355.2465; Specific Rotation: $[\alpha]_D^{33}$ +37.2 (*c* = 0.900, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *S* enantiomer of product prepared through the use of the *R* enantiomer of ligand.)

Preparation of *o*-quinone methide precursor.[44] ***tert*-Butyl-(2-formyl-4-methoxyphenyl)carbonate (4.68):** To a flame-dried round bottom flask was added 2-hydroxy-5-methoxybenzaldehyde (**4.67**, 3.00 g, 19.7 mmol), Boc_2O (4.73 g, 21.7 mmol) and thf (19.7 mL). The yellow solution was allowed to stir at 22 °C for 5 min before the addition of dimethylaminopyridine (dmap, 0.398 g, 3.25 mmol). After 12 h, the solution was concentrated under reduced pressure to provide a yellow oil that was purified by silica gel chromatography (10% Et_2O/hexanes) to afford 4.97 g of *t*-butyl (2-formyl-4-methoxylphenyl)carbonate as a white solid (19.7 mmol, >98% yield). IR (neat): 2990 (w), 2939 (w), 2862 (w), 1756 (s), 1693 (w), 1605 (w), 1585 (w), 1492 (s), 1462 (w), 1426 (w), 1395 (w), 1371 (w), 1323 (w), 1269 (w), 1256 (w), 1202 (m), 1138 (s), 1033 (m), 1012 (w), 936 (m), 885 (w), 818 (w), 771 (m), 755 (m), 733 (m), 706 (w), 632 (w), 576 (w), 454 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 10.20 (1H, s), 7.34 (1H, d, $J = 2.8$ Hz), 7.17–7.15 (2H, m), 3.84 (3H, s), 1.56 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.4, 157.7, 151.9, 146.4, 128.7, 124.3, 122.3, 112.5, 84.5, 56.0, 27.8; HRMS (ESI+): Calcd for $C_{13}H_{17}O_5$ $[M+H]^+$: 253.1076, Found: 253.1069.

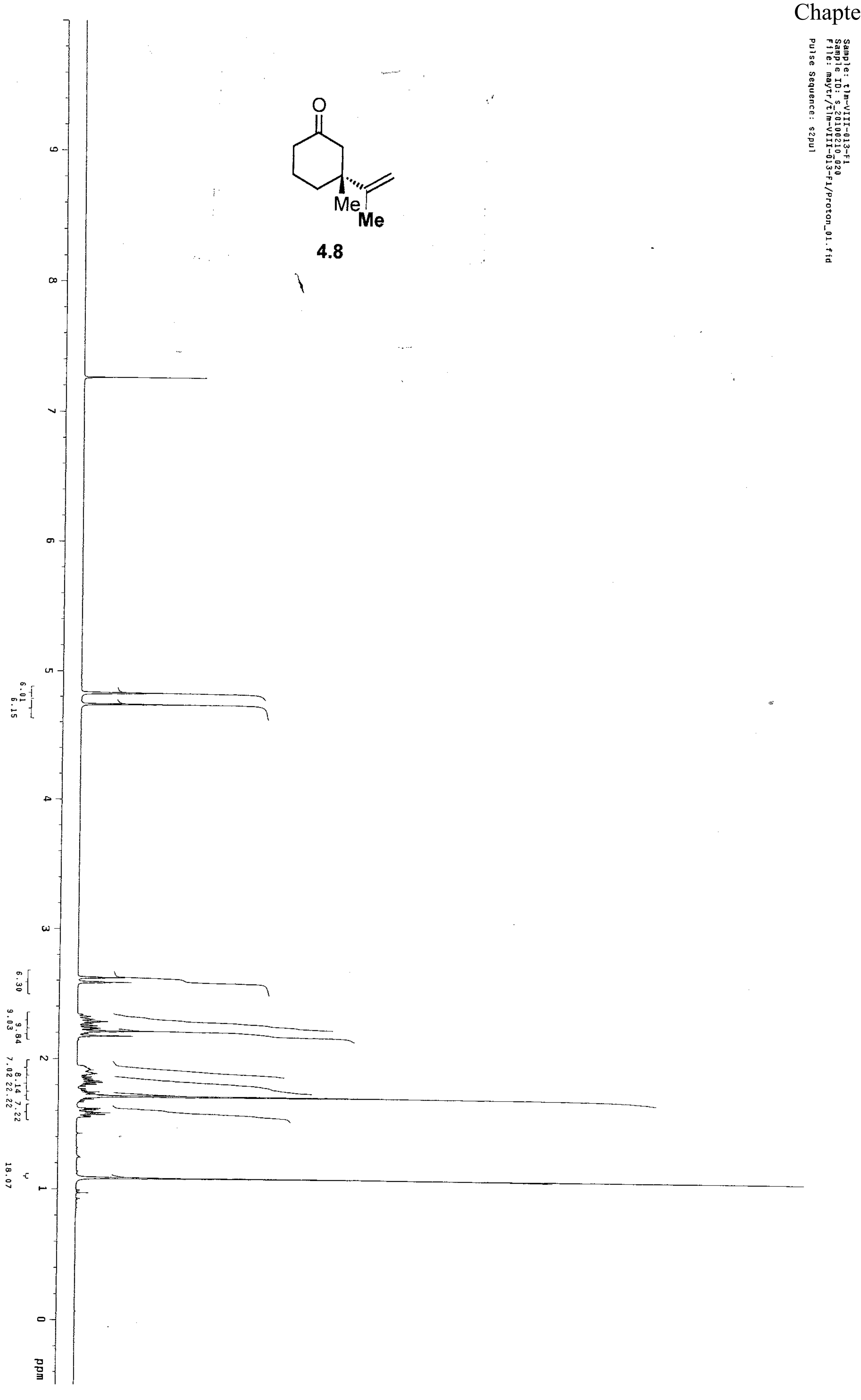
***tert*-Butyl-(2-(hydroxymethyl)-4-methoxyphenyl)carbonate (4.69):** To a flame-dried round bottom flask under N_2 was added *tert*-butyl (2-formyl-4-methoxyphenyl) carbonate (**4.68**, 5.04 g, 20.2 mmol) in thf (34 mL) and H_2O (34 mL). The solution was allowed to cool to 0 °C and $NaBH_4$ (0.812 g, 21.6 mmol) was added in one portion; the clear and colorless solution effervesces. The reaction was quenched after 1 min with 3.0 M HCl (30 mL). The aqueous layer was washed with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (2 x 30 mL), brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated to provide a yellow oil that was purified by silica gel column chromotagraphy (10% Et_2O in hexanes) to afford the titled compound as a white solid (3.15 g, 12.4 mmol, 62% yield). IR (neat): 3430 (br m), 2980 (w), 2937 (w), 1753 (s), 1610 (w), 1592 (w), 1497 (m), 1460 (w), 1431 (w), 1395 (m), 1370 (w), 1273 (s), 1257 (s), 1201 (w), 1142 (s), 1034 (m), 930 (w), 886 (m), 810 (w), 784 (w), 751 (w), 711 (w), 576 (w), 464 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.05–7.00 (2H, m), 6.83 (1H, dd, $J = 9.2, 3.2$ Hz), 4.63–4.55 (2H, m), 3.80 (3H, s), 1.55 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 152.9, 142.4, 134.0, 122.9, 114.4, 114.3, 84.0, 60.7, 55.8, 27.8; HRMS (ESI+): Calcd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1232, Found: 255.1228.

Synthesis of Tertiary Alcohol (4.72): An oven-dried vial was charged with enol acetate **4.61** (20.0 mg, 0.065 mmol) and thf (650 μL). The solution was allowed to cool to 0 °C before the addition of *n*-BuLi (83.0 μL, 0.131 mmol, 1.58 M). The yellow mixture was allowed to warm to 22 °C and stir for 1.5 h. A separate oven-dried vial was charged with *tert*-butyl (2-(hydroxymethyl)-4-methoxyphenyl) carbonate (82.0 mg, 0.352 mmol) and thf (704 μL) and was allowed to cool to −78 °C. Freshly prepared *t*-butylmagnesium chloride (0.477 mL, 0.357 mmol, 0.748 M) was added dropwise (the solution goes from clear and colorless to yellow). The lithium enolate was cannula transferred to the vial containing the in situ generated *o*-quinone methide at −78 °C. The yellow solution was allowed to warm to 22 °C and stir for 1 h. After 1 h, the yellow solution was cannula transferred to another five equiv of the *o*-quinone methide at −78 °C. The solution was allowed to warm to 22 °C and stir. After 12 h, the reaction was quenched by the addition of H_2O (10 mL) and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yellow oil before purification by silica gel chromatography (10% Et_2O/hexanes) to afford the desired product and an inseparable impurity. The material was taken forward without further purification. An oven-dried vial was charged with alkylated product (26.9 mg, 0.067 mmol) and thf (670 μL) was allowed to cool to 0 °C. Methyllithium (149 μL, 0.336 mmol, 2.24 M) was added dropwise and the solution was allowed to warm to 22 °C and stir. After 3 h, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (2 mL). The aqueous layer was washed with Et_2O (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a yellow oil that was purified by silica gel chromatography (10% Et_2O/hexanes → 15% Et_2O/hexanes) to afford 19.0 mg of 2-((6*R*-)-2-hydroxy-2,6-dimethyl-6-((*Z*)-4-methyl-1-(trimethylsilyl)penta-1,3-dienyl-1-yl)cyclohexyl)methyl-4-methoxyphenol as a white solid (0.0478 mmol, 70% yield). IR (neat): 3355 (br s), 2953 (s), 2928 (s), 2869 (m), 1701 (w), 1609 (w), 1499 (s), 1464 (m), 1433 (m), 1378 (m), 1203 (m), 1151 (s), 1108 (s), 1042 (w), 979 (s), 806 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.89–6.82 (1H, m), 6.73 (1H, d, *J* = 8.4 Hz), 6.34–6.59 (2H, m), 6.25 (1H, br d, *J* = 11.2 Hz), 2.91–2.84 (1H, br m), 2.91–2.84 (1H, m), 2.43 (1H, d, *J* = 14.4 Hz), 2.11–1.94 (1H, m), 1.82 (3H, s), 1.79 (3H, s), 1.74–1.57 (4H, m), 1.31–1.23 (7H, m), 0.87 (3H, brs), 0.38 (9H, br s); ^{13}C NMR (CDCl$_3$, 100 MHz) (data collected as a 3:2 mixture of diastereomers): δ 153.8, 149.4, 148.6, 136.2, 135.2, 131.2, 124.8, 117.3, 116.9, 115.7, 114.7, 112.9, 111.6, 73.9, 73.1, 55.8, 52.7, 52.2, 49.8, 46.0, 43.3, 43.0, 42.9, 39.6, 39.1, 37.8, 33.0, 32.6, 31.7, 30.5, 29.8, 29.3, 27.2, 26.9, 26.2, 26.0, 25.9, 25.9, 25.8, 24.1, 23.7, 21.7, 21.2, 18.2, 18.0, 17.8, 14.3, 4.3; HRMS (ESI+): Calcd for $C_{25}H_{40}O_3NaSi$ [M+Na]$^+$: 439.2644, Found: 439.2649.

Synthesis of Tetrasubstituted Olefin (4.73):[42] A flame-dried vial was charged with the tertiary alcohol (9.1 mg, 0.02 mmol) and freshly distilled pyridine (81 μL). The clear and colorless solution was allowed to cool to 0 °C. Thionyl chloride (1.6 μL, 0.22 mmol) was added and the yellow solution was allowed to warm to 22 °C for 1 h. After 1 h, Et$_2$O (1 mL) and H$_2$O (1 mL) were added and the aqueous layer was washed with Et$_2$O (3 x 2 mL). The combined organic layers were washed with 1.0 M HCl (3 x 2 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated to yield yellow oil that was purified by silica gel chromatography (10% Et$_2$O/hexanes) to afford 5.3 mg of **4.73** as a clear and colorless oil (0.0020 mmol, 61% yield). IR (neat): 3390 (br w), 2956 (m), 2923 (s), 2853 (m), 1727 (w), 1665 (w), 1604 (w), 1506 (w), 1463 (w), 1433 (w), 1376 (w), 1260 (s), 1202 (w), 1174 (w), 1092 (m), 1019 (s), 852 (w), 798 (s), 760 (w), 690 (w), 570 (w), 515 (w), 482 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.75–6.56 (4H, m), 6.17 (1H, d, *J* = 12.0 Hz), 5.36 (1H, brd, *J* = 32.8 Hz), 3.76 (3H, s), 2.88–2.81 (1H, m), 2.63–2.49 (1H, m), 2.18–1.96 (3H, m), 1.79 (3H, s), 1.73 (3H, s), 1.44 (3H, s), 1.39 (3H, s), 1.26–1.06 (3H, m), 0.28 (9H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 153.9, 148.1, 146.5, 138.3, 135.4, 133.3, 130.0, 124.6, 122.2, 116.6, 116.5, 112.1, 55.8, 47.2, 44.8, 32.9, 30.4, 29.9, 26.8, 24.3, 24.1, 18.0, 4.1; HRMS (ESI+): Calcd for $C_{25}H_{39}O_2Si$ [M+H]$^+$: 399.2719, Found: 399.2732; Specific Rotation: $[\alpha]_D^{25}$ +6.66 (*c* = 0.120, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er.

Protodesilylation: A flame-dried vial equipped with a stir bar was charged with tetrabutylammonium fluoride (61.0 mg, 0.193 mmol) in a N_2 filled glovebox. The vial was sealed with a septum cap and removed from the glovebox. A solution of **4.73** (7.70 mg, 0.0193 mmol) in DMSO (0.193 mL) was added and the clear, colorless solution was heated to 110 °C for 6 h, at which time the solution turned dark brown. The solution was allowed to cool to 22 °C and water (2 mL) and EtOAc (2 mL) were added. The layers were separated and the aqueous layer was washed with EtOAc (2 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a light brown oil that was purified by silica gel chromatography (10% Et_2O/hexanes) to afford 4.00 mg of riccardiphenol B as a clear and colorless oil (0.012 mmol, 62% yield).

Riccardiphenol B: IR (neat): 3432 (br w), 3364 (br w), 3216 (br w), 2956 (m), 2922 (s), 2853 (w), 1709 (w), 1664 (w), 1606 (w), 1507 (w), 1458 (m), 1450 (m), 1430 (m), 1376 (w), 1258 (w), 1202 (m), 1152 (m), 1090 (w), 1039 (s), 1016 (s), 798 (s), 758 (m) cm^{-1}; (We have found that NMR peaks of this compound can be concentration dependent and can shift +/– 0.2 ppm.) ^1H NMR ($CDCl_3$, 400 MHz): δ 6.72–6.59 (3H, m), 6.18 (1H, dd, *J* = 15.6, 10.8 Hz), 5.74 (1H, brd, *J* = 12.8 Hz), 5.54 (1H, d, *J* = 15.2 Hz), 5.32 (1H, br d, *J* = 23.2 Hz), 4.68 (1H, brs), 3.73 (3H, s), 3.39 (1H, d, *J* = 17.6 Hz), 3.30 (1H, d, *J* = 17.6 Hz), 2.15–1.89 (6H, m), 1.72 (3H, s), 1.70 (3H, s), 1.55 (3H, s) 1.09 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 147.9, 140.5, 133.3, 132.6, 131.0, 128.2, 12534, 124.6, 115.6, 115.5, 110.8, 55.7, 41.8, 38.9, 32.6, 29.7, 25.9, 25.3, 21.0, 18.5, 18.4; HRMS (ESI+): Calcd for $C_{22}H_{31}O_2$ $[M+H]^+$: 327.2324, Found: 327.2340; Specific Rotation: $[\alpha]_D^{24}$ –5.45 (*c* = 0.222, $CHCl_3$) for an enantiomerically enriched sample of 98.5:1.5 er. (Rotation was measured with the *R* enantiomer of product prepared through the use of the *R* enantiomer of ligand.)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9
8
7
6
5
4
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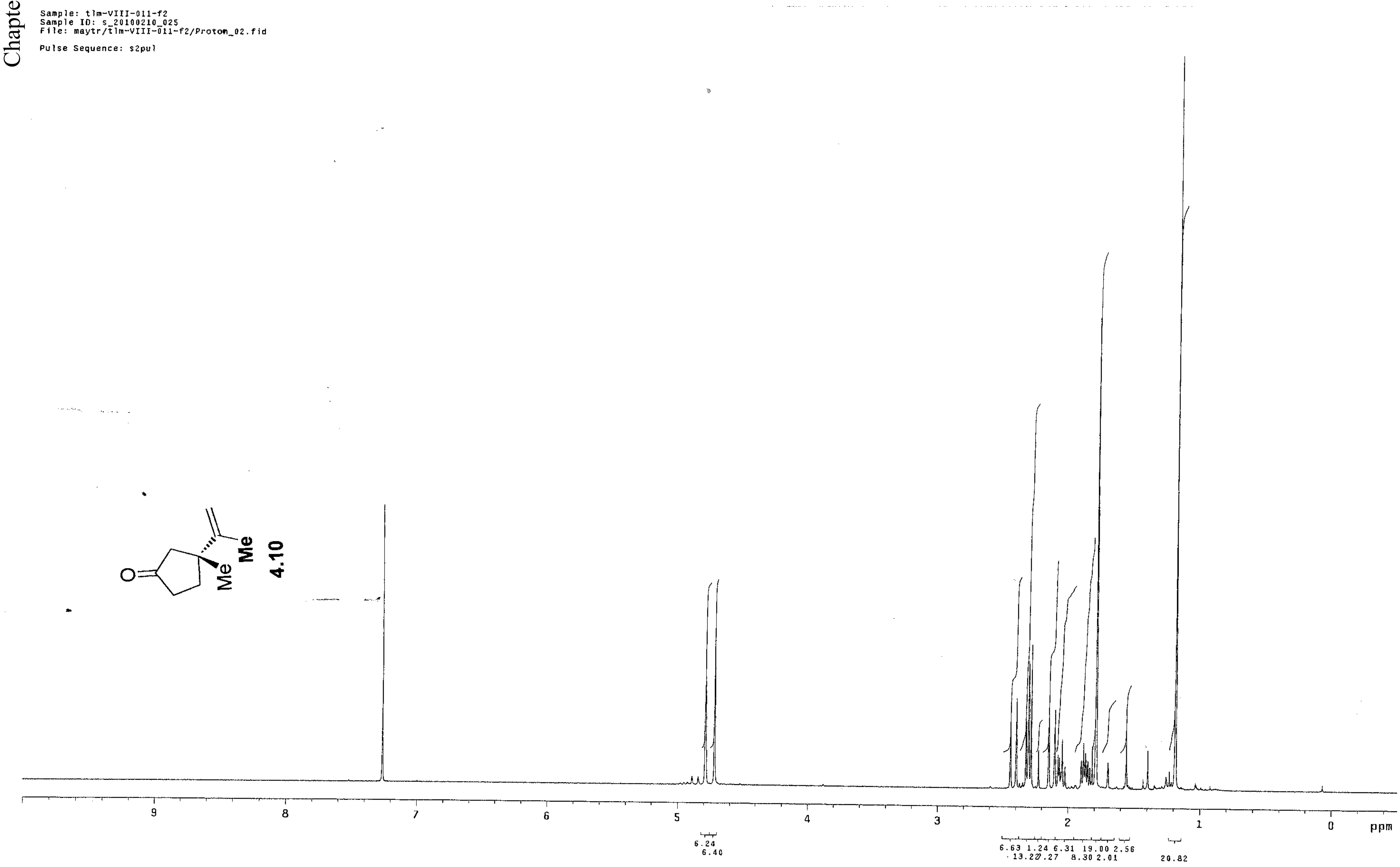
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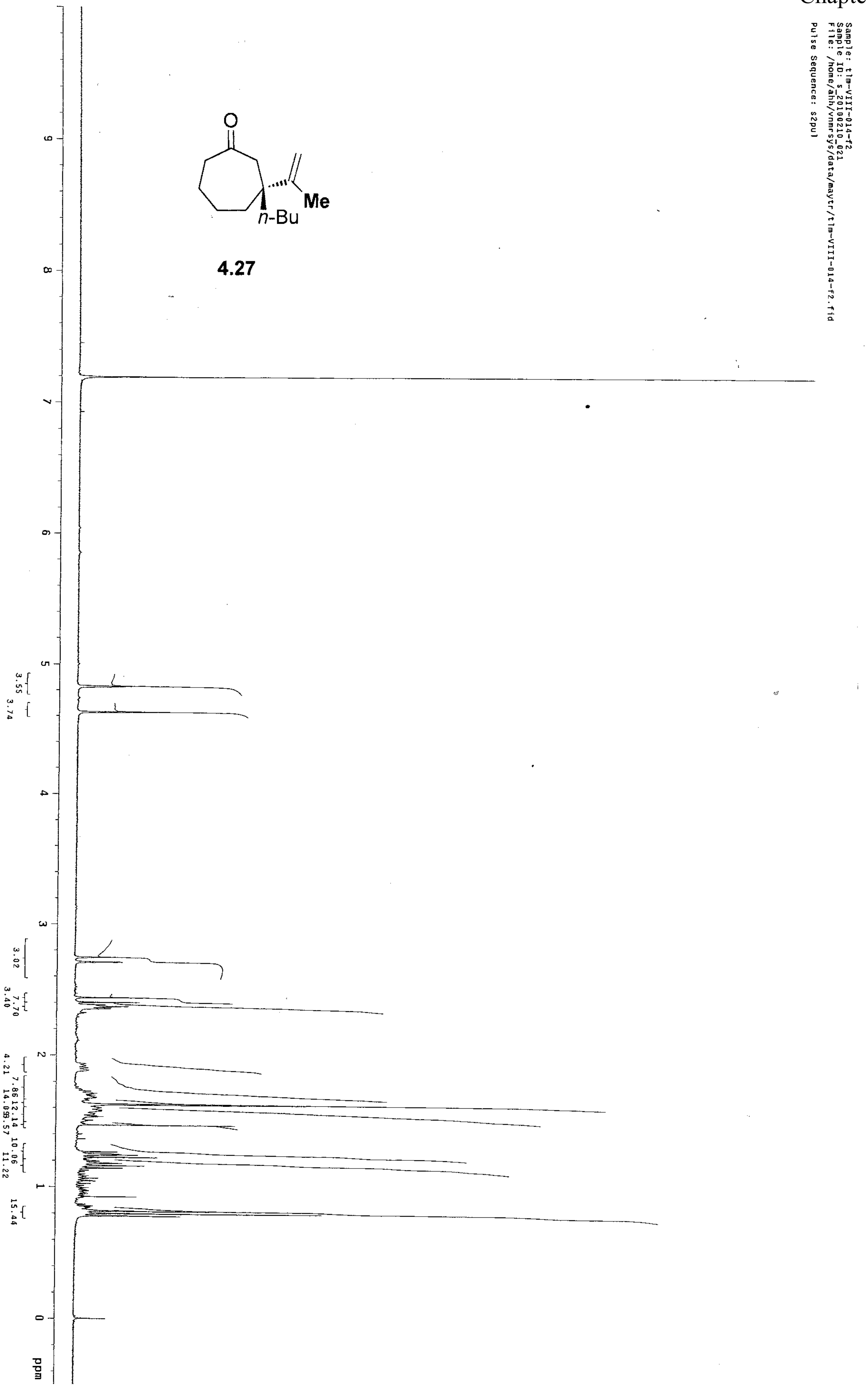
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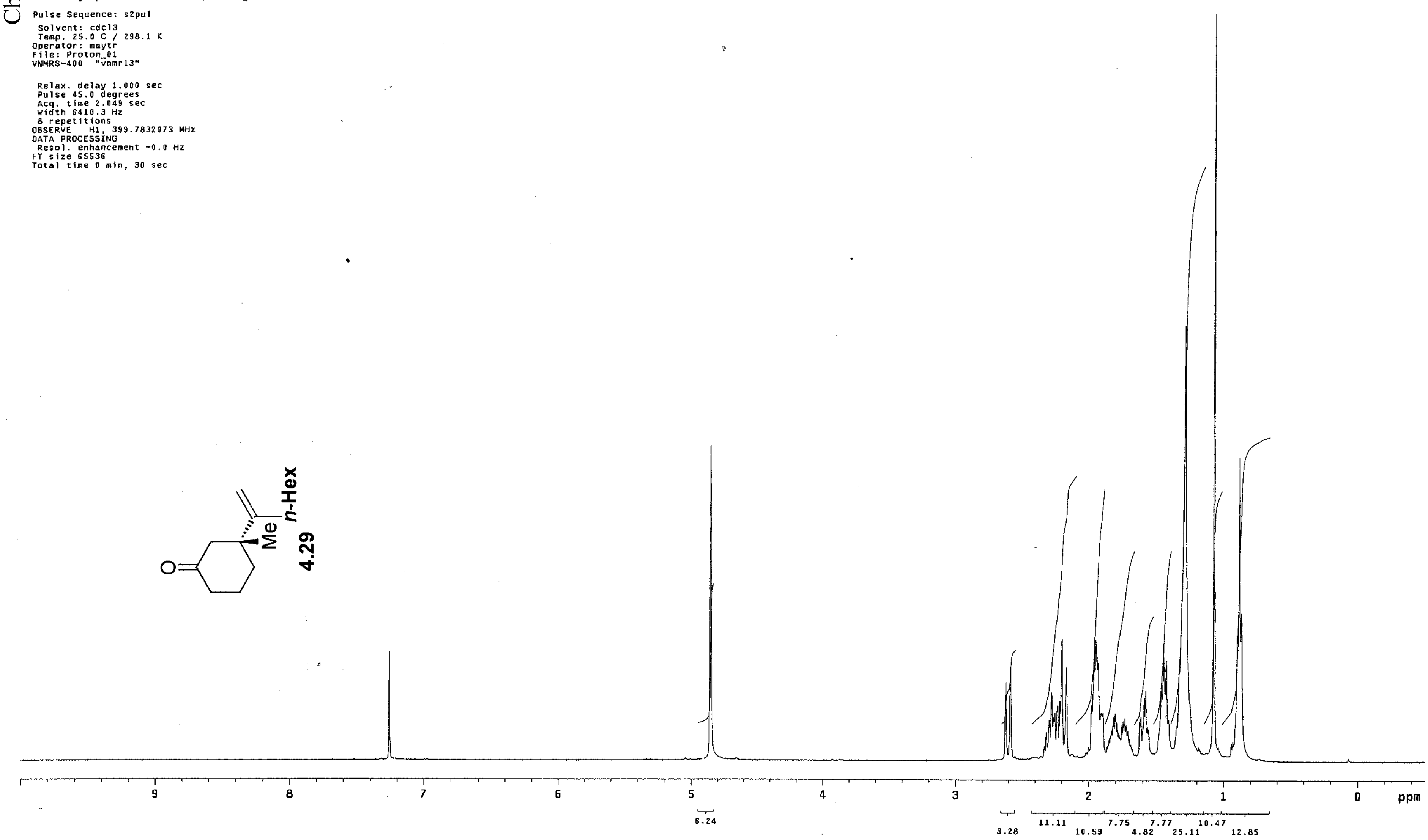
11.22
15.44

