DEVELOPMENT OF NICKEL-CATALYZED CYCLOADDITION AND COUPLING REACTIONS

by

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To my mother Tikirimenike and my wife Shyama

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ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
atm	atmosphere
BARF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate)
BDE	Bond Dissociation Energy
Bn	benzyl
BIPHEP	bis(diphenylphosphanyl)biphenyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
t-Bu	*tert*-butyl
COD	1,5-cyclooctandienyl
cot	cyclooctatetraene

Cp	cyclopentadienyl
Cy	cyclohexyl
^{o}C	temperature in degrees centigrade
d	day(s)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethylene
DFT	discrete Fourier transform
DIBAL	diisobutylaluminum hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DPEphos	bis(2-diphenylphosphinophenyl)ether
DIPHOS	1,2-bis(diphenylphosphino)ethane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMSO	dimethyl sulfoxide

Et	ethyl
equiv	equivalent
EWG	Electron Withdrawing Group
ESTA	ethyl trimethylsilylacetate
h	hour(s)
Hex	hexanes
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
IMes	1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
LOBA	lithium-1,1,3,3-tetramethylbutyl-*tert*-butylamide
Me	methyl
MEM	methoxyethoxy
min	minute(s)

NHC	*N*-heterocyclic carbene
Nu	Nucleophile
PCC	pyridinium chlorochromate
Pent	pentyl
Ph	phenyl
PMB	*p*-Methoxybenzyl ether
PMP	*p*-Methoxyphenyl
i-Pr	isopropyl
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBSH	*t*-butyldimethylsilane
TESH	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPSH	triisopropylsilane
TLC	thin layer chromatography
Tol	toluene

TPSH	triphenylsilane
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TsCl	*p*-toluenesulfonyl chloride
TsOH	*p*-toluenesulfonic acid

ABSTRACT

DEVELOPMENT OF NICKEL-CATALYZED CYCLOADDITION AND COUPLING REACTIONS

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Chair: John Montgomery

Nickel-catalyzed carbon-carbon bond-forming reactions provide a potentially useful strategy to generate a variety of organic compounds efficiently, regioselectively, chemoselectively, and stereoselectively. The versatility of these types of reactions makes them a powerful tool in organic synthesis. This dissertation mainly focuses on methodology development involving nickel catalysis. In this work, a number of highly selective reactions of readily available precursors, such as alkynes, enals and enones were developed.

In one application, a novel, nickel-catalyzed [3+2] cycloaddition of enals and alkynes was explored. This reaction provides a diastereoselective and chemoselective entry to five-membered rings, which are a common structural

motif in many architecturally complex and biologically active natural products. This nickel-catalyzed reaction is the first catalytic, intermolecular route to this scaffold, and during the development of this process, we uncovered significant effects of ligands on the intramolecular and intermolecular reactions. For example, the intramolecular reaction could be carried out with either bidentate or monodentate phosphine ligands; however, the intermolecular reaction is effective only with monodentate phosphine ligands. Additionally, the product distribution of the reaction could be varied by changing the ligand structure.

In another application, a novel, nickel-catalyzed intermolecular reductive coupling of enones and alkynes was developed. The key feature of this reaction is the chemoselective coupling of two potential Michael acceptors such as enones and alkynoates. The direct participation of alkynes as an alternative to preparing and handling sensitive vinyl cuprate reagents provides potentially significant improvements in accessing γ,δ-unsaturated ketones.

An intriguing, nickel-catalyzed, intermolecular reductive coupling of enals and alkynes has also been developed. The unique features of this reaction are the construction of geometrically pure *Z*-enol silanes and high functional group tolerance. The direct participation of enals, alkynes and silanes as an alternative to existing methods provides potentially significant improvements in accessing enol silanes. Additionally, this reaction provides direct evidence for the catalytic involvement of a seven-membered oxametallacycle intermediate.

A novel, nickel-catalyzed intermolecular three-component coupling of aldehydes, alkynes, and enones has been developed. This new process involves an internal redox mechanism and proceeds in the absence of reducing agents that have previously been required in related nickel-catalyzed couplings. The high extent of chemoselectivity is unusual, particularly for aldehyde, enone, alkyne couplings that involve three different π-components. Moreover, deuterium labeling experiments illustrate a unimolecular hydrogen migration and rule out alternate mechanisms that could involve a preformed nickel-hydride active catalyst. Together, these new methods provide access to interesting chemical scaffolds and greatly expand the versatility of nickel-catalyzed reactions.

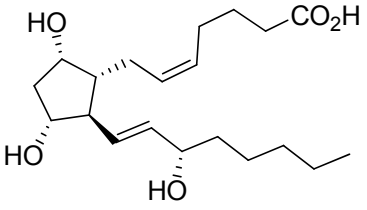
CHAPTER 1

NICKEL-CATALYZED [3+2] REDUCTIVE CYCLOADDITION OF ENALS AND ALKYNES

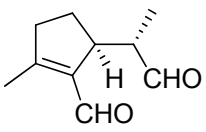
1.1 Introduction

Five-membered carbocycles are important building blocks for many biologically active molecules.[1,2] Moreover, substituted cyclopentenones such as cyclopentenone prostaglandins exhibit characteristic biological activity.[3] A few representative natural products containing highly functionalized five-membered rings are listed in Scheme 1, and all of them have been identified as important synthetic targets due to their biological activities.

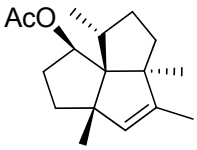
Scheme 1. Representative Cyclopentanoid Natural Products



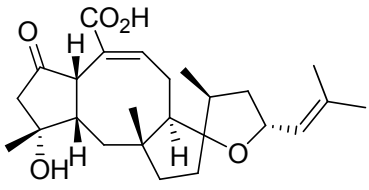
$PGF_{2\alpha}$



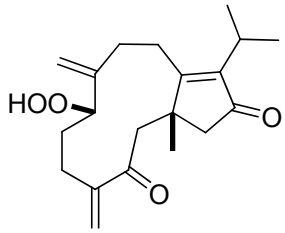
Chrysomelidial



1-Acetoxy-isocomene



Ophiobolin A



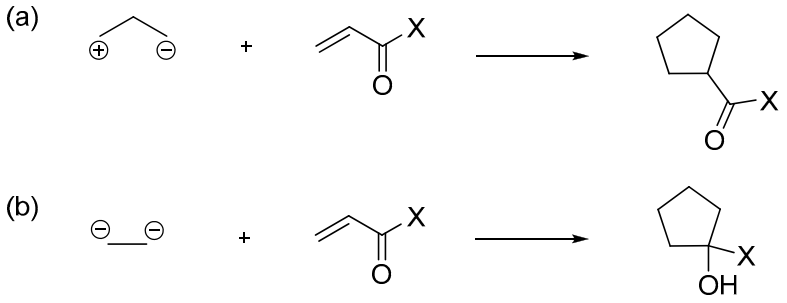
Dolabellane diterpenes

Efficient synthesis of highly functionalized cyclopentane rings continues to remain an important challenge in organic synthesis. Current methods for the formation of five-membered rings are based on cycloadditions involving either four π-electrons ([$3_{2\sigma}$ + $2_{2\pi}$], [$3_{2\pi}$ + $2_{2\pi}$]) or six electrons ([$3_{4\pi}$ + $2_{2\pi}$], [$4_{4\pi}$ + $1_{2\pi}$], [$2_{2\pi}$ + $2_{2\pi}$ + $1_{2\pi}$]).

1.1.1 [3+2] Cycloaddition

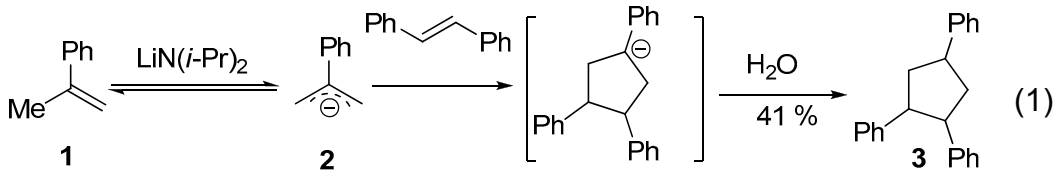
The most efficient method for the construction of five-membered carbocyclic rings is a [3+2] cycloaddition process.[4-6] Anionic,[7] cationic,[8,9] free radical mediated[10] and transition metal catalyzed[2,4,6] [3+2] cycloadditions have been investigated. The most widely used method is one in which dipolar three carbon units are coupled with electron deficient olefins (Scheme 2a) with the involvement of 4π electrons from the dipole and 2π electrons from the alkene. However, the [3+2] cycloaddition between dianionic building blocks and dicationic building blocks are less common (Scheme 2b).[11,12]

Scheme 2. (a) [3+2] Cycloaddition of Dipolar Three Carbon and Two Carbon Units and (b) Dianionic Two Carbon and Dicationic Three Carbon Units

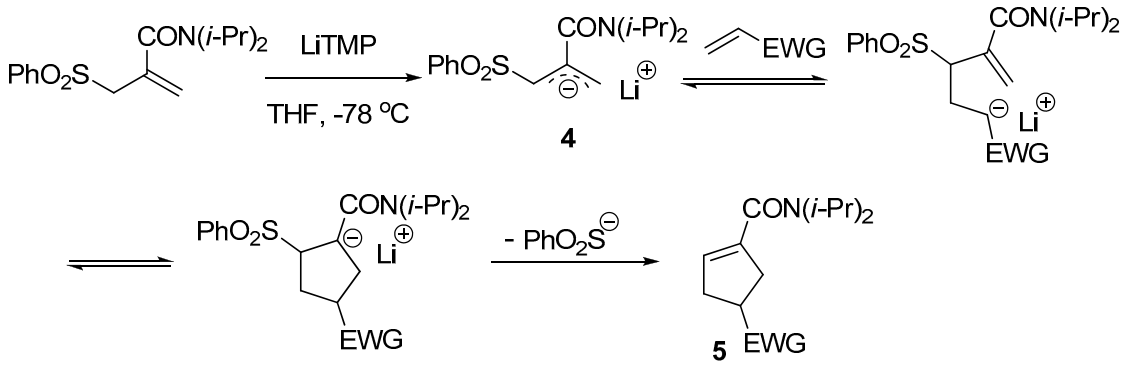


1.1.1.1 Anionic [3+2] Cycloaddition

Early methods of generating five-membered carbocycles involved anionic [3+2] cycloaddition of allyl anions or allyllithium compounds to double or triple bonds. In 1972, Kauffman and co-workers reported the use of anionic [3+2] cycloaddition to generate cyclopentanes (eq 1).[13] The allyl anion **2** was generated by treatment of α-methyl styrene **1** with lithium diisopropylamide and was reacted with stilbene to generate cyclopentane **3**.



Scheme 3. Anionic [3+2] Cyclization/Elimination

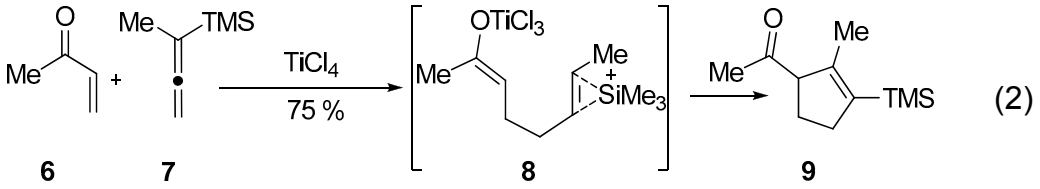


In the late 1980s, Beak and co-workers reported an anionic [3 + 2] cyclization/elimination route to synthesize cyclopentenes.[7] Allyl lithium **4** underwent coupling with olefins bearing an electron-withdrawing group to generate cyclopentenes **5** in high yields (Scheme 3). The formation of cyclopentenes **5** occurs in a stepwise fashion. Initial highly regioselective addition

to the electron-deficient olefin by the allyllithium reagent **4** followed by a 5-endo-trig cyclization and elimination of benzenesulfinate generated the cyclopentenes **5**. The β´-(phenylsulfonyl) group activates the β´-hydrogen for metalation and provides a stable allyllithium reagent **4**, which directs a highly regioselective addition to the electron deficient olefin.

1.1.1.2 Cationic [3+2] Cycloaddition

In 1981, Danheiser and co-workers employed trimethylsilylallenes as the three carbon component in [3+2] annulations to produce highly substituted cyclopentenes (eq 2).[14] A unique feature of this annulation is its ability to regiospecifically generate highly substituted five-membered rings which are functionally equipped for further synthetic transformations.

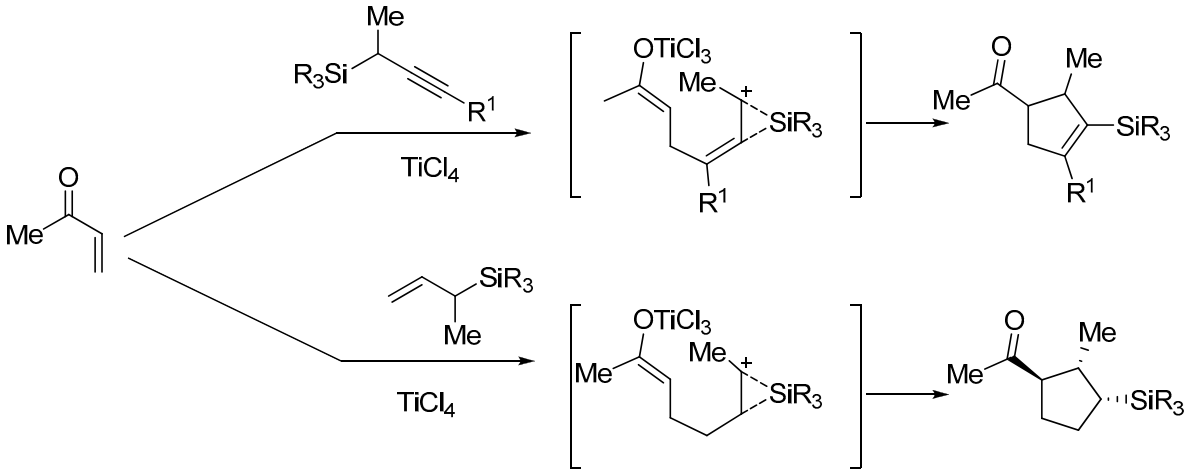


(2)

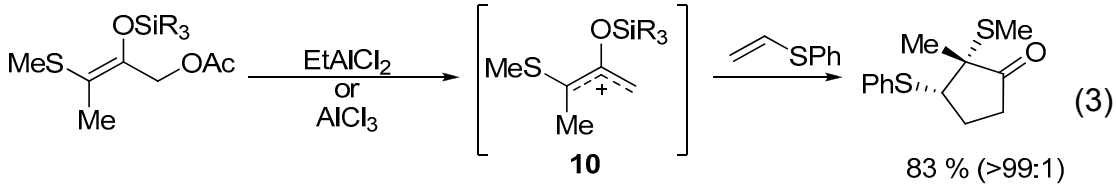
Initial complexation of $TiCl_4$ to methyl vinyl ketone **6** generates an alkoxy allylic carbocation, which initiates regiospecific electrophilic substitution of the (trimethylsilyl)allene **7** at C(3). The generated carbocation is stabilized by the β-silyl group. A 1,2 shift of the trimethylsilyl group then affords an isomeric cation **8** which is intercepted by the titanium enolate to produce a five-membered ring **9**. This method was further developed by introducing propargyl and allyl silanes as the three-carbon component in a [3+2] annulation strategy to generate five-

membered carbocycles (Scheme 4).[15] Large trialkylsilyl groups were employed to avoid the known desilylation pathway leading to allenes.

Scheme 4. Propargyl and Allyl Silane as Three-carbon Components in [3+2] Cycloaddition



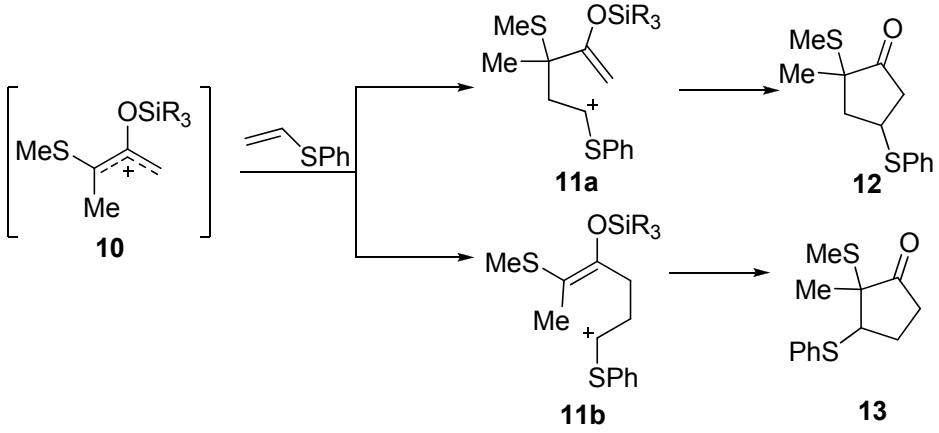
The Kuwajima group developed a new synthetic method for functionalized cyclopentanones by employing 1-(methylthio)-2-siloxyallyl cationic species **10** as the three carbon unit (eq 3).[9] Under the influence of a Lewis acid, silyl enol ether **10** reacted with a nucleophilic olefin to afford intermediate **11a** or **11b**. Then the enol silyl ether moiety and the cationic intermediate could undergo cyclization to yield cyclopentanone **12** or **13** (Scheme 5). The more sterically hindered regioisomer **13** was predominantly formed with high stereoselectivity.



(3)

83 % (>99:1)

Scheme 5. Siloxyallyl Cationic Species as a Three Carbon Unit



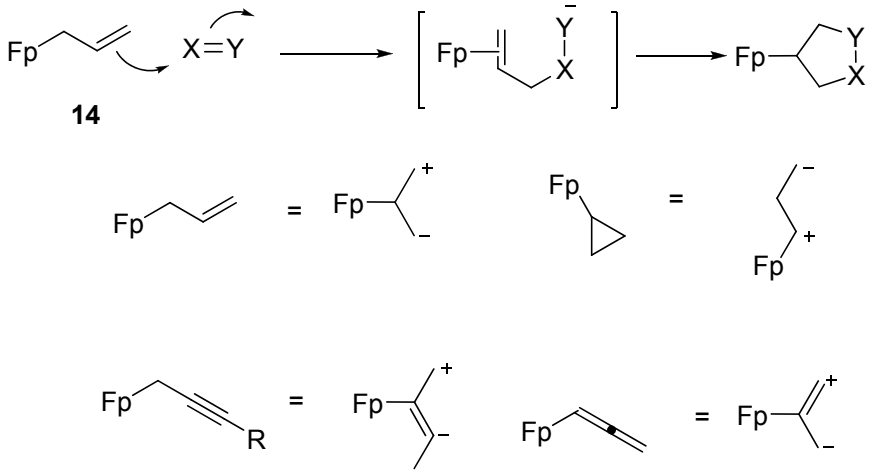
1.1.1.3 Transition Metal Catalyzed [3+2] Cycloaddition

Many classical cycloadditions require the presence of polarized functional groups as substrates. Furthermore, the reaction between unactivated substrates is poor and extreme conditions or special methodologies are required to obtain good yields of cycloadducts. Additionally, these cycloadditions can be promoted by heat, light, and Lewis acid etc. However, the evolution of metal catalysis has provided new opportunities to eliminate these drawbacks of cycloaddition with unactivated substrates.

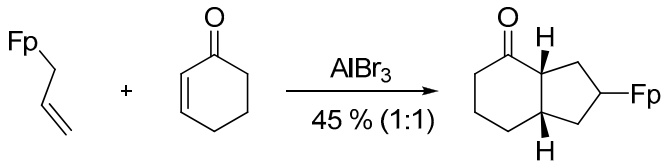
Metal-assisted formation of 1,3-dipoles has played a major role in facilitating the use of the [3+2] cycloaddition reaction in modern organic synthesis. One of the earliest examples of metal assisted 1,3-dipole formation involves transition metal alkenyl complexes.[16] Iron η^1-allyl complexes, such as **14**, and its congeners have been shown to behave as 1,3 dipoles (Scheme 6).[17] All of these complexes react with electron deficient olefins to generate metal-substituted cyclopentanes. These reactions most likely occur via a stepwise

mechanism. One of the disadvantages of these early metal-assisted [3+2] cycloaddition reactions is the requirement that the alkene component be very electron deficient. This problem was solved by adding Lewis acids to activate the α,β-unsaturated ketone. The [3+2] cycloaddition between iron η^1-allyl complexes and enones in the presence of a Lewis acid was first reported by the Rosenblum group (eq 4).[18]

Scheme 6. Iron η^1-Allyl Complexes and Its Congeners



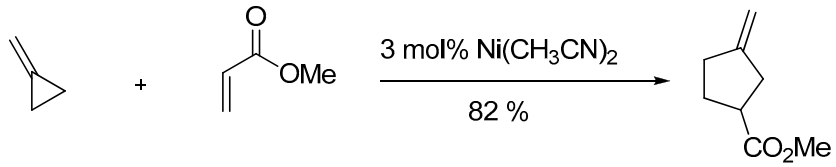
Fp = $CpFe(CO)_2$, Cp = η^5-cyclopentadienyl



(4)

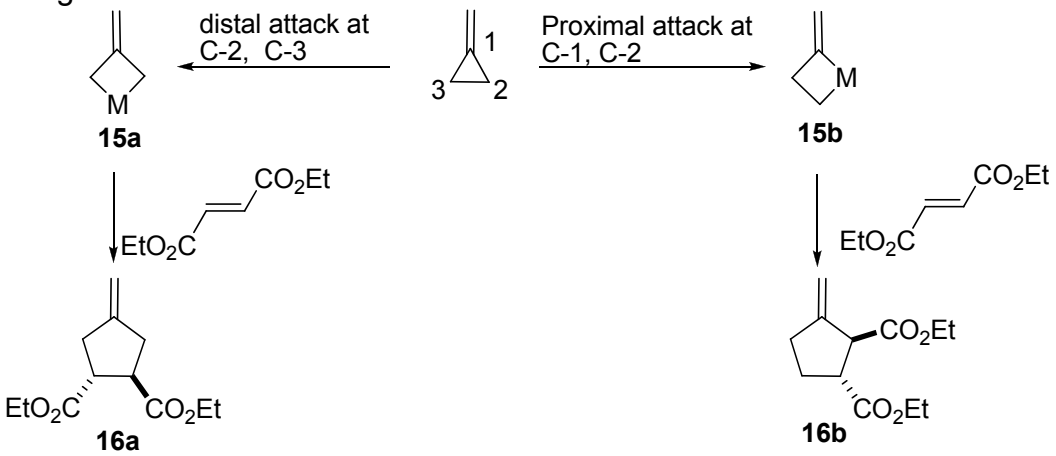
Various transition metals are known to insert into the strained bonds of cyclopropanes to generate metallacyclobutanes, which can be trapped by an olefin to produce cyclopentanes. In 1970, Noyori and co-workers reported a nickel catalyzed [3+2] cycloaddition of methylene cyclopropane with methyl

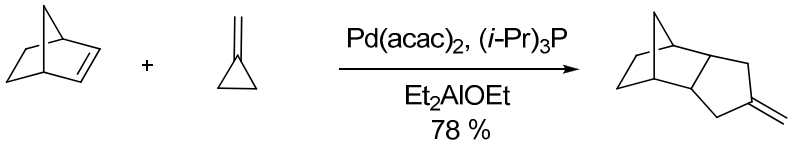
acrylate (eq 5).[19] This reaction can proceed via two different reaction pathways, which lead to regioisomers **16a** and **16b** (Scheme 7). Oxidative addition could occur either into the distal bond (C-2 and C-3) or proximal bond (C-1 and C-3) to generate two different metallacyclobutanes (**15a** and **15b**) followed by carbometalation of the double bond and reductive elimination to produce cyclopentanes. Noyori observed a mixture of cycloadducts derived from both distal and proximal ring opening with methylene cyclopropane and dimethyl fumarate in the presence of a catalytic amount of nickel catalyst (Scheme 7).[20] However, the cycloaddition reaction of methylene cyclopropane with Pd catalysts occurs exclusively at the distal bond (eq 6).[21]



(5)

Scheme 7. Possible Reaction Pathways of Methylene Cyclopropane Ring Opening

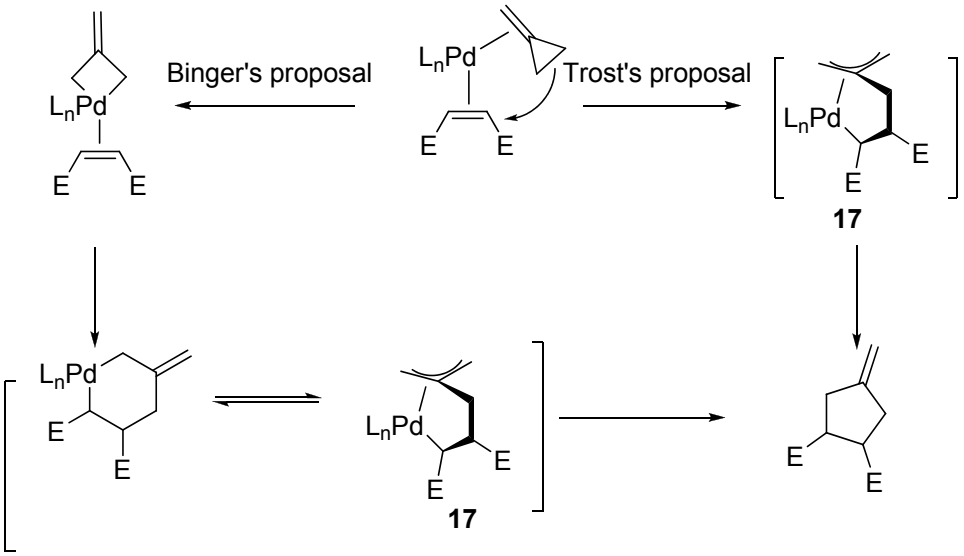




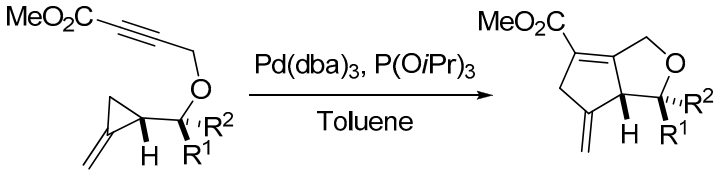
(6)

Binger has proposed that the distal ring opening might be initiated by prior coordination of both reaction partners to the metal, followed by an oxidative addition of the palladium into the distal bond.[22] In contrast, Trost proposed that after pre-coordination, the distal bond directly attacks the double bond of the acceptor to generate π-allyl complex **17** (Scheme 8).[2]

Scheme 8. Binger's Proposal vs. Trost's Proposal



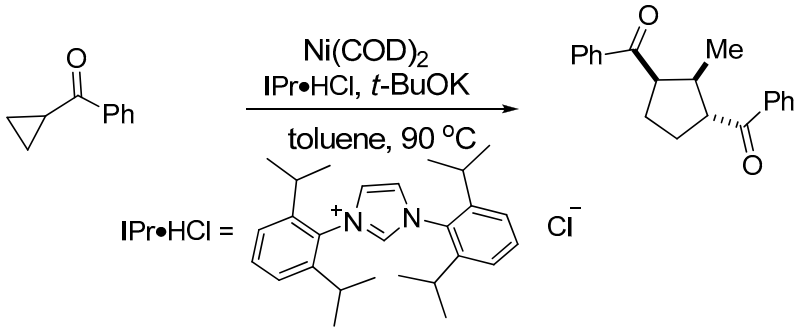
Additionally, intramolecular [3+2] cycloaddition of methylene cyclopropanes with alkynes has been used to produce bicycles with high stereoselectivity (eq 7).[23]



(7)

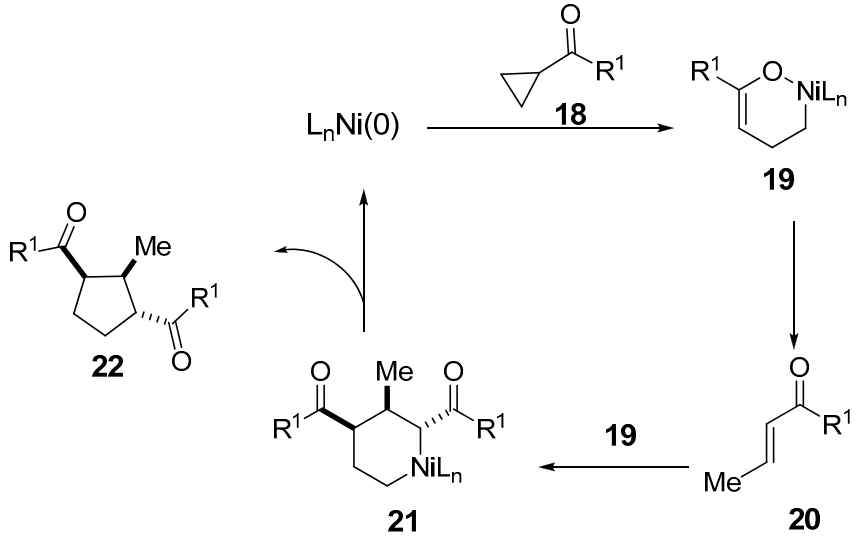
Recently, the Montgomery group developed a nickel catalyzed cyclization process employing cyclopropyl ketones, which underwent highly diastereoselective dimerization to produce trisubstituted cyclopentanes (eq 8).[24]

Cross-coupling of cyclopropyl ketones with enones was achieved by employing Lewis acids. The proposed mechanism is depicted in Scheme 9. Oxidative addition of Ni(0) with cyclopropyl ketone **18** generates metallacycle **19**, which could undergo β-hydride elimination to afford enone **20**. Then enone **20** and intermediate **19** could react to generate metallacycle **21**, which could undergo reductive elimination to produce [3+2] cycloaddition product **22**.

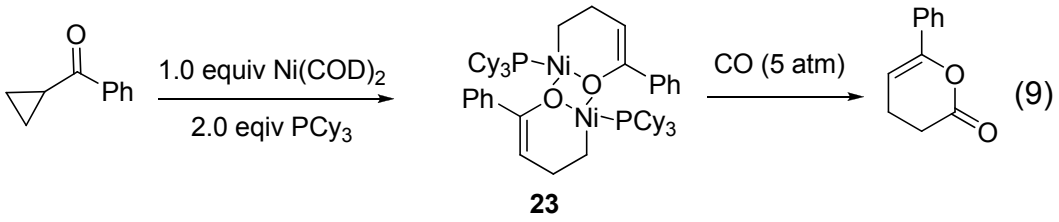


(8)

Scheme 9. Proposed Mechanism for the Dimerization of Cyclopropyl Ketones



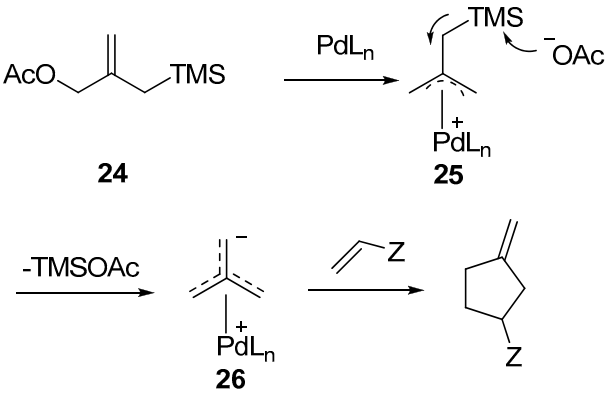
Ogoshi reported the same dimerization reaction of cyclopropyl ketones with a Ni(0)/phosphine catalyst and isolated nickelacycle **23** by using stoichiometric amounts of Ni and two equivalents of phosphine ligand (eq 9).[25]



23 (9)

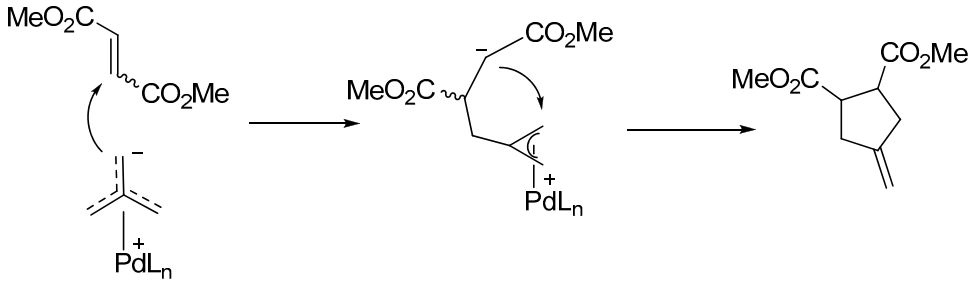
The Trost group demonstrated that palladium-trimethylenemethane (Pd-TMM) complexes can be used as a 1,3-dipolar unit to construct five-membered rings (Scheme 10).[26-28] Pd-TMM complexes are accessible by treatment of an allyl acetate **24** with a Pd(0) catalyst. The π-allylpalladium intermediate **25** readily undergoes loss of trimethylsilyl acetate to generate Pd-TMM complex **26**, which reacts with olefins to produce methylene cyclopentanes.

Scheme 10. Generation of the Pd-TMM Complex



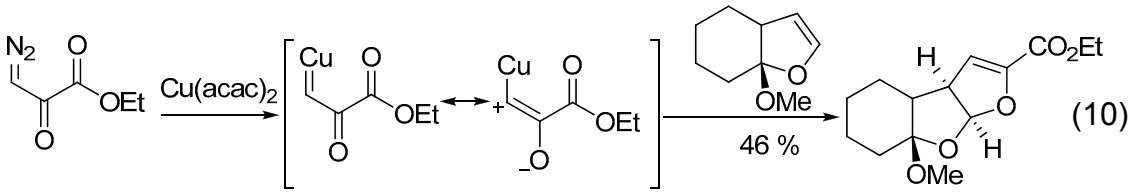
The stereoselectivity of the reaction depends on the alkene geometry. The reaction with *E*-olefins was stereoselective, whereas reaction with *Z*-olefins generated *cis/trans* mixtures of methylenecyclopentanes.[29,30] This lack of stereospecificity suggests a stepwise mechanism for this reaction (Scheme 11).

Scheme 11. Stepwise Mechanism



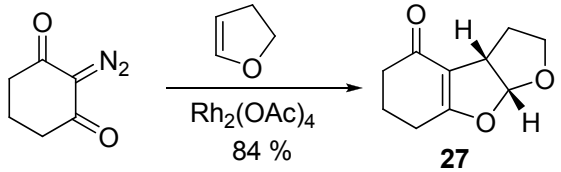
26

Additionally metal carbenoids have been coupled with electron rich olefins to produce cyclopentanes. In 1983, Wenkert and co-workers showed that copper carbenoids can serve as 1,3-dipoles and react stereoselectively with dihydrofurans to construct tricyclic ethers (eq 10).[31]



(10)

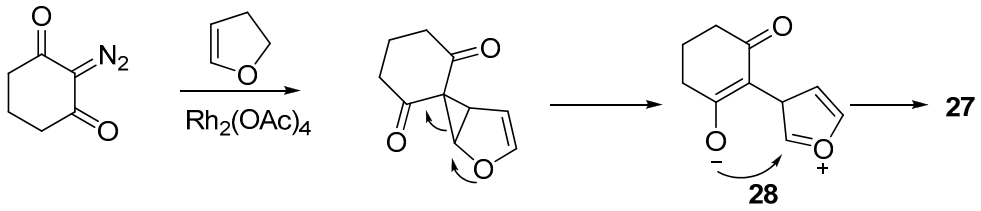
Later, Pirrung introduced a rhodium carbenoid to produce tricyclic compounds via a [3+2] cycloaddition (eq 11).[32] The proposed mechanism involves initial cyclopropanation of the furan followed by fragmentation to the zwitterion **28**, which is stabilized by the carbonyl group. Then *O*-alkylation of the enolate with the oxonium ion could generate tricyclic ketone **27** (Scheme 12).



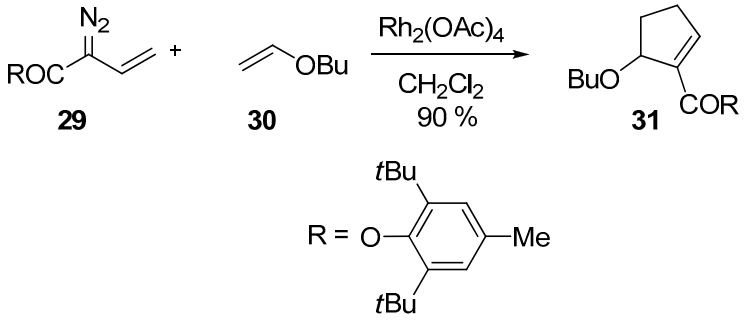
27

(11)

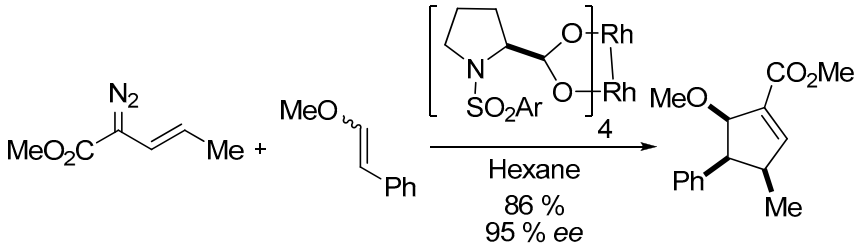
Scheme 12. Rhodium Carbenoid Mediated [3+2] Cycloaddition



Rhodium(II)-stabilized vinylcarbenoids have been reacted with alkenes to produce cyclopentenes. Davies and co-workers observed formation of cyclopentene **31** in the presence of vinyldiazocarbonyl **29** and vinyl ether **30** with $Rh(OAc)_4$ (eq 12).[33] Related asymmetric catalytic cycloadditions involving diazoacetates have been extensively developed by Davies to synthesize highly functionalized cyclopentenes with high enantioselectivity (eq 13).[34]



(12)

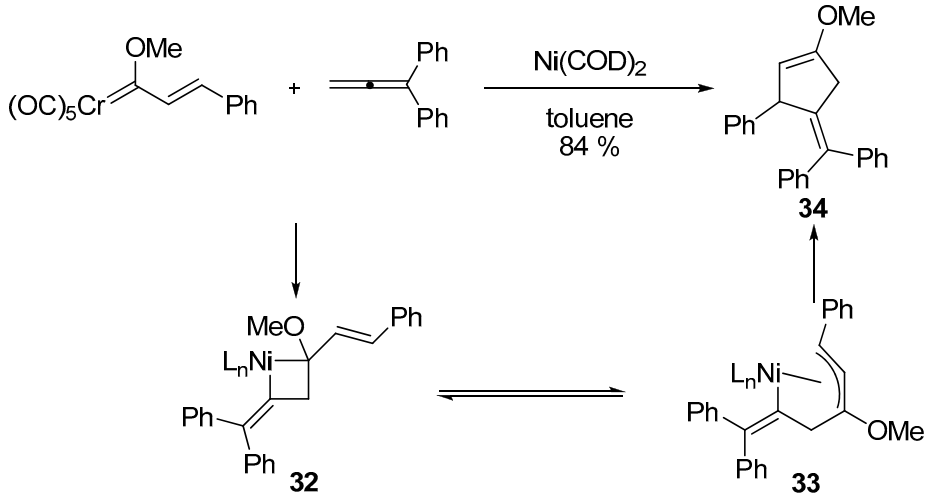


(13)

In 2004, the Barluenga group reported nickel(0)-mediated [3+2] cycloadditions of chromium Fischer carbene complexes and allenes involving the *in situ* generation of a nickel carbene complex by chromium-nickel exchange.[35,36]

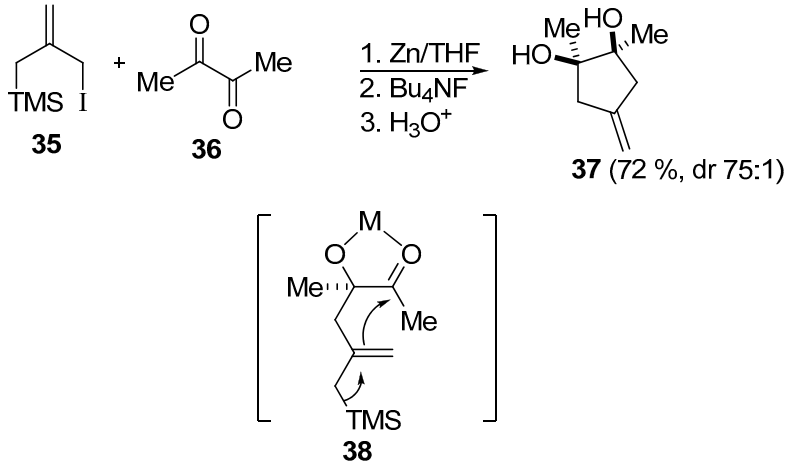
As illustrated in Scheme 13, [2+2] cycloaddition between the nickel carbene and allene could generate the intermediates **32** and **33**, followed by reductive elimination to produce cyclopentene **34**.

Scheme 13. [3+2] Cycloadditions of Chromium Fischer Carbene Complexes



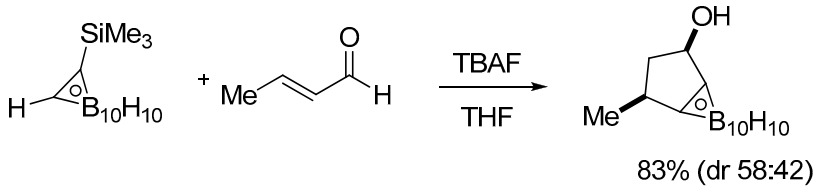
1.1.1.4 Involvement of Dianionic and Dicationic Building Blocks in [3+2] Cycloaddition

[3+2] Cycloaddition between dianionic and dicationic building blocks are less common than 1,3-dipolar cycloadditions. In 1986, Molander and co-workers developed a stereoselective [3+2] cycloaddition using 3-iodo-2-[(trimethylsilyl)methyl]propene **35** and 1,2-diones (eq 14).[11] An allylic zinc reagent could attack the 1,2-dione **36** to generate intermediate **38**, which could then undergo an intramolecular nucleophilic attack with the carbonyl to generate diol **37**. Intramolecular chelation could control the stereochemistry of the addition.



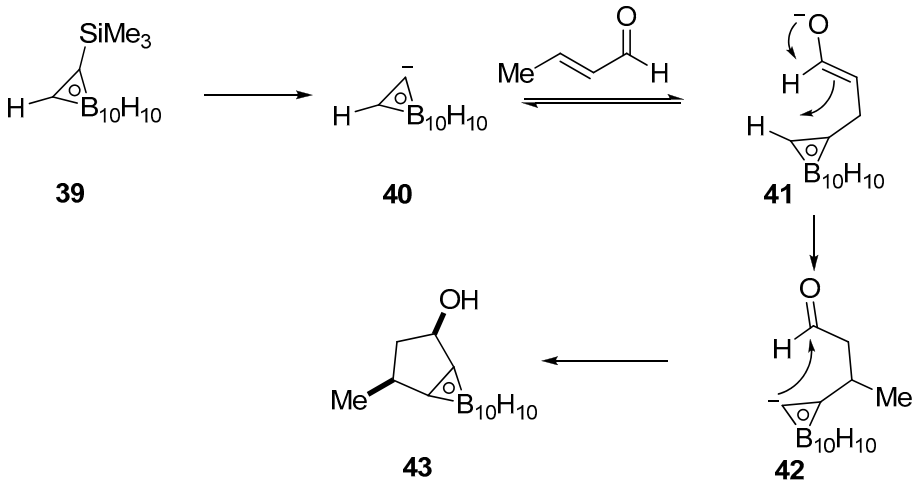
(14)

Later, Yamamoto discovered a novel [3+2] annulation between *ortho*-carboranyltrimethylsilane and conjugated carbonyl compounds (eq 15).[12] A possible mechanism for this novel reaction was proposed (Scheme 14). The reaction of the trimethylsilane compound **39** with TBAF would form an anionic intermediate **40**, which could react with the enal in a 1,4-manner to form intermediate **41**. The thermodynamically favored **41** would undergo proton exchange to afford the 1,2-carborane anion **42**, which could undergo intramolecular ring closure to produce alcohol **43**.



(15)

Scheme 14. [3+2] Annulation between *Ortho*-carboranyltrimethylsilane and Conjugated Carbonyl Compounds

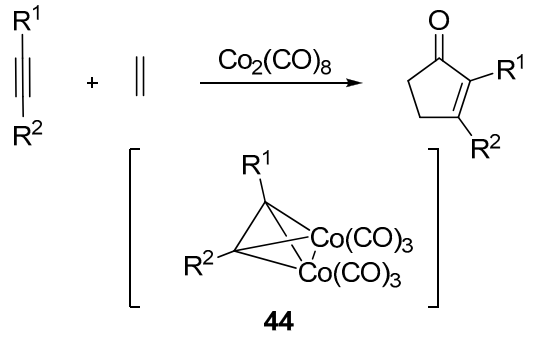


1.1.2 [2+2+1] Cycloaddition

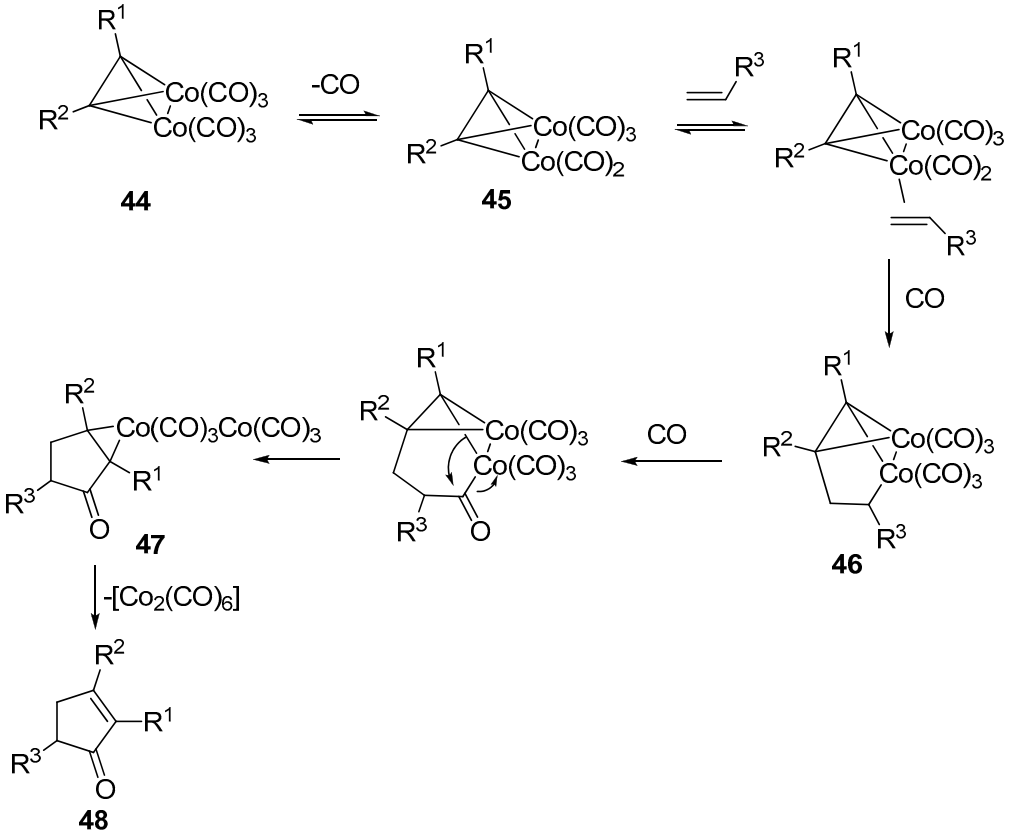
In 1971, Pauson and Khand discovered a cobalt-catalyzed [2+2+1] cycloaddition to construct five-membered rings.[37,38] The Pauson-Khand reaction combines an alkene, an alkyne and carbon monoxide into a cyclopentenone ring in the presence of stoichiometric amounts of dicobalt octacarbonyl (Scheme 15). More commonly, the alkyne has been converted to its hexacarbonyldicobalt complex **44**, which undergoes reaction with the alkene.

The mechanism for the stoichiometric reaction was proposed by Magnus *et al.* in 1985 (Scheme 16).[39,40] Initially, formation of hexacarbonyldicobalt complex **44**, followed by the loss of one CO ligand creates a vacant coordination site in the intermediate **45**. Next, the alkene coordinates with the cobalt and then inserts into a cobalt-carbon bond to form the intermediate **46**. Finally, insertion of CO could generate intermediate **47**, which could undergo reductive elimination to form the cyclopentenone **48**.

Scheme 15. The Pauson-Khand Reaction

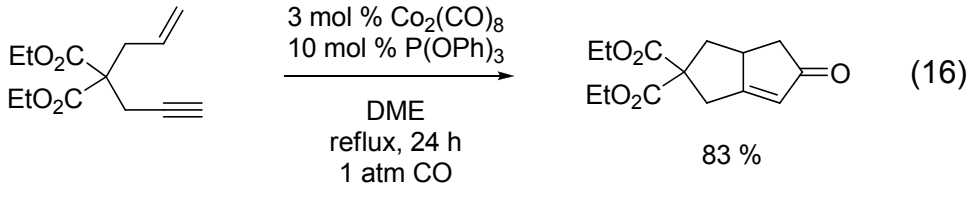


Scheme 16. The Mechanism of Pauson-Khand Reaction

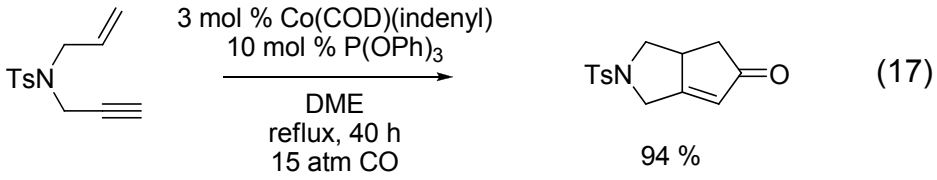


In the early 1990s, Jeong and co-workers developed the first effective catalytic intramolecular Pauson-Khand reaction by using triphenyl phosphite as an additive (eq 16).[41] This method was further developed into an efficient

catalytic intramolecular version using a Co(I) complex with an indenyl ligand as the catalyst under 15 atm of CO (eq 17).[42]

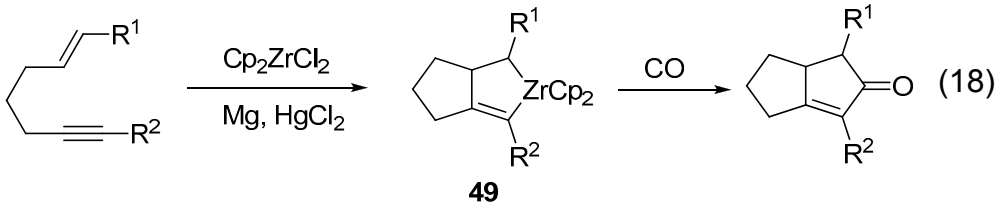


(16)



(17)

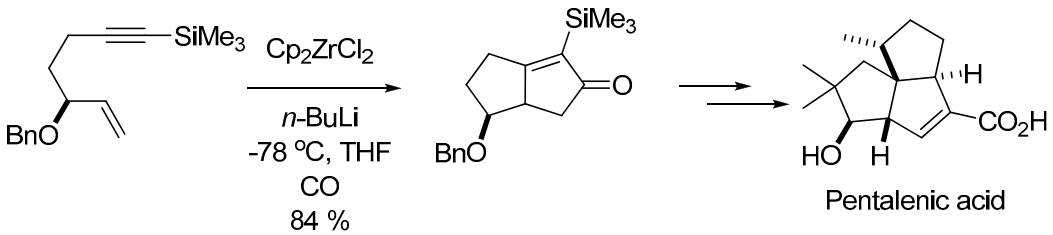
Alternatively, [2+2+1] reactions can also be catalyzed by Zr, Ti, and Ir complexes. In 1985, Negishi and co-workers showed that the zirconacycles **49** could be directly carbonylated to generate bicyclic cyclopentenones (eq 18).[43] Negishi utilized his zirconium-promoted [2+2+1] cycloaddition in the total synthesis of pentalenic acid (Scheme 17).[44]



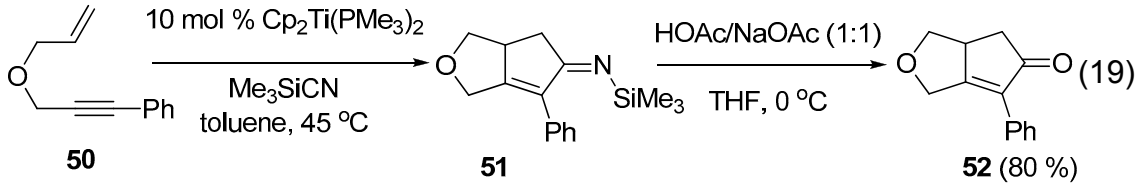
49

(18)

Scheme 17. Total Synthesis of Pentalenic Acid



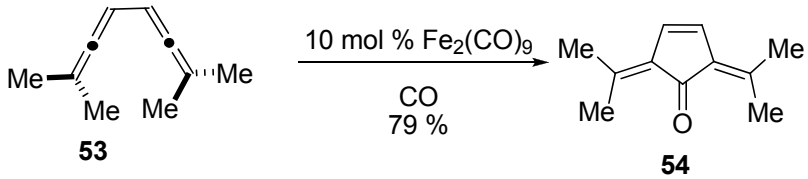
Later, Buchwald and co-workers developed a titanocene-catalyzed [2+2+1] process to generate bicyclic iminocyclopentenes (eq 19).[45] In the presence of a catalytic amount of $Cp_2Ti(PMe_3)_2$, trialkylsilyl cyanide and enyne **50** provided iminocyclopentene **51**. Mild hydrolysis then afforded cyclopentenone **52**.



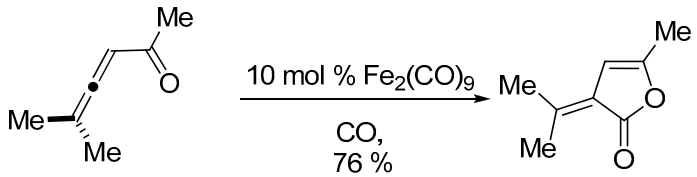
50 **51** **52** (80 %)

1.1.3 [4+1] Cycloaddition

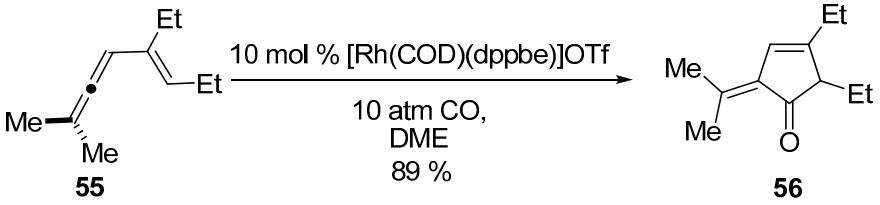
Only a few general [4+1] routes to five-membered carbocycles have been reported to date. In 1992, Eaton and co-workers reported iron mediated [4+1] cycloaddition to construct cyclopentenone.[46] Conjugated bis-allene **53** reacted with carbon monoxide in the presence of a catalytic amount of iron pentacarbonyl to produce **54** (eq 20). Later, this methodology was modified by replacing one of the allenes with a carbonyl group to produce lactones (eq 21).[47] Ito and co-workers demonstrated that the reaction of vinylallene **55** with carbon monoxide in the presence of a catalytic amount of [Rh(COD)(dppbe)]OTf led to the formation of cyclopentenone **56** via a [4+1] cycloaddition (eq 22).[48,49]



53 **54**



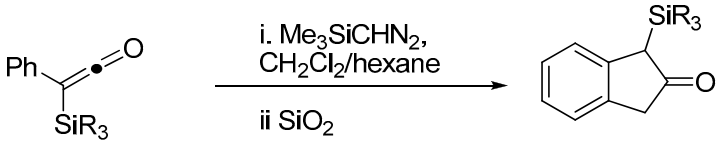
(21)



55 **56**

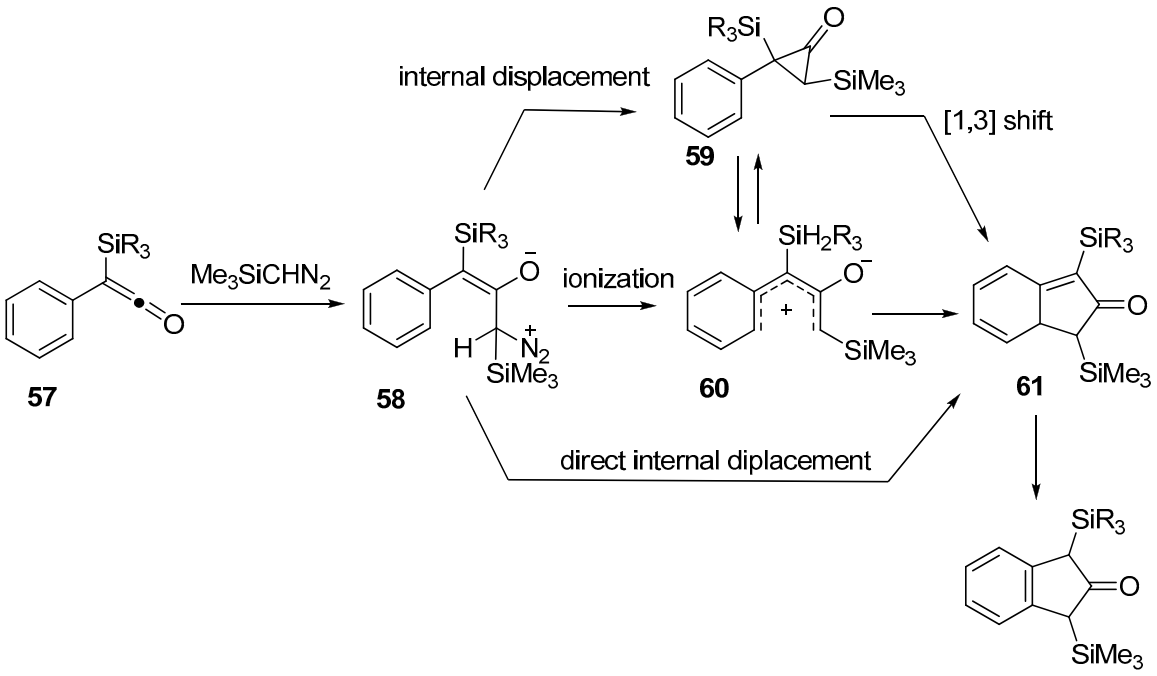
(22)

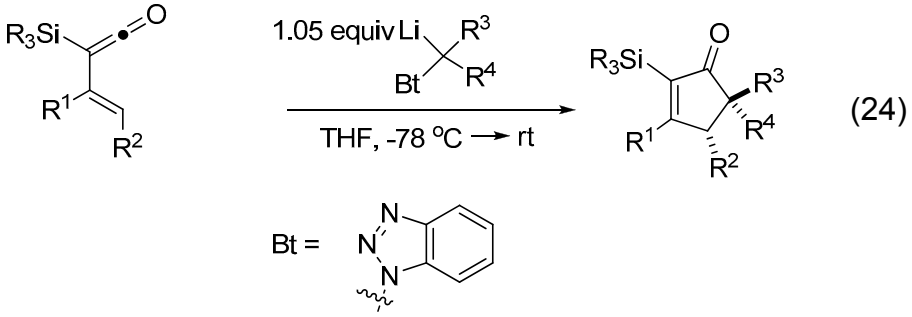
In 2002, Danheiser and co-workers developed a new [4 + 1] annulation strategy for the synthesis of 2-indanones by reacting (trialkylsilyl)arylketenes with (trimethylsilyl)diazomethane (eq 23).[50] The proposed mechanism is outlined in Scheme 18. Several alternative reaction pathways were proposed. Addition of TMS-diazomethane to the silylketene **57** could generate the (*Z*)-enolate **58**. Cyclization could then occur via ionization to form the cation **60**, which could undergo stereospecific conrotatory electrocyclic closure to ketone **61**. Alternatively, cyclization of intermediate **58** could occur to form the 2,3-bis(silyl)cyclopropanone **59**, which could undergo [1,3] shift to produce product **61**. Later, this methodology was modified by employing α-benzotriazolyl organolithium compounds and trialkylsilyl vinyl ketenes to stereoselectively access highly substituted cyclopentenones (eq 24).[51]



(23)

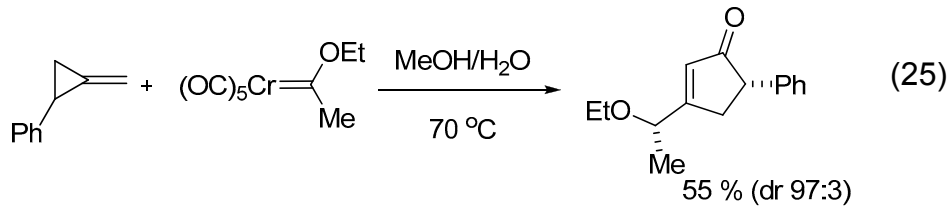
Scheme 18. Proposed Mechanism for the [4+1] Cycloaddition



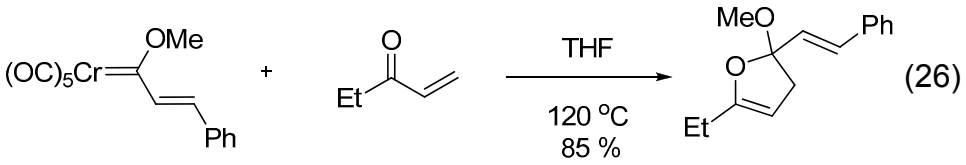


(24)

Furthermore, de Meijere reported that Fischer carbene chromium complexes could be reacted with methylene cyclopropanes to generate cyclopentenones via [4+1] cycloaddition (eq 25).[52] Recently, the Barluenga group illustrated that Fischer carbenes could also be reacted with enone to generate 2,3-dihydrofurans via [4+1] cycloaddition (eq 26).[53]



(25)



(26)

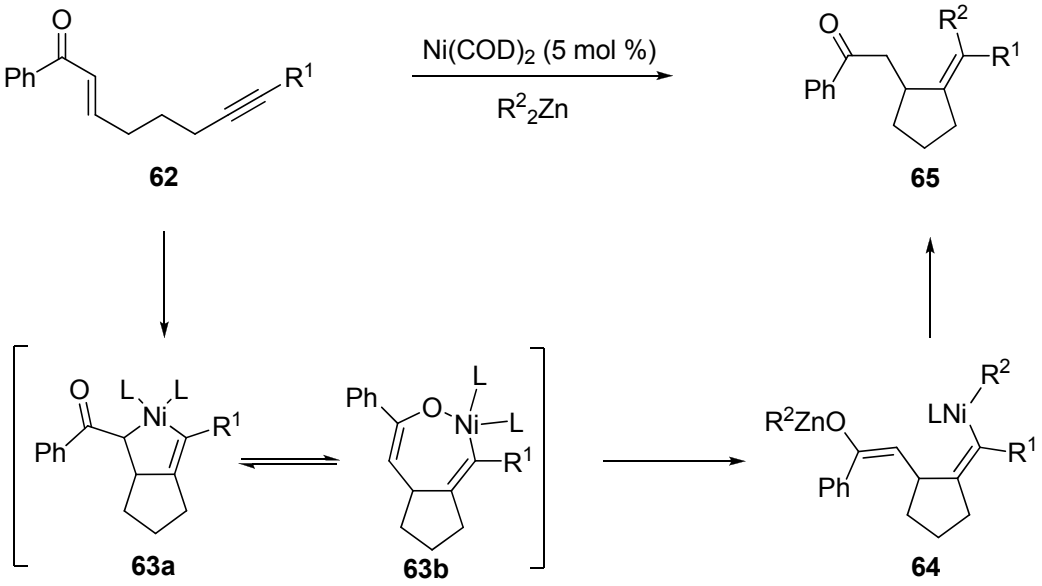
1.1.4 Nickel-Catalyzed Cyclization of Alkynyl Enones

Metal catalyzed cascade reactions are among the most important methods for assembling complex polycyclic molecules from simple polyunsaturated precursors.[54] Such processes usually begin with migratory insertion of various unsaturated units into a highly active metal–carbon bond. Subsequent transformations such as carbonylation, transmetallation, and reductive elimination lead to highly complex molecules in one reaction pot.[55,56]

Transition metal enolates have been proposed as intermediates in numerous organic transformations, and their modes of reactivity are diverse.[57] In 1996, the Montgomery group reported that alkynyl enones such as **62** underwent cyclization when initiated by $Ni(COD)_2$ and an organozinc reducing agent. Aryl, alkenyl and alkyl substituted organozincs participated in coupling to produce β-alkenyl ketones with complete control of olefin geometry (Scheme 19).[58,59] In the presence of an organozinc bearing β-hydrogens, reductive cyclization products were formed as a minor product. Use of excess triphenylphosphine with an

organozinc bearing β-hydrogens produced the reductive cyclization product as a major product (Scheme 20). Using this methodology, *E* or *Z*, tri- or tetra-substituted alkenes could be selectively prepared from a common alkynyl enone.

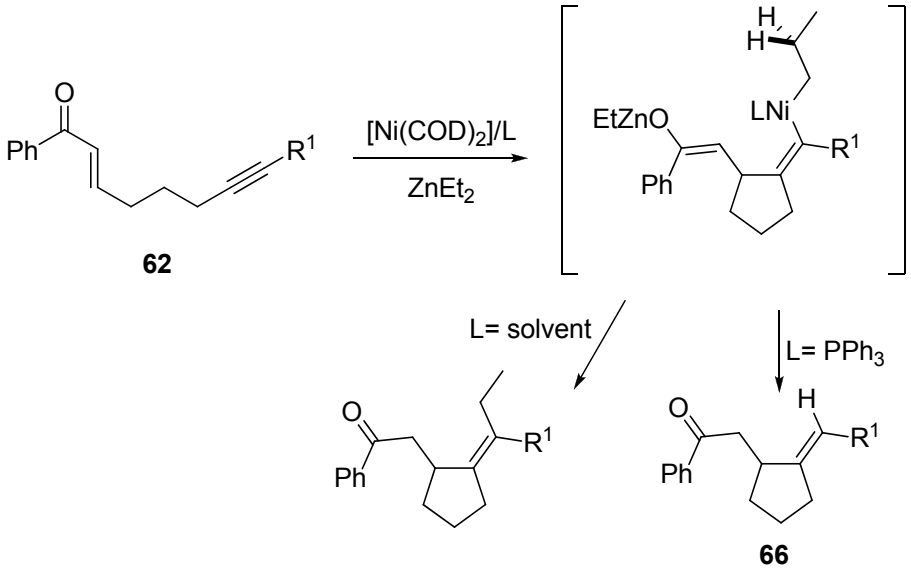
Scheme 19. Nickel-Catalyzed Alkylative Cyclization



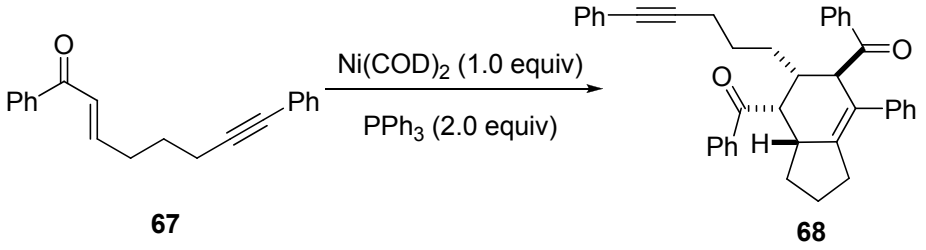
The mechanism is proposed to start with oxidative cyclization of alkynyl enone **62** to generate a nickel metallacycle, which could exist as either carbon bound **63a** or the oxygen-bound tautomer **63b** (Scheme 19). Transmetallation of the organozinc to the metallacycle would generate the intermediate **64**, which could undergo reductive elimination to generate the product **65**.

In the presence of triphenylphosphine, β-hydride elimination occurs to generate reductive coupling product **66**, instead of reductive elimination (Scheme 20). The σ-donating ability of the ligands likely controls the products formed in the reaction.

Scheme 20. Nickel-Catalyzed Reductive Cyclization



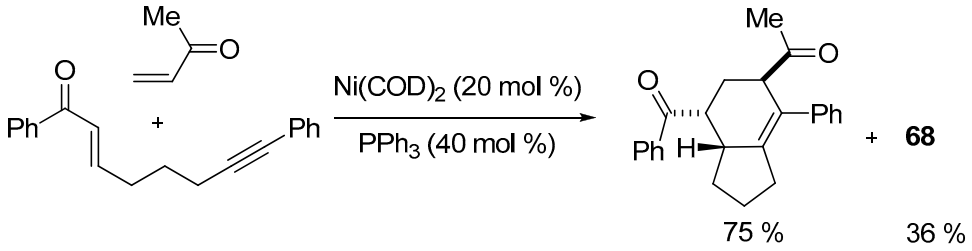
To support the mechanism in Scheme 19, several attempts were made to isolate the metallacyclic intermediate **63**. Treatment of alkynyl enone **67** with stoichiometric amount of $Ni(COD)_2/PPh_3$ (1:2) in the absence of an organozinc provided unexpected dimerization product **68** in quantitative yield as a single isomer (eq 27).



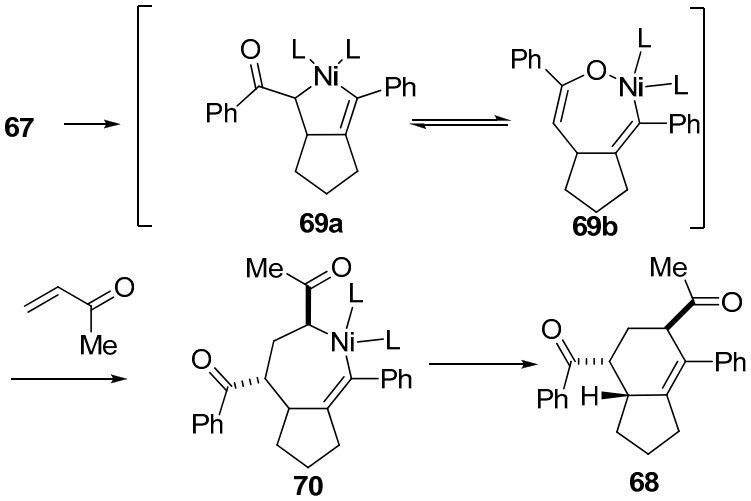
(27)

Later, this [2+2+2] cycloaddition process was developed to access highly functionalized cyclohexenes in high diastereoselectivity (Scheme 21).[60] The mechanism could involve formation of metallacycle **69**, followed by insertion of enone to generate metallacycle **70**. Reductive elimination then could generate the product **68** (Scheme 22).

Scheme 21. Nickel-Catalyzed [2+2+2] Cycloaddition

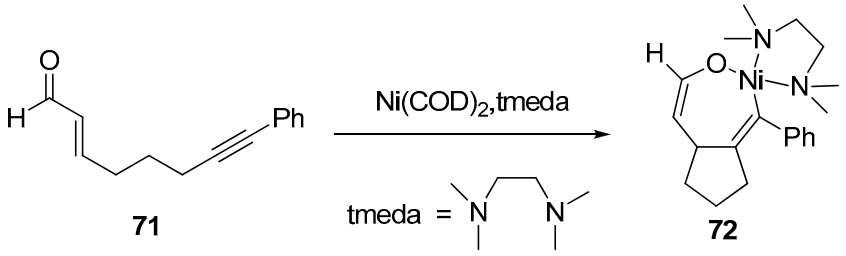


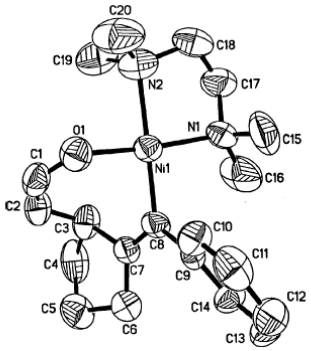
Scheme 22. The Mechanism of the Nickel-Catalyzed [2+2+2] Cycloaddition



Recognizing that dimerization involved dissociation of one of monodentate ligands and coordination of the second enone to the reactive metallacycle, bidentate ligands were used to stabilize the metallacycle and suppress the uptake of a second equivalent of enone. Treatment of alkynyl enal **71** with a stoichiometric amount of $Ni(COD)_2$/tmeda(1:1) or $Ni(COD)_2$/bpy afforded the structurally well-defined Ni(II) enolate **72** as the major product after recrystallization (Scheme 23).[61] The oxametallacycle structure was confirmed by both X-ray crystallography and NMR characterization data.

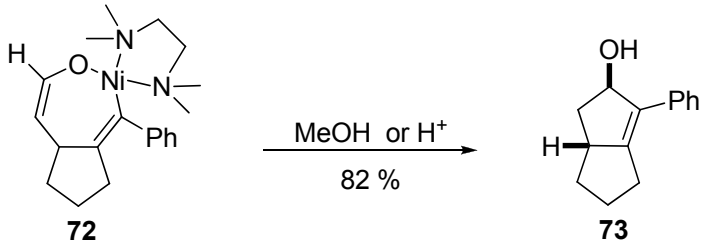
Scheme 23. Isolation of the η^1 Nickel *O*-Enolate Intermediate





X-ray crystal structure of metallacycle **72**

Reactivity of the isolated metallacycle was investigated. After treatment of alkynyl enal **71** with Ni(COD)$_2$/tmeda for 1 h at room temperature, the resulting red solution was quenched with either methanol or dilute aqueous acid. Surprisingly, an unexpected bicyclooctenol **73** was observed in 82% yield with excellent control of stereochemistry (eq 28).[62,63]

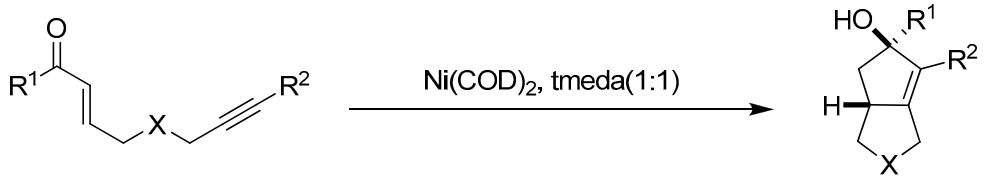


(28)

1.1.5 Nickel Catalyzed [3+2] Cycloaddition

This novel nickel-promoted reductive [3+2] cycloaddition reaction is different from conventional [3+2] cycloaddition reactions. Most standard [3+2] cycloaddition reactions required specialized substrate classes that cannot be carried through routine synthetic sequences and are sometimes difficult to install into complex molecules. However, this novel reaction requires an easily installed α,β-unsaturated carbonyl as the three-carbon unit. Additionally, this intramolecular [3+2] cycloaddition reaction can tolerate both enone and enal structures and alkyne substitution with either aliphatic, aromatic or silyl groups (Table 1, entry 1-4). However, terminal alkynes and alkynoates were poor substrates (Table 1, entry 5).[63]

Table 1. Substrate Scope of [3+2] Cycloaddition

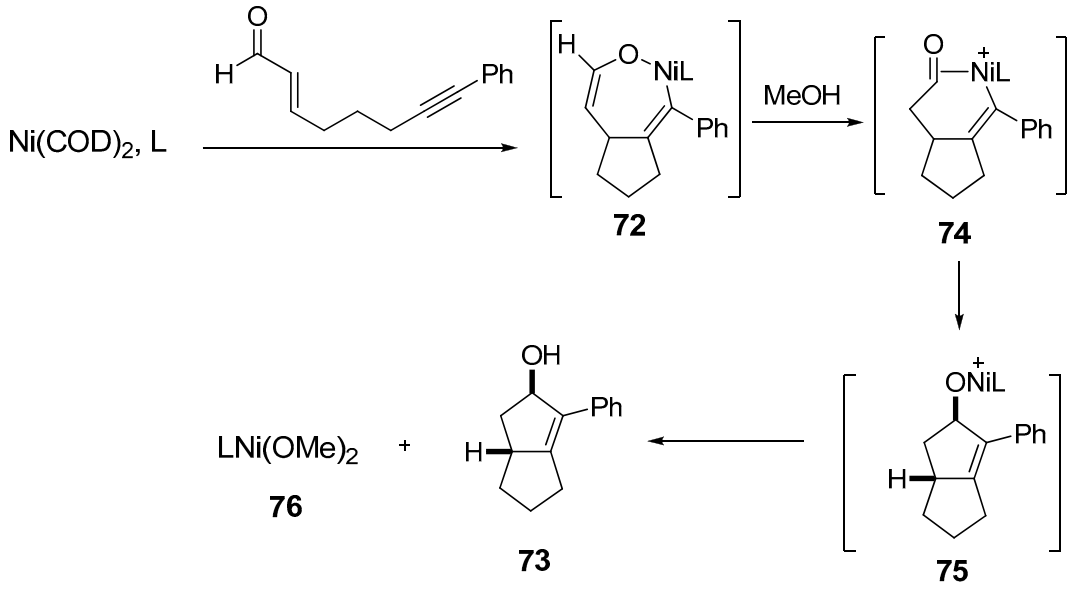


Entry	X	R^1	R^2	yield (%)
1	CH_2	H	Ph	82
2	CH_2	H	CH_3	72
3	CH_2	H	$SiMe_3$	55
4	O	H	Ph	78
5	CH_2	H	$COCH_3$	15
6	CH_2	Ph	Ph	71

The proposed mechanism for this reaction is depicted in Scheme 24. Oxidative cyclization could generate the metallacycle **72**. Monoprotonation of metallacycle **72** could produce vinyl nickel intermediate **74** and finally a rapid

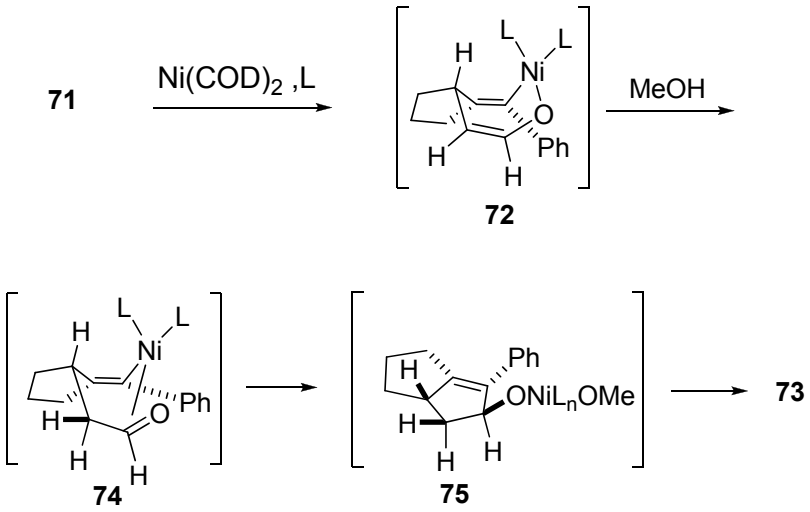
insertion of the vinylic Ni-C bond into the coordinated carbonyl would produce nickel alkoxide **75**. Then the protonation of the nickel alkoxide **75** could generate [3+2] cycloadduct **73** and nickel alkoxide **76**.

Scheme 24. Proposed Mechanism for the Nickel-Catalyzed [3+2] Cycloaddition



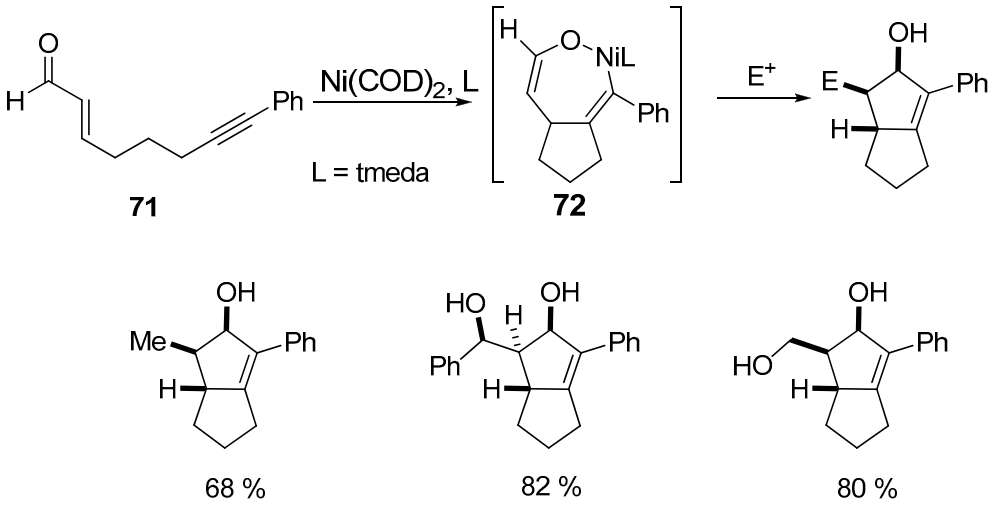
The explanation for the observed diastereoselectivity is outlined in Scheme 25. The conversion of vinyl nickel intermediate **74** into nickel alkoxide **75** is most likely irreversible. Therefore, the observed diastereoselectivity is likely due to either the kinetic selectivity of binding to the two prochiral faces of the carbonyl in **74** or the kinetic selectivity for the carbonyl insertion from rapidly equilibrating diastereomers of **74**. If the overall conformation of the metallacycle is preserved in each of the mechanistic steps, the observed diastereoselectivity directly correlates to the initial metallacycle conformation.

Scheme 25. Diastereoselectivity of the [3+2] Cycloaddition

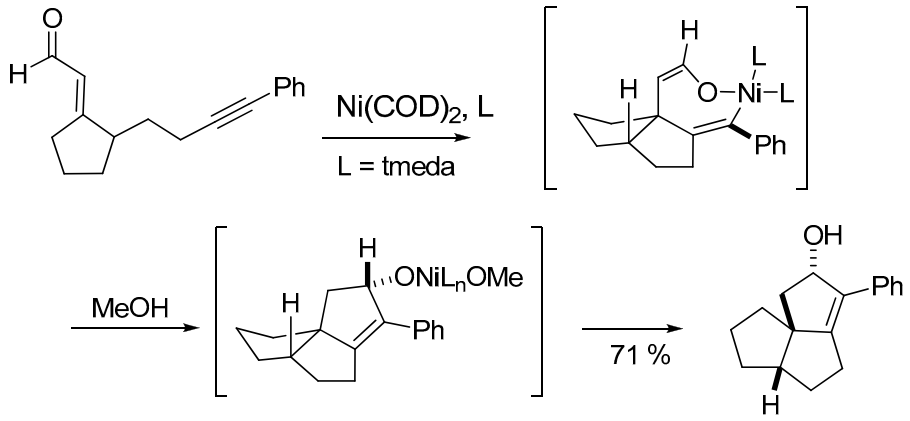


To explore the scope of this new reaction, the metallacycle **72** was quenched with electrophiles such as methyl iodide, benzaldehyde, and formaldehyde to generate highly functionalized cyclopentenols with high diastereoselectivity (Scheme 26). An intriguing feature of this reaction is the ability to use trisubstituted alkenes to produce tricyclic alcohols possessing a quaternary center as a single isomer in high yield (Scheme 27).

Scheme 26. Synthesis of Highly Functionalized Bicyclooctenol



Scheme 27. Synthesis of Tricyclic Compounds



The major drawback of this nickel enolate-mediated cyclization is that the reaction is restricted to the stoichiometric intramolecular five-membered ring-forming version. However, several attempts to develop an efficient catalytic process were unsuccessful. Use of several reducing agents such as Znº, Mnº, diorganozincs and organosilanes failed either due to poor turnover efficiencies or due to premature interception of a reactive intermediate.

1.2 Results and Discussion

1.2.1 Development of a Catalytic Version of the [3+2] Cycloaddition

As discussed in the previous section our group developed an intramolecular [3+2] cycloaddition process using a stoichiometric amount of nickel/ligand. The major drawback of this process is the requirement of stoichiometric amount of nickel/ligand. Therefore the development of a catalytic version of [3+2] cycloaddition was nessasary. Several attempts were made to develop the catalytic version of this reaction. However, none of them provided

promising results. The main focuses of my research are (i) the development of a catalytic version of the nickel-catalyzed [3+2] cycloaddition, (ii) increase the reaction scope, and (iii) explore the asymmetric version of this reaction.

A requirement for efficient catalysis is the presence of a Ni(0) species, a reducing agent and a Brønsted acid in the reaction mixture. In 2001, Tamaru and co-workers reported nickel catalyzed homoallylation of aldehydes by the use of triethylborane and protic solvents,[64] and later Jamison and co-workers used triethylborane and a hydroxylic solvent to develop nickel(0)-catalyzed reductive coupling of alkynes and imines (Scheme 28).[65] During these investigations, it was determined that organoboron reagents and hydroxylic solvents were crucial for these reactions to proceed. We recognized that these reactions involved the three required components for a catalytic version of the [3+2] cycloaddition, namely a low valent nickel species, a weak Brønsted acid (MeOH or H_2O) and a reducing agent (Et_3B).

Based on this analysis, we planned to investigate organoboranes and hydroxylic solvents for a catalytic version of the [3+2] cycloaddition. The initial nickel (0)-catalyzed [3+2] cycloaddition was carried out by reacting alkynyl enal **71** with 20 mol % of $Ni(COD)_2$/tmeda (1:1) and 3.0 equivalents of Et_3B in MeOH/MeOAc (6:1) as a solvent. Under these conditions, the reaction provided the [3+2] cycloaddition product **73** in 28% yield and the MeOH incorporated product **78** in 18% yield (Table 2, entry 1). The reaction was also carried out in MeOH/THF (6:1); however, the yield of [3+2] cycloaddition product remained nearly the same under both sets of conditions indicating that MeOAc has no role

and THF may be applicable for the reaction (Table 2, entry 2). Assuming that MeOH incorporation (as evidenced by product **78**) could interrupt the [3+2] cyclization pathway, the reaction was carried out with a decreased amount of MeOH and increased amount of Et_3B. Consistent with this assumption, treatment of alkynyl enal **71** with 10 mol% of $Ni(COD)_2$ /tmeda (1:1) and 20 equivalent of Et_3B cleanly afforded the [3+2] adduct **73** as a single diastereomer in 64% yield (Table 2, entry 3). The same reaction using 10 mol % $Ni(COD)_2$ and 10 equivalants of Et_3B in THF/MeOH (7:1) provided a superior result (Table 2, entry 4). Attempts with smaller amounts of Et_3B or MeOH showed a substantial decrease in yield. However, the use of 10 equivalents of Et_3B reduces the practicality of the reaction.

Scheme 28. Coexistence of Nickel, Brønsted Acid and Reducing Agent

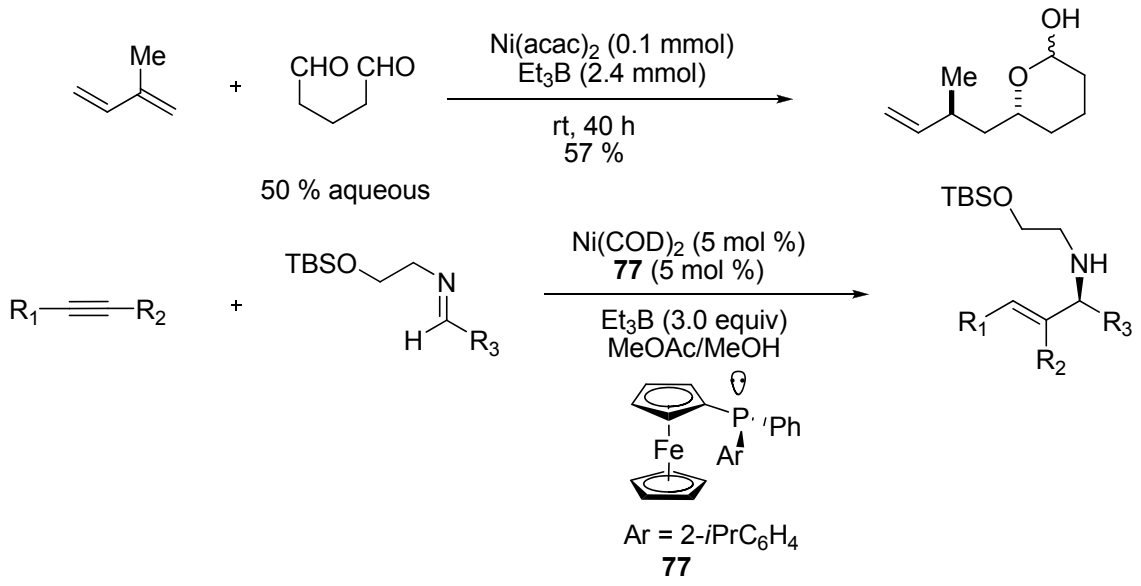
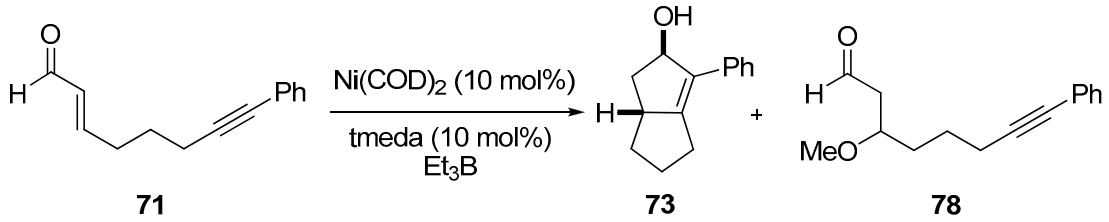


Table 2. Optimization of Catalytic Version of the [3+2] Cycloaddition

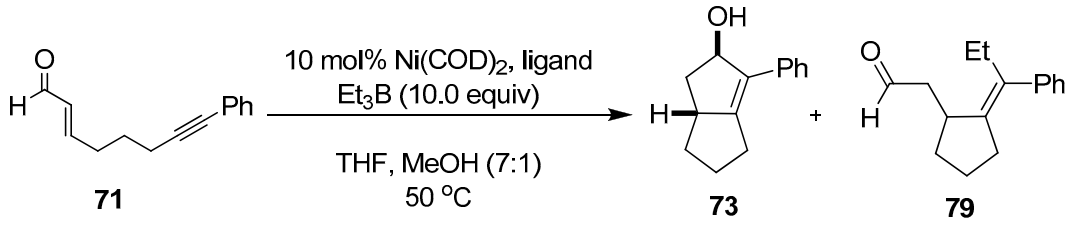


71 **73** **78**

entry	Et_3B	Solvent	**73** (yield,%)	**78** (yield,%)
1	*3 equiv	MeOH/MeOAc(6:1)	28	18
2	*3 equiv	MeOH/THF(6:1)	29	18
3	20 equiv	MeOH/THF(1:7)	64	0
4	10 equiv	MeOH/THF(1:7)	77	0

* Dr. Minsoo Song PhD thesis

Table 3. Scope of Ligands



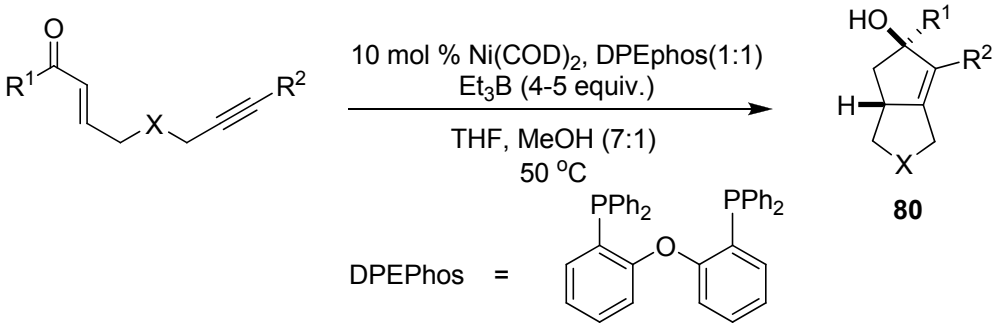
71 **73** **79**

Entry	Ligand	**73** (yield,%)	**79** (yield,%)
1	tmeda	77	-
2	DIPHOS	47	-
3	PBu_3	50	-
4	DPEphos	87[a]	-
5	dppf	82[b]	-
6	PPh_3	24	-
7	Pyridine	8	35
8	PCy_3	17	-

a - 4 equiv of Et_3B, b - 3 equiv of Et_3B

Although tmeda (Table 3, entry 1) provided a good yield of the desired product, we were interested in examining the scope of ligands. Screening different ligands demonstrated that bidentate phosphine ligand bis(2-diphenylphosphinophenyl)ether (DPEphos) was the best ligand for the [3+2] cycloaddition (Table 3, entry 4). Using DPEphos, the yield of the reaction was increased to 87% while the amount of Et_3B could be decreased to 4.0 equivalents. Later, we found that 1,1'-bis(diphenylphosphino)ferrocene (dppf) is a better ligand than DPEphos and required only 3.0 equivalant of Et_3B (Table 3, entry 5).

Table 4. Substrate Scope with DPEphos

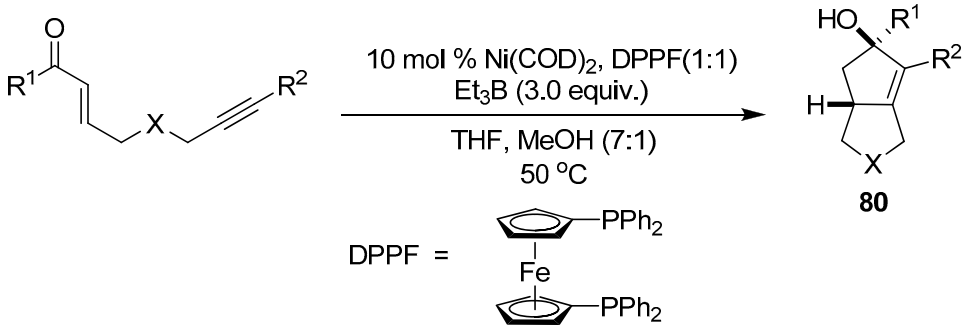


Entry	X	R^1	R^2	**80** (yield.%)
1	CH_2	H	Ph	87
2	CH_2	H	CH_3	78
3	CH_2	H	$SiMe_3$	-
4	O	H	Ph	44
5	CH_2	H	H	62
6	CH_2	Ph	CH_3	74[a]
7	CH_2	CH_3	H	35[a]

a - 20 mol % $Ni(COD)_2$/L

The scope of the catalytic reaction with DPEphos is illustrated in Table 4. Enals are the most efficient substrates in the reaction (entries 1, 2). Additionally, aromatic enones provided satisfactory yields (entry 7). It is important to note that a single diastereomer is observed in each reaction, which is described in Table 4. The scope of the catalytic reaction with dppf is illustrated in Table 5.

Table 5. Substrate Scope with DPPF

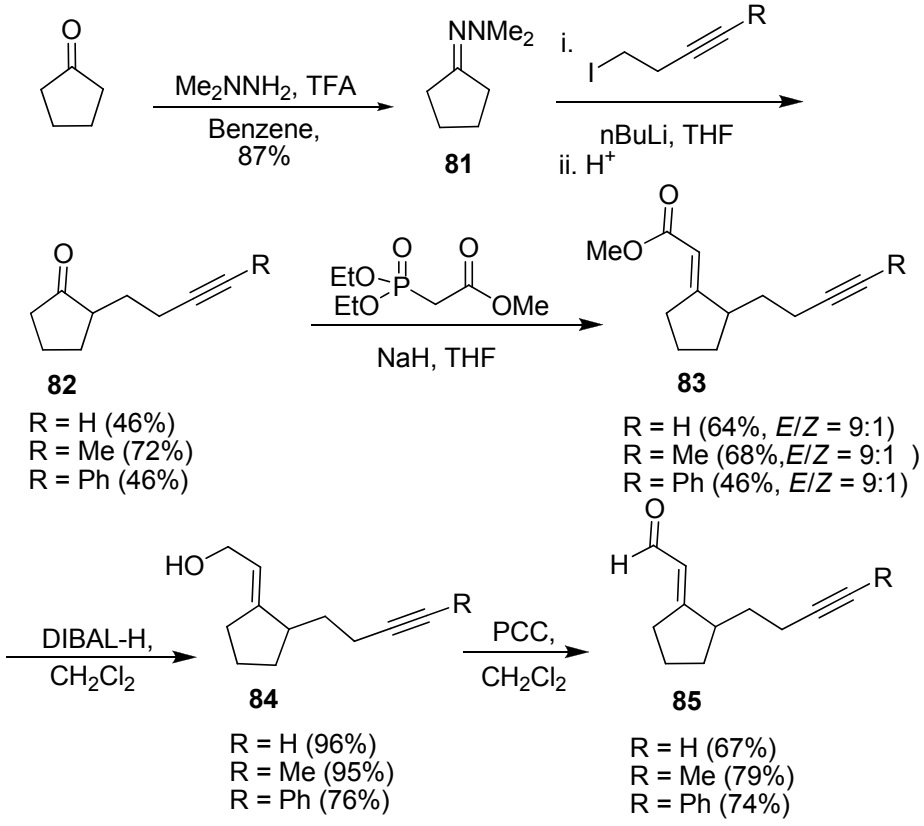


Entry	X	R^1	R^2	**80** (yield, %)
1	CH_2	H	Ph	82
2	CH_2	H	CH_3	76
3	CH_2	H	$SiMe_3$	-
4	O	H	Ph	62
5	CH_2	H	H	52
6	CH_2	Ph	CH_3	60
7	CH_2	CH_3	H	38

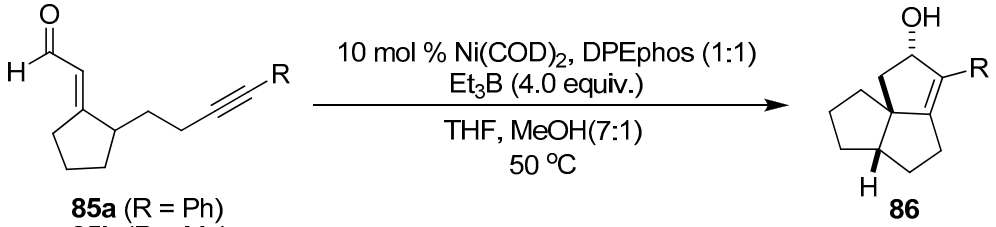
To examine the participation of trisubstituted alkenes, enal **85** was prepared using standard methods (Scheme 29). Ketones **82** were prepared from cyclopentanone *N,N*-dimethylhydrazone **81**, which was derived from cyclopentanone and *N,N*-dimethylhydrazine using trifluoroacetic acid as a catalyst, was subjected to deprotonation with *n*-BuLi, alkylation with alkyl iodides, followed by hydrolysis. Ketones **82** were obtained in high to moderate yields.

Then Horner-Emmons-Wadsworth olefination conditions were employed to produce corresponding ester **83** as a 9: 1 mixture of *E* and *Z* isomers in high yield. The *E*-isomers were separated by column chromatography and subjected to reduction to generate alcohols **84** in high yield. Then oxidation of the resulting alcohol with PCC gave enals **85** in high yields. Enals were then treated with $Ni(COD)_2$/DPEphos(1:1) in THF/MeOH(7:1) at 50 ^oC. The cyclization proceeded efficiently to produce tricyclic compound **86** as a single isomer in high yield (Scheme 30).

Scheme 29. Preparation of Trisubstituted Enal



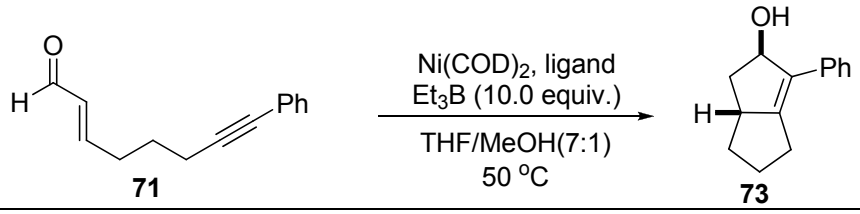
Scheme 30. Synthesis of Angular Triquinanes



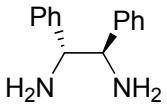
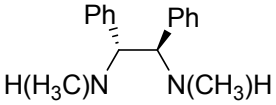
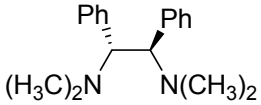
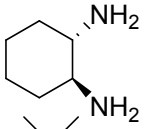
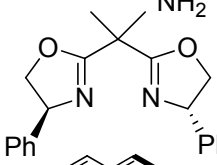
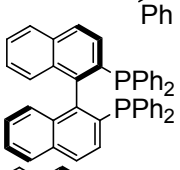
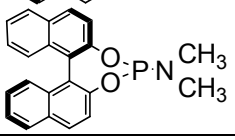
85a (R = Ph)
85b (R = Me)
85c (R = H)

86
86a (74 %)
86b (79 %)
86c (60 %)

Table 6. The Influence of the Ligand Structure on the Enantioselectivity



71 **73**

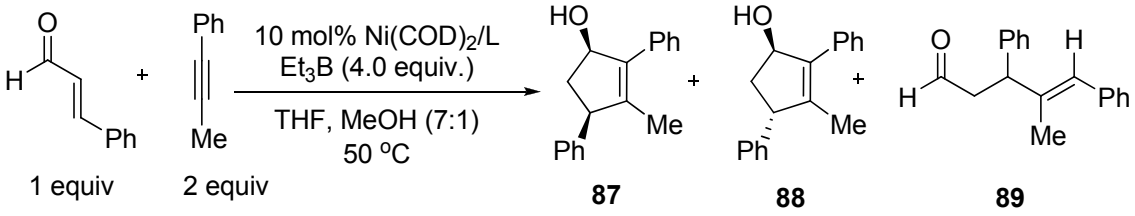
Entry	Ligand	**73** (yield,%)	e.e. %
1		50	10
2		48	11
3		26	10
4		46	20
5		37	12
6		43	11
7		30	10

We used different chiral ligands to investigate the potential for an enantioselective process; however, we only observed poor enantioselectivities (10-20 % *e.e.*) with all chiral ligands screened (Table 6).

1.2.2 Intermolecular Nickel Catalyzed [3+2] Cycloaddition of Alkynes and Enals

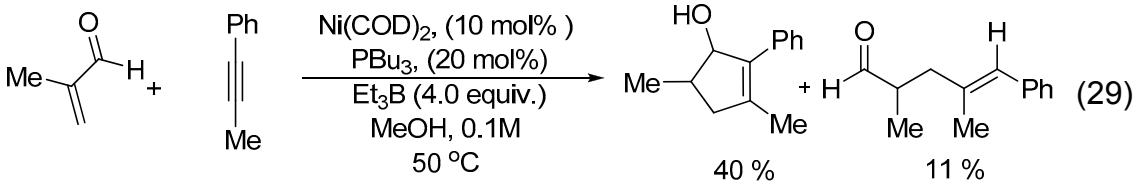
Having successfully developed a catalytic intramolecular version, we were interested in exploring an intermolecular version of this reaction. First, the nickel(0)-catalyzed [3+2] cycloaddition of phenylpropyne and *trans*-cinnamaldehyde was attempted with 10 mol % of $Ni(COD)_2$/DPEphos(1:1) and 4.0 equivalents of Et_3B in THF/MeOH (7:1) as a solvent. Unfortunately, under these conditions, the reaction provided no [3+2] cycloadduct (Table 7, entry 4).

Table 7. Scope of Ligands for Intermolecular Version



entry	L	**87** (% yield)	**88** (% yield)	**89** (% yield)
1	PBu_3	47	14	16
2	PMe_3	28	12	-
3	DPPF	-	-	-
4	DPEphos	-	-	-
5	PPh_3	-	-	58
6	bipy	-	-	-
7	tmeda	-	-	-

Screening of different ligands demonstrated that tributylphosphine (PBu_3) was the best ligand for the intermolecular version of this reaction (Table 7, Entry 1). Also screening different solvent ratios of MeOH/THF indicated that MeOH was the best solvent for the intermolecular reaction. However, the use of MeOH as a solvent resulted in low yields for other substrates (eq 29). We believe that the low solubility of $Ni(COD)_2$ in MeOH could be the reason for low yields. Thus, the reaction conditions were optimized by using an increased amount of MeOH and decreased amount of THF (MeOH:THF, 8:1), and also the substrate concentration was lowered to 0.06M. The reaction was performed by initially dissolving $Ni(COD)_2$ in THF and then adding tributylphosphine into the reaction mixture. Finally, substrates were added as methanol solutions.

