

PART 1. NEW MECHANISTIC INSIGHTS AND PROCEDURES FOR THE PREPARATION OF ORGANOLITHIUM COMPOUNDS BY REDUCTIVE LITHIATION.

PART 2. THE MOST STEREOSELECTIVE REDUCTION OF ALCOHOLS USING LITHIUM AND HYDRATED SALTS OF COMMON TRANSITION METALS.

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PART 1. NEW MECHANISTIC INSIGHTS AND PROCEDURES FOR THE PREPARATION OF ORGANOLITHIUM COMPOUNDS BY REDUCTIVE LITHIATION.

PART 2. THE STEREOSELECTIVE REDUCTION OF KETONES TO THE MOST THERMODYNAMICALLY STABLE ALCOHOLS USING LITHIUM AND HYDRATED SALTS OF COMMON TRANSITION METALS.

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University of Pittsburgh, 2015

Part 1: A widely used method of preparing organolithium compounds is by the reductive lithiation of alkyl phenyl thioethers or usually less conveniently, alkyl halides, with either aromatic radical-anions of lithium or lithium metal in the presence of a catalytic amount of an aromatic electron transfer reagent. The work presented here shows, in two parts, that (i) a catalytic amount of *N,N*-dimethylaniline (DMA) and lithium ribbon can achieve reductive lithiation and (ii) lithium dispersion can achieve reductive lithiation in the absence of the electron transfer agent. These procedures are more efficient and surprisingly, in both methods of reductive lithiation, the order of relative reactivity of the substrates differs from that of the method using preformed aromatic radical-anion. Moreover, DMA is significantly cheaper than alternative reductive lithiation catalysts, therefore, can be recycled during work-up, which makes this process more cost-effective. The methodology was expanded to, but may not be limited to, (i) the DMA catalyzed reductive lithiation of phenyl thioethers and alkyl chlorides and (ii) the lithium dispersion reductive lithiation of phenyl thioethers, alkyl chlorides, acrolein diethyl acetal, and isochroman.

Part 2: An operationally simple method is presented for the highly stereoselective reductions of a variety of ketones to the most thermodynamically stable alcohols. In this procedure, the ketone is treated with lithium dispersion and either $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ or $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in THF at room temperature. This protocol is both more convenient and efficient than those commonly used for the diastereoselective reduction of five- and six- membered cyclic ketones.

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LIST OF ABBREVIATIONS

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degrees celsius
$^1\text{H NMR}$	proton nuclear magnetic resonance
$^{13}\text{C NMR}$	carbon nuclear magnetic resonance
9-BBN	9-borabicyclo[3.3.1]nonyl
BDE	bond dissociation energy
CaH_2	calcium hydride
CDCl_3	deuterated chloroform
CHCl_3	chloroform
CH_2Cl_2	methylene chloride
CH_3Li	methyl lithium
$\text{CuBr}\cdot\text{SMe}_2$	copper bromide dimethyl sulfide
$\text{CuCl}_2\cdot 2\text{H}_2\text{O}$	copper (II) chloride hydrate
D_2O	deuterium oxide
DBB	<i>p,p'</i> -di- <i>tert</i> -butyl biphenyl
$\text{DIBAO}_3\text{SCH}_3$	<i>Al</i> -methanesulfonyldiisobutylalane
disp.	dispersion
DMA	<i>N,N</i> -dimethylaniline
DMAN	1-(dimethylamino)-naphthalene
DMF	<i>N,N</i> -dimethylformamide
DMOT	<i>N,N</i> -dimethyl- <i>o</i> -toluidine
dr	diastereomeric ratio
e^-	electron
E2	bimolecular elimination
EI	electron ionization
equiv	equivalents
ES^+	positive electrospray ionization (MS)
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FeCl_3	ferric chloride
$\text{FeCl}_2\cdot 4\text{H}_2\text{O}$	iron (II) chloride tetrahydrate
GLC	gas-liquid chromatography
h	hour(s)
HCl	hydrochloric acid
H_2O	water
<i>i</i> Pr	isopropyl

I ₂	iodine
In	indium
IR	infrared spectroscopy
KMnO ₄	potassium permanganate
KHSO ₅	potassium peroxymonosulfate (oxone)
LDBB	lithium <i>p,p'</i> -di- <i>tert</i> -butyl biphenylide
LDMA	lithium <i>N,N</i> -dimethylanilinide
LDMAN	lithium 1-(dimethylamino)-naphthalenide
LDMOT	lithium <i>N,N</i> -dimethyl- <i>o</i> -toluidinide
Li	lithium
LiAlH ₄	lithium aluminum hydride
LN	lithium naphthalenide
LUMO	lowest unoccupied molecular orbital
MgSO ₄	magnesium sulfate
min	minute(s)
MS	mass spectrometry
MVK	methyl vinyl ketone
NaBH ₄	sodium borohydride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaOH	sodium hydroxide
NaSPh	sodium thiophenoxide
NH ₃	ammonia
NiCl ₂ •2H ₂ O	nickel (II) chloride dihydrate
Np	naphthalene
PAA	<i>p</i> -anisaldehyde
PdCl ₂	palladium (II) chloride
POCl ₃	phosphoryl chloride
ppm	parts per million
RC1	alkyl chloride
RLi	alkyl lithium
RSPH	alkyl phenyl sulfide
rt	room temperature
S _H 2	bimolecular homolytic substitution
S _N 2	bimolecular nucleophile substitution
temp.	temperature
<i>tert</i>	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TOF	time-of-flight
UV	ultraviolet

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1.0 NEW MECHANISTIC INSIGHTS AND PROCEDURES FOR THE PREPARATION OF ORGANOLITHIUM COMPOUNDS BY REDUCTIVE LITHIATION.

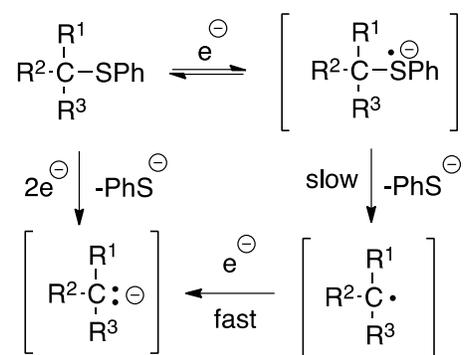
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1.1 BACKGROUND

1.1.1 Lithium Radical-Anion Reagents.

Functionalized organometallic reagents have become versatile intermediates for the preparation of complex polyfunctional molecules.¹ In this vast area, organolithium compounds constitute an essential class of reagents that introduce different functionalities into an organic skeleton using only one reaction step. Organolithium reagents can be prepared from different starting materials, replacing a carbon-X bond of the precursors by a carbon-lithium bond. Previously, deprotonation and halogen-lithium exchange have represented the most versatile routes for the preparation of organolithium intermediates. Thus, other methodologies are considered attractive processes that expand the approaches to these interesting reagents for synthetic purposes.¹

Reductive lithiation, the replacement of a C-heteroatom bond with a C-Li bond, using aromatic radical-anions proves to be a viable method for the synthesis of organolithiums. The lithium aromatic radical-anion causes the reductive cleavage of a carbon-X bond leading to a carbon-radical, which is further reduced to a carbanion stabilized by lithium.¹ An important advantage of reductive lithiation with an aromatic radical-anion is that it is often the case that the less stable the organolithium, the greater the ease of its generation by reductive lithiation.² The reason is that the mechanism involves the reversible transfer of an electron from the aromatic radical-anion to the substrate to form a new radical-anion followed by homolytic cleavage of the bond between the organic moiety and the leaving group resulting in an anionic leaving group and a carbon radical ([Scheme 1.1](#)).³ Since this step is rate determining, the rate of the reaction is determined largely by the stability of the intermediate radical (tertiary > secondary > primary, and $sp^3 > sp^2$), rather than that of the carbanion, to which the radical is rapidly reduced by the second equivalent of radical-anion reducing agent.³



Scheme 1.1 Mechanism of Reductive Lithiation of Phenyl Thioethers.

In reductive lithiations using aromatic electron transfer agents, the aromatic radical-anions are formed as a result of the abstraction of an electron from an alkali metal, usually Li, by an aromatic hydrocarbon.⁴ The electron donated by the metal is believed to occupy the π^* orbital (LUMO) of the corresponding aromatic compound.⁴ Aromatic radical-anions including: lithium naphthalenide (LN), lithium 1-(dimethylamino)naphthalenide (LDMAN), and lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) are currently in use (Figure 1.1). All three radical-anion reducing agents can be easily generated in THF, the solvent universally used in synthetic procedures involving aromatic radical-anions. Other commonly used solvents have been found ineffective except dimethyl ether, in which LDMAN can be prepared.⁵ The rapidity of lithium metal electron donation in THF compared to the sluggishness of the same reactions in other solvents can be ascribed to the ability of the lithium metal cation to coordinate to the lone pair of electrons of THF. This greater solvating power promotes the donation of electrons from Li metal to the aromatic hydrocarbon.⁶

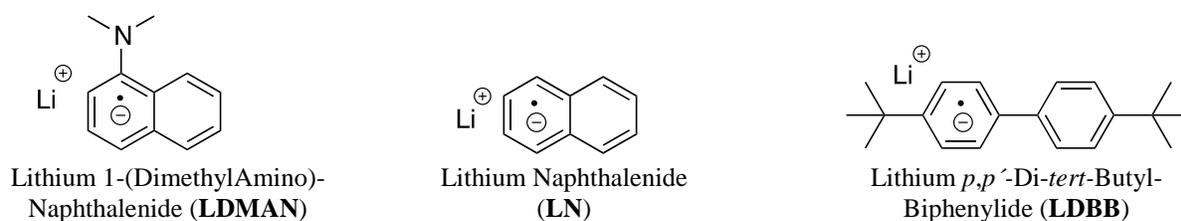
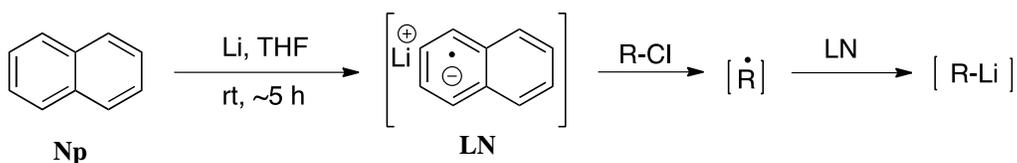


Figure 1.1 Aromatic Radical-Anion Reducing Agents.

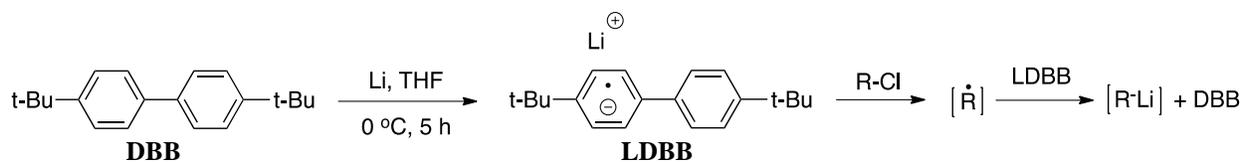
The formation of aromatic radical-anions is dependent on the nature of the metal, the aromatic hydrocarbon and the temperature. Screttas, in 1972, was the first to report aromatic

radical-anions formed from lithium and naphthalene (Np).⁷ The latter acts as an acceptor of lithium's electron, and the resulting radical-anion LN is used for a very rapid reduction of an alkyl halide to generate an alkyl radical, which then accepts another electron from a second LN molecule in order to form an alkyllithium, RLi ([Scheme 1.2](#)).⁷



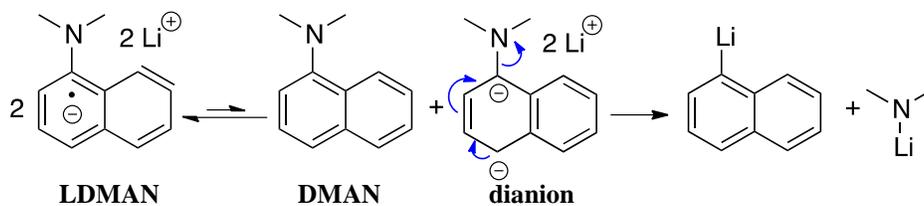
Scheme 1.2 Formation of LN and the Reductive Lithiation of an Alkyl Chloride.

The lithium radical-anion reagent LDBB is formed from Li metal and the aromatic hydrocarbon 4,4'-di-*tert*-butylbiphenyl (DBB). The bulky *tert*-butyl groups effectively prevent participation in side-reactions by sterically shielding positions in both aromatic rings while allowing it to participate in single electron reductions.⁸ On the other hand, both naphthalene and its radical-anion LN are susceptible to attack by the intermediate radical (R•) or by the newly formed organolithium (RLi). LDBB is a more powerful electron donor than LN. This allows reductive lithiation to be performed at a lower temperature and for a shorter amount of time.⁸ Unfortunately, the use of LDBB for the preparation of various alkyllithiums is limited by separation issues between the final product and the aromatic hydrocarbon by-product DBB ([Scheme 1.3](#)). When the reaction is complete, the DBB can be removed either by a chromatography column, if the desired product is fairly polar, or by vacuum distillation, which is usually destructive and results in low isolated yields of the desired product.



Scheme 1.3 Formation of **LDBB** and the Reductive Lithiation of an Alkyl Chloride.

In 1980, a solution to the problem of removal of DBB was found in the Cohen Laboratory.⁹ When LDMAN was used as the reducing agent, the basic aromatic by-product, 1-(dimethylamino)naphthalene (DMAN), could easily be removed and recovered by a dilute acid wash. DMAN appears to accept an electron from the lithium metal far faster than DBB; THF solutions of LDMAN can be generated at -55 °C in 5 h. while THF solutions of LDBB are generated at 0 °C in 5 h. A disadvantage of LDMAN is that above -52 °C it decomposes to 1-lithionaphthalene and lithium dimethylamide ([Scheme 1.4](#)). Because of the great instability of aryl radicals, it was thought that the decomposition of LDMAN at this low temperature was probably not due to the homolytic cleavage of the C-N bond, the usual mode in radical-anion decompositions. Rather, it was postulated that the aromatic dianion was generated in an unfavorable equilibrium with the radical anion and was decomposing directly to the relatively stable 1-lithionaphthalene and lithium dimethylamide.⁹



Scheme 1.4 LDMAN Decomposition the Aromatic Dianion in Equilibrium with LDMAN.²

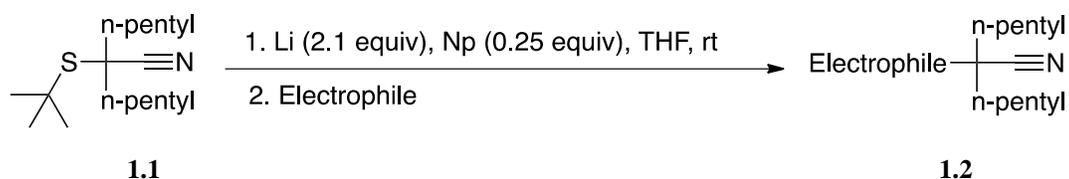
Fortunately, this often appeared to be only a minor disadvantage since most reductive lithiations are successful at $-78\text{ }^{\circ}\text{C}$. As a result, the use of LDMAN is rather widespread,^{2,5,9-11} but considerably less so than the use of LDBB.¹²⁻¹³ For optimum yield, it is necessary to maintain a temperature of $-55 \pm 3\text{ }^{\circ}\text{C}$ by manual control for 5 h for the synthesis of LDMAN.¹³ When this procedure was followed, every example tested provided higher yields than the use of either LDBB or LN in reductive lithiations.¹⁴

1.1.2 Catalytic Method of Reductive Lithiation.

Because LDMAN decomposes to 1-lithionaphthalene above $-52\text{ }^{\circ}\text{C}$ (Scheme 1.4), a “catalytic” variation of reductive lithiation, which employs a catalytic amount of the aromatic hydrocarbon rather than a stoichiometric amount of the preformed radical-anion, was devised in this laboratory, thus allowing reactions with LDMAN to be performed at higher temperatures.⁹ DMAN and Li metal react over a period of hours to produce LDMAN while most reductive lithiations are extremely rapid. Therefore, it was reasoned that if the substrate to be reduced is dissolved in THF with a substoichiometric amount of DMAN, the latter would act as a conduit for electrons to the substrate undergoing reductive lithiation. As a result, the concentration of the radical-anion would

remain extremely low until the reductive lithiation was complete. Thus, the equilibrium in [Scheme 1.4](#) would be driven even further to the left, resulting in a negligible concentration of the unstable dianion and consequently in a very slow decomposition of LDMAN.²

Nagata appears to be the first to employ organic cleavage reactions under catalytic reductive lithiation conditions in 1973. By evaluating the lithium reduction of α,α -dialkylated- α -*t*-butyl-esters, ketones, and nitriles in liquid ammonia, the Nagata group stumbled upon an unexpected result pertaining to the nitriles. Because of its quasihalogen nature, a cyano group itself undergoes ready reductive cleavage with alkali metals in liquid ammonia giving an alkane.¹⁵ However, mechanistic considerations led the group to change the electron-transfer medium from liquid ammonia to catalytic amounts of naphthalene in THF for the reductive lithiation of nitrile **1.1**. This change gave excellent results when trapping the organolithium intermediate with various electrophiles to provide product **1.2**, at room temperature ([Scheme 1.5](#)).¹⁵



Scheme 1.5 Reductive Lithiation of α,α -Dialkylated- α -(*tert*-Butylthio)-Acetonitrile, **1.1**.¹⁵

More recently, Yus and co-workers introduced an alternative procedure for catalytic reductive lithiation of alkyl chlorides and alkyl phenyl sulfides.¹⁶ In their work¹⁷⁻¹⁹ a solution of the substrate to be reduced, in THF, is mixed with 1-5 mol% of the aromatic hydrocarbon, usually naphthalene or DBB, and a large excess of specially prepared lithium powder, usually a 4 to 7 fold

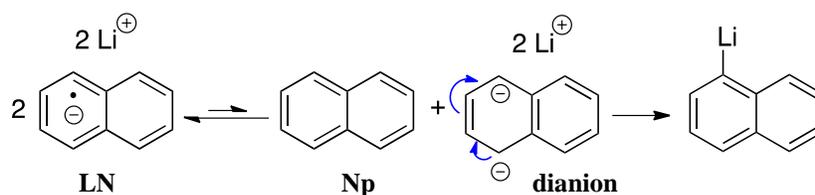
molar excess ([Scheme 1.6](#)). They have demonstrated that a large variety of organic compounds can be reductively lithiated and that this method eases the separation of the aromatic byproduct from the reaction product.¹⁶⁻¹⁹ In a number of these papers, Yus claims that the catalytic aromatic method, in which the radical-anion is continually generated and rapidly destroyed by electron transfer to substrate, is far more powerful than the use of a stoichiometric amount of preformed aromatic radical-anion.^{2,20-23}



Scheme 1.6 Yus's Catalytic Reductive Lithiation of Alkyl Chlorides.

The theoretical basis appears inconsistent with the fact that radical-anion formation is always far slower than the reductive lithiation. Thus, in most cases the rate-determining step in the catalytic aromatic reductive lithiation would be the transfer of an electron from the surface of the metal to the aromatic catalyst.² The net result would be that the process of reductive lithiation would be slower at any given temperature than the preformed radical-anion process.² Such long reaction times can translate into destruction of some organolithium compounds. Of course, damage is minimized in the Yus protocol, in which the radical-anion formation is accelerated by supplying the Li metal as a specially prepared powder rather than large chunks with less surface area, as well as the use of a large excess of the lithium powder. This dramatically increases the overall price and complexity of the catalytic method.²⁴

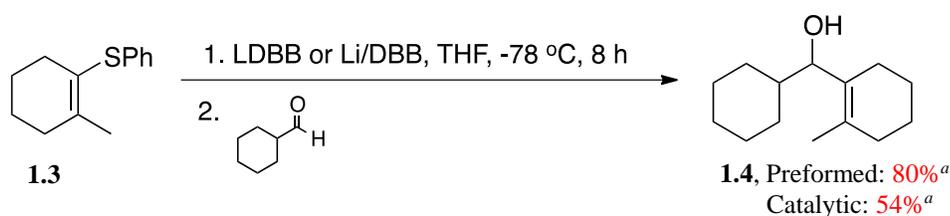
Yus has proposed the following mechanistic explanation to account for the alleged superiority of the catalytic method: there is a greater concentration of aromatic dianion during reduction by the catalytic method and that dianion is expected to be a more powerful reducing agent than the monoanion.²¹ In reality, there should be a far *lower* concentration of the aromatic dianion in the catalytic method compared to the preformed radical-anion method. In the case of preformed aromatic radical-anion, the concentration of dianion is at the maximum since virtually all of the aromatic is in the form of the radical-anion and the concentration of neutral aromatic is negligible.² On the other hand, in the catalytic method, the concentration of dianion is minimal since the rapid transfer of an electron from the slowly formed radical-anion to the substrate maintains a negligible concentration of aromatic radical-anion and virtually all of the aromatic hydrocarbon is in the neutral form.² For example consider naphthalene, as shown in [Scheme 1.7](#), to illustrate this mechanistic explanation. This reasoning is correct as evidenced in the case of DMAN: the green-black color of LDMAN only became evident when all of the substrate had reacted.⁹



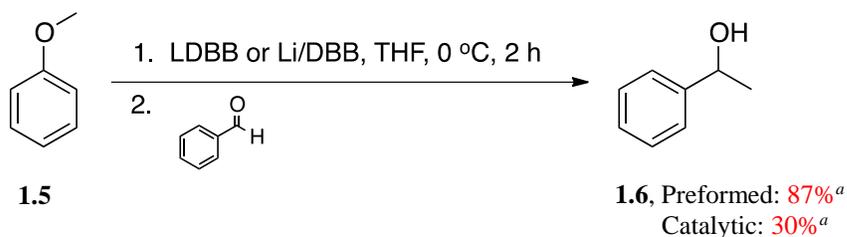
Scheme 1.7 Lithium Naphthalenide, LN, in Equilibrium with Neutral Naphthalene and the Dianion.

In 2006, our lab published a paper comparing the preformed radical-anion and catalytic methods to determine the relative advantages of each.² Through many reductive lithiation

examples, Cohen *et. al.* demonstrated a major disadvantage of the catalytic method; that is at any given temperature, the catalytic method is slower than using a stoichiometric amount of preformed aromatic radical-anion. In cases in which the organolithium is not entirely stable to the reaction conditions, significant decreases in yield are observed in going from the preformed radical-anion to the catalytic method.² Examples include the reductive lithiation of 2-methyl-1-(phenylthio)-cyclohexene, **1.3**, a vinyl phenyl sulfide, ([Scheme 1.8](#)) and anisole, **1.5**, ([Scheme 1.9](#)), which cannot undergo reductive lithiation in the absence of DBB.²

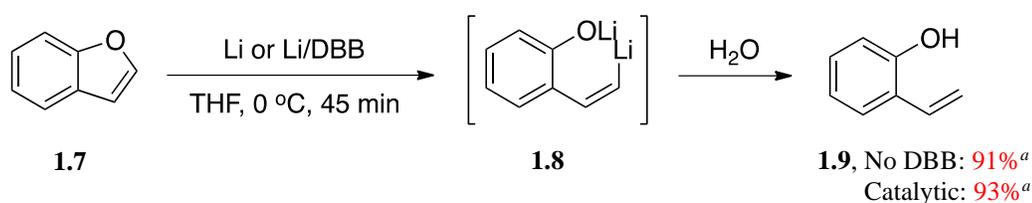


Scheme 1.8 Preformed Radical-Anion vs. Catalytic Method of Reductive Lithiation of 2-Methyl-1-(Phenylthio)-Cyclohexene, **1.3**. ^a Ref. 2.



Scheme 1.9 Preformed Radical-Anion vs. Catalytic Method of Reductive Lithiation of Anisole, **1.5**. ^a Ref. 2.

Furthermore, Cohen and co-workers demonstrated that some compounds previously believed by the Yus group to undergo catalytic reductive lithiation, such as 2,3-benzofuran, **1.7**, pick up an electron and cleave as fast in the absence as in the presence of the aromatic catalyst ([Scheme 1.10](#)).² The radical-anion derived from this substrate has extensive delocalization, probably greater than that in the LDBB.

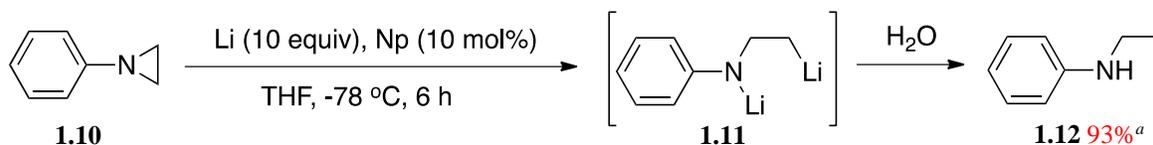


Scheme 1.10 Non-Catalyzed vs. Catalytic Method of Reductive Lithiation of 2,3-Benzofuran, **1.7**. ^a Ref. 2.

1.1.3 Reductive Cleavage of *N*-phenylaziridine.

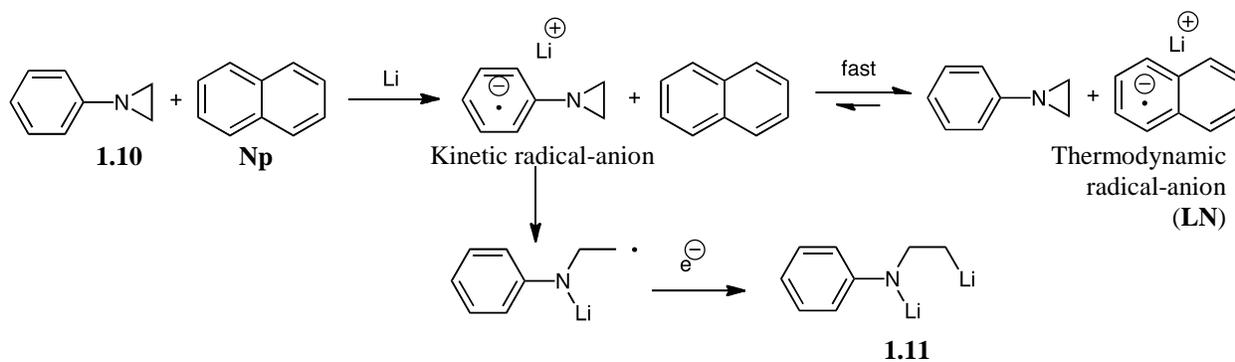
In a search for the reason for the statements by Yus in his claim that the catalytic method is superior to the preformed radical-anion method, Cohen *et. al.* reexamined work that Yus often cited, namely the reductive cleavage of *N*-phenylaziridine, **1.10**. It was reported that for *N*-phenylaziridine, because of the ring strain, the three-membered ring can be opened by excess Li metal with a catalytic amount of the aromatic electron carrier naphthalene in 93% yield of **1.12**, even at -78 °C ([Scheme 1.11](#)).²⁵ Furthermore, Yus claims that aziridines do not undergo reductive opening by preformed aromatic radical-anions, such as LN, at low temperatures.²⁶ As a result, the Cohen lab directly compared the catalytic and preformed radical-anion methods as applied to the reductive cleavage of *N*-phenylaziridine.² Surprisingly, the reductive lithiation under preformed radical-

anion conditions with lithium naphthalenide (LN) did not cause the desired cleavage at the temperature and time reported. However, under the catalytic reductive lithiation conditions the reported result was produced.



Scheme 1.11 Catalytic Reductive Lithiation of *N*-phenylaziridine, **1.10**. ^a Ref. 25.

A possible explanation of this result is the transfer of an electron from the surface of the lithium to the *N*-phenylaziridine, **1.10**, occurs more rapidly than the transfer of an electron to the naphthalene ([Scheme 1.12](#)). However, in the presence of naphthalene (Np), the resulting radical-anion of *N*-phenylaziridine can transfer an electron to the naphthalene to generate the more thermodynamically stable LN ([Scheme 1.12](#)).² In other words, the radical-anion generated from the *N*-phenylaziridine is the kinetic product of electron transfer from the lithium but the LN is the thermodynamic radical-anion.² Since the kinetic radical-anion is the immediate precursor of the ring-opened product, its concentration is directly proportional to the rate of ring cleavage. The higher the concentration of naphthalene, the lower the rate of ring cleavage.² Thus, the naphthalene in this case is actually an inhibitor rather than a catalyst. By behaving as a sink for electrons, naphthalene reduces the concentration of the kinetic radical-anion and therefore inhibits the reductive ring opening. As a result, the aziridine was opened at -78 °C in the absence of the naphthalene “catalyst” with a higher yield than when the naphthalene was present.²

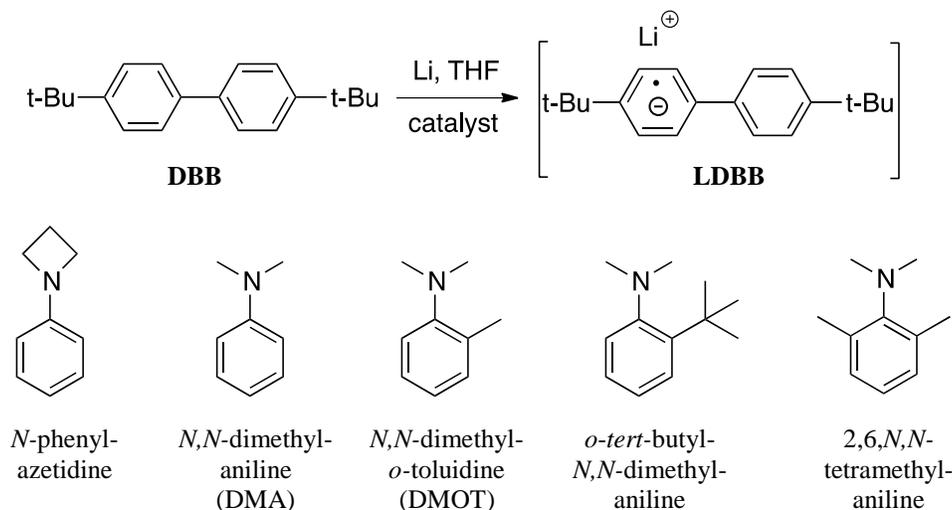


Scheme 1.12 Mechanistic Explanation for the Preformed Radical-Anion Method of Reductive Lithiation of *N*-phenylaziridine, **1.10**.²

The reason that *N*-phenylaziridine accepts an electron more rapidly from lithium is not known; however, this finding is consistent with DMAN forming a lithium radical-anion at $-55\text{ }^{\circ}\text{C}$, which is faster than naphthalene does so at room temperature.² One can speculate that the amino group complexes with a lithium cation on the surface of the metal, thus, increasing the electrophilicity of the ring while at the same time increasing the electron donating power of the metal surface. As a result, this leads to a more rapid transfer of an electron to the π^* system of the aromatic.²

Because *N*-phenylaziridine acquires an electron from Li metal faster than naphthalene does and the resulting radical-anion can transfer the electron rapidly to naphthalene, *N*-phenylaziridine “catalyzes” the formation of LN.² However, the *N*-phenylaziridine radical-anion is unstable and easily undergoes ring opening at $-78\text{ }^{\circ}\text{C}$. Thus, more stable analogues of *N*-phenylaziridine were tested as catalysts for the formation of LDBB ([Scheme 1.13](#)).²⁷ *N*-phenylazetidine was the first to be tried as a catalyst because it is the closest analog of *N*-phenylaziridine and it decomposes extremely slowly at $-78\text{ }^{\circ}\text{C}$ in the presence of Li. However, it produced the same results as LDBB in the absence of catalyst. On the other hand, when *N,N*-dimethylaniline (DMA), *N,N*-dimethyl-*o*-

toluidine (DMOT), *o*-*t*-butyl-*N,N*-dimethylaniline, and 2,6,*N,N*-tetramethylaniline were used as catalysts, the yields of LDBB increased from that obtained without catalysis under the same conditions.²⁷ As a result, these are the first catalysts discovered for the formation of aromatic radical-anions.



Scheme 1.13 Amino Catalysts for the Formation of LDBB.²⁷

1.1.4 Reductive Lithiation of Phenyl Thioethers.

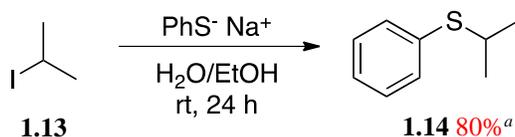
Since its introduction in 1978,²⁸⁻²⁹ reductive lithiation of phenyl thioethers using aromatic radical-anions has been demonstrated to be one of the most versatile methods known for generating organolithiums.³⁰⁻³¹ The superiority of alkyl phenyl thioethers as substrates for reductive lithiation arises from their almost unique ease of construction, as well as the ability of the phenylthio group to enter a molecule as a nucleophile, electrophile, or radical.² In addition, these substrates are almost always able to withstand the powerful nucleophiles/bases that are present in the reductive

lithiation conditions. For example, alkyl halides, sulfates, and sulfonates are subject to ready nucleophilic substitution as well as base-induced elimination, thus limiting their use largely to the preparation of primary alkyl lithiums unless an aryl or vinyl group is present to increase the rate of reductive lithiation and favor it over the competing process.² Another considerable advantage is that the aromatic hydrocarbon and the thiophenol are recoverable and thus a stoichiometric amount of lithium metal is the only reagent that is destroyed, making this the most economical method available since lithium metal is far less expensive than any organic form of lithium.²

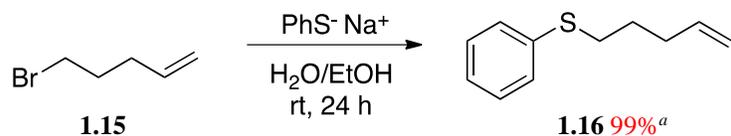
1.2 RESULTS AND DISCUSSION

1.2.1 Preparation of Phenyl Thioethers.

Isopropyl phenyl sulfide, **1.14**, ([Scheme 1.14](#)) and 5-(phenylthio)-1-pentene, **1.16**, ([Scheme 1.15](#)) were prepared in high yields by the S_N2 reaction between NaSPh, generated from thiophenol and sodium hydroxide in water solution, and the corresponding commercially available alkyl halides. The benzenethiolate anion ranks among the most-powerful nucleophiles in protic solvents.³²



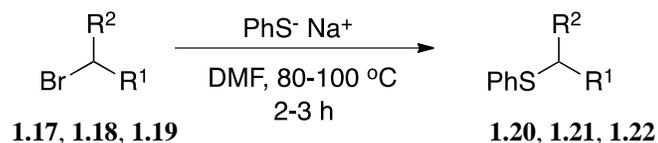
Scheme 1.14 Preparation of Isopropyl Phenyl Sulfide **1.14**. ^a Isolated crude yield.

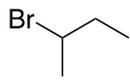
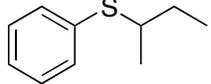
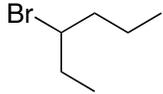
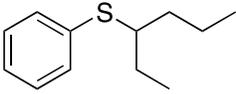
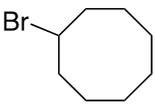
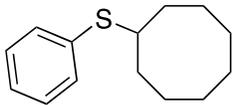


Scheme 1.15 Preparation of 5-(Phenylthio)-1-Pentene **1.16**. ^a Isolated crude yield.

2-(Phenylthio)-butane, **1.20**, 3-(phenylthio)-hexane, **1.21**, and cyclooctyl phenyl sulfide, **1.22**, were synthesized via $\text{S}_{\text{N}}2$ reactions of sodium thiophenoxide, generated from thiophenol and sodium hydride in DMF, and the corresponding commercially available alkyl bromide at a high temperature ([Table 1.1](#)).³³ The solvent was changed to the polar aprotic DMF in order to prevent an E_2 reaction.

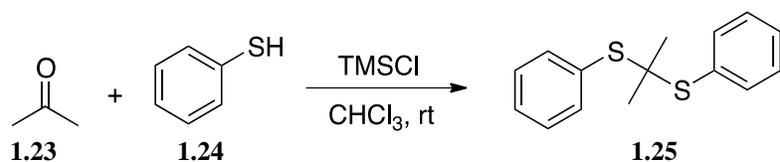
Table 1.1 Preparation of Alkyl Phenyl Sulfides 1.20 – 1.22.



Entry	Alkyl Halide	Product	%Yield ^a
1	 1.17	 1.20	89
2	 1.18	 1.21	99
3	 1.19	 1.22	52

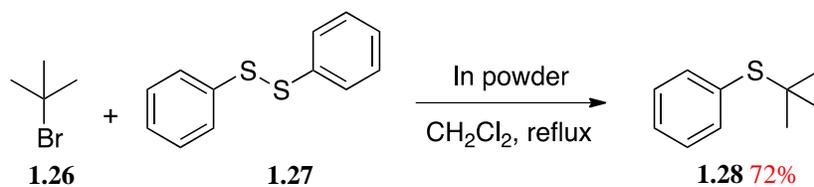
^a Isolated yield after column chromatography (basic aluminum oxide, hexanes) based on the starting material.

The thioacetal 2,2-bis(phenylthio)propane, **1.25**, was synthesized utilizing the method developed in this laboratory,³⁴ which involves the Lewis acid-catalyzed condensation of acetone with thiophenol ([Scheme 1.16](#)).

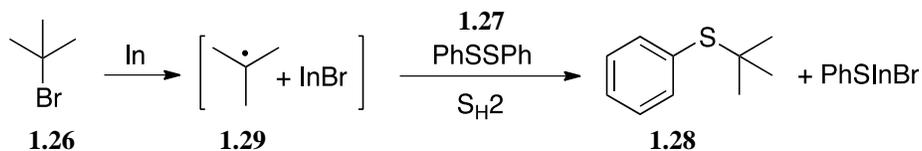


Scheme 1.16 Thioacetalization for the Preparation of 2,2-Bis(phenylthio)propane, **1.25**.

Tert-butyl phenyl sulfide, **1.28**, was synthesized via two diverse methods. First, the one-pot indium-mediated reaction between *tert*-butyl bromide and diphenyl disulfide produced **1.28** in 72% yield ([Scheme 1.17](#)).³⁵ According to the proposed mechanism ([Scheme 1.18](#)),³⁶ indium metal reduces **1.26** to generate the alkyl radical, **1.29**, followed by an S_H2 reaction with diphenyl disulfide to form **1.28**.

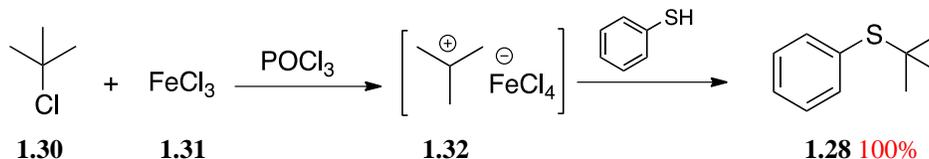


Scheme 1.17 Indium Metal-Mediated Synthesis of *tert*-Butyl Phenyl Sulfide, **1.28**.



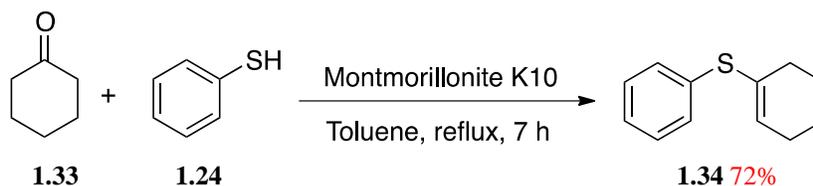
Scheme 1.18 Plausible Mechanism for the Reaction of **1.26** with **1.27** in the Presence of Indium.³⁶

Because indium powder is expensive (5 g for \$94.90),³⁷ an alternative method was chosen for the synthesis of *tert*-butyl phenyl sulfide. Screttas and co-workers prepared alkyl phenyl sulfides via the catalyzed displacement of certain nucleophiles by the thiophenoxy group. Thiophenol exhibits a marked reactivity toward carbenium ions, being capable of displacing various nucleophiles at a carbenium ion center.³⁸ *Tert*-butyl chloride, **1.30**, was found to react with thiophenol in POCl₃ solvent in the presence of catalytic amounts of anhydrous ferric chloride, **1.31** ([Scheme 1.19](#)).³⁸ Under these conditions *tert*-butyl chloride ionizes to the carbenium ion, **1.32**, which readily reacts with thiophenol at room temperature yielding quantitative *tert*-butyl phenyl sulfide.³⁸ In our work, employing glacial acetic acid, in place of POCl₃, and *tert*-butyl bromide, **1.26**, as the alkyl halide, **1.28** was synthesized in 35% yield.



Scheme 1.19 Screttas Synthesis of *tert*-Butyl Phenyl Sulfide, **1.28**.³⁸

1-(Phenylthio)-1-cyclohexene, **1.34**, was synthesized from a procedure developed by Villemin.³⁹ Using an acidic clay catalyst and thiophenol, **1.24**, cyclohexanone, **1.33**, was converted into the desired product in one pot ([Scheme 1.20](#)). This method appeared to be the shortest available with the added benefit of using cheap, readily available, non-corrosive reagents. The yield obtained in our work, 72%, was lower than that which is reported in the literature due to the use of non-purified reagents, **1.24** and **1.33**.

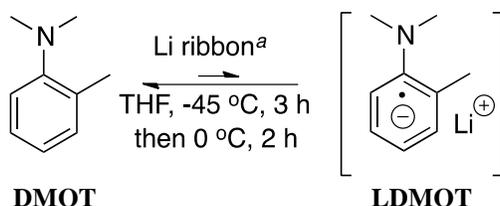


Scheme 1.20 Preparation of 1-(Phenylthio)-1-Cyclohexene, **1.34**.

1.2.2 Catalytic Reductive Lithiation with *N,N*-Dimethyl-*o*-Toluidine (DMOT).

To generate the commonly used radical-anion reducing agent LDBB, for reductive lithiation, an equimolar amount of DBB and Li metal at 0 °C for 5 h is required.²⁴ This extended length of time presents a problem; however, the subsequent reductive lithiation between the preformed LDBB

reactions, is scraped free of the oxide coating prior to weighing.⁴³ Unlike DMAN, which turns a green-black color upon LDMAN formation, the DMOT reaction mixture remained colorless, and DMOT was completely recovered. This implies that a discernible radical-anion lithium (*N,N*-dimethyl)-*o*-toluidinide (LDMOT) had not formed. In the case of DMAN, the ability to readily form a radical-anion is hypothesized to be due to the amino group complexing with a lithium cation on the surface of the metal to increase the electrophilicity of the ring, as well as the electron donating power of the metal surface. This may lead to a more rapid transfer of an electron to the π^* system of the aromatic.² In the case of DMOT, unlike that of DMAN, the equilibrium in the conversion to its radical-anion may be unfavorable due to the reduced electron delocalization in LDMOT as compared to LDMAN.

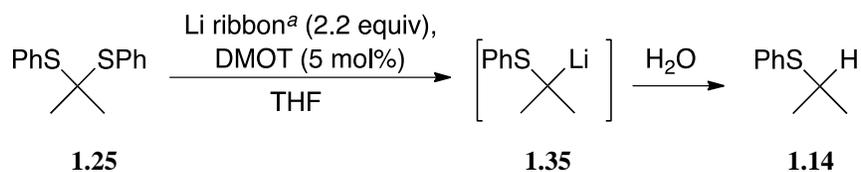


Scheme 1.22 Aromatic Radical-Anion, **LDMOT**, Formation.
^a Oxide coating on Li ribbon was scraped prior to the reaction.

Here we present our results of the DMOT catalyzed reductive lithiation of **1.25**, in which the organolithium intermediate, **1.35**, was trapped with water rather than being subjected to conjugate addition with methyl vinyl ketone, as in Ivanov's work ([Scheme 1.21](#)). DMOT catalysis was measured by isolating the yield of isopropyl phenyl sulfide, **1.14**, at different temperatures.

As shown in [Table 1.2](#), **1.14** was produced in the highest yield at -45 °C after 60 min. When 100 mol% of DMOT was employed, the yield of **1.14** only increased to 24% (entry 5).

Table 1.2 DMOT Catalyzed Reductive Lithiation of 1.25.

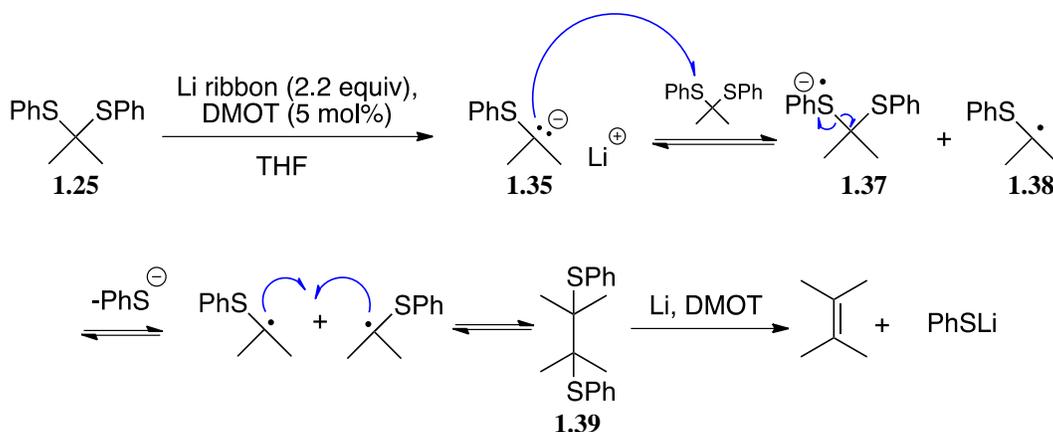


Entry	Temp. (°C)	Rxn Time (min)	%Yield ^b
1	0	45	13
2	-22	20	12
3	-22	60	15
4	-45	60	20
5	-45	40	24 ^c

^a Oxide coating on Li ribbon was scraped prior to the reaction. ^b Isolated yield of **1.14** after column chromatography (silica gel, hexanes) based on the starting material. ^c 100 mol% DMOT.

Since the yield did not significantly increase with an increase in DMOT, it seemed likely that the organolithium intermediate, **1.35**, was reacting with the starting material, which would prevent the conversion to product. Given the extreme steric crowding of the tertiary carbon, the mechanism of the thiophenoxy displacement clearly cannot be S_N2. Thus, a single electron transfer mechanism is proposed in order to explain the depletion of **1.35** ([Scheme 1.23](#)). This process results in the transfer of an electron from **1.35** to **1.25**.^{3b} Upon acquisition of the electron, the thioether forms a radical-anion, **1.37**, which then decomposes to a carbon radical, **1.38**, and thiophenoxide ion (dissociative electron transfer). If the **1.37** decomposes to a radical and

thiophenoxide ion before the original radical can diffuse away from it, the two radicals can combine to form the 2,3-bis(phenylthio)-2,3-dimethylbutane byproduct, **1.39**, (radical pair mechanism). The resulting alkene would be expected to be lost by evaporation. Because the ^1H NMR of **1.39** matches that of **1.25**, a ^{13}C NMR may have confirmed the presence of **1.39** due to a shift in the methyl carbon, but rather, the substrate was changed to commercially available methyl phenyl sulfide, **1.40**.

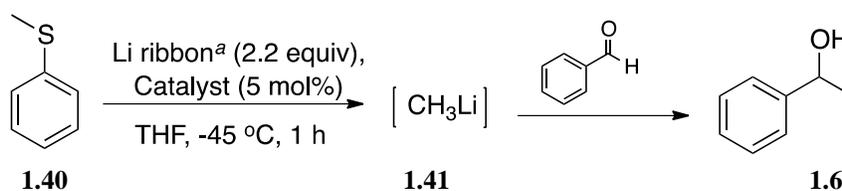


Scheme 1.23 Single Electron Transfer Reaction of **1.35** Resulting from the Reductive Lithiation of **1.25**.

Methyl phenyl sulfide, **1.40**, was chosen to test the catalytic power of DMOT, and the methyl-lithium intermediate, **1.41**, which is significantly less reactive, was trapped with benzaldehyde, rather than water, to yield an isolable alcohol product, 1-phenylethanol, **1.6** ([Table 1.3](#)). The DMOT catalyzed reductive lithiation of methyl phenyl sulfide was compared to the known electron transfer catalysts, DBB and DMAN. As shown in [Table 1.3](#), DMOT catalyzed the reductive lithiation of **1.40** to the same degree as DMAN (entry 2) and both amines catalyzed the reductive lithiation better than the most widely used catalyst, DBB (entry 4). DMA, which is

significantly cheaper than both DMOT and DBB,⁴⁴ was tested as a catalyst because it was found to catalyze the formation of LDBB (Scheme 1.13).²⁷ DMA produced a result similar to those of DMOT and DMAN (entry 3). In order to support the theory that the nitrogen impacts the transfer of electrons by coordinating to the lithium metal surface, cumene, which is structurally similar to DMA but lacks nitrogen, was tested as a possible electron transfer catalyst but did not catalyze the reductive lithiation of **1.40**. DMOT, DMA, and DMAN were completely recovered after washing the organic layer with aqueous hydrochloric acid. Removing the amino aromatic from the product simplifies the isolation of the product via column chromatography, and would allow recycling of the presumed catalyst.

Table 1.3 Catalytic Reductive Lithiation of Methyl Phenyl Sulfide.



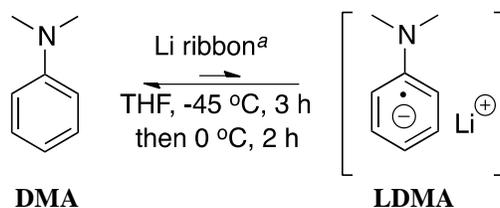
Entry	Catalyst	% Yield ^b
1	DMOT	65
2	DMAN	72
3	DMA	68
4	DBB	48
5	Cumene	42
6	None	39

^a Oxide coating on Li ribbon was scraped prior to the reaction.

^b Isolated yield of **1.6** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

1.2.3 Catalytic Reductive Lithiation with *N,N*-Dimethyl-Aniline (DMA).

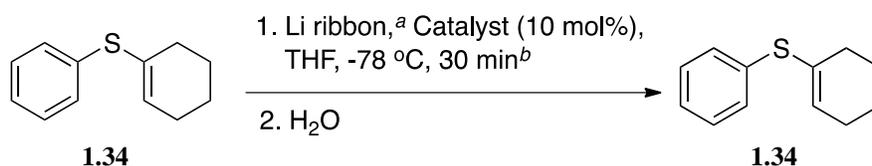
DMA catalyzed the reductive lithiation of methyl phenyl sulfide just as well as DMOT and DMAN ([Table 1.3](#)); however, DMA is a much cheaper catalytic alternative to DMOT⁴⁴ and DMAN. Therefore, DMA was considered to be a successful electron transfer mediator and the study of its catalysis ensued. DMA was treated with lithium ribbon in THF for several hours in order to determine if a perceptible aromatic radical-anion was produced ([Scheme 1.24](#)). Similar to DMOT ([Scheme 1.22](#)), the reaction mixture remained colorless, Li metal remained unreacted, and DMA was completely recovered. This implies that a discernible stable radical-anion lithium (*N,N*-dimethyl)-anilide (LDMA) was not generated.



Scheme 1.24 Aromatic Radical-Anion, **LDMA**, Formation.
^a Oxide coating on Li ribbon was scraped prior to the reaction.

To further investigate the DMA catalyzed reductive lithiation of phenyl thioethers, the yields of unreacted starting material of an alternative substrate, 1-(phenylthio)-1-cyclohexene, **1.34**, were compared at a lower temperature and higher percentage of catalyst. As shown in [Table 1.4](#), DMA and DBB catalyzed the cleavage of **1.34** at similar rates (entries 1 and 2) when the reaction was terminated after 30 min.

Table 1.4 Catalytic Reductive Lithiation of 1-(Phenylthio)-1-Cyclohexene.

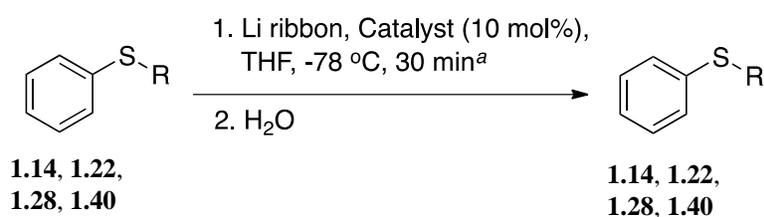


Entry	Catalyst	%(1.34) ^c
1	DBB	76
2	DMA	79
3	None	100

^a Oxide coating on Li ribbon was scraped prior to the reaction. ^b Reaction terminated after 30 min. ^c % of recovered starting material after column chromatography (silica gel, hexanes).

In Tables 1.3 and 1.4 the efficacy of DMA as an electron transfer reagent was compared to known reductive lithiation catalysts. In order to gain an understanding of relative rates of cleavage in the DMA catalyzed reductive lithiation of alkyl phenyl sulfides, the amount of unreacted starting material was recovered when the reaction was terminated after 30 min. As shown in [Table 1.5](#), **1.40** cleaves considerably faster than **1.14**, **1.22**, and **1.28** rather than slower, as would be predicted for the pre-formed radical-anion method.^{30a,31s,45} The relative reactivity is reversed in going from the preformed radical-anion method ([Scheme 1.1](#)) to the DMA catalytic method. This unique finding results from a steric effect rather than an electronic effect. By comparing the relative rates of cleavage of two secondary alkyl phenyl sulfides, **1.14** and **1.22**, the result is that an increase in bulkiness of the alkyl group led to a sharp increase in unreacted starting material.

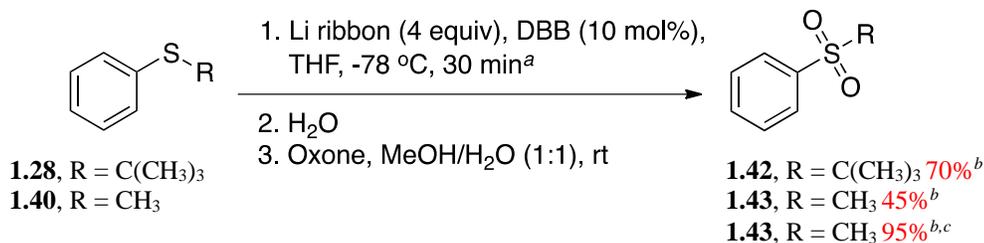
Table 1.5 Catalytic Reductive Lithiation of Alkyl Phenyl Sulfides.



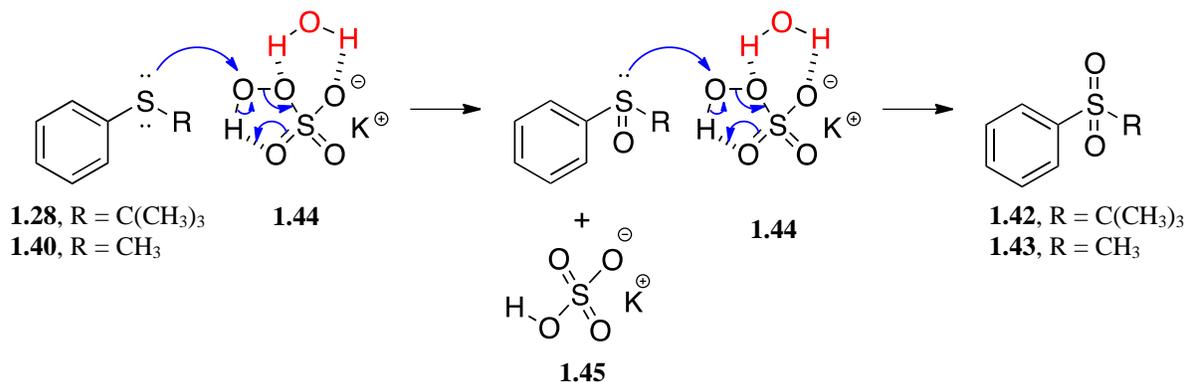
Entry	SM	R	Catalyst	(%) ^b
1	1.14	CH(CH ₃) ₂	DMA	62
2	1.22	<i>c</i> -C ₈ H ₁₅	DMA	95
3	1.28	C(CH ₃) ₃	DMA	60
4	1.40	CH ₃	DMA	31
5	1.40	CH ₃	DMA	30 ^c
6	1.40	CH ₃	DMAN	29 ^c

^a Reaction terminated after 30 min. ^b % of recovered starting material after column chromatography (silica gel, hexanes). ^c Oxide coating on Li ribbon was *not* scraped prior to the reaction.

The same relative reactivity was observed for the DBB catalyzed reductive lithiation of alkyl phenyl sulfides, in which **1.40** cleaved more rapidly than **1.28** ([Scheme 1.25](#)). The unreacted starting material was oxidized to a sulfone ([Scheme 1.26](#)),^{46,47} with Oxone®, in order to facilitate separation from DBB via column chromatography. Thus, the catalyzed reductive lithiation of alkyl phenyl sulfides must be fundamentally different from the preformed radical-anion method.



Scheme 1.25 DBB Catalyzed Reductive Lithiation of Methyl Phenyl Sulfide and *tert*-Butyl Phenyl Sulfide.
^a Reaction terminated after 30 min. ^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes).
^c Oxide coating on lithium ribbon was *not* scraped prior to reaction.

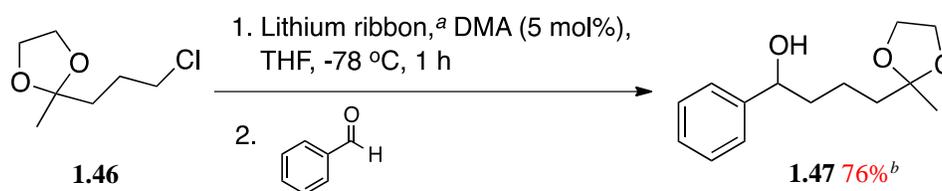


Scheme 1.26 Proposed Mechanism for the MeOH/H₂O Promoted Oxidation of *tert*-Butyl Phenyl Sulfide and Methyl Phenyl Sulfide with Oxone® (**1.44** is the active component, KHSO₅ or potassium peroxomonosulfate, and **1.45** is the by-product, KHSO₄ or potassium bisulfate).⁴⁷

In our recent publication in *The Journal of Organic Chemistry*, we reveal that, in the absence of an aromatic electron carrier, the reductive lithiation of phenyl thioethers with lithium dispersion occurs at the surface of the Li metal and the order of reactivity is reversed from the preformed aromatic radical-anion method.⁴⁵ Based on the results from [Table 1.5](#) and [Scheme 1.25](#), the catalytic method of reductive lithiation has the same selectivity as the lithium dispersion

method, thus the cleavage of the C-S bond must also occur at the Li metal surface. The role of the catalyst is predicted to activate and replenish the surface of the lithium, which enhances the electron donating power of the lithium metal.⁴⁸ This is especially evident with DMA and DMAN, in which the amino group can complex with a lithium cation on the surface and promote surface reconstruction. Thus, the oxide coating does not need to be removed prior to the reaction (Table 1.5, entries 2 and 3). Alternatively, with DBB, the shiny surface, free of the oxide coating, needs to be exposed for successful reductive lithiation (Scheme 1.25). The exact mechanism of electron transfer, including the transition state, is unknown and difficult to study because the cleavage occurs at the Li metal surface.

Yus and co-workers have performed a large number of catalyzed reductive lithiations of alkyl chlorides,^{16,49} including 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, **1.46**. In order to determine if **1.46** could be lithiated under our DMA catalyzed conditions, we treated this substrate with a catalytic amount of DMA and lithium ribbon at -78 °C. As a result, the corresponding alcohol product **1.47** was successfully obtained after capturing the organolithium intermediate with benzaldehyde (Scheme 1.27).



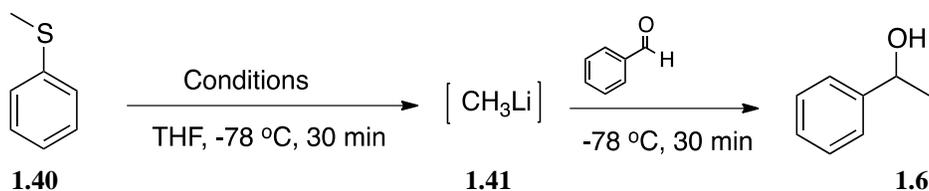
Scheme 1.27 DMA Catalyzed Reductive Lithiation of 2-(3-Chloropropyl)-2-Methyl-1,3-Dioxolane, **1.46**.

^aOxide coating on Li ribbon was *not* scraped prior to the reaction.

^bIsolated yield after column chromatography (silica gel, EtOAc/hexanes).

The lithium source was changed from lithium ribbon to lithium dispersion (disp., 25 wt% in mineral oil) containing 0.1% sodium. An important advantage of this dispersion is that it can be weighed and transferred to the designated flask open to the air without the lithium reacting. The mineral oil that coats the lithium metal can then be removed under argon by rinsing with hexanes so that the lithium remains unreacted under argon until the solvent and the substrate are added. Again, DMA was compared to the well known reductive lithiation catalyst, DBB, as well as the preformed radical-anion method with LDBB (Table 1.6). Non-catalyzed reductive lithiation, that is, the lithium dispersion alone without an aromatic electron transfer reagent, was used as the control. Surprisingly, the lithium dispersion reductive lithiation of **1.40** (entry 4) produced **1.6** in a yield comparable to those achieved via the preformed radical-anion and catalytic reductive lithiation methods.

Table 1.6 Catalytic, Preformed Radical-Anion, and Lithium Dispersion Reductive Lithiation of Methyl Phenyl Sulfide.

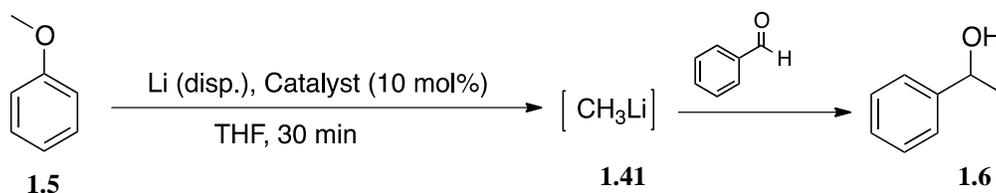


Entry	Conditions	%Yield ^a
1	LDBB	79
2	Li (disp.), DMA (10 mol%)	77
3	Li (disp.), DBB (10 mol%)	74
4	Li (disp.)	73

^a Isolated yield of **1.6** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

Because methyl phenyl sulfide reacted with lithium dispersion alone, as well as, in the presence of a “catalyst,” the role of DMA could not be determined. There were two factors to be measured occurring in one reaction pot, the non-catalyzed and catalyzed reductive lithiation, which may be happening simultaneously or affecting one another. Therefore, the study of the catalyzed reductive lithiation of anisole, **1.5**, which was found to not readily undergo non-catalyzed reductive lithiation,² ensued ([Table 1.7](#)). In that way, the role of DMA as an electron transfer catalyst could properly be evaluated. DBB successfully catalyzed the reductive lithiation of anisole at 0 °C to form 1-phenylethanol, **1.6**, after trapping the organolithium intermediate with benzaldehyde (entry 1). In the presence of DMA, no product was formed, even after 24 h at room temperature (entry 5). With these results, it was concluded that DMA may *not* be an effective electron transfer reagent when lithium dispersion is the Li metal source.

