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 SATLS OF COMMON TRANSITION METALS.

by

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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 FeCl$_2$$\cdot$4H$_2$O or CuCl$_2$$\cdot$2H$_2$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

\( \delta \) chemical shift (ppm)

\( ^{9}C \) degrees celsius

\(^{1}H\) NMR proton nuclear magnetic resonance

\(^{13}CNMR\) 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\(_2\)Cl\(_2\) methylene chloride

CH\(_3\)Li methyl lithium

CuBr•SMe\(_2\) copper bromide dimethyl sulfide

CuCl\(_2\)•2H\(_2\)O copper (II) chloride dehydrate

D\(_2\)O deuterium oxide

DBB \(p,p´-\)di-\(\text{tert}\)-butyl biphenyl

DIBAO\(_3\)SCH\(_3\) \(Al\)-methanesulfonyldiisobutylalane

disp. dispersion

DMA \(N,N\)-dimethylaniline

DMAN 1-(dimethylamino)-naphthalene

DMF \(N,N\)-dimethylformamide

DMOT \(N,N\)-dimethyl-o-toluidine

dr diastereomeric ratio

e\(^{-}\) electron

E\(_2\) bimolecular elimination

EI electron ionization

equiv equivalents

ES\(^{+}\) positive electrospray ionization (MS)

Et\(_2\)O diethyl ether

EtOAc ethyl acetate

EtOH ethanol

FeCl\(_3\) ferric chloride

FeCl\(_2\)•4H\(_2\)O iron (II) chloride tetrahydrate

GLC gas-liquid chromatography

h hour(s)

HCl hydrochloric acid

H\(_2\)O water

\(i\)Pr isopropyl
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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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{3}

\[ \text{Scheme 1.1 Mechanism of Reductive Lithiation of Phenyl Thioethers.} \]
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.\textsuperscript{4} The electron donated by the metal is believed to occupy the $\pi^*$ orbital (LUMO) of the corresponding aromatic compound.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6}

![Figure 1.1 Aromatic Radical-Anion Reducing Agents.](image)

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).\(^7\)

\[ 
\text{Np} \xrightarrow{\text{Li, THF, rt, \sim 5 h}} \left[ \begin{array}{c} \text{Li} \\ \text{N} \\ \end{array} \right] \xrightarrow{\text{R-Cl}} \left[ \begin{array}{c} \text{R} \\ \text{LN} \end{array} \right] \xrightarrow{\text{LN}} \left[ \text{RLi} \right] 
\]

**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.
In 1980, a solution to the problem of removal of DBB was found in the Cohen Laboratory. 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.
Fortunately, this often appeared to be only a minor disadvantage since most reductive lithiations are successful at -78 °C. As a result, the use of LDMAN is rather widespread, but considerably less so than the use of LDBB. For optimum yield, it is necessary to maintain a temperature of -55 ± 3 °C by manual control for 5 h for the synthesis of LDMAN. When this procedure was followed, every example tested provided higher yields than the use of either LDBB or LN in reductive lithiations.

1.1.2 Catalytic Method of Reductive Lithiation.

Because LDMAN decomposes to 1-lithionaphthalene above -52 °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. 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

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.\textsuperscript{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.\textsuperscript{2,20-23}

![Scheme 1.6 Yus’s Catalytic Reductive Lithiation of Alkyl Chlorides.](image)

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9}

\begin{center}
\begin{tikzpicture}
    \node[draw] at (0,0) (LN) {Lithium Naphthalenide, LN};
    \node[draw] at (2,0) (Np) {Neutral Naphthalene, Np};
    \node[draw] at (4,0) (dianion) {Dianion};
    \node[draw] at (4.5,0) (Li) {Li};
    \draw[<->] (LN) -- (Np); \node at (1,-0.5) {2 \text{Li}^\ominus};
    \draw[<->] (Np) -- (dianion) \node at (3,-0.5) {2 \text{Li}^\ominus};
    \draw[<->] (dianion) -- (Li); \node at (3.5,-0.5) {Li};
\end{tikzpicture}
\end{center}

\textbf{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.\textsuperscript{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. 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.

\[
\text{Scheme 1.10 Non-Catalyzed vs. Catalytic Method of Reductive Lithiation of 2,3-Benzofuran, 1.7.} \quad \text{\textsuperscript{a}Ref. 2.}
\]

1.1.3 Reductive Cleavage of \textit{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 \textit{N}-phenylaziridine, 1.10. It was reported that for \textit{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 \textit{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.

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). 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. 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. 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.
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 °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 \(\pi^*\) 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 °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 °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.

\[
\text{Scheme 1.13 Amino Catalysts for the Formation of LDBB.}^{27}
\]

### 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 lithums unless an aryl or vinyl group is present to increase the rate of reductive lithiation and favor it over the competing process. 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.

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. *Isolated crude yield.](image-url)
Scheme 1.15 Preparation of 5-(Phenylthio)-1-Pentene 1.16. *Isolated crude yield.

2-(Phenylthio)-butane, 1.20, 3-(phenylthio)-hexane, 1.21, and cyclooctyl phenyl sulfide, 1.22, were synthesized via S\textsubscript{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).\textsuperscript{33} The solvent was changed to the polar aprotic DMF in order to prevent an E\textsubscript{2} reaction.
Table 1.1 Preparation of Alkyl Phenyl Sulfides 1.20 – 1.22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyl Halide</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhS&lt;sup&gt;−&lt;/sup&gt; R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhS&lt;sup&gt;−&lt;/sup&gt; R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>3</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhS&lt;sup&gt;−&lt;/sup&gt; R&lt;sub&gt;1&lt;/sub&gt;Br  R&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

*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,<sup>34</sup> which involves the Lewis acid-catalyzed condensation of acetone with thiophenol (Scheme 1.16).
Thioacetalization for the Preparation of 2,2-Bis(phenylthio)propane, 1.25.

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 $S_\text{H2}$ reaction with diphenyl disulfide to form 1.28.

Scheme 1.17 Indium Metal-Mediated Synthesis of *tert*-Butyl Phenyl Sulfide, 1.28.
Because indium powder is expensive (5 g for $94.90), 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. \( \text{Tert-butyl chloride, 1.30, was found to react with thiophenol in POCl}_3 \text{ solvent in the presence of catalytic amounts of anhydrous ferric chloride, 1.31 (Scheme 1.19).} \) 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. In our work, employing glacial acetic acid, in place of POCl\(_3\), and tert-butyl bromide, 1.26, as the alkyl halide, 1.28 was synthesized in 35% yield.

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

1.2.2 Catalytic Reductive Lithiation with N,N-Dimethyl-α-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
and thioether takes no longer than 10 min. Thus, the more important issue, especially in large-scale preparations, is that two equivalents of DBB must be separated from each equivalent of product. In order to overcome the drawbacks of the preformed aromatic radical-anion method, an alternative to Yus’s catalytic aromatic method was developed by Roman Ivanov in this lab. It consisted of the reaction between Li metal and the corresponding alkyl thioether, \( \text{1.25} \), in the presence of a catalytic amount of the aromatic additive DMAN, which is far more active in forming a radical-anion than DBB or naphthalene (Scheme 1.21).  

![Scheme 1.21 DMAN Catalyzed Reductive Lithiation of 2,2-Bis(phenylthio)propane.]

This reductive lithiation was tested with commercially available \( \text{N,N-dimethyl-\( \alpha \)-toluidine (DMOT)} \), which had been found to readily catalyze the formation of LDBB (Scheme 1.13). In his unpublished work, Roman Ivanov discovered that 5 mol% of DMOT catalyzed the reductive lithiation of \( \text{1.25} \) faster than 5 mol% of DMAN. Since the lab notebook that contained these experiments was not recovered, the DMOT catalyzed reductive lithiation of \( \text{1.25} \) was repeated.