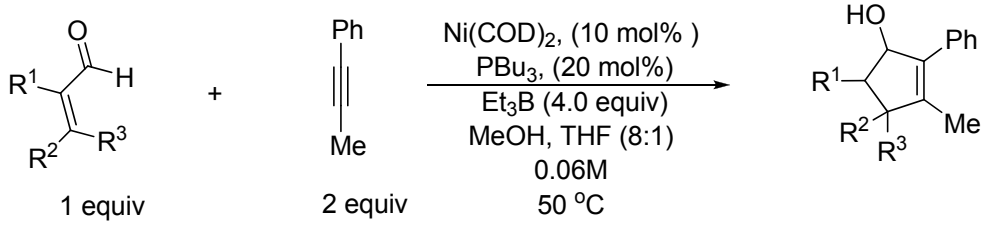


(29)

This optimized procedure provided high to moderate yields for most of the substrates with excellent control of stereochemistry (Table 8, Table 9). A wide range of enals underwent diastereoselective and regioselective reductive [3+2] cycloadditions with 1-phenylpropyne (Table 8). The reaction tolerates both alkyl (Table 8, entry 1) and aryl (Table 8, entry 2) substituents at the β-carbon and alkyl substitution at the α-carbon of the enal (Table 8, entry 3) as well as α,β-disubstituted enals (Table 8, entry 4, 5) and cyclic enals (Table 8, entry 6). Additionally, this reaction can tolerate a wide range of alkyne structures such as dialkyl, diaryl and silyl (Table 9).[66] In one case, the reductive coupling product

was observed as the major product, which was seen as minor products in other cases (Table 9, entry 5).

Table 8. Scope of Enals



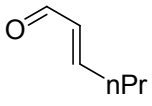
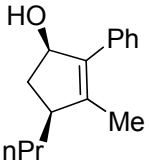
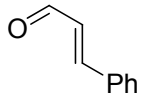
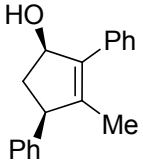
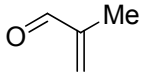
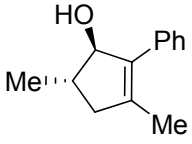
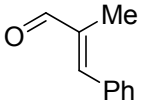
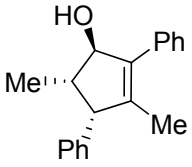
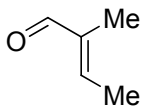
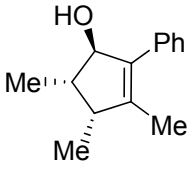
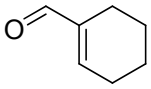
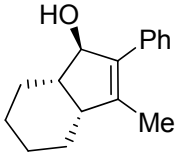
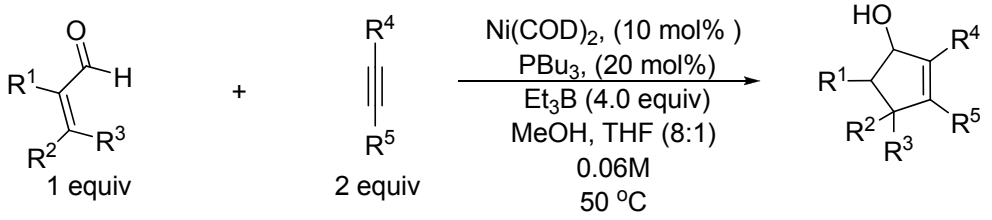
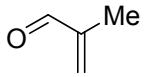
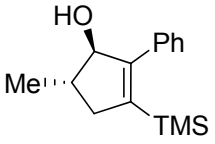
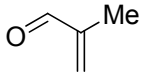
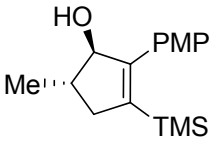
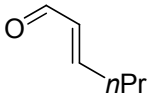
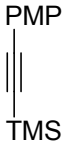
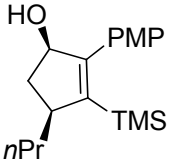
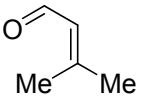
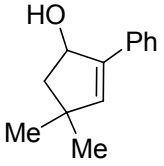
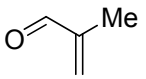
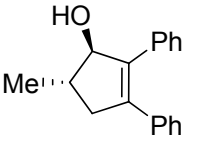
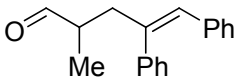
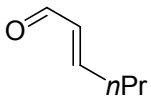
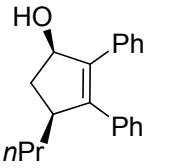
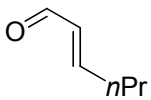
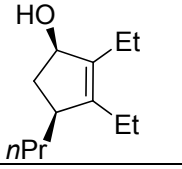
Entry	Substrates	Products	Yield(%)	dr
1			85	87:13
2			56	81:19
3			80	90:10
4			57	81:11:8
5			75	71:17:12
6			68	87:13

Table 9. Scope of Alkynes

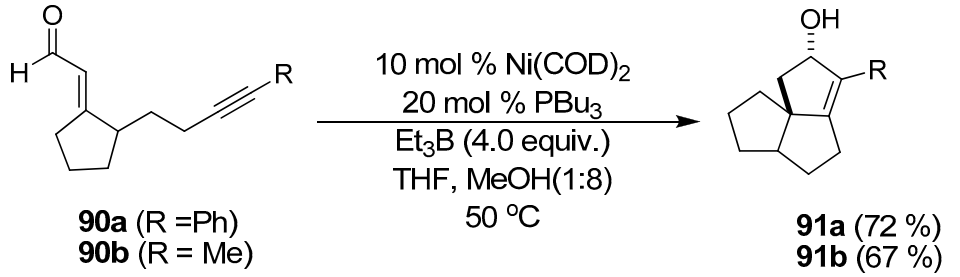


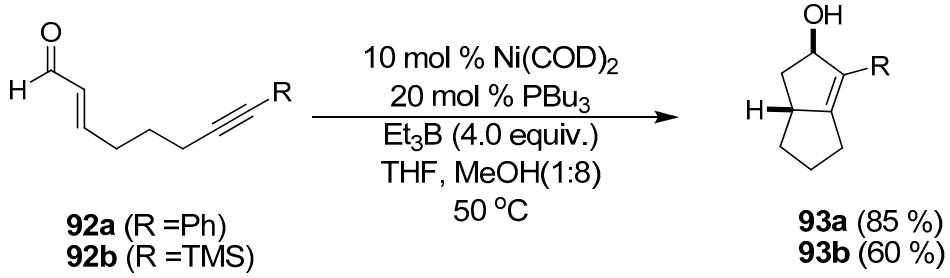
Entry	Substrates		Products	Yield(%)	dr
1				60	82:18
2				69	90:10
3				78	92:8
4				60	-
5				30	84:16
				60	
6				74	82:18
7				64	63:37

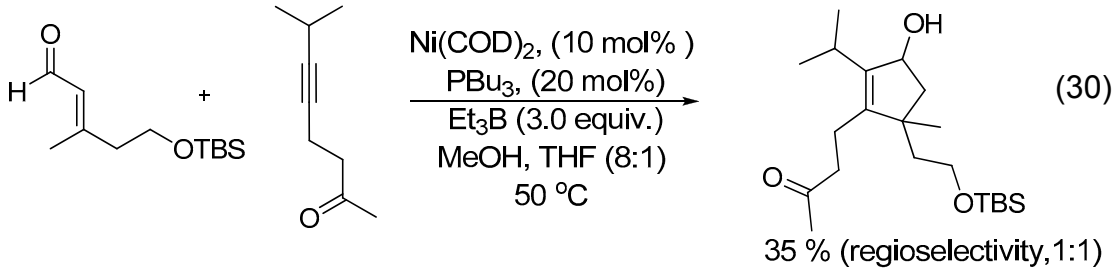
TMS - trimethylsilyl, PMP - *p*-methoxyphenyl

This new catalytic procedure with PBu_3 could be applied to intramolecular reactions to access bicyclic or tricyclic structures (Scheme 31). It is noteworthy that this method allows cyclization of more sterically demanding alkyne structures such as trimethylsilyl alkyne **92b**, which were not effective with bidentate ligands (Table 4, entry 3). Additionally, highly substituted cyclopentenols could be accessed by employing this methodology (eq 30). Unfortunately the regioselectivity and the yield of the reaction were low.

Scheme 31. Intramolecular [3+2] Cycloaddition





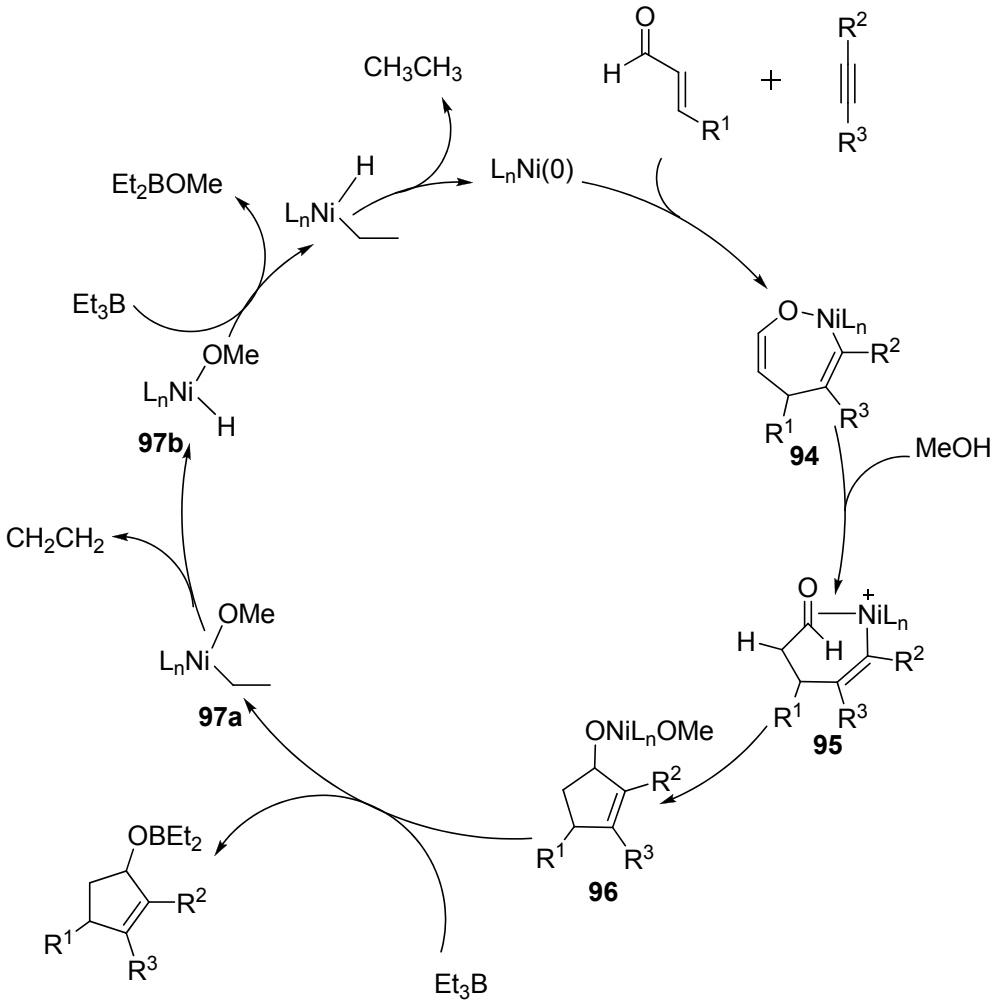


(30)

We propose that the mechanism of this novel catalytic process likely involves a selective monoprotonation of the nickel enolate **94** by methanol (Scheme 32). Once the selective monoprotonation occurs to generate

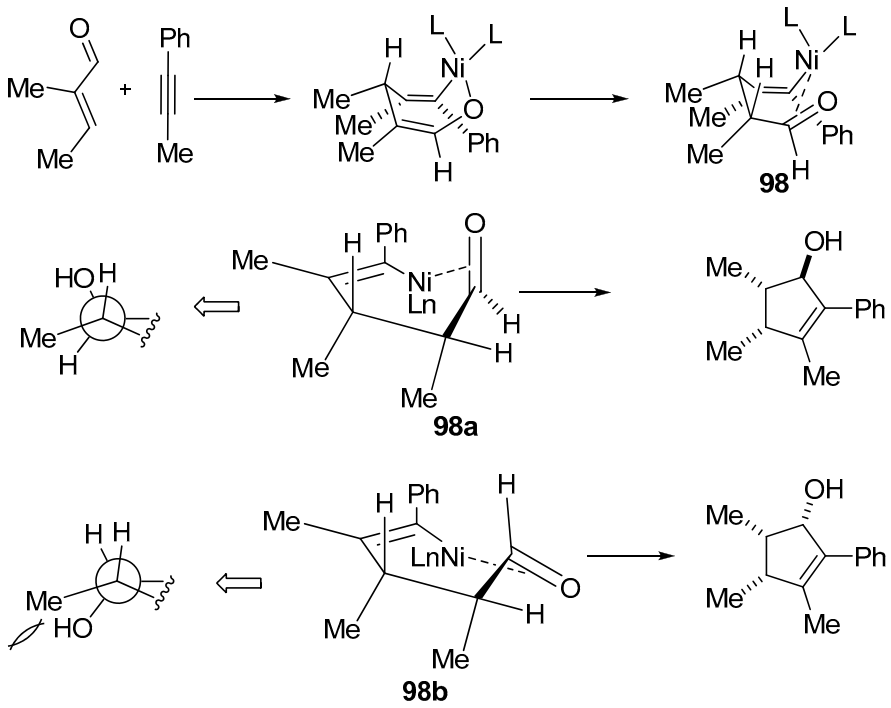
intermediate **95**, a rapid insertion of the vinylic Ni-C bond into the coordinated carbonyl would give nickel alkoxide **96**. Transmetallation of the nickel alkoxide **96** with Et_3B would generate the observed [3+2] cycloadduct upon acidic workup. The methoxy ethyl nickel species **97a** would then undergo β-hydride elimination to give **97b**. Finally, transmetallation followed by reductive elimination would eventually regenerate the Ni(0)/ligand complex to complete the catalytic cycle.

Scheme 32. Proposed Mechanism of the Novel [3+2] Cycloaddition Reaction

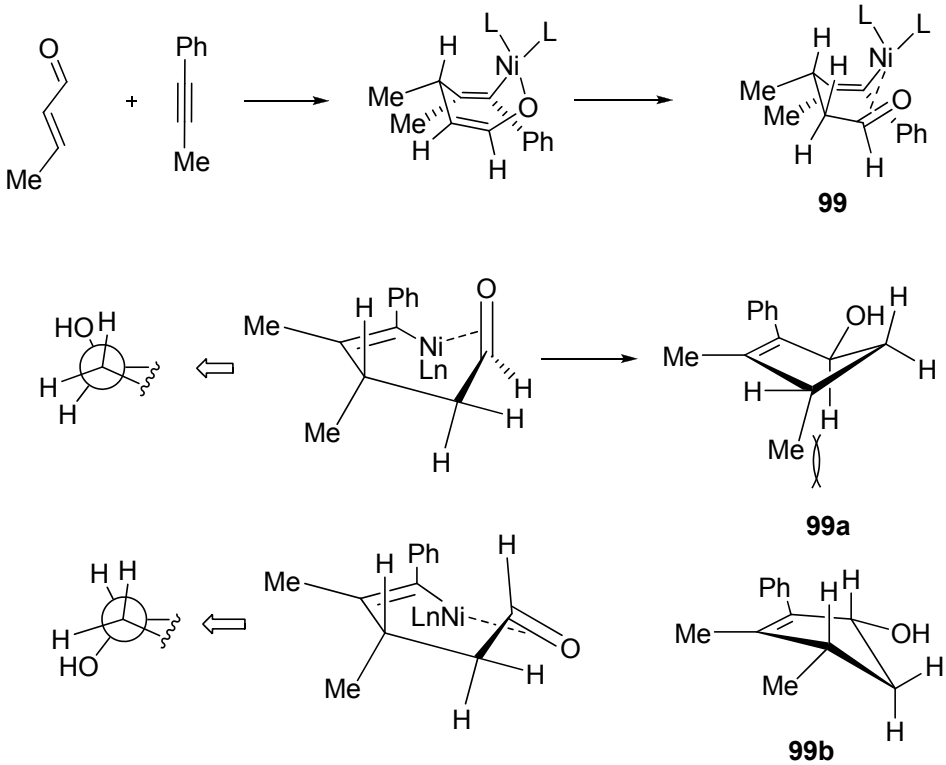


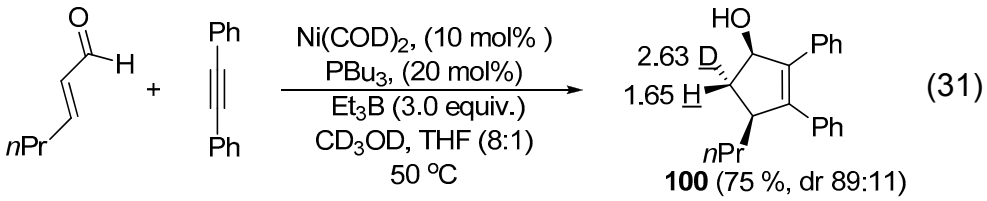
The observed diastereoselectivities could be explained as outlined in the Scheme 33 and Scheme 34. When α,β-disubstituted enals are used, monoprotonation of the metallacycle could determine the stereochemical outcome (Scheme 33). Protonation could occur from the opposite side of the β-substituent to generate intermediate **98**. Insertion of the vinyl nickel carbon into the aldehyde could occur from two prochiral faces (conformer **98a** and **98b**). Vinyl nickel insertion from conformer **98b** is unstable due to developing gauche interaction between the methyl group and the hydroxyl group. However, conformer **98a** is stable compared to conformer **98b**. Therefore vinyl nickel insertion to the carbonyl would preferentially occur via intermediate **98a** to generate the major diastereomer. Additinally, complex **98a** should be kinetically favored considering the cup-shaped conformation of the metallacycle. When β-substituted enals are used, the stereochemical outcome may be governed by product-like steric interactions that developed in the transition state for addition of the vinyl nickel unit to the aldehyde (Scheme 34). Formation of the product **99a** could be unfavorable due to steric interaction between the pseudoaxial methyl and the aldehyde proton, whereas this interaction is absent in the transition state leading to diastereomer **99b**. Therefore the formation of the product **99b** would be favorable.

Scheme 33. Diastereoselectivity with α,β-Disubstituted Enals



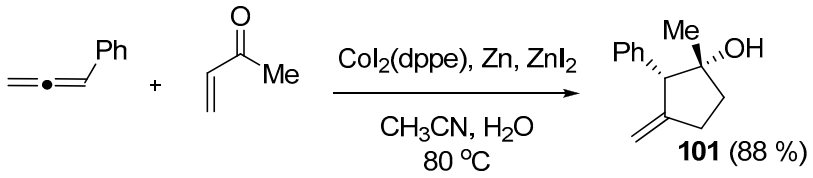
Scheme 34. Diastereoselectivity with β-Substituted Enals





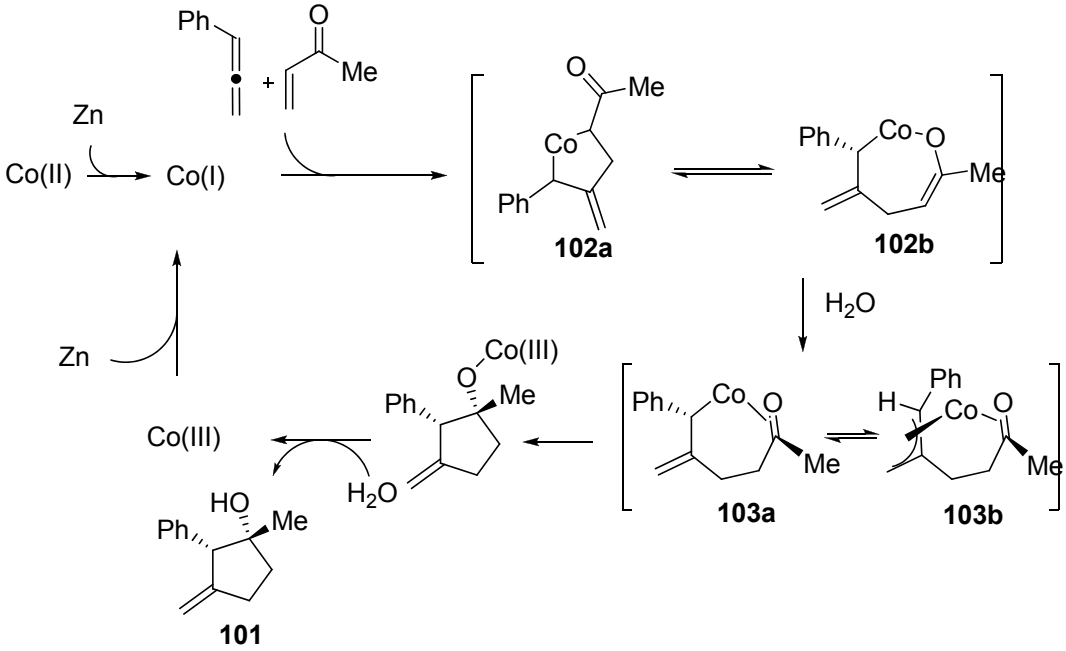
(31)

To understand the role of MeOH and to elucidate the mechanism of the present catalytic reaction, an isotope labeling experiment using CD_3OD instead of MeOH for the reductive [3+2] cycloaddition of *trans*-hexenal and diphenylacetylene was carried out (eq 31). The results showed that the C(5) position in the cyclopentenol ring was diastereoselectively deuterated. The stereoselectivity was determined by comparing the ^1H NMR spectra.



(32)

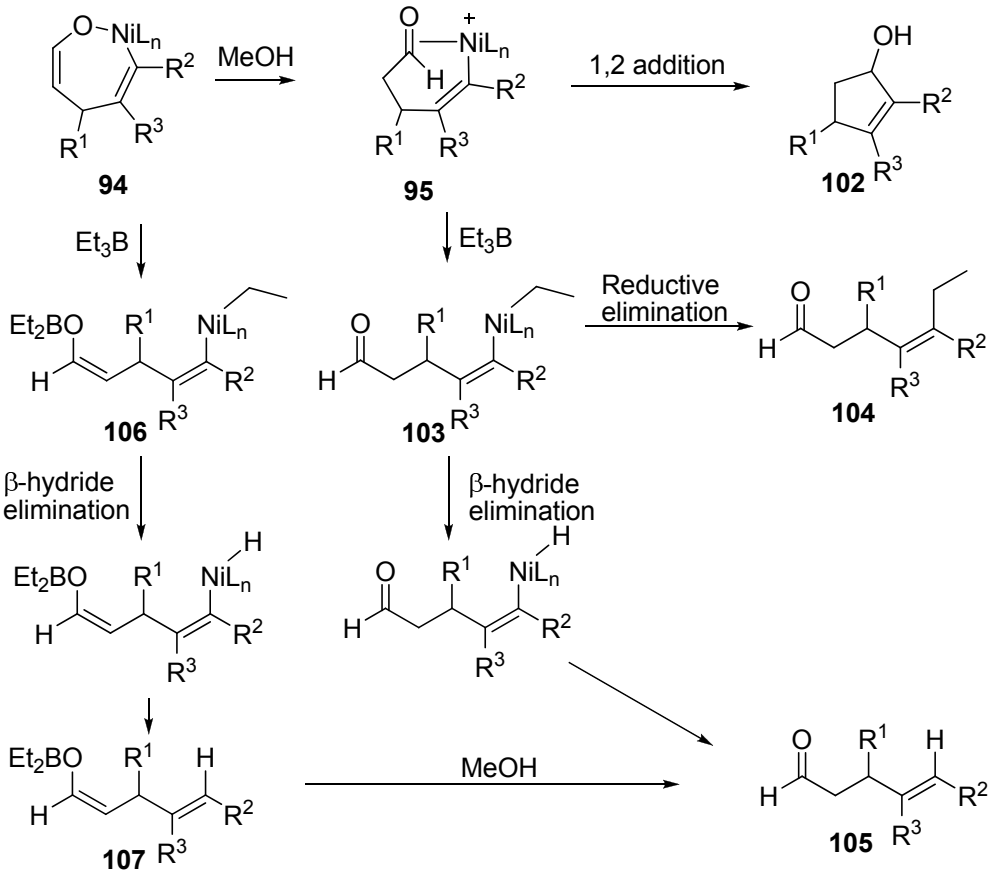
Scheme 35. Cobalt-Catalyzed [3+2] Cycloaddition



Recently, Cheng reported a similar reaction by employing cobalt catalysis. Treatment of allenes and enones with a catalytic amount cobalt catalyst produced reductive [3+2] cycloadduct in high diastereoselectivity (eq 32).[67] As illustrated in Scheme 35, the catalytic cycle could be initiated by the reduction of Co(II) to Co(I) by zinc dust, followed by oxidative addition to form cobalt cyclopentane intermediate **102a**, which is in equilibrium with *O*-enolate **102b**. Then monoprotonation of **102b** to generate intermediate **103** followed by insertion of the cobalt carbon into the carbonyl could produce the cyclopentanol **101** upon protonation.

The formation of the reductive coupling product **105** could occur through the same metallacycle **94** through two possible reaction pathways (Scheme 36)**.** Monoprotonation would generate intermediate **95**. Then it could undergo either 1,2 addition to generate [3+2] adduct **102** or ethyl transfer could generate intermediate **103**, which could undergo either reductive elimination to generate **104** or β-hydride elimination followed by reductive elimination to generate the reductive coupling product **105**. Alternatively, metallacycle **94** could undergo transmetallation with Et_3B to generate the intermediate **106**, which could undergo β-hydride elimination followed by reductive elimination to generate product **107.** Then protonation of intermediate **107** would yield product **105**. As evidenced by [3+2] cycloaddition, the protonation of the metallacycle **94** by methanol could be faster than the transmetallation step. Therefore the reaction is most likely to occur via intermediate **95**.

Scheme 36. Other Possible Reaction Pathways



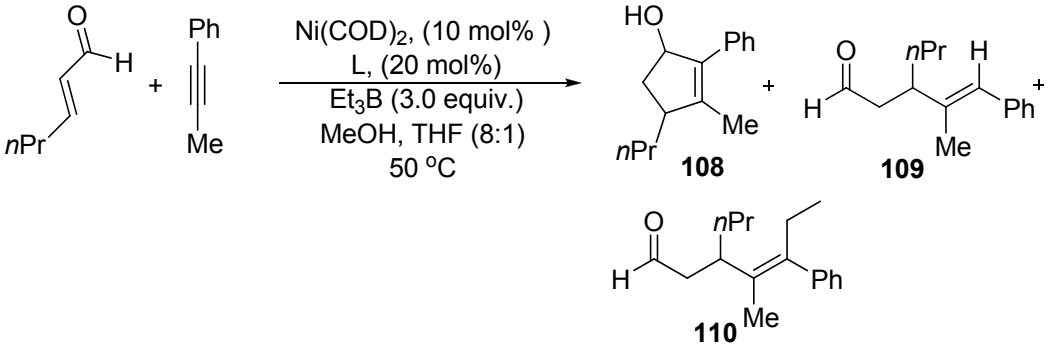
1.2.3 Effect of Ligand Structure on Product Distribution

By varying the ligand structure on nickel, distribution of the products could be varied. The mechanism proposed above suggests that if the rate of reductive elimination from the intermediate **103** is faster relative to the β-hydride elimination, then the product **104** should be obtained in high yield. Thus, the selective synthesis of product **104** could be achieved by employing nickel catalysts supported by bulky phosphine ligands that are known to be highly effective at promoting reductive elimination reactions.[68] If the rate of reductive elimination could be minimized, the reaction may be directed toward product **105**.

The two classes of phosphine ligands that are well documented in their ability to decrease the rate of reductive elimination are small, electron rich ligands and bidentate ligands with small bite angles.[58,59,69]

Experiments with monodentate ligands demonstrated that selectivity is highly dependent on the steric bulk and the electronic nature of the ligand (Table 10). Extremely bulky ligand P(o-tol)$_3$ (cone angle 198^o) favored the formation of product **110** in high yield, whereas use of the smaller electron-rich ligands such as PMe_3 and PBu_3 provided exclusively [3+2] adduct **108**. However, use of bulky electron-rich phosphine ligands PCy_3 and P(*t*-Bu)$_3$ resulted in low reactivity. The selectivity for **109** increased with medium sized aryl phosphine ligands such as PPh_3 and PPh_2Me.

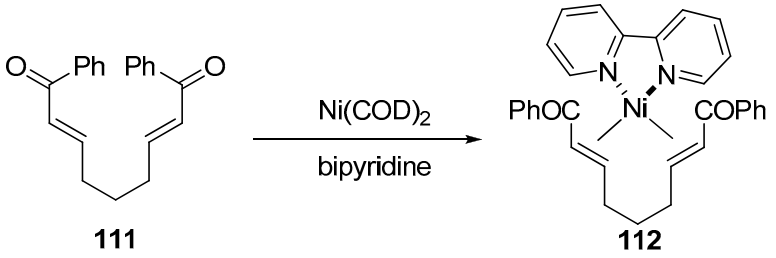
Table 10. Effect of Ligand Structure on Product Distribution



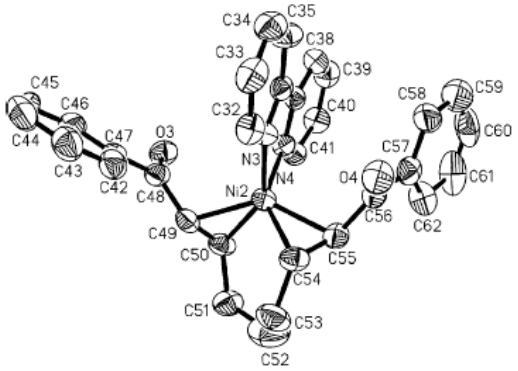
L	cone angle	**108** (% yield)	**109** (% yield)	**110** (% yield)
PMe_3	118	42	-	-
PBu_3	136	85	-	-
PPh_2Me	136	29	38	-
PPh_3	145	12	51	13
PCy_3	170	-	-	-
P(*t*Bu)$_3$	182	-	-	-
P(*o*-tolyl)$_3$	194	-	6	70

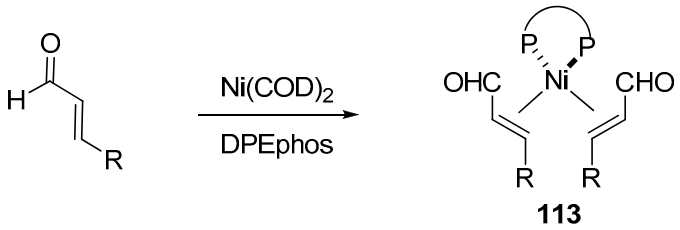
Use of bidentate ligands for the intermolecular version resulted in no [3+2] or reductive coupling product. Treatment of the enal and alkyne with 10 mol % of $Ni(COD)_2$/DPEphos (1:1) resulted in a deep red solution, but only starting materials were recovered. It is well known from previous literature reports that the enones could coordinate with nickel and form very stable tetrahedral Ni(0) bis π complexes (Scheme 37).[70] Treatment of bis-enone **111** with stoichiometric quantities of $Ni(COD)_2$ and bipyridine resulted in the formation of tetrahedral Ni(0) bis π complex **112**.

Scheme 37. X-ray Structure of Tetrahedral Ni(0) Bis π Complex



111 **112**



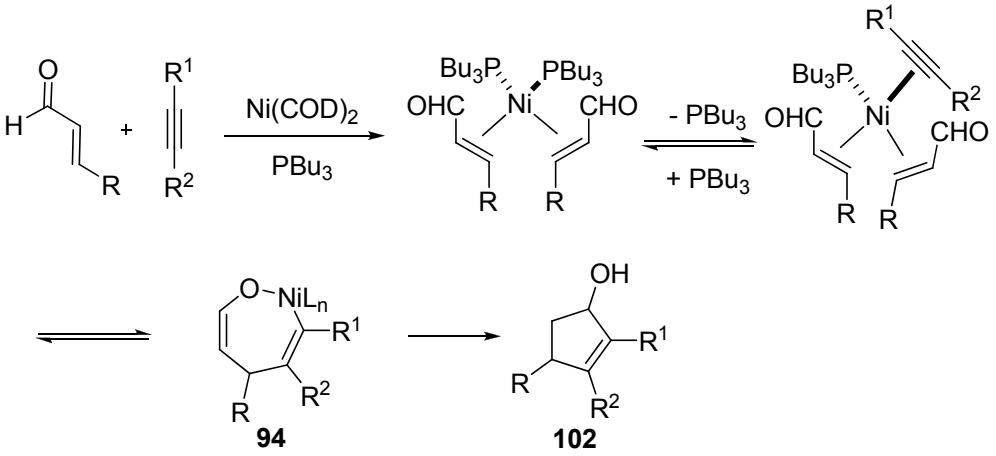


113

(33)

We believe that enals could also form a similar kind of tetrahedral Ni(0) bis π complex **113** as shown in eq 33. Tetrahedral Ni(0) bis π complex **113** could be very stable and that could prevent the coordination of the alkyne, thereby shutting down the intermolecular [3+2] cycloaddition reaction. However, monodentate ligands are more labile than bidentate ligands. Therefore dissociation of one of monodentate ligands and coordination of alkyne to the complex could generate a reactive metallacycle, which could lead to the formation of the [3+2] cycloadduct in the presence of monodentate ligands (Scheme 38). In the intramolecular case, the alkyne is already tethered to the enal, which could lead to the formation of a reactive metallacycle. Bidentate ligands could also suppress uptake of a second equivalent of enal.

Scheme 38. Intermolecular [3+2] Cycloaddition with Monodentate Ligands

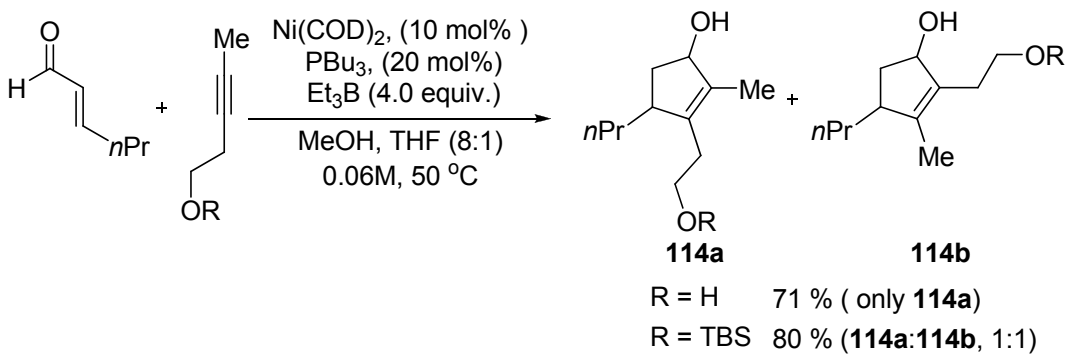


1.2.4 Unusual Regioselectivity with Alkynol

The [3+2] cycloaddition between *trans*-hexenal and 3-pentyn-1-ol provided regioisomer **114a** as a major product. However, the reaction with silyl protected 3-pentyn-1-ol generated a mixture of regioisomers (Scheme 39). This might be

due to a hydroxyl group directing effect. In 2005, Micalizio and co-workers reported hydroxyl group directed titanium mediated coupling of alkynes and aldehydes (Scheme 40)[71,72] and Jamison *et al.* reported olefin directed nickel catalyzed coupling of aldehydes and alkynes (eq 34).[73,74] Based on these results, the hydroxyl group directing effect on nickel catalyzed [3+2] cycloaddition can be explained (Scheme 41). First, Ni(0) could coordinate to the alkyne and hydroxyl group on the alkyne to form intermediate **116**. The hydroxyl group could act as a ligand which is more labile than tributylphosphine. Hydroxyl dissociation and enal coordination with retention of configuration at nickel would favor formation of metallacycle **118**, leading to the production of **114a**. If the reaction occours via hydroxyl group coordinated intermediate, product **114b** could be favored. The mechanism of this hydroxyl group directed reaction is noteworthy. In the Micalizio method, the proposed mechanism involves hydroxyl group coordinated titanium complex **115** and that governs the regiochemical outcome of the reaction (Scheme 40). However, in this reaction the regiochemical outcome is dictated by the intermediate **117**, which is the reversed regioisomer compared to Micalizio's method.

Scheme 39. [3+2]Cycloaddition with Alkynol

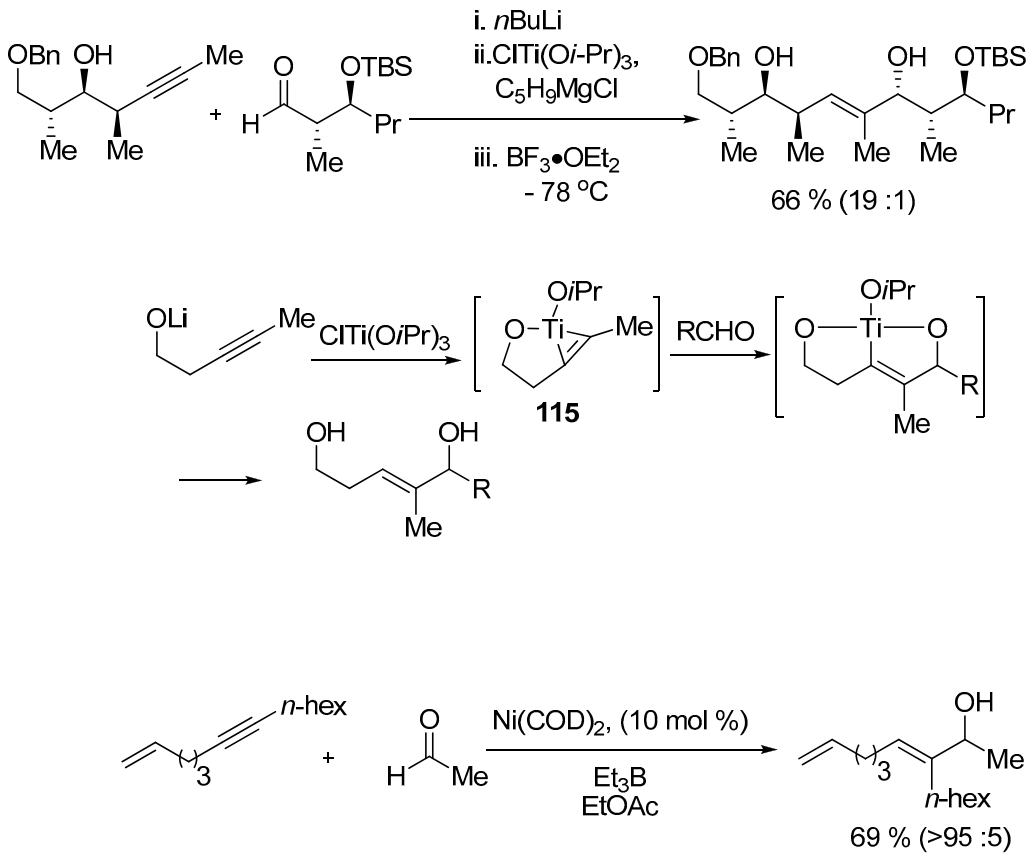


114a **114b**

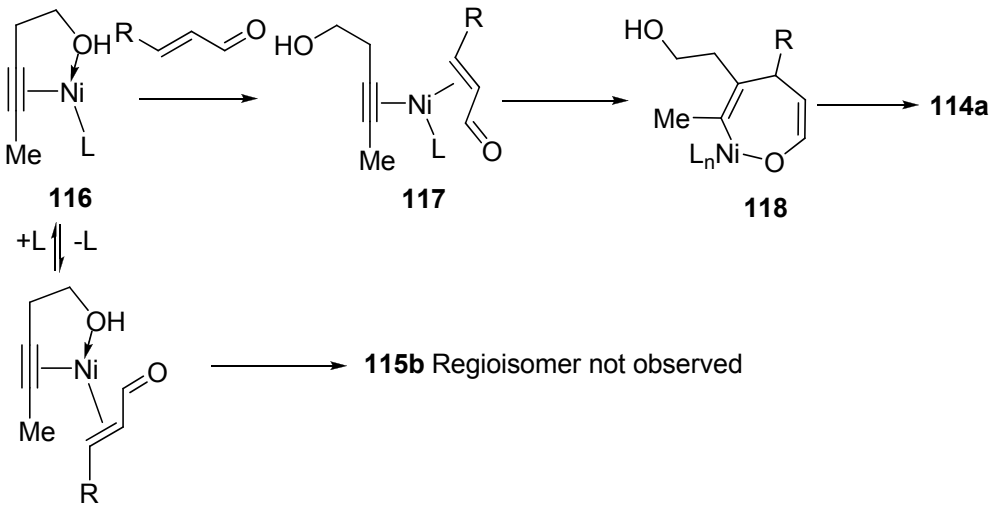
R = H 71 % (only **114a**)

R = TBS 80 % (**114a**:**114b**, 1:1)

Scheme 40. Titanium Alkoxide-Mediated Coupling



Scheme 41. Explanation of the Regioselectivity



1.3 Summary

A novel, nickel-catalyzed [3+2] cycloaddition of enals and alkynes has been developed. This new reaction provides a diastereoselective and chemoselective entry to five-membered rings, which are a common structural motif in many architecturally complex and biologically active natural products. These are the first intermolecular versions and the first catalytic versions of the process. The effect of ligands on intramolecular and intermolecular reactions is noteworthy. Intramolecular reactions could be carried out with either bidentate or monodentate phosphine ligands. However, intermolecular reactions are effective only with monodentate phosphine ligands. Additionally, the product distribution of this reaction could be varied by changing the ligand structure.

CHAPTER 2

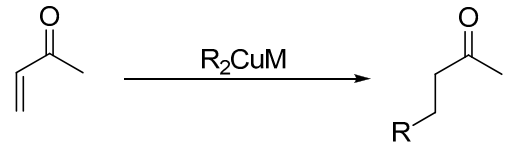
NICKEL-CATALYZED INTERMOLECULAR REDUCTIVE COUPLING OF ENONES AND ALKYNES

2.1 Introduction

Carbon-carbon bond formation by conjugate addition of organometallic reagents to α,β-unsaturated enones is an efficient and powerful tool for the synthesis of β-substituted carbonyl compounds. Various organometallic reagents such as organocopper,[75] organozirconium,[76] organozinc,[77] organoaluminium,[78,79] organomercury,[80] organoboron,[81] organosilane[82,83] and organotin[84] reagents are widely used. Among them, organocopper reagents and vinyl zirconium reagents are arguably the most versatile compounds employed for the synthesis of γ,δ-unsaturated ketones.

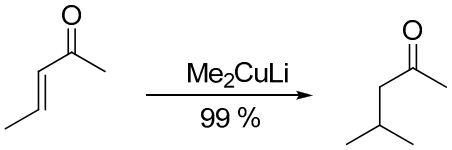
2.1.1 Conjugate Addition of Organocopper Reagents

Nucleophilic organocopper(I) reagents are used either in a catalytic or stoichiometric manner in organic chemistry to synthesize β-substituted carbonyl compounds. Metal organocuprates, generally formulated as R_2CuM, with a variety of metal (M) and organic groups (R), are uniquely effective synthetic reagents for nucleophilic delivery of hard anionic nucleophiles such as alkyl, vinyl and aryl anions (eq 35).

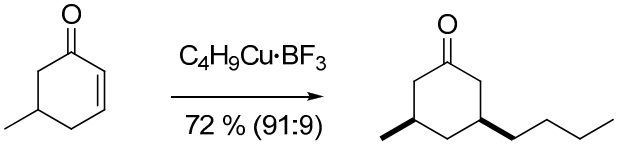


(35)

In 1941, Kharasch and Tawney observed the conjugate addition of a Grignard reagent to α,β-unsaturated ketones in the presence of CuCl.[85] Later House and co-workers reported the 1,4-addition reaction of a lithium diorganocuprate(I) reagent, which was discovered by Gilman in 1952 (eq 36).[86,87] In 1982, Yamamoto et al. discovered a Lewis acid-mediated conjugate addition of organocuprate reagents to α,β-unsaturated ketones, esters and acids (eq 37).[88]

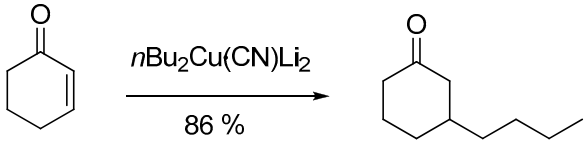


(36)



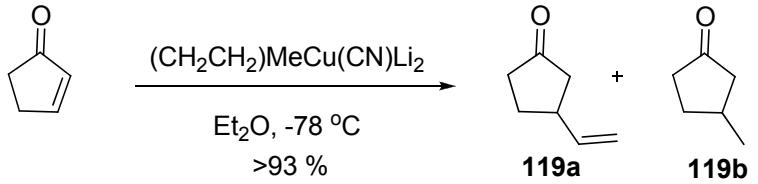
(37)

The solubility and stability of the Gilman reagent was very low. To overcome this problem many groups employed different additives such as Me_2S, LiBr, HMPA, $P(OEt)_3$, and PBu_3. Later, Lipshutz introduced high order organocuprates $R_2Cu(CN)Li_2$ instead of Gilman reagents to access β-substituted ketones (eq 38).[89,90] This methodology was efficient and no additives were required.



(38)

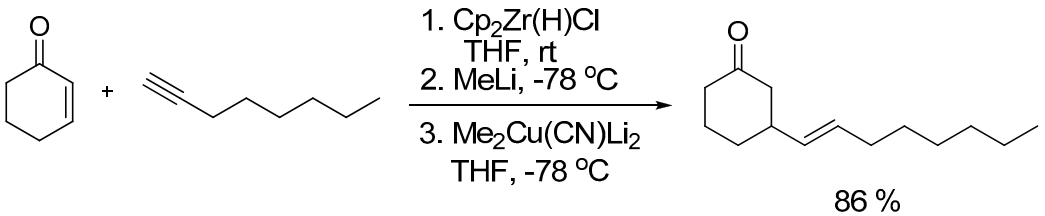
With lower order homoorganocuprates $[R_2Cu]^-$, in most cases, the reagent can transfer only one of the two R ligands to the target electrophile, and one R ligand is lost during the work-up, thereby decreasing the efficiency of the reaction. Thus efficiency of this reaction was increased by the introduction of mixed higher order cuprates $[R(Y)Cu]^{2-}$, containing two different ligands. One ligand is replaced with a "dummy" ligand, such as a metalated acetylene or anions of heteroatom-containing species where back bonding or strong sigma bonding to Cu is present (eq 39)[91]



(39)

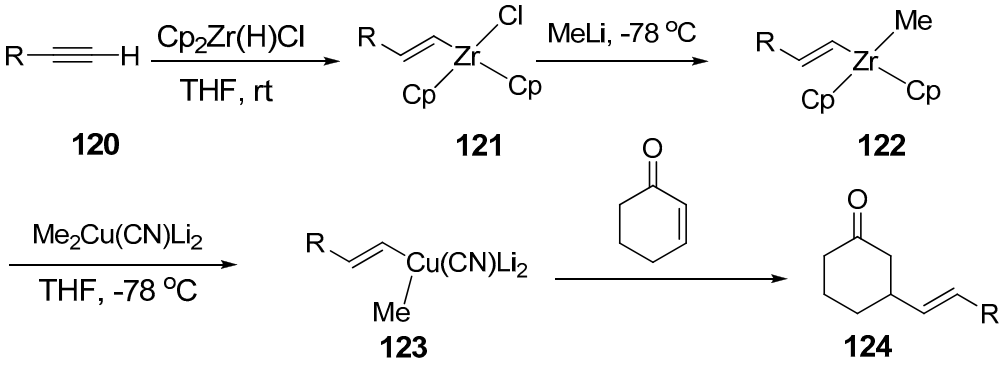
119a : 119b =142 : 1

In 1990, Lipshutz used a hydrozirconation-transmetallation sequence to synthesize γ,δ-unsaturated ketones (eq 40).[92] Treatment of alkyne **120** with Schwartz's reagent, $Cp_2Zr(H)Cl$, yielded product **121**. Then the resulting intermediate is reacted with MeLi to afford **122**. A cooled solution of $Me_2Cu(CN)Li_2$ is added to generate cuprate **123**, which is then reacted with an enone to produce ketone **124** (Scheme 42). This new one pot process can be applied to acetylenes which possess a nitrile, ester, or chloride.[93] However, in these procedures, a stoichiometric amount of copper(I) salts was necessary.

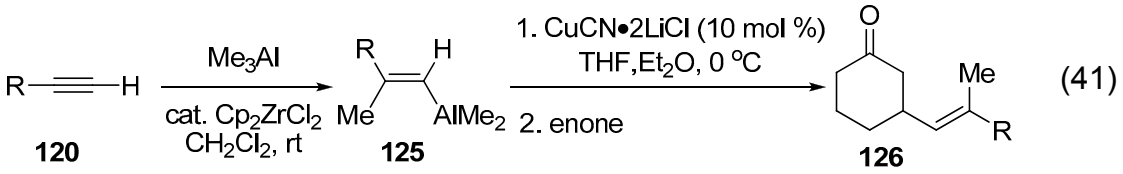


(40)

Scheme 42. Cyanocuprate Addition to Enones



Vinylic zirconates, stannanes, and tellurides readily exchange vinylic ligands with alkyl groups on copper. Lipshutz used this strategy to develop a new methodology by employing a vinylic alane and Cu(I) catalyst (eq 41). Treatment of alkyne **120** with Me_3Al and a catalytic amount of Cp_2ZrCl_2 generates vinylic alane **125**, which is reacted with CuCN·2LiCl to generate vinylic copper intermediate. Then addition of enone to the intermediate generates 1,4-adduct **126** in high yields.

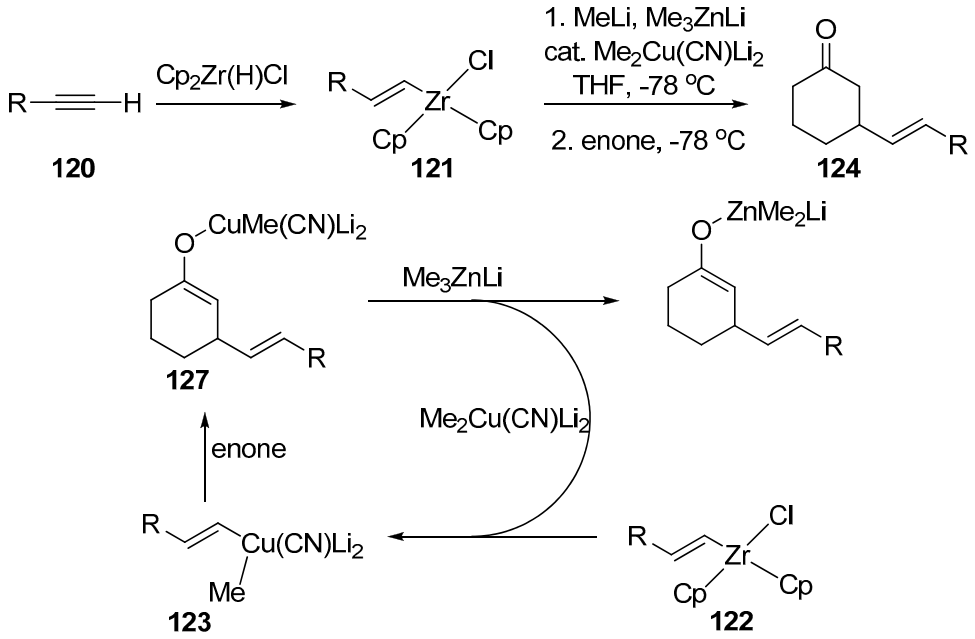


(41)

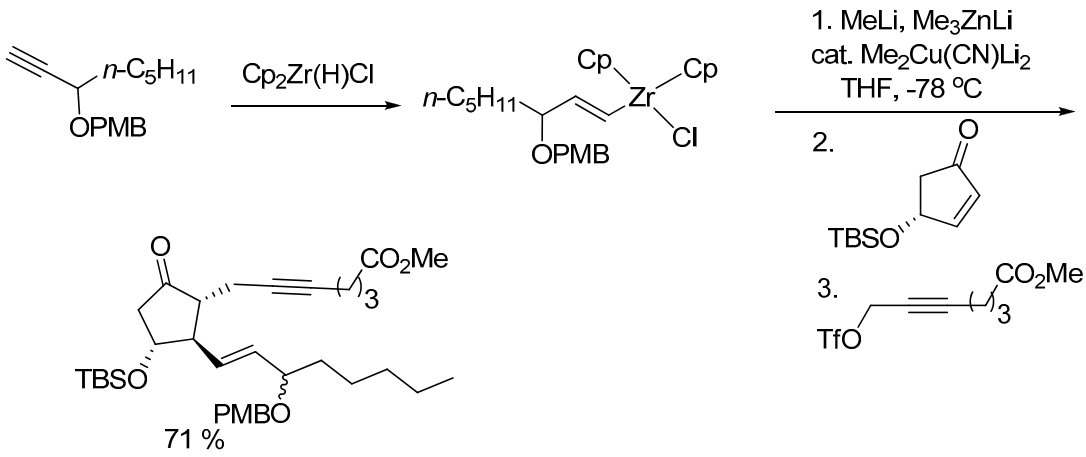
Later, the same group developed a cyanocuprate-catalyzed 1,4-addition of vinylic zirconocenes using a zincate as an organolithium “shuttle”. Zincate (Me_3ZnLi) was employed as a source of methyl anion to regenerate these higher order cuprates.[94] Zincate transported the elements of MeLi to copper in enolate **127** (Scheme 43). This new procedure allowed the amount of cuprate to be decreased to 5 mol %. The extension of this novel methodology by the Lipshutz

group led to the short efficient syntheses of prostaglandin and non-prostaglandin derivatives from alkyne precursors and functionalized cyclopentenones (Scheme 44).[95-97]

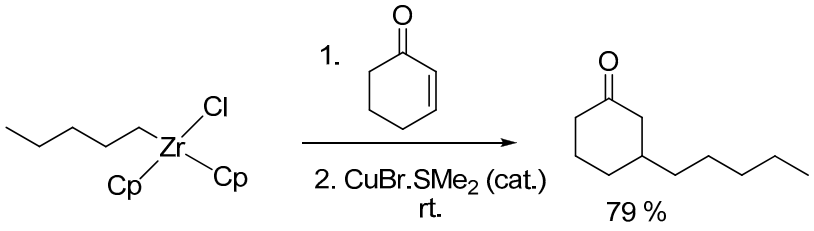
Scheme 43. Cyanocuprate-Catalyzed 1,4-Additions to Enones



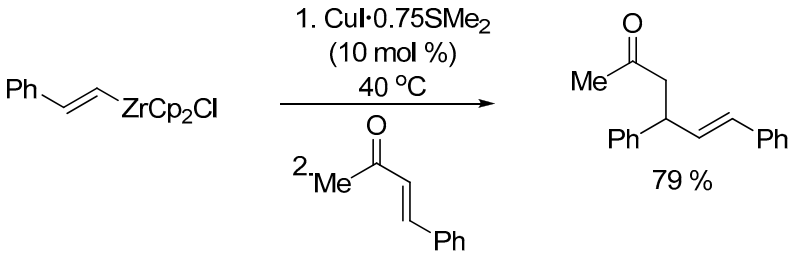
Scheme 44. Three-Component Coupling Approach to Prostaglandins



In 1991, Wipf reported an *in situ* protocol for the copper-catalyzed conjugate addition of organozirconocenes to enones.[98] In the presence of 10 mol % of $CuBr{\cdot}SMe_2$, 1 equiv of 1-hexyl-zirconocene and enone provided a β-substituted ketone in high yield (eq 42). Recently, the Bergdahl group modified the above methodology to access γ,δ-unsaturated ketones and aldehydes (eq 43).[99]

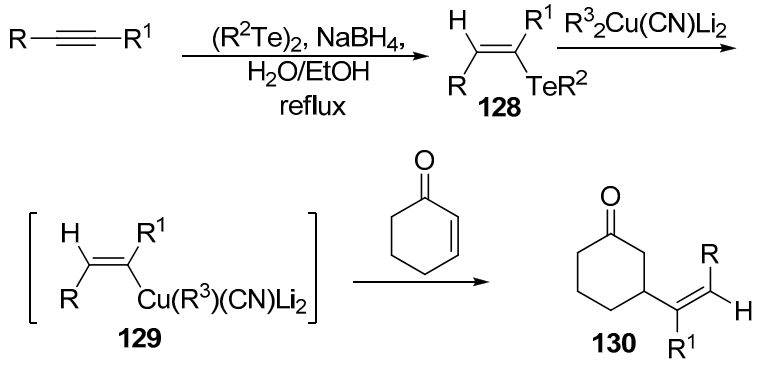


(42)



(43)

Scheme 45. Preparation of *Z*-Vinylic Cuprates from *Z*-Vinylic Tellurides

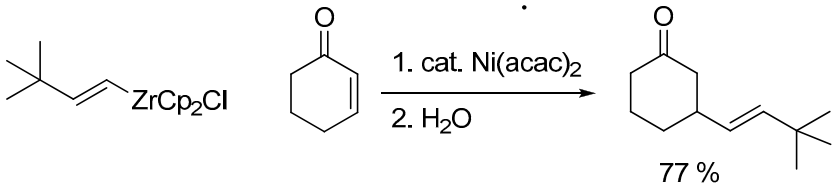


Commasseto and Marino reported the preparation of *Z*-vinylic cuprates from *Z*-vinylic tellurides.[100] Hydrotelluration of alkynes yielded *Z*-vinylic tellurides **128**, which are transformed into *Z*-vinylic higher order cyanocuprates **129** by

reacting with $Me_2Cu(CN)Li_2$ or *n*-$Bu_2Cu(CN)Li_2$. The resulting vinyl cuprates **129** reacted with enones to give the corresponding 1,4-adducts **130** in high yields (Scheme 45).

2.1.2 Conjugate Addition of Organozirconium Reagents

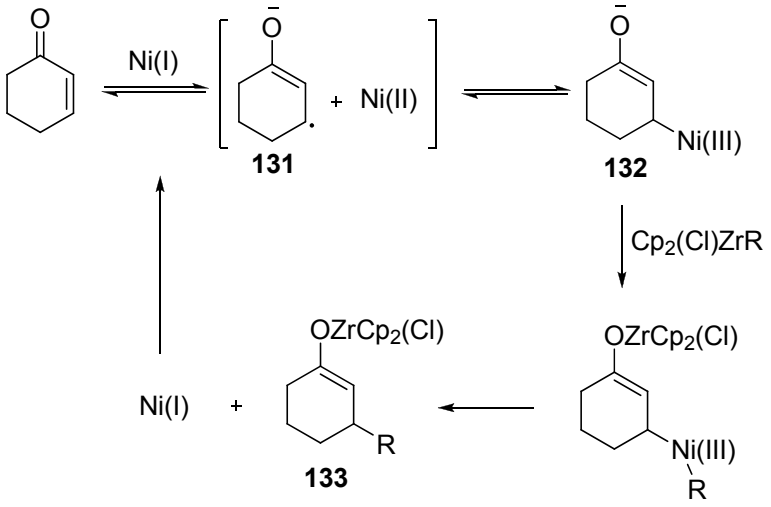
Although organocopper complexes have been widely used, other related reactions catalyzed by transition metals have provided additional applications and extension of this methodology. In 1979 Schwartz reported a nickel catalyzed conjugate addition of an alkenylzirconium species to α,β-unsaturated ketones.[76] When a mixture of alkenylzirconium and enone was treated with a catalytic amount of $Ni(acac)_2$, the 1,4-adduct was obtained in high yield (eq 44).



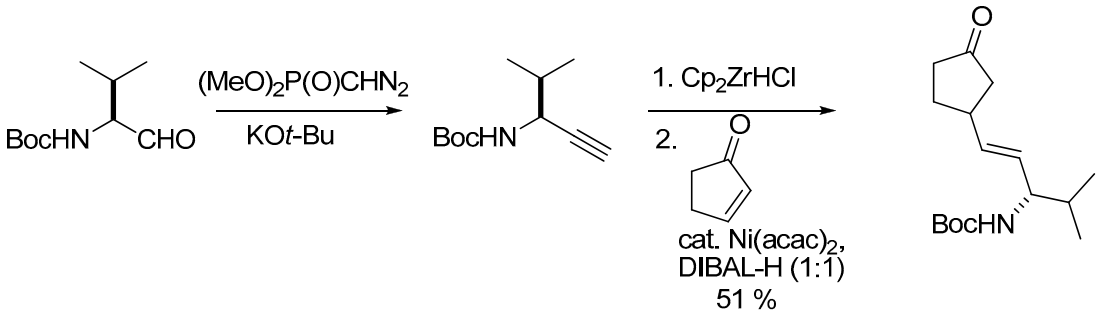
(44)

Alkenylzirconium reagents derived from internal alkynes resulted in modest yields. The reduction of $Ni(acac)_2$ with 1 equiv of DIBAL-H, prior to reaction, provided improved yields.[101] A one-electron transfer mechanism was proposed for these nickel catalyzed reactions (Scheme 46).[102,103] Initial electron transfer from a Ni(I) species to the unsaturated ketone generates intermediate **131**, which could attack Ni(II) to produce intermediate **132**. The organonickel(III) intermediate **132** then could undergo transmetallation with the alkenylzirconium followed by reductive elimination to generate product **133** and Ni(I).

Scheme 46. One-electron Transfer Mechanism

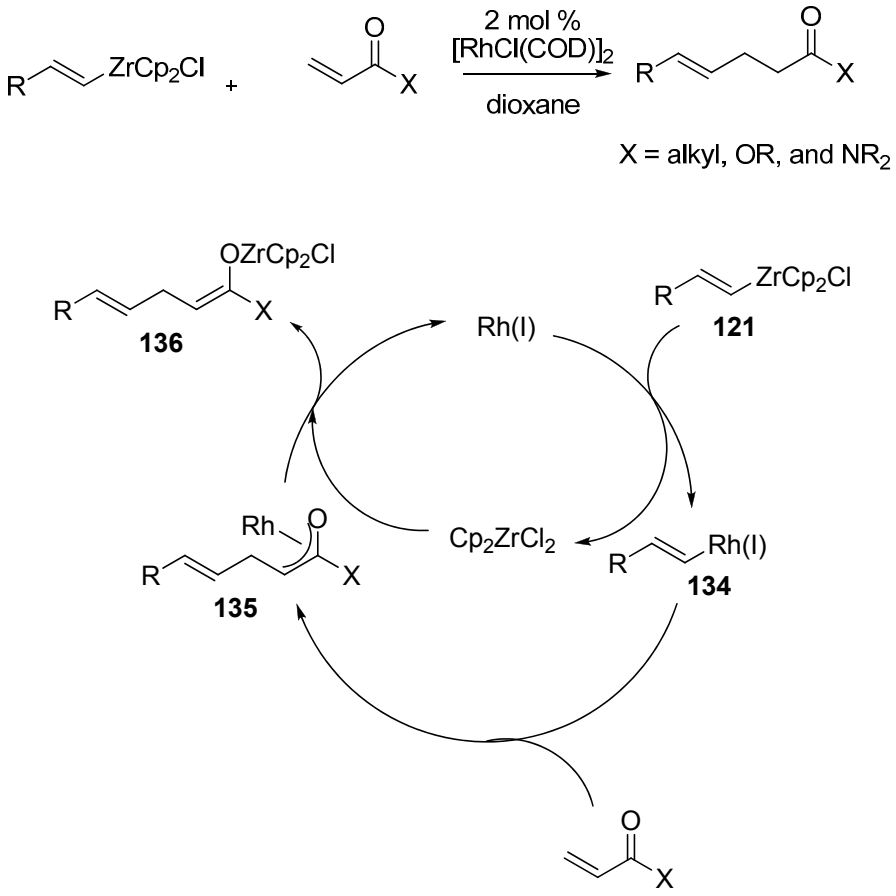


Scheme 47. Conversion of Amino Aldehydes Directly into Chiral Allyl Amines

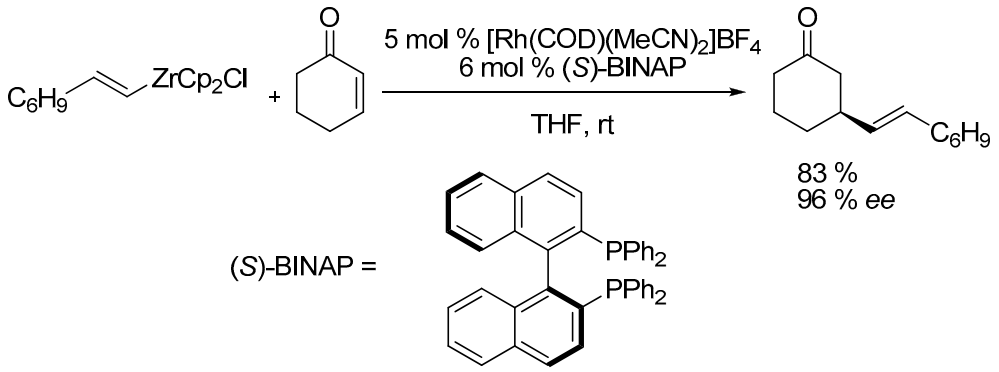


Hauske utilized this methodology with both cyclic and acyclic enones in their investigations to convert amino aldehydes directly into chiral allyl amines (Scheme 47).[104] The same group also employed this methodology to synthesize FKBP inhibitors.[105] In 2004, Hanzawa *et al.* reported the rhodium-catalyzed 1,4-addition of alkenylzirconocene chlorides to electron deficient alkenes such as enones, α,β-enoic acids esters and α,β-enoic acid amides (Scheme 48).[106]

Scheme 48. Rhodium-Catalyzed 1,4-Addition of Alkenylzirconocenes



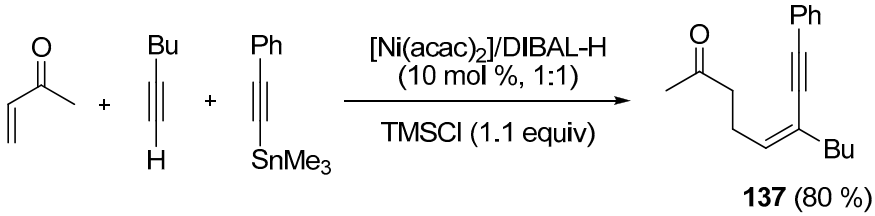
The mechanism is likely to involve the formation of alkenylrhodium species **134** by transmetallation at the initial step (Scheme 48). Then 1,4-addition of alkenylrhodium **134** to enone would generate the oxa-π-allylrhodium enolate **135**, which could then react with the zirconium complex to produce zirconium enolate **136** and rhodium(I). Later, Inoue and Oi employed a similar catalytic system to develop an asymmetric conjugate addition of alkenylzirconium reagents to α,β-unsaturated ketones.[107] The chiral rhodium complex was generated from $[Rh(COD)(MeCN)_2]BF_4$ and (*S*)-BINAP (eq 45).



(45)

2.1.3 Transition Metal Catalyzed Coupling of Enones and Alkynes

Efficient transition metal-catalyzed coupling of two unsaturated components in a chemoselective and stereoselective fashion is particularly useful in the synthesis of complex organic molecules. In 1994, Sato and Ikeda reported the intermolecular coupling of enones, alkynes, and alkynyltins to generate conjugated enynes such as **137** (eq 46).[108] Both internal and terminal alkynes can be employed while terminal alkynes provided high regio and stereoselectivity.

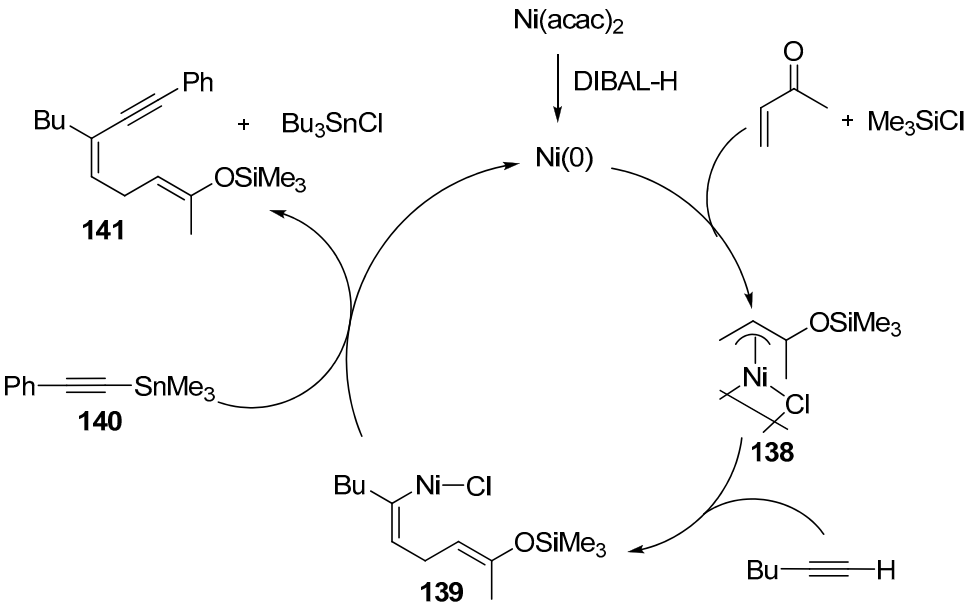


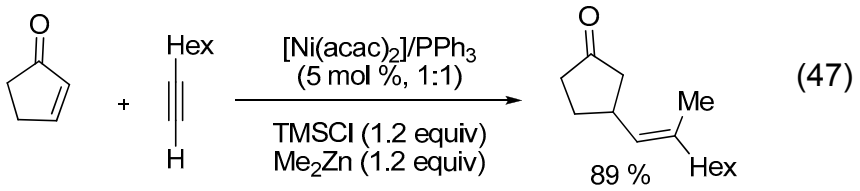
(46)

The proposed mechanism involves the reaction of a nickel complex with Me_3SiCl to generate [1-[(trimethylsilyl)oxy]allyl]nickel complex **138**, which could react with alkyne to form vinylnickel species **139**. Transmetallation of vinyl nickel species **139** with alkyne **140**, followed by reductive elimination could generate the coupling product **141** and regenerate the nickel complex (Scheme 49). Later,

the same group reported a nickel-catalyzed tandem coupling of chlorotrimethylsilane, enones, alkynes, and dimethylzinc (eq 47).[109]

Scheme 49. Proposed Mechanism for the Nickel-Catalyzed Coupling of Enones, Alkynes, and Alkynyltins





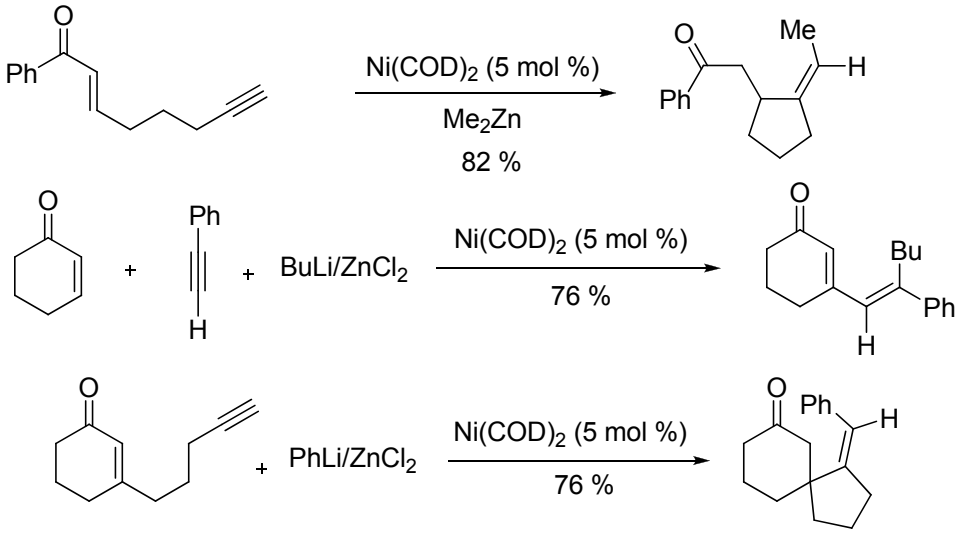
(47)

The corresponding intermolecular couplings with alkynylzincs also proceed to generate conjugated enynes.[109,110] However, yields and regioselectivities of the alkyne insertion are lower than in the alkynyltin reagent variant.

As mentioned in the previous chapter (Section 1.1.4), our group has introduced nickel-catalyzed three component couplings of enones, alkynes and

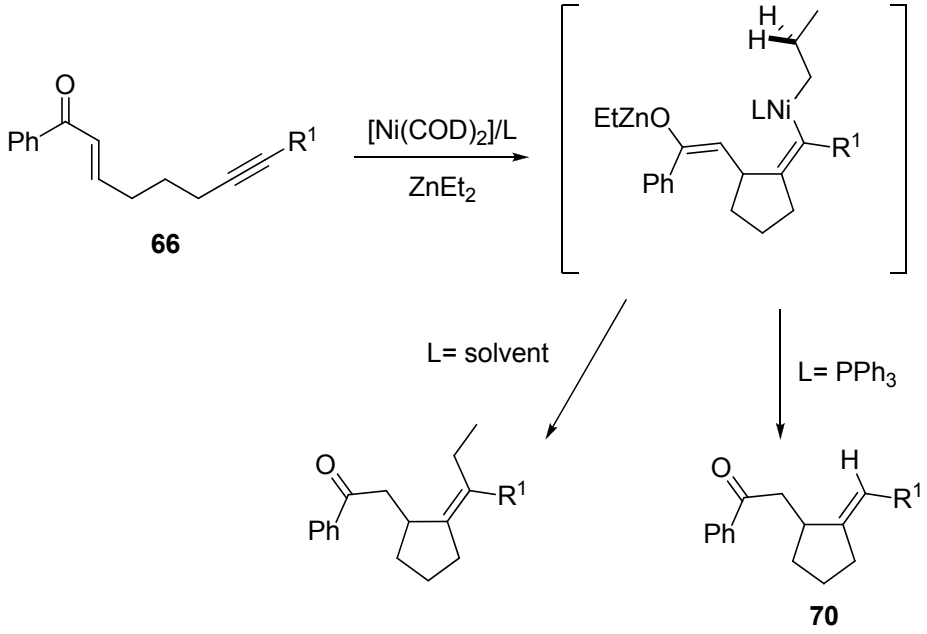
organozinc reagents to produce highly substituted γ,δ-unsaturated ketones in a completely stereoselective fashion. This reaction can be carried out in an intermolecular or intramolecular fashion (Scheme 50).[58]

Scheme 50. Nickel-Catalyzed Three Component Couplings of Enones, Alkynes and Organozinc

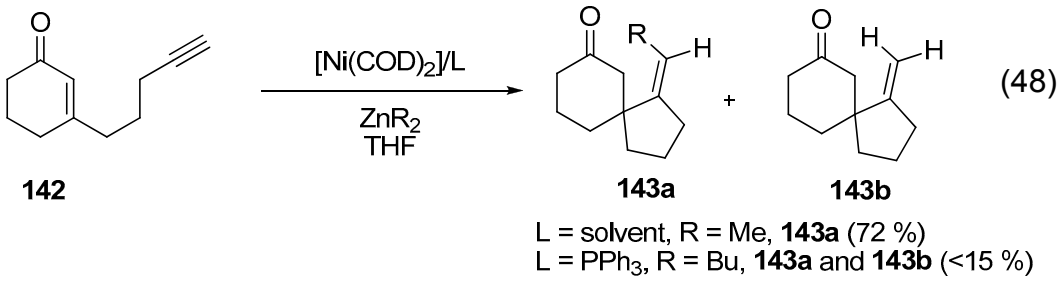


Organozinc reagents that bear β-hydrogen atoms provided reductive coupling products when the nickel catalyst was pretreated with excess triphenylphosphine (Scheme 51). The σ-donating ability of the ligand promotes the β-hydrogen elimination reaction pathway. In the absence of triphenylphosphine, the unreacted enone substrate could coordinate to the nickel intermediate and lead to an acceleration of the rate of reductive elimination due to the decreased electron density on the metal center.

Scheme 51. Intramolecular Reductive Coupling of Enones and Alkynes

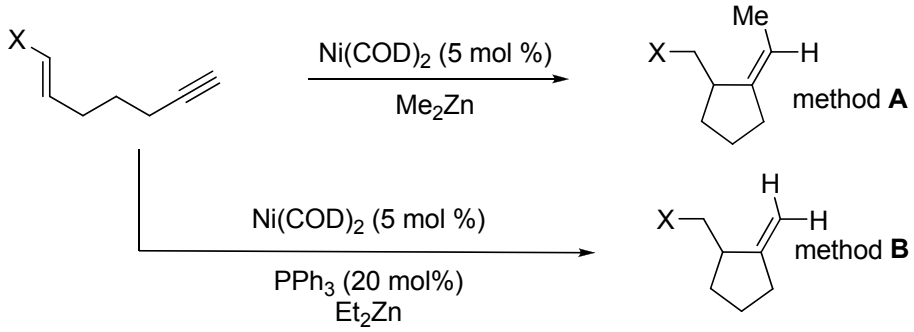


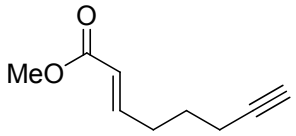
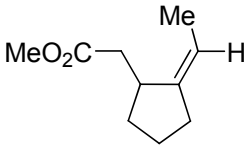
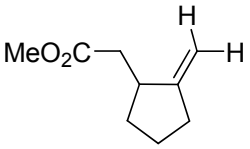
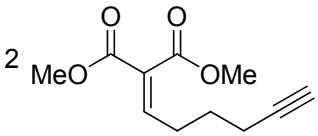
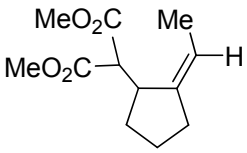
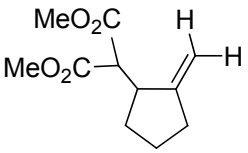
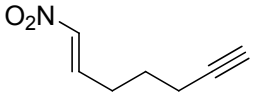
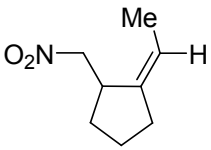
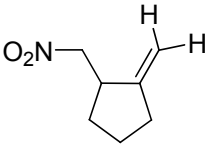
These reactions can tolerate a wide range of electron deficient alkenes such as enones, nitroalkenes, alkylidene malonates, and unsaturated β-ketoesters (Table 11). However, enoates are poor substrates in this class of reactions (Table 11, entry 1).[59] Both alkylative cyclization and reductive cyclization gave modest yields with internal alkynes. Reductive cyclization of terminal alkynes was more efficient than with internal alkynes. Additionally, alkylative cyclizations were more efficient than reductive cyclizations with sterically-demanding substrates such as **142** (eq 48).



(48)

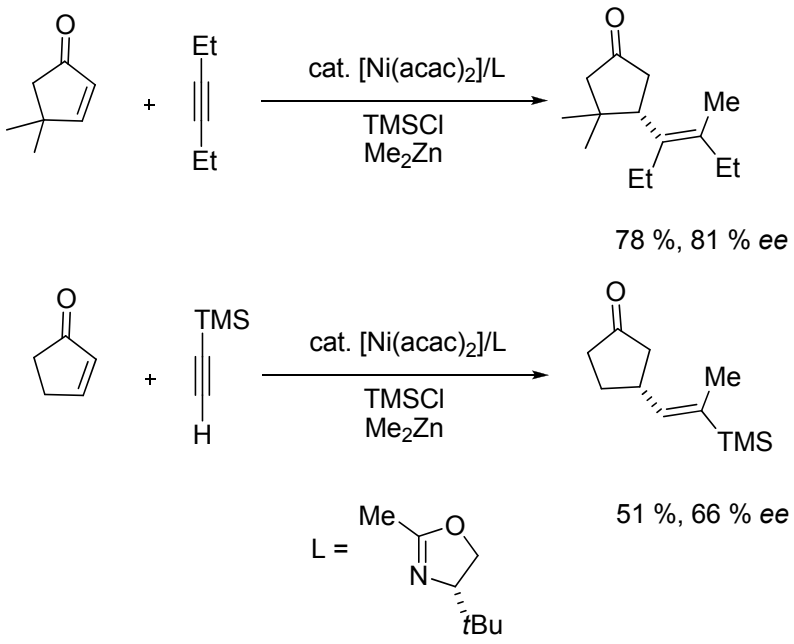
Table 11. Substrate Scope of Intramolecular Alkylative and Reductive Coupling



entry	substrate	Product method **A** (% yield)	method **B** (% yield)
1		 15-20 %	 -
2		 74 %	 83 %
3		 39 %	 13 %

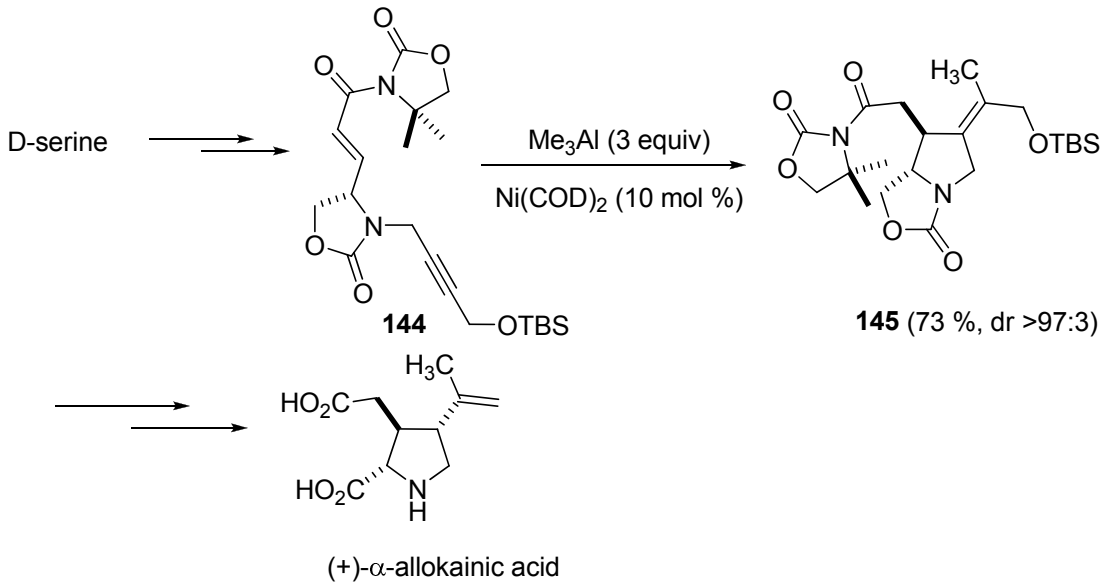
Later Ikeda *et al*. reported an asymmetric version of the intermolecular coupling of enones, alkynes, and dimethylzinc.[111] Chiral monodentate oxazoline ligands were employed to access γ,δ-usaturated ketones in moderate to good enantioselectivity (Scheme 52).

Scheme 52. Asymmetric Version of the Intermolecular Coupling

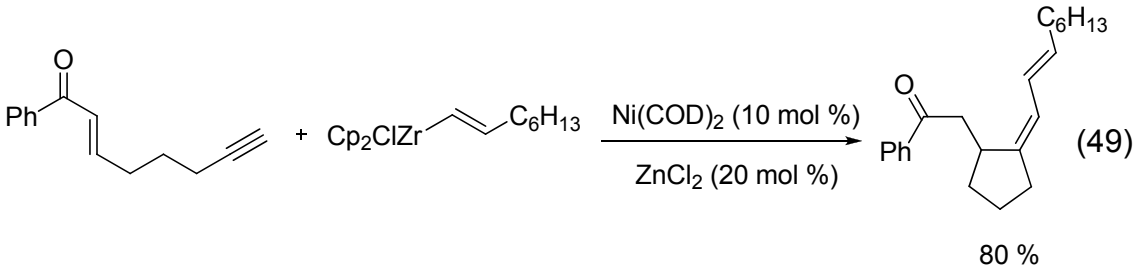


In 2000, the Montgomery group employed organoaluminums instead of organozincs in the total synthesis of (+)-α-allokainic acid (Scheme 53).[112] Substrate **144** was efficiently cyclized in the presence of trimethylaluminum and a catalytic amount of $Ni(COD)_2$ to generate **145** in high diastereoselectivity.

Scheme 53. Total Synthesis of (+)-α-Allokainic acid



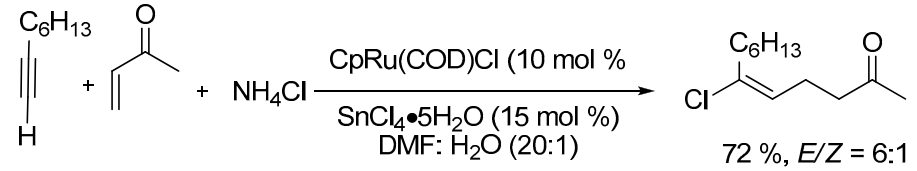
Vinylzirconium reagents were also effective in these types of cyclizations. It was found that alkyne-derived vinylzirconium reagents could be employed in the intramolecular enone-alkyne couplings with nickel catalysis.[113] This new coupling process provided a novel route to highly substituted 1,3-dienes (eq 49).



(49)

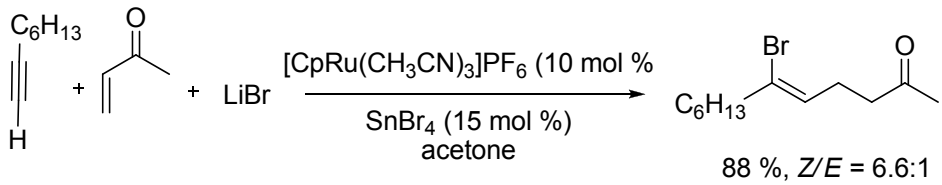
80 %

Trost and co-workers developed ruthenium-catalyzed three component couplings of enones, alkynes, and ammonium chloride to generate *E*-vinyl chlorides (eq 50).[114] Later, this method was extended to access *Z*-vinyl bromides by employing the halide-free ruthenium catalyst, $[CpRu(CH_3CN)_3]PF_6$, as a catalyst (eq 51).[115]



(50)

72 %, *E*/*Z* = 6:1



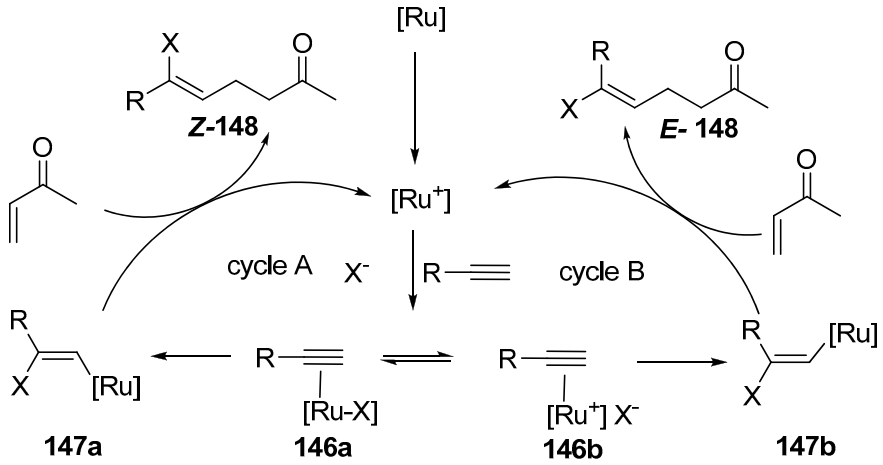
(51)

88 %, *Z*/*E* = 6.6:1

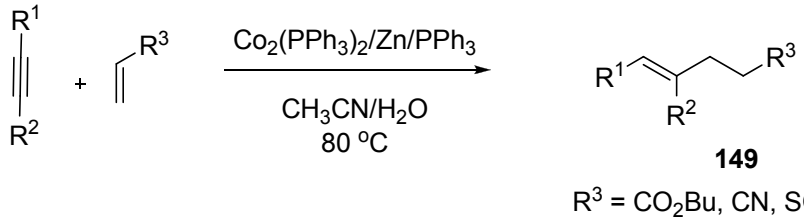
The proposed mechanism is shown in Scheme 54. A cationic ruthenium species could coordinate to the alkyne and the halide either covalently **146a** or as an ion pair **146b**. The ion pair **146b** would lead to a *trans*-haloruthenation to form intermediate **147b**, which could react with an enone to generate the product

***E*-148**. The covalently bound complex **146a** could lead to intermediate **147a** via *cis*-haloruthenation, followed by the insertion of an enone to produce the product ***Z*-148**.

Scheme 54. Proposed Mechanism for the Ruthenium-Catalyzed Stereoselective Synthesis of Vinyl Bromides

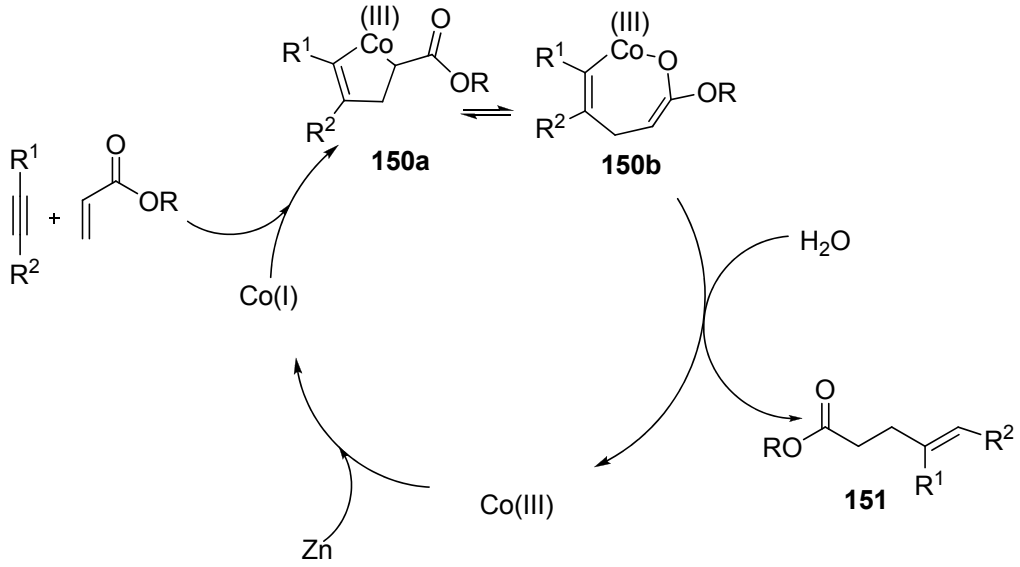


In 2002, Cheng *et al.* reported a cobalt-catalyzed intermolecular reductive coupling of alkynes with conjugated alkenes (eq 52).[116] Treatment of electron deficient alkenes such as *n*-butyl acrylate, acrylonitrile and phenyl vinyl sulfone, with alkynes in the presence of $Co(PPh_3)_2I_2$ (5 mol %), PPh_3 (16 mol %) and Zn powder in acetonitrile/water provided coupling products **149** in high yields. Oxidative cyclization could generate metallacycle **150a** or **150b**. Protonation of intermediate **150** would give the product **151** and Co(III), which is then reduced by Zn to regenerate the active catalyst (Scheme 55).



(52)

Scheme 55. Proposed Mechanism for the Cobalt-Catalyzed Reductive Coupling



2.1.4 Synthesis of Silyl Enol Ethers

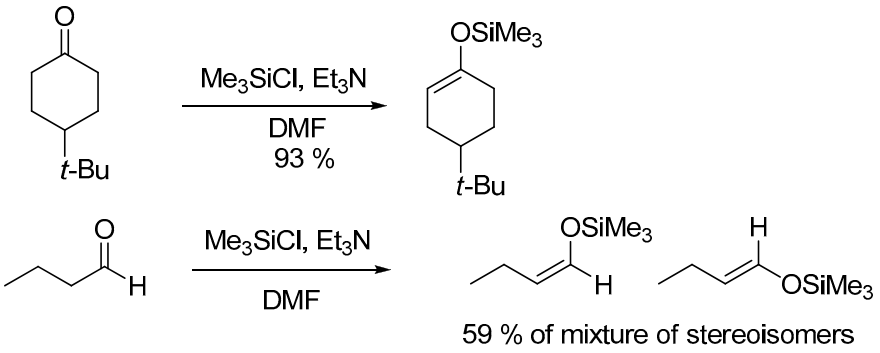
Although many conjugate addition processes are terminated by enolate protonation to generate ketone products, silylation processes that generate silyl enol ethers have been widely explored. Additionally, direct enolization of carbonyls in the presence of silyl electrophiles affords an alternate entry to silyl enol ethers. Since a segment of the results to be described in this thesis provide a new entry to silyl enol ethers, a general description of preparative methods for this important functional group class will be described here.

Silyl enol ethers are important intermediates in organic synthesis. Considerable attention has recently been focused on the synthesis of silyl enol ethers due to their usefulness in various synthetic transformations such as Mukaiyama aldol condensations, and Mannich reactions.[117,118] Enol silanes offer tremendous potential as synthetic enol equivalents, and many cases provide distinct advantages over conventional enols. Silyl enol ethers also can react as nucleophiles in alkylations, haloketone formation with halogens, and acyloin formation by organic oxidation with mCPBA.

One of the early and still one of the most frequently used methods to synthesize (*E*)- or (*Z*)-silyl enol ethers is the trapping of ketone or aldehyde enolates generated under either kinetic- or equilibrium-controlled conditions. These compounds are generally prepared by thermodynamic reactions of carbonyl compounds with silylating reagents in the presence of tertiary amines, or by kinetic reactions of metal enolates which are formed by treatment of carbonyl compounds with metal amides or alkoxides.[119,120]

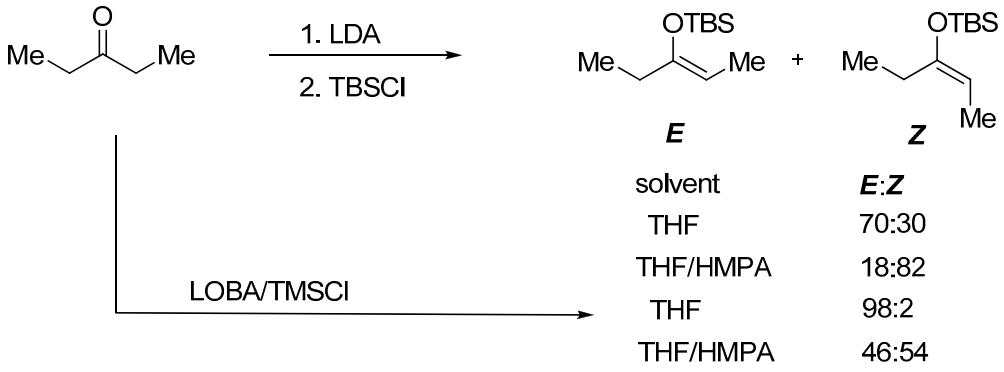
In 1968, Stork and Hudrlik reported the first method to generate silyl enol ethers from ketones using sodium hydride as a base.[121,122] A year later, House and co-workers reported a method for the preparation of trimethylsilyl enol ethers from aldehydes and ketones.[119] Reaction of ketones and aldehydes with chlorotrimethylsilane (TMSCl) and triethylamine (Et_3N) in dimethylformamide (DMF) solution provided trimethylsilyl enol ethers in high yield (Scheme 56).

Scheme 56. Preparation of Silyl Enol Ether from Enolates



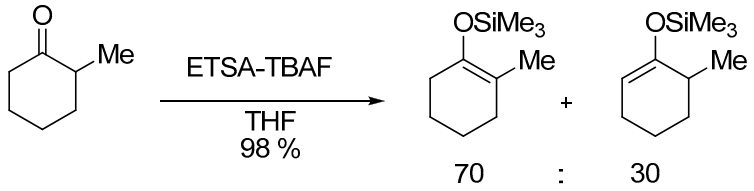
In 1976, Ireland and co-workers demonstrated that an enolization of pentanone with lithium diisopropylamide (LDA) followed by trapping with chlorotrialkylsilane resulted predominantly in the formation of the *E*-enolate in THF and *Z*-enolate in THF/HMPA (Scheme 57).[123] In 1984, Corey and Gross employed a more hindred base, lithium-1,1,3,3-tetramethylbutyl-*tert*-butylamide (LOBA), to increase the selectivity of the *E*-isomer (Scheme 57).[124] Several control experiments suggest that the enolizations occur under exclusively kinetic control and addition of HMPA breaks up enolate aggregation and increases the rate of equilibration.[120,125]

Scheme 57. Kinetic Control Enolization



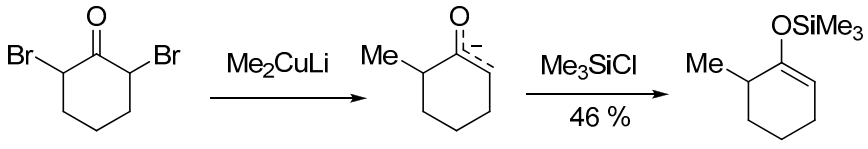
Although these methods for the preparation of silyl enol ethers provided high yields, separation of moisture-sensitive products from a large amount of

inorganic or amine salts was difficult. In 1976, Kuwajima and co-workers have reported an improved method of silylation of ketones with ethyl trimethylsilylacetate-tetrabutylammonium fluoride (ETSA-TBAF), where relatively volatile ethyl acetate is the by-product which can be removed easily (eq 53).[126] However, this method was limited to enones.

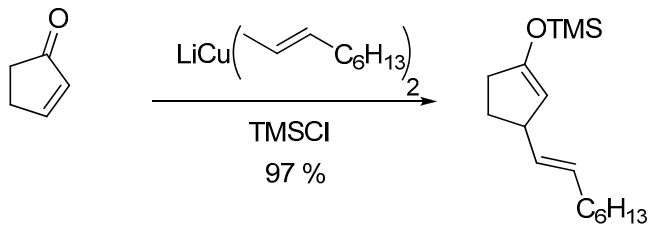


(53)

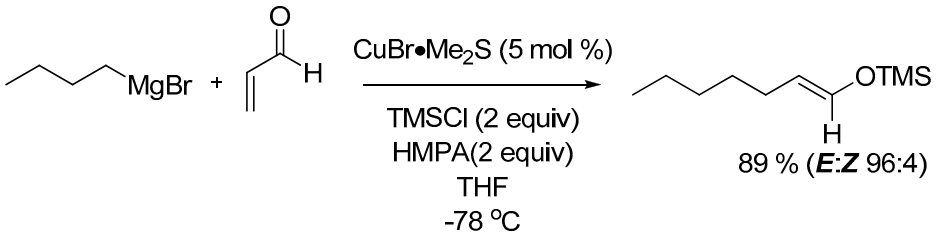
In 1975 Posner *et al*. reported the reaction of α,α'-dibromoketones with organocopper reagents to generate enolate ions in a regiospecific manner. Then these enolates were trapped with chlorosilanes to produce the corresponding silyl enol ethers (eq 54).[127] Similarly, silyl enol ethers generated by nucleophilic conjugate addition of organocuprates to enones have also been reported (eq 55).[128,129] Patterson and Fried employed this methodology in the synthesis of deoxy prostaglandins. Later, Kuwajima and co-workers further developed this method to synthesize enol silyl ethers of aldehydes in high stereoselectivity (eq 56).[130,131]



(54)



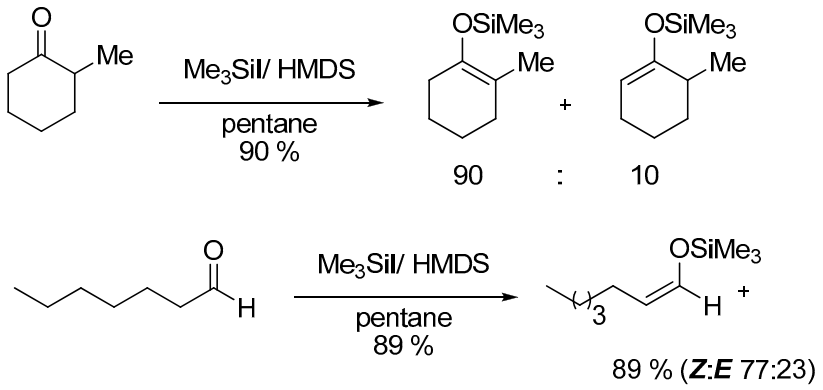
(55)

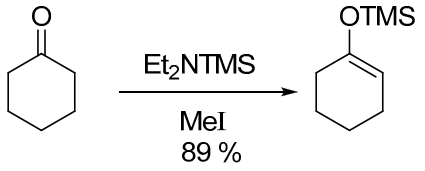


(56)

Miller and co-workers developed an improved method to prepare trimethylsilyl enol ethers in high yield at room temperature (Scheme 58).[132] Treatment of ketones or aldehydes with iodotrimethylsilane (TMSI) and hexamethyldisilazane (HMDS) produce silyl enol ethers in high yields. These mild conditions led to the formation of the thermodynamically more stable product. One of the highlights of this reaction is that aldehydes generated enol ethers in favor of the *Z*-isomer. In 1997, Yamamoto and co-workers reported a similar method for the preparation of silyl enol ethers from ketones. The reaction of ketones with silyl amines and methyl iodide resulted in enol silanes in high yield (eq 57).[133] The isolation of products was comparatively easy, as the ammonium salts formed during the reaction can be removed by filtration.

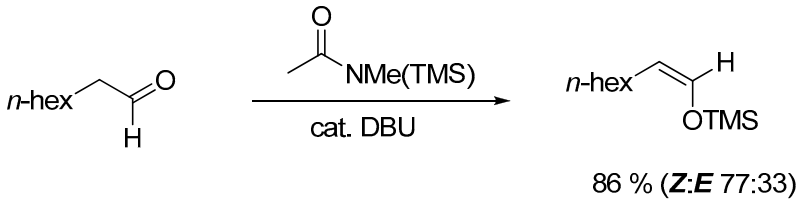
Scheme 58. TMSI and HMDS Promoted Synthesis of Enol Silanes





(57)

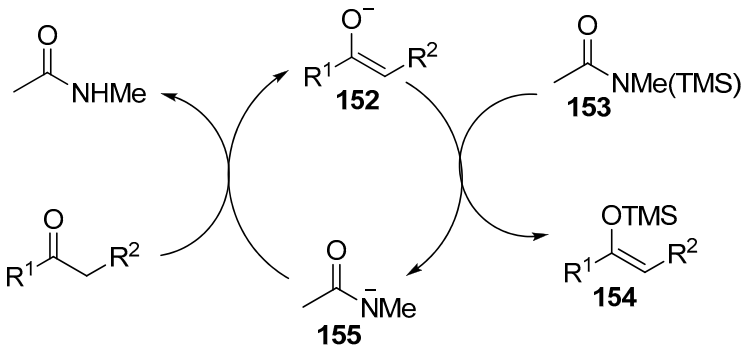
In 2002, Tanabe and co-workers developed an efficient method using novel agents such as TMS-acetamide with catalytic amount of base (eq 58).[134] The reaction introduced the TMS group chemoselectively into aldehydes and ketones under mild conditions. The plausible mechanism is outlined in Scheme 59. First, base deprotonates the carbonyl compound to form enolate **152**, which is then trapped with TMS-acetamide **153** to produce the silyl enol ether **154**. The resulting amidate anion **155** deprotonates the carbonyl compound to complete the catalytic cycle.



86 % (***Z*:*E*** 77:33)

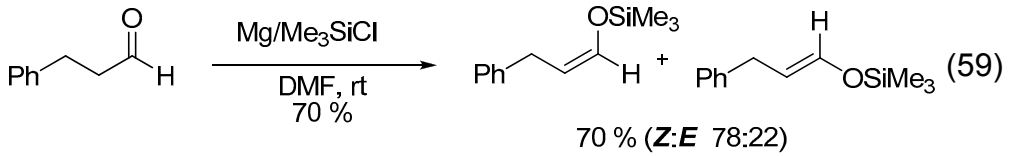
(58)

Scheme 59. Proposed Mechanism for TMS-acetamide Promoted Enolization

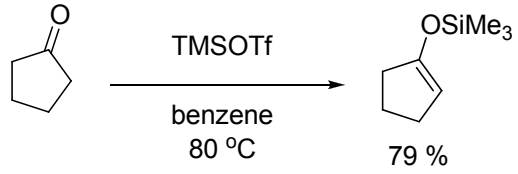


Furthermore, Ishino *et al*. reported Mg-promoted coupling of aliphatic carbonyl compounds with trimethylsilyl chloride (TMSCl) at room temperature to

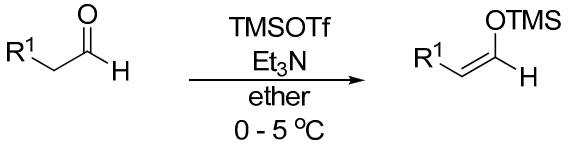
give the corresponding silyl enol ethers in excellent to good yields (eq 59).[135] This method generated *Z*-enol silanes selectively with aldehydes.