4.27



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File: Proton_01
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FT size 65536
Total time 0 min, 30 sec
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4.29

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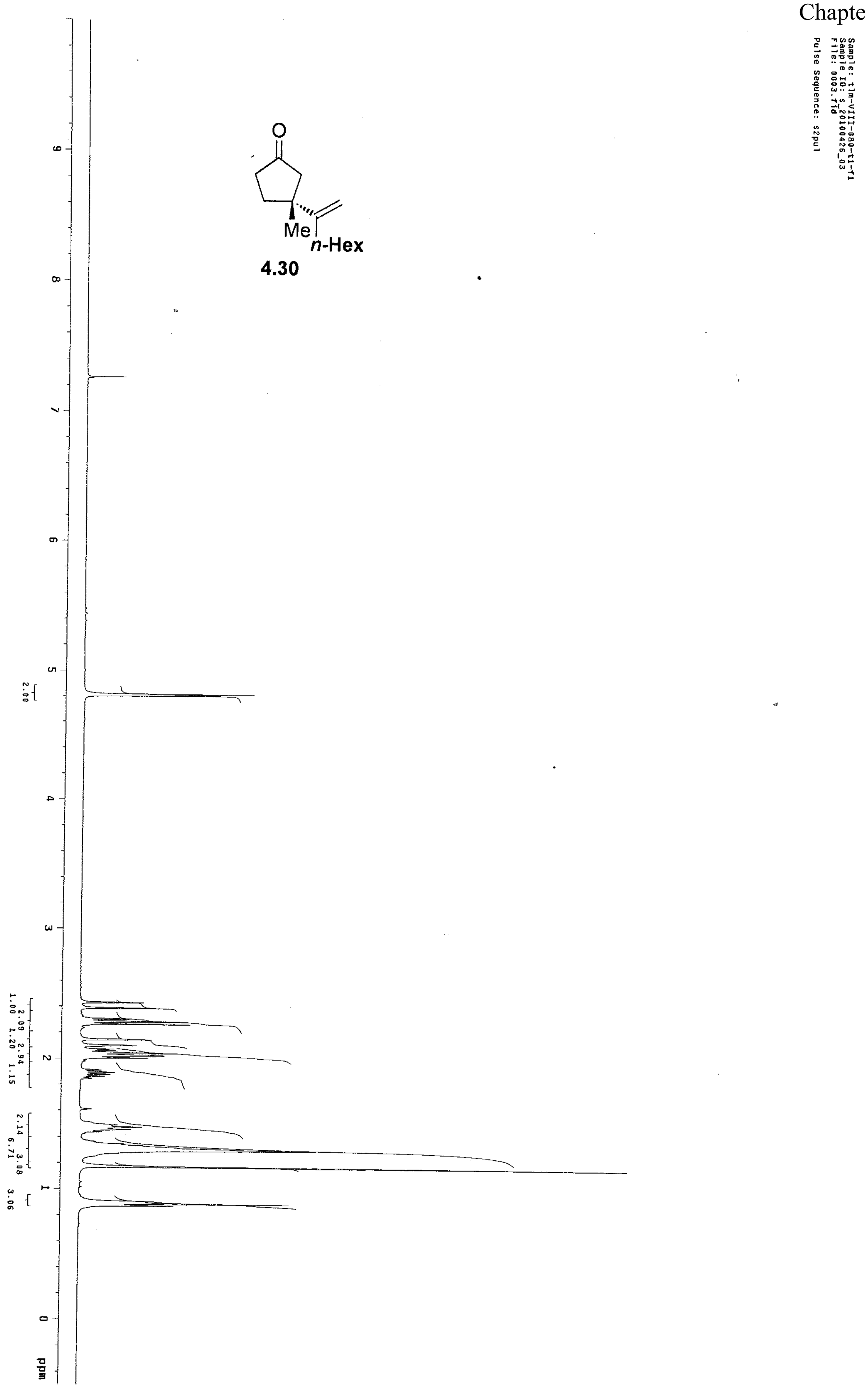
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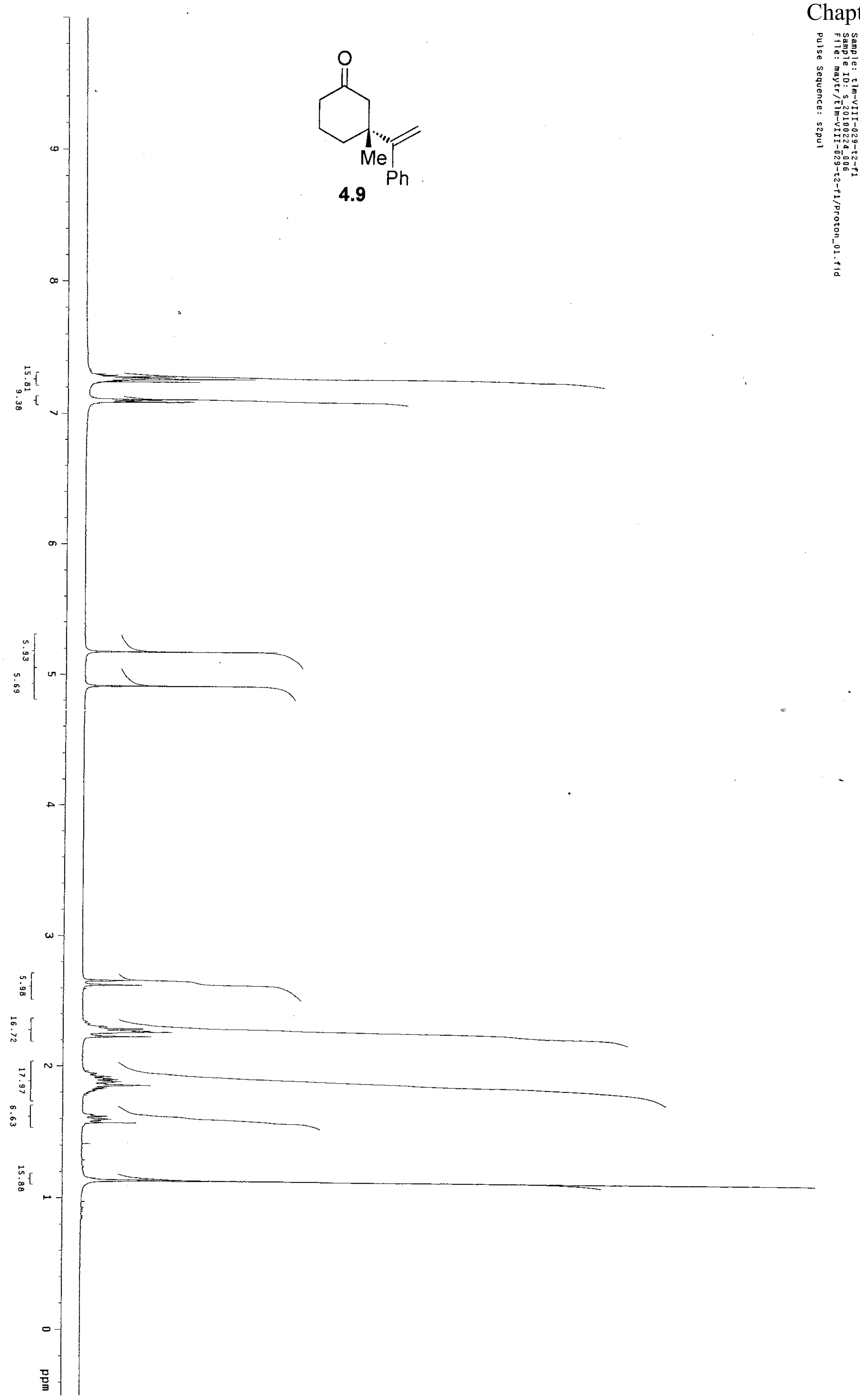
4.30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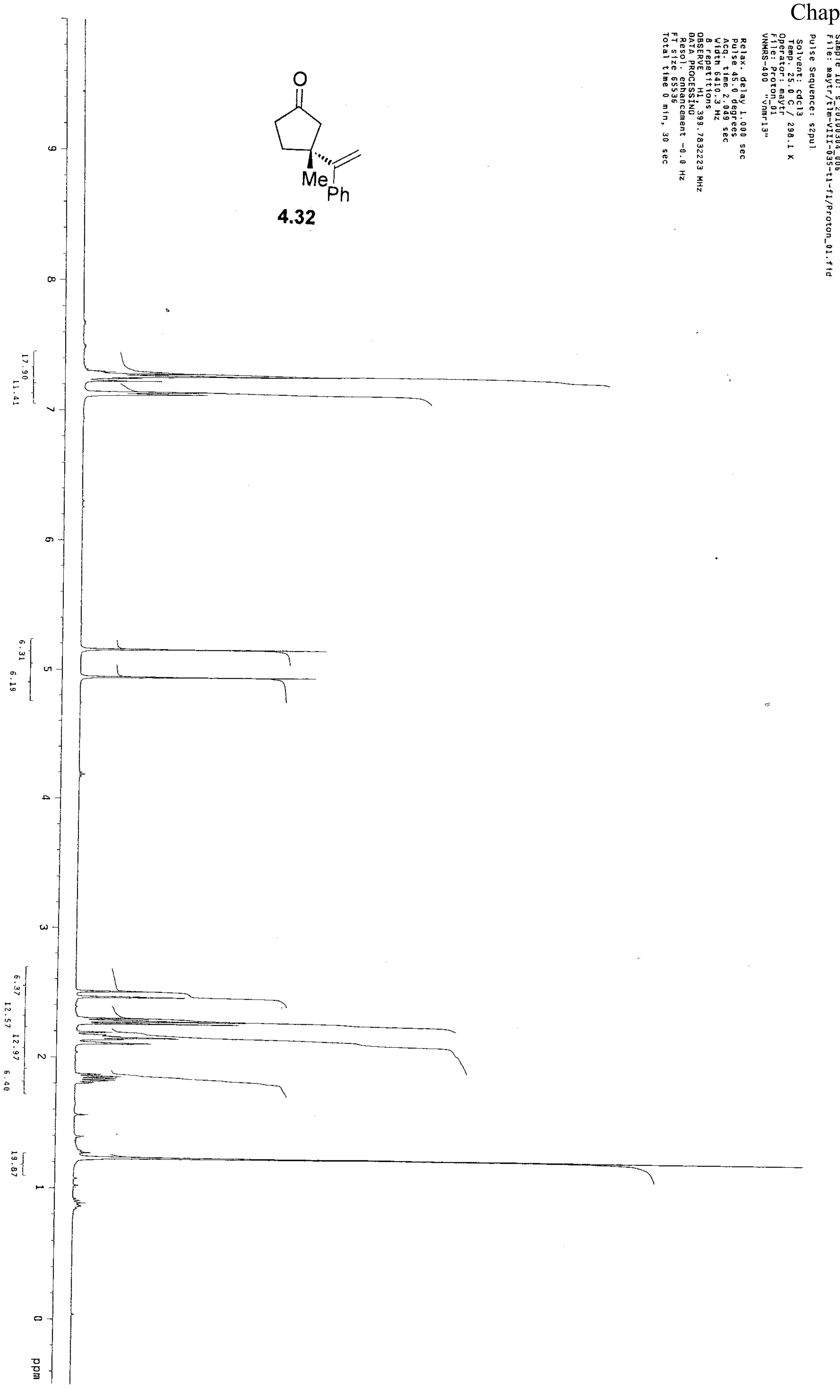
15.88

4.9



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File: Proton_01
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  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
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Total time 0 min, 30 sec
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 Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

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 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
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DATA PROCESSING
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FT size 65536
Total time 0 min, 30 sec
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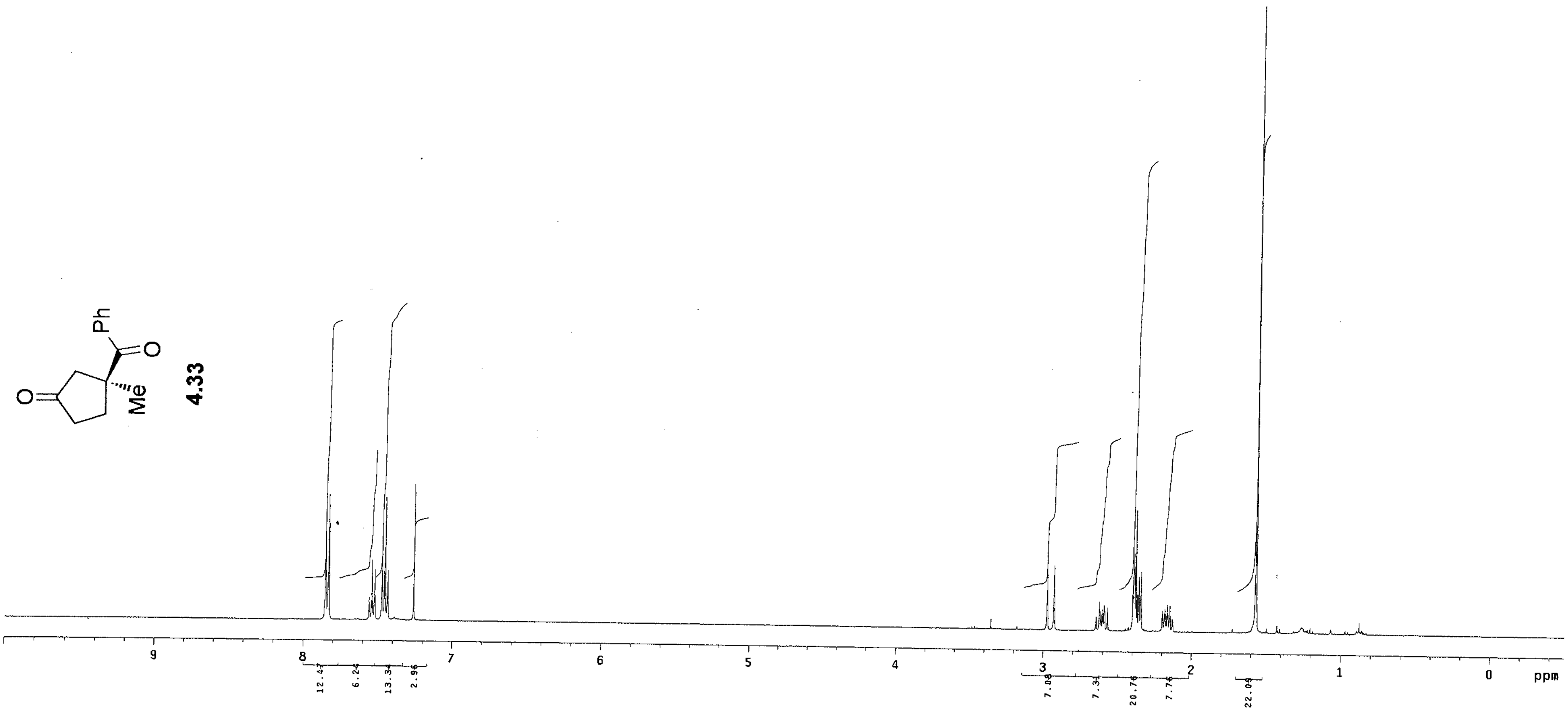

4.33

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Pulse Sequence: s2pul

 Solvent: cdcl3
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Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

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 Pulse 45.0 degrees
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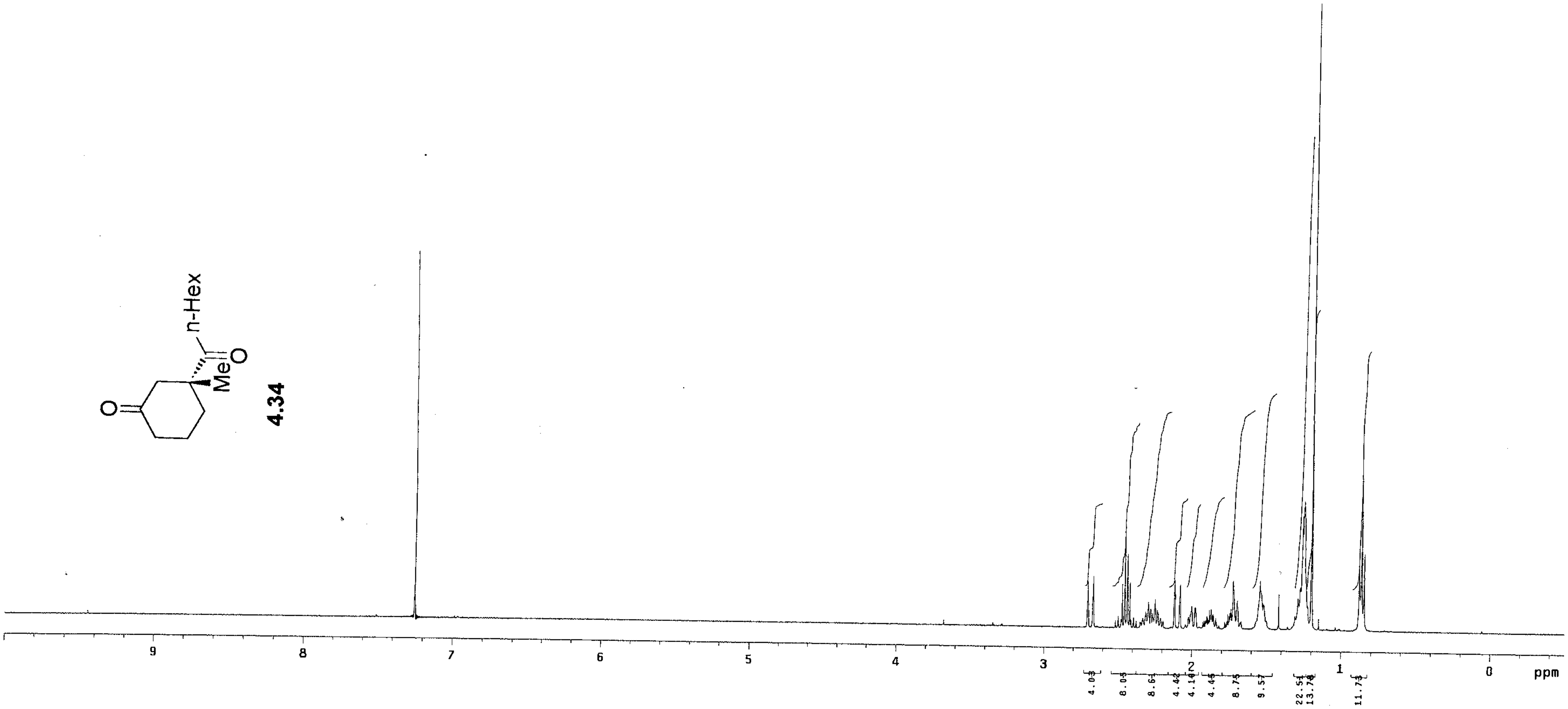
4.34



