EVALUATION OF
1,1-DIMETHYL-5,7-DI-\(t\)-BUTYLSPIRO[2.5]OCTA-4,7-DIEN-6-ONE
AS A MECHANISTIC PROBE FOR SINGLE ELECTRON TRANSFER

by

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Evaluation of 1,1-Dimethyl-5,7-di-t-butylspiro[2.5]octa-4,7-dien-6-one as a Mechanistic Probe for Single Electron Transfer

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(ABSTRACT)

Single electron transfer (SET) mechanisms are becoming ubiquitous in modern organic chemistry. However, it is often difficult to distinguish SET mechanisms from polar mechanisms. Kinetics, products and product distributions, and response to perturbation in solvent and substituents are often identical between the two mechanisms. Detection techniques such as EPR, CIDNP, and UV absorption can often detect “blind” pathways and thus cannot provide unambiguous evidence regarding the true mechanism of interest. In recent years mechanistic probes have been developed which can test for single electron transfer in the mechanism of interest in a more unambiguous manner, although a given probe is often applicable to a narrower range of reactions.

In this work 1,1-dimethyl-5,7-di-t-butylspiro[2.5]octa-4,7-dien-6-one (6) is presented as a new “hypersensitive” probe for single electron transfer to conjugated carbonyl compounds. This new probe functions in a rather unique fashion, allowing interpretation of the mechanism at work on the basis of the regiochemistry of spirocyclic ring opening. This “regiodifferentiation” based probe was studied with a variety of nucleophiles (particularly Grignard reagents) and has been found to be effective in differentiating SET from polar processes, although surprising results indicative of polar pathways in the case of reaction of 6 with Grignard reagents other than methyl Grignard were found. Additional insight into the mechanism of the reaction of Grignard reagents with conjugated ketones is also presented.
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DEDICATION
This work is dedicated to Scott McIntyre, a man with a true love of chemistry and a great willingness to share that passion with others.
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Chapter 1. Historical Introduction to SET Probes.

1.1 Introduction.

Single electron transfer, or SET, has emerged as a ubiquitous process in organic chemistry over the past few decades. SET leads to paramagnetic intermediates (free radicals, radical anions, and radical cations.) Free radicals have been studied extensively and are fairly well understood. Less work has been done with radical ions. But in both cases, both types of species are being found to be increasingly important in mechanisms previously considered to be well understood. There are many reasons why such mechanisms may be important. Foremost is the simple fact that transfer of charge to a substrate often increases its reactivity by an incredible amount.

The two ways to transfer charge are proton transfer and electron transfer. In proton transfer, the elementary particle of positive charge activates the substrate. This method is so common in organic chemistry that its significance is often overlooked. Consider the protonation of a carbonyl prior to nucleophilic attack (Scheme 1.1). Preprotonation of the carbonyl oxygen significantly increases the rate of attack by the nucleophile. Instead of the simple resonance partial positive charge on carbon of the unprotonated carbonyl, there is now a much more significant positive charge on the carbon; thus reaction rate with the nucleophile is enhanced. It is also possible to increase reactivity by the removal of a proton (proton transfer away from the substrate). For instance, methoxide is a much better nucleophile than methanol.

**Scheme 1.1**
Similarly, electron transfer also enhances reactivity. Now the charge being transferred is the elementary particle of negative charge. As in proton transfer, activation can occur by transfer of an electron either to or from the substrate of interest. A neutral molecule can undergo one electron reduction to give a radical anion, or one electron oxidation to give a radical cation. Both species are more reactive than the corresponding neutral molecule. Consider the case of toluene acidity (Scheme 1.2). Neutral toluene has a pK$_a$ of 41. However, after undergoing a one electron oxidation to the corresponding radical cation, the pK$_a$ is –15. That is a difference of 56 pK$_a$ units; the radical cation is fifty-six orders of magnitude more acidic than the neutral molecule.$^{1,2,3,4}$

**Scheme 1.2**

Another example is chlorobenzene. As a neutral molecule, chlorobenzene is quite stable and not prone to either homolytic or heterolytic cleavage of the carbon-chlorine bond. However, the one electron reduction product of chlorobenzene (chlorobenzene radical anion) rapidly dissociates to give phenyl radical and chloride ion (Scheme 1.3).$^5$
In the preceding examples, transfer of charge greatly enhances the reactivity of the species involved. This is due primarily to diminution of bond order, particularly in the case of electron transfer. In the case of a single electron oxidation, an electron is generally being removed from a bonding molecular orbital. In single electron reduction, an electron is being added to an antibonding molecular orbital. In either case, the net result is a decrease in bond order and corresponding increase in reactivity. Furthermore, the introduction of charge itself also increases substrate reactivity.

To consider the potential for SET in conventional organic reactions, let us consider a simple generic $S_N2$ type reaction as occurring via either a polar or SET mechanism (Scheme 1.4). This is a commonplace organic reaction taught universally in introductory organic texts as occurring via a concerted polar process involving backside attack by the nucleophile to displace a leaving group leading to inversion of stereochemical configuration. However, it is entirely possible that some “$S_N2$” reactions proceed via single electron transfer from the nucleophile to the alkyl halide, giving a nucleophile radical and an alkyl halide radical anion that would then rapidly dissociate to an alkyl radical and a halide ion. If these processes, as well as the subsequent nucleophile radical
alkyl radical coupling, occurred in cage as a geminate cage pair, then inversion of configuration and all other conventional S\textsubscript{N}2 criteria would be met.\textsuperscript{6,7}

\textbf{Scheme 1.4}

\[
\begin{array}{c}
\text{polar} \\
\text{SET} \\
\text{SET}
\end{array}
\begin{array}{c}
\text{Nu}^- + \text{R-X} \rightarrow \text{Nu-R} + \text{X}^- \\
\text{[Nu} \cdot \text{R-X}^- \text{]} \rightarrow \text{[Nu} \cdot \text{R} \cdot \text{X}^- \text{]}
\end{array}
\]

As single electron transfer has emerged as an increasingly important mechanistic pathway, reactions previously thought to occur through strictly conventional polar (electron pair) pathways are now being re-examined and are often found to contain a significant SET element to their mechanism. Examples in the current literature tend to focus on the reaction of carbonyl compounds, particularly ketones and aldehydes. There exists significant evidence for SET to carbonyl compounds in Grignard reactions,\textsuperscript{8} the Clemmenson reduction,\textsuperscript{9,10} the aldol condensation,\textsuperscript{11,12,13} the Wittig reaction and its variations,\textsuperscript{14} reaction with organolithium reagents,\textsuperscript{15,16} the Meerwein-Ponndorf-Verley reduction,\textsuperscript{17} lithium dialkylamides,\textsuperscript{18,19,20} NADH analogs,\textsuperscript{21,22,23} complex metal hydrides,\textsuperscript{24} and radical mediated reductions involving trialkylstannyl\textsuperscript{25} and trialkylsilyl\textsuperscript{26} radicals.

As just one example, reconsider the generic reaction of a carbonyl with an anionic nucleophile (Scheme 1.5). Such a reaction can occur \textit{via} either a conventional two electron (polar) process or a single electron (SET) process.

\textbf{Scheme 1.5}

\[
\begin{array}{c}
\text{polar} \\
\text{SET} \\
\text{SET}
\end{array}
\begin{array}{c}
\text{Nu}^- + \text{O} \rightarrow \text{Nu} \cdot \text{O}^- \\
\text{Nu} \cdot + \text{O} \rightarrow \text{Nu}^- \cdot \text{O} \\
\end{array}
\]

4
In either case differentiation by product analysis is not a simple process. In this generic example, as well as most potential situations, precisely the same products are produced according to the same kinetics. Both mechanisms will generally respond similarly (although not always identically) to perturbations in solvent, substituents, temperature and other typically varied parameters. Thus the need has arisen for firm detection and elucidation of single electron transfer mechanisms in organic chemistry.

1.2 The Development of Mechanistic Probes for SET.

Seemingly the easiest way to detect paramagnetic intermediates is through the use of ESR (electron spin resonance, also known as EPR or electron paramagnetic resonance) techniques, which can unambiguously identify the presence of paramagnetic species in a reaction sample, often at extremely low concentrations. There are two unfortunate drawbacks to this method. First, although ESR can unambiguously identify the presence of such species, it cannot necessarily identify the absence of such species. The lifetimes of paramagnetic intermediates may not be sufficiently long or the species may not build up in sufficient concentrations for them to be detected. So while seeing radicals or radical ions by ESR confirms their presence, not seeing them does not confirm their absence. Secondly, there is no ability with ESR to confirm the significance of the detected paramagnetic species. They may or may not partake in the reaction of interest. It is entirely possible that any paramagnetism detected by ESR is simply an artifact, or a “blind” pathway, not leading to product formation. Other methods used for detecting radicals and radical ions have included chemically induced dynamic nuclear polarization (CIDNP), ultraviolet absorption, inhibition or trapping by radical scavengers, and kinetic isotope effects. All these methods suffer from either insensitivity or potential detection of blind pathways, or both. It would be desirable to establish a method that can detect the presence of paramagnetic intermediates, their importance to the mechanism of interest, and potentially even their role or lifetimes.
Thus the concept of developing mechanistic probes for electron transfer reactions has become very important. Rather than attempting to detect paramagnetic intermediates with instrumentation, it has become desirable to detect them unambiguously via chemical reaction with a probe molecule, preferably in such a manner as to confirm the significance of the paramagnetic intermediates to the mechanism under study as well as confirming their mere presence or absence. Two main classes of mechanistic probes have evolved. The first class is the group collectively known as fragmentation probes.

Fragmentation probes are generally neutral molecules that contain substituents which can be ejected as stable ions if an electron is transferred to (or from) the probe molecule. One such group of probes, the $\alpha$-haloacetophenones studied primarily by Tanner et al., is shown in Scheme 1.6 to illustrate the class.\textsuperscript{36,37,38} Elucidation of SET pathways is then accomplished by product analysis.

It is presumed that products from Nu$^\bullet$ / neutral radical coupling (PhCOCH$_2$Nu) or from hydrogen atom abstraction by the neutral radical (acetophenone) are indicative of a
SET process. The former is advantageous as it can show that the SET pathway is the mechanism that actually leads to product formation. Unfortunately in this case a direct polar $S_{N2}$ substitution at the $\alpha$-carbon cannot be ruled out as an alternative mechanism to product formation. Meanwhile the products observed from hydrogen atom abstraction, radical dimerization, or pinacol coupling of the radical anions can only indicate that SET has occurred, but are unable to indicate significance to the mechanism of interest. The single electron transfer event could be strictly a side reaction not involved in the product determining pathway of interest.

The successful use of fragmentation probes in the identification of SET relies on the essential irreversibility of the fragmentation step ($k_1$), and its rate being faster than any competitive processes of the radical anion ($e.g.$, $k_2$ and $k_3$). The presence of the product of the $k_2$ step is solely indicative of non product determining SET. The product of the $k_3$ step cannot be differentiated from direct polar 1,2-nucleophilic addition to the carbonyl. (Scheme 1.7).

**SCHEME 1.7**

![Scheme 1.7](image)
Other fragmentation probes have been developed along similar lines. One example is the incorporation of the fragmenting moiety onto the aromatic ring. This is particularly useful when nucleophiles that are too basic to be used with substrates containing acidic protons (such as those α to a carbonyl.) Monosubstituted benzophenones can be used in these cases. A wide variety of these and other probes have been studied by Tanner et al., yielding a spectrum of rate constants for both fragmentation and competing processes. Unfortunately, all of these probes, as a class, suffer from the problems enumerated above.

Thus it is the second class of probes, rearrangement probes, that have attempted to overcome the shortcomings of the fragmentation probes. Rearrangement probes work on the basis of “intramolecular trapping” of a paramagnetic intermediate. Instead of fragmenting upon electron transfer to the probes, the resulting radical anions instead undergo a chemical rearrangement of some sort.

There are three subgroups to this class of probe, based upon the type of rearrangement (Scheme 1.8). The first subgroup rearranges based upon geometric (cis to trans) isomerizations (I). The second subgroup (II) involves cyclization (generally exo) through a remote intramolecular carbon-carbon double bond. The third involves rupture of small (three- or four-membered) rings (III).

**Scheme 1.8**

\[ \text{I} \quad X \equiv Y \quad \text{e}^- \quad [X \equiv Y]^+ \quad \rightarrow \quad [X \equiv Y]^+ \]

\[ \text{II} \quad \text{C} - \text{C} \quad \text{A} = \text{B} \quad \text{e}^- \quad \text{C} - \text{C} \quad \text{A} - \text{B}^- \quad \rightarrow \quad \text{C} - \text{A} \quad \text{B}^- \]

\[ \text{III} \quad \text{A} = \text{B} \quad \text{e}^- \quad \text{A} - \text{B}^- \quad \rightarrow \quad \text{A} - \text{B}^- \]
All three types have found some utility in detecting SET as rearrangement probes. Types II and III are based upon very well known, well documented, extensively studied rearrangements of the corresponding neutral radicals. This statement is also somewhat true of type I, but much less so than the other two types. Examples of neutral radical rearrangements that would correspond to a type II radical anion rearrangement would be the $\Delta^5$-hexenyl family of rearrangements as well as the similar $o$-allyloxyphenyl rearrangement. The classic cyclopropylcarbinyl $\rightarrow$ homoallyl (or “allylcarbinyl” as it is occasionally known) rearrangement is the premier example of the neutral radical version of type III. In many of these neutral radical rearrangements, absolute rate constants are known. For such systems, Griller and Ingold have coined the term “free radical clocks” and this terminology has entered into the general vocabulary of the field. The significance of the term is that when absolute rate constants for the rearrangements are known, absolute rate constants for competing bimolecular processes can also be determined by simple product analysis.

This level of sophistication has not yet been reached in the field of radical ion rearrangements. It is a much newer field that is just beginning to see meaningful investigation, although progress is being made. In the past it has often been simply assumed that the same structural feature which lead to neutral radical rearrangements will by analogy induce similar rearrangements in radical ions. This may very well not be the case. Often radical ions can be inherently different than the corresponding neutral radicals, either due to the presence of charge, or because of some structural difference. A case in point is the rearrangement of cyclopropylketyl radical anions. At first glance, these seem that they should be analogous to the cyclopropylcarbinyl free radicals, so a ring-opening rearrangement is anticipated. In many cases, particularly of the radical anions of phenyl cyclopropyl ketones, this is not so.

The cyclopropylcarbinyl $\rightarrow$ homoallyl rearrangement has received extensive study and is known to occur with a rate constant on the order of $10^8$ s$^{-1}$, and the rearrangement is essentially complete (i.e., virtually irreversible, a large equilibrium constant favors the ring-opened form almost completely.) As such the analogous “type III”
radical anion rearrangements have been studied as the most promising of the rearrangement probes due to the belief that they would rearrange faster, more reliably, and less reversibly than the type I and II probes, and without the potential for anionic (polar) cyclization that has been documented in the case of some type II probes. Until recently, it was generally assumed that the ketyl radical anions derived from cyclopropyl ketones should behave at least reasonably similarly to cyclopropylcarbinyl radicals. This would allow for their use as probes for electron transfer mechanisms in various reactions involving carbonyls. For instance, these molecules have seen fairly extensive use as potential probes to test for SET involvement in the addition of nucleophiles to ketones (Scheme 1.9).  

\[ \text{SCHEME 1.9} \]

The basis for the use of such species as probes is simple. If direct polar addition is taking place, it is expected that only addition product 2 will be formed. However if there is a SET mechanism at work, ketyl radical anion 3 is formed. If the rearrangement of 3 to ring opened distonic enolate radical anion 4 is rapid enough to be competitive with coupling of 3 with Nu\textsuperscript{•}, then ring-opened addition product 5 should be produced to some extent. If the rearrangement is significantly faster and than radical-radical coupling and is mostly irreversible then 5 should be the dominant product. It has always been acknowledged that product 2 is not strict evidence for a polar mechanism but is actually inconclusive, as it is possible that it arises from rapid coupling of 3 with Nu\textsuperscript{•} (relative to
rearrangement). Nonetheless, production of 5 was assumed to be indicative of SET. Recently though, there has appeared evidence in the literature that product 5 can be produced by a polar pathway through a Michael type addition.

