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Regio- and Stereoselective Construction of Tertiary and Quaternary Stereogenic Carbon Centers via Allylic Substitution with Alkyl- and Arylcopper Reagents

Thesis by

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Doctor of Philosophy

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List of Abbreviations

Ac	acetyl
acac	acetylacetonato
Ar	aryl
n-Bu	<i>normal</i> -butyl
Bn	benzyl
CT	chirality transfer
cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
<i>o</i> -DPPB	<i>ortho</i> -diphenylphosphanylbenzoate
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
Me	methyl
Ms	methanesulfonyl
nd	not determined
NMO	4-methylmorpholine <i>N</i> -oxide
NOE	nuclear overhauser effect
Ph	phenyl
Pic	2-pyridinecarboxylate
Piv	pivaloyl
PMB	<i>para</i> -methoxybenzyl
Pr	propyl
py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	<i>tertiary</i> -butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	<i>para</i> -toluenesulfonyl

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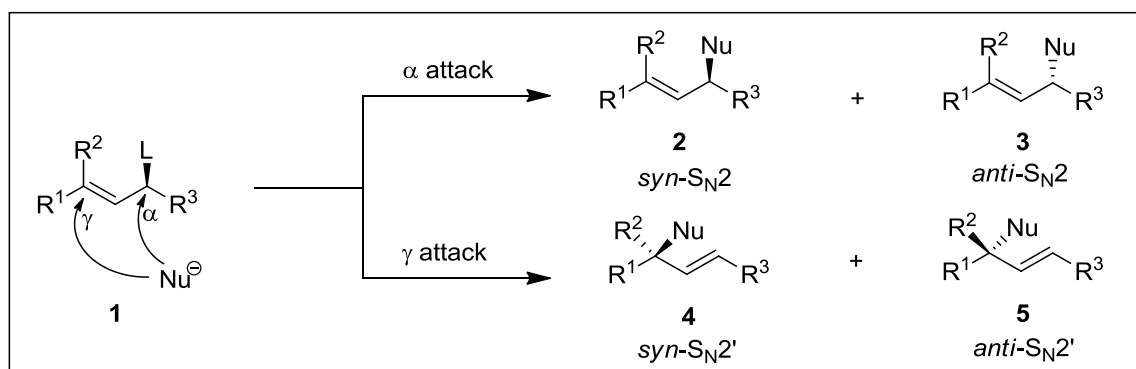
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Chapter 1 General Introduction

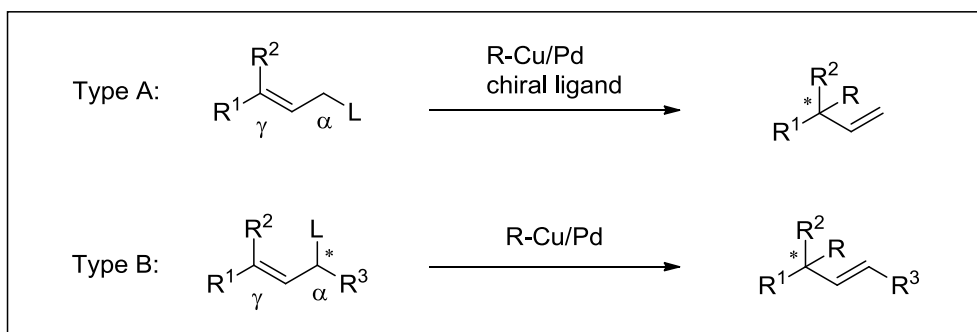
1.1 General Introduction

Organocopper reagents were originally prepared (from PhMgI and CuCl) by H. Gilman and co-workers in 1936,¹ which are unstable and show moderate reactivity. In 1952, H. Gilman made a remarkable progress, firstly prepared lithium dimethylcuprate (also named Gilman reagent), which presents high reactivity and can be soluble in diethyl ether and THF. In 1967, Gilman reagent was employed by E. Corey and G. Posner for forming C-C bond, including substitution of allylic substrates², opening the gate for allylic substitution with organocopper reagents. Inspired by E. Corey and G. Posner, allylic substitution with organocopper reagents generating S_N2' product was first reported by P. Grabbé, et al in 1969,³ and has become one of the most fundamental methods to form C-C bond.⁴ Allylic substitution with secondary esters **1a** and **1b** gives *syn*-S_N2, *anti*-S_N2, *syn*-S_N2' and *anti*-S_N2' products **2-5** in theory (**Scheme 1.1**), in consequence of α or γ attack of nucleophile with *syn*- or *anti*-manner. As a result, it is essential to obtain one single isomer by controlling the regio- and stereoselectivity among all the four possible products.



Scheme 1.1 Allylation Producing Four Possible Products

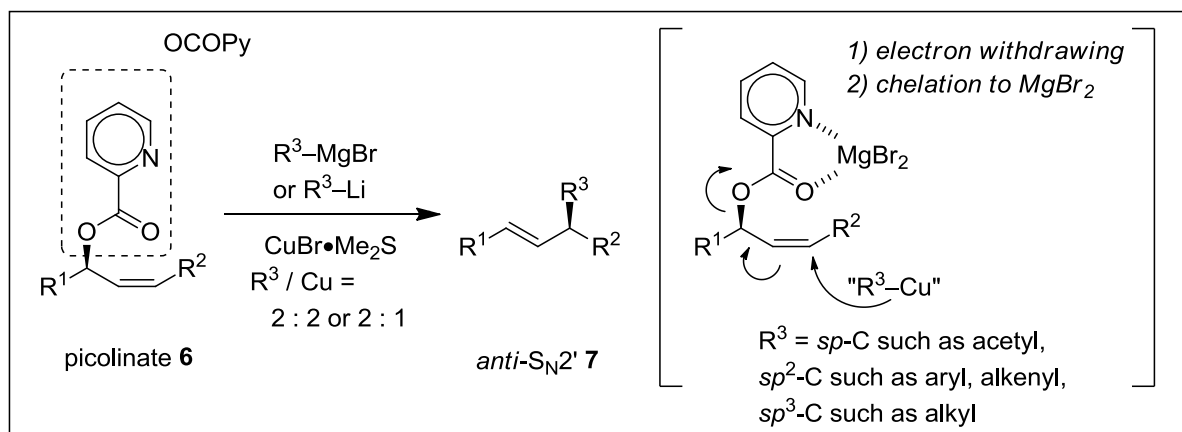
Generally, two types of allylic substitution have been reported (**Scheme 1.2**) to produce S_N2' products.⁴ Type A in the presence of a chiral ligand generates optically active products with terminal olefin. Type B constructs chiral centers with internal olefin via full CT (chirality transfer) of enantiomerically enriched substrates. Furthermore, due to generation of internal olefin in the S_N2' products, which can be transformed to various skeletons by many available methods, type B has its own advantage for further applications.



Scheme 1.2 Allylation Producing Four Possible Products

Since preparation of asymmetric allylic alcohols with excellent enantiomeric purity is well investigated,⁵ allylic substitution of chiral esters with complete CT became one of the most important methods to generate stereogenic centers.¹ Due to the high energy of 3d orbital of copper,⁶ which contains full 10 electrons, organocopper reagents present high potency to generate *anti*-S_N2' product selectively. For instance, Breit et al reported an interesting protocol via *o*-DPPB-directed allylic substitution, regio- and stereoselectively affording *anti*- or *syn*-S_N2' products.⁷ Knochel and co-workers on the other hand employed the OCOC₆F₅ leaving group to asymmetrically afford *anti*-S_N2' products⁸ and to synthesize chiral quaternary carbons, which were then successively transformed to chiral tertiary alcohols and amines.^{8b} Sawamura et al employed boron reagents to afford various allylation products using Cu and Pd as catalysts.⁹

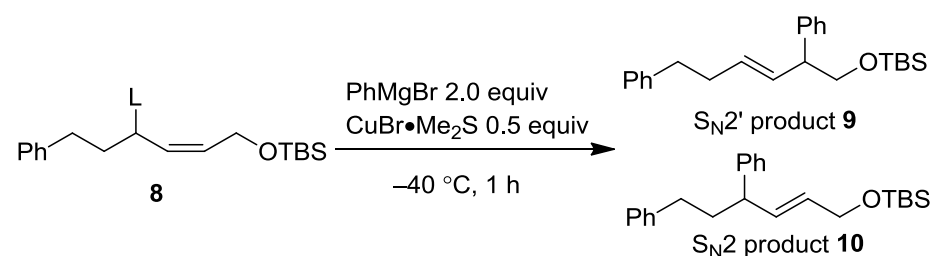
Despite these impressive achievements, many unsolved problems including limitation with scope of C-C bonds have remained.⁴ Recently, allylic picolinate **6** has been developed by us¹⁰ to make several kinds of C-C bonds with alkyl (*sp*³-C), aryl and alkenyl (*sp*²-C), and even alkynyl (*sp*-C) groups regio- and stereoselectively because of the high potency of the new leaving group OCOPy (Py = 2-pyridyl), which is activated by the following two effects (**Scheme 1.3**): (1) Electron-withdrawing from pyridyl group; (2) Chelation to MgBr₂.



Scheme 1.3 Synergistic Activation of the Picolinoxyl Group

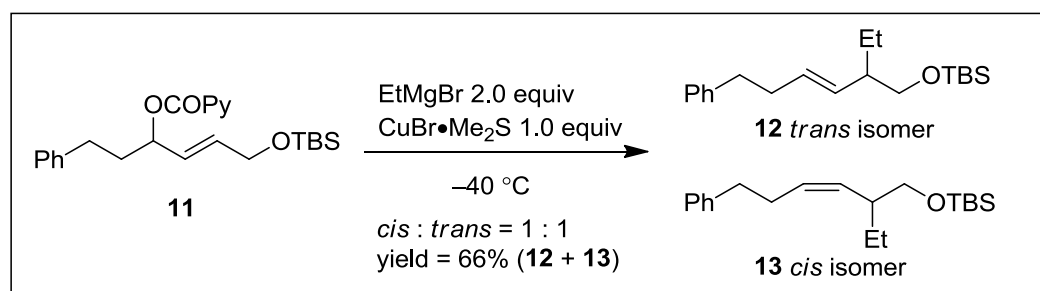
These activations are verified by reactions using several similar leaving groups (**Table 1.1**).¹⁰ The conversion decreases a lot in case of no nitrogen atom and even no reaction occurs with a nitrogen atom at *para* position of aromatic ring (entries 2 and 3); the reactivity is similar to that with *ortho* position (entry 1) when nitrogen atoms are at both *para* and *ortho* positions (entry 4). Hence, chelation of the nitrogen atom and the carbonyl oxygen to MgBr₂ activates the picolinoxy leaving group very much.

Table 1.1 Exploration of Leaving Groups



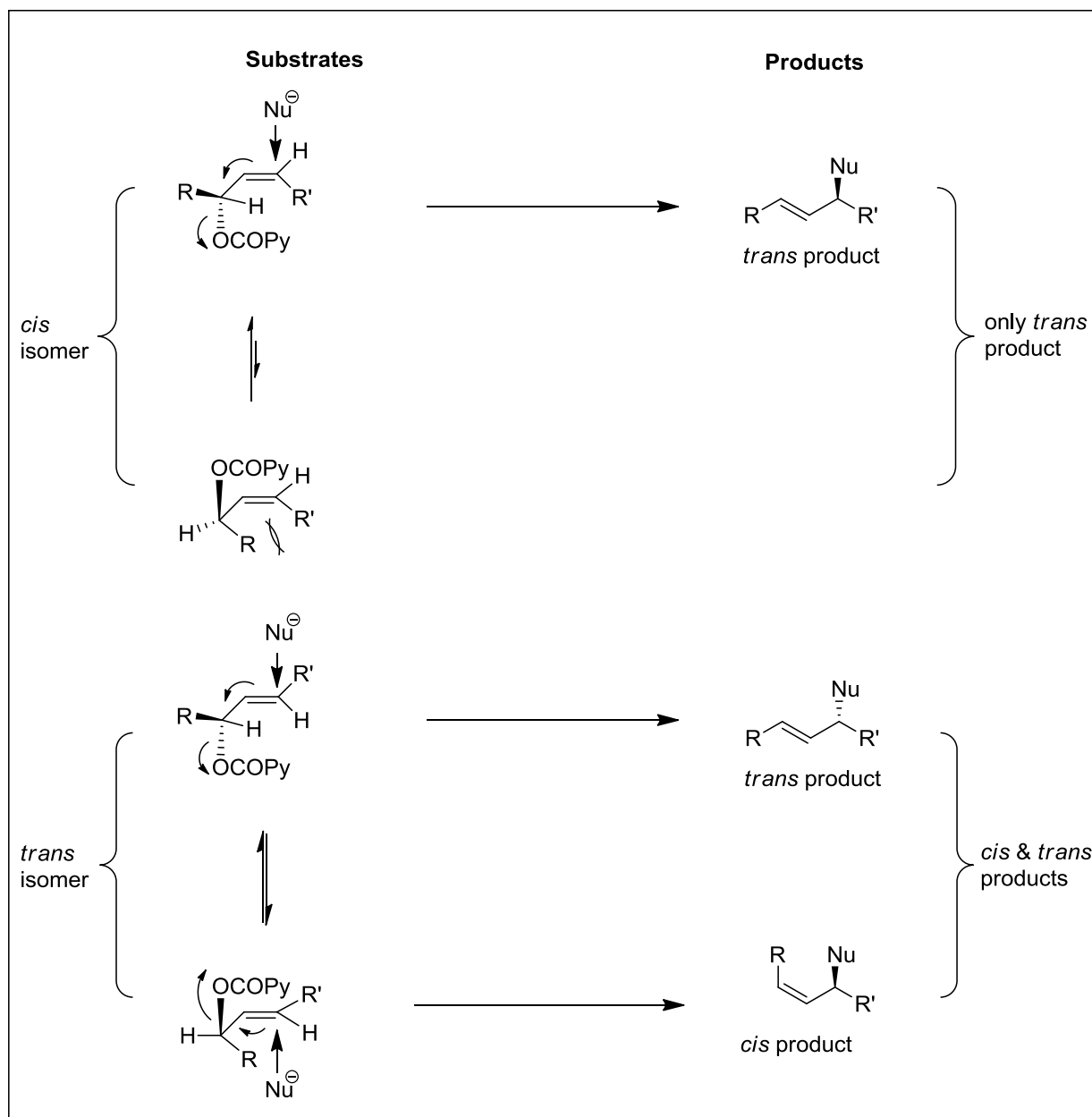
Entry	Leaving Group	9 : 10	Yield
1		99 : 1	90%
2		—	46%
3		—	no reaction
4		99 : 1	94%

Moreover, the effect of olefinic geometry of picolinate has been investigated. *trans*-Olefin **11** forms a mixture of *cis*- and *trans*-products **12** and **13** (**Scheme 1.4**), whereas *cis*-olefin gives *trans*-product **9** selectively as mentioned above (**Table 1.1**, entry 1).



Scheme 1.4 Allylation of *trans* Olefinic Picolinate

As demonstrated in **Scheme 1.5**, the mechanism^{4h} that the 1,3-allylic strain (steric hindrance between R and R') in the *cis* allylic picolinate **8** corresponds to its high selectivity giving *trans* isomer **9**, while the conformational freedom of *trans*-olefin substrate **11** corresponds to giving a mixture of *cis* and *trans*-isomers (**12** and **13**) with low selectivity.

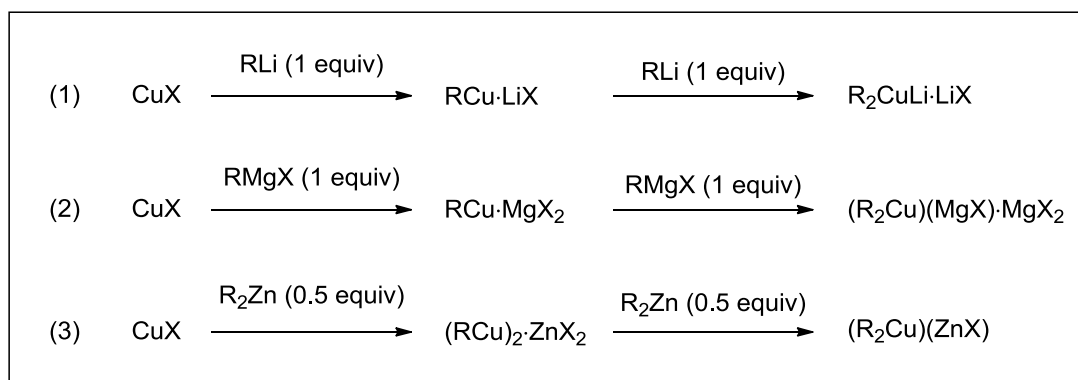


Scheme 1.5 Allylic Substitution of Picolates Containing *cis/trans* Olefin

In addition, comparing with *o*-DPPB (1,917 JPY/mmol), OCOC₆F₅ (240 JPY/mmol) leaving groups, OCOPy (4 JPY/mmol) leaving group is much cheaper,¹¹ thus has its advantage for applications.

Finally, the reagents used for allylic substitution of picolates are generally "RCu" and "R₂Cu[−]" species corresponding to R/Cu in 1:1 and 2:1 ratios (**Scheme 1.6**).⁴ In case of Cu(II) such as Cu(acac)₂

(acac = acetylacetonate), one equivalent of R^- (from $RMgX$, RLi , etc.) is necessary to reduce $Cu(II)$ to $Cu(I)$,¹² subsequently undergoing the same transmetalation as $Cu(I)$.



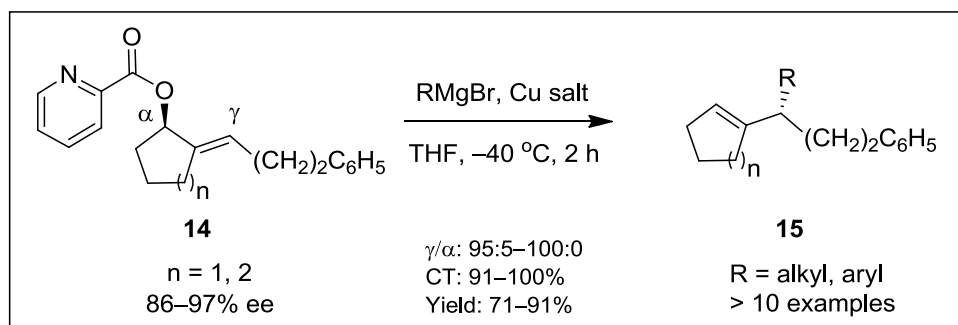
Scheme 1.6 Transmetalation between Copper and $RLi/RMgX/R_2Zn$ ($X = Cl, Br$, etc)

1.2 Introduction of Each Chapter

Based on these investigations, the author was interested in allylic substitution of optically active cyclic and acyclic picolates to construct chiral tertiary and quaternary carbon centers:

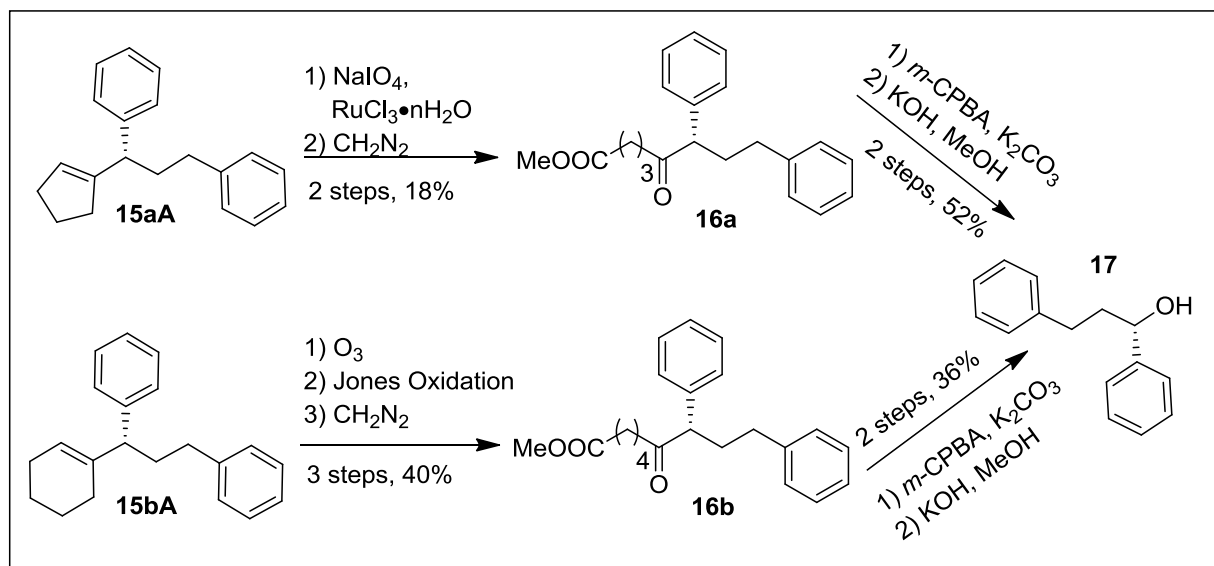
Chapter 2 Installation of a Chiral Side Chain to a 2-Alkylidene-1-cycloalkan-1-ol Unit by Using Allylic Substitution

Firstly, the author was interested in allylic substitution of cycloalkenyl picolates because bioactive steroids such as vitamin D contain the five-membered ring and the chiral side chain on the D ring. Hence, construction of such structural unit is important for synthesizing steroids. To obtain fundamental aspect such as reactivity, regio- and stereoselectivities, the author investigated allylic substitution of γ -alkyl substituted allylic cycloalkenyl picolates **14** with $RMgBr$ -based copper reagents ($R = Bu, Ph$, etc.), producing anti S_N2' products **15** (**Scheme 1.7**).



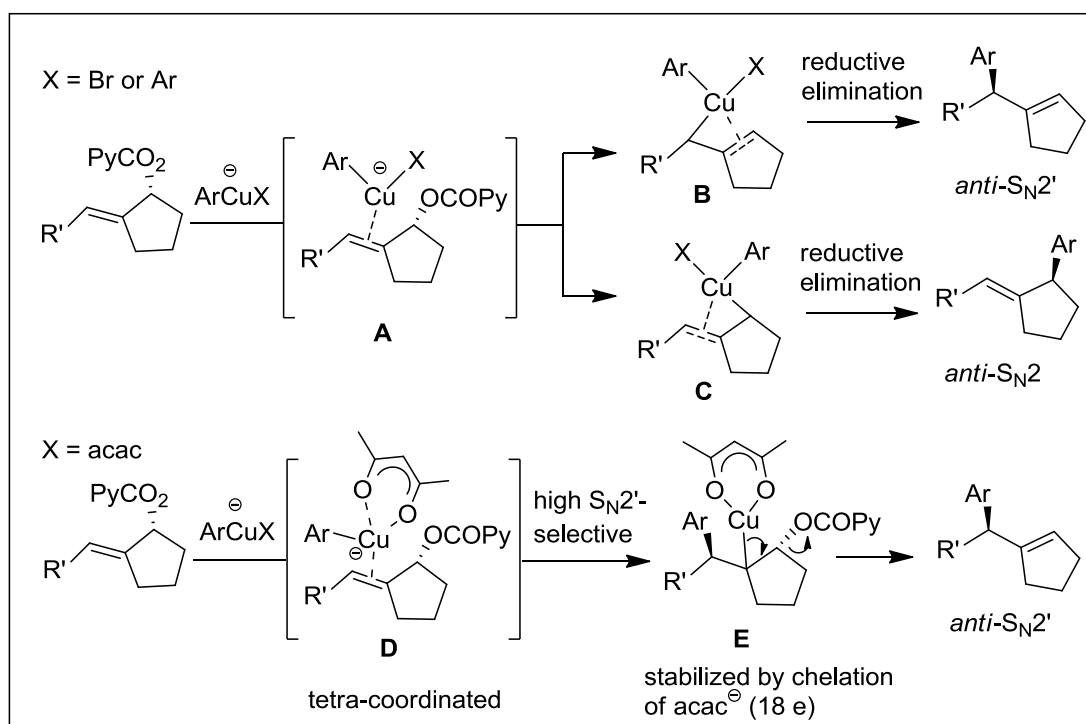
Scheme 1.7 Allylation of Optically Active Cycloalkenyl Picolates

The absolute configuration of **15aA** ($n = 1$, $R = \text{Ph}$) and **15bA** ($n = 2$, $R = \text{Ph}$) was determined by degradation to known compound **17** and comparing the $[\alpha]_D$ value of that reported (**17** from **15aA**, $[\alpha]_D^{23} -13$ (c 0.17, CHCl_3); **17** from **15bA**, $[\alpha]_D^{23} -23$ (c 0.25, CHCl_3) (lit.¹³ $[\alpha]_D^{20} -27$ (c 0.52, CHCl_3) for the *S* enantiomer of >99% ee), respectively (**Scheme 1.8**), thus stabilizing *anti* $\text{S}_{\text{N}}2'$ pathway of the allylic substitution.



Scheme 1.8 Degradation of 15aA and 15bA to Known Compound 17

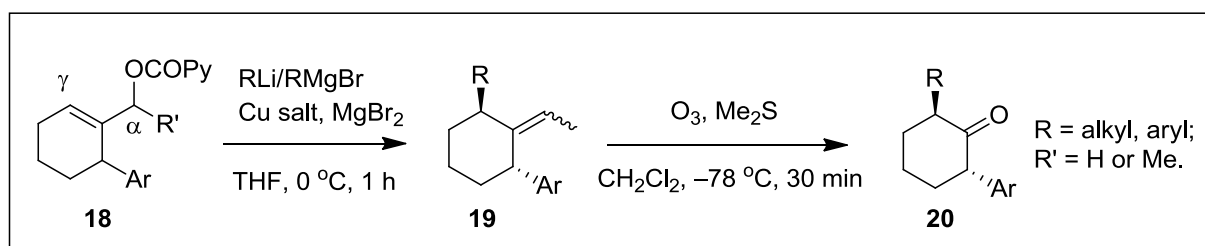
In detail, $\text{Cu}(\text{acac})_2$ was found to be a better copper salt than $\text{CuBr} \cdot \text{Me}_2\text{S}$. A possible mechanism was presented (**Scheme 1.9**). Due to high energy of 3d orbital of copper, which has a comparable energy level to R^- , the $\text{R}-\text{Cu}$ bond is more like a covalent bond rather than an ionic bond, thus acting like a nucleophile when interacting with $\text{C}=\text{C}$ bond.^{6, 14} As a result, in case of $\text{X} = \text{Br}$ or Ar , firstly, $[\text{Ar}-\text{Cu}-\text{X}]^-$ coordinates to $\text{C}=\text{C}$ bond to form a T-shaped complex **A**, which controls the stereochemistry of this transformation and subsequently affording an tri-coordinated organocopper “ $\text{Cu}(\text{III})$ ” intermediate, which is oftentimes assumed to be an important transition state and unstable by computational analysis.^{14d,15} Oxidative addition of $\text{C}=\text{C}$ bond and subsequent cleavage of $\text{C}-\text{O}$ bond produce π complexes **B** and **C**, which are tetra-coordinated complexes preferred by copper.^{14d,16} Then reductive elimination generates the *anti*- $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ products. In contrast, in case of $\text{X} = \text{acac}$, the T-shape complex **D** is already tetra-coordinated, the Ar^- attacks the γ position and a tri-coordinated organocopper “ $\text{Cu}(\text{III})$ ” intermediate **E** is formed, which is usually unstable.^{14d,15} However, due to chelation of acac^- , the complex consists of 18 electrons, and thus stable (according to the classic 18 electron rule), and probably could be an experimentally observable stabilized tri-coordinated organocopper(III) species. In this transition state, on the other hand, it is quite unstable in case of $\text{X} = \text{Br}$ or Ar . The following elimination generates *anti*- $\text{S}_{\text{N}}2'$ product with solid regioselectivity.



Scheme 1.9 Possible Mechanism

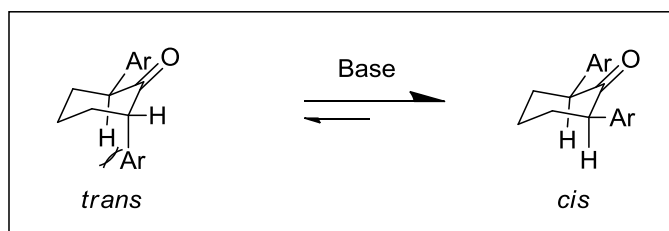
Chapter 3 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanone via Allylic Substitution of *exo*-Cyclic Picolinates Followed by Ozonolysis

Alpha position of ketones usually plays as nucleophile such as in aldol reaction. Thus anion is generated at alpha position of carbonyl group and is attacking electrophiles to generate various products. In this study (**Scheme 1.10**), a strategy was developed by allylic substitution of cyclic picolinates **18** with nucleophiles and ozonolysis to generate 2,6-disubstituted cyclohexanones **20** (nucleophiles were attached to α position of carbonyl group indirectly).



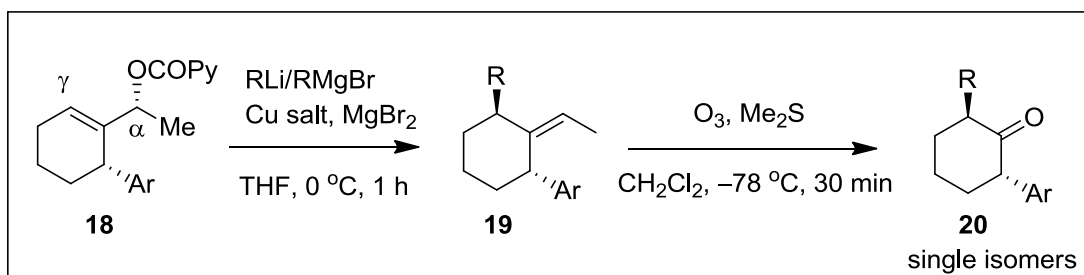
Scheme 1.10 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanones

Furthermore, due to steric factor (**Scheme 1.11**), reactions afford α,α -disubstituted cyclohexanones preferring syn isomer, whereas, in this work, products **20** are in an *anti*-manner, which was determined by NOE analysis as well as comparing ¹H NMR with that reported.



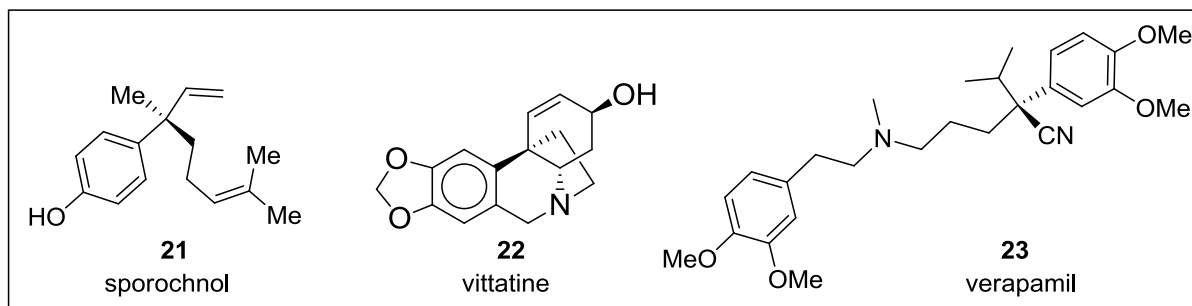
Scheme 1.11 Transformation from *trans* to *cis* Isomers

In addition, single isomers **20a** (Ar = Ph, R = Me), **20b** (Ar = Ph, R = Me), and **20c** (Ar = R = Ph) were synthesized by using optically active substrate, respectively (**Scheme 1.12**).



Scheme 1.12 Synthesis of Single Isomers

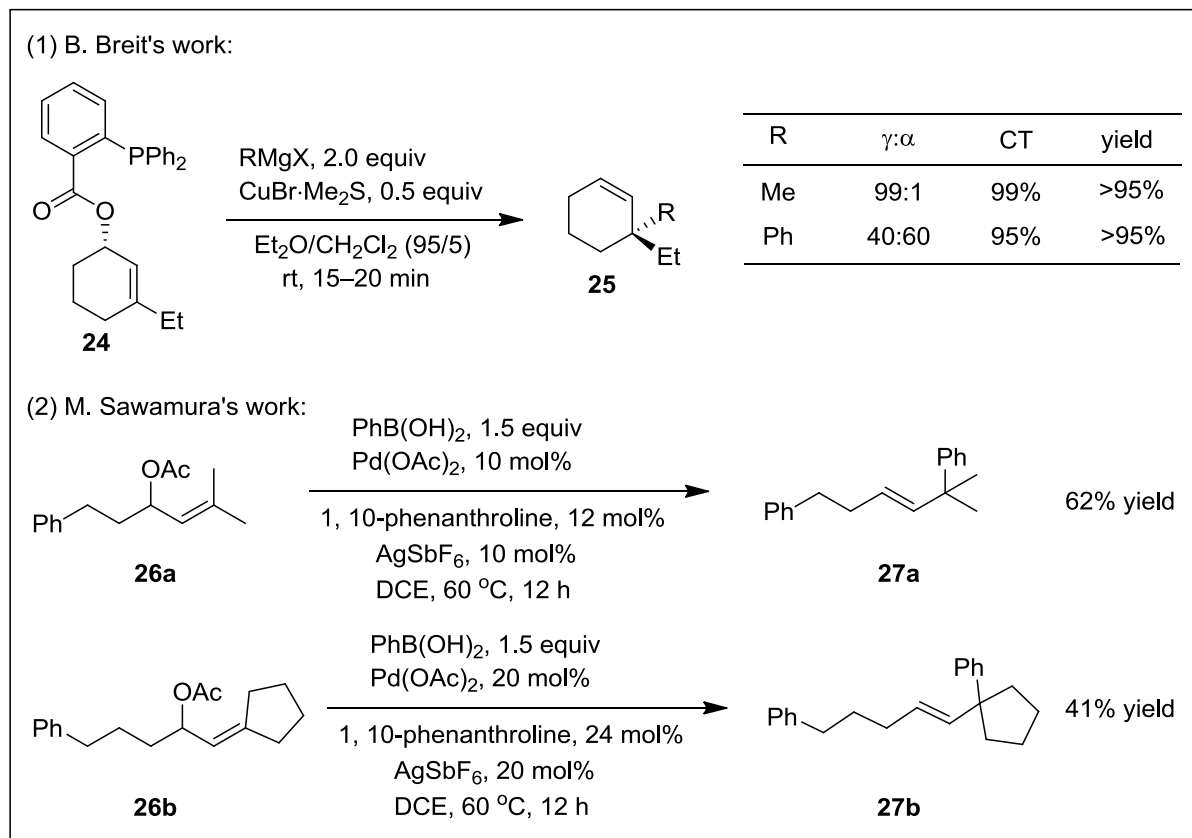
Chapter 4 Construction of Chiral Quaternary Carbon Centers with Arylcopper Reagents



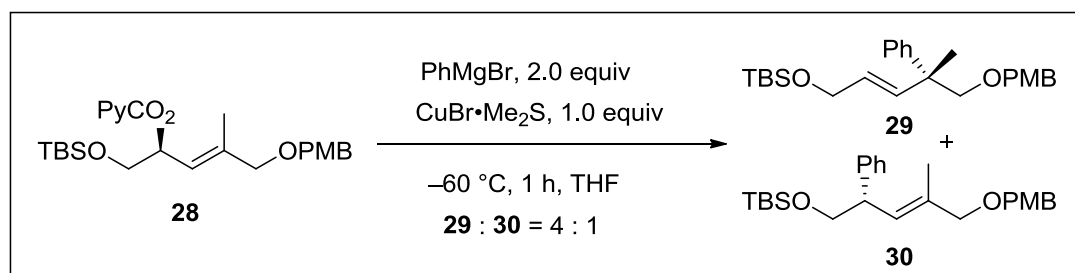
Scheme 1.13 Quaternary Carbon Centers Found in Natural Products

Quaternary centers are very common in biologically active natural products such as those shown in **Scheme 1.13** and asymmetric preparation of quaternary centers is an important synthetic problem. Allylic substitution is one of the most valuable approaches. However, allylic substitution of secondary esters affording S_N2' products with excellent selectivity is limited to alkyl groups. For example, B. Breit^{7b,7c} and M. Sawamura^{9d} reported protocols (**Schemes 1.14**) for construction of quaternary centers with aromatic groups, however, due to the larger steric hindrance as well as lower reactivity of Ph group, the former protocol applying *o*-DPPB leaving group afforded *syn*- S_N2' product **25b** (R = Ph) with 40% regioselectivity and Pd-catalyzed allylic substitution with PhB(OH)_2 turned out low yield of **27a** and

27b (62% and 41% yield) respectively. Likewise, OCOPy leaving group was also employed previously^{10b} in our laboratory and the conventional catalyst CuBr·Me₂S was used to deliver Ph group to form *anti*-S_N2' product **29** with a chiral quaternary carbon center with 82% regioselectivity (**Scheme 1.15**).



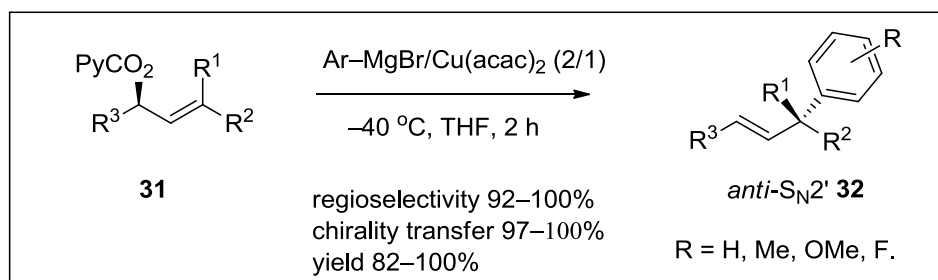
Scheme 1.14 Construction of Quaternary Carbons by B. Breit and M. Sawamura



Scheme 1.15 Previous Work in Our Laboratory

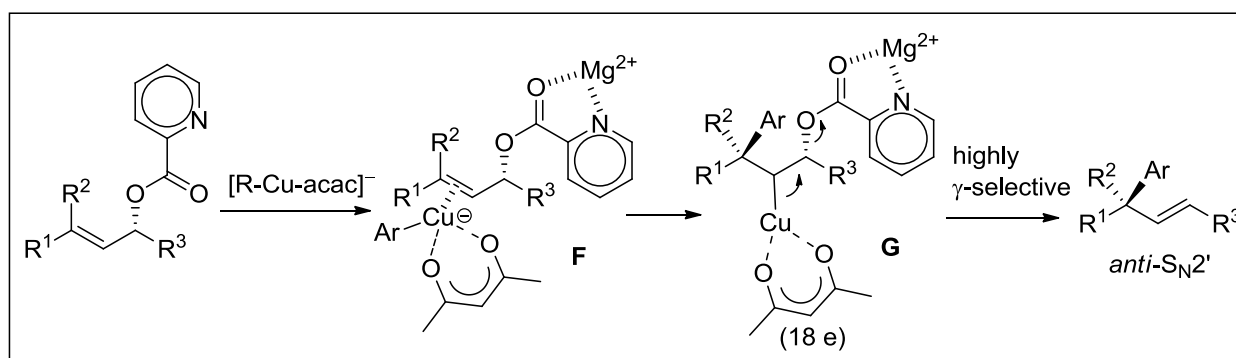
In this chapter, firstly, CuBr·Me₂S as well as ZnI₂-driven protocol^{10e} were applied, still resulting in a mixture of S_N2' and S_N2 products. In contrast, Ph group was successfully transferred by Cu(acac)₂ to the quaternary carbon centers with excellent regio- and stereo-selectivity as shown in **Scheme 1.16**. The absolute configuration of **32a** (R = H) was determined by comparing [α]_D value ([α]_D²³ +2.5 (c 0.16, CHCl₃)) with this reported (lit.^{10b} [α]_D³⁰ +1.5 (c 0.40, CHCl₃)) as well as the retention time on chiral

HPLC analysis, establishing *anti*- γ pathway. Additionally, PhMgBr/Cu(acac)₂/ZnI₂ in a 3:1:1 ratio was found to be a good reagent system too, implying the important role played by Zinc in turn.



Scheme 1.16 This Work

In a view of mechanism (**Scheme 1.17**), coordination of organocopper reagents to C=C bond, resulting a T-shaped complex **F**, which is already tetra-coordinated. Then the Ar group attacks γ position generates tri-coordinated organocopper species **G**. Chelation of acac[−] to copper stabilized the Cu-C σ bond (18 electron rule), which is usually unstable, following by excellent γ -selective pathway.

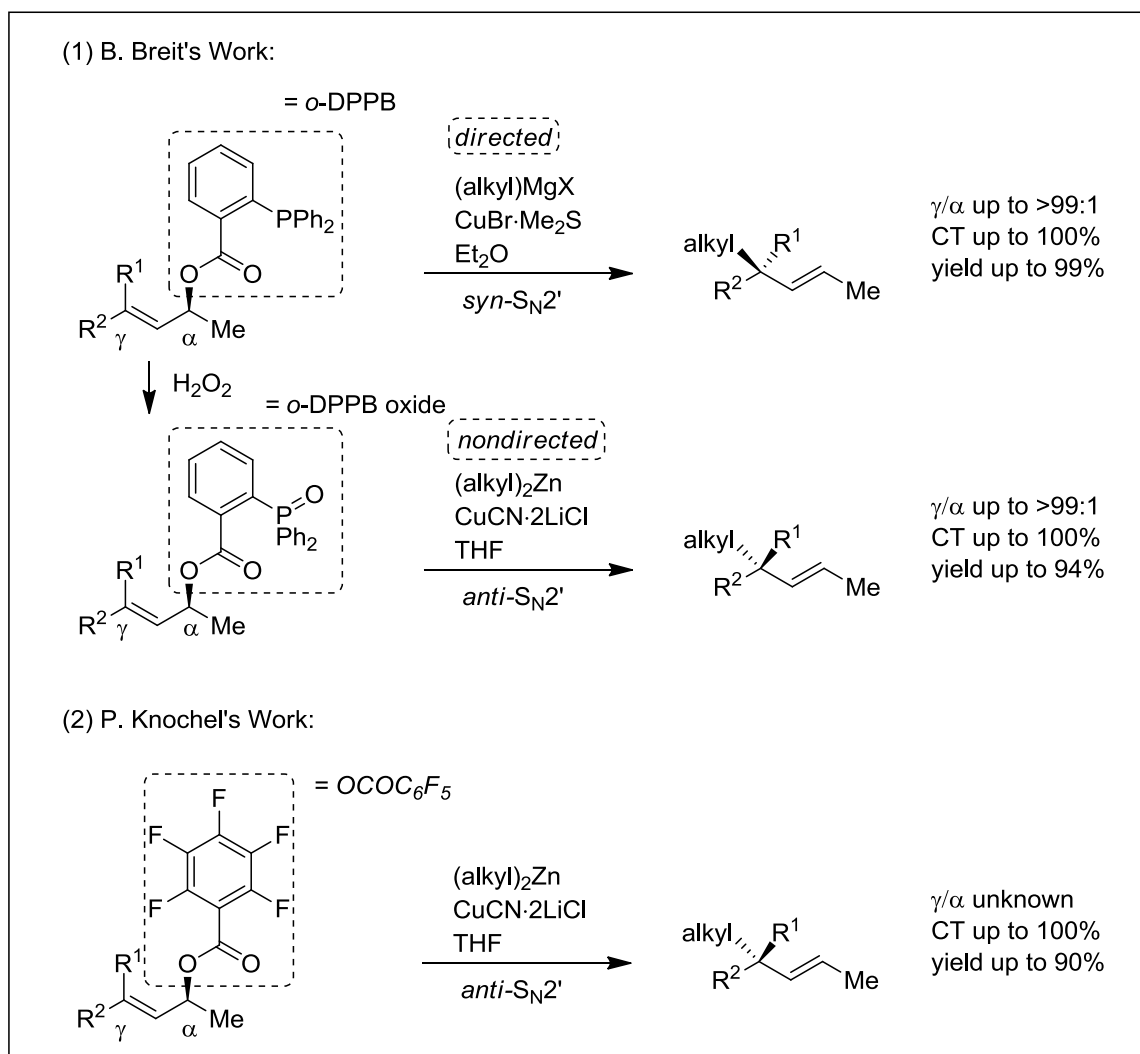


Scheme 1.17 Possible Mechanism

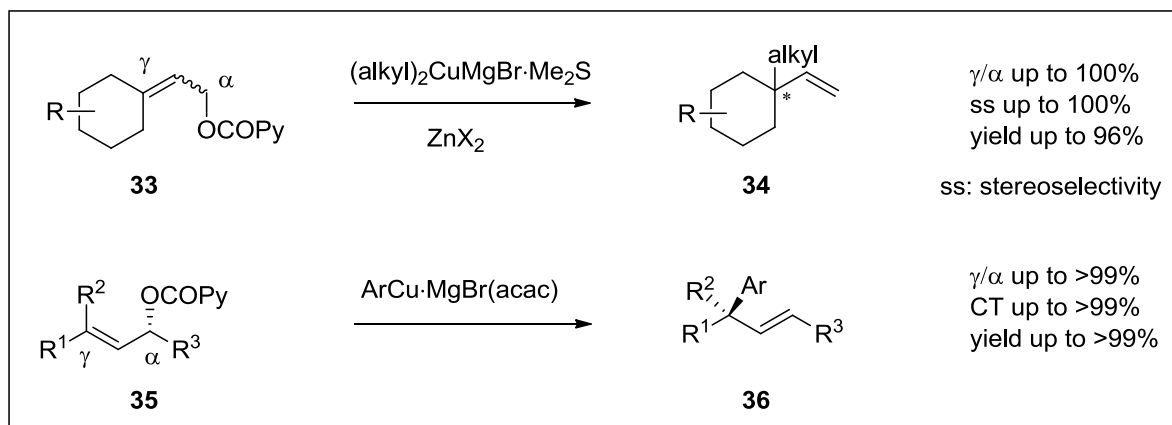
Chapter 5 Construction of Chiral Quaternary Carbon Centers with Alkylcopper Reagents

With respect to excellent *o*-DPPB and OCOC₆F₅ leaving groups (**Scheme 1.18**) for construction of quaternary carbon centers regio- and stereoselectively developed by B. Breit⁷ and P. Knochel⁸ respectively, recently, we have introduced the PyCO₂ leaving group to establish allylic substitution of secondary allylic esters,¹⁰ and the protocol was applied to construction of all carbon quaternary centers on cyclic and acyclic structures (**Scheme 1.19**).^{10e,g} In the latter case, an aryl (Ar) group was delivered to the γ position by using ArCu(acac)MgBr, which was in turn derived from ArMgBr and Cu(acac)₂ in the 2:1 ratio.^{10g} Later, this reagent system was applied to BuCu(acac)MgBr, a representative alkylcopper reagent, to produce a mixture of products, among which the desired S_N2' product was detected by ¹H NMR and TLC analysis. In this chapter, the author presents the continuous investigation

of finding alkylcopper reagents for construction of chiral quaternary carbon centers by allylic substitution of optically active acyclic picolinates.



Scheme 1.18 Construction of Chiral Quaternary Carbons by B. Breit and P. Knochel



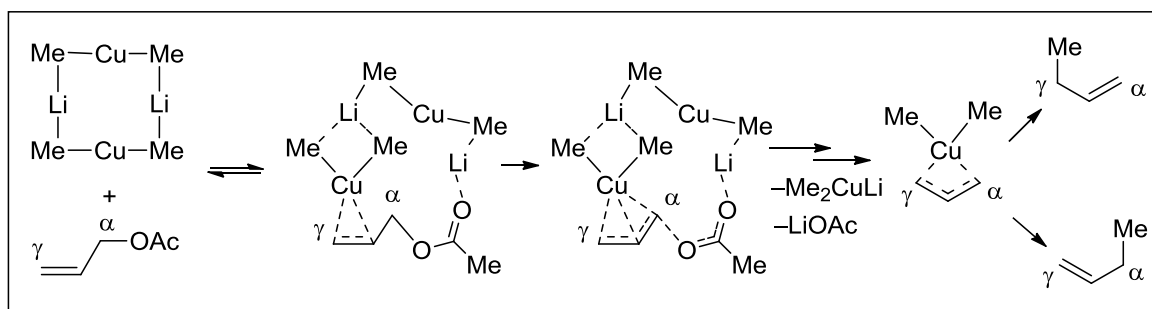
Scheme 1.19 Previous Work

ZnI_2 was found to promote regio- and stereoselective substitution of acyclic γ,γ -disubstituted secondary allylic picolates with alkylcopper reagents derived from alkyl-MgBr and $\text{CuBr}\cdot\text{Me}_2\text{S}$ in a 2:1 ratio to furnish quaternary carbon centers in good yields (**Scheme 1.20**). Alkyl groups delivered efficiently were the primary, secondary, and benzyl classes such as Me, Et, Bu, $\text{C}_{16}\text{H}_{33}$, $\text{Ph}(\text{CH}_2)_2$, $\text{Ph}(\text{CH}_2)_3$, $c\text{-C}_6\text{H}_{11}$, and Bn. As an application, allylic picolates with the (*E*)- or (*Z*)-olefin afforded quaternary carbon centers that are the enantiomers each other.

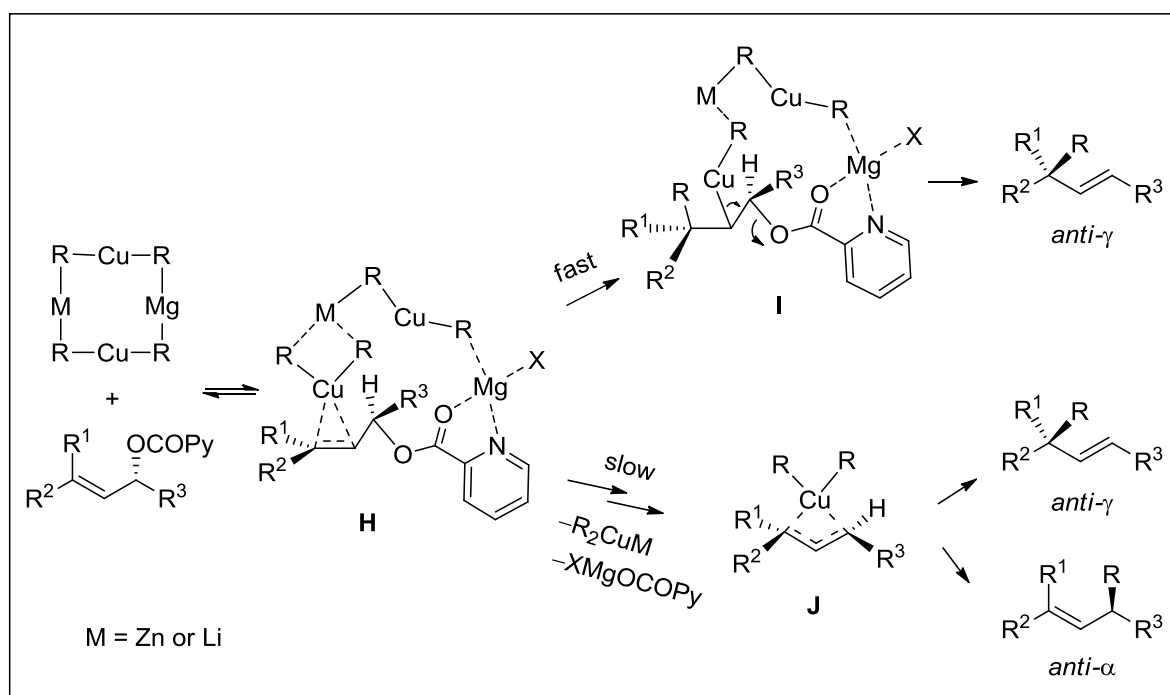


Scheme 1.20 Present Work

Zn salts were studied and a mechanism was proposed to explain the effect of Zn salt. With respect to the mechanism for allylic substitution of allylic acetate illustrated by E. Nakamura et al (**Scheme 1.21**),^{14c} Zn was proposed to form a trimetallic intermediate with Cu instead of Li in our reagent system as described in **Scheme 1.22**. Experimentally, it was proved that Zn cannot replace Cu as well as Mg. The possible position for Zn is the position of Li in the mechanism demonstrated by E. Nakamura.^{14c} Additionally, LiI was also found to promote the regioselectivity as ZnI_2 did, indicating similar role played by Zn and Li, on the other hand, suggesting Zn works as Li in the mechanism reported by E. Nakamura.^{14c}



Scheme 1.21 Mechanism Illustrated by E. Nakamura, et al



Scheme 1.22 Proposed Mechanism

Chapter 6 Summary

The results presented in **Chapters 2–5** are summarized briefly in this chapter.

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Chapter 2 Installation of a Chiral Side Chain to a 2-Alkylidene-1-cycloalkan-1-ol Unit by Using Allylic Substitution

2.1 Introduction

Recently, allylic substitution of secondary allylic esters with organocopper reagents prepared in situ or generated under catalytic conditions has been actively investigated with highly potent leaving groups¹ such as $o(\text{PPh}_2)\text{C}_6\text{H}_4\text{CO}_2$, $o(\text{P}(\text{O})\text{Ph}_2)\text{C}_6\text{H}_4\text{CO}_2$, $\text{C}_6\text{F}_5\text{CO}_2$, $(\text{RO})_2\text{PO}_2$ and 2-PyCO₂ groups. By using these leaving groups alkyl copper reagents as well as less reactive aryl, alkenyl, heteroaryl and alkynyl reagents can take part in the substitution to furnish γ products with high regio- and stereoselectivity.^{2,3} The 2-PyCO₂ leaving group introduced by us is activated by Mg^{2+} and/or Zn^{2+} to allow participation of the above classes of reagents.³ Furthermore, ArMgBr -based copper reagents could be used for constitution of a quaternary carbon in an efficient manner.⁴

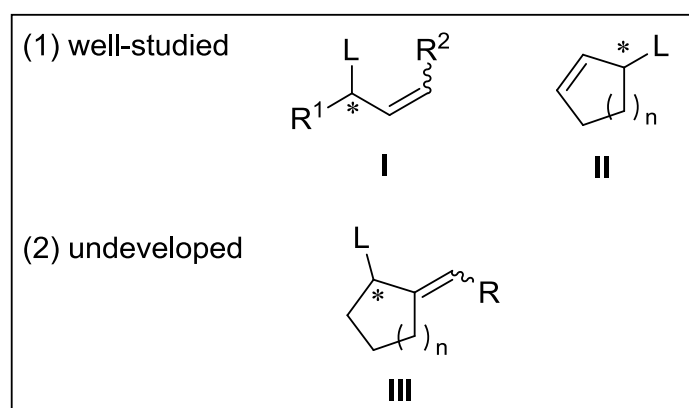
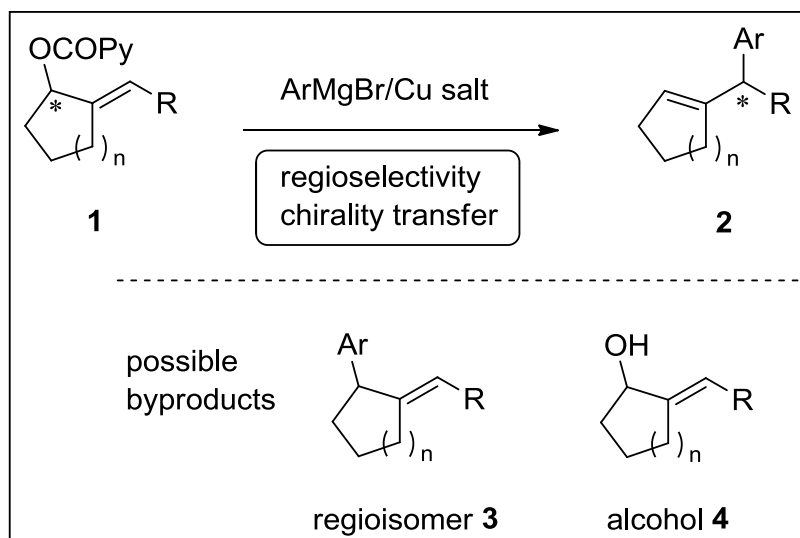


Figure 2.1 Substrate Types for the Allylic Substitution (L = Leaving Group)

During the investigation, we became aware that acyclic and cyclic allylic esters of types **I** and **II** shown in **Figure 2.1** have been used as test substrates and that exocyclic allylic esters **III** that are in part cyclic and acyclic have been studied in a few cases. In brief, methylation of a 2-butyldiene-1-cyclopentyl alcohol derivatives **III** (Z-olefin, $n = 1$, $\text{R} = \text{Pr}$, $\text{L} = \text{OCO-}t\text{Bu}$, OCONHPh) afforded the desired γ product regioselectively.⁵ However, a scope of reagents including those of the aromatic class is unclear.⁶ In contrast, 2-benzylidene-1-cycloalkyl acetates **III** (E-olefin, $n = 1, 2$, $\text{R} = \text{Ph}$, $\text{L} = \text{OAc}$) upon CuCl -catalyzed substitution with alkyl- and aryl-MgBr gave γ products with 65~100% regioselectivity depending on the ring size of the substrates and the reagents.⁷ With these publications in mind, we selected picolinates **1** of $n = 1, 2$ as **III**, and studied allylic substitution with aryl copper reagents as depicted in **Scheme 2.1** and with an alkyl copper reagent. The structure of the γ products **2** evokes several biologically active compounds such as the classical steroids, vitamin D family, OSW-1

series, ophiobolins, biyouyanagin A, zingiberene and heliannuols (**Figure 2.2**), which are characterized by chiral side chains. Herein, we present results of this investigation, focusing on regioselectivity (2 over 3) and chirality transfer (C.T.).^{8,9}



Scheme 2.1 Aim of the Present Allylic Substitution

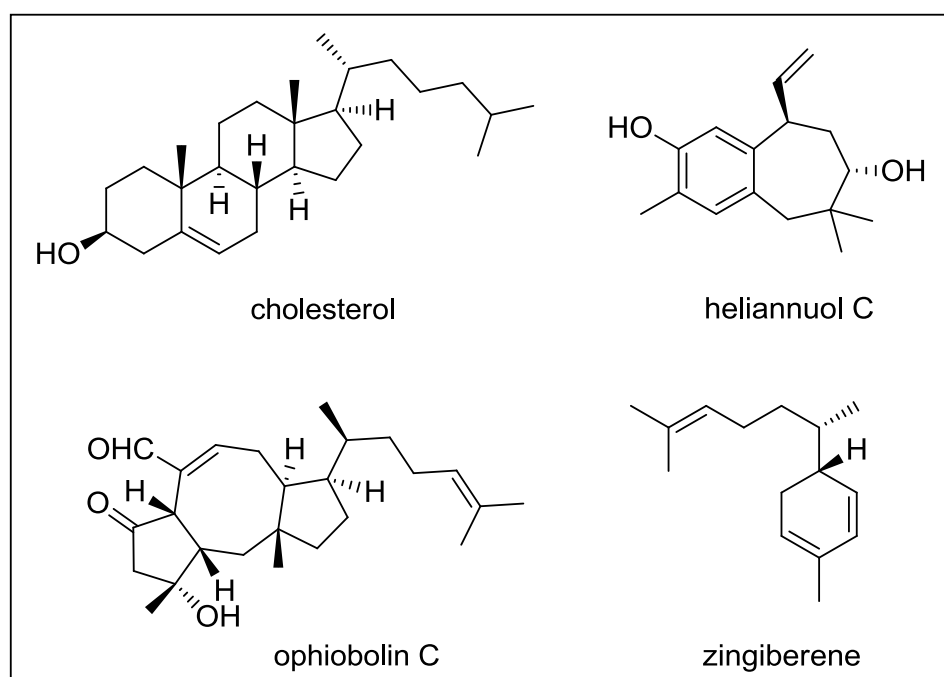


Figure 2.2 Natural Products Possessing a Chiral Carbon on a Side Chain

2.2 Results and Discussion

Allylic substrates shown in **Figure 2.3** were synthesized by methods delineated in **Scheme 2.2**. In brief, aldol reaction of cyclopentane and 3-phenylpropionaldehyde followed by elimination of the hydroxyl group with MsCl and Et₃N produced *E*-olefin **5a** in 40% unoptimized yield. Examination of the ¹H NMR spectrum of crude **5a** indicated absence of the *Z*-isomer (olefinic H of **5a**, 6.50–6.63 (m) ppm; H of *Z*-isomer, probably 5.6–6.0 ppm¹⁰). CBS reduction¹¹ using (*S*)-MeCBS was applied to the enone and the resulting alcohols (*R*)-**4a** was converted to picolinates (*R*)-**1a** in 72% yield by DCC-mediated condensation with PyCO₂H. Enantiomeric purity of (*R*)-**1a** prepared twice were 94 and 97% ee by chiral HPLC analysis. Likewise, picolinate (*R*)-**1b** with 86% ee was synthesized from cyclohexanone through enone **5b**.¹² For preliminary investigation, racemic picolinates *rac*-**1a** and **-1b** were synthesized in 73–80% yields from enones **5a** and **5b** by reduction with NaBH₄ followed by DCC-assisted esterification with PyCO₂H. Similarly, enone **5c** was prepared via aldol condensation of cyclopentanone with isobutyraldehyde and converted to racemic picolinate *rac*-**1c**, which was used to examine steric influence of the bulky side chain on the allylic substitution.

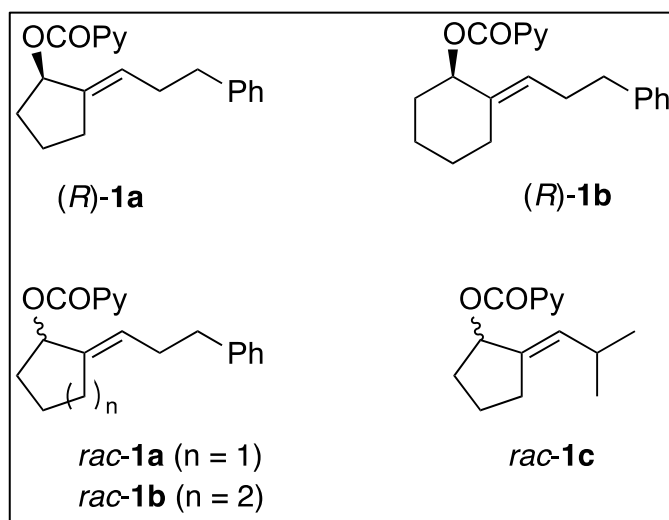
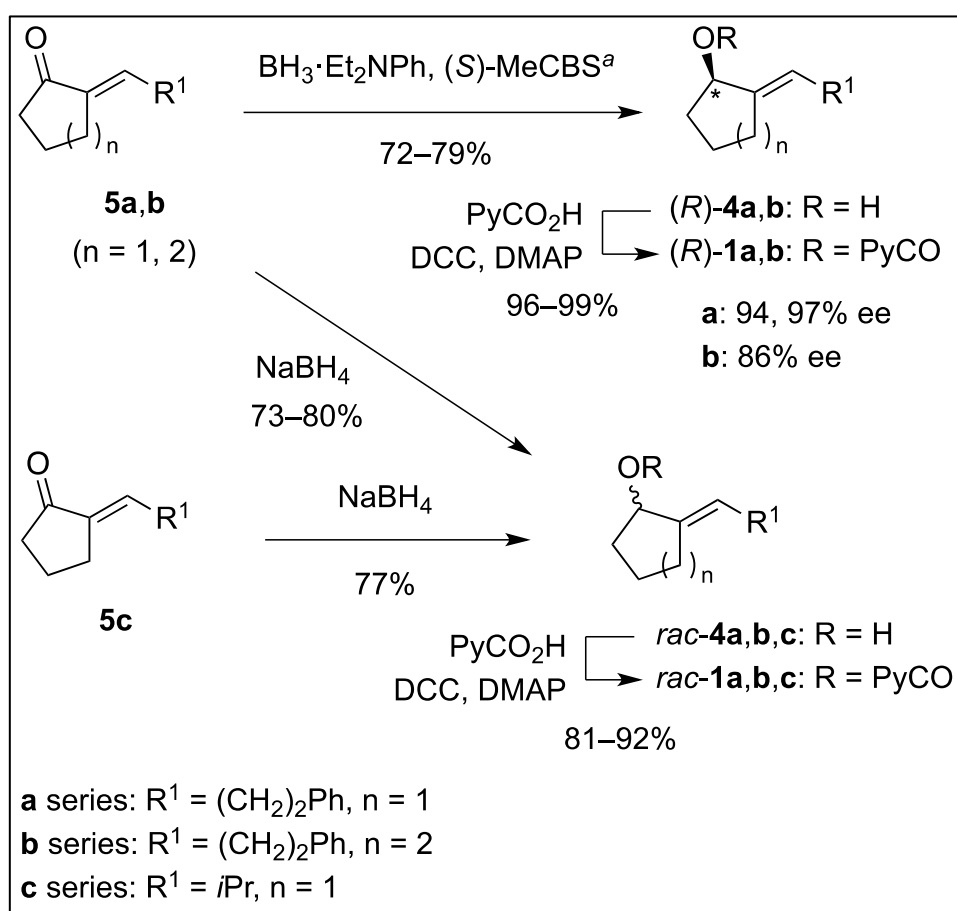


Figure 2.3 Substrates for the Present Study

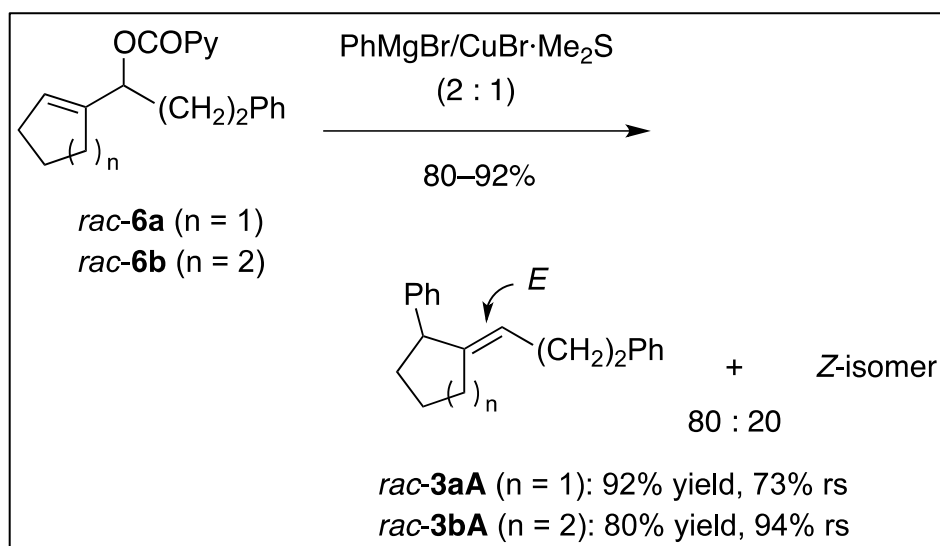
Allylic substitution of *rac*-**1a** was investigated first with Ph reagents derived from PhMgBr and CuBr·Me₂S in 1:1 and 2:1 compositions in THF at an initial temperature of –40 or –30 °C, which was gradually increased to –10 or 0 °C over 2 h to afford *rac*-**2aA** as the major product. For those reactions started at 0 °C, the reaction was carried out at 0 °C over 1 h. To calculate regioselectivity of *rac*-**2aA** over *rac*-**3aA** by ¹H NMR spectroscopy, allylation of the regioisomeric substrate *rac*-**6a**¹³ with 2:1 PhMgBr/CuBr·Me₂S was carried out to produce *rac*-**3aA** as a mixture with the *Z*-isomer in a 4:1 ratio (**Scheme 2.3**).¹⁴ The 1:1 PhMgBr/CuBr·Me₂S reagent (1.5 equiv) proceeded regioselectively, 93%

regioselectivity at 0 °C (**Table 2.1**, Entry 1) and 92% at –30 °C but 14% of *rac*-**1a** remained (Entry 3). On the other hand, 3 equiv of the reagent consumed the substrate completely to afford *rac*-**2aA** with 96% regioselectivity (Entry 4). Substitution of *rac*-**1a** with 1 equiv of 2:1 PhMgBr/CuBr·Me₂S afforded *rac*-**2aA** with similar regioselectivity (Entries 2, 5 and 8). Completion of the reaction within 2 h even with 1 equiv of the reagent suggests participation of 1:1 PhMgBr/CuBr·Me₂S produced in situ by the reaction with the 2:1 reagent. In fact, the 1:1 reagent produces *rac*-**2aA** regioselectively (Entries 1, 3 and 4). The 2:1 reagent in the presence of ZnI₂ resulted in somewhat low regioselectivity (Entries 9). The reagent derived from PhMgBr and Cu(acac)₂ in a 2:1 ratio furnished *rac*-**2aA** with 96% regioselectivity (Entry 10). Moreover, phenylcopper reagents derived from PhMgCl and CuBr·Me₂S/CuCl in a 2:1 ratio produced *rac*-**2aA** with slightly higher regioselectivity (Entries 6 and 7).



Scheme 2.2 Synthesis of the Substrates ((*S*)-MeCBS, (*S*)-3,3-Diphenyl-1-methylpyrrolidino[1,2-*c*]-1,3,2-oxazaborole)

The reagent types of Entries 4 and 8–10 were applied to *p*Tol-MgBr. The Cu(acac)₂-based reagent showed high regioselectivity (98%),¹⁵ producing *rac*-**2aB** (**B** refers to the *p*Tol group) (Entry 14), whereas low regioselectivity was observed with the CuBr·Me₂S-based reagents (Entries 11–13).



Scheme 2.3 Synthesis of Regioisomers (rs: Regioselectivity)

Table 2.1 Optimization of Conditions for Allylic Substitution with Arylcopper Reagents

Entry	Substrate	ArMgBr (equiv)	Cu salt (equiv)	Ar/Cu	ZnI ₂ (equiv)	T ^[a] (°C)	2 : 3 : 4 : 1 ^[b]	Yield ^[c,d]
	<i>rac-1a</i>	Ar = Ph <i>pTol</i>	<i>rac-2aA</i> <i>rac-2aB</i>	<i>rac-3aA</i> <i>rac-3aB</i>	<i>rac-4a</i>			
1	<i>rac-1a</i>	PhMgBr (1.5)	CuBr·Me ₂ S (1.5)	1:1	–	0	93:7:0:0	nd
2	<i>rac-1a</i>	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	0	95:5:0:0	nd
3	<i>rac-1a</i>	PhMgBr (1.5)	CuBr·Me ₂ S (1.5)	1:1	–	–30	79:7:0:14	nd
4	<i>rac-1a</i>	PhMgBr (3.0)	CuBr·Me ₂ S (3.0)	1:1	–	–30	96:4:0:0	nd
5	<i>rac-1a</i>	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	–30	92:2:0:6	nd
6	<i>rac-1a</i>	PhMgCl (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	–30	>99:1:0:0	nd
7	<i>rac-1a</i>	PhMgCl (2.2)	CuCl (1.0)	2:1	–	–30	97:3:0:0	nd
8	<i>rac-1a</i>	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	–40	95:5:0:0	85
9	<i>rac-1a</i>	PhMgBr (3.0)	CuBr·Me ₂ S (1.5)	2:1	1.5	–40	90:10:0:0	>99
10	<i>rac-1a</i>	PhMgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	96:4:0:0	>99
11	<i>rac-1a</i>	<i>pTol</i> -MgBr (3.0)	CuBr·Me ₂ S (3.0)	1:1	–	–40	80:20:0:0	nd
12	<i>rac-1a</i>	<i>pTol</i> -MgBr (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	–40	60:40:<5:0	80
13	<i>rac-1a</i>	<i>pTol</i> -MgBr (3.0)	CuBr·Me ₂ S (1.5)	2:1	1.5	–40	86:14:<5:0	>95

14	<i>rac-1a</i>	<i>pTol</i> -MgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	98:2:0:0	88
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$\text{Ar} = \text{Ph} \quad \text{Ar} = p\text{Tol}$
rac-2bA *rac-2bB* *rac-3bA* *rac-3bB* *rac-4b*

15	<i>rac-1b</i>	PhMgBr (3.0)	CuBr·Me ₂ S (3.0)	1:1	–	–40	94:5:1:0	93
16	<i>rac-1b</i>	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	2:1	–	–40	94:0:0:6	79
17	<i>rac-1b</i>	PhMgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	99:1:0:0	nd
18	<i>rac-1b</i>	<i>pTol</i> -MgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	96:4:0:0	82

$\text{Ar} = \text{Ph} \quad \text{Ar} = p\text{Tol}$
rac-2cA *rac-2cB* *rac-3cA* *rac-3cB* *rac-4c*

19	<i>rac-1c</i>	PhMgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	99:1:0:0	96
20	<i>rac-1c</i>	<i>pTol</i> -MgBr (3.0)	Cu(acac) ₂ (1.5)	2:1	–	–40	95:5:0:0	87

[a] Reaction temperature was kept at 0 °C over 1 h or raised gradually from –40 or –30 to –10 or 0 °C over 2 h. [b] Determined by ¹H NMR spectroscopy. [c] Isolated yield of (2+3). [d] nd: Not determined.

With the above results in hand, the six-membered ring substrate *rac-1b* was sacrificed to substitution with Ph and *pTol* copper reagents. The regioisomer *rac-3bA* with the Ph substituent was independently synthesized by reaction shown in **Scheme 2.3** to extract the diagnostic absorbance in the ¹H NMR spectrum for estimation of the regioselectivity. As summarized in Entries 17 and 18 Cu(acac)₂-derived Ph and *pTol* reagents afforded *rac-2bA* and *-2bB*, respectively, with high regioselectivity (99%, 96%).¹⁵ A similar regioselectivity was recorded in the phenylation using 1:1 and 2:1 PhMgBr/CuBr·Me₂S reagents (Entries 15 and 16).

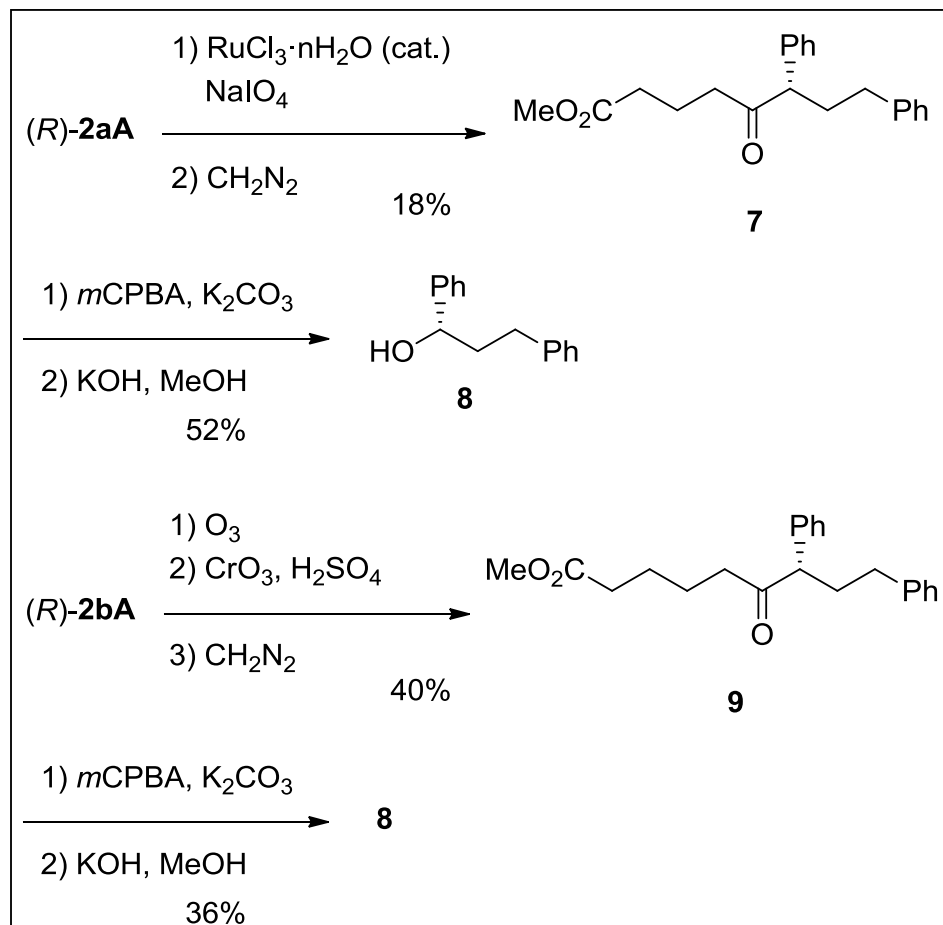
Next, steric influence on the regioselectivity was examined with the *iPr*-substituted substrate *rac-1c*, to which the Cu(acac)₂-derived Ph and *pTol* reagents were subjected. The reactions proceeded without delay and afforded *rac-2cA* and *-2cB* regioselectively¹⁵ (Entries 19 and 20).

Entry	Substrate ^[a]	ArMgBr [equiv]	Copper source [equiv]	Product	2:3	C.T. ^[b]	Yield [%] ^[c]
	(<i>R</i>)- 1a			(<i>R</i>)- 2aA~F	3aA~F		
1	(<i>R</i>)- 1a	PhMgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aA , ^[d] Ar = Ph	>99 : 1	>99%	80
2	(<i>R</i>)- 1a	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	(<i>R</i>)- 2aA , Ar = Ph	98:2	98%	89
3	(<i>R</i>)- 1a	<i>p</i> Tol-MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aB , Ar = <i>p</i> Tol	>99 : 1	>99%	80
4	(<i>R</i>)- 1a	<i>o</i> Tol-MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aC , Ar = <i>o</i> Tol	98 : 2	96%	87
5	(<i>R</i>)- 1a	<i>p</i> MeOC ₆ H ₄ MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aD , Ar = <i>p</i> MeOC ₆ H ₄	>99 : 1	97%	91
6	(<i>R</i>)- 1a	<i>o</i> MeOC ₆ H ₄ MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aE , Ar = <i>o</i> MeOC ₆ H ₄	95 : 5	91%	82
7	(<i>R</i>)- 1a	<i>p</i> FC ₆ H ₄ MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2aF , Ar = <i>p</i> FC ₆ H ₄	>99 : 1	96%	86
	(<i>R</i>)- 1b			(<i>R</i>)- 2bA,-2bD,-2bE	3bA,D,E		
8	(<i>R</i>)- 1b	PhMgBr (2.2)	CuBr·Me ₂ S (1.0)	(<i>R</i>)- 2bA , ^[d] Ar = Ph	>99 : 1	>99%	89
9	(<i>R</i>)- 1b	<i>p</i> MeOC ₆ H ₄ MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2bD , Ar = <i>p</i> MeOC ₆ H ₄	>99 : 1	93%	87
10	(<i>R</i>)- 1b	<i>o</i> MeOC ₆ H ₄ MgBr (3.0)	Cu(acac) ₂ (1.5)	(<i>R</i>)- 2bE , Ar = <i>o</i> MeOC ₆ H ₄	97 : 3	96%	71

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Throughout the above examination the 2:1 ArMgBr/Cu(acac)₂ reagents (Ar = Ph, *p*Tol) provided high regioselectivity in all the entries. As for the 2:1 ArMgBr/CuBr·Me₂S, the Ph reagent was highly regioselective, but the *p*Tol reagent was not. With these results in hand allylic substitution of (*R*)-**1a** (94 and 97% ee) and (*R*)-**1b** (86% ee) was studied to evaluate chirality transfer (C.T.)⁸ and to determine the stereochemical course. The 2:1 PhMgBr/Cu(acac)₂ reagent was first subjected to reaction with the five-membered substrate (*R*)-**1a** to produce (*R*)-**2aA** (Ar = Ph) with >99% C.T. and >99% regioselectivity in 80% isolated yield (**Table 2.2**, Entry 1). The 2:1 PhMgBr/CuBr·Me₂S reagent produced (*R*)-**2aA** with 98% C.T. as well (Entry 2). Similarly, *p*Tol, *p*MeOC₆H₄ and *p*FC₆H₄ reagents participated in the substitution to afford (*R*)-**2aB**, **-2aD** and **-2aF** efficiently (Entries 3, 5 and 7). Steric congestion by the Me and MeO groups in *o*Me- and *o*MeOC₆H₄ reagents slightly decreased C.T. and regioselectivity, but the selectivity is probably still in an acceptable level (Entries 4 and 6). Comparable results were also observed with the six-membered substrate (*R*)-**1b** (Entries 8–10).

Scheme 2.4 shows transformation¹⁶ of (*R*)-**2aA** and **-2bA** to the known alcohol **8**, and the specific rotations of **8** were compared with the literature value¹⁷ to establish not only the *R* configuration of **2aA** and **2bA** but also anti S_N2' pathway of the allylic substitution. Configuration of the other products was determined by analogy.

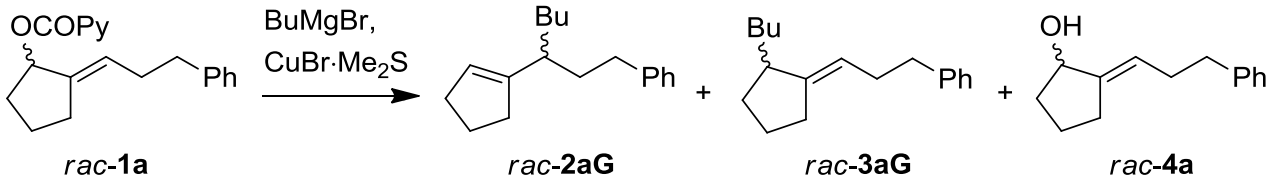
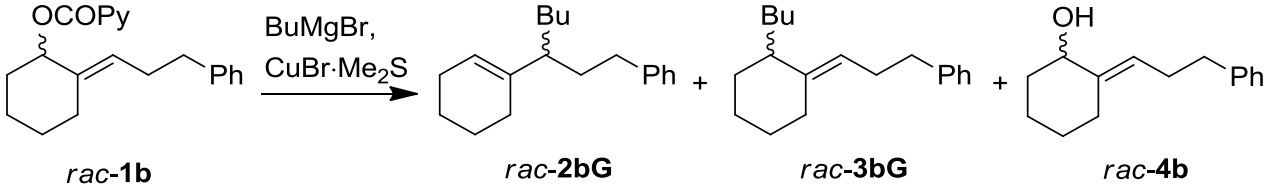


Scheme 2.4 Transformation of (*R*)-2aA and -2bA to the Known Alcohol (*S*)-8

We turned our attention to a Bu copper reagent as a typical example of alkylcopper reagents. Surprisingly, 2:1 BuMgBr/CuBr·Me₂S was less regioselective (74% rs) (**Scheme 2.5**).¹⁸ As observed in the previous experiment, regioselectivity of (*R*)-2aG was highly improved to 99% by addition of ZnI₂. In contrast, 2:1 BuMgBr/Cu(acac)₂ was regioselective to produce (*R*)-2aG, which was, however, contaminated with unidentified product(s).¹⁹ Nonetheless, the conditions optimization for allylic substitution of *rac*-1a and -1b were described in **Table 2.3**. In case of *rac*-1a, BuMgBr and CuBr·Me₂S in a 1:1 ratio showed higher regioselectivity than those in a 2:1 ratio at 0 °C (Entry 1 vs 2). On the other hand, at −30 or −40 °C, regioselectivity of BuMgBr and CuBr·Me₂S in a 2:1 ratio could be enhanced a lot by addition of ZnI₂ (Entries 4 vs 3, 6 vs 5), which is consistent with reported results.⁴ However, in case of *rac*-1b, good conditions for allylic substitution with phenylcopper reagents did not work well, only 80–87% regioselectivity was observed (Entries 8 and 9). To our surprise, ZnI₂-assisted protocol, which showed excellent

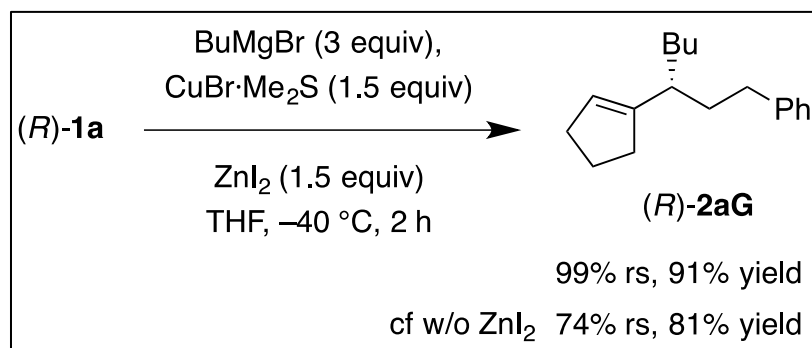
regioselectivity for allylic substitution of *rac-1a* with butylcopper reagent, only generated S_N2' product *rac-2bG* with 86% regioselectivity (Entry 10). Other conditions including BuMgBr and CuBr·Me₂S in 1:1, 1:2, as well as 1:3 ratios in the presence or absence of different quantities of ZnI₂ only synthesized S_N2' product *rac-2bG* with poor to moderate regioselectivity (Entries 7, and 11–14). The ring number of substrates **1a** and **1b** is apparently to take responsibility for different regioselectivity since it probably influenced the interaction geometry of organocopper reagents with double bonds, therefore changing the reactivities of the organocopper reagents.^{20c}

Table 2.3 Allylic Substitution of *rac-1a* and -1b with Alkylcopper Reagents

Entry	Substrate	BuMgBr (equiv)	CuBr·Me ₂ S (equiv)	Ar/Cu	ZnI ₂ (equiv)	T ^[a] (°C)	2 : 3 : 4 : 1 ^[b]	Yield ^[c]
 <i>rac-1a</i> → <i>rac-2aG</i> + <i>rac-3aG</i> + <i>rac-4a</i>								
1	<i>rac-1a</i>	1.5	1.5	1:1	–	0	89:4:0:7	78
2	<i>rac-1a</i>	2.2	1.0	2:1	–	0	86:10:0:4	nd ^[d]
3	<i>rac-1a</i>	3.0	1.5	2:1	–	–30	69:31:0:0	nd
4	<i>rac-1a</i>	3.0	1.5	2:1	1.5	–30	>99:0:0:0	76
5	<i>rac-1a</i>	3.0	1.5	2:1	–	–40	74:26:0:0	81
6	<i>rac-1a</i>	3.0	1.5	2:1	1.5	–40	>99:0:0:0	72
 <i>rac-1b</i> → <i>rac-2bG</i> + <i>rac-3bG</i> + <i>rac-4b</i>								
7	<i>rac-1b</i>	1.5	1.5	1:1	–	–40	55:20:0:25	89
8	<i>rac-1b</i>	3.0	3.0	1:1	–	–40	87:13:<5:<5	60
9	<i>rac-1b</i>	2.2	1.0	2:1	–	–40	76:19:0:5	72

10	<i>rac</i> - 1b	3.0	1.5	2:1	1.5	−40	86:14:<1:<5	nd
11	<i>rac</i> - 1b	3.0	1.5	2:1	0.5	−40	77:23:<5:0	nd
12	<i>rac</i> - 1b	6.0	3.0	2:1	1.5	−40	76:24:<5:0	nd
13	<i>rac</i> - 1b	4.5	1.5	3:1	–	−40	84:16:0:0	nd
14	<i>rac</i> - 1b	4.7	1.5	3:1	1.5	−40	88:12:<5:0	70

[a] Reaction temperature was kept at 0 °C over 1 h or raised gradually from −40 or −30 to −10 or 0 °C over 2 h. [b] Determined by ¹H NMR spectroscopy. [c] Isolated yield (%) of (**2+3**). [d] nd: Not determined.

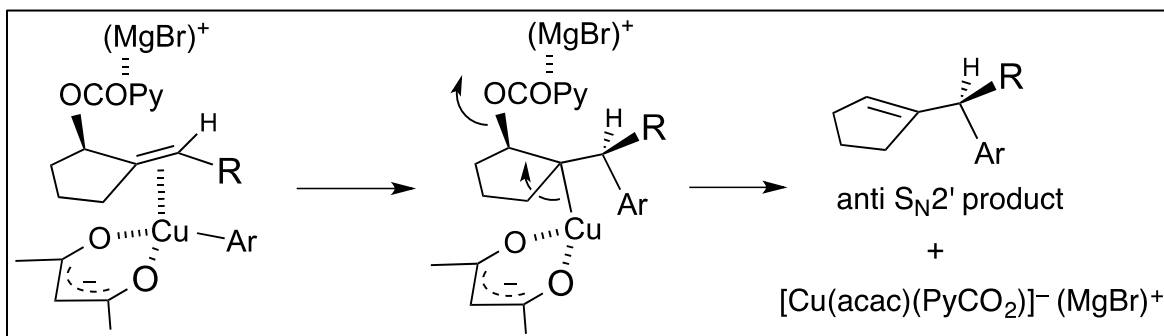


Scheme 2.5 Reaction with Bu Copper Reagent

2.3 Mechanism

As illustrated in **Scheme 1.9 (Chapter 1)**, in case of $[\text{ArCu}(\text{acac})]^-$, the T-shape complex is already tetra-coordinated. The Ar^- attacks the γ position and a tri-coordinated organocopper “Cu(III)” intermediate is formed, which consists of 18 electrons, and thus stable (according to the classic 18 electron rule), and probably could be an experimentally observable stabilized tri-coordinated organocopper(III) species,²¹ which is seldom characterized.^{20a}

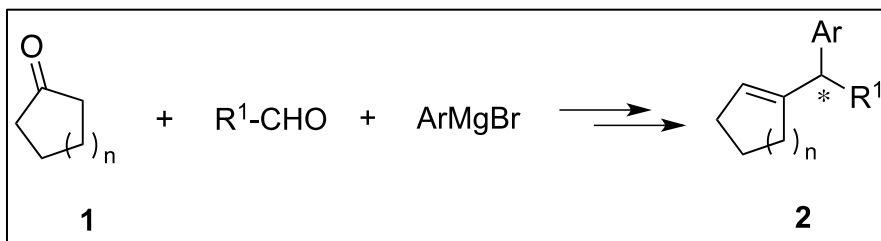
Nevertheless, a possible pathway is illustrated in **Scheme 2.6** on the basis of the recent mechanism for allylic substitution.^{2b,c,20} Reaction of ArMgBr and $\text{Cu}(\text{acac})_2$ in the 2:1 ratio produces $[\text{ArCu}(\text{acac})]^-$ species and $(\text{MgBr})^+$. This Ar-Cu species coordinates to the double bond, while the later cation activates the PyCO_2 leaving group by chelation, which facilitates the subsequent elimination of the PyCO_2 group to produce anti $\text{S}_{\text{N}}2'$ product with high γ -selectivity. The key stabilized intermediate consisting of 18 electrons due to coordination of acac takes responsibility for excellent γ -selectivity.



Scheme 2.6 Plausible Mechanism

2.4 Conclusion

We have developed a method for construction of cycloalkenyl-substituted carbon unit by using allylic substitution with the 2:1 ArMgBr/Cu(acac)₂ reagents, which proceeded with excellent regioselectivity and high C.T.. Furthermore, sterically demanding reagents as well as electron-donating and -withdrawing reagents could be used in the reaction successfully. The present results in total offers a transformation depicted in Scheme 2.7. Total synthesis of biologically active compounds employing this transformation will be reported in near future.

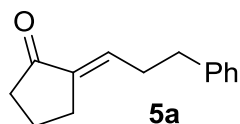


Scheme 2.7 Overall Transformation

2.5 Experimental Section

General Methods: The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were measured in CDCl_3 using SiMe_4 ($\delta = 0$ ppm) and the centerline of triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). Chemical shifts of carbons accompany minus (for C and CH_2) and plus (for CH and CH_3) signs of APT experiments. The following solvents were distilled beforehand: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions were finished, the organic extracts were concentrated by using a evaporator and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60 N). $\text{Cu}(\text{acac})_2$ was purchased from TCI, Jpn, and used without purification, whereas $\text{CuBr}\cdot\text{Me}_2\text{S}$ was prepared as described previously.^{3e}

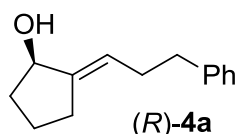
Synthesis of Picolimates (*R*)-1a and *rac*-1a



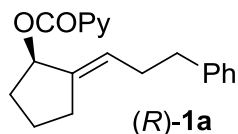
(*E*)-2-(3-Phenylpropylidene)cyclopentanone (5a): To an ice-cold solution of diisopropylamine (0.80 mL, 5.69 mmol) in THF (8 mL) was added $n\text{BuLi}$ (3.0 mL, 1.65 M in hexane, 4.95 mmol) dropwise. The solution was stirred for 15 min at 0 °C and cooled to -70 °C. Cyclopentanone (0.30 mL, 3.47 mmol) was added to the solution. After 30 min of stirring at -70 °C to -50 °C, 3-phenylpropionaldehyde (0.30 mL, 2.28 mmol) was added to the solution dropwise at -70 °C. After 30 min of stirring at -70 °C, the solution was poured into a mixture of EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over MgSO_4 , and concentrated to give a residue, which was passed through a short column of silica gel (hexane/ EtOAc) to afford the aldol, which was used for the next reaction without further purification.

To an ice-cold solution of the above alcohol, Et_3N (0.45 mL, 3.26 mmol) and DMAP (29.0 mg, 0.237 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.17 mL, 2.18 mmol) dropwise. The solution

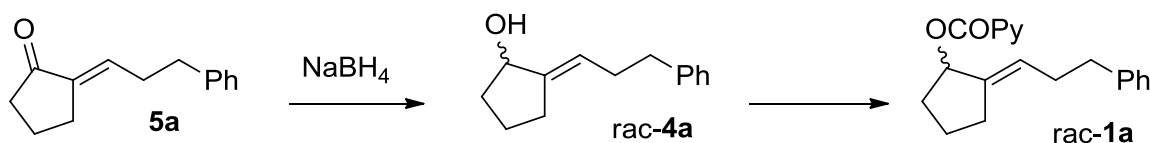
was allowed to warm to rt over 2 h, and diluted with saturated NaHCO₃ with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ twice. The extracts were washed with brine, dried over MgSO₄, and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **5a** (182 mg, 40% over two steps). IR (neat): ν = 1723, 1651, 1454, 747, 699 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.87 (quint., J = 8 Hz, 2 H), 2.30 (t, J = 8 Hz, 2 H), 2.40–2.53 (m, 4 H), 2.77 (t, J = 8 Hz, 2 H), 6.50–6.63 (m, 1 H), 7.16–7.38 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 19.8 (–), 26.8 (–), 31.7 (–), 34.6 (–), 38.7 (–), 126.2 (+), 128.47 (+), 128.50 (+), 134.7 (+), 138.0 (–), 141.2 (–), 207.2 (–) ppm. HRMS (EI): calcd. for C₁₄H₁₆O [M]⁺ 200.1201; found 200.1202.



(R,E)-2-(3-Phenylpropylidene)cyclopentanol ((R)-4a): To a solution of (S)-methyl oxazaborolidine (0.11 mL, 1.0 M in toluene, 0.11 mmol) and *N,N*-diethylaniline borane (0.11 mL, 0.619 mmol) at –20 °C in THF (3 mL) was added a solution of enone **5a** (110.4 mg, 0.551 mmol) in THF (3 mL) over 60 min. After being stirred at –20 °C for 1 h, the reaction was quenched by cold MeOH (3 mL, –20 °C) carefully. After additional stirring for 1 h at rt, the solution was concentrated to afford a residue, which was passed through a pad of silica gel (hexane/EtOAc) to furnish alcohol **(R)-4a** (80.1 mg, 72%). IR (neat): $\tilde{\nu}$ = 3348, 1496, 1453, 1080, 748, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.45 (br s, 1 H), 1.53–1.66 (m, 2 H), 1.74–1.90 (m, 2 H), 2.04–2.16 (m, 1 H), 2.22–2.38 (m, 3 H), 2.69 (t, J = 7.5 Hz, 2 H), 4.34 (br s, 1 H), 5.53–5.62 (m, 1 H), 7.15–7.22 (m, 3 H), 7.25–7.32 (m, H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 22.0 (–), 27.0 (–), 31.3 (–), 35.6 (–), 35.7 (–), 75.7 (+), 123.3 (+), 125.9 (+), 128.4 (+), 128.5 (+), 142.1 (–), 146.8 (–) ppm. HRMS (EI): calcd. for C₁₄H₁₈O [M]⁺ 202.1358; found 202.1356.



(R,E)-2-(3-Phenylpropylidene)cyclopentyl Picolinate ((R)-1a): To an ice-cold solution of (*R*)-**4a** (80.1 mg, 0.396 mmol) in CH₂Cl₂ (5 mL) were added DCC (109 mg, 0.528 mmol), DMAP (49.0 mg, 0.401 mmol), and picolinic acid (59.0 mg, 0.479 mmol). The mixture was stirred at rt for 2 h and diluted with Et₂O. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (*R*)-**1a** (120 mg, 99%). ¹H NMR (400 MHz, CDCl₃): δ = 1.66–1.77 (m, 1 H), 1.84–2.07 (m, 3 H), 2.10–2.22 (m, 1 H), 2.29–2.42 (m, 3 H), 2.61–2.76 (m, 2 H), 5.74–5.82 (m, 2 H), 7.13–7.20 (m, 3 H), 7.20–7.27 (m, 2 H), 7.46 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.83 (dt, *J* = 2, 8 Hz, 1 H), 8.08 (dt, *J* = 8, 1 Hz, 1 H), 8.78 (dm, *J* = 5 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 22.8 (–), 27.3 (–), 31.7 (–), 33.1 (–), 35.4 (–), 79.1 (+), 125.1 (+), 125.8 (+), 126.7 (+), 127.1 (+), 128.3 (+), 128.6 (+), 136.9 (+), 141.3 (–), 142.0 (–), 148.7 (–), 150.1 (+), 165.1 (–) ppm. HRMS (EI): calcd. for C₂₀H₂₁NO₂ [M]⁺ 307.1572; found 307.1578. The enantiomeric purity (97% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 98/2, 0.5 mL/min, 25 °C, *t*_R/min = 40.8 (*R*-isomer), 46.0 (*S*-isomer). The reaction was repeated to obtain (*R*)-**1a** of 94% ee.

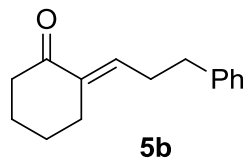


(E)-2-(3-Phenylpropylidene)cyclopentyl Picolinate (rac-1a): To an ice-cold solution of **5a** (70.4 mg, 0.352 mmol) and CeCl₃·7H₂O (135 mg, 0.362 mmol) in MeOH (4 mL) was added NaBH₄ (13.0 mg, 0.344 mmol). After being stirred at rt for 1 h, the solution was diluted with 1 N HCl and Et₂O with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with Et₂O three times. The combined extracts were dried over MgSO₄ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish alcohol *rac*-**4a** (55.4 mg, 80%). The ¹H NMR spectrum was identical with that of (*R*)-**4a**.

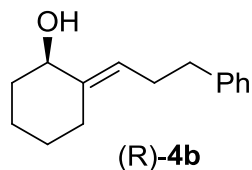
According to the procedure for synthesis of (*R*)-**1a**, *rac*-**4a** (55.0 mg, 0.272 mmol) was subjected to esterification with picolinic acid (42.0 mg, 0.341 mmol), DCC (74.0 mg, 0.359

mmol) and DMAP (34.0 mg, 0.278 mmol) in CH₂Cl₂ (2 mL) at rt for 2 h to furnish *rac*-**1a** (73.1 mg, 87%). The ¹H NMR and ¹³C NMR spectra were identical with those of (*R*)-**1a**.

Synthesis of Picolinates (*R*)-**1b** and *rac*-**1b**

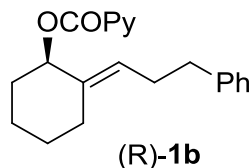


(*E*)-2-(3-Phenylpropylidene)cyclohexanone (5b): According to the procedure for synthesis of **5a**, cyclohexanone (2.30 mL, 22.3 mmol) was converted to the aldol as a mixture of diastereomers by reaction with 3-phenylpropionaldehyde (2.00 mL, 15.2 mmol) using diisopropylamine (6.30 mL, 44.8 mmol) and *n*BuLi (23.0 mL, 1.62 M in hexane, 37.3 mmol) THF (50 mL). The aldol was subjected to reaction with MsCl (1.90 mL, 24.5 mmol), Et₃N (5.10 mL, 36.6 mmol) and DMAP (1.50 g, 12.3 mmol) in CH₂Cl₂ (40 mL) at 0 °C–rt for 2 h to furnish **5b** (1.73 g, 53% over two steps). ¹H NMR (300 MHz, CDCl₃): δ = 1.59–1.72 (m, 2 H), 1.75–1.87 (m, 2 H), 2.30–2.48 (m, 6 H), 2.70–2.79 (m, 2 H), 6.63 (tt, *J* = 8, 2 Hz, 1 H), 7.12–7.32 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.4 (–), 23.6 (–), 26.7 (–), 29.8 (–), 34.7 (–), 40.3 (–), 126.2 (+), 128.5 (+), 137.0 (–), 138.0 (+), 141.3 (–), 201.3 (–) ppm. HRMS (EI): calcd. for C₁₅H₁₈O [*M*]⁺ 214.1358; found 214.1363. The ¹H and ¹³C NMR spectra were consistent with those reported.¹²

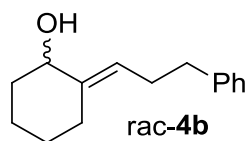


(*R,E*)-2-(3-Phenylpropylidene)cyclohexanol ((*R*)-4b): According to the procedure for synthesis of (*R*)-**4a**, a solution of enone **5b** (202 mg, 0.942 mmol) in THF (9 mL) was added over 50 min to a solution of (*S*)-methyl oxazaborolidine (0.20 mL, 1.0 M in toluene, 0.200 mmol) and *N,N*-diethylaniline borane (0.18 mL, 1.01 mmol) in THF (5 mL) at –20 °C. The solution was stirred at –20 °C for 30 min to afford alcohol (*R*)-**4b** (162 mg, 79%). ¹H NMR (300 MHz, CDCl₃): δ = 1.23–1.62 (m, 5 H), 1.68–1.96 (m, 3 H), 2.26–2.40 (m, 3 H), 2.66 (t, *J* = 8 Hz, 2 H), 4.00–4.08

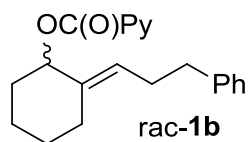
(m, 1 H), 5.39 (dt, $J = 1, 7$ Hz, 1 H), 7.12–7.20 (m, 3 H), 7.22–7.29 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 23.0$ (–), 26.1 (–), 27.2 (–), 28.9 (–), 36.2 (–), 36.3 (–), 73.8 (+), 120.1 (+), 125.8 (+), 128.2 (+), 128.5 (+), 141.7 (–), 142.0 (–) ppm. HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{20}\text{O}$ $[\text{M}]^+$ 216.1514; found 216.1518.



(R,E)-2-(3-Phenylpropylidene)cyclohexyl Picolinate ((R)-1b): According to the procedure for synthesis of **(R)-1a**, a solution of **(R)-4b** (162 mg, 0.749 mmol), picolinic acid (115.6 mg, 0.939 mmol), DCC (214 mg, 1.04 mmol) and DMAP (91.7 mg, 0.751 mmol) in CH_2Cl_2 (8 mL) was stirred at rt for 2 h to furnish **(R)-1b** (231 mg, 96%). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.28$ – 1.42 (m, 1 H), 1.44–1.64 (m, 2 H), 1.76–1.98 (m, 3 H), 2.09–2.19 (m, 1 H), 2.22–2.40 (m, 3 H), 2.65 (t, $J = 8$ Hz, 2 H), 5.49–5.56 (m, 2 H), 7.10–7.18 (m, 3 H), 7.18–7.26 (m, 2 H), 7.46 (ddd, $J = 8, 5, 1$ Hz, 1 H), 7.82 (dt, $J = 1, 8$ Hz, 1 H), 8.09 (d, $J = 8$ Hz, 1 H), 8.79 (dm, $J = 5$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 22.6$ (–), 26.0 (–), 26.7 (–), 28.9 (–), 33.0 (–), 35.9 (–), 77.3 (+), 123.6 (+), 125.0 (+), 125.7 (+), 126.6 (+), 128.2 (+), 128.6 (+), 136.67 (–), 136.86 (+), 141.8 (–), 148.7 (–), 150.0 (+), 164.1 (–) ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_2$ $[\text{M}]^+$ 321.1729; found 321.1729. The enantiomeric purity (86% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 98/2, 0.8 mL/min, 25 °C, t_{R} /min = 29.0 (*R*-isomer), 32.7 (*S*-isomer).

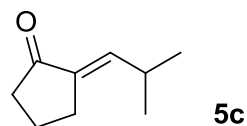


(E)-2-(3-Phenylpropylidene)cyclohexanol (rac-4b): According to the procedure for synthesis of **rac-4a**, reduction of **5b** (183 mg, 0.855 mmol) with NaBH_4 (32.4 mg, 0.856 mmol) was carried out in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (330 mg, 0.885 mmol) in MeOH (9 mL) at rt for 1 h to furnish racemic alcohol **rac-4b** (135 mg, 73%). The ^1H NMR and ^{13}C NMR spectra were identical with those of **(R)-4b**.



(E)-2-(3-Phenylpropylidene)cyclohexyl Picolinate (*rac*-1b): According to the procedure for synthesis of *rac*-1a, condensation of *rac*-4b (135 mg, 0.624 mmol) with picolinic acid (99.5 mg, 0.808 mmol) was carried out with DCC (175 mg, 0.848 mmol) and DMAP (73.5 mg, 0.602 mmol) in CH₂Cl₂ (7 mL) at rt for 2 h to furnish *rac*-1b (163 mg, 81%). The ¹H NMR and ¹³C NMR spectra were identical with those of (*R*)-1b.

Synthesis of Picolinate *rac*-1c

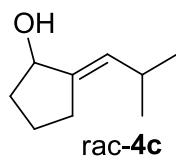


(E)-2-(2-Methylpropylidene)cyclopentanone (5c): According to the procedure for synthesis of 5a, cyclopentanone (1.48 mL, 16.7 mmol) was converted to the aldol as a mixture of diastereomers by reaction with isobutyraldehyde (1.02 mL, 11.1 mmol) using diisopropylamine (4.66 mL, 33.2 mmol) and *n*BuLi (17.2 mL, 1.60 M in hexane, 27.5 mmol) in THF (36 mL).

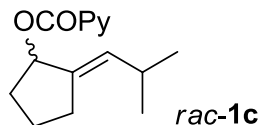
To an ice-cold solution of the above aldol and Et₃N (4.64 mL, 33.3 mmol) in CH₂Cl₂ (30 mL) was added MsCl (1.72 mL, 22.2 mmol) dropwise. The solution was stirred between 0 °C and rt for 2 h and poured into saturated NaHCO₃ with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ twice. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to afford the corresponding mesylate.

To an ice-cold solution of the above mesylate in THF (40 mL) was added DBU (3.31 mL, 22.2 mmol). The mixture was stirred at rt for 1 h and diluted with aqueous 1 N HCl and Et₂O with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with Et₂O twice. The combined extracts were dried over MgSO₄ and concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish 5c (715 mg, 47% over three steps). ¹H NMR (400 MHz, CDCl₃): δ = 1.04 (d, *J* = 6 Hz, 6 H), 1.94 (tt, *J* = 8, 8 Hz, 2 H), 2.33 (t, *J* = 8 Hz, 2 H), 2.41–2.55 (m, 1 H), 2.60 (dt, *J* = 2.5, 7 Hz, 2 H), 6.38 (dt, *J* = 10,

2.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 19.9 (–), 21.8 (+), 26.6 (–), 29.2 (+), 38.6 (–), 135.0 (–), 142.6 (+), 207.9 (–) ppm.

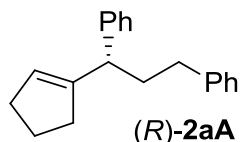


(E)-2-(2-Methylpropylidene)cyclopentanol (*rac*-4c): According to the procedure for synthesis of ***rac*-4a**, reduction of enone **5c** (89.6 mg, 0.648 mmol) with NaBH_4 (25.0 mg, 0.661 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (250 mg, 0.671 mmol) in MeOH (7 mL) gave alcohol ***rac*-4c** (70.2 mg, 77%). ^1H NMR (400 MHz, CDCl_3): δ = 0.966 (d, J = 7 Hz, 3 H), 0.971 (d, J = 7 Hz, 3 H), 1.54–1.73 (m, 2 H), 1.75–1.91 (m, 2 H), 2.14–2.26 (m, 1 H), 2.30–2.46 (m, 2 H), 4.33–4.41 (m, 1 H), 5.36 (dm, J = 9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 22.2 (–), 22.6 (+), 22.8 (+), 26.7 (–), 28.9 (+), 35.6 (–), 75.8 (+), 131.8 (+), 143.6 (–) ppm.



(E)-2-(2-Methylpropylidene)cyclopentyl picolinate (*rac*-1c): According to the procedure for synthesis of ***rac*-1a**, condensation of ***rac*-4c** (180 mg, 1.28 mmol) with picolinic acid (198.6 mg, 1.61 mmol) in CH_2Cl_2 (12 mL) was carried out with DCC (348.4 mg, 1.69 mmol) and DMAP (155.5 mg, 1.27 mmol) at rt for 1 h to furnish picolinate ***rac*-1c** (291 mg, 92%): IR (neat): ν = 1714, 1304, 1245, 1127 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ = 0.95 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.69–1.85 (m, 1 H), 1.85–2.11 (m, 3 H), 2.21–2.54 (m, 3 H), 5.54 (dm, J = 9.5 Hz, 1 H), 5.76 (tm, J = 4 Hz, 1 H), 7.43 (ddd, J = 8, 5, 1 Hz, 1 H), 7.80 (dt, J = 2, 8 Hz, 1 H), 8.07 (dm, J = 8 Hz, 1 H), 8.75 (dm, J = 5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 22.5 (+), 22.6 (+), 22.9 (–), 27.1 (–), 29.2 (+), 33.1 (–), 79.3 (+), 125.1 (+), 126.6 (+), 135.4 (+), 136.9 (+), 138.1 (–), 148.8 (–), 150.0 (+), 165.0 (–) ppm. HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ $[\text{M}]^+$ 245.1416; found 245.1420.

General Procedure for the Allylation



(R)-1-(1-(Cyclopent-1-en-1-yl)propane-1,3-diyl)dibenzene ((R)-2aA). **Table 2.2, Entry 1:** Allylation with CuBr·Me₂S: To an ice-cold suspension of CuBr·Me₂S (20.4 mg, 0.0992 mmol) in THF (1 mL) was added phenylmagnesium bromide (0.23 mL, 0.91 M in THF, 0.21 mmol) slowly. The mixture was stirred at 0 °C for 30 min, cooled to −40 °C, and added a solution of picolinate (*R*)-**1a** (30.3 mg, 97% ee, 0.0986 mmol) in THF (1 mL). The resulting mixture was allowed to warm to −10 °C over 1 h to give (*R*)-**2aA** (23.0 mg, 89%). [α]_D²¹ +27 (*c* 0.12, CHCl₃). IR (neat): ν = 3025, 1602, 1494, 1452, 699 cm^{−1}. ¹H NMR (400 MHz, CDCl₃): δ = 1.76–1.84 (m, 2 H), 2.00–2.25 (m, 4 H), 2.27–2.39 (m, 2 H), 2.43–2.62 (m, 2 H), 3.32 (t, *J* = 7 Hz, 1 H), 5.52 (s, 1 H), 7.10–7.23 (m, 6 H), 7.23–7.35 (m, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (−), 32.4 (−), 33.7 (−), 34.1 (−), 35.8 (−), 47.2 (+), 123.9 (+), 125.8 (+), 126.2 (+), 128.0 (+), 128.4 (+), 128.5 (+), 142.6 (−), 143.9 (−), 147.3 (−) ppm. HRMS (EI): calcd. for C₂₀H₂₂ [M]⁺ 262.1722; found 262.1725. The enantiomeric purity (94% ee) was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*PrOH = 99.6/0.4, 0.3 mL/min, 25 °C, *t*_R/min = 34.4 (*S*-isomer), 39.4 (*R*-isomer).

Table 2.2, Entry 2: Allylation with Cu(acac)₂: To an ice-cold suspension of Cu(acac)₂ (281.3 mg, 1.07 mmol) in THF (7 mL) was added phenylmagnesium bromide (2.00 mL, 1.05 M in THF, 2.10 mmol) slowly. The mixture was stirred at 0 °C for 60 min, cooled to −40 °C, and added a solution of picolinate (*R*)-**1a** (220.0 mg, 94% ee, 0.716 mmol) in THF (3 mL). The resulting mixture was allowed to warm to −5 °C over 2 h to afford (*R*)-**2aA** (149.5 mg, 80%). The enantiomeric purity (95% ee) was determined by chiral HPLC analysis.

Allylation Products

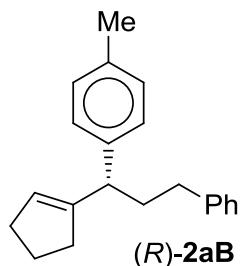


Table 2.2, Entry 3: (R)-1-(1-(Cyclopent-1-en-1-yl)-3-phenylpropyl)-4-methylbenzene ((R)-2aB): Colorless oil (80% yield). IR (neat): $\nu = 1604, 1512, 1496, 1454, 699 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 1.72\text{--}1.84$ (m, 2 H), $1.97\text{--}2.23$ (m, 4 H), 2.33 (s, 3 H), $2.27\text{--}2.35$ (m, 2 H), 2.51 (t, $J = 8 \text{ Hz}$, 2 H), 3.29 (t, $J = 8 \text{ Hz}$, 1 H), 5.50 (s, 1 H), $7.05\text{--}7.20$ (m, 6 H), $7.23\text{--}7.29$ (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.1$ (+), 23.3 (–), 32.4 (–), 33.7 (–), 34.1 (–), 35.8 (–), 46.8 (+), 123.7 (+), 125.7 (+), 127.9 (+), 128.3 (+), 128.5 (+), 129.0 (+), 135.6 (–), 140.9 (–), 142.7 (–), 147.5 (–) ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{24} [\text{M}]^+$ 276.1878; found 276.1882. The enantiomeric purity (97% ee) was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*PrOH = 99.6/0.4, 0.3 mL/min, 25 °C, t_{R} /min = 25.1 (S-isomer), 31.7 (R-isomer).

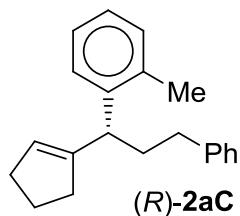


Table 2.2, Entry 4: (R)-1-(1-(Cyclopent-1-en-1-yl)-3-phenylpropyl)-2-methylbenzene ((R)-2aC): Colorless oil (87% yield). $[\alpha]_{\text{D}}^{21} -4$ (c 0.47, CHCl_3). IR (neat): $\nu = 1603, 1454, 754, 729, 699 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 1.72\text{--}1.86$ (m, 2 H), $1.98\text{--}2.07$ (m, 1 H), $2.07\text{--}2.14$ (m, 2 H), 2.23 (s, 3 H), $2.15\text{--}2.26$ (m, 1 H), $2.28\text{--}2.35$ (m, 2 H), $2.48\text{--}2.63$ (m, 2 H), 3.60 (t, $J = 7 \text{ Hz}$, 1 H), 5.47 (s, 1 H), $7.06\text{--}7.21$ (m, 6 H), $7.23\text{--}7.29$ (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.6$ (+), 23.2 (–), 32.3 (–), 33.6 (–), 34.0 (–), 35.6 (–), 42.1 (+), 124.1 (+), 125.66 (+), 125.71 (+), 126.0 (+), 126.5 (+), 128.3 (+), 128.4 (+), 130.2 (+), 136.2 (–), 141.8 (–), 142.5 (–), 146.5 (–) ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{24} [\text{M}]^+$ 276.1878; found 276.1871. The enantiomeric purity (90% ee) was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*PrOH = 92/8, 0.3 mL/min, 25 °C, t_{R} /min = 16.5 (R-isomer), 17.8 (S-isomer).

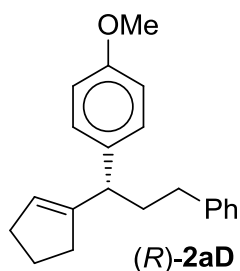


Table 2.2, Entry 5: (R)-1-(1-(Cyclopent-1-en-1-yl)-3-phenylpropyl)-4-methoxybenzene ((R)-2aD): Colorless oil (91% yield). $[\alpha]_D^{27} +27$ (c 0.47, CHCl₃). IR (neat): ν = 1609, 1507, 1246, 1176, 1039 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.69–1.85 (m, 2 H), 1.93–2.23 (m, 4 H), 2.24–2.38 (m, 2 H), 2.50 (t, J = 8 Hz, 2 H), 3.26 (t, J = 7 Hz, 1 H), 3.79 (s, 3 H), 5.47 (s, 1 H), 6.82 (d, J = 8 Hz, 2 H), 7.03–7.19 (m, 5 H), 7.20–7.26 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.2 (–), 32.3 (–), 33.6 (–), 34.0 (–), 35.8 (–), 46.2 (+), 55.2 (+), 113.6 (+), 123.5 (+), 125.6 (+), 128.2 (+), 128.4 (+), 128.8 (+), 135.9 (–), 142.6 (–), 147.6 (–), 157.9 (–) ppm. HRMS (EI): calcd. for C₂₁H₂₄O [M]⁺ 292.1827; found 292.1825. The enantiomeric purity (91% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 99.8/0.2, 0.4 mL/min, 25 °C, t_R /min = 24.7 (*S*-isomer), 26.6 (*R*-isomer).

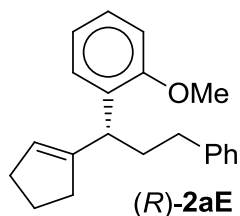


Table 2.2, Entry 6: (R)-1-(1-(Cyclopent-1-en-1-yl)-3-phenylpropyl)-2-methoxybenzene ((R)-2aE): Colorless oil (82% yield). $[\alpha]_D^{20} +12$ (c 0.26, CHCl₃). IR (neat): ν = 1599, 1492, 1241, 1031, 751, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.71–1.87 (m, 2 H), 1.94–2.05 (m, 1 H), 2.09–2.20 (m, 3 H), 2.32 (tt, J = 7, 2.5 Hz, 2 H), 2.49 (ddd, J = 14, 10, 6 Hz, 1 H), 2.58 (ddd, J = 14, 10, 6 Hz, 1 H), 3.80 (s, 3 H), 3.92 (t, J = 7 Hz, 1 H), 5.50 (s, 1 H), 6.87 (d, J = 8 Hz, 1 H), 6.92 (dt, J = 1, 8 Hz, 1 H), 7.12–7.20 (m, 5 H), 7.22–7.28 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (–), 32.5 (–), 34.20 (–), 34.22 (–), 35.9 (–), 38.6 (+), 55.6 (+), 110.7 (+), 120.6 (+), 123.8 (+), 125.6 (+), 126.9 (+), 127.8 (+), 128.2 (+), 128.4 (+), 132.4 (–), 143.0 (–), 147.0 (–), 157.4 (–) ppm. HRMS (EI): calcd. for C₂₁H₂₄O [M]⁺ 292.1827; found 292.1828. The

enantiomeric purity (85% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 99.9/0.1, 1.0 mL/min, 25 °C, *t_R*/min = 9.5 (*S*-isomer), 10.3 (*R*-isomer).