Table 1.7 Catalyzed Reductive Lithiation of Anisole.



Entry	Temp. (°C)	Catalyst	% Yield ^a
1	0	DBB	59
2	0	DBB	30 ^b
3	0	DMAN	66
4	0	DMA	0
5	rt	DMA	0 ^c

^a Isolated yield of **1.6** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Results from 2006 *Tetrahedron* article: 14 equiv of lithium dispersion and 2 h at 0 °C then warming to room temperature after the addition of benzaldehyde.² ^c After 24 h.

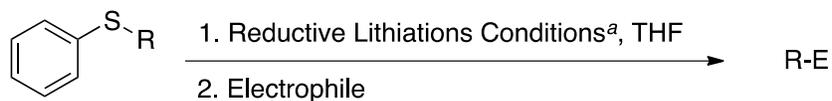
1.2.4 Lithium Dispersion Reductive Lithiation of Phenyl Thioethers.

Thus, our attention was focused on optimizing the lithium dispersion reductive lithiation of phenyl thioethers, as well as expanding the methodology to diverse substrates, which have previously undergone either catalytic or preformed radical-anion reductive lithiation. Four phenyl thioethers, including: isopropyl phenyl sulfide (**1.14**; [Scheme 1.14](#)),⁵⁰ 5-(phenylthio)-1-pentene (**1.16**; [Scheme 1.15](#)),⁵¹ 1-(phenylthio)-1-cyclohexene (**1.34**; [Scheme 1.20](#)),³⁹ and methyl phenyl sulfide, **1.40** were surveyed. Unlike Yus's procedure, which generally uses a large excess of lithium, prepared in a special apparatus⁵² not generally available in synthetic labs, the procedure developed here uses a slight stoichiometric excess (2.4 equivalents) of the commercially available lithium dispersion.

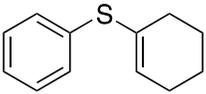
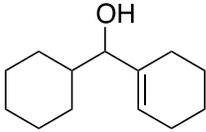
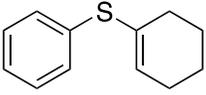
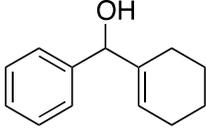
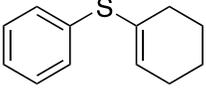
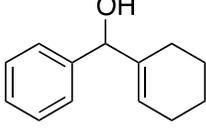
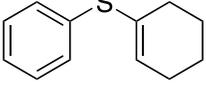
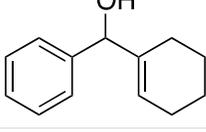
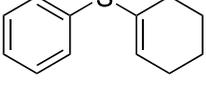
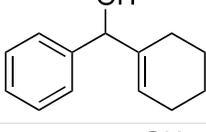
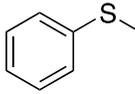
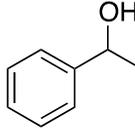
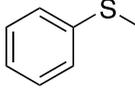
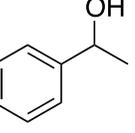
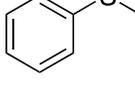
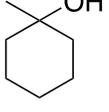
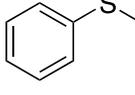
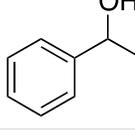
As a result, excellent yields of the corresponding products were obtained after the organolithium intermediates were captured with benzaldehyde (80-95% yield) ([Table 1.8](#)). With the optimum conditions developed for each substrate, including reaction time and temperature, 10 mol% of DBB was added in order to determine the significance of DBB in the reductive lithiation of these phenyl thioethers. As shown in [Table 1.8](#) (entries 2, 11, and 15), DBB did not significantly affect the isolated yield under identical reaction conditions. Furthermore, less time was required for the lithium dispersion reductive lithiations of **1.34** and **1.40** (entries 8, 9, 15 and 16) in comparison to the catalytic and preformed aromatic radical-anion reductive lithiations of these substrates at the same temperature.^{16,53} Lastly, similar amounts of unreacted starting material **1.16** were recovered, in both the presence of and absence of 10 mol% of DBB (entries 6 and 7), after the organolithium intermediate was quenched with water. Thus, it was determined that DBB does not catalyze the reductive lithiation of phenyl thioethers when lithium dispersion is the Li metal source.

In order to determine if granular lithium behaved in a manner similar to that of lithium dispersion, the Li source was changed to commercially available granular lithium (0.5% sodium), which presumably has less surface area due to the large chunks of granular metal. Under identical reaction conditions, the granular lithium reductive lithiation of **1.16** and **1.34** produced a slightly lower isolated yield ([Table 1.8](#), entries 5 and 13), despite the granular lithium having five times the amount of sodium compared to the lithium dispersion.⁵⁴ Thus, the increase in the surface area of the Li metal, from the granular to the dispersion, apparently somewhat enhanced the rate of reductive lithiation.

Table 1.8 Reductive Lithiation of Phenyl Thioethers Using Lithium Dispersion and Some Comparisons with the Use of Granular Lithium and DBB Catalysis.



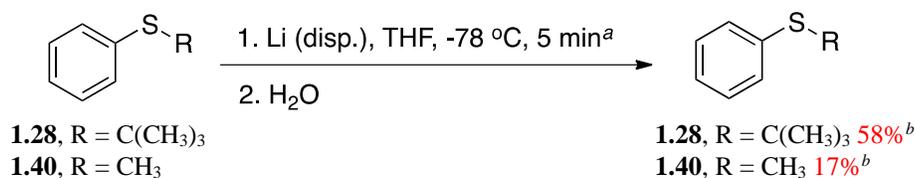
Entry	Phenyl Thioether	Temp. (°C)	Time (min)	Method ^a	Electrophile	Product	% Yield ^b
1	 1.14	-78	90	A	PhCOH	 1.48	87
2	 1.14	-78	90	B	PhCOH	 1.48	87
3	 1.16	0	15	A	PhCOH	 1.49	80
4	 1.16	-78	60	A	PhCOH	 1.49	83
5	 1.16	-78	60	C	PhCOH	 1.49	77
6	 1.16	-78	10	D	H ₂ O	 1.16	11
7	 1.16	-78	10	E	H ₂ O	 1.16	10
8	 1.34	0	15	A	PhCOH	 1.50	88

9	 1.34	0	30	F	<i>c</i> -C ₆ H ₁₁ COH	 1.51	63 ^c
10	 1.34	-45	60	A	PhCOH	 1.50	88
11	 1.34	-78	60	A	PhCOH	 1.50	84
12	 1.34	-78	60	B	PhCOH	 1.50	86
13	 1.34	-78	60	C	PhCOH	 1.50	64
14	 1.40	0	15	A	PhCOH	 1.6	95
15	 1.40	-78	60	A	PhCOH	 1.66	95
16	 1.40	-78	150	G	$\overline{(\text{CH}_2)_5\text{CO}}$	 1.52	92 ^d
17	 1.40	-78	60	B	PhCOH	 1.6	88

^a **Method A:** Li (disp., 2.4 equiv); Benzaldehyde. **Method B:** Li (disp., 2.4 equiv), DBB (10 mol%); Benzaldehyde. **Method C:** Li granular (2.4 equiv); Benzaldehyde. **Method D:** Li (disp., 2.4 equiv), reaction terminated after 10 min; H₂O. **Method E:** Li (disp., 2.4 equiv), DBB (10 mol%), reaction terminated after 10 min; H₂O. **Method F:** LN; Cyclohexanecarboxaldehyde.^{53a} **Method G:** Li powder, Np (1 mol%); Cyclohexanone.¹⁶ ^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^c Ref. 53a. ^d Ref. 16.

The finding that phenyl thioethers were reductively lithiated by lithium metal with no aromatic catalyst present was surprising. In the past, with very few exceptions, the overwhelming number of reductive lithiations of phenyl thioethers were performed in the presence of either preformed aromatic radical-anions or an aromatic catalyst that acts as an electron carrier. The only exceptions of which we are aware are the findings of Screttas *et. al.* that a few phenyl thioethers can be reductively lithiated by a substantial excess of specially prepared lithium dispersion alone²⁸ and that allylic phenyl thioethers can be reductively lithiated under highly unusual conditions, that is with an excess of lithium chips in solutions of diethyl ether, rather than the standard THF, at ice bath temperature.⁵⁵

In [Table 1.8](#), overall yields were used to compare the efficacy of the procedures for different substrates. In order to gain an understanding of the relative rates of cleavage of two different substrates, **1.28** and **1.40**, the yields of the unreacted starting materials after a 5-minute reductive lithiation were determined. As shown in [Scheme 1.28](#), **1.40** cleaves significantly faster than **1.28** rather than slower, as would be predicted for the preformed radical-anion method.^{30,31s,45} The reaction selectivity is reversed in going from the preformed radical-anion method ([Scheme 1.29](#)) to the lithium dispersion method ([Scheme 1.28](#)). Thus, the preformed radical-anion method of reductive lithiation must be fundamentally different from the lithium dispersion method.

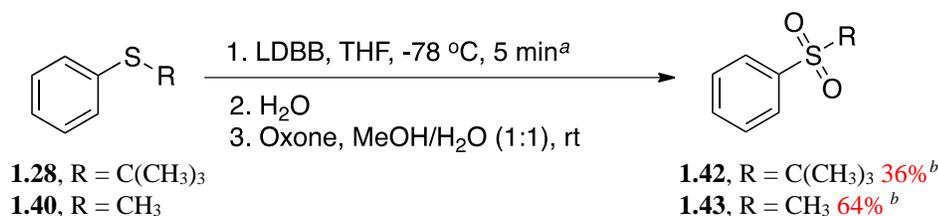


Scheme 1.28 Lithium Dispersion Reductive Lithiation of *tert*-Butyl Phenyl Sulfide and Methyl Phenyl Sulfide.

^a Reaction terminated after 5 min.

^b % of recovered starting material after column chromatography (silica gel, hexanes).

Under the preformed radical-anion method with LDBB ([Scheme 1.29](#)), the unreacted starting material was oxidized to a sulfone⁴⁶ in order to facilitate separation from DBB via column chromatography. Thus, as expected, **1.28** cleaved more rapidly than **1.40**.



Scheme 1.29 LDBB Reductive Lithiation of *tert*-Butyl Phenyl Sulfide and Methyl Phenyl Sulfide.

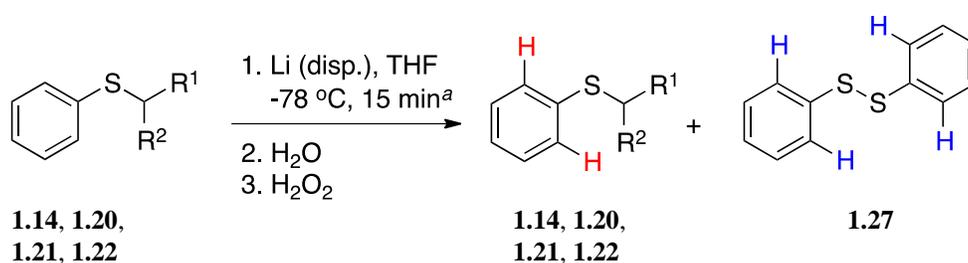
^a Reaction terminated after 5 min.

^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

Further evidence includes the lithium dispersion reductive lithiation of a 1:1 mixture of **1.28** and **1.40** being selective for methyl phenyl sulfide, resulting in a 7:1 ratio of unreacted starting material ([Scheme 1.30](#) and [Figure 1.2](#)).

dispersion and the lithium thiophenoxide products were oxidized to diphenyl disulfide, **1.27** (Table 1.9) with hydrogen peroxide, a strong oxidizing agent. The ratio of the starting material (SM) to **1.27** was determined by comparing the ratio of the *ortho* aromatic protons of each product in the crude ^1H NMR spectrum. The result is that the rate is very sensitive to steric effects; an increase in bulkiness of the alkyl group led to a sharp increase in unreacted starting material. This thus is a steric effect rather than an electronic effect.

Table 1.9 Lithium Dispersion Reductive Lithiation of 2° Alkyl Phenyl Sulfides.



Entry	2° Alkyl Phenyl Sulfide	Ratio of SM (H) to Diphenyl Disulfide (H) ^b	Figure
1	1.14	3:1	1.3
2	1.20	8:1	1.4
3	1.21	34:1	1.5
4	1.22	36:1	1.6

^a Reaction terminated after 15 min. ^b Ratio determined from crude ^1H NMR.

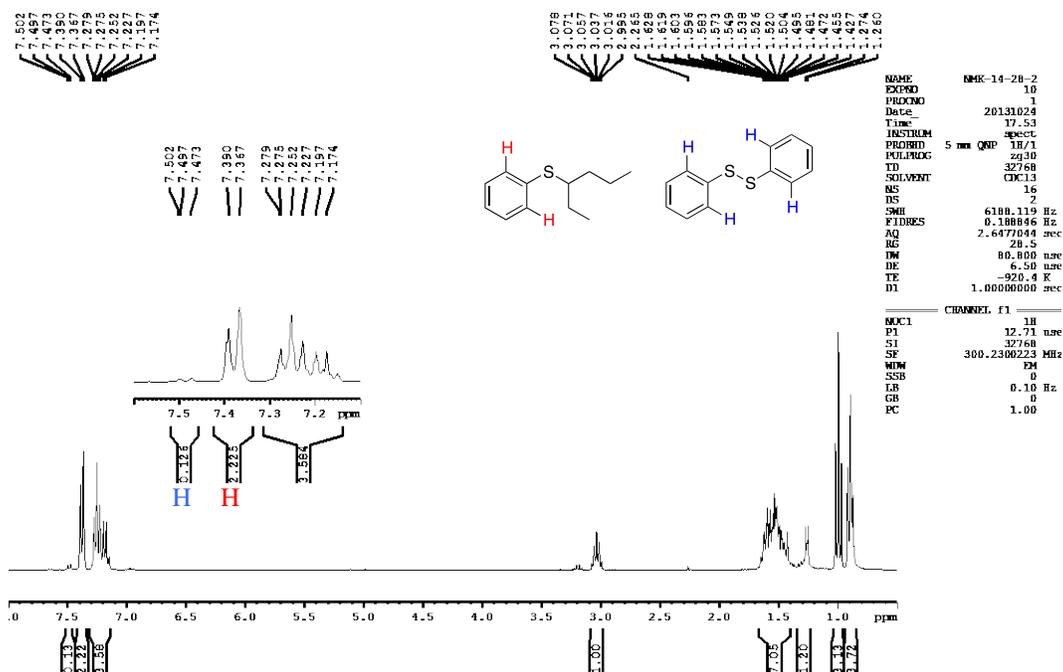


Figure 1.5 Crude ¹H NMR of 3-(Phenylthio)-Hexane and Diphenyl Disulfide.

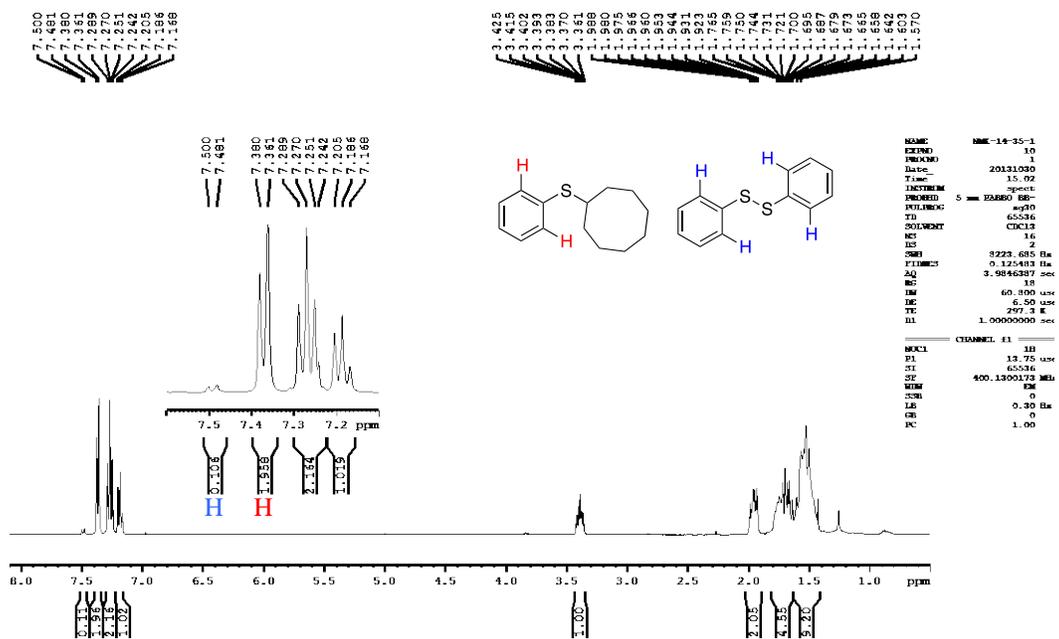
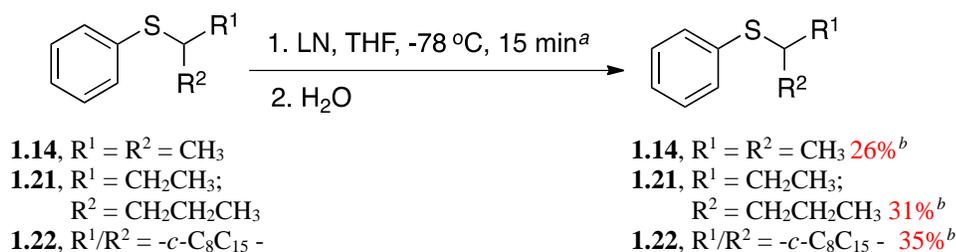


Figure 1.6 Crude ¹H NMR of Cyclooctyl Phenyl Sulfide and Diphenyl Disulfide.

The preformed radical-anion reductive lithiation of some of these substrates was explored in order to determine whether there are similar or different steric effects on the rate of reductive lithiation when compared to the lithium dispersion method. The ratio of the starting material to **1.27** could not be determined by ^1H NMR due to overlap of the aromatic protons with naphthalene; therefore, the unreacted starting material was isolated. As shown in [Scheme 1.31](#), compounds **1.14**, **1.21**, and **1.22** have similar rates of cleavage under the preformed radical-anion reaction conditions. There was little to no discrepancy observed in the percentages of the unreacted SM ([Scheme 1.31](#)) in comparison to the considerable difference observed in the ratios of the SM to **1.27** in [Table 1.9](#).



Scheme 1.31 LN Reductive Lithiation of 2° Alkyl Phenyl Sulfides.

^a Reaction terminated after 15 min.

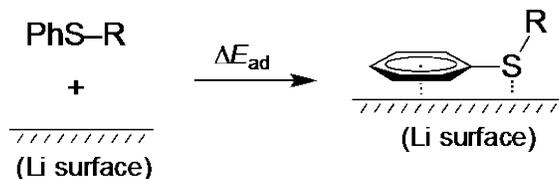
^b % of recovered starting material after column chromatography (silica gel, hexanes).

1.2.5 Calculations of C-S Bond Cleavage of Alkyl Phenyl Sulfides on the Lithium Surface.

In collaboration with computational organic chemists, Dr. Peng Liu and Dr. Gang Lu, lithium surface calculations supported our experimental results.⁴⁵ The reductive lithiation of alkyl phenyl

sulfides with lithium dispersion is expected to occur through the dissociative adsorption mechanism on the lithium surface. This process involves molecular adsorption of the alkyl phenyl sulfide on the lithium surface, followed by C-S bond cleavage to form a thiophenoxyl radical and an alkyl radical adsorbed on the lithium surface. The adsorption energies of the alkyl phenyl sulfides were surprisingly similar regardless of the very different size of the alkyl groups (Table 1.10). Thus, the reactivity dictating the cleavage rate and reaction selectivity does not depend on the adsorption of the substrate onto the Li metal.

Table 1.10 Substrate Adsorption Energy on Li Surface.⁴⁵



Entry	Substrate	Substrate on Li Surface (*)	ΔE_{ad} (kcal/mol)
1	1.5	PhO-Me + * \rightarrow PhO-Me*	-6.3
2	1.14	PhS- <i>i</i> -Pr + * \rightarrow PhS- <i>i</i> -Pr*	-15.5
3	1.20	PhS-2-butyl + * \rightarrow PhS-2-butyl*	-14.4
4	1.21	PhS-3-hexyl + * \rightarrow PhS-3-hexyl*	-15.1
5	1.28	PhS- <i>t</i> -Bu + * \rightarrow PhS- <i>t</i> -Bu*	-15.1
6	1.40	PhS-Me + * \rightarrow PhS-Me*	-12.0

The C-S bond cleavage on the Li surface was found to be exothermic and the exothermicity parallels the reactivity trend (Table 1.11).⁴⁵ The reaction with **1.40** was the most favorable thermodynamically, although the PhS-Me bond is the strongest in terms of gas phase bond

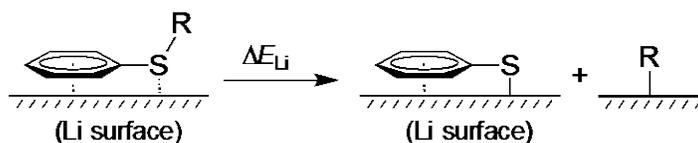
dissociation energies (entry 5). The bulkier alkyl groups, **1.21** and **1.28**, resulted in much less exothermic C-S bond cleavage on the Li surface (entries 3 and 4)

Table 1.11 Calculated C-S Bond Dissociation Energies.⁴⁵

(a) bond dissociation energy in gas phase



(b) bond dissociation energy on Li surface



Entry	Substrate	R	ΔE_{gas} (kcal/mol)	ΔE_{Li} (kcal/mol)
1	1.14	<i>i</i> -Pr	60.2	-27.1
2	1.20	2-butyl	60.7	-26.4
3	1.21	3-hexyl	60.7	-24.5
4	1.28	<i>t</i> -Bu	57.1	-24.8
5	1.40	Me	68.1	-38.0

The origin of the more favorable C-S bond dissociation with smaller alkyl groups is attributed to the stronger binding of the sterically less hindered alkyl radical to the Li surface. The adsorption of the methyl radical on Li was the most exothermic and the adsorption energy decreases as the bulkiness of the alkyl group increases ([Table 1.12](#)). Again, an electronic explanation, rather than a steric one, is quite unlikely since there was not a noticeable difference in the adsorption energies between the secondary radicals. In summary, the lithium surface

calculations indicate that the relative rates of cleavage of the phenyl thioethers are controlled by the steric repulsions between the alkyl group and the lithium surface in the adsorbed alkyl radical complex.⁴⁵

Table 1.12 Calculated Radical Adsorption Energies.⁴⁵

Entry	Substrate	Radical Adsorption on Li Surface (*)	ΔE_{ad} (kcal/mol)
1	1.14	$i\text{-Pr}\bullet + * \rightarrow i\text{-Pr}^*$	-30.2
2	1.20	$2\text{-butyl}\bullet + * \rightarrow 2\text{-butyl}^*$	-28.9
3	1.21	$3\text{-hexyl}\bullet + * \rightarrow 3\text{-hexyl}^*$	-27.7
4	1.28	$t\text{-Bu}\bullet + * \rightarrow t\text{-Bu}^*$	-24.3
5	1.40	$\text{Me}\bullet + * \rightarrow \text{Me}^*$	-45.4

1.2.6 Reductive Lithiation of Additional Substrates.

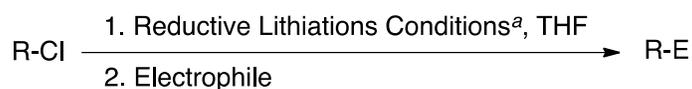
In order to determine if other functional groups behaved in a manner similar to that of the phenyl thioether, that is picking up an electron from lithium metal in the absence of an aromatic electron transfer reagent, the lithium dispersion reductive lithiation of some diverse substrates, which have previously undergone either catalytic or preformed radical-anion reductive lithiation, was investigated. The importance of the lithium dispersion reductive lithiation methodology is currently demonstrated in the industrial production of commercially available organolithium reagents. This procedure involves the exothermic reaction of the alkyl chloride with lithium dispersion (0.5-2% Na) in the desired hydrocarbon solvent.⁵⁴ Afterwards, the lithium chloride is removed and the solution is concentrated.

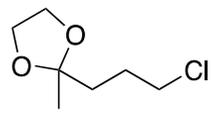
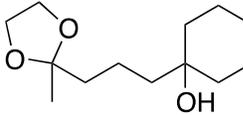
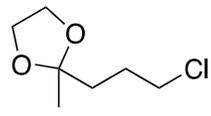
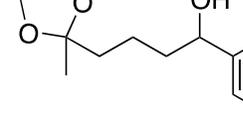
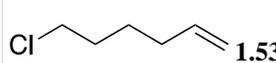
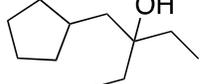
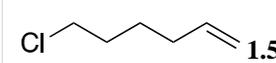
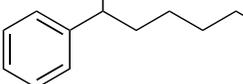
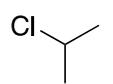
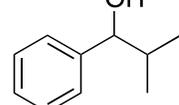
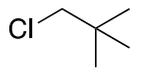
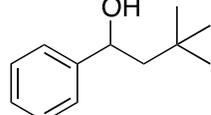
Yus and co-workers have performed a large number of catalyzed lithiation reactions of alkyl chlorides.^{16,21a,49} In two blank reactions, in the absence of an aromatic electron carrier, the

lithiation of two different primary alkyl chlorides resulted in one failed reaction, with 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, **1.46** ([Table 1.13](#), entry 1),¹⁶ and one successful reaction, with 6-chloro-1-hexene, **1.53** (entry 3).^{49f} In order to determine if **1.46** could be lithiated under the reductive lithiation conditions developed in our work, we treated this substrate with lithium dispersion, also at -78 °C. As a result, the corresponding alcohol product **1.47** was successfully obtained, in half the amount of time, after capturing the organolithium intermediate with benzaldehyde (entry 2).

Unlike the cyclopentyl product, **1.57**, that Yus isolated (entry 3), our reductive lithiation of **1.53** gave no rearranged product (entry 4). In the process of C-S bond cleavage on the Li surface, no free alkyl radical is formed. The calculated large adsorption energies suggest the alkyl group remains strongly adsorbed on the surface.⁴⁵ Furthermore, the short C-Li distance in the adsorbed complexes⁴⁵ indicates bonding interaction with the radical carbon, which will likely prevent the radical cyclization to form the cyclopentylmethyl radical. The lithium dispersion method of reductive lithiation of isopropyl chloride, **1.54**, and neopentyl chloride, **1.55**, provided excellent yields of the corresponding alcohol products, **1.48** and **1.59**, after the organolithium intermediates were trapped with benzaldehyde ([Table 1.13](#), entries 5 and 6). It is probably safe to assume that the reductive lithiation of alkyl chlorides, like that of phenyl thioethers, is general in the absence of added aromatic electron carriers under our very mild conditions.

Table 1.13 Reductive Lithiation of Alkyl Chlorides.



Entry	Alkyl Chloride	Temp. (°C)	Time (min)	Method ^a	Electrophile	Product	% Yield ^b
1	 1.46	-78	240	A	$(\text{CH}_2)_5\text{CO}$	 1.56	0 ^c
2	 1.46	-78	120	B	PhCOH	 1.47	85
3	 1.53	-30	50	C	Et ₂ CO	 1.57	83 ^d
4	 1.53	-45	60	A	PhCOH	 1.58	78
5	 1.54	-45	30	A	PhCOH	 1.48	79
6	 1.55	-45	30	A	PhCOH	 1.59	99

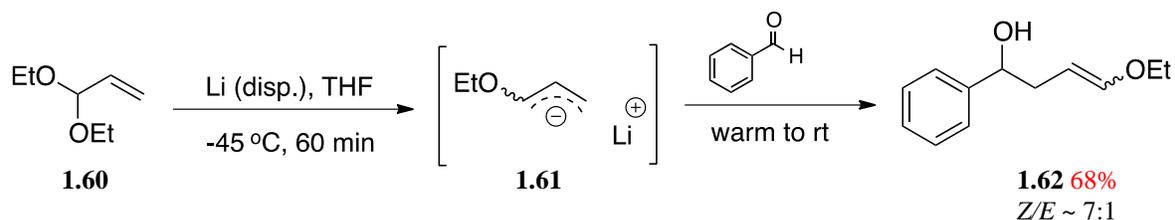
^a **Method A:** Li powder (Aldrich 325 mesh, 99.9%, 10 equiv); Cyclohexanone. **Method B:** Li (disp., 2.4 equiv); Benzaldehyde. **Method C:** Li powder (specially prepared,⁵² 7 equiv); 3-Pentanone. ^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^c Ref. 16. ^d Ref. 49f.

A 2006 report of the reductive cleavage of anisole, **1.5**, at the alkyl C-O bond, at 0 °C indicated that using 14 equivalents of Li but no DBB gave no product.² When anisole was

subjected to the reductive lithiation conditions developed in this work, no cleavage product was formed; rather starting material, benzaldehyde, and the pinacol coupling product of benzaldehyde were isolated, even after 24 h at room temperature. This result was puzzling because the bond dissociation energy values for the homolytic cleavage of the methyl-heteroatom bond of anisole (63.8 ± 1 kcal/mol) and of methyl phenyl sulfide (69.4 ± 2 kcal/mol) are close in energy.⁵⁶ Therefore, under the same reductive lithiation conditions, the rate at which the methyl radical is formed from each compound should be similar. Lithium surface calculations revealed that the energy of anisole adsorbed onto the surface of lithium is significantly less exothermic than the lithium surface adsorption energies of alkyl phenyl sulfides ([Table 1.10](#)).⁴⁵ The more favorable adsorption energies of the alkyl phenyl sulfides compared to anisole is presumably due to the greater polarizability of sulfur compared to oxygen. For this reason, the phenyl thioethers can pick up an electron more readily from Li metal itself, in the absence of an aromatic electron carrier when lithium dispersion is the Li metal source.

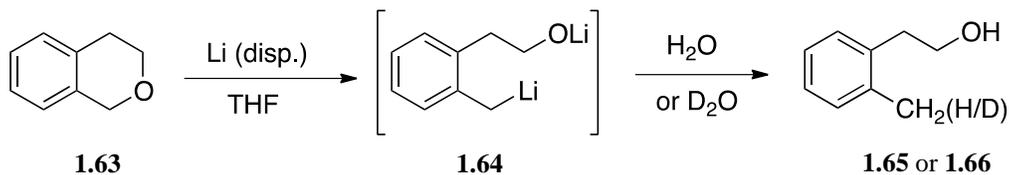
In that same 2006 report, Cohen and co-workers performed the aromatic radical-anion reductive cleavage of acrolein diethyl acetal, **1.60**.^{2,57} When acrolein diethyl acetal was subjected to the lithium dispersion reductive lithiation conditions developed in this work, the reductive cleavage occurred smoothly at -45 °C to provide the allylic organolithium intermediate, **1.61**, which was trapped with benzaldehyde to provide a 68% yield of **1.62** in a *Z/E* ratio of 7:1 ([Scheme 1.32](#)). The major *Z*-isomer was determined from the vicinal coupling constants (*J* values) on the olefin, $\delta 6.08$ (d, *J* = 6.3 Hz) ppm corresponding to the *Z*-isomer and $\delta 6.30$ (d, *J* = 12.6 Hz) ppm, which corresponds to the *E*-isomer.⁵⁸ This yield closely matches that obtained from the preformed radical-anion reductive cleavage of **1.60** after 90 min at -50 °C.² Furthermore, the yield of **1.60**

achieved in this work surpasses the 34% yield obtained with Yus's catalytic method, in which a 4-fold excess of lithium and Barbier conditions were employed.⁵⁹



Scheme 1.32 Lithium Dispersion Reductive Lithiation of Acrolein Diethyl Acetal, **1.60**.

In 1995, Yus and co-workers reported that isochroman, **1.63**, can be converted into lithium 2-(2-lithiomethylphenyl)ethanolate, **1.64**, via the reductive ring-opening by an excess of lithium powder (20 molar) and a catalytic amount of DBB ([Table 1.14](#), entries 1 and 3).⁶⁰ Furthermore, the claim is made that in the absence of the DBB, lithiation times were longer (*ca.* 3 h) and yields were considerably lower.⁶⁰ When **1.63** was subjected to the reductive lithiation conditions developed in our present work, 2-(2-methylphenyl)ethanol, **1.65**, was isolated in excellent yields at both 0 °C and -78 °C (entries 2 and 5). The formation of **1.64** was confirmed by quenching the reaction mixture with D₂O (entry 4) to obtain 2-(2-deuteriomethylphenyl)ethanol, **1.66**. Thus, only 2.4 molar equivalents of lithium dispersion was necessary to achieve similar yields as Yus *et. al.*, even at lower temperatures.

Table 1.14 Reductive Lithiation of Isochroman.

Entry	Temp. (°C)	Time (min)	Product	%Yield ^a
1	20	45	H (1.65)	89 ^b
2	0	30	H (1.65)	78
3	20	45	D (1.66)	86 ^b
4	0	30	D (1.66)	70
5	-78	120	H (1.65)	99

^a Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^b Ref 60.

1.3 CONCLUSIONS

In conclusion, we have demonstrated two efficient and cost-effective methods for the production of organolithium compounds via the reductive lithiation of alkyl phenyl thioethers as well as various other substrates. A new aromatic electron transfer reagent, DMA, was compared to the most common reductive lithiation catalysts and has been shown to catalyze the reductive lithiation to the same degree, if not better. Additionally, the lithium ribbon does not need to be scraped free from the oxide coating when DMA is used as the catalyst. Most impressively, the relative reactivity of the catalyzed reductive lithiation method is just the opposite of the preformed aromatic radical-anion method.

Alternatively, when lithium dispersion is the source of the Li metal, many reductive lithiations, previously thought to be possible only in the presence of electron transfer reagents, can

be performed with no electron transfer reagent present. Unlike Yus's procedure, which generally uses a large excess of lithium, specially prepared in an apparatus not generally available in synthetic labs, the procedure developed here uses a slight stoichiometric excess of commercially available lithium. Similar to the catalyzed method, the absence of the preformed aromatic radical-anion can completely change and even reverse the selectivity of reduction of different but very similar substrates. Phenyl thioethers with smaller alkyl groups are much more reactive than those with bulkier substituents. Lithium surface calculations reveal that the key step of alkyl phenyl sulfide cleavage on the lithium surface involves the formation of a thiophenoxyl and an alkyl radical adsorbed on the surface. Sterically less hindered alkyl radicals bind the surface more strongly, and thus lead to more exothermic cleavage of the alkyl phenyl sulfide. Thus, the transfer of an electron from the Li surface is proportional to binding, whereas poor binding requires an aromatic electron transfer reagent. The methodology developed in this work includes, but may not be limited to, the reductive lithiation of phenyl thioethers, alkyl chlorides, acrolein diethyl acetal, and isochroman.

1.4 EXPERIMENTAL

1.4.1 General Methods

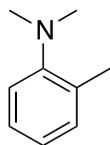
All reactions were carried out under a positive pressure of dry argon gas in oven-dried (120 °C) flasks and standard precautions against moisture were taken. A dry ice/acetone bath was used to obtain -78 °C, an ice bath was used to obtain 0 °C, and a dry ice/acetonitrile bath was used to obtain -45 °C. Flash chromatography (low pressure) was performed with either Dynamic Adsorbents Inc.

Flash silica gel (32-63 μm) or Sigma-Aldrich aluminum oxide, activated basic or neutral. Thin-layer chromatography was performed on glass supported (0.25 mm) silica plates (EMD Chemicals). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light, aqueous solution of KMnO_4 or *p*-Anisaldehyde (PAA). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer operating at 300 MHz or 400 MHz for ^1H and 75 MHz for ^{13}C at 22 $^\circ\text{C}$ unless otherwise noted. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of the CHCl_3 triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), and br (broad). Coupling constants, J , are reported in Hz.

Commercial solvents and reagents, from Sigma-Aldrich or Fisher Scientific, were used as received with the following exceptions: THF was distilled over sodium metal in the presence of benzophenone as indicator, hexanes was freshly distilled over CaH_2 , and benzaldehyde was washed with saturated $\text{NaHCO}_{3(\text{aq})}$, extracted with Et_2O , and vacuum distilled (~ 20 mm Hg).⁶¹ Lithium ribbon (0.75 mm thick, 0.45 mm wide, 99.9%) and lithium powder (325 mesh, 99.9%) were commercially available from Sigma-Aldrich. Lithium ribbon was prepared by scraping off the dark oxide coating from the surface while submerged in mineral oil. The shiny metal was dipped into hexanes and weighed in a tared beaker containing mineral oil. The metal was sliced into smaller pieces and then was dipped in hexanes prior to addition to the flask. Lithium dispersion (25 wt% in mineral oil) was commercially available from Sigma-Aldrich. Toward the end of the work described here, Sigma-Aldrich discontinued offering lithium dispersion; however, recipes

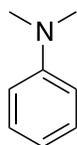
for its preparation are available.⁶² Furthermore, as described here, granular lithium (4-10 mesh, high sodium, 99%), from Sigma Aldrich, is only slightly less effective than the dispersion.

Attempted Production of the LDMOT ([Scheme 1.22](#))



An oven dried 25 mL round-bottom flask was charged with DMOT (1.0 mL, 6.9 mmol) and THF (12 mL) and then was cooled to -45 °C under argon. Lithium ribbon (40 mg, 5.8 mmol) was added to the flask. The reaction mixture was stirred for 3 h at -45 °C and then was warmed slowly to 0 °C and was stirred for an additional 2 h. No color was observed. The reaction mixture was quenched with H₂O and was extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo in order to completely recover the DMOT (1.0 g, 100% yield). ¹H NMR (CDCl₃) δ (ppm): 7.14-7.13 (m, 1H), 7.12-7.11 (m, 2H), 7.00 (dd, *J* = 8.6, 1.0 Hz, 1H), 6.93 (td, *J* = 7.3, 1.1 Hz, 1H), 2.67 (s, 6H), 2.31 (s, 3H).

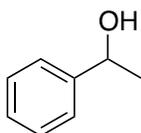
Attempted Production of LDMA ([Scheme 1.24](#))



An oven dried 5 mL round-bottom flask was charged with DMA (0.10 mL, 0.79 mmol) and THF (2 mL) and then was cooled to -45 °C under argon. Lithium ribbon (5 mg, 0.7 mmol) was added to the round-bottom flask. The reaction mixture was stirred for 3 h at -45 °C and then was warmed slowly to 0 °C and stirred an additional 2 h. No color change was observed. The reaction mixture

was quenched with H₂O and the product was extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo in order to completely recover the DMA (0.10 g, 100% yield). ¹H NMR (CDCl₃) δ (ppm): 7.23 (t, *J* = 7.2 Hz, 2 H), 6.74-6.69 (m, 3H), 2.91 (s, 6H).

1.4.2 1-Phenylethanol (**1.6**).



Catalytic Reductive Lithiation of **1.40** (Table 1.3)

An oven dried 25 mL round-bottom flask was charged with methyl phenyl sulfide, **1.40** (1.0 mL, 8.5 mmol), 5 mol% of catalyst (0.40 mmol), and THF (10 mL). The solution was cooled to -45 °C under argon and lithium ribbon (0.16 g, 23 mmol) was added. The reaction was stirred at -45 °C for 60 min followed by the dropwise addition of benzaldehyde (1.6 mL, 15 mmol). The mixture was stirred for 15 min and then was quenched with H₂O. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1-phenylethanol, **1.6**, as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.33-7.27 (m, 4H), 7.26-7.22 (m, 1H), 4.82 (q, *J* = 6.4 Hz, 1 H), 2.37 (br, 1H), 1.44 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 146.0, 128.4, 127.3, 125.5, 70.2, 25.2. These NMR data compare well with the literature values.²

- With DBB (0.11 g), 0.50 g (48%) of **1.6** was obtained.
- With cumene (0.06 mL), 0.43 g (42%) of **1.6** was obtained.

- With DMA (0.05 mL), 0.71 g (68%) of **1.6** was obtained. During the extraction, the combined organic layers were washed with 5% HCl_(aq).
- With DMAN (0.07 mL), 0.75 g (72%) of **1.6** was obtained. During the extraction, the combined organic layers were washed with 5% HCl_(aq).
- With DMOT (0.06 mL), 0.68 g (65%) of **1.6** was obtained. During the extraction, the combined organic layers were washed with 5% HCl_(aq).
- With 0 mol% of catalytic additive, 0.41 g (39%) of **1.6** was obtained.

*LDBB Reductive Lithiation of **1.40*** ([Table 1.6](#), entry 1)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (3 mL) was added and the mixture was stirred at room temperature. A solution of DBB (0.64 g, 2.7 mmol) in THF (2 mL) was added to the flask and the reaction mixture was stirred at room temperature for 5 min and then was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then was cooled to -78 °C. A solution of methyl phenyl sulfide, **1.40** (0.11 mL, 1.0 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 30 min. Benzaldehyde (0.12 mL, 1.2 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 30 min. The mixture was then quenched with H₂O and the product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1-phenylethanol, **1.6** (96 mg, 79% yield).

Catalytic and Non-Catalytic Reductive Lithiation of **1.40** ([Table 1.6](#), entries 2-4)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was then cooled to -78 °C and THF (1 mL) was added. A solution of 10 mol% of catalyst (0.10 mmol) in THF (0.5 mL) was added dropwise to the flask. Immediately following, was the dropwise addition of a solution of methyl phenyl sulfide, **1.40** (0.11 mL, 1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at -78 °C for 30 min. Benzaldehyde (0.12 mL, 1.2 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 30 min. The mixture was then quenched with H₂O and the product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1-phenylethanol, **1.6**.

- With DBB (27 mg), 90 mg (74%) of **1.6** was obtained.
- With DMA (12 mg), 94 mg (77%) of **1.6** was obtained. During the extraction, the combined organic extracts were washed with 1% HCl_(aq).
- With 0 mol% of catalytic additive, 89 mg (73%) of **1.6** was obtained.

Catalytic Reductive Lithiation of Anisole ([Table 1.7](#))

An oven-dried 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.22 g, 7.9 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was then cooled to 0 °C and THF (3 mL) was added followed by 10 mol% of catalyst (0.40 mmol). Anisole, **1.5** (0.40 mL, 3.7 mmol) was added dropwise and the reaction proceeded for 30 min at 0 °C and then was cooled to -45 °C under argon. Benzaldehyde (0.46 mL, 4.5 mmol) was added dropwise and the mixture was stirred for 15 min at -45 °C. The

mixture was then quenched with H₂O and the product was extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1-phenylethanol, **1.6**.

- With DBB (98 mg), 0.26 g (59%) of **1.6** was obtained.
- With DMAN (0.06 mL), 0.30 g (66%) of **1.6** was obtained. During the extraction, the combined organic extracts were washed with 1% HCl_(aq).
- With DMA (0.05 mL), 0% of **1.6** was obtained. During the extraction, the combined organic extracts were washed with 1% HCl_(aq).
- With DMA (0.05 mL) at room temperature, 0% of **1.6** was obtained. During the extraction, the combined organic extracts were washed with 1% HCl_(aq).

Lithium Dispersion Reductive Lithiation of **1.40** (Table 1.8, entries 14 and 15)

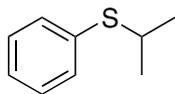
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to 0 °C and THF (3.5 mL) was added. A solution of methyl phenyl sulfide, **1.40** (0.25 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.6** (0.23 g, 95% yield).

- At -78 °C for 60 min, 0.23 g of **1.6** was obtained (95% yield).

DBB Catalyzed Reductive Lithiation of **1.40** ([Table 1.8](#), entry 17)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to -78 °C and THF (3 mL) was added. A solution DBB (53 mg, 0.2 mmol) in THF (0.5 mL) was added to the flask followed by the dropwise addition of methyl phenyl sulfide, **1.40** (0.25 g, 2.0 mmol) in THF (0.5 mL). The reaction mixture was stirred for 60 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.6** (0.22 g, 88% yield).

1.4.3 Isopropyl Phenyl Sulfide (**1.14**)



Synthesis of **1.14** ([Scheme 1.14](#))

A 100 mL round-bottom flask was charged with H₂O (45 mL) and NaOH (1.7 g, 44 mmol). Thiophenol (4.0 mL, 39 mmol) was added dropwise to the solution. The reaction mixture was stirred for 30 min. to insure the complete formation of sodium thiophenoxide. Isopropyl iodide (4.0 mL, 40 mmol) in EtOH (7 mL) was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with CH₂Cl₂ and the combined organic extracts were washed with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The crude colorless oil **1.14** was used

without purification (4.9 g, 80% yield). ^1H NMR (CDCl_3) δ (ppm): 7.39 (d, $J = 8.0$ Hz, 2H), 7.28, (t, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 3.36 (septet, $J = 6.8$ Hz, 1H), 1.29 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (CDCl_3) δ (ppm): 135.5, 131.9, 128.7, 126.6, 38.2, 23.1. These NMR data compare well with the literature values.⁵⁰

DMOT Catalyzed Reductive Lithiation of 2,2-Bis(phenylthio)propane (Table 1.2)

An oven dried 25 mL round-bottom flask was charged with of 2,2-bis(phenylthio)propane, **1.25** (1.0 g, 3.8 mmol), DMOT (0.030 mL, 0.21 mmol), and THF (10 mL). The solution was cooled to 0 °C under argon and lithium ribbon (60 mg, 8.6 mmol) was added. The reaction was stirred at 0 °C for 45 min and then was quenched with H_2O . The product was extracted with Et_2O and the combined organic extracts were washed with 5% $\text{HCl}_{(\text{aq})}$ followed by H_2O . The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography on silica gel (100% hexanes) afforded product **1.14** (76 mg, 13% yield).

- At -22 °C for 20 min, 70 mg (12%) of **1.14** was obtained.
- At -22 °C for 60 min, 90 mg (15%) of **1.14** was obtained.
- At -45 °C for 60 min, 0.12 g (20%) of **1.14** was obtained.
- At -45 °C for 40 min with 100 mol% of DMOT (0.56 mL, 3.8 mmol), 0.14 g (24%) of **1.14** was obtained. The aqueous extract was neutralized with 1M $\text{NaOH}_{(\text{aq})}$. The DMOT was extracted with Et_2O . The combined organic extracts were washed with H_2O , dried over MgSO_4 , and concentrated in vacuo in order to completely recover the DMOT (0.56 g, 100% yield).

DMA Catalyzed Reductive Lithiation of **1.14** ([Table 1.5](#))

An oven dried 10 mL round-bottom flask was charged with DMA (6.1 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of isopropyl phenyl sulfide, **1.14** (76 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.14** (47 mg, 62%).

Lithium Dispersion Reductive Lithiation of **1.14** ([Table 1.9](#))

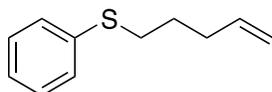
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of isopropyl phenyl sulfide, **1.14** (0.15 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then H₂O (5 mL) was added slowly and the mixture was warmed to room temperature. Hydrogen peroxide (30 wt%, 9.8 M, 0.10 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the **1.14** to the diphenyl disulfide, **1.27**, as 3:1.

LN Reductive Lithiation of **1.14** ([Scheme 1.31](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL)

under argon. THF (1.5 mL) was added to the flask followed by a solution of naphthalene (0.17 g, 1.3 mmol) in THF (1 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then cooled to -78 °C and a solution of isopropyl phenyl sulfide, **1.14** (76 mg, 0.50 mmol) in THF (0.25 mL) was added dropwise. The reaction mixture was stirred for 15 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.14** (16 mg, 26%).

1.4.4 5-(Phenylthio)-1-Pentene (**1.16**)



Synthesis of **1.16** ([Scheme 1.15](#))

A 100 mL round-bottom flask was charged with H₂O (45 mL) and NaOH (1.7 g, 45 mmol). Thiophenol (4.3 g, 39 mmol) was added dropwise to the solution. The reaction mixture was stirred for 30 min. to insure the complete formation of sodium thiophenoxide. 5-Bromo-1-pentene (3.7 mL, 31 mmol) in EtOH (6 mL) was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with CH₂Cl₂ and the combined organic extracts were washed twice with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The crude colorless oil **1.16** was used without purification (6.0 g, 99% yield). ¹H NMR (CDCl₃) δ (ppm): 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 5.78 (ddt, *J* = 13.6, 10.4, 6.8, Hz, 1H), 5.05-4.97 (m, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.19 (q, *J* = 7.2 Hz, 2H), 1.74 (pentet, *J* = 7.2 Hz, 2H); ¹³C NMR

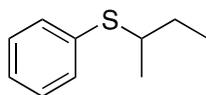
(CDCl₃) δ (ppm): 137.6, 136.7, 129.1, 128.9, 125.8, 115.4, 33.0, 32.7, 28.3. These NMR data compare well with the literature values.⁶³

Reductive Lithiation of **1.16** in the Presence and Absence of DBB (Table 1.8, entries 6 and 7)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1 mL) was added. A solution DBB (27 mg, 0.10 mmol) in THF (0.5 mL) was added to the flask followed by the dropwise addition of a solution of 5-(phenylthio)-1-pentene, **1.16** (0.18 g, 1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred for 10 min at -78 °C and then was quenched with H₂O. The mixture was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.16** (18 mg, 10%).

- With 0 mol% of catalyst, 20 mg (11%) of **1.16** was recovered.

1.4.5 2-(Phenylthio)-Butane (**1.20**)



Synthesis of **1.20** (Table 1.1, entry 1)

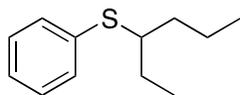
Sodium hydride (60 wt% in mineral oil, 0.60 g, 15 mmol) was charged to a 3-neck 25 mL round-bottom flask equipped with a condenser. The NaH was washed three times with hexanes (3 mL). DMF (5 mL) was added and the reaction mixture was stirred at room temperature. Thiophenol (1.0 mL, 9.8 mmol) was added dropwise to the reaction mixture followed by 2-bromobutane (0.70 mL,

6.4 mmol). The reaction mixture was stirred at approximately 80 °C for 2 h under argon and then was cooled to room temperature and quenched with H₂O. The product was extracted with hexanes and the combined organic extracts were washed twice with 1 M NaOH_(aq) followed by H₂O). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on basic alumina (100% hexanes) afforded **1.20** as a colorless oil (0.95 g, 89% yield). ¹H NMR (CDCl₃) δ (ppm): 7.36 (dd, *J* = 8.2, 2.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 3.13 (sextet, *J* = 6.6 Hz, 1H), 1.71-1.42 (m, 2H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 135.6, 131.9, 128.7, 126.6, 44.9, 29.5, 20.5, 11.4. These NMR data compare well with the literature values.⁶⁴

Lithium Dispersion Reductive Lithiation of **1.20** (Table 1.9)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of 2-(phenylthio)-butane, **1.20** (0.17 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then H₂O (5 mL) was added slowly and the mixture was warmed to room temperature. Hydrogen peroxide (30 wt%, 9.8 M, 0.10 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the **1.20** to the diphenyl disulfide, **1.27**, as 8:1.

1.4.6 3-(Phenylthio)-Hexane (1.21)



Synthesis of 1.21 (Table 1.1, entry 2)

Sodium hydride (60 wt% in mineral oil, 1.2 g, 30 mmol) was charged to a 3-neck 25 mL round-bottom flask equipped with a condenser. The NaH was washed three times with hexanes (6 mL). DMF (10 mL) was added and the reaction mixture was stirred at room temperature. Thiophenol (2.0 mL, 19.6 mmol) was added dropwise to the reaction mixture followed by 3-bromohexane (1.8 mL, 12.8 mmol). The reaction mixture was stirred at 100 °C for 2 h under argon and then was cooled to room temperature and quenched with H₂O. The product was extracted with hexanes and the combined organic extracts were washed twice with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on basic alumina (100% hexanes) afforded **1.21** as a colorless oil (2.4 g, 99% yield). ¹H NMR (CDCl₃) δ (ppm): 7.36 (d, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.14-7.09 (m, 1H), 3.01 (pentet, *J* = 6.2 Hz, 1H), 1.63-1.41 (m, 6H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 6.9 Hz); ¹³C NMR (CDCl₃) δ (ppm): 136.0, 131.8, 128.7, 126.4, 50.4, 36.2, 27.3, 20.1, 14.0, 11.1; IR (thin film) 3073 (s); 2959 (m); 2930 (m); 2872 (m); 1584 (s); 1477 (s); 1459 (s); 1439 (s); 1378 (s); 1091 (s); 1025 (s); 740 (m); 692 (m) cm⁻¹; TOF MS (EI⁺) exact mass calculated for C₁₂H₁₈S is 194.1129, found 194.1126.

Lithium Dispersion Reductive Lithiation of 1.21 (Table 1.9)

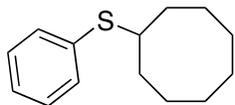
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of 3-

(phenylthio)-hexane, **1.21** (0.19 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then H₂O (5 mL) was added slowly and the mixture was warmed to room temperature. Hydrogen peroxide (30 wt%, 9.8 M, 0.10 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the **1.21** to the diphenyl disulfide, **1.27**, as 34:1.

LN Reductive Lithiation of **1.21** ([Scheme 1.31](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (1.5 mL) was added to the flask followed by a solution of naphthalene (0.17 g, 1.3 mmol) in THF (1 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then cooled to -78 °C and a solution of 3-(phenylthio)-hexane, **1.21** (97 mg, 0.50 mmol) in THF (0.25 mL) was added dropwise. The reaction mixture was stirred for 15 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.21** (30 mg, 31%).

1.4.7 Cyclooctyl Phenyl Sulfide (**1.22**)



Synthesis of **1.22** ([Table 1.1](#), entry 3)

Sodium hydride (60 wt% in mineral oil, 0.7 g, 15 mmol) was charged to a 3-neck 25 mL round-bottom flask equipped with a condenser. The NaH was washed three times with hexanes (3 mL). DMF (5 mL) was added and the reaction mixture was stirred at room temperature. Thiophenol (1.1 mL, 11 mmol) was added dropwise to the reaction mixture followed by cyclooctyl bromide (1.0 g, 5.2 mmol). The reaction mixture was stirred at 100 °C for 3 h under argon and then was cooled to room temperature and quenched with H₂O. The product was extracted with hexanes and the combined organic extracts were washed twice with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on basic alumina (100% hexanes) afforded **1.22** as a colorless oil (0.81 g, 52% yield). ¹H NMR (CDCl₃) δ (ppm): 7.37 (dd, *J* = 7.2, 0.8 Hz, 2H), 7.27 (dd, *J* = 15.2, 1.6 Hz, 2H), 7.19 (td, *J* = 6.8, 1.2 Hz, 1H), 3.43-3.36 (m, 1H), 2.00-1.93 (m, 2H), 1.79-1.50 (m, 12H); ¹³C NMR (CDCl₃) δ (ppm): 136.3, 131.5, 128.9, 126.5, 47.8, 32.1, 27.3, 26.0, 25.3. These NMR data compare well with the literature values.³³

DMA Catalyzed Reductive Lithiation of **1.22** ([Table 1.5](#))

An oven dried 10 mL round-bottom flask was charged with DMA (6.1 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of cyclooctyl phenyl sulfide, **1.22** (0.11 g, 0.50 mmol) in THF (0.5 mL)

was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.22** (0.10 g, 95%).

Lithium Dispersion Reductive Lithiation of **1.22** ([Table 1.9](#))

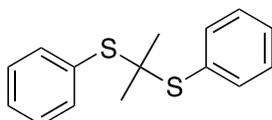
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of cyclooctyl phenyl sulfide, **1.22** (0.22 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then H₂O (5 mL) was added slowly and the mixture was warmed to room temperature. Hydrogen peroxide (30 wt%, 9.8 M, 0.10 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the **1.22** to the diphenyl disulfide, **1.27**, as 36:1.

LN Reductive Lithiation of **1.22** ([Scheme 1.31](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (1.5 mL) was added to the flask followed by a solution of naphthalene (0.17 g, 1.3 mmol) in THF (1 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then cooled to -78 °C and a solution of cyclooctyl phenyl sulfide, **1.22** (0.11 g, 0.50 mmol) in THF (0.25 mL) was added dropwise. The reaction mixture was stirred for 15 min

at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.22** (30 mg, 35%).

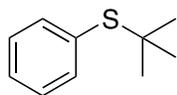
1.4.8 2,2-Bis(phenylthio)propane (**1.25**)



Synthesis of **1.25** ([Scheme 1.16](#))

To a solution of acetone (2.9 mL, 40 mmol), thiophenol (8.2 mL, 80 mmol), and CHCl₃ (40 mL) was added TMSCl (7.6 mL, 60 mmol) over a period of 45 min. The resulting mixture was stirred at room temperature for 1 h and then washed twice with 5% NaOH_(aq). The organic layer was dried over MgSO₄ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes) afforded **1.25** as a colorless oil (7.8 g, 76% yield). ¹H NMR (CDCl₃) δ (ppm): 7.66-7.63 (m, 4H), 7.38-7.34 (m, 6H), 1.50 (s, 6H); ¹³C NMR (CDCl₃) δ (ppm): 137.0, 132.4, 129.1, 128.6, 59.5, 30.9. These NMR data compare well with the literature values.³⁴

1.4.9 *tert*-Butyl Phenyl Sulfide (**1.28**)



Synthesis of **1.28** (Scheme 1.17)³⁵

A mixture of indium powder (1.0 g, 8.7 mmol), diphenyl disulfide (1.9 g, 8.7 mmol), and *tert*-butyl bromide (2.0 mL, 18 mmol) in CH₂Cl₂ (50 mL) was heated at reflux for 2 h under argon. The reaction mixture was cooled to room temperature and then was then quenched with 1 M HCl_(aq). The product was extracted with CH₂Cl₂ and the combined organic extracts were washed twice with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford **1.28** (2.1 g, 72% yield) as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.53-7.52 (m, 2H), 7.36-7.29 (m, 3H), 1.29 (s, 9H); ¹³C NMR (CDCl₃) δ (ppm): 137.4, 132.7, 128.6, 128.4, 45.8, 31.0. These NMR data compare well with the literature values.^{35,65}

Synthesis of **1.28** (Scheme 1.19)³⁸

A mixture of *tert*-butyl bromide (5.5 mL, 51 mmol), thiophenol (5.0 mL, 49 mmol), anhydrous FeCl₃ (0.71 g, 4.4 mmol) and glacial acetic acid (25 mL) was stirred at room temperature for 46 h. The reaction was quenched with H₂O and the product was extracted with Et₂O. The combined organic extracts were washed with saturated NaHCO_{3(aq)} followed by 1 M NaOH_(aq). The organic layer was dried over MgSO₄ and concentrated in vacuo to afford **1.28** (2.9 g, 35% yield) as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.53-7.52 (m, 2H), 7.36-7.29 (m, 3H), 1.29 (s, 9H); ¹³C NMR (CDCl₃) δ (ppm): 137.4, 132.7, 128.6, 128.4, 45.8, 31.0. These NMR data compare well with the literature values.⁶⁵

DMA Catalyzed Reductive Lithiation of **1.28** ([Table 1.5](#))

An oven dried 10 mL round-bottom flask was charged with DMA (6.1 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of *tert*-butyl phenyl sulfide, **1.28** (83 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.28** (50 mg, 60%).

Lithium Dispersion Reductive Lithiation of **1.28** ([Scheme 1.28](#))

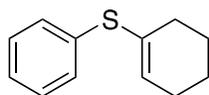
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of *tert*-butyl phenyl sulfide, **1.28** (83 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 5 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.28** (48 mg, 58%).

Reductive Lithiation of **1.40** in the Presence of **1.28** ([Scheme 1.30](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of *tert*-

butyl phenyl sulfide, **1.28** (83 mg, 0.50 mmol) and methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) and in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. ¹H NMR ratio of **1.28** to **1.40** as 7:1.

1.4.10 1-(Phenylthio)-1-Cyclohexene (**1.34**)



Synthesis of **1.34** (Scheme 1.20)

³⁹

Thiophenol (2.0 mL, 20 mmol), cyclohexanone (2.1 mL, 20 mmol), Montmorillonite K10 (4.0 g) and toluene (200 mL) were added under argon to a 250 mL three neck round-bottom flask equipped with a Dean Stark trap and condenser. The light beige slurry was heated at reflux for 6 h and then was cooled to ambient temperature and was filtered. The filter pad was washed with toluene and the filtrate was washed twice with 1 M NaOH_(aq) followed by H₂O. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) afforded **1.34** (2.8 g, 72% yield) as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.31-7.23 (m, 4H), 7.17-7.14 (m, 1H), 6.06 (s, 1H), 2.13 (m, 4H), 1.62 (dd, *J* = 24.2, 3.8 Hz, 4H); ¹³C NMR (CDCl₃) δ (ppm): 135.2, 132.7, 131.3, 130.0, 128.8, 126.2, 29.9, 26.7, 23.6, 21.6. These NMR data compare well with the literature values.³⁹

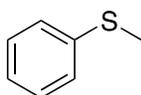
Catalytic Reductive Lithiation of **1.34** (Table 1.4)

An oven dried 10 mL round-bottom flask was charged with 10 mol% catalyst (0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78

°C under argon. A solution of 1-(phenylthio)-1-cyclohexene, **1.34** (95 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.34**.

- With DBB (13 mg), 72 mg (76%) of **1.34** was recovered.
- With DMA (6.1 mg), 75 mg (79%) of **1.34** was recovered.
- With 0 mol% of catalyst, 95 mg (100%) of **1.34** was recovered.

1.4.11 Methyl Phenyl Sulfide (**1.40**)



DMA Catalyzed Reductive Lithiation of **1.40** (Table 1.5)

An oven dried 10 mL round-bottom flask was charged with DMA (6.1 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.40** (19 mg, 31%).