Furthermore (and most importantly), the method is also flawed by the assumption that these ketyl radical anions will behave similarly to the corresponding neutral carbinyl radicals. It has recently been firmly demonstrated that this assumption is incorrect.

**Scheme 1.10**

![Scheme 1.10](image)

In the case of phenyl cyclopropyl ketones in particular (Scheme 1.10), these assumptions break down.\(^{57,58,59}\) The radical ion behaves virtually nothing like the neutral cyclopropylcarbinyl radical it is intended to emulate. The resonance stabilized ketyl radical anion (essentially a benzylic radical) which results from electron transfer to the ketone does not significantly ring open. There are two competing factors at work. Relief of cyclopropyl ring strain drives the rearrangement (as in the neutral radical rearrangement), but loss of resonance energy retards the ring opening. One might argue that while the ring-closed form has a resonance stabilized radical, the ring-opened form is a styrene rather than an isolated double bond. However this is flawed logic, as the difference between an olefin and a styrene is not significant compared to the difference between an alkyl radical and a benzylic radical. If a resonance stabilizing substituent is
not added to the cyclopropyl ring, resonance effects prevail almost completely, and ring opening does not occur to a significant extent. Thus these probes would fail to detect *bona fide* SET processes. If a phenyl or vinyl group is added to the ring, it is possible to give the ring-opened form resonance stability as well, thus allowing the rearrangement to occur to a greater extent. This is just one prime example of the different factors that must be taken into account in designing mechanistic probes for single electron transfer.

Perhaps a better comparison to the radical anion of phenyl cyclopropyl ketone would be the phenylcyclopropylcarbinyl radical (the benzylic radical of benzylcyclopropane) rather than merely cyclopropylcarbinyl radical. This is a better direct comparison. In this case the neutral radical still ring opens with a forward rate constant of $10^6 \text{ s}^{-1}$ but is completely reversible, with an equilibrium constant $K = 10^{-1.60}$. This is still a far cry from the forward rate constant of $k \leq 2 \text{ s}^{-1}$ and $K < 10^{-7}$ for the unsubstituted radical anion of phenyl cyclopropyl ketone. Thus extreme caution must be used in drawing inferences about radical ions from their corresponding neutral radicals.

Although placing a phenyl or vinyl group on the cyclopropyl ring does appear to bring thermodynamics and kinetics into a slightly favorable regime for use as a probe, there is still the problem of Michael type contamination of the probe (*i.e.*, giving “rearranged” product *via* a polar pathway, Scheme 1.11). Also, it would be desirable to create a probe in which the ring opening is favored by both the relief of cyclopropyl ring strain and by an increase in (not simply a maintaining of) resonance energy.

**Scheme 1.11**

1.3 Development of a “Hypersensitive” Probe for SET to Carbonyls.

The need for a mechanistic molecular probe for detecting single electron transfer, the title compound has been described. It was believed that a probe based on the cyclopropyl
ring opening paradigm could have great promise. A rearrangement probe is desirable as it helps eliminate the possibility of detecting a “blind” pathway (one in which the paramagnetism detected is not a part of the product forming mechanism.) However there are two additional factors to be overcome. The first is to eliminate the possibility of “false positives” (results where the probe “detects” SET that is not occurring), such as in the case of Michael type addition to the cyclopropyl ketones described above. The second is to get all possible chemical forces to work in favor of rearrangement (i.e., both relief of cyclopropyl ring strain and a net increase in resonance energy upon rearrangement.)

It was believed that the title compound, 1,1-dimethyl-5,7-di-\textit{t}-butylspiro[2.5]octa-4,7-dien-6-one (6), would fit the bill for such a probe. The molecule is fairly easily reduced (reduction potential of $-2.557 \pm 0.005$ V vs. 0.1 M Ag\textsuperscript{+}/Ag) and the resulting ketyl-type radical anion 7 subsequently undergoes a chemically distinct but rapid \((k > 10^7$ s\textsuperscript{-1}) and thermodynamically favorable \((\Delta G^\circ \approx -13.3$ kcal/mol) ring opening.\textsuperscript{63} This ring opening rearrangement is preferentially (albeit not exclusively) to the tertiary distonic radical anion 8 (Scheme 1.12).

\begin{center}
\textbf{SCHEME 1.12}
\end{center}

This rearrangement potentially allows the title compound to be used as a mechanistic probe for nucleophilic addition to ketones, based not whether ring opened products are formed, but rather on the regiochemistry of that ring opening (Scheme 1.13).
If the addition of a nucleophile is occurring via a conventional polar process, conjugate addition to the least hindered carbon on the three-membered ring is expected, yielding substitution at the least-hindered carbon (product 10). If a SET mechanism is at work then the title compound (6) will be reduced to the radical anion (7) which will then preferentially open to the more substituted distonic radical anion (8). The resultant Nu• would couple with 8 to give apparent substitution at the most-hindered carbon, yielding product 9. In neither case is direct 1,2-addition to the carbonyl expected or observed. It is believed that the steric bulk of the vicinal t-butyl groups precludes such an event, just as it also prevents the polymerization that occurs in unsubstituted spiro[2.5]octadienones. Thus the probe will always result in spiro ring opening and “conjugate” addition, but the regiochemistry of the addition products is indicative of the mechanism at work. The term “regiodifferentiation” has been coined for this phenomenon.

Thus it was decided that the title compound had excellent potential as a regiodifferentiation based mechanistic probe molecule to differentiate SET and polar pathways in the addition of nucleophiles to carbonyl containing species (particularly conjugate addition of nucleophiles to conjugated ketones.) An investigation of this potential probe through bulk electrolysis, addition of nucleophiles with known and
unknown mechanisms of addition, and mechanistically “self-diagnostic” nucleophiles, with an emphasis on Grignard reagents is presented herein.
Chapter 2. Initial Investigations.

2.1 Bulk Electrolysis.

The first step in exploring the utility of the title compound (6) as a regiodifferentiation based probe for single electron transfer was to examine exactly what happens when an electron is transferred to the molecule. Such results were first reported by this group in 1994, but the experiments have recently been replicated and re-reported (by this experimenter) to give better percent recoveries and proof of products. The constant current bulk electrolysis was performed in N,N-dimethylformamide (DMF) with a tenfold excess of electrolyte (tetra-n-butylammonium perchlorate, or TBAP) in a standard electrochemical “H-cell” using a gold foil working electrode, Ag+/Ag reference electrode, and a platinum wire auxiliary electrode. By simply (if crudely) “pumping in electrons” it is possible to examine the behavior of 6 upon acceptance of an electron. Since there is no opportunity for a polar process in this case, it was hoped that the bulk electrolysis results would give information about the “true” behavior of the probe in a strictly SET environment (Scheme 2.1).

![Scheme 2.1](image)

Product yields are percentages of electrolysis products. Actual “mass balance” (actually “mole balance” is reported, since that is more appropriate) was 93%, including 13% unreacted starting material, quantitated as the two alcohols, 14 and 15, that are the hydrolysis products of unreacted 6 upon exposure to acidic workup conditions (Scheme 2.2). Quantitation was by GC analysis of independently obtained samples versus 2,6-di-t-butylphenol, as an internal standard. The percentages in Scheme 2.1 are of the 80% detected electrolysis products.
Products 11 and 13 are obviously the result of ring opening to the tertiary distonic radical anion, while product 12 results from the primary radical anion. Thus ring opening favors the tertiary radical over the primary radical in just over a 9:1 ratio. The proposed mechanism of formation of these products is outlined in Scheme 2.3.
The reduction of 6 to radical anion to ketyl-type radical anion 7 is followed by ring opening rearrangement to distonic radical anions 8 and 14 in a fast but distinct followup chemical step. Product formation could occur via either disproportionation or hydrogen atom abstraction, but as 4-alkenylphenol (13) is formed in roughly equal amounts to the 4-alkylphenols (11 and 12), disproportionation appears to be dominant. The major products are those resulting from radical ion rearrangement to give the thermodynamically favorable tertiary distonic radical anion. This seems reasonable, as ring opening of 7 to the tertiary radical (8) is estimated to be roughly 8 kcal/mol more favorable than ring opening to the primary radical (16). (∆G° calculated to be -13.3 kcal/mol vs. –5.3 kcal/mol, respectively). For a detailed analysis of kinetics, thermodynamics, and more sophisticated electrochemistry of this sort of spirooctadienones, refer to recent work from the Tanko group.63

2.2 Initial Grignard Experiments.

2.2.1 Literature Precedent for SET.

The mechanisms of Grignard reagents, both formation and reaction, have been under study and debate virtually since their discovery at the beginning of this century.64 The debate has ranged over a wide array of polar and radical pathways. Inherent to the debate are a variety of issues. The form, purity, and particle size of magnesium used in formation of the reagent;65,66 the effects of any impurities in the magnesium, particularly catalysis by transition metal impurities;65,66,67 the specific halide (Cl, Br, or I) in the alkyl halide used to form the reagent;68 any entraining methods used to initiate or sustain formation;69 any salts present either due to entraining or due to intentional perturbation;69,70 the solvent in use for both formation and reaction;66,71 the physical structure(s) of the Grignard reagent itself;72,73 the nature of the specific Grignard reagent in question, particularly its stability as an alkyl radical;66,68 the nature66,68 and ease of reduction of the substrate… all these factors play a role in the potential mechanism. Despite nearly a century of study, these factors are not fully cataloged and correlated. Nor has one concrete mechanism been found to be true in all cases.
Nonetheless, there is significant evidence for SET mechanism(s) in the reaction of Grignard reagents. In particular this is true of the reaction of Grignards with conjugated carbonyls. The two major factors at work in such a case are the stability of the alkyl radical (\(\text{R}^\bullet\)) of the Grignard reagent (“RMgX”), and the ease of reduction of the carbonyl. For instance, if the Grignard is very stable as a radical (such as \(t\)-butyl or benzyl), it may react via SET with virtually any ketone. On the other hand, if the Grignard in question has a high energy radical (non-stabilized methyl, primary, and to some extent secondary) a much more eager electron acceptor is needed (\(\text{e.g.,}\), benzophenone, or some other well-conjugated ketone.) Benzophenone has generally been shown to react via SET with virtually all Grignard reagents studied, including methyl magnesium bromide or iodide. For the spirodienone probe (6) in question, it is believed that the second situation is true. Compound 6 is a very willing electron acceptor, as shown by its reduction potential and by its ability to gain aromaticity after accepting an electron. Thus evidence for electron transfer from even methyl and primary Grignards to easily reduced conjugated carbonyls is outlined below.

Some of the earliest work in giving actual evidence (as opposed to mere conjecture) for electron transfer was provided by Hammett plot studies conducted by Torkil Holm.\(^8\) This was by no means conclusive in and of itself, but it gave the field of inquiry a huge push and provided impetus for further study. Holm has also performed a large number of kinetic studies with varying the structure of the Grignard reagent to provide further mechanistic detail,\(^74\) and all studies to date seem to point to at least some SET component in all the Grignard reactions to conjugated carbonyls he has studied.

Ashby is another pioneer in the field of SET from Grignard reagents. He has attacked the problem in a number of ways, throughout much of his career. These especially include providing evidence for SET by a variety of rearrangements. One method used by Ashby is the \(\text{cis-} \rightarrow \text{trans-}\) isomerization (“type I”) probes discussed earlier to detect at least some SET from both methyl and \(t\)-butyl Grignard reagents.\(^75\) Ashby has also made use of rearrangements that can occur in the alkyl group of the Grignard reagent after electron transfer, such as the rearrangement of 1,1-dimethyl-5-
hexenyl to the (dimethylcyclopentyl)carbinyl in the reaction of that Grignard with benzophenone. Ashby also did much of the initial early ESR and UV work on determining paramagnetic intermediacy, although as discussed in the previous chapter, these techniques are not as conclusive as some other methods. However, by coupling kinetic analysis to the ESR results the data becomes more convincing.

The third of the “big three” pioneers to study SET from Grignard reagents is Cheves Walling, who focuses much of his work on kinetic analysis. Until Walling, most researchers ruled out the possibility of freely diffusing radical intermediates as impossible. It had been assumed that if freely diffusing radicals were the case, little reaction of Grignard with substrate would be seen due to the numerous competitive reactions (assorted dimerizations, disproportionations, and hydrogen atom abstractions) that the free alkyl radicals could undergo. However Walling has shown through a detailed kinetic analysis that if only one of two species (in this case free alkyl radicals) in a bimolecular process can rapidly react away via other pathways and the other (here the ketyl radical anion) cannot generally react except via that bimolecular process, the latter will very quickly build up in sufficient concentration to make the bimolecular process the dominant one. There is currently much debate and conflicting evidence as to the cage or non-cage nature of the resulting radical/radical-ion coupling which follows SET in the reaction of Grignards with ketones, but Walling has shown it to be a definite possibility. Garst, another power in the field, also weighs in on the side of freely diffusing intermediates in the case of Grignard formation (as opposed to, but complimentary with, Walling’s freely diffusing reaction model) with detailed evidence stemming from 5-hexenyl studies and other detailed product analysis.

More recent evidence includes kinetic isotope effect studies of both carbon ($^{12}$C, $^{13}$C, and $^{14}$C) and hydrogen (H/D). One paper seems to indicate rate determining C-C bond formation. In other cases electron transfer seems to be rate limiting. The general conclusion is that it varies from Grignard to Grignard and substrate to substrate, with methyl and other alkyl Grignards showing predominantly rate determining C-C bond formation.
Formation of both R-R dimers\textsuperscript{88} and pinacol formation from the resulting ketyl species\textsuperscript{66,89,90} provide evidence of freely diffusing radical species (although not necessarily along the lines of the product-forming pathway.)