DMOT was treated with lithium ribbon in THF for several hours in order to determine if a perceivable aromatic radical-anion was generated (Scheme 1.22). Lithium ribbon, which is commonly used in both catalytic and preformed aromatic radical-anion reductive lithiation
reactions, is scraped free of the oxide coating prior to weighing.\textsuperscript{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 (\textit{N,N-}
dimethyl)-\textit{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 \( \pi^* \) system of the aromatic.\textsuperscript{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.

\[\text{DMOT} \quad \xrightarrow{\text{Li ribbon}^a} \quad \text{THF, -45 } ^\circ\text{C, 3 h then 0 } ^\circ\text{C, 2 h}} \quad [\text{LDMOT}] \]

\textbf{Scheme 1.22} Aromatic Radical-Anion, LDMOT, Formation.
\textsuperscript{a}Oxide coating on Li ribbon was scraped prior to the reaction.

Here we present our results of the DMOT catalyzed reductive lithiation of \textbf{1.25}, in which the organolithium intermediate, \textbf{1.35}, was trapped with water rather than being subjected to conjugate addition with methyl vinyl ketone, as in Ivanov’s work (\textbf{Scheme 1.21}). DMOT catalysis was measured by isolating the yield of isopropyl phenyl sulfide, \textbf{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Rxn Time (min)</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>45</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>-22</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>-22</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>-45</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>-45</td>
<td>40</td>
<td>24c</td>
</tr>
</tbody>
</table>

"Oxide coating on Li ribbon was scraped prior to the reaction. Isolated yield of 1.14 after column chromatography (silica gel, hexanes) based on the starting material. 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 SN2. 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. 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, \textbf{1.39}, (radical pair mechanism). The resulting alkene would be expected to be lost by evaporation. Because the $^1$H NMR of \textbf{1.39} matches that of \textbf{1.25}, a $^{13}$C NMR may have confirmed the presence of \textbf{1.39} due to a shift in the methyl carbon, but rather, the substrate was changed to commercially available methyl phenyl sulfide, \textbf{1.40}.

\begin{center}
\textbf{Scheme 1.23} Single Electron Transfer Reaction of \textbf{1.35} Resulting from the Reductive Lithiation of \textbf{1.25}.
\end{center}

Methyl phenyl sulfide, \textbf{1.40}, was chosen to test the catalytic power of DMOT, and the methyl-lithium intermediate, \textbf{1.41}, which is significantly less reactive, was trapped with benzaldehyde, rather than water, to yield an isolable alcohol product, 1-phenylethanol, \textbf{1.6} (\textit{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 \textit{Table 1.3}, DMOT catalyzed the reductive lithiation of \textbf{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, was tested as a catalyst because it was found to catalyze the formation of LDBB (Scheme 1.13). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>%Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMOT</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>DMAN</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>DMA</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>DBB</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>Cumene</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>39</td>
</tr>
</tbody>
</table>

<sup>a</sup> Oxide coating on Li ribbon was scraped prior to the reaction.<br><sup>b</sup> 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 DMOT\(^{44}\) 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)-anilinide (LDMA) was not generated.

![Diagram](image)

**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.

![Catalytic Reductive Lithiation Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>% of (1.34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBB</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>DMA</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>100</td>
</tr>
</tbody>
</table>

* Oxide coating on Li ribbon was scraped prior to the reaction. 
\(^a\) 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.

\[
\begin{align*}
\text{Entry} & \quad \text{SM} & \quad \text{R} & \quad \text{Catalyst} & \quad (\%)^a \\
1 & 1.14 & \text{CH(CH}_3)_2 & \text{DMA} & 62 \\
2 & 1.22 & c-\text{C}_8\text{H}_{15} & \text{DMA} & 95 \\
3 & 1.28 & \text{C(CH}_3)_3 & \text{DMA} & 60 \\
4 & 1.40 & \text{CH}_3 & \text{DMA} & 31 \\
5 & 1.40 & \text{CH}_3 & \text{DMA} & 30^c \\
6 & 1.40 & \text{CH}_3 & \text{DMAN} & 29^c \\
\end{align*}
\]

\(a\) 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), 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.\textsuperscript{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,\textsuperscript{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).

\begin{equation}
\text{Scheme 1.27 DMA Catalyzed Reductive Lithiation of 2-(3-Chloropropyl)-2-Methyl-1,3-Dioxolane, 1.46.}
\end{equation}

\textsuperscript{a} Oxide coating on Li ribbon was not scraped prior to the reaction.

\textsuperscript{b} Isolated 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDBB</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>Li (disp.), DMA (10 mol%)</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Li (disp.), DBB (10 mol%)</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>Li (disp.)</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^a\) 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>DBB</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>DBB</td>
<td>30(^b)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>DMAN</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>DMA</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>rt</td>
<td>DMA</td>
<td>0(^c)</td>
</tr>
</tbody>
</table>

\(^a\) 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.

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 apparatus\(^{52}\) 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.\textsuperscript{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.\textsuperscript{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.

\[
\text{Ph-S-R} \xrightarrow{\text{1. Reductive Lithiations Conditions}^a, \text{THF}} \text{R-E} \xrightarrow{\text{2. Electrophile}} \text{PhCOH}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenyl Thioether</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Method(^c)</th>
<th>Electrophile</th>
<th>Product</th>
<th>%Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>-78</td>
<td>90</td>
<td>A</td>
<td>PhCOH</td>
<td><img src="image2" alt="Image" /></td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td>-78</td>
<td>90</td>
<td>B</td>
<td>PhCOH</td>
<td><img src="image4" alt="Image" /></td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td>0</td>
<td>15</td>
<td>A</td>
<td>PhCOH</td>
<td><img src="image6" alt="Image" /></td>
<td>80</td>
</tr>
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<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td>-78</td>
<td>60</td>
<td>A</td>
<td>PhCOH</td>
<td><img src="image8" alt="Image" /></td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Image" /></td>
<td>-78</td>
<td>60</td>
<td>C</td>
<td>PhCOH</td>
<td><img src="image10" alt="Image" /></td>
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<tr>
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<td><img src="image11" alt="Image" /></td>
<td>-78</td>
<td>10</td>
<td>D</td>
<td>H(_2)O</td>
<td><img src="image12" alt="Image" /></td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Image" /></td>
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<td>10</td>
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<tr>
<td>8</td>
<td><img src="image15" alt="Image" /></td>
<td>0</td>
<td>15</td>
<td>A</td>
<td>PhCOH</td>
<td><img src="image16" alt="Image" /></td>
<td>88</td>
</tr>
</tbody>
</table>
| Method | 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. Method G: Li powder, Np (1 mol%); Cyclohexanone. Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. Ref. 53a. Ref. 16.

| Method | 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. Method G: Li powder, Np (1 mol%); Cyclohexanone. Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. Ref. 53a. Ref. 16.

| Method | 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. Method G: Li powder, Np (1 mol%); Cyclohexanone. Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. Ref. 53a. Ref. 16.

| Method | 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. Method G: Li powder, Np (1 mol%); Cyclohexanone. Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. Ref. 53a. 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 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 alone 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.

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. 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.

Reaction terminated after 5 min.

% 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 sulfone 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.

Reaction terminated after 5 min.

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).
In order to determine if this unique finding results from an electronic effect or a steric effect, the relative rates of reductive lithiation of secondary alkyl phenyl sulfides, increasing in bulkiness, were compared. Four substrates were individually reductively lithiated with lithium.
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 $^1$H 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2° Alkyl Phenyl Sulfide</th>
<th>Ratio of SM (H) to Diphenyl Disulfide (H)</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.14</td>
<td>3:1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1.20</td>
<td>8:1</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>1.21</td>
<td>34:1</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>1.22</td>
<td>36:1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

a Reaction terminated after 15 min. b Ratio determined from crude $^1$H NMR.
Figure 1.3 Crude \(^1\text{H}\) NMR of Isopropyl Phenyl Sulfide and Diphenyl Disulfide.

Figure 1.4 Crude \(^1\text{H}\) NMR of 2-(Phenylthio)-Butane and Diphenyl Disulfide.
Figure 1.5 Crude $^1$H NMR of 3-(Phenylthio)-Hexane and Diphenyl Disulfide.

Figure 1.6 Crude $^1$H 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 $^1$H 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.