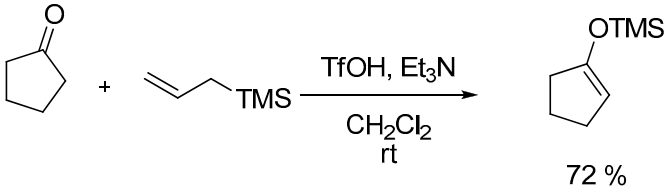
The formation of silyl enol ethers was also achieved by the silylation of ketones and aldehydes by trimethylsilyl trifluoromethanesulfonate (TMSOTf).[136] In 1976, Simchen and Kober employed TMSOTf to generate silyl enol ether from ketones (eq 60).[137] This methodology was further developed by adding Et_3N as a base to quench the formed triflic acid, and this modification led to the stereoselective formation of enol silanes from aldehydes (eq 61). Later, Olah and co-workers modified this method by employing allyltrimethylsilane and trifluoromethanesulfonic acid with triethyl amine at room temperature (eq 62).[138]



(60)



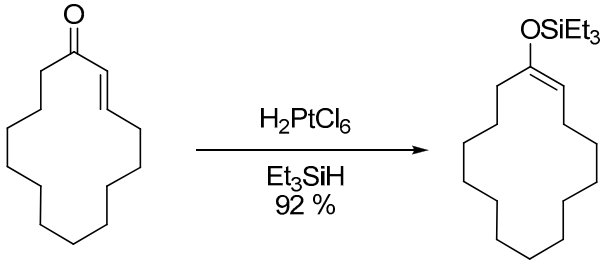
(61)



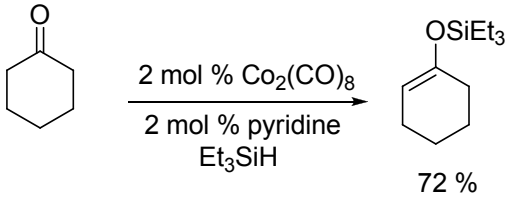
(62)

The 1,4-addition of hydrosilanes to α,β-unsaturated carbonyls has been used to construct enol silanes. In 1975, Stork and MacDonald demonstrated the

isomerization of α,β-unsaturated ketones in the presence of a platinum-catalyst and hydrosilanes (eq 63).[139] A year later, Sakurai and co-workers developed a clean and convenient method of preparing silyl enol ether using the catalytic dehydrogenation from ketone and hydrosilane (eq 64).[140] Dicobalt octacarbonyl was employed as a catalyst with hydrosilanes.

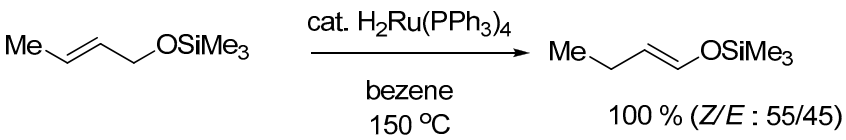


(63)

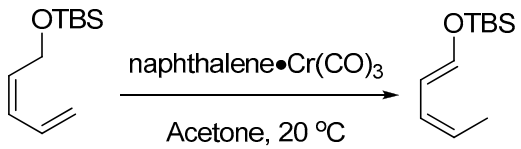


(64)

The catalytic isomerization of allyl ethers is another convenient and straightforward method that allows the large-scale preparation of silyl enol ethers.[141-143] In 1979, Suzuki *et al*. reported isomerization of allyl silyl ethers in the presence of catalytic amount of ruthenium hydride complexes to produce the corresponding silyl enol ethers in high yields (eq 65).[143] A decade later, Shibasaki and co-workers developed a new method for the synthesis of silyl dienol ethers using a chromium catalyst (eq 66).[144]

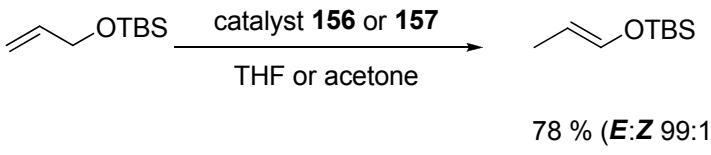


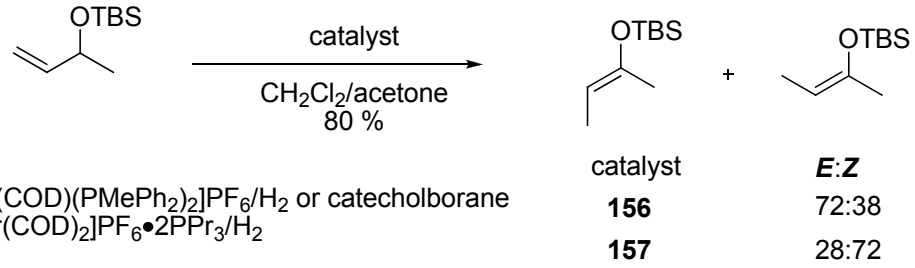
(65)



(66)

Scheme 60. Isomerization of Allyl Silyl Ethers



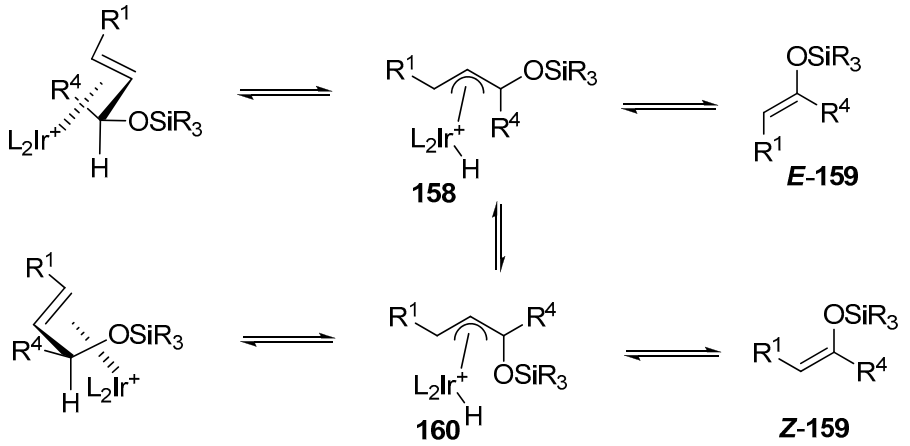


catalyst	*E*:*Z*
156	72:38
157	28:72

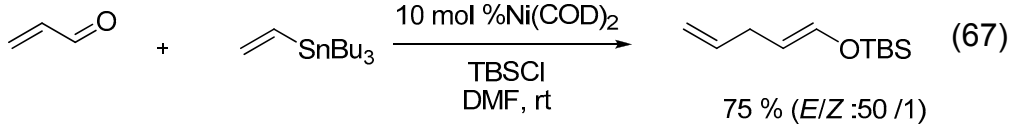
In 1998, Miyaura and co-workers reported a stereoselective isomerization of allyl silyl ethers to (*E*)- or (*Z*)-silyl enol ethers using cationic iridium complexes.[145,146] Primary allyl silyl ethers produced *E*-enol ethers and secondary allyl ethers generated *Z*-enol ethers or *E*-enol ethers depending on the reaction conditions (Scheme 60). The ^{1}H NMR studies led to propose two isomerization pathways (Scheme 61). The isomerization proceeds through the oxidative addition of allylic C-H bond to the metal giving a *syn*-π-allyl intermediate **158**, which selectively led to the product (*E*)-**159**. This kinetically controlled product (*E*)-**159** could be equilibrated to thermodynamically controlled product (*Z*)-**159** via the *anti*-π-allyl **160**. The thermodynamic pathway is slow in a solvent having medium donor strength such as acetone. Thus, the stereochemistry of the product (*Z*)-**159** was highly dependent on the catalyst, the solvent, reaction time, and the substrate. Primary allyl ethers led to the kinetically controlled product (*E*)-

159 in acetone/CH_2Cl_2. On the other hand, secondary allyl ethers produced *Z*- and *E*-enol ethers depending on the reaction conditions.

Scheme 61. The Mechanism of Isomerization

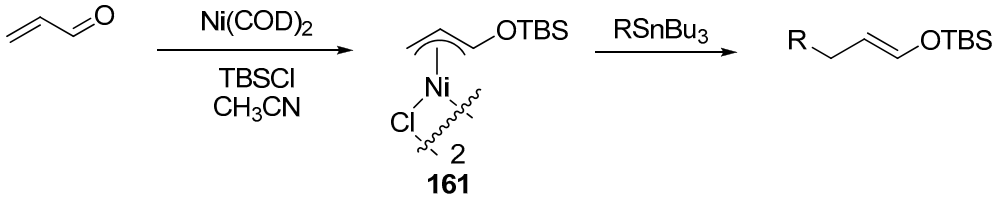


Chain extension methods represent an important protocol to construct silyl enol ethers. Mackenzie developed nickel-catalyzed, chlorotrialkylsilane-assisted conjugate addition of alkenyltributyltin reagents to α,β-unsaturated aldehydes to produce *E*-enol silanes (eq 67).[147,148] Treatment of an enal with $Ni(COD)_2$ and *t*-butyldimethylsilyl chloride generated oxy-allyl species **161**, which underwent transmetallation with an alkenyltin to generate the *E*-enol silane (Scheme 62).

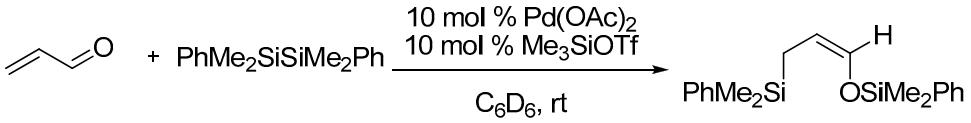


(67)

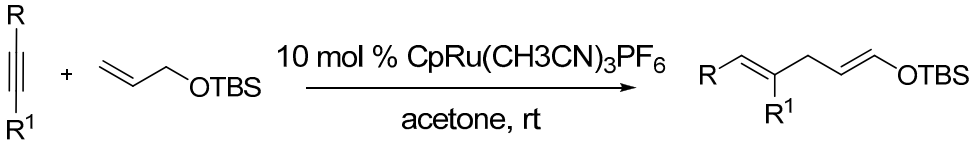
Scheme 62. Bis[(μ-chloro)(1-((trialkylsilyl)oxy)allyl]-nickel(II)] Complex



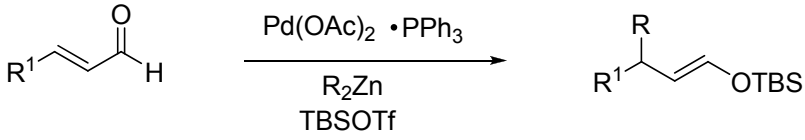
Later, Ogoshi developed a similar method using palladium catalysis with trimethylsilyl trifluoromethanesulfonate (TMSOTf). The reaction of α,β-unsaturated carbonyl compounds with diphenyltetramethyldisilane proceeded to generate 1,4-bis-silylation product in high yields (eq 68).[149] In 2001, Trost and co-workers developed an atom economical chain extension method to construct *E*-enol silanes. Treatment of silyl protected allyl alcohol and alkyne with ruthenium catalyst generated *E*-enol silanes in high yield (eq 69).[150] Recently, Marshall developed a palladium and organozinc mediated method to synthesize *E*-enol silanes starting with enals (eq 70).[151]



99 % (*E*/*Z* :58 /42) (68)

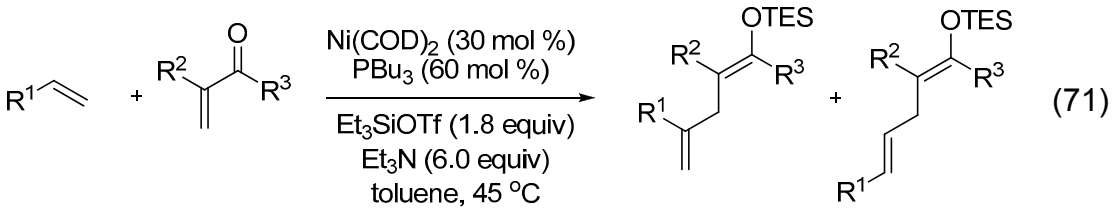


(69)



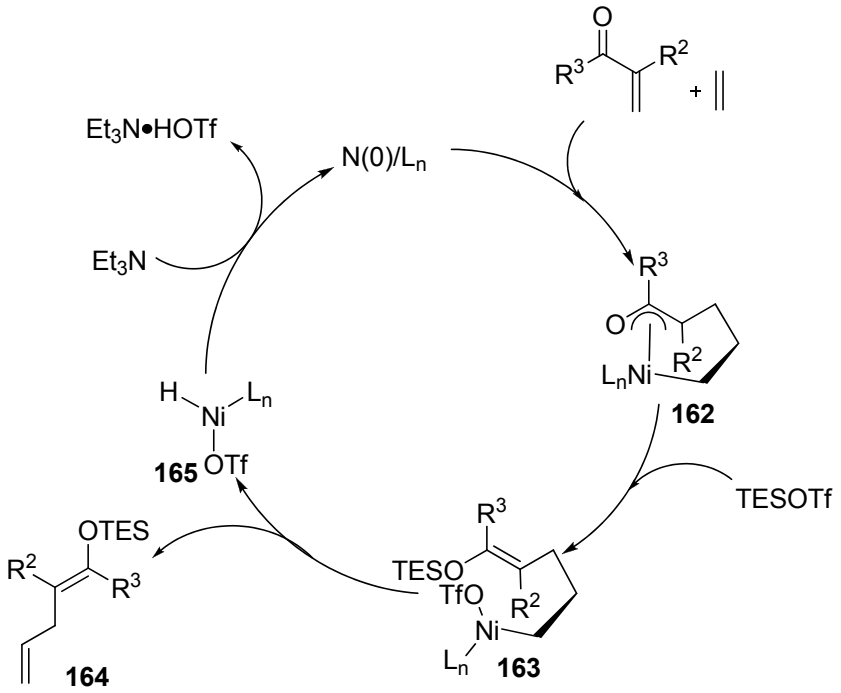
(70)

More recently, the Jamison group reported a nickel-catalyzed coupling of alkenes and enals or enones to generate silyl enol ethers.[152] In the presence of $Ni(COD)_2$, PBu_3, TESOTf and Et_3N, alkenes and enals underwent stereoselective coupling to generate silyl enol ethers in high yield (eq 71).



(71)

Scheme 63. Proposed Mechanism for the Jamison Approach

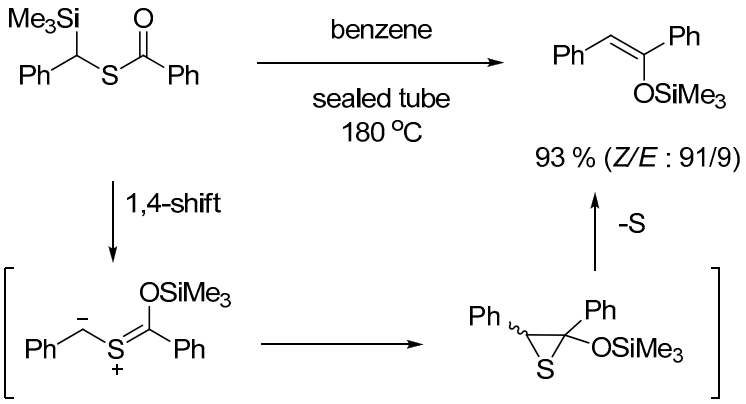


Jamison proposed that the mechanism occurs via an oxa-π-allyl nickel complex **162** (Scheme 63). Then the silyl triflate reacts with the nickel complex **162** to produce enol silane **163**, which undergoes β-hydride elimination to form the product **164** and nickel hydride **165**. Abstraction of TfOH from nickel hydride **165** by Et_3N regenerates nickel(0).

In 2001, Komatsu *et al.* developed a novel method to generate silyl enol ethers from *S*-α-silylbenzyl thioesters via silicon migration, under completely neutral conditions. The reaction involves a thermal 1,4-shift of the silyl group onto

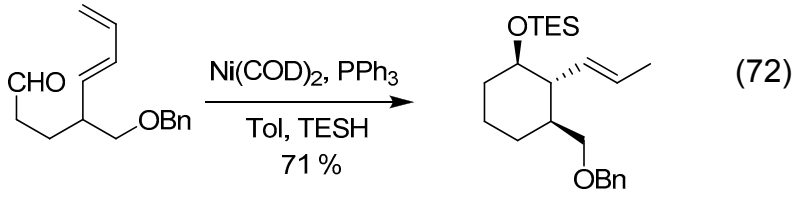
the oxygen of the carbonyl function, followed by C-C bond formation (Scheme 64).[153]

Scheme 64. 1,4-Silatropic Shift



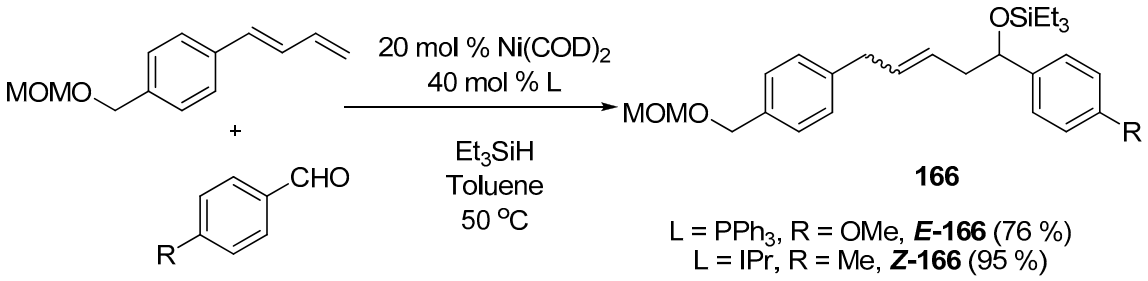
2.1.5 Nickel-Catalyzed Processes Involving Trialkylsilanes

Mori and co-workers reported the first use of trialkylsilanes as a reducing reagent for nickel-catalyzed diastereoselective intramolecular cyclization of aldehydes and 1,3-dienes (eq 72).[154,155] This reaction was later modified to the intermolecular version using N-heterocyclic carbenes as a ligand (Scheme 65).[156,157] Furthermore, the intermolecular version provided different selectivity with different ligands.

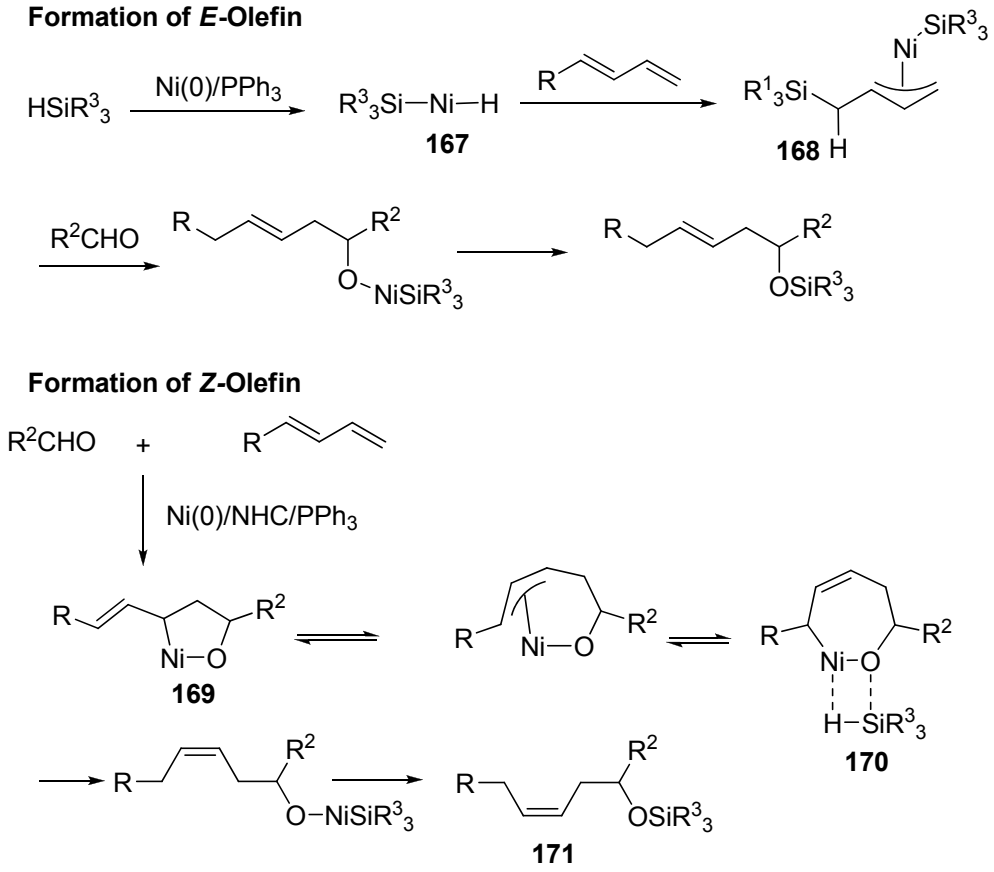


(72)

Scheme 65. Intermolecular Coupling of Aldehydes and 1,3-Dienes



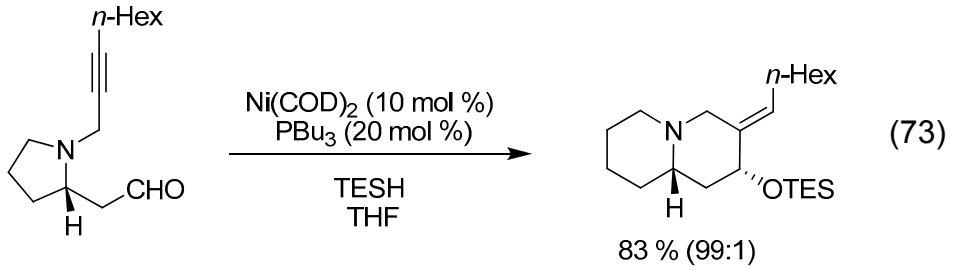
Scheme 66. Possible Reaction Pathways for the *Z*- and *E*-Olefin Formation



It was proposed that, with the phosphine ligand system, the reactions occur through oxidative addition of silane to nickel to produce Ni-hydride **167** (Scheme 66). Then the insertion of the diene moiety into the nickel-hydride

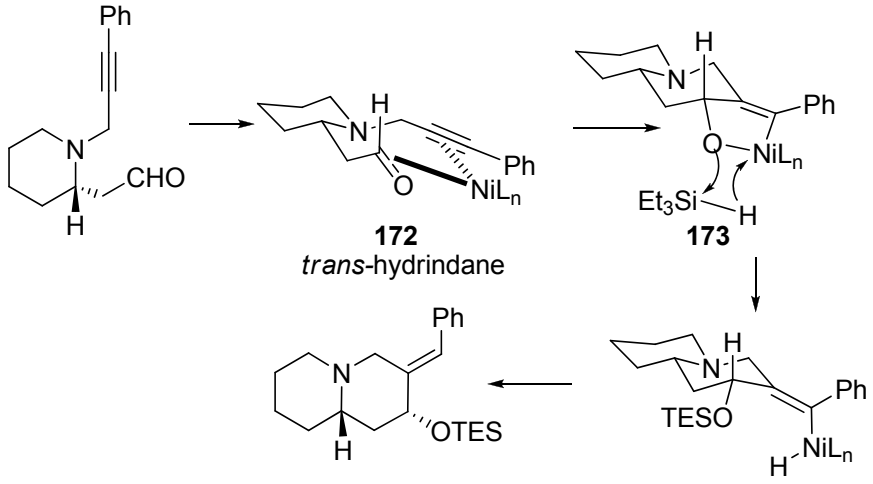
generates the *syn*-π-allylnickel complex **168,** which is coupled with the aldehyde followed by silicon-oxygen bond formation to give the *E*-olefin. In contrast, the reaction of a Ni-NHC complex could occur via metallacyclic intermediate **169**. Then σ-bond metathesis between **170** and hydrosilane could generate *Z*–olefin **171** (Scheme 66).[157]

In 1999, the Montgomery group developed an intramolecular aldehyde alkyne reductive coupling to construct nitrogen-containing bicyclic compounds in high diastereoselectivity by employing triethylsilane as a reducing agent (eq 73).[158] In addition, this methodology was utilized in the total synthesis of (+)-allopumiliotoxin 267A.



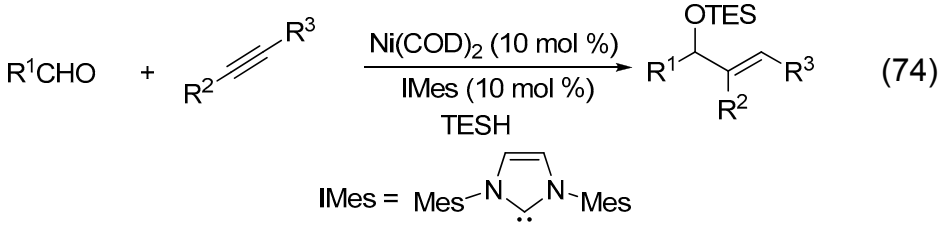
(73)

Scheme 67. Intramolecular Aldehyde and Alkyne coupling



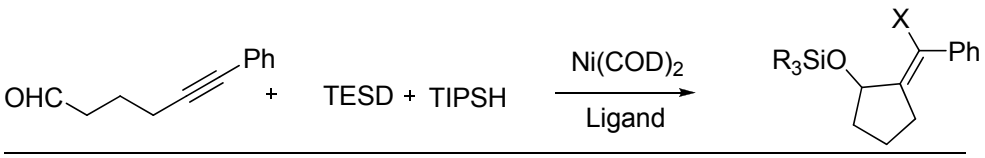
The proposed mechanism is depicted in Scheme 67. The initial complexation of Ni(0) to the alkyne and aldehyde π-systems could lead to the formation of oxametallacycle **173**. Finally, σ-bond metathesis of triethylsilane and the nickel-oxygen bond of **173** could form the product. The stereochemical outcome could be dictated by the initial complexation of the starting material in *trans*-hydrindane conformation **172**.[159]

Even though the intramolecular version gave high yields and high diastereoselectivity, the intermolecular reductive coupling reaction of aldehydes and alkynes was not possible under these conditions due to trimerization of alkynes. Later, this difficulty was overcome by employing N-heterocyclic carbenes instead of phosphine ligands. The reactions provided high regioselectivity with aryl alkynes and conjugated enynes (eq 74).[160]



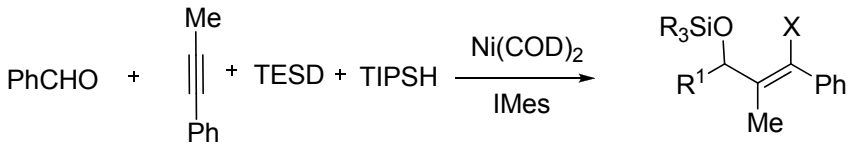
(74)

Table 12. Ligand Dependence on Product Distribution of the Crossover Reaction



entry	X	SiR_3	relative % from IMes	relative % from PBu_3
1	H	TES	< 2	25
2	D	TES	55	34
3	H	TIPS	41	23
4	D	TIPS	< 2	18

Table 13. Intermolecular Crossover Reaction

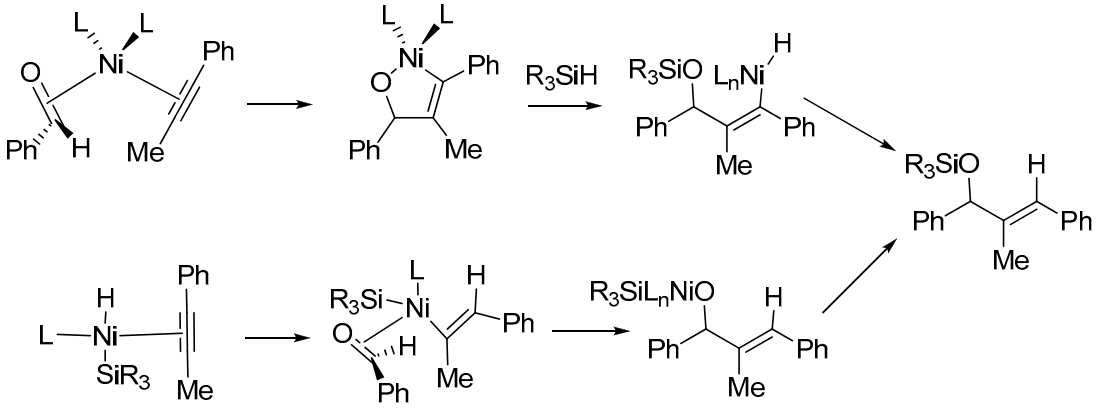


Entry	X	SiR_3	relative %
1	H	TES	<1
2	D	TES	48
3	H	TIPS	50
4	D	TIPS	<1

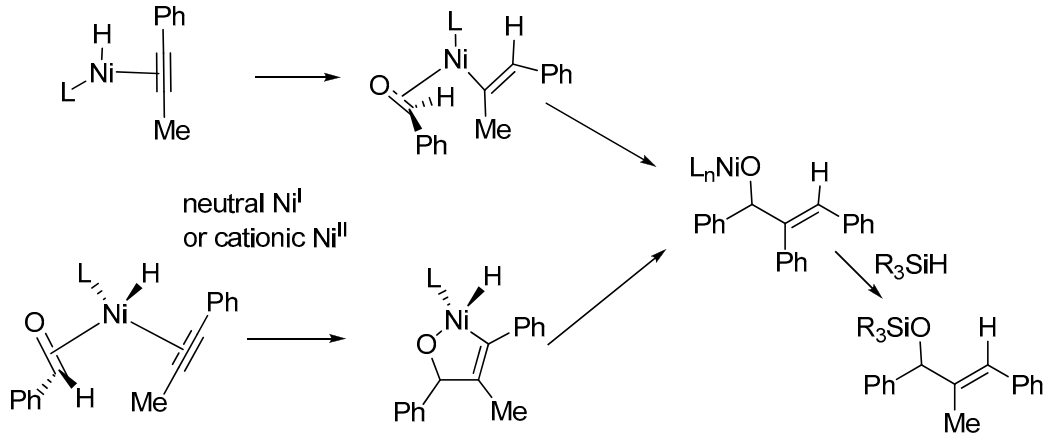
Crossover deuterium-labelling experiments demonstrated that the catalyst formulations involving PBu_3 and the N-heterocyclic carbene ligand proceed through fundamentally different mechanisms. The crossover experiments using isotopically labeled triethylsilane were carried out in intra- and intermolecular reductive coupling reactions (Table 12 and Table 13). Very little crossover was observed when using the IMes ligand, while PBu_3 provided a significant amount of crossover products. The lack of crossover products suggests that the addition of the hydride and the silane occur simultaneously. However, in the presence of PBu_3, a significant amount of crossover products are formed, indicating that the hydride and silane are added in separate steps (Scheme 68).

Scheme 68. Proposed Mechanisms of Ni-Catalyzed Aldehyde and Alkyne Coupling

Mechanism Consistent with No Crossover



Mechanism Consistent with Crossover



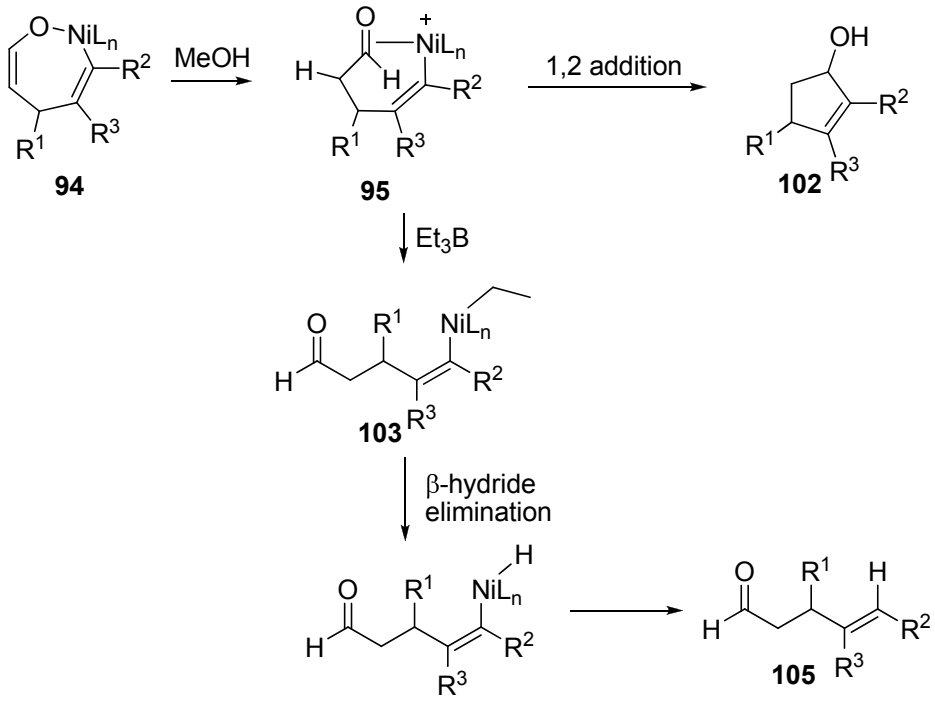
2.2 Results and Discussion

2.2.1 Nickel-Catalyzed Intermolecular Reductive Coupling of Alkynes and Enones

As mentioned in the previous chapter (Section 1.2.2, Table 9), in the course of studying nickel-catalyzed [3+2] cycloadditions of enals and alkynes, we observed the reductive coupling product as a minor pathway. Selectivity between [3+2] cycloaddition vs. reductive coupling depended on the relative rates of 1,2-addition vs. Et_3B transmetallation from a common intermediate **95** (Scheme 69),

and we anticipated that the use of enones would disfavor the 1,2-addition, thus favoring the reductive coupling product. Our exploratory experiments thus focused on the catalytic addition of enones and alkynes with Ni(0) catalysts in the presence of triethylborane and protic solvents. We were pleased to observe that the same reaction conditions with enones instead of enals provided exclusively the reductive coupling product (Scheme 70).

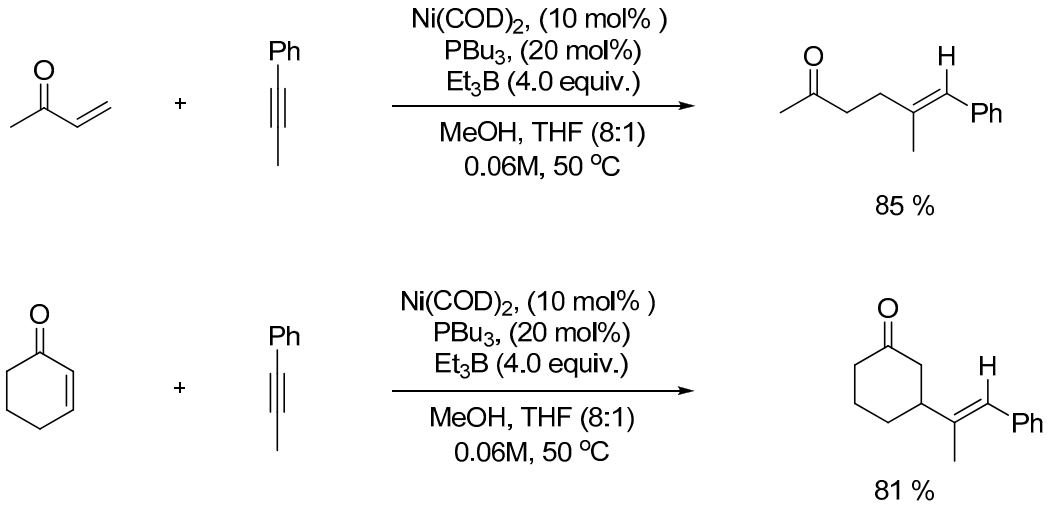
Scheme 69. 1,2-Addition vs. Transmetallation



Several aspects of this novel reductive coupling are noteworthy. First, this is the first example of a catalytic intermolecular reductive coupling of enones and alkynes. Typically, γ,δ-unsaturated ketones were prepared by conjugate addition of terminal alkyne-derived vinyl organometallics. Earlier studies from our laboratory illustrated that alkynyl enones undergo nickel-catalyzed reductive cyclization processes using diethylzinc as reducing agent. Unfortunately, the

scope of this process was limited to five-membered ring cyclizations on very simple substrates, and the use of triethylborane under aprotic conditions was also ineffective. Additionally, attempts with intermolecular versions, sterically hindered cyclizations, or larger ring cyclizations were entirely unsatisfactory. Finally, the direct participation of alkynes as an alternative to preparing and handling sensitive vinyl cuprate reagents provides potentially significant improvements in accessing γ,δ-unsaturated ketones.

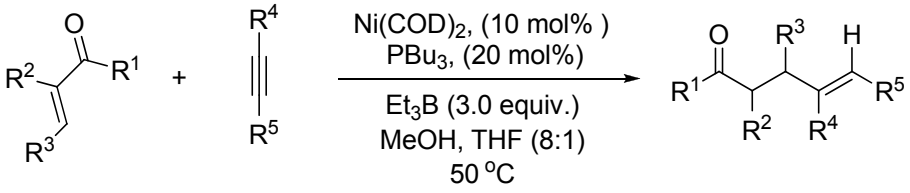
Scheme 70. A New Reductive Coupling of Enones



As illustrated in Table 14, a wide range of conjugated enones underwent catalytic intermolecular reductive couplings with 1-phenylpropyne.[161] This reaction tolerates a wide variety of enones, including methyl vinyl ketone (Table 14, entry 1), a longer chain simple vinyl ketone (Table 14, entry 2), aromatic vinyl ketones with β-alkyl substitution (Table 14, entry 3), an α-alkyl enone (Table 14, entry 4) an α′-siloxy(vinyl)ketone (Table 14, entries 5 and 8), a β-substituted enone bearing a free hydroxyl group (Table 14, entry 6) and a cyclic enone (Table 14, entry 7). Additionally this reaction can tolerate different alkyne

structures such as a terminal alkyne (Table 15, entry 1), hydroxyl-bearing alkynes (Table 15, entries 3 and 4), dialkyl alkynes (Table 15, entries 2, 5, and 6), and diaryl alkyne (Table 15, entries 7-10). Coupling with aromatic or terminal alkynes provided high regioselectivity (Table 14, entries 1-8 and Table 15, entry 1), whereas nonaromatic internal alkynes afforded mixtures of regioisomers (Table 15, entries 2-4).

Table 14. Scope of Enones



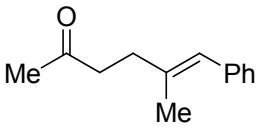
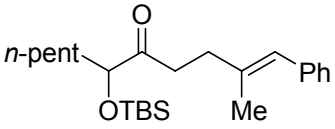
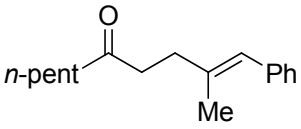
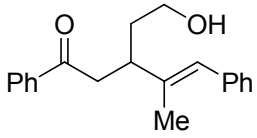
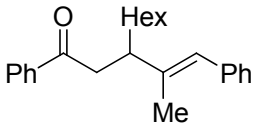
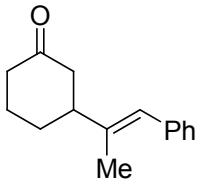
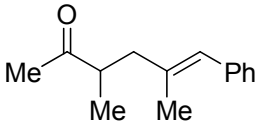
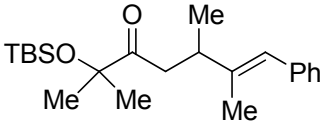
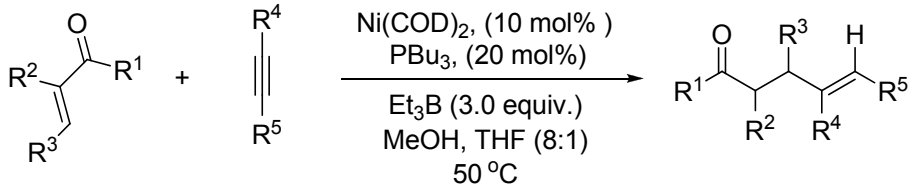
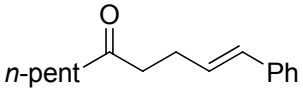
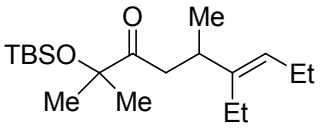
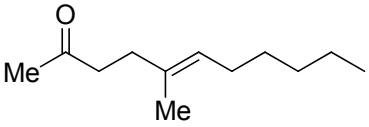
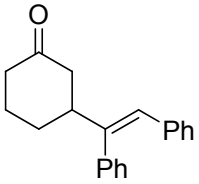
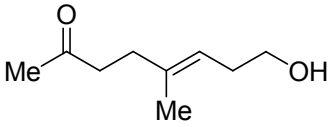
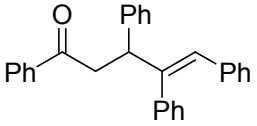
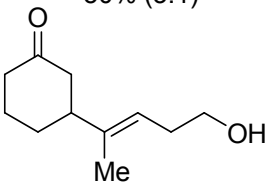
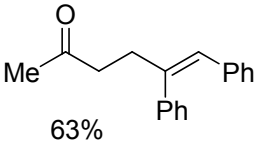
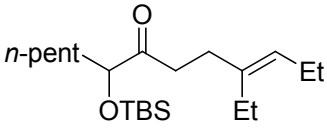
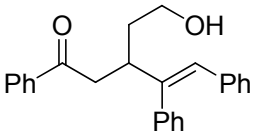
entry	Product Yield (regioselectivity)	entry	Product Yield (regioselectivity)
1	 85% (>95:5)	5	 72% (>95:5)
2	 78% (>95:5)	6	 84% (>95:5)
3	 65% (>95:5)	7	 80% (>95:5)
4	 80% (>95:5)	8	 92% (>95:5)

Table 15. Scope of Alkynes

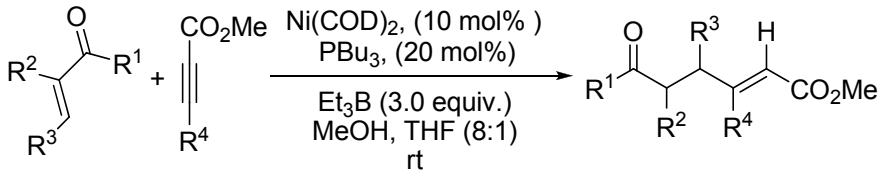


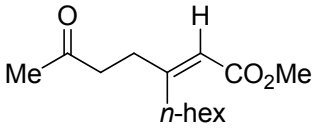
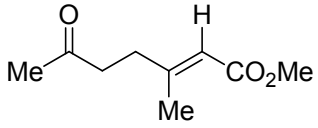
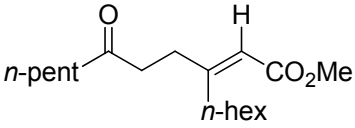
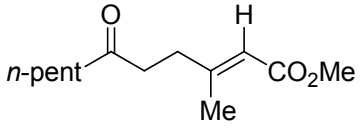
entry	Product Yield (regioselectivity)	Entry	Product Yield (regioselectivity)
1	 74% (>95:5)	6	 75%
2	 42% (2:1)	7	 70%
3	 50% (3:1)	8	 65%
4	 62% (1:1)	9	 63%
5	 72%	10	 84%

The unique characteristics of this new process are best illustrated by the chemoselective coupling of enones and ynoates (Table 16). Both ynoates and enones are potential Michael acceptors. However, they undergo highly

regioselective, stereoselective, and chemoselective heterocouplings at room temperature without requiring a large excess of either starting material or careful control of reagent addition.

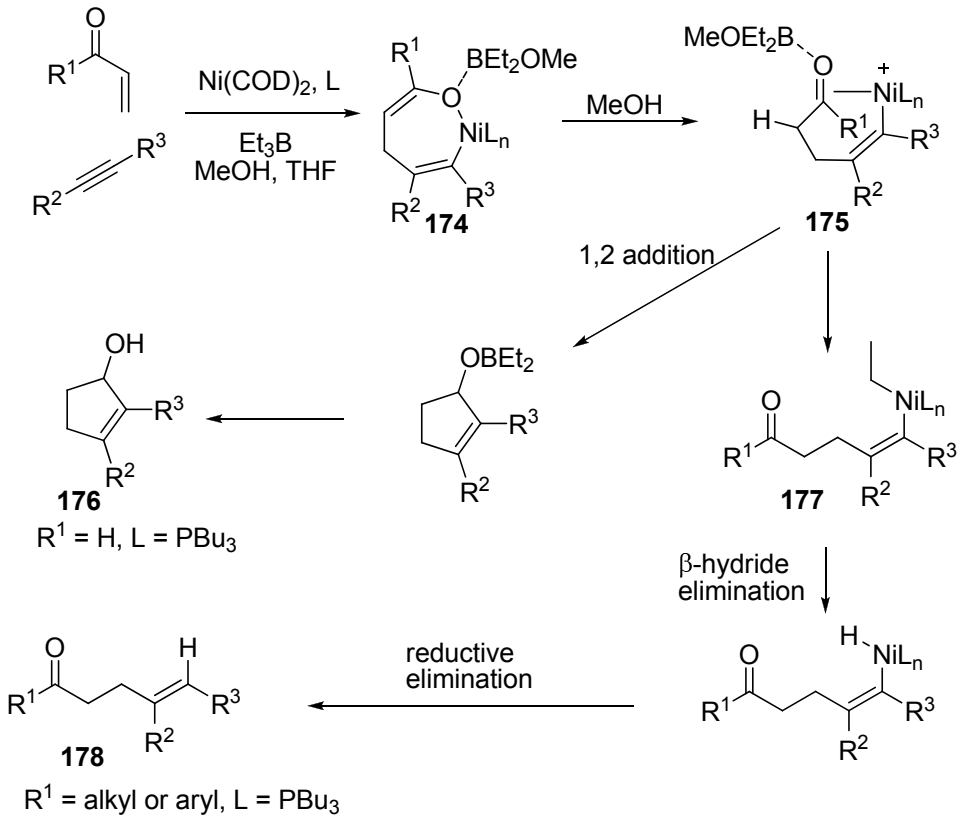
Table 16. New Reductive Coupling of Enones and Ynoates



entry	Product Yield (regioselectivity)	entry	Product Yield (regioselectivity)
1	 80% (>95:5)	3	 74% (>95:5)
2	 78% (>95:5)	4	 72% (>95:5)

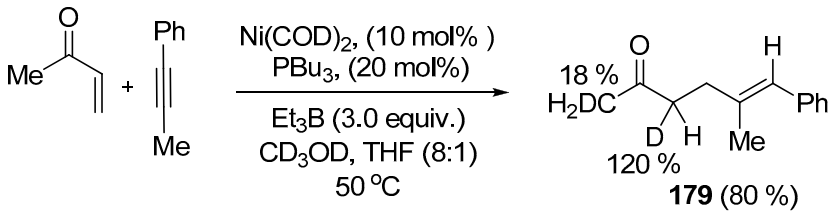
This novel reductive coupling reaction has several advantages over hydrometallation strategies and organocuprate conjugate addition methodologies. Hydrometallation of ynoates could be problematic since they could have potential to exhibit lack of chemoselectivity or reversed regioselectivity. Organocuprate formation via traditional lithiation sequences is typically difficult in the presence of electrophilic functional groups such as esters. Additionally this novel reaction can tolerate free hydroxyl groups, whereas traditional organocuprate methodologies cannot tolerate free hydroxyl groups.

Scheme 71. Proposed Mechanism of the Intermolecular Reductive Couplings



The divergent reactivity of enals compared with enones can be explained by using Scheme 71. Formation of metallacycle **174**, followed by monoprotonation would generate alkenyl nickel species **175**, which could act as a common intermediate for the [3+2] reductive cycloadduct **176** and reductive coupling product **178**. From intermediate **175**, using an enal, vinyl nickel addition to the tethered aldehyde would afford [3+2] cycloadduct **176**. Alternatively, if carbonyl addition is sterically unfavorable in ketone (R^1 = alkyl or aryl) derivatives when an enone is employed, then ethyl transfer from boron to nickel would generate **177**. Finally β-hydride elimination and reductive elimination would produce product **178**.

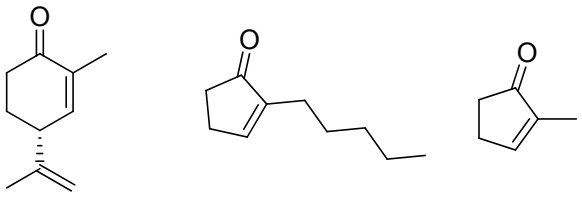
To understand the role of methanol, and to help elucidate the mechanism, an isotopic-labeling experiment using CD_3OD (99.9%) was carried out (eq 75). The results showed that the α-methyl protons and one of the protons of the α-methylene group of the product **179** were deuterated in 18% and 120%, respectively. No deuterium incorporation at the alkenyl position was observed. Deuteration at the α-carbon could result from enolization. However, the alkenyl proton represents a kinetically controlled result.



(75)

Attempts to couple α-substituted cyclic enones with alkynes were unsuccessful. No expected coupled products were observed, and in each of those cases starting materials were recovered quantitatively (Figure 1).

Figure 1.



Reactions with *S*-trans enones could occur via a five-membered *C*-enolate metallacycle **180** (Scheme 72). The above observation can be explained by the increase in steric bulk by α-substitution of cyclic enones which could potentially prevent the formation of the metallacycle **180**.

Scheme 72. Possible Mechanism with *S*-Trans Enones

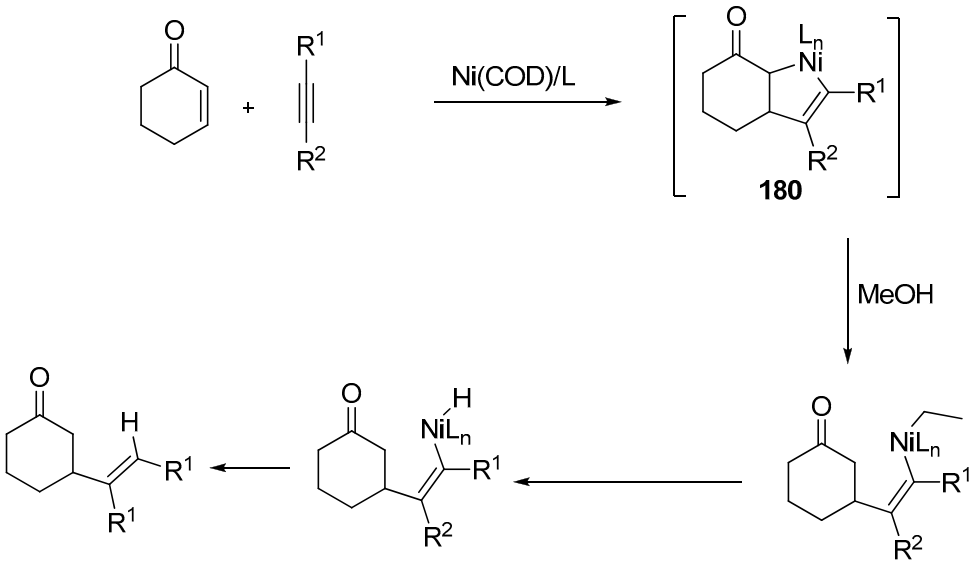
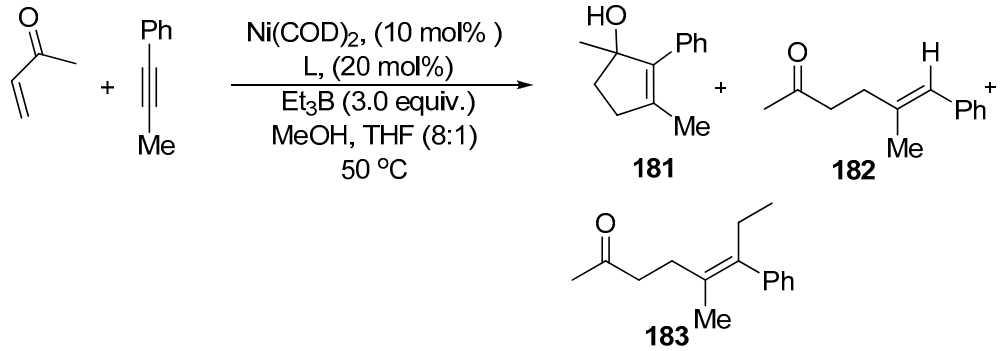


Table 17. Scope of Ligands for the Reductive Coupling



L	cone angle	**181** (% yield)	**182** (% yield)	**183** (% yield)
PMe_3	118	21	32	-
PBu_3	136	10	85	-
PPh_3	145	20	41	-
PCy_3	170	-	74	-
$P(t\text{Bu})_3$	182	-	-	-
$P(o\text{-tolyl})_3$	194	-	46	45

Similar ligand effects as in intermolecular [3+2] cycloaddition were observed for the intermolecular reductive coupling of enones and alkynes.

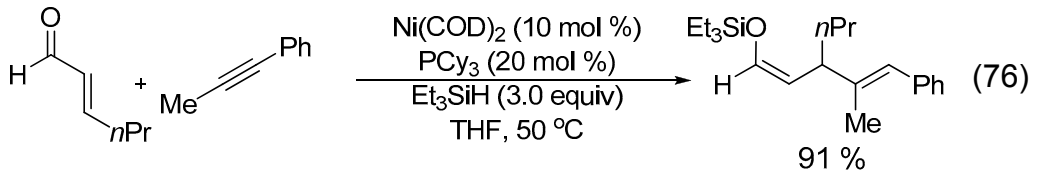
Screening of different monodentate phosphine ligands demonstrated that product distribution could be varied by changing the ligand structure (Table 17).

2.2.2 Summary of Reductive Coupling of Alkynes and Enones

A novel, nickel-catalyzed intermolecular reductive coupling of enones and alkynes has been developed. The key feature of this reaction is the chemoselective coupling of two potential Michael acceptors such as enones and alkynoates. The direct participation of alkynes as an alternative to preparing and handling sensitive vinyl cuprate reagents provides potentially significant improvements in accessing γ,δ-unsaturated ketones.

2.2.3 Nickel-Catalyzed Intermolecular Reductive Coupling of Alkynes and Enals

Due to our recent success with intermolecular enone and alkyne coupling, we decided to further investigate the reductive coupling of enal and alkynes considering the modest selectivities described in chapter 1 (Table 10), where reductive coupling was observed as a minor product during the [3+2] cycloaddition process. During those studies of ligand structure on product distribution, triphenylphosphine provided the reductive coupling product as a major product. However, the efficiency and the substrate scope of the reaction with triphenylphosphine were very low. Thus, we decided to investigate different reducing agents for the reductive coupling of enals and alkynes. Screening a variety of reducing agents led to the finding that triethylsilane was superior, and provided the enol silane as a single product in 91 % yield (eq 76).



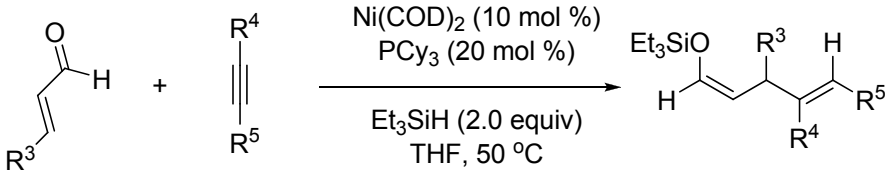
(76)

Several aspects of this process are noteworthy. First, this is a rare example of conjugate addition of vinyl species to a α,β-unsaturated aldehyde. Typically, organocuprate additions to aldehydes favor 1,2-addition, or the kinetic enolate from conjugate addition could directly undergo aldol addition to the aldehyde. Secondly, the stereoselective synthesis of enol silanes is important, because alkene geometry can influence the stereochemistry of subsequent events. Finally, enol silanes are starting materials in a wide variety of enantioselective transformations. Thus, the nickel-catalyzed synthesis of *Z*-enol silanes provides a new route to important highly substituted enol silanes, which are difficult to access with high selectivity by enolization of an aldehyde.

Recognizing the potential impact of this transformation as a complement to the above synthetic methods for generating *Z*-enol silanes, we set out to examine the scope of this new reductive coupling process. Reaction optimization suggests that optimal conditions for this transformation involve treatment of an enal and alkyne with $Ni(COD)_2$, PCy_3 and triethylsilane in THF at 50 °C. Using these optimal conditions, different alkynes were screened. As illustrated in Table 18, this reaction tolerates dialkyl alkynes (Table 18, entry 2), diaryl alkynes (Table 18, entry 3), terminal alkynes (Table 18, entry 4), alkynoates (Table 18, entry 5), and alkynes with free hydroxyl groups (Table 18, entries 7 and 8), alkynes with ketones (Table 18, entry 9), alkynes with aldehydes (Table 18, entry

10), and alkynes with secondary amines (Table 18, entry 11). Additionally, the reaction can generate *Z*-enol silanes with enals that possess β-aryl and β-aliphatic substitution. However, the reaction with acrolein provided very low conversion with triethylsilane as the reducing agent. Thus, we decided to investigate different silanes for this reaction. In varying the silane structure, we found that this reaction can tolerate a variety of silanes such as, *tert*-butyldimethylsilane (Table 19), dimethylphenylsilane (Scheme 73), and triphenylsilane (Table 20). Triphenylsilane and *tert*-butyldimethylsilane afforded identical products, whereas reaction with dimethylphenylsilane provided the deprotected aldehyde after column purification (Scheme 73). Additionally, the scope of the reaction was increased by the use of bulky silanes which provided the corresponding silane in high yield with acrolein (Table 19, entry 2 and Table 20, entries 3 and 4).

Table 18. Coupling of Enals, Alkynes, and Triethylsilane



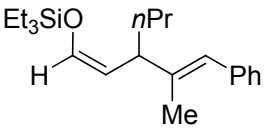
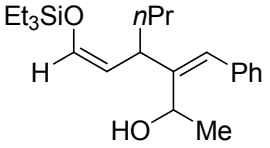
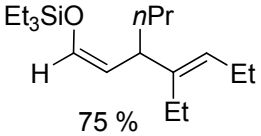
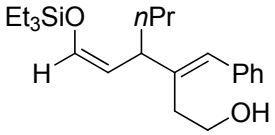
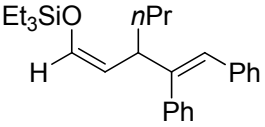
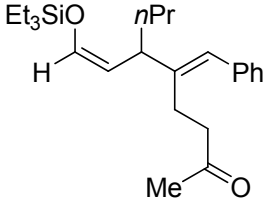
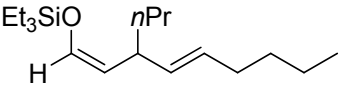
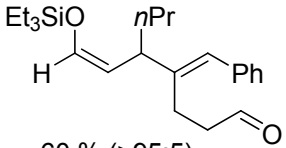
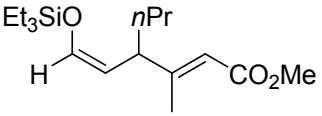
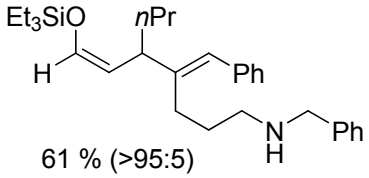
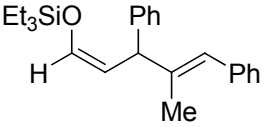
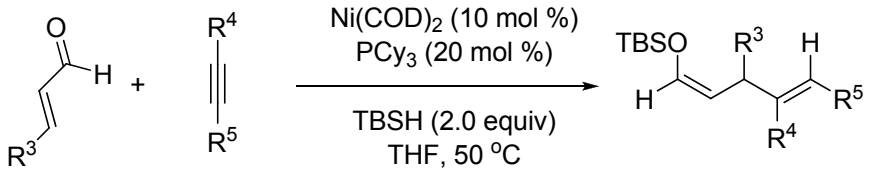
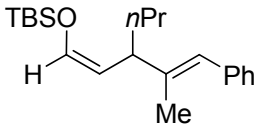
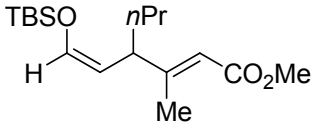
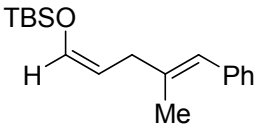
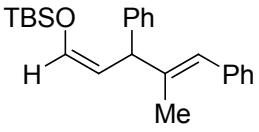
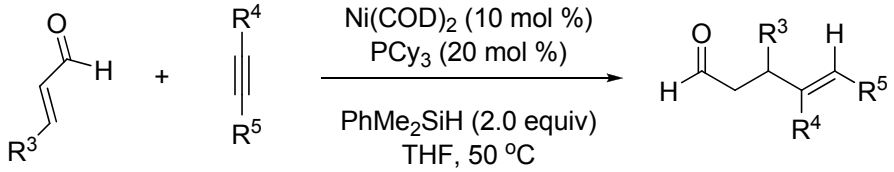
entry	Product Yield (regioselectivity)	entry	Product Yield (regioselectivity)
1	 91 % (>95:5)	7	 87 % (dr 79:21, >95:5)
2	 75 %	8	 91 % (>95:5)
3	 76 %	9	 65 % (>95:5)
4	 45 % (80:20)	10	 60 % (>95:5)
5	 40 % (>95:5)	11	 61 % (>95:5)
6	 87 % (>95:5)		

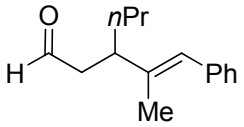
Table 19. Coupling of Enals, Alkynes, and TBSH



entry	Product Yield (regioselectivity)	Entry	Product Yield (regioselectivity)
1	 85 % (>95:5)	3	 49 % (>95:5)
2	 52 % (>95:5)	4	 74 % (>95:5)

Scheme 73. Coupling of Enals, Alkynes, and Dimethylphenylsilane




184 (86 %, >95:5)

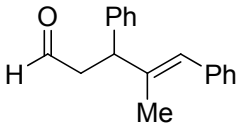
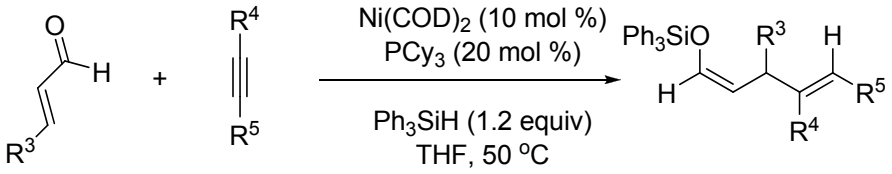
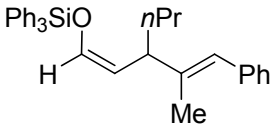
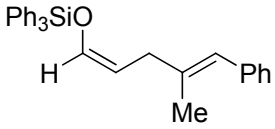
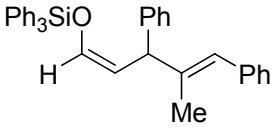
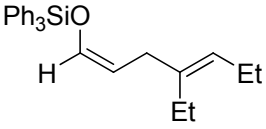

185 (81 %, >95:5)

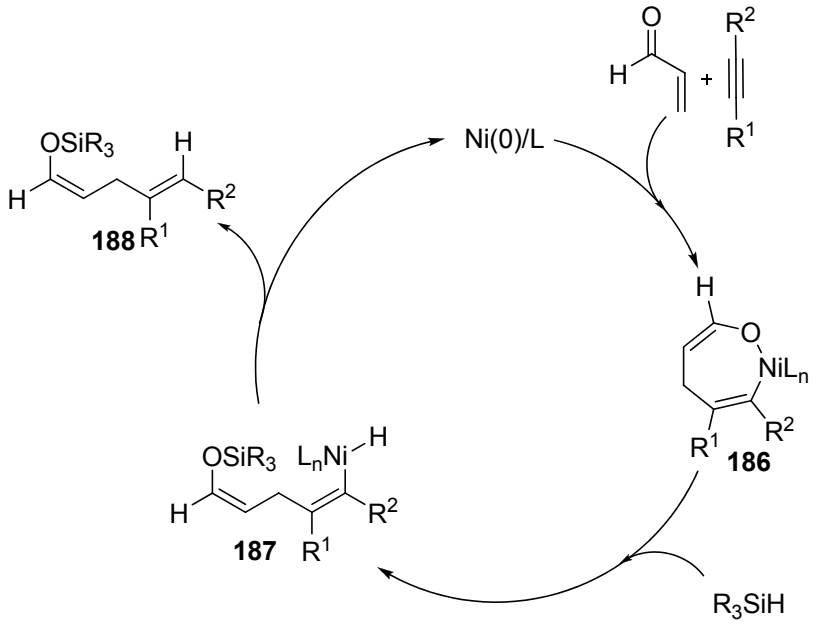
Table 20. Coupling of Enals, Alkynes, and Triphenylsilane



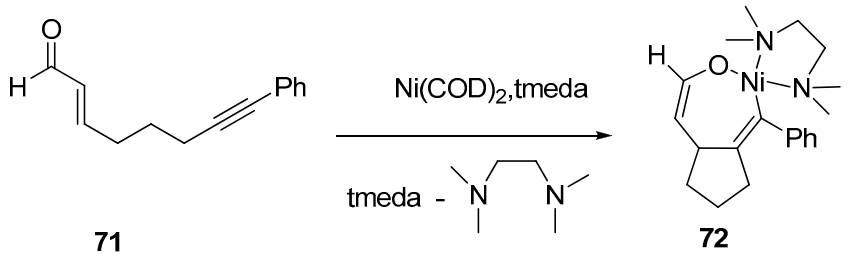
entry	Product Yield (regioselectivity)	Entry	Product Yield (regioselectivity)
1	 88 % (>95:5)	3	 69 % (>95:5)
2	 92 % (>95:5)	4	 59 % (>95:5)

A number of features of the above examples, particularly the range of alkyne substitution patterns, the tolerance of free hydroxyls, and free amines, illustrate complementarity to alternative procedures. However, the unique feature of this new process is perhaps best illustrated by the stereoselective coupling of alkynes containing ketones and alkynes containing aldehydes with enals to produce *Z*-enol silanes in high yields. This is a rare example of selective enolization of aldehydes in the presence of ketones or other aldehydes. Typically, existing methods could dimerize the starting material or generate a mixture of products. Additionally, the selective coupling of an alkyne in the presence of an aldehyde is unusual in nickel-catalyzed reductive couplings.

Scheme 74. Mechanism of Reductive Coupling of Enals and Aldehyds



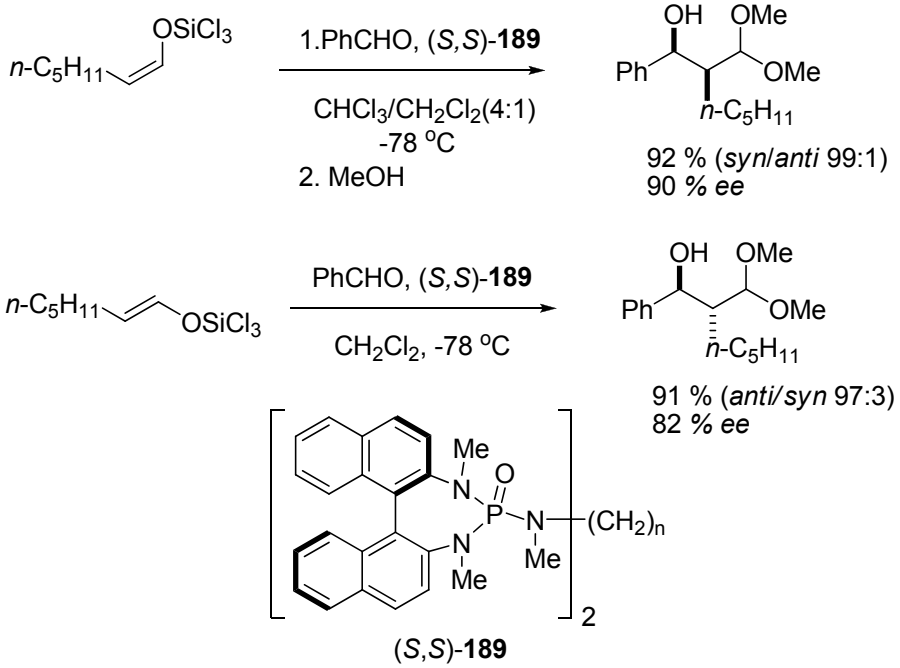
We suggest that the mechanism of this process proceeds by metallacyclic intermediate **186** (Scheme 74). Oxidative cyclization of alkyne and enal to metallacycle **186** followed by σ-bond metathesis could generate the intermediate **187**. Then, the reductive elimination would afford the enol silane **188**. The *Z* selectivity thus appeared to be dictated by the metallacycle **186**, which is consistent with the observed sense of enol and the alkene geometry. This is the first evidence for the formation of metallcyclic intermediate **186** in a catalytic reaction. As mentioned in the chapter 1 (Section 1.1.4), our group isolated such a metallacycle **71** by treating alkynyl enal **72** with a stoichiometric amount of $Ni(COD)_2$/tmeda(1:1) or $Ni(COD)_2$/bpy (1:1) (eq 77).[61] If the *C*-bound enolate or oxy-allyl species involved, then the *E*-isomer of the enol silane product would be expected. For example, the Mackenzie and Jamison methods involve the formation of *E*-enol silanes via electrophilic silylation of oxy-allyl species.[147,151]



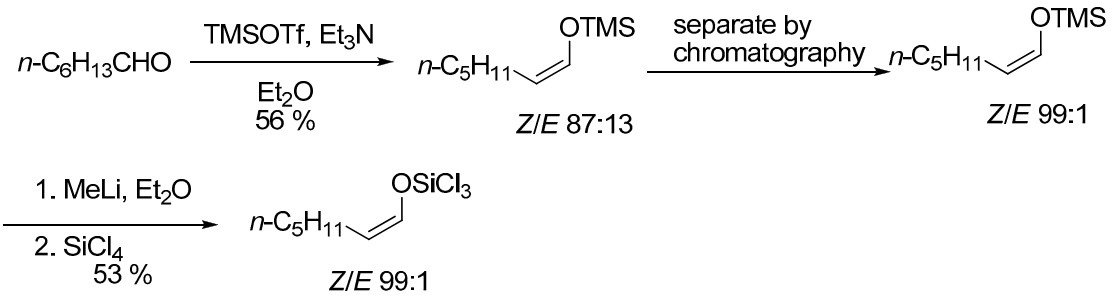
71 72 (77)

One of the early and still one of the most frequently used methods to synthesize *Z*-silyl enol ethers is the trapping of ketone enolates generated under equilibrium-controlled conditions. Although a number of different methods have been described to generate enol silanes, none were capable of delivering the *Z*-enol silanes with such high levels of geometric purity. Recent reports from Denmark demonstrated the importance of stereochemistry of the enol silanes in aldol additions. In 2001, Denmark and Ghosh developed a Lewis base catalyzed diastereoselective and enantioselective crossed aldol reaction of aldehydes and enol silanes.[162] The reaction with geometrically pure *Z*-enoxytrichlorosilane provided high *syn* selectivity, whereas the reaction with *E*- enoxytrichlorosilane resulted in high *anti* selectivity (Scheme 75). Synthesis of *Z*-enol silane was achieved by direct enolization of aldehyde followed by trapping of the resulted enolate with trimethylsilylchloride. Then the resulting mixture of isomers was separated by chromatography to isolate the *Z*-enol silane, which was treated MeLi and quenched with excess $SiCl_4$ to produce the geometrically enriched *Z*-enoxytrichlorosilane (Scheme 76). We believe that our methodology would give a more selective and more direct method to synthesize geometrically pure *Z*-enol silanes.

Scheme 75. Lewis Base Catalyzed Mukiyama Aldol Reaction



Scheme 76. Synthesis of Trichlorosilyl Enol



2.2.4 Summary of Reductive Coupling of Alkynes and Enals

A novel, nickel-catalyzed intermolecular reductive coupling of enals and alkynes has been developed. The unique features of this reaction are the construction of geometrically pure *Z*-enol silanes and high functional group tolerance. The direct participation of enals, alkynes and silanes as an alternative

to existing methods provides potentially significant improvements in accessing enol silanes. Additionally, this reaction provides direct evidence for the catalytic involvement of a seven-membered oxametallacycle intermediate.

CHAPTER 3

INTERMOLECULAR NICKEL-CATALYZED THREE-COMPONENT COUPLINGS VIA INTERNAL REDOX

3.1 Introduction

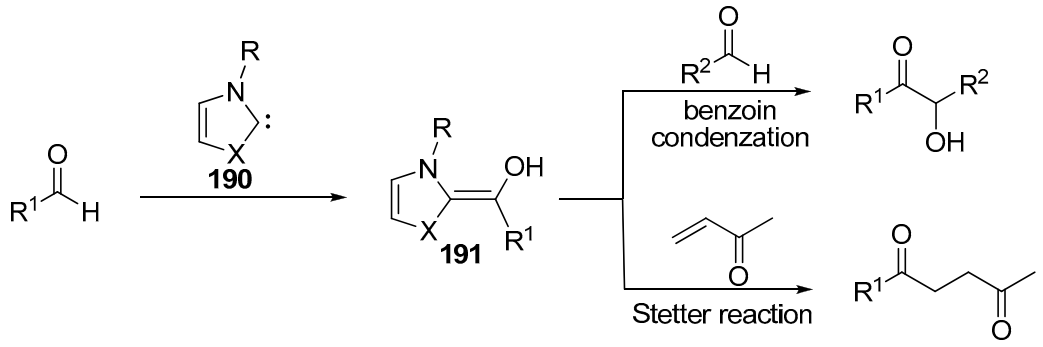
Redox reactions or oxidation-reduction reactions have a number of similarities to acid-base reactions. Fundamentally, redox reactions are a family of reactions that are concerned with the transfer of electrons between species. Oxidation refers to the loss of electrons, while reduction refers to the gain of electrons. An internal redox reaction is defined as the reaction that undergoes oxidation and reduction within the reactive partners without participation of an external reducing agent or oxidant.

Many high yielding organic reactions are non-catalytic, lacking atom economy, and frequently require harsh reaction conditions. It has been a challenge to improve known methods and develop new procedures that will avoid the production of stoichiometric or larger amounts of byproducts and provide mild conditions that will allow the use of sensitive substrates. Using an internal redox mechanism in organic reactions provides new opportunities to increase the atom economy and the efficiency of the reaction. Some commonly reported internal redox reactions and the observation of a novel nickel catalyzed three component coupling reaction are discussed in the current chapter.

3.1.1 Organocatalyzed Internal Redox Reactions

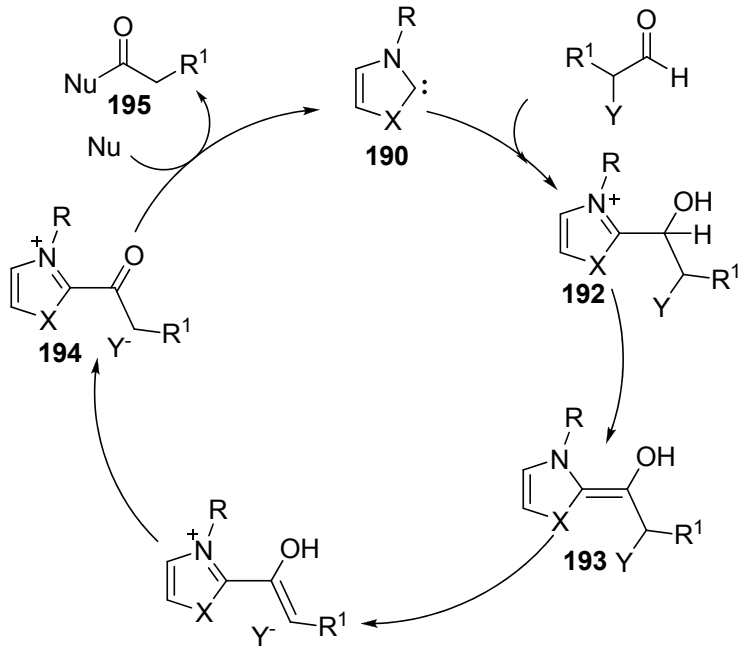
Organocatalytic processes mediated by N-heterocyclic carbenes (NHCs) have provided several advantages over standard chemical reactions. These reactions are atom economical, simple to operate, and also provide the possibility of nontraditional retrosynthetic bond disconnections. Earlier, NHCs have been used as a catalyst to develop benzoin and Stetter reactions (Scheme 77).[163] Recently, the utility of the proposed acyl anion equivalent **191** (Breslow's intermediate) was further extended with the use of a leaving group at the α-position (Scheme 78) or in a conjugated system (Scheme 80).[164]

Scheme 77. Benzoin and Stetter Reaction

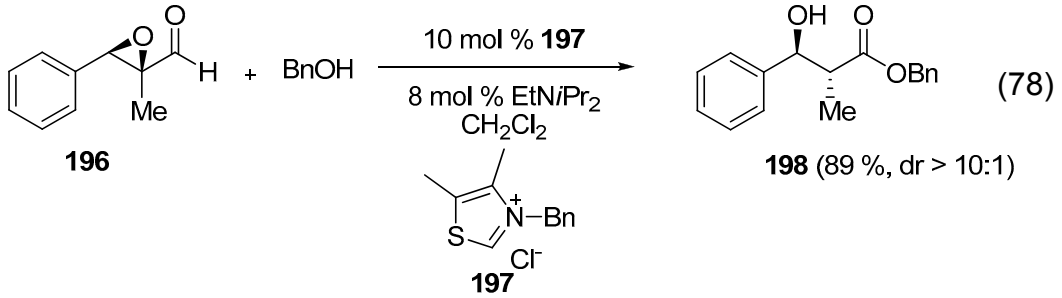


The nucleophilic attack of carbene **190** to an aldehyde would generate acyl anion equivalent **192** which can be further functionalized by using α-heteroatomic aldehydes, such as α-halo aldehydes and α,β-epoxy aldehydes (Scheme 78). The intermediate **194** can be formed via an internal redox reaction by elimination of the leaving group Y, followed by isomerization. The reaction with nucleophiles generates product **195** and regenerates the catalyst **190**.

Scheme 78. Nucleophilic Carbene Catalyzed Internal Redox Reaction

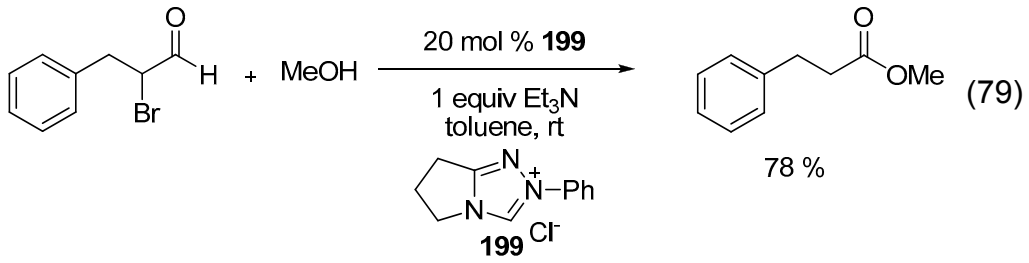


In 2004, Bode and co-workers discussed the use of epoxy aldehydes to generate *anti*-β-hydroxy esters in high stereoselectivity (eq 78).[165] Treatment of the aldehyde **196** with thiazolium pre-catalyst **197** in the presence of benzyl alcohol resulted in the formation of ester **198** in high yield. The product **198** is proposed to be formed by an epoxide ring opening step from intermediate **193** followed by a nucleophilic attack of the alcohol (Scheme 78).



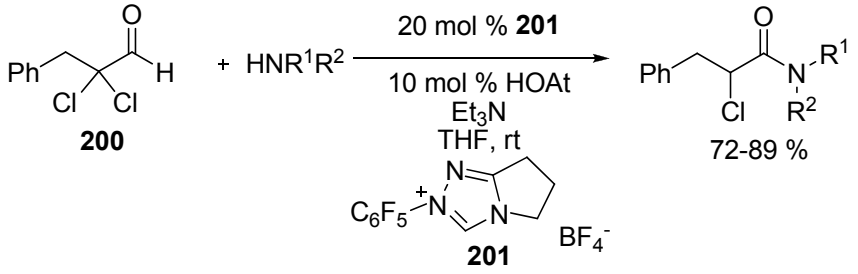
(78)

Simultaneously, Rovis and co-workers reacted secondary and tertiary α-halo aldehydes with catalytic amounts of triazolium-derived carbene **199** in the presence of an alcohol to generate esters (eq 79).[166]



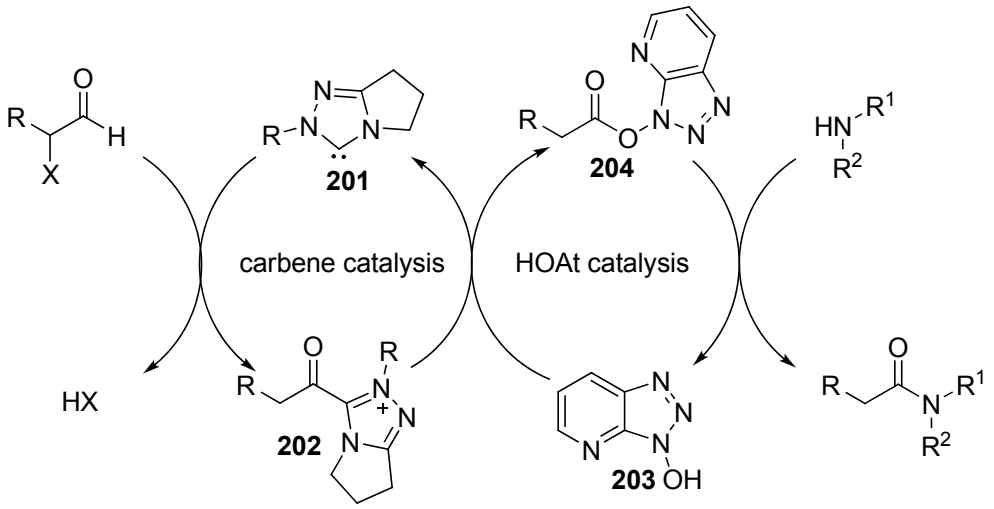
(79)

Recently, the same group also reported a α-redox amidation process using α-halo-aldehyde **200** in the presence of carbene **201** and co-catalyst 1-hydroxy-7-azabenzotriazole (HOAt) (eq 80).[167] The proposed catalytic cycle is depicted in Scheme 79. First, carbene **201** undergoes nucleophilic addition to the aldehyde to generate acyl azolium intermediate **202**, which undergoes acyl transfer with co-catalyst **203** to produce the activated carboxylate **204**. Then nucleophilic attack by the amine forms the amide and regenerates the co-catalyst **203**.

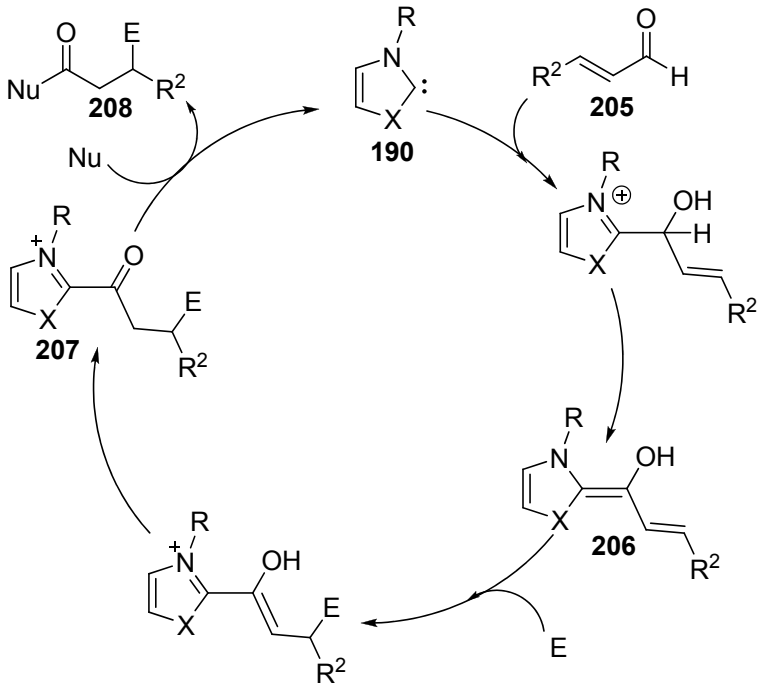


(80)

Scheme 79. The Mechanism of Redox Amidation



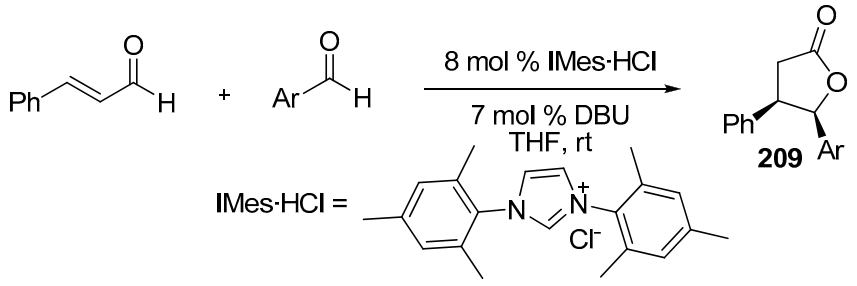
Scheme 80. Organocatalytic Internal Redox Reaction of Enals



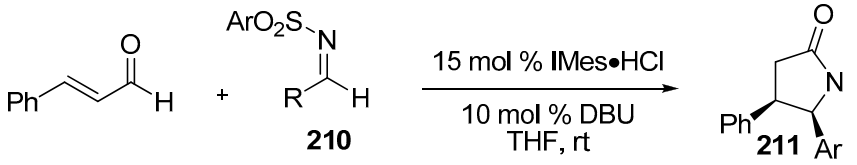
Alternatively, α,β-unsaturated aldehydes **205** can be used to generate the acylazolium species **206**, which can undergo electrophilic trapping followed by tautomerization to form the intermediate **207** (Scheme 80). Reactions with

appropriate nucleophiles in an intermolecular or intramolecular fashion generate the product **208** and regenerate the catalyst **190**.

In 2004, Bode and Glorius independently reported an organocatalytic reaction of enals with aldehydes to afford γ-butyrolactones (eq 81).[168,169] The stereoselective synthesis of γ-butyrolactones was achieved by a one step procedure via homoenol intermediates such as **206**. The conjugated acyl anion equivalent **206** reacts with an aldehyde to afford the alkoxide intermediate, which is then trapped in an intramolecular fashion to produce γ-butyrolactone **209**. Later, the Bode group extended this methodology by employing imines **210** as the electrophilic partner to access disubstituted γ-lactams **211** (eq 82).[170]

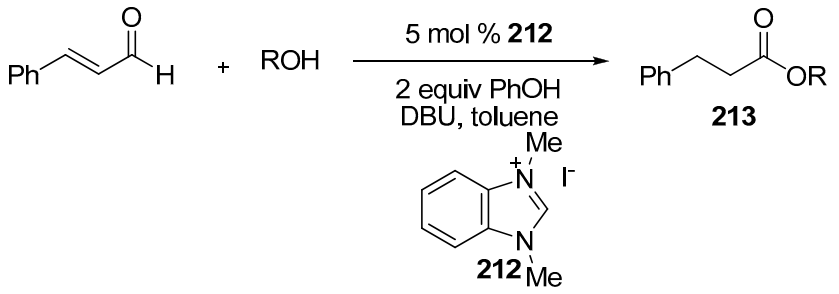


(81)



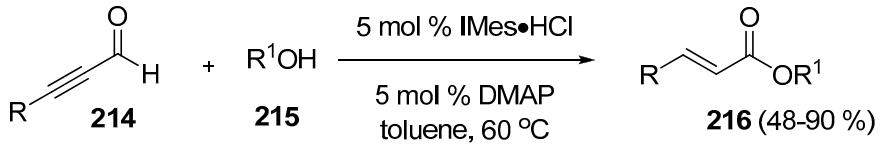
(82)

The above process was also explored by Scheidt and Chan. They reported that the resulting homoenolate could be protonated by using phenol as a proton source and coupled with another alcohol to generate the corresponding esters **213** in high yields (eq 83).[171]

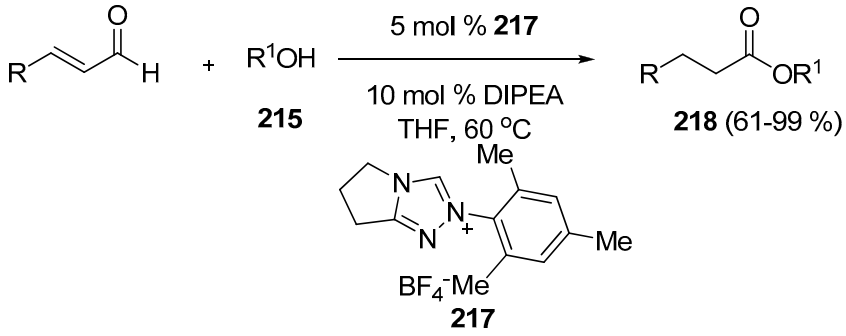


(83)

The stereoselective sythesis of (*E*)-α,β-unsaturated esters via carbene-catalyzed redox esterification was accomplished by Zeitler (eq 84).[172] Treatment of alkynyl aldehydes **214** with IMes and alcohol **215** resulted in the formation of carboxylic esters **216** in high stereoselectivity.



(84)



(85)

Bode and co-workers showed that a weaker base could be used as a catalytic proton shuttle to promote the in situ protonation of the homoenolate without an additional proton source (eq 85).[173] The nucleophilic attack of alcohol **215** generated the esters **218** in moderate to high yields.

3.1.2 Transition Metal-Catalyzed Internal Redox Reactions

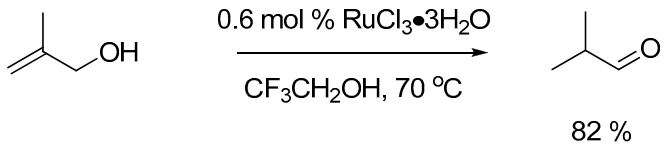
Transition-metal-catalyzed reductive coupling reactions have been known for many years and many of the reactions require the use of stoichiometric

reductants, such as elemental hydrogen, silanes, boranes, or organozincs, to regenerate the active catalyst. In these reactions, two π-systems such as aldehydes, enones, alkynes, dienes, or allenes are typically combined with a reducing agent. During the reaction, two π-systems are coupled to form C-C bonds via a net two-electron reduction, while the reducing agent undergoes a net two-electron oxidation. In contrast, many transition-metal catalyzed reactions such as isomerization of allylic alcohols, cycloisomerization, and hydroacylation reactions do not require reducing agents and react via β-hydride elimination reaction pathways or internal redox mechanism.

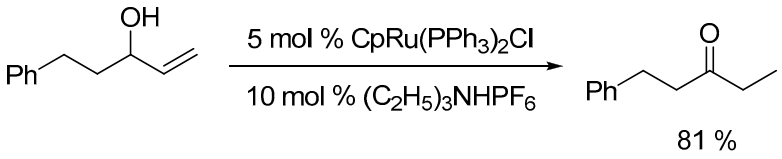
3.1.2.1 Isomerization of Allylic Alcohols

A one-pot catalytic isomerization of unsaturated alcohols into the corresponding ketone or aldehyde is an attractive strategy to access ketones and aldehydes compared to traditional oxidation procedures. Many transition-metal-catalyzed isomerizations of allylic alcohols have been developed.[174] Among them, ruthenium catalysts have been widely used in these types of transformations.

In 1975, Strohmeier and Weigelt reported the ruthenium-catalyzed isomerization of allylic alcohols into the corresponding aldehydes (eq 86).[175] Later, Trost and co-workers reported a ruthenium-catalyzed intramolecular redox reaction of an allylic alcohol to produce the corresponding ketone (eq 87).[176] This reaction can isomerize allylic alcohols selectively in the presence of free alcohols, esters, carbonyl groups, alkynes, and terminal alkynes.



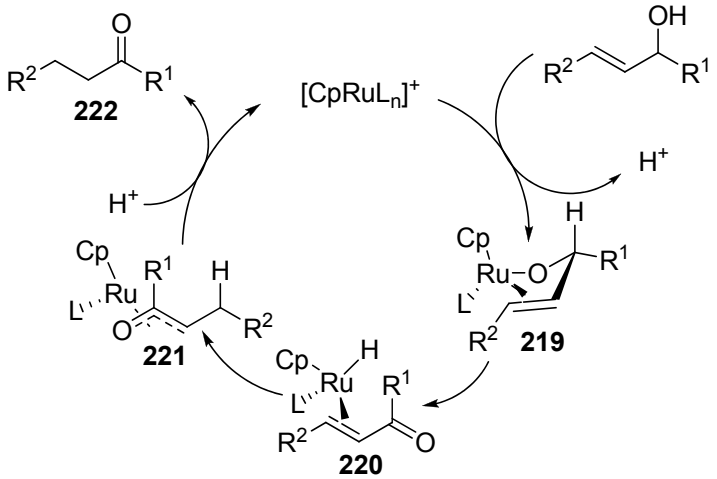
(86)



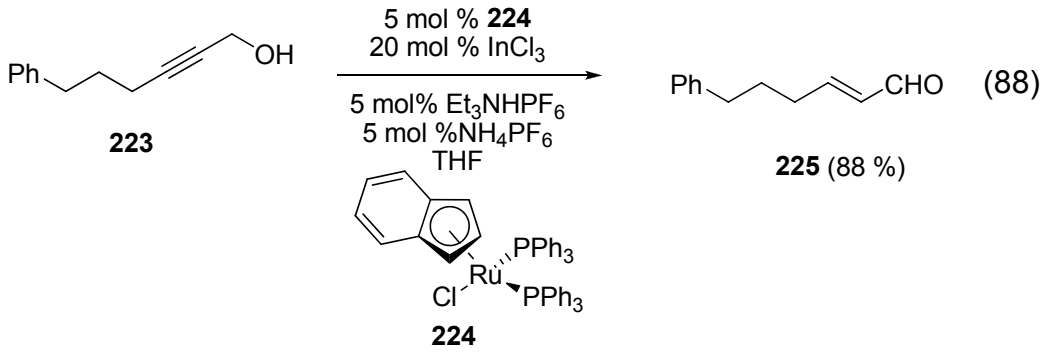
(87)

The proposed mechanism is shown in Scheme 81. First, coordination of the olefin and the allylic alcohol could generate complex **219**. Subsequent β-hydride elimination could lead to ruthenium hydride species **220**. Then allylic C-H insertion gives intermediate **221**. Finally, protonation of intermediate **221** could produce the ketone **222**. Several other ruthenium complexes have been used to isomerize allylic alcohols such as ruthenium hydride species,[174] tetrapropylammonium perruthenate (TPAP),[177] and the Grubbs vinylidene-metathesis catalyst.[178]

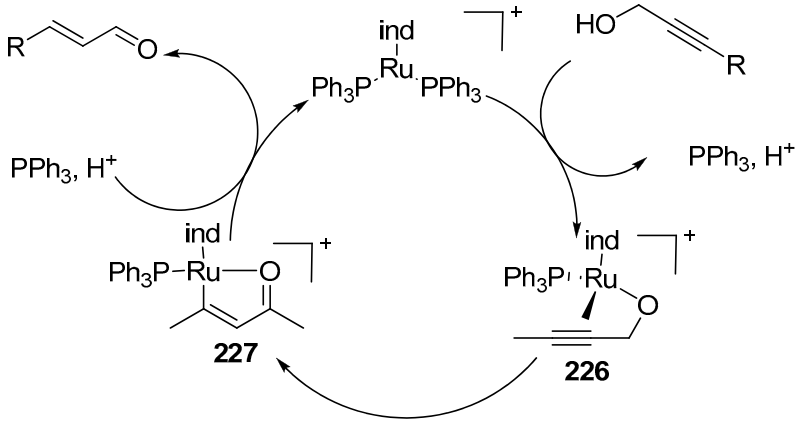
Scheme 81. Redox Isomerization of Allylic Alcohols



In 1995, Trost *et al*. developed redox isomerization of propargyl alcohols to the corresponding enals and enones (eq 88).[179] In the presence of indenyl catalyst **224** and co-catalyst indium(III) chloride, propargyl alcohol **223** underwent redox isomerization to produce enal **225** in 88 % yield. The reaction is highly chemoselective and tolerates the presence of carbonyl, hydroxyl, and alkene functionalities.



Scheme 82. Redox Isomerization of Propargyl Alcohols

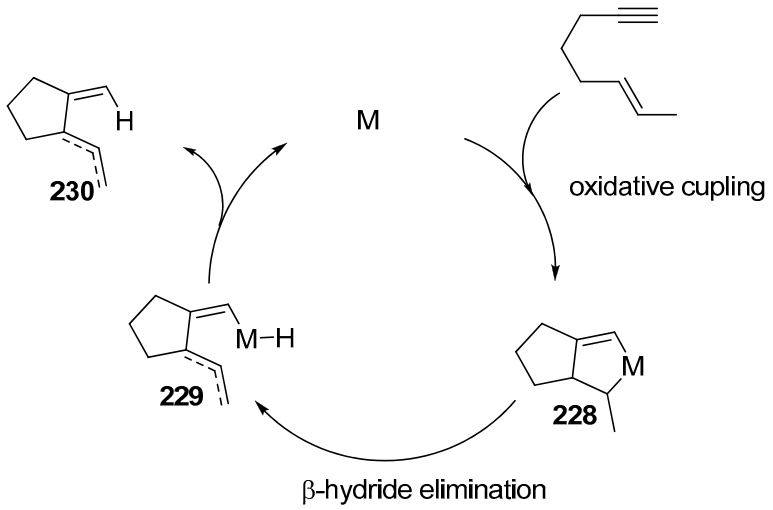


Mechanistic work demonstrated that an intramolecular 1,2-hydride transfer is the critical step that leads to the vinylruthenium species **227** from **226** (Scheme 82). The indium salt serves as a halophile, which enables the formation of the coordinatively unsaturated ruthenium cation.

3.1.2.2 Cycloisomerization of Enynes

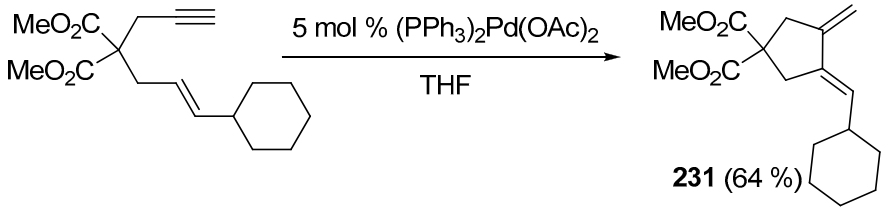
Transition-metal-catalyzed cycloisomerization of enynes has emerged as an attractive and unique tool for the synthesis of different cyclic compounds in a one-pot process. Cyclization of enynes or dienes has been achieved with a wide range of transition-metals such as palladium, ruthenium, cobalt, rhodium, iridium, and titanium. The main steps of the catalytic cycle are depicted in Scheme 83. The formation of metallacyclopentene **228** followed by β-hydride elimination would generate metal hydride **229**. Finally, reductive elimination could generate either one or a mixture of 1,3- and 1,4-dienes **230**. Depending on the regioselectivity of the β-hydride elimination of two dienes, the 1,3- or 1,4-diene could be obtained.

Scheme 83. General Mechanism for the Metal-Catalyzed Cycloisomerization

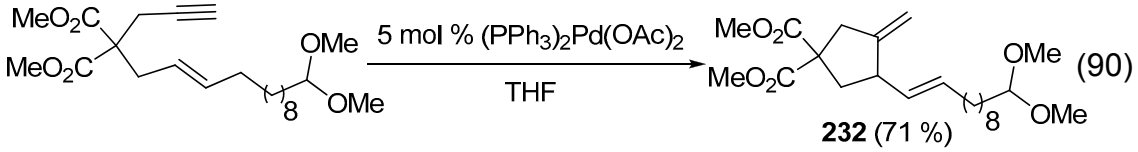


In 1985, Trost and Lautens reported the cyclization of 1,6-enynes in the presence of a palladium catalyst to construct 1,3-dienes (eq 89 and 90).[180] Steric factors influence the regioselectivity of the cyclization. Branching at the allylic

position leads exclusively to the 1,3-diene **231**, whereas an allylic methylene group generates the Alder-ene type 1,4-diene **232**.

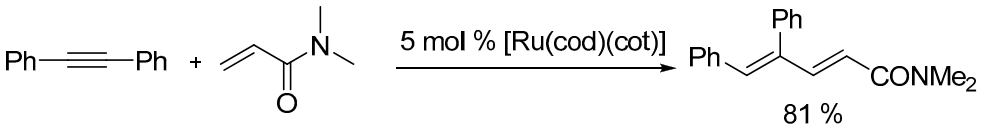


(89)



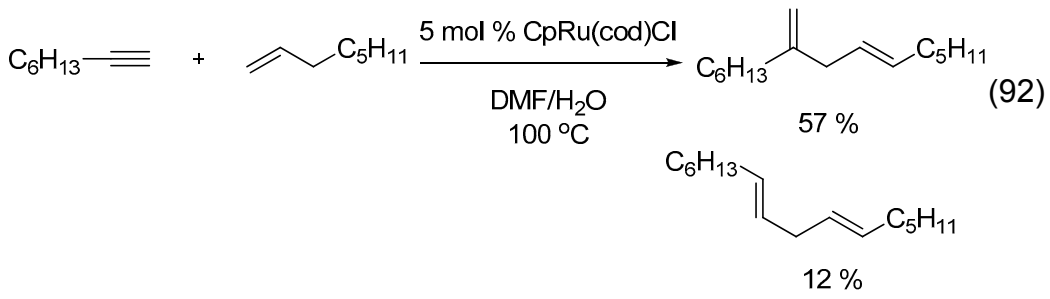
(90)

Intermolecular alkene-alkyne coupling is not feasible with the palladium catalyst. Furthermore, 1,4- vesus 1,3-diene formation is often substrate dependent.[180,181] A decade later, Watanabe *et al*. showed that 1,3-dienes can also be obtained by using ruthenium catalysis in an intermolecular fashion from alkynes and α,β-unsaturated olefins (91).[182]



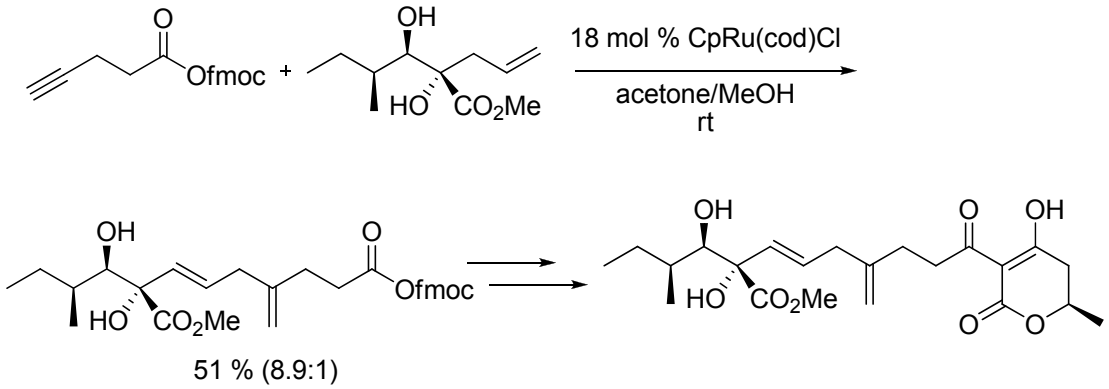
(91)

Trost and co-workers further explored this methodology and developed a ruthenium catalyzed addition of alkenes to acetylenes.[183] This reaction could generate two regioisomeric products. In the presence of a catalytic amount of a ruthenium catalyst, using monosubstituted alkenes and alkynes, 1,4-dienes are formed in favor of the branched isomer (eq 92). The observed selectivity was explained based on steric interactions. The power of this methodology was explained in the formal synthesis of alternaric acid (Scheme 84).[184]



(92)

Scheme 84. Formal Synthesis of Alternaric Acid



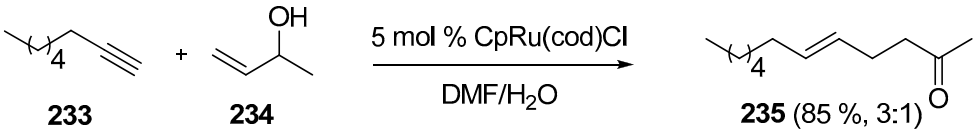
51 % (8.9:1)

Recently, the same group discovered that the use of the cationic ruthenium catalyst $[CpRu(CH_3CN)_3]^+ PF_6^-$ tolerates 1,2-di- and tri-substituted alkenes and allows the cycloisomerization of 1,6- and 1,7-enynes.[185] The ruthenium reaction selectively generates the 1,4-dienes (eq 93).

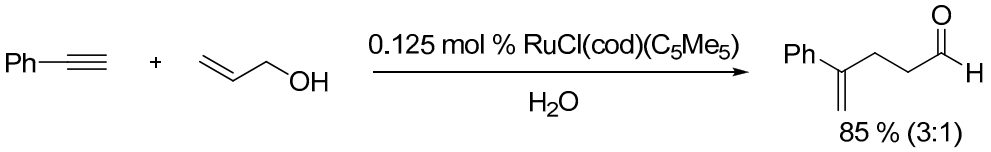
(93)

In addition to palladium and ruthenium complexes, iridium,[186] cobalt,[187] and rhodium[188] complexes also catalyze similar reactions. In 1993, the Trost group discovered a ruthenium-catalyzed coupling of allyl alcohols and alkynes to access γ,δ-unsaturated ketones (eq 94).[189] Exposure of allyl alcohol **233** and

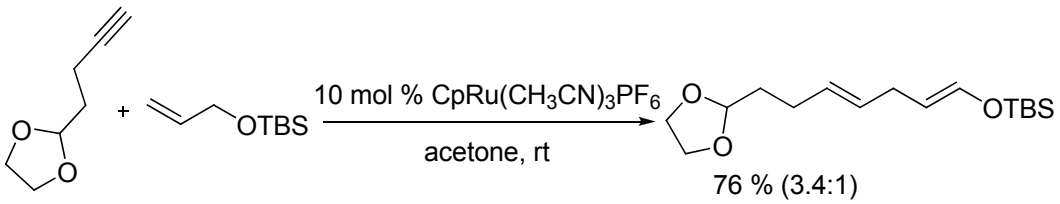
alkyne **234** to a phosphine free ruthenium catalyst resulted in the formation of γ,δ-unsaturated ketone **235** in high yield. However, this reaction provided mixtures of branched and linear products. Dixneuf and co-workers also developed similar reactions to access γ,δ-unsaturated aldehydes (eq 95).[190] In a further extension of this methodology, silyl enol ethers[150] and enamides[191] can be constructed from silyl protected alcohols and allyl amides (eq 96 and 97).



