J. Am. Chem. Soc. **2001,** *123,* 6527−6535

The Regioselectivity of Addition of Organolithium Reagents to Enones and Enals: The Role of HMPA

William H. Sikorski and Hans J. Reich*

Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received January 4, 2001

Abstract: The role of polar solvents (particularly HMPA) in controlling the ratio of 1,2 to 1,4 addition of sulfur-substituted organolithium reagents to cyclohexenones and hexenal was studied. Low-temperature, multinuclear NMR studies provided quantitative information about the ratio of contact (CIP) and solvent-separated (SIP) ion pairs in solutions of dithianyllithiums and phenylthiobenzyllithiums in THF−HMPA solutions. The ratio of contact and separated ion pairs was manipulated by changes in the strength of solvation (generally through the addition of HMPA). Although the results are consistent with the CIP/SIP distribution being an important factor in determining the regioselectivity of these additions (Curtin−Hammett limitations prevent a direct correlation), it cannot be the only one. Changes in diastereomeric product ratios upon addition of HMPA suggest that complexation of HMPA to lithium has two effects. First, it causes ion pair separation, which enhances 1,4 addition. Second, it lowers the Lewis acidity and catalytic effectiveness of the lithium cation, which also favors 1,4 addition. For most sulfur-stabilized lithium reagents, 2 equiv of HMPA suffice to achieve >95% 1,4 addition, whereas 4 equiv of DMPU are required to achieve identical regiochemical and stereochemical results.

Introduction

Hexamethylphosphoramide (HMPA) is a highly polar, aprotic solvent that has found extensive use as a solvent additive in organolithium chemistry. Its usefulness stems from its ability to coordinate to lithium very strongly—by one measurement approximately 300 times more strongly than tetrahydrofuran (THF).[1a] HMPA is frequently used to accelerate organolithium reactions, but far more intriguing are the instances where it has been used to alter the course of a chemical reaction. For example, it has been used to change the stereochemistry of enolate formation,[2a] alkylation,[2b] and protonation,[2c] as well as the regiochemistry of imine metalation,[3a] allyl anion alkylations,[3b] and additions to α,β-unsaturated carbonyl compounds (Figure 1).[1b,4,5] This last effect will be the topic of this paper.

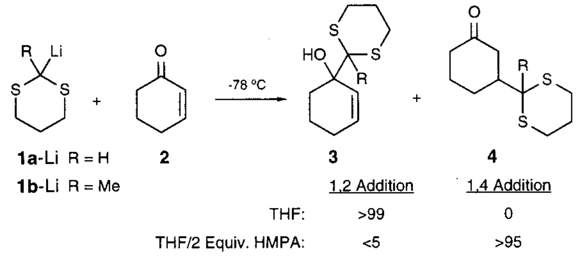


Figure 1. A demonstration of the effect of HMPA on the *kinetic* selectivity of enone addition.[5]

A mechanistic understanding of such results has been hampered by a lack of information about the solution structures of organolithium reagent/HMPA complexes, particularly the ion pair structure. Two distinctions will be made: contact ion pairs (CIP), in which there is a C−Li bond, and separated ion pairs (SIP), in which the carbanion and lithium counterion are separated by at least one layer of solvent molecules (yet remain intimately associated based on chemical shift[1c] and reactivity[6] effects). We have developed a low-temperature, multinuclear NMR technique for determining the nature of ion-pairing, aggregation, HMPA-solvation, and intramolecular chelation of organolithium reagents in solution.[1c]

Background

The addition chemistry to α,β-unsaturated carbonyl compounds can only be of practical synthetic utility if one of the two regioisomers is generated selectively. The synthetic importance of these reactions is reflected by the extensive efforts directed toward elucidating the effects that changes in solvent,

---

(1) (a) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273−274. (b) Preliminary communication: Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14−15. (c) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728−8741. (d) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869−5880. (e) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444−3445. (f) Reich, H. J.; Green, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729−8731. (g) Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835−1837. (h) Reich, H. J.; Sikorski, W. H.; Gudmundsson, B. Ö.; Dykstra, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4035−4036. (i) Sikorski, W. H.; Sanders, A. W.; Reich, H. J. *Magn. Reson. Chem.* **1998**, *36*, S118−S124. (j) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201−7210. (k) Reich, H. J.; Gudmundsson, B. Ö. *J. Am. Chem. Soc.* **1996**, *118*, 6074−6075. (l) Reich, H. J.; Dykstra, R. R. *Organometallics* **1994**, *13*, 4578.

(2) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. (b) Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579−1588. (c) Panek, E. J.; Rodgers, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 6921−6928.

(3) (a) Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081−2083. (b) Wolf, G.; Würthwein, E.-U. *Tetrahedron Lett.* **1988**, *29*, 3647−3650.

(4) Hunt, D. A. *Org. Prep. Proced. Int.* **1989**, *21*, 705−749.

(5) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100−101.

(6) (a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307−318. (b) Smid, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 112−127.(c) Smid, J. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, J., Ed.; Wiley: New York, 1972; Chapter 3.

10.1021/ja010053w CCC: $20.00

temperature, and steric bulk as well as main group and transition metal additives have on the regioselectivity of addition of organolithium reagents to enones and enals.[2,7−15]

The first demonstration that the 1,4:1,2 ratio could in some cases be controlled by proper choice of temperature or solvent appeared in 1977,[7] when it was found that the kinetic preference for 1,2 addition by metalated 2-phenyl-1,3-dithiane could be overcome by performing the reaction at higher temperatures and in more polar solvent, leading to the thermodynamically favored 1,4 product. A year later, for a reaction determined to be entirely under kinetic control, the opposite temperature dependence was observed: lower temperatures favored the 1,4 product and higher temperatures favored the 1,2 product.[8] No explanation was offered.

In 1977, Dolak and Bryson observed that isopropyl(phenylthio)methyllithium underwent 1,4 addition to cyclohexenone.[9] They attributed this unexpected regioselectivity to the presence of HMPA, which was needed to perform the difficult metalation of isobutyl phenyl sulfide. In a footnote they theorized that the HMPA "may be forming solvent separated ion pairs that allow the lithium ion to complex with oxygen while the sulfur bearing carbon adds to the terminus of the conjugated system."[9] Seyden-Penne and Krief subsequently showed that in the absence of HMPA this lithium reagent (generated by Li−Se exchange) gave exclusively 1,2 addition in THF, but confirmed that when 80:20 THF/HMPA was used, only 1,4 addition was observed.[10a] More importantly, they demonstrated that this was an HMPA-promoted *kinetic* 1,4 addition: when the HMPA was added subsequently to the addition reaction, no equilibration occurred. As little as 1 or 2 equiv of HMPA can have quite a dramatic effect on the kinetic regioselectivity, as exemplified in Figure 1 in which an essentially complete reversal of regioselectivity was observed by Brown and Yamaichi for the addition of 2-lithio-1,3-dithiane (**1a**-Li) and several substituted dithianes (including **1b**-Li) to cyclohexenone (Figure 1).[5]

In 1987, Cohen extended the separated ion pair hypothesis of Dolak and Bryson to explain temperature and solvent effects for the addition of bis(phenylthio)methyllithium to 2-cyclohexenone.[11] Lower temperatures and the addition of HMPA favored 1,4 addition, conditions also known to favor separated ion pairs.[6] Cohen rationalized that separated ion pairs react to give predominantly 1,4 addition, while contact ion pairs, which are favored at higher temperatures, undergo 1,2 addition via a four-centered transition state, since simultaneous formation of the O−Li bond is necessary to compensate for the rupture of the C−Li bond (the 1,4:1,2 product ratio was shown to be concentration independent, ruling out termolecular reactions which could provide a mechanism for the CIP to add 1,4). This hypothesis could not be directly tested since no information about the solution structures of organolithium reagent/HMPA complexes was available.

One plausible explanation for the propensity of SIP's to add 1,4 is that the higher HOMO of the SIP vs the CIP promotes a single electron transfer (SET) reaction, leading to conjugate addition. However, a mechanistic study using radical probes failed to demonstrate that trapable radicals were involved in the reactions of lithiodithianes.[13]

Other explanations have been proposed to account for the effect of HMPA in promoting 1,4 addition. Ab initio calculations indicate that the carbonyl coefficient of the enone LUMO is increased relative to that of the remote carbon when lithium coordinates to the carbonyl, and hence coordination should promote 1,2 addition. It is suggested, therefore, that HMPA coordination renders the lithium less electrophilic, making carbonyl activation insignificant and leading to more 1,4 addition.[12]

In the research that follows, we used our NMR technique to test Cohen's proposal.[11] We were looking for a correlation between the amount of CIP and SIP present in solution (which we are in a position to determine quantitatively) and the amount of 1,2 and 1,4 addition produced. We limited this study to stabilized organolithium reagents which are known or expected to be monomeric in THF, to simplify the analysis.