1.14, $R^1 = R^2 = CH_3$
1.21, $R^1 = CH_2CH_3$; $R^2 = CH_2CH_2CH_3$
1.22, $R^1/R^2 = \text{c-C}_8\text{C}_15$

1.14, $R^1 = R^2 = CH_3 26\%^b$
1.21, $R^1 = CH_2CH_3$; $R^2 = CH_2CH_2CH_3 31\%^b$
1.22, $R^1/R^2 = \text{c-C}_8\text{C}_15 35\%^b$

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. 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.

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

The C-S bond cleavage on the Li surface was found to be exothermic and the exothermicity parallels the reactivity trend (Table 1.11). 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.\(^{45}\)

<table>
<thead>
<tr>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

(a) bond dissociation energy in gas phase

\[
\text{PhS} - \text{R} \xrightarrow{\Delta E_{\text{gas}}} \text{PhS} \cdot + \text{R} \cdot
\]

(b) bond dissociation energy on Li surface

\[
\begin{array}{ccc}
\text{R} & \Delta E_{\text{Li}} & \text{R} \\
\text{(Li surface)} & \text{Li surface} & +
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>(\Delta E_{\text{gas}}) (kcal/mol)</th>
<th>(\Delta E_{\text{Li}}) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.14</td>
<td>(i)-Pr</td>
<td>60.2</td>
<td>-27.1</td>
</tr>
<tr>
<td>2</td>
<td>1.20</td>
<td>2-butyl</td>
<td>60.7</td>
<td>-26.4</td>
</tr>
<tr>
<td>3</td>
<td>1.21</td>
<td>3-hexyl</td>
<td>60.7</td>
<td>-24.5</td>
</tr>
<tr>
<td>4</td>
<td>1.28</td>
<td>(t)-Bu</td>
<td>57.1</td>
<td>-24.8</td>
</tr>
<tr>
<td>5</td>
<td>1.40</td>
<td>Me</td>
<td>68.1</td>
<td>-38.0</td>
</tr>
</tbody>
</table>

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.**\(^45\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Radical Adsorption on Li Surface (*)</th>
<th>(\Delta E_{ad}) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.14</td>
<td>(i\text{-Pr}^* + * \rightarrow i\text{-Pr}^*)</td>
<td>-30.2</td>
</tr>
<tr>
<td>2</td>
<td>1.20</td>
<td>(2\text{-butyl}^* + * \rightarrow 2\text{-butyl}^*)</td>
<td>-28.9</td>
</tr>
<tr>
<td>3</td>
<td>1.21</td>
<td>(3\text{-hexyl}^* + * \rightarrow 3\text{-hexyl}^*)</td>
<td>-27.7</td>
</tr>
<tr>
<td>4</td>
<td>1.28</td>
<td>(t\text{-Bu}^* + * \rightarrow t\text{-Bu}^*)</td>
<td>-24.3</td>
</tr>
<tr>
<td>5</td>
<td>1.40</td>
<td>(\text{Me}^* + * \rightarrow \text{Me}^*)</td>
<td>-45.4</td>
</tr>
</tbody>
</table>

### 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, $\mathbf{1.46}$ (Table 1.13, entry 1), and one successful reaction, with 6-chloro-1-hexene, $\mathbf{1.53}$ (entry 3). In order to determine if $\mathbf{1.46}$ 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 $\mathbf{1.47}$ was successfully obtained, in half the amount of time, after capturing the organolithium intermediate with benzaldehyde (entry 2).

Unlike the cyclopentyl product, $\mathbf{1.57}$, that Yus isolated (entry 3), our reductive lithiation of $\mathbf{1.53}$ 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. Furthermore, the short C-Li distance in the adsorbed complexes 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, $\mathbf{1.54}$, and neopentyl chloride, $\mathbf{1.55}$, provided excellent yields of the corresponding alcohol products, $\mathbf{1.48}$ and $\mathbf{1.59}$, 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyl Chloride</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Method(^a)</th>
<th>Electrophile</th>
<th>Product</th>
<th>% Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="" /> 1.46</td>
<td>-78</td>
<td>240</td>
<td>A</td>
<td>(CH(_2))(_3)CO</td>
<td>![image] 1.56</td>
<td>0(^c)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="" /> 1.46</td>
<td>-78</td>
<td>120</td>
<td>B</td>
<td>PhCOH</td>
<td>![image] 1.47</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="" /> 1.53</td>
<td>-30</td>
<td>50</td>
<td>C</td>
<td>Et(_2)CO</td>
<td>![image] 1.57</td>
<td>83(^d)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="" /> 1.53</td>
<td>-45</td>
<td>60</td>
<td>A</td>
<td>PhCOH</td>
<td>![image] 1.58</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="" /> 1.54</td>
<td>-45</td>
<td>30</td>
<td>A</td>
<td>PhCOH</td>
<td>![image] 1.48</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="" /> 1.55</td>
<td>-45</td>
<td>30</td>
<td>A</td>
<td>PhCOH</td>
<td>![image] 1.59</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) 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, 72 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. 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). 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. 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, δ6.08 (d, J = 6.3 Hz) ppm corresponding to the Z-isomer and δ6.30 (d, J = 12.6 Hz) ppm, which corresponds to the E-isomer. This yield closely matches that obtained from the preformed radical-anion reductive cleavage of 1.60 after 90 min at -50 °C. 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.](image)

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>45</td>
<td>H (1.65)</td>
<td>89(^a)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>30</td>
<td>H (1.65)</td>
<td>78(^b)</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>45</td>
<td>D (1.66)</td>
<td>86(^b)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>30</td>
<td>D (1.66)</td>
<td>70(^b)</td>
</tr>
<tr>
<td>5</td>
<td>-78</td>
<td>120</td>
<td>H (1.65)</td>
<td>99(^a)</td>
</tr>
</tbody>
</table>

\(^a\) 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 KMnO₄ or p-Anisaldehyde (PAA). ¹H and ¹³C NMR spectra were recorded on a Bruker DPX-300 spectrometer operating at 300 MHz or 400 MHz for ¹H and 75 MHz for ¹³C at 22 °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 ¹³C are referenced to the central peak of the CHCl₃ 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 CaH₂, and benzaldehyde was washed with saturated NaHCO₃(aq), extracted with Et₂O, and vacuum distilled (~ 20 mm Hg). 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. 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)*

![Chemical Structure]

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).

\[ ^1H \text{NMR (CDCl}_3 \text{) } \delta \text{ (ppm): } 7.14-7.13 \text{ (m, 1H), } 7.12-7.11 \text{ (m, 2H), } 7.00 \text{ (dd, } J = 8.6, 1.0 \text{ Hz, 1H), } 6.93 \text{ (td, } J = 7.3, 1.1 \text{ Hz, 1H), } 2.67 \text{ (s, 6H), } 2.31 \text{ (s, 3H).} \]

**Attempted Production of LDMA** *(Scheme 1.24)*

![Chemical Structure]

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 H\textsubscript{2}O and the product was extracted with Et\textsubscript{2}O. The combined organic extracts were dried over MgSO\textsubscript{4} and concentrated in vacuo in order to completely recover the DMA (0.10 g, 100\% yield). \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 7.23 (t, \(J = 7.2\) Hz, 2 H), 6.74-6.69 (m, 3 H), 2.91 (s, 6 H).