Meanwhile, EPR\textsuperscript{28,72,73,77,78,79,91,92,93} and UV\textsuperscript{77,79} studies show transient paramagnetic intermediates in the case of most all Grignard reactions, including those not involving species particular favoring SET by stabilization of either radical or radical anion formed by SET (although again this could well be a “blind” pathway), including primary Grignard reagents. Stop-flow techniques have also successfully indicated the occurrence of SET.\textsuperscript{72,92,94}

A variety of probes,\textsuperscript{68,75,76,95,96} including one by Liotta\textsuperscript{95} that is structurally similar to 6, have provided good evidence for SET from Grignards to a conjugated ketone much like that reported herein. It should also be noted that Liotta’s probe showed complete cyclization of 5-hexenyl to cyclopentylcarbinyl in the reaction of 5-hexenyl lithium. Since Liotta showed independently that the lithiate itself underwent zero cyclization, this provided very good evidence for freely diffusing radicals (since the hexenyl rearrangement is not sufficiently fast to occur within the lifetime of a solvent cage.) Other hexenyl systems are providing stereochemical evidence for SET.\textsuperscript{97,98} The cyclopropylcarbinyl Grignard has even been studied at extremely low temperatures with very easily reduced, very reactive ketones (benzoquinone) giving rearrangement that Wigal has shown to be strictly radical in nature, and is potentially indicative of freely diffusing paramagnetic intermediates.\textsuperscript{99}

Thus it appears that there is a large body of evidence to conclusively support at least some SET component to the reaction of almost any Grignard with relatively easily reduced conjugated ketones. Admittedly the structure of the Grignard itself, the nature of the “R•” species (or whether it is a RMgX•+ instead), the cage or noncage nature of the coupling, the role of transition metal impurities and a host of other variables are as yet uncertain. Nonetheless, the fact that the reaction of even methyl Grignard with conjugated ketones under “typical” synthetic conditions (using plain reagent grade
magnesium (and its inherent trace iron impurities) at typical concentrations with or without entraining by EDB, in ethereal solvents, etc.) has at least some SET component is essentially beyond dispute, although this may well be in competition with a polar process since it appears that if SET is stopped by radical inhibition, a polar process is still possible in most cases.

2.2.2 Experimental Results.

Thus methyl Grignard was chosen as an initial nucleophile with which to test the title compound (6) as a probe for SET. Since methyl Grignard is basically the least reducing Grignard reagent available, and the least likely to transfer an electron, it was felt that it would be an excellent one to examine to see if SET was able to be detected in a somewhat borderline case where SET is known to be occurring, but a polar process is almost certainly competitive. Commercial methyl magnesium bromide was the first methyl Grignard to be used with 6, with preliminary results already reported. These in fact do turn out to be the best results and are outlined below (Scheme 2.4).

**Scheme 2.4**

\[
\begin{array}{c}
\text{Ar} = \begin{array}{c}
\text{t-Bu} \\
\text{Ar} \\
\text{t-Bu}
\end{array} \\
\text{OH} \\
\text{t-Bu}
\end{array}
\]

Product analysis was performed similarly to that done for the bulk electrolysis, using correction factors and retention times from independently obtained or previously isolated products. Unreacted starting material was again quantitated as the two alcohols, 14 and 15, which are the result of hydrolysis of 6 upon dilute acid workup (Scheme 2.2).
GC analysis showed quantitative results. The major addition product (17) shows substitution at the most hindered carbon, a definite SET product. 17 is present in nearly three times greater amount than the least hindered substitution product (18). Some 18 is expected even if a strictly SET process is occurring, as seen from the 10% ring opening to the primary distonic radical ion in the bulk electrolysis (Schemes 2.1 and 2.3). This can account for some or even all of the observed less-hindered product. The fact that roughly 25% less-hindered substitution is seen, versus roughly 10% in the bulk electrolysis is indicative of one of two things. Either some competitive polar process is occurring at a rate just slightly slower than the SET process and is thus increasing the amount of less hindered product, or the difference is simple deviation based on varying solvent (from DMF to THF) and counter ion (from a tetra-n-butylammonium ion to a Mg\textsuperscript{II} species). Regardless, significant SET is occurring, either with or without a slower but competitive polar process.

In addition to unreacted starting material, the three non-addition products seen in the bulk electrolysis are also observed here. The formation of the 4-alkylphenols 11 and 12, present in trace amounts, are further evidence of SET as the only reasonable mechanism of formation for these species is the disproportionation outlined in Scheme 2.3. Alkene 13 is the “partner” to 11 and 12 in said disproportionation, but as such should only be present in an amount equal to the sum of 11 and 12. As yields of 11 and 12 are just above the detection and/or quantitation limits of the techniques used, their ratios are subject to significant error, but nonetheless not nearly enough of these two alkylphenols is present to explain the significant amount of 13 produced. The best explanation for the vast majority of 13 formed is a competing polar elimination (E\textsubscript{2}) process (Scheme 2.5).
Another possibility for the formation of excess 13 (relative to 11 and 12) is the disproportionation of 8 with an intermediate methyl radical. This seems slightly less likely, but possible, especially due to the relatively low percent conversions of these reactions. This would yield 13 through a radical pathway without producing any 11 or 12, but methane instead, which would likely not be detected, although no bubbling of methane out of solution was observed. If this pathway is responsible for significant formation of 13, it could explain the apparently lower selectivity of ring opening in the addition products as this mechanism can consume tertiary radical 8, but not primary radical 16.

This experimenter attempted to repeat the reaction of methyl Grignard and 6 using methyl magnesium iodide prepared just prior to use from methyl iodide and standard 98% magnesium turnings, and very slight entraining with 1,2-dibromoethane (EDB). Difficulties were experienced due to solubility problems, both in formation and reaction of the Grignard. The net result was an inhomogeneous reaction mixture with significant precipitation of the Grignard reagent despite the use of a more dilute reaction mixture. As a result reaction time was greatly increased, even at room temperature, but results were very similar and may well be statistically identical (within the limits posed by the GC and the correction factors used), beyond the fact of less net reaction in general (Scheme 2.6).

Although, due to the difficulties encountered and the lack of repetition, these numbers are less reliable than those previously reported, they do show good agreement with results already published and, in general, little sensitivity to the slight increase in temperature, the lower concentrations, and the inhomogeneity of the reaction mixture, other than the mentioned sluggishness of the reaction.
In all, these initial investigations (utilizing bulk electrolyses and simple Grignard reagents) provide significant evidence for the utility of 6 as a mechanistic probe for detecting SET to conjugated carbonyls by regiodifferentiation.

Scheme 2.6
Chapter 3. Nucleophiles Which Can Rearrange After ET.

3.1 Introduction to the Concept.

Since preliminary investigations showed the title compound to have great promise as a regiodifferentiation based probe for SET to conjugated carbonyls, further experiments were designed to test this notion. One way to add a level of confirmation about the radical nature of a reaction (as well as possibly further elucidate the overall mechanism) is to study nucleophiles that incorporate a SET probe moiety as well (Scheme 3.1). For instance, if the nucleophile does not rearrange as an anion, but can rearrange as the paramagnetic species resulting from transferring an electron (to the carbonyl in the case of interest), then four potential addition products are possible (Scheme 3.2).

![Scheme 3.1](image)

These four products consist of both rearranged and unrearranged nucleophile attached at either the most- or least-hindered position.

![Scheme 3.2](image)

If there is truly no anionic cyclization whatsoever, then product 20 should be the only product to arise from a strictly polar pathway. On the other hand, it is potentially possible to obtain all four addition products, 19-22, via a SET mechanism. Scheme 3.3 outlines the mechanism for obtaining each potential product.
If a SET pathway is at work, then the nucleophile will transfer an electron to 6, which will then rapidly ring open preferentially to 8 but also to a lesser extent to 16. (Bulk electrolysis of 6 gives a crude estimate of a 9:1 ratio of 8 to 16, but only a 3:1 product distribution was seen with MeMgX, either due to a competitive polar process, or because of solvent and counter-ion effects.) Regardless of the ratio of 8 to 16 formed (although 8 should definitely dominate), if coupling of the radical anions (8 and 16) with...
Nu• is faster than rearrangement of Nu•, then 9 and 10 predominate, yielding 19 and 20 upon workup. However, if radical rearrangement of Nu• is faster than coupling of Nu• to 8 and 16, then 9' and 10' predominate, yielding 20 and 21 on workup. Thus using these sorts of nucleophiles which can rearrange after transferring an electron will allow both a confirmation of paramagnetic intermediacy, and some further information about kinetics and mechanism.

3.2 Cyclopropylcarbinyl Phenyl Sulfone.

3.2.1 Introduction.

Very recently Chanon and Stirling reported preliminary results demonstrating that the anion derived from deprotonation at the carbinyl position of cyclopropylcarbinyl phenyl sulfone can be used as a probe for SET based on the cyclopropylcarbinyl → homoallyl radical rearrangement (Scheme 3.4). The anion (they used the lithiate) absolutely does not rearrange. The phenyl sulfone provides excellent stabilization of this anion, and both theory and experiment support the fact that 23 will not rearrange to give 24. On the other hand, the carbinyl radical 25 (which results if anion 23 transfers and electron to an acceptor) is not stabilized by the phenyl sulfone and thus rearranges rapidly to relieve cyclopropyl ring strain (k ≈ 10^8 s⁻¹, similar to the normal cyclopropylcarbinyl radical rearrangement).

![Scheme 3.4](image-url)
Both the extreme speed of the radical rearrangement, and the utter lack of any corresponding anionic rearrangement make this species an ideal nucleophile with which to further investigate the title compound (6) and was chosen as the first attempt to use a \( \text{Nu}^- \rightarrow \text{Nu}^- \rightarrow \text{Nu}^- \) system to probe the title compound.

### 3.2.2 Experimental Results.

The anion 23 was generated from cyclopropylcarbinyl phenyl sulfone with \( n \)-butyl lithium. The presence of the anion was confirmed by a \( \text{D}_2\text{O} \) quench experiment followed by both \( ^1\text{H} \) and \( ^2\text{H} \) NMR which showed nearly complete deuteration at the \( \alpha \)-position with no other deuteration seen. Nor was any rearrangement of the anion observed, either at \(-78^\circ\text{C}\) or upon stirring at room temperature for several hours. A \( \text{THF} \) solution of the lithiate of 23 was then added to a \( \text{THF} \) solution of 6 slowly at \(-78^\circ\text{C}\). The solution was allowed to warm to room temperature and react for 22 hours, then worked up as usual. GC quantitation was not possible due to decomposition of the products in the injector ports, but via a combination of preparative HPLC, preparative TLC, and crude NMR integration the results shown in Scheme 3.5 were obtained, with a mass balance of over 90%.

**Scheme 3.5**

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{nBuLi (hex)} \quad \text{THF} \quad (-78^\circ\text{C} \rightarrow \text{RT}) \quad \text{SO}_2\text{Ph} \\
\text{SO}_2\text{Ph} & \quad \text{6} \quad \text{THF} \quad (-78^\circ\text{C} \rightarrow \text{RT}) \\
\text{Ar} & \text{= t-Bu} \quad \text{OH} \quad \text{t-Bu}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>12%</td>
</tr>
<tr>
<td>27</td>
<td>63%</td>
</tr>
<tr>
<td>28</td>
<td>13%</td>
</tr>
<tr>
<td>11</td>
<td>12%</td>
</tr>
<tr>
<td>12</td>
<td>13%</td>
</tr>
<tr>
<td>13</td>
<td>11%</td>
</tr>
<tr>
<td>Unreacted SM</td>
<td></td>
</tr>
</tbody>
</table>
Unfortunately, a polar process obviously predominated. Least hindered attachment of the nucleophile (24) predominated in a 5:1 excess, and absolutely no rearrangement of the cyclopropylcarbinyl phenyl sulfone moiety was observed. These results are thoroughly indicative of a polar process. The small amount of most hindered substitution product (25) observed is probably due to a small amount of SET, but with very fast Nu• coupling to radical anion 7, since no rearrangement to Nu’• is observed in any of the products. The three usual non-addition products (11-13) were formed, but not well quantitated relative to each other. Alkene 13 dominated, and is believed to make up most or potentially all of the indicated 12%, with 11 and 12 seemingly present in only trace amounts. This makes sense, with 13 presumably arising predominately as a result of a polar elimination, with only trace amounts of 11, 12, and 13 formed via disproportionation of intermediates formed during the very small amount of SET which is occurring.

The reason for the failure of 23 to transfer an electron should have been obvious, although it was overlooked in the zeal of discovering such a potentially good nucleophile with which to further examine 6. As was previously mentioned, the anion (23) is extremely well stabilized by the phenyl sulfone; so well so that it does not rearrange to give anion 24 at all, despite the significant ring strain and opening to a primary anion. The radical 25 is not at all stabilized by the phenyl sulfonyl group. So to go from the extremely well stabilized anion to the unstabilized radical is very unfavorable (i.e., anion 23 is a poor reducing agent.) In this case the energetics favoring electron transfer to 6 are not sufficient to make ΔG for electron transfer favorable, so ET is not a significant mechanistic pathway in this reaction.

3.2.3 Phenylsulfonylcyclopropylcarbinyl Anion with “SpiroAnthrone”.

At this point significant time and effort had been put into the cyclopropylcarbinyl phenyl sulfone, and it was not desired to discard it immediately. If a more easily reduced substrate than 6 could be found, electron transfer might be made favorable enough to be a significant mechanistic contributor. It just so happened that another group member was
working with just such a substrate at the same time that the cyclopropylcarbinyl phenyl sulfone experiments were being conducted.

The substrate, 29, dubbed “SpiroAnthrone” by this group, had been synthesized by Mr. Phillip Schwartz (via a published route much simpler than that used for the title compound, 6, and its analogs)\textsuperscript{102,103} and was under initial electrochemical investigation at the time. SpiroAnthrone is more easily reduced than 6 by several hundred millivolts,\textsuperscript{104} so it was thought that perhaps electron transfer from 23 to 29 might be possible. So an experiment similar to that of 23 with 6 was set up with the SpiroAnthrone (Scheme 3.6).

**Scheme 3.6**

\[
\text{SO}_2\text{Ph} \quad \text{nBuLi (hex)} \quad \text{THF} \quad (-78^\circ \text{C} \rightarrow \text{RT}) \quad \text{SO}_2\text{Ph} \]

\[
\text{29} \quad + \quad \text{23} \quad \text{THF} \quad (-78^\circ \text{C} \rightarrow \text{RT}) \quad \text{NO RXN} \quad (97\% \text{ RECOVERED 29})
\]

No reaction whatsoever was observed at room temperature regardless of time. Reaction times from 20 minutes to 8 days were attempted; all yielded a minimum of 97% recovered starting material. Deuterium oxide quench experiments followed by proton and deuterium NMR again confirmed formation of 23, but there was simply no reaction.

SpiroAnthrone should be less susceptible to polar attack (and the results show it is indeed) and more prone to SET (according to its reduction potential it is, but apparently not sufficiently so to react with 23). To use 23 in the desired manner, an even more easily reduced substrate would have to be used. Benzoquinone might be utilized for instance, to parallel Wigal’s recent work in that area, but it is obvious that 23 will not be useful in evaluating the class of probes reported herein under study. Thus it was decided to return to the title compound (6), and use a more conventional and well-studied Nu$- \rightarrow$
Nu• → Nu’• system to further investigate the mechanism and utility of the spirooctadienone as a mechanistic probe for SET to conjugated carbonyls.

3.3 Δ⁵-Hexenyl Grignard.

3.3.1 Introduction.

The hex-5-en-1-yl (or “Δ⁵-hexenyl”) → cyclopentylcarbinyl radical rearrangement is one of the best-studied rearrangements in all of radical chemistry (Scheme 3.7). It has been used extensively as a free radical clock over the past 25 years, and several variations have also been used.

\[ \text{Scheme 3.7} \]

\[ \text{30} \xrightarrow{\text{SLOW}} \text{31} \]

\[ -e^- \]

\[ \text{32} \rightarrow \text{33} \quad k = \sim 10^5 \text{ s}^{-1} \]

In addition, carbonyl species with a remote carbon-carbon double bond (generally δ,ε unsaturated ketones) have been used as “type II” cyclization radical ion probes for SET. These radical ion cyclizations are fairly well studied compared to other radical ion systems, but not compared to the Δ⁵-hexenyl free radical reaction. Most of the work in the field, and the most reliable data, come from incorporating the hexenyl moiety into the nucleophile to detect the neutral free radical produced after the nucleophile transfers an electron.