Results and Discussion

Solution Structure of Lithiodithianes. We began by investigating the synthetically useful lithiodithianes,[16] starting with the 2-methyl derivative **1b**-Li. By titrating small amounts of HMPA to a solution of the lithium reagent and studying the solution by NMR spectroscopy at −135 °C, we can detect the individual HMPA-solvated lithium species, determine the number of HMPA molecules coordinated to the lithium, and detect when the transition from a contact to a separated ion occurs. The method for making these assignments has been described elsewhere.[1d−g]

We have not experimentally addressed the aggregation states of the lithiodithianes, but previous work has shown that both **1a**-Li and **1b**-Li[17d] as well as the 2-*tert*-butyl analog[1d] in THF show C−Li coupling to only a single lithium in the ^{13}C NMR spectra, so the species either are monomeric or are dimerized by S−Li bridging, as found for the crystals of the **1b**-Li·TMEDA complex grown from hydrocarbon solvent.[17e] Cryoscopic measurements in THF confirm that **1a**-Li is monomeric in solution,[17a] and we presume that **1b**-Li is also monomeric, since higher levels of alkyl substitution at a carbanion center invariably lead to lower levels of aggregation. The HMPA titration technique[1c] can also detect aggregation, since dimers and higher aggregates usually show a more complex sequence of HMPA solvates in the $^{6/7}$Li and ^{31}P NMR spectra than do

---

(7) Ostrowski, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549−3552.

(8) Ogura, K.; Yamashita, M.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1978**, 1303−1306.

(9) Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961−1964.

(10) (a) Wartski, L.; El Bouz, M.; Seyden-Penne, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, 1543−1546. (b) Lucchetti, J.; Krief, A. *J. Organomet. Chem.* **1980**, *194*, C49−C52. (c) Krief, A. *Tetrahedron* **1980**, *36*, 2531−2640. (d) Dumont, W.; Lucchetti, J.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1983**, 66−68.

(11) Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923−7924.

(12) Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597−2605.

(13) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1984**, *49*, 935−939. Juaristi, E.; Gordillo, B.; Aparicio, D. M. *Tetrahedron Lett.* **1985**, *26*, 1927−1930.

(14) (a) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, *51*, 3983−3992. (b) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Org. Chem.* **1989**, *54*, 1960−1968. (c) Hirama, M. *Tetrahedron. Lett.* **1981**, *22*, 1905−1908. (d) Wilson, S. R.; Price, M. F. *Synth. Commun.* **1982**, *12*, 657−663. (e) Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, 2659−2662. (f) Loupy, A.; Lefour, J.-M.; Deschamps, B.; Seyden-Penne, J. *Nouv. J. Chim.* **1980**, *4*, 121−126. (g) Seebach, D.; Locher, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 957−958.

(15) (a) Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett* **1994**, 519−520. (b) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091−9092.

(16) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075−1077.

(17) (a) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972−1988. (b) Ahlbrecht, H.; Harbach, J.; Hoffman, R. W.; Ruhland, T. *Liebigs Ann.* **1995**, 211−216. (c) Ruhland, T.; Hoffman, R. W.; Shade, S.; Boche, G. *Chem. Ber.* **1995**, *128*, 551−556. (d) Seebach, D.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta* **1984**, *67*, 1083−1099. (e) Amstutz, R.; Seebach, D.; Seiler, P.; Schweizer, W. B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 53−54. (f) Zarges, W.; Marsch, M.; Harms, K.; Koch, W.; Frenking, G.; Boche, G. *Chem. Ber.* **1991**, *124*, 543−549. (g) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395−4399.

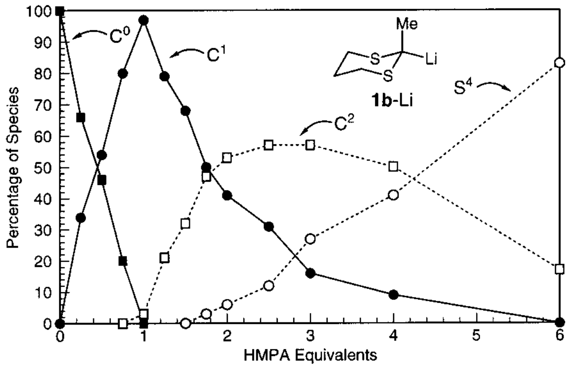


Figure 2. Graph of the percentage of each ion pair species as a function of HMPA for 0.16 M 2-methyl-1,3-dithianyllithium (**1b**-Li) in 3:2 THF/Et_2O at −135 °C.

monomers. Thus, mono and bis HMPA complexes of the dimers of PhLi,[1j] 2-(dimethylaminomethyl)phenyllithium,[1k] MeSLi,[1c] LiCl,[1c] $LiPPh_2$,[11] $LiNiPr_2$,[18a] and lithium bis(trimethylsilyl)amide[18b] have been observed, in addition to one or more monomer HMPA complexes. Studies of the effect of HMPA on the parent 2-lithio-1,3-dithiane **1a**-Li, as well as on the 2-silyl-, 2-phenyl-, and 2-*tert*-butyl-substituted lithiodithianes, revealed an effect of HMPA on ion pairing,[1d] but gave no indication of the presence of dimers.

The results from the NMR study are shown graphically in Figure 2, where the relative amounts of each of the species based on curve fitting of the ^7Li spectra[19] are plotted. In a notation that will be used throughout this paper, the various organolithium species will be designated as C^n or S^n, where C and S denote contact ion pair and solvent-separated ion pair, respectively, and the superscript indicates the number of HMPA molecules coordinated to the lithium. The addition of HMPA converts the C^0 species first to C^1, then to C^2, followed by a jump in coordination to the separated ion, S^4 (this is, in effect, a disproportionation of C^3 to a C^2 and an S^4). Only the first molecule of HMPA coordinates quantitatively; subsequent coordinations occur with increasing difficulty (i.e., C^2 maximizes at 2.75 equiv of HMPA), probably due to both steric and electronic effects. Free HMPA is detectable in the solution (by ^{31}P NMR) as early as 1.0 equiv of HMPA, which is characteristic for strongly contact ions (separated ions show no free HMPA until >3 equiv of HMPA). A very important result for the purposes of this study is that the separated ion, S^4, is not detectable until after 1.5 equiv of HMPA, and it does not become the dominant species until after 4.25 equiv of HMPA.

Regioselectivity of Lithiodithiane Additions. With this detailed knowledge of which species are present in solution, we looked for a correlation with the regiochemistry of additions of **1b**-Li to 2-cyclohexenone (**2**) and *trans*-2-hexenal (**5**).[10b] The reactions were performed in the same solvent and at comparable temperatures as the NMR studies. Refer to the Experimental Section for a description of how we addressed the technical problem of adding the electrophile to the lithium reagent at these very low temperatures while maintaining good temperature control and efficient mixing.

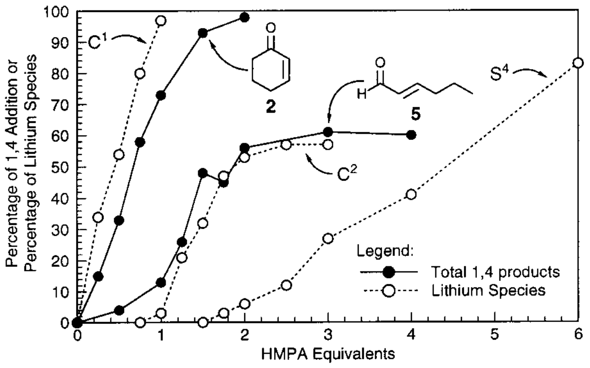
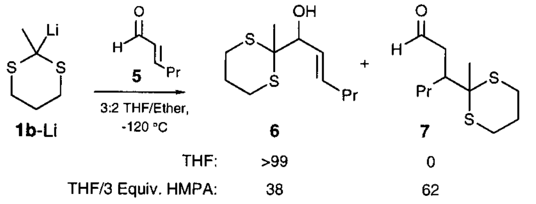


Figure 3. Graph of the percentage of each HMPA-containing ion pair species for **1b**-Li (dotted lines) overlaid with the percentage of 1,4 addition of 2-methyl-1,3-dithianyllithium (**1b**-Li) toward 2-cyclohexenone (**2**) and *trans*-2-hexenal (**5**) as functions of HMPA for 0.16 M **1b**-Li in 3:2 THF/Et_2O at −125 °C (solid lines).

The results of the reactivity studies of **1b**-Li with **2** (to give **3b** and **4b**) and **5** (to give **6** and **7**) are shown in Figure 3, overlaid with the growth of each HMPA-containing lithium species. The graph demonstrates that there is no direct correlation between the amount of separated ion S^4 and the amount of 1,4 addition produced in the reactions with either **2** or **5**.