1.4.2 1-Phenylethanol (1.6).

\[
\begin{align*}
\text{OH} \\
\text{\includegraphics[width=0.1\textwidth]{phenylethanol.png}}
\end{align*}
\]

*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 H\textsubscript{2}O. The product was extracted with Et\textsubscript{2}O; the combined organic extracts were dried over MgSO\textsubscript{4} and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1-phenylethanol, 1.6, as a light yellow oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 7.33-7.27 (m, 4 H), 7.26-7.22 (m, 1 H), 4.82 (q, \(J = 6.4\) Hz, 1 H), 2.37 (br, 1 H), 1.44 (d, \(J = 6.4\) Hz, 3 H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 146.0, 128.4, 127.3, 125.5, 70.2, 25.2. These NMR data compare well with the literature values.\textsuperscript{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)

![Structure of 1.14](image)

**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). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (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\(_3\)) \(\delta\) (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\(_2\)O. The product was extracted with Et\(_2\)O and the combined organic extracts were washed with 5% HCl\(_{(aq)}\) followed by H\(_2\)O. 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 NaOH\(_{(aq)}\). The DMOT was extracted with Et\(_2\)O. The combined organic extracts were washed with H\(_2\)O, 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)

\[
\begin{align*}
\text{S} & \quad \text{C} - \text{C} - \text{C} - \text{C} - \text{C} \\
\end{align*}
\]

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)**

![Structure of 2-(Phenylthio)-Butane](image)

**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-(Phenythio)-Hexane (1.21)

\[
\text{1.21}
\]

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 (El⁺) exact mass calculated for C_{12}H_{18}S 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, \textbf{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 H$_2$O (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 Et$_2$O; the combined organic extracts were dried over MgSO$_4$ and concentrated \textit{in vacuo}. Crude $^1$H NMR provided a ratio of the \textbf{1.21} to the diphenyl disulfide, \textbf{1.27}, as 34:1.

\textit{LN Reductive Lithiation of \textbf{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, \textbf{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 H$_2$O. The product was extracted with hexanes; the combined organic extracts were dried over MgSO$_4$ and concentrated \textit{in vacuo}. Flash chromatography on silica gel (100% hexanes) led to recovered starting material \textbf{1.21} (30 mg, 31%).
1.4.7 Cyclooctyl Phenyl Sulfide (1.22)

\[
\text{\includegraphics[width=0.2\textwidth]{cyclooctylphenylsulfide.png}}
\]

**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). \(^1\)H 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); \(^1\)C 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)

![2,2-Bis(phenylthio)propane](image)

*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)

\[
\text{\includegraphics[width=0.1\textwidth]{sulfide.png}}
\]

**Synthesis of 1.28 (Scheme 1.17)**

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.

**Synthesis of 1.28 (Scheme 1.19)**

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 NaHCO₃(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.
DMA Catalyzed Reductive Lithiation of $\textbf{1.28}$ (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, $\textbf{1.28}$ (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 $\textbf{1.28}$ (50 mg, 60%).

Lithium Dispersion Reductive Lithiation of $\textbf{1.28}$ (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, $\textbf{1.28}$ (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 $\textbf{1.28}$ (48 mg, 58%).

Reductive Lithiation of $\textbf{1.40}$ in the Presence of $\textbf{1.28}$ (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)**

![Chemical structure of 1-(Phenylthio)-1-Cyclohexene (1.34)](attachment:image)

*Synthesis of 1.34 (Scheme 1.20)*

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)

![Methyl Phenyl Sulfide](image)

**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)

\[
\begin{array}{c}
\text{SO} \\
\text{C}_6\text{H}_4 \\
\text{S} \\
\end{array}
\]

**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 Et$_2$O; the combined organic extracts were
dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography on silica gel
(EtOAc/hexanes) afforded **1.43** (35 mg, 45% yield) as a white solid. $^1$H NMR (CDCl$_3$) $\delta$ (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); $^{13}$C NMR
(CDCl$_3$) $\delta$ (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 H$_2$O. The product was extracted with hexanes; the combined
organic extracts were dried over MgSO$_4$ and concentrated in vacuo. To the crude product, a 1:1
solution of MeOH/H$_2$O (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 Et$_2$O; the
combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Flash
chromatography on silica gel (Et$_2$O/hexanes) afforded **1.43** (50 mg, 64% yield).
1.4.14 2-(4-Hydroxy-4-Phenylbutyl)-2-Methyl-1,3-Dioxolane (1.47)

![Chemical Structure](attachment:chemical_structure.png)

**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.

**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 °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 1.47 (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 °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 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) as a light yellow oil. ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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).
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 \textit{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 \textit{in vacuo}. Flash chromatography on
silica gel (EtOAc/hexanes) afforded **1.50** (0.33 g, 88% yield) as a light yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ (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); $^{13}$C NMR (CDCl$_3$) $\delta$ (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 C$_{13}$H$_{15}$O 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 H$_2$O in an ice-water bath. The product was extracted with Et$_2$O; the combined organic extracts were dried over MgSO$_4$ 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 °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 °C and then was quenched with H$_2$O. The product was extracted with Et$_2$O; 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. $^1$H 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)

![Chemical Structure](image)

**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: $^1$H NMR (CDCl$_3$) $\delta$ (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$_3$) $\delta$ (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)

![2-(2-Methylphenyl)Ethanol](image)

*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$_2$O. The product was extracted with Et$_2$O; 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. $^1$H NMR (CDCl$_3$) $\delta$ (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$_3$) $\delta$ (ppm): 136.5, 136.5, 130.4, 129.7, 126.0, 126.0, 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)

![Chemical Structure](image)

*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 D$_2$O. The product was extracted with diethyl ether; the combined organic extracts were dried over MgSO$_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 1.66 (96 mg, 70% yield) as a colorless oil. $^1$H NMR (CDCl$_3$) $\delta$ (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); $^{13}$C NMR (CDCl$_3$) $\delta$ (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. 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. 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. 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. Several valuable
protocols have been devised for the synthesis of the more stable equatorial alcohols; 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’s 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\textsuperscript{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 unavailable\textsuperscript{83} 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.\textsuperscript{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 CuCl\textsubscript{2}•2H\textsubscript{2}O\textsuperscript{82} and an 8:1 molar ratio of lithium powder to FeCl\textsubscript{2}•4H\textsubscript{2}O.\textsuperscript{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 CuCl\textsubscript{2}•2H\textsubscript{2}O and in the case of the more highly hydrated FeCl\textsubscript{2}•4H\textsubscript{2}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 \textsuperscript{1}H NMR spectra and the major
product was determined by comparing literature NMR values and/or the \( J \) values of cyclohexane (Figure 2.1).\(^{58}\)

![Diagram of cyclohexane](image)

**Figure 2.1** Coupling \( J \) Values for Cyclohexane.

In the reduction of 4-\textit{tert}-butylcyclohexanone, \textbf{2.3}, (Table 2.1), in which the bulky \textit{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, \textit{trans}-4-\textit{tert}-butylcyclohexanol, \textbf{2.4a} (entries 1 and 2). Based on the \( J \) values shown in Figure 2.1, the CH-OH at \( \delta \) 3.52 (tt, \( J = 10.8, 4.2 \text{ Hz} \)) ppm (see Figure 2.2) confirms the equatorial position of the alcohol and the \textit{trans} structure of the alcohol product.\(^{84}\) This selectivity result resembles those obtained with the most common metal hydrides LiAlH\(_4\) 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 \textit{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 \textbf{2.3} with 1.1 equivalents of \textit{Al}-methanesulfonyldiisobutylalane (DIBAO\(_3\)SCH\(_3\)) at room temperature to obtain 99% (as determined by GC after 72 h.) of the more stable \textit{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 DIBAO\(_3\)SCH\(_3\) 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** $^1$H NMR of cis- and trans-4-tert-Butylcyclohexanol.
Table 2.1 Stereoselective Reduction of 4-tert-Butylcyclohexanone.