- With the oxide coating not removed (Li ribbon cut into 2 smaller pieces), 19 mg (31%) of **1.40** was recovered.

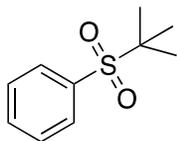
DMAN Catalyzed Reductive Lithiation of **1.40** ([Table 1.5](#))

An oven dried 10 mL round-bottom flask was charged with DMAN (8.6 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (un-scraped, 14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.40** (18 mg, 29%).

Lithium Dispersion Reductive Lithiation of **1.40** ([Scheme 1.28](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 5 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) led to recovered starting material **1.40** (11 mg, 17%).

1.4.12 *tert*-Butyl Phenyl Sulfone (**1.42**)



DBB Catalyzed Reductive Lithiation of **1.28** ([Scheme 1.25](#))

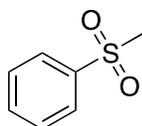
An oven dried 10 mL round-bottom flask was charged with DBB (13 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of *tert*-butyl phenyl sulfide, **1.28** (83 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. To the crude reaction mixture a 1:1 solution of H₂O/MeOH (4 mL) was added followed by oxone (0.92 g, 1.5 mmol). The reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.42** (69 mg, 70% yield) as a white solid. ¹H NMR (CDCl₃) δ (ppm): 7.89 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 1.34 (s, 9H); ¹³C NMR (CDCl₃) δ (ppm): 135.4, 133.5, 130.4, 128.6, 59.8, 23.6. These NMR data compare well with the literature values.⁶⁶

LDBB Reductive Lithiation of **1.28** ([Scheme 1.29](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (2 mL) was added and the mixture was stirred at room temperature. A solution

of DBB (0.36 g, 1.4 mmol) in THF (0.5 mL) was added to the flask and the reaction mixture was stirred at room temperature for 5 min and then was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then was cooled to -78 °C. A solution of *tert*-butyl phenyl sulfide, **1.28** (83 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred 5 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. To the crude product, a 1:1 solution of MeOH/H₂O (5 mL) was added followed by oxone (0.92 g, 1.5 mmol). The reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (Et₂O/hexanes) afforded **1.42** (36 mg, 36% yield).

1.4.13 Methyl Phenyl Sulfone (1.43)



DBB Catalyzed Reductive Lithiation of **1.40** (Scheme 1.25)

An oven dried 10 mL round-bottom flask was charged with DBB (13 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (14 mg, 2.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C and then was quenched with brine. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. To the crude reaction mixture a 1:1 solution of H₂O/MeOH (4 mL) was added followed by oxone (0.92 g, 1.5 mmol). The reaction mixture was stirred overnight

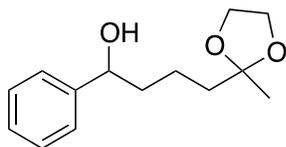
at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.43** (35 mg, 45% yield) as a white solid. ¹H NMR (CDCl₃) δ (ppm): 7.95 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 2H), 3.06 (s, 3H); ¹³C NMR (CDCl₃) δ (ppm): 140.6, 133.6, 129.3, 127.2, 44.4. These NMR data compare well with the literature values.⁶⁷

- With the oxide coating not removed (Li ribbon cut into 2 smaller pieces), 74 mg (95%) of **1.43** was obtained.

LDBB Reductive Lithiation of **1.40** ([Scheme 1.29](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (33 mg, 1.2 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (2 mL) was added and the mixture was stirred at room temperature. A solution of DBB (0.36 g, 1.4 mmol) in THF (0.5 mL) was added to the flask and the reaction mixture was stirred at room temperature for 5 min and then was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then was cooled to -78 °C. A solution of methyl phenyl sulfide, **1.40** (62 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred 5 min at -78 °C and then was quenched with H₂O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. To the crude product, a 1:1 solution of MeOH/H₂O (5 mL) was added followed by oxone (0.92 g, 1.5 mmol). The reaction mixture was stirred overnight at room temperature. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (Et₂O/hexanes) afforded **1.43** (50 mg, 64% yield).

1.4.14 2-(4-Hydroxy-4-Phenylbutyl)-2-Methyl-1,3-Dioxolane (**1.47**)



DMA Catalyzed Reductive Lithiation of **1.46** ([Scheme 1.27](#))

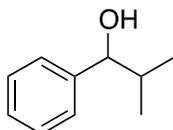
An oven dried 25 mL round-bottom flask was charged with DMA (6.1 mg, 0.050 mmol) and THF (1.5 mL). Lithium ribbon (un-scraped, 28 mg, 4.0 mmol) was added and the mixture was cooled to -78 °C under argon. A solution of 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, **1.46** (0.16 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 1 h and then benzaldehyde (0.12 mL, 1.2 mmol) was added dropwise. The mixture was warmed to room temperature and then was quenched with brine in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.47** (0.18 g, 76% yield) as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.35-7.29 (m, 5H), 4.66 (m, 1H), 3.90 (d, *J* = 4.8 Hz, 4H), 2.50 (br, 1H), 1.79-1.41 (m, 6H), 1.30 (s, 3H); ¹³C NMR (CDCl₃) δ (ppm): 144.8, 128.3, 127.4, 125.8, 110.0, 74.3, 64.5, 39.1, 38.7, 23.6, 20.3. These NMR data compare well with the literature values.⁶⁸

Lithium Dispersion Reductive Lithiation of **1.46** ([Table 1.13](#))

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to -78 °C and THF (1.5 mL) was added. A solution of 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, **1.46** (0.16 g, 1.0 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred for 2 h. Benzaldehyde (0.12 mL, 1.2 mmol) was

added dropwise and the reaction mixture was stirred for an additional hour at $-78\text{ }^{\circ}\text{C}$ and then was quenched with H_2O . The product was extracted with Et_2O ; the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc /hexanes) afforded **1.47** (0.20 g, 85% yield).

1.4.15 2-Methyl-1-Phenylpropan-1-ol (**1.48**)



Lithium Dispersion Reductive Lithiation of **1.14** ([Table 1.8](#), entry 1)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to $-78\text{ }^{\circ}\text{C}$ and THF (3.5 mL) was added. A solution of isopropyl phenyl sulfide, **1.14** (0.30 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 90 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H_2O in an ice-water bath. The product was extracted with Et_2O ; the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc /hexanes) afforded **1.48** (0.26 g, 87% yield) as a light yellow oil. ^1H NMR (CDCl_3) δ (ppm): 7.33-7.23 (m, 5H), 4.31 (d, $J = 6.8$ Hz, 1H), 2.08 (br, 1H), 1.93 (sextet, $J = 6.8$ Hz, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 143.6, 128.0, 127.2, 126.5, 79.8, 35.1, 18.9, 18.2. These NMR data compare well with the literature values.⁶⁹

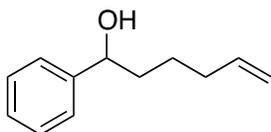
DBB Catalyzed Reductive Lithiation of **1.14** ([Table 1.8](#), entry 2)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to -78 °C and THF (3 mL) was added. A solution DBB (53 mg, 0.2 mmol) in THF (0.5 mL) was added to the flask followed by the dropwise addition of isopropyl phenyl sulfide, **1.14** (0.30 g, 2.0 mmol) in THF (0.5 mL). The reaction mixture was stirred for 90 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.48** (0.26 g, 87% yield).

Lithium Dispersion Reductive Lithiation of **1.54** ([Table 1.13](#))

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.34 g, 12.2 mmol). The lithium was washed three times with hexanes (5 mL) and once with THF (5 mL) under argon. The lithium was cooled to -45 °C and THF (5 mL) was added. Isopropyl chloride, **1.54** (0.50 mL, 5.5 mmol) was added dropwise and the reaction mixture was stirred for 30 min. Benzaldehyde (0.67 mL, 6.6 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 min at -45 °C and then was quenched with H₂O. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.48** (0.65 g, 79% yield).

1.4.16 1-Phenylhex-5-en-1-ol (**1.49**)



Lithium Dispersion Reductive Lithiation of **1.16** (Table 1.8, entries 3 and 4)

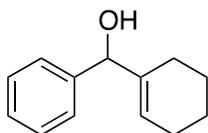
A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to 0 °C and THF (3.5 mL) was added. A solution of 5-(phenylthio)-1-pentene, **1.16** (0.36 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.49** (0.28 g, 80% yield) as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.34-7.23 (m, 5H), 5.77 (ddt, *J* = 14.0, 10.4, 6.4 Hz, 1H), 5.00-4.92 (m, 2H), 4.64-4.61 (m, 1H), 2.08 (br, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.82-1.65 (m, 2H), 1.54-1.32 (m, 2H); ¹³C NMR (CDCl₃) δ (ppm): 145.0, 138.7, 128.5, 127.5, 126.0, 114.8, 74.5, 38.5, 33.7, 25.2; TOF MS (ES⁺) exact mass calculated for C₁₂H₁₅O is 175.1123, found 175.1114. These NMR data compare well with the literature values.⁷⁰

- At -78 °C for 60 min, 0.29 g of **1.49** was obtained (83% yield).

Granular Lithium Reductive Lithiation of **1.16** ([Table 1.8](#), entry 5)

A 10 mL round-bottom flask was charged with granular lithium (34 mg, 4.8 mmol) and THF (3.5 mL). The flask was cooled to -78 °C and then a solution of the 5-(phenylthio)-1-pentene, **1.16** (0.36 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 60 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product **1.49** (0.27 g, 77% yield).

1.4.17 1-(1'-Cyclohexenyl)-1-Phenylmethanol (1.50)



Lithium Dispersion Reductive Lithiation of **1.34** ([Table 1.8](#), entries 8, 10, and 11)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to 0 °C and THF (3.5 mL) was added. A solution of 1-(phenylthio)-1-cyclohexene, **1.34** (0.38 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 15 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on

silica gel (EtOAc/hexanes) afforded **1.50** (0.33 g, 88% yield) as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.32-7.23 (m, 5H), 5.82-5.77 (m, 1H), 5.03 (s, 1H), 2.17 (br, 1H), 2.06 (m, 2H), 1.89 (d, *J* = 16 Hz, 1H), 1.73 (d, *J* = 16 Hz, 1H), 1.54 (m, 4H); ¹³C NMR (CDCl₃) δ (ppm): 142.6, 139.6, 128.2, 127.3, 126.3, 123.5, 78.3, 25.0, 24.0, 22.5, 22.4; TOF MS (ES⁺) exact mass calculated for C₁₃H₁₅O is 187.1123, found 187.1143. These NMR data compare well with the literature values.⁷¹

- At -45 °C for 60 min, 0.33 g of **1.50** was obtained (88% yield).
- At -78 °C for 60 min, 0.32 g of **1.50** was obtained (84% yield).

Granular Lithium Reductive Lithiation of **1.34** (Table 1.8, entry 13)

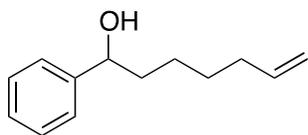
A 10 mL round-bottom flask was charged with granular lithium (34 mg, 4.8 mmol) and THF (3.5 mL). The flask was cooled to -78 °C and then a solution of the 1-(phenylthio)-1-cyclohexene, **1.34** (0.38 g, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 60 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product **1.50** (0.24 g, 64% yield).

DBB Catalyzed Reductive Lithiation of **1.34** (Table 1.8, entry 12)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to -78 °C and THF (3 mL) was added. A solution DBB (53

mg, 0.2 mmol) in THF (0.5 mL) was added to the flask followed by the dropwise addition of 1-(phenylthio)-1-cyclohexene, **1.34** (0.38 g, 2.0 mmol) in THF (0.5 mL). The reaction mixture was stirred for 60 min and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then the mixture was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.50** (0.32 g, 86% yield).

1.4.18 1-Phenylhept-6-en-1-ol (**1.58**)

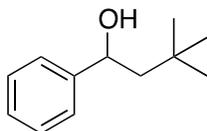


Lithium Dispersion Reductive Lithiation of **1.53** (Table 1.13)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.23 g, 8.2 mmol). The lithium was washed three times with hexanes (5 mL) and once with THF (5 mL) under argon. The lithium was cooled to -45 °C and THF (5 mL) was added. 6-Chloro-1-hexene, **1.53** (0.50 mL, 3.8 mmol) was added dropwise and the reaction mixture was stirred for 60 min at -45 °C. Benzaldehyde (0.46 mL, 4.5 mmol) was added dropwise and the reaction mixture was warmed to room temperature and then was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.58** (0.56 g, 78% yield) as a light yellow oil. ¹H NMR (CDCl₃) δ (ppm): 7.32-7.24 (m, 5H), 5.78 (ddt, *J* = 13.6, 10.0, 6.8 Hz, 1H), 5.00-4.91 (m, 2H), 4.64 (t, *J* = 6.8 Hz, 1H), 2.03 (d, *J* = 6.8 Hz, 2H), 1.95 (br, 1H), 1.83-

1.6.5 (m, 2H), 1.42-1.28 (m, 4H); ^{13}C NMR (CDCl_3) δ (ppm): 144.9, 138.9, 128.4, 127.5, 125.9, 114.4, 74.6, 38.9, 33.7, 28.8, 25.3. These NMR data compare well with the literature values.⁷²

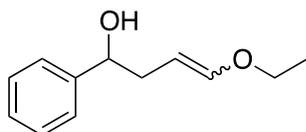
1.4.19 3,3-Dimethyl-1-Phenylbutan-1-ol (**1.59**)



Lithium Dispersion Reductive Lithiation of **1.55** (Table 1.13)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.25 g, 9.0 mmol). The lithium was washed three times with hexanes (5 mL) and once with THF (5 mL) under argon. The lithium was cooled to $-45\text{ }^\circ\text{C}$ and THF (5 mL) was added. Neopentyl chloride, **1.55** (0.50 mL, 4.1 mmol) was added dropwise and the reaction mixture was stirred for 30 min. Benzaldehyde (0.50 mL, 4.9 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 min at $-45\text{ }^\circ\text{C}$ and then was quenched with H_2O . The product was extracted with Et_2O ; the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc /hexanes) afforded **1.59** (0.72 g, 99% yield) as a light yellow oil. ^1H NMR (CDCl_3) δ (ppm): 7.32-7.31 (m, 4H), 7.28-7.22 (m, 1H), 4.78 (d, $J = 5.2$ Hz, 1H), 1.88 (br, 1H), 1.73 (dd, $J = 14.4, 8.4$ Hz, 1H), 1.58 (dd, $J = 13.3, 3.4$ Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (CDCl_3) δ (ppm): 146.4, 128.4, 127.2, 125.7, 72.4, 52.8, 30.4, 30.1. These NMR data compare well with the literature values.⁷³

1.4.20 4-Ethoxy-1-Phenylbut-3-en-1-ol (**1.62**)



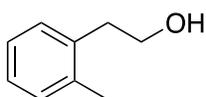
Lithium Dispersion Reductive Lithiation of **1.60** (Scheme 1.32)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.13 g, 4.8 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. The lithium was cooled to -45 °C and THF (3.5 mL) was added. A solution of the acrolein diethyl acetal, **1.60** (0.30 mL, 2.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 60 min at -45 °C and then benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then was quenched with H₂O in an ice-water bath. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.62** (0.26 g, 68% yield, Z/E ≈ 7:1) as a light yellow oil. *E*- and *Z*-isomers could not be separated. The following data concern the mixture of these two compounds: IR (thin film) 3429, 3031, 2977, 2925, 1664, 1494, 1453, 1382, 1305, 1247, 1192, 1040, 984, 759, 701 cm⁻¹; TOF MS (EI⁺) exact mass calculated for C₁₂H₁₅O₂ is 191.1072, found 191.1057.

- *Z*-Isomer: ¹H NMR (CDCl₃) δ (ppm): 7.38-7.30 (m, 5H), 6.08 (d, *J* = 6.3 Hz, 1H), 4.72 (dd, *J* = 7.5, 5.1 Hz, 1H), 4.38 (q, *J* = 6.9 Hz, 1H), 3.78 (q, *J* = 7.0 Hz, 2H), 2.62-2.50 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 146.6, 144.2, 127.9, 126.9, 125.7, 101.6, 73.7, 67.5, 33.9, 15.0.

- *E*-Isomer: ^1H NMR (CDCl_3) δ (ppm): 7.38-7.30 (m, 5H), 6.30 (d, $J = 12.6$ Hz, 1H), 4.61 (dd, $J = 7.5, 5.1$ Hz, 1H), 4.38 (q, $J = 6.9$ Hz, 1H), 3.69 (q, $J = 7.0$ Hz, 2H), 2.47-2.27 (m, 2H), 1.23 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 148.4, 144.9, 128.0, 127.1, 125.7, 98.8, 73.7, 64.5, 37.8, 14.5.

1.4.21 2-(2-Methylphenyl)Ethanol (**1.65**)

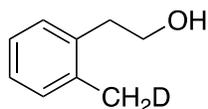


Lithium Dispersion Reductive Lithiation of **1.63** (Table 1.14)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to 0 °C and THF (1.5 mL) was added. A solution of isochroman, **1.63** (0.13 g, 1.0 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then was quenched with H_2O . The product was extracted with Et_2O ; the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc /hexanes) afforded **1.65** (0.11 g, 78% yield) as a colorless oil. ^1H NMR (CDCl_3) δ (ppm): 7.14 (m, 4H), 3.80 (t, $J = 7.0$ Hz, 2H), 2.88 (t, $J = 6.8$ Hz, 2H), 2.32 (s, 3H), 1.79 (br, 1H); ^{13}C NMR (CDCl_3) δ (ppm): 136.5, 136.5, 130.4, 129.7, 126.6, 126.0, 62.6, 36.4, 19.5. These NMR data compare well with the literature values.⁷⁴

- At -78 °C for 2 h, 0.13 g of **1.65** was obtained (99% yield).

1.4.22 2-(2-Deuteriomethylphenyl)Ethanol (1.66)



Lithium Dispersion Reductive Lithiation of **1.63** (Table 1.14)

A 10 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. The lithium was cooled to 0 °C and THF (1.5 mL) was added. A solution of isochroman, **1.63** (0.13 g, 1.0 mmol) in THF (0.5 mL) was then added dropwise. The reaction mixture was stirred for 30 min and then was quenched with D₂O. The product was extracted with diethyl ether; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **1.66** (96 mg, 70% yield) as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.20 (m, 4H), 3.85 (t, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 2.37 (d, *J* = 5.2 Hz, 2H), 2.05 (br, 1H); ¹³C NMR (CDCl₃) δ (ppm): 136.4, 130.3, 129.5, 126.5, 126.0, 62.5, 36.3, 19.1 (t, *J* = 19.5 Hz). These NMR data compare well with the literature values.⁷⁴

2.0 THE STEREOSELECTIVE REDUCTION OF KETONES TO THE MOST THERMODYNAMICALLY STABLE ALCOHOLS USING LITHIUM AND HYDRATED SALTS OF COMMON TRANSITION METALS.

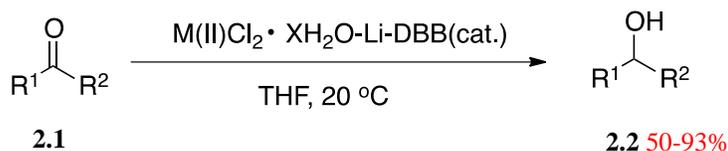
This chapter is based on results presented in: Kennedy, N.; Cohen, T. *J. Org. Chem.* **2015**, *80*, 8134-8141. DOI: 10.1021/acs.joc.5b01232.

2.1 BACKGROUND

The reduction of unsaturated organic substrates represents one of the most widely used and valuable functional group transformations in synthetic organic chemistry. Metal-mediated reductions by electron- or hydride-transfer, are interesting alternatives to catalytic hydrogenation, because of their practical and fundamental importance.⁷⁵ These reactions are convenient in both large- or lab-scale synthesis since there is no need to employ high hydrogen pressure or to use hazardous reducing agents.⁷⁵ Among the various reducible substrates, ketones are of great relevance in order to obtain the corresponding alcohols. Specifically, the stereoselective reduction of cyclic ketones is an extremely important reaction in organic synthesis, in which most of the published results consist of using metal hydrides or complex reducing agents.^{76,77} In general, for 6-membered rings, bulky reducing agents favor the approach to the carbonyl group via an equatorial trajectory, giving the thermodynamically less stable axial alcohol.⁷⁸ Several valuable

protocols have been devised for the synthesis of the more stable equatorial alcohols;⁷⁹ however, a simple, consistently high yielding method is unavailable.

Presented here is a new, simple and effective methodology to accomplish the diastereoselective reduction of mono- and poly-cyclic ketones under very mild conditions to afford the thermodynamically more stable alcohol product. This method was developed during our investigation of the protocol by Yus and co-worker's⁸⁰ for the reduction of unsaturated groups. Their procedure makes use of the hydrates of transition metal salts FeCl₂•4H₂O, NiCl₂•2H₂O, or CuCl₂•2H₂O in the presence of lithium metal and catalytic amounts of *p,p'*-di-*tert*-butyl biphenyl (DBB) (Scheme 2.1). The role of the latter additive is to pick up an electron from the Li to form an aromatic radical-anion, which then transfers the electron to another component of the solution thus acting as an electron transfer agent.



Scheme 2.1 Yus's Reduction of Carbonyl Compounds. M = Cu, Ni or Fe, X = 2 or 4.

In Chapter 1, it was revealed that the reductive lithiation of alkyl phenyl thioethers, as well as various other substrates, previously performed only in the presence of such aromatic electron transfer agents, does not actually require the use of such reagents when the Li metal is a dispersion or granular. This led to the investigation of whether or not the same is true of ketone reductions

performed by Yus^{75,81,82} in the presence of the hydrates of transition metal salts. The studies were restricted to the commercially available copper and iron salts. The commercially unavailable⁸³ and toxic nickel salts were not examined. It turns out that in the reduction of ketones by this procedure the aromatic electron transfer agent is indeed not required. Furthermore, most surprisingly, in many important cases, the diastereoselectivity is just the opposite in the presence or absence of such agents.⁷⁵ We have not been able to reproduce some of these reported stereoselectivity results.

2.2 RESULTS AND DISCUSSION

2.2.1 Stereoselective Reduction with Lithium Dispersion.

Yus and co-workers employed an 8:1 molar ratio of lithium sand to $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ⁸² and an 8:1 molar ratio of lithium powder to $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$.⁷⁵ There is no mention as to why they use different types of lithium or what their lithium sources are. In the work presented here, a 4:1 molar ratio of lithium dispersion, (25 wt% in mineral oil) containing 0.1% sodium, to $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and in the case of the more highly hydrated $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, a 6:1 molar ratio to achieve the diastereoselective reduction of cyclic ketones in moderate to excellent yields. An important advantage of this dispersion is that it can be weighed and transferred to the designated flask open to the air without the lithium reacting. The mineral oil that coats the lithium metal can then be removed under argon by rinsing with hexanes so that the lithium remains unreacted under argon until the solvent and the substrate are added. According to following tables, the hydrated metal salt equivalents and allotted reaction times were employed in order to achieve the maximum yield of alcohol products. The diastereomeric ratios were assigned from the isolated product ¹H NMR spectra and the major

product was determined by comparing literature NMR values and/or the J values of cyclohexane (Figure 2.1).⁵⁸

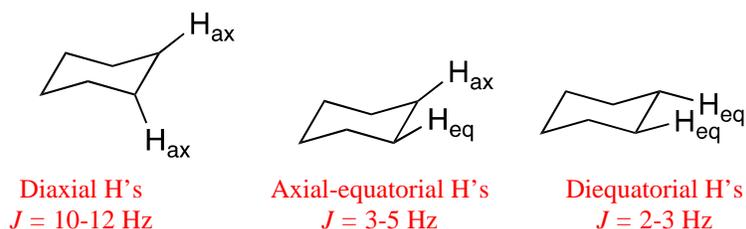


Figure 2.1 Coupling J Values for Cyclohexane.

In the reduction of 4-*tert*-butylcyclohexanone, **2.3**, (Table 2.1), in which the bulky *tert*-butyl group is locked in the equatorial position and is removed from the carbonyl reaction center, the resulting product was the thermodynamically more stable equatorial alcohol, *trans*-4-*tert*-butylcyclohexanol, **2.4a** (entries 1 and 2). Based on the J values shown in Figure 2.1, the CH-OH at δ 3.52 (tt, $J = 10.8, 4.2$ Hz) ppm (see Figure 2.2) confirms the equatorial position of the alcohol and the *trans* structure of the alcohol product.⁸⁴ This selectivity result resembles those obtained with the most common metal hydrides LiAlH₄ or 9-BBN (Table 2.1, entries 3 and 4)⁸⁵ or the complex reducing agents of Caubère's group (entry 5).⁸⁶ Lithium metal in liquid ammonia afforded only the *trans* isomer, although in much lower yield (57%) than ours (Table 2.1, entry 6).⁸⁷ More recently, Cha and co-workers performed the reduction of **2.3** with 1.1 equivalents of Al-methanesulfonyldiisobutylalane (DIBAO₃SCH₃) at room temperature to obtain 99% (as determined by GC after 72 h.) of the more stable *trans*-alcohol in a ratio of 94:6 eq./ax (Table 2.1, entry 7).^{79g} Their procedure not only requires the preparation of the DIBAO₃SCH₃ reagent but also

a significantly longer reaction time in order to achieve a diastereoselectivity that is similar to that obtained in our present work.

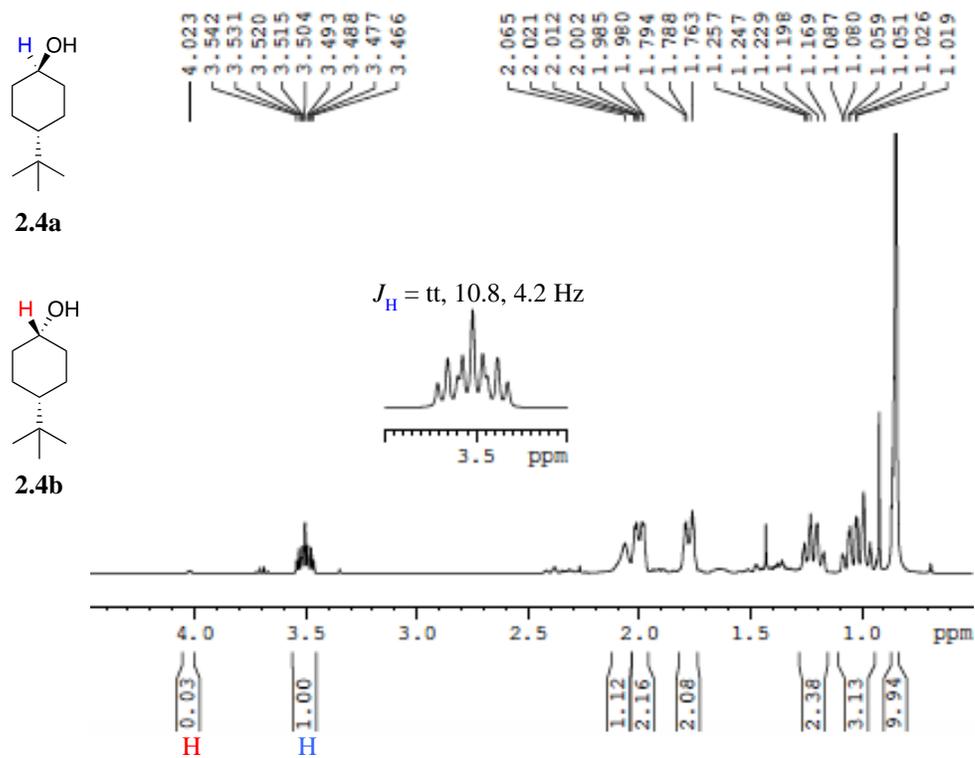
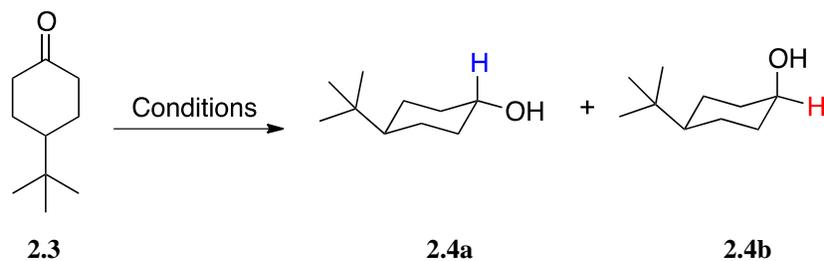


Figure 2.2 ^1H NMR of *cis*- and *trans*-4-*tert*-Butylcyclohexanol.

Table 2.1 Stereoselective Reduction of 4-*tert*-Butylcyclohexanone.



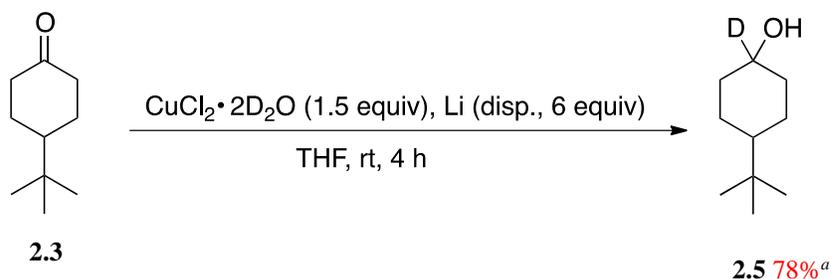
Entry	Conditions	% Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h	83	99:1
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h	77	100:0 ^c
3	LiAlH ₄ , THF	-	90:10 ^d
4	9-BBN, THF	-	92:8 ^d
5	NaH- <i>tert</i> -AmONa-Ni(OAc) ₂ -LiBr, THF, 40 °C, 4 h	93	92:8 ^e
6	Li (1 equiv), NH ₃ (liquid), Et ₂ O, reflux, 30 min	57	100:0 ^f
7	DIBAO ₃ SCH ₃ (1.1 equiv), Et ₂ O, rt, 72 h	99 ^g	94:6 ^g

^a Isolated yield of **2.4** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c See ¹H NMR in [Appendix](#). ^d Ref. 85. ^e Ref. 86. ^f Ref. 87.

^g Determined by GC, Ref. 79g.

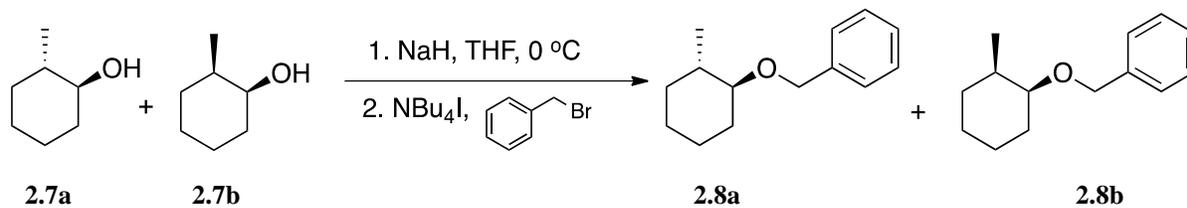
In our work, using the deuterated salt $\text{CuCl}_2 \cdot 2\text{D}_2\text{O}$, prepared from anhydrous CuCl_2 and D_2O , instead of the hydrated one, furnished the corresponding alcohol, **2.5**, deuterated at the 1-position ([Scheme 2.2](#)).



Scheme 2.2 Reduction of 4-*tert*-Butylcyclohexanone with $\text{CuCl}_2 \cdot 2\text{D}_2\text{O}$.
^aDeuterium incorporation approximately 85% by ^1H NMR (see [Appendix](#)).

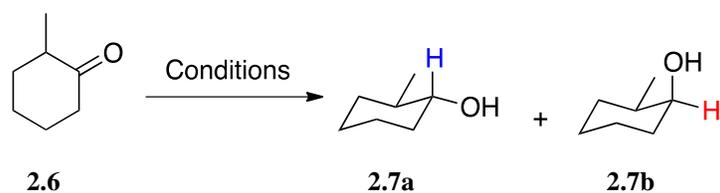
The reduction of the more hindered ketone, 2-methylcyclohexanone, **2.6**, ([Table 2.2](#), entries 1 and 2), produced the thermodynamically more stable equatorial alcohol, *trans*-2-methylcyclohexanol, **2.7a**, after only 10 minutes. Based on the *J* values shown in [Figure 2.1](#), the CH-OH at δ 3.10 (td, *J* = 9.6, 4.2 Hz) ppm (see [Figure 2.3](#)) confirms the equatorial position of the alcohol, when the 2-methyl group is also equatorial in order to prevent 1,3-diaxial interactions, and the *trans* structure of the alcohol product. The crude alcohol was protected as a benzyl ether,⁸⁸ **2.8** ([Scheme 2.3](#)) to ease the isolation process. The diastereoselectivity that we obtained surpasses that observed with common reducing systems LiAlH_4 , NaBH_4 , 9-BBN ([Table 2.2](#), entries 3-5).⁸⁹ The metal-ammonia reduction of **2.6** affords nearly exclusive formation of the equatorial alcohol, **2.7a**; however, a significantly lower yield (63%) was collected after 100 min ([Table 2.2](#), entry 6).^{79a} In the work by Cha *et. al.*, a longer reaction time, when compared to our procedure, was

employed in their reduction of **2.6** with *Al*-trifluoromethanesulfonyldiisobutylalane (DIBAO₃SCF₃) to produce 94% (as determined by GC after 1 h.) of the more stable *trans*-alcohol, **2.7a**, in a ratio of 91:9 eq./ax (entry 7).^{79h}



Scheme 2.3 Crude Alcohol **2.7** Protected as Benzyl Ether.

Table 2.2 Stereoselective Reduction of 2-Methylcyclohexanone.



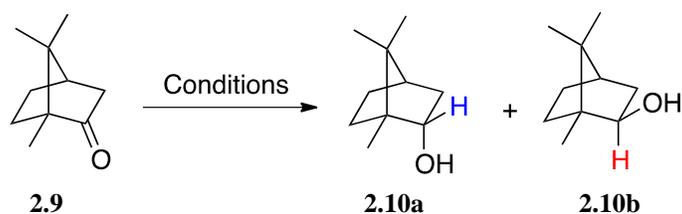
Entry	Conditions	% Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 10 min	80 ^c	92:8
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 10 min	99 ^c	95:5 ^d
3	LiAlH ₄ , THF	-	65:35 ^e
4	9-BBN, THF	-	60:40 ^e
5	NaBH ₄ , THF	-	69:31 ^e
6	Li, NH ₃ (liquid), Et ₂ O, EtOH, 100 min	63	100:0 ^f
7	DIBAO ₃ SCF ₃ (1.1 equiv), Et ₂ O, rt, 1 h	94 ^g	91:9 ^g

^a Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c Isolated yield of benzyl-ether product, **2.8**. ^d See [Figure 2.3](#). ^e Ref. 89.

^f Ref. 79a. ^g Determined by GC, Ref. 79h.

Table 2.3 Stereoselective Reduction of (±)-Camphor.



Entry	Conditions	%Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (2 equiv), Li (disp., 8 equiv), THF, rt, 24 h	65	96:4
2	FeCl ₂ •4H ₂ O (2 equiv), Li (disp., 12 equiv), THF, rt, 24 h	78	95:5 ^c
3	CuCl ₂ •2H ₂ O (2 equiv), DBB (10 mol%) Li (powder, 16 equiv), THF, rt, 24 h	55	85:15 ^d
4	FeCl ₂ •4H ₂ O (2 equiv), DBB (10 mol%) Li (powder, 16 equiv), THF, rt, 24 h	62	90:10 ^d

^a Isolated yield of **2.10** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c See [Figure 2.4](#). ^d Ref. 75.

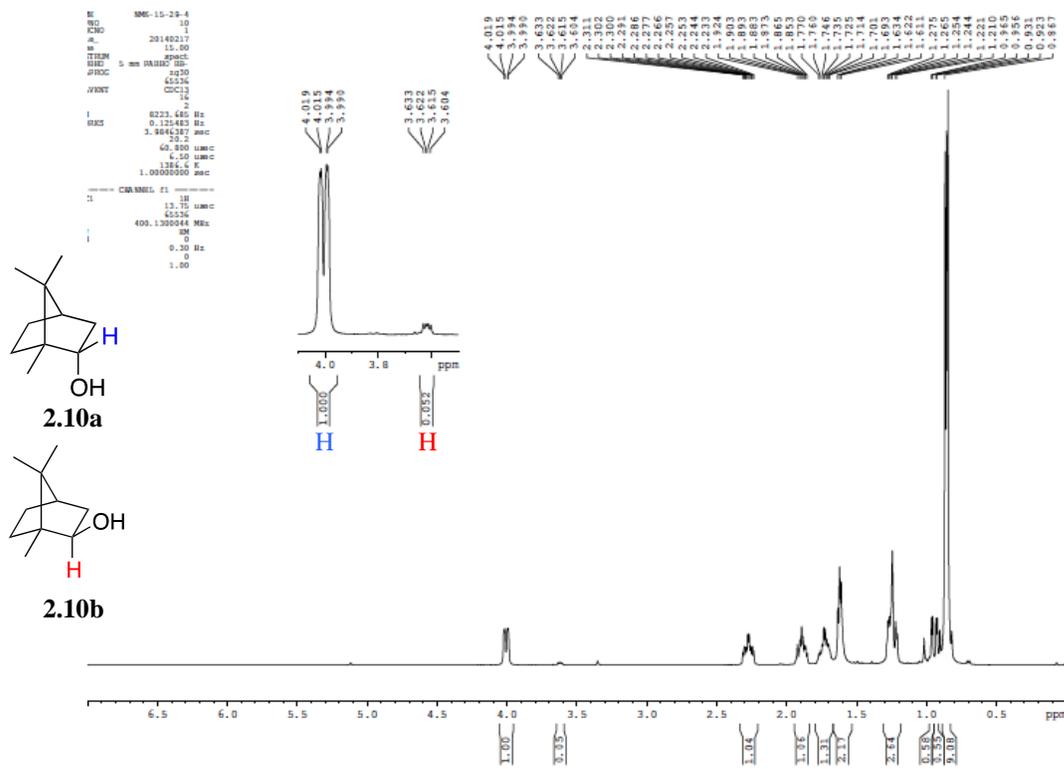
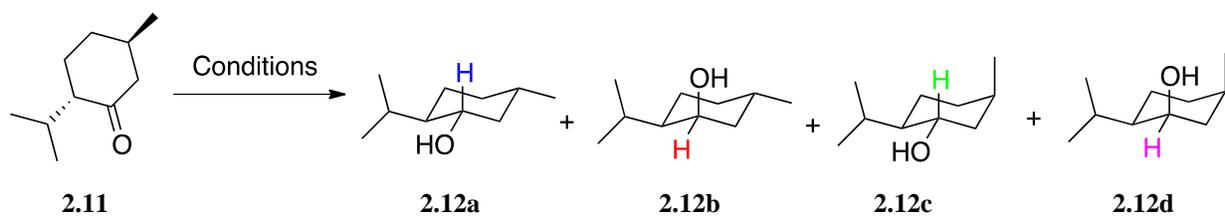


Figure 2.4 ^1H NMR of *endo*- and *exo*-Borneol (Table 2.3, entry 2).

In the reduction of (-)-menthone, **2.11** (Table 2.4, entries 1 and 2) the alcohol that is so favorably produced, (-)-menthol, **2.12a**, is capable of an all-equatorial configuration. Based on the J values shown in Figure 2.1, the CH-OH at δ 3.41 (td, $J = 10.2, 3.6$ Hz) ppm (see Figure 2.5) confirms the equatorial position of the alcohol when the *iso*-propyl group is also equatorial in order to prevent 1,3-diaxial interactions. Solodar and co-workers obtained less of **2.12**, 74% (-)-menthol, **2.12a**, to 26% mixture of *neo*-, **2.12b**, *iso*-, **2.12c**, and *neois*-menthol, **2.12d**, in their stereoselective reduction of **2.11** with 3 equivalents of lithium metal and 1 equivalent of water in ether at ambient temperature (entry 3).⁹¹

Table 2.4 Stereoselective Reduction of (-)-Menthone.



Entry	Conditions	%Yield ^a	Ratio (a:b:c:d) ^b
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h	86	96:4:0:0 ^c
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h	99	95:5:0:0
3	Li (3 equiv), Et ₂ O (wet), rt	87	74:9:13:4 ^d

^a Isolated yield of **2.12** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c See [Figure 2.5](#). ^d Ref. 91.

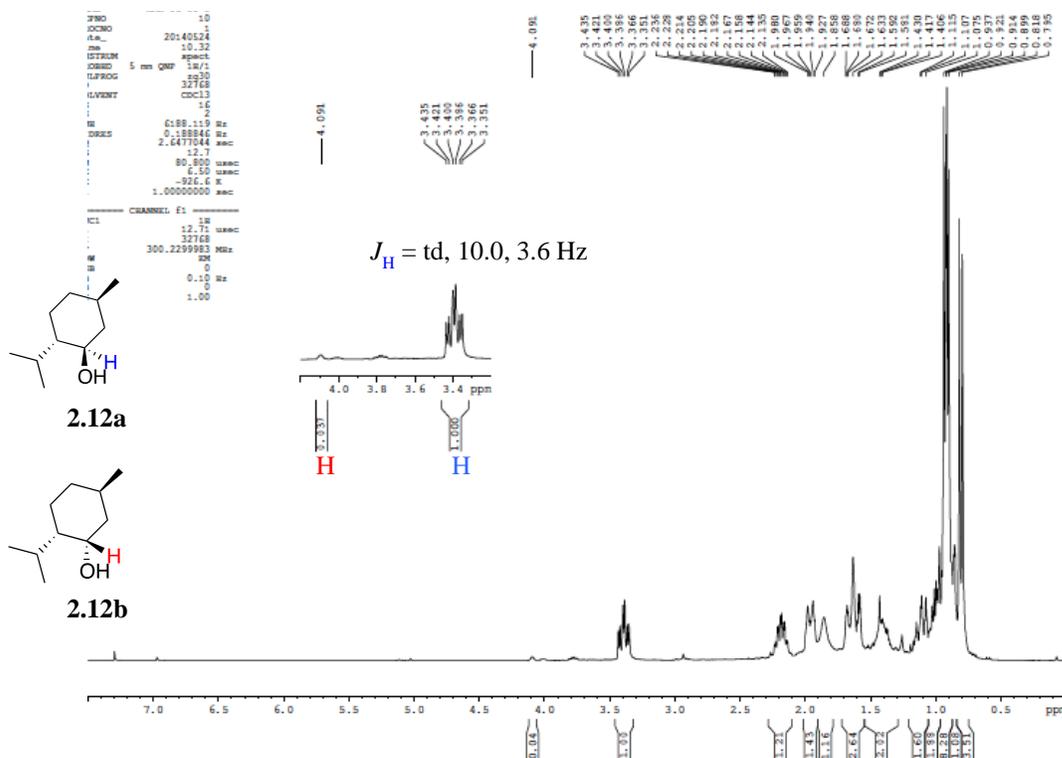
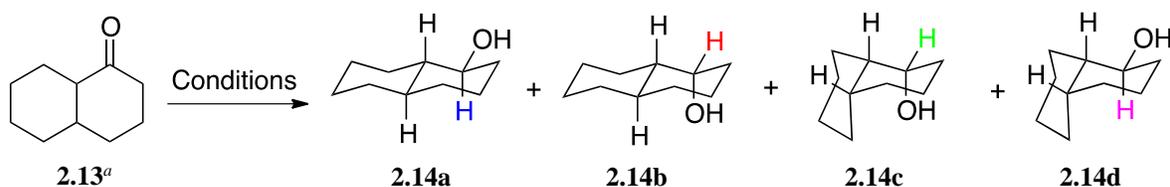


Figure 2.5 Crude ^1H NMR of *neo*- and (-)-Menthol (Table 2.4, entry 1).

When our methodology was applied to a mixture of *cis*- and *trans*-1-decalone, **2.13** (Table 2.5, entries 1 and 2), the major diastereomeric product, (\pm)-*trans,cis*-decahydro-1-naphthol, **2.14a**, was that which would result from the reduction of pure *trans*-1-decalone, despite the starting material containing a mixture of isomers. Presumably, the *trans*-isomer of 1-decalone reacts faster than the *cis*-isomer. (\pm)-*Cis,cis*-decahydro-1-naphthol, **2.14d**, was not produced in either reduction reaction, as determined by the lack of a signal at δ 3.80 ppm.⁸⁴ Houk and co-workers observed only 60% of the thermodynamically stable equatorial alcohol after 24 h. with the NaBH_4 reduction of *trans*-1-decalone (Table 2.5, entry 3).⁹² Yus *et. al.* isolated the less thermodynamically stable

axial alcohol, (\pm)-*trans,trans*-decahydro-1-naphthol,⁹³ **2.14b**, with their M(II)Cl₂•XH₂O-Li-DBB reduction of *trans*-1-decalone (Table 2.5, entries 4 and 5).⁷⁵

Table 2.5 Stereoselective Reduction of 1-Decalone.



Entry	Conditions	%Yield ^b	Ratio (a:b:c ⁸⁴ :d) ^c
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 2 h	82	92:5:3:0 ^d
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 2 h	95	94:4:2:0
3	NaBH ₄ , MeOH, rt, 24 h	-	60:40:0:0 ^e
4	CuCl ₂ •2H ₂ O (1.5 equiv), DBB (10 mol%) Li (powder, 12 equiv), THF, rt, 3 h	84	1:99:0:0 ^f
5	FeCl ₂ •4H ₂ O (1.5 equiv), DBB (10 mol%) Li (powder, 12 equiv), THF, rt, 3 h	91	1:99:0:0 ^f

^a Commercially available unknown mixture of *cis* and *trans* from Sigma-Aldrich. ^b Isolated yield of **2.14** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^c Diastereomeric ratio determined by ¹H NMR. ^d See Figure 2.6. ^e *trans*-1-decalone starting material; Ref. 92. ^f *trans*-1-decalone starting material; Ref. 75.

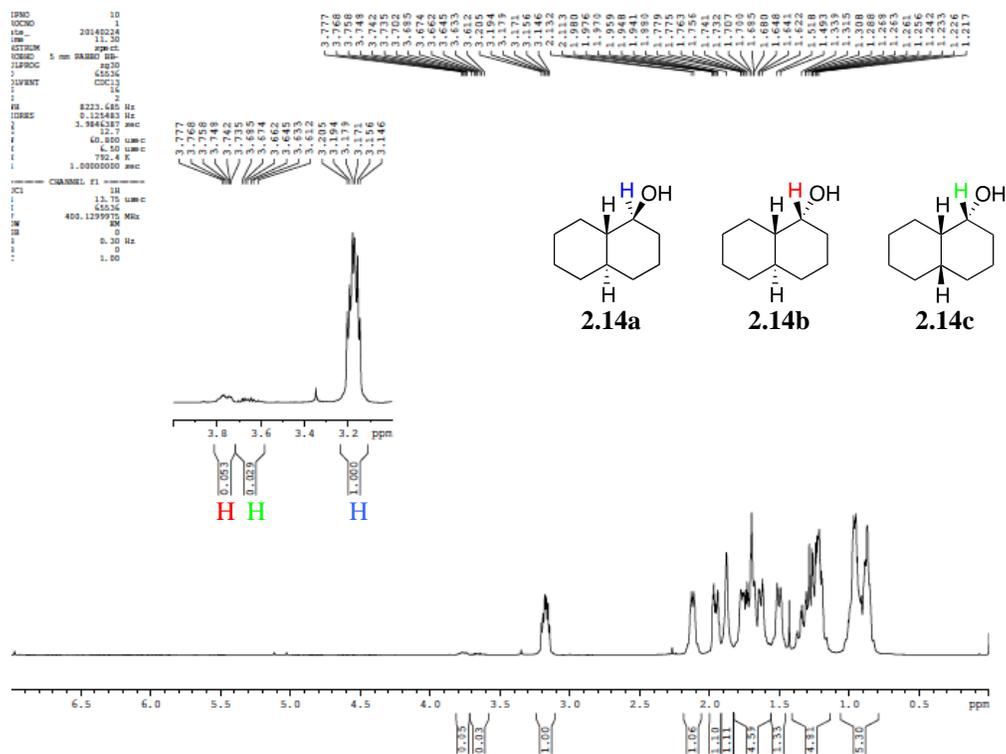
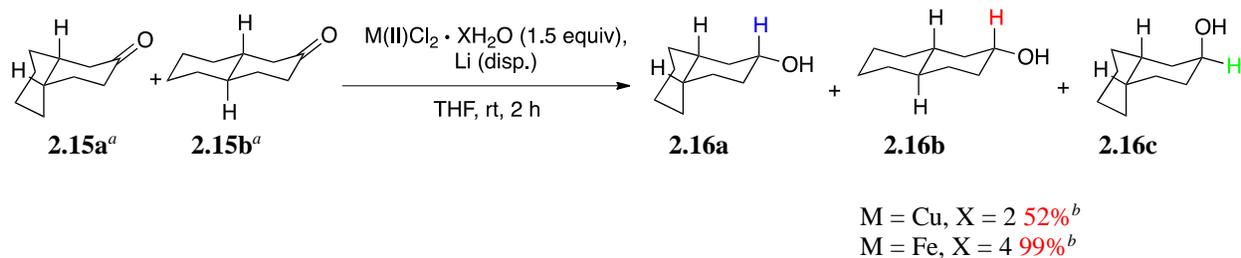


Figure 2.6 ^1H NMR of (\pm)-*trans,trans*-, (\pm)-*cis,trans*-, and (\pm)-*trans,cis*-Decahydro-1-naphthol (Table 2.5, entry 1).

Unfortunately, the reduction of a mixture of *cis*- and *trans*-2-decalone, **2.15** (~20:80, Figure 2.7)⁹⁴ under the conditions developed in our work, was not stereoselective (Scheme 2.4). The inseparable decahydro-2-naphthols, **2.16**, [(\pm)-*cis,trans*, **2.16a**, (\pm)-*trans,trans*, **2.16b**, and (\pm)-*cis,cis*, **2.16c**] were isolated in almost equal amounts, as determined by ^1H NMR (see Appendix). Product **2.16** was confirmed by comparing the ^1H NMR to the literature values.⁸⁴



Scheme 2.4 Reduction of 2-Decalone. ^aCommercially available mixture of *cis* and *trans* (~20:80, see [Figure 2.7](#)). ^bIsolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

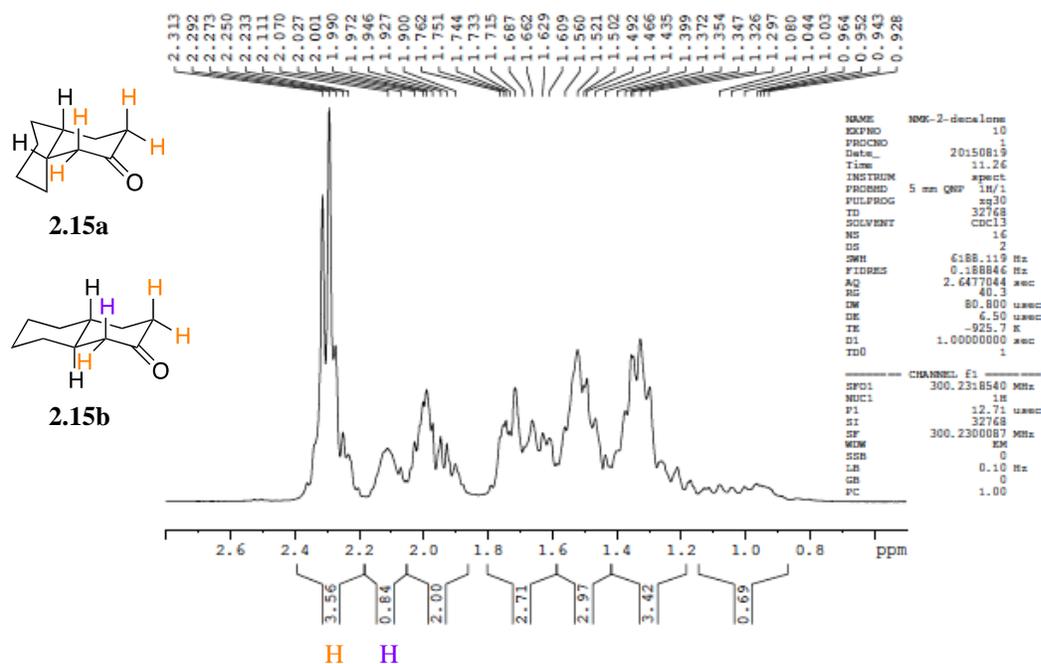


Figure 2.7 ¹H NMR of *cis*- and *trans*-2-Decalone.

In the case of 3,3,5-trimethylcyclohexanone, **2.17** ([Table 2.6](#), entries 1 and 2), a significantly higher yield of the thermodynamically stable equatorial alcohol, *cis*-3,3,5-trimethylcyclohexanol, **2.18a**, was isolated with the $FeCl_2 \cdot 4H_2O$ in comparison to the

CuCl₂•2H₂O. Furthermore, 2 equiv of CuCl₂•2H₂O were required to reduce the ketone to an isolable amount; regardless, the diastereoselectivity was still excellent. Based on the *J* values shown in [Figure 2.1](#), the CH-OH at δ 3.72 (tt, *J* = 11.2, 4.5 Hz) ppm (see [Figure 2.8](#)) confirms the equatorial position of the alcohol when the 5-methyl group is also equatorial in order to prevent 1,3-diaxial interactions. More recently, Cha and co-workers performed the reduction of **2.17** with their DIBAO₃SCF₃ to obtain the more stable *cis*-alcohol in a ratio of 98:2 eq./ax. after 72 h,^{79h} that is with less diastereoselectivity than in our reduction after only 1 h (entry 3).

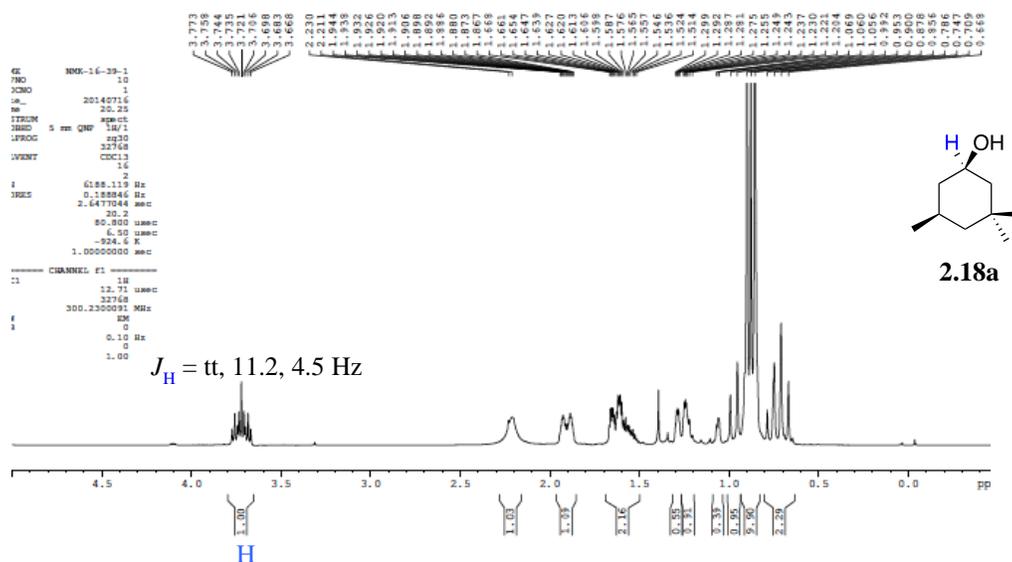
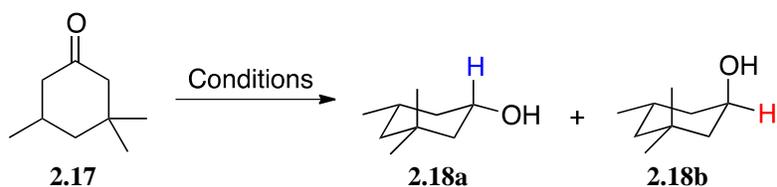


Figure 2.8 ¹H NMR of *cis*-3,3,5-Trimethylcyclohexanol ([Table 2.6](#), entries 1 and 2).

Table 2.6 Stereoselective Reduction of 3,3,5-Trimethylcyclohexanone.



Entry	Conditions	%Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (2 equiv), Li (disp., 8 equiv), THF, rt, 1 h	26	100:0 ^c
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 1 h	70	100:0 ^c
3	DIBAO ₃ SCF ₃ (1.1 equiv), Et ₂ O, rt, 72 h	99.8 ^d	98:2 ^d

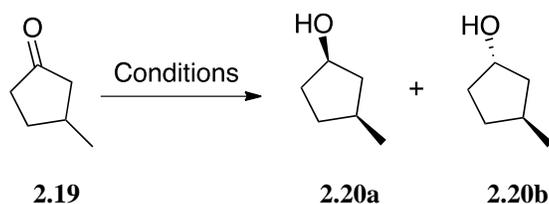
^a Isolated yield of **2.18** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c See [Figure 2.8](#). ^d Determined by GC, Ref. 79h.

Examination of the conformation of 3-methylcyclopentanone shows that the 3-methyl group prefers to occupy a *pseudo-equatorial* position⁹⁵ of an envelope conformation.⁹⁶ Under our conditions, the reduction of 3-methylcyclopentanone, **2.19** ([Table 2.7](#), entries 1 and 2) led to 3-methylcyclopentanol, in only 5 min., with an excess of the *cis*-isomer, **2.20a** (see [Figure 2.9](#)). Product **2.20a** was confirmed by comparing the ¹H NMR to the literature methyl peaks at δ 1.06 ppm and δ 0.99 ppm.⁹⁶ The LiAlH₄ reduction of **2.19** also provides a 60:40 *cis* to *trans* ratio of 3-

methylcyclopentanol (entry 3).⁹⁷ Similar to the case of **2.7**, the reduction product was protected as a benzyl ether to afford **2.21** ([Scheme 2.5](#)).

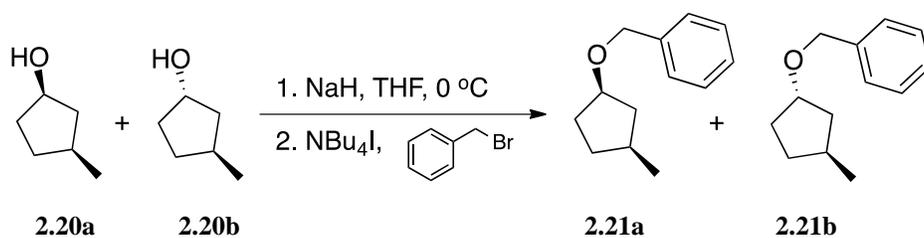
Table 2.7 Stereoselective Reduction of 3-Methylcyclopentanone.



Entry	Conditions	% Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (1 equiv), Li (disp., 3 equiv), ^c THF, rt, 5 min	63 ^d	60:40 ^e
2	FeCl ₂ •4H ₂ O (1 equiv), Li (disp., 5 equiv), ^f THF, rt, 5 min	70 ^d	60:40 ^e
3	LiAlH ₄ , THF	-	60:40 ^g

^a Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c 3:1 ratio of lithium dispersion to CuCl₂•2H₂O. ^d Isolated yield of benzyl-ether product, **2.21**. ^e See [Figure 2.9](#). ^f 5:1 ratio of lithium dispersion to FeCl₂•4H₂O. ^g Determined by IR, Ref. 97.



Scheme 2.5 Crude Alcohol **2.20** Protected as Benzyl Ether.

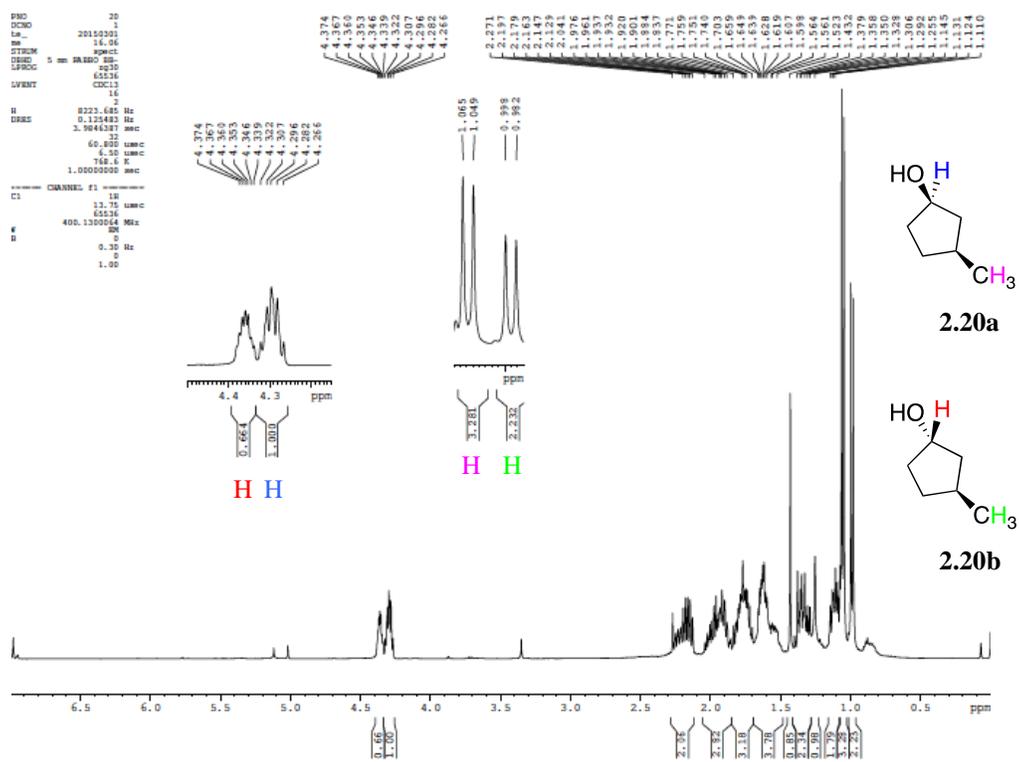
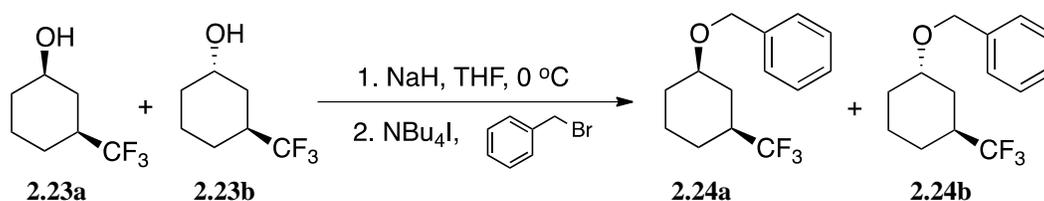


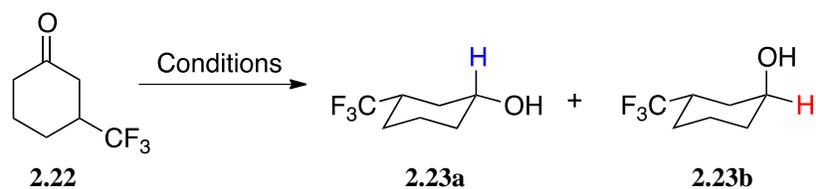
Figure 2.9 Crude ^1H NMR of *cis*- and *trans*-3-Methylcyclopentanol ([Table 2.7](#), entries 1 and 2).