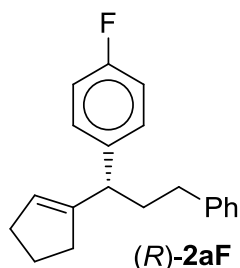


Table 2.2, Entry 7: (R)-1-(1-(cyclopent-1-en-1-yl)-3-phenylpropyl)-4-fluorobenzene ((R)-2aF): Colorless oil (86% yield). $[\alpha]_D^{21} +22$ (*c* 0.36, CHCl₃). IR (neat): ν = 1602, 1508, 1498, 1223, 1156 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.73–1.87 (m, 2 H), 1.96–2.25 (m, 4 H), 2.27–2.36 (m, 2 H), 2.50 (t, *J* = 8 Hz, 2 H), 3.30 (t, *J* = 8 Hz, 1 H), 5.50 (s, 1 H), 6.98 (tt, *J* = 8, 2.5 Hz, 2 H), 7.09–7.21 (m, 5 H), 7.23–7.30 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (–), 32.4 (–), 33.7 (–), 34.0 (–), 35.9 (–), 46.4 (+), 115.1 (d, *J* = 21 Hz) (+), 124.1 (+), 125.8 (+), 128.4 (+), 128.5 (+), 129.3 (d, *J* = 8 Hz) (+), 139.5 (d, *J* = 3 Hz) (–), 142.4 (–), 147.2 (–), 161.4 (d, *J* = 242 Hz) (–) ppm. HRMS (EI): calcd. for C₂₀H₂₁F [M]⁺ 280.1627; found 280.1621. The enantiomeric purity (90% ee) was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*PrOH = 99.6/0.4, 1.0 mL/min, 25 °C, *t_R*/min = 8.7 (*S*-isomer), 10.8 (*R*-isomer).

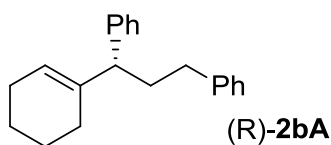


Table 2.2, Entry 8: (R)-1-(1-(Cyclohex-1-en-1-yl)propane-1,3-diyl)dibenzene ((R)-2bA): Colorless oil (89% yield). $[\alpha]_D^{21} -3$ (*c* 0.26, CHCl₃). IR (neat): ν = 3025, 1602, 1494, 1451, 699 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.44–1.62 (m, 4 H), 1.65–1.90 (m, 2 H), 1.92–2.22 (m, 4 H), 2.42–2.62 (m, 2 H), 3.13 (t, *J* = 7 Hz, 1 H), 5.62 (s, 1 H), 7.08–7.32 (m, 10 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 22.8 (–), 23.2 (–), 25.6 (–), 26.7 (–), 34.3 (–), 34.6 (–), 52.6 (+), 121.6 (+), 125.6 (+), 126.0 (+), 127.9 (+), 128.1 (+), 128.2 (+), 128.4 (+), 139.8 (–), 142.6 (–), 144.2 (–) ppm. HRMS (EI): calcd. for C₂₁H₂₄ [M]⁺ 276.1878; found 276.1875. The enantiomeric purity (86% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 100/0, 0.8 mL/min, 20 °C, *t_R*/min = 13.2 (*S*-isomer), 14.1 (*R*-isomer).

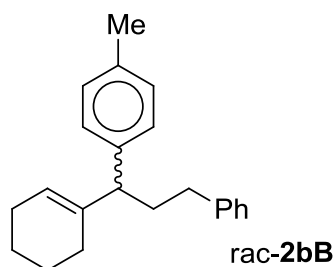


Table 2.1, Entry 18: 1-(1-(Cyclohex-1-en-1-yl)-3-phenylpropyl)-4-methylbenzene (*rac*-2bB):

Colorless oil (82% yield). IR (neat): ν = 1511, 1496, 1453, 698 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 1.48–1.56 (m, 4 H), 1.67–1.87 (m, 2 H), 1.94–2.17 (m, 4 H), 2.32 (s, 3 H), 2.46–2.62 (m, 2 H), 3.10 (t, J = 7.0 Hz, 1 H), 5.62 (s, 1 H), 7.06–7.30 (m, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 21.1 (+), 22.8 (–), 23.1 (–), 25.5 (–), 26.6 (–), 34.2 (–), 34.6 (–), 52.1 (+), 121.5 (+), 125.7 (+), 127.9 (+), 128.3 (+), 128.5 (+), 128.9 (+), 135.5 (–), 140.1 (–), 141.3 (–), 142.8 (–) ppm. HRMS (EI): calcd. for $\text{C}_{22}\text{H}_{26}$ (M^+) 290.2035; found 290.2035.

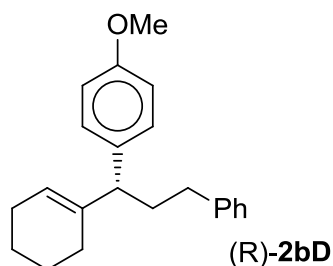


Table 2.2, Entry 9: (R)-1-(1-(Cyclohex-1-en-1-yl)-3-phenylpropyl)-4-methoxybenzene ((R)-2bD):

Colorless oil (87% yield). $[\alpha]_{\text{D}}^{21}$ –2 (c 0.498, CHCl_3). IR (neat): ν = 1608, 1509, 1246, 1177, 1039 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 1.46–1.60 (m, 4 H), 1.66–1.86 (m, 2 H), 1.92–2.16 (m, 4 H), 2.44–2.59 (m, 2 H), 3.08 (t, J = 8 Hz, 1 H), 3.80 (s, 3 H), 5.61 (s, 1 H), 6.83 (dm, J = 9 Hz, 2 H), 7.09–7.20 (m, 4 H), 7.23–7.29 (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 22.7 (–), 23.1 (–), 25.4 (–), 26.6 (–), 34.2 (–), 34.7 (–), 51.6 (+), 55.3 (+), 113.5 (+), 121.4 (+), 125.7 (+), 128.3 (+), 128.5 (+), 128.8 (+), 136.4 (–), 140.2 (–), 142.8 (–), 157.9 (–) ppm. HRMS (EI): calcd. for $\text{C}_{22}\text{H}_{26}\text{O}$ [M] $^+$ 306.1984; found 306.1981. The enantiomeric purity (80% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 99.9/0.1, 1.0 mL/min, 20 $^{\circ}\text{C}$, t_{R} /min = 16.7 (*S*-isomer), 22.5 (*R*-isomer).

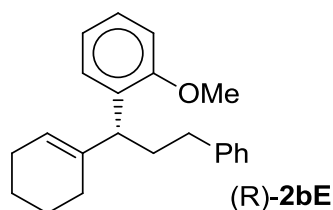


Table 2.2, Entry 10: (R)-1-(1-(Cyclohex-1-en-1-yl)-3-phenylpropyl)-2-methoxybenzene ((R)-2bE): Colorless oil (71% yield). $[\alpha]_D^{20} +6$ (c 0.36, CHCl₃). IR (neat): $\nu = 1598, 1490, 1460, 1241 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.44\text{--}1.64$ (m, 4 H), 1.76–1.87 (m, 2 H), 1.87–1.99 (m, 1 H), 2.00–2.14 (m, 3 H), 2.47 (ddd, $J = 14, 10, 6 \text{ Hz}$, 1 H), 2.59 (ddd, $J = 14, 10, 6 \text{ Hz}$, 1 H), 3.71 (t, $J = 8 \text{ Hz}$, 1 H), 3.79 (s, 3 H), 5.61 (s, 1 H), 6.82–6.88 (m, 1 H), 6.91 (t, $J = 7 \text{ Hz}$, 1 H), 7.11–7.21 (m, 5 H), 7.22–7.28 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.8$ (–), 23.2 (–), 25.5 (–), 27.7 (–), 34.3 (–), 35.1 (–), 43.6 (+), 55.6 (+), 110.7 (+), 120.5 (+), 121.3 (+), 125.6 (+), 126.8 (+), 127.6 (+), 128.2 (+), 128.5 (+), 133.0 (+), 139.5 (+), 143.2 (+), 157.7 (+) ppm. HRMS (EI): calcd. for C₂₂H₂₆O [M]⁺ 306.1984; found 306.1986. The enantiomeric purity (83% ee) was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*PrOH = 99.9/0.1, 1.0 mL/min, 20 °C, t_R /min = 9.9 (*S*-isomer), 11.3 (*R*-isomer).

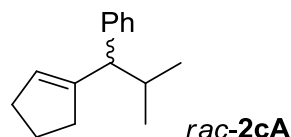


Table 2.1, Entry 19: (1-(Cyclopent-1-en-1-yl)-2-methylpropyl)benzene (rac-2cA): Colorless oil (96% yield). IR (neat): $\nu = 1493, 1451, 702 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃): $\delta = 0.71$ (d, $J = 6 \text{ Hz}$, 3 H), 0.96 (d, $J = 6 \text{ Hz}$, 3 H), 1.77 (tt, $J = 8, 8 \text{ Hz}$, 2 H), 2.06–2.23 (m, 3 H), 2.23–2.35 (m, 2 H), 3.00 (d, $J = 10 \text{ Hz}$, 1 H), 5.52 (s, 1 H), 7.13–7.21 (m, 3 H), 7.22–7.29 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 21.3$ (+), 22.0 (+), 23.3 (–), 30.1 (+), 32.2 (–), 32.9 (–), 56.7 (+), 124.5 (+), 125.9 (+), 128.1 (+), 128.4 (+), 143.7 (–), 146.8 (–) ppm. HRMS (EI): calcd. for C₁₅H₂₀ [M]⁺ 200.1565; found 200.1559.

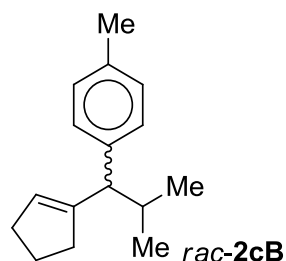
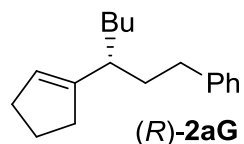


Table 2.1, Entry 20: 1-(1-(Cyclopent-1-en-1-yl)-2-methylpropyl)-4-methylbenzene (*rac*-2cB):

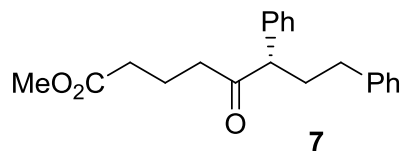
Colorless oil (87% yield). IR (neat): $\nu = 1512, 1465, 1384, 815 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.71$ (d, $J = 6.5 \text{ Hz}$, 3 H), 0.94 (d, $J = 6.5 \text{ Hz}$, 3 H), $1.72\text{--}1.83$ (m, 2 H), $2.07\text{--}2.36$ (m, 5 H), 2.31 (s, 3 H), 2.97 (d, $J = 10 \text{ Hz}$, 1 H), 5.50 (s, 1 H), $7.03\text{--}7.12$ (m, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.1$ (+), 21.3 (+), 22.0 (+), 23.3 (–), 30.1 (+), 32.2 (–), 32.9 (–), 56.3 (+), 124.2 (+), 128.3 (+), 128.8 (+), 135.2 (–), 140.6 (–), 147.0 (–) ppm. HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{22} [\text{M}]^+$ 214.1722; found 214.1722.



Scheme 2.5: (R)-(3-(Cyclopent-1-en-1-yl)heptyl)benzene ((R)-2aG): Colorless oil (91% yield).

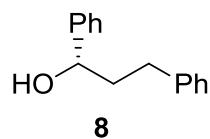
IR (neat): $\nu = 1500, 1455, 1260, 1032, 804, 698 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.87$ (t, $J = 7 \text{ Hz}$, 3 H), $1.15\text{--}1.40$ (m, 6 H), $1.58\text{--}1.72$ (m, 2 H), 1.85 (quint, $J = 7 \text{ Hz}$, 2 H), $2.12\text{--}2.27$ (m, 3 H), $2.27\text{--}2.36$ (m, 2 H), $2.40\text{--}2.60$ (m, 2 H), $5.36\text{--}5.41$ (m, 1 H), $7.13\text{--}7.19$ (m, 3 H), $7.23\text{--}7.30$ (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2$ (+), 22.9 (–), 23.5 (–), 29.8 (–), 31.0 (–), 32.1 (–), 33.5 (–), 34.0 (–), 35.6 (–), 41.0 (+), 125.1 (+), 125.6 (+), 128.3 (+), 128.5 (+), 143.2 (–), 147.1 (–) ppm.

Determination of the configuration of (*R*)-2aA



(*S*)-Methyl 5-oxo-6,8-diphenyloctanoate (7): To an ice-cold solution of (*R*)-2aA (43.9 mg, 0.167 mmol) in CCl₄ (2 mL), MeCN (2 mL), and H₂O (3 mL) were added NaIO₄ (150 mg, 0.701 mmol) and RuCl₃·*n*H₂O (ca. 16 mg). The mixture was stirred at rt for 7 h and diluted with CH₂Cl₂ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ twice. The combined organic layers was dried by MgSO₄ and concentrated to afford a residue, which was passed through a pad of Celite with Et₂O to remove the remaining Ru species. The filtrate was concentrated to afford a crude oil, which was passed through a short column and used for the next reaction without further purification.

To an ice-cold solution of the above oil in Et₂O (2 mL) was added a solution of CH₂N₂ in Et₂O (2 mL). After 5 min at °C, the solution was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **7** (9.7 mg, 18% from (*R*)-2aA). ¹H NMR (400 MHz, CDCl₃): δ = 1.68–1.86 (m, 2 H), 1.94–2.07 (m, 1 H), 2.08–2.26 (m, 2 H), 2.26–2.45 (m, 3 H), 2.49 (tm, *J* = 7 Hz, 2 H), 3.53–3.61 (m, 1 H), 3.57 (s, 3 H), 7.08–7.13 (m, 2 H), 7.15–7.19 (m, 3 H), 7.22–7.28 (m, 3 H), 7.28–7.34 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 18.9 (–), 32.9 (–), 33.4 (–), 40.6 (–), 51.6 (+), 58.2 (+), 126.0 (+), 127.4 (+), 128.44 (+), 128.48 (+), 128.53 (+), 129.1 (+), 138.7 (–), 141.6 (–), 173.6 (–), 209.4 (–) ppm.

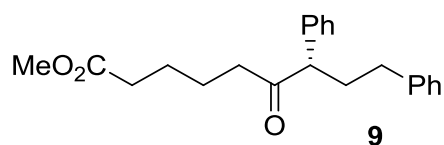


(*S*)-1,3-Diphenylpropan-1-ol (8): To a solution of **7** (15.3 mg, 0.0472 mmol) in CH₂Cl₂ (5 mL) were added K₂CO₃ (72.2 mg, 0.522 mmol) and *m*CPBA (92.3 mg, 77% purity, 0.412 mmol). The reaction was carried out at rt for 40 h and quenched by addition of aqueous Na₂S₂O₃ and CH₂Cl₂. The organic layer was separated and the aqueous phase was extracted with EtOAc twice. The combined extracts was dried by MgSO₄, concentrated, and passed through a short column

(hexane/EtOAc) to afford a residue, which was used for the following reaction without further purification.

A mixture of the above product and aqueous KOH (1.8 N, 0.10 mL) in MeOH (1 mL) was stirred at rt overnight and diluted with H₂O and Et₂O. The organic layer was separated and the aqueous phase was extracted with Et₂O three times. The combined extracts were dried by MgSO₄, concentrated, and purified by chromatography on silica gel (hexane/EtOAc) to furnish **8** (5.2 mg, 52% over two steps). $[\alpha]_D^{23} -13$ (c 0.17, CHCl₃) (cf. $[\alpha]_D^{20} -27.1$ (c 0.52, CHCl₃) for the *S* enantiomer of >99% ee.^[17] ¹H NMR (400 MHz, CDCl₃): δ = 1.84 (br s, 1 H), 1.97–2.20 (m, 2 H), 2.62–2.81 (m, 2 H), 4.70 (dd, *J* = 8 Hz, 5.5 Hz, 1 H), 7.15–7.22 (m, 3 H), 7.25–7.32 (m, 3 H), 7.33–7.37 (m, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 32.2 (–), 40.6 (–), 74.0 (+), 125.95 (+), 126.01 (+), 127.7 (+), 128.48 (+), 128.52 (+), 128.62 (+), 141.8 (–), 144.6 (–) ppm. The ¹H and ¹³C NMR spectra were consistent with those reported.¹⁷

Determination of the configuration of (*R*)-2bA



(*S*)-Methyl 6-oxo-7,9-diphenylnonanoate (9): A stream of ozone in oxygen was slowly bubbled into a solution of (*R*)-**2bA** (43.1 mg, 0.156 mmol) in CH₂Cl₂ (8 mL) at –78 °C until the solution turned to pale blue (5 min). Excess ozone remaining in the solution was removed by bubbling argon at –78 °C for 5 min and PPh₃ (52.0 mg, 0.198 mmol) was added. The solution was gradually warmed to rt, stirred overnight, and concentrated to afford a residue, which was passed through a short column (hexane/EtOAc) to furnish a crude aldehyde, which was used for the next reaction without further purification.

To a solution of the above crude aldehyde in acetone (5 mL) was added Jones reagent (9 drops, 4 M) at 0 °C. After 30 min at 0 °C, *i*PrOH was added to quench the excess reagent. After concentration, the residue was passed through a short column and the filtrate was concentrated to afford a residue, which was used directly for the next reaction without further purification.

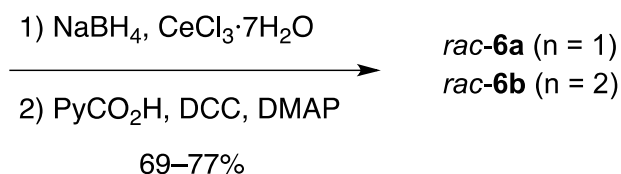
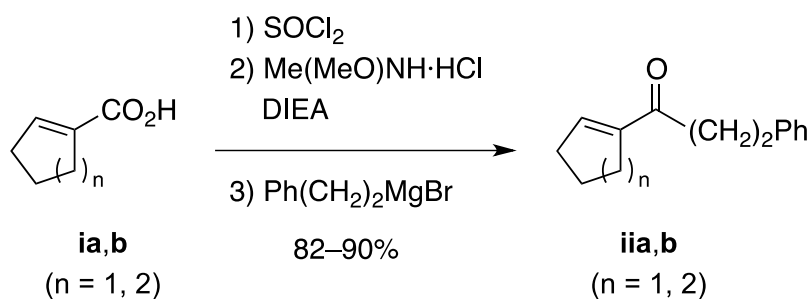
To an ice-cold solution of the above residue in Et₂O (2 mL) was added a solution of CH₂N₂ in Et₂O (2 mL). After 5 min, the solution was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish ester **9** (21.3 mg, 40% from (*R*)-**2bA**). ¹H NMR (300 MHz, CDCl₃): δ = 1.38–1.66 (m, 4 H), 1.94–2.10 (m, 1 H), 2.15–2.25 (m, 2 H), 2.28–2.44 (m, 3 H), 2.45–2.56 (m, 2 H), 3.54–3.65 (m, 1 H), 3.62 (s, 3 H), 7.06–7.21 (m, 5 H), 7.21–7.36 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.2 (–), 24.3 (–), 33.42 (–), 33.45 (–), 33.8 (–), 41.3 (–), 51.6 (+), 58.2 (+), 126.0 (+), 127.4 (+), 128.44 (+), 128.45 (+), 128.52 (+), 129.0 (+), 138.8 (–), 141.6 (–), 173.9 (–), 209.8 (–) ppm.

According to the above procedure, a mixture of **9** (21.3 mg, 0.0629 mmol), K₂CO₃ (105 mg, 0.760 mmol) and *m*CPBA (128.3 mg, 77% purity, 0.0572 mmol) in CH₂Cl₂ (6 mL) was stirred at rt for 48 h to afford the ester product, which was subjected to hydrolysis with aqueous KOH (1.8 N, 0.15 mL) in MeOH (2 mL) at rt overnight to furnish **8**: (4.8 mg, 36% from **9**): $[\alpha]_D^{23}$ –23 (c 0.25, CHCl₃) (cf. $[\alpha]_D^{20}$ –27.1 (c 0.52, CHCl₃) for the *S* enantiomer of >99% ee).¹⁷

2.6 References and Notes

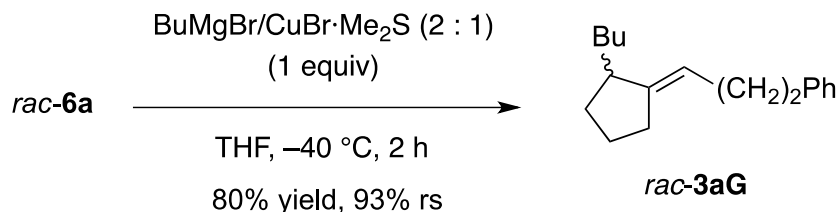
1. Reviews: a) d) J. F. Teichert, B. L. Feringa, *Angew. Chem., Int. Ed.* **2010**, 49, 2486–2528; b) B. Breit, Y. Schmidt, *Chem. Rev.* **2008**, 108, 2928–2951; c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, 108, 2824–2852; d) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, 108, 2796–2823; e) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765–3780; f) H. Yorimitsu, K. Oshima, *Angew. Chem., Int. Ed.* **2005**, 44, 4435–4439.
2. Recent publications: a) R. Shintani, K. Takatsu, M. Takeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2011**, 50, 8656–8659; b) H. Ohmiya, U. Yokobori, Y. Makida, M. Sawamura, *J. Am. Chem. Soc.* **2010**, 132, 2895–2897; c) H. Ohmiya, N. Yokokawa, M. Sawamura, *Org. Lett.* **2010**, 12, 2438–2440; d) H. Ohmiya, Y. Makida, T. Tanaka, M. Sawamura, *J. Am. Chem. Soc.* **2008**, 130, 17276–17277; e) D. Soorukram, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, 45, 3686–3689; f) P. Demel, M. Keller, B. Breit, *Chem. Eur. J.* **2006**, 12, 6669–6683; g) B. Breit, P. Demel, D. Grauer, C. Studte, *Chem. Asian J.* **2006**, 1, 586–597; h) B. Breit, P. Demel, C. Studte, *Angew. Chem., Int. Ed.* **2004**, 43, 3786–3789.
3. a) Q. Wang, Y. Kobayashi, *Org. Lett.* **2011**, 13, 6252–6255; b) Y. Kiyotsuka, Y. Kobayashi, *Tetrahedron* **2010**, 66, 676–684; c) Y. Kiyotsuka, Y. Kobayashi, *J. Org. Chem.* **2009**, 74, 7489–7495; d) Y. Kiyotsuka, Y. Katayama, H. P. Acharya, T. Hyodo, Y. Kobayashi, *J. Org. Chem.* **2009**, 74, 1939–1951; e) Y. Kiyotsuka, H. P. Acharya, Y. Katayama, T. Hyodo, Y. Kobayashi, *Org. Lett.* **2008**, 10, 1719–1722.
4. a) C. Feng, Y. Kobayashi, *J. Org. Chem.* **2013**, 78, 3755–3766; b) Y. Kaneko, Y. Kiyotsuka, H. P. Acharya, Y. Kobayashi, *Chem. Commun.* **2010**, 46, 5482–5484.
5. T. B. RajanBabu, W. A. Nugent, D. F. Taber, P. J. Fagan, *J. Am. Chem. Soc.* **1988**, 110, 7128–7135.
6. C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, 51, 2884–2891.
7. M. C. Warner, A. Nagendiran, K. Bogár, J.-E. Bäckvall, *Org. Lett.* **2012**, 14, 5094–5097.
8. Defined as (% ee of **2**) x 100 / (% ee of **1**).

9. Previous production of compounds corresponding to the γ products: a) C. S. Yi, D. W. Lee, *Organometal.* **2010**, 29, 1883–1885; b) J. Almena, F. Foubelo, M. Yus, *Tetrahedron* **1997**, 53, 5563–5572.
10. a) J. K. Crandall, J. P. Arrington, J. Hen, *J. Am. Chem. Soc.* **1967**, 89, 6208–6213; b) S. Nakamura, T. Hayakawa, T. Nishi, Y. Watanabe, T. Toru, *Tetrahedron* **2001**, 57, 6703–6711; c) K. Shimoda, N. Kubota, H. Hamada, M. Kaji, T. Hirata, *Tetrahedron: Asymmet.* **2004**, 15, 1677–1679.
11. E. J. Corey, C. J. Helal, *Angew. Chem., Int. Ed.* **1998**, 37, 1986–2012.
12. a) J. R. Falck, A. He, L. M. Reddy, A. Kundu, D. K. Barma, A. Bandyopadhyay, S. Kamila, R. Akella, R. Bejot, C. Mioskowski, *Org. Lett.* **2006**, 8, 4645–4647; b) A. Yanagisawa, R. Goudou, T. Arai, *Org. Lett.* **2004**, 6, 4281–4283.
13. The substrates *rac*-**6a** and **-6b** were synthesized by the method shown below.



14. The diagnostic olefin protons in the ^1H NMR spectrum: *rac*-**3aA** and the *Z*-isomer in a 4:1 ratio, δ 4.93 (tt, $J = 7, 2.5$ Hz, 0.8 H) and 5.47 (tm, $J = 7$ Hz, 0.2 H); *rac*-**3bA** and the *Z*-isomer in a 4:1 ratio, δ 4.66 (t, $J = 7$ Hz, 0.8 H) and 5.43 (t, $J = 7$ Hz, 0.2 H). The major absorbance at δ 4.93 and 4.66 were coincident with the minor signals seen in the spectra of *rac*-**2aA** and **-2bA**, respectively. On the other hand, the olefin protons of *rac*-**3aG** and the *Z*-isomer overlapped each other at δ 5.12–5.32 (m, 1 H).

- 15 The olefin and/or allylic signals of *rac*-**3aB**, -**3bB**, -**3cA** and -**3cB** in ^1H NMR spectroscopy were assigned by analogy of *rac*-**3aA** and -**3bA**, respectively.
- 16 Although RuCl_3 -catalysed oxidation of (*R*)-**2aA** with NaIO_4 followed by esterification with CH_2N_2 suffered from low yield of ketone **7** due to difficulty to separate the side product(s), Baeyer-Villiger oxidation of **7** and subsequent hydrolysis gave enough quantity of **8** for determination of the specific rotation. To avoid the problem, ozonolysis followed by Jones oxidation was applied to (*R*)-**2bA** to produce ketone **9** in moderate yield, and further transformation furnished **8** as well.
- 17 Z. Cao, Z. Liu, Y. Liu, H. Du, *J. Org. Chem.* **2011**, 76, 6401–6406.
- 18 Regioisomer *rac*-**3aG** (E + Z isomers and Z isomer was not shown) was synthesized as shown below. The ^1H NMR spectrum of *rac*-**3aG** was used as reference for calculation of the regioselectivity of (*R*)-**2aG**.

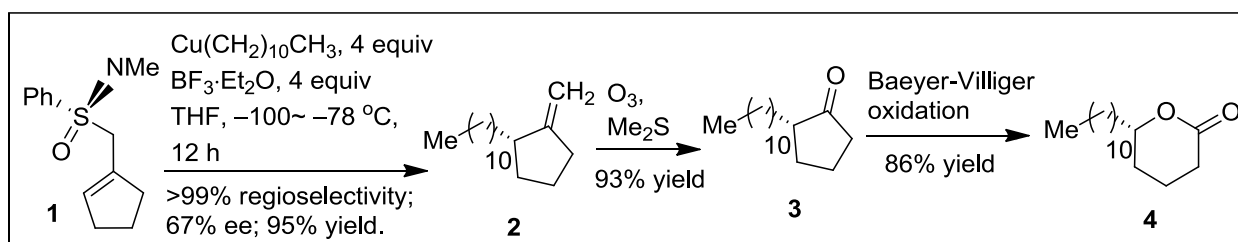


- 19 The stereochemistry was speculated. e.e. of the product and thus C.T. could not be determined by HPLC analysis with attempted six chiral columns.
- 20 a) N. Yoshikai, E. Nakamura, *Chem. Rev.* **2012**, 112, 2339–2372; b) N. Yoshikai, S.-L. Zhang, E. Nakamura, *J. Am. Chem. Soc.* **2008**, 130, 12862–12863; c) S. Mori, E. Nakamura, *Tetrahedron Lett.* **1999**, 40, 5319–5322.
- 21 Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nature Chemistry*, **2011**, 3, 377–381.

Chapter 3 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanone via Allylic Substitution of *exo*-Cyclic Picolinates Followed by Ozonolysis

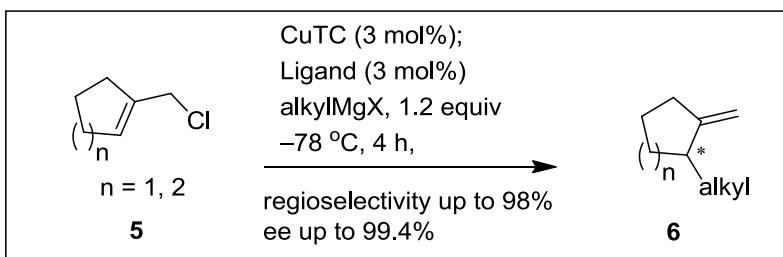
3.1 Introduction

Allylic substitution of exocyclic substrates was investigated in a few cases. For instance, in 1991, regioselective and enantioselective allylic substitution of β,β -disubstituted exocyclic substrate **1** and the following transformation to lactone **4** by ozonolysis and Baeyer-Villiger oxidation was initially investigated by J. Bund and co-workers¹ as shown in **Scheme 3.1**. The regioselectivity was achieved more than 99% with alkylcopper reagents, however, only 67% ee of **2** was obtained.



Scheme 3.1 Allylic Substitution of Sulfoximine **1** and Transformation to Lactone **4**

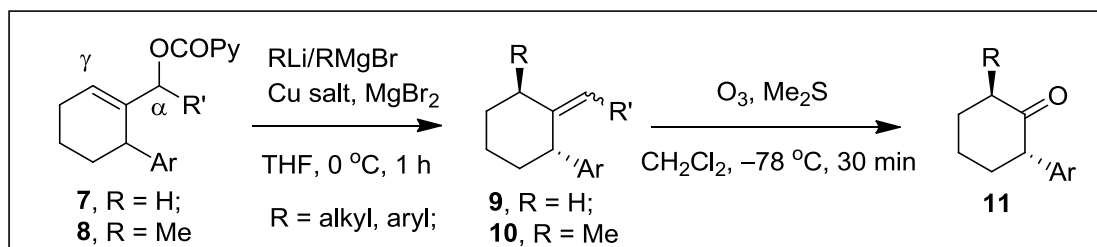
In 2006, Alexakis et al² reported Cu-catalyzed allylic substitution of β,β -disubstituted exocyclic substrate **5** by employing chiral ligand to asymmetrically synthesize $\text{S}_{\text{N}}2'$ product **6** (**Scheme 3.2**).



Scheme 3.2 Asymmetrical Substitution of Allylic Chloride **5** with Chiral Ligand

In this chapter, exocyclic substrate **7** and **8** were synthesized and the steric effects of Ar group in allylic substitution of **7/8** with both alkyl and aryl groups were investigated. The

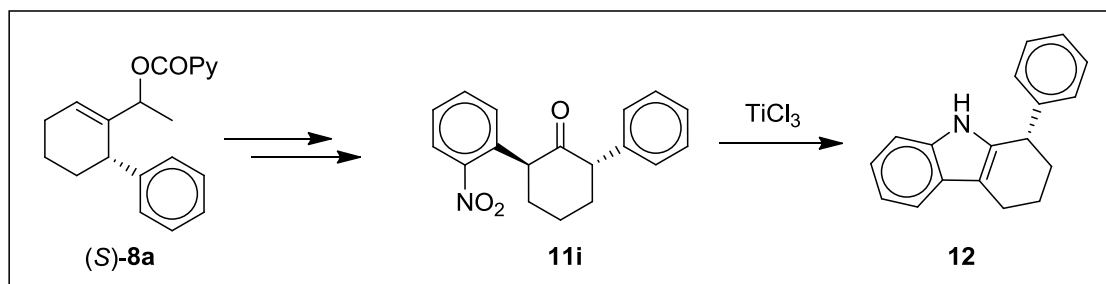
stereochemistry of S_N2' reaction was found to be controlled by Ar group as well, based on NOE analysis as well as comparing ^1H NMR spectrum with that reported. Ozonolysis of S_N2' product **9/10** generated 2,6-*trans*-disubstituted cyclohexanone **11** with *trans* stereochemistry, which was hardly constructed by other methods.



Scheme 3.3 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanones

On the other hand, anion generated at alpha position of carbonyl group reacts with electrophiles to generate various products. Among them, 2,6-disubstitued cyclohexanones are valuable intermediates for synthesis of some medicines such as potential HIV inhibitors,³ alkaloids,⁴ as well as indoles.^{5d} However, methods for synthesis of 2,6-disubstituted skeleton oftentimes generate a mixture of *cis*- and *anti*-isomers.⁵ In this chapter, a strategy was developed by allylic substitution of exocyclic picolates **7** with nucleophiles, followed by ozonolysis to generate 2,6-disubstituted cyclohexanones **11** (**Scheme 3.3**).

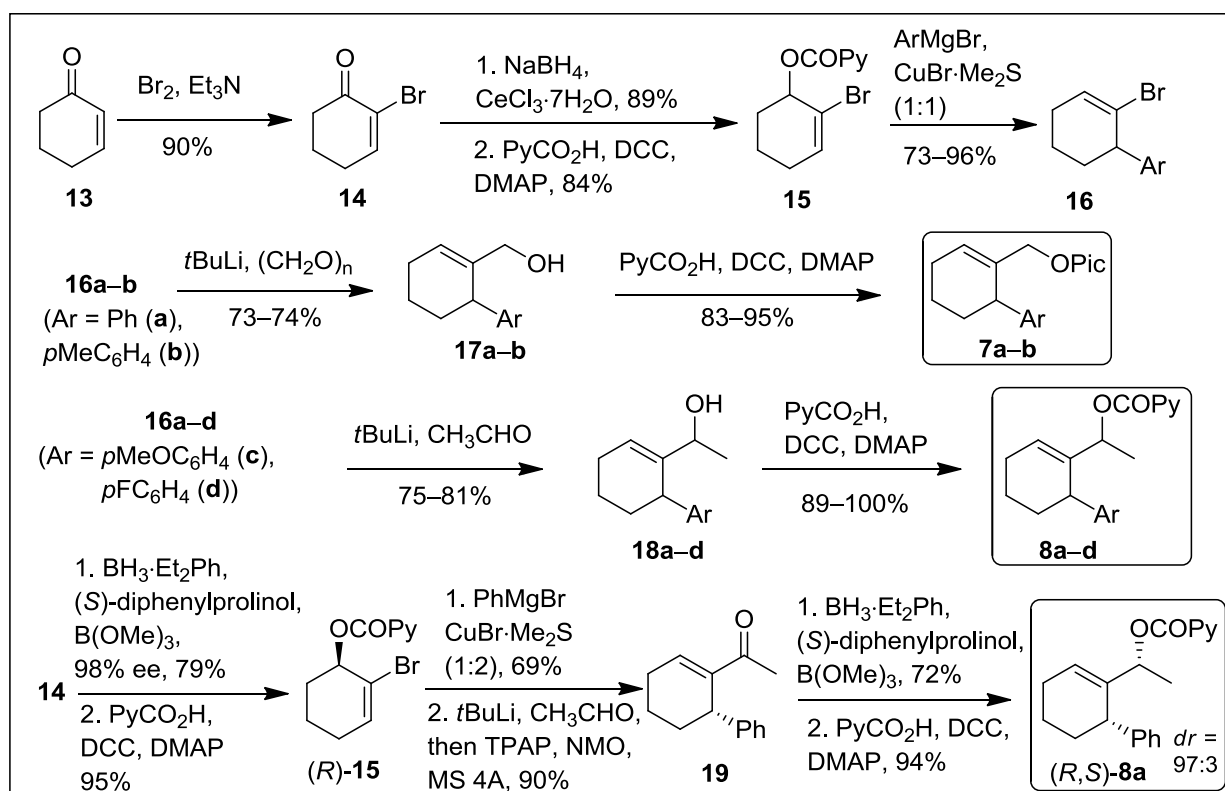
Furthermore, chiral (*R,S*)-**8a** was synthesized by employing CBS reduction and allylic substitution of (*R,S*)-**8a** as well as ozonolysis to generate single isomer of **11a** (R = Me, Ar = Ph) and **11b** (R = Ph, Ar = Ph) has been investigated. Possible application of the above transformation for synthesis of optically active indole **12** from (*S*)-**8a** is under investigation (**Scheme 3.4**).^{5d}



Scheme 3.4 Possible Application for Synthesis of Indole 12

3.2 Results and Discussion

Firstly, allylic picolinate **7** and **8** were synthesized according to T. Hirotsu's master thesis completed in our laboratory previously. In brief, bromination of enone **13**, followed by reduction with NaBH₄ and DCC-mediated condensation generated picolinate **15**, allylic substitution of which with Arylcopper reagents furnished intermediates **16a-d**, respectively (**a**, Ar = Ph; **b**, Ar = *p*MeC₆H₄; **c**, Ar = *p*MeOC₆H₄; **d**, Ar = *p*FC₆H₄). **16a-b** reacted with *t*BuLi and (CH₂O)_n, and then esterification afforded picolinate **7a-b**. Likewise, picolinate **8a-d** were synthesized respectively. (*R,S*)-**8a** (dr = 97:3 by ¹H NMR) was synthesized by applying CBS reductions.⁶

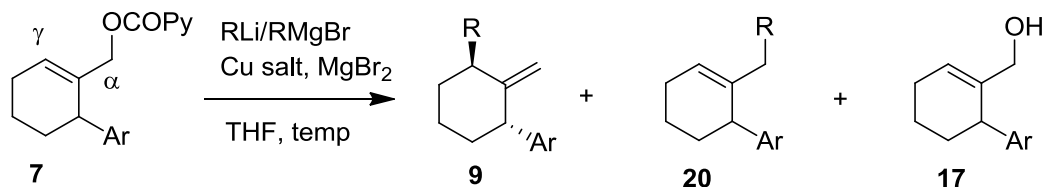


Scheme 3.5 Synthesis of Picolinate 7 and 8

Allylation of Picolinate 7. Picolinate **7a** was employed for preliminary study. First, methylcopper reagent generated from MeLi or MeMgBr and CuBr·Me₂S in a 1:1 ratio was investigated, affording S_N2' product **9a** (anti-stereochemistry was determined by NOE analysis, see **Figure 3.1**) more than ca. 90% regioselectivity over S_N2 product **20a** in good yields (entries 1 and 2). Then BuLi and CuBr·Me₂S in a 1:1 ratio smoothly generated S_N2' product **9b** with 97%

regioselectivity in 82% yield (entry 3). The above results suggest that allylic substitution of picolinate **7a** with alkylcopper reagents generated from alkyl–Li or alkyl–MgX and CuBr·Me₂S in a 1:1 ratio regioselectively affords S_N2' products **9**.

Table 3.1 Allylic Substitution of Picolinate 7a–b (a, Ar = Ph; b, Ar = *p*MeC₆H₄)



Entry ^a	RMgBr/RLi (equiv)	Cu salt (equiv)	Additive (equiv)	T/°C	Time	9:20:17:7 ^b	Yield ^c (%)
1	MeLi (2.7)	CuBr·Me ₂ S (3.0)	MgBr ₂ (3.0)	0	1 h	90:7:3:0	96%
2	MeMgBr (1.5)	CuBr·Me ₂ S (1.5)	—	0	1 h	88:6:6:<1	89%
3	BuLi (2.7)	CuBr·Me ₂ S (3.0)	MgBr ₂ (3.0)	0	1 h	94:3:3:<1	82%
4	PhLi (3.0)	CuBr·Me ₂ S (3.0)	MgBr ₂ (3.0)	0	1 h	53:35:12:0	—
5	PhMgBr (3.2)	Cu(acac) ₂ (1.5)	—	0	1 h	80:18:2:0	—
6	PhLi (4.0)	Cu(acac) ₂ (2.0)	MgBr ₂ (2.0)	–40	2 h	0:0:40:60	—
7	PhLi (6.0)	Cu(acac) ₂ (2.0)	MgBr ₂ (2.0) + ZnI ₂ (2.0)	–40	2 h	0:0:70:30	—
8	PhMgBr (3.0)	Cu(acac) ₂ (1.5)	—	–40	2 h	24:1:5:70	—
9	PhMgBr (6.0)	Cu(acac) ₂ (3.0)	—	–40	2 h	36:8:16:40	—
10	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	—	–40	2 h	20:70:10:0	—
11	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	ZnI ₂ (1.5)	–40	2 h	37:4:20:39	—
12	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	ZnI ₂ (1.0)	–40	2 h	55:3:17:25	—
13	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	ZnI ₂ (2.0)	–40	2 h	<5:<5:44:56	—
14	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	ZnI ₂ (1.5)	–40	12 h	84:7:5:4	81%
15	PhMgBr (4.6)	Cu(acac) ₂ (1.5)	ZnI ₂ (1.5)	–40	12 h	76:12:5:7	72%

^a Substrate of entries 1–14: **7a**; substrate of entry 15: **7b**. ^b Determined by ¹H NMR. ^c Combined yield of **9** and **20**.

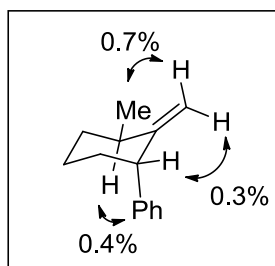


Figure 3.1 NOE Analysis of **9a**

Next, arylcopper reagents were examined. In construct, at 0 °C, arylcopper reagent generated PhLi and CuBr·Me₂S in a 1:1 ratio only generated a mixture of S_N2' and S_N2 products **9c** and **20c** (entry 4). PhMgBr and Cu(acac)₂ in a 2:1 ratio, which is a good reagent system for aryl groups (see **Chapter 2**), improved the regioselectivity to moderate ca. 82% (entry 5). At lower temperature (−40 °C), PhLi and Cu(acac)₂ in a 2:1 and 3:1 ratios only generated percentages of corresponding alcohol **17c** with/without addition of ZnI₂ (entries 6 and 7), whereas phenylcopper reagents showed poor conversion of picolinate **7a** (entries 8 and 9). PhMgBr and Cu(acac)₂ in a 3:1 ratio generated S_N2 product **20c** as the major product, whereas addition of ZnI₂ improved regioselectivity even though picolinate **7a** remained (entries 10 and 11). Attempts trying different quantities of ZnI₂ were unsuccessful (entries 12 and 13). However, acceptable result was obtained by carrying outh the reaction for longer time (12 h) and S_N2' product **9c** was furnished with 92% regioselectivity in 81% isolated yield (entry 14). However, allylic substitution of picoliant **7b** resulted in lower regioselectivity, demonstrating bigger steric hindrance of *p*MeC₆H₄ group (entry 15). As a result, allylic substitution of primary exocyclic picolinate **7** with alkylcopper reagents generate S_N2' products with high regioselectivity while with arylcopper reagents unsatisfactory regioselectivity was obtained.

Next, secondary piclinate **8a** (Ar = Ph) was applied for further investigation. As illustrated in **Table 3.2**, good conditions for allylic substitution of **7a** (**Table 3.1**, entries 1 and 3) still worked well for substrate **8a** and S_N2' products **10a** (R = Me, Ar = Ph) and **10b** (R = Bu, Ar = Ph) were obtained as *Z* and *E* (ca. 1:1) isomeric mixtures with high regioselectivity in good yields respectively (**Table 3.2**, entries 1 and 2). In addition, stereochemistry of **10a** was determined by NOE analysis (**Figure 3.2**) and was assigned to the others. Moreover, PhLi and CuBr·Me₂S in a

1:1 ratio in the presence of MgBr_2 generated $\text{S}_{\text{N}}2'$ product **10c** ($\text{R} = \text{Ph}$, $\text{Ar} = \text{Ph}$) with 94% regioselectivity in 85% yield (entry 3), implying higher activity of secondary picolinate **8a** than **7a**. Phenylcopper reagent derived from PhMgBr and $\text{CuBr}\cdot\text{Me}_2\text{S}$ in a 1:1 ratio afforded **10c** with 95% regioselectivity in 80% yield as well (entry 4). Then, picolinate **8b** ($\text{Ar} = \text{ptolyl}$) was subjected to conditions of entry 3, furnishing **10d** ($\text{R} = \text{Ph}$, $\text{Ar} = \text{ptolyl}$) with 98% regioselectivity in 79% yield (entry 5), demonstrating generality of the above conditions. Attempt by lithiation of $p\text{MeC}_6\text{H}_4\text{Br}$ with BuLi ⁷ generated unidentified products perhaps due to uncompleted lithiation (entry 6), whereas ptolylmagnesium bromide and $\text{CuBr}\cdot\text{Me}_2\text{S}$ or $\text{Cu}(\text{acac})_2$ in a 1:1 or 2:1 ratio afforded $\text{S}_{\text{N}}2'$ product **10e** ($\text{R} = \text{ptolyl}$, $\text{Ar} = \text{ptolyl}$) with high regioselectivity in good yields (entries 7 and 8). Stereic hindered group otolyl group was also transferred to synthesize $\text{S}_{\text{N}}2'$ product **10f** ($\text{R} = \text{otolyl}$, $\text{Ar} = \text{ptolyl}$) with 93% regioselectivity in 85% yield (entry 9). Allylic substitution of picolines **8c** ($\text{Ar} = p\text{MeOC}_6\text{H}_4$) and **8d** ($\text{Ar} = p\text{FC}_6\text{H}_4$) with PhLi and $\text{CuBr}\cdot\text{Me}_2\text{S}$ in a 1:1 ratio generated $\text{S}_{\text{N}}2'$ products **10g** ($\text{R} = \text{Ph}$, $\text{Ar} = p\text{MeOC}_6\text{H}_4$) and **10h** ($\text{R} = \text{Ph}$, $\text{Ar} = p\text{FC}_6\text{H}_4$) with 97% and 96% regioselectivity in good yields respectively (entries 10 and 11).

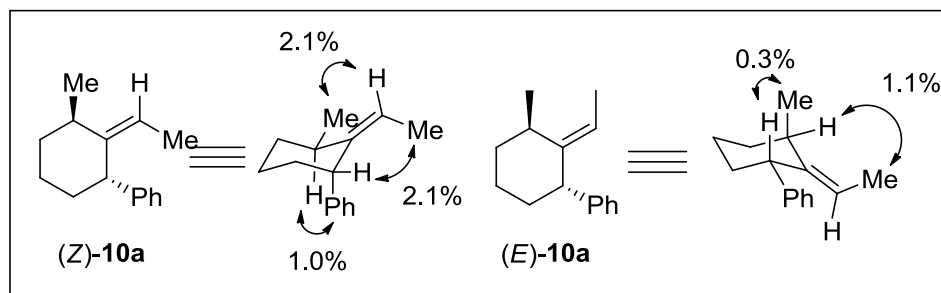


Figure 3.2 NOE Analysis of 10a

Table 3.2 Allylic Substitution of Picolinates 8a-d

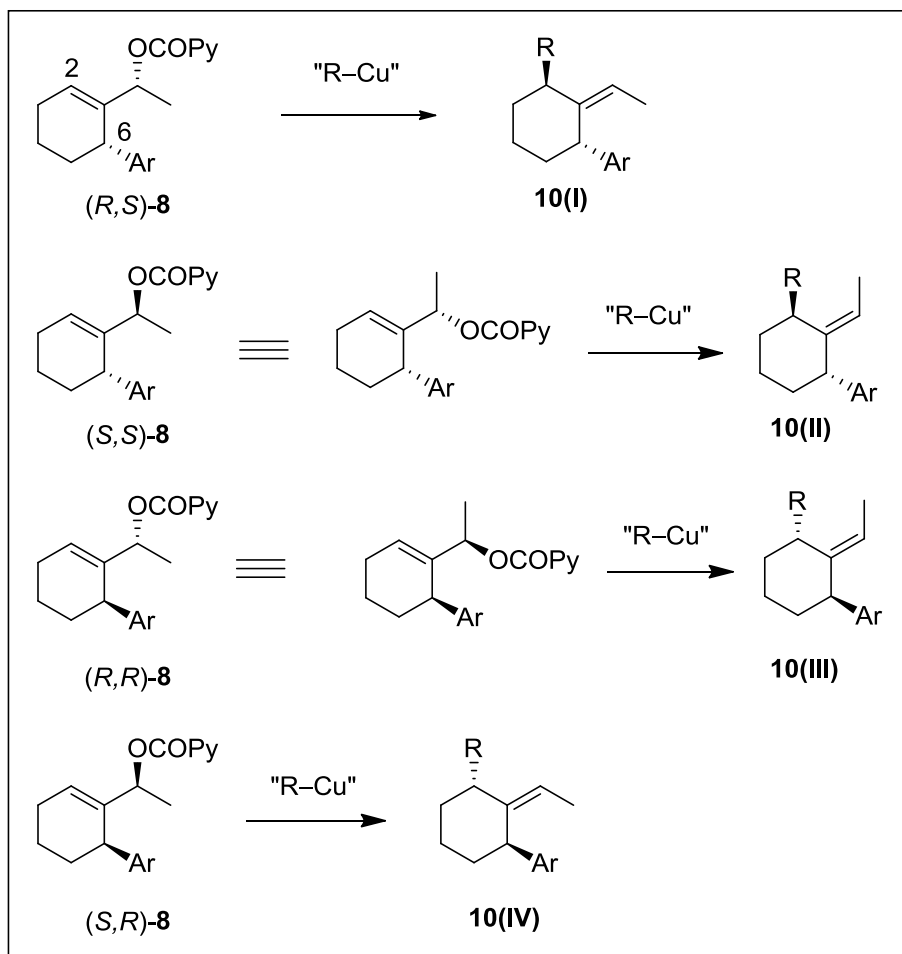
Reaction scheme: Substrate **8** (cyclohexene with OCOPy and Ar) reacts under conditions in THF at 0 °C for 1–2 h to yield products **10** and **21**.

Entry	Substrate	RLi/RMgBr (equiv)	CuBr·Me ₂ S (equiv)	MgBr ₂ (equiv)	Prod.	10:21 ^a	Isolated yield ^b (%)
1	8a , Ar = Ph	MeLi (2.7)	3.0	3.0	10a	97:3	81
2	8a	BuLi (2.7)	3.0	3.0	10b	>98:2	85
3	8a	PhLi (2.7)	3.0	3.0	10c	94:6	83
4	8a	PhMgBr (1.5)	1.5	—	10c	95:5	80
5	8b , Ar = <i>p</i> tolyl	PhLi (2.7)	3.0	3.0	10d	98:2	80
6 ^c	8b	<i>p</i> MeC ₆ H ₄ Br (3.0), BuLi (2.7)	3.0	3.0	—	— ^d	— ^d
7	8b	<i>p</i> MeC ₆ H ₄ MgBr (1.5)	1.5	—	10e	99:1	92
8	8b	<i>p</i> MeC ₆ H ₄ MgBr (3.0)	1.5 ^e	—	10e	99:1	82
9	8b	<i>o</i> MeC ₆ H ₄ MgBr (1.5)	1.5	—	10f	93:7	67
10	8c , Ar = <i>p</i> MeOC ₆ H ₄	PhLi (2.7)	3.0	3.0	10g	97:3	78
11	8d , Ar = <i>p</i> FC ₆ H ₄	PhLi (2.7)	3.0	3.0	10h	96:4	83

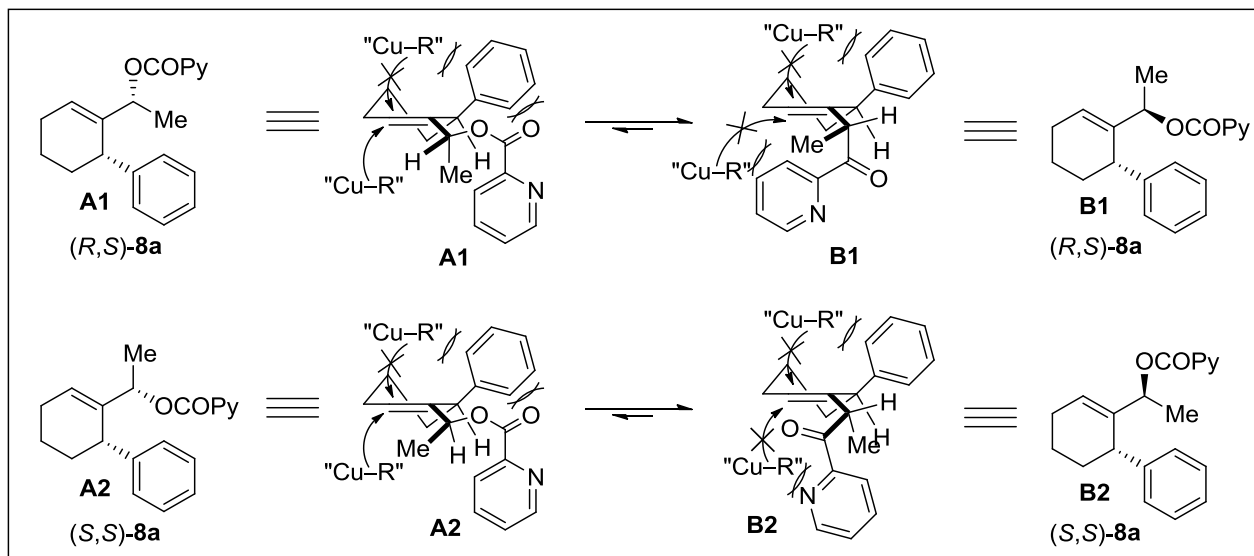
^aDetermined by ¹H NMR. ^bCombined yield of **10** and **21**. ^c*p*MeC₆H₄Br was treated by BuLi for 30 min at 0 °C. ^dUnidentified products. ^eCu(acac)₂ was used.

Apparently, the geometry of the olefin as well as stereochemistry of S_N2' products **10** are controlled by two effects: (1) *anti*-S_N2' pathway of allylic substitution of allylic picolinates; (2) antiparallel attack of nucleophiles (nucleophiles attack from the *trans* side of Ar group at the 6 position of the 6-membered ring) (Scheme 3.6). In detail, the geometry of the olefin of **10** is controlled by the absolute configuration of OCOPy leaving group and the stereochemistry (antiparallel attack) of allylic substitution of nucleophiles is controlled by absolute configuration

of Ar group at 6 position of the 6-membered ring. For example, as shown in **Scheme 3.7**, even conformation **B** of (*R,S*)-**8a** or (*S,S*)-**8a** is favored over conformation **A** due to steric hindrance between Ph and OCOPy groups. However, both sides of conformation **B** are blocked by Ph or OCOPy groups, as a result, organocopper reagents react with (*R,S*)-**8a** or (*S,S*)-**8a** as conformation **A**, generating **10(I)** or **10(II)** (Ar = Ph) shown in **Scheme 3.6**. It is worth noting that most of the S_N2' products **10**, except **10f** (R = *o*-tolyl, Ar = *p*-tolyl), were generated as a ca. 1:1 mixture of *E* and *Z* olefin. However, **10f** was generated with *E* olefin as the major product (*E*:*Z* = 4 : 1), demonstrating steric hindrance between “*o*-tolyl-Cu” and Me group of **A2**, which does not exist in **A1**. In addition, RLi or RMgBr (R = Bu or Ph) and CuBr·Me₂S in a 2:1 ratio in the absence of ZnI₂ lost regioselectivity when performing allylic substitution of both picolines **7a** and **8a** (data not shown).



Scheme 3.6 Allylic Substitution of Picolines **8**



Scheme 3.7 Mechanism of Allylic Substitution of (S,S)-8a

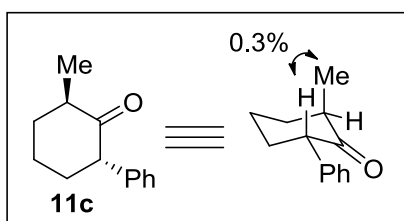


Figure 3.3 NOE Analysis of 11c

Subsequently, S_N2' products **10a–h** were transferred to 2,6-*trans*-disubstituted cyclohexanones **11a–h** by ozonolysis in 72–92% yields (**Table 3.3**). The *trans* configuration of **11a** and **11c** was determined by NOE analysis (**Figure 3.3**) as well as comparing ^1H NMR with that reported⁴ respectively and was assigned to the others. Additionally, **9a** and **9b** were transferred to **11a** and **11b** by ozonolysis as above and *trans*:*cis* = >98:2.

Reaction scheme showing the synthesis of cyclohexanone derivatives **11** from cyclohexenyl derivatives **10** using O_3 , Me_2S , and CH_2Cl_2 at -78°C for 30 min.

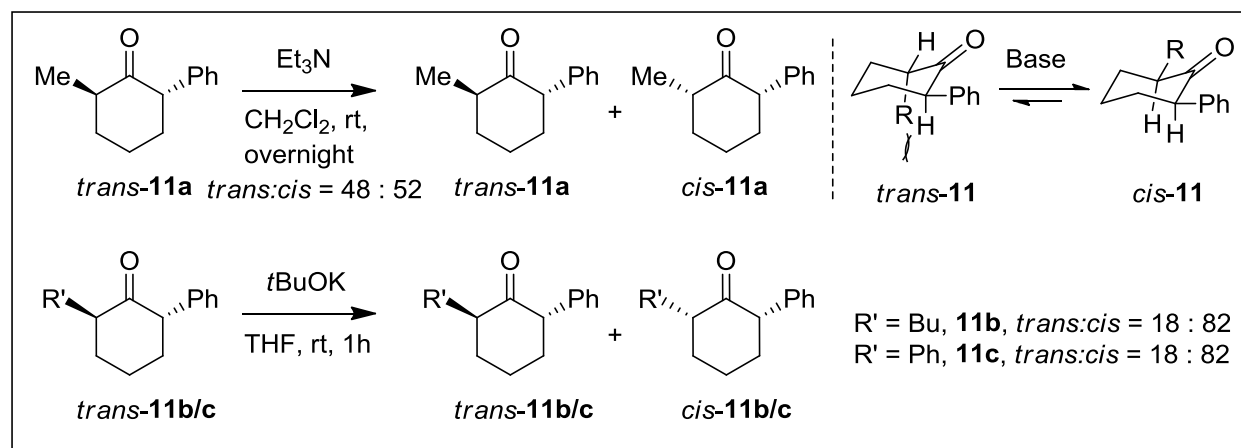
General reaction:

10 (Cyclohexenyl derivative with R and Ar substituents) $\xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 30 \text{ min}]{\text{O}_3, \text{Me}_2\text{S}}$ **11** (Cyclohexanone derivative with R and Ar substituents)

Specific examples of products **11**:

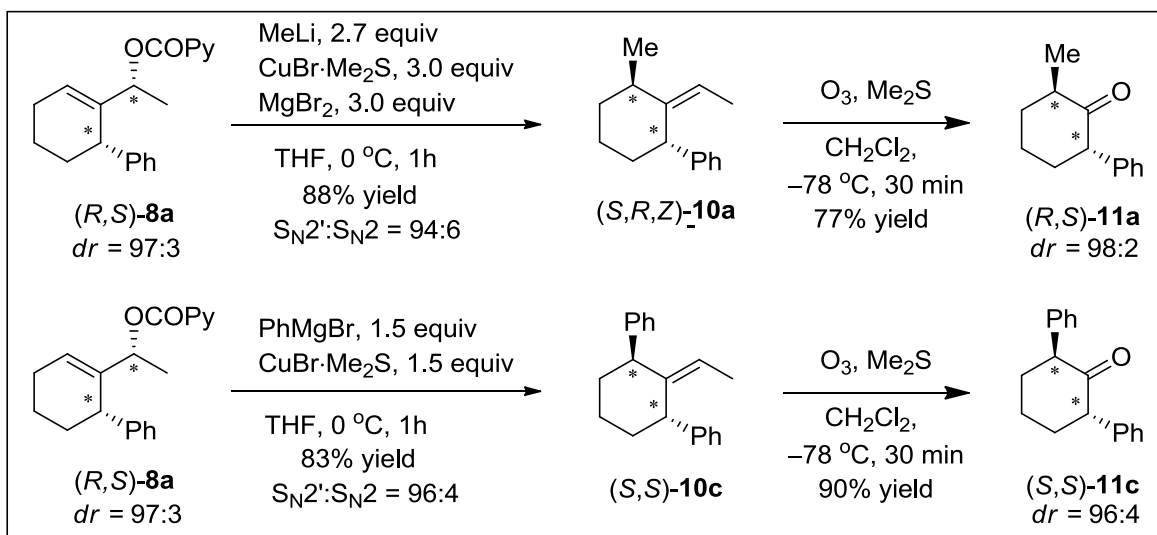
- 11a**: 87% yield^a, *trans*:*cis* = >98:2^b
- 11b**: 86% yield, *trans*:*cis* = 97:3
- 11c**: 79% yield, *trans*:*cis* = >99:1
- 11d**: 82% yield, *trans*:*cis* = 99:1
- 11e**: 72% yield, *trans*:*cis* = >98:2
- 11f**: 85% yield, *trans*:*cis* = >98:2
- 11g**: 88% yield, *trans*:*cis* = >98:2
- 11h**: 83% yield, *trans*:*cis* = >98:2

In addition, *trans*-**11** can be easily transformed to a mixture of *trans*- and *cis*-**11**. For example, *trans*-**11a** was only treated by Et₃N at rt overnight, isomerization took place and a mixture of *trans*- and *cis*-**11a** (*trans*:*cis* = 48:52) was formed (**Scheme 3.8**).



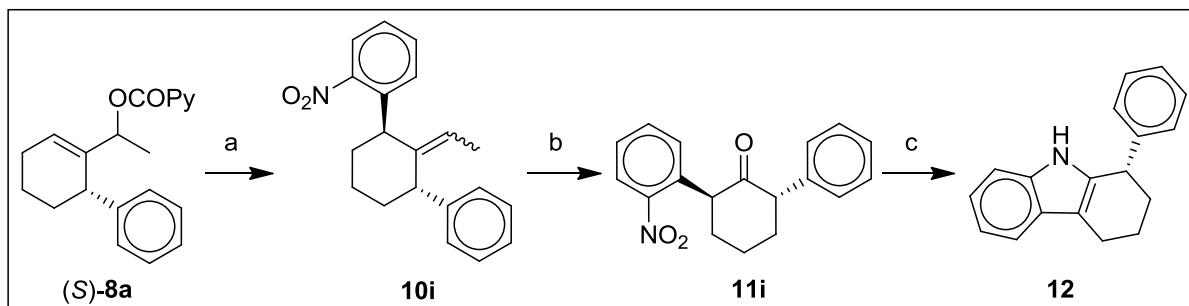
Next, single isomer (*R,S*)-**8a** (*dr* was determined by ¹H NMR) was synthesized by employing CBS reduction (**Scheme 3.5**). According to **Scheme 3.6**, only one single isomer will be

generated. Experimentally (**Scheme 3.9**), allylic substitution of (*R,S*)-**8a** with methyl- and phenylcopper reagents generated from MeLi/PhLi and CuBr·Me₂S in a 1:1 ratio afforded (*S,R,Z*)-**10a** and (*S,S*)-**10c** respectively. Following ozonolysis synthesized corresponding 2,6-*trans*-disubstituted cyclohexanones (*R,S*)-**11a** and (*S,S*)-**11c** (*dr* was determined by chiral HPLC) in completed chirality transfer.



Scheme 3.9 Synthesis of Single Isomer (*R,S*)-**11a** and (*S,S*)-**11c**

Since ozonolysis cleavages C=C bond of the olefin **10**, and the geometry of the olefin is controlled by absolute configuration of OCOPy leaving group, it is not necessary to install the optically active OCOPy leaving group. As an application (**Scheme 3.10**), synthesis of enantioenriched indole **12** is being investigated starting from (*S*)-**8a**, which contains racemic OCOPy leaving group. Briefly, Allylic substitution of picolinate (*S*)-**8a** with organocopper reagent derived from (2-nitrophenyl)magnesium bromide⁸ and CuBr·Me₂S in a 1:1 ratio is supposed to generate **10i**, which can be transferred to **11i** through ozonolysis. Reduction of **11i** by TiCl₃ can generate chiral indole **12** in good yield.^{5d}



Scheme 3.10 Supposed Synthesis of Chiral Indole 12

Reagents: a, (2-Nitrophenyl)magnesium Bromide and $\text{CuBr} \cdot \text{Me}_2\text{S}$; b, O_3 , Me_2S ; c, TiCl_3

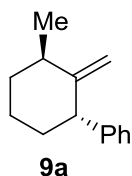
3.3 Conclusion

In conclusion, 2,6-*trans*-disubstituted cyclohexanones were synthesized by allylic substitution of exocyclic picolates and ozonolysis with high regioselectivity as well as good yields. Both alkyl and aryl groups were successfully installed to the cyclohexane ring in an antiparallel substitution manner. The geometry of the olefin as well as stereochemistry of S_N2' products are found to be controlled by two effects: (1) *anti*-S_N2' pathway of allylic substitution of allylic picolates; (2) antiparallel attack of nucleophiles.

3.4 Experimental Section

General Remarks. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were measured in CDCl_3 using SiMe_4 ($\delta = 0$ ppm) and the centerline of triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). Chemical shifts in the ^{13}C NMR spectra accompany minus (for C and CH_2) and plus (for CH and CH_3) signs of APT experiments. The following solvents were distilled beforehand: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions were finished, the organic extracts were concentrated by using evaporators and the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60 N).

Generally Procedure for Allylation:



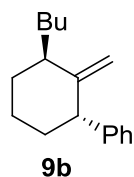
(trans-3-Methyl-2-methylenecyclohexyl)benzene (9a). Allylation with $\text{CuBr}\cdot\text{Me}_2\text{S}$ and MeLi : (**Table 3.1, entry 1**): To an ice-cold suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (52.7 mg, 0.256 mmol) in THF (1 mL) was added methyllithium (0.18 mL, 1.14 M in diethyl ether, 0.21 mmol) slowly. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 10 min, and then MgBr_2 (1.28 mL, 0.20 M in THF, 0.26 mmol) was added before a solution of picolinate **7a** (24.5 mg, 0.0835 mmol) in THF (1 mL) was added dropwise. After being stirring at $0\text{ }^\circ\text{C}$ for 1 h, the resulting mixture was diluted by saturated NH_4Cl and extracted with hexane twice. The combined extracts were dried over MgSO_4 , concentrated, and passed through chromatography on silica gel to furnish **9a** (15.0 mg, 96% yield).

Allylation with $\text{CuBr}\cdot\text{Me}_2\text{S}$ and MeMgBr (**Table 3.1, entry 2**): To an ice-cold suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (25.9 mg, 0.126 mmol) in THF (1 mL) was added methylmagnesium bromide (0.14 mL, 0.97 M in THF, 0.136 mmol) slowly. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 10 min,

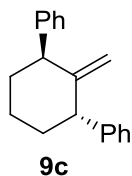
and then a solution of picolinate **7a** (25.0 mg, 0.0852 mmol) in THF (1 mL) was added dropwise. After being stirring at 0 °C for 1 h, the resulting mixture was diluted by saturated NH₄Cl and extracted with hexane twice. The combined extracts were dried over MgSO₄, concentrated, and passed through chromatography on silica gel to furnish **9a** (14.1 mg, 89% yield).

Product **9a**: ¹H NMR (300 MHz, CDCl₃): δ = 1.12 (d, J = 7 Hz, 3 H), 1.30–1.44 (m, 1 H), 1.58–1.79 (m, 3 H), 1.79–1.92 (m, 1 H), 2.06–2.20 (m, 1 H), 2.30–2.43 (m, 1 H), 3.60 (dd, J = 7, 5 Hz, 1 H), 4.45 (d, J = 1 Hz, 1 H), 4.81 (s, 1 H), 7.13–7.23 (m, 2 H), 7.23–7.36 (m, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 19.2, 21.7, 32.6, 35.8, 36.2, 46.8, 108.0, 125.9, 128.1, 128.2, 143.3, 156.3 ppm.

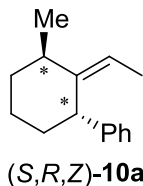
Allylation Products:



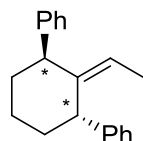
((1R,3R)-3-Butyl-2-methylenecyclohexyl)benzene (9b) (Table 3.1, entry 3): According to the general procedure, to a suspension of CuBr·Me₂S (52.8 mg, 0.26 mmol), butyllithium (0.15 mL, 1.64 M in hexane, 0.25 mmol), and MgBr₂ (1.28 mL, 0.20 M in THF, 0.26 mmol) in THF (1 mL) was added picolinate **7a** (25.0 mg, 0.0852 mmol) in THF (1 mL) at 0 °C dropwise. Then the reaction mixture was stirred at 0 °C for 1 h to afford **9b** (15.9 mg, 82% yield): ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (t, J = 7 Hz, 3 H), 1.09–1.46 (m, 6 H), 1.56–1.81 (m, 4 H), 1.85–1.96 (m, 2 H), 2.27–2.35 (m, 1 H), 3.42 (dd, J = 9, 5.5 Hz, 1 H), 4.14 (br s, 1 H), 4.71 (br s, 1 H), 7.14–7.24 (m, 3 H), 7.26–7.34 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (+), 21.9 (–), 22.9 (–), 30.0 (–), 32.0 (–), 33.2 (–), 33.7 (–), 43.5 (+), 46.2 (+), 108.8 (–), 126.0 (+), 128.2 (+), 128.5 (+), 143.6 (–), 155.6 (–) ppm. HRMS (EI) calcd for C₁₇H₂₄ (M⁺) 228.1878, found 228.1881.



(*trans*-2-Methylenecyclohexane-1,3-diyl)dibenzene (9c) (Table 3.1, Entry 14): To an ice-cold suspension of Cu(acac)₂ (33.9 mg, 0.130 mmol) and anhydrous ZnI₂ (40.2 mg, 0.126 mmol) in THF (1 mL) was added phenylmagnesium bromide (0.46 mL, 0.85 M in THF, 0.391 mmol) slowly. The reaction mixture was stirred at 0 °C for 1 h, and then the mixture was cooled to –40 °C. A solution of picolinate **7a** (24.9 mg, 0.0849 mmol) in THF (1 mL) was added dropwise to the mixture, which was allowed to be warmed to 0 °C slowly. After being stirring at 0 °C overnight, the resulting mixture was diluted with saturated NH₄Cl and extracted with hexane twice. The combined extracts were dried over MgSO₄ and concentrated. The residue was passed through a column of silica gel to furnish **9c** (17.1 mg, 81% yield): ¹H NMR (300 MHz, CDCl₃): δ = 1.75 (dt, *J* = 12, 6 Hz, 2 H), 1.86–2.00 (m, 2 H), 2.16–2.30 (m, 2 H), 3.55 (dd, *J* = 7, 4.5 Hz, 2 H), 4.61 (s, 2 H), 7.12–7.26 (m, 4 H), 7.26–7.40 (m, 6 H) ppm.

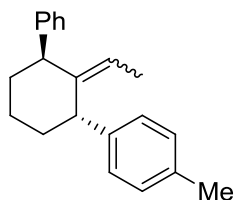


((1*S*,3*R,Z*)-2-Ethylidene-3-methylcyclohexyl)benzene ((*S,R,Z*)-10a) (Scheme 3.9): According to the general procedure, to a suspension of CuBr·Me₂S (50.4 mg, 0.245 mmol), methyllithium (0.19 mL, 1.14 M in diethyl ethyl, 0.22 mmol), and MgBr₂ (1.23 mL, 0.20 M in THF, 0.25 mmol) in THF (1 mL) was added picolinate (*R,S*)-**8a** (*dr* = 97:3) (25.5 mg, 0.0830 mmol) in THF (1 mL) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 1 h to afford (*S,R,Z*)-**10a** (14.6 mg, 88% yield): ¹H NMR (400 MHz, CDCl₃): δ = 1.00 (d, *J* = 7 Hz, 3 H), 1.50–1.74 (m, 5 H), 1.69 (dd, *J* = 6.5, 2 Hz, 3 H), 1.97–2.10 (m, 1 H), 2.46 (dm, *J* = 13 Hz, 1 H), 4.08–4.16 (m, 1 H), 5.45 (dq, *J* = 1.5, 7 Hz, 1 H), 7.14–7.21 (m, 1 H), 7.24–7.34 (m, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 13.0, 18.8, 21.9, 30.0, 33.9, 37.5, 39.5, 115.4, 125.4, 127.5, 128.4, 143.0, 145.5 ppm. HRMS (EI) calcd for C₁₅H₂₀ (M⁺) 200.1565, found 200.1562.



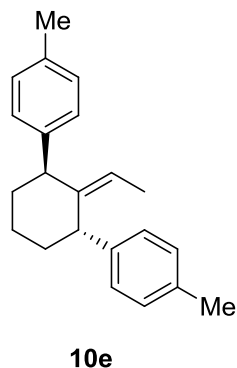
(*S,S*)-**10c**

((1*S*,3*S*)-2-Ethylidenecyclohexane-1,3-diyl)dibenzene ((*S,S*)-10c**) (Scheme 3.9):** According to the general procedure, to a suspension of CuBr·Me₂S (30.2 mg, 0.150 mmol), methylmagnesium bromide (0.16 mL, 0.94 M in THF, 0.15 mmol) was added picolinate (*R,S*)-**8a** (*dr* = 97:3) (30.2 mg, 0.0982 mmol) in THF (1 mL) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 1 h to afford (*S,S*)-**10c** (21.2 mg, 83% yield): ¹H NMR (300 MHz, CDCl₃): δ = 1.56 (dd, *J* = 7, 2 Hz, 3 H), 1.64–1.96 (m, 5 H), 2.58 (dm, *J* = 14 Hz, 1 H), 3.18–3.36 (m, 1 H), 4.14–4.28 (m, 1 H), 4.80 (dq, *J* = 2, 7 Hz, 1 H), 7.06–7.50 (m, 10 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 13.0 (+), 22.1 (–), 29.8 (–), 34.3 (–), 39.6 (+), 46.9 (+), 120.1 (+), 125.7 (+), 126.1 (+), 127.5 (+), 128.2 (+), 128.6 (+), 128.9 (+), 142.5 (–), 143.9 (–), 145.2 (–) ppm. HRMS (EI) calcd for C₂₀H₂₂ (M⁺) 262.1722, found 262.1721.



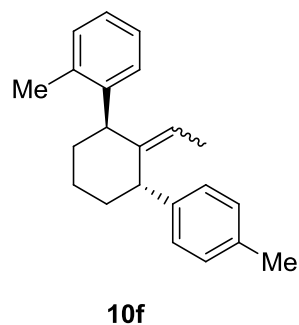
10d

1-(*trans*-2-Ethylidene-3-phenylcyclohexyl)-4-methylbenzene (10d) (Table 3.2, Entry 5): According to the general procedure, to a suspension of CuBr·Me₂S (59.0 mg, 0.287 mmol), phenyllithium (0.24 mL, 1.07 M in cyclohexane and diethyl ethyl, 0.26 mmol), and MgBr₂ (1.42 mL, 0.20 M in THF, 0.28 mmol) in THF (1 mL) was added picolinate **8b** (30.4 mg, 0.0946 mmol) in THF (1 mL) at 0 °C dropwise. The reaction was carried out at 0 °C for 1 h to afford **10d** (21.0 mg, 80% yield) as a 1:1 olefin mixture: ¹H NMR (400 MHz, CDCl₃): δ = 1.22–1.37 (m, 1 H), 1.56 (dd, *J* = 7, 2.5 Hz, 1 H), 1.64–1.90 (m, 3 H), 2.34 (s, 1.5 H), 2.36 (s, 1.5 H), 2.51–2.62 (m, 1 H), 3.18–3.31 (m, 1 H), 4.12–4.22 (m, 1 H), 4.77 (dq, *J* = 2, 7 Hz, 0.5 H), 4.82 (dq, *J* = 2, 7 Hz, 0.5 H), 7.00–7.40 (m, 9 H) ppm. HRMS (EI) calcd for C₂₁H₂₄ (M⁺) 276.1878, found 276.1881.



4,4'-(*trans*-2-Ethylidenecyclohexane-1,3-diyl)bis(methylbenzene) (10 e) (Table 3.2, Entry 7):

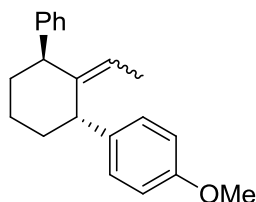
According to the general procedure, to a suspension of CuBr·Me₂S (29.0 mg, 0.141 mmol) and *p*-tolylmagnesium bromide (0.15 mL, 0.91 M in THF, 0.14 mmol) was added picolinate **8b** (30.1 mg, 0.0936 mmol) in THF (1 mL) at 0 °C dropwise. The reaction was carried out at 0 °C for 1 h to afford **10e** (25.1 mg, 92% yield): ¹H NMR (400 MHz, CDCl₃): δ = 1.51–1.59 (m, 3 H), 1.64–1.87 (m, 5 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.55 (d, *J* = 13 Hz, 1 H), 3.23 (dm, 12 Hz, 1 H), 4.14 (s, 1 H), 4.80 (dq, *J* = 2, 7 Hz, 1 H), 7.04 (d, *J* = 8 Hz, 2 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 7.18 (d, *J* = 8 Hz, 2 H), 7.26 (d, *J* = 7.5 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.0, 22.1, 29.9, 34.5, 39.2, 46.5, 119.8, 127.4, 128.8, 128.9, 129.3, 135.1, 135.5, 139.4, 140.9, 145.3 ppm.



1-(*trans*-2-Ethylidene-3-(*p*-tolyl)cyclohexyl)-2-methylbenzene (10f) (Table 3.2, Entry 9):

According to the general procedure, to a suspension of CuBr·Me₂S (28.5 mg, 0.139 mmol) and *o*-tolylmagnesium bromide (0.15 mL, 0.93 M in THF, 0.14 mmol) was added picolinate **8b** (30.5 mg, 0.0949 mmol) in THF (1 mL) at 0 °C dropwise. The reaction was carried out at 0 °C for 1 h to afford **10f** (18.5 mg, 67% yield) as a 4:1 olefin mixture: ¹H NMR (400 MHz, CDCl₃): δ = 1.58 (dd, *J* = 7, 1.5 Hz, 3 H), 1.64–2.02 (m, 5 H), 2.06 (s, 2.4 H), 2.08 (s, 0.6 H), 2.35 (s, 2.4 H), 2.38 (s, 0.6 H), 2.50–2.62 (m, 1 H), 3.31 (d, *J* = 10 Hz, 0.8 H), 3.73 (d, *J* = 10 Hz, 0.2 H), 4.09 (t, *J* =

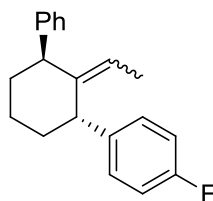
6 Hz, 0.2 H), 4.18 (s, 0.8 H), 4.68 (dq, $J = 1.5, 6.5$ Hz, 0.8 H), 4.83 (dq, $J = 1.5, 6.5$ Hz, 0.2 H), 7.00–7.38 (m, 8 H) ppm.



10g

1-(*trans*-2-Ethylidene-3-phenylcyclohexyl)-4-methoxybenzene (10g) (Table 3.2, Entry 10):

According to the general procedure, to a suspension of CuBr·Me₂S (61.9 mg, 0.301 mmol), phenyllithium (0.25 mL, 1.07 M in cyclohexane and diethyl ethyl, 0.27 mmol), and MgBr₂ (1.47 mL, 0.20 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **8c** (33.7 mg, 0.0999 mmol) in THF (1 mL) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 1 h to afford **10g** (22.8 mg, 78% yield) as a 3:2 olefin mixture: ¹H NMR (400 MHz, CDCl₃): δ = 1.54–1.59 (m, 3 H), 1.64–1.92 (m, 5 H), 2.48–2.62 (m, 1 H), 3.17–3.30 (m, 1 H), 3.81 (s, 1.2 H), 3.83 (s, 1.8 H), 4.10–4.15 (m, 0.6 H), 4.15–4.20 (m, 0.4 H), 4.77 (dq, $J = 2, 7$ Hz, 0.6 H), 4.82 (dq, $J = 2, 7$ Hz, 0.4 H), 6.84–6.95 (m, 2 H), 7.04–7.17 (m, 2 H), 7.18–7.40 (m, 5 H) ppm. HRMS (EI) calcd for C₂₁H₂₄O (M⁺) 292.1827, found 292.1833.



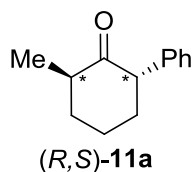
10h

1-(*trans*-2-Ethylidene-3-phenylcyclohexyl)-4-fluorobenzene (10 h) (Table 3.2, Entry 11):

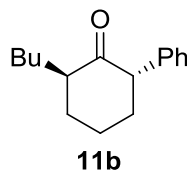
According to the general procedure, to a suspension of CuBr·Me₂S (113.9 mg, 0.554 mmol), phenyllithium (0.47 mL, 1.07 M in cyclohexane and diethyl ethyl, 0.50 mmol), and MgBr₂ (2.77 mL, 0.20 M in THF, 0.55 mmol) in THF (2 mL) was added picolinate **8c** (60.2 mg, 0.185 mmol) in THF (1 mL) at 0 °C dropwise. The reaction was carried out at 0 °C for 1 h to afford **10g** (43.0 mg, 83% yield) as a 1:1 olefin mixture: ¹H NMR (400 MHz, CDCl₃): δ = 1.48–1.60 (m, 3 H), 1.60–1.98 (m, 5 H), 2.43–2.62 (m, 1 H), 3.10–3.35 (m, 1 H), 4.03–4.16 (m, 0.5 H), 4.16–4.29 (m,

0.5 H), 4.65–4.83 (m, 1 H), 6.85–7.40 (m, 9 H) ppm. HRMS (EI) calcd for C₂₀H₂₁F (M⁺) 280.1627, found 280.1622.

2,6-*trans*-Disubstituted Cyclohexanone

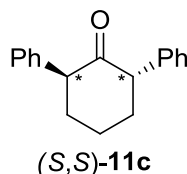


(2*R*,6*S*)-2-Methyl-6-phenylcyclohexanone ((*R,S*)-11a) (Scheme 3.9): General procedure of ozonolysis: To a solution of (*S,R,Z*)-**10a** (12.5 mg, 0.0664 mmol) in CH₂Cl₂ (2 mL) was bubbled O₃ at –78 °C until the solution changed to pale blue (30 min). Argon was bubbled into the solution for 5 min, and Me₂S (0.50 mL, 6.8 mmol) was added. After being stirred at –78 °C for 30 min, the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The solution was washed with brine, dried over MgSO₄ and concentrated to afford a residue, which was purified by chromatography on silica gel to furnish (*R,S*)-**11a** (9.0 mg, 77% yield): ¹H NMR (400 MHz, CDCl₃): δ = 1.11 (d, *J* = 7 Hz, 3 H), 1.55–1.66 (m, 1 H), 1.78–1.98 (m, 2 H), 1.98–2.07 (m, 1 H), 2.07–2.18 (m, 1 H), 2.36–2.46 (m, 1 H), 2.52–2.63 (m, 1 H), 3.80 (t, *J* = 6.5 Hz, 1 H), 7.18–7.28 (m, 3 H), 7.30–7.37 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 15.7 (+), 21.1 (–), 32.0 (–), 35.4 (–), 43.2 (+), 54.0 (+), 126.8 (+), 127.7 (+), 128.7 (+), 138.5 (–), 214.1 (–) ppm. The enantiomeric ratio (98:2) was determined by chiral HPLC analysis: Chiralcel IC, hexane/*i*PrOH = 99/1, 1.0 mL/min, 26 °C, *t*_R/min = 19.4 and 20.0, (2*S*,6*S*-isomer and 2*R*,6*R*-isomer), 24.7 (2*R*,6*S*-isomer), 25.7 (2*S*,6*R*-isomer).

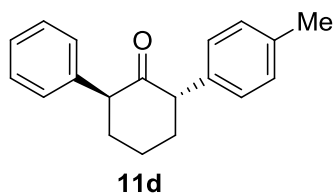


***trans*-2-Butyl-6-phenylcyclohexanone (11b) (Table 3.3):** (14.2 mg, 86%). ¹H NMR (300 MHz, CDCl₃): δ = 0.88 (t, *J* = 7 Hz, 3 H), 1.13–1.49 (m, 5 H), 1.67–1.72 (m, 4 H), 1.72–2.06 (m, 1 H), 2.09–2.34 (m, 2 H), 2.40–2.52 (m, 1 H), 3.77 (dd, *J* = 8.5, 6 Hz, 1 H), 7.10–7.39 (m, 5 H) ppm.

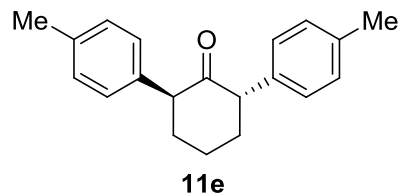
^{13}C NMR (100 MHz, CDCl_3): δ = 14.0 (+), 21.2 (–), 22.7 (–), 29.5 (–), 30.3 (–), 33.0 (–), 33.1(–), 49.4 (+), 54.2 (+), 126.8 (+), 128.0 (+), 128.6 (+), 138.7 (–), 213.5 (–) ppm.



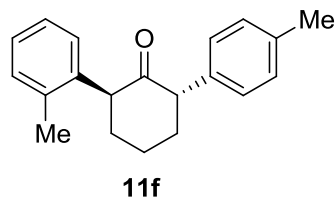
((1*S*,6*S*)-2-Methylenecyclohexane-1,3-diyl)dibenzene ((*S,S*)-11c**) (Scheme 3.9):** (18.3 mg, 90% yield). ^1H NMR (400 MHz, CDCl_3): δ = 2.01 (dt, J = 12, 6 Hz, 2 H), 2.18–2.28 (m, 2 H), 2.37–2.49 (m, 2 H), 3.83 (dd, J = 7.5, 5.5 Hz, 2 H), 7.18–7.23 (m, 4 H), 7.24–7.30 (m, 2 H), 7.32–7.39 (m, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 21.7 (–), 32.8 (–), 54.5 (+), 127.0 (+), 127.9 (+), 128.7 (+), 138.2 (–), 210.7 (–) ppm. The er (96:4) and dr (>98:2) were determined by chiral HPLC analysis: Chiralcel IC, hexane/*i*PrOH = 99/1, 1.0 mL/min, 28 °C, t_R /min = 7.3 (2*R*,6*S*-isomer), 23.4 (2*R*,6*R*-isomer), 25.3 (2*S*,6*S*-isomer).



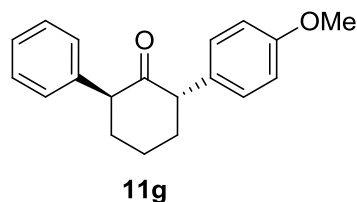
***trans*-2-Phenyl-6-(*p*-tolyl)cyclohexanone (**11d**):** (14.1 mg, 82% yield). ^1H NMR (400 MHz, CDCl_3): δ = 1.99 (dt, J = 12, 6 Hz, 2 H), 2.15–2.27 (m, 2 H), 2.34 (s, 3 H), 2.36–2.47 (m, 2 H), 3.79 (dd, J = 7.5, 5.5 Hz, 1 H), 3.83 (dd, J = 8, 5.5 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 7.14–7.22 (m, 4 H), 7.23–7.30 (m, 1 H), 7.32–7.40 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 21.1, 21.7, 32.8, 32.9, 54.0, 54.3, 127.0, 127.7, 127.9, 128.7, 129.5, 135.1, 136.6, 138.2, 211.1 ppm. HRMS (EI) calcd for $\text{C}_{19}\text{H}_{20}\text{O}$ (M^+) 264.1514, found 264.1513.



***trans*-2,6-di-*p*-Tolylcyclohexanone (11e):** (31.6 mg, 72%). ^1H NMR (400 MHz, CDCl_3): δ = 1.98 (dt, J = 12, 6 Hz, 2 H), 2.14–2.24 (m, 2 H), 2.29–2.46 (m, 2 H), 2.34 (s, 3 H), 3.79 (dd, J = 7, 5.5 Hz, 2 H), 7.08 (d, J = 8 Hz, 4 H), 7.16 (d, J = 8 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 21.1 (+), 21.7 (–), 32.9 (–), 53.9 (+), 127.7 (+), 129.4 (+), 135.1 (–), 136.5 (–), 211.3 (–) ppm. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{O}$ (M^+) 278.1671, found 278.1671.

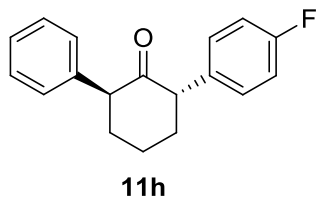


***trans*-2-(*o*-Tolyl)-6-(*p*-tolyl)cyclohexanone (11f):** (19.2 mg, 85%). ^1H NMR (400 MHz, CDCl_3): δ = 1.92–2.40 (m, 5 H), 1.97 (s, 3 H), 2.35 (s, 3 H), 2.64 (d, J = 14.5 Hz, 1 H), 3.83–3.94 (m, 2 H), 7.08–7.26 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 19.7 (+), 21.1 (+), 22.2 (–), 30.6 (–), 34.1 (–), 50.6 (+), 54.3 (+), 126.0 (+), 126.9 (+), 127.2 (+), 127.6 (+), 129.6 (+), 130.4 (+), 134.6 (–), 136.58 (–), 136.61 (–), 137.2 (–), 210.6 (–) ppm. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{22}\text{O}$ (M^+) 278.1671, found 278.1671.



***trans*-2-(4-Methoxyphenyl)-6-phenylcyclohexanone (11g):** (19.3 mg, 88% yield). ^1H NMR (400 MHz, CDCl_3): δ = 2.00 (dt, J = 12, 6 Hz, 2 H), 2.15–2.28 (m, 2 H), 2.32–2.48 (m, 2 H), 3.77 (dd, J = 8, 5.5 Hz, 1 H), 3.81 (s, 3 H), 3.83 (dd, J = 8, 5.5 Hz, 1 H), 6.90 (dt, J = 8.5, 2.5 Hz, 2 H), 7.12 (dm, J = 8.5 Hz, 2 H), 7.20 (d, J = 7.5 Hz, 2 H), 7.24–7.30 (m, 1 H), 7.36 (tm, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 21.7, 32.8, 33.0, 53.6, 54.3, 55.3, 114.2, 127.0,

127.8, 128.7, 128.8, 130.2, 138.2, 158.5, 211.2 ppm. HRMS (EI) calcd for $C_{19}H_{20}O_2$ (M^+) 280.1463, found 280.1471.



***trans*-2-(4-Fluorophenyl)-6-phenylcyclohexanone (11h):** (34.1 mg, 83% yield). 1H NMR (300 MHz, $CDCl_3$): δ = 1.88–2.14 (m, 2 H), 2.14–2.38 (m, 3 H), 2.42–2.56 (m, 1 H), 3.77 (dd, J = 9, 6 Hz, 1 H), 3.82 (t, J = 6 Hz, 1 H), 6.96–7.16 (m, 4 H), 7.16–7.42 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (–), 32.2 (–), 33.5 (–), 53.6 (+), 54.4 (+), 115.5 (d, J = 21 Hz) (+), 127.0 (+), 127.7 (+), 128.8 (+), 129.5 (d, J = 8 Hz) (+), 134.0 (d, J = 3 Hz) (–), 138.0 (–), 161.9 (d, J = 244 Hz) (–), 210.5 (–) ppm. HRMS (EI) calcd for $C_{18}H_{17}FO$ (M^+) 268.1263, found 268.1263.

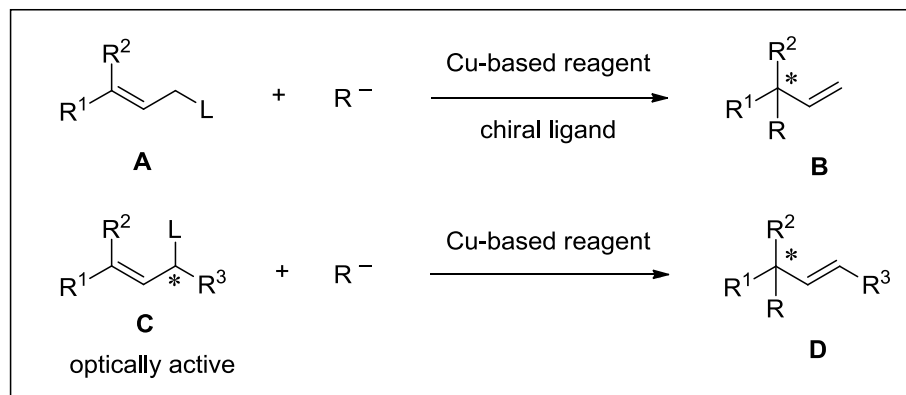
3.5 References:

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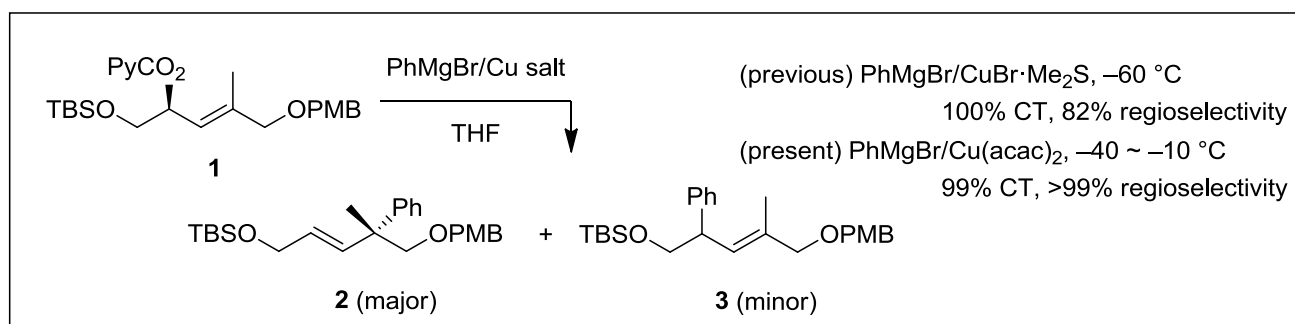
Chapter 4 Construction of Chiral Quaternary Carbon Centers with Arylcopper Reagents

4.1 Introduction

Exploration of a method for construction of a quaternary carbon in an enantiomerically enriched form has been an active area of investigation in connection with synthesis of biologically important molecules.¹ In the past decade, two types of allylic substitution shown in **Scheme 4.1** have been studied actively for this purpose.² Until now, the former substitution using primary allylic substrates of type **A** proceeds with alkyl as well as alkenyl-, allenyl-, and alkynylcopper reagents, producing olefin **B** with high efficiency in terms of enantio- and regioselectivity.³ Substitution with aryl copper reagents was also reported in one case.^{3f} On the other hand, a group of copper reagents that react with secondary allylic esters of type **C** to produce **D** is limited to the alkyl group.⁴ As for aryl reagents, the substitution shown in **Scheme 4.2** resulted in 82% regioselectivity using the picolinoxy leaving group.⁵ However, the regioselectivity is somewhat lower than that observed in the substitution of the allylic picolates of type **4** (**Figure 4.1**).^{6,7} Similarly, application of other highly potent leaving groups such as *o*-(PPh₂)C₆H₄CO₂ and *o*-(P(O)Ph₂)C₆H₄CO₂ originally developed for allylic substitution of type **5** (**Figure 4.1**) suffers from low regioselectivity.^{4b,4d} Low nucleophilicity of aryl reagents and increased congestion around secondary substrate and aryl reagent as such are likely reasons for the low efficiency. Recently, Pd/Ag-catalyzed substitution of allylic acetates with PhB(OH)₂ was applied to allylic acetates of type **C** (L = OAc),⁸ but stereoselectivity and reactivity were uncertain.⁹ Due to importance of this subject in organic synthesis,^{2,10} substitution of allylic picolates was reinvestigated to find highly efficient reagents derived from ArMgBr and Cu(acac)₂ as presented in this chapter.



Scheme 4.1 Two Types of Allylic Substitution for Construction of a Quaternary Carbon



Scheme 4.2 Previous and Present Results

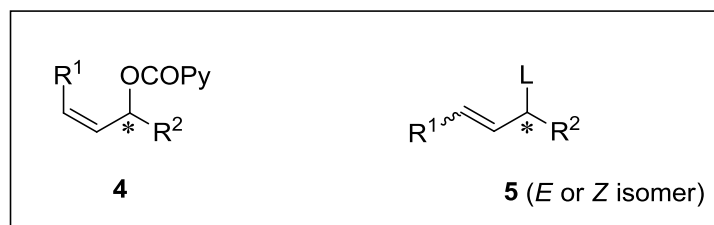
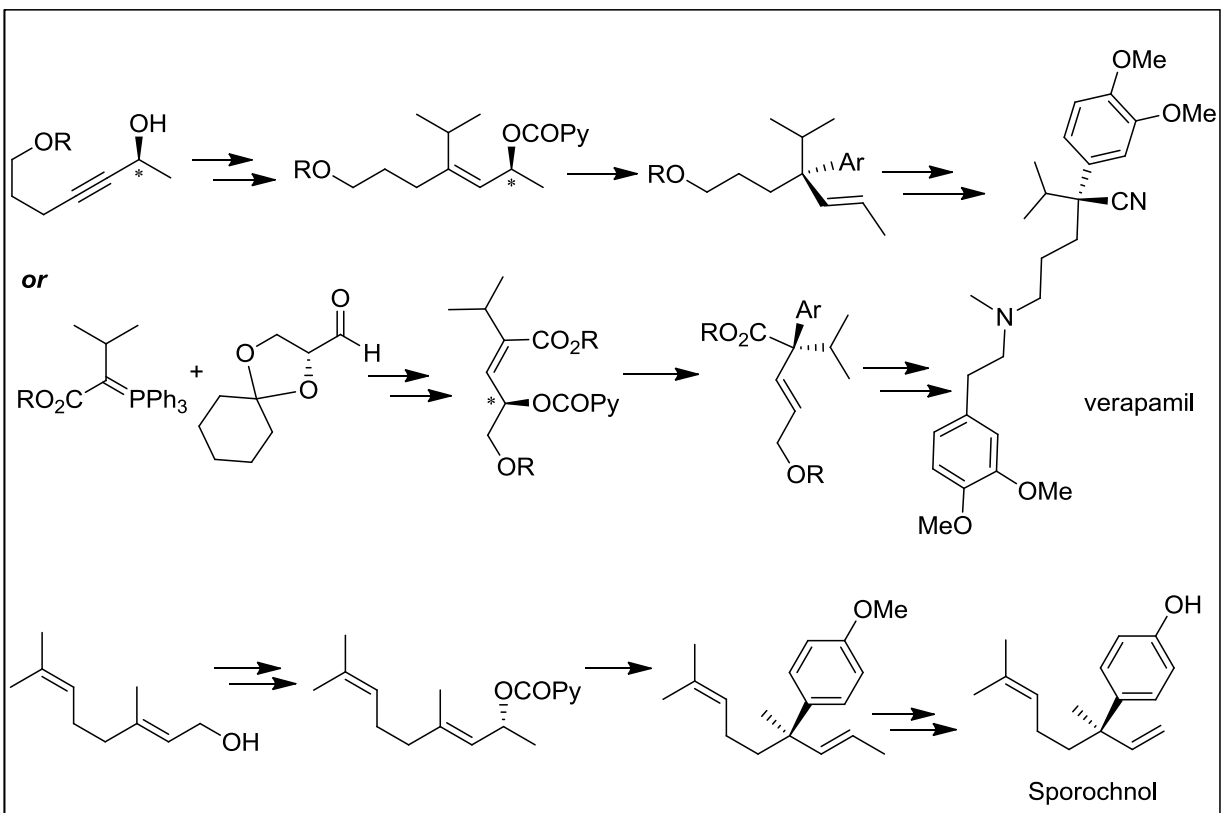
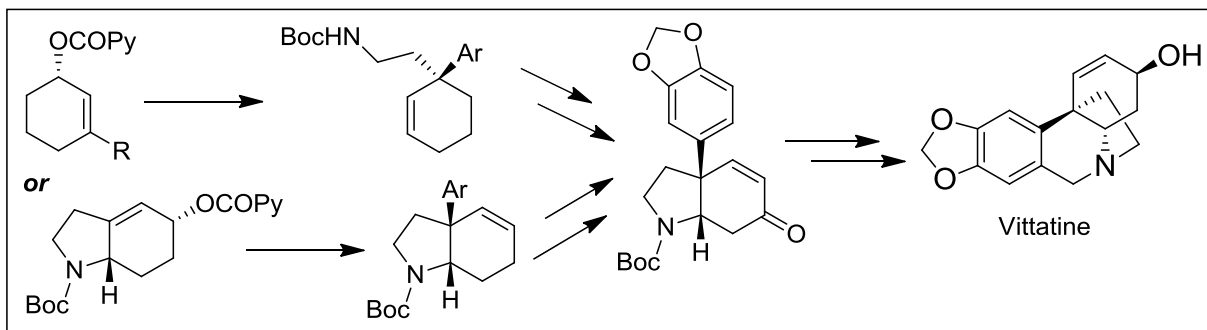


Figure 4.1 Allylic Substrates 4 and 5

For synthetic applications, allylic substitution of chiral picolinate asymmetrical construction of quaternary carbons could be key steps for synthesis of verapamil, spirochnol and vattatine (Schemes 4.3 and 4.4).



Scheme 4.3 Synthesis of Verapamil and Sporochnol Employing Allylic Substitution of Acyclic Picolimates



Scheme 4.4 Synthesis of Alkaloid Such As Vittatine by Allylic Substitution of Cyclic Picolimates

4.2 Results and Discussion

Preparation. Allylic picolinate shown in **Figure 4.2** were used for the present investigation (**Scheme 4.3**). The picolinate **1** (**Scheme 4.4**) and **14** were prepared by the methods published previously,^{5,7} while other picolinate **6–8** and **9–13** were synthesized by methods delineated in **Scheme 4.5**. Briefly, after protection by cyclohexanone, mannitol was oxidized to generate an aldehyde in 85% yield, which was transferred to an alcohol by a Wittig olefination in 90% yield and a reduction with DIBAL in 87% yield. Following protection by PMB group and cleavage of cyclohexanone group generated a diol in 51% yield over 2 steps. Then the primary alcohol was protected by TBS group quantitatively and the resulting chiral secondary alcohol was esterified to afford optically active picolinate **1** (98% ee) in 91% yield. For synthesis of the other picolinate **6–8** and **9–13**, Grignard addition to aldehyde **19** produced racemic alcohol **17**, which upon DCC condensation with PyCO₂H afforded picolinate **6** in 74% yield. Similarly, aldehydes **20** and **22**, prepared from geraniol and nerol by oxidation, were converted to **7** and **8**, respectively. For preparation of optically active picolinate **9–12**, CBS reduction of the corresponding ketones with (*S*)-MeCBS¹¹ was used for our convenience to afford alcohols **24–27**, which were in 60–82% ee by chiral HPLC analysis.¹² The alcohols were then converted to picolinate **9–12**. The absolute configuration of alcohol **24** was determined by comparison of the $[\alpha]_D$ value with that reported¹³ and was consistent with the sense of the CBS reduction. The same configuration was assigned to the other alcohols **25–27** by analogy.

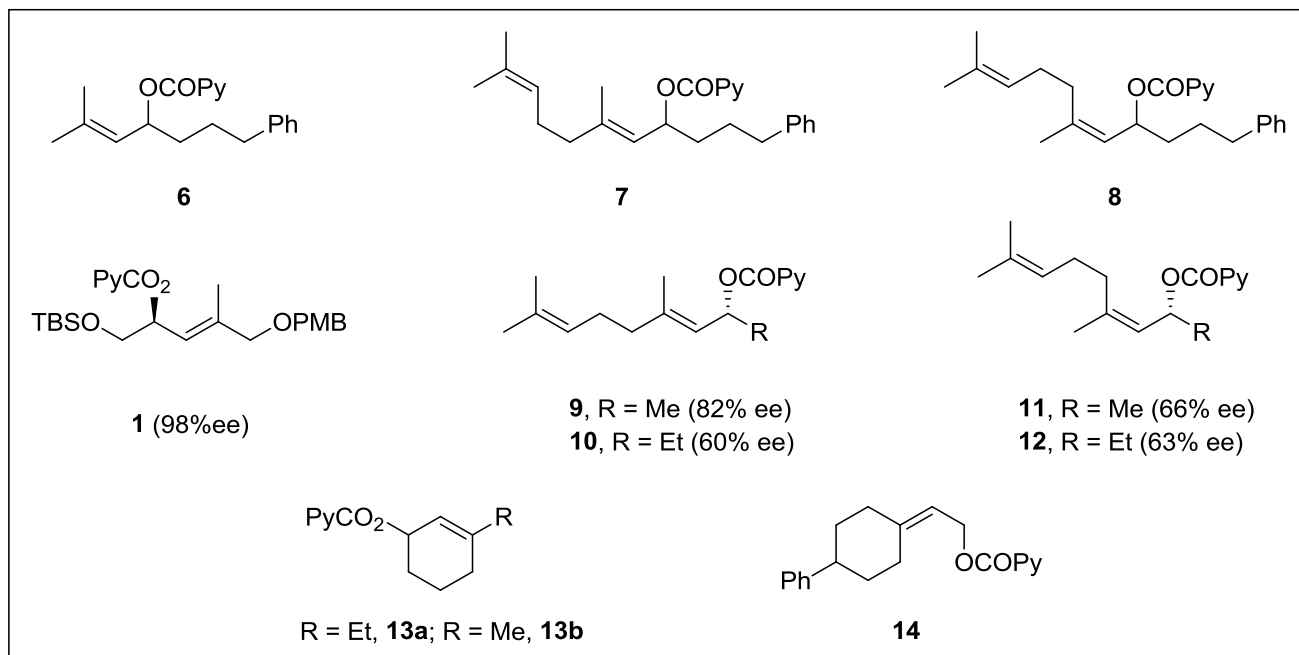
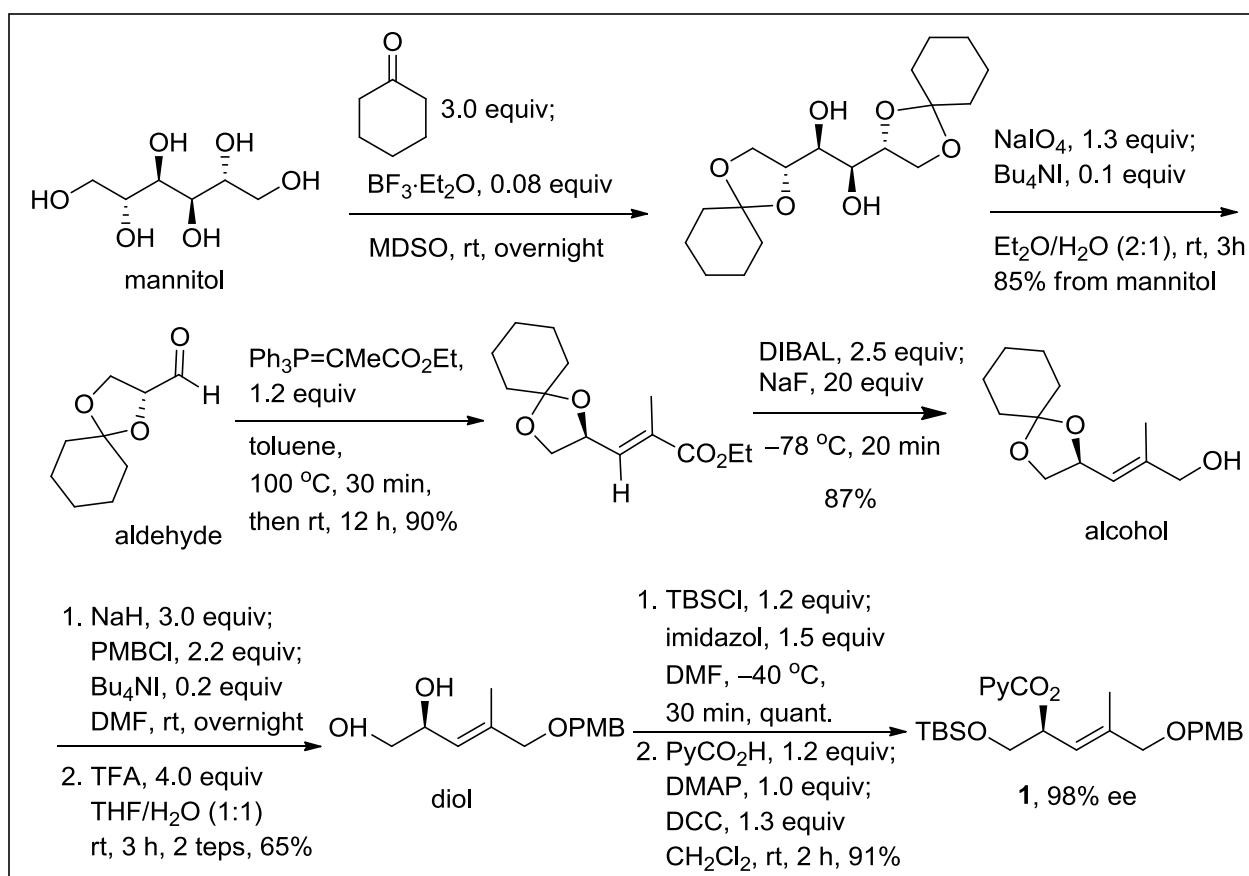
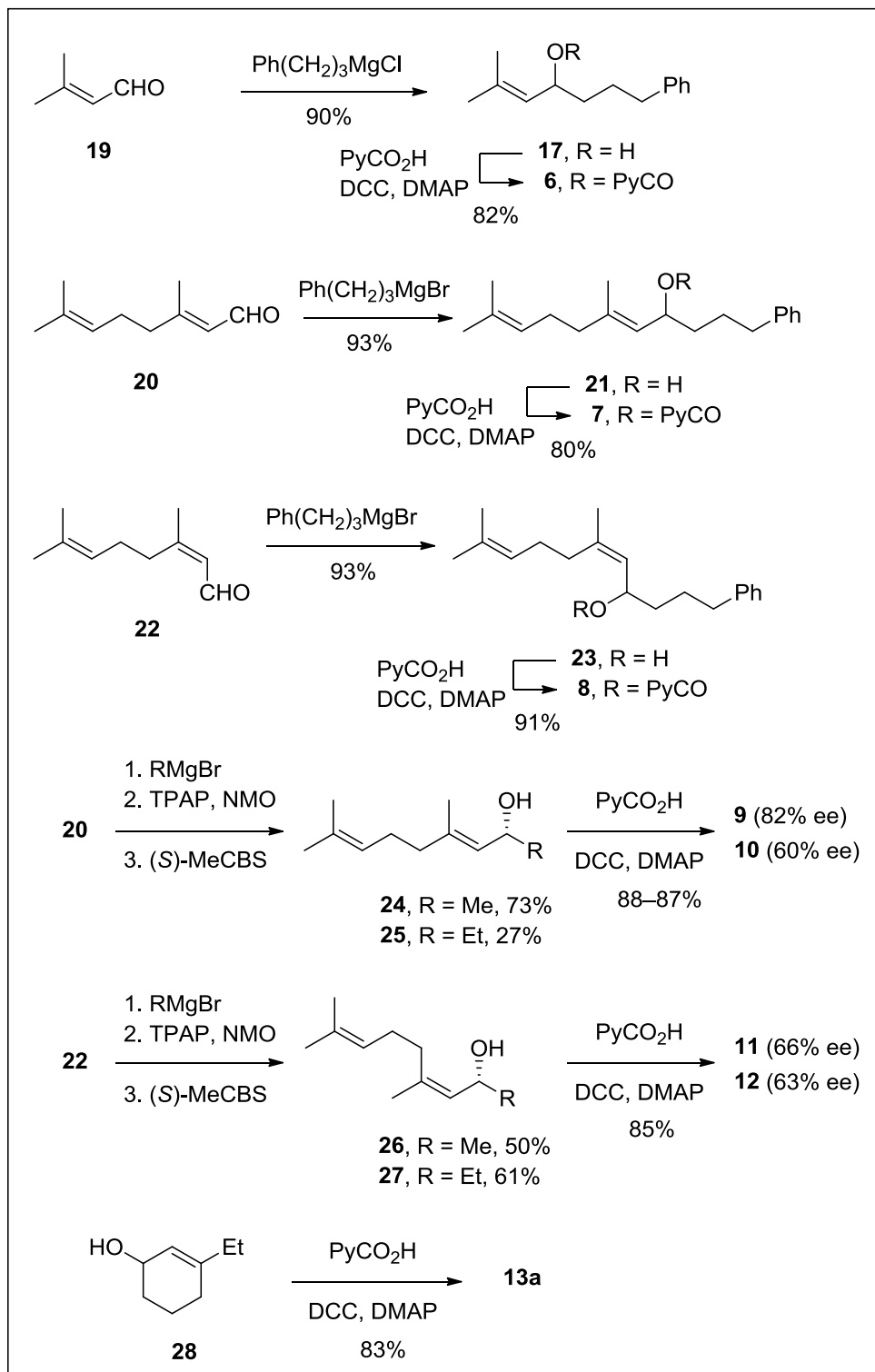


Figure 4.2 Substrates Examined (Py = 2-Pyridyl)



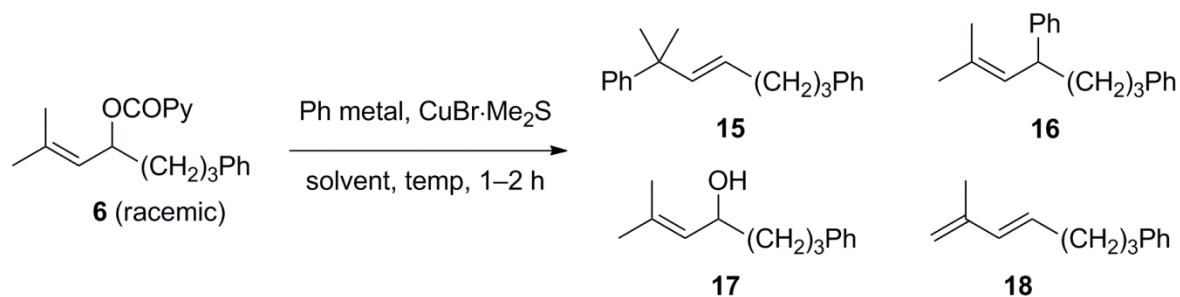
Scheme 4.4 Preparation of Picolinate 1



Scheme 4.5 Synthesis of Picolinate 6–8 and 9–13

Phenylation of Allylic Picolinate 6. Substitution of picolinate **6** with phenylcopper reagents derived from CuBr·Me₂S and PhMgX or PhLi was studied preliminarily, and the results are summarized in **Table 4.1**. The procedure developed by us⁵ for the picolinate **4** was examined first with the Ph reagent derived from PhMgBr and CuBr·Me₂S (2:1) in THF to afford a mixture of the expected product **15**, regioisomer **16**, alcohol **17**, and the starting picolinate **6** (entry 20).¹⁴ The calculated regioselectivity of **15** over **16** was 76%, which is similar to that obtained for picolinate **1** (82%). Additionally, diene **18** was observed occasionally by other conditions. No cis isomer was detected by ¹H NMR spectroscopy analysis of the crude product mixtures. At a higher temperature (−18 °C), the reaction proceeded completely, but with low regioselectivity (entry 1). The ZnI₂-assisted protocol, developed for allylation of cyclic substrates such as **14**,⁷ was applied then, however, even with different kinds of Zn salts, only a mixture was obtained and regioselectivity was not successfully improved (entries 2–7). At −40 °C, PhMgBr and CuBr·Me₂S in a 1:1 ratio produced S_N2' product **15** in 89% regioselectivity (entry 8), however, addition of ZnI₂ (1.5 equiv) prevented the reaction and picolinate **6** was recovered (data not shown). PhMgBr and CuBr·Me₂S in a 2:1 ratio with or without ZnI₂ at −40 °C afforded similar results (entries 9–14) to conditions at −18 °C described above. Higher ratios (3:1 or 5:1) of PhMgBr/CuBr·Me₂S with different quantities of ZnI₂ were also employed, however, still low regioselectivity emerged (entries 15–17). In Et₂O, a mixture of **15–17** and diene **18** was produced (entry 18), whereas, the ZnI₂-promoted reaction generated diene **18** as the major product (entry 19). To seek higher selectivity lower temperature was tried next. However, the organocopper reagents examined in entries 21–23, 27 and 28 did not provided satisfactory results. Furthermore, reaction in CH₂Cl₂-THF, the mixed solvent for the allylic substitution with alkynyl copper reagents,¹⁵ was not more selective (entry 24 vs. entry 22). The PhLi-based reagent in the presence or absence of ZnI₂ produced **18** as the major product in ca. 60% yields (entries 25, 26). As a result, various possible conditions based on CuBr·Me₂S with or without ZnI₂ did not afforded S_N2' product **15** with high regioselectivity.

Table 4.1 Allylation of Racemic 6 with CuBr·Me₂S-based Organocopper Reagents:



Entry	Ph metal (equiv)	CuBr·Me ₂ S (equiv)	Ph/Cu	Additive	Solvent	T/ °C	15:16:17:18:6 ^a
1	PhMgBr (3.0)	1.5	2:1	–	THF	–18	54:45:1:0:0
2	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	THF	–18	78:13:3:6:0
3	PhMgBr (3.0)	1.5	2:1	ZnI ₂ (1.5)	THF	–18	82:7:1:0:10
4	PhMgBr (3.2)	1.5	2:1	ZnBr ₂ (1.5)	THF	–18	60:28:12:0:0
5	PhMgBr (3.0)	1.5	2:1	ZnCl ₂ (1.5)	THF	–18	62:37:1:0:0
6	PhMgBr (3.0)	1.5	2:1	Zn(OTs) ₂ (1.5)	THF	–18	55:12:2:3:28
7	PhMgBr (3.0)	1.5	2:1	Zn(OCOPh) ₂ (1.5)	THF	–18	76:13:3:8:0
8	PhMgBr (1.5)	1.5	1:1	–	THF	–40	81:10:5:4:0
9	PhMgBr (3.2)	1.5	2:1	–	THF	–40	54:14:20:0:12
10	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	THF	–40	74:26:0:0:0
11	PhMgBr (3.0)	1.5	2:1	–	THF	–40	79:21:0:0:0
12	PhMgBr (3.0)	1.5	2:1	ZnI ₂ (1.5)	THF	–40	67:19:14:0:0
13	PhMgBr (3.0)	1.5	2:1	ZnBr ₂ (1.5)	THF	–40	66:20:6:0:8
14	PhMgBr (3.0)	1.5	2:1	Zn(OCOPh) ₂ (1.5)	THF	–40	78:20:2:0:<1
15	PhMgBr (6.0)	2.0	3:1	ZnI ₂ (2.0)	THF	–40	19:69:15:0:0
16	PhMgBr (2.5)	0.5	5:1	ZnI ₂ (1.5)	THF	–40	59:20:7:0:14
17	PhMgBr (2.5)	0.5	5:1	ZnI ₂ (0.5)	THF	–40	30:62:8:0:0
18	PhMgBr (3.2)	1.5	2:1	–	Et ₂ O	–40	22:40:21:17:0
19	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	Et ₂ O	–40	0:40:0:60:0
20	PhMgBr (2.0)	1.0	2:1	–	THF	–60	53:17:16:0:14
21	PhMgBr (4.0)	2.0	2:1	–	THF	–60	39:28:33:0:0
22	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	THF	–60	69:21:10:0:0

23	PhMgBr (6.0)	1.5	4:1	ZnI ₂ (1.5)	THF	−60	16:49:35:0:0
24	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	CH ₂ Cl ₂ - THF ^b	−60	62:26:9:3:0
25	PhLi (3.2), MgBr ₂ (4.0)	1.5	2:1	–	THF	−60	0:20:16:64:0
26	PhLi (3.2), MgBr ₂ (4.0)	1.5	2:1	ZnI ₂ (1.5)	THF	−60	0:14:27:58:0
27	PhMgBr (3.2)	1.5	2:1	–	THF	−70	74:12:14:0:0
28	PhMgBr (3.2)	1.5	2:1	ZnI ₂ (1.5)	THF	−70	66:28:6:0:0

^aDetermined by ¹H NMR analysis of unpurified reaction mixture and integration ratios of the protons at δ 5.44 (dt, 1 H) and 5.64 (d, 1 H) for **15**, 5.26 (d, 1 H) for **16**, 5.15 (dm, 1 H) for **17**, 6.15 (d, 1 H) and 4.87 (s, 2 H) for **18**, and 5.80–5.89 (m, 1 H) for **6**. ^bTHF:CH₂Cl₂ = 7:1.