![Diagram of ketone and products](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
<th>Ratio (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂•2H₂O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h</td>
<td>83</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂•4H₂O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h</td>
<td>77</td>
<td>100:0°</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄, THF</td>
<td>-</td>
<td>90:10°</td>
</tr>
<tr>
<td>4</td>
<td>9-BBN, THF</td>
<td>-</td>
<td>92:8°</td>
</tr>
<tr>
<td>5</td>
<td>NaH-tert-AmONa-Ni(OAc)₂-LiBr, THF, 40 °C, 4 h</td>
<td>93</td>
<td>92:8°</td>
</tr>
<tr>
<td>6</td>
<td>Li (1 equiv), NH₃ (liquid), Et₂O, reflux, 30 min</td>
<td>57</td>
<td>100:0°</td>
</tr>
<tr>
<td>7</td>
<td>DIBAO₃SCH₃ (1.1 equiv), Et₂O, rt, 72 h</td>
<td>99°</td>
<td>94:6°</td>
</tr>
</tbody>
</table>

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 CuCl₂•2D₂O, prepared from anhydrous CuCl₂ and D₂O, 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 CuCl₂•2D₂O.](image)

*Deuterium 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, 2.8 (Scheme 2.3) to ease the isolation process. The diastereoselectivity that we obtained surpasses that observed with common reducing systems LiAlH₄, NaBH₄, 9-BBN (Table 2.2, entries 3-5). 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). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>% Yield$^{a}$</th>
<th>Ratio (a:b)$^{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$$^\cdot$2H$_2$O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 10 min</td>
<td>80$^c$</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_3$$^\cdot$4H$_2$O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 10 min</td>
<td>99$^c$</td>
<td>95:5$^d$</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$, THF</td>
<td>-</td>
<td>65:35$^e$</td>
</tr>
<tr>
<td>4</td>
<td>9-BBN, THF</td>
<td>-</td>
<td>60:40$^f$</td>
</tr>
<tr>
<td>5</td>
<td>NaBH$_4$, THF</td>
<td>-</td>
<td>69:31$^e$</td>
</tr>
<tr>
<td>6</td>
<td>Li, NH$_3$ (liquid), Et$_2$O, EtOH, 100 min</td>
<td>63</td>
<td>100:0$^f$</td>
</tr>
<tr>
<td>7</td>
<td>DIBAO$_3$SCF$_3$ (1.1 equiv), Et$_2$O, rt, 1 h</td>
<td>94$^g$</td>
<td>91:9$^g$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.
$^b$ Diastereomeric ratio determined by $^1$H 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.
Interestingly, the reduction of (±)-camphor, 2.9 (Table 2.3, entries 1 and 2) required 2 equivalents of the metal (II) salts and a longer reaction time (24 h) leading to ratios of 96:4 and 95:5 of the more stable endo-borneol, 2.10a, to exo, 2.10b. Product 2.10a was confirmed by comparing the $^1$H NMR to the literature values. Yus reported that, for the same reaction time and equivalents, the reduction of 2.9 yielded 55% of borneol (endo/exo 85:15, entry 3) with CuCl$_2$•2H$_2$O and 62% of borneol (endo/exo 90:10, entry 4) with FeCl$_2$•4H$_2$O. Thus, a higher yield and diastereoselectivity was obtained under our conditions, that is, in the absence of an aromatic electron transfer reagent.
Table 2.3 Stereoselective Reduction of (±)-Camphor.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield$^a$</th>
<th>Ratio (a:b)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$$\cdot$2H$_2$O (2 equiv), Li (disp., 8 equiv), THF, rt, 24 h</td>
<td>65</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$$\cdot$4H$_2$O (2 equiv), Li (disp., 12 equiv), THF, rt, 24 h</td>
<td>78</td>
<td>95:5$^c$</td>
</tr>
<tr>
<td>3</td>
<td>CuCl$_2$$\cdot$2H$_2$O (2 equiv), DBB (10 mol%), Li (powder, 16 equiv), THF, rt, 24 h</td>
<td>55</td>
<td>85:15$^d$</td>
</tr>
<tr>
<td>4</td>
<td>FeCl$_2$$\cdot$4H$_2$O (2 equiv), DBB (10 mol%), Li (powder, 16 equiv), THF, rt, 24 h</td>
<td>62</td>
<td>90:10$^d$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield of 2.10 after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. $^b$ Diastereomeric ratio determined by $^1$H NMR. $^c$ See Figure 2.4. $^d$ Ref. 75.
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 $\delta$ 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 neoiso-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).
Table 2.4 Stereoselective Reduction of (-)-Menthone.

![Menthone reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
<th>Ratio (a:b:c:d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂•2H₂O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h</td>
<td>86</td>
<td>96:4:0:0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂•4H₂O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h</td>
<td>99</td>
<td>95:5:0:0</td>
</tr>
<tr>
<td>3</td>
<td>Li (3 equiv), Et₂O (wet), rt</td>
<td>87</td>
<td>74:9:13:4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield of 2.12 after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. <sup>b</sup> Diastereomeric ratio determined by <sup>1</sup>H NMR. <sup>c</sup> See Figure 2.5. <sup>d</sup> Ref. 91.
When our methodology was applied to a mixture of cis- and trans-1-decalone, Figure 2.5 (Table 2.5, entries 1 and 2), the major diastereomeric product, (±)-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. (±)-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. Houk and co-workers observed only 60% of the thermodynamically stable equatorial alcohol after 24 h. with the NaBH₄ reduction of trans-1-decalone (Table 2.5, entry 3). Yus et. al. isolated the less thermodynamically stable
axial alcohol, (±)-trans,trans-decahydro-1-naphthol, with their M(II)Cl₂•XH₂O-Li-DBB reduction of trans-1-decalone (Table 2.5, entries 4 and 5).

Table 2.5 Stereoselective Reduction of 1-Decalone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
<th>Ratio (a:b:c:d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂•2H₂O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 2 h</td>
<td>82</td>
<td>92:5:3:0²⁴</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂•4H₂O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 2 h</td>
<td>95</td>
<td>94:4:2:0</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄, MeOH, rt, 24 h</td>
<td>-</td>
<td>60:40:0:0²⁶</td>
</tr>
<tr>
<td>4</td>
<td>CuCl₂•2H₂O (1.5 equiv), DBB (10 mol%), Li (powder, 12 equiv), THF, rt, 3 h</td>
<td>84</td>
<td>1:99:0:0²⁷</td>
</tr>
<tr>
<td>5</td>
<td>FeCl₂•4H₂O (1.5 equiv), DBB (10 mol%), Li (powder, 12 equiv), THF, rt, 3 h</td>
<td>91</td>
<td>1:99:0:0²⁷</td>
</tr>
</tbody>
</table>

² Commercially available unknown mixture of cis and trans from Sigma-Aldrich. ²⁴ Isolated yield of 2.14 after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. ²⁶ Diastereomeric ratio determined by ¹H NMR. ²⁷ See Figure 2.6. ²⁸ trans-1-decalone starting material; Ref. 92. ²⁹ trans-1-decalone starting material; Ref. 75.
Unfortunately, the reduction of a mixture of cis- and trans-2-decalone, 2.15 (~20:80, Figure 2.7)\textsuperscript{94} under the conditions developed in our work, was not stereoselective (Scheme 2.4). The inseparable decahydro-2-naphthols, 2.16, [(±)-cis,trans, 2.16a, (±)-trans,trans, 2.16b, and (±)-cis,cis, 2.16c] were isolated in almost equal amounts, as determined by \( ^1 \)H NMR (see Appendix). Product 2.16 was confirmed by comparing the \( ^1 \)H NMR to the literature values.\textsuperscript{84}
Scheme 2.4 Reduction of 2-Decalone. "Commercially available mixture of cis and trans (~20:80, see Figure 2.7).\(^b\) Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.