In order to further assess the reduction capability of our method in the presence of various functional groups, other than alkyl substituents, we have successfully reduced ketones containing a trifluoromethyl group, a hydroxyl group, a methoxy group, and a tertiary amine. 3-(Trifluoromethyl)cyclohexanone, **2.22**, was reduced to the more thermodynamically stable *cis*-3-(trifluoromethyl)cyclohexanol, **2.23a**, in excellent diastereoselectivity (Table 2.8, entries 1 and 2). Based on the *J* values in [Figure 2.1](#), the CH-OH at δ 3.61 (tt, *J* = 10.8, 4.2 Hz) ppm (see [Figure 2.10](#)) confirms the equatorial position of the alcohol when the 3-(trifluoromethyl) group is also equatorial in order to prevent 1,3-diaxial interactions. The crude alcohol was protected as a benzyl ether, **2.24**, in order to ease the isolation and purification of the product ([Scheme 2.6](#)). To the best of our knowledge, the only other reduction of **2.22** occurred with microorganisms, in which 3-(trifluoromethyl)cyclohexanone was reduced with *Streptomyces* C53 in 94% in a ratio of 55:45 *cis*-3-(trifluoromethyl)cyclohexanol, **2.23a**, to *trans*, **2.23b**, after 24 h (entry 3).⁹⁸



Scheme 2.6 Crude Alcohol **2.23** Protected as Benzyl Ether.

Table 2.8 Stereoselective Reduction of 3-(Trifluoromethyl)cyclohexanone.



Entry	Conditions	%Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 1 h	70 ^c	95:5
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 1 h	85 ^c	97:3 ^d
3	<i>Streptomyces</i> C53, EtOH, 24 h	94	55:45 ^e

^a Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c Isolated yield of benzyl-ether product, **2.24**. ^d See [Figure 2.10](#).

^e Determined by GLC, Ref. 98.

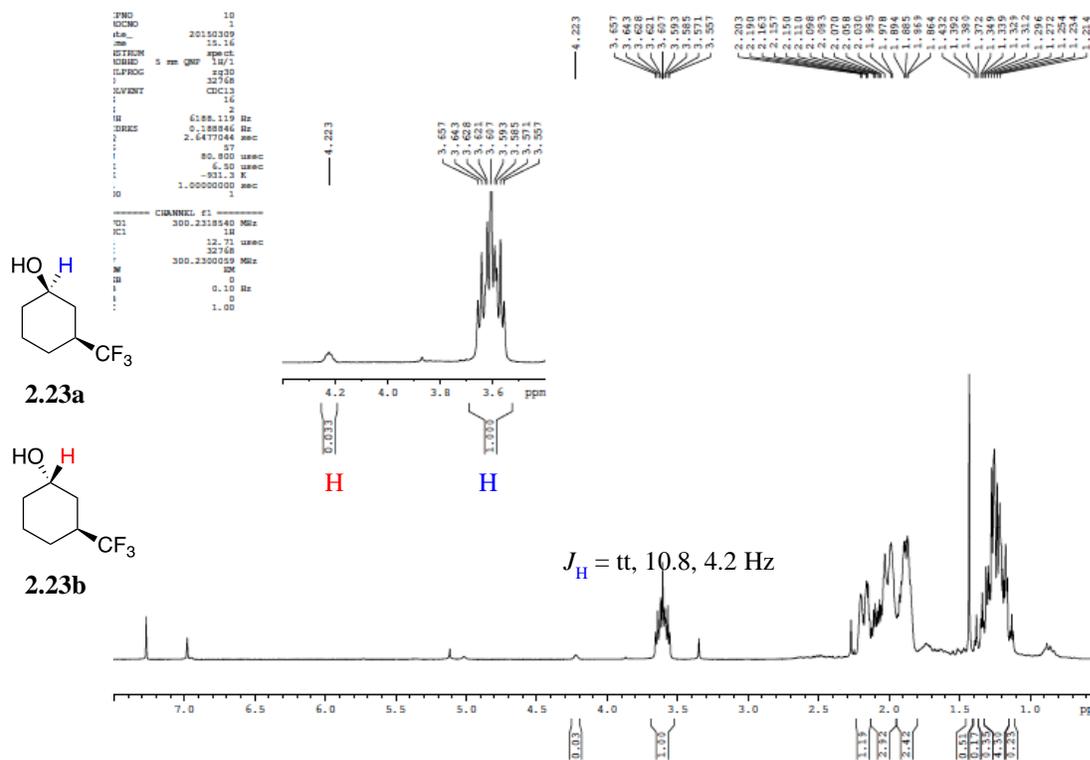
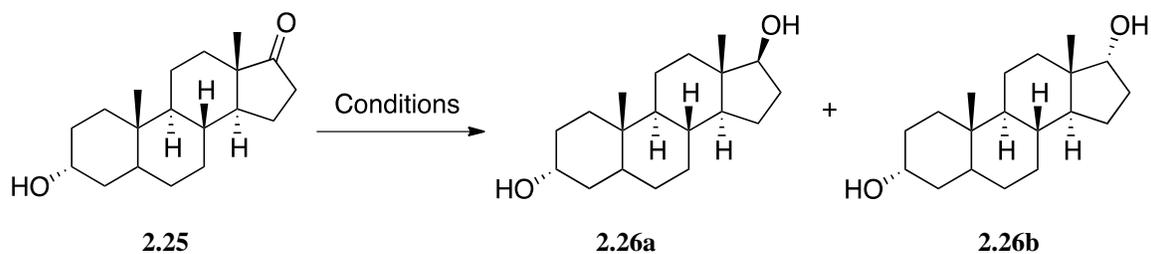


Figure 2.10 Crude ^1H NMR of *cis*- and *trans*-3-(Trifluoromethyl)cyclohexanol (Table 2.8, entry 2).

The hindered steroidal ketone, 3 α -hydroxy-5 α -androstane-17-one, **2.25**, was diastereoselectively reduced to 5 α -androstane-3 α ,17 β -diol, **2.26a** (Table 2.9, entries 1 and 2). Product **2.26a** was confirmed by comparing the ^1H NMR to the literature values at δ 4.04 ppm and δ 3.63 ppm (see Figure 2.11).⁹⁹ The free 3 α -hydroxy group did not affect the ketone reduction. Satoh and co-workers indicated that the reduction of **2.25** with NaBH_4 alone is difficult; therefore, they employed a large excess of NaBH_4 (10 equiv) and PdCl_2 in their reduction of 3 α -hydroxy-5 α -androstane-17-one to obtain **2.26a** in 96% yield (entry 3).¹⁰⁰

Table 2.9 Stereoselective Reduction of 3 α -Hydroxy-5 α -Androstan-17-one.



Entry	Conditions	%Yield ^a	Ratio (a:b) ^b
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h	75	100:0 ^c
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h	96	100:0 ^c
3	NaBH ₄ (10 equiv), PdCl ₂ (2 equiv), MeOH, rt, 1 h	96	100:0 ^d

^a Isolated yield of **2.26** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

^b Diastereomeric ratio determined by ¹H NMR. ^c See [Figure 2.11](#). ^d Determined by GLC, Ref. 100.

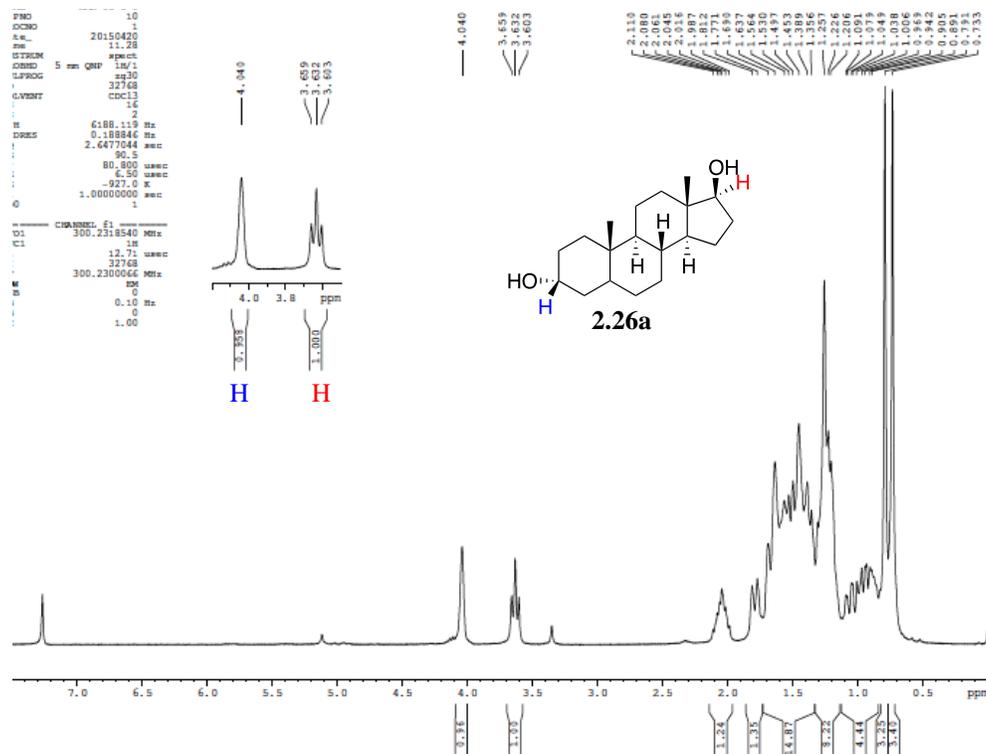
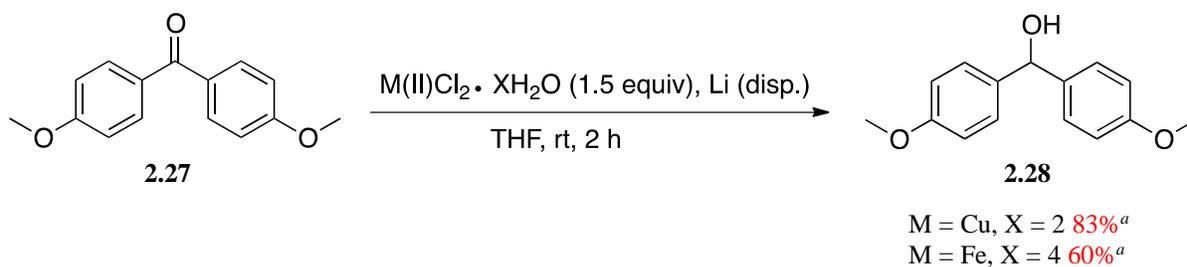


Figure 2.11 ^1H NMR of 5α -Androstane- $3\alpha,17\beta$ -diol (Table 2.9, entries 1 and 2).

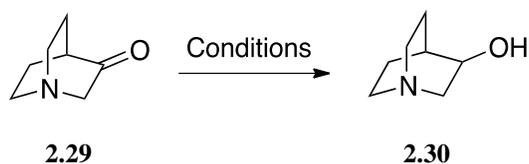
The reduction of 4,4'-dimethoxybenzophenone, **2.27**, (Scheme 2.7) yielded bis(4-methoxyphenyl)methanol, **2.28**, in moderate or good yield depending on whether the iron or copper salt was employed.



Scheme 2.7 Reduction of 4,4'-Dimethoxybenzophenone.

^aIsolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

There have been many reports of biological reductions¹⁰¹ and asymmetric hydrogenations¹⁰² of 3-quinuclidinone, **2.29**, and/or the hydrochloride salt of **2.29**. As shown in [Table 2.10](#) (entries 1 and 2), **2.29** was reduced to 3-quinuclidinol, **2.30**, in moderate yield under our mild reduction conditions. Product **2.30** was confirmed by comparing the ¹H NMR to the literature values.^{102a}

Table 2.10 Reduction of 3-Quinuclidinone.

Entry	Conditions	%Yield ^a
1	CuCl ₂ •2H ₂ O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 24 h	65
2	FeCl ₂ •4H ₂ O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 24 h	65
3	<i>M. piriformis</i> (2.0 g/L), 12 days, Amberlite IR-120	73 ^b
4	Ru(S _p ,S _N) (0.005%), <i>t</i> -BuOK, 2-propanol, H ₂ (30 atm), 6 h	50 ^c

^a Isolated yield of **2.30** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

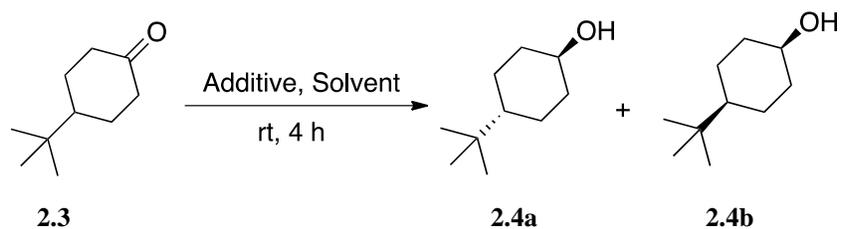
^b Ref. 101d. ^c Ref. 102b.

2.2.2 Effects of Reaction Variables on the Reduction of 4-*tert*-Butylcyclohexanone.

Further experiments were performed on the reduction of 4-*tert*-butylcyclohexanone, **2.3**, in order to determine the effect of variables such as solvent, the presence or absence of the copper salt, and the state of hydration ([Table 2.11](#)). When the solvent was changed from THF to hexanes, the reduction of **2.3** with CuCl₂•2H₂O produced approximately a 30% lower yield of **2.4a** ([Table 2.11](#), entry 2) presumably because, unlike THF, hexanes cannot complex the lithium metal or the

intermediate carbonyl radical-anion. In the absence of a proton donor source from the hydrate of the Cu(II) salt, as in entries 3 and 4, a considerably lower yield of **2.4a** was isolated. Because some of the reduction product was observed in these cases, the carbonyl radical-anion intermediate most likely reacts with atmospheric moisture to form the alkoxy radical, which would then be further reduced to an alkoxide ion.¹⁰⁴ This is evident when both 1.1 equiv and a stoichiometric amount of water were introduced into the reaction mixture and the yield of **2.4a** increased ([Table 2.11](#), entries 5 and 6); however, these yields remain significantly lower than those achieved in the presence of the metal(II) hydrate salts. When the reaction mixture was quenched with D₂O, rather than water, there was no change in the amount of **2.4a**. This further supports the fact that the hydrogen at the 1-position of the reduction product alcohol indeed comes from the hydrate of the metal(II) salt and not from the THF solvent.

Table 2.11 Effects of Some Reaction Variables on the Stereoselective Reduction of 4-*tert*-Butylcyclohexanone.



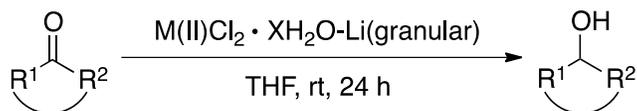
Entry	Additive	Cu(II)	Product ^a	%Yield ^b	dr ^c
1	THF	CuCl ₂ •2H ₂ O	 2.4a	83	99:1
2	hexanes	CuCl ₂ •2H ₂ O	 2.4a	54	100:0
3	THF	CuCl ₂ (anhydrous)	 2.4a	28	98:2
4	THF	-	 2.4a	26	95:5
5	THF	Water (1.1 equiv)	 2.4a	42	99:1
6	THF	Water (2.2 equiv)	 2.4a	48	94:6

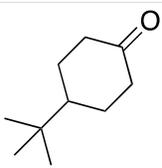
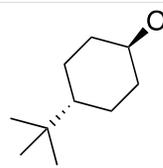
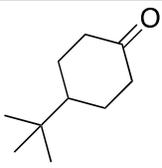
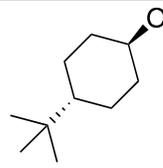
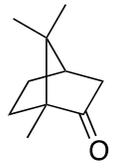
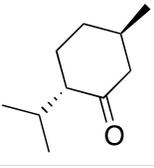
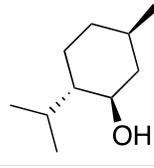
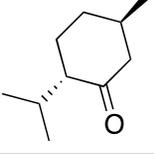
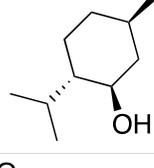
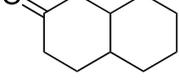
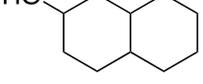
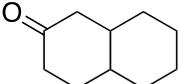
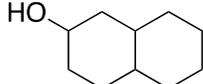
^aThe structure of the major diastereoisomer is shown. ^bIsolated yield of **2.4a** after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^cDiastereomeric ratio of **2.4a** to **2.4b** determined by ¹H NMR.

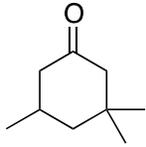
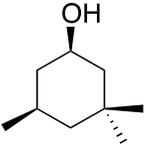
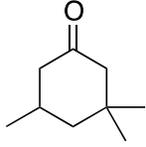
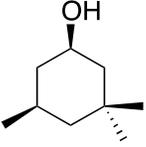
2.2.3 Stereoselective Reduction with Granular Lithium.

In order to determine if granular lithium behaved in a manner similar to that of lithium dispersion, the Li source was changed to commercially available granular lithium (0.5% sodium), which presumably has less surface area due to the large chunks of granular metal. A slight excess of the granular lithium, in comparison to the amount of lithium dispersion, was employed because the granular Li metal does not have the protective mineral oil coating that the dispersion has, and therefore, can react with moisture in the air upon transferring to the desired flask. Furthermore, a longer reaction time (24 h) was necessary to achieve the diastereoselective reduction of cyclic ketones in moderate to excellent yields ([Table 2.12](#)). Thus, the increase in the surface area of the Li metal, from the granular to the dispersion, apparently somewhat enhances the rate of electron transfer for the reduction of ketones, despite the granular lithium having five times the amount of sodium compared to the lithium dispersion.⁵⁴ The diastereoselectivities remained the same as, or very similar to, those observed with the lithium dispersion reduction conditions ([Table 2.12](#)). The only major discrepancy in yield in going from the dispersion to the granular was in the case of **2.17** ([Table 2.12](#), entry 10), in which a significantly lower yield of **2.18a** was isolated with the $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, regardless of whether the equivalents of the Fe(II) salt employed was increased or decreased. This result remains puzzling and perhaps a better understanding of the reduction mechanism would provide an explanation.

Table 2.12 Reduction of Cyclic Ketones with Granular Lithium and either CuCl₂•2H₂O or FeCl₂•4H₂O.



Entry	Ketone	Metal (II)	Equiv	Product ^a	% Yield ^b	dr ^c
1	 2.3	Cu	1.5	 2.4a	86	96:4
2	 2.3	Fe	1.5	 2.4a	85	100:0
3	 2.9	Cu	2	 2.10a	44	100:0
4	 2.9	Fe	1	 2.10a	64	90:10
5	 2.11	Cu	1.5	 2.12a	99	93:7
6	 2.11	Fe	1.5	 2.12a	99	94:6
7	 2.15 ^d	Cu	1.5	 2.16	73	-
8	 2.15 ^d	Fe	1.5	 2.16	83	-

9	 2.17	Cu	1.5	 2.18a	56	100:0
10	 2.17	Fe	1.5	 2.18a	31	100:0

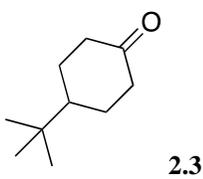
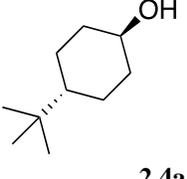
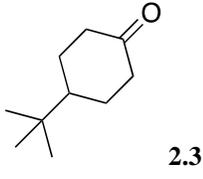
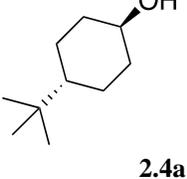
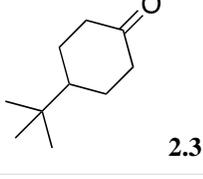
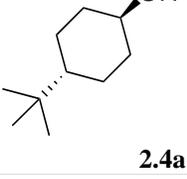
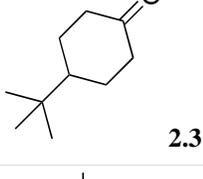
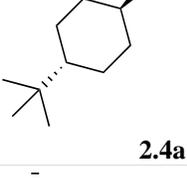
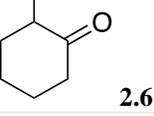
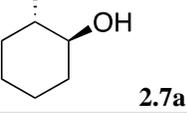
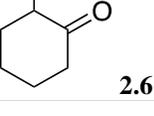
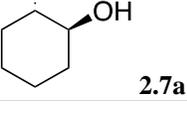
^a The structure of the major diastereoisomer is shown. ^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^c Diastereomeric ratio determined by ¹H NMR. ^d Commercially available mixture of *cis* and *trans* (~20:80).

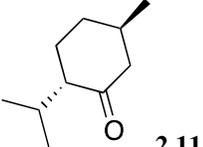
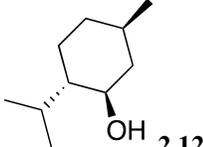
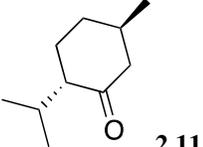
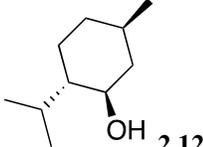
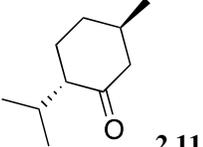
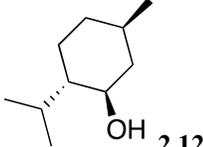
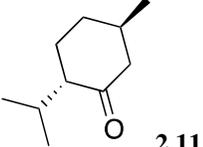
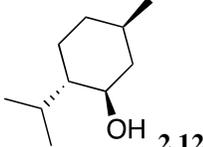
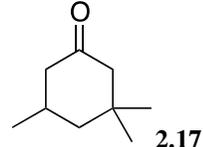
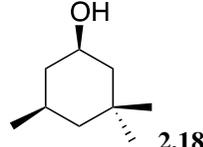
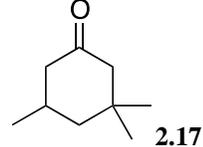
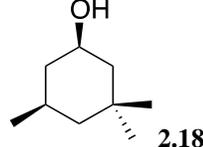
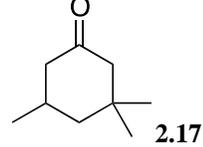
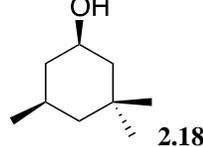
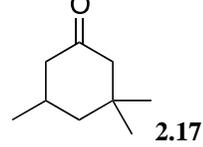
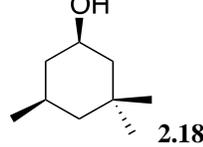
2.2.4 Reduction of Cyclic Ketones in the Presence and Absence of DBB.

In a blank reaction, Yus and co-workers attempted to reduce an alkyne, 1-ethynylcyclohexanol, to the corresponding alkane in the absence of an arene electron carrier catalyst and the yield of 1-ethylcyclohexanol decreased from 70% to less than 5%.¹⁰³ It was thus determined that the role of the arene was crucial for the reaction to proceed, and therefore, an arene electron transfer catalyst, either naphthalene or DBB, has been included in Yus's metal(II) reduction reaction conditions.^{75,80-}
⁸²In order to determine the significance of an arene electron transfer catalyst in our work, 10 mol% of DBB was added to the CuCl₂•2H₂O-granular lithium reduction of various substrates ([Table 2.13](#)). The ratio of the starting material (SM) to the product was determined from ¹H NMR and compared to the ratio obtained from the reduction of the same substrates in the absence of the DBB. The reduction conditions were repeated with the Fe(II) salt. As shown in [Table 2.13](#), DBB did not affect the rate of the reduction or the diastereoselectivity observed under either the CuCl₂•2H₂O or the FeCl₂•4H₂O reaction conditions. Surprisingly, Yus *et. al.* isolated the less

thermodynamically stable alcohol, *cis*-2-methylcyclohexanol, **2.7b**, with their M(II)Cl₂•XH₂O-Li-DBB reduction of **2.6**,⁷⁵ which is the opposite of what we observed ([Table 2.13](#), entries 5 and 6).

Table 2.13 Stereoselective Reduction of Cyclic Ketones in Presence or Absence of DBB after 4 h.^a

Entry	Ketone	Metal (II)	DBB	Product ^b	Ratio SM/Product ^c	dr ^d	Figure
1	 2.3	Cu	Yes	 2.4a	2:1	90:10	2.12
2	 2.3	Cu	No	 2.4a	2:1	95:5	2.13
3	 2.3	Fe	Yes	 2.4a	17:1	100:0	2.14
4	 2.3	Fe	No	 2.4a	19:1	100:0	2.15
5	 2.6	Cu	Yes	 2.7a	- ^e	91:9	-
6	 2.6	Fe	Yes	 2.7a	- ^e	98:2	-

7	 2.11	Cu	Yes	 2.12a	12:1	100:0	2.16
8	 2.11	Cu	No	 2.12a	8:1	100:0	2.17
9	 2.11	Fe	Yes	 2.12a	9:1	100:0	2.18
10	 2.11	Fe	No	 2.12a	14:1	100:0	2.19
11	 2.17	Cu	Yes	 2.18a	4:1	96:4	2.20
12	 2.17	Cu	No	 2.18a	1.5:1	94:6	2.21
13	 2.17	Fe	Yes	 2.18a	7:1	97:3	2.22
14	 2.17	Fe	No	 2.18a	2:1	97:3	2.23

^a Reaction terminated after 4 h. ^b The structure of the major diastereoisomer is shown. ^c Ratio determined by ¹H NMR. ^d Diastereomeric ratio determined by ¹H NMR. ^e Ratio not provided because the reduction of **2.6** was not performed with granular lithium in the absence of DBB; therefore, the ratio would be ambiguous.

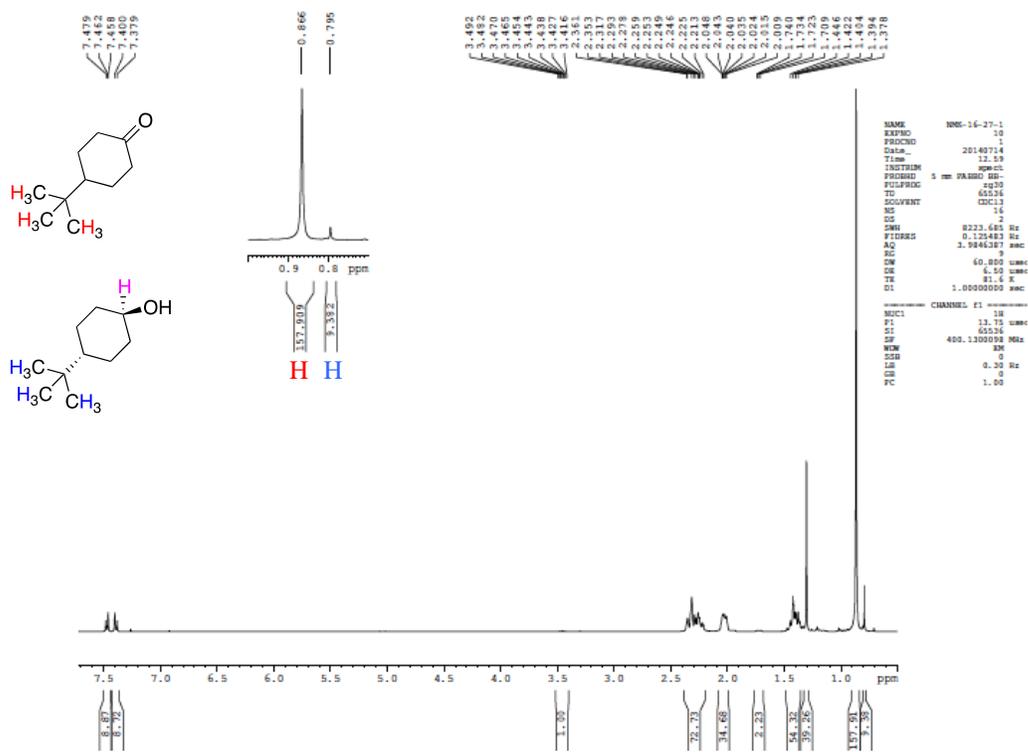


Figure 2.14 Crude ^1H NMR of DBB Catalyzed Reduction of **2.3** with $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (Table 2.13, entry 3).

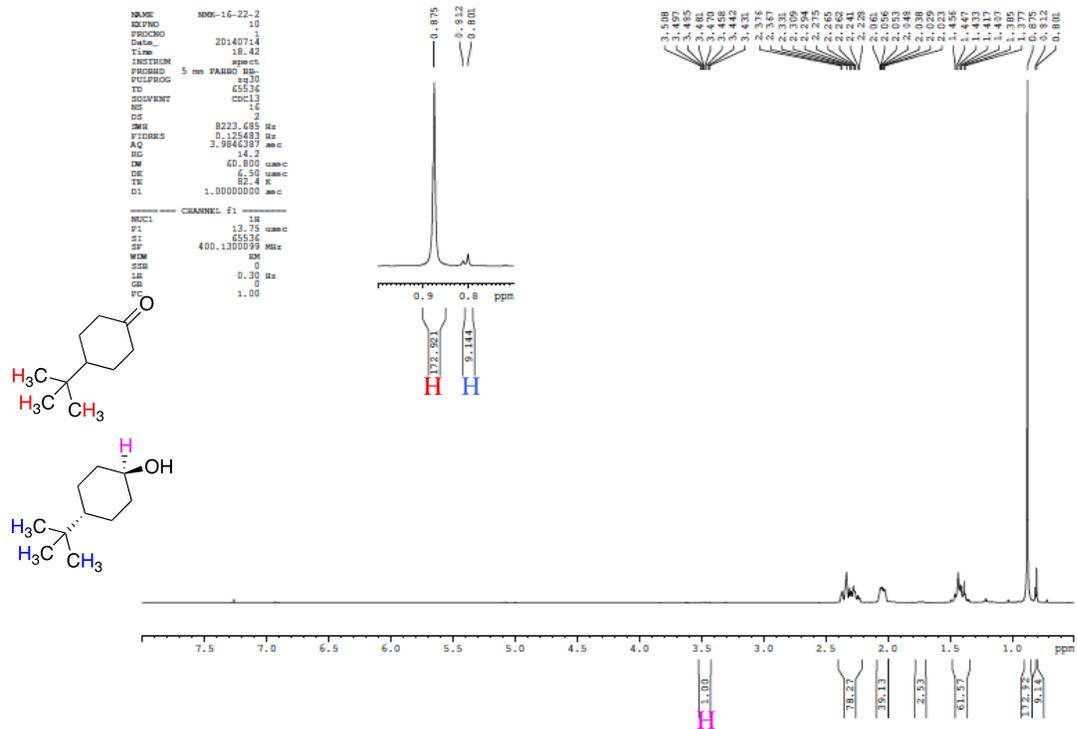


Figure 2.15 Crude ^1H NMR of Non-Catalyzed Reduction of **2.3** with $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (Table 2.13, entry 4).

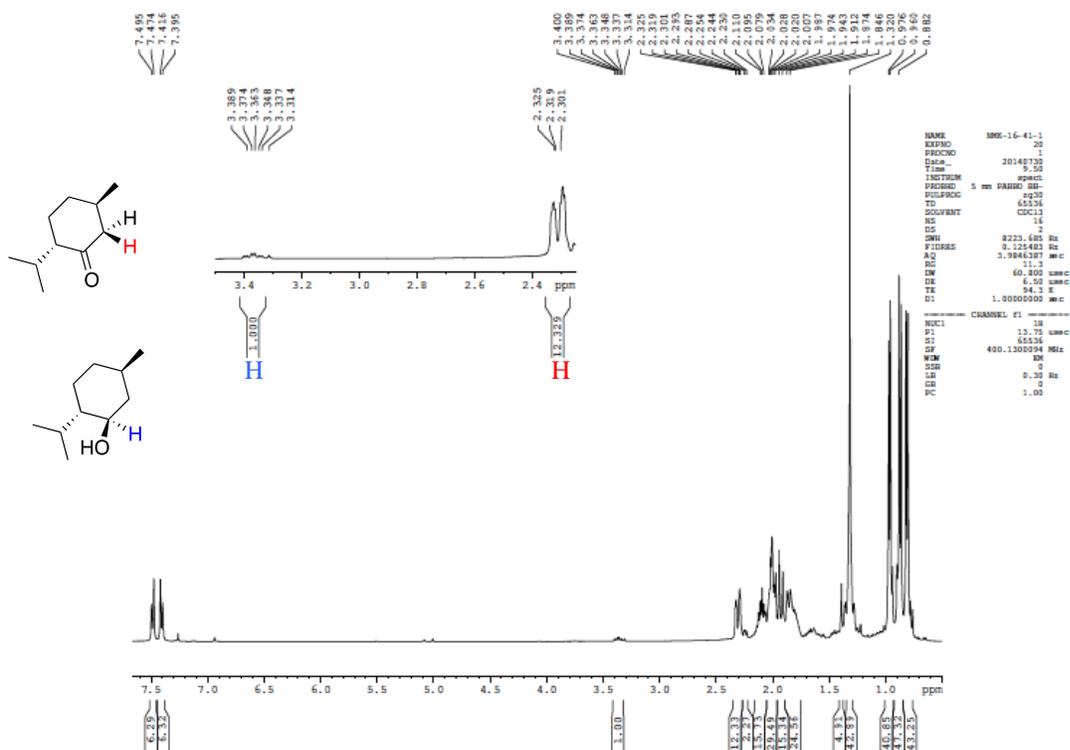


Figure 2.16 Crude ^1H NMR of DBB Catalyzed Reduction of **2.11** with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (Table 2.13, entry 7).

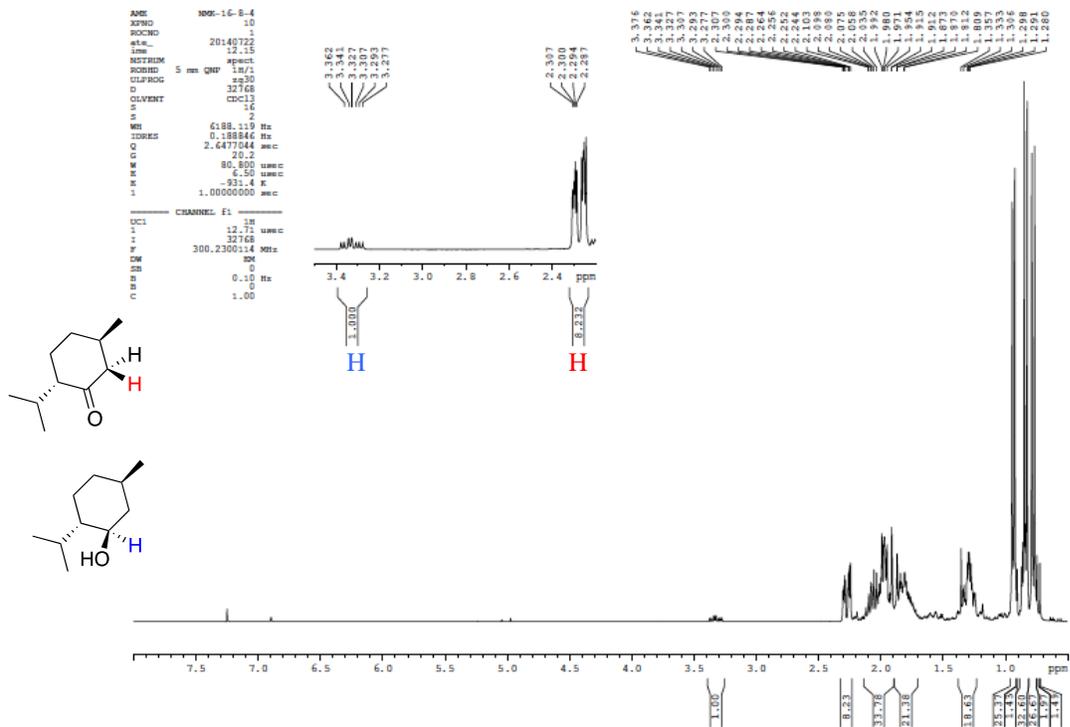


Figure 2.17 Crude ^1H NMR of Non-Catalyzed Reduction of **2.11** with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (Table 2.13, entry 8).

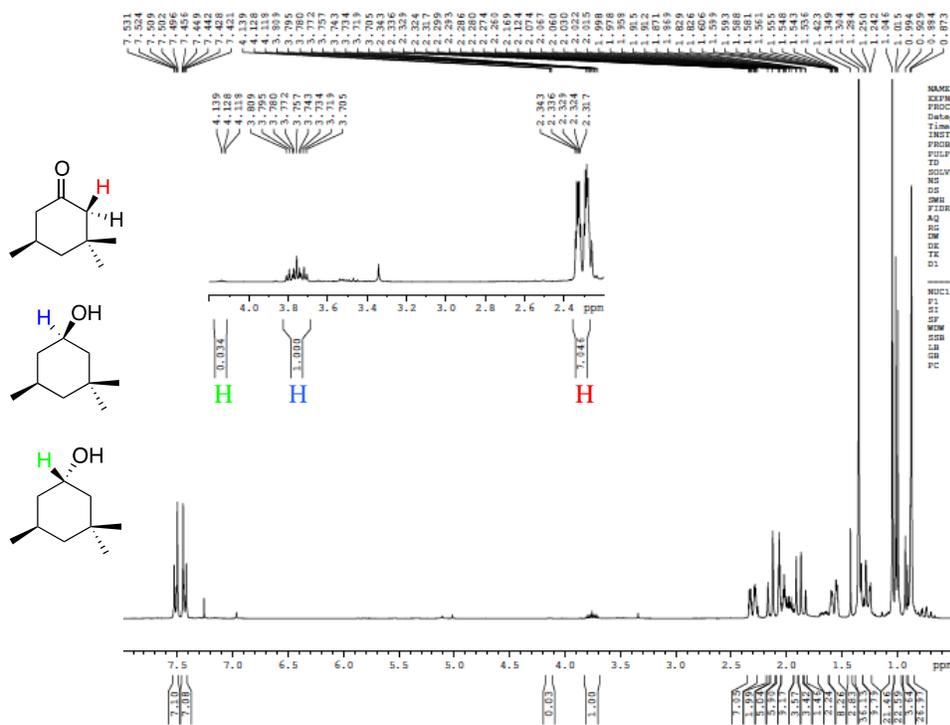


Figure 2.22 Crude ¹H NMR of DBB Catalyzed Reduction of **2.17** with FeCl₂·4H₂O (Table 2.13, entry 13).

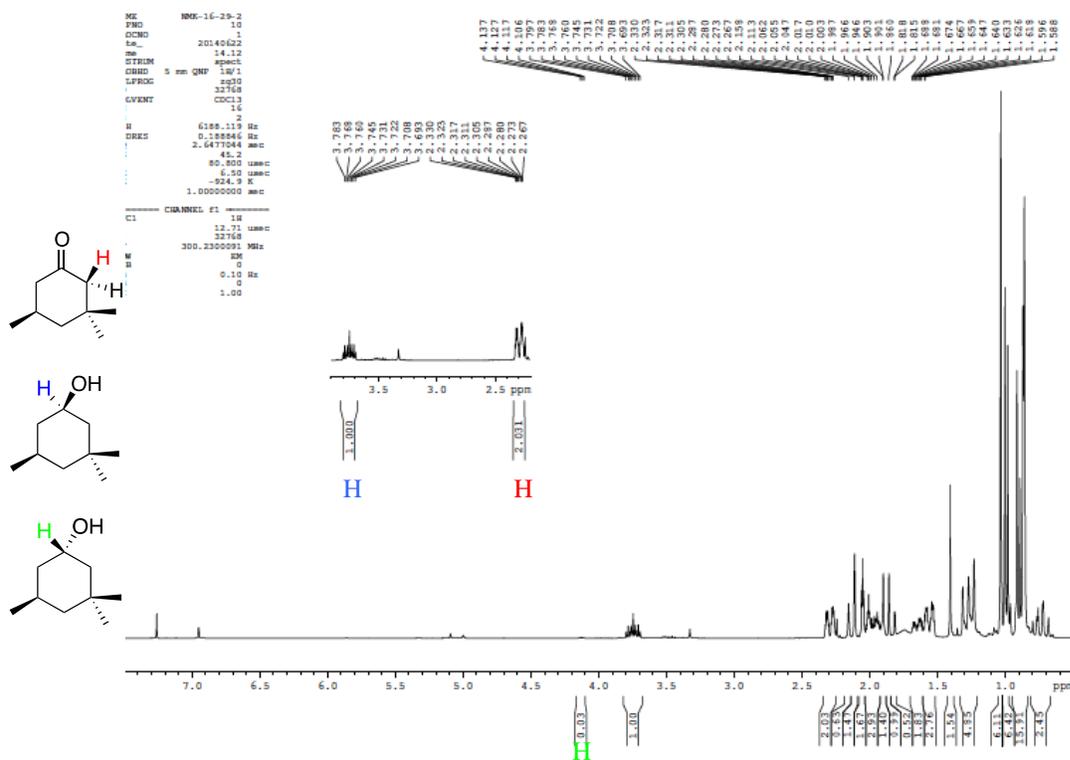
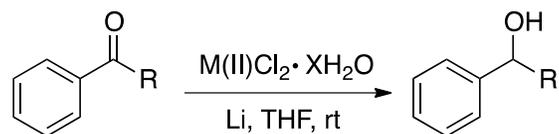


Figure 2.23 Crude ¹H NMR of Non-Catalyzed Reduction of **2.17** with FeCl₂·4H₂O (Table 2.13, entry 14).

2.2.5 Reduction of Aromatic Ketones.

When the lithium dispersion reduction conditions were expanded to include acyclic ketones, other than 4,4'-dimethoxybenzophenone, **2.27**, the reduction of acetophenone, **2.31**, led to low isolated yields of 1-phenylethanol, **1.6**, using both $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (Table [2.14](#), entries 1 and 3). Changing the lithium source, from dispersion to granular, slightly increased the yield of **1.6** to 38% after 24 h with 1.5 equiv of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (entry 2). The main product was the pinacol diol, presumably formed by the coupling of the intermediate radical-anion of acetophenone. This intermediate must couple faster than be reduced to the dianion. A similar mechanistic result is observed in the metal-ammonia reduction of ketones.¹⁰⁴ However, in the reduction of benzophenone, **2.32**, which also contains a benzoyl group, the pinacol diol was not observed, most likely because the coupling of the radical-anion is sterically inhibited, and therefore a nearly quantitative yield of 1,1-diphenylmethanol, **2.33**, was obtained (Table [2.14](#), entries 4 and 5). Benzophenone was treated with 1.5 equiv of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ for 4 h so that the yield of **2.33** could be compared to that achieved by Yus and co-workers (75%) under similar reaction conditions.⁸² Our conditions were repeated with $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, in order to compare the effectiveness of each salt in the reduction of **2.32**, and in each case, our isolated yields greatly exceeded those obtained by Yus.⁷⁵

Table 2.14 Reduction of Aromatic Ketones with Lithium and Metal(II) Hydrate Salts.

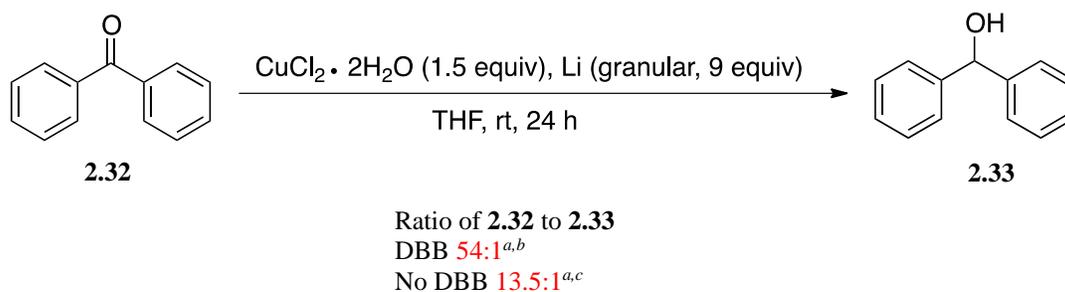


Entry	Ketone	Metal (II)	Equiv	Rxn. Time (h)	Product ^a	% Yield ^b
1	2.31	Cu	1.5	4	1.6	16 ^c
2	2.31	Cu	1.5	24	1.6	38 ^{c,d}
3	2.31	Fe	1.5	1	1.6	38 ^c
4	2.32	Cu	1.5	4	2.33	99
5	2.32	Fe	1.5	4	2.33	99

^a The structure of the reduction product is shown. ^b Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ^c Product isolated with pinacol diol, yield calculated from ¹H NMR. ^d Granular lithium.

In order to determine the significance of DBB in the aromatic ketone reduction of benzophenone, 10 mol% of DBB was added to the CuCl₂•2H₂O-granular lithium reduction of **2.32** (Scheme 2.8). The ratio of the starting material (SM) to the product was determined from ¹H NMR

and compared to the ratio obtained from the reduction of the same substrate in the absence of the DBB. As shown in [Scheme 2.8](#), DBB appeared to hinder the rate of the reduction of **2.32** rather than enhance it. Perhaps an understanding of the reduction mechanism would provide an explanation for this result.



Scheme 2.8 Reduction of Benzophenone in the Presence and Absence of DBB (10 mol%).

^a Ratio determined by crude ¹H NMR. ^b See [Figure 2.24](#). ^c See [Figure 2.25](#).

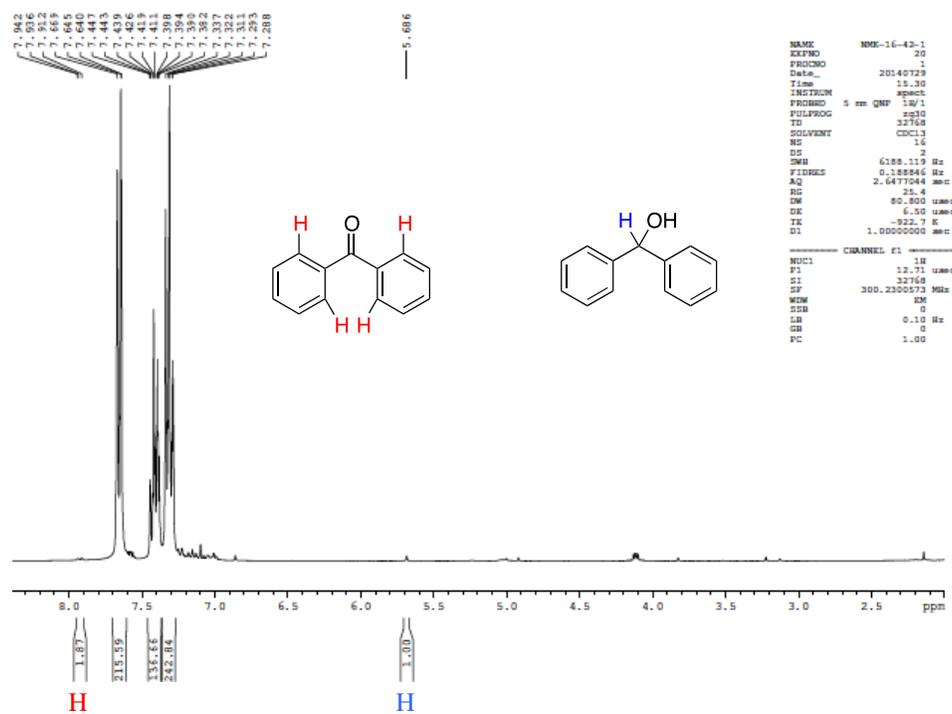


Figure 2.24 Crude ¹H NMR of DBB Catalyzed Reduction of 2.32 with CuCl₂·2H₂O (Scheme 2.8).

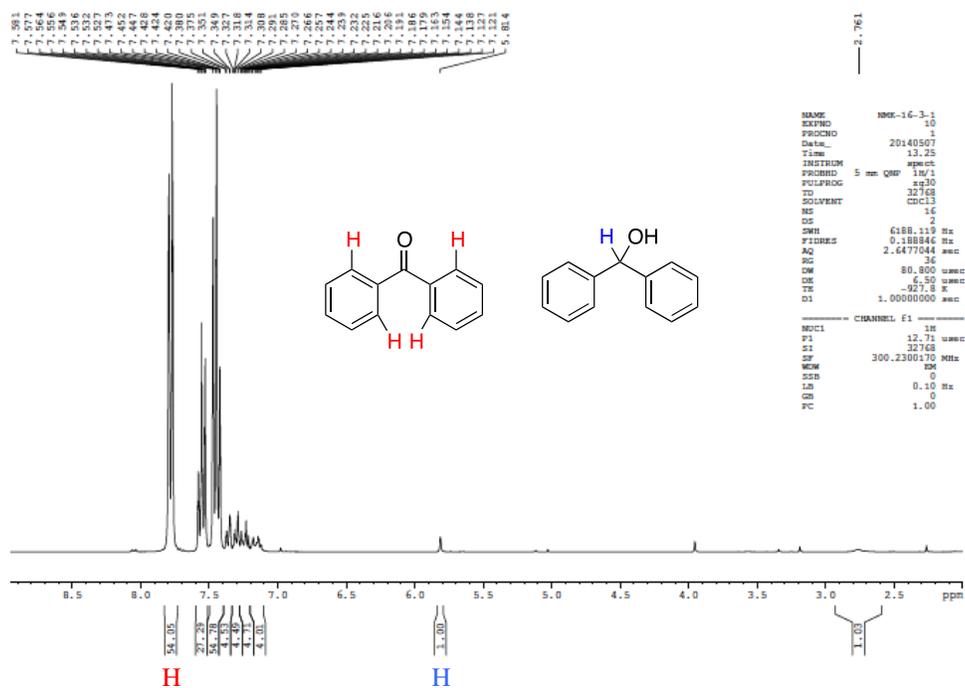


Figure 2.25 Crude ¹H NMR of Non-Catalyzed Reduction of 2.32 with CuCl₂·2H₂O (Scheme 2.8).

2.3 CONCLUSIONS

It was found that the reductions of monocyclic and bicyclic 6-membered ring ketones using lithium and either $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ or $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in the presence of DBB, the system promulgated by Yus and collaborators,^{75,82} is just as effective in the absence of the latter electron transfer agent provided that the lithium is a dispersion in mineral oil or the commercially available granular form. Under our very mild conditions, the reduction is highly stereoselective, affording the most thermodynamically stable alcohol in moderate to excellent yields. The procedure presented here is more efficient than the most commonly reported reduction protocols due to the use of commercially available reagents at room temperature and a shorter reaction time in most cases. The source of the carbinol proton is the hydrate of the transition metal salts. It is most surprising and inexplicable that in two important cases, that of 2-methylcyclohexanone and *trans*-1-decalone, Yus *et. al.* obtained the opposite diastereoselectivity, which is the least thermodynamically stable alcohol products, under their reduction conditions;⁷⁵ our attempts to repeat these results were unsuccessful. The $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ -Li and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ -Li reducing systems developed here should become the default protocol for the kind of ketone reductions studied here.

2.4 EXPERIMENTAL

2.4.1 General Methods.

All reactions were carried out under a positive pressure of dry argon gas in oven-dried (120 °C) flasks and standard precautions against moisture were taken. An ice bath was used to obtain 0 °C.

Flash chromatography (low pressure) was performed with Dynamic Adsorbents Inc. Flash silica gel (32-63 μm). Thin-layer chromatography was performed on glass supported (0.25 mm) silica plates (EMD Chemicals). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; aqueous solution of KMnO_4 ; solution of *p*-anisaldehyde (PAA); or iodine (I_2). Commercial solvents and reagents, from Sigma-Aldrich or Fisher Scientific, were used as received with the following exceptions. THF was distilled over sodium metal in the presence of benzophenone as indicator. Hexanes was freshly distilled over CaH_2 . Lithium dispersion (25 wt% in mineral oil) was commercially available from Sigma-Aldrich. Toward the end of the work described here, Sigma-Aldrich discontinued offering lithium dispersion; however, recipes for its preparation are available.⁶² Furthermore, as described here, granular lithium is only slightly less effective than the dispersion. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz or 400 MHz for ^1H and 75 MHz for ^{13}C at 22 $^\circ\text{C}$ unless otherwise noted. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of CHCl_3 triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), and br (broad). Coupling constants, J , are reported in Hz.

General Method A.

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and Lithium Dispersion.

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil. The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. Copper(II) chloride dihydrate was added at once followed by the dropwise addition of a solution of the

substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

General Method B.

FeCl₂•4H₂O and Lithium Dispersion Reduction.

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil. The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate was added at once followed by the dropwise addition of a solution of the substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

General Method C.

CuCl₂•2H₂O and Granular Lithium Reduction.

A 25 mL round-bottom flask was charged with granular lithium. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. Copper(II) chloride dihydrate was added at once followed by the dropwise addition of a solution of the substrate (1.0 mmol) in THF (0.5

mL). The reaction mixture was stirred at room temperature and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

General Method D.

FeCl₂•4H₂O and Granular Lithium Reduction.

A 25 mL round-bottom flask was charged with granular lithium. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate was added at once followed by the dropwise addition of a solution of the substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

General Method E.

CuCl₂•2H₂O, DBB, and Granular Lithium Reduction.

A 25 mL round-bottom flask was charged with granular lithium (62 mg, 9.0 mmol). THF (3 mL) was added to the lithium and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.26 g, 1.5 mmol) was added at once followed by a solution of DBB (27 mg, 0.10 mmol) in THF. A solution of the substrate (1.0 mmol) in THF (0.5 mL) was added dropwise and the

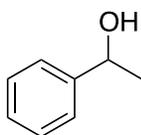
reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the starting material to the product.

General Method F.

FeCl₂•4H₂O, DBB, and Granular Lithium Reduction.

A 25 mL round-bottom flask was charged with granular lithium (83 mg, 12 mmol). THF (3 mL) was added to the lithium and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol) was added at once followed by a solution of DBB (27 mg, 0.10 mmol) in THF. A solution of the substrate (1.0 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Crude ¹H NMR provided a ratio of the starting material to the product.

2.4.2 1-Phenylethanol (1.6).



General Method A ([Table 2.14](#), entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), acetophenone, **2.31** (0.12 g, 1.0 mmol), and a reaction time of 4 h afforded **1.6** (20 mg, 16% yield).

^1H NMR (CDCl_3) δ (ppm): 7.33-7.27 (m, 4H), 7.26-7.22 (m, 1H), 4.82 (q, $J = 6.4$ Hz, 1 H), 2.37 (br, 1H), 1.44 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 146.0, 128.4, 127.3, 125.5, 70.2, 25.2. These NMR data compare well with the literature values.²

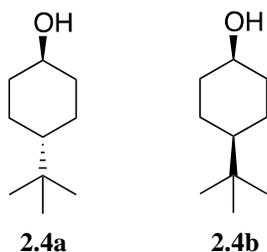
General Method B (Table 2.14, entry 3)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride dihydrate (0.30 g, 1.5 mmol), acetophenone, **2.31** (0.12 g, 1.0 mmol), and a reaction time of 1 h afforded **1.6** (46 mg, 38% yield).

General Method C (Table 2.14, entry 2)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), acetophenone, **2.31** (0.12 g, 1.0 mmol), and a reaction time of 24 h afforded **1.6** (46 mg, 38% yield).

2.4.3 4-*tert*-Butylcyclohexanol (2.4).



General Method A (Table 2.1, entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 4 h afforded **2.4a** (0.13 g, 83% yield) as a white solid with a *trans* to *cis* ratio of 99:1. ^1H NMR (CDCl_3) δ (ppm): 3.52 (tt, $J = 10.8, 4.2$ Hz 1H), 2.00 (d, $J = 10.5$ Hz, 2H), 1.78 (d, $J = 10.2$ Hz, 2H), 1.57 (br, 1H), 1.26-1.10

(m, 2H), 1.06-0.96 (m, 3H), 0.85 (s, 9H); ^{13}C NMR (CDCl_3) δ (ppm): 71.1, 47.1, 35.9, 32.2, 27.6, 25.5. These NMR data compare well with the literature values.⁸⁴

General Method B (Table 2.1, entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 4 h afforded **2.4a** (0.12 g, 77% yield).

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and Lithium Dispersion Reduction of **2.3** in Hexanes (Table 2.11, entry 2)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed four times with hexanes (3 mL) under argon. Hexanes (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.26 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) in hexanes (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then was quenched with H_2O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et_2O . The filtrate was further extracted with Et_2O ; the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc /hexanes) afforded **2.4a** (83 mg, 54% yield).

CuCl_2 (anhydrous) and Lithium Dispersion Reduction of **2.3** in THF (Table 2.11, entry 3)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. THF (3.5 mL) was added to the lithium and the mixture was stirred at room

temperature. Copper(II) chloride anhydrous (0.20 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **2.4a** (44 mg, 28% yield) with a *trans* to *cis* ratio of 98:2.

Lithium Dispersion Reduction of **2.3** in THF (Table 2.11, entry 4)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. A solution of 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **2.4a** (40 mg, 26% yield) with a *trans* to *cis* ratio of 95:5.

Lithium Dispersion Reduction of **2.3** in Wet THF (Table 2.11, entry 5)

A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.11 g, 4.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with non-anhydrous THF (3 mL) under argon. Non-anhydrous THF (3.5 mL) was added to the lithium and H₂O (0.02 mL, 1.1 mmol) were added to the lithium and the mixture was stirred at room temperature. A

solution of 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) in non-anhydrous THF (0.5 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **2.4a** (65 mg, 42% yield) with a *trans* to *cis* ratio of 99:1.

- Under the same conditions but 0.14 g of lithium dispersion (5.0 mmol) and 2.2 equiv of H₂O (0.04 mL, 2.2 mmol), **2.4a** (75 mg, 48% yield) was obtained with a *trans* to *cis* ratio of 94:6 ([Table 2.11](#), entry 6).

General Method C ([Table 2.12](#), entry 1)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.4a** (0.13 g, 86% yield) with a *trans* to *cis* ratio of 96:4.

General Method D ([Table 2.12](#), entry 2)

Granular (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.4a** (0.13 g, 85% yield).

General Method E ([Table 2.13](#), entry 1)

4-*tert*-Butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) provided a ratio of **2.3** to **2.4a** as 2:1 with a *trans* to *cis* ratio of 90:10.

General Method C ([Table 2.13](#), entry 2)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.3** to **2.4a** as 2:1 with a *trans* to *cis* ratio of 95:5.

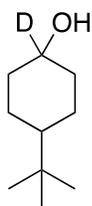
General Method F ([Table 2.13](#), entry 3)

4-*tert*-Butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol) provided a ratio of **2.3** to **2.4a** as 17:1.

General Method D ([Table 2.13](#), entry 4)

Granular lithium (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 4-*tert*-butylcyclohexanone, **2.3** (0.15 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.3** to **2.4a** as 19:1.

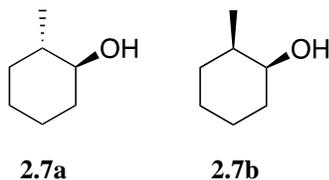
2.4.4 1-Deuterio-4-*tert*-Butylcyclohexan-1-ol (**2.5**). ([Scheme 2.2](#))



A 25 mL round-bottom flask was charged with 25 wt% lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL) under argon. THF (3.5 mL) was added to the lithium and the mixture was stirred at room temperature. $\text{CuCl}_2 \cdot 2\text{D}_2\text{O}$ (prepared from anhydrous CuCl_2 and D_2O ; 0.26 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **2.3**, (0.15

g, 1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then was quenched with H₂O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et₂O. The filtrate was further extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded **2.5** (0.12 g, 78% yield) as a white solid with a D/H ratio of ~85:15. ¹H NMR (CDCl₃) δ (ppm): 2.15 (br, 1H), 1.96 (d, *J* = 12.0 Hz, 2H), 1.74 (d, *J* = 9.6 Hz, 2H), 1.22-1.14 (m, 2H), 1.06-0.92 (m, 3H), 0.81 (s, 9H); ¹³C NMR (CDCl₃) δ (ppm): 71.0, 70.8, 70.6, 70.3, 47.1, 35.9 (d, *J* = 8.2 Hz), 32.2, 27.6, 25.5 (d, *J* = 7.5 Hz); FTMS +p ESI exact mass calculated for C₁₀H₂₀²HO is 158.16497, found 158.16455.

2.4.5 2-Methylcyclohexanol (2.7).



General Method A ([Table 2.2](#), entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 2-methylcyclohexanone, **2.6** (0.11 g, 1.0 mmol), and a reaction time of 10 min afforded **2.7a** as a crude oil with a *trans* to *cis* ratio of 92:8. ¹H NMR (CDCl₃) δ (ppm): 3.10 (td, *J* = 9.6, 4.2 Hz, 1H), 1.95-1.91 (m, 1H), 1.74-1.57 (m, 4H), 1.30-1.16 (m, 4H), 0.99 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 76.6, 40.4, 35.6, 33.8, 25.8, 25.3, 18.7. These NMR data compare well with the literature values.⁸⁴

General Method B ([Table 2.2](#), entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 2-methylcyclohexanone, **2.6** (0.11 g, 1.0 mmol), and a reaction time of 10 min afforded **2.7a** as a crude oil with a *trans* to *cis* ratio of 95:5

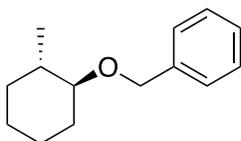
General Method E ([Table 2.13](#), entry 5)

2-methylcyclohexanone, **2.6** (0.11 g, 1.0 mmol) provided a *trans* to *cis* ratio of 91:9.