Therefore, SIPs can only be responsible for the 1,4 product if two conditions are met: the SIPs are exceedingly more reactive than the CIPs, and the SIPs and CIPs are in rapid equilibrium. This is a manifestation of the Curtin−Hammett principle,[20] which states that if two reactive species interconvert more readily than they react, then the product ratio will not reflect the ground-state distribution (which is what is measured by the NMR experiment), but, rather, it will be a function of the energy difference between the product-forming transition states for the two reactive species. In other words, although the CIPs are the ground-state structures (the NMR results prove this), the product distribution could be dominated by more reactive SIPs in rapid equilibration with the CIPs, even though their equilibrium concentrations might be negligible.



Even before the fully HMPA-solvated S^4 species becomes detectable, SIPs with lower HMPA coordination numbers will exist in equilibrium with their CIP counterparts (Scheme 1). As the HMPA coordination number of the CIP increases, the equilibrium constant favoring the SIP increases (i.e., $K^0_{eq} < K^1_{eq} < K^2_{eq}$) and the rate at which the CIP equilibrates with its SIP probably also increases (i.e., $k_{S0} < k_{S1} < k_{S2}$). Thus the apparent correlation of the 1,4-addition product of cyclohexenone with the fraction of C^1 in Figure 2 could actually be a correlation with the undetected species S^1 in equilibrium with it, if $K^1_{eq} \cdot k^{S1}_{14} \gg k^{C1}_{12}$. Under this analysis, C^0 and S^1 are the principal 1,2- and 1,4-forming species, respectively, and the product distribution reflects the C^0/C^1 equilibrium.

Alternatively, the rate of formation of the SIP (k_{S0} and/or k_{S1}) could be rate determining for the 1,4 addition, since the ion pair separation is substantially endothermic when little or no HMPA is present. With no HMPA present, $k^{C0}_{12} > k_{S0}$ and the 1,2 product predominates, whereas when HMPA is present,

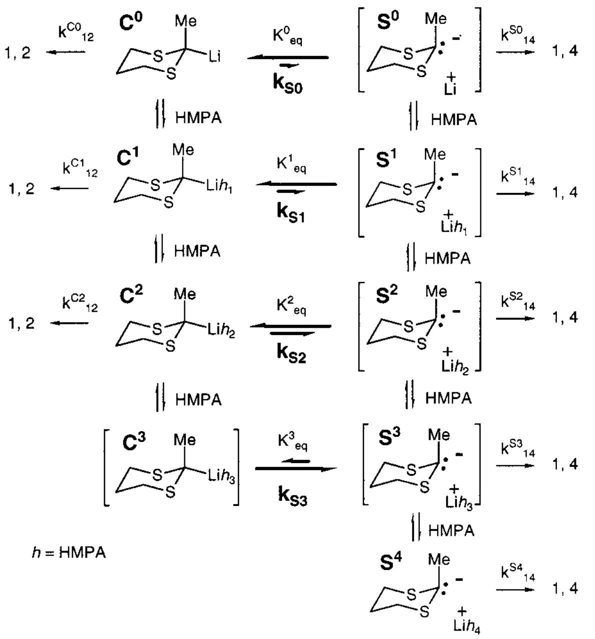
---

(18) (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751−5757. (b) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475−3483. (c) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 3546−3553.

(19) Reich, H. J. WinDNMR: Dynamic NMR Spectra for Windows. In *J. Chem. Educ.: Software, Ser. D* **1996**, *3D*, No. 2.

(20) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111−128.

Scheme 1. Expected Rates and Equilibria for **1b**-Li in THF/HMPA Solution



$k^{C1}_{12} < k_{S1}$ and the 1,4 product predominates. In this case one can make the prediction that by switching to a sufficiently reactive substrate, one could tip the balance in favor of k^{C1}_{12}, since k_{S1} is independent of substrate and k^{C1}_{12} would now be larger. We have tested this hypothesis with the enal **5**, expected to be 3 orders of magnitude more reactive than the enone.[21] In Figure 3, the growth of the 1,4 addition curve for the enal no longer follows C^1, but rather parallels the growth of the C^2 species remarkably well. This suggests that when C^2 is present, the enal is reacting with the S^2 that is in equilibrium with it (and whose concentration is always directly proportional to it). With less HMPA present, in the absence of C^2, the enal reacts with C^0 or C^1, i.e., the rates of conversion of these CIPs to their SIPs (k_{S0} and k_{S1}) are too slow to permit significant reaction between the enal and S^0 or S^1. Note that in this system, the SIP produces a 60:40 ratio of 1,4:1,2 addition rather than pure 1,4 addition.

The rates of all of the reactions discussed in this paper are too fast to measure by the techniques and analytical methods used (>90% complete in <1 min at −120 °C), so a more direct test of the proposed explanation is not possible. We therefore turned to stereochemical probes to provide further insight into the reactive intermediates involved.

Stereochemistry of Additions. We used the chiral enone 5-trimethylsilyl-2-cyclohexen-1-one (**8**)[22] with **1a** and the chiral lithium reagent phenylthio(3-methyl)benzyllithium (**9**-Li) in the hope that the CIPs and SIPs would exhibit unique signatures or fingerprints in the form of diastereomeric product ratios which would allow their participation in addition reactions to be tracked. We switched to the parent dithianyllithium **1a**-Li from the methyl homologue **1b**-Li used above because the bis(sulfur)-substituted carbon has an easily observable proton for NMR analysis of the diastereomeric product mixtures. The HMPA titration of **1a**-Li has been previously reported,[1d] and the profile is very comparable to that of **1b**-Li (Figure 2) and will not be reproduced here. To test the proposal that small amounts of SIPs in equilibrium with the ground-state CIPs were producing the 1,4 product, we also performed a series of experiments in which we substituted for THF the less polar analogue 2,5-dimethyltetrahydrofuran, in the hopes of disfavoring the SIPs. The results of the experiments in both solvent systems are shown in Figure 4.

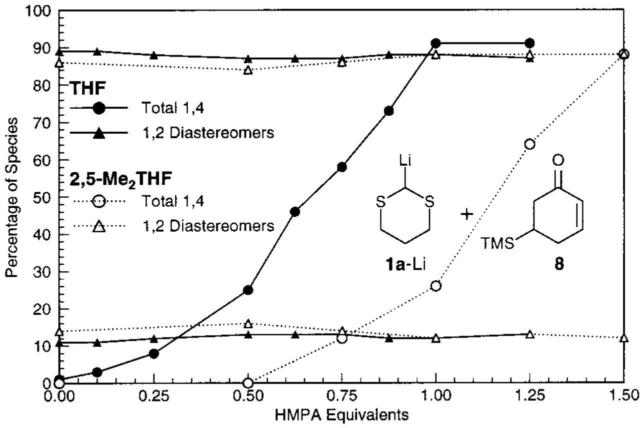
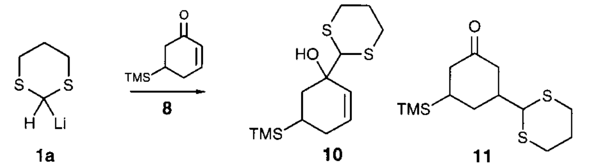
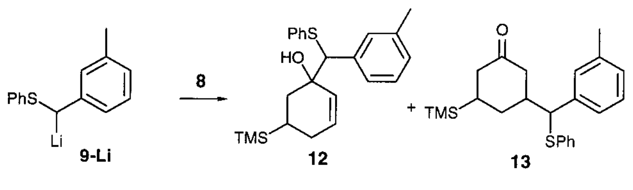


Figure 4. Graph of 1,4 addition and 1,2 diastereomer distribution as functions of HMPA for the reaction of 1,3-dithianyllithium (**1a**-Li) with 5-trimethylsilyl-2-cyclohexenone (**8**) at −120 °C in 3:2 THF/Et$_2$O and in 3:2 Me$_2$THF/Et$_2$O.



The diastereoselectivities for this system to form the adducts **10** and **11** were constant; however, they were too large[23] (and therefore had too little dynamic range available) to use them as evidence that a CIP was solely responsible for the 1,2 addition and a SIP was solely responsible for the 1,4 addition. For simplicity, only the 1,2 diastereomer distributions are shown (the selectivity was even greater for the 1,4 products **11**, more than 95:5 throughout in favor of the trans product of axial attack). The most significant aspect of this graph is the phase shift of the total 1,4 addition curves between the two solvent systems. The change in solvent polarity and donor strength is not likely to appreciably change the relative ratios of C^0, C^1, and C^2 over the range of 0 to 1.5 equiv of HMPA for this strongly contact ion, because they are formed essentially quantitatively at these HMPA levels even in THF. What the change in solvent is likely to do is affect the stabilization of any small amounts of separated ions that are in equilibrium with these contact ions, through primary and secondary solvent shells. Hence, the sharp rise in the total 1,4 addition occurs at a later point in the less polar solvent system.