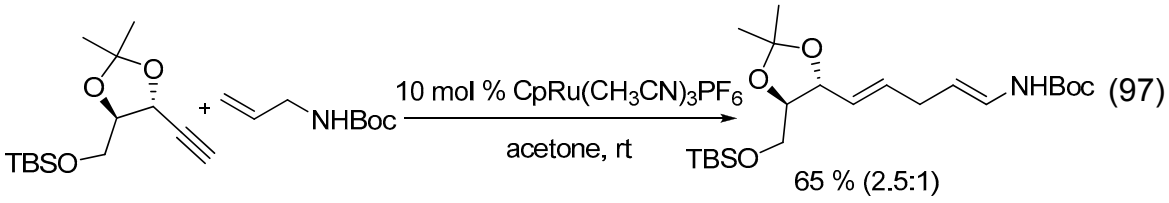
(94)



(95)



(96)



(97)

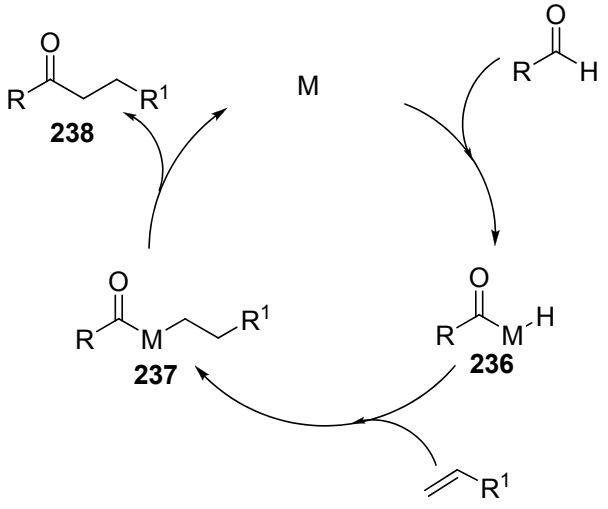
3.1.2.3 Hydroacylation

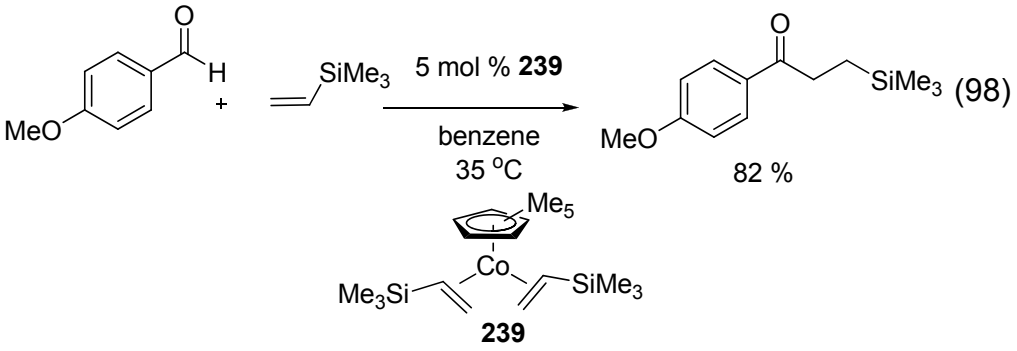
The ability of transition metals to decarbonylate aldehydes via acyl metal hydride intermediates has been used to construct ketones via an overall hydroacylation process in an efficient manner (Scheme 85). The aldehyde C-H bond can be cleaved to generate acyl metal hydride **236**, followed by insertion of

the hydride into an olefin to give acylmetal alkyl complex **237**. Then reductive elimination of acylmetal alkyl **237** gives ketone **238**.

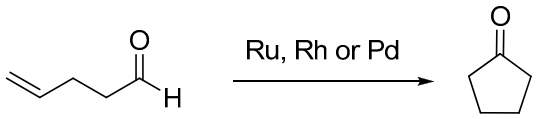
Rhodium catalyzed hydroacylation has also been reported to generate ketones. However, the early variations of the reaction were limited to ethylene.[192] Later, Watanabe and co-workers utilized a carbonyl ruthenium(0) complex.[193] Common olefins such as cyclohexene can be employed in this process, but the reaction requires harsh conditions to obtain the products. A few years later, Brookhart and Lenges developed a mild cobalt catalyzed intermolecular hydroacylation of vinylsilane (eq 98).[194] However, the reaction was limited to vinylsilane.

Scheme 85. General Mechanism for Hydroacylation

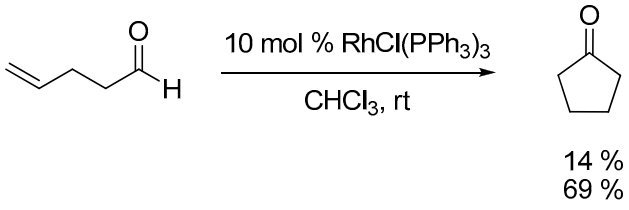




Another important use of transition-metal catalyzed intramolecular hydroacylation is the construction of cyclopentanone derivatives (eq 99). The first example of an intramolecular version was described in 1972 by Sakai.[195] The first catalytic example was reported a few years later by Miller.[196] Later, these conditions were modified by introducing ethylene into the reaction mixture to obtain cyclopentanone derivatives in higher yield (eq 100).[197]

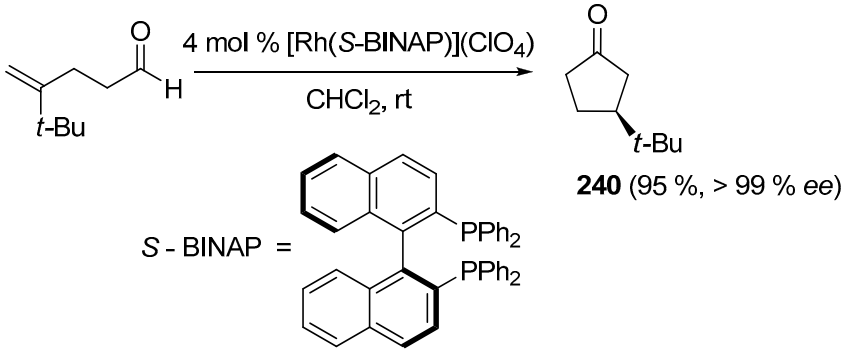


(99)



(100)

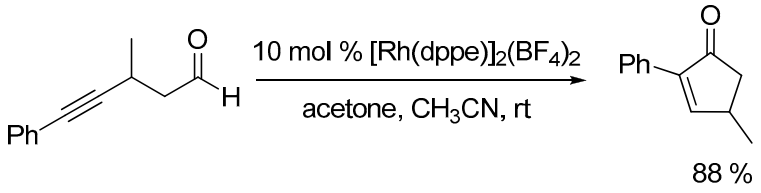
Asymmetric cyclization of substituted pent-4-enals was achieved by employing rhodium complexes bearing a chiral diphosphine ligand (eq 101). Bosnich and co-workers used a [Rh(*S*-BINAP)](ClO_4) complex to convert 4-*t*-butyl-pent-4-enal to cyclopentanone **240** with high enantioselectivity.[198]



(101)

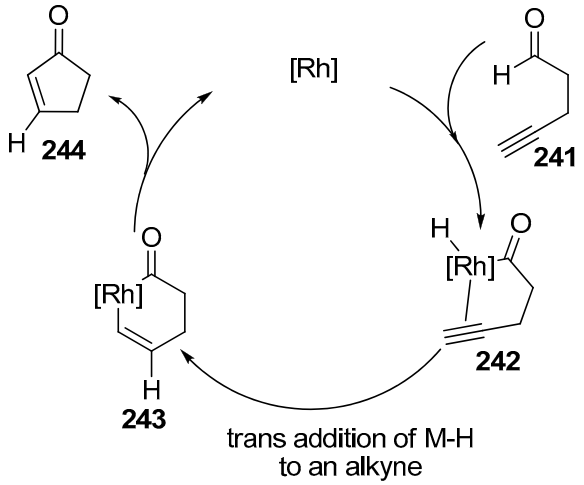
In 2002, Fu and co-workers used 4-alkynal instead of 4-alkenals to afford a cyclopentenone (eq 102).[199] The proposed mechanism is analogous to the

cyclization of 4-alkenals (Scheme 86). First, the oxidative addition of the aldehyde **241** C-H bond to Rh(I) generates the Rh(III) acyl hydride **242**. Next, the rhodium hydride adds in a trans fashion to the alkyne to generate rhodium metallacyclohexene **243**. Finally, reductive elimination occurs to generate product **244**.

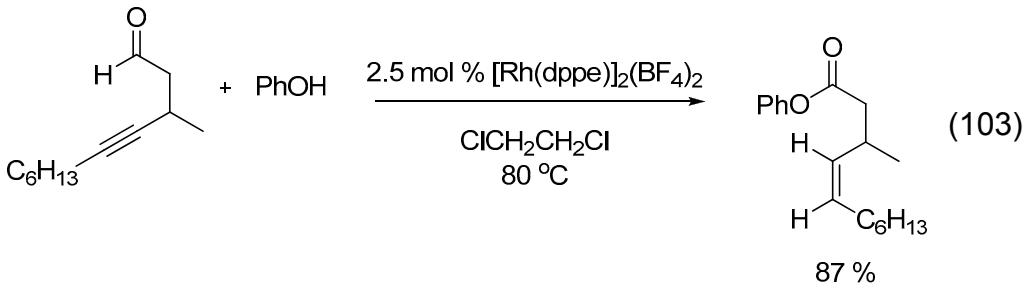


(102)

Scheme 86. Rhodium-Catalyzed Cyclization of 4-Alkynal

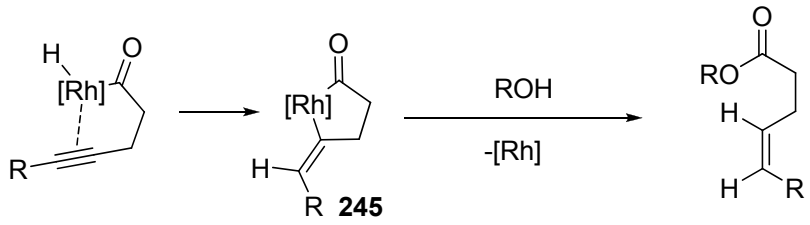


During the mechanistic investigation of this reaction, Fu and co-workers discovered a novel rhodium-catalyzed tandem redox reaction of a 4-alkynal with an alcohol to afford a *cis*-alkenoate (eq 103).[200] The mechanism is illustrated in Scheme 87. Rhodium metallacycle **245** was trapped with a nucleophile such as an alcohol.

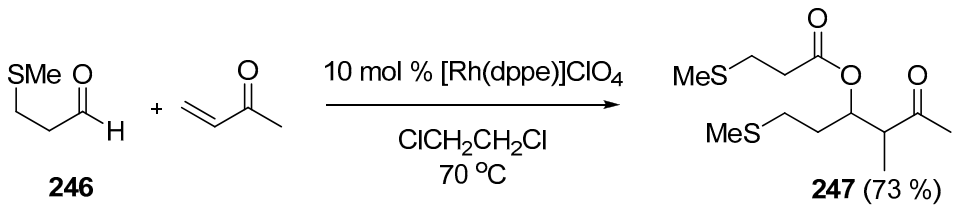


(103)

Scheme 87. Rhodium-Catalyzed Tandem Redox Reaction

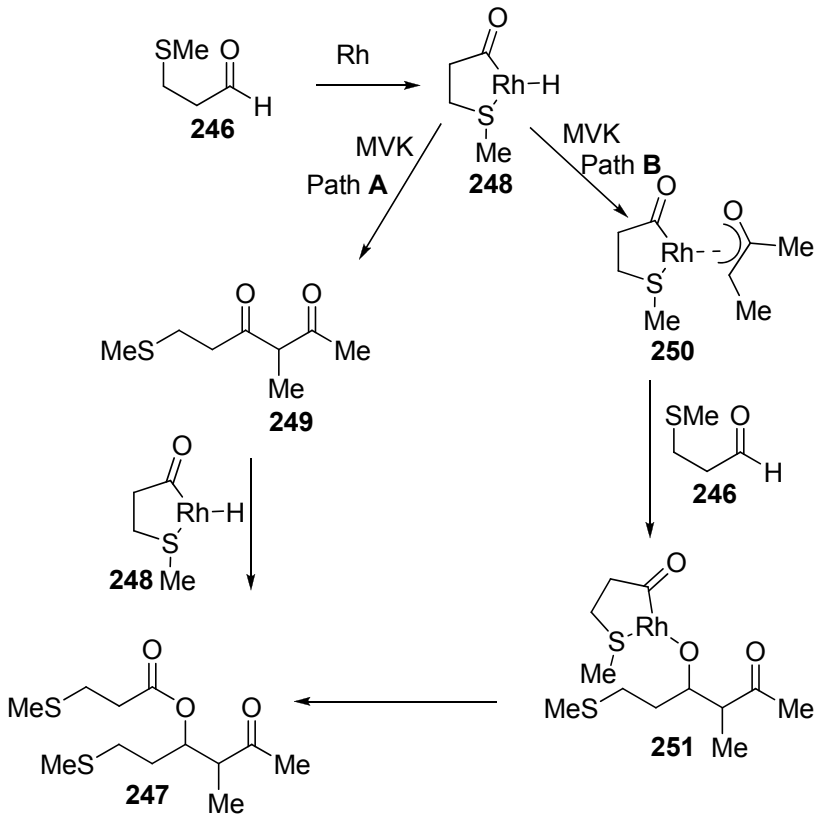


Recently, a rhodium-catalyzed reductive aldol reaction was reported using aldehydes as the stoichiometric reductant.[201] In the presence of a Rh(I) catalyst β-methyl sulfide-substituted propanal **246** and methyl vinyl ketone (MVK) generated ketone **247** in high yield (eq 104). Two possible mechanisms are outlined in Scheme 88. First, the oxidative addition of the aldehyde **246** C-H bond could generate the chelated acyl rhodium hydride **248**. In path **A**, hydroacylation could generate ketone **249**, which could undergo reduction with another equivalent of acyl rhodium hydride **248** to afford ester **247**. In path **B**, conjugate addition of the hydride could generate rhodium enolate **250**, which could add to another equivalent of the aldehyde **246** to afford aldolate **251**. Reductive elimination of the aldolate **251** would generate product **247**.

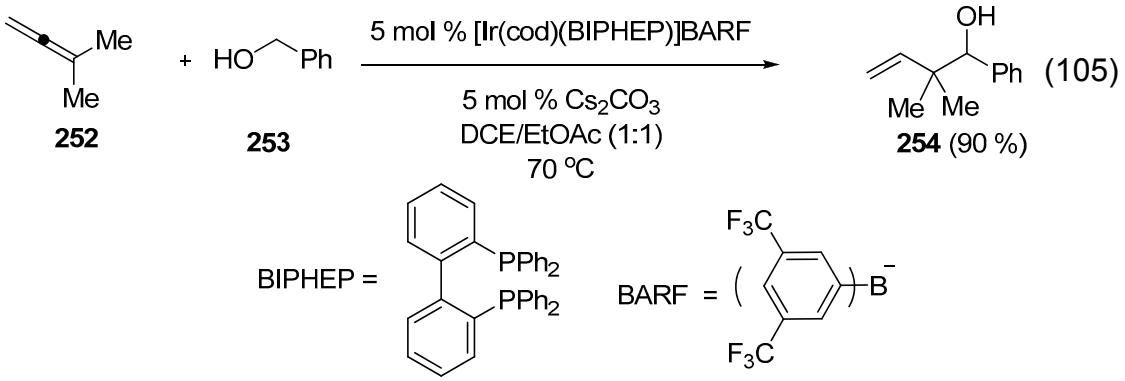


(104)

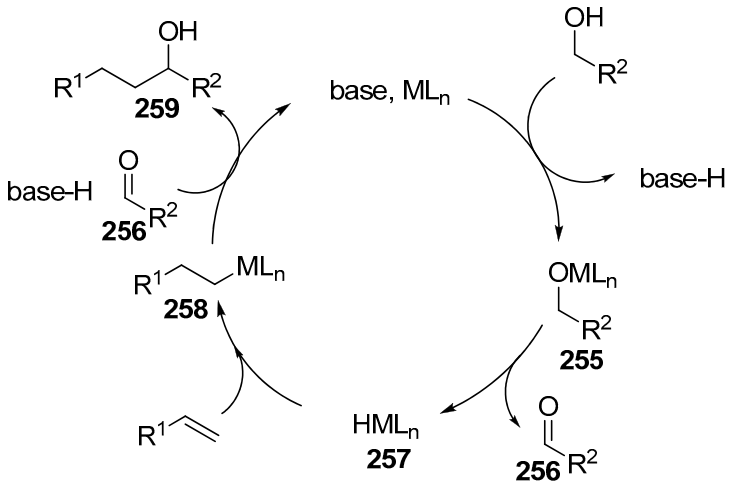
Scheme 88. Rhodium-Catalyzed Reductive Aldol Reaction



More recently, Krische and co-workers developed an iridium-catalyzed C-C bond formation via hydrogen autotransfer (eq 105).[202] In this reaction, allene **252** is coupled with alcohol **253** to generate alcohol **254** in high yield. The reaction is believed to be occurring through hydrogen autotransfer.[203]

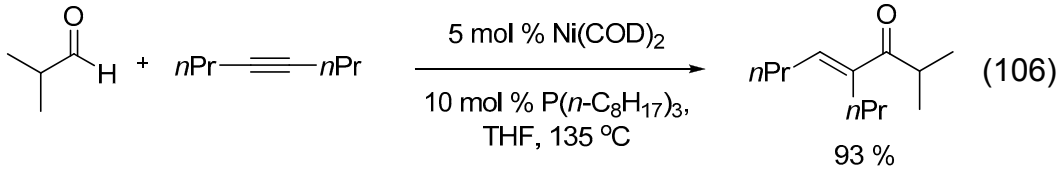


Scheme 89. Iridium-Catalyzed C-C Bond Formation via Hydrogen Autotransfer



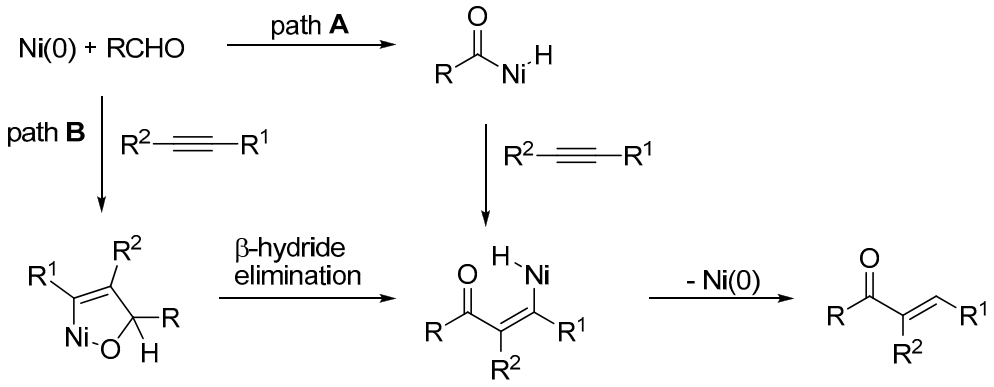
The proposed catalytic cycle is shown in Scheme 89. First, β-hydride elimination of intermediate **255** could generate metal hydride **257** and aldehyde **256**. Then, hydrogenation of the alkene would produce metal alkyl species **258**, which could react with aldehyde **256** to generate product **259**.

In 1990, Tsuda *et al*. reported a nickel-catalyzed coupling of alkynes with aldehydes to produce enones (eq 106).[204] Two possible reaction pathways were proposed. Path **A** involves the β-hydride elimination and path **B** involves hydroacylation (Scheme 90).

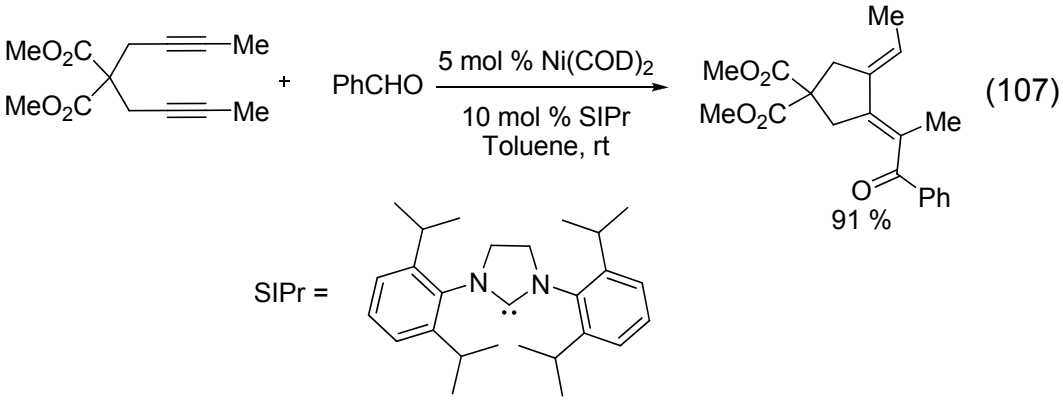


(106)

Scheme 90. Nickel-Catalyzed Coupling of Alkynes and Aldehydes

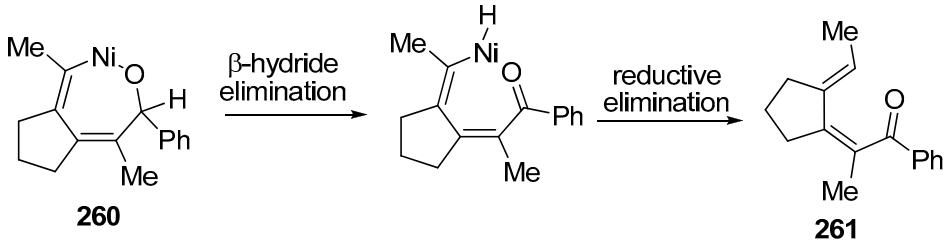


Later, Louie and co-workers observed a similar process during the nickel-catalyzed cycloaddition of diynes and aldehydes (eq 107).[205] Nickel-NHC complexes were used to mediate the reaction. The reaction is likely to occur through metallacycle **260**. The β-hydride elimination from metallacycle **260** followed by reductive elimination generated the product **261** (Scheme 91).



(107)

Scheme 91. Nickel-Catalyzed Cycloaddition of Diynes and Aldehydes

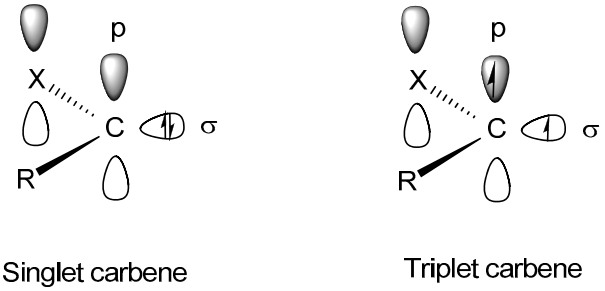


260 **261**

3.2 Carbenes

Carbenes are neutral species in which the carbon center contains six valence electrons, two of the electron pairs are bonding and one is non-bonding. Carbenes can be considered to be sp^2 hybridized. The two non-bonding orbitals are non-degenerate: an in-plane sp^2 orbital is labelled as σ and a perpendicular p orbital labeled as p. For a generic carbene the distribution of these non-bonding electrons, and hence the multiplicity of the ground state, is governed by the relative orbital energies and electron-electron repulsion (Figure 2).

Figure 2



Singlet carbene Triplet carbene

For a ground state singlet carbene, the energy required to excite one of these electrons to the vacant p orbital exceeds the energy of repulsion between these two electrons. Therefore, in the ground state singlet, the two electrons occupy the in-plane (σ) orbital. For a ground state triplet carbene, the energy required to promote one electron from the σ orbital to the p orbital is less than the absolute value of electron-electron repulsion (Figure 2).

Heteroatoms such as oxygen, sulfur, nitrogen and halogens stabilize the singlet state substantially. Substituting one fluorine atom for hydrogen stabilizes the singlet state by 15 kcal/mol. Substitution of a second fluorine further

increases the stability of the singlet state.[206] NHCs were reported to have an energy difference as high as 79 kcal/mol (Figure 3). [207]

Figure 3

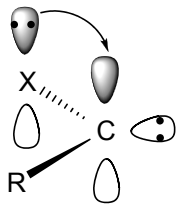
$E_{triplet} - E_{singlet}$ (kcal/mol)	-10	15	56	79

The driving force of a carbene reaction, in general, is the completion of the octet at the electron deficient carbon. Therefore, we would expect carbenes to behave as electrophiles and react rapidly with electron rich substrates. The chemistry of carbenes that contain π-donor substituents, such as oxygen, sulfur and nitrogen, linked directly to the carbene center exhibit different properties than those of other carbenes; these carbenes behave as nucleophiles.

3.2.1 Nucleophilic Carbenes

The major contributing factor for the stabilization of the singlet state of carbenes with heteroatoms is the conjugative donation of non-bonding electrons from the heteroatom to the vacant p-orbital of the carbene carbon (Figure 4).

Figure 4

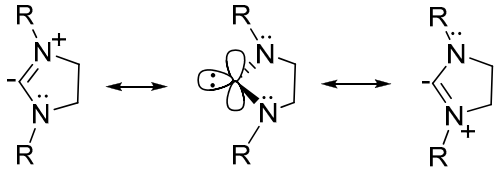


X = OR, SR, NR_2

This electron donation increases the energy of the p orbital. In addition, the inductive effect of the electronegative substituents lowers the energy of the σ

orbital. These two effects in combination increase the singlet - triplet gap substantially so that these carbenes exist primarly in the singlet state. Additionally, nucleophilicity of the N-heterocyclic carbenes are increased by resonance stabilization from the nitrogen lone pair (Figure 5).

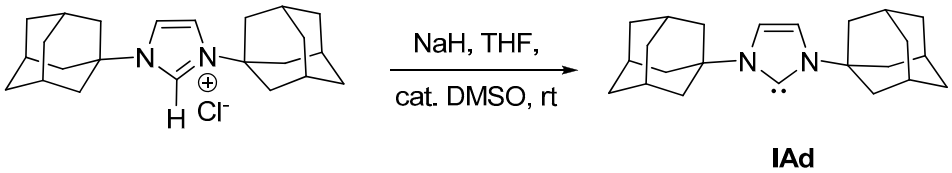
Figure 5.



3.2.2 N-Heterocyclic Carbenes vs. Phosphine ligands

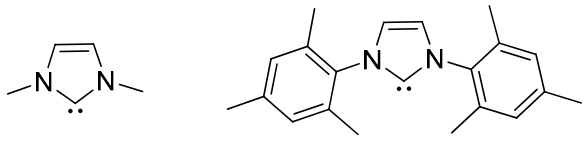
In the late 1960s, Wanzlick and Öfele independently reported the first use of N-heterocyclic carbenes as ligands for metal complexes.[208,209] Later, in 1991, Arduengo and coworkers isolated the first stable N-heterocyclic carbene IAd (Scheme 92).[210] The stability of the carbene was achieved by employing sterically demanding adamantyl groups.

Scheme 92. 1,3-Diadamantyl-imidazol-2-ylidene



Although the N,N-dimethyl-substituted imidazolium-derived IMe is less stable than IAd, it can be stored in solution without decomposition for days. Additionally, IMes can be isolated as a neutral carbene and be synthesized and crystallized without dimerization due to the combination of steric and electronic effects (Figure 6).

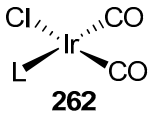
Figure 6.



IMe IMes

Due to both similarities and differences compared to phosphine ligands, the use of NHCs as ligands has been rapidly increasing as a substitute for phosphine ligands. The σ-donating ability of the N-heterocyclic carbenes was quantified by comparing the stretching frequencies of CO ligands attached to the metals. These studies revealed that N-heterocyclic carbenes are more electron rich than the most basic trialkyl phosphines (Figure 7).[211,212]

Figure 7. Relationship between the Tolman Electronic Parameters and IR Stretching Frequencies for Complex **262**



262

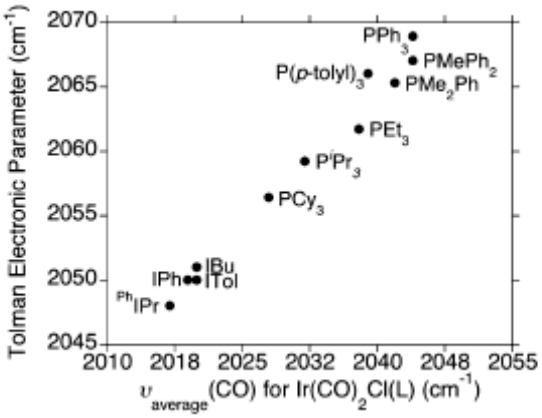
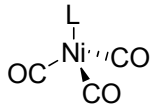


Figure taken from *Organometallics* **2004**, *23*, 2461-2468

Additionally, computational studies also explained that the metal carbon bond of the carbene metal complex has high σ-bond character, which stabilizes

the high oxidation state of metal complexes. Saturated and unsaturated NHCs form very stable bonds with transition metals whereas phosphine ligands generally form much weaker bonds (Table 21).[213] As a result, NHCs generate more robust metal ligand complexes compared to phosphine ligands.

Table 21. DFT-calculated M-NHC Bond Dissociation Energies for Complex **263**

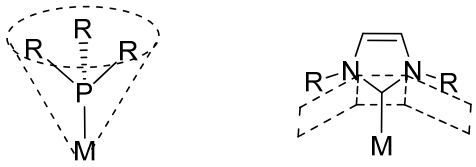


263

Ligand	BDE of L in **263** kcal mol^{-1}
IMes	41.1
SIMes	40.2
IPr	38.5
SIPr	38.0
ICy	39.6
IAd	20.4
PPh_3	26.7
P*t*Bu_3	28.0

The shape of a phosphine metal complex and NHC metal complex are very different (Figure 8). In phosphine metal complexes, the substituent R groups point away from the metal, resulting in a cone-like shape. Whereas, in NHC metal complexes the substituent R groups point towards the metal center resulting in the formation of a pocket. Therefore, the steric demand of phosphine ligands is described by cone angle[214] and with N-heterocyclic carbenes is described by the percent volume buried ($\%V_{bur}$).[213]

Figure 8.

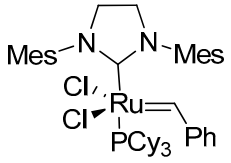


3.3 Nickel-Catalyzed Reactions Involving *N*-Heterocyclic Carbenes

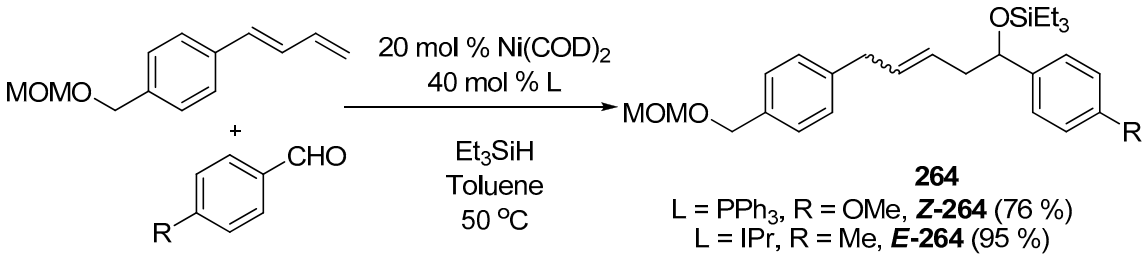
Due to the close analogy of NHCs to trialkylphophines, and their excellent σ-donating properties, this makes them the ligand of choice for many transition metals. Their complexes are found to be much more effective than conventional catalysis in a number of reactions such as the Heck reaction and olefin metathesis. The most impressive application of using the NHC ligands is Grubbs' 2nd generation catalyst for olefin metathesis reactions (Figure 9).

As mentioned in the previous chapter (Chapter 2, section 2.1.5), Mori and co-workers reported nickel-catalyzed coupling of aldehydes and 1,3-dienes to generate the homoallylic alcohol.[156,215] The use of NHCs as ligands resulted in a complete reversal of the olefin geometry. The reaction with a phosphine ligand provided the *trans*-olefin whereas with NHC ligands, the reaction provided the *cis*-olefin geometry (Scheme 93).

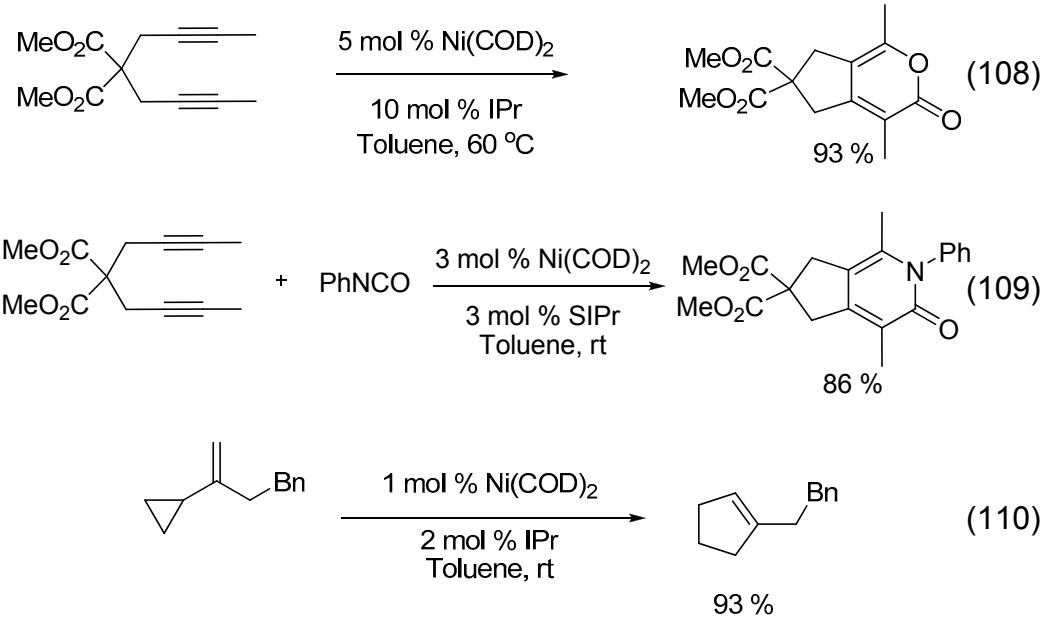
Figure 9. Grubbs' 2nd Generation Catalyst



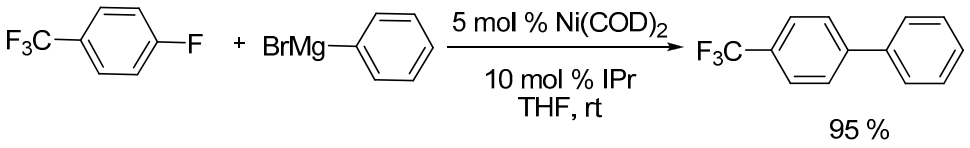
Scheme 93. Nickel-Catalyzed Coupling of Aldehydes and 1,3-Dienes



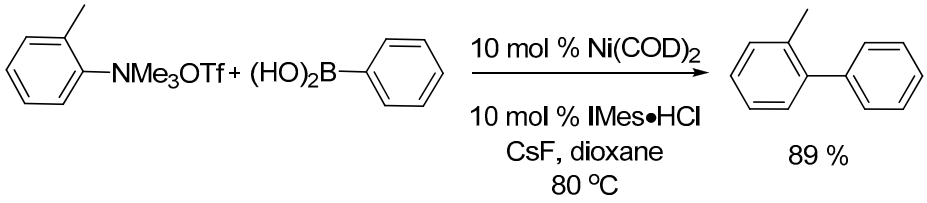
A similar effect of changing the reactivity by the use of an N-heterocyclic carbene ligand was also observed by the Louie group. The treatment of diynes and CO_2 with a catalytic amount of an NHC and nickel(0) resulted in the formation of 2-pyrones in high yields (eq 108).[216] The addition of NHCs instead of phosphines provided greatly improved reactivity and a broader substrate scope. The same catalytic system was also employed to produce 2-pyridones very efficiently (eq 109).[217] The efficient isomerization of unactivated vinyl cyclopropanes to cyclopentanes was achieved by using the same catalytic system (eq 110).[218]



In 2001, the Herrmann group showed that NHC ligands can remarkably enhance the reactivity of unreactive reaction partners, such as a species containing a C(sp^2)-F. Catalytic C-C bond formation through selective activation of C-F bonds was achieved by using a nickel/NHC complex (eq 111).[219] Later, MacMillan and co-workers demonstrated nickel-catalyzed Suzuki cross-couplings of aryltrimethylammonium salts to generate biaryl compounds very efficiently in the presence of a nickel/NHC catalyst (eq 112).[220]

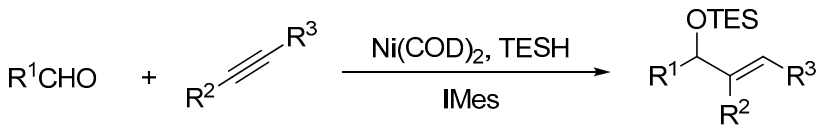


(111)



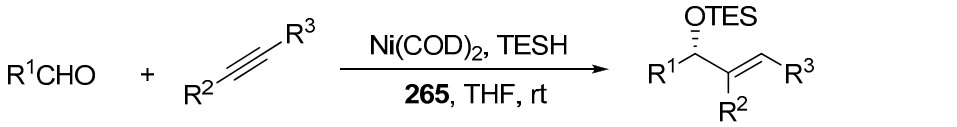
(112)

As mentioned in the previous chapter (section 2.1.5), our group employed nickel(0)/NHC complexes to develop intermolecular aldehyde/alkyne reductive coupling reactions using alkylsilane reducing agents. Early studies with phosphine ligands proved that the intermolecular reductive coupling of alkynes, aldehydes, and trialkylsilanes were not possible due to alkyne trimerization, whereas the desired heterocoupling of an aldehyde and alkyne was achieved by using nickel(0)/N-heterocyclic carbene complexes (eq 113). Crossover deuterium-labelling experiments demonstrated that catalyst formulations involving PBu_3 and the N-heterocyclic carbene ligand proceed through fundamentally different mechanisms.

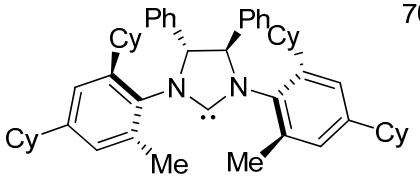


(113)

Recently, an asymmetric version of nickel-catalyzed intermolecular aldehyde and alkyne coupling was achieved with chiral N-heterocyclic carbene **265** which selectively provided the protected alcohol in moderate to good enantiomeric excess (eq 114).[221]



(114)

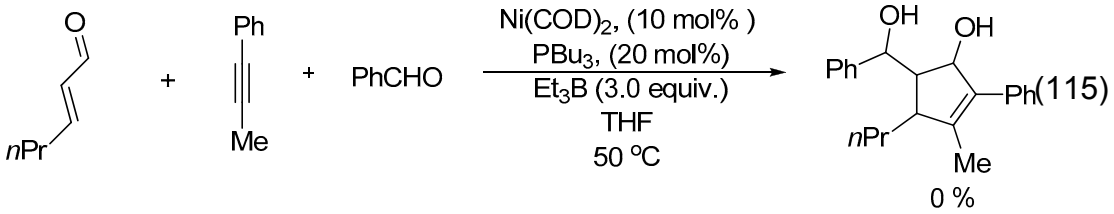


265

3.4 Results and Discussion

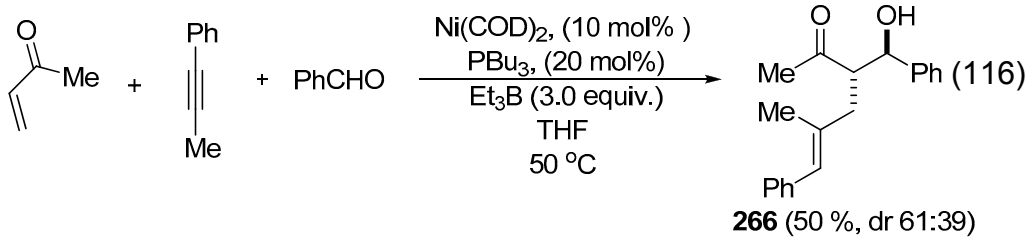
3.4.1 Nickel-Catalyzed Three-Component Couplings of Alkynes, Enones and Aldehydes

In the course of studying nickel-catalyzed [3+2] cycloadditions of enals and alkynes, we considered replacing the Brønsted acid (methanol) with an electrophile to access highly functionalized cyclopentenols. Unfortunately, all attempts to obtain the cyclopentenol with enals failed (eq 115).



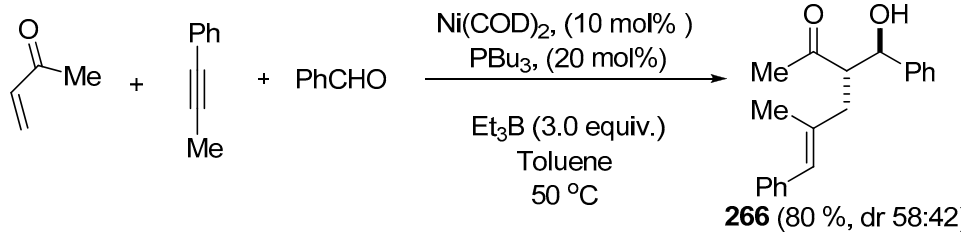
(115)

Later, we were excited to find that highly functionalized γ,δ-unsaturated ketones could be synthesized by employing aldehydes as an electrophilic component instead of methanol (eq 116). An initial experiment was performed by treatment of methyl vinyl ketone, 1-phenylpropyne and benzaldehyde with 10 mol % of $Ni(COD)_2/PBu_3$(1:1) and 3.0 equiv of Et_3B in THF to provide the desired product **266** in 50 % yield. The reaction was optimized by employing toluene as a solvent and controlling the addition of substrates (eq 117).



(116)

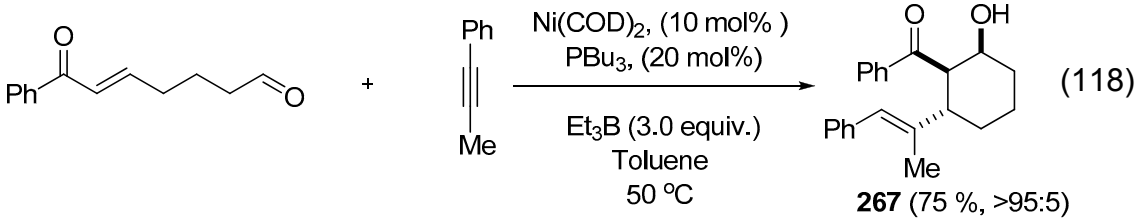
266 (50 %, dr 61:39)



(117)

266 (80 %, dr 58:42)

A key feature of this reaction is that enones tethered to an aldehyde are also effective substrates to allow generation of highly functionalized cyclohexanes in high yield with high stereoselectivity (eq 118).



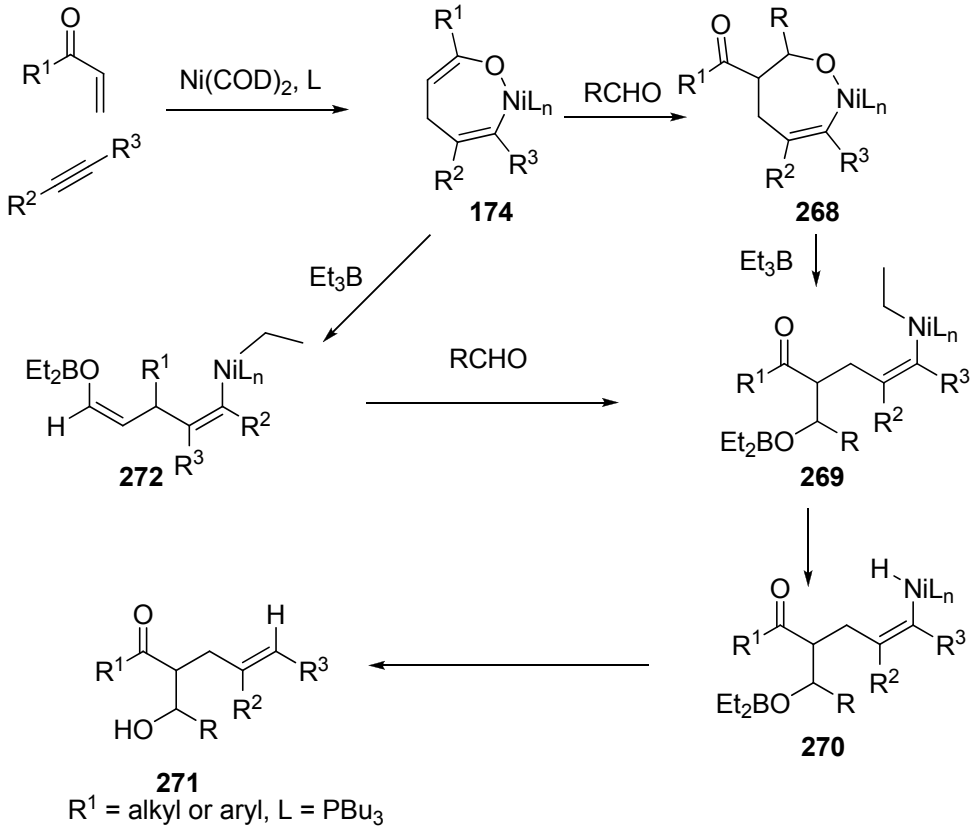
(118)

267 (75 %, >95:5)

The proposed mechanism for the formation of the product is shown in Scheme 94. Metallacycle **174** could undergo aldol addition to aldehyde to

generate the nickel aldolate **268**, then transmetallation followed by β-hydride elimination would generate **270**, and finally reductive elimination followed by protonation would generate alcohol **271**. Alternatively, metallacycle **174** could undergo transmetallation with triethylborane to generate enol borane **272**, which could undergo aldol addition with aldehyde to generate aldol adduct **269**. However, this aldol reaction is most likely to occur via nickel aldolate **268**. Initial studies demonstrated that the reductive coupling of enones and alkynes was not effective in the absence of protic solvents. These observations suggest that the reaction most likely occurs through protonation of the metallacycle followed by transmetallation (Chapter 2, section 2.2.1). Therefore we could eliminate the reaction pathway, which involves enol borane **272**.

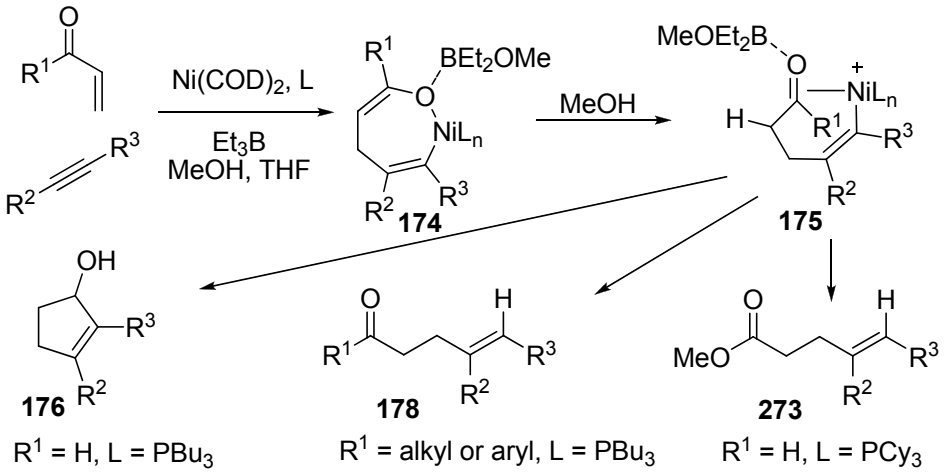
Scheme 94. Proposed Mechanism for the Three-Component Couplings



3.4.2 Intermolecular Nickel-Catalyzed Three-Component Couplings via Internal Redox

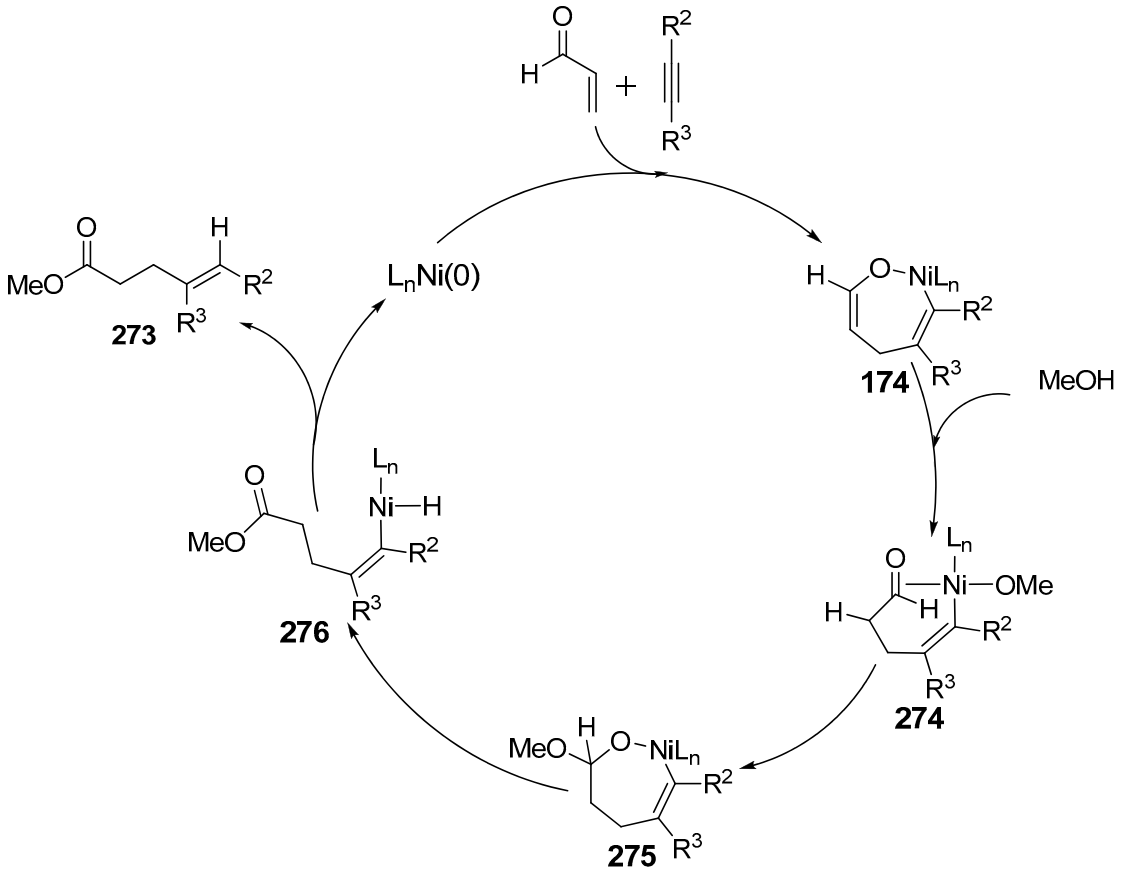
At the same time another colleague in our group (Wei Li) observed that a minor reaction pathway is possible in the coupling of enals with alkynes to generate methyl ester **273**, when tricyclohexylphosphine (PCy_3) is used as a ligand (Scheme 95). Yields for the production of **273** were greatly improved in the absence of a reducing agent. We believe that the formation of **176** and **178** is formally a reductive cycloaddition or coupling, however, the generation of **273** may involve an internal redox process, wherein the aldehyde is oxidized and the alkyne is reduced.

Scheme 95. Divergent Reaction Pathways



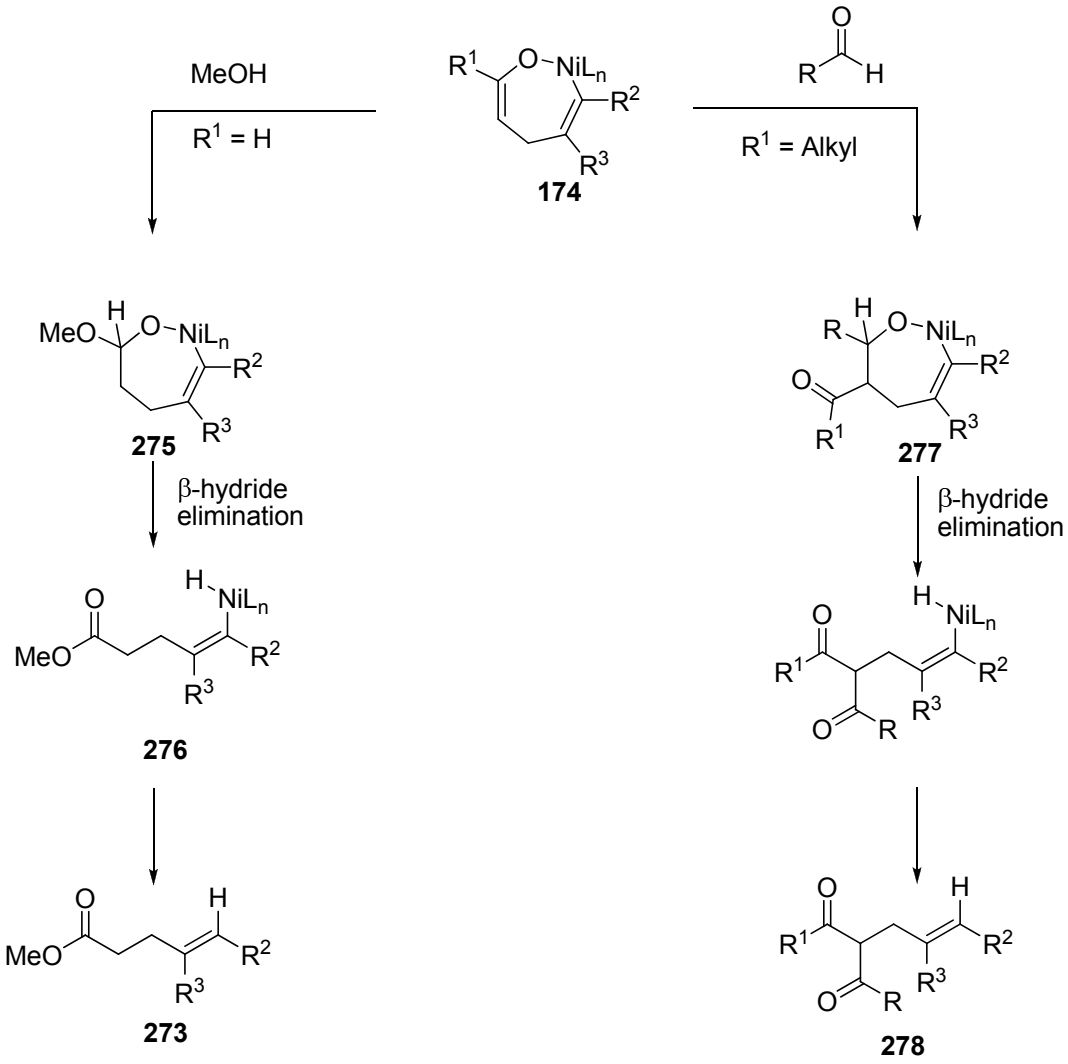
Initially we considered that this reaction could occur through an internal redox mechanism (Scheme 96). First, formation of the metallacycle **174** and monoprotonation could generate intermediate **274**. Then, 1,2 addition of methoxide could occur to generate **275**, which could undergo β-hydride elimination to form **276**. Finally, reductive elimination would generate product **273** and Ni(0).

Scheme 96. Proposed Mechanism of Enal, Alkyne, Alcohol Couplings



Inspired by these results we envisioned that the same mechanism might provide access to 1,3-diketones. The requirement for the proposed mechanistic pathway is the generation of a metallacyclic alkoxide **275**, which possesses an accessible β-hydrogen. Similar metallacycle **277** can be accessed by using an aldehyde instead of methanol (Scheme 97). Then β-hydride elimination, followed by reductive elimination could generate 1,3-diketone **278**.

Scheme 97. Proposed Metallacyclic Intermediates



The reaction was carried out with methyl vinyl ketone, 1-phenyl propyne and benzaldehyde in the presence of a catalytic amount of $Ni(COD)_2$ and ligand. Screening different ligands illustrated that IPr and PCy_3 are the best ligands for this reaction. The reaction was optimized by employing toluene as a solvent at 90 ^oC. A series of examples were examined to investigate the scope of this novel internal redox process. Treatment of a mixture of an enone, an aldehyde and an alkyne with $Ni(COD)_2$ and either PCy_3 or IPr as the ligand in toluene at 90 ^oC

directly afforded 1,3-diketone products in good yield with a high degree of chemoselectivity (Table 22 and Table 23).[222] This reaction can tolerate different enones such as methyl vinyl ketone (Table 22, entries 1,4 and 6, and Table 23, entries 1,4 and 6), a longer chain simple vinyl ketone (Table 22, entries 2 and 3 and Table 23, entries 2, 3, and 7-9), and an α-alkyl enone (Table 22, entry 5 and Table 23, entry 5). However, β-substitution on the enone is not tolerated. Additionally, this reaction can tolerate a wide range of alkyne structures such as aromatic alkynes, dialkyl alkynes, and terminal alkynes (Table 22 and Table 23). Another interesting observation was that the alkyne regioselectivities can be reversed depending on the choice of ligand (Scheme 98). Use of IPr ligand resulted the smaller substituents of the alkynes at the terminal position whereas use of PCy_3 resulted in the completely reversed regioisomer.

Scheme 98. Ligand Effect on Regioselectivity

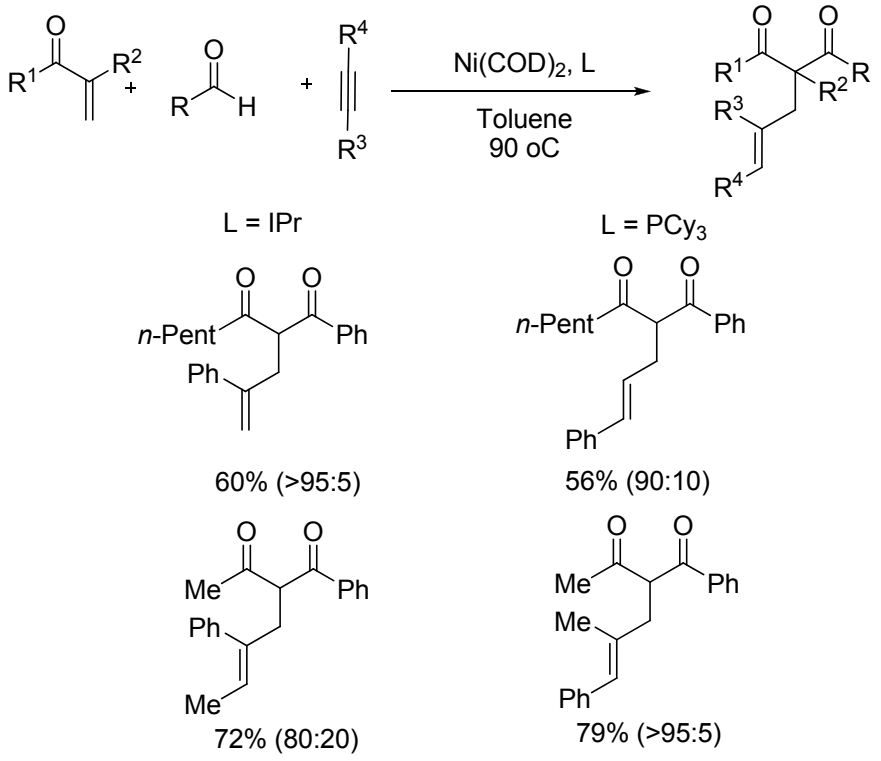
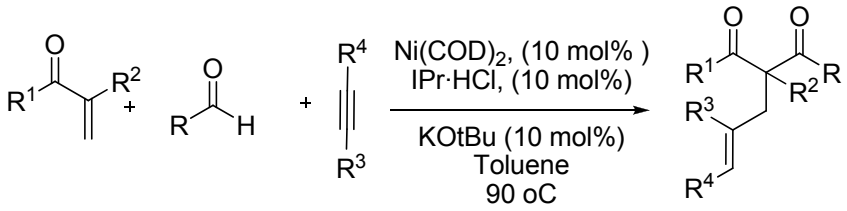


Table 22. Three-Component Couplings with IPr Ligand



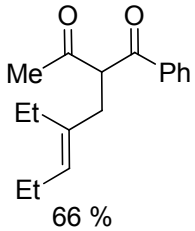
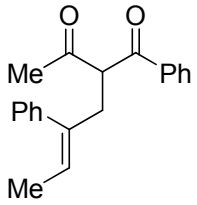
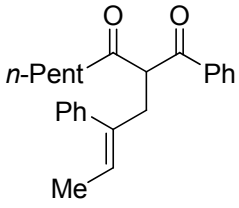
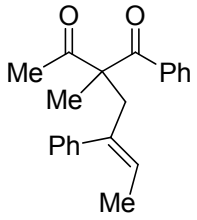
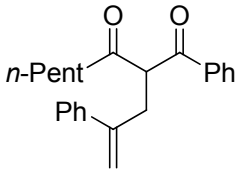
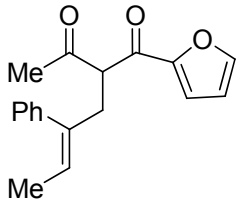
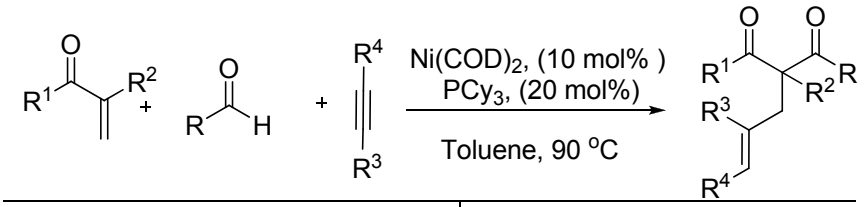
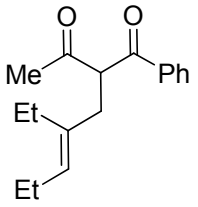
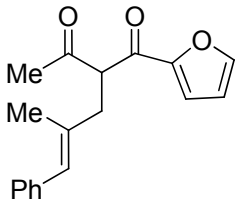
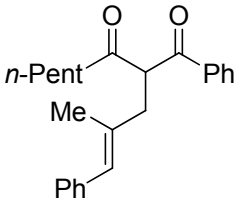
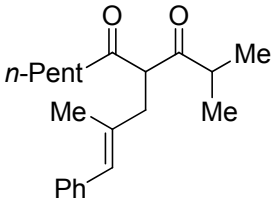
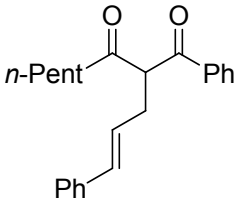
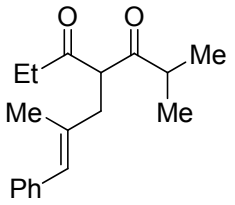
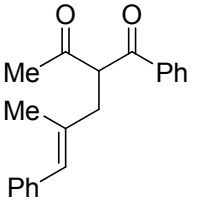
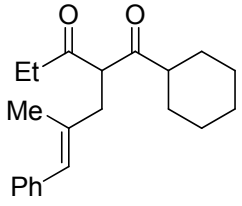
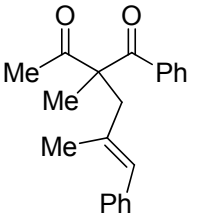
entry	Product Yield (regioselectivity)	entry	Product Yield (regioselectivity)
1	 66 %	4	 72% (80:20)
2	 61% (72:28)	5	 47% (61:39)
3	 60% (>95:5)	6	 86% (80:20)

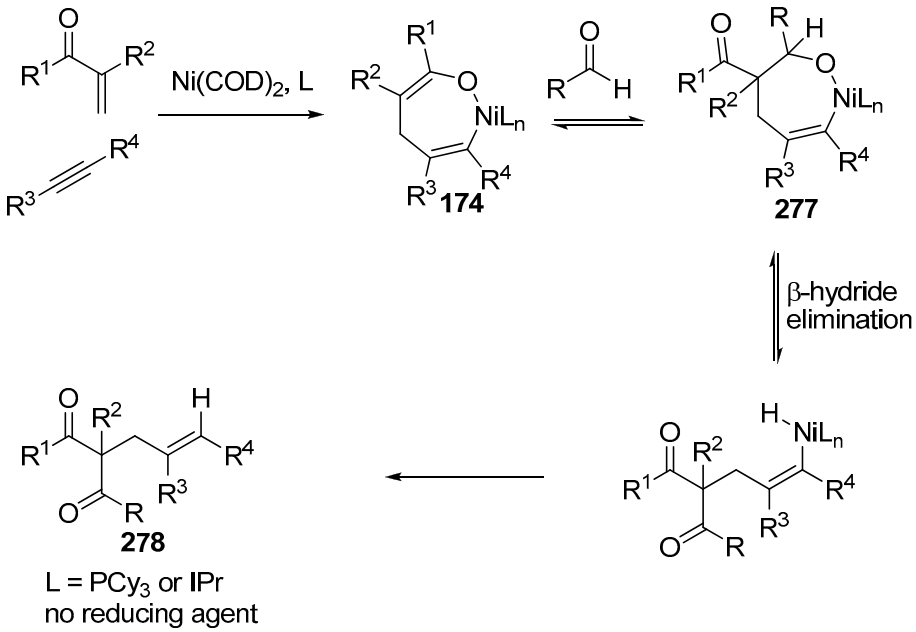
Table 23. Three-Component Couplings with PCy_3 Ligand



entry	Product Yield (regioselectivity)	entry	Product Yield (regioselectivity)
1	 70%	6	 77% (>95:5)
2	 76% (72:28)	7	 50 % (>95:5)
3	 56% (90:10)	8	 42 % (>95:5)
4	 79% (>95:5)	9	 46 % (>95:5)
5	 65% (87:13)		

The proposed mechanism for the intermolecular three component couplings is depicted in Scheme 99. Aldol addition of nickel enolate **174** to the aldehyde would generate the nickel aldolate **277**. The resulting aldolate **277** could undergo β-hydride elimination followed by reductive elimination to produce 1,3-diketone **278**. This method provides a novel internal redox mechanism that avoids the use of reducing agents.

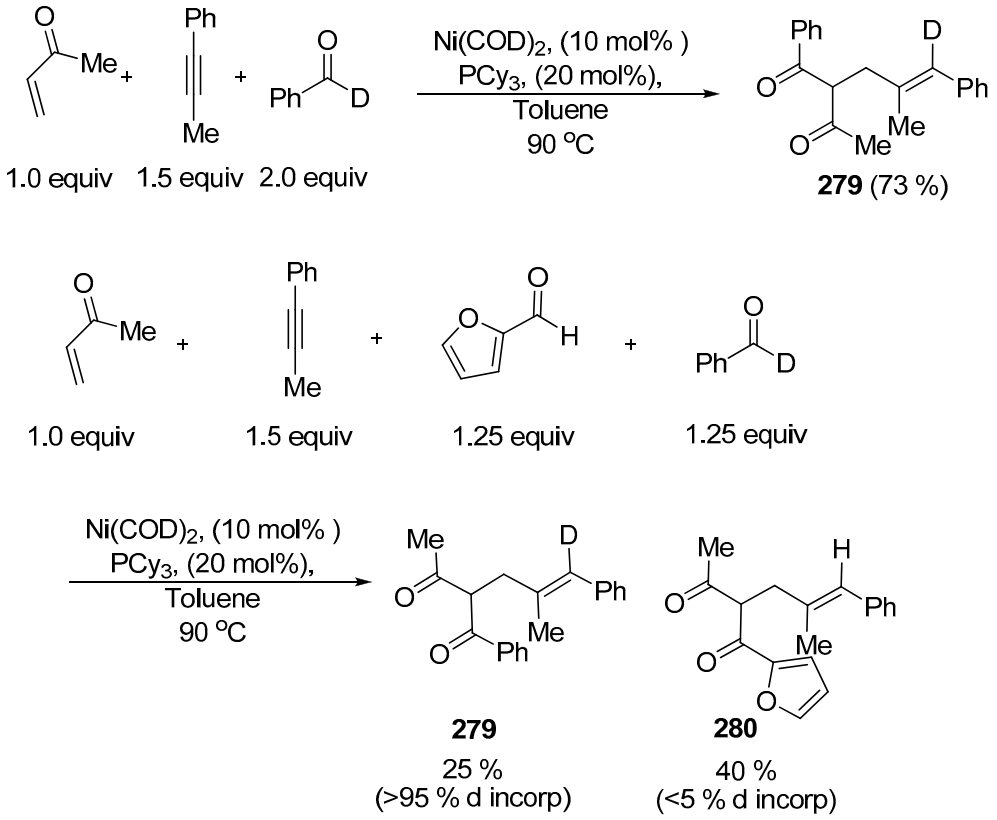
Scheme 99. The Proposed Mechanism of Enone, Alkyne, Aldehyde Coupling



To support this mechanism, a deuterium-labeling experiment was carried out using $Ni(COD)_2/PCy_3$, d_1-benzaldehyde, methyl vinyl ketone and phenyl propyne (Scheme 100). Deuterated product **279** was obtained in 73% yield with > 95% deuterium incorporation at the expected alkenyl position. To probe the molecularity of hydrogen migration, a crossover experiment was carried out by using 1.25 equiv each of d_1-benzaldehyde and 2-furaldehyde, methyl vinyl ketone (1.0 equiv), 1-phenyl propyne (1.5 equiv), $Ni(COD)_2$ (0.1 equiv) and PCy_3

(0.2 equiv). Product **279** was obtained in 25 % yield with > 95 % deuterium incorporation, whereas product **280** was obtained in 40 % yield with < 5 % deuterium incorporation. These experiments illustrate a unimolecular hydrogen migration and rule out alternate mechanisms that could involve a preformed nickel-hydride active catalyst.

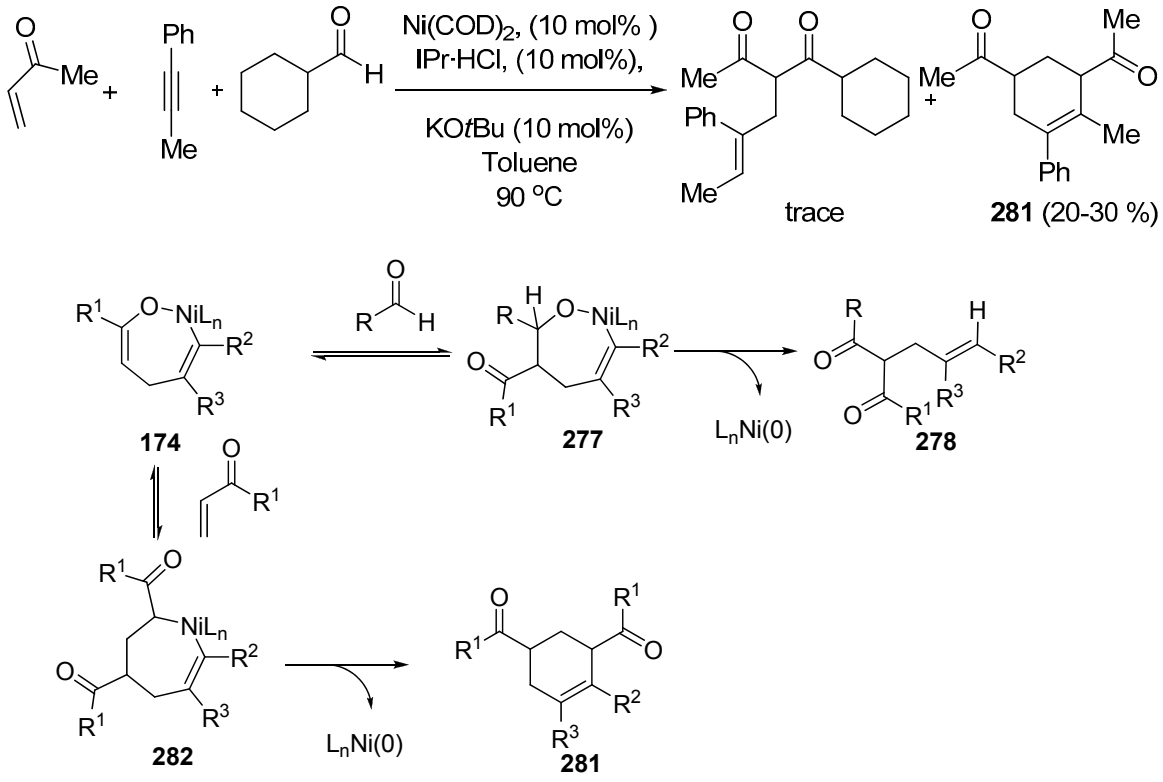
Scheme 100. Deuterium-Labelling Studies



The participation of aliphatic aldehydes requires PCy_3, whereas aromatic aldehydes participate with either PCy_3 or IPr. With aliphatic aldehydes, in the presence of IPr ligand only a trace amount of desired product was obtained and around 30% of the undesired six-membered ring **281** was observed. The formation of this product could be explained as depicted in scheme 101. Metallacycle **174** could undergo aldol addition with aldehyde to generate **277**. At

the same time, metallacycle **174** could undergo 1,4-addition with the enone to generate metallacycle **282**, followed by reductive elimination to generate **281**. The aldol reaction could be reversible and β-hydride elimination with an aliphatic aldehyde could be very slow compared to the reductive elimination step. Thus, the reaction could funnel through the formation of product **281**.

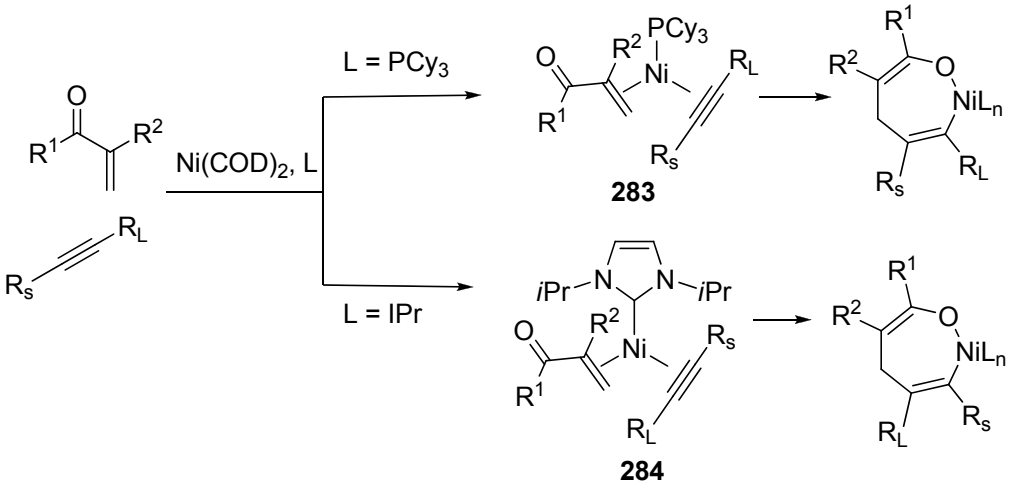
Scheme 101. Other Reaction Pathways



The rationale for the regioselectivity is depicted in Scheme 102. The orientation in which the alkyne complexes to nickel is dependent upon both the steric environment around the enone and that surrounding the ligand. With a relatively small ligand, such as PCy_3, R_L (Ph) is placed proximal to the ligand to minimize interactions between the β-carbon of the enone and the alkyne (**283**). Whereas with the sterically demanding IPr ligand, interactions between the ligand

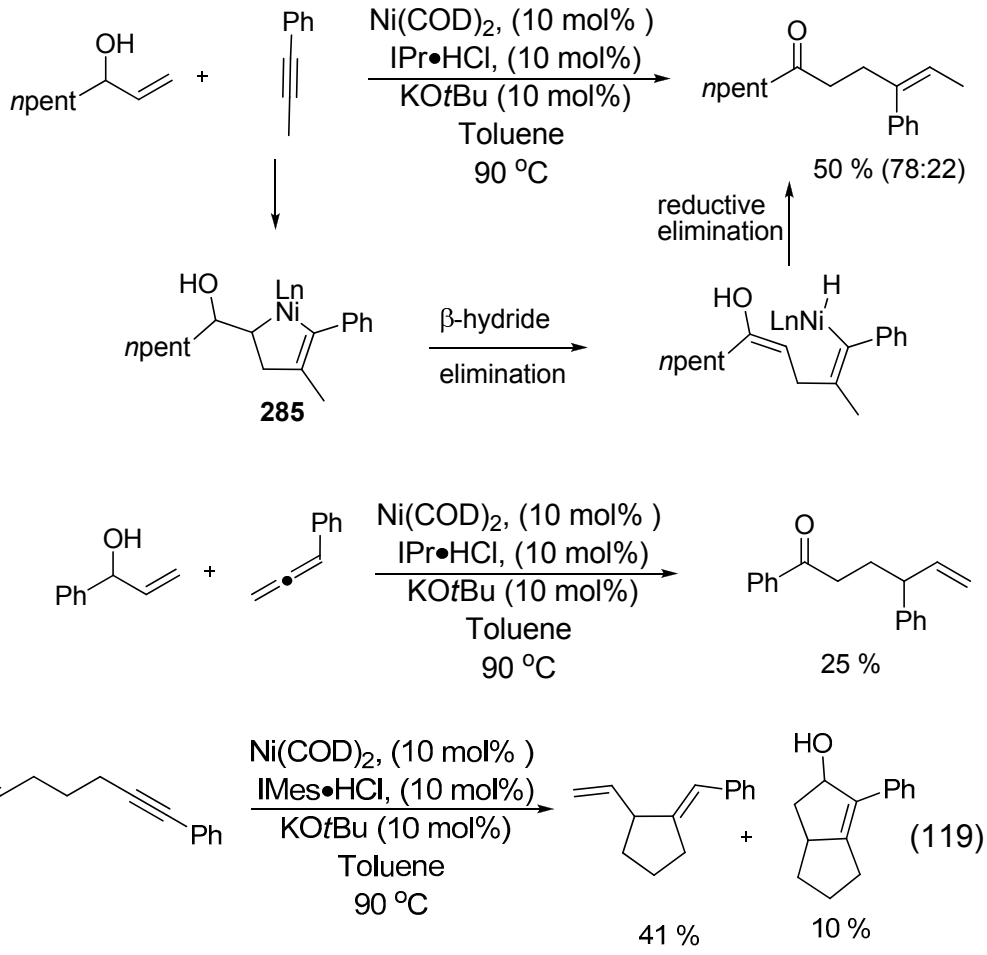
and R_L (Ph) force complexation to occur such that R_L is placed distal to the ligand (**284**), favoring formation of the reversed regioisomer.

Scheme 102. Rationale of Regioselectivity



Additionally, alkynes or allenes could be coupled with secondary allyl alcohols using the reaction condition used in the internal redox process to generate corresponding ketones in moderate yields (Scheme 103). The reaction could occur through *C*-bound metallacycle **285**. The resulting metallacycle **285** could undergo β-hydride elimination followed by reductive elimination to produce the corresponding ketone. However, treatment of a primary allyl alcohol tethered to alkyne with the same reaction condition resulted the formation of 1,4-dienes in moderate yield (eq 119).

Scheme 103. Coupling of Allyl Alcohols with Alkynes and Allenes



3.5 Summary

A novel, nickel-catalyzed intermolecular three-component coupling of aldehydes, alkynes, and enones has been developed. This new process involves an internal redox mechanism and proceeds in the absence of reducing agents that have previously been required in many nickel-catalyzed couplings of these classes. The high extent of chemoselectivity is unusual, particularly for aldehyde, enone, alkyne couplings that involve three different π-components. Moreover, deuterium labeling experiments illustrate a unimolecular hydrogen migration and

rule out alternate mechanisms that could involve a preformed nickel-hydride active catalyst.

CHAPTER 4

EXPERIMENTAL SECTION

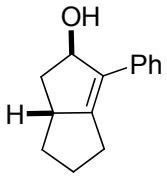
4.1 Reaction Procedures and Spectral Data of Chapter 1

Unless otherwise noted, reagents were commercially available and were used without purification. Tetrahydrofuran (THF) was treated under nitrogen using a solvent purification system (Innovative Technology, Inc., Model # SPS-400-3). Freshly distilled PBu_3 (tributylphosphine) was used in all reactions. $Ni(COD)_2$, DPEphos, and DPPF (Strem Chemicals, Inc., used as received) were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under a nitrogen or argon atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

4.1.1 General Procedure for the $Ni(COD)_2$/DPEphos or DPPF Promoted [3+2] Cycloaddition of Enals and Alkynes

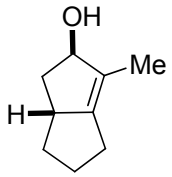
THF (2 mL) was added to a solid mixture of DPEphos or DPPF (0.03 mmol) and $Ni(COD)_2$ (0.03mmol) at rt. After stirring for 5-10 min at rt, the reaction mixture became deep red. A solution of enal or enone (0.3 mmol) at rt. in THF (1.5 mL) and MeOH (0.5 mL) was added, and then Et_3B (1.2 mmol) was added. The reaction mixture was stirred at 50 ^oC until TLC analysis indicated disappearance of the enal. The reaction mixture was concentrated *in vacuo*. The residue was purified via flash chromatography (SiO_2) to afford the desired product.

(2R*,6aR*)-3-Phenyl-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 4, entry 1)



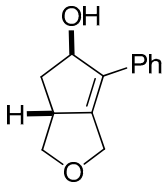
Following the general procedure, (*E*)-8-phenyloct-2-en-7-ynal (51 mg, 0.26 mmol), $Ni(COD)_2$ (7 mg, 0.026 mmol), DPEphos (14 mg, 0.026 mmol), and Et_3B (149 µL, 1.03 mmol) were stirred for 3 h at 50°C. The product (45 mg, 87%) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes). Spectroscopic data were identical to that previously reported data.[63]

(2R*,6aR*)-3-Methyl-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 4, entry 2)



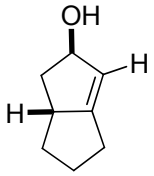
Following the general procedure, (*E*)-non-2-en-7-ynal (31 mg, 0.24 mmol), $Ni(COD)_2$ (7 mg, 0.023 mmol), DPEphos (12 mg, 0.023 mmol), and Et_3B (132 µL, 0.91 mmol) were stirred for 3 h at 50°C. The product (25 mg, 78%) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes). Spectroscopic data were identical to that previously reported data.[63]

(3aR*,5R*)-6-Phenyl-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan-5-ol (Table 4, entry 4)



Following the general procedure, (*E*)-4-(3-phenylprop-2-ynyloxy)but-2-enal (40 mg, 0.20 mmol), $Ni(COD)_2$ (6 mg, 0.02 mmol), DPEphos (11 mg, 0.02 mmol), and Et_3B (145 µL, 1.0 mmol) were stirred for 2 h at 50°C. The product (18 mg, 44 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes). Spectroscopic data were identical to that previously reported data.[63]

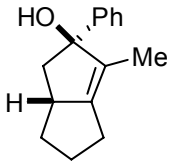
(2R*,6aR*)-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 4, entry 5)



Following the general procedure, (*E*)-oct-2-en-7-ynal (61 mg, 0.50 mmol), $Ni(COD)_2$ (14 mg, 0.05 mmol), DPEphos (27 mg, 0.05 mmol), and Et_3B (290 µL, 2.0 mmol) were stirred for 20 min at 50°C. The product (44 mg, 62 %) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H

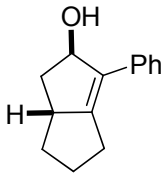
NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.95 (d, *J* = 4.8 Hz, 1H), 3.12 (m, 1H), 2.27 (m, 1H), 2.16 (dt, *J* = 6.8, 12.4 Hz, 1H), 2.06-1.92 (m, 4H), 1.68 (dt, *J* = 5.6, 10.8 Hz, 1H), 1.52 (bs, 1H), 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 120.2, 82.9, 49.5, 41.1, 31.9, 28.4, 23.6; IR (film,cm^{-1}) 3335, 2941, 1695, 1447; HRMS (EI) *m/z* calcd for $C_8H_{12}O$ [M^+] 124.0888, found 124.0883.

(2S*,6aR*)-3-methyl-2-phenyl-1,2,4,5,6,6a-hexahydropentalen-2ol (Table 4, entry 6)



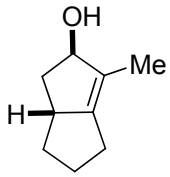
Following the general procedure, (E)-9-phenylnon-3-en-8-yn-2-one (59 mg, 0.28 mmol), $Ni(COD)_2$ (15 mg, 0.06 mmol), DPEphos (30 mg, 0.06 mmol), and Et_3B (201 µL, 1.4 mmol) were stirred for 30 min at 50°C. The product (44 mg, 74 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 3.00 (ddd, *J* = 2.0, 8.8, 16.4 Hz, 1H), 2.45 (m, 1H), 2.30 (dd, *J* = 2.0, 16.4 Hz, 1H), 2.15 (m, 1H), 1.93 (m, 1H), 1.87 (t, *J* = 2.0 Hz, 3H), 1.82-1.74 (m, 3H), 1.58 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 136.7, 128.1, 127.8, 126.7, 98.2, 48.3, 41.9, 38.5, 34.8, 25.5, 11.1; IR (film,cm^{-1}) 3333, 3024, 1695, 1447; HRMS (EI) *m/z* calcd for $C_{15}H_{18}O$ [M^+] 214.1358, found 214.1350.

(2R*,6aR*)-3-Phenyl-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 5, entry 1)



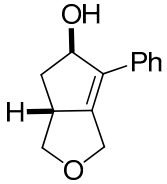
Following the general procedure, (*E*)-8-phenyloct-2-en-7-ynal (68 mg, 0.34 mmol), $Ni(COD)_2$ (9 mg, 0.034 mmol), DPPF (19 mg, 0.034 mmol), and Et_3B (246 µL, 1.7 mmol) were stirred for 1h at 50°C. The product (56 mg, 82%) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

(2R*,6aR*)-3-Methyl-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 5, entry 2)



Following the general procedure, (*E*)-non-2-en-7-ynal (44 mg, 0.32 mmol), $Ni(COD)_2$ (9 mg, 0.032 mmol), DPPF (18 mg, 0.032 mmol), and Et_3B (142 µL, 0.97 mmol) were stirred for 1h at 50°C. The product (34 mg, 76 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

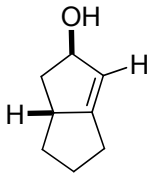
(3aR*,5R*)-6-Phenyl-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan-5-ol (Table 5, entry 4)



Following the general procedure, (*E*)-4-(3-phenylprop-2-ynyloxy)but-2-enal (54 mg, 0.27 mmol), $Ni(COD)_2$ (7 mg, 0.027 mmol), DPPF (14 mg, 0.027 mmol), and Et_3B (117 µL, 0.81 mmol) were stirred for 1h at 50°C. The product (34 mg,

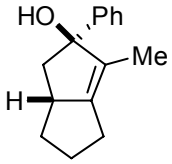
62 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

(2R*,6aR*)-1,2,4,5,6,6a-hexahydropentalen-2-ol (Table 5, entry 5)



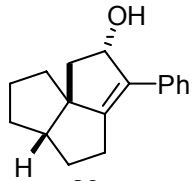
Following the general procedure, (*E*)-oct-2-en-7-ynal (28 mg, 0.23 mmol), $Ni(COD)_2$ (6 mg, 0.023 mmol), DPEphos (13 mg, 0.023 mmol), and Et_3B (100 µL, 0.69 mmol) were stirred for 2h at 50°C. The product (15 mg, 52 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

(2S*,6aR*)-3-methyl-2-phenyl-1,2,4,5,6,6a-hexahydropentalen-2ol (Table 5, entry 6)



Following the general procedure, (E)-9-phenylnon-3-en-8-yn-2-one (50 mg, 0.24 mmol), $Ni(COD)_2$ (6 mg, 0.024 mmol), DPPF (13 mg, 0.024 mmol), and Et_3B (100 µL, 0.69 mmol) were stirred for 3h at 50°C. The product (31 mg, 60 %) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

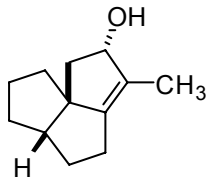
3-Phenyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol



86a

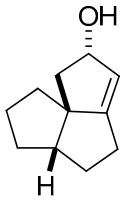
Following the general procedure, aldehyde **85a** (38 mg, 0.16 mmol), $Ni(COD)_2$ (4 mg, 0.016 mmol), DPEphos(10 mg, 0.016 mmol), and Et_3B (92 µL, 0.64 mmol) were stirred for 3h at 50°C. The product (28 mg, 74 %) was obtained as white solid after SiO_2 chromatography (30 % Et_2O in Hexanes). Spectroscopic data were identical to that previously reported and the structural assignment was confirmed by single crystal X-Ray analysis.[63]

3-Methyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol



86b

Following the general procedure, aldehyde **85b** (40 mg, 0.23 mmol), $Ni(COD)_2$ (6 mg, 0.02 mmol), DPEphos (12 mg, 0.02 mmol), and Et_3B (164 µL, 1.14 mmol) were stirred for 2h at 50°C. The product (32 mg, 79 %) was obtained as light yellow color oil after SiO_2 chromatography (30 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (d, *J* = 6.4 Hz, 1H), 2.11 (m, 2H), 1.95 (m, 4H), 1.82-1.72 (m, 3H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.68-1.54 (m, 3H), 1.44 (s, 1H), 1.33 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 127.6, 85.4, 64.1, 49.7, 47.7, 41.6, 35.4, 35.2, 27.6, 22.9, 12.4; IR (film,cm^{-1}) 3333, 2942, 1699, 1447; HRMS (EI) *m/z* calcd for $C_{12}H_{18}O$ [M^+] 178.1358, found 178.1350. NOE data were consistent with the proposed structure and the assignment was deemed secure by similarity of ^1H NMR J values and chemical shifts to compound **86a**.



86c

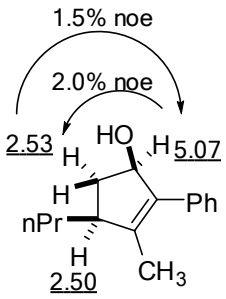
Following the general procedure, aldehyde **85c** (35 mg, 0.22 mmol), $Ni(COD)_2$ (6 mg, 0.02 mmol), DPEphos (12 mg, 0.02 mmol), and Et_3B (164 µL, 1.14 mmol) were stirred for 3h at 50°C. The product (22 mg, 60 %) was obtained as a colorless oil after SiO_2 chromatography (30 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (t, *J* = 2.4 Hz, 1H), 4.82 (s, 1H), 2.26-2.13 (m, 2H), 2.03-1.56 (m, 10H), 1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 119.6, 81.2, 63.8, 50.3, 47.4, 42.0, 35.4, 35.3, 27.8, 24.8; IR (film,cm^{-1}) 3335, 2941, 1698, 1447.

4.1.2 General Procedure for the $Ni(COD)_2/PBu_3$ Promoted [3+2] Cycloaddition of Enals and Alkynes

To a solution of $Ni(COD)_2$ (0.03 mmol) in THF (0.6 mL) was added dropwise tributylphosphine (PBu_3) (0.06 mmol) at room temperature. After stirring for 5-10 min at rt, the reaction mixture became bright yellow. A solution of enal (0.3 mmol) and alkyne (0.6 mmol) at rt. in MeOH (4.4 mL) was added, and then Et_3B (1.2 mmol) was added. The reaction mixture was stirred at 50 ^oC until TLC analysis indicated disappearance of the enal. The reaction mixture was concentrated *in vacuo*. The residue was purified via flash chromatography (SiO_2) to afford the desired product. Diastereomeric ratios were determined on crude reaction mixtures using NMR, GC or GC-MS. GC's with FID detection were

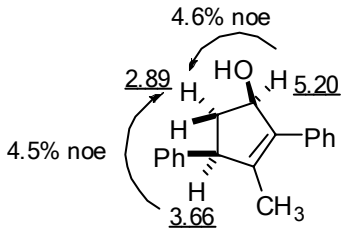
carried on an Agilent 6890N Network GC System with a HP-5MS column (30m x 0.252 mm x 0.25 μm). GCMS analyses were carried on a HP 6890 Series GC System with a HP-5MS column (30m x 0.252 mm x 0.25 μm).

(1R*,4R*)-3-Methyl-2-phenyl-4-propylcyclopent-2-enol (Table 8, entry 1)



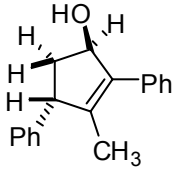
Following the general procedure, *trans*-2-hexen-1-al (35 μL, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (174 μL, 1.20 mmol) were stirred for 1 h at 50°C. The product (55 mg, 85%, dr 87:13) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 87:13 product ratio (major isomer 1H signal at 5.07 ppm; minor isomer 1H signal at 5.00 ppm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 4H), 7.23-7.19 (m, 1H), 5.07 (m, 1H), 2.53 (dt, *J* = 12.8, 7.6 Hz, 1H), 2.50 (m, 1H), 1.75 (s, 3H), 1.72 (m, 1H), 1.57 (bs, 1H), 1.46-1.21 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 138.5, 136.2, 128.4, 128.3, 126.6, 78.2, 47.7, 38.5, 36.8, 20.6, 14.3, 14.1; IR(film, cm^{-1}) 3388, 2956, 1598, 1442; HRMS (EI) *m/z* calcd for $C_{15}H_{20}O$ [M^+] 216.1514, found 216.1509. The structural assignment of the product was confirmed by Dess-Martin oxidation followed by L-selectride reduction[1] to re-afford the cis isomer.

(1R*,4R*)-3-Methyl-2,4-diphenylcyclopent-2-enol (Major, Table 8, entry 2)



Following the general procedure, *trans*-cinnamaldehyde (41 mg, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 3 h at 50°C. The product (42 mg, 56%, dr 81:19) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 10H), 5.20 (m, 1H), 3.66 (t, *J* = 7.2 Hz, 1H), 2.89 (ddd, *J* = 13.9, 7.8, 8.4 Hz, 1H), 1.76 (ddd, *J* = 13.9, 4.8, 6.0 Hz, 1H), 1.73 (bs, 1H), 1.59 (t, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 140.9, 140.1, 136.0, 128.6, 128.5, 128.4, 128.0, 127.0, 126.4, 78.4, 54.6, 42.4, 14.5; IR(film, cm^{-1}) 3400, 3024, 1599, 1494; HRMS (EI) *m/z* calcd for $C_{18}H_{18}O$ [M^+] 250.1358, found 250.1366.

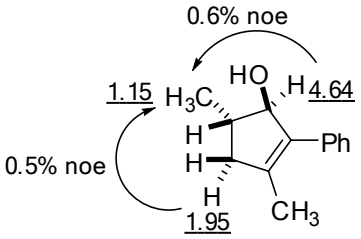
(1R*,4S*)-3-Methyl-2,4-diphenylcyclopent-2-enol (Minor, Table 8, entry 2)



^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.12 (m, 10H), 5.30 (m, 1H), 4.02 (t, *J* = 6.8 Hz, 1H), 2.31 (m, 2H), 1.77 (bs, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

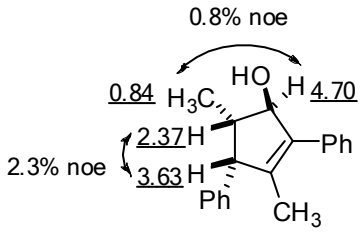
δ 144.5, 142.0, 139.8, 136.1, 128.6, 128.44, 128.37, 127.6, 127.0, 126.4, 79.3, 54.8, 43.4, 14.2; IR(film, cm^{-1}) 3400, 3024, 1599, 1494; HRMS (EI) *m/z* calcd for $C_{18}H_{18}O$ [M^+] 250.1358, found 250.1366.

(1R*,5S*)-3,5-Dimethyl-2-phenylcyclopent-2-enol (Table 8, entry 3)



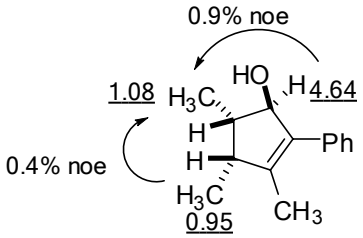
Following the general procedure, methacrolein (25 μL, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (174 μL, 1.20 mmol) were stirred for 15 minutes at 50°C. The product (45 mg, 80%, dr 90:10) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 90:10 product ratio (major isomer 1H signal at 4.64 ppm; minor isomer 1H signal at 4.80 ppm). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 4H), 7.21 (m, 1H), 4.64 (m, 1H), 2.75 (dd, *J* = 8.0, 16.8 Hz, 1H), 2.11 (m, 1H), 1.95 (ddt, *J* = 16.8 , 5.6 , 1.2 Hz, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.62 (bs, 1H), 1.15 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.5, 136.3, 128.30, 128.28, 126.6, 86.8, 44.6, 40.9, 19.2, 15.7; IR (film,cm^{-1}) 3366, 2954, 1599, 1440; HRMS (EI) *m/z* calcd for $C_{13}H_{16}O$ [M^+] 188.1201, found 188.1209.

(1R*,4S*,5S*)-3,5-Dimethyl-2,4-diphenylcyclopent-2-enol (Table 8, entry 4)



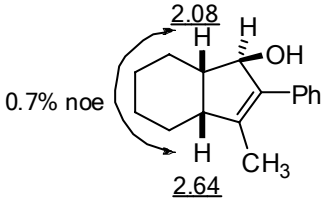
Following the general procedure, α-methyl-*trans*-cinamaldehyde (44 mg, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 5h at 50°C. The product (45 mg, 57%, dr 81:11:8) was obtained as a white solid after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 81:11:8 product ratio (major isomer 1H signal at 4.70 ppm; minor isomers 1H signal at 4.80 ppm and 4.65 ppm). ^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.18-7.06(m, 4H), 6.95 (d, *J* = 6.8 Hz, 2H), 4.70 (m, 1H), 3.63 (d, *J* = 8.8 Hz, 1H), 2.37 (m, 1H), 1.57 (d, *J* = 0.4 Hz, 3H), 1.16 (d, *J* = 5.6 Hz, 1H), 0.84 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 140.2, 140.1, 135.8, 128.9, 128.4, 128.3, 127.0, 126.5, 84.6, 58.5, 46.3, 14.8, 14.6; IR (film, cm^{-1}) 3311, 2872, 1599, 1493; HRMS (ESI) m/z calcd for $C_{19}H_{20}ONa$ $[M+Na]^+$ 287.1412, found 287.1411.

(1R*,4S*,5S*)-3,4,5-Trimethyl-2-phenylcyclopent-2-enol (Table 8, entry 5)



Following the general procedure, *trans*-2-methyl-2-butenal (29 µL, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 2h at 50°C. The product (45 mg, 75%, dr 71:17:12) was obtained as a white solid after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 71:17:12 product ratio (major isomer 1H signal at 4.64 ppm; minor isomers 1H signal at 5.12 ppm and 4.70 ppm). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H), 7.23-7.19 (m, 1H), 4.64 (dt, *J* = 5.6, 1.6 Hz, 1H), 2.71 (quint, *J* = 7.2 Hz, 1H), 2.14 (dquint, *J* = 7.2, 6.0 Hz, 1H), 1.76 (t, *J* = 1.2 Hz, 3H), 1.54 (bs, 1H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 137.4, 136.4, 128.3, 128.2, 126.6, 84.7, 45.1, 44.5, 13.8, 13.6, 13.5**;** IR (film,cm^{-1}) 3118, 2960, 1646, 1449; HRMS (ESI) m/z calcd for $C_{14}H_{18}ONa$ $[M+Na]^+$ 225.1255, found 225.1246.

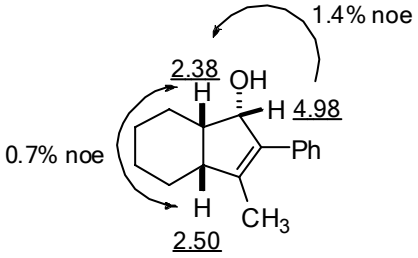
(1R*,3aR*,7aS*)-3-Methyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-ol (Major, Table 8, entry 6)



Following the general procedure, 1-cyclohexene-1-carboxaldehyde (34µL, 0.30 mmol), 1-phenyl-1-propyne (70 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 2h at 50°C. The product (47 mg, 68%, dr 87:13) was obtained as a white solid after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ

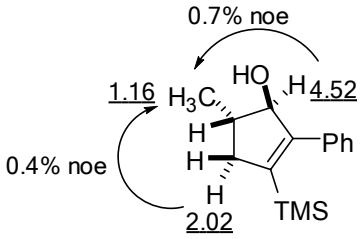
7.35-7.28 (m, 4H), 7.20 (m, 1H), 4.74 (m, 1H), 2.64 (q, *J* = 6.8 Hz, 1H), 2.08 (quint, *J* = 6.4 Hz, 1H), 1.81 (m, 1H), 1.78 (s, 3H), 1.71-1.53 (m, 2H), 1.52-1.36 (m, 4H), 1.34-1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.4, 136.7, 128.24, 128.22, 126.5, 81.3, 46.4, 45.6, 28.2, 25.3, 23.8, 23.2, 13.7; IR(film,cm^{-1}) 3116, 2917, 1646, 1493; HRMS (ESI) m/z calcd for $C_{16}H_{20}ONa$ $[M+Na]^+$ 251.1412 found 251.1409. The structural assignment of the product was confirmed by Dess-Martin oxidation followed by L-selectride reduction[1] to re-afford the same compound as the minor product of the catalytic reaction.

(1S*,3aR*,7aS*)-3-Methyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-ol (Minor, Table 8, entry 6)



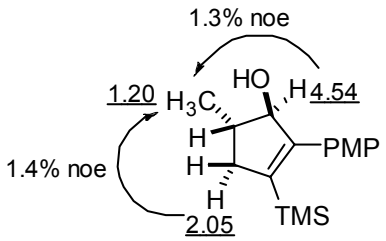
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 4H), 7.25 (m, 1H), 4.98 (m, 1H), 2.50 (q, *J* = 6.4 Hz, 1H), 2.38 (quint, *J* = 7.2 Hz, 1H), 1.83 (m, 3H), 1.80 (m, 1H), 1.61 (m, 4H), 1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 138.2, 136.6, 128.4, 128.2, 126.5, 81.0, 46.2, 41.2, 28.1, 24.3, 23.5, 22.6, 13.6; IR(film,cm^{-1}) 3116, 2917, 1646, 1493; HRMS (ESI) m/z calcd for $C_{16}H_{20}ONa$ $[M+Na]^+$ 251.1412, found 251.1409.

(1R*,5S*)-5-Methyl-2-phenyl-3-(trimethylsilyl)cyclopent-2-enol (Table 9, entry 1)



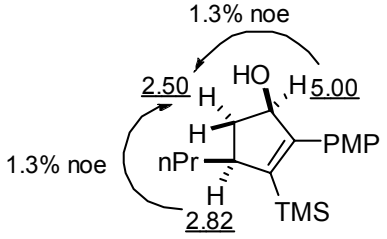
Following the general procedure, methacrolein (25 µL, 0.30 mmol), 1-phenyl-2-(trimethylsilyl)acetylene (118 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 1h at 50°C. The product (45 mg, 60%, dr 82:18) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). GCMS analysis of the crude reaction mixture (start temp. 70 ^oC, end temp. 250 ^oC, 10 ^oC/ min) indicated an 82:18 product ratio (major isomer retention time = 13.3 min; minor isomer retention time = 13.5 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 4.52 (d, *J* = 5.2 Hz, 1H), 2.73 (ddd, *J* = 1.6, 7.6, 16 Hz, 1H), 2.12 (sept, *J* = 6.8 Hz, 1H), 2.02 (ddd, *J* = 1.6 ,16.0, 6.8 Hz, 1H), 1.56 (bs, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), -0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 141.4, 138.4, 128.5, 128.0, 127.2, 88.4, 43.3, 42.5, 18.6, -0.9; IR (film,cm^{-1}) 3332, 2954, 1591, 1442, 1248; HRMS (EI) *m/z* calcd for $C_{15}H_{22}OSi$ [M^+] 246.1440, found 246.1437.

(1R*,5S*)-2-(4-Methoxyphenyl)-5-methyl-3-(trimethylsilyl)cyclopent-2-enol (Table 9, entry 2)



Following the general procedure, methacrolein (25 µL, 0.30 mmol), (4-methoxyphenylethynyl)trimethylsilane (130 µL, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 2h at 50°C. The product (57 mg, 69 %, dr 90:10) was obtained as light yellow oil after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 90:10 product ratio (major isomer 1H signal at 4.54 ppm; minor isomer 1H signal at 4.60 ppm). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 2H), 6.87 (m, 2H), 4.54 (d, *J* = 5.6 Hz, 1H), 3.82 (s, 3H), 2.76 (ddd, *J* = 1.6, 7.6, 16.0 Hz, 1H), 2.14 (sept, *J* = 6.8 Hz, 1H), 2.05 (ddd, *J* = 1.6, 16.4, 6.8 Hz, 1H), 1.57 (bs, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), -0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 154.5, 140.5, 130.6, 129.6, 113.4, 88.3, 55.2, 43.2, 42.5, 18.6, -0.8; IR (film,cm^{-1}) 3365, 2954, 1612, 1508, 1247; HRMS (EI) *m/z* calcd for $C_{16}H_{24}O_2Si$ [M^+] 276.1546, found 276.1543.