TIM-VIII-110F8

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 Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_02
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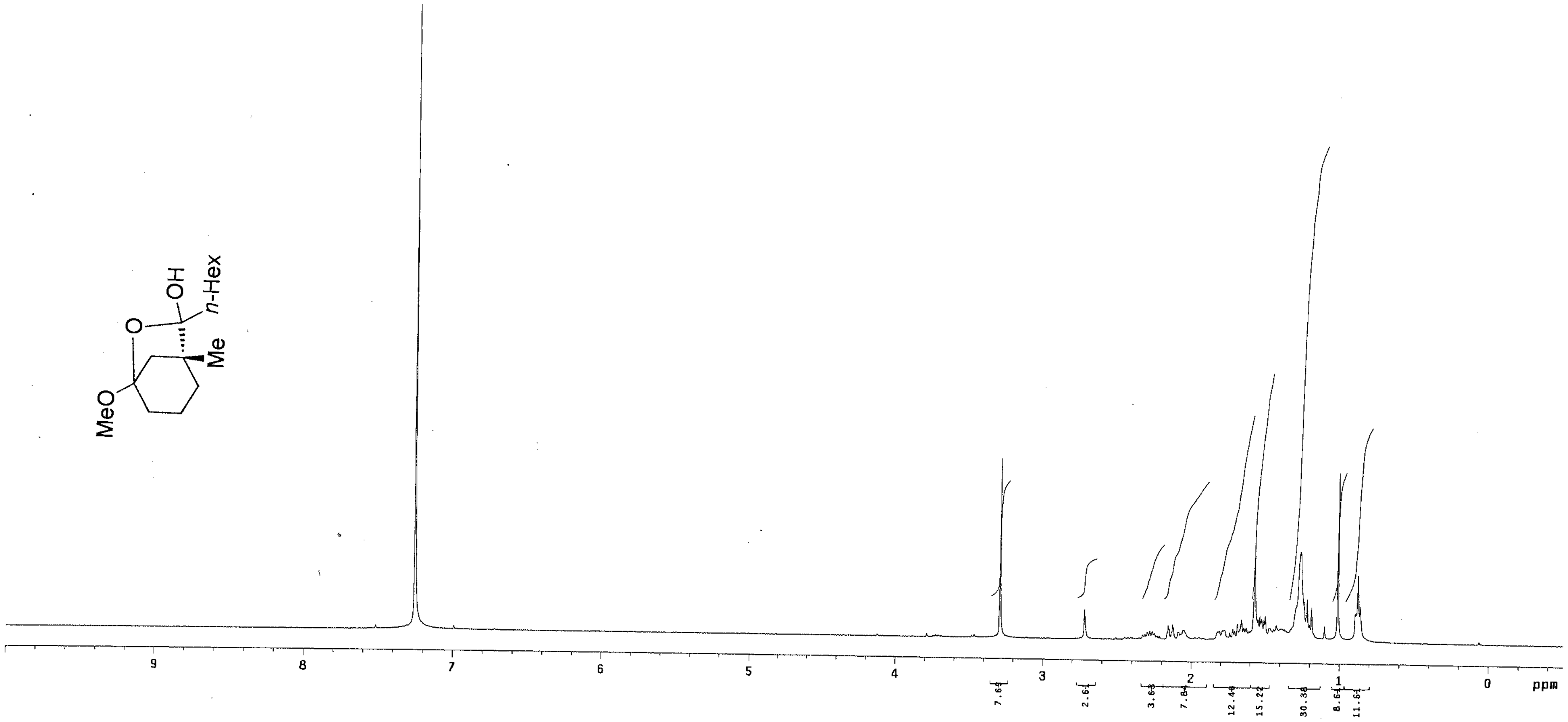

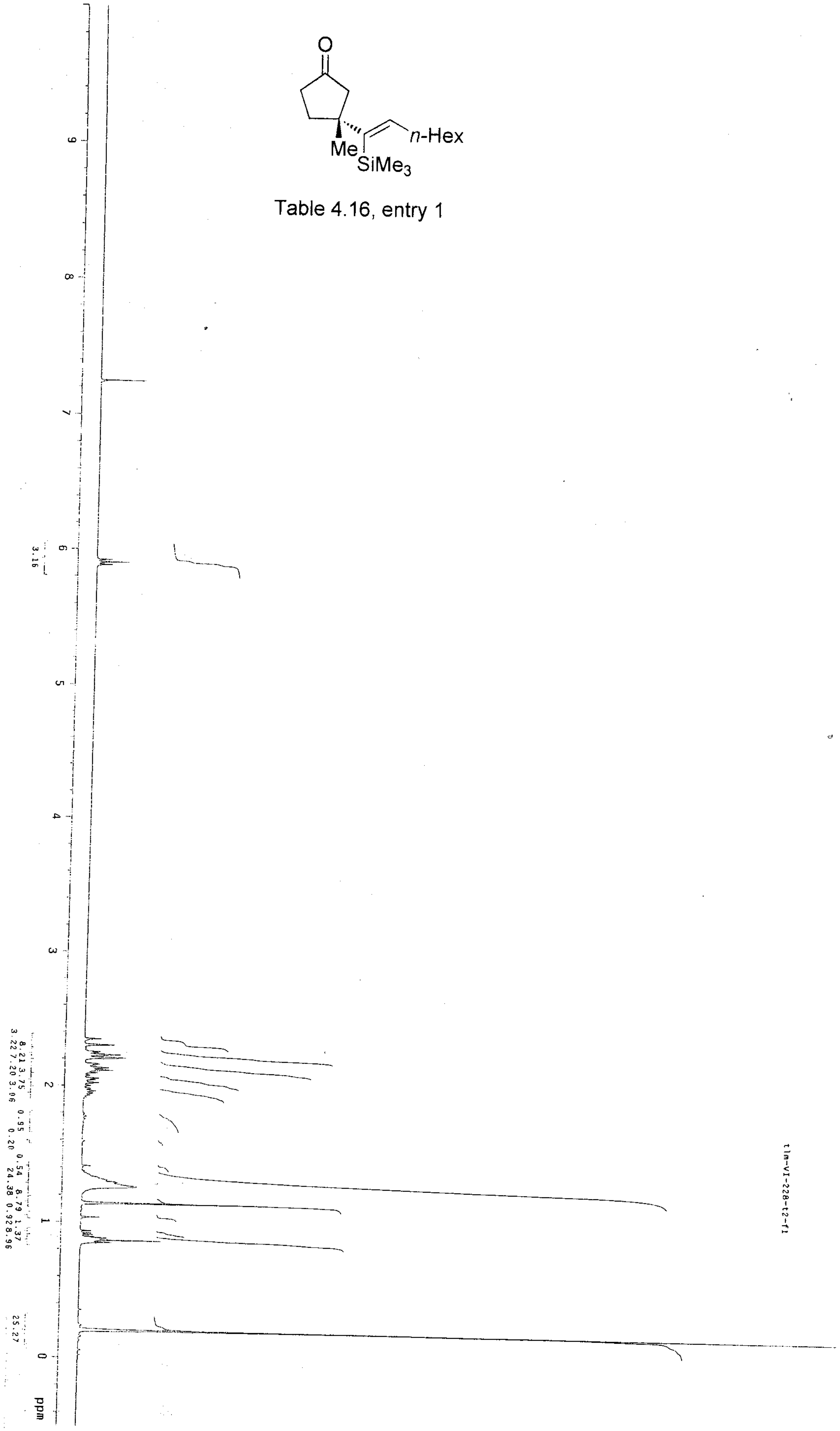

Table 4.16, entry 1

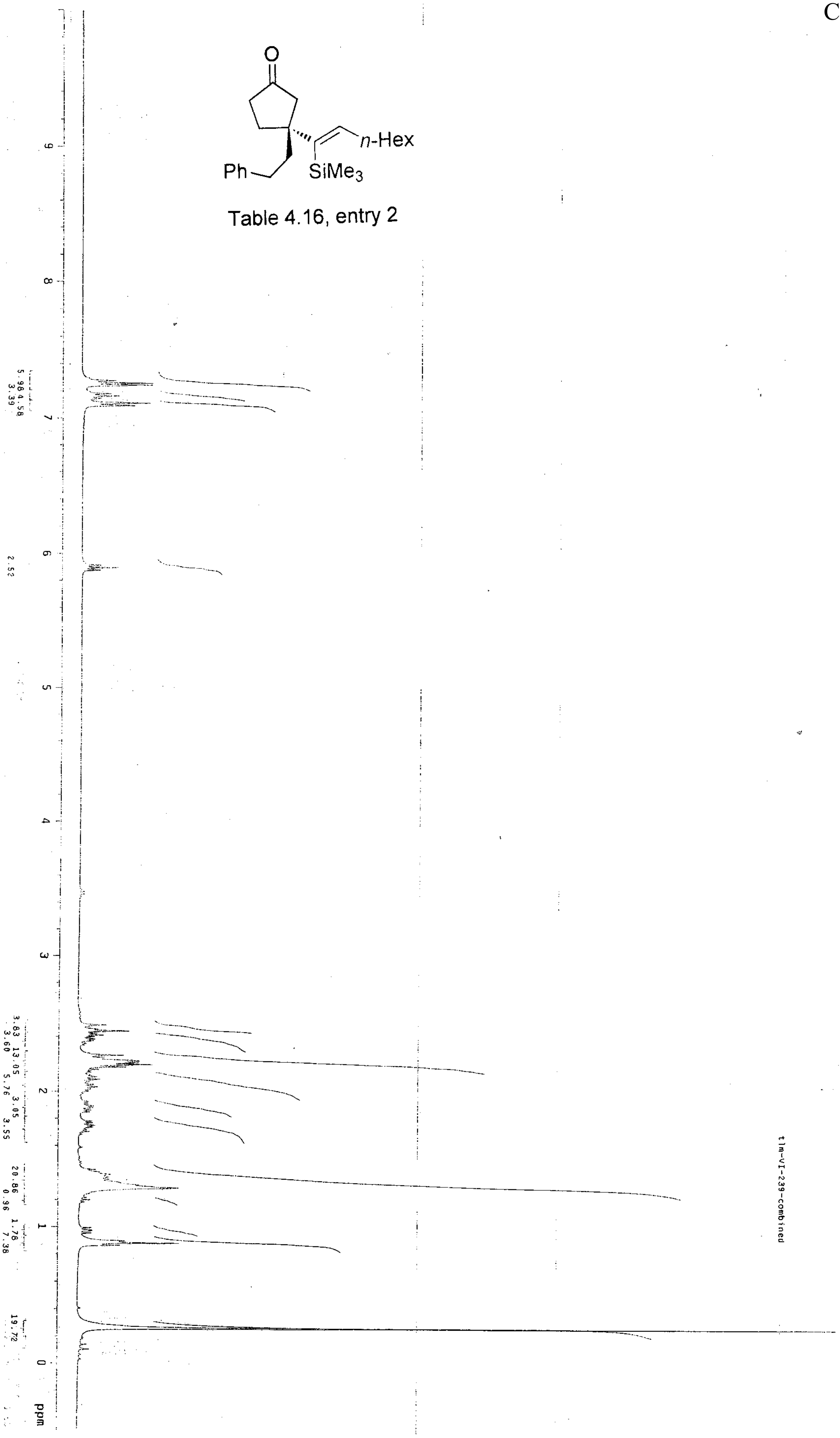

Table 4.16, entry 2

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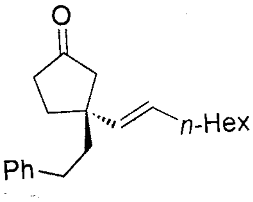
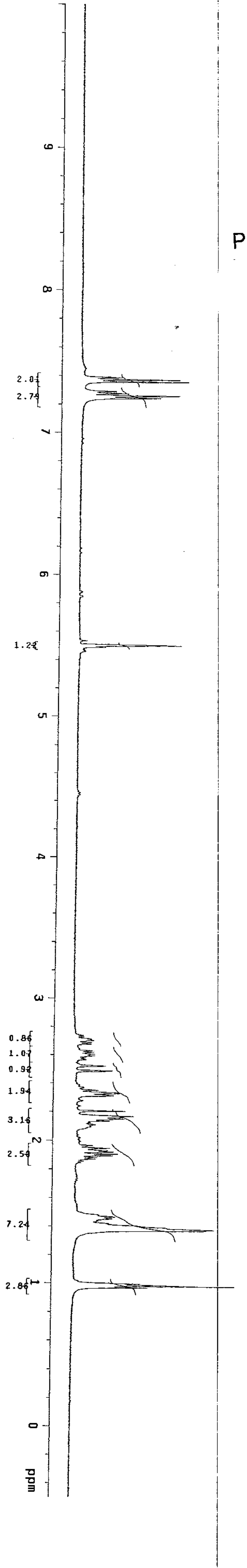
new experiment
Sample: JAD-I-021Fr6
File: exp

Pulse Sequence: s2pul
  Solvent: cdcl3
  Ambient temperature
Operator: ahh
VNMRS-500 "nmr15"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 8012.8 Hz
  32 repetitions
OBSERVE   H1, 499.8807529 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 44 sec
```





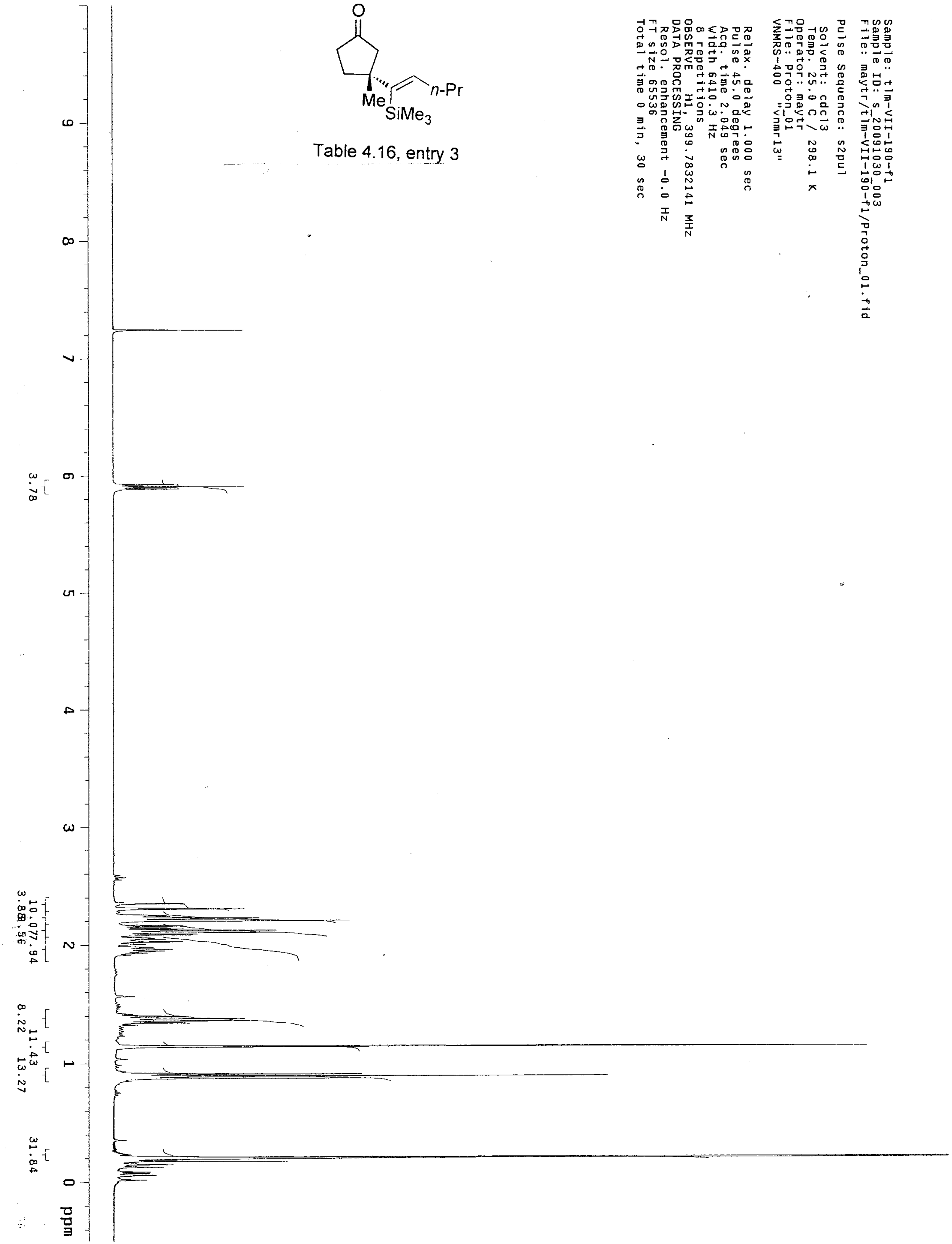


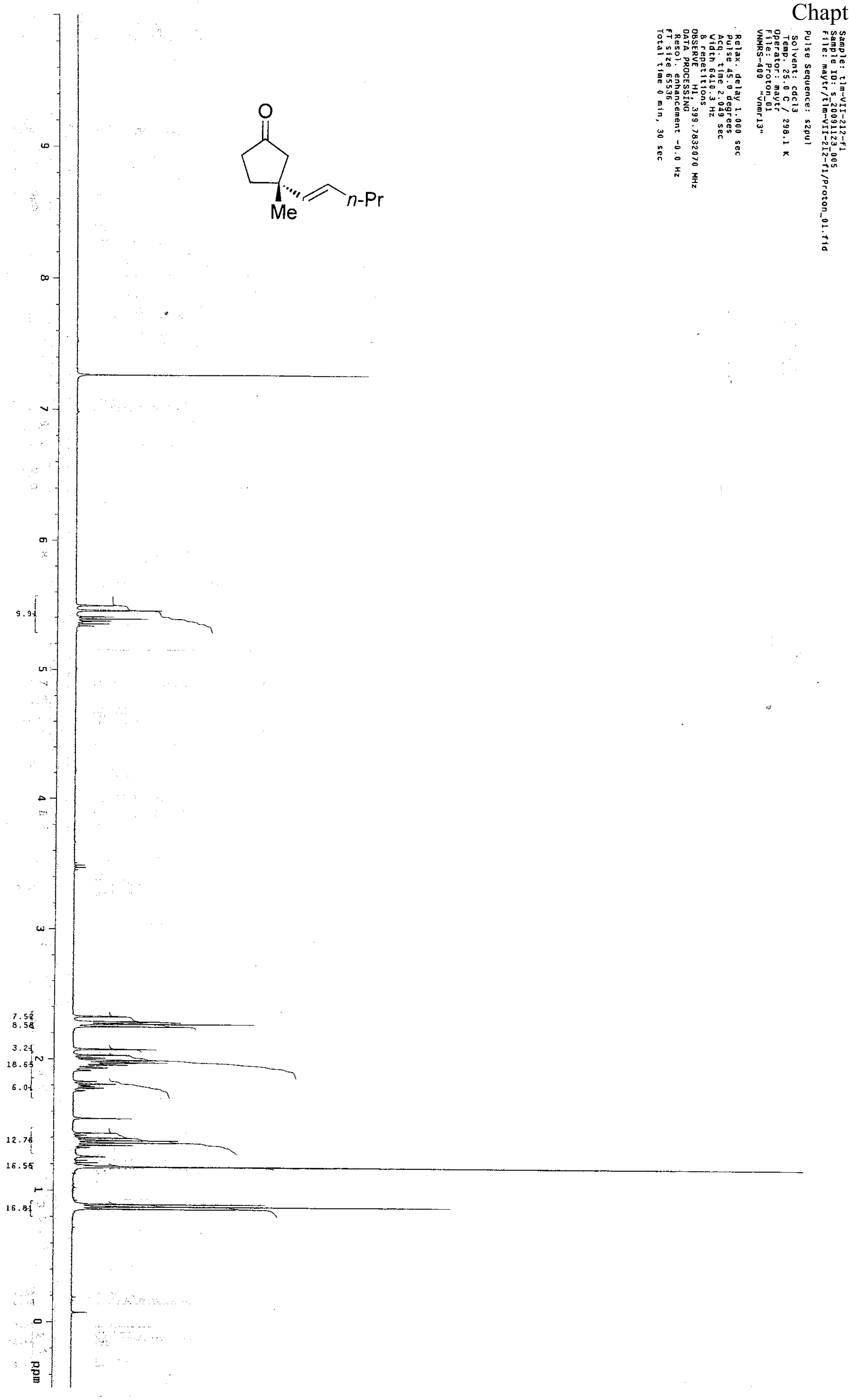
Table 4.16, entry 3

```
Sample: tlm-VII-190-f1
Sample ID: s_20091030_003
File: maytr/tlm-VII-190-f1/Proton_01.fid