The kinetics of the free radical cyclization are well studied, as are product distributions for the parent system and a number of derivatives. The rearrangement is essentially irreversible. The rate constant for cyclization at room temperature is on
Different researchers have reported a variety of values from zero to ten percent endo cyclization\textsuperscript{55} (to give the cyclohexyl radical), but exo cyclization definitively dominates in all cases of this rearrangement. Furthermore, unlike the phenylsulfonylcyclopropylcarbinyl anion (23) described above, the \( \Delta^5 \)-hexenyl system is slightly contaminated by an anionic cyclization which occurs eight to ten orders of magnitude slower than the radical process. It is believed that the major cause of this dramatic difference in rates is merely a result of charge localization in the anion by the counter-ion. In addition to this slow strictly anionic cyclization, there is also some evidence that the commonly used \( \Delta^5 \)-hexenyl organometallic reagents can auto-cyclize through an undetermined (although probably radical) mechanism.\textsuperscript{82,97,105} These issues have been addressed in a variety of ways, including using the 1-methyl derivative and determining the cis- to trans- ratio of cyclization products.\textsuperscript{97} A ratio of 4.5:1 favoring cis- is considered indicative of 100% radical character. It is also potentially possible to use just the standard \( \Delta^5 \)-hexenyl system and perform a parallel experiment without substrate at the same temperature and concentration for the same duration, then quench and quantitate 1-hexene \textit{versus} methylcyclopentane. This should give the amount of cyclization (anionic or autocyclization) \textit{not} resulting from direct reaction with the substrate.

Another problem that has occasionally arisen is the failure of the organometallic compounds of the unsubstituted primary \( \Delta^5 \)-hexenyl to give SET. This was not considered to be a problem in the case of the title compound. First of all there was significant literature precedent for SET from methyl and primary Grignards to conjugated carbonyls, as outlined in section 2.2.1 (pp. 18-22) above. Second, and more directly, 6 had already been shown to undergo electron transfer from methyl Grignard, and primary Grignards are more reducing than methyl Grignard. For instance n-butyl magnesium bromide has a \( E^\circ_{\text{ox}} \) of \(-0.53 \text{ V} \text{ vs. normal hydrogen electrode (NHE)} \) in diethyl ether, and ethyl magnesium bromide has a \( E^\circ_{\text{ox}} \) of \(-0.66 \text{ V} \text{ vs. NHE} \) in ether, while methyl magnesium bromide has a \( E^\circ_{\text{ox}} \) of \(-0.25 \text{ V} \text{ vs. NHE} \) in ether. These numbers themselves are not particularly significant, but they do indicate that primary Grignards should show more electron transfer than methyl Grignard. (The trend continues, with isopropyl
magnesium bromide having a $E_{\text{ox}}$ of $-0.95$ V vs. NHE in ether, and $t$-butyl magnesium bromide having a $E_{\text{ox}}$ of $-1.07$ V vs. NHE in ether.) So, the more substituted the Grignard, the more reducing it is. Furthermore, the more sterically hindered the Grignard is, the slower polar nucleophilic attack should be (although admittedly this should be only a minor factor in primary, especially linear primary, versus methyl Grignard.) However, in cases where ET does not dominate, more directly substituted $\Delta^5$-hexenyl systems have been used (e.g., 1-methyl- and 1,1-dimethyl-5-hexenyl Grignards) as well as a more hindered “neopentyl type” $\Delta^5$-hexenyl Grignard (2,2-dimethyl-5-hexenyl Grignard). In the case of 6, the use of such derivatives was not deemed necessary.

A final problem is the potential for false detection of SET by cyclization if electron transfer is reversible (permitting ET, rearrangement, back ET, and polar addition.) However the precedent of ET from methyl Grignard, the extreme improbability of undergoing back electron transfer, and the virtual impossibility of undergoing back ET all seem to rule this out. In any case, the title compound itself should confirm ET by giving most-hindered substitution if ET is part of the product forming mechanism, but not if it is a “blind” pathway.

So it was that the $\Delta^5$-hexenyl magnesium bromide was chosen as the next nucleophile with which to study the title compound (6). This allowed for study with a class of reagent that had already been shown to transfer an electron to 6, and the envisioned difficulty of potential anionic or organometallic cyclization would be compensated for by running parallel experiments sans substrate and quantitating rearrangement upon quenching. The direct precedent that was used was a recent and very similar study by Wigal in which the reaction of benzoquinone with both $\Delta^5$-hexenyl Grignard and cyclopropylcarbinyl Grignard was studied, and the rate of radical coupling was pinned down to between the rate constants for the two rearrangements. Initially a collaboration was envisioned to allow study of 6 with cyclopropylcarbinyl magnesium bromide as well.
3.3.2 Experimental Results.

The first run of this experiment between 6 and $\Delta^5$-hexenyl magnesium bromide was run to get an initial feel for products produced, and possibly to isolate products for more definitive analysis and better quantitation of future runs. This was partially successful. GC indicated that there were four high-mass products produced (Figure 1). GC-MS confirmed masses of 344 amu for the last four peaks in the GC trace, and it was believed that all four products, 34-37, were produced (Scheme 3.8).

Figure 1. Reaction of 6 with 5-Hexenyl Magnesium Bromide, GC-MS Total Ion Chromatogram.
However isolation of any of the compounds proved impossible by both HPLC and TLC at a variety of concentrations and conditions. It was possible to separate the addition products from non-addition products 11-15, also produced, by preparatory TLC or by Kugelrohr distillation, but separation of the addition products from one another was simply not possible with the means available.

To reduce the number of potential products to two, and aid in characterization, a reaction of 6 with cyclopentylcarbinyl magnesium bromide was run, yielding a roughly 90/10 mixture of two addition products, isolated as a mixture by prep TLC and Kugelrohr distillation. The NMR of this mixture is presented in Figure 2.
Figure 2. Reaction of 6 with Cyclopentylmethyl Magnesium Bromide, $^1$H NMR of Addition Products.

Peak A (aromatic) integrates to 24H. Peak B integrates to 2H. Peak C integrates to 13H. Peak D integrates to 2H. C is obviously the one proton phenol peak for both compounds in the mixture, with A being the two aromatic protons of the major isomer and B being the aromatic peak of the minor isomer. The presence of a two proton
benzylic methylene peak (D) that corresponds perfectly to B indicates that the minor product is the more-hindered (SET) addition product (35) and that surprisingly the major product is the less-hindered (polar) addition product (37). The resolution of peaks A and B is also supportive of this assignment, as a quaternary carbon ortho to the aromatic protons will result in a slightly more downfield shift than a secondary carbon.

The major product of the cyclopentylcarbinyl Grignard reaction corresponds to the peak at retention time 14.9 minutes in the GC trace (Figure 1). Meanwhile the minor product corresponds to either the peak at 15.5 or 15.8 minutes. Resolution of those peaks was too poor to allow structure determination simply on the basis of matching retention times.

To conclusively elucidate which peaks were hexenyl and which were cyclopentylmethyl, a few drops of elemental bromine was added to the reaction mixture. Bromination of the hexenyl double bond caused the peaks at 13.7 and 15.8 minutes to disappear, while the peaks at 14.9 and 15.5 minutes were unaffected. Thus it is that 13.7 and 15.8 are the two hexenyl products (34 and 36) while 14.9 is the less-hindered cyclopentylmethyl product 37 and 15.5 is the more-hindered cyclopentylmethyl product 35.

Meanwhile mass spectral fragmentations provided the final evidence necessary to complete characterization of the four peaks. All four addition products should fragment along the C1-C2 bond of the 4-alkyl group to give 4-hydroxy benzylic cation. The more-hindered products (34 and 35) fragment to give a primary benzylic cation with a mass of 219 amu. Meanwhile the less-hindered addition products (36 and 37) should give rise to a mass 247 amu peak corresponding to the tertiary benzylic cation (Scheme 3.9).
These fragmentations do indeed dominate, and in the case of all four GC peaks, one of the two masses is the base peak of the mass spectra. Retention times 13.7 and 14.9 give nearly identical mass spectra (Figures 3 and 4, respectively) with mass 247 being the base peak. Meanwhile retention times 15.5 and 15.8 also give nearly identical mass spectra (Figures 5 and 6, respectively), but with 219 being the base peak. Thus mass spectrometry confirms the structure of 37, already demonstrated by NMR, confirms the structure of 35, already implied as the minor product by NMR, and conclusively distinguishes between 34 and 36.

The retention times and structures are as follows. At 13.7 minutes, reacts with elemental bromine, tertiary benzylic cation fragment in MS, therefore less-hindered unrearranged product (36). At 14.9 minutes, inert to Br₂, no benzylic protons in NMR, tertiary benzylic cation fragment in MS, thus less-hindered rearranged addition product (37). At 15.5 minutes, inert to Br₂, primary benzylic cation fragment in MS, benzylic protons present in NMR, therefore it is more-hindered rearranged product (35). And at 15.8 minutes, reactive with Br₂, primary benzylic cation fragment in MS, thus more-hindered unrearranged product (34).
Figure 3. Mass Spectrum of 13.7 min Peak.

Figure 4. Mass Spectrum of 14.9 min Peak.
The final yield information from the first run is now presented in Scheme 3.10, on the basis of crude GC area percents. As correction factors were not yet available, these results are sufficiently crude that each percentage should be considered to have an error of 20-25% of its own value.
These product ratios lead to the surprising conclusion that a polar process is dominating the reaction of 5-hexenyl Grignard with 6, contrary to what would be expected on the basis of the methyl Grignard results, the reducing power of primary Grignards (relative to MeMgX), and steric factors. Nonetheless, these are the results, and the considerable evidence described above completely supports this interpretation. The NMR data described above for the reaction of 6 with cyclopentylmethyl Grignard are also indicative of a dominant polar process.

A parallel quench experiment of the same Grignard, after the same duration, albeit not at the same concentration (the parallel quench Grignard solution was significantly more concentrated than the reaction mixture and should have yielded, if anything, more anionic rearrangement than the reaction mixture) gave roughly 10% cyclization (Scheme 3.11).
The major pathway of the reaction of 6 with 5-hexenyl magnesium bromide is a polar one which leads predominantly to 36. The small amount of 37 formed is due strictly to anionic cyclization, as it is less than 10% of the less-hindered products formed. There is no enhancement of cyclization in the course of the reaction for the less-hindered products. However, the formation of 34 and 35 likely occurs by a slower but competitive SET process. The mere occurrence of more-hindered products (34 and 35) may be indicative of this, as is the presence of disproportionation products 11 and 12. However the clincher is the dramatic increase in 5-hexenyl → cyclopentylcarbinyl rearrangement in the more-hindered addition products. Cyclization is up to 60% of the more-hindered addition products, with at most 10% of that due to anionic cyclization. This cyclization provides further information that will be discussed later in this document. Products 11 and 12 are again the result of disproportionation, while 13 can arise from both radical disproportionation or from polar elimination.

The recovery of products from the initial experiments with 5-hexenyl and cyclopentylmethyl Grignards also enabled crude GC correction factors (again versus 2,6-di-tert-butylphenol) to be obtained for addition products in general versus the non-addition products observed. This allowed for subsequent experiments to be run to confirm the above results and examine the effects of concentration with a slightly greater degree of precision. Error limits from this point on should be considered to be roughly 10% of the value of a given number, instead of the 25% error imposed on the previous figures. Product yields of the initial experiment and five additional experiments are summarized in Table 1 below. All yields were quantitative within error limits (and usually were found to be slightly above 100%, most likely due to the slightly lower hydrophobicity of the internal standard, 2,6-di-tert-butylphenol, relative to the addition products.)

Table 2 includes the ratio of more- to less-hindered substitution occurring. This can be taken to be a crude indicator of the amount of SET versus polar mechanism, at least in pathways leading to substitution. Also included are the amount of anionic cyclization (from parallel quench experiments), amount of cyclization in the less-hindered (polar) products, and amount of cyclization in the more-hindered (SET) products. It is obvious
that the polar process dominates in all six runs. The amount of anionic cyclization is a very good approximation of the amount of cyclization in the polar products, whereas there is significant enhancement of cyclization in the addition products arising from SET.

**Table 1. Reaction of 6 with 5-Hexenyl Magnesium Bromide, Product Yields.**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.150</td>
<td>44</td>
<td>6%</td>
<td>6%</td>
<td>59%</td>
<td>1%</td>
<td>9%</td>
<td>2%</td>
<td>1%</td>
<td>15%</td>
</tr>
<tr>
<td>0.122</td>
<td>20</td>
<td>6%</td>
<td>9%</td>
<td>26%</td>
<td>2%</td>
<td>18%</td>
<td>14%</td>
<td>1%</td>
<td>24%</td>
</tr>
<tr>
<td>0.089</td>
<td>45</td>
<td>8%</td>
<td>2%</td>
<td>11%</td>
<td>0.3%</td>
<td>41%</td>
<td>3%</td>
<td>0.5%</td>
<td>35%</td>
</tr>
<tr>
<td>0.066</td>
<td>44</td>
<td>5%</td>
<td>4%</td>
<td>43%</td>
<td>1%</td>
<td>21%</td>
<td>2%</td>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>0.027</td>
<td>44</td>
<td>2%</td>
<td>4%</td>
<td>32%</td>
<td>1%</td>
<td>35%</td>
<td>2%</td>
<td>1%</td>
<td>23%</td>
</tr>
<tr>
<td>0.017</td>
<td>45</td>
<td>0.6%</td>
<td>0.5%</td>
<td>5.3%</td>
<td>0.1%</td>
<td>57%</td>
<td>0.9%</td>
<td>0.3</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Table 2. Reaction of 6 with 5-Hexenyl Magnesium Bromide, Selectivity and Rearrangement Data.**

<table>
<thead>
<tr>
<th>[6] M</th>
<th>t, hrs</th>
<th>most to least hindered ratio</th>
<th>extent of parallel anionic cyclization</th>
<th>extent of cyclization in less- hindered products</th>
<th>Extent of cyclization in more- hindered products</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.150</td>
<td>44</td>
<td>0.2 : 1</td>
<td>&lt; 1%</td>
<td>2.3%</td>
<td>52%</td>
</tr>
<tr>
<td>0.122</td>
<td>20</td>
<td>0.5 : 1</td>
<td>~ 10%</td>
<td>7.1%</td>
<td>60%</td>
</tr>
<tr>
<td>0.089</td>
<td>45</td>
<td>0.9 : 1</td>
<td>2.4%</td>
<td>2.6%</td>
<td>17%</td>
</tr>
<tr>
<td>0.066</td>
<td>44</td>
<td>0.2 : 1</td>
<td>&lt; 1%</td>
<td>2.3%</td>
<td>48%</td>
</tr>
<tr>
<td>0.027</td>
<td>44</td>
<td>0.2 : 1</td>
<td>&lt; 1%</td>
<td>2.5%</td>
<td>65%</td>
</tr>
<tr>
<td>0.017</td>
<td>45</td>
<td>0.2 : 1</td>
<td>2.1%</td>
<td>2.6%</td>
<td>49%</td>
</tr>
</tbody>
</table>

The results in both tables show a significant amount of scatter, and ratios of small numbers in particular must always be interpreted cautiously. Nonetheless, polar processes consistently dominate. A slower but competitive SET process is also observed however, and where SET occurs, significant additional 5-hexenyl → cyclopentylcarbinyl rearrangement is also observed beyond that seen in the parallel quench experiments. Concentration does not seem to have much effect other than the obvious effect on extent of reaction. The variability in anionic cyclization and to some lesser extent the variability in amount of SET occurring demonstrates the significant variability from batch to batch of Grignard reagent, but the consistency within a given batch. Further implications of these results are presented in the discussion section, including further insight provided into the mechanism of reaction.
Chapter 4. Other Investigations.