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 FeCl₂·4H₂O in comparison to the
CuCl\(_2\)•2H\(_2\)O. Furthermore, 2 equiv of CuCl\(_2\)•2H\(_2\)O 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 \(\delta 3.72\) (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 DIBAO\(_3\)SCF\(_3\) 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** \(^1\)H NMR of cis-3,3,5-Trimethylcyclohexanol  (Table 2.6, entries 1 and 2).
Table 2.6 Stereoselective Reduction of 3,3,5-Trimethylcyclohexanone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield$^a$</th>
<th>Ratio (a:b)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$$^\bullet$2H$_2$O (2 equiv), Li (disp., 8 equiv), THF, rt, 1 h</td>
<td>26</td>
<td>100:0$^c$</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$$^\bullet$4H$_2$O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 1 h</td>
<td>70</td>
<td>100:0$^c$</td>
</tr>
<tr>
<td>3</td>
<td>DIBAO$_3$SCF$_3$ (1.1 equiv), Et$_2$O, rt, 72 h</td>
<td>99.8$^d$</td>
<td>98:2$^d$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield of 2.18 after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.  
$^b$ Diastereomeric ratio determined by $^1$H 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 position$^{95}$ 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 $^1$H NMR to the literature methyl peaks at $\delta$ 1.06 ppm and $\delta$ 0.99 ppm.$^{96}$ The LiAlH$_4$ reduction of 2.19 also provides a 60:40 cis to trans ratio of 3-
methylcyclopentanol (entry 3). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
<th>Ratio (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$$\cdot$2H$_2$O (1 equiv), Li (disp., 3 equiv), THF, rt, 5 min</td>
<td>63$^d$</td>
<td>60:40$^e$</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$$\cdot$4H$_2$O (1 equiv), Li (disp., 5 equiv), THF, rt, 5 min</td>
<td>70$^d$</td>
<td>60:40$^e$</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$, THF</td>
<td>-</td>
<td>60:40$^e$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after column chromatography (silica gel, EtOAc/hexanes) based on the starting material.
$^b$ Diastereomeric ratio determined by $^1$H NMR. $^c$ 3:1 ratio of lithium dispersion to CuCl$_2$$\cdot$2H$_2$O. $^d$ Isolated yield of benzyl-ether product, 2.21. $^e$ See Figure 2.9. $^f$ 5:1 ratio of lithium dispersion to FeCl$_2$$\cdot$4H$_2$O. $^g$ Determined by IR, Ref. 97.
Scheme 2.5 Crude Alcohol 2.20 Protected as Benzyl Ether.

Figure 2.9 Crude $^1$H NMR of cis- and trans-3-Methylocyclopentanol (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-\text{OH} at δ 3.61 (tt, \( J = 10.8, 4.2 \text{ Hz} \)) 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 \textit{Streptomyces} C53 in 94% in a ratio of 55:45 \textit{cis}-3-(trifluoromethyl)cyclohexanol, 2.23a, to \textit{trans}, 2.23b, after 24 h (entry 3). 98

![Scheme 2.6 Crude Alcohol 2.23 Protected as Benzyl Ether.](image-url)
Table 2.8 Stereoselective Reduction of 3-(Trifluoromethyl)cyclohexanone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ratio (a:b)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl&lt;sub&gt;2&lt;/sub&gt;•2H&lt;sub&gt;2&lt;/sub&gt;O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 1 h</td>
<td>70&lt;sup&gt;c&lt;/sup&gt;</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>FeCl&lt;sub&gt;2&lt;/sub&gt;•4H&lt;sub&gt;2&lt;/sub&gt;O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 1 h</td>
<td>85&lt;sup&gt;c&lt;/sup&gt;</td>
<td>97:3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><em>Streptomyces</em> C53, EtOH, 24 h</td>
<td>94</td>
<td>55:45&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> Diastereomeric ratio determined by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield of benzyl-ether product, 2.24. <sup>d</sup> See Figure 2.10.

<sup>e</sup> Determined by GLC, Ref. 98.
The hindered steroidal ketone, 3α-hydroxy-5α-androstan-17-one, 2.25, was diastereoselectively reduced to 5α-androstane-3α,17β-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 3α-hydroxy group did not affect the ketone reduction. Satoh and co-workers indicated that the reduction of 2.25 with NaBH4 alone is difficult; therefore, they employed a large excess of NaBH4 (10 equiv) and PdCl2 in their reduction of 3α-hydroxy-5α-androstan-17-one to obtain 2.26a in 96% yield (entry 3).100
Table 2.9 Stereoselective Reduction of 3α-Hydroxy-5α-Androstan-17-one.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
<th>Ratio (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$$\cdot$2H$_2$O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 4 h</td>
<td>75</td>
<td>100:0$^c$</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$$\cdot$4H$_2$O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 4 h</td>
<td>96</td>
<td>100:0$^c$</td>
</tr>
<tr>
<td>3</td>
<td>NaBH$_4$ (10 equiv), PdCl$_2$ (2 equiv), MeOH, rt, 1 h</td>
<td>96</td>
<td>100:0$^d$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield of 2.26 after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. $^b$ Diastereomeric ratio determined by $^1$H NMR. $^c$ See Figure 2.11. $^d$ Determined by GLC, Ref. 100.
The reduction of 4,4′-dimethoxybenzophenone, \textbf{2.27}, (Scheme \textbf{2.7}) yielded bis(4-methoxyphenyl)methanol, \textbf{2.28}, in moderate or good yield depending on whether the iron or copper salt was employed.
Scheme 2.7 Reduction of 4,4\textsuperscript{-}Dimethoxybenzophenone.

\begin{align*}
\text{M(II)Cl}_2 \cdot XH_2O (1.5 \text{ equiv}), \text{Li (disp.)} & \rightarrow \\
\text{THF, rt, 2 h} & \rightarrow \\
\text{M = Cu, } X = 2 & 83\%^a \\
\text{M = Fe, } X = 4 & 60\%^a \\
\end{align*}

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

There have been many reports of biological reductions\textsuperscript{101} and asymmetric hydrogenations\textsuperscript{102} 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 \textsuperscript{1}H NMR to the literature values.\textsuperscript{102a}
Table 2.10 Reduction of 3-Quinuclidinone.

![Conversion of 2.29 to 2.30](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl$_2$•2H$_2$O (1.5 equiv), Li (disp., 6 equiv), THF, rt, 24 h</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$•4H$_2$O (1.5 equiv), Li (disp., 9 equiv), THF, rt, 24 h</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td><em>M. piriformis</em> (2.0 g/L), 12 days, Amberlite IR-120</td>
<td>73$^b$</td>
</tr>
<tr>
<td>4</td>
<td>Ru(S$<em>{p}$S$</em>{N}$) (0.005%), t-BuOK, 2-propanol, H$_2$ (30 atm), 6 h</td>
<td>50$^c$</td>
</tr>
</tbody>
</table>

$^a$ 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 CuCl$_2$•2H$_2$O 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.\textsuperscript{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 D\textsubscript{2}O, 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.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Cu(II)</th>
<th>Product</th>
<th>% Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>CuCl₂•2H₂O</td>
<td>2.4a</td>
<td>83</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>hexanes</td>
<td>CuCl₂•2H₂O</td>
<td>2.4a</td>
<td>54</td>
<td>100:0</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>CuCl₂ (anhydrous)</td>
<td>2.4a</td>
<td>28</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>-</td>
<td>2.4a</td>
<td>26</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>Water (1.1 equiv)</td>
<td>2.4a</td>
<td>42</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>Water (2.2 equiv)</td>
<td>2.4a</td>
<td>48</td>
<td>94:6</td>
</tr>
</tbody>
</table>

*a The structure of the major diastereoisomer is shown. *b Isolated yield of 2.4a after column chromatography (silica gel, EtOAc/hexanes) based on the starting material. *c Diastereomeric 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.\(^\text{54}\) 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 FeCl₂•4H₂O, 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.

