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

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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 phenylthiobenzylolithiums 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 alklylation,2b and protonation,2d as well as the regiochemistry of imine metalation,3a allyl anion alkylations,3b and additions to α,β-unsaturated carbonyl compounds (Figure 1).3b,4,5 This last effect will be the topic of this paper.

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 shift1c and reactivity6 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,

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

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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.\textsuperscript{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,\textsuperscript{7} when it was found that the kinetic preference for 1,2 addition by metalled 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.\textsuperscript{8} No explanation was offered.

In 1977, Dolak and Bryson observed that isopropyl(phenylthio)methyl lithium underwent 1,4 addition to cyclohexene.\textsuperscript{9} They attributed this unexpected regioselectivity to the presence of HMPA, which was needed to perform the difficult metallation of isobutyl phenyl sulide. 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."\textsuperscript{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.\textsuperscript{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 cyclohexene (Figure 1).\textsuperscript{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)methyl lithium to 2-cyclohexene.\textsuperscript{11} Lower temperatures and the addition of HMPA favored 1,4 addition, conditions also known to favor separated ion pairs.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12}

In the research that follows, we used our NMR technique to test Cohen's proposal.\textsuperscript{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,\textsuperscript{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.\textsuperscript{14–g}

We have not experimentally addressed the aggregation states of the lithiodithianes, but previous work has shown that both 1a-Li and 1b-Li\textsuperscript{17d} as well as the 2-tert-butyl analog\textsuperscript{17d} in THF show C–Li coupling to only a single lithium in the $^1$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.\textsuperscript{17e} Cryoscopic measurements in THF confirm that 1a-Li is monomeric in solution,\textsuperscript{17a} and we presume that 1b-Li is also monomeric, since higher levels of alkyl substitution at a carbamion center invariably lead to lower levels of aggregation. The HMPA titration technique\textsuperscript{16} can also detect aggregation, since dimers and higher aggregates usually show a more complex sequence of HMPA solvates in the $^6$Li and $^{31}$P NMR spectra than do

monomers. Thus, mono and bis HMPA complexes of the dimers of PhLi, LiCl, LiPPh₂, LiNiPr₂, and lithium bis(trimethylsilyl)amide 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, 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 ³Li spectra are plotted. In a notation that will be used throughout this paper, the various organolithium species will be designated as C₀ or S⁴, 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 C₀ species first to C₁, then to C₂, followed by a jump in coordination to the separated ion, S⁴ (this is, in effect, a disproportionation of C₁ to C² and an S⁴). Only the first molecule of HMPA coordinates quantitatively; subsequent coordinations occur with increasing difficulty (i.e., C² maximizes at 2.75 equiv of HMPA), probably due to both steric and electronic effects. Free HMPA is detectable in the solution (by ³¹P 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, S⁴, 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.

**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/Et₂O at −135 °C.

**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-cyclohexene (2) and trans-2-hexenal (5) as functions of HMPA for 0.16 M 1b-Li in 3:2 THF/Et₂O at −125 °C (solid lines).

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 S⁴ 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, 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 equilibrium with the CIPs, even though their equilibrium concentrations might be negligible.

Even before the fully HMPA-solvated S⁴ 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., K₁₂ < K₁₄ < K₂₄) and the rate at which the CIP equilibrates with its SIP probably also increases (i.e., kₕ₁₂ < kₕ₁₄ < kₕ₂₄). Thus, the apparent correlation of the 1,4-addition product of cyclohexene with the fraction of C¹ in Figure 2 could actually be a correlation with the undetected species S¹ in equilibrium with it, if K₁₂/kₕ₁₂ ≫ K₂₄. Under this analysis, C⁰ and S⁴ are the principal 1,2- and 1,4-forming species, respectively, and the product distribution reflects the C⁰/C¹ equilibrium.