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: maytr
File: Proton_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832141 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```



```
Sample: tlm-VII-212-f1
Sample ID: s_20091123_005
File: maytr/tlm-VII-212-f1/Proton_01.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: maytr
File: Proton_01
VNMRS-400 "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832070 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

O
Me
n-Pr
9
8
7
6
9.91
5
4
3
7.52
8.58
3.21
2
18.65
6.01
12.76
16.55
1
16.81
0
ppm

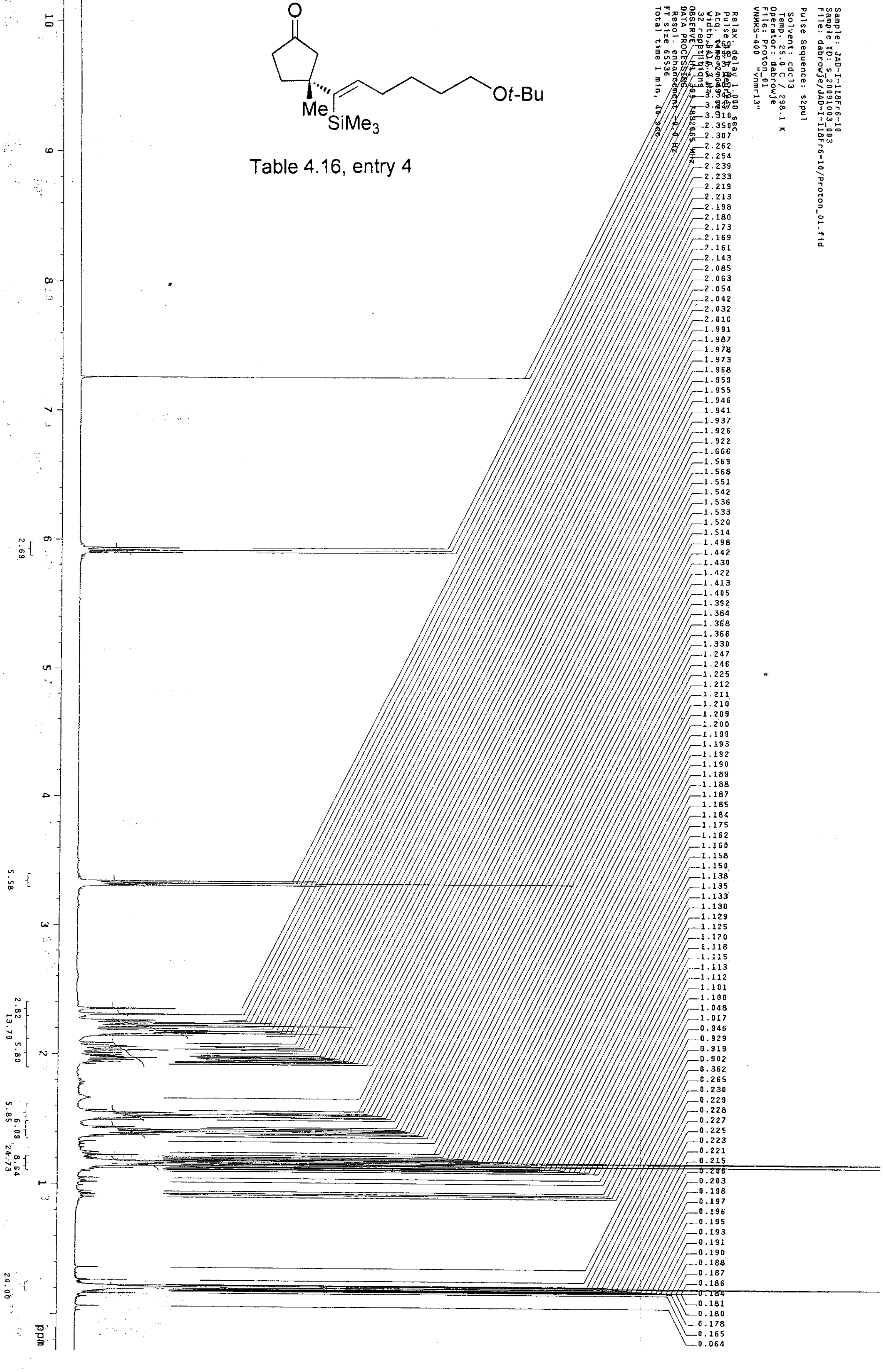


Table 4.16, entry 4

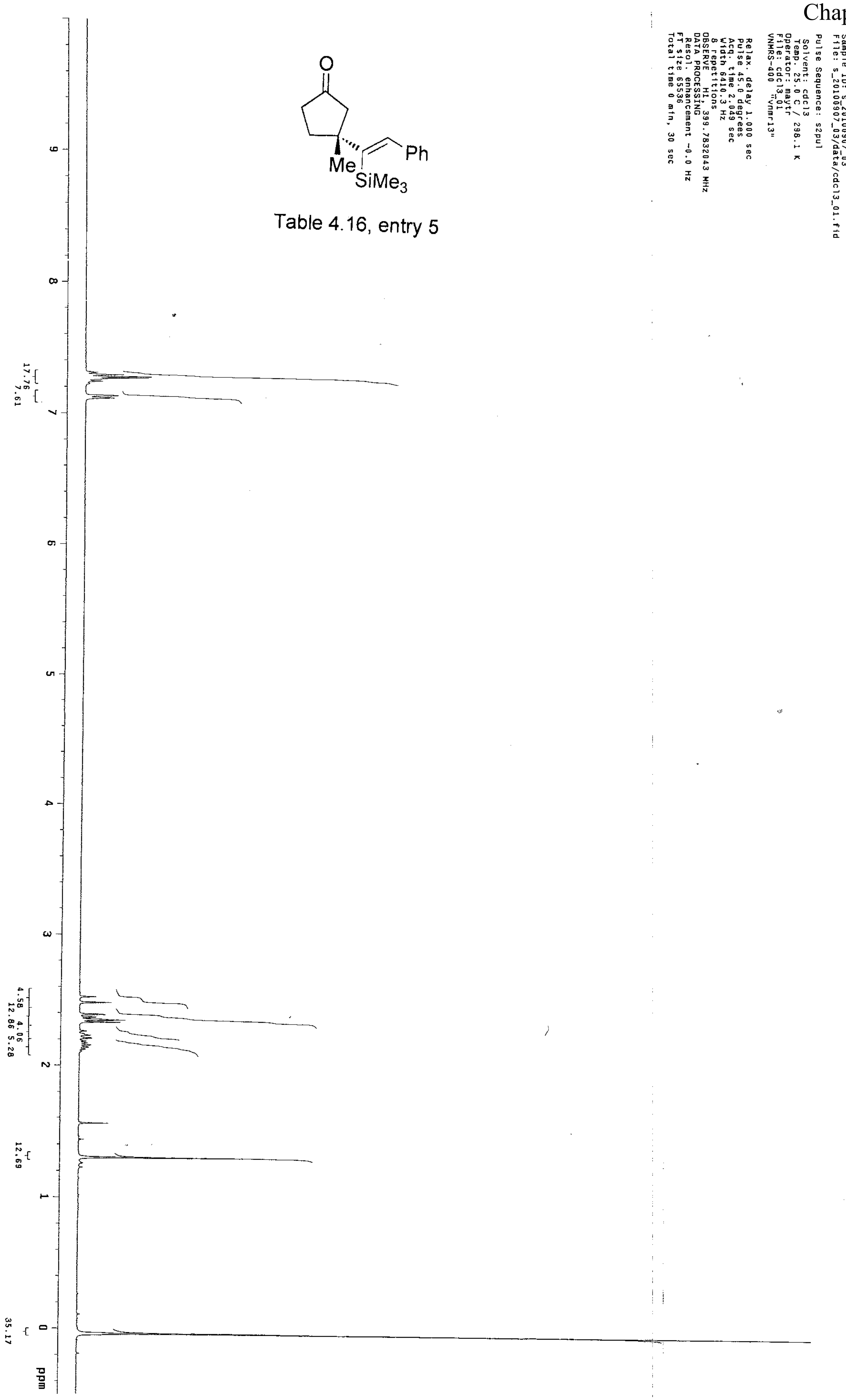


Table 4.16, entry 5

```
Sample: tlm-VIII-210-t1-f1
Sample ID: s_20100907_03
File: s_20100907_03/data/cdcl3_01.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
OBSERVE   H1, 399.7832043 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

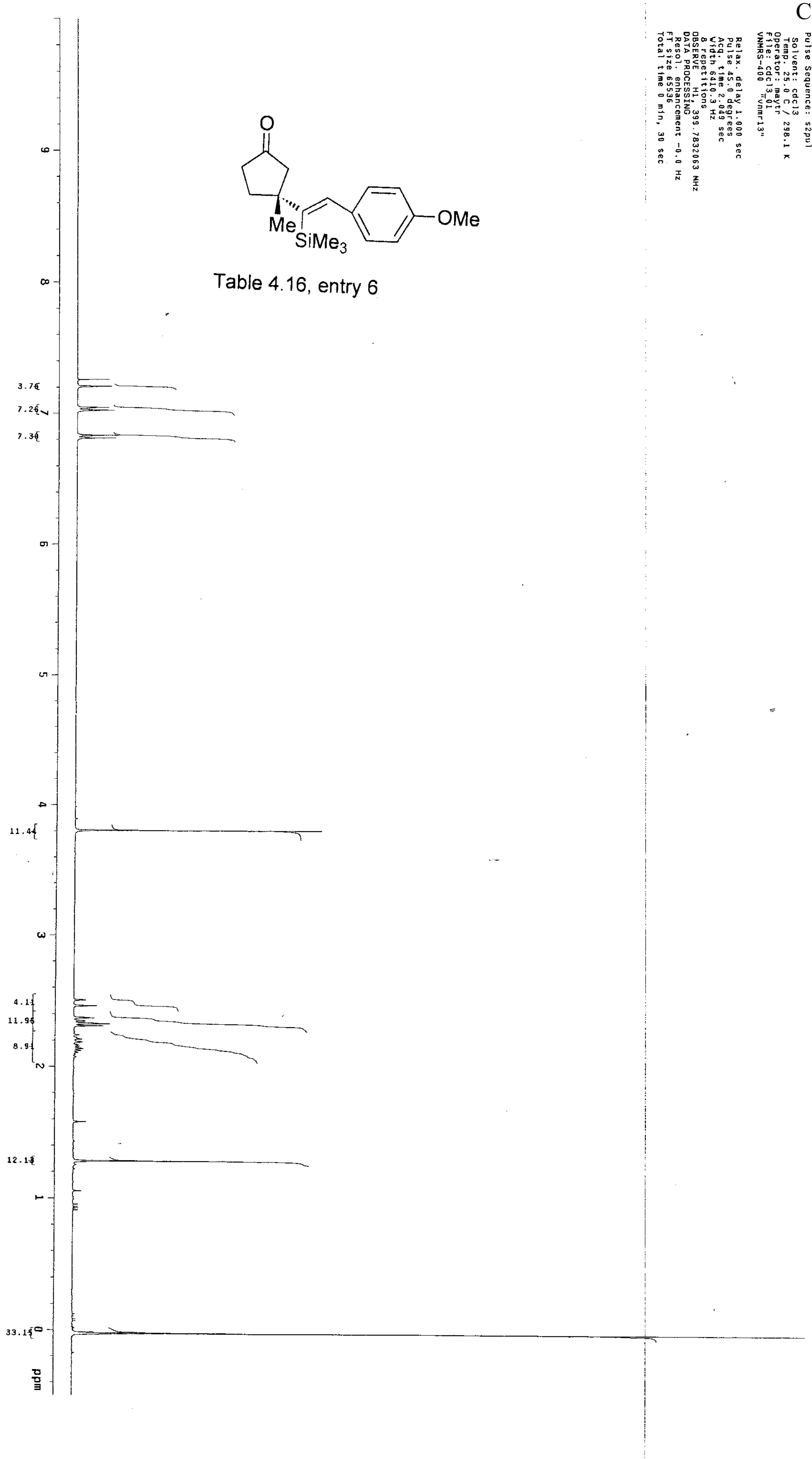


Table 4.16, entry 6

```
Sample: tlm-VIII-207-f1
Sample ID: s_20100903_06
File: s_20100903_06/data/cdcl3_01.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 25.0 C / 298.1 K
Operator: maytr
file: cdcl3_01
VNMRS-400 "vnmr13"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
OBSERVE   H1, 399.7832063 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

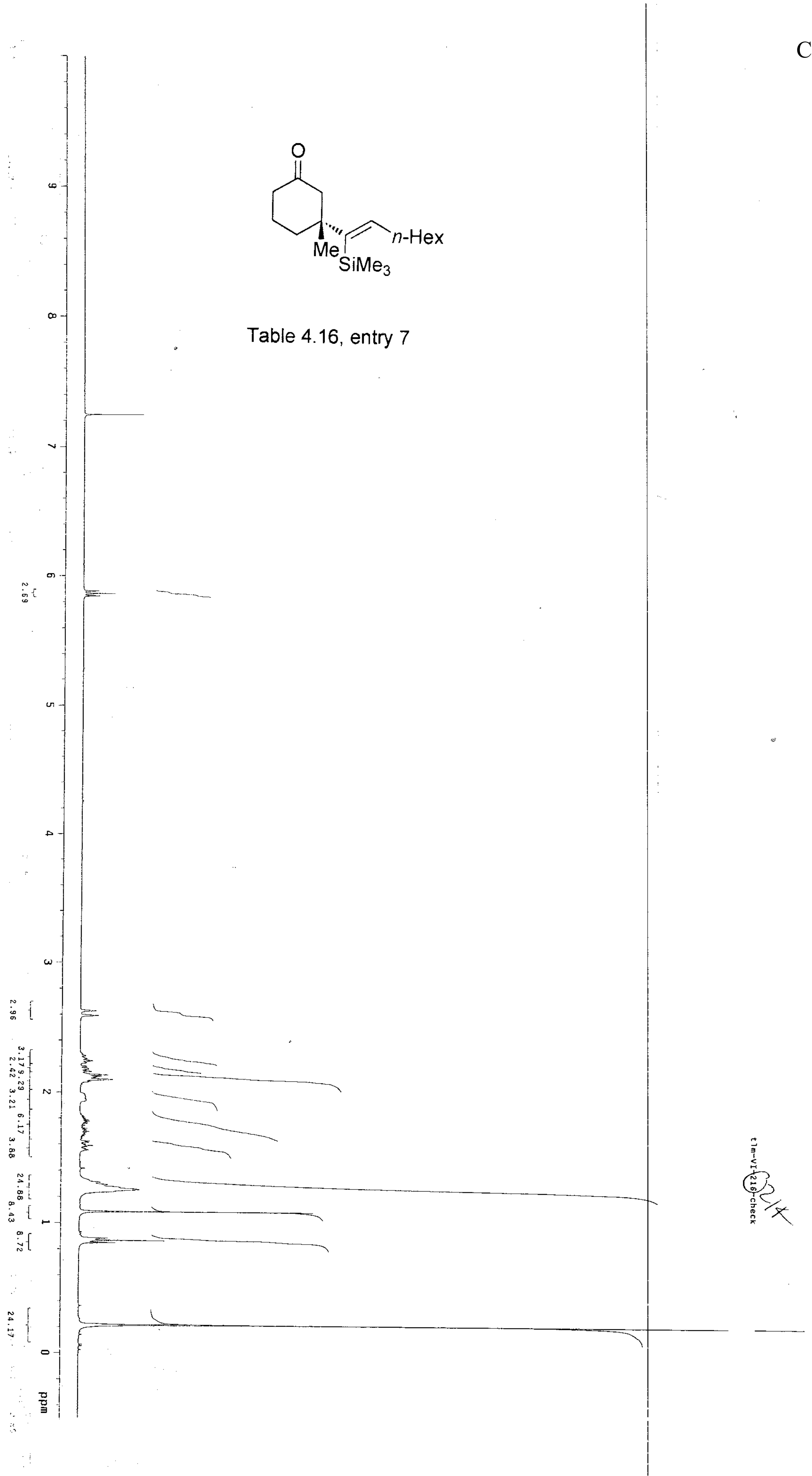
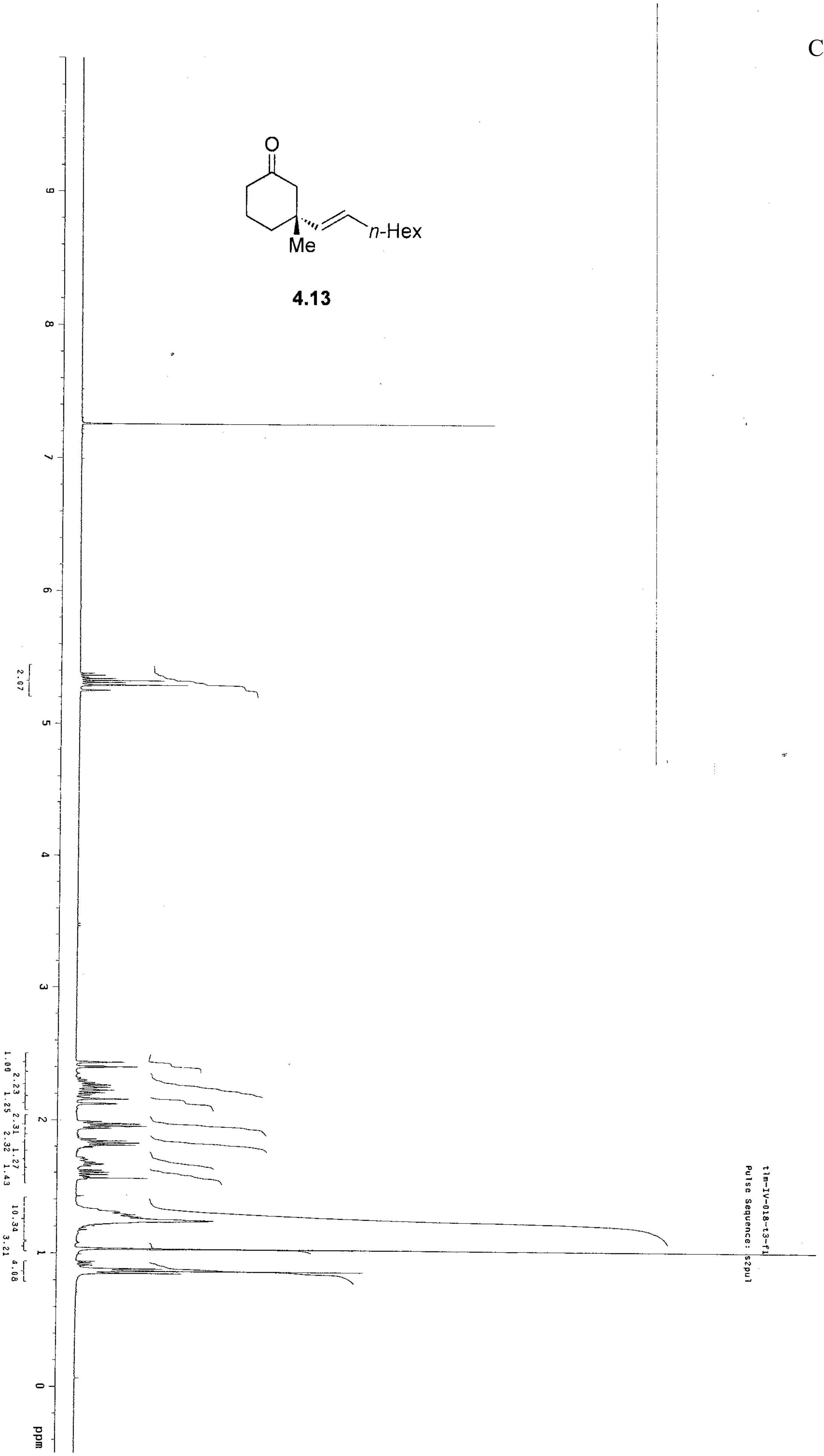


Table 4.16, entry 7


O
Me
n-Hex
9
8
7
6
5
4
3
2
1
0
ppm
2.07
2.23
1.00
1.25
2.31
2.32
1.27
1.43
10.34
3.21
4.08
tlm-IV-018-t3-f1
Pulse Sequence: s2pul

4.13

```
Sample: tlm-VII-253-t1-c
Sample ID: s_20100106_002
File: meesa/tlm-VII-253-t1-c/Proton_01.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: meesa
File: Proton_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832069 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