4.1 Introduction.

In this brief chapter, two sets of experiments done early in the Tanko group investigation of the title compound are described. These experiments were performed by Dr. Larry E. Brammer as part of his doctoral research, and have been reported at least preliminarily in the chemical literature.\textsuperscript{62,100} They are reviewed only briefly here as they pertain to ultimate evaluation of 6 as a mechanistic probe for SET to conjugated carbonyls.

4.2 Methyl Lithium.

Organolithium reagents are well preceded in the literature as reacting \textit{via} SET, much like Grignard reagents.\textsuperscript{15,16,113,114,115} In many cases, the two are studied side by side. Many of the key points from the discussion of Grignard mechanisms earlier in this work hold true for organolithium reagents as well. Prior work done by this research group is described below, primarily to demonstrate two major points. The first is that 6 is not limited strictly to detecting SET from Grignards. The second is to show that there was some reason to have believed that the phenylsulfonylcyclopropylcarbinyl lithiate (23) could have transferred an electron, and more importantly, that had it transferred an electron, the title compound 6 would have been able to detect it. Methyl lithium was chosen for its commercial availability, its ability to parallel the methyl magnesium halides previously described, and to show that even the methyl species could transfer an electron to 6 (since once again methyl should be less reducing than primary which is less reducing than secondary, which is less reducing than tertiary). Results are reported in Scheme 4.1.
Only two products, formed in nearly equal amounts, were detected. There was the alkene, 13, which is almost certainly the result of a polar elimination process, since no other disproportionation products were detected. Again, disproportionation with a methyl radical intermediate cannot be conclusively ruled out, although it is considered unlikely due to the lack of either 11 or 12 which would result from the competing disproportionation reactions. Nor was any bubbling of methane out of solution observed. The only addition product detected was 17, where the methyl group is attached at the more-hindered position, completely indicative of a SET process. Total recovery was 96%, but percent conversion was only 26% with the remainder being accounted for by unreacted starting material. Reasons for the low amount of conversion after 20 hours (compared to MeMgBr) could include the lower concentrations used as well as the possibility of an intrinsic reactivity difference due to the lithium counter-ion (as opposed to a Mg\textsuperscript{II} species).

It should be noted that although zero least hindered substitution product (18) was observed, if the “predicted” 9:1 ratio were indeed present, it would have been at the limits of detection of the techniques used. Similarly, one cannot rule out the possibility that a small fraction of the 13 formed was due to disproportionation, with the correspondingly small amounts of 11 and/or 12 that would also have to be formed being below the detection limits as well. However these would all be trace products and their presence or absence is not particularly relevant to the discussion at hand.

In summary, the results do indeed demonstrate that organolithium reagents do undergo SET to conjugated carbonyls, and 6 is able to confirm this by
regiodifferentiation. Even the least reducing of the normal (alkyl) organolithium reagents will transfer an electron to 6. Thus the failure of 23 to transfer an electron to 6 is a result of the stabilization of the anion by the phenyl sulfonyl group as described earlier, and is not merely an artifact of the counter-ion used.

4.3 Lithium Dimethyl Cuprate.

Another of Brammer’s experiments is described below. In this case, lithium dimethyl cuprate is studied with 6. This was one early study to use 6 to actually investigate a mechanism that was under debate. There is an immense amount of conflicting information in the literature as to the mechanism of lithium dialkyl cuprates. The general consensus has been that there is at least some degree of SET to their mechanism of reaction with carbonyls and other species if the substrates are sufficiently easy to reduce. A general guideline has been suggested by House that substrates with reduction potentials $\leq -2.35$ V vs. SCE should react with lithium dimethyl cuprate via SET. Since 6 has a reduction potential of $-2.22$ V vs. SCE, it was expected to fall into the SET mechanistic regime. The results of Brammer’s reaction of lithium dimethyl cuprate with 6 are outlined in Scheme 4.2.

![Scheme 4.2](image)

The only product observed, in 98% purity and 73% recovery was the addition product 18, where the methyl group has added to the least hindered carbon, through what should by now be definitively indicative of a polar process. Thus SET did not occur even though 6 does fall within House’s range for species that should react via SET with Me$_2$CuLi. Admittedly 6 is near the limit of House’s range, and there could be some variability in behavior of Me$_2$CuLi near that limit. Also one might imagine that reduction
potential alone may not be the sole determinant, and some unknown factor may also play a role. An entirely different compound from 6 with the same reduction potential may or may not react similarly with Me₂CuLi.

Nonetheless, this experiment establishes some good evidence for the use of 6 as a probe for SET. First of all, 6 is able to detect when SET is not at work by giving least hindered substitution. Also, this experiment with Me₂CuLi is the first demonstration of the utility of 6 in determining the occurrence of SET in a case where there is doubt about a mechanism. The other reactions studied to date have generally been ones where the mechanisms were fairly well known and were under study primarily to evaluate 6, and not vice versa.
Chapter 5. Discussion.

5.1 Discussion and Interpretation of Results.

Brief interpretations of results have been given as the results were presented. Here a more detailed and comprehensive overview of the results of the research will be presented and discussed, particularly as it pertains to the use of the title compound as a mechanistic probe for single electron transfer to conjugated carbonyl compounds.

The initial bulk electrolysis results demonstrate that when the title compound is reduced (6 → 7), it undergoes rapid and irreversible ring opening, preferentially to the tertiary radical anion (8). Some opening to the less favored primary radical anion (16) does also occur. The ratio of tertiary to primary ring opening observed was just over 9:1. This may serve as a crude indication for the selectivity of ring opening in a totally ET process. One should remember, however, that this number is almost certainly solvent and counter-ion dependent to some extent. It may also be dependent on both relative and absolute concentrations, as these could potentially affect coordination and rate of ring opening. Nonetheless, previous work indicates not only the reduction potential of 6, but also the fact that the follow-up chemistry (spirocyclic ring opening) is faster than the ET step (from an electrode), but is still a chemically distinct step from ET and is not concerted with electron transfer. Most importantly, the bulk electrolysis confirms that upon accepting an electron, 6 will ring open, and do so to the tertiary radical anion with a significant degree of selectivity.

Initial investigations with reagents (i.e., methyl Grignards and methyl lithium) known to transfer an electron to this sort of conjugated carbonyl confirmed the bulk electrolysis results by giving predominately more-hindered substitution products. The significance of counter-ion and concentration was demonstrated again by the difference in both rate of reaction and selectivity. A competing E2 process is definitely observed, as this is the best explanation for the significant amount of alkene 13 produced in abundant excess of the two 4-alkylphenols (11 and 12) which are the other disproportionation products. Since 11 and 12 can arise from disproportionation or hydrogen atom
abstraction, the sum of the yields of 11 and 12 set a maximum for the amount of 13 that can be accounted for by a disproportionation mechanism. The remainder (the majority of the 13 produced) is due to a competing polar elimination process. A competing polar substitution process may also be at work in the case of methyl Grignard. The selectivity of most- to least-hindered substitution is less than 3:1. This could be due to a difference of selectivity on changing concentration, solvent (THF vs. DMF) and counter-ion (Mg²⁺ vs. Bu₄N⁺). However it could also be the result of a slower but competitive direct polar attack by the nucleophile at the least-hindered carbon. This is a definite possibility, especially in light of the presence of a competitive polar elimination process. In the case of methyl lithium, the competitive E2 process is just as significant as SET-addition, but no least-hindered substitution arising from SET or polar pathways is observed. It should, however, be noted that at the low percent conversions obtained, to see a 9:1 ratio would be at the limits of detection. These two sets of experiments confirm the SET nature of the reactions of MeLi and MeMgX with conjugated carbonyls while at the same time providing substantial evidence for the utility of 6 to detect and distinguish SET on the basis of observed regiochemistry. They also further illustrate the significance of counter-ion, solvent, and concentration. It is also interesting to note that inhomogeneity in the case of MeMgI slowed the rate of reaction but did not significantly affect product ratios, indicating that surface reaction either did not occur or occurred via a chemically similar process to the solution phase reaction.

Brammer’s experiment using lithium dimethyl cuprate shows two distinct and interesting facts. The first is the simple fact that 6 can and will detect non-SET processes by giving least-hindered substitution products. Thus 6 truly can be useful as a probe for SET because it will detect (fairly unambiguously) both polar and SET processes and distinguish between them on the basis of observed regiochemistry. The second fact elucidated in this experiment is the mildly surprising fact that SET is not at work in this reaction. This is another piece of evidence for a polar mechanism in the reaction of dialkyl lithium cuprates with conjugated carbonyls. It is still very likely that SET is important in many such reactions, as the body of evidence, although split, does in general favor SET. However, Me₂CuLi does not appear to transfer an electron to a relatively
easily reduced ketone such as 6. It has however been shown to do so with even more easily reduced carbonyls (benzophenone, etc.). So it may well be that House’s window of SET from Me₂CuLi to carbonyls with a reduction potential between –1.40 to –2.35 vs. SCE is just a bit too wide, or it may be that near the border of this window other factors may predominate and reduction potentials are not the sole or even major determinant to the mechanism. This experiment was also significant in that it was the first true test of the title compound in a case where the mechanism was not well established.

Next the search for a nucleophile that could probe for SET in conjunction with the title compound to give confirmation of SET detection, and potentially more information regarding specifics of the mechanism was underway. The first attempt in this area was to use the anion of cyclopropylcarbinyl phenyl sulfone (23) with a lithium counter-ion, since Chanon and Stirling had recently demonstrated the rapid ring opening of the carbinyl radical but zero ring opening of the anion. The stability of this particular cyclopropylcarbinyl anion is due to extreme stabilization effected by the phenyl sulfonyl group. This piece of information, along with the conditions Chanon and Stirling had to use to form the radical, should have been indicative of the trouble that awaited. The anion is simply too stable and $\Delta G^\circ$ for electron transfer, even to as good a substrate as 6, is too unfavorable. Crude analysis of products showed a polar mechanism predominating, with no rearrangement of the phenylsulfonylcyclopropylcarbinyl moiety in the addition products, and predominately least hindered substitution (27). Formation of small amounts of most hindered substitution (28) may have been due to a competitive but slower SET process, but this would have to involve in cage coupling, as no rearrangement of the phenylsulfonylcyclopropylcarbinyl moiety was observed. A polar process such as that described by Tanko and Brammer for the more-hindered substitution of thiophenoxide is another possibility that cannot be ruled out.¹⁰⁰,¹²³ Regardless of the mechanism of formation of the minor product, it is clear that direct polar addition occurred as the predominate pathway. If paramagnetic species were involved in any minor pathways, the lifetime of the phenylsulfonylcyclopropylcarbinyl radical was significantly less than $10^{-8}$ seconds, since absolutely no rearrangement of the phenylsulfonylcyclopropylcarbinyl moiety was observed.
In a brief effort to continue to use 23, since significant effort had already been put into synthesis and studies of the formation of the anion via proton and deuterium NMR, it was decided to investigate the reaction of 23 with “SpiroAnthrone” (29). Regardless of time, and even at room temperature, no reaction occurred, with quantitative recovery of both 29 and cyclopropylcarbinyl phenyl sulfone. Cyclopropylcarbinyl anion 23 simply is unwilling to give up the anionic stabilization of the phenylsulfonyle group and transfer an electron to the substrate. So 23 was abandoned in favor of a more conventional and well-studied radical clock and investigation of 6 continued.

The clock that was at least a partial success was the next one tried, the 5-hexenyl → cyclopentylcarbinyl rearrangement. 5-Hexenyl Grignards and similar derivatives have been very well studied in the past few decades. It was expected that since methyl Grignard shows predominately SET in reaction with 6, a primary Grignard should show even more SET, since there is very slightly more steric bulk and a more negative reduction potential. The only thing left to contend with is the rearrangement of the “nucleophile” either through an anionic pathway during reaction, or by a radical or polar process during Grignard formation. This was addressed in a two-pronged manner. First, some of the Grignard was quenched right after titration and before use. “Initial extent of cyclization” was found by quantitating 1-hexene vs. methylcyclopentane (by GC vs. 2,3-dimethylbutane.) Second, by also running parallel experiments where the Grignard solution was syringed into an equal volume of THF as the experimental run, but without any 6, and allowing it to stir at the same temperature and for the same duration as the experimental run, and then quenching and again quantitating 1-hexene vs. methylcyclopentane, the total extent of parallel anionic cyclization was obtained. This figure gives the total amount of extraneous cyclization that was the result of anything other than SET to 6. This can then be subtracted from the amount of cyclization in the experimental run. It is interesting to note that the extraneous cyclization occurred from nearly zero to up to about 10%, and that under the conditions used virtually all extraneous cyclization was due to initial cyclization during the formation of the Grignard reagent. That is, virtually no increase in extent of cyclization occurred even at room temperature over 40+ hours in the parallel experiments (sans 6.) This seems to indicate that anionic
cyclization of the Grignard reagent itself (once it is formed) is not nearly as much of a problem as literature seems to present, and that it is cyclization during the formation of the Grignard reagent that can confound the experiments if care is not taken to evaluate it.

With parallel experiments in place to assess the extent of extraneous cyclization, the reaction of 6 with 5-hexenyl Grignard was run a number of times, with three different batches of Grignard reagent, at varying concentrations. It is hard to see much of a trend in the data as far as concentration, but only concentrations from 0.017 M to 0.155 M were able to be studied, just under an order of magnitude difference. The one obvious (and expected) trend is the net decrease in extent of reaction as the solutions become increasingly dilute, and the corresponding increase in unreacted starting material. Surprisingly, increased concentration may lead to less polar (E₂) elimination, but this may be due to error and not a true relationship. Other than that there is not much of an observable trend based on concentration. The data is fairly consistent, with similar amounts of SET and similar amounts of hexenyl cyclization for the SET products regardless of concentration (although there is a fairly significant amount of scatter.) The one run at 0.089 M appears to be an anomaly, as it does not fit the trend for extent of reaction or amount of elimination based on concentration, nor is there a similar amount of SET to the other five runs.

The one thing that truly does leap out is how amazingly little SET is occurring. Of the addition products, roughly 20% are at the favored more-hindered site. This is compared to roughly 75% for the methyl Grignard runs. This is completely unexpected on the basis of increased steric bulk and greater reducing power of primary Grignard reagents over methyl Grignard. More SET should be occurring, not less. No readily apparent explanation for these data exists, but the data themselves are beyond question. The product analysis presented in 3.3.2 (pp. 35-44) is conclusive, and the results have been replicated no less than five times. The role played by the grade of magnesium, amount of extra MgBr₂ present (due to entraining of the Grignard formation with EDB), and other undetermined factors is not well understood, but there was no significant change in any of these between the methyl Grignard runs and the 5-hexenyl Grignard
runs. The run used in isolating a single product to aid in analysis of the mixture, using cyclopentylcarbinyl magnesium bromide also yielded predominant polar products, in nearly a 9:1 excess. So perhaps it is that the methyl Grignard runs are the anomalies, although the data there too appears to be beyond question. Perhaps there is an undiscovered fundamental difference in the reactivities of methyl Grignard and primary Grignards, not based on reduction potentials or steric bulk. Nonetheless the data is as presented, albeit without any substantial explanation for such unexpected results. Nonetheless, the title compound does still appear to be proving itself successful at distinguishing mechanism, even when the explanation for why that mechanism occurs is lacking.