Recently, Cu(acac)₂-based alkynyl reagents were found to be highly reactive and regioselective in the substitution of cyclic allylic picolates.¹⁶ By intuition, we envisaged high efficiency with reagents derived from PhMgBr and Cu(acac)₂. In fact, a Ph copper reagent derived from PhMgBr and Cu(acac)₂ in a 2 : 1 ratio at −60 °C for 2 h produced **15** with almost perfect regioselectivity, though a few % of alcohol **17** and picolinate **6** were found in the ¹H NMR spectrum of the crude product (entry 1). The reaction attempted in the presence of ZnI₂ was unsuccessful (entries 2), similar to reaction with PhMgBr, CuBr·Me₂S, and ZnI₂ in a 2:1:1 ratio. In contrast, more quantities of PhMgBr reduced regioselectivity even full conversion was observed (entries 3 and 5). Moreover, although picolinate **6** was recovered (entry 4), ZnI₂ highly improved regioselectivity by using PhMgBr/Cu(acac)₂ in a 3:1 ratio (entries 4 vs 3), which is also a remarkable difference from the results of CuBr·Me₂S based organocopper species (**Table 4.1**). Nevertheless, we investigated the substitution at higher temperatures than −60 °C. At −40 °C, the 2:1 PhMgBr/Cu(acac)₂ reagent produced **15** exclusively in quantitative yield (entry 6). This reagent was sufficiently regioselective even at −30 and −20 °C (entries 12 and 13), whereas regioselectivity was decreased at 0 °C (entry 14). In contrast, addition of ZnI₂ again prevented the reaction at all (entry 7). Different from the 2:1 Ph/Cu reagent, ZnI₂ this time assisted the 3:1 Ph/Cu reagent to proceed with high regioselectivity with full conversion of picolinate **6** (entry 9 vs. entry 8). Similar results were also gained by utility of ZnBr₂ and ZnCl₂ (entries 10 and 11).

An attempted reaction with a 1:1 PhMgBr/Cu(acac)₂ reagent even at 0 °C did not produce the allylation products **15/16**; Instead, picolinate **6** was recovered (data not shown). We also examined reagents derived from Cu(OAc)₂ and Cu(OMe)₂. As shown in entry 15, a reagent derived from Cu(OAc)₂ produced diene **18** as the major product, while that prepared from Cu(OMe)₂ afforded **15** with somewhat low regioselectivity of 88% (entry 16).¹⁷ The attempted reaction with 10 mol% of Cu(acac)₂ afforded a mixture of **15/16/17** in a 20:56:24 ratio (data not shown).

Table 4.2 Allylation of Racemic 6 with CuX₂-based Organocopper Reagents (X=acac, etc.):

Reaction scheme: Racemic 6 (OCOPy, (CH₂)₃Ph) reacts with PhMgBr and Cu(II) salt in THF at various temperatures to yield products 15, 16, 17, and 18.						
Entry	PhMgBr (equiv)	Cu(acac) ₂ (equiv) ^a	Ph/Cu	Additive (equiv)	T/ °C	15:16:17:18:6 ^b
1	3.0	1.5	2:1	–	–60	86:0:6:0:8
2	3.2	1.5	2:1	ZnI ₂ (1.5)	–60	no reaction
3	4.7	1.5	3:1	–	–60	45:42:13:0:0
4	4.7	1.5	3:1	ZnI ₂ (1.5)	–60	54:0:9:0:37
5	6.0	1.5	4:1	–	–60	27:56:17:0:0
6	3.0	1.5	2:1	–	–40	>99:0:0:0:0 ^c
7	3.0	1.5	2:1	ZnI ₂ (1.5)	–40	no reaction
8	4.7	1.5	3:1	–	–40	44:41:15:0:0
9	4.7	1.5	3:1	ZnI ₂ (1.5)	–40	98:2:0:0:0 ^c
10	4.7	1.5	3:1	ZnBr ₂ (1.5)	–40	97:3:0:0:0 ^c
11	4.7	1.5	3:1	ZnCl ₂ (1.5)	–40	94:5:1:0:0
12	3.0	1.5	2:1	–	–30	99:1:0:0:0
13	3.0	1.5	2:1	–	–20	95:3:2:0:0
14	3.0	1.5	2:1	–	0	85:13:2:0:0

15	3.0	Cu(OAc) ₂ (1.5)	2:1	–	–40	18:13:0:69:0 ^d
16	3.0	Cu(OMe) ₂ (1.5)	2:1	–	–40	88:12:0:0:0 ^d

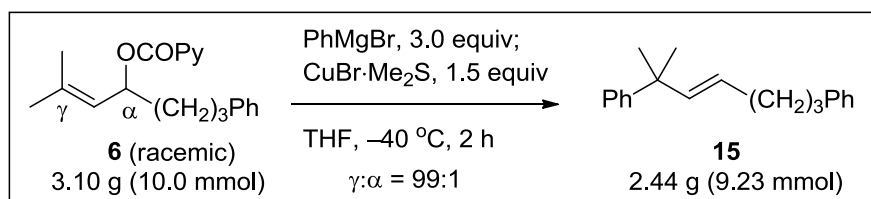
^aCu(acac)₂ (1.5 equiv) was used in entries 1–14. ^bDetermined by ¹H NMR analysis of unpurified reaction mixture and integration ratios of the protons at δ 5.44 (dt, 1 H) and 5.64 (d, 1 H) for **15**, 5.26 (d, 1 H) for **16**, 5.15 (dm, 1 H) for **17**, 6.15 (d, 1 H) and 4.87 (s, 2 H) for **18**, and 5.80–5.89 (m, 1 H) for **6**. ^cIsolated yield of **15** and **16**: 100% (entry 6), 87% (entry 9), and 90% (entry 10). ^dUnidentified products were also formed.

In summary of the preliminary investigation, regioselectivity and reactivity of the phenylation of picolinate **6** were highly dependent on the copper source, composition, and ZnI₂. The reagent systems of high performance based on results of Tables 4.1 and 4.2 are summarized in Table 4.3 with those related. First, Cu(acac)₂ was found to be a better source of the copper reagent than CuBr·Me₂S (result 1). Second, ZnI₂ was found to raise the regioselectivity of the 3:1 PhMgBr/Cu(acac)₂ reagent (result 4 vs. result 3), whereas the reaction with the 2:1 reagent was totally prevented by ZnI₂ (result 2). As mentioned in the above paragraph, no reaction took place with the supposed 1:1 PhMgBr/Cu(acac)₂ reagent. Consequently, it is likely that 1 equiv of PhMgBr per Cu(acac)₂ is consumed stoichiometrically to reduce Cu(acac)₂ to a Cu⁺ species¹⁸ and that use of 2 and 3 equivs of PhMgBr per Cu(acac)₂ produces Ph-Cu and Ph₂Cu[–] species, respectively. Thus, the Ph-Cu species derived from PhMgBr and Cu(acac)₂ is more regioselective in the phenylation of picolinate **6** than the Ph₂Cu[–] species, whereas the low regioselectivity of the Ph₂Cu[–] reagent is highly improved by addition of ZnI₂ without substantial loss of the reactivity. From a practical point of view, we are thinking that the 2:1 PhMgBr/Cu(acac)₂ reagent would be the first choice on the basis of the quantity of PhMgBr. Additionally, the procedure using the 2:1 PhMgBr/Cu(acac)₂ reagent could be scaled up to 3.1 g of **6** (10 mmol), which afforded **15** with 99% regioselectivity and 92% yield after purification by chromatography (**Scheme 4.6**).

Table 4.3 Potential of the Reagents

Result	Entry	Ph/Cu ^a	ZnI ₂	Conversion of 6 (%)	Regioselectivity ^b (%)
1	6, Table 4.2	2:1	–	100	>99
2	7, Table 4.2	2:1	added ^c	0	–
3	8, Table 4.2	3:1	–	100	52
4	9, Table 4.2	3:1	added^c	100	98

^aQuantity of Cu(acac)₂ was 1.5 equiv per picolinate **6**, and that of PhMgBr were 3–3.1 and 4.5–4.7 equivs for the 2:1 and 3:1 ratios. ^bBased on the products **15** and **16**. ^c1.5 equiv.

**Scheme 4.6 Large-scale Allylic Substitution of Picolinate 6**

Allylic Substitution with aryl reagents. The reagent system used in entry 6 of **Table 4.2** was applied to allylic substitution summarized in **Table 4.4**. The reactions in the all entries were complete within 2 h. However, regioselectivity and yields varied slightly. Thus, the Me substituent at the para and ortho positions furnished similar regioselectivity and yield (entries 1, 2), whereas the MeO group at the ortho position slightly lowered the selectivity and yield (entry 4 vs. entries 1–3). The reaction with the *p*-F-C₆H₄ reagent proceeded efficiently as well (entry 5). Substitution of picolates **7** and **8** was not affected by the bulkiness of the alkyl groups on the reacting carbon (γ position) and S_N2' product **34** was obtained selectively (entries 6, 7). A similar selectivity was observed in entry 8 to produce **35**.

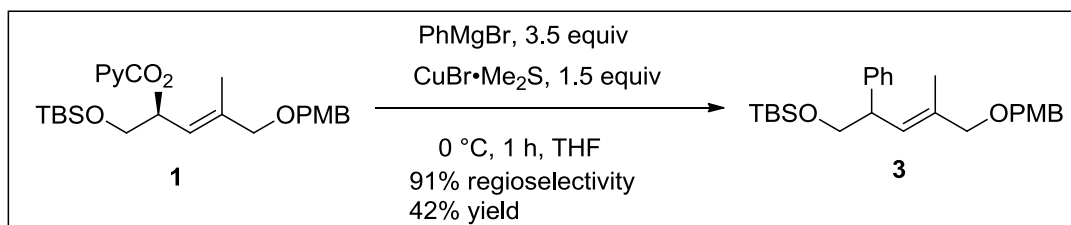
Table 4.4 Allylic Substitution of Racemic 6–8 with ArMgBr/Cu(acac)₂^a

Entry	Picolate	Product	Regioselectivity, % ^b	Isolated yield, %
1	6	29 , Ar = <i>p</i> -MeC ₆ H ₄	>99	93
2	6	30 , Ar = <i>o</i> -MeC ₆ H ₄	96	96
3	6	31 , Ar = <i>p</i> -MeOC ₆ H ₄	98	82
4	6	32 , Ar = <i>o</i> -MeOC ₆ H ₄	90	65
5	6	33 , Ar = <i>p</i> -FC ₆ H ₄	98	84
6	7	34 , Ar = Ph	>99	95
7	8	34 , Ar = Ph	99	88
8	7 + 8 (3:2)	35 , Ar = <i>p</i> -FC ₆ H ₄	99	80

^aArMgBr (3 equiv), Cu(acac)₂ (1.5 equiv), THF, −40 ~ −20 or −10 °C, 2 h. ^bDetermined by ¹H NMR.

Arylation of Enantiomerically Enriched Allylic Picolates. The above reagent system consisting of 2:1 ArMgBr/Cu(acac)₂ was applied to enantiomerically enriched picolates **1**¹⁹ and **9–12** to determine chirality transfer (CT) of the allylic substitution (**Table 4.5**). Substitution of **1** (98% ee) with the Ph copper reagent for 3 h, however, afforded a mixture of **2** and the starting picolate **1** (entry 1 and footnote e), suggesting lower reactivity of **1** than the substrates examined above. Fortunately, full conversion was attained by doubling the quantity of the reagent to produce **2** with >99% regioselectivity and 99% CT in 91% yield (entry 2). The regioisomer **3** was synthesized with 91% regioselectivity (**Scheme 4.7**) along with alcohol **42** using the CuBr·Me₂S-based copper reagent in 42% yield according to **Table 4.1**, entry 1, which

in turn afforded a mixture of **16** and **15** in a 45:55 from substrate **6**.²⁰ The different regioselectivity between **1** and **6** implies that the γ position of **1** is more prohibited than **6**, rendering the position less accessible, probably due to the oxygen atom near the γ position of **1**, which reduced the reactivity of the γ position of **1**. The absolute configuration of **2** was determined by the specific rotation ($([\alpha]^{23}_{\text{D}} + 2.5$ (c 0.16, CHCl_3)) with this reported (lit.²¹ $[\alpha]^{30}_{\text{D}} + 1.5$ (c 0.40, CHCl_3)) and retention time on chiral HPLC (experimental section),²¹ establishing anti $\text{S}_{\text{N}}2'$ pathway. Similarly, substituted aryl reagents shown in entries 3–5 and 7 afforded **36**–**38** and **40** with high CT in high yields. These results demonstrate high potency of the $\text{ArMgBr}/\text{Cu}(\text{acac})_2$ reagents, which would not be influenced by steric and electronic biases. In addition, **39** was also produced with 92% regioselectivity in 81% yield, however, contaminated with 2,2'-dimethoxy-1,1'-biphenyl (entry 6). Meanwhile, the enantiomers of **2**, **36**–**40** for HPLC analysis were synthesized through a Mizunobu reaction (**Scheme 4.8**).

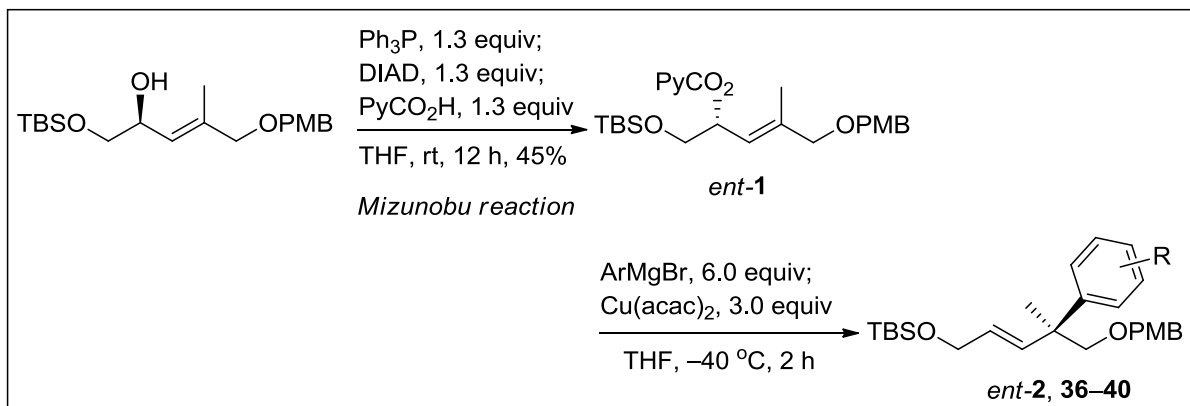


Scheme 4.7 Synthesis of Regioisomer 3

Table 4.5 Substitution of Chiral Picolinates with Aryl Copper Reagents

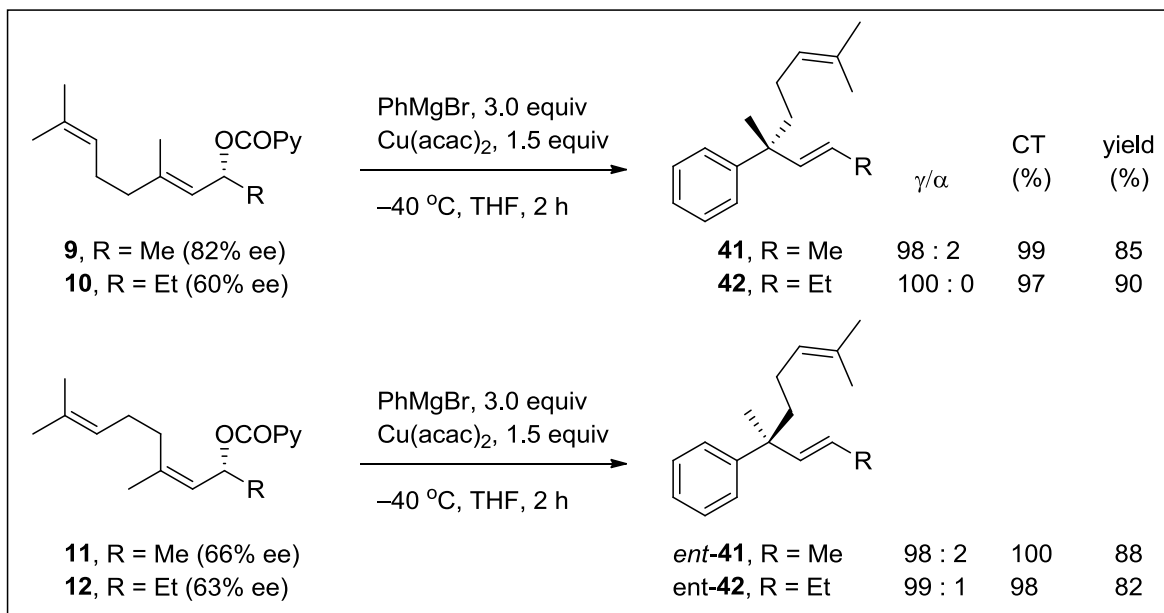
Entry	Reagents (equiv)	Time (h)	Product	γ/α^a	Yield ^b (%)	CT ^c (%)	
1 ^d	PhMgBr (3), Cu(acac) ₂ (1.5)	3		96 : 4	49	98	
2	PhMgBr (6), Cu(acac) ₂ (3)	2	2	100 : 0	91	99	
3	<i>p</i> -MeC ₆ H ₄ MgBr (6), Cu(acac) ₂ (3)	2		92 : 8	93	99	
4	<i>o</i> -MeC ₆ H ₄ MgBr (6), Cu(acac) ₂ (3)	2		96 : 4	95	100	
5	<i>p</i> -MeOC ₆ H ₄ MgBr (6), Cu(acac) ₂ (3)	2		93 : 7	94	99	
6	<i>o</i> -MeC ₆ H ₄ MgBr (6), Cu(acac) ₂ (3)	2		92 : 8	81	— ^e	
7	<i>p</i> -FC ₆ H ₄ MgBr (6), Cu(acac) ₂ (3)	2		100 : 0	100	100	

^aDetermined by ¹H NMR analysis. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. CT (chirality transfer) was calculated by (ee substrate) x 100 / (ee product). ^dRemaining **1** was detected by ¹H NMR and TLC analysis. **1** still remained even after 7 h. ^eCT was not determined due to the difficulty of separation of **38a** from 2,2'-dimethoxy-1,1'-biphenyl.



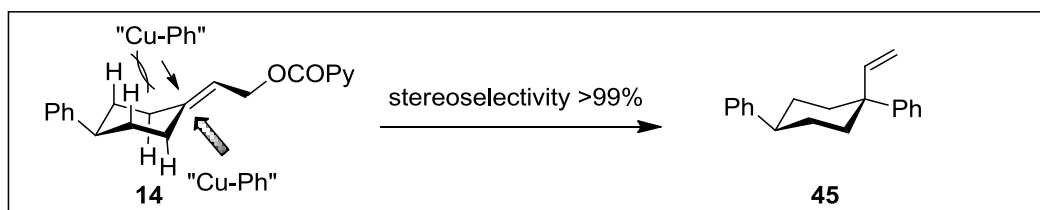
Scheme 4.8 Synthesis of Enantiomers of 2, 36–39

Next, reaction of picolates **9–12** was examined to find a higher reactivity than **1** (**Scheme 4.9**). Thus, the reactions proceeded with the standard quantity of the Ph reagent to afford **41** and **42** from **9** and **10**, and *ent*-**41** and *ent*-**42** from **11** and **12**, respectively, with high CT and regioselectivity in good yields.²² In addition, the absolute configuration of *anti*- $\text{S}_{\text{N}}2'$ products **41** and **42** can be switched by geometry of the olefin of picolates **9** and **10**, which would be an advantage for synthetic applications.

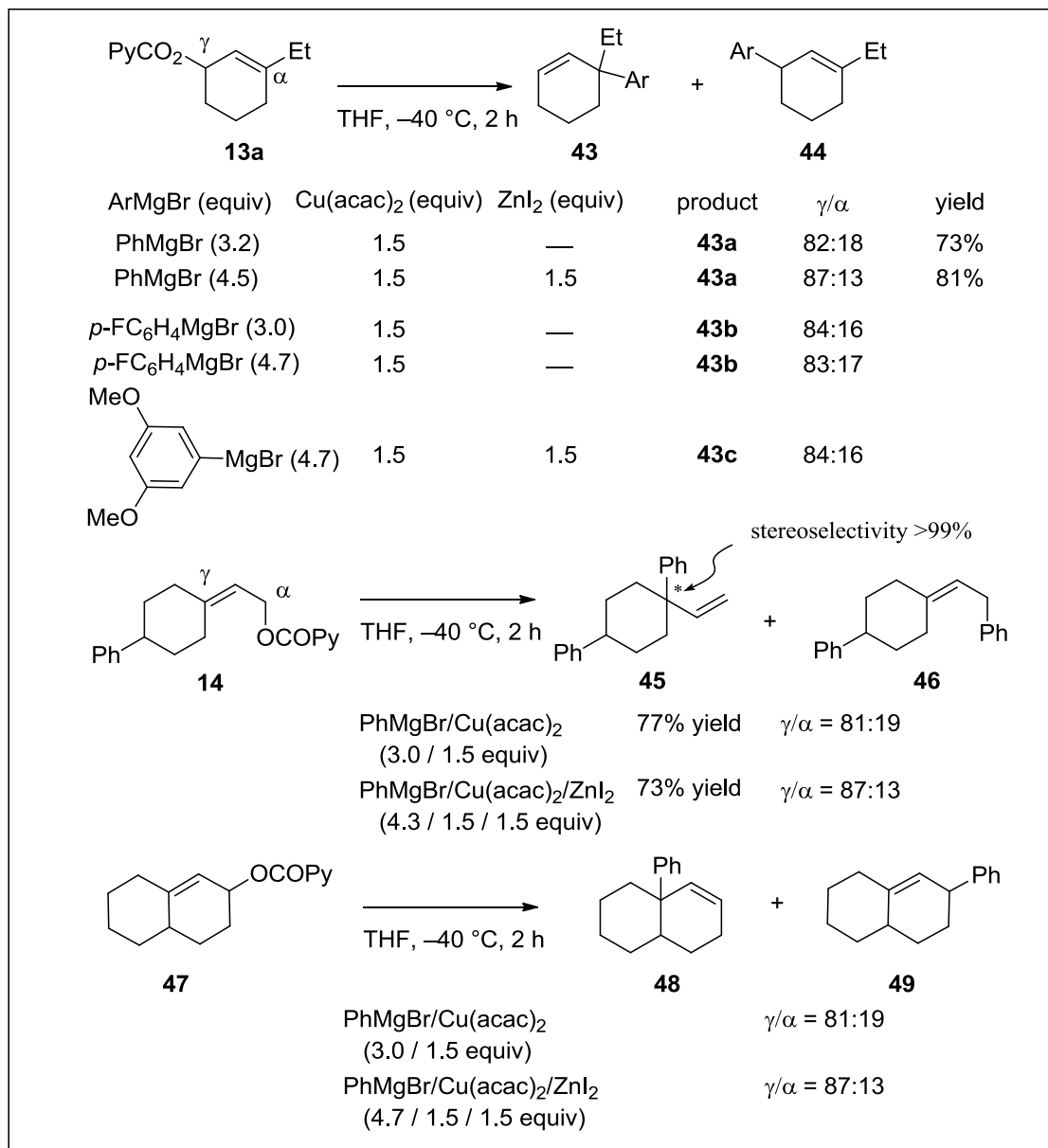


Scheme 4.9 Allylic Substitution of Picolates 9-12

Construction of a Quaternary Carbon on the Cyclohexane Ring. The above protocol was applied to picolinates to create a quaternary carbon on the cyclohexane ring (**Scheme 4.10**). Reaction of **13a** with the 2:1 PhMgBr/Cu(acac)₂ and 3:1:1 PhMgBr/Cu(acac)₂/ZnI₂ reagents gave **43a** with 82–87% regioselectivity over the regioisomer **44a** in good yields. Likewise, *p*-FC₆H₄ and 3,5-dimethoxyphenyl groups were installed to quaternary carbon center with 83–84% regioselectivity. The next substrate was **14**, in which the α carbon is less congested than that of the other substrates examined above, thus rendering the γ position less reactive than α. Nevertheless, both of the reagents afforded the desired product **45** with >81% regioselectivity over the regioisomer **46**. Furthermore, the ¹H NMR spectrum of **45** indicates >99% stereoselectivity, and the *trans* 1,4-diphenyl stereochemistry is assigned on the basis of the previous results with alkyl copper reagents (**Scheme 4.11**).⁷ S_N2' product **48** was also produced with 81% and 87% regioselectivity respectively by using PhMgBr/Cu(acac)₂ (2:1) as well as PhMgBr/Cu(acac)₂/ZnI₂ (3:1:1) reagent systems. In consequence of the cyclic carbon skeleton (for example, picolinates **13** shown in **Figure 4.3**), γ position of cyclic picolinates has larger steric hindrance than that of acyclic picolinates. Therefore, even with reagents derived from ArMgBr/Cu(acac)₂, which show high selectivity for allylic substitution of cyclic picolinates, only moderate regioselectivity was observed.



Scheme 4.11 Stereochemistry of Allylic Substitution of Picolinate 14



Scheme 4.10 Construction of a Quaternary Carbon on the Cyclohexane Ring

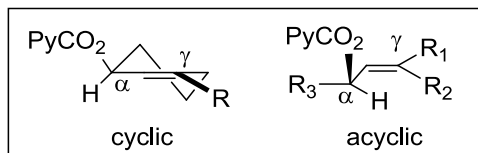
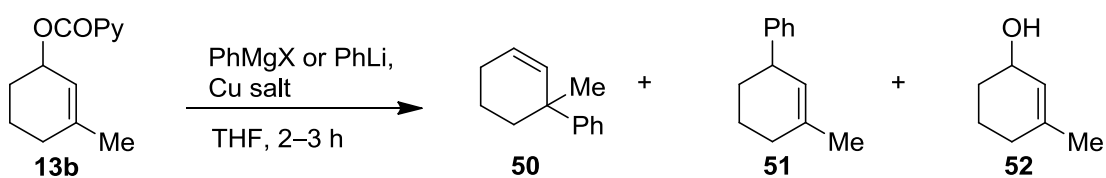


Figure 4.3 Cyclic and Acyclic Picolimates

Further investigation of allylic substitution of cyclic picolinate **13b** based on **Table 4.3** is unsuccessful (**Table 4.6**). PhMgX (X = Br or Cl) and Cu(acac)₂ in a 2:1 ratio reacted with cyclic picolinate **13b** generated S_N2' product **50** with 72–85% regioselectivity (entries 1–3), whereas PhLi and Cu(acac)₂ in a 2:1 ratio in the presence of MgBr₂ only produced a mixture of corresponding alcohol **52** and substrate **13b** (entry 4). PhMgX (X = Br or Cl)/Cu(acac)₂ in a 3:1 ratio with different quantities of ZnX₂ (X = Br or I) at both –40 °C and –78 °C did not improve the efficiency of the reaction (entries 5–10). TMSCl and phen were reported to promote S_N2' product,²⁹ but produced byproducts with picolinate **13b** (entries 11 and 12).

Table 4.6 Allylic Substitution of Cyclic Picolinate 13b

							
Entry	Ph metal	Cu(acac) ₂	Ph/Cu	Additive	T/°C	50:51:52:13b ^a	γ/α
1	PhMgBr, 3.0 equiv	1.5 equiv	2:1	—	–40	54:11:<1:35	83:17
2	PhMgBr, 6.0 equiv	3.0 equiv	2:1	—	–40	79:14:7:0	85:15
3	PhMgCl, 3.0 equiv	1.5 equiv	2:1	—	–40	48:19:<1:33	72:28
4	PhLi, 3.0 equiv	1.5 equiv	2:1	MgBr ₂ , 2.0 equiv	–40	0:0:29:71	—
5	PhMgCl, 4.7 equiv	1.5 equiv	3:1	ZnI ₂ , 1.5 equiv	–40	79:21:<1:0	79:21
6	PhMgBr, 4.5 equiv	1.5 equiv	3:1	ZnI ₂ , 1.5 equiv	–40	82:18:<1:0	82:18
7	PhMgCl, 4.7 equiv	1.5 equiv	3:1	ZnBr ₂ , 2.0 equiv	–40	65:29:6:0	69:31
8	PhMgBr, 9.0 equiv	3.0 equiv	3:1	ZnI ₂ , 3.0 equiv	–40	85:15:<1:0	85:15
9	PhMgBr, 4.3 equiv	1.5 equiv	3:1	ZnI ₂ , 1.5 equiv	–78	85:15:0:0	85:15
10	PhMgCl, 4.7 equiv	1.5 equiv	3:1	ZnI ₂ , 2.0 equiv	–78	75:25:0:0	75:25
11	PhMgBr, 2.2 equiv	1.0 equiv	2:1	TMSCl, 1.0 equiv	0	— ^b	—
12	PhMgBr, 3.0 equiv	1.5 equiv	2:1	phen, ^c 1.5 equiv	–40	— ^b	—

^aDetermined by ¹H NMR analysis of unpurified reaction mixtures. ^bByproduct. ^c1,10-Phenanthroline.

Moreover, several Cu(acac)₂-like Cu salts were examined (**Table 4.7**), however, Cu(acac)₂ was found afford the highest regioselectivity comparing with other Cu salts (entries 3 vs 1, 5, and

7). Conditions with addition of ZnI_2 with different Cu salts did not proceed with better results (entries 2 and 4 vs 3, 6 vs 5, 8 vs 7).

Table 4.7 Allylic Substitution of Cyclic Picolinate 13b with $\text{Cu}(\text{acac})_2$ -like Cu salts

Entry	PhMgBr	Reagents ^a	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2^b$
1	3.0 equiv	$\text{Cu}(\text{TFAA})$, 1.5 equiv	78:22
2	9.0 equiv	$\text{Cu}(\text{acac})_2$, 3.0 equiv + ZnI_2 , 3.0 equiv	85:15
3	6.0 equiv	$\text{Cu}(\text{acac})_2$, 3.0 equiv	85:15
4	4.5 equiv	$\text{Cu}(\text{acac})_2$, 1.5 equiv + ZnI_2 , 1.5 equiv	82:18
5	3.0 equiv	$\text{Cu}(\text{TMHD})_2$, 1.5 equiv	80:20
6	4.5 equiv	$\text{Cu}(\text{TMHD})_2$, 1.5 equiv + ZnI_2 , 1.5 equiv	85:15
7	3.2 equiv	$\text{Cu}(\text{FOD})_2$, 1.5 equiv	byprod.
8	4.6 equiv	$\text{Cu}(\text{FOD})_2$, 1.5 equiv + ZnI_2 , 1.5 equiv	74:26

^aacac showed highest egioselectivity among acac, TMHD, TFAA and FOD (**Figure 4.4**).

^bDetermined by ^1H NMR.

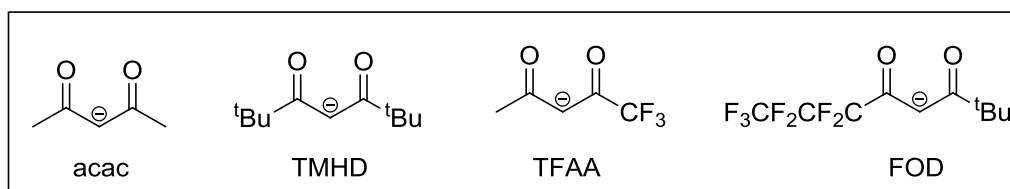


Figure 4.4 Ligands Applied in Table 4.7

Conditions summarized in **Table 4.3** were also employed for allylic substitution of picolinate **13a**, however, similar results observed (entries 4–11, **Table 4.8**) with those of allylic substitution

of **13b**. Organocopper reagents derived from CuBr·Me₂S in the presence or absence of ZnI₂ afforded 61–81% regioselectivity (entries 1–3). Likewise, Cu(OAc)₂-based reagents failed to improve the regioselectivity and only a mixture of S_N2' product **43** and S_N2 product **44** was obtained (entries 12 and 13).

Table 4.8 Allylic Substitution of Cyclic Picolinate 13 with Organocopper Reagents

Entry	PhMgBr (equiv)	Cu salt (equiv)	Ph/Cu	ZnI ₂ (equiv)	43:44:28:13a	S _N 2':S _N 2	Yield ^a
1	1.6	CuBr·Me ₂ S (1.5)	1:1	—	21:5:28:46	81:19	13%
2	3.2	CuBr·Me ₂ S (1.5)	2:1	—	59:38:3:0	61:39	82%
3	3.2	CuBr·Me ₂ S (1.5)	2:1	1.5	60:14:11:15	81:19	55%
4	3.0	Cu(acac) ₂ (1.5)	2:1	—	84:16:<5:0	84:16	52%
5	3.2	Cu(acac) ₂ (1.5)	2:1	—	71:16:0:13	82:18	73%
6	3.7	Cu(acac) ₂ (1.5)	2.5:1	—	86:14:<1:0	86:14	94%
7	4.0	Cu(acac) ₂ (2.0)	2:1	—	79:21:0:0	79:21	90%
8 ^b	3.2	Cu(acac) ₂ (1.5)	2:1	—	11:1:18:70	87:13	—
9 ^b	3.0	Cu(acac) ₂ (1.5)	2:1	—	—	87:13	22%
10	4.5	Cu(acac) ₂ (1.5)	3:1	1.5	87:13:0:0	87:13	81%
11	4.7	Cu(acac) ₂ (1.5)	3:1	0.5	60:29:11:0	67:33	—
12	3.0	Cu(OAc) ₂ (1.5)	2:1	—	62:14:24:0	85:15	21%
13	4.7	Cu(OAc) ₂ (1.5)	3:1	1.5	82:18:<1:0	82:18	88%

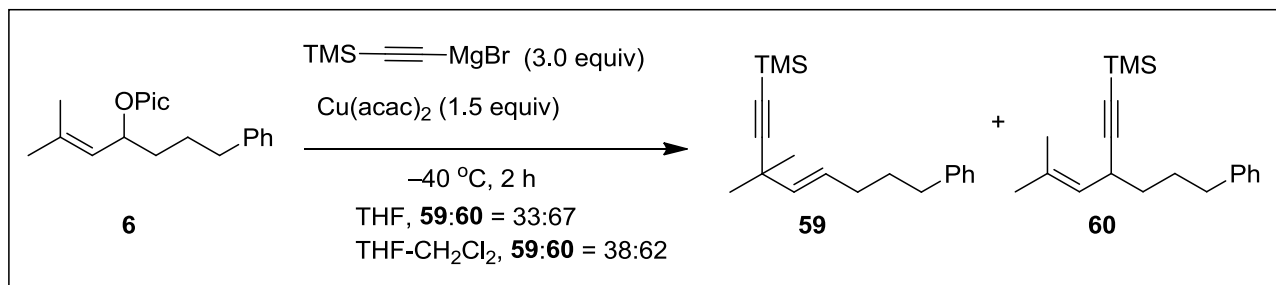
^aIsolated yield. ^bReaction was carried out at –60 °C.

Attempts by using Pd/Cu-catalyzed allylic substitution of picolinate **13b** were unsuccessful. As shown in **Table 4.9**, conditions using Pd(OAc)₂ (20 mol%)^{29b} generated a mixture of **50a** and **52** (entry 1), whereas conditions using Cu(acac)₂ (20 mol%) generated S_N2 product **51** as the major product (entry 2). Although characterization of **50a** was difficult because **50a** was decomposed during chromatography, **50a** was assigned among three possible S_N2' products in connection with three possible nucleophiles (Ph⁻, Br⁻, AcO⁻) in conditions of entry 1. At -40 °C, no reaction occurred by using Pd(OAc)₂ (20 mol%) as the catalyst along with PhMgBr and PhLi (entries 3 and 4).

Table 4.9 Pd/Cu-catalyzed Allylic Substitution of Picolinate 13b

13b Pd/Cu catalyst 50 51 52 MgBr₂ (2.0 equiv) quinoline, 24–30 mol% R = Ph, 50 R = Ph, 51 R = OH, 52 R = Br, 50a R = Br, 51a				
Entry	Ph metal (equiv)	Catalyst	Condition	Result
1	PhMgBr (1.5)	Pd(OAc) ₂ , 20 mol%	THF, 0 °C, overnight	50a:51a:52:13b = 46:0:54:0
2	PhMgBr (1.5)	Cu(acac) ₂ , 20 mol%	THF, 0 °C, overnight	50:51:52:13b = 24:65:11:0
3	PhMgBr (2.0)	Pd(OAc) ₂ , 20 mol%	THF, -40 °C, 2 h	no reaction
4	PhLi (2.0)	Pd(OAc) ₂ , 20 mol%	THF, -40 °C, 2 h	no reaction

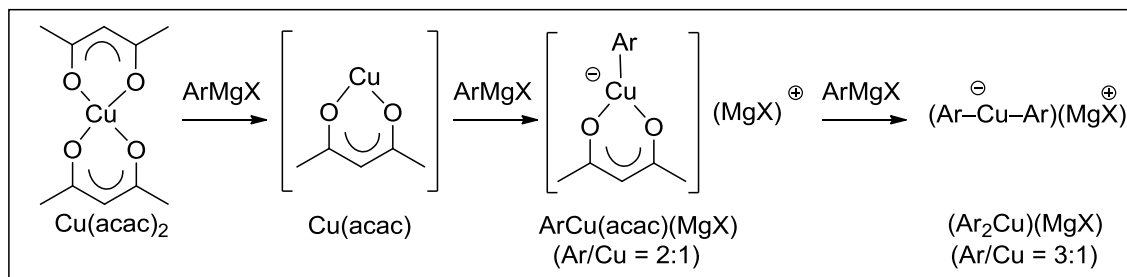
In addition, construction of quaternary with *sp* carbon group and Cu(acac)₂ only afforded a mixture of S_N2' and S_N2 products **59** and **60** in both THF and THF-CH₂Cl₂ solvent system (**Scheme 4.12**). No alcohol or remaining **6** were detected by ¹H NMR analysis of crude reaction mixtures.



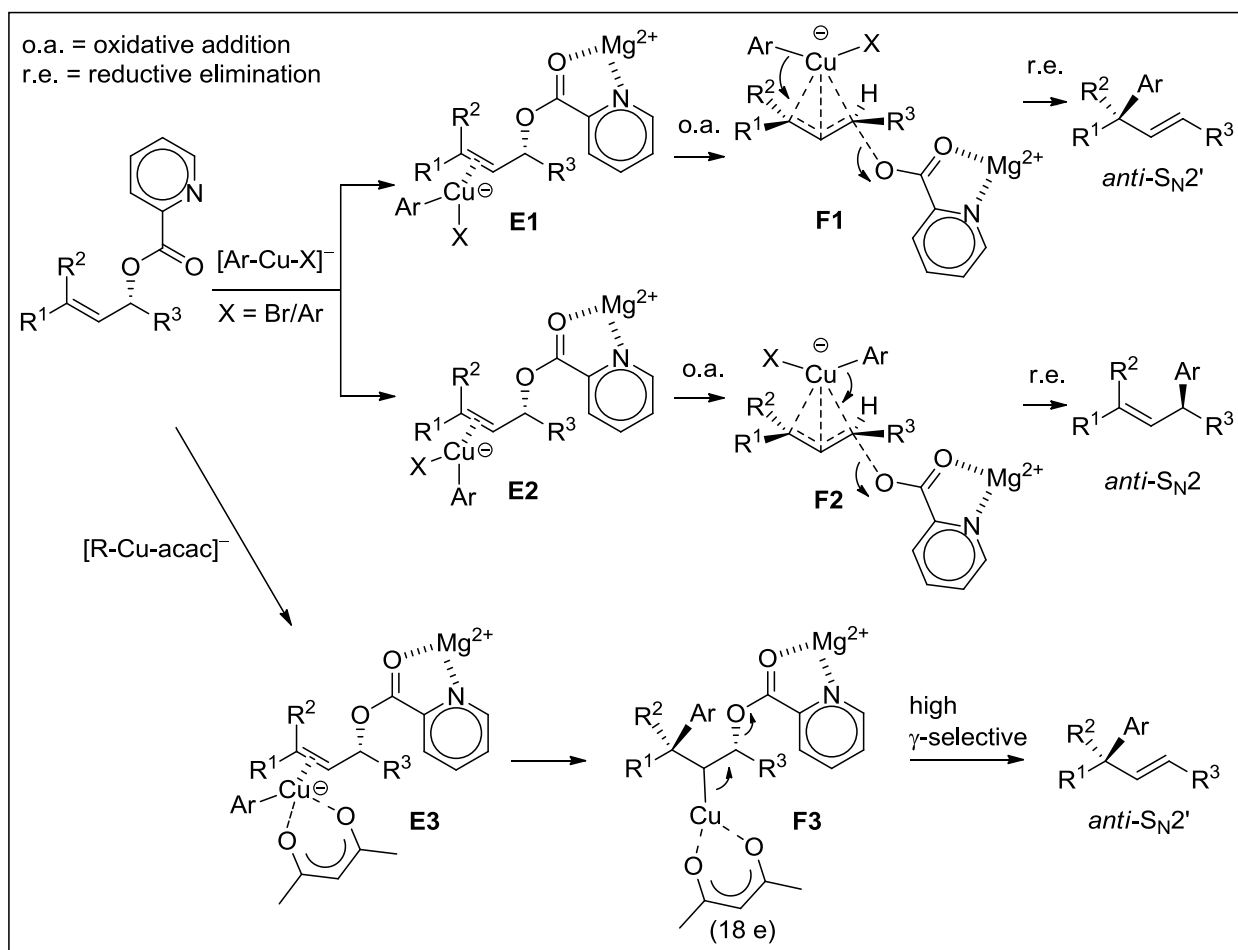
Scheme 4.12 Construction of Quaternary Carbons with *sp*-Carbon Group

4.3 Mechanism

Finally, we turned our attention to work out a possible pathway for the above reactions. Even though allylic substitution with organocopper reagents has been fully studied,³⁰ the above results somehow demonstrate importance of chelation of acac^- to copper other than types of organocopper reagents (“R–Cu” or “ R_2Cu^- ” species), rendering organocopper(III) species rather than neutral organocopper(I) intermediate. In view of mechanism, 1 equiv of PhMgBr per $\text{Cu}(\text{acac})_2$ is consumed stoichiometrically to reduce $\text{Cu}(\text{acac})_2$ to a Cu^+ species¹⁸ and use of 2 and 3 equivs of PhMgBr per $\text{Cu}(\text{acac})_2$ produces Ph–Cu and Ph_2Cu^- species, respectively (**Scheme 4.13**). Apparently, the larger dissymmetry of organocopper species $[\text{ArCu}(\text{acac})]^-$ derived from $\text{Cu}(\text{acac})_2$ and ArMgBr in a 1:2 ratio than $[\text{ArCuX}]^-$ (X = Br or Ar) derived from $\text{CuBr}\cdot\text{Me}_2\text{S}$ and ArMgBr in a 1:1 or 1:2 ratio is supposed to perform an obligation to $\text{S}_{\text{N}}2'$ -selectivity. On the other hand, the excellent γ -regioselectivity of $[\text{ArCu}(\text{acac})]^-$ species strongly implies a different pathway from $[\text{ArCuX}]^-$ (X = Br or Ar). Herein, an interesting possible transformation shown in **Scheme 4.14** is proposed. Basically, $[\text{ArCuX}]^-$ (X = Br or Ar) coordinates to olefin to form T-shaped complex **E1/E2**. Oxidative addition affords tetra-coordinated intermediate **F1/F2** subsequently and both $\text{S}_{\text{N}}2'$ and $\text{S}_{\text{N}}2$ products are possible to be produced via reductive elimination. Instead of the acknowledged T-shaped transient complex **E1/E2**, $[\text{ArCu}(\text{acac})]^-$ chelates to double bonds advantageously to form a stabilized organocopper intermediate **E3**, which is already tetra-coordinated. Subsequently, addition of Ar group at γ position results in formation of stable 18 electron organocopper(III) intermediate **F3**, which undergoes *anti*- β -elimination to produce *anti*- $\text{S}_{\text{N}}2'$ product with solid γ -selectivity. Therefore, acac^- originates stable tetra-coordinated as well as 18 electron transient organocopper intermediates, constituting high *anti*- $\text{S}_{\text{N}}2'$ selective pathway. In addition, $\text{Cu}(\text{OAc})_2$ and $\text{Cu}(\text{OMe})_2$ (**Table 4.2**, entries 15 and 16), although containing Cu–O bonds, did not provide high regioselectivity as $\text{Cu}(\text{acac})_2$. No generation of stable 18 electron intermediate such as $\text{Cu}(\text{acac})_2$ is a likely reason.



Scheme 4.13 Organocopper Reagents Derived from $\text{Cu}(\text{acac})_2$



Scheme 4.14 Possible Mechanism

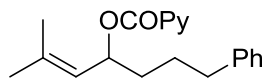
4.4 Conclusion

In conclusion, we have developed the 2:1 ArMgBr/Cu(acac)₂ and 3:1:1 ArMgBr/Cu(acac)₂/ZnI₂ reagents for construction of a quaternary carbon by allylic substitution, which proceeds with high stereo-, regio- and product-selectivities. We found furthermore that the olefin geometry in allylic picolinate does not affect CT and regioselectivity, but just dictates chirality of the product. This fact would be synthetically convenient for designing biologically important compounds, which consist of a chiral quaternary carbon possessing an aryl group.²³ Applications of above conditions for construction of quaternary carbons on cyclic ring turn out 81–87% regioselectivity in about 80% yield.

4.5 Experimental Section

General Remarks. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were measured in CDCl_3 using SiMe_4 ($\delta = 0$ ppm) and the centerline of triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). Chemical shifts in the ^{13}C NMR spectra accompany minus (for C and CH_2) and plus (for CH and CH_3) signs of APT experiments. The following solvents were distilled beforehand: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions were finished, the organic extracts were concentrated by using evaporators and the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60 N). $\text{Cu}(\text{acac})_2$ was purchased from TCI, Jpn, and used without purification, whereas $\text{CuBr}\cdot\text{Me}_2\text{S}$ was prepared as described previously.^{6b} Picolinates **1** (98% ee) and **14** were prepared according to the literature procedures published from our laboratory.^{5,7}

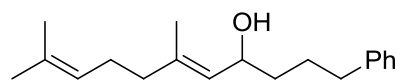
Synthesis of Racemic Picolinates 6–8, 13, and 52



6 (racemic)

2-Methyl-7-phenylhept-2-en-4-yl Picolinate (6). To an ice-cold solution of 3-methyl-2-butenal (**19**) (1.14 g, 13.6 mmol) in THF (60 mL) was added $\text{Ph}(\text{CH}_2)_3\text{MgCl}$ (26.5 mL, 0.77 M in THF, 20.4 mmol). The solution was stirred at rt for 2 h, and saturated NH_4Cl and EtOAc were added with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried over MgSO_4 , washed with brine, and concentrated to afford a residue, which was purified by chromatography on silica gel with hexane/ EtOAc to furnish alcohol **17** (2.49 g, 90%): IR (neat) 3361, 1453, 748, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.28–1.34 (m, 1 H), 1.42–1.54 (m, 1 H), 1.55–1.74 (m, 2 H), 1.67 (d, $J = 1$ Hz, 3 H), 1.72 (d, $J = 1$ Hz, 3 H), 2.63 (t, $J = 7$ Hz, 2 H), 4.35 (dt, $J = 8, 6$ Hz, 1 H), 5.15 (dm, $J = 9$ Hz, 1 H), 7.14–7.21 (m, 3 H), 7.25–7.31 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.3 (+), 25.9 (+), 27.4 (–), 36.0 (–), 37.4 (–), 68.6 (+), 125.8 (+), 128.2 (+), 128.4 (+), 128.5 (+), 135.4 (–), 142.5 (–). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{20}\text{O}$ (M^+) 204.1514, found 204.1516.

To an ice-cold suspension of picolinic acid (1.67 g, 13.6 mmol) in CH₂Cl₂ (30 mL) were added DMAP (746 mg, 6.11 mmol) and DCC (3.29 g, 15.9 mmol). The mixture was stirred at 0 °C for 30 min, and a solution of alcohol **17** (2.49 g, 12.2 mmol) in CH₂Cl₂ (20 mL) was added. The resulting mixture was stirred at 0 °C for 2 h, diluted with Et₂O and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel with hexane/EtOAc to afford picolinate **6** (3.09 g, 82%): IR (neat) 1737, 1713, 1245, 1133, 747, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.63–1.78 (m, 3 H), 1.73 (d, *J* = 1 Hz, 3 H), 1.80 (d, *J* = 1 Hz, 3 H), 1.87–1.98 (m, 1 H), 2.65 (t, *J* = 7 Hz, 2 H), 5.29 (dm, *J* = 10 Hz, 1 H), 5.80–5.89 (m, 1 H), 7.14–7.20 (m, 3 H), 7.23–7.30 (m, 2 H), 7.44 (ddd, *J* = 8, 5, 1 Hz, 1 H), 7.81 (dt, *J* = 8, 2 Hz, 1 H), 8.10 (dt, *J* = 8, 1 Hz, 1 H), 8.77 (ddd, *J* = 5, 2, 1 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 18.7 (+), 25.9 (+), 27.2 (–), 34.6 (–), 35.7 (–), 73.3 (+), 123.4 (+), 125.2 (+), 125.8 (+), 126.7 (+), 128.4 (+), 128.5 (+), 136.9 (+), 138.2 (–), 142.2 (–), 148.7 (–), 150.0 (+), 164.7 (–). HRMS (EI) calcd for C₂₀H₂₃NO₂ (M⁺) 309.1729, found 309.1730.

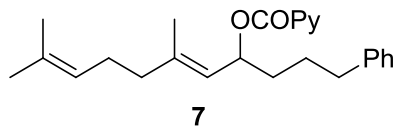


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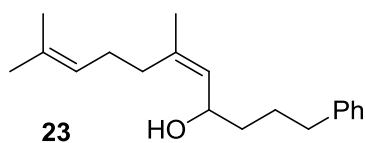
(E)-6,10-Dimethyl-1-phenylundeca-5,9-dien-4-ol (21). To a suspension of molecular sieves 4A (1.65 g), TPAP (116.0 mg, 0.330 mmol), and NMO (590.0 mg, 5.04 mmol) in CH₂Cl₂ (20 mL) was added a solution of geraniol (501.6 mg, 3.25 mmol) in CH₂Cl₂ (10 mL). The mixture was stirred at rt for 1 h and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **20** (433.9 mg, 88%): ¹H NMR (400 MHz, CDCl₃) δ 1.61 (s, 3 H), 1.69 (s, 3 H), 2.15–2.28 (m, 4 H), 2.17 (s, 3 H), 5.04–5.12 (m, 1 H), 5.88 (d, *J* = 8 Hz, 1 H), 10.00 (d, *J* = 8 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 17.7 (+), 17.8 (+), 25.7 (+), 25.8 (–), 40.7 (–), 122.7 (+), 127.5 (+), 133.0 (–), 163.9 (–), 191.4 (+). The ¹H and ¹³C NMR spectra were consistent with those reported.²⁴

According to the Grignard addition to aldehyde **19**, aldehyde **20** (433.9 mg, 2.85 mmol) in THF (25 mL) was subjected to reaction with Ph(CH₂)₃MgBr (5.00 mL, 0.80 M in THF, 4.00 mmol) at rt for 1 h to produce alcohol **21** (723.7 mg, 93%): IR (neat) 3377, 1453, 748, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (br s, 1 H), 1.42–1.54 (m, 1 H), 1.57–1.74 (m, 3 H), 1.59 (s, 3 H), 1.67 (s, 6 H), 2.01 (t, *J* = 7.5 Hz, 2 H), 2.05–2.14 (m, 2 H), 2.63 (t, *J* = 7 Hz, 2 H), 4.37 (dt,

$J = 9, 6 \text{ Hz}, 1 \text{ H}$), 5.07 (t, $J = 7 \text{ Hz}, 1 \text{ H}$), 5.16 (d, $J = 9 \text{ Hz}, 1 \text{ H}$), 7.14–7.20 (m, 3 H), 7.23–7.30 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.7 (+), 17.8 (+), 25.7 (+), 26.4 (–), 27.3 (–), 36.0 (–), 37.3 (–), 39.6 (–), 68.5 (+), 124.0 (+), 125.8 (+), 128.0 (+), 128.3 (+), 128.5 (+), 131.8 (–), 138.7 (–), 142.5 (–). HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{28}\text{ONa}$ $[(\text{M}+\text{Na})^+]$ 295.2038, found 295.2036.



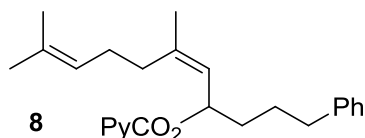
(E)-6,10-Dimethyl-1-phenylundeca-5,9-dien-4-yl Picolinate (7). According to the preparation of picolinate **6**, alcohol **21** (155.8 mg, 0.572 mmol) was subjected to condensation with picolinic acid (95.9 mg, 0.779 mmol), DMAP (69.6 mg, 0.570 mmol), and DCC (156.0 mg, 0.756 mmol) in CH_2Cl_2 (3 + 2 mL) at rt for 2 h to afford picolinate **7** (172.1 mg, 80%): IR (neat) 1738, 1713, 1245, 1132, 746, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.54–1.82 (m, 3 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.79 (d, $J = 2 \text{ Hz}, 3 \text{ H}$), 1.86–1.98 (m, 1 H), 1.98–2.14 (m, 4 H), 2.66 (t, $J = 7 \text{ Hz}, 2 \text{ H}$), 5.05 (tm, $J = 7 \text{ Hz}, 1 \text{ H}$), 5.28 (dd, $J = 9, 1 \text{ Hz}, 1 \text{ H}$), 5.86 (dt, $J = 9, 6 \text{ Hz}, 1 \text{ H}$), 7.13–7.20 (m, 3 H), 7.22–7.30 (m, 2 H), 7.44 (ddd, $J = 7.5, 5, 1 \text{ Hz}, 1 \text{ H}$), 7.81 (dt, $J = 2, 7.5 \text{ Hz}, 1 \text{ H}$), 8.10 (dt, $J = 7.5, 1 \text{ Hz}, 1 \text{ H}$), 8.76 (dm, $J = 5 \text{ Hz}, 1 \text{ H}$); ^{13}C NMR (100 MHz, CDCl_3) δ 17.0 (+), 17.8 (+), 25.7 (+), 26.3 (–), 27.1 (–), 34.6 (–), 35.7 (–), 39.6 (–), 73.2 (+), 123.2 (+), 123.9 (+), 125.2 (+), 125.8 (+), 126.6 (+), 128.4 (+), 128.5 (+), 131.8 (–), 136.9 (+), 141.4 (–), 142.2 (–), 148.8 (–), 150.0 (+), 164.7 (–). HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_2\text{Na}$ $[(\text{M}+\text{Na})^+]$ 400.2252, found 400.2253.



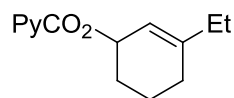
(Z)-6,10-Dimethyl-1-phenylundeca-5,9-dien-4-ol (23). According to the oxidation of geraniol, a mixture of nerol (501.6 mg, 3.25 mmol), TPAP (114.0 mg, 0.324 mmol), NMO (570.0 mg, 4.87 mmol), and molecular sieves 4A (1.63 g) in CH_2Cl_2 (20 + 10 mL) was stirred at rt for 1 h to furnish **22** (445.5 mg, 90%): ^1H NMR (400 MHz, CDCl_3) δ 1.59 (s, 3 H), 1.68 (d, $J = 1 \text{ Hz}, 3 \text{ H}$), 1.98 (d, $J = 1 \text{ Hz}, 3 \text{ H}$), 2.24 (dt, $J = 7, 7.5 \text{ Hz}, 2 \text{ H}$), 2.59 (t, $J = 7.5 \text{ Hz}, 2 \text{ H}$), 5.10 (tm, $J = 7 \text{ Hz}, 1 \text{ H}$), 5.88 (d, $J = 8 \text{ Hz}, 1 \text{ H}$), 9.90 (d, $J = 8 \text{ Hz}, 1 \text{ H}$); ^{13}C NMR (100 MHz, CDCl_3) δ 17.8 (+),

25.1 (+), 25.7 (+), 27.1 (–), 32.7 (–), 122.4 (+), 128.8 (+), 133.8 (–), 163.9 (–), 190.9 (+). The ^1H and ^{13}C NMR spectra were consistent with those reported.²⁵

According to the Grignard addition to aldehyde **19**, aldehyde **22** (445.5 mg, 2.93 mmol) in THF (25 mL) was subjected to reaction with $\text{Ph}(\text{CH}_2)_3\text{MgBr}$ (5.10 mL, 0.80 M in THF, 4.08 mmol) at rt for 1 h to furnish alcohol **23** (737.7 mg, 93%): IR (neat) 3364, 1452, 748, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (br s, 1 H), 1.41–1.53 (m, 1 H), 1.55–1.77 (m, 3 H), 1.59 (s, 3 H), 1.68 (s, 3 H), 1.72 (d, J = 1 Hz, 3 H), 2.00–2.17 (m, 4 H), 2.63 (t, J = 7 Hz, 2 H), 4.33 (dt, J = 9, 6 Hz, 1 H), 5.06–5.14 (m, 1 H), 5.18 (d, J = 9 Hz, 1 H), 7.13–7.20 (m, 3 H), 7.23–7.30 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.7 (+), 23.37 (+), 23.39 (+), 25.7 (+), 26.6 (–), 27.5 (–), 32.4 (–), 36.0 (–), 37.2 (–), 68.0 (+), 124.0 (+), 125.8 (+), 128.3 (+), 128.5 (+), 129.1 (+), 132.5 (–), 138.9 (–), 142.5 (–). HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{28}\text{ONa}$ $[(\text{M}+\text{Na})^+]$ 295.2038, found 295.2066.

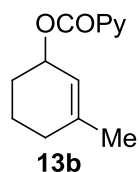


(Z)-6,10-Dimethyl-1-phenylundeca-5,9-dien-4-yl Picolinate (8). According to the preparation of picolinate **6**, alcohol **23** (294.1 mg, 1.08 mmol) was subjected to condensation with picolinic acid (167.9 mg, 1.36 mmol), DMAP (101.1 mg, 0.828 mmol), and DCC (297.5 mg, 1.44 mmol) in CH_2Cl_2 (8 + 2 mL) at rt for 2 h to produce picolinate **8** (369.3 mg, 91%): IR (neat) 1738, 1713, 1245, 1132, 747, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.58 (s, 3 H), 1.62 (s, 3 H), 1.74 (d, J = 1.5 Hz, 3 H), 1.64–1.80 (m, 3 H), 1.86–1.98 (m, 1 H), 2.00–2.20 (m, 3 H), 2.28–2.38 (m, 1 H), 2.65 (t, J = 7 Hz, 2 H), 5.11 (tm, J = 7 Hz, 1 H), 5.31 (dd, J = 10, 1 Hz, 1 H), 5.89 (dt, J = 10, 7 Hz, 1 H), 7.12–7.20 (m, 3 H), 7.22–7.29 (m, 2 H), 7.43 (ddd, J = 8, 5, 1 Hz, 1 H), 7.80 (dt, J = 2, 8 Hz, 1 H), 8.10 (dt, J = 8, 1 Hz, 1 H), 8.76 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.7 (+), 23.4 (+), 25.7 (+), 26.7 (–), 27.3 (–), 32.7 (–), 34.8 (–), 35.8 (–), 72.8 (+), 123.9 (+), 124.0 (+), 125.2 (+), 125.8 (+), 126.6 (+), 128.4 (+), 128.5 (+), 132.0 (–), 136.9 (+), 141.7 (–), 142.1 (–), 148.8 (–), 149.9 (+), 164.6 (–). HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_2$ $[(\text{M}+\text{H})^+]$ 378.2433, found 378.2441.



13a (racemic)

3-Ethylcyclohex-2-enyl Picolinate (13a). According to the preparation of picolinate **6**, alcohol **28**²⁶ (208.1 mg, 1.65 mmol) was subjected to condensation with picolinic acid (245.0 mg, 1.99 mmol), DMAP (202.1 mg, 1.65 mmol), and DCC (450.0 mg, 2.18 mmol) in CH₂Cl₂ (14 + 2 mL) to give picolinate **13a** (318.4 mg, 83%): IR (neat) 1736, 1713, 1245, 1133, 911, 748, 709 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.03 (t, J = 7.5 Hz, 3 H), 1.65–1.76 (m, 1 H), 1.81–2.11 (m, 7 H), 5.57–5.66 (m, 2 H), 7.45 (dm, J = 7.5 Hz, 1 H), 7.83 (dt, J = 1.5, 7.5 Hz, 1 H), 8.13 (d, J = 7.5 Hz, 1 H), 8.78 (dm, J = 5 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 11.9 (+), 19.5 (–), 28.4 (–), 28.5 (–), 30.4 (–), 70.9 (+), 118.1 (+), 125.2 (+), 126.7 (+), 136.9 (+), 146.7 (–), 148.9 (–), 150.0 (+), 165.1 (–). HRMS (FAB) calcd for C₁₄H₁₈NO₂ (M)⁺ 232.1338, found 232.1343.

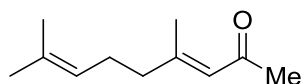


3-Methylcyclohex-2-en-1-yl picolinate (13b). To an ice-cooled solution of 3-methylcyclohex-2-enone (717.1 mg, 6.51 mmol) and CeCl₃·7H₂O (2.45 g, 6.58 mmol) in MeOH (20 mL) was added NaBH₄ (254.7 mg, 6.73 mmol). After further stirring at 0 °C for 30 min, the reaction was quenched with saturated NaHCO₃ and extracted with EtOAc twice. The combined extracts was washed with brine, dried over MgSO₄, and concentrated to afford a residue, which was purified by chromatography to furnish an alcohol **52** (606.6 mg, 83%): ¹H NMR (400 MHz, CDCl₃) δ 1.50–1.62 (m, 2 H), 1.68 (s, 3 H), 1.70–1.83 (m, 2 H), 1.83–2.02 (m, 2 H), 4.12–4.22 (m, 1 H), 5.46–5.52 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 19.1 (–), 23.6 (+), 30.1 (–), 31.7 (–), 65.8 (+), 124.4 (+), 138.5 (–). The ¹H and ¹³C NMR spectra were identical to those reported.³¹

According to the preparation of picolinate **6**, alcohol **52** (200.8 mg, 1.79 mmol) was subjected to condensation with picolinic acid (287.2 mg, 2.33 mmol), DMAP (108.0 mg, 0.884 mmol), and DCC (481.2 mg, 2.33 mmol) in CH₂Cl₂ (7 + 2 mL) to give picolinate **13b** (341.2 mg, 88%): ¹H NMR (300 MHz, CDCl₃) δ 1.62–1.80 (m, 2 H), 1.73 (s, 3 H), 1.80–2.10 (m, 4 H), 5.52–5.65 (m, 2 H), 7.43 (ddd, J = 7.5, 5, 1.5 Hz, 1 H), 7.80 (dt, J = 7.5, 1.5 Hz, 1 H), 8.10 (dt, J

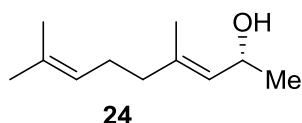
= 7.5, 1 Hz, 1 H), 8.75 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.4 (–), 23.8 (+), 28.1 (–), 30.1 (–), 70.8 (+), 119.9 (+), 125.1 (+), 126.7 (+), 136.9 (+), 141.6 (–), 148.9 (–), 150.0 (+), 165.0 (–).

Synthesis of Optically Active Picolinates 9–12



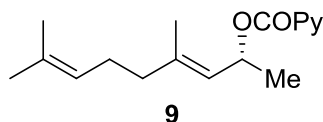
(E)-4,8-Dimethylnona-3,7-dien-2-one. According to the Grignard addition to aldehyde **19**, aldehyde **20** (466.5 mg, 3.06 mmol) in THF (30 mL) was subjected to reaction with MeMgBr (4.60 mL, 0.99 M in THF, 4.55 mmol) at rt for 1 h to furnish racemic alcohol *rac*-**24** (467.1 mg, 91%).

According to the oxidation of geraniol, a mixture of *rac*-**24** (228.2 mg, 1.36 mmol), TPAP (47.2 mg, 0.134 mmol), NMO (318.0 mg, 2.71 mmol), and molecular sieves 4A (677.0 mg) in CH_2Cl_2 (12 + 2 mL) was stirred at rt for 2 h to furnish the title ketone (188.1 mg, 83%): ^1H NMR (400 MHz, CDCl_3) δ 1.61 (s, 3 H), 1.69 (s, 3 H), 2.10–2.20 (m, 4 H), 2.13 (d, J = 1 Hz, 3 H), 2.17 (s, 3 H), 5.02–5.12 (m, 1 H), 6.06 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.7 (+), 19.3 (+), 25.7 (+), 26.2 (–), 31.8 (+), 41.2 (–), 123.1 (+), 123.7 (+), 132.6 (–), 158.3 (–), 198.9 (–). The ^1H and ^{13}C NMR spectra were identical with those reported.²⁷

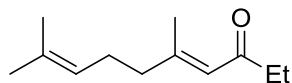


(R,E)-4,8-Dimethylnona-3,7-dien-2-ol (24). To a solution of (S)-methyl oxazaborolidine (0.030 mL, 1.0 M in toluene, 0.030 mmol) and *N,N*-diethylaniline borane (0.036 mL, 0.202 mmol) in THF (1 mL) at $-20\text{ }^\circ\text{C}$ was added a solution of the above ketone (30.2 mg, 0.182 mmol) in THF (2 mL) over 5 h. After the addition, the solution was stirred at $-20\text{ }^\circ\text{C}$ for further 3 h. Cold MeOH (3 mL) was added slowly to the solution at $-20\text{ }^\circ\text{C}$, and the cooling bath was removed. The solution was stirred at rt for 1 h and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **24** (29.7 mg, 97%): $[\alpha]_{\text{D}}^{24} +23$ (c 0.60, CHCl_3) (cf. $[\alpha]_{\text{D}}^{20} +21.6$ (c 0.3, CHCl_3) for the *R* enantiomer of 98% ee),¹³ ^1H NMR (400 MHz,

CDCl₃) δ 1.23 (d, J = 6 Hz, 3 H), 1.43 (br s, 1 H), 1.60 (s, 3 H), 1.679 (s, 3 H), 1.682, (s, 3 H), 1.99 (t, J = 7 Hz, 2 H), 2.05–2.14 (m, 2 H), 4.57 (dq, J = 8, 6 Hz, 1 H), 5.08 (tm, J = 7 Hz, 1 H), 5.21 (dm, J = 8, 1 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 16.5 (+), 17.7 (+), 23.7 (+), 25.7 (+), 26.5 (–), 39.5 (–), 64.8 (+), 124.0 (+), 129.2 (+), 131.7 (–), 137.6 (–). HRMS (EI) calcd for C₁₁H₂₀O (M⁺) 168.1514, found 168.1514. The ¹H and ¹³C NMR spectra were identical with those reported.²⁷ The enantiomeric purity of 82% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH = 99.5/0.5, 0.700 mL/min, 30 °C, t_R /min = 19.7 (*R*-isomer), 20.7 (*S*-isomer).



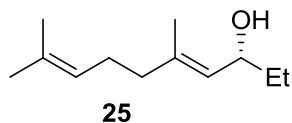
(*R,E*)-4,8-Dimethylnona-3,7-dien-2-yl Picolinate (9). According to the preparation of picolinate **6**, alcohol **24** (29.7 mg, 0.176 mmol) was subjected to condensation with picolinic acid (31.2 mg, 0.253 mmol), DMAP (21.7 mg, 0.178 mmol), and DCC (47.7 mg, 0.231 mmol) in CH₂Cl₂ (1 + 1 mL) at rt for 2 h to afford **9** (42.4 mg, 88%): [α]_D²³ –17 (*c* 0.26, CHCl₃); IR (neat) 1738, 1715, 1132, 747, 708 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (d, J = 6 Hz, 3 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 1.78 (d, J = 1 Hz, 3 H), 1.99–2.05 (m, 2 H), 2.06–2.15 (m, 2 H), 5.07 (tm, J = 7 Hz, 1 H), 5.37 (dq, J = 9, 1 Hz, 1 H), 5.95 (dq, J = 9, 6 Hz, 1 H), 7.44 (ddd, J = 8, 4.5, 1 Hz, 1 H), 7.82 (dt, J = 2, 8 Hz, 1 H), 8.12 (dt, J = 8, 1 Hz, 1 H), 8.77 (ddd, J = 5, 2, 1 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 16.8 (+), 17.7 (+), 21.0 (+), 25.7 (+), 26.3 (–), 39.5 (–), 70.0 (+), 123.9 (+), 124.4 (+), 125.1 (+), 126.6 (+), 131.7 (–), 136.9 (+), 140.2 (–), 148.8 (–), 149.9 (+), 164.7 (–). HRMS (EI) calcd for C₁₇H₂₃NO₂ (M⁺) 273.1729, found 273.1733.



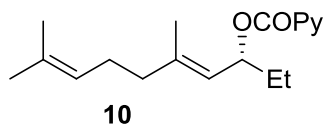
(*E*)-5,9-Dimethyldeca-4,8-dien-3-one. According to the Grignard addition to aldehyde **19**, aldehyde **20** (410.9 mg, 2.70 mmol) in THF (25 mL) was subjected to reaction with EtMgBr (4.80 mL, 0.80 M in THF, 3.84 mmol) at rt for 1 h to furnish racemic alcohol *rac*-**25** (463.0 mg, 94%).

According to the oxidation of geraniol, a mixture of alcohol *rac*-**25** (212.1 mg, 1.16 mmol), TPAP (41.0 mg, 0.117 mmol), NMO (260.0 mg, 2.22 mmol), and molecular sieves 4A (598.4

mg) in CH₂Cl₂ (10 + 2 mL) was stirred at rt for 2 h to produce the title ketone (176.8 mg, 84%): IR (neat) 1688, 1621, 1122 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.07 (t, *J* = 7 Hz, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 2.10–2.22 (m, 4 H), 2.14 (s, 3 H), 2.44 (q, *J* = 7 Hz, 2 H), 5.02–5.12 (m, 1 H), 6.05 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 8.2 (+), 17.7 (+), 19.4 (+), 25.7 (+), 26.2 (–), 37.5 (–), 41.3 (–), 123.0 (+), 123.1 (+), 132.5 (–), 157.9 (–), 201.8 (–). HRMS (EI) calcd for C₁₂H₂₀O (*M*⁺) 180.1514, found 180.1510.

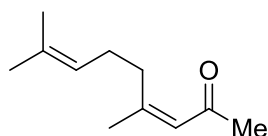


(*R,E*)-5,9-Dimethyldeca-4,8-dien-3-ol (25). According to the CBS reduction to afford alcohol **24**, a solution of the above ketone (77.6 mg, 0.426 mmol) in THF (2 mL) was added to a solution of (*S*)-methyl oxazaborolidine (0.090 mL, 1.0 M in toluene, 0.090 mmol) and *N,N*-diethylaniline borane (0.080 mL, 0.450 mmol) in THF (4 mL) at –40 °C over 60 min and the solution was allowed to warm to –20 °C over 3 h. Cold MeOH (3 mL) was added at –20 °C and the solution was stirred at rt for 1 h to furnish alcohol **25** (26.8 mg, 34%): IR (neat) 3369, 1454, 1378 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, *J* = 8 Hz, 3 H), 1.38–1.54 (m, 2 H), 1.60 (s, 3 H), 1.680 (s, 3 H), 1.683 (s, 3 H), 2.02 (t, *J* = 8 Hz, 2 H), 2.06–2.16 (m, 2 H), 4.28 (dt, *J* = 8.5, 7 Hz, 1 H), 5.09 (tm, *J* = 7 Hz, 1 H), 5.16 (dd, *J* = 8.5, 1 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.8 (+), 16.7 (+), 17.7 (+), 25.7 (+), 26.5 (–), 30.6 (–), 39.7 (–), 70.1 (+), 124.0 (+), 127.9 (+), 131.7 (–), 138.7 (–). HRMS (EI) calcd for C₁₂H₂₂O (*M*⁺) 182.1671, found 182.1671. The ¹H and ¹³C NMR spectra were identical with those reported.²⁸ The enantiomeric purity of 60% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH = 99.8/0.2, 0.700 mL/min, 30 °C, *t*_R/min = 18.8 (*R*-isomer), 19.6 (*S*-isomer).



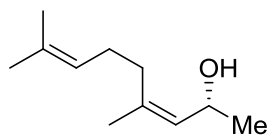
(*R,E*)-5,9-Dimethyldeca-4,8-dien-3-yl Picolinate (10). According to the preparation of picolinate **6**, alcohol **25** (26.8 mg, 0.147 mmol) was subjected to condensation with picolinic acid (24.2 mg, 0.197 mmol), DCC (40.0 mg, 0.194 mmol), and DMAP (17.8 mg, 0.146 mmol) in CH₂Cl₂ (1 + 1 mL) at rt for 2 h to give picolinate **10** (36.6 mg, 87%): [*α*]_D²⁶ –11 (c 0.31, CHCl₃):

IR (neat) 1714, 1438, 1245, 1134, 747, 708 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.94 (t, $J = 7$ Hz, 3 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.66–1.78 (m, 1 H), 1.80 (d, $J = 1$ Hz, 3 H), 1.84–1.96 (m, 1 H), 2.00–2.16 (m, 4 H), 5.07 (tm, $J = 7$ Hz, 1 H), 5.29 (dm, $J = 7$ Hz, 1 H), 5.76 (dt, $J = 9, 7$ Hz, 1 H), 7.44 (ddd, $J = 7.5, 5, 1$ Hz, 1 H), 7.82 (dt, $J = 2, 7.5$ Hz, 1 H), 8.12 (dt, $J = 7.5, 1$ Hz, 1 H), 8.77 (ddd, $J = 5, 2, 1$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.6 (+), 17.0 (+), 17.7 (+), 25.6 (+), 26.3 (–), 28.0 (–), 39.6 (–), 74.6 (+), 123.1 (+), 123.9 (+), 125.1 (+), 126.5 (+), 131.7 (–), 136.8 (+), 141.3 (–), 148.8 (–), 149.9 (+), 164.7 (–). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$ (M^+) 287.1885, found 287.1887.



(Z)-4,8-Dimethylnona-3,7-dien-2-one. According to the Grignard addition to aldehyde **19**, aldehyde **22** (520.0 mg, 3.42 mmol) in THF (25 mL) was subjected to reaction with MeMgBr (5.18 mL, 0.99 M in THF, 5.13 mmol) at rt for 2 h to produce racemic alcohol *rac*-**26** (492.0 mg, 86%).

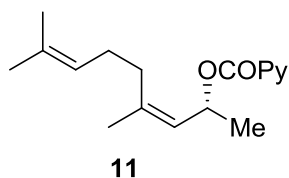
According to the oxidation of geraniol, a mixture of *rac*-**26** (267.5 mg, 1.59 mmol), TPAP (53.4 mg, 0.152 mmol), NMO (381.0 mg, 3.25 mmol), and molecular sieves 4A (800.1 mg) in CH_2Cl_2 (12 + 3 mL) was stirred at rt for 3 h to produce the title ketone (204.8 mg, 77%): ^1H NMR (400 MHz, CDCl_3) δ 1.63 (s, 3 H), 1.68 (s, 3 H), 1.87 (d, $J = 1$ Hz, 3 H), 2.09–2.19 (m, 2 H), 2.15 (s, 3 H), 2.58 (t, $J = 7.5$ Hz, 2 H), 5.14 (tm, $J = 7.5$ Hz, 1 H), 6.06 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6 (+), 25.6 (+), 25.7 (+), 26.8 (–), 31.7 (+), 33.8 (–), 123.8 (+), 124.3 (+), 132.2 (–), 158.9 (–), 198.2 (–). The ^1H and ^{13}C NMR spectra were identical with those reported.²⁷



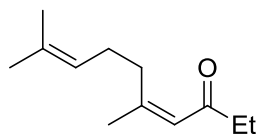
26

(R,Z)-4,8-Dimethylnona-3,7-dien-2-ol (26). According to the CBS reduction to afford alcohol **24**, a solution of the above ketone (109.2 mg, 0.657 mmol) in THF (4 mL) was mixed with a solution of (*S*)-methyl oxazaborolidine (0.13 mL, 1.0 M in toluene, 0.13 mmol) and *N,N*-

diethylaniline borane (0.13 mL, 0.731 mmol) in THF (5 mL) at $-20\text{ }^{\circ}\text{C}$ over 4 h and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for 3 h. Cold MeOH (3 mL) was added dropwise at $-20\text{ }^{\circ}\text{C}$ and the solution was stirred at rt for 1 h to furnish alcohol **26** (82.5 mg, 75%): $[\alpha]_{\text{D}}^{20} +14$ (c 0.80, CHCl_3); IR (neat) 3340 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.22 (d, $J = 6\text{ Hz}$, 3 H), 1.46 (br s, 1 H), 1.61 (s, 3 H), 1.70 (s, 3 H), 1.72 (d, $J = 1\text{ Hz}$, 3 H), 2.02–2.16 (m, 4 H), 4.53 (dq, $J = 9, 6\text{ Hz}$, 1 H), 5.07–5.15 (m, 1 H), 5.23 (dd, $J = 9, 1\text{ Hz}$, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.7 (+), 23.3 (+), 23.6 (+), 25.7 (+), 26.5 (–), 32.3 (–), 64.3 (+), 124.0 (+), 130.3 (+), 132.5 (–), 137.7 (–). The ^1H and ^{13}C NMR spectra were identical with those reported.²⁷ The enantiomeric purity of 66% ee was determined by chiral HPLC analysis of the corresponding picolinate as described below.

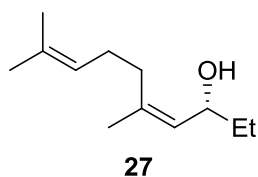


(*R,Z*)-4,8-Dimethylnona-3,7-dien-2-yl Picolinate (11). According to the preparation of picolinate **6**, alcohol **26** (82.5 mg, 0.490 mmol) was subjected to condensation with picolinic acid (82.5 mg, 0.670 mmol), DCC (131.6 mg, 0.638 mmol), and DMAP (56.2 mg, 0.460 mmol) in CH_2Cl_2 (2 + 1 mL) at rt for 2 h to afford **11** (114.5 mg, 85%): $[\alpha]_{\text{D}}^{22} -76$ (c 0.53, CHCl_3); IR (neat) 1713, 1245, 1127, 747, 708 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.45 (d, $J = 6\text{ Hz}$, 3 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 1.75 (d, $J = 1\text{ Hz}$, 3 H), 2.00–2.22 (m, 3 H), 2.28–2.39 (m, 1 H), 5.06–5.16 (m, 1 H), 5.39 (d, $J = 9.5\text{ Hz}$, 1 H), 5.95 (dq, $J = 9.5, 6\text{ Hz}$, 1 H), 7.44 (ddd, $J = 8, 5, 1\text{ Hz}$, 1 H), 7.82 (dt, $J = 2, 8\text{ Hz}$, 1 H), 8.12 (dt, $J = 8, 1\text{ Hz}$, 1 H), 8.76 (ddd, $J = 5, 2, 1\text{ Hz}$, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6 (+), 21.2 (+), 23.3 (+), 25.7 (+), 26.6 (–), 32.5 (–), 69.6 (+), 123.8 (+), 125.1 (+), 125.2 (+), 126.6 (+), 132.0 (–), 136.8 (+), 140.5 (–), 148.8 (–), 149.9 (+), 164.6 (–). HRMS (EI) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_2$ (M^+) 273.1729, found 273.1722. The enantiomeric purity of 66% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH = 99/1, 0.300 mL/min, $30\text{ }^{\circ}\text{C}$, $t_{\text{R}}/\text{min} = 46.4$ (*R*-isomer), 53.7 (*S*-isomer).



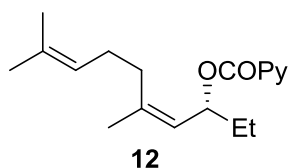
(Z)-5,9-Dimethyldeca-4,8-dien-3-one. According to the Grignard addition to aldehyde **19**, aldehyde **22** (440.3 mg, 2.89 mmol) in THF (25 mL) was subjected to addition reaction with EtMgBr (5.10 mL, 0.80 M in THF, 4.08 mmol) at rt for 1 h to furnish racemic alcohol *rac*-**27** (459.8 mg, 87%).

According to the oxidation of geraniol, a mixture of *rac*-**27** (206.3 mg, 1.13 mmol), TPAP (36.5 mg, 0.104 mmol), NMO (267.8 mg, 2.29 mmol), and molecular sieves 4A (570.2 mg) in CH₂Cl₂ (9 + 2 mL) was stirred at rt for 3 h to give the title ketone (162.6 mg, 80%): IR (neat) 1688, 1621, 1125 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.06 (t, *J* = 7 Hz, 3 H), 1.62 (s, 3 H), 1.67 (d, *J* = 1 Hz, 3 H), 1.87 (d, *J* = 1 Hz, 3 H), 2.07–2.20 (m, 2 H), 2.42 (q, *J* = 7 Hz, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 5.13 (tm, *J* = 7.5 Hz, 1 H), 6.03 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 8.2 (+), 17.7 (+), 25.6 (+), 25.7 (+), 26.9 (–), 33.9 (–), 37.4 (–), 123.7 (+), 123.9 (+), 132.1 (–), 158.5 (–), 201.2 (–). HRMS (EI) calcd for C₁₂H₂₀O (M⁺) 180.1514, found 180.1519.



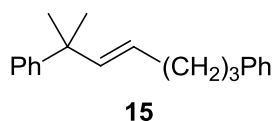
(R,Z)-5,9-Dimethyldeca-4,8-dien-3-ol (27). According to the CBS reduction to afford alcohol **24**, a solution of the above ketone (96.3 mg, 0.534 mmol) in THF (3 mL) was added to a solution of (*S*)-methyl oxazaborolidine (0.11 mL, 1.0 M in toluene, 0.11 mmol) and *N,N*-diethylaniline borane (0.11 mL, 0.619 mmol) in THF (5 mL) at –20 °C over 2 h and the solution was stirred at –20 °C for 6 h. Cold MeOH (3 mL) was added at –20 °C and the solution was stirred at rt for 1 h to furnish alcohol **27** (83.9 mg, 88%): [α]_D²² +3 (c 0.68, CHCl₃); IR (neat) 3357, 1448, 1002, 959 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.89 (t, *J* = 8 Hz, 3 H), 1.34–1.66 (m, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.73 (d, *J* = 1.5 Hz, 3 H), 2.00–2.20 (m, 4 H), 4.23 (dt, *J* = 9, 7 Hz, 1 H), 5.06–5.14 (m, 1 H), 5.17 (d, *J* = 9 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.9 (+), 17.7 (+), 23.3 (+), 25.7 (+), 26.6 (–), 30.4 (–), 32.4 (–), 69.5 (+), 124.0 (+), 128.9 (+), 132.4 (–), 138.9 (–). HRMS (EI)

calcd for $C_{12}H_{22}O$ (M^+) 182.1671, found 182.1672. The enantiomeric purity of 63% ee was determined by chiral HPLC analysis of the corresponding picolinate as described below.



(*R,Z*)-5,9-Dimethyldeca-4,8-dien-3-yl Picolinate (12). According to the preparation of picolinate **6**, alcohol **27** (83.9 mg, 0.460 mmol) was subjected to condensation with picolinic acid (78.8 mg, 0.640 mmol), DCC (139.1 mg, 0.674 mmol), DMAP (64.8 mg, 0.530 mmol) in CH_2Cl_2 (4 + 1 mL) at rt for 2 h to afford picolinate **12** (112.0 mg, 85%): $[\alpha]_D^{23}$ -64 (c 0.60, $CHCl_3$); IR (neat) 1714, 1245, 1137, 747, 707 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7 Hz, 3 H), 1.61 (s, 3 H), 1.62–1.78 (m, 1 H), 1.65 (s, 3 H), 1.76 (d, J = 1.5 Hz, 3 H), 1.82–1.96 (m, 1 H), 2.00–2.20 (m, 3 H), 2.32–2.42 (m, 1 H), 5.10–5.18 (m, 1 H), 5.32 (d, J = 10 Hz, 1 H), 5.79 (dt, J = 10, 7 Hz, 1 H), 7.44 (ddd, J = 8, 5, 1 Hz, 1 H), 7.81 (dt, J = 2, 8 Hz, 1 H), 8.12 (dt, J = 8, 1 Hz, 1 H), 8.76 (ddd, J = 5, 2, 1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (+), 17.6 (+), 23.4 (+), 25.6 (+), 26.6 (–), 28.1 (–), 32.6 (–), 74.2 (+), 123.8 (+), 123.9 (+), 125.1 (+), 126.5 (+), 131.9 (–), 136.8 (+), 141.7 (–), 148.8 (–), 149.9 (+), 164.6 (–). HRMS (EI) calcd for $C_{18}H_{25}NO_2$ (M^+) 287.1885, found 287.1887. The enantiomeric purity of 63% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH = 99/1, 0.500 mL/min, 30 °C, t_R /min = 28.1 (*R*-isomer), 30.5 (*S*-isomer).

Substitution of Allylic Picolines



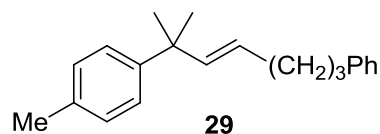
General Procedure for the Allylation: Synthesis of (*E*)-(6-Methylhept-4-ene-1,6-diyl)dibenzene (15). (Table 4.2, entry 6) To an ice-cold suspension of $Cu(acac)_2$ (38.1 mg, 0.146 mmol) in THF (1 mL) was added a solution of $PhMgBr$ (0.36 mL, 0.81 M in THF, 0.292 mmol) slowly. The mixture was stirred at 0 °C for 60 min and cooled to -40 °C before addition of a solution of picolinate **6** (30.0 mg, 0.0970 mmol) in THF (1 mL). The resulting mixture was

allowed to warm to $-20\text{ }^{\circ}\text{C}$ over 2 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over MgSO_4 , and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **15** (25.9 mg, 100%).

(**Table 4.2**, entry 9) To an ice-cold suspension of $\text{Cu}(\text{acac})_2$ (38.3 mg, 0.146 mmol) and ZnI_2 (46.8 mg, 0.147 mmol) in THF (1 mL) was added PhMgBr (0.56 mL, 0.81 M in THF, 0.454 mmol). After being stirred at $0\text{ }^{\circ}\text{C}$ for 1 h, the mixture was cooled to $-40\text{ }^{\circ}\text{C}$ and a solution of picolinate **6** (29.7 mg, 0.0960 mmol) in THF (1 mL) was added. The mixture was allowed to warm to $-10\text{ }^{\circ}\text{C}$ over 2 h to afford **15** (22.4 mg, 87%) after purification by chromatography.

Large-scale reaction: A solution of picolinate **6** (3.10 g, 10.0 mmol) in THF (15 mL) was added to a mixture of $\text{Cu}(\text{acac})_2$ (3.93 g, 15.0 mmol) in THF (15 mL) and PhMgBr (32.0 mL, 0.95 M in THF, 30 mmol), which had been stirred at $0\text{ }^{\circ}\text{C}$ for 1 h and cooled to $-40\text{ }^{\circ}\text{C}$ before the addition. The reaction mixture was allowed to warm to $-10\text{ }^{\circ}\text{C}$ over 2 h to afford **15** (2.44 g, 92%) after purification by chromatography on silica gel.

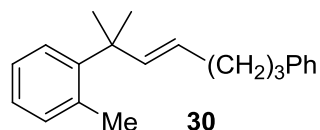
Product **15**: IR (neat) 1495, 1454, 975, 763, 746, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.38 (s, 6 H), 1.72 (quint., $J = 7\text{ Hz}$, 2 H), 2.09 (dt, $J = 7, 7\text{ Hz}$, 2 H), 2.62 (t, $J = 8\text{ Hz}$, 2 H), 5.44 (dt, $J = 16, 7\text{ Hz}$, 1 H), 5.64 (d, $J = 16\text{ Hz}$, 1 H), 7.13–7.21 (m, 4 H), 7.22–7.32 (m, 4 H), 7.32–7.38 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 29.0 (+), 31.5 (–), 32.2 (–), 35.5 (–), 40.4 (–), 125.70 (+), 125.73 (+), 126.1 (+), 126.2 (+), 128.1 (+), 128.3 (+), 128.5 (+), 140.6 (+), 142.7 (–), 149.4 (–). HRMS (EI) calcd for $\text{C}_{20}\text{H}_{24}$ (M^+) 264.1878, found 264.1881.



(E)-1-Methyl-4-(2-methyl-7-phenylhept-3-en-2-yl)benzene (29). (**Table 4.4**, entry 1)

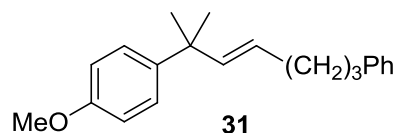
According to the general procedure a solution of **6** (30.0 mg, 0.0970 mmol) in THF (1 mL) was added to a mixture of $p\text{-MeC}_6\text{H}_4\text{MgBr}$ (0.34 mL, 0.86 M in THF, 0.292 mmol) and $\text{Cu}(\text{acac})_2$ (38.0 mg, 0.146 mmol) in THF (1 mL) at $-40\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to $-20\text{ }^{\circ}\text{C}$ over 2 h to afford **29** (25.1 mg, 93%): IR (neat) 1512, 1454, 975, 817, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36 (s, 6 H), 1.66–1.76 (m, 2 H), 2.04–2.12 (m, 2 H), 2.31 (s, 3 H), 2.62 (t,

$J = 8$ Hz, 2 H), 5.43 (dt, $J = 16, 7$ Hz, 1 H), 5.62 (d, $J = 16$ Hz, 1 H), 7.06–7.13 (m, 2 H), 7.14–7.20 (m, 3 H), 7.21–7.30 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0 (+), 29.1 (+), 31.5 (–), 32.3 (–), 35.5 (–), 40.0 (–), 125.7 (+), 125.9 (+), 126.1 (+), 128.3 (+), 128.6 (+), 128.8 (+), 135.2 (–), 140.8 (+), 142.7 (–), 146.5 (–). HRMS (EI) calcd for $\text{C}_{21}\text{H}_{26}$ (M^+) 278.2035, found 278.2036.



(E)-1-Methyl-2-(2-methyl-7-phenylhept-3-en-2-yl)benzene (30). (Table 4.4, entry 2)

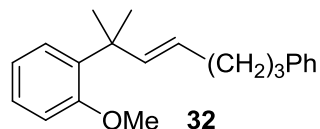
According to the general procedure a solution of **6** (30.1 mg, 0.0973 mmol) in THF (1 mL) was added to a mixture of *o*-MeC₆H₄MgBr (0.33 mL, 0.87 M in THF, 0.287 mmol) and Cu(acac)₂ (38.1 mg, 0.146 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -20 °C over 2 h to afford **30** (26.0 mg, 96%): IR (neat) 1495, 1454, 975, 760, 728, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.43 (s, 6 H), 1.63–1.73 (m, 2 H), 2.02–2.10 (m, 2 H), 2.39 (s, 3 H), 2.60 (t, $J = 8$ Hz, 2 H), 5.32 (dt, $J = 16, 7$ Hz, 1 H), 5.66 (d, $J = 16$ Hz, 1 H), 7.10–7.20 (m, 5 H), 7.24–7.30 (m, 3 H), 7.35–7.39 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.7 (+), 29.4 (+), 31.4 (–), 32.3 (–), 35.6 (–), 41.1 (–), 125.67 (+), 125.73 (+), 126.1 (+), 126.2 (+), 126.3 (+), 128.3 (+), 128.5 (+), 132.4 (+), 137.1 (–), 140.5 (+), 142.7 (–), 146.4 (–). HRMS (EI) calcd for $\text{C}_{21}\text{H}_{26}$ (M^+) 278.2035, found 278.2037.



(E)-1-Methoxy-4-(2-methyl-7-phenylhept-3-en-2-yl)benzene (31). (Table 4.4, entry 3)

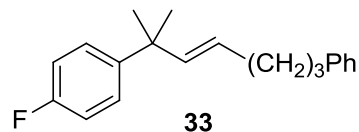
According to the general procedure a solution of **6** (29.5 mg, 0.0953 mmol) in THF (1 mL) was added to a mixture of *p*-MeOC₆H₄MgBr (0.32 mL, 0.93 M in THF, 0.298 mmol) and Cu(acac)₂ (37.8 mg, 0.144 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -10 °C over 2 h to afford **31** (23.1 mg, 82%): IR (neat) 1511, 1250, 1181, 1037, 829, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36 (s, 6 H), 1.66–1.76 (m, 2 H), 2.04–2.12 (m, 2 H), 2.62 (t, $J = 8$ Hz, 2 H), 3.78 (s, 3 H), 5.41 (dt, $J = 16, 7$ Hz, 1 H), 5.62 (d, $J = 16$ Hz, 1 H), 6.83 (dm, $J = 9$ Hz, 2 H), 7.14–7.20 (m, 3 H), 7.22–7.30 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 29.2 (+), 31.5 (–),

32.2 (–), 35.5 (–), 39.8 (–), 55.3 (+), 113.4 (+), 125.7 (+), 125.9 (+), 127.2 (+), 128.3 (+), 128.5 (+), 140.9 (+), 141.6 (–), 142.7 (–), 157.6 (–). HRMS (EI) calcd for C₂₁H₂₆O (M⁺) 294.1984, found 294.1986.



(E)-1-Methoxy-2-(2-methyl-7-phenylhept-3-en-2-yl)benzene (32). (Table 4.4, entry 4)

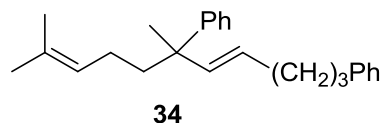
According to the general procedure a solution of **6** (30.4 mg, 0.0983 mmol) in THF (1 mL) was added to a mixture of *o*-MeOC₆H₄MgBr (0.33 mL, 0.89 M in THF, 0.294 mmol) and Cu(acac)₂ (38.0 mg, 0.145 mmol) in THF (1 mL) at –40 °C, and the mixture was allowed to warm to –20 °C over 2 h to afford **32** (18.8 mg, 65%): IR (neat) 1490, 1455, 1241, 1031, 750, 699 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 6 H), 1.63–1.74 (m, 2 H), 2.02–2.11 (m, 2 H), 2.61 (t, *J* = 8 Hz, 2 H), 3.78 (s, 3 H), 5.32 (dt, *J* = 15.5, 7 Hz, 1 H), 5.78 (dt, *J* = 15.5, 2 Hz, 1 H), 6.83–6.92 (m, 2 H), 7.12–7.22 (m, 4 H), 7.22–7.30 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 27.9 (+), 31.6 (–), 32.3 (–), 35.4 (–), 39.9 (–), 55.1 (+), 111.8 (+), 120.3 (+), 125.2 (+), 125.7 (+), 127.2 (+), 127.3 (+), 128.3 (+), 128.6 (+), 137.2 (–), 140.4 (+), 142.9 (–), 158.3 (–). HRMS (EI) calcd for C₂₁H₂₆O (M⁺) 294.1984, found 294.1983.



(E)-1-Fluoro-4-(2-methyl-7-phenylhept-3-en-2-yl)benzene (33). (Table 4.4, entry 5)

According to the general procedure a solution of **6** (29.8 mg, 0.0963 mmol) in THF (1 mL) was added to a mixture of *p*-FC₆H₄MgBr (0.32 mL, 0.92 M in THF, 0.294 mmol) and Cu(acac)₂ (38.4 mg, 0.147 mmol) in THF (1 mL) at –40 °C, and the mixture was allowed to warm to –10 °C over 2 h to afford **33** (22.8 mg, 84%): IR (neat) 1508, 1230, 1163, 976, 834, 699 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (s, 6 H), 1.66–1.77 (m, 2 H), 2.03–2.13 (m, 2 H), 2.62 (t, *J* = 8 Hz, 2 H), 5.42 (dt, *J* = 16, 7 Hz, 1 H), 5.60 (dt, *J* = 16, 1 Hz, 1 H), 6.91–7.00 (m, 2 H), 7.14–7.21 (m, 3 H), 7.23–7.32 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 29.2 (+), 31.5 (–), 32.2 (–), 35.5 (–), 40.0 (–), 114.7 (d, *J* = 21 Hz) (+), 125.8 (+), 126.4 (+), 127.7 (d, *J* = 8 Hz) (+), 128.4 (+),

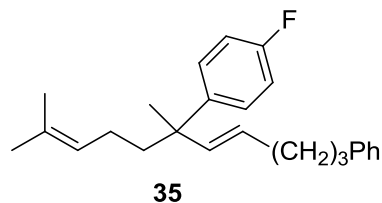
128.5 (+), 140.4 (+), 142.6 (–), 145.1 (d, $J = 3$ Hz) (–), 161.1 (d, $J = 242$ Hz) (–). HRMS (EI) calcd for $C_{20}H_{23}F$ (M^+) 282.1784, found 282.1792.



(E)-(6,10-Dimethylundeca-4,9-diene-1,6-diyl)dibenzene (34). (Table 4.4, entry 6) According to the general procedure a solution of **7** (38.4 mg, 0.102 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.31 mL, 1.02 M in THF, 0.316 mmol) and Cu(acac)₂ (39.6 mg, 0.151 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -10 °C over 2 h to afford **34** (32.1 mg, 95%).

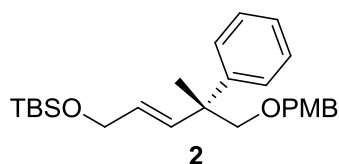
(Table 4.4, entry 7) According to the general procedure a solution of **8** (37.1 mg, 0.0983 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.29 mL, 1.02 M in THF, 0.296 mmol) and Cu(acac)₂ (38.9 mg, 0.149 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -10 °C over 2 h to afford **34** (28.9 mg, 88%).

Product **34**: IR (neat) 1495, 1453, 1445, 698 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), 1.60–1.90 (m, 6 H), 2.10 (dt, $J = 8, 8$ Hz, 2 H), 2.62 (t, $J = 8$ Hz, 2 H), 5.02–5.12 (m, 1 H), 5.42 (dt, $J = 16, 7$ Hz, 1 H), 5.63 (dt, $J = 16, 1$ Hz, 1 H), 7.10–7.20 (m, 4 H), 7.20–7.33 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (+), 23.6 (–), 25.8 (+), 25.9 (+), 31.6 (–), 32.5 (–), 35.6 (–), 41.8 (–), 43.6 (–), 124.8 (+), 125.56 (+), 125.64 (+), 126.6 (+), 127.1 (+), 128.0 (+), 128.2 (+), 128.4 (+), 131.2 (–), 139.3 (+), 142.5 (–), 148.2 (–). HRMS (FAB) calcd for $C_{25}H_{32}Na$ [$(M+Na)^+$] 355.2402, found 355.2393.



(E)-1-(2,6-Dimethyl-11-phenylundeca-2,7-dien-6-yl)-4-fluorobenzene (35). (Table 4.4, entry 8) According to the general procedure a solution of **7** and **8** (3 : 2) (37.8 mg, 0.100 mmol) in THF (1 mL) was added to a mixture of *p*-FC₆H₄MgBr (0.33 mL, 0.92 M in THF, 0.304 mmol) and Cu(acac)₂ (39.4 mg, 0.151 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to

warm to $-10\text{ }^{\circ}\text{C}$ over 2 h to afford **35** (28.2 mg, 80%): IR (neat) 1603, 1508, 1232, 834, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.34 (s, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), 1.60–1.90 (m, 6 H), 2.10 (dt, $J = 8, 8\text{ Hz}$, 2 H), 2.62 (t, $J = 8\text{ Hz}$, 2 H), 5.03–5.10 (m, 1 H), 5.42 (dt, $J = 16, 7\text{ Hz}$, 1 H), 5.61 (dt, $J = 16, 1\text{ Hz}$, 1 H), 6.91–7.00 (m, 2 H), 7.14–7.21 (m, 3 H), 7.22–7.31 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6 (+), 23.4 (–), 25.8 (+), 25.9 (+), 31.5 (–), 32.4 (–), 35.5 (–), 41.9 (–), 43.2 (–), 114.7 (d, $J = 21\text{ Hz}$) (+), 124.7 (+), 125.8 (+), 127.4 (+), 128.2 (d, $J = 8\text{ Hz}$) (+), 128.4 (+), 128.5 (+), 131.4 (–), 139.3 (+), 142.6 (–), 144.0 (d, $J = 3\text{ Hz}$) (–), 161.1 (d, $J = 242\text{ Hz}$) (–). HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{31}\text{F}$ [(M) $^{+}$] 350.2410, found 350.2410.



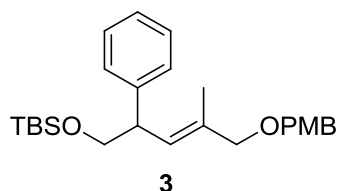
(*R,E*)-tert-Butyl((5-((4-methoxybenzyl)oxy)-4-methyl-4-phenylpent-2-en-1-

yl)oxy)dimethylsilane (2). According to the general procedure a solution of **1** (98% ee, 30.5 mg, 0.0647 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.38 mL, 1.00 M in THF, 0.38 mmol) and $\text{Cu}(\text{acac})_2$ (50.1 mg, 0.191 mmol) in THF (1 mL) at $-40\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ over 2 h to afford **2** (23.6 mg, 86%).

(**Table 4.5**, entry 2) According to the general procedure a solution of **1** (98% ee, 14.0 mg, 0.0297 mmol) in THF (0.5 mL) was added to a mixture of PhMgBr (0.17 mL, 1.02 M in THF, 0.17 mmol) and $\text{Cu}(\text{acac})_2$ (23.1 mg, 0.0882 mmol) in THF (1 mL) at $-40\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ over 2 h to afford **2** (11.6 mg, 92%).

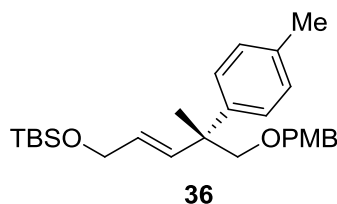
Product **2**: $[\alpha]_{\text{D}}^{25} +2.5$ (c 0.16, CHCl_3) (cf. $[\alpha]_{\text{D}}^{30} +1.5$ (c 0.40, CHCl_3) for the *R* enantiomer of 98% ee);⁴ ^1H NMR (400 MHz, CDCl_3) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.43 (s, 3 H), 3.55 (d, $J = 9\text{ Hz}$, 1 H), 3.60 (d, $J = 9\text{ Hz}$, 1 H), 3.80 (s, 3 H), 4.20 (dd, $J = 5, 1.5\text{ Hz}$, 2 H), 4.42 (s, 2 H), 5.55 (dt, $J = 16, 5\text{ Hz}$, 1 H), 5.91 (dt, $J = 16, 1.5\text{ Hz}$, 1 H), 6.84 (d, $J = 8\text{ Hz}$, 2 H), 7.14–7.21 (m, 2 H), 7.24–7.35 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.0 (+), 18.5 (–), 23.8 (+), 26.1 (+), 44.9 (–), 55.3 (+), 64.3 (–), 73.0 (–), 77.6 (–), 113.7 (+), 126.1 (+), 127.1 (+), 128.07 (+), 128.12 (+), 129.1 (+), 130.7 (–), 136.7 (+), 145.8 (–), 159.1 (–). The ^1H NMR and ^{13}C NMR spectra were consistent with data reported in the literature.⁵ The enantiomeric purity of 97% ee was

determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99/1, 0.300 mL/min, 30 °C, t_R /min = 24.9 (*S*-isomer), 33.6 (*R*-isomer).



(*E*)-tert-Butyl((5-((4-methoxybenzyl)oxy)-4-methyl-2-phenylpent-3-en-1-

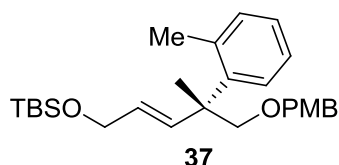
yl)oxy)dimethylsilane (regioisomer 3). To an ice-cold suspension of CuBr·Me₂S (19.8 mg, 0.0963 mmol) in THF (1 mL) was added a solution of PhMgBr (0.25 mL, 0.90 M in THF, 0.225 mmol) slowly. The mixture was stirred at 0 °C for 30 min and a solution of picolinate **1** (30.1 mg, 0.0638 mmol) in THF (1 mL) was added. The mixture was stirred at 0 °C for 2 h and diluted with hexane and saturated NH₄Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the regioisomer **3** and **2** in a 91:9 ratio (11.3 mg, 42%): ¹H NMR (400 MHz, CDCl₃) δ −0.07 (s, 3 H), −0.06 (s, 3 H), 0.82 (s, 9 H), 1.69 (s, 3 H), 3.70–3.82 (m, 3 H), 3.80 (s, 3 H), 3.91 (s, 2 H), 4.37 (s, 2 H), 5.69 (d, *J* = 7 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 7.14–7.35 (m, 7 H); ¹³C NMR (100 MHz, CDCl₃) δ −5.4 (+), 14.5 (+), 18.4 (−), 25.9 (+), 47.1 (+), 55.3 (+), 67.9 (−), 71.0 (−), 75.8 (−), 113.8 (+), 126.3 (+), 128.1 (+), 128.3 (+), 128.5 (+), 129.4 (+), 130.7 (−), 134.1 (−), 142.7 (−), 159.2 (−).



(*R,E*)-tert-Butyl((5-((4-methoxybenzyl)oxy)-4-methyl-4-(4-methylphenyl)pent-2-en-1-

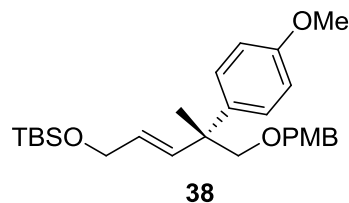
yl)oxy)dimethylsilane (36). (Table 4.5, entry 3) According to the general procedure a solution of **1** (98% ee, 34.9 mg, 0.0740 mmol) in THF (1 mL) was added to a mixture of *p*-MeC₆H₄MgBr (0.48 mL, 0.93 M in THF, 0.446 mmol) and Cu(acac)₂ (58.4 mg, 0.223 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to 0 °C over 2 h to afford **36** (30.2 mg, 93%): $[\alpha]_D^{22}$ +1.9 (c 0.16, CHCl₃); IR (neat) 1513, 1249, 1098, 836 cm^{−1}; ¹H NMR (400 MHz, CDCl₃)

δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.41 (s, 3 H), 2.31 (s, 3 H), 3.52 (d, J = 9 Hz, 1 H), 3.58 (d, J = 9 Hz, 1 H), 3.80 (s, 3 H), 4.19 (dd, J = 5, 1 Hz, 2 H), 4.42 (s, 2 H), 5.54 (dt, J = 16, 5 Hz, 1 H), 5.90 (d, J = 16 Hz, 1 H), 6.84 (d, J = 8 Hz, 2 H), 7.06–7.12 (m, 2 H), 7.15–7.27 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ –5.0 (+), 18.5 (–), 21.0 (+), 23.8 (+), 26.1 (+), 44.6 (–), 55.3 (+), 64.4 (–), 73.0 (–), 77.7 (–), 113.7 (+), 126.9 (+), 128.0 (+), 128.8 (+), 129.1 (+), 130.8 (–), 135.6 (–), 136.9 (+), 142.8 (–), 159.1 (–). HRMS (FAB) calcd for $\text{C}_{27}\text{H}_{39}\text{O}_3\text{Si}$ $[(\text{M}-\text{H})^+]$ 439.2668, found 439.2669. The enantiomeric purity of 97% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.8, 0.300 mL/min, 30 °C, t_{R} /min = 30.5 (*S*-isomer), 40.1 (*R*-isomer).



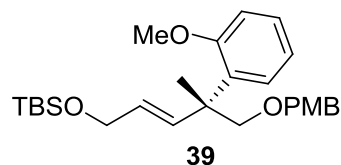
(*R,E*)-*tert*-Butyl((5-((4-methoxybenzyl)oxy)-4-methyl-4-(2-methylphenyl)pent-2-en-1-yl)oxy)dimethylsilane (37). (Table 4.5, entry 4)

According to the general procedure a solution of **1** (98% ee, 34.8 mg, 0.0738 mmol) in THF (1 mL) was added to a mixture of *o*-MeC₆H₄MgBr (0.52 mL, 0.85 M in THF, 0.442 mmol) and Cu(acac)₂ (58.2 mg, 0.222 mmol) in THF (1 mL) at –40 °C, and the mixture was allowed to warm to –10 °C over 2 h to afford **37** (30.9 mg, 95%): $[\alpha]_{\text{D}}^{22}$ –7 (c 0.52, CHCl_3); IR (neat) 1613, 1513, 1463, 1250, 1097, 836 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 6 H), 0.90 (s, 9 H), 1.49 (s, 3 H), 2.31 (s, 3 H), 3.59 (d, J = 9 Hz, 1 H), 3.63 (d, J = 9 Hz, 1 H), 3.80 (s, 3 H), 4.14 (dd, J = 5, 1.5 Hz, 2 H), 4.45 (s, 2 H), 5.38 (dt, J = 16, 6 Hz, 1 H), 5.94 (dt, J = 16, 1.5 Hz, 1 H), 6.85 (dm, J = 9 Hz, 2 H), 7.06–7.16 (m, 3 H), 7.20 (dm, J = 9 Hz, 2 H), 7.34–7.40 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ –5.0 (+), 18.5 (–), 22.9 (+), 24.5 (+), 26.0 (+), 45.7 (–), 55.3 (+), 64.2 (–), 73.0 (–), 77.2 (–), 113.7 (+), 125.6 (+), 126.4 (+), 127.6 (+), 128.0 (+), 129.2 (+), 130.7 (–), 132.4 (+), 136.9 (+), 137.1 (–), 143.3 (–), 159.1 (–). HRMS (FAB) calcd for $\text{C}_{27}\text{H}_{39}\text{O}_3\text{Si}$ $[(\text{M}-\text{H})^+]$ 439.2668, found 439.2669. The enantiomeric purity of 98% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.5/0.5, 0.300 mL/min, 30 °C, t_{R} /min = 35.4 (*S*-isomer), 40.0 (*R*-isomer).



(*R,E*)-tert-Butyl((5-((4-methoxybenzyl)oxy)-4-(4-methoxyphenyl)-4-methylpent-2-en-1-yl)oxy)dimethylsilane (38). (Table 4.5, entry 5)

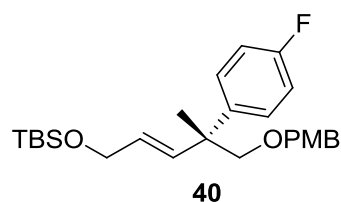
According to the general procedure a solution of **1** (98% ee, 47.2 mg, 0.100 mmol) in THF (1 mL) was added to a mixture of *p*-MeOC₆H₄MgBr (0.64 mL, 0.93 M in THF, 0.595 mmol) and Cu(acac)₂ (78.2 mg, 0.299 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford **38** (43.1 mg, 94%): [α]_D²¹ −1 (c 0.79, CHCl₃); IR (neat) 1513, 1249, 834 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.41 (s, 3 H), 3.51 (d, *J* = 9 Hz, 1 H), 3.56 (d, *J* = 9 Hz, 1 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.19 (dd, *J* = 5, 2 Hz, 2 H), 4.42 (s, 2 H), 5.53 (dt, *J* = 16, 5 Hz, 1 H), 5.88 (dt, *J* = 16, 2 Hz, 1 H), 6.80–6.87 (m, 4 H), 7.15–7.21 (m, 2 H), 7.21–7.27 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ −5.0 (+), 18.5 (−), 23.9 (+), 26.1 (+), 44.3 (−), 55.3 (+), 64.3 (−), 73.0 (−), 77.7 (−), 113.4 (+), 113.7 (+), 127.9 (+), 128.1 (+), 129.1 (+), 130.8 (−), 137.0 (+), 137.9 (−), 157.9 (−), 159.1 (−). HRMS (FAB) calcd for C₂₇H₄₀O₄SiNa [(M+Na)⁺] 479.2594, found 479.2613. The enantiomeric purity of 97% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99/1, 0.500 mL/min, 30 °C, *t*_R/min = 35.6 (*S*-isomer), 46.3 (*R*-isomer).



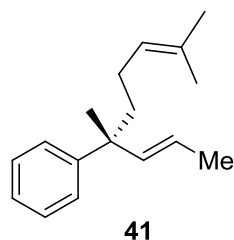
(*R,E*)-tert-Butyl((5-((4-methoxybenzyl)oxy)-4-(2-methoxyphenyl)-4-methylpent-2-en-1-yl)oxy)dimethylsilane (39). (Table 4.5, entry 6)

According to the general procedure a solution of **1** (98% ee, 30.0 mg, 0.0636 mmol) in THF (1 mL) was added to a mixture of *o*-MeOC₆H₄MgBr (0.38 mL, 1.01 M in THF, 0.38 mmol) and Cu(acac)₂ (50.0 mg, 0.191 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to 0 °C over 2 h to afford **39** (23.4 mg, 81%): ¹H NMR (300 MHz, CDCl₃) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.49 (s, 3 H), 3.68 (s, 3 H), 3.71–3.79 (m, 2 H), 3.76 (s, 3 H), 4.15 (dd, *J* = 5, 1.5 Hz, 2 H), 4.38 (s, 2 H), 5.44 (dt, *J* = 16, 5 Hz, 1 H), 6.06 (dt, *J* = 16, 1.5 Hz, 1 H), 6.74–7.04 (m, 4 H), 7.08–7.36 (m, 4 H); ¹³C NMR (100

MHz, CDCl₃) δ -5.0, 18.5, 22.8, 26.1, 44.7, 55.1, 55.3, 64.5, 72.9, 76.1, 111.7, 120.4, 126.9, 127.6, 129.1, 136.9, 157.1, 159.0.

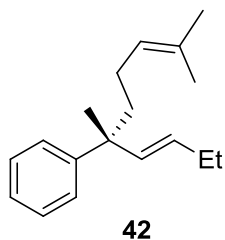


(*R,E*)-tert-Butyl((4-(4-fluorophenyl)-5-((4-methoxybenzyl)oxy)-4-methylpent-2-en-1-yl)oxy)dimethylsilane (40). (Table 4.5, entry 7) According to the general procedure a solution of **1** (98% ee, 48.4 mg, 0.103 mmol) in THF (1 mL) was added to a mixture of *p*-FC₆H₄MgBr (0.65 mL, 0.92 M in THF, 0.598 mmol) and Cu(acac)₂ (77.9 mg, 0.298 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to 0 °C over 2 h to afford **40** (45.6 mg, >99%): [α]_D²¹ -2.7 (*c* 0.33, CHCl₃); IR (neat) 1510, 1249, 1097, 835, 777 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.41 (s, 3 H), 3.52 (d, *J* = 9 Hz, 1 H), 3.55 (d, *J* = 9 Hz, 1 H), 3.80 (s, 3 H), 4.19 (dd, *J* = 5, 2 Hz, 2 H), 4.42 (s, 2 H), 5.53 (dt, *J* = 16, 5 Hz, 1 H), 5.88 (dt, *J* = 16, 2 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.91–7.00 (m, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 7.24–7.31 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ -5.0 (+), 18.5 (-), 24.0 (+), 26.1 (+), 44.5 (-), 55.3 (+), 64.2 (-), 73.0 (-), 77.5 (-), 113.7 (+), 114.7 (d, *J* = 21 Hz), 128.3 (+), 128.7 (d, *J* = 8 Hz), 129.1 (+), 130.5 (-), 136.4 (+), 141.4 (d, *J* = 3 Hz), 159.1 (-), 161.3 (d, *J* = 243 Hz). HRMS (FAB) calcd for C₂₆H₃₆FO₃Si [(M-H)⁺] 443.2418, found 443.2406. The enantiomeric purity of >97% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99/1, 0.300 mL/min, 30 °C, *t*_R/min = 26.7 (*S*-isomer), 33.6 (*R*-isomer).

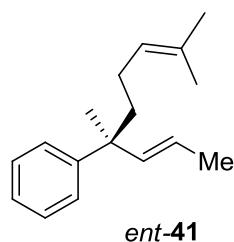


(*R,E*)-(4,8-Dimethylnona-2,7-dien-4-yl)benzene (41). According to the general procedure a solution of **9** (82% ee, 31.5 mg, 0.115 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.34 mL, 1.01 M in THF, 0.343 mmol) and Cu(acac)₂ (45.0 mg, 0.172 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -10 °C over 2 h to afford **41** (22.3 mg, 85%):

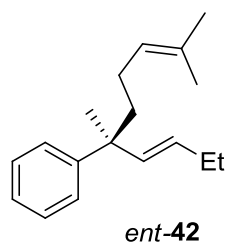
$[\alpha]_D^{24} +3$ (c 0.75, CHCl_3); IR (neat) 1445, 973, 762, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36 (s, 3 H), 1.51 (s, 3 H), 1.62–1.90 (m, 4 H), 1.65 (s, 3 H), 1.72 (dd, J = 6, 1.5 Hz, 3 H), 5.04–5.12 (m, 1 H), 5.43 (dq, J = 16, 6 Hz, 1 H), 5.65 (dq, J = 16, 1.5 Hz, 1 H), 7.13–7.19 (m, 1 H), 7.24–7.34 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6 (+), 18.3 (+), 23.5 (–), 25.6 (+), 25.8 (+), 41.9 (–), 43.6 (–), 122.1 (+), 125.0 (+), 125.6 (+), 126.7 (+), 128.0 (+), 131.3 (–), 140.1 (+), 148.5 (–). The enantiomeric purity of 81% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 30 °C, t_R /min = 17.8 (*S*-isomer), 18.9 (*R*-isomer). HRMS (EI) calcd for $\text{C}_{17}\text{H}_{24}$ (M^+) 228.1878, found 228.1873.



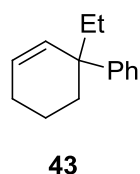
(*R,E*)-(5,9-Dimethyldeca-3,8-dien-5-yl)benzene (42). According to the general procedure a solution of **10** (60% ee, 23.3 mg, 0.0811 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.24 mL, 1.01 M in THF, 0.242 mmol) and $\text{Cu}(\text{acac})_2$ (31.6 mg, 0.121 mmol) in THF (1 mL) at -40 °C, and the mixture was allowed to warm to -10 °C over 2 h to afford **42** (17.7 mg, 90%): $[\alpha]_D^{24} +4$ (c 0.22, CHCl_3); IR (neat) 1445, 977, 763, 699 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.00 (t, J = 7.5 Hz, 3 H), 1.35 (s, 3 H), 1.51 (s, 3 H), 1.62–1.92 (m, 4 H), 1.65 (s, 3 H), 2.02–2.14 (m, 2 H), 5.02–5.12 (m, 1 H), 5.45 (dt, J = 16, 6 Hz, 1 H), 5.60 (dt, J = 16, 1 Hz, 1 H), 7.10–7.18 (m, 1 H), 7.22–7.34 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (+), 17.6 (+), 23.5 (–), 25.7 (+), 25.8 (+), 26.0 (–), 41.9 (–), 43.4 (–), 125.0 (+), 125.6 (+), 126.7 (+), 128.0 (+), 129.3 (+), 131.2 (–), 137.8 (+), 148.6 (–). The enantiomeric purity of 59% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 30 °C, t_R /min = 21.3 (*S*-isomer), 22.6 (*R*-isomer). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{26}$ (M^+) 242.2035, found 242.2033.