Alternatively, the rate of formation of the SIP (kₕ₁₂ and/or kₕ₁₄) 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, kₕ₁₂ > k₅₀ and the 1,2 product predominates, whereas when HMPA is present,

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

\[
\begin{align*}
C_0 & \quad k_{12}^{C_0} \\
C_1 & \quad k_{12}^{C_1} \\
C_2 & \quad k_{12}^{C_2} \\
S_0 & \quad k_{12}^{S_0} \\
S_1 & \quad k_{12}^{S_1}
\end{align*}
\]

The reactivity of the reactive intermediates involved. Turned to stereochemical probes to provide further insight into the proposed explanation is not possible. We therefore used their SIPs (\(k_{12}^{C_1}, k_{12}^{S_1}\)) and SIPs (\(k_{12}^{C_0}, k_{12}^{S_0}\)) to test the hypothesis that the C2 species remarkably well. This suggests that when C2 is present, the enal is reacting with the \(S_1\) that is in equilibrium with it (and whose concentration is always directly proportional to it). With less HMPA present, in the absence of C2, the enal reacts with C0 or C1, i.e., the rates of conversion of these CIPs to their SIPs (\(k_{12}^{C_0}, k_{12}^{S_0}\)) are too slow to permit significant reaction between the enal and S0 or S1. 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 \(-120^\circ C\)), 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)benzyl lithium (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.

The diastereoselectivities for this system to form the adducts 10 and 11 were constant; however, they were too large23 (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 C0, C1, and C2 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-

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lithium (9-Li). Benzyl lithium itself is monomeric in THF, and α-phenylthiobenzyl lithium crystallizes as a monomeric trisolvate from THF. Other benzyllithium reagents such as 2-phenyl-1,3-dithiane, α-methylsulfonylbenzyl lithium, and α-dimethylaninobenzyl lithium are also monomeric in THF solution. 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° directly to S1. 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 Et2O with incremental amounts of THF added, and also in 3:2 THF/Et2O (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 Et2O 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 Et2O solution increases the solvent strength enough to stabilize small amounts of SIP (S°), which are solely responsible for the 1,4 product under THF/Et2O conditions (Mechanism B).

We have checked the effect of concentration of 9-Li on the ratio of 1,2 to 1,4. 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)methyl lithium. 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.

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). 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, for Yamamoto’s bulky aluminum catalysts. 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 addition 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.

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

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(23) The high stereoselectivity in this system is surprising, since the addition of 1a-Li to 4-tert-butylcyclohexane gives a 60:40 ratio of axial to equatorial attack: Juáristi, 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.
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, \(\Delta G^\circ > 19\) kcal/mol.\(^{(28)}\) The reaction of 9-Li with cyclohexenone has \(\Delta G^\circ < 9.7\) 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.\(^{(29)}\)

Figure 8 shows the results for the 1,2 diastereomers. Only the Et_2O/THF experiments are shown because 1,4 addition 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).

**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 benzenophenone ketyl before use. Hexamethylyphosphoramidite (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.


\(^{(27)}\) 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.


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

Syntheses: 5-Trimethylsilyl-2-cyclohexene-1-one (8). This compound was synthesized according to a literature procedure and purified by distillation (60–63 °C at 1 mmHg [lit. 65.5–67 °C at 2.0 mmHg]).


A syringe was used to transfer 4.0 mL of (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 N2 pressure.

A dried, N2-purged, 5 mL conical flask fitted with a septum was charged with 0.6 mL of THF, 0.4 mL of Et2O, and 12.0 µL (11.9 mg, 0.124 mmol) of 2, and both flasks were cooled under positive N2 pressure to −120 °C using an N2/pentane slurry. A N2 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 N2 pressure inside being dissipated through the cannula, purging it of any liquids and preventing a back flow. The N2 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 EtO (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 EtO/hexane were added. The solution was washed with 3 × 20 mL of H2O, dried over anhydrous MgSO4, and concentrated by rotary evaporation.

The ratios of products were determined using the following 1H NMR signals in CDCl3:

1-[2-(2-Methyl-1,3-dithianyl)-2-cyclohexene-1-ol (3b): 1,2 product 1b-Li and 2, Rf (20% EtOAc/hexane): 0.32. 1H NMR (300 MHz, CDCl3): δ 1.70–2.10 (m, 8H), 1.77 (CH3, s, 3H), 2.28 (OH, s, 1H), 2.89–2.98 (m, 4H), 5.97–6.05 (CH, m, 1H). 13C NMR (75.4 MHz, CDCl3): δ 18.33 (CH3), 24.31 (CH2), 25.00 (CH3), 25.13 (CH2), 26.69 (CH2), 26.82 (CH3), 31.01 (CH), 59.44 (SC), 75.62 (COH), 128.35 (SCH), 132.84 (SCH), IR (neat): 3466 cm−1 (OH). MS: M+ 230.0793 (calcd for C11H18OS2, 230.07991).