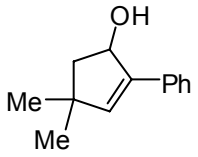
(1R*,4S*)-2-(4-Methoxyphenyl)-4-propyl-3-(trimethylsilyl)cyclopent-2-enol (Table 9, entry 3)



Following the general procedure, *trans*-2-hexen-1-al (35 µL, 0.30 mmol), (4-methoxyphenylethynyl)trimethylsilane (130 µL, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 4h at 50°C. The product (71 mg, 78 %, dr 92:8) was obtained as light yellow oil after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the

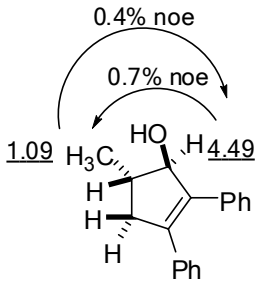
crude reaction mixture indicated a 92:8 product ratio (major isomer 1H signal at 5.00 ppm; minor isomer 1H signal at 4.88 ppm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 2H), 6.88 (m, 2H), 5.00 (m, 1H), 3.83 (s, 3H), 2.83 (m, 1H), 2.50 (dt, *J* = 14.0, 8.0 Hz, 1H), 1.72 (m, 1H), 1.54-1.44 (m, 2H), 1.36-1.20 (m, 3H), 0.96 (t, *J* = 7.2 Hz, 3H), -0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.0, 145.6, 130.5, 129.8, 113.5, 81.0, 55.2, 49.0, 39.6, 38.6, 20.8, 14.2, 0.1; IR (film,cm^{-1}) 3425, 2956, 1612, 1508, 1247; HRMS (ESI) m/z calcd for $C_{18}H_{28}O_2SiNa$ $[M+Na]^+$ 327.1756, found 327.1758.

4,4-Dimethyl-2-phenylcyclopent-2-enol (Table 9, entry 4)



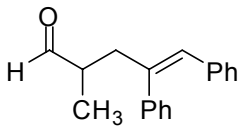
Following the general procedure, 3-methyl-2-buten-1-al (30 µL, 0.30 mmol), phenylacetylene (67 µL, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 8h at 50°C. The product (34 mg, 60 %) was obtained as yellow oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.36 (m, 2H), 7.27 (m, 1H), 6.13 (s, 1H), 5.28 (dd, *J* = 3.2, 7.2 Hz, 1H), 2.27 (dd, *J* = 7.2, 14.0 Hz, 1H), 1.81 (dd, *J* = 3.2, 13.6 Hz, 1H), 1.60 (bs, 1H), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.4, 134.6, 128.5, 127.4, 126.2, 77.1, 49.5, 43.6, 30.3, 29.2; IR (film,cm^{-1}) 3351, 2951, 1598, 1446; HRMS (ESI) m/z calcd for $C_{13}H_{16}ONa$ $[M+Na]^+$ 211.1099, found 211.1096.

(1R*, 5S*)-5-Methyl-2,3-diphenylcyclopent-2-enol (Table 9, entry 5)



Following the general procedure, methacrolein (25 μL, 0.30 mmol), diphenylacetylene (107 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (174 μL, 1.20 mmol) were stirred for 2h at 50°C. The product (23 mg, 30 %, dr 84:16) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). NMR analysis of the crude reaction mixture indicated an 84:16 product ratio (major isomer 1H signal at 4.49 ppm; minor isomer 1H signal at 4.66 ppm). ^1H NMR (400 MHz, C_6D_6) δ 7.32-6.95 (m, 10H), 4.49 (m, 1H), 2.93 (m, 1H), 2.14 (m, 2H), 1.33 (d, 1H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.6, 139.3, 138.3, 137.6, 129.7, 129.0,128.9, 128.7, 127.8, 127.6, 87.9, 43.4, 41.6, 19.3; IR (film,cm^{-1}) 3344, 2954, 1598, 1492, 1443; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}ONa$ $[M+Na]^+$ 273.1255, found 273.1258.

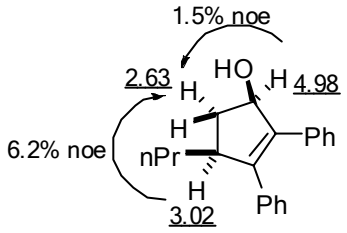
(Z)-2-Methyl-4,5-diphenylpent-4-enal (Table 9, entry 5)



Following the general procedure, methacrolein (25 μL, 0.30 mmol), diphenylacetylene (107 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (174 μL, 1.20 mmol) were stirred for 2h at 50°C. The

product (45 mg, 60 %) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 1.6 Hz, 1H), 7.30-7.22 (m, 3H), 7.13 (m, 2H), 7.07 (m, 3H), 6.90 (m, 2H), 6.46 (s, 1H), 3.00 (ddd, *J* = 1.2, 5.6, 13.6 Hz, 1H), 2.42 (ddd, *J* = 0.8, 8.8, 13.6 Hz, 1H), 2.34 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 139.8, 139.4, 136.8, 129.0, 128.80,128.77, 128.6, 127.9, 127.4, 126.5, 44.2, 41.6, 13.0; IR (film,cm^{-1}) 2930, 2718, 1722, 1599, 1442; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}ONa$ $[M+Na]^+$ 273.1255, found 273.1255.

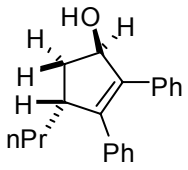
(1R*,4R*)-2,3-Diphenyl-4-propylcyclopent-2-enol (Major, Table 9, entry 6)



Following the general procedure, *trans*-2-hexen-1-al (35 µL, 0.30 mmol), phenyacetylene (107 mg, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 1h at 50°C. The product (62 mg, 74 %, dr 82:18) was obtained as white solid after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.09 (m, 10H), 4.98 (dt, *J* = 3.6, 7.2 Hz, 1H), 3.02 (septet, *J* = 4.0 Hz, 1H), 2.63 (dt, *J* = 14.0, 8.0 Hz, 1H), 1.81 (d, *J* = 6.8 Hz, 1H), 1.66 (dt, *J* = 13.6, 4.0 Hz, 1H), 1.60-1.50 (m, 1H), 1.40 (m, 1H), 1.32-1.19 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 139.2, 137.2, 136.5, 128.8, 128.7, 128.1, 128.0, 127.0, 126.8, 79.9, 47.2, 38.7, 37.3, 21.0, 14.1; IR (film,cm^{-1}) 3364, 2955, 1612,

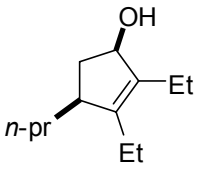
1442; HRMS (ESI) m/z calcd for $C_{20}H_{22}ONa$ $[M+Na]^+$ 301.1568, found 301.1557. The structural assignment of the product was confirmed by Dess-Martin oxidation followed by L-selectride reduction[1] to re-afford the cis isomer.

(1R*,4S*)-2,3-Diphenyl-4-propylcyclopent-2-enol (Minor, Table 9, entry 6)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.05 (m, 10H), 5.34 (m, 1H), 3.35 (m, 1H), 2.15 (m, 2H), 1.63 (d, *J* = 4.8 Hz, 1H), 1.45-1.28 (m, 2H), 1.25-1.16 (m, 1H), 1.05 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 139.4, 136.9, 135.4, 128.8, 128.5, 128.3, 128.2, 126.99, 126.95, 79.1, 47.2, 38.7, 36.1, 20.4, 14.2; IR (film,cm^{-1}) 3364, 2955, 1612, 1442; HRMS (ESI) m/z calcd for $C_{20}H_{22}ONa$ $[M+Na]^+$ 301.1568, found 301.1557.

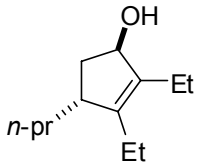
(1R*,4R*)-2,3-Diethyl-4-propylcyclopent-2-enol (Major, Table 9, entry 7)



Following the general procedure, *trans*-2-hexen-1-al (35 µL, 0.30 mmol), 3-hexyne (68 µL, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (174 µL, 1.20 mmol) were stirred for 3h at 50°C. The product (35 mg, 64 %, dr 63:37) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (t, *J* = 5.6 Hz, 1H), 2.48 (m, 1H), 2.42 (dt, *J* = 13.2, 7.6 Hz, 1H), 2.15 (m, 3H), 1.98 (sext, *J* = 7.6 Hz,

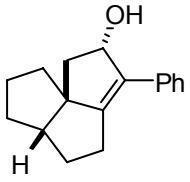
1H), 1.65 (m, 1H), 1.44-1.19 (m, 4H), 1.10 (m, 1H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 138.7, 77.5, 43.7, 39.1, 36.8, 20.7, 19.4, 18.6, 14.3, 13.3, 13.2; IR (film,cm^{-1}) 3325, 2961, 1653, 1559, 1457; HRMS (EI) *m/z* calcd for $C_{12}H_{22}O$ [M^+] 182.1671, found 182.1679.

(1R*,4S*)-2,3-Diethyl-4-propylcyclopent-2-enol (Minor, Table 9, entry 7)



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (bs, 1H), 2.78 (m, 1H), 2.15 (m, 2H), 1.96 (sext, *J* = 7.2 Hz, 1H), 1.82 (m, 2H), 1.60-1.52 (m, 2H), 1.38-1.15 (m, 4H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 138.6, 77.9, 43.6, 39.8, 36.1, 20.3, 19.3, 18.7, 14.3, 13.3, 12.7; IR (film,cm^{-1}) 3325, 2961, 1653, 1559, 1457; HRMS (EI) *m/z* calcd for $C_{12}H_{22}O$ [M^+] 182.1671, found 182.1679.

3-Phenyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol

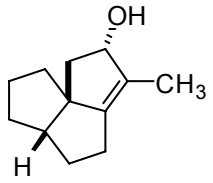


91a

Following the general procedure, 2 [2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetaldehyde[2] (15 mg, 0.064 mmol), $Ni(COD)_2$ (2 mg, 0.006 mmol), PBu_3 (3 µL, 0.012 mmol), and Et_3B (37 µL, 0.26 mmol) were stirred for 3h

at 50°C. The product (11 mg, 72 %) was obtained as white solid after SiO_2 chromatography (30 % Et_2O in Hexanes). Spectroscopic data were identical to that previously reported and the structural assignment was confirmed by single crystal X-Ray analysis.[2]

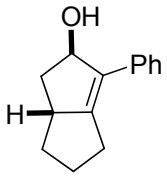
3-Methyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol



91b

Following the general procedure, 2-(2-(pent-3-ynyl)cyclopentylidene)acetaldehyde[2] (70 mg, 0.40 mmol), $Ni(COD)_2$ (11 mg, 0.04 mmol), PBu_3 (19 µL, 0.08 mmol), and Et_3B (232 µL, 1.60 mmol) were stirred for 3h at 50°C. The product (47 mg, 67 %) was obtained as light yellow color oil after SiO_2 chromatography (30 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (d, *J* = 6.4 Hz, 1H), 2.11 (m, 2H), 1.95 (m, 4H), 1.82-1.72 (m, 3H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.68-1.54 (m, 3H), 1.44 (s, 1H), 1.33 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 127.6, 85.4, 64.1, 49.7, 47.7, 41.6, 35.4, 35.2, 27.6, 22.9, 12.4; IR (film,cm^{-1}) 3333, 2942, 1699, 1447; HRMS (EI) *m/z* calcd for $C_{12}H_{18}O$ [M^+] 178.1358, found 178.1350. NOE data were consistent with the proposed structure and the assignment was deemed secure by similarity of ^1H NMR J values and chemical shifts to compound **91a**.

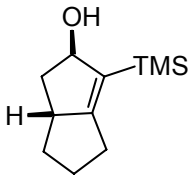
(2R*,6aR*)-3-Phenyl-1,2,4,5,6,6a-hexahydropentalen-2-ol



93a

Following the general procedure, (*E*)-8-phenyloct-2-en-7-ynal (32 mg, 0.16 mmol), $Ni(COD)_2$ (4 mg, 0.016 mmol), PBu_3 (8 µL, 0.032 mmol), and Et_3B (93 µL, 0.64 mmol) were stirred for 30 min at 50°C. The product (27 mg, 84%) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes).

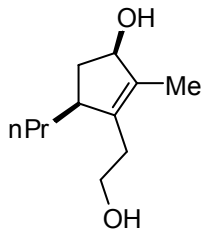
(2R*,6aR*)-3-(trimethylsilyl)-1,2,4,5,6,6a-hexahydropentalen-2-ol



93b

Following the general procedure, (*E*)-8-(trimethylsilyl)oct-2-en-7-ynal (32 mg, 0.16 mmol), $Ni(COD)_2$ (4 mg, 0.016 mmol), PBu_3 (8 µL, 0.032 mmol), and Et_3B (93 µL, 0.64 mmol) were stirred for 2h at 50°C. The product (35 mg, 60%) was obtained as colorless oil after SiO_2 chromatography (20 % EtOAc in Hexanes). Spectroscopic data were identical to that previously reported data.[63]

(1R*,4R*)-2-(2-Hydroxyethyl)-3-methyl-4-propylcyclopent-2-enol



114a

Following the general procedure, *trans*-2-hexen-1-al (35 μL, 0.30 mmol), 3-pentyn-1-ol (55 μL, 0.60 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (174 μL, 1.20 mmol) were stirred for 3h at 50°C. The product (39 mg, 71 %, dr 82:18) was obtained as colorless oil after SiO_2 chromatography (80 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (m, 1H), 3.62 (m, 2H), 2.45 (m, 3H), 2.30 (dt, *J* = 13.6, 6.4 Hz, 1H), 1.72 (d, *J* = 0.8 Hz, 3H), 1.69-1.61 (m, 3H), 1.43-1.05 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.8, 79.5, 61.0, 44.5, 39.0, 36.9, 30.1, 20.6, 14.2, 11.3; IR (film,cm^{-1}) 3328, 2954, 1683, 1456; HRMS (ESI) m/z calcd for $C_{11}H_{20}O_2$ Na $[M+Na]^+$ 207.1361, found 207.1353.

4.2 Reaction Procedures and Spectral Data of Chapter 2

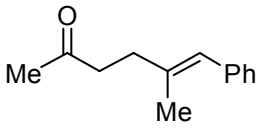
Unless otherwise noted, reagents were commercially available and were used without purification. Enals were distilled prior to use. Tetrahydrofuran (THF) was treated under nitrogen using a solvent purification system (Innovative Technology, Inc., Model # SPS-400-3). Freshly distilled PBu_3 (tributylphosphine) was used in all reactions. $Ni(COD)_2$ and PCy_3 (Strem Chemicals, Inc. and Aldrich, used as received) were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical

shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

4.2.1 General Procedure for the $Ni(COD)_2/PBu_3$ Promoted Reductive Coupling of Enones and Alkynes

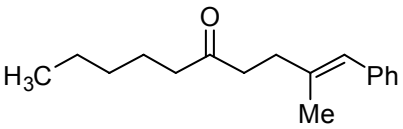
To a solution of $Ni(COD)_2$ (0.03 mmol) in THF (0.6 mL) was added dropwise tributylphosphine (PBu_3) (0.06 mmol) at room temperature. After stirring for 5-10 min at rt, the reaction mixture became bright yellow. A solution of enone (0.3 mmol) and alkyne (0.45 mmol) at rt in MeOH (4.4 mL) was added, and then Et_3B (0.9 mmol) was added. The reaction mixture was stirred at 50 ^oC until TLC analysis indicated disappearance of the enone. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated and residue was purified by column chromatography on silica gel. Regioisomeric ratios were determined on crude reaction mixtures using ^1H NMR. The alkene stereochemistry was determined by NOE for the following examples: Table 14, entries 2, 5, 6, and 7, Table 15, entries 3, 5, and 9 and Table 16, entries 1 and 4. Analysis of coupling constants was satisfactory for the 1,2-disubstituted alkene of Table 15, entry 1.

(*E*)-5-Methyl-6-phenylhex-5-en-2-one (Table 14, entry 1)



Following the general procedure, 3-buten-2-one (25 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at 50 °C. The product (48 mg, 85 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.22 (m, 3H), 6.29 (s, 1H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 1.87 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 138.1, 137.3, 128.7, 128.0, 126.0, 125.3, 42.2, 34.4, 29.9, 17.8; IR (film, cm^{-1}) 3055, 2917, 1714, 1599, 1442; GCMS calcd for $C_{13}H_{16}O$ [M^+] 188, found 188. This compound was previously reported and no spectral data was reported.[1]

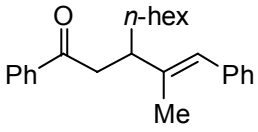
(*E*)-2-Methyl-1-phenyldec-1-en-5-one (Table 14, entry 2)



Following the general procedure, 1-octen-3-one (45 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at 50 °C. The product (57 mg, 78 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m,

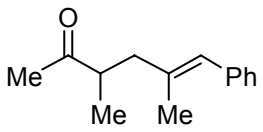
2H), 7.22 (m, 3H), 6.29 (s, 1H), 2.64 (m, 2H), 2.46 (m, 4H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.62 (quint, *J* = 7.2 Hz, 2H), 1.31 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 138.1, 137.5, 128.7, 128.0, 126.0, 125.3, 42.9, 41.2, 34.4, 31.4, 23.5, 22.4, 17.8, 13.9; IR (film, cm^{-1}) 2931, 1715, 1444; HRMS (EI) *m/z* calcd for $C_{17}H_{24}O$ [M+Na]$^+$ 267.1725, found 267.1722.

(*E*)-1-Phenyl-3-(1-phenylprop-1-en-2-yl)nonan-1-one (Table 14, entry 3)



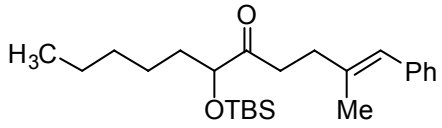
Following the general procedure, (*E*)-1-phenylnon-2-en-1-one (55 mg, 0.25 mmol), 1-phenyl-1-propyne (44 mg, 0.38 mmol), $Ni(COD)_2$ (7 mg, 0.025 mmol), PBu_3 (14 µL, 0.05 mmol), and Et_3B (108 µL, 0.75 mmol) were stirred for 10 h at 50 °C. The product (54 mg, 65 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.49 (m, 2H), 7.32 (m, 2H), 7.20 (m, 3H), 6.30 (s, 1H), 3.10 (m, 2H), 2.91 (quint, *J* = 7.2 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.54 (m, 2H), 1.30 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 139.7, 138.2, 137.4, 132.8, 128.9, 128.5, 128.1, 127.9, 126.6, 125.9, 45.6, 43.4, 33.3, 31.8, 29.3, 27.4, 22.6, 14.2, 14.1; IR (film,cm^{-1}) 3058, 2926, 1684, 1598, 1448; HRMS (ESI) m/z calcd for $C_{24}H_{30}ONa$ [M+Na]$^+$ 357.2194, found 357.2193.

(*E*)-3,5-Dimethyl-6-phenylhex-5-en-2-one (Table 14, entry 4)



Following the general procedure, 3-methyl-3-buten-2-one (29 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at 50 °C. The product (49 mg, 80 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.22 (m, 3H), 6.30 (s, 1H), 2.81 (sext, *J* = 6.8 Hz, 1H), 2.55 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.19 (s, 3H), 2.16 (m, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 138.0, 135.8, 128.8, 128.0, 127.3, 126.1, 45.3, 43.9, 28.3, 17.6, 15.9; IR (film, cm^{-1}) 3055, 2970, 1712, 1599, 1444; HRMS (EI) *m/z* calcd for $C_{14}H_{18}O$ [M^+] 202.1358, found 214.1349.

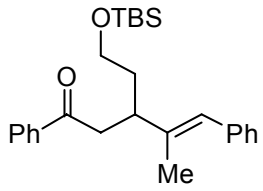
(*E*)-6-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylundec-1-en-5-one (Table 14, entry 5)



Following the general procedure, 4-(*tert*-butyldimethylsilyloxy)non-1-en-3-one (40 mg, 0.15 mmol), 1-phenyl-1-propyne (26 mg, 0.22 mmol), $Ni(COD)_2$ (4 mg, 0.015mmol), PBu_3 (8 μL, 0.03 mmol), and Et_3B (65 μL, 0.45 mmol) were stirred for 1 h at 50 °C. The product (42 mg, 72 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % Et_2O in hexanes). ^1H NMR (400 MHz, C_6D_6) δ 7.34-7.18 (m, 5H), 6.30 (s, 1H), 4.06 (dd, *J* = 6.8, 5.2 Hz, 1H), 2.77 (m, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.87 (d, *J* = 0.8 Hz, 3H), 1.62 (m, 2H), 1.29 (m, 6H), 0.94 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 138.3, 137.8, 128.8, 128.0, 126.0, 125.2, 78.9, 35.9, 34.9, 33.7, 31.7, 25.8, 24.5, 22.4, 18.1, 17.9, 14.0, -4.9; IR (film, cm^{-1}) 3023,

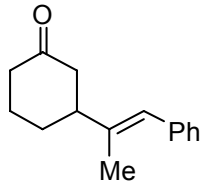
1719, 1462, 1256; HRMS (ESI) m/z calcd for $C_{24}H_{40}O_2SiNa$ $[M+Na]^+$ 411.2695, found 411.2689.

(*E*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-methyl-1,5-diphenylpent-4-en-1-one (Table 14, entry 6)



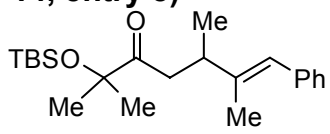
Following the general procedure, (E)-5-hydroxy-1-phenylpent-2-en-1-one (53 mg, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.9 mmol) were stirred for 10 hrs at 50 °C. The product (74 mg, 84 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (50 % Et_2O in hexanes). The alcohol was protected as its TBS ether for characterization. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.30 (m, 2H), 7.18 (m, 3H), 6.28 (s, 1H), 3.65 (m, 2H), 3.11 (m, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.79 (q, *J* = 6.8 Hz, 2H), 0.90 (s, 9H), 0.059 (s, 3H), 0.055 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 139.1, 138.0, 137.2, 132.8, 128.9, 128.5, 128.1, 127.9, 126.8, 126.0, 61.1, 43.3, 42.4, 36.2, 25.9, 18.2, 14.3, -5.3 ; IR (film,cm^{-1}) 3057, 2953, 1686, 1598, 1448; HRMS (ESI) m/z calcd for $C_{26}H_{36}O_2SiNa$ $[M+Na]^+$ 431.2382, found 431.2378.

(*E*)-3-(1-Phenylprop-1-en-2-yl)cyclohexanone (Table 14, entry 7)



Following the general procedure, 2-cyclohexen-1-one (29 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 6 h at 50 °C. The product (52 mg, 80 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.23 (m, 3H), 6.33 (s, 1H), 2.57-2.41 (m, 4H), 2.34 (m, 1H), 2.15 (m, 1H), 2.01 (m, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 140.3, 137.9, 128.9, 128.0, 126.2, 124.8, 48.3, 46.7, 41.2, 30.1, 25.2, 15.7; IR (film,cm^{-1}) 3054, 2937, 1710, 1599; HRMS (EI) *m/z* calcd for $C_{15}H_{18}O$ [M^+] 214.1358, found 214.1358.

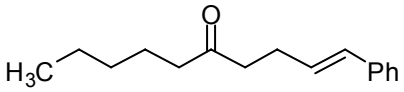
(*E*)-2-(*tert*-butyldimethylsilyloxy)-2,5,6-trimethyl-7-phenylhept-6-en-3-one (Table 14, entry 8)



Following the general procedure, (E)-2-(tert-butyldimethylsilyloxy)-2-methylhex-4-en-3-one (73 mg, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 4h at 50°C. The product (99 mg, 92 %) was obtained as colorless oil after SiO_2 chromatography (5 % Et_2O in Hexanes).^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.13 (m, 5H), 6.30 (s, 1H), 2.80 (m, 3H), 1.81 (d, *J* = 1.6 Hz, 3H), 1.31 (d, *J* = 3.6 Hz, 6H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.12 (d, *J* = 4.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 142.6, 138.4, 128.9, 127.9, 125.8, 124.1, 80.2, 42.1, 38.0, 27.1, 27.0, 25.8, 19.5, 18.1, 15.3, -2.2; IR (film,cm^-

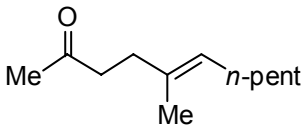
[1]) 3024, 2931, 1720, 1600, 1462; HRMS (ESI) m/z calcd for $C_{22}H_{36}O_2SiNa$ $[M+Na]^+$ 383.2382, found 383.2379.

(*E*)-1-Phenyldec-1-en-5-one (Table 15, entry 1)



Following the general procedure, 1-octen-3-one (45 μL, 0.30 mmol), phenylacetylene (50 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 2 h at 50 °C. The product (51 mg, 74 %, >95:5) was obtained as a yellow oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H), 6.37 (d, *J* = 15.6 Hz, 1H), 6.16 (dt, *J* = 16.0, 6.8 Hz, 1H), 2.54 (m, 2H), 2.46 (m, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.56 (quint, *J* = 7.2 Hz, 2H), 1.24 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 137.4, 130.6, 129.0, 128.4, 127.0, 125.9, 42.9, 42.2, 31.4, 27.1, 23.5, 22.4, 13.9; IR (film, cm^{-1}) 3026, 2930, 1713, 1448; HRMS (EI) *m/z* calcd for $C_{16}H_{22}O$ $[M+Na]^+$ 253.1568, found 253.1569.

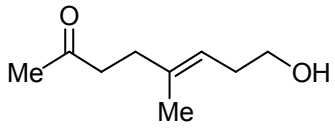
(E)-5-methylundec-5-en-2-one (Table 15, entry 2)



Following the general procedure, 3-buten-2-one (41 μL, 0.50 mmol), 2-octyne (109 μL, 0.75 mmol), $Ni(COD)_2$ (14 mg, 0.05 mmol), PBu_3 (24 μL, 0.01

mmol), and Et_3B (217 µL, 1.50 mmol) were stirred for 3 h at 50°C. The product (38 mg, 42 %, 2:1) was obtained as colorless oil after SiO_2 chromatography (10 % Et2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (q, J = 6.8 Hz, $1H_{min}$), 5.14 (tq, J = 7.2, 1.2 Hz, $1H_{maj}$) 2.52 (m, $2H_{maj}$ + $2H_{min}$), 2.53 (t, J = 8.4 Hz, $2H_{maj}$ + $2H_{min}$), 2.15 (s, $3H_{maj}$ + $3H_{min}$), 1.97 (m, $2H_{maj}$ + $2H_{min}$), 1.60 (s, $3H_{maj}$), 1.57 (d, J = 6.8 Hz, $3H_{min}$), 1.31 (m, $6H_{maj}$ + $6H_{min}$), 0.893 (t, J = 7.2 Hz, $3H_{min}$), 0.887 (t, J = 7.2 Hz, $3H_{maj}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + minor) δ 209.0, 138.8, 133.2, 125.4, 118.8, 42.6, 42.4, 33.6, 31.8, 31.5, 30.7, 30.3, 29.9, 29.8, 29.4, 27.84, 27.79, 22.6, 16.0, 14.1, 13.2; IR(film, cm^{-1}) 2934, 1715, 1442; HRMS (EI) *m/z* calcd for $C_{12}H_{22}ONa$ $[M+Na]^+$ 205.1568, found 205.1561.

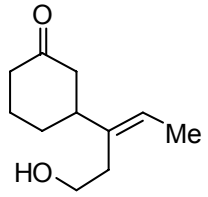
(*E*)-8-Hydroxy-5-methyloct-5-en-2-one (Table 15, entry 3)



Following the general procedure, 3-buten-2-one (25 µL, 0.30 mmol), 3-pentyn-1-ol (42 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.90 mmol) were stirred for 1 h at rt. The product (23 mg, 50 %, 3:1) was obtained as a colorless oil after SiO_2 chromatography (50 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (q, J = 6.8 Hz, $1H_{min}$), 5.14 (t, J = 7.6 Hz, $1H_{maj}$) 3.67 (t, J = 6.4 Hz, $2H_{min}$), 3.61 (t, J = 6.4 Hz, $2H_{maj}$), 2.55 (m, $2H_{maj}$ + $2H_{min}$), 2.28 (m, $4H_{maj}$ + $4H_{min}$), 2.14 (s, $3H_{maj}$ + $3H_{min}$), 1.70 (m, $1H_{maj}$ + $1H_{min}$), 1.64 (s, $3H_{maj}$), 1.62 (d, J = 6.4 Hz, $3H_{min}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + minor) 208.8, 137.0, 134.7, 121.8, 120.7, 62.3, 60.8, 42.1, 33.6, 33.4,

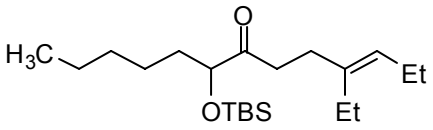
31.4, 30.5, 30.3, 30.0, 29.9, 16.2, 13.4; IR (film, cm^{-1}) 3411, 2933, 1713, 1440; HRMS (CI-NH_3) m/z calcd for $C_9H_{16}O_2$ $[M+H]^+$ 157.1229, found 157.1228.

(*E*)-3-(5-Hydroxypent-2-en-3-yl)cyclohexanone (Table 15, entry 4)



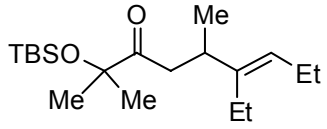
Following the general procedure, 2-cyclohexen-1-one (29 µL, 0.30 mmol), 3-pentyn-1-ol (42 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.90 mmol) were stirred for 5 h at 50 °C. The product (34 mg, 62 %, 53:47) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.42 (q, *J* = 6.8 Hz, $1H_{maj}$), 5.20 (t, *J* = 6.8 Hz, $1H_{min}$) 3.62 (m, $2H_{maj}$ + $2H_{min}$), 2.33 (m, $7H_{maj}$ + $7H_{min}$), 2.06 (m, $1H_{maj}$ + $1H_{min}$), 1.88 (m, $1H_{maj}$ + $1H_{min}$), 1.65 (m, $6H_{maj}$ + $6H_{min}$); ^{13}C NMR (100 MHz, $CDCl_3$) 211.81, 211.8, 140.2, 138.4, 121.5, 120.1, 62.3, 61.2, 47.6, 47.4, 46.8, 45.3, 41.22, 41.2, 32.6, 31.3, 30.8, 30.1, 25.2, 25.1, 14.2, 13.5; IR (film, cm^{-1}) 3410, 2938, 1710, 1448; HRMS (ESI) m/z calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1197.

(*E*)-8-(*tert*-Butyldimethylsilyloxy)-4-ethyltridec-3-en-7-one (Table 15, entry 5)



Following the general procedure, 4-(*tert*-butyldimethylsilyloxy)non-1-en-3-one (40 mg, 0.15 mmol), 3-hexyne (26 µL, 0.22 mmol), $Ni(COD)_2$ (4 mg, 0.015mmol), PBu_3 (8 µL, 0.03 mmol), and Et_3B (65 µL, 0.45 mmol) were stirred for 1 h at 50 °C. The product (38 mg, 72 %) was obtained as a colorless oil after SiO_2 chromatography (5 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.08 (t, *J* = 7.2 Hz, 1H), 4.02 (dd, *J* = 5.2, 7.0 Hz, 1H), 2.64 (m, 2H), 2.22 (t, *J* = 8.0 Hz, 2H), 2.01 (sext, *J* = 7.2 Hz, 4H), 1.58 (m, 2H), 1.28 (m, 6H), 0.99-0.86 (m, 9H), 0.93 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 139.2, 126.2, 78.9, 36.2, 34.9, 31.7, 29.6, 25.7, 24.5, 23.3, 22.5, 20.8, 18.1, 14.6, 14.0, 13.2, -4.92, -4.94; IR (film, cm^{-1}) 2959, 1717, 1463, 1254; HRMS (ESI) m/z calcd for $C_{21}H_{42}O_2SiNa$ $[M+Na]^+$ 377.2852, found 377.2842.

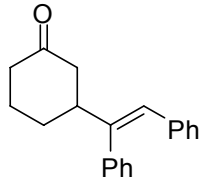
(*E*)-2-(*tert*-butyldimethylsilyloxy)-6-ethyl-2,5-dimethylnon-6-en-3-one (Table 15, entry 6)



Following the general procedure, (E)-2-(tert-butyldimethylsilyloxy)-2-methylhex-4-en-3-one (50 mg, 0.20 mmol), 3-hexyne (34 µL, 0.30 mmol), $Ni(COD)_2$ (6 mg, 0.02 mmol), PBu_3 (12 µL, 0.04 mmol), and Et_3B (87 µL, 0.60 mmol) were stirred for 4h at 50°C. The product (49 mg, 75 %) was obtained as colorless oil after SiO_2 chromatography (5 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) 5.09 (t, *J* = 6.8 Hz, 1H), 2.70 (m, 3H), 2.02 (sext, *J* = 7.2 Hz, 4H), 1.31 (s, 6H), 0.98 (m, 9H), 0.92 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 144.9, 124.9, 80.1, 42.9, 34.5, 27.1, 27.0, 25.8, 22.7, 20.8, 20.3, 18.1,

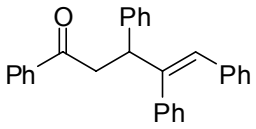
14.6, 14.1, -2.22, -2.25; IR(film,cm-1) 2962, 1721, 1462; HRMS (ESI) m/z calcd for $C_{19}H_{38}O_2SiNa$ $[M+Na]^+$ 349.2539, found 349.2538.

(*Z*)-3-(1,2-diphenylvinyl)cyclohexanone (Table 15, entry 7)



Following the general procedure, 2-cyclohexen-1-one (29 µL, 0.30 mmol), diphenylacetylene (80 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.90 mmol) were stirred for 1 h at 50°C. The product (58 mg, 70 %) was obtained as colorless oil after SiO_2 chromatography (20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.10 (m, 5H), 6.86 (m, 2H), 6.46 (s, 1H), 2.87 (m, 1H), 2.56 (m, 1H), 2.39 (m, 2H), 2.28 (m, 1H), 2.09 (m, 2H) 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 145.0, 139.7, 136.6, 129.0, 128.9, 128.6, 127.8, 127.2, 126.5, 126.3, 48.0, 46.9, 41.1, 30.3, 25.1; IR(film, cm^{-1}) 3022, 2936, 1710, 1598, 1446; HRMS (EI) *m/z* calcd for $C_{20}H_{20}O$ $[M^+]$ 276.1514, found 276.1518.

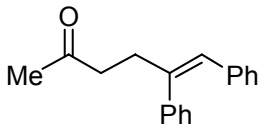
(*Z*)-1,3,4,5-tetraphenylpent-4-en-1-one (Table 15, entry 8)



Following the general procedure, (E)-chalcone (62 mg, 0.30 mmol), diphenylacetylene (80 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.90 mmol) were stirred for 12h at 50°C. The product (76 mg, 65 %) was obtained as white solid after SiO_2 chromatography

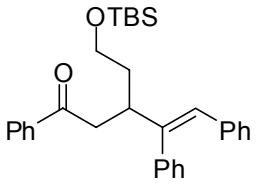
(20 % Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.56 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.46 (m, 2H), 7.30-7.20 (m, 8H), 7.06 (m, 3H), 6.96 (m, 2H), 6.87 (m, 2H), 6.56 (s, 1H), 4.62 (t, *J* = 7.6 Hz, 1H), 3.66 (dd, *J* = 7.2, 16.8 Hz, 1H), 3.50 (dd, *J* = 7.2, 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 144.7, 141.8, 140.4, 137.2, 136.9, 133.0, 129.13, 129.07, 128.6, 128.33, 128.28, 128.0, 127.8, 127.2, 127.0, 126.6, 126.4, 49.7, 42.5; IR (film,cm^{-1}) 3057, 2929, 1684, 1598; HRMS (EI) m/z calcd for $C_{29}H_{24}O$ $[M]^+$ 388.1827, found 388.1826.

(*Z*)-5,6-Diphenylhex-5-en-2-one (Table 15, entry 9)



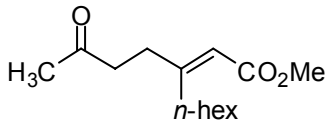
Following the general procedure, 3-buten-2-one (25 µL, 0.30 mmol), diphenylacetylene (80 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.90 mmol) were stirred for 1 h at 50 °C. The product (47 mg, 63 %) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-6.92 (m, 10H), 6.50 (s, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 141.4, 140.3, 137.0, 129.0, 128.62, 128.56, 127.8, 127.1, 126.9, 126.3, 42.0, 34.5, 30.0; IR (film, cm^{-1}) 3019, 2945, 1597, 1442; GCMS calcd for $C_{18}H_{18}O$ $[M^+]$ 250, found 250. Spectral data for this compound was previously reported and matched with the current data.

(*Z*)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,4,5-triphenylpent-4-en-1-one (Table 15, entry 10)



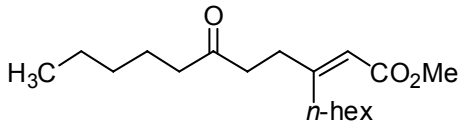
Following the general procedure, (E)-5-hydroxy-1-phenylpent-2-en-1-one (53 mg, 0.30 mmol), diphenylacetylene (80 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.9 mmol) were stirred for 10 hrs at 50 °C. The product (90 mg, 84 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (50 % Et_2O in hexanes). The alcohol was protected as its TBS ether for characterization. ^{1}H NMR (400 MHz, C_6D_6) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34 (m, 2H), 7.21 (dd, t, *J* = 7.6, 1.6 Hz, 2H), 7.10 (m, 3H), 6.88 (m, 2H), 6.52 (s, 1H), 3.82 (m, 2H), 3.48 (m, 1H), 2.28 (dd, *J* = 7.6, 16.0 Hz, 1H), 3.08 (dd, *J* = 6.4, 16.0 Hz, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.3, 144.1, 140.1, 137.2, 137.0, 132.8, 129.3, 129.0, 128.50, 128.48, 128.1, 127.9, 127.7, 127.0, 126.2, 61.0, 43.0, 41.7, 36.3, 25.9, 18.2, -5.3; IR (film,cm^{-1}) 3081, 2928, 1690, 1598, 1447; HRMS (ESI) *m/z* calcd for $C_{31}H_{38}O_2SiNa$ $[M+Na]^+$ 493.2539, found 493.2546.

(*E*)-Methyl 3-(3-oxobutyl)non-2-enoate (Table 16, entry 1)



Following the general procedure, 3-buten-2-one (25 μL, 0.30 mmol), methyl-2-nonynoate (76 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at rt. The product (43 mg, 60 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.67 (s, 3H), 2.58 (m, 4H), 2.42 (m, 2H), 2.17 (s, 3H), 1.42 (m, 2H), 1.29 (m, 6H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 166.6, 163.2, 114.9, 50.8, 41.3, 32.4, 31.7, 31.6, 30.0, 29.5, 28.6, 22.6, 14.0; IR (film,cm^{-1}) 2929, 1722, 1643, 1434, 1148; GCMS calcd for $C_{14}H_{24}O_3$ [M^+] 240, found 240. Spectral data for this compound was previously reported and matched with the current data.

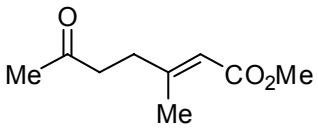
(*E*)-Methyl 3-hexyl-6-oxoundec-2-enoate (Table 16, entry 2)



Following the general procedure, 1-octen-3-one (45 μL, 0.30 mmol), methyl-2-nonynoate (76 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 2 h at rt. The product (67 mg, 76 %, 96:4) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.67 (s, 3H), 2.57 (m, 4H), 2.41 (m, 4H), 1.58 (quint, *J* = 7.6 Hz, 2H), 1.43 (m, 2H), 1.29 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 166.6, 163.4, 114.8, 50.8, 42.9, 40.4, 32.4, 31.8, 31.6, 31.4, 29.5, 28.6, 23.5, 22.6, 22,4, 14.1, 13.9; IR (film,cm^{-1}) 2930, 1720, 1644,

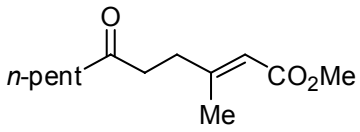
1434, 1149; HRMS (ESI) m/z calcd for $C_{18}H_{32}O_3Na$ $[M+Na]^+$ 319.2249, found 319.2241.

(*E*)-Methyl 3-methyl-6-oxohept-2-enoate (Table 16, entry 3)



Following the general procedure, 3-buten-2-one (25 μL, 0.30 mmol), methyl 2-butynoate (45 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at rt. The product (38 mg, 74 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (q, *J* = 1.2 Hz, 1H), 3.69 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.18 (s, 3H), 2.17 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 166.9, 158.3, 115.5, 50.8, 41.1, 34.2, 30.0, 18.8; IR (film,cm^{-1}) 2958, 1714, 1688, 1462, 1148; HRMS (EI) calcd for $C_9H_{14}O_3$ $[M^+]$ 170.0943, found 170.0945.

(*E*)-Methyl 3-methyl-6-oxoundec-2-enoate (Table 16, entry 4)



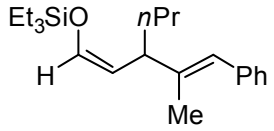
Following the general procedure, 1-octen-3-one (45 μL, 0.30 mmol), methyl 2-butynoate (45 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at rt. The product (49 mg, 72 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (q, *J*

= 1.2 Hz, 1H), 3.68 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 4H), 2.16 (d, *J* = 1.2 Hz, 3H), 1.56 (quint, *J* = 7.2 Hz, 2H), 1.27 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 167.0, 158.6, 115.4, 50.8, 42.9, 40.1, 34.3, 31.3, 23.5, 22.4, 18.5, 13.9; IR (film,cm^{-1}) 2954, 1716, 1650, 1435, 1150; HRMS (EI) *m/z* calcd for $C_{13}H_{22}O_3$ [M^+] 226.1569, found 226.1577.

4.2.2 General Procedure for the $Ni(COD)_2/PCy_3$ Promoted Reductive Coupling of Enals and Alkynes

THF (2 mL) was added to a solid mixture of tricyclohexylphosphine (0.06 mmol), and $Ni(COD)_2$ (0.03 mmol) at rt. The resulting solution was stirred for 5-10 min. Then a solution of enal (0.3 mmol), alkyne (0.45 mmol), and trialkylsilane (0.6 mmol) at rt in THF (2.0 mL) was added. The reaction mixture was stirred at 50 ^{o}C until TLC analysis indicated disappearance of the enal. The reaction mixture was concentrated *in vacuo*. The residue was purified via flash chromatography (SiO_2) to afford the desired product.

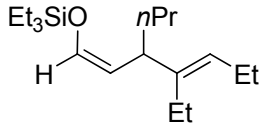
Triethyl((*Z*)-3-((*E*)-1-phenylprop-1-en-2-yl)hex-1-enyloxy)silane (Table 18, entry 1)



Following the general procedure, trans-2-hexenal (35 µL, 0.3 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (90 mg, 91 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 6.35

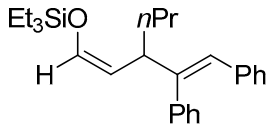
(s, 1H), 6.29 (d, *J* = 5.6 Hz, 1H), 4.47 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.42 (q, *J* = 7.6 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.61-1.29 (m, 4H), 1.02 (t, *J* = 7.6 Hz, 9H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.69 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.0, 138.4, 128.9, 127.9, 125.6, 124.1, 112.9, 43.4, 36.0, 20.6, 15.4, 14.1, 6.6, 4.5; IR (film, cm^{-1}) 3023, 2954, 1651, 1456; HRMS (EI) *m/z* calcd for $C_{21}H_{34}OSi$ [M^+] 330.2379, found 330.2387.

Triethyl((1*Z*,4*E*)-4-ethyl-3-propylhepta-1,4-dienyloxy)silane (Table 18, entry 2)



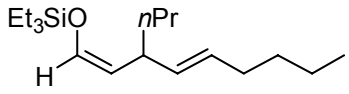
Following the general procedure, trans-2-hexenal (35 µL, 0.3 mmol), 3-hexyne (51 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (67mg, 75 %) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 6.0 Hz, 1H), 5.10(t, *J* = 7.2 Hz, 1H), 4.28 (dd, *J* = 5.6, 9.6 Hz, 1H), 3.24 (q, *J* = 7.2 Hz, 1H), 2.02 (m, 4H), 1.47-1.23 (m, 4H), 1.01-0.96 (m, 12H); 0.95 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.65 (q, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.6,124.8, 114.5, 39.7, 36.6, 22.6, 20.9, 20.7, 14.8, 14.2, 14.1, 6.5, 4.5; IR (film, cm^{-1}) 2958, 1651, 1456; HRMS (CI) *m/z* calcd for $C_{18}H_{36}OSiH$ [M+H] $^+$ 297.2614, found 297.2600.

((*Z*)-3-((*Z*)-1,2-diphenylvinyl)hex-1-enyloxy)triethylsilane (Table 18, entry 3)



Following the general procedure, trans-2-hexenal (35 μL, 0.3 mmol), diphenylacetylene (59 mg, 0.33 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 μL) were stirred for 2 h at 50 °C. The product (89 mg, 76 %) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-6.81 (m, 10H), 6.42 (s, 1H), 6.25 (d, *J* = 6.0 Hz, 1H), 4.37 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.67 (q, *J* = 8.0 Hz, 1H), 1.52-1.23 (m, 4H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.62 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 141.2, 138.5, 137.8, 129.2, 129.0, 128.1, 127.7, 126.5, 125.9, 125.8, 112.7, 43.3, 36.5, 20.6, 14.1, 6.5, 4.5; IR (film, cm^{-1}) 3053, 2955, 1651, 1598, 1456; HRMS (EI) *m/z* calcd for $C_{26}H_{36}OSi$ [M^+] 392.2535, found 392.2532.

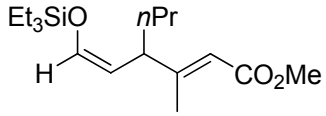
Triethyl((1*Z*,4*E*)-3-propylnona-1,4-dienyloxy)silane (Table 18, entry 4)



Following the general procedure, *trans*-2-hexenal (35 μL, 0.3 mmol), 1-hexyne (42 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 μL) were stirred for 2 h at 50 °C (substrates and triethylsilane were added slowly over 1h as a THF solution). The product (40 mg, 45 %, 80:20) was obtained as a colorless oil after SiO_2

chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, J = 6.0 Hz, $1H_{minor}$), 6.21 (d, J = 6.0 Hz, $1H_{major}$), 5.40 (dt, J = 15.2, 6.4 Hz, $1H_{major}$), 5.59 (dd, J = 7.2, 15.6 Hz, $1H_{major}$), 4.75 (s, $1H_{minor}$), 4.70 (s, $1H_{major}$), 4.30 (dd, J = 6.0, 9.2 Hz, $1H_{major}$), 4.27 (dd, J = 6.0, 8.8 Hz, $1H_{minor}$), 3.24 (m, $1H_{major}$ + $1H_{minor}$), 2.58 (m, $1H_{major}$), 2.41 (q, J = 7.2 Hz, $1H_{minor}$), 2.14 (q, J = 7.2 Hz, $1H_{minor}$), 1.99 (quint, J = 6.8 Hz, $1H_{major}$) , 1.57-1.26 (m, $8H_{major}$+ $8H_{minor}$), 0.99 (t, J = 8.0 Hz, $9H_{major}$+ $9H_{minor}$), 0.95-0.87 (m, $6H_{major}$+ $6H_{minor}$), 066 (q, J = 8.0 Hz, $6H_{major}$+ $6H_{minor}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + minor) δ 137.6, 133.8, 128.7, 114.1, 39.4, 38.1, 36.8, 36.3, 34.6, 32.3, 31.8, 30.3, 22.6, 22.2, 20.6, 20.3, 14.1, 14.0, 6.5, 4.5; IR (film, cm^{-1}) 2955, 1652, 1456; HRMS (EI) *m/z* calcd for $C_{18}H_{36}OSi$ $[M]^+$ 296.2535, found 296.2610.

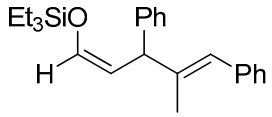
(*E*)-Methyl 3-methyl-4-((*Z*)-2-(triethylsilyloxy)vinyl)hept-2-enoate (Table 18, entry 5)



Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), methyl 2-butynoate (45 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (37 mg, 40 %, 92:8) was obtained as a colorless oil after SiO_2 chromatography (10 % EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (dd, J = 0.8, 5.6 Hz, 1H), 5.72 (t, J = 0.8 Hz, 1H), 4.32 (dd, J = 6.0, 9.2 Hz, 1H), 3.68 (s, 3H), 3.34 (q, J = 8.0 Hz, 1H), 2.13 (d, J = 1.6 Hz, 3H), 1.58-1.21 (m, 4H), 0.97 (t, J = 8.0 Hz, 9H), 0.89 (t, J = 7.2 Hz, 3H), 0.65 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 163.5, 139.6, 114.3, 111.0, 50.7, 43.9, 35.6,

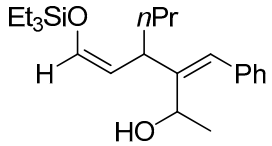
20.4, 16.6, 14.0, 6.5, 4.4; IR (film, cm^{-1}) 2955, 1718, 1647, 1456; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_3SiNa$ $[M+Na]^+$ 335.2018, found 335.2023.

Triethyl((1*Z*,4*E*)-4-methyl-3,5-diphenylpenta-1,4-dienyloxy)silane (Table 18, entry 6)



Following the general procedure, *trans*-cinnamaldehyde (41 mg, 0.30 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (95 mg, 87 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 10H), 6.49 (s, 1H), 6.40 (d, *J* = 5.6 Hz, 1H), 4.88 (dd, *J* = 5.6, 9.6 Hz, 1H), 4.75 (q, *J* = 9.6 Hz, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.67 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.8, 138.9, 138.7, 128.9, 128.2, 128.0, 127.95, 125.92, 125.87, 125.8, 111.2, 48.8, 16.8, 6.5, 4.5; IR (film, cm^{-1}) 3056, 2954, 1648, 1598, 1490; HRMS (EI) *m/z* calcd for $C_{24}H_{32}OSi$ $[M^+]$ 364.2222, found 364.2225.

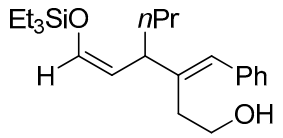
(*Z*)-3-Benzylidene-4-((*Z*)-2-(triethylsilyloxy)vinyl)heptan-2-ol (Table 18, entry 7)



Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), 4-phenyl-3-butyne-2-ol (66 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17

mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (92 mg, 85 %, dr 79:21, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 6.40 (s, 1H), 6.20 (dd, *J* = 1.2, 5.6 Hz, 1H), 4.86 (quint, *J* = 5.6 Hz, 1H), 4.57 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.52 (dt, *J* = 6.0, 8.8 Hz, 1H), 2.91 (d, *J* = 8.0 Hz, 1H), 1.62-1.33 (m, 4H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.71 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 137.6, 137.0, 128.8, 128.0, 126.3, 125.4, 116.3, 66.2, 38.7, 32.4, 22.1, 20.8, 14.1, 6.4, 4.3; IR (film, cm^{-1}) 3499, 3023, 2955, 1650, 1456; HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_2SiNa$ $[M+Na]^+$ 383.2382, found 383.2393.

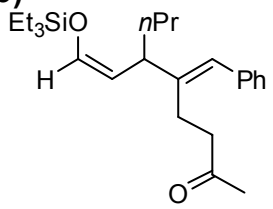
(*E*)-3-Benzylidene-4-((*Z*)-2-(triethylsilyloxy)vinyl)heptan-1-ol (Table 18, entry 8)



Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), 4-phenylbut-3-yn-1-ol (66 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (98 mg, 91 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.48 (s, 1H), 6.29 (d, *J* = 6.0 Hz, 1H), 4.42 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.79 (m, 2H), 3.43 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.62 (quint, *J* = 6.8 Hz, 1H), 2.52 (quint, *J* = 6.8 Hz, 1H), 1.65-1.36 (m, 5H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.68 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.5,

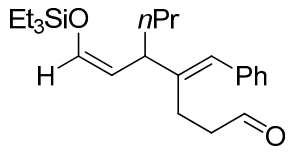
138.4, 128.7, 128.1, 126.8, 126.1, 113.6, 61.4, 39.6, 36.9, 34.0, 20.7, 14.1, 6.5, 4.4; IR (film, cm^{-1}) 3338, 3023, 2954, 1651, 1456; HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_2SiNa$ $[M+Na]^+$ 383.2382, found 383.2372.

(*E*)-5-Benzylidene-6-((*Z*)-2-(triethylsilyloxy)vinyl)nonan-2-one (Table 18, entry 9)



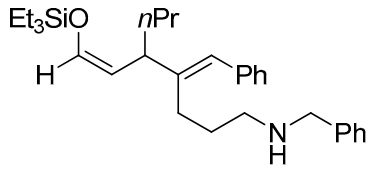
Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), 6-phenylhex-5-yn-2-one (77 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 µL) were stirred for 2 h at 50 °C. The product (75 mg, 65 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (m, 5H), 6.32 (s, 1H), 6.28 (dd, *J* = 0.8, 5.6 Hz, 1H), 4.35 (dd, *J* = 6.0, 9.2 Hz, 1H), 3.34 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.61-2.49 (m, 4H), 2.06 (s, 3H), 1.66-1.24 (m, 4H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.66 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208, 145.3, 138.51, 138.47, 128.4, 128.1, 126.0, 124.6, 113.3, 42.8, 40.1, 36.6, 29.6, 24.8, 20.7, 14.1, 6.5, 4.4; IR (film, cm^{-1}) 3023, 2955, 1717, 1651, 1456; HRMS (ESI) *m/z* calcd for $C_{24}H_{38}O_2SiNa$ $[M+Na]^+$ 409.2539, found 409.2520.

(*E*)-4-Benzylidene-5-((*Z*)-2-(triethylsilyloxy)vinyl)octanal (Table 18, entry 10)



Following the general procedure, *trans*-2-hexenal (35 μL, 0.3 mmol), 5-phenylpent-4-ynal (71 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triethylsilane (0.6 mmol, 96 μL) were stirred for 2 h at 50 °C. The product (67 mg, 60 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (10 % EtOAc in hexanes).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.33-7.17 (m, 5H), 6.37 (s, 1H), 6.30 (dd, *J* = 0.8, 6.0 Hz, 1H), 4.35 (dd, *J* = 5.6, 9.6 Hz, 1H), 3.37 (dt, *J* = 5.6, 8.8 Hz, 1H), 2.59 (s, 4H), 1.64-1.27 (m, 4H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.68 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 144.7, 138.7, 138.4, 128.4, 128.2, 126.1, 124.9, 113.2, 43.0, 39.8, 36.5, 23.2, 20.7, 14.1, 6.5, 4.4; IR (film, cm^{-1}) 3023, 2955, 1725, 1650, 1457; HRMS (ESI) *m/z* calcd for $C_{23}H_{36}O_2SiNa$ $[M+Na]^+$ 395.2382, found 395.2372.

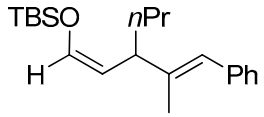
(*E*)-*N*-benzyl-4-benzylidene-5-((*Z*)-2-(triethylsilyloxy)vinyl)octan-1-amine(Table 18, entry 11)



Following the general procedure, *trans*-2-hexenal (22 μL, 0.18 mmol), N-benzyl-5-phenylpent-4-yn-1-amine (70 mg, 0.28 mmol), $Ni(COD)_2$ (5 mg, 0.018 mmol), PCy_3 (10 mg, 0.036 mmol), and triethylsilane (0.36 mmol, 57 μL) were stirred for 2 h at 50 °C. The product (51 mg, 61 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.15 (m, 10H), 6.32 (s, 1H), 6.28 (dd, *J* = 0.8, 6.0 Hz, 1H), 4.37 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.75 (s, 2H), 3.43 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.63

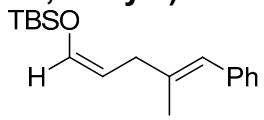
(bs, 2H), 2.29 (m,2H), 1.70 (quint, *J* = 7.2 Hz, 2H), 1.63-1.13 (m, 5H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.67 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.0, 138.3, 128.6, 128.3, 128.05, 128.03, 126.8, 125.7, 123.8, 113.8, 53.9, 49.5, 39.8, 36.7, 29.1, 28.4, 20.7, 14.2, 6.6, 4.5; IR (film, cm^{-1}) 3024, 2954, 1652, 1598, 1456; HRMS (CI) *m/z* calcd for $C_{30}H_{45}NOSiH$ $[M+H]^+$ 464.3349, found 464.3342.

tert-Butyldimethyl((_Z_)-3-((_E_)-1-phenylprop-1-en-2-yl)hex-1-enyloxy)silane (Table 19, entry 1)



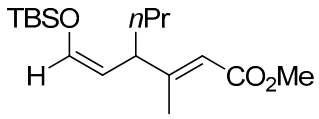
Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and *tert*-butyldimethylsilane (0.6 mmol, 98 µL) were stirred for 2 h at 50 °C. The product (84 mg, 85 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 6.33 (s, 1H), 6.25 (dd, *J* = 0.8, 5.6 Hz, 1H), 4.46 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.39 (q, *J* = 7.6 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.60-1.28 (m, 4H), 0.95 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 138.9, 138.5, 128.9, 127.9, 125.6, 124.2, 112.9, 43.5, 36.0, 25.6, 20.7, 18.2, 15.4, 14.1, -5.4; IR (film, cm^{-1}) 3024, 2955, 1652, 1599, 1471; HRMS (EI) *m/z* calcd for $C_{21}H_{34}OSi$ $[M^+]$ 330.2379, found 330.2384.

***tert*-Butyldimethyl((1*Z*,4*E*)-4-methyl-5-phenylpenta-1,4-dienyloxy)silane (Table 19, entry 2)**



Following the general procedure, propenal (25 μL, 0.3 mmol), 1-phenyl-1-propyne (56 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and *tert*-butyldimethylsilane (0.6 mmol, 98 μL) were stirred for 2 h at 50 °C (substrates and *tert*-butyldimethylsilane were added slowly over 1h as a THF solution). The product (45 mg, 52 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.17 (m, 5H), 6.33 (td, *J* = 0.8, 5.6 Hz, 1H), 6.32 (s, 1H), 4.58 (q, *J* = 7.2 Hz, 1H), 2.97 (d, *J* = 7.2 Hz, 2H), 1.88 (s, 3H), 0.96 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 138.8, 138.6, 128.8, 128.0, 125.7, 124.4, 107.8, 34.6, 25.6, 18.3, 17.8, -5.3; IR (film, cm^{-1}) 3024, 2955, 1652, 1599, 1471; HRMS (EI) *m/z* calcd for $C_{18}H_{28}OSi$ [M^+] 288.1905, found 288.1905.

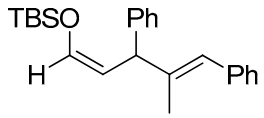
((*E*)-methyl 4-((*Z*)-2-(*tert*-butyldimethylsilyloxy)vinyl)-3-methylhept-2-enoate (Table 19, entry 3)



Following the general procedure, *trans*-2-hexenal (35 μL, 0.3 mmol), methyl 2-butynoate (45 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and *tert*-butyldimethylsilane (0.6 mmol, 98 μL) were stirred for 2 h at 50 °C. The product (45 mg, 49 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 0.8, 5.6 Hz, 1H), 5.72 (s, 1H), 4.34 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.68 (s,

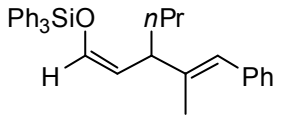
3H), 3.33 (q, *J* = 8.0 Hz, 1H), 2.13 (d, *J* = 1.2 Hz, 3H), 1.53-1.21 (m, 4H), 0.92 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.125 (s, 3H), 0.118 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 163.5, 139.6, 114.3, 111.0, 50.7, 44.0, 35.6, 25.5, 20.4, 18.1, 16.6, 14.0, -5.4; IR (film, cm^{-1}) 2955, 1717, 1645, 1434; HRMS (CI) *m/z* calcd for $C_{17}H_{32}O_3SiH$ $[M+H]^+$ 313.2199, found 313.2194.

tert-butyldimethyl((1*Z*,4*E*)-4-methyl-3,5-diphenylpenta-1,4-dienyloxy)silane (Table 19, entry 4)



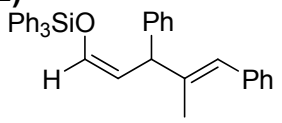
Following the general procedure, *trans*-cinnamaldehyde (41 mg, 0.30 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and *tert*-butyldimethylsilane (0.6 mmol, 98 µL) were stirred for 2h at 50 °C. The product (81 mg, 74 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (m, 10H), 6.52 (s, 1H), 6.39 (dd, *J* = 0.8, 5.6 Hz, 1H), 4.91 (dd, *J* = 5.6, 9.2 Hz, 1H), 4.76 (q, *J* = 9.2 Hz, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 0.95 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.7, 139.0, 138.6, 128.9, 128.2, 128.0, 127.95, 125.94, 125.88, 111.2, 48.9, 25.6, 18.2, 16.8, -5.30, -5.34; IR (film, cm^{-1}) 3056, 2927, 1651, 1599, 1491; HRMS (EI) *m/z* calcd for $C_{24}H_{32}OSi$ $[M^+]$ 364.2222, found 364.2225.

Triphenyl((*Z*)-3-((*E*)-1-phenylprop-1-en-2-yl)hex-1-enyloxy)silane (Table 20, entry 1)



Following the general procedure, *trans*-2-hexenal (35 µL, 0.3 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triphenylsilane (0.36 mmol, 94 mg) were stirred for 1h at 50 °C. The product (125 mg, 88 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.16 (m, 20H), 6.38 (s, 1H), 6.35 (dd, *J* = 0.8, 6.0 Hz, 1H), 4.56 (dd, *J* = 6.0, 9.2 Hz, 1H), 3.60 (q, *J* = 7.6 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.61-1.30 (m, 4H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.8, 138.2, 135.4, 133.2, 130.3, 129.0, 128.0, 127.9, 125.6, 124.6, 114.0, 44.0, 36.0, 20.7, 15.4, 14.2; IR (film, cm^{-1}) 3067, 2954, 1651, 1589, 1428; HRMS (EI) *m/z* calcd for $C_{33}H_{34}OSi$ [M^+] 474.2379, found 474.2369.

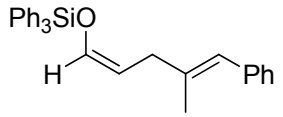
((1*Z*,4*E*)-4-Methyl-3,5-diphenylpenta-1,4-dienyloxy)triphenylsilane (Table 20, entry 2)



Following the general procedure, *trans*-cinnamaldehyde (41 mg, 0.30 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triphenylsilane (0.36 mmol, 94 mg) were stirred for 4h at 50 °C. The product (140 mg, 92 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.22 (m,

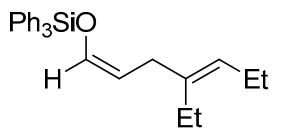
25H), 6.55 (s, 1H), 6.47 (d, *J* = 5.2 Hz, 1H), 5.00 (dd, *J* = 5.6, 9.6 Hz, 1H), 4.96 (d, *J* = 9.6 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.4, 138.7, 138.5, 135.4, 133.0, 130.4, 129.0, 128.3, 128.1, 127.98, 127.95, 126.2, 126.0, 125.9, 112.2, 49.3, 16.8; IR (film, cm^{-1}) 3066, 1648, 1738, 1598, 1428; HRMS (EI) *m/z* calcd for $C_{36}H_{32}OSi$ [M^+] 508.2222, found 364.2208.

((1*Z*,4*E*)-4-Methyl-5-phenylpenta-1,4-dienyloxy)triphenylsilane (Table 20, entry 3)



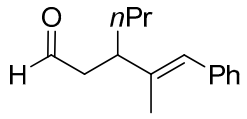
Following the general procedure, propenal (25 µL, 0.3 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triphenylsilane (0.36 mmol, 94 mg) were stirred for 3h at 50 °C (substrates and triphenylsilane were added slowly over 1h as a THF solution). The product (90 mg, 69 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.19 (m, 20H), 6.44 (dt, *J* = 5.6, 1.2 Hz, 1H),6.34 (s, 1H), 4.67 (dt, *J* = 6.0, 7.2 Hz, 1H), 3.12 (d, *J* = 7.2 Hz, 2H), 1.88 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.7, 138.3, 135.4, 133.2, 130.4, 128.8, 127.98, 127.95, 125.7, 124.7, 108.8, 34.9, 17.9; IR (film, cm^{-1}) 3066, 2924, 1652, 1588, 1427; HRMS (EI) *m/z* calcd for$C_{30}H_{28}OSi$ [M^+] 432.1909, found 432.1911.

((1*Z*,4*E*)-4-Ethylhepta-1,4-dienyloxy)triphenylsilane (Table 20, entry 4)



Following the general procedure, propenal (25 μL, 0.3 mmol), 3-hexyne (51 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and triphenylsilane (0.36 mmol, 94 mg) were stirred for 3h at 50 °C (substrates and triphenylsilane were added slowly over 1h as a THF solution). The product (71 mg, 59 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 6H), 7.49-7.40 (m, 9H), 6.66 (dt, *J* = 6.0, 1.2 Hz, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.57 (dt, *J* = 7.6, 6.0 Hz, 1H), 2.96 (d, *J* = 7.6 Hz, 2H), 2.04 (m, 4H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 138.5, 135.4, 133.3, 130.3, 127.9, 126.0, 109.9, 31.0, 23.2, 20.9, 14.7, 13.3; IR (film, cm^{-1}) 3066, 2924, 1652, 1427; HRMS (EI) *m/z* calcd for $C_{27}H_{30}OSi$ [M^+] 398.2066, found 398.2074.

(*E*)-3-(1-phenylprop-1-en-2-yl)hexanal (Scheme 73)

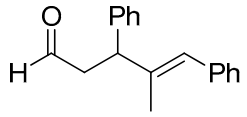


184

Following the general procedure, *trans*-2-hexenal (35 μL, 0.3 mmol), 1-phenyl-1-propyne (56 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and dimethylphenylsilane (0.6 mmol, 93 μL) were stirred for 1h at 50 °C. The product (56 mg, 86 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.4 Hz, 1H), 7.35-7.19 (m, 5H), 6.39 (s, 1H), 2.83 (m, 1H), 2.53 (dd, *J* = 2.8, 8.0 Hz, 1H), 2.52 (dd, *J* = 2.0, 6.8 Hz, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.42 (m, 4H),

0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 139.0, 137.8, 128.9, 128.0, 127.0, 126.2, 47.6, 43.7, 35.5, 20.4, 14.0, 13.9; IR (film,cm^{-1}) 2958, 1724, 1599, 1442; HRMS (EI) *m/z* calcd for $C_{15}H_{20}O$ [M^+] 216.1514, found 216.1511.

(*E*)-4-methyl-3,5-diphenylpent-4-enal



185

Following the general procedure, *trans*-cinnamaldehyde (41 mg, 0.30 mmol), 1-phenyl-1-propyne (56 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PCy_3 (17 mg, 0.06 mmol), and dimethylphenylsilane (0.6 mmol, 93 µL) were stirred for 4h at 50 °C. The product (61 mg, 81 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 2.0 Hz, 1H), 7.37-7.21 (m, 10H), 6.52 (s, 1H), 4.08 (t, *J* = 8.0 Hz, 1H), 3.04 (ddd, *J* = 2.4, 8.0, 16.4 Hz, 1H), 2.96 (ddd, *J* = 2.0, 7.6, 16.4 Hz, 1H), 1.75 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 141.6, 139.3, 137.6, 129.0, 128.6, 128.1, 127.8, 126.9, 126.4, 126.1, 48.6, 47.0, 16.6; IR (film, cm^{-1}) 3024, 2914, 1723, 1598, 1492; HRMS (EI) *m/z* calcd for $C_{18}H_{18}O$ [M^+] 250.1358, found 250.1354.

4.3 Reaction Procedures and Spectral Data of Chapter 3

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3). Aldehydes were distilled prior to use. $Ni(COD)_2$ (Strem Chemicals, Inc., used as received),

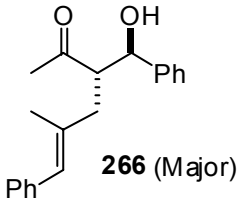
tricyclohexylphosphine (PCy_3), 1,3-Bis(2,6-di-*iso*-propylphenyl) imidazolium chloride (IPr·HCl) and potassium *tert*-butoxide were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

Regioisomeric ratios were determined on crude reaction mixtures using NMR, GC or GC-MS. GC's with FID detection were carried on an Agilent 6890N Network GC System with a HP-5MS column (30m x 0.252 mm x 0.25 μm). GCMS analyses were carried out on an HP 6890 Series GC System with a HP-5MS column (30m x 0.252 mm x 0.25 μm). The alkene stereochemistry was determined by NOE in the following cases: Table 22, entry 4 and Table 23, entries 2, 4, 6, and 9. Analysis of coupling constants was satisfactory for the 1,2-disubstituted alkene of Table 23, entry 3.

4.3.1 General Procedure for the $Ni(COD)_2/PBu_3$ Promoted Three-Component Coupling of Enones, Alkynes, and Aldehydes

To a solution of $Ni(COD)_2$ (0.03 mmol) in THF (1.0 mL) was added dropwise tributylphosphine (PBu_3) (0.06 mmol) at room temperature. After stirring for 5-10 min at rt, the reaction mixture became bright yellow. Aldehyde (0.6 mmol) and Et_3B (0.9 mmol) were added. A solution of enone (0.3 mmol) and alkyne (0.45 mmol) in THF (2.0 mL) was prepared. Ten percent of this solution was added at once, the reaction mixture was heated to 50 ^{o}C, and the remaining enone alkyne solution was added by syringe pump over 1.5-2 h. The reaction mixture was stirred at 50 ^{o}C until TLC analysis indicated disappearance of the enone. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated and residue was purified by column chromatography on silica gel.

(S*,E)-3-((R*)-hydroxy(phenyl)methyl)-5-methyl-6-phenylhex-5-en-2-one

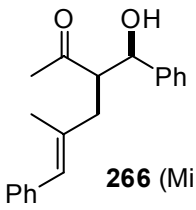


266 (Major)

Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), buten-2-one (25 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 µL, 0.06 mmol), and Et_3B (130 µL, 0.9 mmol) were stirred for 3 h at 50 °C. The product (71 mg, 80 %, 58:42) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes). ^{1}H NMR (400 MHz,

$CDCl_3$) (Major) δ 7.35-7.11 (m, 10H), 6.22 (s, 1H), 4.79 (dd, *J* = 5.6, 7.2 Hz, 1H), 3.21 (ddd, *J* = 5.2, 7.2, 10.0 Hz, 1H), 2.93 (d, *J* = 5.6 Hz, 1H), 2.43 (ddd, *J* = 0.8, 10.0, 13.2 Hz, 1H), 3.12 (dd, *J* = 5.6, 12.4 Hz, 1H), 2.08 (s, 3H), 1.76 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3, 142.3, 137.7, 134.8, 128.7, 128.6, 128.04, 127.98, 127.8, 126.3, 75.8, 57.3, 40.7, 32.5, 17.7; IR (film, cm^{-1}) 3430, 3058, 2921, 1707, 1598, 1492; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_2$ $[M+Na]^+$ 317.1517, found 317.1508. Stereochemical assignments were achieved by comparing *J* values between two chiral centers. *Syn* aldol products typically display *J* values of 3-6 Hz between the two chiral centers whereas *anti* aldol products display *J* values of 5-9 Hz.[223]

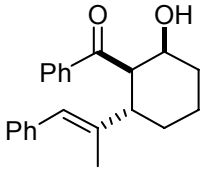
(R*,*E*)-3-((R*)-Hydroxy(phenyl)methyl)-5-methyl-6-phenylhex-5-en-2-one



266 (Minor)

^{1}H NMR (400 MHz, $CDCl_3$) (Minor) δ 7.35-7.11 (m, 10H), 6.21 (s, 1H), 4.94 (dd, *J* = 2.4, 5.6 Hz, 1H), 3.15 (quint, *J* = 4.8 Hz, 1H), 2.90 (d, *J* = 2.4 Hz, 1H), 2.52 (m, 2H), 1.95 (s, 3H), 1.74 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 141.6, 137.8, 135.8, 128.7, 128.5, 128.0, 127.8, 127.5, 126.20, 126.15. 73.9, 57.7, 38.4, 32.2, 17.7;

((1R*,2S*,6S*)-2-Hydroxy-6-((*E*)-1-phenylprop-1-en-2-yl)cyclohexyl)(phenyl)methanone



270

Following the general procedure, (*E*)-7-oxo-7-phenylhept-5-enal (48 mg, 0.24 mmol), 1-phenyl-1-propyne (41 mg, 0.36 mmol), $Ni(COD)_2$ (2 mg, 0.024 mmol), PBu_3 (12 µL, 0.05 mmol), and Et_3B (104.0 µL, 0.72 mmol) were stirred for 1 h at 50 °C. The product (56 mg, 75 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.54-7.03 (m, 6H), 6.82 (d, *J* = 7.6 Hz, 2H), 6.24 (s, 1H), 4.22 (d, *J* = 1.6 Hz, 1H), 3.72 (dd, *J* = 1.6, 11.6 Hz, 1H), 3.65 (bs, 1H), 3.00 (td, *J* = 3.2, 12.0 Hz, 1H), 2.02-1.83 (m, 4H), 1.61 (d, *J* = 1.2 Hz, 3H), 1.55-1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 139.7, 137.9, 137.5, 133.4, 128.69, 128.67, 128.2, 127.8, 126.7, 125.9, 66.7, 51.1, 44.6, 31.8, 31.2, 19.4, 15.8; IR (film, cm^{-1}) 3468, 3055, 2932, 1683, 1596, 1446; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_2Na$ $[M+Na]^+$ 343.1674, found 343.1674.

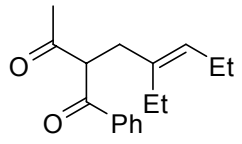
4.3.2 General Procedure for the $Ni(COD)_2$/IPr Promoted Three-Component Coupling of Enones, Alkynes, and Aldehydes

Toluene (1 mL) was added to a solid mixture of IPr•HCl (0.03 mmol), potassium *t*-butoxide (0.03 mmol) and $Ni(COD)_2$ (0.03 mmol) at rt. The resulting solution was stirred for 20-30 min until the color turned to dark red. Aldehyde (0.6 mmol) was added. Then a solution of enone (0.3 mmol) and alkyne (0.45 mmol) at rt in

toluene (2.0 mL) was added. The reaction mixture was stirred at 90 °C until TLC analysis indicated disappearance of the enone. The reaction mixture was concentrated *in vacuo*. The residue was purified via flash chromatography (SiO_2) to afford the desired product.

Note: Table 22, entries 1-4 and 6 exist as tautomeric mixtures.

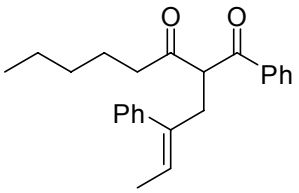
(*E*)-2-(2-Ethylpent-2-enyl)-1-phenylbutane-1,3-dione (Table 22, entry 1)



Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 3-buten-2-one (25 µL, 0.30 mmol), 3-hexyne (51 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 1 h at 90 °C. The product (51 mg, 66 %) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 72:28 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, $2H_{keto}$), 7.61-7.34 (m, $3H_{keto}$+ $5H_{enol}$), 5.18 (t, J = 7.2 Hz, $1H_{enol}$), 5.10 (t, J = 7.2 Hz, $1H_{keto}$), 4.65 (t, J = 7.2 Hz, $1H_{keto}$), 2.94 (d, J = 1.6 Hz, $2H_{enol}$), 2.70 (m, $2H_{keto}$), 2.20 (s, $3H_{enol}$), 2.16 (s, $3H_{keto}$), 2.15-1.90 (m, $4H_{keto}$+ $4H_{enol}$), 0.98 (t, J = 7.6 Hz, $3H_{enol}$), 0.96 (t, J = 7.6 Hz, $3H_{keto}$), 0.94 (t, J = 7.6 Hz, $3H_{enol}$), 0.85 (t, J = 7.6 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 204.2, 200.5, 196.3, 182.6, 138.9, 136.6, 136.4, 136.0, 133.5, 130.2, 128.84, 128.76, 128.7, 128.0, 127.5, 126.7, 107.0, 62.0, 35.4, 34.7, 27.9, 24.8, 24.5, 23.0, 20.9, 20.8, 14.6,

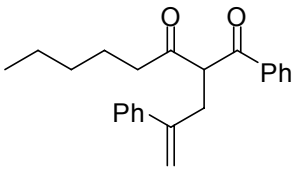
14.3, 13.0, 12.9; IR (film,cm^{-1}) 3060, 2963, 1720, 1677, 1596; HRMS (ESI) *m/z* calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ 281.1517, found 281.1512.

(*Z*)-1-Phenyl-2-(2-phenylbut-2-enyl)octane-1,3-dione (Table 22, entry 2)



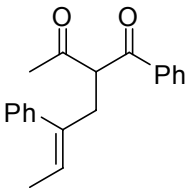
Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 1-octen-3-one (45 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 1 h at 90 °C. The product (64 mg, 61 %, 72:28) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). An 88:12 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 0.8, 8.4 Hz, 2H), 7.56-7.03 (m, 8H), 5.57 (q, *J* = 6.8 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 3.01 (dd, *J* = 7.2, 14.0 Hz, 1H), 3.04 (dd, *J* = 6.8, 14.4 Hz, 1H), 2.32 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.40 (quint, *J* = 7.2 Hz, 2H), 1.22-1.05 (m, 4H), 0.78 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (keto only) δ 205.6, 196.3, 139.3, 137.5, 136.5, 133.4, 128.8, 128.65, 128.64, 128.2, 126.9, 124.6, 60.8, 41.2, 38.2, 31.1, 23.0, 22.3, 14.7, 13.8; IR (film, cm^{-1}) 3056, 2954, 1715, 1673, 1596, 1447; HRMS (EI) *m/z* calcd for $C_{24}H_{28}O_2Na$ $[M+Na]^+$ 371.1987, found 371.1986.

1-Phenyl-2-(2-phenylallyl)octane-1,3-dione (Table 22, entry 3)



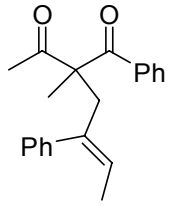
Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 1-octen-3-one (45 µL, 0.30 mmol), phenylacetylene (50 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 2 h at 90 °C. The product (60 mg, 60 %, >95:5) was obtained as a yellow oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 98:2 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.52-7.21 (m, 8H), 5.19 (d, *J* = 1.0 Hz, 1H), 5.03 (d, *J* = 1.0 Hz, 1H), 4.56 (t, *J* = 7.0 Hz, 1H), 3.20 (ddd, *J* = 1.0, 7.0, 15.0 Hz, 1H), 3.13 (ddd, *J* = 1.0, 7.0, 15.0 Hz, 1H), 2.37 (dt, *J* = 7.5, 17.5 Hz, 1H), 2.28 (dt, *J* = 7.5, 17.5 Hz, 1H), 1.42 (dquint, *J* = 1.0, 7.0 Hz, 2H), 1.28-1.04 (m, 4H), 0.77 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 196.2, 145.0, 140.1, 136.6, 133.6, 128.73, 128.67, 128.5, 127.8, 126.4, 115.2, 60.7, 41.4, 34.6, 31.1, 23.0, 22.3, 13.8; IR (film, cm^{-1}) 3057, 2975, 1715, 1673, 1595, 1447; HRMS (EI) *m/z* calcd for $C_{23}H_{26}O_2Na$ $[M+Na]^+$ 357.1830, found 357.1833.

(*Z*)-1-Phenyl-2-(2-phenylbut-2-enyl)butane-1,3-dione (Table 22, entry 4)



Following the general procedure, benzaldehyde (61 μL, 0.6 mmol), 3-buten-2-one (25 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 1 h at 90 °C. The product (63 mg, 72 %, 4:1) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). An 83:17 ratio of keto:enol forms was observed in the ^1H NMR spectrum.^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.07 (m, $10H_{maj}$ + $10H_{enol}$), 5.64 (q, *J* = 6.8 Hz, $1H_{keto}$), 5.60 (q, *J* = 6.8 Hz, $1H_{enol}$), 4.45 (t, *J* = 6.8 Hz, $1H_{keto}$), 3.25 (m, $2H_{enol}$), 3.07 (m, $2H_{keto}$), 2.30 (s, $3H_{enol}$), 2.09 (s, $3H_{keto}$), 1.66 (dt, *J* = 6.8, 2.0 Hz, $3H_{enol}$), 1.51 (d, *J* = 6.8 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 203.6, 200.1, 196.2, 183.3, 141.2, 140.2, 139.2, 137.4, 136.4, 136.0, 133.5, 130.4, 128.74, 128.66, 128.3, 128.1, 127.8, 127.4, 127.0, 126.8, 124.6, 122.1, 106.8, 61.4, 38.3, 37.3, 28.2, 24.8, 14.7; IR (film, cm^{-1}) 3056, 2917, 1717, 1675, 1595, 1447; HRMS (ESI) m/z calcd for $C_{20}H_{20}O_2Na$ $[M+Na]^+$ 315.1361, found 315.1351.

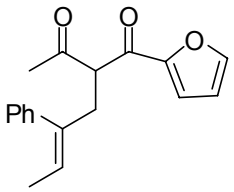
(*Z*)-2-Methyl-1-phenyl-2-(2-phenylbut-2-enyl)butane-1,3-dione (Table 22, entry 5)



Following the general procedure, benzaldehyde (61 μL, 0.6 mmol), 3-methyl-3-buten-2-one (29 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 3 h at 90 °C. The product (43 mg, 47 %, 61:39) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in

hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-6.89 (m, $10H_{maj}$ + $10H_{min}$), 6.16 (s, $1H_{min}$), 5.41 (q, J = 6.8 Hz, $1H_{maj}$), 3.23 (d, J = 14.4 Hz, $1H_{maj}$), 3.11 (d, J = 14.4 Hz, $1H_{maj}$), 3.02 (d, J = 14.4 Hz, $1H_{min}$), 2.95 (d, J = 14.4 Hz, $1H_{min}$), 2.10 (s, $3H_{min}$), 1.87 (s, $3H_{maj}$), 1.62 (d, J = 1.2 Hz, $3H_{min}$) 1.48 (s, $3H_{min}$), 1.46 (d, J = 6.8 Hz, $3H_{maj}$), 1.28 (s, $3H_{maj}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + minor) δ 207.9, 207.8, 199.2, 198.6, 139.6, 137.7, 136.2, 136.01, 135.95, 133.9, 133.0, 132.6, 130.4, 129.1, 128.89, 128.86, 128.8, 128.5, 128.4, 128.0, 127.7, 127.0, 126.6, 126.3, 65.21, 65.17, 46.2, 44.2, 27.4, 27.1, 20.33, 20.27, 19.4, 14.7; IR (film, cm^{-1}) 3062, 2957, 1713, 1672, 1355; HRMS (ESI) m/z calcd for $C_{21}H_{22}O_2Na$ $[M+Na]^+$ 329.1517, found 329.1522. The major:minor ratio was determined by crude ^{1}H NMR, and the spectrum of purified material attached shows an altered ratio.

(*Z*)-1-(Furan-2-yl)-2-(2-phenylbut-2-enyl)butane-1,3-dione (Table 22, entry 6)



Following the general procedure, 2-furaldehyde (50 µL, 0.6 mmol), 3-buten-2-one (25 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IPr•HCl (13 mg, 0.03 mmol), and *t*-BuOK (3 mg, 0.03 mmol) were stirred for 1 h at 90 °C. The product (73 mg, 86 %, 4:1) was obtained as a colorless oil after SiO_2 chromatography (10 % EtOAc in hexanes). An 89:11 ratio of keto:enol forms was observed in the ^{1}H NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, $1H_{enol}$), 7.51 (dd, J = 0.8, 2.0 Hz, $1H_{keto}$) 7.30-7.18 (m, $3H_{keto}$+ $3H_{enol}$), 7.05-7.02 (m, $3H_{keto}$+ $3H_{enol}$), 6.48 (dd, J = 2.0, 3.6 Hz, $1H_{enol}$), 6.46 (dd, J

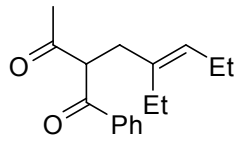
= 2.0, 4.0 Hz, $1H_{keto}$), 5.58 (q, *J* = 6.8 Hz, $1H_{keto}$), 5.41 (tq, *J* = 2.0, 6.8 Hz, $1H_{enol}$) 4.16 (t, *J* = 7.2 Hz, $1H_{keto}$), 3.50 (m, $2H_{enol}$), 2.99 (m, $2H_{keto}$), 2.23 (s, $3H_{enol}$), 2.07 (s, $3H_{keto}$), 1.52 (dt, *J* = 7.2, 2.0 Hz, $3H_{enol}$), 1.47 (dt, *J* = 6.8, 0.8 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + enol) δ 203.1, 184.3, 152.0, 147.1, 145.5, 141.6, 139.1, 137.3, 128.7, 128.3, 128.2, 128.0, 126.9, 126.8, 124.7, 121.0, 118.8, 117.0, 112.6, 112.0, 61.5, 37.8, 35.7, 28.7, 24.6, 14.7, 14.6; IR (film,cm^{-1}) 3132, 2917, 1720, 1678, 1566, 1464; HRMS (ESI) m/z calcd for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1154, found 305.1149.

4.3.3 General Procedure for the $Ni(COD)_2/PCy_3$ Promoted Three-Component Coupling of Enones, Alkynes, and Aldehydes

Toluene (1 mL) was added to a solid mixture of tricyclohexylphosphine (0.06 mmol), and $Ni(COD)_2$ (0.03 mmol) at rt. The resulting solution was stirred for 5-10 min. Aldehyde (0.6 mmol) was added. Then a solution of enone (0.3 mmol) and alkyne (0.45 mmol) at rt in toluene (2.0 mL) was added. The reaction mixture was stirred at 90 ^oC until TLC analysis indicated disappearance of the enone. The reaction mixture was concentrated *in vacuo*. The residue was purified via flash chromatography (SiO_2) to afford the desired product.

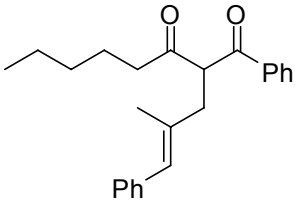
Note: Table 23, entries 1-4 and 6-9 exist as tautomeric mixtures.

(*E*)-2-(2-Ethylpent-2-enyl)-1-phenylbutane-1,3-dione (Table 23, entry 1)



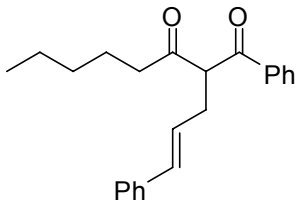
Following the general procedure, benzaldehyde (61 μL, 0.6 mmol), 3-buten-2-one (25 μL, 0.30 mmol), 3-hexyne (51 μL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (54 mg, 70 %) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). Spectral data is identical to that obtained in entry 1.

(*E*)-2-(2-Methyl-3-phenylallyl)-1-phenyloctane-1,3-dione (Table 23, entry 2)



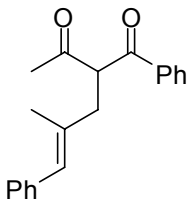
Following the general procedure, benzaldehyde (61 μL, 0.6 mmol), 3-octen-2-one (45 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (79 mg, 76 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 96:4 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.63-7.11 (m, 8H), 6.30 (s, 1H), 4.79 (t, *J* = 7.2 Hz, 1H), 2.89 (d, *J* = 7.2 Hz 2H), 2.50 (m, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.53 (quint, *J* = 7.2 Hz, 2H), 1.22 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (keto) δ 205.7, 196.0, 137.6, 136.6, 134.8, 133.6, 128.8, 128.7, 128.6, 128.0, 127.6, 126.2, 61.4, 40.9, 39.4, 31.1, 23.0, 22.3, 17.9, 13.8; IR (film, cm^{-1}) 3056, 2954, 1715, 1673, 1596, 1447; HRMS (EI) *m/z* calcd for $C_{24}H_{28}O_2Na$ $[M+Na]^+$ 371.1987, found 371.1986.

2-Cinnamyl-1-phenyloctane-1,3-dione (Table 23, entry 3)



Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 3-octen-2-one (45 µL, 0.30 mmol), phenylacetylene (50 µL, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (56 mg, 56 %, 90:10) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.63-7.20 (m, 8H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.14 (dt, *J* = 16.0, 7.6 Hz, 1H), 4.62 (t, *J* = 7.2 Hz, 1H), 2.90 (tt, *J* = 1.6, 7.2 Hz, 2H), 2.51 (dt, *J* = 17.6, 7.2 Hz, 1H), 2.42 (dt, *J* = 17.6, 7.2 Hz, 1H), 1.53 (m, 2H), 1.21 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 195.8, 137.0, 136.4, 133.7, 132.6, 128.9, 128.7, 128.5, 127.4, 126.1, 62.6, 41.1, 32.4, 31.1, 23.0, 22.4, 13.8; IR (film,cm^{-1}) 3057, 2975, 1715, 1673, 1595, 1447; HRMS (EI) *m/z* calcd for $C_{23}H_{26}O_2Na$ $[M+Na]^+$ 357.1830, found 357.1833.

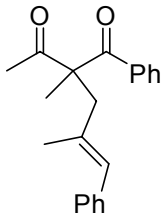
(*E*)-2-(2-Methyl-3-phenylallyl)-1-phenylbutane-1,3-dione (Table 23, entry 4)



Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 3-buten-2-one (25 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg,

0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (69 mg, 79 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 77:23 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, $2H_{keto}$), 7.58-7.07 (m, $8H_{keto}$ + $10H_{enol}$), 6.31 (s, $1H_{enol}$), 6.28 (s, $1H_{keto}$), 4.74 (t, *J* = 7.2 Hz, $1H_{keto}$), 3.09 (s, $2H_{enol}$), 2.86 (d, *J* = 7.2 Hz, $2H_{keto}$), 2.24 (s, $3H_{enol}$), 2.17 (s, $3H_{keto}$), 1.84 (d, *J* = 0.8 Hz, $3H_{enol}$), 1.82 (d, *J* = 1.2 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 203.6, 200.0, 196.0, 183.4, 138.0, 137.8, 137.6, 136.5, 136.0, 134.6, 133.7, 133.5, 130.3, 128.8, 128.73, 128.72, 128.6, 128.2, 128.1, 128.0, 127.7, 127.4, 126.25, 126.22, 125.3, 106.8, 61.9, 39.4, 38.2, 28.0, 24.8, 18.8, 17.8; IR (film, cm^{-1}) 3056, 2917, 1717, 1675, 1595, 1447; HRMS (ESI) m/z calcd for $C_{20}H_{20}O_2Na$ $[M+Na]^+$ 315.1361, found 315.1351.

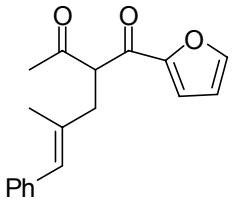
(*E*)-2-Methyl-2-(2-methyl-3-phenylallyl)-1-phenylbutane-1,3-dione (Table 23, entry 5)



Following the general procedure, benzaldehyde (61 µL, 0.6 mmol), 3-methyl-3-buten-2-one (29 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 3 h at 90 °C. The product (60 mg, 47 %, 87:13) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-6.89 (m, $10H_{maj}$ + $10H_{min}$), 6.16 (s, $1H_{maj}$), 5.41 (q, *J* = 6.8 Hz, $1H_{min}$), 3.23 (d, *J* = 14.4 Hz, $1H_{min}$), 3.11 (d, *J* = 14.4 Hz, $1H_{min}$), 3.02 (d, *J* = 14.4

Hz, 1H$_{maj}$), 2.95 (d, *J* = 14.4 Hz, 1H$_{maj}$), 2.10 (s, 3H$_{maj}$), 1.87 (s, 3H$_{min}$), 1.62 (d, *J* = 1.2 Hz, 3H$_{maj}$) 1.48 (s, 3H$_{maj}$), 1.46 (d, *J* = 6.8 Hz, 3H$_{min}$), 1.28 (s, 3H$_{min}$); ^{13}C NMR (100 MHz, $CDCl_3$) (major + minor) δ 207.9, 207.8, 199.2, 198.6, 139.6, 137.7, 136.2, 136.01, 135.95, 133.9, 133.0, 132.6, 130.4, 129.1, 128.89, 128.86, 128.8, 128.5, 128.4, 128.0, 127.7, 127.0, 126.6, 126.3, 65.21, 65.17, 46.2, 44.2, 27.4, 27.1, 20.33, 20.27, 19.4, 14.7; IR (film, cm^{-1}) 3062, 2957, 1713, 1672, 1355; HRMS (ESI) m/z calcd for $C_{21}H_{22}O_2Na$ [M+Na]$^+$ 329.1517, found 329.1522.

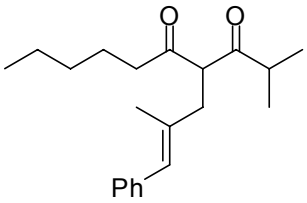
(*E*)-1-(Furan-2-yl)-2-(2-methyl-3-phenylallyl)butane-1,3-dione (Table 23, entry 6)



Following the general procedure, 2-furaldehyde (50 µL, 0.6 mmol), 3-buten-2-one (25 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (65 mg, 77 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (10 % EtOAc in hexanes). An 85:15 ratio of keto:enol forms was observed in the ^{1}H NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H$_{keto}$) 7.54 (m, 1H$_{enol}$), 7.28-7.01 (m, 6H$_{keto}$+ 6H$_{enol}$), 6.53 (dd, *J* = 1.6, 3.6 Hz, 1H$_{keto}$), 6.47 (dd, *J* = 1.6, 3.6 Hz, 1H$_{enol}$), 6.26 (s, 1H$_{keto}$), 6.19 (s, 1H$_{enol}$) 4.53 (t, *J* = 7.2 Hz, 1H$_{keto}$), 3.38 (s, 2H$_{enol}$), 2.81 (m, 2H$_{keto}$), 2.23 (s, 3H$_{enol}$), 2.20 (s, 3H$_{keto}$), 1.94 (d, *J* = 1.2 Hz, 3H$_{enol}$), 1.82 (d, *J* = 1.2 Hz, 3H$_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 203.1, 199.0, 184.3, 171.0, 152.2, 147.2, 145.6, 138.0, 137.6,

136.5, 134.5, 128.74, 128.72, 128.01, 127.96, 127.7, 126.2, 126.1, 124.5, 118.7, 117.2, 112.8, 112.0, 105.6, 61.6, 38.8, 36.9, 28.7, 24.6, 18.8, 17.7; IR (film,cm^{-1}) 3132, 2917, 1720, 1678, 1566, 1464; HRMS (ESI) m/z calcd for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1154, found 305.1149.

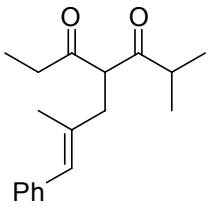
(*E*)-2-Methyl-4-(2-methyl-3-phenylallyl)decane-3,5-dione (Table 23, entry 7)



Following the general procedure, 2-methylpropionaldehyde (57 μL, 0.6 mmol), 1-octen-3-one (45 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (47 mg, 50 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 43:57 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.16 (m, $5H_{keto}$ + $5H_{enol}$), 6.28 (s, $1H_{keto}$), 6.16 (s, $1H_{enol}$), 4.12 (t, *J* = 7.2 Hz, $1H_{keto}$), 3.11 (d, *J* = 0.8 Hz, $2H_{enol}$), 2.75 (m, $3H_{keto}$ + $1H_{enol}$), 2.50 (dd, *J* = 3.2, 7.2 Hz, $1H_{keto}$), 2.49 (dd, *J* = 3.2, 7.2 Hz, $1H_{keto}$) 2.40 (t, *J* = 7.6 Hz, $2H_{enol}$), 1.93 (d, *J* = 1.2 Hz, $3H_{enol}$), 1.86 (d, *J* = 1.2 Hz, $3H_{keto}$) 1.66-1.54 (m, $2H_{keto}$ + $2H_{enol}$), 1.36-1.20 (m, $4H_{keto}$ + $4H_{enol}$), 1.15 (d, *J* = 6.8 Hz, $6H_{enol}$), 1.11 (d, *J* = 6.8 Hz, $3H_{keto}$), 1.09 (d, *J* = 6.8 Hz, $3H_{keto}$), 0.88 (m, $3H_{keto}$ + $3H_{enol}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 205.9, 198.0, 196.5, 138.1, 137.6, 137.3, 134.7, 128.7, 128.1, 127.7, 126.3, 126.1, 124.8, 105.0, 64.3, 41.3, 41.2, 39.3, 36.0, 35.6, 32.3, 31.7,

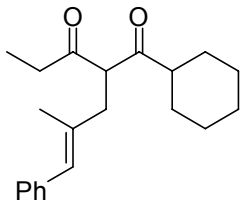
31.2, 25.2, 23.0, 22.5, 22.4, 19.6, 18.8, 18.2, 17.9, 17.8, 13.91, 13.86; IR (film, cm^{-1}) , 2957, 2871, 1717, 1698, 1598; HRMS (ESI) m/z calcd for $C_{21}H_{30}O_2Na$ $[M+Na]^+$ 337.2144, found 337.2133.

(*E*)-2-Methyl-4-(2-methyl-3-phenylallyl)heptane-3,5-dione (Table 23, entry 8)



Following the general procedure, 2-methylpropionaldehyde (57 μL, 0.6 mmol), 1-penten-3-one (30 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (34 mg, 42 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 65:35 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.16 (m, $5H_{keto}$ + $5H_{enol}$), 6.28 (s, $1H_{keto}$), 6.16 (s, $1H_{enol}$), 4.13 (t, *J* = 7.2 Hz, $1H_{keto}$), 3.11 (s, $2H_{enol}$), 2.73 (m, $3H_{keto}$ + $1H_{enol}$), 2.49 (m, $2H_{keto}$ + $2H_{enol}$), 1.93 (s, $3H_{enol}$), 1.86 (d, *J* = 1.2 Hz, $3H_{keto}$), 1.150 (d, *J* = 6.8 Hz, $6H_{enol}$), 1.149 (t, *J* = 7.2 Hz, $3H_{enol}$), 1.12 (d, *J* = 6.8 Hz, $3H_{keto}$), 1.08 (d, *J* = 6.8 Hz, $3H_{keto}$), 1.05 (t, *J* = 7.2 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 209.8, 206.4, 198.1, 196.4, 138.0, 137.6, 137.2, 134.7, 128.73, 128.71, 128.1, 127.7, 126.3, 126.1, 124.7, 104.6, 64.0, 41.2, 39.4, 35.9, 34.6, 32.0, 29.1, 19.5, 18.8, 18.1, 18.0, 17.8, 9.4, 7.6; IR (film, cm^{-1}) , 3023, 2929, 1722, 1694, 1598; HRMS (ESI) m/z calcd for $C_{18}H_{24}O_2Na$ $[M+Na]^+$ 295.1674, found 295.1667.

(*E*)-1-Cyclohexyl-2-(2-methyl-3-phenylallyl)pentane-1,3-dione (Table 23, entry 9)



Following the general procedure, cyclohexanecarboxaldehyde (73 μL, 0.6 mmol), 1-penten-3-one (30 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The product (43 mg, 46 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (5 % EtOAc in hexanes). A 51:49 ratio of keto:enol forms was observed in the ^1H NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.16 (m, $5H_{keto}$ + $5H_{enol}$), 6.28 (s, $1H_{keto}$), 6.18 (s, $1H_{enol}$), 4.12 (t, *J* = 7.2 Hz, $1H_{keto}$), 3.11 (s, $2H_{enol}$), 2.74 (dd, *J* = 7.2, 14.0 Hz, $1H_{keto}$), 2.68 (dd, *J* = 7.2, 14.0 Hz, $1H_{keto}$), 2.48 (m, $3H_{keto}$ + $3H_{enol}$), 1.93 (s, $3H_{enol}$), 1.86 (d, *J* = 1.2 Hz, $3H_{keto}$), 1.81- 1.52 (m, $4H_{keto}$+ $4H_{enol}$), 1.25 (m, $6H_{keto}$+ $6H_{enol}$), 1.15 (t, *J* = 7.2 Hz, $3H_{enol}$), 1.04 (t, *J* = 7.2 Hz, $3H_{keto}$); ^{13}C NMR (100 MHz, $CDCl_3$) (keto + enol) δ 208.9, 206.4, 198.2, 195.4, 138.1, 137.7, 137.4, 134.8, 128.72, 128.70, 128.1, 127.6, 126.3, 126.1, 124.8, 104.9, 64.2, 51.1, 42.6, 39.2, 36.0, 34.6, 29.4, 29.2, 28.4, 28.1, 25.9, 25.7, 25.65, 25.56, 25.4, 18.7, 17.8, 9.4, 7.6; IR (film, cm^{-1}) , 3022, 2852, 1727, 1694, 1448; HRMS (ESI) m/z calcd for $C_{21}H_{28}O_2Na$ $[M+Na]^+$ 335.1987, found 335.1978.

Crossover Experiment (Scheme 101)

d_1-Benzaldehyde was prepared by $LiAlD_4$ reduction followed by PCC oxidation.Following the general procedure, d_1-benzaldehyde (41 mg, 0.38 mmol), 2-furaldehyde (32 µL, 0.38 mmol) 1-buten-3-one (25 µL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), and PCy_3 (17 mg, 0.06 mmol) were stirred for 1 h at 90 °C. The products **279** (22 mg, 25 %, >95 % d incorp) and **280** (34 mg, 40 %, <5 % d incorp) were obtained as colorless oils after SiO_2 chromatography (5 % EtOAc in hexanes). The ^1H NMR spectrum of **282** illustrated > 95 % deuterium incorporation of the alkenyl CH (δ 6.31_{enol} and δ 6.28_{keto}). ^1H NMR spectrum of **279** is attached and may be compared with Table 23, entry 4 spectrum.