The rearrangement of the 5-hexenyl moiety does provide some further information. The less-hindered (presumably polar) products show no significant enhancement of 5-hexenyl → cyclopentylcarbinyl rearrangement relative to the amount of anionic cyclization. The data presented in Table 2 (p. 44) show that the numbers for anionic cyclization versus those for cyclized less-hindered addition products are generally within error limits of one another. Meanwhile the amount of cyclization in the more-hindered (presumably SET) products shows dramatic enhancement of the rearrangement. Again consulting Table 2, the data shows anionic cyclization from < 1% up to about 10%, while the amount of cyclization in the more-hindered products is in the 48-65% range (ignoring the one anomalous run at 0.089 M). This dramatic increase in cyclization confirms an SET pathway as dominant in the formation of most-hindered products. At least 48-65% of the more-hindered addition products are from SET, and that is a theoretical minimum based on the assumption that only the more-hindered containing the cyclopentylcarbinyl moiety arise from SET. It is much more likely that nearly all of the more-hindered addition products arise from an SET mechanism. Meanwhile the lack of increased cyclization in the less-hindered products provides good evidence that these arise from a polar process. Although strictly speaking they could arise from in-cage radical coupling occurring much faster than hexenyl cyclization, this is deemed extremely unlikely, based on the selectivity of less- to more-hindered substitution, previous results with 6, and the fact that the hexenyl radicals known to exist in the formation of the more-hindered
products do have time to rearrange. Thus the most likely explanation is that there are two competing processes at work. A polar $S_N2$-type pathway, like that described in Scheme 1.13 (p. 13), leads to less-hindered substitution products without any enhanced rearrangement of the 5-hexenyl moiety. Meanwhile a slower but competitive radical process is leading to more-hindered substitution products, and the intermediate hexenyl radicals exist on a sufficiently long time scale to allow rearrangement, which implies at least some amount of freely diffusing radical intermediates in the SET reaction of Grignard reagents with conjugated carbonyls, as per Walling’s\textsuperscript{80} and Wigal’s\textsuperscript{99} assertions.

**5.2 Conclusions.**

The results discussed above lead to a number of significant conclusions. The first is a better understanding of the mechanism of the reaction of Grignard reagents with 6, and presumably, by extension, to other similar easily reduced conjugated carbonyl compounds. There appears to be varying amounts of SET and polar processes at work, depending on the nucleophilic reagent used. The dominance of one mechanistic pathway over the other is not well predicted by currently understood features such as steric bulk or reducing power of the Grignard reagents. The polar process is a simple and obvious pathway, just as described in Scheme 1.13. The significant result that can be garnered here is a better understanding of the potential SET mechanism. Even though SET is not necessarily the dominant mechanism in all or even most cases, it is almost always somewhat competitive, and greater insight into this mechanism has been gained.

The basic outline of potential SET mechanisms is presented in Scheme 5.1. In the scheme, only spirocyclic ring opening of 7 to 8 is shown, although $7 \rightarrow 16$ also occurs to a lesser extent. Thus, anywhere 8 is in the scheme, 16 occurs to a lesser extent. Similarly, 19 implies 20 and 21 implies 22 to the same extent that 8 implies 16. $k_{ET}$ is the rate constant for electron transfer from the Grignard reagent to 6; $k_{open}$ is a combined rate constant for the spirocyclic ring opening of 7 to both distonic radical anions 8 and 16; $k_{diff}$ is the rate constant for diffusion of the alkyl radical from either 7, 8, or 16 (all can be assumed to be about the same, and if $k_{open} < k_{diff}$ then it is diffusion of $\textit{R}^\bullet$ from 7,
whereas if $k_{\text{open}} > k_{\text{diff}}$ then it is diffusion of $R^\cdot$ from 8 or 16 depending on the direction that 7 opens; $k_{\text{in-cage}}$ is the rate constant for in-cage coupling of $R^\cdot$ to 8 (or 16) and is only a factor if $k_{\text{open}} > k_{\text{diff}}$; $k_{\text{free}}$ is the rate constant for coupling of freely diffusing $R^\cdot$ and 8 (or 16); $k_{\text{rearr}}$ and $k_{\text{free'}}$ only apply if the alkyl radical $R^\cdot$ has the potential to rearrange to $R'^\cdot$, such as the 5-hexenyl radical, and then $k_{\text{rearr}}$ is the rate constant for that rearrangement ($\sim 10^5$ s$^{-1}$ for 5-hexenyl at room temperature) and $k_{\text{free'}}$ is the rate constant for the coupling of 8 (or 16) to the free $R'^\cdot$ radical.

Scheme 5.1 outlines just the mechanism for SET reaction of 6 with Grignard reagents, and is in competition with any polar processes, such as the direct polar “$S_N2$-type” attack described in Scheme 1.13, or the polar E$_2$ elimination described in Scheme 2.5. The SET mechanism begins with electron transfer from the Grignard to 6, yielding radical anion 7 and $R^\cdot$. Here is the first potential divergence. It is known that ring opening of 7 to tertiary and primary distonic radicals (8 and 16, respectively) is fast, with $k_{\text{open}} > 10^7$ s$^{-1}$. If $k_{\text{open}} > 10^{10}$ s$^{-1}$, then ring opening can occur within a cage lifetime as depicted in Scheme 5.1. If $k_{\text{open}}$ is significantly less than $10^{10}$ s$^{-1}$, then $k_{\text{diff}} > k_{\text{open}}$ and spirocyclic ring opening occurs after diffusion out of the solvent cage. Assuming that $k_{\text{open}}$ is fast enough to occur within a cage lifetime, then there is the possibility for in-cage coupling of $R^\cdot$ to 8 or 16 ($k_{\text{in-cage}}$). If spirocyclic ring opening does not occur in-cage, then $k_{\text{in-cage}}$ is not significant, since no 1,2-addition products are observed. Regardless of whether there is any in-cage coupling of $R^\cdot$ and 8 (or 16) to yield 19 (or 20), the presence of 5-hexenyl → cyclopentylcarbinyl rearrangement in the addition products indicates that there is an out-of-cage process at work (either exclusively or in addition to an in-cage process). $R^\cdot$ and the radical anion(s) present in-cage (be they 7, 8, and/or 16) diffuse apart with a rate constant $k_{\text{diff}}$ that is roughly equal to $10^{10}$ s$^{-1}$, give or take an order of magnitude. Any 7 left would then open to the distonic radicals 8 and 16. This is where the possibilities for these radicals and radical ions open up. Once there are freely diffusing paramagnetic species, abstraction of a hydrogen atom from solvent or disproportionation become possible. These likely do occur in most cases, but to a small extent. As Walling predicts in his detailed kinetic analysis$^{80}$, these can occur until there
is a large imbalance of the two paramagnetic species, but then the kinetics dictate that coupling processes will dominate. It is also during this time that rearrangement of $\text{R} \cdot \rightarrow \text{R}' \cdot$ can occur. If there are no in-cage processes, then the 5-hexenyl data suggests that coupling occurs roughly at the same rate as the $\sim 10^5 \text{s}^{-1}$ 5-hexenyl $\rightarrow$ cyclopentylcarbinyl rearrangement, and thus about half of the freely diffusing $\text{R} \cdot$ radicals have time to rearrange to $\text{R}' \cdot$ (i.e., $k_{\text{in-cage}} \approx 0, k_{\text{rearr}} \approx k_{\text{free}}$). However, if most of the coupling to give 19 (and 20) is in-cage, and only about half of the radicals diffuse ($k_{\text{in-cage}} \approx k_{\text{diff}}$), then the $\text{R} \cdot$ radicals that do escape the cage must almost all rearrange to $\text{R}' \cdot$, and $k_{\text{rearr}} \gg k_{\text{free}}$.

**Scheme 5.1**
More importantly, the major and most significant conclusion that can be drawn from the results discussed above is the very heart and soul of this endeavor. That is the evaluation of \(6\) as a mechanistic probe for single electron transfer to conjugated carbonyl compounds. In this regard the project was a definitive success. The title compound is successfully able to differentiate SET from polar processes on the basis of observed regiochemistry. The concept of a “regiodifferentiation” probe has been successfully demonstrated. Difficulties in the use of \(6\) as a probe include the facts that \(6\) is not quite as reactive as some other probes and conjugated carbonyls, it is not quite as easily reduced, the synthesis of \(6\) is still non-trivial, and isolation (or independent synthesis) or the different regioisomers can prove difficult since the structures are often very similar. However mass spectral evidence based on fragmentation patterns and the presence or absence of benzylic protons in the NMR spectra is a very good indicator of whether most- or least-hindered substitution has occurred. Previous work has also shown that the use of \(6\) in protic solvent is limited\(^{100}\), as the potential for carbocationic pathways then exists which could confound any study using \(6\) as a probe. Lastly, some unexpected and currently unexplainable results as to when SET occurs were found. Nonetheless, the evidence presented herein clearly demonstrates that (at least in ethereal solvents) this probe is indeed a useful tool in the growing arsenal of probes and other methods for use in mechanistic elucidation, and is very good for unambiguous detection of a SET pathway in the reaction of a nucleophile. Results should be generalizable to other carbonyl species (usually conjugated carbonyls) with similar reduction potentials to \(6\). This is indeed the entire goal of both this document and the entire research effort. The title compound can be used to aid in elucidating a mechanism, and this result can be generalized to other carbonyl species.

Other information that was garnered throughout the duration of this study is also potentially useful. 5-Hexenyl Grignard is a useful tool for evaluating the presence of freely diffusing alkyl radical intermediates. Anionic contamination is present (in 0-10% under the conditions used) but can be successfully accounted for by performing parallel “blank” experiments at the same temperature and concentration, then quenching and quantitating 1-hexene vs. methylcyclopentane. It was also demonstrated that it is
possible to use unsubstituted 5-hexenyl Grignard with limited success, although the 1,1- or 2,2-dimethyl-5-hexen-1-yl derivatives have been shown to undergo more cyclization and thus potentially more SET, and would have been a somewhat better choice for study to achieve more SET and thus easier analysis of 6 as a probe for SET.

The phenylsulfonylcyclopropylcarbinyl anion 23, though interesting, was not particularly useful in evaluating 6. This was due to the extreme stability of anion 23 (as a result of the stabilizing influence of the phenylsulfonyl group), and the resultant unwillingness of 23 to transfer an electron to 6 (or even 29) to give 25 and 7 (or the radical anion of 29.) “SpiroAnthrone” (29) may have some utility in the future, but in the case studied here was simply too unreactive, even though it is more easily reduced than 6.

Thus a good deal of relevant information was garnered in the evaluation of 6 as a mechanistic probe for SET to conjugated carbonyl compounds, but most significant is the fact that 6 is indeed a successful tool for mechanistic investigations.
Chapter 6. Experimental.

6.1 Instrumentation and Materials.

6.1.1 Instrumentation.

Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected and reported to the nearest half-degree centigrade. Nuclear magnetic resonance spectra were obtained on a variety of Fourier-transform instruments, including Bruker WP 200 MHz, WP 270 MHz, and AM 360MHz instruments, and a Varian Unity 400 MHz instruments. Routine $^1$H and $^{13}$C spectra were obtained on any of the four, while high resolution and two-dimensional spectra were recorded on the Varian instrument. In many cases, $^{13}$C assignments were aided by the attached proton test (APT) performed on any of the four instruments. $^2$H (deuterium) spectra were obtained by Mr. Bill Bebout on the 200MHz Bruker instrument. All chemical shift values are reported in δ units in CDCl$_3$, relative either to TMS (δ = 0.00 ppm) or to residual CHCl$_3$ (δ = 7.24 ppm), except for $^2$H spectra which were taken in the solvent of the quench experiment, normal THF. Infrared spectra were recorded on a Perkin-Elmer model 1600 FT-IR spectrometer, with all data reported in cm$^{-1}$. Ultraviolet-visible spectroscopy was performed using a Perkin Elmer Lambda 4 UV-Vis Spectrophotometer. Unit mass resolution GC-MS was performed on a Hewlett Packard HP 5890 gas chromatograph with interfaced to a HP 5970 low resolution mass spectrometer and a HP series computer. High-resolution mass spectrometry was performed by Mr. Kim Harich on a VG-7070E HF double-focusing magnetic sector high-resolution mass spectrometer using electron impact ionization at 70 eV.

Gas chromatography was performed on a Hewlett Packard 5890A gas chromatograph equipped with a flame ionization detector and an HP 3393A recording integrator, on either of two Alltech Econocap EC-5 (SE-54) capillary columns. Most analyses were performed on a 15 m x 0.53 mm ID x 1.2 µm column with a head pressure of 5 psi. More volatile materials were analyzed on a 30 m x 0.25 mm ID x 0.25 µm column with a head pressure of 15 psi. A variety of oven temperature ramping profiles were used, with an injector temperature of 275°C and detector temperature of 300°C.
Correction factors *versus* either 2,6-di-\textit{t}-butylphenol [Aldrich] or 2,3-dimethylbutane (DMB) [Aldrich, 98\%] were used wherever authentic samples were available.

High performance liquid chromatography was performed using a Beckman System Gold 128 model solvent pump system with a 166 model UV-Visible detector (at wavelengths from 254-275 nm, as appropriate.) Preparative separations were attempted on a Beckman C-18 reverse phase preparatory column (21.2mm x 150mm) with acetonitrile/water [both from Mallinckrodt, chromatography/biological grade] solvent mixtures at flow rates from 15-25 mL/min. Analytical separations were performed on either a Beckman C-18 reverse phase analytical column (4.6 mm x 250 mm) with acetonitrile/water solvent mixtures at a flow rate of 1 mL/min, or on the preparatory column as described above, simply with smaller sample volumes. Bulk electrolyses were performed on an EG&G Princeton Applied Research model 273 potentiostat/galvanostat interfaced to a PC in a MS-DOS environment.

### 6.1.2 Solvents and Purification.

Tetrahydrofuran (THF) [Mallinckrodt, EM Science, or Fisher] and diethyl ether [Mallinckrodt or EM Science] were dried over lithium aluminum hydride [Aldrich, 95\%] and distilled immediately prior to use. Acetonitrile [Mallinkrodt] was dried over CaH$_2$ and distilled prior to use. N,N-Dimethylformamide (DMF) [EM Science, 98\%] was dried over CuSO$_4$ [Aldrich, 98\%] and activated alumina [Aldrich, neutral, Brockman activity I] (flame dried under vacuum) for a minimum of three days and then vacuum distilled just prior to use. Pyridine (Aldrich, 99+\%) was dried over potassium hydroxide [Mallinckrodt] for a minimum of seven days and was then distilled just prior to use. Deionized water refers to house water supply purified by reverse osmosis, and distilled water refers to deionized water that was distilled prior to use. All other solvents were used as received, from the chemical supplier noted in square brackets (vendor is only noted the first time that a solvent is used, unless vendors changed over experiments.)
6.1.3 Titrations.

Grignard reagents were titrated versus 10 µL of 2-butanol [Aldrich, 98%] in THF with N-phenylnapthylamine [Aldrich, 98%] as an indicator just prior to use. Alkyl lithium reagents were titrated versus 2,5-dimethoxybenzyl alcohol [Aldrich, 99%] in. This is a self-indicating titration.