2-Methyl-1,3-dithianithium (1b-Li) and 2-cyclohexene (2): HMPA dependence in 3:2 THF/Et2O 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 Et2O, 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 cooled inside. The flask (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 N2 inlet needle was introduced into the flask, purging the flask and the cannula. When purging was complete, the free end of the cannula was plunged by imbedding it into a thick piece of septum. A stock solution of 1b-Li 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 Et2O (the resulting solution is 0.20 M in 5). A syringe was used to transfer 1 mL (0.22 mmol) of 5 to the conical flask. For these experiments, 1 equiv of HMPA = 34.8 µL. Product ratios were determined using the following 1H NMR signals in CDCl3:

1. Product ratios were determined using the following 1H NMR signals in CDCl3: δ 3.91 (CH3, s), 22.98 (CH2), 26.61 (CH3), 38.45 (CH2), 129.23 (CH), 151.20 (CH), 199.81 (C).
1-[2-(2-Methyl-1,3-dithianyl)]-2-hexen-1-ol (6b; 1 product of 1b-Li and S): Rf (20% EtOAc/hexane): 0.41. 1H NMR (300 MHz, CDCl3): δ 0.91 (CH3, t, J = 7.4 Hz, 3H), 1.39 (H8, s, 3H), 1.44 (H7, q, J = 7.3, 7.2 Hz, 2H), 1.80–1.96 (m, 1H), 2.02–2.15 (m, 3H), 2.65 (SCH3, dm, J = 14.2 Hz, 2H), 2.80 (OH, br s, 1H), 3.03 (SCH3, ddd, J = 14.3, 11.2, 6.1, 2.9 Hz, 2H), 4.47 (OCH, br d, J = 6.1 Hz, 1H), 5.64 (CH=C=, ddt, J = 15.3, 6.1, 1.5 Hz, 1H), 5.85 (CH=C=, dt, J = 15.4, 6.8, 1.1 Hz). 13C NMR (75.4 MHz, CDCl3): δ 13.65 (CH3), 22.17 (CH2), 22.26 (CH2), 23.42 (CH2), 25.75 (CH2), 26.12 (CH2), 34.47 (CH2), 53.29 (SCh2), 125.67 (C=CH), 134.91 (C). IR (neat): 3466 cm−1 (OH). MS: M+ 232.0963 (calcd for C11H20O2S2, 232.0956).

1,3-Dithianyllithium (1a-Li) and 5-trimethylsilyl-2-cyclohexen-1-one (8): Effect of HMPA in 3:2 THF/EtO 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 metatation is instantaneous, using 1.8 mL of THF, 1.2 mL of EtO, 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 1H NMR signals in CDCl3: 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), 4.01 (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 1H NMR signals in CD2Cl2: starting material, δ 3.95 (s, 2H); 1,2 diastereomers (12), 0.421 (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-[Phenyliothio(3-methyl)benzyl]-5-(trimethylsilyl)-2-cyclohexen-1-one (11: 1,2 products of 9-Li and 8, four diastereomers A, B, C, and D): Rf (20% EtOAc/hexane): 0.56. 1H NMR (300 MHz, CD2Cl2): δ −0.23 (SiMe3 A), −0.13 (SiMe3 D), −0.11 (SiMe3 C), −0.10 (SiMe3 B), 0.60–1.90 (m, 6H), 2.00–2.35 (m, 4H), 2.69 (B, dm, J = 13.6 Hz), 4.21 (SCH2 A), 4.29 (SCH2 C), 4.38 (SCH2 B), 4.43 (SCH2 D), 5.39 (SCH2 B, dm, J = 10.3 Hz), 5.56 (SCH2 B, ddd, J = 10.1, 4.4, 2.8 Hz), 5.68 (SCH2 A, ddd, J = 10.1, 4.4, 2.8 Hz), 5.78–5.94 (SCH2 A, dm, J = 10.1 Hz), 6.33 (SCH2 B, dm, J = 10.6 Hz), 6.46 (SCH2 A, dm, J = 10.1 Hz). IR (neat): 3348 cm−1 (OH), 3541 cm−1 (O). MS: M+ 382.1781 (calcd for C23H28O3S2, 382.1787).