General Method F ([Table 2.13](#), entry 6)

2-methylcyclohexanone, **2.6** (0.11 g, 1.0 mmol) provided a *trans* to *cis* ratio of 98:2.

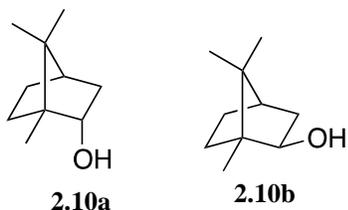
2.4.6 Benzyl *trans*-2-Methylcyclohexyl Ether (**2.8**). ([Scheme 2.3](#))



A 10 mL round-bottom flask was charged with 60 wt% sodium hydride in mineral oil (80 mg, 2.0 mmol). The NaH was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (4 mL) was added to the flask and the mixture was cooled to 0 °C. A solution of the crude alcohol **2.7** (~0.19 g, 1.7 mmol) in THF (0.25 mL) was added dropwise. Tetrabutylammonium iodide (60 mg, 0.16 mmol) was added to the reaction mixture at once followed by the dropwise addition of benzyl bromide (0.20 mL, 1.7 mmol). The ice-water bath was removed and reaction mixture was stirred at room temperature for 24 h and then was quenched

with H₂O. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (100% hexanes) afforded **2.8** as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.34-7.21 (m, 5H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 2.89 (m, 1H), 2.14-2.11 (m, 1H), 1.75-1.69 (m, 2H), 1.61-1.44 (m, 2H), 1.26-1.21 (m, 4H), 1.01 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 139.3, 128.2, 127.6, 127.3, 83.6, 70.6, 38.4, 33.9, 31.1, 25.6, 25.0, 18.9. These NMR data compare well with the literature values.¹⁰⁵ TOF MS (EI⁺) exact mass calculated for C₁₄H₂₀O is 204.1514, found 204.1551; IR (film) 697, 735, 926, 986, 1028, 1072, 1096, 1160, 1205, 1250, 1303, 1355, 1453, 1496, 2856, 2927, 3031, 3064 cm⁻¹.

2.4.7 Borneol (2.10).



General Method A (Table 2.3, entry 1)

Lithium dispersion (0.22 g, 8.0 mmol), copper(II) chloride dihydrate (0.34 g, 2.0 mmol), (±)-camphor, **2.9** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.10a** (0.10 g, 65% yield) as a white solid with an *endo* to *exo* ratio of 96:4. ¹H NMR (CDCl₃) δ (ppm): 4.00 (dd, *J* = 10.0, 1.6 Hz, 1H), 2.31-2.23 (m, 1H), 1.92-1.85 (m, 1H), 1.77-1.69 (m, 1H), 1.63-1.61 (m, 2H), 1.28-1.21 (m, 2H), 0.94 (dd, *J* = 10.0, 3.4 Hz, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H); ¹³C NMR (CDCl₃) δ (ppm): 77.3, 49.4, 48.0, 45.1, 39.0, 28.2, 25.9, 20.2, 18.6, 13.3. These NMR data compare well with the literature values.⁹⁰

General Method B ([Table 2.3](#), entry 2)

Lithium dispersion (0.33 g, 12 mmol), iron(II) chloride tetrahydrate (0.40 g, 2.0 mmol), (±)-camphor, **2.9** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.10a** (0.12 g, 78% yield) with an *endo* to *exo* ratio of 95:5.

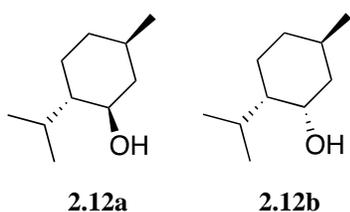
General Method C ([Table 2.12](#), entry 3)

Granular lithium (83 mg, 9.0 mmol), copper(II) chloride dihydrate (0.34 g, 2.0 mmol), (±)-camphor, **2.9** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.10a** (68 mg, 44% yield).

General Method D ([Table 2.12](#), entry 4)

Granular (56 mg, 12 mmol), iron(II) chloride tetrahydrate (0.20 g, 1.0 mmol), (±)-camphor, **2.9** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.10a** (98 mg, 64% yield) with an *endo* to *exo* ratio of 90:10.

2.4.8 Menthol (2.12).



General Method A ([Table 2.4](#), entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 4 h afforded **2.12a** (0.13 g, 86% yield) as a white solid with an *equatorial* to *axial* ratio of 94:6. ¹H NMR (CDCl₃) δ (ppm): 3.41 (td, *J* = 10.0, 3.6 Hz, 1H), 2.17 (pent, *J* = 5.7 Hz, 1H), 1.96 (d, *J* = 11.4 Hz, 1H), 1.64 (t, *J* = 13.2 Hz,

2H), 1.45 (m, 2H), 1.15-1.08 (m, 1H), 0.94-0.90 (m, 9H), 0.81 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 71.4, 50.0, 45.0, 34.5, 31.6, 25.7, 23.0, 22.1, 21.0, 16.0. These NMR data compare well with the literature values.¹⁰⁶

General Method B ([Table 2.4](#), entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 4 h afforded **2.12a** (0.15 g, 99% yield) with an *equatorial* to *axial* ratio of 95:5.

General Method C ([Table 2.12](#), entry 5)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.12a** (0.15 g, 99% yield) with an *equatorial* to *axial* ratio of 93:7.

General Method D ([Table 2.12](#), entry 6)

Granular (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.12a** (0.15 g, 99% yield) with an *equatorial* to *axial* ratio of 94:6.

General Method E ([Table 2.13](#), entry 7)

(-)-menthone, **2.11** (0.15 g, 1.0 mmol) provided a ratio of **2.11** to **2.12a** as 12:1.

General Method C ([Table 2.13](#), entry 8)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.11** to **2.12a** as 8:1.

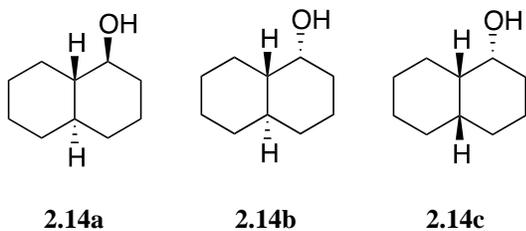
General Method F ([Table 2.13](#), entry 9)

(-)-menthone, **2.11** (0.15 g, 1.0 mmol) provided a ratio of **2.11** to **2.12a** as 9:1.

General Method D ([Table 2.13](#), entry 10)

Granular lithium (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), (-)-menthone, **2.11** (0.15 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.11** to **2.12a** as 14:1.

2.4.9 Decahydro-1-Naphthol (**2.14**).



General Method A ([Table 2.5](#), entry 1)

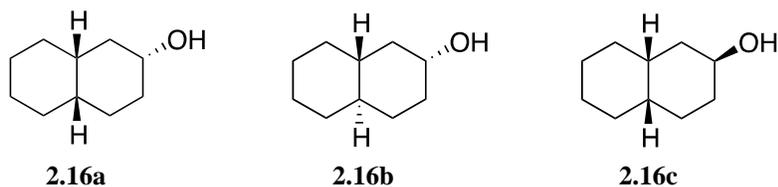
Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 1-decalone (mixture of *cis* and *trans*), **2.13** (0.15 g, 1.0 mmol), and a reaction time of 2 h afforded **2.14a** (0.13 g, 82% yield) as a white solid with a *trans,cis*, **2.14a**, to *trans,trans*, **2.14b**, to *cis,trans*, **2.14c**, ratio of 92:5:3.

- (\pm)-*trans,cis*-decahydro-1-naphthol (**2.14a**) ^1H NMR (CDCl_3) δ (ppm): 3.18 (tt, $J = 7.6$, 4.2 Hz, 1H), 2.12 (d, $J = 7.6$ Hz, 1H), 1.98-1.94 (m, 1H), 1.88 (br, 1H), 1.78-1.62 (m, 4H), 1.51 (d, $J = 10.0$ Hz, 1H), 1.34-1.19 (m, 4H), 0.97-0.87 (m, 5H); ^{13}C NMR (CDCl_3) δ (ppm): 74.9, 50.4, 41.1, 35.7, 33.5, 33.4, 28.9, 26.3, 26.1, 24.0. These NMR data compare well with the literature values.¹⁰⁷ The 3 isomers could not be separated; therefore, the following data concern the mixture of these 3 compounds: IR (thin film) 3369 (br); 2919 (s); 2853 (s); 1641 (w); 1448 (m); 1358 (w); 1238 (w); 1141 (w); 1059 (m); 1040 (m); 1020 (w); 953 (w); 915 (w); 839 (w); 823 (w) cm^{-1} ; TOF MS (ES^+) exact mass calculated for $\text{C}_{10}\text{H}_{17}\text{O}$ is 153.1279, found 153.1284.
- (\pm)-*trans,trans*-decahydro-1-naphthol (**2.14b**) ^1H NMR (CDCl_3) δ (ppm): 3.78-3.74 (m, 1H).⁹³
- (\pm)-*cis,trans*-decahydro-1-naphthol (**2.14c**) ^1H NMR (CDCl_3) δ (ppm): 3.70-3.61 (m, 1H).⁸⁴

General Method B ([Table 2.5](#), entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 1-decalone (mixture of *cis* and *trans*), **2.13** (0.15 g, 1.0 mmol), and a reaction time of 2 h afforded **2.14a** (0.15 g, 95% yield) with a *trans,cis*, **2.14a**, to *trans,trans*, **2.14b**, to *cis,trans*, **2.14c**, ratio of 94:4:2.

2.4.10 Decahydro-2-Naphthol (**2.16**).



General Method A ([Scheme 2.4](#))

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 2-decalone (mixture of *cis* and *trans*), **2.15** (0.15 g, 1.0 mmol), and a reaction time of 2 h afforded **2.16** (80 mg, 52% yield) as a mixture of *cis,trans*, **2.16a**, to *trans,trans*, **2.16b**, to *cis,cis*, **2.16c**.

- (\pm)-*cis,trans*-Decahydro-2-naphthol (**2.16a**) ^1H NMR (CDCl_3) δ (ppm): 3.83 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); ^{13}C NMR (CDCl_3) δ (ppm): 71.4, 35.6, 35.4, 34.6, 31.6, 30.3, 30.0, 26.6, 25.8, 20.9. These NMR data compare well with the literature values.¹⁰⁸
- (\pm)-*trans,trans*-decahydro-2-naphthol (**2.16b**) ^1H NMR (CDCl_3) δ (ppm): 3.65-3.55 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); ^{13}C NMR (CDCl_3) δ (ppm): 70.6, 43.1, 42.2, 41.1, 35.7, 33.7, 33.2, 31.9, 26.5, 26.2. These NMR data compare well with the literature values.⁸⁴
- (\pm)-*cis,cis*-decahydro-2-naphthol (**2.16c**) ^1H NMR (CDCl_3) δ (ppm): 3.65-3.55 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); ^{13}C NMR (CDCl_3) δ (ppm): 66.8, 41.1, 35.6, 35.3, 34.6, 30.3, 29.6, 25.8, 24.8, 20.9. These NMR data compare well with the literature values.^{84,109}

General Method B ([Scheme 2.4](#))

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 2-decalone (mixture of *cis* and *trans*), **2.15** (0.15 g, 1.0 mmol), and a reaction time of 2 h afforded **2.16** (0.15 g, 99% yield) as a mixture of *cis,trans*, **2.16a**, to *trans,trans*, **2.16b**, to *cis,cis*, **2.16c**.

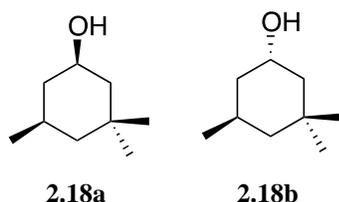
General Method C ([Table 2.12](#), entry 7)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 2-decalone (mixture of *cis* and *trans*), **2.15** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.16** (0.11 g, 73% yield) as a mixture of *cis,trans*, **2.16a**, to *trans,trans*, **2.16b**, to *cis,cis*, **2.16c**.

General Method D ([Table 2.12](#), entry 8)

Granular (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 2-decalone (mixture of *cis* and *trans*), **2.15** (0.15 g, 1.0 mmol), and a reaction time of 24 h afforded **2.16** (0.13 g, 83% yield) as a mixture of *cis,trans*, **2.16a**, to *trans,trans*, **2.16b**, to *cis,cis*, **2.16c**.

2.4.11 3,3,5-Trimethylcyclohexanol (**2.18**).



General Method A ([Table 2.6](#), entry 1)

Lithium dispersion (0.22 g, 8.0 mmol), copper(II) chloride dihydrate (0.34 g, 2.0 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 1 h afforded **2.18a** (37 mg, 26% yield) as a white solid. ^1H NMR (CDCl_3) δ (ppm): 3.72 (tt, $J = 11.2, 4.5$ Hz, 1H), 2.21 (br, 1H), 1.91 (d sextet, $J = 15.6, 1.8$ Hz, 2H), 1.67-1.51 (m, 2H), 1.26 (d pent, $J = 16.0, 1.8$ Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.73 (q, $J = 10.0$ Hz, 2H); ^{13}C NMR (CDCl_3) δ (ppm): 67.8, 48.2, 47.6, 44.6, 33.1, 32.2, 27.2, 25.7, 22.3; IR (thin film) 3412 (br); 2951 (m); 2922 (m);

2925 (m); 1641 (m); 1460 (w); 1365 (w); 1080 (w); 1026 (w) cm^{-1} ; TOF MS (ES^+) exact mass calculated for $\text{C}_9\text{H}_{17}\text{O}$ is 141.1279, found 141.1265.

General Method B ([Table 2.6](#), entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 1 h afforded **2.18a** (0.10 g, 70% yield).

General Method C ([Table 2.12](#), entry 9)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 24 h afforded **2.18a** (80 mg, 56% yield).

General Method D ([Table 2.12](#), entry 10)

Granular (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 24 h afforded **2.18a** (40 mg, 31% yield).

General Method E ([Table 2.13](#), entry 11)

3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol) provided a ratio of **2.17** to **2.18a** as 4:1 with a *cis* to *trans* ratio of 96:4.

General Method C ([Table 2.13](#), entry 12)

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.17** to **2.18a** as 1.5:1 with a *cis* to *trans* ratio of 94:6.

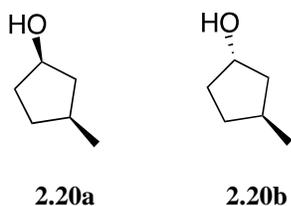
General Method F ([Table 2.13](#), entry 13)

3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol) provided a ratio of **2.17** to **2.18a** as 7:1 with a *cis* to *trans* ratio of 97:3.

General Method D ([Table 2.13](#), entry 14)

Granular lithium (83 mg, 12 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3,3,5-trimethylcyclohexanone, **2.17** (0.14 g, 1.0 mmol), and a reaction time of 4 h provided a ratio of **2.17** to **2.18a** as 2:1 with a *cis* to *trans* ratio of 97:3.

2.4.12 3-Methylcyclopentanol (**2.20**).



General Method A ([Table 2.7](#), entry 1)

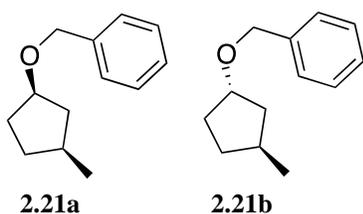
Lithium dispersion (82 g, 3.0 mmol), copper(II) chloride dihydrate (0.17 g, 1.0 mmol), 3-methylcyclopentanone, **2.19** (98 mg, 1.0 mmol), and a reaction time of 5 min afforded **2.20** as a crude oil with a *cis* to *trans* ratio of 60:40.

- *cis*-3-Methylcyclopentanol (**2.20a**) ^1H NMR (CDCl_3) δ (ppm): 4.29 (tt, $J = 10.0, 6.2$ 1H), 2.27-2.13 (m, 1H), 2.04-1.09 (m, 6H), 1.06 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 73.7, 44.1, 35.4, 32.9, 32.2, 21.0. These NMR data compare well with the literature values ⁹⁶
- *trans*-3-Methylcyclopentanol (**2.20b**) ^1H NMR (CDCl_3) δ (ppm): 4.36 (pent, $J = 2.8$ Hz, 1H), 2.27-2.13 (m, 1H), 2.04-1.09 (m, 6H), 0.99 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3) δ (ppm): 73.7, 44.3, 35.2, 32.4, 31.8, 20.6. These NMR data compare well with the literature values ⁹⁶

General Method B ([Table 2.7](#), entry 2)

Lithium dispersion (0.14 g, 5.0 mmol), iron(II) chloride tetrahydrate (0.20 g, 1.0 mmol), 3-methylcyclopentanone, **2.19** (98 mg, 1.0 mmol), and a reaction time of 5 min afforded **2.20** as a crude oil with a *cis* to *trans* ratio of 60:40.

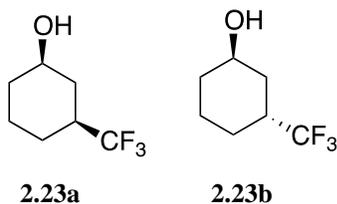
2.4.13 Benzyl 3-Methylcyclopentyl Ether (2.21). ([Scheme 2.5](#))



A 10 mL round-bottom flask was charged with 60 wt% sodium hydride in mineral oil (40 mg, 1.0 mmol). The NaH was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (1.8 mL) was added to the flask and the mixture was cooled to 0 °C. A solution of the crude alcohol **2.20** (~90 mg) in THF (0.5 mL) was added dropwise. Tetrabutylammonium iodide (40 mg, 0.10 mmol) was added to the reaction mixture at once followed by the dropwise addition

of benzyl bromide (0.13 mL, 1.1 mmol). The ice-water bath was removed and reaction mixture was stirred at room temperature for 24 h and then was quenched with H₂O. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (Et₂O/hexanes) afforded **2.21** as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.33-7.26 (m, 5H), 4.45 (d, *J* = 4.2 Hz, 2H), 3.98 (q, *J* = 5.7 Hz, 1H), 2.19-2.08 (m, 1H), 1.94-1.68 (m, 4H), 1.36-1.20 (m, 2H), 1.04 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃) δ (ppm): 139.0, 128.2, 127.5, 127.3, 80.9, 70.8, 41.3, 32.9, 32.4, 32.2, 20.9; TOF MS (AP⁺) exact mass calculated for C₁₃H₁₉O is 191.1436; found 191.1434; IR (film) 649, 699, 733, 908, 1028, 1068, 1095, 1205, 1376, 1496, 2868, 2955, 3032, 3066, 3089 cm⁻¹.

2.4.14 3-(Trifluoromethyl)cyclohexanol (2.23).



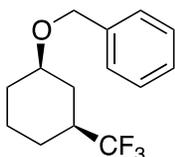
General Method A ([Table 2.8](#), entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 3-(trifluoromethyl)cyclohexanone, **2.22** (0.17 g, 1.0 mmol), and a reaction time of 1 h afforded **2.23a** as a crude oil with a *cis* to *trans* ratio of 95:5. ¹H NMR (CDCl₃) δ (ppm): 3.61 (tt, *J* = 10.8, 4.2 Hz, 1H), 2.20-2.15 (m, 1H), 2.11-1.86 (m, 4H), 1.43-1.12 (m, 4H); ¹³C NMR (CDCl₃) δ (ppm): 132.7, 129.0, 125.3, 121.6, 69.3, 40.9 (q, *J* = 27.0 Hz), 34.7, 34.0 (q, *J* = 2.2 Hz), 24.0 (q, *J* = 2.2 Hz), 22.7. These NMR data compared well with the literature values.⁹⁸

General Method B ([Table 2.8](#), entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3-(trifluoromethyl)cyclohexanone, **2.22** (0.17 g, 1.0 mmol), and a reaction time of 1 h afforded **2.23a** as a crude oil with a *cis* to *trans* ratio of 97:3.

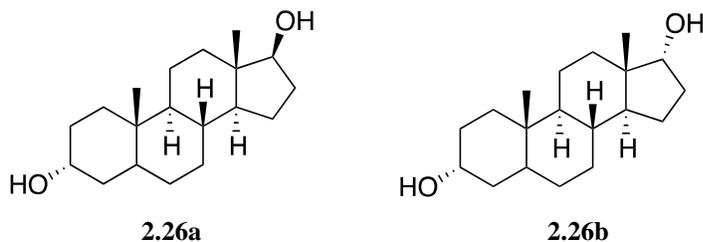
2.4.15 Benzyl *cis*-3-(Trifluoromethyl)cyclohexyl Ether (**2.24**). ([Scheme 2.6](#))



A 10 mL round-bottom flask was charged with 60 wt% sodium hydride in mineral oil (57 mg, 1.4 mmol). The NaH was washed three times with hexanes (2 mL) and once with THF (2 mL) under argon. THF (1.7 mL) was added to the flask and the mixture was cooled to 0 °C. A solution of the crude alcohol **2.23** (~0.16 g) in THF (0.5 mL) was added dropwise. Tetrabutylammonium iodide (35 mg, 0.095 mmol) was added to the reaction mixture at once followed by the dropwise addition of benzyl bromide (0.14 mL, 1.2 mmol). The ice-water bath was removed and reaction mixture was stirred at room temperature for 24 h and then was quenched with H₂O. The product was extracted with Et₂O; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography on silica gel (Et₂O/hexanes) afforded **2.24** as a colorless oil. ¹H NMR (CDCl₃) δ (ppm): 7.36-7.27 (m, 5H), 4.57 (s, 2H), 3.34-3.33 (m, 1H), 2.31 (d, *J* = 11.5 Hz, 1H), 2.13-2.02 (m, 2H), 1.88 (m, 2H), 1.33-1.23 (m, 4H); ¹³C NMR (CDCl₃) δ (ppm): 138.6, 128.4, 127.8, 127.5, 127.5, 76.0, 70.0, 41.0 (q, *J* = 26.2 Hz), 31.8, 31.1 (d, *J* = 1.2 Hz), 24.4 (d, *J* = 2.5 Hz), 22.8; ¹⁹F NMR (CDCl₃) δ (ppm): -73.6 (d, *J* = 5.0 Hz); TOF MS (AP⁺) exact mass calculated

for $C_{14}H_{17}OF_3$ is 258.1232; found 258.1251; IR (film) 698, 736, 1028, 1089, 1122, 1173, 1213, 1253, 1278, 1320, 1360, 1454, 1496, 2867, 2945, 3031, 3065 cm^{-1}

2.4.16 5 α -Androstane-Diol (2.26).



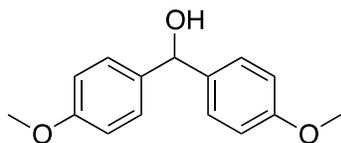
General Method A (Table 2.9, entry 1)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 3 α -hydroxy-5 α -androstan-17-one, **2.25** (0.29 g, 1.0 mmol), and a reaction time of 4 h afforded **2.26a** (0.22 g, 75% yield) as a white solid. 1H NMR ($CDCl_3$) δ (ppm): 4.04 (m, 1H), 3.63 (t, $J = 8.4$ Hz, 1H), 2.11-1.99 (m, 1H), 1.79 (d, $J = 12.3$ Hz, 1H), 1.69-0.89 (m, 22H), 0.79 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 82.0, 66.5, 54.5, 51.1, 43.0, 39.2, 36.8, 36.2, 35.9, 35.6, 32.2, 31.6, 30.5, 29.0, 28.4, 23.4, 20.4, 11.2, 11.1. These NMR data compared well with the literature values.⁹⁹ TOF MS (EI^+) exact mass calculated for $C_{19}H_{31}O_2$ is 291.2324, found 291.2347.

General Method B (Table 2.9, entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3 α -hydroxy-5 α -androstan-17-one, **2.25** (0.29 g, 1.0 mmol), and a reaction time of 4 h afforded **2.26a** (0.28 g, 96% yield).

2.4.17 Bis(4-methoxyphenyl)methanol (**2.28**). ([Scheme 2.7](#)).



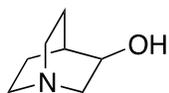
General Method A

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 4,4'-dimethoxybenzophenone, **2.27** (0.24 g, 1.0 mmol), and a reaction time of 2 h afforded **2.28** (0.20 g, 83% yield) as a white solid. ¹H NMR (CDCl₃) δ (ppm): 7.24 (d, *J* = 8.4 Hz, 4H), 6.83 (d, *J* = 8.4 Hz, 4H), 5.70 (s, 1H), 3.75 (s, 6H), 2.44 (br, 1H); ¹³C NMR (CDCl₃) δ (ppm): 158.8, 136.4, 127.7, 113.7, 75.2, 55.2. These NMR data compared well with the literature values.¹¹⁰

General Method B

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 4,4'-dimethoxybenzophenone, **2.27** (0.24 g, 1.0 mmol), and a reaction time of 2 h afforded **2.28** (0.15 g, 60% yield).

2.4.18 3-Quinuclidinol (**2.30**).



General Method A ([Table 2.10](#), entry 1)

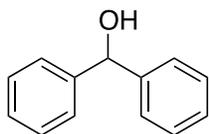
Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), 3-quinuclidinone, **2.29** (0.12 g, 1.0 mmol), and a reaction time of 24 h afforded **2.30** (0.83 mg, 65%

yield) as a white solid. ^1H NMR (CDCl_3) δ (ppm): 3.81 (t, $J = 4.0$ Hz, 1H), 3.31 (br, 1H), 3.10 (dq, $J = 14.1, 8.3, 5.7, 2.0$ Hz, 1H), 2.94-2.84 (m, 1H), 2.76-2.55 (m, 4H), 1.98-1.87 (m, 1H), 1.78 (q, $J = 3.0$ Hz, 1H), 1.71-1.61 (m, 1H), 1.50-1.29 (m, 2H); ^{13}C NMR (CDCl_3) δ (ppm): 67.4, 58.0, 47.4, 46.3, 28.4, 24.8, 18.9. These NMR data compared well with the literature values.^{101,102}

General Method B (Table 2.10, entry 2)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), 3-quinuclidinone, **2.29** (0.12 g, 1.0 mmol), and a reaction time of 24 h afforded **2.30** (0.83 mg, 65% yield).

2.4.19 1,1-Diphenylmethanol (**2.33**).



General Method A (Table 2.14, entry 4)

Lithium dispersion (0.17 g, 6.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), benzophenone, **2.32** (0.18 g, 1.0 mmol), and a reaction time of 4 afforded **2.33** (0.18 g, 99% yield) as a white solid. ^1H NMR (CDCl_3) δ (ppm): 7.33-7.22 (m, 10H), 5.73 (s, 1H), 2.53 (br, 1H); ^{13}C NMR (CDCl_3) δ (ppm): 143.8, 128.4, 127.4, 126.5, 76.1. These NMR data compare well with the literature vales.¹¹¹

General Method B ([Table 2.14](#), entry 5)

Lithium dispersion (0.25 g, 9.0 mmol), iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol), benzophenone, **2.32** (0.18 g, 1.0 mmol), and a reaction time of 4 h afforded **2.33** (0.18 g, 99% yield).

General Method E ([Scheme 2.8](#))

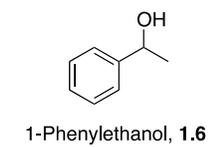
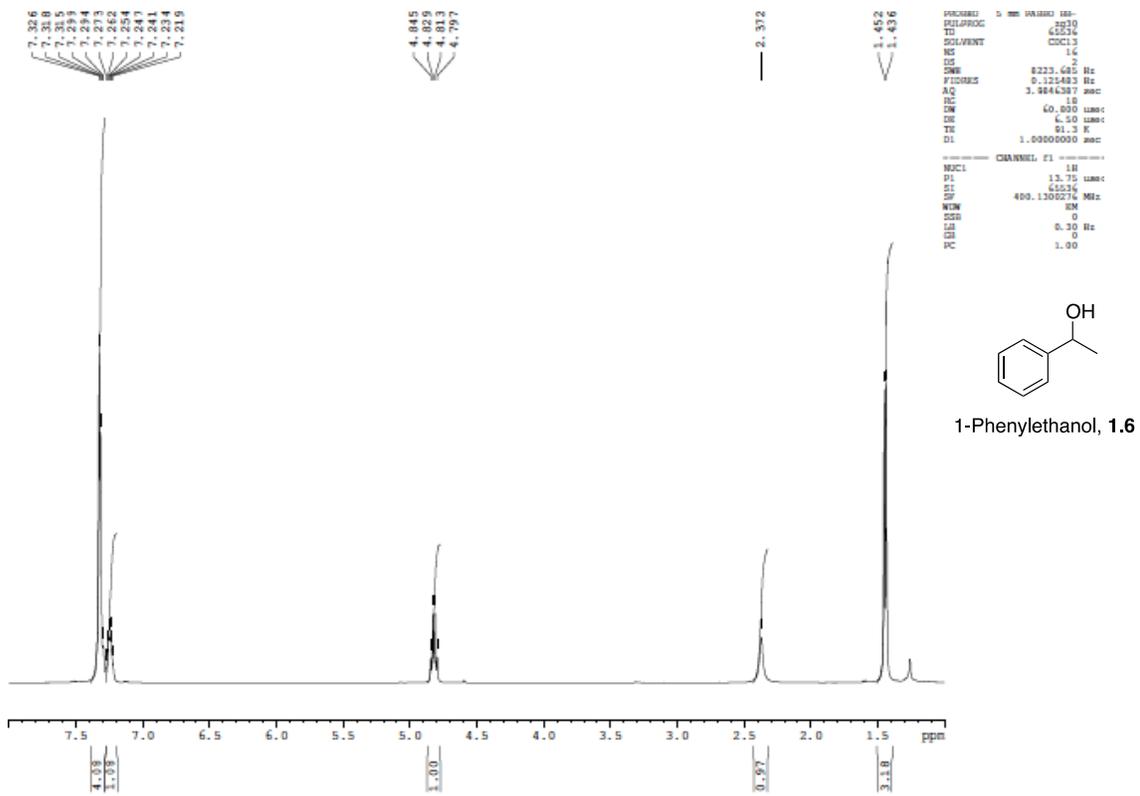
benzophenone, **2.32** (0.18 g, 1.0 mmol) and a reaction time of 24 h provided a ratio of **2.32** to **2.33** as 54:1.

General Method C ([Scheme 2.8](#))

Granular lithium (62 mg, 9.0 mmol), copper(II) chloride dihydrate (0.26 g, 1.5 mmol), benzophenone, **2.32** (0.18 g, 1.0 mmol), and a reaction time of 24 h provided a ratio of **2.32** to **2.33** as 13.5:1.

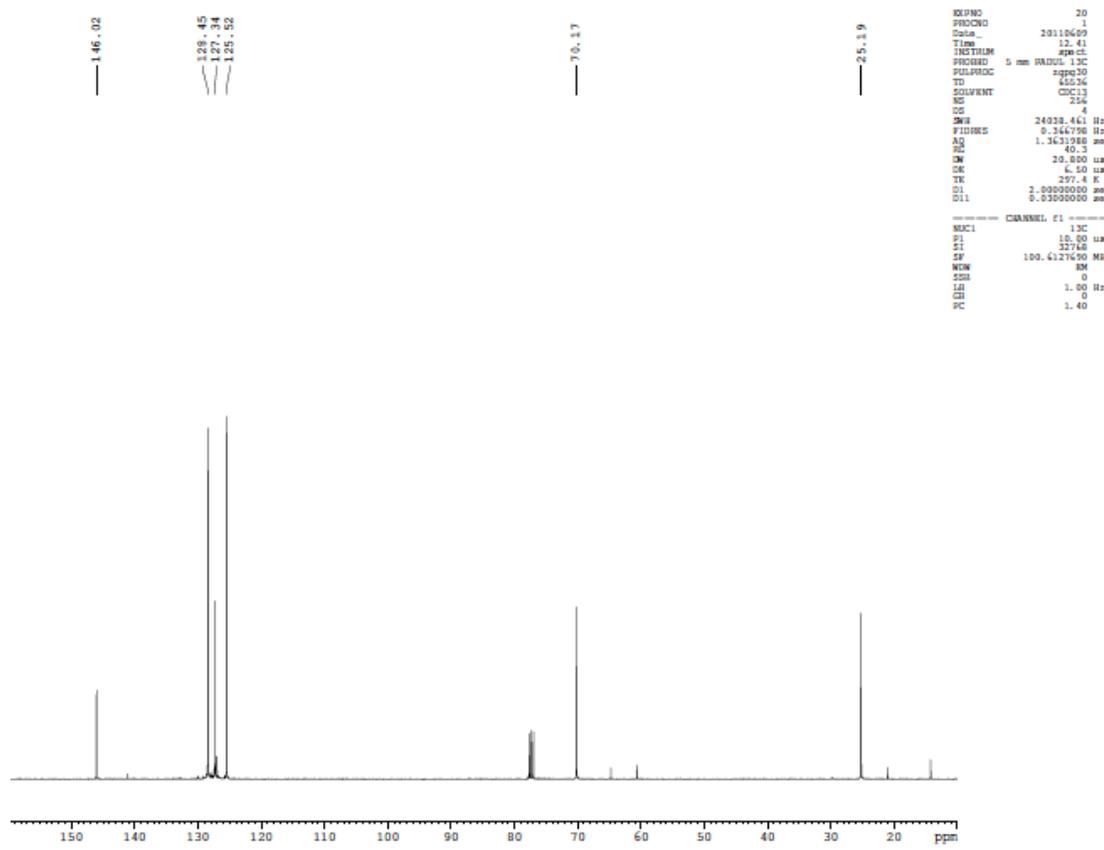
APPENDIX

^1H and ^{13}C NMR Spectra of Synthetically Prepared Compounds



5 mm PABBO HD-
 PROBO 45236
 TO 14
 SOLVENT CDCl3
 NS 14
 DS 2
 SWS 8223.685 Hz
 FIDRES 0.125483 Hz
 AQ 3.984387 sec
 SC 18
 SW 60.800 umsec
 DE 4.50 umsec
 TE 91.3 K
 DI 1.0000000 sec

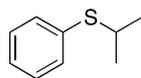
CHANNEL F1
 NUC1 1H
 P1 13.75 umsec
 SI 65336
 SF 400.1300276 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



20
 PROBO 1
 Date_ 20110609
 Time 12.41
 INSTRUM spect
 PROBO 5 mm PABBO 13C
 PABBO 45236
 SOLVENT CDCl3
 NS 14
 DS 4
 SWS 24938.461 Hz
 FIDRES 0.346798 Hz
 AQ 1.3631988 sec
 SC 40.3
 SW 20.800 umsec
 DE 4.50 umsec
 TE 297.4 K
 DI 2.0000000 sec
 D11 0.2300000 sec

CHANNEL F1
 NUC1 13C
 P1 15.00 umsec
 SI 32746
 SF 100.627650 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

7.401
7.381
7.296
7.277
7.258
7.224
7.205
7.187



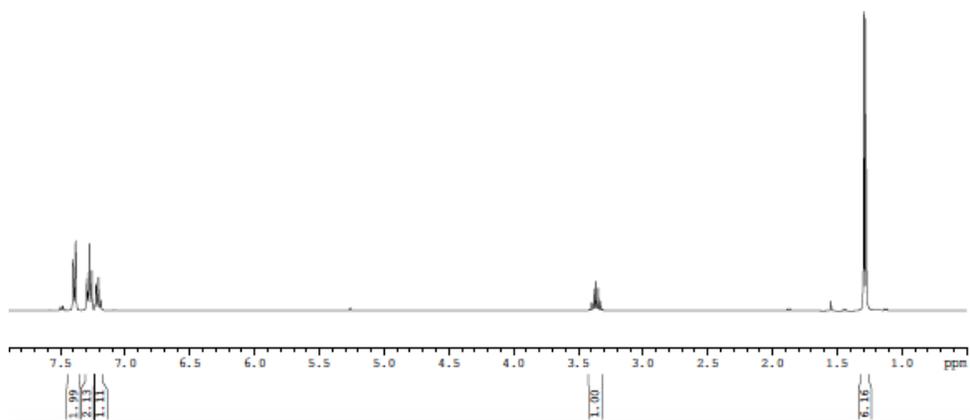
Isopropyl Phenyl Sulfide, 1.14

3.415
3.399
3.381
3.365
3.349
3.331
3.315

1.295
1.279

Date_ 20110825
Time 14.49
INSTRUM spect
PROBHD 5 mm VADCL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 8223.650 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 32
DM 60.800 usec
DE 6.50 usec
TE 299.1 K
D1 1.0000000 sec

===== CHANNEL f1 =====
NUC1 13
P1 9.31 usec
S1 65536
SF 400.1300205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



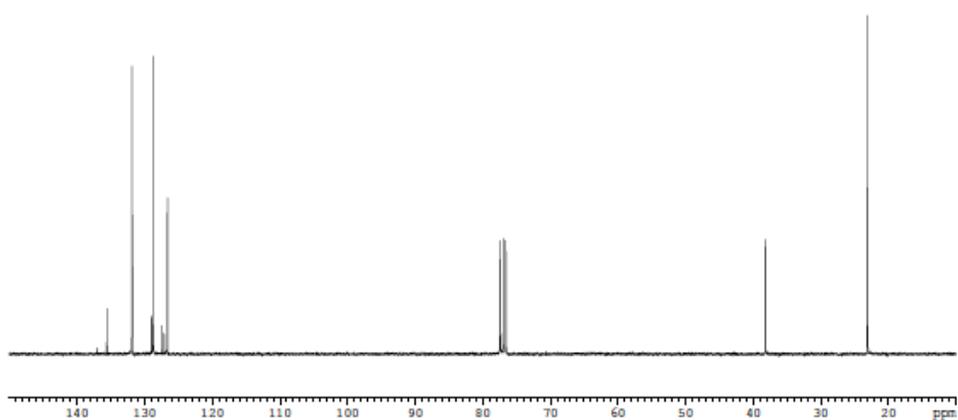
135.53
131.86
128.71
126.62

39.16

23.10

Time 16.19
INSTRUM spect
PROBHD 5 mm QNP 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 18028.846 Hz
FIDRES 0.275098 Hz
AQ 1.0175818 sec
RG 287
DM 27.733 usec
DE 6.50 usec
TE 299.1 K
D1 2.0000000 sec
D11 0.0300000 sec
TDD 1

===== CHANNEL f1 =====
SFO1 75.500428 MHz
NUC1 13C
P1 12.00 usec
S1 32768
SF 75.4928992 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



7.333
7.313
7.289
7.220
7.210
7.178
7.160
7.142

5.829
5.802
5.801
5.795
5.786
5.769
5.751
5.744
5.727

5.053
5.010
5.005
4.997
4.972

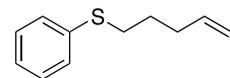
2.937
2.901

2.215
2.197
2.179
2.162

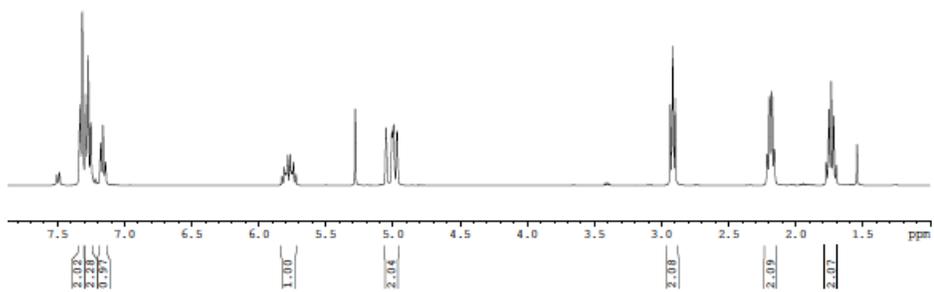
1.775
1.757
1.720
1.702

```

NAME      5-pentylthio-1-pentene
EXPNO     2
PROCNO    2
PROCNAME  2
INSTRUM   zgpg30
PROBHD    zgpg30
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         4
SWH        8221.400 Hz
FIDRES     0.131483 Hz
AQ         3.9044307 sec
RG         327
WDW         EM
SSB         0
LB         0.140 umsec
GB         0
PC         284.6 Hz
DC         0
SFO        100.626100 MHz
===== CHANNEL f1 =====
NUC1       13C
P1         8.00 umsec
PL1        0.00 dB
PC1        0.00 dB
SFO1       100.626100 MHz
WDW1       EM
SSB1       0
LB1        0.140 Hz
GB1        0
PC1        1.00
  
```



5-(Phenylthio)-1-Pentene, 1.16



137.59
136.73

125.07
124.86
123.79

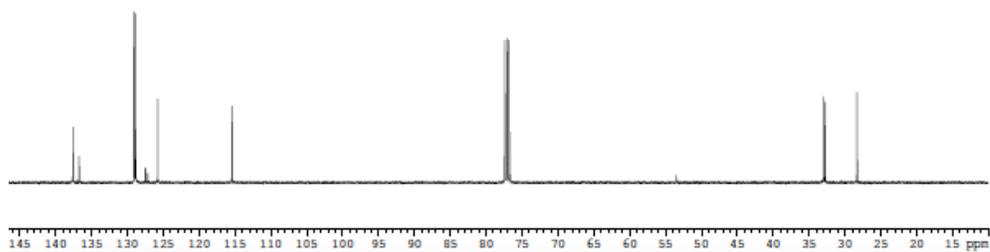
115.42

32.96
32.72

28.29

```

===== CHANNEL f1 =====
NAME      5-pentylthio-1-pentene
EXPNO     2
PROCNO    2
PROCNAME  2
INSTRUM   zgpg30
PROBHD    zgpg30
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         4
SWH        8221.400 Hz
FIDRES     0.131483 Hz
AQ         3.9044307 sec
RG         327
WDW         EM
SSB         0
LB         0.140 umsec
GB         0
PC         284.6 Hz
DC         0
SFO        100.626100 MHz
===== CHANNEL f1 =====
NUC1       13C
P1         8.00 umsec
PL1        0.00 dB
PC1        0.00 dB
SFO1       100.626100 MHz
WDW1       EM
SSB1       0
LB1        0.140 Hz
GB1        0
PC1        1.00
  
```

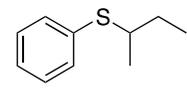


7.382
7.375
7.358
7.357
7.347
7.259
7.255
7.248
7.226
7.211
7.206
7.197
7.177
7.173
7.162
7.153
7.144
7.134
7.129

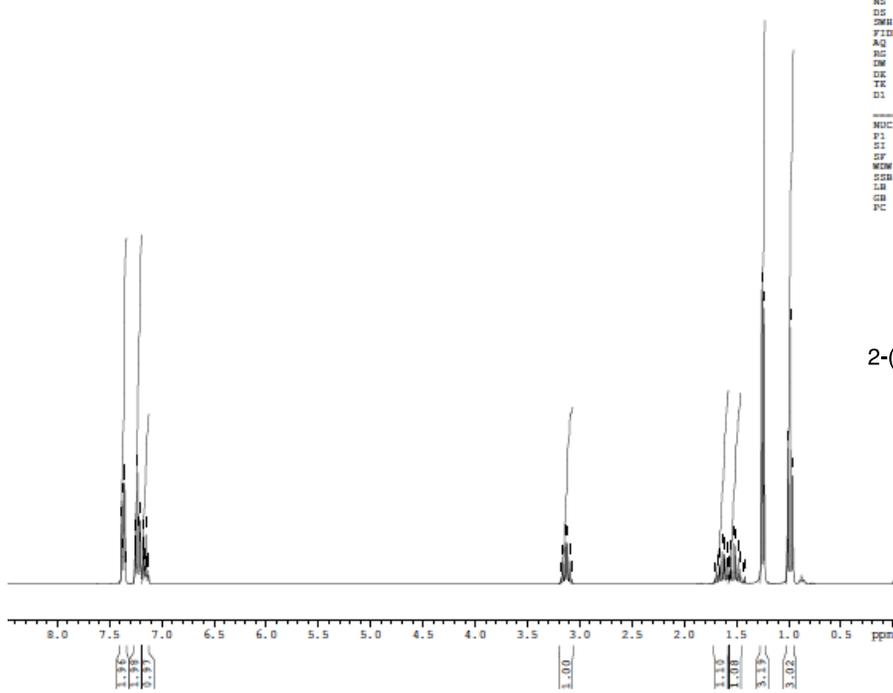
3.183
3.161
3.117
3.095
3.073
1.709
1.684
1.658
1.638
1.617
1.613
1.595
1.575
1.568
1.554
1.530
1.507
1.480
1.436
1.416
1.377
1.357
1.009
0.985

```

NAME      10
EXPNO     1
PROCNO    1
Date_     20130926
Time      9.33
INSTRUM   spect
PROBHD    5 mm QNP
PULPROG   zgpg30
TD         32768
SOLVENT   CDCl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.6477044 sec
RG         16
DM         80.850 usec
DE         6.50 usec
TE         -92.7 K
D1         1.00000000 sec
----- CHANNEL f1 -----
NUC1       1H
P1         12.71 usec
SI         32768
SF         300.2300391 MHz
WDW        EM
SSB        0
LB         0.10 Hz
GB         0
PC         1.00
  
```



2-(Phenylthio)-Butane, 1.20

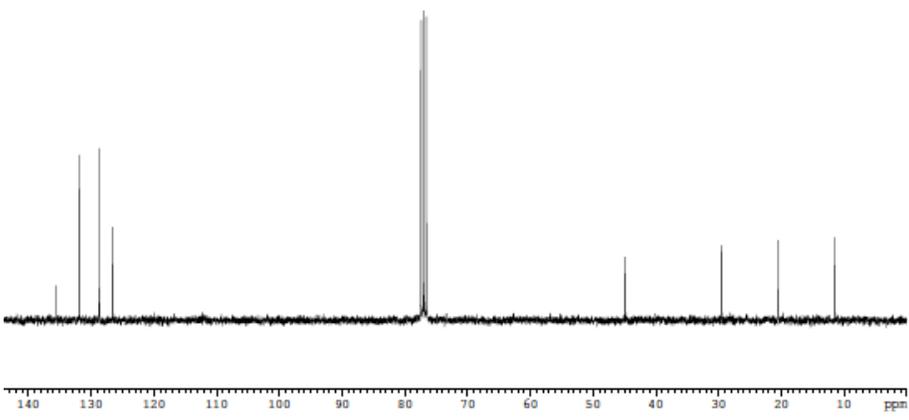


130.55
131.88
128.73
126.55

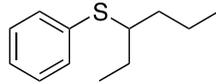
44.86
29.48
8.51
11.44

```

NAME      10
EXPNO     1
PROCNO    1
Date_     20130927
Time      12.32
INSTRUM   spect
PROBHD    5 mm QNP
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         256
DS         4
SWH        18028.846 Hz
FIDRES     0.275098 Hz
AQ         1.8175818 sec
RG         362
DM         27.753 usec
DE         6.50 usec
TE         -92.4 K
D1         2.00000000 sec
D11        0.03000000 sec
----- CHANNEL f1 -----
NUC1       13C
P1         12.00 usec
SI         32768
SF         75.4928954 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
  
```

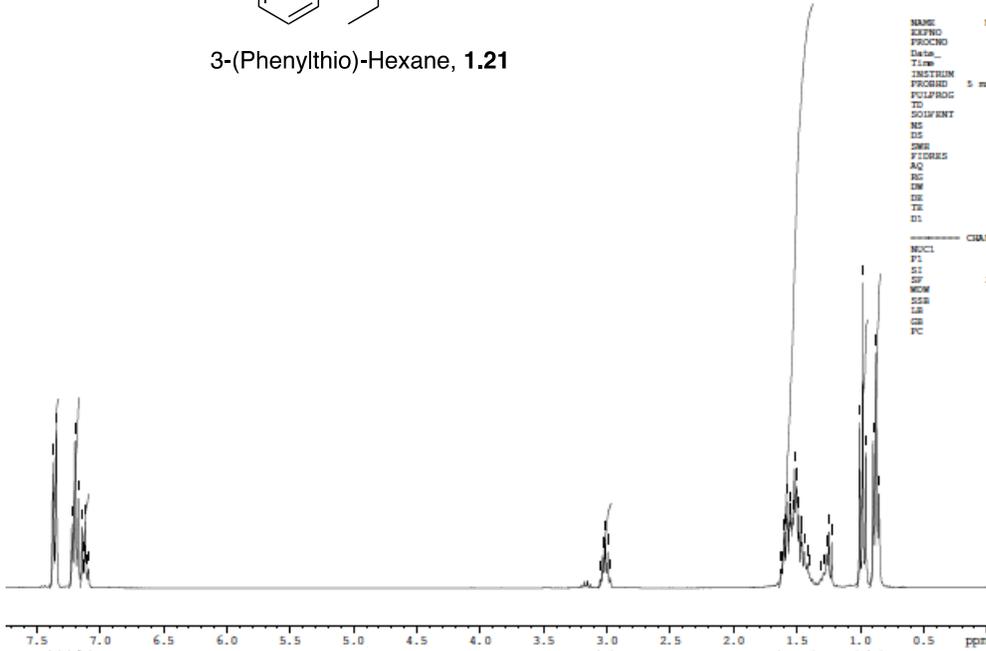


7.371
7.282
7.199
7.173
7.142
7.117
7.109
7.093



3-(Phenylthio)-Hexane, 1.21

3.054
3.033
2.993
2.972
1.629
1.620
1.596
1.573
1.560
1.550
1.530
1.504
1.501
1.484
1.480
1.444
1.417
1.406
1.389
1.267
1.249
1.226
0.986
0.957
0.899



```

NAME      NMR-13-46-1
EXPNO    10
PROCNO    1
Date_     20130813
Time      16.42
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zgpg30
ID        32768
SOLVENT   CDCl3
NS        16
DS        2
SWH       6188.119 Hz
FIDRES    0.188846 Hz
AQ        2.6477044 sec
RG        12.7
SQ        80.800 u
DE        6.50 u
TE        -92.61 K
D1        1.00000000 sec
----- CHANNEL f1 -----
NUC1      13C
P1        12.71 u
SFO       300.2300535 MHz
MCHM      RM
SGB       0
LB        0.10 Hz
GB        0
PC        1.00
  
```

2.25
2.26
1.12

1.00

0.9

1.19
1.13

135.99
131.80
128.73
126.42

50.43

36.21

27.30

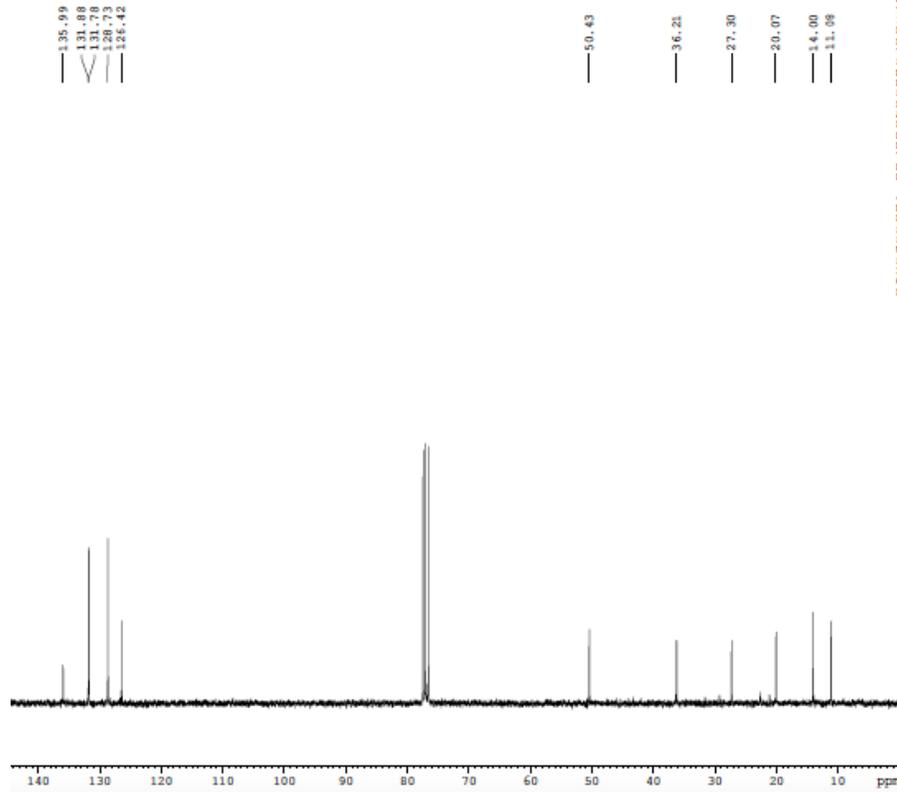
20.07

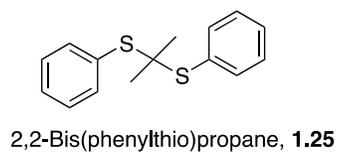
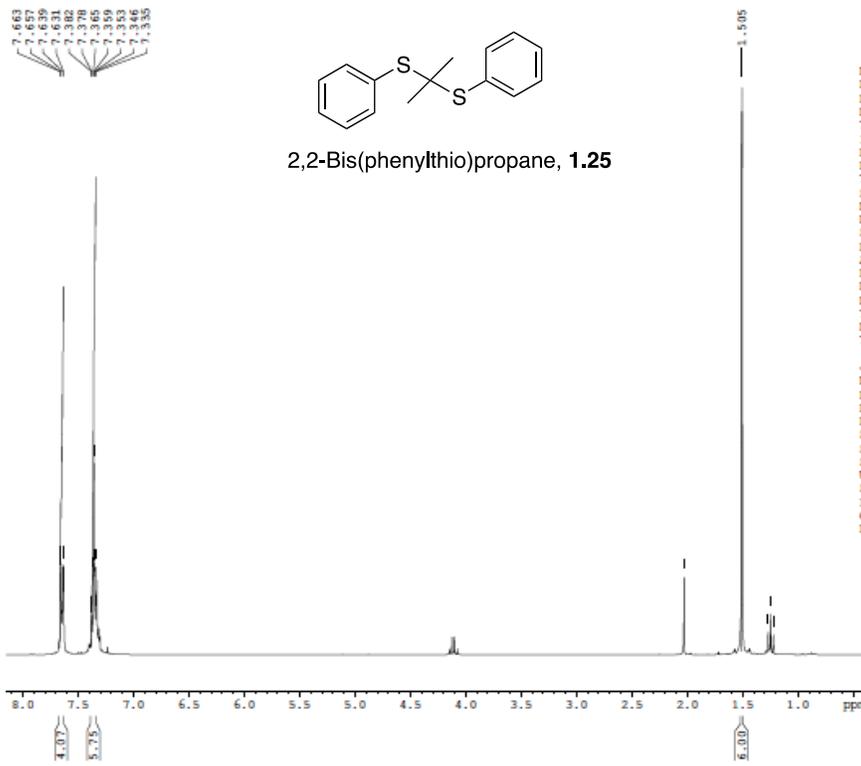
14.00

11.09

```

NAME      41130813
EXPNO    10.27
PROCNO    1
Date_     20130813
Time      16.42
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zgpg30
ID        32768
SOLVENT   CDCl3
NS        16
DS        2
SWH       18028.846 Hz
FIDRES    0.275098 Hz
AQ        1.8175818 sec
RG        362
SQ        27.733 u
DE        6.50 u
TE        -92.29 K
D1        2.00000000 sec
D11       0.03000000 sec
----- CHANNEL f1 -----
NUC1      13C
P1        12.00 u
SFO       75.4928959 MHz
MCHM      RM
SGB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```



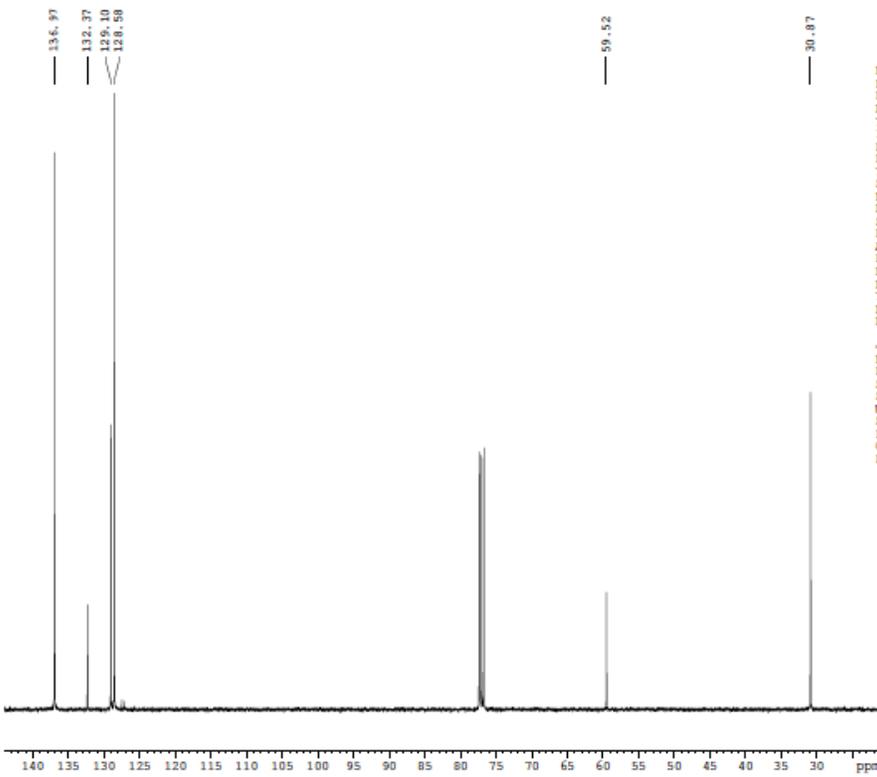


```

NAME      NMK-3-1-1
EXPNO    1
PROCNO   1
Date_    20110211
Time     12.23
INSTRUM  spect
PROBHD   5 mm Multinucl
PULPROG  zg30
TD       32768
SOLVENT  CDCl3
NS       16
DS       2
SWH      6188.119 Hz
FIDRES   0.188846 Hz
AQ       2.6477044 sec
RG       32
DW       80.800 usec
DE       6.50 usec
TE       295.1 K
D1       1.00000000 sec
TD0      1
  
```

```

----- CHANNEL f1 -----
NUC1     1H
P1       13.20 usec
PL1      -2.00 dB
PL1W     18.20942116 W
SFO1     300.2318540 MHz
SI       32768
SF       300.2300163 MHz
WDW      EM
SSB      0
LB       0.10 Hz
GB       0
PC       1.00
  
```

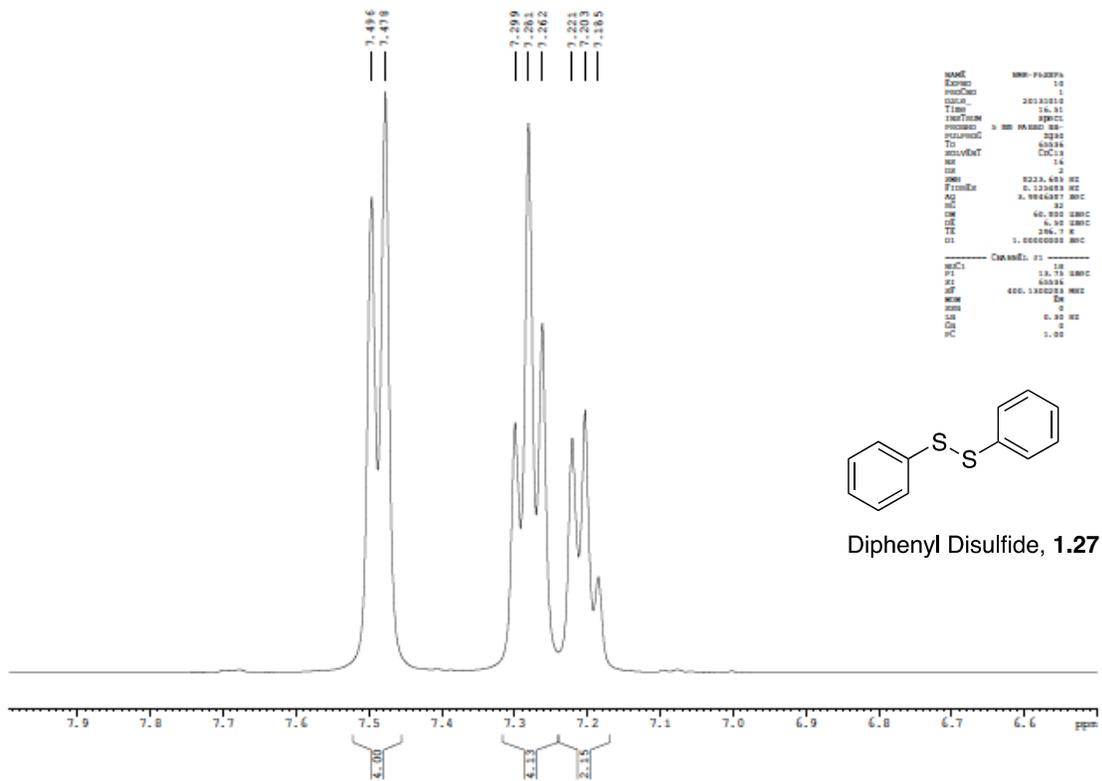


```

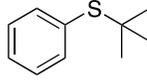
NAME      NMK-2, 2-Bis (phenylt)
EXPNO    10
PROCNO   1
Date_    20120108
Time     18.50
INSTRUM  spect
PROBHD   5 mm PADUL 13C
PULPROG  zgpg30
TD       65536
SOLVENT  CDCl3
NS       256
DS       4
SWH      24038.461 Hz
FIDRES   0.366798 Hz
AQ       1.3631988 sec
RG       36
DW       20.800 usec
DE       6.50 usec
TE       297.1 K
D1       2.00000000 sec
D11      0.03000000 sec
  
```