APPENDIX

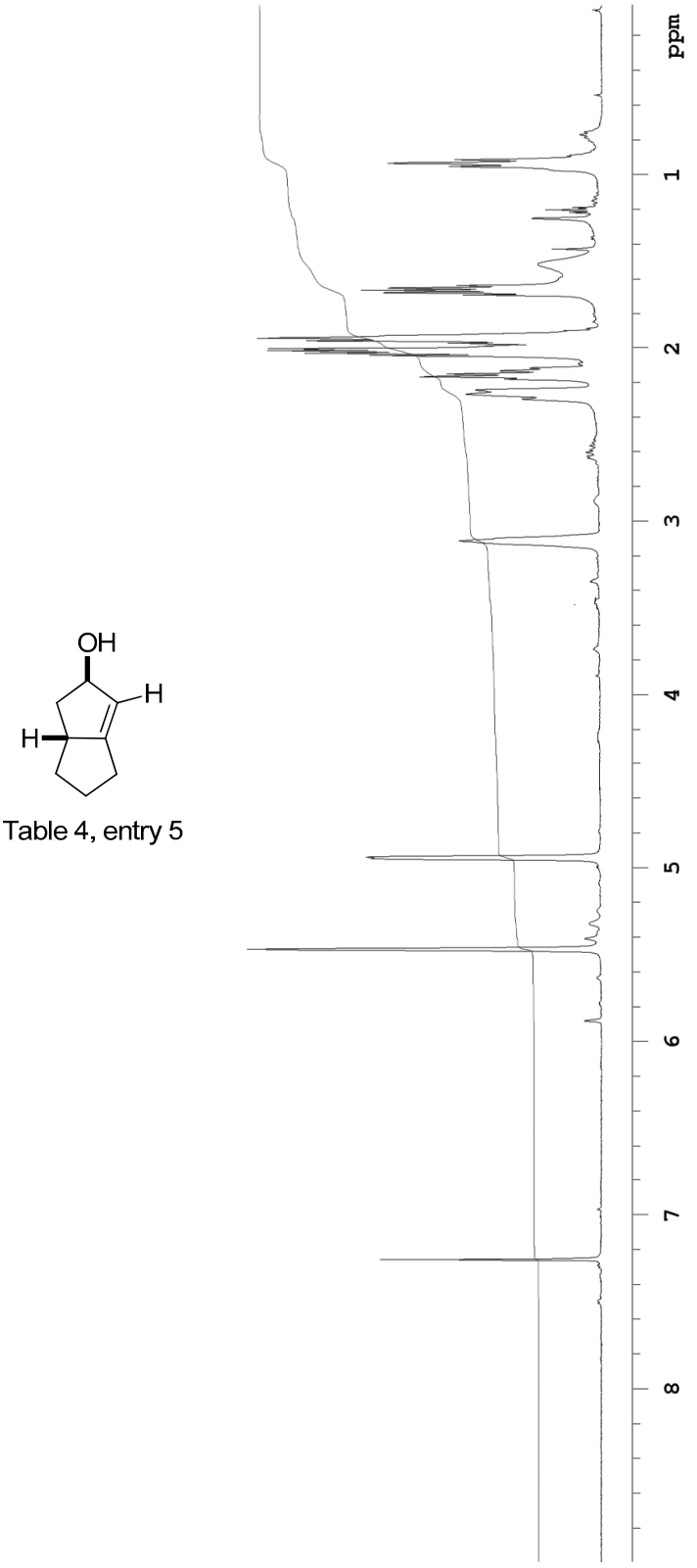


Table 4, entry 5

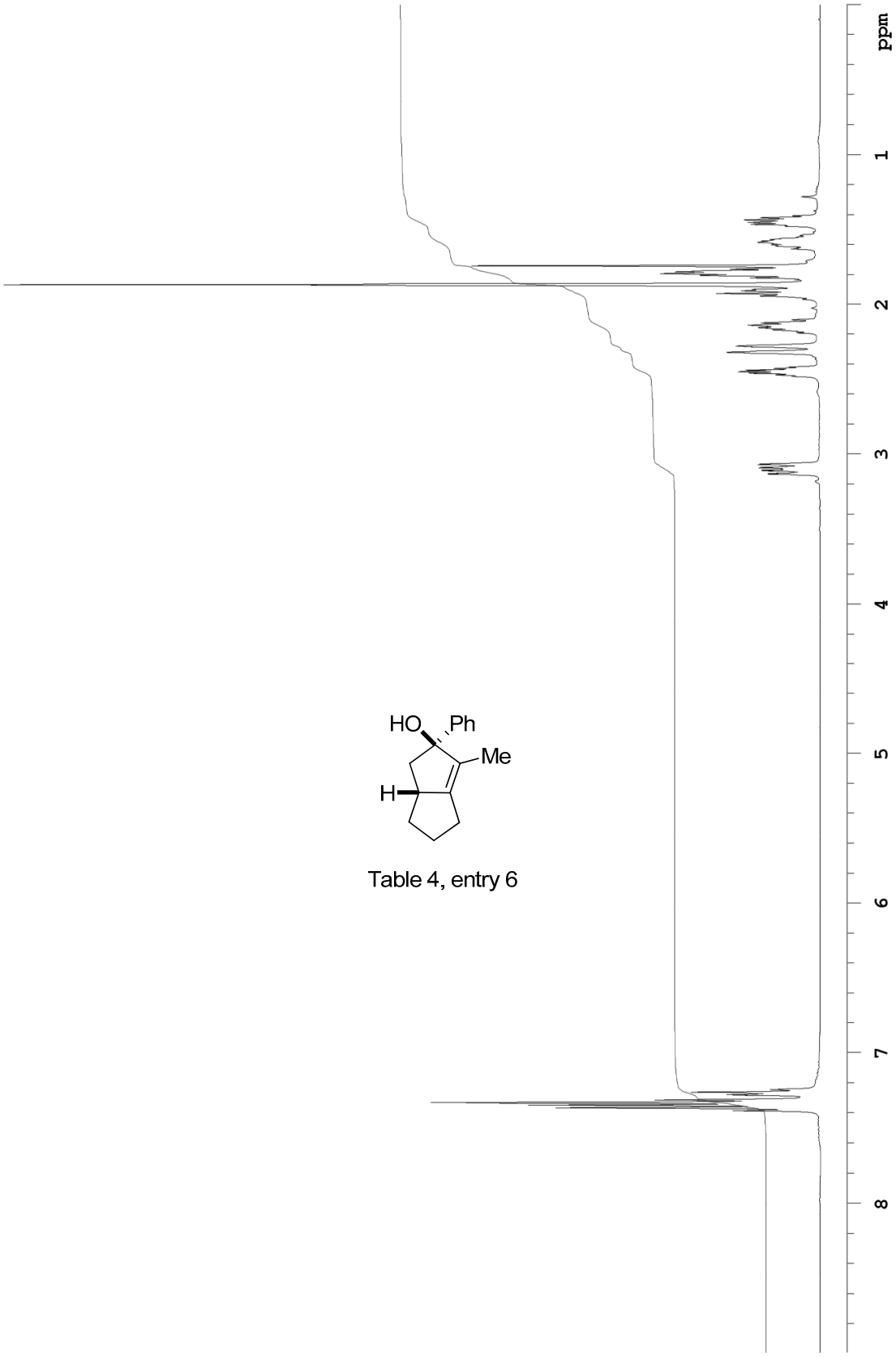
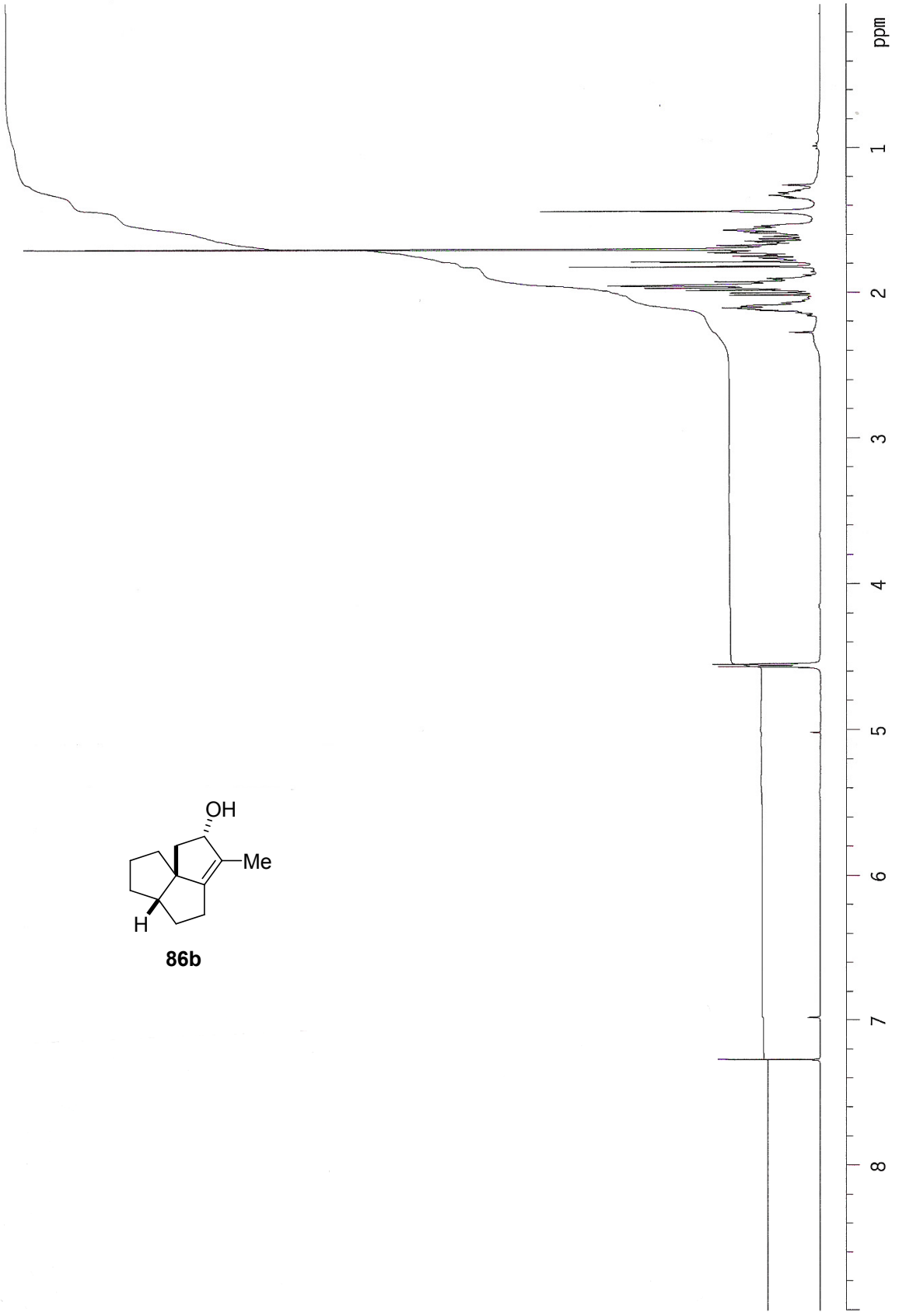
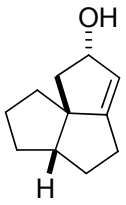


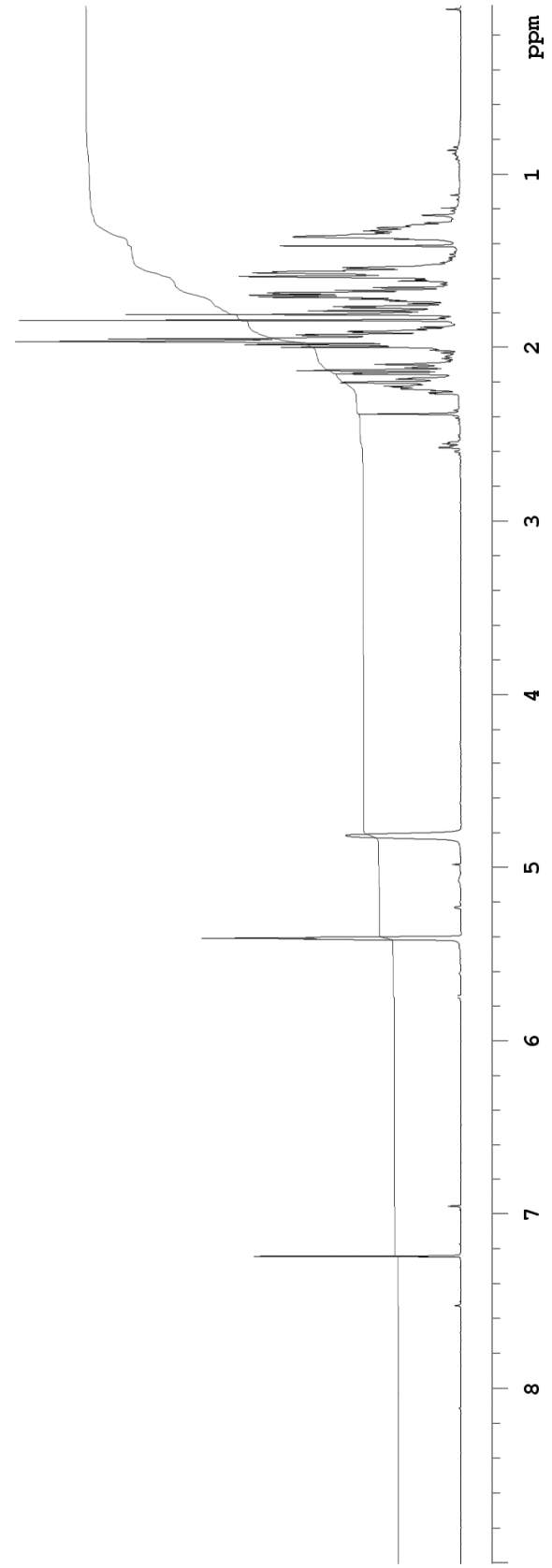
Table 4, entry 6



86b



90c



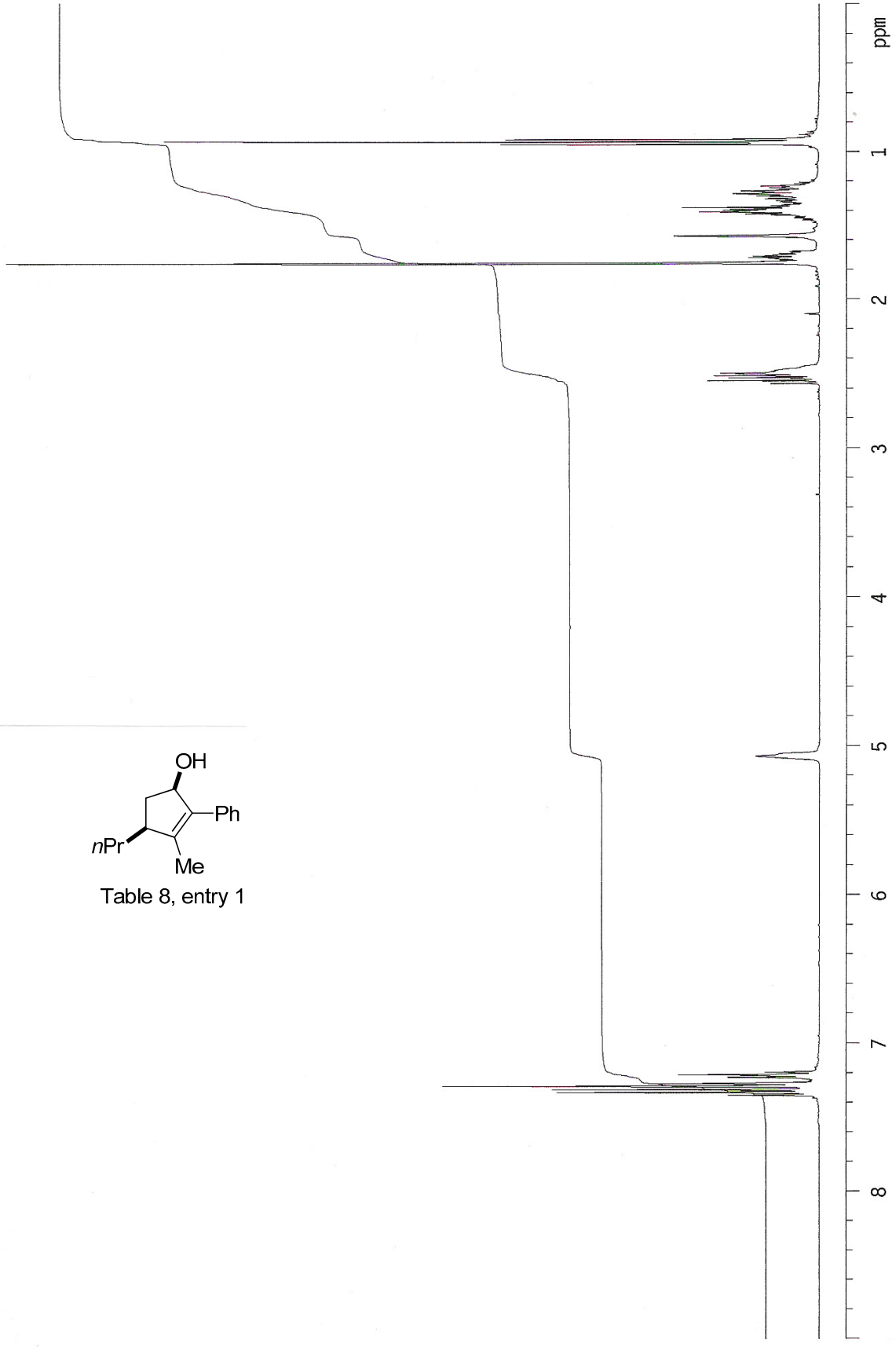
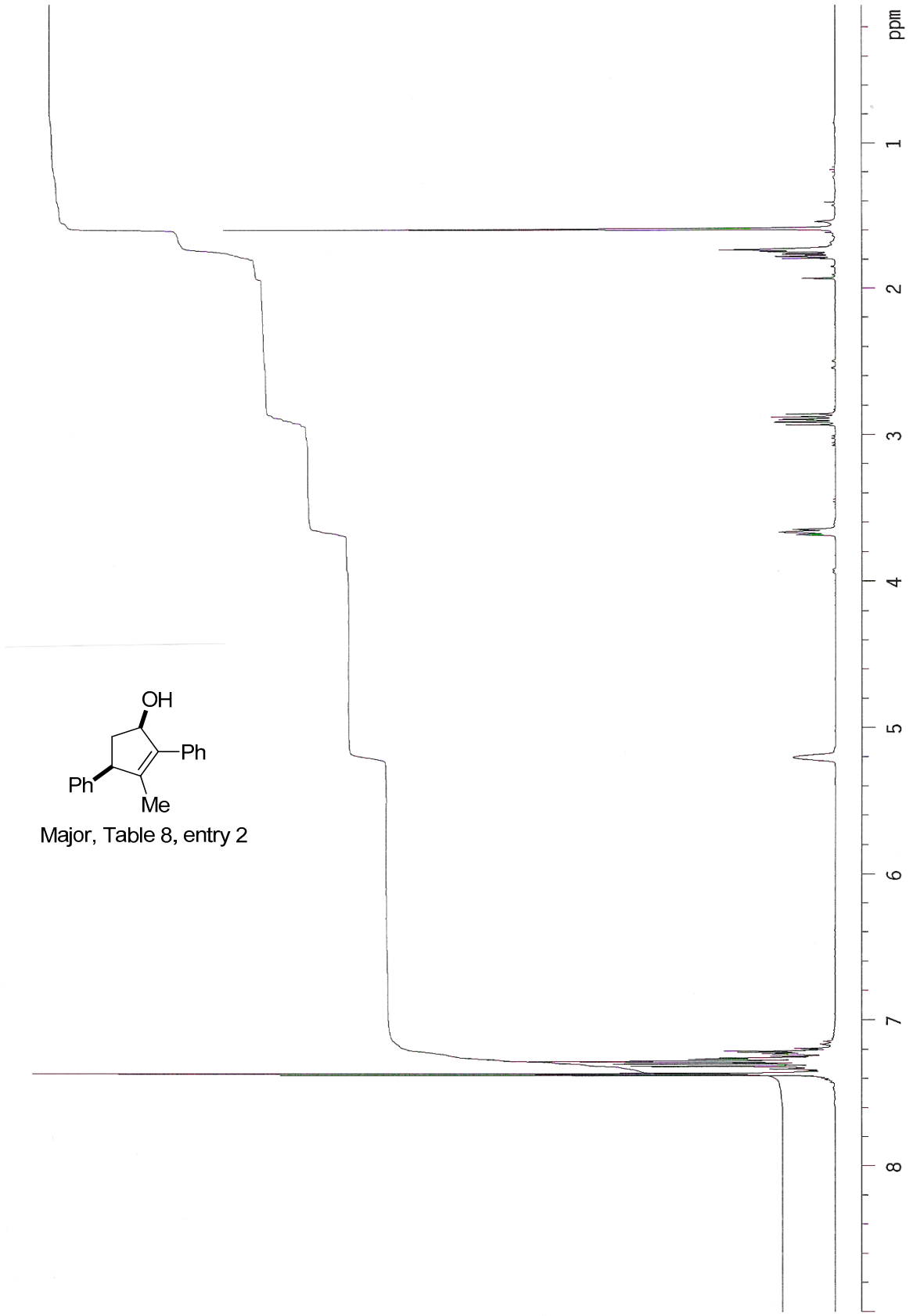
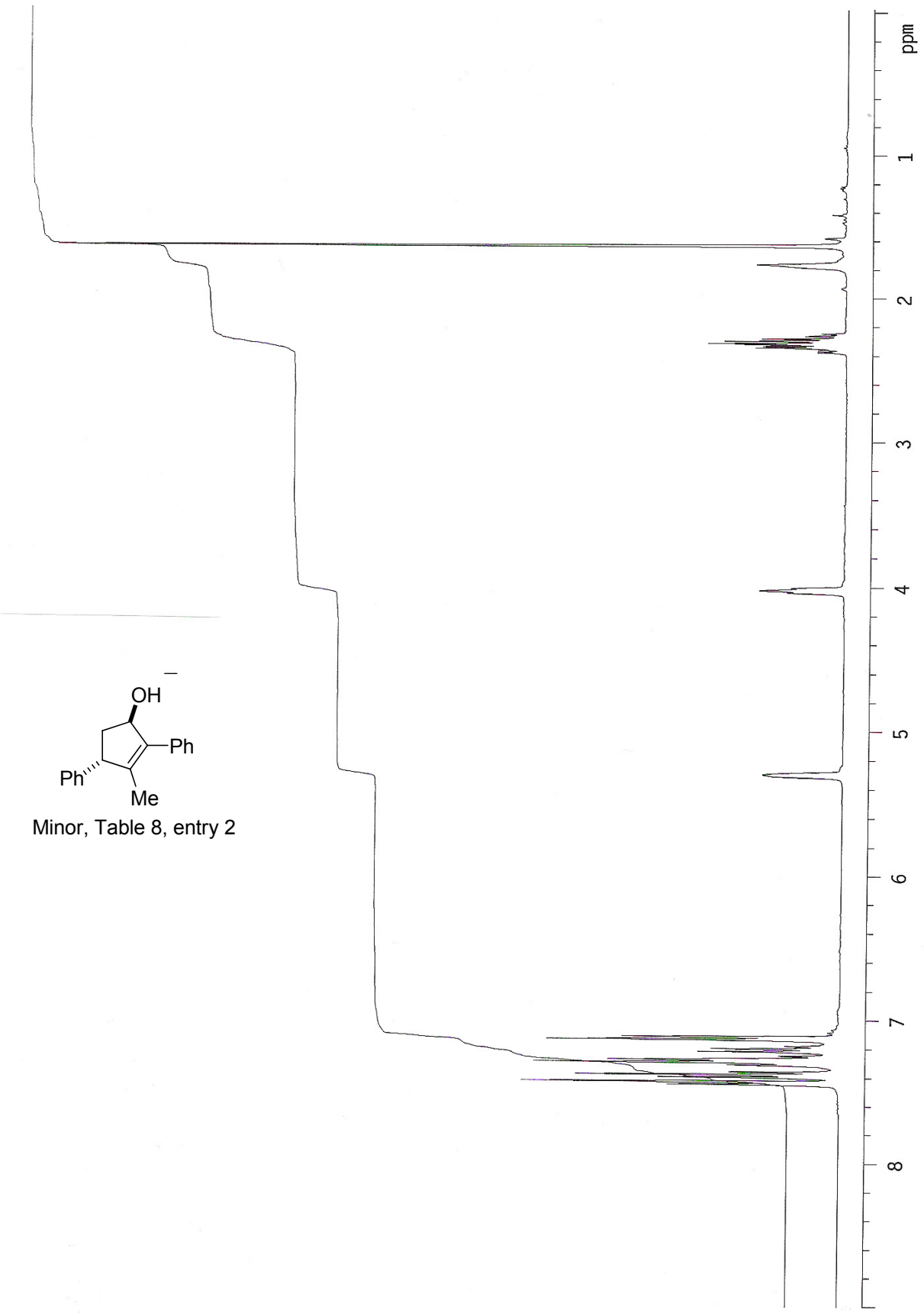


Table 8, entry 1



Major, Table 8, entry 2



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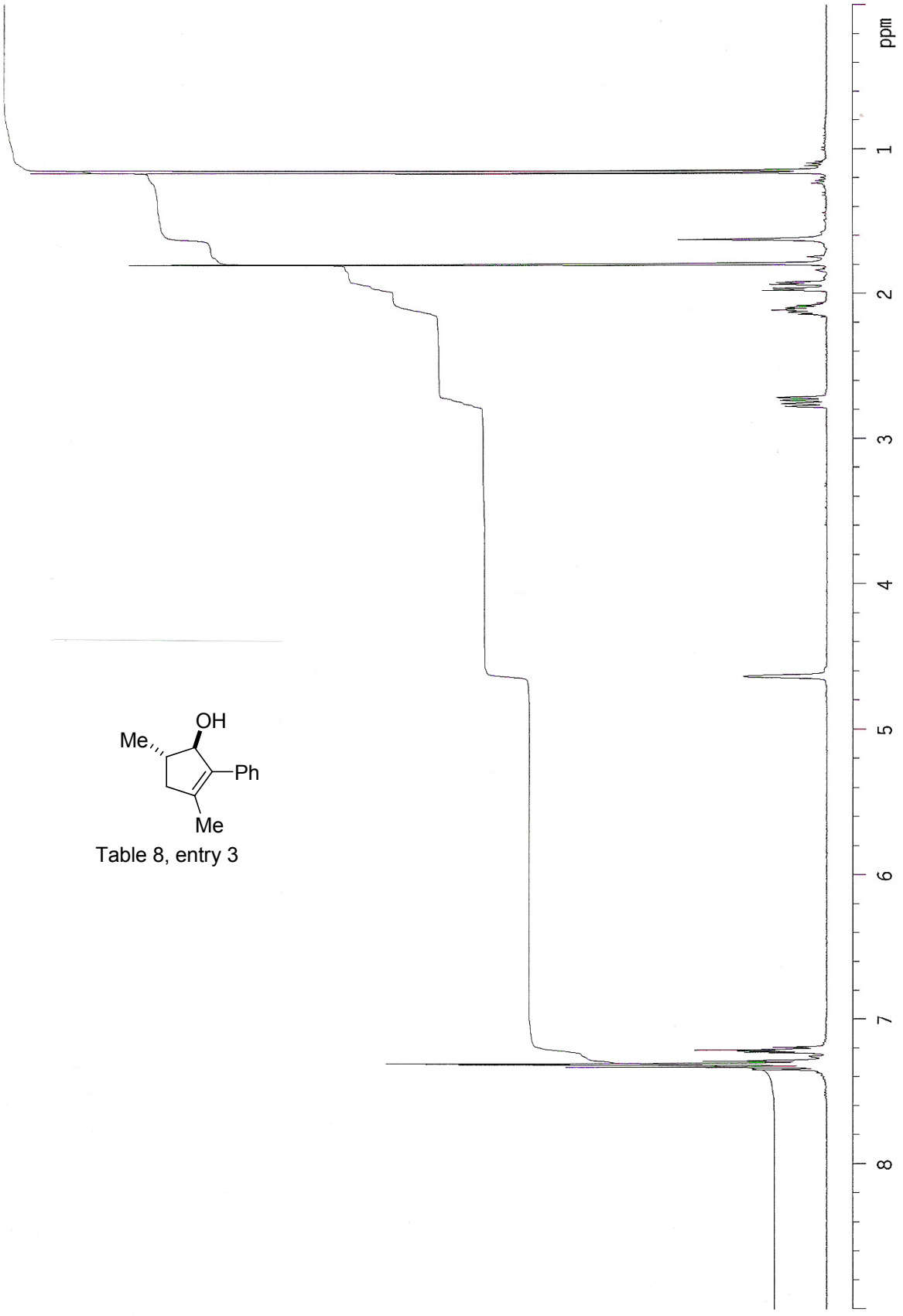


Table 8, entry 3

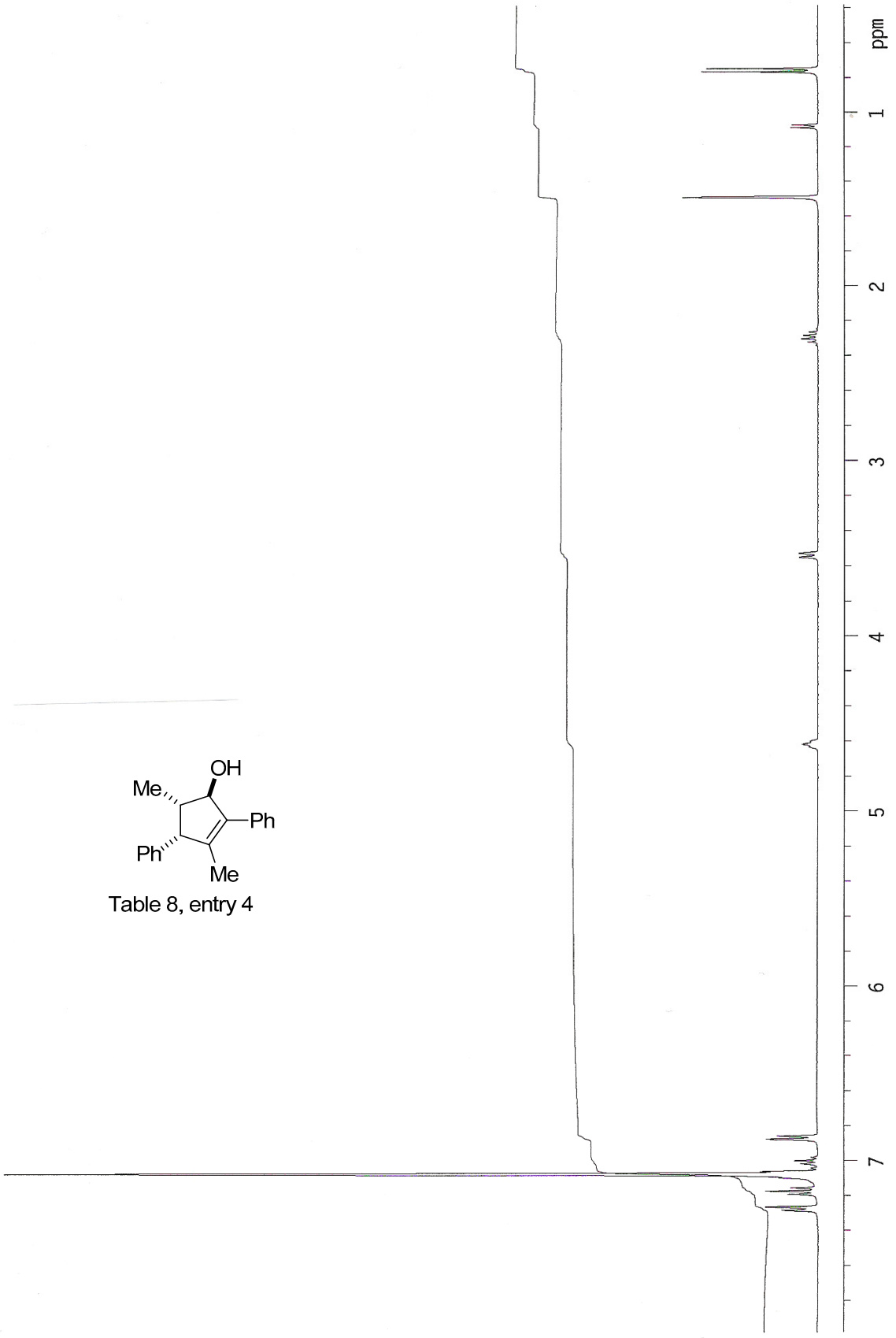
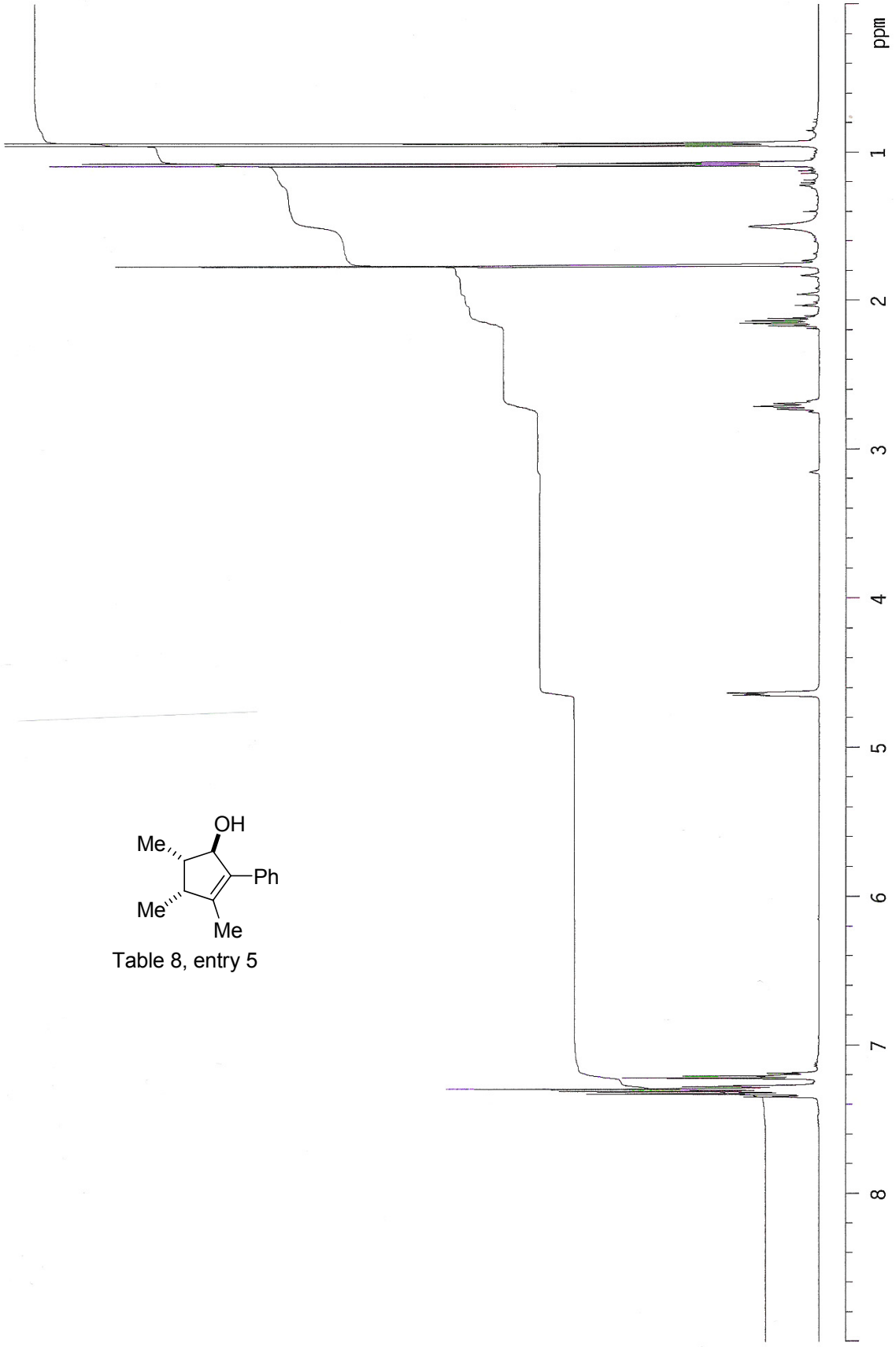


Table 8, entry 4



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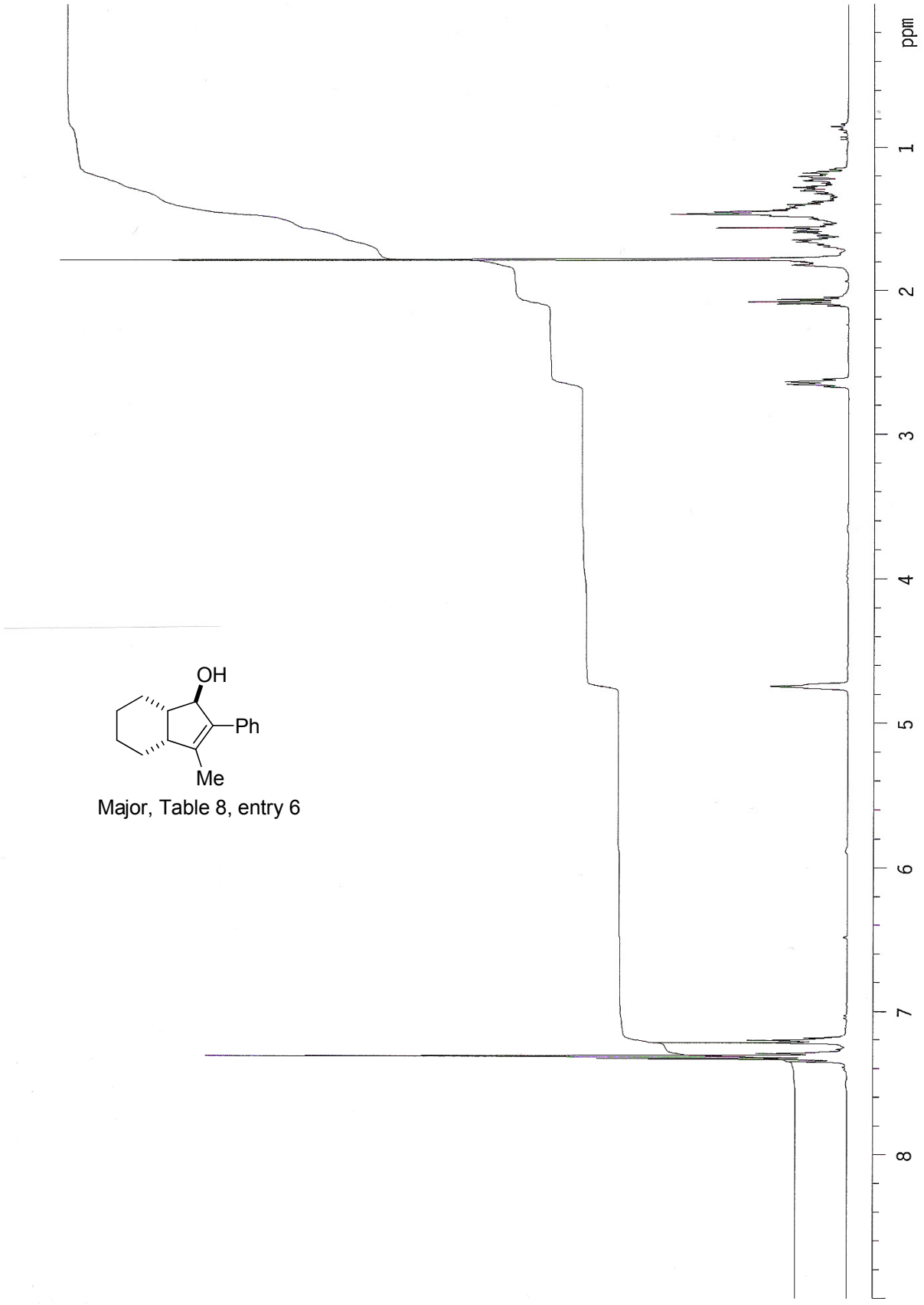

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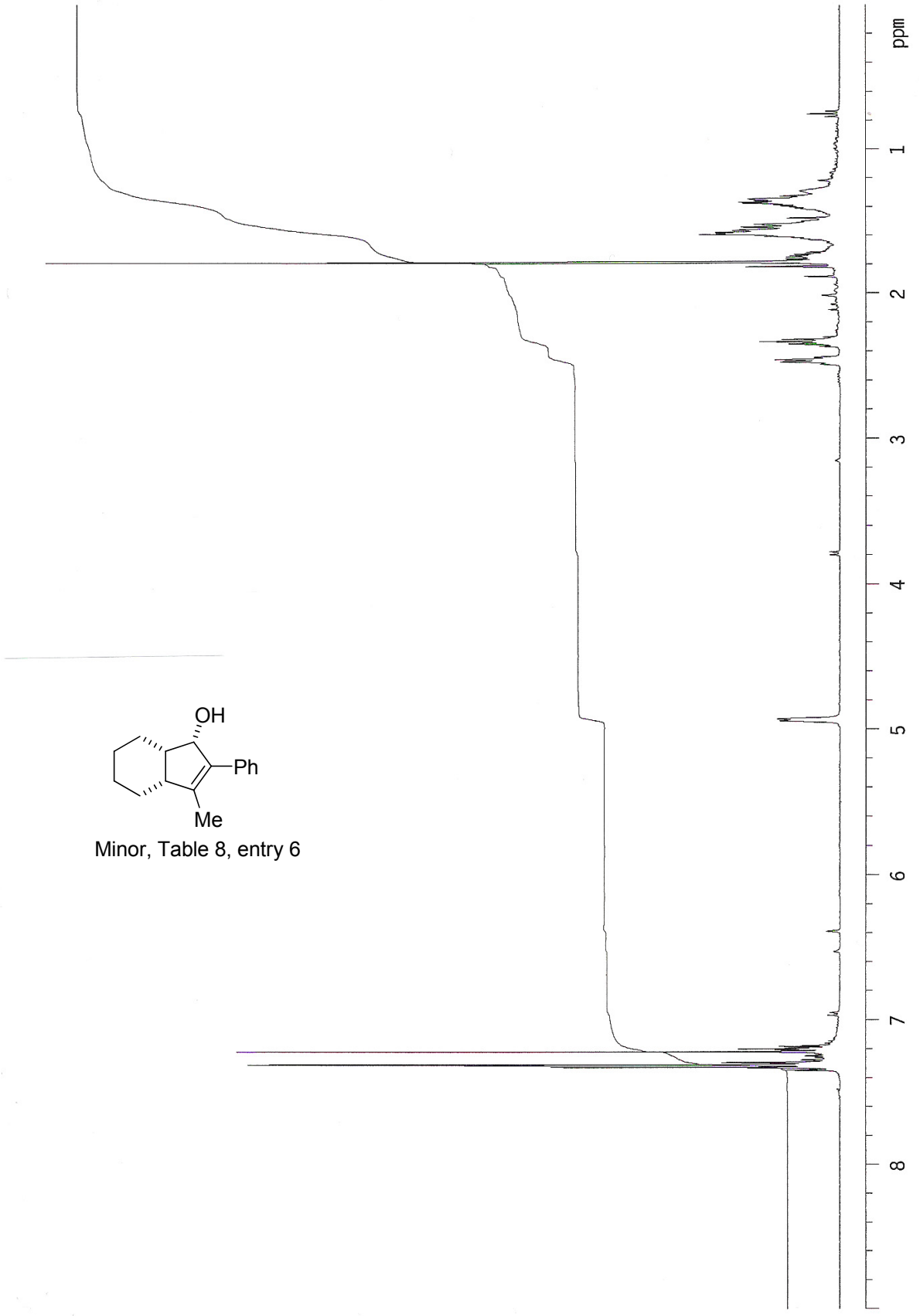

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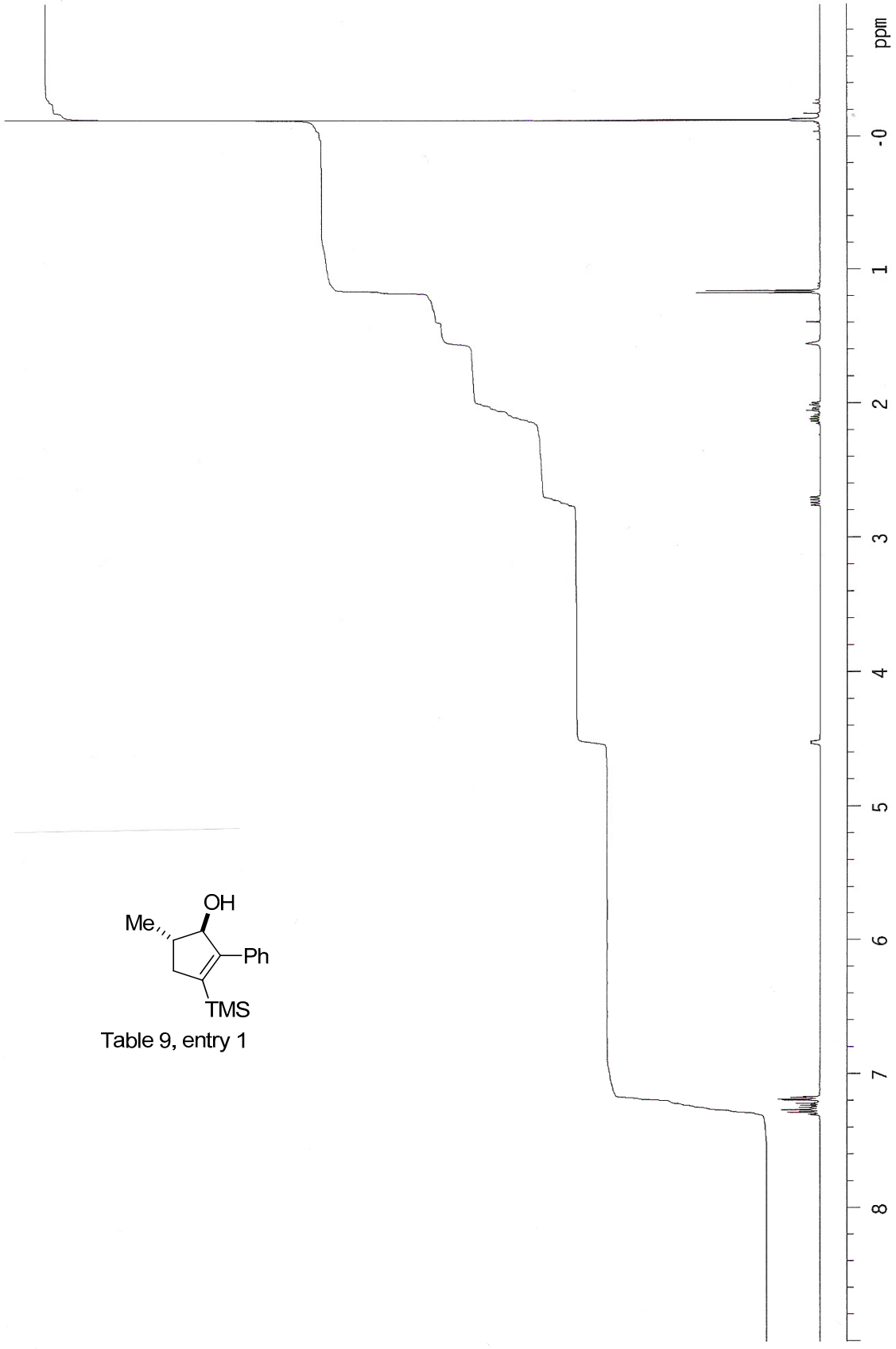

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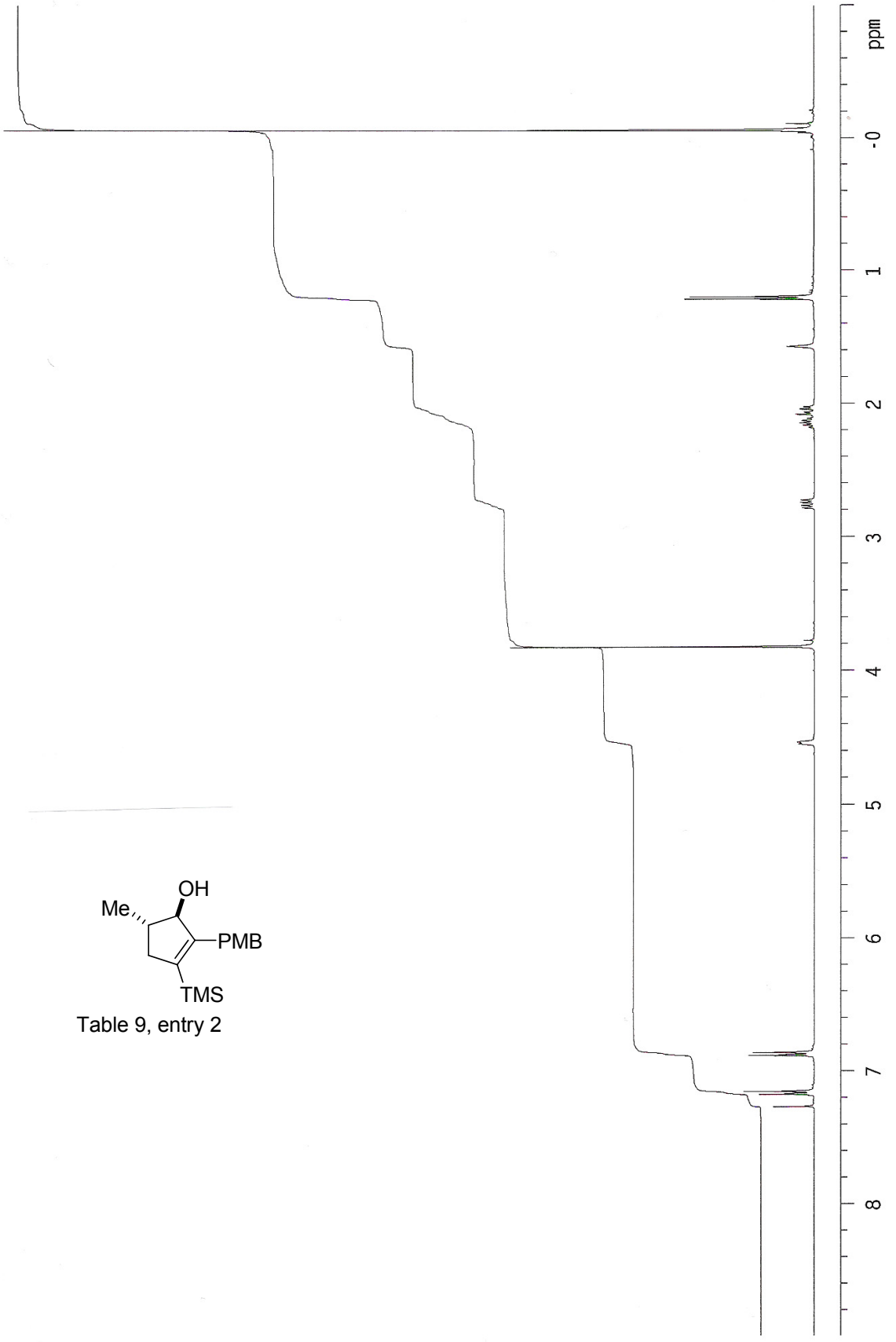

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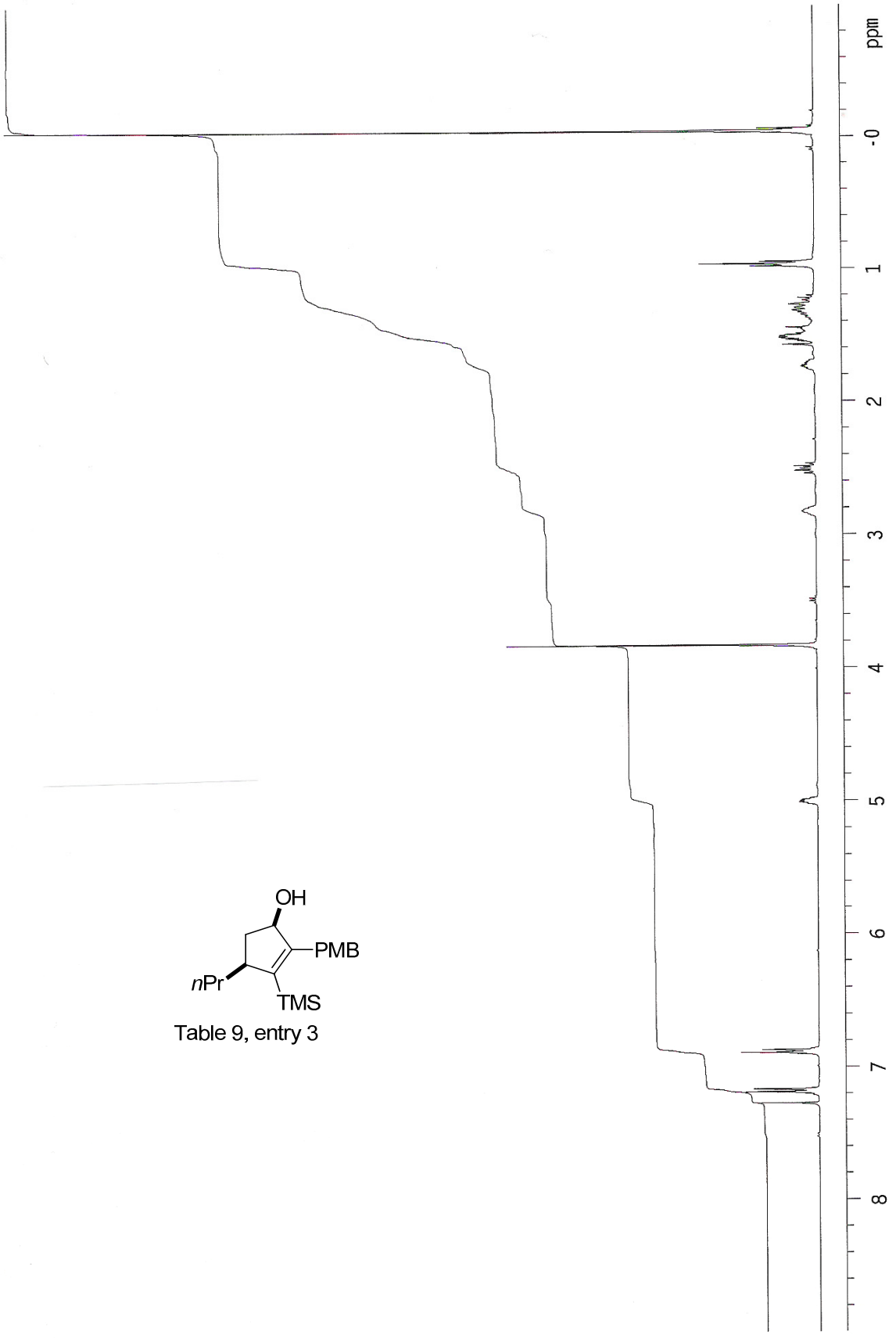

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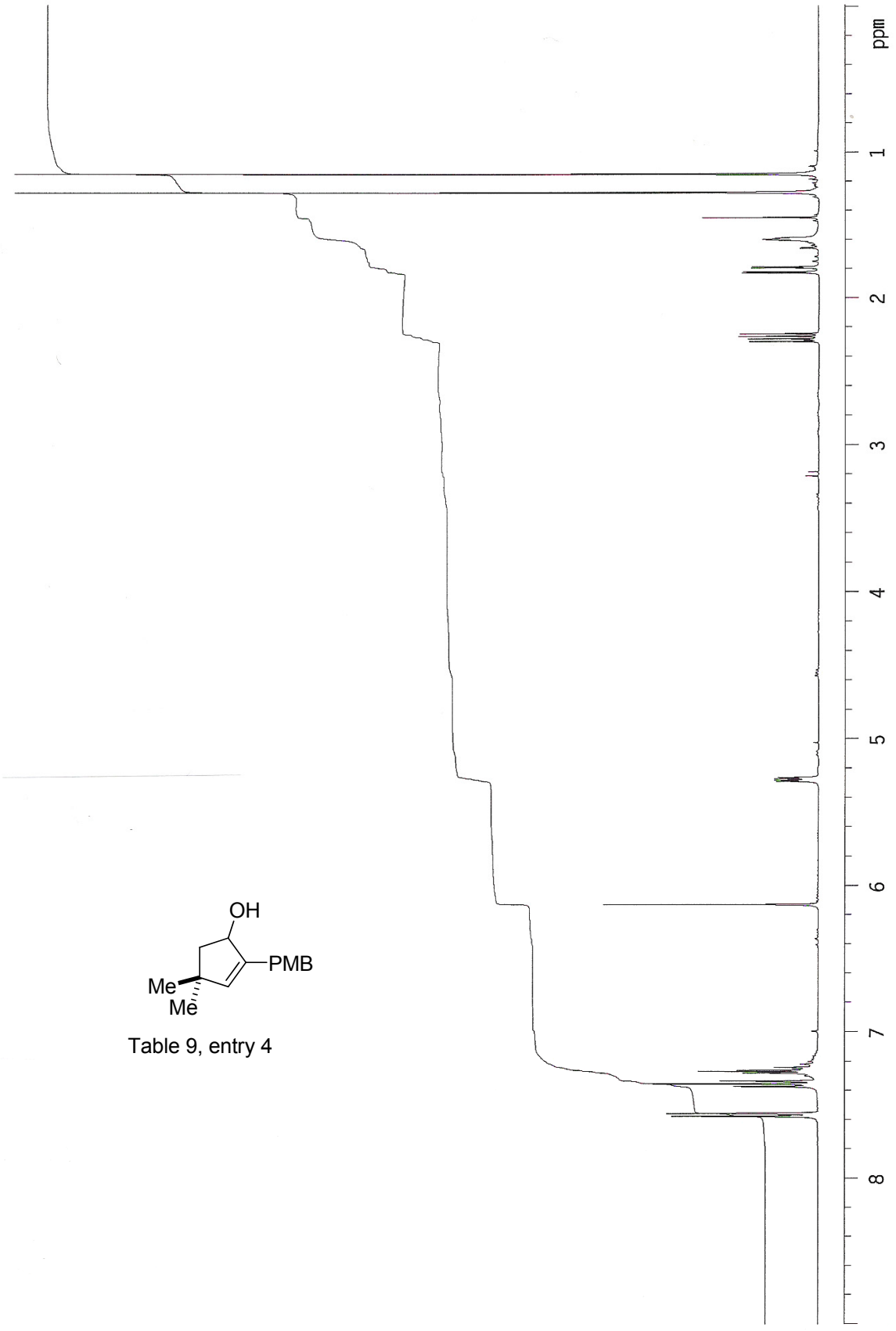

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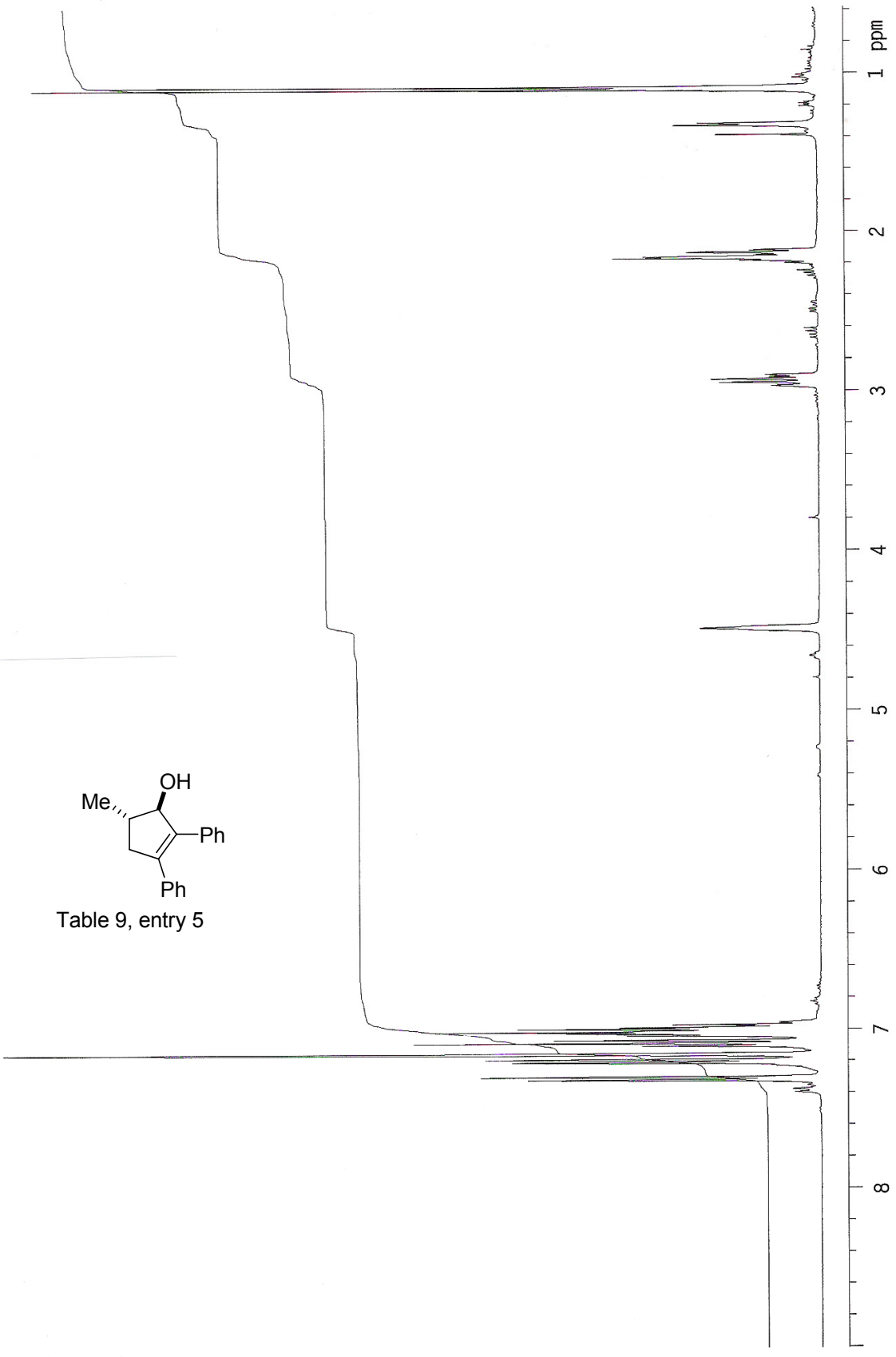

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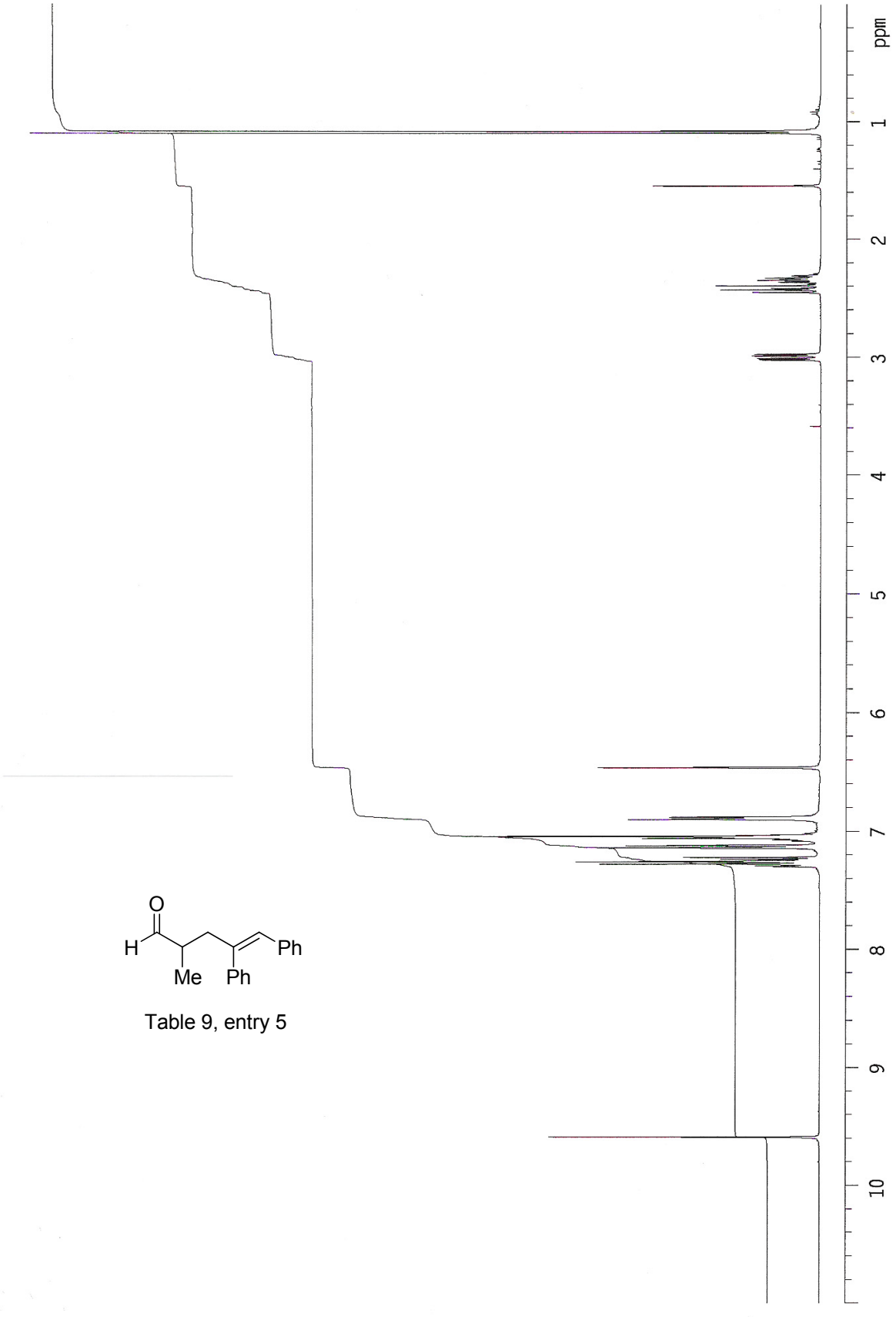

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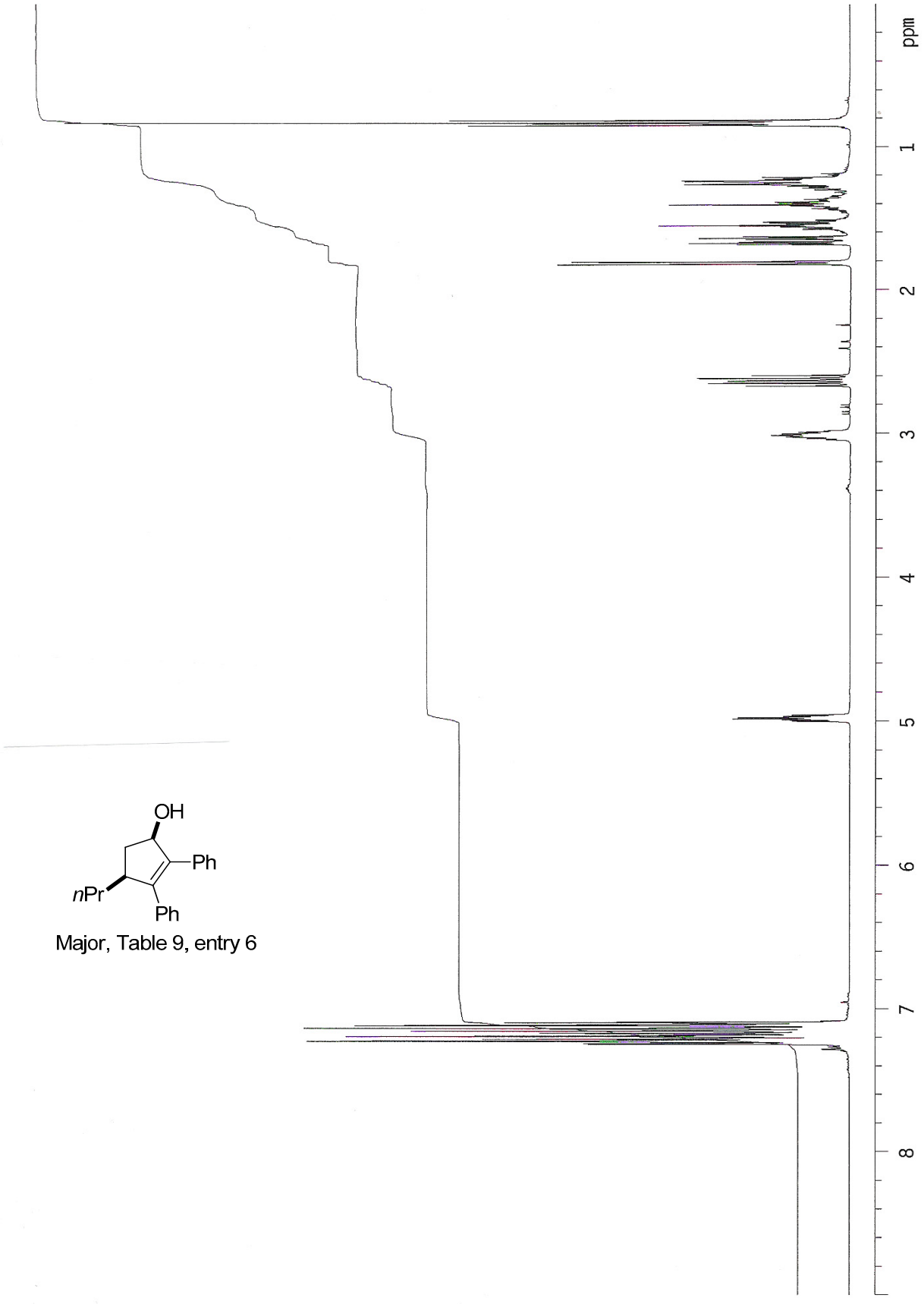
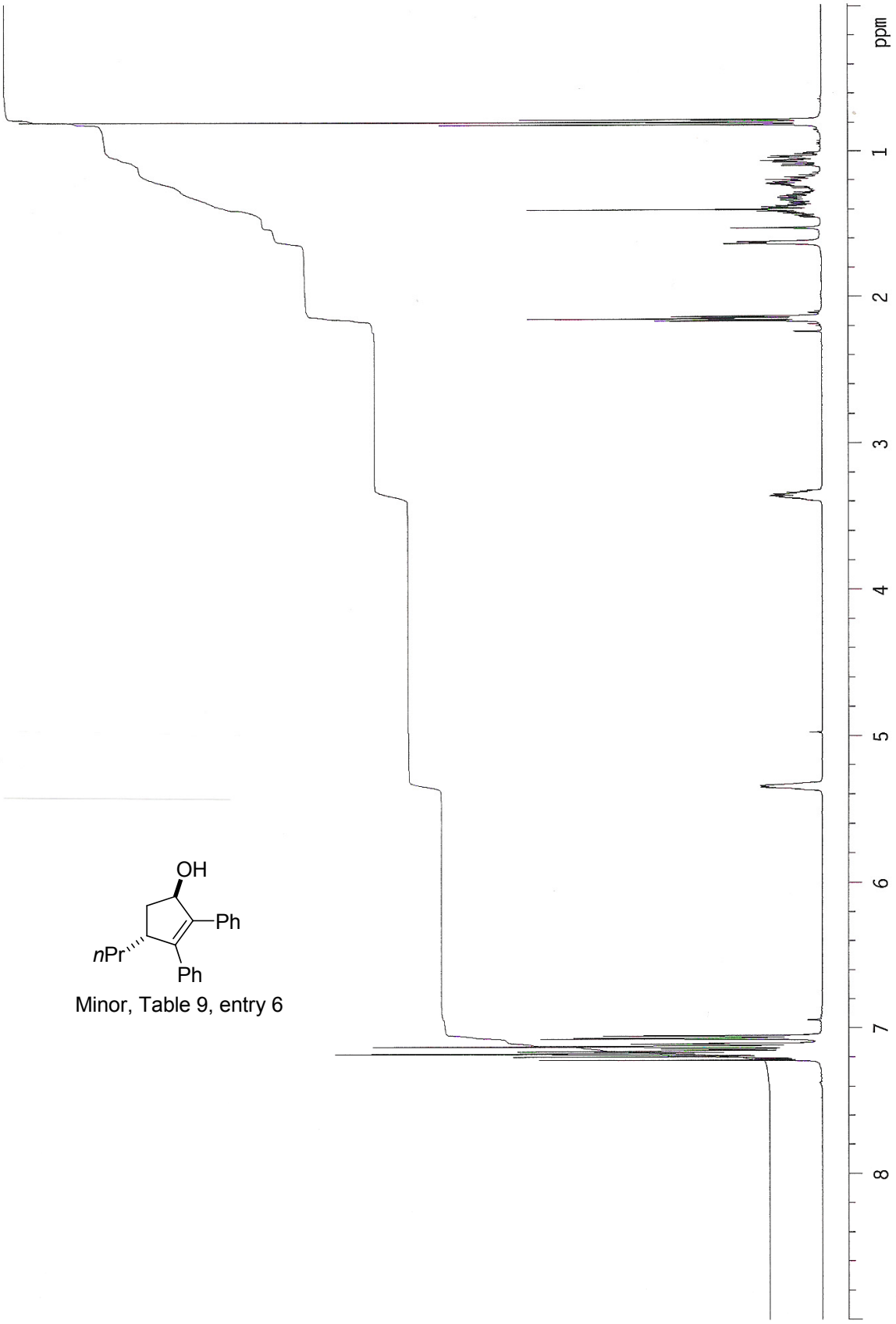


Major, Table 9, entry 6



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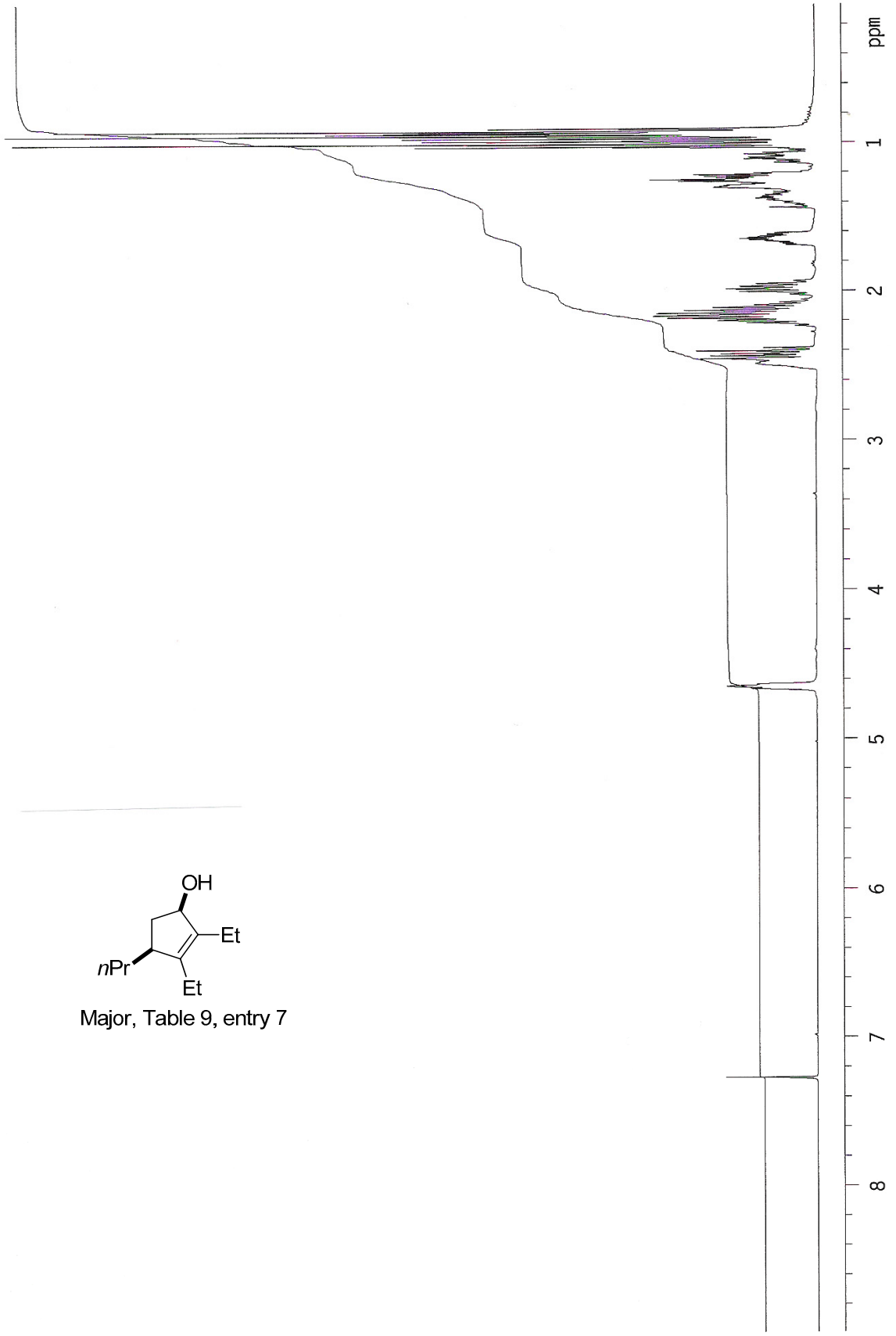
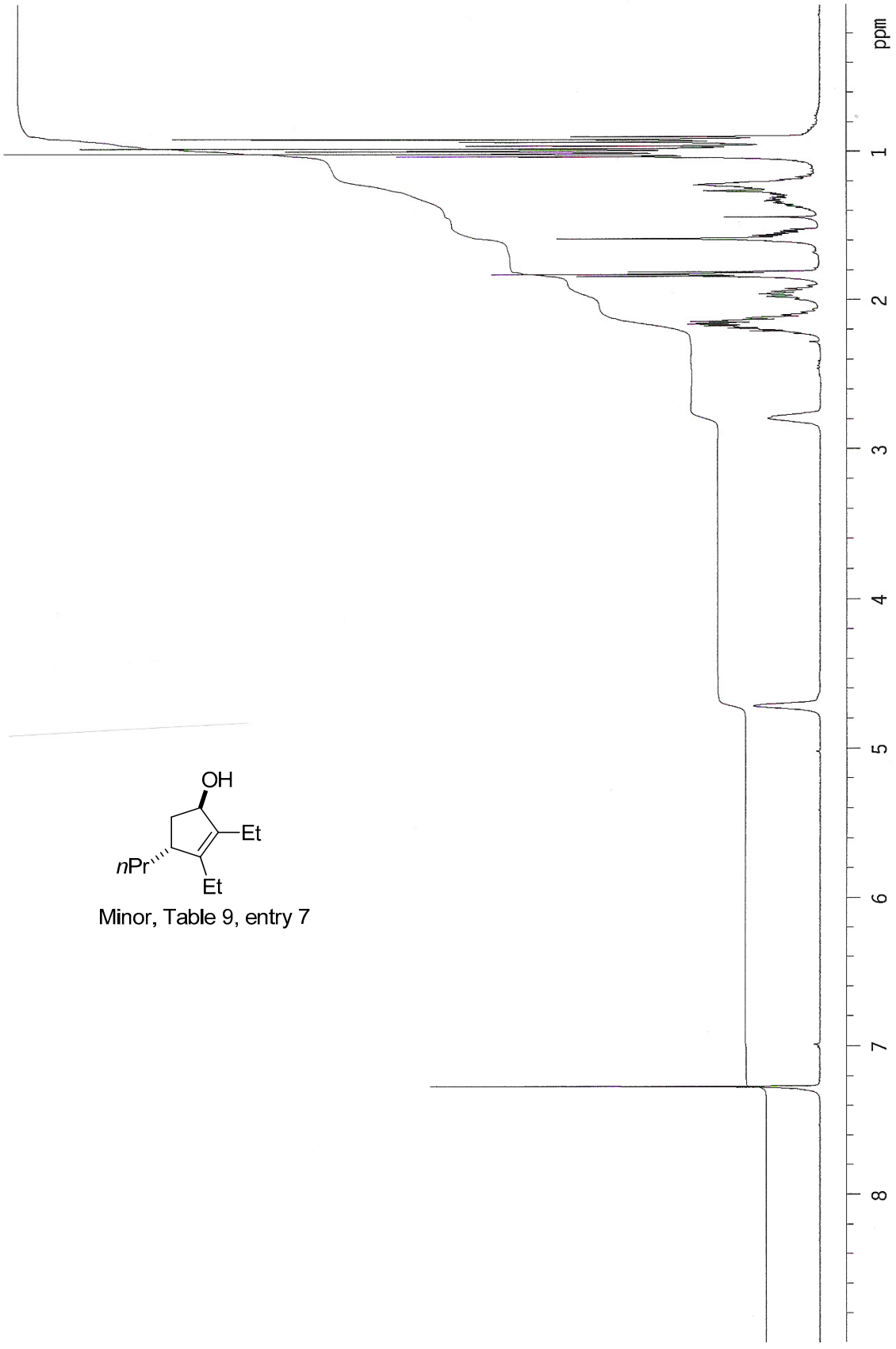
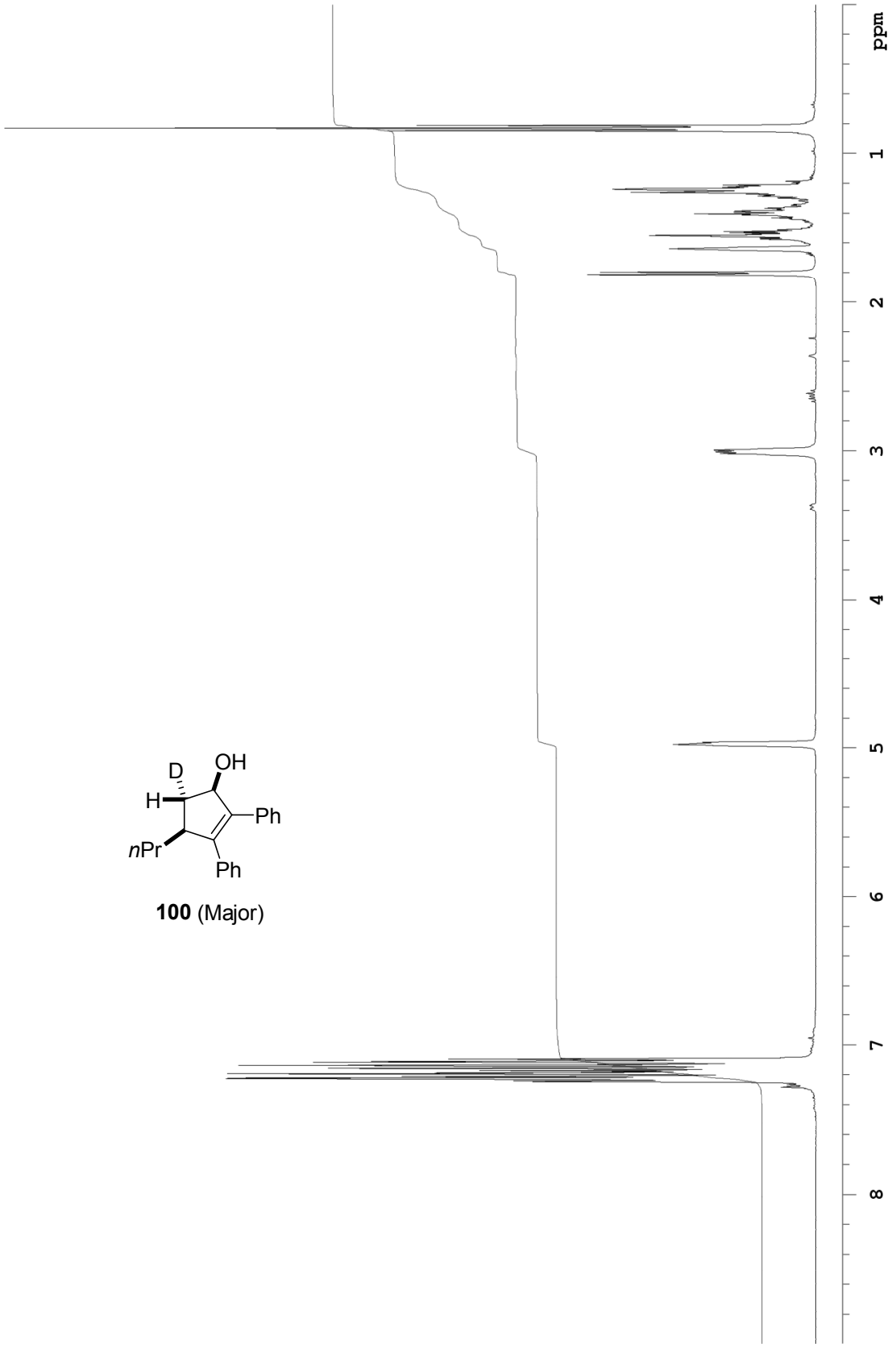


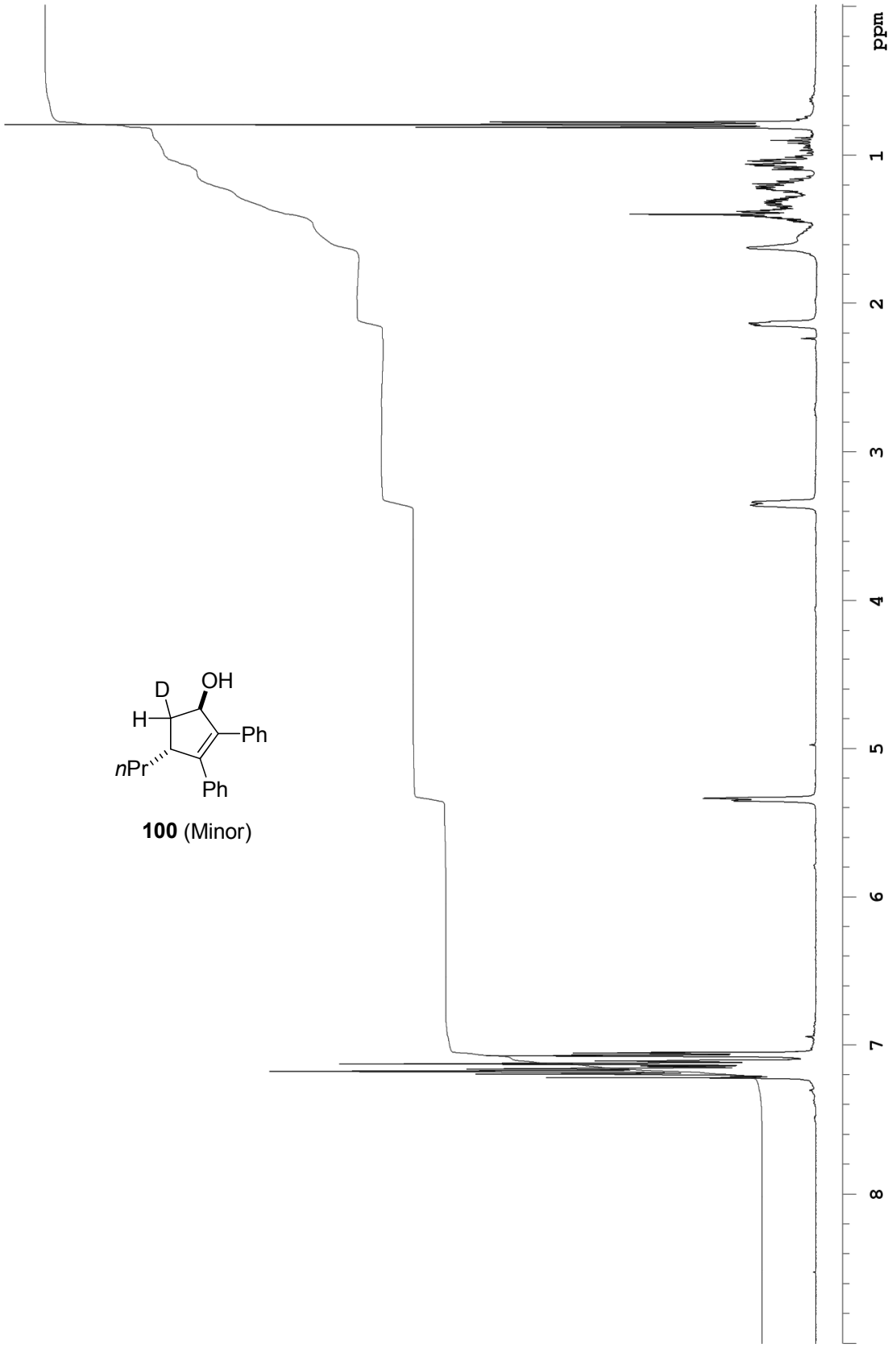
Major, Table 9, entry 7



Minor, Table 9, entry 7



100 (Major)



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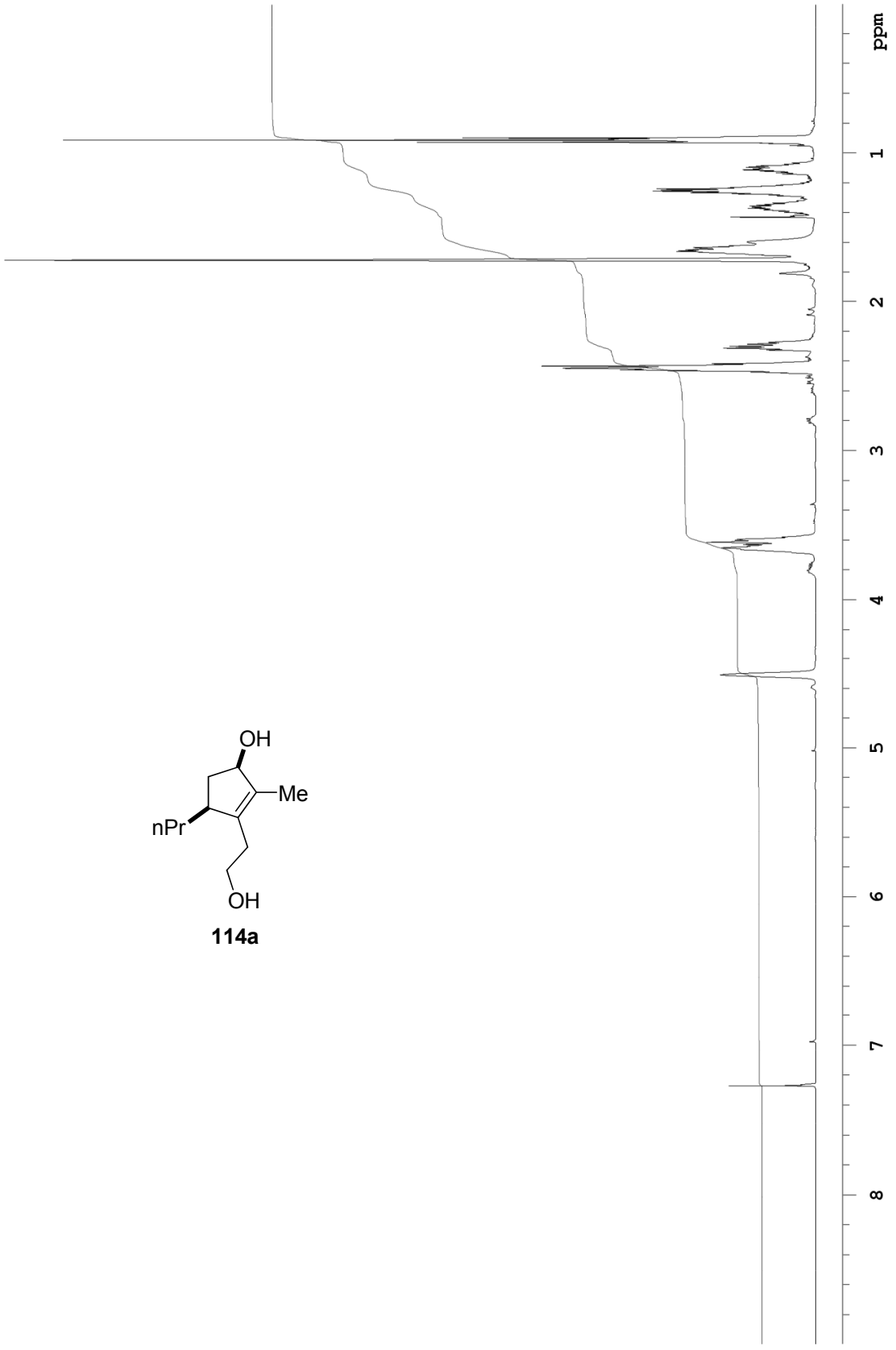

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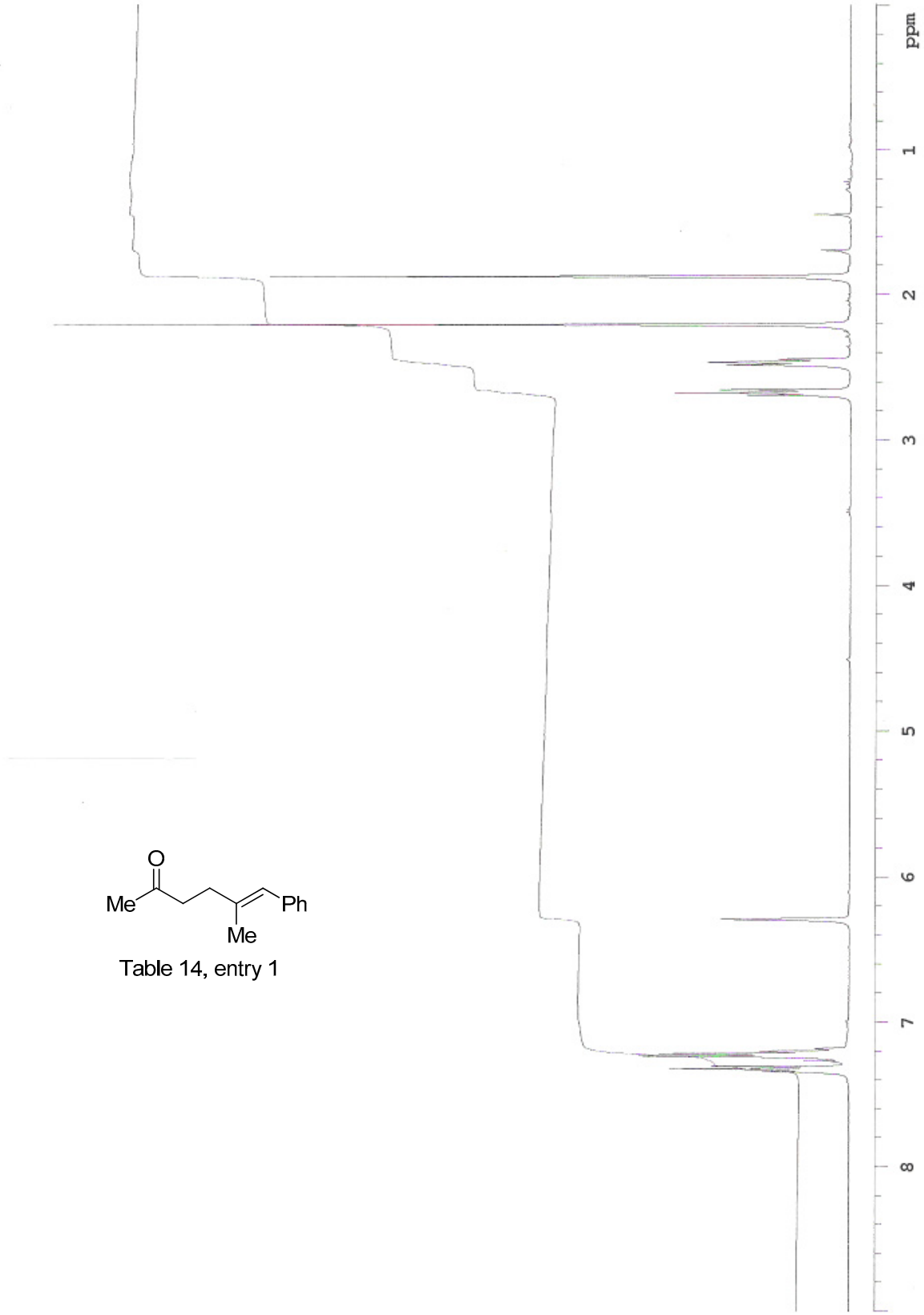

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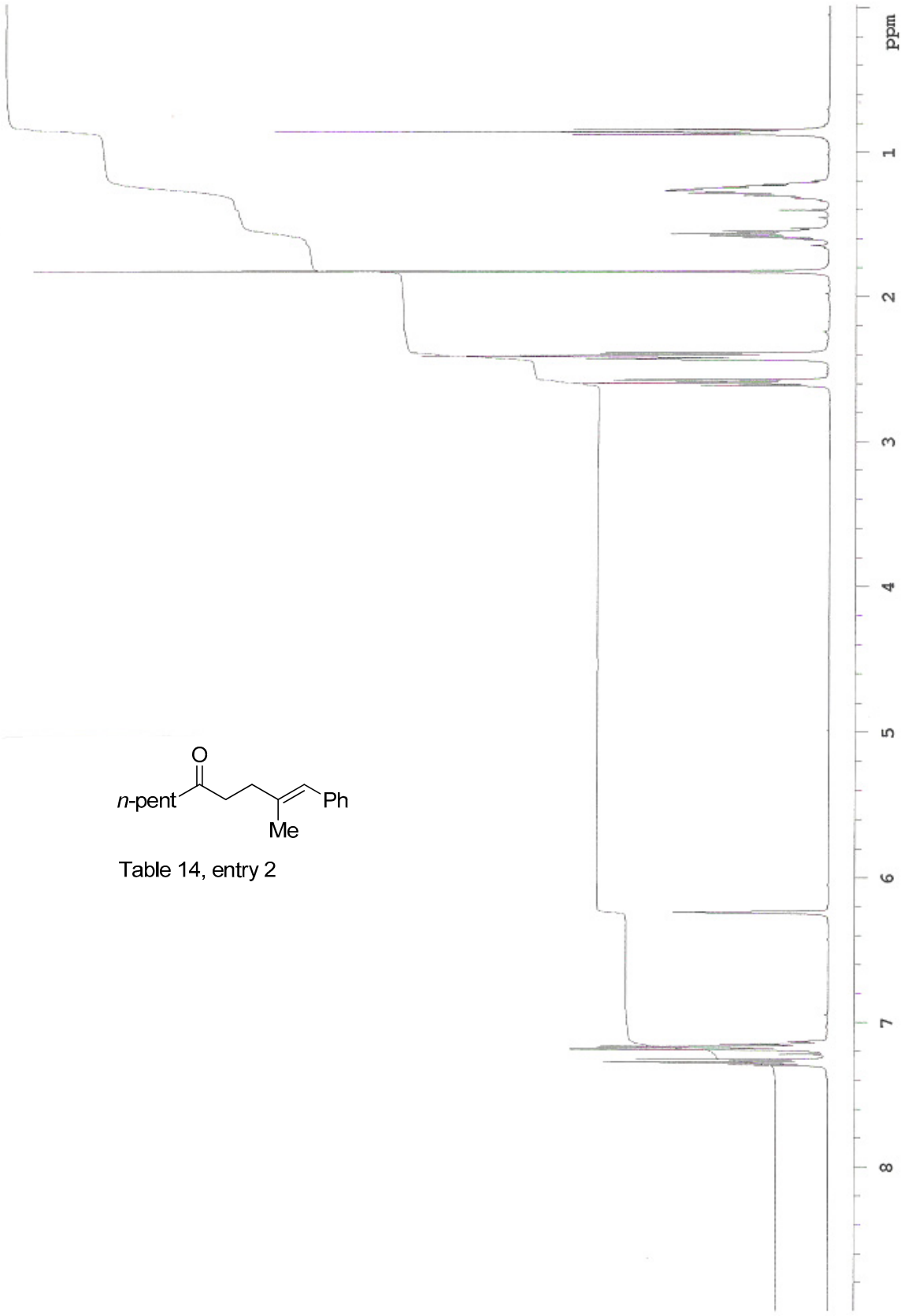

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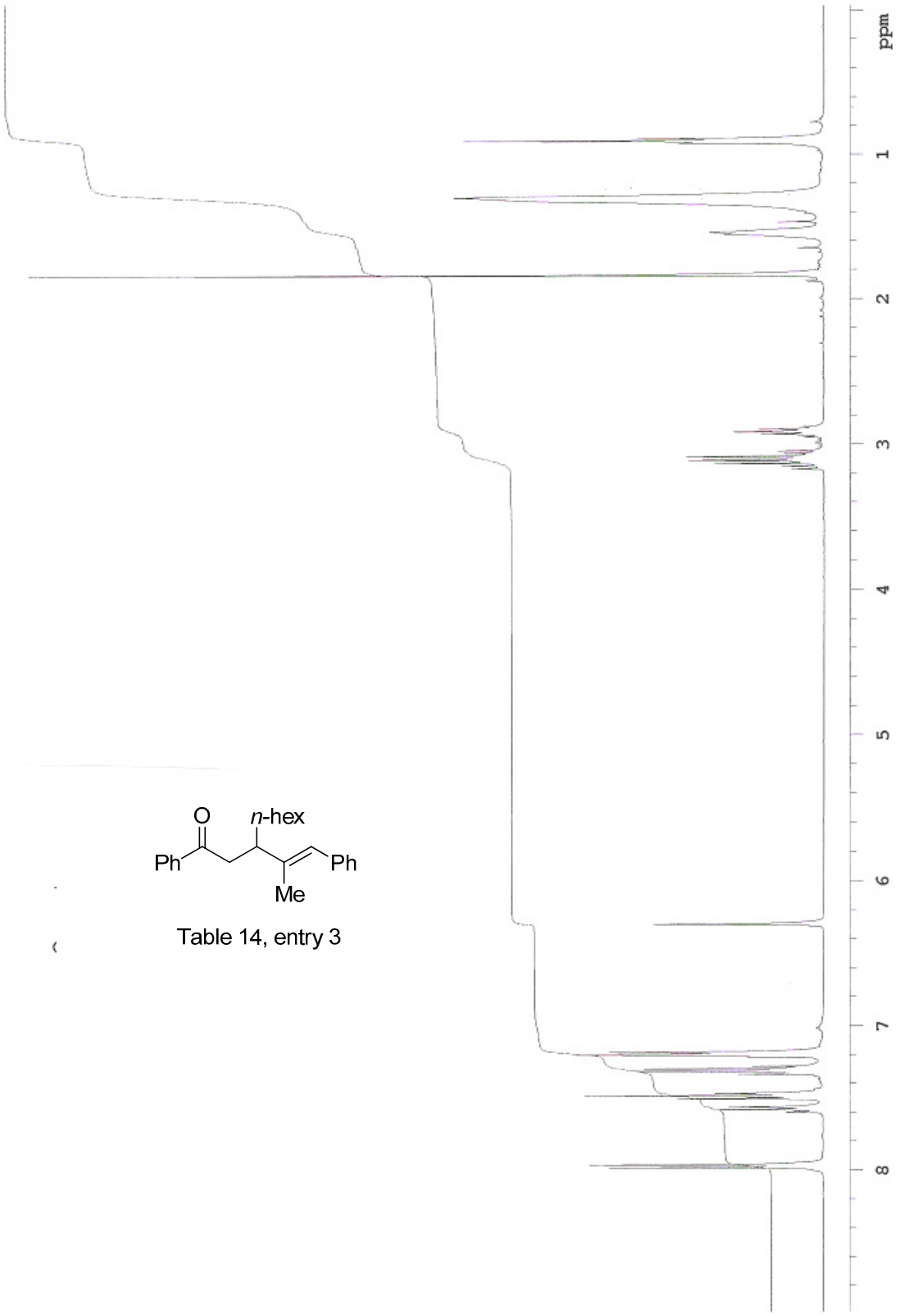
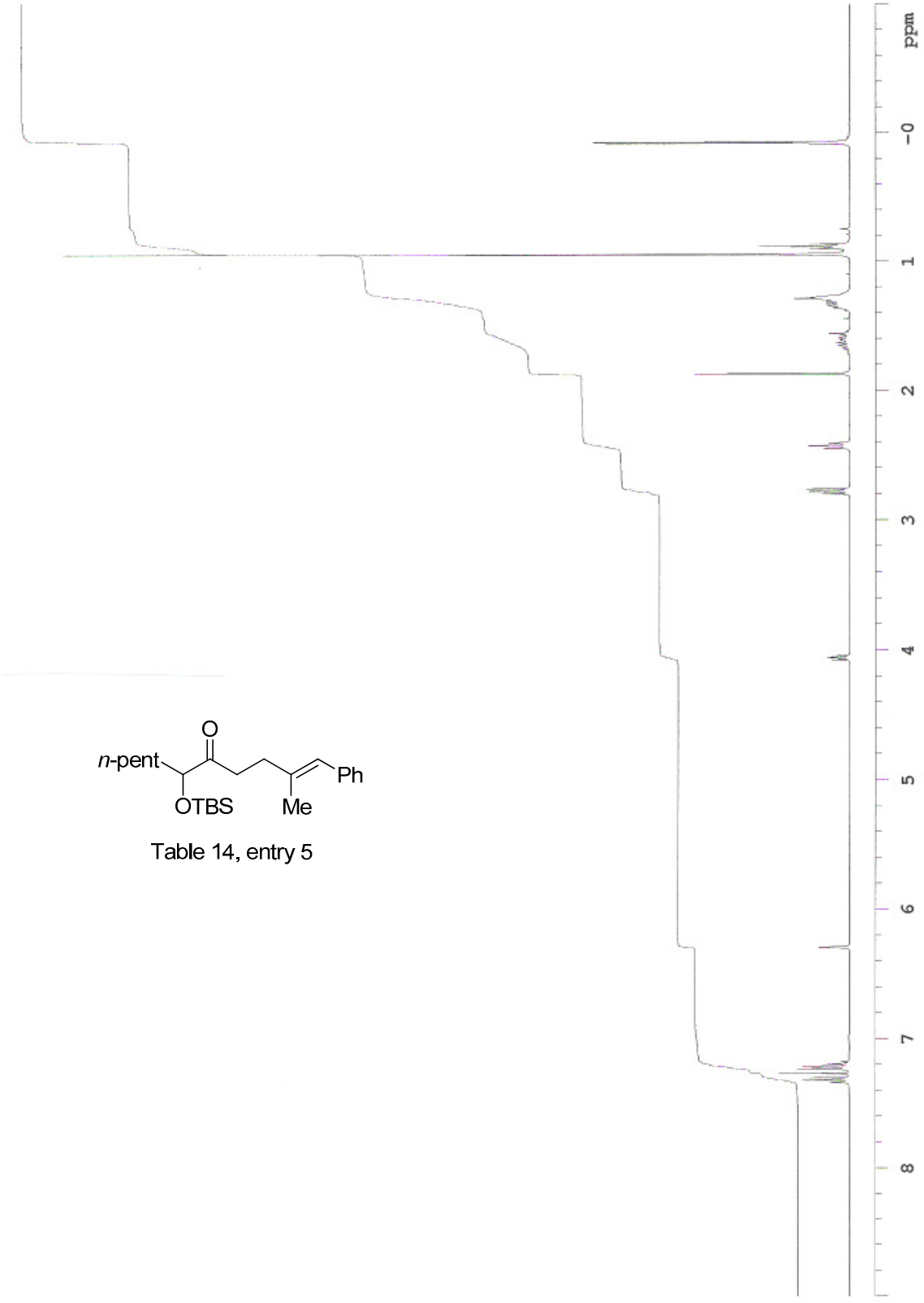