(*S,E*)-(4,8-Dimethylnona-2,7-dien-4-yl)benzene (*ent*-41). According to the general procedure a solution of **11** (66% ee, 29.5 mg, 0.108 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.33 mL, 1.01 M in THF, 0.333 mmol) and Cu(acac)₂ (42.7 mg, 0.163 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford *ent*-**41** (21.6 mg, 88%): [α]_D²³ −2 (*c* 0.76, CHCl₃). The ¹H and ¹³C NMR spectra were identical with those for **41**. The enantiomeric purity of 66% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 30 °C, *t*_R/min = 19.3 (*S*-isomer), 20.8 (*R*-isomer).



(*S,E*)-(5,9-Dimethyldeca-3,8-dien-5-yl)benzene (*ent*-42). According to the general procedure, a solution of **12** (63% ee, 29.9 mg, 0.104 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.31 mL, 1.01 M in THF, 0.313 mmol) and Cu(acac)₂ (41.2 mg, 0.157 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford *ent*-**42** (20.7 mg, 82%): [α]_D²³ −3 (*c* 0.27, CHCl₃). The ¹H and ¹³C NMR spectra were identical with those for **42**. The enantiomeric purity of 62% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 30 °C, *t*_R/min = 29.4 (*S*-isomer), 31.2 (*R*-isomer).

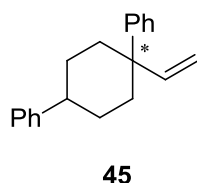


1-Ethyl-1-phenyl-2-cyclohexene (43). Phenylation with 2:1 PhMgBr/Cu(acac)₂: A solution of **13a** (24.6 mg, 0.106 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.35 mL, 0.98 M

in THF, 0.343 mmol) and Cu(acac)₂ (42.3 mg, 0.162 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford a mixture of **43** and **44** in a 82:18 ratio (14.4 mg, 73%).

Phenylation with 3:1:1 PhMgBr/Cu(acac)₂/ZnI₂: To an ice-cold suspension of Cu(acac)₂ (42.5 mg, 0.162 mmol) and ZnI₂ (51.0 mg, 0.160 mmol) in THF (1 mL) was added PhMgBr (0.63 mL, 0.77 M in THF, 0.485 mmol). After being stirred at 0 °C for 1 h, the mixture was cooled to −40 °C and a solution of picolinate **13a** (25.3 mg, 0.109 mmol) in THF (1 mL) was added. The mixture was allowed to warm to −10 °C over 2 h to afford a mixture of **43** and **44** in a 87:13 ratio (16.5 mg, 81%).

Product **43**: ¹H NMR (400 MHz, CDCl₃) δ 0.73 (t, *J* = 7.5 Hz, 3 H), 1.45–2.08 (m, 8 H), 5.85 (dm, *J* = 10 Hz, 1 H), 5.90 (dt, *J* = 10, 3 Hz, 1 H), 7.13–7.23 (m, 2 H), 7.24–7.34 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 8.7 (+), 19.0 (−), 25.6 (−), 35.1 (−), 36.7 (−), 43.1 (−), 125.4 (+), 127.3 (+), 127.93 (+), 127.95 (+), 132.9 (+), 148.3 (−). The ¹H NMR spectrum was consistent with data reported in the literature.^{4b}



1,4-Diphenyl-1-vinylcyclohexane (45). Phenylation with 2:1 PhMgBr/Cu(acac)₂: A solution of **14**⁷ (29.6 mg, 0.0963 mmol) in THF (1 mL) was added to a mixture of PhMgBr (0.26 mL, 1.14 M in THF, 0.296 mmol) and Cu(acac)₂ (39.0 mg, 0.149 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford a mixture of **45** and **46** in a 81:19 ratio (19.4 mg, 77%).

Phenylation with 3:1:1 PhMgBr/Cu(acac)₂/ZnI₂: To an ice-cold suspension of Cu(acac)₂ (38.0 mg, 0.145 mmol) and ZnI₂ (46.4 mg, 0.145 mmol) in THF (1 mL) was added PhMgBr (0.49 mL, 0.85 M in THF, 0.417 mmol). After being stirred at 0 °C for 1 h, the mixture was cooled to −40 °C and a solution of picolinate **14** (29.5 mg, 0.0960 mmol) in THF (1 mL) was added. The mixture was allowed to warm to −10 °C over 2 h to afford a mixture of **45** and **46** in a 87:13 ratio (18.4 mg, 73%).

Product **45**: ^1H NMR (400 MHz, CDCl_3) δ 1.80–1.96 (m, 6 H), 2.28 (dm, $J = 10$ Hz, 2 H), 2.50–2.64 (m, 1 H), 5.16 (dd, $J = 18$, 1 Hz, 1 H), 5.33 (dd, $J = 11$, 1 Hz, 1 H), 5.88 (dd, $J = 18$, 11 Hz, 1 H), 7.16–7.26 (m, 4 H), 7.27–7.35 (m, 4 H) 7.39–7.44 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.5 (–), 36.4 (–), 44.0 (–), 44.3 (+), 115.1 (–), 125.9 (+), 126.0 (+), 126.2 (+), 127.0 (+), 128.2 (+), 128.4 (+), 144.6 (+), 147.5 (–), 149.3 (–). HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{22}$ (M^+) 262.1722, found 262.1720.

4.6 References and Notes

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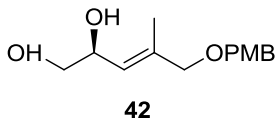
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(19) The enantiomer of **1** (i.e., *ent-1*) was synthesized via Mitsunobu inversion of the corresponding alcohol for chiral HPLC analysis of **1** and **2**.

(20) In addition to **3** and **2**, alcohol **42**⁵ was also formed: **3/2/42** = 66:7:27.



(21) Retention time on chiral HPLC, see Experimental Section. Specific rotation: synthesized [α]_D²⁵ +2.5 (c 0.16, CHCl₃); lit.⁵ [α]_D³⁰ +1.5 (c 0.40, CHCl₃).

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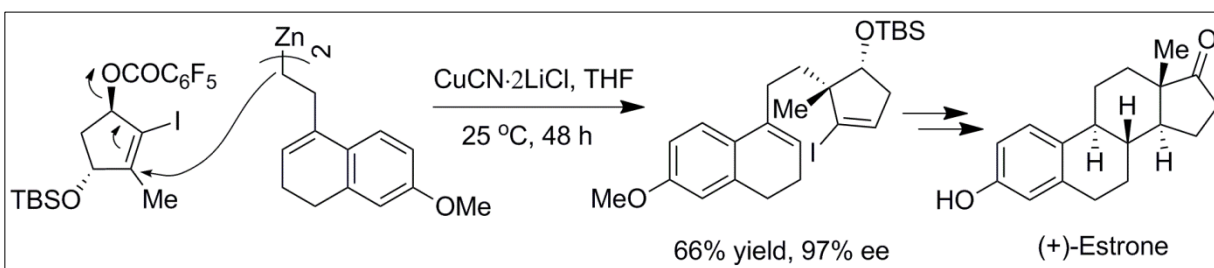
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Chapter 5 Construction of Chiral Quaternary Carbon Centers with Alkylcopper Reagents

5.1 Introduction

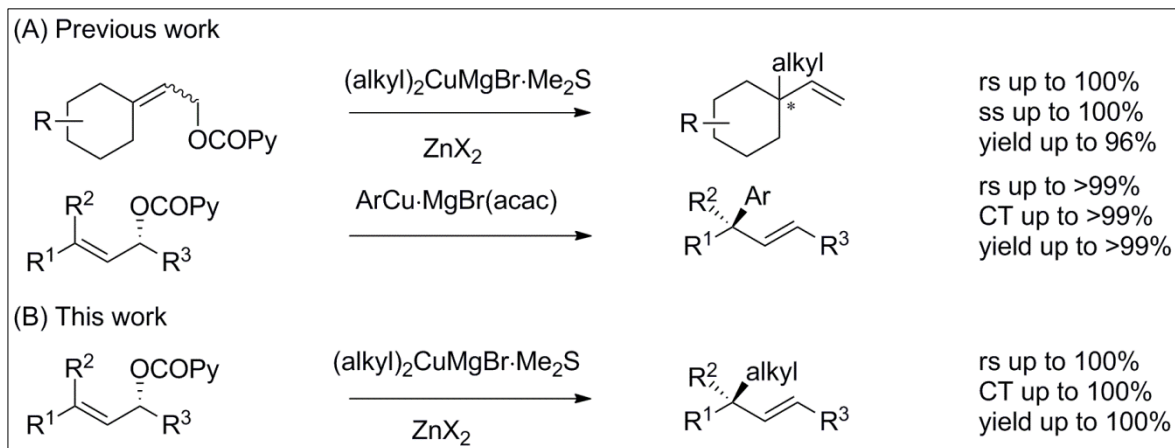
Organocopper reagents have been successfully applied for allylic substitution, representing one of the most valuable methods to form C-C bonds,¹ especially in connection with construction of chiral quaternary carbon centers, which is a great challenge during the past decades² and oftentimes the key step for synthesis of important natural products.³ For example, P. Knochel et al synthesized (+)-Estrone by using allylic substitution with alkylcopper reagent to construction of a quaternary carbon center as the key step (**Scheme 5.1**).^{3a} Since preparation of asymmetric allylic alcohols with high enantiomeric purity is well investigated,⁴ allylic substitution of chiral esters with full CT (chirality transfer) became one of the most essential methods to generate all-carbon quaternary stereogenic centers.¹ For instance, Breit et al reported an interesting protocol via *o*-DPPB-directed allylic substitution, regio- and stereoselectively affording chiral quaternary carbon centers.⁵ Knochel and co-workers on the other hand applied OCOC₆F₅ leaving group to asymmetrically synthesize quaternary carbons, which were then successively transformed to chiral tertiary alcohols and amines.⁶



Scheme 5.1 Synthesis of Estrone by P. Knochel et al

Recently, as part of our efforts to establish new reagent systems for allylic substitution, OCOPy leaving group has been investigated to regio- and stereoselectively construct all carbon quaternary centers on cyclohexane rings as well as those possessing Ar groups (**Scheme 5.2A**),⁷ demonstrating high potency of OCOPy leaving group. However, allylic substitution of γ,γ -disubstituted acyclic picolates with alkylcopper reagents as well as CT of this type were not yet examined.^{7d} Herein, we continued the investigation of constructing chiral quaternary carbon

centers by allylic substitution of optically active acyclic picolinates with alkylcopper reagents and excellent chirality transfer, high regioselectivity as well as good yields were achieved (**Scheme 5.2B**).



Scheme 5.2 Previous and present work (rs/ss: regio-/stereo-selectivity)

5.2 Results and Discussion

Picolinates **1–3**, (*Z*)- and (*E*)-**4** were prepared according to **Chapter 4**. At the beginning of our study, racemic picolinate **1**^{7e} was synthesized for condition optimization and the results were summarized in Table 5.1. In general, two types of organocopper reagents, “BuCu” and “Bu₂Cu[–]” reagents were generated by using BuMgBr and CuBr•Me₂S in 1:1 and 2:1 ratios, respectively.⁸ The product distribution was calculated based on ¹H NMR analysis of corresponding olefinic protons as an unpurified reaction mixture.

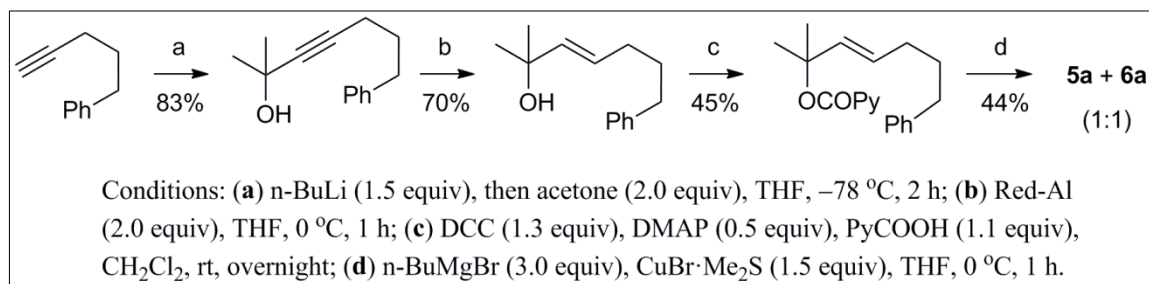
Table 5.1 Condition Optimization

1	5a	6a	7			
Entry	BuMgBr (equiv)	CuBr•Me ₂ S (equiv)	Bu/Cu	ZnI ₂ (equiv)	T (°C)	5a : 6a : 7 : 1 ^a
1	1.5	1.5	1 : 1	–	0	68 : 8 : 24 : 0 ^b
2	1.5	1.5	1 : 1	1.5	0	39 : 7 : 54 : 0 ^b
3	3.0	1.5	2 : 1	–	0	41 : 56 : 3 : 0
4	3.0	1.5	2 : 1	1.5	0	90 : 9 : 1 : 0
5	1.5	1.5	1 : 1	–	–18	75 : 4 : 3 : 18
6	1.5	1.5	1 : 1	1.5	–18	44 : 4 : 2 : 50
7	3.0	1.5	2 : 1	–	–18	33 : 56 : 11 : 0
8	3.0	1.5	2 : 1	1.5	–18	96 : 4 : 0 : 0
9	3.0	1.5	2 : 1	–	–40	54 : 46 : 0 : 0
10	3.0	1.5	2 : 1	1.5	–40	> 99 : 1 : 0 : 0^c
11	3.0	1.5	2 : 1	1.0	–40	97 : 2 : 1 : 0
12	3.0	1.5	2 : 1	0.5	–40	92 : 3 : 5 : 0

^aDetermined by ¹H NMR analysis of unpurified reaction mixtures. ^bUnidentified product was produced. ^c91% Isolated yield.

At 0 °C, the former “BuCu” species gave S_N2' product **5a** (no cis product was detected by ¹H NMR) in ca. 89% regioselectivity (68/(68+8)×100%) over S_N2 product **6a** (no cis product was detected by ¹H NMR) (entry 1), while addition of ZnI₂, in consequence of the importance of Zn

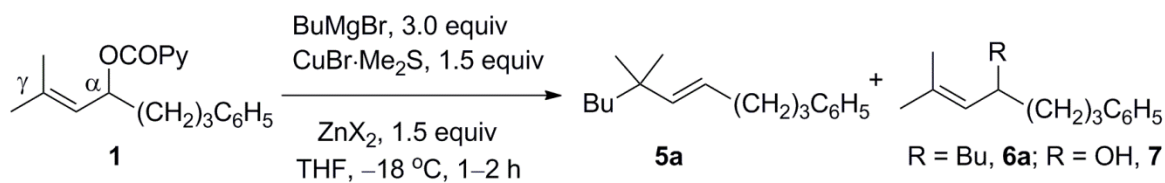
salts to the regioselectivity discovered previously,^{7d} afforded much alcohol **7** (entry 2). Meanwhile, the regioisomer **6a** was prepared according to the transformation shown in **Scheme 5.3**. In addition, both the above conditions (entries 1 and 2) generated unidentified product as the major product, whereas “Bu₂Cu[−]” species afforded mixture of **5a** and **6a** without producing such unidentified byproduct (entry 3). Moreover, addition of ZnI₂ improved the regioselectivity to ca. 91% (entry 4).



Scheme 5.3 Synthesis of 6a

At −18 °C, “BuCu” species gave S_N2’ product **5a** in ca. 95% regioselectivity over S_N2 product **6a** (entry 5), yet somehow lower conversion of substrate **1** than that of “Bu₂Cu[−]” species took place, although a mixture of **5a** and **6a** was afforded (entry 7). Furthermore, ZnI₂ was employed with “BuCu” species, but prevented the reaction (entry 6). In contrast, by utilizing “Bu₂Cu[−]” species, regioselectivity was greatly enhanced to 96% in the presence of ZnI₂ (entries 8 vs 7) and almost perfection at −40 °C (entries 10 vs 9). Even with less quantities of ZnI₂ (1.0 equiv and 0.5 equiv), high regioselectivity was still observed (entries 11 and 12), representing the essential role played by Zn salts, which chelated to the Py ring to activate the OCOPy leaving group^{7a, c} as a stronger Lewis acid instead of MgBr₂.^{7d} However, Zn salts only work well in case of “Bu₂Cu[−]” reagent by comparison with “BuCu[−]” organometallic reagent (entries 2 vs 4; 6 vs 8).

Table 5.2 Examination of Various Zn Salts



Entry	X =	5a : 6a : 7 : 1 ^a	γ/α
1	F	35 : 65 : 0 : 0	35 : 65
2	Cl	40 : 7 : 3 : 50	85 : 15
3	Br	78 : 6 : 5 : 11	93 : 7
4	PhCOO	96 : 4 : 0 : 0	96 : 4
5	OAc	88 : 12 : 0 : 0	88 : 12
6	OTs	91 : 5 : 0 : 4	95 : 5
7	OSO ₂ CF ₃	40 : 58 : 2 : 0	41 : 59

^a Determined by ¹H NMR analysis of unpurified reaction mixtures.

Despite the excellent regioselectivity accomplished by addition of ZnI₂, a variety of Zn salts were examined then (Table 5.2). Conditions with ZnF₂ mainly gave S_N2 product, whereas with ZnCl₂, which is hygroscopic, substrates remained (entries 1 and 2). In contrast, ZnBr₂, Zn(OTs)₂ and Zn(PhCOO)₂ successfully improved the regioselectivity to more than ca. 93% (entries 3, 5 and 6). Zn(OAc)₂ generated the S_N2' product with 88% regioselectivity but Zn(OSO₂CF₃)₂ generated a mixture instead (entries 4 and 7). As a result, ZnI₂ works the best; ZnBr₂, Zn(PhCOO)₂, and Zn(OTs)₂ are the second choice; Zn(OAc)₂ could be another choice.

Table 5.3 Allylic substitution picolinates with various of alkyl copper reagents

entry	substrate	RMgX	product	$\gamma:\alpha^b$	yield ^c (%)
1	1	MeMgBr	5b R = Me	>99 : 1	88
2	1	EtMgBr	5c R = Et	98 : 2	84
3	1	C ₆ H ₅ CH ₂ MgCl	5d R = C ₆ H ₅ CH ₂	98 : 2	95
4	1	C ₆ H ₅ (CH ₂) ₂ MgBr	5e R = C ₆ H ₅ (CH ₂) ₂	>99 : 1	94
5	1	C ₆ H ₅ (CH ₂) ₃ MgBr	5f R = C ₆ H ₅ (CH ₂) ₃	98 : 2	87
6	1	<i>n</i> -C ₁₆ H ₃₃ MgBr	5g R = <i>n</i> -C ₁₆ H ₃₃	98 : 2	100
7	1	CyMgBr	5h R = Cy	92 : 8	90
8	1	<i>t</i> -BuMgCl	5i R = <i>t</i> -Bu	32 : 68	38 ^d
9	2	BuMgBr	8a R = Bu	99 : 1	79
10	2	CyMgBr	8b R = Cy	97 : 3	81

^aConditions: RMgX, 3.0 equiv; CuBr·Me₂S, 1.5 equiv; ZnI₂, 1.5 equiv, −40 °C, 1–2 h.

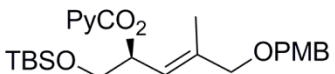
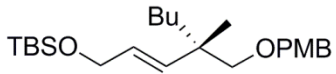
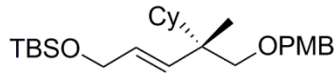
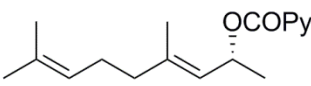
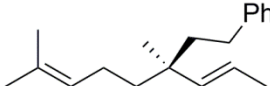
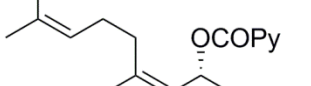
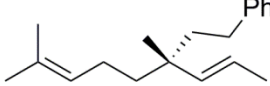
^bDetermined by ¹H NMR analysis. ^cIsolated yield after purification by chromatography. ^dNo picolinate remained based on TLC and ¹H NMR analysis of unpurified mixtures.

Subsequently, different alkyl groups were examined (Table 5.3). Me and Et groups were transferred successfully and the S_N2' products were obtained with 99% and 98% regioselectivity in good yields respectively (entries 1 and 2). The Bn, Ph(CH₂)₂ and Ph(CH₂)₃ groups were examined and excellent regioselectivity as well as high yields were observed as above (entries 3–5), suggesting Ar groups within the alkyl chain is also greatly acceptable to our reagent system. It was worth noting that *o*-DPPB leaving group did not work well for Bn group, resulting in only 53% yield.⁵ Furthermore, a long alkyl chain (*n*-C₁₆H₃₃) was impressively transferred to the quaternary carbon centers with 98% regioselectivity quantitatively (entry 6), demonstrating high efficiency of the above reagent system. Afterward, cyclohexyl as a secondary alkyl group was selected to study the steric factor, still resulting in 92% regioselectivity (entry 7). However, the introduction of *t*-Bu group, as shown in entry 8, proceeded with the S_N2 product as the major

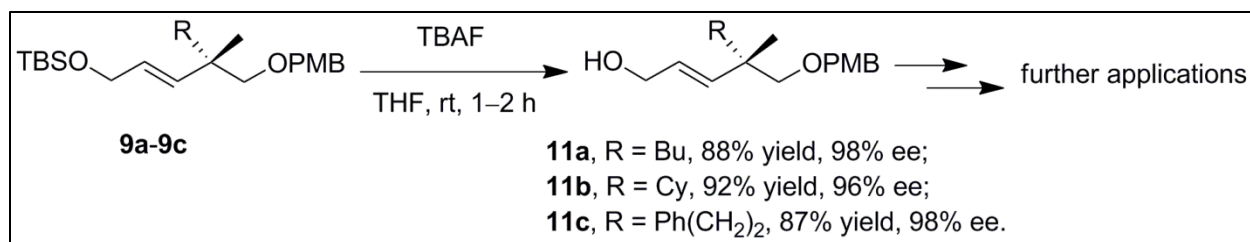
product and unknown side products were also detected by ^1H NMR analysis of unpurified reaction mixture, due to the more steric hindrance and stronger basicity of *t*-butylcopper species. $\text{Cu}(\text{acac})_2$ was also applied but afforded unidentified byproduct, although 95% regioselectivity was observed by using $\text{BuMgBr}/\text{Cu}(\text{acac})_2$ in both 2/1 and 3/1 ratios at -40°C (data not shown). Next, cyclic picolinate **2**^{7e} was also examined and $\text{S}_{\text{N}}2'$ products **8a**^{5b} and **8b** were correspondingly synthesized, bearing quaternary carbon centers on the cyclohexane ring with excellent regioselectivity (entries 9 and 10).

Encouraged by these satisfactory results, we turned our attention to subject optically active picolines **3** (98% ee), *E*-**4** (82% ee) and *Z*-**4** (66% ee) to the above conditions to create asymmetric quaternary carbon centers. As described in **Table 5.4**, without Zn salt, the $\text{S}_{\text{N}}2'$ product was obtained with 83% regioselectivity (entry 1), whereas with both 0.5 equiv and 1.5 equiv of ZnI_2 , the $\text{S}_{\text{N}}2'$ product **9a** was generated with >99% regioselectivity, with 99% and >99% CT respectively (entries 2 and 3). In contrast, allylic substitution of **3** with standard phenylcopper reagents (generated from 3 equiv of PhMgBr and 1.5 equiv of $\text{Cu}(\text{acac})_2$) suffers from low conversion (**Chapter 4**) reveals the high activity of alkylcopper species. The absolute configuration of **9a** was confirmed by comparing the $[\alpha]_{\text{D}}$ value with that reported ($[\alpha]_{\text{D}}^{23} = +5.4$ (*c* 0.40, CHCl_3) for the *S* isomer of 98% ee; cf. $[\alpha]_{\text{D}}^{27} = +3.2$ (*c* 0.50, CHCl_3) for the *S* isomer of 96% ee; $[\alpha]_{\text{D}}^{22} = -5.7$ (*c* 0.615, CHCl_3) for the *R* isomer of 93% ee).^{5b} Thus the anti- $\text{S}_{\text{N}}2'$ pathway was established and it was assigned to the others. ZnBr_2 gave **9a** with high selectivity likewise (entry 4), whereas $\text{Zn}(\text{PhCOO})_2$ and $\text{Zn}(\text{OTf})_2$ somewhat resulted in a lower yield due to generation of alcohol, nevertheless >98% and >99% regio- and stereo-selectivity was observed (entries 5 and 6). Cyclohexyl and $\text{Ph}(\text{CH}_2)_2$ groups were examined later and the anti- $\text{S}_{\text{N}}2'$ products **9b** and **9c** were obtained with high selectivity in good yields (entries 7 and 8). Notably, allylic substitution of (*E*)- and (*Z*)-**4** generated the stereoisomers (*S*)- and (*R*)-**10** respectively (entries 9 and 10), illustrating the absolute configuration of the product is also controlled by the geometry of the olefin, which would be a synthetic convenience for its application.

Table 5.4 Allylic Substitution of Optically Active Picolinates with Alkylcopper Reagents^a

Entry	substrate	Organocopper reagents (equiv)	ZnX ₂ (equiv)	Product	$\gamma:\alpha^b$	CT ^c %	Yield ^d %
1	 3 (98% ee)	Bu ₂ CuMgBr·MgBr ₂ (1.5)	—	 9a	83:17	97	77
2	3	Bu ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (0.5)	9a	>99:1	99	85
3	3	Bu ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (1.5)	9a	>99:1	>99	92
4	3	Bu ₂ CuMgBr·MgBr ₂ (1.5)	ZnBr ₂ (1.5)	9a	>99:1	99	89
5	3	Bu ₂ CuMgBr·MgBr ₂ (1.5)	Zn(PhCOO) ₂ (1.5)	9a	99:1	>99	78
6	3	Bu ₂ CuMgBr·MgBr ₂ (1.5)	Zn(OTs) ₂ (1.5)	9a	98:2	>99	74
7	3	Cy ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (1.5)	 9b	94:6	98	82
8	3	(Ph(CH ₂) ₂) ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (1.5)	 9c	99:1	>99	86
9	 (E)-4 (82% ee)	(Ph(CH ₂) ₂) ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (1.5)	 (S)-10	98:2	>99	90
10	 (Z)-4 (66% ee)	(Ph(CH ₂) ₂) ₂ CuMgBr·MgBr ₂ (1.5)	ZnI ₂ (1.5)	 (R)-10	97:3	98	82

^a Reaction conditions: THF, −40 °C, 1–2 h. ^b Determined by ¹H NMR of the unpurified reaction mixtures. ^c Determined by chiral HPLC analysis of the corresponding alcohols after removing TBS group for entries 1–8 and the products of entries 9–10. ^d Isolated yield.

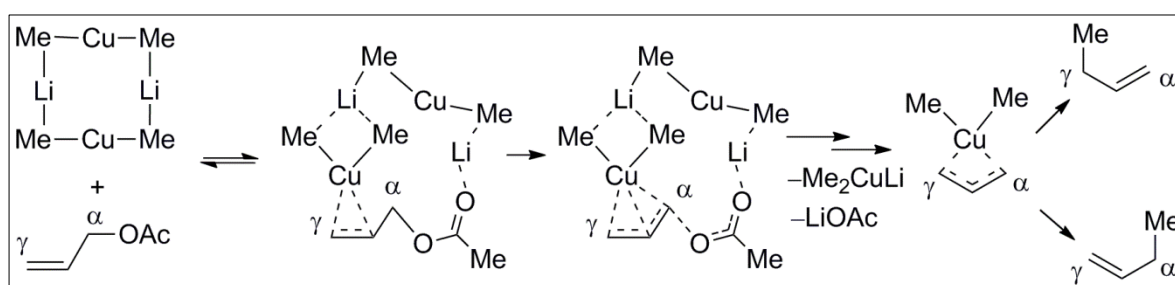


Scheme 5.4 Corresponding Alcohols of 9a-9c

Additionally, due to the difficulty of separation of enantiomers of **9a-9c** by chiral HPLC, the enantiomeric purity of **9a-9c** was determined by chiral HPLC analysis of the corresponding alcohols **11a-11c** after removing TBS group as illustrated in **Scheme 5.5**, which, on the other hand, could be chiral pools containing quaternary carbon centers (96-98% ee) for further applications.

5.3 Mechanism

For an in-depth understand the anti-S_N2' pathway established as shown above, a question remains: **why zinc**? Since mechanism of allylic substitution as well as conjugate addition with organocopper reagents has been well studied in both experimental and theoretical view,^{1h,9,10} especially, the mechanism of allylic substitution with organocopper reagents illustrated by E. Nakamura et al,^{10c} indicating a bimetallic cluster consists of copper and lithium (**Scheme 5.5**). The regioselectivity is lost after cleavage of the C–O bond to remove OAc leaving group, affording α and γ products equally.



Scheme 5.5 Mechanism Proposed by E. Nakamura et al

According to the above mechanism, considering the picolinate reagent system, 3 possible positions, **P¹**, **P²**, and **P³** were proposed for Zn²⁺ respectively (**Figure 5.1**).

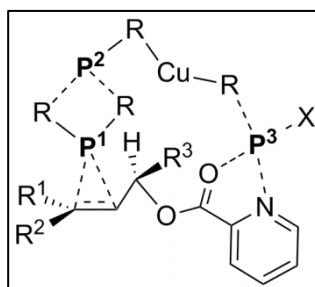
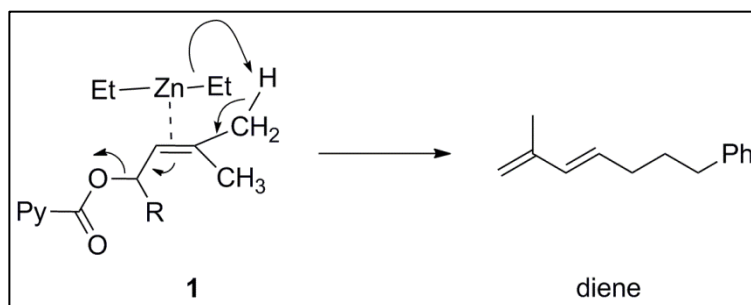


Figure 5.1 Three Possible Positions (P¹, P², and P³) for Zinc

So far as we know, the role of Zn²⁺ was probably to chelate to the picolinoxy group as a stronger Lewis acid instead of Mg²⁺,^{7d} but further study on Zn salts suggests a different story. As described in **Table 5.5**, without CuBr·Me₂S, EtMgBr and ZnI₂ in 1:1 and 2:1 ratios generated diene respectively (entries 1 and 2), suggesting Zn could not chelate directly to C=C bond of substrate **1** to transfer the Et group as metal-centered nucleophiles but as a Lewis acid to C=C

bond (**Scheme 5.6**), due to the low-lying 3d orbital of zinc,⁹ though zinc and copper are in a neighborhood in the periodic table. As a result, position **P**¹ is not the possible position for Zinc.



Scheme 5.6 Zinc works as Lewis Acid in the Absence of Copper

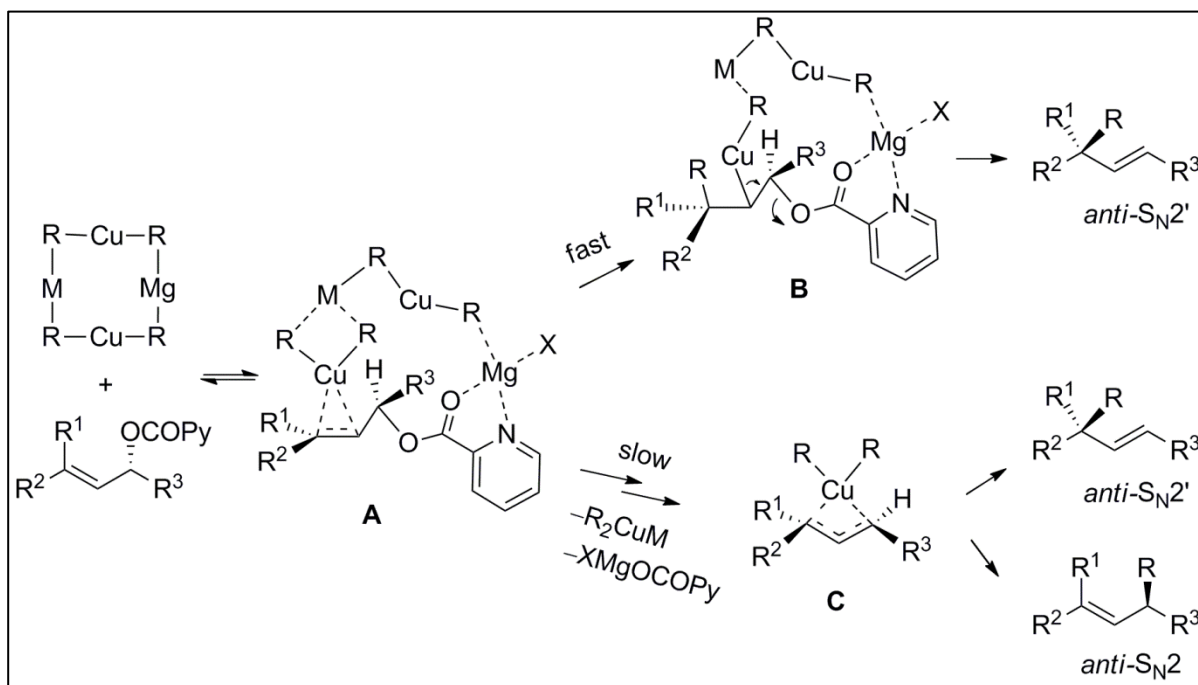
To examine whether OCOPy leaving group was activated by Zn^{2+} or Mg^{2+} , Et_2Zn reagent was employed as the alkyl reagent source. In addition, Et_2Zn and $\text{CuBr}\cdot\text{Me}_2\text{S}$ in a 1:2 and 1:1 ratios generates $\text{EtCu}\cdot\text{ZnBr}_2\cdot\text{Me}_2\text{S}$ and $\text{Et}_2\text{CuZnBr}\cdot\text{Me}_2\text{S}$ respectively (**Chapter 1, Scheme 1.6**). At -40°C , almost no reaction occurred with $\text{Et}_2\text{Zn}/\text{Cu}$ in a 1:2 ratio (entry 3), and with 1.5 equiv of MgBr_2 , picolinate **1** remained although ca. 96% regioselectivity was observed (entry 4), demonstrating Et/Cu in a 1:1 ratio has poor reactivity. On the other hand, MgBr_2 enhanced the reaction greatly in case of Et/Cu in a 2:1 ratio (entry 6 vs 5). However, addition of ZnI_2 only afforded ca. 10% of alcohol **7** and ca. 90% of substrate **1**, and both $\text{S}_{\text{N}}2'$ and $\text{S}_{\text{N}}2$ products were not detected by ^1H NMR (entry 7), indicating it is the Mg^{2+} that chelates to the Py ring to active OCOPy leaving group but not Zn^{2+} . Additionally, LiI was also applied but did not complete the reaction (entry 8). Next, BuLi was used to confirm that MgBr_2 is much better than ZnI_2 to active OCOPy. Use of MgBr_2 afforded $\text{S}_{\text{N}}2'$ product **5a** with 98% regioselectivity (entries 11 vs 9) while use of ZnI_2 prevented the reaction (entry 10 vs 9). As a result, ZnI_2 improved the regioselectivity is not because of chelation to the Py ring to active OCOPy leaving group instead of MgBr_2 . In other words, position **P**³ is not the possible position for zinc.

Table 5.5 Study of Mechanism

Reaction scheme: $\text{1} \xrightarrow[\text{THF, 1 h}]{\text{R-M, CuBr}\cdot\text{Me}_2\text{S}}$ $\text{5a} + \text{6a} + \text{7}$

Entry	R-M (equiv)	CuBr•Me ₂ S (equiv)	R/Cu	Additive (equiv)	T (°C)	5a : 6a : 7 : 1 ^a	γ/α
1	EtMgBr (1.5)	–	–	ZnI ₂ (1.5)	–40	diene ^b	–
2	EtMgBr (3.0)	–	–	ZnI ₂ (1.5)	–40	diene ^b	–
3	Et ₂ Zn (0.75)	1.5	1 : 1	–	–40	0 : 0 : 1 : 99	–
4 ^c	Et ₂ Zn (0.75)	1.5	1 : 1	MgBr ₂ (1.5)	–40	46 : 2 : 4 : 48	96 : 4
5	Et ₂ Zn (1.5)	1.5	2 : 1	–	–40	27 : 1 : 3 : 69	97 : 3
6 ^c	Et ₂ Zn (1.5)	1.5	2 : 1	MgBr ₂ (1.5)	–40	96 : 4 : 0 : 0	96 : 4
7	Et ₂ Zn (1.5)	1.5	2 : 1	ZnI ₂ (1.5)	–40	0 : 0 : 10 : 90	–
8	Et ₂ Zn (1.5)	1.5	2 : 1	Lil (1.5)	–40	65 : 4 : 6 : 25	95 : 5
9	BuLi (3.0)	1.5	2 : 1	–	–40	25 : 73 : 2 : 0	25 : 75
10	BuLi (3.0)	1.5	2 : 1	ZnI ₂ (1.5)	–40	0 : 0 : 10 : 90	–
11 ^c	BuLi (3.0)	1.5	2 : 1	MgBr ₂ (1.5)	–40	93 : 2 : 5 : 0	98 : 2
12	BuMgBr (3.0)	1.5	2 : 1	ZnI ₂ (1.5)	–18	96 : 4 : 0 : 0	96 : 4
13	BuMgBr (3.0)	1.5	2 : 1	Lil (1.5)	–18	97 : 3 : 0 : 0	97 : 3

^aDetermined by ¹H NMR. ^bAs shown in Scheme 5.5. ^cMgBr₂ (0.20 M in THF) was used.



Scheme 5.7 Possible Mechanism (M = Zn/Li, R = alkyl, X = Br, I, etc.)

Nevertheless, Zn was proposed to form a trimetallic intermediate with Cu instead of Li in our reagent system as described in **Scheme 5.7** and the role of Zn²⁺ is suggested to be at the position **P**² (**Figure 5.1**), because Zn²⁺ was proved not to chelate to the Py ring as above (position **P**³ is not possible) and not to interact with C=C bond as nucleophile (position **P**¹ is not possible). In other words, Li⁺, which is also at the position **P**² (**Scheme 5.5** and **Figure 5.1**), probably increases the selectivity as Zn²⁺ does, which was proved by addition of LiI affording the same level selectivity as well as reactivity to ZnI₂ (Table 5.5, entries 12 and 13). Hence oxidative addition of alkylcopper reagent to C=C bond of picolinate forms the complex **A** first, in which Mg²⁺ chelates to Py to activate OCOPy leaving group. Then one alkyl group is delivered to form complex **B**, which undergoes reductive elimination to generate *anti*-S_N2' product. Meanwhile, **A** also generates **C** as described by E. Nakamura (**Scheme 5.6**), which loses the regioselectivity to afford *anti*-S_N2' and *anti*-S_N2 products. Because of different leaving ability of OCOPy from the OAc leaving group (conditions of entry 12 was also applied to OAc leaving group instead of OCOPy leaving group of substrate **1**, no reaction occurred even after stirring for overnight), **A** is supposed to generate **B** much faster than **C**, thus resulting in high regioselectivity, which is consistent with the above experimental results, although more evidences could be obtained by computational method to explain why the pathway **A** to **B** is preferred over the other pathway **A**

to **C**. In addition, stoichiometric alkylcopper reagent of type **A** is unreactive,^{1h} which explains reactions did not proceeded well with R/Cu/Zn (R = alkyl) in a 1:1:1 ratio (Table 5.1, entry 6; Table 5.5, entries 3 and 4).

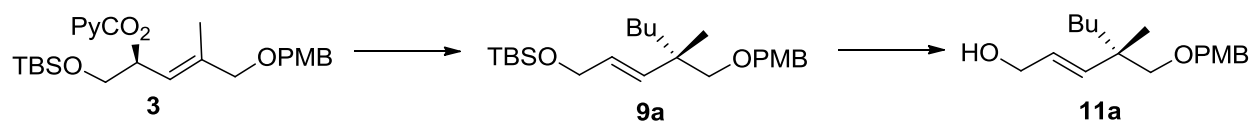
On the other hand, there is still a chance that Zn may act as Lewis acid associating organocopper reagents to attack the γ position directly.

5.4 Conclusion

In conclusion, allylic substitution of γ , γ -disubstituted chiral picolines with primary and secondary alkylcopper reagents generating anti-S_N2' products with high regio- and stereoselectivity in good yields was established and presented an efficient method for construction of chiral quaternary carbon centers. Various Zn salts were examined with different quantities implying mild reaction conditions. Notably, the absolute configuration of the anti-S_N2' product can be switched by the geometry of the olefin, which would be an advantage for synthetic application. Further study implies that zinc, copper and magnesium form trimetallic complex, which affords anti-S_N2' product selectively and zinc could be replaced by lithium. Further investigation for synthesis of natural products is currently going on and will be reported by us in the near future.

5.5 Experimental Section

General Remarks. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were measured in CDCl_3 using SiMe_4 ($\delta = 0$ ppm) and the centerline of triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). Chemical shifts in the ^{13}C NMR spectra accompany minus (for C and CH_2) and plus (for CH and CH_3) signs of APT experiments. The following solvents were distilled beforehand: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions were finished, the organic extracts were concentrated by using evaporators and the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60 N).

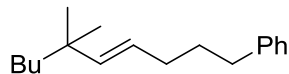


Typical procedure for construction of a chiral quaternary carbon: To a suspension of anhydrous ZnI_2 (32.5 mg, 0.102 mmol) and $\text{CuBr}\cdot\text{Me}_2\text{S}$ (21.1 mg, 0.103 mmol) in THF (1 mL) was added BuMgBr (0.25 mL, 0.87 M in THF, 0.22 mmol). After further stirring at 0°C for 30 min, to the above reaction mixture was added a solution of picolinate **3** (32.1 mg, 0.0681 mmol) in THF (1 mL) at -40°C . Then the reaction mixture was allowed to be warmed to -15°C over 1 h and was quenched by NH_4Cl (aq). The resulting mixture was extracted by hexane three times. The combined extracts were washed by brine and dried by MgSO_4 . The solvents were evaporated and the remaining residue was purified by chromatography (hexane) to furnish **9a** (25.4 mg, 92% yield): (25.4 mg, 92% yield). $[\alpha]_D^{23} = +5.4$ (c 0.50, CHCl_3). IR (neat) 1613, 1514, 1249, 837, 776 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.06 (s, 6 H), 0.86 (t, $J = 8$ Hz, 3 H), 0.90 (s, 9 H), 1.00 (s, 3 H), 1.10–1.20 (m, 2 H), 1.20–1.30 (m, 2 H), 1.32–1.40 (m, 2 H), 3.17 (d, $J = 9$ Hz, 1 H), 3.19 (d, $J = 9$ Hz, 1 H), 3.80 (s, 3 H), 4.16 (dd, $J = 5$, 1 Hz, 2 H), 4.42 (s, 2 H), 5.47 (dt, $J = 16$, 5 Hz, 1 H), 5.60 (dm, $J = 16$ Hz, 1 H), 6.86 (dm, $J = 8$ Hz, 2 H), 7.24 (dm, $J = 8$ Hz, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ -4.9 (+), 14.2 (+), 18.5 (-), 21.7 (+), 23.6 (-), 26.1(+), 26.2 (-), 37.8 (-), 40.0 (-), 55.3 (+), 64.6 (-), 73.0 (-), 77.9 (-), 113.7 (+), 127.3 (+), 129.0 (+), 131.1 (-), 137.4

(+), 159.1 (-). HRMS (FAB) calcd for $C_{24}H_{42}O_3SiNa [(M+Na)^+]$ 429.2801, found 429.2822. The 1H and ^{13}C NMR spectra of **9a** were identical with those reported (Ref. 5b).

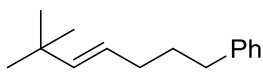
TBS ester **9a** (25.4 mg, 0.062 mmol) was then dissolved in THF (3.0 mL) and treated by TBAF (0.13 mL, 1.0 M in THF, 0.13 mmol) for 1 h at rt to afford the corresponding alcohol **11a**: (16.1 mg, 98% ee, 100% CT, 88% yield). $[\alpha]_D^{24} = +9.3$ (c 0.20, $CHCl_3$). IR (neat) 3398, 1612, 1513, 1245, 1092 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, $J = 7$ Hz, 3 H), 1.00 (s, 3 H), 1.08–1.20 (m, 2 H), 1.20–1.32 (m, 2 H), 1.32–1.40 (m, 2 H), 3.19 (s, 2 H), 3.80 (s, 3 H), 4.11 (d, $J = 5$ Hz, 2 H), 4.43 (s, 2 H), 5.57 (dt, $J = 16, 6$ Hz, 1 H), 5.66 (d, $J = 16$ Hz, 1 H), 6.87 (d, $J = 9$ Hz, 2 H), 7.24 (d, $J = 9$ Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (+), 21.6 (+), 23.5 (-), 26.2 (-), 37.7 (-), 40.1 (-), 55.4 (+), 64.3 (-), 73.0 (-), 77.7 (-), 113.8 (+), 127.0 (+), 129.1 (+), 130.9 (-), 139.4 (+), 159.2 (-). HRMS (FAB) calcd for $C_{16}H_{28}O_3Na [(M+Na)^+]$ 315.1936, found 315.1936. The enantiomeric purity was determined by chiral HPLC analysis: Chiralcel AS-H, hexane/*i*-PrOH = 97/3, 0.500 mL/min, 30 °C, t_R /min = 26.4 (*R*-isomer), 31.8 (*S*-isomer).

Other products:



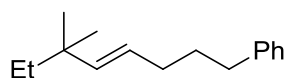
5a

(E)-(6,6-Dimethyldec-4-en-1-yl)benzene 5a: According to the typical procedure, to a suspension of ZnI_2 (55.4 mg, 0.174 mmol), $CuBr \cdot Me_2S$ (35.6 mg, 0.173 mmol), and $BuMgBr$ (0.48 mL, 0.77 M in THF, 0.37 mmol) in THF (1 mL) was added picolinate **1** (35.8 mg, 0.116 mmol) in THF (1 mL) at -40 °C dropwise. Then the reaction mixture was allowed to warm to -10 °C over 1 h to afford **5a** (25.7 mg, 91% yield): 1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3 H), 0.95 (s, 6 H), 1.12–1.32 (m, 6 H), 1.62–1.74 (m, 2 H), 2.04 (dt, $J = 7, 7$ Hz, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 5.28 (dt, $J = 16, 6$ Hz, 1 H), 5.36 (d, $J = 16$ Hz, 1 H), 7.14–7.30 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (+), 23.6 (-), 27.0 (-), 27.5 (+), 31.6 (-), 32.4 (-), 35.4 (-), 35.7 (-), 43.1 (-), 125.4 (+), 125.7 (+), 128.3 (+), 128.6 (+), 141.1 (+), 142.8 (-). HRMS (EI) calcd for $C_{18}H_{28} (M^+)$ 244.2191, found 244.2193.



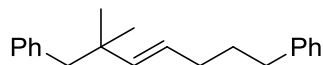
5b

(E)-(6,6-Dimethylhept-4-en-1-yl)benzene 5b: According to the typical procedure, to a suspension of ZnI_2 (47.0 mg, 0.147 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (29.5 mg, 0.143 mmol), and MeMgBr (0.30 mL, 0.97 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (30.9 mg, 0.0999 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -5°C over 1 h to afford **5b** (17.7 mg, 88% yield). ^1H NMR (400 MHz, CDCl_3) δ 0.99 (s, 9 H), 1.62–1.74 (m, 2 H), 2.02 (dt, $J = 7, 7$ Hz, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 5.31 (dt, $J = 16, 7$ Hz, 1 H), 5.45 (d, $J = 16$ Hz, 1 H), 7.14–7.32 (m, 5 H). ^{13}C NMR (100 MHz, CDCl_3) δ 29.9, 31.5, 32.2, 32.9, 35.4, 124.3, 125.7, 128.3, 128.6, 142.1, 142.8.



5c

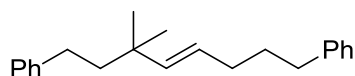
(E)-(6,6-Dimethyloct-4-en-1-yl)benzene 5c: According to the typical procedure, to a suspension of ZnI_2 (46.9 mg, 0.147 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (29.5 mg, 0.143 mmol), and EtMgBr (0.30 mL, 0.98 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (29.8 mg, 0.0963 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -5°C over 1 h to afford **5c** (17.5 mg, 84% yield). ^1H NMR (300 MHz, CDCl_3) δ 0.78 (t, $J = 7.5$ Hz, 3 H), 0.94 (s, 6 H), 1.28 (q, $J = 7.5$ Hz, 2 H), 1.56–1.76 (m, 2 H), 2.04 (dt, $J = 7, 7$ Hz, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 5.28 (dt, $J = 16, 6$ Hz, 1 H), 5.35 (d, $J = 16$ Hz, 1 H), 7.12–7.32 (m, 5 H). ^{13}C NMR (75 MHz, CDCl_3) δ 9.1 (+), 27.0 (+), 31.7 (–), 32.4 (–), 35.4 (–), 35.5 (–), 35.9 (–), 125.67 (+), 125.71 (+), 128.3 (+), 128.6 (+), 140.6 (+), 142.8 (–).



5d

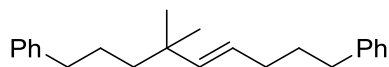
(E)-(2,2-Dimethylhept-3-ene-1,7-diyl)dibenzene 5d: According to the typical procedure, to a suspension of ZnI_2 (46.7 mg, 0.146 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (30.1 mg, 0.146 mmol), and BnMgCl (0.66 mL, 0.44 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (29.9 mg, 0.0966 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to –

10 °C over 2 h to afford **5d** (25.5 mg, 95% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.97 (s, 6 H), 1.59–1.73 (m, 2 H), 2.03 (dt, *J* = 7, 7 Hz, 2 H), 2.55 (s, 2 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 5.22 (dt, *J* = 16, 6.5 Hz, 1 H), 5.46 (d, *J* = 16 Hz, 1 H), 7.06–7.34 (m, 10 H). ¹³C NMR (75 MHz, CDCl₃) δ 27.2 (+), 31.5 (–), 32.4 (–), 35.4 (–), 36.9 (–), 49.6 (–), 125.7 (+), 125.8 (+), 125.9 (+), 127.5 (+), 128.3 (+), 128.5 (+), 130.7 (+), 139.2 (–), 140.3 (+), 142.8 (–).



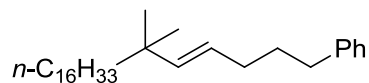
5e

(E)-(3,3-Dimethyloct-4-ene-1,8-diyl)dibenzene 5e: According to the typical procedure, to a suspension of ZnI₂ (47.3 mg, 0.148 mmol), CuBr·Me₂S (29.2 mg, 0.142 mmol), and Ph(CH₂)₂MgBr (0.37 mL, 0.78 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (29.9 mg, 0.0966 mmol) in THF (1 mL) at –40 °C dropwise. Then the reaction mixture was allowed to warm to –5 °C over 1 h to afford **5e** (26.5 mg, 94% yield). ¹H NMR (300 MHz, CDCl₃) δ 1.04 (s, 6 H), 1.50–1.62 (m, 2 H), 1.62–1.80 (m, 2 H), 2.07 (dt, *J* = 7.5, 7.5 Hz, 2 H), 2.46–2.56 (m, 2 H), 2.63 (t, *J* = 7.5 Hz, 2 H), 5.36 (dt, *J* = 16, 6 Hz, 1 H), 5.44 (d, *J* = 16 Hz, 1 H), 7.10–7.34 (m, 10 H). ¹³C NMR (100 MHz, CDCl₃) δ 27.5 (+), 31.4 (–), 31.6 (–), 32.4 (–), 35.4 (–), 35.9 (–), 45.4 (–), 125.6 (+), 125.7 (+), 126.2 (+), 128.3 (+), 128.35 (+), 128.38 (+), 128.5 (+), 140.3 (+), 142.7 (–), 143.5 (–).



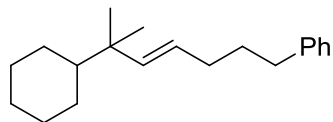
5f

(E)-(6,6-Dimethylnon-4-ene-1,9-diyl)dibenzene 5f: According to the typical procedure, to a suspension of ZnI₂ (44.9 mg, 0.141 mmol), CuBr·Me₂S (30.3 mg, 0.147 mmol), and Ph(CH₂)₃MgBr (0.32 mL, 0.90 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (30.0 mg, 0.0970 mmol) in THF (1 mL) at –40 °C dropwise. Then the reaction mixture was allowed to warm to –5 °C over 1 h to afford **5f** (25.9 mg, 87% yield). ¹H NMR (300 MHz, CDCl₃) δ 0.95 (s, 6 H), 1.24–1.36 (m, 2 H), 1.46–1.74 (m, 4 H), 2.02 (dt, *J* = 6.5, 6.5 Hz, 2 H), 2.50–2.66 (m, 4 H), 5.26 (dt, *J* = 16, 6 Hz, 1 H), 5.35 (d, *J* = 16 Hz, 1 H), 7.12–7.32 (m, 10 H). ¹³C NMR (100 MHz, CDCl₃) δ 26.7 (–), 27.5 (+), 31.6 (–), 32.4 (–), 35.4 (–), 35.7 (–), 36.8 (–), 43.0 (–), 125.7 (+), 128.3 (+), 128.5 (+), 128.6 (+), 140.8 (+), 142.8 (–), 143.0 (–).



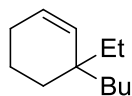
5g

(E)-(6,6-Dimethyldocos-4-en-1-yl)benzene 5g: According to the typical procedure, to a suspension of ZnI_2 (46.5 mg, 0.146 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (29.7 mg, 0.144 mmol), and $n\text{-C}_{16}\text{H}_{33}\text{MgBr}$ (0.58 mL, 0.50 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (29.8 mg, 0.0963 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -10°C over 2 h to afford **5g** (39.8 mg, >99% yield). ^1H NMR (300 MHz, CDCl_3) δ 0.88 (t, $J = 7$ Hz, 3 H), 0.94 (s, 6 H), 1.10–1.40 (m, 30 H), 1.61–1.78 (m, 2 H), 2.03 (dt, $J = 6.5, 6.5$ Hz, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 5.27 (dt, $J = 16, 6$ Hz, 1 H), 5.36 (d, $J = 16$ Hz, 1 H), 7.12–7.34 (m, 5 H). ^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (–), 22.8 (–), 24.7 (–), 27.5 (+, 2 C), 29.5 (–), 29.76 (–) and 29.80 (–) (9 C), 30.6 (–), 31.6 (–), 32.0 (–), 32.4 (–), 35.4 (–), 35.7 (–), 43.4 (–), 125.4 (+), 125.7 (+), 128.3 (+), 128.6 (+), 141.1 (+), 142.8 (–). HRMS (EI) calcd for $\text{C}_{30}\text{H}_{52}$ (M^+) 412.4069, found 412.4079.



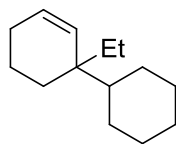
5h

(E)-(6-Cyclohexyl-6-methylhept-4-en-1-yl)benzene 5h: According to the typical procedure, to a suspension of ZnI_2 (46.7 mg, 0.146 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (30.2 mg, 0.147 mmol), and CyMgBr (0.42 mL, 0.70 M in THF, 0.29 mmol) in THF (1 mL) was added picolinate **1** (30.6 mg, 0.0989 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -10°C over 1 h to afford **5h** (24.1 mg, 90% yield). ^1H NMR (300 MHz, CDCl_3) δ 0.80–1.28 (m, 5 H), 0.91 (s, 6 H), 1.52–1.80 (m, 8 H), 2.04 (dt, $J = 7, 7$ Hz, 2 H), 2.61 (t, $J = 7$ Hz, 2 H), 5.25 (dt, $J = 16, 6$ Hz, 1 H), 5.37 (d, $J = 16$ Hz, 1 H), 7.12–7.32 (m, 5 H). ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (+), 26.8 (–), 27.3 (–), 27.8 (–), 31.7 (–), 32.5 (–), 35.5 (–), 38.3 (–), 48.0 (+), 125.67 (+), 125.71 (+), 128.3 (+), 128.6 (+), 140.6 (+), 142.9 (–). HRMS (EI) calcd for $\text{C}_{20}\text{H}_{30}$ (M^+) 270.2348, found 270.2350.



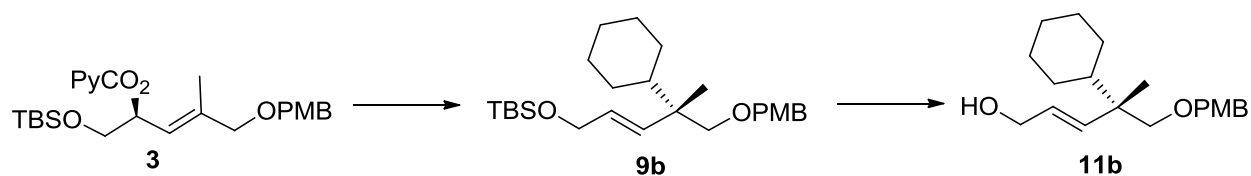
8a

3-Butyl-3-ethylcyclohex-1-ene 8a: According to the typical procedure, to a suspension of ZnI_2 (41.8 mg, 0.131 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (26.9 mg, 0.131 mmol), and BuMgBr (0.30 mL, 0.87 M in THF, 0.26 mmol) in THF (1 mL) was added picolinate **2** (20.3 mg, 0.0878 mmol) in THF (1 mL) at $-40\text{ }^\circ\text{C}$ dropwise. Then the reaction mixture was allowed to warm to $-5\text{ }^\circ\text{C}$ over 2 h to afford **8a** (11.5 mg, 79% yield). ^1H NMR (400 MHz, CDCl_3) δ 0.79 (t, $J = 7.5$ Hz, 3 H), 0.89 (t, $J = 7$ Hz, 3 H), 1.12–1.38 (m, 8 H), 1.38–1.44 (m, 2 H), 1.53–1.64 (m, 2 H), 1.86–1.97 (m, 2 H), 5.42 (d, $J = 10.5$ Hz, 1 H), 5.63 (dt, $J = 10.5, 3.5$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ 8.2 (+), 14.3 (+), 19.2 (–), 23.8 (–), 25.4 (–), 26.0 (–), 32.0 (–), 32.2 (–), 36.7 (–), 39.1 (–), 125.9 (+), 136.1 (+). The ^1H NMR and ^{13}C NMR were identical to those reported.^{5b}



8b

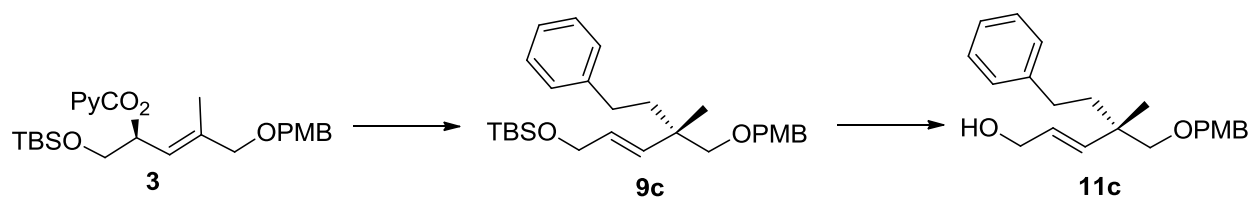
1-Ethyl-[1,1'-bi(cyclohexan)]-2-ene 8b: According to the typical procedure, to a suspension of ZnI_2 (42.3 mg, 0.132 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (26.9 mg, 0.131 mmol), and CyMgBr (0.37 mL, 0.70 M in THF, 0.26 mmol) in THF (1 mL) was added picolinate **2** (21.2 mg, 0.0917 mmol) in THF (1 mL) at $-40\text{ }^\circ\text{C}$ dropwise. Then the reaction mixture was allowed to warm to $-5\text{ }^\circ\text{C}$ over 1 h to afford **8b** (14.2 mg, 81% yield). ^1H NMR (400 MHz, CDCl_3) δ 0.78 (t, $J = 7.5$ Hz, 3 H), 0.86–1.49 (m, 10 H), 1.49–1.80 (m, 7 H), 1.84–1.94 (m, 2 H), 5.39 (d, $J = 10$ Hz, 1 H), 5.67 (dt, $J = 10, 3.5$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ 8.3 (+), 19.6 (–), 25.2 (–), 26.8 (–), 27.0 (–), 27.4 (–), 27.5 (–), 27.8 (–), 28.9 (–), 30.1 (–), 39.3 (–), 44.3 (+), 126.3 (+), 135.5 (+).



(*S,E*)-*tert*-Butyl((4-cyclohexyl-5-((4-methoxybenzyl)oxy)-4-methylpent-2-en-1-

yl)oxy)dimethylsilane **9b**: According to the typical procedure, to a suspension of ZnI_2 (30.0 mg, 0.0940 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (19.3 mg, 0.0939 mmol), and CyMgBr (0.28 mL, 0.72 M in THF, 0.20 mmol) in THF (1 mL) was added picolinate **3** (30.1 mg, 0.0638 mmol) in THF (1 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -10°C over 2 h to afford **9b** (22.7 mg, 82% yield): $[\alpha]_D^{24} = +9.3$ (c 0.30, CHCl_3). IR (neat) 1514, 1250, 1097, 837 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.06 (s, 6 H), 0.84–1.28 (m, 4 H), 0.90 (s, 9 H), 0.95 (s, 3 H), 1.43 (t, $J = 12\text{ Hz}$, 1 H), 1.58–1.78 (m, 6 H), 3.22 (d, $J = 8.5\text{ Hz}$, 1 H), 3.25 (d, $J = 8.5\text{ Hz}$, 1 H), 3.80 (s, 3 H), 4.16 (d, $J = 5\text{ Hz}$, 2 H), 4.40 (s, 2 H), 5.45 (dt, $J = 16, 5\text{ Hz}$, 1 H), 5.66 (d, $J = 16\text{ Hz}$, 1 H), 6.86 (d, $J = 8.5\text{ Hz}$, 2 H), 7.23 (d, $J = 8.5\text{ Hz}$, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ -4.9 (+), 18.5 (–), 18.7 (+), 26.1 (+), 26.8 (–), 27.13 (–), 27.15 (–), 27.3 (–), 27.6 (–), 42.5 (–), 43.1 (+), 55.3 (+), 64.7 (–), 73.0 (–), 76.4 (–), 113.7 (+), 127.6 (+), 129.1 (+), 131.1 (–), 136.6 (+), 159.1 (–). HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{43}\text{O}_3\text{Si}$ $[(\text{M}-\text{H})^+]$ 431.2981, found 431.2970.

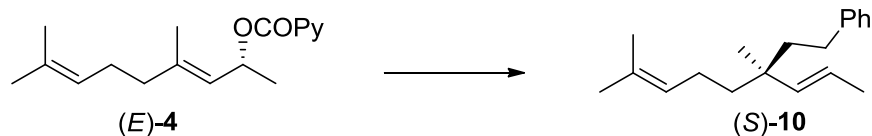
The TBS ester **9b** (8.9 mg, 0.0206 mmol) was treated by TBAF (0.04 mL, 1.0 M in THF, 0.04 mmol) at rt for 1 h to afford **11b**: (6.0 mg, 96% ee, 98% CT, 92% yield). $[\alpha]_D^{24} = +14$ (c 0.20, CHCl_3). IR (neat) 3416, 1612, 1513, 1248, 1087 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.80–1.24 (m, 4 H), 0.95 (s, 3 H), 1.42 (tt, $J = 12, 2.5\text{ Hz}$, 1 H), 1.48–1.78 (m, 6 H), 3.22 (d, $J = 9\text{ Hz}$, 1 H), 3.26 (d, $J = 9\text{ Hz}$, 1 H), 3.81 (s, 3 H), 4.12 (d, $J = 6\text{ Hz}$, 2 H), 4.41 (s, 2 H), 5.56 (dt, $J = 16, 6\text{ Hz}$, 1 H), 5.71 (d, $J = 16\text{ Hz}$, 1 H), 6.87 (d, $J = 8\text{ Hz}$, 2 H), 7.23 (d, $J = 8\text{ Hz}$, 2 H). ^{13}C NMR (100 MHz, CDCl_3) δ 18.4 (+), 26.8 (–), 27.09 (–), 27.13 (–), 27.3 (–), 27.6 (–), 42.7 (–), 43.1 (+), 55.4 (+), 64.4 (–), 73.0 (–), 76.3 (–), 113.8 (+), 127.4 (+), 129.1 (+), 130.9 (–), 138.9 (+), 159.2 (–). HRMS (EI) calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3$ $(\text{M})^+$ 318.2195, found 318.2199. The enantiomeric purity was determined by chiral HPLC analysis: Chiralcel AS-H, hexane/*i*-PrOH = 97/3, 0.500 mL/min, 30°C , $t_R/\text{min} = 20.3$ (*R*-isomer), 23.9 (*S*-isomer).



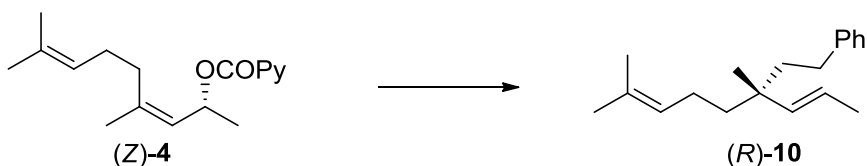
(*S,E*)-*tert*-Butyl((4-(((4-methoxybenzyl)oxy)methyl)-4-methyl-6-phenylhex-2-en-1-

yl)oxy)dimethylsilane 9c: According to the typical procedure, to a suspension of ZnI_2 (10.9 mg, 0.0341 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (6.9 mg, 0.034 mmol), and $\text{Ph}(\text{CH}_2)_2\text{MgBr}$ (0.080 mL, 0.78 M in THF, 0.062 mmol) in THF (0.5 mL) was added picolinate **3** (8.7 mg, 0.018 mmol) in THF (0.5 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -10°C over 2 h to afford **9c** (7.2 mg, 86% yield). ^1H NMR (400 MHz, CDCl_3) δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.09 (s, 3 H), 1.69 (t, $J = 8.5$ Hz, 2 H), 2.49 (t, $J = 8.5$ Hz, 2 H), 3.22 (d, $J = 9$ Hz, 1 H), 3.26 (d, $J = 9$ Hz, 1 H), 3.80 (s, 3 H), 4.19 (d, $J = 5$ Hz, 2 H), 4.43 (s, 2 H), 5.55 (dt, $J = 16, 5$ Hz, 1 H), 5.68 (d, $J = 16$ Hz, 1 H), 6.86 (d, $J = 9$ Hz, 2 H), 7.10–7.30 (m, 7 H). ^{13}C NMR (100 MHz, CDCl_3) δ -4.9 (+), 18.5 (–), 21.7 (+), 26.1 (+), 30.7 (–), 40.1 (–), 40.2 (–), 55.3 (+), 64.4 (–), 73.0 (–), 77.7 (–), 113.7 (+), 125.6 (+), 127.9 (+), 128.3 (+), 128.4 (+), 129.1 (+), 130.9 (–), 136.6 (+), 143.3 (–), 159.1 (–). HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{42}\text{O}_3\text{SiNa}$ $[(\text{M}+\text{Na})^+]$ 477.2801, found 477.2793.

The TBS ester **9c** (20.2 mg, 0.0444 mmol) was treated by TBAF (0.09 mL, 1.0 M in THF, 0.09 mmol) at rt for 1 h to afford **11c**: (13.2 mg, 98% ee, 100% CT, 87% yield). ^1H NMR (400 MHz, CDCl_3) δ 1.10 (s, 3 H), 1.63–1.78 (m, 2 H), 2.42–2.56 (m, 2 H), 3.24 (s, 2 H), 3.80 (s, 3 H), 4.12 (d, $J = 5$ Hz, 2 H), 4.44 (s, 2 H), 5.63 (dt, $J = 16, 5$ Hz, 1 H), 5.70 (d, $J = 16$ Hz, 1 H), 6.87 (d, $J = 8.5$ Hz, 2 H), 7.10–7.30 (m, 7 H). ^{13}C NMR (100 MHz, CDCl_3) δ 21.6 (+), 30.6 (–), 40.0 (–), 40.3 (–), 55.3 (+), 64.1 (–), 73.1 (–), 77.5 (–), 113.8 (+), 125.6 (+), 127.5 (+), 128.3 (+), 128.4 (+), 129.2 (+), 130.7 (–), 138.6 (+), 143.1 (–), 159.1 (–). The enantiomeric purity was determined by chiral HPLC analysis: Chiralcel AS-H, hexane/*i*-PrOH = 97/3, 0.500 mL/min, 30°C , $t_{\text{R}}/\text{min} = 31.4$ (*R*-isomer), 34.2 (*S*-isomer).



(S,E)-(3,7-Dimethyl-3-(prop-1-en-1-yl)oct-6-en-1-yl)benzene (S)-10: According to the typical procedure, to a suspension of ZnI_2 (26.4 mg, 0.0827 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (16.9 mg, 0.0822 mmol), and $\text{Ph}(\text{CH}_2)_2\text{MgBr}$ (0.23 mL, 0.78 M in THF, 0.18 mmol) in THF (0.5 mL) was added picolinate (E)-4 (15.4 mg, 0.0563 mmol) in THF (0.5 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -5°C over 2 h to afford (S)-10 (13.0 mg, 83% ee, 100% CT, 90% yield). ^1H NMR (400 MHz, CDCl_3) δ 1.02 (s, 3 H), 1.32 (t, $J = 8$ Hz, 2 H), 1.52–1.64 (m, 2 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.71 (d, $J = 4.5$ Hz, 3 H), 1.84–1.96 (m, 2 H), 2.46–2.56 (m, 2 H), 5.10 (t, $J = 7$ Hz, 1 H), 5.28–5.43 (m, 2 H), 7.12–7.32 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.7 (+), 18.4 (+), 23.0 (–), 23.4 (+), 25.8 (+), 30.9 (–), 38.8 (–), 41.3 (–), 43.5 (–), 122.2 (+), 125.2 (+), 125.6 (+), 128.37 (+), 128.41 (+), 131.1 (–), 139.7 (+), 143.6 (–). HRMS (EI) calcd



for $\text{C}_{19}\text{H}_{28}$ (M^+) 256.2191, found 256.2192. The enantiomeric purity was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 35°C , $t_{\text{R}}/\text{min} = 15.9$ (S-isomer), 16.7 (R-isomer).

(R,E)-(3,7-Dimethyl-3-(prop-1-en-1-yl)oct-6-en-1-yl)benzene (R)-10: According to the typical procedure, to a suspension of ZnI_2 (26.8 mg, 0.0840 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (16.8 mg, 0.0817 mmol), and $\text{Ph}(\text{CH}_2)_2\text{MgBr}$ (0.23 mL, 0.78 M in THF, 0.18 mmol) in THF (0.5 mL) was added picolinate (Z)-4 (15.8 mg, 0.0578 mmol) in THF (0.5 mL) at -40°C dropwise. Then the reaction mixture was allowed to warm to -5°C over 2 h to afford (R)-10 (12.2 mg, 65% ee, 98% CT, 82% yield). ^1H and ^{13}C NMR spectra were identify with those of (S)-10. The enantiomeric purity was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/*i*-PrOH = 99.8/0.2, 0.300 mL/min, 35°C , $t_{\text{R}}/\text{min} = 15.9$ (S-isomer), 16.6 (R-isomer).

5.6 References and Notes

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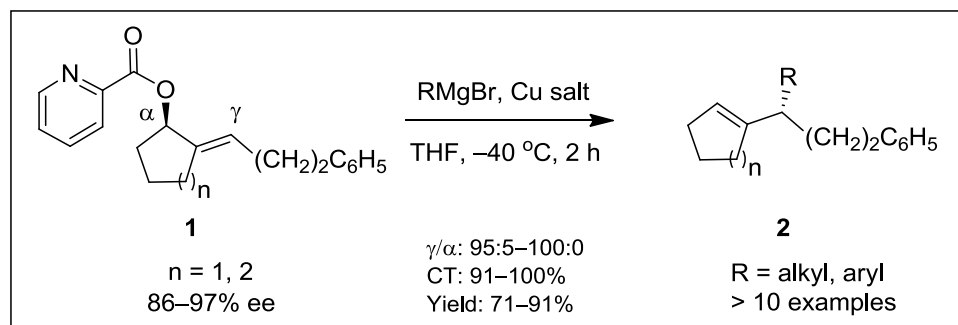
Chapter 6 Summary

Since preparation of asymmetric allylic alcohols with excellent enantiomeric purity is well investigated, allylic substitution of chiral esters with complete CT (chirality transfer) became one of the most important methods to generate stereogenic centers. New OCOPy leaving group was developed previously in our laboratory, presenting a new reagent system for allylic substitution.

The author investigated allylic substitution of enantioenriched cyclic and acyclic picolates to construct chiral tertiary and quaternary carbon centers. The results presented in **Chapters 2-5** were summarized in this chapter.

Chapter 2 Installation of a Chiral Side Chain to a 2-Alkylidene-1-cycloalkan-1-ol Unit by Using Allylic Substitution

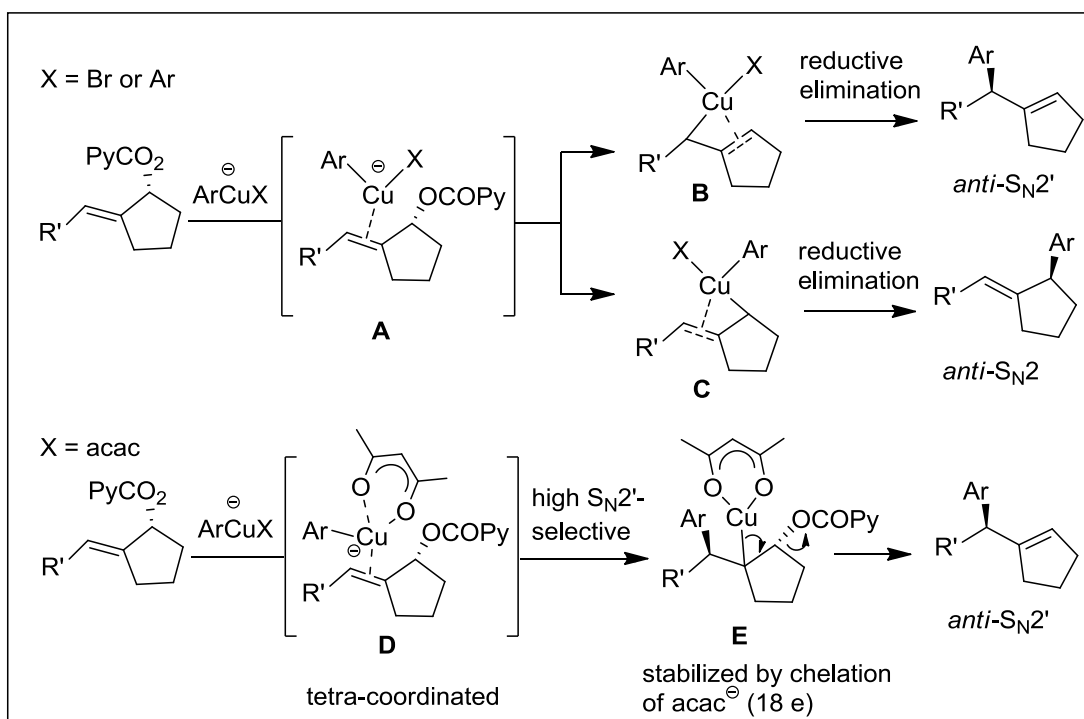
Firstly, the author studied to install chiral side chains to a 2-alkylidene-1-cycloalkan-1-ol unit by allylic substitution of picolates, which is important for synthesizing steroids containing D ring. To obtain fundamental aspect such as reactivity, regio- and stereoselectivities, the author investigated allylic substitution of γ -alkyl substituted allylic cycloalkenyl picolates **1** with RMgBr-based copper reagents (R = Bu, Ph, etc.), producing *anti* S_N2' products **2** (**Scheme 6.1**).



Scheme 6.1 Allylation of Optically Active Cycloalkenyl Picolates

Cu(acac)₂ was found to be a better copper salt than CuBr·Me₂S. A possible mechanism was presented (**Scheme 6.2**). In case of X = Br or Ar, [Ar-Cu-X][–] coordinates to C=C bond to form a T-shaped complex **A**, which controls the stereochemistry of this transformation and subsequently affording an tri-coordinated organocopper “Cu(III)” intermediate. Oxidative addition of C=C

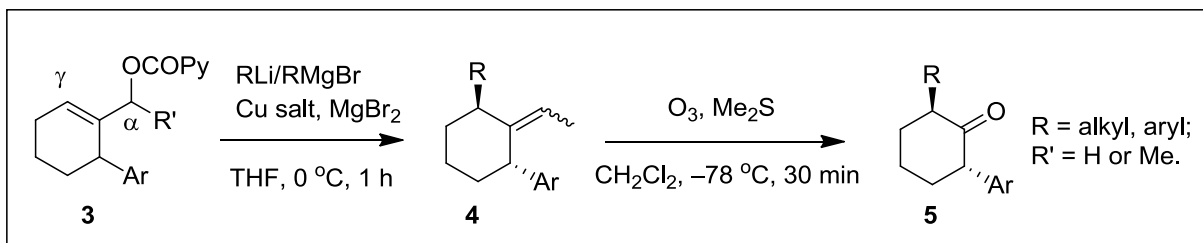
bond and subsequent cleavage of C–O bond produce tetra-coordinated π complexes **B** and **C**. Then reductive elimination generates the *anti*- S_N2' / S_N2 products. In contrast, in case of $X = \text{acac}$, the T-shape complex **D** is already tetra-coordinated, the Ar^- attacks the γ position, forming a stabilized tri-coordinated organocopper “Cu(III)” intermediate **E**, which consists of 18 electrons. Subsequent elimination generates *anti* S_N2' products with excellent regioselectivity.



Scheme 6.2 Plausible Mechanism

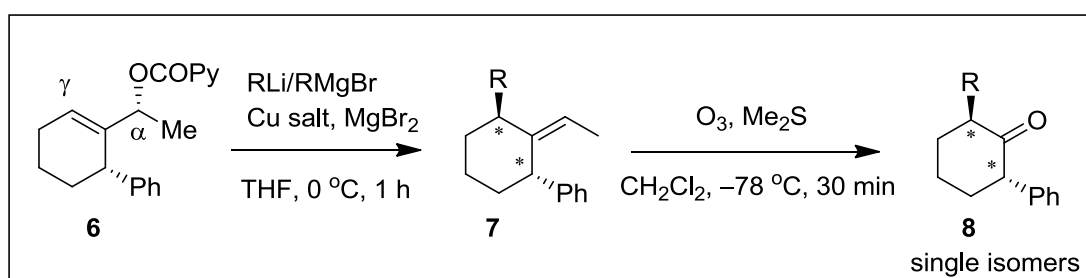
Chapter 3 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanone via Allylic Substitution of *exo*-Cyclic Picolinate Followed by Ozonolysis

Available methods oftentimes generate a mixture of 2,6-*trans*- and *cis*-disubstituted cyclohexanones. In this chapter, a strategy was developed by allylic substitution of exocyclic picolinate **3** with nucleophiles and ozonolysis to generate 2,6-disubstituted cyclohexanones **5** (nucleophiles were attached to α position of carbonyl group indirectly) (**Scheme 6.3**).



Scheme 6.3 Synthesis of 2,6-*trans*-Disubstituted Cyclohexanones

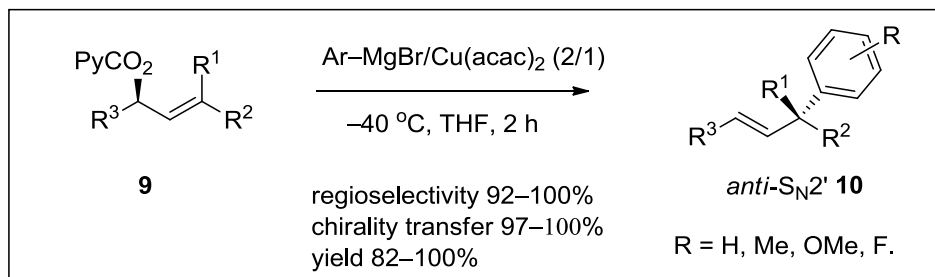
In addition, single isomer **8** (R = Me or Ph) were synthesized by allylic substitution of optically active picolinate **6**, respectively (**Scheme 6.4**).



Scheme 6.4 Synthesis of Single Isomers

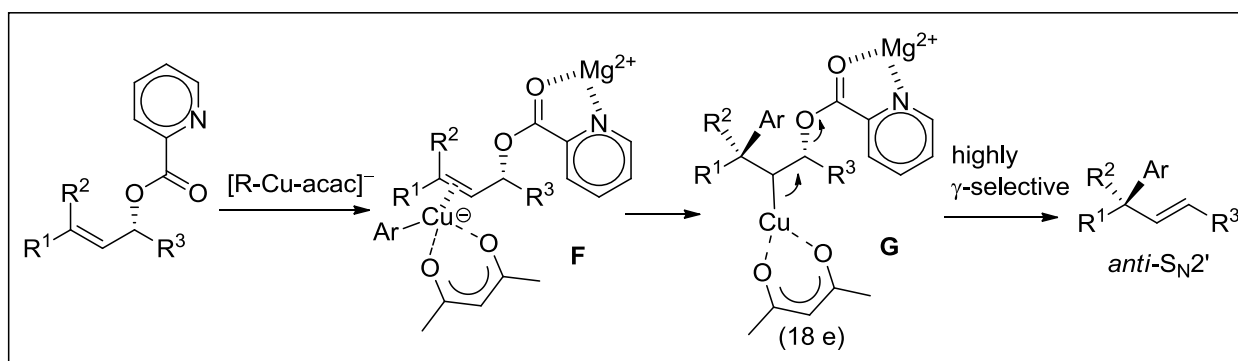
Chapter 4 Construction of Chiral Quaternary Carbon Centers with Arylcopper Reagents

Quaternary centers are very common in biologically active natural products and asymmetric preparation of quaternary centers is an important synthetic problem. Allylic substitution is one of the most valuable approaches. However, allylic substitution of secondary esters affording S_N2' products with excellent selectivity is limited to alkyl groups. In this chapter, aryl (Ar) groups were successfully transferred by $\text{Cu}(\text{acac})_2$ to the quaternary carbon centers of **10** with excellent regio- and stereoselective allylic substitution of optically active picolates **9** as shown in **Scheme 6.5**. Additionally, $\text{PhMgBr}/\text{Cu}(\text{acac})_2/\text{ZnI}_2$ in a 3:1:1 ratio was found to be a good reagent system as well.



Scheme 6.5 Construction of Chiral Quaternary Carbons Possessing Aryl groups

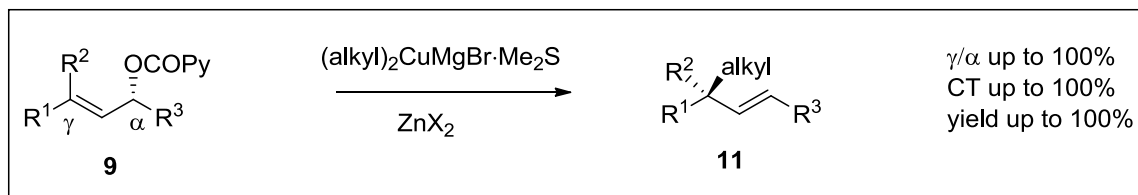
In a view of mechanism (**Scheme 6.6**), coordination of organocopper reagents to C=C bond, resulting a T-shaped complex **F**, which is already tetra-coordinated. Then the Ar group attacks γ position generates tri-coordinated organocopper species **G**. Chelation of acac^- to copper stabilized the Cu-C σ bond (18 electron rule), which is usually unstable, following by excellent γ -selective pathway.



Scheme 6.6 Possible Mechanism

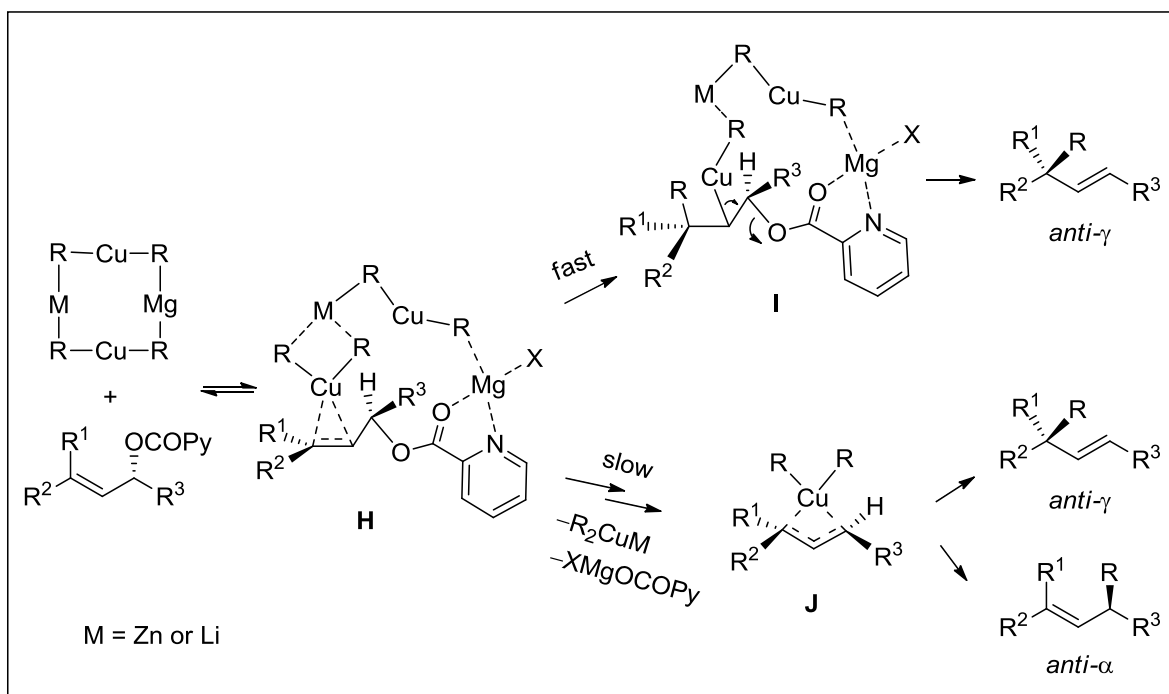
Chapter 5 Construction of Chiral Quaternary Carbon Centers with Alkylcopper Reagents

A protocol was successfully developed to construct all carbon quaternary centers possessing Ar group (**Chapter 4**). In this chapter, the author presents the continuous investigation of finding alkylcopper reagents for construction of chiral quaternary carbon centers by allylic substitution of optically active acyclic picolinates. ZnI_2 was found to promote regio- and stereoselective substitution of acyclic γ,γ -disubstituted secondary allylic picolinates **9** with alkylcopper reagents derived from alkyl-MgBr and $\text{CuBr}\cdot\text{Me}_2\text{S}$ in a 2:1 ratio to furnish *anti* S_N2' products **11** in good yields, which contain chiral quaternary carbon centers (**Scheme 6.7**).



Scheme 6.7 Construction of Chiral Quaternary Carbon Centers with Alkylcopper Reagents

Experimentally, it was proved that zinc cannot replace copper as well as magnesium in our reagent system. As a result, zinc was proposed to form a tri-metallic transition complex **H** like lithium (**Scheme 6.8**). The favorable transformation of **H** to **I** plays the key step for high regioselectivity to generate *anti* $\text{S}_{\text{N}}2'$ products over $\text{S}_{\text{N}}2$ products.



Scheme 6.8 Proposed Mechanism

Publications:

- [1] Feng, C.; Kobayashi, Y. “Allylic Substitution for Construcion of A Chiral Quaternary Carbon Possessing An Aryl Group”, *J. Org. Chem.* **2013**, 78, 3755–3766.
- [2] Feng, C.; Kaneko, Y.; Kobayashi, Y. “Construction of Quaternary Carbon Centers by Using Substitution of γ,γ -Disubstituted Secondary Allylic Picolimates With AlkylCopper Reagents”, *Tetrahedron Lett.* **2013**, 54, 4629–4632.
- [3] Feng, C.; Kobayashi, Y. “Installation of A Chiral Side Chain on Cycloalkenyl-substituted Carbon Unit by Using Substitution of Allylic Picolimates”, *Eur. J. Org. Chem.* *in press*.
- [4] Feng, C.; Ikoma, A.; Hirotsu, H.; Kobayashi, Y. “Synthesis of 2,6-*trans*-Disubstituted Cyclohexanone via Allylic Substitution of *exo*-Cyclic Picolimates Followed by Ozonolysis”, *Manuscript in preparation*.

Other Publication:

Kobayashi, Y.; Igarashi, J.; Feng, C.; Tojo, T. “Efficient Synthesis of Substituted Quinolines through Intramolecular Addition of Aryl Anion to Carbonyl Carbon”, *Tetrahedron Lett.* **2012**, 53, 3742–3745.

Oral Presentations:

- [1] Feng, C.; Kobayashi, Y. “Allylic Substitution of Picolimates for Construcion of A Quaternary Carbon Possessing An Aryl Group”, Japan Chemical Society 93rd Annual Meeting, Ritsumeikan University, Japan, 2013.
- [2] Feng, C.; Kobayashi, Y. “Asymmetrical Construction of Cycloalkenyl-substituted Carbon Unit by Using Substitution of Allylic Picolimates”, Japan Chemical Society 92nd Annual Meeting, Koei University, Japan, 2012.

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冯 超 (Chao Feng)

2013.6.17

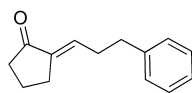
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Chapter 3: S27-S34

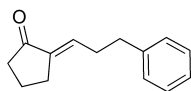
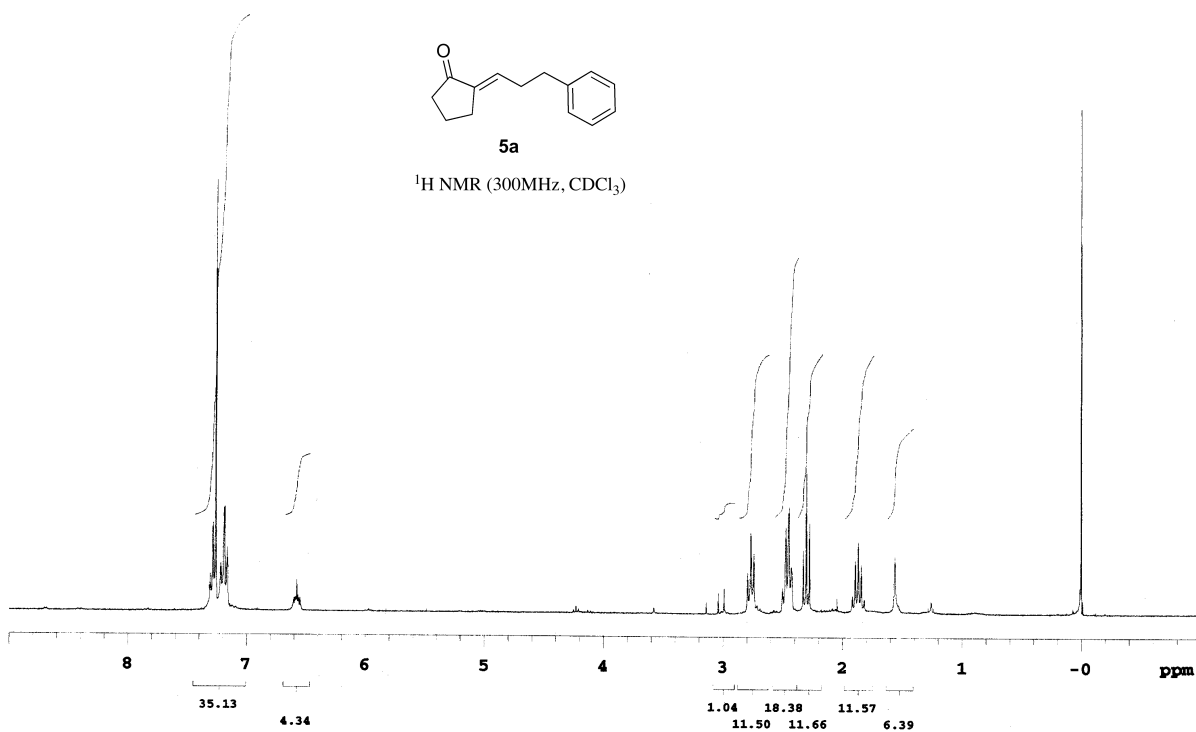
Chapter 4: S35-S77

Chapter 5: S78-S92



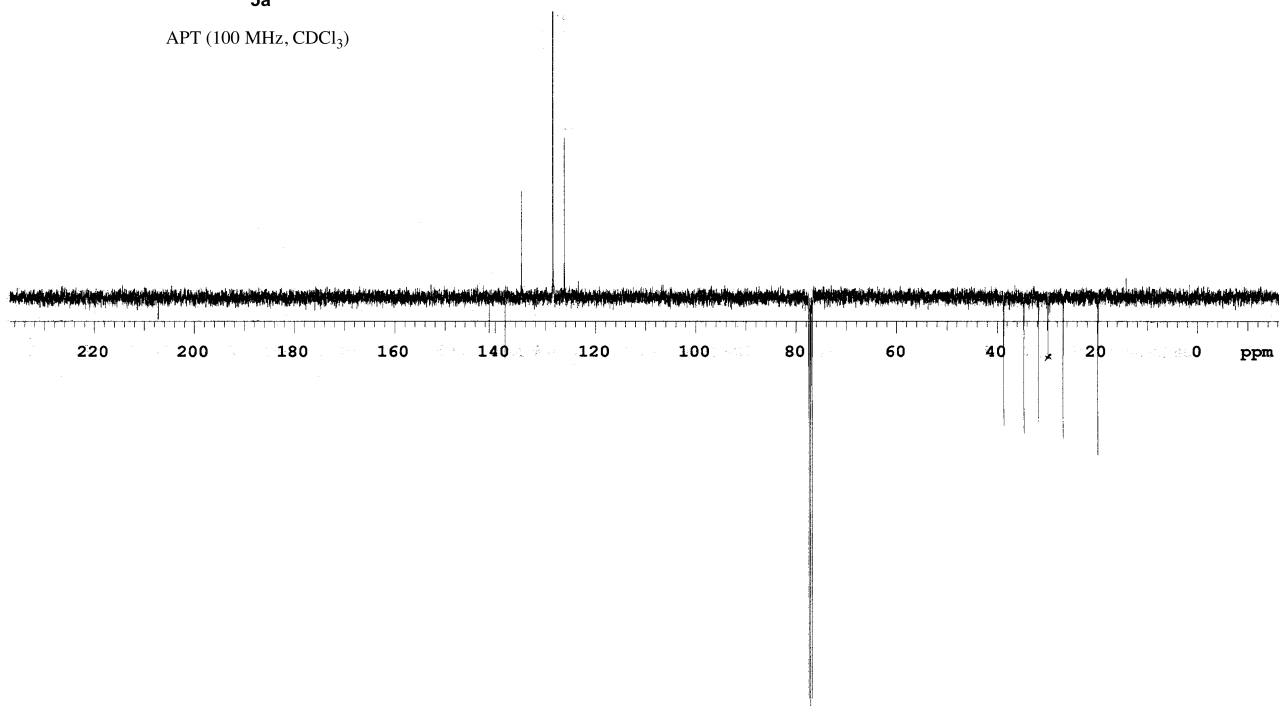
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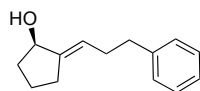
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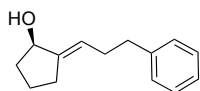
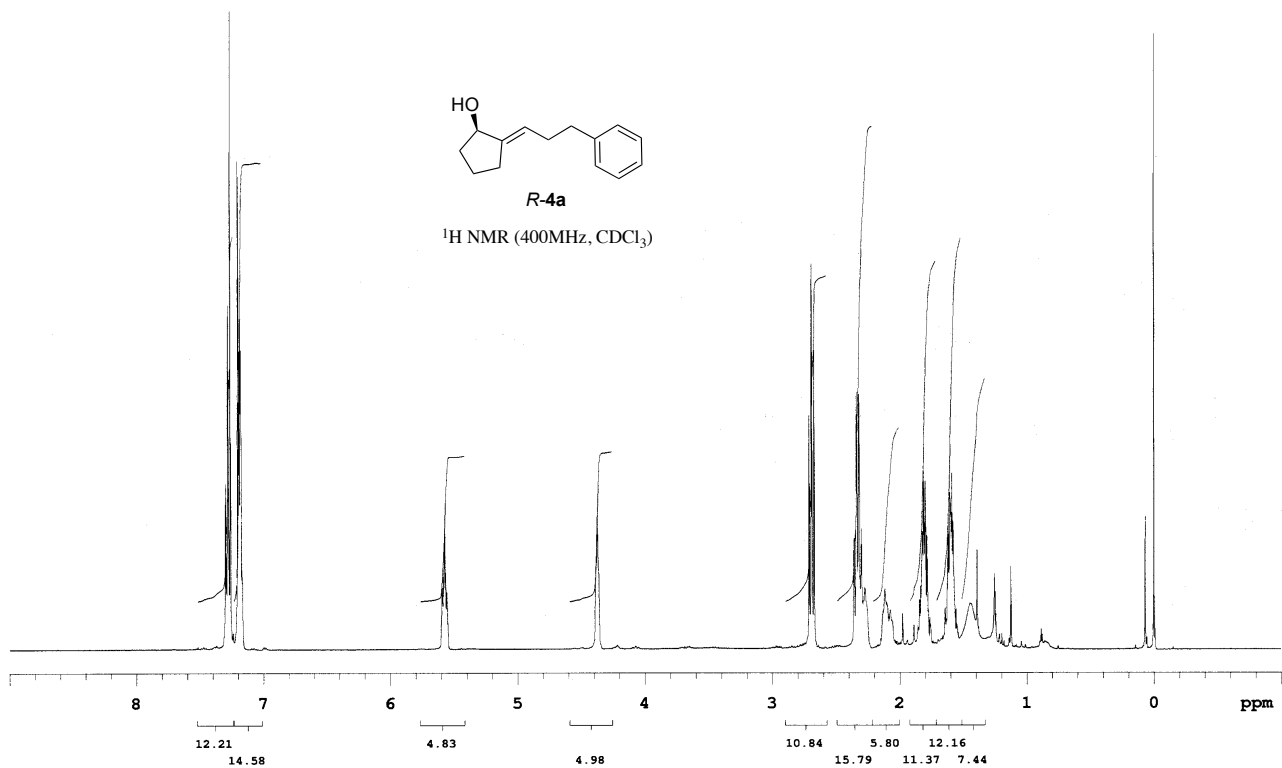
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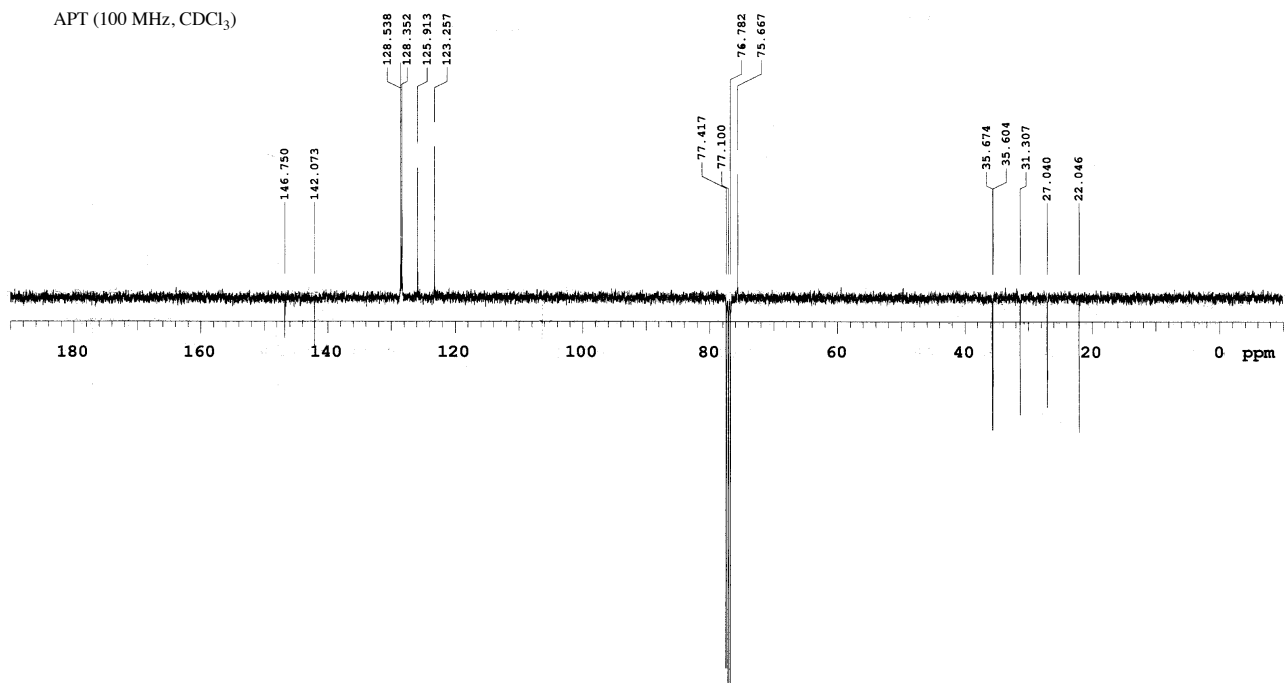
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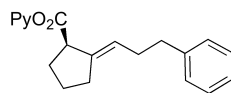
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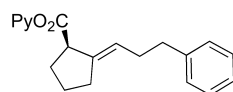
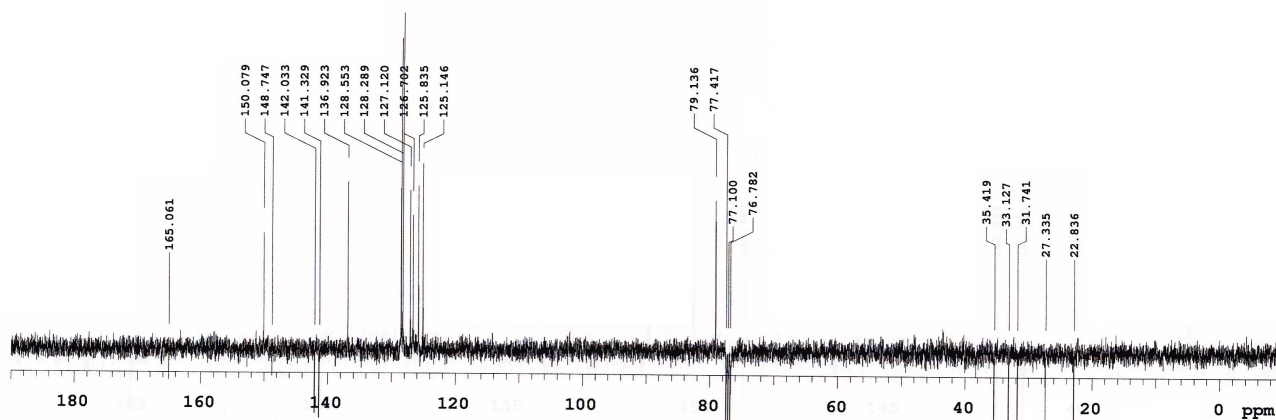
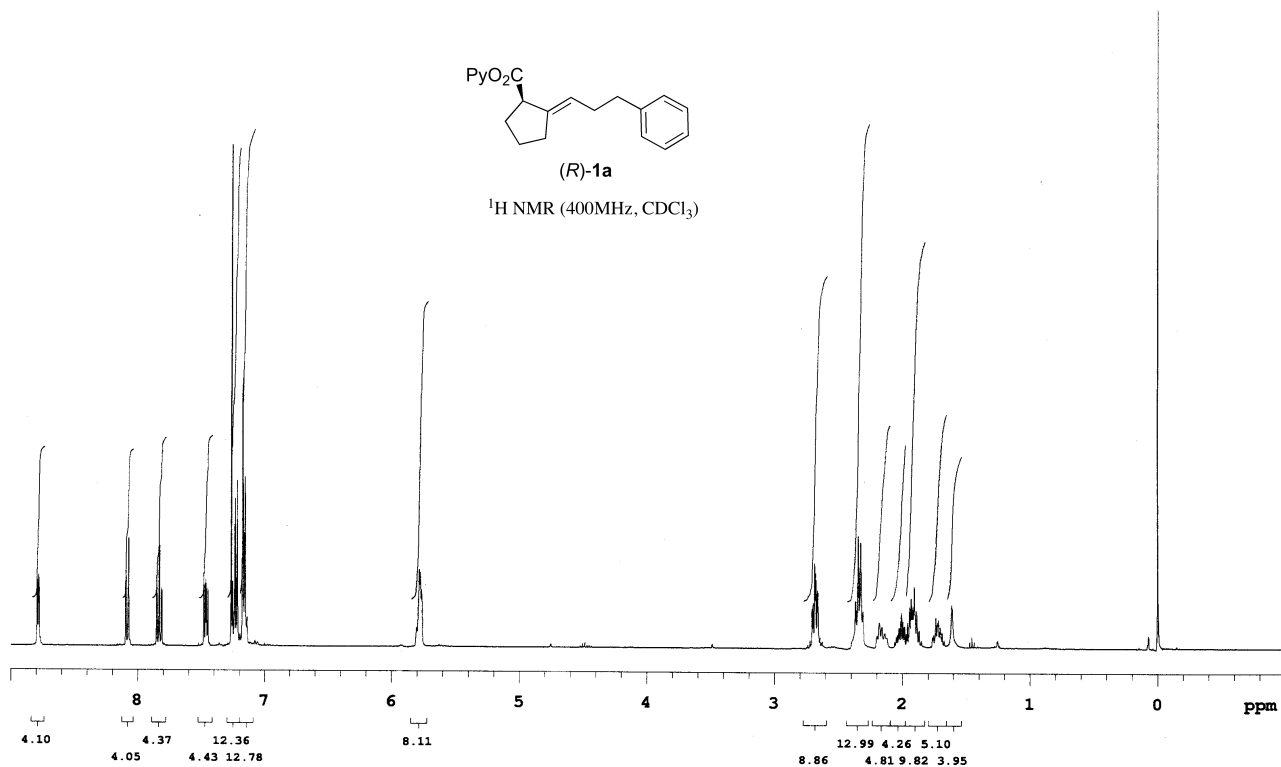
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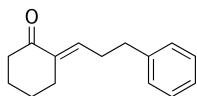
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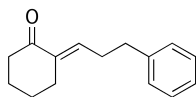
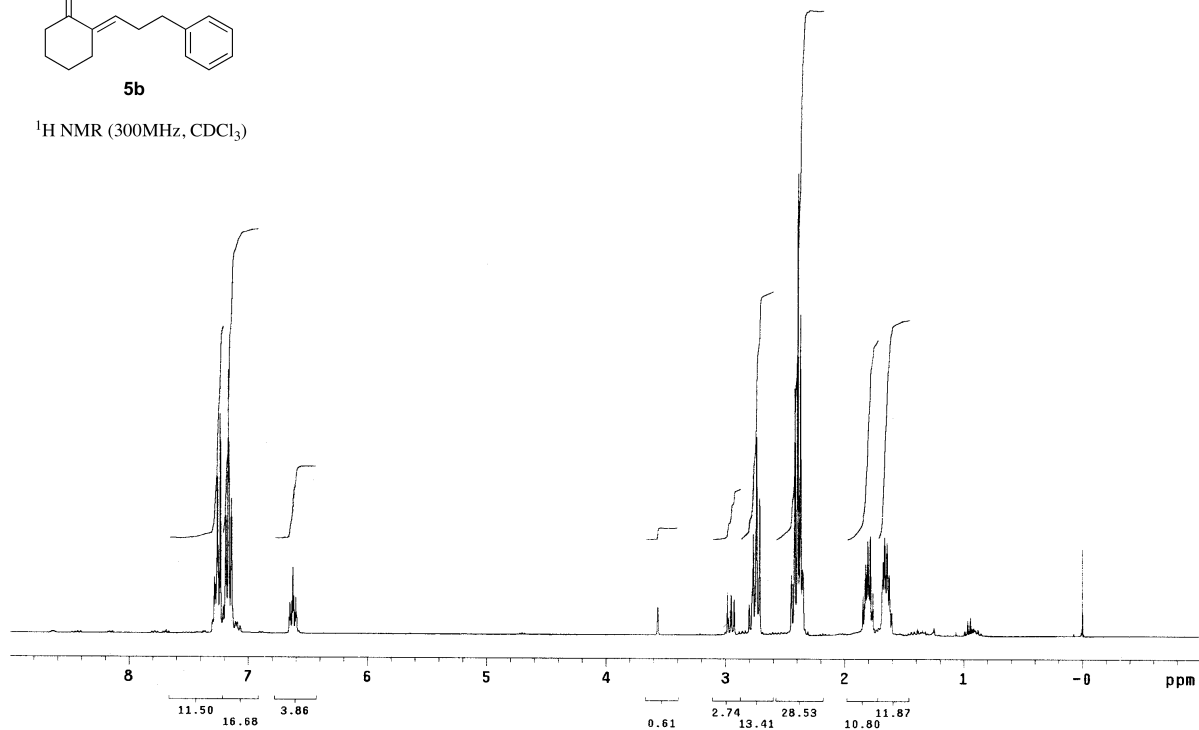
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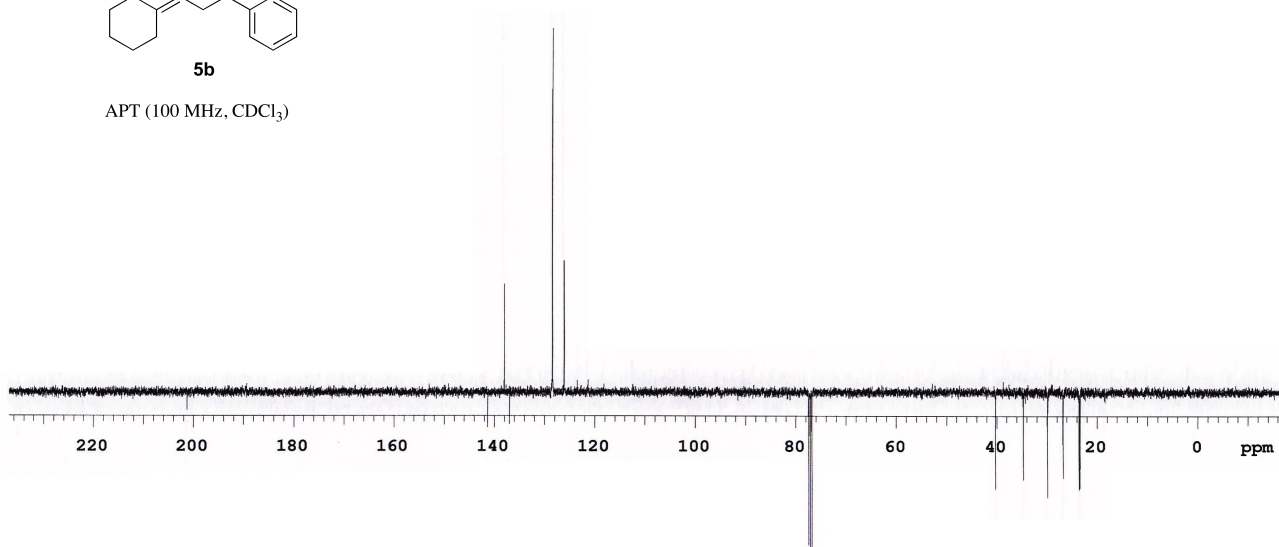
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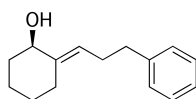
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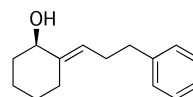
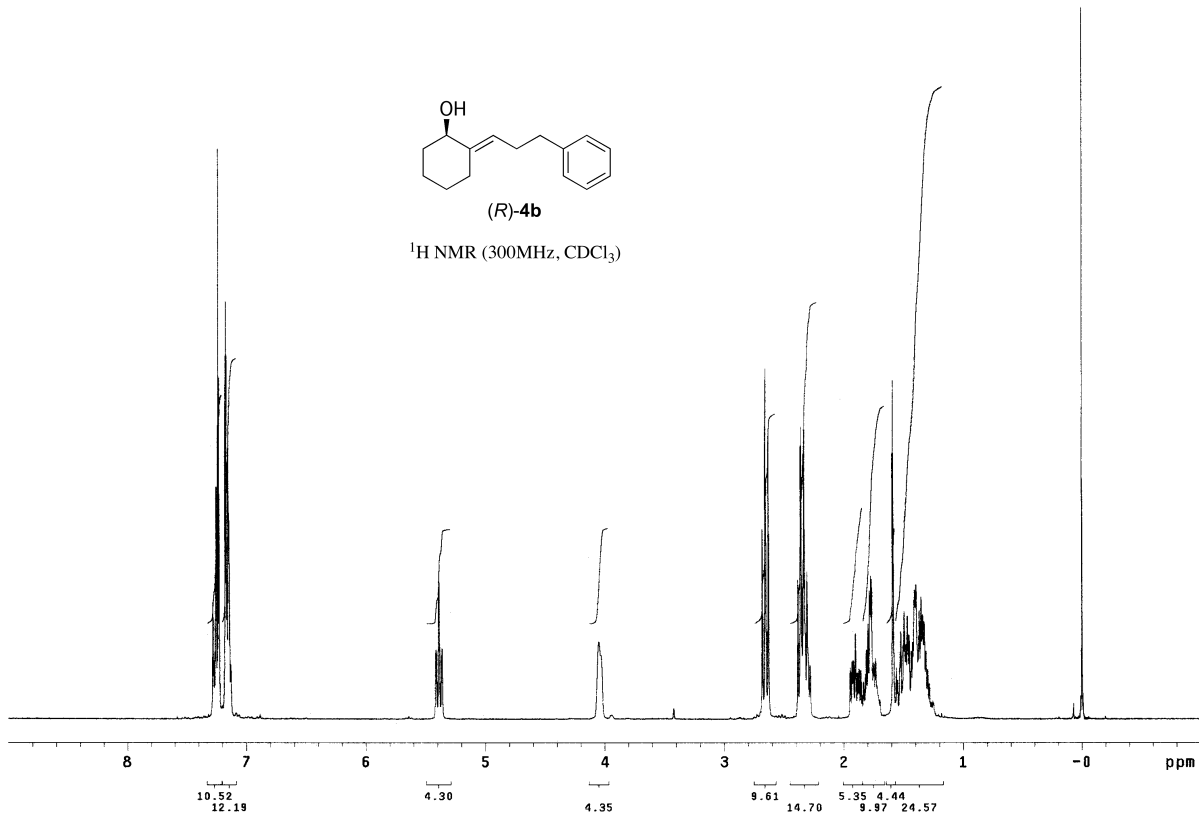
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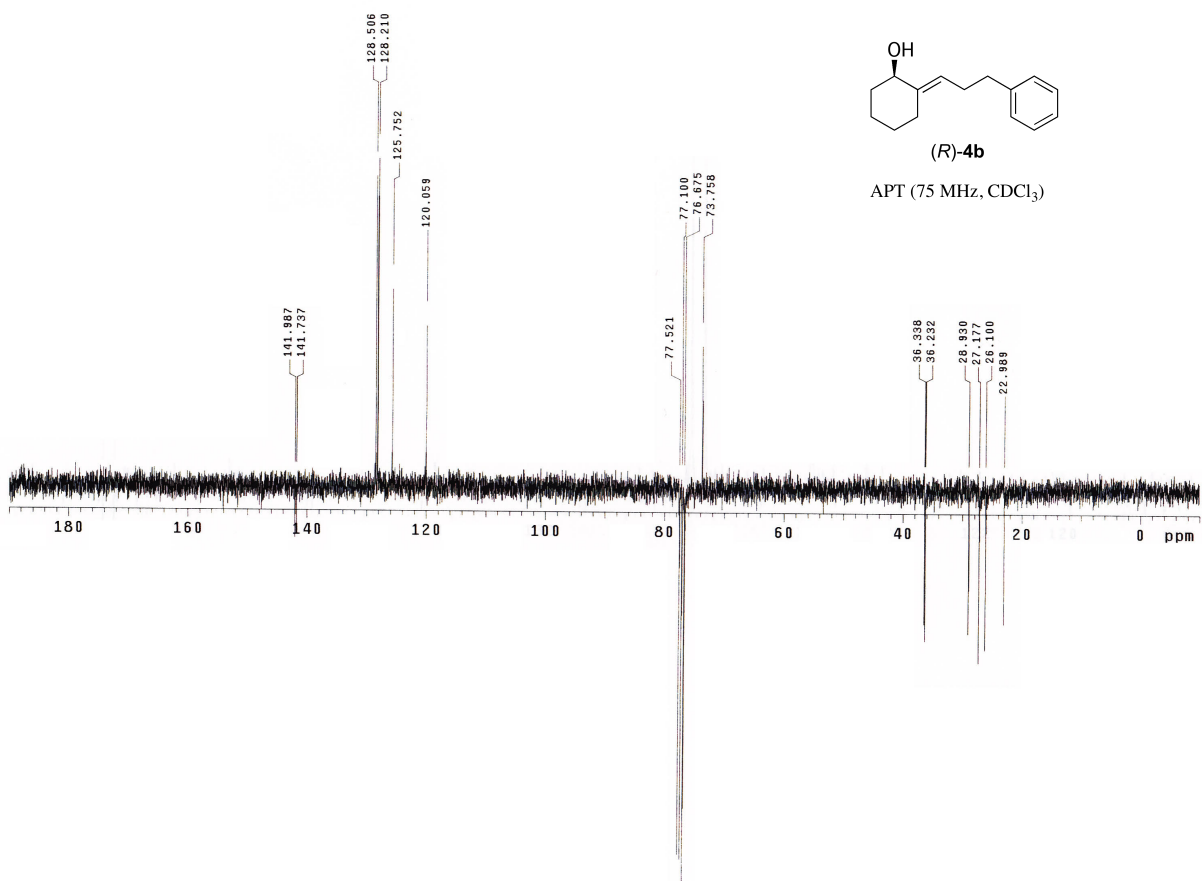
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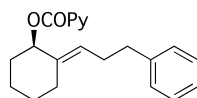
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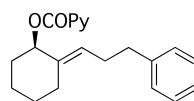
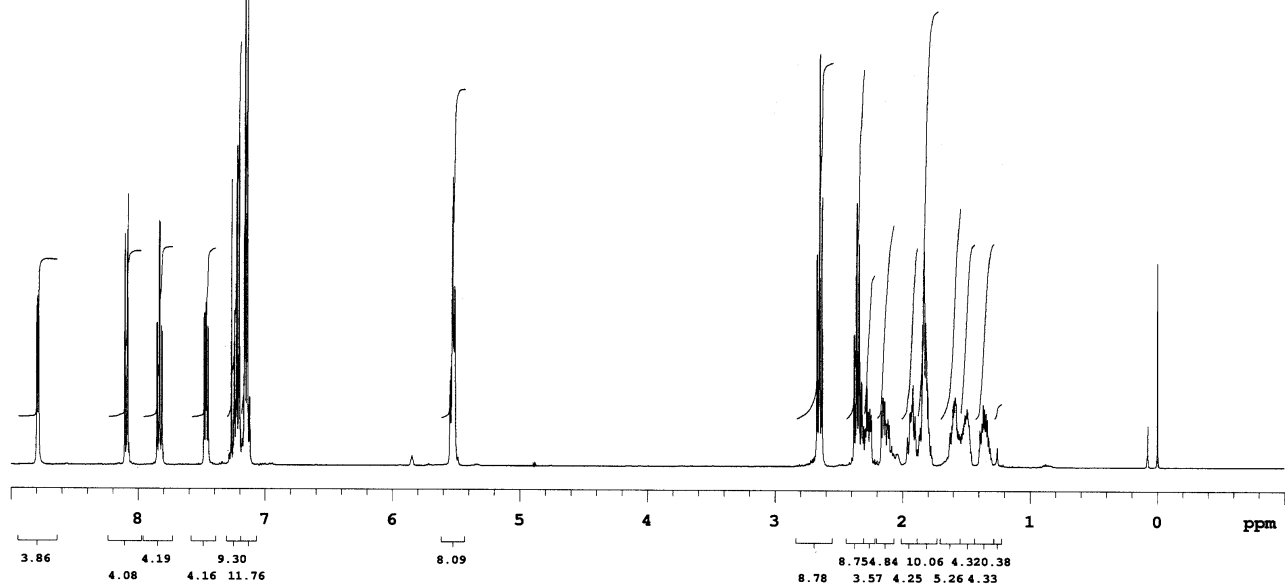
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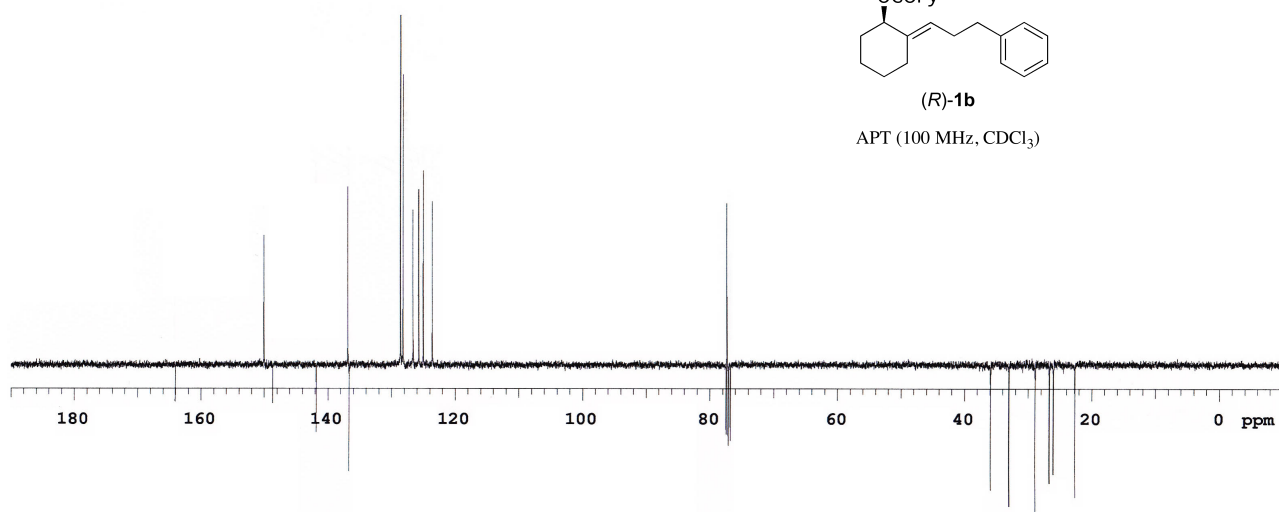
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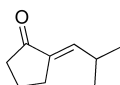
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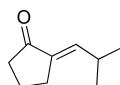
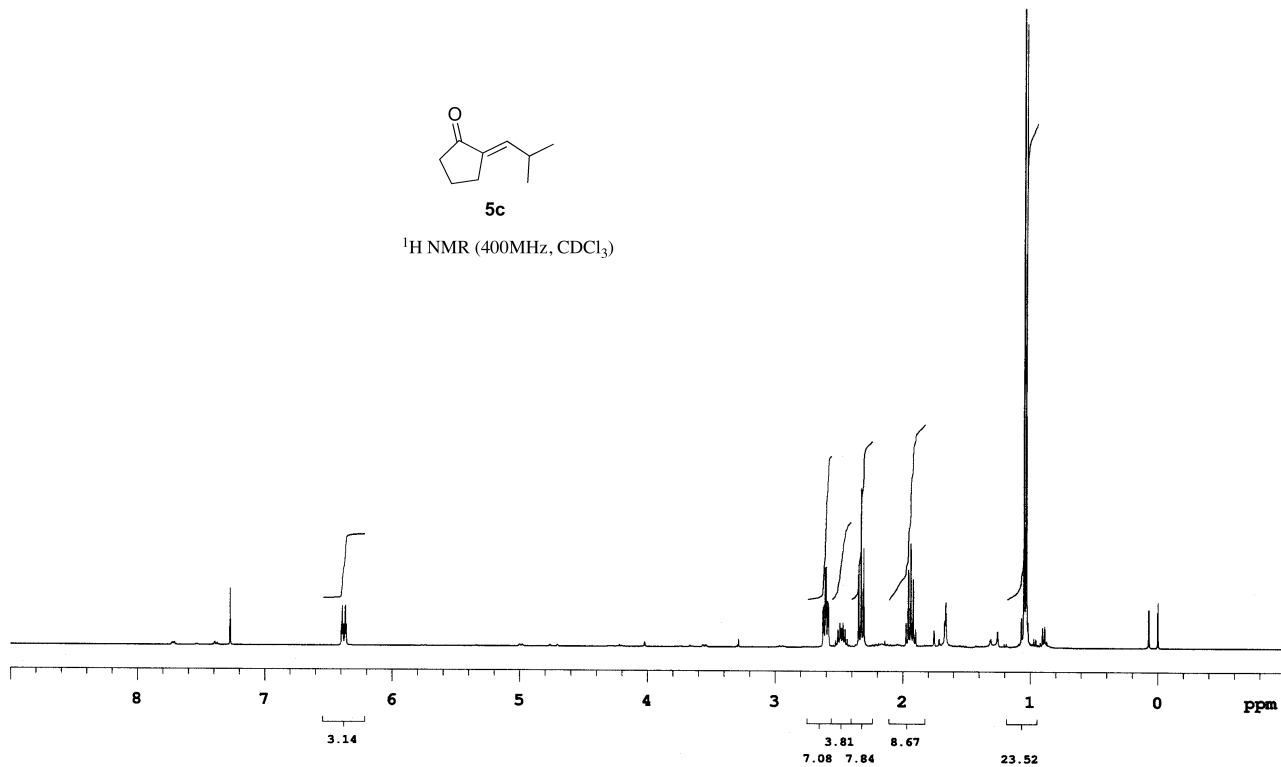
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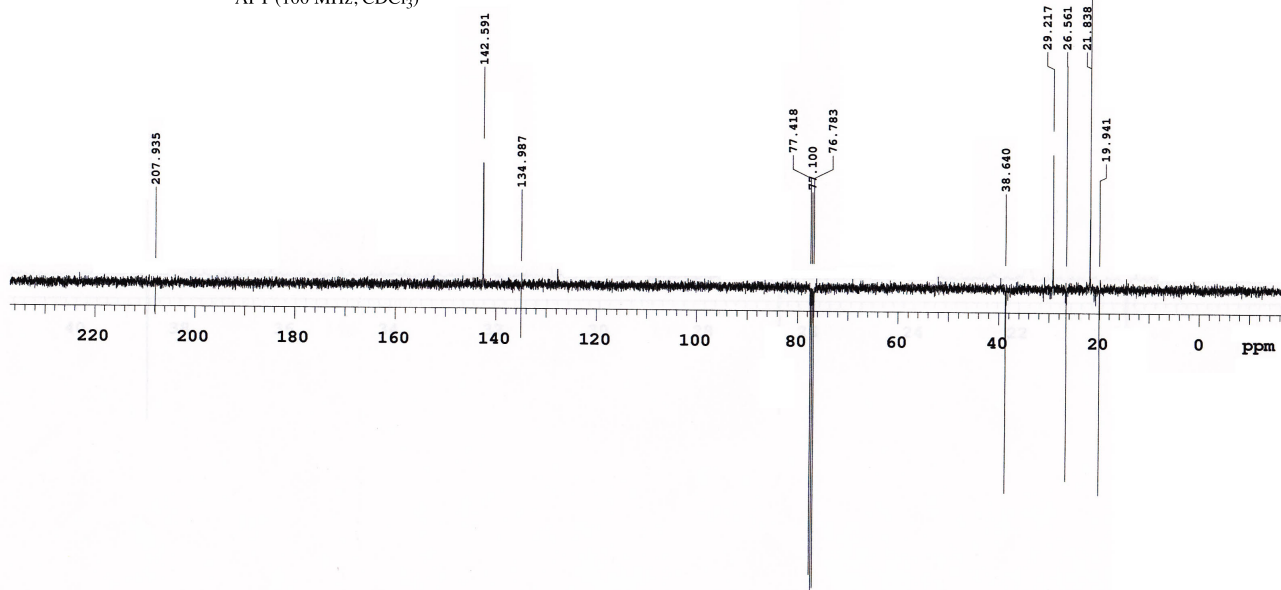
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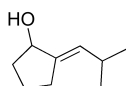
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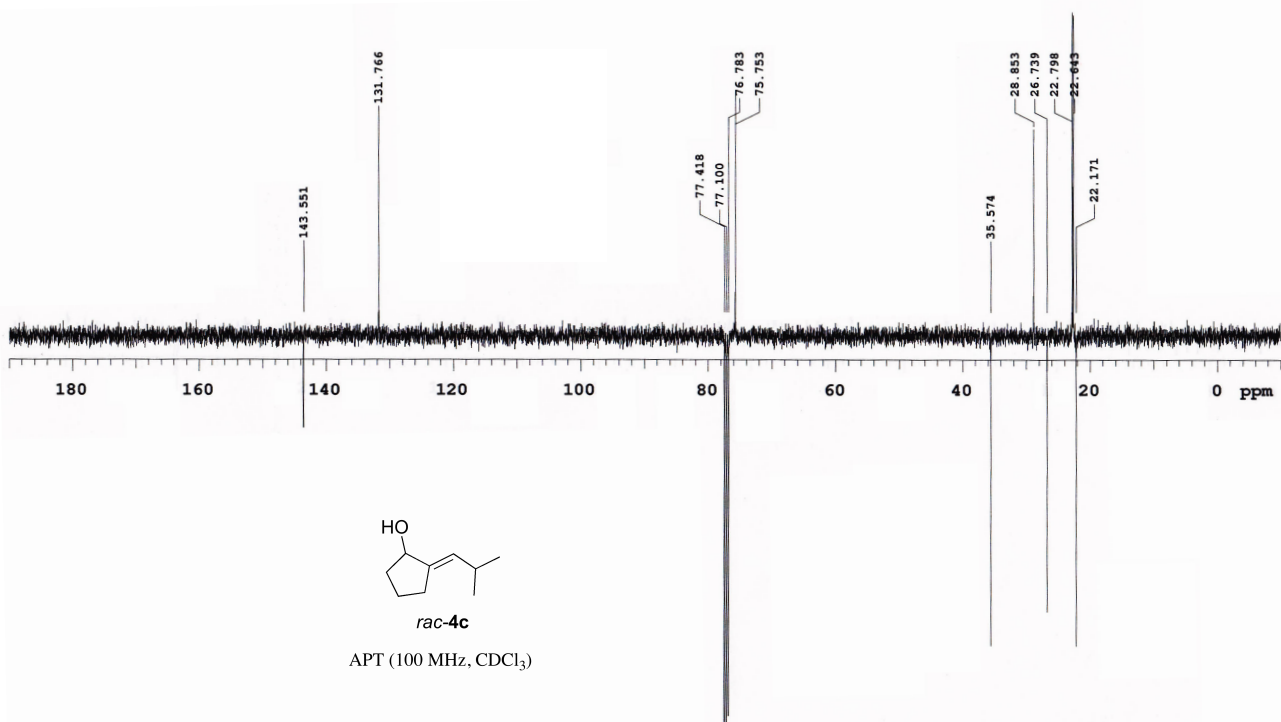
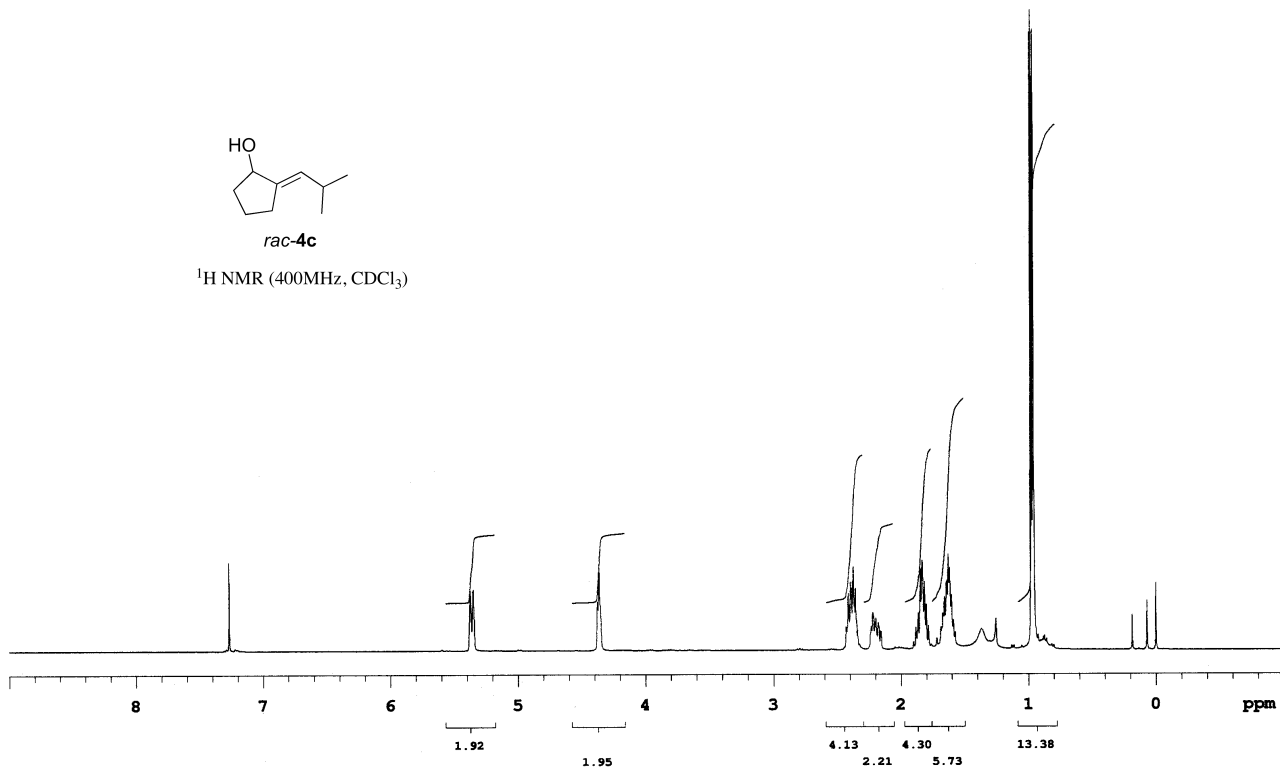
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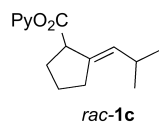