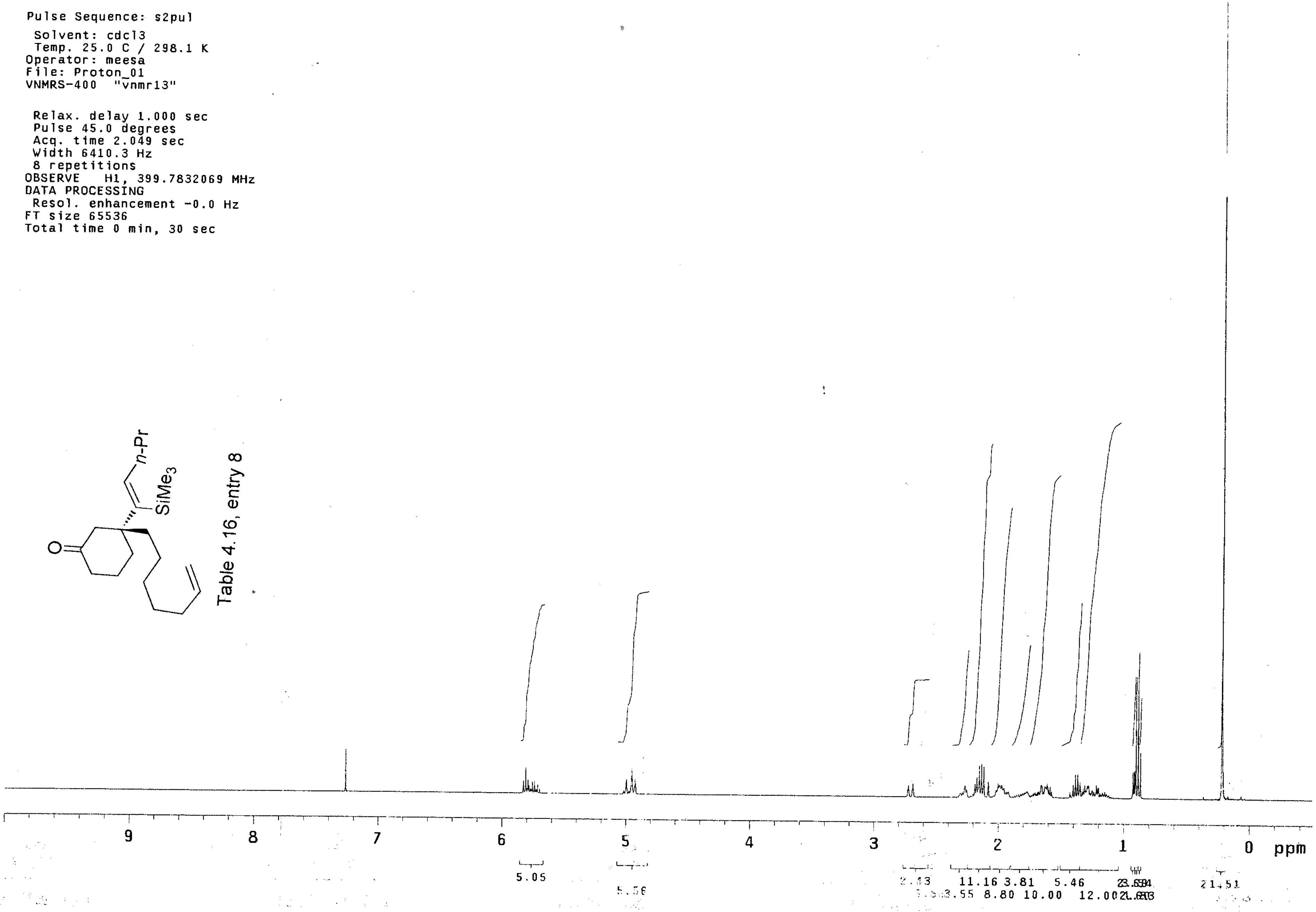


Table 4.16, entry 8

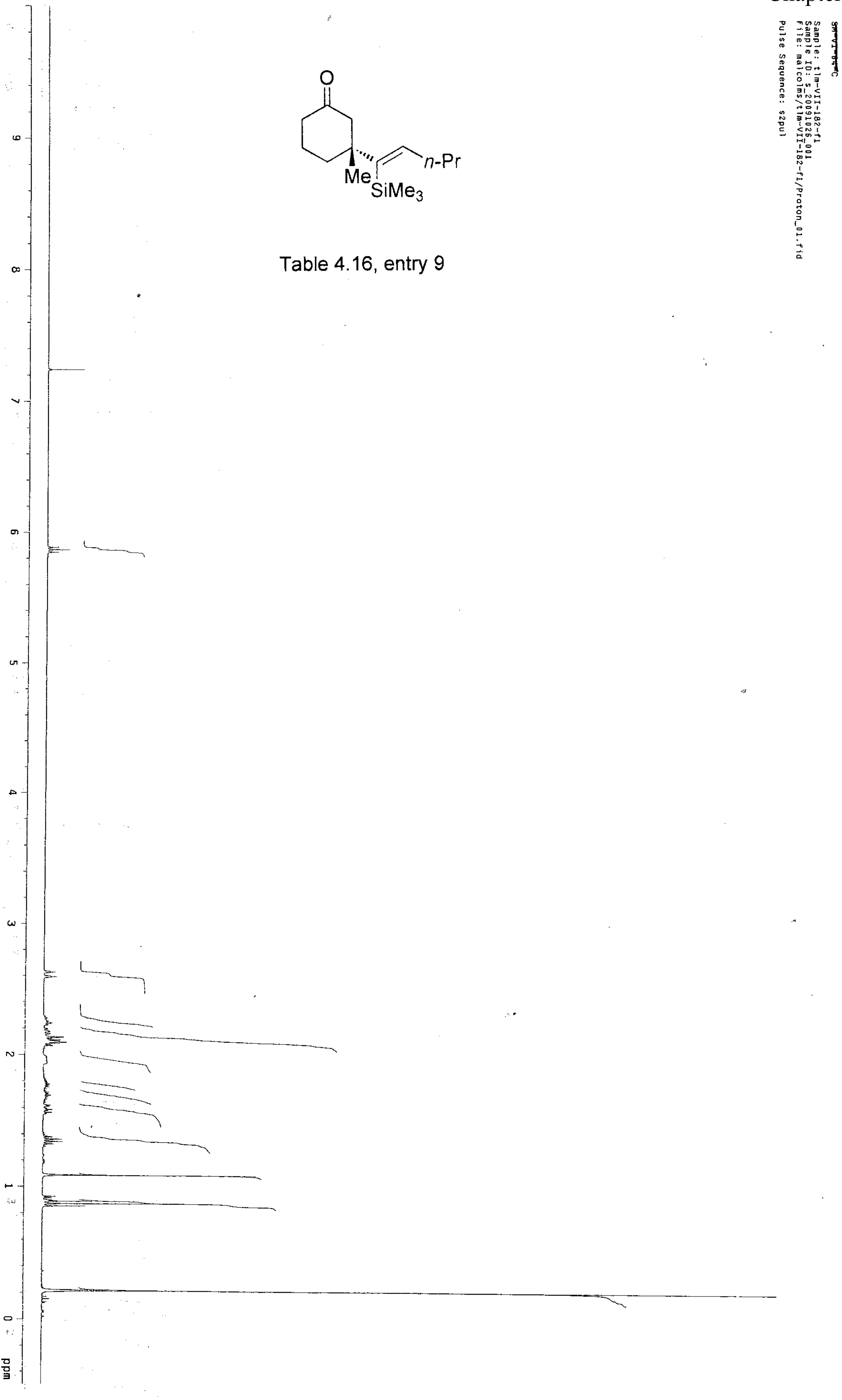
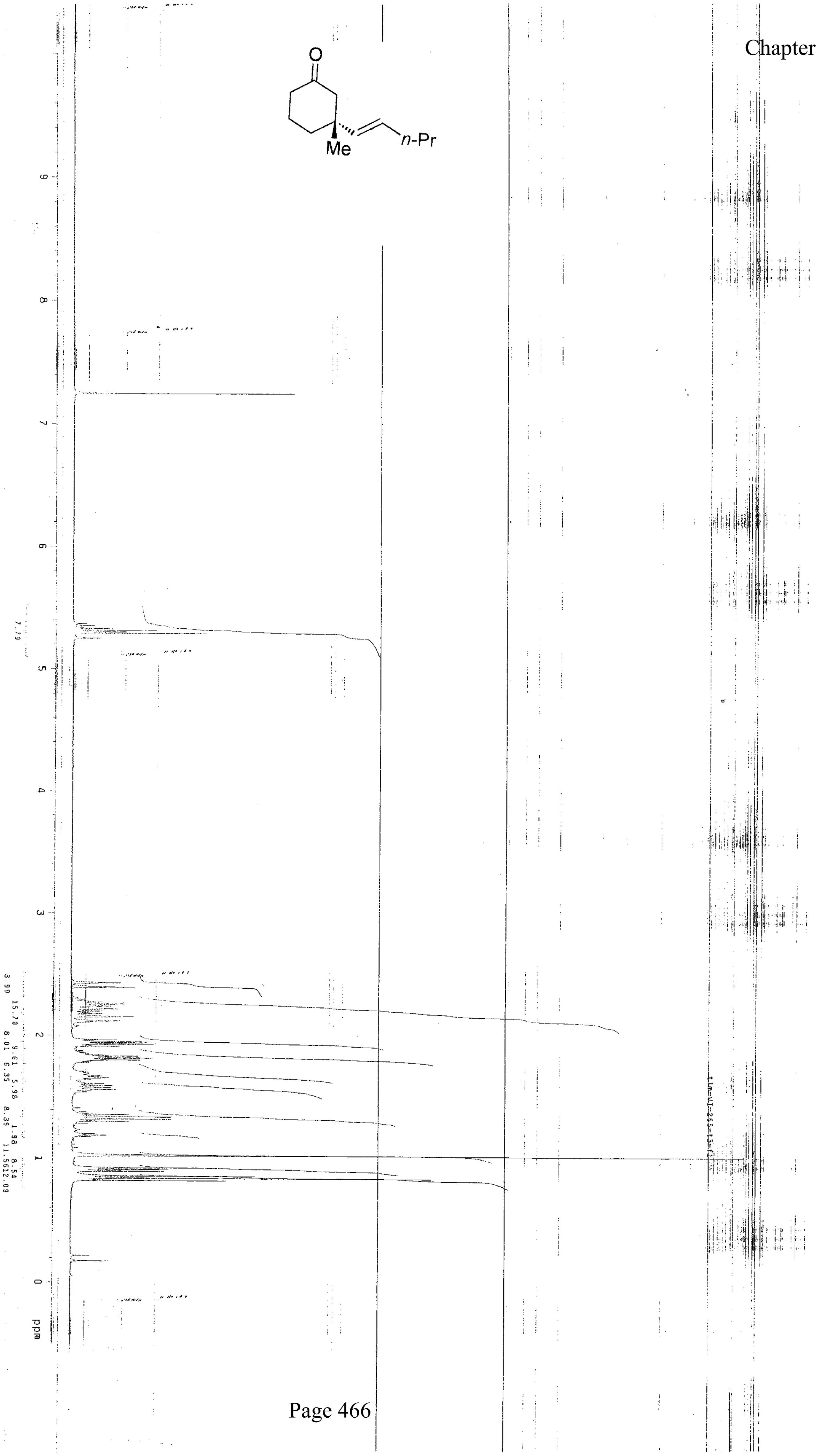


Table 4.16, entry 9


O
Me
n-Pr
9
8
7
6
5
4
3
2
1
0
ppm
7.79
3.99 15.70 8.01 6.35 9.61 5.98 8.39 1.98 11.56 8.54 12.09
tlm-VI-265-t3-f1

```
Sample: JAD-I-172-2Fr12-20
File: /home/ahh/vnmrsys/data/JAD/JAD-I-172-2Fr12-20.fid

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: dabrowje
File: JAD-I-172-2Fr12-20
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 28 repetitions
OBSERVE   H1, 399.7832069 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 44 sec
```

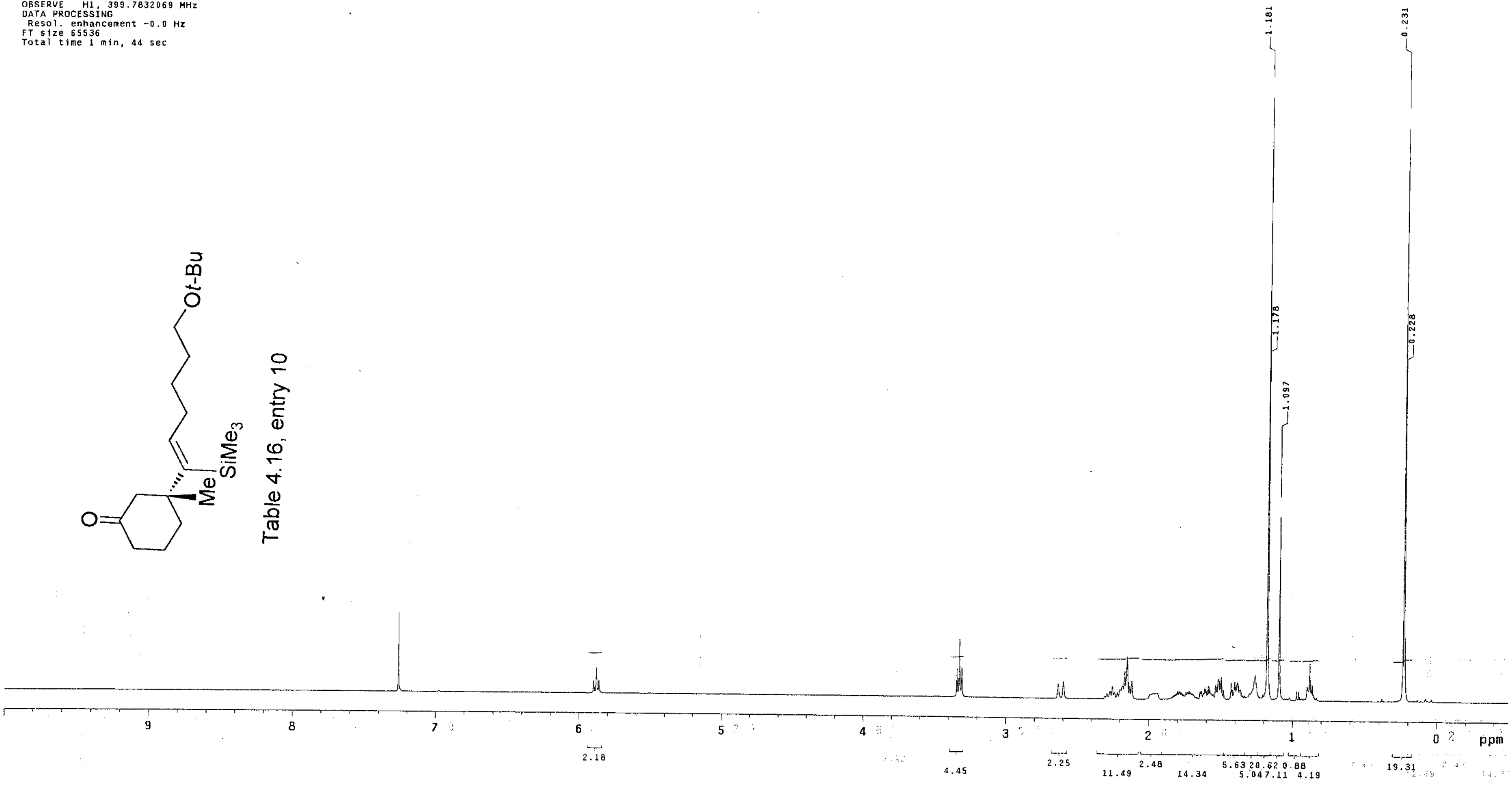


Table 4.16, entry 10

```
Sample: tlm-VIII-208-t1-f1-2
Sample ID: s_20100906_03
File: s_20100906_03/data/cdcl3_01.fid

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832093 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

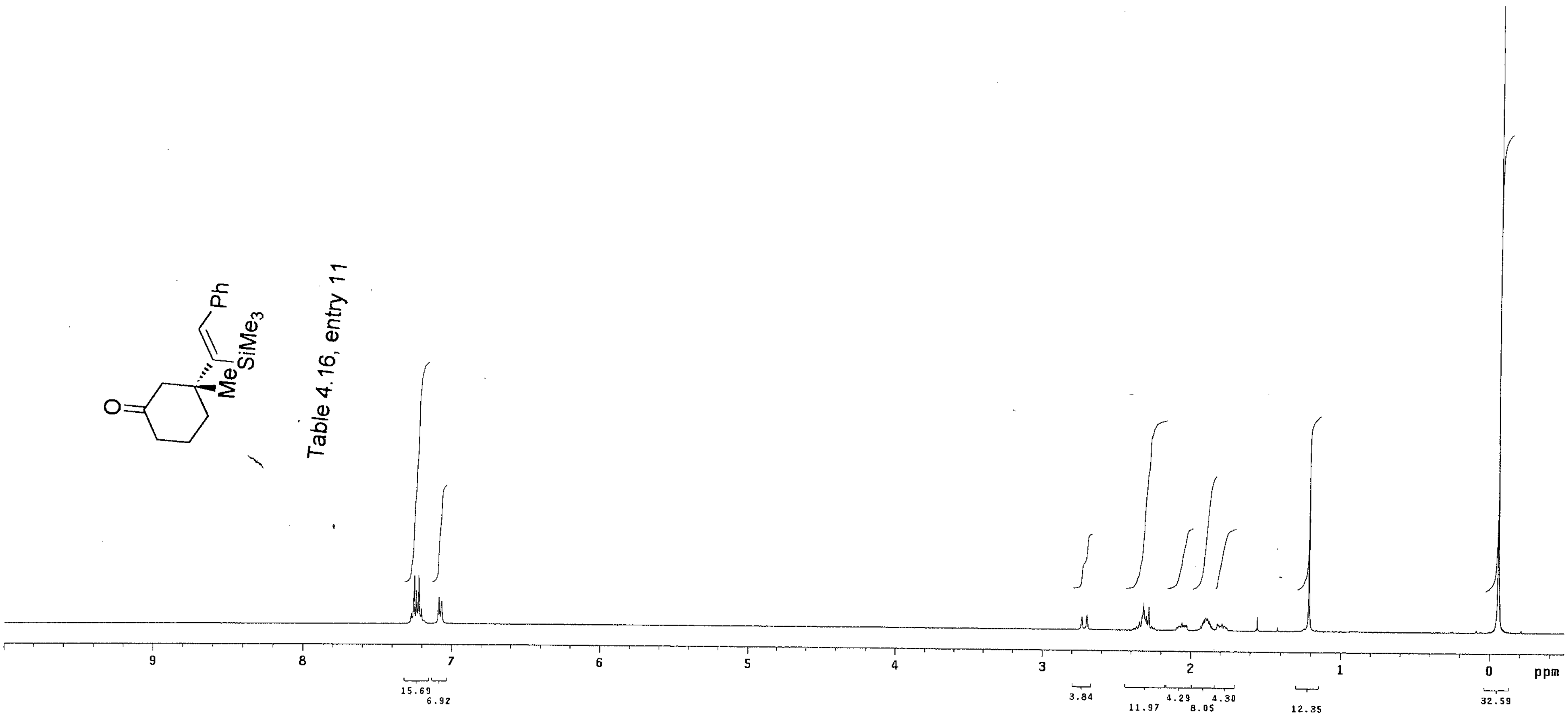


Table 4.16, entry 11

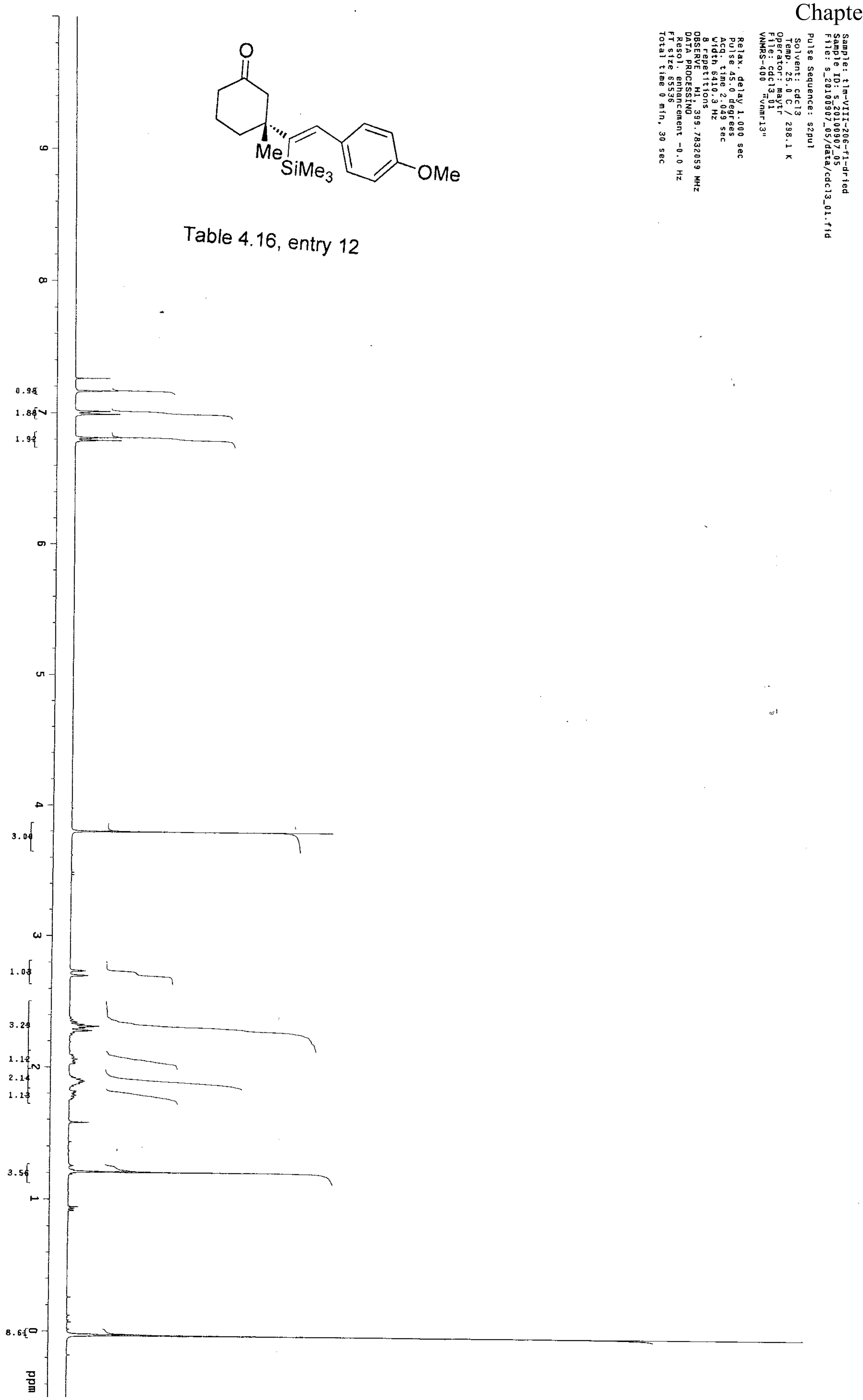
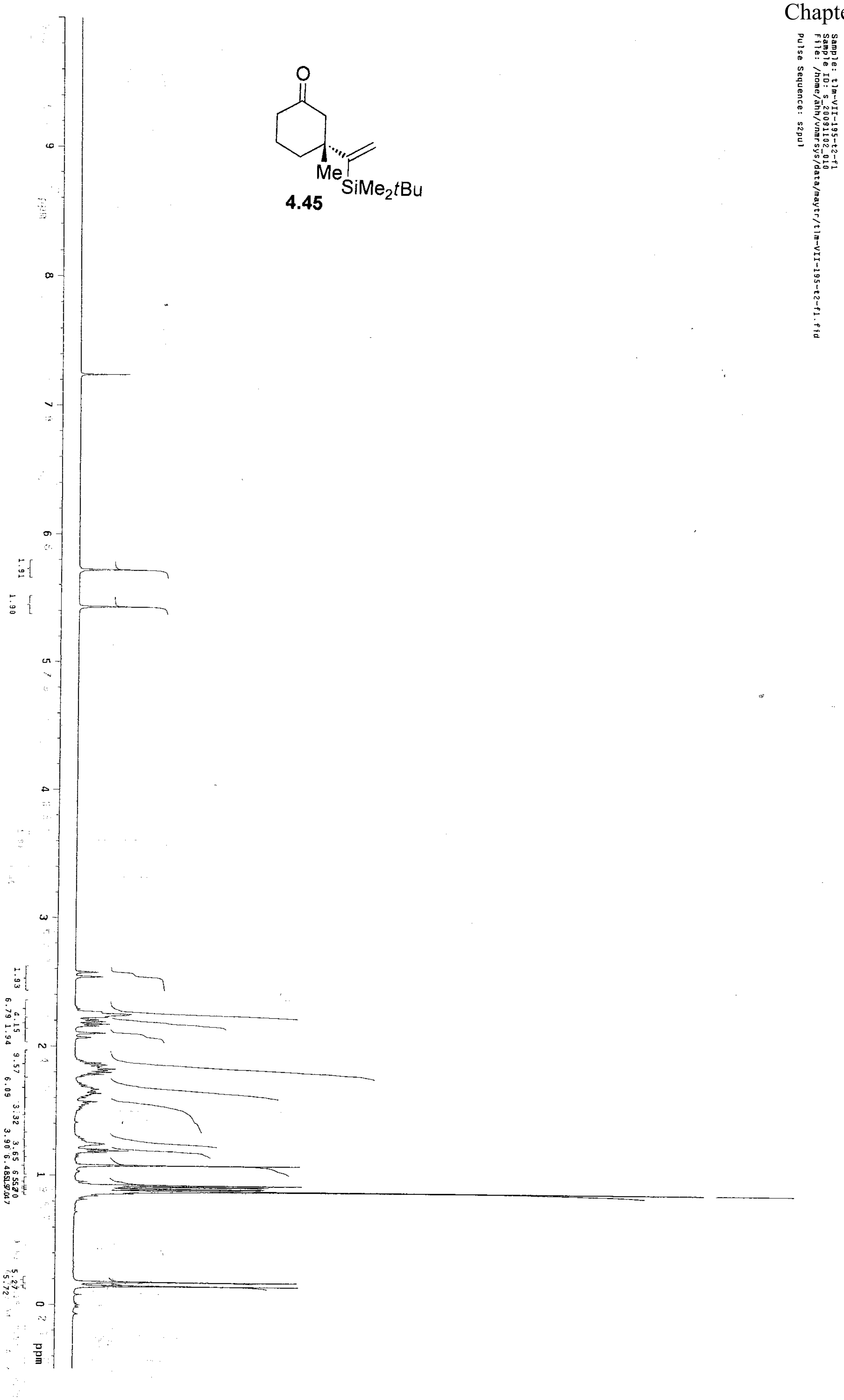
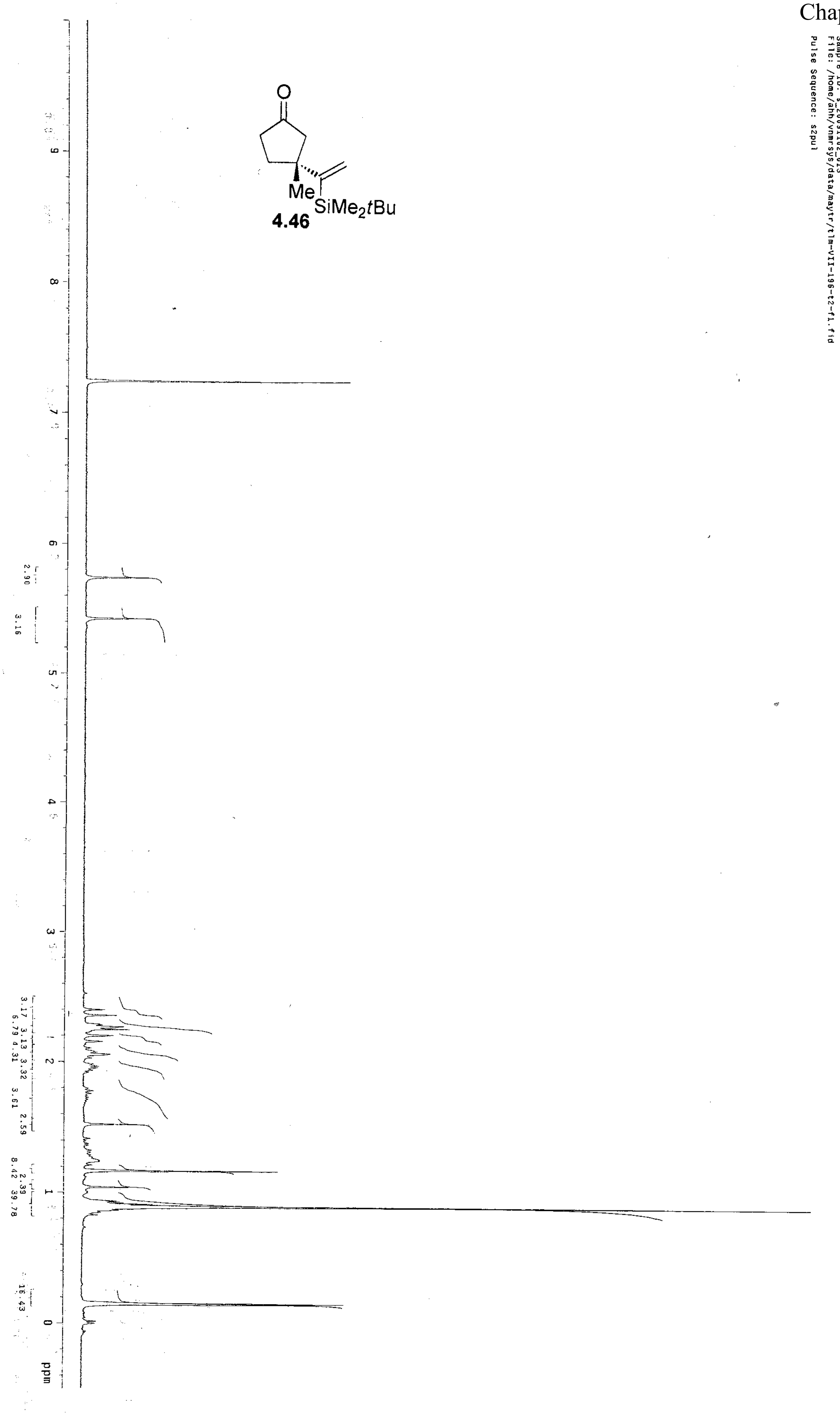
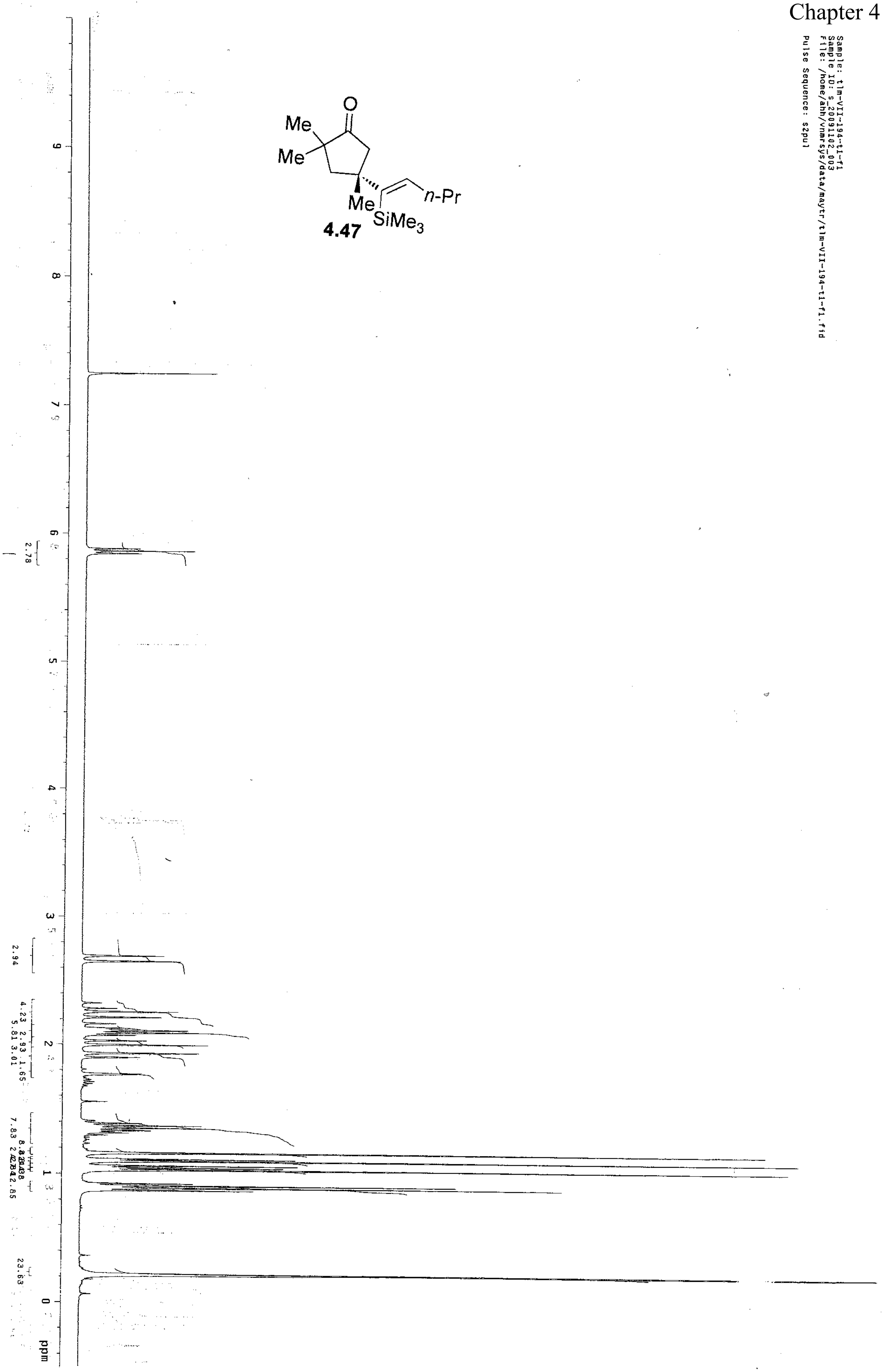


Table 4.16, entry 12

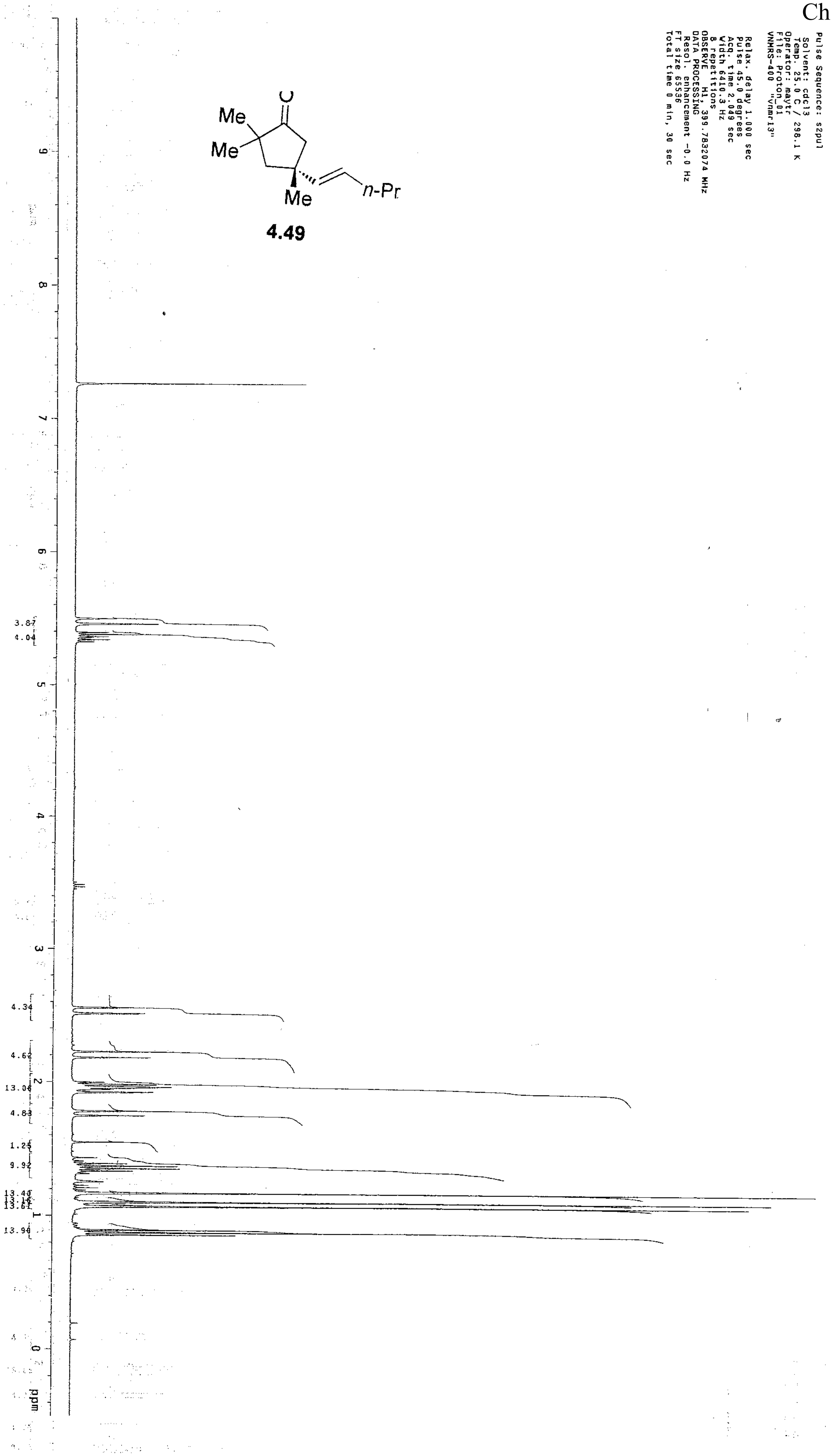

O
Me
SiMe₂tBu
Sample: tlm-VII-195-t2-f1
Sample ID: s_20091102_010
File: /home/ahh/vnmrsys/data/maytr/tlm-VII-195-t2-f1.fid
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
1.91
1.90
1.93
4.15
6.79
1.94
9.57
6.09
3.32
3.90
3.65
6.48
6.55
5.27
5.72

4.45


4.46
O
Me
SiMe$_2$tBu
Sample: tlm-VII-196-t2-f1
Sample ID: s_20091102_013
File: /home/ahh/vnmrsys/data/maytr/tlm-VII-196-t2-f1.fid
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
2.90
3.16
3.17
6.79
3.13
4.31
3.32
3.61
2.59
2.39
8.42
39.78
16.43


Sample: tlm-VII-194-t1-f1
Sample ID: s_20091102_003
File: /home/ahh/vnmrsys/data/maytr/tlm-VII-194-t1-f1.fid
Pulse Sequence: s2pul
Me
Me
O
Me
SiMe3
n-Pr
9
8
7
6
5
4
3
2
1
0
ppm
2.78
2.94
4.23
2.93
1.65
5.81
3.01
7.83
23.63

4.47