Table 14, entry 3

Table 14, entry 4



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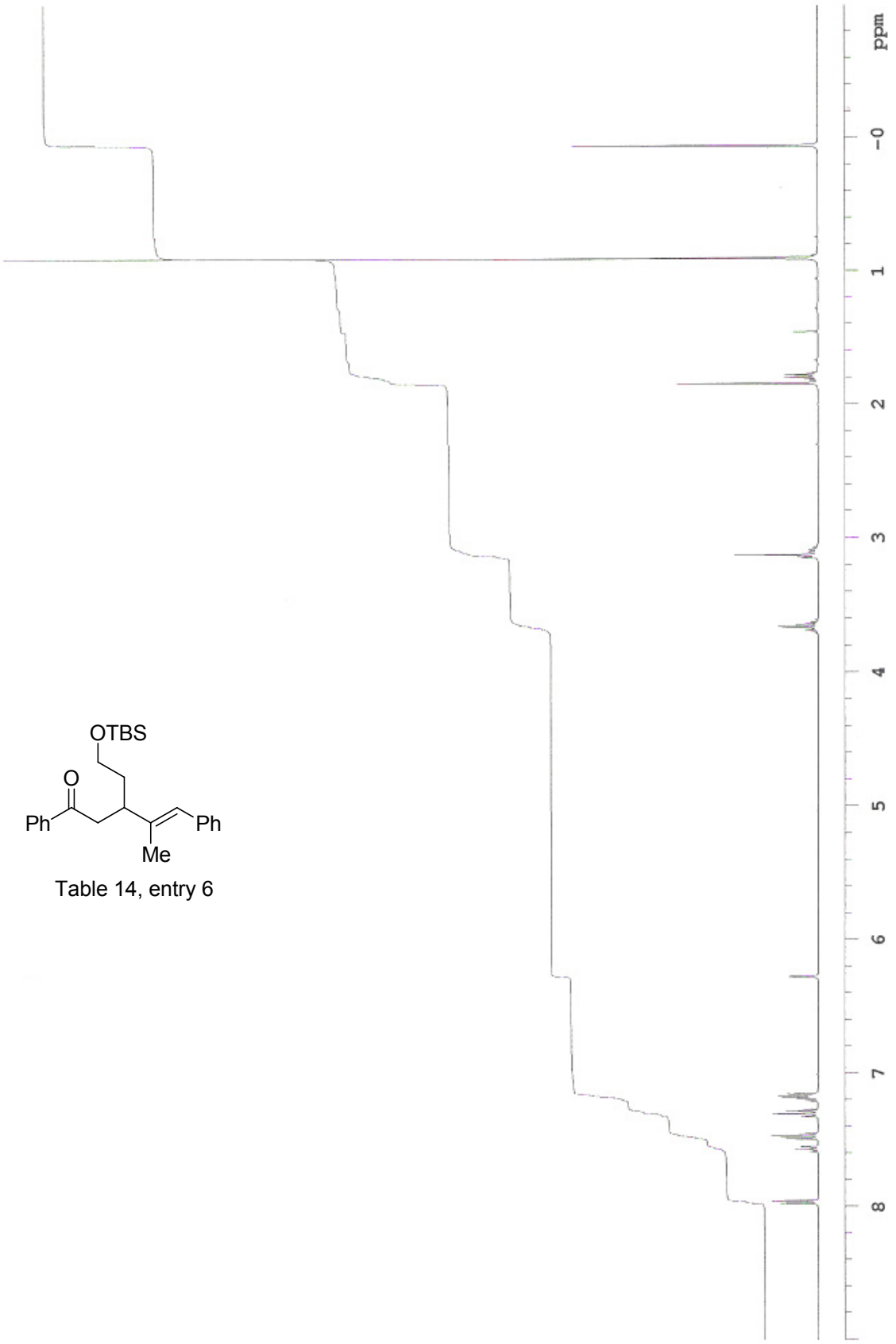

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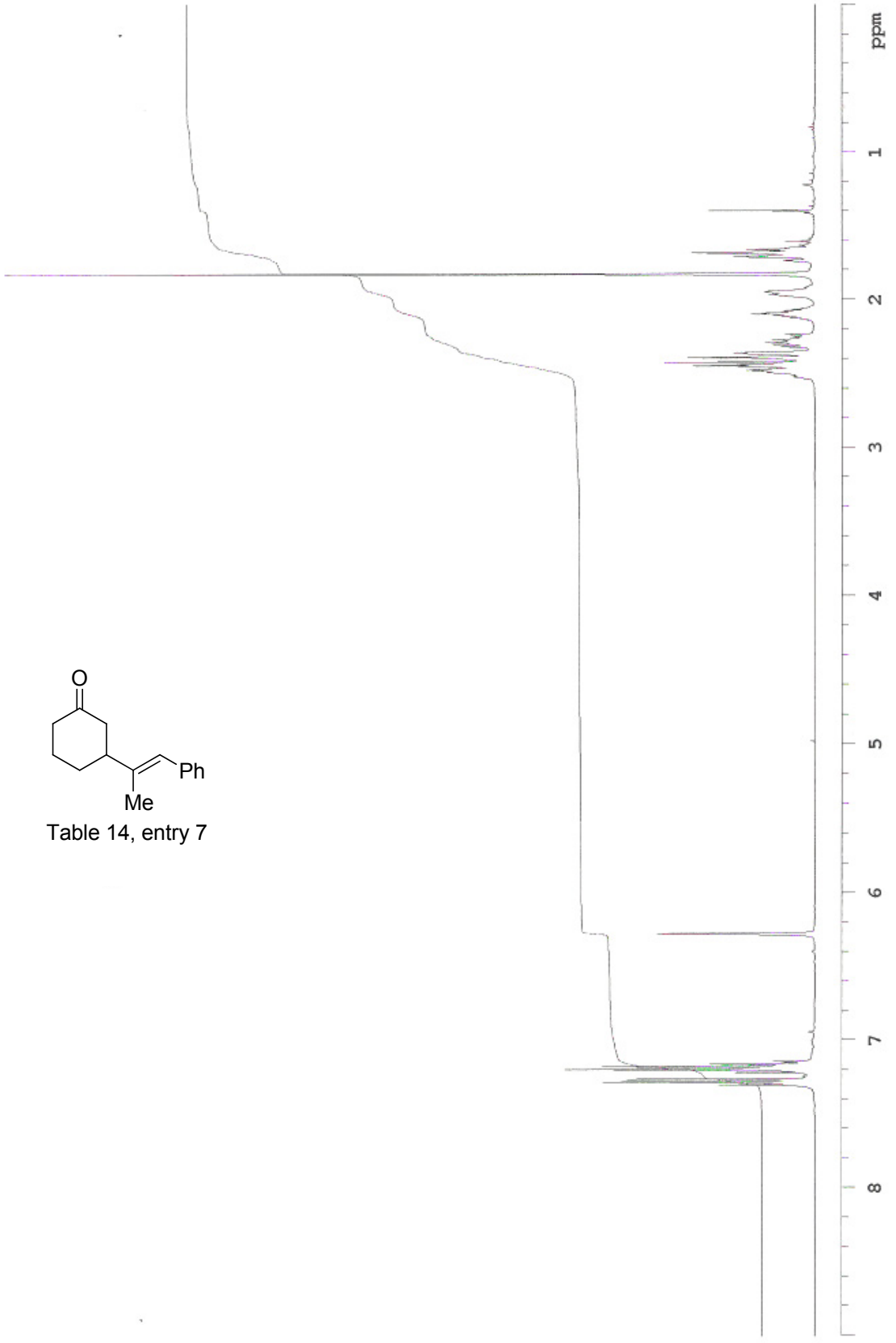

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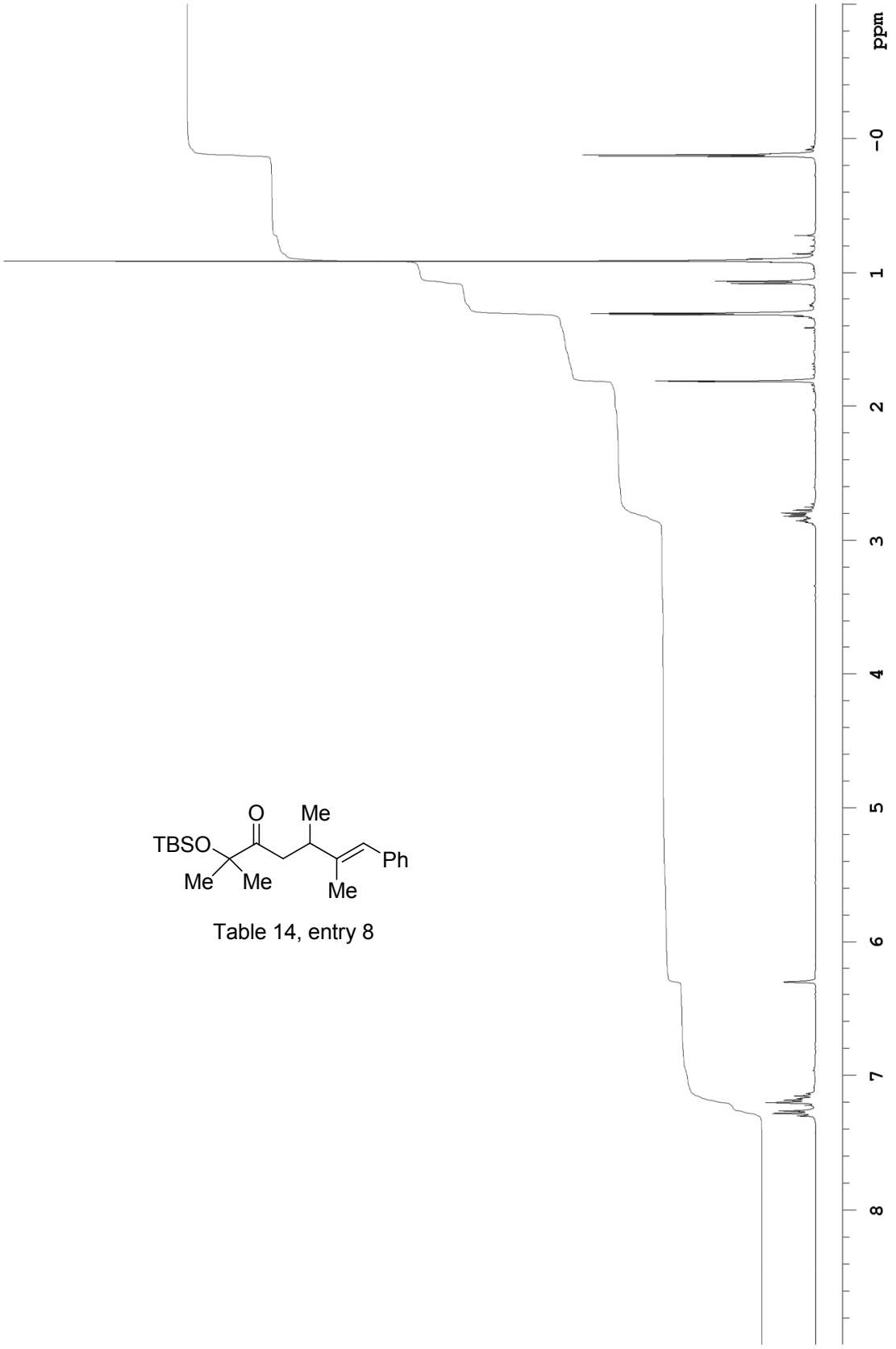

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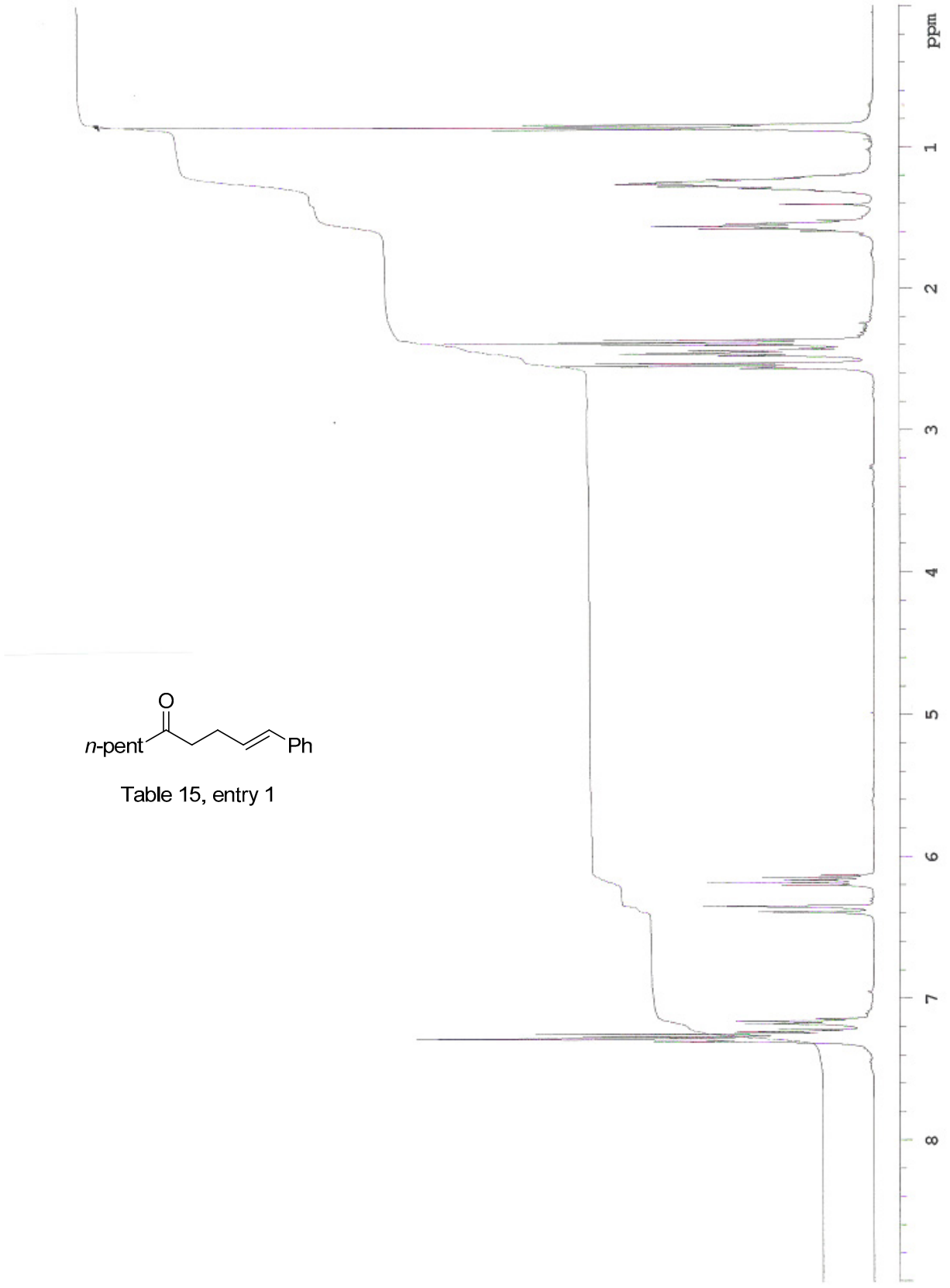

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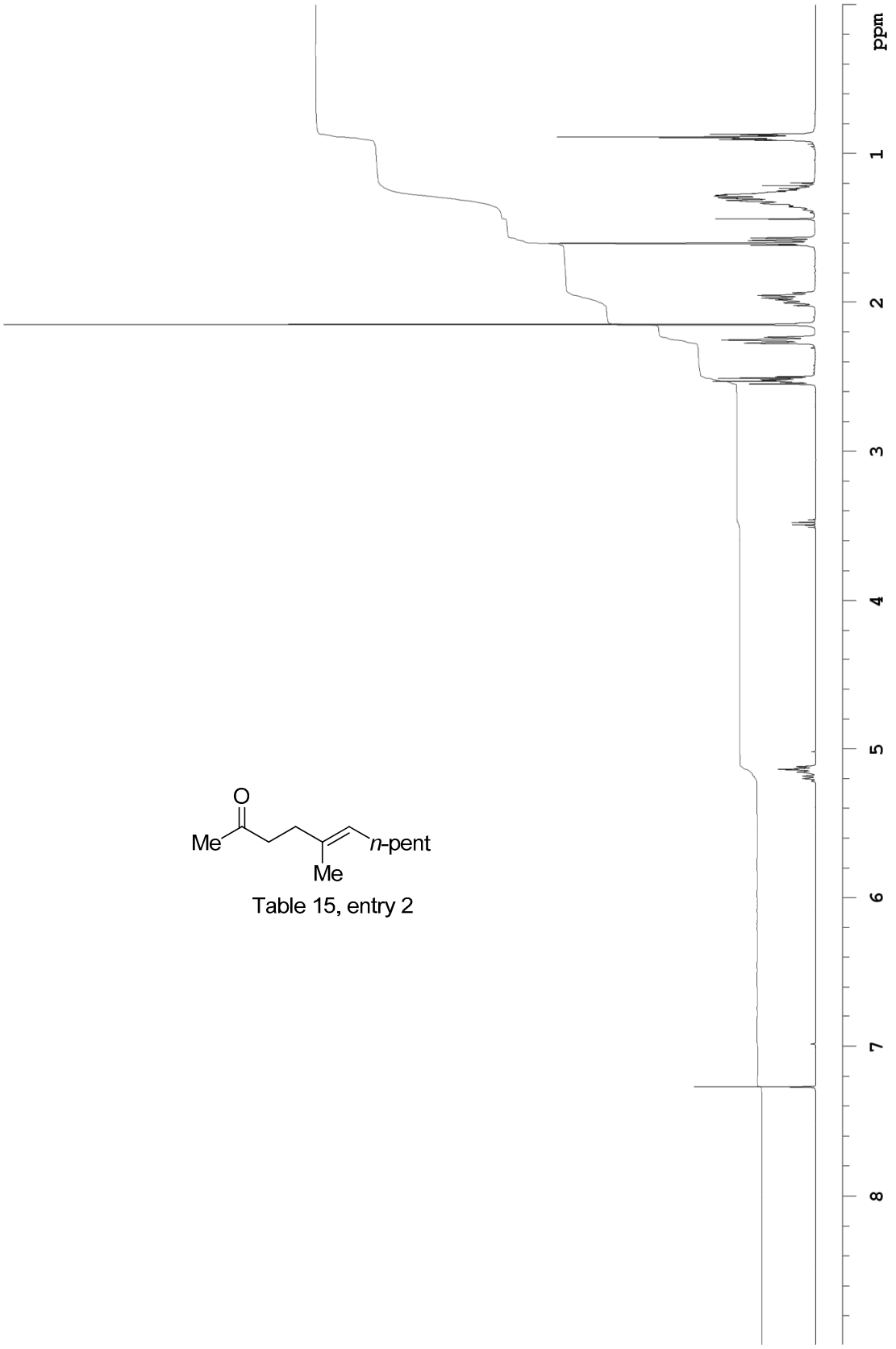

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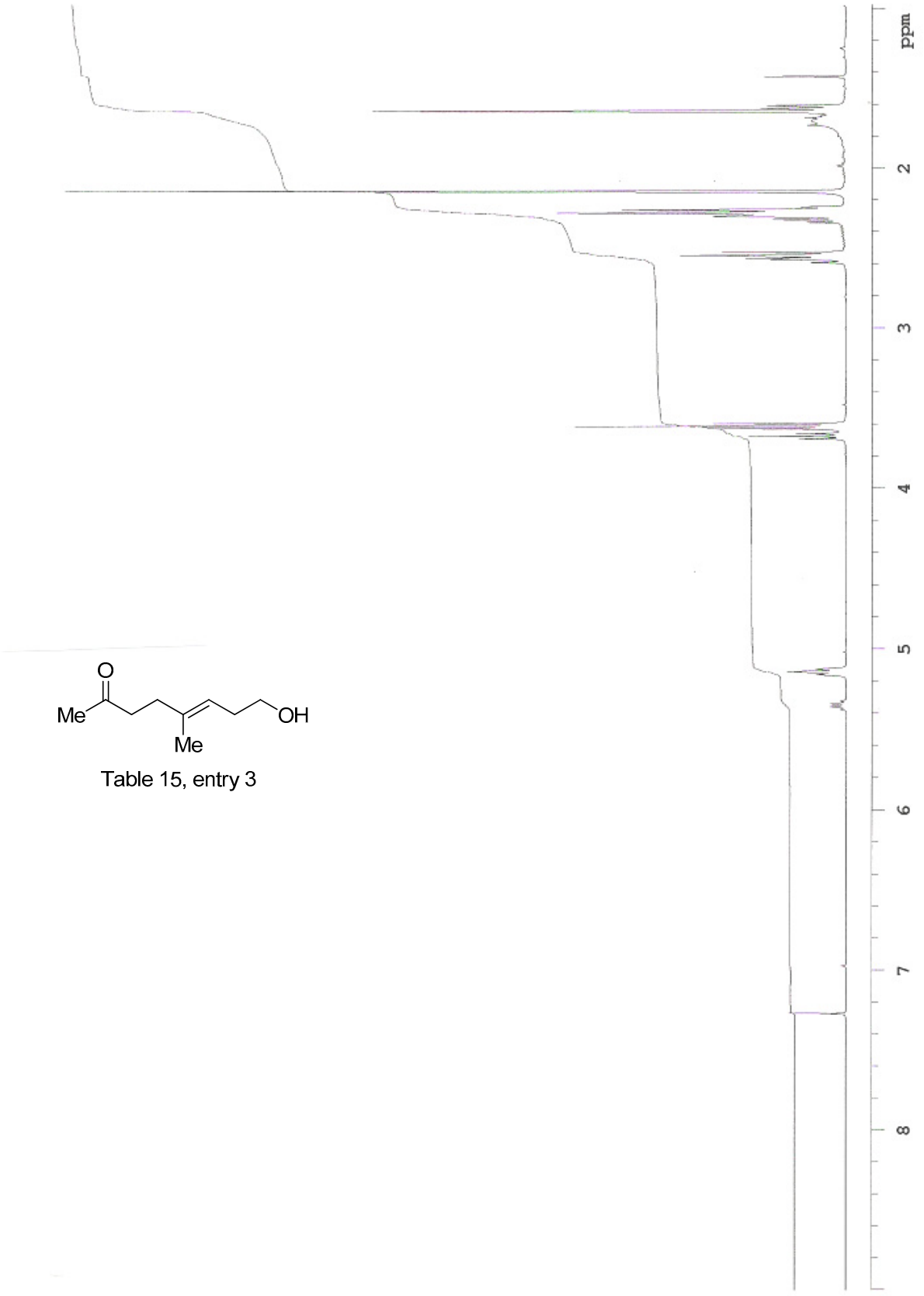

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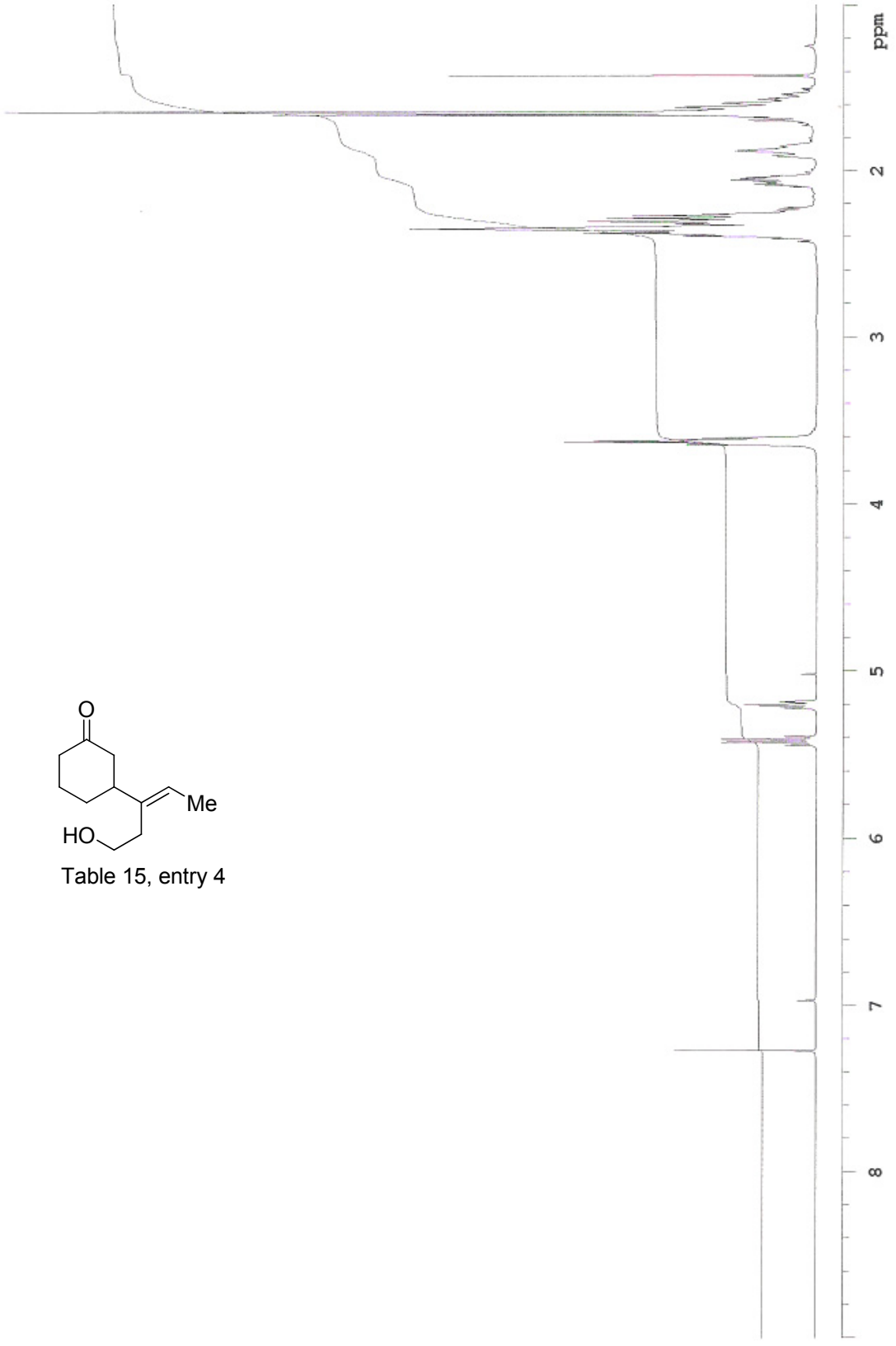

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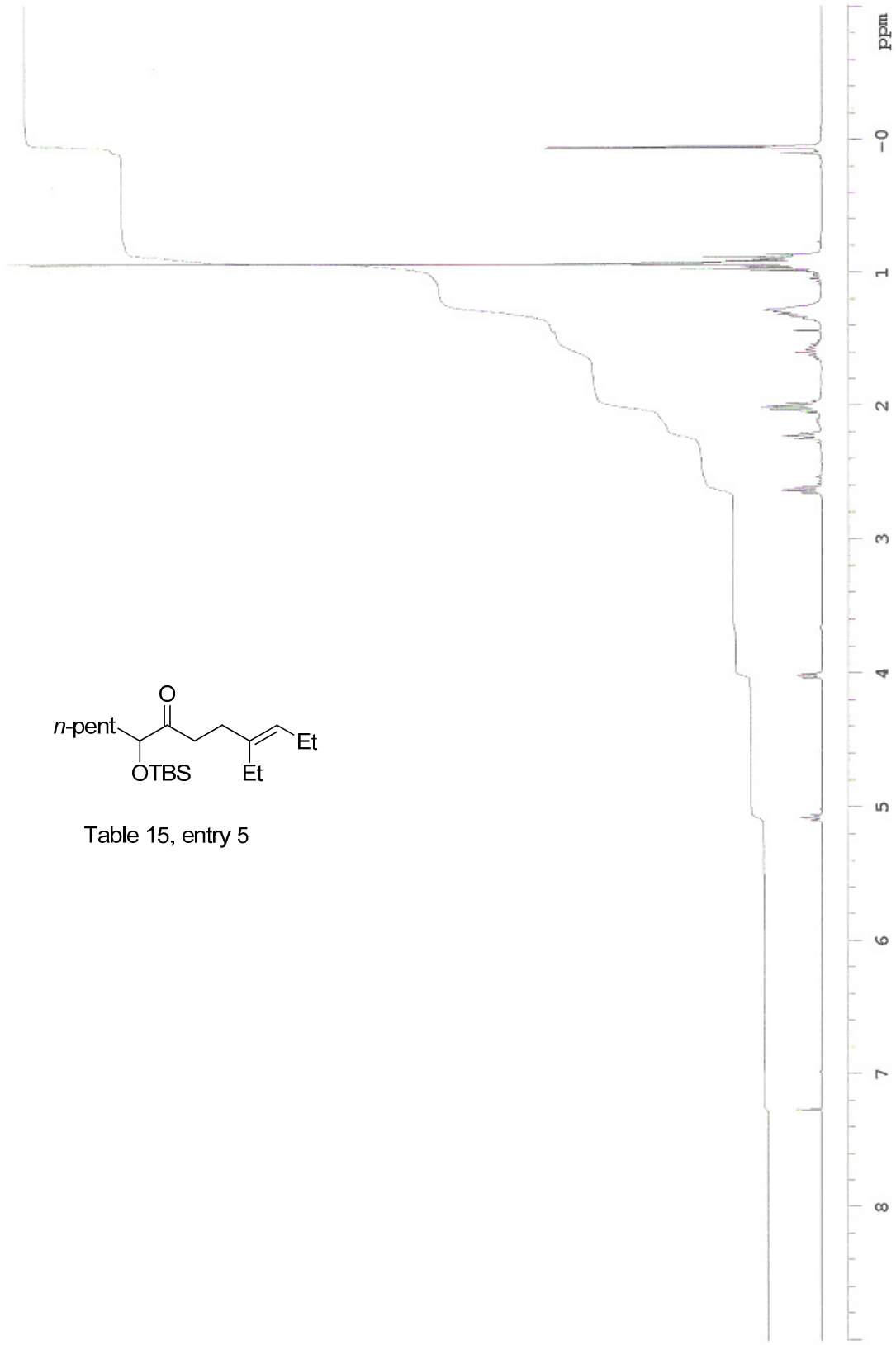

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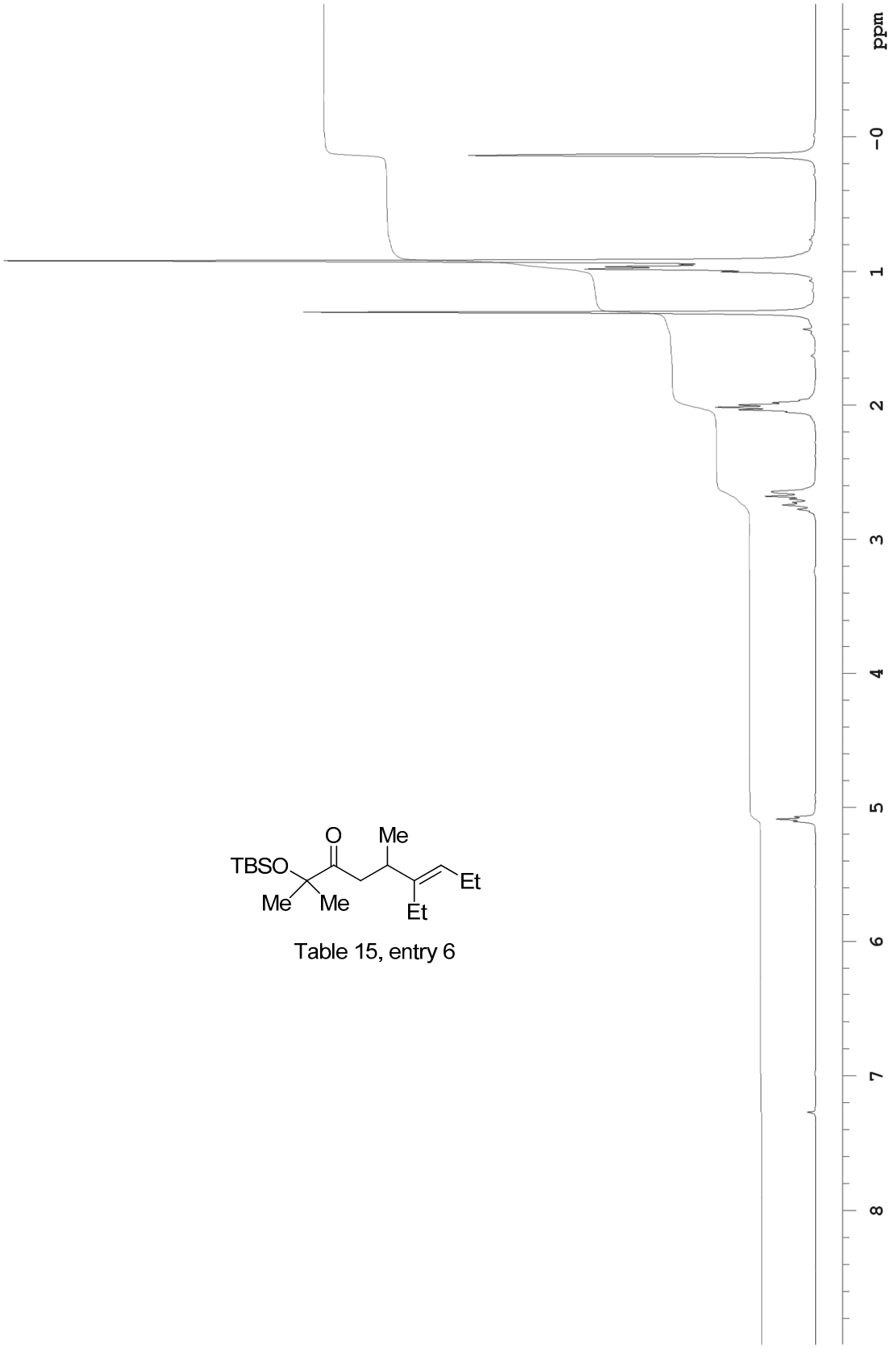

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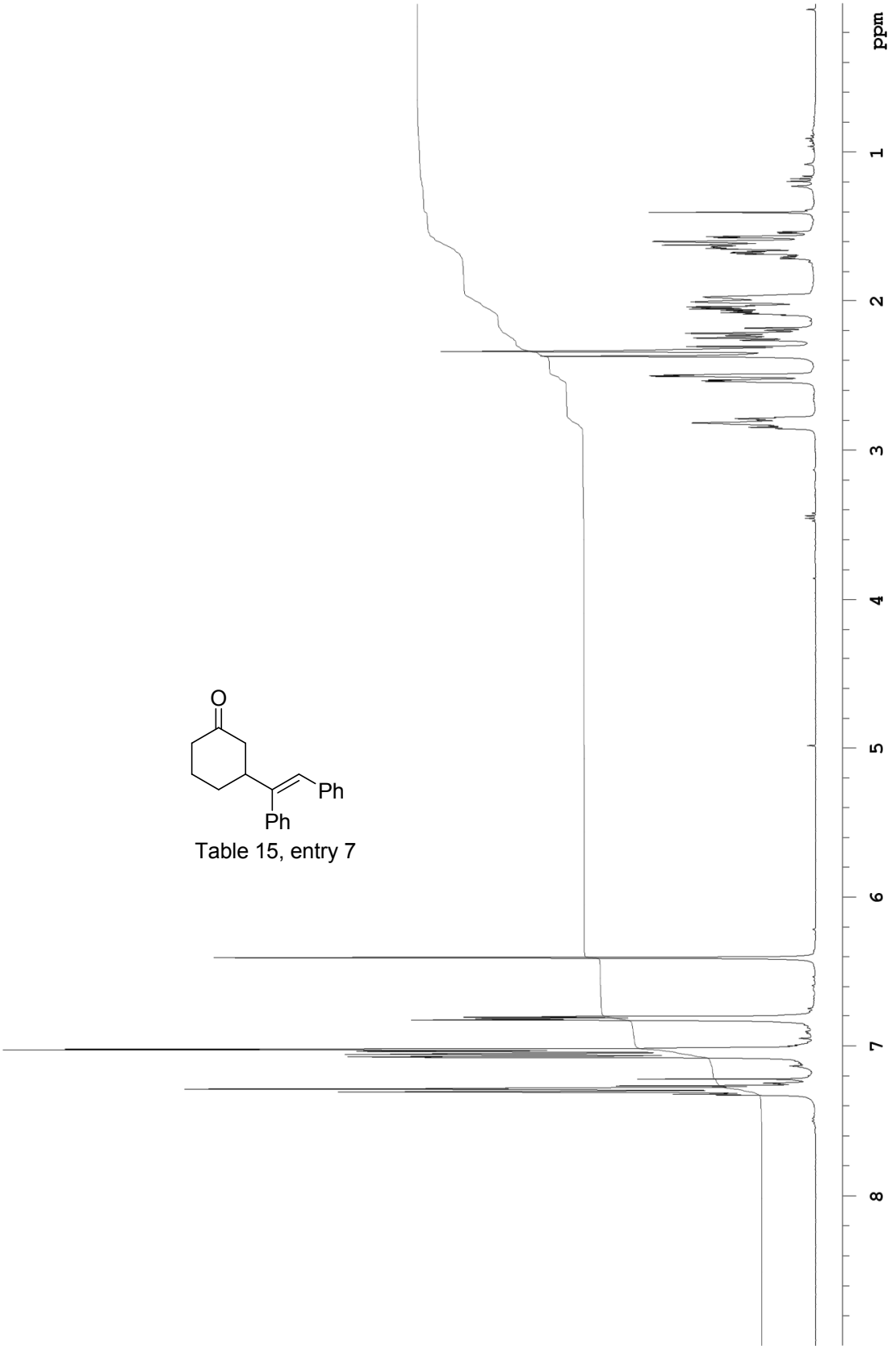

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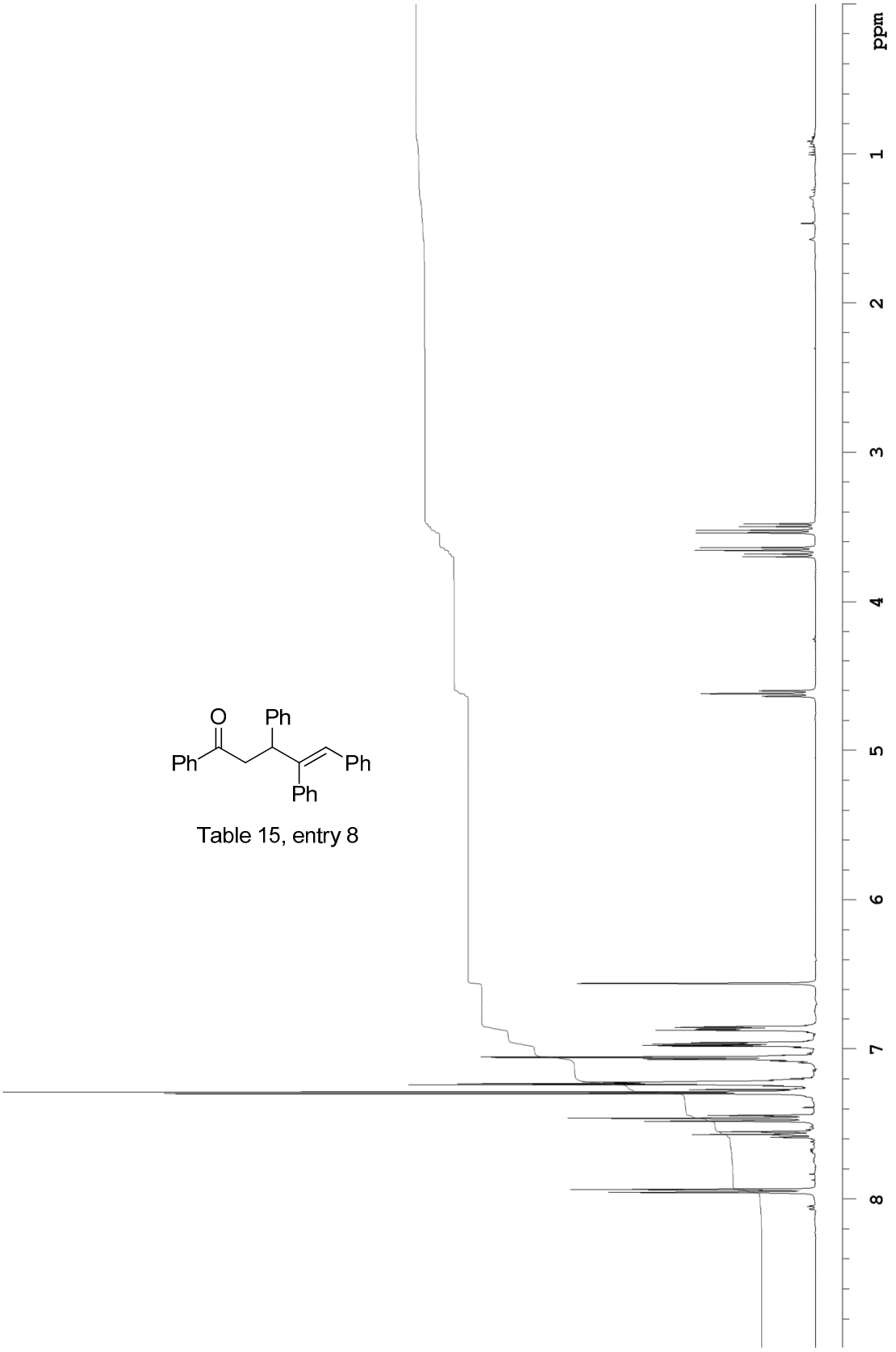

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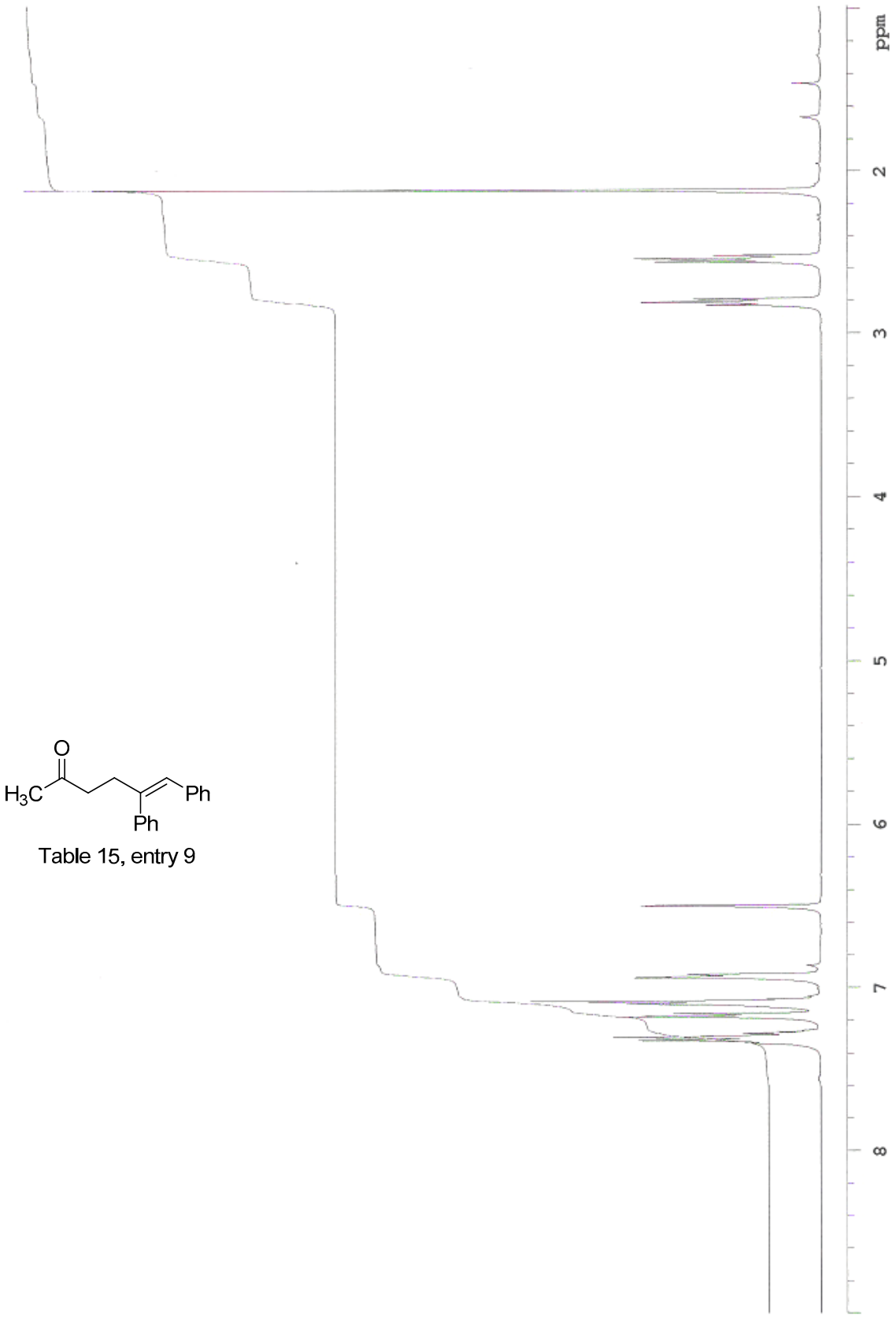

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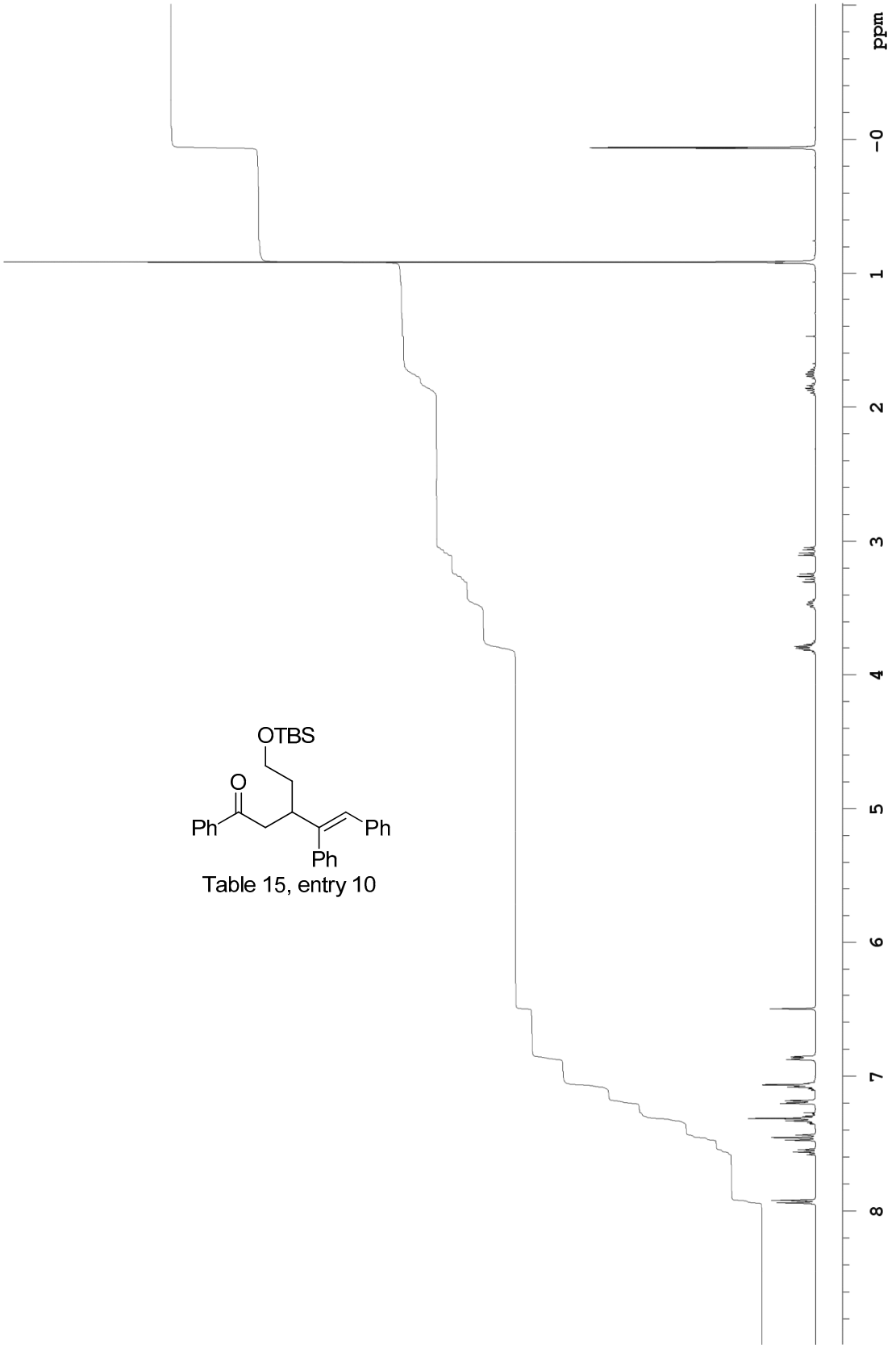

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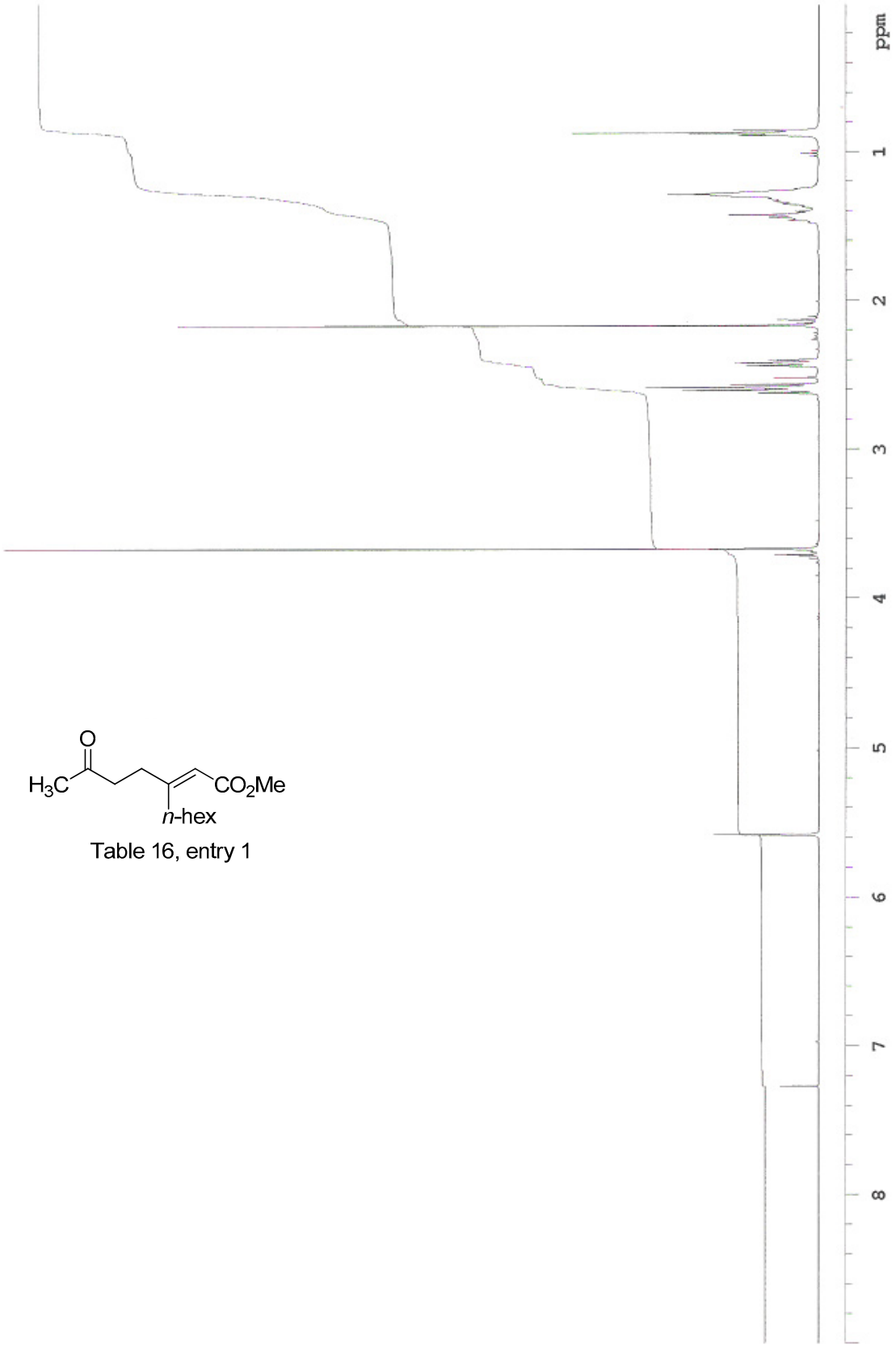

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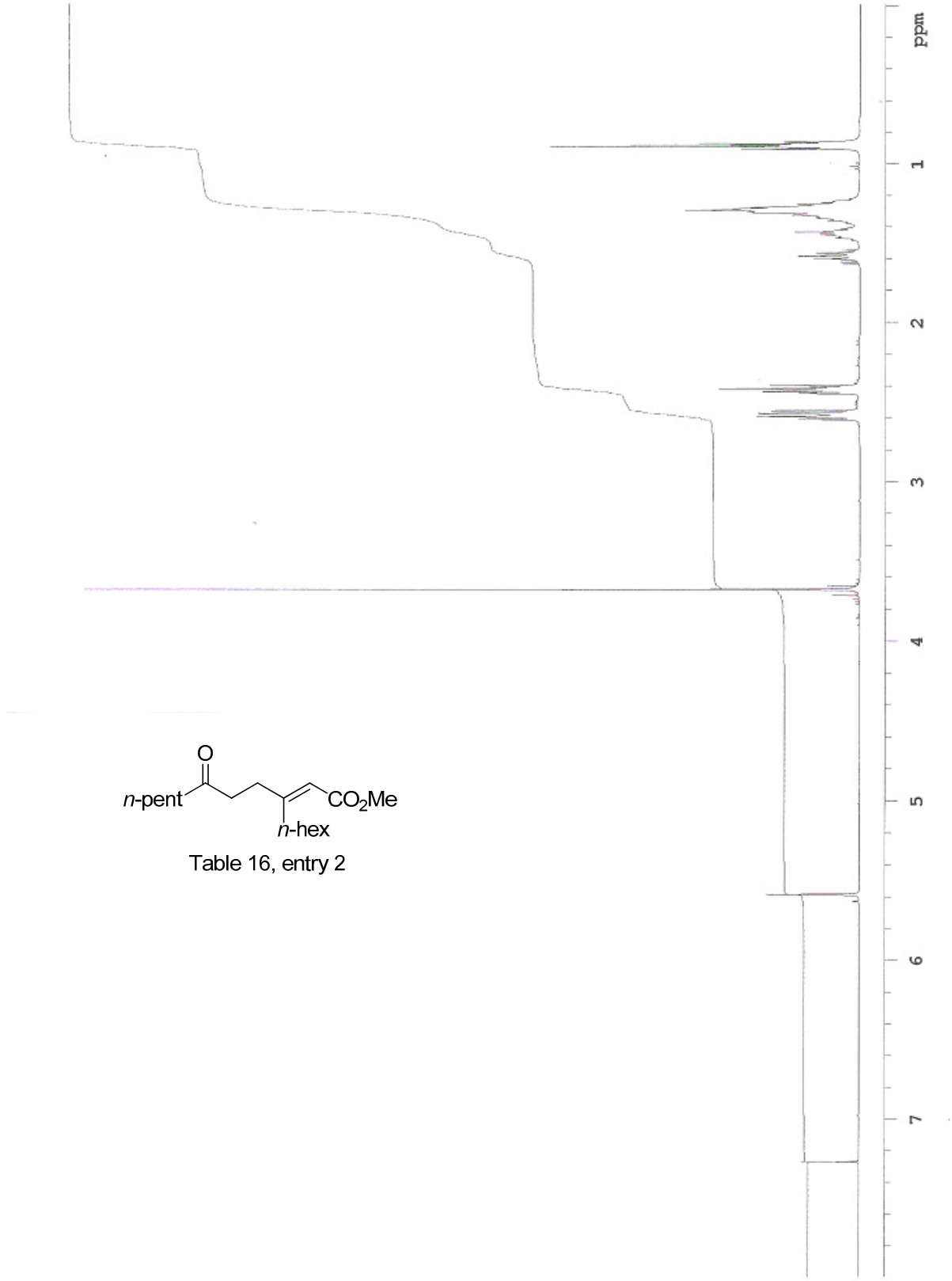

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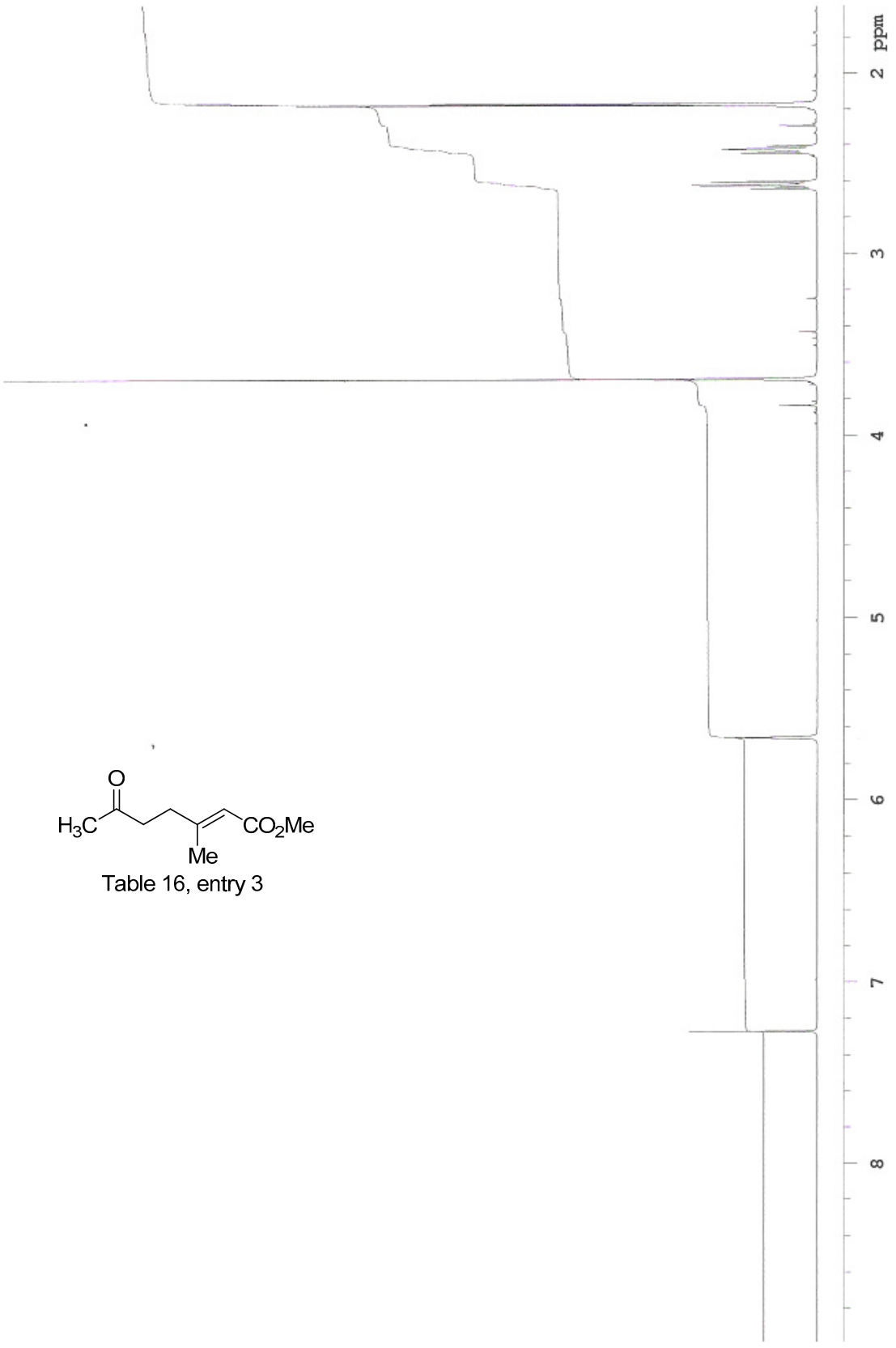

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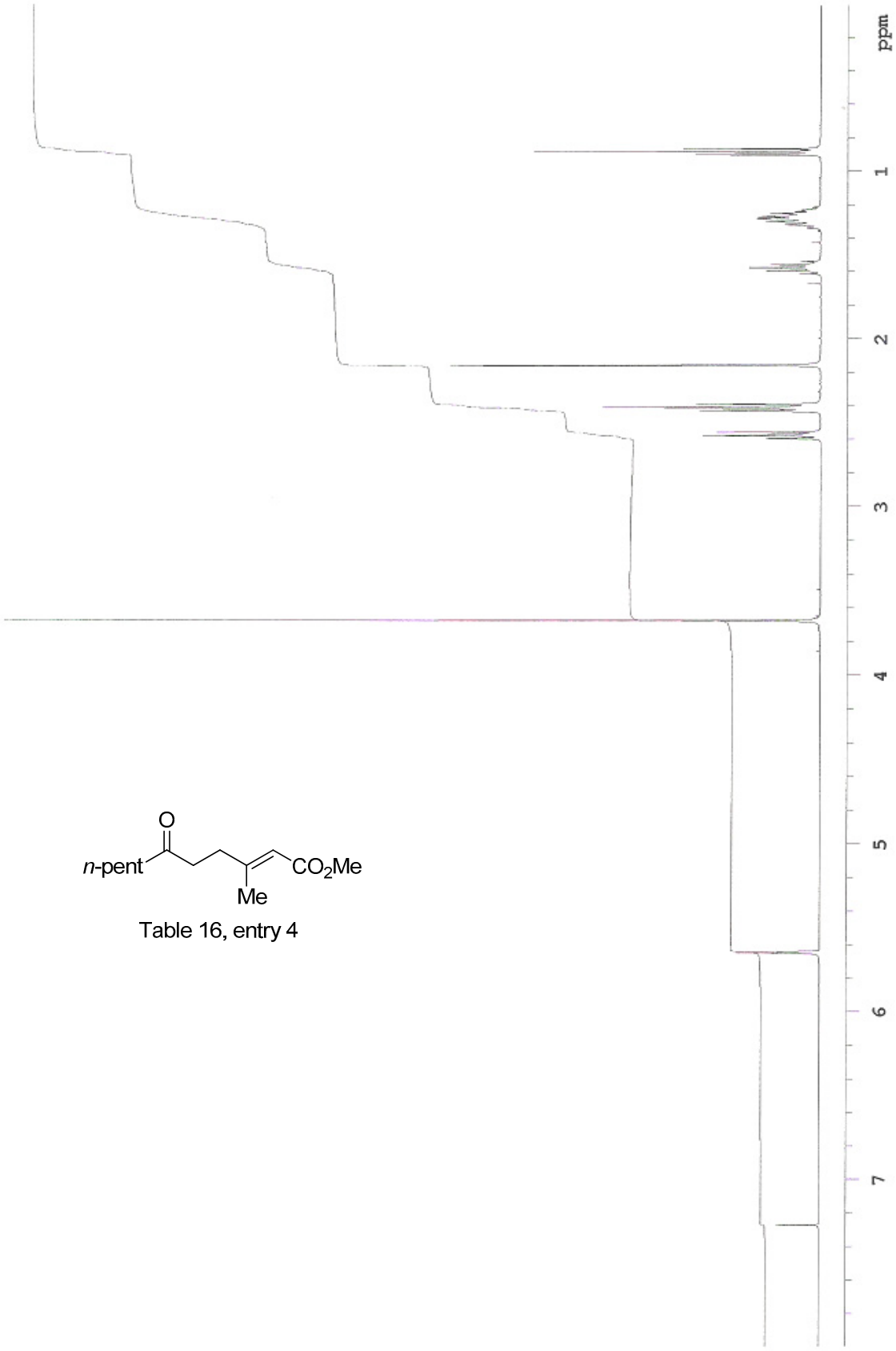

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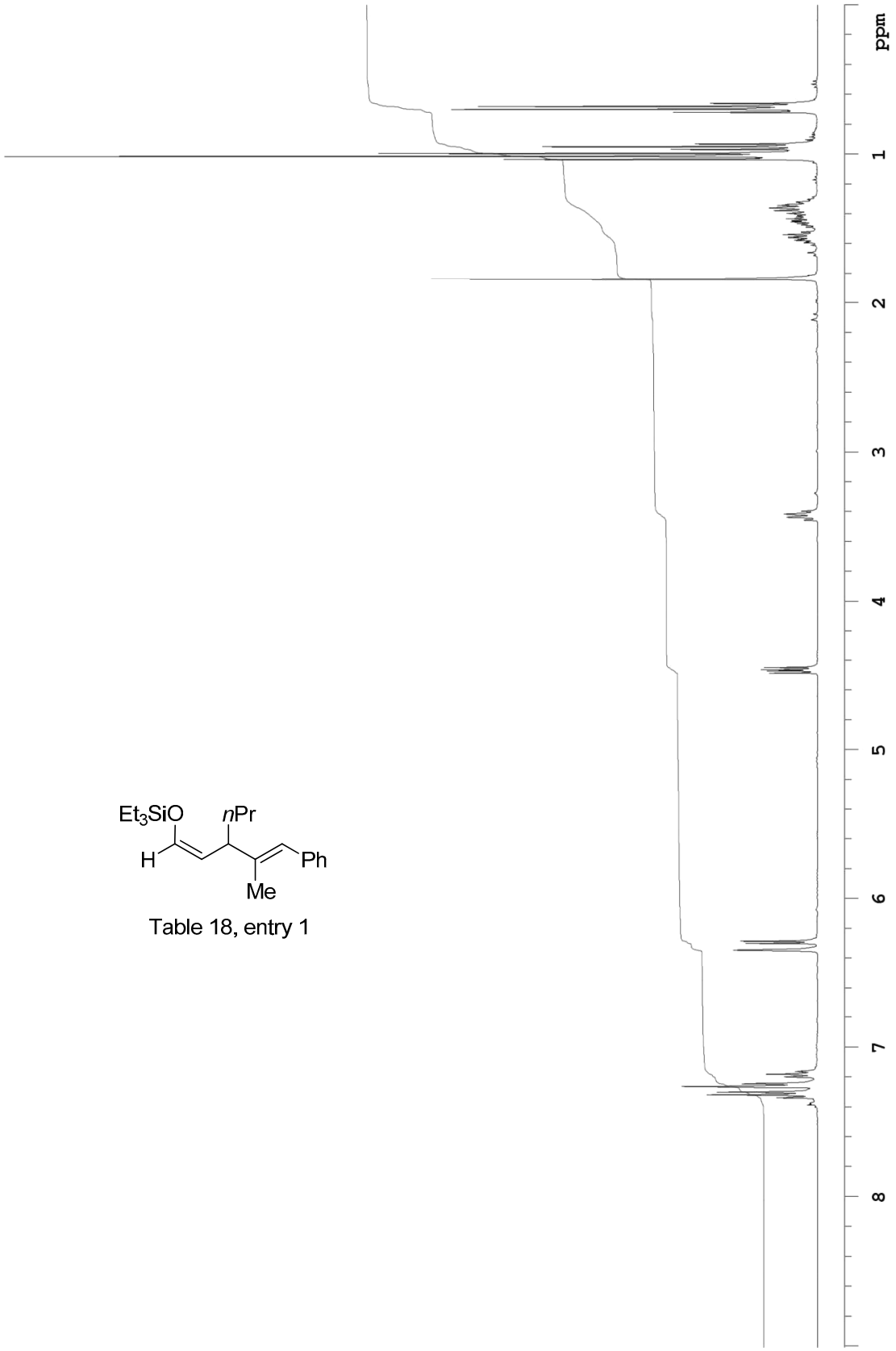

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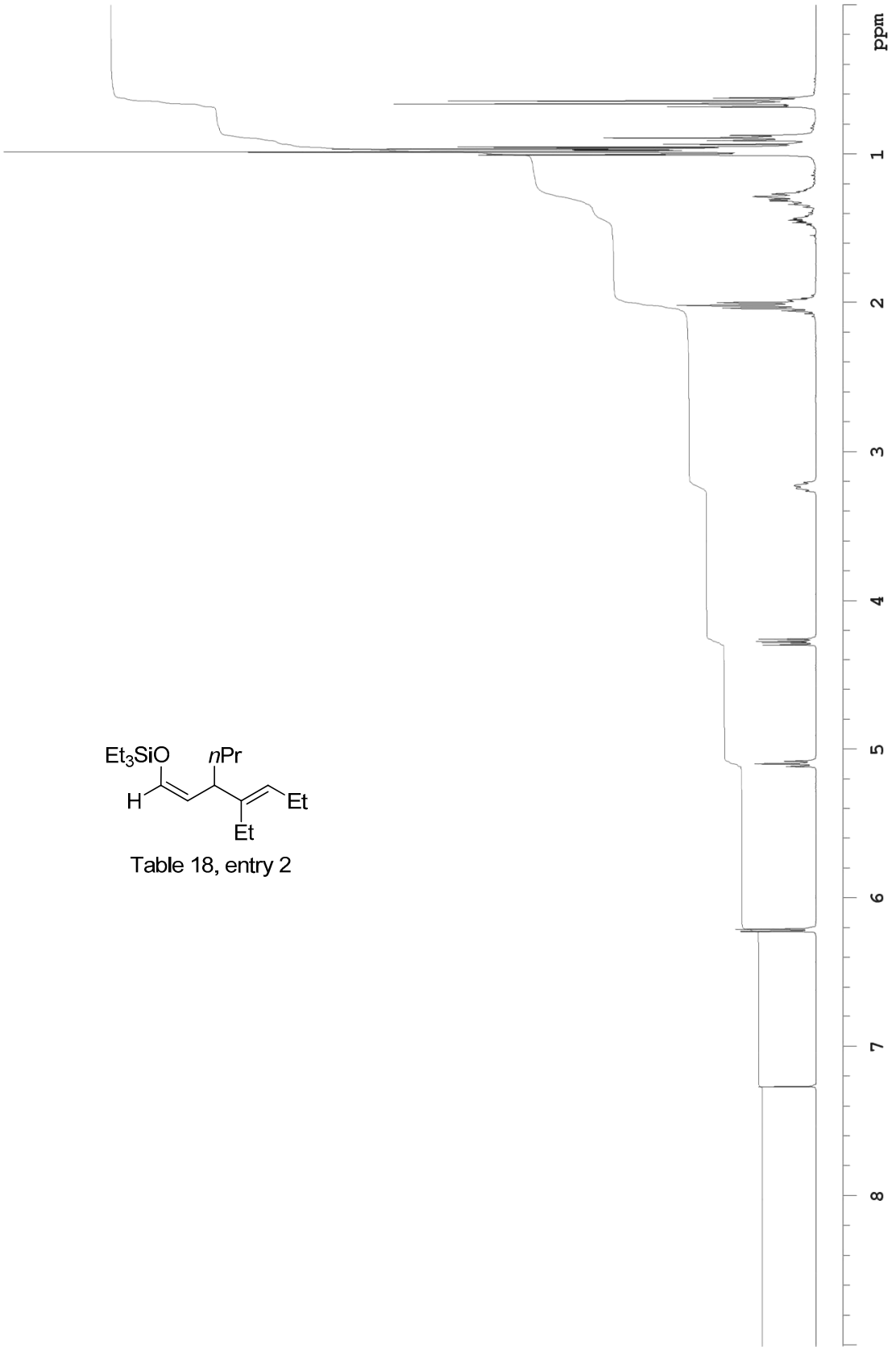

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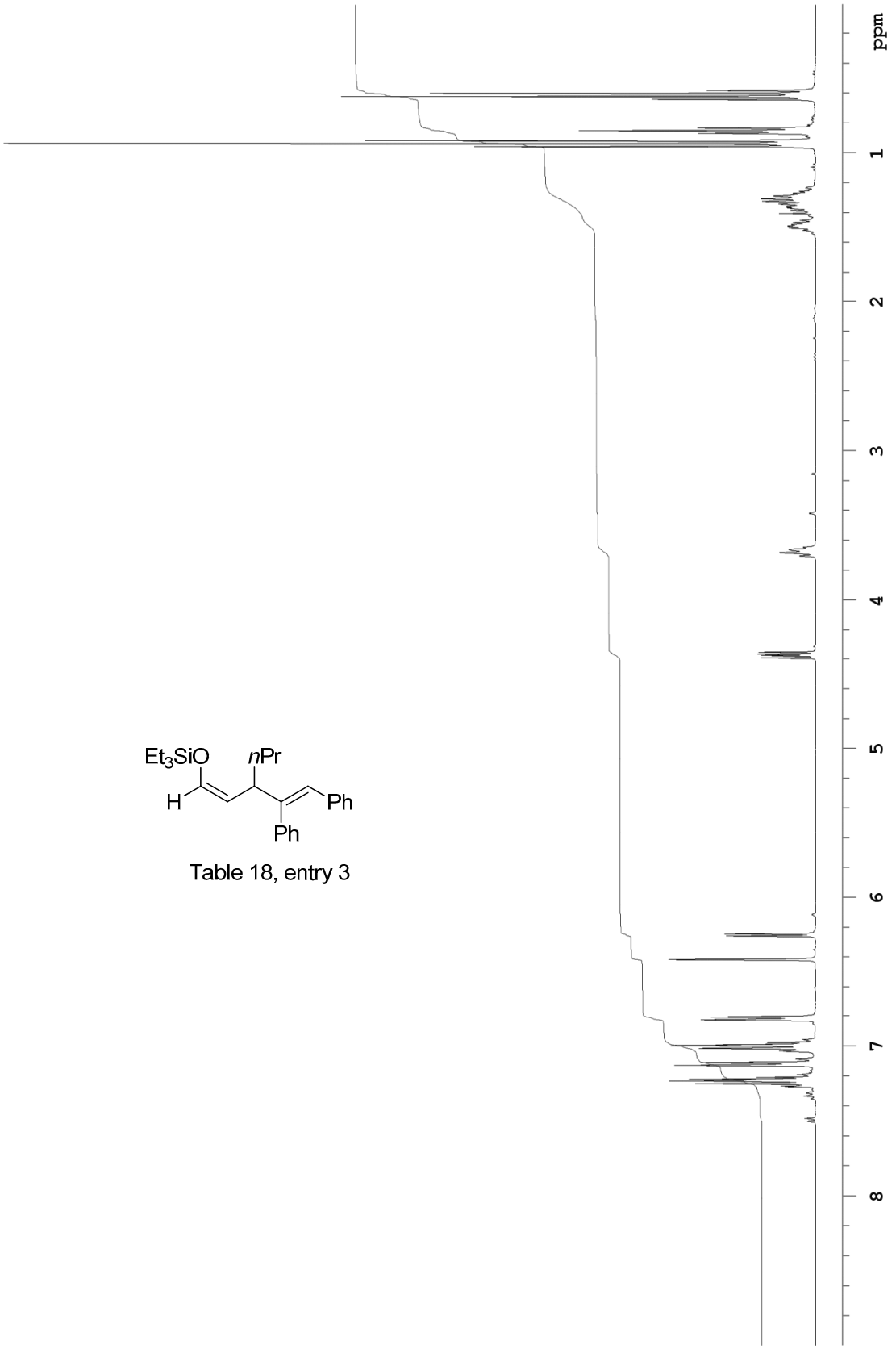

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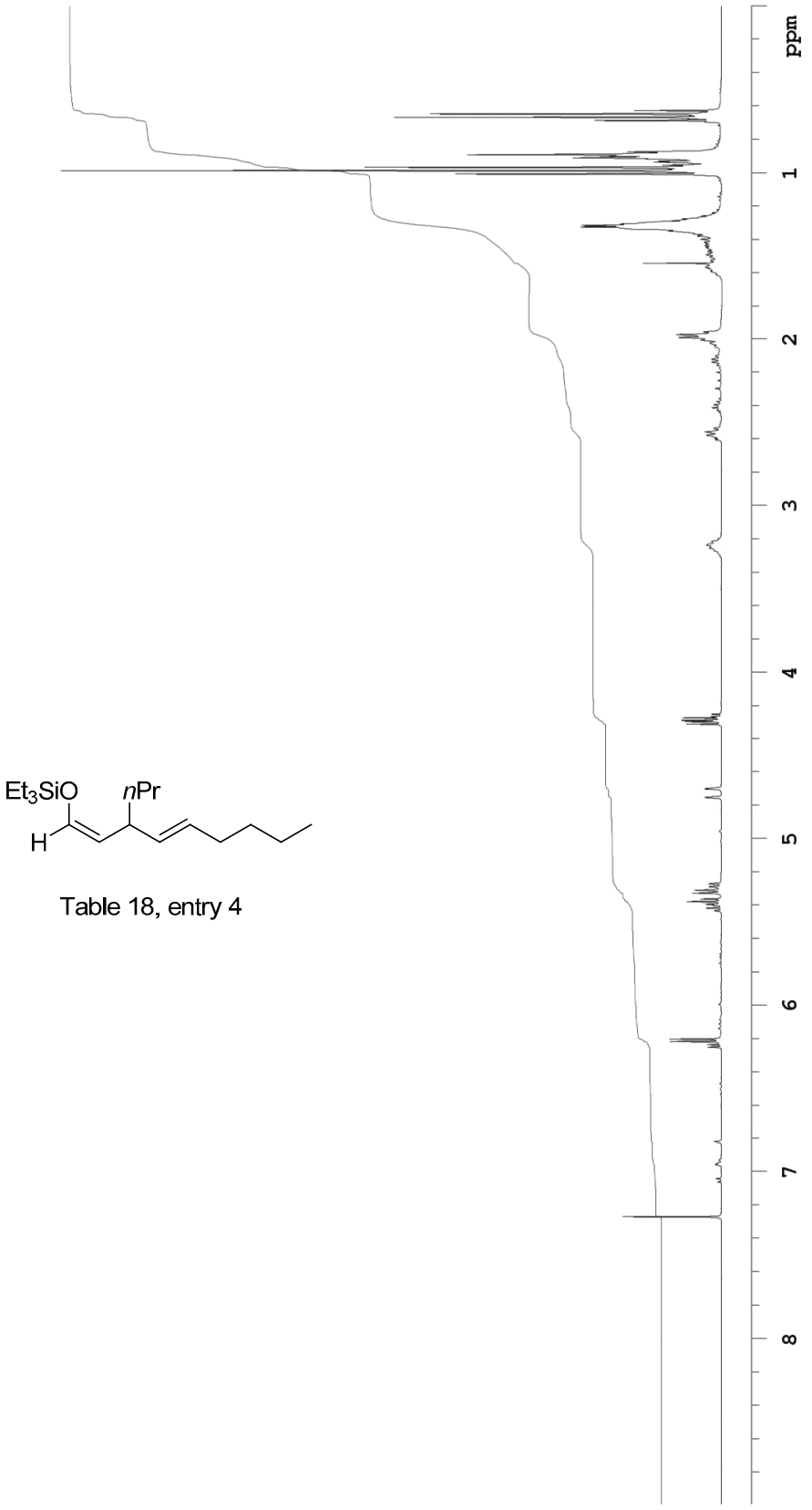

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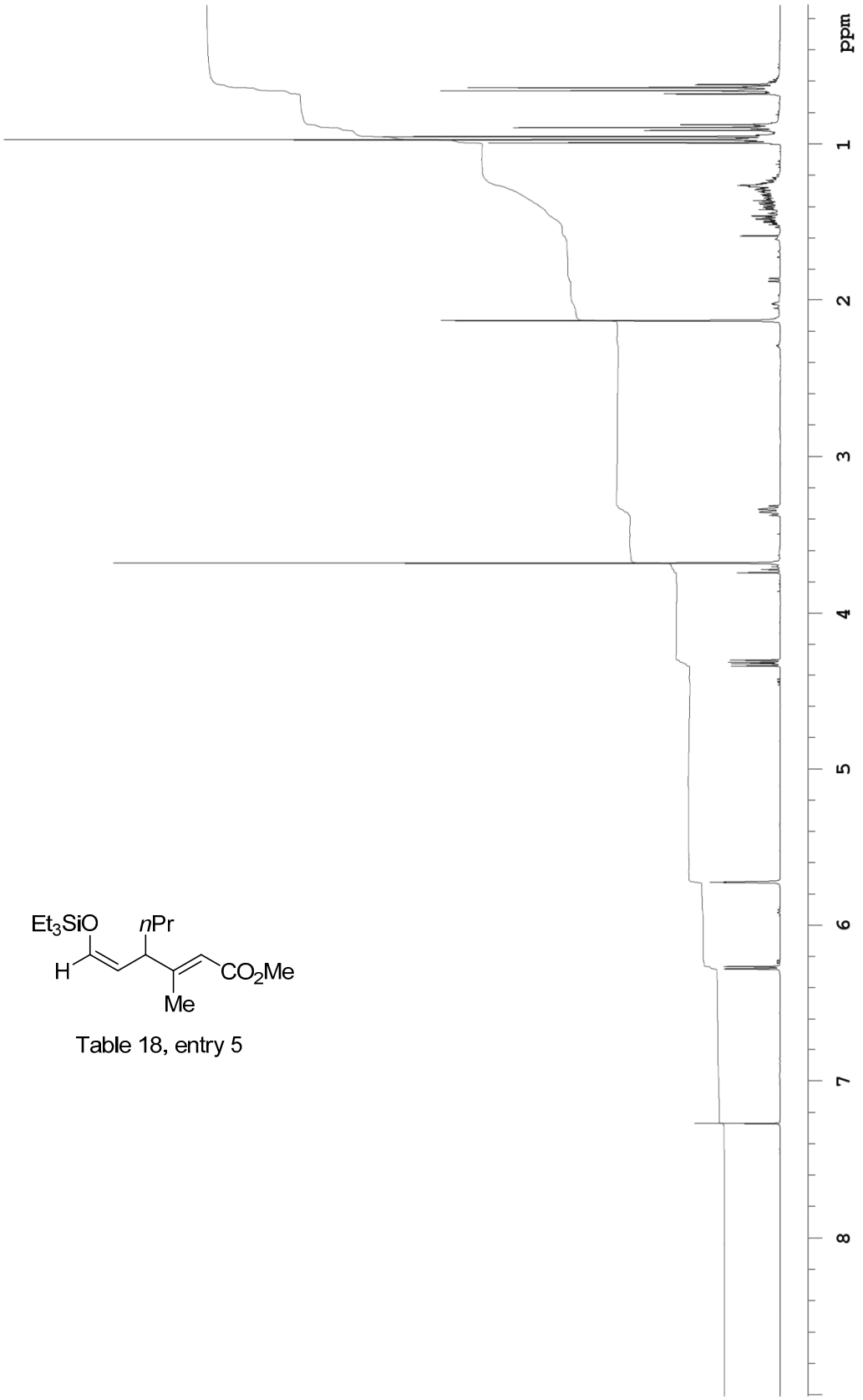

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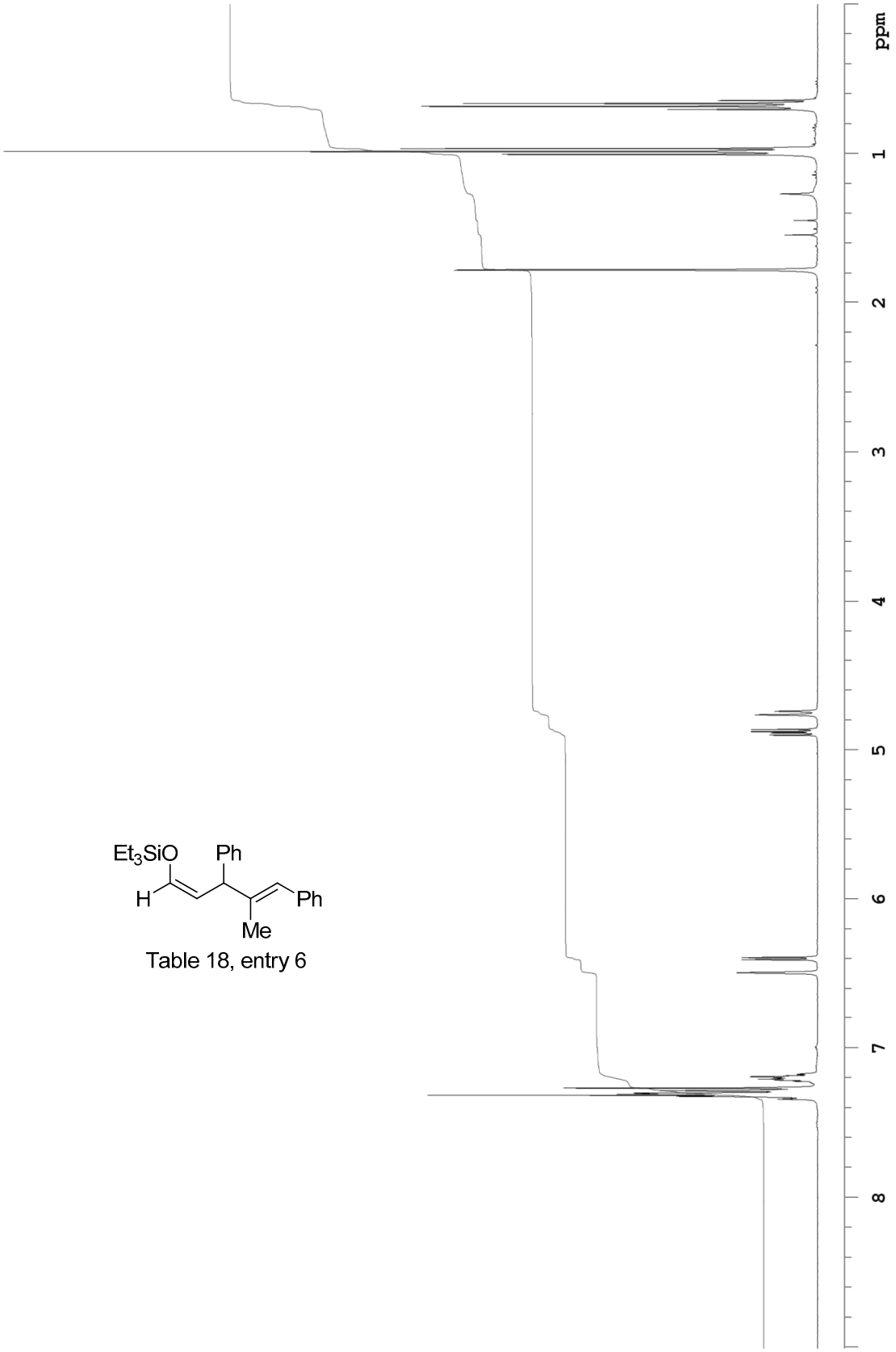

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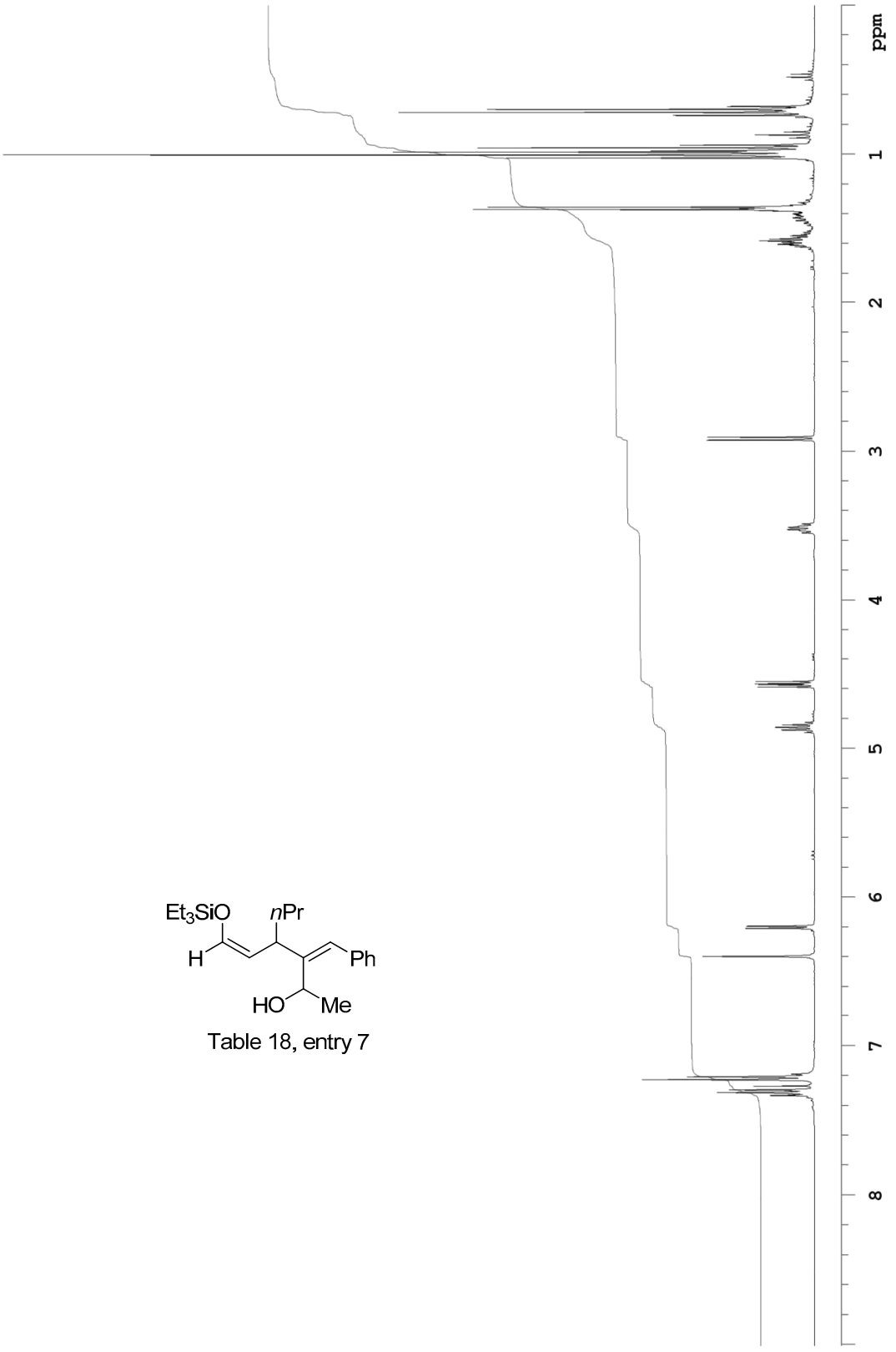

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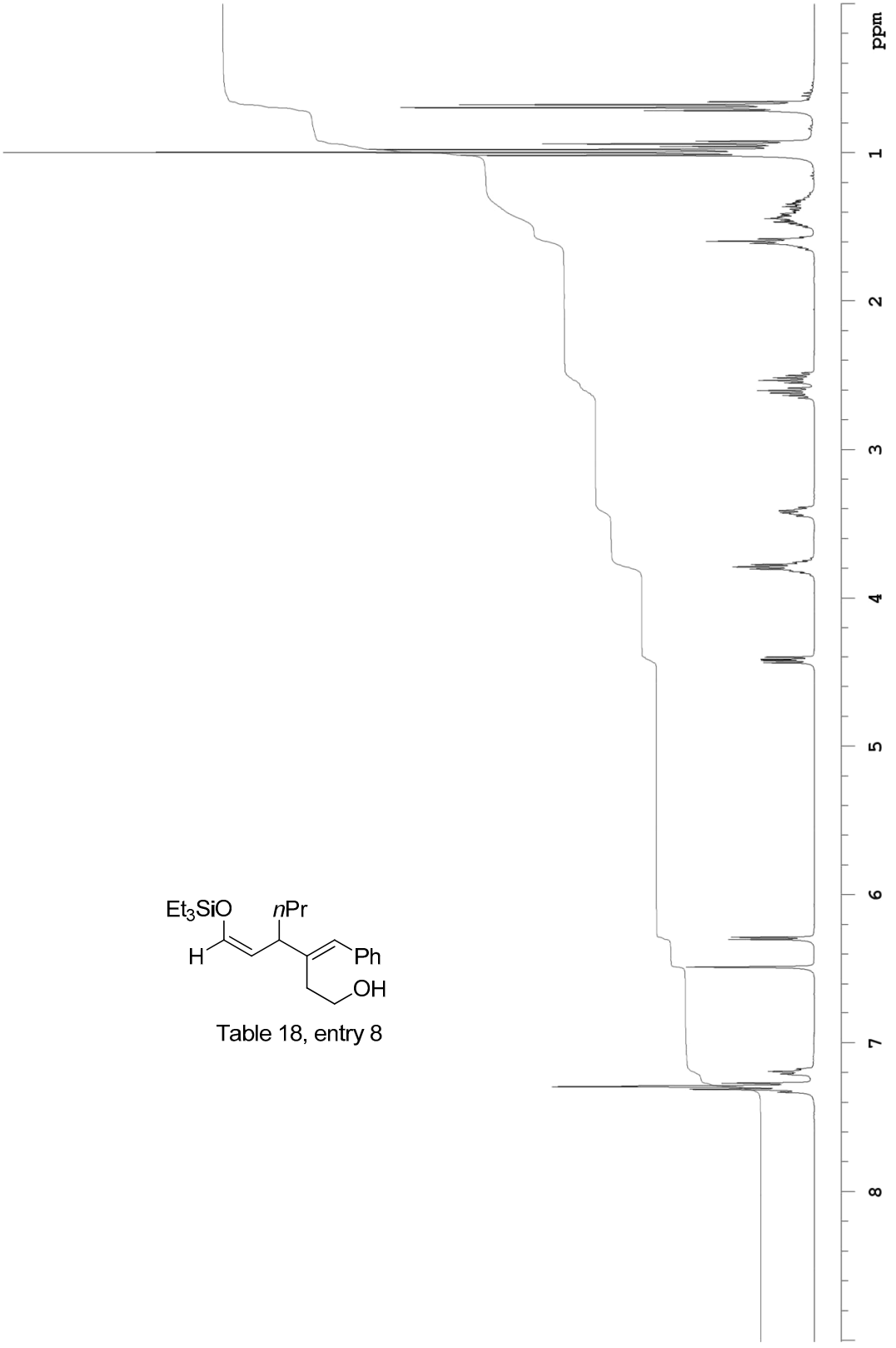

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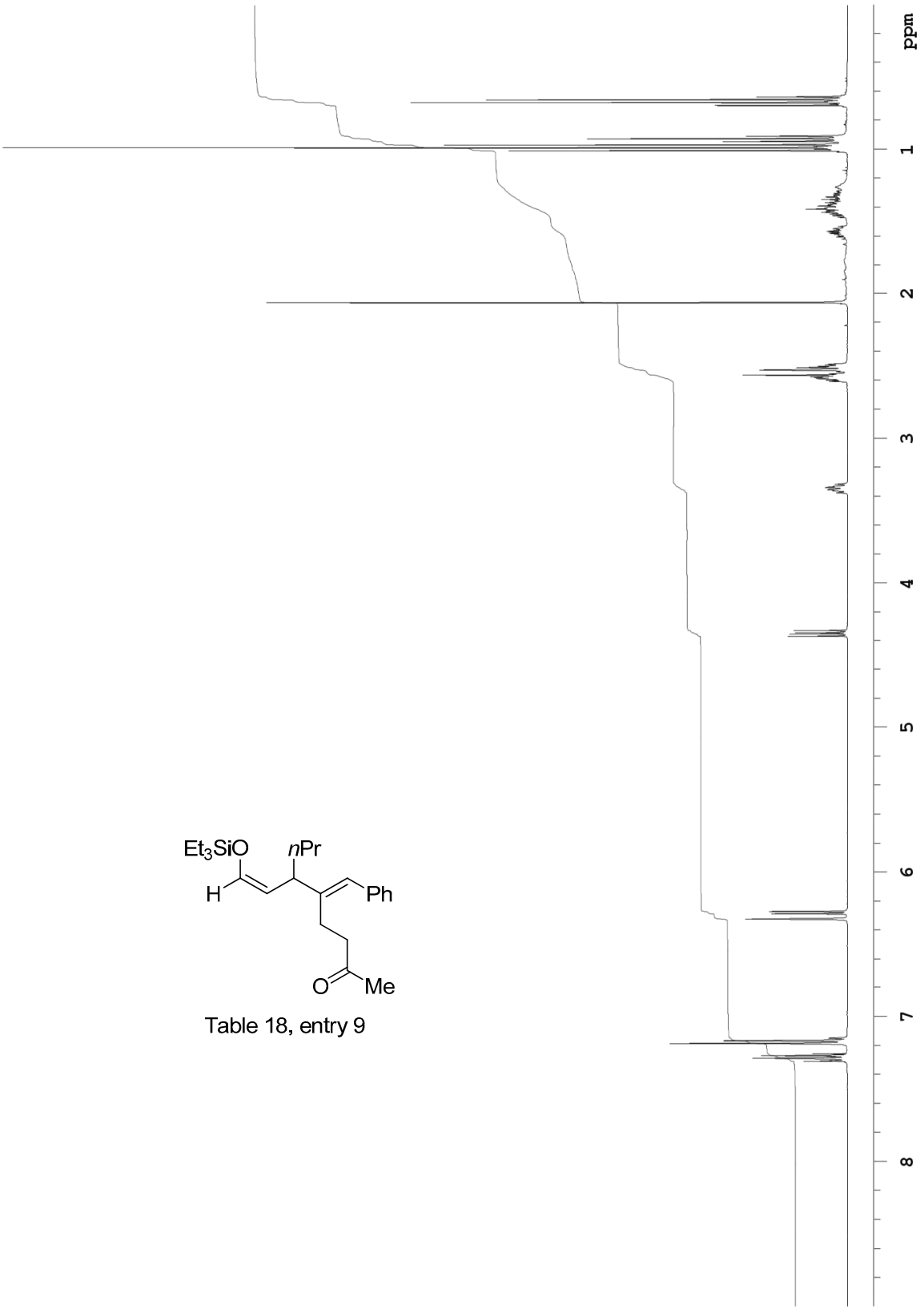

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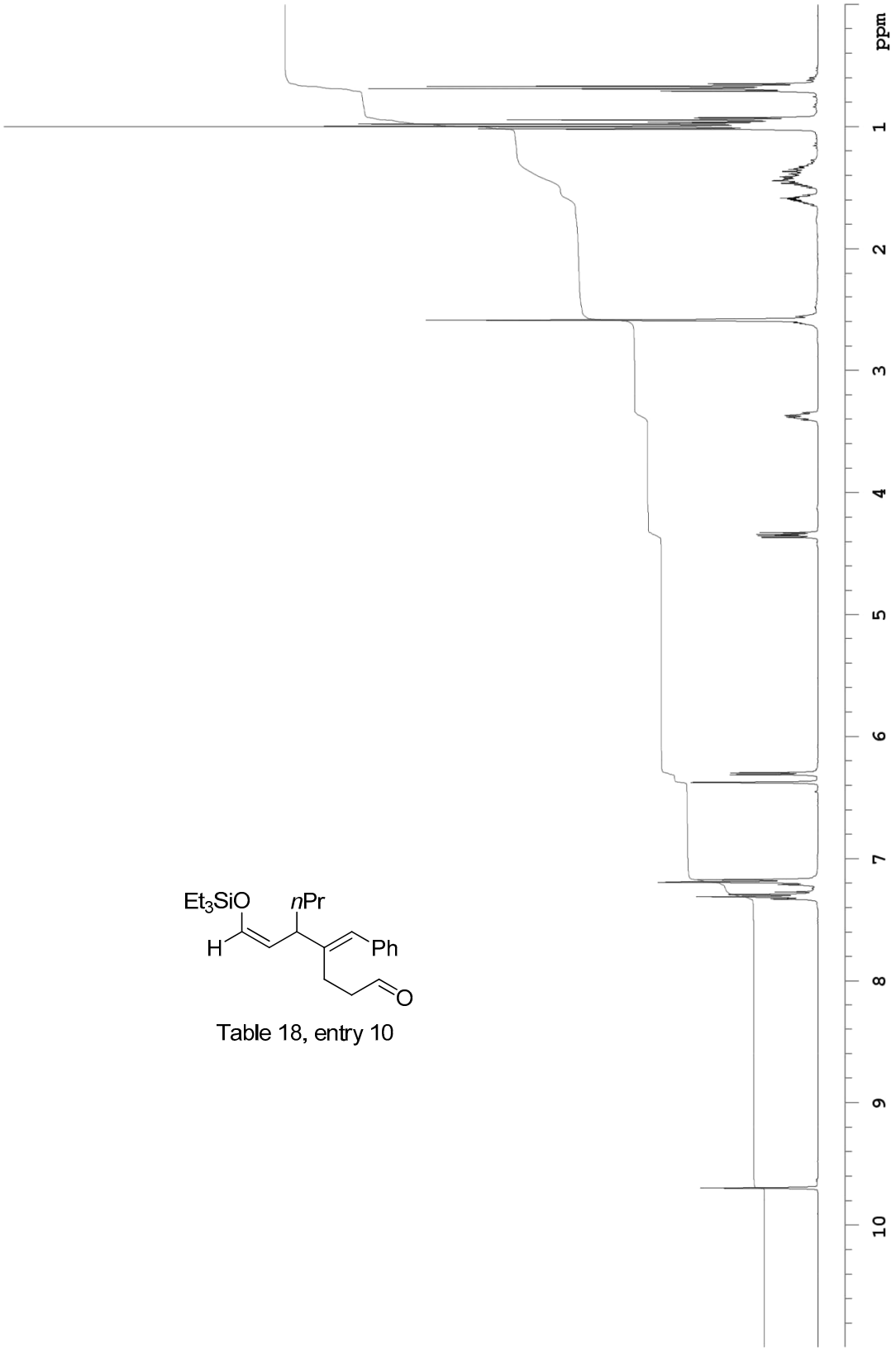

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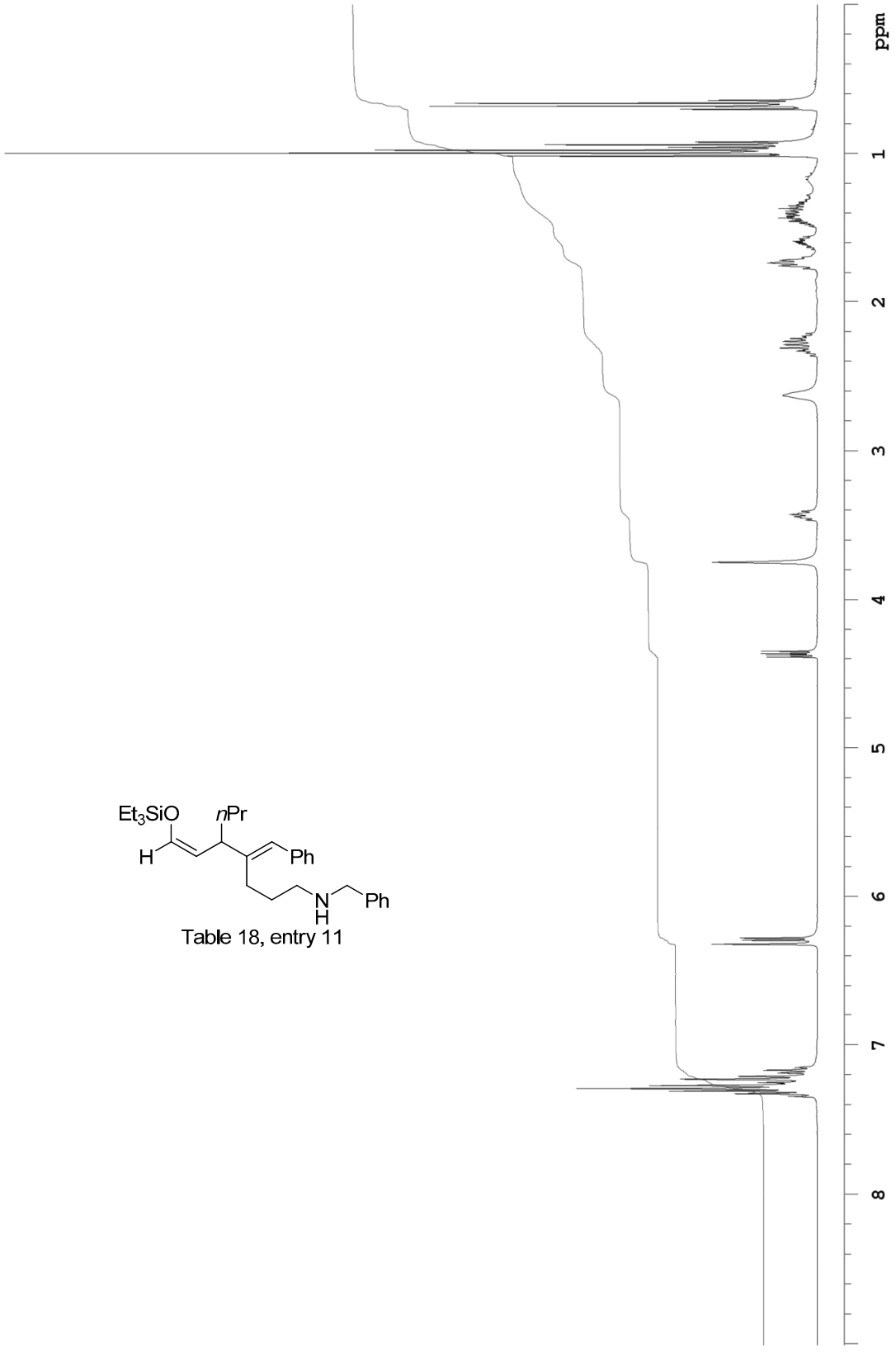