We obtained our most dramatic stereochemical results using the chiral organolithium reagent phenylthio(3-methyl)benzyl-

---

(21) Pentanal is 2700 times as reactive as cyclohexanone toward pinacolone lithium enolate in THF ($\Delta\Delta G^{\ddagger}$ =3.1 kcal/mol): Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302−1312. Benzaldehyde is >3000 times more reactive than benzophenone toward methylmagnesium bromide: Holm, T. *J. Org. Chem.* **2000**, *65*, 1188−1192.

(22) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669−5672.

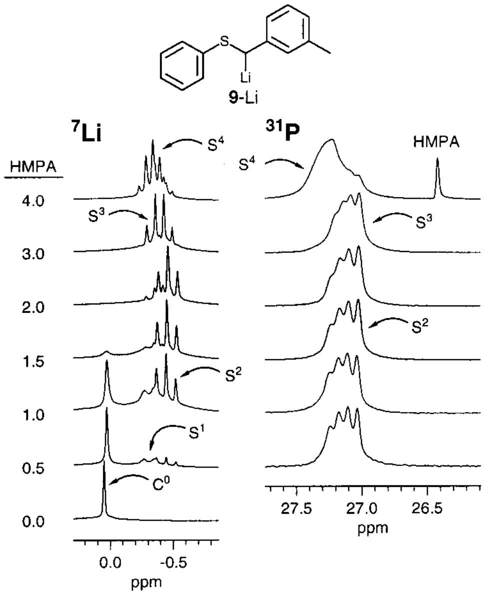


Figure 5. ^{7}Li and ^{31}P NMR spectra from an HMPA titration of 0.16 M phenylthio(3-methyl)benzyllithium (**9**-Li) in 3:2 THF/Et$_2$O at −129 °C.

lithium (**9**-Li). Benzyllithium itself is monomeric in THF,[17g] and α-phenylthiobenzyllithium crystallizes as a monomeric tris-solvate from THF.[17f] Other benzyllithium reagents such as 2-phenyl-1,3-dithiane, α-methylsulfonylbenzyllithium, and α-dimethylaminobenzyllithium are also monomeric in THF solution.[17b] We therefore assume that **9**-Li is monomeric.

Compound **9**-Li is unambiguously a contact ion in THF, but a very weak one. This is shown by the HMPA titration (Figure 5), in which the addition of HMPA converts C^0 directly to S^1. Consistent with this, a substantial fraction of 1,4 addition occurs even without the addition of HMPA. It was necessary to reduce solvent polarity to pure ether before 1,4 addition was fully suppressed.

Reactivity studies were performed in Et$_2$O with incremental amounts of THF added, and also in 3:2 THF/Et$_2$O (which corresponds to 90 equiv of THF) with incremental amounts of HMPA added. Reaction of **9**-Li with the chiral enone **8** produced four diastereomers of both the 1,2 and 1,4 products **12** and **13**. The diastereomer distribution of the 1,4 products will be considered first (Figure 6).

The most significant result from Figure 6 is that the 1,4 diastereomer ratio was essentially invariant as THF was added to an Et$_2$O solution, despite a change in the total amount of 1,4 addition from 0 to 65%. The constant diastereomer ratio is consistent with the 1,4 products being produced by the same species throughout. In the absence of THF, only 1,2 addition was observed, and we propose that a CIP (Mechanism A in Scheme 2) is the only reactive species. The addition of THF to the Et$_2$O solution increases the solvent strength enough to stabilize small amounts of SIP (S^0), which are solely responsible for the 1,4 product under THF/Et$_2$O conditions (Mechanism B). We have checked the effect of concentration of **9**-Li on the ratio of 1,2 to 1,4 addition. 1,4-Addition to 2-cyclohexenone is constant within experimental error over a 12-fold change in concentration (61% 1,4 product at 0.02 M, 60% at 0.08 M, 64% at 0.25 M), and the ratio of addition to **8** is constant over a 4-fold range of concentrations (41% 1,4 product at 0.02 M, 39% at 0.08 M), as also found previously for bis(phenylthio)methyllithium.[11] This rules out a difference in molecularity (i.e., from bimolecular to unimolecular in RLi) as the origin of the changes in the ratio of 1,2 and 1,4 additions which we have attributed to a switch from Mechanism A to Mechanism B.

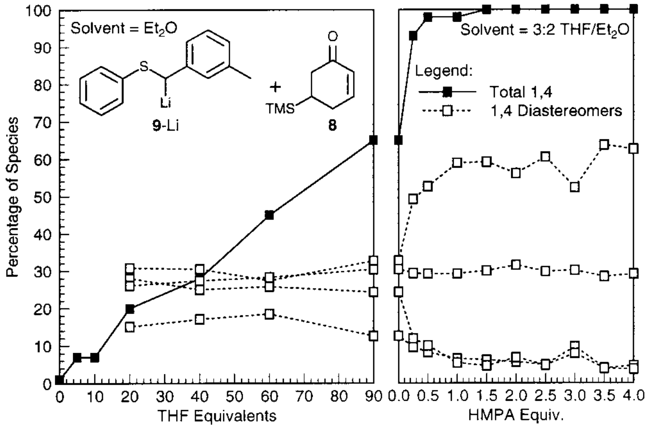
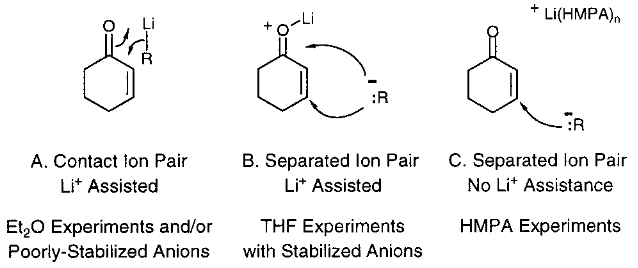


Figure 6. Graphs of total 1,4 addition and 1,4 diastereomer distribution as functions of THF in ether (left) and HMPA in 3:2 THF/ether (right) for the reaction of **9**-Li with **8** at −120 °C.

Scheme 2. Mechanistic Proposal



The addition of HMPA causes a dramatic change in the 1,4 diastereomer distribution as well as the total 1,4 addition. We propose that the change in diastereomer ratios signals the onset of an uncatalyzed pathway (Mechanism C, Scheme 2), which strongly favors 1,4 addition (this is consistent with calculations which predict that Lewis acid complexation of the carbonyl enhances 1,2 addition[12]). The diastereoselectivity reaches a limiting value at 1.0 equiv of HMPA, suggesting that with this system an HMPA-coordinated lithium is a catalytically inactive species. HMPA certainly does create more SIPs (this is clear from the NMR experiment), but the increase in diastereoselectivity from 30:28:26:16 to 59:30:5:6 is the result of a concomitant destruction of lithium catalysis, and it is the combination of these effects which accounts for the potent ability of HMPA to promote 1,4 addition.

An alternative explanation might be that the dramatic effect of HMPA is steric in nature, as for Yamamoto's bulky aluminum catalysts.[15] We disfavor this rationalization, since Yamamoto's catalysts are strongly electrophilic, whereas an HMPA-solvated lithium would be expected to be much less so. Further, the diastereoselectivity change is very sensitive to only the first equivalent of HMPA. If the effect were purely steric in nature, continued changes might be expected as additional HMPA was added. Yet, from 1 to 4 equiv of HMPA, the diastereoselectivity remains essentially constant.[24]

More evidence against the steric explanation comes from a study of the effect of alternative lithium-complexing agents such

---

(23) The high stereoselectivity in this system is surprising, since the addition of **1a**-Li to 4-*tert*-butylcyclohexanone gives a 60/40 ratio of axial to equatorial attack: Juaristi, E.; Cruz-Sánchez, J. S.; Ramos-Morales, F. R. *J. Org. Chem.* **1984**, *49*, 4912−4917.

(24) With large excesses of HMPA, the results become less reproducible and there is a greater scattering of data. Apparently, in this highly polar medium the reaction becomes sensitive to other, unknown variables which are not being properly controlled in these experiments.