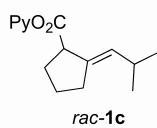
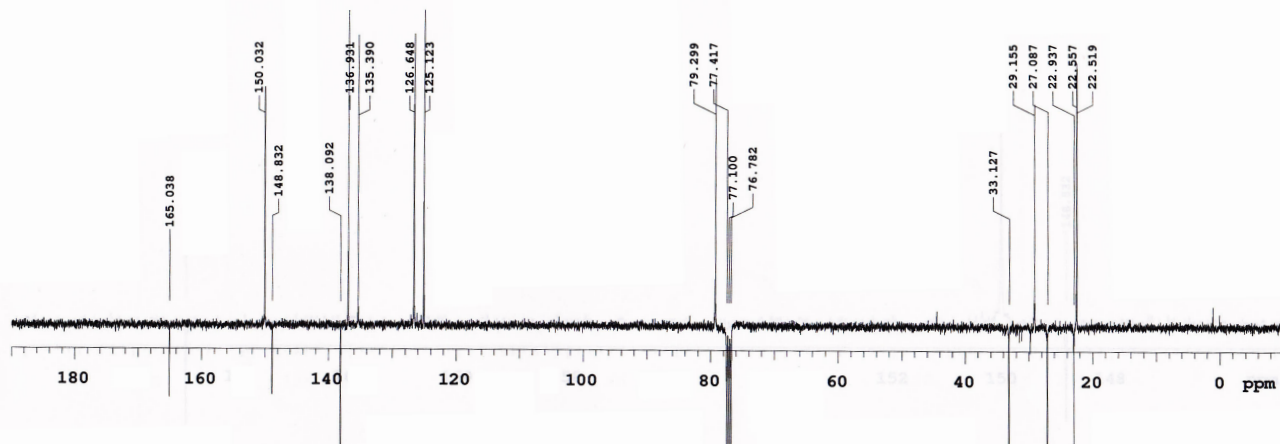
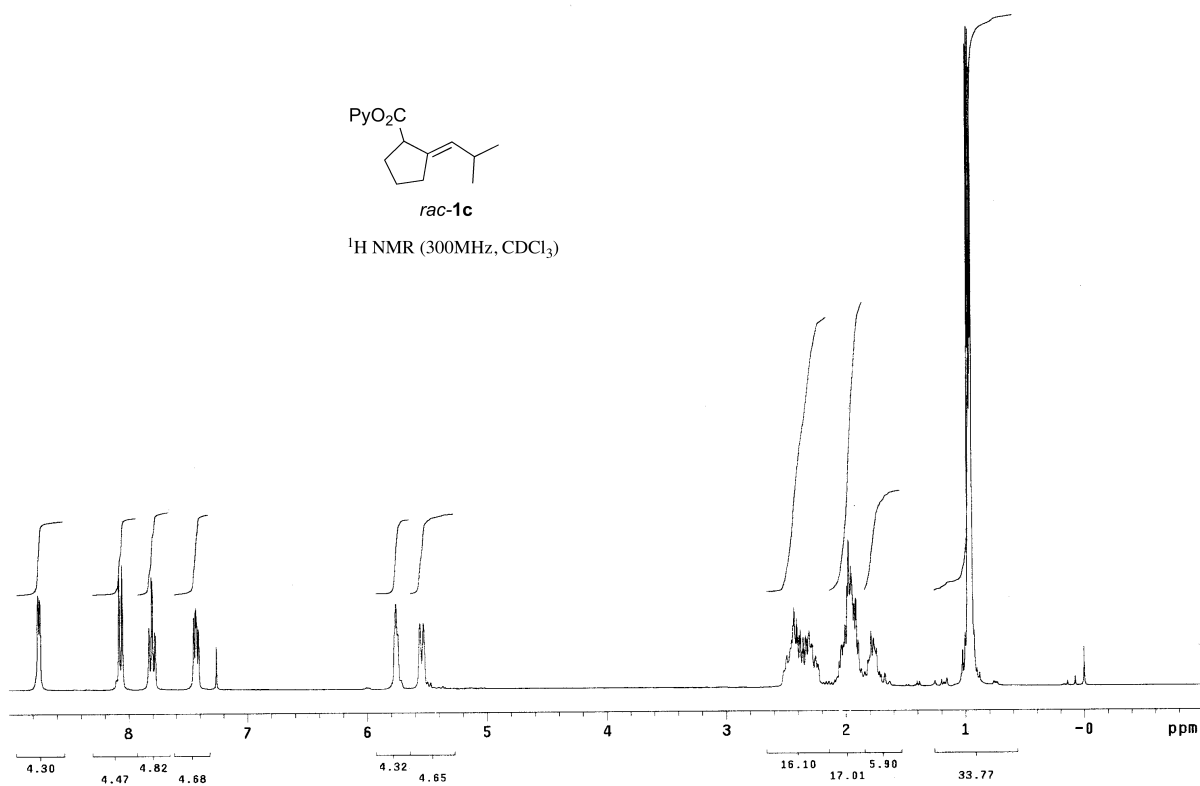
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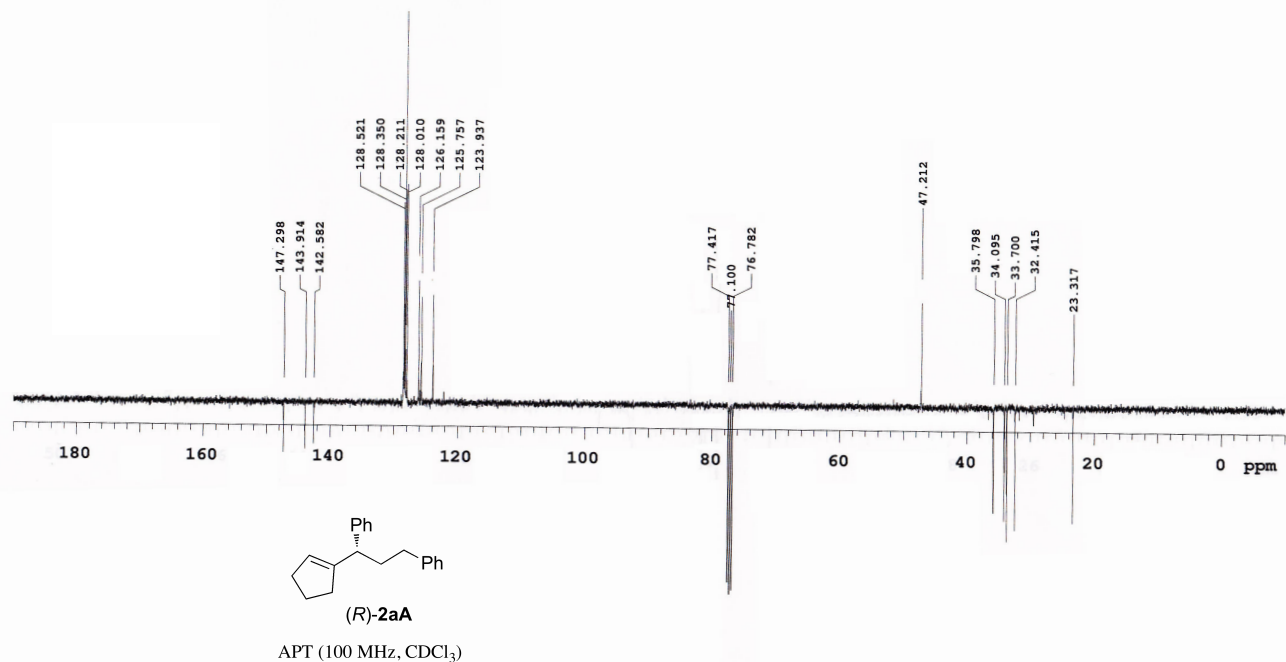
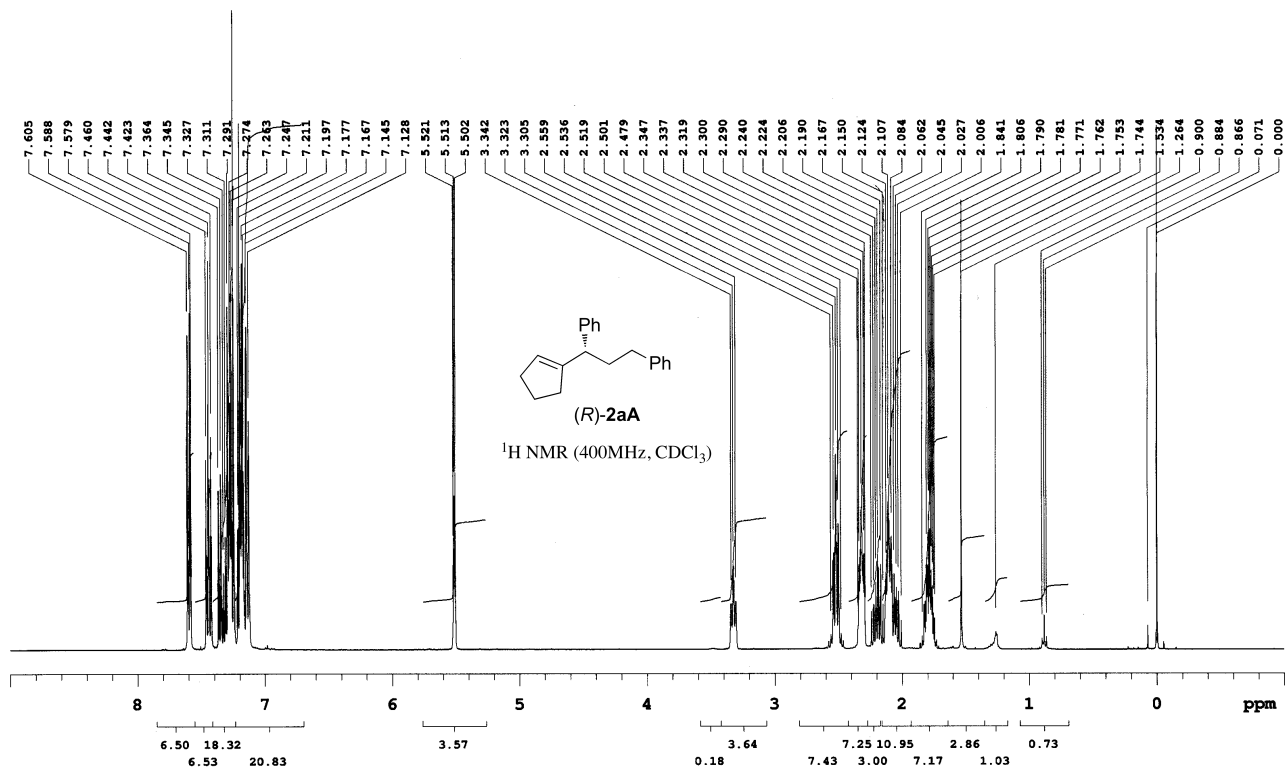


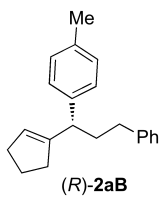


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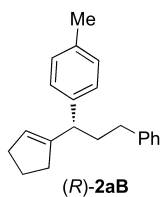
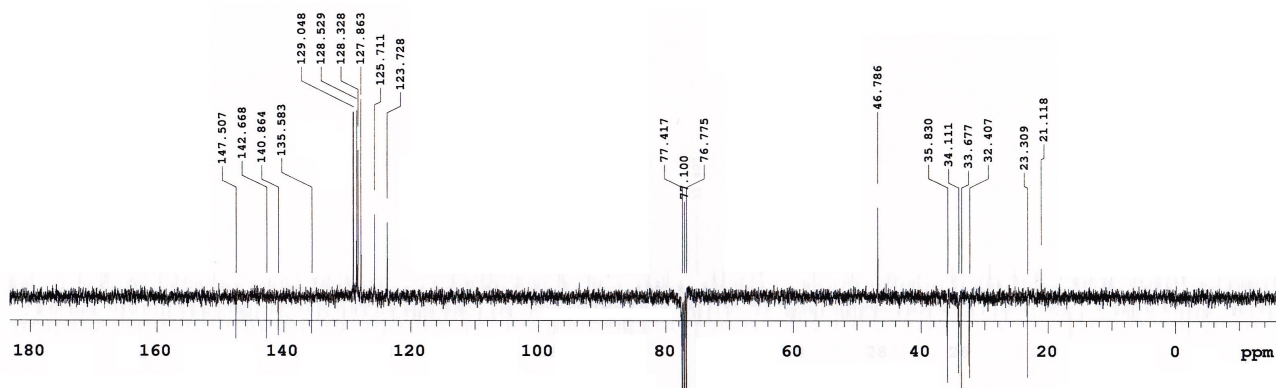
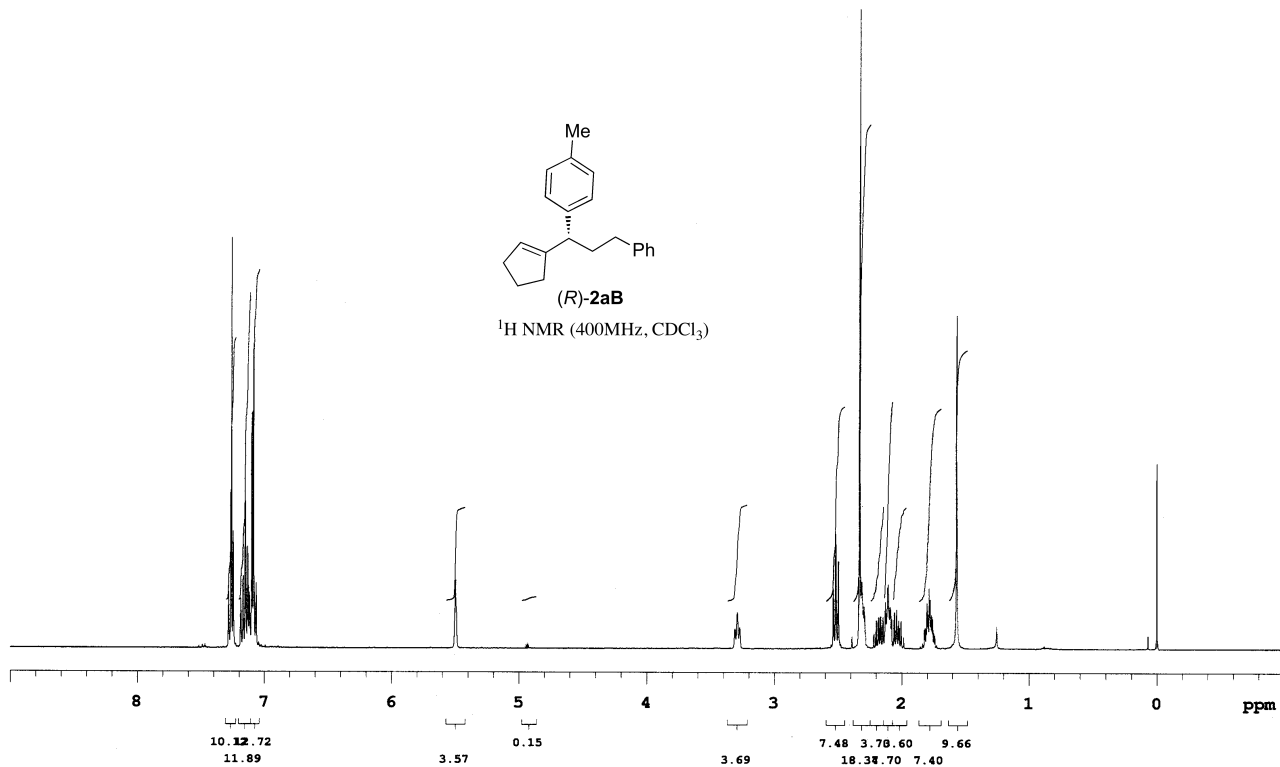


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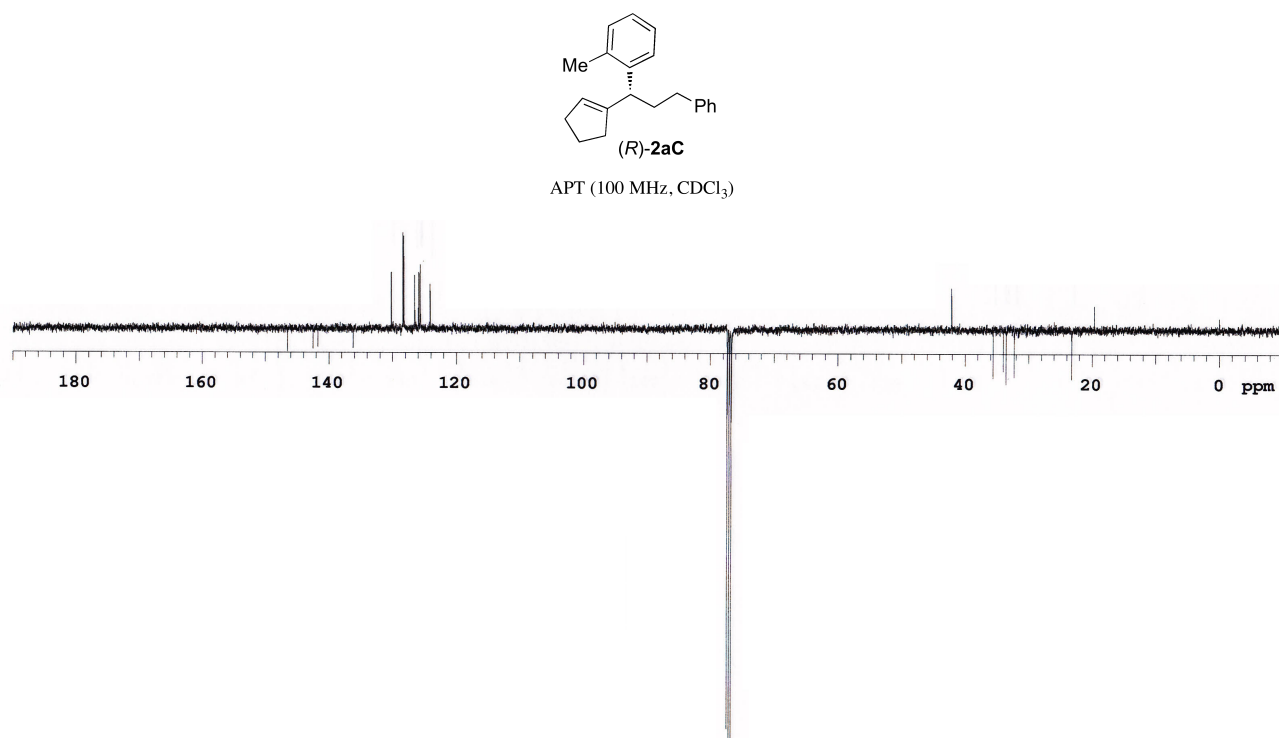
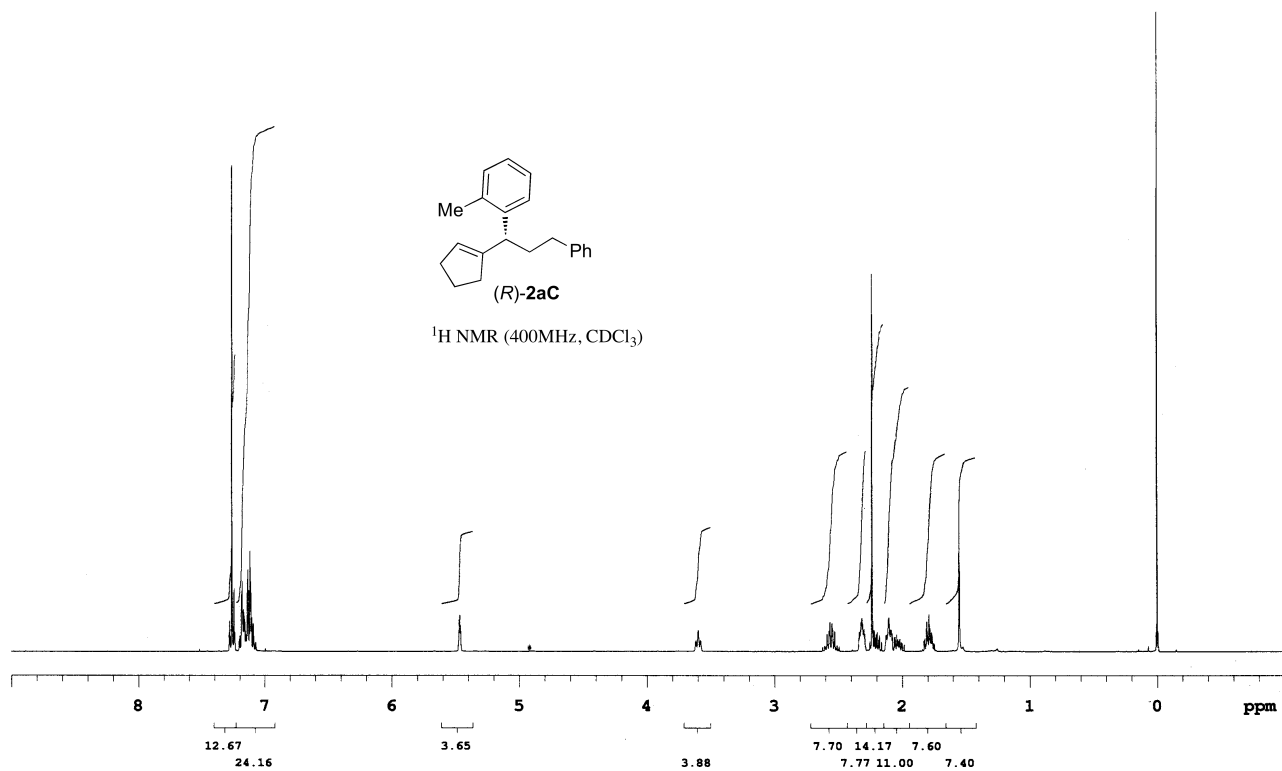


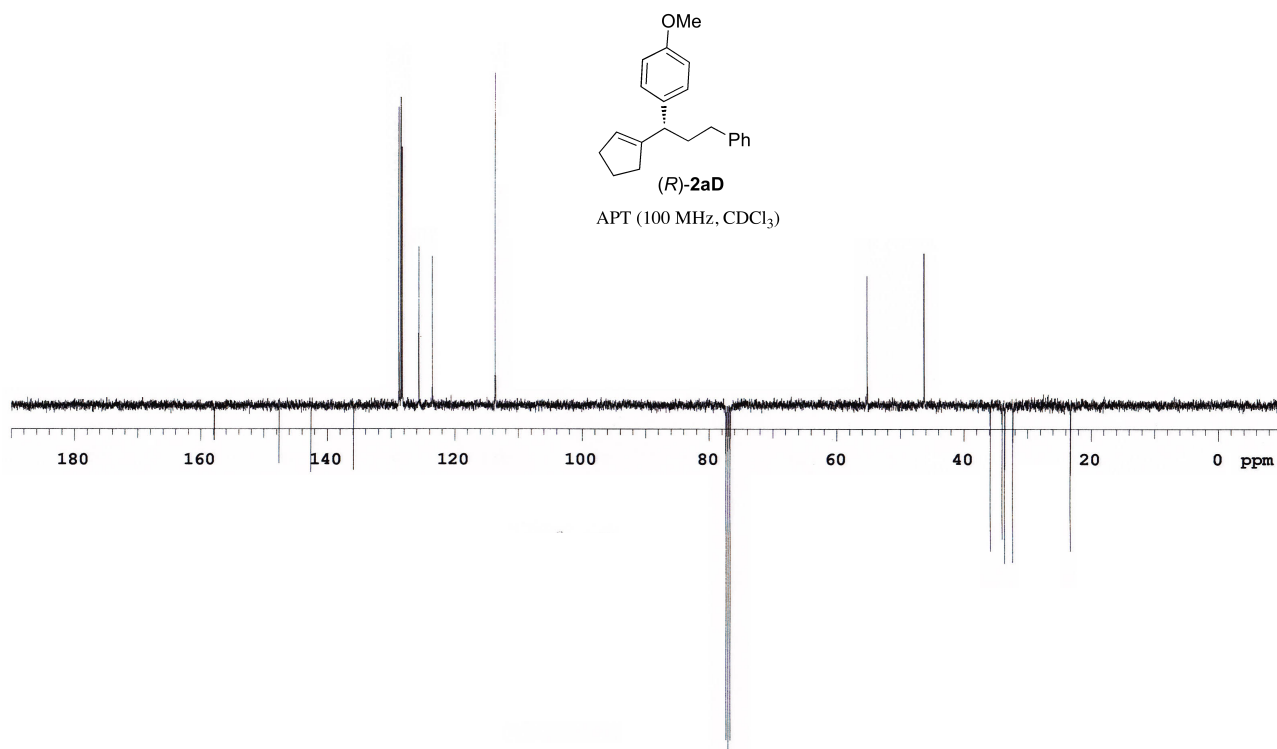
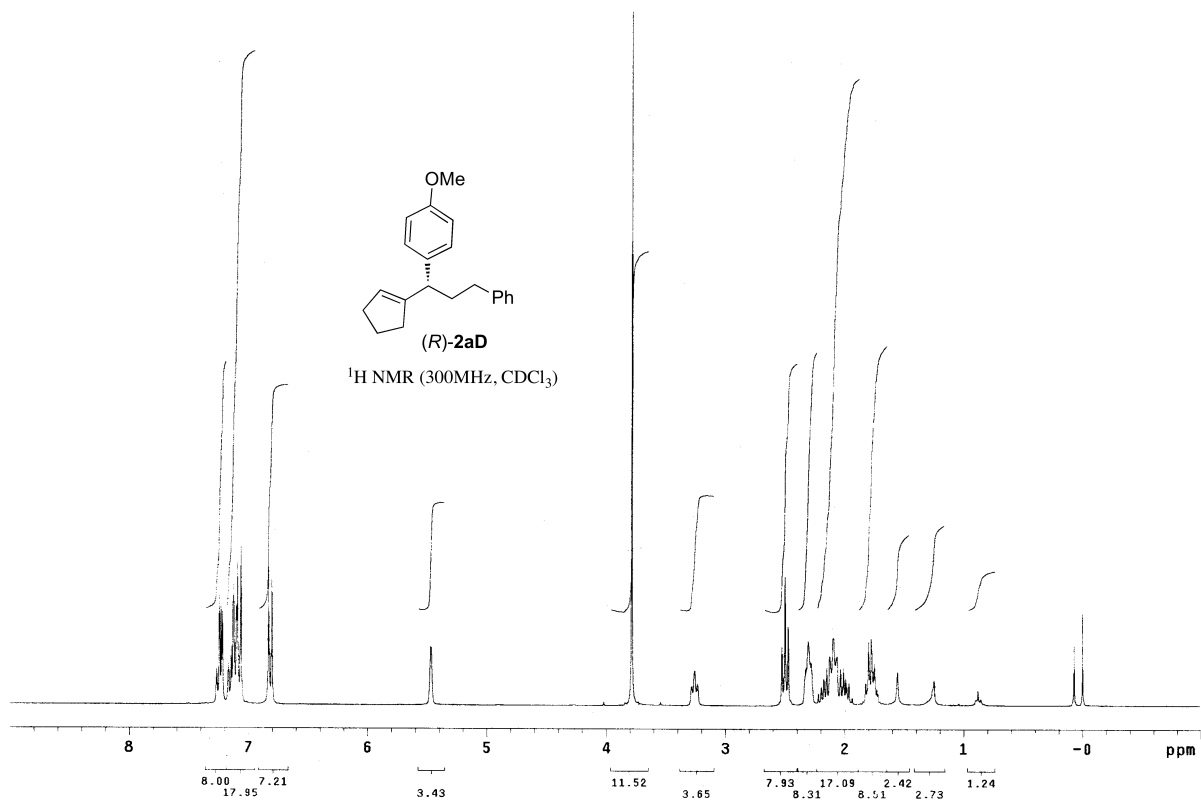


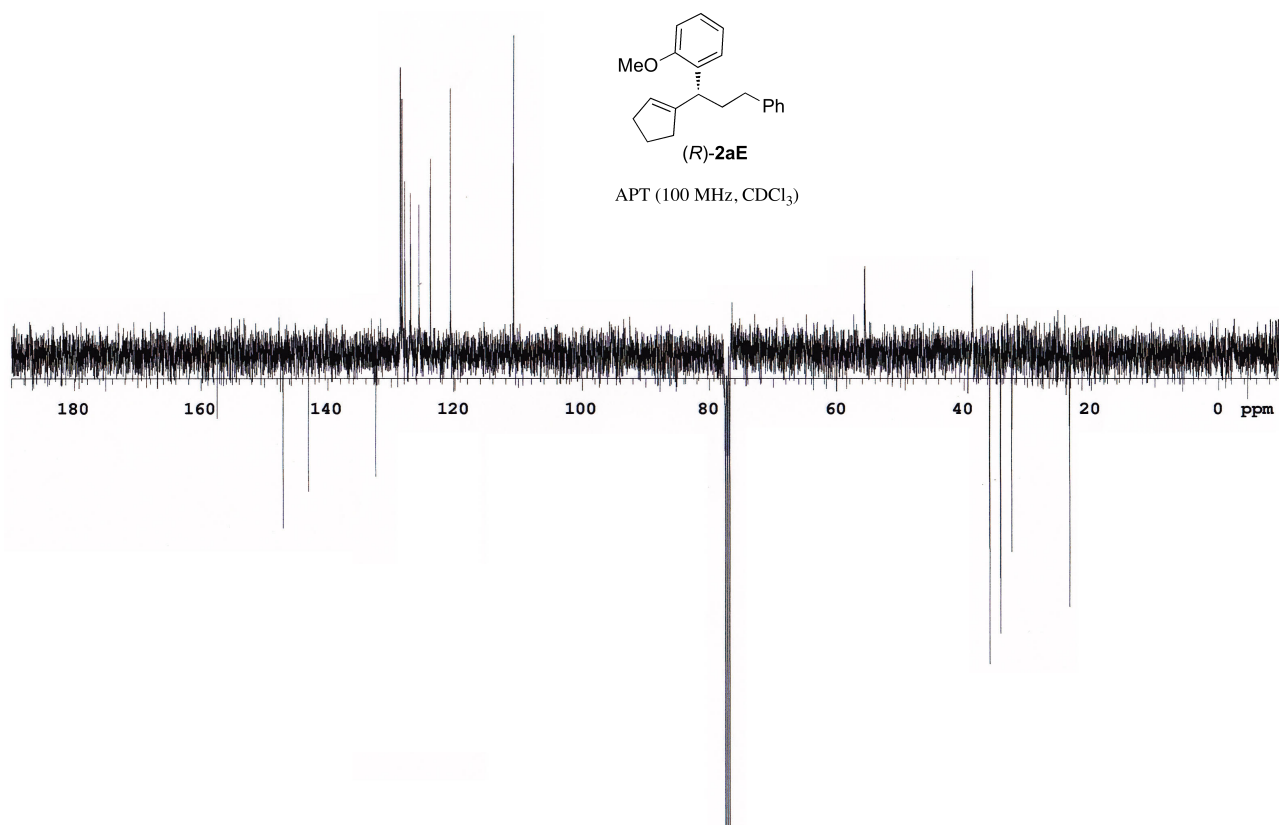
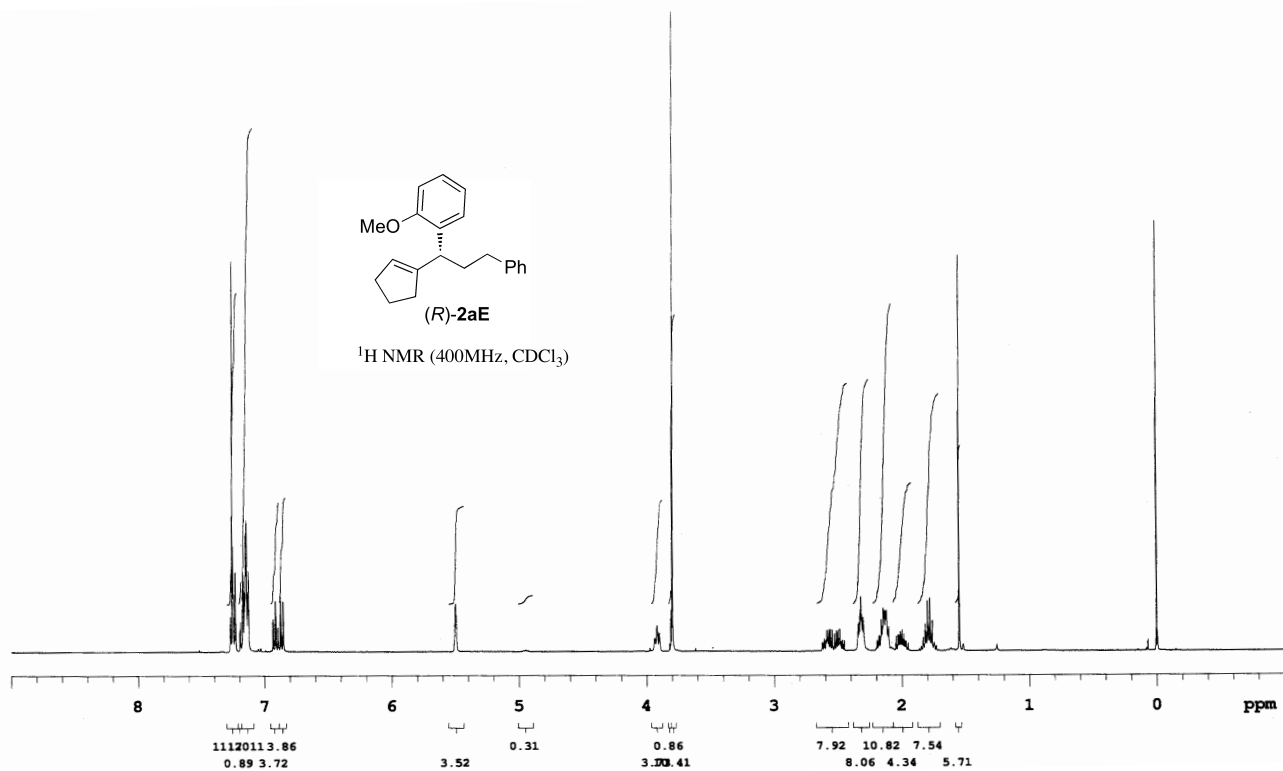
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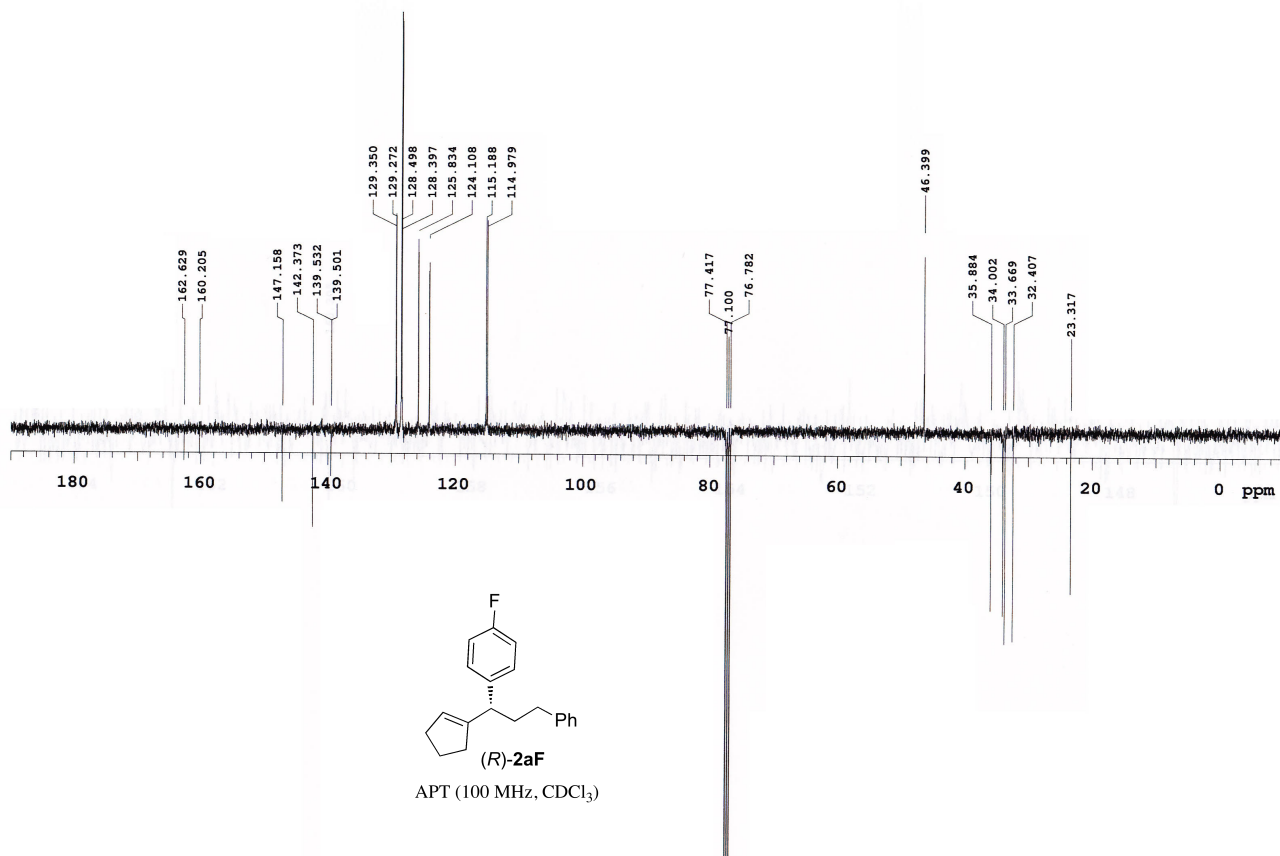
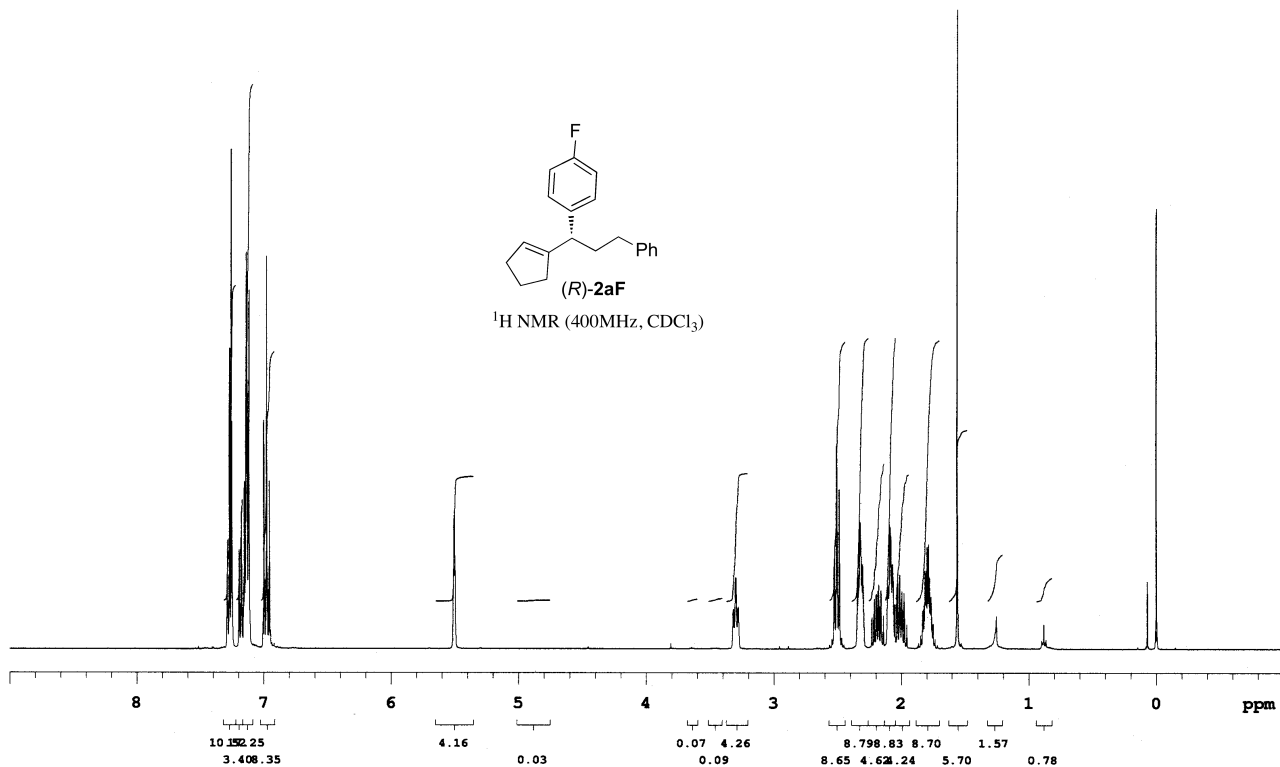


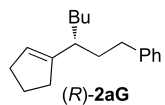
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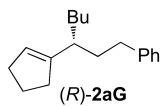
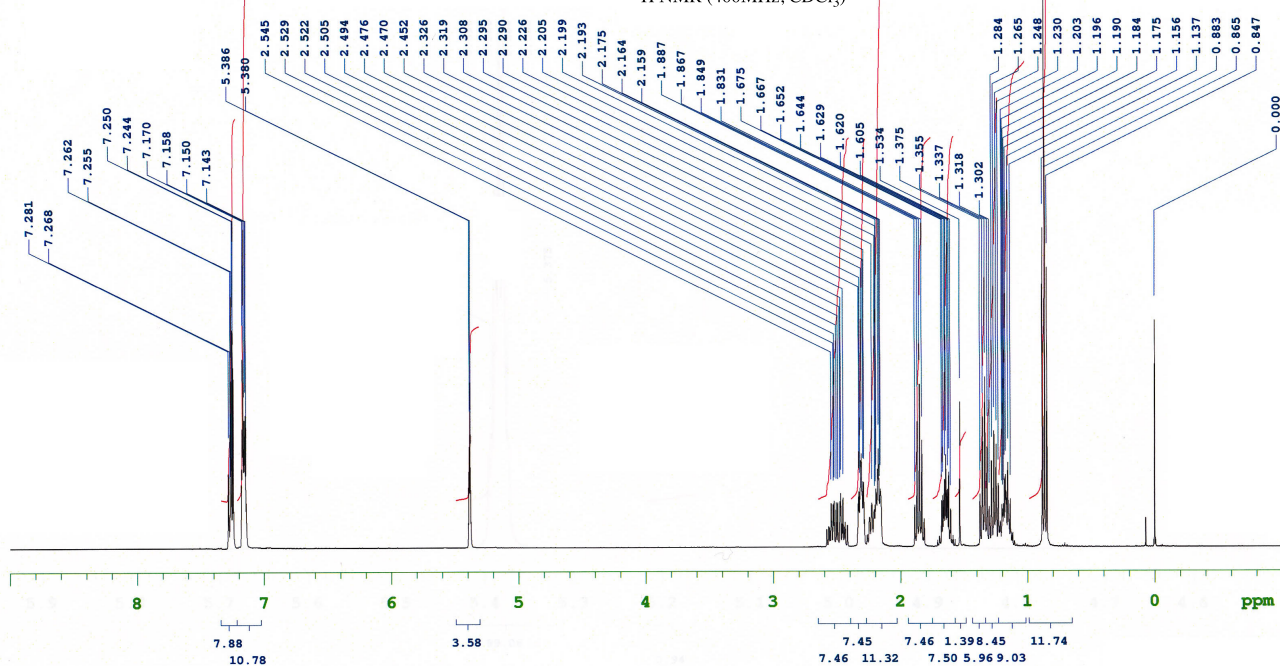




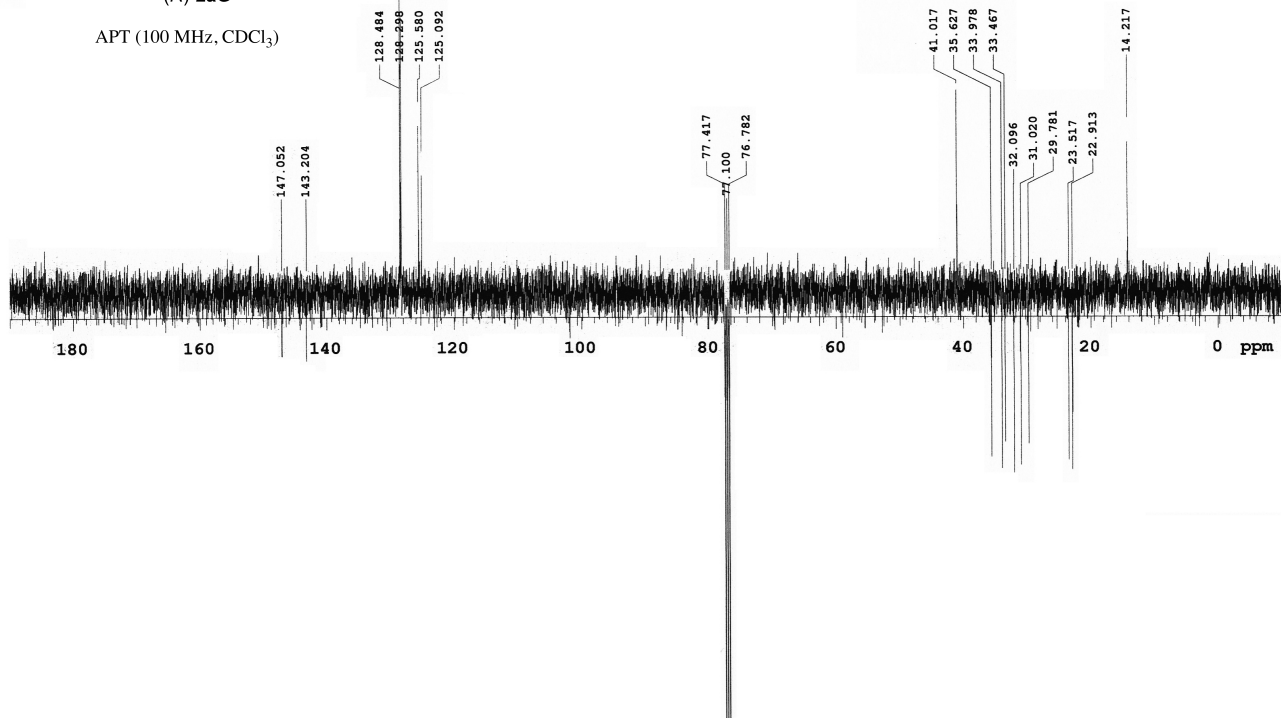


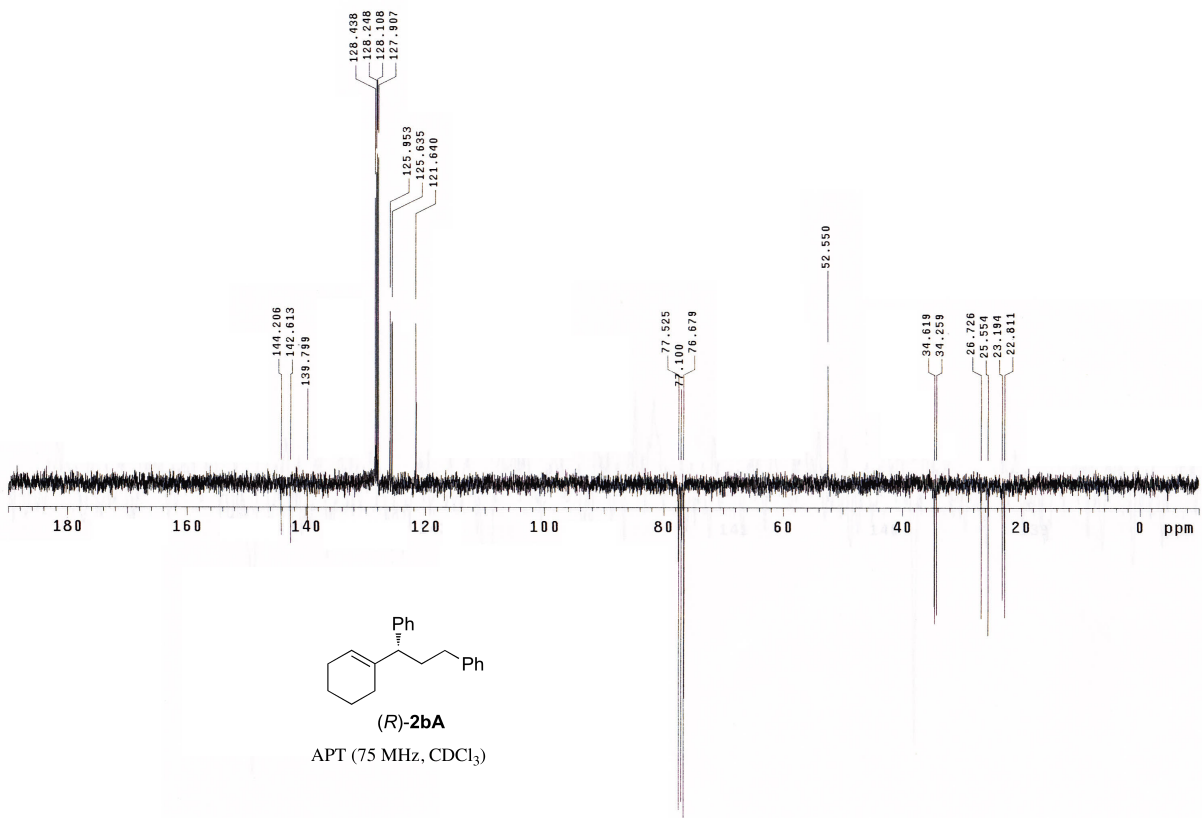
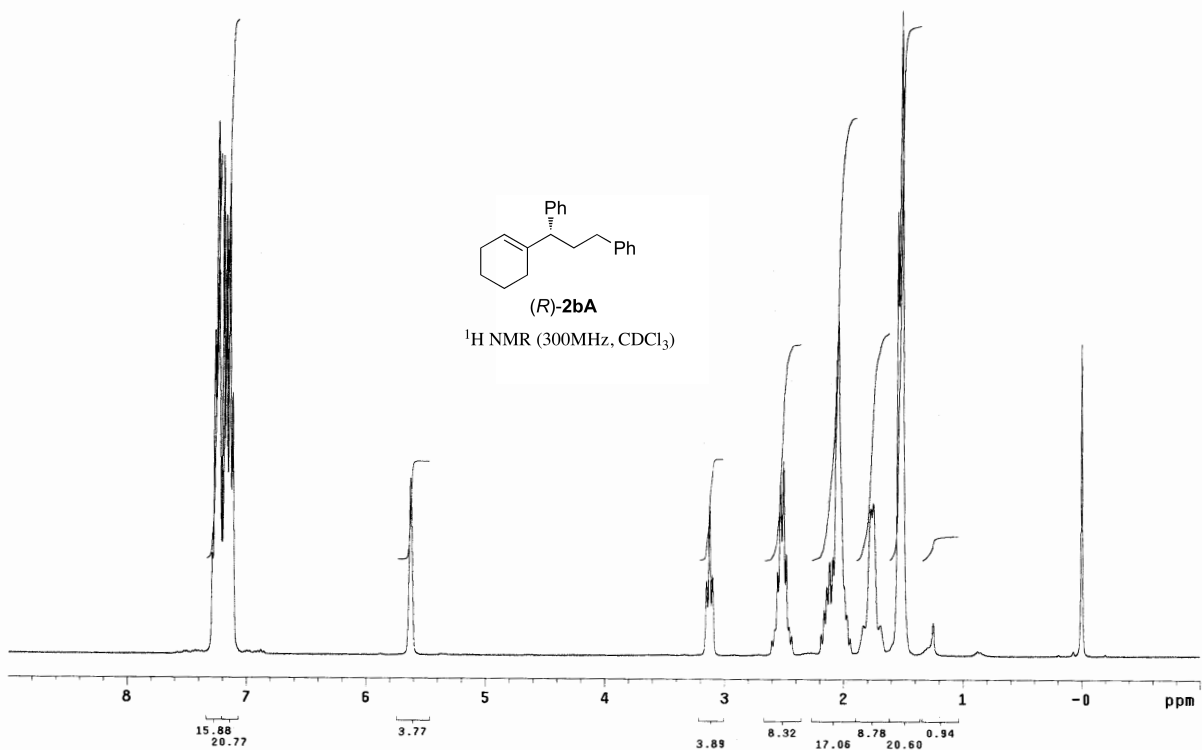


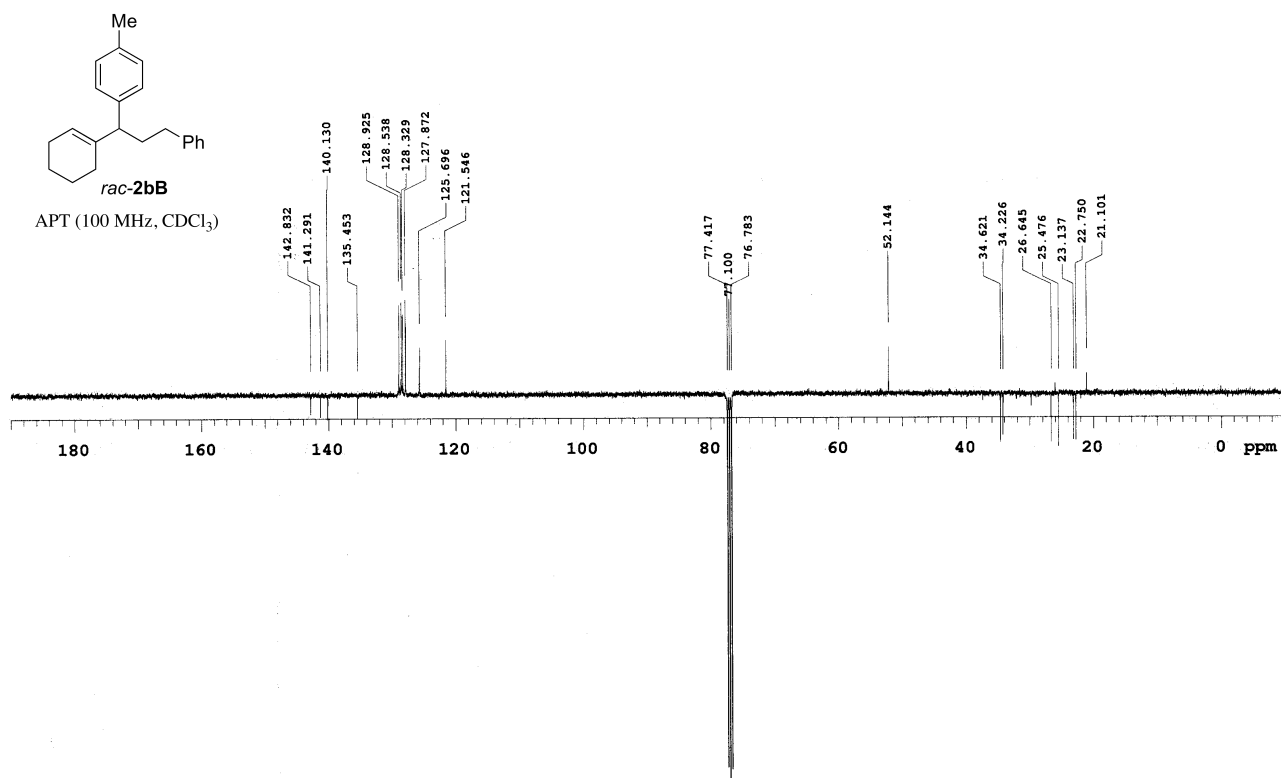
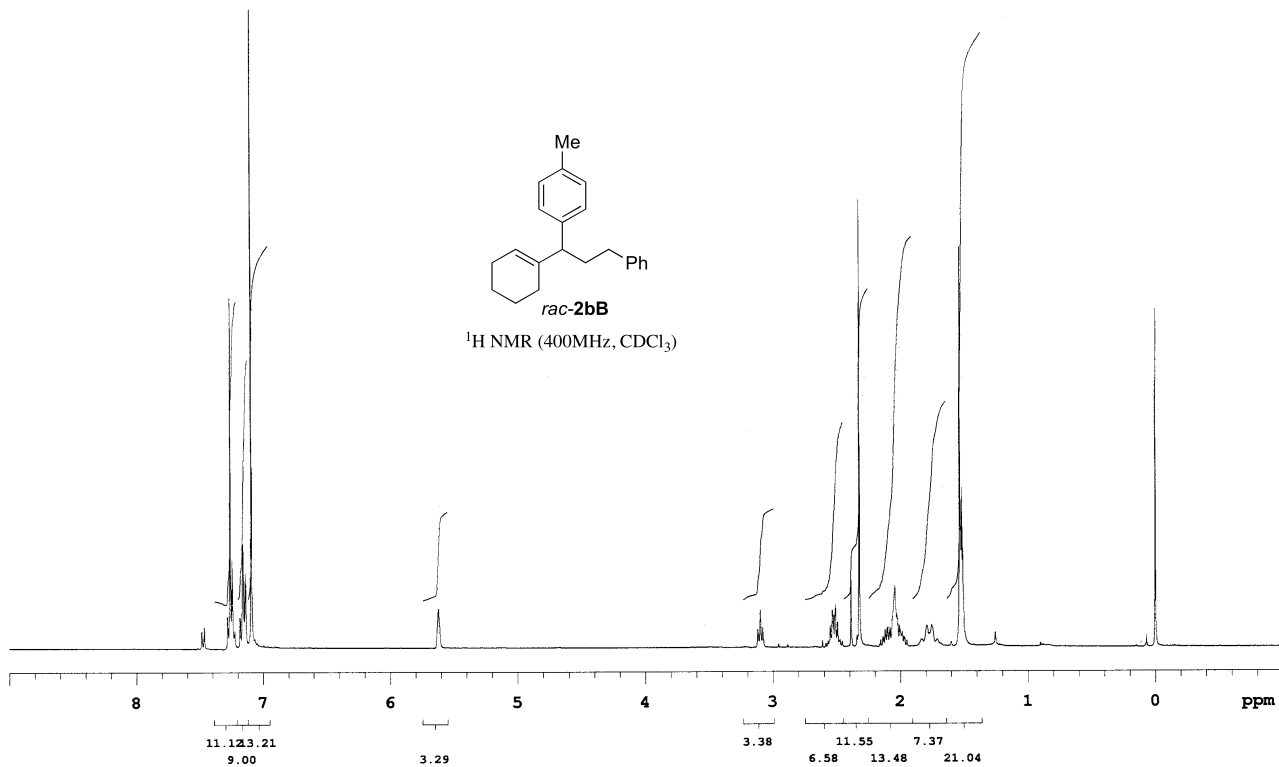
¹H NMR (400MHz, CDCl₃)

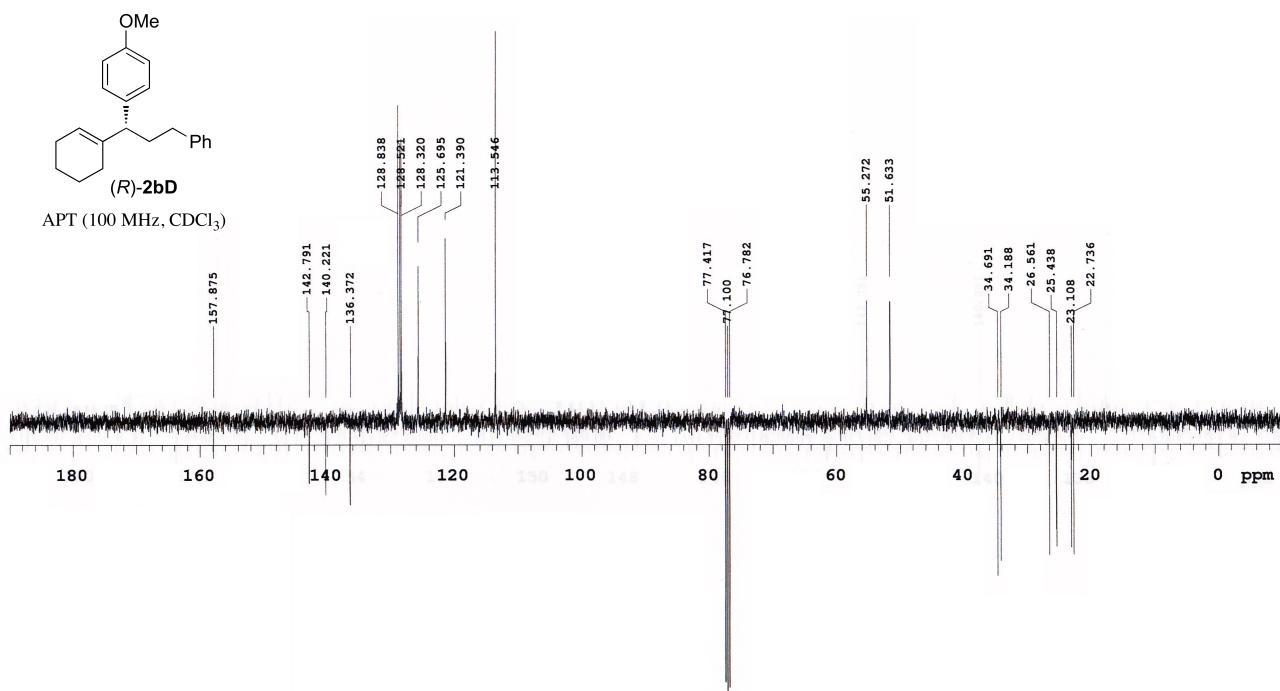
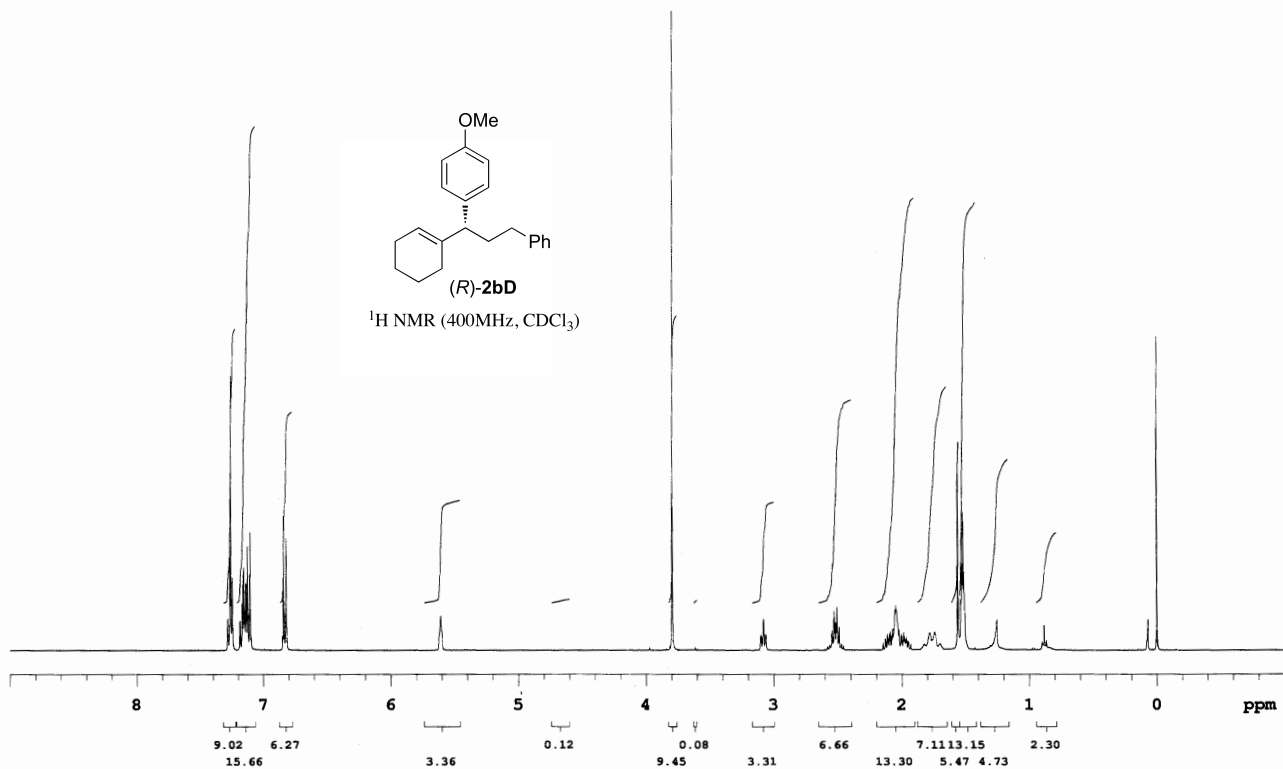


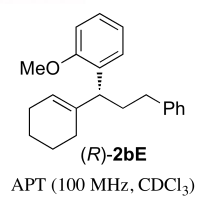
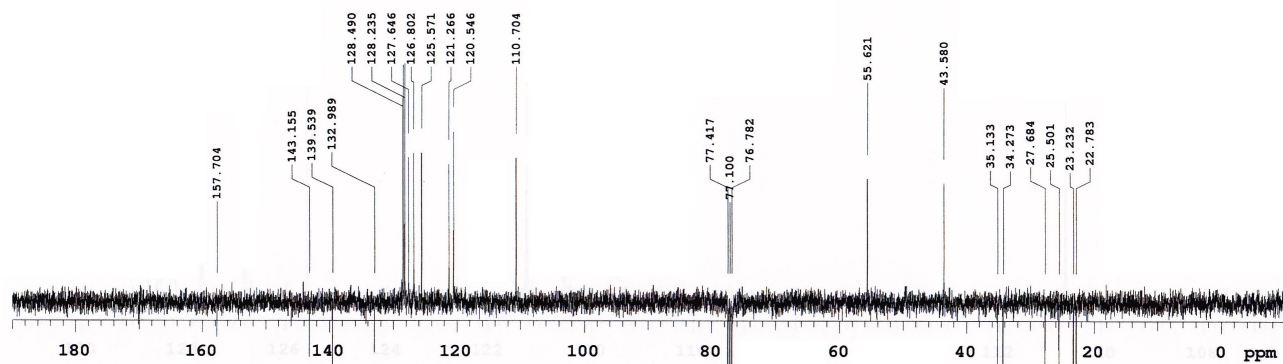
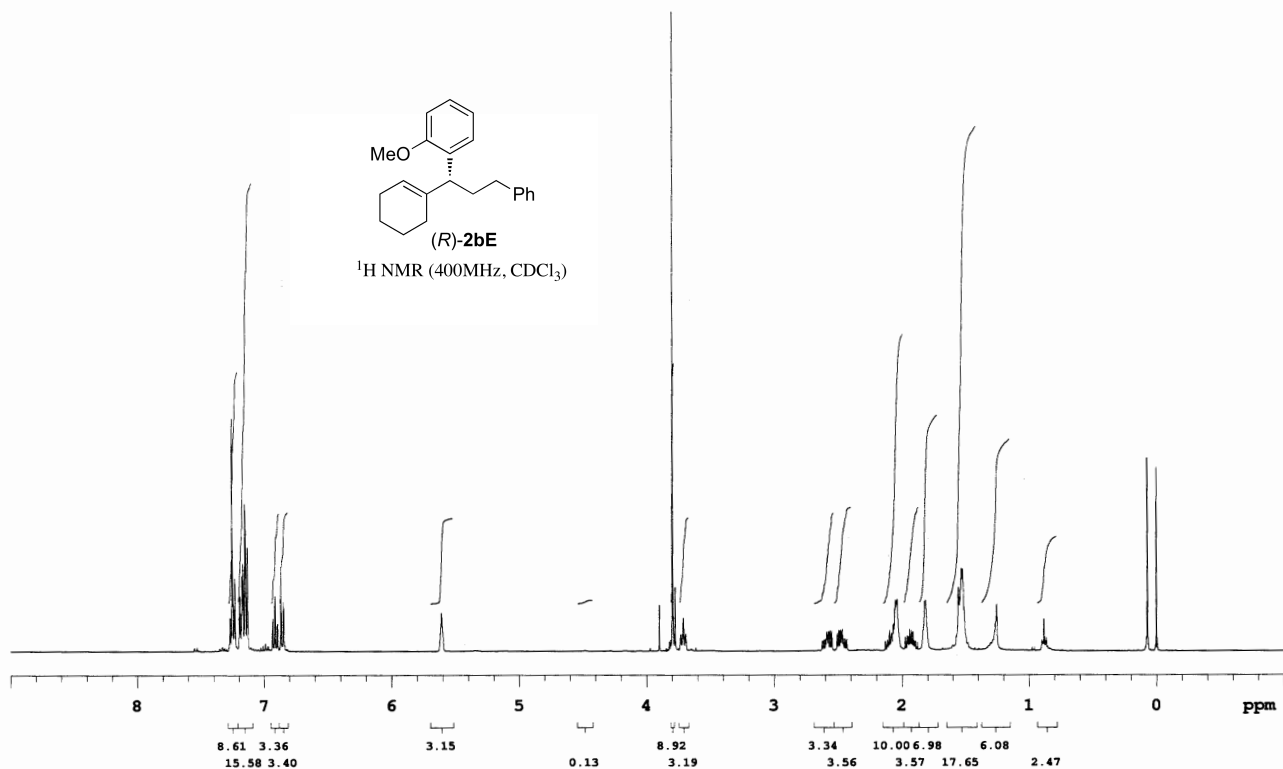
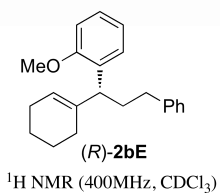
APT (100 MHz, CDCl₃)

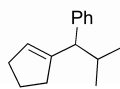






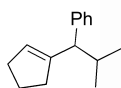
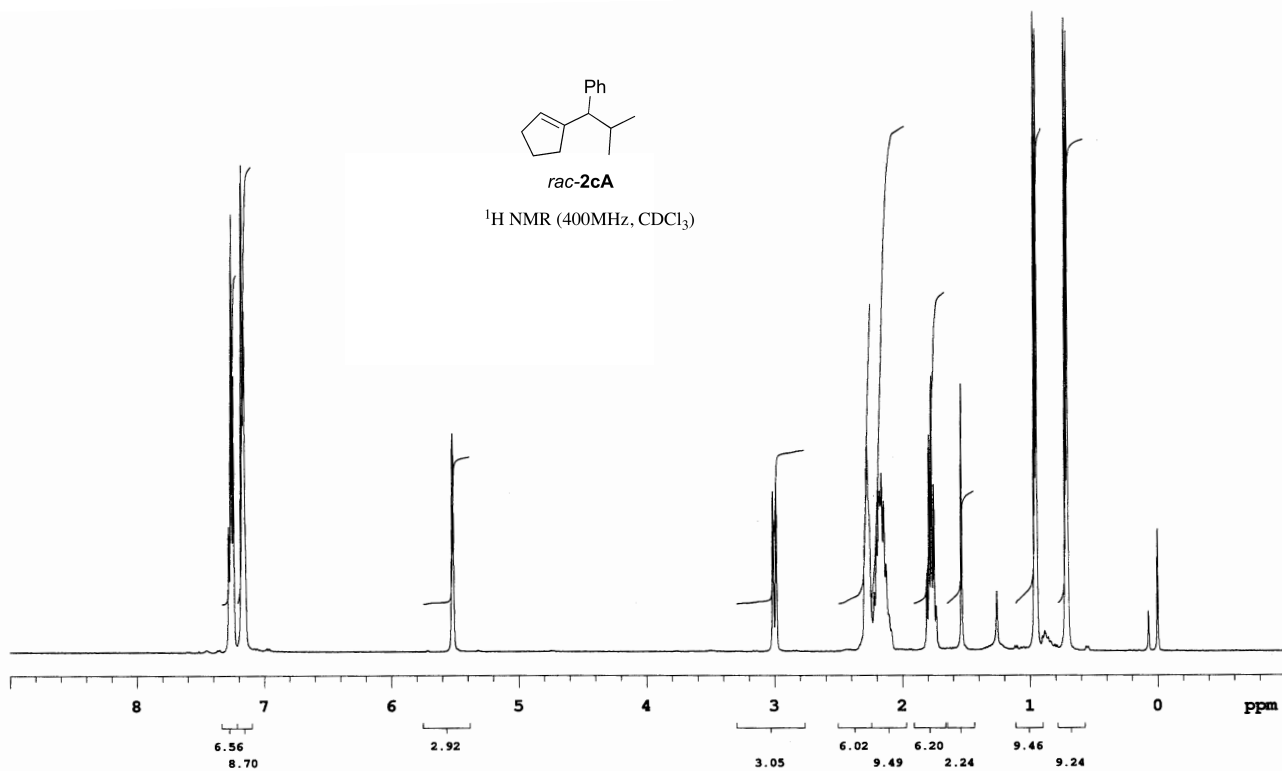






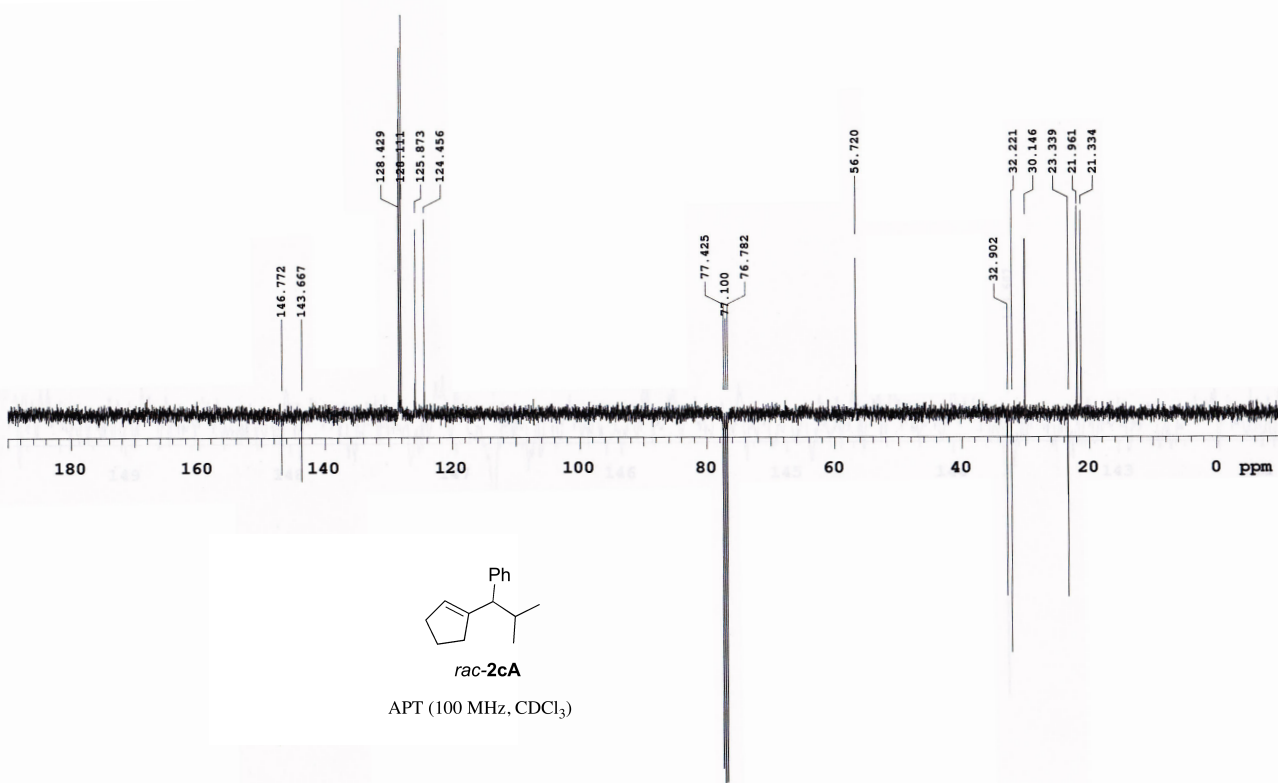
rac-2cA

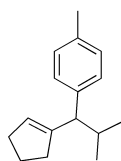
^1H NMR (400MHz, CDCl_3)



rac-2cA

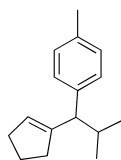
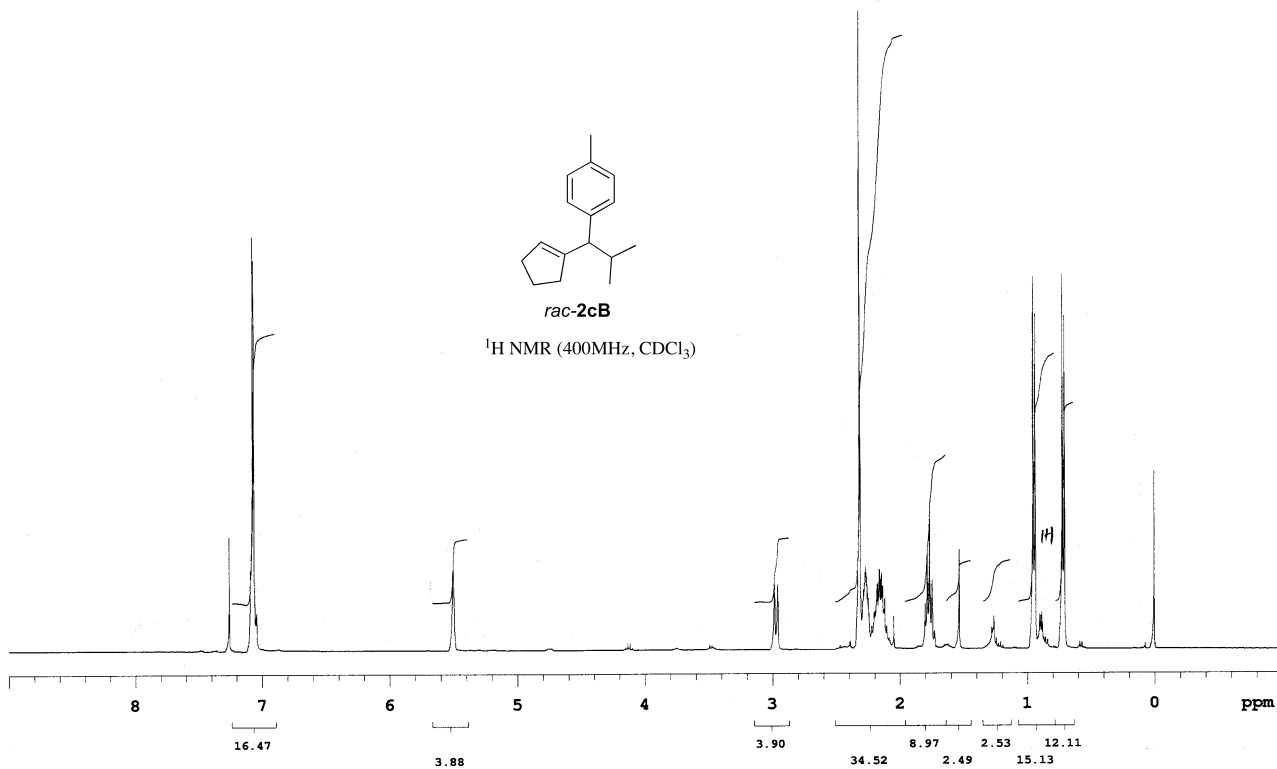
APT (100 MHz, CDCl_3)





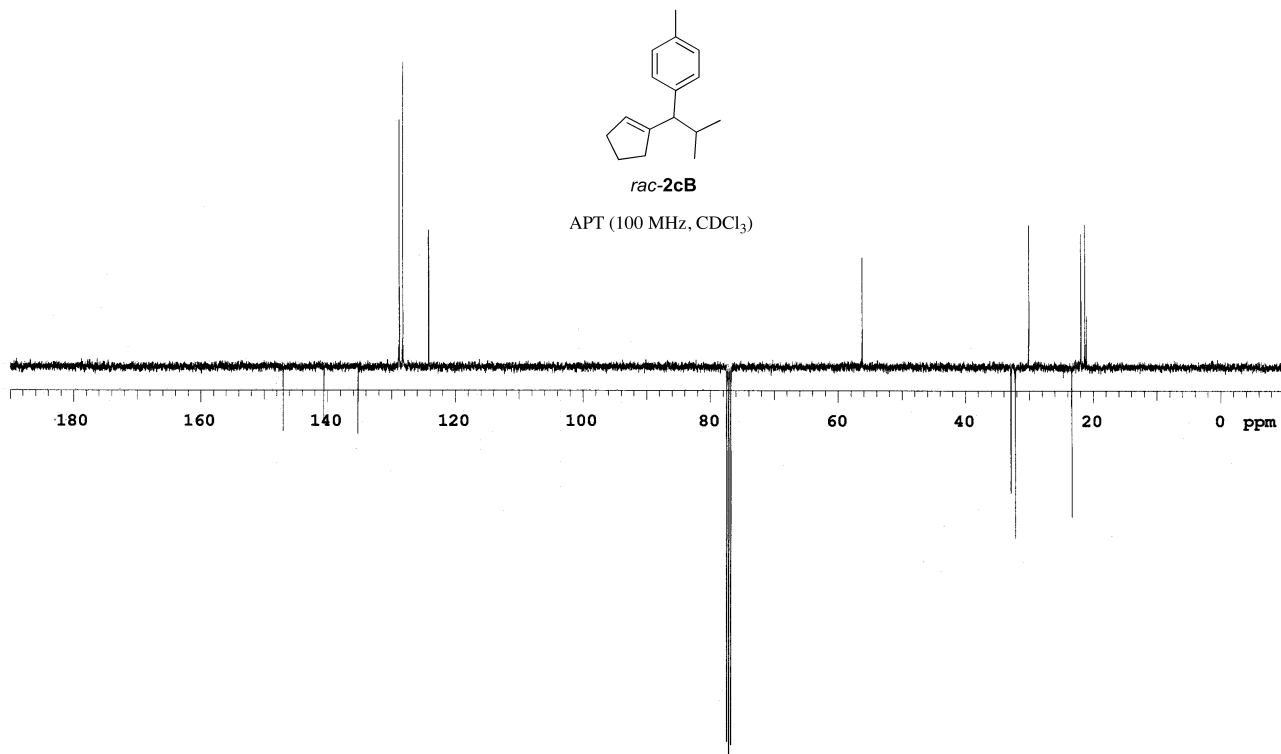
rac-2cB

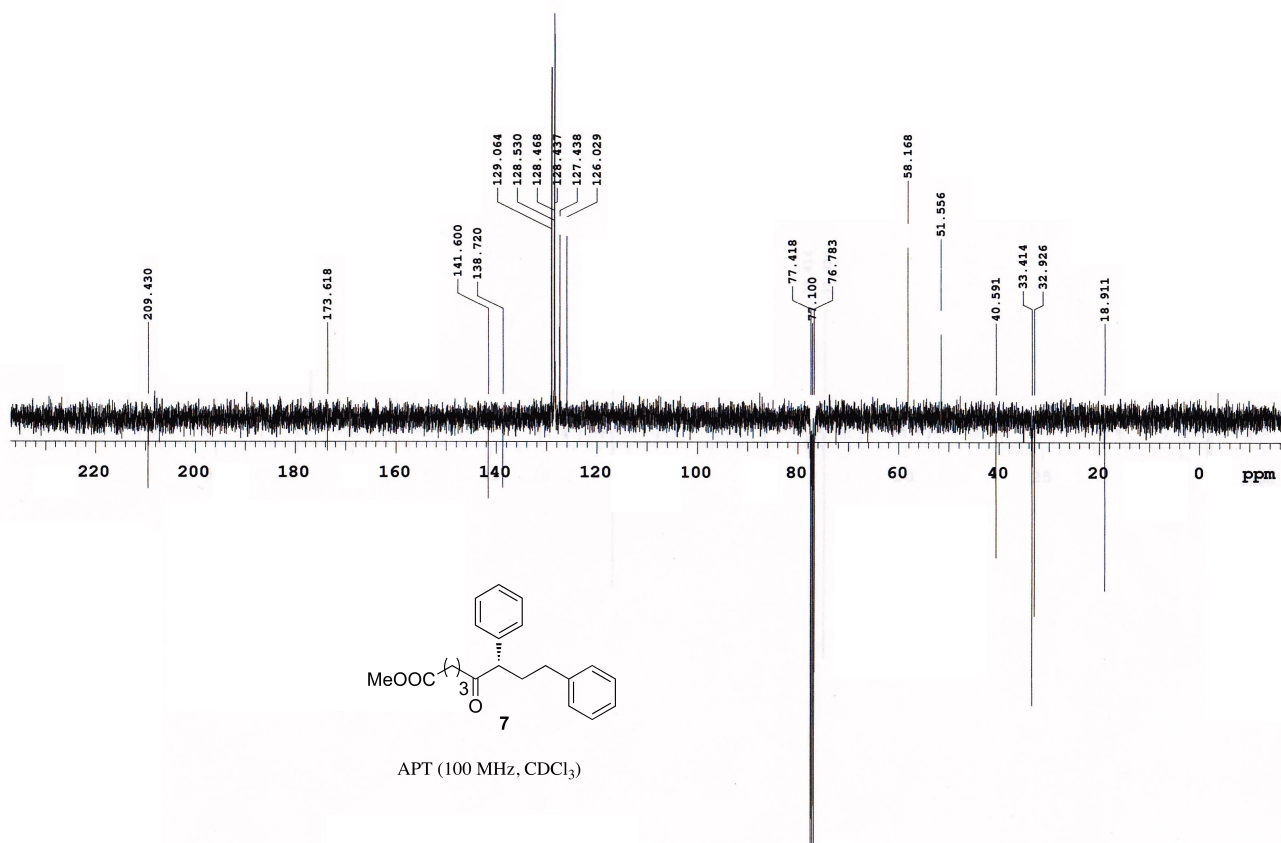
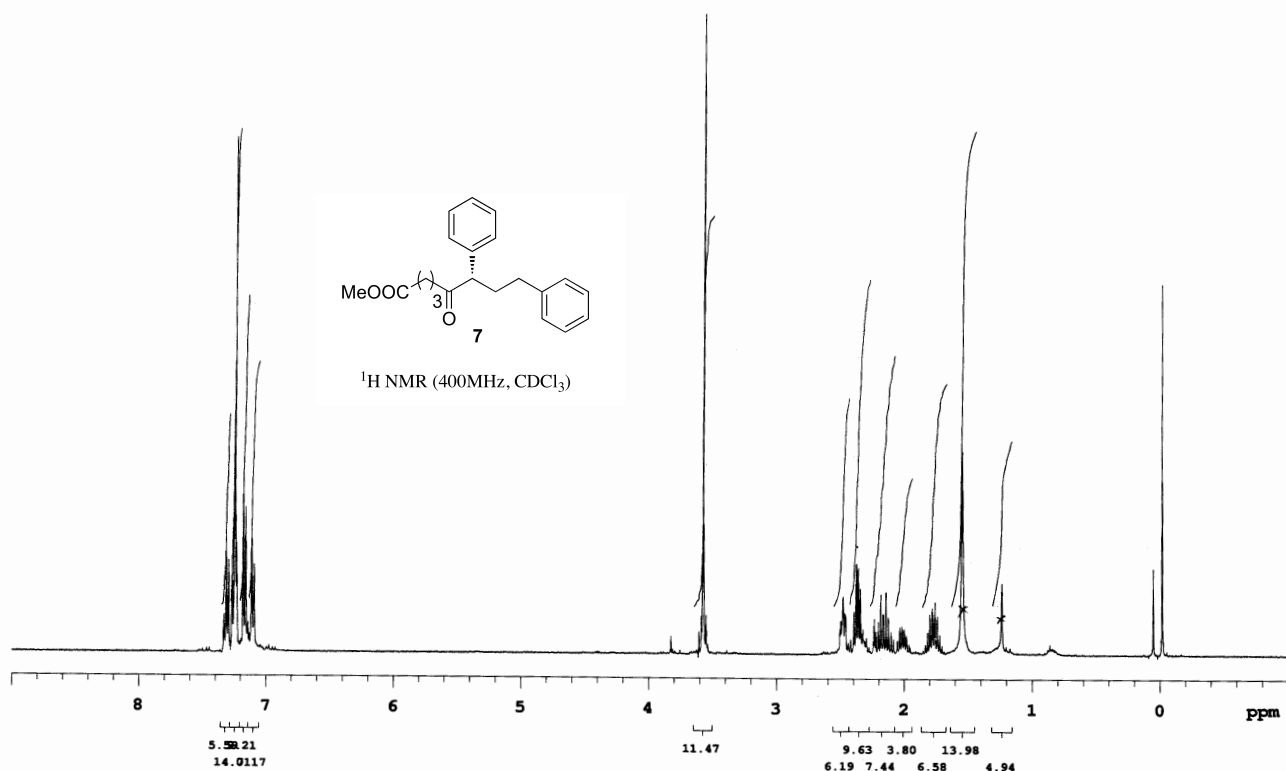
¹H NMR (400MHz, CDCl₃)

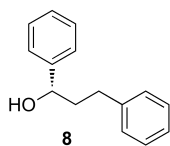


rac-2cB

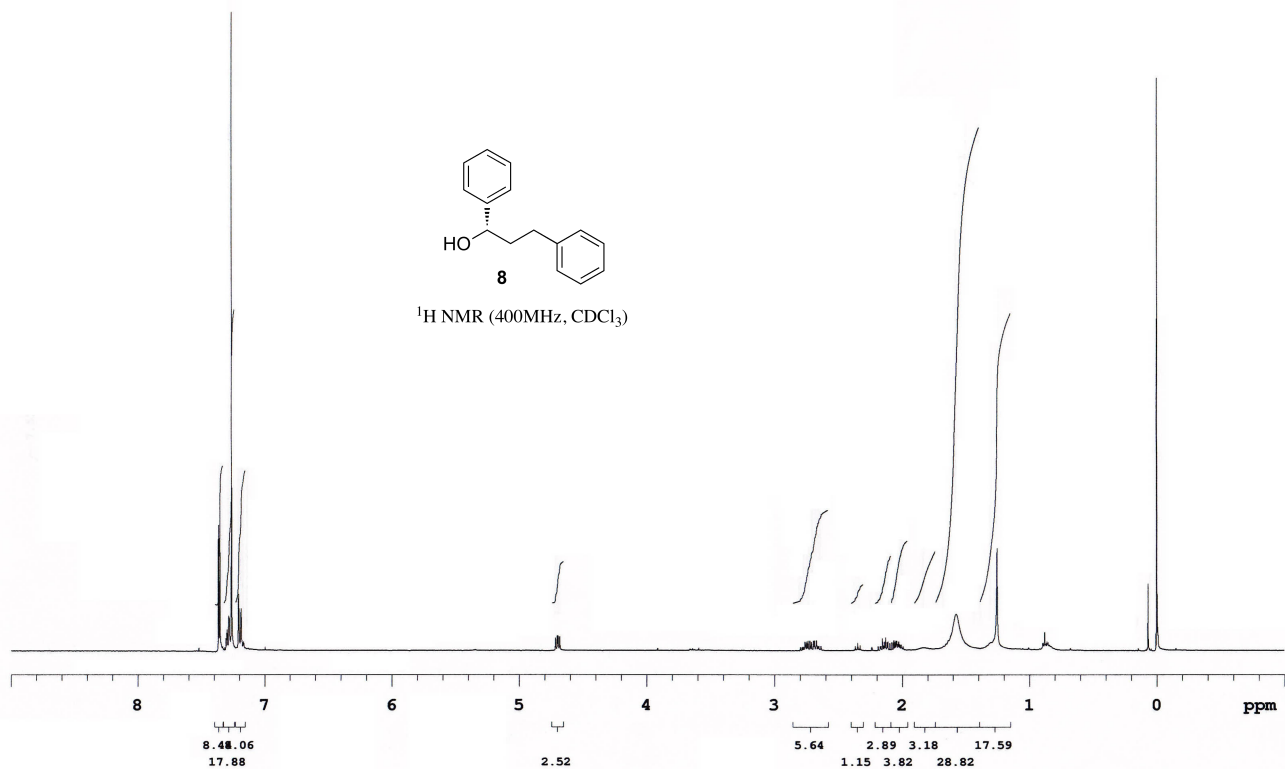
APT (100 MHz, CDCl₃)



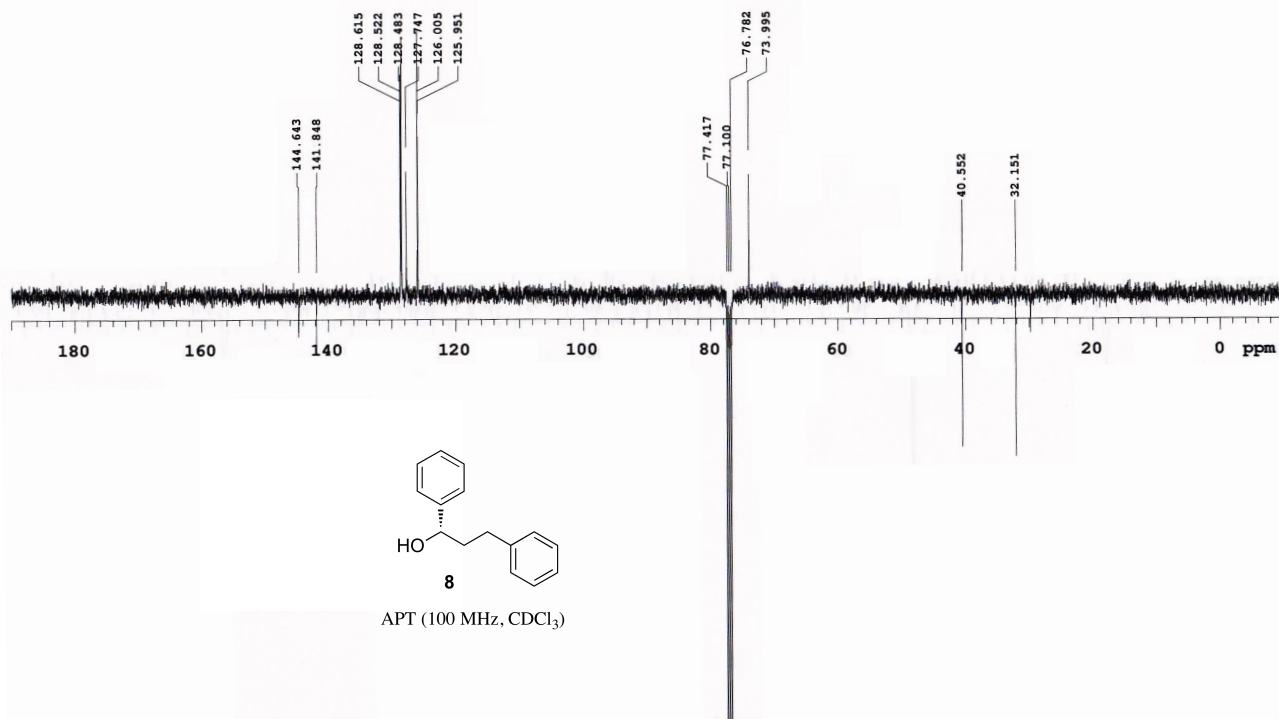


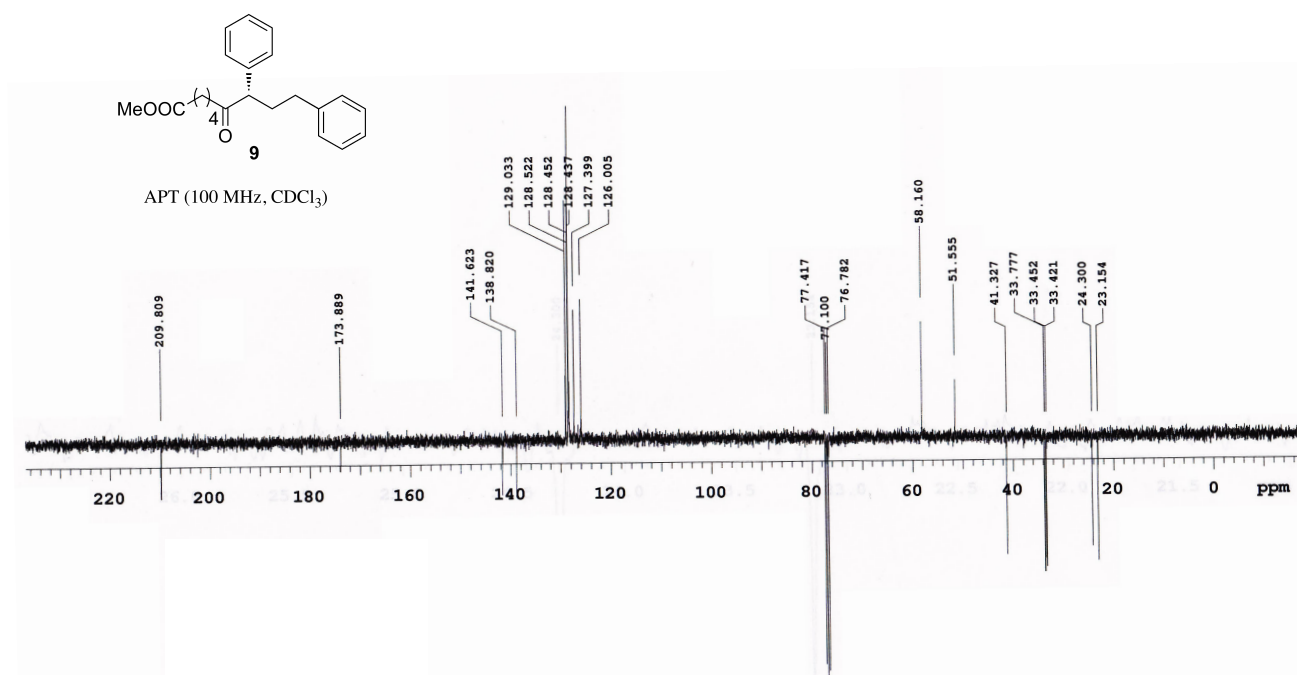
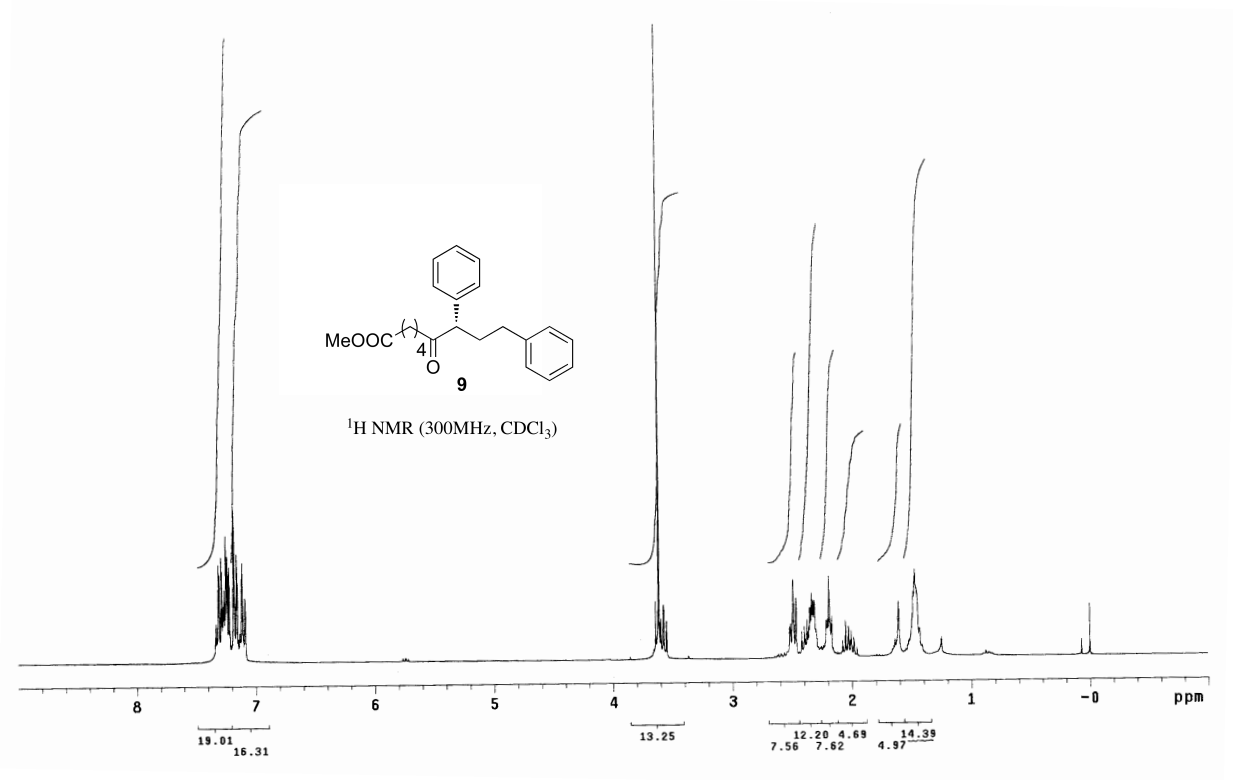


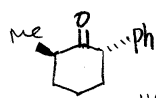
^1H NMR (400MHz, CDCl_3)



APT (100 MHz, CDCl_3)



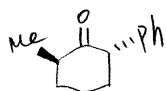
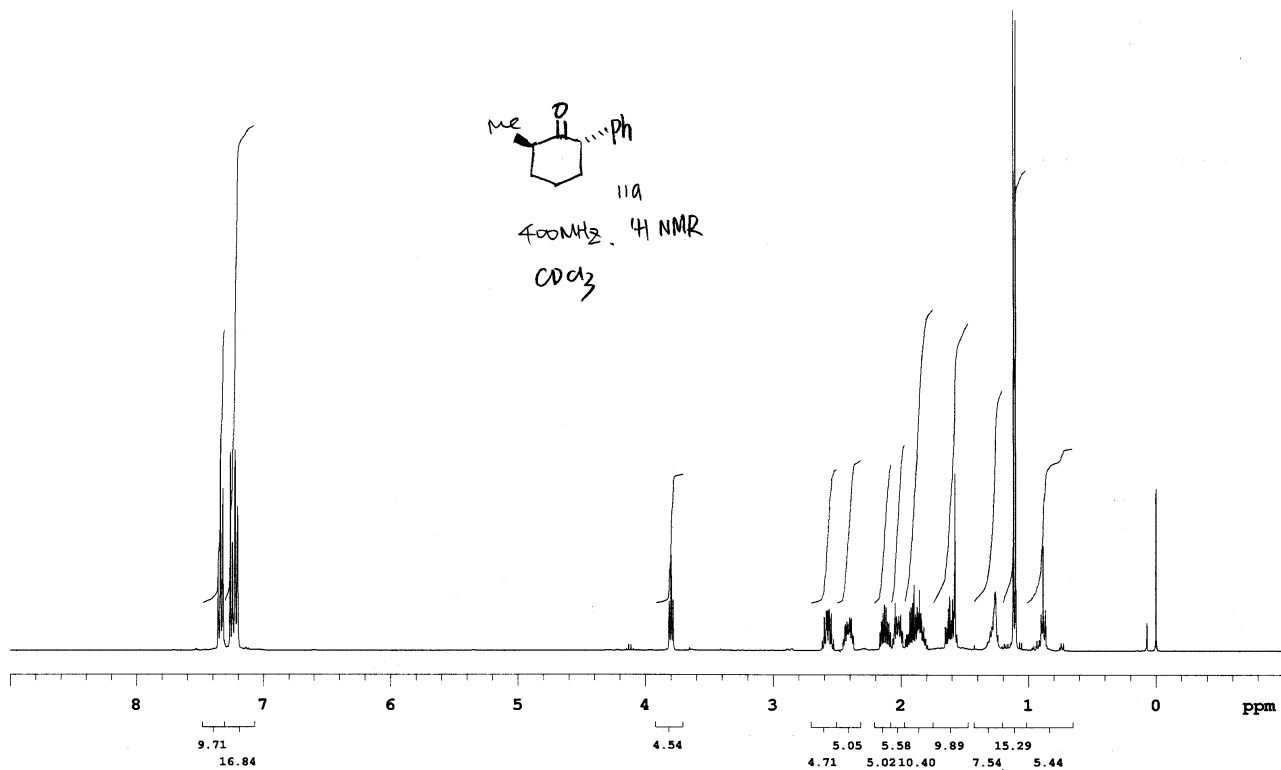