\[
\begin{array}{cccccc}
\text{Entry} & \text{Ketone} & \text{Metal (II)} & \text{Equiv} & \text{Product}^c & \% \text{Yield}^b & \text{dr}^c \\
1 & \begin{array}{c}
\text{Cyclic ketone} \\
2.3
\end{array} & \text{Cu} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.4a
\end{array} & 86 & 96:4 \\
2 & \begin{array}{c}
\text{Cyclic ketone} \\
2.3
\end{array} & \text{Fe} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.4a
\end{array} & 85 & 100:0 \\
3 & \begin{array}{c}
\text{Cyclic ketone} \\
2.9
\end{array} & \text{Cu} & 2 & \begin{array}{c}
\text{Product image} \\
2.10a
\end{array} & 44 & 100:0 \\
4 & \begin{array}{c}
\text{Cyclic ketone} \\
2.9
\end{array} & \text{Fe} & 1 & \begin{array}{c}
\text{Product image} \\
2.10a
\end{array} & 64 & 90:10 \\
5 & \begin{array}{c}
\text{Cyclic ketone} \\
2.11
\end{array} & \text{Cu} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.12a
\end{array} & 99 & 93:7 \\
6 & \begin{array}{c}
\text{Cyclic ketone} \\
2.11
\end{array} & \text{Fe} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.12a
\end{array} & 99 & 94:6 \\
7 & \begin{array}{c}
\text{Cyclic ketone} \\
2.15^d
\end{array} & \text{Cu} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.16
\end{array} & 73 & - \\
8 & \begin{array}{c}
\text{Cyclic ketone} \\
2.15^d
\end{array} & \text{Fe} & 1.5 & \begin{array}{c}
\text{Product image} \\
2.16
\end{array} & 83 & - \\
\end{array}
\]
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 \(^1\)H 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. \(^{75,80-82}\) In order to determine the significance of an arene electron transfer catalyst in our work, 10 mol% of DBB was added to the CuCl\(_2\)•2H\(_2\)O-granular lithium reduction of various substrates (Table 2.13). The ratio of the starting material (SM) to the product was determined from \(^1\)H 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 CuCl\(_2\)•2H\(_2\)O or the FeCl\(_2\)•4H\(_2\)O 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, 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Metal (II)</th>
<th>DBB</th>
<th>Productb</th>
<th>Ratio SM/Productc</th>
<th>drd</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3</td>
<td>Cu</td>
<td>Yes</td>
<td>2.4a</td>
<td>2:1</td>
<td>90:10</td>
<td>2.12</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>Cu</td>
<td>No</td>
<td>2.4a</td>
<td>2:1</td>
<td>95:5</td>
<td>2.13</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>Fe</td>
<td>Yes</td>
<td>2.4a</td>
<td>17:1</td>
<td>100:0</td>
<td>2.14</td>
</tr>
<tr>
<td>4</td>
<td>2.3</td>
<td>Fe</td>
<td>No</td>
<td>2.4a</td>
<td>19:1</td>
<td>100:0</td>
<td>2.15</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>Cu</td>
<td>Yes</td>
<td>2.7a</td>
<td>e</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2.6</td>
<td>Fe</td>
<td>Yes</td>
<td>2.7a</td>
<td>e</td>
<td>98:2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2.11</td>
<td>Cu</td>
<td>Yes</td>
<td>2.12a</td>
<td>12:1</td>
<td>100:0</td>
<td>2.16</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>----</td>
<td>-----</td>
<td>-------</td>
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</tr>
<tr>
<td>8</td>
<td></td>
<td>Cu</td>
<td>No</td>
<td>2.12a</td>
<td>8:1</td>
<td>100:0</td>
<td>2.17</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Fe</td>
<td>Yes</td>
<td>2.12a</td>
<td>9:1</td>
<td>100:0</td>
<td>2.18</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Fe</td>
<td>No</td>
<td>2.12a</td>
<td>14:1</td>
<td>100:0</td>
<td>2.19</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Cu</td>
<td>Yes</td>
<td>2.18a</td>
<td>4:1</td>
<td>96:4</td>
<td>2.20</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>Cu</td>
<td>No</td>
<td>2.18a</td>
<td>1.5:1</td>
<td>94:6</td>
<td>2.21</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Fe</td>
<td>Yes</td>
<td>2.18a</td>
<td>7:1</td>
<td>97:3</td>
<td>2.22</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>Fe</td>
<td>No</td>
<td>2.18a</td>
<td>2:1</td>
<td>97:3</td>
<td>2.23</td>
</tr>
</tbody>
</table>

\(^a\) Reaction terminated after 4 h. \(^b\) The structure of the major diastereoisomer is shown. \(^c\) Ratio determined by \(^1\)H NMR. \(^d\) Diastereomeric ratio determined by \(^1\)H 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 2.12 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.3 with CuCl$_2$·2H$_2$O (Table 2.13, entry 1).

Figure 2.13 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.3 with CuCl$_2$·2H$_2$O (Table 2.13, entry 2).
Figure 2.14 Crude $^1\text{H}$ NMR of DBB Catalyzed Reduction of 2.3 with FeCl$_2$$\cdot$4H$_2$O (Table 2.13, entry 3).

Figure 2.15 Crude $^1\text{H}$ NMR of Non-Catalyzed Reduction of 2.3 with FeCl$_2$$\cdot$4H$_2$O (Table 2.13, entry 4).
Figure 2.16 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.11 with CuCl$_2$·2H$_2$O (Table 2.13, entry 7).

Figure 2.17 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.11 with CuCl$_2$·2H$_2$O (Table 2.13, entry 8).
Figure 2.18 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.11 with FeCl$_2$·4H$_2$O (Table 2.13, entry 9).

Figure 2.19 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.11 with FeCl$_2$·4H$_2$O (Table 2.13, entry 10).
Figure 2.20 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.17 with CuCl$_2$·2H$_2$O (Table 2.13, entry 11).

Figure 2.21 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.17 with CuCl$_2$·2H$_2$O (Table 2.13, entry 12).
Figure 2.22 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.17 with FeCl$_2$·4H$_2$O (Table 2.13, entry 13).

Figure 2.23 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.17 with FeCl$_2$·4H$_2$O (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 CuCl\(_2\)\(\cdot\)2H\(_2\)O and FeCl\(_2\)\(\cdot\)4H\(_2\)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 CuCl\(_2\)\(\cdot\)2H\(_2\)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 CuCl\(_2\)\(\cdot\)2H\(_2\)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 FeCl\(_2\)\(\cdot\)4H\(_2\)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.

\[
\begin{align*}
\text{Entry} & \quad \text{Ketone} & \quad \text{Metal (II)} & \quad \text{Equiv} & \quad \text{Rxn. Time (h)} & \quad \text{Product}^a & \quad \%Yield^b \\
1 & \begin{array}{c}
2.31
\end{array} & \text{Cu} & 1.5 & 4 & \begin{array}{c}
\text{Product}
\end{array} & 1.6 \\
2 & \begin{array}{c}
2.31
\end{array} & \text{Cu} & 1.5 & 24 & \begin{array}{c}
\text{Product}
\end{array} & 38^c,d \\
3 & \begin{array}{c}
2.31
\end{array} & \text{Fe} & 1.5 & 1 & \begin{array}{c}
\text{Product}
\end{array} & 38^e \\
4 & \begin{array}{c}
2.32
\end{array} & \text{Cu} & 1.5 & 4 & \begin{array}{c}
\text{Product}
\end{array} & 99 \\
5 & \begin{array}{c}
2.32
\end{array} & \text{Fe} & 1.5 & 4 & \begin{array}{c}
\text{Product}
\end{array} & 99
\end{align*}
\]

*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 $^1$H 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 CuCl$_2$$\cdot$2H$_2$O-granular lithium reduction of 2.32 (Scheme 2.8). The ratio of the starting material (SM) to the product was determined from $^1$H 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%).

Ratio of 2.32 to 2.33
DBB 54:1\textsuperscript{a,b}
No DBB 13.5:1\textsuperscript{a,c}

\textsuperscript{a} Ratio determined by crude \textsuperscript{1}H NMR. \textsuperscript{b} See Figure 2.24. \textsuperscript{c} See Figure 2.25.
Figure 2.24 Crude $^1$H NMR of DBB Catalyzed Reduction of 2.32 with CuCl$_2$·2H$_2$O (Scheme 2.8).

Figure 2.25 Crude $^1$H NMR of Non-Catalyzed Reduction of 2.32 with CuCl$_2$·2H$_2$O (Scheme 2.8).
2.3 CONCLUSIONS

It was found that the reductions of monocyclic and bicyclic 6-membered ring ketones using lithium and either FeCl₂•4H₂O or CuCl₂•2H₂O 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 FeCl₂•4H₂-O-Li and CuCl₂•2H₂-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 \(\mu m\)). 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 KMnO4; solution of p-anisaldehyde (PAA); or iodine (I2). 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 CaH2. 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. \(^1\)H and \(^{13}\)C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz or 400 MHz for \(^1\)H and 75 MHz for \(^{13}\)C at 22 °C unless otherwise noted. Chemical shift data are reported in units of \(\delta\) (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for \(^{13}\)C are referenced to the central peak of CHCl3 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.**

\(\text{CuCl}_2\cdot2\text{H}_2\text{O and Lithium Dispersion.}\)

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).
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).