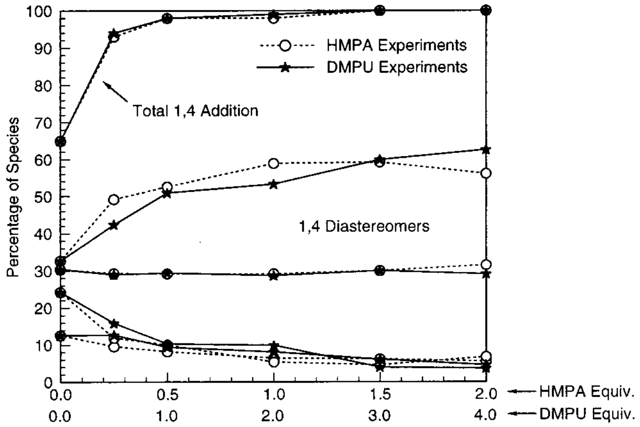


Figure 7. Graph of 1,4 addition and 1,4 diastereomer distribution as functions of HMPA and DMPU for the reaction of **9**-Li with **8** at −120 °C. Twice as much DMPU relative to HMPA is necessary for the curves to overlap.

as *N*,*N*′-dimethylpropylene urea (DMPU), which has been proposed as an alternative to the carcinogenic HMPA,[25] and [2.1.1]cryptand.[26] When the series of experiments was repeated using the sterically different DMPU, the same limiting diastereomer ratio was reached (Figure 7). Note, however, that twice as much DMPU relative to HMPA is needed[27] to reach both the same 1,4:1,2 ratio and the same diastereomer distribution. This suggests an electronic rather than a steric effect.

Finally, essentially the same limiting diastereomer ratio was observed with 1 equiv of [2.1.1]cryptand (53/11/5/31) as was found for 1 equiv of HMPA (59/7/5/29) or 2 equiv of DMPU (53/8/10/29). The barrier to intermolecular exchange of lithium cations complexed to [2.1.1]cryptand has been measured in several solvents, $\Delta G^{\ddagger} > 19$ kcal/mol.[28] The reaction of **9**-Li with cyclohexenone has $\Delta G^{\ddagger} < 9.7$ kcal/mol, so in the presence of excess cryptand participation by free lithium is not possible because lithium cannot escape at a fast enough rate (i.e., the Curtin−Hammett principle does not apply here). However, a cryptand-encapsulated lithium could conceivably still act as a catalyst.[18c,29]

Figure 8 shows the results for the 1,2 diastereomers. Only the Et_2O/THF experiments are shown because 1,2 addition became negligible as soon as the first 0.25 equiv of HMPA was added.

There was a noticeable change with two of the diastereomers upon adding 5 equiv of THF to the Et_2O solution. This jump is reproducible and very likely represents a change in the nature of the C^0 species that is generating the 1,2 product (from one that is Et_2O solvated to one that is THF solvated). With further addition of THF, there was a mild drift in the diastereomer ratio. This can be interpreted as a direct effect of the change in bulk solvent polarity, or as an indirect effect resulting from the stabilization of a small amount of an S^0 species in equilibrium with C^0, which is also capable of some 1,2 addition, but through Mechanism B (Scheme 2), hence producing a different diastereomer ratio. In this interpretation the 1,2 diastereomer distribution at 5 equiv of THF represents the diastereoselectivity of the THF-solvated C^0 (operating through Mechanism A). That at 90 equiv of THF represents a significant influence of S^0 in producing the 1,2 product (through Mechanism B).

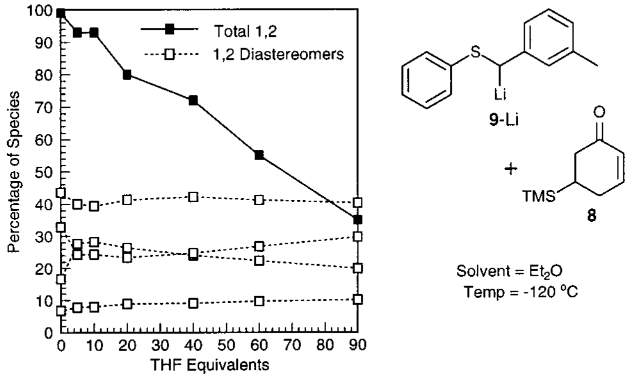


Figure 8. Graph of total 1,2 addition and 1,2 diastereomer distribution as functions of THF for the reaction of phenylthio(3-methyl)benzyllithium (**9**-Li) with 5-trimethylsilyl-2-cyclohexen-1-one (**8**) in Et_2O at −120 °C.

Summary

Curtin−Hammett limitations precluded us from proving a correlation between the ratio of CIP and SIP and the amount of 1,2 and 1,4 addition. Unless a system can be found where the lithium reagent reacts more readily than its CIPs and SIPs interconvert, such a correlation will not be possible. However, the large amount of circumstantial evidence that we have collected indicates that the type of ion pair is an important factor, but it cannot be the only one. In addition to inducing CIP to SIP transitions, we believe that HMPA also affects the 1,4:1,2 ratio by decreasing or preventing lithium catalysis. We propose that the absence of Li catalysis is an important factor in achieving clean 1,4 addition. For well-stabilized anions in the absence of HMPA, when lithium catalysis is possible and SIPs are energetically accessible reactive intermediates, mixtures of 1,2 and 1,4 addition are observed.

Many stabilized lithium reagents can be induced to cleanly add either 1,4 or 1,2 to enones. The addition of HMPA or DMPU favors 1,4 addition (there is rarely an advantage to the use of more than 2 equiv of HMPA or 4 equiv of DMPU). Conversely, the use of Et_2O as a solvent leads in most cases to clean 1,2 addition (although with strongly contact ions such as dithianyllithium, exclusive 1,2 addition is achieved even in THF).

Experimental Section

General. Tetrahydrofuran (THF) and Et_2O were freshly distilled from sodium benzophenone ketyl before use. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 at reduced pressure and stored under N_2 over molecular sieves. Glassware was placed overnight in a 110 °C oven or flame-dried before purging with N_2 to remove moisture. Common lithium reagents were titrated using *n*-propanol in THF with 1,10-phenanthroline as an indicator.[30] Temperatures of −78 °C were achieved with a dry ice/acetone bath and −120 °C with an $N_{2(l)}$/pentane bath. Melting and boiling points are not corrected.

---

(25) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385−391.

(26) (a) Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron Lett.* **1969**, *34*, 2885−2888. (b) Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron Lett.* **1969**, *34*, 2889−2892. (c) Lehn, J. M. *Pure Appl. Chem.* **1980**, *52*, 2303−2319.

(27) This is consistent with other studies on DMPU,[25] and with several NMR studies that we have performed which show that twice as much DMPU is needed to reach the same SIP/CIP ratio in solution.

(28) Cahen, Y. M.; Dye, J. L.; Popov, A. I. *J. Phys. Chem.* **1975**, *79*, 1292−1295. Shamsipur, M.; Popov, A. I. *J. Phys. Chem.* **1986**, *90*, 5997−5999.

(29) For the X-ray crystal structure of a [2.1.1]cryptand complex of $EtMg^+$ see: Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 432−435.

(30) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

Commercially available starting materials and reagents (Aldrich Chemical Co.) include the following: α-chloro-*m*-xylene, 2-cyclohexenone (**2**), 1,3-dithiane (**1a**-H), hexamethylphosphoramide (HMPA), 2-methyl-1,3-dithiane (**1b**-H), thiophenol, *trans*-2-hexenal (**5**), and triethylamine.

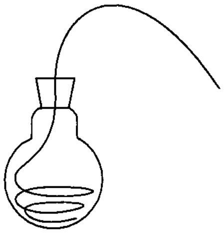
Syntheses: 5-Trimethylsilyl-2-cyclohexen-1-one (**8**). This compound was synthesized according to a literature procedure[22] and purified by distillation (60−63 °C at 1 mmHg [lit.[22] 65.5−67 °C at 2.0 mmHg]). Density: 0.9020 g/mL. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.22 (CH_3, s, 9H), 1.18 (H_5, dddd, $^3J_{5-6a} = 14.9$ Hz, $^3J_{5-4a} = 11.6$ Hz, $^3J_{5-4e} = 4.8$ Hz, $^3J_{5-6e} = 3.9$ Hz), 1.94 (H_{4a}, ddt, $^2J_{4a-4e} = 18.9$ Hz, $^3J_{4a-5} = 11.4$ Hz, $^3J_{4a-3} = {}^4J_{4a-2} = 2.6$ Hz), 1.96 (H_{6a}, dd, $^2J_{6a-6e} = 16.6$ Hz, $^3J_{6a-5} = 14.5$ Hz), 2.08 (H_{4e}, dtt, $^2J_{4e-4a} = 19.1$ Hz, $^3J_{4e-3e} = {}^3J_{4e-5} = 5.2$ Hz, $^4J_{4e-2} = {}^4J_{4e-6e} = 1.3$ Hz), 2.17 (H_{6e}, ddt, $^2J_{6e-6a} = 16.4$ Hz, $^3J_{6e-5} = 3.9$ Hz, $^4J_{6e-2} = {}^4J_{6e-4e} = 1.1$ Hz), 5.74 (H_2, ddt, $^3J_{2-3} = 9.8$ Hz, $^4J_{2-4a} = 2.7$ Hz, $^4J_{2-4e} = {}^4J_{2-6e} = 1.1$ Hz), 6.79 (H_3, $^3J_{3-2} = 10.1$ Hz, $^3J_{3-4e} = 5.5$ Hz, $^3J_{3-4a} = 2.6$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ −3.91 (CH_3), 22.98 (CH), 26.61 (CH_2), 38.45 (CH_2), 129.23 (CH), 151.20 (CH), 199.81 (C).