1-[Phenyliothio(3-methyl)benzyl]-5-trimethylsilylcyclohexane (13): 1,4 products of 9-Li and 8, four diastereomers A, B, C, and D): Rf (20% EtOAc/hexane): 0.44. 1H NMR (300 MHz, CD2Cl2): δ −0.22 (SiMe3 D), −0.07 (SiMe3 A), −0.02 (SiMe3 B or C), 0.01 (SiMe3 B or C), 0.85–1.63 (m, 2H), 1.75–3.06 (m, 9H), 3.85 (SCH2 A, d, J = 10.3 Hz), 3.95 (SCH2 C, d, J = 10.7 Hz), 4.00 (SCH2 B, d, J = 7.0 Hz), 4.09 (SCH2 A, d, J = 5.9 Hz). 13C NMR (75.4 MHz, CD2Cl2, selected signals): δ −3.83 (SiMe3 A), −3.71 (SiMe3 D), −3.68 (SiMe3 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 (O). MS: M+ 382.1799 (calcd for C23H28O3S2, 382.1877).

Phenyliothio(3-methyl)benzilithium (9-Li) and 5-trimethylsilyl-2-cyclohexenone (8): Effect of addition of THF to EtO at −120 °C. The previous procedure, used for the HMPA experiments, was replaced in the following way: 3 mL of EtO was used as the solvent for the solid 9-H; 1 mL of EtO 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.

Phenyliothio(3-methyl)benzilithium (9-Li) and 5-trimethylsilyl-2-cyclohexenone (8): Effect of 1 equiv of [2.1][Cryptand] in 3:2 THF/EtO at −120 °C. For the characterization of synthesized compounds, 1H and 13C NMR spectra were acquired on a Bruker AC-300 spectrometer with CDCl3 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 (1H) or 145.784 MHz (13C). The digital resolution was 0.51 Hz for 1H and 0.61 Hz for 13C. For a typical 0.15 M solution, excellent signal-to-noise ratios were obtained after 32 transients for 1H and 80 for 13C. 1H and 13C 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 \((\text{digital resolution})/\text{GB}\).

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 \(\text{N}_2\) 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 \(-78^\circ \text{C}\) until the experiment was performed. Since nondeuterated solvents were used, the spectrometer was run unlocked, and shimming was performed on the \(^{13}\text{C}\) 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 \(-78^\circ \text{C}\) 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 \(^{13}\text{C}\) NMR chemical shift thermometer.\(^{\text{11}}\)

2-Methyl-1,3-dithianyllithium (1b-Li). To a dried, \(\text{N}_2\)-purged, 10 mm NMR tube fitted with a septum and maintained under positive \(\text{N}_2\) 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\(_2\)O. The NMR tube was cooled to \(-78^\circ \text{C}\) and 0.25 mL (0.540 mmol) of 2.13 M \(n\)-BuLi in pentane was added. The NMR tube was warmed to \(-20^\circ \text{C}\) for 5 h to complete the metalation. A series of \(^7\text{Li}\) and \(^{31}\text{P}\) NMR spectra at \(-135^\circ \text{C}\) were taken during an HMPA titration (1 equiv of HMPA = 93.8 \(\mu\)L).

\(\alpha\)-(Phenylthio)(3-methyl)benzylolithium (9-Li). To a dried, \(\text{N}_2\)-purged, 10 mm NMR tube fitted with a septum and maintained under positive \(\text{N}_2\) pressure were added 103 \(\mu\)L (108 mg, 0.504 mmol) of 3-methylbenzyl phenyl sulfide (9-H), 1.8 mL of THF, and 1.2 mL of Et\(_2\)O. The NMR tube was cooled to \(-78^\circ \text{C}\) and 0.27 mL (0.513 mmol) of 1.9 M \(n\)-BuLi in pentane was added. A series of \(^7\text{Li}\) and \(^{31}\text{P}\) NMR spectra at \(-127^\circ \text{C}\) were taken during an HMPA titration (1 equiv of HMPA = 87.7 \(\mu\)L).

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Supporting Information Available: \(^7\text{Li}\) and \(^{31}\text{P}\) spectra of an HMPA titration of 1b-Li, and \(^1\text{H}\) and \(^{13}\text{C}\) 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.

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