![1-Phenylethanol](image)

**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).
$^1$H NMR (CDCl$_3$) δ (ppm): 7.33-7.27 (m, 4H), 7.26-7.22 (m, 1H), 4.82 (q, $J = 6.4$ Hz, 1H), 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).

![Chemical structures of 2.4a and 2.4b](image)

**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. $^1$H 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$_3$) $\delta$ (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).

*CuCl$_2$$\cdot$2H$_2$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$_2$O in an ice-water bath. The mixture was filtered through a celite pad and washed with Et$_2$O. The filtrate was further extracted with Et$_2$O; 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. CuCl\(_2\)•2D\(_2\)O (prepared from anhydrous CuCl\(_2\) and D\(_2\)O; 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).

![2.7](image_url)

*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, \( \text{2.6} \) (0.11 g, 1.0 mmol), and a reaction time of 10 min afforded \( \text{2.7a} \) as a crude oil with a *trans* to *cis* ratio of 95:5

**General Method E** (Table 2.13, entry 5)

2-methylcyclohexanone, \( \text{2.6} \) (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, \( \text{2.6} \) (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)

![Scheme 2.3](image)

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 \( \text{2.7} \) (~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).

2.12a 2.12b

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. $^1$H NMR (CDCl3) $\delta$ (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$_3$) $\delta$ (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).

![Chemical structures](2.14a:2.14b:2.14c)

**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.
• (±)-trans,cis-decahydro-1-naphthol (2.14a) $^1$H 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 (s); 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 C$_{10}$H$_{17}$O is 153.1279, found 153.1284.

• (±)-trans,trans-decahydro-1-naphthol (2.14b) $^1$H NMR (CDCl$_3$) δ (ppm): 3.78-3.74 (m, 1H).

• (±)-cis,trans-decahydro-1-naphthol (2.14c) $^1$H NMR (CDCl$_3$) δ (ppm): 3.70-3.61 (m, 1H).

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.

- (±)-cis,trans-Decahydro-2-naphthol (2.16a) \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (ppm): 3.83 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) (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.\(^{108}\)

- (±)-trans,trans-decahydro-2-naphthol (2.16b) \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (ppm): 3.65-3.55 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) (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.\(^{84}\)

- (±)-cis,cis-decahydro-2-naphthol (2.16c) \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (ppm): 3.65-3.55 (m, 1H), 2.26 (br, 1H), 1.98-0.84 (m, 16H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) (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, \(2.16\text{a}\), to trans,trans, \(2.16\text{b}\), to cis,cis, \(2.16\text{c}\).

**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, \(2.16\text{a}\), to trans,trans, \(2.16\text{b}\), to cis,cis, \(2.16\text{c}\).

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

![OH](image)

**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 \(2.18\text{a}\) (37 mg, 26% yield) as a white solid. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (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); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) (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); 152
2925 (m); 1641 (m); 1460 (w); 1080 (w); 1026 (w) cm$^{-1}$; TOF MS (ES$^+$) exact mass calculated for C$_9$H$_{17}$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).**

![Cis and trans isomers of 3-methylcyclopentanol](image)

**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) \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (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); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) (ppm): 73.7, 44.1, 35.4, 32.9, 32.2, 21.0. These NMR data compare well with the literature values.

• _trans_-3-Methylcyclopentanol (2.20b) \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (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); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) (ppm): 73.7, 44.3, 35.2, 32.4, 31.8, 20.6. These NMR data compare well with the literature values.

_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).

![2.23a](image1)

![2.23b](image2)

**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)*

![Chemical Structure](image)

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\textsubscript{14}H\textsubscript{17}OF\textsubscript{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\(\alpha\)-Androstan-Diol (2.26).

\begin{center}
\includegraphics[width=0.4\textwidth]{2.26.png}
\end{center}

\textit{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\(\alpha\)-hydroxy-5\(\alpha\)-androstan-17-one, 2.25 (0.29 g, 1.0 mmol), and a reaction time of 4 h afforded 2.26\(a\) (0.22 g, 75% yield) as a white solid. \(^1\text{H NMR (CDCl}_3\text{)}\) \(\delta\) (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);

\(^{13}\text{C NMR (CDCl}_3\text{)}\) \(\delta\) (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\textsubscript{19}H\textsubscript{31}O\textsubscript{2} is 291.2324, found 291.2347.

\textit{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\(\alpha\)-hydroxy-5\(\alpha\)-androstan-17-one, 2.25 (0.29 g, 1.0 mmol), and a reaction time of 4 h afforded 2.26\(a\) (0.28 g, 96% yield).
2.4.17 Bis(4-methoxyphenyl)methanol (2.28). (Scheme 2.7).

![Chemical structure of Bis(4-methoxyphenyl)methanol](image)

**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. $^1$H NMR (CDCl$_3$) $\delta$ (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); $^{13}$C NMR (CDCl$_3$) $\delta$ (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).

![Chemical structure of 3-Quinuclidinol](image)

**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. $^1$H 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).

![1,1-Diphenylmethanol](image)

**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. $^1$H 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 values.$^{111}$
**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

$^1$H and $^{13}$C NMR Spectra of Synthetically Prepared Compounds
5-(Phenylthio)-1-Pentene, 1.16
2-(Phenylthio)-Butane, 1.20
3-(Phenylthio)-Hexane, 1.21
2,2-Bis(phenylthio)propane, 1.25
Diphenyl Disulfide, 1.27
1-(Phenythio)-1-Cyclohexene, 1.34
tert-Butyl Phenyl Sulfone, 1.42
Methyl Phenyl Sulfone, 1.43
2-(4-Hydroxy-4-Phenylbutyl)-2-Methyl-1,3-Dioxolane, 1.47
1-Phenylhex-5-en-1-ol, 1.49
(Z)-4-Ethoxy-1-Phenylbut-3-en-1-ol, 1.62

(E)-4-Ethoxy-1-Phenylbut-3-en-1-ol, 1.62
2-(2-Deuteriomethylphenyl)Ethanol, 1.66
1-deutero-4-tert-Butylcyclohexanol, 2.5
trans-2-Methylcyclohexanol, 2.7a

cis-2-Methylcyclohexanol, 2.7b
Benzyl trans-2-Methylcyclohexyl Ether, 2.8
Endo-Borneol, 2.10a

Exo-Borneol, 2.10b
(-)-Menthol, 2.12a

Neo-Menthol, 2.12b

189
(±)-trans,cis-Decahydro-1-naphthol, 2.14a

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

(±)-cis,trans-Decahydro-1-naphthol, 2.14c
(±)-cis,trans-Decahydro-2-naphthol, 2.16a

(±)-trans,trans-Decahydro-2-naphthol, 2.16b

(±)-cis,cis-Decahydro-2-naphthol, 2.16c
cis-3,3,5-Trimethylcyclohexanol, 2.18a
Benzyl cis-3-Methylcyclopentyl Ether, 2.21a

Benzyl trans-3-Methylcyclopentyl Ether, 2.21b
cis-3-(Trifluoromethyl)cyclohexanol, 2.23a

trans-3-(Trifluoromethyl)cyclohexanol, 2.23b
Benzyl cis-3-(Trifluoromethyl)cyclohexyl Ether, 2.24
Benzyl cis-3-(Trifluoromethyl)cyclohexyl Ether, 2,24
5α-Androstane-3α,17β-Diol, 2.26a
Bis(4-Methoxyphenyl)methanol, 2.28
3-Quinuclidinol, 2.30
1,1-Diphenylmethanol, 2.33


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Unpublished work, Roman Ivanov’s lab notebooks.


*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.


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


61 Wilfred, W. L. F.; Chai, C. L. L. Purification of Laboratory Chemicals. Elsevier, 2003; Ed. 5, pp 119


83 NiCl$_2$$	extperiodcentered$2H$_2$O is prepared from commercially available NiCl$_2$$	extperiodcentered$6H$_2$O 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.


104 According to Huffman and Charles, in the metal-ammonia reduction of ketones, the $\pi^*$ 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.\textsuperscript{79a}