```
Sample: tlm-VII-206-f1
Sample ID: s_20091123_003
File: maytr/tlm-VII-206-f1/Proton_01.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
   Temp. 25.0 C / 298.1 K
Operator: maytr
File: Proton_01
VNMRS-400  "vnmr13"

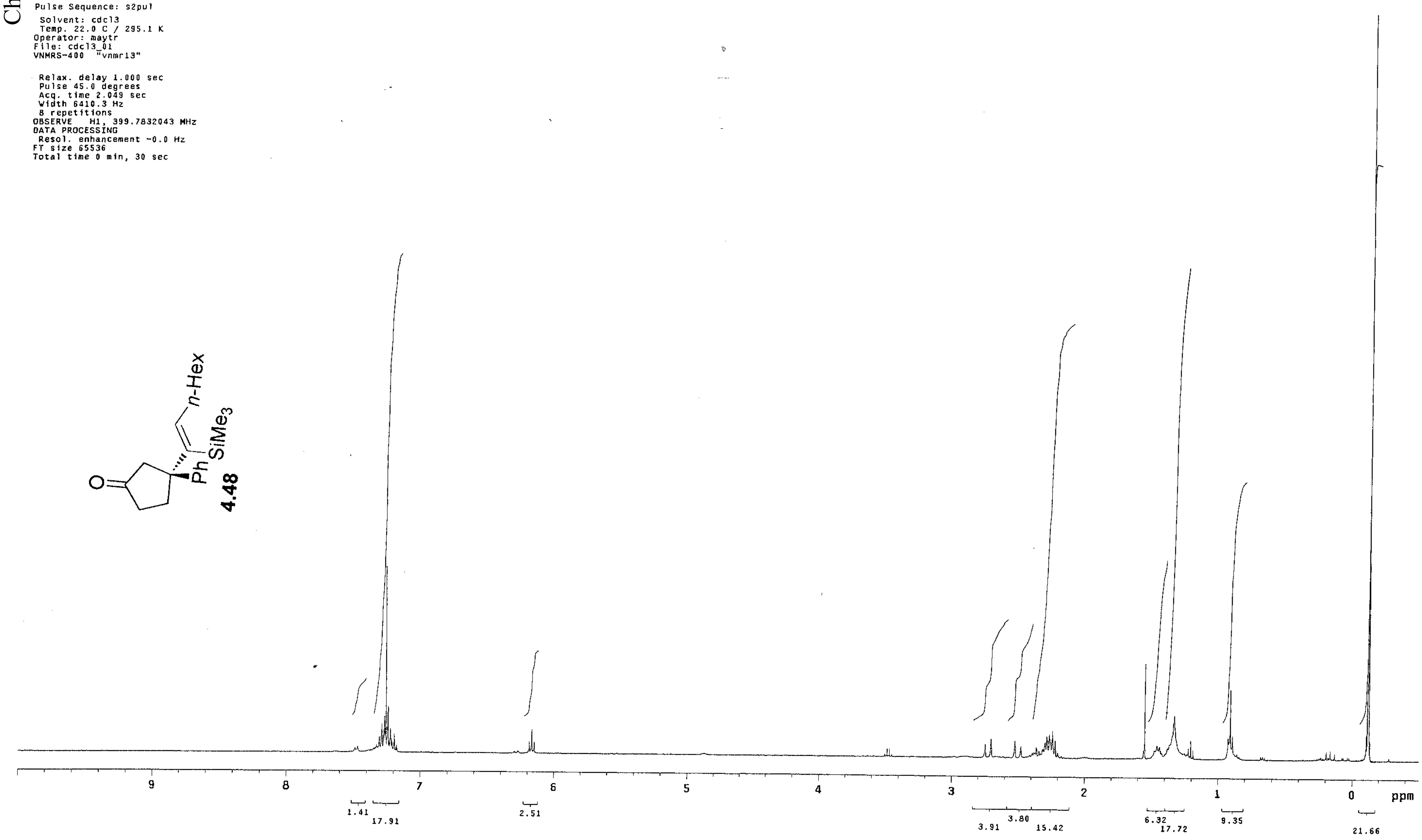
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832074 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

```
Sample: tlm-VIII-190-f1
Sample ID: s_20100823_03
File: s_20100823_03/data/cdcl3_01.fid

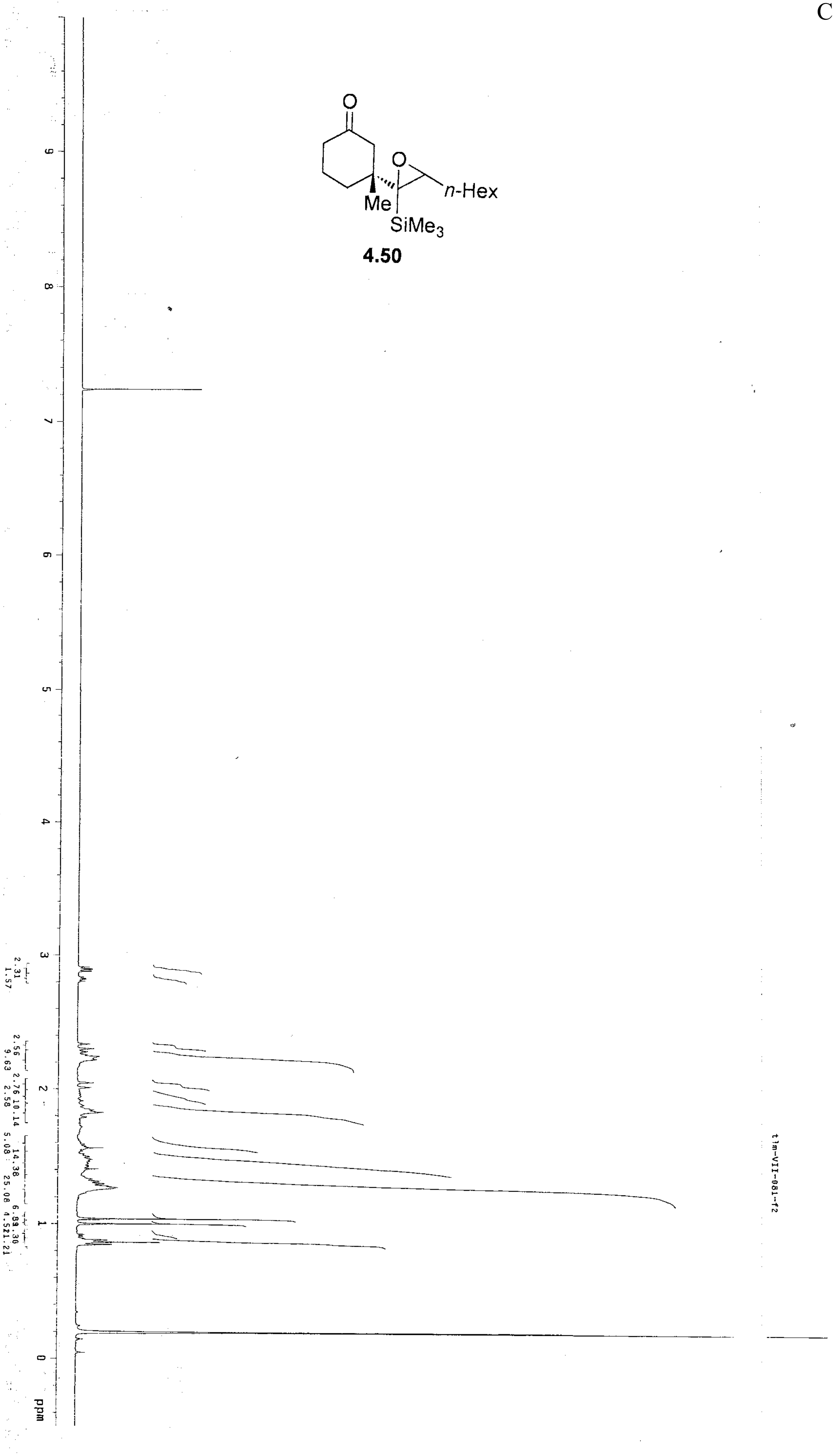
Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 22.0 C / 295.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832043 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

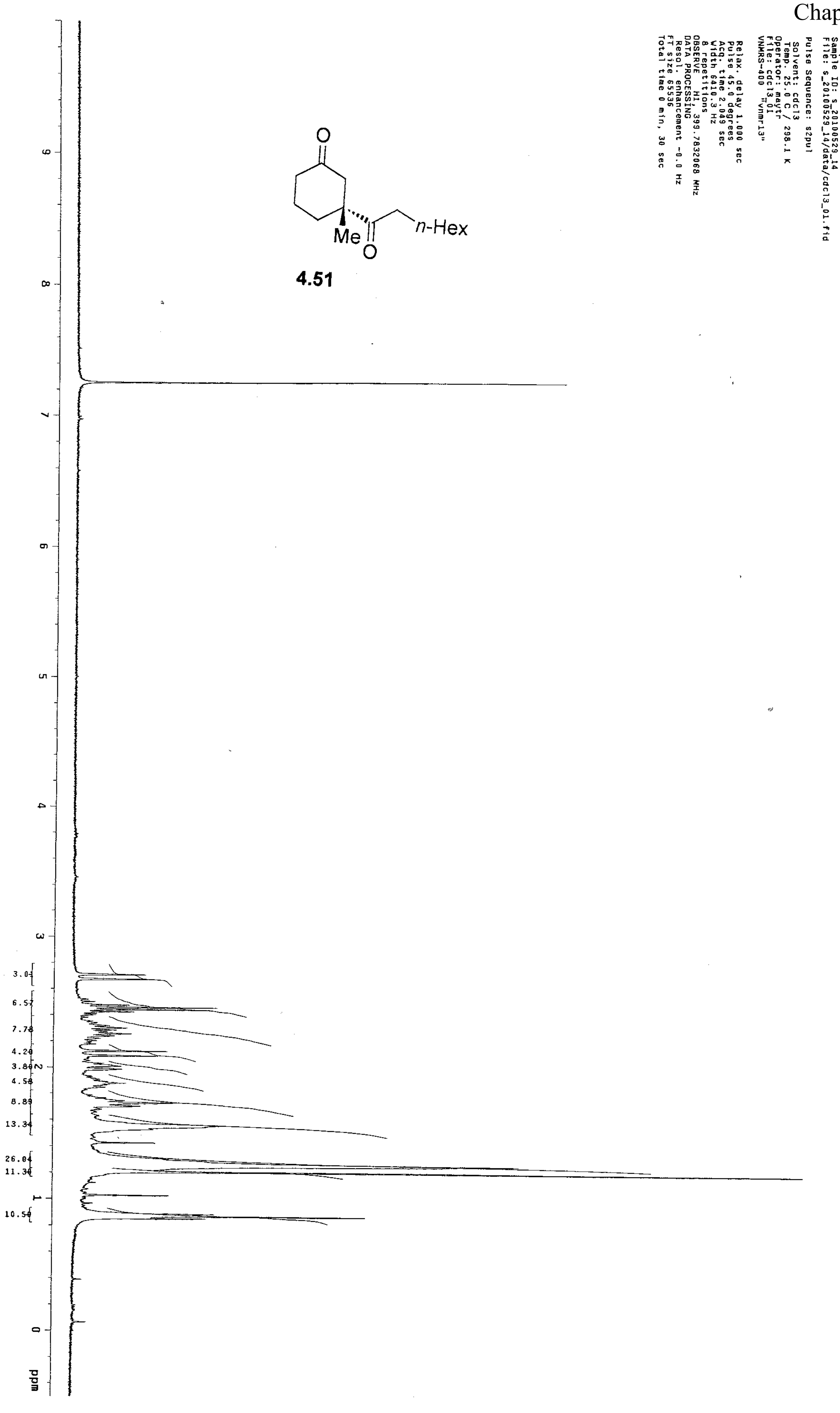


4.48



4.50

O
O
n-Hex
Me
SiMe$_3$
9
8
7
6
5
4
3
2
1
0
ppm
2.31
1.57
2.56
9.63
2.76
10.14
2.58
14.38
5.08
25.08
6.89
4.52
1.30
1.21
tlm-VII-081-f2



4.51