```

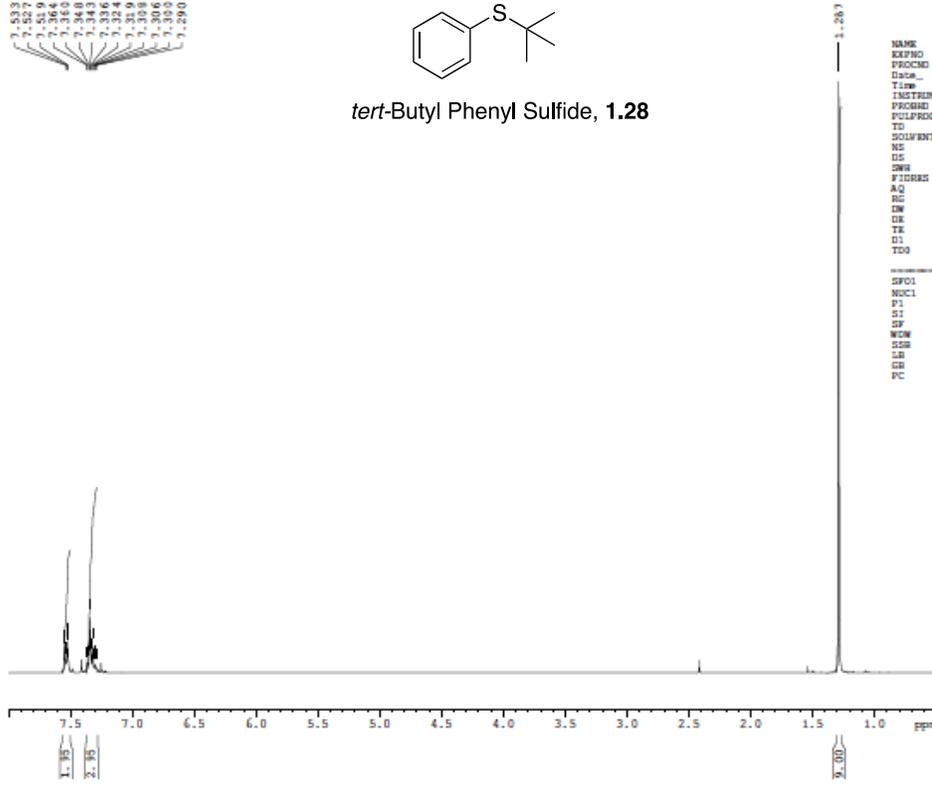
----- CHANNEL f1 -----
NUC1     13C
P1       10.00 usec
PL1      0
PL1W     100.6127690 MHz
SI       65536
SF       100.6127690 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
  
```



7.553
7.527
7.520
7.364
7.360
7.348
7.338
7.332
7.324
7.319
7.308
7.305
7.290



tert-Butyl Phenyl Sulfide, 1.28



```

NAME      NMC-17-37-5M
EXPNO     10
PROCNO    1
Date_     20150208
Time      13.11
INSTRUM   spect
PROBHD    5 mm QNP
PULPROG   zg30
TD         32768
SOLVENT   CDCl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.6477044 sec
RG         30.5
DW         80.800 usec
DE         6.50 usec
TE         -930.9 K
D1         1.00000000 sec
TDO       1
----- CHANNEL f1 -----
SFO1      300.231840 MHz
NUC1      1H
P1        12.71 usec
SI        32768
SF        300.2300113 MHz
WOW       EM
SFO       0
LB        0.10 Hz
GB        0
PC        1.00

```

137.45
132.73
128.61
126.61

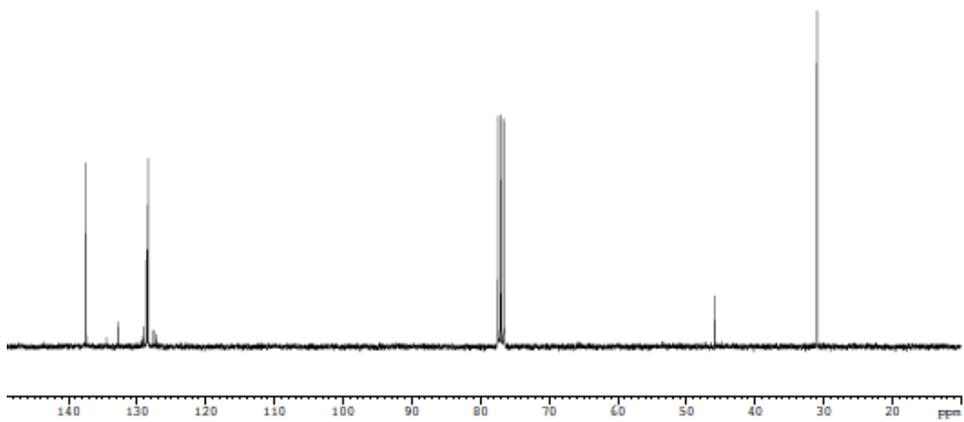
45.79

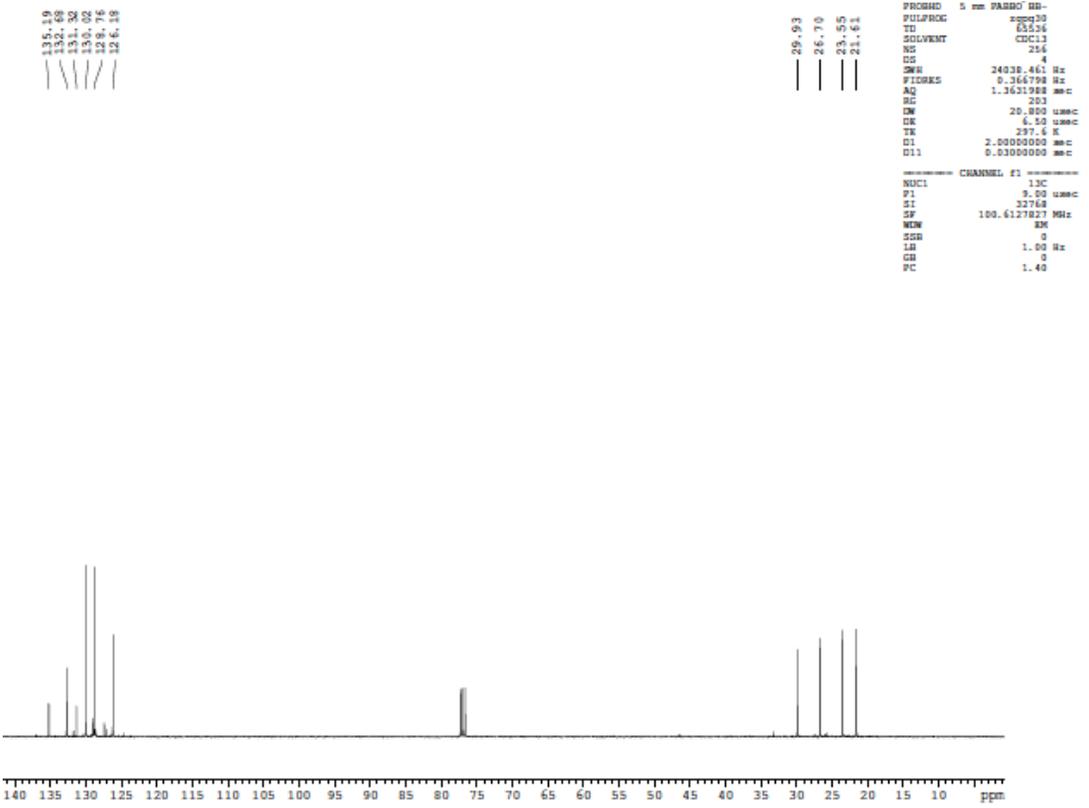
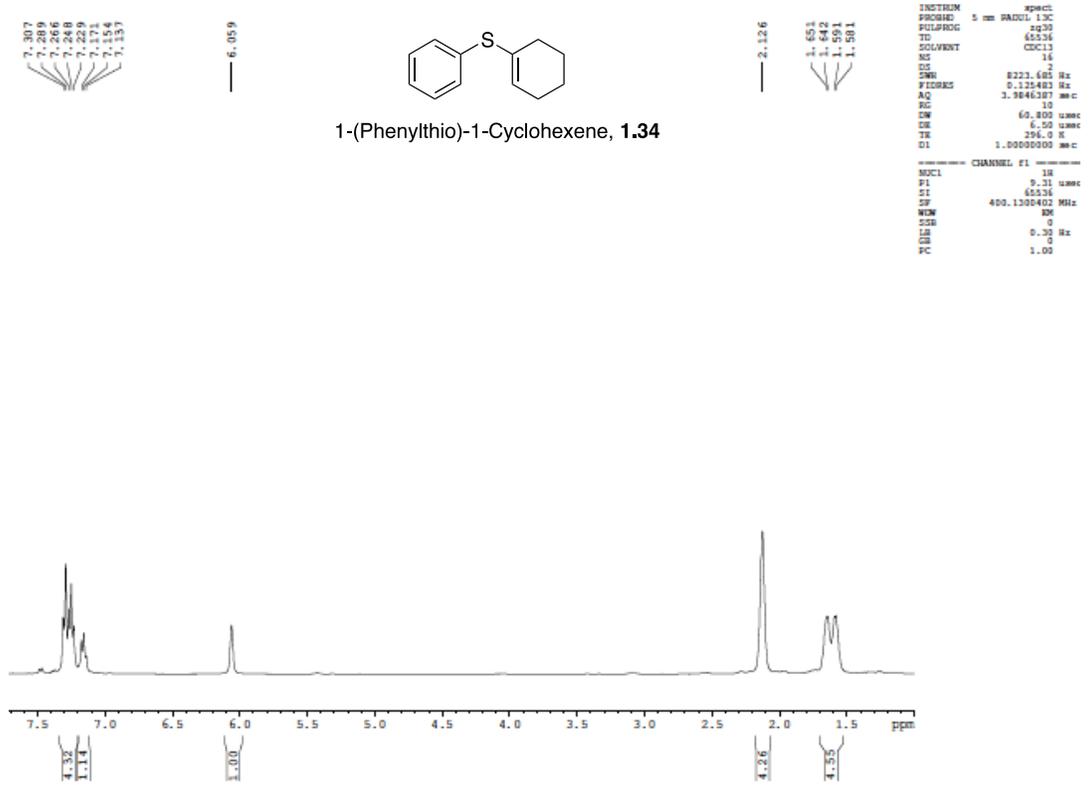
30.95

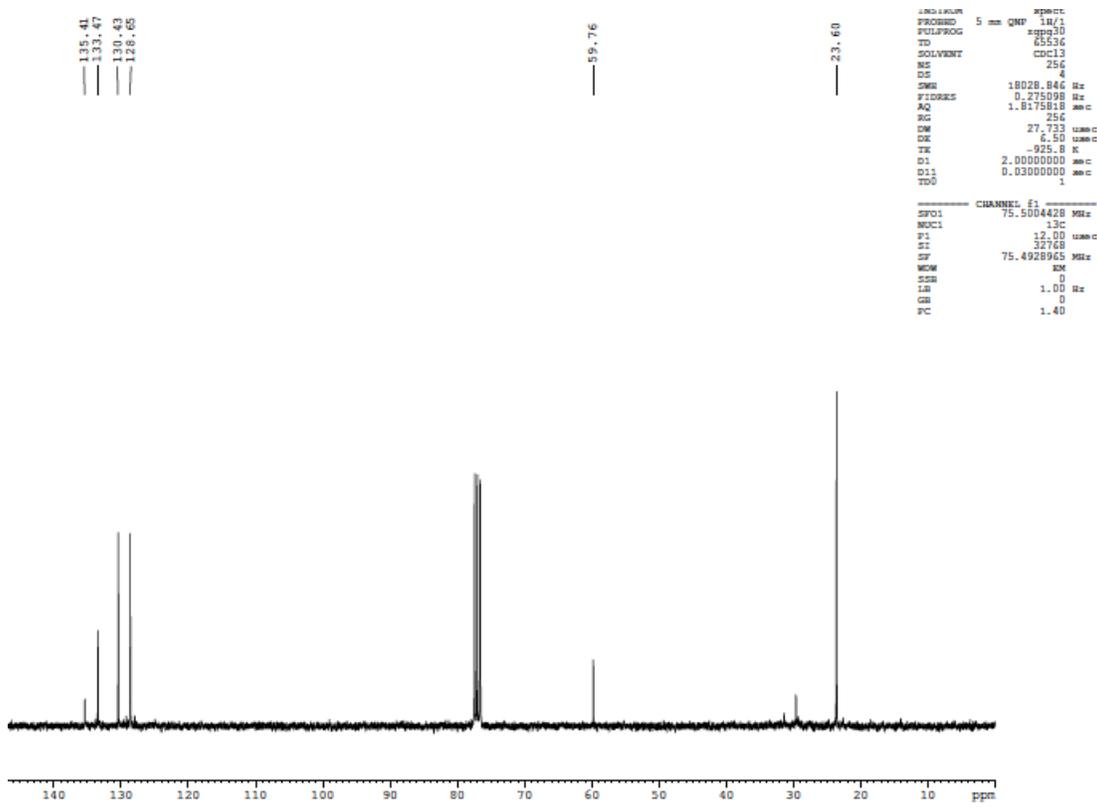
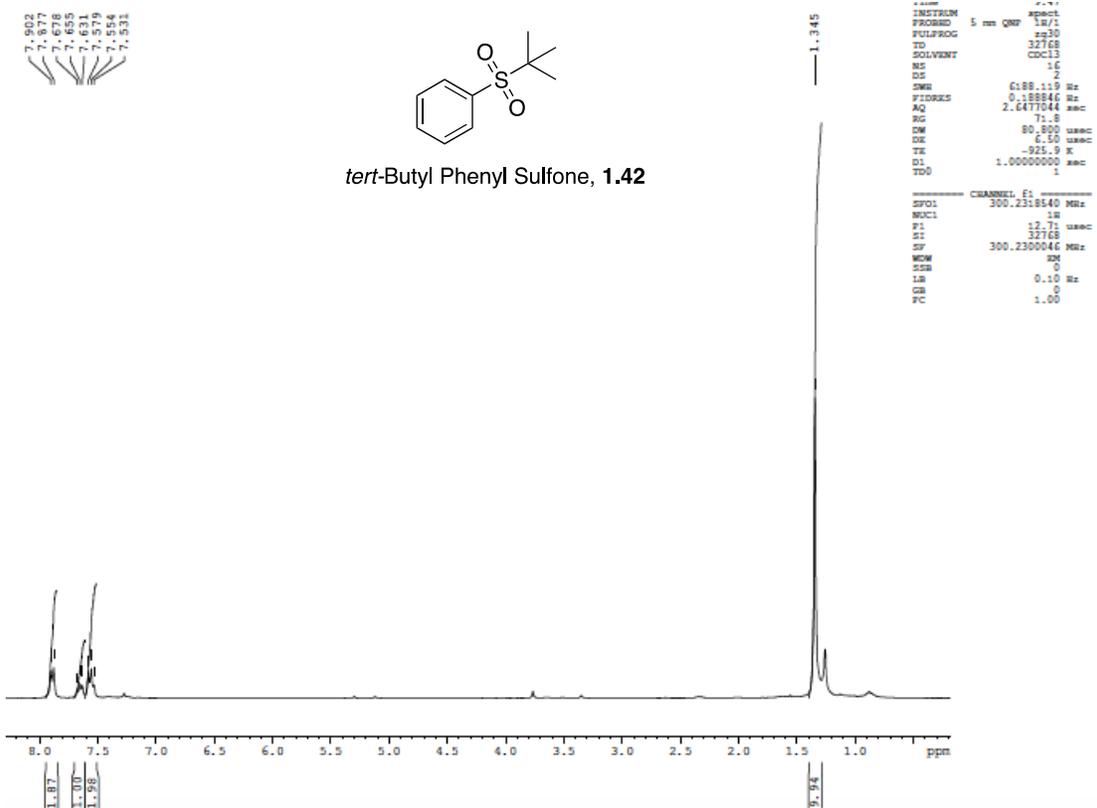
```

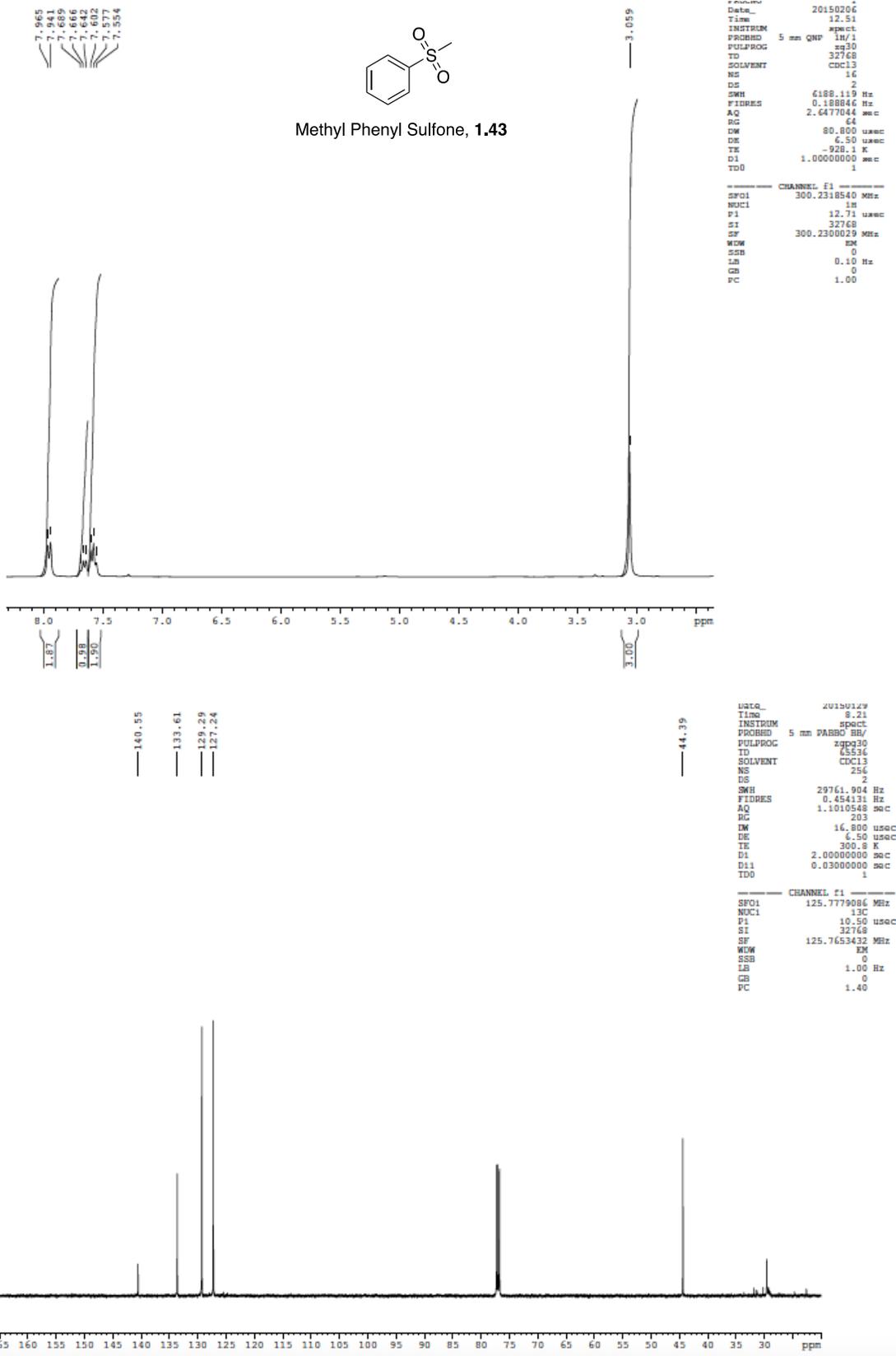
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         256
DS         4
SWH        18028.846 Hz
FIDRES     0.275098 Hz
AQ         1.8175812 sec
RG         287
DW         27.733 usec
DE         6.50 usec
TE         -930.8 K
D1         2.00000000 sec
D11        0.03000000 sec
TDO       1
----- CHANNEL f1 -----
SFO1      75.5004428 MHz
NUC1      13C
P1        12.00 usec
SI        32768
SF        75.4928954 MHz
WOW       EM
SFO       0
LB        1.00 Hz
GB        0
PC        1.40

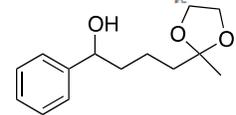
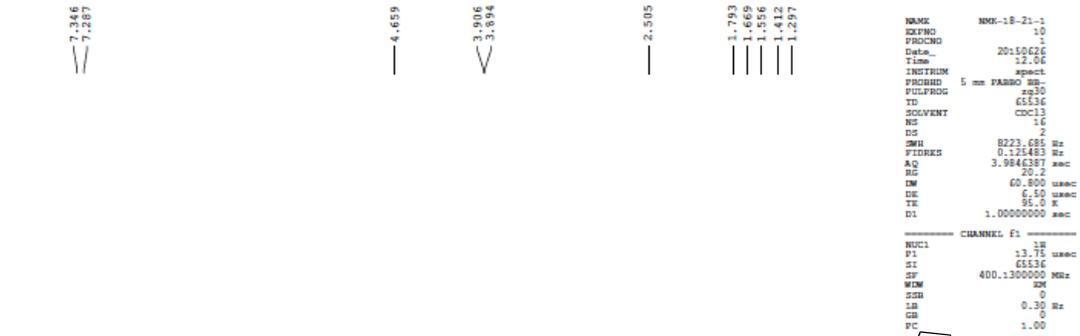
```



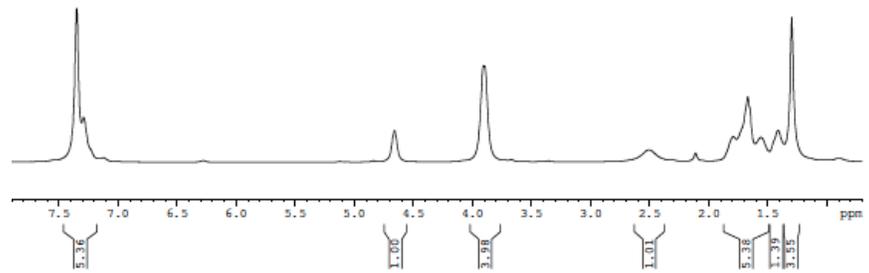








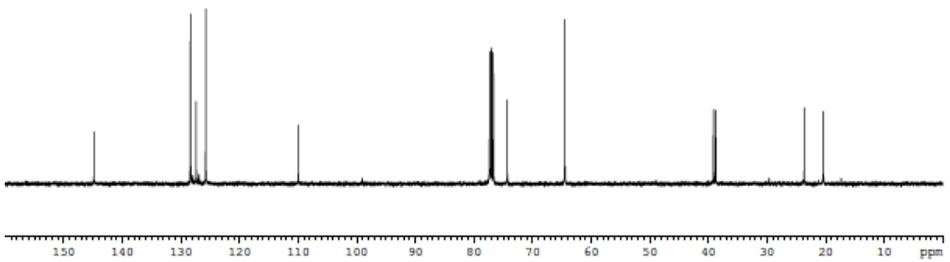
2-(4-Hydroxy-4-Phenylbutyl)-2-Methyl-1,3-Dioxolane, **1.47**

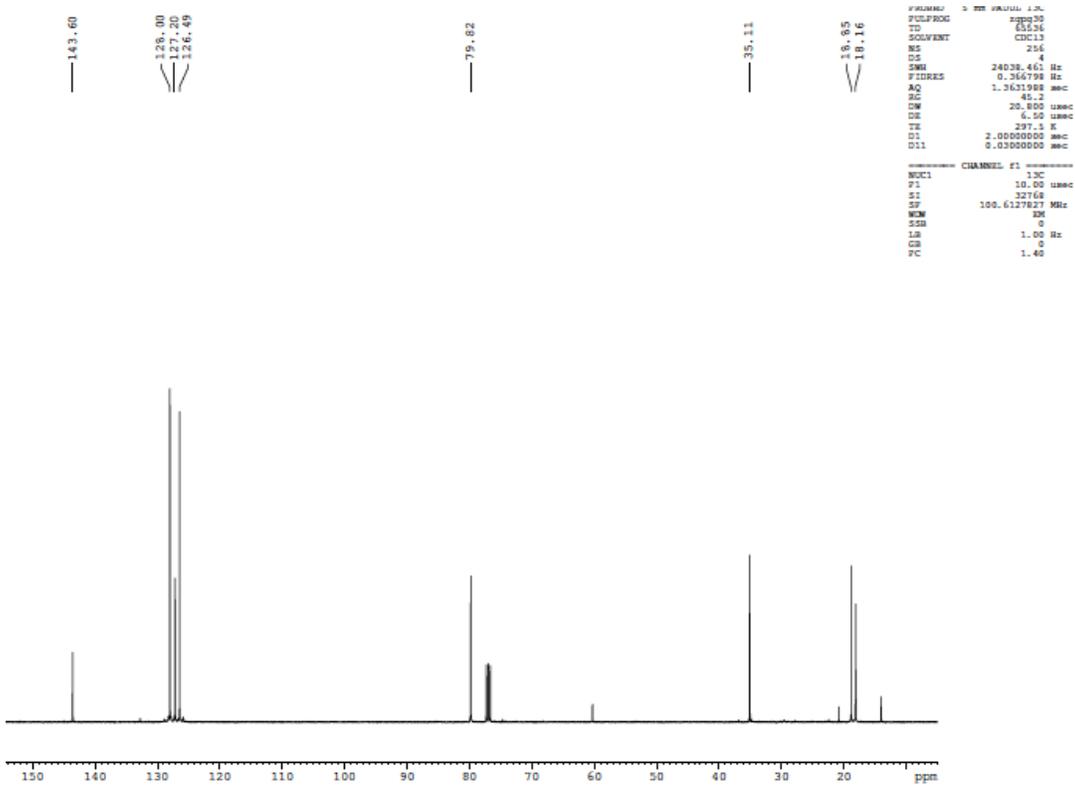
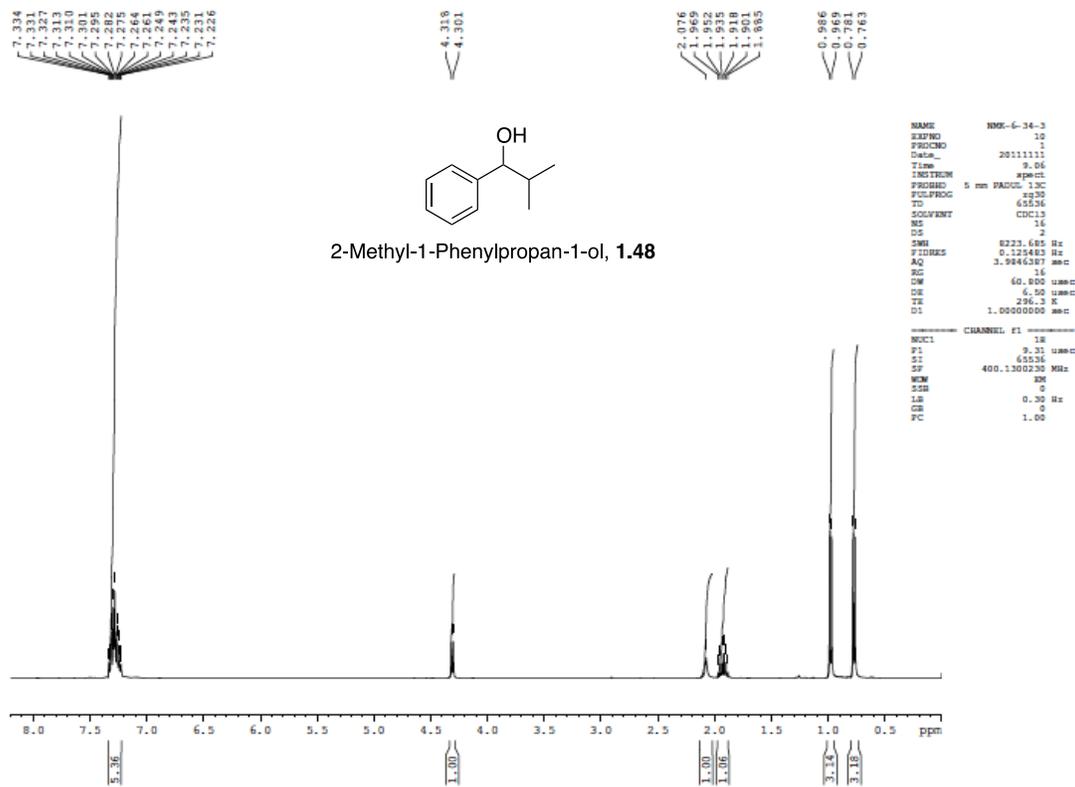


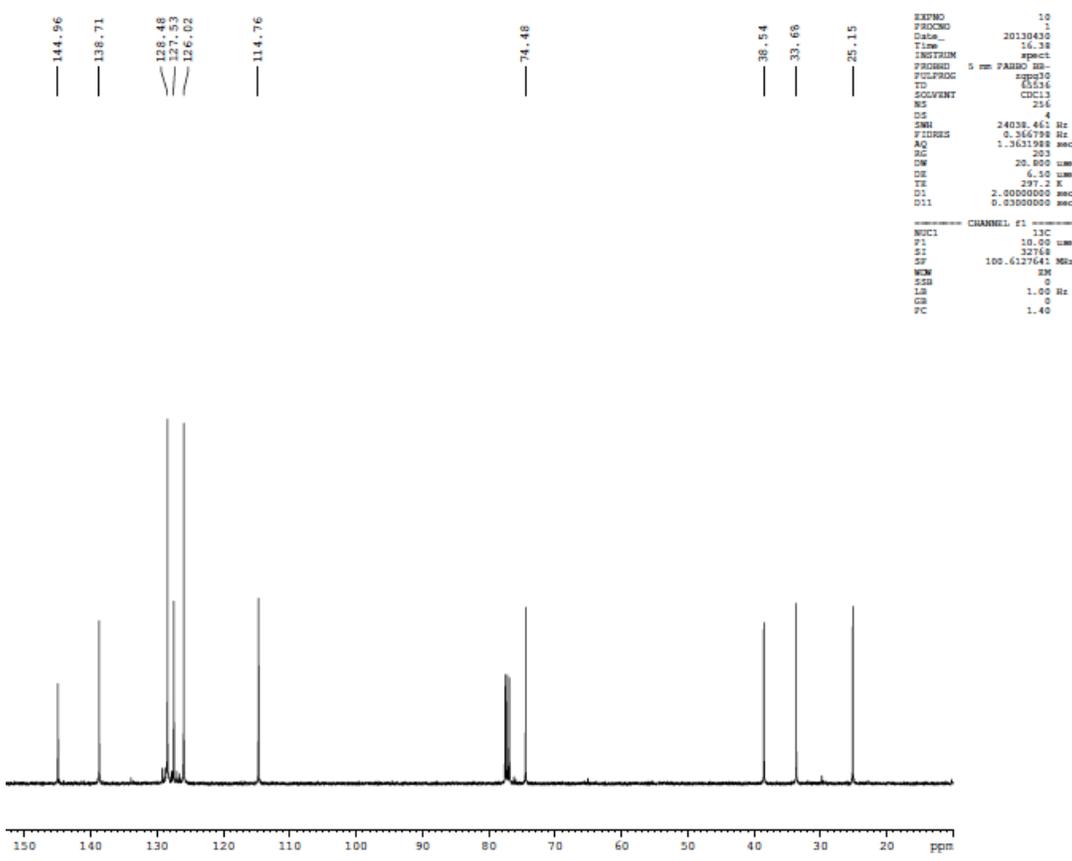
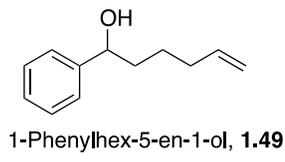
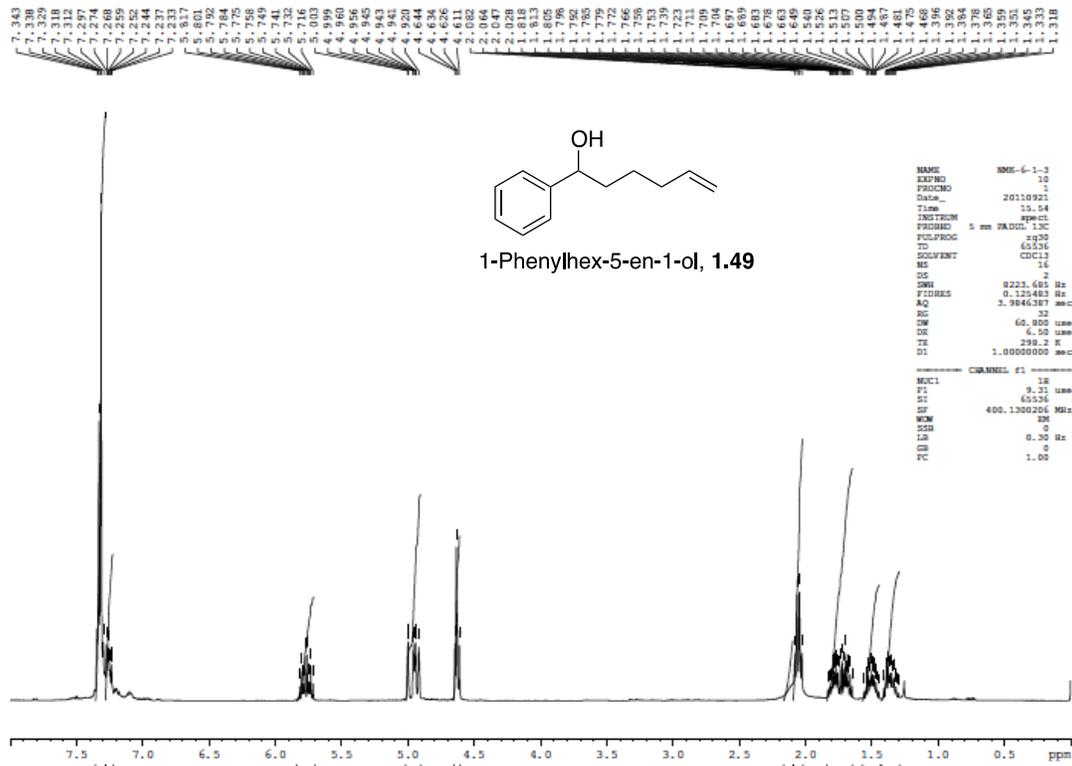
```

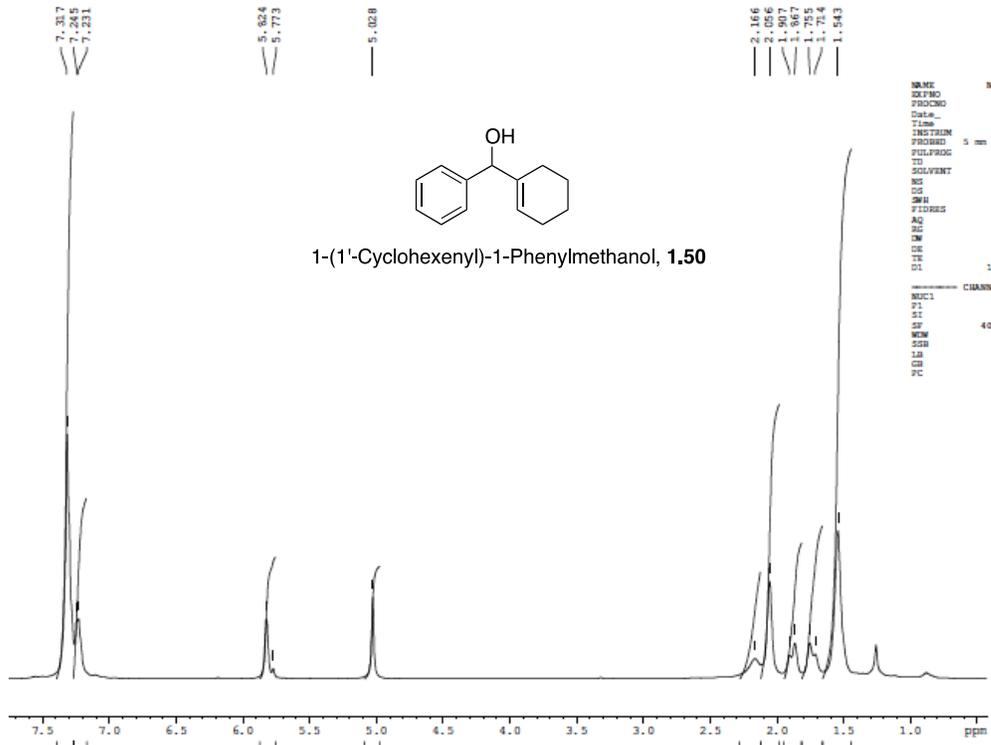
NAME NMR-18-21-1C13
EXPNO 10
PROCNO 1
Date_ 20150221
Time 12.22
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT cdcl3
NS 256
DS 4
SWH 24038.461 Hz
FIDRES 0.364798 Hz
AQ 1.3631988 sec
RG 181
SQ 20.800 usec
DE 6.50 usec
TE 95.1 K
SI 2.0000000 sec
D1 0.0300000 sec
----- CHANNEL f1 -----
NUC1 13C
P1 10.00 usec
SI 32768
SF 100.6127791 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

```



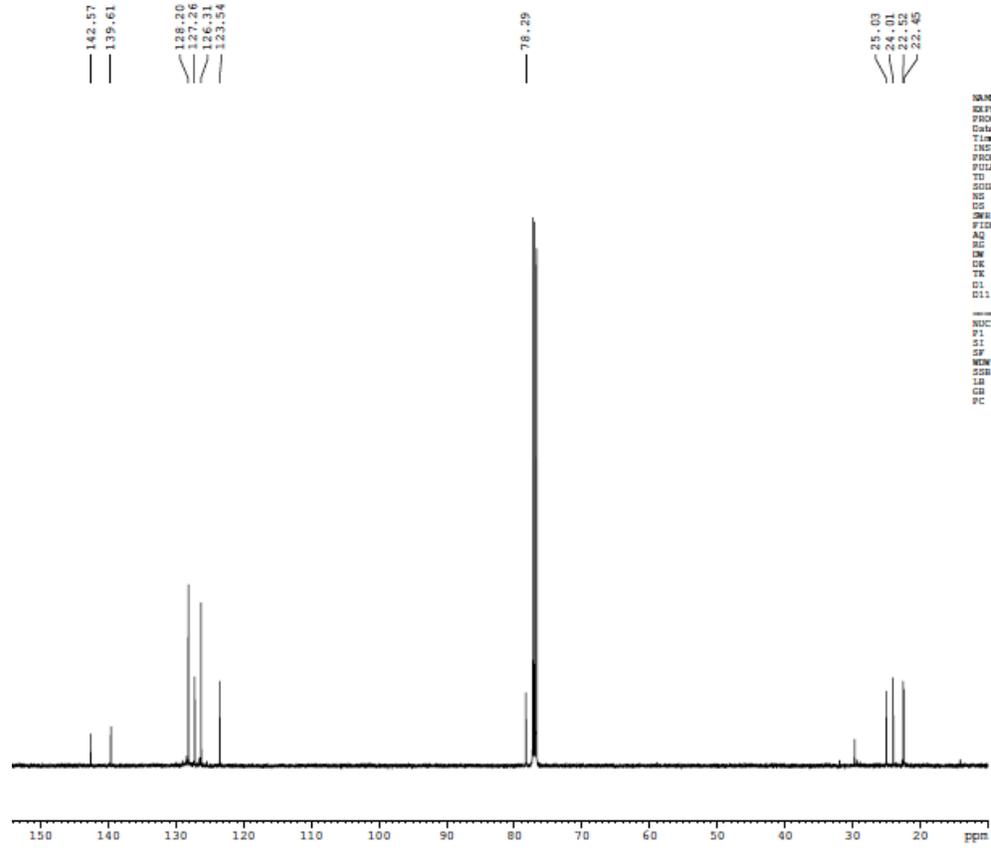






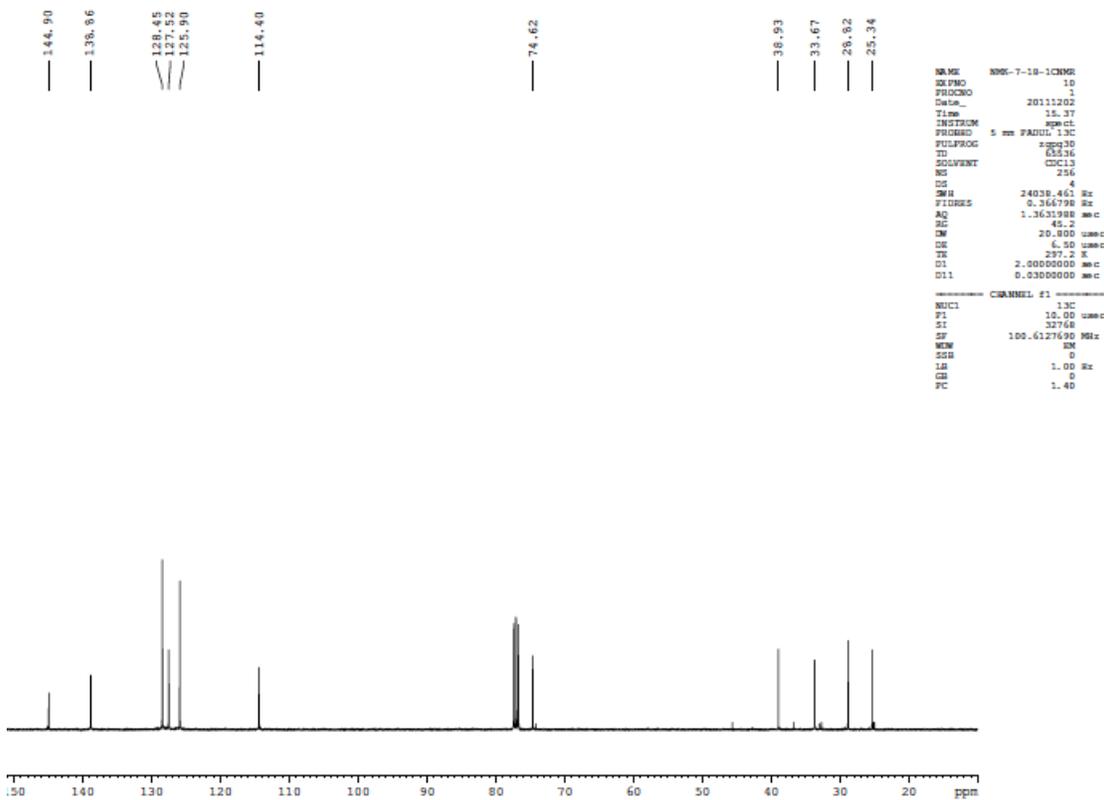
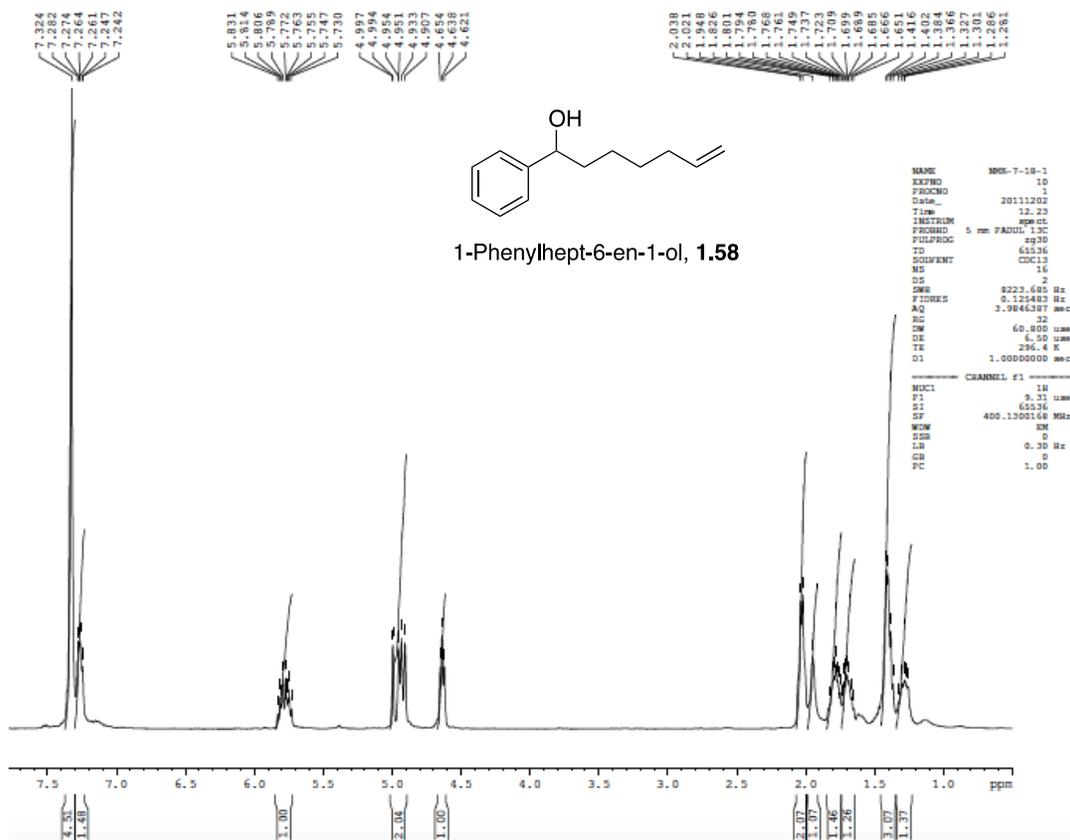
```

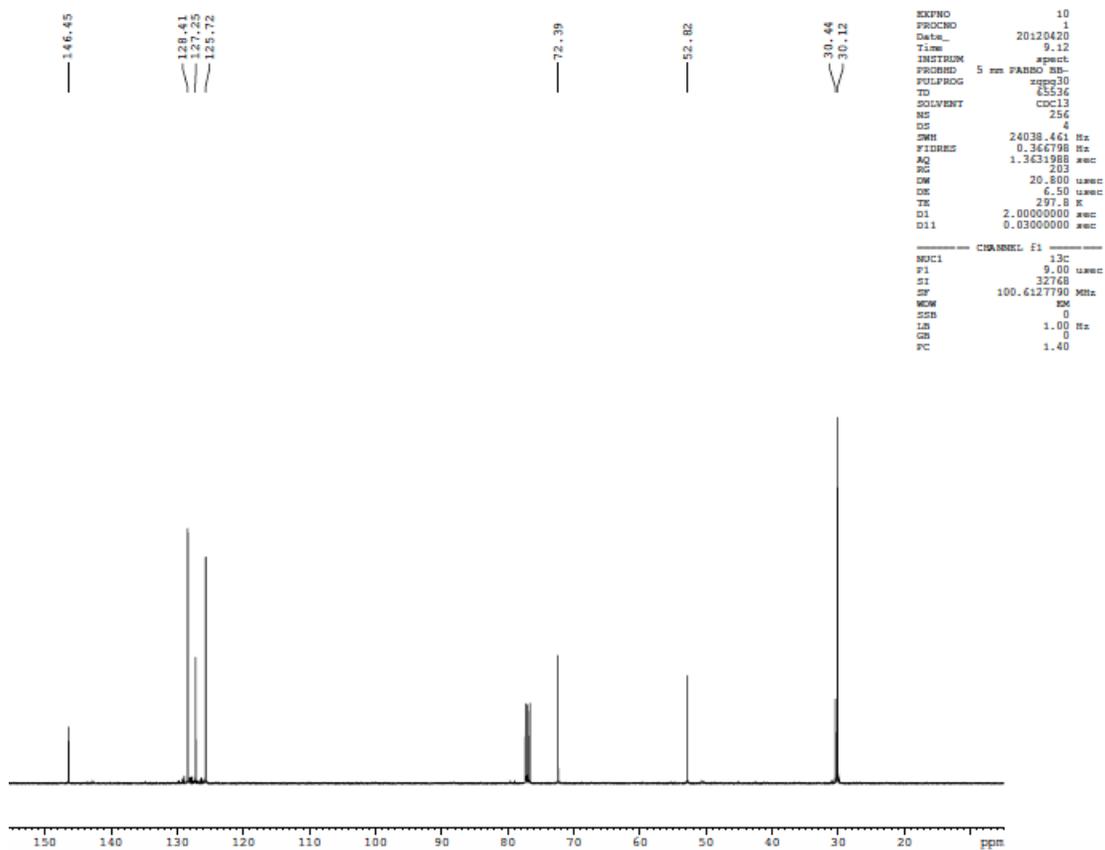
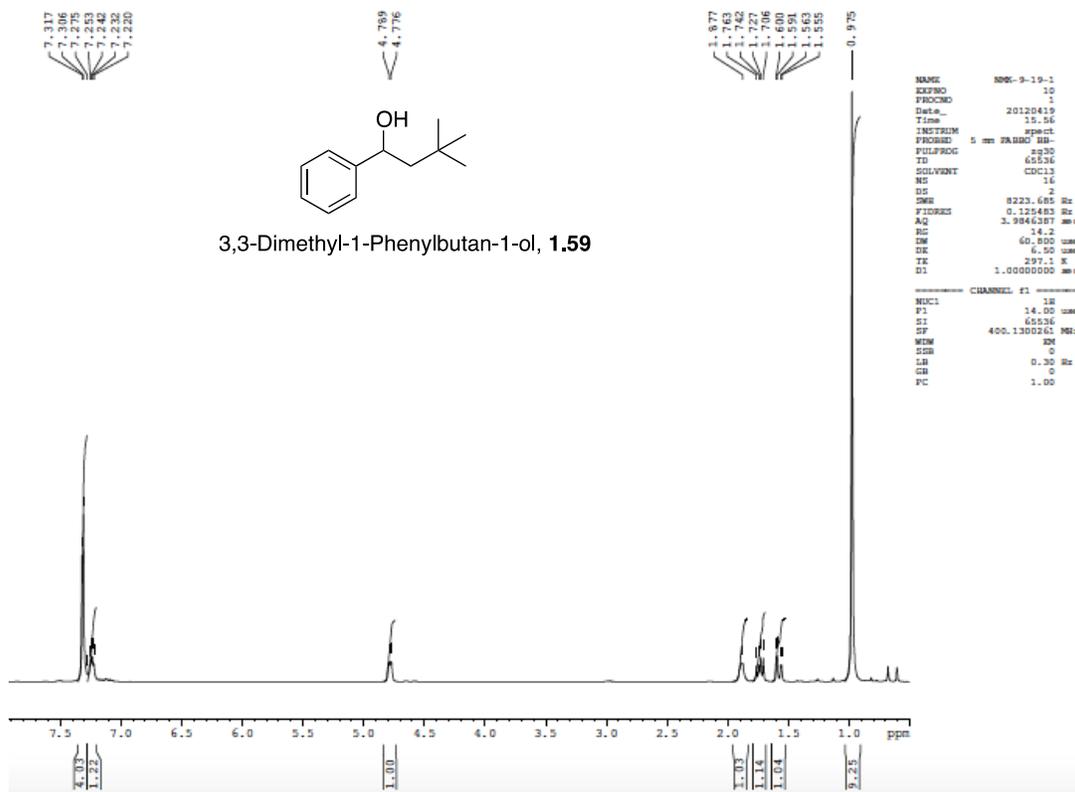
NAME      NMR-7-39-2
EXPNO    10
PROCNO   1
Date_    20111228
Time     16.41
INSTRUM  spect
PROBHD   5 mm PABBO 13C
PULPROG  zg30
TD        65536
SOLVENT  CDCl3
NS        2
DS        4
SWH       8222.665 Hz
FIDRES    0.121483 Hz
AQ        3.9846387 sec
RG        14.2
DM        60.000 umm
DE        6.50 umm
TE        297.0 K
D1        1.0000000 sec
  
```

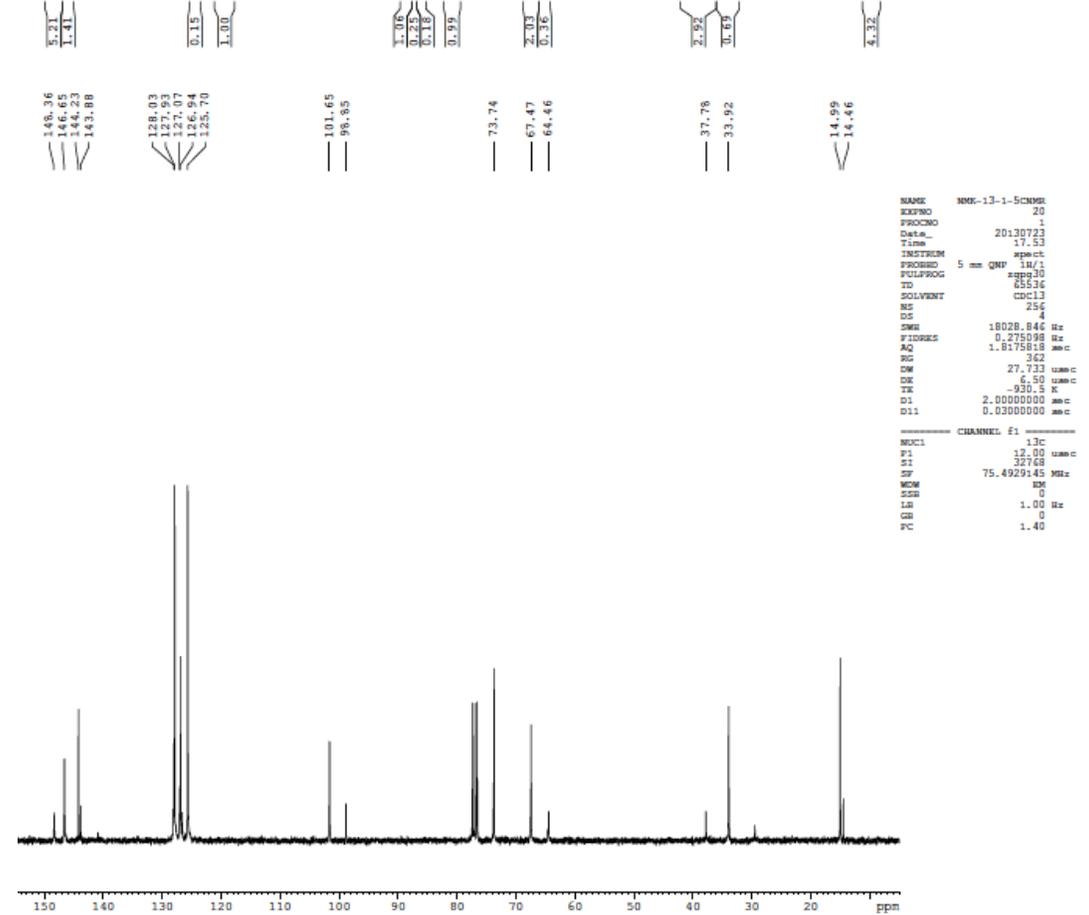
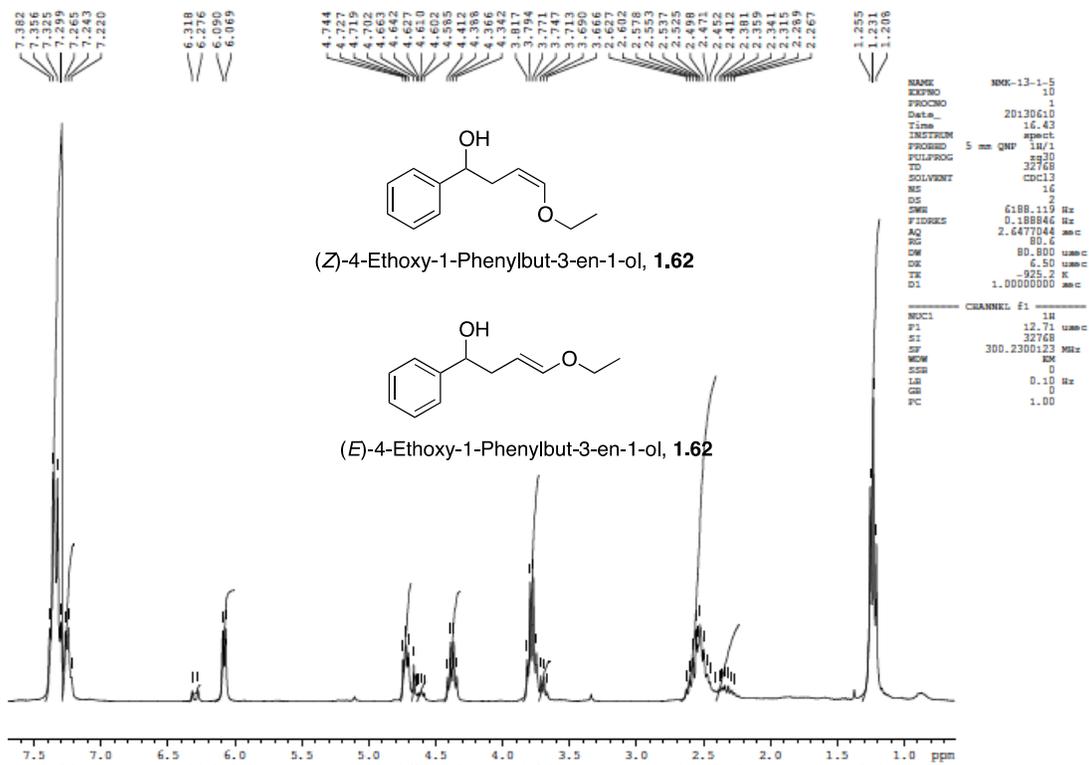


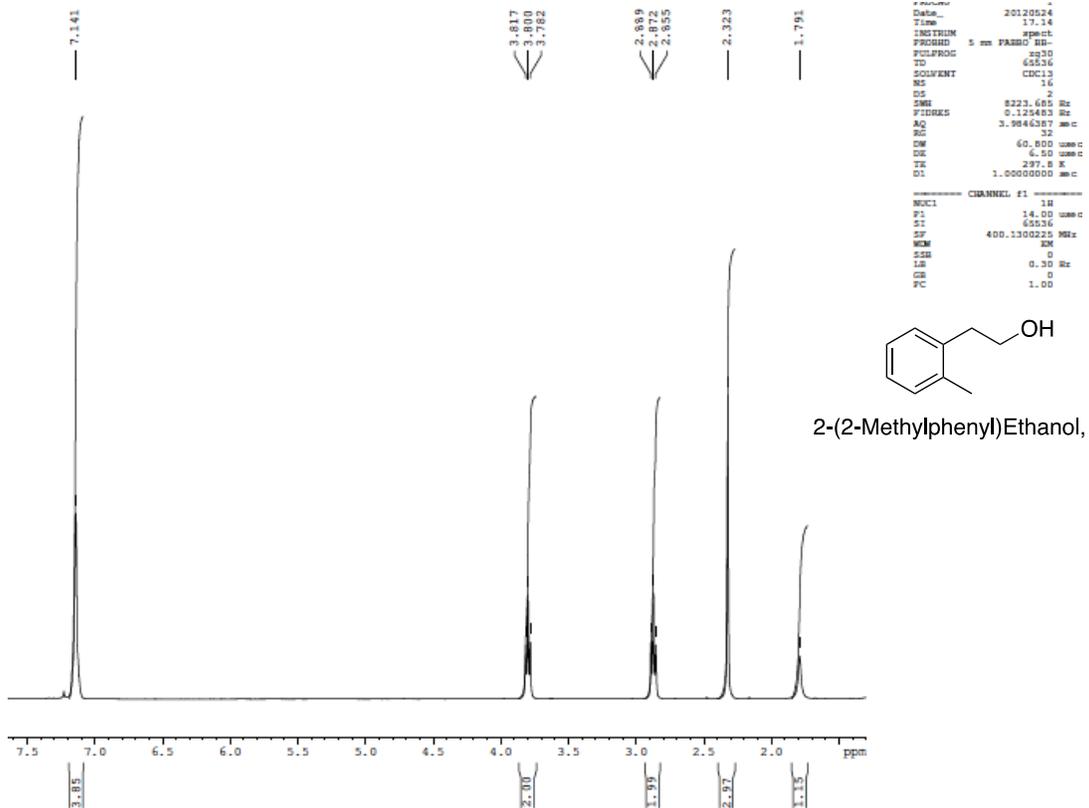
```

NAME      NMR-7-40-18-CBGG
EXPNO    1
PROCNO   1
Date_    20111228
Time     11.53
INSTRUM  spect
PROBHD   5 mm PABBO 13C
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        4
DS        4
SWH       29761.904 Hz
FIDRES    0.484131 Hz
AQ        1.1015548 sec
RG        283
DM        16.000 umm
DE        6.50 umm
TE        298.0 K
D1        2.0000000 sec
D11       0.0300000 sec
  
```





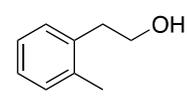




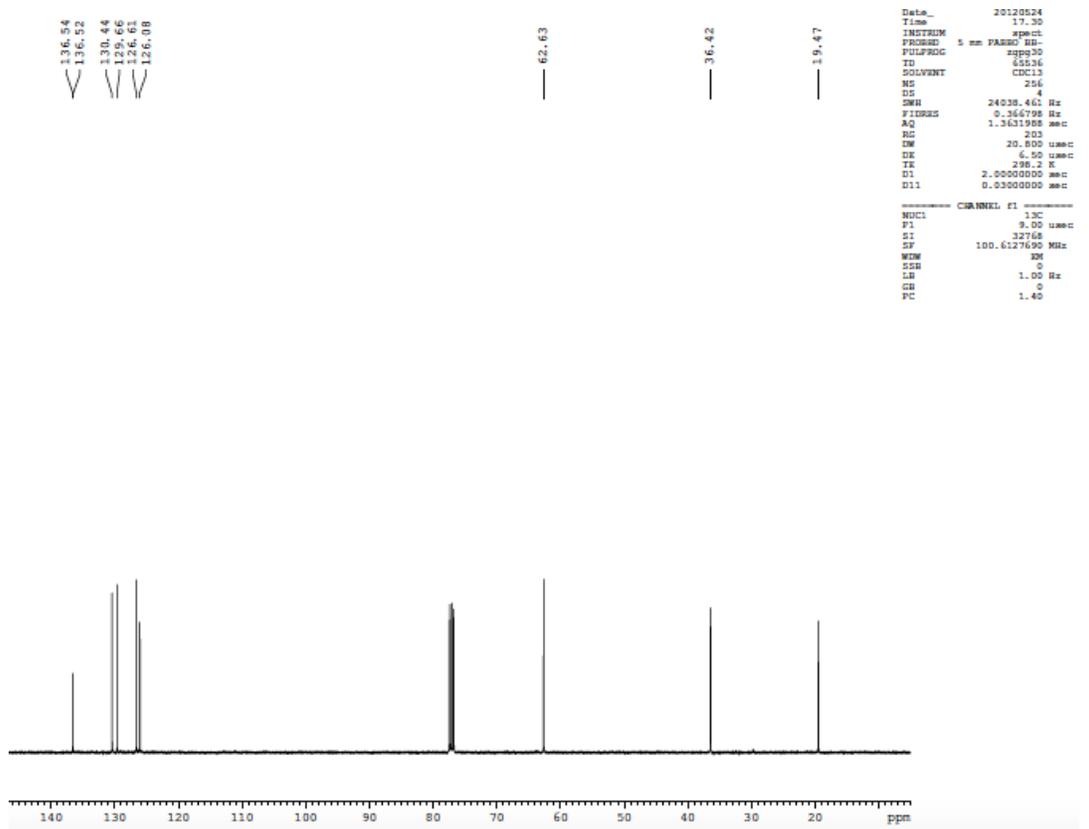
```