6.1.4 Thin Layer Chromatography.

Analytical thin layer chromatography (TLC) was performed on 20 cm x 20 cm precoated polyester silica gel (250 µm layer) plates with fluorescent indicator [Whatman] cut and sized as needed. Preparatory TLC was performed on 20 cm x 20 cm fluorescent indicating precoated glass plates with either 1500 µm or 2000 µm layer of silica gel [Alltech]. In both cases, plates were spotted with homemade micro-pipettes, developed in varying concentration Ethyl Acetate [EM Science] / Hexanes [EM Science] mixtures of varying concentration, and visualized using a short-wave UV lamp.

6.1.5 Reagents.

Tetra-\textit{n}-butylammonium perchlorate was prepared according to the method of House,\textsuperscript{124} recrystallized a minimum of four times from ethyl acetate / hexanes, and then dried in a vacuum oven immediately prior to use. Methyl iodide [Aldrich, 99%] was distilled under nitrogen in a darkened room, taking the middle 10 mL of 15 mL distilled, and stored in a flask wrapped in aluminum foil under nitrogen in a –20 °C freezer. Magnesium used for each individual set of experiments was of a single batch of 98% magnesium turnings [Aldrich], stored under argon, and discarded if any visible oxidation was present on the metal surface. Cyclopropylcarbinyl phenyl sulfone was prepared by the method of Chanon and Stirling (and their references therein)\textsuperscript{101} without significant modification (although it was discovered that cyclopropyl phenyl sulfone is not stable to the conditions of gas chromatography, nor will it give a parent ion in either direct probe or GC- or direct probe MS with either electron impact or chemical ionization techniques) All other reagents were used as received, from the vendor noted in square brackets. A vendor is only noted for a given reagent the first time a reagent is mentioned, unless vendors changed between experiments.
6.2 Synthesis of 1,1-Dimethyl-5,7-di-tert-butylspiro[2.5]octa-4,7-dien-6-one (6).

The synthesis of the title compound is a Tanko group modification of a variety of published procedures and is outlined below in Scheme 6.1. A detailed experimental procedure for each step follows. A very similar procedure was reported by Brammer in his doctoral dissertation, but significant improvements in yield, purity, and analysis have been made, and the synthesis is therefore reported herein.

**SCHEME 6.1**

6.2.1 Synthesis of 38.

To 40 mL (382 mmol) of isobutyroyl chloride [Aldrich, 96%, or synthesized in the usual fashion from isobutyric acid and thionyl chloride] was added 44 g (330 mmol) AlCl$_3$ [Aldrich, 98%] with mechanical stirring under flowing argon in a salt-ice-water bath. To this solution was added dropwise a solution of 53 g (257 mmol) of 2,6-di-tert-butylphenol [Aldrich] in an additional 50 mL (475 mmol) isobutyroyl chloride. Two minutes after addition was complete, the resulting purple mixture was slowly added to roughly 1300 mL swirling ice-water. The resulting fluffy yellow suspension was extracted twice with ether. This ethereal solution was washed three times with 10%
aqueous sodium hydroxide [Mallinckrodt], then three times with deionized water. The organics were then dried over anhydrous magnesium sulfate [Mallinckrodt] and filtered through a glass wool plug. Solvent was removed in vacuo, leaving 71.5 g rust colored solid. Multiple recrystallizations from boiling 95% ethanol [Aaper], including further retrieval of material from the mother liquors yielded 68.8 g (97%) pale yellow solid (38) mp 128.5-131 °C, literature¹²⁵ mp 125-127 °C.

¹H NMR (CDCl₃, 270.134 MHz) δ 1.22 (d, 6H, dimethyl), 1.50 (s, 18H, di-t-butyl), 3.39 (m, 1H, methine), 5.76 (s, 1H, phenol), 7.90 (s, 2H, aromatic).

6.2.2 Synthesis of 39.

To 325 mL of a 3:2 mixture of ethyl acetate and chloroform [EM Science] was added 47.5 g (172 mmol) 38. This was stirred roughly 10 minutes until dissolution occurred. Then 87.0 g (390 mmol) CuBr₂ [Aldrich, 99%] was added slowly with continued magnetic stirring. The reaction mixture was brought to reflux and allowed to stand. After 2.5 hours the hot pea green opaque mixture was vacuum filtered through Celite [Aldrich], treated with decolorizing carbon, and filtered again through Celite, washing with ethyl acetate each time. The now clear, deep green solution was passed through a 2” plug of neutral alumina on top of a bed of Celite on a fritted glass vacuum filter to give a clear pale yellow solution, which reeked of HBr after removal of solvent in vacuo. The 53.4 g of yellow solid obtained was redissolved in chloroform and solvent was again removed in vacuo, leaving the solid under vacuum for an hour to help remove additional HBr. The resulting solid was washed with ice-cold hexanes and dried on a vacuum pump overnight, yielding 49.5 (81%) of a nearly white solid powder (39).

mp 141-143 °C, literature mp¹²⁵ 141-142 °C.

¹H NMR (CDCl₃, 200.132 MHz) δ 1.47 (s, 18H, di-t-butyl), 2.05 (s, 6H, dimethyl), 5.72 (s, 1H, phenol), 8.16 (s, 2H, aromatic).

6.2.3 Synthesis of 15.

To 49.3 g (139 mmol) 39 stirring (mechanical) under argon in 1200 mL ethyl ether was added 10.4 g (274 mmol) lithium aluminum hydride. The ice bath was removed and the solution was brought to reflux with continued vigorous stirring. After 3 hours at
reflux, the reaction was allowed to cool to room temperature, and was then quenched by
the addition of 300 mL cold deionized water, followed by 300 mL 10% aqueous sulfuric
acid (Fisher). The layers were separated, and the organic layer was dried over
magnesium sulfate, gravity filtered, and the solvent was removed in vacuo to yield 37.6 g
(97%) fine white powder (15).

mp 148-150 °C, literature mp 149.8-150.3 °C.

1H NMR (CDCl3, 399.951 MHz) δ 1.32 (s, 6H, dimethyl), 1.45 (s, 18H, di-t-butyl),
1.56 (s, broad, 1H, alkyl hydroxy), 3.57 (d, J = 6 Hz, 2H, methylene), 5.12 (s, broad, 1H,
phenol), 7.18 (s, 2H, aromatic)

13C NMR (CDCl3, 50.323 MHz) δ 25.5 (dimethyl), 30.3 (di-t-butyl methyl groups),
34.5 (di-t-butyl quaternary), 39.9 (quaternary), 73.3 (methylene), 122.8 (aromatic C-H),
135.4 (2,6-aromatic quaternary), 136.3 (4-aromatic quaternary), 152.0 (phenolic C-OH).

6.2.4 Synthesis of 40.

To 25.4 g (91.2 mmol) 15 stirring under argon in 300 mL pyridine, well chilled in a
salt-ice-water bath, was added 21 g (110 mmol) tosyl chloride [Eastman]. The bath was
left in place but not maintained with additional ice so that reaction gradually came to
room temperature. Reaction was allowed to stand stirring for 26 hours, after which time
the mixture was poured into 350 mL chilled deionized water and extracted four times
with diethyl ether. The organics were wased three times with deionized water and then
rotary evaporated under water aspirator at 40 °C until roughly 200 mL of a brown
solution remained. This was diluted to 500 mL with benzene [Fisher] and rotary
evaporated nearly to dryness (benzene azeotropes pyridine) and this was repeated several
times until all trace of a pyridine odor was gone. The resulting pale yellow solid was
dried overnight on a vacuum pump to yield 37.1 g (94%) 40.

mp 98 °C (rapidly decomposed to a bright red liquid), literature mp 100-102 °C.

1H NMR (CDCl3, 200.132 MHz) δ 1.31 (s, 6H, dimethyl), 1.41 (s, 18H, di-t-butyl),
2.43 (s, 3H, tosylate methyl), 3.93 (s, 2H, methylene), 5.13 (s, 1H, phenol), 7.07 (s, 2H,
aromatic), 7.28 (d, J = 8.5 Hz, 2H, tosylate aromatic), 7.68 (d, J = 8.1 Hz, 2H, tosylate
aromatic)
6.2.5 Synthesis of 6.

To 2.0 g (4.6 mmol) 40 stirring under argon in 12 mL THF was added 0.61 g (5.4 mmol) potassium t-butoxide [Aldrich, 95%]. The reaction mixture was allowed to stand stirring for 4 hours, after which time the reaction mixture was poured into 35 mL diethyl ether. The organics were washed three times with 1% aqueous sodium hydroxide, dried over magnesium sulfate, vacuum filtered, and the solvent was removed \textit{in vacuo} to yield 1.15 g (96%) of a yellow crystalline crude product melting at 88-92.5°C. The product was purified by two recrystallizations from boiling hexanes, followed by repeated washing with ice-cold hexanes, and dried on a vacuum pump overnight to yield 0.53 g (46%) of a very fine fine white powder (6).

\text{mp } 91.5-93 \degree C, \text{ literature}^{126} \text{ mp } 92-94 \degree C

$^1$H NMR (CDCl$_3$, 270.133 MHz) $\delta$ 1.26 (s, 18H, di-t-butyl), 1.40 (s, 6H, dimethyl), 1.60 (s, 2H, methylene), 6.46 (s, 2H, dienone).

6.3 Bulk Electrolysis of 6.

6.3.1 Electrolysis.

A standard H-cell electrolysis apparatus was used, with a gold foil working electrode, a 0.1 M (in acetonitrile) Ag+/Ag reference electrode, and a copper wire auxiliary electrode. Both compartments were filled with 25 mL of a 0.2 M TBAP solution in DMF. To the working compartment was added 96.0 mg (0.369 mmol) 6 and the apparatus was continuously stirred (magnetically) and bubbled with argon prior to and throughout the electrolysis. Solution was electrolyzed for 43 min at 30 mA (2.2 equivalents of electrons). Electrolysis was quenched by the addition of 2% aqueous sulfuric acid, and 2,6-di-t-butylphenol was added as an internal standard for gas chromatographic analysis. Products were analyzed by GC with comparison to independently synthesized compounds, as described in the 6.3.2. Products were found to be 11 (27.1%), 12 (7.3%), 13 (43.9%), with unreacted 6 quantitated as the two alcohols which are the result of hydrolysis upon acidic workup, 14 (11.8%) and 15 (2.6%). This is a total of 92.7% recovery, with 7.3% unaccounted for, although this is within error limits of being quantitative.
6.3.2 Product Analysis.

Products enumerated above were quantitated by GC versus 2,6-di-t-butylphenol, matching retention times to authentic products already in hand, as described below. Product 12 (2,4,6-tri-t-butylphenol) is commercially available [Aldrich, 96%]. Product 15 is an intermediate of the synthesis of 6 and preparation and characterization is described above.

Product 13 can be prepared cleanly and quantitatively via thermolysis of 6 under an inert atmosphere. In a glass vial under argon, 0.30 g (1.15 mmol) 6 was heated on low heat on a hot plate for 2.5 hours to yield 0.30 g (1.15 mmol, 100%) 11, a thick yellow oil.

$^1$H NMR (CDCl$_3$, 270.133 MHz) $\delta$ 1.45 (s, 18H, di-t-butyl), 1.68 (s, 3H, methyl), 3.26 (s, 2H, methylene), 4.73 (s, broad, 1H, vinylic), 4.80 (s, broad, 1H, vinylic), 5.06 (s, 1H, phenol), 6.99 (s, 2H, aromatic).

$^{13}$C NMR (CDCl$_3$, 67.925 MHz) $\delta$ 22 (methyl), 30 (di-t-butyl methyls), 35 (di-t-butyl quaternary), 45 (methylene), 111 (vinyllic methylene), 125 (aromatic C-H), 130 (4-aromatic quaternary), 136 (2,4-aromatic quaternary), 146 (vinyllic quaternary), 152 (phenolic C-OH).

HRMS mass found 260.214218, mass calculated (C$_{18}$H$_{28}$O) 260.2140158, error 0.8ppm.

UV (MeOH) $\lambda_{max}$ = 275 nm.

IR (neat) cm$^{-1}$ 3647.9, 3072.0, 2954.5, 2911.9, 2873.0, 1648.7, 1613.5, 1431.3.

Product 14 can be prepared by acid hydrolysis of 6. In a separatory funnel, 0.19 g (0.73 mmol) 6 was dissolved in 35 mL ether and shaken with 35 mL 1% aqueous sulfuric acid for 5 min, layers were separated, organics were dried (MgSO$_4$) and filtered, and solvent was removed in vacuo to yield 0.20 g (0.72 mmol, 99% crude yield) 14 which was purified by successive recrystalizations from boiling 95% ethanol to yield .05 g (0.18 mmol, 25% yield) extremely pure 14, as a fine white powder.

mp 89-92 °C, literature$^{127}$ mp 92-93 °C.

$^1$H NMR and IR also compared well to literature.$^{127}$
Product 11 can be prepared via ionic hydrogenation of 38 (an intermediate in the synthesis of 6, reported above). Into a small round bottom flask was charged 2.00 g (7.24 mmol) 38. To this was added 3.0 mL (38.94 mmol) trifluoroacetic acid [Aldrich, 99%] with stirring until dissolution was complete, followed by dropwise addition of 2.9 mL (18.15 mmol) triethylsilane [Aldrich, 99%]. The reaction mixture stood stirring for 40 min after addition was complete, and then 30 mL deionized water and 20 mL ether was added. The layers were separated, and the aqueous layer was washed twice with additional ether. All ethereal layers were combined, dried (MgSO$_4$), and filtered. Ether was removed in vacuo to yield a yellow oil containing 38, 11, and small amounts of triethylsilane and trifluoroacetic acid. Purification by repeated flash column chromatography on silica gel with various ethyl acetate / hexane mixtures eventually afforded 0.92 g (3.51 mmol, 48%) 11 as a thick, clear, colorless oil freezing slightly below room temperature.

$^1$H NMR (CHCl$_3$, 360.434 MHz) $\delta$ 0.91 (d, 6H, dimethyl), 1.43 (s, 18H, di-$t$-butyl), 1.74-1.82 (m, 1H, methine), 2.37 (d, 2H, methylene), 5.00 (s, 1H, phenol), 6.92 (s, 2H, aromatic).

$^{13}$C NMR (CHCl$_3$, 100.578 MHz) $\delta$ 22.6 (dimethyl), 30.0 (methine), 30.6 (di-$t$-butyl methyls), 34.4 (di-$t$-butyl quaternary), 45.6 (methylene), 125.6 (aromatic C-H), 132.3 (4-aromatic quaternary), 135.5 (2,6-aromatic quaternary), 151.8 (phenolic C-OH).

HRMS mass found 262.2311, mass calculated (C$_{18}$H$_{30}$O) 262.2297, error 5.3 ppm.

GC-MS m/z (abundance) 262 (23), 247 (38), 219 (100), 57 (15).

IR cm$^{-1}$ 3648.8, 3074.0, 2957.4, 2908.4, 2868.4, 2844.4, 1434.7, 1233.4, 1158.2.