3-Methylbenzyl Phenyl Sulfide (9-H**).** To a 250 mL round-bottom flask with a stir bar were added 125 mL of MeCN, 5.32 g (37.8 mmol) of α-chloro-*m*-xylene, and 4.18 g (38.0 mmol) of PhSH. With vigorous stirring, 3.85 g (38 mmol) of Et_3N was added dropwise. The solid Et_3N•HCl was filtered using a fritted glass funnel, and the solid was rinsed with an additional 50 mL of MeCN. The solution was concentrated by rotary evaporation, taken up in 100 mL of 1:1 Et_2O/hexane, and washed with 2 × 50 mL of 10% NaOH, 50 mL of H_2O, and 50 mL of brine. The solution was dried over anhydrous $MgSO_4$, the solvents were removed by rotary evaporation, and the product was distilled (109−110 °C at 0.02 mmHg), yielding 5.19 g (24.2 mmol, 64.1%) of a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (CH_3, s), 4.06 (CH_2, s), 7.00−7.33 (Ar, m, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.29 (CH_3), 38.88 (CH_2), 125.80 (CH), 126.16 (CH), 127.90 (CH), 128.31 (CH), 128.75 (CH), 129.52 (CH), 129.56 (CH), 136.57 (C), 137.18 (C), 138.07 (C). Mass Spec: M^+ 214.0819 (calcd for $C_{14}H_{14}S$, 214.0816).

Trapping Studies. All of the enone trapping studies were performed using the same general procedure, which is written out in detail for the reaction between 2-methyl-1,3-dithianyllithium (**1b**-Li) and 2-cyclohexenone (**2**). Because of the potential problem that the product alkoxides and enolates, which are good electron pair donors, could displace HMPA from lithium, thereby changing the ratio of HMPA to unreacted lithium reagent at latter stages in the reaction, generally 0.5 equiv of the electrophile was added and the remaining lithium reagent was quenched with a propionic acid/Et_2O solution, which does not freeze under the reaction conditions.

2-Methyl-1,3-dithianyllithium (1b-Li) and 2-cyclohexenone (2): HMPA dependence in 3:2 THF/Et_2O at −120 °C. A stock solution of **1b**-Li was prepared by dissolving 0.24 mL (0.27 g, 2.0 mmol) of **1b**-H in 18.6 mL of THF and 12.4 mL of Et_2O, cooling to −78 °C, adding 0.95 mL (2.02 mmol) of 2.13 M *n*-BuLi in pentane, and storing overnight at −20 °C (the resulting solution, 0.0626 M in **1b**-Li, is good for at least 1 week at −20 °C).

A 10 mL round-bottom flask was prepared in advance with one end of a cannula coiled inside. The flask (with cannula and stir bar) was dried overnight in an oven. The external end of the cannula was poked through the bottom of a septum, and the septum was passed along it into position. An N_2 inlet needle was introduced into the flask, purging the flask and the cannula. When purging was complete, the free end of the cannula was plugged by imbedding it into a thick piece of septum.



A syringe was used to transfer 4.0 mL (0.25 mmol) of the **1b**-Li stock solution to the flask containing the cannula, the necessary amount of HMPA (1 equiv = 43.5 μL) was added, and the flask was cooled to −78 °C under positive N_2 pressure.

A dried, N_2-purged, 5 mL conical flask fitted with a septum was charged with 0.6 mL of THF, 0.4 mL of Et_2O, and 12.0 μL (11.9 mg, 0.124 mmol) of **2**, and both flasks were cooled under positive N_2 pressure to −120 °C using an $N_{2(l)}$/pentane slurry. A N_2 inlet needle was introduced into the conical flask containing **2** and turned on momentarily to build up pressure. The septum plug was removed from the exposed end of the cannula, and the cannula was immediately inserted into the conical flask, with the N_2 pressure inside being dissipated through the cannula, purging it of any liquids and preventing a back flow. The N_2 gas through the inlet needle was again turned on, and the end of the cannula was submerged in the liquid of the conical flask, transferring the solution to the lithium reagent over the course of approximately 5 s (occasionally an experiment had to be abandoned due to a plugged cannula).

After 1 min at this temperature, 3 mL (0.8 mmol) of 0.27 M propionic acid in Et_2O (1:49 v/v) were added via syringe to quench the unreacted lithium reagent. The solution was allowed to warm to room temperature, the contents were transferred to a separatory funnel, and 20 mL of 1:1 Et_2O/hexane were added. The solution was washed with 3 × 20 mL of H_2O, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation.

The ratios of products were determined using the following ^{1}H NMR signals with C_6D_6 as the solvent (300 MHz spectrometer): starting material, δ 3.81 (CH, q, $J = 7.0$ Hz, 1H); 1,2 product (**3b**), δ 6.32 (=CH, dq, $J = 10.3$, 1.8 Hz, 1H); and 1,4 product (**4b**), δ 2.96 (CH, dq, $J = 12.9$, 2.5 Hz, 1H). Although, in general, a relaxation delay was not used during the NMR acquisitions, occasionally the reliability of the integrations was checked by introducing delays of up to 20 s, which, without exception, had absolutely no effect on either the ratio of the two products or their ratios to the returned starting material.

The samples from experiments which strongly favored one or the other isomer were pooled together, and the major component was isolated by preparative TLC for characterization.

1-[2-(2-Methyl-1,3-dithianyl)]-2-cyclohexen-1-ol (3b: 1,2 product of 1b-Li and 2). R_f (20% EtOAc/hexane): 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70−2.10 (m, 8H), 1.77 (CH_3, s, 3H), 2.28 (OH, S, 1H), 2.88−2.98 (m, 4H), 5.97−6.05 (=CH, m, 1H), 6.10−6.17 (=CH, m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.83 (CH_2), 24.31 (CH_3), 25.00 (CH_2), 25.13 (CH_2), 26.69 (CH_2), 26.82 (CH_2), 31.01 (CH_2), 59.44 (S_2C), 75.62 (COH), 128.35 (=CH), 132.84 (=CH). IR (neat): 3466 cm^{-1} (OH). MS: M^+ 230.0793 (calcd for $C_{11}H_{18}OS_2$, 230.07991).

3-[2-(2-Methyl-1,3-dithianyl)]cyclohexanone (4b: 1,4 product of 1b-Li and 2). R_f (20% EtOAc/hexane): 0.41. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50−1.70 (m, 2H), 1.62 (OH, s, 1H), 1.90−2.03 (m, 2H), 2.10−2.45 (m, 6H), 2.77−2.90 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.40 (CH_3), 24.84 (CH_2), 25.06 (CH_2), 26.07 (CH_2), 26.21 (CH_2), 26.29 (CH_2), 41.09 (CH_2), 43.08 (CH_2), 46.27 (CH), 52.50 (S_2C), 211.34 (C=O). IR (neat): 1708 cm^{-1} (C=O). MS: M^+ 230.0804 (calcd for $C_{11}H_{18}OS_2$, 230.07991).

2-Methyl-1,3-dithianyllithium (1b-Li) and *trans*-2-hexenal (5): HMPA dependence in 3:2 THF/Et_2O at −120 °C. The general procedure was used with the following changes. A stock solution of **1b**-Li was prepared by dissolving 0.24 mL (0.27 g, 2.0 mmol) of **1b**-H in 23.25 mL of THF and 15.50 mL of Et_2O, cooling to −78 °C, adding 1.0 mL (2.0 mmol) of 2.0 M *n*-BuLi in pentane, and storing overnight at −20 °C (the resulting solution, 0.052 M in **1b**-Li, is stable at least 1 week at −20 °C). A syringe was used to transfer 4.0 mL (0.21 mmol) of **1**b-Li to the flask containing the cannula. A stock solution of **5** was also prepared, with 0.23 mL (0.20 g, 2.0 mmol) of **5** in 5.86 mL of THF and 3.91 mL of Et_2O (the resulting solution is 0.20 M in **5**). A syringe was used to transfer 1 mL (0.2 mmol) of **5** to the conical flask. For these experiments, 1 equiv of HMPA = 34.8 μL. Product ratios were determined using the following ^{1}H NMR signals in $CDCl_3$: starting material, δ 4.13 (S−CH−S, q, $J = 7.0$ Hz, 1H); 1,2 product (**6b**), δ 4.47 (O−CH, dm, $J = 6.2$ Hz, 1H); and 1,4 product (**7b**), δ 9.86 (CHO, t, $J = 2.6$ Hz, 1H).