```
Sample: tlm-VIII-112-f5
Sample ID: s_20100529_14
File: s_20100529_14/data/cdcl3_01.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400 "vnmr13"

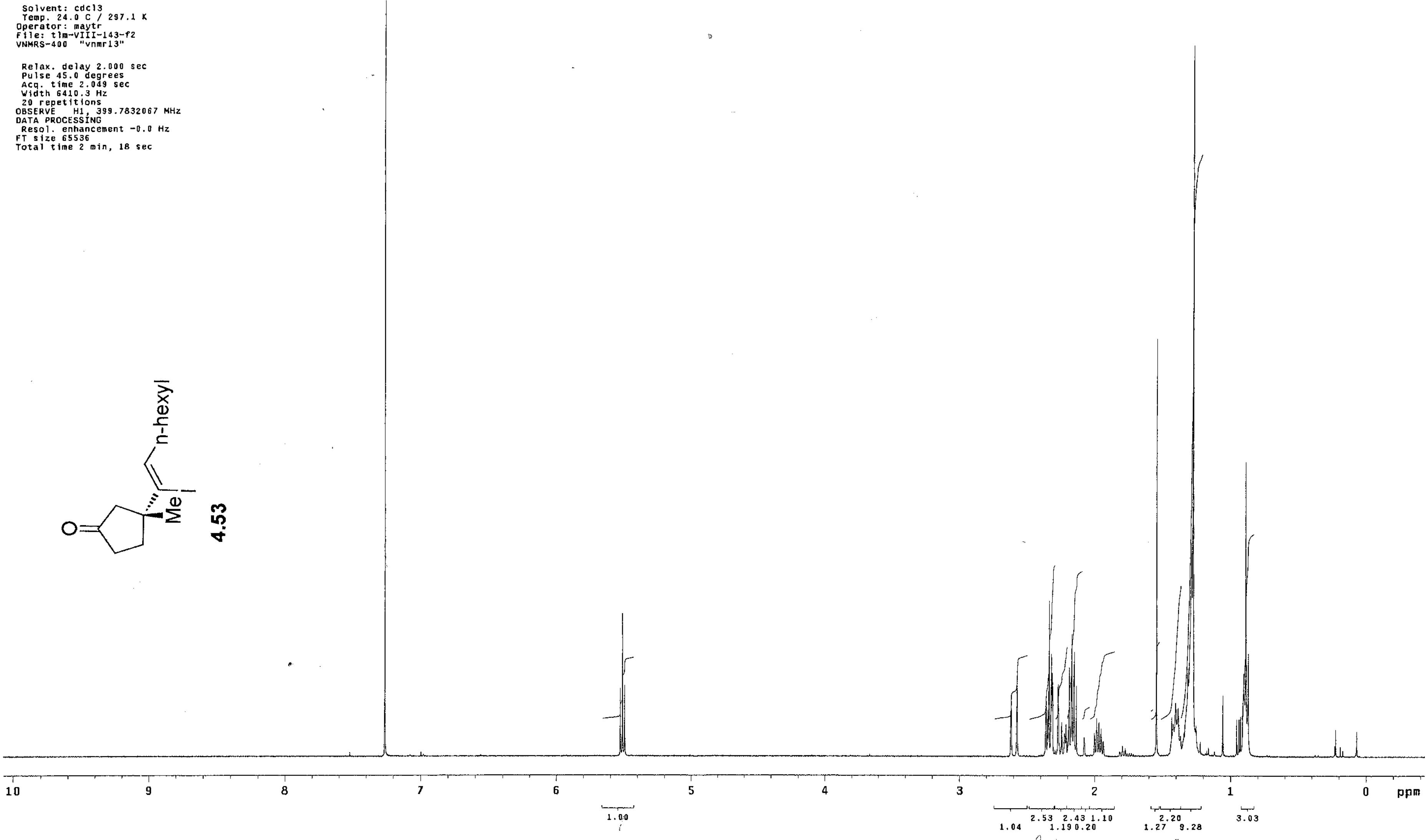
  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
OBSERVE   H1, 399.7832068 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

Me
n-Hex
9
8
7
6
5
4
3
2
1
0
ppm
3.01
6.57
7.78
4.20
3.80
4.58
8.89
13.34
26.04
11.38
10.50

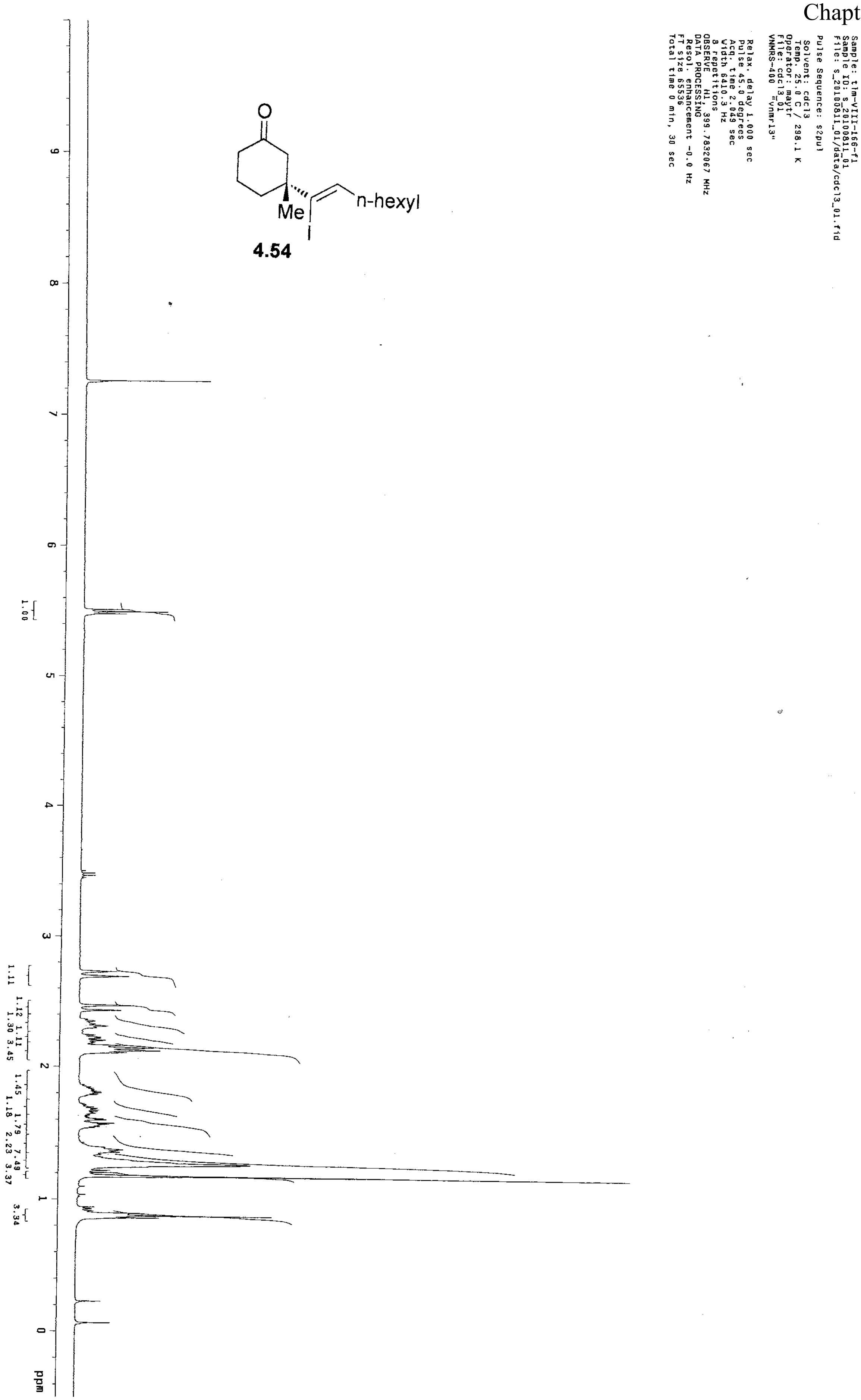
```
Sample: tlm-VIII-143-f2
File: /home/ahh/vnmrsys/data/maytr/tlm-VIII-143-f2.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: maytr
File: tlm-VIII-143-f2
VNMRS-400  "vnmr13"

 Relax. delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 20 repetitions
OBSERVE   H1, 399.7832067 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 2 min, 18 sec
```



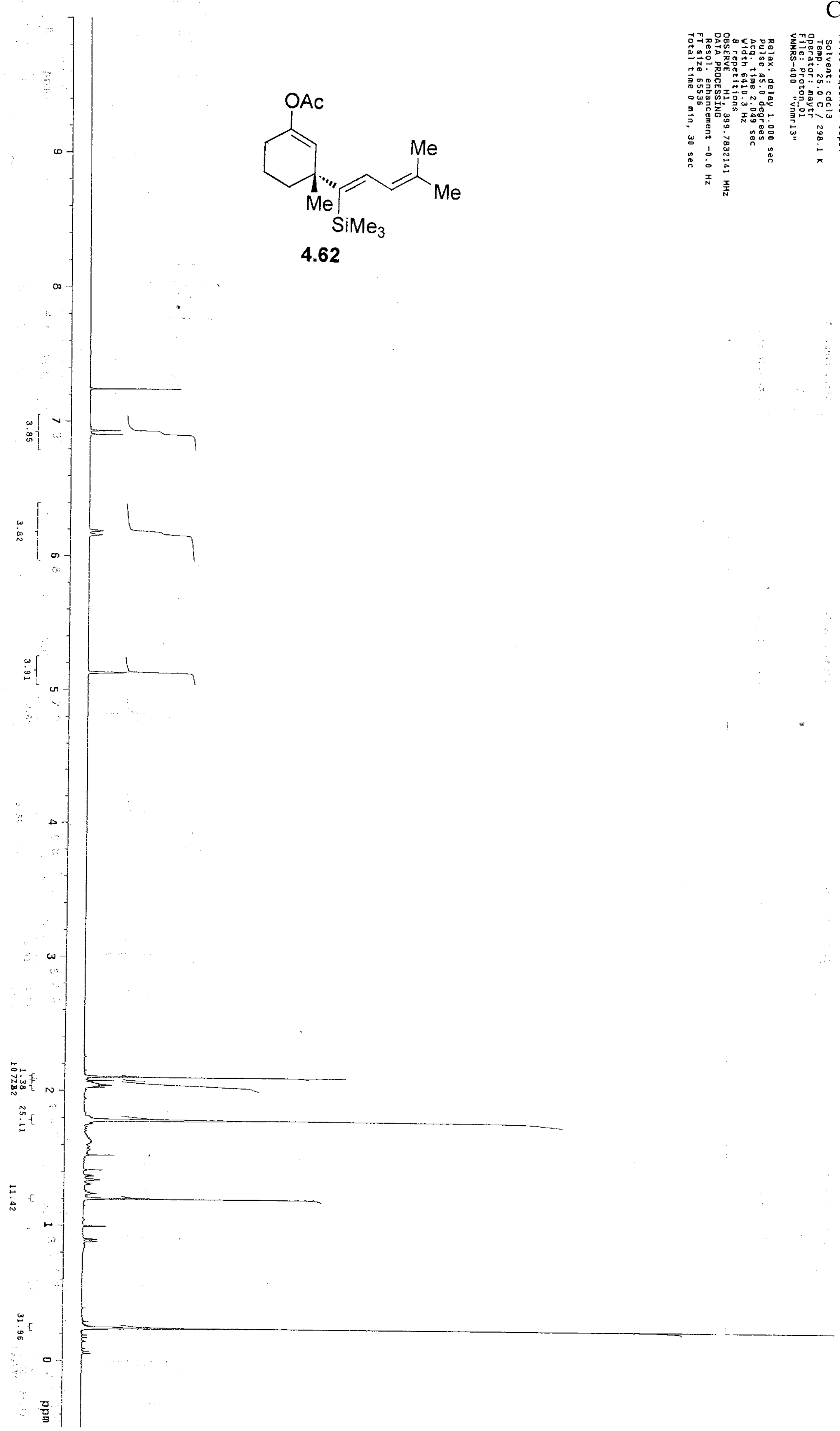
4.53


O
Me
I
n-hexyl
4.54
Sample: tlm-VIII-166-f1
Sample ID: s_20100811_01
File: s_20100811_01/data/cdcl3_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400 "vnmr13"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7832067 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.11
1.12
1.11
1.30
3.45
1.45
1.18
1.79
2.23
7.49
3.37
3.34

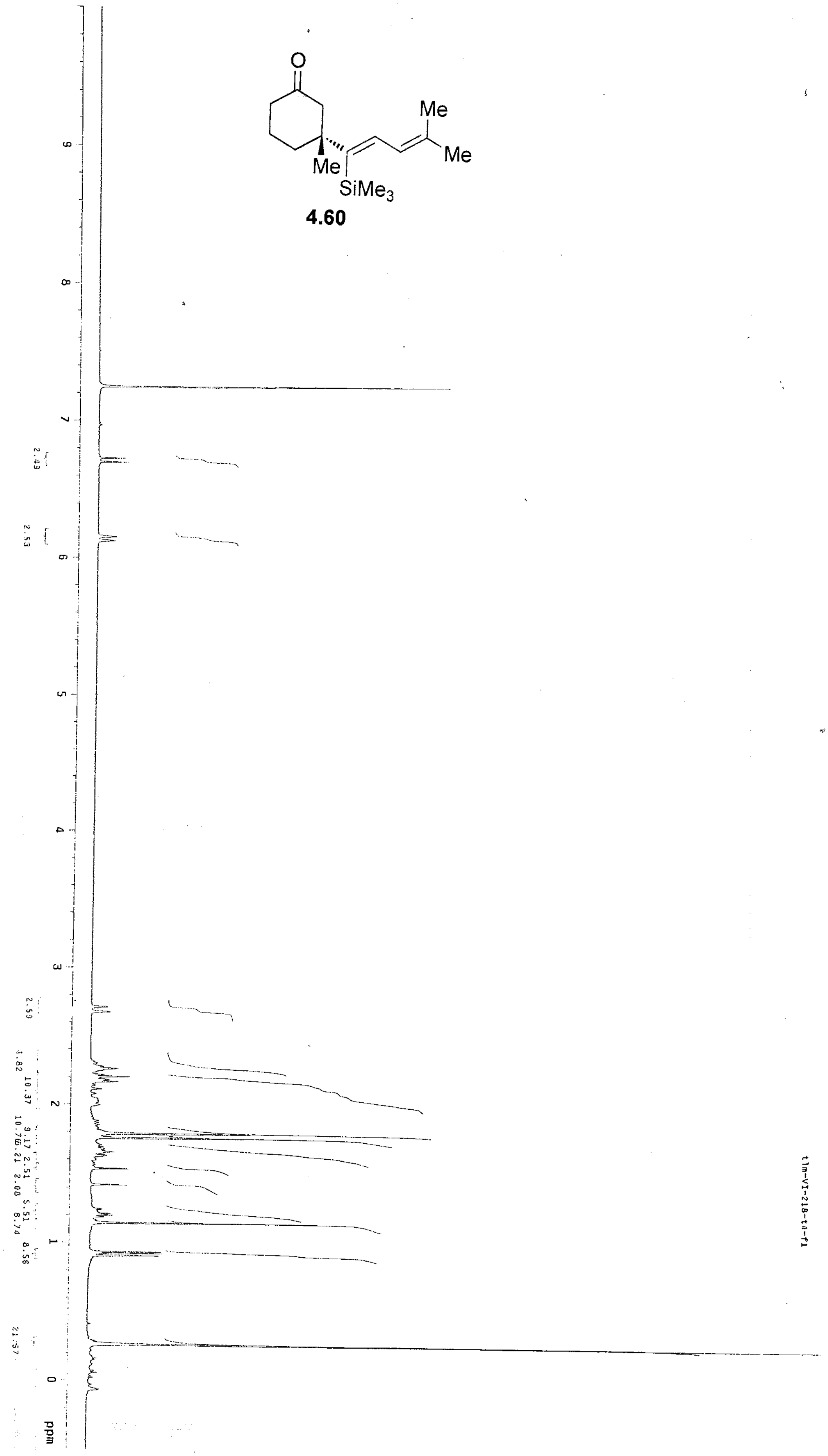
```
Sample: tlm-VII-169-f1
Sample ID: s_20091003_010
File: maytr/tlm-VII-169-f1/Proton_01.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 25.0 C / 298.1 K
Operator: maytr
File: proton_01
VNMRS-400  "vnmr13"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
OBSERVE   H1, 399.7832141 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

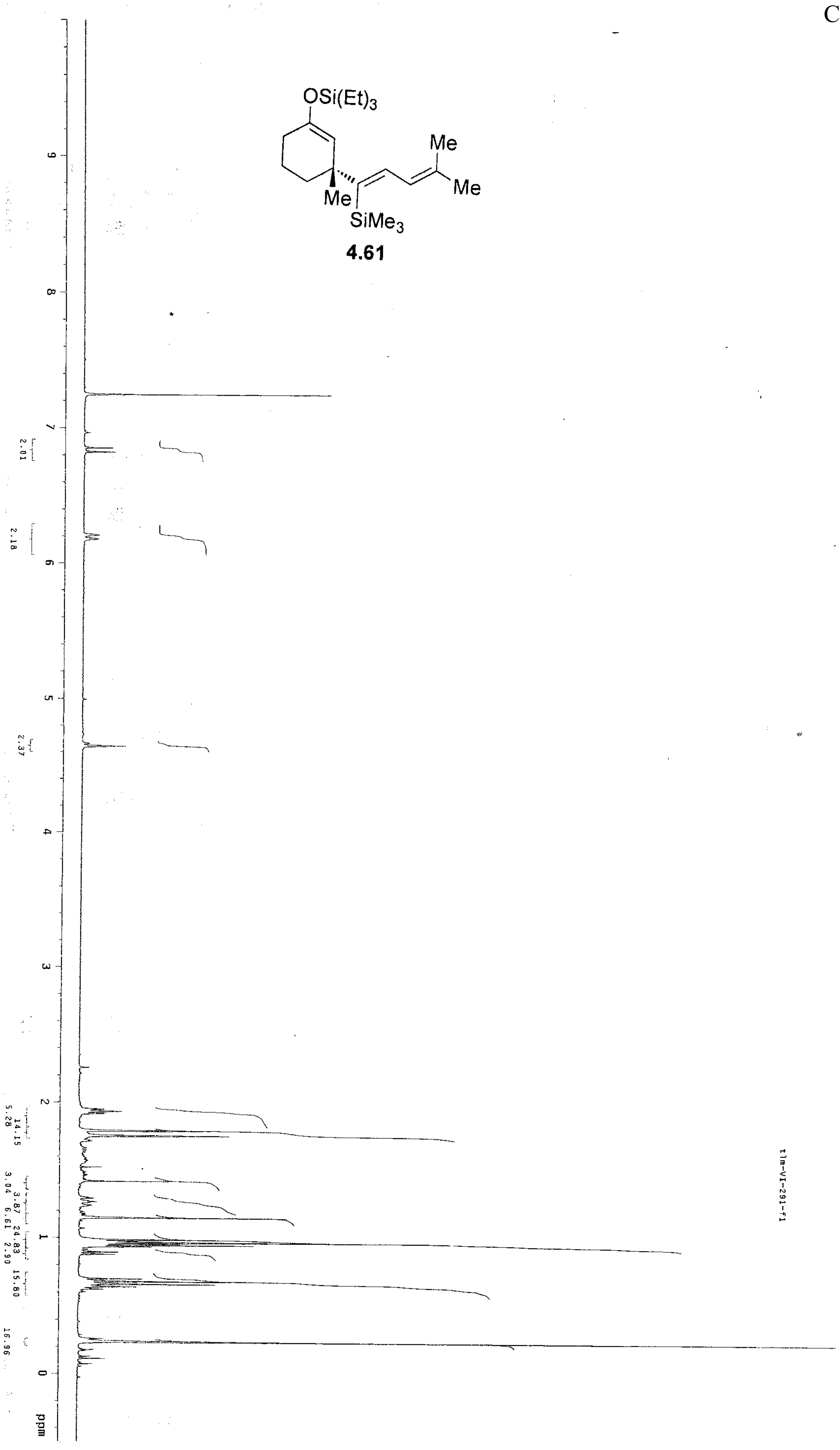


4.62

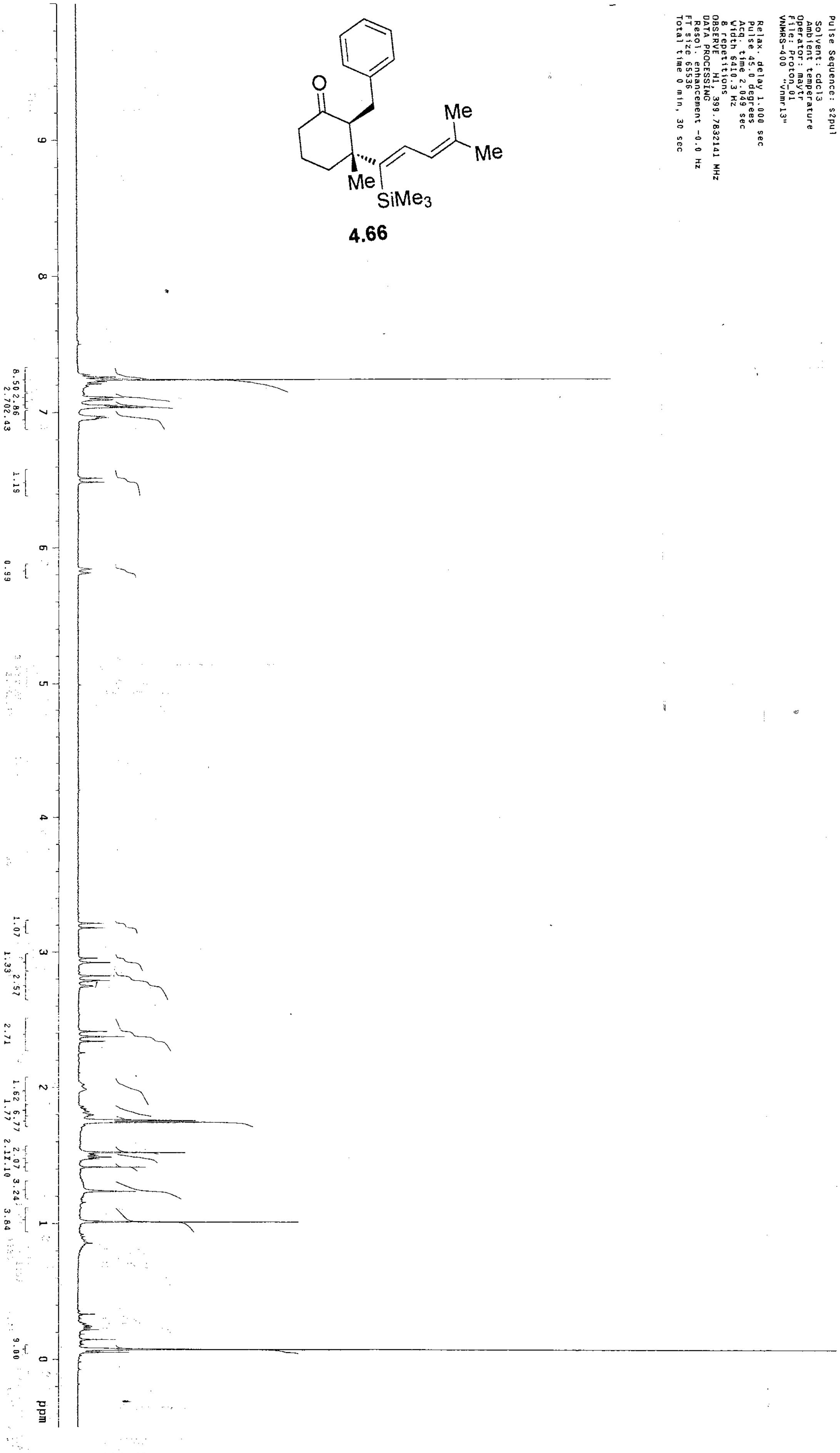


4.60

O
Me
Me
Me
SiMe3
9
8
7
6
5
4
3
2
1
0
ppm
2.49
2.53
2.53
4.82
10.37
10.76
6.21
9.17
2.51
2.08
5.51
8.74
8.56
21.57
tlm-VI-218-t4-f1


OSi(Et)$_3$
Me
Me
Me
SiMe$_3$
9
8
7
6
5
4
3
2
1
0
ppm
2.01
2.18
2.37
14.15
5.28
3.87
3.04
24.83
6.61
2.90
15.80
16.96
tlm-VI-291-f1

4.61



4.66