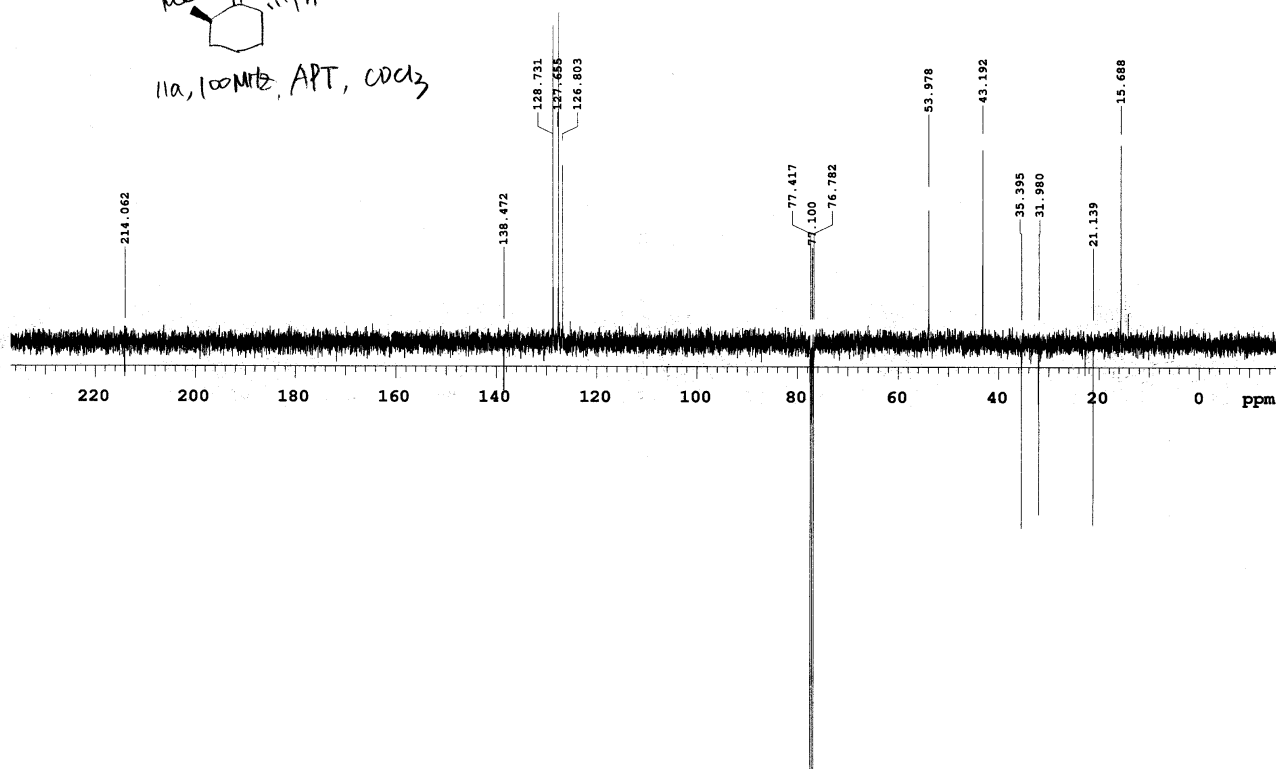
11a

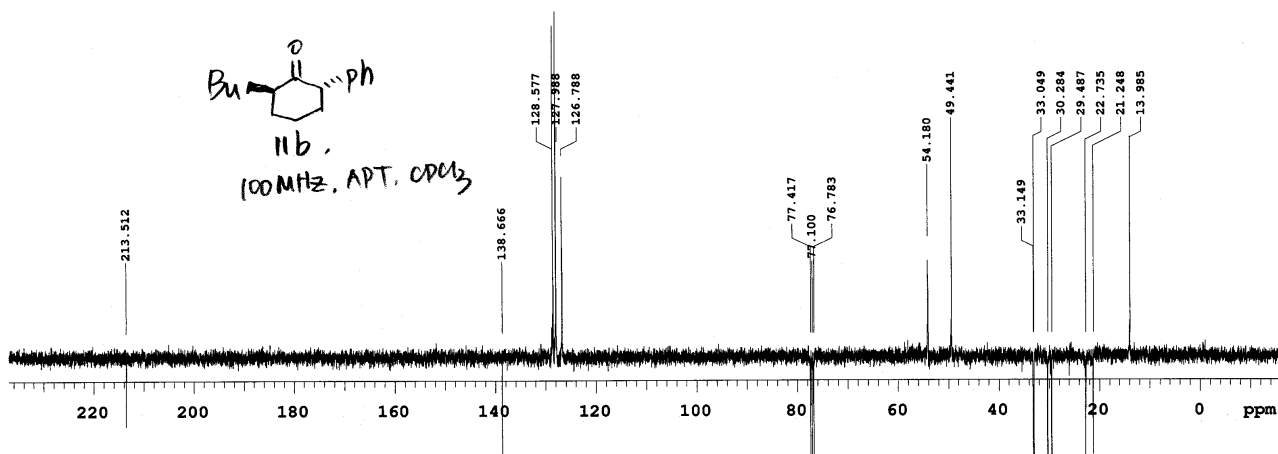
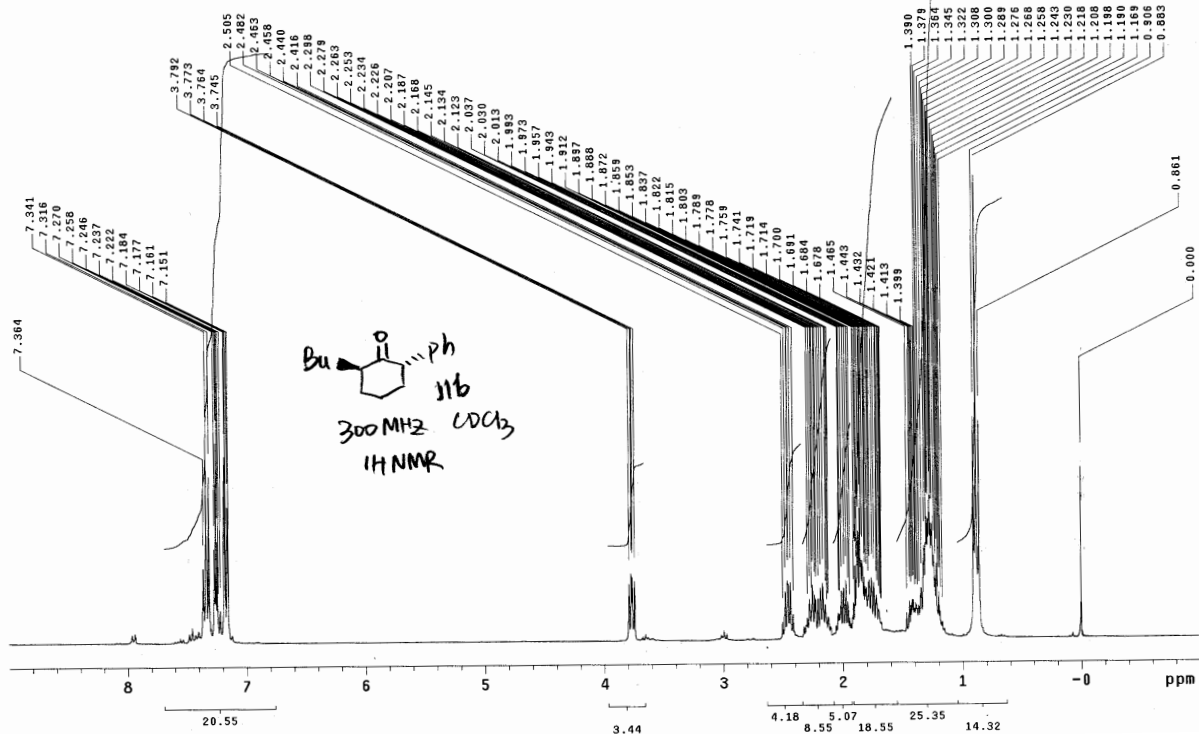
400MHz, ¹H NMR

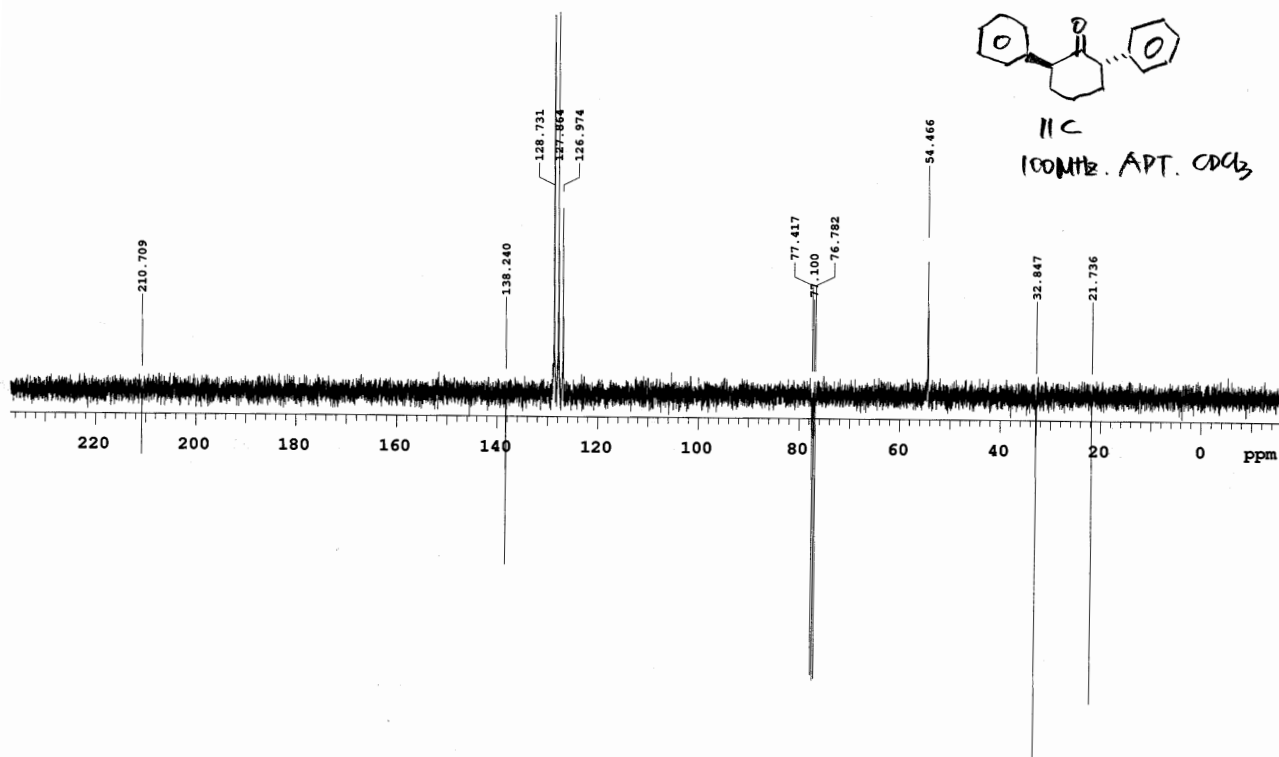
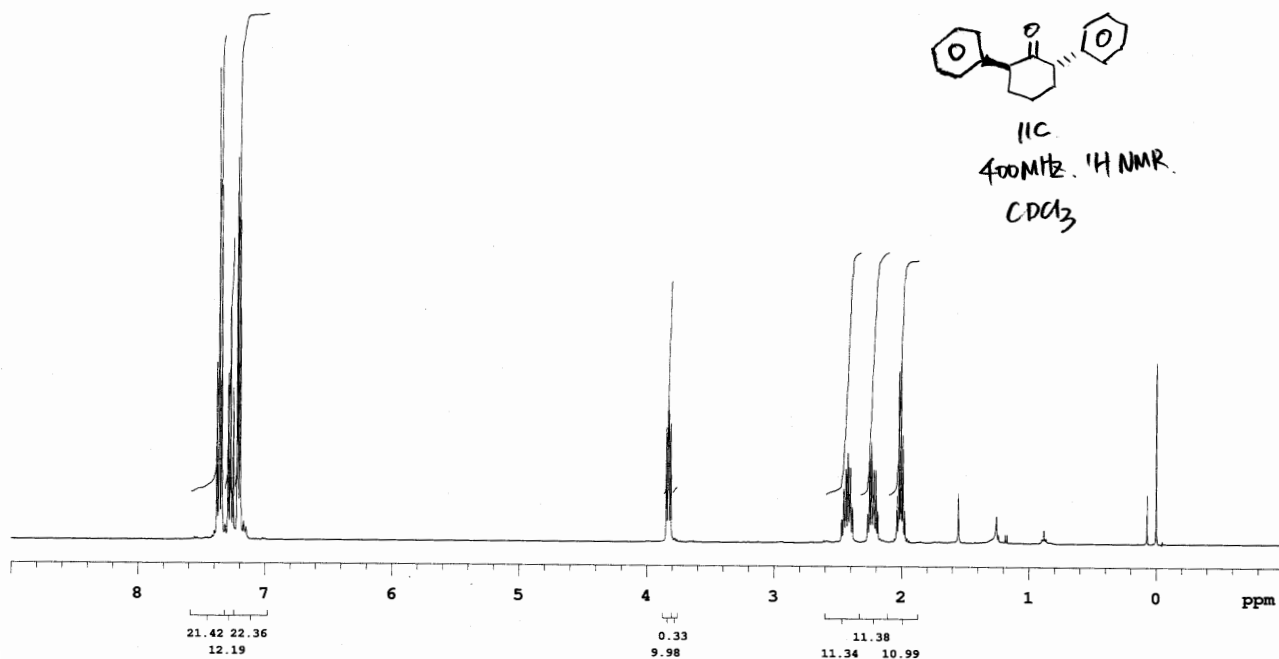
CDCl₃

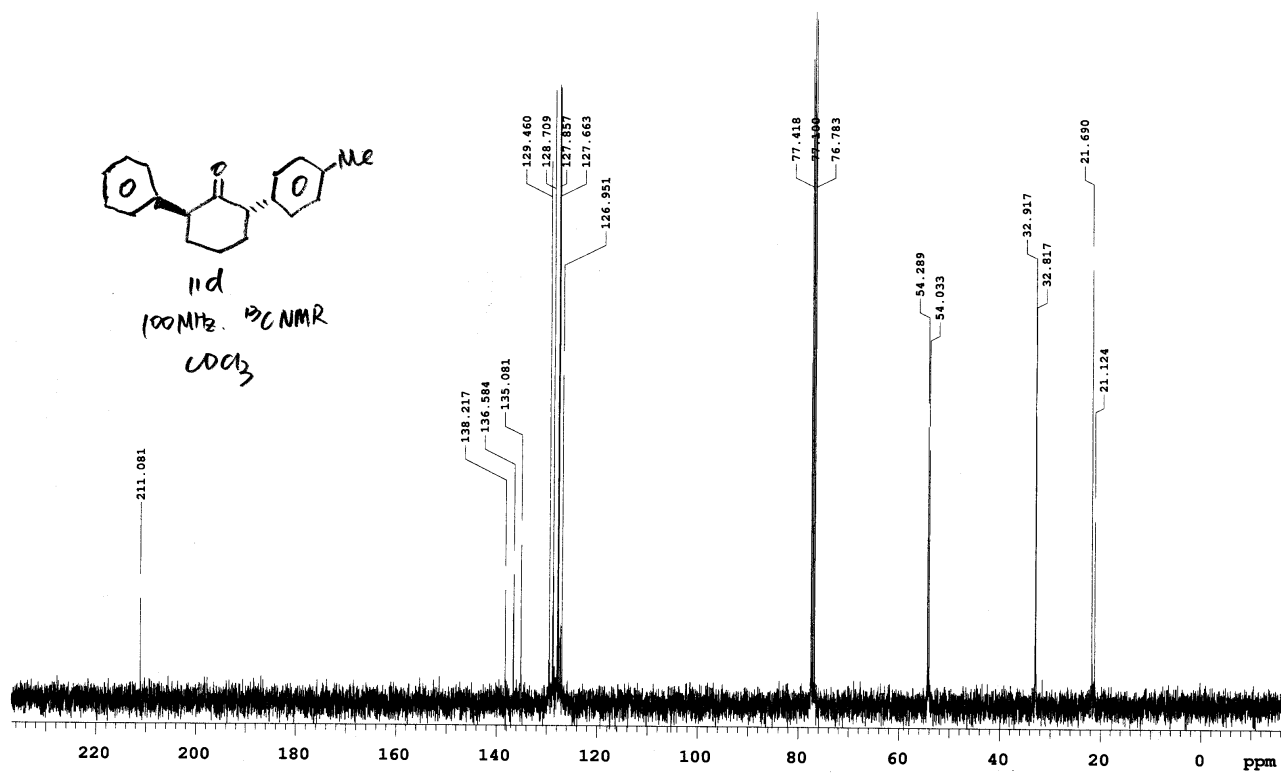
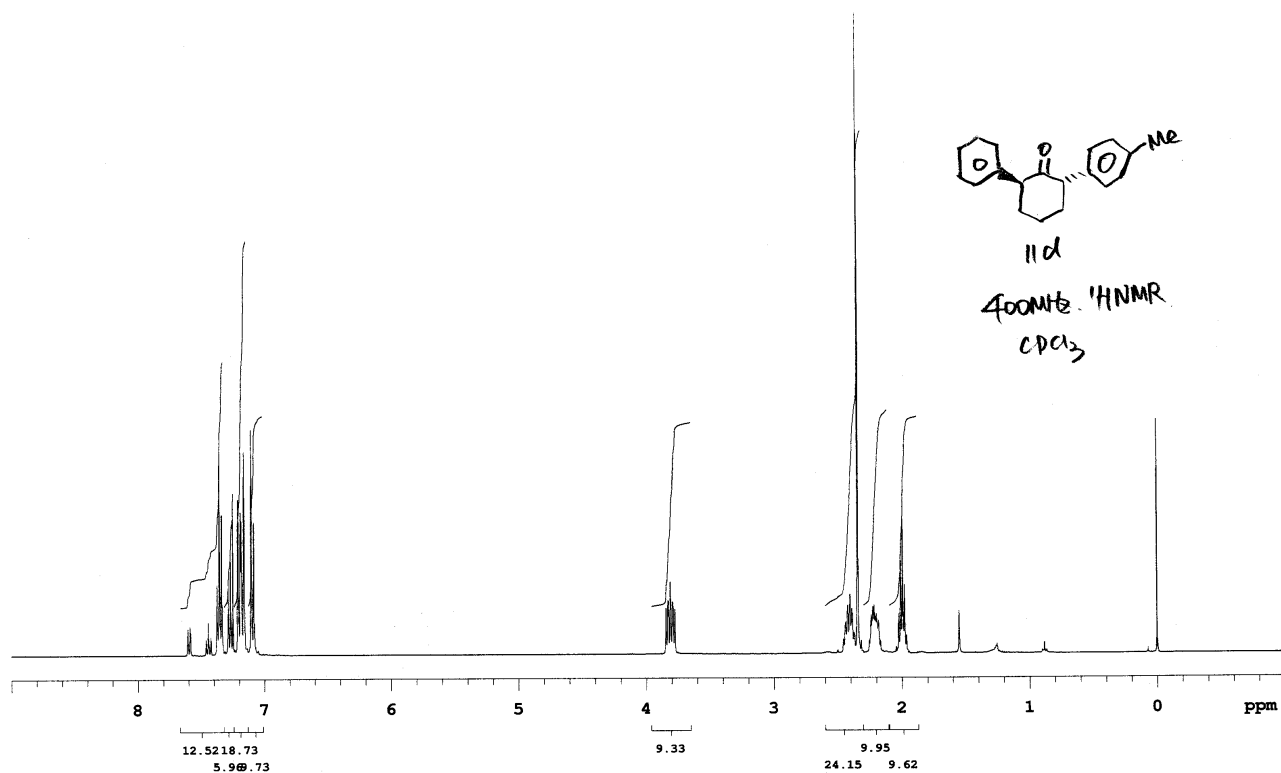


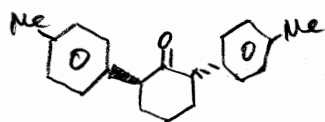
11a, 100MHz, APT, CDCl₃



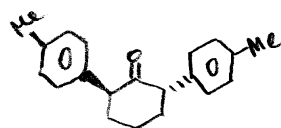
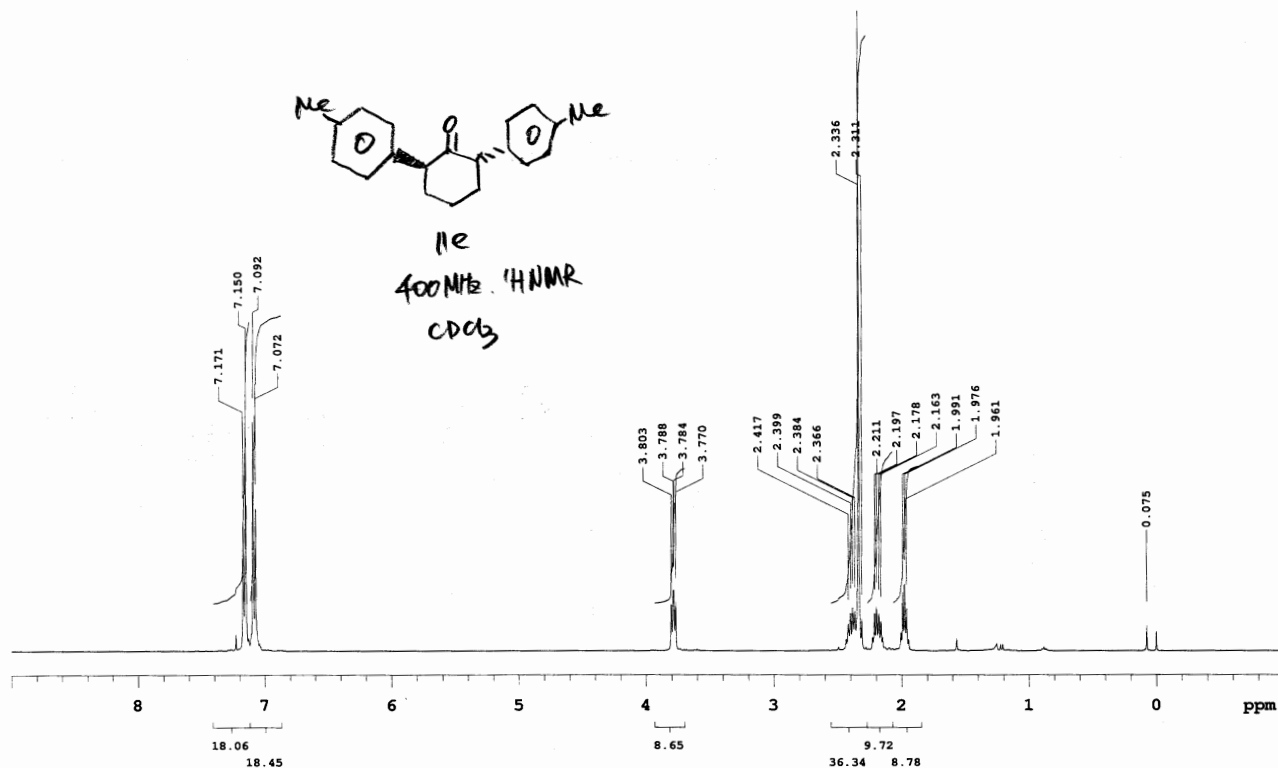




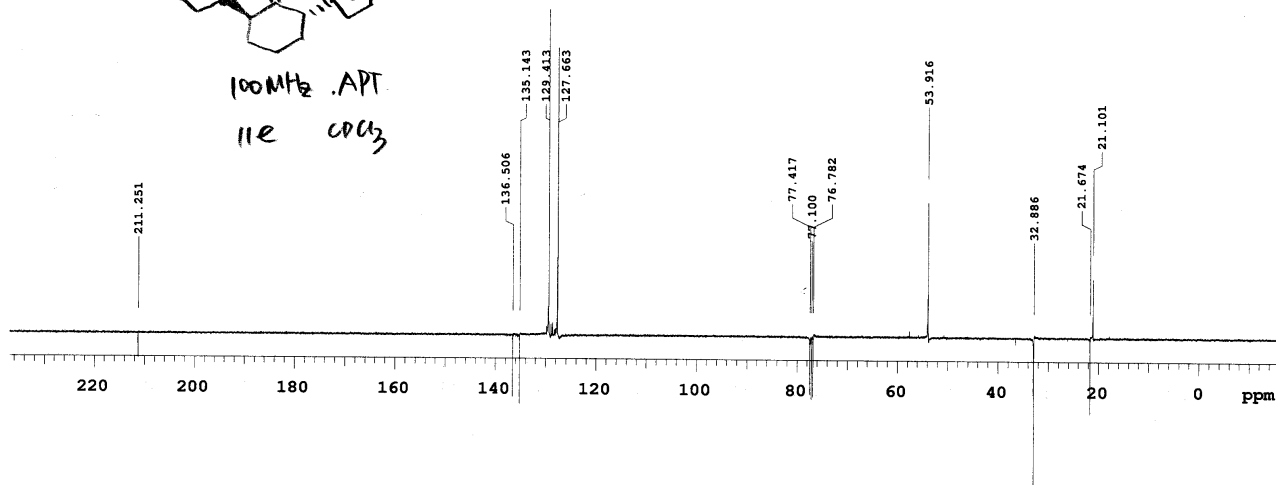


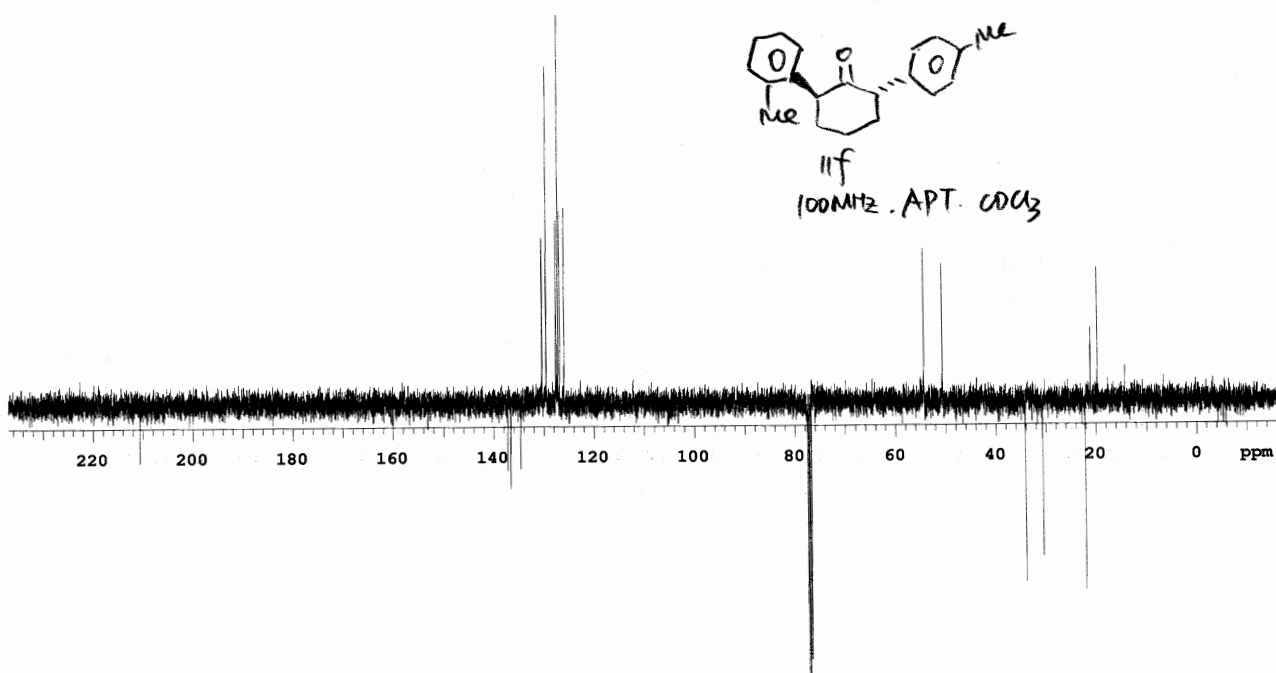
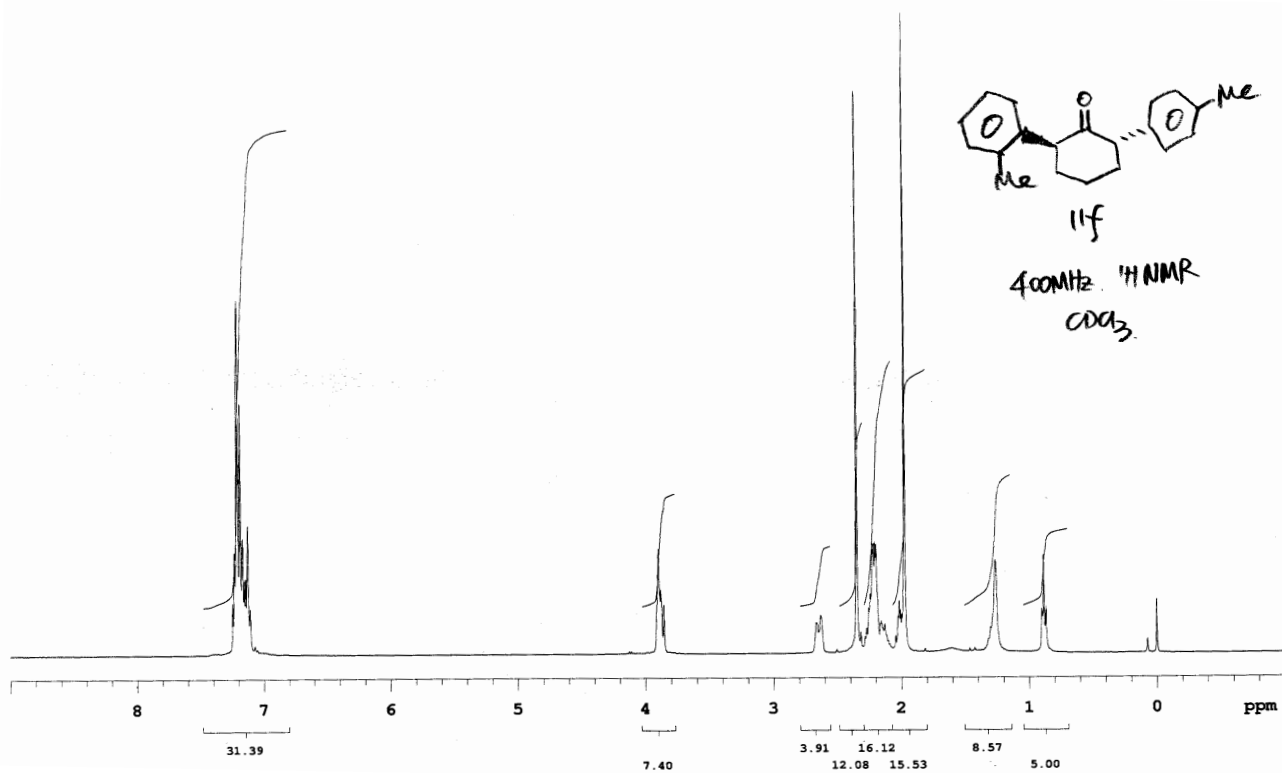


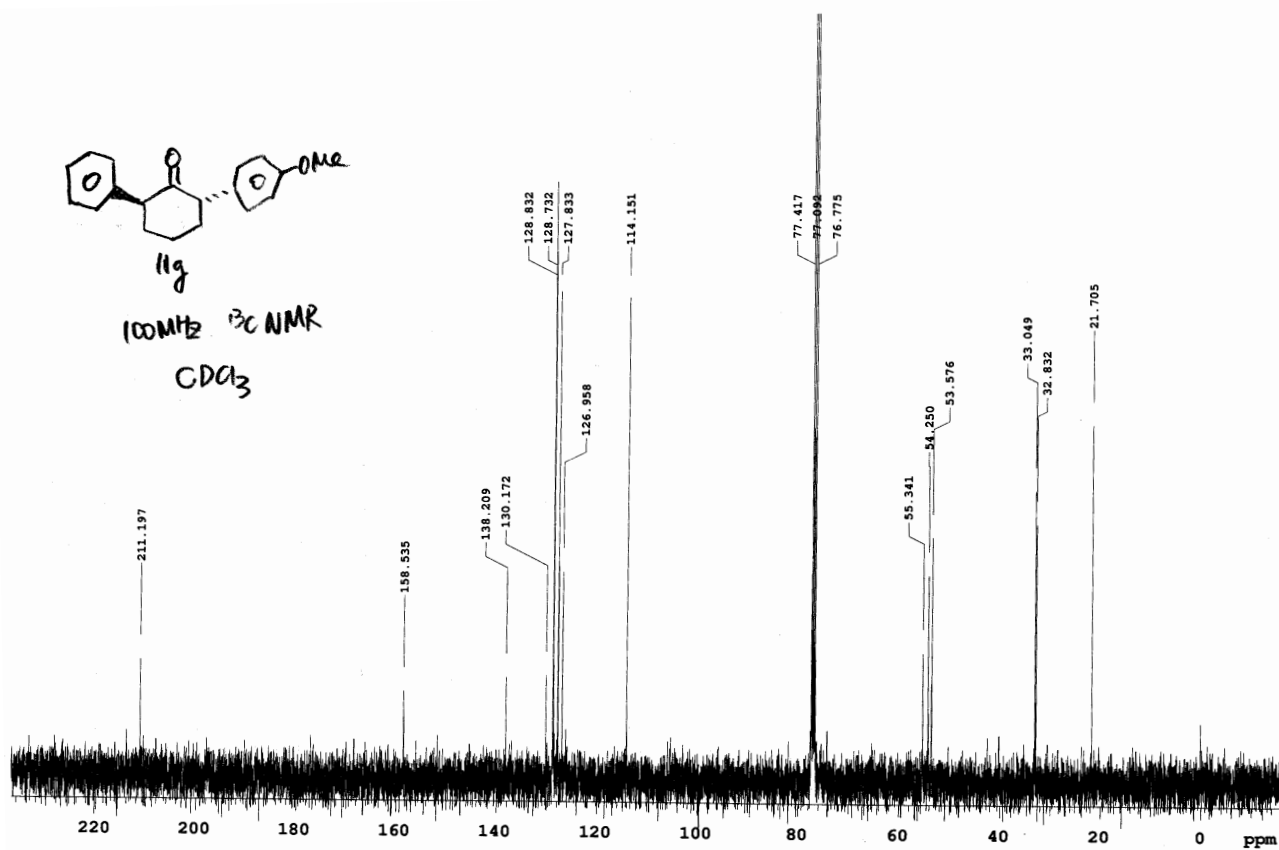
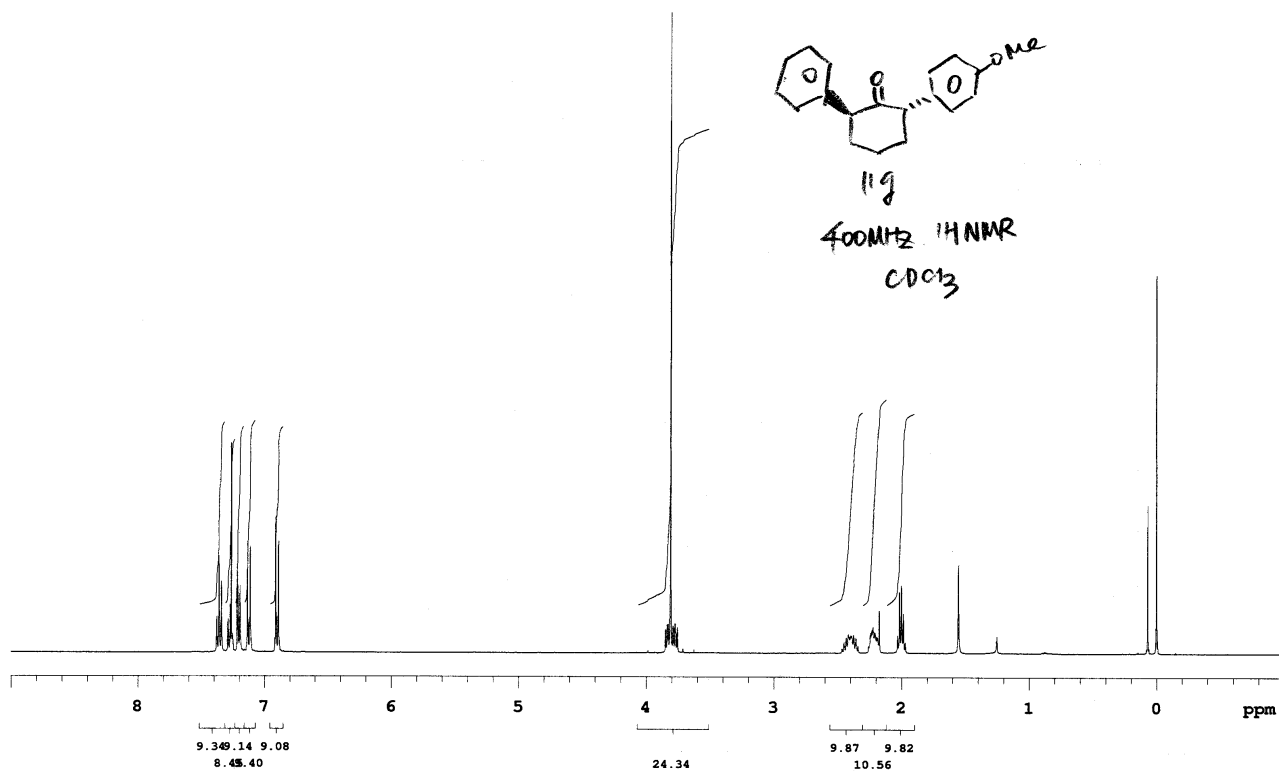
11e
400MHz ¹H NMR
CDCl₃



100MHz .APT
11e CDCl₃







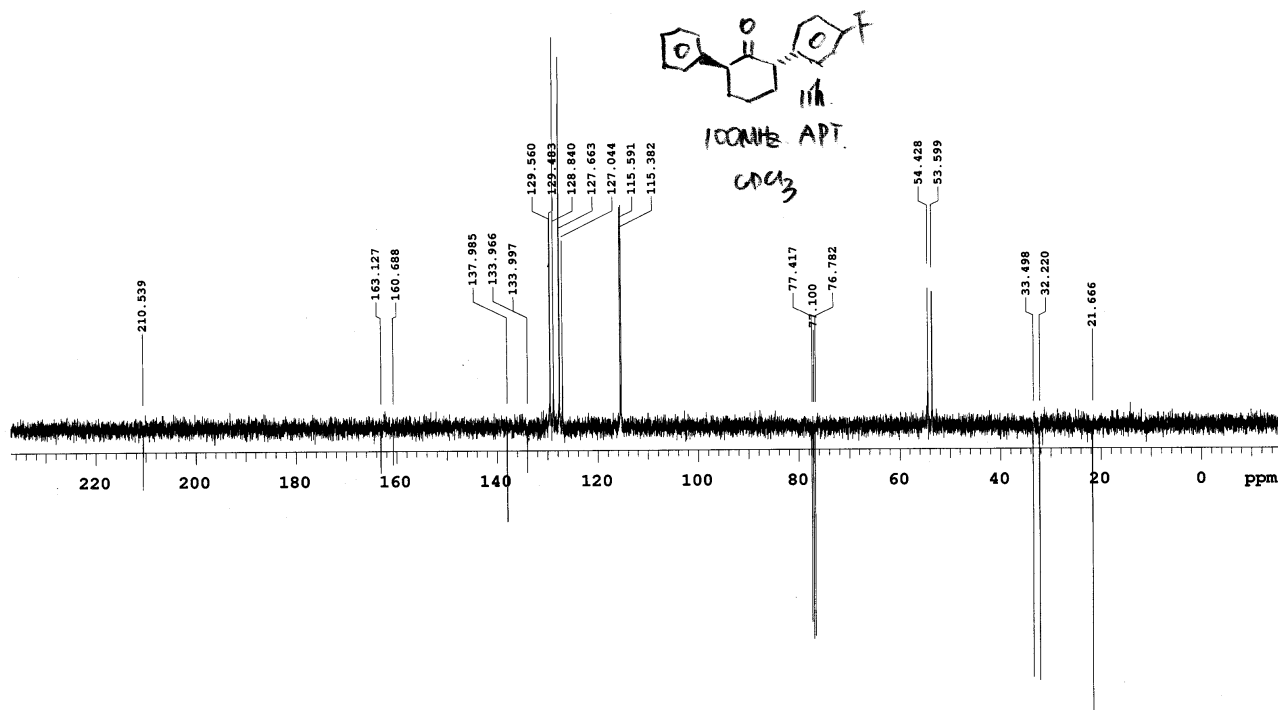
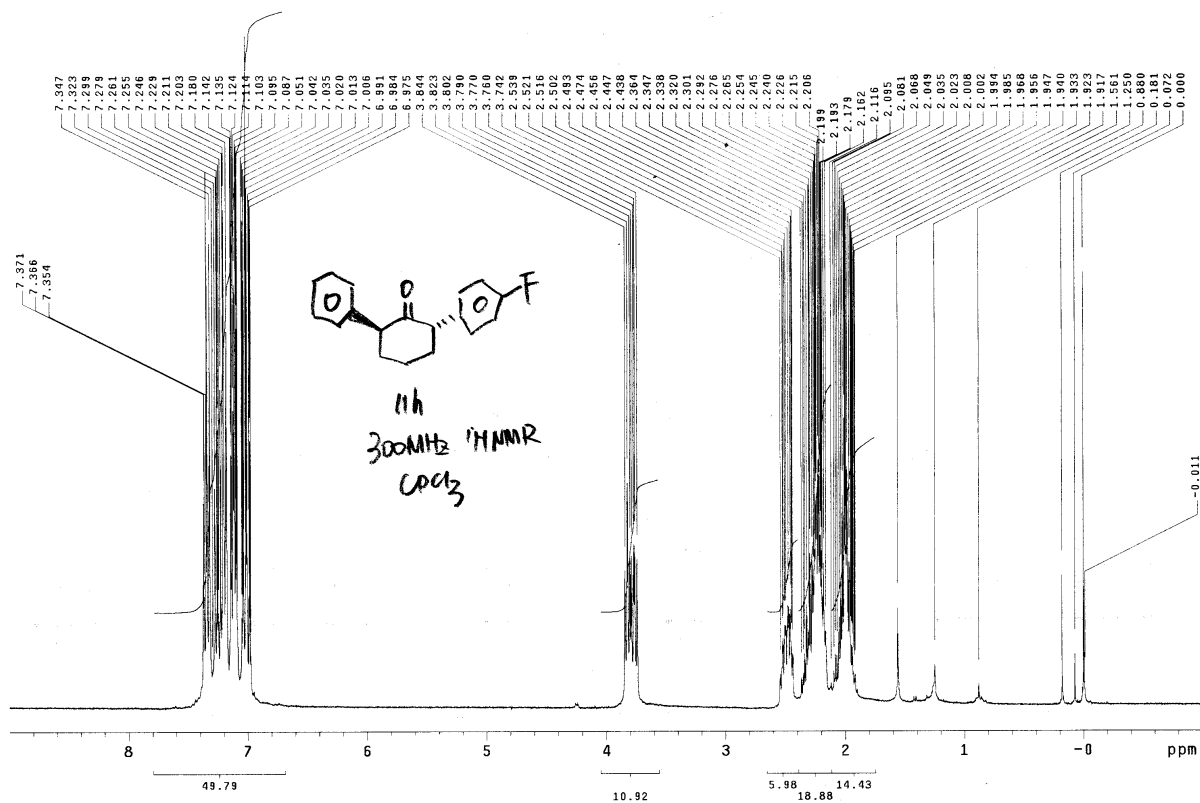


Table 1, entry1

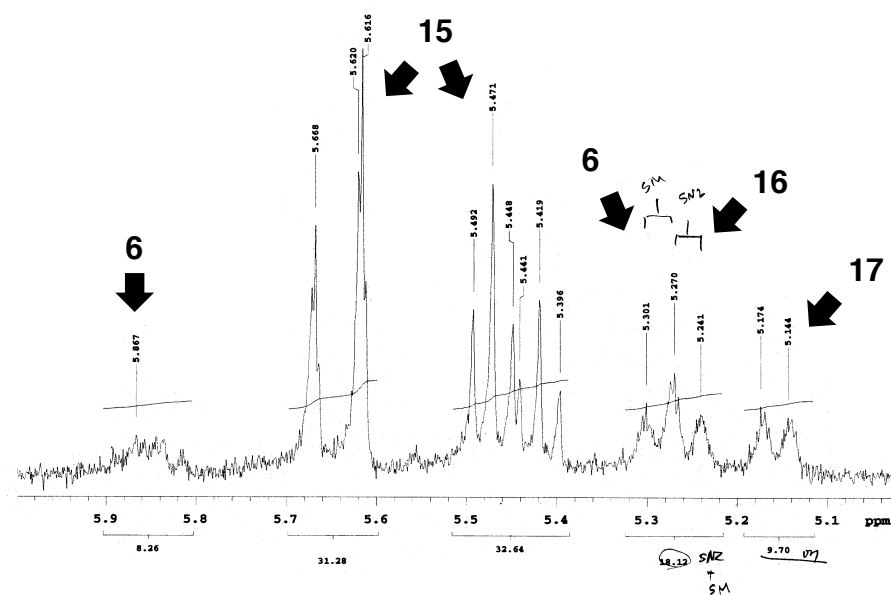
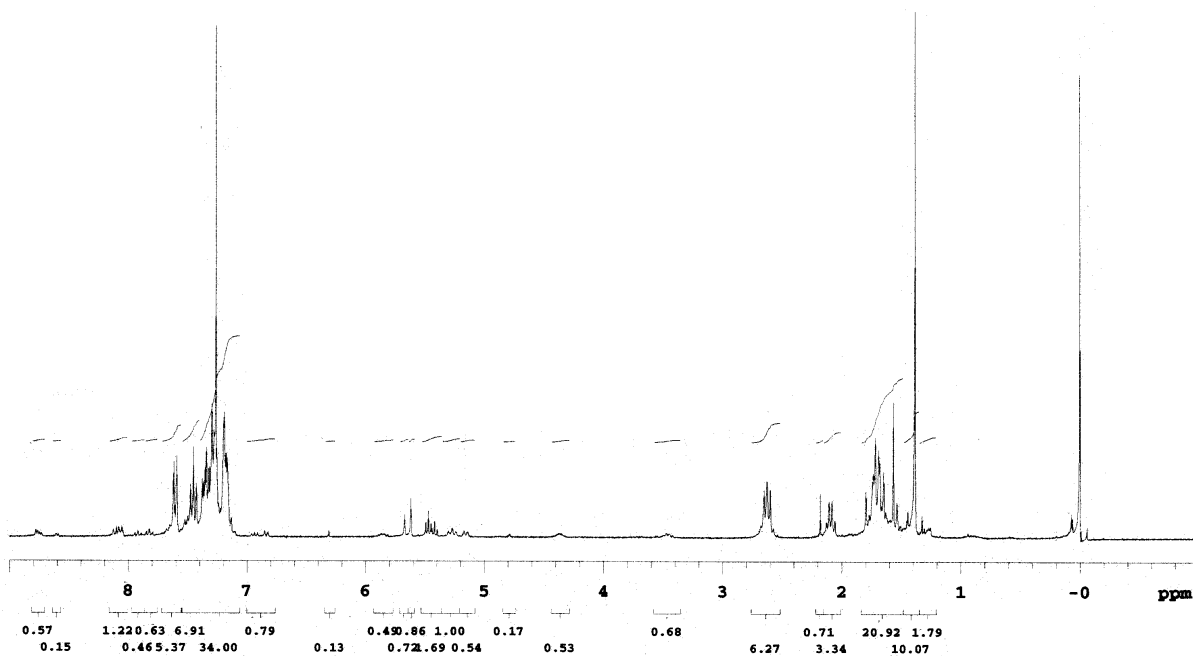
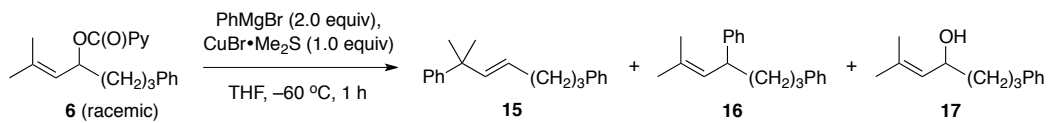
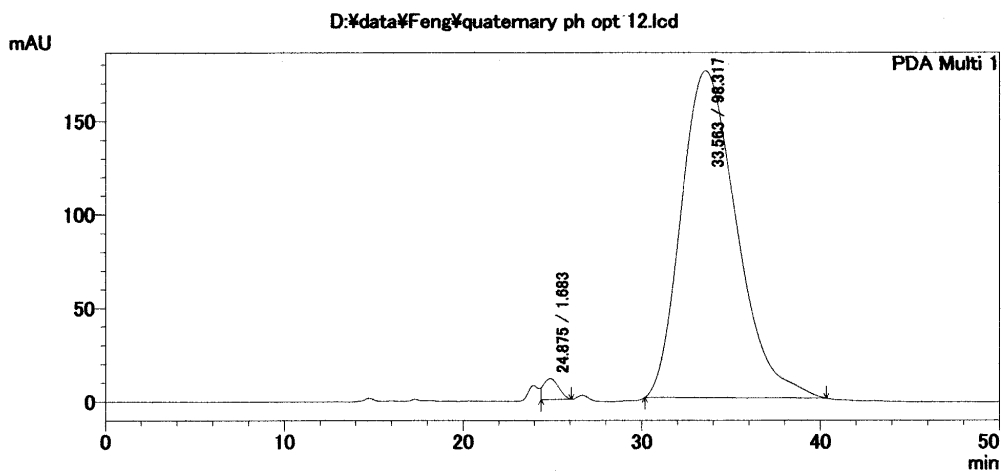


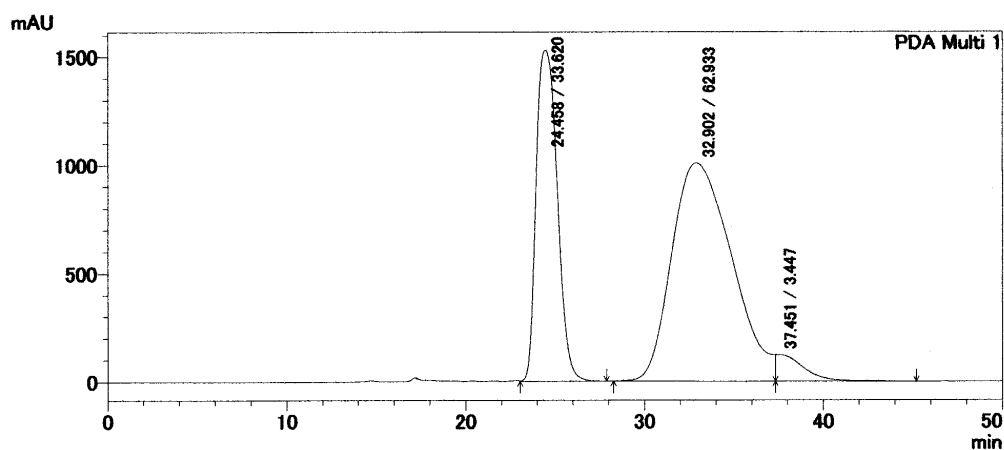
Table 4, entry 2



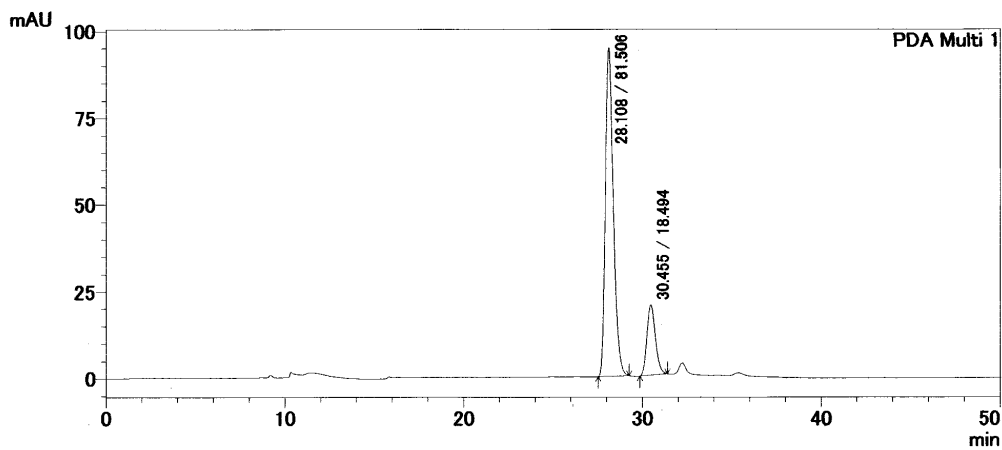
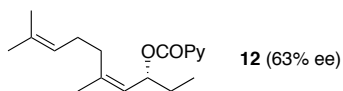
<クロマトグラム>



$ee. = 97\%$ $at. = 99\%$
OT-H. Flow = 0.3 mL conc = 1% 30°C.



substrate for Table 4, entry 10



1 PDA Multi 1/259nm 4nm

OD-H 0.500 mL/min Flow
 1% conc 30°C

$$ee = \frac{81.506 - 18.494}{81.506 + 18.494} \times 100\% = 63.0\% = 63\%$$

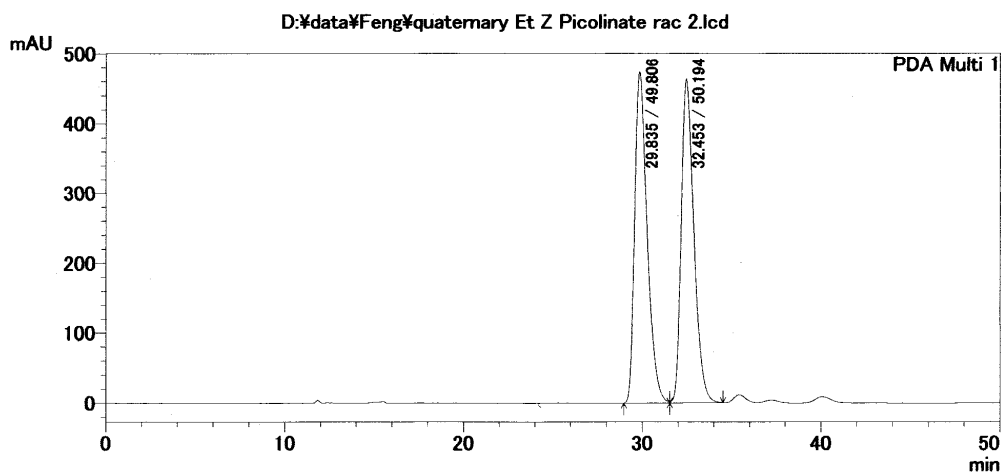
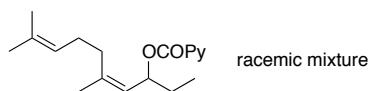
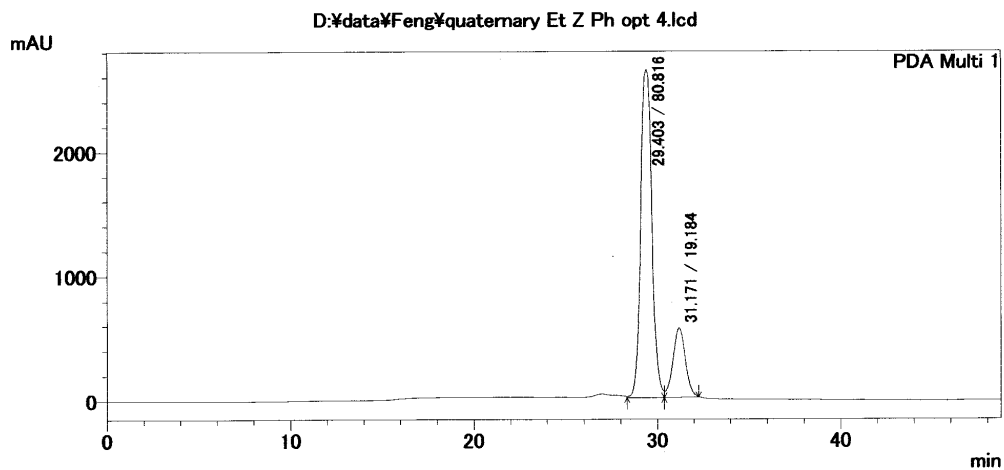
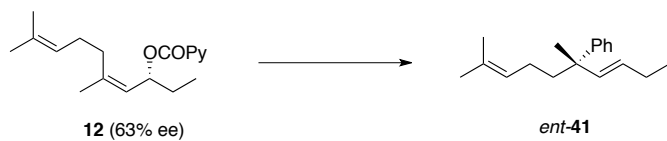


Table 4, entry 10



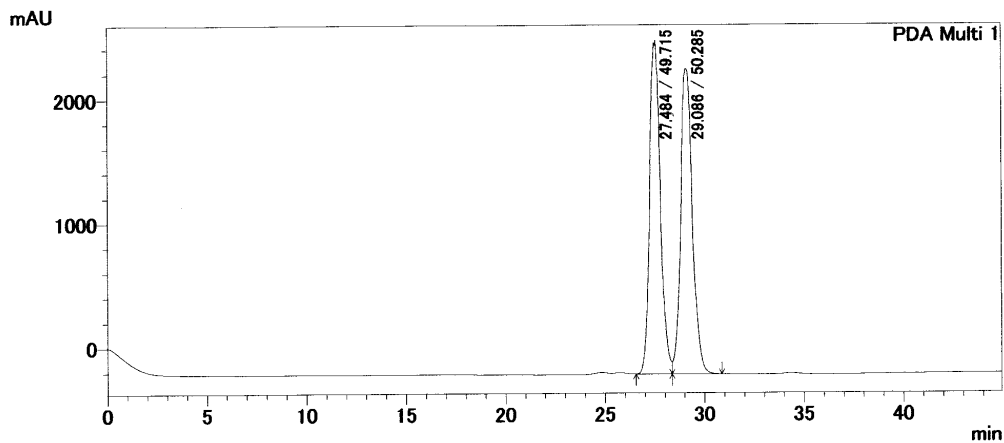
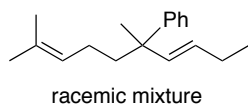
1 PDA Multi 1/192nm 4nm

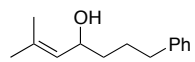
OJ-H. 0.300 mL/min Flow

0.2% conc. 30°C

$$ee = \frac{80.816 - 19.184}{100} \times 100\% = 61.6\% = 62\%$$

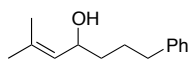
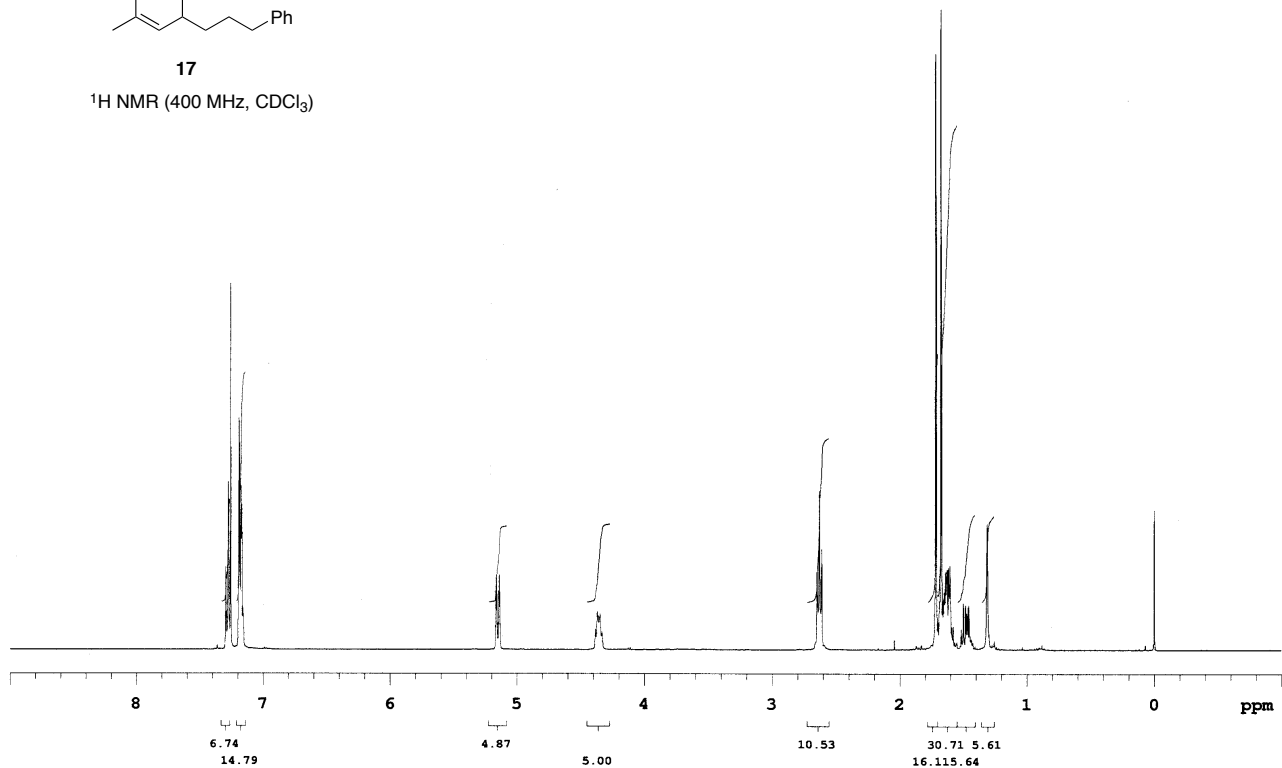
$$C.T. = \frac{61.6\%}{63.0\%} \times 100\% = 98\%$$





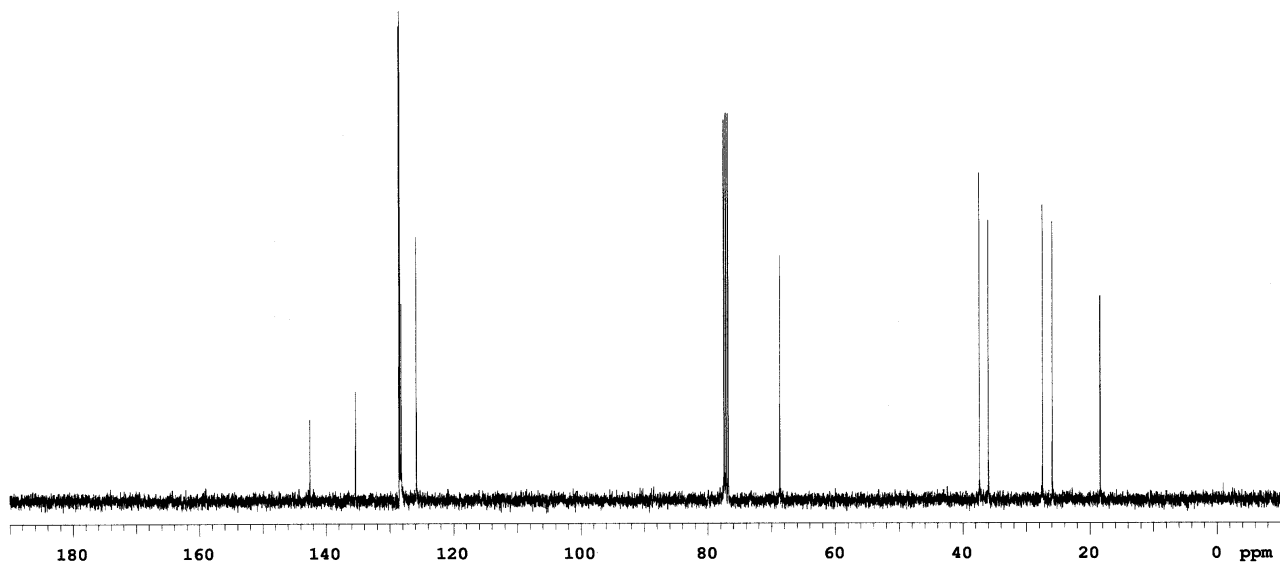
17

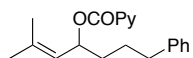
^1H NMR (400 MHz, CDCl_3)



17

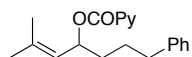
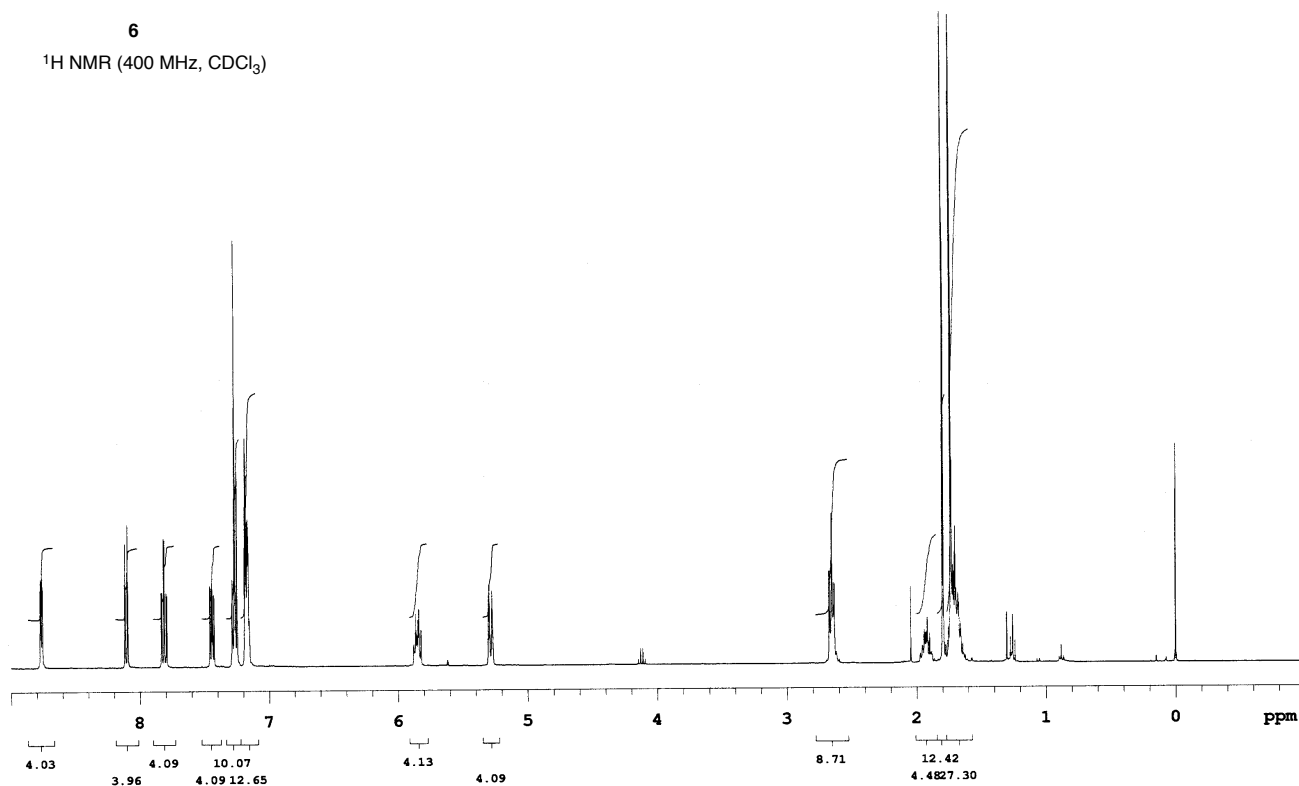
^{13}C NMR (100 MHz, CDCl_3)





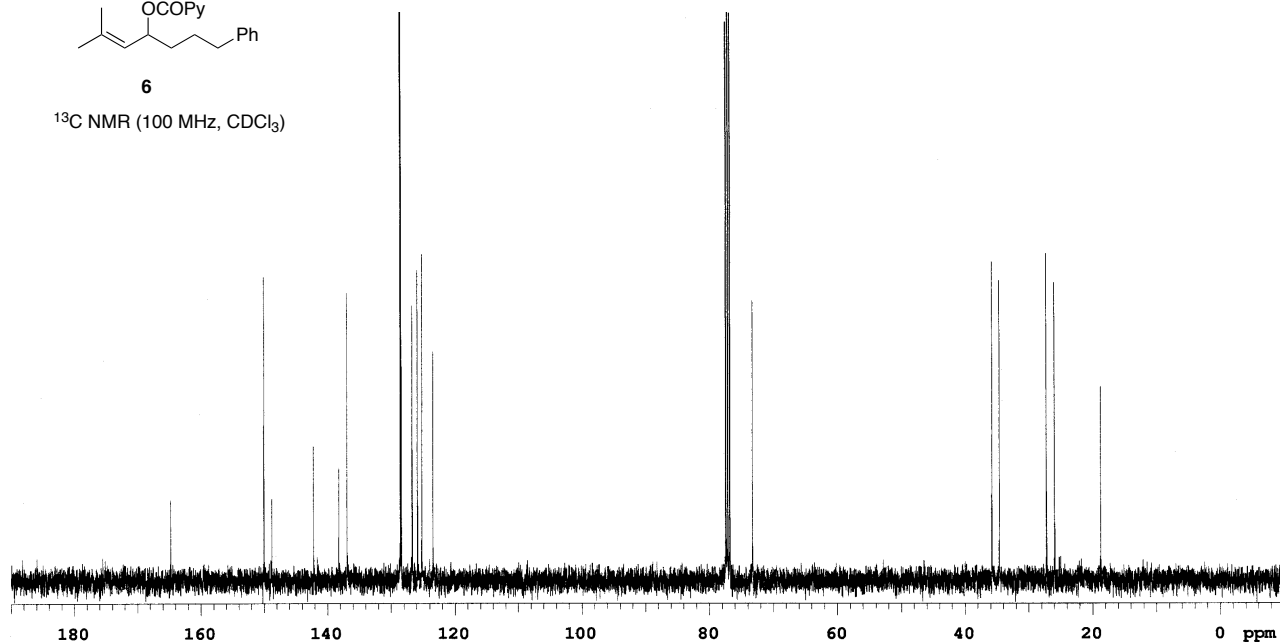
6

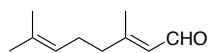
^1H NMR (400 MHz, CDCl_3)



6

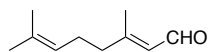
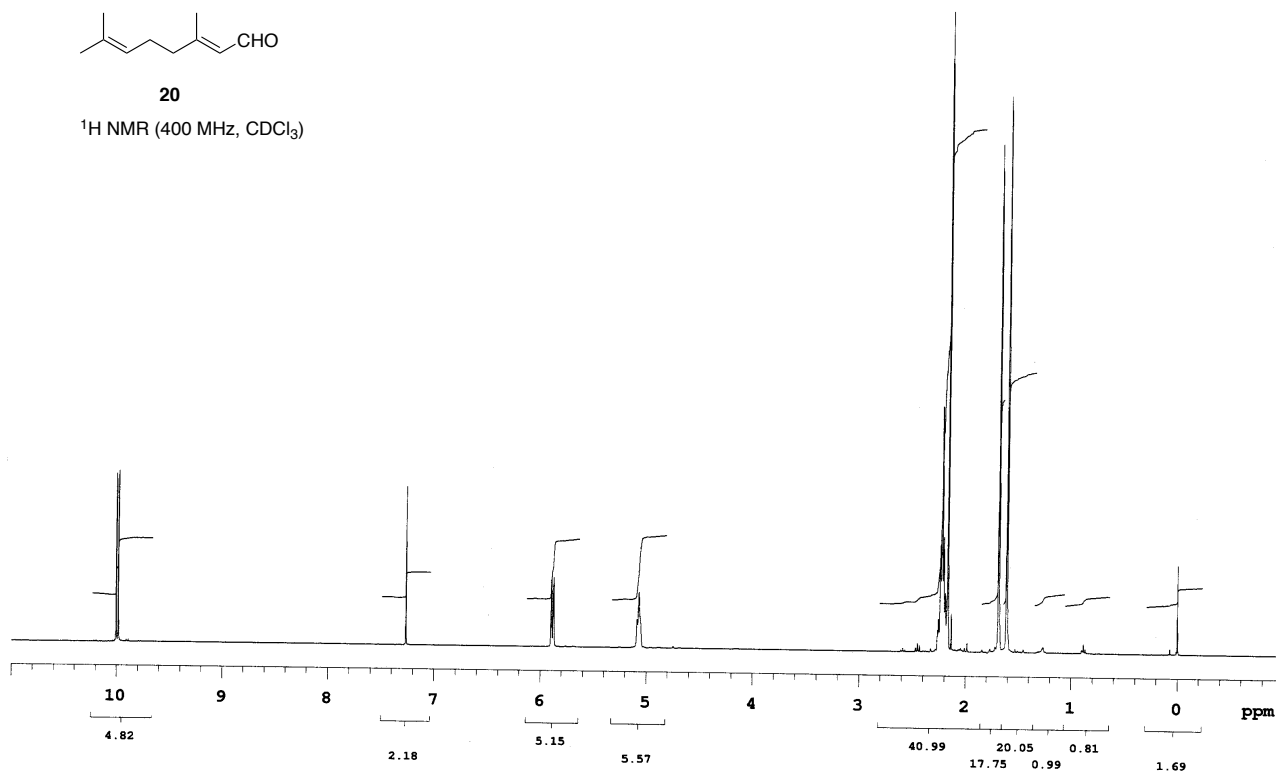
^{13}C NMR (100 MHz, CDCl_3)





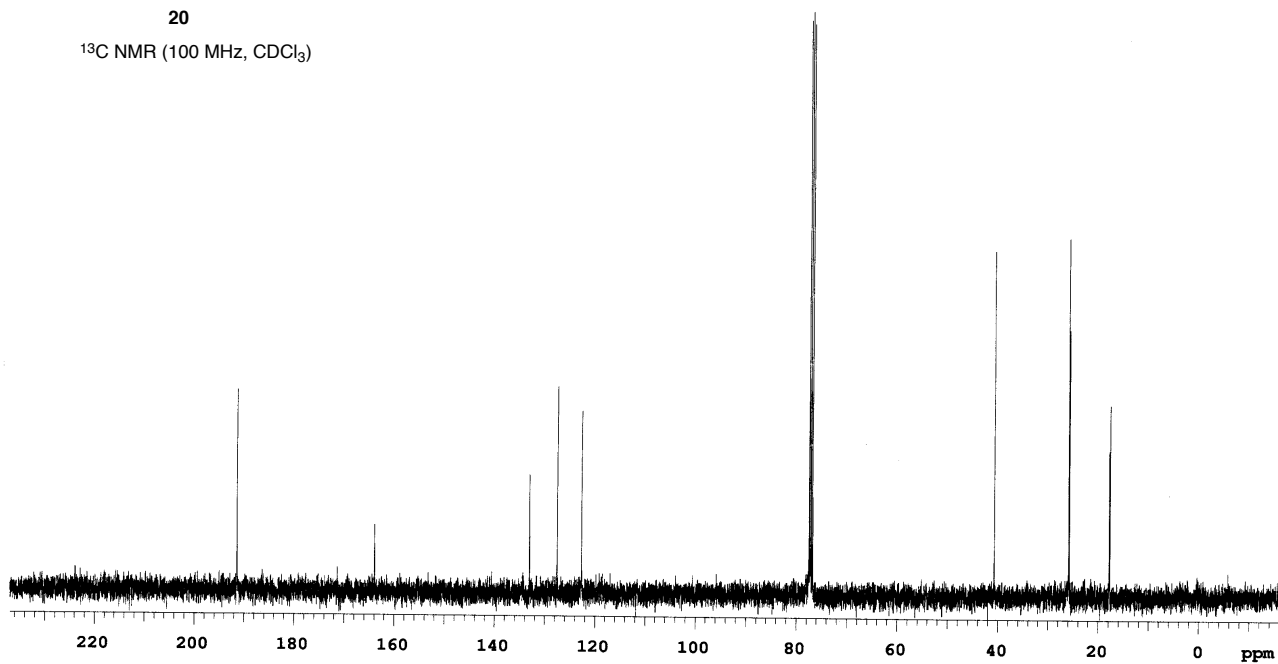
20

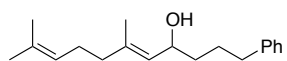
^1H NMR (400 MHz, CDCl_3)



20

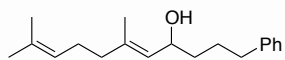
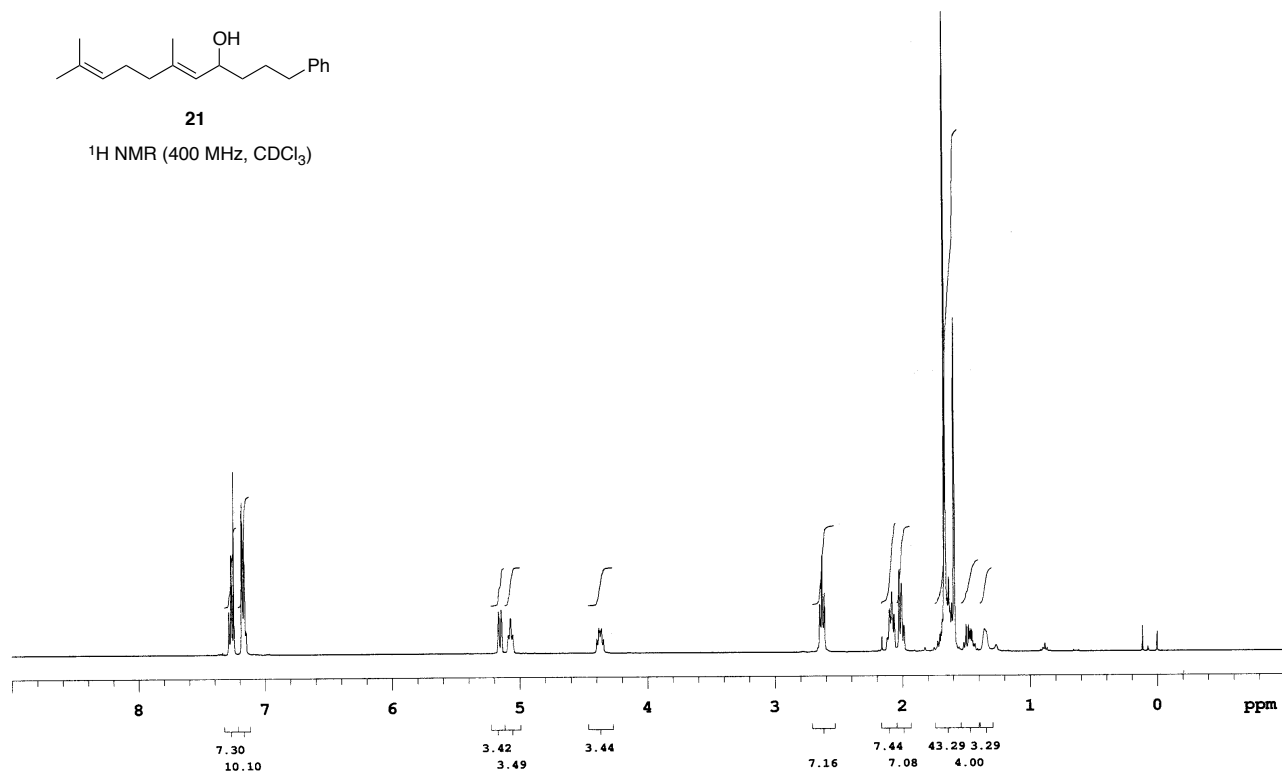
^{13}C NMR (100 MHz, CDCl_3)





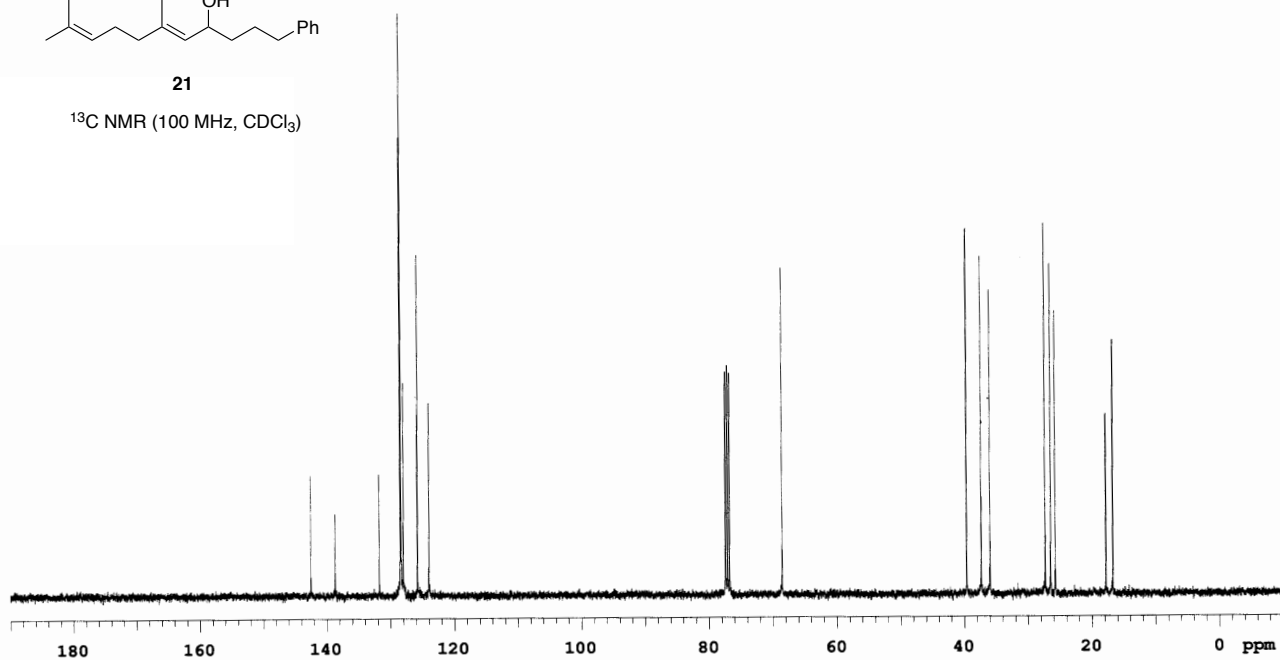
21

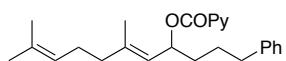
^1H NMR (400 MHz, CDCl_3)



21

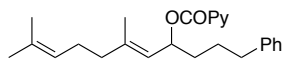
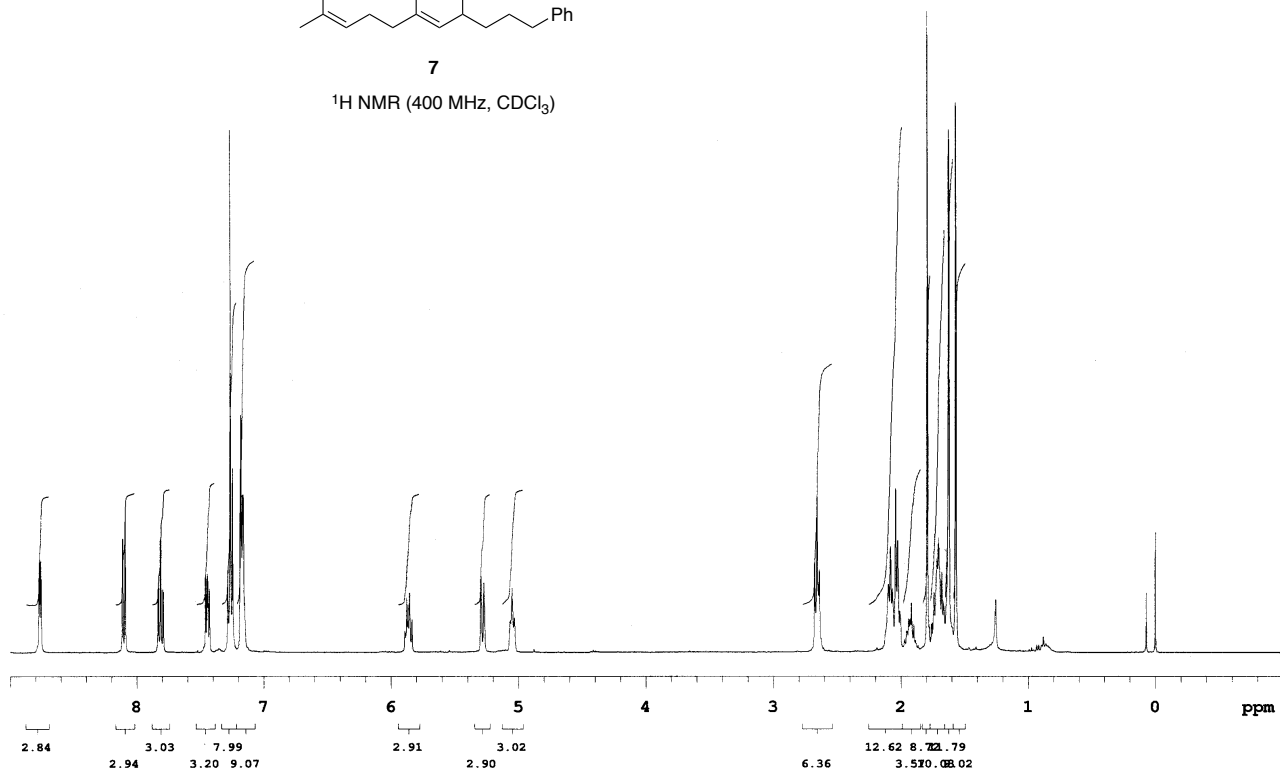
^{13}C NMR (100 MHz, CDCl_3)





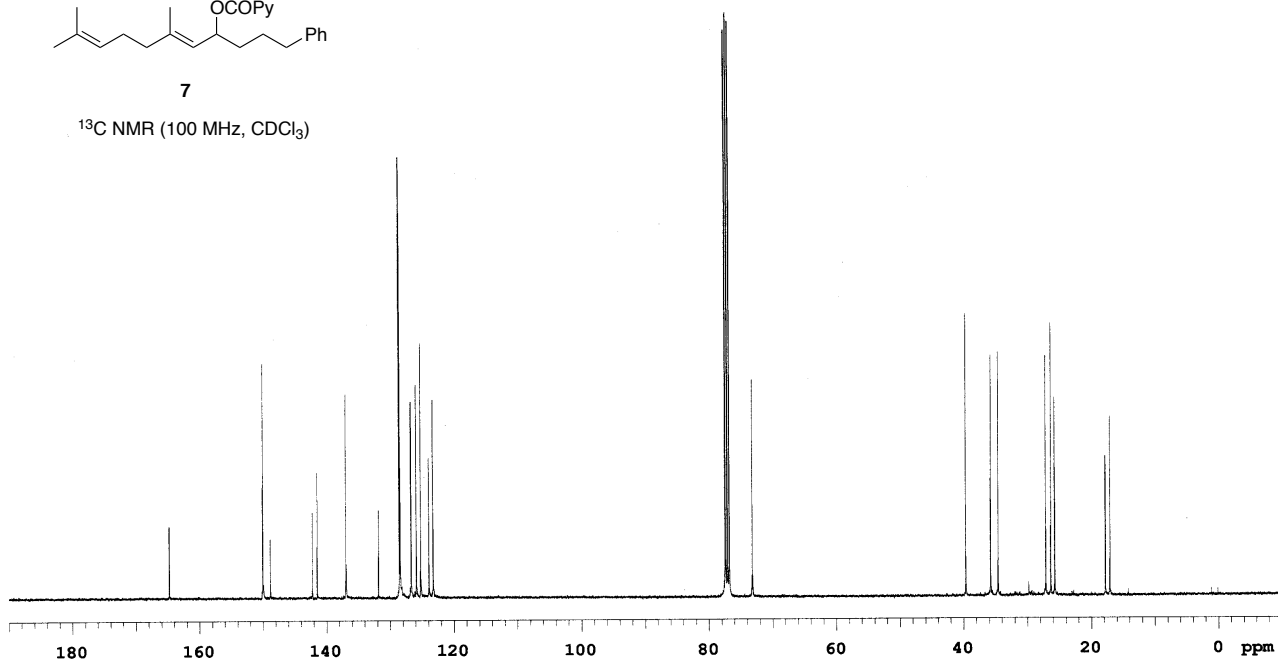
7

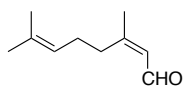
¹H NMR (400 MHz, CDCl₃)



7

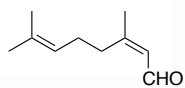
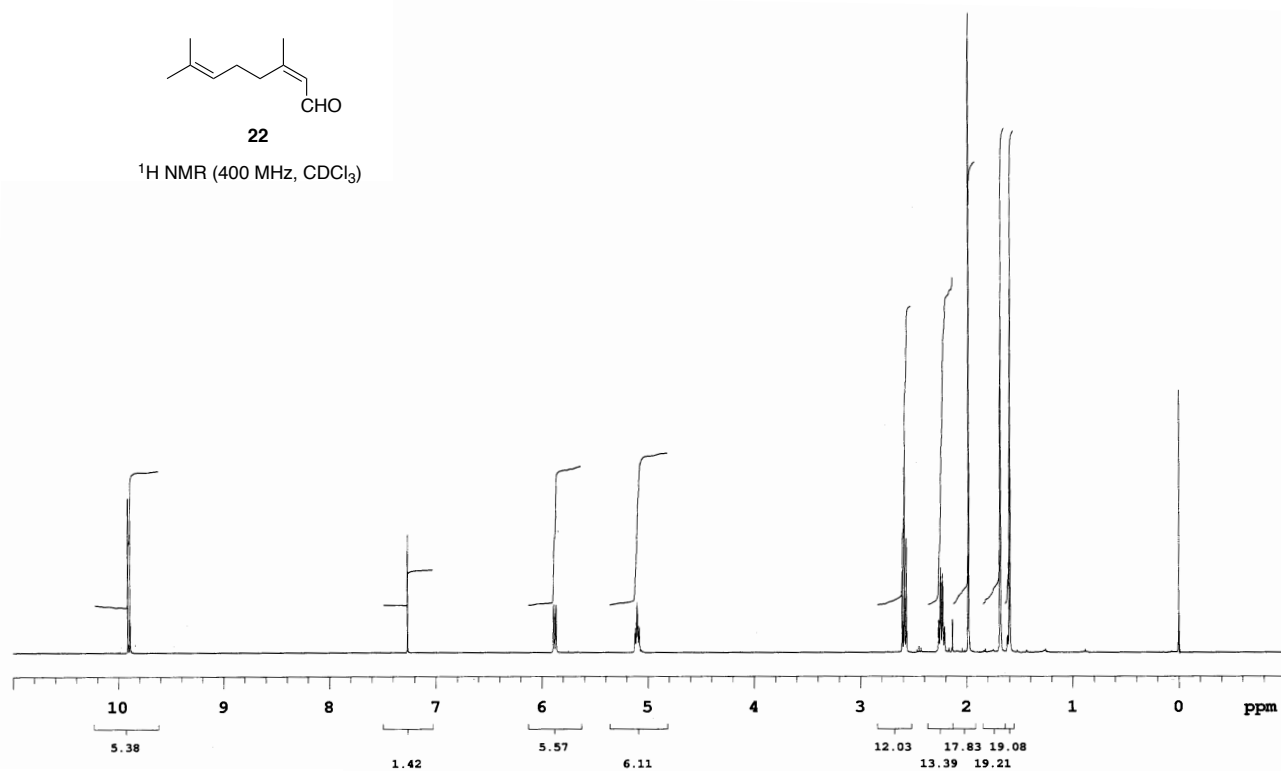
¹³C NMR (100 MHz, CDCl₃)





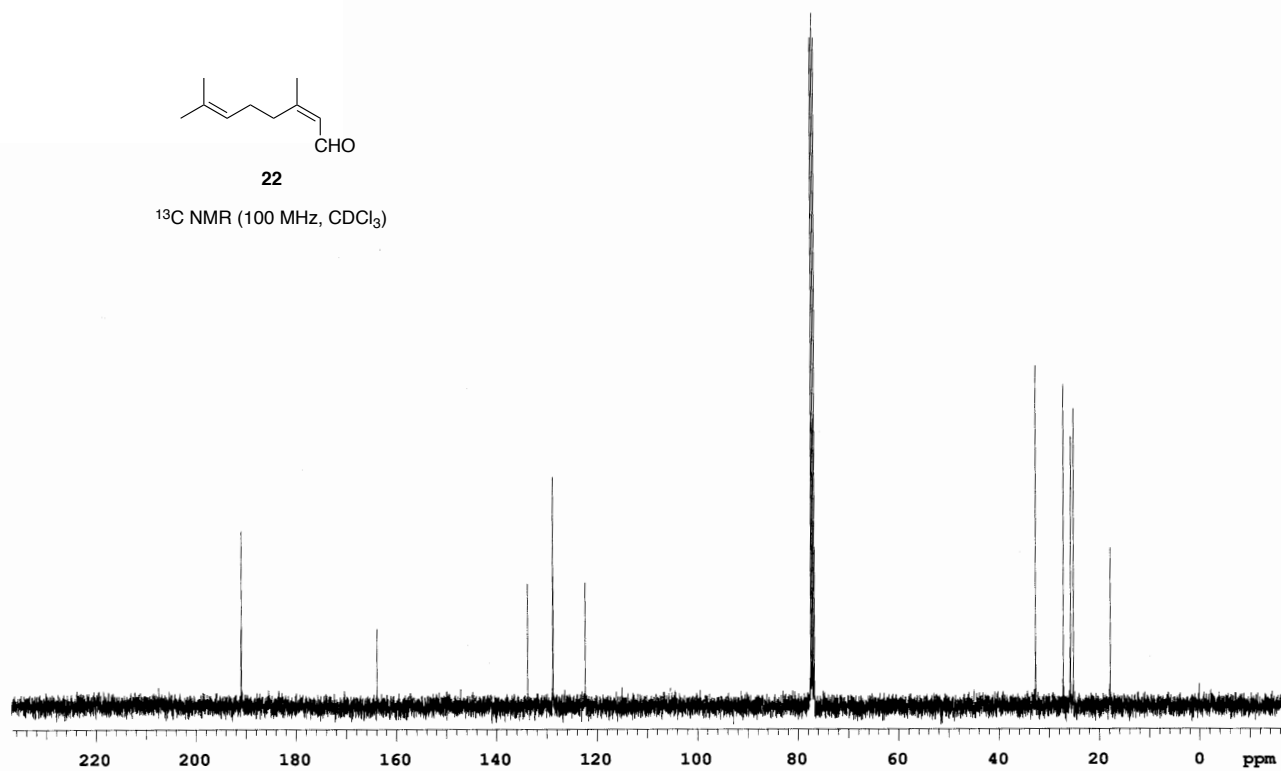
22

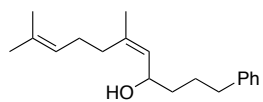
^1H NMR (400 MHz, CDCl_3)



22

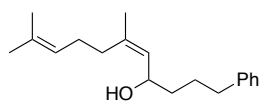
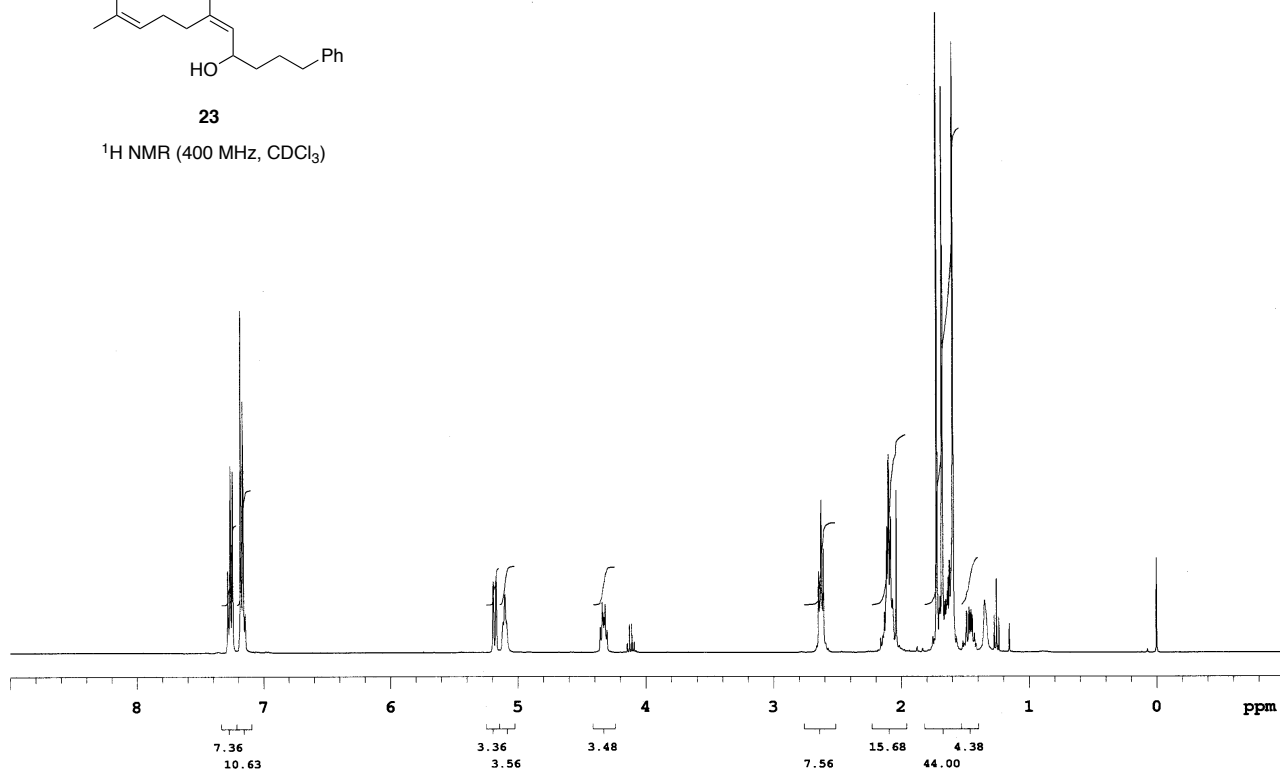
^{13}C NMR (100 MHz, CDCl_3)





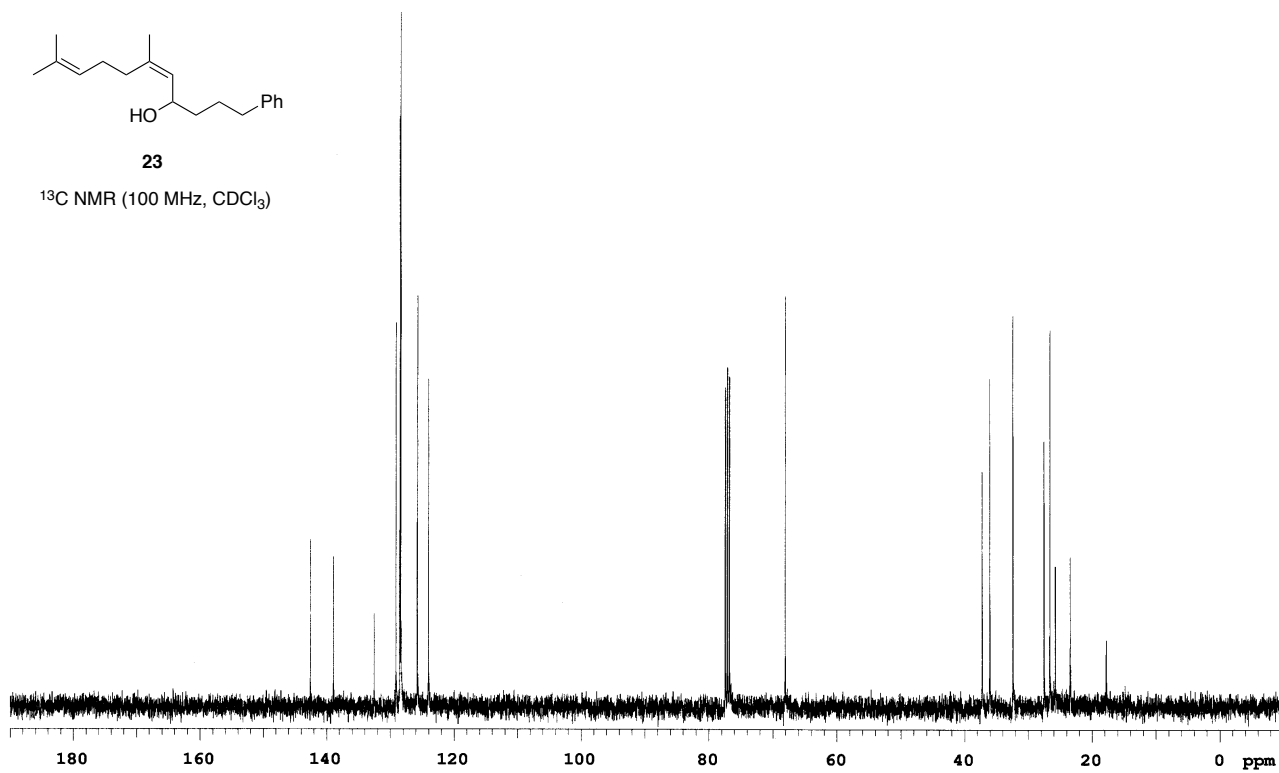
23

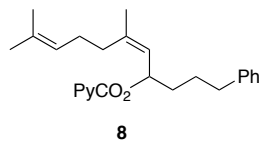
¹H NMR (400 MHz, CDCl₃)



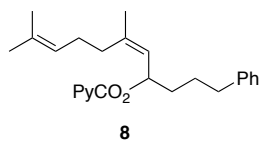
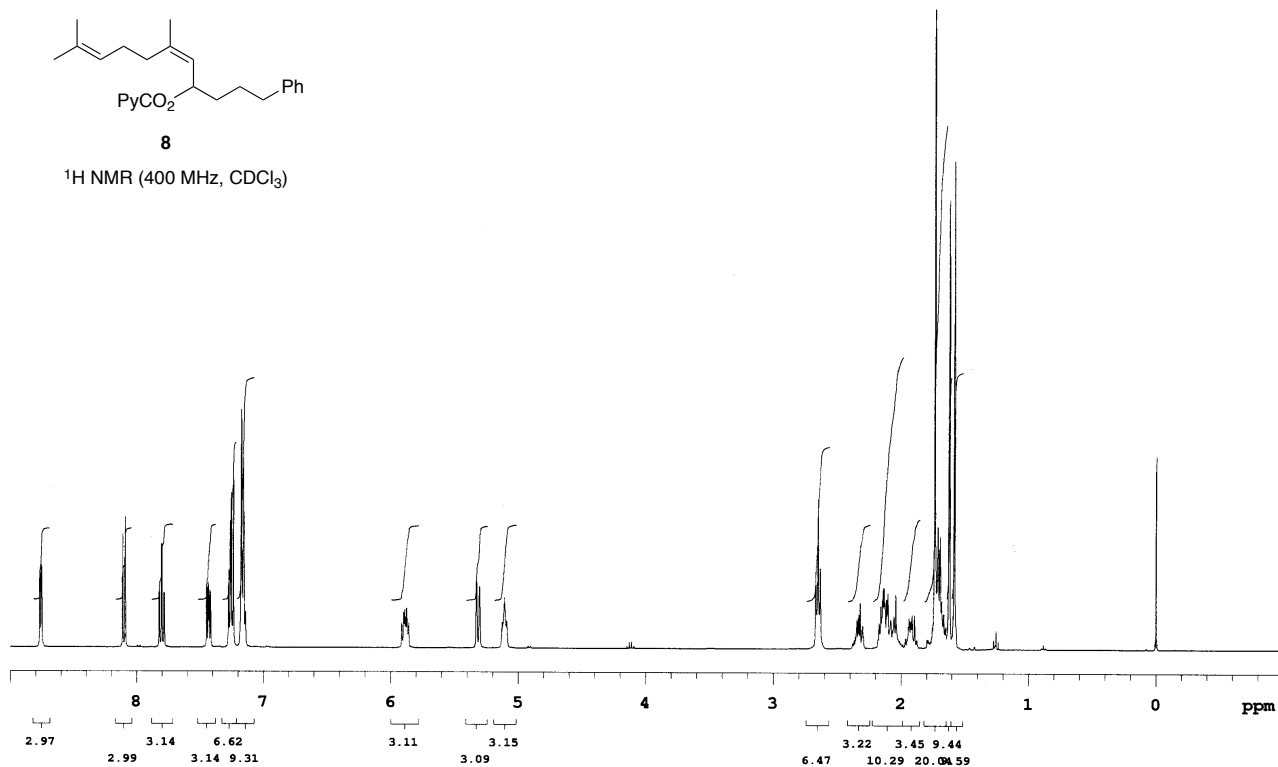
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¹³C NMR (100 MHz, CDCl₃)

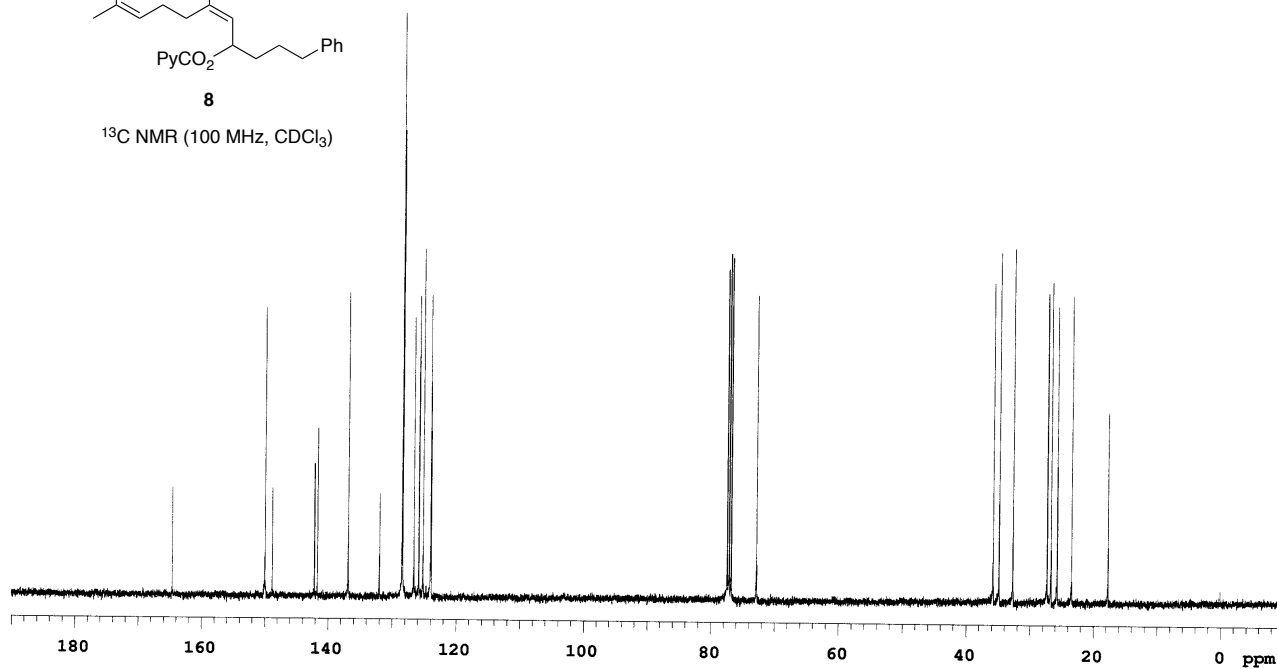


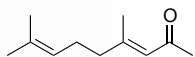


^1H NMR (400 MHz, CDCl_3)

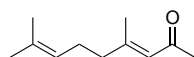
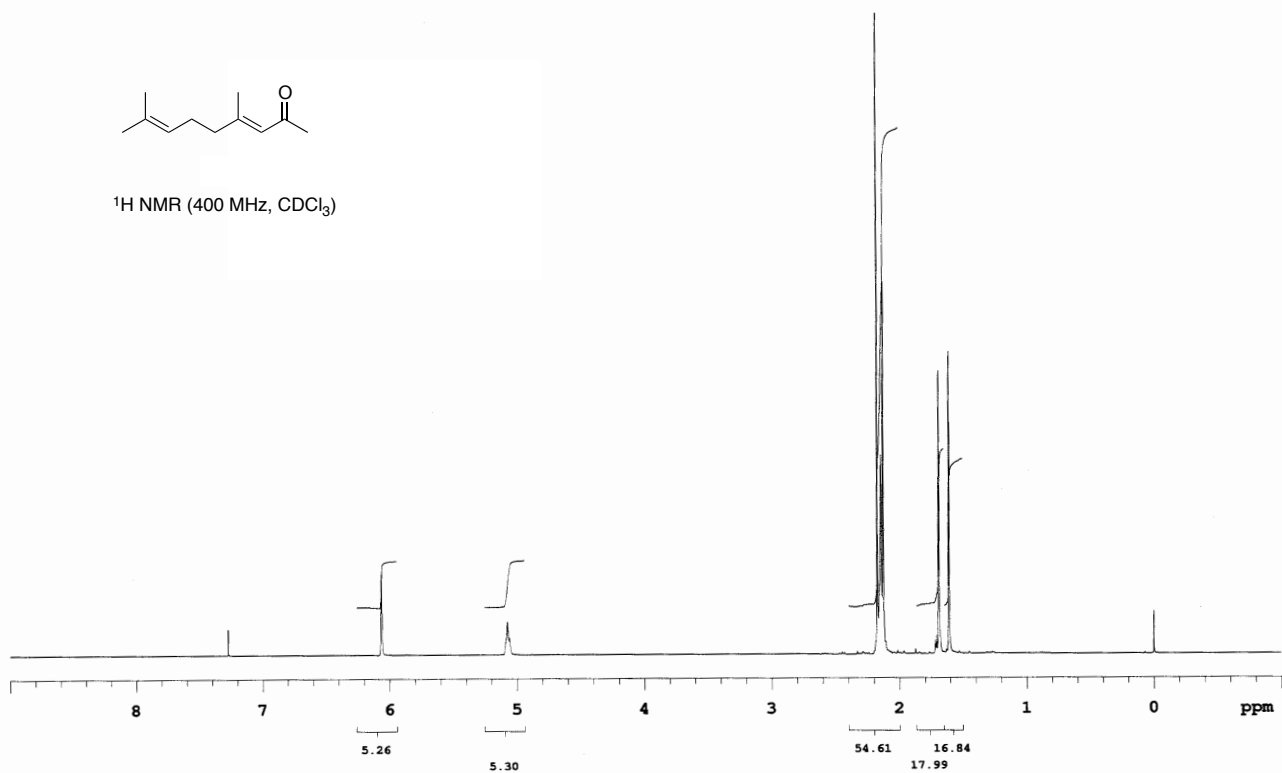


^{13}C NMR (100 MHz, CDCl_3)

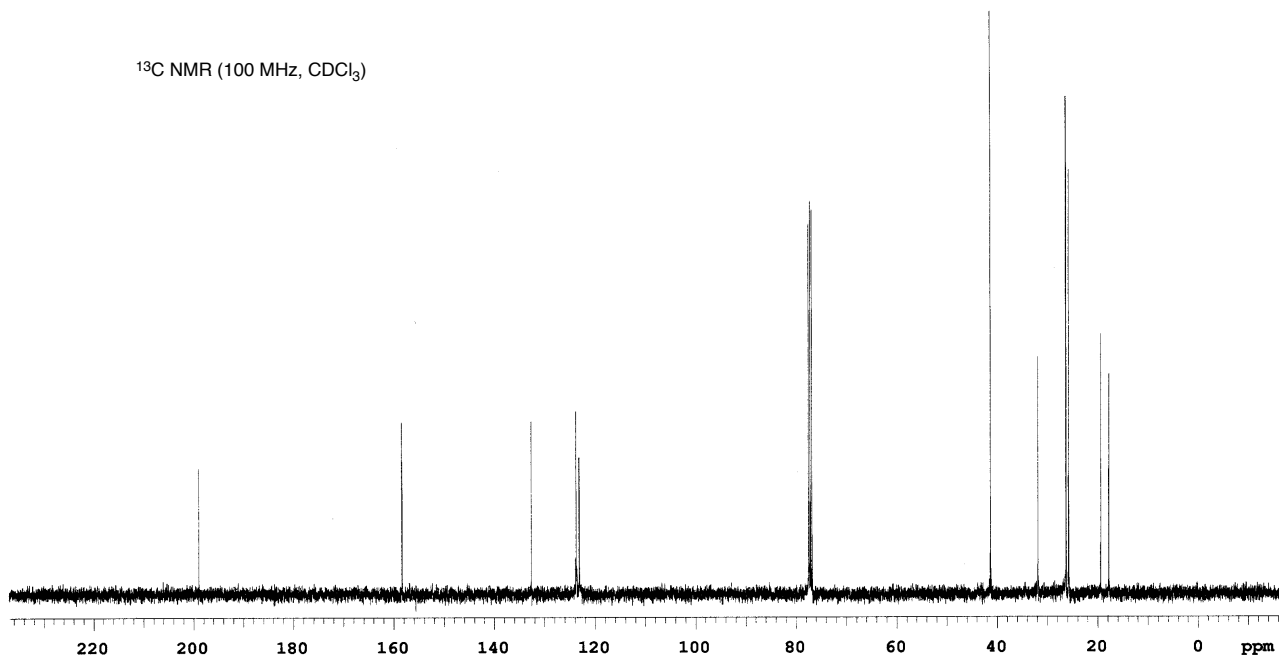


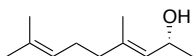


^1H NMR (400 MHz, CDCl_3)



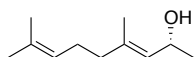
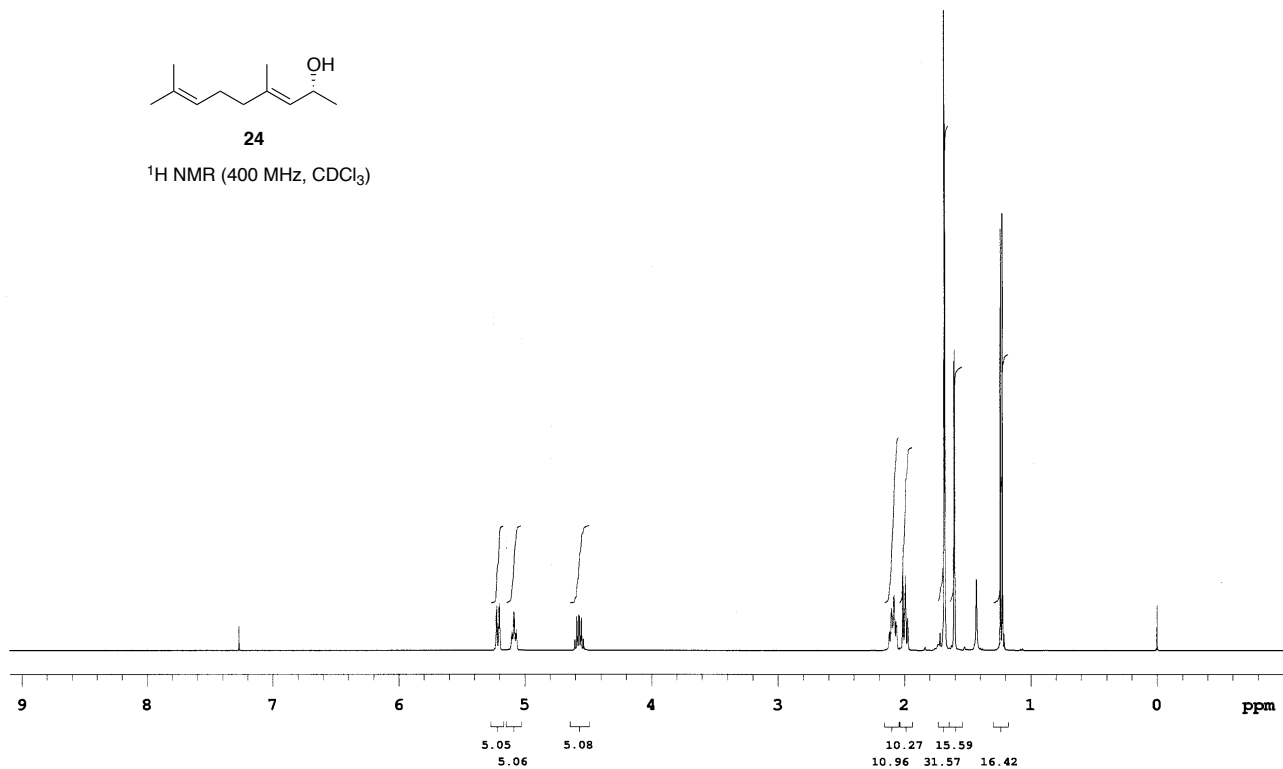
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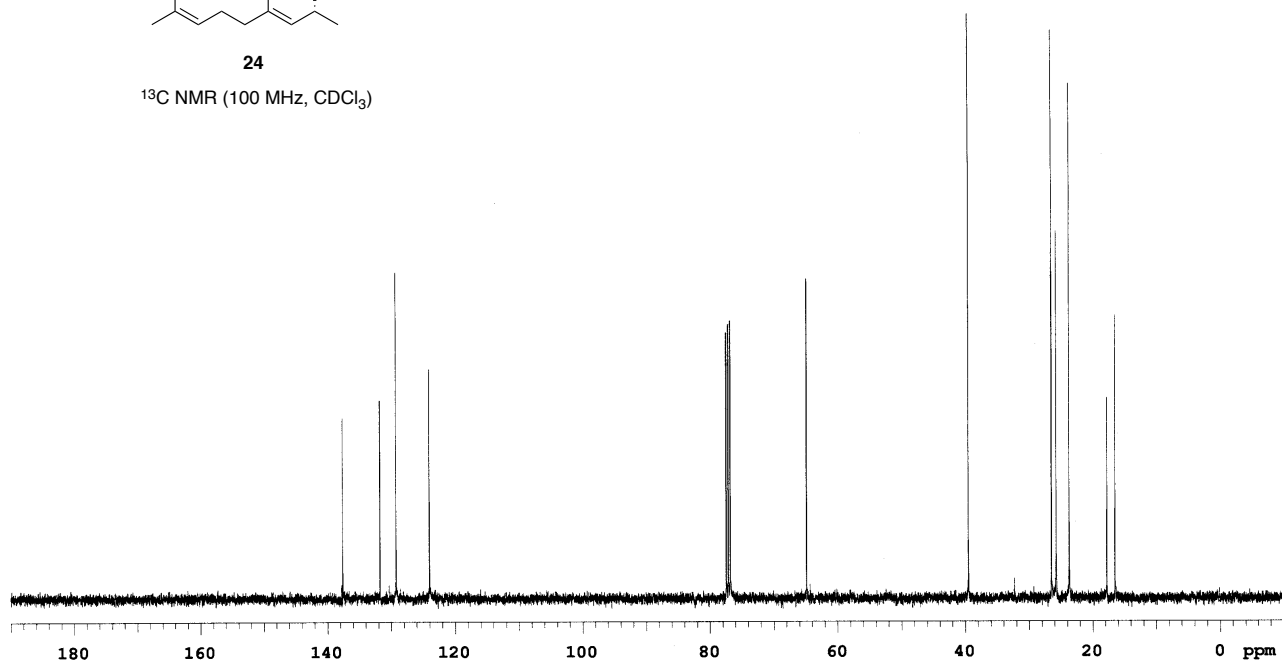
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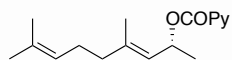
¹H NMR (400 MHz, CDCl₃)