1-[2-(2-Methyl-1,3-dithianyl)]-2-hexen-1-ol (6b: 1,2 product of 1b-Li and 5). R_f (20% EtOAc/hexane): 0.41. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.91 (CH$_3$, t, J = 7.4 Hz, 3H), 1.39 (H,^{6} s, 3H), 1.44 (H,^{5} qt, J = 7.3, 7.3 Hz, 2H), 1.80−1.96 (m, 1H), 2.02−2.15 (m, 3H), 2.65 (SCH$_{eq}$, dm, J = 14.2 Hz, 2H), 2.80 (OH, br s, 1H), 3.03 (SCH$_{ax}$, dddd, J = 14.3, 11.2, 6.1, 2.9 Hz, 2H), 4.47 (OCH, br d, J = 6.1 Hz, 1H), 5.64 (CH^2═, ddt, J = 15.3, 6.1, 1.5 Hz, 1H), 5.85 (═CH^3, dtd, J = 15.4, 6.8, 1.1 Hz). ^{13}C NMR (75.4 MHz, CDCl$_3$): δ 13.65 (CH$_3$), 22.17 (CH$_2$), 22.26 (CH$_3$), 24.32 (CH$_2$), 25.75 (CH$_2$), 26.12 (CH$_2$), 34.47 (CH$_2$), 53.29 (S$_2$C), 72.72 (COH), 125.67 (C^{2}H═), 134.91 (═C^{3}H). IR (neat): 3466 cm^{-1} (OH). MS: M$^+$ 232.0963 (calcd for C$_{11}$H$_{20}$OS$_2$, 232.0956).

3-[2-(2-Methyl-1,3-dithianyl)]hexanal (7b: 1,4 product of 1b-Li and 5). R_f (20% EtOAc/hexane): 0.56. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.94 (CH$_3$, t, J = 7.2 Hz, 3H), 1.05−1.50 (m, 3H), 1.42 (CH$_3$, s, 3H), 1.80−2.10 (m, 3H), 2.29 (ddd, J = 17.1, 4.6, 1.3 Hz, 1H), 2.57 (dddd, J = 14.3, 5.9, 3.3, 0.7 Hz, 1H), 2.68 (dddd, J = 14.5, 6.1, 3.3, 0.7 Hz, 1H), 2.75−2.85 (m, 2H), 2.90−3.00 (m, 2H), 9.86 (CHO, t, J = 1.3 Hz). ^{13}C NMR (75.4 MHz, CDCl$_3$): δ 14.12 (CH$_3$), 21.82 (CH$_2$), 23.54 (CH$_3$), 24.55 (CH$_2$), 26.18 (CH$_2$), 26.34 (CH$_2$), 33.31 (CH$_2$), 39.65 (CH), 45.42 (CH$_2$), 52.99 (C), 200.12 (C═O). IR (neat): 1719 cm^{-1} (C═O).

1,3-Dithianyllithium (1a-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): Effect of HMPA in 3:2 THF/Et$_2$O at −120 °C. The general procedure was used with the following changes: the lithium reagents was made fresh for each experiment, directly in the flask containing the cannula at −78 °C, using 1.8 mL of THF, 1.2 mL of Et$_2$O, 60.2 mg (0.5 mmol) of **1a**-H, 0.26 mL (0.52 mmol) of 2.02 M *n*-BuLi in pentane, and warming to −20 °C for 2 h. For these experiments, 1 equiv of HMPA = 87.0 μL. The lithium reagent was trapped with a solution of 46.6 μL (42.0 mg, 0.25 mmol) of **8**. Product ratios were determined using the following ^{1}H NMR signals in C$_6$D$_6$: starting material, δ 3.35 (s, 2H); 1,2 diastereomers (**10**), δ 4.13 (s, 1H), 4.25 (s, 1H); 1,4 diastereomers (**11**), δ 3.73 (d, J = 4.5 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H).

1-[2-(1,3-Dithianyl)]-5-trimethylsilyl-2-cyclohexen-1-ol (10: 1,2 product of 1a-Li and 8, major diastereomer). R_f (20% EtOAc/hexane): 0.31. ^{1}H NMR (300 MHz, CDCl$_3$): δ −0.03 (SiCH$_3$, s, 9H), 0.99 (SiCH, s, 1H), 1.34 (dd, J = 14.3, 13.2 Hz, 1H), 1.76−1.93 (m, 2H), 1.94−2.10 (m, 2H), 2.32 (OH, broad s, 1H), 2.37 (dm, J = 13.2 Hz, 1H), 2.76−2.96 (m, 4H), 4.37 (S$_2$CH, s, 1H), 5.80 (CH═, dm, J = 9.9 Hz, 1H), 5.86 (CH═, ddd, J = 10.1, 3.9, 2.2 Hz, 1H). ^{13}C NMR (75.4 MHz, CDCl$_3$): δ 3.87 (SiCH$_3$), 18.91 (SiCH), 25.55 (CH$_2$), 25.69 (CH$_2$), 30.13 (CH$_2$), 30.33 (CH$_2$), 34.42 (CH$_2$), 57.93 (S$_2$CH), 73.12 (COH), 130.63 (CH═), 131.27 (CH═). IR (neat): 3448 cm^{-1} (OH). MS: M$^+$ 288.1031 (calcd for C$_{13}$H$_{24}$OS$_2$Si, 288.1038).

***trans*-3-[2-(1,3-Dithianyl)]-5-trimethylsilylcyclohexanone (11: 1,4 product of 1a-Li and 8).** R_f (20% EtOAc/hexane): 0.33. ^{1}H NMR (500 MHz, CDCl$_3$): δ 0.00 (SiCH$_3$, s, 9H), 1.29 (tt, J = 11.2, 4.4 Hz, H$_{5a}$), 1.77 (ddd, J = 13.9, 10.9, 4.7 Hz, H$_{4a}$), 1.85 (dtt, J = 14, 9.6, 4.9 Hz, H$_{4'}$), 2.10 (m, H$_{4e}$, H$_{4'}$), 2.17 (ddd, J = 14.4, 11.2, 0.9 Hz, H$_{6a}$), 2.34 (ddt, J = 14.4, 4.9, 1.5 Hz, H$_{6e}$), 2.42 (d p, J = 8.6, 5.3 Hz, H$_{3e}$), 2.49 (dd, J = 14.2, 5.3 Hz, H$_{2a}$), 2.74 (ddt, J = 14.2, 5.9, 1.5 Hz, H$_{2e}$), 2.80−2.88 (m, 4H, SCH$_2$), 3.97 (d, J = 8.6 Hz, S$_2$CH). The minor cis diastereomer had a signal at δ 4.09 (S$_2$CH, d, J = 4.6 Hz). The trans stereochemistry for the major isomer was assigned on the basis of the large H$_{6a}$−H$_{5a}$ trans-diaxial coupling of 11.2 Hz (5-SiMe$_3$ group equatorial), vs the smaller H$_{2a}$−H$_{3e}$ coupling of 5.3 Hz (3-dithianyl group axial). Assignments were confirmed by a COSY spectrum. ^{13}C NMR (75.4 MHz, CDCl$_3$): δ −3.42 (SiCH$_3$), 21.46 (SiCH), 25.83 (CH$_2$), 27.77 (CH$_2$), 30.42 (CH$_2$), 30.46 (CH$_2$), 41.52 (CH), 41.61 (CH$_2$), 43.83 (CH$_2$), 50.83 (S$_2$CH), 211.62 (C═O). IR (neat): 1709 cm^{-1} (C═O). MS: M$^+$ 288.1045 (calcd for C$_{13}$H$_{24}$OS$_2$Si, 288.1038).

1,3-Dithianyllithium (1a-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): HMPA dependence in 3:2 dimethyl-THF/Et$_2$O at −120 °C. The preceding experiment was repeated, substituting 2,5-dimethyltetrahydrofuran for THF in both the lithium reagent and the enone solutions.

Phenylthio(3-methyl)benzyllithium (9-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): HMPA dependence in 3:2 THF/Et$_2$O at −120 °C. The general procedure was used with the following changes: the lithium reagent was made fresh for each experiment, directly in the flask containing the cannula at −78 °C, because the metalation is instantaneous, using 1.8 mL of THF, 1.2 mL of Et$_2$O, 49.0 μL (52.7 mg, 0.25 mmol) of **9**-H, and 0.125 mL (0.25 mmol) of 2.0 M *n*-BuLi in pentane. For these experiments, 1 equiv of HMPA = 43.5 μL. The lithium reagent was trapped with 46.6 μL (42.0 mg, 0.25 mmol) of **8**. Different NMR solvents had to be used to determine the diastereomer ratios of the 1,2 and 1,4 products, due to coincident signals. The 1,4 product ratios were determined using ^{1}H NMR signals in CDCl$_3$: starting material δ 4.04 (s, 2H); 1,4 diastereomers (**13**), δ 3.85 (d, J = 10.3 Hz, 1H), 3.95 (d, J = 10.7 Hz, 1H), 4.00 (d, J = 7.0 Hz, 1H), 4.09 (d, J = 5.9 Hz, 1H); 1,2 diastereomers (**12**), δ 4.17 (two coincident signals), 4.25, 4.39. The 1,2 product ratios were determined using ^{1}H NMR signals in C$_6$D$_6$: starting material, δ 3.82 (s, 2H); 1,2 diastereomers (**12**), δ 4.21 (s, 1H), 4.29 (s, 1H), 4.38 (s, 1H), 4.44 (s, 1H); 1,4 diastereomers (**13**), δ 3.87 (d, J = 10.9 Hz), 3.90 (two coincident signals, d, J = 6.6 Hz), 4.10 (d, J = 10.5 Hz).