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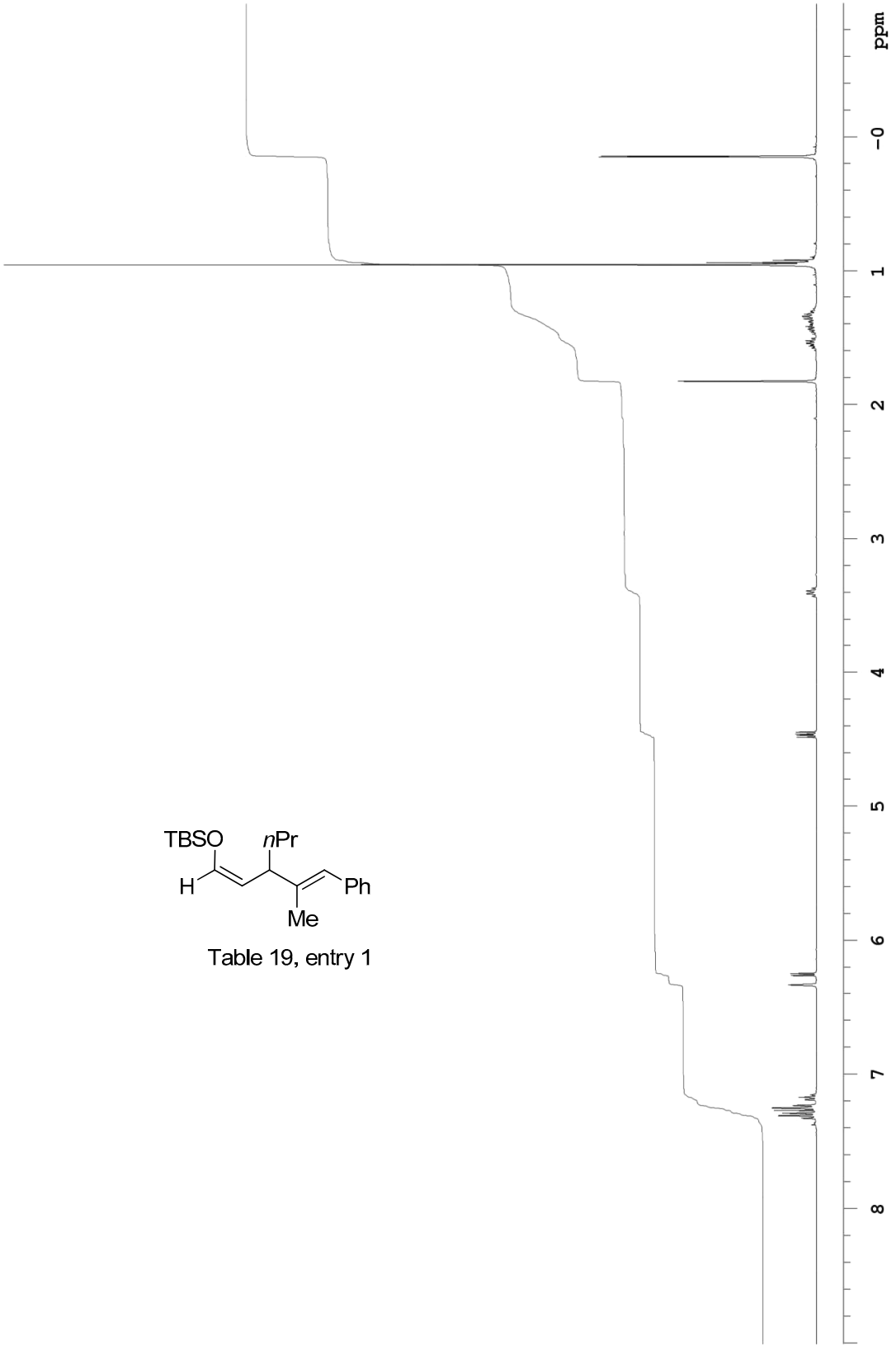

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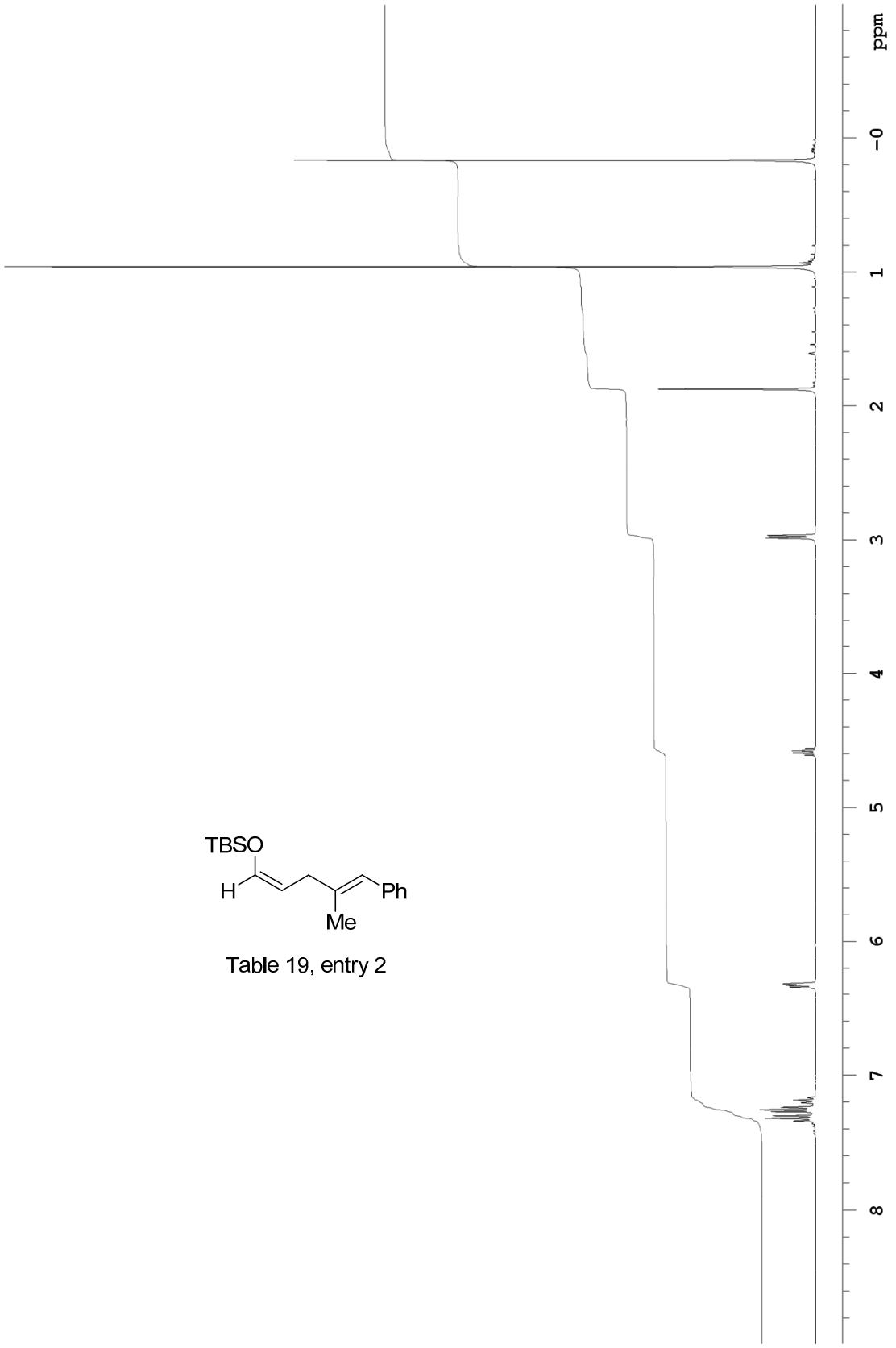

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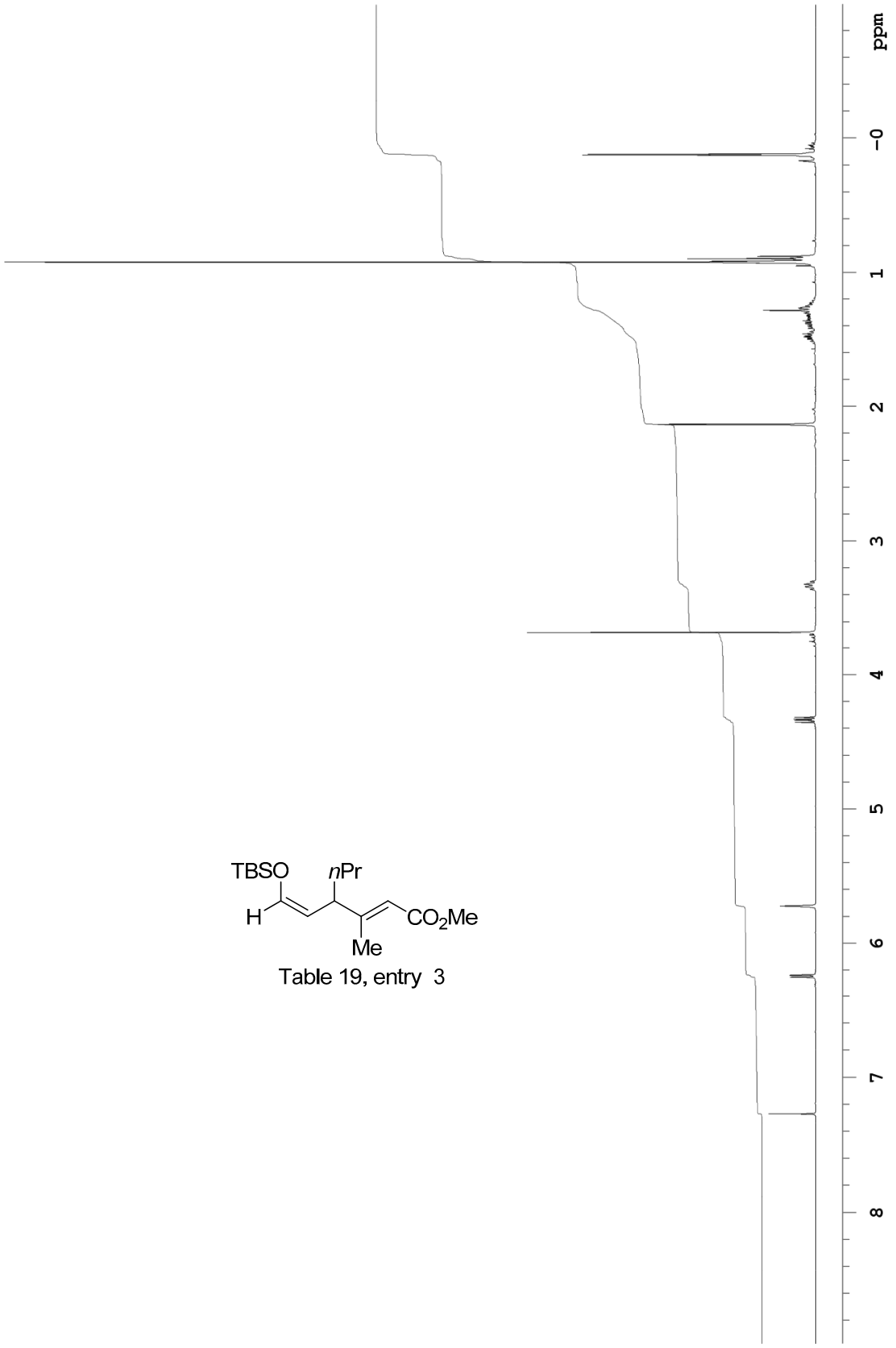

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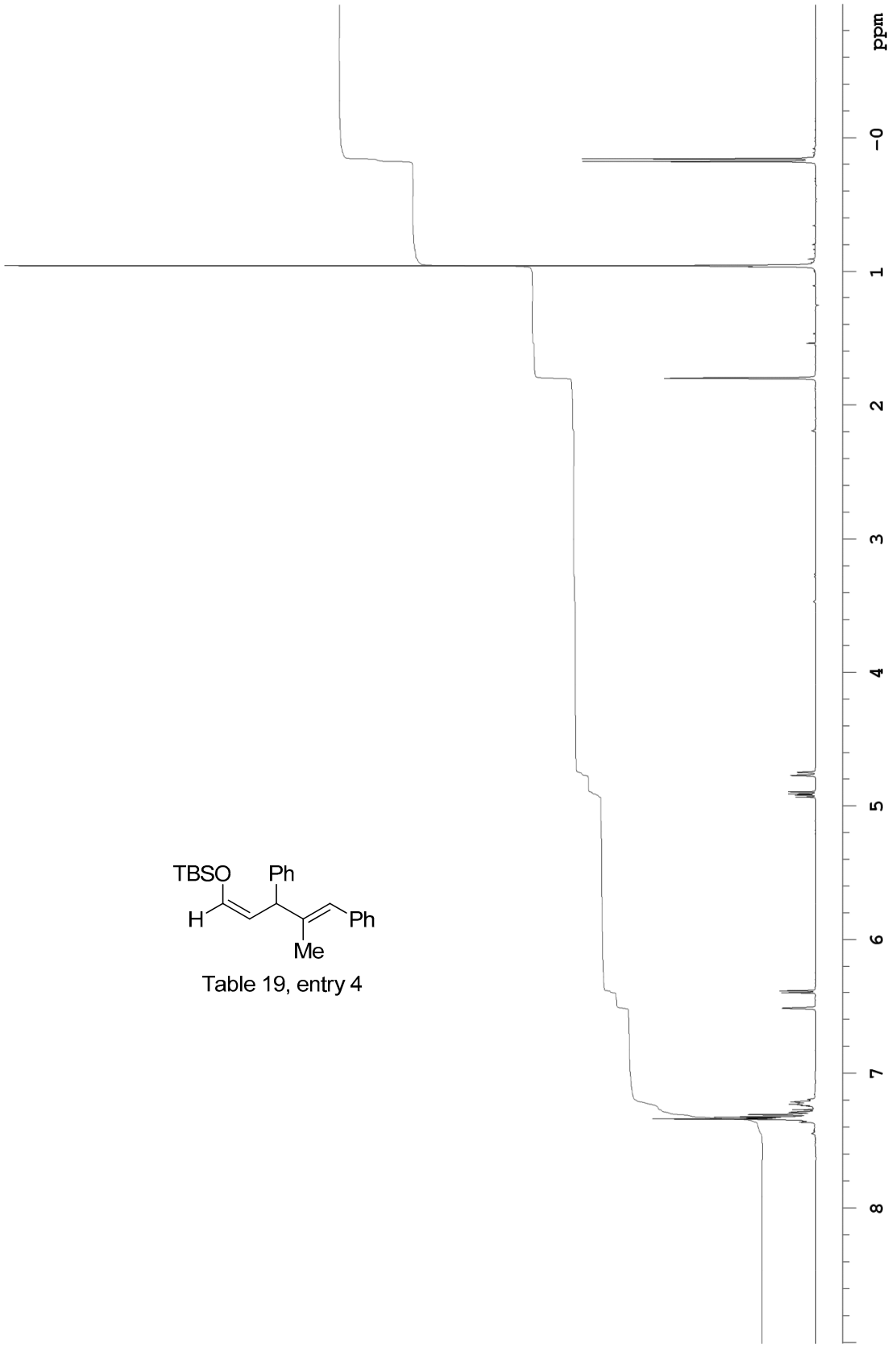

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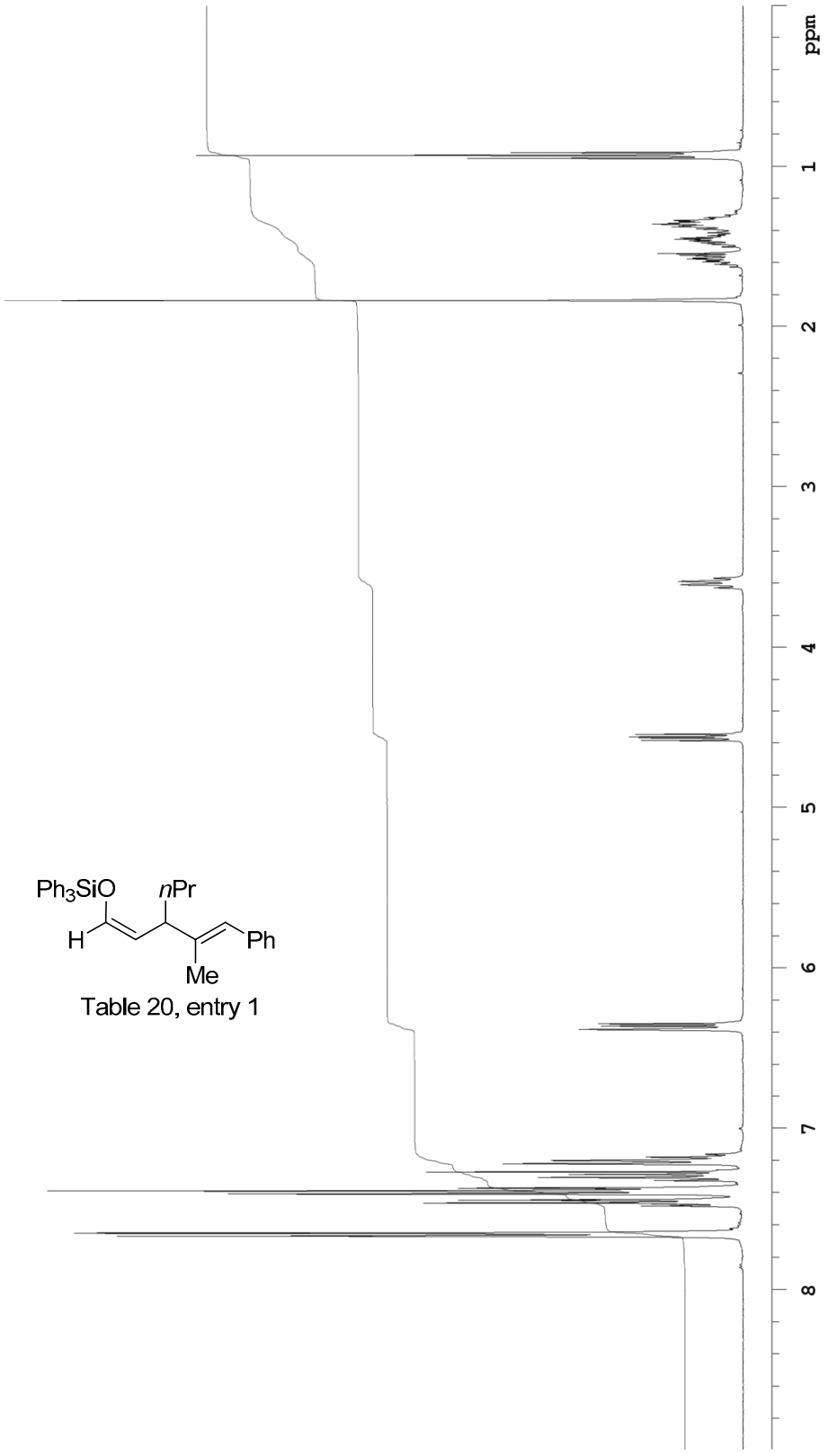

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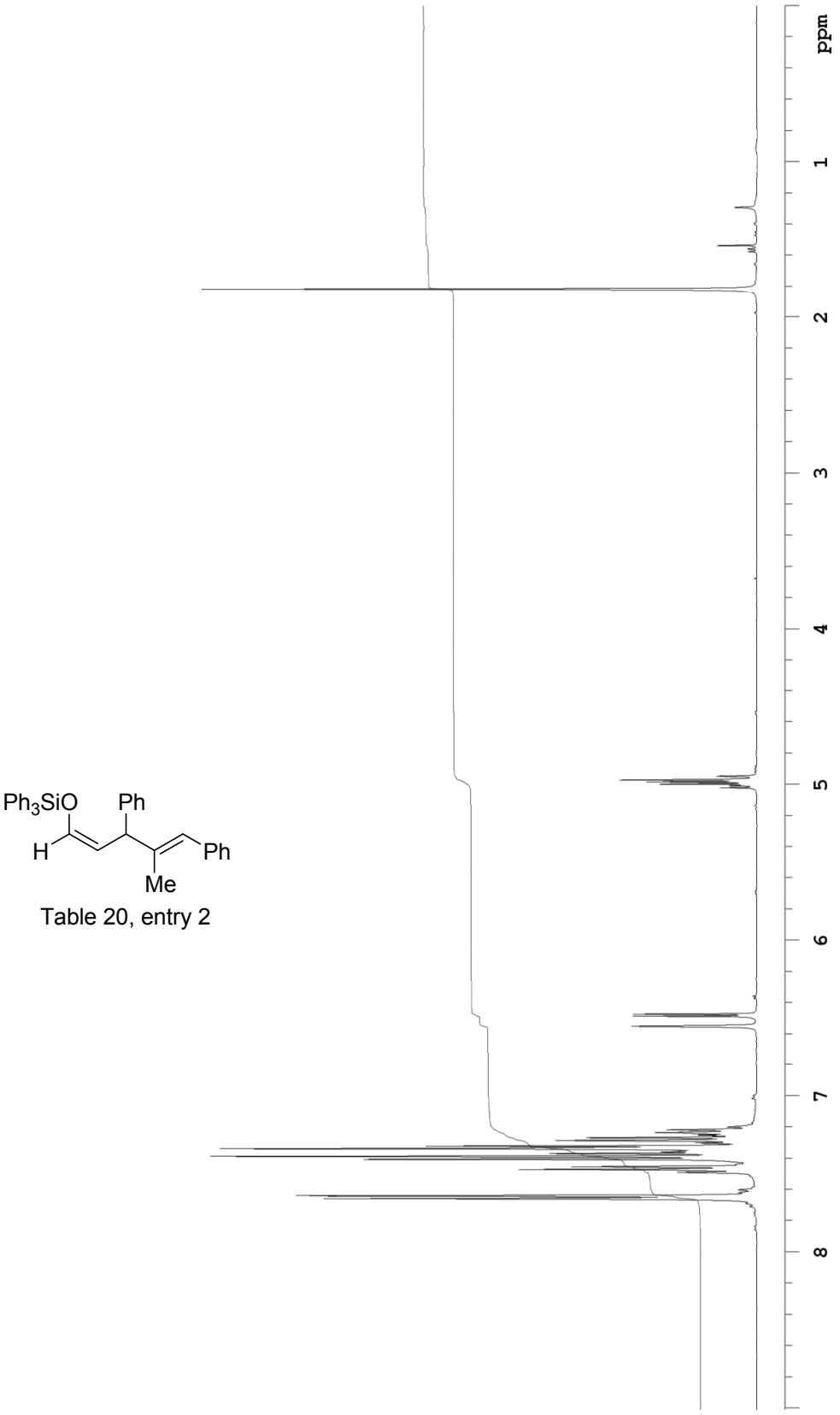

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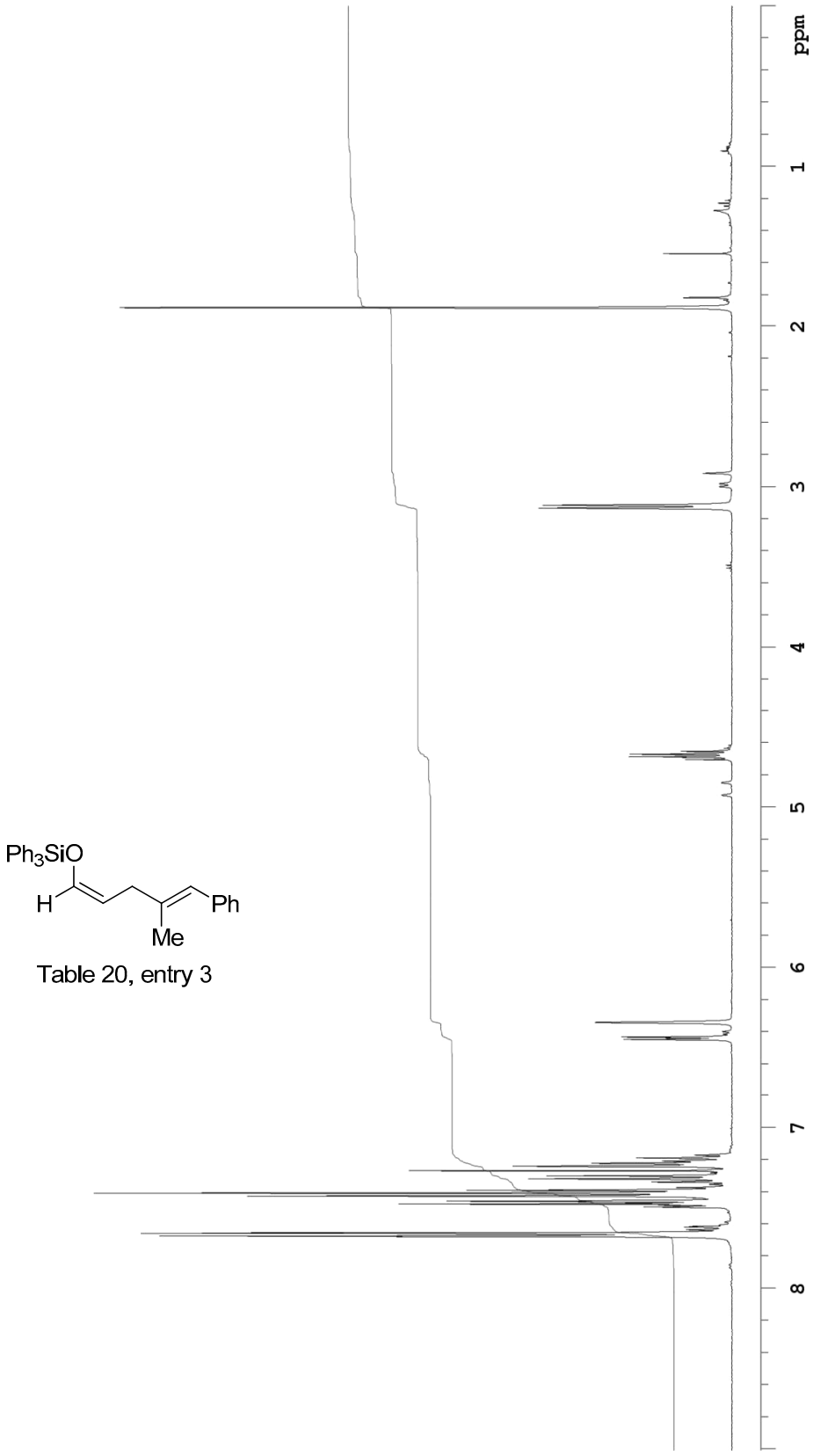

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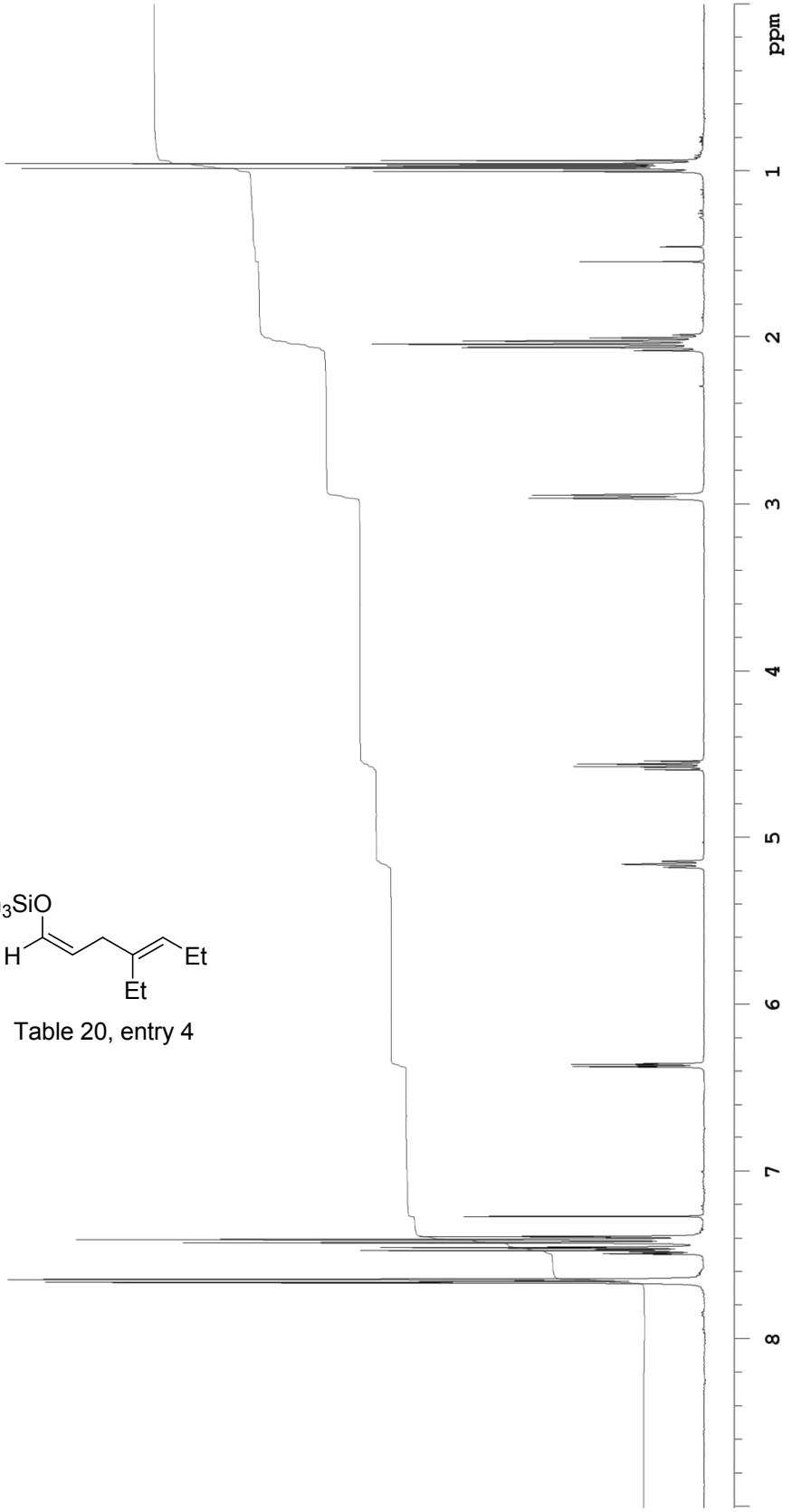

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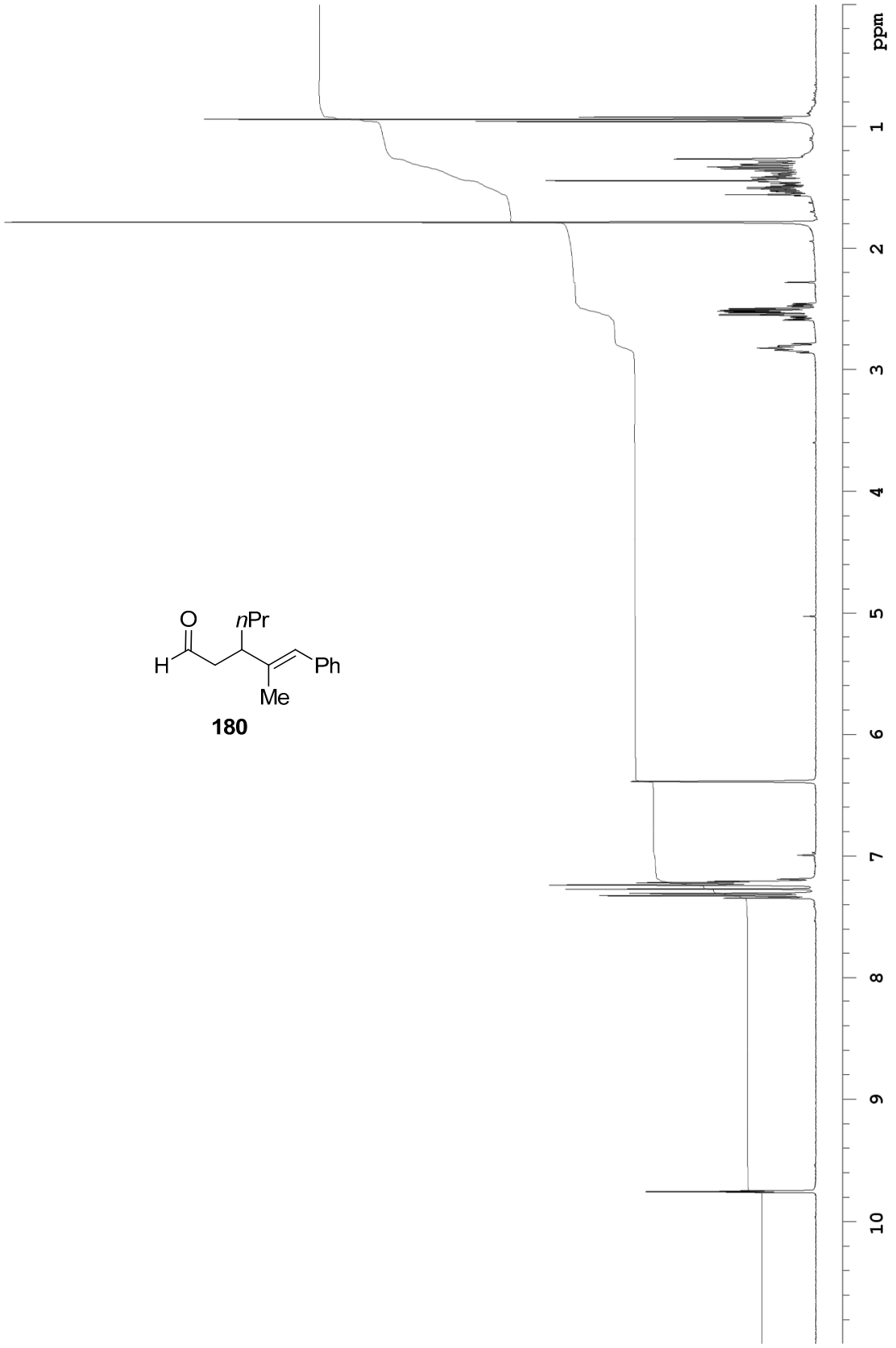

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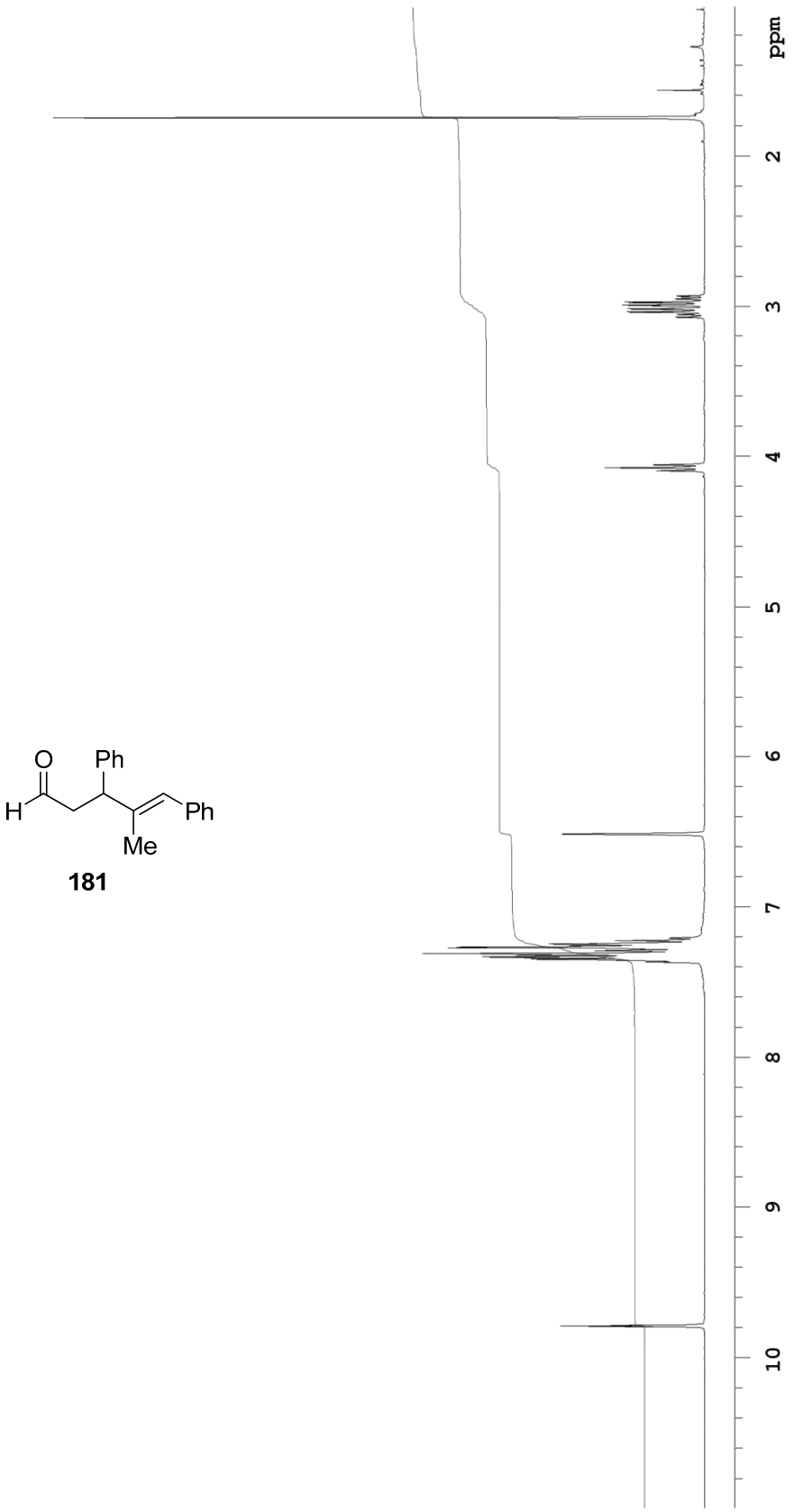

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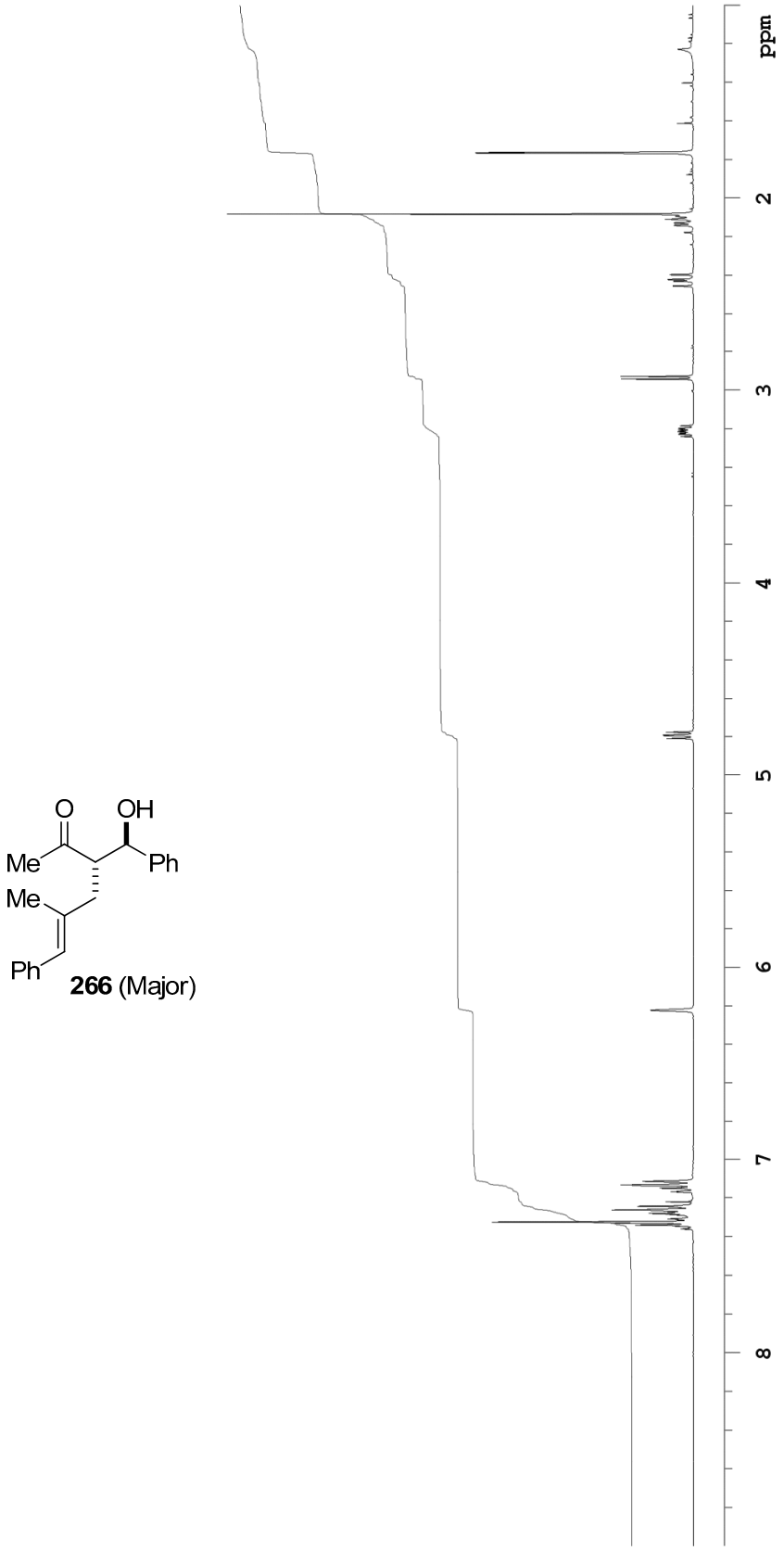
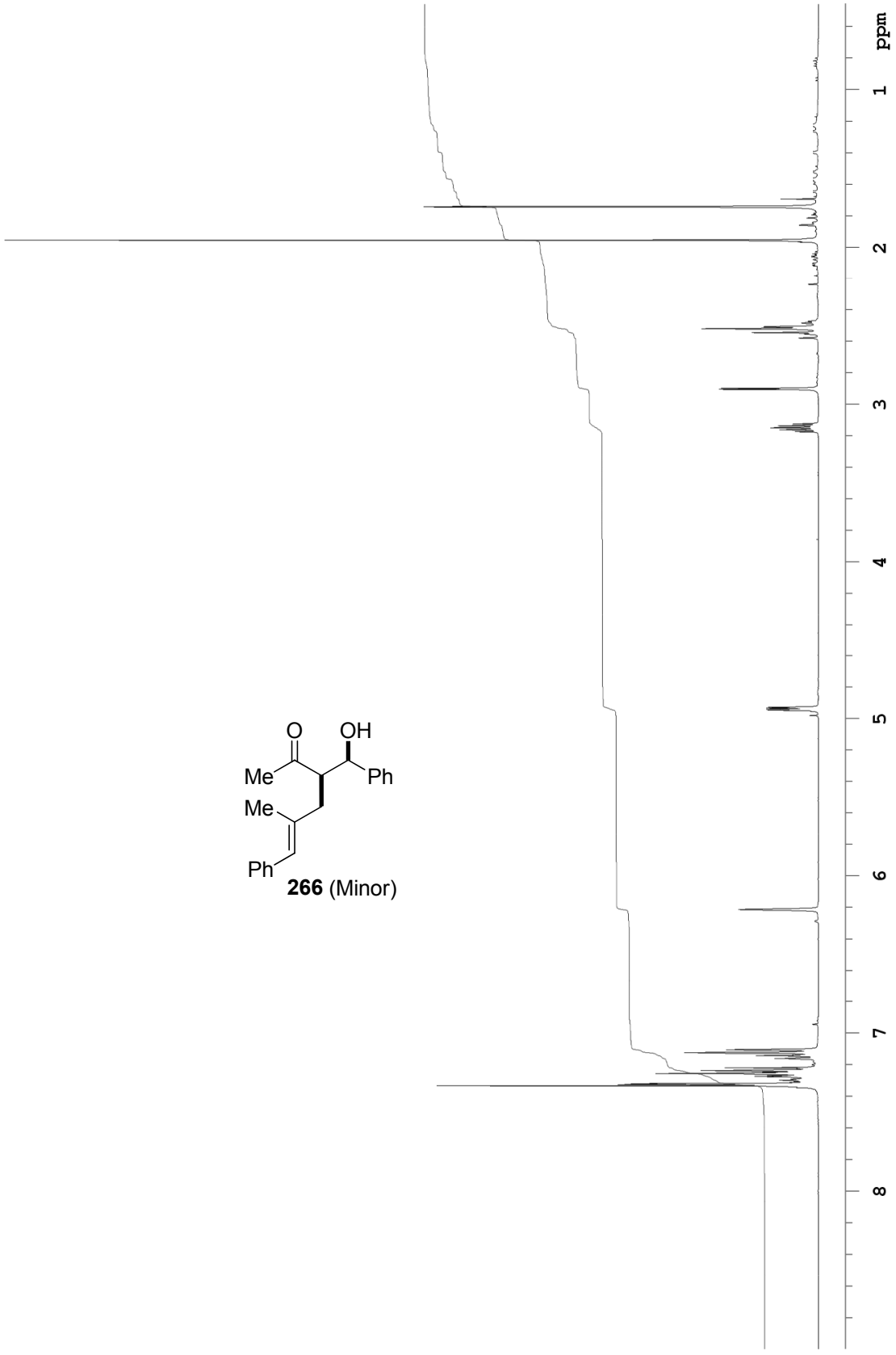
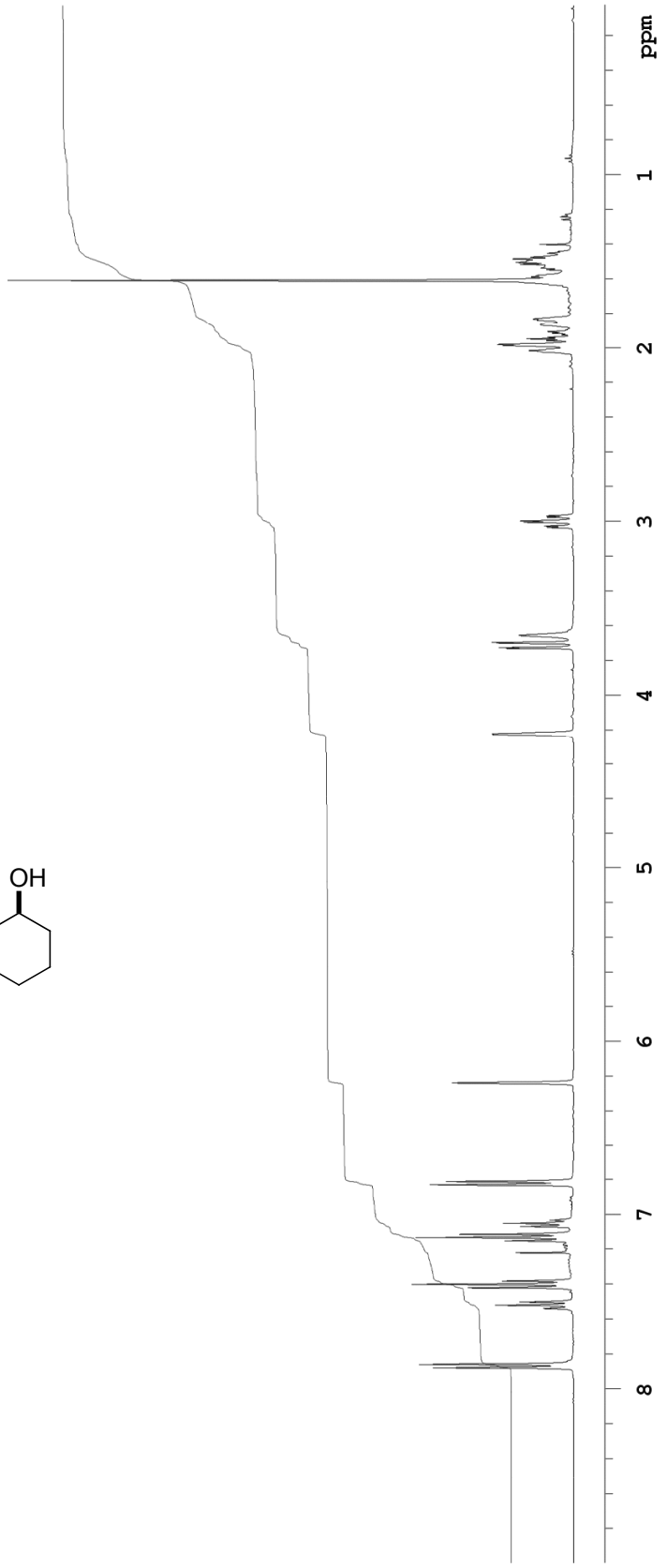
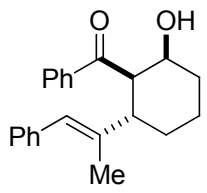


266 (Major)



266 (Minor)





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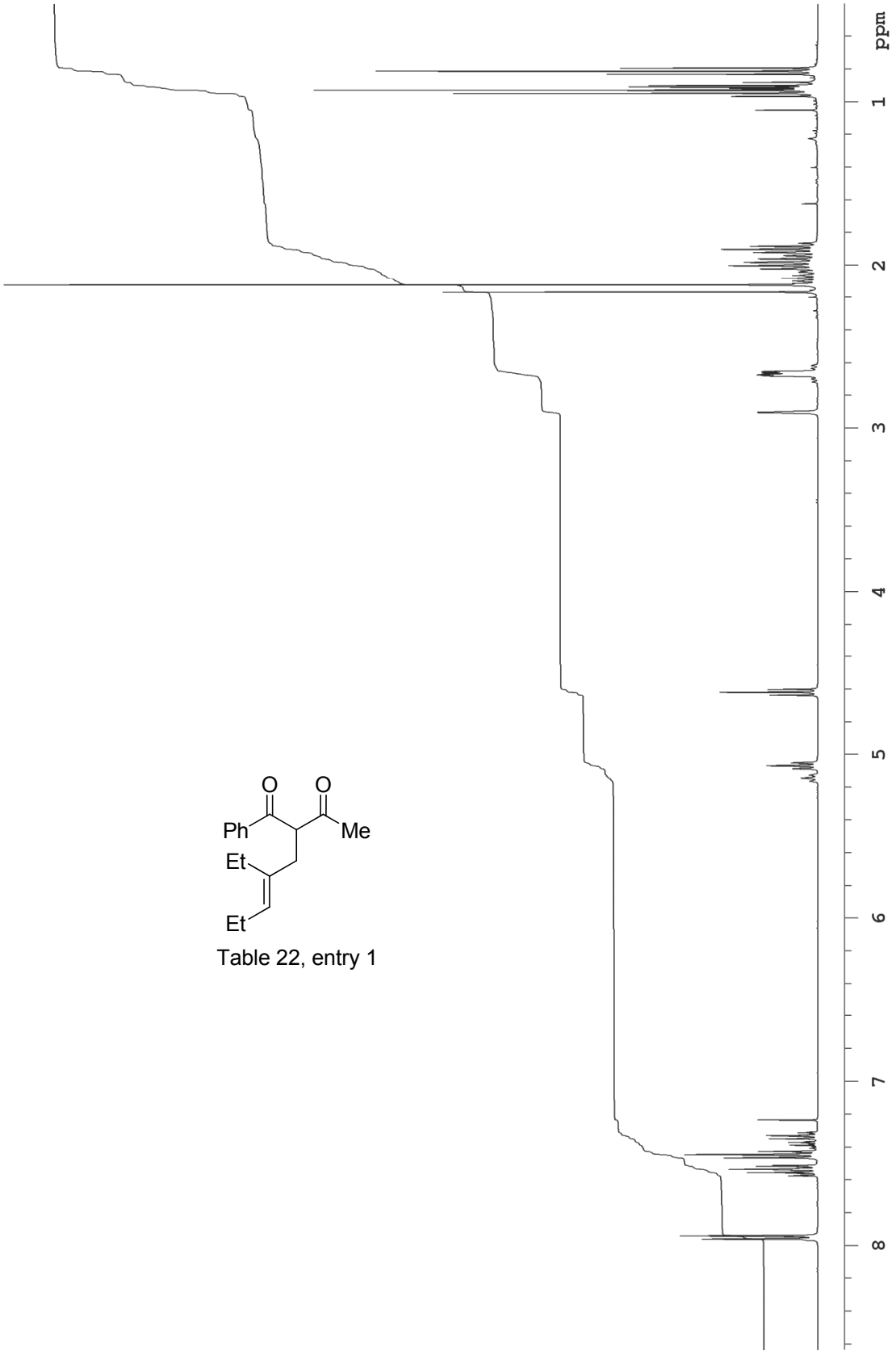

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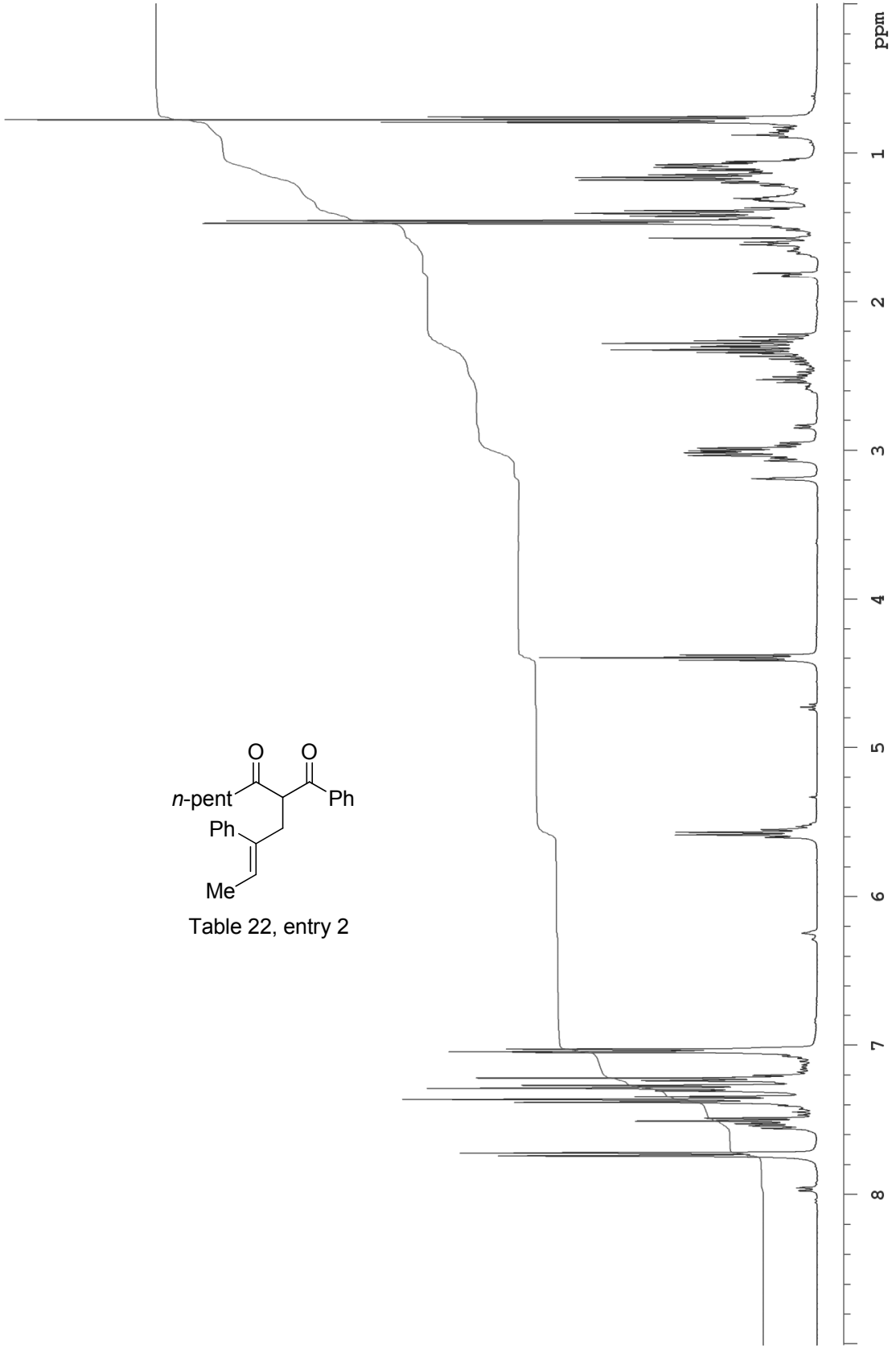

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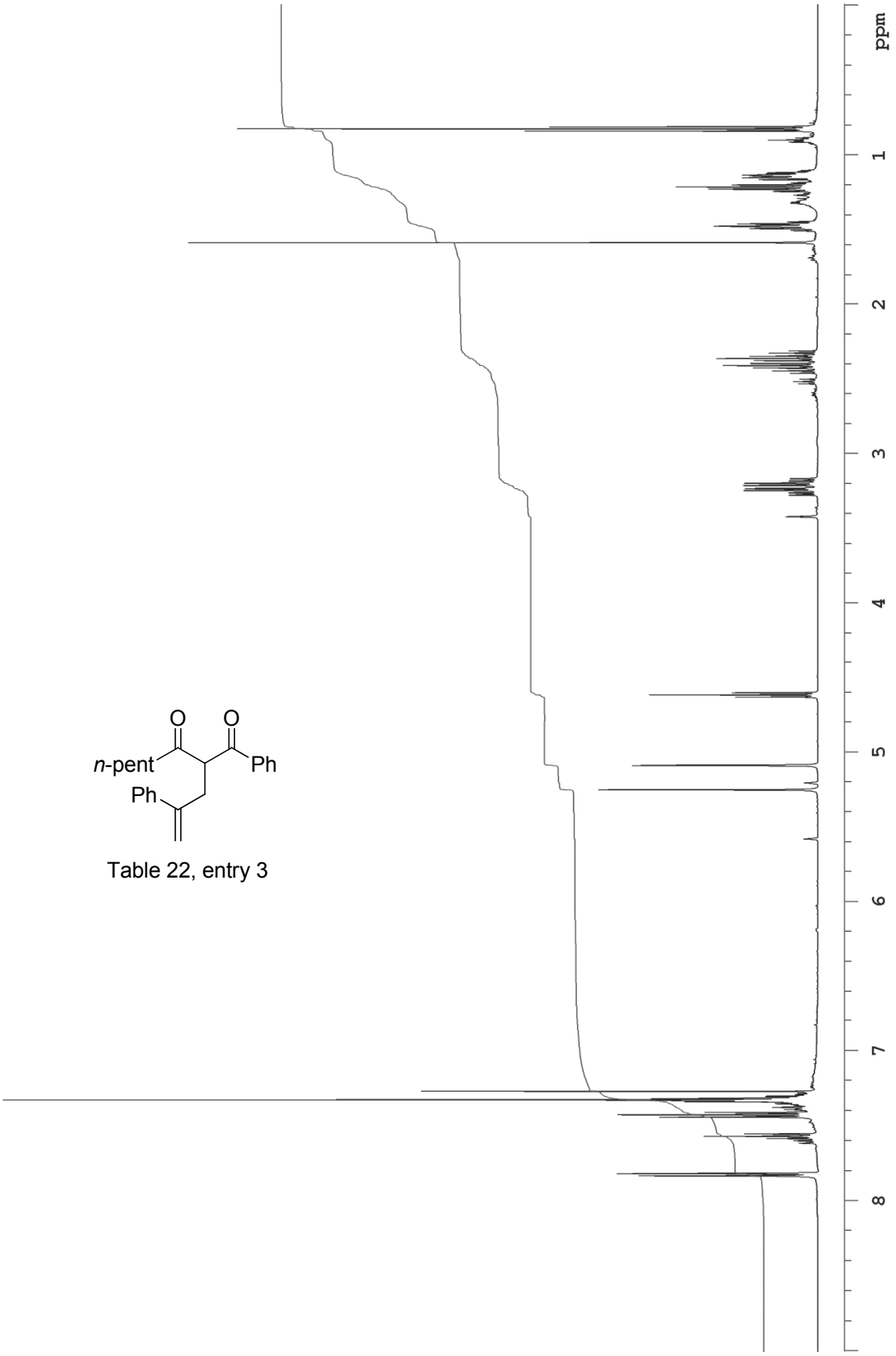

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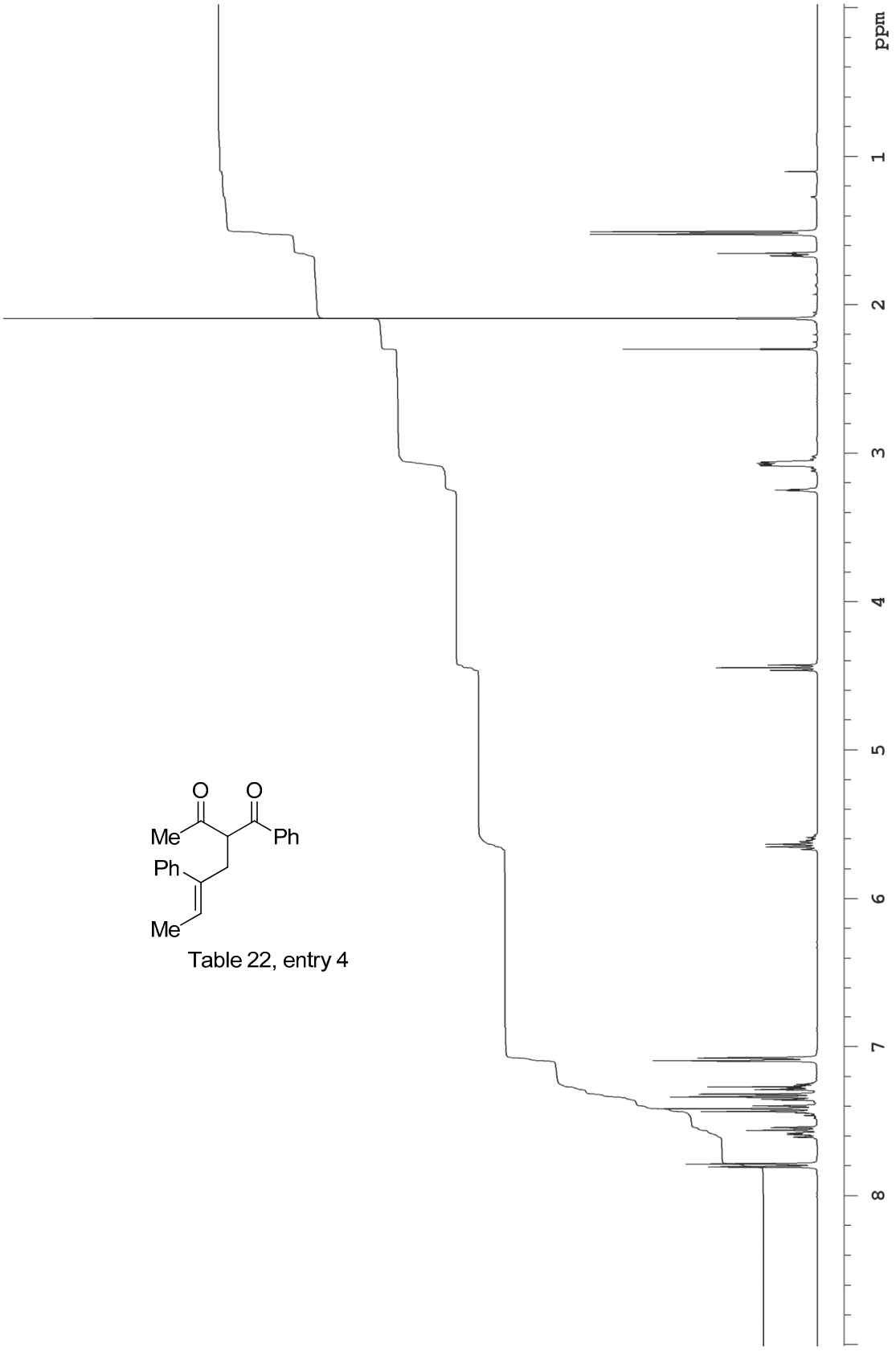

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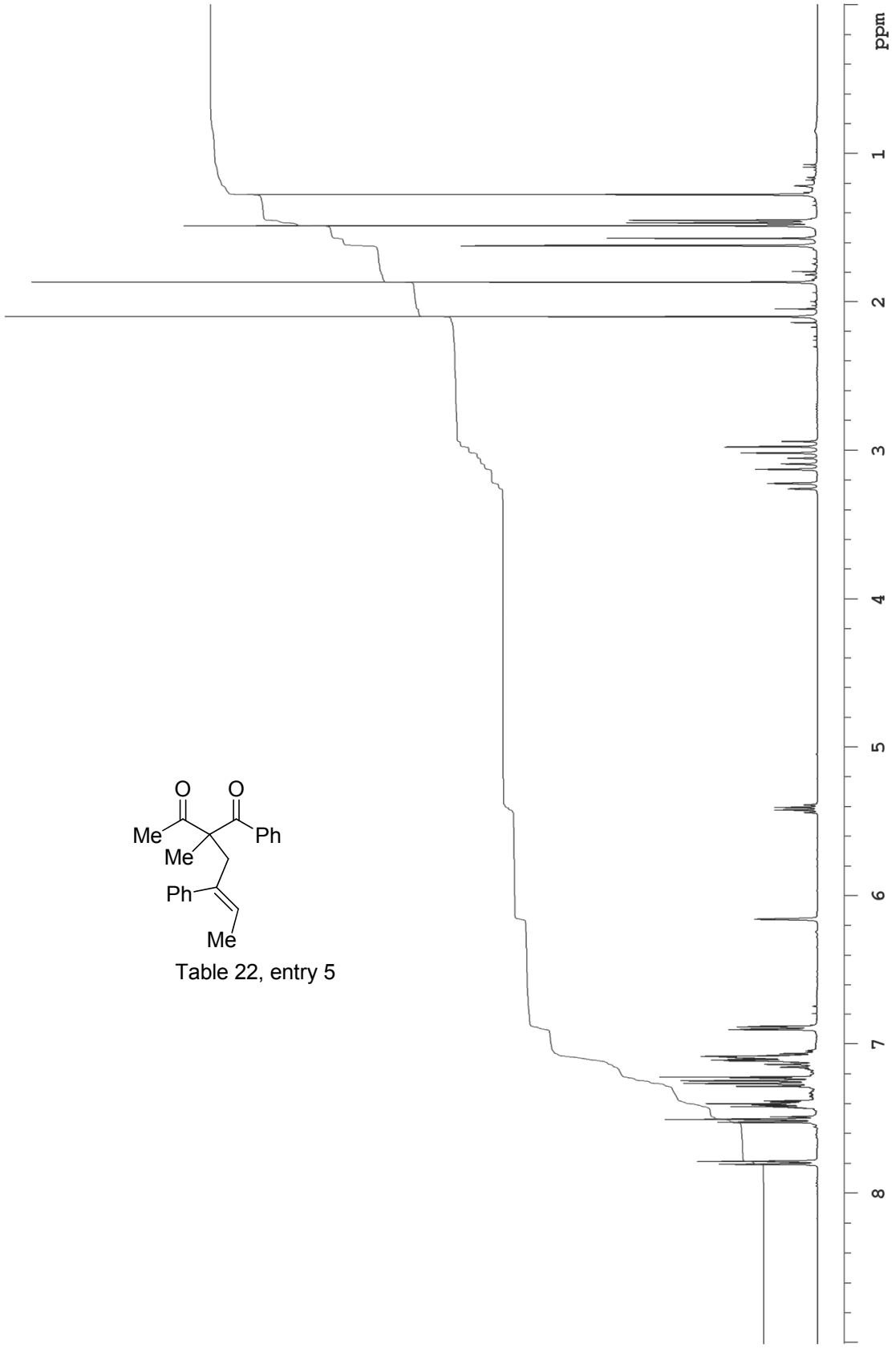

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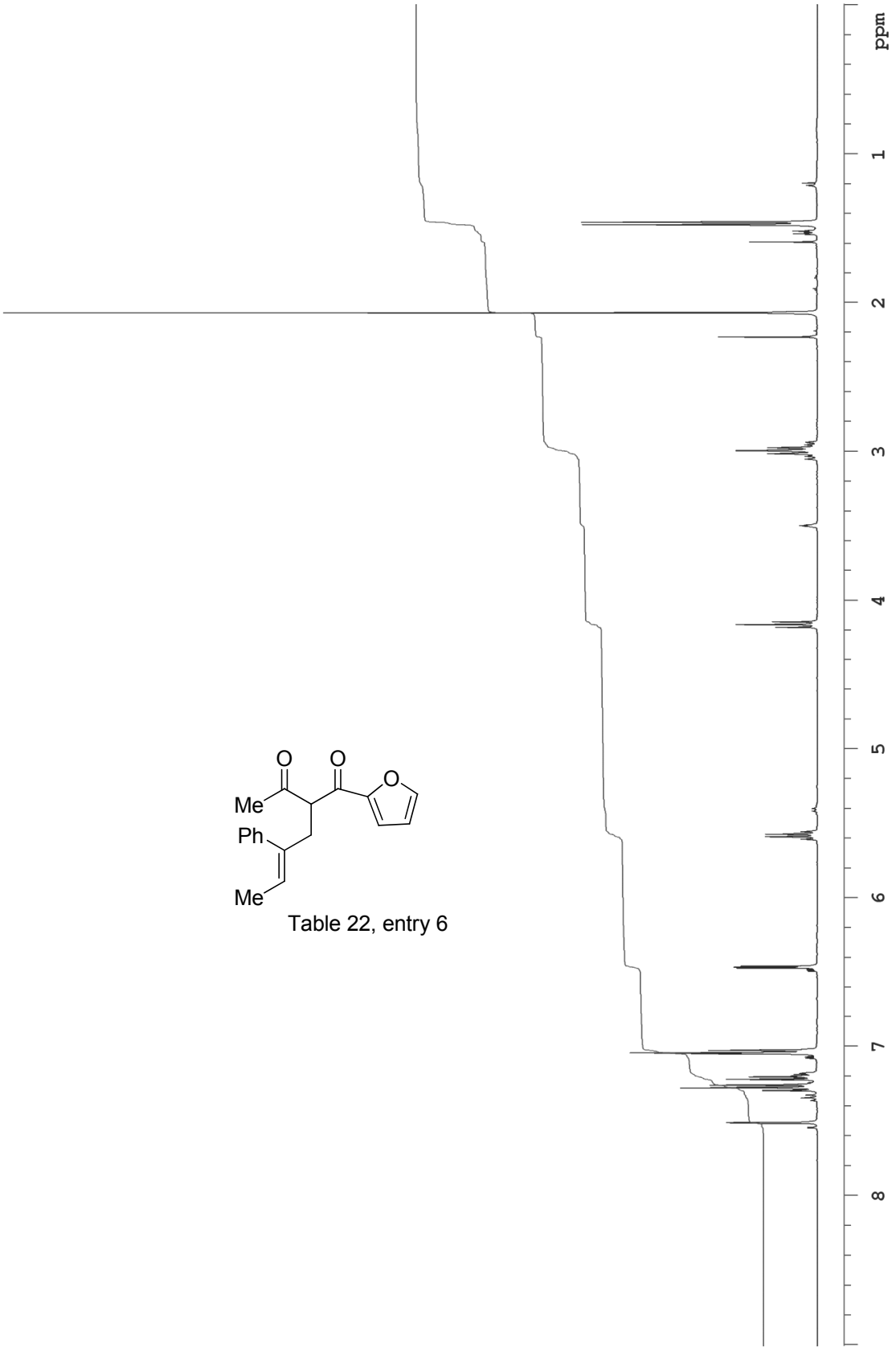

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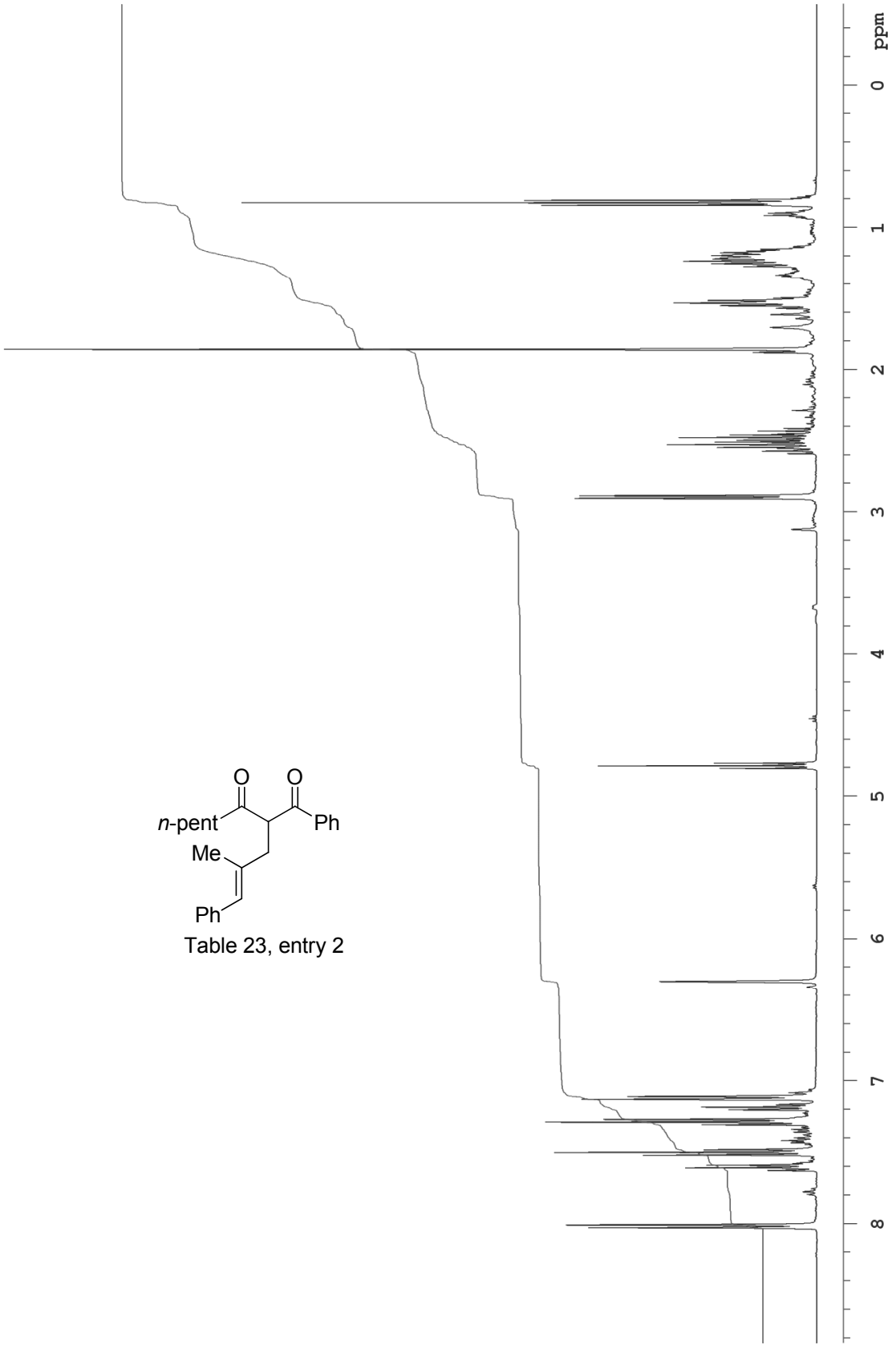

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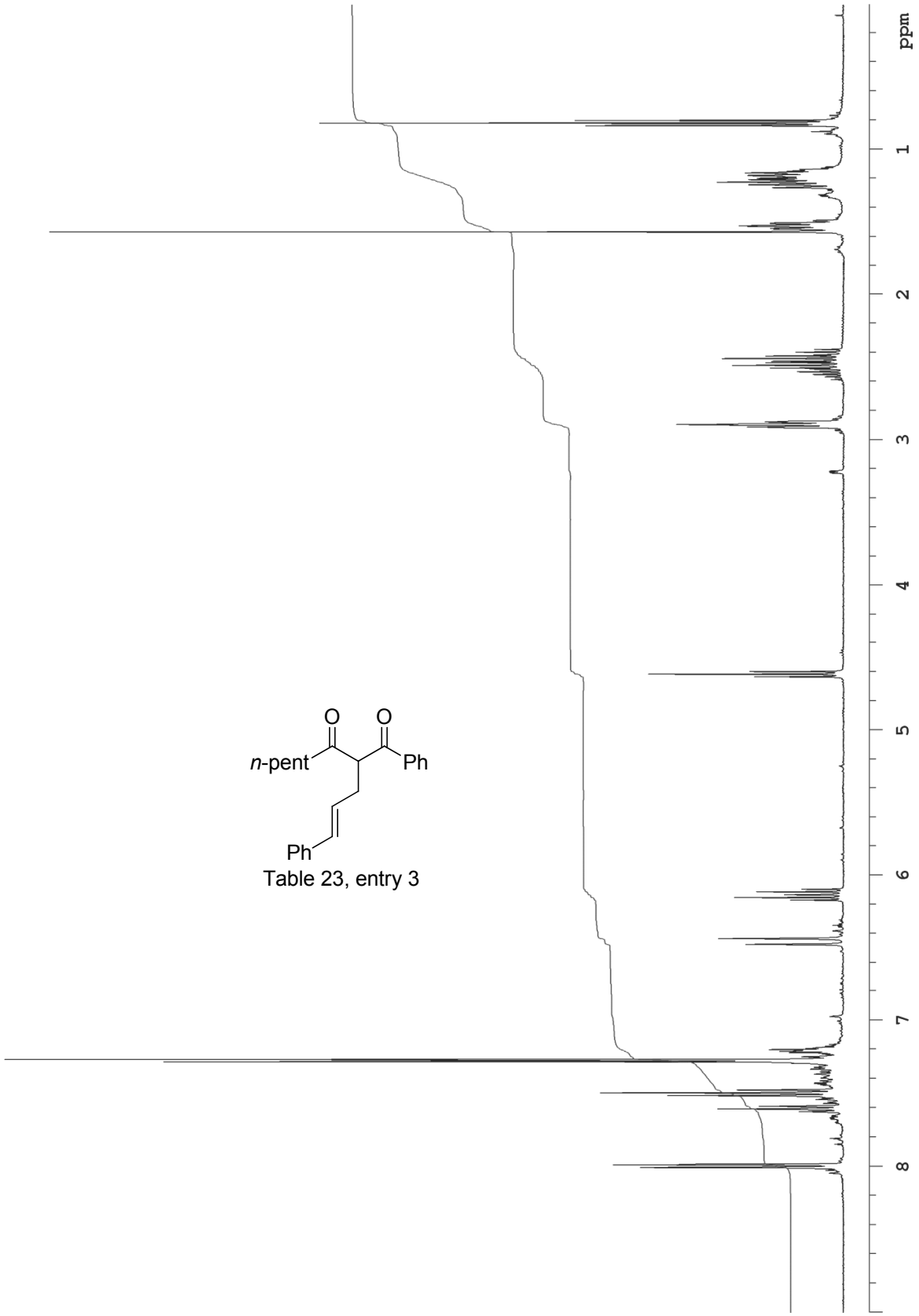

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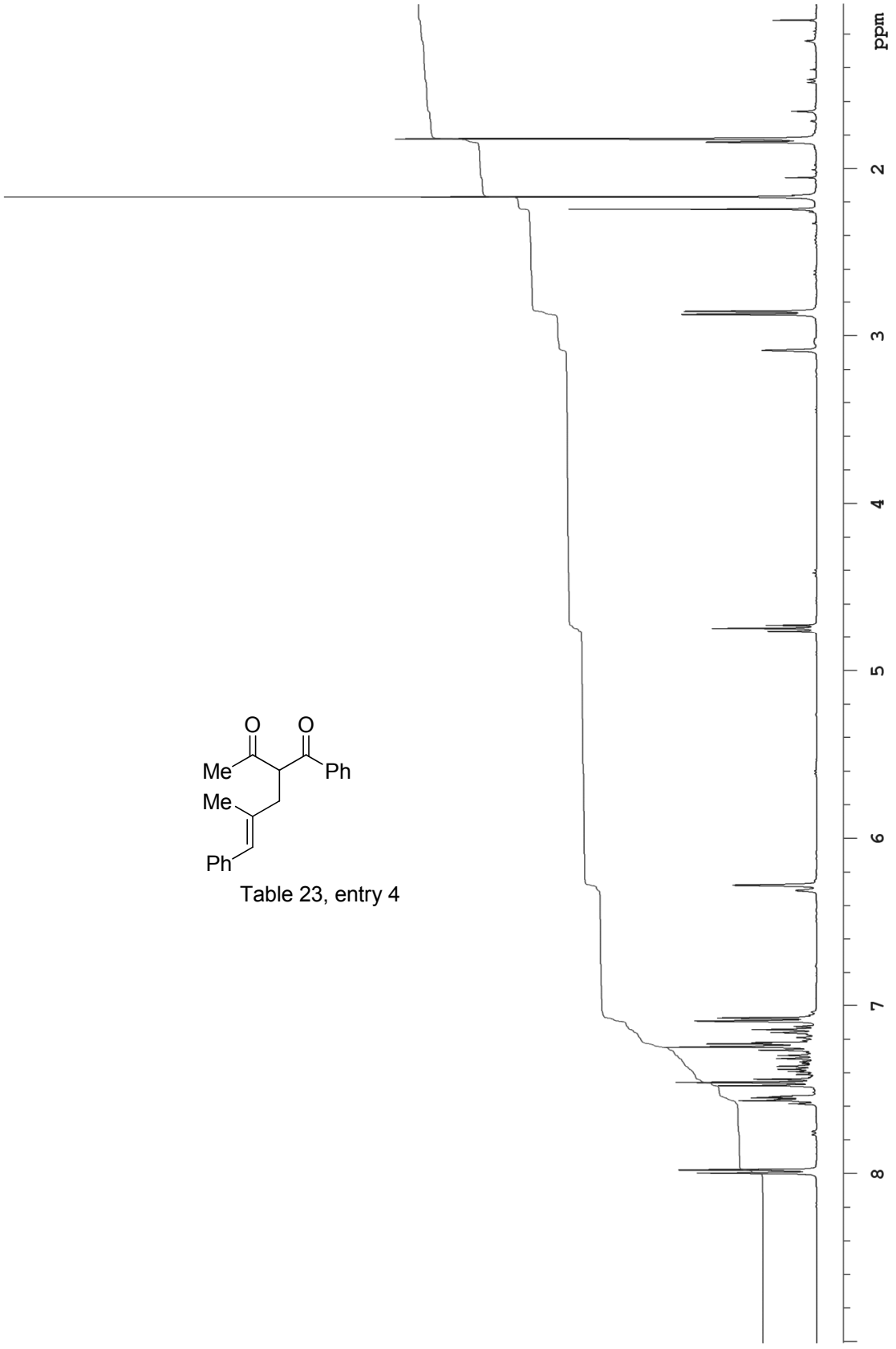

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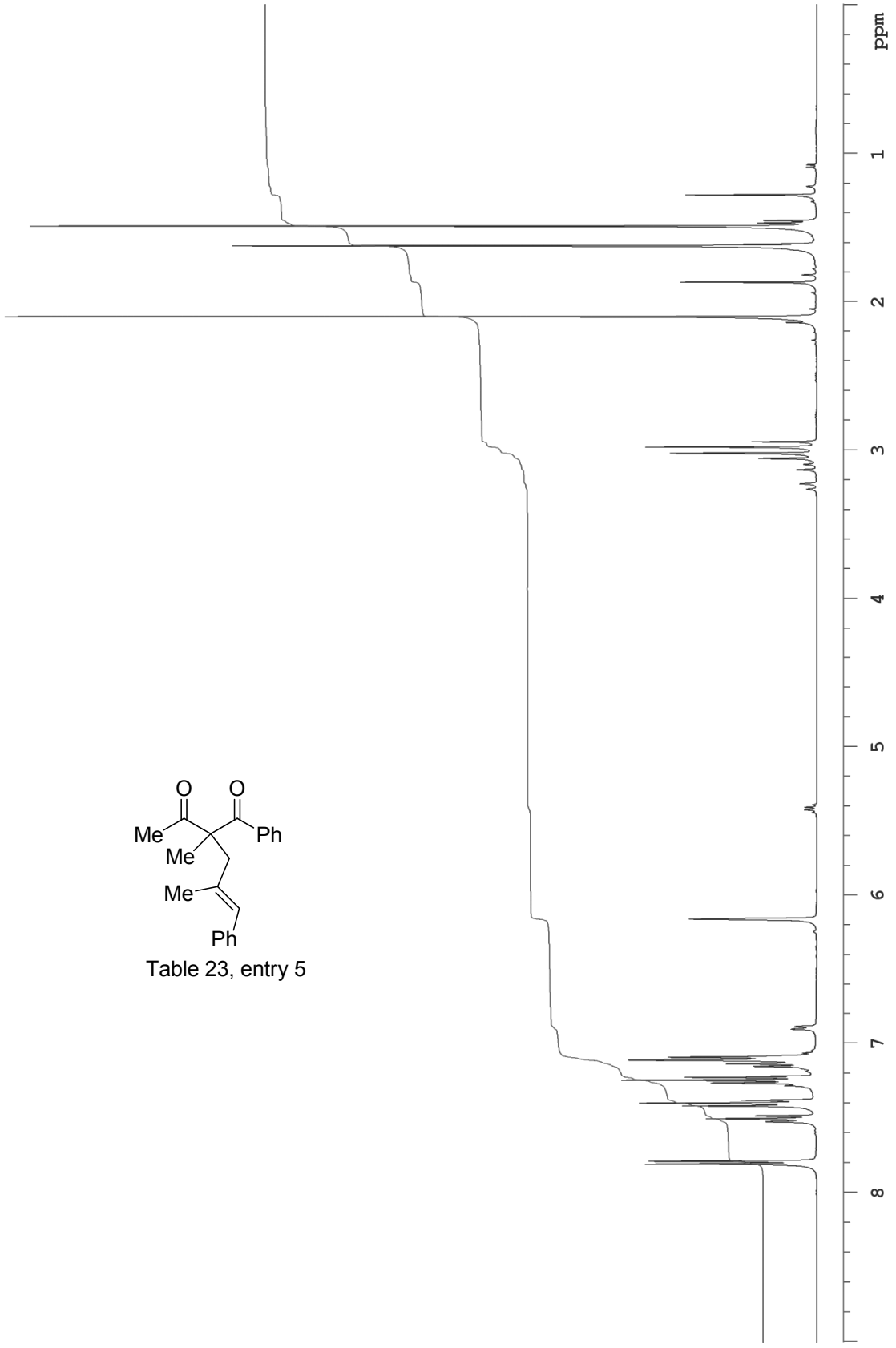

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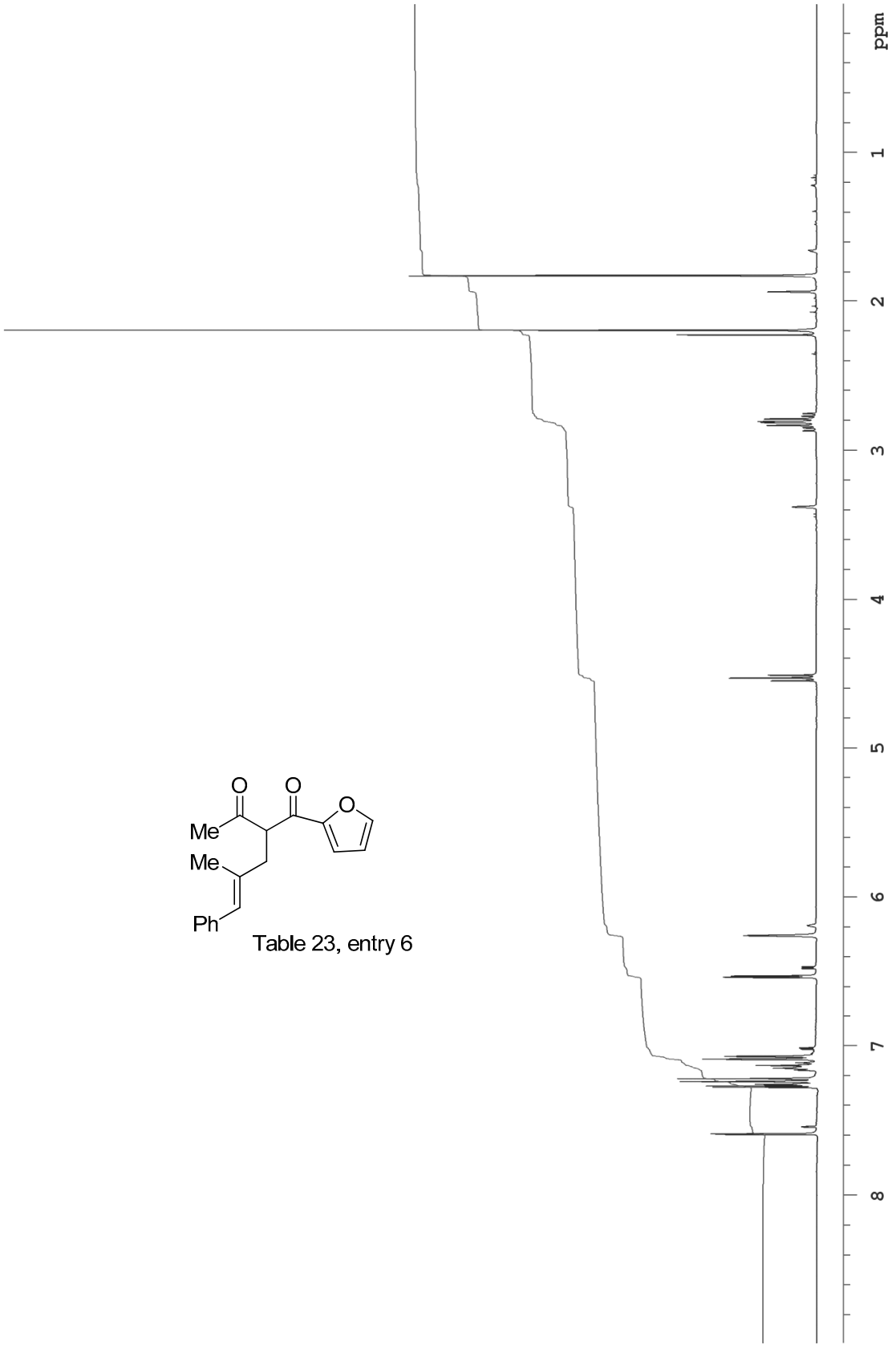

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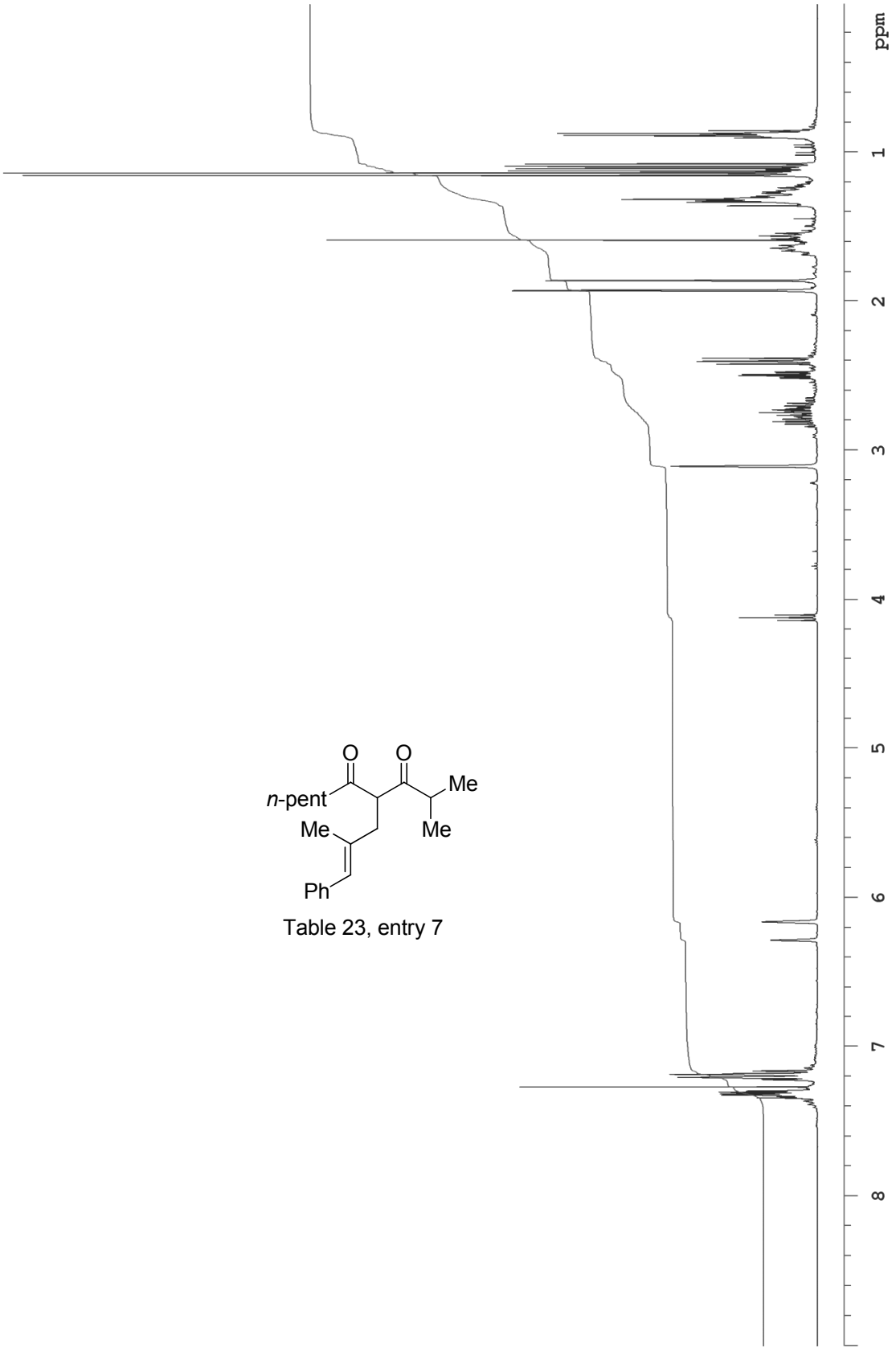

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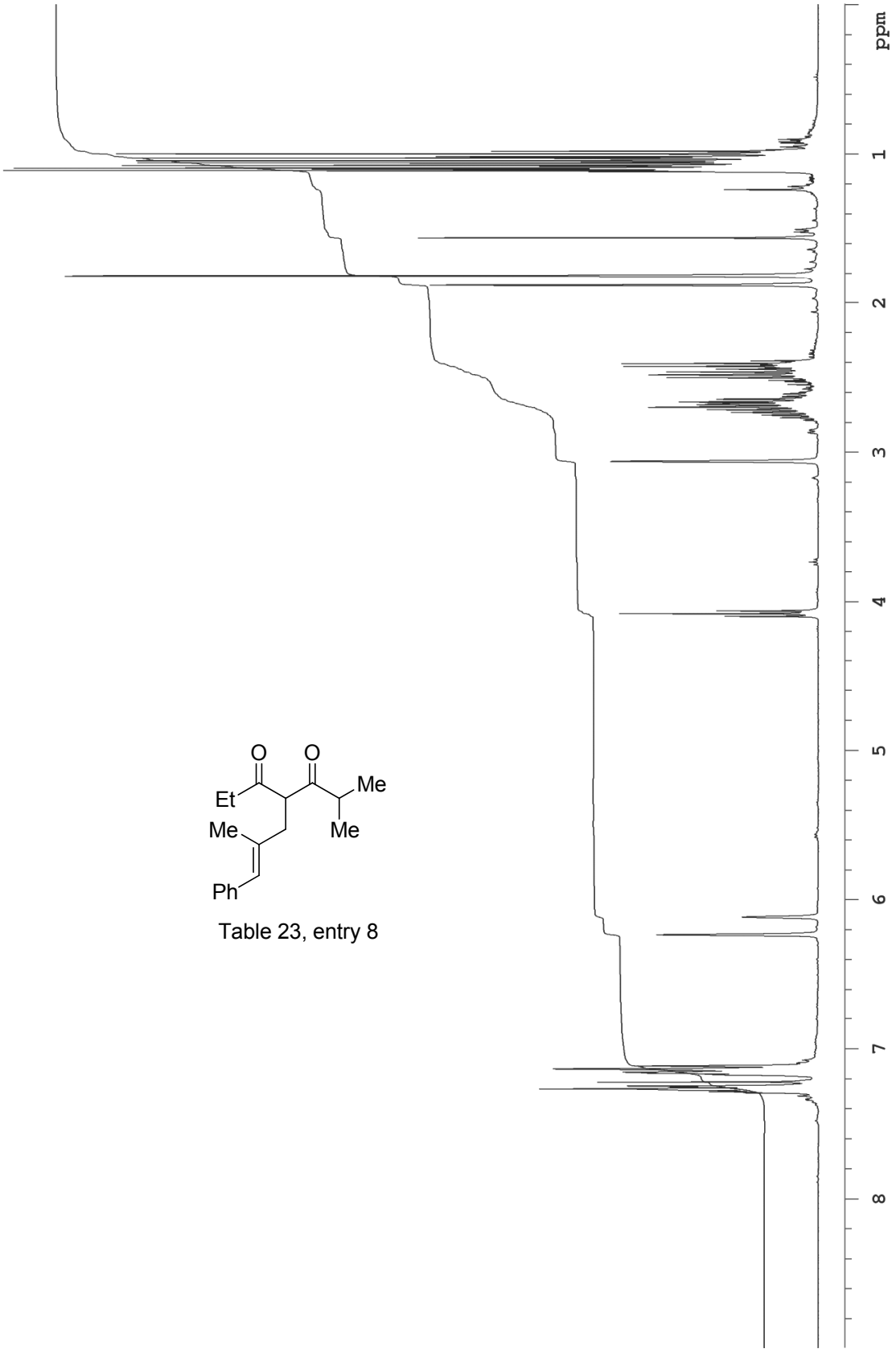

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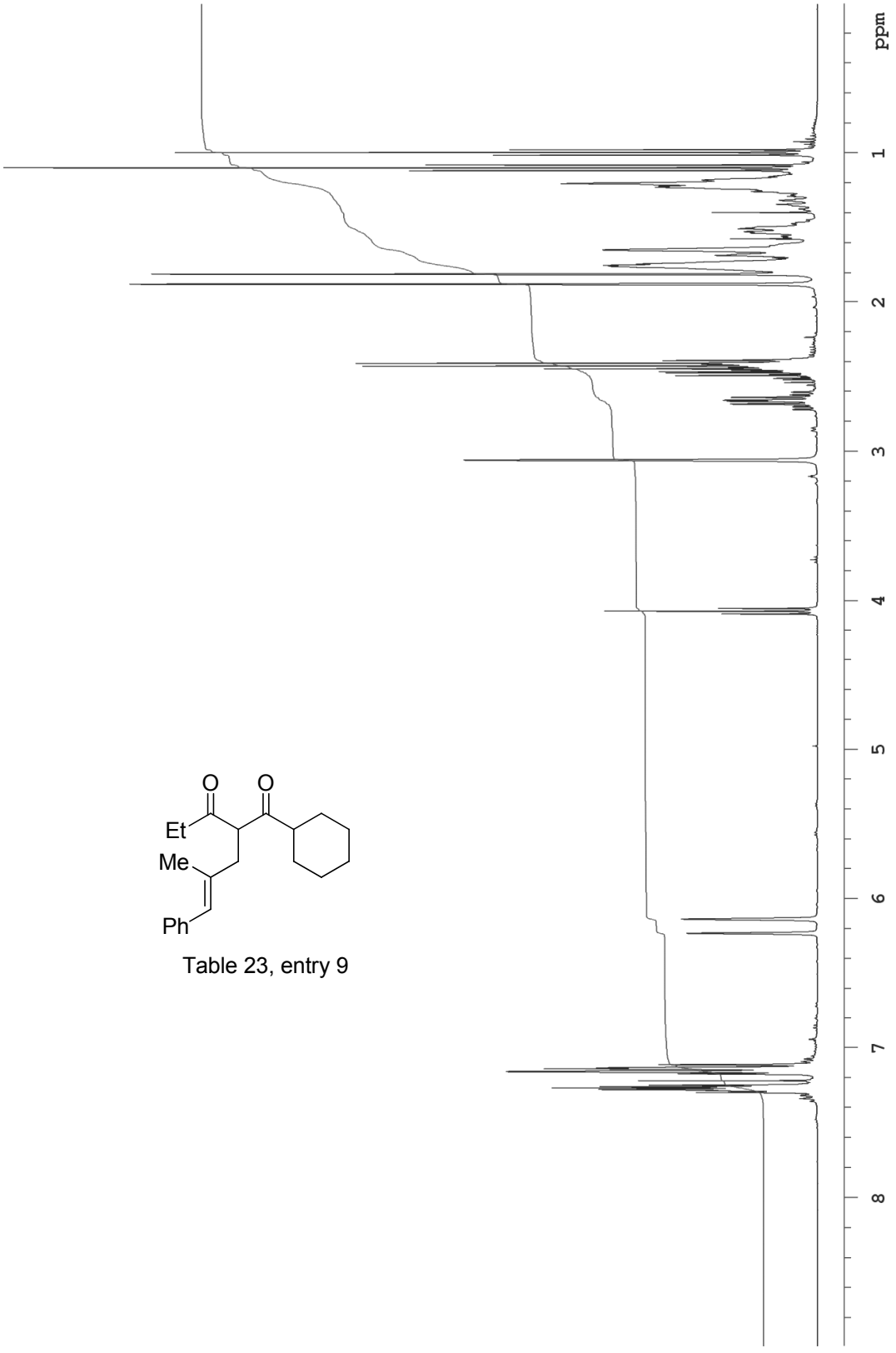

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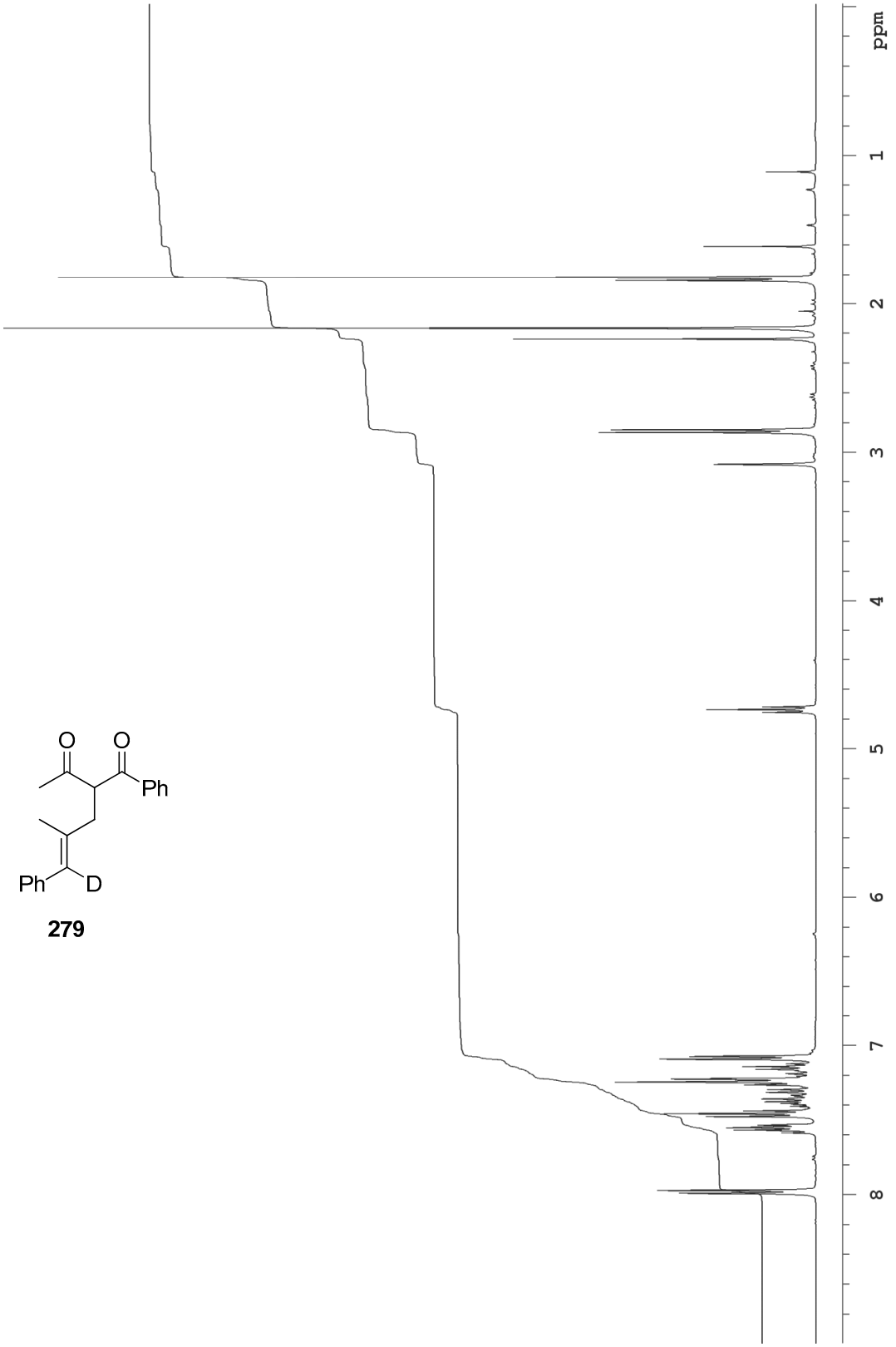

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