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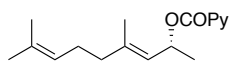
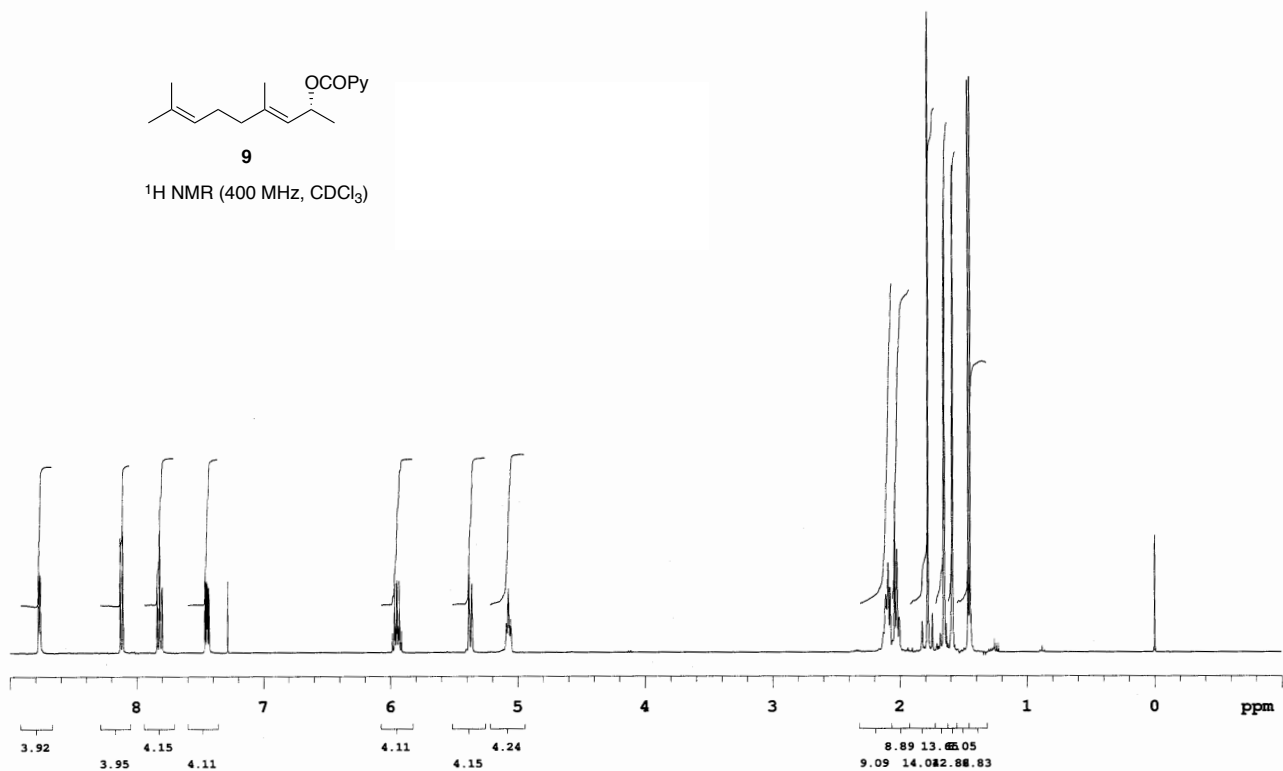
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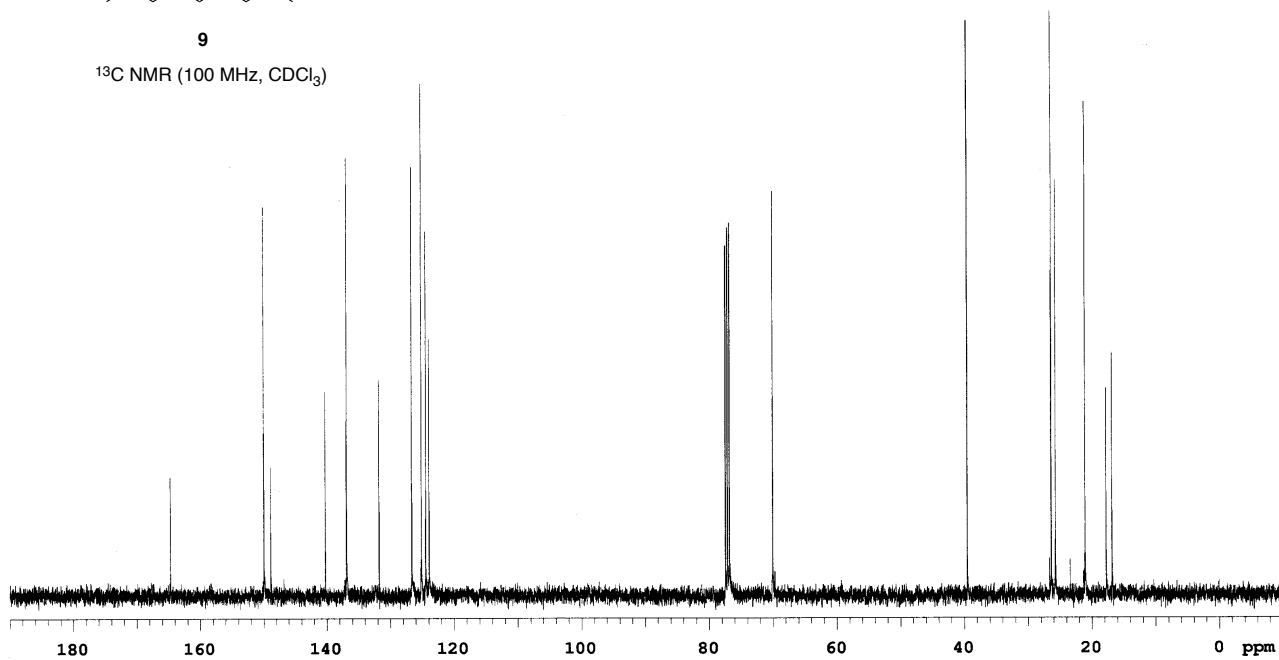
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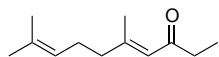
¹H NMR (400 MHz, CDCl₃)



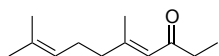
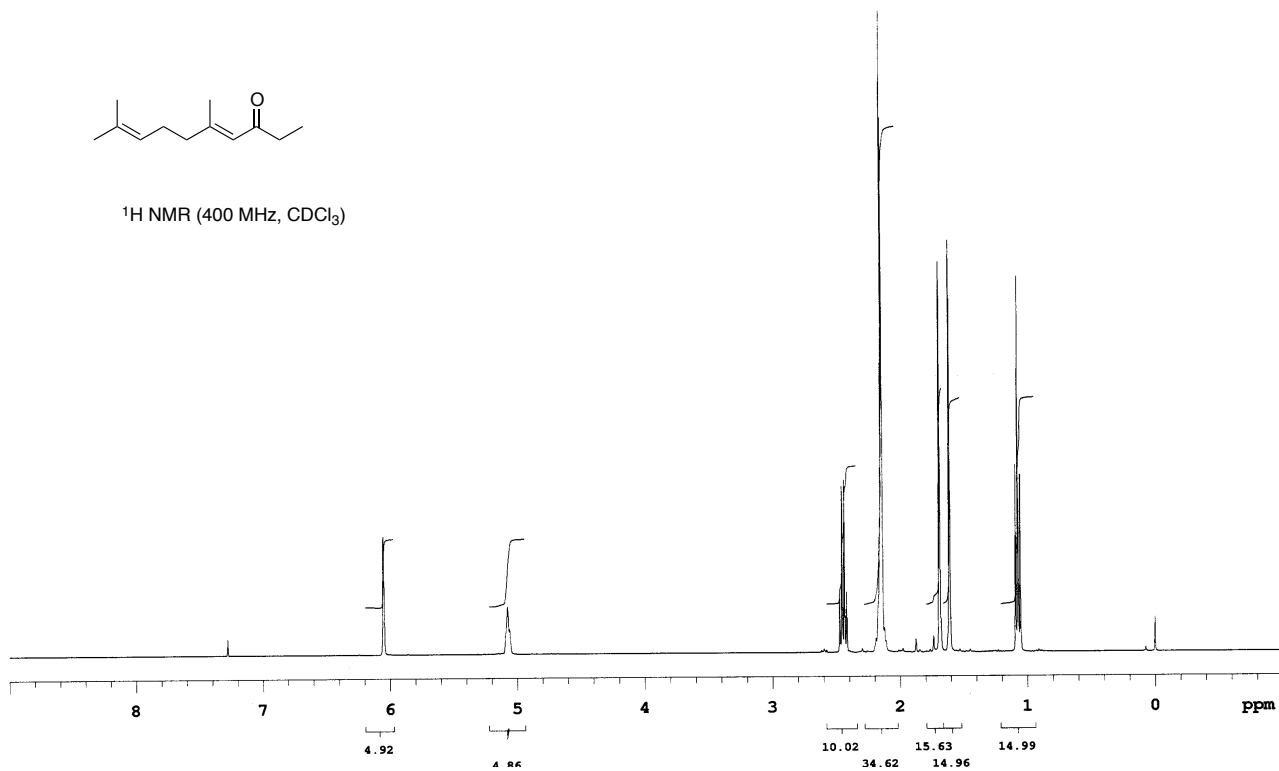
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¹³C NMR (100 MHz, CDCl₃)

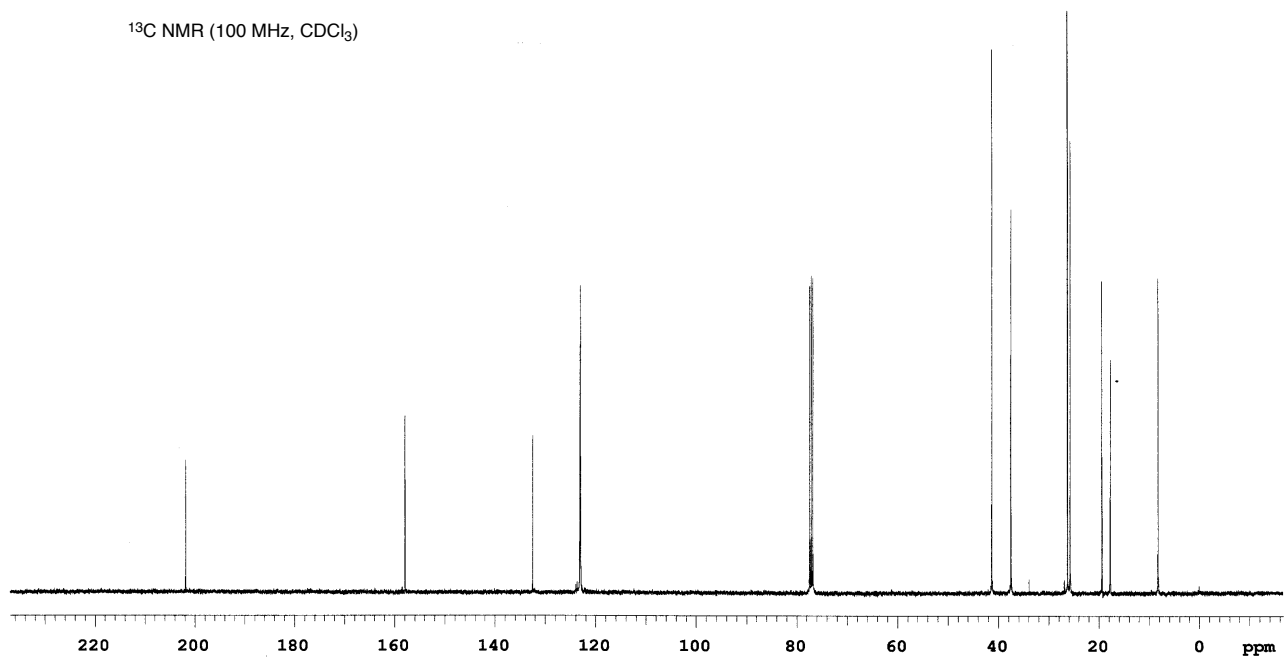


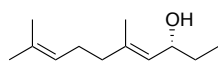


^1H NMR (400 MHz, CDCl_3)



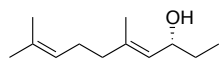
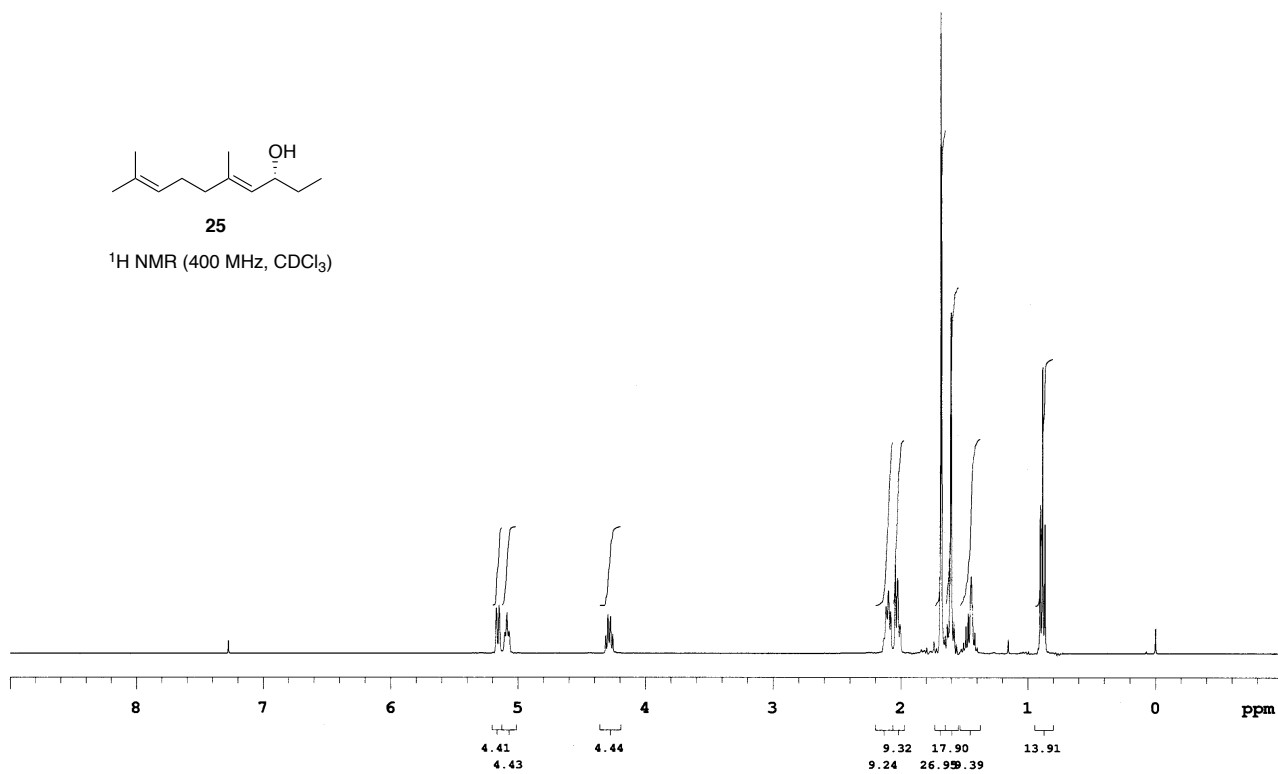
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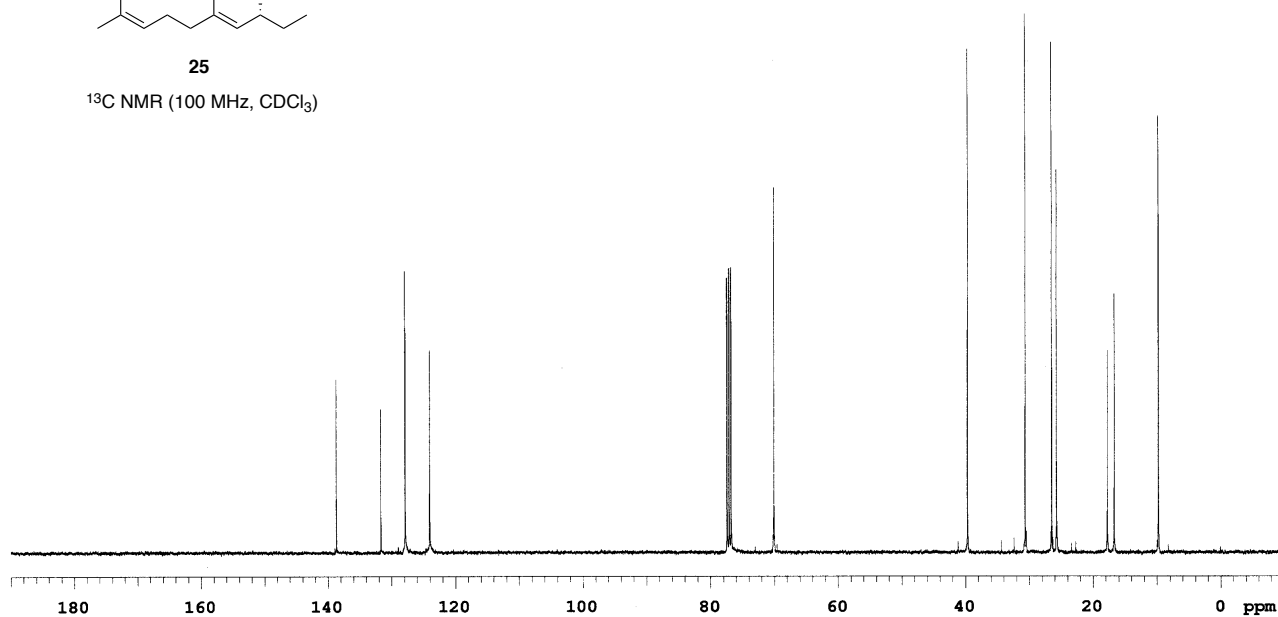
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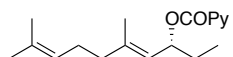
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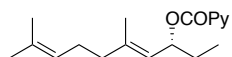
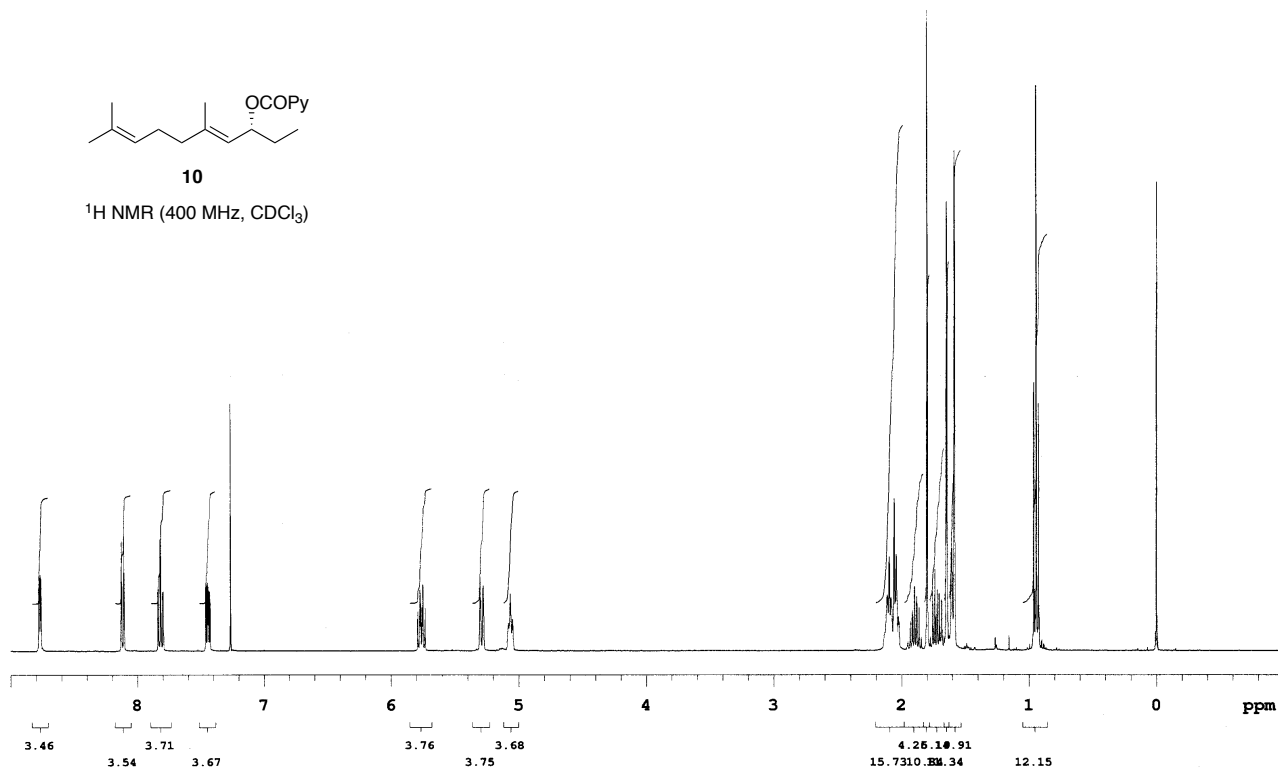
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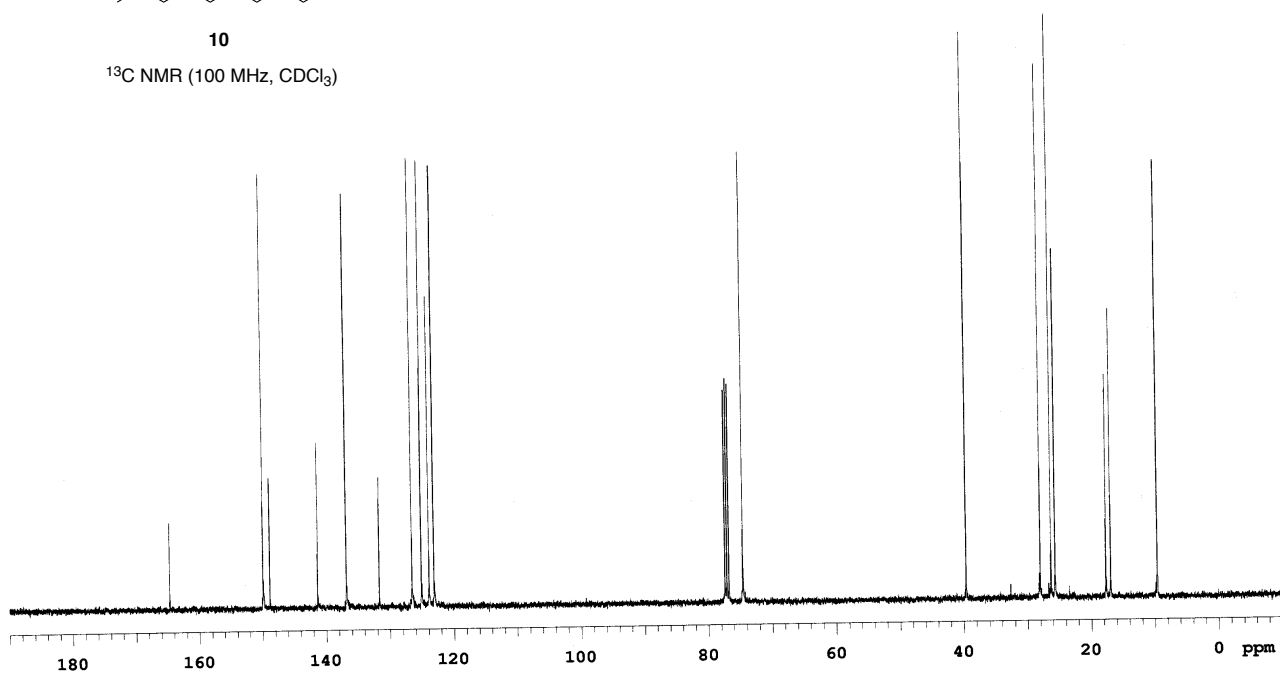
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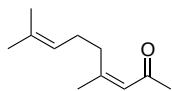
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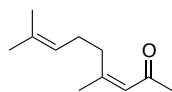
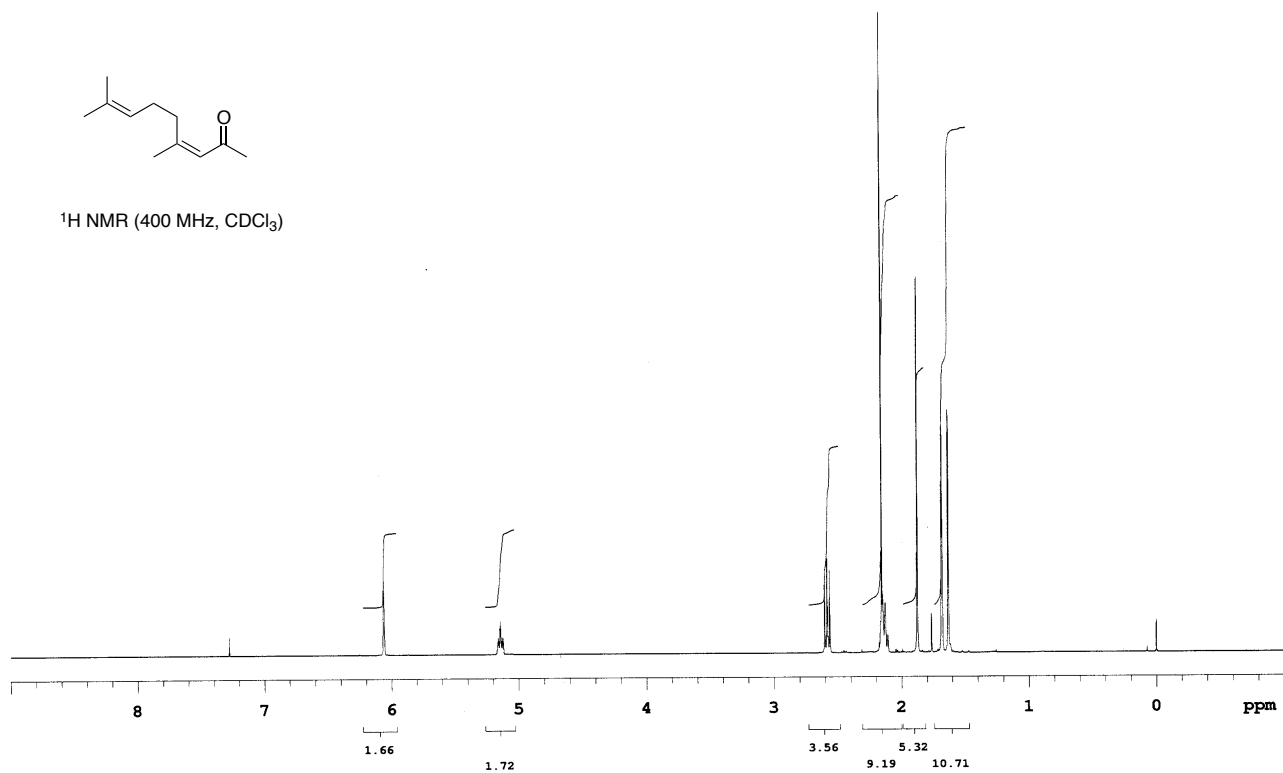
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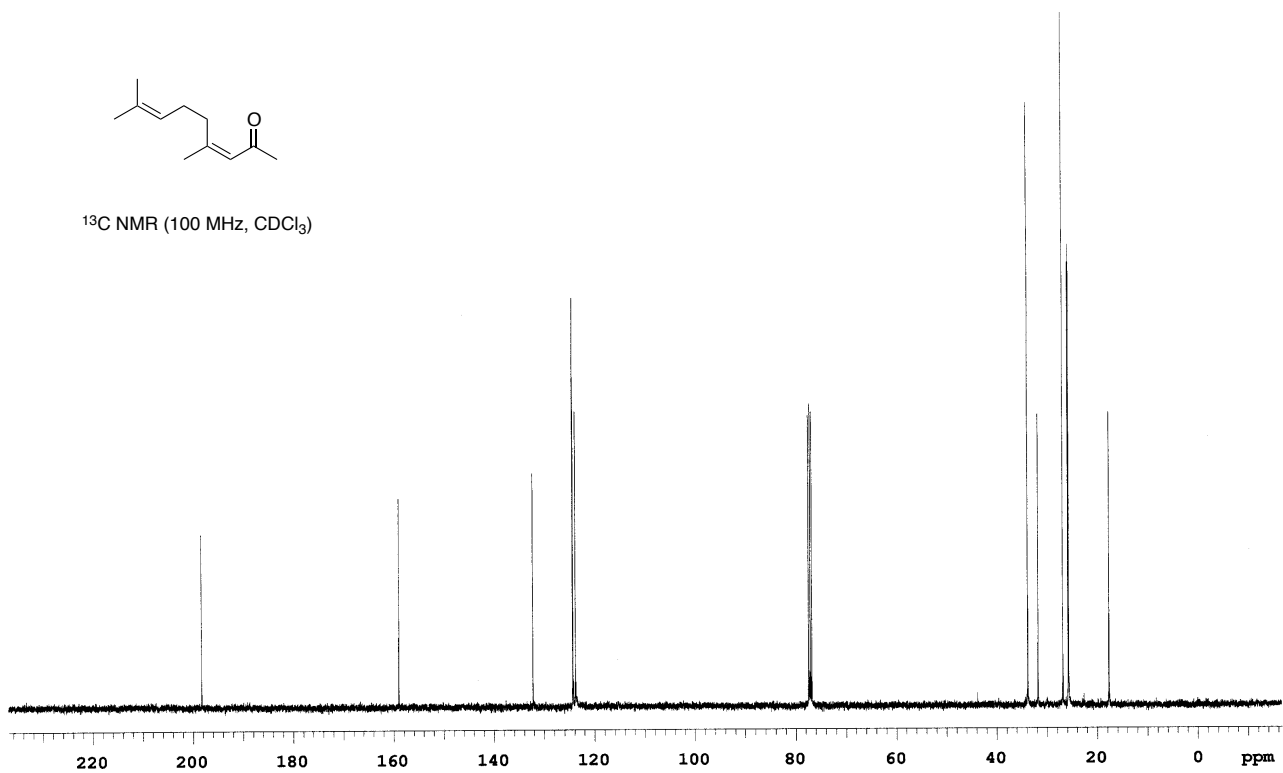


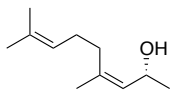


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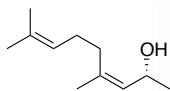
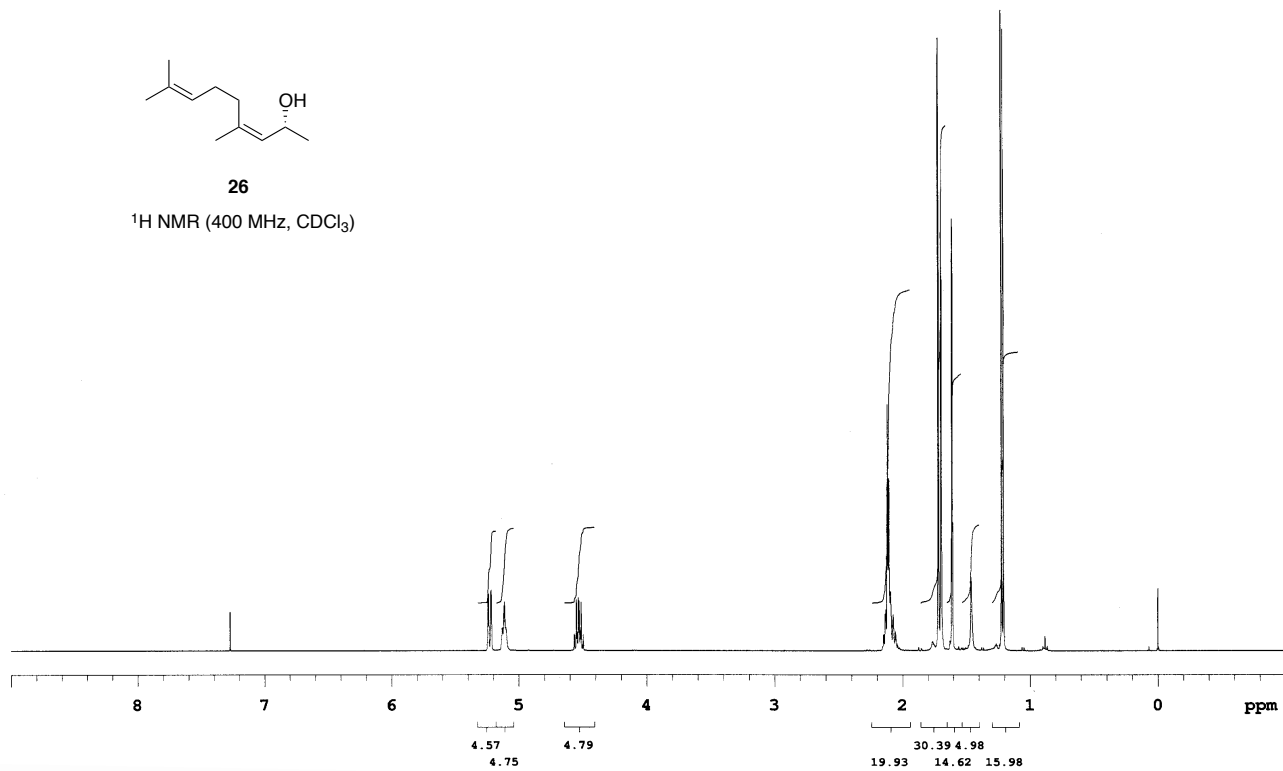
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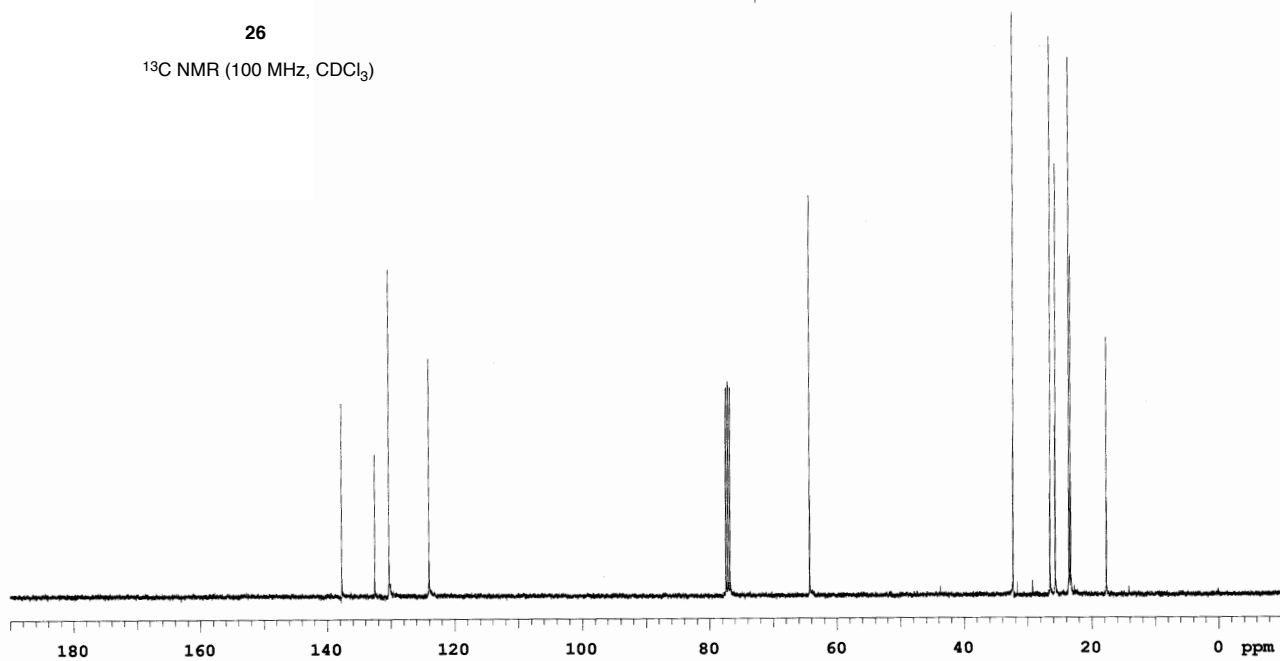
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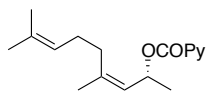
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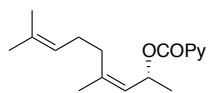
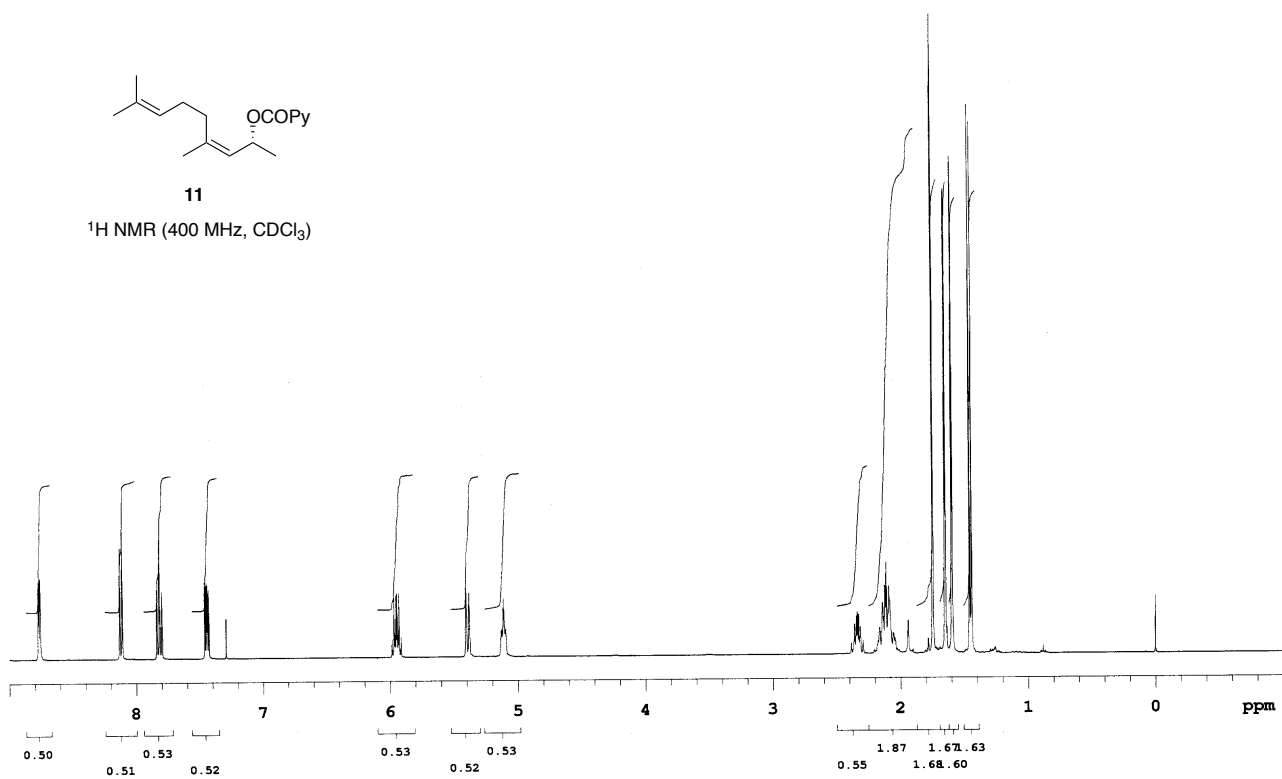
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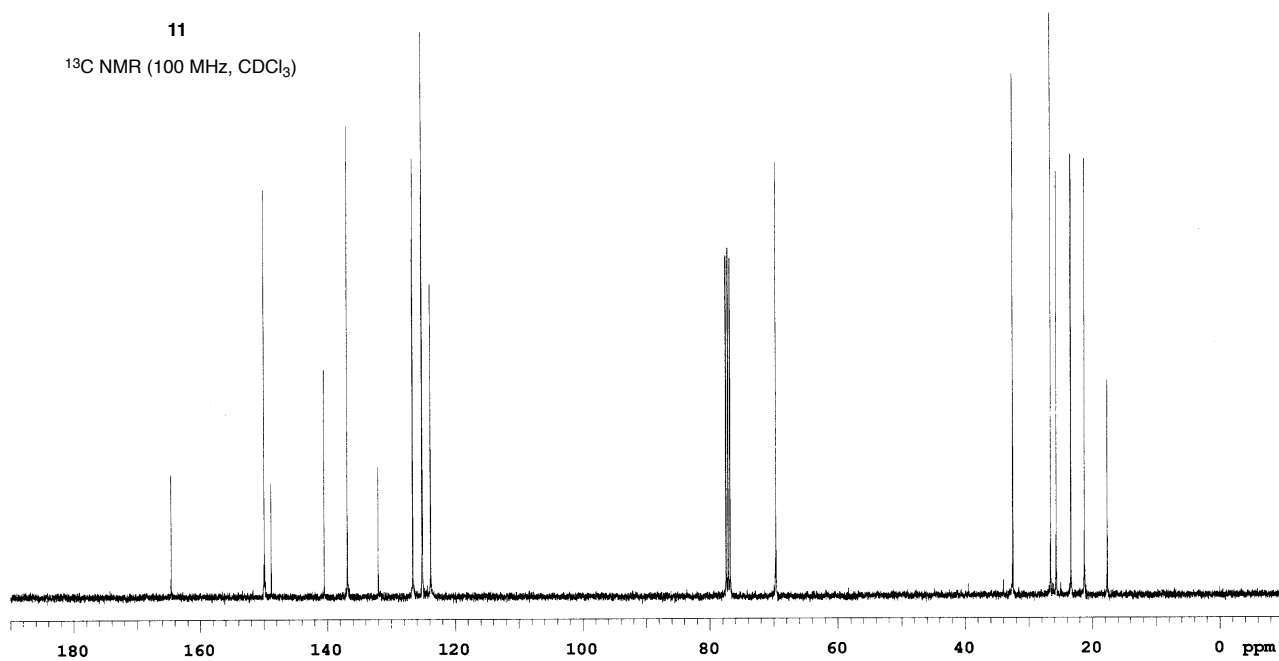
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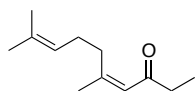
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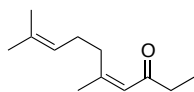
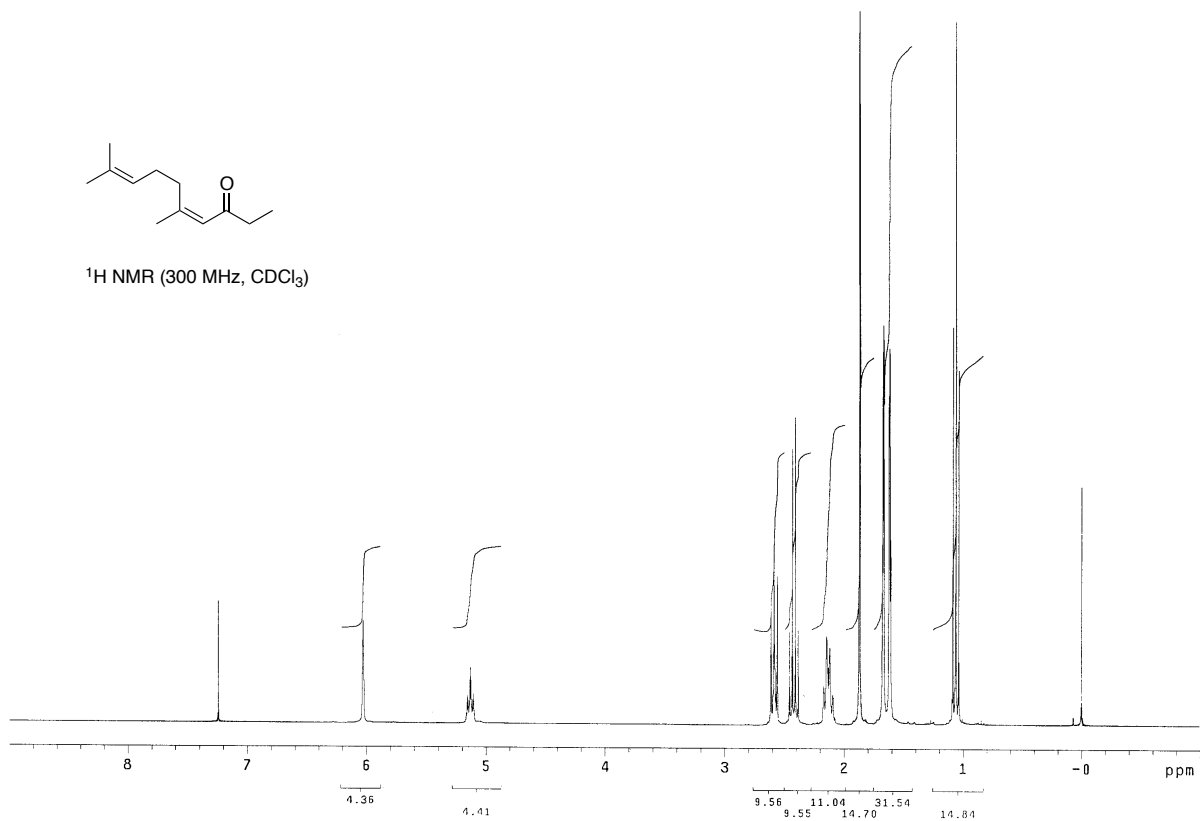
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^{13}C NMR (100 MHz, CDCl_3)

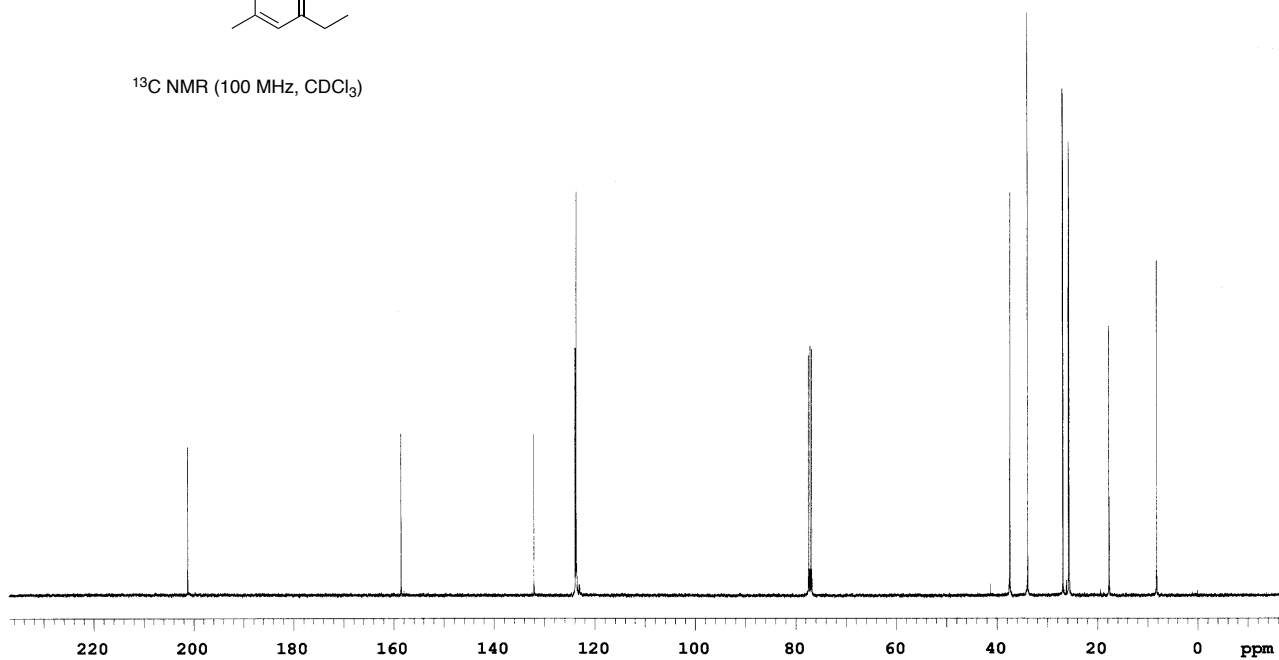


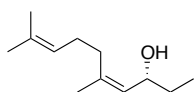


^1H NMR (300 MHz, CDCl_3)



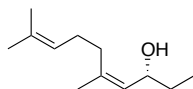
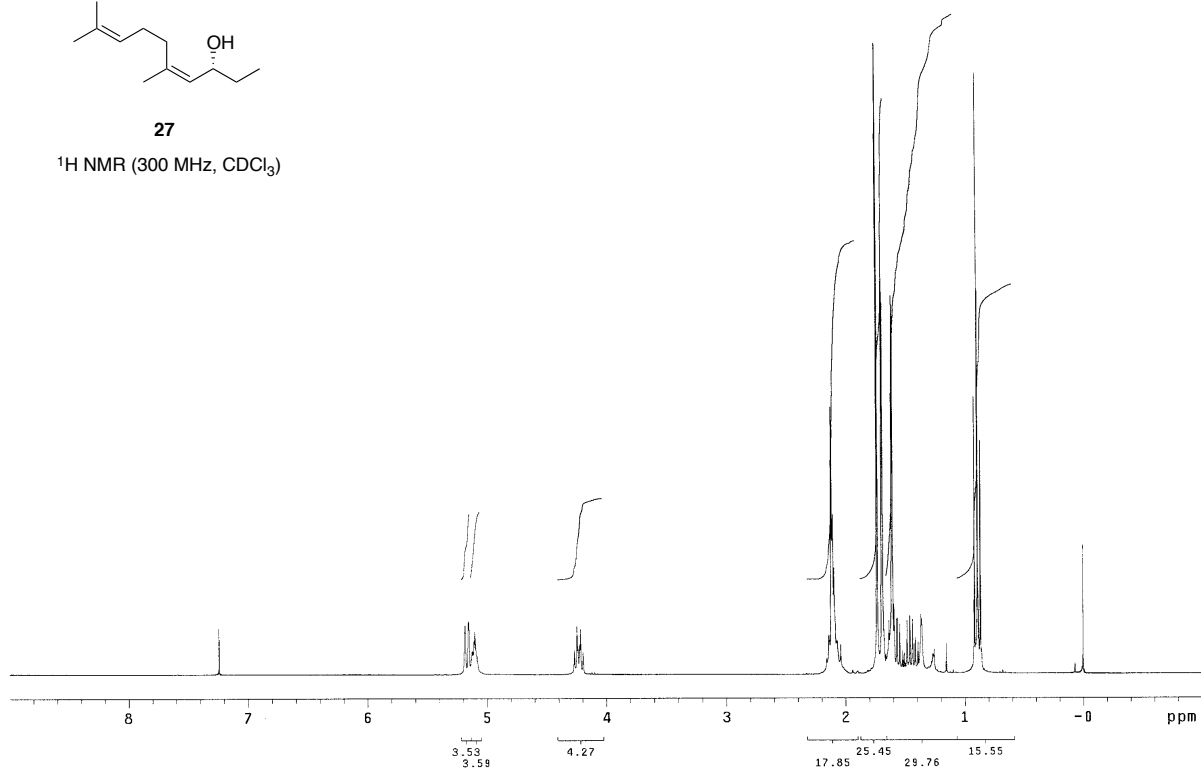
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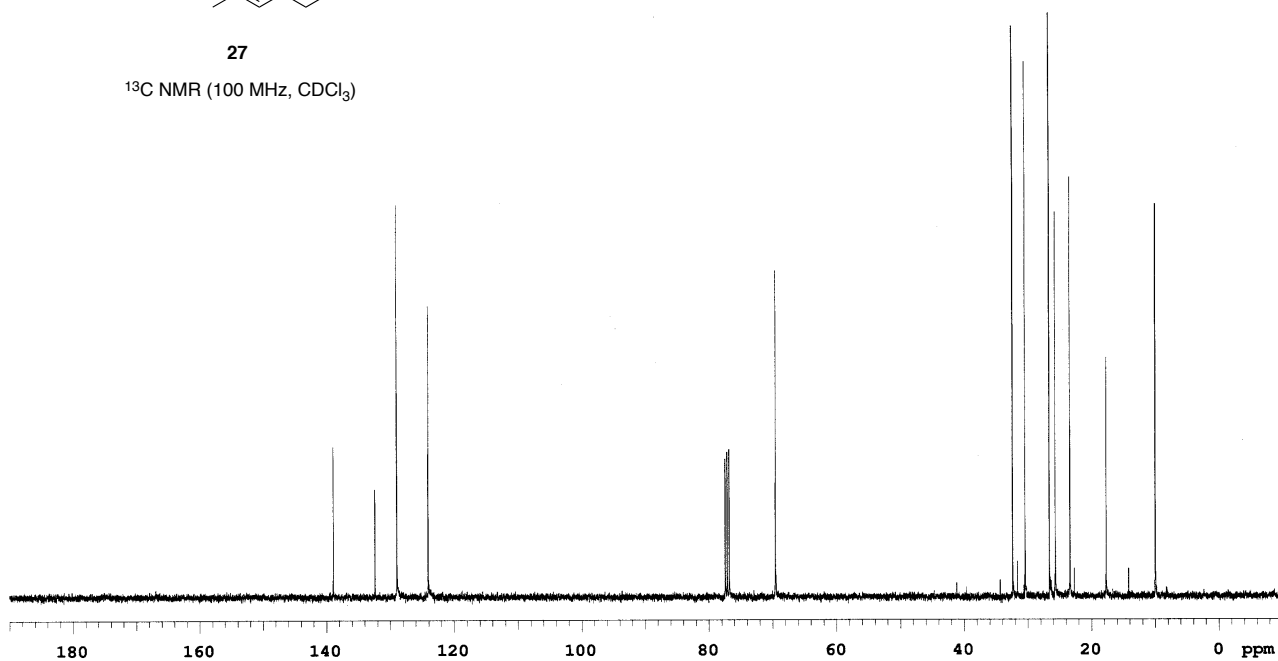
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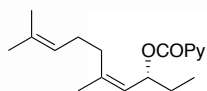
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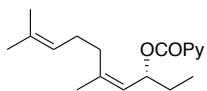
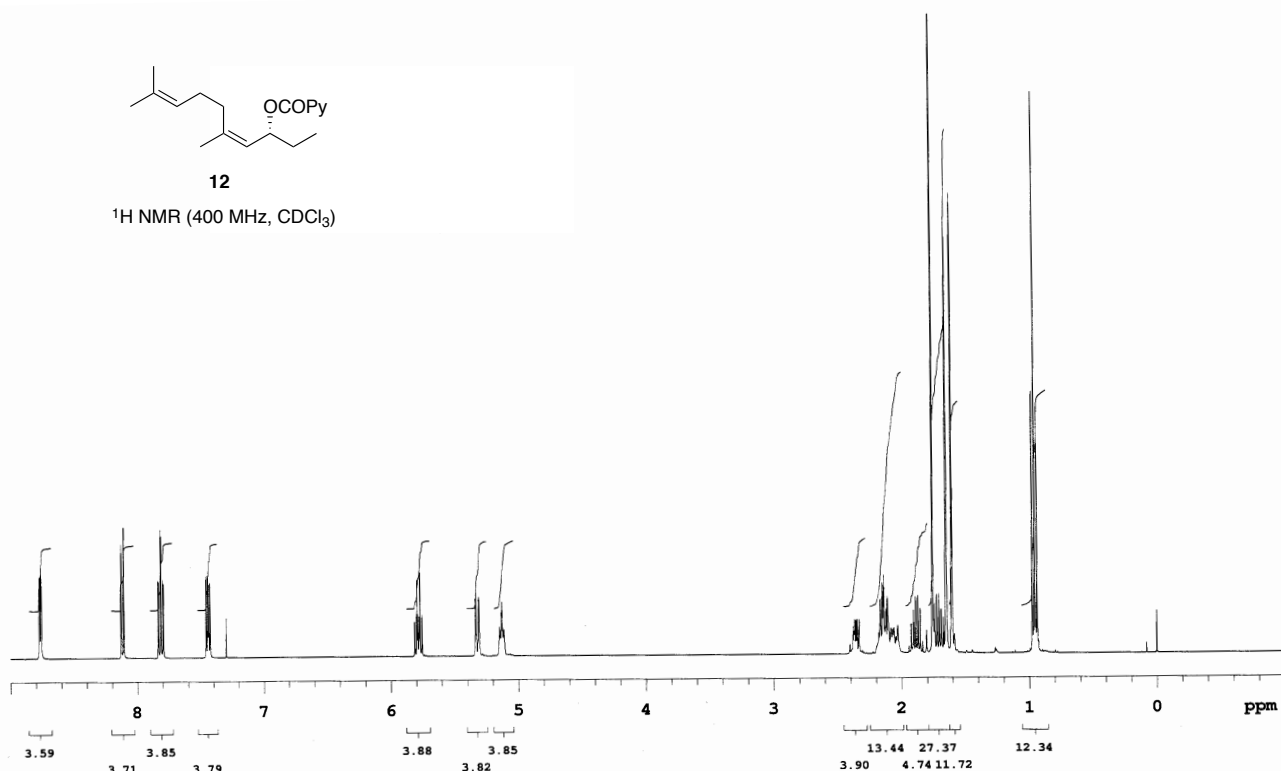
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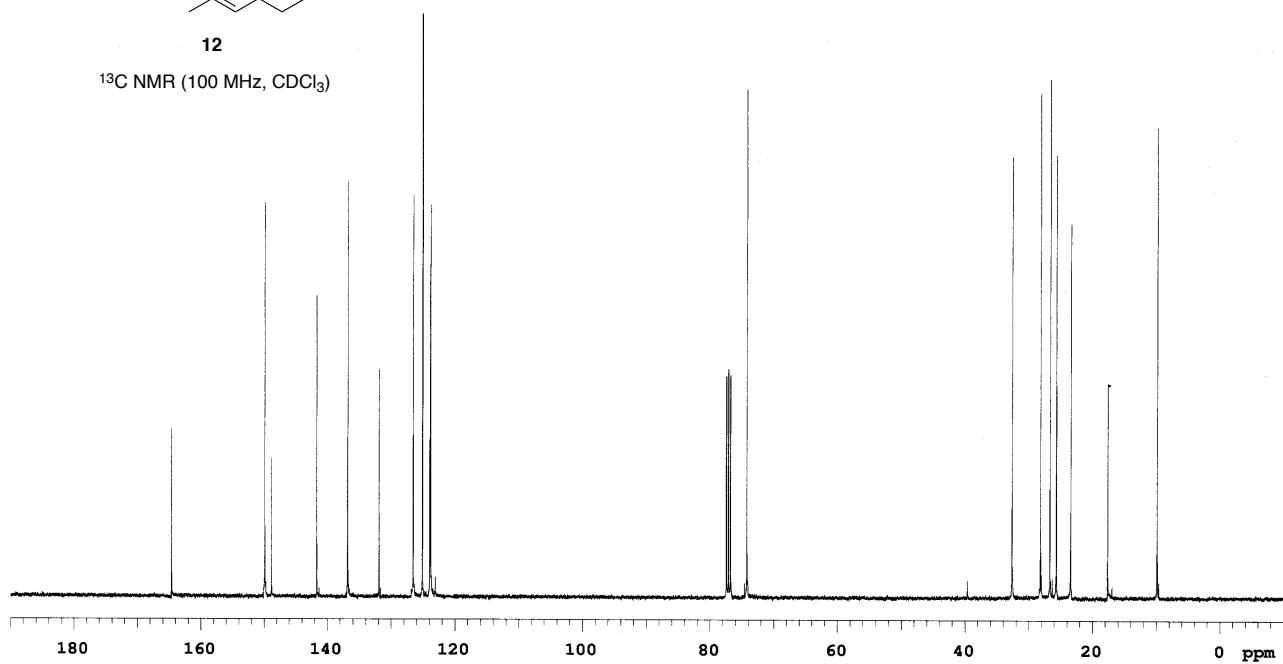
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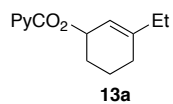
¹H NMR (400 MHz, CDCl₃)



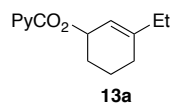
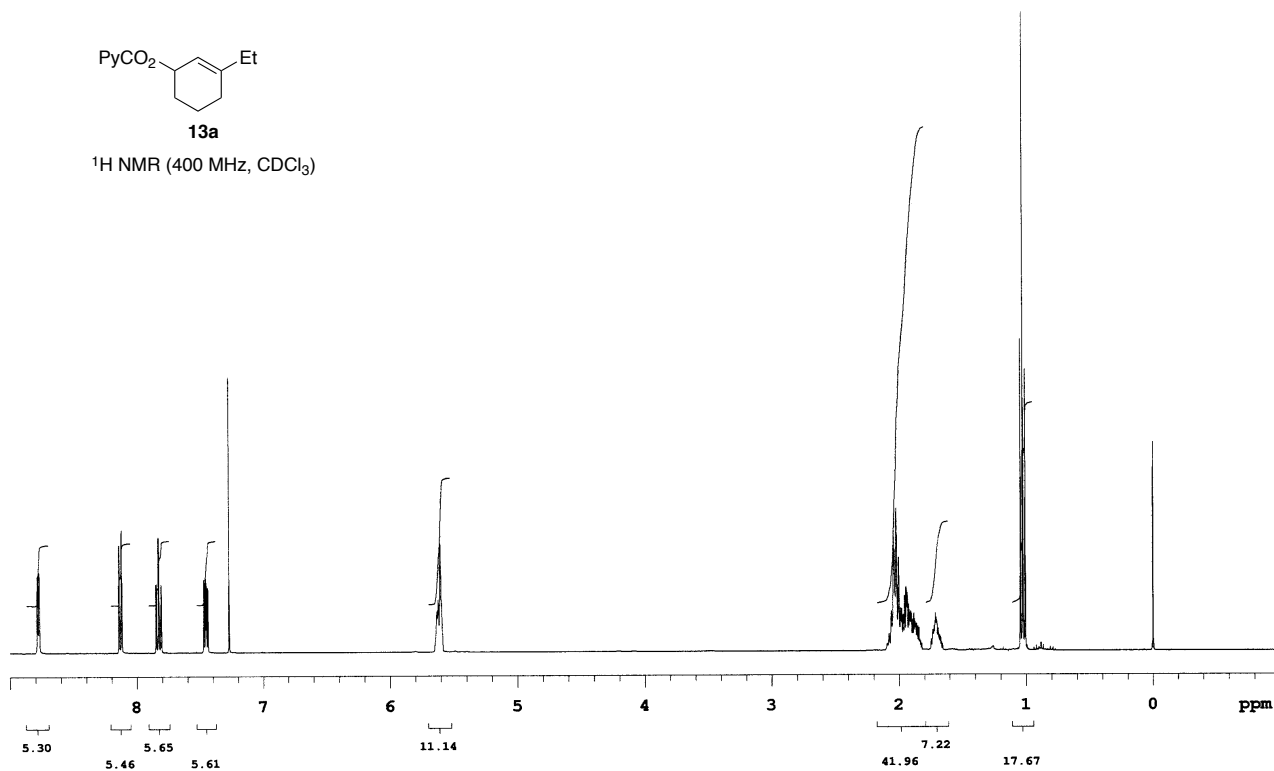
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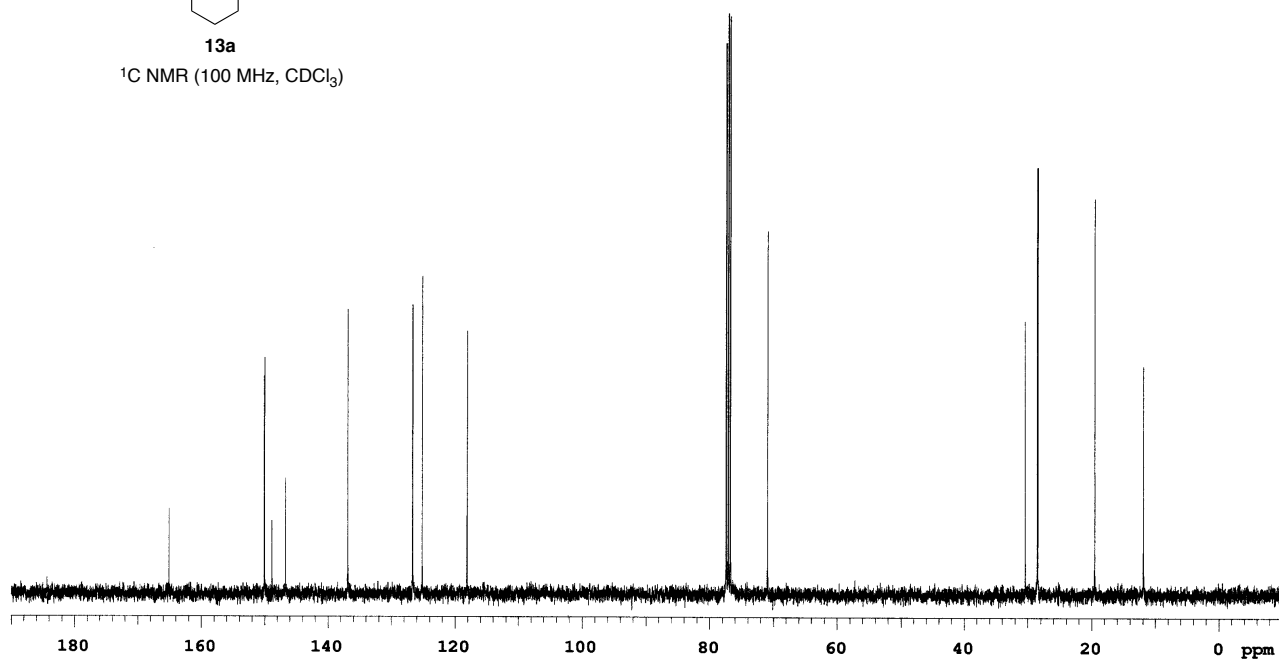


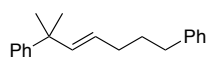


^1H NMR (400 MHz, CDCl_3)



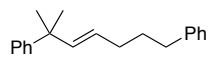
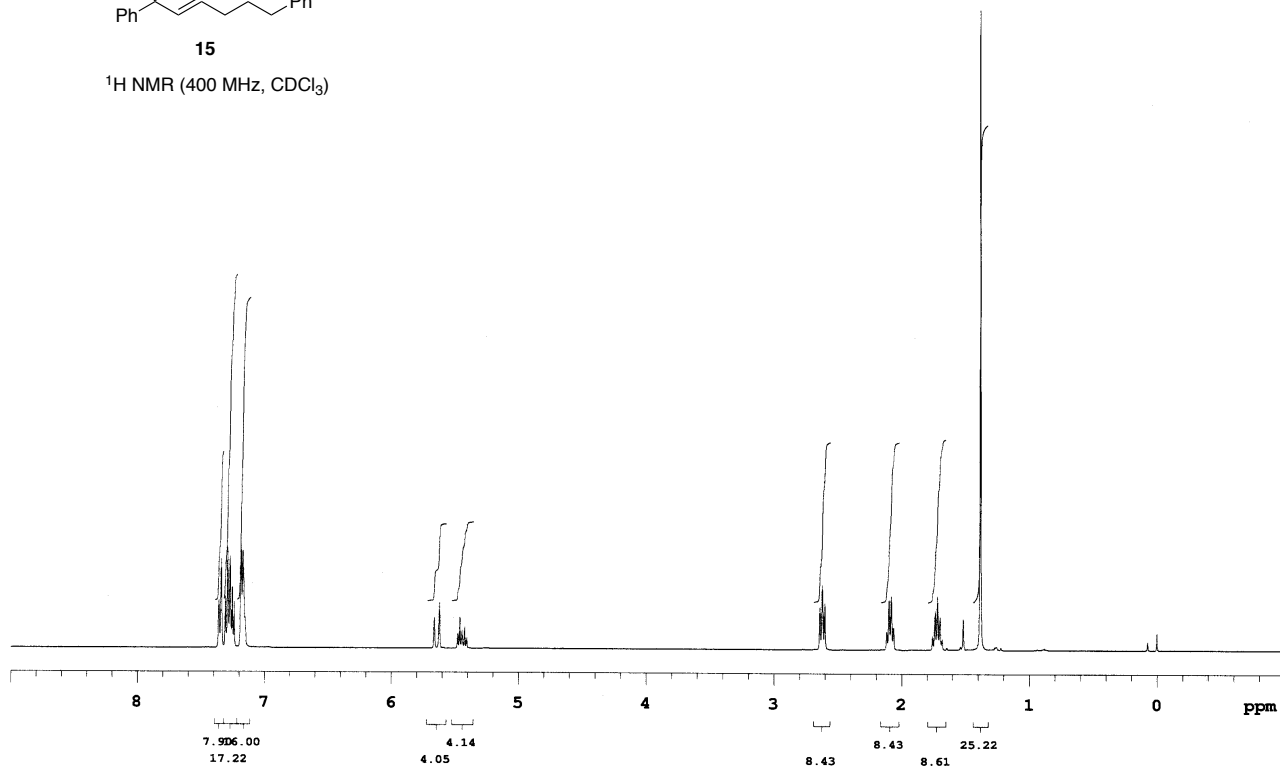
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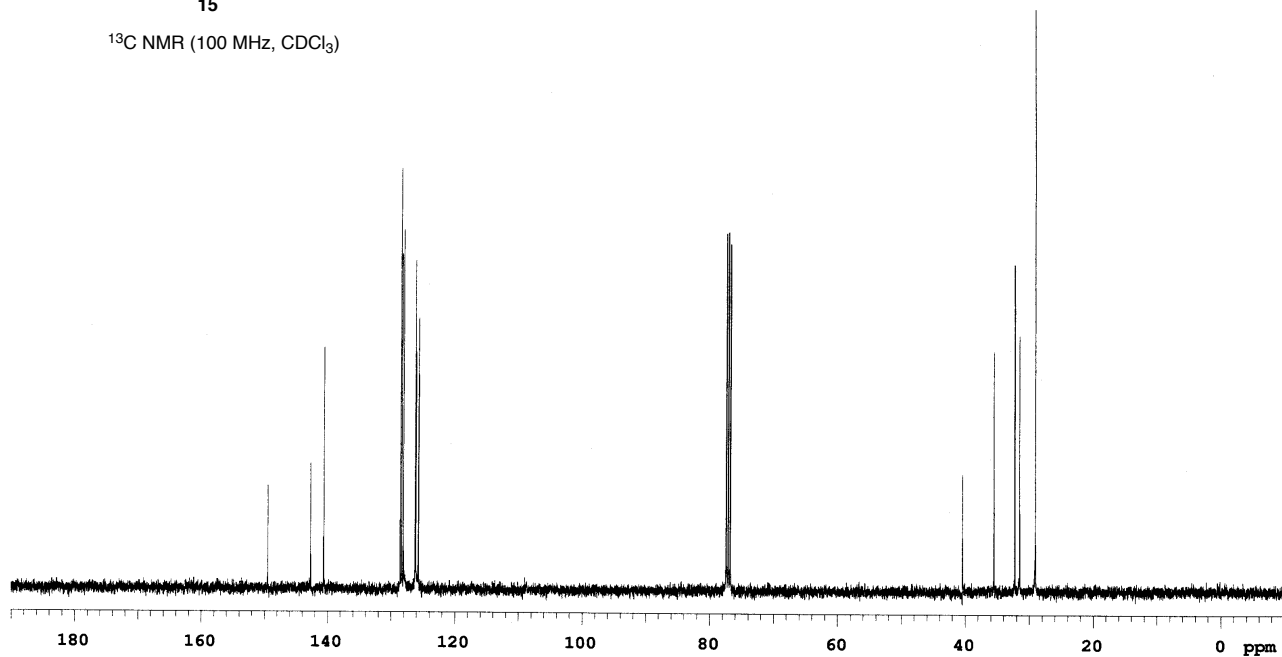
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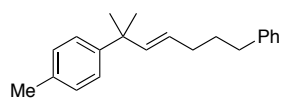
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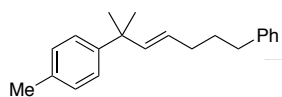
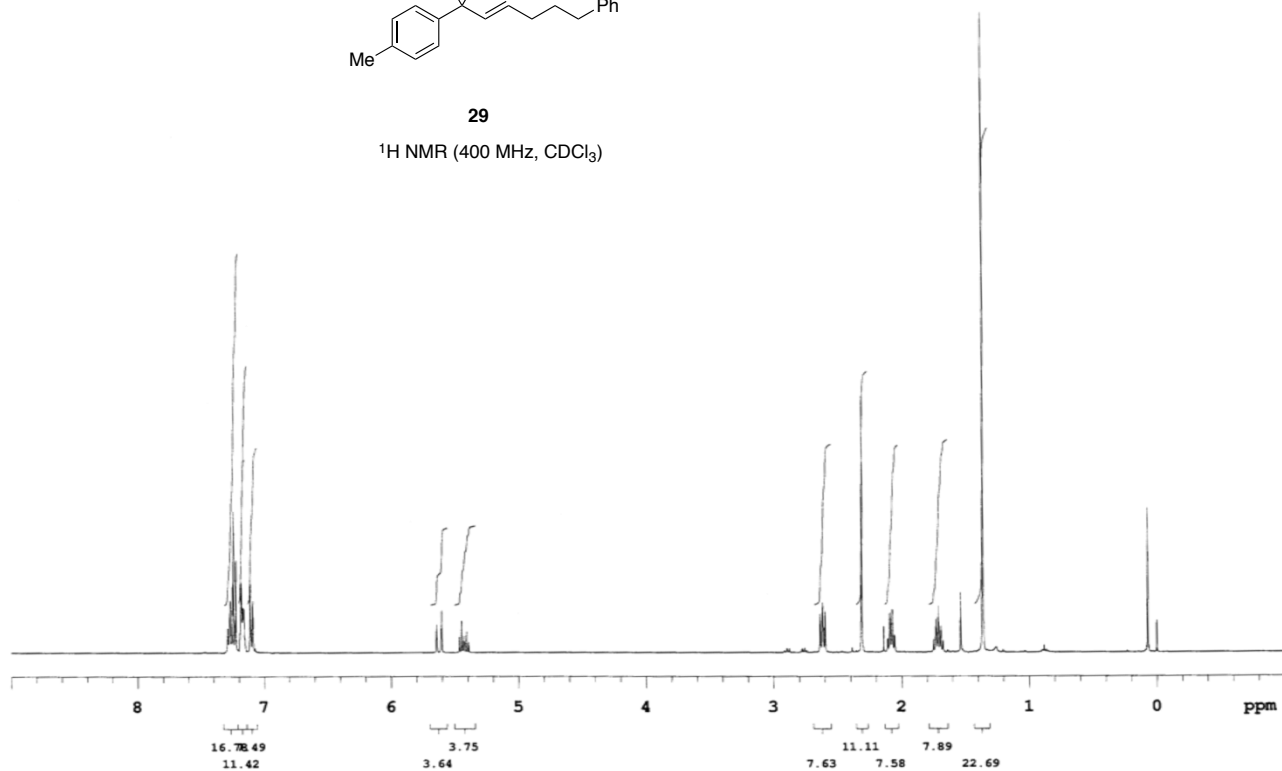
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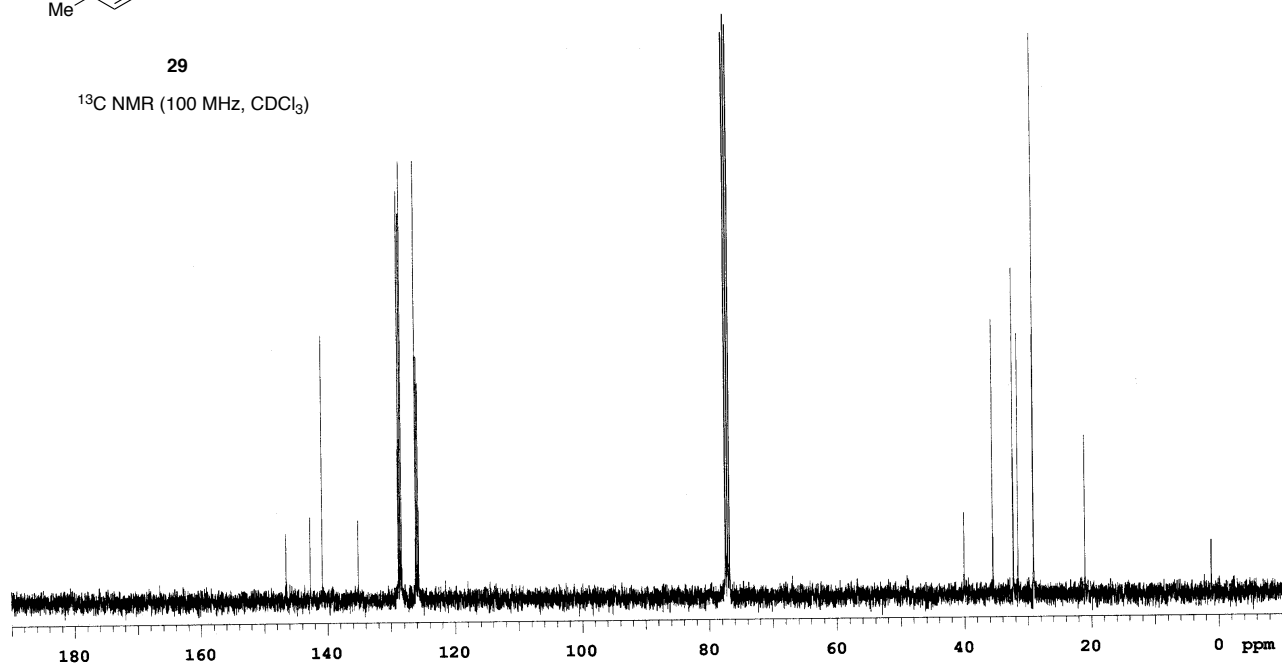
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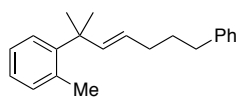
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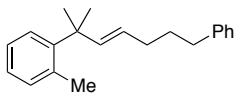
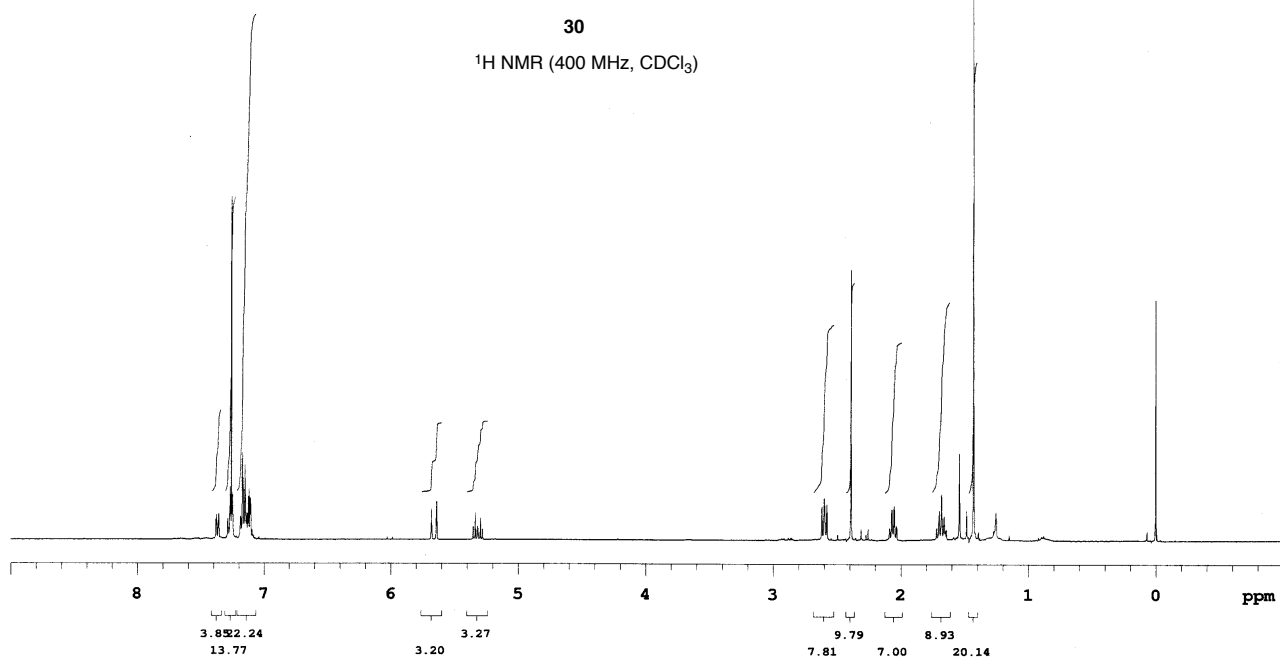
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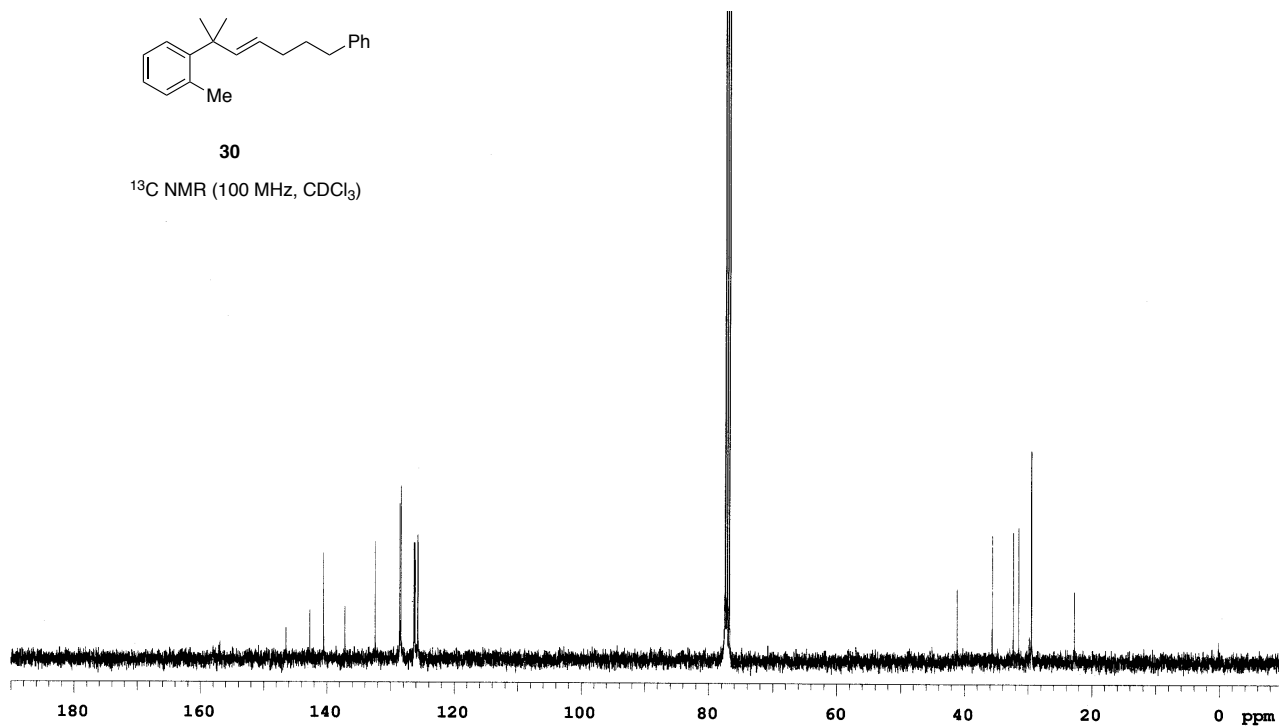
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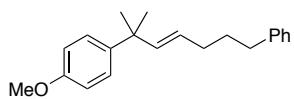
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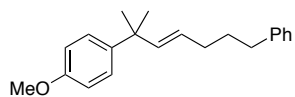
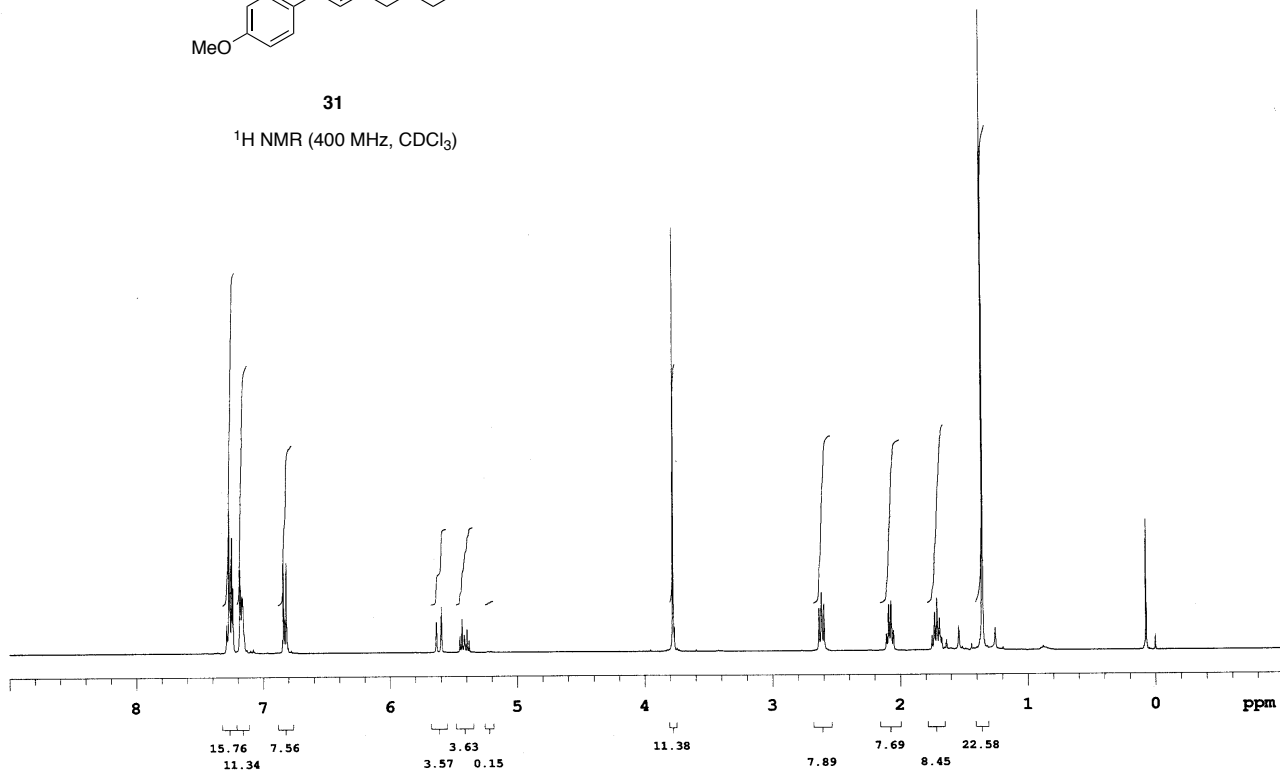
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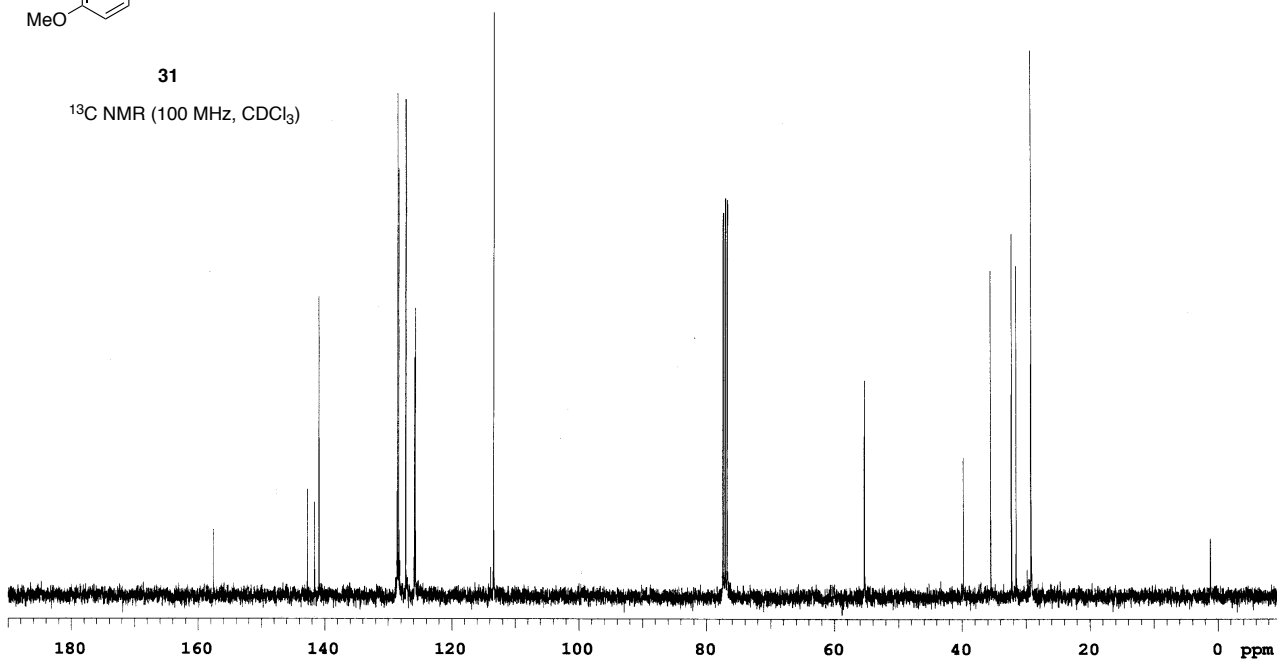
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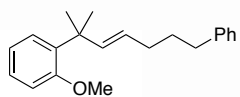
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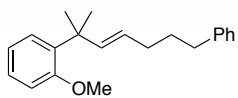
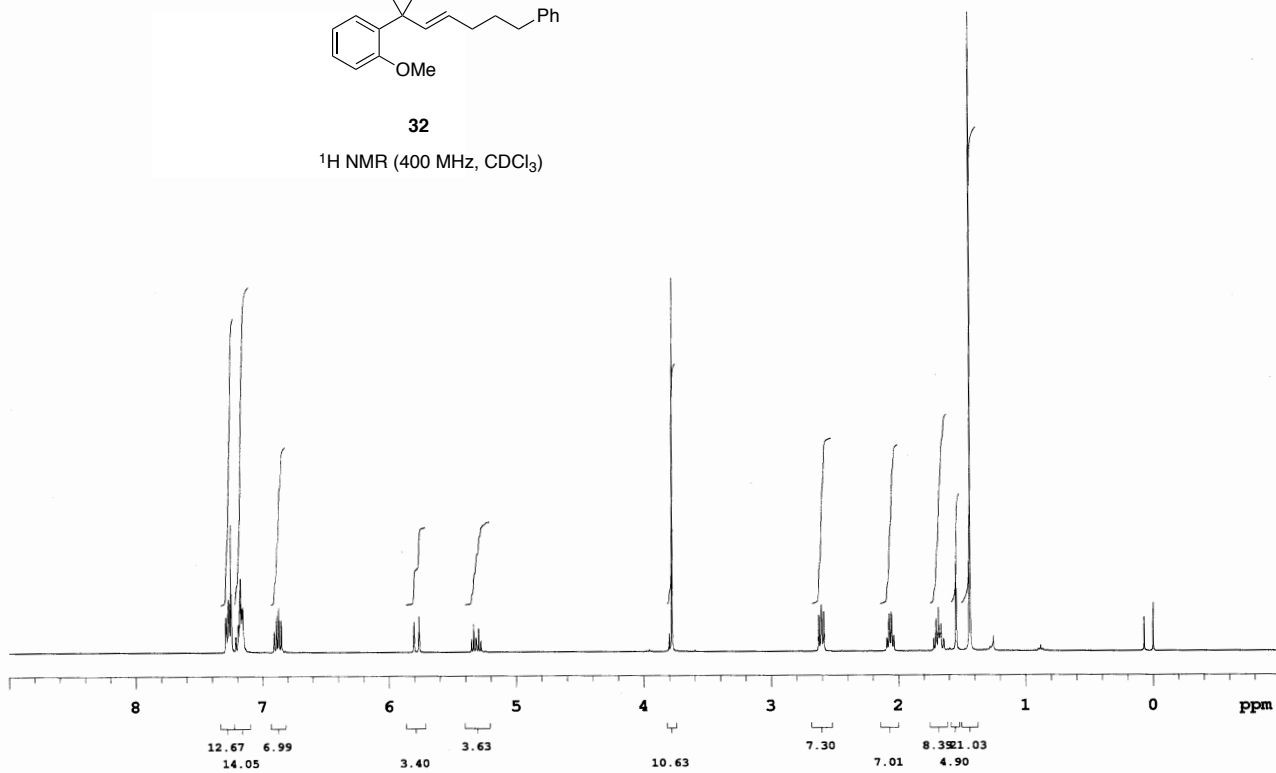
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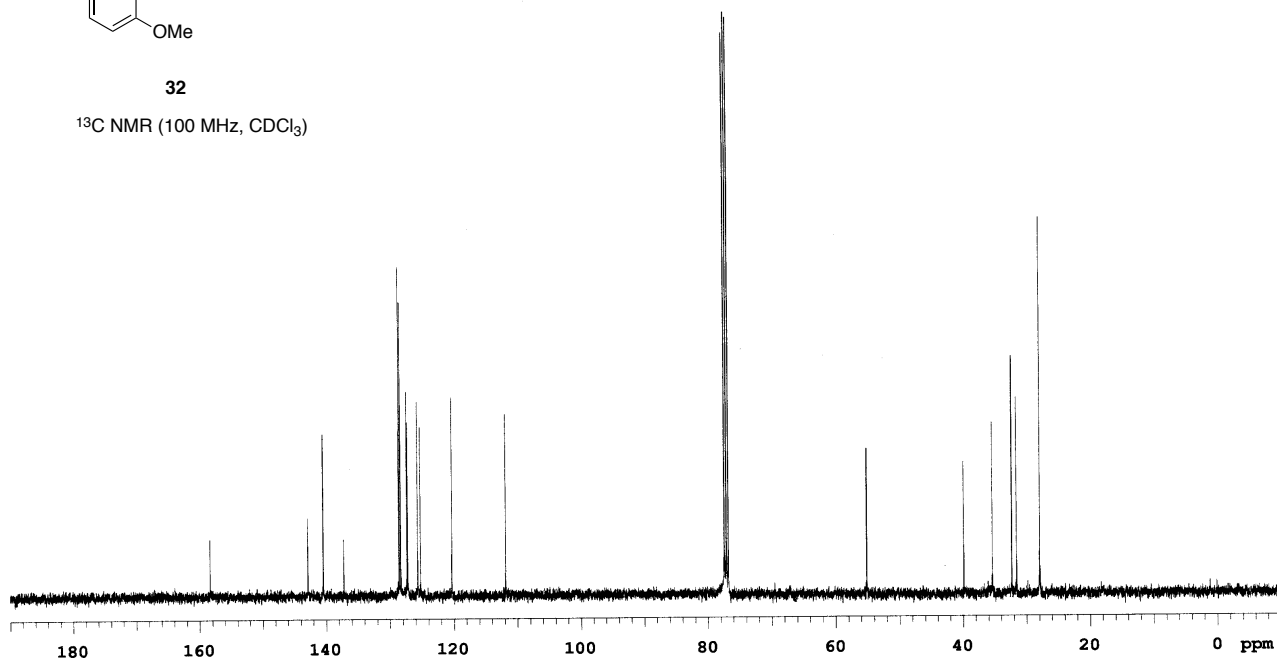
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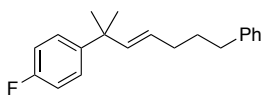
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32

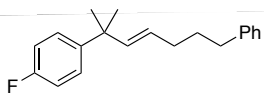
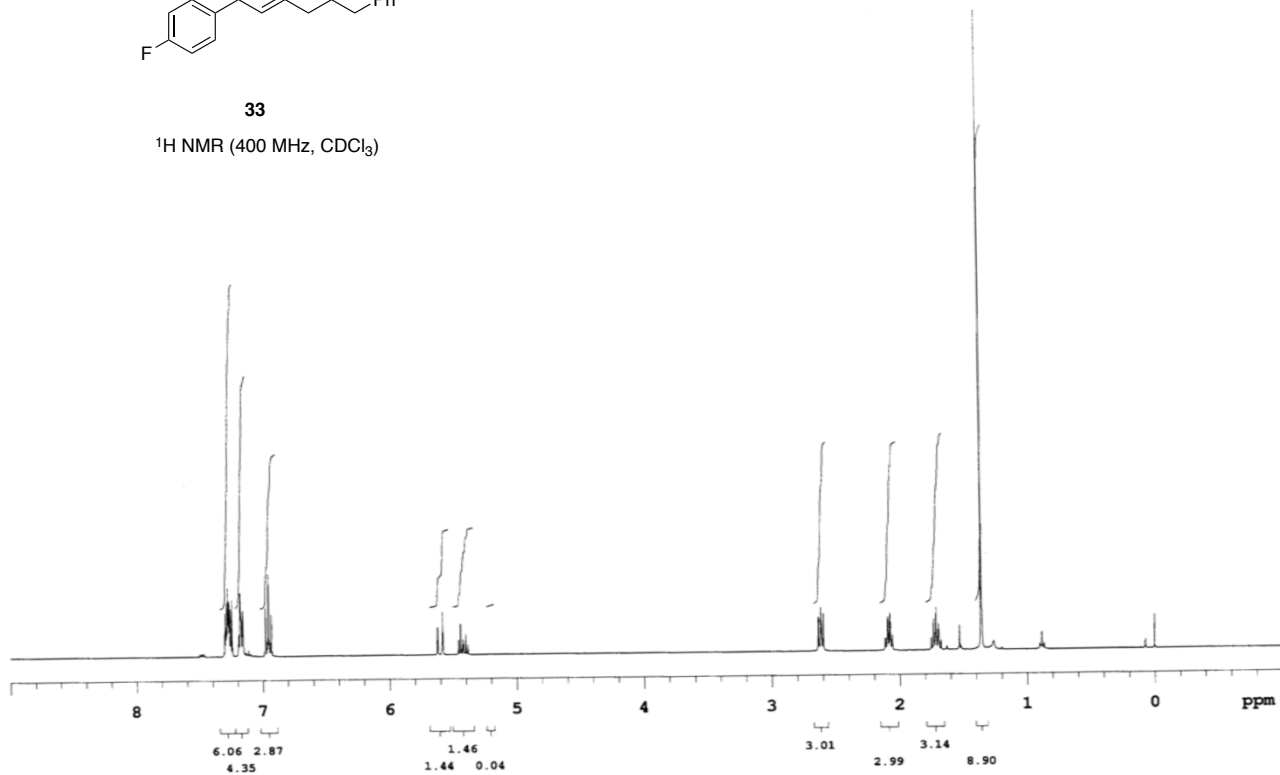
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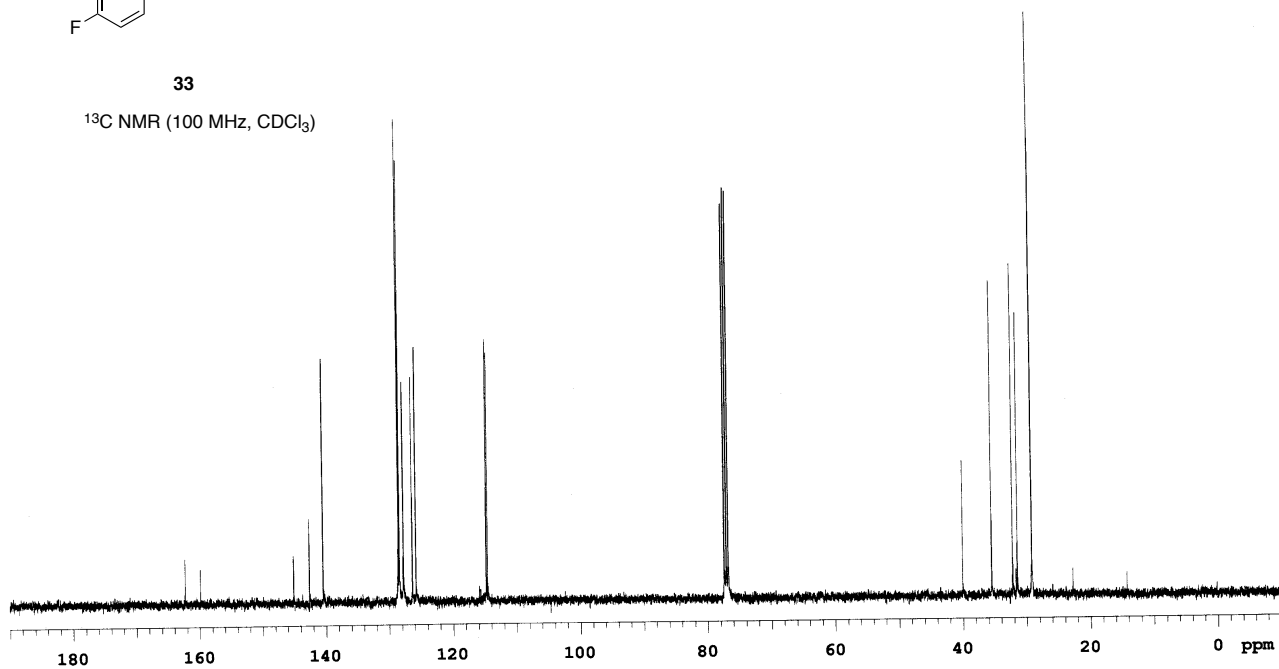
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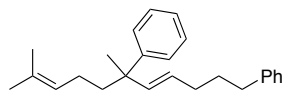
^1H NMR (400 MHz, CDCl_3)



33

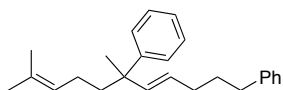
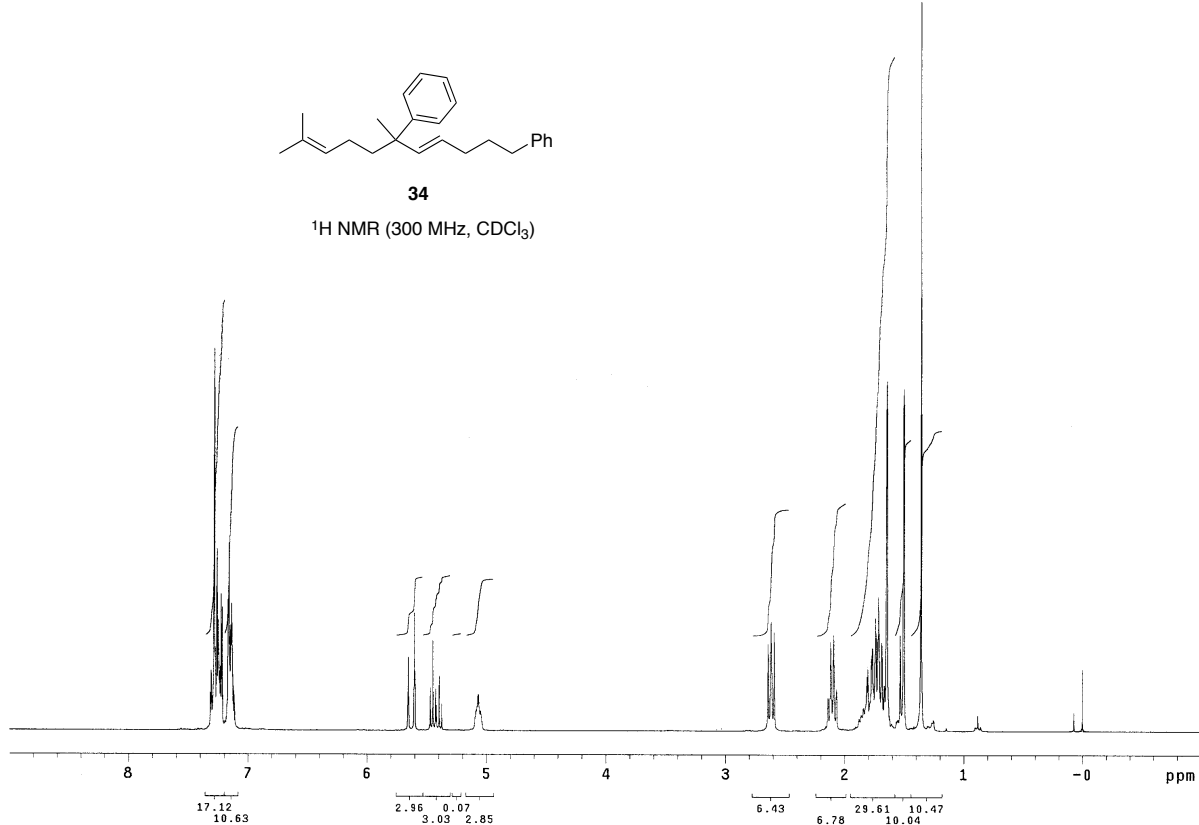
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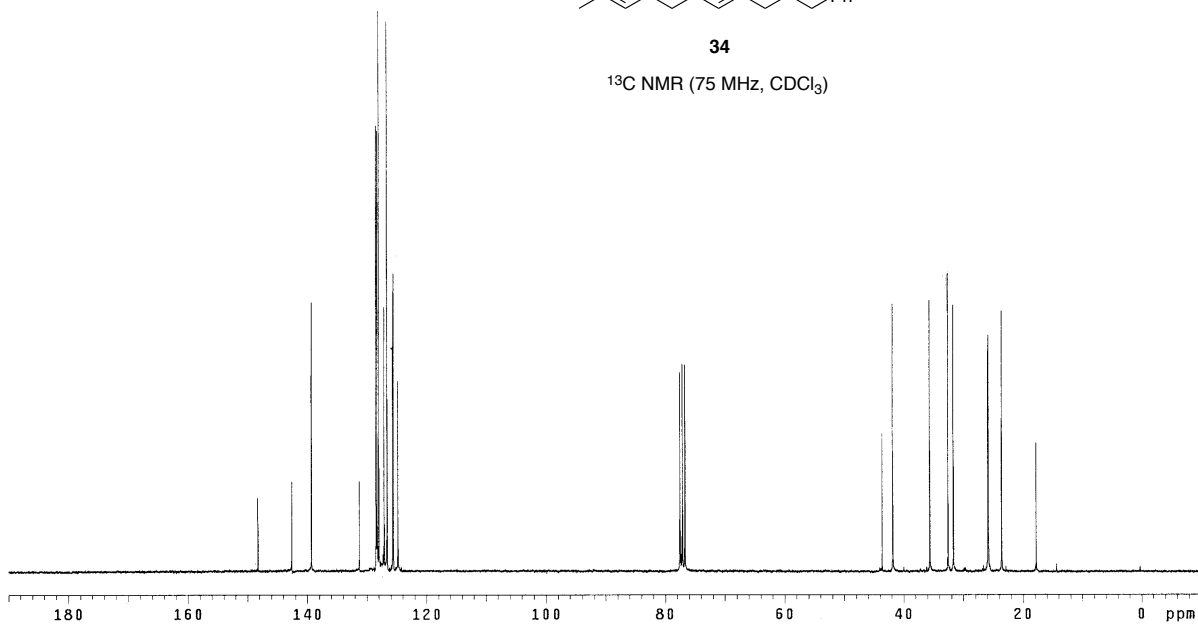
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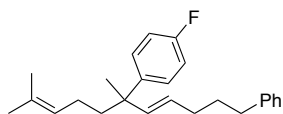
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34

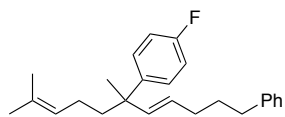
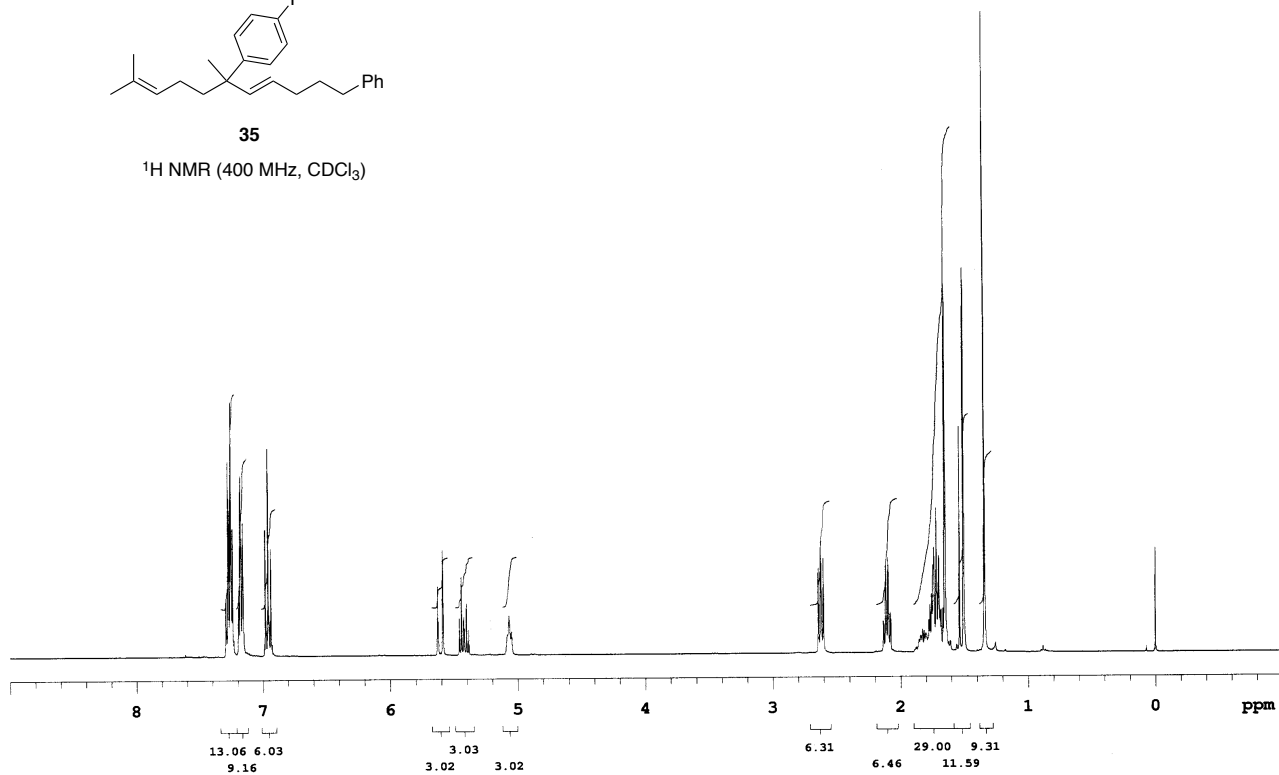
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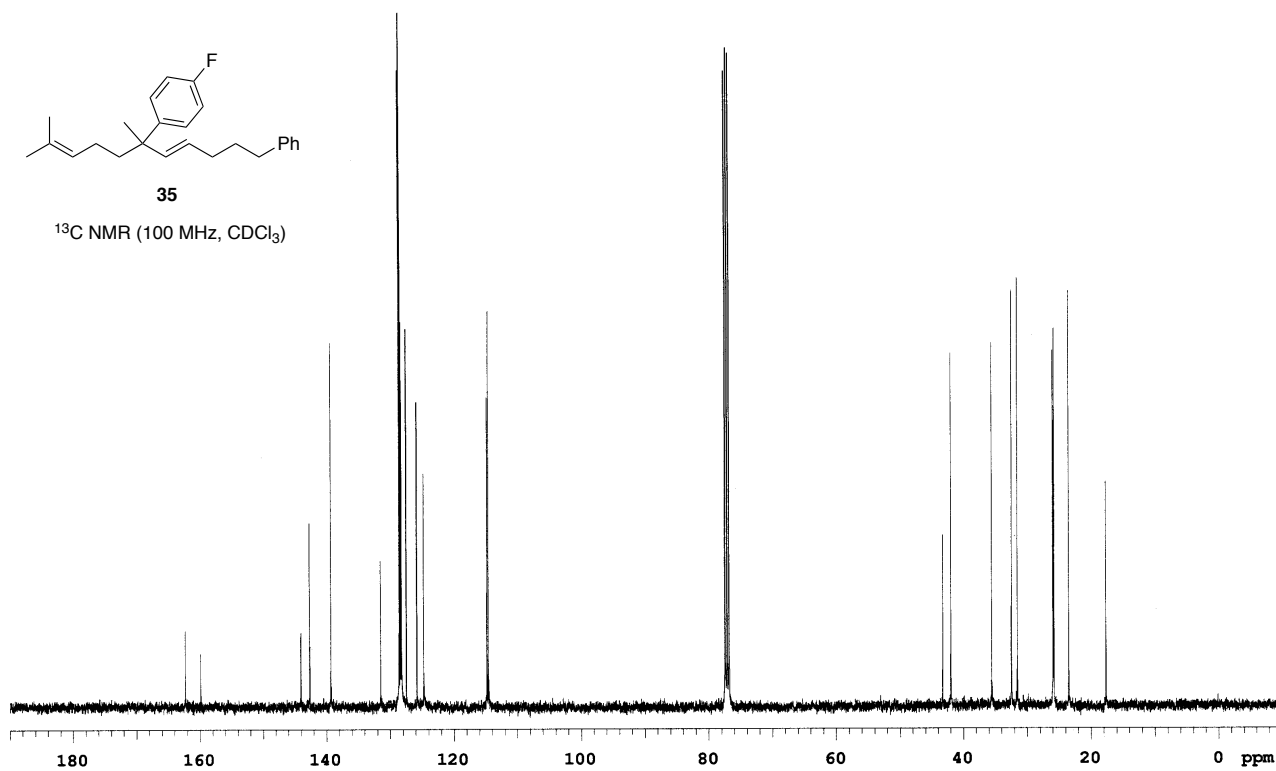
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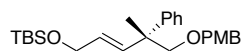
¹H NMR (400 MHz, CDCl₃)



35

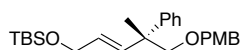
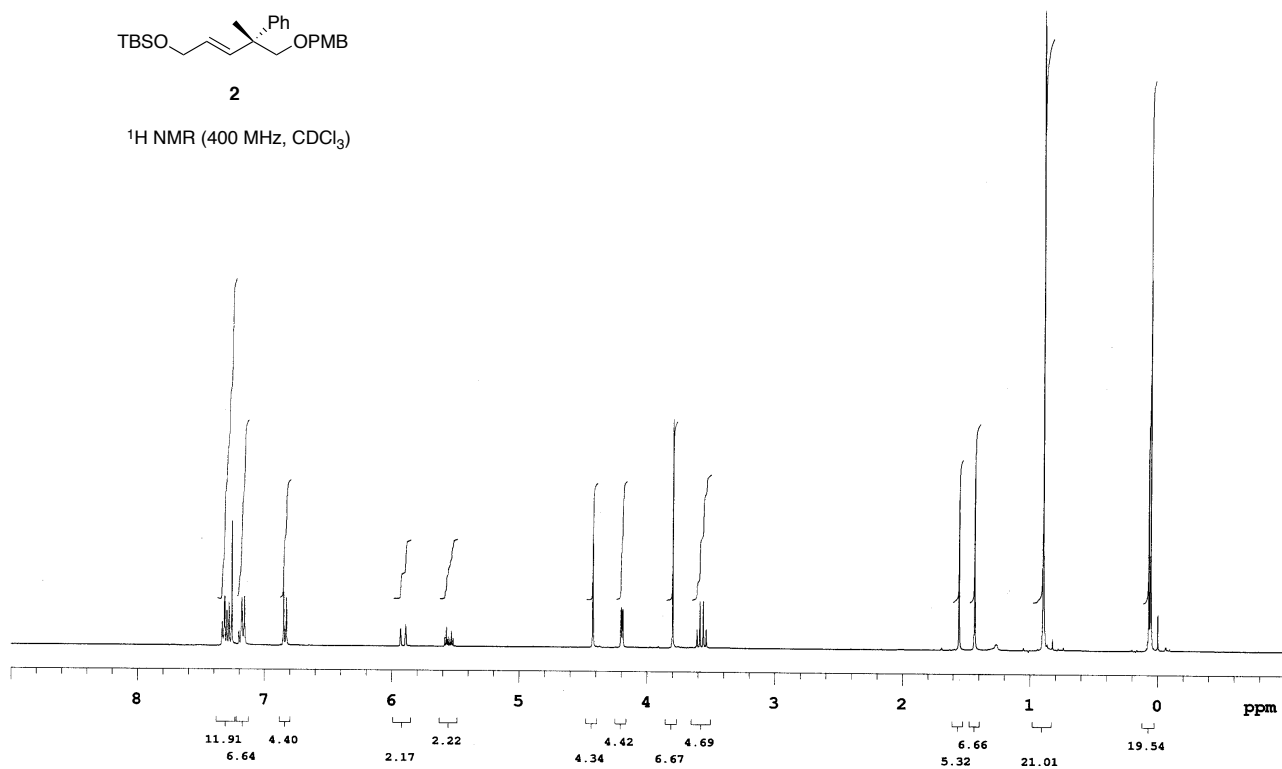
¹³C NMR (100 MHz, CDCl₃)





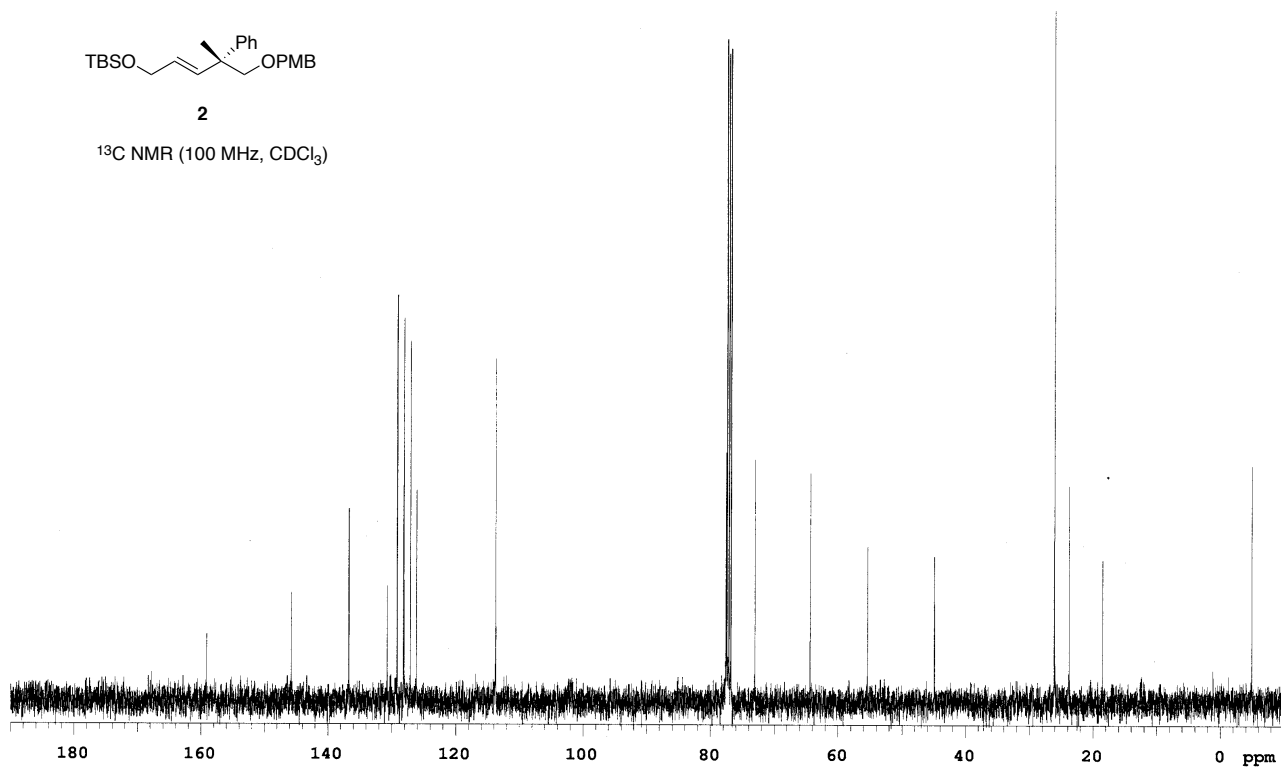
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^1H NMR (400 MHz, CDCl_3)