```
Sample: tlm-VII-095-flashed
Sample ID: s_20090912_003
File: maytr/tlm-VII-095-flashed/Proton_01.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
Operator: maytr
File: Proton_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832141 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

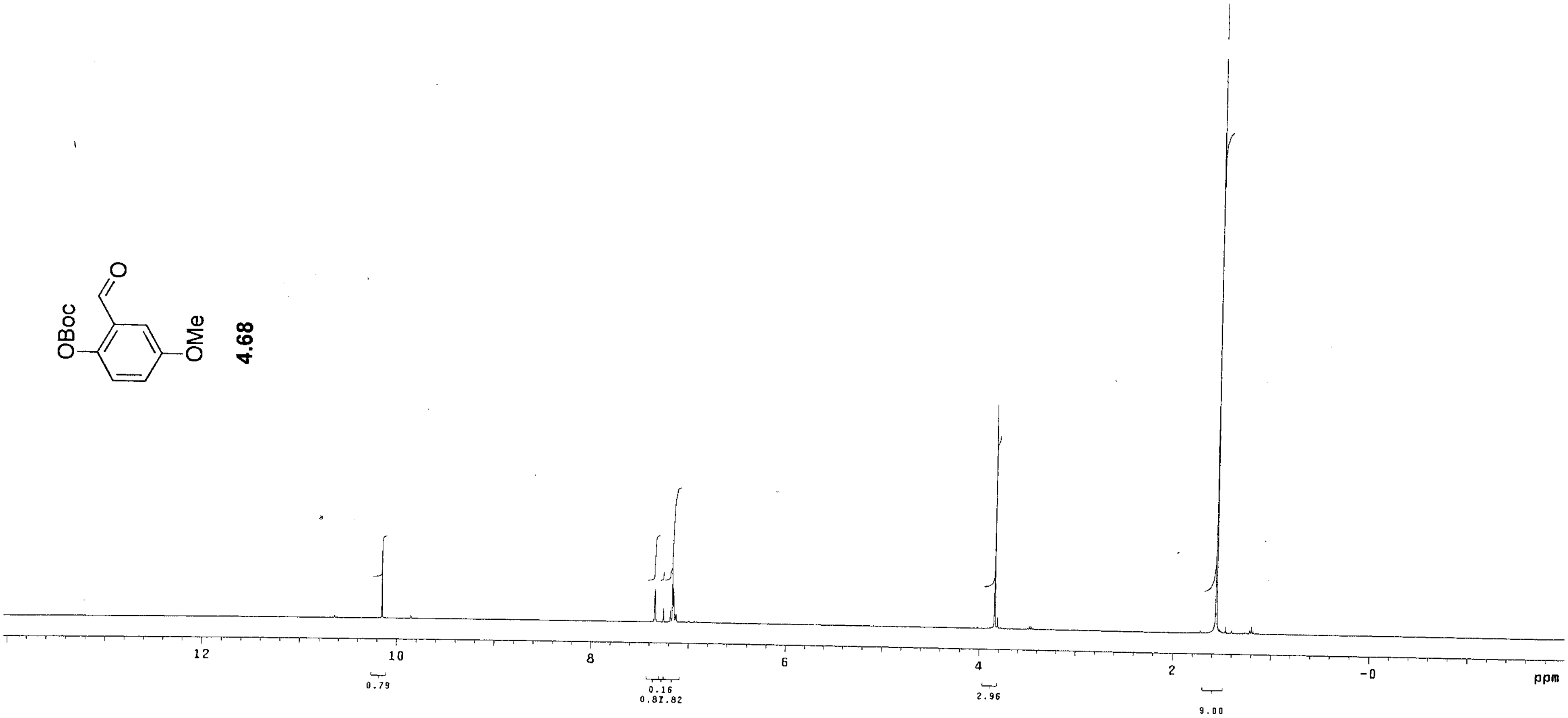
```
Sample: tlm-VIII-099-f1-dried
Sample ID: s_20100513_01
File: s_20100513_01/data/cdcl3_01.fid

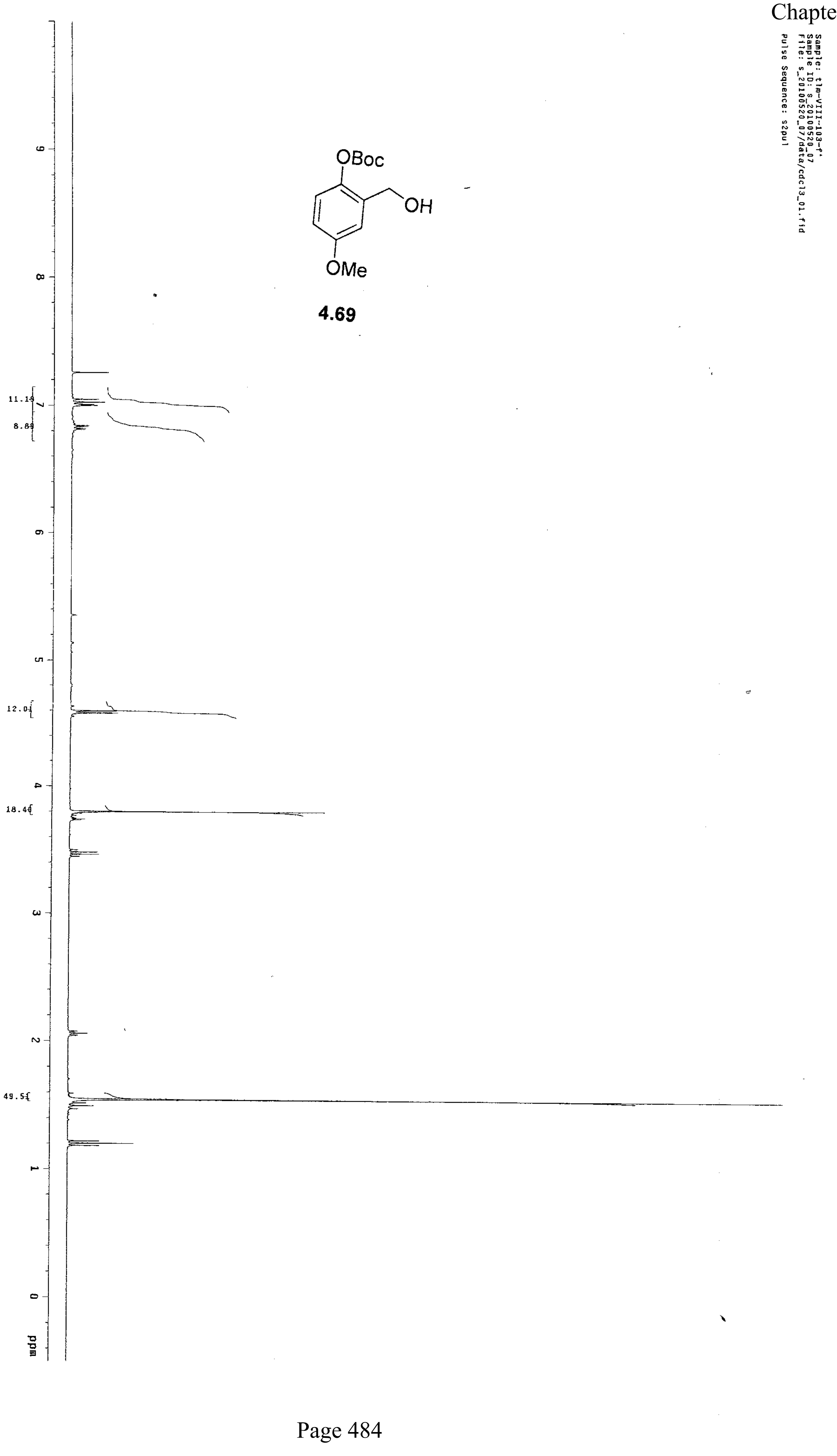
Pulse Sequence: s2pul

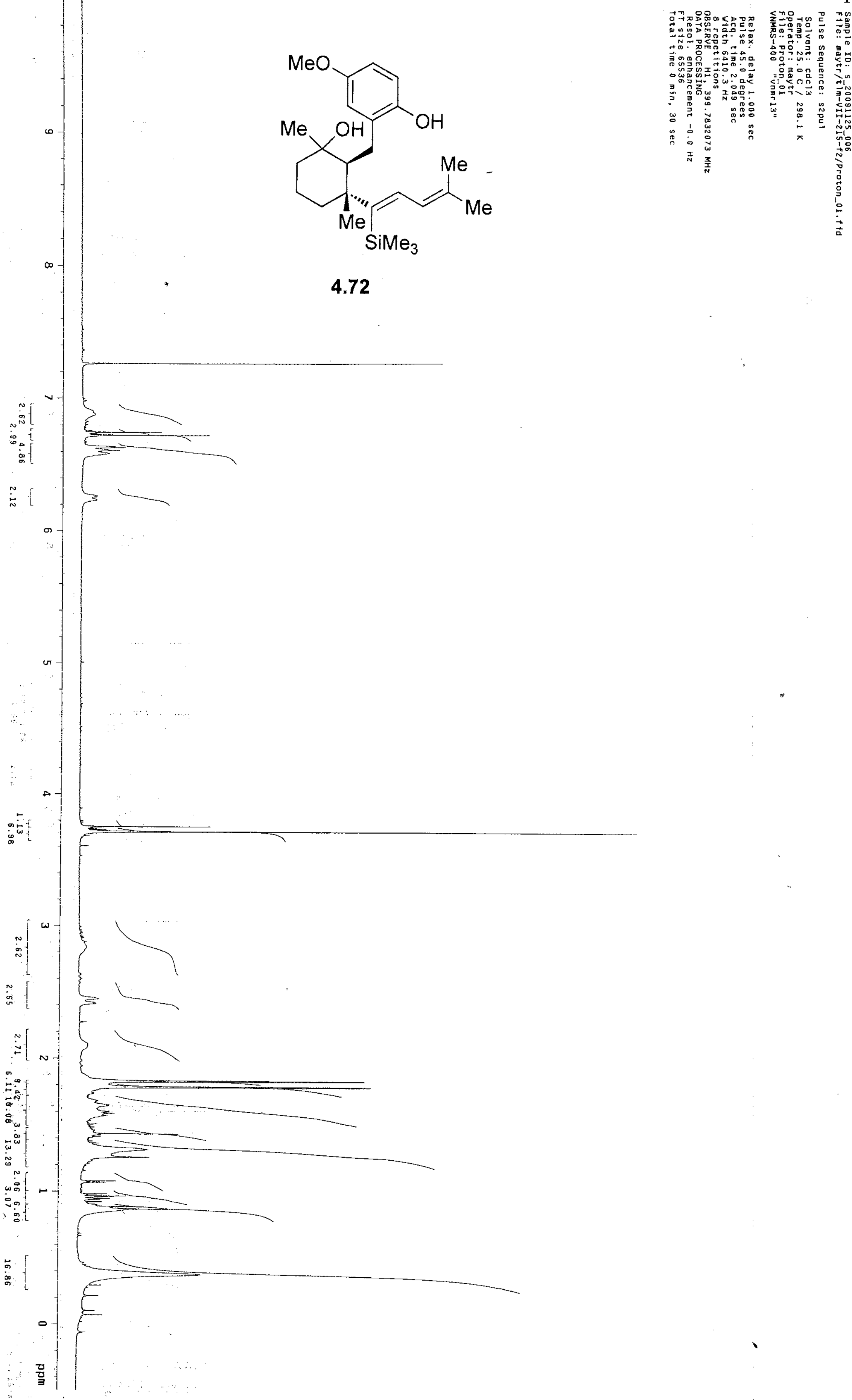
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: maytr
File: cdcl3_01
VNMRS-400  "vnmr13"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE   H1, 399.7832059 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
```

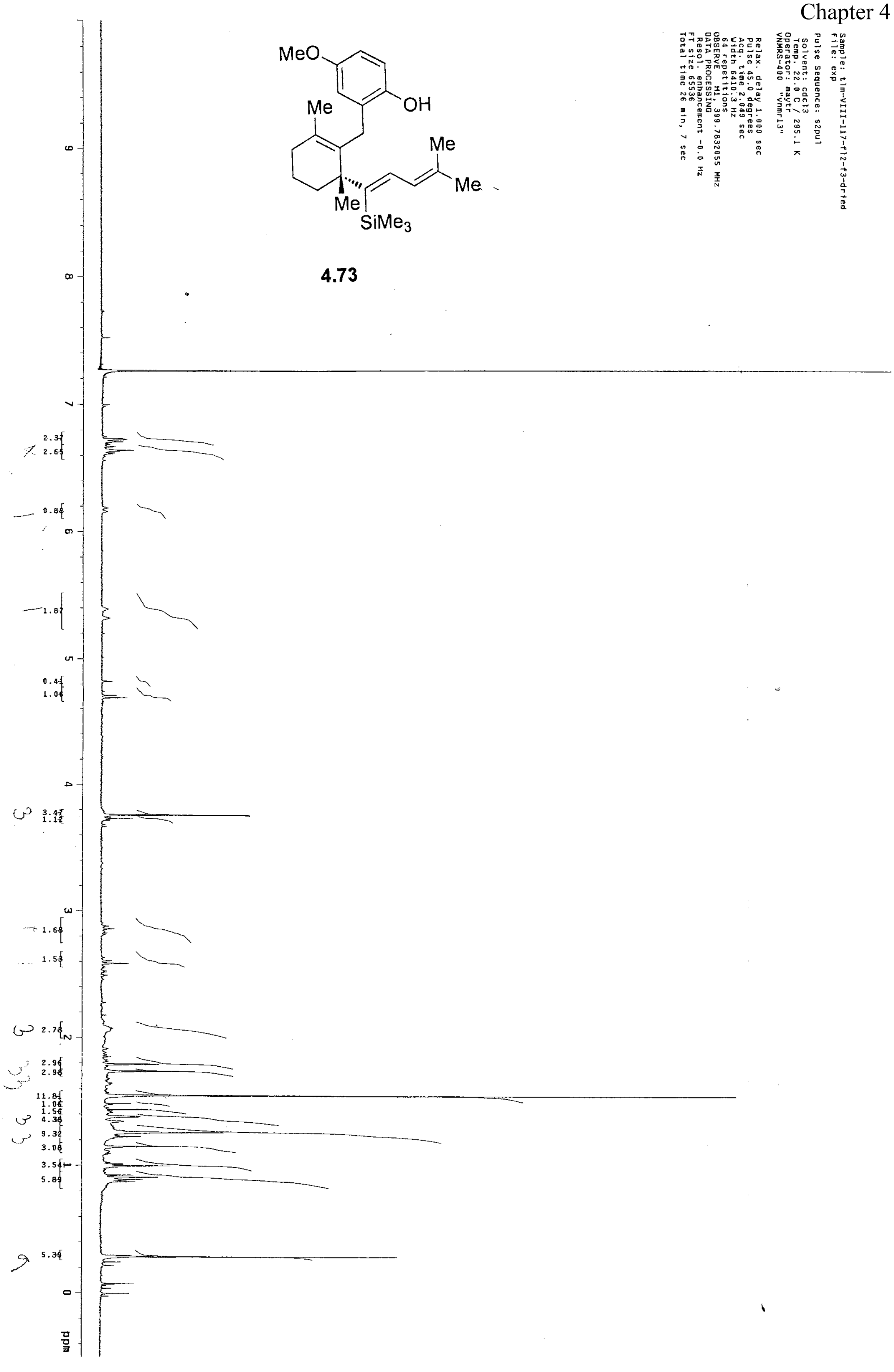
4.68




Sample: tlm-VIII-103-f'.
Sample ID: s_20100520_07
File: s_20100520_07/data/cdcl3_01.fid
Pulse Sequence: s2pul
OBoc
OH
OMe
4.69
11.14
8.89
12.04
18.40
49.51
9
8
7
6
5
4
3
2
1
0
ppm


Sample: tlm-VII-215-f2
Sample ID: s_20091125_006
File: maytr/tlm-VII-215-f2/Proton_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: maytr
File: Proton_01
VNMRS-400 "vnmr13"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7832073 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
MeO
OH
Me
OH
Me
Me
Me
SiMe3
9
8
7
6
5
4
3
2
1
0
ppm
2.62
2.99
4.86
2.12
1.13
6.98
2.82
2.65
2.71
9.42
6.11
10.08
3.83
13.29
2.06
3.07
6.60
16.86

4.72

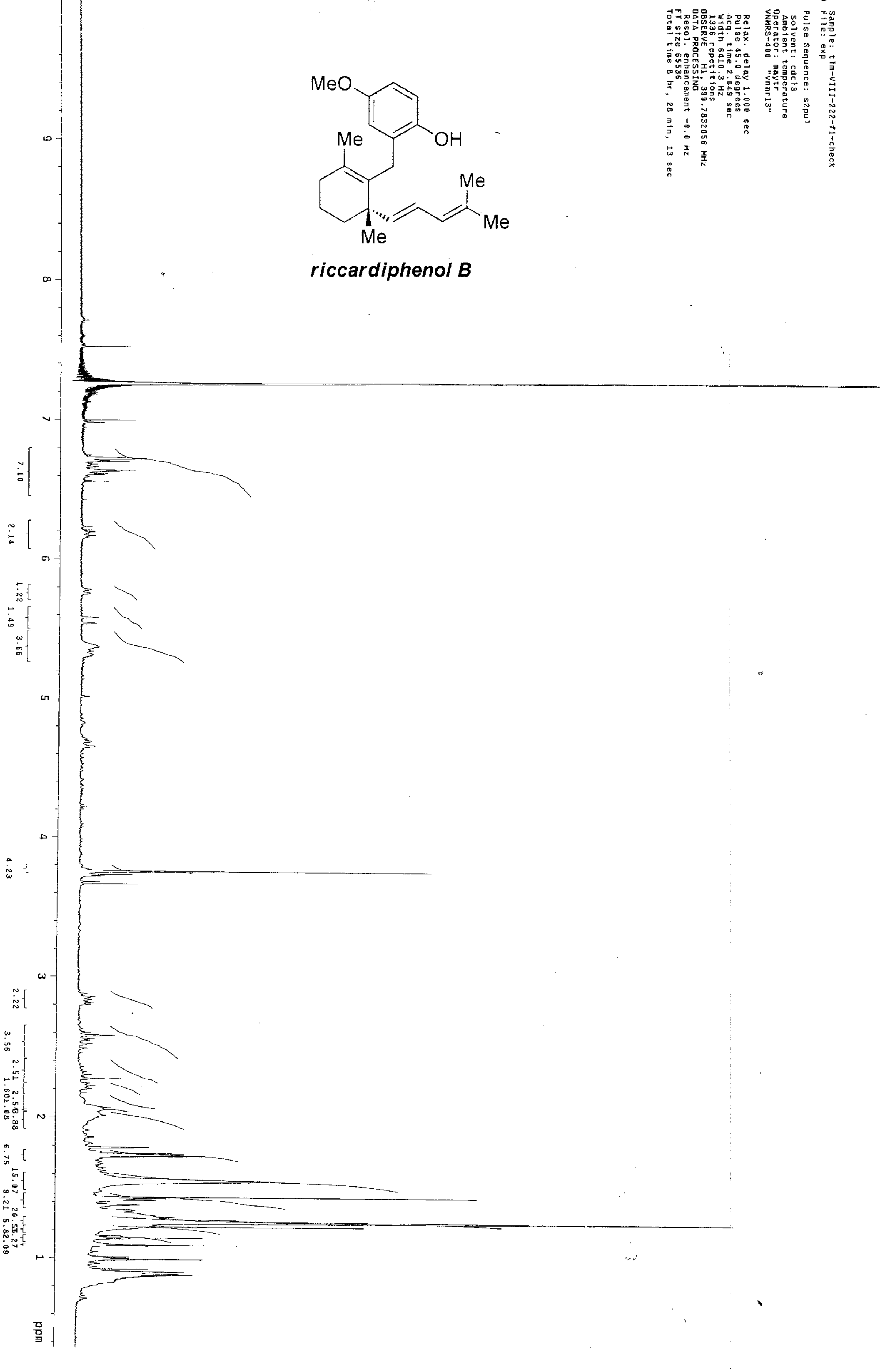


4.73

```
Sample: tlm-VIII-117-f12-f3-dried
File: exp

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 22.0 C / 295.1 K
Operator: maytr
VNMRS-400  "vnmr13"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  64 repetitions
OBSERVE   H1, 399.7832055 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 26 min, 7 sec
```


MeO
OH
Me
Me
Me
Me
Me
riccardiphenol B
Sample: tlm-VIII-222-f1-check
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: maytr
VNMRS-400 "vnmr13"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
1336 repetitions
OBSERVE H1, 399.7832056 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 8 hr, 28 min, 13 sec
9
8
7
6
5
4
3
2
1
ppm
7.10
2.14
1.22
1.49
3.66
4.23
2.22
3.56
2.51
1.60
1.08
2.50
0.88
6.75
15.07
9.21
20.55
5.82
3.27
2.09