6.4 Reaction of 6 with MeMgI.

Methyl magnesium iodide was prepared from 0.032 g (1.32 mmol) magnesium turnings and 70 $\mu$L (1.12 mmol) distilled methyl iodide in a total of 1.4 mL THF, for 3 hours. To the crude, heterogenous Grignard solution was added 0.10 g (0.38 mmol) 6 dissolved in 0.4 mL THF over a period of 5 minutes. Reaction was allowed to proceed with vigorous stirring under argon for 17 hours after the addition of 6. The reaction was quenched with 1% aqueous sulfuric acid, and extracted three times with ether. The
organics were washed three times with deionized water, dried over magnesium sulfate, and filtered. Solvent was removed \textit{in vacuo} to yield 0.114 g of a thick yellow-brown oil. This oil was taken up in dichloromethane [EM Science] along with 2,6-di-\textit{t}-butylphenol (as an internal standard) and quantitated by gas chromatography. Products were determined to be 17 (18%), 18 (6%), 11 (2%), 12 (< 1%), and 13 (21%) with 49% unreacted starting material quantitated as hydrolysis products 14 and 15, for a total of 97% recovery, well within error limits of being quantitative. Products were matched to 11-15 as described above for the bulk electrolysis, and to authentic samples of 17 and 18 isolated by HPLC by Brammer from his previous experiments with MeMgBr\textsuperscript{62,100}.

17 – $^1$H NMR (CDCl\textsubscript{3}, 270 MHz) $\delta$ 0.90 (s, 9H, alkyl \textit{t}-butyl), 1.45 (s, 18H, di-\textit{t}-butyl), 2.40 (s, 2H, methylene), 5.02 (s, 1H, phenol), 6.90 (s, 2H, aromatic).

18 – $^1$H NMR (CDCl\textsubscript{3}, 270 MHz) $\delta$ 0.72 (t, J = 7.4 Hz, 3H, methyl), 1.24 (s, 6H, dimethyl), 1.45 (s, 18H, di-\textit{t}-butyl), 1.65 (q, J = 7.5 Hz, 2H, methylene), 5.01 (s, 1H, phenol), 7.13 (s, 2H, aromatic).

6.5 Reactions of Cyclopropylcarbinyl Phenyl Sulfone.

6.5.1 Formation of Phenylsulfonylcyclopropylcarbinyl Lithium (23).

Cyclopropylcarbinyl phenyl sulfone was prepared according to the method of Chanon and Stirling (and references therein).\textsuperscript{101} The carbinyl anion, 23, was formed as the lithiate by addition of 1.0 M \textit{n}-BuLi [Aldrich, in hexanes, titrated prior to use] to a solution of the sulfone in THF at -78°C followed by warming to room temperature for 40 minutes. Formation of the appropriate anion was confirmed by a D\textsubscript{2}O [Aldrich, 99.9 atom % D] and $^2$H NMR (of the crude THF / hexanes solution) and $^1$H NMR of the isolated cyclopropyldeuteriocarbinyl phenyl sulfone in CDCl\textsubscript{3} which indicated greater than 90% deuteration, and zero ring opening or deuteration at any other position.

6.5.2 Reaction of 23 with 6.

To 12 mL of a 0.13 M solution of 23 (1.58 mmol) in THF (prepared as described above) and recooled to -78 °C was added a solution of 0.30 g (1.15 mmol) 6 in 6 mL THF. The reaction was kept under argon at all times and vigorous stirring proceeded
throughout the experiment. After one hour at –78 °C the reaction was allowed to warm to room temperature and stood stirring for 22 hours. The mixture was again cooled and the reaction was quenched by the addition of deionized water followed by 5% aqueous sulfuric acid. The mixture was extracted three times with ether and the combined organics were washed once with deionized water, dried over magnesium sulfate, and gravity filtered. In vacuo removal of solvent yielded a quantitative mass balance.

It was discovered that the addition products were not stable to either GC, GC-MS, or direct probe MS of any source, seriously limiting analysis. Repeated preparatory TLC and HPLC eventually afforded four fractions. The first was a small amount of recovered cyclopropylcarbinyl phenyl sulfone. The other three were derived from 6, and after isolation accounted for roughly a 92% mass balance. One fraction was a mixture of 14 and 15 (the result of hydrolyzed unreacted 6) found to account for 11% of the recovered products containing the 4-substituted-2,6-di-t-butyl moiety, identified by GC of the isolated fraction. Another fraction contained three non-addition products 11, 12, and 13 for a total of 12% of the reacted 6 recovered. Although not strictly quantitated relative to each other, GC and NMR indicate that 13 was the dominant component of this fraction. The final fraction contained a total of just over 76% of the recovered isolated products derived from 6. Analytical HPLC indicated two products in a roughly 80/20 mixture, but they were not separable by preparatory methods. NMR confirmed a completely intact cyclopropyl ring derived from 23, the typical 4-substituted-2,6-di-t-butyl moiety, and no vinylic signals that would have arisen from cyclopropylcarbinyl → homoallyl rearrangement of 23. The two non-rearranged addition isomers (27 and 28) were quantitated on the basis of the presence or absence of the benzylic methylene signal in the NMR, relative to the area of the phenol singlet (identical for both.) These results indicated that of this final mixture 17% had the benzylic methylene (28) and the rest did not (27). This was in good accord with the area ratio in the analytical HPLC. So 27 dominated the addition products, and of the 92% isolated mass balance the final results are reported as 63% 27, 13% 28, 11% unreacted 6 (as alcohols 14 and 15), and 12% non-addition products 11-13 (predominately 13). Error for this experiment is high as a result of the crude analysis techniques employed, and error bars are considered to be almost
20% of each reported figure. Nonetheless it is evident that 27 was the major product and SET was very minor for this reaction.

6.5.3 Reaction of 23 with 29.

“SpiroAnthrone” 29 was prepared according to reported methods\textsuperscript{102,103} by another group member and used as supplied in an identical procedure to that reported above for reaction of 23 with 6. Reaction times ranging from 20 minutes to 186 hours were employed, all with quantitative recovery (97-102% mass balance) of both 29 and cyclopropylcarbiny1 phenyl sulfone. Analytical HPLC indicated no other products, and the recovered peaks matched authentic materials perfectly. \textsuperscript{1}H NMR provided further confirmation of no reaction, even though deuterium oxide quench experiments showed that anion 23 was being formed in at least 90%.

6.6 5-Hexenyl Grignard Experiments.

6.6.1 Formation of Cyclopentylmethyl Magnesium Bromide.

Cyclopentylmethyl Bromide was prepared from cyclopentanemethanol [Aldrich, 98\%] in the following manner. To 15.4 g (58.7 mmol) triphenylphosphine [Aldrich, 99\%] was added a solution of 4.9 g (48.9 mmol) cyclopentanemethanol in 50 mL DMF with continuous stirring under argon until dissolution occurred. Elemental bromine [Acros] was added via addition funnel through a water condenser to the reaction vessel in a dropwise fashion until a deep orange color persisted (~3-4 mL Br\textsubscript{2}). The reaction vessel was then hooked to a crude vacuum distillation apparatus and all volatile materials (100 °C, 18 mmHg) were removed from the phosphorous containing compounds. The orange sludge left in the still pot was discarded. The distillate (collected in a liquid nitrogen bath) was allowed to come to room temperature, and 60 mL distilled water was added with stirring. The resulting biphasic mixture was extracted four times with ether. The combined organics were washed once with deionized water, twice with saturated aqueous CuSO\textsubscript{4} (to remove residual DMF), once more with deionized water, and once with brine, and were then dried over magnesium sulfate and filtered. Solvent was removed \textit{in vacuo} to afford 5.30 g slightly yellow clear oil which was vacuum distilled.
(35 °C, 9 mmHg) to give 4.64 (58%) perfectly clear colorless oil, found by GC versus an authentic sample to by 99.3% cyclopentylmethyl bromide (with 0.5% cyclopentane methanol and 0.2% DMF.)

The Grignard reagent was prepared immediately prior to use as follows. To 0.66 g (27 mmol) magnesium turnings stirring in 3 mL THF under argon was added 50 µL (0.58 mmol) 1,2-dibromoethane (ethylene dibromide, EDB) [Fisher] was added to cleanse the magnesium surface. To this was then slowly added a solution of 3.1 g (19 mmol) cyclopentylmethyl bromide in 5 mL THF, with continuous entraining with an additional 150 µL (1.7 mmol) EDB. After addition was complete, solution was diluted with an additional 10 mL THF and a final 50 µL (0.58 mmol) EDB was added. The mixture was allowed to stand stirring overnight for 16 more hours. In the morning the solution was transferred away from the remaining magnesium via syringe. The solution was titrated just prior to use, and the presence of the appropriate Grignard was confirmed by quenching a small aliquot and detecting methylcyclopentane only on the GC.

6.6.2 Reaction of 6 with Cyclopentylmethyl Magnesium Bromide.

To 0.80 g (3.1 mmol) 6 in 10 mL THF stirring under argon was added 22 mL of a 0.14 M solution of cyclopentylmethyl magnesium bromide in THF over a period of 40 min. Reaction mixture stood stirring for 92 hours, at which point the reaction was quenched by addition of 2% aqueous sulfuric acid. The biphasic mixture was extracted twice with ether and the combined organics were washed one with brine, dried (MgSO₄), and filtered. The solvents were removed in vacuo and the resulting thick brown oil was taken up in chloroform for GC analysis, which indicated small amounts of 11-15, as well as two higher mass peaks. The two higher mass peaks were isolated as a mixture from the remainder of the compounds by successive combinations preparatory TLC and Kugelrohr distillation, but the two peaks themselves were inseparable. The ¹H NMR presented in Figure 2 was obtained, along with the mass spectra presented in Figures 4 and 5 (for the major and minor isomers, respectively). These data provided sufficient evidence to declare the major isomer to be 37, and the minor isomer to be 35, present in just less than a 9:1 ratio.
6.6.3 Formation of 5-Hexenyl Magnesium Bromide.

5-Hexenyl magnesium bromide was formed directly from commercially available 6-bromo-1-hexene [Aldrich, 95%] in a manner directly analogous to that described above for cyclopentylmethyl magnesium bromide.

6.6.4 5-Hexenyl Grignard Quench Experiments.

Initial quench experiments were performed on all 5-hexenyl magnesium bromide formed by crudely syringing an aliquot of Grignard solution into a mixture of THF and methanol and adding a known amount of 2,3-dimethylbutane (DMB) [Aldrich, 97%] as an internal standard for GC quantitation of 1-hexene versus methylcyclopentane. Parallel quench experiments were run for each experimental run of 6 plus 5-hexenyl Grignard by adding the same amount of Grignard solution to the same amount of THF, but without the presence of 6, followed by the same reaction time, temperature, and workup procedures, and then again quantitating by GC. In all cases only 1-hexene and methylcyclopentane were observed. No cyclohexane was ever detected. It is also notable that parallel quench results always yielded extremely similar results to the initial quench experiments, and the percentage of methylcyclopentane produced varied per batch of Grignard from a low of near zero to a high of 10%.

6.6.5 Reaction of 6 with 5-Hexenyl Magnesium Bromide.

To 0.40 g (1.54 mmol) 6 stirring in 17 mL THF under argon was added 6.3 mL of a 0.247 M THF solution of 5-hexenyl magnesium bromide (1.56 mmol) over a period of 5 minutes. After 44 hours reaction was quenched by the addition of 5 mL deionized water followed by 6 mL 5% aqueous sulfuric acid. Then 0.05290 g (0.256 mmol) 2,6-di-t-butylphenol was added as an internal standard. The mixture was extracted twice with ether and washed once with deionized water. Solvent was removed in vacuo and the resulting brown oil was taken up in chloroform for GC analysis of products. The analysis and characterization of products and assignment of structures is given in detail in section 3.3.2 and is not repeated here. The structure and the methods used to confirm them are
indicated in the following yield information (reported as percentages of the 102% mass balance as found by GC):

34 – 4.6% (MS, reacts with Br₂).
35 – 4.3% (MS, ¹H NMR, does not react with Br₂, minor isomer of 6 plus cyclopentylmethyl magnesium bromide).
36 – 43.1% (MS, reacts with Br₂).
37 – 1.0% (MS, ¹H NMR, does not react with Br₂, major isomer of 6 plus cyclopentylmethyl magnesium bromide).
11 – 2.4% (independent synthesis and characterization reported above).
12 – 1.6% (commercially available).
13 – 22.0% (independent synthesis and characterization reported above).
14 – 14.6% (independent synthesis and characterization reported above).
15 – 6.4% (synthesized and characterized as an intermediate in synthesis of 6 as reported above)
Works Cited


8 For a review, see Holm, T. *Acta Chem. Scand., Ser. B* 1983, 37, 567. Extensive discussion and references for SET from Grignard reagents to carbonyls is presented in section 2.2.1 of this thesis.


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Vita

Jason George Gillmore was born July 10, 1975, the first of two children, to George and Ginny Gillmore in a rural western New Jersey town, where he lived the first eighteen years of his life, and where his family still resides. Always a bright and interested student, Jason had many diverse academic interests. However, upon his first exposure to chemistry in the tenth grade, at North Hunterdon High School in Annandale, NJ, Jason knew this was the subject he would devote his life to. He never wavered, and has ever since been narrowing his focus.

Jason began his undergraduate studies in chemistry at Virginia Polytechnic Institute and State University in the fall of 1993, accepting generous National Merit, university, and departmental scholarships. He was first introduced to organic chemistry by his future research advisor, Professor James Tanko, in his first semester at Virginia Tech. He found the physical side of the subject fascinating, but was also drawn to the artistic side of synthesis. After one summer away from chemistry Jason returned refreshed and determined not to miss out on another summer chemistry opportunity. To this end, Professor Tomas Hudlicky helped Jason secure a position doing a model study related to natural products synthesis over the next summer with Professor John Benbow at Lehigh University, provided Jason first carry out a semester of undergraduate research in the Hudlicky research group. Those two early synthetic experiences were of immense value.

For a change of pace, Jason chose to join the Tanko research group on a project in physical organic chemistry, albeit with a synthetic slant. The plan was to return to a strictly synthetic research group at another institution for a Ph.D. after completing a bachelor of science degree in honors (with the requisite thesis) in the Tanko group. This plan began to change when Jason discerned both financial and academic benefits to graduating a semester early with the lower “Commonwealth Scholar” honors degree (sans thesis) and then pursuing a thesis-based master of science degree with Professor Tanko for another three semesters, still planning on moving to a synthesis based Ph.D. at another institution after finishing. Jason completed his Bachelor of Science, *cum laude,*
with the “Commonwealth Scholar” distinction in December of 1996. This thesis will mark the completion of his Master of Science degree during the summer of 1998. During his final semesters as an undergraduate and throughout his career as a master's candidate, Jason truly enjoyed teaching a variety of lab and recitation sections in organic and general chemistry. Originally contemplating a financially rewarding industrial career after obtaining a doctoral degree, Jason is now seriously considering the intellectual freedom and the rewards of teaching offered by an academic career.

After all this time, the physical side of things has truly captivated Jason and he has been won over, perhaps to Tanko’s much beloved “Dark Side” of organic chemistry. The how and why of organic chemistry now intrigue him even more than the beauty of synthesis. As such, Jason has decided to continue doing physical organic chemistry and will turn down generous offers by Cornell and Princeton, among others, to accept the prestigious Sproull and Sherman Clarke fellowships at the University of Rochester. Braving heavy snow and perpetual gray skies, Jason will begin his Ph.D. there in August of 1998 with Professor Joseph Dinnocenzo on a materials-oriented photoinduced electron transfer / radical cation project with a focus on potential application in the area of holographic data storage.