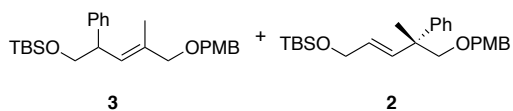


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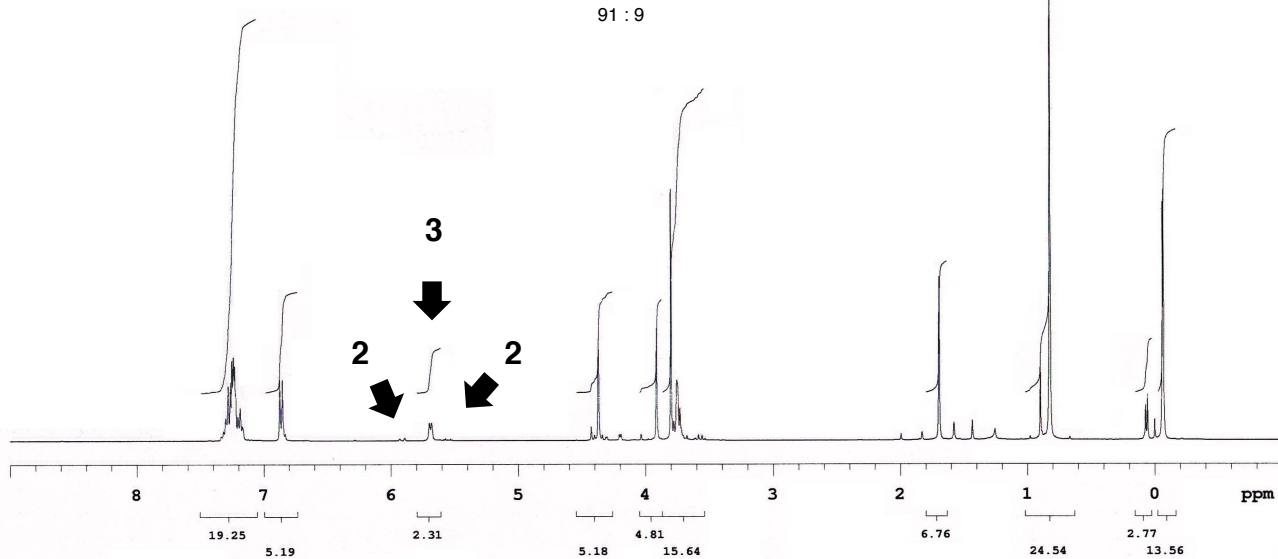
^{13}C NMR (100 MHz, CDCl_3)



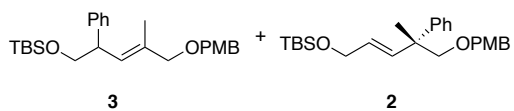
^1H NMR (400 MHz, CDCl_3)



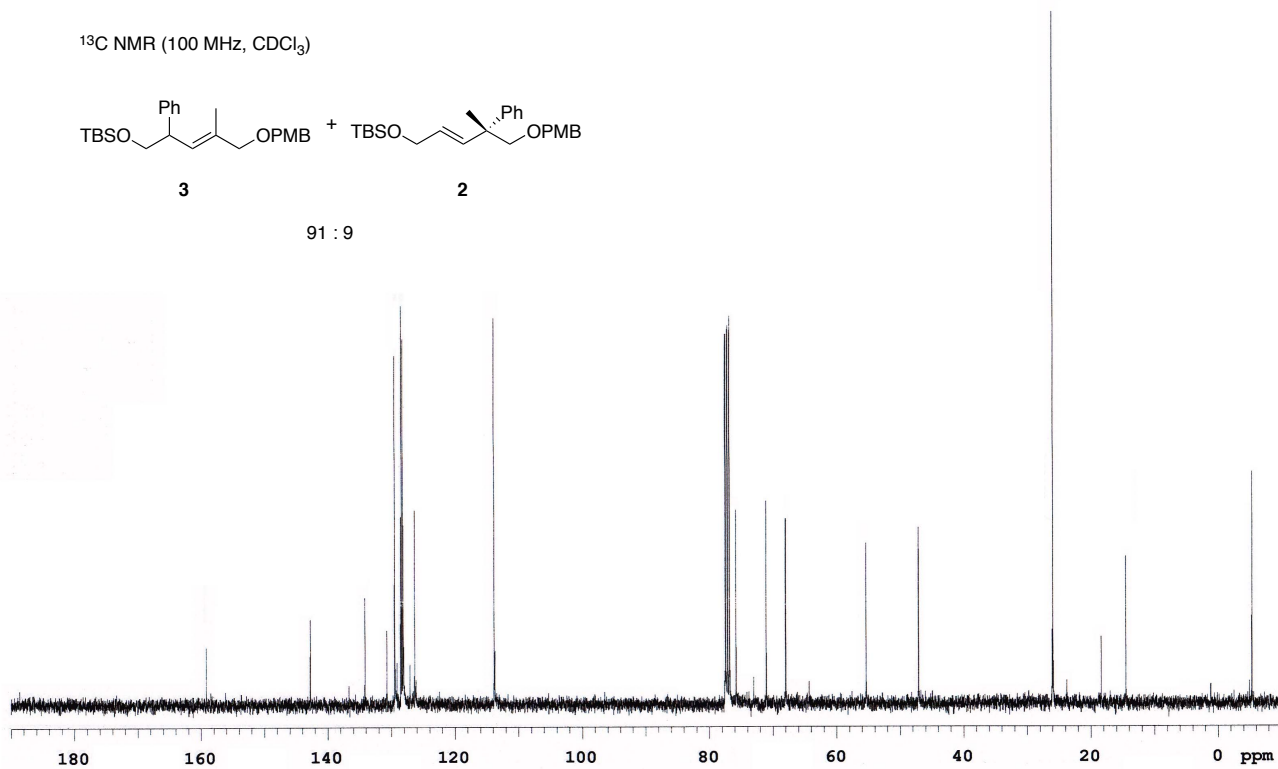
91 : 9

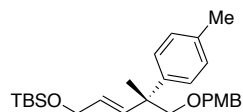


^{13}C NMR (100 MHz, CDCl_3)



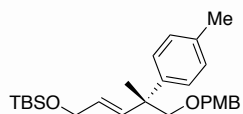
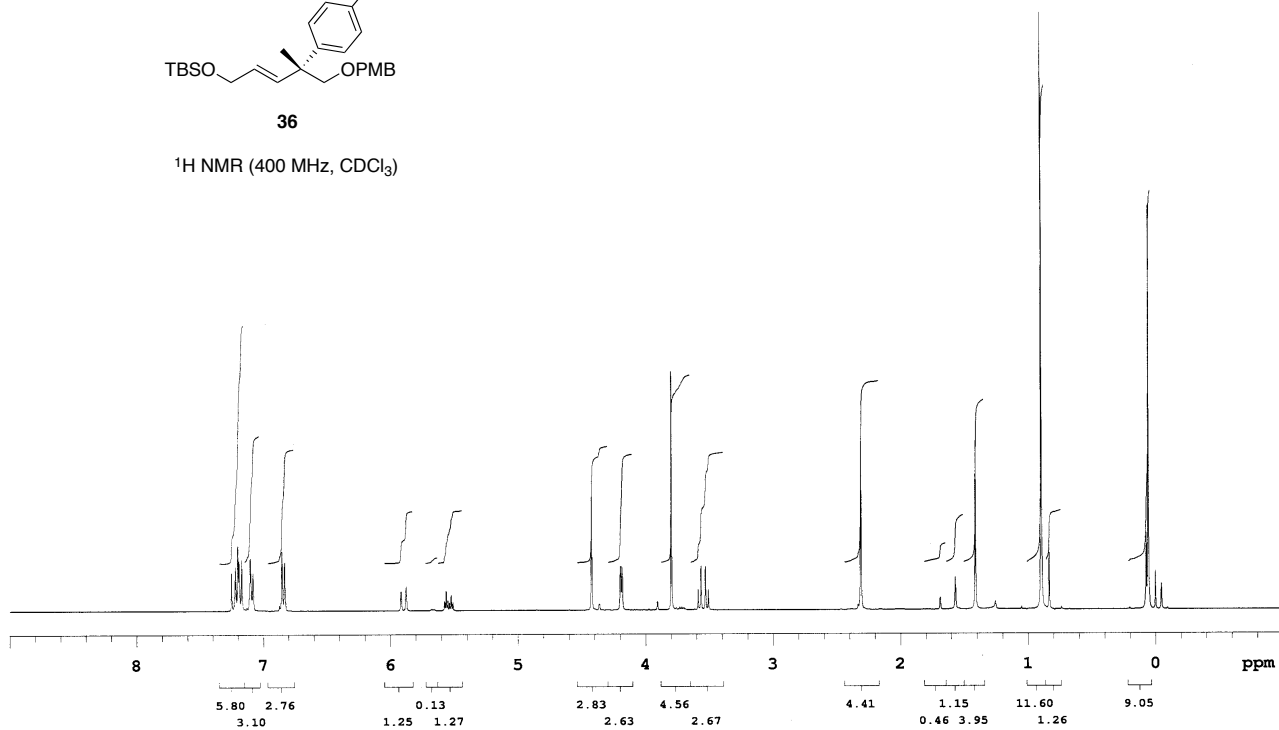
91 : 9





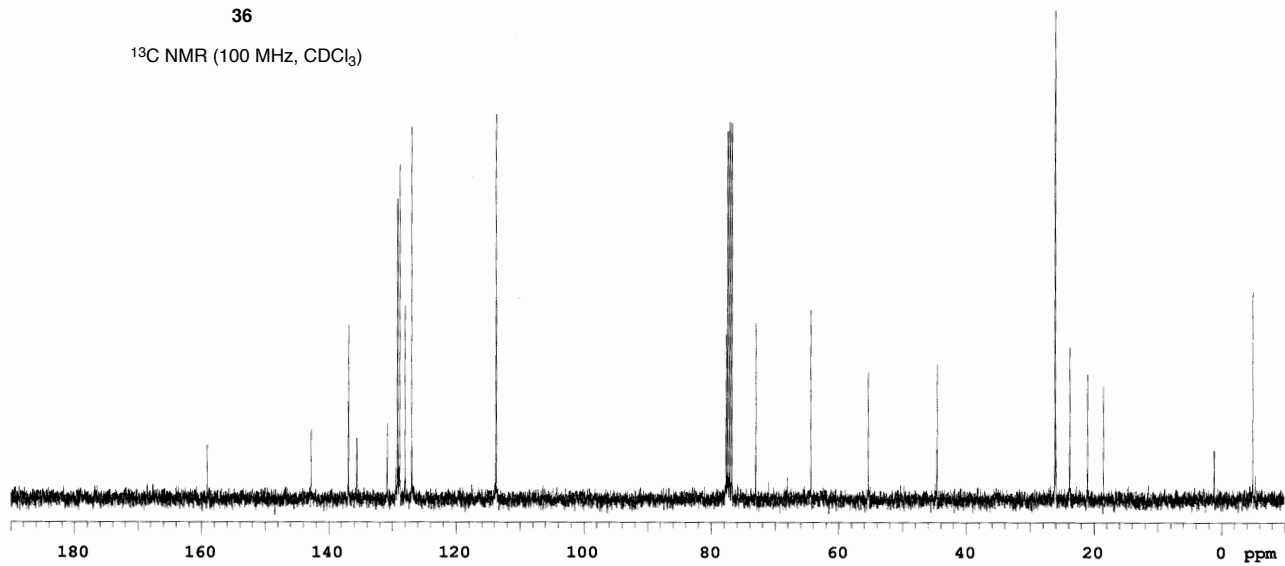
36

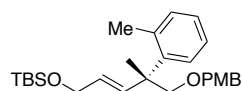
^1H NMR (400 MHz, CDCl_3)



36

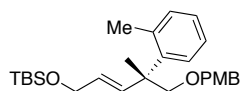
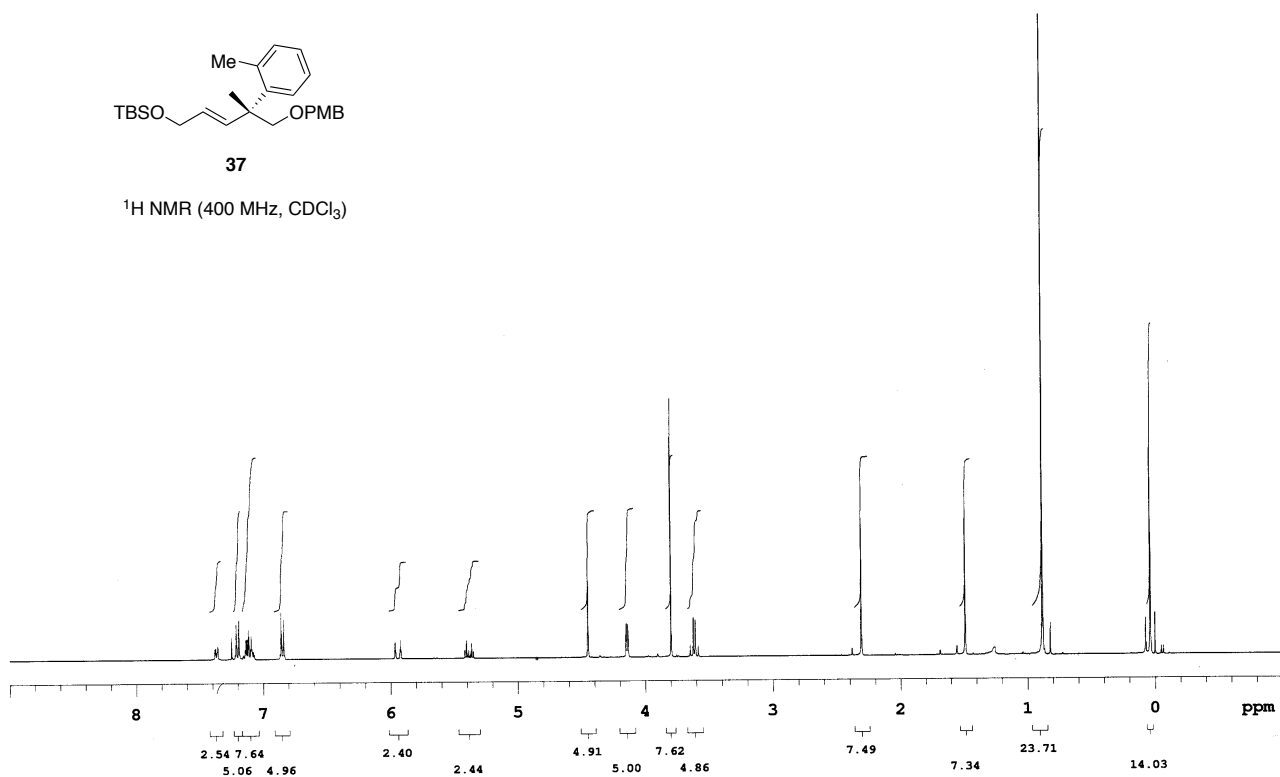
^{13}C NMR (100 MHz, CDCl_3)





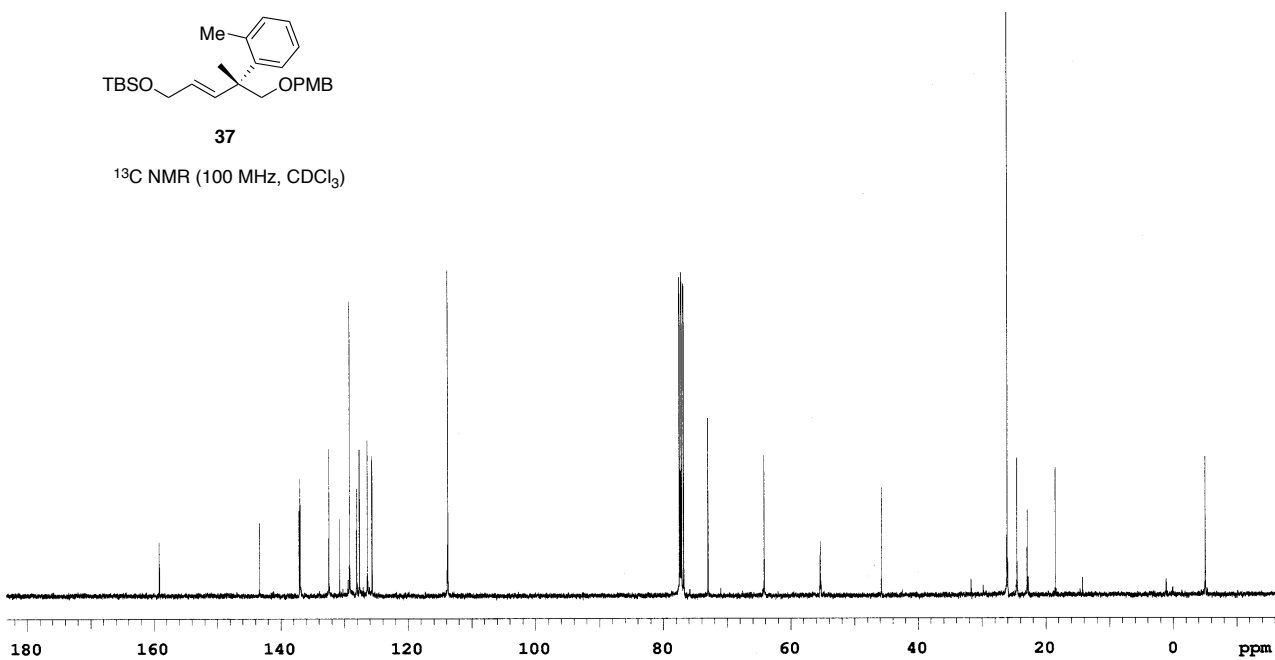
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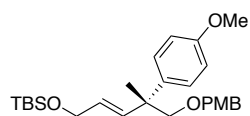
¹H NMR (400 MHz, CDCl₃)



37

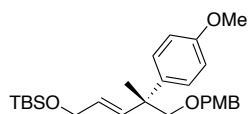
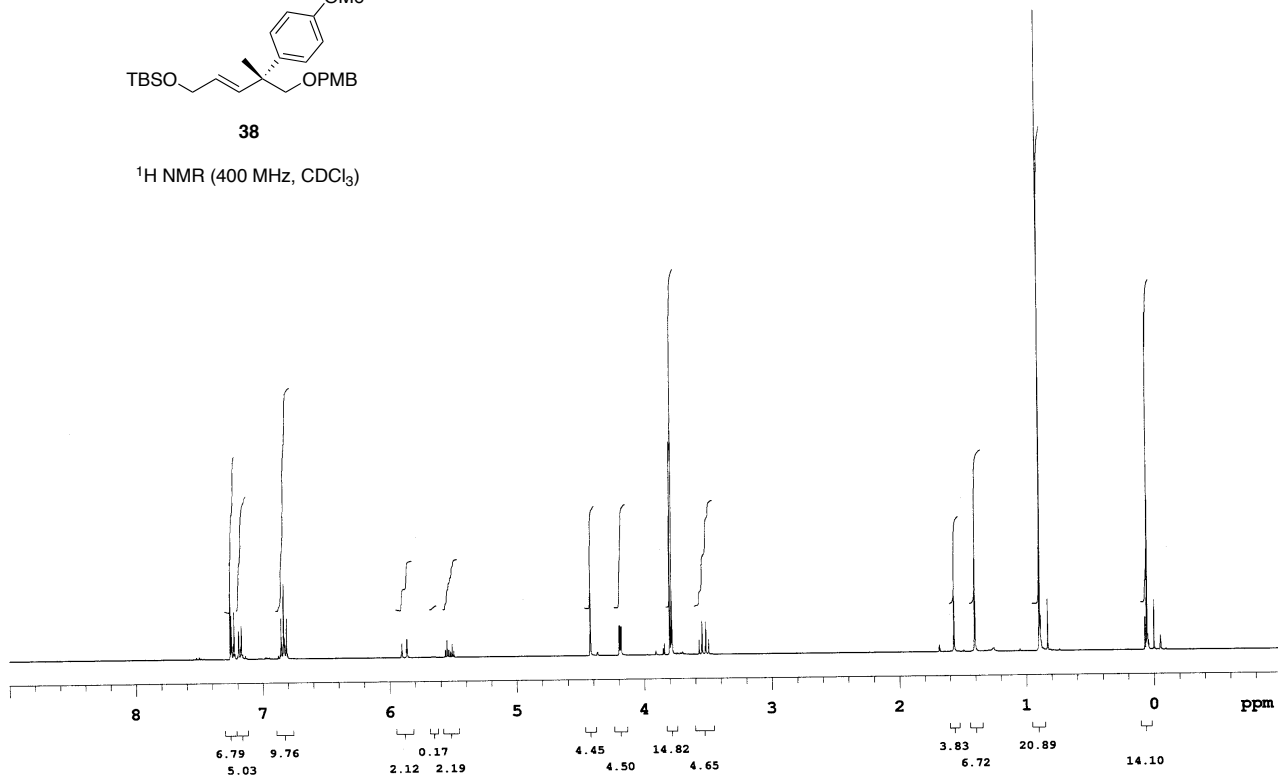
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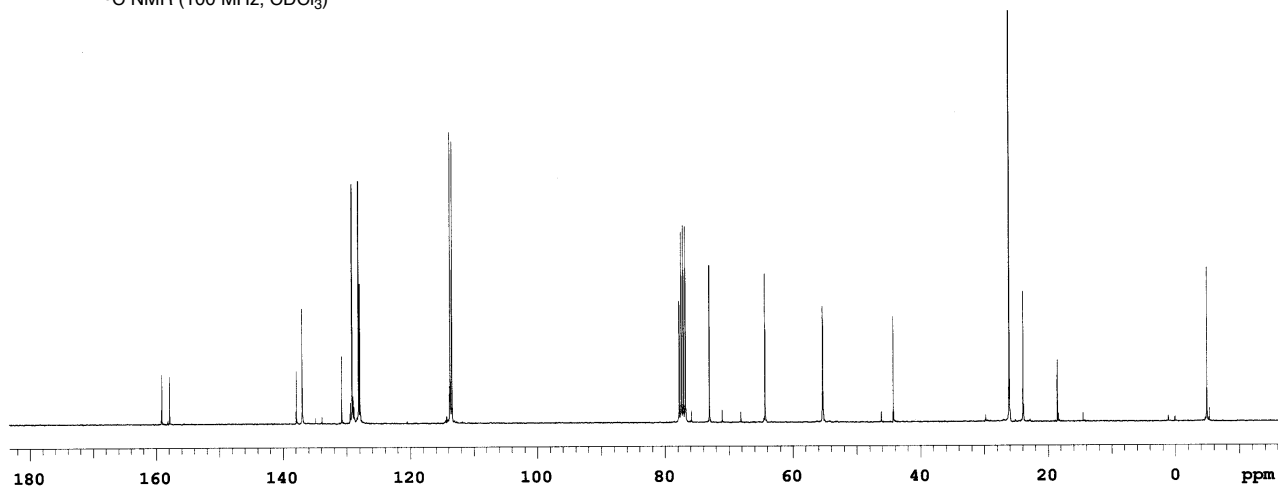
38

^1H NMR (400 MHz, CDCl_3)



38

^{13}C NMR (100 MHz, CDCl_3)





40

^1H NMR (400 MHz, CDCl_3)

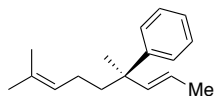
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40

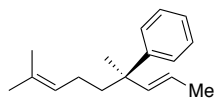
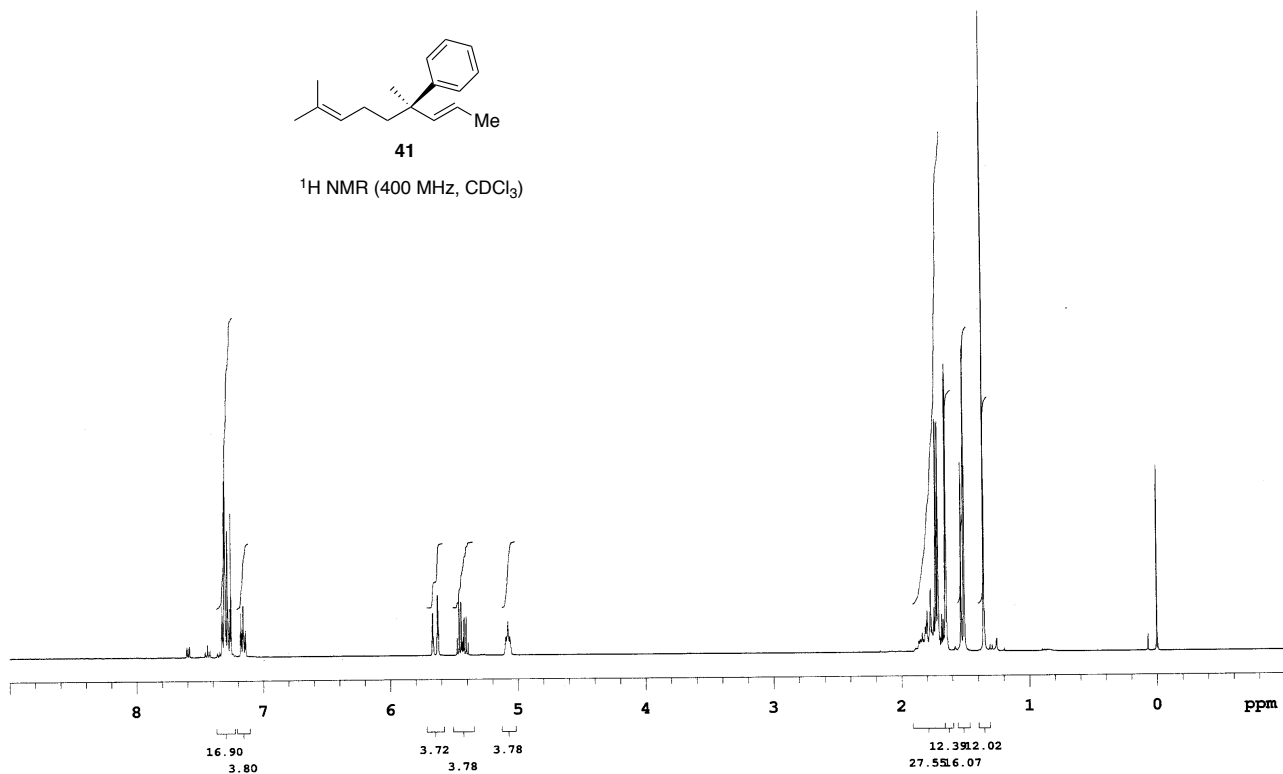
^1C NMR (100 MHz, CDCl_3)

180 160 140 120 100 80 60 40 20 0 ppm



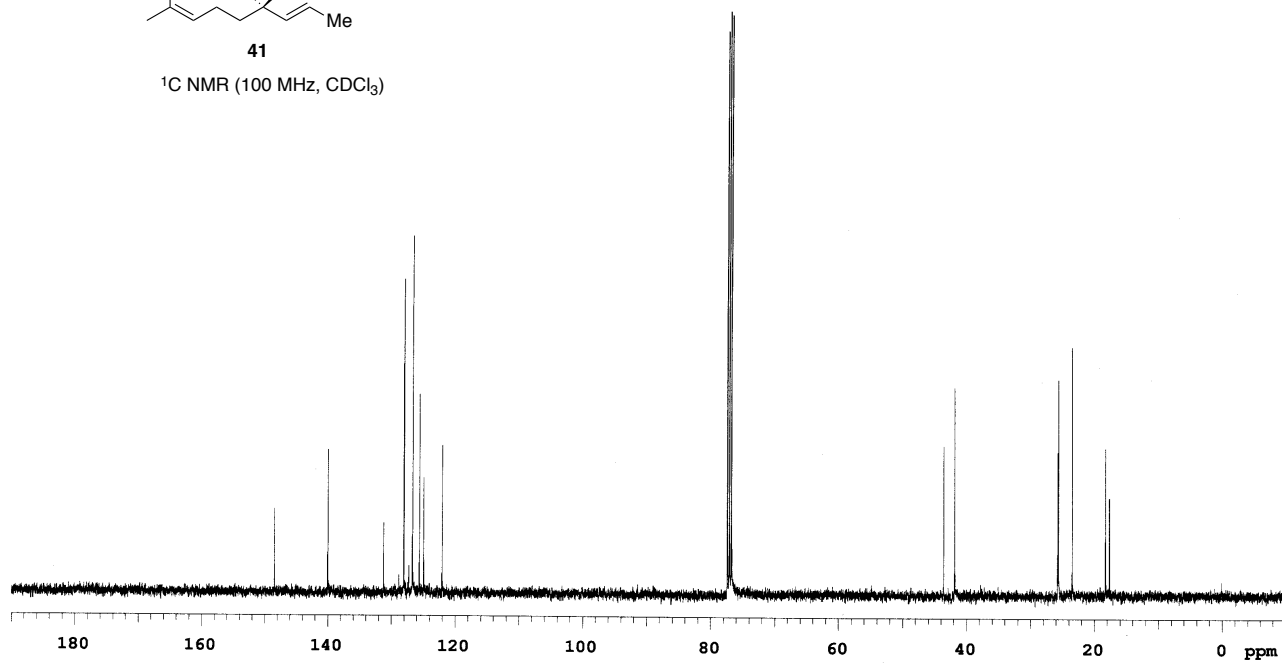
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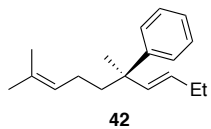
^1H NMR (400 MHz, CDCl_3)



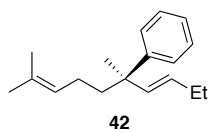
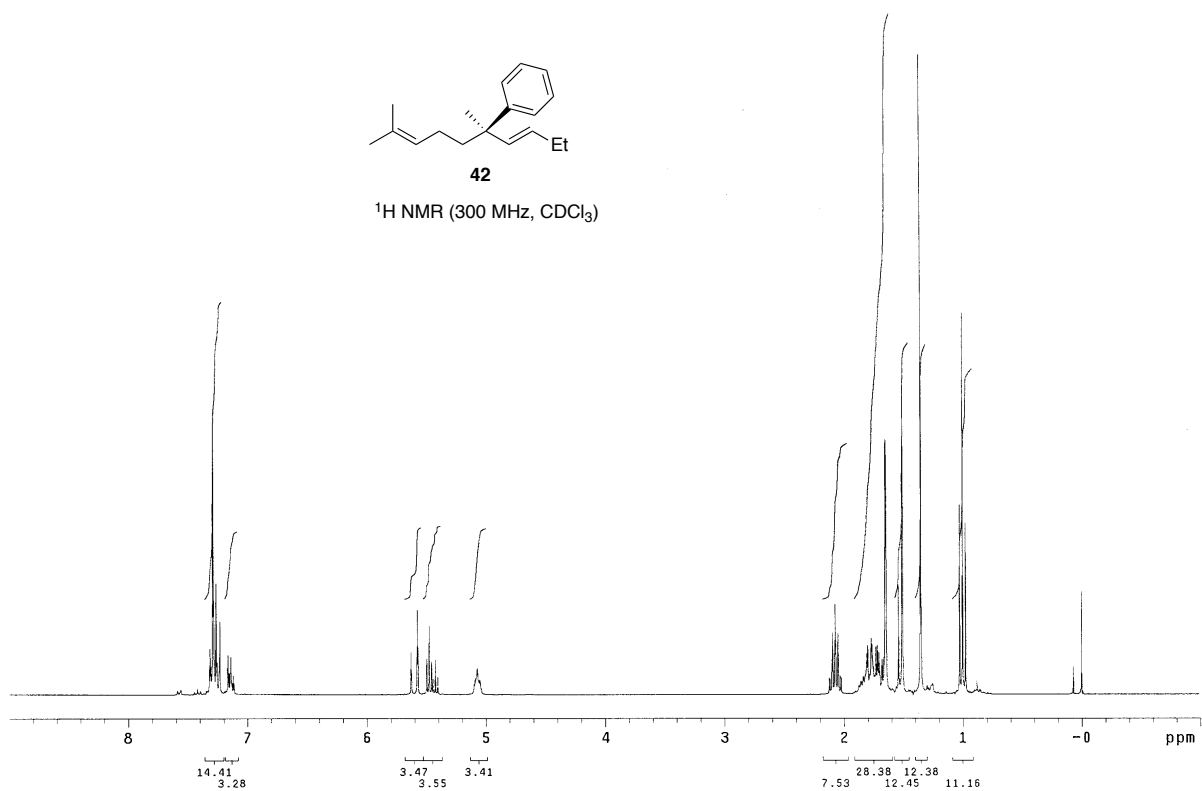
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^{13}C NMR (100 MHz, CDCl_3)

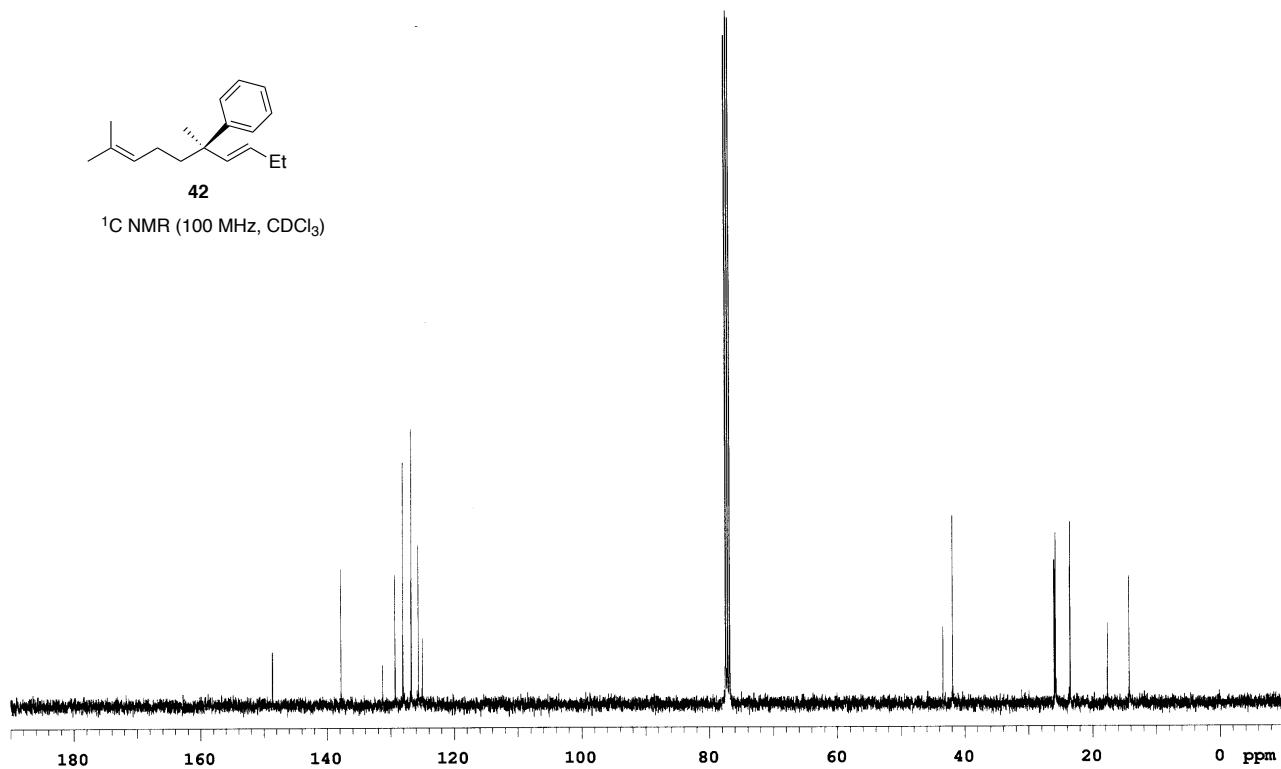


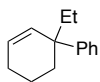


^1H NMR (300 MHz, CDCl_3)



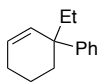
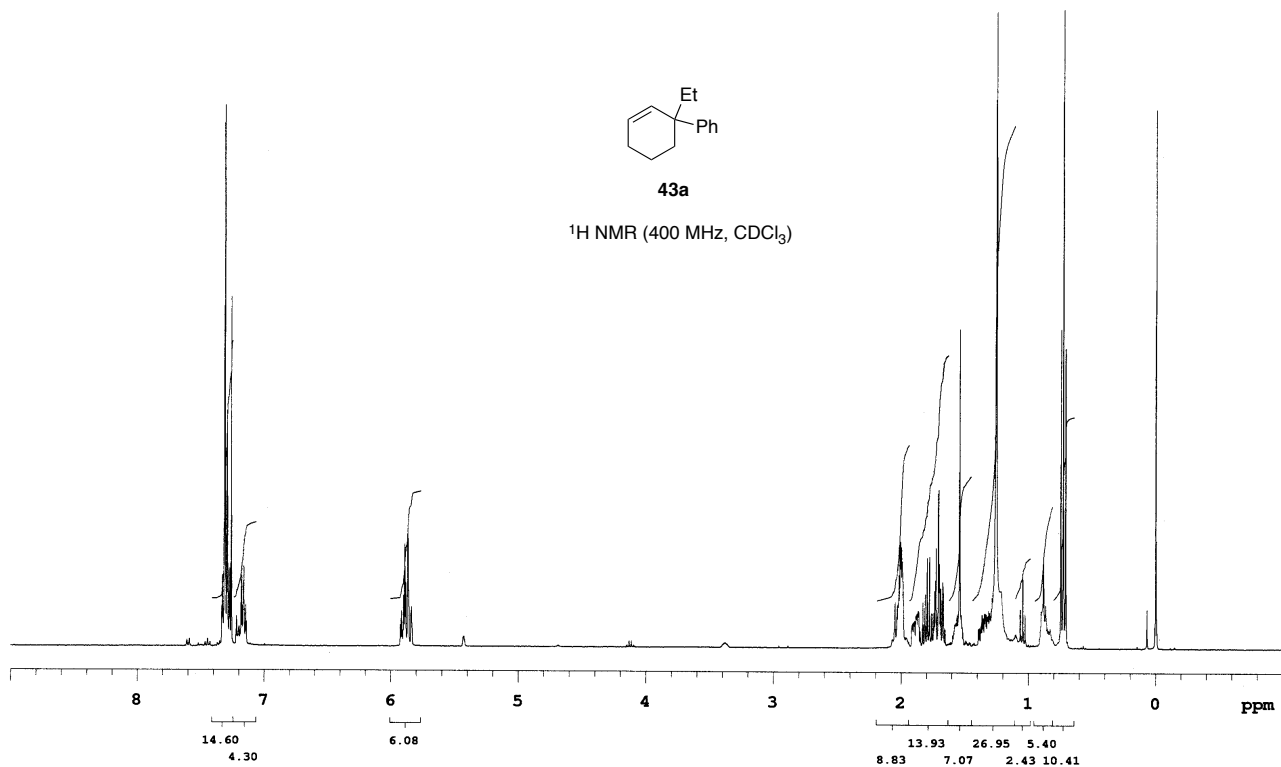
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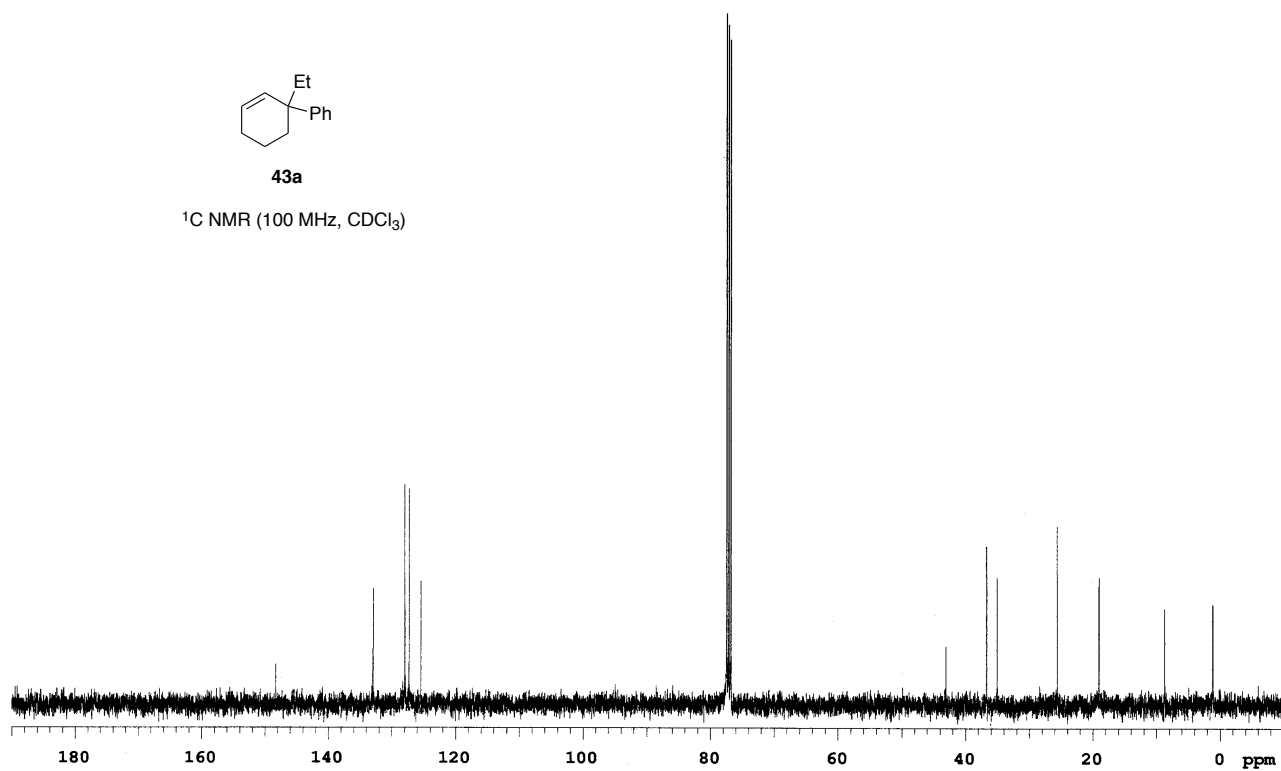
43a

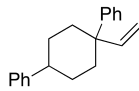
^1H NMR (400 MHz, CDCl_3)



43a

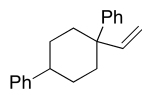
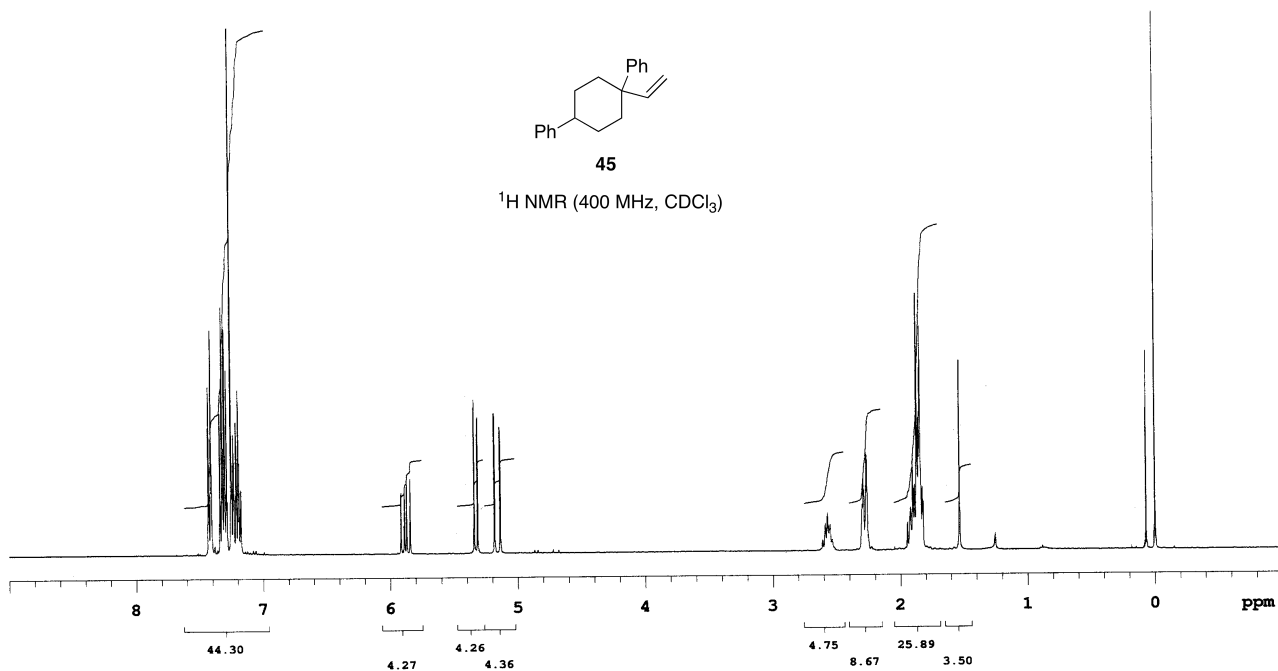
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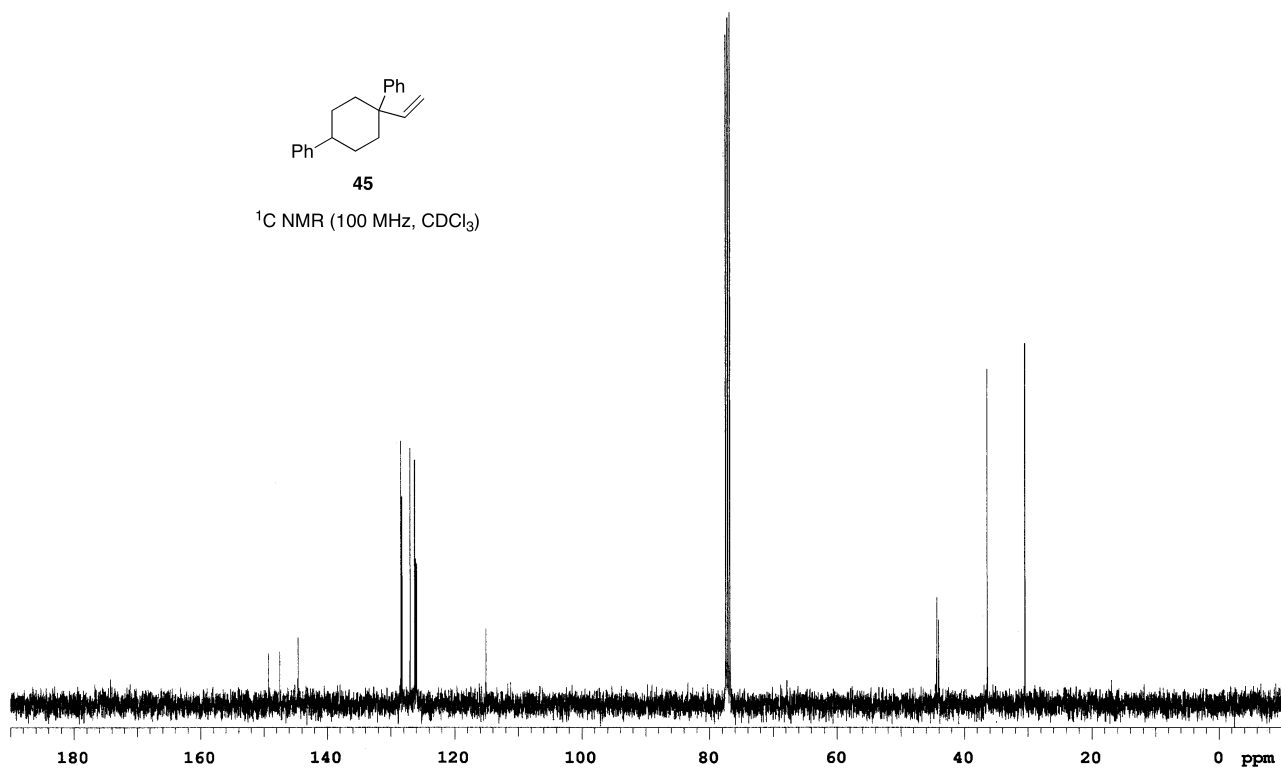
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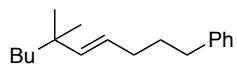
^1H NMR (400 MHz, CDCl_3)



45

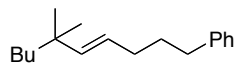
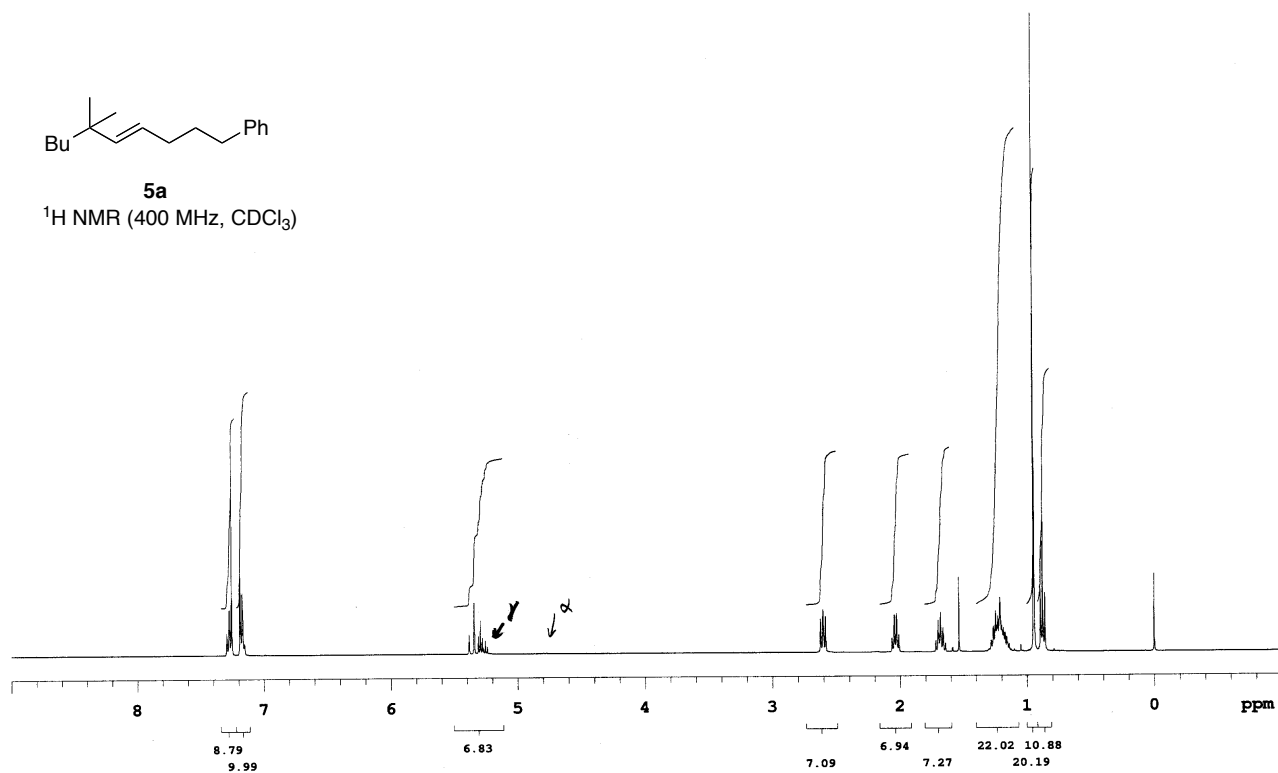
^{13}C NMR (100 MHz, CDCl_3)





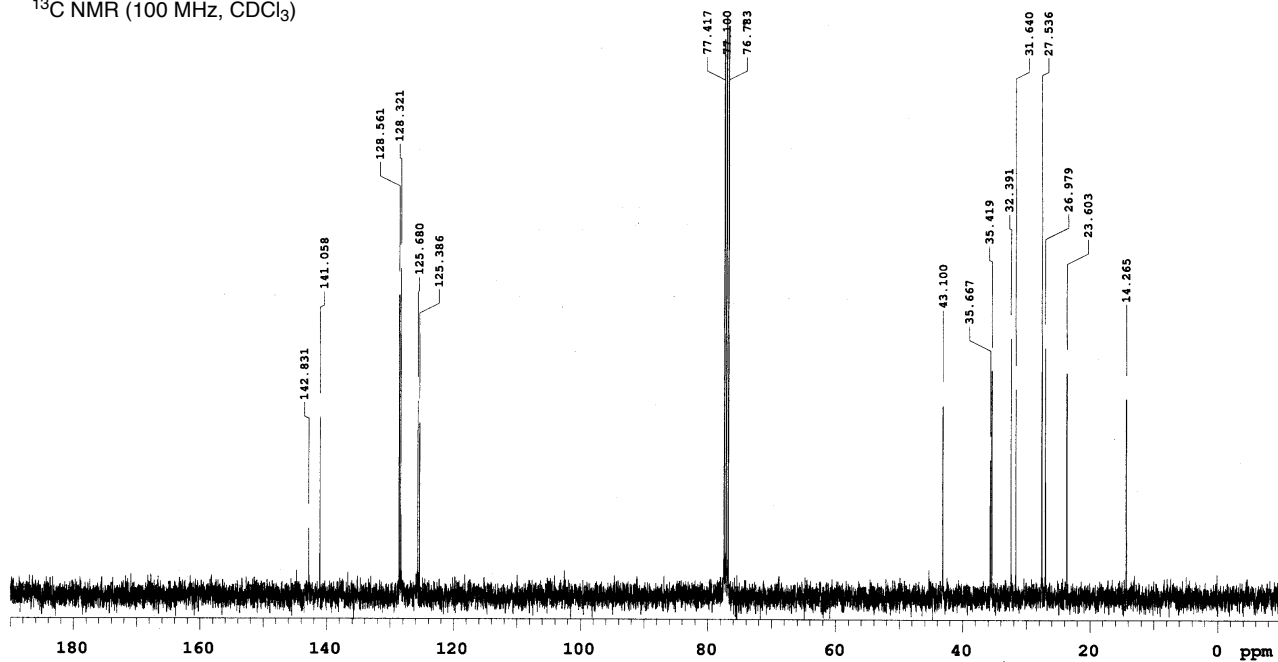
5a

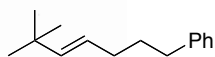
¹H NMR (400 MHz, CDCl₃)



5a

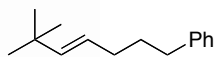
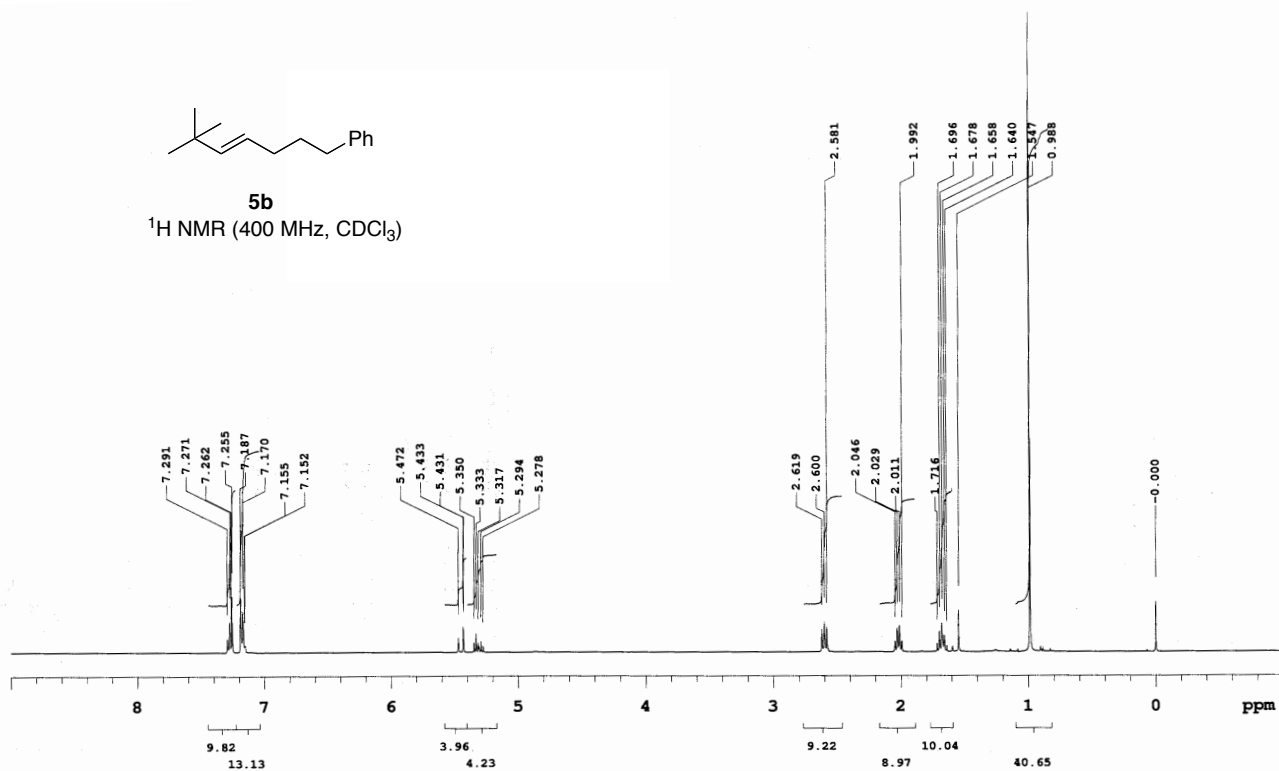
¹³C NMR (100 MHz, CDCl₃)





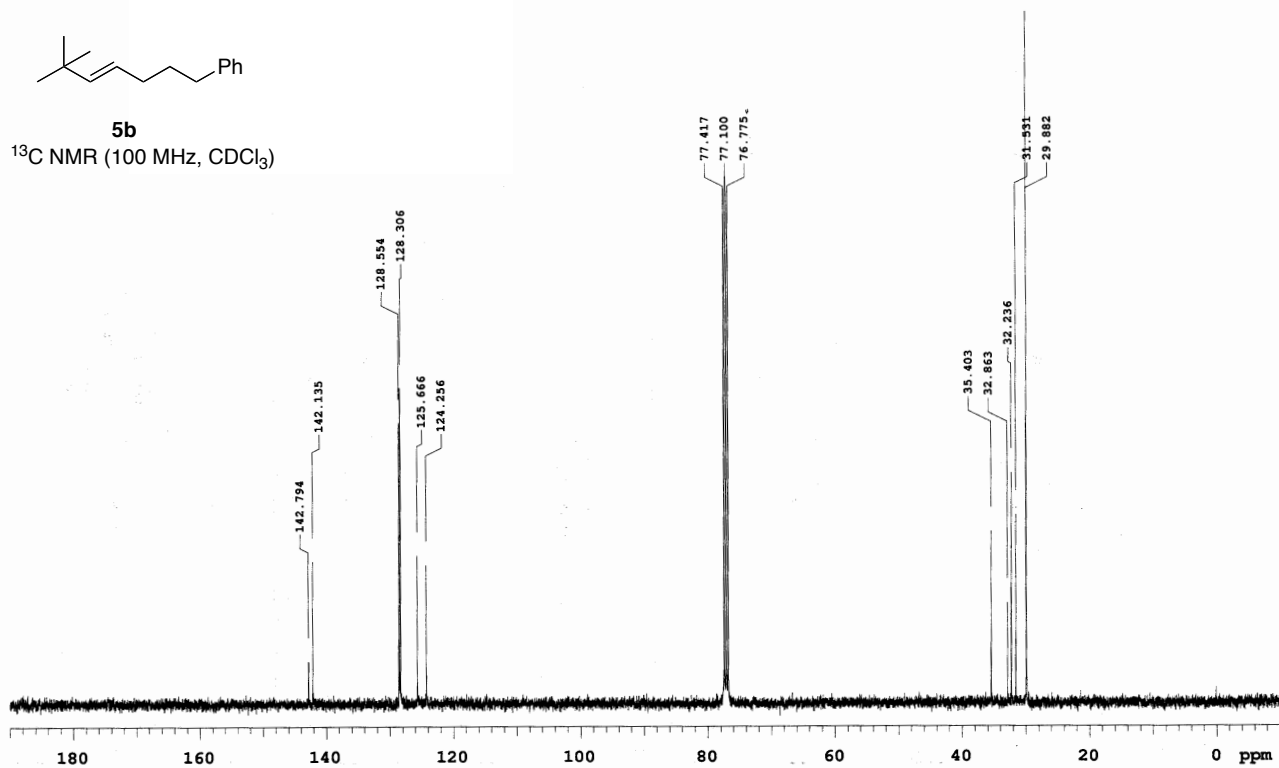
5b

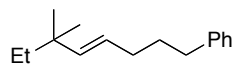
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5b

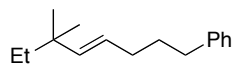
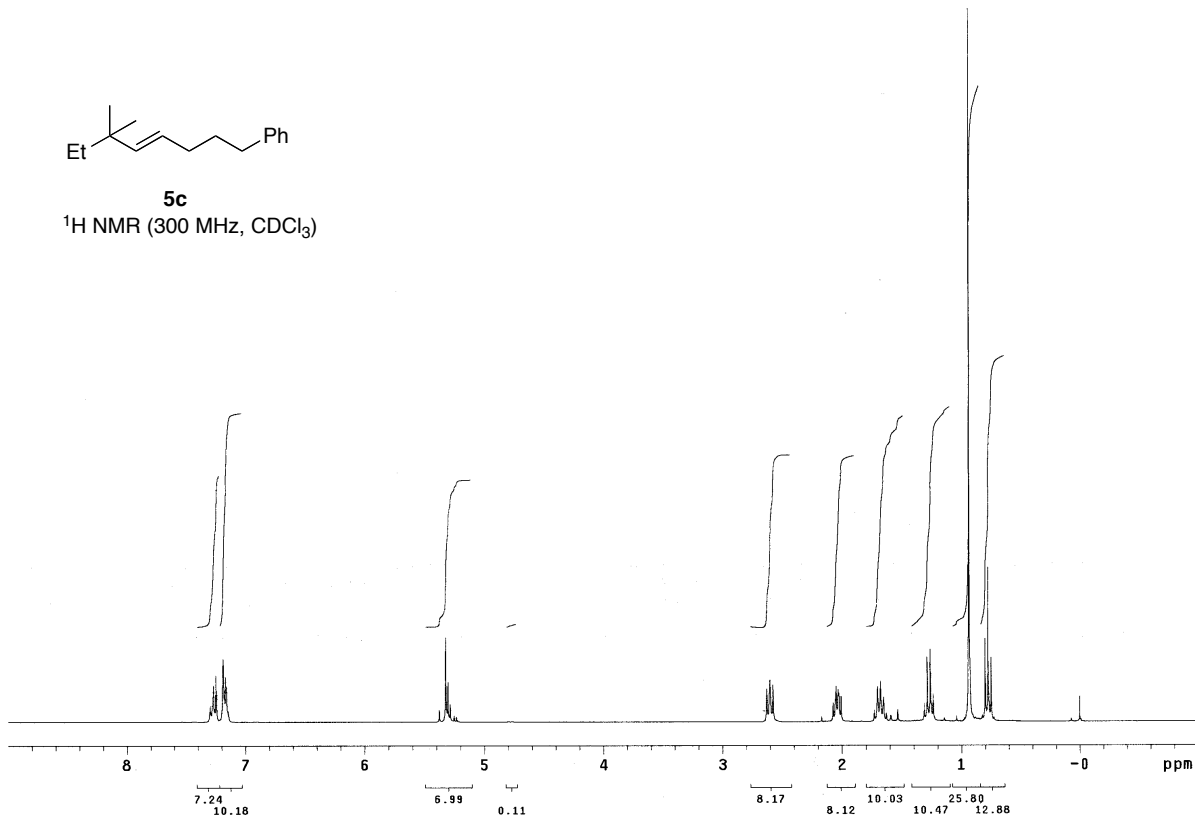
^{13}C NMR (100 MHz, CDCl_3)





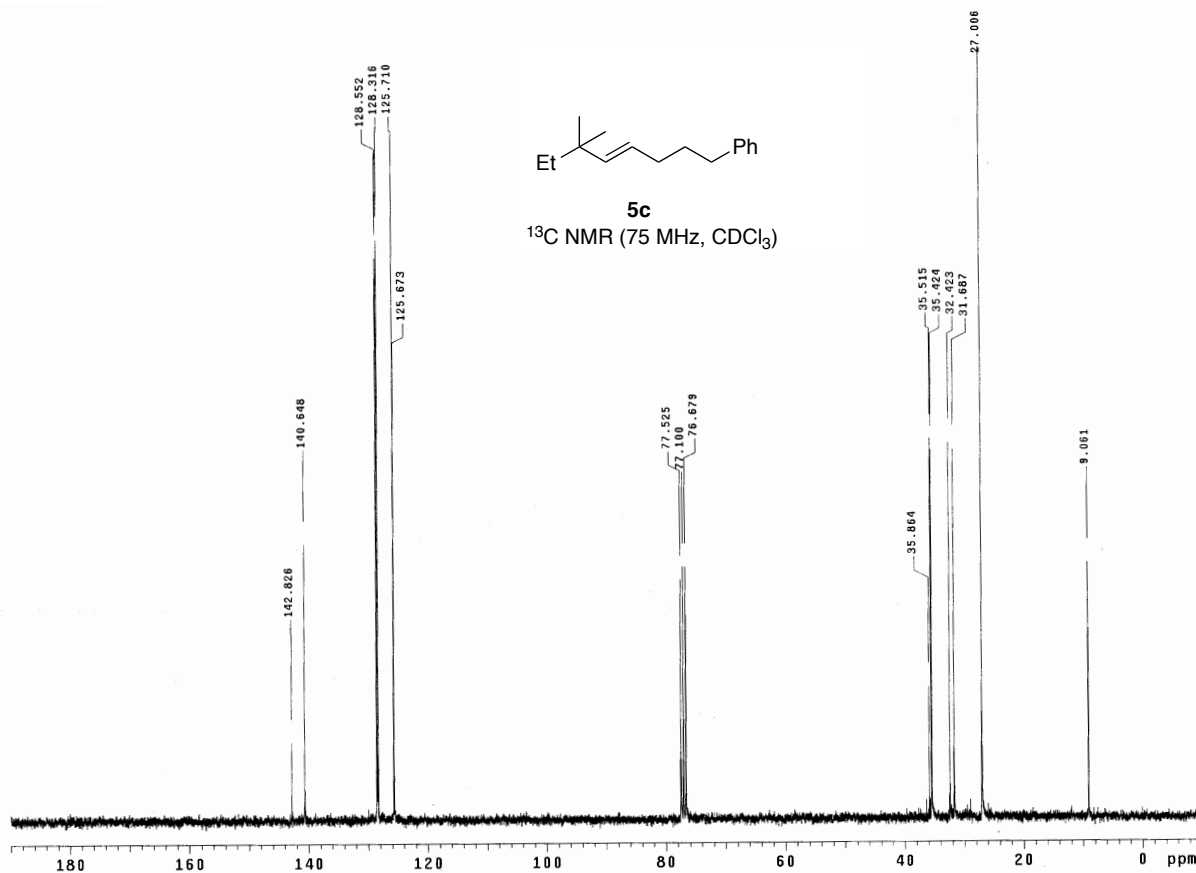
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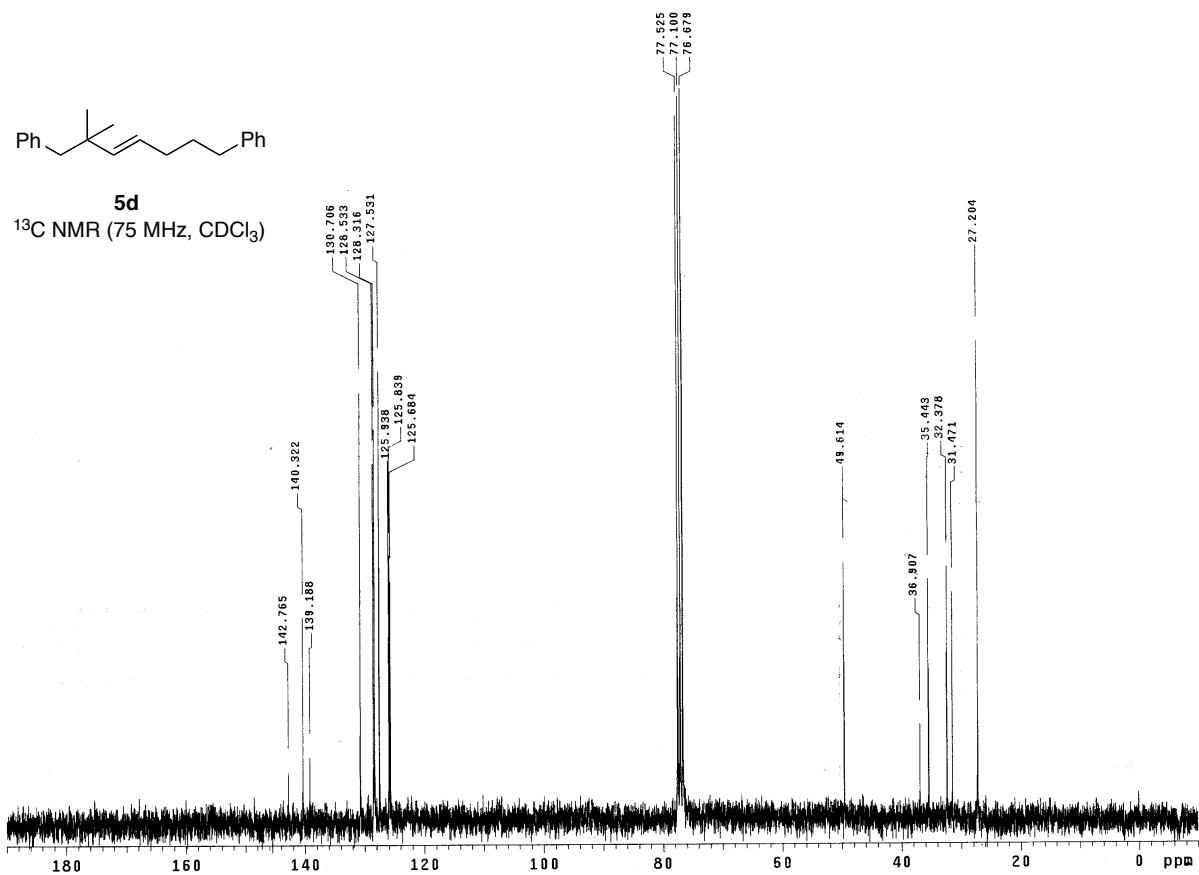
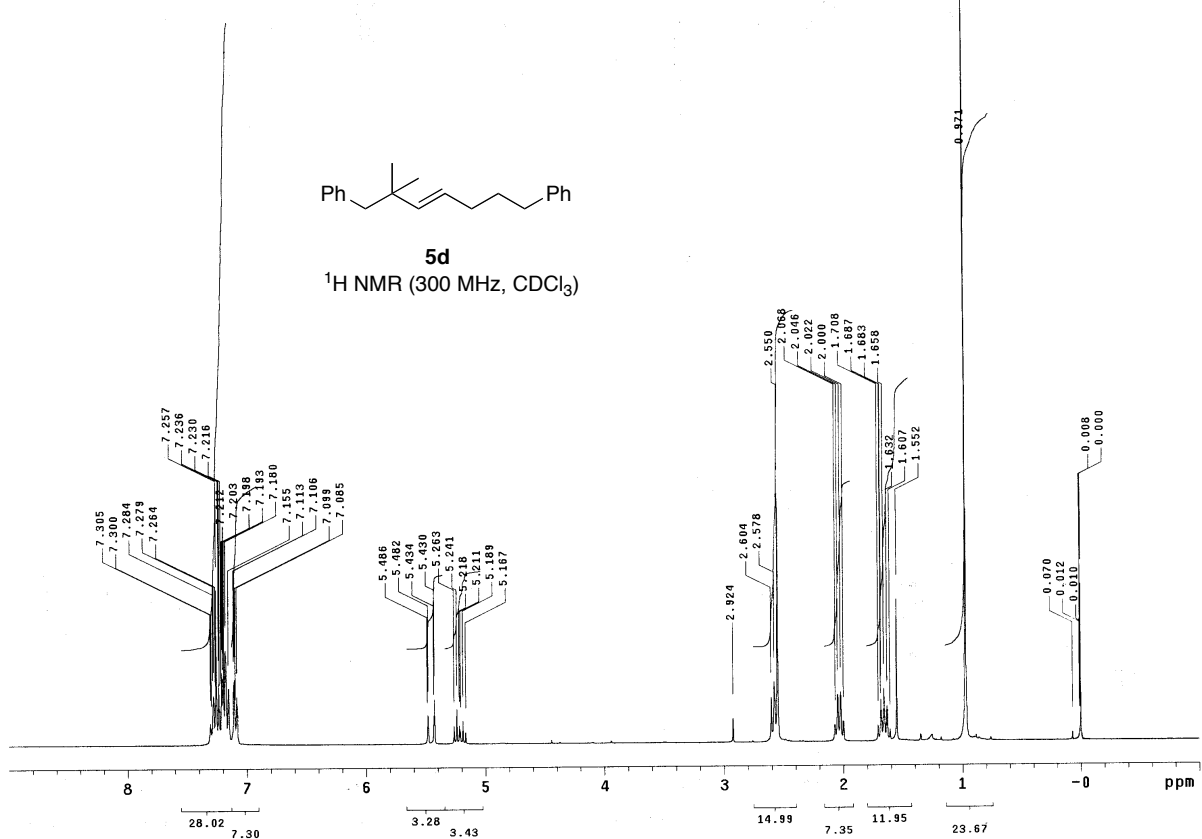
¹H NMR (300 MHz, CDCl₃)

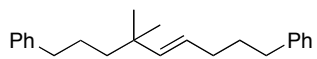


5c

¹³C NMR (75 MHz, CDCl₃)

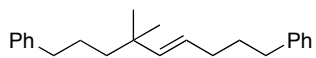
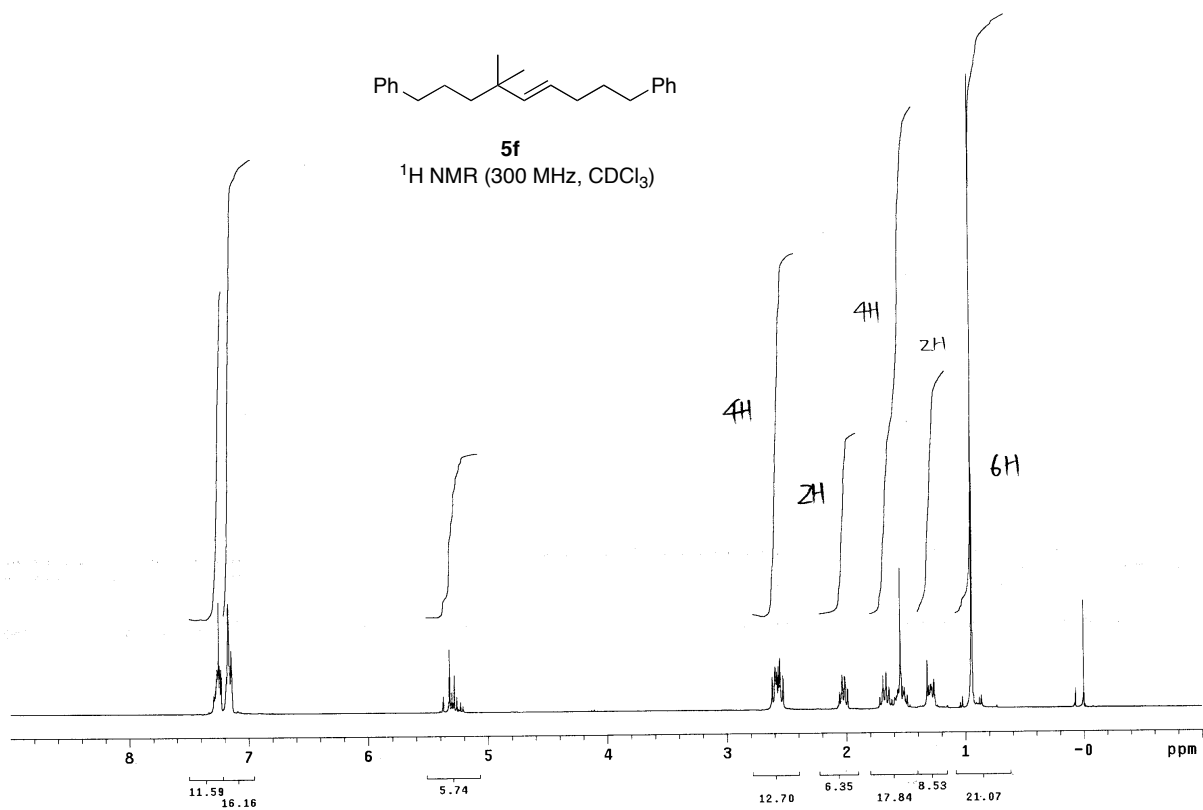






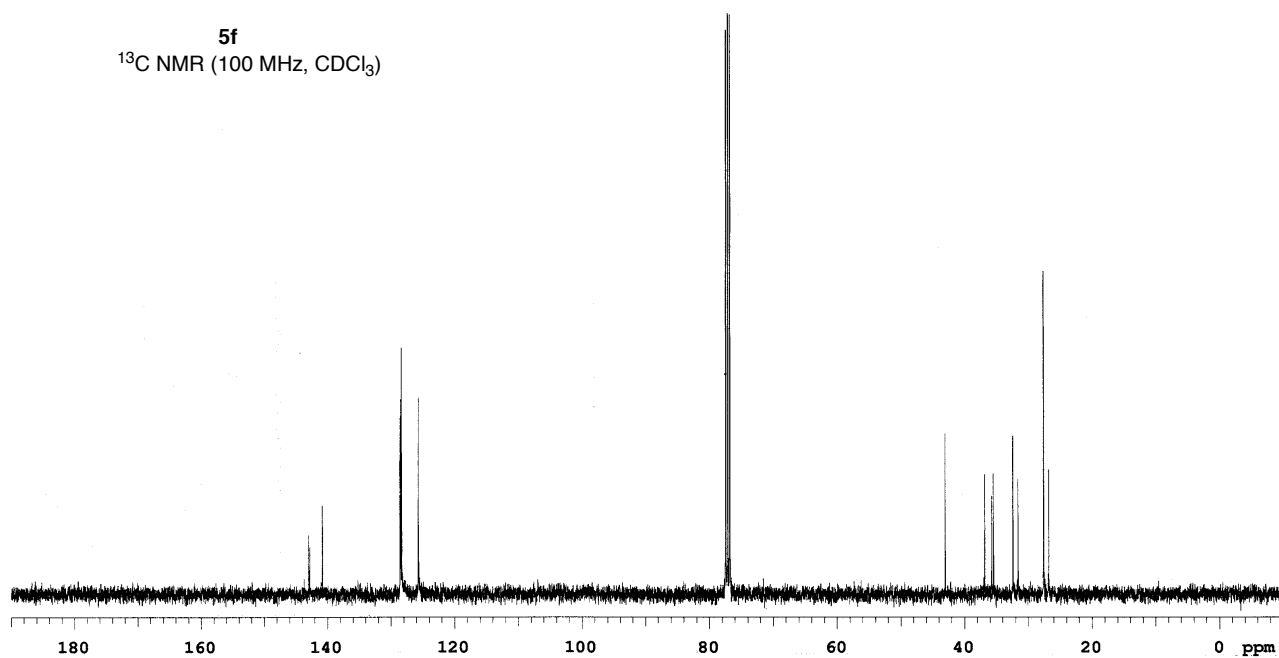
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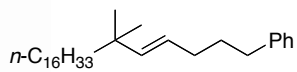
^1H NMR (300 MHz, CDCl_3)



5f

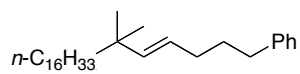
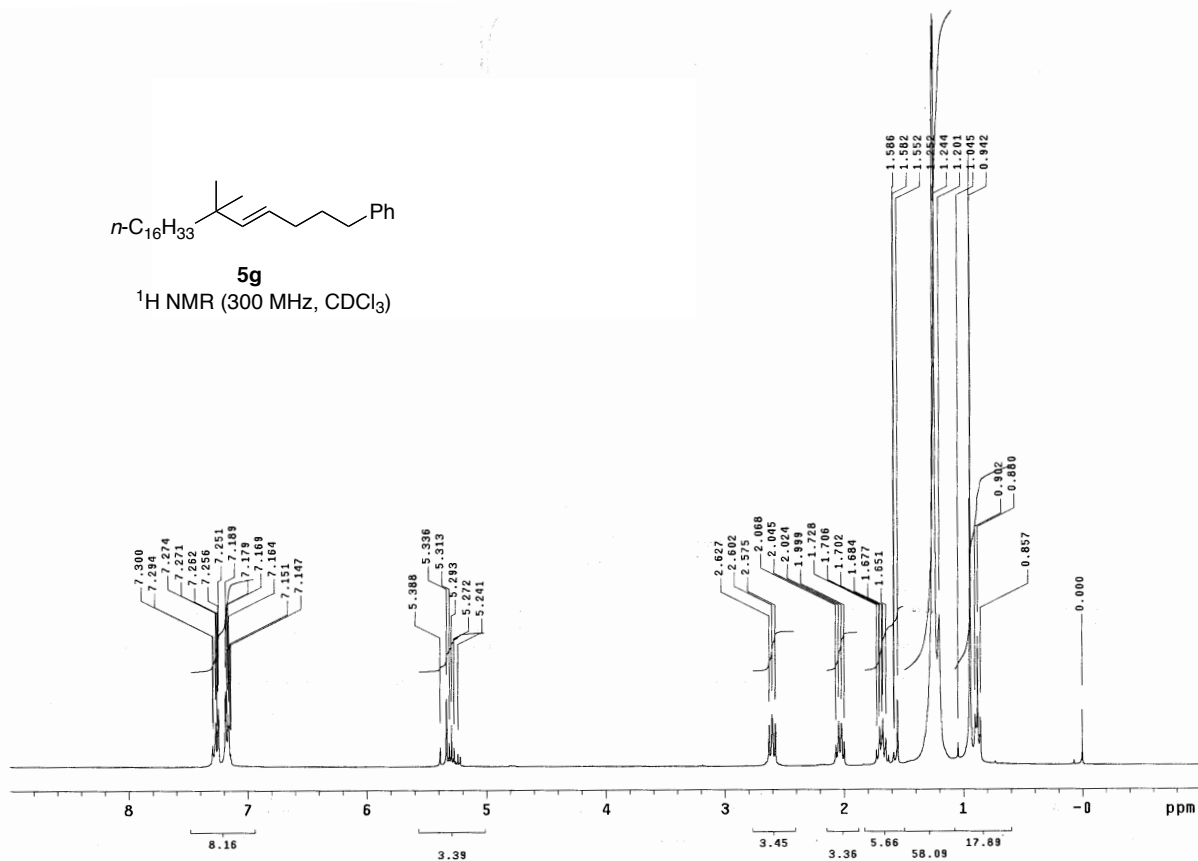
^{13}C NMR (100 MHz, CDCl_3)





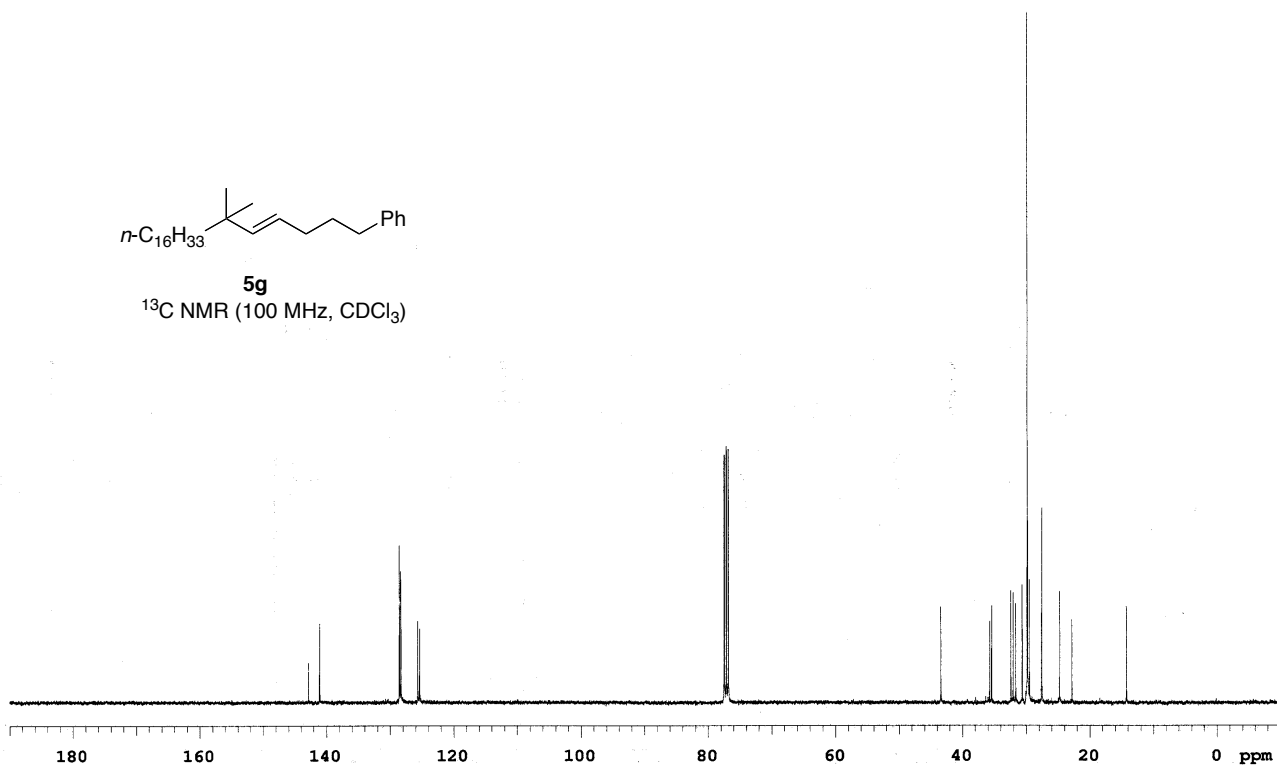
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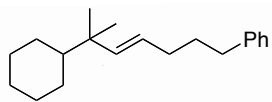
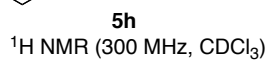
^1H NMR (300 MHz, CDCl_3)

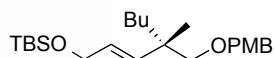


5g

^{13}C NMR (100 MHz, CDCl_3)

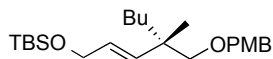
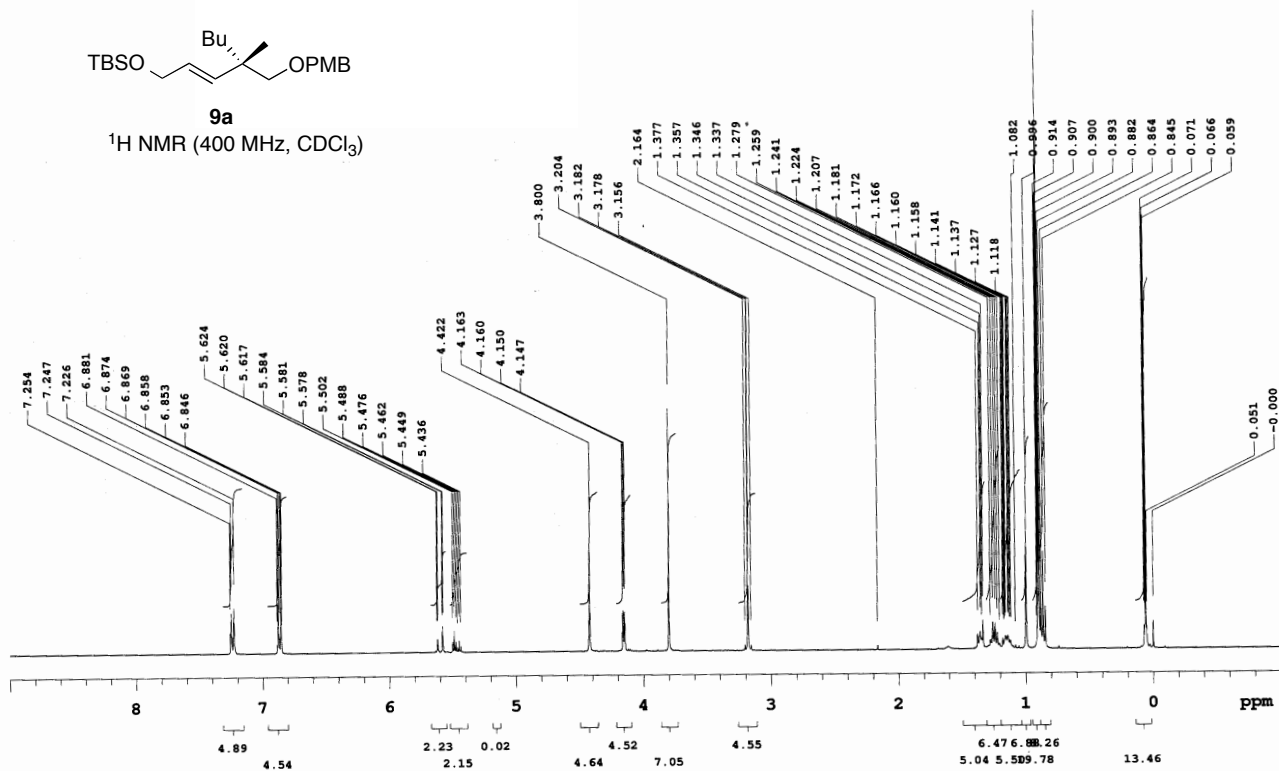






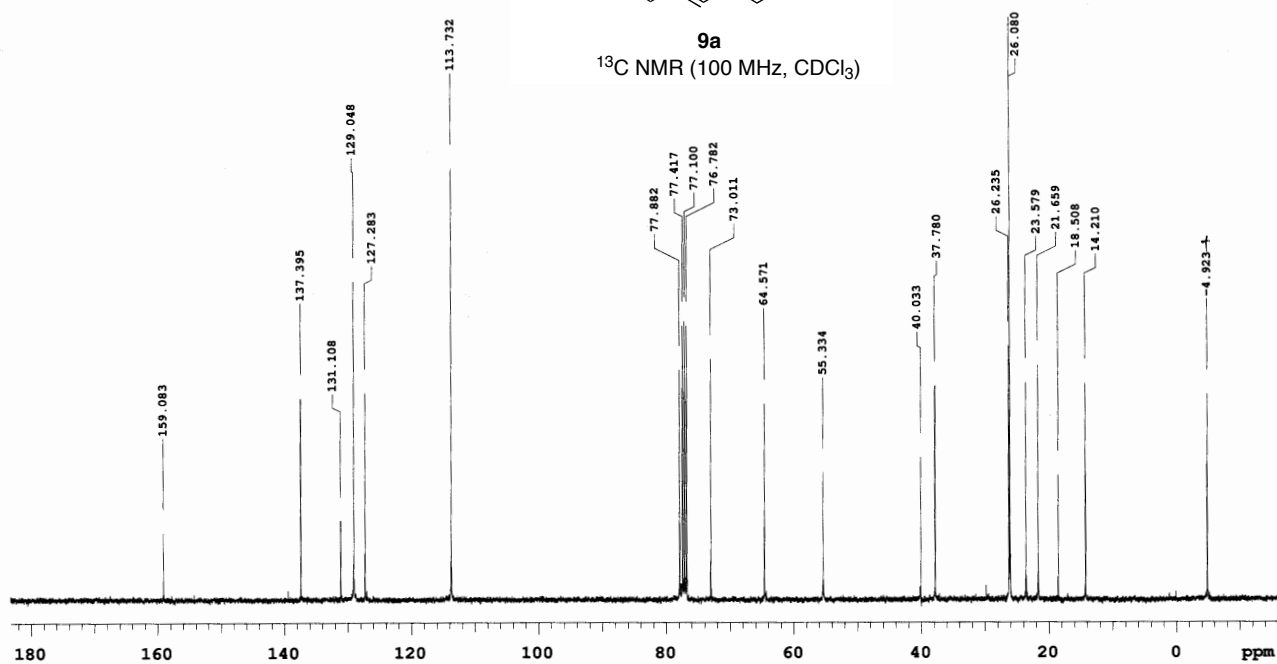
9a

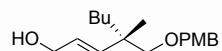
¹H NMR (400 MHz, CDCl₃)



9a

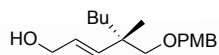
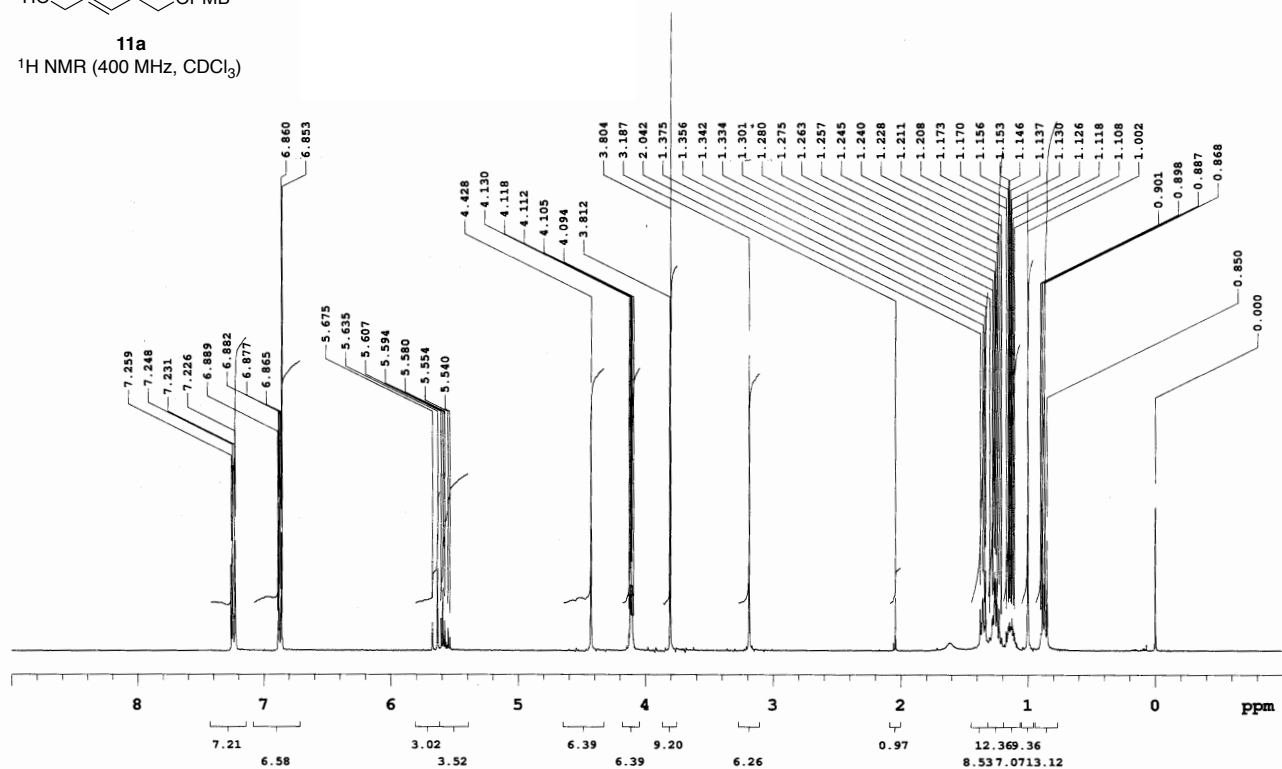
¹³C NMR (100 MHz, CDCl₃)





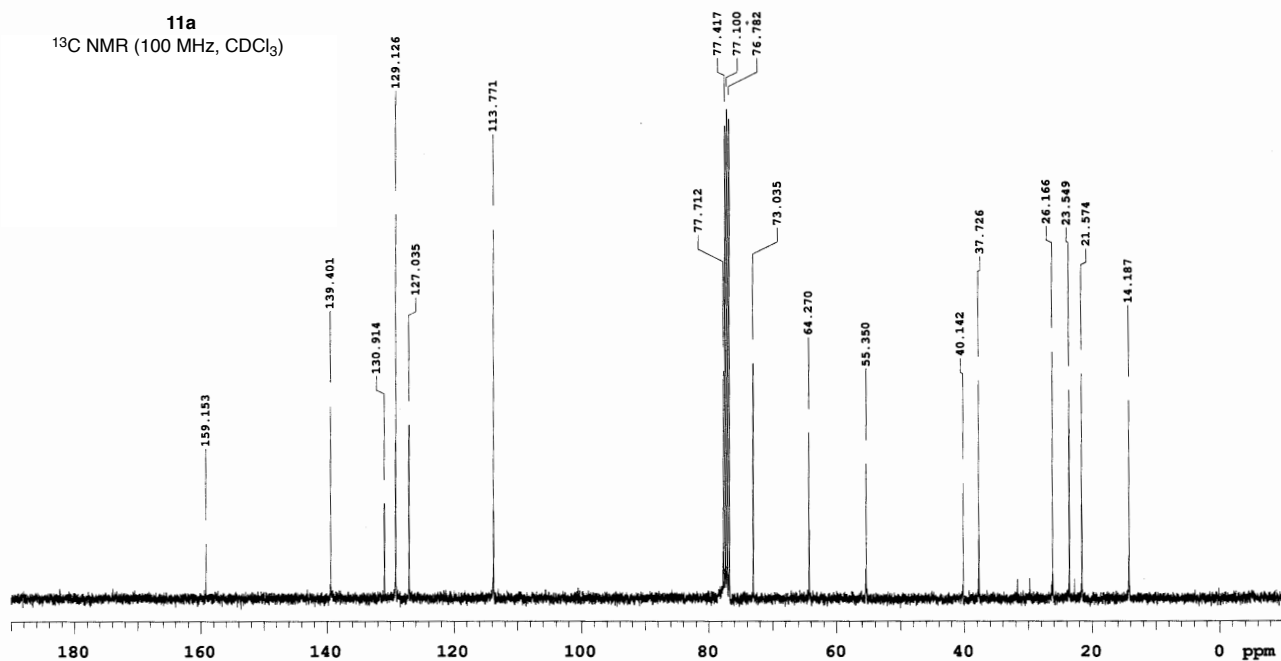
11a

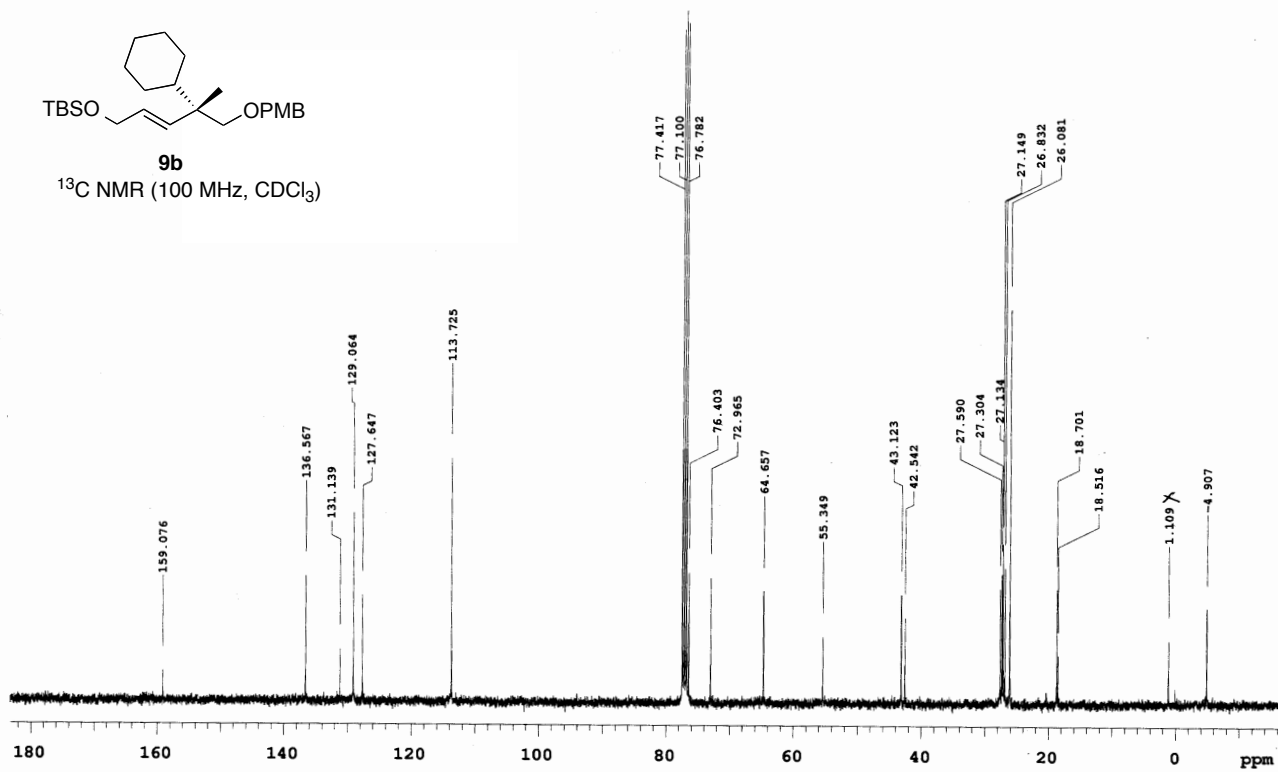
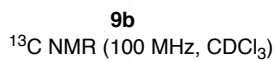
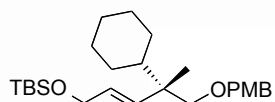
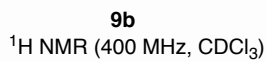
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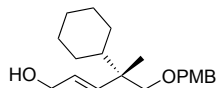


11a

¹³C NMR (100 MHz, CDCl₃)

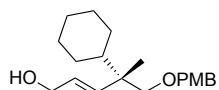
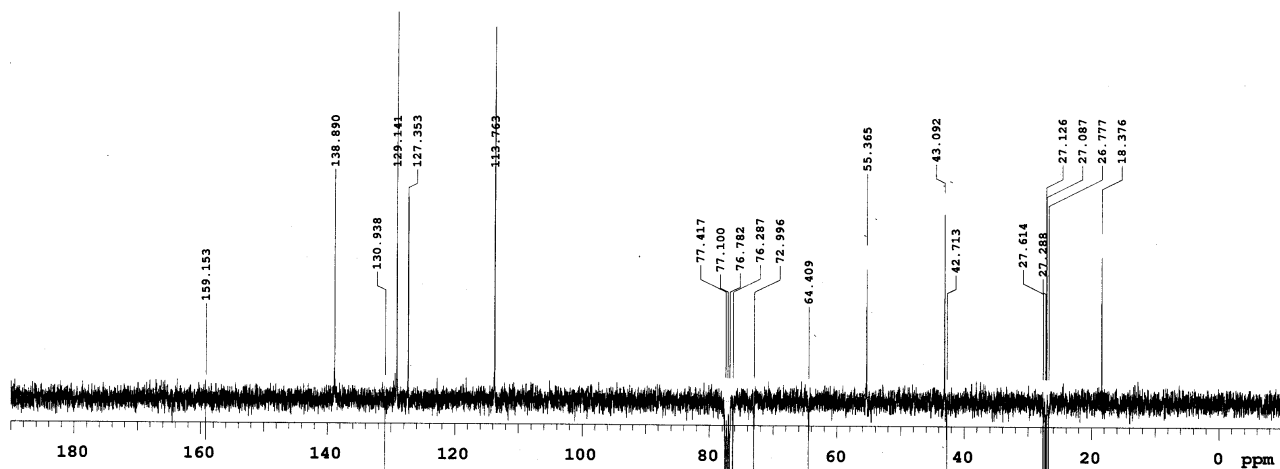
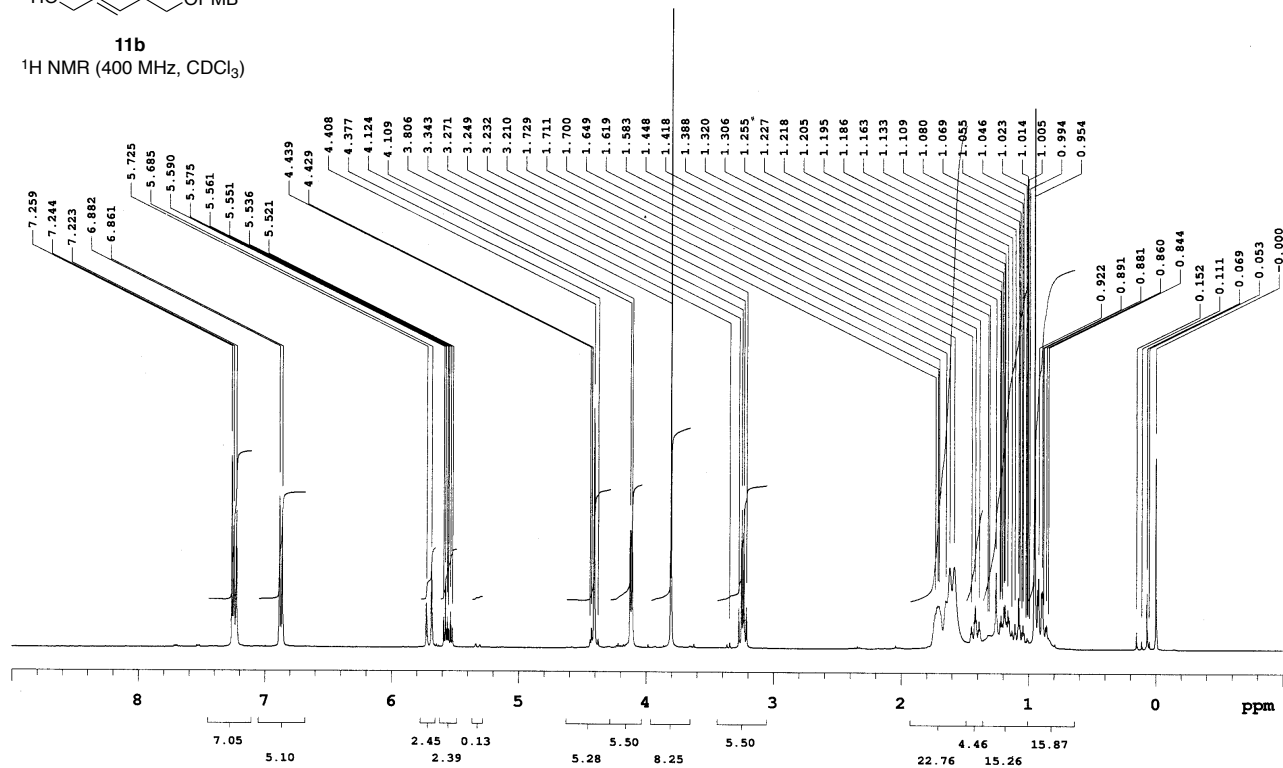






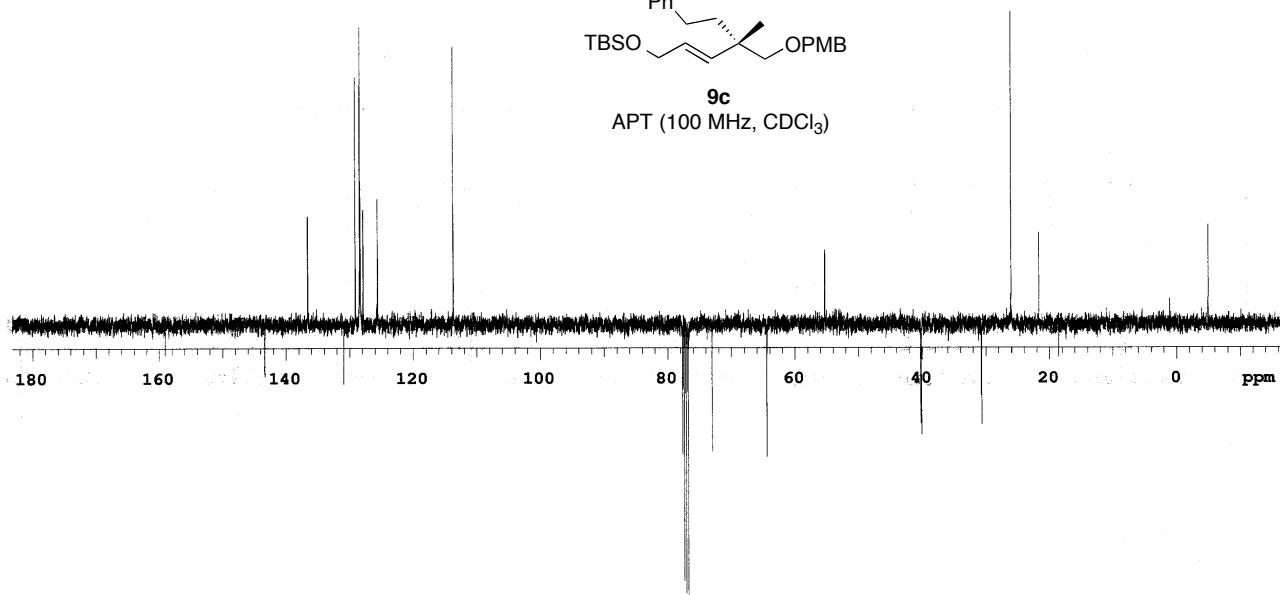
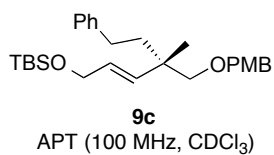
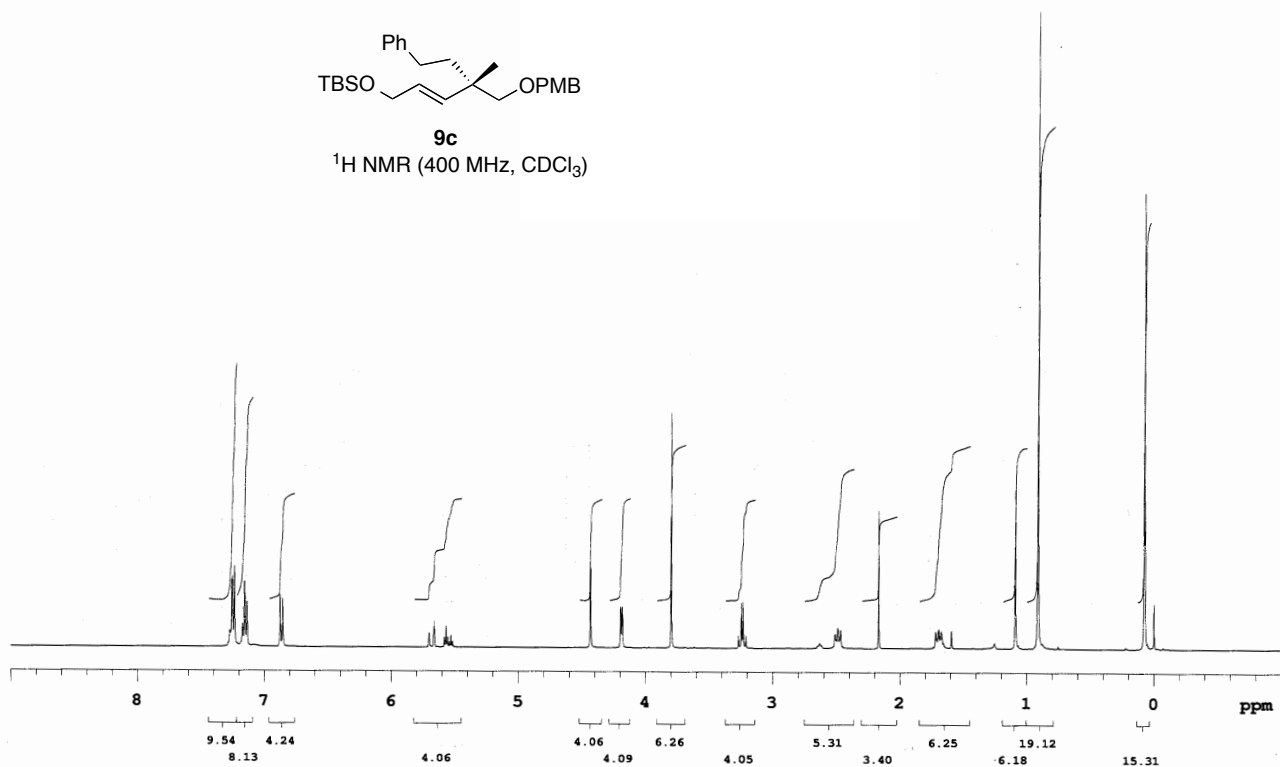
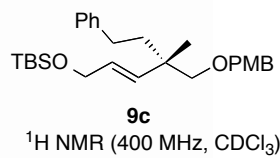
11b

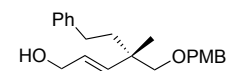
^1H NMR (400 MHz, CDCl_3)



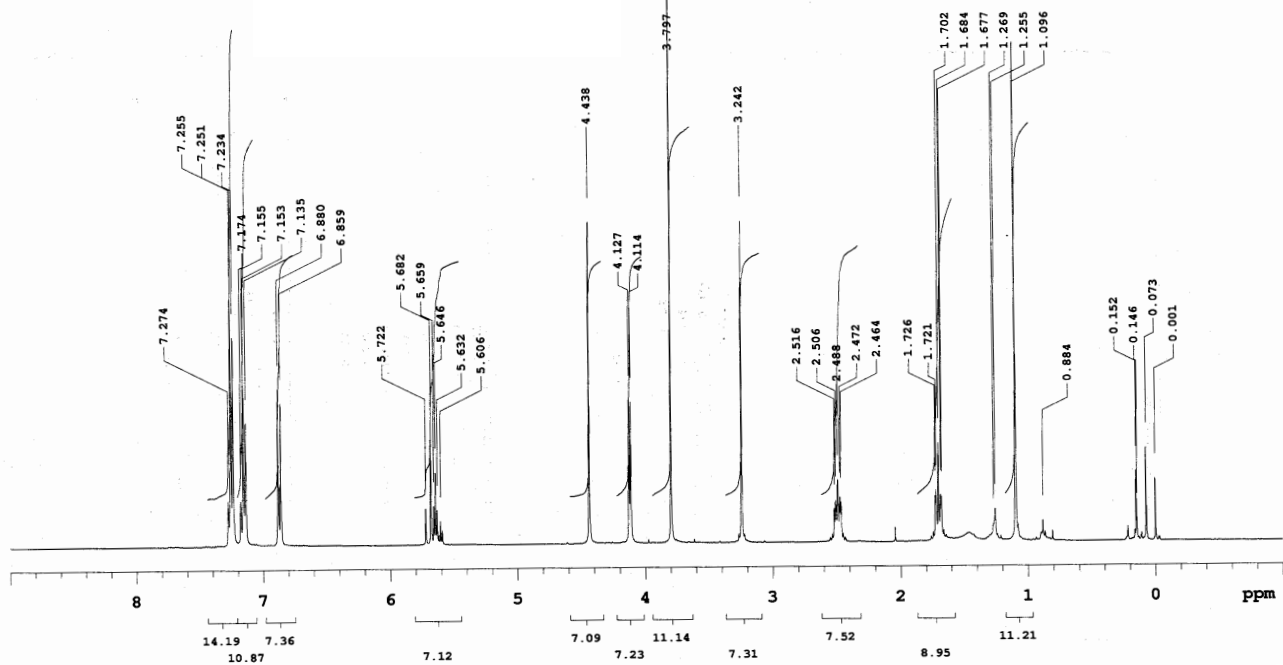
11b

APT (100 MHz, CDCl_3)

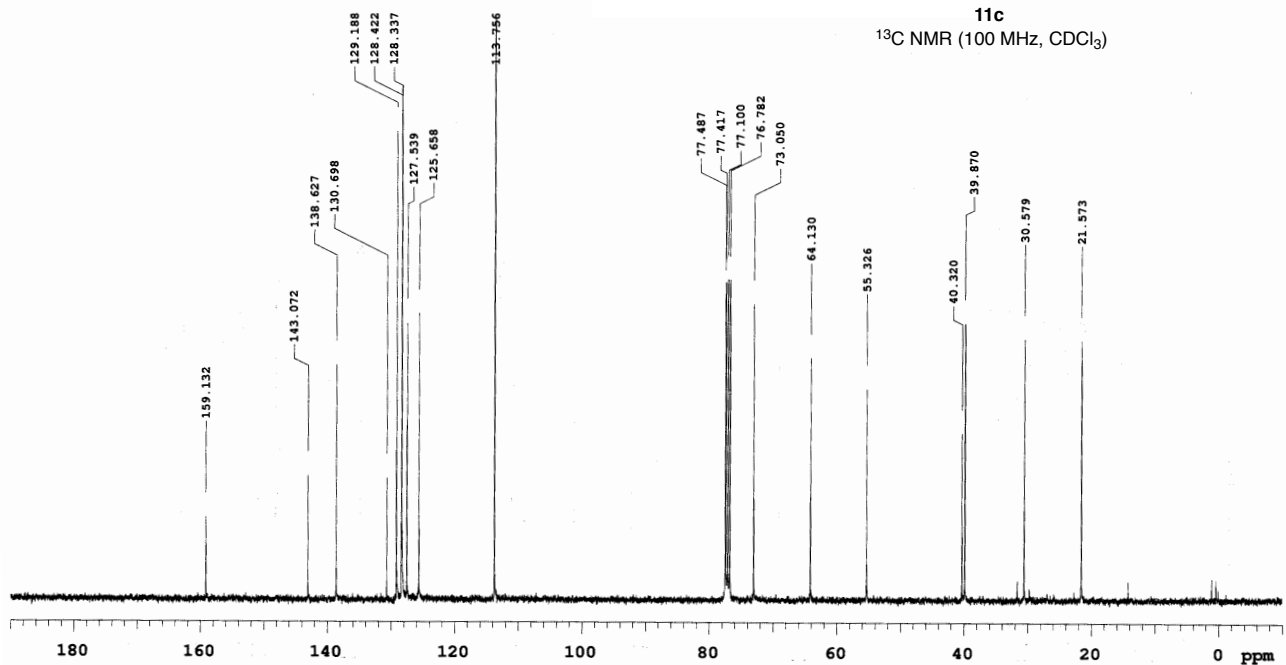


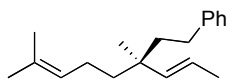


11c
¹H NMR (400 MHz, CDCl₃)

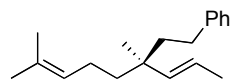
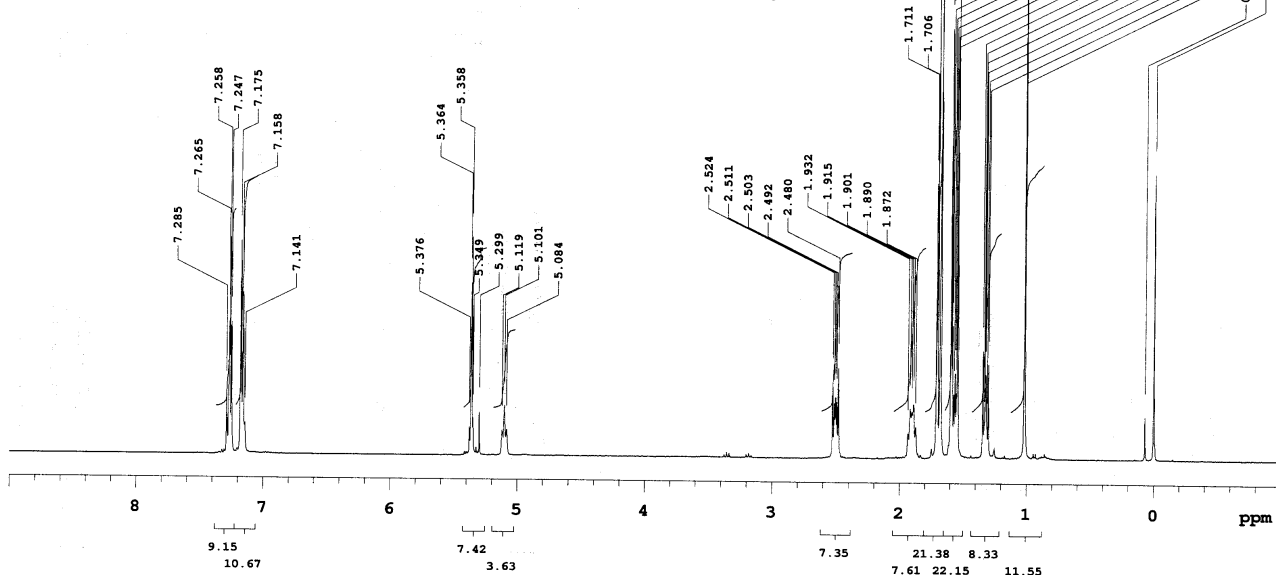


11c
¹³C NMR (100 MHz, CDCl₃)





(S)-10
 ^1H NMR (400 MHz, CDCl_3)



(S)-10
 ^{13}C NMR (100 MHz, CDCl_3)