Date_      20120524
Time       17.14
INSTRUM    spect
PROBHD     5 mm FAIMS2 BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH        8321.685 Hz
FIDRES     0.112483 Hz
AQ         3.9546287 sec
RG         32
WDW        EM
DE         60.800 usec
TE         297.2 K
D1         1.00000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         14.00 usec
SI         62536
SF         400.1300225 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
  
```



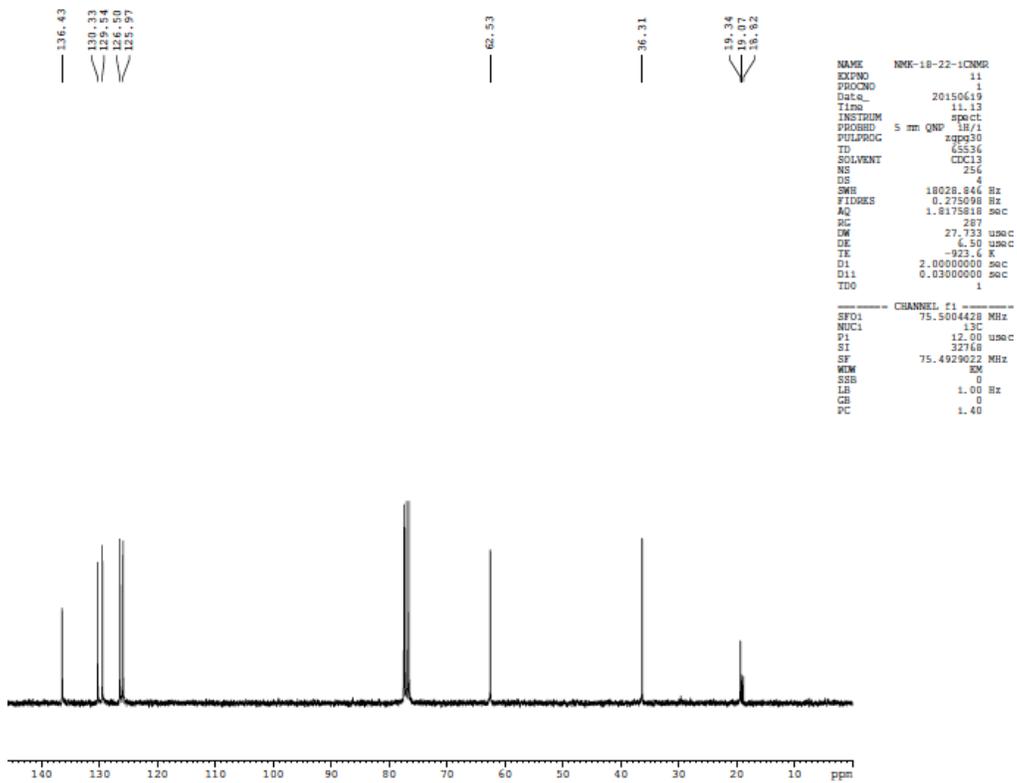
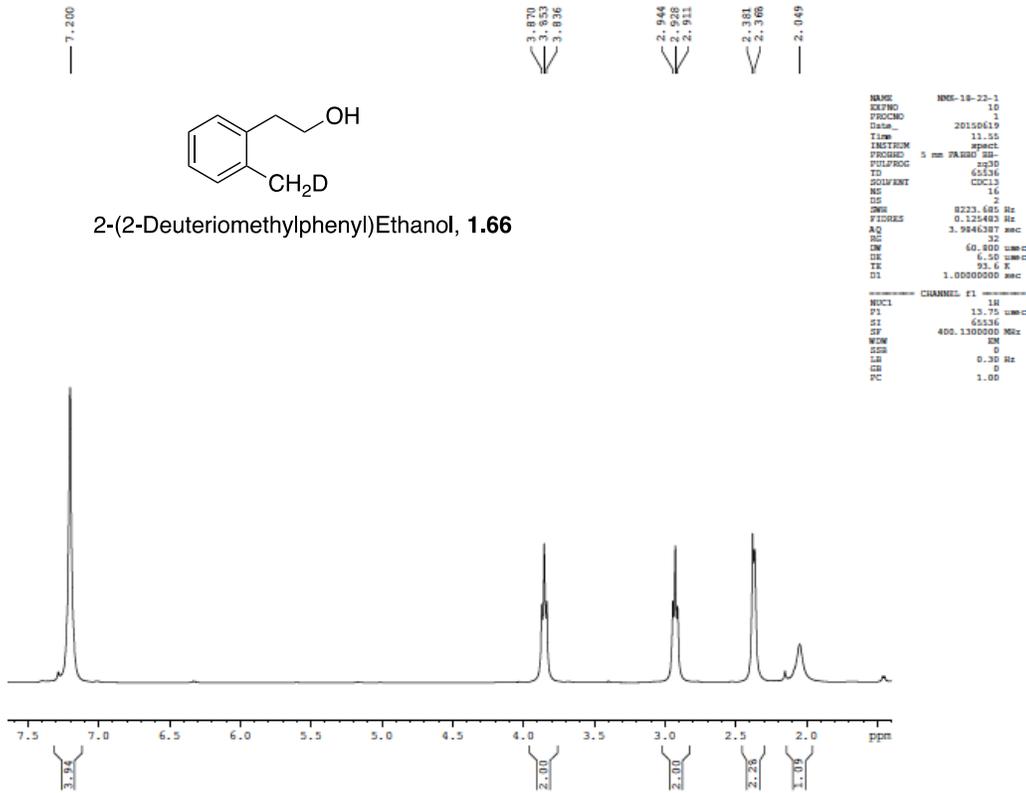
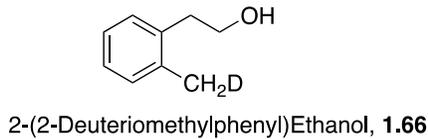
2-(2-Methylphenyl)Ethanol, **1.65**



```

Date_      20120524
Time       17.30
INSTRUM    spect
PROBHD     5 mm FAIMS2 BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         256
DS         4
SWH        24938.46 Hz
FIDRES     0.364798 Hz
AQ         1.3631988 sec
RG         203
WDW        EM
DE         20.800 usec
TE         298.2 K
D1         2.00000000 sec
D11        0.03000000 sec

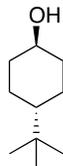
===== CHANNEL f1 =====
NUC1       13C
P1         9.00 usec
SI         32768
SF         100.6127690 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
  
```



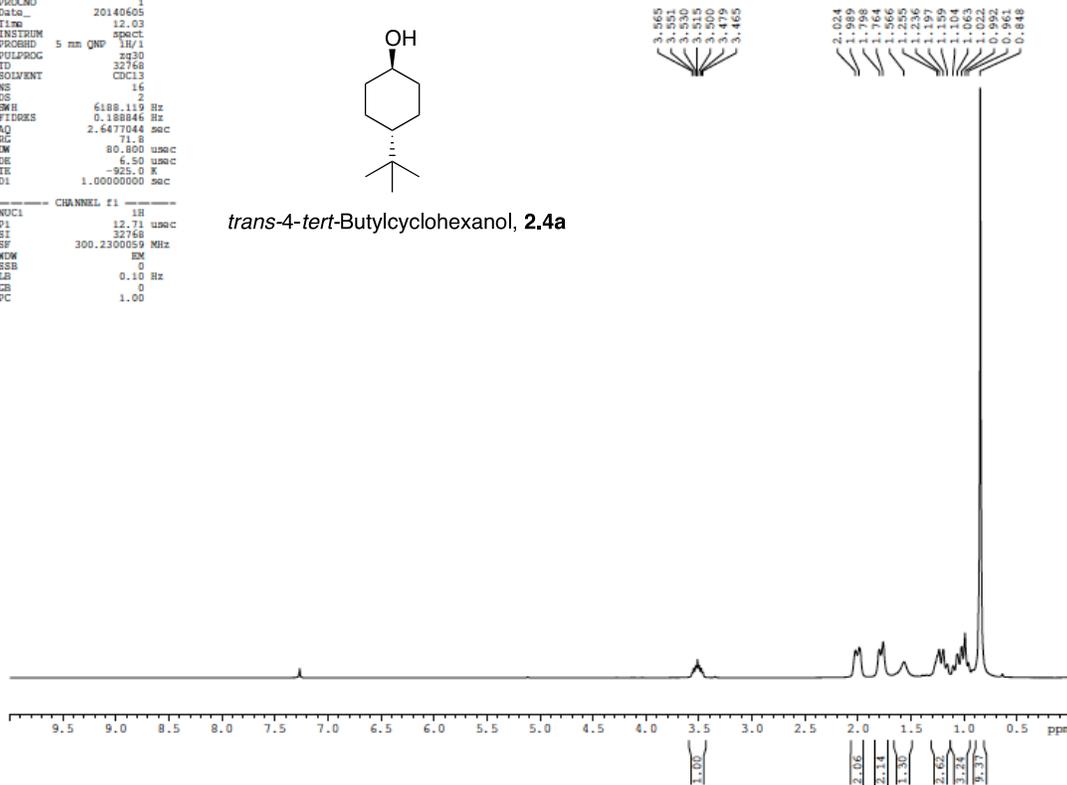
```

PULPROG 1
Date_ 20140605
Time 12.03
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 2
DS 16
SWH 6188.119 Hz
FIDRES 0.188846 Hz
AQ 2.6477044 sec
RG 71.8
EM 80.800 usec
DE 6.50 usec
TE -925.0 K
D1 1.0000000 sec

```



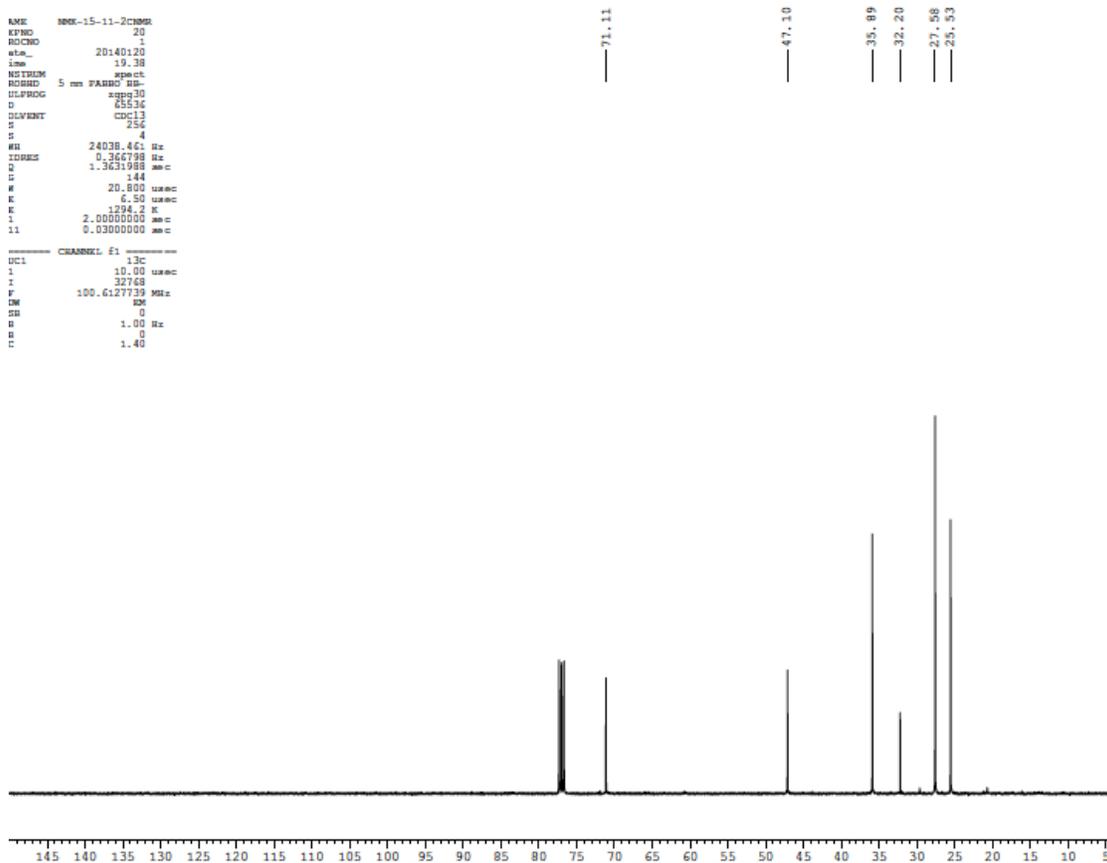
trans-4-*tert*-Butylcyclohexanol, 2,4a



```

NAME 00K-15-11-2000K
EXPNO 20
PROCNO 1
Date_ 20140120
Time 19.38
INSTRUM spect
PROBHD 5 mm F4000 QNP
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 4
DS 256
SWH 24038.441 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 344
EM 20.800 usec
DE 6.50 usec
TE 1294.2 K
D1 2.0000000 sec
D11 0.0300000 sec

```



```

EXPNO      10
PROCNO     1
Data_      20140901
Time       12.16
INSTRUM    spect
PROBHD     5 mm QNP 1H/1
PULPROG    zg30
TD          32768
SOLVENT    CDCl3
NS          16
DS          2
SWH         6188.119 Hz
FIDRES     0.188846 Hz
AQ          2.6471044 sec
RG          28.5
RW          80.800 usec
DE          6.50 usec
TE          -923.7 K
D1          1.0000000 sec
TD0         1

----- CHANNEL f1 -----
SFO1       300.2318540 MHz
NUC1        1H
P1          12.71 usec
SI          32768
SF          300.2300095 MHz
WEM         EM
SSB         0
LB          0.10 Hz
GB          0
PC          1.00

```



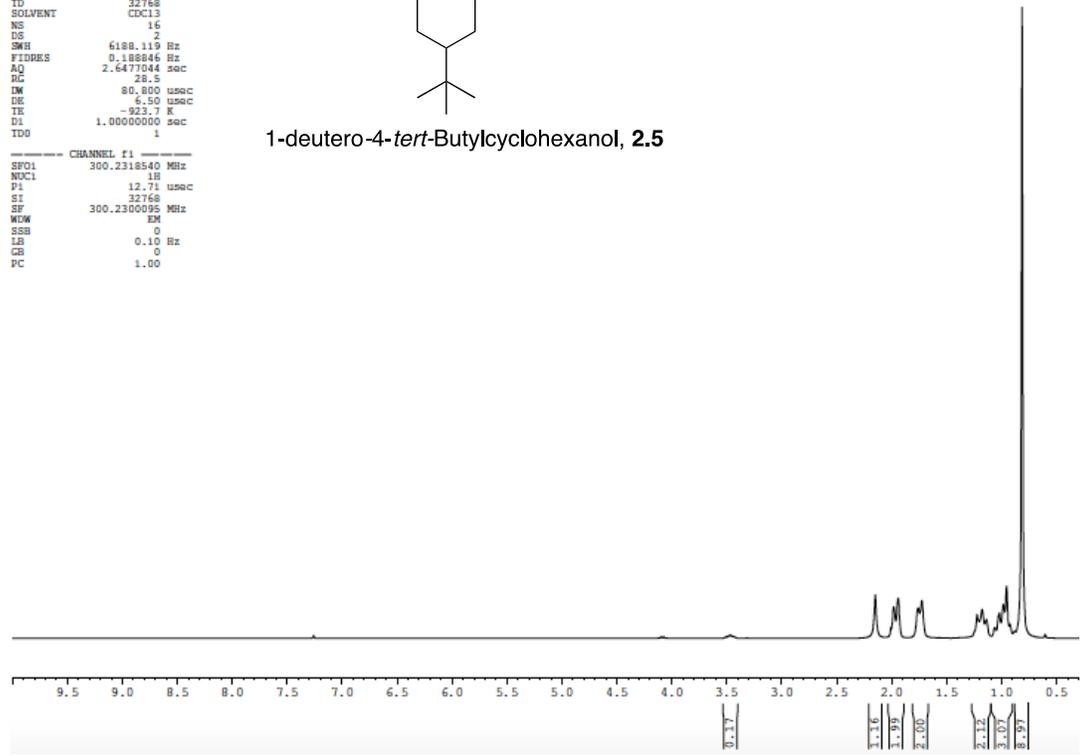
1-deutero-4-*tert*-Butylcyclohexanol, 2,5

```

3.439
3.375
3.483
3.469
3.454
3.433
3.419

2.148
1.980
1.940
1.756
1.724
1.776
1.137
1.062
1.019
0.979
0.923
0.832

```



```

PROBHD     5 mm QNP 1H/1
PULPROG    zgpg30
TD          65536
SOLVENT    CDCl3
NS          256
DS          4
SWH         18028.846 Hz
FIDRES     0.275098 Hz
AQ          1.8175818 sec
RG          287
RW          27.733 usec
DE          6.50 usec
TE          -923.6 K
D1          2.0000000 sec
D11         0.0300000 sec
TD0         1

----- CHANNEL f1 -----
SFO1       75.5004428 MHz
NUC1        13C
P1          12.00 usec
SI          32768
SF          75.4928981 MHz
WEM         EM
SSB         0
LB          1.00 Hz
GB          0
PC          1.40

```

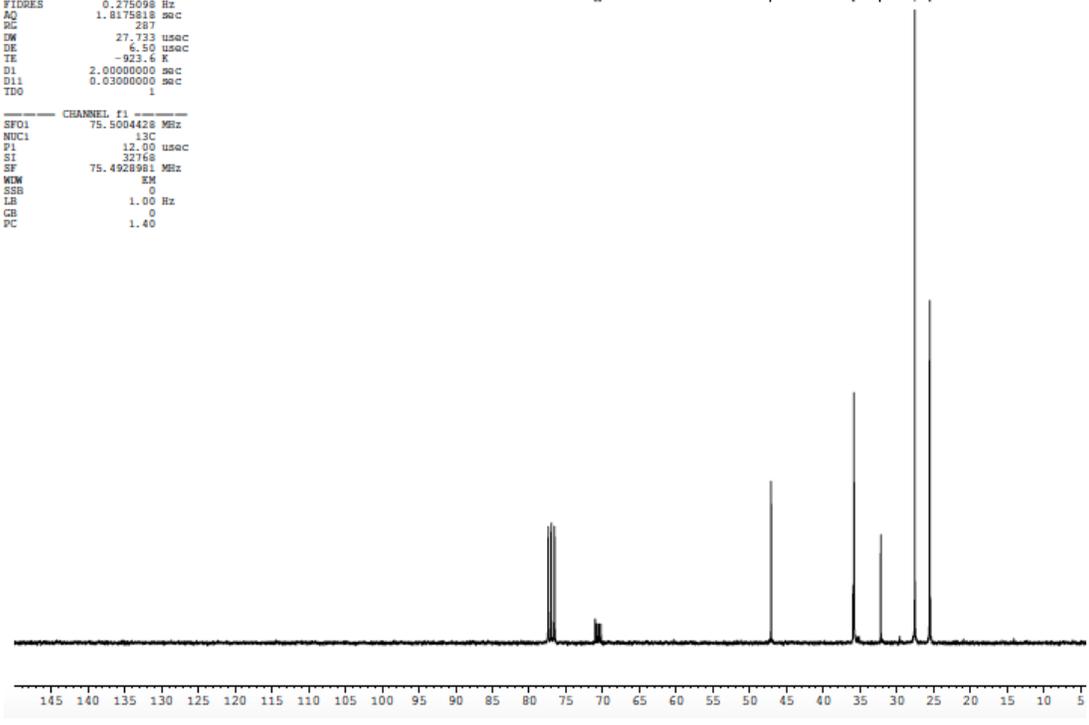
```

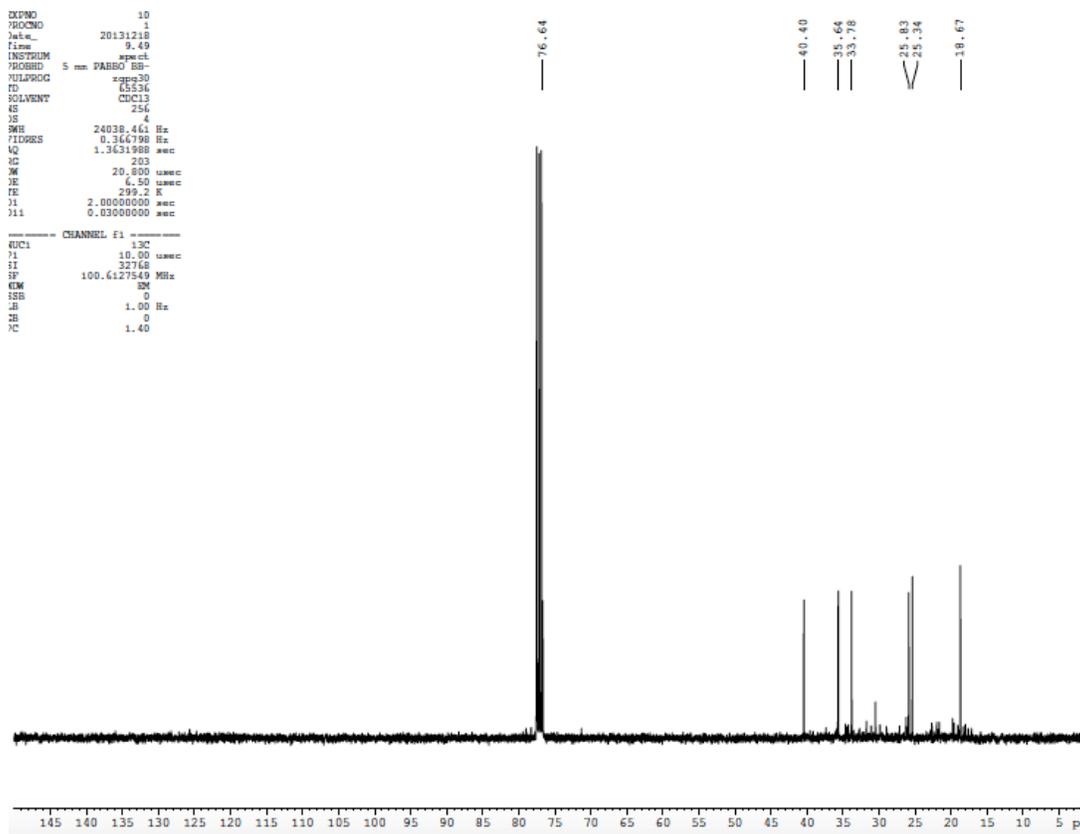
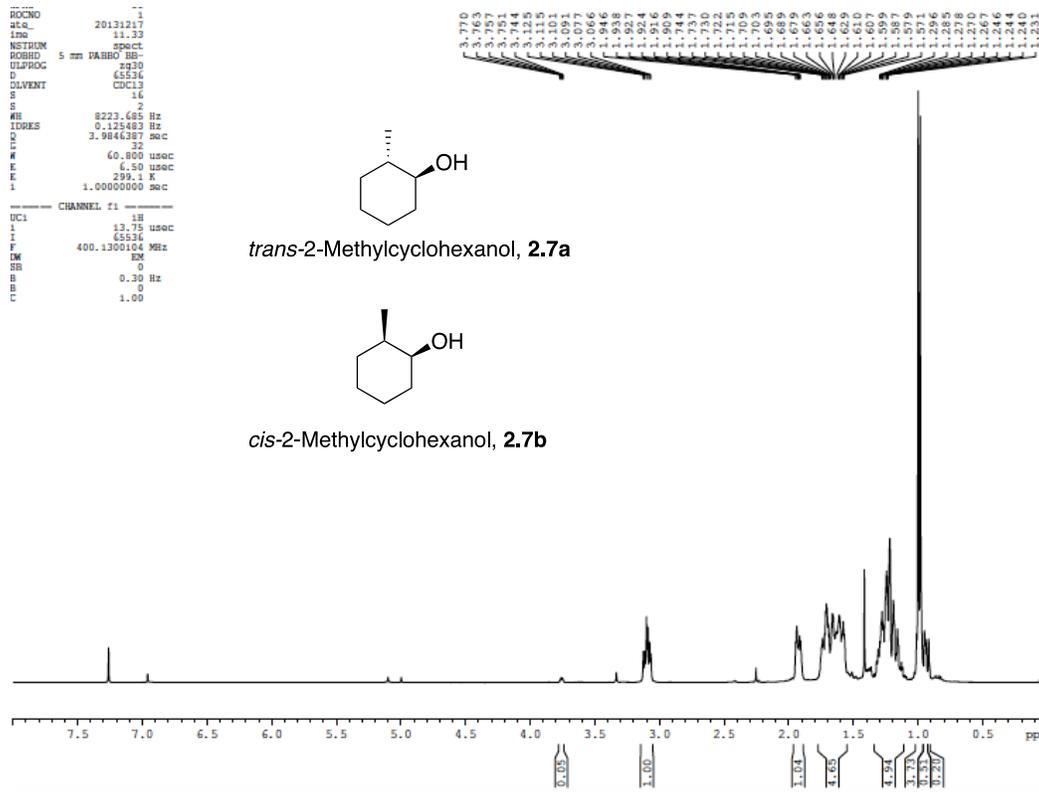
71.03
70.83
70.55
70.26

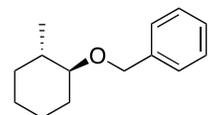
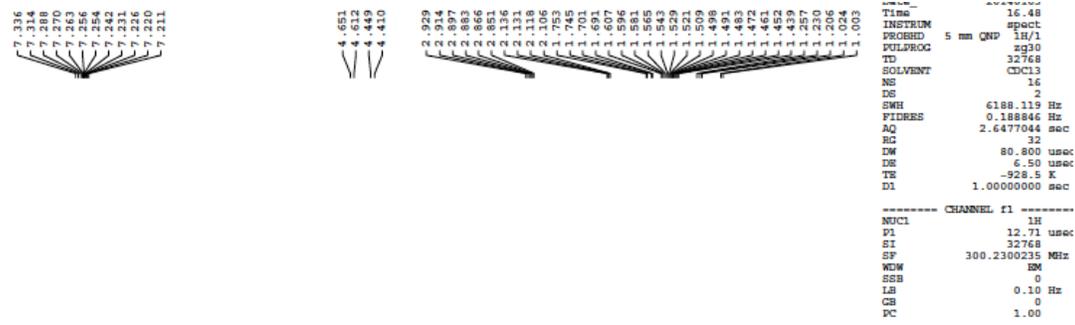
47.12

35.95
35.84
32.19
27.57
25.85
25.45

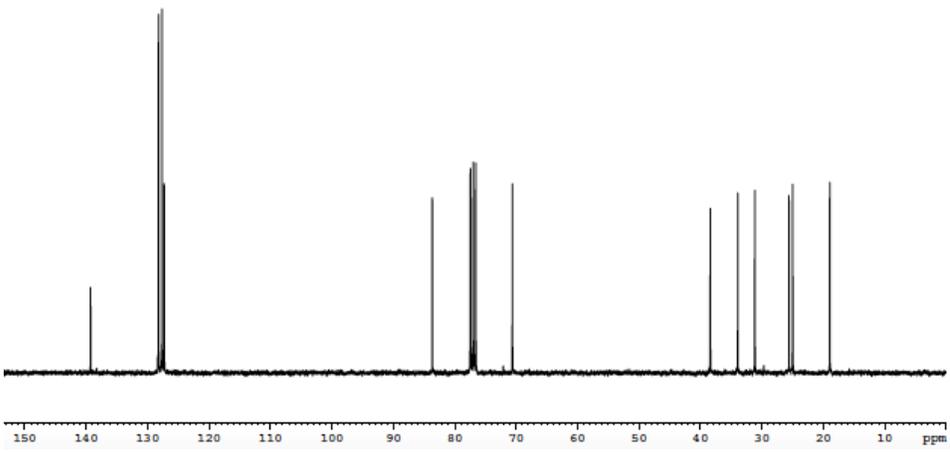
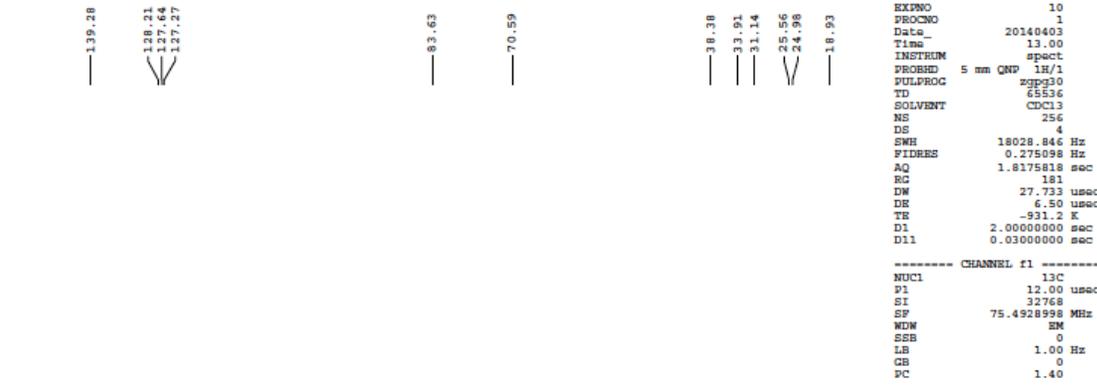
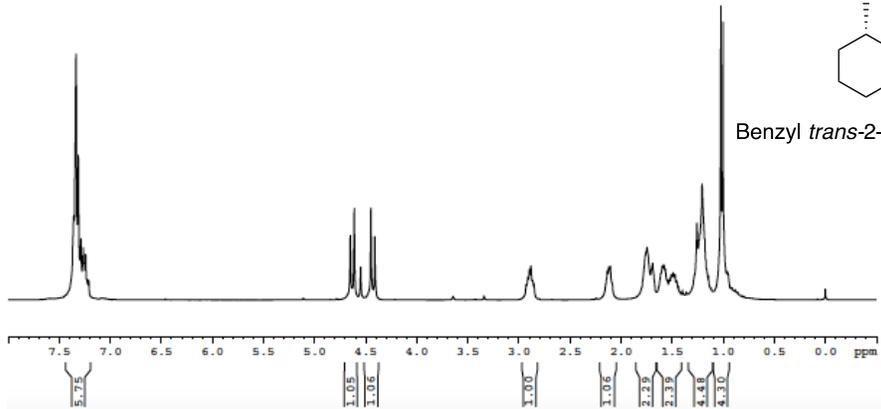
```







Benzyl *trans*-2-Methylcyclohexyl Ether, 2.8



```

NAME      NMR-15-29-4
EXPNO     10
PROCNO    1
Date_     20140217
Time      15.00
INSTRUM   spect
PROBHD    5 mm PARBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH        8233.685 Hz
FIDRES     0.125483 Hz
AQ         3.9846387 sec
RG         20.2
LW         60.800 usec
DE         6.50 usec
TE         1386.4 K
D1         1.00000000 sec

----- CHANNEL f1 -----
NUC1       1H
P1         13.75 usec
SI         65536
SF         400.1300044 MHz
MSB        0
LB         0.30 Hz
GB         0
PC         1.00

```

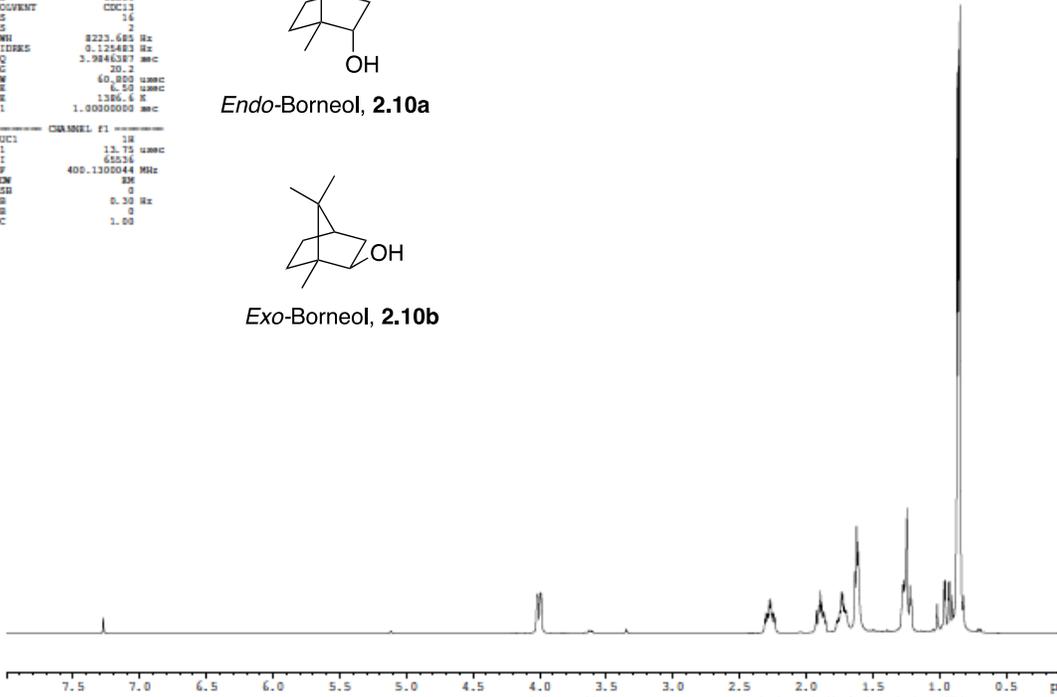


Endo-Borneol, 2.10a



Exo-Borneol, 2.10b

4.019
4.015
3.984
3.980
3.633
3.622
3.615
3.604
3.302
2.291
2.286
2.287
2.257
2.253
2.244
2.233
1.984
1.903
1.893
1.873
1.865
1.853
1.720
1.710
1.746
1.725
1.725
1.701
1.693
1.634
1.622
1.622
1.275
1.265
1.254
1.244
1.221
1.210
0.965



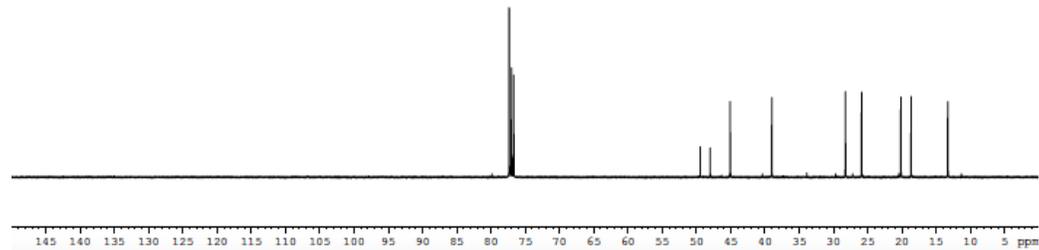
```

CPMG      10
PROCNO    1
Date_     20140217
Time      15.16
INSTRUM   spect
PROBHD    5 mm PARBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         256
DS         4
SWH        24038.464 Hz
FIDRES     0.366798 Hz
AQ         1.3431988 sec
RG         20.3
LW         20.800 usec
DE         6.50 usec
TE         1898.4 K
D1         2.00000000 sec
D11        0.03000000 sec

----- CHANNEL f1 -----
NUC1       13C
P1         10.00 usec
SI         32768
SF         100.6127717 MHz
MSB        0
LB         1.00 Hz
GB         0
PC         1.40

```

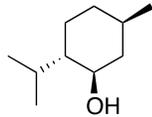
77.32
49.45
47.98
45.06
38.98
26.24
25.88
20.15
16.64
13.29



```

NAME_      20140528
EXP_       21.03
INSTRUM    spect
PROBHD     5 mm QNP 1H/1
PULPROG    zgpg30
D          32768
SOLVENT    CDCl3
S          16
SI         2
FIDRES     6188.119 Hz
AQRES      0.188844 sec
Z         2.6477044 sec
D          50.8
E         80.800 usec
S         6.50 usec
K         -925.9 K
SI         1.0000000 sec

```

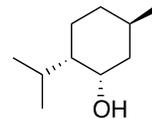


(-)-Menthol, 2.12a

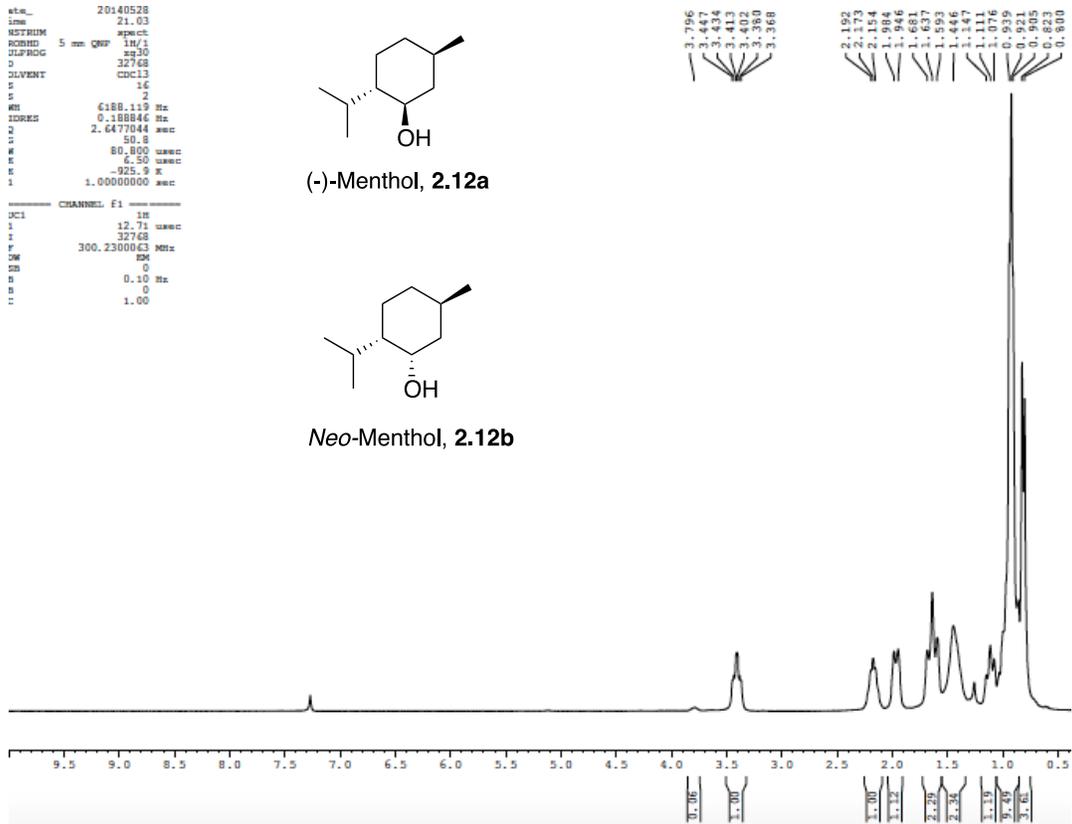
```

----- CHANNEL f1 -----
NUC1       13C
P1         12.71 usec
S          32768
F          300.2300063 MHz
DM         RM
SB         0
S          0.10 Hz
SI         0
SI         1.00

```



Neo-Menthol, 2.12b



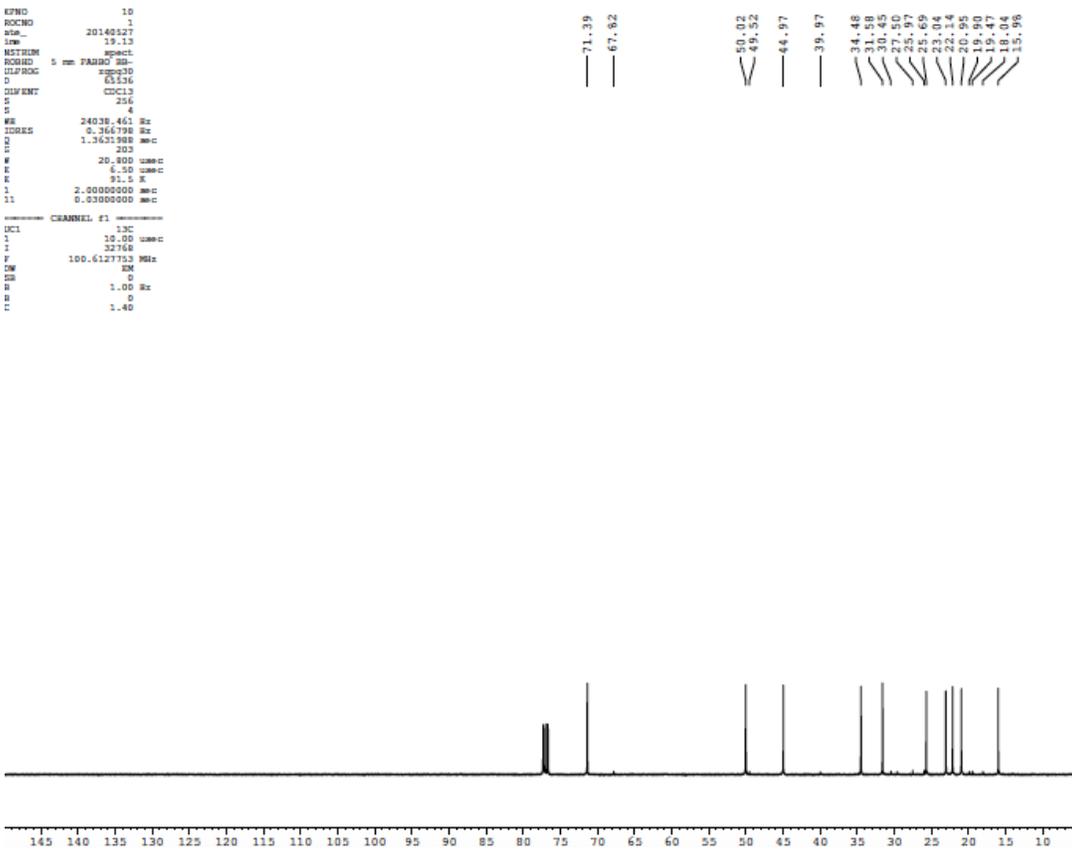
```

ETHC       10
ROBHD      1
EXP_       20140527
EXP_       19.13
INSTRUM    spect
PROBHD     5 mm PABBO BB
PULPROG    zgpg30
D          65536
SOLVENT    CDCl3
S          256
SI         4
FIDRES     24038.461 Hz
AQRES      0.366798 Hz
Z         1.3631988 sec
DM         RM
SB         0
S          20.800 usec
E         6.50 usec
K         91.5 K
SI         2.0000000 sec
SI         0.0000000 sec

```



(-)-Menthol, 2.12a

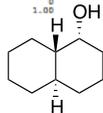


```

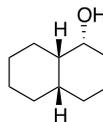
NAME      1
PROCNO    1
DATA_     20140224
Date_     11.30
INSTRUM   spect
PROBHD    5 mm PABBO 2H-
PULPROG   zgpg30
ID        65536
SOLVENT   CDCl3
NS        16
DS        4
SWH       8233.685 Hz
FIDRES    0.125483 Hz
AQ        3.2846387 sec
RG        12.7
SM        60.800 usec
JE        6.50 usec
TE        293.2 K
DE        792.4 Hz
SI        1.00000000 sec
SI1       1.00000000 sec

===== CHANNEL f1 =====
NUC1      13C
P1        12.00 usec
SI        32748
SF        75.4928987 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

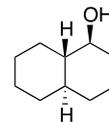
```



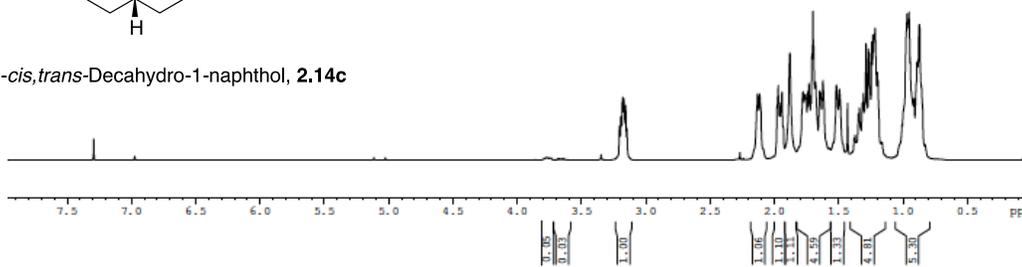
(±)-*trans,trans*-Decahydro-1-naphthol, **2.14b**



(±)-*cis,trans*-Decahydro-1-naphthol, **2.14c**



(±)-*trans,cis*-Decahydro-1-naphthol, **2.14a**

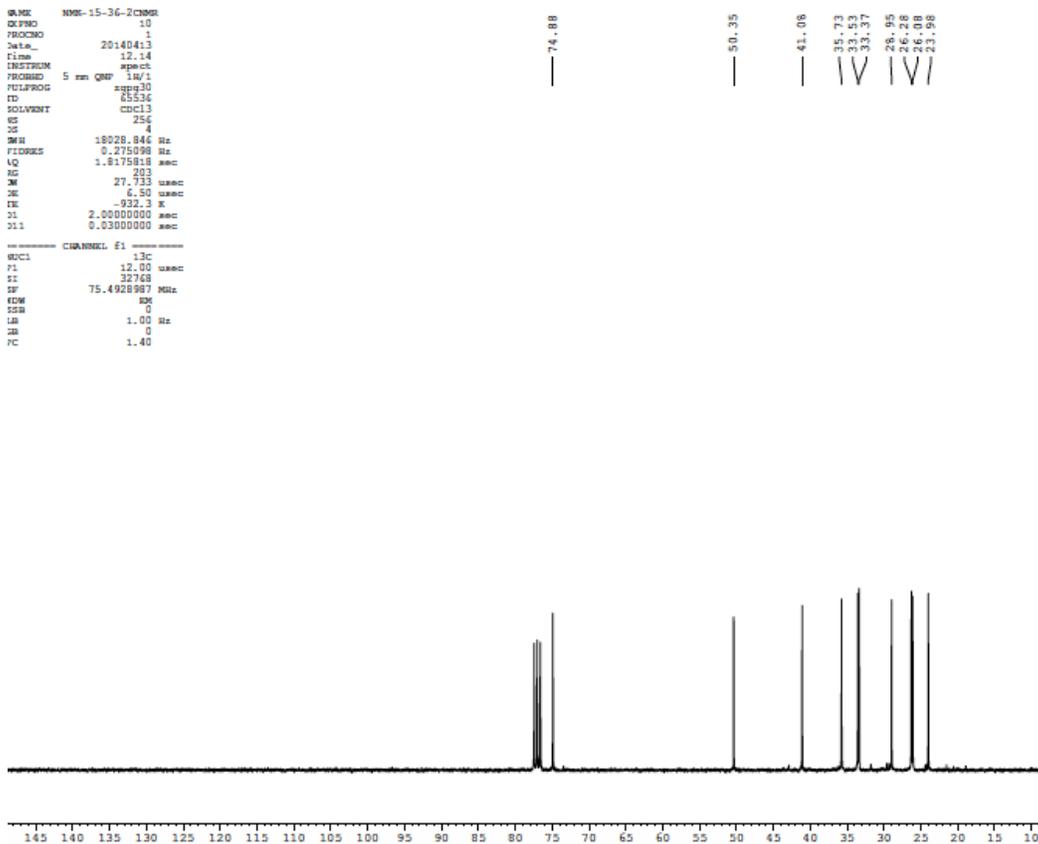


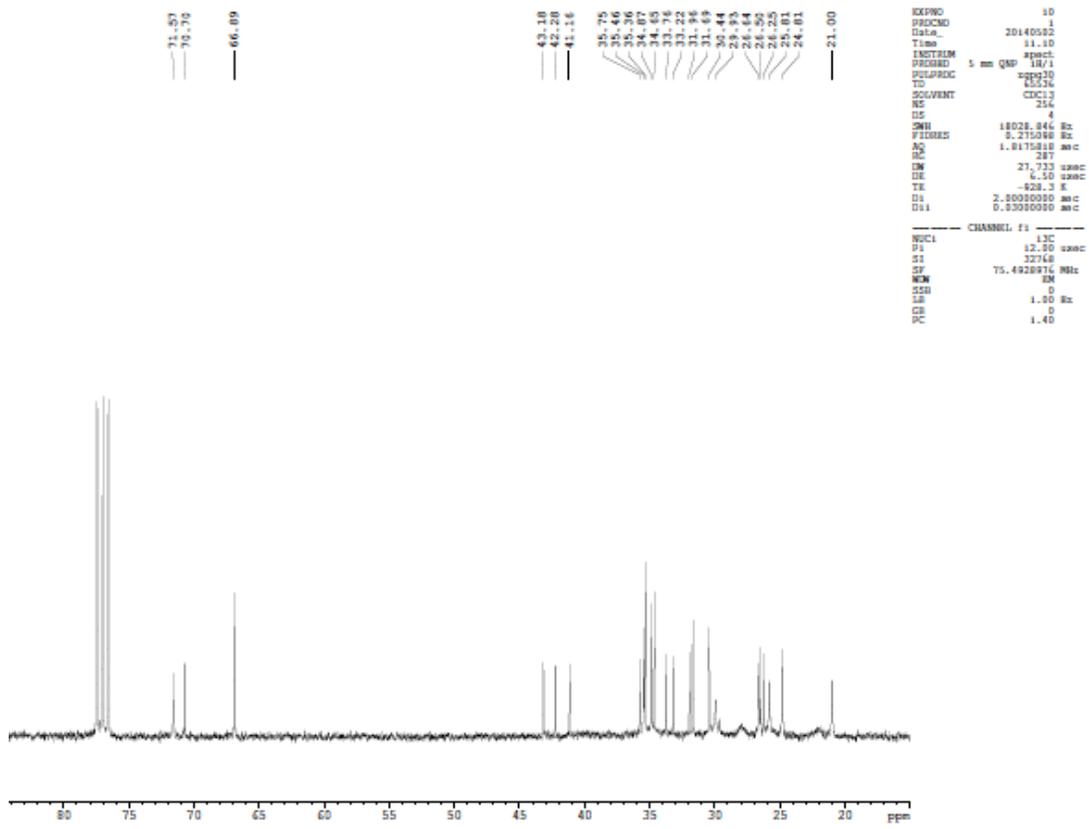
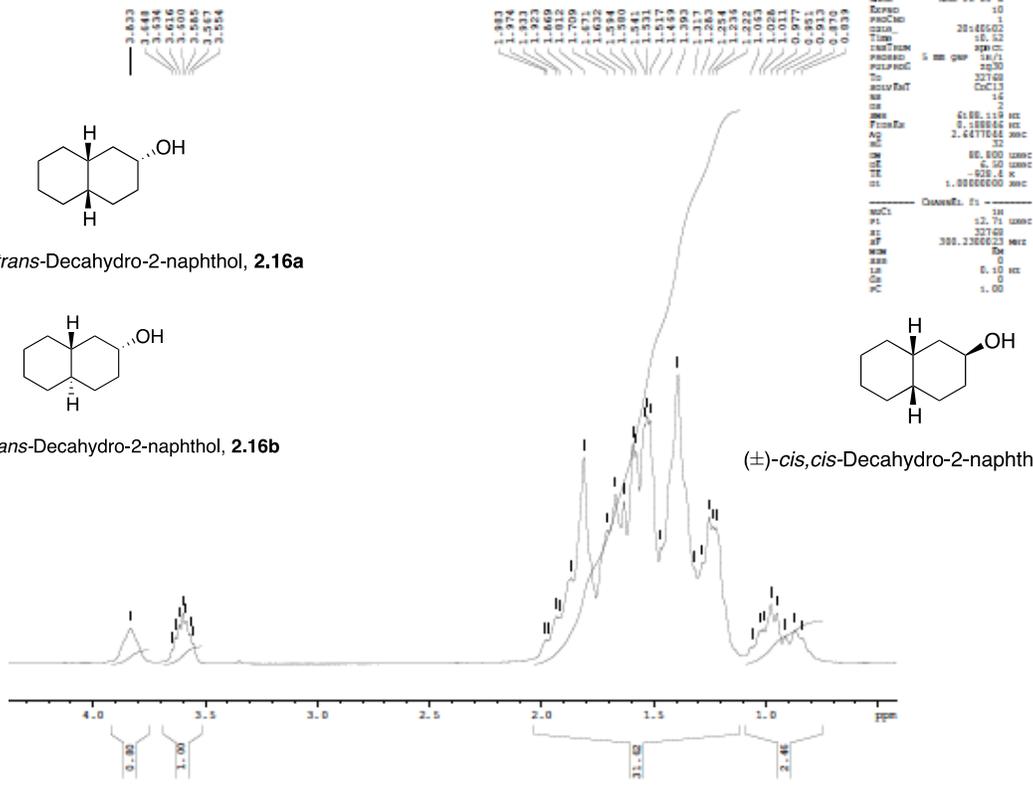
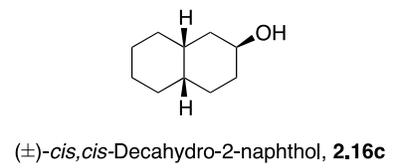
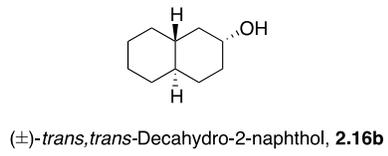
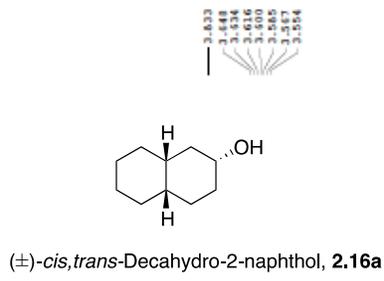
```

NAME      NMR-15-36-2CHMR
PROCNO    1
DATA_     20140413
Date_     12.14
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zgpg30
ID        65536
SOLVENT   CDCl3
NS        256
DS        4
SWH       18028.846 Hz
FIDRES    0.275098 Hz
AQ        1.8175818 sec
RG        203
SM        27.733 usec
JE        6.50 usec
TE        -932.3 K
DE        2.00000000 sec
SI        0.23000000 sec
SI1       0.23000000 sec

===== CHANNEL f1 =====
NUC1      13C
P1        12.00 usec
SI        32748
SF        75.4928987 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```



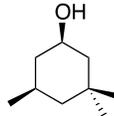


```

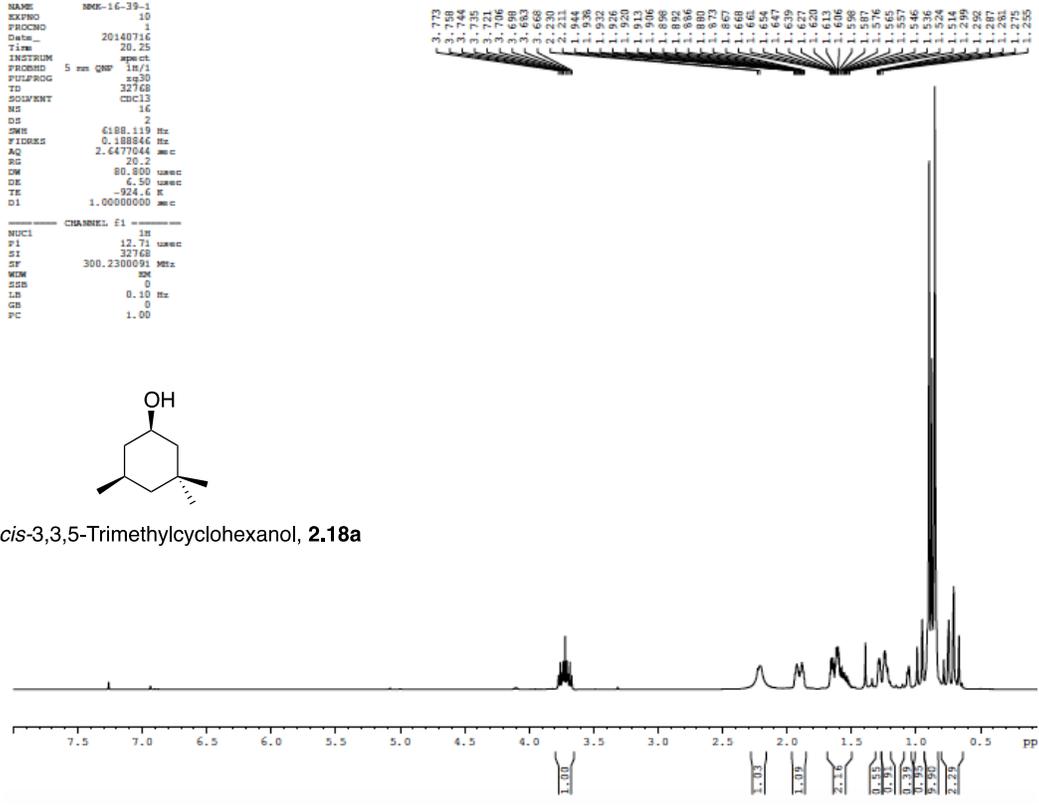
NAME      NMR-16-39-1
EXPNO    10
PROCNO   1
Date_    20140716
Time     20.25
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zg30
TD        32768
SOLVENT  CDCl3
NS        16
DS        2
SWH       6188.119 Hz
FIDRES    0.188844 Hz
AQ        2.6477044 sec
RG        20.2
DM        80.800 usec
DE        6.50 usec
TE        -82.4 K
D1        1.00000000 sec
  
```

```

----- CHANNEL f1 -----
NUC1      1H
P1        12.71 usec
SI        32768
SF        300.2300091 MHz
WDW       EM
SSB       0
LB        0.10 Hz
GB        0
PC        1.00
  
```



cis-3,3,5-Trimethylcyclohexanol, **2.18a**

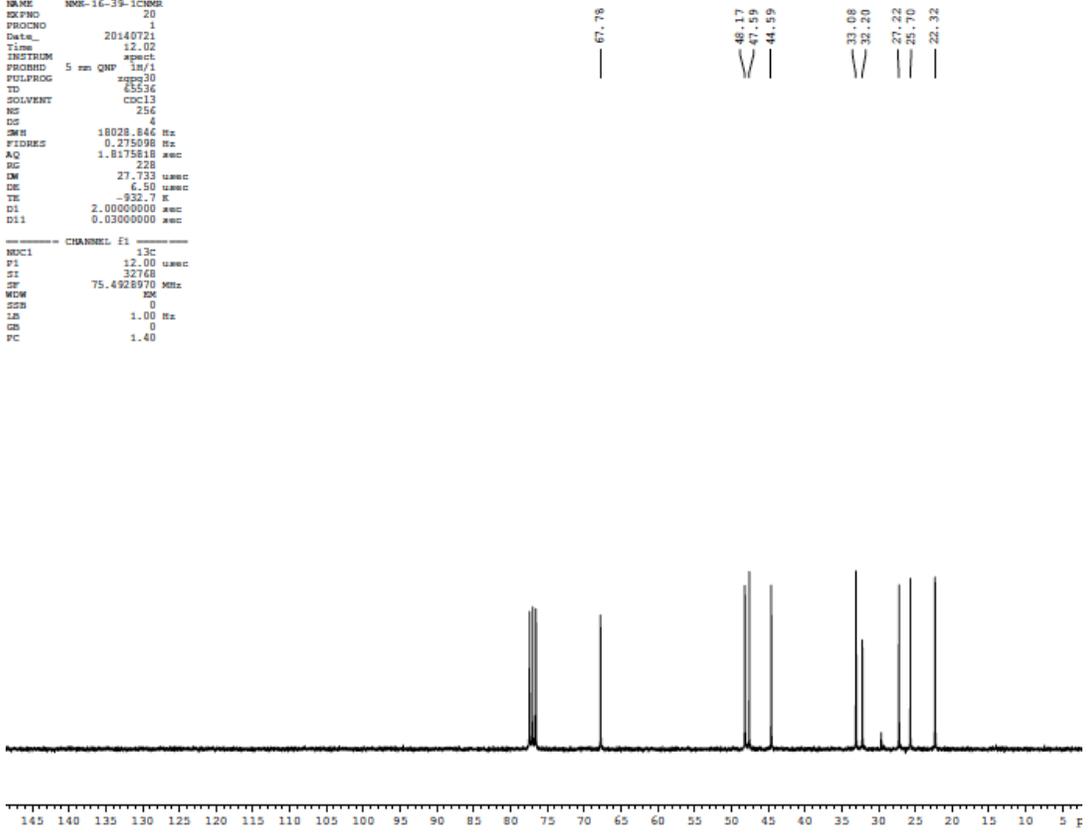


```

NAME      NMR-16-39-1CHMR
EXPNO    20
PROCNO   1
Date_    20140721
Time     12.02
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        256
DS        4
SWH       18028.844 Hz
FIDRES    0.275098 Hz
AQ        1.8175818 sec
RG        228
DM        27.733 usec
DE        6.50 usec
TE        -82.7 K
D1        2.00000000 sec
D11       0.03000000 sec
  
```

```

----- CHANNEL f1 -----
NUC1      13C
P1        12.00 usec
SI        32768
SF        75.4928970 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```



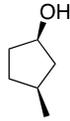
```

KPCNO 20
ROCN0 1
ata_ 20150301
ime 16.06
NSTRUM spect
ROBHD 5 mm PABBO BB-
ULFROG zg30
D 65536
OLVENT CDC13
S 16
S 4
MH 8223.685 Hz
IDRES 0.125483 Hz
Q 3.9846387 sec
C 32
W 60.800 usec
E 6.50 usec
R 768.0 K
I 1.00000000 sec