1-[Phenylthio(3-methyl)benzyl]-5-(trimethylsilyl)-2-cyclohexen-1-ol (12: 1,2 products of 9-Li and 8, four diastereomers A, B, C, and D). R_f (20% EtOAc/hexane): 0.56. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ −0.23 (SiMe$_3$ **A**), −0.13 (SiMe$_3$ **D**), −0.11 (SiMe$_3$ **C**), −0.10 (SiMe$_3$ **B**), 0.60−1.90 (m, 6H), 2.00−2.35 (m, 4H), 2.69 (**B**, dm, J = 13.6 Hz), 4.21 (SCH **D**), 4.29 (SCH **C**), 4.38 (SCH **B**), 4.43 (SCH **A**), 5.39 (═CH **B**, dm, J = 10.3 Hz), 5.56 (═CH **B**, ddd, J = 10.1, 4.4, 2.8 Hz), 5.68 (═CH **A**, ddd, J = 10.1, 4.4, 2.4 Hz), 5.78−5.94 (═CH, m, 1H), 6.33 (═CH **D**, dm, J = 10.1 Hz), 6.46 (═CH **A**, dm, J = 10.1 Hz), 6.78−6.94 (m, 4H), 7.00−7.10 (m, 1H), 7.28−7.40 (m, 4H). ^{13}C NMR (75.4 MHz, C$_6$D$_6$, selected signals): δ −3.89 (SiMe$_3$ **A**), −3.71 (SiMe$_3$ **D**), −3.68 (SiMe$_3$ **C**), 64.83 (SCH **A**), 65.51 (SCH **B**), 65.83 (SCH **D**), 66.93 (SCH **C**), 71.19 (COH **D**), 71.57 (COH **C**), 73.50 (COH **A**), 73.54 (COH **B**). IR (neat): 3456 (OH), 3541 cm^{-1} (OH). MS: M$^+$ 382.1781 (calcd for C$_{23}$H$_{30}$OSSi, 382.1787).

3-[Phenylthio(3-methyl)benzyl]-5-trimethylsilylcyclohexanone (13: 1,4 products of 9-Li and 8, four diastereomers A, B, C and D). R_f (20% EtOAc/hexane): 0.44. ^{1}H NMR (300 MHz, CDCl$_3$): δ −0.22 (SiMe$_3$ **D**), −0.07 (SiMe$_3$ **A**), −0.02 (SiMe$_3$ **B** or **C**), 0.01 (SiMe$_3$ **C** or **B**), 0.85−1.63 (m, 2H), 1.75−3.06 (m, 9 H), 3.85 (SCH **D**, d, J = 10.3 Hz), 3.95 (SCH **C**, d, J = 10.7 Hz), 4.00 (SCH **B**, d, J = 7.0 Hz), 4.09 (SCH **A**, d, J = 5.9 Hz). ^{13}C NMR (75.4 MHz, CDCl$_3$, selected signals): δ −3.83 (SiCH$_3$ **A**), −3.77 (SiCH$_3$ **D**), −3.46 (SiCH$_3$ **B** or **C**), 56.93 (SCH **B** or **C**), 57.71 (SCH **D**), 59.31 (SCH **A**), 59.96 (SCH **C** or **B**), 211.45 (C═O **A**), 211.77 (C═O **D**). IR (neat): 1709 cm^{-1} (C═O). MS: M$^+$ 382.1799 (calcd for C$_{23}$H$_{30}$OSSi, 382.1787).

Phenylthio(3-methyl)benzyllithium (9-Li) and 5-trimethylsilyl-2-cyclohexenone (8): Effect of addition of THF to Et$_2$O at −120 °C. The previous procedure, used for the HMPA experiments with the system, was adapted in the following way: 3 mL of Et$_2$O were used as the solvent for **9**-H; 1 mL of Et$_2$O was used as the solvent for **8**; and THF was used in place of HMPA (5 equiv = 0.10 mL). The metalation was performed at 0 °C for 10 min before cooling to −120 °C.

Phenylthio(3-methyl)benzyllithium (9-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): DMPU dependence in 3:2 THF/Et$_2$O at −120 °C. The procedure for the HMPA experiments with this system was modified by substituting DMPU for HMPA (1 equiv of DMPU = 30.2 μL).

Phenylthio(3-methyl)benzyllithium (9-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): Effect of 1 equiv of [2.1.1]Cryptand in 3:2 THF/Et$_2$O at −120 °C. The procedure for the HMPA experiments with this system was modified by substituting [2.1.1]cryptand for HMPA (1 equiv of [2.1.1]cryptand = 65.7 μL).

NMR Spectroscopy. For the characterization of synthesized compounds, ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC-300 spectrometer with CDCl$_3$ as the solvent (unless otherwise stated) and tetramethylsilane as the internal standard. All multinuclear NMR experiments were performed in 10 mm NMR tubes using a wide-bore AM-360 spectrometer at 139.962 MHz (^{7}Li) or 145.784 MHz (^{31}P). The digital resolution was 0.51 Hz for ^{7}Li and 0.61 Hz for ^{31}P. For a typical 0.15 M solution, excellent signal-to-noise ratios were obtained after 32 transients for ^{7}Li and 80 for ^{31}P. ^{7}Li and ^{31}P spectra were generally transformed with Gaussian multiplication, with the GB parameter set to the fractional duration of the FID and the LB parameter set to −(digital resolution)/GB.

The lithium reagent samples were prepared in 10 mm thin-walled NMR tubes which were oven-dried, fitted with a septum (9 mm i.d.), and N_2 flushed. The outside top portion of the tube was lightly greased to make a better seal for the septum, which was held securely in place with Parafilm. Silicon grease was placed on the septum top to seal punctures, and the tubes were stored at −78 °C until the experiment was performed. Since nondeuterated solvents were used, the spectrometer was run unlocked, and shimming was performed on the ^{13}C FID of carbon 3 of THF. Although the spectrometer was unlocked during the acquisition, the field was generally very stable and only occasionally did a spectrum have to be reacquired due to a field shift. When a substance had to be added (HMPA, for example), the sample was ejected and placed in a −78 °C bath. To get HMPA to dissolve, the tube had to be repeatedly shaken, but each time was returned quickly to the cold bath. Temperatures were measured using a thermocouple submerged in a second NMR tube containing the same solvent mixture, or with an internal ^{13}C NMR chemical shift thermometer.[1i]

2-Methyl-1,3-dithianyllithium (1b-Li). To a dried, N_2-purged, 10 mm NMR tube fitted with a septum and maintained under positive N_2 pressure were added 72.5 mg (0.540 mmol) of 2-methyl-1,3-dithiane (**1b**-H), 2.1 mL of THF, and 1.4 mL of Et_2O. The NMR tube was cooled to −78 °C and 0.25 mL (0.540 mmol) of 2.13 M *n*-BuLi in pentane was added. The NMR tube was warmed to −20 °C for 5 h to complete the metalation. A series of ^{7}Li and ^{31}P NMR spectra at −135 °C were taken during an HMPA titration (1 equiv of HMPA = 93.8 μL).

α-(Phenylthio)(3-methyl)benzyllithium (9-Li). To a dried, N_2-purged, 10 mm NMR tube fitted with a septum and maintained under positive N_2 pressure were added 103 μL (108 mg, 0.504 mmol) of 3-methylbenzyl phenyl sulfide (**9**−H), 1.8 mL of THF, and 1.2 mL of Et_2O. The NMR tube was cooled to −78 °C and 0.27 mL (0.513 mmol) of 1.9 M *n*-BuLi in pentane was added. A series of ^{7}Li and ^{31}P NMR spectra at −127 °C were taken during an HMPA titration (1 equiv of HMPA = 87.7 μL).

Acknowledgment. We thank the National Science Foundation for financial support of this work and Procter and Gamble for a fellowship for W.H.S.

Supporting Information Available: ^{7}Li and ^{31}P spectra of an HMPA titration of **1b**-Li, and ^{1}H and ^{13}C spectra of **8**, **9**-H, and the products of the trapping experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010053W