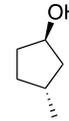
----- CHANNEL F1 -----
DC1 1H
I 13.75 usec
F 400.1300064 MHz
SW KM
SB 0
B 0.30 Hz
C 1.00

```

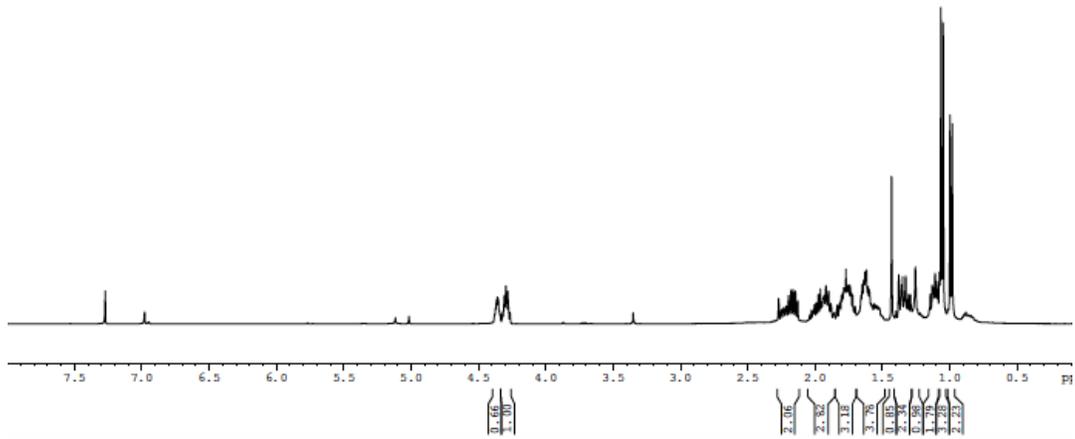
4.374
4.367
4.360
4.353
4.346
4.322
4.307
4.296
4.282
2.275
2.197
2.179
2.163
2.147
2.131
2.049
1.976
1.961
1.937
1.932
1.920
1.884
1.884
1.837
1.771
1.759
1.740
1.740
1.703
1.659
1.649
1.639
1.618
1.607
1.598
1.564
1.561
1.532
1.432
1.379
1.358
1.350
1.328
1.306
1.292
1.285



cis-3-Methylcyclopentanol, **2.20a**



trans-3-Methylcyclopentanol, **2.20b**



```

ARS NMR-1 F-4U-1105K
XPRO 30
ROCN0 1
ata_ 20150303
ime 13.23
NSTRUM spect
ROBHD 5 mm PABBO BB-
ULFROG zg30
D 65536
OLVENT CDC13
S 256
S 4
MH 24038.461 Hz
IDRES 0.366798 Hz
Q 1.5631988 sec
C 203
W 20.800 usec
E 6.50 usec
R 770.9 K
I 2.00000000 sec
I1 0.03000000 sec

----- CHANNEL F1 -----
DC1 13C
I 10.00 usec
F 100.6127783 MHz
SW KM
SB 0
B 1.00 Hz
C 1.40

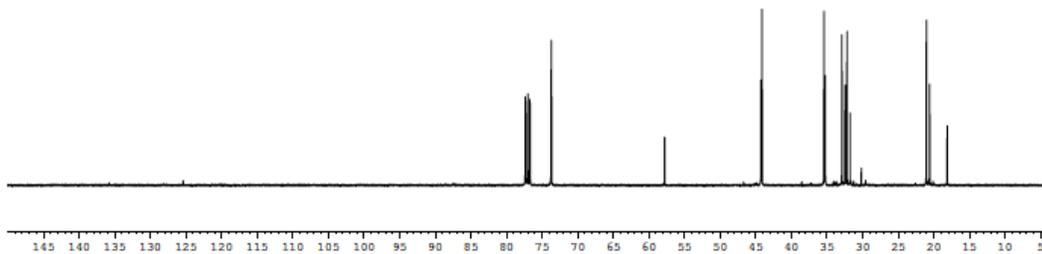
```

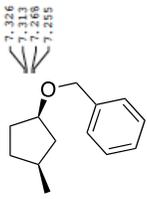
73.72
73.66

44.27
44.10

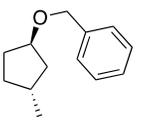
35.40
35.24
32.89
32.43
31.75

31.03
30.56





Benzyl *cis*-3-Methylcyclopentyl Ether, **2.21a**



Benzyl *trans*-3-Methylcyclopentyl Ether, **2.21b**

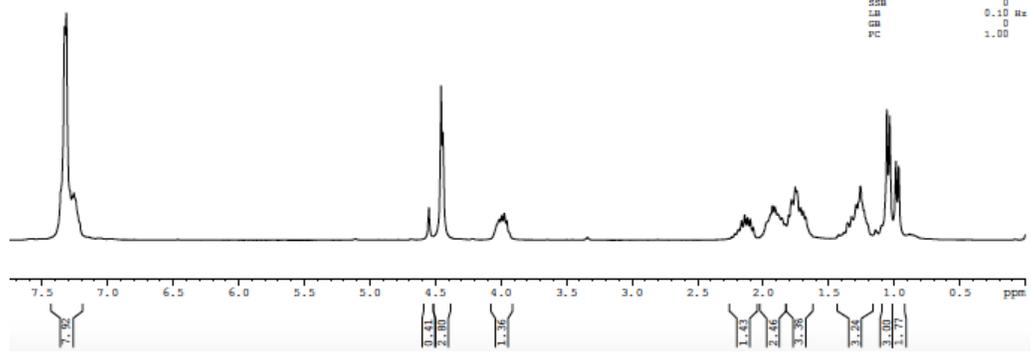
4.549
4.456
4.442

4.012
3.983
3.974
3.956

2.212
2.189
2.164
2.141
2.119
2.094
2.075
1.944
1.930
1.911
1.892
1.887
1.833
1.804
1.783
1.742
1.715
1.694
1.676
1.656
1.377
1.317
1.291
1.268
1.250
1.231
1.056
1.034
0.988
0.966

```

NAME      INE-17-43-2
EXPNO    30
PROCNO   1
Date_    20150307
Time     12.00
INSTRUM  spect
PROBHD   5 mm QNP
PULPROG  zgpg30
TD       32768
SOLVENT  CDCl3
NS       16
DS       2
SWH      6188.119 Hz
FIDRES   0.188846 Hz
AQ       2.6477044 sec
RG       32
DM       80.800 um
SFE      6.50 um
TK       -93.1 K
D1       1.0000000 sec
TD0      1
  
```



139.02
136.28

126.34
126.24
127.71
127.53
127.26

80.88

72.09
70.83
70.55

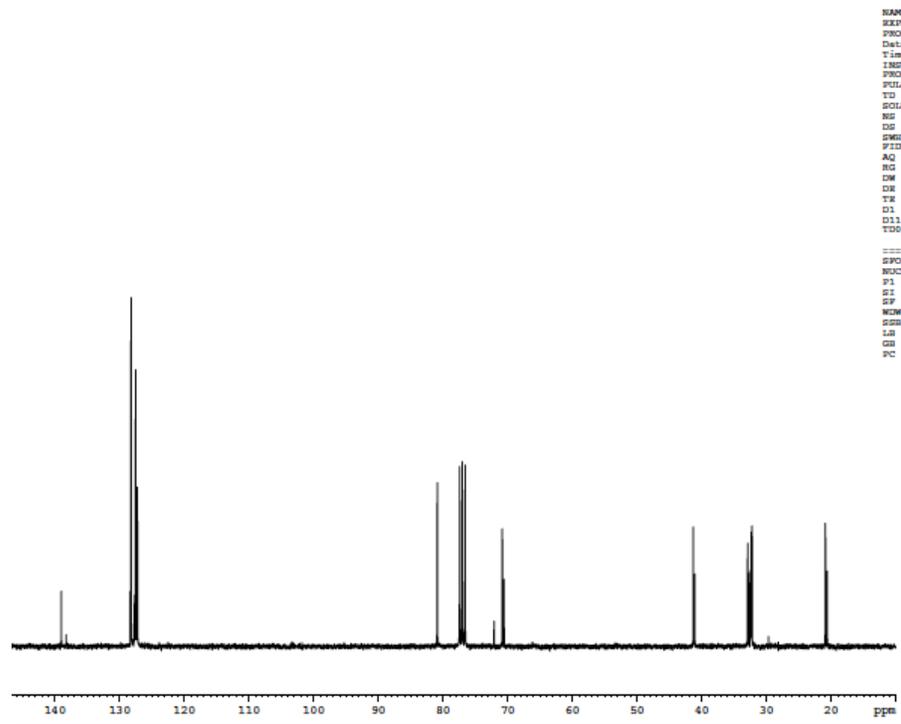
41.20

32.89
32.72
32.35
32.21
32.19

20.88
20.58

```

===== CHANNEL f1 =====
SFO1     300.2318540 MHz
NUC1     1H
P1       12.71 um
SI       32768
SF       300.2302040 MHz
WDW      EM
SSB      0
LB       0.10 Hz
GB       0
PC       1.00
  
```



```

NAME      INE-17-43-2CONH
EXPNO    10
PROCNO   1
Date_    20150307
Time     12.31
INSTRUM  spect
PROBHD   5 mm QNP
PULPROG  zgpg30
TD       65536
SOLVENT  CDCl3
NS       256
DS       4
SWH      18028.846 Hz
FIDRES   0.275098 Hz
AQ       1.8178818 sec
RG       322
DM       27.733 umsec
SFE      6.50 umsec
TK       -93.8 K
D1       2.0000000 sec
D11      0.0300000 sec
TD0      1
  
```

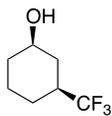
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===== CHANNEL f1 =====
SFO1     75.5004428 MHz
NUC1     13C
P1       12.00 umsec
SI       32768
SF       75.4929003 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
  
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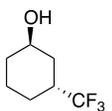
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NAME      NMR-17-46-1
EXPNO    10
PROCNO   1
Date_    20150309
Time     15.16
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zg30
TD        32768
SOLVENT  CDCl3
NS        16
DS        2
SWE       6188.119 Hz
FIDRES   0.188846 Hz
AQ        2.6477044 sec
RG         57
DM        80.800 usec
DE        6.50 usec
TE        -931.3 K
D1        1.0000000 sec
D11       1
TDO       1

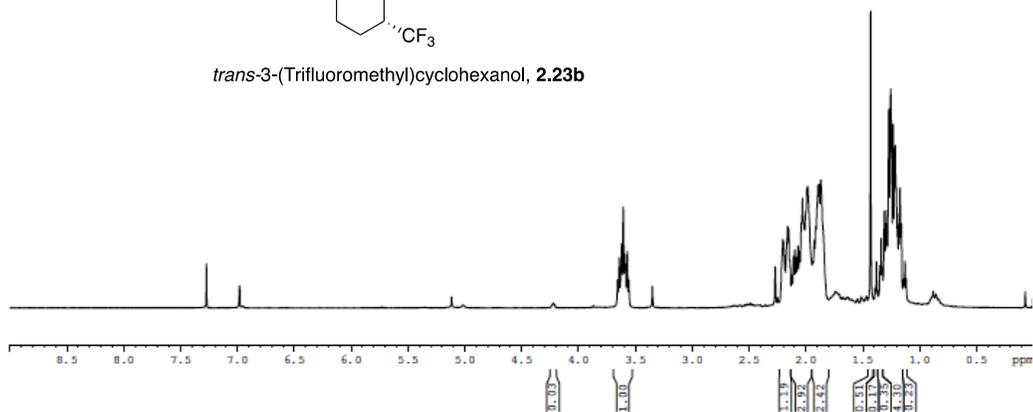
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cis-3-(Trifluoromethyl)cyclohexanol, **2.23a**



trans-3-(Trifluoromethyl)cyclohexanol, **2.23b**



132.68
129.00
125.31
121.62

69.28

41.42
41.06
40.70
40.34
34.72
34.02
33.99
24.02
23.99
23.96
23.92
22.71

```

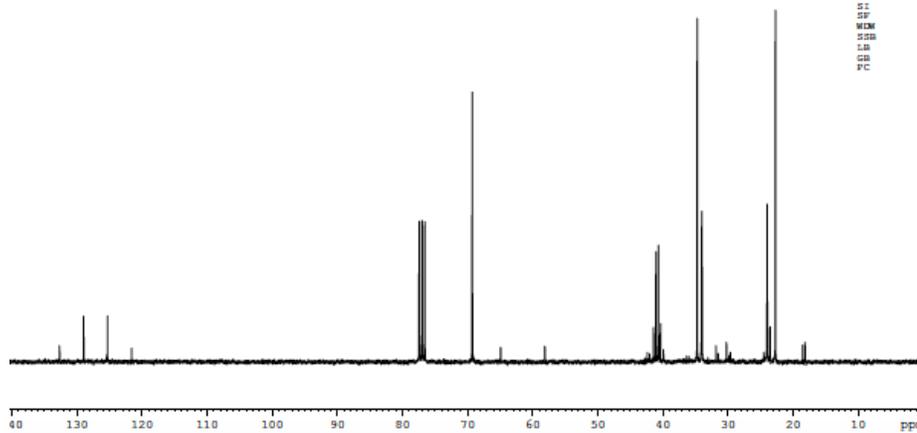
NAME      NMR-17-46-1COND
EXPNO    10
PROCNO   1
Date_    20150322
Time     15.02
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        256
DS        4
SWE       18028.846 Hz
FIDRES   0.275598 Hz
AQ        1.8175818 sec
RG         322
DM        27.733 usec
DE        6.50 usec
TE        -928.0 K
D1        2.0000000 sec
D11       0.0300000 sec
D12       1
TDO       1

```

```

CHANNEL F1
SF01     75.5004428 MHz
NUC1     13C
P1       12.00 usec
SI       32768
SF       75.4908984 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40

```



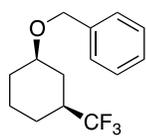
7.362
7.359
7.352
7.348
7.342

4.567

3.361
3.333

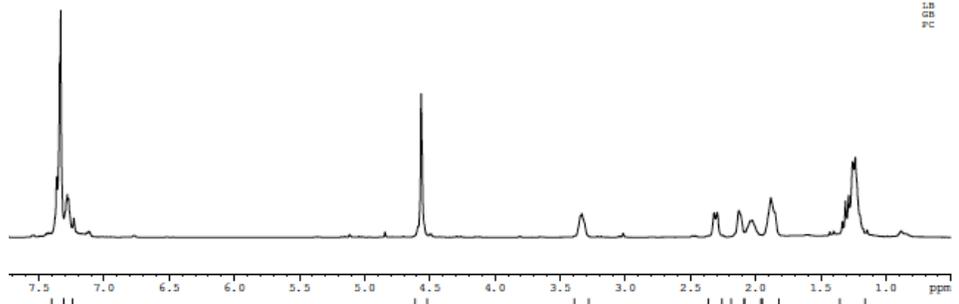
2.318
2.295
2.081
2.061
2.032
2.025
1.983

1.333
1.309
1.286
1.266
1.234



Benzyl *cis*-3-(Trifluoromethyl)cyclohexyl Ether, **2.24**

NAME NMR-17-47-3
EXPNO 10
PROCNO 1
Date_ 20150331
Time 10.57
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
FIDRES 0.16
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.800 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 32
RC 32
CW 50.000 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TDO 1



CHANNEL F1
SFO1 500.1430887 MHz
NUC1 1H
P1 11.45 usec
SI 65536
SF 500.1400272 MHz
WCH RM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

136.61
128.39
127.75
127.53
127.48

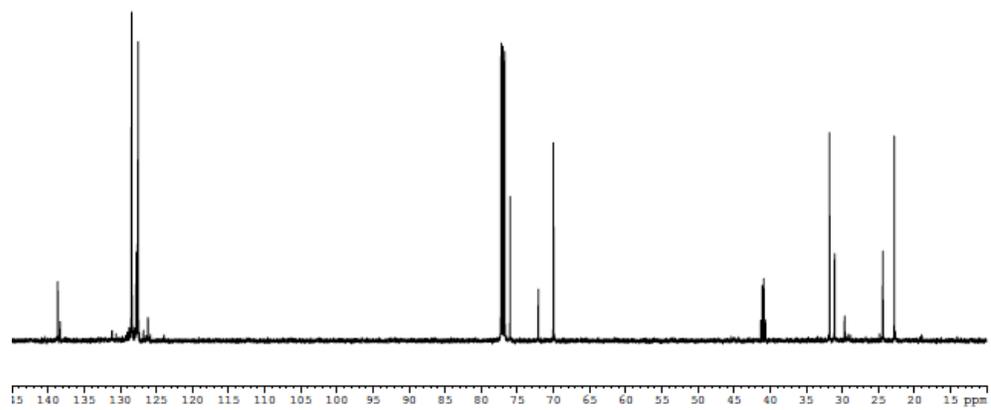
76.02
72.10
70.01

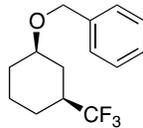
41.28
41.07
40.84
40.64

31.78
31.66
24.38
24.36
22.80

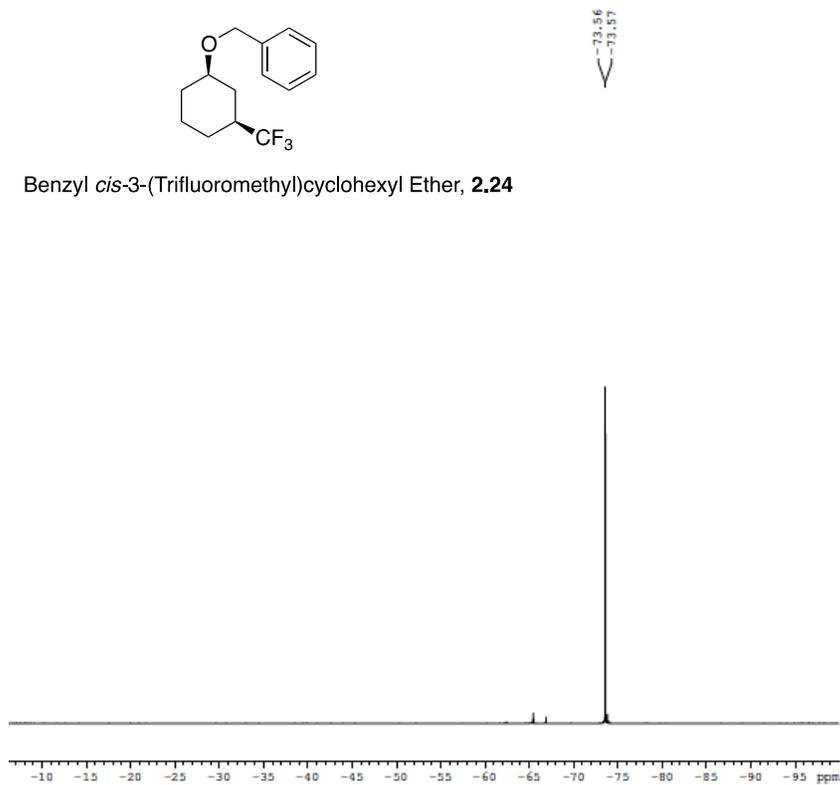
NAME 47170321
Time 11.12
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
FIDRES 0.16
SOLVENT CDCl3
NS 256
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
RC 203
CW 16.800 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1

CHANNEL F1
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
SI 32768
SF 125.7653386 MHz
WCH RM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



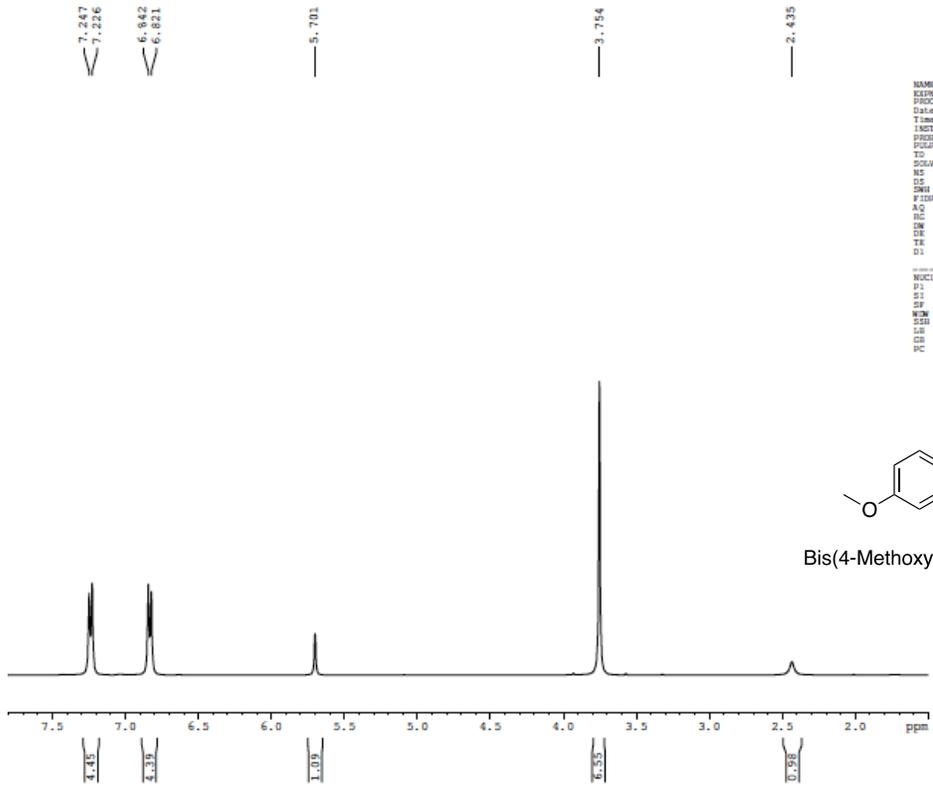


Benzyl *cis*-3-(Trifluoromethyl)cyclohexyl Ether, **2,24**



NAME NMK-17-47-3-FMHR
EXPNO 20
PROCNO 1
Date_ 20150403
Time 16.38
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 113636.367 Hz
FIDRES 0.866977 Hz
AQ 0.5767668 sec
RG 203
RW 4.400 usec
DE 6.50 usec
TE 297.3 K
DI 1.0000000 sec
TD0 1

CHANNEL f1
SFO1 470.5735434 MHz
NUC1 19F
P1 5.00 usec
SI 65536
SF 470.6206054 MHz
WDW EM
SSB 0
LB 0.30 Hz
CB 0
PC 1.00

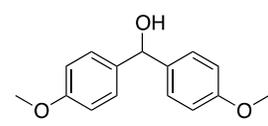


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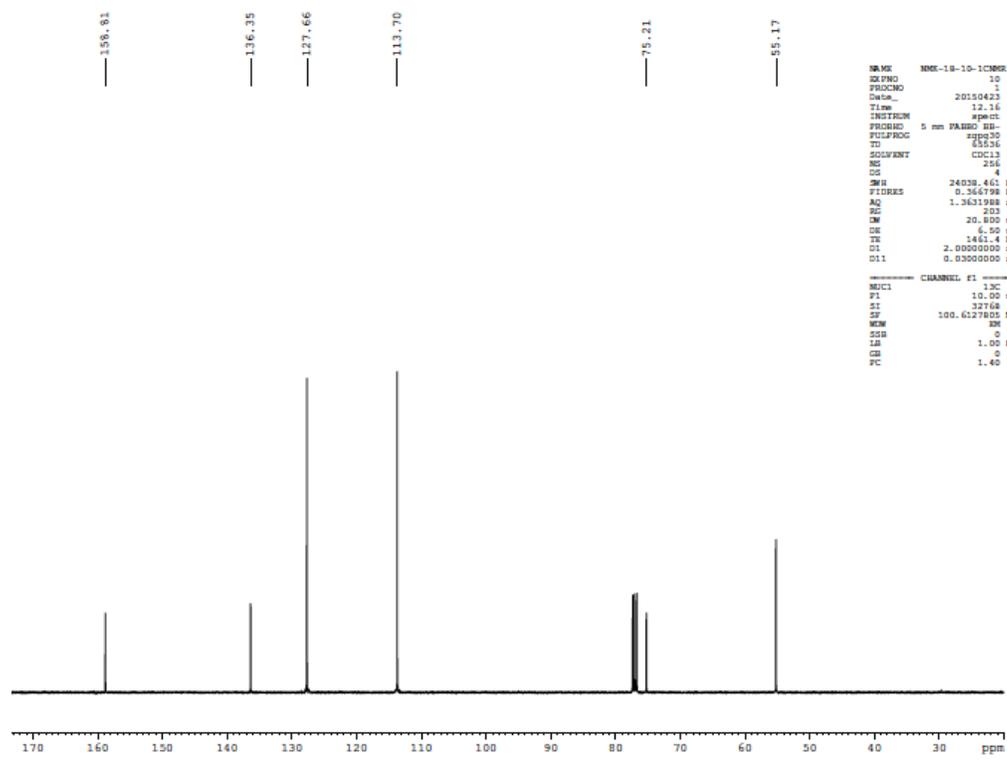
NAME      NMR-18-10-1
EXPNO     10
PROCNO    1
Date_     20150423
Time      11.52
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         14
DS         4
SWH        8223.643 Hz
FIDRES    0.125483 Hz
AQ         3.904307 sec
RG         323
RC         32
DM         64.800 umsec
DE         6.50 umsec
TE         293.2 K
SI         1.00000000 sec
DI         1.00000000 sec

----- CHANNEL f1 -----
NUC1      1H
P1         13.75 umsec
SI         65536
SF         400.1300232 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00

```



Bis(4-Methoxyphenyl)methanol, 2,28

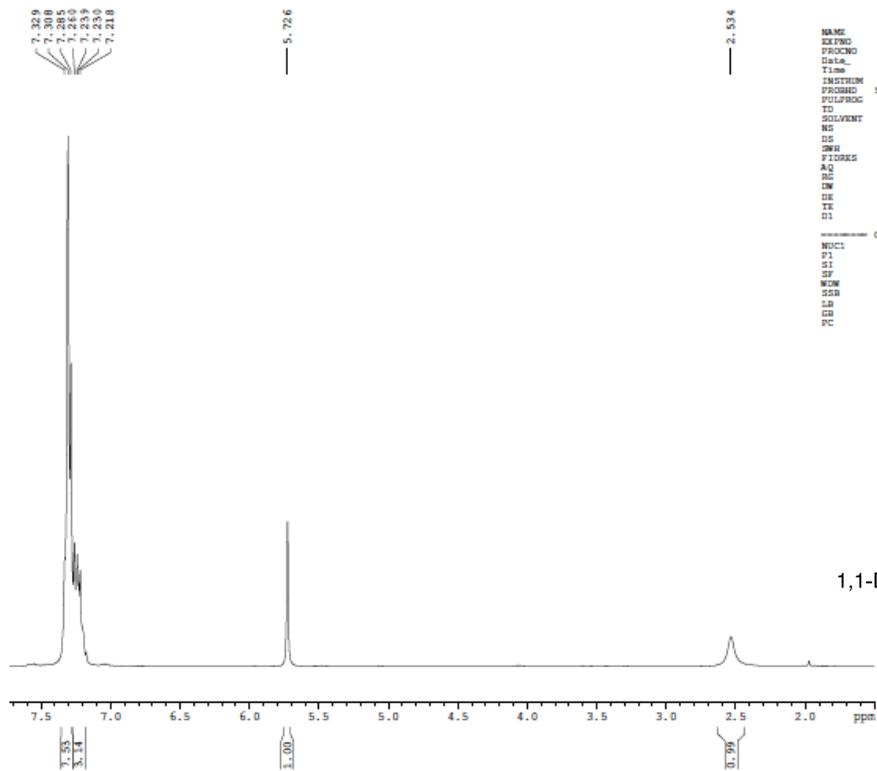


```

NAME      NMR-18-10-1C100R
EXPNO     10
PROCNO    1
Date_     20150423
Time      12.16
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         256
DS         4
SWH       24038.463 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
RC         203
DM         20.800 umsec
DE         6.50 umsec
TE         1461.4 K
SI         2.00000000 sec
DI         0.03000000 sec

----- CHANNEL f1 -----
NUC1      13C
P1         10.00 umsec
SI         32768
SF        100.6127805 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40

```

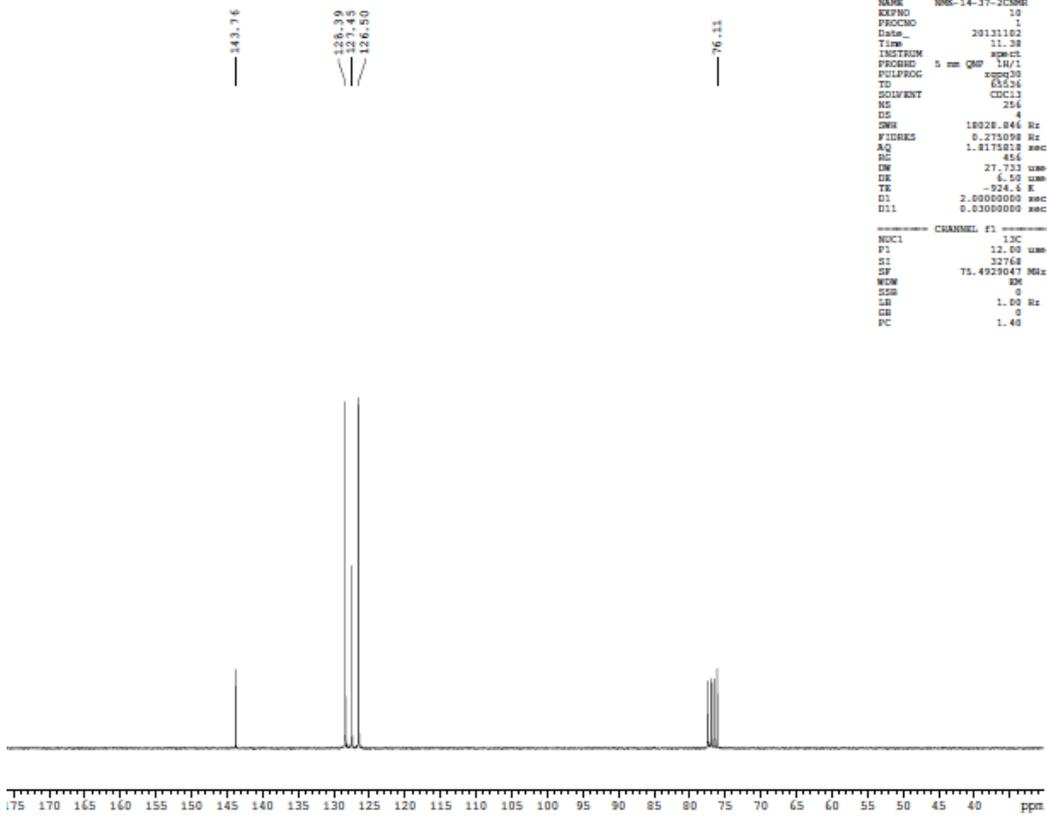
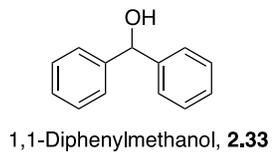



```

NAME      NMR-14-37-2
EXPNO     10
PROCNO    1
Date_     20131102
Time      11.20
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
TD         32768
SOLVENT   CDCl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.647584 sec
RG         45.2
EW         80.800 usec
DE         6.50 usec
TE         -924.8 K
D1         1.0000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         12.71 usec
SI         32768
SF         300.2300340 MHz
WOW        2K
SSB        0
LB         0.10 Hz
GB         0
PC         1.00

```



```

NAME      NMR-14-37-2C001
EXPNO     10
PROCNO    1
Date_     20131102
Time      11.38
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         256
DS         4
SWH        18028.846 Hz
FIDRES     0.278598 Hz
AQ         1.8175818 sec
RG         456
EW         27.733 usec
DE         6.50 usec
TE         -924.6 K
D1         2.0000000 sec
D11        0.0300000 sec

===== CHANNEL f1 =====
NUC1       13C
P1         12.00 usec
SI         32768
SF         75.4929047 MHz
WOW        2K
SSB        0
LB         1.00 Hz
GB         0
PC         1.40

```

BIBLIOGRAPHY

- ¹ Guijarro, D.; Pastor, I. M.; Yus, M. *Current Organic Chemistry* **2011**, *15*, 375-400.
- ² Yang, A.; Butela, H.; Deng, K.; Doubleday, M.; Cohen, T. *Tetrahedron* **2006**, *62*, 6526-6535.
- ³ (a) Severin, M. G.; Arévalo, M. C.; Farnia, G.; Vianello, E. *J. Phys. Chem.* **1987**, *91*, 466-472;
(b) Kulkarni, V.; Cohen, T. *Tetrahedron* **1997**, *53*, 12089-12100.
- ⁴ Holy, N. L. *Chem. Rev.* **1974**, *74*, 243-277.
- ⁵ Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni, V. *J. Am. Chem. Soc.* **2001**, *123*, 3478-3483.
- ⁶ Eisch, J. J. *J. Org. Chem.* **1963**, *28*, 707-710.
- ⁷ Screttas, C. G. *J. Chem. Soc. Chem. Commun.* **1972**, 752-753.
- ⁸ Feeman, P. K.; Hutchinson, L. L. *Tetrahedron Lett.* **1976**, *17*, 1849-1852.
- ⁹ Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311-317.
- ¹⁰ (a) Deng, K.; Bensari-Bouguerra, A.; Whetston, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360-2372; (b) Deng, K.; Bensari, A.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291-3304; (c) Shook, C. A.; Romberger, M. L.; Jung, S. H.; Xiao, M.; Sherbine, J. P.; Zhang, B.; Lin, F. T.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855-3865; (d) Cabral, J. A.; Cohen, T.; Doubleday, W. W.; Duchelle, E. F.; Fraenkel, G.; Guo, B. S.; Yü, S. H. *J. Org. Chem.* **1992**, *57*, 3680-3684; (e) McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727-9736; (f) Cohen, T.; Jung, S. H.; Romberger, M. L.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 25-26; (g) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710-4711; (h) Cohen, T.; Guo, B. S. *Tetrahedron* **1986**, *42*, 2803-2808; (i) Cohen, T.; Sherbine, J. P.; Mendelson, S. A.; Myers, M.

Tetrahedron Lett. **1985**, *26*, 2965-2968; (j) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245-3252; (k) Cohen, T.; Lin, M. *J. Am. Chem. Soc.* **1984**, *106*, 1130-1131; (l) Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520-525; (m) Cohen, T.; Ouellette, D.; Senaratne, K. P. A.; Yu, L. C. *Tetrahedron Lett.* **1981**, *22*, 3377-3380; (n) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900-6902; (o) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1994**, *50*, 12793-12810.

¹¹ (a) Streiff, S.; Ribeiro, N.; Désaubry, L. *J. Org. Chem.* **2004**, *69*, 7592-7598; (b) Giannini, A.; Coquerel, Y.; Greene, A. E.; Deprés, J. P. *Tetrahedron Lett.* **2004**, *45*, 6749-6751; (c) Tsai, T. Y.; Shia, K. S.; Liu, H. J. *Synlett.* **2003**, 97-101; (d) Perales, J. B.; Makino, N. F.; Van Vranken, D. L. *J. Org. Chem.* **2002**, *67*, 6711-6717; (e) Shimizu, M.; Hiyama, T.; Matsubara, T.; Yamabe, T. *J. Organomet. Chem.* **2000**, *611*, 12-19; (f) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **2000**, *122*, 12806-12812; (g) Nowak, A.; Schaumann, E. *Synthesis* **1998**, 899-904; (h) Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361-12378; (i) Tamao, K.; Kawachi, A. *Organometallics* **1995**, *14*, 3108-3111; (j) Block, E.; Guo, C.; Thiruvazhi, M.; Toscano, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 3492-3499; (k) Tanaka, K.; Minami, K.; Funaki, I.; Suzuki, H. *Tetrahedron Lett.* **1990**, *31*, 2727-2730; (l) McDougal, P. G.; Condon, B. D. *Tetrahedron Lett.* **1989**, *30*, 789-790; (m) Keys, B. A.; Eliel, E. L.; Juaristi, E. *Israel J. Chem.* **1989**, *29*, 171-186; (n) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Selim, M. R. *Tetrahedron Lett.* **1987**, *28*, 693-696; (o) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915-916; (p) Barluenga, J.; Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183-194; (q) Yus, M.; Concellón, J. M.; Bernad, P.; Alvarez, F. *J. Chem. Res. (S)* **1985**, 128-129; (r) Lyle, T. A.; Mereyala, H. B.; Pascual, A.; Frei, B. *Helv. Chim. Acta.* **1984**, *67*,

- 774-778; (s) Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3019-3026;
- (t) Kuwajima, I.; Takeda, R. *Tetrahedron Lett.* **1981**, 22, 2381-2384.
- ¹² (a) Yus, M. in *The Chemistry of Organolithium Compounds*, Rappoport, Z. Marek, I., Ed. Wiley: Chichester, **2004**; Part 2, Chap. 11; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225-237.
- ¹³ Recent Reviews: (a) Strohmman, C.; Schildbach, D. in *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley: New York, **2004**, Chap. 15; (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: London, **2002**; Chap. 4. Recent papers reporting the use of LDBB: (a) Merten, J.; Hennig, A.; Schwab, P.; Frohlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144-1161; (b) Chen, W.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett.* **2006**, 8, 2087-2090; (c) Morin, M. D. Rychnovsky, S. D. *Org. Lett.* **2005**, 7, 2051-2053; (d) La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, 7, 1873-1875; (e) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, 7, 1853-1856; (f) Cooksey, J.; Gunn, A.; Kocienski, P. J.; Kuhl, A.; Uppal, S.; Christopher, J. A.; Bell, R. *Org. Biomol. Chem.* **2004**, 2, 1719-1731; (g) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, 6, 569-572.
- ¹⁴ Ivanov, R.; Marek, I.; Cohen, T. *Tetrahedron Lett.* **2010**, 51, 174-176.
- ¹⁵ Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synthetic Commun.* **1973**, 3, 265-272.
- ¹⁶ Yus, M.; Ramon, D. J. *J. Chem. Soc. Chem. Commun.* **1991**, 398-400.
- ¹⁷ Reviews: (a) Yus, M. *Chem. Soc. Rev.* **1996**, 155-161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225—237; (c) Yus, M. in *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, **2004**; Chap. 11.
- ¹⁸ (a) Alonso, F.; Dacunha, B.; Melendez, J.; Yus, M. *Tetrahedron* **2005**, 61, 3437-3450; (b) Gómez, C.; Maciá, B.; Yus, M. *Arkivoc.* **2005**, 10-20; (c) Yus, M.; Gomis, J. *Tetrahedron* **2003**, 59, 4967-4971.

- ¹⁹ Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525-8542.
- ²⁰ (a) Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 5047-5051; (b) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017-7026.
- ²¹ (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455-3458; (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574-2584.
- ²² Foubelo, F.; Moreno, B.; Soler, T.; Yus, M. *Tetrahedron* **2005**, *61*, 9082-9096.
- ²³ Gil, J. F.; Ramon, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 3437-3446.
- ²⁴ Ivanov, R. A. Ph.D. Thesis, University of Pittsburgh, **2008**, pp 76 and 181.
<http://etd.library.pitt.edu/ETD/available/etd-02142008-151714/>
- ²⁵ Almena, J.; Yus, M.; Foubelo, F. *Tetrahedron Lett.* **1993**, *34*, 1649-1652.
- ²⁶ Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2001**, *66*, 2809-2813.
- ²⁷ Yang, A. Ph.D. Thesis, University of Pittsburgh, **2007**, pp 30.
- ²⁸ (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064-1071; (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713-719.
- ²⁹ (a) Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665-4668; (b) Cohen, T.; Weisenfeld, R. B. *J. Org. Chem.* **1979**, *44*, 3601-3603.
- ³⁰ Reviews: (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161; (b) Cohen, T. in *Heteroatom Chemistry*; Block, E., Ed.; VCH Publishers: New York, **1990**; Chapter 7, 129-142; (c) Foubelo, F.; Yus, M. *Chem. Soc. Rev.* **2008**, *37*, 2620-2633.
- ³¹ Recent uses of reductive lithiation of phenyl thioethers: (a) Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M.; Steele, B. R. *Tetrahedron Lett.* **2005**, *46*, 4357-4360; (b) Tang, T.; Ruan, Y. P.; Ye, J. L.; Huang, P. Q. *Synlett.* **2005**, 231-234; (c) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853-1856; (d) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569-572;

(e) Cooksey, J.; Gunn, A.; Kocienski, P. J.; Kuhl, A.; Uppal, S.; Christopher, J. A.; Bell, R. *Org. Biomol. Chem.* **2004**, *2*, 1719-1731; (f) Streiff, S.; Ribeiro, N.; Desaubry, L. *J. Org. Chem.* **2004**, *69*, 7592-7598; (g) Bourque, E.; Kocienski, P. J.; Stocks, M.; Yuen, J. *Synthesis* **2005**, 3219-3224; (h) Gómez, C.; Maciá, B.; Yus, M. *Tetrahedron* **2005**, *61*, 9325-9330; (i) Merten, J.; Hennig, A.; Schwab, P.; Frohlich, R.; Tokalov, S.; V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144-1161; (j) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 3256-3260; (k) Huang, P. Q. *Synlett.* **2006**, 1133-1149; (l) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459-490; (m) Abou, A.; Foubelo, F.; Yus, M. *Arkivoc.* **2007**, 196-205; (n) Huckins, J. R.; de Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757-4760; (o) Malathong, V.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 4220-4223; (p) Zheng, X.; Chen, G.; Ruan, Y. P.; Huang, P. Q. *Sci. China Ser. B* **2009**, *52*, 1631-1638; (q) Biggs-Houck, J. E.; Davis, R. L.; Wei, J. Q.; Mercado, B. Q.; Olmstead, M. M.; Tantillo, D. J.; Shaw, J. T. *J. Org. Chem.* **2012**, *77*, 160-172; (r) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660-663; (s) Perry, M. A.; Rychnovsky, S. D. *Nat. Prod. Rep.* **2015**, *32*, 517-533; (t) Azzena, U.; Pisano, L. *Lithium Compounds in Organic Synthesis-from Fundamentals to Applications*. Luisi, R.; Capriati, V., Ed.; Wiley: Weinheim, Germany, **2014**, pp. 351-373 and references cited therein.

³² Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16-24.

³³ Masson, E.; Leroux, F. *Helv. Chim. Acta.* **2005**, *88*, 1375-1386.

³⁴ Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569-11584.

³⁵ Munbunjong, W.; Lee, E. H.; Ngermaneerat, P.; Kim, S. J.; Singh, G.; Chavasiri, W.; Jang, D. O.; *Tetrahedron* **2009**, *65*, 2467-2471.

³⁶ Munbunjong, W.; Lee, E. H.; Chavasiri, W.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 8769-8771.

- ³⁷ Indium Powder 99.99% Strem Chemicals; [7440-74-6]; 2012 ThermoFisher Scientific; www.fishersci.com
- ³⁸ Micha-Screttas, M.; Screttas, C. G. *J. Org. Chem.* **1977**, *42*, 1462-1465.
- ³⁹ Labiad, B.; Villemin, D. *Synthesis* **1989**, 143-144.
- ⁴⁰ Unpublished work, Roman Ivanov's lab notebooks.
- ⁴¹ (a) Kuwaiima, I.; Takeda, R. *Tetrahedron Lett.* **1981**, *22*, 2381-2384; (b) Ramig, K. Dong, Y.; Van Arnum, S. D. *Tetrahedron Lett.* **1996**, *37*, 443-446; (c) Streif, S.; Ribeiro, N.; Désaubry, L. *Chem. Commun.* **2004**, 346-347 and references therein.
- ⁴² (a) Wynberg, H.; Bantjes, A. *J. Am. Chem. Soc.* **1960**, *82*, 1447-1450; (b) Pérez-Baldo, C.; Markó, I. E. *Tetrahedron* **2006**, *62*, 2331-2349; (c) Okimoto, M.; Kawachi, A.; Yamamoto; Y. J. *Organomet. Chem.* **2009**, *694*, 1419-1426 and references therein.
- ⁴³ Cohen, T.; Sherbine, J. P.; Hutchins, R. R.; Lin, M-T. α -Heteroatom Organolithium Compounds by Reductive Lithiation of Substituted Phenylthioethers Using Lithium 1-(Dimethylamino)Naphthalene (LDMAN). In *Organometallic Syntheses*; King, R. B., Eisch, J. J., Eds.; Elsevier: New York, **1986**; Vol. 3, pp 361-368.
- ⁴⁴ *N,N*-Dimethylaniline, 99% (515124-100 mL-Aldrich) for \$21.30; 4,4'-Di-*tert*-butylbiphenyl, 99% (193801-25g-Aldrich) for \$149.00; and *N,N*-Dimethyl-*o*-toluidine, 99% (409928-250mL-Aldrich) for \$76.00.
- ⁴⁵ Kennedy, N.; Lu, G.; Liu, P.; Cohen, T. *J. Org. Chem.* **2015**, *80*, Just Accepted.
- ⁴⁶ Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290.
- ⁴⁷ Yu, B.; Liu, A-H.; He, L-N.; Li, B.; Diao, Z-F.; Li, Y-N. *Green Chem.* **2012**, *14*, 957-962.
- ⁴⁸ Kennedy, N.; Liu, P.; Cohen, T. *N,N*-Dimethylaniline, A Highly Advantageous Aromatic Electron Transfer Catalyst for Preparing Organolithiums by Reductive Lithiation. *Surprising*

Fundamental Difference between Reductive Lithiations Using Preformed Aromatic Radical-Anions and Those Using Catalytic Amounts of Aromatic Electron Transfer Agents. **2015**, To be submitted.

⁴⁹ (a) Ramón, D. J.; Yus, M. *Tetrahedron* **1996**, *43*, 13739-13750; (b) Huerta, F. F.; Gómez, C.; Guijarro, A.; Yus, M. *Tetrahedron* **1995**, *51*, 3375-3388; (c) Guijarro, A.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 2011-2014; (d) Ramón, D. J.; Yus, M. *J. Org. Chem.* **1991**, *56*, 3825-3831; (e) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574-2584; (f) Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron Lett.* **2002**, *43*, 2957-2960.

⁵⁰ O'Mahoney, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288-3296.

⁵¹ Kleimark, J.; Johansson, C.; Olsson, S.; Håkansson, M.; Hansson, S.; Åkermark, B.; Norrby, P.-O. *Organometallics* **2011**, *30*, 230-238.

⁵² Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119-10124.

⁵³ (a) Dosch Doubleday, M. PhD Thesis, University of Pittsburgh, **1991**, pp. 67-68; (b) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784-4786.

⁵⁴ The sodium initiates the radical pathway and increases the rate. (a) *Organometallics in Organic Synthesis*. Schlosser, M., Ed.; Wiley: New York, **1994**; (b) Kamienski, C.; Esmay, D. *J. Org. Chem.* **1960**, *25*, 1807-1808 and references therein.

⁵⁵ (a) Screttas, C. G. Heropoulos, G. A.; Micha-Screttas, M.; Steele, B. R.; Catsoulacos, D. P. *Tetrahedron Lett.* **2003**, *44*, 5633-5535; (b) Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M.; Steel, B. R. *Tetrahedron Lett.* **2005**, *46*, 4357-4360.

⁵⁶ McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493-532.

⁵⁷ Attempts to cleave acrolein diethyl acetal with 10 eq. of Li dispersion (30% in paraffin), from Alfa Aesar, in the absence of DBB failed.²

- ⁵⁸ Crews, P.; Rodríguez, J.; Jaspars, M. Interpretation and Use of Proton and Carbon Coupling Constants. In *Organic Structure Analysis*; Houk, K. N.; Loudon, G. M., Eds.; Oxford: New York, **2010**; Ed. 2, pp 148-161.
- ⁵⁹ Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 3437-3446.
- ⁶⁰ Almena, J.; Foubleo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365-3374.
- ⁶¹ Wilfred, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*. Elsevier, **2003**; Ed. 5, pp 119
- ⁶² Yakovleva, M.; Gao, Y.; Fitch, K. B.; Palepu, P. T.; Li, Y.; Woltermann, C. J. *Method of Forming a Lithium Dispersion and Stabilized Lithium Metal Powder*. U.S. Patent EP,2186151,B1, Dec 4, 2013.
- ⁶³ Alexakis, A.; Cahiez, C.; Normant, J. F. *J. Organomet. Chem.* **1979**, *177*, 293-298.
- ⁶⁴ Mattiza, J. T.; Meyer, V. J.; Duddeck, H. *Magn. Reson. Chem.* **2010**, *48*, 192-197.
- ⁶⁵ Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 8696.
- ⁶⁶ Gibson (née Thomas) S. E.; Guillo, N.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2575-2581.
- ⁶⁷ Jereb, M. *Green Chem.* **2012**, *14*, 3047-3052.
- ⁶⁸ Ramón, D. J.; Yus, M. *J. Org. Chem.* **1991**, *56*, 3825-3831.
- ⁶⁹ Guijarro, D.; Yus, M.; *Tetrahedron* **1994**, *50*, 3447-3452.
- ⁷⁰ Peñafiel, I.; Pastor, I. M.; Yus, M. *Tetrahedron* **2010**, *66*, 2928-2935.
- ⁷¹ Miura, K.; Wang, D.; Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366-9367.
- ⁷² Trahanovsky, W. S.; Fox, N. S. *J. Am. Chem. Soc.* **1974**, *96*, 7968-7974.

- ⁷³ Scholz, R.; Hellmann, G.; Rohs, S.; Özdemir, D.; Raabe, G.; Vermeeren, C.; Gais, H-J. *Eur. J. Org. Chem.* **2010**, 4588-4616.
- ⁷⁴ Almena, J.; Foubleo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365-3374.
- ⁷⁵ Moglie, Y.; Alonso, F.; Vitale, C.; Yus, M.; Radivoy, G. *Tetrahedron* **2006**, *62*, 2812-2819.
- ⁷⁶ (a) Noyce, D. S.; Denney, D. B. *J. Am. Chem. Soc.* **1950**, *72*, 5743-5745; (b) Umland, J. B.; Jefraim, M. I. *J. Am. Chem. Soc.* **1956**, *78*, 2788-2790; (c) Dauben, W. G.; Fonken, G. J., Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579-2582; (d) Brown, H. C.; Bigley, D. B. *J. Am. Chem. Soc.* **1961**, *83*, 3166-3167; (e) House, H. O.; Müller, H. C.; Pitt, C. G.; Wickham, P. P. *J. Org. Chem.* **1963**, *28*, 2407-2416; (f) Huffman, J. W.; Alabran, D. M.; Bethea, T. W.; Ruggles, A. C. *J. Org. Chem.* **1964**, *29*, 2963-2968; (g) Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620-5625; (h) Richer, J-C. *J. Org. Chem.* **1965**, *30*, 324-325; (i) Coulombeau, A; Rassat, A. *Chem. Commun.* **1968**, 1587-1589; (j) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411-2428; (k) Ashby, E. C.; Sevenair, J. P.; Dobbs, F. R. *J. Org. Chem.* **1971**, *36*, 197-199; (l) Brown, H. C.; Varma, V. *J. Org. Chem.* **1974**, *39*, 1631-1636; (m) Wigfield, D. C.; Feiner, S.; Phelps, D. J. *J. Org. Chem.* **1975**, *40*, 2533-2534; (n) Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1976**, *98*, 1965-1967; (o) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890-2903; (p) Hutchins, R. O. *J. Org. Chem.* **1977**, *42*, 920-922; (q) Ashby, E. C.; Lin, J. J.; Goel, A. G. *J. Org. Chem.* **1978**, *43*, 183-188; (r) Ashby, E. C.; Willard, G. F. *J. Org. Chem.* **1978**, *43*, 4094-4098; (s) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1560-1563; (t) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607; (u) Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594-599; (v) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449-462; (w) Asby, E. C.; Noding, S. A.; Goel, A. B. *J. Org. Chem.* **1980**, *45*, 1028-1035; (x) Gemal; A. L.; Luche, J.

L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459; (y) Kim, S.; Moon, Y. C.; Ahn, K. H. *J. Org. Chem.* **1982**, *47*, 3311-3315; (z) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 399-405.

⁷⁷ (a) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351-6388; (b) Yoon, N. M.; Kim, K. E.; Kang, J. J. *Org. Chem.* **1986**, *51*, 226-229; (c) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588-3597; (d) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1990**, *55*, 5911-5915; (e) Sarkar, A.; Rao, B. R. *Tetrahedron Lett.* **1991**, *32*, 1247-1250; (f) Sarkar, A.; Rao, B. R. *Tetrahedron Lett.* **1991**, *32*, 2157-2160; (g) Fort, Y. *Tetrahedron Lett.* **1995**, *36*, 6051-6054; (h) Cha, J. S.; Kwon, O. O. *J. Org. Chem.* **1997**, *62*, 3019-3020; (i) Cha, J. S.; Kwon, O. O.; Kim, J. M.; Cho, S. D. *Synlett.* **1997**, 1465-1466; (j) Dannenberg, J. J. *Chem. Rev.* **1999**, *99*, 1225-1241; (k) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243-1263; (l) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377-1386; (m) Kwon, O. O.; Cha, J. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 659-661; (n) Cha, J. S.; Moon, S. J.; Kwon, O. O.; Lee, Y. R. *Bull. Korean Chem. Soc.* **2000**, *21*, 128-130; (o) Luibrand, R. T.; Taigounov, I. R.; Taigounov, A. A. *J. Org. Chem.* **2001**, *66*, 7254-7262; (p) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40-73; (q) Cha, J. S.; Moon, S. J.; Park, J. H. *J. Org. Chem.* **2001**, *66*, 7514-7515; (r) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Gansäuer, A.; Oltra, J. E. *Tetrahedron Lett.* **2003**, *44*, 1079-1082; (s) Bahia, P. S.; Jones, M. A.; Snaith, J. S. *J. Org. Chem.* **2004**, *69*, 9289-9291; (t) Bahia, P. S.; Jones, M. A.; Snaith, J. S. *J. Org. Chem.* **2004**, *69*, 9289-9291; (u) Cha, J. S. *Org. Process Res. Dev.* **2006**, *10*, 1032-1053; (v) Cha, J. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 2162-2190; (x) Cha, J. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 1808-1846; (y) Hayashi, T.; Kikuchi, S.; Asano, Y.; Endo, Y.; Yamada, T. *Org. Process Res. Dev.* **2012**, *16*, 1235-1240.

⁷⁸ (a) Ourisson, G.; Rassat, A. *Tetrahedron Lett.* **1960**, *1*, 16-19; (b) Brown, H. C.; Varma, V. *J. Am. Chem. Soc.* **1966**, *88*, 2871; (c) Brown, H. C.; Dickason, W. C. *J. Am. Chem. Soc.* **1970**, *92*,

709-710; (d) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159-7161; (e) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100-4102; (f) Hooz, J.; Aklyama, S.; Cedar, F. J.; Bennett, M. T.; Tuggle, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 274-276; (g) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383-3384; (h) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534-2536; (i) Haubenstock, H.; Hong, S. J. *Tetrahedron* **1978**, *34*, 2445-2447; (j) Kim, S.; Ahn, K. H.; Chung, Y. W. *J. Org. Chem.* **1982**, *47*, 4581-4582; (k) Brown, H. C.; Cha, J. S.; Nazer, B. *J. Org. Chem.* **1984**, *49*, 2073-2074; (l) Brown, H. C.; Cha, J. S.; Nazer, B. *Inorg. Chem.* **1984**, *23*, 2929-2931; (m) Brown, H. C.; Cha, J. S.; Nazer, B.; Brown, C. A. *J. Org. Chem.* **1985**, *50*, 549-553; (n) Yoon, N. M.; Kim, K. E.; Kang, J. *J. Org. Chem.* **1986**, *51*, 226-229; (o) Brown, H. C.; Nazer, B.; Cha, J. S.; Sikorski, J. A. *J. Org. Chem.* **1986**, *51*, 5264-5270; (p) Cha, J. S.; Yoon, M. S.; Kim, Y. S.; Lee, K. W. *Tetrahedron Lett.* **1988**, *29*, 1069-1070; (q) Cha, J. S.; Yoon, M. S.; Lee, K. W.; Lee, J. C. *Heterocycles* **1988**, *27*, 1455-1460; (r) Cha, J. S.; Lee, D. Y.; Moon, S. J. *Bull. Korean Chem. Soc.* **2001**, *22*, 661-662; (s) Cho, S. D.; Lim, H. J.; Kim, H. J.; Cha, J. S. *Bull. Korean Chem. Soc.* **2002**, *23*, 1695-1696.

⁷⁹ (a) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486-6492; (b) Maruoka, K.; Sakurai, M.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 3853-3856; (c) Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 5201-5204; (d) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378-6385; (e) Denis, C.; Laignel, B.; Plusquellec, D.; Marouille, J-Y. L.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53-56; (f) Cha, J. S.; Park, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1051-1052; (g) Cha, J. S.; Noh, M. Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 840-844; (h) Cha, J. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 219-224.

- ⁸⁰ Reviews: (a) Alonso, F.; Yus, M. *Chem. Soc. Rev.* **2004**, *33*, 284-293; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009-4091.
- ⁸¹ Alonso, F.; Yus, M. *Tetrahedron* **1998**, *54*, 1921-1928.
- ⁸² Alonso, F.; Vitale, C.; Radivoy, G.; Yus, M. *Synthesis* **2003**, 443-447.
- ⁸³ NiCl₂•2H₂O is prepared from commercially available NiCl₂•6H₂O by heating *in vacuo* (ca. 0.5 torr) at 100 °C in Kugelrohr for 2 h: Alonso, F.; Yus, M. *Tetrahedron Lett.* **1996**, *37*, 6925-6928.
- ⁸⁴ Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nat. Chem.* **2010**, *2*, 478-483.
- ⁸⁵ Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, **1991**; pp 56.
- ⁸⁶ Brunet, J. J.; Mordenti, L.; Caubère, P. *J. Org. Chem.* **1978**, *43*, 4804-4808.
- ⁸⁷ Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594-599.
- ⁸⁸ Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535-3536.
- ⁸⁹ Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Synthesis. Recent Advances and Practical Applications*; Abdel-Magid, A. F., Ed.; ACS Symposium Series *641*; American Chemical Society: Washington, DC, **1996**; pp 21.
- ⁹⁰ (a) Ronald, R.; Maleczka, R. E. *Org. Lett.* **2011**, *13*, 584-587; (b) Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem. Eur. J.* **2009**, *15*, 1713-1722; (c) Abraham, R. J.; Barlow, A. P.; Rowan, A. E. *Magn. Reson. Chem.* **1989**, *27*, 1074-1084.
- ⁹¹ Solodar, J. *J. Org. Chem.* **1976**, *41*, 3461-3464.
- ⁹² Wu, Y-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018-5027.
- ⁹³ Chênevert, R.; Courchesne, G.; Jacques, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3587-3590.
- ⁹⁴ Kerep, P.; Ritter, H. *Macromol. Chem. Phys.* **2007**, *208*, 188-195.

- ⁹⁵ Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521-546.
- ⁹⁶ Fuchs, B.; Haber, R. G. *Tetrahedron Lett.* **1966**, *7*, 1323-1328.
- ⁹⁷ Haber, R. G.; Fuchs, B. *Tetrahedron Lett.* **1966**, *7*, 1447-1451.
- ⁹⁸ Arnone, A.; Bernardi, R.; Blasco, F.; Cardillo, R.; Resnati, G.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **1998**, *54*, 2809-2818.
- ⁹⁹ (a) Świzdor, A.; Panek, A.; Milecka-Tronina, N. *Steroids* **2014**, *82*, 44-52; (b) Hunter, A. C.; Khuenl-Brady, H.; Barrett, P.; Dodd, H. T.; Dedi, C. *J. Steroid Biochem. Mol. Biol.* **2010**, *118*, 171-176.
- ¹⁰⁰ Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, *10*, 1029-1030.
- ¹⁰¹ (a) Isotani, K.; Kurokawa, J.; Itoh, N. *Int. Mol. Sci.* **2012**, *13*, 13542-13553; (b) Wang, Y.; Li, J.; Wu, Q.; Zhu, D. *J. Mol. Catal. B: Enzym.* **2013**, *88*, 14-19; (c) Isotani, K.; Kurokawa, J.; Suzuki, F.; Nomoto, S.; Negishi, T.; Matsuda, M.; Itoh, N. *Appl. Environ. Microbiol.* **2013**, *79*, 1378-1384; (d) Kolet, S. P.; Jadhav, D. D.; Priyadarshini, B.; Swarge, B. N. Thurlasiram, H. V. *Tetrahedron Lett.* **2014**, *55*, 5911-5914; (e) Hou, F.; Miyakawa, T.; Kataoka, M.; Takeshita, D.; Kumashiro, S.; Uzura, A.; Urano, N.; Nagata, K.; Shimizu, S.; Tanokura, M. *Biochem. Biophys. Res. Commun.* **2014**, *446*, 911-915 and references cited therein.
- ¹⁰² (a) Arai, N.; Akashi, M.; Sugizaki, S.; Ooka, H.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2010**, *12*, 3380-3383; (b) Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N.; Ohkuma, T. *J. Am. Chem. Soc.* **2011**, *133*, 10696-10699; (c) Slade, A. T.; Lensink, C.; Falshaw, A.; Clark, G. R.; Wright, L. *J. Dalton Trans.* **2014**, *43*, 17163-17171 and references therein.
- ¹⁰³ Alonso, F.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 149-152.
- ¹⁰⁴ According to Huffman and Charles, in the metal-ammonia reduction of ketones, the π^* LUMO presumably accepts an electron from the lithium metal (or solvated electron) and becomes a

radical-anion. This radical-anion has several competitive reaction paths open: (1) dimerization to the pinacol coupled diol product; (2) protonation of the radical-anion to give an alkoxide radical; and (3) reduction of the radical-anion to the vicinal dianion. Protonation of the radical-anion to the alkoxy radical, which would then be further reduced to an alkoxide ion, results in protonation from the least hindered side of the carbonyl atom. Reduction of the radical-anion to the dianion gives a tetrahedral species, which should give rise to approximately an equilibrium mixture of products, in which the thermodynamically stable isomer predominates.^{79a}

¹⁰⁵ Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730.

¹⁰⁶ Atta-ur-Rahman; Yaqoob, M.; Farooq, A.; Anjum, S.; Asif, F.; Choudhary, M. I. *J. Nat. Prod.* **1998**, *61*, 1340-1342.

¹⁰⁷ Maio, G. D.; Mascia, M. G.; Vecchi, E. *Tetrahedron* **2002**, *58*, 3313-3318.

¹⁰⁸ Oritani, T.; Ichimura, M.; Hanyu, Y.; Yamashita, K. *Agr. Biol. Chem.* **1983**, *47*, 2613-2617.

¹⁰⁹ Oritani, T.; Yamashita, K. *Agr. Biol. Chem.* **1974**, *38*, 1965-1971.

¹¹⁰ Denegri, B.; Kronja, O. *J. Org. Chem.* **2007**, *72*, 8427-8433.

¹¹¹ Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, *7*, 4153-4155.